A STUDY OF THE PRODUCT RESULTING FROM THE REACTION OF ACETYLSALICYLIC ACID AND MORPHINE ACETYLSALICYLIC ACID AND CODEINE

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Acknowledgment is made to Dr. Louis W. Busse for his invaluable aid in carrying out the pharmacological tests on animals.

INTRODUCTION

In 1929 an article appeared in the Journal of the American Pharmaceutical Association under the title of "A Chemical Combination between Morphine and Aspirin" by Jordon and Klemme.(13) Their work can be summarized as follows: A prescription supposed to contain Dover's powder, Acetophenetidin and Acetylsalicylic acid gave more marked soporific effects than was expected. Assays showed the absence of Dover's powder but the presence of Morphine Hydrochloride. Known mixtures of Morphine Hydrochloride and Aspirin when moistened and warmed became hard and produced narcosis in guinea pigs of greater intensity than was expected from its Morphine content. Their conclusions were:

1. The suspected capsules contained Morphine Hydrochloride, Aspirin and Phenacetin.

2. A chemical combination probably took place between the Morphine Hydrochloride and the Aspirin, giving a narcotic effect resembling heroine. They found this to be true because the physical conditions of the contents of the capsule and the pronounced narcotic effect produced indicated it. The contents of the capsule prepared from Morphine Hydrochloride, Aspirin and Phenacetin, slightly moistened and heated on the radiator underwent the same physical change and produced a similar pronounced narcotic effect.

3. They believed that when prescriptions containing Aspirin and Morphine are called for, the pharmacists should be very careful that the materials be dry and the patient should be cautioned.

4. The suspected chemical combination of Morphine and Aspirin should be further investigated.

This problem aroused out interest, since combination of such ingredients are frequently prescribed by the physicians. Therefore, further investigation on the chemical aspect of the problem is called for. The first part of the

study was to repeat several experiments performed by Jordon and Klemme, then attempts were made to prepare a chemical combination of Morphine and Asiprin. Finally, pharmacological experiments were carried out on animals.

HISTORY AND THERAPEUTICS

Morphine: Already in the seventeenth and eighteenth centuries attempts had been made to prepare from opium the "principle" to which it owes its physiological activities and the extracts obtained in the course of these experiments were employed in medicine under the name of "Magisterium Opii." Early in the nineteenth century Bucholz endeavored to crystallize from aqueous extracts of the drug a "Salt which could be used in place of opium; and about the same time Derosne, an apothecary practising in Paris, observed the separation of a crystalline substance when a syrupy aqueous extract of opium was diluted with water. This crystalline material was probably narcotine, or a mixture of the alkaloid with morphine.(12) M.L.G. Torande, the well known Paraisian pharmacist, claimed the honor of discovery of morphine for Courtois who also was an apothecary. He was engaged as preparator by Seguin who assigned Courtois to study opium. On December 24, 1804 Seguin handed to the Institute of France that had extracted from opium a crystalline body possessing an alkaline reaction and capable of forming salts when combined with acids. This paper was not published in the "Annales de Chemie" till 10 years later. Courtois was apparently lacking in confidence.(4) In 1806, Friedrich Wilhelm Adams Serturner made the first report on morphine. In 1817 Serturner was holder and in consequence luckier and has gone down to posterity as the discoverer of morphine.(10)

Morphine is the most important one of the opium alkaloids. Its therapeutic

actions can be considered under four separate headings:

1. Central Nervous System: The most important actions of morphine are on the central nervous system. It depresses the brain especially its higher function. The medullary centers are first stimulated then depressed. The reflexes and spinal functions are mainly stimulated. It is decidedly the strongest hypnotic and analgesic member of the opium alkaloid. Sir William Osler called morphine as God's own medicine for the alleviation of pain.

2. Respiration: Small and moderate doses of morphine 15-10 mg. in man quiet the respiration. The rate is generally moderately slowed; the depth is often rather increased. The regular deep respiration thus induced is more favorable to the air-exchange, so that the respiration is more efficient even when it is slower. Bronchial muscle are slightly relaxed by therapeutic doses of morphine. Unless there is nausea, the secretion of mucous appears diminished, particularly in bronchitis.

3. Circulation: Therapeutic doses of morphine or its derivatives do not effect the circulation materially. In man, there is generally an increase of pulse rate immediately after an injection; this is quickly increased fulness and force (stimulation of Vagus center) or falls slightly by the depression of the vaso-motor nerve.

4. Other actions:

On skin: morphine and its derivatives have a direct mild irritant action on the skin, resulting in erythma, itching and wheals.

On pupils: In man even small scarcely analgesic doses of morphine constrict the pupils.

Spinal cord: Morphine increases the spinal reflexes. Large doses in frogs produce convulsions, mammals generally die from the respiratory depressinn

before the convulsant stage can develope.

Sensory nerves: Opium and its derivatives have practically no action on the sensory endings. Their local use is therefore irrational.

Nausea, emesis and anti-emetic action: Morphine tends to produce nausea and vomiting. The sever ty varies greatly in different individuals. With large doses, the emesis is followed by diminished suspectibility to vomiting.

Constipative action: Morphine produces constipation, even with small doses. This is an undesirable side-effect of its analgesic use, but is valuable for arresting diarrheas and for quieting peristalsis in acute inflammations of the intestines and peritoneum.(29)

Codeine: It resembles morphine in its general effect, but its depressant action is less marked and less prolonged, whilst its stimulating action involves not only the spinal carod but also the lower parts of the brain. In small doses in man it induces sleep which is not so deep as that caused by morphine and in large doses it causes restlessness and increased reflex-excitability rather th an sleep. Although it is less actively analgesic, hypnotic and sedative than morphine, is preferable to the latter when average doses of codeine are effective because it is very much less likely to produce habit and is less constipating. Its usefulness in replacing morphine is limited by the necessity of avoiding overdosage. Codeine is especially useful in cough where average doses are generally effective (overdosage makes cough worse).(12)

Aspirin: Bayer introduced aspirin to physicians in 1900 intended for the relief of rheumatism (26). He obtained his German patent in 1889 and U.S. patent in 1900 under the name of aspirin.(4)

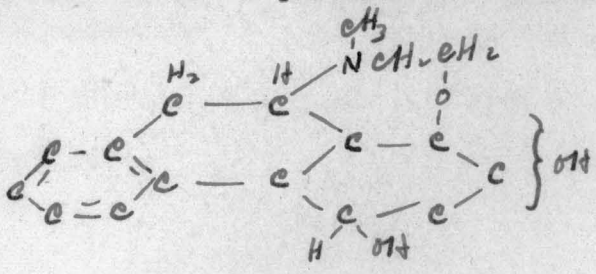
Aspirin is a strong analgesic and antipyretic agent, perhaps because the undecomposed acetyl compound enters the nerve cells more readily. The effects of poisonous doses in animals are similar to other salicylates. When

the dosage of salicylates are raised to the full therapeutic effect there occur usually a series of side action.(34) Mann reported a case of myocardial impairment secondary to aspirin poisoning.(21) Kraus, as early as 1914 reparted a series of cases exhibiting allegic manifestations such as urticaria acute edema, either local or general; erythema and prùritus following ingestion of as little as from 5 - 10 grains of acetylsalicylic acid.(18) While Hanzlik demonstrated acetylsalicylic acid to be one and one fifth times as toxic as sodium salicylate in man.(8) Stiell recorded chronic poisoning with daily dose of 20 grains over a period of six years.(30) The most serious reported reaction in recent years were observed by Lamson ans Thomas. They recorded four cases of sever sensitivity to aspirin contained in a patent asthma powder. One patient died in acute air hunger within an hour following the self-administration of but one half of the recommended dose. The three other cases exhibited a prompt induction or marked aggravation of asthmatic symptoms requiring epinephrine for relief. One of these patients was rendered unconscious by the reaction. The authors concluded that an abnormal response to acetylsalicylic acid is probably more common than to any other drug.(19) Aspirin is sup posed to pass through the stomach unchanged and that the salicylic acid is liberated in the intestine. In fact, it produces some gastric irritation and the intestinal decomposition is slow and incomplete, a part being absorbed unchanged.(34)

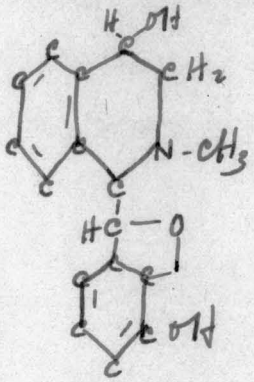
DEVELOPMENT OF MORPHINE FORMULA

1889 Knorr and Ludwig's Oxazine Formula:(15) The appearance of derivatives of ethanol dimethylamine $(CH_3)_2NCH_2CH_2OH$ among the products from degration of alpha methylmorphmethine with acetic anhydride led Knorr to believe that this

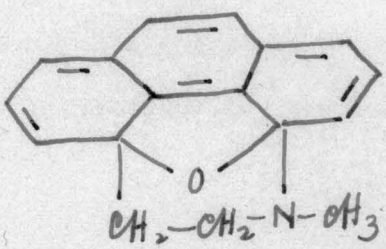
alkamine must be formed through hydrolytic scession of an ether linkage and the ethamine chain on to the phenanthrene nucleus through oxygen.

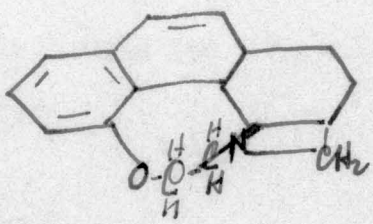


1893 Vis' formula of Morphine:(31) T he formulation which represented morphine as a benzylisoquinoline derivative was put forward unsupported assertion that the phenanthrene nucleus is not present in morphine. This Vis formula is entirely inadequate to explain the complex changes and relationship of morphine.

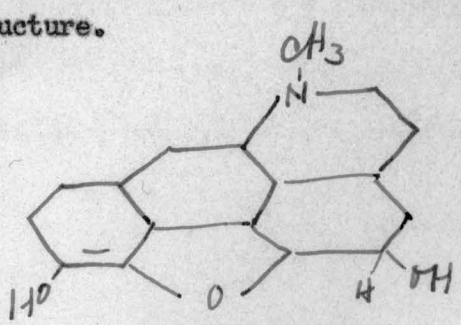


1900 Vongerichten's formula of Morphine:(33) He made two tentative structural proposals in which no conjecture was made as to the location of the alcoholic hydroxyl group or the saturated portion of the nucleus.

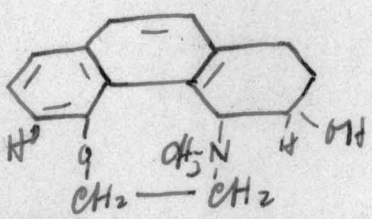




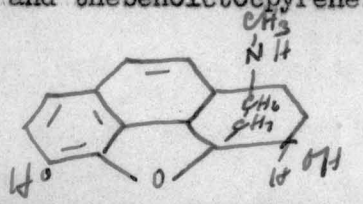
1902 Pschorr, Jaeckel and Feckt's Pyridine Formula:(25) One of the chief advantage seen in this formula is that it places morphine in close relationship to papaverine, narcotine and other isoquinoline opium alkaloids. The formula was modified by Knorr in 1907 which dominated for nearly 20 years the theory of morphine structure.



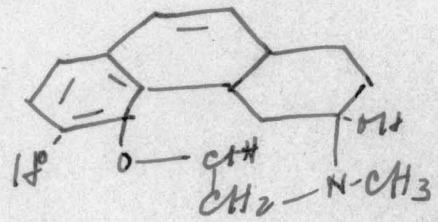
1903 Knorr and Ludwig's formula of Morphine:(16) The position of two of the oxygenations in morphine was determined. The recognition of relationship between thebaine and codeine and conversion of the latter to methyl thebaol, the location of all of the exygen atoms in morphine was accomplished.



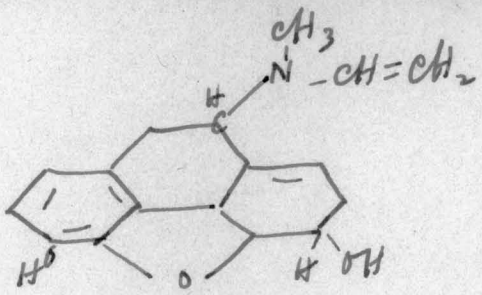
1905 Freund Martin's formula of Morphine:(6) This is a phenanthrene oxide formula. With this formula it was possible to explain the conversion of thebain through thebenine and thebenolctocpyrene.



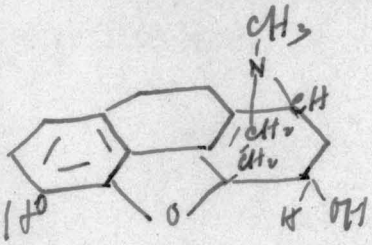
1907 Bucherer Han's formula of Morphine:(2) The formula was believed to account for apomorphine and morphothebaine formation.



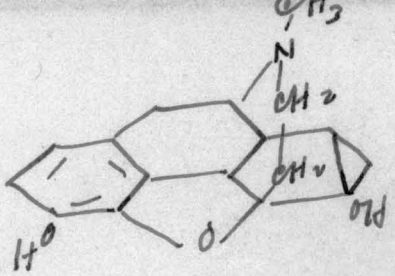
1911 Wieland and Kappelmeier's formula of Morphine:(11) In an attempt to account for the extraordinary ease with which many compounds in the morphine series as codeinone and thebaine, lose the entire ethnanmine side chain.



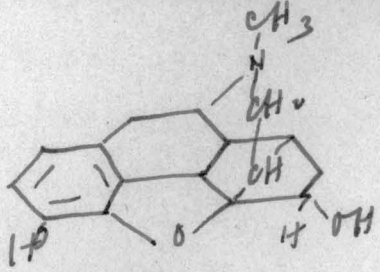
1914 Klee and Gadamer's formula of Morphine:(14) The formula has no experimental basis and constructed only to explain the conversion of thebaine into isothebaine.



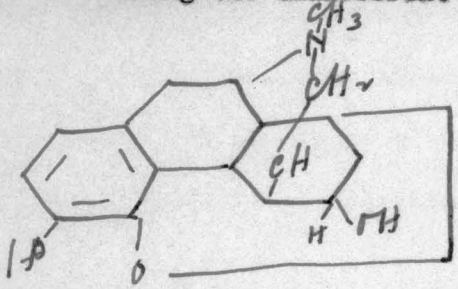
1914. Von Braun and Cahn's formula of Morphine:(32) The fact that morphine and codeine in contrast to thebaine, react with cyanogen bromide with replacement of the nitrogen methyl group by cyanogen, but with no scission of nitrogen ring brough Bon Braun to the conclusion that in these two alkaloids there could be no double bond in carbon 9 and 10.



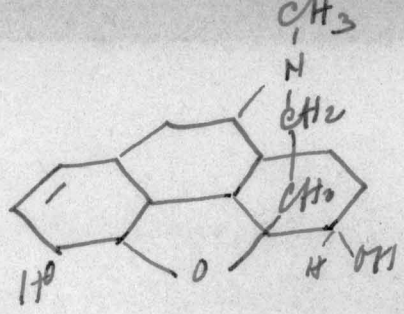
1916 Freund Martin's Camphene formula of Morphine:(22) It lent itself remarkably well to the explanation of the complicated phenomena in morphine chemistry in particular to the mechanism of formation of apomorphine, morphothebaine and thebaine.



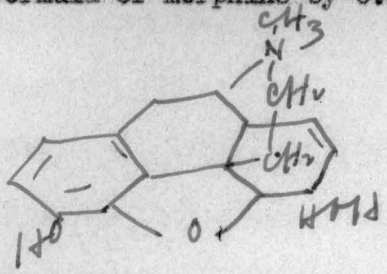
1917 Faltis' formula of Morhpine:(5) Reasoning that the weakness of existing morphine formula lies in their inability to explain satisfactorily many reactions for a hydroxyl group to appear on carbon 8. Faltis constructed the formula consisted in linking the indifferent ether exygen from canbon 4 to carbon 8.



1923 Robinson and Gulland's formula of Morphine:(27) The general property of the bases of morphine series is the tendency to lose the entire entanamine chain exhibited in many degradative processes. Gulland and Robinson proposed the formula which permits the formation of acetylmethylmorphol by acetolysis of methylmorphinethine.



1926 Cahn and Robinson's formula of Morphine:(3) This formula possesses a decided advantage over the older camphene formula in making the codeine, pseudo-codeine rearrangement analogous to the gernaiol-linalool type of change. It is also capable of explaining in a reasonable way the changes of thebaine or codeinone to morphothebain and of morphine to apomorphine. This is the present accepted formula of morphine by U.S.P.XI.



SALTS OF MORPHINE

The following list of morphine derivatives indicate the amount of importance morphine plays in our materia medica and the great amount of work which has been devoted to the chemistry of the compound. However, we have failed to find in the literature a derivative of acetylsalicylic acid either the salt or ester.

Morphine

Nitrate, phosphate, acid phosphate, carbonate, hydrobromide, hydroiodide, mercuriodide, tetraiodide, tetrachloride, bismuthiodiid, hydrofluoride, borofluoride, phosphofluoride, sulphate, thiosulphate, dethionate, thocyanate, perchloride, ferrocyanide, platinocyanide ,, silicotungstate, chromate, dichromate, vanadate, tetrathiocyanato-diamine chromium, formate, acetate,

monochloroacetate, dichloroacetate, triholoroacetate, monobromaacetate, phenylacetate, butyrate, isovalerianate, exalate, lactate, trichlorolactate, malate, citrate, tartrate, acid tartrate, antimonyl tartrate, urate, cyanurate, hippurate, phthalate, benzoate, mellitate, picrate, benzene-thiosulphonate, p-toluene-thiosulphonate, alpha-naphthalene thiosulphonate, beta-naphthalene thiosulphonate, ortho-guaiacol sulphonate, acid salt 5,5' dichlorodiphenyl 3,3' dicarboxylic acid, l-mandelate, l-xylonate, benzalsulphite, meconate, bimeconate, diallylbarbitutate, phenylethylbarbiturate, alloxanmorphinedisulphite, helianthate, d-oximinocyclohexane-4-carboxylate(20), hydrochloride, salicylate.(7)

ESTERS OF MORPHINE

Formyl morphine, alpha-acetylmorphine, beta-acetylmorphine, gemma-acetylmorphine, diacetyl morphine (diamorphine, heroin), triacetyl morphine, chloroacetyl morphine, dichloracetyl morphine, alpha-acetylbenzoyl morphine, acetylbutyl dimorphine, dipropionyl morphine, alpha-butyryl morphine, beta-butyryl morphine, dibutyl morphine, succinyl morphine, camphorylmorphine, benzoylmorphine, dibenzoyl morphine, dibenzoylacetyl morphine, carbomethoxy morphine, carboethoxyl morphine, carbopropoxy morphine, acetylcarbomethoxy morphine, ethyloxyacetyl morphine, p-acetoxybenzoyl morphine, di-alpha-bromaisovaleryl morphine, benzensulphonyl morphine, morphine sulphuric acid, acetyl dimorphine, acetyl butyryl dimorphine. (20)

CHEMICAL AND PHYSICAL PROPERTIES

Morphine: Morphine crystallises from alcohpl in colorless trimetric prisms containing 1 H_2O , becomes anhydrous at 100 c and then melts with decompositinn at 254C. It is bitter to the taste and sparingly soluble in most solvents.

The solubilities given by different observers vary greatly (e.g. boiling alcohol 1 in 30 to 1 in 36, in cold alcohol 1 in 210 to 1 in 300). The physical condition of the alkaloid used affects the solubility to a considerable extent: water(1 in 3,533), ether(1 in 7,632), benzene(1 in 1579), chloroform(1 in 1,525), ethyl acetate (1 in 537). The solubility in amyl alcohol is 1 in 50 at 78C. Morphine is readily soluble in limewater(1 in 100 at 25C) or in alkali hydroxide solutions, but less so in ammonia solution (1 in 117 s.g. 0.97). The base is laevorotatory $[\alpha]_d$ -130.9 in methyl alcohol, -70 in excess of alkali. It is a monoacidic base, and its salts which are usually well crystallized are neutral to titmus and methyl orange.

Detection: Morphine is at most colored faintly pink by cold sulphuric acid but becomes dirty green and brown on warming. With nitric acid it gives an orange red coloration. With sulphuric acid and potassium iodate it yields a brown coloration, and with sulphuric acid containing potassium dichromate, a green tint after a time, and with sulphuric acid containing selenious acid blue changing to green and then brown.(12)

Codeine: Codeine crystallizes 1H from water in large orthorhombic prisms, m.p. 155C(dry), $[\alpha]_d$ -137.7 in alcohol or -111.5 (dry)chloroform, and is generally seen in this form but it separates from dry ether in small anhydrous prisms. Its taste is slightly bitter. Codeine is moderately soluble in water (1 in 120 at 25C, 1 in 59 at 80C), or ammonia solution (1 in 68 at 15.5C), more so in ether (1 in 12.5 at 25C), and readily so in alcohol (1 in 1.6 at 25C, 1 in 0.92 at 60C) or chloroform (1 in 0.66 at 25C). It differs from morphine in being fairly soluble in anisole (1 in 6.5 at 16C) or cold benzene (1 in 10.4), and in its sparingly soluble in aqueous solutions of alkali hydroxides. Codeine is a strong monoacidic base, forming salts, which are neutral to litmus or

methyl orange. The free base and also the sulphate and phosphate are used in medicine.(12)

Acetylsalicylic Acid: Colorless crystals, commonly tabular or needlelike, or a white crystalline powder. Odorless, stable in dry air, in moist air gradually hydrolyzing into salicylic and acetic acids. One gram of Acetylsalicylic Acid is soluble in about 300 cc. of water, in 5cc. of alcohol, in 17 cc. of chloroform and in from 10 to 15cc. of ether, @ 25C. It is less soluble in dehydrated ether. It is also soluble with decomposition in solution of alkali hydroxides and carbonates. Acetylsalicylic Acid has a melting point not below 135C. when it is heated with distilled water for several minutes, then cooled and a drop or two of ferric chloride T.S. added, a violet-red color is produced in the mixture.(34)

EXPERIMENTAL

Attempts were made to repeat several tests performed by Jordon and Klemme. (13) These experiments were devoted mainly to the suspected chemical combination of Aspirin and Morphine Hydrochloride. For carrying out these experiments mixture of Morphine Hydrochloride, Phenacetin and Aspirin were placed in capsules using the following quantities.

A.

Morphine Hydrochloride Phenacetin Aspirin	of each	2 grains

B.

Morphine Hydrochloride	1 grain
Phenacetin	2 grains
Aspirin	2 grains

C.

Dover's Powder Phenacetin Aspirin	of each	2 grains

Twenty capsules of each of the above combinations were made. These are subjected to slight moistening and moderate heat. After one week, the following results were shown in the capsules:

Mixture A turned slightly brown and hard.

Mixture B and C showed no evident change. These three mixtures were further subjected to known color tests in order to further identify the constituents.

Reagent	Mix. A	Mix.B	Mix. C
Sulphuric acid and 0.00 gm. selenious acid	Blue to green to brown	Green to brown	Faint green to light brown
Sulfuric acid and 0.0005 gm. molybdic acid	Purple to pink	Purple to pink	Faint purple
Solution of formaldehyde and 1 drop of sulfuric acid	Purple to wind	Purple to wind	Faint wind

Reagent	Mix. A	Mix. B	Mix. C
Nitric acid	Reddish orange to yellow	Orange red to yellow	Faint red

From these color tests, A and B mixtures showed identical reactions which indicate the presence of morphine. Mixture C showed a very faint color to all hese reactions. This was due to the comparatively small amount of morphine it contained (approx. 0.02 gr./cap.)

The melting point of the above mixtures gave the following results:

Mix. A	Mix. B	Mix. C
Partially melts at 133C decomposes at 250C	Partially melts at 136C decomp. at 252C	Partially melts at 135C decomp. at 250C

From the above melting points, it seems quite certain that after one week there was no evident change taken place in the mixtures.

The Preparation of Morphine Acetylsalicylate (salt)

For the preparation of derivatives of Acetylsalicylic acid and Morphine, there are two kajor possibilities; namely the formation of a salt of Morphine and an ester of Morphine. On this assumption attempts were made to carry out this theory. The first attempt was to prepare the salt and was carried out accordingly.

Procedure: To 2 grams of Morphine, 60cc. of anhydrous alcohol was added and slowly warmed until the Morhine entirely dissolved. 1 gram of Acetyl-salicylic acid was dissolved in anhydrous alcohol. The two solutions were intimately mixed in a round bottom flask and refluxed for two hours over a water-bath. At the end of this time crystals were formed on the side of the flask. The solution was filtered while hot. The crystals were removed and recrystallized in methyl alcohol. These crystals are colorless and rectangular in shape, larger than morphine. The crystals were subjected to the following

tests:

1. Positive alkaloidal test with Mayer's and Wagner's reagent.

2. Soluble in warm waterm slightly soluble in methyl alcohol, insoluble in 50% hydrochloric acid and soluble in 50% potassium hydroxide solution.

3. When boiled with 10cc. of sodium hydroxide T.S. for a few minutes cooled and 10cc. of diluted sulfuric acid was added, a white precipitate of salicylic acid was produced, and the odor of acetic acid was perceptible. The solution was filtered and to the filtrate 3 cc. of alcohol and 3cc. of sulfuric acid was added and warmed, the odor of ethyl acetate became noticeable.

4. Melting point 245C (not corrected) decomposes at 240C.

5. Its aqueous solution is acid in character.

The Estimation of the Molecular Weight

1. By Titration: 50cc. of 0.11015N sodium hydroxide was added to the sample in an erlenmeyer flask and the solution was warmed for 2 minutes. Then it was titrated against 0.10211N sulfuric acid solution. A blank test was carried out in which 53.8 cc. of 0.10211N sulfuric acid solution was required to neutralize 50cc. of 0.11015N sodium hydroxide solution. Correction was made in the final calculation.

Formula for the calculation of molecular weight:

$$\frac{\text{Grams of sodium hydroxide required for neutralization}}{\text{1 gram of the compound}} - \frac{\text{Molecular wgt. of sodium hydroxide } 40}{\text{Molecular wgt. of the compound}}$$

2. By Nitrogen Determination: (24) Dumas' method

Formula for the calculation of molecular weight:

$$\frac{\text{Grams of nitrogen liberated by one gram of sample}}{\text{1 gram of the compound}} \quad \frac{\text{Molecular weight of nitrogen } 14}{\text{Molecular weight of the compound}}$$

The results of molecular weight estimation are as following:

Weight of samples	Molecular weight Found		Calculated	% of Nitrogen Found	Calculated
Titration Method					
1.30000 grams	468		465		
1.12500 grams	464				
1.11500 grams	465	Average 465.6			
1.23500 grams	465				
1.16350 grams	466				
Nitrogen Determination					
0.50710 grams	462		465	3.01%	3.01%
0.68490 grams	465			3.02%	
0.50010 grams	464	Average 464.5		3.00% Av.	3.01%
0.60600 grams	464			3.01%	
0.55450 grams	465			3.01%	

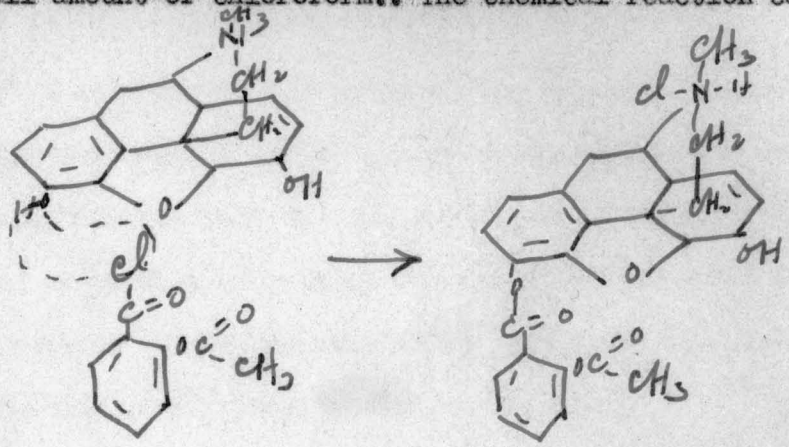
The compound formed was morphine acetylsalicylate, a salt formed by the addition of acetylsalicylic acid on the tri-valent nitrogen of morphine. The probable reaction can be represented as follows:

Morphine Acetylsalicylic Acid Morphine Acetylsalicylate

It becomes apparent that our first experiment resulted in the formation of a salt rather than the ester. In as much as we were interested in the ester type of product further reactions were studied. The general procedure selected was

as follows:

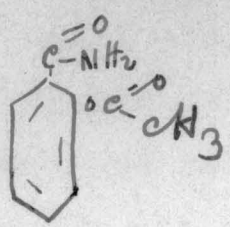
The most common method for the preparation of esters is by reacting an acid halide with an alcohol or phenolic hydroxyl group. To prepare the ester of acetylsalicyl morphine, acetylsalicyl chloride must be used. The reaction was carried out by refluxing morphine in a solution of acetylsalicyl chloride with a small amount of chloroform.. The chemical reaction can be shown as follows:



The Preparation of Acetylsalicyl Chloride:

Procedure: To 80 grams of Acetylsalicylic Acid was added 200 cc. of anhydrous petroleum ether and to this 100 grams of pure phosphorous pentachloride were added slowly. The mixture was refluxed on a water bath until a light yellowish solution resulted. Petroleum ether and phosphorus exychloride were distilled off under diminished pressure (8-12 mm.) Then the heat was increased to 165-175C and the liquid distilled over was colorless. After chilling, the distillate were crystallized and recrystallized in anhydrous petroleum ether and were dried immediately and kept in a well stoppered container. This acid chloride is very unstable and tend to decompose and change to dark color on exposure to light and air.

Characterization: Preparation of o-acetylsalicylamide by the action of dry ammonia gas on O-acetylsalicyl chloride. (23)



Procedure: A solution of 9.5 grams of the chloride in absolute ether was saturated with dry ammonia gas. As soon as the gas passed into the solution, a thick precipitate was formed. The precipitate consisted of ammonia chloride was removed by washing with water and the amide was dried and recrystallized in ethyl acetate. Yield was about 70%. The amide melts at 138C corresponds with the melting point given by the Journal (23).

Physical properties: Acetylsalicyl chloride is soluble in chloroform, acetone, ether and alcohol. It is slightly soluble in water. In warm water it decomposes. It melts at 46C, Auspach reported as 43C.(1)

Preparation of Mono-acetylsalicyl Morphine

Procedure: To 8 grams of pure acetylsalicyl chloride in 10 cc. of chloroform was added 4 grams of morphine. The solution was refluxed on a water-bath for four hours. To this mixture, anhydrous ether was added and a brownish mass precipitated out from the solution. The excess acid chloride was removed by washing with ether several times. The borwnish mass was dried on a porous plate and purified by dissolving it in chloroform and reprecipitated out with anhydrous ether, The precipitate was dried under diminished pressure at 50C. The dried precipitate was crystalline powder, having a light yellowish color. It is soluble in dilute hydrochloric acid, chloroform, water(warmO, propylene gly-

col, alcohol(warm); insoluble in cold water and ether. It melts at 115 C and volatilized at 90 C; it gives alkaloidal and salicylate tests. The compound is very unstable; aqueous and glycol solution turns black on standing and its crystalline powder also truns black and becomes hygroscopic on exposure to light and air. Upon hydrolysis with sodium hydroxide, sodium salicylate was formed and by the addition of an acid, salicylic acid was isolated and identified. A slight odor of acetic acid was also detected and was identified by the formation of ethyl acetate.

Determination of nitrogen content: Dumas method (24)

	Weight of samples	% of Nitrogen found		Calculated Mono-acetylsalicyl Morphine
A.	103.180 mg.	3.06		3.13
B.	100.668 mg.	3.10	Av. 3.10	
C.	103.410 mg.	3.25		
D.	100.898 mg.	2.99		

Preparation of Acetylsalicyl Codeine

Procedure: 2 grams of codeine were dissolved in 20 cc. of chloroform and mixed intimately with 20 cc. of chloroform containing 6 grams of acetylsalicyl chloride. The solution was refluxed for 4 hours on a water-bath. A white precipitate was obtained by the addition of 10 cc. of anhydrous ether. The crystalline powder was dried and recrystallized in anhydrous petroleum ether.

The compound is soluble in warm water, in alcohol, insoluble in ether, chloroform and ethyl acetate; soluble in 10% sodium hydroxide solution and gives test for salicylates and codeine. When hydrolized by boiling with N sodium hydroxide solution for 15 minutes; upon the addition of an acid, salicylic acid precipitated out and acetic acid odor was also perceptible. The compound melts

at 135 C.

Determination of Nitrogen Content: Dumas' method (24)

	Weight of samples	% of Nitrogen Found		Calculated Acetylsalicyl Codeine
A.	99.871 mg.	3.02		2.92%
B.	101.067 mg.	2.99		
C.	102.045 mg.	2.93	Av. 2.98%	
D.	100.245 mg.	2.98		
E.	103.310 mg.	2.98		

TEST FOR ANALGESIA ON RABBITS

This work was carried out to verify our chemical results in that this compound differs from Morphine Hydrochloride and a mixture of Morhine and Aspirin. The test for analgesia was carried out on rabbits, using response to a strong pinch of the tail as an indication for analgesia. These compounds were injected intraveneously using the marginal ear vein. The Morphine Hydrochloride was dissolved in aqueous solution while the acetylsalicyl Morphine was dissolved in fifty percent mixture of propylene glycol and water.

Following chart shows the comparison of the observed pharmacological action of the two compounds.

	No. of Animals	Morphine HCL	No. of Animals	Acetylsalicyl Morphine
M. A. D.*	4	10 mg./kg.	5	2.5 mg./kg.
M. T. D.**	2	100 mg./kg.	3	20 mg./kg.
T. I.		1:10		1:8
Pupils		constrict		dlate

In order to determine the physiological effect of a physical mixture of Morphine and Aspirin, doses of 5 mg./kg. and 20 mg./kg. were administered by injection. These doese contained Morphine and Aspirin in the molecular proportion that they exist in chemical combination of Acetylsalicyl Morphine.

5 mg./kg.	no analgesic
20 mg./kg.	analgesic; physioligical effects were similar to Morphine alone

CONCLUSIONS

1. The Morphine and Codeine esters of Acetylsalicylic acid were prepared. These compounds having chemical and physical properties which differ from the salt of Morphine and Codeine.

2. Upon hydrolysis of these esters Morphine and Salicylic Acid were isolated and identified.

3. Acetylsalicyl Morphine is quite unstable and decomposes when exposed to light and air. It turns black in color and becomes gummy in consistency developing a slight acetic odor.

4. Tests for abalgesic on rabbits showed Acetylsalicyl Morphine to possess strong analgesic properties.

5. The toxic dose of Acetylsalicyl Morphine in rabbits was established at 20 mg./kg.

6. The injection of physical mixtures of Acetylsalicylic acid and Morphine showed the chemical combination of these compounds to be much more toxic as well as much stronger in analgesic properties.

* M. A. D.: Minimum Analgesic Dose is the smallest dose at which the rabbit does not respond to a strong pinch of the tail.

** M. T. D.: Minimum Toxic Dose is the smallest dose which when administered kills 100% of the rabbits.

T. I.: Therapeutic Index is the ratio; M. T. D./M. A. D. T.I.

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BIOLOGICAL TESTS OF ACETYLSALICYL MORPHINE

ON RABBITS

3/19/40

Rabbit #1 I.V.* Morphine HCl 5mg/kg.

No. 1 gray male 0.5% sol. 10.8mg/2.15 kg. -- 2.7cc

2:27 p.m. administered

2:43 still responds to pain in the tail by pinching

2:45 injected 10 mg. ---- 2.0cc more

2:50 no response to tail pinch

3:10 " " " " " the total dose administered 20.8 mg.

No. 2 white male Acetylsalicyl Morphine 5mg/kg.
0.5% sol. (Glycol and water) 10.3mg/2.06 kg. --2.06cc

3:17 injected

3:19 Head up moving from one side to the other;rear legs stretched out showing mild convulsion. Pupils were dilated. Not sensitive to pinch in the ears and analgesic to tail pinch but still has its righting reflex. Breathing was very slow pulse normal.

3:45 Head still on the side (right);attempts to bring it back but remains in the same position. Very hypersentitive to touch and sound and its eye balls twittering showing nystagma. Cord was stimulated and contitual attempts to bring the hind legs close to the body failed.

4:00 Able to pull the hind legs in; still analgesic. Nystigma stopped.

4:30 Head straightened out; tail was still analgesic; ears responded to pinch

3/20/40

Both No. 1 and No. 2 rabbits were in good condition.

3/21/40

No. 3 white male Acetylsalicyl Morphine 2.5 mg/kg.
0.5% sol. (glycol and water) 5.17mg/2.07kg. --- 1.03 cc.

8:55 a.m. injected

9:00 Head tilted slightly towards the right; respiration wea slow and regular; analgesic in the tail but responded to pinching in the ears. No sign of convulsion was observed. No nystigma,; hypersensitive to touch and sound. The animal ~~slept~~ was quietly.

9:30 No more analgesic

9:35 No more hypersensitive to touch and sound.

9:41 Normal

* intravenous injection

No. 4 gray male Acetylsalicyl Morphine 0.5% sol (glycol and water) 2.5 mg/kg. 5.47mg/2.19 kg.----1.09cc

9:20 injected

9:25 completely analgesic in the tail with the head tilted towards the left; hypersensitive towards noise; respiration slow and regular; hind legs stretched out slightly; no nystigma.

9:52 respiration faster; still analgesic in the tail ; not in the ears.

10:05 no more analgesic.

3/25/40

No. 5 white male Morphine & Aspirin (mixture) 0.5% sol (glycol and water) 5 mg/kg. 11.9mg/2.38kg. ----2.4 cc

2:18 p.m. injected

2:25 responded to pinch in tail; action apparently none.

No. 6 grayish white male Acetylsalicyl Morphine 0.5% sol (glycol and water) 5mg/kg. 11.5mg/2.27kg. ----2.3 cc

2:36 injected
immediate effects - slumped down-respiration; other effects were similar to No. 2 rabbit.

2:50 Head over on right side (down)
very sensitive to noise
completely analgesic to pinch in tail and ears.

4:15 no more analgesic

No. 7 white male Acetylsalicyl Morphine 0.5% sol. (glycol and water) 2.5mg/kg. 7.6mg/3.06 kg. ----1.5 cc

3:10 effect similar to the previous test on No. 3 rabbit.

No. 8 brown female Acetylsalicyl Morphine 0.5% sol. (glycol and water) 4 mg/kg. 9.28 mg/2.32kg. ----1.8 cc

3:27 injected

3:32 analgesic no convulsion and rested quietly.

4:15 no more analgesic