[CONTRIBUTION FROM THE EXPERIMENTAL RESEARCH LABORATORIES, BURROUGHS WELLCOME AND COMPANY]

1,2-DIHYDROPAPAVERINE AND MODIFIED SYNTHESES OF PAPAVERINE AND PAPAVERALDINE (XANTHALINE)

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A number of investigations have been carried out on the reduction products of papaverine, but 1,2-dihydropapaverine or 6,7,3′,4′-tetramethoxy-1,2-dihydroprotopapaverine[1] (IV) has not been previously isolated. Pyman[2] described a compound of the same empirical formula, which he supposed to have the structure of the 1,2-derivative. Later[3] he modified this view on the basis of exhaustive methylation experiments, and assigned to it the structure (VIII), naming it Pavine.

The writer has obtained 1,2-dihydropapaverine by a rigid method and has established the structure. Homoveratroyl-ω-amino-acetoveratrone (I), prepared from homoveratroyl chloride and ω-amino-acetoveratrone, was cyclized by means of phosphorus oxychloride, yielding 6,7,3′,4′-tetramethoxy-4-keto-3,4-dihydroprotopapaverine (II). This compound on reduction gave 6,7,3′,4′-tetramethoxy-4-hydroxy-1,2,3,4-tetrahydroprotopapaverine (III), which on appropriate treatment lost the elements of water, 1,2-dihydropapaverine being formed (IV). The structure was established by its smooth reduction (catalytic) to the known tetrahydropapaverine[2] (VII), by its dehydrogenation to papaverine (IX) and by its oxidation to 6,7,3′,4′-tetramethoxy-9-keto-1,2-dihydroprotopapaverine (V), which in turn is readily converted into papaveraldine (VI) or 6,7,3′,4′-tetramethoxy-9-keto-protopapaverine. Papaveraldine is identical with the naturally-occurring alkaloid xanthaline.[4]

The dehydration of (III) to 1,2-dihydropapaverine was carried out by means of phosphorus pentachloride in cold chloroform solution. When heating with phosphorus pentoxide or oxychloride in toluene was employed, only the oxidized product (V) was isolated. The same product was also formed by air oxidation of solutions of 1,2-dihydropapaverine exactly as with 6,7,3′,4′-tetramethoxy-3,4-dihydroprotopapaverine.[5] The parallel is even closer, as 1,2-dihydropapaverine behaves exactly like the latter compound (3,4-dihydropapaverine) when heated with methyl alcoholic potash, both giving papaveraldine (VI).

It was hoped to obtain interesting derivatives from the compounds (II)

[1] The nomenclature of Buck, Perkin and Stevens, *J. Chem. Soc.*, **127**, 1462 (1925), is used except where well-established names exist.

[2] Pyman, *ibid.*, **95**, 1610 (1909).

[3] Pyman and Reynolds, *ibid.*, **97**, 1320 (1910); Pyman, *ibid.*, **107**, 176 (1915).

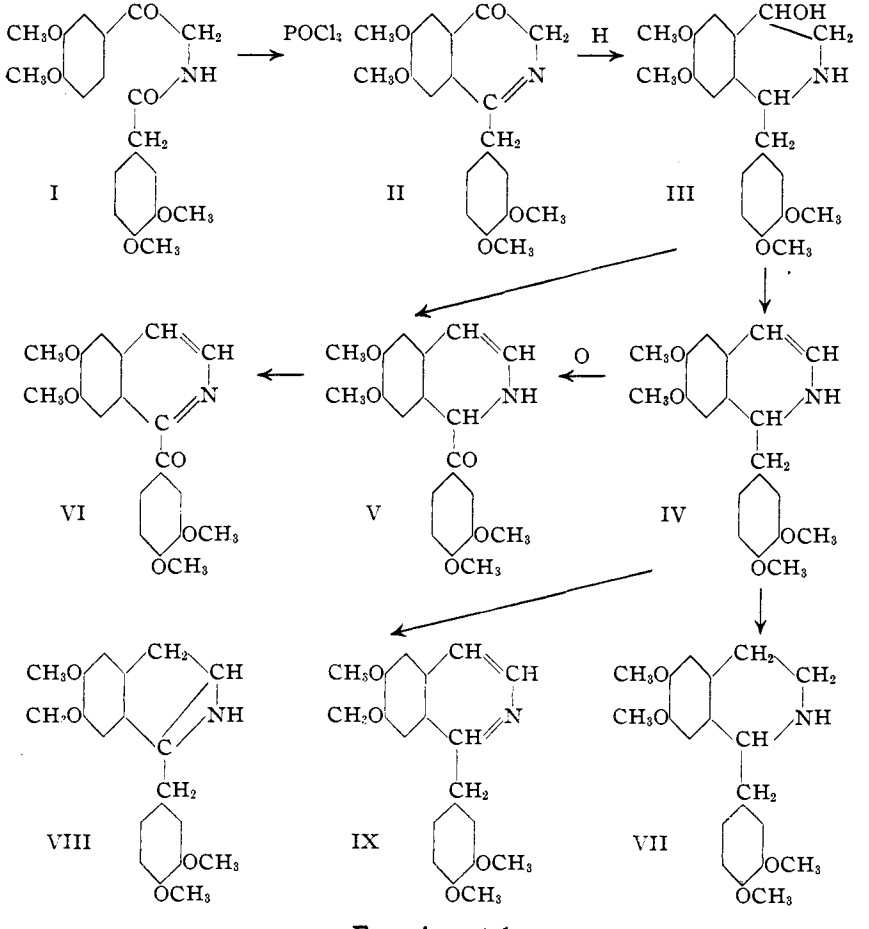
[4] Dobson and Perkin, *ibid.*, **99**, 135 (1911).

[5] Buck, Haworth and Perkin, *ibid.*, **125**, 2176 (1924).

and (III) but they proved to be disappointingly inert. No derivatives of the carbonyl or hydroxyl groups were isolated, and the basic properties are so suppressed that the bases form no well-defined salts. Indeed (III) may be recrystallized unchanged from fairly strong hydrochloric acid.

1,2-Dihydropapaverine is conspicuous by its ready oxidizability in air, when in solution, and by its very insoluble perchlorate. But for this salt it is doubtful whether 1,2-dihydropapaverine could have been isolated in the pure state.

It will be seen that the isolation of papaverine and papaveraldine (xanthaline) in the above series of reactions constitutes new syntheses of these substances.



Experimental

Homoveratroyl-ω-amino-acetoveratrone (I) was prepared from homoveratroyl chloride and ω-amino-acetoveratrone and was found to be identical with the product of

Pictet and Gams.[6] In preparing homoveratric acid[7] it is advantageous to carry out the oxidation of dimethoxyphenylpyruvic acid with 10% or stronger hydrogen peroxide in the presence of ice, and to recrystallize the acid from benzene.

6,7,3',4'-Tetramethoxy-4-keto-3,4-dihydroprotopapaverine (II).—Twenty grams of homoveratroyl-ω-amino-acetoveratrone, 40 cc. of phosphorus oxychloride and 100 cc. of toluene were boiled for forty-five minutes, cooled and petroleum ether added until no more oil separated. The supernatant liquor was decanted, the oil dissolved in alcohol and sodium hydroxide solution added until the mixture was strongly alkaline. The product separated as an oil and soon solidified; yield almost theoretical. Recrystallized from alcohol the compound forms a white felted mass of slender needles, slightly soluble in cold alcohol and moderately soluble in hot. It is insoluble in water, but readily soluble in cold benzene; m. p. 116–117° (uncorr.). The solution in hydrochloric acid is pale yellow and the solution in chloroform has a marked bluish fluorescence.

With cold concentrated sulfuric acid the solid turns bright blue and gives a blue solution which becomes intensely violet on heating. A crystal of potassium nitrate added to the cold solution gives a deep claret color, changing to crimson. Luchini's reagent gives an orange-brown color, changing to greenish-black, Wenzell's reagent, transient violet, becoming golden: Erdmann's reagent, intense red; Mandelin's reagent, golden brown, greenish on heating: Fröhde's reagent, violet, blue on heating.

It was difficult to obtain concordant analyses on this compound, micro-analyses being usually high and macro-analyses usually low.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.54; H, 5.67; N, 3.94; mol. wt., 355. Found: C, 67.45; H, 5.99; N, 3.84; mol. wt., 335, 343.

Methiodide.—This was prepared by heating with benzene and methyl iodide in a sealed tube at 100° for two hours. It forms faintly yellow thin square plates, m. p. 202° (uncorr.) with frothing.

Anal. Calcd. for $C_{21}H_{24}O_5NI$: C, 50.7; H, 4.8. Found: C, 50.5; H, 4.8.

6,7,3,'4'-Tetramethoxy-4-hydroxy-1,2,3,4-tetrahydroprotopapaverine (III).—It was not found possible to reduce the compound (II) successfully with the usual reagents, such as zinc and sulfuric acid, etc. Ultimately a very active catalyst (platinic chloride in hydrochloric acid with the addition of platinum oxide and Skita catalyst) was prepared. This readily caused the absorption of four atoms of hydrogen (acetic acid with hydrochloric acid as solvent). No stage corresponding to two atoms of hydrogen was isolated. After the catalyst had flocculated, the solution was evaporated under reduced pressure, the residue dissolved in methyl alcohol and treated with ammonia. The product crystallizes out on standing. Recrystallized from alcohol, the compound forms white, bulky aggregates of crystals (thin rectangular plates) melting at 123° (uncorr.). It is slightly soluble in hot water, readily soluble in hot alcohol and moderately soluble in hot toluene.

With cold concentrated sulfuric acid the compound gives a colorless solution, becoming pale amethyst on warming. Addition of a crystal of potassium nitrate to the cold acid solution produces an orange-brown color. Luchini's reagent gives a pale gold color; Wenzell's reagent, violet changing to gold; Erdmann's reagent, light golden; Mandelin's reagent, greenish-gold; Fröhde's reagent, green, changing to deep brown.

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.85; H, 6.96. Found: C, 66.72; H, 7.21.

1,2-Dihydropapaverine (IV).—One gram of compound (III) dissolved in 10 cc. of chloroform was treated with 3 g. of phosphorus pentachloride and allowed to stand for forty-eight hours in the cold. The yellow magma which formed was added to crushed ice,

[6] Pictet and Gams, *Ber.*, **42**, 2943 (1909).

[7] Haworth, Perkin and Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

the chloroform layer separated, washed with water and sodium bicarbonate solution and evaporated under reduced pressure. The residual gum was taken up in acetic acid and 20% perchloric acid added. The sparingly soluble perchlorate was filtered off, washed, dried, suspended in benzene and a stream of dry ammonia passed in. After filtration and the addition of petroleum ether, a crop of crystals separated on standing in a refrigerator and was filtered off. The liquor slowly deposits the oxidized compound (V) (below). For this reason, any prolonged operations should be carried out in an atmosphere of inert gas. For analysis, the compound was recrystallized several times from dilute methyl alcohol, after it had been warmed with methyl alcoholic potash to remove impurities. 1,2-Dihydropapaverine forms a bulky white mass of crystals (narrow hexagonal plates) melting at 97–98° (uncorr.). It is easily oxidized in solution by air, or by strong hydrogen peroxide in acetone solution, to the compound (V). It is readily soluble in the usual solvents, sparingly soluble in petroleum ether and practically insoluble in water.

With cold concentrated sulfuric acid it gives a yellow-brown solution which becomes intensely bluish-violet on heating. A crystal of potassium nitrate added to the cold acid solution gives an intense golden-brown color. Boiling acetic anhydride slowly develops a light emerald-green color (see compound V). Luchini's reagent gives a deep red color; Wenzell's reagent, deep violet; Erdmann's reagent, orange-red; Mandelin's reagent, blood-red, golden on heating; Fröhde's reagent, yellow-green, becoming deep green, then violet on heating.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.38; H, 6.74. Found: C, 69.98; H, 6.99.

On catalytic reduction in hydrochloric–acetic acid solution, tetrahydropapaverine is produced. It was isolated and identified by means of the characteristic hydriodide, which was compared with an authentic specimen prepared by Pyman's method. A mixed melting point determination showed no depression.

The dehydrogenation of 1,2-dihydropapaverine went very smoothly when 0.4 g. was heated with 0.2 g. of palladium black[8] in an inert atmosphere for thirty minutes at 170–180°. The melt was extracted with 10% hydrochloric acid and the papaverine precipitated as iodide by the addition of potassium iodide. The iodide was recrystallized from alcohol and identified (properties and mixed melting point determination) by comparison with an authentic specimen, and was then converted into the base and similarly identified as papaverine.

1,2-Dihydropapaverine is very similar to 3,4-dihydropapaverine[5,6] and is best distinguished by means of its oxidation product (V), which shows considerable differences from that derived from the 3,4-compound.

Perchlorate.—This was prepared from the purified base and forms a sphaerocrystalline white powder, melting with blackening at 238° (uncorr.) after sintering. It is very sparingly soluble except in strongly acid solutions.

Anal. Calcd. for $C_{20}H_{23}O_4N \cdot HClO_4$: C, 54.36; H, 5.44. Found: C, 54.31; H, 5.74.

Picrate.—Prepared from the purified base, the picrate forms a lemon-yellow sphaerocrystalline powder, melting at 151° (uncorr.).

Anal. Calcd. for $C_{20}H_{23}O_4N \cdot C_6H_3N_3O_7$: C, 54.74; H, 4.56. Found: C, 54.39; H, 4.72.

6,7,3,'4'-Tetramethoxy-9-keto-1,2-dihydroprotopapaverine.—As already mentioned, this compound is produced by air-oxidation of 1,2-dihydropapaverine or by oxidation by strong hydrogen peroxide in acetone solution. When phosphorus pentoxide or oxychloride is used to remove water from (III), this compound is usually obtained. It

[8] *Cf.* Späth and Polgar, *Monatsh.*, **51**, 190 (1929).

forms a compact mass of thick, irregular prisms from alcohol, melting at 187° (uncorr.). It is moderately soluble in alcohol, soluble in chloroform, somewhat soluble in hot benzene and very sparingly soluble in ether. With cold concentrated sulfuric acid it forms a golden solution, which becomes intensely red on adding a crystal of potassium nitrate. It dissolves in hydrochloric acid with a golden color and in hot acetic anhydride with an intense deep-green color. Luchini's reagent gives a red color; Wenzell's reagent, transient violet; Erdmann's reagent, orange red; Mandelin's reagent, blood red, becoming golden on heating; Fröhde's reagent, brownish, blood-red when heated.

Anal. Calcd. for $C_{20}H_{21}O_6N$: C, 67.54; H, 5.67. Found: C, 67.22; H, 5.94.

When warmed on the steam-bath with methyl alcoholic potash, the compound rapidly changes into papaveraldine, identified by comparison and mixed melting point determinations with the authentic compound and with the alkaloid xanthaline.

Summary

1,2-Dihydropapaverine, hitherto unknown, has been synthesized and its structure established. In the course of the work, papaverine and papaveraldine have been obtained by a new series of reactions.

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AN IODIMETRIC METHOD FOR DETERMINING OXIDASE ACTIVITY[1]

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The usual methods for estimating oxidase activity depend on either the production of a colored substance,[2] or the measurement of the volume of oxygen absorbed.[3] Recently an electrometric method has been suggested.[4] Colorimetric methods are often inapplicable on account of pigments or turbidity in the extracts to be tested. Methods measuring the oxygen uptake require special apparatus. The method to be described here requires no unusual equipment, is easy to use and reasonably accurate. With it as many as sixteen determinations have been made at the same time.

In a previous paper,[5] it was noted that potato juice contains a substance or substances that may be titrated with iodine in acid solution (trichloroacetic acid) and that this titration decreases on exposure to air. Ordinarily five cc. of juice reduces about 0.5 cc. of $N/100$ iodine. However, juice from one lot of potatoes was found to reduce 2.0 cc. of $N/100$ iodine. It was thought that this might be due to a low content of oxidase, the substance responsible for the iodine reaction not being oxidized in the

[1] Herman Frasch Foundation for Research in Agricultural Chemistry, Paper No. 6.

[2] J. A. Dye, *Proc. Soc. Exptl. Biol. Med.*, **24**, 640–642 (1927).

[3] H. H. Bunzel, THIS JOURNAL, **34**, 303–316 (1912).

[4] A. E. Stearn and A. A. Day, *J. Biol. Chem.*, **85**, 299–306 (1929).

[5] F. E. Denny, L. P. Miller and J. D. Guthrie, *Am. J. Botany*, **17**, 483–509 (1930).