# ISOLATION AND CHEMISTRY OF THE ALKALOIDS FROM *Papaver macrostomum* BOISS. *et* HUET* **

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From *Papaver macrostomum* BOISS. *et* HUET (genus *Papaver* L., section *Carinatae* FEDDE), a mixture of alkaloids was isolated. It gave the new 1-benzylisoquinoline alkaloids macrostomine (*I*), dehydronormacrostomine (*IV*), and sevanine (*VII*).

*Papaver macrostomum* BOISS. *et* HUET (Synonyma: *P. oligotrichum* BIENERT, *Closteranda macrostoma* STAPF) is the only one of the six plants categorized by Fedde[1] to the section *Carinatae* FEDDE (genus *Papaver* L.) which so far has been studied for the presence of alkaloids[2,3]. In the plants cultivated in Central Europe (Czechoslovakia, German Democratic Republic), the major alkaloids found therein were rhoeadine and protopine in addition to an other alkaloid of m.p. 195–197°C which was not identified. There were also found the papaverrubines A, B, D and E. The purpose of our work was to study the plant *P. macrostomum* BOISS. *et* HUET collected in the environments of the lake Sevan (Ar. SSR), which is the locality of its natural occurrence.

Chromatography of the nonphenolic fraction of the extract on alumina gave the optically active substance macrostomine whose mass spectrum exhibited a peak $M^+$ 406·1892 (for $C_{24}H_{26}N_2O_4$ calculated 406·1892) and peaks at *m/e* 377 (M – $C_2H_5$), 363 (M – $C_3H_7$), 350 (M – $C_3H_6N$), 348 (M – $C_3H_8N$), 271 (M – $C_8H_7O_2$), 135 ($C_8H_7O_2$, methylenedioxybenzyl ion) and 84 ($C_5H_{10}N$, N-methyl-

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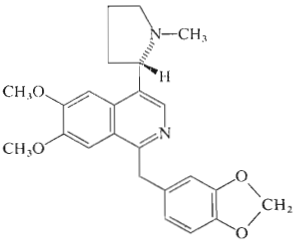
pyrrolinium ion – analogy with nicotine data[4]). The UV spectrum of macrostomine was characteristic for the 1-benzylisoquinoline chromophore. In the IR spectrum, the band at 2792 $cm^{-1}$ indicated the N-methyl group of the tertiary amine[5]. The intense band at 1645 $cm^{-1}$ confirmed the presence of a heteroaromatic ring. In the $^1$H-NMR spectrum (measured in hexadeuteriobenzene), the singlet at 2·13 ppm (3 H) was assigned to the N—$CH_3$ group and the two singlets at 3·47 (3 H) and 3·55 ppm (3 H), which in deuteriochloroform are shifted to 3·90 and 4·00 ppm, to the methoxyl groups with a free *ortho*-position. The singlet at 4·55 ppm (2 H) was ascribed to the protons of the methylene group coupled to the aromatic nucleus and the singlet at 5·30 ppm (2 H) to the protons of the methylenedioxy group. In the region of the aromatic protons there appear an *ortho* doublet ($J$ = 8·0 Hz) at 6·55 ppm (1 H), an *ortho*/*meta* doublet of doublets ($J$ = 8·0 and 1·0 Hz) at 6·80 ppm (1 H), and a *meta* doublet ($J$ = 1·0 Hz) at 6·97 ppm (1 H). Furthermore, this region shows three one-proton singlets at 7·35, 7·87 and 8·72 ppm. The multiplets in the region of 1·5–2·2 ppm (4 H) and 3·0–3·6 ppm (3 H) are attributable, in analogy with the spectrum of nicotine, to the protons of the pyrrolidine moiety. In trifluoroacetic acid, the signal of the N—$CH_3$ group shifts to 3·08 ppm and splits into a doublet ($J$ = 5·0 Hz) which coalesces into a singlet in deuteriotrifluoroacetic acid. The proton in the α-position to the N—$CH_3$ group appears as a multiplet at 3·28 ppm. On the basis of the spectral data, the structure *I* was assigned to macrostomine. The CD spectrum of macrostomine (*I*) shows three negative Cotton effects in the region of the longest wavelength band. In this region, (*S*)-(–)-nicotine[6] and (*S*)-(–)-brevicolline[7] show negative Cotton effects. These compounds also have a heteroaromatic chromophore substituted in the position 3 with a chiral atom of the pyrrolidine ring. We assume that the absolute configuration on the chiral carbon atom of macrostomine is also *S*. Hydrogenation of macrostomine on platinum in acetic acid gave the original compound. Methylation of macrostomine (*I*) with methyl iodide yielded the quaternary salt *II*. According to the $^1$H-NMR spectra, methylation proceeded on both nitrogen atoms. Reduction of the methiodide *II* with zinc in hydrochloric acid gave a compound whose $^1$H-NMR spectrum showed a singlet at 2·20 ppm (6 H) which was assigned to the $N(CH_3)_2$ group and a singlet at 2·47 ppm (3 H) attributable to the N—$CH_3$ group of the tetrahydroisoquinoline moiety. The methoxyl groups and the methylenedioxy group appear as singlets at 3·65, 3·83 and 5·87 ppm. In the region of the aromatic protons there appear an *ortho*-doublet at 6·13 ppm (1 H, $J$ = 8·5 Hz) and a multiplet at 6·53 ppm (4 H). The UV spectrum is typical for tetrahydroisoquinoline derivatives. The mass spectrum contains a small peak $M^+$ 440, for the fragment M – 1 there was found $C_{26}H_{35}N_2O_4$. The base peak *a* is at *m*/*e* 305 ($C_{18}H_{29}N_2O_2$) which arises by elimination of the methylenedioxybenzyl radical. The metastable transition at 221·6 confirmed the fragmentation of the ion *a* to the ion $C_{16}H_{22}NO_2$ (*m*/*e* 260) by elimination of dimethylamine. Other characteristic peaks were observed at *m*/*e* 204 (dimethoxy-N-methylisoquino-

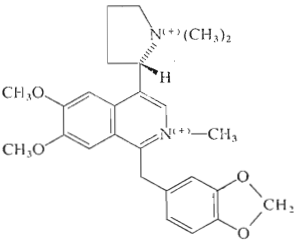
linium), 135 (methylenedioxybenzyl ion), 100 (N,N-dimethylpyrrolidinium), 58 (dimethylmethyleneammonium). The compound was ascribed the structure *III*. During the reaction, reduction of the isoquinoline nucleus and reductive cleavage of the $C-N^{(+)}$ bond in pyrrolidine took place.

In addition to macrostomine (*I*), the nonphenolic fraction contained a second more polar optically inactive alkaloid dehydronormacrostomine. The UV spectrum of this substance differs from that of macrostomine in the region of c. 320 nm. The mass spectrum displays a peak $M^+$ 390·1587 (for $C_{23}H_{22}N_2O_4$ calculated 390·1579). The ion of mass *m/e* 135 indicates substitution of the benzyl nucleus by a methylenedioxy group. Labelling with deuterioethanol leads to a shift of the molecular ion by one unit, to a smaller extent by two units, the ion of mass *m/e* 84 (N-methylpyrrolinium) is absent. The difference between the mass of the molecular peak of macrostomine (*I*) and that of dehydronormacrostomine by $CH_4$ cannot be explained by substitution of two methoxyl groups for one methylenedioxy group. This precludes the presence of an ion at *m/e* 359 ($C_{22}H_{19}N_2O_3$, $M - OCH_3$). On the basis of these data, we propose structure *IV* for dehydronormacrostomine.

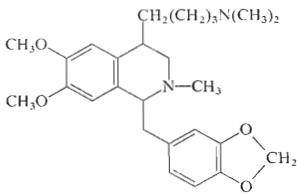
The phenolic fraction contains an optically inactive alkaloid sevanine whose molecular peak $M^+$ 309·0989 corresponds to $C_{18}H_{15}NO_4$ (calculated 309·1001). The only abundant fragment is the ion $M - 1$. The most characteristic small peak is that of the methylenedioxybenzylic ion at *m/e* 135. The UV spectrum of sevanine is almost identical with that of papaverine (*V*). After alkalinization with sodium hydroxide, the longest wavelength band undergoes a bathochromic shift by c. 30 nm. This shift is indicative of the hydroxysubstituted aromatic chromophore[8]. In the $^1$H-NMR spectrum, measured in a mixture of deuteriochloroform–deuteriomethanol 1 : 1, the singlet at 4·03 ppm (3 H) was assigned to the methoxyl group, the singlet at 4·45 ppm (2 H) to the protons of the benzyl methylene group, the protons of the methylenedioxy group produced a singlet at 5·87 ppm. The aromatic region of the spectrum shows five protons, a singlet at 6·72 ppm (3 H), two singlets at 7·10 (1 H) and 7·48 ppm (1 H), doublets at 7·45 (1 H) and 8·23 ppm (1 H, $J$ = 6·0 Hz). We assigned the singlet at 7·48 ppm to the proton at $C_{(8)}$ and the singlet at 7·10 ppm to the proton at $C_{(5)}$. A comparison of the chemical shifts of these protons in hexadeuteriodimethyl sulphoxide and in hexadeuteriodimethyl sulphoxide alkalinized with $CD_3ONa$ shows that H-8 shifted upfield by 0·93 ppm and H-5 by 0·42 ppm. This shift indicates[9] that the hydroxyl group is at $C_{(7)}$. On the basis of these data, the structure of 7-hydroxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*VII*) was assigned to sevanine. Methylation of sevanine with diazomethane gave the already earlier described[10] 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*VI*). An attempt was made to synthesize the authentic isomer *VII* to determine unambiguously the positions of the hydroxyl and methoxyl groups on the isoquinoline nucleus of sevanine. Condensation of 4-benzyloxy-3-methoxybenzaldehyde with nitromethane in a solution of sodium methoxide yielded 1-(4-benzyloxy-3-me-



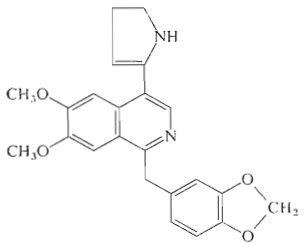
*I*



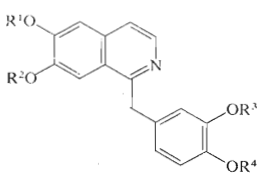
*II*



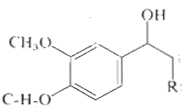
*III*



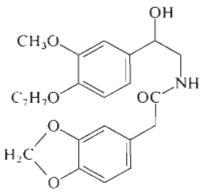
*IV*



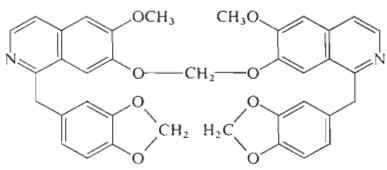
*V*, $R^1 = R^2 = R^3 = R^4 = CH_3$
*VI*, $R^1 = R^2 = CH_3$, $R^3 + R^4 = CH_2$
*VII*, $R^1 = CH_3$, $R^2 = H$, $R^3 + R^4 = CH_2$
*XI*, $R^1 = CH_3$, $R^2 = C_7H_7$, $R^3 + R^4 = CH_2$
*XII*, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$



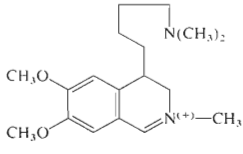
*VIII*, R = $NO_2$
*IX*, R = $NH_2$



V



XIII



a

thoxyphenyl)-2-nitroethanol (*VIII*). On reduction with lithiumaluminiumhydride, this substance afforded 2-amino-1-(4-benzyloxy-3-methoxyphenyl)ethanol (*IX*) which was isolated as an acetate. The acetate of the substance *IX* was acylated with 3,4--methylenedioxyphenylacetyl chloride, prepared from 1-(3,4-methylenedioxyphenyl)-acetic acid, to afford 1-(4-benzyloxy-3-methoxyphenyl)-2-(3,4-methylenedioxyphenylacetamido)ethanol (*X*). Cyclization of the amide X with phosphoric oxychloride in toluene gave 7-benzyloxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*XI*). Debenzylation of this compound in 20% hydrochloric acid gave 7-hydroxy--6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*VII*) which on the basis of the melting point and spectral data was identical with sevanine. The compound *VII* was also prepared by another route. Demethylation of papaverine (*V*) with 47% hydrobromic acid yielded[11] 1-(3,4-dihydroxybenzyl)-7-hydroxy-6-methoxyisoquinoline (*XII*). Reaction of this compound with dichloromethane and sodium hydroxide in dimethyl sulphoxide gave the compound *VII* in 10% yield. The major product of methylation was a substance whose UV spectrum showed maxima at 238 nm ($\log \varepsilon$ 5·10), 287 (4·17), 312 (3·84) and 325 (3·81). In the mass spectrum, the molecular ion $M^+$ 630·2010 ($C_{37}H_{30}N_2O_8$) eliminated the methylenedioxybenzyl radical to give rise to a fragment at *m/e* 495 (metastable transition: 388·9). In the $^1$H-NMR spectrum, the singlet at 3·98 ppm (6 H) was attributed to the methoxyl groups, the singlet at 4·40 ppm (4 H) to the protons of the benzyl fragment. The protons of the methylenedioxy groups exhibited a singlet at 5·73 ppm (4 H). The singlet at 5·85 ppm (2H) was assigned to the methylenedioxy group connecting the two isoquinoline

nuclei. The doublets at 6·45 (2 H) and 6·65 ppm (2 H, $J$ = 8·0 Hz) and the singlets at 6·72 (2 H), 7·10 (2 H), and 7·90 ppm (2 H) were assigned to the aromatic protons. The protons in the position 3, 4 of the isoquinoline nucleus exhibited doublets at 7·43 (2 H) and 8·40 ppm (2 H, $J$ = 5·5 Hz). On the basis of these data, the substance was ascribed the structure *XIII*.

None of the portions of the extract contained rhoeadine and papaverrubine alkaloids which were found in *P. macrostomum* Boiss. *et* Huet already earlier[2,3].

Macrostomine (*I*) has a stronger spasmolytic effect on the smooth muscle of the isolated intestins of rats and rabbits than papaverine (*V*) or thiospasmine; it antagonizes the effect of barium and acetylcholine on the rat duodenum proportionately with higher doses. In the striated muscle of rats, macrostomine (*I*) inhibits the nerve-muscle transfer only slightly. In rabbits, intravenous application produces a marked but transient arythmia. The acute toxicity of macrostomine amounts to 100 mg/kg. Orientatively it was found that macrostomine has no local-anaesthetic effect[12].

## EXPERIMENTAL

The melting points have been determined on the Kofler block and are not corrected. Preparative chromatography was carried out on neutral alumina W 200 (Woelm, GFR), thin-layer chromatography on silica gel G (Merck, GFR) using the solvent systems $S_1$ (cyclohexane–diethylamine, 80 : 20), $S_2$ (cyclohexane–chloroform–diethylamine, 70 : 20 : 10), and $S_3$ (methanol–diethylamine, 80 : 20). The alkaloids were detected with Dragendorff reagent or in UV light. Thin-layer chromatography of papaverrubines was carried out with the solvent systems $S_4$ (benzene–acetone–methanol, 70 : 20 : 10), detection with hydrochloric acid and heating. The $^1$H-NMR spectra were measured on a Varian T-60 in 5% w/v concentration with tetramethylsilane as internal standard. The chemical shifts are given in $\delta$-units (ppm). The UV spectra were measured on a Unicam SP 700 spectrophotometer, the IR spectra on an Infrascan H-900 instrument, the optical rotations on a Hilger-Watts polarimeter, and the CD spectra on a Roussel-Jouan (Model 185) dichrograph at 20°C in cells of 0·01 to 2·00 cm thickness; the values are given as $\lambda_{max}(\Delta\varepsilon)$. The mass spectra were measured on an AEI MS 902 apparatus.

### Isolation of Alkaloids

The flowering plants were collected in June 1971 in the environments of the lake Sevan (Western Caucasus, Arm. SSR). The dried drug (6·2 kg) was gradually extracted with a total of 200 l of methanol, concentrated to c. 1 l, extracted with benzene (2·5 l) and then with acetone (2·5 l). After evaporation of the solvents, the residue was dissolved in 10% sulphuric acid, filtered, the filtrate made alkaline with ammonia and extracted with chloroform. The obtained extract was dissolved in 5% acetic acid (300 ml), filtered, the filtrate made alkaline with $Na_2CO_3$ to c. pH 8 and extracted with ether (500 ml) to give the portion *A* containing 3·4 g, 0·055% of a mixture of crude alkaloids. The aqueous layer was alkalinized with NaOH to c. pH 12 and extracted with ether (300 ml) to give the portion *B* (3 mg) in which quaternary protoberberine alkaloids could not be demonstrated.

The mixture of crude alkaloids of the portion *A* was dissolved in 1% acetic acid (150 ml), made alkaline with NaOH and extracted with ether to give the nonphenolic bases (portion $A_1$,

3·1 g). The aqueous layer was acidified with hydrochloric acid, made alkaline with ammonia and extracted with ether to yield the phenolic bases (portion $A_2$, 0·15 g). Papaverrubines were not detected in any of those extracts. The portion $A_1$ was chromatographed on alumina (250 g, 750 ml fractions) by using an eluotrope series of solvents. The fractions 1—3 (light petroleum–ether, 50 : 50) did not contain any alkaloids. The fractions 4—7 (ether) gave 1·99 g of macrostomine (*I*). The fraction 9 (ether) yielded dehydronormacrostomine (*IV*) (7 mg). The fractions 10—30 were amorphous and only thin-layer chromatography demonstrated therein Dragendorff positive spots of h$R_F$ 38, 27 and 19 ($S_1$). The portion $A_2$ gave directly 50 mg of crystalline sevanine (*VII*) (methanol–ether). The mother liquors were chromatographed on alumina (15 g, 50 ml fractions). The individual fractions were amorphous and thin-layer chromatography demonstrated in them dehydronormacrostomine (*IV*) and sevanine (*VII*).

Macrostomine (*I*)

M.p. 107—110°C (benzene), $[\alpha]_D^{25}$ −51° ± 3° (*c* 0·89 in $CHCl_3$), h$R_F$ 47 ($S_1$) and 59 ($S_2$). UV (ethanol): $\lambda_{max}$ 241, 246 sh, 276 sh, 288, 292 sh, 317 and 332 nm (log ε 4·87, 4·62, 3·87, 3·97, 3·80, 3·74 and 3·77); (ethanol with HCl): $\lambda_{max}$ 259, 290, 319 and 333 sh (log ε 4·63, 3·74, 3·84 and 3·73). CD (ethanol): 273 nm (+0·33), 298 (−0·44), 317 (−0·39) and 331 (−0·46). MS: $M^+$ 406 (25, $C_{24}H_{26}N_2O_4$), 405 (16), 391 (12, $C_{23}H_{23}N_2O_4$), 377 (3·7, $C_{22}H_{21}N_2O_4$), 375 (2·1), 364 (3·7), 363 (13, $C_{21}H_{19}N_2O_4$), 350 (6·3, $C_{21}H_{20}NO_4$), 349 (2·6), 348 (3·7), 322 (2·1), 271 (4·2, $C_{16}H_{19}N_2O_2$), 243 (4·7, $C_{14}H_{15}N_2O_2$), 160 (2·1) 135 (6·8, $C_8H_7O_2$), 84 (100, $C_5H_{10}N$).

Macrostomine Methiodide (*II*)

To a solution of macrostomine (*I*) (200 mg) in methanol (3 ml), methyliodide (2 ml) was added and refluxed for 5 h. The solvent was evaporated and the residue crystallized from methanol to give 220 mg of the methiodide *II*, m.p. 220—230°C (decomposition). $^1$H-NMR (hexadeuteriodimethyl sulphoxide): 3·00 s and 3·12 s ($N^{(+)}(CH_3)_2$ of the pyrrolidine moiety), 3·97 s and 4·20 s (—$OCH_3$); 4·40 s ($N^{(+)}$—$CH_3$); 5·07 bs (Ar—$CH_2$); 5·98 s (O—$CH_2$—O); 6·72 d and 6·88 d, $J$ = 8·0 Hz (5′,6′-H); 6·82 s (2′-H); 7·87 bs (5,8-H); 9·00 s (3-H). UV (ethanol): $\lambda_{max}$ 221, 263 and 339 nm (log ε 4·22, 4·48 and 3·62).

*Reduction with zinc*: The methiodide *II* (120 mg) was stirred under heating (70°C) with zinc powder (400 mg) in 5 ml of 3M-HCl for 3 h. The mixture was filtered, the filtrate made alkaline with ammonia and extracted with ether. The ether extract yielded 50 mg of an oily substance *III* of h$R_F$ 49 ($S_1$). UV (ethanol): $\lambda_{max}$ 228 sh and 282 nm (log ε 4·08 and 3·87). MS: $M^+$ 440 (0·3), 439 (0·5, $C_{26}H_{35}N_2O_4$), 438 (0·6), 437 (0·1), 394 (0·3), 338 (1·7), 318 (1·0), 306 (21), 305 (100, $C_{18}H_{29}N_2O_2$), 303 (4·5), 261 (3·4), 260 (17), 358 (11), 204 (16), 190 (3·9), 189 (2·8), 188 (3·4), 177 (2·3), 160 (2·3), 135 (4·5), 100 (8·5), 83 (9·0), 77 (2·8), 71 (2·8), 58 (36).

Sevanine (*VII*)

M.p. 213—215°C (methanol), h$R_F$ 19 (benzene–ethyl acetate–diethylamine, 70 : 20 : 10). UV (ethanol): $\lambda_{max}$ 241, 277 sh, 285, 291 sh, 321 and 332 nm (log ε 4·74, 3·82, 3·87, 3·85, 3·69 and 3·73); (ethanol with NaOH): $\lambda_{max}$ 256, 292 and 360 nm (log 4·55, 3·95 and 3·71). MS: $M^+$ 309 (62, $C_{18}H_{15}NO_4$), 308 (100), 307 (2·0), 393 (7·0), 392 (7·5), 380 (6·0), 378 (7·5), 365 (6·5), 364 (6·0), 250 (16), 248 (7·0), 236 (14), 235 (8·0), 220 (6·0), 208 (12), 207 (11), 191 (7·5), 178 (8·0), 167 (6·0), 151 (6·0), 150 (7·5), 135 (11), 123 (11), 121 (7·5).

Dehydronormacrostomine (*IV*)

M.p. 193—195°C (acetone), h$R_F$ 38 ($S_1$). UV (ethanol): $\lambda_{max}$ 249, 295, 317 and 333 sh nm (log $\varepsilon$ 4·24, 3·51, 3·46 and 3·43); (ethanol with HCl): $\lambda_{max}$ 235, 263 and 340 nm (log $\varepsilon$ 4·02, 4·00 and 3·51). MS: $M^+$ 390 (76, $C_{23}H_{22}N_2O_4$), 389 (100, $C_{23}H_{21}N_2O_4$), 376 (12), 375 (47, $C_{22}H_{19}N_2O_4$), 373 (7·0), 361 (3·8), 360 (8·1), 359 (23, $C_{22}H_{19}N_2O_3$), 347 (7·6), 345 (6·5), 344 (5·9), 343 (5·4), 331 (11), 317 (5·9), 316 (5·4), 315 (5·4), 180 (11), 135 (22, $C_8H_7O_2$), 77 (10).

O-Methylsevanine (*VI*)

To a solution of sevanine (*VII*) (20 mg) in 1 ml of methanol, a solution (2 ml) of diazomethane in ether was added and the mixture was left standing fo 4 h at room temperature. After evaporation of the solvents, the residue was crystallized from a mixture of benzene–n-hexane to afford 15 mg of the compound *VI*, m.p. 106—108°C (ref.[10] reports m.p. 123°C (benzene) for this substance). MS: $M^+$ 323·1159, for $C_{19}H_{17}NO_4$ calculated 323·1157. $^1$H-NMR ($CDCl_3$): 3·87 s (—$OCH_3$); 3·97 s (—$OCH_3$); 4·47 s (Ar—$CH_2$); 5·82 s (O—$CH_2$—O); 6·68 bs (3 H, Ar—H); 7·00 s (1 H, Ar—H); 7·27 s (1 H, Ar—H); 7·37 d and 8·33 d, $J$ = 5·5 Hz (3·4-H).

1-(4-Benzyloxy-3-methoxyphenyl)-2-nitroethanol (*VIII*)

To a solution of 4-benzyloxy-3-methoxybenzaldehyde (24·2 g) in methanol (200 ml), nitromethane (6·5 ml) was added under cooling and then gradually a solution of 2·76 g of sodium in 50 ml of methanol. After shaking for 20 min, the mixture was acidified with dilute acetic acid. The oil was separated from the liquid phase at —10°C, washed with tetrachloromethane and dried. Yield 15·65 g of a crude product which was purified by chromatography on silica gel. The ethereal eluate gave 13·0 g (43%) of the compound *VIII*, m.p. 105—107°C (ether). For $C_{16}H_{17}NO_5$ (303·3) calculated: 63·36% C, 5·65% H, 4·62% N; found: 63·25% C, 5·74% H, 4·40% N. $^1$H-NMR ($CDCl_3$): 2·87 bs (CH—OH); 3·87 s (—$OCH_3$); 4·57 m ($CH_2$—$NO_2$); 5·13 s (Ar—$CH_2$—O); 5·38 m (CH(OH)—$CH_2$); 6·8—7·1 m (3 H, Ar—H); 7·3—7·5 m (5 H, Ar—H).

2-Amino-1-(4-benzyloxy-3-methoxyphenyl)ethanol (*IX*)

The nitro derivative *VIII* (7·0 g) was extracted in a Soxhlet apparatus into a suspension of 2·1 g of $LiAlH_4$ in 350 ml of ether and the mixture refluxed for 6 h. After decomposition with water and alkalinization, the ethereal portion was separated and the solid residue repeatedly extracted with ethyl acetate (500 ml). The combined extracts gave 2·15 g (28%) of a substance of m.p. 128—136°C (ethyl acetate) which on the basis of the elemental analysis is an acetate of the compound *IX*. For $C_{18}H_{23}NO_5$ (333·3) calculated: 64·84% C, 6·94% H, 4·20% N; found: 64·69% C, 7·09% H, 4·03% N. $^1$H-NMR (hexadeuteriodimethyl sulphoxide): 1·90 s ($CH_3COO$); 2·82 m (2 H); 3·87 s (—$OCH_3$); 4·70 m (5 H); 5·15 s (Ar—$CH_2$—O); 6·8—7·2 m (3 H, Ar—H); 7·48 bs (5 H, Ar—H). MS: $M^+$ 273 (8·1, $C_{16}H_{19}NO_3$), 244 (14), 243 (61, $C_{15}H_{15}O_3$), 153 (9·2), 91 (100), 65 (14), 30 (17).

1-(4-Benzyloxy-3-methoxyphenyl)-2-(3,4-methylenedioxyphenylacetamido)ethanol (*X*)

The acetate of the compound *IX* (2·55 g) was suspended in dichloromethane (20 ml) and water (5 ml). At 0°C, 10% sodium hydroxide (3 ml) was added and a solution of the 1-(3,4-methylenedioxyphenyl)acetyl chloride in dichloromethane (12 ml) were added. (The chloride was prepared from 1·65 g of the acid and was not isolated.) The mixture was stirred for 1 h at room temperature, the organic solvent was separated and the aqueous layer was extracted with dichloromethane.

The residue of the combined extracts crystallized from aqueous methanol to afford 3·21 g (96%) of the compound *X*, m.p. 135–139°C (aqueous ethanol). For $C_{25}H_{25}NO_6$ (435·5) calculated: 68·94% C, 5·78% H, 3·22% N; found: 68·95% C, 6·01% H, 3·06% N. $^1$H-NMR ($CDCl_3$): 3·42 s (—CO—NH); 3·2–3·6 m (3 H, one active hydrogen); 3·82 s (—$OCH_3$); 4·67 m (C<u>H</u>(OH)—$CH_2$); 5·10 s (Ar—$CH_2$—O); 5·90 s (O—$CH_2$—O); 6·5–6·9 m (6 H, Ar—H); 7·1–7·5 m (5 H, Ar—H). UV (ethanol): $\lambda_{max}$ 231 and 282 nm (log ε 4·16 and 3·82). MS: $M^+$ 435 (1·1, $C_{25}H_{25}NO_6$), 417 (3·7, $C_{25}H_{23}NO_5$), 326 (2·7, $C_{18}H_{16}NO_5$), 256 (24, $C_{16}H_{16}O_3$), 243 (7·3, $C_{15}H_{15}O_3$), 240 (2·9, $C_{16}H_{16}O_2$), 193 (14), 165 (10), 164 (8·7, $C_9H_{10}NO_2$), 135 (90), 91 (100), 77 (15), 65 (11).

7-Benzyloxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*XI*)

To a suspension of the compound *X* (1 g) in toluene (20 ml), $POCl_3$ (2·5 ml) was added and refluxed for 3·5 h, evaporated in vacuum, the residue alkalinized with 10% sodium hydroxide, extracted with chloroform, and the chloroform residue purified on alumina in benzene. Yield 0·30 g (32%) of the compound *XI*, m.p. 116–118°C (cyclohexane–benzene, 5 : 1). For $C_{25}H_{21}$·$NO_4$ (399·4) calculated: 75·18% C, 5·30% H, 3·50% N; found: 75·31% C, 5·49% H, 3·29% N. $^1$H-NMR ($CDCl_3$): 4·00 s (—$OCH_3$); 4·38 s (Ar—$CH_2$); 5·18 s (Ar—$CH_2$—O); 5·85 s (O—$CH_2$—O); 6·62 bs (3 H, Ar—H); 7·03 s (1 H, Ar—H); 7·2–7·6 m (7 H, Ar—H); 8·32 d, $J$ = 5·5 Hz (3-H). MS: $M^+$ 399 (30, $C_{25}H_{21}NO_4$), 388 (19), 308 (8·3, $C_{18}H_{14}NO_4$), 91 (100).

7-Hydroxy-6-methoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (*VII*)

*A*. A solution of the compound *XI* (0·34 g) in 20% hydrochloric acid (200 ml) was refluxed for 40 min, filtered, and the filtrate evaporated in vacuum. The residue was extracted with hot chloroform and the extract filtered. After evaporation in vacuum, the residue (0·11 g, 42%) was recrystallized from methanol, m.p. 213–215°C. For $C_{18}H_{15}O_4N$ (309·3) calculated: 69·89% C, 4·89% H, 5·53% N; found: 70·02% C, 4·94% H, 4·39% N.

*B*. A mixture of 1-(3,4-dihydroxybenzyl)-7-hydroxy-6-methoxyisoquinolinium chloride (*XII*) (1·24 g), prepared by demethylation[11] of papaverine (*V*) with hydrobromic acid, and powdered sodium hydroxide (0·64 g) in 10 ml of dichloromethane and 30 ml of dimethyl sulphoxide was heated under nitrogen for 2 h at 120°C. After cooling, the mixture was adjusted to pH 2 with 3M-HCl, and the solvent evaporated in vacuum. The residue was extracted with chloroform and the extract shaken with a saturated solution of $NaHCO_3$. After evaporation of chloroform in vacuum, the yield gave 0·86 g of a mixture which was chromatographed on alumina. The benzene fractions gave 0·42 g of the compound *XIII*, m.p. 189–191°C (benzene). MS: $M^+$ 630 (100, $C_{37}H_{30}N_2O_8$), 629 (5·4), 496 (17), 495 (50), 323 (36), 322 (65), 321 (12), 320 (17), 315 (15), 310 (21), 309 (36), 308 (86), 307 (40), 306 (61), 135 (50). The fractions benzene–chloroform (1 : 1) gave 0·11 g of the compound *VII*, m.p. 213–215°C (methanol).

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