Tetrahedron, 1965, Vol. 21, pp. 2155 to 2158. Pergamon Press Ltd. Printed in Northern Ireland

THE SYNTHESES OF 1,2,9-TRIMETHOXY-10-HYDROXYAPORPHINE AND 2-METHOXY-N-ACETYLNORAPORPHINE

W. H. BAARSCHERS and R. R. ARNDT
National Chemical Research Laboratory, C.S.I.R. Pretoria, S. Africa

(*Received* 9 *February* 1965)

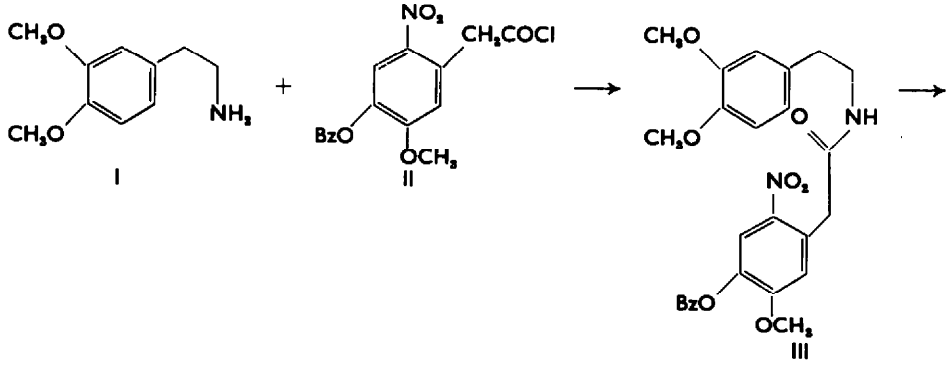
Abstract—1,2,9-Trimethoxy-10-hydroxyaporphine (VII) is the structure recently proposed[1] for rogersine, a natural aporphine alkaloid. An unambiguous synthesis of the compound with this structure proves the structure of rogersine to be in error.

The origin, of 2-methoxy-N-acetylnornuciferine (VIII) which was recently[2] used in an NMR study of aporphine alkaloids, is also now reported.

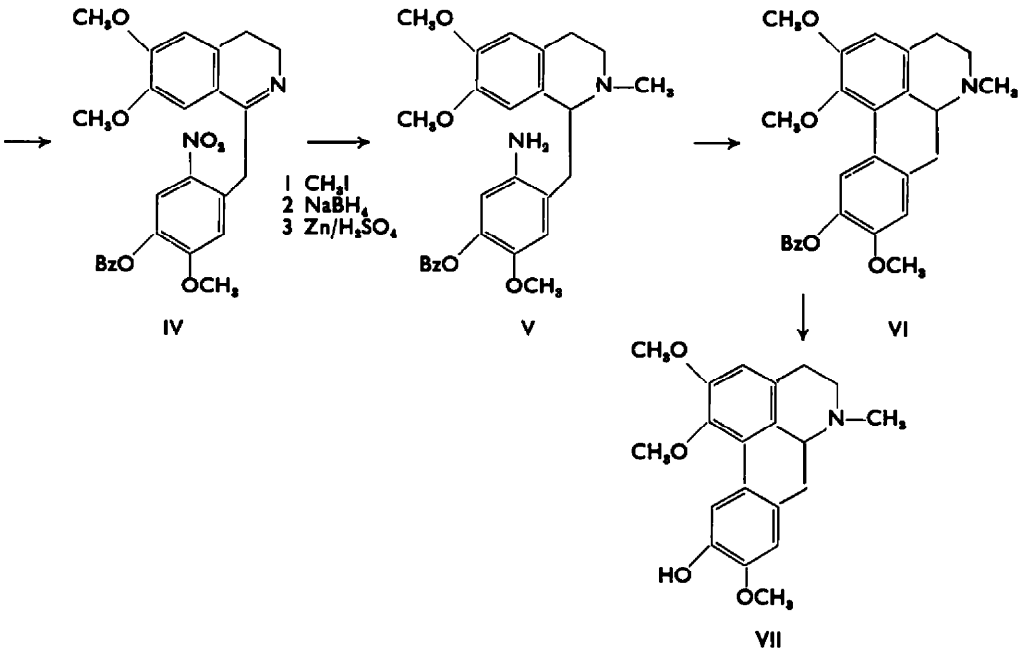
WHEN structure VII was recently suggested[1] for the aporphine alkaloid rogersine, isolated from *Phylica rogersii* Pillans, it was decided to attempt a synthesis of this compound. An unsuccessful attempt to synthesize this compound has been recorded.[3]

The protection of phenol groups by benzylation was first successfully applied to the synthesis of phenolic aporphine alkaloids by Hey and Lobo.[4] The two starting materials, the amine (I) and the nitro-acid chloride (II), were prepared from vanillin according to standard methods, and condensed in the presence of alkali to the amide (III). A Bischler-Napieralski cyclization with phosphorus pentachloride afforded the dihydro-isoquinoline (IV), the methiodide of which, on reduction with sodium borohydride and zinc in sulphuric acid, readily gave the amine (V). This compound, which gave an NMR spectrum in agreement with its structure was then subjected to the Pschorr ring closure reaction.

The crude product from the Pschorr reaction was chromatographed on alumina to give the expected yield (20–25%) of crystalline material. This was found to consist of 2 components, which could only be separated by fractional crystallization from methanol.



[1] R. R. Arndt and W. H. Baarschers, *J. Chem. Soc.* 2244 (1964).
[2] W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach and B. Douglas, *J. Chem. Soc.* 4778 (1964).
[3] R. L. Douglas and J. M. Gulland, *J. Chem. Soc.* 2893 (1931).
[4] D. H. Hey and L. C. Lobo, *J. Chem. Soc.* 2246 (1954).



The less soluble component of the mixture, $C_{27}H_{29}NO_4$, m.p. 149°, gave an NMR spectrum characteristic[2] of a benzylaporphine (VI) alkaloid. Although the removal of a benzyl ether protective group is reported in the literature[5] to be a relatively easy reaction, some difficulty was encountered. Catalytic hydrogenolysis failed under a variety of conditions. However, warming of the benzyl ether in acetic acid–conc. hydrochloric acid gave the desired phenolic product, m.p. 140–145°, which gave NMR and UV spectra in agreement with a 1,2,9,10-tetra-substituted aporphine. The hydroiodide $C_{20}H_{24}NO_4I$ had m.p. 228°.

A comparison of synthetic 1,2,9-methoxy-10-hydroxyaporphine with natural rogersine revealed differences in the IR spectra. The UV spectra of aporphine alkaloids with the same substitution pattern are not very characteristic,[6] when the spectra are run in neutral medium. The spectra in alkaline medium were found to be more typical for isomeric phenolic aporphines, and in the present case revealed a considerable difference between the synthetic and natural products. It is thus clear that the structure proposed for rogersine must be in error. Further comments on the structure of rogersine will be given in the following paper.[7]

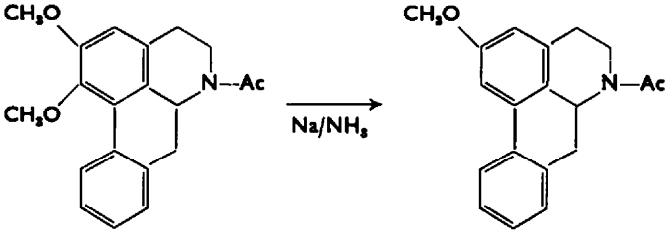
The more soluble component of the mixture obtained from the Pschorr reaction, m.p. ~140°, was thought to be one of the two usual byproducts obtained during the Pschorr ring closure reaction.[8,9] Lack of material prevented an investigation of the structure of this compound.

In the course of a study of the reaction of aporphine alkaloids with sodium and

[5] W. H. Hartung and R. Simonoff, *Org. Reactions* **7**, 263
[6] M. Shamma, *Experientia* **16**, 484 (1960).
[7] K. G. R. Pachler, R. R. Arndt and W. H. Baarschers, *Tetrahedron* **21**, 2059 (1965).
[8] M. Tomita and I. Kikkawa, *J. Pharm. Soc. Japan* **77**, 1015 (1957).
[9] J. A. Weisbach and B. Douglas, *J. Org. Chem.* **27**, 3738 (1962).

liquid ammonia, N-acetylnornuciferine (VIII) was subjected to this reaction. When the work of Tomita *et al.* concerning the same aspect was published,[10] the above study was discontinued. As one of our products was subsequently used in an NMR study of aporphine alkaloids,[2] its preparation is recorded here.

When N-acetylnornuciferine (VIII)[11] was treated with sodium in liquid ammonia, it gave a product $C_{19}H_{19}NO_4$, m.p. 182–183°,



VIII IX

which contained only one methoxy group.

The assignment of structure (IX) to this product was based on its NMR spectrum, which is fully reported elsewhere.[2]

EXPERIMENTAL

The m.ps were corrected and measured in evacuated, sealed capillaries. UV spectra refer to EtOH solutions. NMR spectra were measured with a Varian A-60 instrument, for 5–10% solutions in $CDCl_3$, with tetramethylsilane as an internal standard at $\tau = 10{\cdot}00$.

3-*Methoxy-4-benzyloxy-6-nitrophenyl*-N-2-(3,4-*dimethoxyphenyl*)-*ethyl-acetamide* (III). To 2-nitro-4-benzyloxy-5-methoxyphenyl acetic acid (2 g) in benzene (20 ml) was added thionyl chloride (8 ml) and the mixture shaken and slightly warmed until the acid dissolved. Removal of the solvent and excess of reagent *in vacuo* gave the crude II, which was immediately added, in chloroform (10 ml), to I, (1·4 g) in $CHCl_3$ (15 ml). After shaking for 5 min, 0·2 N KOH (10 ml) was added and the mixture kept at room temp for 2 hr with occasional shaking. The $CHCl_3$ layer was then separated and washed with 2 N KOH, water, 10% HCl, and again with water. Removal of the solvent gave crude III (2·25 g). An analytical sample had m.p. 168–169° from MeOH (lit.[3] 168°) (Found: C, 64·7; H, 5·9; N, 5·7; Calc. for $C_{26}H_{28}N_2O_7$: C, 65·0; H, 5·9; N, 5·8%.) This reaction was repeated 7 times with the same quantities to give a total of 18 g amide.

1-(3-*Methoxy-4-benzyloxy-6-nitrobenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (IV). The above amide (6 g) was added to PCl_5 (12 g) in $CHCl_3$ (50 ml) and allowed to stand at room temp for 2 days. Ice was added and the $CHCl_3$ and $POCl_3$ removed *in vacuo*, to give an oil which soon crystallized. The experiment was repeated twice with the same quantities. The total crude product was recrystallized from MeOH containing a few drops of dil HCl aq, to give the hydrochloride of IV (15·8 g). An analytical specimen had m.p. 205° (lit.[3] 210°) and contained 0·5 mole water of crystallization which could not be removed by prolonged drying *in vacuo*. (Found: C, 61·8; H, 5·6; N, 5·6; Calc. for $C_{26}H_{27}N_2O_6Cl{\cdot}\frac{1}{2}H_2O$: C, 61·5; H, 5·6; N, 5·5%.) The free base, recrystallized from MeOH, had m.p. 143–144° (dec) (lit.[3] 155° from ether), and was found to undergo slow decomposition. (Found: C, 67·1; H, 5·8; Calc. for $C_{26}H_{26}N_2O_6$: C, 67·5; H, 5·7%.)

1-(3-*Methoxy-4-benzyloxy-6-nitrobenzyl*)-2-*methyl*-3,4-*dihydro* - 6,7 - *dimethoxyisoquinoline iodide*. The above amine (IV) (280 mg) was heated on a water-bath in a sealed tube with an excess of MeI for 1 hr. After evaporation of the excess of reagent the residue was triturated with acetone to give the crystalline methiodide, which had m.p. 195° (lit.[3] 196–197°) after recrystallization from wet acetone. (Found: C, 51·8; H, 5·1; N, 4·50; Calc. for $C_{27}H_{29}O_6N_2I{\cdot}H_2O$: C, 52·0; H, 5·0; N,

[10] M. Tomita and K. Fukagawa, *J. Pharm. Soc. Japan* **83**, 293 (1963); *Chem. Abstr.* **59**, 5211b (1963).

[11] The authors thank Dr J. A. Weisbach, Smith, Kline and French Laboratories, Philadelphia, for a gift of this compound.

4·50%.) Prolonged drying *in vacuo* resulted in a hygroscopic product which did not give a satisfactory analysis. The remaining portion of the amine (IV) was converted to its methiodide in the same way.

Reduction of the amine methiodide. The above methiodide (1·8 g) in MeOH (20 ml) was treated with $NaBH_4$ (0·5 g) for 30 min at room temp. Zn dust (6 g) was added, and H_2SO_4 (23 ml 2 M) was added dropwise. The mixture was stirred for 30 min while the temp was kept below 40°. The mixture was filtered and MeOH was removed partly from the filtrate *in vacuo* at room temp. After basification with ammonia, the crystalline product was isolated with methylene dichloride. An analytical sample had m.p. 62–72° (dec) after recrystallization from 96% EtOH. (Found: C, 69·6, 69·7; H, 7·5, 7·2; N, 6·3; Calc. for $C_{27}H_{32}N_2O_4 \cdot H_2O$: C, 69·5; H, 7·4; N, 6·0%.) Attempts at further drying resulted in decomposition. The NMR spectrum had peaks at τ 2·63 (5 protons of the benzyl ether group), 3·45, 3·56, 3·72, 3·76 (4 isolated aromatic protons), 4·92 (2 protons of the benzyl-CH_2 group), 6·17, 6·28, 6·36 (3 three-proton peaks of the methoxy groups), and 7·48 (N-methyl). The material gave a strong blue colour with $FeCl_3$, and could be diazotized and coupled with β-naphtol to give a red dye.

The Pschorr cyclization reaction. The preceding amine (V; 2 g) was diazotized with $NaNO_2$ (0·32 g) and conc. H_2SO_4 (2·4 ml) in MeOH (50 ml). The mixture was kept at 0° for 2 hr after which it was boiled under reflux with Cu-bronze (26 g) for 20 min. After filtration and cooling, MeOH was removed *in vacuo*, and the mixture basified. A brown syrupy mass (1·6 g) was isolated with methylene dichloride, and chromatographed on alumina (40 g). Elution with methylene dichloride gave a crystalline substance, from which the benzylaporphine (VI) could be isolated by crystallization from MeOH. This compound had m.p. 148–150°, and in its NMR spectrum had peaks at τ 1·86, 3·17, 3·42 (3 isolated aromatic protons), 2·60, and 4·78 (resp. 5H and 2H from the benzyl group), 6·04, 6·13, and 6·57 (three-proton peaks, 3 OMe), and 7·46 (N—Me), λ_{max} 302, 381, and 216 mμ (ε 10,860, 13,063, and 25,600, resp.). (Found: C, 75·0; H, 6·9; N, 3·4; $C_{27}H_{29}NO_4$ requires: C, 75·2; H, 6·8; N, 3·3%.)

1,2,9-*Trimethoxy*-10-*hydroxyaporphine.* The benzylaporphine obtained above was dissolved in a mixture of glacial acetic acid and conc. HCl (3:7) and warmed at 60° for 1·5 hr. After cooling, the mixture was basified with Na_2CO_3 and extracted with methylene dichloride. The crude dl-base was treated with NaI in glacial acetic acid to afford the *hydroiodide*, which after recrystallization from EtOH had m.p. 227–228°, λ_{max} 303, 280, and 222 mμ (ε 13,490, 13,800, and 36,310 resp.) λ_{max} in 0·05 N ethanolic KOH, 327, 290, 258, and 232 mμ (ε 8251, 8449, 22,330, and 32,690 resp.). (Found: C, 51·5; H, 5·8; OMe, 20·2; Calc. for $C_{20}H_{24}NO_4I$: C, 51·1; H, 5·2; 3 OMe, 19·9%.) The crystalline free base, m.p. 140–145°, had in its NMR spectrum the following peaks: τ 2·00, 3·24, and 3·42 (3 aromatic protons), 6·10, 6·13, and 6·31 (three-proton peaks, 3 OMe), and 7·43 (N—Me). The free base was different from natural rogersine as indicated by the IR spectra and the UV spectra in alkaline medium.*

Cleavage of N-*acetylnornuciferine* VIII *with sodium in liquid ammonia.* To *N*-acetylnornuciferine (64·5 mg) in tetrahydrofurane (1 ml) and liquid ammonia (5 ml) Na was added in small portions, until a dark blue colour persisted (12 mg). After 15 min, EtOH (1 ml) was added, and the ammonia was allowed to evaporate, the residual mixture was evaporated to dryness and water (15 ml) was added. The aqueous mixture was extracted with $CHCl_3$, and any basic material removed with dil HCl aq. The neutral $CHCl_3$-residue (63 mg) was recrystallized from MeOH, m.p. 182–183°. The NMR spectrum had signals at τ 6·16 (1 OMe) and 7·80 (N—Ac) (Ref. 2), λ_{max} 310, 270, and 211 mμ (ε 4050, 11,920, and 34,760 resp.). (Found: C, 77·6; H, 6·4; N, 4·3; OMe 10·6; $C_{19}H_{19}NO_2$ requires: C, 77·8; H, 6·5; N, 4·8; one OMe, 10·6%.)

Acknowledgement—This work was supported by Messrs. Smith, Kline, and French, Philadelphia, U.S.A.

* When it was stated (Ref. 1) that the neutral UV spectra of rogersine and N-methyl-laurotetanine were identical, an error was made in reporting the ε-values of the former. The correct spectrum of rogersine is: λ_{max} 304, 282, and 219 mμ (ε 12,850, 12,850 and 32,630 resp.), $\lambda_{max}^{0\cdot05N\ KOH}$ 329 and 223 mμ (ε 19,910 and 23,000 resp.).