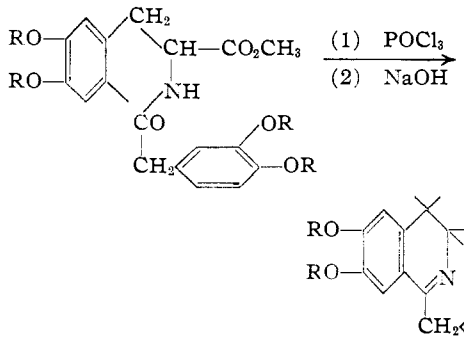
[CONTRIBUTION FROM GALAT CHEMICAL CORPORATION]

Synthesis of Papaverine and Some Related Compounds

BY ALEXANDER GALAT

A synthesis of 3,4-dihydropapaverine, the key intermediate in the syntheses of the three opium alkaloids, papaverine, papaveraldine and laudanosine, is reported. 3,4-Dimethoxyphenylpyruvic acid or α-(N-benzamido)-3,4-dimethoxycinnamic acid are converted by the reaction with ammonia into N-phenylacetyl-3,4-dimethoxyphenylalanine, which is cyclized *via* its methyl ester. 3,4-Dihydropapaverine is obtained by hydrolysis and decarboxylation. Perparine, a tetraethyl analog of papaverine, is prepared by a similar route.

Several 6,7-dialkoxy-3,4-dihydro-3-carboxy-(3′,-4′-dialkoxybenzyl)-isoquinolines were required in this Laboratory for pharmacological studies. These compounds were prepared from the corresponding substituted esters of N-phenylacetylphenylalanine by the conventional ring-closure with phosphorus oxychloride followed by hydrolysis

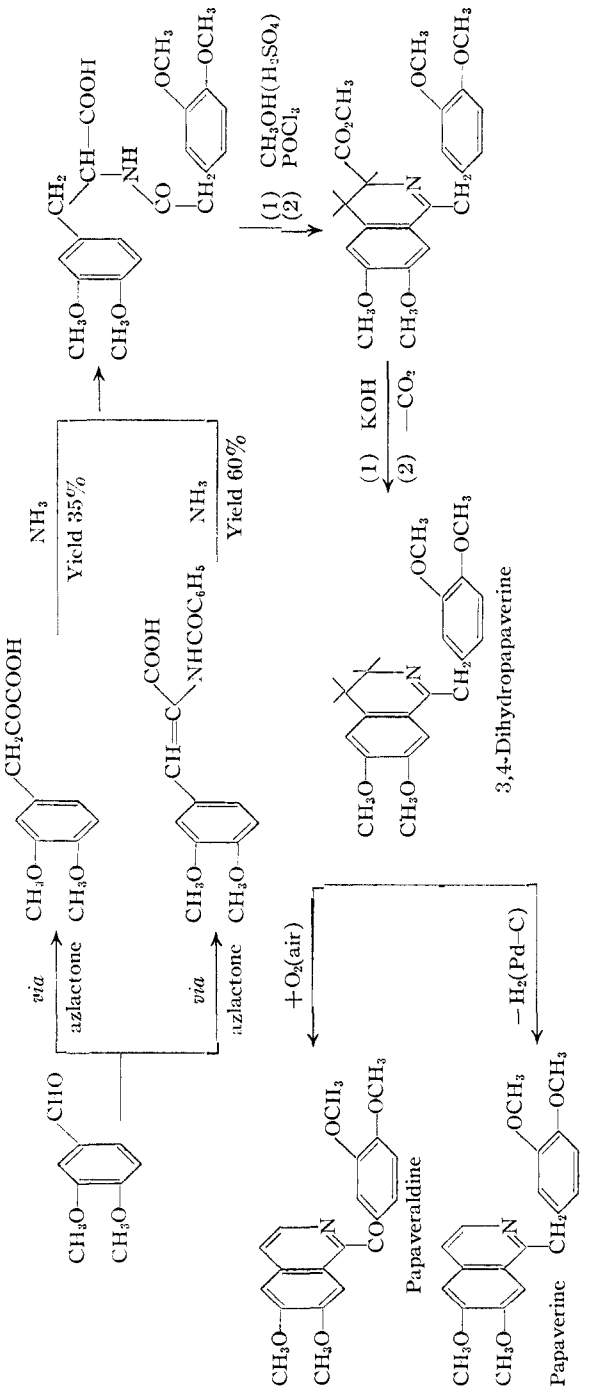


The preparation of the required phenylacetylphenylalanines was reported in a previous paper.[1]

This study was extended in order to include some compounds of biological and pharmacological importance. Thus, 6,7-dimethoxy-3,4-dihydro-3-carboxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline was decarboxylated to 3,4-dihydropapaverine, which is the key intermediate in the synthesis of laudanosine[2] and the penultimate compound in the syntheses of two other opium alkaloids, papaveraldine[3] and papaverine.[4,5] The synthesis of 3,4-dihydropapaverine, papaverine and papaveraldine is represented in the chart.

The tetraethyl analog of papaverine, perparin, which is reported to be more active as antispasmodic than papaverine, was synthesized by an analogous route. It has been recently prepared by a different method.[6]

In a recent communication Snyder and Werber have described a direct route from N-acylphenylalanines to isoquinolines by the use of polyphosphoric acid–phosphorus oxychloride mixture.[7] The application of this method, which appeared after the



(1) A. Galat, THIS JOURNAL, **72**, 4436 (1950).

(2) A. Pictet and M. Finkelstein, *Ber.*, **42**, 1979 (1909).

(3) J. S. Buck, THIS JOURNAL, **52**, 3610 (1930).

(4) K. Kindler and W. Peschke, *Arch. Pharm.*, **272**, 238 (1934).

(5) Shortly after our manuscript describing the new synthesis of 3,4-dihydropapaverine and papaverine had been submitted for publication[1] a communication appeared by H. Wahl (*Bull. soc. chim.*, **17**, 680 (1950)) reporting essentially the same method. However, since Wahl did not isolate or identify 3,4-dihydropapaverine nor provide any experimental data for its preparation, the synthesis of this compound is described in detail in the present paper. In addition, by the use of α-(N-benzamido)-3,4-dimethoxycinnamic acid instead of 3,4-dimethoxyphenylpyruvic acid in the key reaction of the synthesis we have been able to obtain appreciably higher yields than those reported by Wahl.

(6) J. Weijlard, E. F. Swanezy and E. Tashjian, THIS JOURNAL, **71**, 1889 (1949).

(7) H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2962, 2965 (1950).

present work had been completed, is now being investigated as a possible one-step route from N-(3′,4′ - dimethoxyphenylacetyl) - 3,4 - dimethoxyphenylalanine[1] to papaverine.

Experimental

N-(3′,4′-Dialkoxyphenylacetyl)-3,4-dialkoxyphenylalanines were prepared by the method described in a previous paper.[1] In the case of the tetramethoxy derivative (I), because of the very poor filtration properties of the diamide, it was found advantageous to hydrolyze the product to the free acid before its isolation:

N-(3′,4′-Dimethoxyphenylacetyl)-3,4-dimethoxyphenylalanine (I).—Thirty-two and seven-tenths grams (0.10 mole) of α-(N-benzamido)-3,4-dimethoxycinnamic acid, 70 ml. of concentrated ammonium hydroxide and 20 ml. of water was heated in a pressure bottle for 48 hours at 110°. The solution was transferred into a flask, 85 ml. of a 10% sodium hydroxide was added, the solution boiled under reflux for two hours, cooled and made strongly acid with hydrochloric acid. The oil which separated was washed once with water, dissolved in 30 ml. of hot isopropyl alcohol and the product precipitated with isopropyl ether. The crystals were filtered, washed with a mixture of isopropyl alcohol–isopropyl ether (1:1), then with ice-cold isopropyl alcohol and dried; yield 12 g. (60%), m.p. 153–155°. The product recrystallized from dioxane melted at 155–156° (lit.[5,8] 156–157°).

Methyl Ester of (I).—Methyl esters of phenylalanines were prepared in yields of over 90% following the procedure described for the ester of (I): Eight and four-tenths grams of (I) was dissolved in 45 ml. of methyl alcohol containing 0.5 ml. of concentrated sulfuric acid and the solution boiled under reflux for two hours. The ester, which crystallized on cooling, was filtered and washed with a small amount of cold methyl alcohol. The filtrate was re-used to esterify two more batches of (I). The combined weight of the ester from three runs, 8.4 g. of (I) each, was 24.9 g. (95.5%), m.p. 94–96° (lit.[5,9] 86–88°, 89–92°). Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{22}H_{27}O_7N$: C, 63.3; H, 6.47; N, 3.36. Found: C, 63.7; H, 6.30; N, 3.50.

N-(3′-Methoxy-4′-ethoxyphenylacetyl)-3-methoxy-4-ethoxyphenylalanine methyl ester melted at 88–90°.

Anal. Calcd. for $C_{24}H_{31}O_7N$: C, 64.7; H, 6.97; N, 3.15. Found: C, 64.5; H, 7.17; N, 3.25.

N-(3′,4′-Diethoxyphenylacetyl)-3,4-diethoxyphenylalanine methyl ester melted at 103–106°.

Anal. Calcd. for $C_{26}H_{35}O_7N$: C, 66.00; H, 9.50; N, 2.96. Found: C, 66.30; H, 9.41; N, 3.06.

N-(3′,4′-Methylenedioxyphenylacetyl)-3,4-methylenedioxyphenylalanine methyl ester melted at 118–120°.

Anal. Calcd. for $C_{20}H_{19}O_7N$: C, 62.40; H, 4.94; N, 3.64. Found: C, 62.66; H, 4.87; N, 3.80.

6,7-Dialkoxy-3,4-dihydro-3-carbomethoxy-1-(3′,4′-dialkoxybenzyl)-isoquinolines were prepared from the corresponding phenylacetyl-phenylalanine methyl esters by ring-closure with phosphorus oxychoride using the standard procedure.[3] The preparation of the tetramethoxy compound (II) is described:

6,7-Dimethoxy-3,4-dihydro-3-carbomethoxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline (II).—Ten grams of the methyl ester of (I), 25 ml. of phosphorus oxychloride and 50 ml. of toluene were boiled under reflux for 45 minutes. The solution was distilled *in vacuo* to dryness on a water-bath, the residue dissolved in 200 ml. of water, treated with charcoal in the cold and filtered. On the addition of ammonium hydroxide the isoquinoline precipitated. It was filtered, washed with water and dried; yield 8.82 g. (92%), m.p. 132–135°. Recrystallized from methyl alcohol, the product melted at 137–139° (lit.[5,9] 125–128°, 125–126°).

Anal. Calcd for $C_{22}H_{25}O_6N$: C, 66.00; H, 6.27; N, 3.51. Found: C, 66.30; H, 6.20; N, 3.65.

6,7-Dimethoxy-3,4-dihydro-3-carboxy-1-(3′,4′-dimethoxybenzyl)-isoquinoline (III).—Two grams of (II) was heated under reflux with 10 ml. of a 20% solution of potassium hydroxide in methyl alcohol. After ten minutes the solution was diluted with 25 ml. of water and acidified with acetic acid. The crystals were filtered upon cooling, washed with water and dried; yield 1.75 g. (91%), m.p. 140–143° (bubbles). The product recrystallized from isopropyl alcohol melted at 147–148° (bubbles) (lit.[5] 140°).

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.50; H, 5.98; N, 3.64. Found: C, 65.30; H, 5.75; N, 3.58.

3,4-Dihydropapaverine.—Five grams of (III) was heated at 150–155° in an oil-bath in an atmosphere of hydrogen. When the evolution of carbon dioxide ceased (five to ten minutes) the oil was allowed to cool in a current of hydrogen. The product was isolated as perchlorate by the method of Buck[3]: the oil was dissolved in 50 ml. of acetic acid and treated with 30 ml. of a 60% solution of perchloric acid. Upon dilution with water the perchlorate precipitated and was filtered, washed with dilute acetic acid, with water and dried. The dry material, 5 g., melted at 235–238° with decomposition (lit.[3] 238° dec.). The perchlorate was converted into the free base with ammonia gas in benzene.[3] The base had a melting point of 98–99° (lit.[3] 97–98°, 105°). The picrate melted unsharply at 160° (lit.[3] 151°).

Anal. Calcd. for $C_{20}H_{24}O_8NCl$ (perchlorate): C, 54.40; H, 5.44. Found: C, 55.00; H, 5.30.

Papaverine.—Ten grams of 3,4-dihydropapaverine, or 11.3 g. of (III), 1.0 g. of palladium-charcoal (10% Pd) and 15 ml. of tetralin was heated in an oil-bath at 240–250° in a current of nitrogen for three hours. The catalyst was removed by filtration, the filtrate cooled and seeded with papaverine. After about one hour the crystals of papaverine were filtered, washed with a small amount of cold tetralin and dried *in vacuo* at 50–60°; yield 9.0 g., m.p. 140°. The filtrate was reused once to treat another 10 g. of dihydropapaverine (or 11.3 g. of (III)) and yielded 9.6 g. of crude papaverine, m.p. 140°, bringing the yield to about 95% of the theoretical. The crude papaverine was recrystallized from isopropyl alcohol and gave a product melting at 146–147° (lit.[4,5] 145°, 147°). The hydrochloride melted at 231° (lit.[4] 231°) and the oxalate at 200–201° with decomposition (lit.[10] 201° dec.).

Papaveraldine was prepared by the method of Buck[3] by digesting 3,4-dihydropapaverine with alcoholic potassium hydroxide on a water-bath for several minutes. The base crystallized on cooling. It was filtered, washed with methyl alcohol and dried. It melted at 208° (lit.[8] 208°). The sparingly soluble hydrochloride had a melting point of 208–209° (lit.[3] 209°).

6-Methoxy-7-ethoxy-3,4-dihydro-3-carbomethoxy-1,3′-methoxy-4′-ethoxybenzyl)-isoquinoline was prepared by the same procedure as (II) and had a melting point of 149–150°.

Anal. Calcd. for $C_{24}H_{29}O_6N$: C, 67.50; H, 6.80; N, 3.28. Found: C, 67.80; H, 6.55; N, 3.10.

The free acid melted at 132–133° (dec.).

6-Methoxy-7-ethoxy-3-carbomethoxy-1-(3′-methoxy-4′-ethoxybenzyl)-isoquinoline was prepared from the preceding methyl ester by dehydrogenation with sulfur following the standard procedure[9] and had a melting point of 187–189°.

Anal. Calcd. for $C_{24}H_{27}O_6N$: C, 67.70; H, 6.36; N, 3.30. Found: C, 67.95; H, 6.30; N, 3.25.

6-Methoxy-7-ethoxy-(3′-methoxy-4′-ethoxybenzyl)-isoquinoline was prepared by decarboxylation of the corresponding acid (m.p. 180–182°) in methylnaphthalene at 240° in a current of carbon dioxide. The isoquinoline was extracted with dilute hydrochloric acid and precipitated with sodium carbonate. The product, after recrystallization from isopropyl alcohol, melted at 128–129°.

Anal. Calcd. for $C_{22}H_{25}O_4N$: C, 71.9; H, 6.81; N, 3.82. Found: C, 71.5; H, 6.77; N, 4.00.

The hydrochloride melted at 200° with decomposition.

Anal. Calcd. for $C_{22}H_{26}O_4NCl$: N, 3.47; Cl, 8.80. Found: N, 3.60; Cl, 8.90.

6,7-Diethoxy-3,4-dihydro-3-carbomethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline had a m.p. of 108–109°.

Anal. Calcd. for $C_{26}H_{33}O_6N$: C, 68.60; H, 7.25; N, 3.08. Found: C, 68.30; H, 7.00; N, 3.15.

The free acid melted at 132–133° with decomposition.

6,7-Diethoxy-3-carbomethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline was obtained by dehydrogenation of the dihydro methyl ester with sulfur and melted at 166°.

Anal. Calcd. for $C_{26}H_{31}O_6N$: C, 68.9; H, 6.84; N, 3.09. Found: C, 69.10; H, 7.10; N, 3.20.

(8) W. Kropp and H. Decker, *Ber.*, **42**, 1184 (1909).

(9) J. Redel and A. Bouteville, *Bull. soc. chim.*, **16**, 443 (1919).

(10) E. Späth and Berger, *Ber.*, **60**, 704 (1927).

The free acid melted at 172–173°.

6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline (perparine) was obtained by decarboxylation of the preceding acid in methylnaphthalene as described above. It melted at 93–95° (lit.[6] 95–96°).

Anal. Calcd. for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.35; N, 3.54. Found: C, 73.10; H, 7.78; N, 3.80.

126 BUCKINGHAM RD., YONKERS, N. Y.

RECEIVED JANUARY 3, 1951

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

Alkaloids from *Tripterygium wilfordii* Hook.—Wilforine and Wilfordine[1,2]

BY MORTON BEROZA

Wilfordine has been shown by countercurrent distribution to be a mixture of alkaloids. Two very similar alkaloids, designated wilforine and wilfordine, were isolated from the mixture by partition chromatography and proved pure by countercurrent distribution. The compounds are insecticidally active ester alkaloids which, upon saponification, yield 1 mole of benzoic acid, 5 moles of acetic acid, and 2 moles of steam-non-volatile acid per mole of compound.

Acree and Haller[3] have recently reported the isolation of wilfordine, an insecticidal alkaloid from the roots of *Tripterygium wilfordii* Hook. They found wilfordine to be an ester alkaloid consisting of a polyhydroxy nucleus esterified with 5 moles of acetic acid, 1 mole of benzoic acid, and 1 mole of a nitrogen-containing dicarboxylic acid; however, they reported that the formula for the sum of the component parts of wilfordine, $C_{43}H_{49}O_{18}N$, did not agree with the molecular formula, $C_{42}H_{47}O_{19}N$, calculated for the entire alkaloid. An investigation of the discrepancy was undertaken.

Although very little fresh root was available at the outset of this investigation, a large quantity of 9-year old root remained from previous work in this Bureau. Preparations of wilfordine, isolated from both fresh and old root, were compared with a sample kindly supplied by Fred Acree, Jr. The melting points checked within a few degrees and mixed melting points showed no depression. The ultraviolet spectra of the preparations were almost identical, and the crystalline structures likewise seemed identical. The three preparations exhibited the same order of toxicity to newly hatched larvae of the European corn borer.[4] Finally, carbon, hydrogen, nitrogen, molecular weight, saponification equivalent and volatile acids data were in agreement with the results of Acree and Haller.

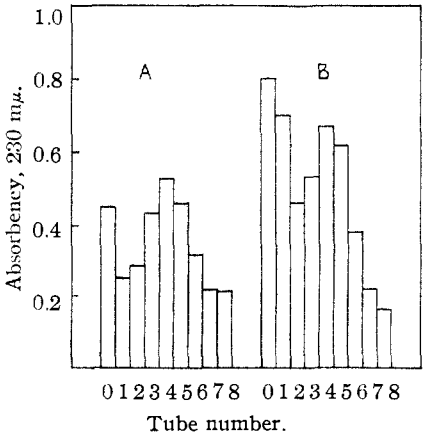


Fig. 1.—Countercurrent distribution of wilfordine (methanol-insoluble fraction), benzene-5% HCl: A, Acree's sample; B, from fresh root.

Wilfordine did not melt sharply but rather changed from a white solid to a clear resin at different temperatures between 167° and 174° for the various lots prepared. This behavior indicated that wilfordine might not be a single compound. Purity studies by chromatography were therefore undertaken, but the results were unsatisfactory. Countercurrent distribution[5,6] proved more successful.

After it had been determined that wilfordine from old root would have a partition coefficient close to 1 when distributed between benzene and 5% hydrochloric acid, a 21-plate countercurrent distribution was performed. The results of this distribution (Fig. 1 in reference 7) show at once that wilfordine is impure and indicated the presence of two principal alkaloids plus smaller amounts of other alkaloids. The two alkaloids were also demonstrated to be present in Acree's sample (Fig. 1,A) and in a sample of wilfordine isolated from fresh root (Fig. 1,B). The latter preparation was recrystallized only once, since additional recrystallizations might remove more of one component than of the others.

The two alkaloids were separated by partition chromatography of the Martin and Synge type.[8] Two main zones were eluted (Fig. 2 in reference 7). The first main compound (C-1) eluted from the column will be called wilforine, while the name, wilfordine, will be retained for the second main compound (C-2). Acree and Haller's wilfordine will henceforth be referred to as the methanol-insoluble fraction.

By countercurrent distribution it was shown that both compounds were not pure. Each zone was then rechromatographed and the alkaloids were isolated in pure form by selecting those zone fractions whose absorbency ratios at 270 and 255 mμ approached a constant value and rechromatographing these combined fractions until a constant ratio was obtained.[7]

(1) Report of a study made under the Research and Marketing Act of 1946. Article not copyrighted.

(2) Part of Ph.D. thesis submitted by M. Beroza to Georgetown University.

(3) Acree and Haller, THIS JOURNAL, **72**, 1608 (1950).

(4) Tests to determine the insecticidal activity of these samples were carried out by D. D. Questel and R. V. Connin of this Bureau.

(5) Craig, *J. Biol. Chem.*, **155**, 519 (1944).

(6) Craig, *Federation Proc.*, **7**, 469 (1948).

(7) Beroza, *Anal. Chem.*, **22**, 1507 (1950).

(8) Martin and Synge, *Biochem. J.*, **35**, 1358 (1941).