Tetrahedron. Vol 26, pp. 4649 to 4653. Pergamon Press 1970. Printed in Great Britain

THE SYNTHESIS OF N-METHYLOVIGERINE

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(*Received in USA* 25 *May* 1970; *Received in the UK for publication* 25 *June* 1970)

Abstract—A synthesis is described for (±)-1,2,10,11-*bis* methylenedioxyaporphine (**2**). The latter proved to be the racemic form of the alkaloid (+)-N-methylovigerine, thus confirming the structures assigned earlier to this alkaloid and to the related base ovigerine on the basis of spectroscopic evidence and chemical transformations.

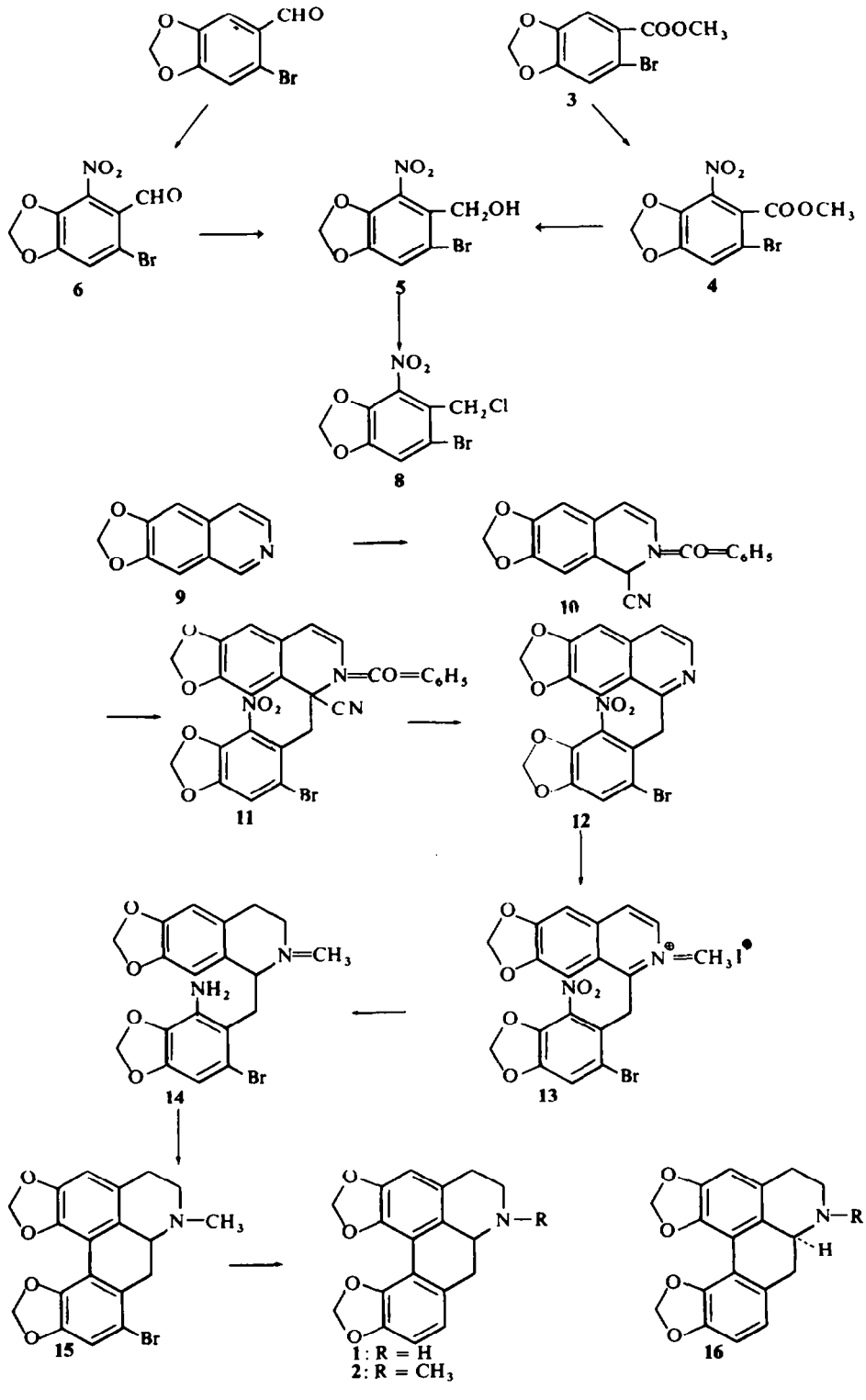
THE isolation of two new non-phenolic aporphine alkaloids, ovigerine and N-methylovigerine, was reported from *Hernandia ovigera* L. in 1966.[1,2] Structures **1** and **2** were assigned to ovigerine and N-methylovigerine, respectively, on the basis of spectroscopic considerations, N-methylation of **1** to **2**, and chemical transformation of **2** to O,O-dimethylmagnoflorine iodide.[1,*] We now report a total synthesis of racemic N-methylovigerine, thus confirming the earlier assigned structures of this natural base and of the related noraporphine, ovigerine.

The synthesis of an aporphine having a 10,11-methylenedioxy substituent has not been reported previously. Such a synthesis involves an interesting synthetic problem, since a suitable intermediate should be a 2-nitro (2-iodo) substituted piperonal or piperonylic acid, although the literature records only the formation of the corresponding 6-substituted compounds by direct electrophilic substitution reactions. Dallacker has reported, however, that nitration of methyl 6-bromopiperonylate (**3**) gives methyl 6-bromo-2-nitropiperonylate (**4**).[3] The latter seemed to be a suitable starting material for our synthesis since the bromine atom of **4** can serve the function of a removable blocking group.

Lithium borohydride reduction of the bromo nitro ester **4** afforded the corresponding alcohol **5**, m.p. 92°. A more convenient alternate route to alcohol **5** consisted in the sodium borohydride reduction of 6-bromo-2-nitropiperonal (**6**, m.p. 89°), which was formed in good yield by the careful low temperature nitration of the readily prepared 6-bromopiperonal (**7**).[4] Reaction of **5** with thionyl chloride gave 6-bromo-2-nitropiperonyl chloride (**8**, m.p. 143°).

Treatment of 6,7-methylenedioxyisoquinoline (**9**) with benzoyl chloride and potassium cyanide gave the previously unreported Reissert compound[5] **10**, m.p. 168°. Alkylation of the latter by chloride **8** was carried out in DMF solution containing sodium hydride[6] to give the alkylated product **11**, which was conveniently hydrolyzed

* No assignment of the absolute configuration of (+)-ovigerine (**1**) or (+)-N-methylovigerine (**2**) was made in our original publication describing their isolation. They may be assumed to have the complete structure (**16**) (R = H or CH_3) on the apparently valid assumption that all dextrorotatory aporphines have the L (or S) configuration at the 6a C atom.[8] A similar assignment is given in Ref 2, in which overigine was independently named "hernovine"


CHO
Br
COOCH3
3
NO2
CHO
6
CH2OH
5
4
CH2Cl
8
9
N=CO=C6H5
CN
10
11
12
N=CH3
NH2
14
N=CH3I
13
15
N–CH3
N–R
1: R = H
2: R = CH3
16
H

in situ by the addition of Triton B[7] to give the crystalline benzylisoquinoline derivative **12**, m.p. 192°. The methiodide (**13**) of the latter was reduced by sodium borohydride, followed by zinc in acetic acid, to give the corresponding aminobenzyl tetrahydroisoquinoline **14** as its hydrochloride, m.p. 178°. Diazotization of amine **14**, followed by slow decomposition of the resulting diazonium solution, gave crude 8-bromo-N-methylovigerine (**15**); the latter was directly reduced by hydrazine hydrate in the presence of palladium to racemic N-methylovigerine (**2**), isolated in 16% yield in the form of its crystalline hydroiodide. The corresponding free base was spectrally identical with the dextrorotatory base isolated from *Hernandia ovigera*.

It is very likely that additional new aporphine alkaloids substituted in the D-ring by only a 10,11-methylenedioxy group will be found in nature. The method described in this paper using halide **8** should be of general applicability to the synthesis of such compounds.

EXPERIMENTAL

Analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. M.ps are uncorrected. NMR spectra were run in $CDCl_3$ (TMS internal standard) using a Varian A-60 instrument. UV spectra were run in 95% EtOH unless otherwise stated, using a Perkin-Elmer Model 202 Spectrophotometer.

Methyl 6-bromo-2-nitropiperonylate (**4**)

A modification of the reported method was employed. Compound **3** (0·250 g, 1 mmol) was added during 10 min to a stirred mixture of red fuming HNO_3 (6 ml) and AcOH (6 ml) at −25°. After 5 additional min, the soln was diluted with water. Crystallization of the ppt from MeOH gave **4**. (0·200 g, 66%), m.p. 131° (lit[3] 131°). The NMR spectrum of **4** showed three sharp singlets at δ 7·28, 6·30 and 3·95 in the expected ratio for the aromatic, methylenedioxy, and ester protons, respectively. An analysis of ester **4** is given below, since analytical values are not recorded in the lit. (Found: C, 35·24; H, 2·13. Calcd. for $C_9H_6NO_6Br$: C, 35·42; H, 1·97%).

6-Bromo-2-nitropiperonal (**6**)

To a mixture of red fuming HNO_3 (6 ml) and AcOH (6 ml) at −25° was added 6-bromopiperonal (0·250 g, 1·1 mmol) with stirring. As soon as the solid dissolved (5 min), the soln was poured onto ice and the yellow ppt was crystallized from aqueous MeOH to give pure **6** (0·210 g, 76%), m.p. 89°. (Found: C, 35·23; H, 1·62; N, 5·16. Calcd. for $C_8H_4NO_5Br$: C, 35·03; H, 1·46; N, 5·11%).

6-Bromo-2-nitropiperonyl alcohol (**5**)

A. *From ester* **4**. $LiBH_4$ (0·200 g, 60 mmol) was added to a stirred soln of **4** (0·500 g, 1·7 mmol) in THF (50 ml) and the soln was refluxed for 3 hr. MeOH (5 ml) was added to destroy excess reductant, the mixture was evaporated *in vacuo*, and the residue was shaken with water and chloroform. Evaporation of the dried organic extract, followed by crystallization of the residue from aqueous MeOH, gave 0·340 g (61%) of **5**, m.p. 92°. (Found: C, 34·71; H, 1·68; N, 4·98. Calcd. for $C_8H_6NO_5Br$: C, 34·70; H, 1·96; N, 5·07%).

B. *From aldehyde* **6**. $NaBH_4$ (0·100 g, 30 mmol) was added to a soln of **6** (0·100 g, 0·5 mmol) in MeOH (10 ml). After refluxing for 5 min, the soln was evaporated *in vacuo* and the product isolated as in Part A to give 0·070 g (69%) of **5** as yellow needles, m.p. 92°, identical (IR) with material prepared from **4**.

6-Bromo-2-nitropiperonyl chloride (**8**)

Thionyl chloride (2 ml) was added to a soln of **5** (0·200 g, 0·7 mmol) in chloroform (10 ml). Evaporation of the solvent and crystallization of the residue from hexane gave 0·200 g (95%) of **8** as yellow needles, m.p. 143°. (Found: C, 32·41; H, 1·60. Calcd. for $C_8H_5NO_4BrCl$: C, 32·65; H, 1·71%).

1-Cyano-2-benzoyl-6,7-methylenedioxy-1,2-dihydroisoquinoline (**10**).

Benzoyl chloride (0·5 ml) was added dropwise to a stirred mixture of **9**[9] (0·500 g, 2·8 mmol), CH_2Cl_2 (20 ml), KCN (0·500 g, 7·5 mmol) and water (2 ml); external ice cooling was maintained during the addition.

After an additional 1 hr stirring, CH_2Cl_2 (50 ml) was added and the organic phase was worked up in the usual manner for the neutral product. White crystals of **10** (0·350 g, 40%), m.p. 168°, were obtained after crystallization from aqueous MeOH. (Found: C, 71·12; H, 3·72; N, 9·05. Calcd. for $C_{18}H_{12}N_2O_3Br$: C, 71·05; H, 3·94; N, 9·21%).

1-(6-*Bromo*-2-*nitropiperonyl*)-6,7-*methylenedioxyisoquinoline* (**12**)

Sodium hydride (0·050 g, 51% in mineral oil) was added to a soln of **10** (0·250 g, 0·8 mmol) and **8** (0·300 g, 1·0 mmol) in dry DMF (20 ml) with external ice cooling. The mixture was stirred for 4 hr under N_2, and the intermediate **11** was then directly hydrolyzed by adding Triton B (4 ml, 40% methanolic benzyltrimethylammonium hydroxide) and keeping the mixture at room temp for an additional 12 hr. Water and chloroform were then added, and the dried chloroform extract was evaporated to give a residue which afforded 0·150 g (43% based on **10**) of yellow **12**, m.p. 192°, after crystallization from aqueous MeOH. The NMR spectrum showed only aromatic hydrogens (1 each at δ 6·7, 6·8, 7·1, 7·3 and 8·0), a benzylic methylene (δ 5·2) and two unsplit methylenedioxy methylenes (δ 5·7 and 5·85). (Found: C, 49·89; H, 2·41; N, 6·39. Calcd. for $C_{18}H_{11}N_2O_6Br$: C, 50·10; H, 2·55; N, 6·49%).

Methiodide (**13**) *of isoquinoline* **12**

A mixture of **12** (0·100 g, 0·25 mmol), MeI (2 ml) and MeOH (5 ml) was refluxed for 2 hr. Evaporation of the soln and crystallization of the residue from MeOH gave 0·035 g (25%) of **13** as yellow needles, m.p. 208°. (Found: C, 39·50; H, 2·61; N, 4·60. Calcd. for $C_{19}H_{14}N_2O_6BrI$: C, 39·72; H, 2·43; N, 4·86%).

1-(6-*Bromo*-2-*aminopiperonyl*)-2-*methyl*-5,6-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline* (**14**)

A soln of **12** (0·200 g, 0·34 mmol) and $NaBH_4$ (0·200 g) in MeOH (10 ml) was kept for 2 hr at room temp. AcOH (2 N, 10 ml) was added slowly, followed by Zn dust (0·05 g), and the mixture was stirred overnight. The diluted and basified reaction was extracted with benzene, and the dried and the concentrated extract was passed through a short column of alumina. HCl was passed into the benzene eluate and the resulting solid was crystallized from MeOH to give 0·080 g (50%) of the *hydrochloride* of **14**, m.p. 178°. (Found: C, 49·98; H, 4·21. Calcd. for $C_{19}H_{20}N_2O_4BrCl$: C, 50·11; H, 4·39%).

N-*Methylovigerine* (**2**)

A soln of the hydrochloride of **14** (0·100 g) in HCl (2 N, 10 ml) was cooled to 0° and a soln of $NaNO_2$ (0·100 g) in water (2 ml) was added. After a further 1 hr at 0°, the reaction soln was kept for 3 hr at room temp and then heated on the steam bath until it gave a negative naphthol test. Zn dust was added to reduce colored by-products and heating was continued for 30 min. The cooled soln was extracted with benzene, then made basic with ammonia and extracted with chloroform. Evaporation of the chloroform gave a residue of crude **15**, which was directly refluxed with hydrazine hydrate (5 ml) and 30% Pd–C (0·1 g) for 12 hr. The cooled mixture was filtered and the catalyst washed with EtOH, the filtrate diluted with water, extracted with chloroform, and the organic extract evaporated. The residue was purified by chromatography (benzene) on alumina to give amorphous **2**, identical by IR, NMR, and TLC (chloroform, silica gel) with the natural alkaloid. The yield of synthetic **2** from several runs (total amount of amine **14** = 0·250 g or 0·6 mmol) was 0·030 g (16%). The synthetic base was analyzed as its hydroiodide, which formed yellow-white crystals from MeOH, m.p. 241–243° dec. (Found: C, 50·40; H, 3·90; N, 3·00. Calcd. for $C_{19}H_{18}NO_4I$: C, 50·44; H, 3·98; N, 3·09%).

Acknowledgement—We thank the National Institutes of Health for a grant (CA 11445) in support of this work.

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