Studies on the Syntheses of Heterocyclic Compounds. Part 678.† Photoracemisation and Photoepimerisation of the Phthalidylisoquinoline Alkaloids (—)-α-Narcotine and (—)-β-Hydrastine

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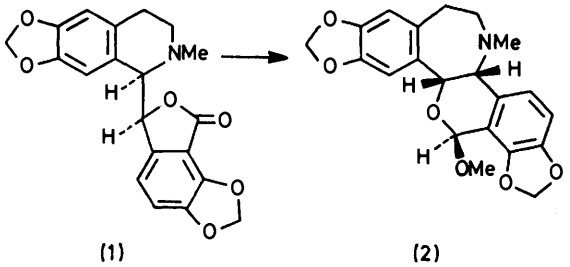
Irradiation of (−)-α-narcotine (3) in tetrahydrofuran gave a mixture of racemates of two epimers, (±)-α-narcotine (5) and (±)-β-narcotine (7). Similarly, irradiation of (−)-β-hydrastine (4) afforded (±)-α-hydrastine (8) and (±)-β-hydrastine (6).

PHTHALIDYLISOQUINOLINE alkaloids are characterised by the presence of a γ-lactone ring and closely resemble rheadan alkaloids. The transformation of phthalidylisoquinolines into rheadans has been suggested as a biogenetic sequence.[1] In fact, the phthalidylisoquinoline

† Part 677, T. Kametani, Y. Satoh, M. Takemura, Y. Ohta, M. Ihara, and K. Fukumoto, *Heterocycles*, 1976, **5**, 175.

[1] F. Šantavý, J. L. Kaul, L. Hruban, L. Dolejš, V. Hanus, K. Bláha, and A. D. Cross, *Coll. Czech. Chem. Comm.*, 1965, **30**, 335, 3479; J. Hrbek, jun., F. Šantavý, and L. Dolejš, *ibid.*, 1970, **35**, 3712.

alkaloid (—)-bicuculline (1) has been converted into the naturally occurring (+)-rhoeadine (2).[2]

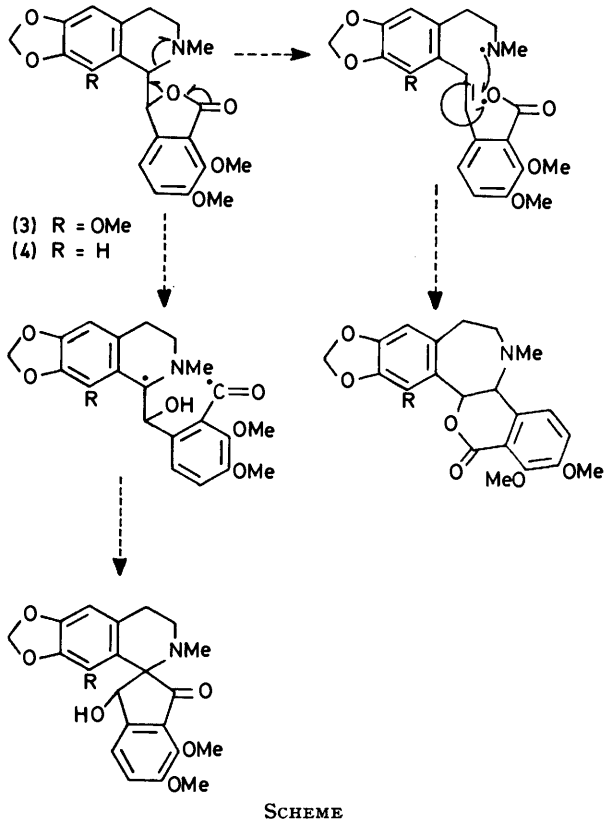


(1) (2)

We have previously[3] reported the synthesis of the phthalidylisoquinoline alkaloids cordrastine and hydrastine by addition of a diazomethylbenzoate to a 3,4-dihydroisoquinolinium iodide, probably *via* an aziridinium salt. In this reaction, no rheadan-type compound was detected. We have now investigated the possibility of achieving the photochemical transformation of phthalidylisoquinoline alkaloids into rheadan alkaloids and/or other alkaloids by a mechanism of the type shown in the Scheme.

Irradiation of (—)-α-narcotine (3), $[\alpha]_D$ —198° ($CHCl_3$), in dry tetrahydrofuran through Pyrex with a 450 W mercury lamp did not give the expected products, but a mixture of racemates of two epimers [(5) and (7)] together with a small amount of 6,7-dimethoxyphthalide (9). These products could be separated by chromatography on silica gel. Compound (5) was characterised from microanalytical and spectral data. Its i.r. spectrum [$\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1}] showed the presence of a five-membered lactone ring, and its n.m.r. spectrum was identical with that of natural narcotine, but the i.r. spectrum of a KBr disc was different from that of the natural product. Moreover, the compound showed no optical rotation. These data confirmed that the compound was (±)-α-narcotine (5).

resonances, a methylenedioxy-signal, and resonances for three aromatic protons at δ 6.30 (5-H), 6.90 (5′- or 6′-H, d, *J* 8 Hz), and 7.16 (5′- or 6′-H, d, *J* 8 Hz). These data indicated that the product was (±)-β-narcotine (7), which was confirmed by direct comparison with an

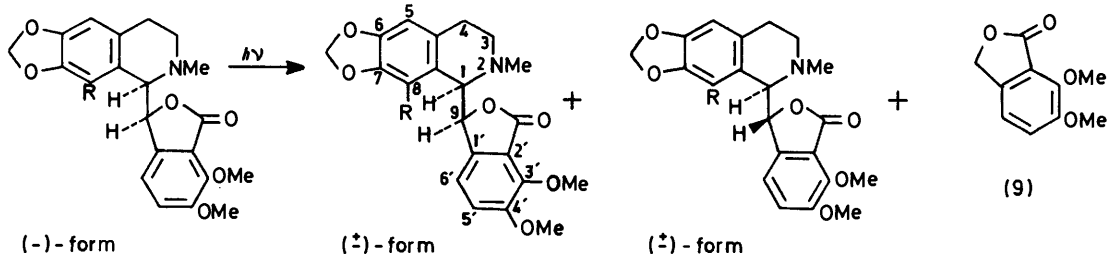


(3) R = OMe
(4) R = H

SCHEME

authentic sample of the (—)-form.[4,5] Irradiation of (—)-α-narcotine in methanol gave only the phthalide (9).

Similarly, irradiation of (—)-β-hydrastine (4), $[\alpha]_D$



(-)-form (±)-form (±)-form (9)
(3) R = OMe (5) R = OMe (7) R = OMe
(4) R = H (6) R = H (8) R = H

The other product (6), $C_{22}H_{23}NO_7$, also contained a five-membered lactone ring [$\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1}] and showed no optical rotation. Its n.m.r. spectrum showed an *N*-methyl resonance at high field (δ 2.20) and two methine signals at δ 4.23 (1-H, d, *J* 2.5 Hz) and 5.51 (9-H, d, *J* 2.5 Hz) in addition to three *O*-methyl

—68° ($CHCl_3$), gave two stereoisomeric compounds in their racemic forms [(6) and (8)], identified on the basis of spectral data.

This photochemical racemisation and epimerisation is the first example to be reported in the isoquinoline alkaloid series, although optically active isoquinoline

[2] W. Klötzer, S. Teilte, and A. Brossi, *Helv. Chim. Acta*, 1971, **54**, 2057.
[3] T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *Heterocycles*, 1975, **3**, 1091; *J.C.S. Perkin I*, 1976, 1221.
[4] M. A. Marshall, F. L. Puman, and R. Robinson, *J. Chem. Soc.*, 1934, 1315.
[5] M. Ohta, H. Tani, S. Morozumi, and S. Kodaira, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 1080.

alkaloids can be racemised with Adams catalyst in ethanol.[6]

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro apparatus, i.r. spectra with a Hitachi EPI-3 recording spectrophotometer, and n.m.r. spectra with a JEOL JNM-PMX 60 spectrophotometer.

Photoreaction of (−)-α-*Narcotine* (3).—A stirred solution of natural (−)-α-narcotine (1 g) in tetrahydrofuran (500 ml) was irradiated with a Riko 450 W high-pressure mercury lamp equipped with Pyrex filter at room temperature for 5 h. Evaporation gave a reddish gum, which was chromatographed on silica gel (50 g) with benzene [fractions (50 ml) 1—5], benzene–ethyl acetate (9 : 1 v/v; fractions 6—13), and benzene–ethyl acetate (8 : 2 v/v; fractions 14—18) as eluants. Fractions 3—5 gave needles which were recrystallised from methanol to afford 6,7-dimethoxyphthalide (9) (20 mg) as needles, m.p. 102—103° (lit.,[7] 102—103°), $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1} (C=O); δ ($CDCl_3$) 3.90 (3 H, s, OMe), 5.17 (2 H, s, ArCH_2·O), 7.07 (1 H, d, *J* 8 Hz, ArH), and 7.23 (1 H, d, *J* 8 Hz, ArH). Fractions 6—12 afforded a pale yellow solid, which was recrystallised from ethanol to yield (±)-α-narcotine (5) (145 mg) as needles, m.p. 227—230° (lit.,[7] 229—232°) (Found: C, 64.3; H, 5.5; N, 3.25. Calc. for $C_{22}H_{23}NO_7$: C, 63.9; H, 5.6; N, 3.4%), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O), δ ($CDCl_3$) 2.54 (3 H, s, NMe), 3.82, 4.00, and 4.07 (each 3 H, s, OMe), 4.36 (1 H, d, *J* 4.5 Hz, 1-H), 5.54 (1 H, d, *J* 4.5 Hz, 9-H), 5.89 (2 H, s, O·CH_2·O), 6.08 (1 H, d, *J* 7.5 Hz, 6′-H), 6.28 (1 H, s, 5-H), and 6.93 (1 H, d, *J* 7.5 Hz, 5′-H), $[\alpha]_D^{18}$ 0° (*c* 0.50 in $CHCl_3$). Fractions 15—18 afforded a pale yellow solid, which was recrystallised from ethanol to give (±)-β-narcotine (7) (72 mg) as needles, m.p. 184—186° (lit.,[7] 188—189°) (Found: C, 64.2; H, 5.5; N, 3.4%), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O), δ ($CDCl_3$) 2.20 (3 H, s, NMe), 3.89, 3.94, and 4.09 (each 3 H, s, OMe), 4.23 (1 H, d, *J* 2.5 Hz, 1-H), 5.51 (1 H, d, *J* 2.5 Hz, 9-H), 5.84 (2 H, s, O·CH_2·O), 6.30 (1 H, s, 5-H), 6.90 (1 H, d, *J* 8 Hz, 5′- or 6′-H), and 7.16 (1 H, d, *J* 8 Hz, 5′- or 6′-H), $[\alpha]_D^{18}$ 0° (*c* 0.50 in $CHCl_3$).

(−)-β-*Narcotine*.—According to the procedure reported by Robinson[4] and Ohta,[5] (−)-α-narcotine was converted into (−)-β-narcotine, m.p. 181—182° (lit.,[5] 177—179°), $[\alpha]_D^{20}$ −87.5° (*c* 1.00 in $CHCl_3$); i.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) spectra were identical with those of the (±)-β-narcotine.

Photoreaction of (−)-β-*Hydrastine* (4).—Irradiation of (−)-β-hydrastine (1 g) as above gave a reddish gum, which was chromatographed on silica gel (50 g) with benzene [fractions (50 ml) 1—5], benzene–ethyl acetate (9 : 1 v/v; fractions 6—12), and benzene–ethyl acetate (8 : 2 v/v; fractions 13—20) as eluants. Fractions 3—5 gave 6,7-dimethoxyphthalide (9) (14 mg) as needles, identical with an authentic sample. Fractions 6—10 afforded a pale yellow solid, which was recrystallised from methanol–ether to give (±)-α-hydrastine (8) (64 mg) as needles, m.p. 149—150° (lit.,[8] 151—152°) (Found: C, 65.3; H, 5.65; N, 3.5. Calc. for $C_{21}H_{21}NO_7$: C, 65.8; H, 5.5; N, 3.65%), $\nu_{max.}$ ($CHCl_3$) 1 750 cm^{-1} (C=O), δ ($CDCl_3$) 2.53 (3 H, s, NMe), 3.84 and 3.97 (each 3 H, s, OMe), 5.53 (1 H, d, *J* 3.5 Hz, 9-H), 5.76 (1 H, d, *J* 1 Hz, O·CH_2·O), 5.81 (1 H, d, *J* 1 Hz, O·CH_2·O), 6.36 (1 H, s, 5-H), 6.63 (1 H, s, 8-H), 7.02 (1 H, d, *J* 8 Hz, 5′- or 6′-H), and 7.26 (1 H, d, *J* 8 Hz, 5′- or 6′-H), $[\alpha]_D^{18}$ 0° (*c* 0.50 in $CHCl_3$). Fractions 14—20 yielded (±)-β-hydrastine (6) (120 mg), identified by comparison with an authentic sample.[3]

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