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ERRATA

page 4, line 2. Instead of Illicium religiosum read
Illicium religiosum Siebold.

page 4, line 6. Instead of Illicium verum read
Illicium verum Hooker f.

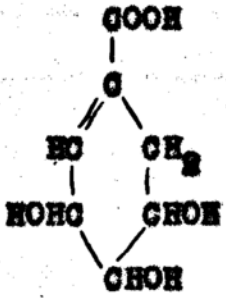
page 4, line 14. Instead of Illicium religiosum read
Illicium religiosum Siebold.

page 4, line 15. Instead of Illicium verum read
Illicium verum Hooker f.

page 8, line 16. Instead of Illicium religiosum read
Illicium religiosum Siebold.

Table of Contents

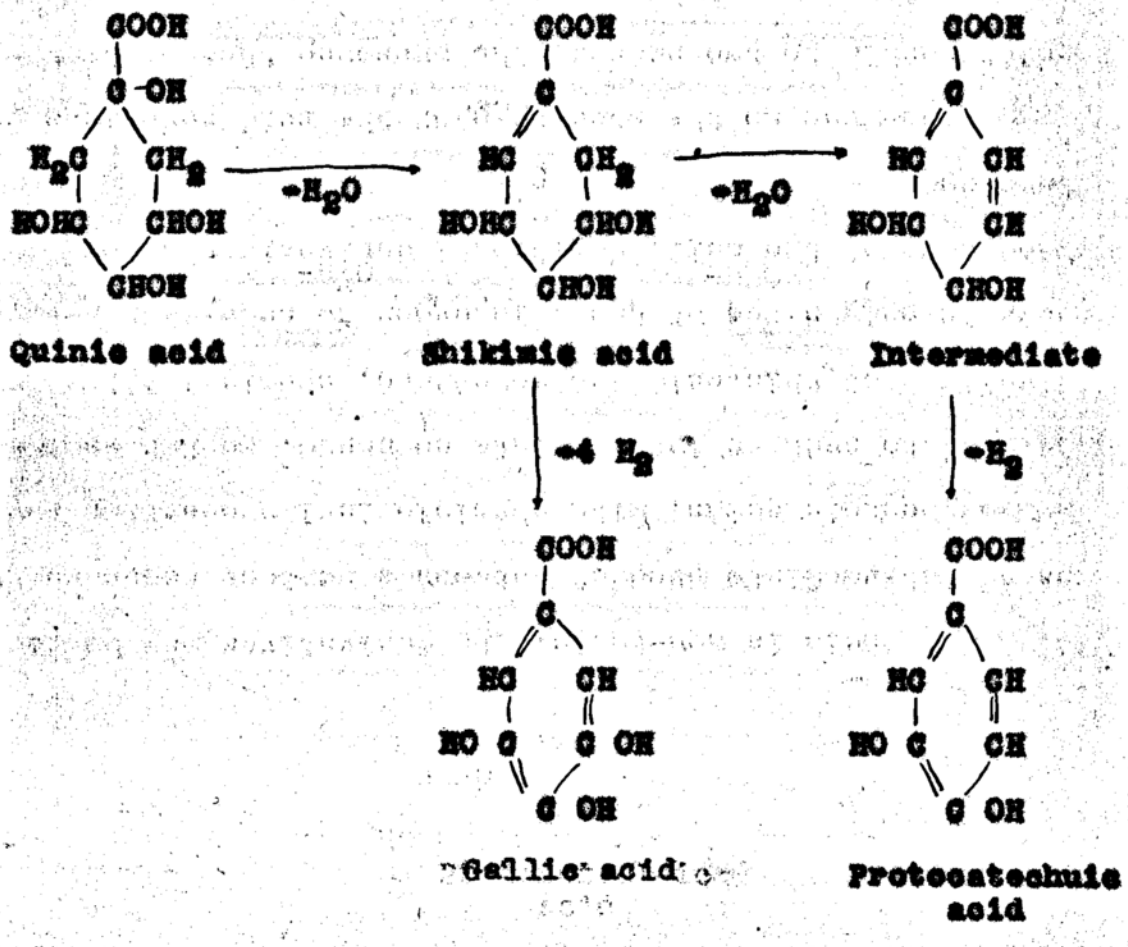
Introduction. The only natural representative of the trihydroxy-cyclohexene carboxylic acids at present known is shikimic acid which is found in rather large amount, up to 16 per cent, in the fruits of Hang Tsao, a Chinese drug. The structure of the acid, as suggested by H.O.L. Fisher[1], is



This acid is non-toxic. Its derivatives may be regarded as an intermediate product between a heptose sugar and the hydroxybenzoic acids, with physiological properties appertaining to such an intermediate compound. So far as the derivatives of this acid are concerned, chemical literature reveals only a few of them. In order to acquire a better knowledge of the acid, additional derivatives have been synthesized.

Inas-much as the structure of the acid reveals a possible relationship to the sugars, the presence thereof to the extent of 16 per cent in the fruit, raised the question of whether or not it may be regarded as a reserve material. Cyclisation of heptose, accompanied by oxidation and dehydration, may pro-

duce this acid. In this connection, it is noteworthy that Armstrong[2] classifies shikimic acid together with quinic acid and inosite as a group of cyclic carbohydrates. Oisvold[3] considers this acid an intermediate product in the formation of protocatechuic and gallic acids from quinic acid.

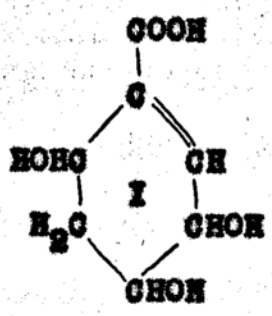


An answer to this question might be expected from assays of both the seed and the carpel of the fruit. Assays seem to reveal the absence of the acid in the seeds, hence it cannot be looked upon as a reserve material. The presence of much material which appears to be more or less closely related to sugars in the carpel naturally raises other physiological questions.

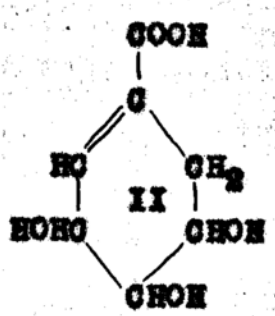
While these assays were being made, note was taken of the micro-chemical study of Editha Siersch[4] who in 1928 showed that, while shikimic acid was found in the carpels of both species of Illicium, the seeds of both were devoid of this acid. The assays repeated in the experimental part (see Appendix) supplement quantitatively the observations of Editha Siersch.

1) Helv. Chim. Acta, 17, pp. 1200-1207
2) Armstrong, ., Carbohydrate Chemistry, p. 155 , (1934).
3) Gisvold, O., and Rogers, C., Chemistry of Plant Constituents, pp. 172-178, (1938).
4) Pharm. Zeitsch., 69, p. 581, (1928).

History. Shikimic acid was discovered by Eykman[1] in 1885, while in Japan, in the fruit of Illicium religiosum, the poisonous star anise, Hang Tsao in Chinese, Shikimi no Ki in Japanese. Its name is derived from the Japanese word. In the following year, he found that it also occurred in the fruit of Illicium verum, the ordinary or true star anise.[2] In 1891, the acid was reported in connection with a chemical study of true star anise by Oswald.[3] In the same year Eykman,[4] in an endeavor to determine the constitution of the acid, published a detailed study of its physical and chemical properties. He assigned formula I to it.



3,4,5-trihydroxy-Δ^1-tetra-hydro benzoic acid



3,4,5-trihydroxy-Δ^1-tetra-hydro benzoic acid

In 1928, Editha Siersch,[5] by means of micro-chemical tests, showed that the carpels of both fruits contain shikimic acid, those of Illicium religiosum containing much more than those of Illicium verum. The seeds of both plants are devoid of the acid. In 1929, S.Y. Chen[6] reported on the acid in connection with his phytochemical study of Illicium religiosum, Siebold.

In the following year, 1930, Yamashita and Sato[7] reported its occurrence in the leaves of Ginko biloba L., but only in small amount.

So far as the structure of shikimic acid was concerned, it had not been definitely proven. Recently, Herman O.L. Fischer,[8] by a series of reactions analogous to those employed in the degradation of quinic acid,[9] demonstrated the position of the double linkage and the positions of the three hydroxyl groups. (Formula II).

1) Trav. chim. d. Pays-Bas, 4, pp. 32, (1885).
2) Ibid., 5, p. 299, (1886).
3) Arch. d. Pharm., 299, p. 84, (1891).
4) Ber. 24, p. 1278, (1891).
5) Pharm. Zeitsch., 69, p. 581, (1928).
6) Am. Jour. Pharm., 101, p. 687, (1929).
7) Jour. Pharm. Soc. Jap., 50, pp. 19 and 113, (1930).
8) Helv. Chim. Acta, 17, p. 1200, (1934).
9) Ibid., 17, p. 1196, (1934).

Occurrence. Thus far, shikimic acid has been isolated from three species representing two families.

Taxaceae.

Ginkgo biloba L.

Yamashita and Sato, in 1930, isolated the acid from the leaves.[1]

Magnoliaceae.

Illicium religiosum Sieb.

As already pointed out, the acid was first isolated from poisonous star anise, the Hang Tsao of the Chinese, by Eykman in 1885.[2]

Illicium verum Hooker f.

A year later, Eykman[3] observed its occurrence in the true star anise.

Inasmuch as the structure of the acid reveals a possible relationship to the sugars, the presence thereof to the extent of 16 per cent in the fruit raised the question of whether or not it may be regarded as a reserve material. In this connection, it is noteworthy that Armstrong lists shikimic acid with the carbohydrates. An answer to this question might be expected from the assays of both the seed and the carpel of the fruits. The results of these assays will be found in the experimental part. These assays seem to reveal the absence of the acid in the seed, hence it cannot be looked upon as a reserve material. The presence of so much material that appears to be more or

less closely related to the sugars in the carpels naturally raises other physiological questions.

While these assays were being made, note was taken of the micro-chemical study of Editha Siersch[4] who in 1928 showed that, while shikimic acid was seen in the carpels of both species of Illicium, the seeds of both were devoid of this acid. The assays reported in the experimental part supplement quantitatively the quantitative observations of Editha Siersch.

1) Jour. Pharm. Soc. Jap., 50, p. 19 and p. 115, (1930).
2) Trav. Chim. d. Pays-Bas, 4, pp. 52-54, (1885).
3) Ibid., 5, p. 299, (1886).
4) Pharm. Zeitsch., 69, p. 581, (1928).

Preparation. Eijkman, who discovered shikimic acid in 1885,[1] obtained it originally as a byproduct in the distillation of the volatile oil. After water distillation of the green leaves and fruits, the residue in the still was expressed and the liquid thus obtained evaporated to a syrup. To this, alcohol was added to cause precipitation. From the filtrate, the alcohol was removed by distillation and the residue evaporated farther still. This concentrated extract was warmed with a little alcohol and, after cooling, 5 to 6 times its volume of ether were added. The ethereal solution separated from the insoluble portion (A.) deposited, upon standing, crystals (B.). Both of these portions, also a portion (E.) not described by the author, are said to have consisted principally of a peculiar acid which he designates shikimic acid.

A year later, Eijkman found the same acid to occur in Illicium religiosum, though in lesser amount, but he does not describe the method by which he obtained it.[2]

Oswald[3] in 1891 followed the method of Eijkman essentially.

For her microscopic examinations, Hiersch[4] macerated the comminuted carpels with alcohol for several days and studied the crystals that resulted upon evaporation of the tincture on a watch glass.

S.Y. Chen[5] prepared shikimic acid on a larger scale by extracting 17.5 Kg. of finely powdered poisonous star anise with alcohol in a Lloyd extractor, evaporating the extractive

to dryness and percolating the residue with acetone. 3.12 Kg., corresponding to 18.0 per cent, were left in the percolator "consisting mainly of shikimic acid."[5]

Sato[6] and collaborers extracted shikimic acid from Ginkgo biloba with ether.

I. 8 Kg. of finely ground, 10 mesh, fruits obtained from Shanghai in 1936 were extracted with 95 per cent alcohol in a Lloyd extractor. To the concentrated extract, acetone was added slowly and with constant stirring until no more precipitation resulted. The acetone solution, after filtration and concentration, yielded, upon cooling, a colored crystalline mass which was washed with acetone. Thus partly purified, the crude shikimic acid melted at 185-186°.

II. In a second operation, 2 Kg. of powdered, 20 mesh, fruits obtained from Eli Lilly and Co., in 1937, were first extracted with petroleum ether, yielding 91 grams of a brownish oil. The drug thus treated was then extracted with three successive portions of alcohol. To the concentrated alcoholic percolate, acetone was added until no further precipitation resulted. The acetone filtrate was concentrated, and after several days, 99 grams had settled out. To remove the green color, it was washed with alcohol leaving about 22 grams of shikimic acid melting at 187°. Recrystallised from alcohol and decolorised with charcoal, the melting point was raised to 188-189°.

The residue obtained upon spontaneous evaporation of the alcoholic washings was stirred with acetone until most of the

color had been removed. Upon filtration, about 16 grams of impure, yellowish-white shikimic acid, m.p. 175-180° after one recrystallization resulted. The acetone washings left, upon evaporation, 46 grams of a green syrupy mass.

The second alcoholic extraction yielded, upon like treatment, 22 grams of a very impure shikimic acid. A third alcoholic extraction of the mare yielded, when treated in like manner, practically nothing.

The three alcoholic extractions yielded about 38 grams of crude shikimic acid, or less than 2 per cent of the fruit.

III. 1 Kg. of powdered, 20 mesh fruit, obtained from Eli Lilly and Co., in 1937, was percolated to exhaustion with alcohol. To the alcoholic concentrate, acetone was added, but little precipitate resulted. The acetone mixture was allowed to evaporate somewhat, and the concentrate was shaken out with petroleum ether. The petroleum ether solution, upon evaporation, yielded 60.8 grams of oil. The brownish mass which had separated from the acetone solution (after shaking with petroleum ether) weighed 30.5 grams. Recrystallized once and decolorized with charcoal, 15 grams of impure shikimic acid, m.p. 175-180° resulted. In addition, about 75 grams of syrupy mass were obtained upon evaporation of the solvents.

IV. 10 Kg. of 10 mesh powder (Eli Lilly and Co., 1937) were percolated in the Lloyd extractor, and the extract was treated as in experiment I. About 180 grams of yellowish-brown shikimic acid, m.p. 180-183°, were obtained. The acetone filtrate was allowed to evaporate, yielding a dark brown, syrupy mass.

V. Another 10 Kg. of 20 mesh powder (Eli Lilly and Co., 1937) were percolated in the Lloyd extractor, and the concentrated percolate shaken with petroleum ether. The separated hydrocarbon layer, upon recovery of the solvent, yielded 697 grams of the oil. The hydro-alcoholic layer, after the removal of the petroleum ether, yielded about 500 grams of a dark brown mass, mostly shikimic acid. Upon standing, the mother liquid yielded a semi-solid mass weighing about 45 grams. The crude shikimic acid was recrystallized twice, decolorizing it each time with charcoal. Thus purified, the 75 grams of acid had a m.p. 186-187°. The mother liquids resulting upon recrystallization were combined and evaporated to dryness. Yield 125 grams.

VI. 1 Kg. of poisonous star anise left by S.Y. Chen (1929) was twice extracted by continuous percolation, each time for 24 hours. Both extracts (a and b), after concentration, were shaken with petroleum ether, and the hydrocarbon solution was drawn off. Upon evaporation, the petroleum ether yielded 151 grams and 0.9 grams respectively. Thus two products were obtained, viz.

1) the petroleum ether extractives (a and b) which were mixed and turned over to S.C. Chen.
2) the alcoholic extracts shaken out with petroleum ether (a and b). The first alcoholic extract formed a solid mass of crystals of shikimic acid, m.p. 175-178°. The 133 grams obtained were then further purified by recrystallization from 95 per cent alcohol after de-

colorization with norite active charcoal. The acid thus obtained, about 80 grams, was snow white, with a m.p. of 187-188°.

VII. The last 11.85 Kg. of ground fruits (20 mesh, Eli Lilly and Co., 1937) were extracted as described under V. In addition to 576 grams of oil, about 280 grams of crude shikimic acid were obtained.

Summary. It becomes apparent that both yield and purity of the product are largely dependent upon the condition of the crude drug. Thus, whereas prime quality drug used by S.Y. Chen (1929) yielded as much as 16 per cent by the simple process of extraction with alcohol and washing (by percolation) the solid extract with acetone, the dark drug of 1937 yielded at most but 3 per cent, no matter how the process was modified.

It would seem that the dark 1937 drug* had not been cured properly, resulting not only in a possible destruction of shikimic acid, but also in the formation of highly colored substances which interfered seriously with the purification of the acid sought.

Instead of evaporating the alcoholic extract to dryness and washing out the impurities by percolation as S.Y. Chen did, the alcoholic extract, if concentrated sufficiently, can be diluted with petroleum ether, thereby not only precipitating the shikimic acid, but also holding in solution oily substances as well as the bulk of the pigments.

* It was smaller as well as dark, hence may have been harvested before maturity had been attained, as well as improperly cured.

1) Trav. Chim. Pays-Bas, 4, p. 49, (1885).
2) Ibid., 5, p. 299, (1886).
3) Arch. d. Pharm., 299, p. 84, (1891).
4) Pharm. Zentralhalle für Deutschland, 69, p. 584,
5) Am. Jour. Pharm., 101, pp. 563 and 588, (1929).
6) Jour. Pharm. Soc. Jap., 50, pp. 19 and 113, (1930).

Purification. The crude acid left by S.Y. Chen[1] was purified in the following manner:

One hundred grams were refluxed with 500 cc. of 95 per cent alcohol for half an hour, leaving a dark, resinous-like material (1). The filtrate was concentrated by recovering 300 cc. of alcohol. To the concentrated alcoholic solution, acetone was added so long as it produced a precipitate (2). From the second filtrate, most of the acetone was recovered by distillation. Upon cooling, white micro-crystals separated (3). The results of five such purifications are herewith tabulated:

	I	II	III	IV	V	Total
(1) Material insoluble in hot alcohol	19	19.5	15	20	19	92.5
(2) Material precipitated by acetone	15	15.0	12	15	20	75.0
(3) Purified shikimic acid	65	48.0	69	61	60	303.0

Hence, from 500 grams of crude acid, 303 grams of purified acid were obtained, and 8.9 per cent are unaccounted for.

(1) The material insoluble in alcohol was not studied.

(2) That precipitated with acetone yielded an osazone, crystallizing in long needles, m.p. 204-205°, corresponding to glucosazone.

(3) The partly purified shikimic acid was further purified by boiling with a minimum amount of alcohol and animal charcoal. The shikimic acid so obtained melted at 188-189° u.c.

The melting points recorded in the literature are as follows:

melting point	investigator
184°	Eykman [2]
183-184°	Oswald [3]
185°	S.Y. Chem [4]
184-185°	Yamashita and Sato [5]

The specific angle of rotation at 25° was observed at -350°. Eykman reports -246.5° .

All later preparations were purified as follows:

The crude shikimic acid was dissolved in a suitable amount of 95 per cent alcohol, and the solution decolorized with norite active charcoal. This process was repeated several times until a colorless solution was obtained. When concentrated to about half its original volume and cooled, (standing in an ice box over night) snow white micro-crystals separated out. The shikimic acid so obtained melted at 187-188°. The mother liquor was again concentrated and decolorized if necessary. Thus, more shikimic acid was obtained.

1) This had been prepared in the following manner: (Am. Jour. Pharm., 101, p. 563, 688, (1929)).
17.5 Kg. of finely powdered fruit had been exhausted with alcohol in a Lloyd extractor. After removal of the alcohol from the percolate, the concentrated extract was percolated with acetone until the readily soluble material had practically all been removed. 3.12 Kg. of solid substance were left in the percolator, consisting mainly of shikimic acid.
2) Trav. Chim. d. Pays-Bas, 4, p. 80, (1885).
3) Arch. d. Pharm., 299, p. 105, (1891).
4) Am. Jour. Pharm., 101, p. 689, (1929).
5) Jour. Pharm. Soc. Jap., 50, p. 19, (1930).

Properties. Shikimic acid crystallizes in snow white micro-crystals. Its physical properties as reported by Nykman[1] are: M.p. 184°; d_{14} is 1.599; $[\alpha]_D$ is -246°; Λ_∞ is 305°; ΔH is 13.1 cal/mol.;** It is readily soluble in water, less soluble in alcohol, and almost insoluble in other organic solvents such as ether, chloroform, benzene, acetone, and heptane.

Since it is a hydroxy acid, it possesses the characteristics of both alcohols and acid. Thus the presence of the carboxyl group leads to the formation of salts, esters, and acid amides. The hydroxy hydrogens are replaceable by alkyl and acyl radicals, hence the methyl ethers and the acetyl derivatives are easily prepared.

When its salts are heated, shikimic acid may lose two molecules of water and one molecule of carbon dioxide, yielding a phenol. This was demonstrated by Oswald[2] and the scheme of the reaction may be shown as follows:

$$C_6H_6(OH)_3COOH \longrightarrow C_6H_5OH + 2H_2O + CO_2$$

Since shikimic acid contains one double bond, it can take on two atoms of hydrogen or two of bromine to form the corresponding dihydro- or di-brom shikimic acid. The double bond can also take on two hydroxyl groups, forming a quercite carboxylic acid.

* Λ_∞ is the conductivity at infinite dilutions.
** ΔH is the heat of neutralization.

When oxidized with stronger oxidizing agents such as HIO_3, shikimic acid can be decomposed into acenitic acid[3] from which its structure has been proved. When heated with acetone-zinc chloride solution, shikimic acid can be converted into an isopropylidene compound, a reaction used in the preparation of acetone sugar in carbohydrate chemistry.

The acid can absorb bromine readily, but does not absorb iodine. Hydrogen chloride and hydrogen bromide gave no crystalline derivatives. In strong alkaline solution, it reduces cupric sulphate to cuprous oxide and to metallic copper. When heated with an ammoniacal solution of mercuric acetate, a black precipitate was produced. The acid decolorizes potassium permanganate solution very readily, but causes no change in the color of iodine in potassium iodide solution. It reduces an acid solution of potassium bichromate, changing the color of the solution from orange to green, and then to violet after standing. Neutral salt solutions (sodium, potassium, and ammonium) of the acid gave an orange red color with ferric chloride solution.

1) Eijkman, J., Rec., 24, p. 1279, (1891).
2) Oswald, F., Arch. d. Pharm., 229, p. 111, (1891).
3) Fischer, H., Helv. Chim. Acta, 18, p. 1204, (1935).

Derivatives.

Salts of Shikimic Acid.

Salts of Metals.

The following salts of metals have been described thus far, viz., those of sodium, potassium, magnesium, calcium, strontium, barium, and lead. Apparently, the three hydroxyl groups in shikimic acid interfere with the isolation of simple salts in crystalline form. Previous work has been repeated, and new salts have been prepared.

Lithium Shikimate. This was made by the action of shikimic acid on lithium carbonate in the presence of water. The product was amorpheus. Being difficultly soluble in organic solvents, recrystallisation did not prove satisfactory. When heated with xylene to remove moisture (3.4 p.c.), it was obtained in slightly colored scales. Analyses yielded the following results:

1. 0.2001 Gm. gave 0.059 Gm. of Li_2SO_4, corresponding to 3.72 p.c. Li.
2. 0.2045 Gm. gave 0.061 Gm. of Li_2SO_4, corresponding to 3.76 p.c. Li.

The theoretical percentage is 3.86 p.c.

Sodium Shikimate. This is one of the few salts previously described. It was obtained by Eykman[1] in 1891 as "large rhombic sphenoids." It was again prepared by S.Y. Chen[2] in 1929. No difficulty was experienced in its preparation. When analysed, the following results were obtained:

1. 0.2675 Gm. yielded 0.0830 Gm. Na_2SO_4 = 10.05 p.c. Na.

2. 0.3220 Gm. yielded 0.1005 Gm. Na_2SO_4 = 10.11 p.c. Na.

Calculated for $C_6H_8(OH)_3COONa$..... 11.74 p.c.

$C_6H_8(OH)_3COONa.2H_2O$..... 9.91 p.c.

$C_6H_8(OH)_3COONa.H_2O$..... 10.75 p.c.

Potassium Shikimate. This salt was obtained in an amorphous condition by S.Y. Chen [3] in 1929. Repetition of the experiment yielded crystals as large as those of the sodium salt. However, when prepared from an alcoholic medium, needle-shaped crystals resulted.

When analyzed, the following results were obtained:

1. 0.3172 Gm. yielded 0.1332 Gm. K_2SO_4 = 18.84 p.c. K.

2. 0.2035 Gm. yielded 0.0835 Gm. K_2SO_4 = 18.41 p.c. K.

Computed for $C_6H_8(OH)_3COOK$ ..... 18.45 p.c. K.

Silver Shikimate. This salt was obtained by heating the acid with freshly precipitated silver oxide in the presence of water. Recrystallized from water, it was obtained in prisms.

Upon analysis, the following results were obtained:

1. 0.2527 Gm. yielded 0.0892 Gm. Ag corresponding to 58.33 p.c. Ag.

2. 0.2270 Gm. yielded 0.1020 Gm. Ag, corresponding to 58.24 p.c. Ag.

Computed for $C_6H_8(OH)_3COOAg$ = 58.41 p.c.

Copper Shikimate. This was obtained by heating the acid with freshly precipitated cupric hydroxide suspended in water. A brownish-green, crystalline product resulted upon evaporation of the filtrate (from the excess $Cu(OH)_2$). It is insoluble in

organic solvents, but dissolves in concentrated alkali (without precipitation of cupric hydroxide).

Distilled with xylene, it yielded 7.4 p.c. of water, corresponding to a di-hydrate. The dehydrated salt was red in color. When analysed, the following results were obtained;

1. 0.1910 Gm. yielded 0.0320 Gm. CuO corresponding to 13.38 p.c. Cu.
2. 0.1447 Gm. yielded 0.0247 Gm. CuO corresponding to 13.63 p.c. Cu.

Computed for $(C_6H_6(OH)_3COO)_2Cu$ ..... 15.82 p.c.

Computed for $(C_6H_6(OH)_3COO)_2Cu.5H_2O$ ..... 15.71 p.c.

Chen in 1929 called attention to the fact that a strongly alkaline solution of shikimic acid mixed with a solution of copper sulphate yields a solution similar to Fehling's solution.[3] Like tartaric acid, shikimic acid is a hydroxy acid.

Magnesium Shikimate. This was reported by S.Y. Chen in 1929.[4] The salt was obtained in an amorphous condition from magnesium carbonate and shikimic acid in the presence of water. The amorphous mass is very hygroscopic and difficultly soluble in organic solvents. When heated with xylene to remove moisture (15 p.c.), slightly colored micro-scales were obtained which are no longer hygroscopic.

Analysis yielded the following results:

1. 0.1792 Gm. sample gave 0.0190 Gm. MgO corresponding to 6.63 p.c. Mg.
2. 0.1870 Gm. sample gave 0.0201 Gm. MgO corresponding to 6.48 p.c. Mg.

Computed for $(C_7H_9O_5)_2Mg$ is 6.56 p.c.

Calcium Shikimate. It was prepared by Oswald in 1891 [6]; also by S.Y. Chen in 1929. [6] The salt was made by neutralising shikimic acid with milk of lime. A crystalline compound was obtained. It can be precipitated from its aqueous solution by methyl alcohol, and can be recrystallised from diluted alcohol.

Analysis yielded the following results:

1. 0.2040 Gm. sample gave 0.0627 Gm. $CaSO_4$ corresponding to 9.05 p.c. Ca.
2. 0.2493 Gm. sample gave 0.0765 Gm. $CaSO_4$ corresponding to 9.04 p.c. Ca.

Computed for $(C_7H_9O_5)_2Ca$ ..... 10.37 p.c.

Computed for $(C_7H_9O_5)_2Ca.5H_2O$ ..... 9.11 p.c.

The salt may be crystallised with three molecules of water. Oswald reported it with $6H_2O$.

Strontium Shikimate. It was also prepared by Oswald in 1891 [7]; again by S.Y. Chen in 1929. [6] Repetition of their experiments yielded a powder. It is slightly soluble in acetone and very difficultly soluble in other organic solvents.

Analysis yielded the following results:

1. 0.2492 Gm. sample gave 0.0982 Gm. $SrSO_4$ corresponding to 18.37 p.c. Sr.
2. 0.2524 Gm. sample gave 0.0997 Gm. $SrSO_4$ corresponding to 18.84 p.c. Sr.

Computed for $(C_7H_9O_5)_2Sr$ ..... 20.21 p.c.

Computed for $(C_7H_9O_5)_2Sr.2H_2O$ ..... 18.66 p.c.

Oswald also reported $2H_2O$ of crystallisation.

Barium Shikimate. This was likewise prepared by Oswald[9] in 1891; also by S.Y. Chen in 1929.[10] An amorphous, brittle mass was obtained by heating barium carbonate and shikimic acid with water. Like the lithium salt it is very difficultly soluble in organic solvents.

Analysis yielded the following results:

1. 0.2102 Gm. sample gave 0.0877 Gm. $BaSO_4$ corresponding to 24.56 p.c. Ba.
2. 0.2672 Gm. sample gave 0.1120 Gm. $BaSO_4$ corresponding to 24.67 p.c. Ba.

Computed for $(C_7H_9O_5)_2Ba$ ..... 28.42 p.c.

Computed for $(C_7H_9O_5)_2Ba.4H_2O$ ..... 24.74 p.c.

Oswald reported no water of crystallization.

Lead Shikimate. This was made by the action of shikimic acid on lead carbonate in the presence of water. An amorphous, brittle mass was obtained as Chen reported in 1929. Attempts to recrystallize it from organic solvents were not successful. When heated with xylene to remove moisture (5.5 p.c.), it was obtained in yellowish-brown scales.

Analysis yielded the following results:

1. 0.321 Gm. sample gave 0.169 Gm. $PbSO_4$ corresponding to 35.97 p.c. Pb.
2. 0.3085 Gm. sample gave 0.162 Gm. $PbSO_4$ corresponding to 35.87 p.c. Pb.

Computed for $(C_7H_9O_5)_2Pb$ ..... 37.45 p.c.

Computed for $(C_7H_9O_5)_2Pb.2H_2O$ ..... 35.98 p.c.

Zinc Shikimate. This salt was obtained from zinc carbonate and shikimic acid in aqueous solution. It can be purified by recrystallization from water or by dissolving in water and then precipitating it with alcohol. It was obtained in crystalline form.

Upon analysis, the following results were obtained:

1. 0.1988 Gm. yielded 0.0395 Gm. ZnO corresponding to 15.96 p.c. Zn.
2. 0.1484 Gm. yielded 0.03 Gm. ZnO corresponding to 16.23 p.c. Zn.
3. 0.1059 Gm. yielded 0.0211 Gm. ZnO corresponding to 15.96 p.c. Zn.

The theoretical percentage is 15.89.

1) Eykman, J., Ber. 24, 1281, (1891).
2) Chen, S.Y., Am. Jour. Pharm., 101, 690, (1929).
3) Ibidem, p. 688.
4) Ibidem.
5) Oswald, F., Arch. Pharm., 229, 105, (1891).
6) Chen, S.Y., Am. Jour. Pharm., 101, 690, (1929).
7) Chen, S.Y., Arch. Pharm., 229, 106, (1929).
8) Chen, S.Y., Am. Jour. Pharm., 101, 688, (1929).
9) Oswald, F., Arch. Pharm., 229, 107, (1891).
10) Chen, S.Y., Am. Jour. Pharm., 101, 688, (1929).

Salts of Ammonia and Substituted Ammonias.

Ammonium Shikimate. This was first prepared by Eykman[1] in 1891 and described by him. It was also prepared by S.Y. Chen[2] in 1929. Repetition of these experiments yielded satisfactory results.

Analysis: (by Kjeldahl method)

1. 0.2125 Gm. of substance required 11.09 cc. of 0.1N HCl equivalent to 7.23 p.c. of N.
2. 0.3055 Gm. of substance required 11.22 cc. of 0.1444N HCl equivalent to 7.36 p.c. of N.

The theoretical percentage of nitrogen in the formula $C_6H_6(OH)_3COONH_4$ 7.33 p.c.

Methylamine Shikimate. This was prepared by S.Y. Chen in 1929,[3] melting point given as 162°. Repetition of his experiment yielded a compound with m.p. 163-164°.

n-Propylamine Shikimate. This was prepared as follows: An excess of propylamine solution was refluxed on a water bath with alcoholic shikimic acid for about two hours. After the removal of most of the solvent by evaporation, a thick, stieky syrup remained which could not be crystallised.

n-Amylamine Shikimate. This was prepared like the propylamine salt and yielded like unsatisfactory results.

Benzylamine Shikimate. This was made from a hot alcoholic mixture of shikimic acid and benzylamine. The reaction takes place immediately, and the resulting compound crystallises in the form of white needles from alcohol. M.p. 195-196°.

Nitrogen determinations according to the Kjeldahl method gave the following results:

1. 0.2825 Gm. of substance required 7.25 cc. of 0.1444N HCl corresponding to 5.19 p.c. N.
2. 0.3352 Gm. of substance required 8.5 cc. of 0.1444N HCl corresponding to 5.01 p.c. N.

Calculated for

$C_6H_6(OH)_3COO\,NH_3\,CH_2C_6H_5$ ..... 4.98 p.c.

$C_6H_6(OH)_3CO.NH.CH_2C_6H_5$ ..... 5.33 p.c.

Aniline Shikimate. This was reported by S.Y. Chen in 1929[4], and the melting point given was 178°. Repetition of the experiment yielded a powder which melted at 194-195°. Its aqueous solution was acidic to litmus paper.

Analysis gave the following results:

1. 0.248 Gm. of substance required 9.3 cc. of 0.1N HCl equivalent to 5.32 p.c. N.
2. 0.252 Gm. of substance required 9.6 cc. of 0.1N HCl equivalent to 5.33 p.c. N.

Calculated for

$C_6H_6(OH)_3COO.NH_3.C_6H_5$ ..... 5.25 p.c.

$C_6H_6(OH)_3CONH.C_6H_5$ ..... 5.62 p.c.

o-Toluidine Shikimate. This was made by refluxing the alcoholic mixture of shikimic acid and the base on a water bath for one hour. The product was a powder melting at 178-180°.

Analysis gave the following results:

1. 0.2035 Gm. of substance required 7.3 cc. of 0.1N HCl equivalent to 5.03 p.c. N.
2. 0.2148 Gm. of substance required 7.8 cc. of 0.1N HCl equivalent to 5.09 p.c. N.

Calculated for

$C_6H_6(OH)_3COO.NH_3.C_6H_4CH_3$ ..... 4.98 p.c.

$C_6H_6(OH)_3CONH.C_6H_4CH_3$ ..... 5.33 p.c.

Pyridine Shikimate. This was prepared by S.Y. Chen in 1929.[5] M.p. 184°. Repetition of the experiment yielded microscopic plates melting at 184-185°.

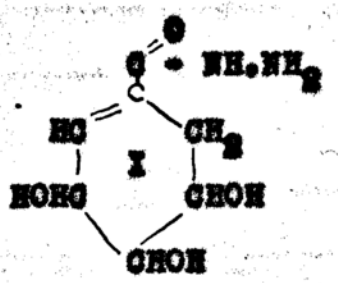
Analysis gave the following results:

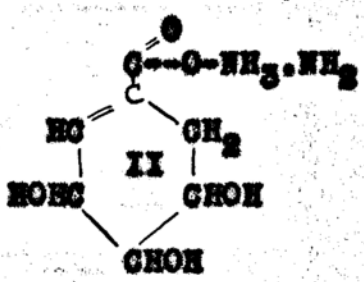
1. 0.291 Gm. of substance required 11.01 cc. of 0.1N HCl equivalent to 5.30 p.c. N.
2. 0.3012 Gm. of substance required 11.6 cc. of 0.1N HCl equivalent to 5.49 p.c. N.

Calculated for

$C_6H_6(OH)_3COO\underset{H}{N}.C_5H_5$ ..... 5.54 p.c.

Hydrazine Shikimate. In an attempt to produce a condensation product of hydrazine with shikimic acid (I), an addition product (II) resulted.





When equivalent amounts of the two substances were mixed at room temperature, a thick paste resulted with the evolution of considerable heat. After heating for ten minutes on a water bath, alcohol was added and the heating was continued for an hour supplemented by a mechanical stirrer. A white crystalline product resulted, m.p. 147-148°.

The nitrogen content was determined by the Dumas method.

1. 0.1045 Gm. yielded 13.1 cc. N at 30° and under 735 mm. pressure, corresponding to 13.14 p.c. N.
2. 0.1068 Gm. yielded 13.2 cc. N at 30° and under 743 mm. pressure, corresponding to 13.13 p.c. N.

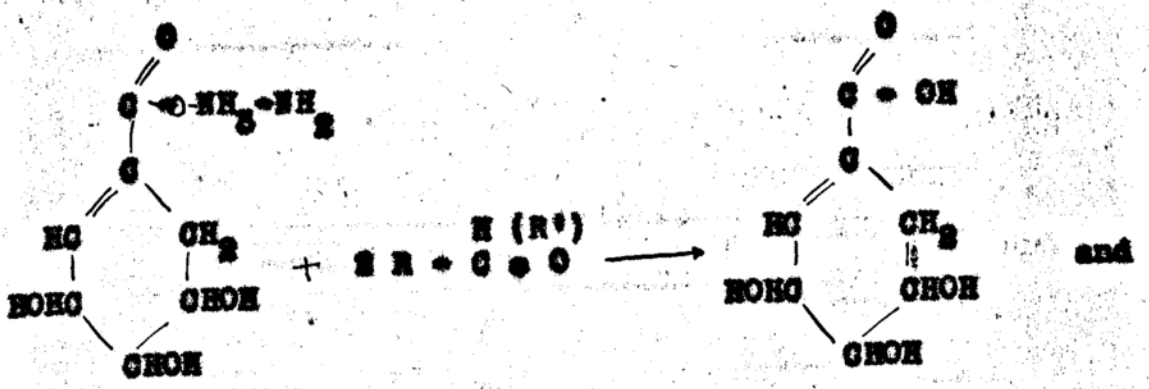
Computed for above formulae:

I	II
14.89 p.c.	13.59 p.c.

Preparation of Azines through the action of hydrazine shikimate on the corresponding aldehydes or ketones.

When hydrazine shikimate was treated with aldehydes or ketones (aromatic), the shikimic acid was found to be split

off, and in turn the hydrazine condensed with the aldehydes or ketones to form the corresponding azines. Thus



and

This reaction took place almost instantaneously and quantitatively. The preparation was carried out as follows: A mixture of 1 gram of hydrazine shikimate and an equivalent amount of an aldehyde or ketone dissolved in 5 cc. of 95 per cent alcohol was warmed on a water bath for two minutes. The condensation product separated from either the hot solution or after it had cooled. The crystals were filtered off by suction and then recrystallised from a suitable amount of alcohol. The properties and analyses of the compounds prepared are shown in the following tables.

Table I.

Physical Properties of the Azines.

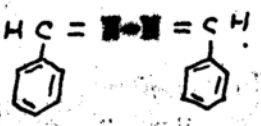
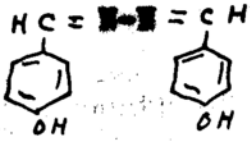
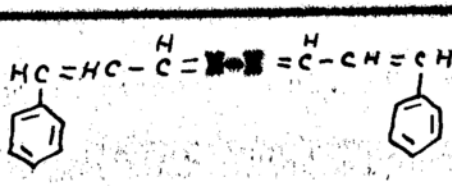
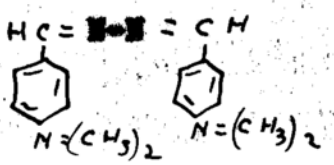
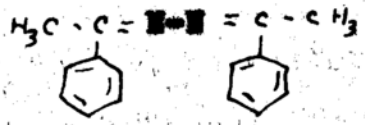
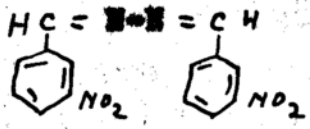
Azine	Structure	M.p. u.c.	Appearance of crystals
di-benzal-hydrazine		94-95° 6)	yellow needles from 95 p.c. alcohol
di-p-hydroxy-benzal-hydrazine		274-275°	golden plates from 95 p.c. alcohol
di-cinnamal hydrazine		165-166° 7)	deep yellow long plates from 95 p.c. alcohol
di-p-dimethyl amino-benzal-hydrazine		262-263°	deep yellow fine plates from 95 p.c. alcohol
methyl-phenyl-ketazine		122-123° 8)	shining yellow plates from 95 p.c. alcohol
3,3'-dinitro-benzaldazine		195-196° 9)	sulphur yellow fine plates from 95 p.c. alcohol

Table II.

Analysis of the Azines.

Azines	Formula	Sample Gms.	Vol N_2(CC)	P. (mm)	T. C^0	P.c. of N_2. Found	Calc.
di-benzal-hydrazine	$C_{14}H_{12}N_2$	0.0662	8.1	739.4	29	13.02	13.46
		0.0664	8.3	739.4	29	13.31	
di-p-hydroxy-benzal-hydrazine	$C_{14}H_{12}O_2N_2$	0.0504	5.5	741.6	33	11.28	11.67
		0.0508	5.6	741.2	33	11.50	
di-cinnamal-hydrazine	$C_{18}H_{16}N_2$	0.0855	8.0	739.2	27	10.06	10.77
		0.0825	7.9	740.5	25	10.41	
di-p-dimethyl amino-benzal-hydrazine	$C_{18}H_{22}N_4$	0.0515	9.2	739.6	28	19.11	19.05
		0.0650	11.4	741.0	29	18.70	
methyl-phenyl-ketazine	$C_{16}H_{16}N_2$	0.0730	8.6	735.0	31	12.06	11.87
		0.0535	6.0	741.6	28	12.31	
3,3'-di-nitro-benzald-azine	$C_{14}H_{10}O_4N_4$	0.0557	9.7	736.2	31	18.22	18.72
		0.0555	9.5	742.2	26	18.19	

Piperidine Shikimate. When equi-molecular amounts of shikimic acid and piperidine were mixed, a large amount of heat was evolved. When alcohol was added to the mixture, a homogeneous solution resulted. This solution was heated on a water bath for a few minutes, filtered, and allowed to evaporate spontaneously. A yellowish-brown syrup was obtained. Chen[10] reported the salt as a syrup also.

Quinine Shikimate. This was prepared as follows: two grams of shikimic acid were dissolved in 10 cc. of water with the aid of heat. An excess of quinine base was then added, shaking until most of the base had gone into solution. The solution was filtered after cooling. Quinine shikimate crystallized out as colorless needles. The salt can be crystallized from alcohol. It melted at 221-222°.

Analysis: (modification of the methods described by Jenkins and DuMez[11]) the amount of base was determined gravimetrically.

1. 0.3666 Gm. sample yielded 0.2382 Gm. quinine corresponding to 64.97 p.c.
2. 0.3604 Gm. sample yielded 0.2338 Gm. quinine corresponding to 64.80 p.c.

The calculated amount for

$C_6H_6(OH)_3COOH.C_{20}H_{24}O_2N_2$ is 65.08 p.c. quinine.

Quinidine Shikimate. This salt was prepared like that of quinine. From diluted (60 p.c.) alcohol, it was obtained in colorless needles, m.p. 224-226°.

When heated on an air bath for four hours at a tempera-

ture of between 100 and 110°, it did not lose weight, indicating the absence of water of crystallization. The melting point of the salt thus treated was 225-226°.

Because of the large molecule, elementary analysis did not seem satisfactory. Hence it was resolved into its components. The quinidine was determined by the U.S.P., method[12] for the assay of codeine phosphate; the shikimic acid gravimetrically as its ammonium salt.

0.56 grams yielded 0.3650 grams of quinidine and 0.2162 grams of ammonium shikimate, corresponding to 65.18 p.c. of quinidine and 34.97 p.c. of shikimic acid respectively. Calculated for

$C_{20}H_{24}O_2N_2.C_6H_6(OH)_3COOH$ base = 65.08 p.c.
acid = 34.92 p.c.

Codeine Shikimate. This salt was prepared like those of quinine and quinidine. From diluted alcohol, it was obtained in crystals somewhat resembling cubes. While sintering at 160°, they melted at 175-4°.

The analysis was carried out by the Dumas method.

1. 0.1015 Gm. gave 2.9 cc. of N at 738.6 mm., and 27.5°, corresponding to 3.06 p.c. N.
2. 0.1006 Gm. gave 2.9 cc. of N at 738 mm., and 28°, corresponding to 3.04 p.c. N.

Calculated for

$C_{18}H_{21}O_3N.C_6H_6(OH)_3COOH$ ..... 2.96 p.c. N.

Strychnine Shikimate. This was prepared from the strychnine base and aqueous shikimic acid as carried out in the preparation of the quinine salt. The salt crystallized out as colorless, long plates, m.p. 234-236° (sintered at 154°).

Analysis: this was carried out as for quinine shikimate, except that chloroform was used instead of ether as the extracting solvent.

1. 0.1176 Gm. sample yielded 0.077 Gm. strychnine, corresponding to 65.48 p.c. base.

Calculated for

$C_6H_6(OH)_3COOH.C_{21}H_{22}O_2N_2$ is 65.75 p.c. base.

Ephedrine Shikimate. Equivalent amounts of shikimic acid and ephedrine were refluxed on a water bath with 95 p.c. alcohol as solvent for about half an hour. Upon cooling, the shikimate crystallized out as large crystals. They can be purified by recrystallising from alcohol. M.p. 162-163°.

Analysis: The determination of nitrogen was carried out by the Dumas method.

1. 0.2093 Gm. gave 8.5 cc. of N at 24° and 742.4 mm., corresponding to 4.46 p.c. N.
2. 0.1040 Gm. gave 4.3 cc. of N at 25° and 738 mm., corresponding to 4.49 p.c. N.

Calculated as addition product

$C_{10}H_{15}ON.C_6H_6(OH)_3COOH$, N = 4.13 p.c.

Calculated as condensation product

$C_{10}H_{14}ON.C_6H_6(OH)_3CO$, N = 4.53 p.c.

Nicotine Shikimate. This was prepared by heating equi-molecular amounts of nicotine and shikimic acid in alcoholic solution as in the preparation of the previous salts. This salt was obtained as a brown, sticky syrup. Attempts to crystallise it from acetone or alcohol or a mixture of them were without success.

Cinchonine Shikimate. Like the other alkaloidal salts, cinchonine shikimate was prepared by heating equi-molecular quantities of cinchonine base and shikimic acid in alcoholic solution. The salt was purified by recrystallization from 95 p.c. alcohol. The yield was almost quantitative. The purified salt crystallized out in the form of prisms and melted at from 194 to 197°.

For analysis, the salt was resolved into its components. Thus:

0.3169 Gm. of salt yielded

0.1982 Gm. of base corresponding to 62.56 p.c. and

0.1500 Gm. of acid (ammonium salt) corresponding to 37.37 p.c.

Calculated for

$C_{19}H_{22}N_2O.C_6H_6(OH)_3COOH$, base = 62.84 p.c. and

acid = 37.16 p.c.

Chloroplatinate of Cinchonine Shikimate. It was found that if the cinchonine shikimate was treated with chloroplatinic acid, the shikimic acid was split off, and instead of the chloroplatinate of cinchonine shikimate, cinchonine chloroplatinate was obtained. This procedure was followed in the preparation:

0.5 grams of cinchonine shikimate were dissolved in 5 cc. of 95 p.c. alcohol and 0.5 cc. of hydrochloric acid (sp. gr. 1.12). When a trifle more than the theoretically calculated quantity of a 10 p.c. solution of chloroplatinic acid in water was added, a yellow crystalline substance precipitated out at once. This was filtered off by suction, washed with a small quantity of the cold solvent, and recrystallized from diluted alcohol.

Analysis yielded 27.84 , 27.92 , and 27.63 p.c. of Pt. respectively.

Calculated for

$C_{19}H_{22}N_2O.C_6H_6(OH)_3COOH.H_2PtCl_6$ equals 22.28 p.c. Pt.

$C_{19}H_{22}N_2O.H_2PtCl_6$ equals ..... 27.80 p.c. Pt.

Picrate of Cinchonine Shikimate. This was prepared as follows:

Equi-molecular amounts of the cinchonine shikimate and picric acid were mixed in a test tube to which was then added a few cc. of alcohol. This was heated on a steam bath for ten minutes. The mixture was allowed to cool, and the reaction product was recrystallized from alcohol. The compound crystallized in the form of yellow irregular plates which melted at 178-182°.

The melting point of cinchonine picrate as given in the literature is 193-194°.

Cinchonidine Shikimate. This compound was also obtained with good yield as in the case of cinchonine shikimate. The compound crystallized from 95 p.c. alcohol is in the form of

prisms. It melted at 205-206°.

For analysis, the salt was resolved into its components.

0.4129 Gm sample gave:

0.2569 Gm. base corresponding to 62.47 p.c.

0. 1689 Gm. acid (ammonium salt) corresponding to 37.20 p.c.

Calculated for

$C_{19}H_{22}N_2O.C_6H_6(OH)_3COOH$ ..... 62.84 p.c. base

Chloroplatinate of Cinchonidine Shikimate. As in the preparation of cinchonine shikimate chloroplatinate, it was found that shikimic acid was split off, and cinchonidine chloroplatinate was obtained instead.

This upon analysis yielded 26.55 and 26.50 p.c. of Pt.

Calculated for

$C_{19}H_{22}N_2O.C_6H_6(OH)_3COOH.H_2PtCl_6$ equals 22.28 p.c. Pt.

$C_{19}H_{22}N_2O.H_2PtCl_6$ ..... equals 27.80 p.c. Pt.

$C_{19}H_{22}N_2O.H_2PtCl_6.2H_2O$ ..... equals 26.37 p.c. Pt.

Picrate of Cinchonidine Shikimate. This was prepared just as was the picrate of cinchonine shikimate. The picrate crystallized from 95 p.c. alcohol as yellow, long, rectangular, prisms mixed with an amorphous powder. The substance melted at 177-179°.

The melting point of cinchonidine picrate as given in the literature is 208-209° with decomposition.

Optochin Shikimate. Like the other alkaloidal salts, this was prepared by heating equi-molecular amounts of optochin and

shikimic acid in alcoholic solution. The salt was purified by recrystallisation from alcohol. The rectangular plates melted at 184-185°.

For analysis, it was resolved into its components.

0.4469 Gm. sample yielded

0.2888 Gm. of base corresponding to 64.56 p.c.

Calculated for

$C_{19}H_{22}O_2N_2.C_6H_6(OH)_3COOH$ ..... equals 64.05 p.c. of base.

Morpholine Shikimate. Shikimic acid is insoluble in morpholine. When morpholine was added to the acid, a large amount of heat was evolved and a plaster-like material resulted. Heating of an alcoholic solution of shikimic acid with morpholine yielded a heavy oily substance which was insoluble in alcohol and formed a layer beneath the alcoholic solution. When the alcohol was evaporated, a thick syrup remained. Treatment with picric acid yielded a picrate melting at 148-149°. Morpholine picrate melts at 148°.

Colchicine Shikimate. This was prepared by heating colchicine with shikimic acid in alcoholic solution. The salt crystallised from alcohol as a yellowish, crystalline powder. It melted at between 101 and 105° (gas bubbles evolved).

For analysis, the salt was resolved into its components. 0.329 Gm. sample yielded 0.2285 Gm. base corresponding to 69.45 p.c. base.

Calculated for

$C_{22}H_{25}NO_6 . C_6H_6(OH)_3COOH$ is 69.64 p.c. base.

Pilocarpine Shikimate. This was prepared by heating equivalent amounts of pilocarpine and shikimic acid in alcoholic solution. The compound obtained was a sticky syrup which could not be crystallised from either alcohol or acetone.

Cocaine Shikimate. This was prepared just as was the pilocarpine salt, and yielded like unsatisfactory results.

Atropine Shikimate. The same method was followed as for the preparation of the pilocarpine salt, and the results were again unsatisfactory.

Homatropine Shikimate. This was prepared by following the method employed in the case of pilocarpine shikimate. The result was unsatisfactory.

Hyoscyamine Shikimate. It was prepared like the pilocarpine salt, and the results were unsatisfactory.

Physostigmine Shikimate. Following the method employed in the preparation of the pilocarpine salt, the physostigmine salt obtained was unsatisfactory.

Caffeine and Allantoin Shikimates were also tried. It was found that they did not react with shikimic acid.

1) Eykman, J., Ber., 24, p. 1281, (1891). For a crystallographic studyof the large crystals obtained from water see Groth, Chemische Kristallographie 3, p. 639.
2) Chen, S.Y., Am. Jour. Pharm., 101, p. 689, (1929).
3) Ibid., p. 691.
4) Ibid., p. 691.
5) Ibid., p. 691.
6) Curtius, J., Jour. prakt. Chem., (2) 39, p. 44, (1889).
7) Ibid., p. 49.
8) Curtius, T., und Thun, K., Jour. prakt. Chem., (2) 44, p. 167, (1891).
9) Minunni, G., et Carta-Satta, Gazz. chim. Ital., 29, II, p. 476, (1899).
10) Chen, S.Y., Am. Jour. Pharm., 101, p. 689, (1929).
11) Jenkins, G., and Dumez, A., Quant. Pharm. Chem., 1 ed., p. 297, (1931).
12) U.S.P. XI, p. 126, (1930).

Esters.

Methyl Shikimate. This was the only ester reported in the literature, having been prepared by Fischer and Dangschat in 1934.[1] They prepared it by condensing methyl alcohol with shikimic acid with the aid of 0.5 p.c. HCl, and also by methylation of the acid with diazomethane. Repetition of the first method yielded very low results until an improvement was introduced, whereupon yields of over 90 p.c. were obtained.

Ten grams of pure shikimic acid were refluxed with 20 cc. of absolute methyl alcohol and either 0.2 cc. of concentrated sulphuric acid or 0.2 cc. of concentrated hydrochloric acid in the presence of 1 gram of finely precipitated copper (from $CuSO_4$ by means of Zn) for about five hours. To the pink filtrate (when the shikimic acid was impure, the color was reddish-brown), an equal volume of petroleum ether or ether was added. The pink or reddish-brown crystalline mass which had been deposited over night was recrystallized from ethyl acetate. The pinkish color remaining was removed by decolorization with animal charcoal, using ethyl acetate as medium.

The white crystals of methyl shikimate melt at 113-114°; reported m.p. 113-114°. The yield was 10 grams or 92.6 p.c. of the theoretical.

The saponification value of the ester was found to be 302.1 and 297.1 respectively for two determinations,

(av. 299.8) whereas the theoretical saponification value for methyl shikimate is 298.4

The amount of carbon and hydrogen was determined in a semi-micro combustion analysis. The results are:

0.0505 Gm. sample yielded 0.095 Gm. CO_2 and 0.0285 Gm. H_2O corresponding to 51.51 p.c. of carbon and 6.27 p.c. of hydrogen respectively.

Calculated for

$C_6H_6(OH)_3COOCH_3$ are 51.06 p.c. carbon and 6.38 p.c. hydrogen.

1) Fischer, H.O.L., and Dangschat, G., Helv. Chim. Acta, 17, p. 1202, (1934).

Methylation of Methyl Shikimate. Five grams of methyl shikimate were dissolved in 15 cc. of methyl iodide contained in a flask fitted with a reflux condenser. About 30 grams of dry, powdered silver oxide were added in small successive portions, shaking the mixture after each addition. The reaction, when once started, was very vigorous. This was moderated by external cooling. After all of the silver oxide had been added and the spontaneous reaction had ceased, the mixture was heated on a water bath until there was no further formation of silver iodide. The methylated product was separated by means of ether extraction, and the ethereal solution was dried over anhydrous calcium chloride. After the removal of the solvent by distillation, there remained an oily liquid.

When distilled at 4mm. pressure and 210° bath temperature, a slightly yellowish oil was obtained. From analysis, this product seemed to be di-methyl-methyl shikimate instead of the tri-methyl-methyl ester expected.

1. 0.0625 Gm. sample yielded 0.1277 Gm. CO_2 and 0.0413 Gm. H_2O corresponding to 55.72 p.c. carbon and 7.34 p.c. hydrogen respectively.
2. 0.0676 Gm. sample yielded 0.1384 Gm. CO_2 and 0.044 Gm. H_2O corresponding to 55.84 p.c. carbon and 7.25 p.c. hydrogen respectively.
3. 0.0569 Gm. sample yielded 0.1165 Gm. CO_2 and 0.036 Gm. H_2O corresponding to 55.84 p.c. carbon and 7.35 p.c. hydrogen respectively.

Calculated for

$C_6H_6(OCH_3)_3COOCH_3$ are 57.39 p.c. carbon and 7.83 p.c. hydrogen.

$C_6H_6(OH)(OCH_3)_2COOCH_3$ are 55.56 p.c. carbon and 7.41 p.c hydrogen.

Benzoylation of Methyl Shikimate. One gram (1 mol.) of methyl shikimate was dissolved in 5 cc. of pyridine, and after the solution was chilled in an ice bath, 2.24 grams or 1.84 cc. (3 mols.) of benzoyl chloride were added dropwise while shaking the reaction mixture violently. Pyridine hydrochloride crystallised out. After having stood over night, the pyridine and its salts were dissolved in diluted (5 or 10 p.c.) sulphuric acid, leaving the benzoylated product as an oily layer at the bottom of the solution. After this was dissolved in ether, the ethereal solution was washed three times with diluted sulphuric acid, and then thoroughly with water until the washings were free from acid. When the ether was evaporated, a sticky syrup was obtained. From the following analyses, it seemed to be di-benzoyl methyl shikimate instead of the tri-benzoyl compound.

1. 0.0489 Gm. sample yielded 0.1205 Gm. CO_2 and 0.0244 Gm. H_2O corresponding to 67.21 p.c. carbon and 5.54 p.c. hydrogen respectively.
2. 0.0462 Gm. sample yielded 0.1128 Gm. CO_2 and 0.0226 Gm. H_2O corresponding to 66.12 p.c. carbon and 5.44 p.c. hydrogen.

Calculated for

$C_6H_6(OCOC_6H_5)_3COOCH_3$ are 69.60 p.c. carbon and
4.80 p.c. hydrogen.

$C_6H_6(OH)(OCOC_6H_5)_2COOCH_3$ are 66.67 p.c. carbonand
5.05 p.c. hydrogen.

Acetone Methyl Shikimate. This can be prepared by either of the following methods:

I. A mixture of 1 gram of methyl shikimate, dissolved in 5 cc. of acetone, and 0.5 gram of fused zinc chloride were warmed on a water bath for five minutes, until all of the ester had gone into solution. When this was filtered and cooled, the zinc chloride was precipitated with quinoline or pyridine. The acetone solution was first warmed on a water bath to remove the solvent, and then distilled under reduced pressure in an oil bath. A heavy, colorless oil distilled over under 4 mm. pressure and at a bath temperature of 220°C. The yield was about 0.9 grams, or 74.2 p.c. of the theoretical.

II. One gram of methyl shikimate was dissolved in 5 cc. of acetone containing 1 - 2 p.c. of hydrochloric acid. After the mixture had been warmed on a water bath for five minutes, the hydrochloric acid was precipitated as lead chloride and filtered off. The filtrate was first warmed on a water bath to drive off the excess solvent, and then distilled under reduced pressure in an oil bath. A colorless, heavy oil distilled over at 130-140°, under 4 mm. pressure and 220° oil bath temperature as in the first case. The yield was about 1 gram, or about 76 p.c. of the theoretical.

Fischer also reported this compound as an oil, but he obtained it by distilling at 0.5 mm. pressure and 150° bath temperature.

Shikimic Amide. The methyl ester of shikimic acid was mixed with an excess of concentrated ammonium hydroxide in a strong, glass stoppered bottle. The mixture was shaken vigorously for about 15 minutes, and then allowed to stand over night. Upon evaporation of most of the solvent, a gelatinous mass was obtained.

Ethyl Shikimate. Twenty cc. of absolute alcohol were refluxed with 10 grams of shikimic acid for about ten hours, using 0.2 cc. of concentrated hydrochloric or sulphuric acid in the presence of 1 gram of finely precipitated Cu as a condensing agent. The filtrate from the reaction mixture was treated as described in the preparation of the methyl ester. The ester can be purified by recrystallisation from ethyl acetate. Yield about 9.5 grams; m.p. 92-93°.

The saponification value of the ester was found to be 300.1 and 295.2 in two determinations. The theoretical saponification value for ethyl shikimate is 292.2.

Carbon and hydrogen were determined by combustion. 0.06 Gm. sample yielded 0.1172 Gm. CO_2 and 0.0349 Gm. H_2O corresponding to 53.28 p.c. carbon and 6.46 p.c. hydrogen. Calculated for

$C_6H_8(OH)_3COOC_2H_5$ are 55.47 p.c. carbon and 6.93 p.c. hydrogen.

n-Propyl Shikimate. It also was obtained in the same way as the methyl ester, using 0.2 cc. of concentrated sulphuric acid as condensing agent. It can be purified by dissolving in chloroform and adding petroleum ether to the point of turbidity. The ester crystallized either as white plates or needles. Yield about 7 grams; m.p. 68-70°.

Carbon and hydrogen were determined by combustion. 0.0539 Gm. sample yielded 0.1096 Gm. CO_2 and 0.036 Gm. H_2O corresponding to 55.46 p.c. carbon and 7.42 p.c. hydrogen.

Calculated for

$C_6H_8(OH)_3COOC_3H_7$ are 55.56 p.c. carbon and 7.41 p.c. hydrogen.

n-p-Butyl Shikimate. This ester is very readily obtained. Thirty cc. of freshly distilled n-p-butyl alcohol, 10 grams of shikimic acid, and 0.2 cc. of concentrated sulphuric acid were refluxed for five hours in an oil bath. By allowing the filtrate to stand over night, a reddish-brown, crystalline mass was precipitated. It was purified by boiling its solution in ethyl acetate with animal charcoal. The yield was almost quantitative. M.p. 112-113°. The saponification value was found to be 247.6 and 235.8 in two determinations (av. 241.7). The computed value is 243.9.

Carbon and hydrogen were determined by combustion. 0.0512 Gm. sample yielded 0.1073 Gm. CO_2 and 0.037 Gm. H_2O corresponding to 57.16 p.c. carbon and 8.03 p.c. of water, respectively.

Calculated for

$C_8H_8(OH)_3COOC_4H_9$ are 57.39 p.c. carbon and 7.82 p.c. hydrogen.

n-p-Amyl Shikimate. This was prepared in the same way as was the methyl ester, again using sulphuric acid as the condensing agent. The ester crystallizes from ethyl acetate in shining plates which melt at 67-69°.

Carbon and hydrogen were determined by combustion.

0.0553 Gm. sample yielded 0.1197 Gm. CO_2 and 0.0395 Gm. H_2O corresponding to 59.03 p.c. carbon and 7.94 p.c. hydrogen, respectively.

Calculated for

$C_6H_6(OH)_3COOC_6H_{11}$ are 59.01 p.c. carbon and 8.20 p.c. hydrogen.

Attempts to prepare the shikimates of menthol, borneol, and geraniol were unsuccessful. Benzyl alcohol, when heated with shikimic acid in the presence of 2 p.c. sulphuric acid, yielded an oily liquid with a very pleasant odor, boiling above 290°, but not constantly.

Dihydroshikimic Acid.

Dihydroshikimic acid was first prepared by Eykman[1] by means of reduction with sodium amalgam. In 1929, Chen[2] obtained it by catalytic reduction, and in 1934, H.O.L. Fischer[3] reported the acid obtained from the hydrolysis of methyl dihydroshikimate which was prepared by the hydrogenation of methyl shikimate with Pd - $BaSO_4$ as catalyst. Recently, 1935, Fischer[4] again prepared it directly by means of reduction in the presence of Pd catalyst. Both methods, viz., that with sodium amalgam and the catalytic reduction have been repeated. It was found that the catalytic reduction gave good results. Instead of using palladium black as Chen did, platinum oxide was used as catalyst. After a preliminary experiment, alcohol instead of water, as Chen described, was found to be the better medium for this purpose. Platinum oxide seems better than palladium black as a catalyst because in using platinum oxide, the reduction can be completed within three hours, instead of three days as Chen reported. The results and the details of the procedure are herewith given:

Preparation of Platinum Oxide.- In a 150 cc. porcelain casserole a solution is made of 2 grams of chloroplatinic acid and 5 cc. of water. To this, 20 grams of sodium nitrate are added. The mixture is heated gently over a Bunsen burner and stirred with a glass rod while the water is being expelled. The residue is then heated as high as is possible

with the flame until complete fusion takes place. Stirring and heating are continued until the evolution of the oxides of nitrogen has practically ceased. The mass is allowed to cool while stirring, and 50 cc. of water are added. The brown precipitate which remains undissolved is filtered off and washed free from inorganic salts. The product thus prepared should be kept in a desiccator until needed.

Reduction of Shikimic Acid.- To a solution of 5 grams of pure shikimic acid in 50 cc. of 95 p.c. alcohol or of water, 0.5 grams of platinum oxide catalyst made as above were added. The mixture was reduced under 25 to 30 pounds pressure of hydrogen in the apparatus described by Adams and Marvel.[5] The reduction was continued until no more hydrogen was absorbed. After the reduction was finished, about two or three hours, the catalyst was filtered off and dried over sulphuric acid in a desiccator where it was kept for later use. The filtrate was concentrated either by distillation under diminished pressure or by evaporation in a vacuum desiccator. When the concentrated solution was chilled, the dihydroshikimic acid crystallised out. It was collected on a filter and washed thoroughly with 95 p.c. alcohol. The filtrate was again concentrated and chilled, with a second crop resulting. The yields were different, depending upon the medium used. It was found that when alcohol was used as the medium, about 0.4 grams, or 8 p.c., of non-crystallizable residue was left. The yield of dihydroshikimic acid was about 92 p.c. If water was used as the medium, the amount of non-crystallizable residue was larger, about 1.6 grams from 5 grams of shikimic

acid, or 28 p.c. The yield of pure dihydroshikimic acid was only 72 p.c. of the theoretical. The dihydroshikimic acid thus obtained melted at 180-181°; $[\alpha]_D^{25}$ = + 18.0

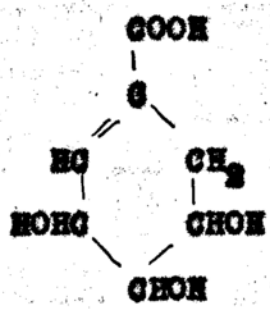
This acid is more soluble in water than is shikimic acid. It crystallizes in irregular plates. Its physical properties as described in the literature are:

Investigator	Melting Point	$[\alpha]_D$
Eykman	175°	+ 18.2 at 25°
S.Y. Chen	180°	+ 12.8 at 26.5°
H.O.L. Fischer	176-178°; 180°	+ 13.45 at 26°

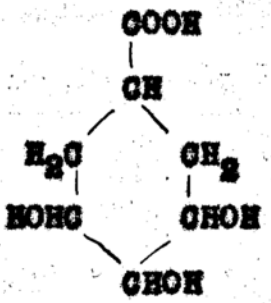
1) Eykman, J., Ber., 24, 1287, (1891).
2) Chen, S.Y., Am. Jour. Pharm., 101, p. 692, (1929).
3) Fischer, H.O.L., Helv. chim. Acta, 17, p. 1202, (1934).
4) Fischer, H.O.L., Helv. chim. Acta, 18, p. 1208, (1935).
5) Univ. of Ill. Bull., 20, No. 8, v. 3, p. 61. (Adkins, H., Practice of Organic Chemistry, p. 277, (1925)).

Salts of Dihydroshikimic Acid.

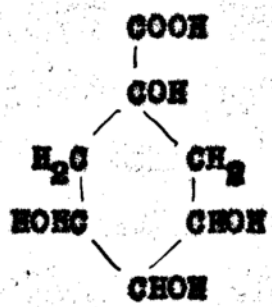
For a better understanding of shikimic acid, comparisons with more or less related acids, e.g., quinic acid and gallic acid seemed desireable, but above all with dihydroshikimic acid



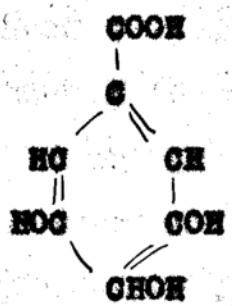
Shikimic acid



Dihydroshikimic acid



Quinic acid



Gallic acid

The dihydroshikimic acid used in the preparation of the salts to be described was made by catalytic reduction.

Lithium Dihydroshikimate. This salt was prepared by the action of the acid on lithium carbonate in the presence of water. Filtration and evaporation of the water resulted in a crystalline residue which was purified by recrystallization.

The product was heated to 120° until of constant weight.

1. 0.1141 Gm. lost 0.006 Gm. corresponding to 5.55 p.c. of water.
2. 0.1065 Gm. lost 0.0046 Gm. corresponding to 5.26 p.c. of water.

Computed for

$C_6H_8(OH)_3COO\,Li$ equals 5.68 p.c. of water

The lithium content was determined by weighing it as Li_2SO_4.

1. 0.1081 Gm. yielded 0.0321 Gm. Li_2SO_4, corresponding to 5.75 p.c. Li.
2. 0.1009 Gm. yielded 0.0299 Gm. Li_2SO_4, corresponding to 5.74 p.c. Li.

Computed for

$C_6H_8(OH)_3COO\,Li$ equals ..... 5.81 p.c.

Sodium Dihydroshikimate. Upon neutralization of dihydroshikimic acid with sodium hydroxide, using phenolphthalein as indicator, long plates or granular crystals resulted. These can be purified by recrystallization from a minimum amount of water and washing with alcohol.

The amount of water of crystallization did not agree

with either one or two molecules.

1. 0.2000 Gm. lost 0.0223 Gm. corresponding to 11.15 p.c. of water
2. 0.1760 Gm. lost 0.0200 Gm. corresponding to 11.36 p.c. of water.

Computed for

$C_6H_8(OH)_3COO\,Na.H_2O$ equals ..... 8.33 p.c.

$C_6H_8(OH)_3COO\,Na.\,1\frac{1}{2}H_2O$ equals ..... 12.10 p.c.

The sodium content was determined as sulphate.

1. 0.1777 Gm. yielded 0.0635 Gm. Na_2SO_4 corresponding to 11.57 p.c.
2. 0.1560 Gm. yielded 0.0560 Gm. Na_2SO_4 corresponding to 11.65 p.c.

Computed for

$C_6H_8(OH)_3COONa$ ..... 11.61 p.c.

Potassium Dihydroshikimate. This salt was prepared like the sodium salt. It crystallised in plates which can be recrystallised from a minimum amount of water. When heated to 120°, no loss in weight was observed. The potassium was determined as the sulphate.

1. 0.1201 Gm. yielded 0.0481 Gm. of K_2SO_4 corresponding to 17.98 p.c. K.
2. 0.1211 Gm. yielded 0.0492 Gm. of K_2SO_4 corresponding to 18.23 p.c. K.

Computed for

$C_6H_8(OH)_3COOK$ ..... 18.26 p.c. K.

Silver Dihydroshikimate. This salt was prepared by double decomposition of sodium dihydroshikimate and silver nitrate. The dihydroshikimic acid was first neutralised with sodium hydroxide in aqueous solution. Then, the requisite amount of solid silver nitrate was added. The mixture was shaken until the silver nitrate dissolved completely. After the solution was filtered, alcohol was added to the point of turbidity. While being chilled and stirred, the silver salt of dihydroshikimic acid came out. It was filtered through a force filter, washed thoroughly with alcohol, and dried in a vacuum desiccator over sulphuric acid. The salt was obtained as a white, crystalline powder which became somewhat brown after standing. It was not stable at higher temperatures and decomposed to a black residue (AgO and C) when dried at 100°. For this reason, the water of crystallization of this salt could not be determined by drying above 100° in an oven.

Analysis yielded the following results:

1. 0.1015 Gm. yielded 0.0364 Gm. Ag, corresponding to 35.93 p.c. Ag.
2. 0.0545 Gm. yielded 0.0194 Gm. Ag, corresponding to to 35.58 p.c. Ag.

Calculated for

$C_6H_8(OH)_3COOAg$ ..... 35.14 p.c. Ag.

$C_6H_8(OH)_3COOAg.H_2O$ ..... 33.86 p.c. Ag.

Copper Dihydroshikimate. It was obtained by heating dihydroshikimic acid with freshly precipitated cupric hydroxide suspended in water. A very beautiful, green, crystalline

product resulted upon the spontaneous evaporation of the filtrate (from the excess cupric hydroxide) in a vacuum desiccator over sulphuric acid. It was insoluble in alcohol, as was copper shikimate. It dissolved in concentrated alkali without the precipitation of cupric hydroxide. The aqueous solution of the salt was green, but in the presence of alkali, it turned blue.

When analysed, the following results were obtained:

1. 0.1041 Gm. gave 0.0199 Gm CuO corresponding to 15.28 p.c. Cu.
2. 0.1049 Gm. gave 0.0202 Gm. CuO corresponding to 15.38 p.c. Cu.

Calculated for

$(C_6H_8(OH)_3COO)_2Cu$ ..... 15.37 p.c. Cu.

Magnesium Dihydroshikimate. This was prepared from magnesium carbonate like the lithium salt. Unlike the magnesium salt of shikimic acid, it is not hygroscopic.

The water content was determined in the usual manner.

1. 0.1032 Gm. lost 0.0050 Gm. corresponding to 4.78 p.c. water.
2. 0.1152 Gm. lost 0.0052 Gm. corresponding to 4.51 p.c. water.

Computed for

$(C_6H_8(OH)_3COO)_2Mg.H_2O$ ..... 4.59 p.c.

The magnesium content was determined as the oxide.

1. 0.0982 Gm. yielded 0.0111 Gm. MgO corresponding to 6.82 p.c. Mg.

2. 0.1100 Gm. yielded 0.0121 Gm. MgO corresponding to 6.64 p.c. Mg.

Computed for

$(C_6H_8(OH)_3COO)_2$ Mg ..... 6.50 p.c.

Calcium Dihydroshikimate. This was made by neutralizing the acid with either milk of lime or calcium carbonate in the presence of water. It was purified by precipitation from its concentrated aqueous solution with alcohol. Thus purified, it was obtained as a granular powder.

The water was determined in the usual way.

1. 0.1060 Gm. lost 0.0049 Gm. corresponding to 4.62 p.c. of water.
2. 0.1047 Gm. lost 0.0046 Gm. corresponding to 4.49 p.c. of water.

Computed for

$(C_6H_8(OH)_3COO)_2Ca.H_2O$ ..... 4.41 p.c.

The calcium content was determined as sulphate.

1. 0.1011 Gm. yielded 0.0337 Gm. $CaSO_4$ corresponding to 9.82 p.c. Ca.
2. 0.1001 Gm. yielded 0.0348 Gm. $CaSO_4$ corresponding to 10.24 p.c. Ca.

Computed for

$(C_6H_8(OH)_3COO)_2$ Ca ..... 10.27 p.c.

Strontium Dihydroshikimate. It was made by the action of dihydroshikimic acid on strontium carbonate in aqueous solution. The salt was obtained in crystalline form. It

can be purified by recrystallisation from water. When analysed, the following results were obtained:

1. 0,0840 Gm. sample lost 0,0064 Gm. corresponding to 7,62 p.c. of water.
2. 0.0849 Gm. sample lost 0,0051 Gm. corresponding to 7,77 p.c. of water.

Calculated for

$(C_6H_8(OH)_3COO)_2\ Sr.H_2O$ ..... 5.95 p.c. H_2O.

$(C_6H_8(OH)_3COO)_2\ Sr.2H_2O$ ..... 7.60 p.c. H_2O.

The strontium content was determined as the sulphate.

1. 0.0776 Gm. yielded 0.0323 Gm. $SrSO_4$ corresponding to 19.86 p.c. Sr.
2. 0.0798 Gm. yielded 0.0339 Gm. $SrSO_4$ corresponding to 20.27 p.c. Sr.

Calculated for

$(C_6H_8(OH)_3COO)_2Sr$ ..... 20.02 p.c. Sr.

* It was found that only ½ mol. of water of crystallisation could be driven off when the salt was kept in an oven at 120° for one day. In order to remove all of the water of crystallisation, the salt must be kept at a temperature of 130-135° for several hours.

Barium Dihydroshikimate. When dihydroshikimic acid was allowed to react with an excess of barium carbonate, barium dihydroshikimate was formed. Since the salt was exceedingly soluble in water, it was difficult to crystallise. When an aqueous solution of it was evaporated in a vacuum, a thick

syrup remained which, upon further elimination of water, became a jellied mass. When this mass was stirred with alcohol, a white powder settled out. This was filtered out and dried in a desiccator over sulphuric acid.

Upon analysis, the following results were obtained:

1. 0.0977 Gm. lost 0.0062 Gm. corresponding to 6.35 p.c. of water.
2. 0.0979 Gm. lost 0.0067 Gm. corresponding to 6.84 p.c. of water.

Calculated for

$(C_6H_8(OH)_3COO)_2Ba.2H_2O$ ..... 6.88 p.c.

The barium content was determined as the sulphate.

1. 0.0915 Gm. yielded 0.0435 Gm. $BaSO_4$ corresponding to 27.99 p.c. Ba.
2. 0.0912 Gm. yielded 0. 0436 Gm. $BaSO_4$ corresponding to 28.14 p.c. Ba.

Calculated for

$(C_6H_8(OH)_3COO)_2Ba$ ..... 28.19 p.c.

* Like for the strontium salt, the determination of water of crystallization was carried out at 130-135°. It was found that at 120° only 1 molecule of water of crystallization was driven off.

Lead Dihydroshikimate. As in the preparation of the lead shikimate, this salt was made by the action of dihydroshikimic acid on lead carbonate in the presence of water. An amorphous, brittle mass was obtained upon the spontaneous evaporation of the filtrate (from the excess lead carbonate) in a vacuum

desiccator over sulphuric acid. It is unstable at higher temperatures, hence its water of crystallisation has been calculated from the following analysis:

1. 0.0533 Gm. gave 0.0215 Gm. $PbSO_4$ corresponding to 27.56 p.c. Pb.
2. 0.1053 Gm. gave 0.0415 Gm. $PbSO_4$ corresponding to 26.99 p.c. Pb.
3. 0.0868 Gm. gave 0.0349 Gm. $PbSO_4$ corresponding to 27.48 p.c. Pb.

Calculated for

$(C_6H_8(OH)_3COO)_2Pb$ ..... 31.19 p.c. Pb.
$(C_6H_8(OH)_3COO)_2Pb.11H_2O$ ..... 27.44 p.c. Pb.
$(C_6H_8(OH)_3COO)_2Pb.12H_2O$ ..... 26.80 p.c. Pb.

Zinc Dihydroshikimate. This was prepared by the action of dihydroshikimic acid on zinc carbonate in aqueous solution. The salt produced was exceedingly soluble in water, and like the barium salt, it could be crystallised only with a good deal of difficulty. When an aqueous solution of it was concentrated in a vacuum, it became a thick syrup which upon further removal of water became a gel-like mass, as did the barium salt. It was obtained as a powder by stirring this mass with 95 p.c. alcohol, filtering, and then drying it in a desiccator over sulphuric acid. The salt is unstable at higher temperatures, above 100°, hence its water of crystallization cannot be determined by the usual method. It was calculated from the following analysis:

1. 0.1221 Gm. sample yielded 0.0221 Gm. ZnO equivalent to 14.54 p.c. Zn.

2. 0.0424 Gm. sample yielded 0. 0077 Gm. ZnO equivalent to 14.59 p.c. Zn.

Calculated for

$(C_6H_8(OH)_3COO)_2Zn$ ..... 15.74 p.c. Zn.

$(C_6H_8)OH)_3COO)_2Zn.2H_2O$ ..... 14.48 p.c. Zn.

Salts of Ammonia and Substituted Ammonias.

Ammonium Dihydroshikimate. The salt was prepared by neutralizing an aqueous solution of dihydroshikimic acid with ammonium hydroxide, using phenolphthalein as indicator. Unlike the ammonium shikimate, which crystallized well, ammonium dihydroshikimate was a thick, syrupy substance.

n-Amylamine Dihydroshikimate. This salt was prepared from n-amylamine and dihydroshikimic acid in alcoholic solution, and like the corresponding shikimic acid salt, it was a thick syrup.

Benzylamine Dihydroshikimate. The salt was prepared as was that of benzylamine shikimate, but unlike the latter, which was in good crystalline form, the benzylamine dihydroshikimate was obtained as a thick, brown syrup.

Codeine Dihydroshikimate. The salt was prepared by heating equivalent amounts of base and acid in alcoholic solution. It crystallized well from 95 p.c. alcohol as rectangular plates which melted at 201-203°.

For analysis, the salt was resolved into its components: 0.3081 Gm. sample yielded 0.1928 Gm. base corresponding to 62.58 p.c. of base, and 0.1228 Gm. of ammonium dihydroshikimate corresponding to 36.35 p.c. acid.

Computed for

$C_{18}H_{21}O_3N.C_6H_8(OH)_3COOH$ is 62.96 p.c. base and 37.04 p.c. acid.

Quinine Dihydroshikimate. This salt was obtained from equivalent amounts of quinine and dihydroshikimic acid in alcoholic solution as in the preparation of the other alkaloidal salts. It crystallized from alcohol as rectangular plates mixed with a powder. M.P. 200-202°.

For analysis, the salt was resolved into its components: 0.3239 Gm. sample gave 0.210 Gm. of base corresponding to 64.84 p.c. of base, and 0.1252 Gm. of ammonium dihydroshikimate corresponding to 35.26 p.c. of acid.

Computed for

$C_{20}H_{24}O_2N_2.C_6H_8(OH)_3COOH$ is 64.81 p.c. of base and 35.19 p.c. of acid.

Quinidine Dihydroshikimate. This salt was obtained as a yellow, gelatinous mass from alcoholic solution. When recrystallized from acetone, however, it separated in the form of prisms mixed with powder. It melted at 171-172°.

For analysis, the salt was resolved into its components: 0.3281 Gm. of sample yielded 0.2120 Gm. of base corresponding to 64.62 p.c. of base, and 0.1289 Gm. of acid (ammonium salt) corresponding to 35.74 p.c. of free acid.

Computed for

$C_{20}H_{24}O_2N_2.C_6H_8(OH)_3COOH$ is 64.81 p.c. of base and 35.19 p.c. of acid.

Cinchonine Dihydroshikimate. The salt was obtained as a thick syrup from alcoholic solution, but it changed into a crystalline powder when stirred and warmed with acetone.

the product so obtained melted at 188-190°.

For analysis, the salt was resolved into its components: 0.3178 Gm. sample yielded 0.2005 Gm. base corresponding to 63.09 p.c.

Calculated for

$C_{19}H_{22}ON_2.C_6H_8(OH)_3COOH$ is 62.57 p.c. of base.

Cinchinidine Dihydroshikimate. The salt was obtained by heating equivalent amounts of cinchonidine base and dihydroshikimic acid in alcoholic solution. It crystallised from hot alcohol as very fine needles mixed with powder. The salt melted at 190-191°.

For analysis, the salt was resolved into its components: 0.3207 Gm. sample yielded 0.2014 Gm. of base corresponding to 62.80 p.c. of base and 0.1301 Gm. of ammonium dihydroshikimate corresponding to 36.99 p.c. of acid.

Calculated for

$C_{19}H_{22}ON_2.C_6H_8(OH)_3COOH$ is 62.57 p.c. of base and 37.43 p.c. of acid.

Strychnine Dihydroshikimate. This was prepared in alcoholic solution as in the cases of the other alkaloidal salts. It was purified by recrystallisation from a mixture of acetone and alcohol (1 : 1), from which it separated in the form of rectangular plates. M.p. 235-238° (sintered at 185°).

For analysis, the salt was resolved into its components: 0.3228 Gm. sample yielded 0.2114 Gm. of base corresponding

to 65.49 p.c. of base and 0.1211 Gm. of ammonium shikimate corresponding to 34.21 p.c. of acid.

Calculated for

$C_{21}H_{22}O_2N_2.C_6H_8(OH)_3COOH$ is 65.51 p.c. of base and 34.49 p.c. of acid.

Nicotine Dihydroshikimate. The salt was prepared from nicotine base and dihydroshikimic acid in alcoholic solution. A brownish-yellow, syrupy substance was obtained. Attempts to crystallize it failed.

Esters.

Methyl Dihydroshikimate. This was prepared by the catalytic reduction of methyl shikimate. Five grams of methyl shikimate, dissolved in 50 cc. of alcohol (95 p.c.), were reduced under a pressure of 25-30 pounds with platinum oxide as catalyst, just as in the preparation of dihydroshikimic acid. A colorless oil which distilled between 180 and 220° under 9 mm. of mercury was obtained. The oil had an index of refraction of n^{20} = 1.5025.

Both carbon and hydrogen were determined by combustion. 0.057 Gm. sample yielded 0.1064 Gm. CO_2 and 0.0387 Gm. H_2O corresponding to 50.91 p.c. carbon and 7.54 p.c. of water, respectively.

Calculated for

$C_6H_8(OH)_3COOCH_3$ are 50.53 p.c. carbon and 7.37 p.c. hydrogen.

It was found that the methyl ester was more easily reduced than was the shikimic acid. For complete reduction, only one and one-half hours were required for 5 grams of ester.

Fischer[1] showed that when methyl dihydroshikimate was distilled, the corresponding lactone resulted.

1) Fischer, H.O.L., and Dangschat, G., Helv. Chim. Acta, 17, p. 1202, (1934).

Dihydroshikimic Hydrazide. This was prepared as follows:

One gram of methyl dihydroshikimate was heated under a reflux condenser for twelve hours with 5 cc. of absolute alcohol and 0.3 cc. of hydrazine hydrate. After cooling and standing over night, the compound appeared in the form of large crystals. These were filtered off and recrystallized from 95 p.c. alcohol. They melted at 200-201°. The compound was reported by Fischer[1] who recorded its melting point as 200-201°. It has the formula:

$$C_6H_8(OH)_3CO\ NHNH_2.$$

1) Fischer, H.O.L., Helv. Chim. Acta, 17, p. 1204, (1934).

Dihydroshikimic Amide. This was prepared by shaking methyl dihydroshikimate with concentrated ammonia. As in the preparation of shikimic amide, a gelatinous substance was obtained which could not be crystallised.

Dihydroshikimic Acid Lactone.

This compound was first prepared by Fischer.[1] His procedure was modified to read as follows:

One gram of dihydroshikimic acid was heated on an oil bath. The acid melted when the bath reached 185°. It was held at this temperature for a few minutes until the melted acid became a homogeneous liquid and gas bubbles were no longer evolved. It was then distilled under a pressure of 3 mm. with a bath temperature of 240-250°. The distillation was very slow, and only a small amount of crystals were deposited in the side-arm of the distilling flask. These were dissolved in ether, and upon evaporation of the solvent, beautiful crystals remained. The yield was very poor, with only 0.3 grams or 30 p.c. being obtained from 1 gram of dihydroshikimic acid. M.p. 145-146°.

Fischer reported the melting point as 146-147° and

$[\alpha]_D^{20}$ = -45.25.

1) Fischer, H.O.L., Helv. chim. Acta, 18, p. 1209, (1935).

Diacetyl-dihydroshikimic Acid Lactone.

Two grams of dihydroshikimic acid were boiled with 8 cc. of acetic acid anhydride on an oil bath for one hour. The excess acetic anhydride or acid was then distilled off. The residue was taken up with hot 98 p.c. alcohol from which beautiful long, hexagonal and rectangular plates crystallised out upon cooling. These were then purified by recrystallisation from alcohol. The compound so obtained melted at 144-145°.

Fischer[1] prepared this compound in the same way. The melting point recorded by him was 145-146° with

$[\alpha]_D^{20}$ = -138.2 .

1) Fischer H.O.L., Helv. chim. Acta., 18, p. 1210, (1935).

Triacetyl-dihydroshikimic Acid.

This was prepared by the reduction of triacetyl-shikimic acid with acetic acid as the solvent and platinum oxide as catalyst. The reduction was carried out just as in the preparation of dihydroshikimic acid. It was a jelly-like mass as was the triacetyl-shikimic acid, and was distilled under high vacuum of 1 mm. pressure and a bath temperature of 200-210°. The acid value, in two determinations, was found to be 170 and 169.5, respectively, while the theoretical acid value calculated for $C_6H_8(OCOCH_3)_3COOH$ is 169.

This compound was prepared by Fischer (1) by decomposing triacetyl-dihydroshikimic acid anhydride with potassium carbonate.

(1) Fischer, H.O.L., Helv. chim. Acta., 18, p. 1209, (1935).

Triacetyl-dihydroshikimic Chloride.

This was prepared by heating triacetyl-dihydroshikimic acid with thionyl chloride (5 grams of each) on a water bath for two hours, until practically no more HCl and SO_2 came off. The reaction mixture was then distilled under reduced pressure on a water bath to remove the excess of thionyl chloride, if any. The yellowish-brown, liquid residue left in the flask was mostly triacetyl-dihydroshikimic chloride. This was reserved for the preparation of the corresponding anilide.

Triacetyl-dihydroshikimic Anilide.

It was prepared by heating the triacetyl-dihydroshikimic chloride previously mentioned with aniline. The reaction product crystallised from alcohol in the form of needles which melted at 148°.

Fischer[1] reported the melting point of this compound as 145-147°.

1) Fischer, H.O.L., Helv. chim. Acta., 18, p. 1209. (1935.)

Acetone Shikimic Acid.

Since shikimic acid is closely related to quinic acid, the corresponding compound, acetone shikimic acid, corresponding to acetone quinic acid which was first prepared by Fischer[1] was expected to be obtained. This was first prepared by Chen[2] in 1929, and by Fischer in 1935.[3] By modifying Chen's method, a product with better yield, about 80 p.c., was obtained.

Five grams of freshly fused zinc chloride were dissolved in 50 cc. of acetone. To this solution, 10 grams of shikimic acid were added and the mixture was refluxed, with occasional shaking, on a water bath for 30 minutes. All the shikimic acid went into solution. After filtration, beautiful shining plates of acetone shikimic acid were obtained upon cooling. The yield was 10 grams, or 81 p.c. of the theoretical. Acetone shikimic acid can be purified by recrystallization from acetone. The purified product has a melting point of 186-187°C.

The acid value of this compound was determined in aqueous solution. It was found to be 263.8 and 261.7 for two determinations, whereas the theoretical acid value of

$$C_7H_{10}O_5 + CH_3CO\,CH_3 + H_2O = 262.1$$

Acetone shikimic acid can also be prepared by heating shikimic acid in acetone solution containing 1 or 2 p.c. of

hydrochloric acid. For example: 1 gram of shikimic acid dissolved in 10 cc. of a 1 or 2 p.c. solution of hydrochloric acid in acetone was refluxed on a water bath for one hour, until all of the shikimic acid had gone into solution. After the liquid was filtered and cooled, the acetone shikimic acid crystallised out in shining plates as in the first case.

Methylation of Acetone Shikimic Acid. One mol. of acetone shikimic acid was dissolved in an excess (3 mols.) of methyl iodide contained in a flask fitted with a reflux condenser, and then, dry powdered silver oxide (1.5 mols.) was added in small, successive portions, shaking the mixture after each addition. The reaction did not begin spontaneously, but could be induced by heating gently, and when once started the reaction was very vigorous. It was moderated by external cooling. After this initial reaction had ceased, the mixture was heated on a water bath until there was no further formation of silver iodide. The methylated product was then separated from the silver iodide by means of extraction with ether. After the solvent was removed from the extract, an oily liquid remained. This was distilled at atmospheric pressure, and two fractions were collected: one distilled over between 95 and 100°; the second was collected above 100°. After standing for a few days, it was found that crystals in the form of needles melting at 114-115° had appeared in the first fraction, but not in the second. When both fractions were stirred with ether, more of the same crystalline sub-

stance was obtained from each. These were filtered off, washed with ether, and their melting points were determined. It was found that the crystals obtained from the two different fractions had the same melting point, 114-115°. When mixed with an authentic sample of methyl shikimate, m.p. 114°, no depression of the melting point was observed. The liquid fractions left after the removal of the crystals were found to be a mono-methyl ether of shikimic acid which was soluble in alcohol and ether, but not in water. Their acid values were determined:

	Fraction 95-100°	Fraction above 100°
	297	302.1
	307.5	308.5
	295.9	315.6
Av.	300.1	308.7

Calculated for

$C_6H_8(OCH_3)(O_2 eCe (CH_3)_2 COOH$ ..... A.V. 246.1

$C_6H_8OCH_3 (OH)_2COOH$ ..... A.V. 298.4

1) Fischer, H.O.L., Ber., 54, p. 775, (1921).
2) Chen, S.Y., Am. Jour. Pharm., 101, p. 692, (1929).
3) Fischer, H.O.L., Helv. chim. Acta., 18, p. 1210, (1935).

Salts of Acetone Shikimic Acid.

Salts of Metals.

Sodium Acetone Shikimate. This salt was obtained by neutralising acetone shikimic acid with sodium hydroxide. The product was a crystalline powder.

Analysis yielded the following results:

1. 0.2885 Gm. gave 0.087 Gm. Na_2SO_4 corresponding to 9.74 p.c. Na.
2. 0.2158 Gm. gave 0.069 Gm. Na_2SO_4 corresponding to 9.66 p.c. Na.

Theoretical percentage for the formula

$C_6H_6(OH)(O_2{\cdot}C_2(CH_3)_2)COONa$ is 9.75 p.c.

Potassium Acetone Shikimate. This was obtained by neutralising acetone shikimic acid with potassium hydroxide. The salt crystallised in plates.

Analysis yielded the following results:

1. 0.2502 Gm. gave 0.068 Gm. K_2SO_4 corresponding to 15.52 p.c. K.

Calculated for

$C_6H_6(OH)(O_2{\cdot}C_2(CH_3)_2)COOK$ is 15.8 p.c.

Copper Acetone Shikimate. This salt was prepared by the action of acetone shikimic acid on freshly precipitated cupric hydroxide. The product obtained was a crystalline powder with a greenish-blue color. Like copper shikimate

and copper dihydroshikimate, it can be dissolved in concentrated alkali without the precipitation of cupric hydroxide.

Analysis yielded the following results:

1. 0.1018 Gm. gave 0.0147 Gm. CuO corresponding to 11.54 p.c. Cu.
2. 0.1017 Gm. gave 0.0148 Gm. CuO corresponding to 11.67 p.c. Cu.

Calculated for

$(C_6H_6(OH)(O_2 \cdot Ce(CH_3)_2)COO)_2Cu$ ..... 12.99 p.c.

$(C_6H_6(OH)(O_2 \cdot Ce(CH_3)_2)COO)_2Cu \cdot 2H_2O$ ..... 12.09 p.c.

$(C_6H_6(OH)(O_2 \cdot Ce(CH_3)_2)COO)_2Cu \cdot 3H_2O$ ..... 11.69 p.c.

Since the salts of acetone shikimic acid are not stable at high temperatures, their water of crystallization was calculated from the analyses.

Magnesium Acetone Shikimate. Like magnesium shikimate, this salt was also obtained in an amorphous condition from magnesium carbonate and acetone shikimic acid in the presence of water. The amorphous mass was difficultly soluble in organic solvents, but it was not hygroscopic as was the magnesium shikimate.

Analysis yielded the following results:

1. 0.2717 Gm. yielded 0.0234 Gm. MgO corresponding to 5.20 p.c. Mg.
2. 0.2066 Gm. yielded 0.0161 Gm. MgO corresponding to 5.28 p.c.

Calculated for

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Mg$ ..... 5.40 p.c.

Calcium Acetone Shikimate. It was prepared by the action of acetone shikimic acid upon calcium carbonate in the presence of water. The salt was obtained as a crystalline powder.

Analysis yielded the following results:

1. 0.1000 Gm. yielded 0.0310 Gm. $CaSO_4$ corresponding to 9.13 p.c. Ca.
2. 0.1175 Gm. yielded 0.0342 Gm. $CaSO_4$ corresponding to 8.57 p.c. Ca.

Calculated for

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Ca$ ..... 8.60 p.c.

Strontium Acetone Shikimate. This salt was made from strontium carbonate and an aqueous solution of acetone shikimate acid. It crystallized in prisms.

Analysis yielded the following results:

1. 0.215 Gm. yielded 0.0735 Gm. $SrSO_4$ corresponding to 16.46 p.c. Sr.
2. 0.209 Gm. yielded 0.07 Gm. $SrSO_4$ corresponding to 16.66 p.c. Sr.

Calculated for

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Sr$ ..... 17.06 p.c.

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Sr \cdot H_2O$ ..... 16.46 p.c.

Barium Acetone Shikimate. Like barium shikimate, this was an amorphous, brittle mass. It was prepared from barium carbonate and acetone shikimic acid in the presence of water. It was very difficultly soluble in organic solvents.

Analysis yielded the following results:

1. 0.3135 Gm. yielded 0.1206 Gm. $BaSO_4$ corresponding to 22.72 p.c. Ba.
2. 0.1235 Gm. yielded 0.0468 Gm. $BaSO_4$ corresponding to 22.85 p.c. Ba.

Calculated for

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Ba$ ..... 24.39 p.c.

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Ba.2H_2O$ ..... 22.95 p.c.

Zinc Acetone Shikimate. As in the preparation of zinc shikimate and zinc dihydroshikimate, this salt was made from zinc carbonate and acetone shikimic acid in aqueous solution. The reaction was carried out at room temperature. A white, crystalline powder remained after evaporation of the filtrate in a vacuum desiccator.

Analysis yielded the following results:

1. 0.1049 Gm. yielded 0.0177 Gm. ZnO corresponding to 13.55 p.c. Zn.
2. 0.1095 Gm. yielded 0.0185 Gm. ZnO corresponding to 13.57 p.c. Zn.

Calculated for

$(C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COO)_2Zn$ ..... 13.50 p.c.

Salts of Substituted Ammonias.

Benzylamine Acetone Shikimate. This was made from a hot alcoholic mixture of acetone shikimic acid and benzylamine. The salt which crystallised in rectangular plates from alcohol melted at 155-156°.

A nitrogen determination according to the Kjeldahl method gave the following results:

1. 0.291 Gm. of substance required 9.32 cc. of 0.1N HCl equivalent to 4.49 p.c. N.
2. 0.270 Gm. of substance required 8.48 cc. of 0.1N HCl equivalent to 4.4 p.c. N.

That calculated for

$C_6H_6(OH)(O_2CC(CH_3)_2)COONH_3CH_2C_6H_5$ is 4.36 p.c.

$C_6H_6(OH)(O_2CC(CH_3)_2)CONH\,CH_2C_6H_5$ is 4.62 p.c.

o-Toluidine Acetone Shikimate. This was prepared as follows: An excess of alcoholic o-toluidine solution was refluxed on a water bath with alcoholic acetone shikimic acid. After the removal of most of the solvent by evaporation, the salt crystallised out in white, shining plates. M.p. 192-193°. The salt was not analysed.

n-Propylamine Acetone Shikimate. This was prepared like the o-toluidine salt, but after evaporating the solvent, a thick, stieky syrup remained. It was just like n-propylamine shikimate, which could not be crystallised either.

n-Amylamine Acetone Shikimate. This was prepared just like the n-propylamine salt and yielded like unsatisfactory results.

Strychnine Acetone Shikimate. The same as in the preparation of strychnine shikimate, the salt obtained was a jelly-like mass, but beautiful crystals were obtained when this substance was warmed with acetone. It had a melting point of 275-277°.

Time did not allow for analysis.

Codeine Acetone Shikimate. This was prepared by heating codeine and acetone shikimic acid in alcoholic solution as in the preparation of codeine shikimate. At first, this salt was a sticky mass which could not be crystallised from either acetone or alcohol, but when desiccated over sulphuric acid, the mass crystallised in the form of scales. The salt was not hydrolysed for analysis.

Chloroplatinate and Chloraurate of Acetone Shikimic Acid. When codeine acetone shikimate was treated with chloro-platinic acid, inthe manner as described under the double salt of cinchonine shikimate, the chloroplatinate of the alakloidal salt was obtained, which crystallised with five molecules of water of crystallisation and melted at 215 - 217°C. However, when codeine acetone shikimate was treated with chloraurie acid under similar conditions, it was found that acetone shikimic acid had been split off, and codeine chloraurate resulted instead. These conclusions are drawn

from the following analyses:

Analysis of the chloroplatinate:

1. 0.0508 Gm. sample yielded 0.0097 Gm. Pt corresponding to 19.10 p.c. Pt.
2. 0.0293 Gm. sample yielded 0. 0057 Gm. Pt corresponding to 19.45 p.c. Pt.

Calculated for

$C_{18}H_{21}O_3N.C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COOH.H_2PtCl_6$ is 21.14 p.c. Pt.

$C_{18}H_{21}O_3NC_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2).H_2PtCl_6.5H_2O$ is 19.27 p.c. Pt.

Analysis of the chloraurate:

1. 0.0532 Gm. sample yielded 0.0162 Gm. Au corresponding to 30.45 p.c. Au.
2. 0.0502 Gm. sample yielded 0.0151 Gm. Au corresponding to 30.08 p.c. Au.

Calculated for

$C_{18}H_{21}O_3N.C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COOH.HAuCl_4$ is 23.11 p.c. Au.

$C_{18}H_{21}O_3N.HAuCl_4$ is 30.85 p.c. Au.

Morpholine Acetone Shikimate. This was prepared by heating equivalent amounts of morpholine and acetone shikimic acid in alcoholic solution. The compound usually crystallised out as large and beautiful crystals. It could be purified by recrystallisation from alcohol. The compound

melted at 178-179°.

The nitrogen content was determined by the Kjeldahl-Gunning-Arnold method. The result is given herewith:

1. 0.1862 Gm sample yielded 0.008504 Gm. N corresponding to 4.57 p.c. N.

Calculated for

$C_8H_9NO.C_6H_8(OH)(O_2\ aCe\ (CH_3)_2)COOH$ is 4.65 p.c. N.

Colchicine Acetone Shikimate. This was prepared by heating colchicine and acetone shikimic acid in alcoholic solution as in the preparation of colchicine shikimate. The salt was obtained as a yellow, crystalline powder when the solvent was evaporated in a vacuum desiccator. The compound melted at from 71-74°.

For analysis, the salt was resolved into its components.

0.4972 Gm. sample yielded 0.322 Gm. base corresponding to 64.76 p.c. base.

Calculated for

$C_{22}H_{25}NO_6.C_6H_8(OH)(O_2\ aCe\ (CH_3)_2)COOH$ is 65.1 p.c. base.

Piperidine Acetone Shikimate. As in the preparation of piperidine shikimate, when piperidine and acetone shikimic acid were mixed, heat was evolved. The mixture formed a homogeneous solution with alcohol. Upon evaporation of the solvent, a yellowish brown syrup resulted.

Cinchonine Acetone Shikimate. This was prepared from cinchonine and acetone shikimic acid in the usual manner. As

it came out of alcoholic solution, the salt was a gelatinous mass, but after this was recrystallized from acetone, it separated in the form of rectangular plates. They melted at 255-257°.

For analysis, the salt was resolved into its components.

0.2065 Gm. yielded 0.1189 Gm. base corresponding to

57.58 p.c. of base.

Calculated for

$C_{19}H_{22}N_2O.C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COOH$ is 57.85 p.c.

Quinine Acetone Shikimate. This was prepared by heating equivalent amounts of quinine and acetone shikimic acid in alcoholic solution. When this solution was evaporated, the salt was a thick, sticky syrup. From hot acetone, it crystallized in the form of long needles. They melted at 125-127°.

For analysis, the salt was resolved into its components.

0.3154 Gm. sample yielded 0.1893 Gm. of base corresponding to 60.02 p.c. of base, and 0.134 Gm. of ammonium acetone shikimate corresponding to 39.36 p.c. acid.

Calculated for

$C_{20}H_{24}O_2N_2.C_6H_6(OH)(O_2 \cdot C \cdot (CH_3)_2)COOH$ are

60.24 p.c. base and

39.76 p.c. acid.

Quinidine Acetone Shikimate. Like the quinine salt, this one was prepared by heating acetone shikimic acid in alcoholic solution with quinidine, the base. The salt crys-

tallized from alcohol in long plates. It had a melting point of 144-145°.

For analysis, the salt was resolved into its components. 0.5 Gm. sample yielded 0.1799 gm. base corresponding to 59.97 p.c. base, and 0.1266 Gm. ammonium acetone shikimate corresponding to 39.09 p.c. acid.

Calculated for

$C_{20}H_{24}O_2N_2 \cdot C_6H_6(OH)(O_2 aCm (CH_3)_2)COOH$ are

60.24 p.c. base and

39.76 p.c. acid.

Nicotine Acetone Shikimate. It was obtained as a brown, sticky syrup by heating nicotine and acetone shikimic acid in alcoholic solution. Like nicotine shikimate, this salt could not be crystallized from alcohol, acetone, or a mixture of the two. When heated with pinric acid, a picrate with the same melting point as nicotine picrate (219-220°) was obtained. Evidently, acetone shikimic acid was split off in the reaction and nicotine picrate was formed instead.

Pilocarpine Acetone Shikimate. This was prepared by heating the base with the acid dissolved in alcoholic solution. The salt crystallized in plates and needles from a mixture of acetone and alcohol. It melted at 115-117°.

The nitrogen content was determined by the Kjeldahl method:

1. 0.1989 Gm. sample yielded 0.01324 Gm. N corresponding to 6.66 p.c. N.

2. 0.1101 Gm. sample yielded 0.00757 Gm. N corresponding to 6.87 p.c. N.

Calculated for

$C_{11}H_{16}O_2N_2 \cdot C_6H_6(OH)(O_2 \cdot Ce\ (CH_3)_2)COOH$ is 6.65 p.c. N.

Cinchonidine Acetone Shikimate. This was prepared in the usual manner. The salt was obtained in the form of needles from a mixture of alcohol and acetone. It melted at 128-129°.

The nitrogen content was determined by the Kjeldahl method.

0.1196 Gm. sample yielded 0.00654 Gm. N corresponding to 5.47 p.c. N.

Calculated for

$C_{19}H_{22}ON_2 \cdot C_6H_6(OH)(O_2 \cdot Ce\ (CH_3)_2)COOH$ is 5.51 p.c. N.

The acetone shikimates of ephedrine, cocaine, atropine, homatropine, eptechin, hyoscyamine, and physostigmine were prepared, following the method generally employed. Each All of them were amorphous, jelly-like masses which could not be crystallized from acetone, alcohol, or a mixture of the two.

Triacetyl Shikimic Acid.[1]

Two methods were tried:

I. Sixty cc. of acetic anhydride were heated with 20 grams of shikimic acid under a reflux condenser on a water bath for 24 hours. The unchanged anhydride and acetic acid were removed by distilling in an oil bath under reduced pressure (water pump) until nothing more distilled over (temp. of oil in bath was about 140°). While still hot, the residue was poured into a beaker. An amorphous, semi-solid was obtained after cooling. Every attempt to crystallize the compound failed.

II. Two grams of shikimic acid (1 mol.), dissolved in 10 cc. of pure pyridine, were treated with 3.2 grams of acetyl chloride (3.5 mols.), the chloride being added with vigorous stirring to the well cooled mixture. After all of the acetyl chloride had been added, the mixture became semi-solid owing to the separation of pyridine hydrochloride. After standing over night, an excess of dilute sulphuric acid (10 p.c.) was added to the mixture, and the acetyl derivative was separated from the soluble pyridine salts by means of ether extraction. The extract was washed thoroughly, first with diluted acid, and then with water. The ether was removed, and a semi-solid remained just as that obtained in experiment I.

The acid value of the product was found to be 188.6 and 187.2 in two determinations, whereas the theoretical acid

value for triacetyl shikimic acid is 186.9.

Solubility Tests.

Solvent	Cold	Hot
Water	•	very slightly
Alcohol	•	+
Chloroform	+	+
Petroleum ether	•	slightly
Benzol	+	+
Ethyl acetate	+	+
Ether	+	+

Tribenzoyl Shikimic Acid. S.Y. Chem[8] attempted to benzoylate shikimic acid according to the Schotten-Baumann method, but obtained no satisfactory results. Repetition of his experiments was equally unsuccessful. However, in pyridine solution the reaction runs smoothly with an almost quantitative yield.

To a solution of 2 grams (1 mol.) of shikimic acid in 10 cc. of of pyridine (solution chilled in an ice bath) 4.65 grams (3 mols.) of benzoyl chloride were added while shaking the reaction mixture vigorously. Pyridine hydrochloride crystallised out. After having stood over night, the pyridine was dissolved in diluted (10 p.c.) sulphuric acid, leaving the tribenzoyl shikimic acid. Washed with water and crystallized from alcohol, or dissolved in acetone and precipitated

therefrom with alcohol, the product melted at 198-200°, but began to sinter at 165°.

The saponification value of the product was found to be 456.3 and 463.8 in two determinations (av. 459.9), whereas the theoretical saponification value for the dibenzoate is 461.1.

1) Eykman, J., Ber., 24, p. 1283, (1891).
2(Chen, S.Y., Am. Jour. Pharm., 101, p. 692, (1929).

Dibromshikimic Acid.

When the double bond of shikimic acid takes on bromine, dibromshikimic acid is formed. This dibromide was first prepared by Eykman[1] in 1891, with the melting point given as 188°. In 1929, S.Y. Chen[2] also reported the compound, but with a melting point of 214-215°. It is found that in the addition of bromine, both temperature and concentration of the aqueous shikimic acid solution must be controlled carefully, otherwise different results will be obtained (see bromolactone). By several trials, a procedure with a yield of about 65 p.c. of the theoretical was arrived at. It is as follows:

Twenty grams of shikimic acid were dissolved in 20 cc. of water with the aid of heat, and the solution was cooled in an ice bath to a temperature below 10°C. A calculated amount of bromine was added from a dropping funnel, drop by drop, shaking vigorously after each addition. When all the bromine had been added, the whole contents were stirred with a mechanical stirrer for one hour. After having stood over night, the dibromide came out; filtered with suction, washed with ether or chloroform, it was recrystallized from alcohol. The yield was about 25 grams.

The dibromide crystallizes from aldohol in rhombic sphenoids melting at 187-188°. Its conductivity constant is reported as being about 100 times as large as that of shikimic

acid. It has a specific rotation of $[\alpha]_D$ = -58°. In strong alkaline solution, it reduces copper solution. It can be reconverted by zinc and acetic acid to shikimic acid.

Codeine Dibromshikimate. The salt was prepared as in the preparation of codeine shikimate. It crystallized from alcohol in long hexagonal prystals which melted at 272-273°.

Morpholine Dibromshikimate. This was prepared from morpholine and dibromshikimic acid by heating in alcoholic solution. After standing a few days, it crystallized out in leaf-like, shining plates which melted at 179-180°.

Bromo Lactone of Shikimic Acid.

As stated in the above preparation of dibromshikimic acid, if the temperature and aqueous concentration of shikimic acid varied, different compounds may result. Thus, the brom_lactone can be prepared by the addition of bromine at a higher temperature and more dilute aqueous shikimic acid solution.

Instead of using 50 p.c. aqueous shikimic acid solution, a 10 p.c. solution was used, i.e., 5 grams of the acid were dissolved in 50 cc. of water, keeping the solution at room temperature. A calculated amount of bromine was slowly added while shaking. After all the bromine had been added and absorbed, the whole contents were stirred for one hour. Then the stirring was continued for another hour, keeping the temperature at 80°C. At the end of the experiment, the color of

the mixture became slightly yellow. It was then concentrated on a water bath to one-fourth of its volume and allowed to stand over night, or several days if necessary. Brom lactone came out as beautiful hemimorphic hexagonal needles. It can be recrystallised from water. M.p. 235-236°. It scarcely reduces copper solution, but forms silver bromide upon treatment with silver nitrate.

Brom lactone can also be obtained by evaporating aqueous dibromide solution, or better, by the action of silver oxide on the dibromide solution. This was described in 1891 by Eykman, but no full procedure was given.[3]

1) Eykman, J., Ber., 24, p. 1278, (1891).
2) Chen, S.Y., Am. Jour. Pharm., 101, p. 692, (1929).
3) Eykman, J. Ber., 24, p. 1278, (1891).

Bibliography.

Eykman (Eijkman), J.F. 1881.

Mitteilungen d.d. Ges. f. Natur - u. Voelkerkunde Ostasiens, XXIII. (Ber., 14, p. 1720). (Pharm. Jour. 40, pp. 1046 and 1066).

Eykman, J.F. 1885.

Sur les principes constituants de l'Illicium religiosum (Sieb.) (Shikimi - no - ki en japonais).

Rec. des Trav. Chim. des Pays-Bas 4, p. 32.

From the Pharmaceutical Laboratory at Tokio, the suther reports on the constituents obtained from the volatile oil of the leaves and unripe fruits (eugenol, shikimol, or safrol, and shikimene) and those obtained from the aqueous extract after distillation (protocatechuic acid, shikimic acid, and shikimipicrine). Of the shikimic acid, he reports the elementary analysis and angle of rotation.

Eykman, J.F. 1886.

Sur l'Illicium religiosum.

Rec. des Trav. Chim. des Pays-Bas, 5, p. 299.

The suther reports on the isolation of shikimic acid, $C_7H_{10}O_5$, from the fruit of Illicium anisatum.

Oswald, Ferd. 1891.

Ueber die Bestandteile der Fruechten des Sternanis.

Arch. d. Pharm., 229, p. 84.

After the removal of both the volatile and fatty oils, the author isolated from the aqueous extract protocatechuic and shikimic acids (p. 103) previously discovered by Eykman: elementary analysis, Ca, Sr, and Ba salts; non-convertibility into quinic acid, reduction with HI, oxidation with MnO_2 and H_2SO_4, dry distillation of calcium salt.

Eykman, J.F. 1891.

Ueber die Shikimisaeure.

Ber., 24, p. 1278.

In an endeavor to determine the constitution of shikimic acid, the author determined the following physical constants:

Electrical conductivity

Heat of neutralisation

Optical rotation

Crystalline form

He also prepared the following derivatives:

Triacetylshikimic acid (p. 1284)

Tripropionyl shikimic acid (do)

Tributyril shikimic acid (do)

HCl and HBr gave no crystalline derivatives (p. 1286)

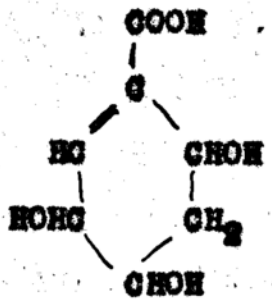
Hydroshikimic acid (p. 1287)

Dibromshikimic acid (p. 1290)

Brom lactone (p. 1292)

Dihydroxyshikimic acid (p. 1294)

He assumes that the following formula expresses the structure of the acid:



Siersch, Editha 1928.

Zur Mikrochemie von Illicium verum Hook. und Illicium religiosum Sieb.

Ph. Zentrh., 69, pp. 581 and 601.

After a critical review of the literature (See p. 504) for references), the auther reports her own experiments on:

1) The detection of shikimic acid (p.584)

2) Extraction of the seeds (p. 601)

She arrives at the following conclusions:

1) Illicium religiosum contains much more Shikimic acid than I. verum.

2) The seeds of both plants are devoid of shikimic acid.

Chen, S.Y. 1929.

Illicium religiosum Siebold. Nang Tsao. A phytochemical study. Am. Jour. Pharm., pp. 550, 622, and 686 (reprint, p. 43.).

A general phytochemical study of the drug with a bibliography of the literature thereon.

Yamashita, T., and Sato, F. 1930.

Shikimin-saeure aus der Blaetter von Gingko biloba, L. Jour. Pharm. Soc. Jap., 50, p. 19 (also 113). (Chem. Abstr., 24, p. 2739; Jahr.)

Extraction with ether yielded shikimic acid; $C_7H_{10}O_5$; m.p. 184-185°; $[\alpha]_D^{52°}$ -181.48°. The ammonium salt and the acetyl derivative were prepared. It adds bromine, and oxidation yields a compound, m.p. 174-175° (probably dihydroxy-shikimic acid).

Fischer, H.O.L., and Dangschat, G. 1934.

Konstitution der Shikimic Saeure (5. Mitteilung ueber Chinasaeure u. Derivate).

Helv. Chim. Acta, 17, pp. 1200-1206.

By a series of reactions analogous to those employed in the degradation of quinic acid, the positions of the double linkage and the three hydroxy groups in the trihydroxy-tetrahydro-benzoic acid , shikimic acid, have been demonstrated.

The following derivatives were prepared:

Methyl shikimate (m.p. 113-114°)

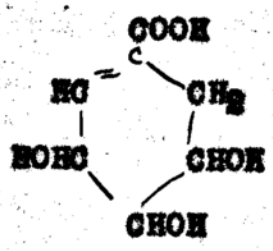
Methyl dihydroshikimate (colorless oil)

Dihydroshikimic acid (m.p. 176-178°)

Acetone methyl dihydroshikimate (b.p. 145-150°)(bath) 10.2 mm.

Monobenzoate of acetone methyl dihydroshikimate (m.p. 121°)

The structure was suggested as:



Fischer, H.O.L., and Dangschat 1935.

Abbau der Shikimisaeure zur Aconitsaeure (6. Mitteilung ueber Chinasaeure und Derivate).

Helv. Chim. Acta, 18, pp. 1204-1206.

By means of careful oxidation, using HIO_3, the authors obtained about 55 p.c. yield of aconitic acid from shikimic acid.

Fischer, H.O.L., and Dangschat 1935.

Zur Konfiguration der Shikimisaeure pp. 1206-1213 (7. Mitteilung ueber Chinasaeure und Derivate).

As a result of various reactions and numerous derivatives, the configuration of shikimic acid was proposed by the authors. The following derivatives were prepared:

Dihydroshikimic acid

Triacetyl dihydroshikimic acid

Triacetyl dihydroshikimic anhydride

Triacetyl dihydroshikimic anilide

Dihydroshikimic acid lactone

Diacetyl dihydroshikimic acid lactone

Acetone shikimic acid

Triacetyl shikimic acid

Methyl propylidene shikimate

Toluene sulphonate of methyl isopropylidene shikimate

Mono-toluene sulphonate of methyl shikimate

Benzoyl methylisopropylidene shikimate

Benzoyl methyl dihydro-isopropylidene shikimate

Mono-benzoyl methyl shikimate

Isopropylidene shikimamide

Mono-acetyl isopropylidene dihydroshikimamide

Mono-benzoate of isopropylidene dihydroshikimic acid . nitrile.

Fischer, H.O.L., and Dangschat, G. 1937.

Quinic Acid and Derivatives (Configuration of Shikimic Acid and degradation to Glucodesonic Acid).

Helv. Chim. Acta, 20, pp. 705-716. (Chem. Abst., 21, p. 7862).

The position of the double bond in shikimic acid relative to the acetonizable pair of hydroxy groups has been established. The optical relationship between the three hydroxy groups of shikimic acid and those of dextrose was pointed out. The following derivatives were prepared by the authors:

Methyl mono-acetyl isopropylidene shikimate

Methyl mono-acetyl isopropylidene pentahydroxy hexahydro-benzoate.

Triacetyl derivative of methyl mono-acetyl isopropylidene pentahydroxy hexahydro-benzoate.

Author Index.

Subject Index.

Toxic principle. K.K. Chen '26, p. 861.

S.Y. Chen '29, pp. 29 and 40.

Triacetyl shikimic ac. Eijkman '91, p. 1284.

Tributyl shikimic ac. Eijkman '91, p. 1284.

Tripropionyl shikimic ac. Eijkman '91, p. 1284.

Approved by Edward Kemers

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