Opium Alkaloids VII

Isolation of a New Benzylisoquinoline Alkaloid. Synthesis and NMR Studies of Papaveroline Trimethyl Ethers

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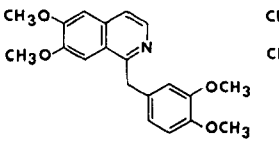
A new phenolic alkaloid was isolated from opium and named palaudine. It was characterized spectroscopically as 1-(3′-hydroxy-4′-methoxybenzyl)-6,7-dimethoxyisoquinoline and the structure confirmed by synthesis. The other three papaveroline trimethyl ethers were also synthesized and their NMR spectra investigated.

1-BENZYLISOQUINOLINE ALKALOIDS containing a hydrogenated heterocyclic ring (1,2,3,4-tetrahydro) are widely distributed in several plant families. On the other hand, very few fully aromatic benzylisoquinolines have been isolated from natural sources, the best known being the opium alkaloid papaverine (I). Investigation of the minor alkaloids of opium has now revealed a new alkaloid of this type. It was isolated from the phenolic alkaloid fraction of powdered opium and purified by preparative thin-layer chromatography on silica gel and by column chromatography on alumina and crystallized from ethanol, m.p. 175–176°. The mass spectrum showed a molecular ion with mass *m/e* 325. The M-1 peak (*m/e* 324) was of greater intensity than the peak of the parent ion. The M-15 peak (*m/e* 310) was also quite pronounced, while the M-31 peak (*m/e* 294) was small. The UV spectrum (in methanol) had maxima at 239, 280, 313.5, and 326.5 mμ and minima at 262, 306.5, and 320 mμ, and was very similar to that of papaverine (1). The NMR spectrum in deuteriochloroform revealed three methoxyl groups resonating at τ 6.01, 612, and 6.19, corresponding to three of the four methoxyl group signals of papaverine. A 2-proton signal at τ 5.51 corresponded to the methylene group signal of papaverine. These spectroscopic data suggested that the new alkaloid had the aromatic benzylisoquinoline structure and a substitution pattern similar to papaverine, *i.e.*, *O*-desmethylpapaverine = papaveroline trimethyl ether. The alkaloid gave a positive test with Gibb's reagent, indicating that it might be unsubstituted in the *para* position to the phenolic hydroxyl group (II). This structure was confirmed by unambiguous synthesis as outlined in Scheme I.

β - Methoxy - β - (3,4 - dimethoxyphenyl)-ethylamine (III) was prepared according to Rosenmund *et al.* (2) by reduction of 1-methoxy-1-(3,4-dimethoxyphenyl)-2-nitroethane with lithium aluminum hydride. The acid chloride (IV) was synthesized from 3-benzyloxy-4-methoxybenzaldehyde *via* the azlactone as described by Robinson and Sugasawa (3). Schotten-Baumann reaction gave the amide (V) which lost methanol and water by treatment with phosphorus oxychloride in toluene.

Acid hydrolysis of VI gave the phenolic base II, which was crystallized from ethanol, m.p. 176°. No melting point depression was observed when mixed with the natural alkaloid. The natural and the synthetic compounds had the same R_f values on silica gel in two different solvent systems (4), and had identical NMR, UV, and IR spectra. Since the new opium alkaloid is closely related to papaverine and has the same pattern of oxygenated substituents as laudanidine, the authors propose to name it palaudine.

Pohl and Wiegrabe (5) have reported the NMR spectrum of papaverine, but the chemical shifts of the individual methoxyl groups have not been established. In order to make these assignments, the three remaining papaveroline trimethyl ethers were synthesized by the same route described for II and illustrated in Scheme I. In this way were obtained 1-(3′,4′-dimethoxybenzyl)-6-methoxy-7-hydroxyisoquinoline (VII), m.p. 163–165°, 1-(3′-methoxy - 4′ - hydroxybenzyl) - 6,7- dimethoxyisoquinoline (VIII), m.p. 165°, and 1 (3′-4′-dimethoxybenzyl) - 6- hydroxy - 7 - methoxyisoquinoline (IX), m.p. 165–167°. Billek (6) has previously synthesized VII and IX by catalytic dehydrogenation of the corresponding 1,2,3,4-tetrahydro derivative. These melting points are in good agreement with his. Boucherle and Alary



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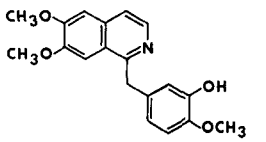

II

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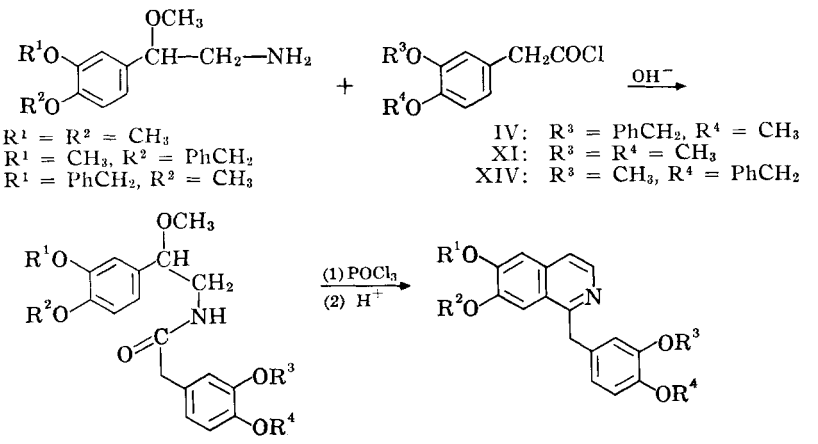

III: $R^1 = R^2 = CH_3$
X: $R^1 = CH_3$, $R^2 = PhCH_2$
XVII: $R^1 = PhCH_2$, $R^2 = CH_3$

IV: $R^3 = PhCH_2$, $R^4 = CH_3$
XI: $R^3 = R^4 = CH_3$
XIV: $R^3 = CH_3$, $R^4 = PhCH_2$

V: $R^1 = R^2 = R^4 = CH_3$, $R^3 = PhCH_2$
XII: $R^1 = R^3 = R^4 = CH_3$, $R^2 = PhCH_2$
XV: $R^1 = R^2 = R^3 = CH_3$, $R^4 = PhCH_2$
XVIII: $R^1 = PhCH_2$, $R^2 = R^3 = R^4 = CH_3$

VI: $R^1 = R^2 = R^4 = CH_3$, $R^3 = PhCH_2$
II: $R^1 = R^2 = R^4 = CH_3$, $R^3 = H$
XIII: $R^1 = R^3 = R^4 = CH_3$, $R^2 = PhCH_2$
VII: $R^1 = R^3 = R^4 = CH_3$, $R^2 = H$
XVI: $R^1 = R^2 = R^3 = CH_3$, $R^4 = PhCH_2$
VIII: $R^1 = R^2 = R^3 = CH_3$, $R^4 = H$
XIX: $R^1 = PhCH_2$, $R^2 = R^3 = R^4 = CH_3$
IX: $R^1 = H$, $R^2 = R^3 = R^4 = CH_3$

Scheme I

(7) have reported obtaining IX by heating of papaverine hydrochloride. However, their product decomposed without melting at 245°, thus leaving some uncertainty as to its identity.

The NMR spectrum of papaverine in deuteriochloroform showed methoxyl groups resonating at τ 6.01, 6.10, 6.18, and 6.23. The methoxyl signal at τ 6.23 was absent from II and could, therefore, be assigned to the 3′-position. Similarly, by comparing the methoxyl signals of papaverine with those of the other papaveroline trimethyl ethers, the chemical shift assignment could be made as shown in Table I.

TABLE I—CHEMICAL SHIFTS (τ) IN DEUTERIOCHLOROFORM

Compd.	6-OMe	7-OMe	4′-OMe	3′-OMe	—CH₂—
I (papaverine)	6.01	6.10	6.18	6.23	5.47
II (palaudine)	6.01	6.12	6.19	...	5.51
VII	5.98	...	6.23	6.28	5.55
VIII	6.00	6.09	...	6.24	5.47
IX	...	6.08	6.18	6.24	5.44

EXPERIMENTAL

The melting points were measured with a Kofler hot-stage micro melting point apparatus and are uncorrected. Ultraviolet spectra were obtained in ethanol solutions with a Cary model 11 spectrophotometer. Infrared spectra were determined in potassium bromide with a Beckman IR-9 spectrophotometer. Nuclear magnetic resonance spectra were measured in deuteriochloroform with a Varian Associates model A-60A nuclear magnetic resonance spectrometer. Tetramethylsilane was used as the internal standard. The mass spectrum was obtained with a Varian M-66 mass spectrometer. The elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, California.

Isolation of Palaudine from Opium—Powdered opium of Indian origin was extracted and the major alkaloid groups separated by liquid–liquid extraction as described in a previous communication (8). The phenolic alkaloid fraction was subjected to preparative thin-layer chromatography on silica gel (9). A broad band having a high R_f value in chloroform–methanol (9:1) consisted of a mixture which was chromatographed on a column of neutral alumina, Merck (activity 4) with chloroform. Twenty-milliliter fractions were collected with an automatic fraction collector. One of the fractions obtained in this way was again subjected to preparative thin-layer chromatography on silica gel with chloroform–methanol (9:1) and gave an alkaloid (7 mg.) which was purified by crystallization from ethanol, m.p. 175–176°. It produced a single spot by thin-layer chromatography in two different solvent systems (4) and gave a single peak by gas chromatography on a polyester column (3% HIEFF 8B, 4 ft., 220°) with a retention time of 162 min. A grayish blue spot was produced on the TLC plate with Gibb's reagent. UV spectrum: $\lambda_{max.}$ at 239, 280, 313.5, and 326.5 mμ (log ϵ, 4.78, 3.89, 3.70, 3.73, respectively); $\lambda_{min.}$ at 262, 306.5, and 319 mμ (log ϵ, 3.81, 3.59, 3.65, respectively). IR spectrum: $\nu_{max.}$ at 3430, 3000, 2868, 2817, 1620, 1589, 1569, 1513, 1478, 1463, 1450, 1432, 1420, 1385, 1350, 1323, 1273, 1235, 1203, 1160, 1130, 1080, 1050, 1030, 988, 961, 921, 894, 860, 823, 810, 788, 761, 652, 600, 565, 560, 500 and 400 cm.$^{-1}$ Mass spectrum: peaks at *m/e* 325 (M), 324 (M-1), 310 (M-15).

Syntheses of—N-(3′-benzyloxy-4′-methoxyphenylacetyl)-β-methoxy-β-(3,4-dimethoxyphenyl)ethylamine(V)—3-Benzyloxy-4-methoxyphenylacetic acid (0.45 Gm.) (3) was refluxed with

0.8 ml. of thionyl chloride in 8 ml. of chloroform for 2 hr. The reaction mixture was concentrated *in vacuo*. Excess of thionyl chloride was removed by repeated addition and evaporation of anhydrous toluene. The oily residue of acid chloride (IV) was dissolved in 10 ml. of anhydrous ether and added dropwise, with stirring and cooling in an ice bath, to a mixture of 10 ml. sodium hydroxide (10%) and 10 ml. of an ether solution of β-methoxy-β-(3,4-dimethoxyphenyl)-ethylamine (III) (2) prepared from 0.52 Gm. of the oxalate. After the addition was completed, stirring was continued for 1 hr. at 0°. The amide crystallized, was filtered off, washed with cold water, and dried. Yield 0.90 Gm. Recrystallization from ethanol gave colorless needles, m.p. 115–116°. The NMR spectrum showed the following proton resonances: Singlet at τ 6.82 for β-methoxyl group, singlet at τ 6.13 for two aromatic methoxyl groups, singlet at τ 6.52 for —CH_2—CO—, and singlet at τ 4.85 for the benzyloxy methylene protons.

Anal.—Calcd. for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.45; H, 6.75; N, 2.92.

1 - (3' - Hydroxy - 4' - methoxybenzyl) - 6,7 - dimethoxyisoquinoline (II)—A mixture of 0.436 Gm. of V, 1.2 ml. of phosphorus oxychloride, and 6 ml. of toluene was heated under reflux for 1.5 hr. The reaction mixture was concentrated *in vacuo* to give an oil of 1-(3'-benzyloxy-4'-methoxybenzyl)-6,7-dimethoxyisoquinoline (VI) hydrochloride. The crude product was refluxed with a mixture of 4 ml. of 18% hydrochloric acid and 2 ml. of ethanol for 2 hr. The solution was concentrated *in vacuo*, made strongly alkaline with 10% sodium hydroxide solution, and washed once with chloroform. Ammonium chloride was added to a pH of about 10 and the liberated phenol extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo* to a brown oil (0.1 Gm.), which crystallized on addition of a small amount of ethanol. Recrystallization from ethanol gave colorless prisms, m.p. 176°. The sample gave no melting point depression in mixture with palaudine isolated from opium. The UV, IR and NMR spectra corresponded to those described for palaudine.

Anal.—Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.91; H, 5.89; N, 4.19.

N - (3',4' - Dimethoxyphenylacetyl) - β - methoxy-β - (3 - methoxy - 4 - benzyloxyphenyl)ethylamine (XII)—The acid chloride (XI) was prepared from 0.25 Gm. of 3,4-dimethoxyphenylacetic acid as described for IV. It was dissolved in 10 ml. of benzene and added dropwise and with stirring and cooling to a mixture of 10 ml. of 1 *N* sodium hydroxide and 10 ml. of a benzene solution of β-methoxy-β-(3-methoxy-4-benzyloxyphenyl)-ethylamine (X) (10) obtained from 0.5 Gm. of the hydrochloride. After 2 hr. of stirring, the benzene layer was separated and washed with water, then with dilute hydrochloric acid and again with water. The benzene layer was dried with anhydrous magnesium sulfate and evaporated *in vacuo* to give the amide (XII) as a brown oil (0.7 Gm.). It was purified by chromatography on a column of neutral alumina, Merck (activity 4) with chloroform. The colorless syrup obtained after evaporation of the solvent gave a single spot by thin-layer chromatography on silica gel with chloroform–methanol (9:1). The NMR spectrum showed the following signals: singlet at τ 6.13 for two aromatic methoxyl groups, singlet at τ 6.52 for —CH_2—CO— and singlet at τ 4.87 for the benzyloxy methylene protons.

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-benzyloxyisoquinoline (XIII)—A mixture of 0.5 Gm. of the amide (XII), 1.5 ml. of phosphorus oxychloride, and 6 ml. of toluene was refluxed for 1.5 hr. After cooling, petroleum ether was added, and a dark brown oil separated. The petroleum ether layer was decanted off, and the residual oil dissolved in methanolic hydrochloric acid and poured into cold 1 *N* sodium hydroxide solution. The mixture was extracted with chloroform, the extract dried over anhydrous magnesium sulfate, and the chloroform removed under reduced pressure. The brown, oily residue was purified by preparative thin-layer chromatography on silica gel with chloroform–methanol (9:1) to give a colorless oil. NMR spectrum: singlets at τ 6.23, 6.18, and 6.01 for three aromatic methoxyl groups, singlet at τ 5.55 for the methylene substituent in position-1, singlet at τ 4.82 for the benzyloxy methylene and doublet at τ 1.65 for the C-3 proton (J = 6 c.p.s.).

1 - (3',4' - Dimethoxybenzyl) - 6 - methoxy - 7-hydroxyisoquinoline (VII)—A solution of XIII (0.095 Gm.) in 2 ml. of ethanol was mixed with 1.5 ml. of hydrochloric acid (38%) and refluxed for 3 hr. The reaction mixture was evaporated to dryness *in vacuo*, the residue dissolved in water, and the solution washed once with chloroform. After addition of sodium hydroxide and ammonium chloride to pH about 10, the solution was extracted with chloroform, the extracts dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residual oil crystallized on treatment with ethanol. Recrystallization from ethanol gave pale brown prisms, m.p. 163–165° [lit. 165–167° (6)]. The substance gave a single spot by thin-layer chromatography on silica gel with chloroform–methanol (9:1).

Anal.—Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.06; H, 5.97; N, 4.45. The NMR signals are given in Table I.

N - (3' - Methoxy - 4' - benzyloxyphenylacetyl)-β - methoxy - β - (3,4-dimethoxyphenyl)ethylamine (XV)—The acid chloride (XIV) was prepared from 0.7 Gm. of 3-methoxy-4-benzyloxyphenylacetic acid (11) and reacted with β-methoxy-β-(3,4-dimethoxyphenyl)ethylamine (III) (from 0.8 Gm. of oxalate) as described for the synthesis of V. The amide which separated (1.3 Gm.) was recrystallized from ethanol to give colorless needles, m.p. 117–118°.

Anal.—Calcd. for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.54; H, 6.60; N, 3.15. The NMR spectrum gave the following proton resonances: singlet at τ 6.83 for the β-methoxyl group, singlet at τ 6.12 for two aromatic methoxyl groups, singlet at τ 6.50 for —CH_2—CO— and a singlet at τ 4.83 for the benzyloxy methylene protons.

1 - (3' - Methoxy - 4' - benzyloxy) - 6,7 - dimethoxyisoquinoline (XVI)—Cyclization of XV (0.6 Gm.) was carried out with phosphorus oxychloride in toluene as described above. The reaction mixture was concentrated *in vacuo*, made alkaline with sodium hydroxide solution, and extracted with chloroform. The chloroform extract was dried and evaporated to a brown oil (0.48 Gm.). The NMR

spectrum showed the following signals: singlets at τ 7.27, 6.12, 5.98 corresponding to three aromatic methoxyl groups, singlet at τ 4.89 for the benzyloxy methylene protons and doublets at τ 1.60 and 2.52 (J = 5.5 c.p.s.) for the C-3 and C-4 protons.

1 - (3' - Methoxy - 4' - hydroxybenzyl) - 6,7 - dimethoxyisoquinoline (VIII)—Hydrolysis of XVI (0.4 Gm.) with ethanolic hydrochloric acid was carried out as described for VII, and the isolated oil (0.1 Gm.) crystallized on standing. Recrystallization from ethanol gave pale tan-colored prisms, m.p. 165° [lit. 165° (6)]. The substance gave a single spot by thin-layer chromatography on silica gel with chloroform–methanol (9:1). The NMR signals are recorded in Table I.

Anal.—Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.87; H, 5.87; N, 4.62.

N-(3',4'-Dimethoxyphenylacetyl)-β-methoxy-β-benzyloxy-4-methoxyphenyl)ethylamine (XVIII)—A benzene solution of the acid chloride (XI), prepared from 0.35 Gm. of acid, was added dropwise with stirring and cooling to a flask containing 10 ml. of sodium hydroxide solution (10%) and 10 ml. of a benzene solution of β-methoxy-β-(3-benzyloxy-4-methoxyphenyl)ethylamine (XVII), prepared from 0.6 Gm. of oxalate. After 2 hr. in an ice bath, the benzene layer was separated, washed with water, then with dilute hydrochloric acid and again with water, dried and evaporated *in vacuo*. The residual oil (0.7 Gm.) showed the following NMR signals: singlet at τ 6.90 for the β-methoxyl group, singlet at τ 6.12 for three aromatic methoxyl groups, singlets at τ 6.52 for the —CH_2CO— group, and at τ 4.87 for the benzyloxy methylene protons.

1 - (3',4' - Dimethoxybenzyl) - 6 - benzyloxy - 7-methoxyisoquinoline (XIX)—Cyclization of XVIII (0.6 Gm.) was carried out as described for XIII. The product was a brown oil (0.45 Gm.) which gave only a single spot by thin-layer chromatography on silica gel with chloroform–methanol (9:1). The NMR spectrum gave the following signals: singlets at τ 6.23, 6.18, and 6.10 corresponding to three aromatic methoxyl groups, singlet at τ 5.47 for the methylene substituent in position 1, and a singlet at τ 4.72 for the benzyloxy methylene protons.

1 - (3',4' - Dimethoxybenzyl) - 6 - hydroxy - 7-methoxyisoquinoline (IX)—The hydrolysis of XIX (0.45 Gm.) was carried out as described above, and the isolated oily compound (0.3 Gm.) purified by preparative thin-layer chromatography on silica gel with chloroform–methanol (9:1). This gave a crystalline substance which was recrystallized from ethanol as prisms having a light tan color, m.p. 165–167° [lit. 165° (6)]. The substance produced a single spot by thin-layer chromatography on silica gel. The NMR data are recorded in Table I.

Anal.—Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.96; H, 5.93; N, 4.35.

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Keyphrases

Opium alkaloids—benzylisoquinoline isolated
Palaudine—isolated, structure confirmed
Column chromatography—separation
TLC—separation
Mass spectrometry—identity
NMR spectrometry—identity
UV spectrophotometry—structure
IR spectrophotometry—structure