

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Alkaloids of Papaveraceous Plants. XXXIV. *Hunnemannia fumariaefolia* Sweet and the Constitution of a New Alkaloid, Hunnemanine

BY RICHARD H. F. MANSKE, LÉO MARION AND ARCHIE E. LEDINGHAM

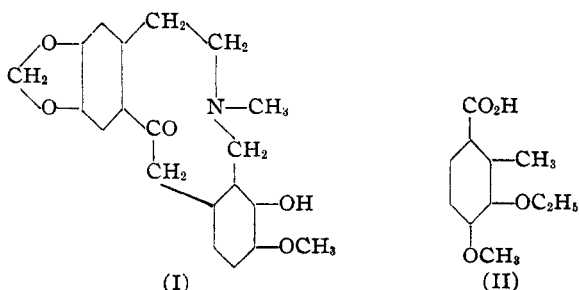
Hunnemannia is a mono-typic genus being represented only by *H. fumariaefolia* Sweet, the so-called tulip poppy. It is native to Mexico and has been successfully introduced into more temperate regions as an ornamental.

There seems to be no record of this plant having been chemically examined. Such an examination seemed to the authors particularly interesting on account of the lone position which the plant occupies in the *Papaveraceae* family.

Four alkaloids have been isolated, two of which, namely protopine and allo-cryptopine, are well-known constituents of many plants of the same family. The remaining two alkaloids appear to be new. One of these, *alkaloid F58*, is non-phenolic and is best represented by $C_{22}H_{21}O_5N$ containing two methoxyl groups. The amount available was too small for further immediate investigation. The second of the new alkaloids (F59) is now termed *hunnemanine* and its constitution has been determined. It is empirically represented by $C_{20}H_{21}O_5N$. It is a mono-hydric phenol, one methoxyl group is present, and on methylation with diazomethane it yields allo-cryptopine ($C_{21}H_{23}O_5N$). This simple observation establishes that hunnemanine is one of the two possible O-desmethyl-allo-cryptopines. That the free hydroxyl is in the sterically hindered 9-position in analogy with many other phenolic alkaloids was highly probable. On this assumption formula (I) has been adopted as a basis for degradative and subsequent synthetic experiments. The deg-

O-ethyl ether of hunnemanine on subjection to the necessary series of reactions yielded two fragments. Since the isolation of one of these, 4,5-methylenedioxy-2- β -dimethylaminoethylbenzaldehyde, could give us no new information, it was not exhaustively purified. The second fragment was isolated in a pure condition and shown by a synthesis to be 2-methyl-3-ethoxy-4-methoxybenzoic acid (II), thus proving formula (I) for hunnemanine. It is pertinent to point out that this alkaloid is the first known example of a phenolic base of the protopine type. The synthesis of the above acid was effected by a very simple route but not until a variety of previous attempts had failed. Oxidation of the mono-basic acid to the known 3-ethoxy-4-methoxyphthalic acid was not practical on account of the small amount available.

The successful synthesis of the above acid was readily achieved by oxidizing the corresponding aldehyde. The synthesis of the aldehyde from 2-ethoxy-3-methoxytoluene proceeded smoothly and with good yield by Gattermann's method. It is worthy of note that in this synthesis the sole product was the desired one since the acid obtained from the crude aldehyde was pure even without recrystallization. It is to be observed in this connection that the nitration of 2,3-dimethoxybenzaldehyde gives the 6-nitro-derivative² almost exclusively, whereas the nitration of 2-ethoxy-3-methoxybenzaldehyde yields for the most part the 5-nitro-compound.³ It is, of course, obvious that the synthetic and degradative acids cannot be identical unless the assigned formula is the correct one. The 2-ethoxy-3-methoxytoluene was prepared by the Clemmensen reduction of the corresponding aldehyde which was obtained by ethylating 2-hydroxy-3-methoxybenzaldehyde. For the last the authors are greatly indebted to the Monsanto Chemical Co., St. Louis, Missouri, who generously donated a liberal amount of it.



radation of alkaloids of this nuclear type as represented by cryptopine is readily carried out by the procedure first detailed by Perkin,¹ but the yield of the final products is not always good. The

Experimental

Isolation of the Alkaloids.—The plant material for this investigation was grown in part in a local garden. The

(1) Perkin, *J. Chem. Soc.*, **100**, 815 (1916).

(2) Perkin and Robinson, *ibid.*, **105**, 2389 (1914).

(3) Davies and Rubenstein, *ibid.*, **123**, 2839 (1923).

greater portion, however, was kindly supplied by Bodger Seeds, Limited, El Monte, California, and special thanks are due to Miss Elizabeth M. Bodger of this firm who personally supervised the collecting and drying of the material. There was available a total of 12 kg. which included the roots. Nearly all of the material was collected during the early flowering stages of the plant. In the course of the chemical examination of the plant it was observed that there were present practically no alkaloids whose hydrochlorides were extractable from aqueous solution by means of chloroform. The procedure devised by one of us⁴ yielded only two fractions, namely, -BS, non-phenolic bases (protopine, allo-cryptopine, and alkaloid F58) and BSE + EES, phenolic bases (hunnemanine).

Protopine and Allo-cryptopine.—The dried base, representing fraction BS, was boiled with methanol and the protopine which then crystallized was filtered off. After recrystallizing it from chloroform-methanol the protopine was obtained in brilliant colorless crystals melting at 209–210° either alone or in admixture with an authentic specimen. Including a small amount obtained from the mother liquor the total yield of protopine was 0.14%.

The methanolic filtrate from the protopine was filtered with the aid of charcoal and evaporated somewhat. The crystals which then separated consisted primarily of allo-cryptopine with some protopine. The mixture was dissolved in dilute hydrochloric acid and the sparingly soluble protopine hydrochloride which then separated was filtered off. The filtrate was basified and the separated base recrystallized from chloroform-methanol. It then melted at 160° either alone or in admixture with an authentic specimen of allo-cryptopine. The yield was 0.03%.

Alkaloid F58.—The final mother liquor from which no more protopine or allo-cryptopine could be crystallized was acidified with hydrochloric acid, boiled to expel the solvents, filtered, basified with ammonia, and the liberated base extracted with ether. The washed extract was evaporated to dryness and the resin treated with an excess of oxalic acid in methanol. The sparingly soluble oxalate which then separated in orange colored plates was converted to free base by shaking with ammonia in the presence of ether. The washed ether solution left a colorless resinous base which crystallized in contact with methanol. The washed base (alkaloid F58) was recrystallized from chloroform-methanol and then consisted of aggregates of colorless fine prisms melting at 174°. It dissolved in sulfuric acid to yield an orange colored solution which changed to a dirty pink color only on heating to a high temperature. Found: C, 69.48, 69.27; H, 5.35, 5.23; N, 3.50, 3.77; OCH₃, 18.39, 18.37. Calcd. for C₂₂H₂₁O₅N: C, 69.65; H, 5.54; N, 3.69; OCH₃, 16.36.

Hunnemanine.—The phenolic base (BSE) precipitated by means of carbon dioxide from its solution in an excess of aqueous sodium hydroxide was dried and boiled with methanol. The cooled mixture was filtered and the crystalline solid recrystallized first from chloroform-methanol and then from a large volume of boiling methanol. Hunnemanine was thus obtained in large colorless rectangular prisms which melted at 209°. A trace of the alkaloid dissolved in sulfuric acid yielded an intensely lilac colored

solution which on gentle heating changed to an olive color. Found: C, 67.95, 67.63; H, 5.93, 5.76; N, 3.51, 3.91; OCH₃, 9.19, 9.27. Calcd. for C₂₀H₂₁O₅N: C, 67.60; H, 5.92; N, 3.94; OCH₃, 8.73. The total yield of hunnemanine was 0.18%.

A small portion of the base was methylated by treating its suspension in methanol with an ethereal solution of diazomethane. The alkaloid dissolved as the brisk evolution of nitrogen proceeded. The non-phenolic product isolated in the usual way was recrystallized from hot methanol and then melted sharply at 160°. In admixture with allo-cryptopine it melted at the same temperature. Calcd. for C₂₁H₂₃O₅N: OCH₃, 16.62. Found: OCH₃, 17.46, 17.53.

Hunnemanine-O-ethyl Ether.—The ethylation of hunnemanine suspended in absolute ethanol was carried out with an ethereal solution of diazo-ethane. The yield was not quite quantitative but no difficulty was experienced in obtaining the non-phenolic base in a pure condition. When recrystallized from hot methanol it was obtained in colorless stout prisms which melted sharply at 168°. From 5 g. of the phenolic base there was obtained 4.3 g. of the ethyl ether. Calcd. for C₂₂H₂₅O₅N: OCH₃ + OC₂H₅ as OCH₃, 16.19. Found: OCH₃, 16.72, 16.82.

Hunnemanine-O-ethyl Ether Methosulfate.—Hunnemanine-O-ethyl ether was added to freshly distilled methyl sulfate and the mixture kept on the steam-bath for thirty minutes. The mixture was then cautiously heated over a small flame until the few remaining crystals had dissolved. The resulting thick, dark sirup was dissolved in a little boiling ethyl acetate, from which solution the methosulfate crystallized in colorless needles melting at 196°.

Tetrahydromethylhunnemanine-O-ethyl Ether.—The methosulfate dissolved in 5% sulfuric acid was reduced with sodium amalgam according to the procedure of Perkin.¹ The product consisted of a thick, light-brown, oily base.

Anhydrotetrahydromethylhunnemanine-O-ethyl Ether.—The oily tetrahydromethylhunnemanine-O-ethyl ether was refluxed for thirty minutes with acetyl chloride. After removal of the excess acetyl chloride, the oily residue was dissolved in hot water, the solution filtered, basified with strong sodium hydroxide and the precipitated base extracted with ether. The ether extract was washed with water and dried over anhydrous potassium carbonate. The oily residue from this solution did not crystallize and failed to yield a crystalline picrolonate.

Oxidation of Anhydrotetrahydromethylhunnemanine-O-ethyl Ether.—Anhydrotetrahydromethylhunnemanine-O-ethyl ether (1.29 g.) was dissolved in purified acetone (100 cc.) and the stirred and cooled (3°) solution treated with finely ground potassium permanganate (1.3 g.) added in small portions. When the oxidation had been completed, the mixture was filtered and the solid washed with acetone. The combined filtrate and washings were distilled under diminished pressure and the viscous residue dissolved in ether. The filtered ether solution was extracted repeatedly with small quantities of dilute acid (1 vol. hydrochloric acid: 3 vol. water), washed with water and extracted with two portions of dilute sodium hydroxide. The combined sodium hydroxide solutions were acidified with hydrochloric acid and the precipitated acid collected in ether.

(4) Manske, *Can. J. Research*, **8**, 210 (1933).

(5) All melting points are corrected.

The ether solution was washed with water, dried over sodium chloride and distilled. The crystalline residue after repeated recrystallization from ether-hexane was finally obtained as short white needles melting at 175°. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.88; H, 6.88. A further quantity of the same acid was obtained by digesting with hot water the manganese dioxide sludge which had been filtered out. The aqueous solution was evaporated down to a volume of ca. 25 cc. and acidified with hydrochloric acid. The chalky precipitate was filtered, dissolved in 5% sodium bicarbonate, the solution filtered and again acidified with hydrochloric acid. The precipitate was dissolved in dilute ammonia and boiled thirty minutes with a little barium chloride. The insoluble barium salt which precipitated was filtered out and the filtrate acidified and extracted with ether. The ether solution, after washing and drying, yielded an acid melting at 168° which after several recrystallizations from ether-hexane melted at 175° and was identical with that obtained as above. A mixture of this acid with a synthetic specimen of 2-methyl-3-ethoxy-4-methoxybenzoic acid melted at 176–177°.

2-Ethoxy-3-methoxy-toluene.—A mixture of 2-ethoxy-3-methoxybenzaldehyde (50 g.), amalgamated zinc (100 g.), toluene (100 cc.) and hydrochloric acid (275 cc.) was boiled under reflux for twenty-four hours. The separated toluene solution was washed with successive portions of aqueous sodium bisulfite, the solvent distilled off, and the residue fractionated *in vacuo*. The portion boiling at 72–74° (4 mm.) weighed 20 g. and consisted substantially of 2-ethoxy-3-methoxytoluene. Calcd. for $C_{10}H_{14}O_3$: C, 72.29; H, 8.43. Found: C, 71.56; H, 8.82.

2-Methyl-3-ethoxy-4-methoxybenzaldehyde.—Aluminum chloride (25 g.) was added to a cooled solution of 2-ethoxy-3-methoxytoluene (17 g.) in dry benzene (50 cc.). To the stirred and cooled mixture was then added anhydrous hydrogen cyanide (17 g.), and a stream of dry hydrogen chloride passed in to saturation. The temperature was then raised to 40° and maintained there for two hours. After remaining at room temperature overnight, the mixture was decomposed with ice, and the aldehyde distilled in a current of steam. It was extracted from the distillate and fractionated *in vacuo*. As thus obtained 2-

methyl-3-ethoxy-4-methoxybenzaldehyde was a colorless oil boiling at 121–123° (3 mm.). On cooling it formed a mass of colorless needles which when pressed out on filter paper melted at 24°. The yield was 14 g. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.35; H, 7.65.

The *oxime* was prepared in aqueous methanol and recrystallized from ether-hexane. It consisted of colorless pearly plates melting at 88°. Calcd. for $C_{11}H_{13}O_3N$: C, 63.15; H, 7.18; N, 6.70. Found: C, 63.36; H, 7.05; N, 7.09.

2-Methyl-3-ethoxy-4-methoxybenzoic Acid.—A suspension of the aldehyde in warm water was vigorously stirred and treated with a saturated solution of potassium permanganate until the color was permanent for five minutes. The solution was then boiled, filtered, decolorized with a little sulfur dioxide, and while still warm acidified with hydrochloric acid. The filtered, washed, and dried acid melted at 176°. It was recrystallized from hot acetone, in which it is only moderately soluble. The large brilliant highly refracting plates thus obtained melted sharply at 177°. The yield was virtually quantitative. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.02; H, 6.83.

Summary

Hunnemannia fumariaefolia Sweet has yielded four alkaloids, two of which, protopine and allo-cryptopine, are well known. A third, *alkaloid F58*, represented as $C_{22}H_{21}O_5N$, was obtained in only minute amounts. The main alkaloid now termed hunnemanine, $C_{20}H_{21}O_5N$, is phenolic, contains one methoxyl group, and on methylation yielded allo-cryptopine. O-Ethylation gave a non-phenolic base which on appropriate degradation yielded 2-methyl-3-ethoxy-4-methoxybenzoic acid, identical with a specimen synthesized for purposes of comparison. Hunnemanine is therefore 9-desmethyl-allo-cryptopine. It is the first alkaloid of the protopine type known to contain a free hydroxyl group.

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