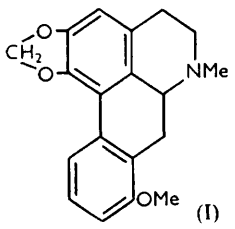
381. *The Aporphine Series. Part IV.* The Synthesis of (±)-Stephanine.*

By D. H. Hey and Ather Husain.

The synthesis of (±)-stephanine by the Bischler–Napieralski–Pschorr method is reported. The structural identity of the racemic product with that of the natural alkaloid is established by comparison of the ultraviolet and infrared absorption spectra of the two bases and their derivatives.

The alkaloid stephanine, $C_{19}H_{19}O_3N$, was isolated, together with related alkaloids of the aporphine group, from *Stephania capitata Spreng* by Tomita and Shirai.[1,2] It was assigned to the aporphine group on the basis of its ultraviolet absorption spectrum and was shown to contain one methoxyl group. The remaining two oxygen atoms were considered to be present as a methylenedioxy-group. Oxidation with permanganate gave 3-methoxyphthalic acid. Hofmann degradation followed by oxidation and decarboxylation gave a derivative of phenanthrene which was regarded as 1-methoxy-5 : 6-methylenedioxyphenanthrene. On the basis of these results the structure (I) was assigned to stephanine. As pointed out by Manske,[3] however, such a structure would be unusual in having a methoxyl group at position 1 in the aporphine system and seems from biogenetic considerations to be improbable. In order to obtain information for or against this structure the synthesis of (±)-stephanine was undertaken by the Bischler–Napieralski–Pschorr method.



(I)

The starting material, 2-methoxy-6-nitrophenylacetic acid, was prepared by Blaikie and Perkin,[4] from 2-hydroxy-6-nitrotoluene by methylation, condensation with ethyl oxalate, and oxidation of the resulting 2-methoxy-6-nitrophenylpyruvic acid. 2-Methoxy-6-nitrophenylacetic acid, erroneously described by them as a new compound, was later prepared by Cook, Loudon, and McCloskey [5] from 2-methoxy-6-nitrobenzyl cyanide, obtained from the corresponding benzyl chloride.[6] The method here used was based on that of Blaikie and Perkin. 2-Methoxy-6-nitrophenylacetic acid was converted in the normal manner into *N*-homopiperonyl-2-methoxy-6-nitrophenylacetamide, which when kept for eight days with phosphorus pentachloride in chloroform solution gave 3 : 4-dihydro-1-(2-methoxy-6-nitrobenzyl)-6 : 7-methylenedioxy*iso*quinoline, which was characterised as the hydrochloride, picrate, and methiodide. Reduction of the methiodide with zinc and hydrochloric acid gave 1-(2-amino-6-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline, which was characterised as the dipicrolonate. The free base, isolated from the dipicrolonate, was diazotised and treated with copper powder. From the resulting product 1-methoxy-5 : 6-methylenedioxyaporphine [(±)-stephanine] was isolated and characterised as the hydrochloride, chloroplatinate, and methiodide.

Ultraviolet absorption spectra were measured in 95% ethanol for natural stephanine, kindly supplied by Professor Tomita, and synthetic (±)-stephanine, as well as for their hydrochlorides and methiodides, and were found to be identical. In addition, infrared absorption spectra were measured in Nujol mulls for the two free bases and for their hydrochlorides and methiodides. So the structural identity of the two series of compounds was confirmed.

* Part III, *J.*, 1957, 2926.

[1] Tomita and Shirai, *J. Pharm. Soc. Japan*, 1942, **62**, 381.
[2] Shirai, *ibid.*, 1944, **64**, 44.
[3] Manske, "The Alkaloids," Academic Press Inc., New York, 1954, Vol. IV, p. 141.
[4] Blaikie and Perkin, *J.*, 1924, **125**, 312.
[5] Cook, Loudon, and McCloskey, *J.*, 1952, 3904.
[6] Buehler, Deebel, and Evans, *J. Org. Chem.*, 1941, **6**, 217.

After completion of this work it was learned that Shirai and Oda [7] had synthesised 1-methoxy-5 : 6-methylenedioxyphenanthrene and shown it to be identical with the compound obtained from stephanine by Hofmann degradation, followed by oxidation and decarboxylation, thus confirming the structure (I) for the alkaloid. Further, Tomita and Hirai [8] had synthesised (±)-1-methoxy-5 : 6-methylenedioxyaporphine and had shown it to be identical in structure with (−)-stephanine by a comparison of the ultraviolet absorption spectra of the methiodides. Tomita and Hirai used a different method for the preparation of their 2-methoxy-6-nitrophenylacetic acid and they obtained their *N*-homopiperonyl-2-methoxy-6-nitrophenylacetamide from the acid chloride and also directly from ω-diazo-2-methoxy-6-nitroacetophenone. The physical constants reported by Tomita and Hirai for their intermediates and derivatives are in good agreement with those recorded below. The synthetic work here reported is on several points more complete than that of Tomita and Hirai.

Experimental

2-Methoxy-6-nitrophenylacetic Acid.—2 : 6-Dinitrotoluene was converted into 2-amino-6-nitrotoluene by Brady and Taylor's method [9] and thence into 2-hydroxy-6-nitrotoluene by Noelting's method.[10] Methylation by Ruggli and Leonhardt's method [11] gave 2-methoxy-6-nitrotoluene, which was converted into 2-methoxy-6-nitrophenylacetic acid, m. p. 170—171°, in 60% yield (Found: C, 51·5; H, 4·2. Calc. for $C_9H_9O_5N$: C, 51·2; H, 4·3%), as described by Blaikie and Perkin.[4]

N-Homopiperonyl-2-methoxy-6-nitrophenylacetamide.—A solution of homopiperonylamine (1·65 g.) in dry benzene (8 ml.) was added to a solution of 2-methoxy-6-nitrophenylacetyl chloride, prepared from the acid (2·1 g.) and thionyl chloride (5 ml.) in chloroform (10 ml.), in dry benzene (15 ml.). 10% Aqueous sodium hydroxide (10 ml.) was then added dropwise. The *amide*, which separated, was collected and crystallised from methanol in needles (3·2 g.), m. p. 157—158° (Found: C, 60·15; H, 5·1. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·1%).

3 : 4-Dihydro-1-(2-methoxy-6-nitrobenzyl)-6 : 7-methylenedioxyisoquinoline.—The homopiperonylamide (2·0 g.) was finely powdered and added to well-cooled phosphorus pentachloride (2·0 g.) in dry chloroform (4 ml.). The closed flask was kept at room temperature for 8 days. The 3 : 4-dihydro*iso*quinoline hydrochloride which was deposited was collected and added at once to cold methanol (4 ml.). After 2 hr. the insoluble hydrochloride (1·4 g.; m. p. 172—174°) was collected. To a solution of the hydrochloride (2·65 g.) in ethanol (20 ml.) was added dilute ammonia solution (20 ml., *d* 0·96) dropwise with shaking. The free *base* which separated crystallised from benzene–light petroleum (b. p. 60—80°) in prismatic needles (2·20 g.), m. p. 148—149° (Found: C, 64·1; H, 4·9. $C_{18}H_{16}O_5N_2$ requires C, 63·5; H, 4·7%). The *picrate*, prepared in the normal manner, separated from ethanol in yellow needles, m. p. 214—215° (decomp.) (Found: C, 50·7; H, 3·9. $C_{18}H_{16}O_5N_2,C_6H_3O_7N_3$ requires C, 50·6; H, 3·4%). The *methiodide* separated from methanol in pale yellow flakes, m. p. 212—213° (decomp.) (Found: C, 47·0; H, 3·8. $C_{18}H_{16}O_5N_2,CH_3I$ requires C, 47·3; H, 3·9%).

1-(2-Amino-6-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxyisoquinoline.—To an ice-cold suspension of the preceding methiodide (1·0 g.) in ethanol (30 ml.) was added concentrated hydrochloric acid (20 ml.) and then zinc dust (4·0 g.) during 10 min. After 30 min. more the mixture was heated on a boiling-water bath for 45 min. and then boiled under reflux for 15 min. The mixture was filtered, cooled in ice, and made alkaline with aqueous ammonia (*d* 0·88). The precipitate was washed twice with water, and the alkaline filtrate was extracted several times with ether. Evaporation of the dried (Na_2SO_4) ethereal extract left a residue to which a hot solution of picrolonic acid (2·0 g.) in ethanol (100 ml.) was added. In the cold the *dipicrolonate* (1·6 g.) separated, having m. p. 194—195° (decomp.) (Found: C, 54·1; H, 5·0. $C_{19}H_{22}O_3N_2,2C_{10}H_8O_5N_4,\frac{1}{2}H_2O$ requires C, 54·2; H, 4·5%).

(±)-Stephanine [(±)-1-Methoxy-5 : 6-methylenedioxyaporphine].—A suspension of the above

[7] Shirai and Oda, *J. Pharm. Soc. Japan*, 1956, **76**, 1287.
[8] Tomita and Hirai, *ibid.*, 1957, **77**, 290.
[9] Brady and Taylor, *J.*, 1920, **117**, 877.
[10] Noelting, *Ber.*, 1904, **37**, 1020.
[11] Ruggli and Leonhardt, *Helv. Chim. Acta*, 1924, **7**, 701.

dipicrolonate (2·5 g.) in cold methanol (10 ml.) was triturated with a cold mixture of concentrated sulphuric acid (2·5 ml.) and methanol (10 ml.). The picrolonic acid (1·45 g.), which separated, was filtered off and washed with methanol. To the combined filtrate and washings was added sodium nitrite (0·21 g.) in water (3·0 ml.) at −5° to 0°. After 10 hr. at 0° copper powder (0·5 g.) was added and a brisk evolution of nitrogen ensued. After being stirred for 30 min. the mixture was boiled under reflux for a similar period. The mixture was filtered and water (25 ml.) was added to the filtrate, followed by concentrated ammonia solution (*d* 0·88; 7·0 ml.). The mixture was then repeatedly extracted with ether (total volume 350 ml.), and the dried extract concentrated to about 5 ml. to which 15% hydrochloric acid (4·0 ml.) was added. The hydrochloride which separated was collected, dissolved in water (5·0 ml.), and extracted once with ether and several times with chloroform (total volume 150 ml.). Evaporation of the dried (Na_2SO_4) chloroform extract left (±)-stephanine hydrochloride, which crystallised from methanol–ether in needles (0·12 g.), m. p. 269—270° (decomp.) (Found: C, 65·35; H, 5·7. Calc. for $C_{19}H_{19}O_3N,HCl$: C, 66·0; H, 5·8%). (±)-Stephanine, liberated from the hydrochloride with ammonia in ethanol, crystallised from aqueous ethanol and then from benzene in needles, m. p. 131—133° (Found: C, 74·25; H, 6·1. Calc. for $C_{19}H_{19}O_3N$: C, 73·8; H, 6·2%). The *chloroplatinate* separated from ethanol in dull yellow needles, m. p. 220—222° (decomp.) (Found: Pt, 23·8. $C_{19}H_{19}O_3N,H_2PtCl_6,6H_2O$ requires Pt, 23·6%). The methiodide, prepared in the normal manner, had m. p. 221—222° (decomp.) (Found: C, 53·2; H, 5·2. Calc. for $C_{19}H_{19}O_3N,CH_3I$: C, 53·0; H, 4·9%). With Erdmann's reagent both the synthetic (±)-stephanine and natural (−)-stephanine gave a yellowish-orange colour; with Frohde's reagent both gave a yellowish-green colour.

The authors thank Professor Tomita, University of Kyoto, for a specimen of natural stephanine and for informing them of his completed synthesis of (±)-stephanine. Thanks are also accorded to the Ministry of Education, Government of Pakistan, for the award (to A. H.) of an Overseas Scholarship.

King's College, University of London,
Strand, London, W.C.2. [*Received, December 16th*, 1957.]