SYNTHETIC APPROACHES TO THE DIHYDROKAVAIN STRUCTURE

By

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INTRODUCTION

The natives of a number of islands of the South Pacific have long employed the root of the Piper methysticum plant to prepare an intoxicating beverage. This drink, commonly known as kava, or kava-kava, if consumed in sufficient amount, produces a state of euphoria followed shortly by muscular relaxation and loss of control of the extremities, and finally a period of dreamless sleep which may last ten hours or more. Upon awakening, there is apparently no hangover or other undesirable effect (1, 2).

Among the constituents of the kava resin, only one, called dihydrokavain, had been shown on experimental animals to produce the characteristic soporific effect. This material was isolated and characterized by Borsche in 1930 (3), but it was not until 1938 that van Veen showed it to have the characteristic narcotic and soporific action of the kava beverage (2, 4, 5).

The rapid onset of action, plus the type of quiet, dreamless sleep it produces, and the lack of hangover indicate that such a substance would make a highly desirable soporific drug. The original objective of this research was the synthesis and subsequent pharmacological study of dihydrokavain. However, after investigating a number of approaches to the solution of the synthetic problem, it

became apparent that the synthesis itself would be a major problem. Several possible routes to the type of structure seen in the dihydrokavain looked promising, and it seemed of interest to investigate these approaches, and to evaluate them, if successful, with respect to yield, convenience and availability of starting materials.

HISTORICAL AND PAST WORK

Probably the first published account of kava was made by Captain James Cook in his "Three Famous Voyages Round the World." It was an important part of the Polynesian materia medica, in addition to its narcotic properties being used as a cure for skin diseases, by causing a "disquamation of the cuticle.... A singular effect of taking a course of ava was the cracking and coming off of the cuticle over the whole body of the patient with which, it is maintained, the system parted with maladies."(6).

As travel among the South Pacific Islands became more common, and more people observed the effects of the beverage, reports of its action and investigation of its constituents began to appear in the scientific literature. Considerable interest and rather widespread usage of the crude resin from the root of the plant is evident from the literature particularly during the latter half of the nineteenth and early twentieth centuries.

The early investigations of physiological activity were concerned with the crude resin rather than the isolated

constituents. Most of the reports were very enthusiastic. Lewin (7) proposed its use as a local anesthetic, stating that hypodermic injection caused an insensibility to thermal, electrical and chemical stimuli, the effect not passing off for five days. After applying a small quantity of the resin to the tongue, the bitterest drug could not be tasted. When instilled into the eye, complete insensitivity of the conjunctiva was produced, the iris retaining its reflex responsiveness. No lesions from hypodermic or external applications appeared. He compared the material favorably with cocaine. Orr (8) reported using the resin for years as a diuretic and urinary antiseptic, especially valuable for sub-acute and chronic infections. Its use as an anti-gonorrheal agent was exploited by the German firm J. D. Heidel-E. de Haën A.-G. (9) who prepared a proprietary remedy, "Gonosan," consisting of a solution of 20% Kava resin and 80% santal oil. This firm also subsidized a major portion of the chemical investigation of its constituents, including the work of Borsche, whose comprehensive study was published in a series of fourteen papers between 1914 and 1933.

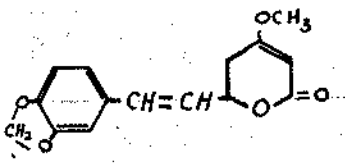
One of the most recent pharmacological studies was carried out by Schubel (10) who attempted to determine what constituents were responsible for certain effects. He ascribed the local anesthetic action to compounds of the benzoic and cinnamic acid group. Allokavain acid (11) (referred to by Schubel as kavain acid) was found to lower reflex excitability and raise blood pressure. A nitrogen containing

oil, not further identified, isolated from the residue by vacuum distillation, produced weak narcotic effects and increased salivary secretion. None of the kava lactones was mentioned as physiologically active.

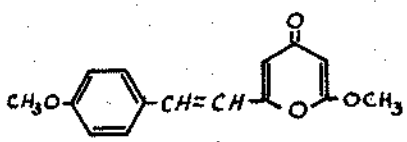
It is curious that of the kava lactones, the principle constituents of the resin, no physiological activity had been reported until the work of van Veen in reproducing the soporific effect with dihydrokavain, and that of the many effects reported from the resin, no definite claims of determination of the responsible ingredients have been reported.

Chemical Investigations

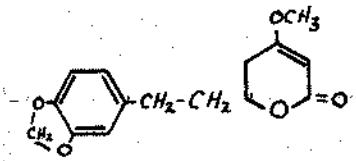
The main constituents isolated from the resin are a group of lactones of the following structures:



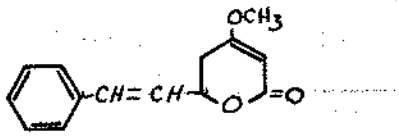
Methysticin



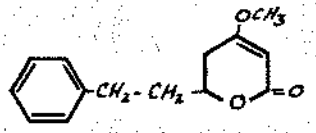
Yangonin



Dihydromethysticin

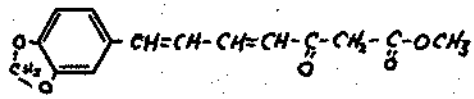


Kavain



Dihydrokavain

The chemical investigation of kava root began in 1860, when Cuzent, a pharmacist in the French navy, and simultaneously Gobley (13) and O'Rorke (14) isolated the crystalline material, methystisin. They reported their results of combustion analysis, but it remained for Pomeranz (15) to establish the empirical formula and postulate a structure. He failed to recognize the presence of the lactone ring, attributing to it the structure of the isomeric methyl piperonyl acetoacetate:

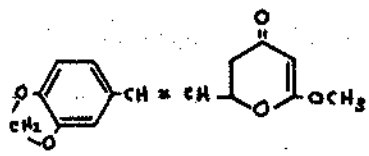


In 1874, a second crystalline substance was isolated, first by Hoelting and Kopp (16). This compound, Yangonin, was investigated by Winzheimer (17), who established the empirical formula and detected the presence of the lactone ring. Later, Borsche and Gerhardt (18) thoroughly investi-

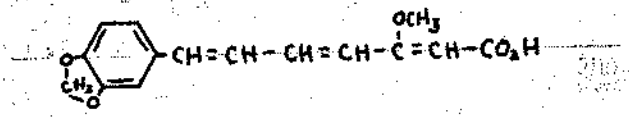
gated this material and arrived at the correct structure which Borsche and Bodenstein confirmed by synthesis (19).

The name "kavain" was very popular with early investigators and was applied indiscriminately to materials which they isolated (13, 20, 21). Frequently upon further examination, these materials proved to be either methysticin or yangonin, which occur in higher amounts and are more readily separated than kavain. Thus, it is not clear if an earlier worker than Borsche deserves credit for the isolation of this material; undoubtedly, Borsche was the first to isolate the pure material, and to establish its structure (3). The structural features were elucidated through work on the more readily isolated methysticin which differs from kavain only in the substitution on the phenyl ring. The similarity in behavior between the parent compounds and respective degradation products made the structural similarity of methysticin and kavain readily apparent.

The formula for methysticin proposed by Pomeranz was accepted until Murayama and Shinozaki noticed its optical activity (22). The compound, $C_{15}H_{14}O_5$, upon treatment with hot 10% sodium hydroxide was converted to an isomeric, non-optically active compound which Murayama and Shinozaki considered to have the Pomeranz structure, methyl piperonyl acetate. On this basis, they proposed a structure with a 2-methoxyl-5,6-dihydro-4-pyrone ring.



Borsche, Rosenthal and Meyer synthesized methyl piperonyl acetate (23) and found it to be different from the material obtained on treatment of methysticin with hot 10% sodium hydroxide. The material dissolved unchanged on warming with dilute carbonate solution or ammonia solution, and upon melting it lost exactly one mole of CO_2 but no methoxyl group. This ruled out the β-keto ester arrangement. Also it was found to be easily hydrolyzed by dilute hydrochloric acid to yield methanol, CO_2, and a doubly unsaturated ketone, $C_{13}H_{12}O_3$, which was identified as piperal acetone $CH_2O_2C_6H_3CH{:}CHCH{:}CHCOCH_3$. Its properties suggested to Borsche a substituted β-methoxy crotonic acid (24), and also suggested a bridge between the methysticinic acid from methysticin and the synthetic methyl piperonyl acetate. The methysticinic acid was treated with diazomethane to convert it to the methyl



Methysticinic Acid

ester. Careful treatment with methanolic hydrochloric acid cleaved the ether methoxyl without attacking the ester linkage, producing a material identical in all respects with his synthetic methyl piperonyl acetate. The reactions are summarized below:

$R = CH_2O_2C_6H_3CH{:}CHCH{:}CH$

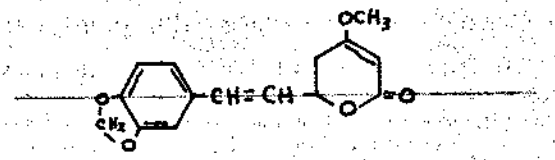
$$R\text{-}CO\text{-}Cl + [CH_3COCHCO_2CH_3]^-Na^+ \longrightarrow RCOCH(COCH_3)CO_2CH_3$$

$$RCOCH(COCH_3)CO_2CH_3 \xrightarrow{\text{aq. } NH_3} RCOCH_2CO_2CH_3$$

$$RCOCH(COCH_3)CO_2CH_3 \xrightarrow{\text{alc. } HCl} RCOCH_2CO_2CH_3$$

$$RC(OCH_3){:}CHCO_2H \xrightarrow{CH_2N_2} RC(OCH_3){:}CHCO_2CH_3$$

Since there was no criterion for the migration of the methoxyl group from the α- to the γ-position in the dihydropyrone ring, as would be necessary if the Mureyama-Shinozaki structure were correct, Borsche concluded that the structure should properly be represented as an α-keto-γ-methoxy dihydropyran:



Kavain acid, $C_{14}H_{14}O_3$, was isolated by Borsche and Rath (25) by treatment of the resin remaining after extraction of methysticin and yangonin with 10% sodium hydroxide solution. They later established this acid to be the methylenedioxy-free analogue of methysticinic acid (26). From this, it was reasoned that there must exist in kava resin a lactone, kavain, $C_{14}H_{14}O_3$, analagous to methysticin. This material was isolated in pure form by a chromatographic procedure (4), and characterized by a series of reactions analogous to those by which methysticin was characterized.

The presence of the dihydro compounds was detected when Borsche and Feitzsch (27), investigating a material which they had called pseudomethysticin, subjected it to hydrogenation and found that it took up only a fraction of the amount of hydrogen necessary to convert methysticin to dihydromethysticin, establishing pseudomethysticin to be a mixture of methysticin and dihydromethysticin. On the basis of the mutual occurrence

of these two substances in kava resin, they looked for and isolated dihydrokavain (3).

The Soporific Principle

In his thirteenth paper (26), Borsche stated that none of the compounds which he had isolated and characterized was responsible for the characteristic effect of the kava beverage. In 1938, van Veen (2, 4) reported the isolation of a substance with which he was able to reproduce the soporific effect. Using an adsorption chromatography technique, and developing an extract of the root on the column, then dividing the column into portions and eluting the adsorbed material, he was able to locate the active material concentrated in one zone on the column, and he isolated the crystalline substance. At first, he believed the material was different from any of the substances isolated by Borsche, but later established it to be dihydrokavain (5). That Borsche had failed to notice the soporific effect was ascribed to the mode of administration. It was found necessary that the material be in a finely emulsified form; the powdered solid was ineffective.

The material, tested on pigeons and monkeys, was found to be very active. Pigeons, after administration orally by pipette of 50 to 70 mg., became sleepy in 8 to 15 minutes, and the sleep which followed lasted for 2 to 10 hours. Upon awakening, the pigeons immediately began eating, and appeared completely normal. Monkeys required 3 to 5 times more drug,

the first sign of response being a loss of control over the extremities within 15 to 30 minutes, after which a deep sleep set in which lasted 15 hours or more. In all cases, the animals recovered with apparently no ill effects.

The foregoing was the situation with regard to the kava constituents and dihydrokavain as revealed by a literature search up to the time this problem was started. Since beginning this work, the author has found in the literature two reported syntheses of kavain. These will be discussed in the next section.

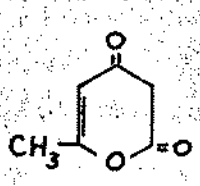
DISCUSSION

The dihydrokavain molecule can best be named as a pyrone rather than as a lactone; namely, 4-methoxy-6-(β-phenyl) ethyl-5,6-dihydro-2-pyrone. Of the possible routes to this pyrone structure, two methods lead to structures unsaturated in the 5,6-position. One was used by Borsche in the synthesis of Yangonin (19). Starting materials for this synthesis included ethyl acetonedicarboxylate and p-methoxy cinnamoyl chloride. Steps required to obtain the final product include condensation of the starting materials, cyclisation, saponification, decarboxylation and methylation.

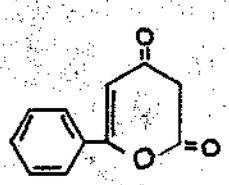
The other method involves an intermolecular condensation between two molecules of the appropriate β-keto ester to give the dehydro acid, as in the well-known synthesis of dehydroacetic acid. Borsche, in his last paper on the kava constituents (28), reported on many of the characteristic reactions of β-keto esters, using ethyl cinnamoyl acetate as the ester. Included in these reactions was the preparation of dehydrocinnamoylacetic acid, but he made no mention of attempting to convert this material into the corresponding pyran-2,4-dione.

In order to arrive at the dihydrokavain structure by either of the above procedures, it is necessary to hydrogenate the double bond in the 5,6-position. Therefore, while investigating these routes to the pyronone structure, attempts

were being made to develop a procedure to selectively hydrogenate this position, using as model compounds 6-methylpyran-2,4-dione (I) and 6-phenylpyran-2,4-dione (II).

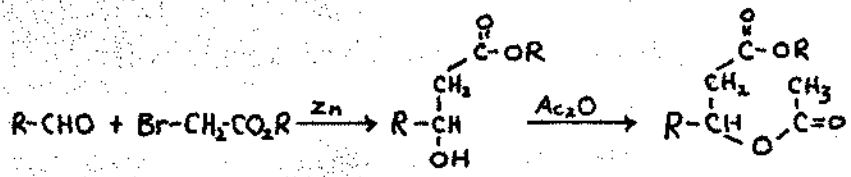


I



II

Two procedures which would preclude this hydrogenation step, and produce the 5,6-dihydro derivative directly were investigated. One depended upon the success of a reaction which might be considered a combination acetoacetic ester condensation-Dieckmann cyclization. The necessary intermediate for this condensation was an acetylated β-hydroxy ester, which was obtained through a Reformatsky reaction followed by acetylation of the hydroxyl group:



The other procedure, also employing a Reformatsky reaction as a key step, involved the condensation of a β-methoxy crotonic ester with the appropriate aldehyde, followed by lactonization.

The experimental work which was done on these approaches, including the pertinent references to related work, will be

solution, but in such small amount it would have been invisible if collected on a filter. Long standing in the refrigerator or at room temperature until the solvent evaporated did not produce any more solid. This step was repeated twice, with slight modifications in procedure and work-up, but similar results were obtained.

In the hope that the material was the acetylated, cyclized product, the next procedure, treatment with 1 N. methanolic sodium hydroxide, was carried out. From this treatment, upon acidification, a solid product which analyzed correctly for the desired product, 5-carbethoxy-6-(β-phenyl) ethyl-pyran-2,4-dione, m.p. 85-6°, was obtained. Hydrolysis of the ester group yielded the 5-carboxy derivative, m.p. 162-162.5° d. Little material was on hand with which to investigate the decarboxylation step, and this was consumed after three attempts. The procedure of Borsche, employing nitrobenzene as the solvent, was used in the first two attempts. In the first run, a small amount of solid material was isolated from the tarry residue which melted smoothly, without evidence of effervescence, at 135-8°, but in insufficient amount for further investigation. In the second run, none of this material was isolated, nor could any starting material or other identifiable product be isolated.

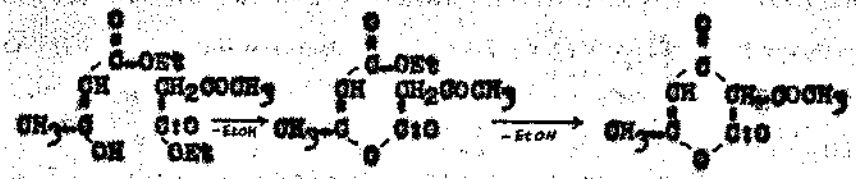
Another attempt, using pyridine as the solvent in a procedure similar to that employed by Corey (30) in decarboxylating half ester of α,β-unsaturated malonic acids, was made with slightly better results. A solid which melted

without decomposition at 139-141° was obtained in an amount about equal to that obtained in the nitrobenzene procedure, but from about half as much starting material. Unfortunately, only about 100 mg. of starting material was available, so the method was not investigated further.

Up to the carboxylic acid stage, the overall yield calculated on the basis of ethylacetonedicarboxylate was about 9%. This was reduced to about 3%, if calculated from citric acid. In view of this low yield, and the fact that there were three further steps, decarboxylation, hydrogenation and methylation, it was not considered worthwhile to repeat the lengthy process to obtain more material to further investigate the decarboxylation reaction.

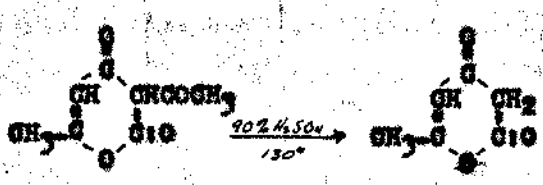
THE DEHYDRO-ACID APPROACH

Certain 6-substituted pyran-2,4-diones can be prepared by an intermolecular condensation between two molecules of a β-keto ester. This condensation was first observed by Guether (31) who obtained dehydroacetic acid upon pyrolysis of ethyl acetoacetate. A method for obtaining dehydroacetic acid in good yield was developed by Arndt and Nachtway (32,33). According to Arndt (32,34) the mechanism involves first a reversible transesterification between the enol form of one molecule and the ester carbonyl of another, followed by a Claisen condensation, catalyzed by base, to yield the product. Because of the reversibility of the first step, it



it is necessary that the alcohol be removed as it is formed in order to force the reaction to completion. A trace of sodium bicarbonate serves to catalyze the subsequent Claisen condensation.

Collie (35) observed that upon treatment of dehydroacetic acid with 90% sulfuric acid, the acyl group was cleaved, resulting in 6-methylpyran-2,4-dione. That structure is very similar to the pyrone ring present in the kava



constituents, requiring only conversion to the enol methyl ether to produce the Yangonin type structure, while hydrogenation of the 5,6-double bond, followed by methylation, would produce the methysticin-kavain type structure.

In order to obtain the proper substituent on the pyrone ring to obtain dihydrokavain, it is necessary to use as the β-keto ester a hydrocinnamoylacetic acid ester. As previously mentioned (p. 11), Borsche prepared ethyl cinnamoyl

acetate from which he obtained dehydrocinnamoyl-acetic acid. By treating the sodio derivative of ethyl acetoacetate with cinnamoyl chloride he obtained ethyl cinnamoyl acetoacetate in good yield, which he isolated and purified as the copper salt. After recovery of the ester from the copper salt, it was treated with 75% acetic acid to yield ethyl cinnamoyl acetate in about 50% yield, together with some benzalacetone and cinnamic acid. Upon subjecting this material to vacuum distillation, only a small amount distilled over unchanged, and from the residue in the distilling flask, dehydro-cinnamoyl acetic acid (3-cinnamoyl-6-styrylpyran-2,4-dione) was recovered.

Also in Borsche's work, ethyl cinnamoyl acetate was hydrogenated with a colloidal palladium catalyst to give ethylhydrocinnamoyl acetate. Upon distillation of this material, some unchanged ester was recovered as distillate, while from the residue the corresponding dehydro acid, 3-hydrocinnamoyl-6-(β -phenyl) ethylpyran-2,4-dione was recovered, m.p. 95°.

In the present work, the investigation of this approach dealt mainly with the hydrogenation of the 5,6-double bond, since the probability of arriving at the desired 6-(β -phenyl) ethylpyran-2,4-dione seemed clearly established. However, in a preliminary examination, a small amount of 3-hydrocinnamoyl-6-(β -phenyl) ethylpyran-2,4-dione was prepared. The procedures used were modifications of Borsche's procedures, using as starting material hydrocinnamoyl chloride rather than cinnamoyl chloride. The product of the condensation

Since it was felt at the time that conditions for hydrogenating the 5,6-double bond could be worked out, a similar sequence of reactions were run, using hydrocinnamoyl chloride instead of p-methoxycinnamoyl chloride, in the hope that ultimately dihydrokavain could be obtained. Ethyl acetonedicarboxylate was prepared from citric acid by the procedure of Ingold and Nicholls (29), then converted to the sodio derivative, and condensed with hydrocinnamoyl chloride. Considerable effort was expended in trying to obtain the product as a solid, since the analogous material prepared by Borsche had been obtained crystalline, m.p. 51-2°. However, no treatment was successful, nor could the product be distilled at reduced pressure without decomposition. When distillation was attempted, the material started darkening before the temperature of the heating bath reached 100°, and when the bath had reached 150°, the flask contents were very black, and no distillate had been obtained. The product was obtained in a pure state, however, through the copper derivative.

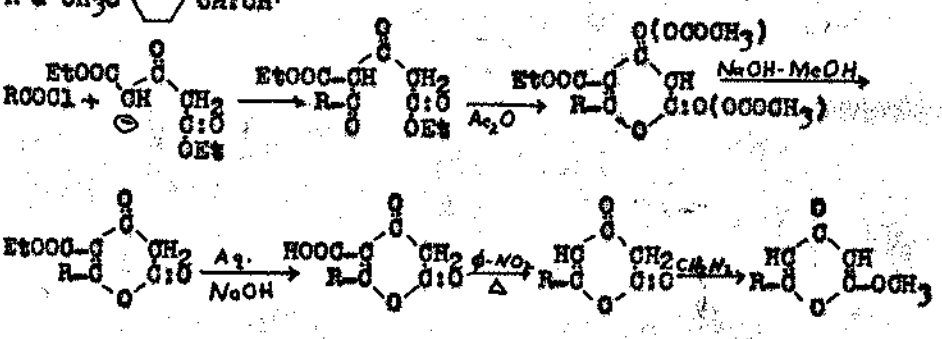
The cyclisation step by Borsche had produced a mixture of O-acetylated lactones, mainly 2-acetoxy-5-carbethoxy-6-p-methoxystyryl-4-pyrone, m.p. 104-5°, and a little of the 4-acetoxy-2-pyrone isomer, m.p. 220°. In this step in the present study an oil was obtained which was again subjected to a variety of treatments in an attempt to obtain a solid product. On treatment with methanol or acetone, just a trace of solid material would separate and remain suspended in the

discussed in the following sections in the order in which they have been mentioned.

It may be well to point out that the naturally occurring products are optically active, and the synthetic products are racemic mixtures, ±-kavain and ±-dihydrokavain. However, for the sake of simplicity in writing, the connotation designating optical activity will be omitted.

THE ETHYL ACETONEDICARBOXYLATE APPROACH

In his synthesis of Yangonin, Borsche (19) condensed p-methoxy cinnamoyl chloride with the sodio derivative of ethyl acetonedicarboxylate, converted the product to the enol-lactone by heating with acetic anhydride, with simultaneous O-acetylation, to get a mixture of isomeric O-acetylated 6-p-methoxy styryl-5-carbethoxypyran-2,4-diones. The acetyl groups were removed by hydrolysis with 1 N. methanolic sodium hydroxide, and the ethyl ester hydrolysed by 2 N. aqueous sodium hydroxide. The carboxyl group was removed by refluxing with nitrobenzene, and the final product obtained by methylation with diazomethane.



of hydrocinnamoyl chloride with the sodic derivative of ethyl acetoacetate formed a copper derivative when treated with a saturated cupric acetate solution, m.p. 130-1° after recrystallization from acetone-petroleum ether. Borsche (28) prepared this material by hydrogenation of ethyl cinnamoyl acetoacetate, and reported the m.p. of the copper compound as 136°.

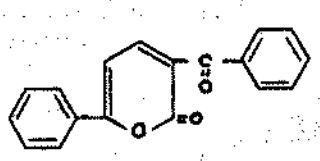
The method by which Borsche had hydrolyzed the acetyl group in ethyl cinnamoyl acetoacetate, employing 75% acetic acid was unsatisfactory for the cleavage of the dihydro product. The method of Shriner, Schmidt and Roll (36), using ammonium chloride and ammonia, was also unsatisfactory, yielding mainly hydrocinnamic acid. However, by using ammonia solution and warming at 60° for one-half hour (23), a product was obtained which, when subjected to vacuum distillation, gave only a few drops of distillate at a bath temperature of 190-200°, but the residue in the distilling flask, upon cooling, deposited long crystalline needles which, when recrystallized from petroleum ether, had m.p. 94-5°, agreeing with the dehydrohydrocinnamoyl-acetic acid of Borsche. Not enough of this material was obtained to attempt the cleavage with 90% sulfuric acid.

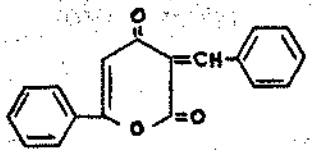
Hydrogenation Experiments

A crucial step in the synthesis of the kavain structure from the dehydroacids is the hydrogenation of the 5,6-double bond. At the time this investigation was undertaken, 6-methyl-5,6-dihydropyran-2,4-dione had been synthesized,

and its physical properties reported (37). During this investigation, the analogous 6-phenyl-5,6-dihydropyran-2,4-dione was reported (38,39,40). Therefore, by choosing as model compounds for the hydrogenation experiments dehydroacetic acid and dehydrobenzoylacetic acid, and especially their derivatives, 6-methylpyran-2,4-dione and the 6-phenyl analogue, successful hydrogenation could be easily verified. The synthesis of the 5,6-dihydropyran-2,4-diones will be discussed later.

Hydrogenation of various pyrones, particularly γ-pyrones, have been extensively investigated (41), and a number of workers have investigated the hydrogenation of dehydroacetic acid. Some of the earliest work was done by Oppenheim and Precht (42) who employed zinc and hydrochloric acid and obtained a product which had lost an oxygen atom, m.p. 187°. On chemical reduction of dehydrobenzoylacetic acid by Perkin (43), who used sodium amalgam, a similar observation was made, i.e., the loss of oxygen occurred. Alternate structures for the resulting compound were proposed by Feist (44), and it was established that the 5,6-double bond was unaffected. The





structures proposed would arise through reduction of a carbonyl group to the alcohol, followed by dehydration.

Much later, Adkins, Connor and Cramer (45) subjected

dehydroacetic acid to hydrogenation at temperatures of 185-190° and pressures of 108-325 atmospheres. The main product they obtained was heptanone-4, but no cyclic hydrogenated products were obtained. They found that upon heating dehydroacetic acid in ethanol at 190° for two hours with or without the nickel catalyst, 70% conversion to acetoacetic ester occurred. This indicated that at least under those conditions, the Claisen condensation postulated by Arndt (32) as the second step in the formation of dehydroacetic acid was also reversible.

Rupe, Pedrini and Collin (46) reportedly obtained the 5,6-dihydro dehydroacetic acid by hydrogenating a neutralized aqueous solution of dehydroacetic acid with a nickel-kieselguhr catalyst. No yields, physical constants nor analytical procedures except combustion analysis data were given. They reported the formation of a mono-semicarbazone from their product, again giving no information as to its physical properties, but rationalising that since -pyrones are unaffected by ketone reagents, the 3-acetyl carbonyl group is involved in formation of the semicarbazone. However, the 6-methyl-5,6-dihydropyran-2,4-dione previously mentioned (37) reportedly yields a semicarbazone readily. By analogy, therefore, the compound claimed by Rupe and co-workers would be expected to yield a di-semicarbazone.

Malachowski and Wanosura (47), using a platinum oxide catalyst, reported the product of their hydrogenation of dehydroacetic acid as 3-ethyl-6-methylpyran-2,4-dione,

m.p. 185°, which gave an oxime, a positive enol test, and on hydrolysis yielded 2,4-heptanedione. Since hydrolysis was carried out under conditions which would not be expected to cause further hydrogenation, the recovery of 2,4-heptanedione seems to clearly establish the correctness of their proposed structure.

Since a high degree of selectivity is required in order to obtain the desired hydrogenated product, no attempts were made under conditions of high temperature and pressure. Since chemical reduction (i.e., zinc and hydrochloric acid or sodium amalgam) apparently attacks the carbonyl group, this type of hydrogenation was avoided. A number of attempts were made with several catalysts under mild conditions, and the results will be discussed. All attempts were carried out in the low pressure catalytic hydrogenation apparatus manufactured by the Parr Instrument Company. This apparatus is very convenient to use, and provides for efficient contact between catalyst and compound in hydrogen atmosphere up to 50 lbs. pressure. Its chief drawback is that the hydrogen absorption cannot be accurately followed when using quantities of less than about 0.05 mole. In this apparatus, absorption of 0.1 mole of hydrogen caused a drop of 8 lbs. on the pressure gauge.

The Dehydro Acids

The hydrogenation of dehydroacetic acid was attempted by a modification of the procedure of Rupe (46) using Raney nickel and a nearly-neutralized aqueous solution of

dehydroacetic acid. One and one-half molar equivalents of hydrogen was absorbed in about four hours, and an additional one-half mole during the next three hours. The only solid product isolated was 6-methylpyran-2,4-dione, evidently resulting from hydrogenolysis of a C-C bond. Hydrogenolysis of this type has been shown to occur when using Raney nickel as a catalyst for hydrogenation of 1,3-diketones (107). Recently an attempt was made to duplicate this result using a less active preparation of Raney nickel, and a solid was obtained which is probably mainly starting material, but has not been obtained pure enough for definite comparison. The behavior of the reaction mixture during the working-up procedure was the same as in the first run.

The reaction obviously produces a complex mixture of substances. The solution, which was acidic before hydrogenation, was distinctly basic after, indicating a decrease in acidic material due to hydrogenation to the alcohol stage or beyond. Acidification of the basic solution produced considerable effervescence, apparently from a readily decarboxylated reaction product. The weight of total ether-soluble material isolatable represented less than 50% of the weight of starting material, apparently because of loss by evaporation of neutral volatile products during the work-up.

Dehydrobenzoylacetic acid was hydrogenated using dioxane as solvent and Raney nickel as catalyst. A yield amounting to about 30% of a substance, m.p. 257-8° without decomposition, was obtained. Carbon-hydrogen analysis agreed closely with the empirical formula $C_{18}H_{14}O_3$, which could arise from hydro-

genolysis of a carbon-oxygen bond to yield 3-benzyl-6-phenyl-pyran-2,4-dione or 3-benzoyl-3,4-dihydro-6-phenyl-2-pyrone. Since the theoretical amount of hydrogen for the reduction of one double bond or carbonyl group was taken up, yet only about 30% of reduced product was recovered, apparently the reduction that had taken place had proceeded beyond the one-mole stage. Further investigation of this material will be undertaken in the future.

Another hydrogenation attempt was carried out on dehydrobenzoylacetic acid also employing dioxane as solvent, but using 5% palladium on carbon as the catalyst. No reduction whatsoever occurred, a slight drop in pressure evidently being due to adsorption of hydrogen on the catalyst or a leak in the system. The original material was recovered quantitatively.

6-Methyl-and 6-Phenylpyran 2,4-dione

Since the structure of most interest in this investigation was the 6-substituted pyran-2,4-dione structure, somewhat more attention was given to these compounds. No reports of investigation of the hydrogenation of these products could be found in the literature. The experiments were limited mainly to the 6-methyl compound, since no suitable solvent could be found for the 6-phenyl compound.

6-Methylpyran-2,4-dione was subjected to a modified Rupe procedure similar to that discussed for dehydroacetic acid. A drop in pressure indicating uptake of 2 moles of hydrogen occurred in about 2 hours, after which the pressure

drop was very slow, only a slight drop being observed over the next six hours. From the reaction mixture, much unreacted starting material and an oily material was obtained which showed no sign of depositing crystals after standing for several weeks. This oil gave no positive tests with carbonyl reagents, nor did it give an enol test with ferric chloride. On treatment with 3,5-dinitrobenzoyl chloride, considerable decomposition occurred, yielding finally a small amount of bicarbonate-insoluble solid which could not be obtained colorless after repeated treatment with Norit. Several recrystallizations by dissolving the material in ether, adding petroleum ether to produce cloudiness, and allowing to crystallize eventually yielded slightly yellowish platelets, m.p. 87-89° after previous sintering at 80°, in too small an amount for further investigation. A repetition of the procedure gave no better results. Apparently the reduction reached the alcohol stage. At least it was evident that the procedure did not produce the desired product.

A number of reduction attempts using methanol or ethanol as solvent established only one fact--that alcohol is a poor solvent for hydrogenation of this material. Using either methanol or ethanol as solvent, attempts were made with Raney Nickel, palladium on charcoal and palladium on strontium carbonate. The mixtures were allowed to shake for periods up to 24 hours. In all cases, the recovery of starting material was practically quantitative. If any re-

duction occurred, the amount was too insignificant to be detected.

Although 6-methylpyran-2,4-dione is only slightly soluble in either, its behavior toward hydrogenation in this solvent was investigated. Palladium on carbon and palladium on barium sulfate were used as catalyst with similar results. Upon evaporation of the ether after filtration to remove the catalyst, a crystalline solid was obtained in an amount corresponding to 15-20% of the starting material but with a much different melting behavior. The product sintered at 120°, effervescence started at 122° and continued to 145° before all solid had disappeared. Recrystallization from ethyl acetate narrowed the melting point range to 124-130°. The melting point of the desired product, 6-methyl-5,6-dihydropyran-2,4-dione has a reported melting point of 123-4°. Recrystallization procedures are continuing in an effort to further narrow the melting range and obtain a pure product.

The problem immediately encountered in working with 6-phenylpyran-2,4-dione was that of finding a solvent for the material. It is very slightly soluble in methanol or ethanol, virtually insoluble in ether, and very slightly soluble in tetrahydrofuran or dioxane. In the first attempt, a suspension of the compound in ethanol was employed, using Raney nickel as the catalyst and a temperature estimated at 60°. The reaction product was recovered from the catalyst by dissolving it in 5% sodium hydroxide. After precipitation

with acid, washing and drying, melting point and mixed melting point confirmed that it was the unchanged starting material.

Upon attempting to use dioxane as solvent, about 1.5 g. of 6-phenylpyran-2,4-dione was dissolved after several hours of refluxing with 150 ml. of dioxane. In the hydrogenation procedure, no hydrogen absorption was indicated by the pressure gauge, but in attempting to isolate the compound from the dioxane solution, even after concentrating to small volume it was necessary to add water to precipitate the solid. The white solid obtained melted about 20° higher than the original 6-phenyl-pyran-2,4-dione, which is a yellow crystalline powder. Mixtures of the two substances melted over a wide range. It was found that the original compound was transformed during the long reflux period with dioxane, the hydrogenation procedure not being required to produce the higher melting compound. The transformed product crystallized from diluted dioxane in rod-like white crystals. Combustion analysis on this material, which melts quite sharply for such a high melting material (264-5°) and forms well-defined crystals, does not agree with any reasonable structure which could be postulated. This material has also been reserved for future investigation.

Since this phase of the work had taken on the aspects of a major problem in itself, and since none of the products obtained resembled in physical properties the known 5,6-dihydro compounds, attention was directed to the solution of other aspects of the problem.

6-Methylpyran-2,4-dione and Derivatives with N-Bromosuccinimide.

During the course of this investigation, Arndt and Avan (48) published a report of their rather comprehensive studies of 6-methylpyran-2,4-dione. Among other things, they stated that the compound titrates 100% as enol with bromine, is methylated by diazomethane to give the 2-methoxy-4-pyrone, m.p. 86-7°, and that with bromine in acetic acid gives the 3-bromo derivative, decomposing above 200°. The 3-bromo derivative with diazomethane gave the 2-methoxy-3-bromo derivative, m.p. 153°. It seemed of interest to investigate the behavior of this compound toward N-bromosuccinimide, particularly the 2-methoxy derivative, since, from the structure, it appeared that this agent should brominate the 6-methyl group, thereby providing a reactive center by means of which the entire pyrone moiety could be provided with a variety of types of 6-substituents. For example, condensation of such a compound with benzyl sodium would produce a dihydroyangonin-type structure.

Treatment of 6-methylpyran-2,4-dione with N-bromosuccinimide yielded a bromo derivative, decomposing above 185°, which had the correct analysis for a monobromo derivative. Since the starting material did not dissolve completely in carbon tetrachloride, the reaction proceeded very slowly, about 24 hours of refluxing being required before no positive bromine test was obtained. The reaction mixture had become very dark, and the yield of the product was poor. Several recrystallizations from glacial acetic acid were required before the decomposition point apparently leveled off

at 185°. The fact that the bromine substitution had involved the 3-position was established by methylation with diazomethane. The methylated product, m.p. 152-3° was identical with the product obtained by the procedure of Arndt.

2-methoxy-6-methyl-4-pyrone, which dissolved readily in carbon tetrachloride, was then treated with N-bromosuccinimide to produce a compound identical to the bromo-methoxy derivative obtained by the first two procedures. This result was somewhat unexpected since the enolic hydrogen had been previously substituted by methoxyl. Buu-Hoï and Lecocq (49) investigated the effect of NBS on a number of heterocyclic compounds, and found that 2,6-dimethyl-4-pyrone readily yielded the bromomethyl derivative. The analogy indicated that the 6-methyl position in 2-methoxy-6-methyl-4-pyrone would be most receptive to bromination, whereas the 3-position is more analogous to the α-position in the β-alkoxy crotonate molecule, a position which is unaffected by NBS. The bromination of the β-alkoxy crotonates will be discussed later.

2-methoxy-3-bromo-6-methyl-4-pyrone was then treated with another equivalent amount of N-bromosuccinimide, and a new compound with the correct analysis for a dibromo derivative was obtained, m.p. 161.5-162°. The fact that this compound was 2-methoxy-3-bromo-6-bromomethyl-4-pyrone was established in the following manner: The mono-bromo compound gave the correct analysis for one C-methyl group (50), while the dibromo compound gave no positive results by this proce-

dure. Upon treatment of the dibromo compound with hexamethylene tetramine by the procedure of Dunn, Waugh, and Dittmer (51), there separated in 89% yield within 10 minutes, a copious addition product which decomposed above 205°. Similar treatment of 6-methylpyran-2,4-dione and 2-methoxy-3-bromo-6-methyl-4-pyrone gave no indication of reaction.

Preliminary attempts were made to convert the dibromo compound to the aldehyde by two methods. The procedure of Dunn et. al. (51) involved dissolution of the material in water, followed by steam distillation. The dibromo compound did not dissolve appreciably in the water, and as heating continued, considerable decomposition occurred. No positive aldehyde tests were obtained from an ether extract of the distillate, nor from the brown, gummy residue in the distilling flask. Angyl and co-workers (52) were successful in obtaining a number of aldehydes by carrying out the reaction between the halomethyl compound and hexamethylenetetramine or the preformed hexaminium salts in 50% acetic acid. The mixtures were boiled under reflux for one-fourth to 5 hours, concentrated hydrochloric acid added and boiling continued for 5 minutes, then the mixture allowed to cool. The aldehydes separated on cooling. When this procedure was followed in the present work, a brown oil separated and was extracted with ether. This oil, on treatment in ethyl alcohol with 2,4-dinitrophenylhydrazine deposited after standing overnight, a small amount of amorphous brown solid which gradually charred above 200° but did not melt below 300°. The amount

was too small to warrant purification attempts for analysis.

Attempts were also made to condense 2-methoxy-3-bromo-6-bromomethyl-4-pyrone with benzyl sodium. The procedure of Smith and Turner (53), who prepared a number of alkyl benzenes in this manner, was followed. Chlorobenzene was added dropwise into a flask containing toluene and sodium wire and filled with dry nitrogen. Continuous stirring was provided, and the temperature was maintained at 30-35° by heating in an oil bath. The mixture became very black as the reaction proceeded, a total of 4 hours was allowed at this temperature. The mixture was then heated to reflux for 35-40 minutes, the heating discontinued, and then a solution of the bromomethylpyrone in toluene introduced with stirring into the hot mixture. After allowing the mixture to cool, unreacted starting material was recovered in practically quantitative yield. This procedure was repeated and starting material was again the only material recovered. When refluxing was allowed to continue for one hour after addition of the bromomethyl compound, only tarry decomposition products were obtained, no starting material being recovered.

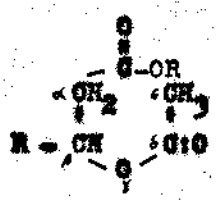
In the procedure of Gilman, Pacevitz and Baine (54) for the formation of benzyl sodium, the reaction mixture upon heating to the reflux temperature, is described as turning from black to brick red, then assuming the "characteristic color of benzyl sodium." However, in the present experiments, no color other than black was observed. It may be, therefore, that failure to get a condensation was due to

the lack of obtaining benzyl sodium.

One attempt was made to see if this material would undergo a Reformatsky reaction. Under the conditions employed, however, no reaction was observed beyond a darkening of the zinc after heating for four hours. The unreacted starting material was recovered.

THE CLAISEN-DIECKMANN CYCLIZATION APPROACH

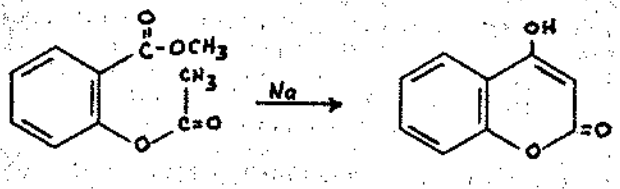
The Claisen condensation or acetoacetic ester condensation is the name usually applied to reactions in which an α-methylene group of an ester molecule is condensed with the carbonyl carbon of another ester molecule to produce a β-keto ester. If the two centers of reaction are within the same molecule such that an intramolecular condensation occurs to produce a cyclic compound, the reaction is generally referred to as a Dieckmann cyclization. In order to undergo such cyclization, the activated methylene group must be in a position δ or ϵ to the carbonyl carbon to which it becomes attached. The configuration of the β-acetoxy esters



fulfills this requirement, but in this case the α-methylene group is also a terminal methyl group--not the usual case in Dieckmann cyclization reactions.

No attempt was made to review the extensive literature on reactions involving cyclization. However, in the compre-

hensive review of Hauser and Hudson (55), no example of a strictly analogous reaction was cited. The usual result of Dieckmann cyclizations is to produce carbocyclic keto compounds, not lactone or pyrone types. One reaction which is closely analogous was accomplished by Pauly and Lackemann (56), who synthesized 4-hydroxycoumarin from methyl acetylsalicylate by the action of sodium. The reaction was brought about by the addition of metallic sodium to the molten methyl acetylsalicylate.



This reaction was investigated by Link and co-workers (57) who had better success by using an inert solvent. In their procedure, sodium and liquid paraffin were heated to 240°, and the methyl acetylsalicylate added slowly. The reaction mixture was maintained at 240-250° for 1½ hours after addition of the ester. In the isolation of the product, they filtered the hot mixture to isolate the sodic derivative, dissolved this in water, and by careful acidification were able to separate most of the acidic impurities, which separated at a higher pH than the 4-hydroxycoumarin.

It might be expected that cyclization in the case of methyl acetylsalicylate would occur more readily than with the β-acetoxy ester. In the salicylate molecule, the

spatial configuration which the trignal carbomethoxy carbon atom can assume is limited to the plane of the phenyl ring. The chance of it being in a position to undergo cyclization therefore is much better than is the case of the corresponding carbon atom of the β-acetoxy ester, in which a high degree of free rotation is permitted. This can be illustrated convincingly by construction of the molecular models.

Attempts to achieve this cyclization were made upon ethyl β-phenyl-β-acetoxy propionate as a model compound and methyl β-acetoxy-δ-phenyl valerate, which would lead to the properly substituted pyrone. Ethyl β-hydroxy-β-phenyl propionate was prepared by the procedure of Hauser and Breslow (58) in about 70% yield. This was acetylated by treatment with excess acetic anhydride in pyridine, the best yield obtained being 80% of pure β-acetoxy ester.

In the preparation of methyl β-acetoxy-δ-phenyl valerate, it was found that the best yields could be obtained by acetylating the crude β-hydroxy product from the Reformatsky reaction. When purification of the β-hydroxy compound by vacuum distillation was employed, the yield was usually about 35%, a yield of 50% being obtained on one occasion. However, when the crude product was acetylated, overall yields of 45% of the β-acetoxy product were obtained.

In the Reformatsky reaction, best yields were obtained by a procedure similar to that employed by Bachmann, Cole and Wilds (59). Hydrocinnamic aldehyde, methyl bromoacetate, zinc and anhydrous benzene were all placed in a round bottom

flask fitted with a reflux condenser protected from atmospheric moisture with a calcium chloride tube. Shortly after addition of a crystal of iodine the reaction started spontaneously and it was necessary to cool the flask occasionally in ice water to keep the reaction from becoming too vigorous. This spontaneous reaction proceeded until virtually all of the zinc was consumed. Usually, an additional small amount of bromoester and zinc was added at this time and the reaction mixture allowed to reflux for another one and one-half to two hours. The reaction mixture was then worked up in the usual manner, using saturated ammonium chloride solution to decompose the zinc intermediate. The benzene solution was dried over anhydrous sodium sulfate, the solvent removed under reduced pressure at room temperature, and the residue treated with acetic anhydride and pyridine to obtain the β-acetoxy product.

Sodium alcoholates, metallic sodium, sodium hydride and sodium amide were employed as condensing agents in the cyclization attempts. In a recent attempt, a preparation of sodium dispersed in submicroscopic particles was used with encouraging results.

Sodium Alcoholate

An attempt was made to bring about the condensation of ethyl β-acetoxy-β-phenyl propionate and sodium ethoxide in ethanol. The only solid product isolatable was cinnamic acid, the dark, oily residue giving no positive indication of formation of an enolic product. Either intramolecular or

inter molecular condensation would be expected to produce enolic material, hence apparently no condensation of the Claisen type occurred.

Methyl β-acetoxy-δ-phenyl valerate was subjected to the action of alcohol-free sodium methoxide under conditions similar to those employed by Bachmann, Cole and Wilds (59) to cyclize the methyl ester of 16-carbomethoxy-dl-equilenin. Apparently these conditions were somewhat milder than those previously employed, because the β-hydroxy acid, m.p. 130-131°, was isolated from this reaction. Also some unreacted starting material (about 30%) was recovered by distillation, leaving a dark, viscous residue which would not distill at a bath temperature of 200° at 1 mm, and gave no detectable enol test or positive reaction with 2,4-dinitrophenylhydrazine reagent.

Metallic Sodium

When ethyl β-acetoxy-β-phenyl propionate was added dropwise into a stirred suspension of finely divided sodium in anhydrous benzene, an immediate vigorous reaction occurred, but the sodium soon became coated with an orange reaction product. Although stirring and refluxing were allowed to continue overnight, much unreacted sodium remained. From this procedure, cinnamic acid was again recovered, and no positive enol test was given by the non-crystallisable residue.

The procedure of Link and co-workers (57) was then applied to methyl β-acetoxy-δ-phenyl valerate. Efficient

stirring was employed throughout the heating period of about 3 hours, and the suspension took on a light brown color, but relatively little decomposition was indicated. However, a large proportion of the sodium did not react. A small amount of methanol was added to decompose any unreacted sodium, and the solid which was a tan, amorphous material collected on a Buchner funnel. From this solid was obtained an acid, m.p. 100-101°, the neutralization equivalent of which agreed for 5-phenyl-2-pentenoic acid. From the liquid petrolatum layer was isolated about 50% of what appeared from its boiling point to be unreacted starting material. No positive enol tests were obtained from any portion of the residue. This procedure was repeated with similar results.

The isolation of the unsaturated acids from these procedures was considered to indicate the presence of moisture in some reactant. Conceivably just a trace of moisture could initiate the hydrolysis, and the resulting dehydration of the hydroxy acid produce moisture for further hydrolysis. However, the utmost care was taken to have conditions as anhydrous as possible. All solvents were dried by accepted procedures, commercial anhydrous alcohols were distilled from magnesium, and liquid reactants were freshly distilled. All apparatus were oven-dried and protected as well as possible from atmospheric moisture during assembly.

The literature was checked to see if similar results had been noticed, and if perhaps another mechanism, such as

α,β-elimination was occurring. Slocum (60) observed that β-acetoxy-β-phenyl propionic acid decomposed above 200° to yield acetic and cinnamic acids when heated alone. Schmidt and Ruts (61) observed that nitro-olefins were obtained on treatment of α-acetoxy nitroparaffins in ether solution with potassium bicarbonate. Sowden and Fischer (62), in applying the reaction to acetylated carbohydrate nitro alcohols, found that only the acetoxy group nearest the nitro group is affected, i.e., β to the functional group. Recently, Linstead, Owen and Webb investigated this reaction (63) and established that elimination was occurring in addition to hydrolysis, by obtaining α,β-unsaturated compounds under conditions by which the corresponding β-hydroxy compounds were not dehydrated. Included in the compounds they investigated were the β-acetoxy-β-phenyl propionate and β-acetoxy-δ-phenyl valerate.

Sodium Hydride

Swamer and Hauser (64) obtained good results in Claisen acylations employing sodium hydride as condensing agent. Employing this agent in the present work, encouraging results were obtained. In the reaction with methyl β-acetoxy-δ-phenyl valerate an enolic substance was formed, and judging by the intensity of the color produced on testing with ferric chloride solution, it was present in an appreciable amount. However, after several attempts with various techniques intended to affect a separation, the enolic substance has not been isolated in a pure state.

When benzene was used as the solvent, a yield amounting to about 3% of the β-hydroxy acid was obtained, about 50% of the starting material was recovered, and the residue gave no positive enol test nor carbonyl test with 2,4-dinitrophenylhydrazine reagent. Upon substitution of n-butyl ether as solvent, however, an enolic substance was formed, a few drops of the pale yellow ether solution, after dilution with ethanol, giving a deep green color upon addition of ferric chloride solution. Removal of the ether under reduced pressure left a clear amber oil which upon standing became very stiff, almost but not quite a glass. On testing with 2,4-dinitrophenylhydrazine reagent, an immediate cloudiness appeared which rapidly became more pronounced and in a short time, red, oily droplets separated from the solution. Repeated attempts to obtain a solid 2,4-dinitrophenylhydrazine were unsuccessful. An attempt to form a semicarbazone yielded a material which invariably separated as a scum on the walls of the container after crystallization attempts.

Upon treatment with saturated cupric acetate solution, a dark blue ether solution was formed from which no solid would separate. Evaporation of the ether solution yielded a dark blue gum soluble in most organic solvents except alcohols and petroleum ether. On treatment with alcohol, an amorphous solid was formed, but the material was insoluble in boiling ethanol. Treatment of solutions of the material in chloroform, benzene or ether with alcohol caused precipitation of the flocculent, amorphous solid. This copper

derivative was purified as well as possible by collecting the solid on a sintered-glass funnel, dissolving it through with a little chloroform, and precipitating it from the chloroform by dilution with alcohol. This was repeated several times until the melting point (or decomposition point) levelled off at about 175-178°, and a sample was analyzed for carbon, hydrogen and copper. Although the material was not considered pure, it was felt that an analysis, particularly for copper content, would give an indication of the type of condensation that had occurred, i.e., intermolecular or intramolecular. For intramolecular condensation, the copper derivative of the compound should contain 15.97% of copper, calculated as copper oxide. For compounds resulting from intermolecular condensation, the copper content would be roughly half, or about 8% for the normal copper derivative resulting from the intermolecular acetoacetic ester condensation between two of the original molecules. Such a molecule would be very large and complex, and one might hesitate to predict that a normal copper derivative would form, but as mentioned previously, the copper derivative of ethyl hydrocinnamoyl acetonedicarboxylate formed readily and analyzed correctly.

The method used in attempting to achieve some degree of purity would tend to eliminate any inorganic copper contaminant which would increase the copper percentage, and would not be so effective in removing organic material not capable of forming a copper derivative, which would lower the copper percentage. The fact that the percentage of

copper found was in much better agreement for intra- than for intermolecular condensation (found 13.91%) was considered to be encouraging evidence that the desired reaction did occur.

Adsorption chromatography procedures were tried unsuccessfully as a means of separation, since the enolic material was adsorbed so strongly on the column (alumina and silicic acid were tried) that it could not be eluted, or even extracted in a Soxhlet extractor from the adsorbent. Upon treatment with diazomethane, a comparatively vigorous reaction occurred, but no crystalline material could be isolated, nor could a crystallisable fraction be obtained after an adsorption chromatography separation. Three rather distinct fractions were eluted from the column, but all formed a glass-like layer in the container after standing until all solvent had evaporated, and they were all readily soluble in all organic solvents but petroleum ether.

Sodium Amide

Sodium amide was employed to see if it would induce the desired reaction and perhaps yield a more pure product. From the reaction with this agent in liquid ammonia upon methyl β-acetoxy-δ-phenyl valerate, there was obtained a good yield of an amide with a carbon, hydrogen, and nitrogen analysis agreeing for the α,β-unsaturated amide, $C_6H_5CH_2CH_2CH{:}CHCONH_2$. Sodium amide in ether gave none of this product, and only a faint positive test for enol was produced by the residue.

Sodium Dispersion

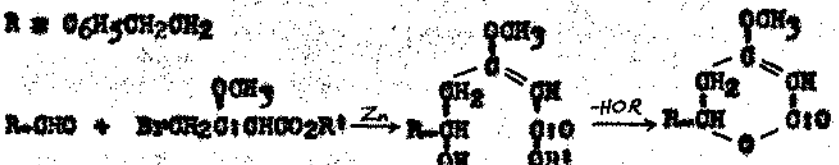
Recently, the use of a sodium dispersion was investigated as a condensing agent in acetoacetic ester condensations (65) and good results obtained. A sample of a sodium dispersion in n-butyl ether in which the particles ranged in size from sub-micron to 10 microns was obtained from U. S. I. Industrial Chemicals Co., 120 Broadway, New York, N. Y. Since some ethyl β-acetoxy-β-phenyl propionate was available, the cyclisation attempt was made with this material. The sodium dispersion was placed in the flask under a nitrogen atmosphere, and the ester in n-butyl ether was added from a dropping funnel with continuous stirring. Reaction was immediate and vigorous, hydrogen was evolved, and considerable heat was generated. The reaction continued during the entire addition of the ester, no heat being applied to the flask until after the addition was complete, then the flask was heated to reflux for one-half hour. After decomposition of excess sodium with glacial acetic acid, the mixture was worked up in the usual way. No crystalline acid could be obtained from the bicarbonate washings of the ether solution, only a slight turbidity developing upon acidification. The ether solution gave an intense, almost black color when treated with ferric chloride solution. After concentration to small volume at reduced pressure and room temperature, dilution of the ether solution with petroleum ether caused precipitation of an amorphous, yellow solid which resinified after standing a short while. A small amount of

this resinous material, after triturating with water on a watch glass, solidified and could be scraped off as a yellow powder. It was unaffected by sodium bicarbonate solution in contrast to the report of Jones (38) that 4-hydroxy-6-phenyl-5,6-dihydro-2-pyrone dissolves with effervescence in sodium bicarbonate solution. At the time of this writing, attempts are continuing to get a substance pure enough for an analysis of this material.

THE β-METHOXY CROTONATE APPROACH

The fact that degradation of the kavain molecule produces a substituted β-methoxy crotonic acid suggested the use of this type of compound in the synthesis of dihydrokavain. It appeared that such an ester, brominated in the γ-position, should undergo a Reformatsky reaction with hydrocinnamic aldehyde, the product from which upon lactonization would produce dihydrokavain directly. Reformatsky condensations with γ-bromo crotonates have been investigated by a number of workers (66,67,68,69,70), and application of the procedure to the present work looked

R = $C_6H_5CH_2CH_2$



promising.

There are a number of procedures whereby β-alkoxy crotonates may be prepared. β-Methoxy and β-ethoxy crotonic

acids were prepared by Friedrich (71) by the action of the corresponding alcoholic potassium hydroxide solution upon the potassium salt of β-chloro crotonic acid. Enke (72) modified this procedure to prepare a number of alkyl β-alkoxy crotonates from the corresponding β-chloro crotonic esters and sodium alkoxides. Ethyl β-methoxy crotonate was prepared by von Peckmann (73) by the treatment of ethyl acetoacetate with diazomethane. β-Methoxy crotonic acid was obtained by Kögl and Veldstra (74) by the dehydrobromination of α-bromo-β-methoxy butyric acid by heating with alcoholic potassium hydroxide. Owen (75) obtained β-ethoxy crotonic acid in a similar manner, and also reported the preparation of two β-alkoxy crotonic acids by the action of sodium alkoxides on tetrolic acid. Ethyl β-ethoxy crotonate was prepared by Claisen (76) by treatment of ethyl acetoacetate with ethyl orthoformate in the presence of acetyl chloride. The same compound was prepared by Curtiss (77) in about 15% yield by passing dry hydrogen chloride through a solution of ethyl acetoacetate in ethyl alcohol.

The first requirement in this approach was necessarily the production of the β-alkoxy crotonate. Three of the above procedures were investigated to determine which could be best adapted as a preparative method for the desired material. The results of these investigations will be taken up individually, and the subsequent bromination and Reformatsky steps discussed.

Diazomethane-Ethyl Acetoacetate Procedure

The procedure of von Pechmann consists of the treatment of ethyl acetoacetate with excess diazomethane in ether solution. Arndt and co-workers (78), in a study of this procedure, found that the presence of some methanol shortened the reaction time and somewhat improved the yield, stating that in this manner, about fifty percent conversion was obtained in two days. In a number of attempts, the yield reported by Arndt could not be duplicated.

The diazomethane was prepared from nitrosomethyl urea after the procedure of Arndt (79). The ether solution was dried over potassium hydroxide for three hours before addition of the ethyl acetoacetate. The ethyl acetoacetate was freshly distilled, and commercial anhydrous methanol (usually about 10 ml. per 25 g. of ethyl acetoacetate) was used. The reaction mixture was always allowed to stand at room temperature for three or more days. The reaction was never vigorous, but evolution of nitrogen was noticeable in every case for at least 24 hours.

In working up the material the ether solution was filtered, and either shaken mechanically for an hour with 2 N. sodium hydroxide, or extracted repeatedly by shaking with 2 N. sodium hydroxide solution in a separatory funnel. This washing was repeated a number of times in the attempt to get a product which no longer gave a positive enol test with ferric chloride solution, a situation that was never realized. In all cases, a few seconds after addition of ferric chloride solution, the characteristic color of the

acetoacetate enol test would appear. It is now believed that this product was not contaminated with any appreciable amount of ethyl acetoacetate, and that a considerable amount of the product was lost through its solubility in the aqueous phase, and possibly some saponification during this washing procedure. The cause of the apparent enol test will be discussed later (p. 58).

The best yield of ethyl β-methoxy crotonate obtained was about 18%, usually somewhat lower. In order to get a reasonable amount of product, it would be necessary to use large quantities of diazomethane, a rather unpleasant material to work with. Therefore, the investigation of other procedures was undertaken, with the expectation of returning to this procedure if necessary.

The Dehydrobromination of α-Bromo-β-Methoxy Butyric Acid.

In their attempts to synthesize dl-threonine, West, Krummel and Carter (80) developed a procedure for obtaining α-bromo-β-methoxybutyric acid in good yield, by adding crotonic acid and bromine simultaneously into a methanolic suspension of silver nitrate. The methanol and bromine first react to form methyl hypobromite, and the liberated bromine ion reacts with silver nitrate and is removed as the insoluble silver bromide. This effectively shifts the reaction toward the methyl hypobromite and greatly decreases the amount of dibromobutyric acid formed.

West and co-workers were unable to isolate more than one dl pair from this reaction, the methyl hypobromite addition evidently occurring in a stereospecific manner.

Therefore the possibility arose that upon dehydrobromination only one geometric isomer would be obtained. In order to be successful in the subsequent procedures, i.e., leading to the lactone structure, it is necessary that the methoxyl group have the trans configuration to the carboxyl group. Apparently this is the configuration obtained, since the β-methoxy crotonic acid obtained by this method, that obtained by saponification of the diazomethane-ethyl acetoacetate product, and that from the β-chlorocrotonic acid have identical melting points.

The dehydrobromination was accomplished by Kögl and Veldstra (74) by heating the α-bromo-β-methoxy butyric acid at 110° for six hours with alcoholic potassium hydroxide. Their α-bromo-β-methoxy butyric acid was prepared in a slightly different manner but should produce the same configuration. It was obtained by treatment of crotonaldehyde with bromine in methanol and subsequent oxidation of the aldehyde to the acid with potassium permanganate.

Owen (75) prepared α-bromo-β-ethoxy butyric acid by the procedure of West, et. al., and refluxed this for six hours with alcoholic sodium ethoxide to effect dehydrobromination, obtaining from 5 g. of starting material an 88% yield of the β-ethoxy acid, m.p. 140°.

During the present work, the procedure of West, Krummel and Carter was used to prepare α-bromo-β-methoxy butyric acid. In two preparations, yields of 43% and 50.5% of acid, m.p. 59.5-61.5° were obtained, representing a total of almost

100 g. of product. Thus if the dehydrobromination could be carried out on a comparable scale, this would be a good preparative method for β-alkoxy acids and the corresponding esters, at least of the lower alcohols.

A number of dehydrobromination experiments were run, using sodium methoxide and sodium ethoxide to bring about the reaction. With sodium methoxide and 10 g. of bromo acid, a yield of 40% of β-methoxy crotonic acid was obtained, but a reflux period of 10 hours was required before an appreciable amount of sodium bromide had separated. A similar run, allowed to reflux for 16 hours, yielded slightly less product. Upon scaling up the reaction to 20 g. of bromo acid, the yield was reduced to 24%. Upon substituting sodium ethoxide, it was noticed that sodium bromide precipitated from the solution within a few minutes. Yields were not improved, but the reflux period was considerably shortened. With a 6-hour reflux period, the yield of β-methoxy crotonic acid was 8.5%. When the reflux period was shortened to 20 minutes, the yield was 40%.

Owen had reported an 88% yield of the β-ethoxy acid from 5 g. of starting material. Kögl and Veldstra, using only 1 g. of the α-bromo-β-methoxy butyric acid, obtained about 46% yield of the β-methoxy acid. Results of the present work indicate that in order to get comparable yields the procedure must be limited to small amounts of starting material, probably not more than 5 g. This behavior greatly decreased the desirability of this procedure as a prepara-

tive route to the β-alkoxy esters. The esterification of the ester with ethereal diazomethane was, of course, accomplished in good yield.

Orthoformic Ester-Acetoacetic Ester Synthesis.

The reaction between ethylorthoformate and ethyl acetoacetate to produce ethyl β-ethoxy crotonate was first observed by Claisen (76). He was investigating the reaction between these two compounds and acetic anhydride, in which ethyl ethoxymethylene acetoacetate, $CH_3COC(:CHOC_2H_5)CO_2C_2H_5$, is produced. Upon substituting acetyl chloride for acetic anhydride, he unexpectedly obtained ethyl β-ethoxy crotonate, O-alkylation having occurred in place of C-alkylation. Blaise and Maire (81) found that better yields were obtained upon substituting a trace of concentrated sulfuric acid for acetyl chloride. Hydrochloric acid (82) and ferric chloride (83) have also been found to serve as catalysts to bring about the reaction in good yield.

The mechanism for this reaction has never been fully determined. Claisen (76) discovered that on distillation in vacuo some ketal, ethyl β,β-diethoxybutyrate, $CH_3C(OC_2H_5)_2CH_2CO_2C_2H_5$, could be recovered, and assumed that this was the primary product of the reaction, being decomposed upon distillation at atmospheric pressure into ethyl β-ethoxy crotonate and ethanol. Michael (83) and later Arndt and co-workers (84) found that, although under many conditions some of the ketal could be found, in runs using a trace of sulfuric acid or ferric chloride (Michael) or an

equivalent of acetyl chloride (Arndt) as catalyst, only the β-ethoxy crotonate could be found. Michael maintained the reaction mixture at -15° and distilled the product at 5-10 mm, at which pressure ethyl β,β-diethoxybutyrate was known to distill without decomposition, but obtained only ethanol, ethyl formate and ethyl β-ethoxy crotonate. He proposed the following scheme as the course of the reaction:

$$CH_3COCH_2CO_2Et + HC(OEt)_3\text{-catalyst} \longrightarrow CH_3C(OEt)\text{-}OCH(OEt)_2\text{-}$$

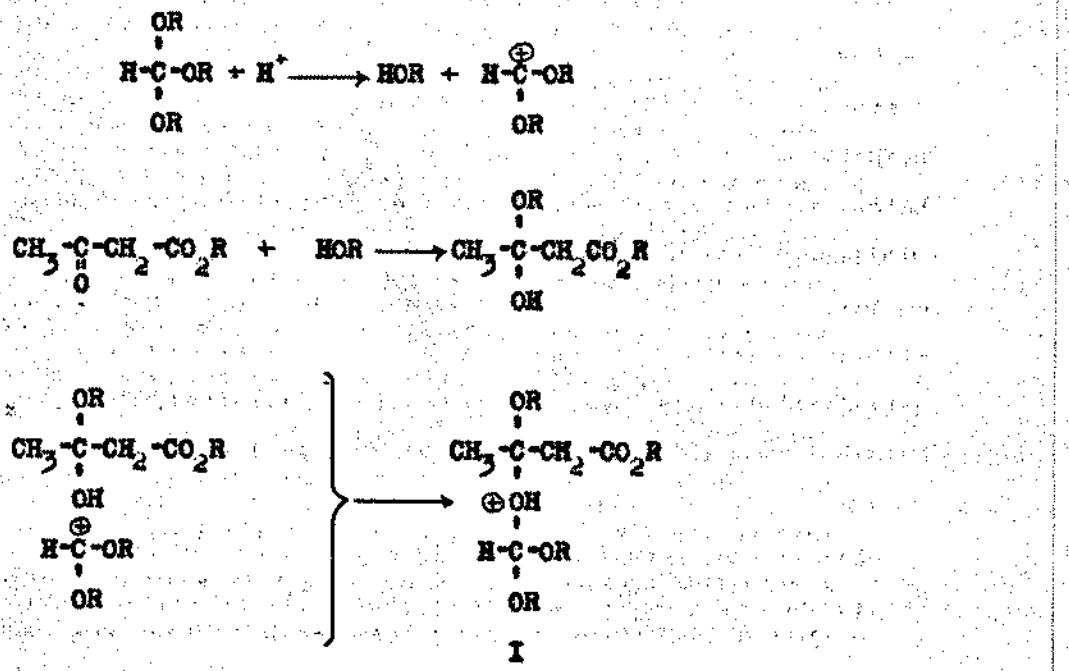
$$\text{catalyst}\text{-}CH_2CO_2Et \longrightarrow CH_3C(OEt){:}CHCO_2Et + \text{-}CH(OH)(OEt)_2\text{-} \longrightarrow$$

$$HCO_2Et + EtOH$$

Another mechanism proposed has been the immediate ethylation of the enol form of ethyl acetoacetate to give the ether and diethyl orthoformate, which immediately breaks down into ethyl formate and ethanol (85).

Although no particular effort was made in the present work to determine the precise mechanism, certain conclusions can be drawn from the observations made in preparing a number of alkyl β-alkoxy crotonates. Little attention has been drawn by previous workers to the color change which occurs during the course of the reaction. Upon addition of the catalyst to the mixture of orthoformic ester-acetoacetic ester, heat is generated and within a few seconds the solution becomes highly colored. For methyl esters, the mixture becomes bright pink, for ethyl a dark amber, and for propyl, n-butyl and isobutyl, a deep red. Upon standing, however,

this color gradually fades until after 24-30 hours the solutions are almost colorless. Evidently this color is due to a transition product which decomposes to produce the products. This same behavior was noticed, and has been reported, on treatment of mixtures of aldehydes or ketones and orthoformic esters with a trace of sulfuric acid, conditions by which acetals or ketals are formed. Curtiss (77) obtained the β-ethoxy crotonate from anhydrous ethanol, ethyl acetoacetate and hydrogen chloride gas, another method for producing acetals and ketals. Such evidence indicates that the same mechanism may be operating in this reaction. A mechanism similar to that proposed for acetal and ketal formation (86) can be postulated to explain both the formation of ethyl β-ethoxy crotonate and ethyl β,β-diethoxybutyrate.



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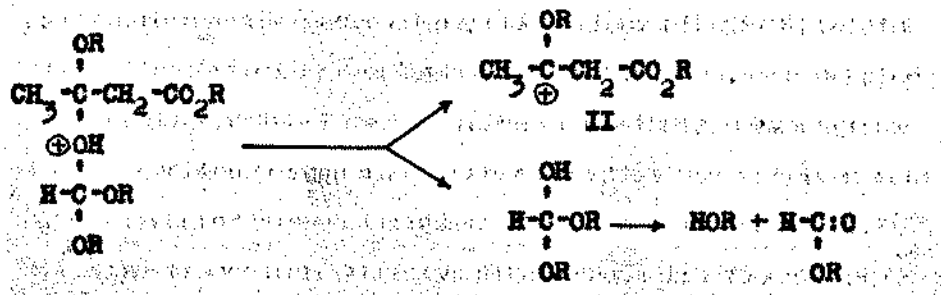
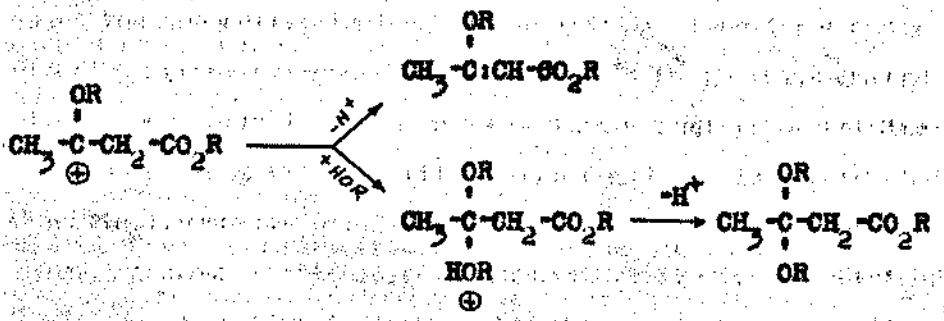


The protonated intermediate I has a counterpart in the case of the reaction with aldehydes and ketones to produce acetals or ketals, and such a form could be responsible for the color.

Carbonium ion II could stabilize itself by elimination of a proton, in which case the β-ethoxy crotonate is formed. It could also coordinate with another alcohol molecule with loss of a proton to produce the β,β-dialkoxybutyrate.



If such a mechanism is operating, it seems logical that the loss of a proton from the α position, which is activated

to some extent by the adjacent carbonyl group, would be the preferred route to stabilization of the molecule, amounting for the predominance, and sometimes the exclusive presence, of the β-ethoxy crotonate product.

Ethyl β-ethoxy crotonate is the only β-alkoxy crotonate reported to have been prepared by this method, but with the criterion clearly established, the use of the procedure for the preparation of the β-methoxy crotonate was investigated. To obtain methylorthoformate, the procedure of Sah and Ma (87) was first employed. In this procedure, metallic sodium is added slowly to a mixture of chloroform and alcohol, the mixture allowed to stand for four hours, the sodium chloride removed by filtration and the product distilled. They prepared seven trialkyl orthoformates in this manner, and reported the yields as 30%.

Three runs were made following this procedure. For the distillation, a fractionating column consisting of two 40 cm. condensers, actually a column approximately 100 cm. high, was used while distilling out excess methanol and chloroform. When the liquid has been reduced to small volume, one of the condensers was removed, and thus a column about 50 cm. high was used to collect the product. The temperature at the distilling head did not rise above 64° until the flask was practically dry, and never rose above 67° while distilling to complete dryness. Other runs were made in which a solution of sodium methoxide was added to a chloroform-methanol solution, final distillation being carried out through a 20 cm.

column packed with glass helices with very carefully controlled heating. The best yield that could be obtained in several runs was approximately six percent.

Since results of this procedure did not appear encouraging, it was decided to try a methyl orthoester other than the orthoformic ester. Conditions for obtaining methyl orthobenzoate in 86% yield have been reported by McElvain and Venerable (88). This procedure, which involves addition of benzotrichloride to a solution of sodium methoxide in methanol, was employed, a yield of 36% being obtained in the first attempt. This was improved to 72% in the second run.

Upon addition of a drop of concentrated sulfuric acid to an equimolar mixture of methyl acetoacetate and methyl orthobenzoate, an immediate, cherry red color was produced. However, after 15 minutes, this had faded to a pale pink, and in less than one-half hour, the solution was completely colorless. After standing 24 hours, followed by neutralization of the acid with potassium carbonate, distillation yielded only a trace of low boiling material (presumably methanol), the remainder being separable into two fractions, b.p. 60-64° at 10 mm. which was practically pure methyl acetoacetate, and amounted to about 85% of the methyl acetoacetate originally employed. A small amount (only a few drops) distilled between 65° and 90°, and the rest, which was fairly pure methyl orthobenzoate, was collected at 90-96°/10 mm.

A number of attempts under more vigorous conditions were made, including warming for several hours on the steam bath, repeated dropwise additions of sulfuric acid until the color persisted for several hours, allowing to stand for periods up to two weeks, treatment with benzoyl chloride followed by allowing to stand at room temperature or at 100°, and use of p-toluenesulfonic acid as catalyst. Generally indications were that some reaction involving the acetoacetate had occurred, since it could not be recovered quantitatively, and a considerable proportion of the reaction mixture was distillable in the 170-180° range (methyl acetoacetate has b.p. 169°, methyl β-methoxy crotonate, 175.5° and methyl benzoate 198-9°). However, except for the starting materials, only methanol and methyl benzoate could be identified, and the 170-180° fraction could not be further purified in several redistillations. On saponification, benzoic acid was the only solid obtainable, in a yield of about 30% if the liquid were considered pure methyl benzoate.

Recently, Alexander and Busch (89) reported the preparation of a number of orthoformic esters by an ester interchange with ethyl orthoformate. By mixing ethyl orthoformate with a higher boiling alcohol, and removing ethanol by distillation as it is formed in the equilibrium reaction, good yields of higher orthoformic esters were obtained. Although this pro-

$$H \cdot C(OC_2H_5)_3 + ROH \longrightarrow H \cdot C(OR)_3 + 3\ C_2H_5OH$$

cedure was not applicable to the preparation of pure methyl

orthoformate, it seemed that if a sufficiently large excess of methanol were employed, and equilibrium with ethyl orthoformate established, conversion to methyl orthoformate should be relatively complete. That the use of an alcoholic solution of orthoformic ester could be employed to produce a β-alkoxy crotonate had been demonstrated by Michael (83) who employed ethanol as solvent for the ethyl orthoformate-ethyl acetoacetate reaction and obtained a yield equally as good as was obtained when no solvent was employed.

Ethyl orthoformate was mixed with a 6-fold excess of methanol (18 moles of methanol per mole of orthoformate) and allowed to reflux overnight. Although equilibrium is undoubtedly established in a shorter time, this procedure involved a minimum of inconvenience and assured establishment of equilibrium. After allowing to cool to room temperature, an equivalent amount of methyl acetoacetate was introduced. The methyl ester was used in order to keep the amount of ethanol available to the equilibrium at a minimum. Upon addition of a trace of concentrated sulfuric acid (generally 4 drops of acid per one-half mole of orthoformic ester), the characteristic pink color develops. This color was observed, although much more intense, when pure methyl orthoformate was used, and was similar to the more transient color which developed when the methyl orthobenzoate-methyl acetoacetate solution was acidified.

This solution was then allowed to stand for 24 hours at room temperature. The color gradually faded, becoming barely

discernable after 12-15 hours, and after 24 hours had completely disappeared. The acid was then neutralised with solid potassium carbonate, and the low boiling materials removed as rapidly as possible by distillation at atmospheric pressure. If the alcohols were removed slowly, there was a probability of transesterification occurring, at least to some extent, and a possibility of transetherification. Although it is not known if transetherification has been observed with β-alkoxy crotonates, it has been shown, with ethyl β-ethoxy acrylate (90) and alcohols boiling higher than ethanol, that in the presence of certain acidic catalysts, considerable transetherification and to a lesser extent transesterification occurred. Therefore, in the interest of obtaining pure methyl β-methoxy crotonate it seemed advisable to attempt to drive over the relatively small amount of ethanol along with the large excess of methanol.

After all the alcohol had been removed, the residual liquid was distilled at reduced pressure. Except for a small amount which distilled below 65°/9 mm. (strong enol test), the bulk of the remaining liquid distilled at 65-69°, all but a few drops distilling at 65.5-67°. On redistillation at atmospheric pressure, a small amount of methanol was recovered, indicating the presence of a little of the β,β-dimethoxybutyrate, and the remainder distilled at 169-173°/733 mm. Upon treatment of a small sample of this material dissolved in ethanol with ferric chloride solution,

no immediate color change appeared, but after standing for a half minute or so, the color gradually darkened to give an apparent positive enol test. Assuming this to be due to a trace of unreacted acetoacetic ester, the material was dissolved in ether and extracted several times by shaking with 10% sodium hydroxide solution. The behavior of the washed material toward ferric chloride was unchanged. Redistillation gave no apparent improvement. Treatment with saturated cupric acetate solution produced no solid copper derivative.

It was therefore concluded that unreacted methyl acetoacetate was not causing the apparently positive enol test; however, on prolonged contact with the acidic ferric chloride solution, the easily hydrolyzed enolic ether was being cleaved to produce the acetoacetate, which subsequently produced the characteristic color. In order to test this hypothesis, a drop of dilute hydrochloric acid was introduced into an alcoholic solution of the material. When tested with ferric chloride solution immediately, or up to one-half minute after introduction of the acid, a delayed positive test was obtained. If, however, one minute or longer was allowed after introduction of the acid, the addition of ferric chloride solution produced an immediate and strongly positive enol test.

In a later preparation, in order to determine if transesterification and transetherification did occur, the reaction mixture, after the usual preliminary steps, was sub-

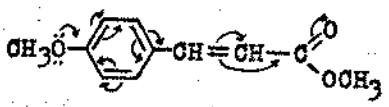
jected to a rather careful fractionation. About 95% of the theoretical amount of methyl formate, b.p. 32°, was obtained, the receiver being immersed in an ice bath to prevent loss by evaporation. Then the temperature rise was fairly gradual to 64°, where a large fraction of methanol was obtained, then the temperature rose even more gradually from 64° to 80°. No attempt was made to separate the ethanol and methanol. When no more distillate would pass over, the heat was increased and when the vapors had risen to the thermometer bulb, the temperature rose very rapidly to 170°, slowly to 174°, and all but a small portion was collected at 174-176°. An additional small fraction distilled between 176° and 180°, by which time the distilling flask was virtually dry. Even under strong heating with a flame, the temperature at the distilling head would not rise above 180°.

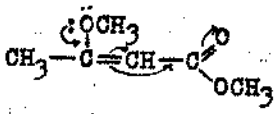
The refractive indices of the 174-176° fraction and the 176-180° fraction were practically the same ($n^{25}D$ 1.4522 and 1.4505 respectively). The $n^{25}D$ of the product from the first procedure, redistilled until two consecutive values were identical, was 1.4402. Upon saponfication, in both cases, pure β-methoxy crotonic acid, m.p. 128-128.5 d. was obtained.

The refractive indices indicate that some transesterification may have occurred, any appreciable transetherification being ruled out by the purity of the acid obtained upon hydrolysis. From the boiling point, since the ethyl β-methoxy crotonate prepared from ethyl acetoacetate and diazomethane distills at 188-190°, it can be assumed that

transesterification was not extensive. This resistance to transesterification may be compared to the behavior of this substance toward saponification. It was found that results of saponification equivalent determinations were consistently too high, but approaching the theoretical value, after refluxing the ester with 0.35 N alcoholic potassium hydroxide for periods of two, four, and six hours. In fact, in determinations which gave acceptable values, the solutions were allowed to reflux overnight(about 12-15 hours).

Rationalization of this behavior follows readily, however, from hydrolysis studies on compounds with electron donating groups conjugated with the ester function (91). For example, the rate of hydrolysis for ethyl p-methoxy benzoate and ethyl p-methoxy cinnamate is considerably slower than for the unsubstituted esters (92). That the effect of conjugated methoxyl in the crotonate esters would be even greater is a distinct probability, because of the greater proximity of the ether group to the ester group, and since there are fewer points at which the effect could be dissipated.





It is generally accepted that alkaline hydrolysis depends upon the low electron density about the carbonyl carbon, and

if electron-donating groups are conjugated with this position, they can supply electrons to the point of low electron density, decreasing the attraction of this position for the hydroxyl ion.

Other Alkyl β-Alkoxy Crotonates

The method was applied to the preparation of other alkyl β-alkoxy crotonates. The procedure of Alexander and Busch (89) was applied for the preparation of n-propyl, n-butyl and isobutyl orthoformates. Upon treatment of methyl or ethyl acetoacetates with these compounds, the characteristic color changes occurred, and the reactions appeared to proceed in a satisfactory manner. However, upon distillation of the reaction mixture, the higher boiling fraction was found to distill over a very wide range. For example, from the reaction between ethyl acetoacetate and n-butyl orthoformate, the higher boiling material distilled over a range of 80°-130° at 10 mm pressure, with the temperature rising steadily and continuously throughout. Upon redistillation through a 30 cm. Vigreaux column, the same result was obtained. The temperature was controlled with a heating mantle, with just sufficient heat to cause vapors to distill. A fraction over an 8-10° boiling range would be collected, then the temperature would drop and no more would pass over. Increasing the temperature of the heat source slightly would produce another fraction of similar size over the next 8-10° range. This behavior continued through the entire range of 50°. A 20 cm. column packed with glass

helices produced the same result, with no apparent break into distinct fractions. Since practically quantitative yields of formic-ester and alcohol were obtained, and the temperature was higher than the boiling point of either of the starting materials, the reaction was evidently complete. A logical explanation for the distilling behavior is that a mixture of all the possible products was formed, namely, ethyl β-butoxy crotonate, butyl β-butoxy crotonate, ethyl β-ethoxy crotonate, butyl β-ethoxy crotonate, and perhaps some β,β-dialkoxy butyrates.

If such were the case, this problem could be avoided by use of the corresponding acetoacetate and orthoformate esters, thereby limiting the reaction to a single available alcohol. The higher alkyl acetoacetates were prepared from methyl acetoacetate by an uncatalyzed ester interchange similar to the method used for the orthoformic esters. A 40 cm. glass-helix packed fractionating column was employed, proportions of about one and one-half mole of alcohol per mole of methyl acetoacetate, and the heat source controlled so that the temperature did not rise above 65° until the theoretical amount of methanol had been collected. The transformation was quantitative in all cases. Using the corresponding esters, the pure β-alkoxy crotonates were obtained in yields of 82-92%, the products distilling over a 2-3° range.

Transesterification of methyl and ethyl acetoacetates with lower alcohols has been studied by Peters (93), but the

reactions were carried out in the presence of basic catalysts. Recently Vogel and co-workers (94) reported the preparation of a number of acetoacetates of higher alcohols (menthol, cholesterol, 1-octanol, 1-dodecanol, etc.) at steam bath temperatures and in the absence of catalysts. No reports have been seen in the literature of the previous preparation of the lower alkyl acetoacetates by this procedure.

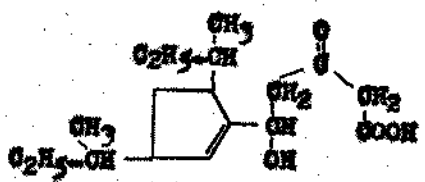
Preparation of the γ-Bromo Derivatives.

The preparation of ethyl γ-bromo-β-ethoxy crotonate was reported by Wohl and Jaschinowski (95) from ethyl β-ethoxy crotonate and N-bromoacetimide. Since the comparatively recent development and investigation of N-bromosuccinimide by Ziegler and co-workers (96), it has become the agent of choice for bromination in the allyl position.

The alkyl β-alkoxy-γ-bromo-crotonates were prepared by means of this agent in very good yields. Equivalent amounts of ester and NBS are employed, dry carbon tetrachloride as solvent, and usually 5 mole percent of freshly recrystallized benzoyl peroxide as catalyst (97). After an initial warming, a rather vigorous exothermic reaction occurred which usually continued for one-half hour or more without application of heat. It was necessary to continue the refluxing for about two hours in most cases before no positive test for bromine (starch-potassium iodide paper) could be obtained. Yields were seldom less than 75%.

Synthesis of Kavain and Homologues

Because of the initial difficulty encountered in the preparation of the β-methoxy crotonate in good yield, the first experiments using this approach were carried out with the more accessible β-ethoxy crotonate. Before any positive results had been obtained, except for the preparation of ethyl γ-bromo-β-ethoxy crotonate using N-bromosuccinimide and attempted Reformatsky condensations with hydrocinnamic aldehyde, two reports were found in the literature which established the practicality of the method. In all cases, the workers had been investigating approaches to compounds related to the plant growth hormone, auxin-b, as formulated by Kögl and co-workers (98). The structure they proposed contained a β-keto-δ-hydroxy acid moiety as would arise from the kavain structure by hydrolysis of the β-methoxy group and the lactone to the free hydroxy keto-acid.

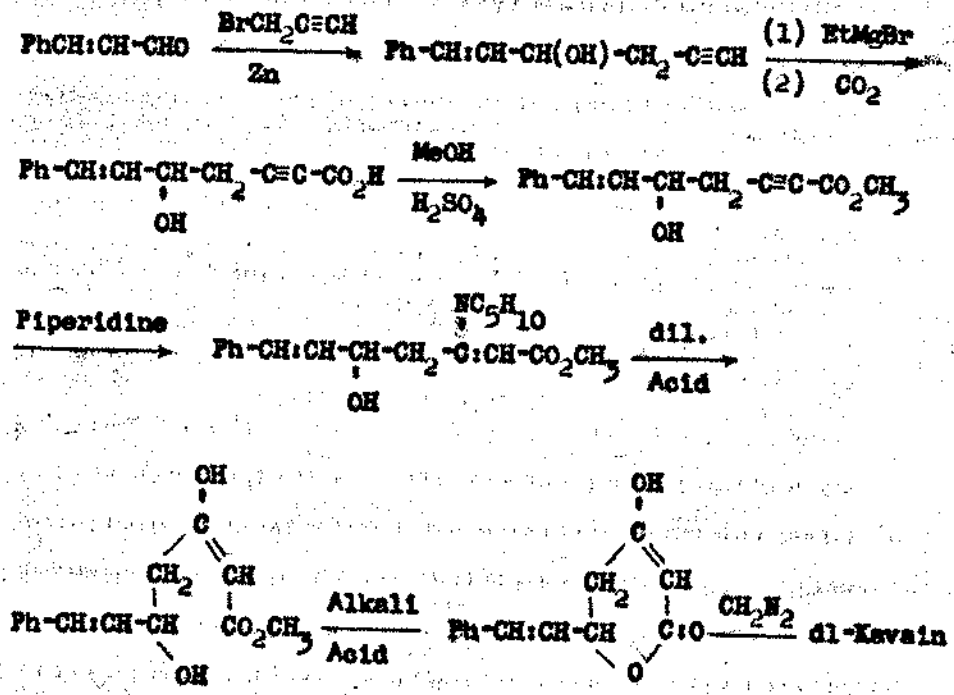


Auxin-b

Jones and co-workers had synthesized the corresponding enol lactone with various substituents on the δ carbon, including the methyl (37) and phenyl (38) which were mentioned previously. Their method involved the Reformatsky condensation of an aldehyde with propargyl bromide to obtain the

acetylenic carbinol. This was converted through the Grignard complex to the carboxylic acid, which was esterified and treated with methanol in the presence of a catalyst to give the methoxy lactone. In an alternative procedure, the acetylenic hydroxy ester was treated with piperidine, which added across the acetylenic bond to give the piperidine adduct. This on treatment with 2 N hydrochloric acid was hydrolysed and lactonised to the 4-hydroxy-6-phenyl-5,6-dihydro.2-pyrone.

An analogous sequence of reactions was employed by Fowler and Henbest (99) with cinnamic aldehyde to produce dl-kavain.



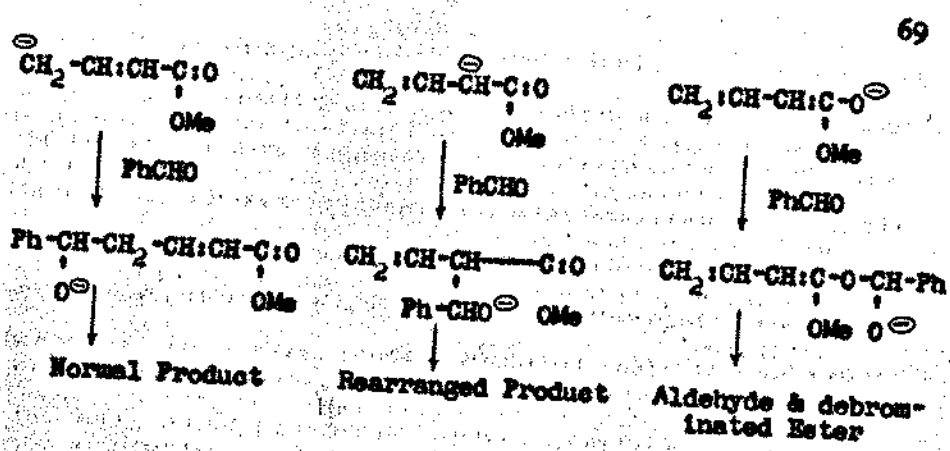
The earliest reports of the use of the β-ethoxy crotonate in preparing auxin-b analogs was by Kögl and de Bruin (39) and independently by Reid and Ruby (40). The γ-bromo derivative was condensed with benzaldehyde in the usual Reformatsky procedure to yield directly, after working up the reaction mixture, the 4-ethoxy-6-phenyl-5,6-dihydro-2-pyrone in good yields. Kögl and de Bruin also employed cyclopentene aldehyde and ethyl β-methoxy crotonate, prepared by the von Peckmann procedure (73) to obtain the cyclopentenyl methoxy analogue.

Shortly afterward, Kostermans (100), who had been associated with Kögl in his investigations of auxin-b, reported the synthesis of kavain by a completely analogous procedure from cinnamic aldehyde and ethyl γ-bromo-β-methoxy crotonate. His yield of kavain was slightly less than 10%.

Before becoming aware of the work of Kostermans, a number of attempts had been made to prepare the ethoxy homologue of dihydrokavain directly from hydrocinnamic aldehyde and ethyl γ-bromo-β-ethoxy crotonate. No solid product had been obtained from any of these attempts in spite of considerable effort. A rather vigorous reaction would occur, and approximately the theoretical amount of zinc would react, but the only products isolatable were unreacted hydrocinnamic aldehyde and ethyl β-ethoxy crotonate. A considerable proportion of high boiling material was formed, some of which would distill at about 175-220° at less than 0.5 mm pressure. It gave no positive test with carbonyl

reagents, and no solid acids could be isolated from attempted hydrolysis of ester linkages, although considerable decomposition occurred on warming with 2 N. alkali. The fact that the product might be a liquid at room temperature and may be present in this high boiling fraction was considered, but later attempts with ethyl γ-bromo-β-methoxy crotonate and the corresponding methyl ester failed to yield a solid product.

The recovery of debrominated esters from Reformatsky reactions has been reported in other cases, and mechanisms proposed for their formation. Newman (101) postulated that a reaction occurs between the bromo-zinc complex and the enol form of the aldehyde or ketone to form the bromo zinc salt of the enol, regenerating the debrominated ester, and, upon acidification, the original carbonyl compound. Van Dorp and Arens (102) use the same explanation for the recovery of β-ionone and ethyl crotonate from the Reformatsky reaction between β-ionone and ethyl γ-bromo crotonate, although an equivalent of zinc is consumed. Jones and coworkers (70) disputed this theory, however, on the basis of similar results with benzaldehyde, in which case enolization is impossible. In their experiments, using ethyl γ-bromo-crotonate also as the ester, they isolated in addition to ethyl crotonate a product which would arise through an abnormal reaction. They postulated a mechanism based on resonance forms of the anion arising from the zinc complex.



As previously mentioned (p.34), hydrocinnamic aldehyde undergoes the Reformatsky reaction with bromoacetic esters in satisfactory yields, yet apparently fails with the β-alkoxy crotonates. A possible explanation for this is that in the case of the saturated aldehyde the phenyl ring can be in a position to offer steric hindrance to the relatively bulky alkoxy crotonate molecule, whereas the smaller acetic ester meets less resistance of this type. Examination of the structure constructed from Fischer-Hirschfelder models supports this view. In the case of the unsaturated cinnamic aldehyde molecule, however, the phenyl ring is held in a position relatively remote from the aldehyde function, so that the approach of the alkoxy crotonate moiety is less inhibited.

Since the desired end had not been attained using hydrocinnamic aldehyde, cinnamic aldehyde was resorted to in order to obtain kavain. The procedure was the same as in the attempts with hydrocinnamic aldehyde, and essentially the

same as that employed by Kostermans. All the reagents, zinc, bromoester and aldehyde were placed in the flask along with dry thiophene-free benzene as solvent. A few crystals of iodine were added to help initiate the reaction, and heat was supplied either by a steam bath, or intermittent application of a low flame. The mixture was frequently shaken vigorously, generally about four hours being allowed before working up the reaction mixture. After the decomposition of the bromo-zinc complex with acid during the work-up, if the benzene solution was diluted with ether, it was found that the product would crystallise in the separatory funnel, virtually all the product separating.

In addition to kavain, the ethoxy homologue was obtained from ethyl β-ethoxy crotonate as starting material. The procedure was analogous throughout, and comparable yields obtained. In the case of the propoxy homologue, a small amount of a brown, amorphous solid was obtained which has as yet not been obtained crystalline nor in satisfactorily pure form for analysis. From reactions involving the butoxy and isobutoxy crotonates, no solid derivatives have been obtained. In all cases, the presence of cinnamic aldehyde and the appropriate debrominated ester have been detected and separated by distillation. These by-products have not been purified and analysed, but their odor is characteristic, they distill at the proper temperatures, and, in the case of the β-ethoxy compound, the ethyl-β-ethoxy crotonate crystallised in the receiver.

Hydrogenation of Kavain and Its Ethoxy Homologue

Borsche had reported the hydrogenation of the naturally occurring kavain to dihydrokavain, using as catalyst colloidal palladium. Using the hydrogenation apparatus previously mentioned (p.22), 5% palladium on carbon as catalyst, and methanol as solvent, results equally as good were obtained.

The hydrogenation was carried out at about 40 ps.i. at room temperature, and shaking allowed to continue for 15 minutes. Eighty to eighty-five percent of the dihydro product was recovered, a small amount of tetrahydrokavaic acid being recovered each time, as reported by Borsche.

The synthetic dl-dihydrokavain has a melting point of 73-74° compared with 60° for the natural optically active compound. Naturally occurring kavain melts at 106°, the synthetic racemic mixture melts at 145°. Cases are known of racemic mixtures melting lower, higher, and at the same temperature as the optically active forms. Evidently kavain and dihydrokavain fall into the higher melting category.

EXPERIMENTAL

All melting points were obtained with Anschutz total-immersion thermometers. Boiling points are uncorrected.

ETHYL ACETONEDICARBOXYLATE APPROACH

Hydrocinnamoyl Chloride

Hydrocinnamic acid (Eastman Kodak white label) was distilled at reduced pressure. The material distilling at 145-146°/7-8 mm. was used.

Forty grams (0.33 mole) of thionyl chloride to which a drop of pyridine had been added was placed in a 200 ml. two-necked round-bottom flask. One neck of the flask was fitted with a reflux condenser carrying a tube from the top leading to a gas trap; the other neck was fitted with a capillary for subsequent distillation. Hydrocinnamic acid (30.1 g., 0.2 mole) was added, and the mixture allowed to reflux on the steam bath for one hour. The reflux condenser was then replaced with a distilling head, and excess thionyl chloride removed at reduced pressure (water aspirator) while warming the flask in an oil bath heated to 75°. After all thionyl chloride had been removed, the temperature of the oil bath was increased to 125°, and the product distilled at 102.5-104°/9-10 mm. Yield was 30.3 g. (90%).

Ethyl Acetonedicarboxylate

The procedure was essentially that of Ingold and Nickolls

(29). One pound of finely powdered U. S. P. citric acid was placed in a three liter round-bottom flask equipped with a mechanical stirrer (hood). Two pounds of fuming sulfuric acid was added, with stirring, as rapidly as possible without allowing the reaction to become too violent. After stirring for 15 minutes, the flask was placed in an ice-salt bath and, with continued stirring, cooled to 0° (about 1½ hours was required.) The mixture assumed a pasty consistency as the acid separated.

The crude acetonedicarboxylic acid was collected on an asbestos-packed Buchner funnel, and pressed and sucked as dry as possible. It was then transferred to a beaker and stirred to a paste with a little ethyl acetate. This was again pressed and sucked dry on the Buchner funnel, and the process repeated. The solid was then transferred to a 2 liter round-bottom flask and 700 g. of absolute alcohol which had been saturated with dry hydrogen chloride gas at room temperature and then cooled to 0° was added. This was placed in a water bath at 45° and shaken until the acid had completely dissolved. The solution was left in the water bath overnight, the bath being allowed to cool to room temperature.

The solution was poured into one liter of ice water in a 3 liter beaker, the mixture then transferred to a 2 liter separatory funnel, the ester layer allowed to separate, and was withdrawn. The aqueous layer was extracted twice with

350 ml. portions of benzene, and the combined ester-benzene layers washed once with 400 ml. of 10% sodium carbonate solution, once with 400 ml. of 10% sulfuric acid, twice with 400 ml. of water, and the solution dried over anhydrous sodium sulfate and Drierite.

The organic solvents were removed by distillation at atmospheric pressure on a steam bath, and the residue distilled at reduced pressure. The fraction distilling at 127-128° at 7-8 mm. was saved. Yield, 153 g. (32% based on citric acid.)

Ethyl Hydrocinnamoyl Acetonedicarboxylate

Into a 1 liter 3-necked round-bottom flask fitted with a mercury-seal stirrer, dropping funnel and a condenser protected at the top with a calcium chloride tube was placed 32.4 g. (0.16 mole) of ethyl acetonedicarboxylate and 300 ml. of anhydrous ether. Finely divided metallic sodium (3.7 g., 0.16 mole) was added, and allowed to react to form the sodio derivative. When this reaction was complete, 26.9 g. (0.16 mole) of hydrocinnamoyl chloride, dissolved in 50 ml. of anhydrous ether, was introduced fairly rapidly from the dropping funnel with continuous stirring. The rate of addition was controlled in a manner to keep the reaction from becoming too vigorous. After addition of the hydrocinnamoyl chloride was complete, the mixture was allowed to reflux for 5 hours. A copious precipitate of sodium chloride separated.

The ether solution was decanted from the sodium chloride into a one liter separatory funnel, the sodium chloride washed once by decantation with 50 ml. of ether, and the ether solution washed once with 10% sulfuric acid, twice with water, and dried over anhydrous sodium sulfate. A small portion of the ether solution was evaporated under a stream of air, and the residual oil treated in a number of ways in an attempt to obtain a solid product, but without success. Another small portion was placed in a 25 ml. Claisen flask and an attempt made to distill the residue in vacuo, but decomposition was extensive, and no distillate could be driven over below 150° at 12 mm.

The bulk of the ether solution was shaken with saturated cupric acetate solution, and after standing overnight in the separatory funnel, no crystallization had occurred. The aqueous layer was withdrawn, the dark blue ether layer washed twice with water, and the ether solution allowed to evaporate spontaneously. A dark blue, almost black semi-solid mass was obtained which was transferred to a Buchner funnel and washed with cold ether with suction. A bright blue-violet solid was obtained, additional material being obtained by similar treatment of the ether washes. After several recrystallizations from methanol-petroleum ether, the melting point was 106.5-107°.

Analysis data:	C	H	Cu (as CuO)
Calc. for $(C_{18}H_{21}O_6)_2Cu$	59.21	5.79	10.89
Found:	59.23	6.06	10.92

Ethyl hydrocinnamoyl acetonedicarboxylate was regenerated by suspending the copper derivative in ether in a separatory funnel and shaking with excess 10% sulfuric acid. The product after removal of the ether was a clear, viscous, slightly amber oil. This pure material would not solidify nor crystallize from any of a number of solvents.

O-Acetylated 5-Carbethoxy-6-(β-phenyl)ethyl pyran-2,4-dione

In a 100 ml. round bottom flask was placed 9.8 g. of ethyl hydrocinnamoyl acetonedicarboxylate, 40.0 g. of acetic anhydride was added, the flask fitted with a reflux condenser, immersed in an oil bath at 145°, and the solution allowed to reflux for four hours. The mixture was then cooled, excess acetic anhydride decomposed with water and the separated oil taken up in ether and washed repeatedly with 2% sodium bicarbonate solution until the washings were alkaline. The ether solution was washed with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the amber, oily residue weighed 7.8 g. This material was readily soluble in most organic solvents except petroleum ether. From dilute methanol or ethanol, dilute acetone, alcohol-petroleum ether, acetone-petroleum ether or benzene-petroleum ether, the material separated as an oil. No apparent reaction occurred upon treatment with saturated cupric acetate solution. This was to be expected if the enolic hydrogen had been substituted by the acetyl group. The crude material was used for the following hydrolysis procedure.

5-Carbethoxy-6-(β-phenyl)ethylpyran-2,4-dione

The crude material from the preceeding procedure (7.8 g.) was dissolved in 50 ml. of approximately 1 N. methanolic sodium hydroxide and shaken mechanically for eight hours at room temperature. The solution was then diluted with water and acidified to congo red paper with 10% sulfuric acid. A solid product separated which formed long, rod-like crystals after standing in the refrigerator. This material was recrystallized from petroleum ether, m.p. 85-6°. Yield 3.5 g. (41% overall from ethyl hydrocinnamoyl acetonedicarboxylate.)

Analysis data:	C	H
Calc. for $C_{16}H_{16}O_5$	66.66	5.60
Found:	66.64	5.70

5-Carboxy-6-(β-phenyl)ethylpyran-2,4-dione.

In a 250 ml. Erlenmeyer flask was placed 3.25 g. of 5-carbethoxy-6-(β-phenyl) ethylpyran-2,4-dione and 100 ml. of 2 N. aqueous sodium hydroxide. This was allowed to stand, with occasional shaking, for sixty hours. The material completely dissolved within a short time. The solution was carefully acidified to congo red paper with 10% sulfuric acid, and allowed to stand in the refrigerator until precipitation was complete. 1.36 g. of solid material, m.p. 162-4° with effervescence, was obtained which after repeated recrystallization from ether-petroleum ether had m.p. 162-162.5° with effervescence.

Analysis data:	C	H
Calc. for $C_{14}H_{12}O_5$	64.61	4.65
Found:	64.01	5.02

Decarboxylation attempts

(a) With nitrobenzene.

In a 50 ml. round bottom flask was placed 0.20 g. of 5-carboxy-6-(β-phenyl) ethylpyran-2,4-dione and 4 ml. of nitrobenzene added. This mixture was heated to reflux on a sand bath for 15 minutes, the mixture becoming very dark. The flask was cooled in ice for some time, but no solid separated, so it was extracted with 10% sodium carbonate solution. Upon acidification of the alkaline extract a milky suspension formed which after standing deposited a small amount of crystalline material (estimated about 10-14 mg.) which after washing and drying on a porous place melted without decomposition at 135-8°. Not enough material was obtained for further investigation.

(b) With pyridine.

The procedure was adapted from Corey (30). In a 50 ml. flask, 0.128 g. of the acid was allowed to reflux with 4 ml. of anhydrous pyridine for four hours. After cooling to room temperature, the pyridine solution was poured into a mixture of 20 ml. of concentrated hydrochloric acid and 30 g. of ice. The solution was extracted with three 15 ml. portions of ether, the ether solution washed three times with 3 ml. portions of 5% sodium bicarbonate solution, and the bicar-

bonate solution acidified with 10% hydrochloric acid. An estimated 15-20 mg. of a white, flocculent precipitate was obtained which after washing and drying on a porous plate melted at 139-141° without effervescence. The quantity was too small for further investigation. Evaporation of the ether solution yielded a small amount of resinous material which could not be obtained solid.

THE DEHYDRO ACID APPROACH

Ethyl Hydrocinnamoyl Acetoacetate.

In a 500 ml. flask fitted with a reflux condenser protected at the top with a calcium chloride tube was placed 23.4 g. (0.18 mole) of ethyl acetoacetate, 200 ml. of anhydrous ether was added, and 4.14 g. (0.18 g. atom) of sodium cut in small pieces was introduced through the condenser. The reaction mixture became quite thick with the solid sodio derivative. The mixture was allowed to stand over the week-end with frequent vigorous shaking. Hydrocinnamoyl chloride (30.3 g., 0.18 mole) was introduced in divided portions through the condenser, allowing the reaction to subside between additions. After addition was complete the mixture was allowed to reflux for one hour, then allowed to stand at room temperature for twenty hours. The separated sodium chloride was removed by filtration, and the ether removed from the filtrate under reduced pressure at room temperature. The resulting oil was distilled at 3-4 mm. pressure, yielding a small fraction at 72-117°, the main fraction distilling at 144-166°, leaving a dark residue that would not distill at a bath temperature above 220°. The 144-166° fraction weighed 16 g. (34% calculated as ethyl hydrocinnamoyl acetoacetate.

Since there was evidence of loss through decomposition upon distillation, the 144-166° fraction was further purified through the copper derivative. The oil was dissolved in

ether and shaken vigorously with saturated cupric acetate solution. After standing overnight, a mass of dark blue solid had separated in the ether layer. This was collected on a Buchner funnel, washed well with water, and sucked dry, m.p. 118-123°. The solid was quite soluble in alcohol, acetone, chloroform, benzene, and slightly soluble in boiling petroleum ether. It was recrystallized by boiling with petroleum ether and adding dropwise sufficient acetone to the boiling mixture to produce a clear solution. On standing at room temperature, clusters of bright blue, tiny needles crystallized from the solution, m.p. 130-131°. Borsche (28) reports m.p. 136° for the copper derivative of ethyl hydrocinnamoyl acetoacetate. The yield, based on the copper derivative of which 18.2 g. was obtained, was 31%.

Ethyl Hydrocinnamoyl Acetate by Hydrolysis of the Acetoacetate.

(a) Attempt with 75% Acetic Acid.

Borsche (28) reported a 50% yield of ethyl cinnamoyl acetate by hydrolysis of the acetoacetate with 75% acetic acid, by warming "for one day on the water bath." About 10 ml. of the oil recovered from the copper salt of ethyl hydrocinnamoyl acetoacetate was placed in a 250 ml. beaker and 40 ml. of 75% acetic acid added. This was allowed to remain on the steam bath for 10 hours. It was then cooled and diluted with about 200 ml. of ice water. The oil was extracted with ether and the ether solution dried over anhydrous sodium sulfate. Upon distillation of the residue

from the ether solution at 2-3 mm., a fraction was obtained, b.p. 149-156°, which was determined through its copper salt to be unreacted starting material. A considerable amount of dark residue remained in the distilling flask from which no pure material was obtained. It was expected that some of the dehydro acid would be present if ethyl hydrocinnamoyl acetate had been produced, but the residue showed no solidifying tendencies after standing or after treatment with solvents. Less than half of the original material was recovered.

(b) Attempt with Ammonia-Ammonium Chloride.

The procedure was essentially that of Shriner et. al. in their preparation of ethyl benzoyl acetate (36). In a 50 ml. Erlenmeyer flask, 3.2 g. (0.06 mole) of ammonium chloride was dissolved in 15 ml. of water and 1 ml. of strong ammonia solution was added. This solution was warmed to 42° in a water bath, and poured quickly onto 6.55 g. (0.025 mole) of ethyl hydrocinnamoyl acetoacetate in another 50 ml. Erlenmeyer flask. The mixture was shaken and placed in a water bath at 42° for ten minutes. The flask was then cooled rapidly in an ice bath, the mixture transferred to a separatory funnel, and extracted three times with 10 ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled at 3 mm., obtaining 3.9 g. at 164-166°, presumed to be unreacted starting material. From the aqueous ammonia solution, upon acidification with dilute sulfuric acid, was obtained an oil which solidified on

agitation in long, broad, colorless crystals, m.p. 47-8°, undepressed on admixture with hydrocinnamic acid. The residue in the distilling flask did not solidify nor could a solid material be obtained.

(c) With Ammonia Solution at 60°.

This procedure was similar to that employed by Borsche (23) to obtain methyl γ-cinnamalacetoacetate from methyl α-(cinnamalacetyl) acetoacetate. Ethyl hydrocinnamoyl acetoacetate (3.1 g., 0.012 mole) was treated with 40 ml. of strong ammonia solution and warmed in a water bath at 60° for one-half hour. The mixture was then cooled in an ice bath, transferred to a separatory funnel, extracted with ether, and the ether solution dried over anhydrous sodium sulfate. When the residue was distilled at 3-4 mm., a few drops distilled at 80-88° while the temperature of the heating bath rose to 180°. When the distilling flask was allowed to cool, the residue became semisolid, and after standing overnight had deposited long, colorless needle crystals. The crystalline material was transferred to a sintered-glass funnel, sucked free of oil, and washed by the dropwise addition of cold ether. The pure white, luminous needles had m.p. 94-5°. This is the melting point reported by Borsche for the hydrogenated product from his dehydrocinnamoylacetic acid.

Dehydroacetin Acid

This material was prepared by the method of Arndt et. al. (34). In a 1 liter two-necked flask equipped with a short

distilling head and nitrogen inlet capillary was placed 600 g. of ethyl acetoacetate and about 5 mg. of sodium bicarbonate. The flask was heated with a heating mantle, the temperature being controlled so that the temperature at the distilling head did not rise above 85°, and under a slow stream of nitrogen, about 50 g. of distillate collected. Then the system was evacuated and unreacted acetoacetic ester removed by distillation. The receiving apparatus was then changed as follows: the distilling head was replaced with a 75° connecting tube combined with a 105° connecting tube leading into a two-necked flask cooled with running water. Into the other neck of the receiving flask was placed a suction adapter for evacuating the system. This set-up permitted warming the column through which the distillate passed to prevent it from becoming plugged with product. The system was evacuated to 3-4 mm. and the dehydroacetic acid distilled, m.p. 108-9°. A yield of about 25% per run was obtained. By reusing the recovered acetoacetic ester, overall yields of 75-80% were obtained.

6-Methylpyran-2,4-dione.

This compound was prepared from dehydroacetic acid by the procedure of Collie (35). Ten grams (about 0.06 mole) of dehydroacetic acid was dissolved in 30 ml. of 90% sulfuric acid in a 125 ml. Erlenmeyer flask. The flask was placed in an oil bath preheated to 150°, and the contents of the flask heated as rapidly as possible to 130°. The flask was removed from the oil bath and cooled in an ice

bath to 10°, then the contents poured with stirring on 60 g. of crushed ice. The solid product was collected on a Buchner funnel, sucked dry, and recrystallized as quickly as possible from water. Yield 6.8 g. (91%) of product m.p. 184-5°. On larger runs (up to 40 g.) yields were appreciably smaller.

Dehydrobenzoylacetic Acid.

The procedure employed was that of Arndt et. al. (34). One hundred grams (0.52 mole) of ethyl benzoyl acetate, 100 ml. of o-dichlorobenzene and approximately 1 mg. of sodium bicarbonate were placed in a 500 ml. flask equipped with a 20 cm. air condenser topped with a distilling head equipped with condenser and receiving flask. The reaction flask was heated with a heating mantle controlled so that the temperature at the distilling head did not rise above 80°. After eight hours, only about 5 ml. of distillate had been collected at 70-80°. On standing overnight, yellow crystalline material separated and was removed by filtration. Yield 4.2 g. Extraction of the filtrate with 10% sodium carbonate solution yielded upon acidification an additional 7.5 g. The o-dichlorobenzene-ethyl benzoyl acetate solution was dried over sodium sulfate and the process repeated until a total of 38.6 g. (51%) of dehydrobenzoylacetic acid was obtained, m.p. 170-1°.

6-Phenylpyran-2,4-dione.

The procedure used was that of Arndt et. al. (34). Ten grams (0.034 mole) of dehydrobenzoylacetic acid was

dissolved in 70 ml. of 90% sulfuric acid in a 125 ml. Erlenmeyer flask and placed in an oil bath preheated to 160°. The solution was warmed as quickly as possible to 138°, and maintained at 138-140° for one minute, then cooled rapidly in an ice bath. When the mixture had cooled to 30°, ice was added with stirring until the mixture became pasty with the separated solid. This brown solid material was collected on a sintered glass funnel, sucked dry, and the solid boiled with ethanol to remove benzoic acid. The 6-phenylpyran-2,4-dione was practically insoluble in the alcohol. After several boilings with ethanol, the product weighed 4.5 g. (70%), m.p. 246-7° d.

Analysis data:	C	H
Calc. for $C_{11}H_8O_3$	70.21	4.26
Found:	69.75	4.58

Hydrogenation of Dehydroacetic Acid.

In the pressure bottle was placed 20.0 g. (0.119 mole) of dehydroacetic acid, about 25 ml. of water, and a drop of phenolphthalein. Sodium hydroxide solution (about 2%) was added with shaking until the solid had just dissolved and the solution remained pink. An additional gram of dehydroacetic acid was added which after shaking made the solution colorless, and 1 teaspoon (about 3 g.) of moist Raney nickel added. The mixture was shaken with hydrogen under an initial pressure of 41.8 lbs. After four hours, the pressure had dropped to 25.2 lbs., representing the absorption of 1½ molar equivalents of hydrogen. During the next three hours, hydrogen amounting to an additional ½ molar equivalent

was absorbed. Shaking was then stopped, the catalyst removed by filtration, and the clear, green solution was found to be distinctly alkaline. The solution was transferred to an evaporating dish and reduced to small volume by evaporation on a steam bath under a current of air. Upon acidification of the concentrated solution with dilute hydrochloric acid, considerable effervescence was noted, and a brown, foamy viscous layer separated and floated on the surface. After standing for several hours, a white crystalline solid separated in the aqueous portion and the gummy layer contained additional crystals. This was transferred to a Buchner funnel and the oil separated by suction filtration. A portion of the solid residue was dried on porous plate, m.p. 152-166° d. The residue was recrystallized several times from 20% ethanol, m.p. 185.5-186° d., undepressed after admixture with 6-methylpyran-2,4-dione.

Analysis data:	C	H
Calc. for $C_6H_6O_3$	57.14	4.80
Found:	57.34	5.06

In a recent attempt to duplicate these results, 8.4 g. (0.05 mole) of dehydroacetic acid was treated in an exactly analogous manner, although it is believed the Raney nickel was less active. Similar behavior was observed, but the solid material isolated is believed to be mainly unreacted starting material. After several recrystallizations from methanol and from ethyl acetate, the separated crystals are somewhat gummy, m.p. 88-94°. After admixture with a little

dehydroacetic acid (m.p. 108-109°), m.p. 88-101°.

The total ether soluble material recovered after concentration and acidification was 4.1 g., less than 50% of the weight of starting material employed.

Hydrogenation of Dehydrobenzoylacetic Acid.

(a) Seven grams (about 0.024 mole) of dehydrobenzoylacetic acid was dissolved in 100 ml. of dioxane by warming, and about 2 g. of moist (alcohol) Raney nickel catalyst added. The heating plate of the hydrogenation apparatus was connected with a Variac set at 60 volts, the mixture in the pressure bottle heated to about 60°, and hydrogen under an initial pressure of 41 p.s.i. was admitted. Shaking was continued until the pressure had dropped 2 lbs., representing the theoretical drop for the absorption of one mole of hydrogen. The solution was then filtered and set aside overnight. Colorless needle crystals separated and were removed by filtration, amounting to 1.3 g. On further cooling of the mother liquor, an additional 0.7 g. was obtained. After several recrystallizations from dioxane, the m.p. was 257-8°.

Analysis data:	C	H
Calc. for $C_{18}H_{14}O_4$:	73.47	4.76
Calc. for $C_{18}H_{14}O_3$:	77.68	5.07
Found:	77.82	5.31

(b) In a pressure bottle, 5.0 g. of dehydrobenzoylacetic acid was dissolved in 100 ml. of dioxane and shaken with

2.0 g. of 5% palladium on carbon under an initial hydrogen pressure of 35.5 p.s.i. After shaking for six hours, the pressure had dropped 1½ lbs., about the amount necessary for the absorption of one molar equivalent of hydrogen. After removal of the catalyst, the solution was allowed to stand overnight, but no solid separated. After concentration of the solution, yellow needle crystals separated, m.p. 169.5-171°. Upon admixture with dehydrobenzoylacetic acid no depression in the melting point occurred. Recovery was essentially quantitative.

Hydrogenation of 6-Methylpyran-2,4-dione.

(a) Modified Rupe procedure.

In a pressure bottle, 3.63 g. (0.029 mole) of 6-methylpyran-2,4-dione in 50 ml. of water was neutralized to about pH 6 with 10% sodium hydroxide solution. About 3 g. of moist Raney nickel was added, and the mixture shaken with hydrogen under an initial pressure of 39.5 p.s.i. The theoretical pressure drop for absorption of one mole of hydrogen occurred in slightly over one hour, then the pressure drop was slow. About six hours shaking was allowed, during which the total drop in pressure was 3.6 lbs. (theoretical for one mole is 2.3 lbs.). The mixture was filtered, the clear solution adjusted to pH 8-9 (pH paper) with 10% sodium hydroxide solution, and concentrated on the steam bath. Upon acidification with 10% hydrochloric acid, a dark oil separated which showed no solidifying tendency after cooling in ice. Treatment of a portion of this material with semi-carbazide hydrochloride (103) gave no sign of reaction nor

a solid derivative except a small amount of biurea, m.p. 249-249.5° d. Upon treatment with freshly prepared 3,5-dinitrobenzoyl chloride (104), the mixture became very black. This was treated with 20 ml. of 5% sodium bicarbonate solution (considerable effervescence), then cooled in ice water, and a brownish-black solid separated. This was removed by filtration, washed on the filter several times with 10% sodium bicarbonate solution, and the residue treated twice in alcohol solution with Norit, which did not remove an appreciable amount of color. The residue was taken up in ether and the ether allowed to evaporate spontaneously, leaving some large, colorless platelets along the walls of the flask as the ether evaporated. These crystals were removed and further purified by recrystallization from ether-petroleum ether, yielding practically colorless platelets, m.p. 87-89° after sintering above 80°, but in too small amount for further investigation.

(b) Attempts in Alcohol Solution with Various Catalysts.

The general procedure for the attempts to hydrogenate 6-methylpyran-2,4-dione in alcohol solution was similar to the procedures given above. Starting material was recovered practically quantitatively each time. Data on several runs are listed below:

Wgt. (g)	Solvent	Catalyst	Pressure (p.s.i.)	Time (hours)
2.65	Methanol	Raney nickel	38.8	11
3.5	Methanol	5% Palladium/carbon	39.9	6
2.0	Ethanol	"	40.0	24
2.0	Methanol	5% Palladium/$SrCO_3$	41.0	9

(c) In Ether.

In a pressure bottle was placed 4.0 g. (0.032 mole) of 6-methylpyran-2,4-dione and 100 ml. of ether. The pyrone did not completely dissolve. 3.0 g. of 5% palladium on barium sulfate was added and the mixture shaken with hydrogen under an initial pressure of 45.0 lbs. The pressure dropped slowly until it reached 42.5 lbs. after eight hours of shaking. The catalyst was removed by filtration, and the ether evaporated under the suction to leave a crystalline solid which, on a melting point determination, sintered at 120°, started to effervesce at 122°, and continued to 145° before all solid had disappeared. Recrystallized from ethyl acetate, the material melted at 124-130° with effervescence. An estimated 15-20% of the total starting material was recovered from the ether solution. Extraction of the catalyst with methanol gave the major portion of the material as unchanged pyrone, m.p. 185-6°.

Attempted Hydrogenation of 6-Phenylpyran-2,4-dione.

In a pressure bottle was placed 9.4 g. (0.05 mole of 6-phenylpyran-2,4-dione, 100 ml. of ethanol and approximately

3 g. of moist Raney nickel. The mixture was heated to about 60° and shaken under hydrogen at 40 p.s.i. No drop in pressure occurred after about six hours. The unchanged starting material was recovered by dissolving it in 5% sodium hydroxide solution, filtering to remove the catalyst, and acidifying with sulfuric acid, m.p. and mixed m.p., 244-7° d.

Effect of Heating 6-Phenylpyran-2,4-dione with Dioxane.

In a 250 ml. flask fitted with a reflux condenser was placed 1.45 g. of 6-phenylpyran-2,4-dione and 150 ml. of dioxane, and the mixture was boiled under reflux until all had dissolved, which required several hours. Concentration of the solution by distillation of dioxane, followed by cooling and long standing failed to yield a precipitate, but upon dilution with water, a white solid separated, m.p. 264-268° d. Recrystallised from dilute dioxane, the material separated in small cylindrical rod-shaped crystals, m.p. 264-265°.

Analysis data:	C	H
Found:	72.15	4.42

6-METHYLPYRAN-2,4-DIONE AND DERIVATIVES WITH NBS

Mono-bromo derivative of 6-methylpyran-2,4-dione.

In a 125 ml. flask were placed 1.26 g. (0.01 mole) of 6-methylpyran-2,4-dione, 1.78 g. (0.01 mole) of N-bromo-succinimide, and 30 ml. of dry carbon tetrachloride. The flask was fitted with a reflux condenser protected at the top with a calcium chloride tube, and warmed with a heating mantle to reflux temperature. The 6-methylpyran-2,4-dione did not all dissolve, but after several hours solid presumed to be succinimide rose to the surface of the liquid. Periodic tests were made of the reaction mixture with starch-potassium iodide paper for the presence of bromine, over twenty-four hours being required before the test was negative. Refluxing was allowed to continue for a total of 36 hours, then the reaction mixture was cooled and the solid removed by filtration. The carbon tetrachloride filtrate, upon evaporation, yielded a small crop of brownish needle crystals, m.p. 182-4° d. after recrystallization from glacial acetic acid. A sodium fusion showed the presence of bromine.

The solid which had been collected on the filter, after washing several times to remove succinimide, had m.p. 165-168° d. Recrystallized from glacial acetic acid, the m.p. was raised to 182.5-183° d. After several recrystallizations from glacial acetic acid, m.p. 185° d.

Analysis data:	C	H
Calc. for $C_6H_5BrO_3$	35.15	2.46
Found:	35.48	2.59

3-Bromo-6-methylpyran-2,4-dione.

This material was prepared by the procedure of Arndt and Avan (48). 6-methylpyran-2,4-dione (0.63 g., 0.005 mole) was dissolved by warming in 10 ml. of glacial acetic acid. To this solution was added dropwise with shaking a solution of 0.5 g. (about 0.062 mole) of bromine in 5 ml. of glacial acetic acid. The bromine was decolorized immediately until the last few drops, representing excess bromine were added. Upon standing, the bromo derivative crystallized as clusters of tiny, colorless needles. Recrystallized from glacial acetic acid, a yield of 0.94 g. (91.5%), m.p. 196.5-197.5° d. was obtained. A mixed melting point with the product from the preceeding (NBS) procedure decomposed at 193-4°.

2-Methoxy-3-bromo-6-methyl-4-pyrone.

(a) Ninety milligrams of the product from the 6-methylpyran-2,4-dione-NBS procedure was added in small portions to an ether solution of diazomethane (from 5 g. of nitrosomethylurea). Each addition was accompanied by vigorous effervescence, with dissolution of the solid. The solution was allowed to stand overnight, the ether removed by evaporation under a current of air, and the solid residue recrystallized from 95% ethanol, m.p. 150.5-153°.

(b) One hundred and fifty milligrams of the 3-bromo product prepared by the procedure of Arndt (48) was covered with anhydrous ether and treated portionwise with an ether solution of diazomethane (from 10 g. of nitrosomethylurea).

Each addition produced vigorous effervescence. Finally, excess of the diazomethane solution was added and the mixture allowed to stand at room temperature overnight. The solid did not all dissolve. The solution was concentrated, cooled, and the solid removed by filtration, m.p. 148.5-151°. This material was recrystallized from benzene, m.p. 152.5-153°, undepressed by admixture with the product from the preceeding procedure.

(c) 2-Methoxy-6-methyl-4-pyrone was prepared by treatment of 6-methylpyran-2,4-dione with diazomethane (48), yielding from 3.1 g. of 6-methylpyran-2,4-dione 2.2 g. (64%) of methoxy product. To a solution of 1.3 g. (0.009 mole) of the methoxy pyrone in 10 ml. of dry carbon tetrachloride was added 1.6 g. (0.009 mole) of NBS and 0.245 g. (about 10 mole %) of benzoyl peroxide. After brief warming, a vigorous reaction occurred which proceeded for some time without further warming. In about ten minutes, the solid had left the bottom of the flask (succinimide) although after five hours of refluxing the test for bromine was still faintly positive. The succinimide was removed by filtration, and concentration of the filtrate yielded a solid which was recrystallized from methanol, m.p. 152-3°, undepressed upon admixture with the product from the two preceeding procedures.

Analysis Data:

Calc. for one CH_3 to Carbon:	6.85%
Found:	6.85%

2-Methoxy-3-bromo-6-bromomethyl-4-pyrone.

A mixture of 3.5 g. of 2-methoxy-3-bromo-6-methyl-4-pyrone, 2.7 g. of NBS, 0.4 g. of benzoyl peroxide and 30 ml. of dry carbon tetrachloride were allowed to reflux for six hours, the test for bromine after that time being faintly positive. After filtration and concentration of the filtrate, the solid residue was removed by filtration and recrystallized three times from methanol, yielding 2.8 g. (62%) of small needle crystals, m.p. 161.5-162°.

Analysis data:	C	H
Calc. for $C_7H_6Br_2O_3$:	28.19	2.03
Found:	28.17	2.76

Upon chromic acid oxidation in the procedure for determination of methyl attached to carbon (50), two drops of 0.0100 N. sodium hydroxide solution was sufficient to bring about the phenolphthalein end point from the first fraction of distillate, indicating the absence of a C-methyl group.

Hexaminium Salt of 2-Methoxy-3-bromo-6-bromomethyl-4-pyrone.

A mixture of 0.52 g. (0.0018 mole) of the dibromo pyrone, 0.244 g. of methenamine and 10 ml. of chloroform were placed in a 50 ml. round-bottom flask and allowed to reflux. A clear solution quickly formed from which, in about ten minutes, a copious precipitate formed. Refluxing was allowed to continue for one hour, then the solid was collected on a Buchner funnel, washed well with ether and air-dried. A yield of 0.68 g. (89%) of a white granular

solid was obtained which resinified at 205-8°.

Attempted Conversion of the Hexaminium Salt of 2-Methoxy-3-bromo-6-bromomethyl-4-pyrone to the aldehyde.

(a) Procedure of Dunn et. al. (51).

In a 100 ml. distilling flask set for steam distillation was placed 0.55 g. of the hexaminium salt and 20 ml. of water. As steam began passing through the system, the solid was converted to a brown gummy material which adhered to the walls of the flask. Distillation was continued until 100-120 ml. of distillate had been collected. The distillate was slightly cloudy with a small amount of oily material floating on the surface. The distillate was acidified with dilute hydrochloric acid, extracted with ether, the ether solution dried over anhydrous sodium sulfate, and the dried solution evaporated under a stream of nitrogen to yield a small amount of brown, oily residue. This residue gave no indication of reaction with sodium bisulfite or 2,4-dinitrophenylhydrazine reagent.

The residue remaining in the distilling flask was virtually insoluble in boiling chloroform or alcohol, readily soluble in dilute hydrochloric acid, but concentration of the acid solution to small volume followed by dilution with alcohol and refrigeration yielded only a brown scum.

(b) Procedure of Angyl et. al. (52).

In a 50 ml. round-bottom flask was placed 0.5 g. (0.0012

mole) of the hexaminium salt and 25 ml. of 50% acetic acid. The flask was fitted with a reflux condenser and immersed in an oil bath at 125°. Refluxing was allowed to continue for thirty minutes, 0.5 ml. of concentrated hydrochloric acid was added, and heating continued for five minutes. Upon cooling, a dark, oily material separated and was extracted with ether. The residue from the ether solution was treated in the usual way with 2,4-dinitrophenylhydrazine (105), to yield, after standing overnight, an estimated 30 mg. of a red, amorphous solid which charred above 200° but did not melt below 300°.

Attempted Condensation of 2-Methoxy-3-bromo-6-bromomethyl-4-pyrone with Benzyl Sodium.

The procedure of Smith and Turner (53) was used for the preparation of benzyl sodium. Into a 200 ml. three-necked flask fitted with a mercury seal stirrer, dropping funnel, condenser, thermometer and nitrogen inlet tube were placed 30 ml. of sodium dried toluene and 0.28 g. (0.012 g. atom) of sodium sand. The air was swept from the system with nitrogen, and with constant stirring 0.68 g. (0.006 mole) of chlorobenzene was introduced slowly from the dropping funnel. The temperature of the reaction mixture was at 30-31° throughout the addition, the mixture becoming very black. After stirring for two hours, the flask was heated in an oil bath for thirty-five minutes, the reflux temperature being about 108°. The heating bath was then removed, and 1.2 g. (0.0043 mole) of the dibromo pyrone added all at

once. The mixture was allowed to stir until it had cooled to room temperature, then solid carbon dioxide added to decompose any unreacted benzyl sodium, followed by a little water to decompose unreacted sodium. A yellow solid separated and remained suspended in the aqueous phase. This, after separation and recrystallization from ethanol, proved to be unreacted starting material. More of this was recovered from the toluene layer. No reaction product, even phenylacetic acid, could be found.

In a similar procedure, the dibromo compound dissolved in toluene was added dropwise. Unreacted starting material was recovered. In another similar run, refluxing was allowed to continue during the addition of a toluene solution of the dibromo compound and for one hour additional. Tarry decomposition products but no solid or pure material could be isolated.

Reformatsky Procedure with 2-Methoxy-3-bromo-6-bromomethyl-4-pyrone and benzaldehyde.

In a 125 ml. round-bottom flask were placed 1.13 g. (0.004 mole) of the dibromo pyrone, 0.5 g. (0.0047 mole) of benzaldehyde, 0.3 g. (0.0046 g. atom) of freshly sand-papered zinc foil cut in small strips, 25 ml. of anhydrous ether and 25 ml. of dry benzene. A crystal of iodine was added, the flask fitted with a reflux condenser protected at the top with a calcium chloride tube, and the mixture heated to reflux on a water bath. Refluxing was continued for four hours,

the pyrone slowly passing into solution, the zinc darkening somewhat but being otherwise apparently unaffected. The ether-benzene solution was decanted from the zinc, and upon cooling deposited crystalline starting material. Recovery was practically quantitative.

THE CLAISSEN-DIECKMANN CYCLIZATION APPROACH

Ethyl β-hydroxy-β-phenyl propionate.

The procedure of Hauser and Breslow (58) was used to prepare this material. From 65 g. (0.61 mole) of benzaldehyde, 84 g. (0.5 mole) of ethyl bromoacetate and 40 g. (0.62 mole) of granulated zinc was obtained 68.5 g. (70.5%) of product, distilling at 120-125° (all but a few drops at 124°) at 1 mm.

Ethyl β-acetoxy-β-phenyl Propionate.

A mixture of 25.8 g. (0.13 mole) of ethyl β-hydroxy-β-phenyl propionate, 41 g. (0.4 mole) of acetic anhydride and 43.6 g. (0.55 mole) of dry pyridine were placed in a 250 ml. Erlenmeyer flask. The flask became quite warm, and a yellow color developed. This was allowed to stand at room temperature for twenty-four hours. The mixture was transferred to a 250 ml. Claisen flask and distilled under reduced pressure (water aspirator) to remove acetic anhydride and pyridine. When the temperature had risen rapidly to 110°, the receiver was changed and the system evacuated to 1 mm. (oil pump). A fraction distilling at 128-134.5° was redistilled to yield 26.4 g. (83.6%) of the acetoxy ester, distilling at 146-147° at 3-4 mm. Saponification equivalent 114.8 (theory 118).

Methyl δ-acetoxy-δ-phenyl Valerate.

Hydrocinnamic aldehyde, Eastman Kodak practical grade,

was distilled at reduced pressure, that portion distilling at 76-77° at 0.5 mm. being employed. Methyl bromoacetate was redistilled at water aspirator pressure, the fraction distilling at 62-5° being used.

In a dry 500 ml. round-bottom flask was placed 16.5 g. (0.25 g. atom) of zinc, 33.5 g. (0.25 mole) of hydrocinnamic aldehyde, 38.3 g. (0.25 mole) of methyl bromoacetate, 100 ml. of dry benzene and 100 ml. of anhydrous ether. A few crystals of iodine were added and the flask was fitted with a reflux condenser protected at the top with a calcium chloride tube. The reaction started spontaneously, gradually becoming more vigorous until after about fifteen minutes it was necessary to control the reaction by cooling the flask intermittently with cold water. The spontaneous reaction continued for about one and one-half hours, when practically all of the zinc had been consumed. About 2 g. of zinc, 10 ml. of methyl bromoacetate and a crystal of iodine were added, and the flask heated on the steam bath with frequent vigorous shaking for an additional hour.

The reaction mixture was transferred to a separatory funnel and shaken with 300 ml. of saturated ammonium chloride solution. The organic layer was separated, the aqueous layer extracted with 50 ml. of ether, and the combined ether-benzene layer washed several times with 10% sodium carbonate solution, once with water and dried over anhydrous sodium sulfate. The solvents were removed from the dried

solution by distillation at reduced pressure and room temperature, finally warming in a water bath at 60° to remove the last traces of solvent.

To the residue was added 100 g. (about 1 mole) of acetic anhydride and 80 g. (about 1 mole) of pyridine. The mixture was allowed to stand for twenty-four hours, then poured into a mixture of about 300 g. of ice and 500 ml. of 10% hydrochloric acid and shaken in a separatory funnel to remove pyridine. Ether was added to facilitate separation, and the ether solution washed repeatedly with 10% sodium carbonate solution until the washings were alkaline. Finally the ether solution was washed with water, dried over anhydrous sodium sulfate and distilled. A fraction distilling at 146-7° at 4-5 mm. was obtained, amounting to 27.2 g. (43.5%). Saponification equivalent 120.0, 124.4 (calculated 125.3).

Attempted Cyclization of Ethyl-α-acetoxy-α-phenyl Propionate with Sodium Ethoxide.

In a 200 ml. three-necked flask fitted with a mercury seal stirrer, reflux condenser and dropping funnel containing 23.6 g. (0.1 mole) of ethyl β-acetoxy-β-phenyl propionate was placed 46 ml. of absolute ethanol (freshly distilled from sodium ethoxide) and 2.3 g. of sodium cut in small pieces was added through the condenser. When the sodium had been completely converted to the ethoxide, the acetoxy ester was introduced slowly with stirring from the dropping funnel. The first few drops of ester caused a violent reaction,

sufficient heat being generated to drive ethanol vapor from the condenser. The contents of the flask became dark brown and rather thick. Subsequent introduction of the acetoxy ester after this vigorous reaction had subsided produced no noticeable effect. After addition of the ester, the condenser was replaced with a distilling head, and the flask heated on the steam bath to remove the alcohol. However, after about 20 ml. of distillate had been collected, it appeared that extensive decomposition and charring was occurring in the flask, so the distillation was discontinued.

The flask was immersed in an ice bath, allowed to become cold, and 75 ml. of a 1:1 mixture of glacial acetic acid and water introduced with stirring. Ether was added to take up the organic layer, the aqueous layer was withdrawn, and the ether solution extracted four times with 5% alkali. From this aqueous solution, after acidification, was obtained an acid, m.p. 129-130° after recrystallization from petroleum ether. After mixing with cinnamic acid, m.p. 131-133°. The oily residue from the mother liquor showed no enolic properties, nor did the oily residue obtained after evaporation of the solvent from the ether solution.

Attempted Cyclization of Methyl β-Acetoxy-δ-phenyl Valerate with Sodium Methoxide.

The procedure similar to that reported by Bachmann, Cole and Wilds was employed. In a 200 ml. three-necked flask fitted with a reflux condenser, nitrogen inlet tube

and an adapter to allow for evacuation was placed about 25 ml. of anhydrous methanol (distilled from magnesium methoxide) and 0.92 g. (0.04 g. atom) of sodium was added through the condenser. The upper end of the condenser was closed with a rubber stopper, and excess methanol removed at reduced pressure. The flask was evacuated to 1 mm. and filled with dry nitrogen. A solution of 5.0 g. (0.02 mole) of methyl β-acetoxy-δ-phenyl valerate in 20 ml. of thiophene-free sodium-dried benzene was added as quickly as possible, and the mixture heated in an oil bath at 90-100° for two hours. During the reflux period the condenser was protected at the top with a calcium chloride tube.

The flask was then cooled in an ice-water bath and 5 ml. of glacial acetic acid was added, followed by a little water, and the flask shaken until the solid had dissolved. The mixture was transferred to a separatory funnel, the aqueous layer withdrawn, and the benzene solution tested for enolic properties, with negative results. The benzene solution was washed with 5% sodium bicarbonate solution until the washings were alkaline. The benzene solution was dried, and the benzene removed at reduced pressure. The viscous residue gave no positive enol test nor positive carbonyl test when treated with 2,4-dinitrophenylhydrazine reagent.

Upon acidification of the alkaline washings, a white precipitate was obtained which was recrystallized from water, m.p. 130-131°. Combustion analysis and neutral

equivalent established it to be β-hydroxy-δ-phenyl valeric acid.

Analysis data:	C	H	Neut.Equiv.
Calculated for $C_{11}H_{14}O_3$:	68.02	7.27	194
Found:	68.07	7.47	196

Attempted Cyclization of Ethyl β-acetoxy-β-phenyl Propionate with Sodium.

In a 150 ml. round-bottom flask fitted with a reflux condenser protected with a calcium chloride tube was placed 40 ml. of dry benzene and 1.2 g. (0.053 g. atom) of finely divided sodium. Ethyl β-acetoxy-β-phenyl propionate (6.5 g., 0.027 mole) was added, followed by a few drops of absolute ethanol. The flask was warmed on a steam bath, and in a short time a vigorous reaction ensued. The flask was frequently shaken, but in a short time the sodium became coated with an orange reaction product and the reaction subsided. The mixture was allowed to reflux on the steam bath overnight.

The mixture was cooled in ice, treated with 6 N. hydrochloric acid, and worked up in the usual way. From the alkaline wash, cinnamic acid was obtained. The residue from the benzene solution had no enolic properties, nor did any solid form after standing for several weeks.

Attempted Cyclization of Ethyl β-Acetoxy-δ-phenyl Valerate with Sodium.

This procedure was a modification of that employed by Link et. al. (57). In a 200 ml. three-necked flask fitted

with a "Trubore" stirrer, dropping funnel and distilling head with a condenser set for distillation and protected from atmospheric moisture was placed about 25 ml. of dry light liquid petrolatum and 0.87 g. (0.038 g. atom) of sodium sand. The flask was heated on a sand bath at 260°, and with stirring 9.0 g. (0.034 mole) of ethyl β-acetoxy-δ-phenyl valerate was allowed to drop in slowly from the dropping funnel. The addition required one-half hour, after which stirring and heating was continued for another hour. At this time, the flask contents had assumed a light brown color and a pasty consistency. The flask was then cooled in an ice bath and 4 ml. of methanol added to decompose any unreacted sodium. The pasty mass was collected on a Buchner funnel, and washed with petroleum ether. The brown solid was dissolved in the minimum amount of water and extracted with ether until the ether extract was colorless. The aqueous solution was then acidified by the dropwise addition of hydrochloric acid. A white crystalline solid separated which had no enolic properties. It was recrystallized from hot water, m.p. 100-101°. It dissolved in 5% sodium bicarbonate solution with effervescence and a neutral equivalent of 178 indicated it to be 5-phenyl-2-pentenoic acid (theoretical neutralization equivalent 176), which has a reported m.p. of 104°. About 0.6 g. of this acid was obtained. From the filtrate, 4.7 g. of unreacted acetoxy ester was recovered (b.p. 138-145° at 1-2 mm.) No portion of the reaction

mixture gave a positive enol test.

Attempted Cyclization of Methyl β-Acetoxy-δ-phenyl Valerate with Sodium Hydride.

In a 300 ml. three-necked flask fitted with a "Trubore" stirrer, dropping funnel, reflux condenser, and a nitrogen inlet tube was placed 1.92 g. (0.08 mole) of sodium hydride and immediately covered with sodium-dried n-butyl ether (Eastman Kodak white label, redistilled). The flask was immersed in an oil bath and preheated to reflux temperature (bath at 160°), and 10.0 g. (0.04 mole) of methyl β-acetoxy-δ-phenyl valerate was introduced slowly with constant stirring over a period of two hours. Refluxing and stirring was continued for six hours.

The flask was cooled in ice and about 2.5 ml. of methanol added to decompose any unreacted sodium hydride. A mixture of 8 ml. of concentrated hydrochloric acid in about 25 ml. of ice and water was added and the mixture stirred until solution was complete. The aqueous layer was withdrawn and a few drops of the ether solution, after dilution with ethanol, gave an intense, dark green coloration after addition of a drop of ferric chloride solution. The ether solution was washed three times with 5% sodium bicarbonate solution. Acidification of the alkaline wash produced only a slight turbidity, and no positive enol test. The residue, after distillation of the solvent, was treated as follows:

(a) A portion of the ether solution was treated with a saturated cupric acetate solution. The ether assumed a deep

green color, but no solid separated after standing for several days. Evaporation of the ether left a dark green gummy residue which solidified after standing for several days. This material was freely soluble in cold ether, benzene, chloroform, or ethyl acetate, but insoluble in alcohol, even after boiling for some time. The solid was purified as well as possible by collecting it on a sintered glass funnel, washing through with chloroform, precipitating it by addition of ethanol, and repeating this process several times.

Analysis data:	C	H	Cu (as CuO)
Calc. for $C_{26}H_{26}O_6Cu$:	62.70	5.26	15.97
Calc. for $C_{54}H_{62}O_{14}Cu$:	64.94	6.26	7.96
Found:	69.23	5.84	13.91

(b) Treatment of a portion of the residue with an ether solution of diazomethane caused a fairly vigorous reaction which quickly subsided but continued to evolve nitrogen slowly for several hours. After allowing to stand until the ether had spontaneously evaporated (three days), a resinous residue remained which still gave a weak positive enol test. Addition of more diazomethane caused no evident reaction. This residue was readily soluble in most organic solvents except petroleum ether, from which, after boiling, filtering and cooling an oil separated.

A small portion of this material was dissolved in a 1:1 mixture of benzene-petroleum ether and placed on an alumina column. The material was eluted with solvents of gradually increasing polarity, starting with benzene-

petroleum ether and proceeding through benzene, benzene-ether, ether, ether-chloroform, chloroform, chloroform-ethanol, ethanol. 50 ml. of each eluant were used, a small amount of material coming out in the ether-benzene eluate, another small amount in chloroform-ether, and the major portion in the chloroform and chloroform-ethanol fractions. None of the eluted material crystallized after standing several days, although it formed a glass-like layer which could be scraped off as a yellow powder. The material was freely soluble in organic solvents, and could not be obtained crystalline, invariably separating as an oil from recrystallization solvents such as dilute alcohol, benzene-petroleum ether, ether-petroleum ether or chloroform-petroleum ether.

Attempted Cyclization of Methyl δ-Acetoxy-δ-phenyl Valerate with Sodium Amide.

(a) In liquid ammonia.

In a 500 ml. three-necked flask immersed in an acetone-dry ice bath and fitted with a dry-ice condenser carrying a soda-lime tube, "Trubore" stirrer and dropping funnel was distilled 100-150 ml. of commercial anhydrous ammonia, the ammonia gas passing through a drying tower filled with potassium hydroxide pellets. A few crystals of ferric nitrate were added and 1.8 g. (0.08 mole) of sodium introduced with stirring. After the sodium had completely reacted, the dry-ice condenser was replaced with an ordinary reflux condenser, the acetone-dry ice bath removed, and a solution

of 10.0 g. (0.04 mole) of methyl β-acetoxy-δ-phenyl valerate in about 100 ml. of anhydrous ether introduced from the dropping funnel. The flask was warmed on a water bath until all ammonia had evaporated, as indicated when the ether commenced to reflux. The reaction mixture was warmed for an additional three hours on a water bath.

The mixture was cooled to room temperature, and the greenish suspension was poured with vigorous stirring onto a mixture of ice and 20 ml. of concentrated hydrochloric acid. The mixture was transferred to a separatory funnel and shaken vigorously. When allowed to separate, a creamy white solid was suspended in the ether layer. The aqueous layer was withdrawn, extracted once with ether, and the ether added to the ether suspension. On vigorous shaking, the solid dissolved in the ether. This solution was dried over drierite, and upon evaporation yielded a mass of white crystalline solid. Recrystallisation from ethyl acetate gave colorless needle crystals, m.p. 127-8°. A sodium fusion of these crystals indicated the presence of nitrogen, and the material had the correct analysis for the amide of 5-phenyl-2-pentenoic acid.

Analysis data:	C	H	N (Kjeldahl)
Calc. for $C_{11}H_{13}NO$:	75.43	7.43	8.00
Found:	75.83	7.43	7.71

The residual oil from the ether solution had the odor of the starting material, a weak but positive enol test, but after standing for several months failed to deposit a solid

product.

(b) In ether.

This procedure differed from the foregoing procedure only in replacement of the ammonia with ether before addition of the acetoxy ester. The reaction mixture gave no indication that any reaction had occurred, no positive enol test was obtained from the ether solution after working up in the usual manner, and extraction of the ether solution with 5% sodium bicarbonate solution produced a small amount of β-hydroxy-δ-phenyl valeric acid.

Attempted Cyclization of Ethyl β-Acetoxy-β-phenyl Propionate with "Sodium Dispersion."

In a 200 ml. three-necked flask fitted with a reflux condenser, nitrogen inlet tube, "Trubore" stirrer and dropping funnel was placed about 2.5 g. of a 50% (weight) dispersion of sodium in n-butyl ether (provided by National Distillers Chemical Company), the apparatus swept out with dry nitrogen, and with stirring a solution of 5.9 g. (0.025 mols) of ethyl β-acetoxy-β-phenyl propionate in about 25 ml. of dry n-butyl ether introduced slowly from the dropping funnel. Immediately upon introduction of the first few drops of acetoxy ester, a vigorous reaction occurred, with gas evolution and sufficient heat to cause the ether to reflux. Refluxing continued throughout the entire addition, which required about one hour, without external application of heat. The reaction assumed an orange-brown color and a pasty consistency. Stirring was continued for an additional

hour, then the reaction mixture was worked up in the usual way. Acidification of the sodium bicarbonate extract produced some turbidity, but even after cooling in the refrigerator for some time, no crystallization or separation occurred. The ether solution, upon testing with ferric chloride solution, gave an intense, almost black color. The ether solution was dried over anhydrous sodium sulfate, and concentrated by distillation of the ether at reduced pressure from a water bath. Upon addition of petroleum ether, an amorphous yellow solid separated which clumped and resinified at the bottom of the flask. Treatment of a portion of this material in ether with saturated cupric acetate solution behaved similarly to the product from the sodium hydride procedure; i.e., no solid would separate from the ether solution, but after evaporation of the ether, a dark blue gummy residue was obtained which was readily soluble in most organic solvents, but insoluble in alcohol, separating as a flocculent precipitate when a chloroform solution was treated with ethanol. The resinous residue from the ether-petroleum ether mixture has not solidified after long standing in the refrigerator.

THE β-METHOXY CROTONATE APPROACH

Ethyl β-Methoxy Crotonate.

The procedure employed was the modification of the von Pechmann procedure as reported by Arndt et. al. (78). Twenty-five grams (0.19 mole) of freshly distilled ethyl acetoacetate containing about 10 ml. of commercial anhydrous methanol was treated with an ether solution of diazomethane (from 40.0 g. of nitrosomethylurea, dried for three hours over potassium hydroxide pellets). Evolution of nitrogen was relatively vigorous for about an hour and proceeded noticeably for about twenty-four hours. The mixture was allowed to stand for three days, then filtered and shaken for one hour mechanically with 100 ml. of 2 N. sodium hydroxide solution. The ether layer was separated, washed with water, dried over anhydrous sodium sulfate, and distilled. The fraction boiling at 185-195° was redistilled, practically all distilling at 187-190°. The best yield obtained in several similar runs was 5 g. (20%).

α-Bromo-β-methoxy Butyric Acid.

This compound was prepared by the procedure of West et. al. (80). In a 2 liter three-necked flask fitted with a mechanical stirrer was placed 500 ml. of commercial anhydrous methanol and 85.0 g. (0.5 mole) of powdered silver

nitrate. The flask was filled with two dropping funnels, one containing 80.0 g. (0.5 mole) of bromine and the other containing a solution of 43.0 g. (0.5 mole) of crotonic acid (redistilled, b.p. 82-4° at 13-14 mm.) in methanol. The flask was immersed in an ice bath, cooled to 0°, and the material from the two dropping funnels allowed to drop in simultaneously, an effort being made to avoid an appreciable excess of either reagent. This addition required about one and one-half hours, after which the mixture was stirred for an additional three hours, then allowed to stand overnight and warm to room temperature.

The sodium bromide was removed by filtration and the clear solution made alkaline to phenolphthalein by addition of 2 N. sodium hydroxide solution. This was concentrated to small volume under reduced pressure and steam bath temperature, then cooled and while immersed in an ice bath carefully acidified by the slow addition of 6 N. sulfuric acid while maintaining vigorous stirring. The acid separated as a colorless oil. The mixture was extracted four times with 100 ml. each of ether, the ether solution washed once with water, and dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled at reduced pressure, b.p. 130-135° (11-12 mm.), practically all distilling at 132-133°. The distillate solidified in the receiver and was removed by dissolving in methanol, the methanol evaporated under a current of air and finally dried twenty-four hours in a vacuum dessicator, m.p. 59.5-61.5°. Yield 49.65 g. (50.5%).

Dehydrobromination of ∝-Bromo-β-methoxy Butyric Acid.

The dehydrobromination was carried out employing sodium methoxide or sodium ethoxide. The general procedure was the same in each case, with variation in time of heating only. The general procedure and the results of several experiments follow:

In a 150 ml. flask fitted with a reflux condenser was placed the bromo methoxy acid and an amount of 2 N. sodium alkoxide to provide about a 2 to 3 molar excess. This was heated to reflux for the times indicated, then allowed to concentrate by heating the open flask on a steam bath. Sufficient water was added to dissolve the solid residue and, while cooling in an ice bath, acidified with slightly more than the calculated amount of 10% sulfuric acid. The precipitate, which was invariably mostly inorganic (sodium sulfate) was collected on a Buchner funnel and washed repeatedly with ether until evaporation of the ether wash yielded no residue. Concentration of the ether solution yielded the β-methoxy crotonic acid which was recrystallised from benzene-petroleum ether.

WEIGHT	ALKOXIDE	REFLUX TIME (HOURS)	YIELD WGT.	%
10.0	methoxide, 100 ml.	10	2.8	48
20.0	methoxide, 175 ml.	16	2.8	24
10.0	ethoxide, 70 ml.	6	0.5	8.5
10.0	ethoxide, 70 ml.	0.33	2.0	40

Methyl Orthoformate.

The procedure of Sah and Ma (87) was employed in several attempts to prepare methyl orthoformate with poor results. The best yield was obtained by the following procedure:

Commercial anhydrous methanol was further dried by distillation from sodium methoxide. The chloroform had been stored over anhydrous potassium carbonate, and was freshly distilled. 69.0 g. (3 g. atoms) of sodium was dissolved in 1 liter of anhydrous methanol in a 2 liter flask. In a 2 liter two-necked flask was placed 110 ml. (about 1 mole) of chloroform and about an equal volume of methanol. One neck of the flask was fitted with a reflux condenser protected at the top with a calcium chloride tube, the other neck attached by a siphon arrangement to the sodium methoxide-containing flask, the flow being controlled by a pinchcock. Shortly after addition of a few ml. of the sodium methoxide solution a vigorous reaction ensued. The reaction flask was cooled in running water and, throughout the addition of the methoxide solution, the reaction was controlled at a moderate reflux rate by intermittent cooling and the rate of sodium methoxide addition.

After standing overnight, the mixture was heated and allowed to reflux for four hours. It was then cooled in an ice bath and the sodium chloride removed by filtration. The filtrate in a 2 liter flask fitted with a 100 cm. column composed of two condensers was heated on a steam bath and

850-900 ml. of distillate collected. The temperature at the distilling head at no time exceeded 64°. The flask was cooled in ice and additional sodium chloride removed. The combined sodium chloride collected to this point, after drying for four hours in a muffle furnace at 220°, weighed 165 g. (94%).

The filtrate was placed in a 250 ml. flask fitted with a 20 cm. glass-helix packed column and distilled. When the temperature at the distilling head rose to 67°, the receiver was changed and the fraction boiling at 67-103° collected, the temperature rise being quite gradual. This fraction was redistilled to yield 8.3 g. (6.4%) of material, b.p. 103-4°, $n^{27}D$ 1.3755. Methyl orthoformate has a reported $n^{25}D$ of 1.3773 (87).

Methyl Orthobenzoate.

The procedure of McElvain and Venerable (88) was employed to prepare methyl orthobenzoate. Commercial anhydrous methanol (1500 ml.) was distilled from magnesium methoxide directly into a 1 liter three-necked flask fitted with a "Trubore" stirrer, reflux condenser protected with a calcium chloride tube and a dropping funnel. Sodium (37 g., 1.6 g. atom) was introduced through the condenser and the flask immersed in an ice-salt bath, cooled below 0°, and 98 g. (0.5 mole) of freshly distilled benzotrichloride (Eastman, white label) was introduced dropwise into the stirred, cooled solution of sodium methoxide. After addition of the benzotrichloride was complete, the mixture was

stirred for an additional hour, then allowed to stand overnight and warm to room temperature. The mixture was then heated and allowed to reflux for five hours. After cooling in an ice bath, the sodium chloride was removed by filtration, and excess methanol removed by distillation. Additional sodium chloride separated during this procedure and was removed by filtration. The yield of sodium chloride, after drying four-five hours in a muffle furnace at 250° was 77 g. (about 89%). After complete removal of methanol, the residue was distilled through a 20 cm. glass-helix packed column at reduced pressure, yielding 66 g. (72%) of methyl orthobenzoate, b.p. 92-4° at 18-20 mm., $n^{25}D$ 1.4862. (McElvain reports $n^{25}D$ 1.4858).

Methyl β-Methoxy Crotonate.

(a) From β-methoxy crotonic acid.

In a 250 ml. Erlenmeyer flask was placed 7.0 gl. (0.6 mole) of β-methoxy crotonic acid, and a dried ether solution of diazomethane (from 20 g. of nitrosomethylurea) was added in small portions. The first few additions were accompanied by vigorous evolution of nitrogen which was allowed to subside before the next addition. Finally the remainder of the diazomethane solution was added and the mixture allowed to stand for twenty-four hours. The solution was then filtered into a 50 ml. Claisen flask and the ether removed at room temperature and reduced pressure. The residue was distilled at atmospheric pressure, all but a small amount of residue distilling at 172-5°. Yield 6.1 g. (81%).

(b) From pure methyl orthoformate.

The procedure of Claisen for the preparation of ethyl β-ethoxy crotonate (76) with the modification of Blaise and Maire (81) was employed. In a 50 ml. Erlenmeyer flask were placed 8.3 g. (0.078 mole) of methyl orthoformate and 9.0 g. (0.078 mole) of methyl acetoacetate and 2 drops of concentrated sulfuric acid added. A pink-violet color quickly developed, and a slight amount of heat was evolved. The mixture was allowed to stand at room temperature for forty-eight hours, during which time the color gradually faded to a pale pink. A few drops of quinoline were added to neutralize the sulfuric acid, and the product distilled at atmospheric pressure. A fraction distilled up to 32° (methyl formate), another to 64° (methanol) then the temperature rose rapidly to 168° and the remaining liquid distilled at 168-172°. This distillate gave a positive enol test, so it was transferred to a separatory funnel, diluted with ether, and extracted with two small portions of 2 N. sodium hydroxide. The ether layer no longer gave an immediate color with ferric chloride solution. The ether solution was washed once with a small amount of water and dried over anhydrous sodium sulfate. Distillation yielded 5.86 g. (58%) of product, b.p. 169-172°.

(c) Attempts with methyl orthobenzoate.

Since attempts to obtain methyl β-methoxy crotonate from methyl orthobenzoate and methyl acetoacetate failed to yield a pure product, and since the behavior was discussed

in the discussion section, experimental details will not be given.

(d) From methanol, ethyl orthoformate and methyl acetoacetate.

In a 1 liter round-bottom flask were placed 74.0 gl. (0.5 mole) of ethyl orthoformate and 288 g. (9 moles) of commercial anhydrous methanol and the flask fitted with a reflux condenser protected with a calcium chloride tube. The solution was allowed to reflux on a steam bath overnight (about 15 hours). The solution was then allowed to cool to room temperature, 58.0 g. (0.5 mole) of methyl acetoacetate and 4 drops of concentrated sulfuric acid added. The characteristic pink color was formed almost immediately after addition of the acid. This was allowed to stand at room temperature for thirty hours. Then solid potassium carbonate (about 0.5 g.) was added and the flask shaken mechanically for one hour.

The solid was removed by filtration and the solution placed in a liter flask equipped with a short distilling head. The low boiling materials (methyl formate, methanol and ethanol) were distilled out as rapidly as possible, the flask being heated with a heating mantle. When the temperature of the distillate reached 80°, the flask was allowed to cool, the receiver changed, and the system evacuated to 9 mm. and one-half hour allowed without heating to remove traces of low boiling material. The residue was then dis-

tilled at 9 mm., a small fraction passing over below 65° (strong enol test) was discarded, and the remainder distilled at 65-9°, all but a few drops distilling at 65.5-67°. This fraction on testing with ferric chloride solution gave no immediate positive reaction, but gradually darkened on standing. The yield was 64.5 g. (theoretical for methyl β-methoxy crotonate, 65.0 g.). This fraction was redistilled at atmospheric pressure through a 20 cm. fractionating column packed with glass helices and surrounded by a heating jacket. A small amount which came over while the temperature was rising rapidly to 169° was discarded, and the remainder distilled at 169-173°, leaving only a small amount of amber residue which would not distill through the column while heating the flask with a micro burner and at a jacket temperature of 175°. Yield 58.0 g. (89%), $n^{25}D$ 1.4402.

Analysis data:

	C	H	OCH_3
Calc. for $C_6H_{10}O_3$:	55.37	7.75	47.68
Found:	54.55	8.20	46.94

Alkyl Orthoformates.

n-Propyl, n-butyl and isobutyl orthoformates were prepared by the procedure of Alexander and Busch (89). The details for the preparation of propyl orthoformate will serve to illustrate the experimental details.

In a 500 ml. flask was placed 74.1 g. (0.5 mole) of ethyl orthoformate and 120 g. (about 2 moles) of n-propyl alcohol. The flask was fitted with a 50 cm. glass-helix packed fractionating column surrounded by a heating jacket,

and heated with a heating mantle with the Variac control set so that the temperature at the distilling head did not rise above 79°. After twenty-four hours, 69.3 g. (about 100.4% of the theoretical amount) of distillate had been collected. The product was then distilled at reduced pressure, b.p. 78-9° at 10 mm., yield 82.5 g. (87%), $n^{25}D$ 1.4066, reported $n^{20}D$ 1.4078 (89).

By this procedure, n-butyl orthoformate was prepared in 93% yield, b.p. 130-2° at 17-18 mm., $n^{25}D$ 1.4175 (reported $n^{20}D$ 1.4184); isobutyl orthoformate, 85% yield, b.p. 97-8°, $n^{25}D$ 1.4112 (reported $n^{20}D$ 1.4122).

Alkyl Acetoacetates.

n-Propyl and isobutyl acetoacetates were prepared from methyl acetoacetate and the corresponding higher alcohol. The preparation of n-propyl acetoacetate will illustrate the procedure.

In a 250 ml. round-bottom flask were placed 35 g. (0.3 mole) of methyl acetoacetate and 36 g. (0.6 mole) of n-propyl alcohol. The flask was fitted with a 50 cm. glass-helix packed, insulated fractionating column. The temperature of the flask was controlled so that the temperature at the distilling head would not rise above 65° (for a brief period, the temperature did rise above that temperature, but the heat was quickly reduced). After twenty-four hours, 10.3 g. of distillate had been collected (theory, 9.6 g.). The residue was distilled at reduced pressure, excess propanol distilling at 28° (14 mm.) then n-propyl acetoacetate

distilled at 82.5-85° at 14 mm. As the temperature rose from 28° to 82.5°, there was no hesitation near 65°, where methyl acetoacetate distills at this pressure. Yield, 40 g. (92%), $n^{25}D$ 1.4203. Reported $n^{25}D$ 1.4205 (106).

By the same procedure, an 85% yield of isobutyl acetoacetate was obtained, b.p. 80-82.5° at 10 mm., $n^{25}D$ 1.4220. Reported $n^{25}D$ 1.4219 (106).

Alkyl β-Alkoxy Crotonates.

The procedure outlined for methyl β-methoxy crotonate was identical to the procedure by which ethyl β-ethoxy crotonate, n-propyl β-n-propoxy crotonate and isobutyl β-isobutoxy crotonate were prepared, with the exception that anhydrous potassium carbonate was substituted for quinoline to neutralise the sulfuric acid. Yields, boiling points and physical constants are as follows:

Ester-Ether	Yield	B.P.	Pres. (mm)	Other Properties
Ethyl	81%	92-6	1	M.p. 29.5-30
n-Propyl	82%	100-2	9	$n^{25}D$ 1.4505, Sap. Equiv. 188.3 (Calc. 186)
Isobutyl	80%	117	9	$n^{25}D$ 1.4474 S. E. 213.1 (Calc. 214)

Bromination of β-Alkoxy Crotonates with N-Bromosuccinimide.

The procedure given below for isobutyl γ-bromo-β-isobutoxy crotonate was general for all alkoxy crotonates.

In a 125 ml. flask was placed 15.0 g. (0.07 mole) of isobutyl β-isobutoxy crotonate, 12.4 g. (0.07 mole) of NBS,

0.7 g. of freshly recrystallized benzoyl peroxide, and about 30 ml. of dry carbon tetrachloride. The flask was fitted with a reflux condenser protected with a calcium chloride tube, and warmed with a heating mantle. Within a few minutes, a vigorous reaction ensued which continued for fifteen to twenty minutes without further application of heat. The contents were then heated to gentle reflux, and tested periodically with starch-potassium iodide paper until the test for bromine was negative. This required about one and one-half hours. The flask was then cooled in ice, and filtered to remove succinimide. Distillation at 2 mm. yielded 12.5 g. (63.5%), b.p. 142-144.5°, $n^{25}D$ 1.4800.

Methyl β-methoxy- γ-bromo crotonate was obtained in 66% yield, b.p. 115-117° at 10-11 mm.

n-Propyl β-n-propoxy- γ-bromo crotonate was obtained was obtained in 90% yield, b.p. 138-142° at 7 mm., $n^{25}D$ 1.4860.

Ethyl β-ethoxy- γ-bromo crotonate was obtained in 81% yield, b.p. 123-5° at 10-11 mm., $n^{25}D$ 1.4936. Reported $n^{29}D$ 1.4912.

Condensation of Alkyl β-Alkoxy- γ-Bromo Crotonates with Cinnamic Aldehyde by the Reformatsky Reaction.

In a 150 ml. round-bottom flask were placed 6.0 g. (0.025 mole) of ethyl β-ethoxy- γ-bromo crotonate, 3.3 g. (0.025 mole) of cinnamic aldehyde, 1.7 g. (0.026 g. atom) of zinc and 50 ml. of dry benzene. A crystal of iodine was added, the flask was fitted with a reflux condenser protected

at the top with a calcium chloride tube, and the flask warmed on a steam bath for three and one-half hours. During the reflux period, two additions of about 1 g. of zinc and a crystal of iodine were made, and the flask was frequently shaken vigorously.

The flask was cooled in ice water, treated with 50 ml. of saturated ammonium chloride solution and worked up in the usual way by washing the benzene solution with 5% sodium bicarbonate solution and drying over anhydrous sodium sulfate. The benzene solution was concentrated to small volume, diluted with petroleum ether but not enough to produce permanent turbidity, and refrigerated overnight. A yellow crystalline solid separated which was recrystallized several times from ether-petroleum ether to give 0.92 g. (15%) of colorless platelets, m.p. 100-100.5°.

Analysis data:	C	H
Calc. for $C_{15}H_{16}O_3$	73.75	6.60
Found:	73.59	6.59

By an analogous procedure, knavain was obtained from cinnamic aldehyde and methyl β-methoxy-γ-bromo crotonate in 18.5% yield, m.p. 145-6°. From the attempted preparation of the n-propoxy homologue, a minute amount of crystalline material separated from the resinous reaction product after standing in the refrigerator for several weeks, m.p. 75.5-77.5°, but in insufficient amount for further investigation. A repetition of the procedure has as yet not yielded a similar crystalline product. From the attempted preparation

of the isobutoxy homologue, no solid product was obtained.

Dihydrokavain and its Ethoxy Homologue.

In the hydrogenation pressure bottle were placed 0.64 g. of kavain, 0.2 g. of 5% palladium on carbon and 50 ml. of methanol. The mixture was shaken under hydrogen at 32 p.s.i. for fifteen minutes. The catalyst was removed by filtration, and the methanol evaporated under a current of air. The residue was taken up in ether, extracted with 0.5 N. sodium hydroxide, the ether solution concentrated and petroleum ether added until cloudiness developed. Upon standing, colorless needle crystals separated. After recrystallization in the same manner, 0.53 g. (81%) of dihydrokavain was obtained, m.p. 73.5-74°.

Analysis data:	C	H
Calc. for $C_{14}H_{16}O_3$:	72.39	6.94
Found:	72.71	7.00

From the alkaline wash was obtained a small amount of acid, m.p. 104-7° after drying on porous plate, and undoubtedly the tetrahydrokavaic acid reported by Borsche, m.p. 109-110°.

The ethoxy homologue was hydrogenated in a similar manner to yield the dihydro derivative, m.p. 60-60.5°.

Analysis data:	C	H
Calc. for $C_{15}H_{18}O_3$:	73.15	7.37
Found:	73.47	7.30

SUMMARY AND CONCLUSIONS

Four distinct approaches to the solution of this problem were investigated. Of these, the approach involving a Reformatsky reaction between cinnamic aldehyde and methyl-γ-bromo-β-methoxy crotonate followed by hydrogenation was successfully employed to prepare dihydrokavain. It was found that the principle drawback in this method involved the lack of a convenient route to the β-methoxy crotonate, and a method was developed for preparing this starting compound in any desired amount from commercially available materials. The same general procedure appeared to be a source of a number of homologous compounds and other alkoxy crotonates were prepared in the hope that they would successfully undergo the required reactions to yield crystalline homologues of dihydrokavain. However, only the ethoxy homologue was obtained as a crystalline compound in isolatable amount.

In the investigation of other approaches to the dihydrokavain synthesis, a number of reactions which did not appear to be leading toward the desired end were not further investigated in order to seek conditions which would lead toward the desired dihydrokavain structure. This left a number of interesting problems unsolved, and future work is planned toward solution of those problems.

The 5,6-double bond in the pyran-2,4-dione structure should yield to selective hydrogenation if the proper con-

ditions can be found. In any event, it would be of interest to thoroughly investigate the fate of this structure under a wide variety of hydrogenation conditions.

The product obtained from the hydrogenation of dehydrobenzoylacetic acid in dioxane solution with Raney nickel, for which a structure was postulated in agreement with the analysis data, will be investigated. It would be of interest to see if dehydroacetic acid under similar conditions will give an analogous product. The fate of dehydroacetic acid in slightly acid aqueous solution with Raney nickel will also be studied to see if a separation and identification of products can be achieved.

2-Methoxy-3-bromo-6-bromomethyl-4-pyrone, which was synthesized during the course of this work, readily yielded a hexaminium salt when treated with hexamethylene tetramine, and should provide a means of supplying the pyran-2,4-dione-type structure with a number of 6-substituents through the reactive 6-bromo-methyl group. The possibility of this will be further explored.

Successful cyclization of β-acetoxy esters would probably be a more convenient route to the dihydrokavain-type structure if good yields could be obtained, since the β-acetoxy esters can generally be prepared in highly satisfactory yield. It is believed that the desired cyclization does occur, but under the conditions employed, condensation of other types apparently occurs to yield a mixture extremely difficult to separate. Separation by distillation does not

seem feasible, since generally the pyran-2,4-dione compounds decompose at or near their melting points. However, the enol ethers generally melt without decomposition, and separation might be achieved through distillation of the product after treatment with diazomethane. The chromatographic procedures employed did not produce the desired result, but this technique should be further studied.

The physiological activity of the synthetic dihydrokavain remains to be investigated, but in general one of the optically active forms of a physiologically active assymetric compound greatly exceeds in activity its enantiomorph or a racemic mixture. Therefore it may well become desirable to separate the synthetic product into its isomers. There seem to be no generally-employed methods for resolving racemic mixtures of neutral compounds, but the dihydrokavain molecule may lend itself to complex formation, or it may be possible to selectively hydrolyze the enol ether and resolve the free enol.

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