Synthesis of (±)-Neolitsine

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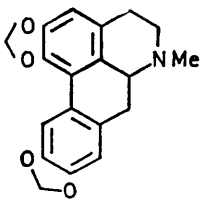
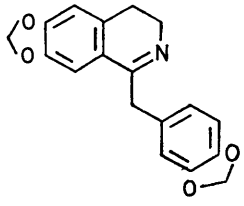
The structure of neolitsine (I) has been confirmed by synthesis of the racemic compound, prepared from benzylisoquinoline derivatives by a photolytic ring closure.

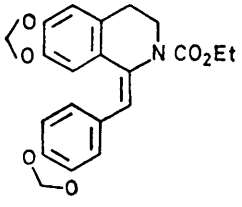
NEOLITSINE, an alkaloid isolated from *Neolitsea pulchella*, was assigned structure (I) [1] on the basis of spectral evidence. We here describe the synthesis of racemic neolitsine (I) which confirms the structure suggested. Among the various methods available for the formation of the tetracyclic ring system of the aporphines, photocyclization has proved to be useful, notably in the synthesis of nuciferine and glaucine.[2]



(I)



(II)



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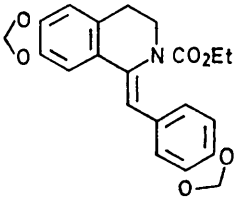
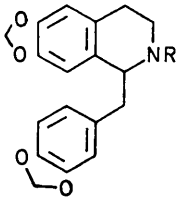
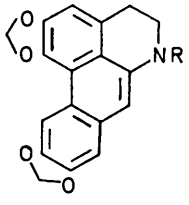


(IV)



(V) R = CO_2Et
(VI) R = H
(VII) R = Me



(VIII) R = CO_2Et
(IX) R = Me

Because compound (II) was already available to us [3] we used it as starting material in the synthesis of (±)-neolitsine (I). Compound (II) [3] was transformed into a mixture of the (*E*), m.p. 108—109°, and (*Z*), m.p. 160—162°, isomers (III) and (IV) by treatment with ethyl chloroformate under Schotten–Baumann conditions. The ratio of the *E*- and *Z*-isomers in the product mixture was *ca.* 1 : 4 and they were separated by silica gel column chromatography (dry method).

The configurations of the two aromatic rings about the double bond in isomers (III) and (IV) were assigned by use of u.v. and n.m.r. spectroscopy. The u.v. spectrum of the high melting isomer (IV) was consistent with it having a *trans*-stilbene group, while the u.v. absorption of isomer (III) suggested a product with *cis*-geometry. These u.v. data agree well with those [4] for compounds of similar structure. The high-field triplet due to the CO_2CH_2Me group appeared at δ 0·90 in the n.m.r. spectrum of isomer (IV) and at 1·20 for isomer (III). In the *Z*-isomer (IV) this methyl group should be more shielded by the aromatic ring of the benzylidene function than in the *E*-isomer (III).

We attempted to provide additional evidence of geometrical isomerism by subjecting compound (IV) to reductive treatment with hydrochloric acid in the presence of amalgamated zinc. This gave a product (V) which was indistinguishable on t.l.c. from that obtained by the same means from compound (III) and from that prepared by ethyl chloroformate treatment of (VI).[3]

Unfortunately compound (V) was not crystalline; however, hydride reduction, in the presence of aluminium chloride, yielded the known [5] isoquinoline derivative (VII).

Solutions of (IV) in Pyrex in ethanol containing iodine and copper(II) acetate, were irradiated with a 400 W high-pressure lamp.[2,4] Samples removed after various times were examined by t.l.c. The results indicated that photochemical cyclization proceeded most readily when the solutions were allowed to warm (45°). Irradiation in quartz does not produce clean products and it appears that the filtering action of the Pyrex towards high energy radiation avoids decomposition of the product (VIII). Attempted irradiation of isomer (III) gave largely tarry material.

That cyclization had occurred in the desired direction, to give the methylenedioxy group at C-9 and C-10 in ring D, was evident from the presence of low-field singlets in the n.m.r. spectra of compound (VIII) and (IX), and which were assigned to H-11 in each of these compounds.

N-Ethoxycarbonyl-6a,7-dehydronoraporphine (VIII) reacted smoothly with lithium aluminium hydride–aluminium chloride in dry tetrahydrofuran to afford the

[1] W. H. Hui, S. N. Loo, and H. R. Arthur, *J. Chem. Soc.*, 1965, 2285.
[2] M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, 1970, **35**, 175.
[3] R. M. Sotelo and D. Giacopello, *Austral. J. Chem.*, 1972, **25**, 385.
[4] N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Letters*, 1966, 2941.
[5] J. S. Buck, W. H. Perkin, and T. S. Stevens, *J. Chem. Soc.*, 1925, 1462.

dehydroaporphine (IX) in good yield. The n.m.r. spectrum of (IX) showed no signals for an ethoxycarbonyl group but had a sharp singlet due to an *N*-methyl group at δ 3·10. Compound (IX) was reduced with amalgamated zinc in 2*N*-hydrochloric acid–ethanol (1 : 1) to yield (±) neolitsine (I), m.p. 148—150° (from acetone), identical with the natural product by chromatographic behaviour and spectroscopic properties.

EXPERIMENTAL

Unless otherwise stated the following generalizations apply. U.v. spectra were measured with a Beckman DK-2 spectrometer for solutions in ethanol. I.r. spectra were determined with a Perkin-Elmer 137B infracord instrument as suspensions in Nujol. N.m.r. spectra were taken for solutions in deuteriochloroform with a Varian A60 spectrometer (tetramethylsilane as internal reference). T.l.c. was carried out on silica plates with chloroform–ethyl acetate (98 : 2) as developing solvent. Solutions in organic solvents were dried over magnesium sulphate.

(E)- *and* (Z)-*Ethyl* 6,7-*Methylenedioxy*-1-(3,4-*methylenedioxybenzylidene*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (III) *and* (IV).—To a mixture of the dihydroisoquinoline (II) (1·2 g), 10% aqueous sodium carbonate (30 ml), and chloroform (60 ml), ethyl chloroformate (0·6 ml) was added dropwise with stirring at 10—15°. After stirring for 45 min, the organic layer was separated, washed with 2*N*-hydrochloric acid (30 ml) and water (2 × 30 ml), and dried. Evaporation to dryness afforded a brown oil (1·3 g) which was chromatographed on silica gel (100 g) with benzene (each fraction 10 ml, 300 ml), benzene–ethyl acetate 97 : 3 (200 ml), 95 : 5 (600 ml), 93 : 7 (200 ml), and 9 : 1 (300 ml) as eluants; elution with benzene–ethyl acetate 97 : 3, 95 : 5, and 93 : 7 gave the (Z)-*isomer* (IV) (800 mg, 80%) as prisms, m.p. 160—162° (from ethanol), R_F 0·50 (Found: C, 66·1; H, 5·3; N, 3·8. $C_{21}H_{19}NO_6$ requires C, 66·1; H, 5·0; N, 3·7%), $\lambda_{max.}$ 217 (log ε 4·55), 244sh (4·50), 298sh (4·22), and 337 nm (4·48), $\nu_{max.}$ 1650 (CO) and 935 (OCH_2O) cm^{-1}, δ 0·90 (3H, t, *J* 7 Hz, OCH_2CH_3), 2·85 (2H, m, NCH_2CH_2), 3·90 (4H, m, NCH_2CH_2 and OCH_2CH_3), 5·91 (4H, s, 2 × OCH_3), 6·55 (1H, s, 5-ArH), 6·60 (1H, d, *J* 5 Hz, 5′-ArH), 6·78 (1H, s, 8-ArH), 6·80 (1H, dd, *J* 5 and 1 Hz, 6′-ArH), 7·00 (1H, d, *J* 1 Hz, 2′-ArH), and 7·13 (1H, s, α-H). Elution with benzene–ethyl acetate (9 : 1) gave the (E)-*isomer* (III) (150 mg, 20%) as needles, m.p. 108—109° (from methanol), R_F 0·18 (Found: C, 63·5; H, 5·6; N, 3·4. $C_{21}H_{19}NO_6$, MeOH requires C, 63·9; H, 5·6; N, 3·4%), $\lambda_{max.}$ 230 (log ε 4·39), 285 (3·88), and 312 nm (3·83), $\nu_{max.}$ 1660 (CO) and 930 (OCH_2O) cm^{-1}, δ 1·20 (3H, t, *J* 7 Hz, OCH_2CH_3), 2·86 (2H, t, *J* 6 Hz), NCH_2CH_2), 4·08 (2H, q, *J* 7 Hz, OCH_2CH_3), 5·92 (2H, s, OCH_2O), 6·02 (2H, s, OCH_2O), 6·70, 6·75, and 7·21 (6H, each s, ArH). The assignment of the proton signals and coupling constants followed from spin-decoupling experiments.

Ethyl 6,7-*Methylenedioxy*-1-(3,4-*methylenedioxybenzyl*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (V).—(*a*) To a warm (50°) and well stirred mixture of zinc dust (500 mg), 3% aqueous mercury(II) chloride (1 ml), and 2*N*-hydrochloric acid (6 ml), was added a solution of the (*Z*)-isomer (IV) (50 mg) in ethanol (5 ml). After 20 min, concentrated hydrochloric acid (0·5 ml) was added, and the stirring was continued for further 20 min at 50°. The suspension was poured into water–dichloromethane (1 : 1; 50 ml) and the solid was filtered. The dichloromethane phase and washings (2 × 25 ml) of the aqueous phase were dried and evaporated *in vacuo*, giving a brown oil (50 mg). Chromatography over silica gel (5 g), eluting with benzene, yielded a product which was sublimed (140°, 10^{-3} mmHg) to give the amorphous *ester* (V), R_F 0·75 (Found: C, 65·3; H, 5·6; N, 3·7. $C_{21}H_{21}NO_6$ requires C, 65·8; H, 5·5; N, 3·6%), $\lambda_{max.}$ 237 (log ε 4·05), and 290 nm (4·06), $\nu_{max.}$ (film) 1670 (CO) and 930 (OCH_2O) cm^{-1}, δ 1·21 (3H, m, OCH_2CH_3), 2·91 (2H, m, OCH_2CH_3), 5·85 (4H, s, 2 × OCH_2O), 6·38 (1H, s, 8-ArH), 6·51, and 6·61 (4H, each s, ArH).

(*b*) Likewise, the (*E*)-isomer (III) (40 mg) in ethanol (5 ml) was added with stirring to a mixture of zinc dust (300 mg), 3% aqueous mercury(II) chloride (1 ml), and 2*N*-hydrochloric acid (5 ml) at 50—60°. Work-up as before gave pure compound (V), identical with the product obtained in (*a*) by t.l.c. and i.r. spectra.

(*c*) Ethyl chloroformate (0·05 ml) was added to a stirred mixture of 6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (VI) hydrochloride [3] (100 mg), chloroform (30 ml), and 10% aqueous sodium carbonate (30 ml) at 15—20°. After 45 min of continuous stirring, the mixture was extracted with chloroform (3 × 30 ml). The extracts were washed with 2*N*-hydrochloric acid (2 × 15 ml), water (2 × 15 ml), dried, and evaporated *in vacuo*. The residue was purified as described in (*a*) to give compound (V).

2-*Methyl*-6,7-*methylenedioxy*-1-(3,4-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydroisoquinoline* (VII).—To a solution of the ester (V) (46 mg) in dry tetrahydrofuran (3·5 ml), a slurry of lithium aluminium hydride–aluminium chloride in tetrahydrofuran (3·5 ml) was added (the slurry contained 23 mg ml^{-1} of lithium aluminium hydride and 40 mg ml^{-1} of aluminium chloride). The mixture was stirred at 55° for 30 min. Then, more slurry (1·5 ml) was added and the stirring continued for a further 20 min. Ethyl acetate (1 ml) was added to decompose the excess of reagent. Dilution of the mixture with water (5 ml) and extraction with dichloromethane (3 × 5 ml) afforded the isoquinoline (VII) (37 mg), m.p. 95—96° (from ether) (lit.,[5] m.p. 96—97°), R_F 0·44 (methanol), $\lambda_{max.}$ 237 (log ε 4·10), and 290 nm (4·10), $\nu_{max.}$ (film) 930 cm^{-1}, δ 2·48 (3H, s, NCH_3), 5·88 and 5·93 (4H, each s, 2 × OCH_2O), 6·26 (1H, s, 8-ArH), 6·53 (1H, s, 5-ArH), 6·63, and 6·68 (3H, s, ArH).

N-*Ethoxycarbonyl*-1,2,9,10-*bismethylenedioxy*-6a,7-*dehydronoraporphine* (VIII).—A solution of the (*Z*)-isomer (IV) (250 mg), copper(II) acetate (100 mg), and iodine (75 mg) in ethanol (625 ml) was divided into eleven portions which were placed in Pyrex test tubes surrounding a 400 W high pressure lamp. The solutions were irradiated with stirring for 6 h and the reaction was monitored by t.l.c. and u.v. spectroscopy. Evaporation of the solvent left a solid which was dissolved in dichloromethane (250 ml), washed with 10% aqueous sodium thiosulphate (100 ml), and water (3 × 100 ml). The dried extract was evaporated to afford a dark brown solid which was chromatographed on silica gel (30 g) with benzene (200 ml), benzene–ethyl acetate 99 : 1 (200 ml), and benzene–ethyl acetate 98 : 2 (400 ml) as eluants. Elution with benzene–ethyl acetate 99 : 1 and 98 : 2 gave the *noraporphine* (VIII) as plates (100 mg), m.p. 206—207° (from ethanol), R_F 0·50 (Found: C, 66·3; H, 4·6; N, 3·8. $C_{21}H_{17}NO_6$ requires C, 66·5; H, 4·5; N, 3·7%), $\lambda_{max.}$ 238 (log ε 4·85), 291sh (4·28), 328 (4·27), 338 (4·28), 360 (3·97), and 380 nm (3·97), $\nu_{max.}$ 1670 (CO) and 950 (OCH_2O) cm^{-1}, δ 1·35 (3H, t, *J* 7 Hz, OCH_2CH_3), 3·16 (2H, t, *J* 6 Hz, NCH_2CH_2), 4·10 (2H, t, *J* 6 Hz, NCH_2CH_2),

4·35 (2H, q, *J* 7 Hz, OCH_2CH_3), 6·01 (2H, s, OCH_2O), 6·25 (2H, s, OCH_2O), 7·03, 7·20, and 7·78 (3H, each s, 3-, 7-, and 8-ArH), and 8·53 (1H, s, 11-ArH).

1,2,9,10-*Bismethylenedioxy*-6a,7-*dehydroaporphine* (IX).—A suspension of lithium hydride (115 mg) and aluminium chloride (200 mg) in tetrahydrofuran (10 ml) was slowly added to a solution of the noraporphine (VIII) (90 mg) in dry tetrahydrofuran (7 ml), and the mixture was heated (50—60°), with stirring for 1 h. After addition of ethyl acetate, 5% aqueous sodium hydroxide (50 ml) was added and the product was extracted with chloroform (3 × 30 ml). The usual work-up gave a residue which was recrystallized from ethanol to afford the *aporphine* (IX) (65 mg), needles, m.p. 201—203° (from ethanol), R_F 0·63 (Found: C, 70·9; H, 4·6; N, 4·2. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·4%), $\lambda_{max.}$ 262 (log ε 4·69), 304 (3·89), and 338 nm (4·05), $\nu_{max.}$ (KBr) 933 (OCH_2O) cm^{-1}, δ 3·00 (3H, s, NCH_3), 3·23 (4H, m, CH_2), 5·96 (2H, s, OCH_2O), 6·13 (2H, s, OCH_2O), 6·85, and 6·98 (3H, each s, 3-, 7-, and 8-ArH), and 8·35 (1H, s, 11-ArH).

(±)-*Neolitsine* (I).—A solution of the aporphine (IX) (80 mg) in ethanol (8 ml) was added dropwise to a warm (50—60°) and well stirred mixture of zinc dust (5 g), 3% aqueous mercury(II) chloride (2 ml), 2*N*-hydrochloric acid (12 ml), and ethanol (2 ml). Stirring and heating were continued for 20 min. Then concentrated hydrochloric acid (1 ml) was added and stirring was continued for a further 30 min. After removal of solids the solution was basified with aqueous ammonia and then extracted with dichloromethane (3 × 35 ml). The extracts were washed with water (2 × 20 ml), dried, and evaporated to leave a viscous oil. Column chromatography over silica gel (3 g), eluting with benzene, benzene–methanol 99 : 1, and benzene–methanol 95 : 5 gave a yellow oil (45 mg) which was chromatographed on alumina (3 g), eluting with benzene. The product, on crystallization from acetone, furnished needles of racemic neolitsine (I), m.p. 148—150° (lit.,[1] m.p. 149—150° for the optically active compound), R_F 0·52, $\lambda_{max.}$ 284 (log ε 3·89) and 310 nm (4·10). The i.r. spectrum of this product in chloroform solution, was superimposable on that for the natural compound.

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