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THE PROBLEM OF THE 1,2,9,10-TETRAOXYGENATED APORPHINES AND THE STRUCTURE OF THE QUATERNARY APORPHINE FROM *FAGARA TINGUASSOIBA*[1]

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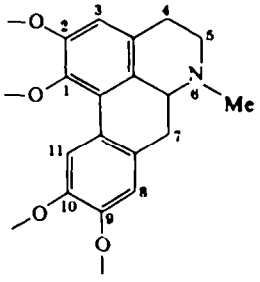
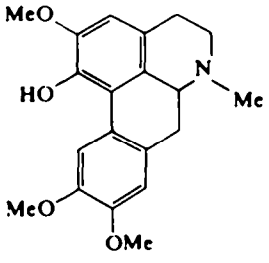
Abstract—Authentic 1-hydroxy-2,9,10-trimethoxyaporphine (II) has been synthesized, and its N-methyl salt shown to correspond to the quaternary alkaloid from *Fagara tinguassoiba*. Natural glaucentrine corresponds to corydine (XIX) rather than to structures II or XI.

THE structural elucidation of the 1,2,9,10-tetraoxygenated aporphine alkaloids (I) varying from one another in the relative number of MeO and OH substituents has resulted in a certain amount of confusion in the literature, and it is the intent of this paper to try to summarize the available information, as well as to present new data which will help clarify the situation.

In 1951, "alkaloid δ" originally isolated from three *Dicentra* species was renamed glaucentrine and assigned structure II.[3] This structural designation was based upon the comparison of derivatives of glaucentrine with synthetic compounds. In one case glaucentrine was O-ethylated with diazoethane and treated with (−)-tartaric acid.

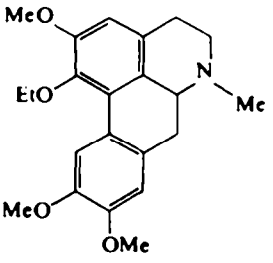


I



II

IIa = N-Methyl salt of II



III

Comparison of the resulting salt through a mixture m.p. determination with the (−)-tartrate salt of the aporphine III obtained by a total synthesis showed no depression in the decomposition point. Similarly, no mixture decomposition point

[1] Part of this paper appeared in a preliminary form; see M. Shamma and W. A. Slusarchyk, *Tetrahedron Letters* No. 20, 1509 (1965).

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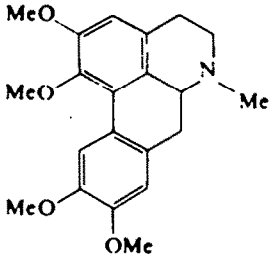
[3] For a discussion of the chemistry of glaucentrine see R. H. F. Manske, *The Alkaloids* Vol. IV; p. 119. Academic Press, New York (1954).

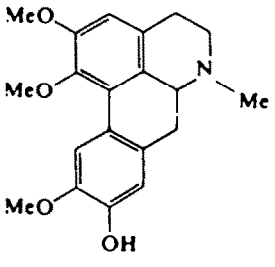
depression was observed when the O-ethyl methiodide salt of glaucentrine was admixed with one of the optically active components of synthetic 1-ethoxy-2,9,10-trimethoxyaporphine methiodide. No degradation reactions were run on glaucentrine, and no UV spectrum was recorded, so that the proof of structure for the alkaloid named glaucentrine rests upon the validity of comparing the decomposition points of two high melting salts. The discussion which follows will deal briefly with the erroneous structural assignments of two aporphines, namely the quaternary base from *Fagara tinguassoiba* and laurelliptine, caused by the misassignment of structure for glaucentrine.

In 1961, the isolation and degradation of a new unnamed quaternary alkaloid obtained from *Fagara tinguassoiba* was described in detail.[4] The alkaloid is a monophenolic trimethoxy aporphine salt, and its UV spectrum is characteristic of a 1,2,9,10-tetrasubstituted aporphine. O-Methylation of the alkaloid iodide gave glaucine (IV) methiodide, thus establishing the oxygenated positions as C-1,2,9, and 10.

Since the salts of the *Fagara* alkaloid had physical properties differing from those of the known aporphine xanthoplanine (Va), the OH function in the former alkaloid could not be placed at C-9. Comparison of the O-ethyl ether of the *Fagara* alkaloid with the corresponding salt of synthetic (±)-10-ethoxy-1,2,9-trimethoxyaporphine revealed the two compounds to be different, hence eliminating the possibility of the OH group being present at C-10. At this stage the remaining positions available for

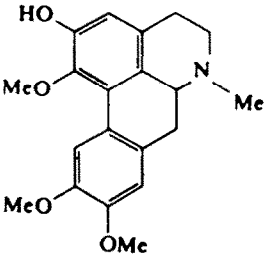


IV



V

Va = N-Methyl salt of V



VI

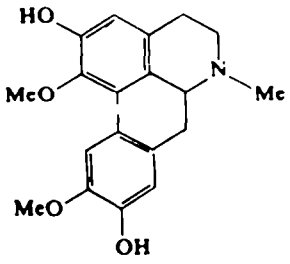
VIa = N-Methyl salt of VI

placement of the OH group were C-1 and C-2. A comparison of the iodide salt of the O-ethyl ether of the *Fagara* alkaloid with the O-ethyl ether of natural glaucentrine methiodide, whose earlier assignment demanded that the O-Et function be at C-1, showed the two quaternary salts again to be different. The OH function in the quaternary aporphine from *F. tinguassoiba* was, therefore, placed at the only remaining possible position, C-2, and structure VIa was assigned to this alkaloid.[4]

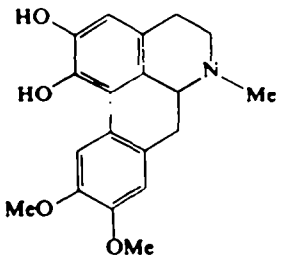
Another alkaloid which needs to be considered at this point is the dimethoxy diphenolic noraporphine laurelliptine found in *Beilschmieda elliptica*.[5] Treatment of N-methyllaurelliptine with diazomethane afforded two products, O,O,N-trimethyllaurelliptine and O,N-dimethyllaurelliptine. The former was found to be identical with an authentic sample of glaucine (IV). The latter product when converted to its methiodide was found to correspond to the quaternary aporphine from *F. tinguassoiba*

[4] N. V. Riggs, L. Antonaccio and L. Marion, *Canad. J. Chem.* **39**, 1330 (1961).
[5] P. S. Clezy, A. W. Nichol and E. Gellert, *Experientia* **19**, 1 (1963).

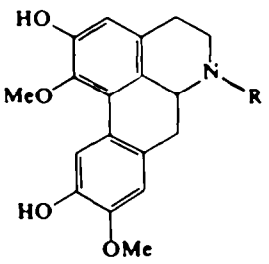
presumed to be VIa, hydroxylated at C-2, so that N-methyllaurelliptine could ostensibly be represented by expressions VII, VIII, or IX in which a OH group is present at position C-2. Structure VII represents the well characterized aporphine boldine, while structure VIII could be eliminated on the basis that laurelliptine gives a negative



VII



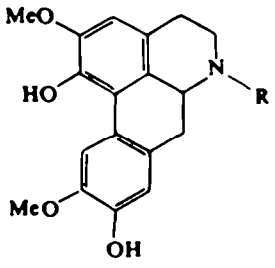
VIII



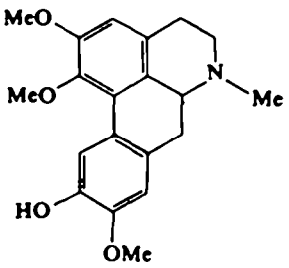
IX, R = Me
IXa, R = H

Quastel test for a 1,2-dihydroxyl group and has the same R_f value on plain and boric acid-sodium acetate treated paper. By a process of elimination, therefore, N-methyllaurelliptine was assigned structure IX, and laurelliptine became 1,9-dimethoxy-2,10-dihydroxynoraporphine (IXa).

Shortly before the original paper on laurelliptine was published, Tomita and his group reported the isolation of the alkaloid isoboldine, for which structure X was advanced on the basis of detailed degradative studies and the clear demonstration that isoboldine methochloride is identical to the well characterized quaternary aporphine laurifoline chloride Xa.[6]



X, R = Me
Xa = Quaternary N-methyl salt of X
Xb, R = H



XI

It is at this stage that we became interested in the structural problem of the 1,2,9,10-tetrasubstituted aporphines. Our approach was first to synthesize authentic 1-hydroxy-2,9,10-trimethoxyaporphine (II) through the classical Pschorr cyclization of intermediate XVII. Comparison of synthetic II and its N-Me quaternary salt with glaucentrine and the quaternary aporphine from *F. tinguassoiba*, respectively, would then either support the original assignments for glaucentrine, the quaternary aporphine from *F. tinguassoiba*, and laurelliptine or alternatively yield information useful in obtaining the corrected structures for these three aporphine alkaloids.

[6] H. Chikamatsu and M. Tomita, *J. Chem. Soc. Japan* **82**, 1708 (1961); and M. Tomita and M. Fujie, *J. Pharm. Soc. Japan* **82**, 1457 (1962).

For this purpose 2-(4-benzyloxy-3-methoxyphenyl)ethylamine was condensed with 3,4-dimethoxyphenylacetic acid to the amide XII which underwent Bischler-Napieralski cyclization to the imine hydrochloride XIII. Treatment of XIII with ammonium hydroxide followed by methyl iodide afforded the new imine methiodide salt XIV which was reduced with sodium borohydride to oily (±)-O-benzylcodamine (XV). Subsequent nitration of base XV with nitric acid in glacial acetic acid gave 6'-nitro-O-benzylcodamine (XVI). Zinc and sulfuric acid reduction of XVI afforded 6'-amino-O-benzylcodamine which when diazotized with sodium nitrite in sulfuric acid and then treated with boiling 25% H_2SO_4, gave the debenzylated racemic aporphine II, m.p. 190–192°, in 22% yield. A side product was the benzylisoquinoline XVIII.

When racemic base II was quaternized with methyl iodide, and the iodide ion then exchanged for picrate, the resulting quaternary salt was identical in its UV spectrum in ethanol, its IR spectrum in acetonitrile solution, and its silica gel thin-layer R_f values in ten different solvent systems with the quaternary alkaloid of *F. tinguassoiba* also in the picrate form. Similarly, comparison of the synthetic N-Me quaternary chloride salt of II, obtained by treatment of the corresponding quaternary iodide with silver chloride, with the *Fagara* alkaloid in the chloride form showed the two compounds to be identical through UV spectra in ethanol, NMR spectra in deuterium oxide with the sodium salt of 3-(trimethylsilyl) propanesulfonic acid as internal standard, and TLC R_f values in six different solvent systems. It follows, therefore, that the old structure VIa for the *F. tinguassoiba* alkaloid should be replaced by expression IIa, and that the structure of glaucentrine had to be reconsidered.

That the identity of the aporphine glaucentrine was, indeed, in error was confirmed by a comparison of our synthetic base II with a sample of natural glaucentrine which showed the two compounds to be different. The sample of glaucentrine which we had received was shown to be identical to corydine (XIX) by means of NMR, IR, UV and TLC R_f comparisons with an authentic sample of corydine. Additionally, a sample of natural glaucentrine hydrochloride turning brown at 234° and blackening between 237–238°, as reported in the literature for this salt, was also found to be identical with corydine hydrochloride. Glaucentrine, therefore, is not a distinct alkaloid but corresponds to the aporphine corydine.

Shortly before the initial publication of our results, Tschesche and coworkers carried out an interesting series of chemical transformations on isoboldine (X) and boldine (VII) which led them to conclude correctly, but by indirect evidence, that the *F. tinguassoiba* alkaloid had to be represented by expression IIa rather than by VIa.[7] However, their revised structure XI for glaucentrine is untenable since glaucentrine actually corresponds to corydine.

Clezy *et al.* have very recently discussed in detail the chemistry of laurelliptine, and this alkaloid is now recognized to possess the structure Xb rather than IXa, so that N-methyllaurelliptine is identical with isoboldine (X).[7,8]

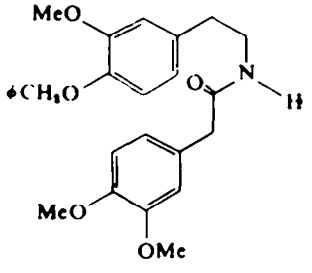
In the course of a study of the alkaloids of *Thalictrum fendleri*, a new tertiary aporphine alkaloid, thaliporphine, m.p. 170–172°, was isolated, which was conclusively shown to possess the structure II originally assigned to glaucentrine. The chemistry of thaliporphine will be described in a separate paper, but the unnamed quaternary aporphine from *F. tinguassoiba* can now be considered to correspond to the

[7] R. Tschesche, P. Welzel and G. Legler, *Tetrahedron Letters* No. 8, 445 (1965).

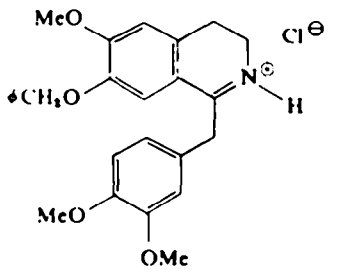
[8] P. S. Clezy, E. Gellert, D. Y. K. Lau and A. W. Nichol, *Austral. J. Chem.* **19**, 135 (1966).

N-methylthaliporphinium cation (IIa).[9] It is interesting to note that the m.p. for thaliporphine is appreciably higher than the value of 148° originally reported for glaucentrine while the m.p. for corydine is 148° or lower, depending upon the mode of recrystallization. This is another indication that glaucentrine corresponds to corydine rather than to thaliporphine.

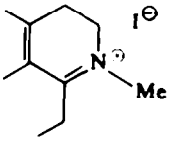
In conclusion, it can be stated that the structure corresponding to 2-hydroxy-1,9,10-trimethoxyaporphine still has not been found in nature. Cocsarmine is the quaternary form of 10-hydroxy-1,2,9-trimethoxy-aporphine, while the natural free base itself is still unknown.[10] The 1-hydroxy-2,9,10-trimethoxyaporphine structure is now assigned to thaliporphine, and the corresponding quaternary N-Me salt has been found in *F. tinguassoiba* and is reported to be present in some samples of *F. rhoifolia*,[11] but not in others.[12] The alkaloids laurotetanine, N-methyllaurotetanine (V), and xanthoplanine (Va) are, respectively, the noraporphine, aporphine, and N-Me quaternary aporphine in the 9-hydroxy-1,2-10-trimethoxy series.



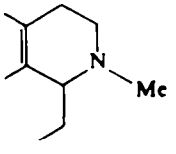
XII



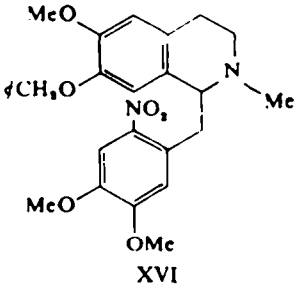
XIII



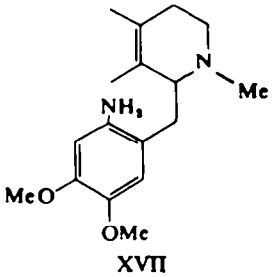
XIV



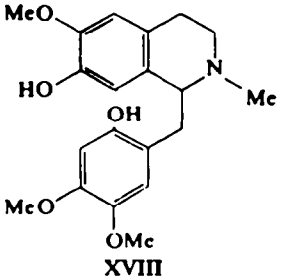
XV



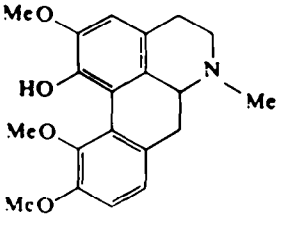
XVI



XVII



XVIII



XIX

[9] M. Shamma, R. J. Shine and B. S. Dudock, *Tetrahedron* in press.
[10] K. G. R. Pachler, R. R. Arndt and W. H. Baarschers, *Tetrahedron* **21**, 2159 (1965).
[11] J. M. Calderwood and F. Fish, *Chem. & Ind.* 237 (1966).
[12] A. M. Kuck, S. M. Albonico and V. Deulofeu, *Chem. & Ind.* 945 (1966).

EXPERIMENTAL

Elemental analyses were performed by Midwest Microlab Inc., Indianapolis, Indiana; all m.ps were taken on a block manufactured by the Nalge Company and are uncorrected. The IR spectra were taken either on a Beckman IR-5 or IR-5A spectrophotometer, and the UV spectra were measured on Cary Model 14 and Model 15 spectrophotometers. NMR spectra were taken on a Varian Associates A-60 spectrometer in $CDCl_3$ sol with TMS as internal standard in microcells provided by Varian Associates. The NMR spectra of the *F. tinguassoiba* alkaloid chloride and our synthetic IIa chloride were taken in D_2O with the Na salt of 3-(trimethylsilyl) propanesulfonic acid monohydrate as internal standard in normal sized tubes.

All compounds gave IR spectra consistent with their structures. All of the TLC was performed on plates made from Adsorbosil-1, manufactured by Applied Science Laboratories, State College, Pennsylvania 16801.

4-Benzyloxy-3-methoxybenzaldehyde. To 152 g (1·00 mole) vanillin in 300 ml 95% EtOH was added a sol of 61 g (1·1 mole) KOH in 60 ml water. The mixture was brought to reflux, 115 ml (1 mole) benzyl chloride was added and heating was continued for 5 hr. The mixture when filtered hot and cooled in an ice bath crystallized yielding the benzyloxy product which upon recrystallization from 95% EtOH gave 170 g (70%) benzylated aldehyde, m.p. 63–64°. Lit. reported m.p. 63–64°.[13]

4-Benzyloxy-3-methoxy-β-nitrosytrene. A mixture of 4 g Na_2CO_3 and 4 g $MeNH_2.HCl$ in 50 ml 95% EtOH was brought to boiling on a steam bath and filtered into a sol of 100 g (0·414 mole) 4-benzyloxy-3-methoxybenzaldehyde in 150 ml 95% EtOH. $MeNO_2$ (25 ml 0·442 mole) was added, and the mixture was stoppered and left in the dark for 3 days. The yellow crystalline product was collected and washed well with 95% EtOH producing 105 g (89%) of product, m.p. 120–121°. Lit. reported 120–121°.[14]

2-(4-Benzyloxy-3-methoxyphenyl)ethylamine. A soln of 85·5 g (0·300 mole) 4-benzyloxy-3-methoxy-β-nitrostyrene in 600 ml THF was added at a mild refluxing rate to a stirred soln of 36·0 g (0·950 mole) LAH in 600 ml THF protected from moisture by means of a $CaCl_2$ tube. After the addition, approximately 1·5 hr, the mixture was stirred until room temp was attained. The complex was decomposed by cautious addition of water using an ice bath to promote cooling. Benzene (200 ml) was added to prevent the mixture from becoming too thick during the addition of the water. After the complex was decomposed, 350 ml 30% NaOHaq was added, and the benzene–THF layer was decanted from the inorganic ppt. More benzene was added and decanted from the ppt, and the benzene–THF mixture was filtered under suction and evaporated to an oil. The oil was taken up in benzene, and the benzene soln was washed well with water, dried over K_2CO_3, and evaporated under reduced press to give 58·5 g (76%) oily amine. Confirmation of the amine was made by preparing its hydrochloride salt derivative using dry ethereal HCl. The hydrochloride salt had m.p. 168–170°. Lit. reported m.p. 169–171°.[14]

3′,4′-Dimethoxyphenyl-2-N-(4-benzyloxy-3-methoxyphenyl)ethylacetamide (XII). A soln of 45·5 g (0·220 mole) N,N′-dicyclohexylcarbodiimide in 50 ml THF distilled from LAH was added to a soln of 39·2 g (0·200 mole) 3,4-dimethoxyphenylacetic acid in 75 ml THF, and the mixture was swirled for 5 min. A soln of 51·4 g (0·200 mole) 2-(4-benzyloxy-3-methoxyphenyl)ethylamine in 125 ml THF was now added to the mixture with swirling. After 5 min of swirling during which time considerable heat was evolved the mixture was left to stand for 5 hr. The crystalline N,N′-dicyclohexylurea was filtered off, and the filtrate was concentrated under reduced press to a red oil which crystallized easily upon addition of anhyd ether only if the workup was performed while the oil was still warm after evaporation of the THF. The yield of amide was 56·8 g (65%), m.p. 124°, after recrystallization from 95% EtOH. Lit. report m.p. 125°.[15]

1-(3′,4′-Dimethoxybenzyl)-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline hydrochloride XIII. Amide XII (50·0 g, 0·115 mole), 50 ml $POCl_3$ and 250 ml toluene were refluxed for 2 hr—a $CaCl_2$ tube being employed. The reaction mixture upon cooling in an ice bath crystallized easily to give the imine hydrochloride salt which was filtered off, washed well with ether, a mixture of abs EtOH–ether, and finally ether again, yielding after drying 45·7 g (87%) salt XIII, m.p. 219–220°. Lit. report m.p. 220–221°.[15]

[13] A. Buzas and C. Dufour, *Ann. Pharm. Fr.* **17**, 453 (1959); *Chem. Abstr.* **54**, 6623 (1960).
[14] D. H. Hey and A. L. Palluel, *J. Chem. Soc.* 2926 (1957).
[15] G. Billek, *Monatsh. Chem.* **87**, 106 (1956).

1-(3',4'-*Dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-3,4-*dihydroisoquinoline iodide* (XIV). Compound XIII (32·0 g, 0·070 mole) was treated with NH_4OH and chf in the cold to give, after drying of the chf extract over K_2CO_3 and subsequent evaporation, the solid free base. The imine dissolved in 150 ml MeOH and 30 ml MeI was left for 2 hr at room temp. Removal of the excess MeI and concentration of the MeOH on the steam bath gave 31·4 g (80%) methiodide salt. Recrystallized from MeOH, m.p. 191–193°. (Found: C, 57·99; H, 5·43. Calc. for $C_{27}H_{30}NO_4I$: C, 57·96; H, 5·41%.)

1(3',4'-*Dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* ((±)-O-*benzyl-codamine*) (XV). To a suspension of 31·0 g (0·055 mole) XIV in 500 ml MeOH was added slowly with stirring and occasional cooling, 10·0 g (0·26 mole) $NaBH_4$. The MeOH was then removed under reduced press, and the residue was taken up in ether and water. The ether extract was washed well with water and dried over K_2CO_3 to yield upon evaporation 23·0 g (97%) pale yellow, oily (±)-O-benzylcodamine.

1-(3',4'-*Dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*hydroxy*-1,2,3,4-*tetrahydroisoquinoline* ((±)-*codamine*) *and its picrate salt*. Refluxing 433 mg (1 mmole) O-benzylcodamine in 10 ml 20% HClaq and 10 ml glacial AcOH for 1·5 hr produced after workup with NH_4OH, chf and $MgSO_4$ as drying reagent, 300 mg (85%) oily (±)-codamine, λ_{max}^{EtOH} 285 mμ (log ε 3·72), characterized as its picrate salt prepared in the following manner.

A hot soln of 72 mg (0·32 mmole) picric acid in 2 ml 95% EtOH was filtered into a previously filtered soln of 90 mg (0·26 mmole) (±)-codamine. After 12 hr the deposited picrate salt was recrystallized from 95% EtOH to give 105 mg (70%) yellow-orange crystals, m.p. 187° (dec). Lit. report m.p. 187°.[16]

1-(2'-*Nitro*-4',5'-*dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (XVI). O-Benzylcodamine (2·17 g, 5 mmoles) was dissolved in 12 ml glacial AcOH, and the soln was frozen in an ice bath. Concentrated HNO_3 (5 ml) was added in 5 portions with the temp being maintained at 5–10°. After the addition the red mixture was poured onto ice, made basic with NH_4OH, and extracted with chf. The extract when dried over K_2CO_3 and evaporated under reduced press gave a red oil which crystallized immediately on addition of MeOH yielding 1·30 g (54%) light sensitive, pale yellow XVI, m.p. 114–116°. (Found: C, 68·07; H, 6·43. Calc. for $C_{27}H_{30}N_2O_6$: C, 67·76; H, 6·32%.)

1-(2'-*Nitro*-4',5'-*dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (XVI) *methiodide*. To 250 mg (0·52 mmole) XVI dissolved in 5–10 ml MeOH was added 1 ml MeI. An hr later the mixture was concentrated on the steam bath until the salt crystallized. After recrystallization from 95% EtOH 300 mg (93%) MeI-salt, m.p. 208°, was obtained. (Found: C, 54·39; H, 5·33. Calc. for $C_{28}H_{33}N_2O_6I$: C, 54·20; H, 5·36%.)

1-(2'-*Nitro*-4',5'-*dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (XVI) *hydrochloride*. To a frozen soln of 15·4 g (0·0355 mole) (±)-O-benzylcodamine (XV) in 75 ml glacial AcOH was added conc HNO_3 (25 ml) in 5 portions, the total time for addition being 3–5 min and the temp being 5–10°. After the first 5 ml portion was added the frozen AcOH was quickly made liquid again by means of vigorous stirring and crushing with a glass rod. After addition of the HNO_3, the red mixture was poured onto ice, made basic with NH_4OH, and extracted thoroughly with chf. The extract was dried over K_2CO_3 and evaporated under reduced press to give a dark red oil. Abs EtOH (30 ml) was added followed by 10 ml conc HCl. The hot mixture when concentrated under reduced press crystallized to give 12·8 g (70%) yellow crystals. Recrystallized from 95% EtOH the hydrochloride salt melted 193–195° with dec. (Found: C, 62·88; H, 6·03. Calc. for $C_{27}H_{30}N_2O_6$.HCl: C, 62·97; H, 6·07%.)

1-(2'-*Amino*-4',5'-*dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*benzyloxy*-1,2,3,4-*tetrahydroisoquinoline* (XVII). Hydrochloride salt of XVI (10·3 g, 0·0200 mole) was dissolved in 200 ml 10% HClaq and 30 ml MeOH. Zn dust (20 g) was added slowly with occasional cooling in an ice bath. The dark mixture was warmed on the steam bath until a yellow or almost colorless soln was formed. After cooling in an ice bath, chf was added, and the mixture was made basic with NH_4OH and filtered by means of suction. The chf layer was separated, and the aqueous layer was extracted further with chf. The combined chf extracts were dried over K_2CO_3 and evaporated under reduced press to give a dark oil which crystallized from 95% EtOH when cooled in an ice bath and scratched slightly with a glass stirring rod. The product in a Buchner funnel was washed well with 95% EtOH, dried under suction for 15 min, washed with ether, and finally dried to give 5·30 g (58%) white solid. After

recrystallization from 95% EtOH the compound melted 128°. (Found: C, 72·65; H, 7·25. Calc. for $C_{37}H_{33}N_3O_4$: C, 72·29; H, 7·19%.)

(±)-1-*Hydroxy*-2,9,10-*trimethoxyaporphine* (II) *and* 1-(2'-*hydroxy*-4',5'-*dimethoxybenzyl*) 2-*methyl*-6-*methoxy*-7-*hydroxy*-1,2,3,4-*tetra-hydroisoquinoline* (XVIII). To a stirred soln of 896 mg (2 mmoles) XVII, 2 ml conc H_2SO_4, 20 ml glacial AcOH and 20 ml water at 5° was added dropwise 152 mg (2·2 mmoles) $NaNO_2$ in 5 ml water. After 15 min stirring the green soln was added dropwise to a boiling soln of 25 ml conc H_2SO_4 and 75 ml water. Zn dust (3 g) was added to the red soln, and heating was continued for 1 hr. The hot yellow soln was diluted with water, filtered, cooled in an ice bath, made basic with NH_4OH and extracted with chf. The extract after drying (K_2CO_3) yielded a dark oil on evaporation. The oil was applied to 4 thin-layer plates (8" × 8", 1 mm thick), and the chromatograms were developed in Et_2O:$CHCl_3$:MeOH (7:2:1) and left to stand for 24 hr after which time the separated components were visible due to the oxidative decomposition on the surface of the silica gel. Extraction of the desired compounds from the silica gel was accomplished by first extracting twice with warm chf:MeOH (2:1), evaporating this extract to dryness and subsequently extracting this new residue with CH_2Cl_2. Filtration and evaporation of the CH_2Cl_2 solns under reduced press gave the oily aporphine and benzylisoquinoline.

The orange-brown band having R_f 0·35 yielded, via the extraction procedure described above, a yellow oil which on addition of anhyd ether and warming on the steam bath produced 150 mg (22%) aporphine II, m.p. 192–194° (dec), after recrystallization from 95% EtOH, λ_{max}^{EtOH} 220, 280 and 305 mμ (log ε 4·52, 4·12 and 4·12). The NMR spectrum showed singlets at 7·47 τ (1 N-Me), 6·12 τ(2 MeO), 6·15 τ(1 MeO) and, 1·92, 3·22 and 3·48 τ(3 aromatic protons). (Found: C, 70·16; H, 6·61. Calc. for $C_{36}H_{33}NO_4$: C, 70·36; H, 6·79%.)

The bright yellow band having R_f 0·52 produced 202 mg (28%) XVIII, although in some runs the yields were as low as 5%. The base had λ_{max}^{EtOH} 289 mμ (log ε 3·72) and 257 mμ (log ε 2·90) and showed a peak in the IR at 2·91 μ and broad bands at 3·7–4·5 μ and 5·3–5·9 μ. The NMR spectrum exhibited singlets at 7·42 τ(1-N-Me), 6·17, 6·20 and 6·26 τ(3 MeO) and 3·27, 3·53, 3·57 and 3·61 τ(4 aromatic protons). It formed a picrate salt which upon 3 recrystallizations from 95% EtOH had m.p. 187–189° with dec. (Found: C, 52·67; H, 5·18. Calc. for $C_{36}H_{33}NO_4.C_6H_3N_3O_7$: C, 53·06; H, 4·80%.)

(±)-1-*Hydroxy*-2,9,10-*trimethoxyaporphine* (II) *methiodide*. A soln of 140 mg (0·41 mmole) II, 4 ml MeOH, and 1 ml MeI was allowed to stand for 2 hr and then concentrated on the steam bath to give 155 mg crystalline MeI salt (78%), m.p. 243–245° (dec), when recrystallized from MeOH–AcOEt. (Found: C, 52·48; H, 5·42. Calc. for $C_{31}H_{36}NO_4I$: C, 52·18; H, 5·42%.)

(±)-1-*Hydroxy*-2,9,10-*trimethoxyaporphine* (II) *methopicrate*. To a hot soln of 50 mg (0·10 mmole) MeI salt of II in 3 ml 95% EtOH, 1 ml acetone and a few drops of water was added a warm soln of 30 mg picric acid in 4 ml 95% EtOH. The mixture was left for 12 hr and concentrated on the steam bath to a volume of about 2 ml at which point the picrate salt crystallized to give 55 mg (94%) orange crystals. Recrystallized from 95% EtOH–acetone the salt had m.p. 223–224° with dec. (Found: C, 55·79; H, 4·76. Calc. for $C_{37}H_{39}N_4O_{11}$: C, 55·48; H, 4·83%.)

(±)-1-*Hydroxy*-2,9,10-*trimethoxyaporphine* (II) *methochloride*. A mixture of 90 mg (0·19 mmole) MeI salt of II, 15 ml water, 5 ml MeOH and approximately 1 g freshly prepared AgCl was stirred for 8 hr. The mixture was centrifuged, and the supernatant liquid was filtered and evaporated to dryness. The resultant residue was extracted with MeOH, and the MeOH extract was filtered and evaporated to an oil which crystallized from acetone–MeOH to give 47 mg (64%) methochloride salt, darkening at 200° and melting with dec at 245–247°. (Found: C, 64·40; H, 6·75. Calc. for $C_{31}H_{36}NO_4Cl$: C, 64·36; H, 6·69%.)

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