Studies on the Syntheses of Heterocyclic Compounds. Part CDLIV.† Abnormal Dienone–Phenol Rearrangement of Procularine

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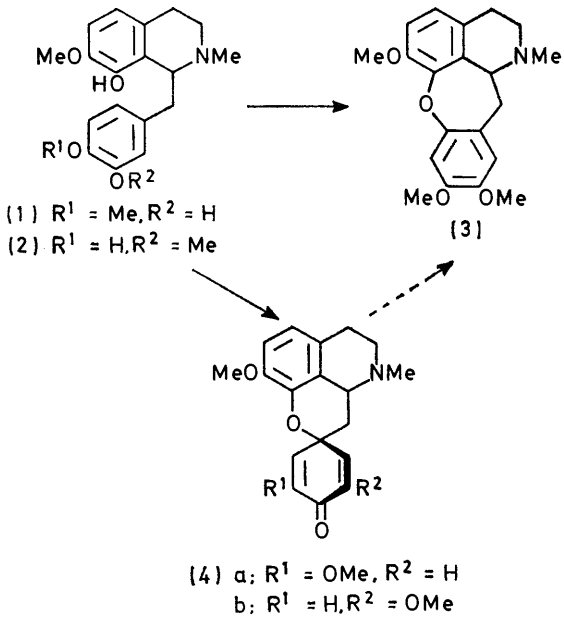
Treatment of procularine A (4a) with sulphuric acid, followed by methylation, gave an abnormal product, 1,9,10-trimethoxyaporphine (5), which was also obtained similarly from procularine B (4b).

THE biogenesis of cularine (3) and related alkaloids may simply involve carbon–oxygen coupling of the diphenolic base (1) by phenolic oxidation. A total synthesis of cularine along these lines has been achieved independently by Jackson [1] and Kametani.[2] Another possible route involves phenolic oxidation of the isomer (2) of the diphenolic isoquinoline (1) to give the procularine (4).[2] A dienone–phenol rearrangement could then generate a cularine-related compound.[3] We have investigated a synthesis of cularine by this method and report an abnormal product from the dienone–phenol rearrangement of the procularine (4).



Four possible products would be expected from the dienone–phenol rearrangement of the procularine, formed by migration of carbon or oxygen functions to either of the two β-positions in the dienone system. The actual course of the reaction would seem to depend upon the stereochemistry of the spiro-ring system [4,5] and the reagents used.[6] We therefore studied the behaviour of procularines A and B on treatment with acids under various conditions.

Treatment of either dienone (4) with trifluoroacetic acid or methanolic hydrochloric acid gave a negative result. Treatment of procularine A (4a) with concentrated sulphuric acid at 5° gave a phenolic base which did not show the signals expected for a cularine system in its n.m.r.[7] and mass spectra.[8] This product was methylated in order to elucidate its structure, and the product was purified to give a non-phenolic isoquinoline which was characterised as its oxalate. Microanalysis and the mass spectrum agreed with the molecular formula $C_{20}H_{23}NO_3$, which indicated that an oxygen function had been eliminated. The u.v. spectrum indicated this product to be an aporphine ($\lambda_{max.}$ 277, 306, and 313sh nm),[9] and the mass spectrum showed a typical aporphine-type fragmentation pattern:[8] *m/e* 324 ($M^+ - 1$), 310, 294, and 282. Moreover, the n.m.r. spectrum revealed, in addition to three *O*-methyl groups and one *N*-methyl group, signals for vicinal aromatic protons [τ 3·11 and 2·93 (d, *J* 9 Hz)] and two isolated protons, one at τ 2·0. These data suggested that the product was 1,9,10-trimethoxyaporphine (5). Procularine B (4b) was also treated with sulphuric acid under the same conditions to give a phenolic base, methylation of which also yielded 1,9,10-trimethoxyaporphine (5). Although the mechanism of

(5)

aporphine formation remains unclear, similar reactions have been reported.[10,11]

† Part CDLIII, T. Kametani, S. Hibino, and S. Takano, preceding paper.

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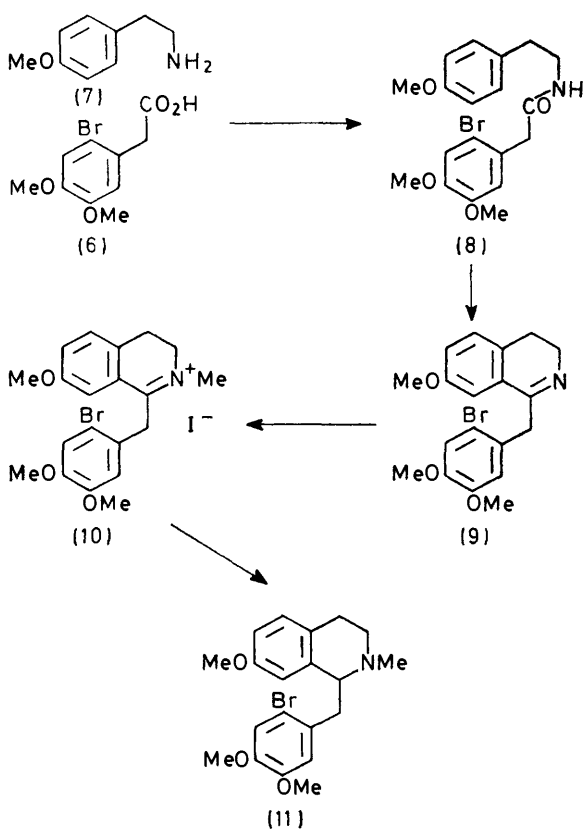
Structure (5) was confirmed by independent synthesis as follows. Fusion of 2-bromo-4,5-dimethoxyphenylacetic acid (6) [12] with 4-methoxyphenethylamine (7) [13] gave the corresponding amide (8), which was cyclised by treatment with phosphorous pentoxide and Celite in boiling benzene–chloroform [14] to give the 3,4-dihydroisoquinoline (9), characterised as its methiodide (10). Reduction of the methiodide (10) with sodium borohydride afforded the 1,2,3,4-tetrahydro-2-methylisoquinoline (11), characterised as its oxalate. Irradiation [15] of the hydrochloride of (11) in aqueous methanol with a 200 W mercury lamp for 8 h gave the aporphine (5), which was identical with the rearrangement product in i.r. and n.m.r. spectral comparisons.

Cularine cannot apparently be obtained *in vitro* by way of the procularine (4), but the formation of the aporphine is of interest from the biogenetic point of view. Although tracer work regarding this rearrangement remains to be done, we suggest that there is some possibility of the biosynthesis of aporphine from procularine.

EXPERIMENTAL

I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, n.m.r. spectra with a Hitachi R-20 spectrometer (tetramethylsilane as an internal standard), and mass spectra with a Hitachi RMU-7 spectrometer.



Dienone–Phenol Rearrangement of the Dienones (4) *with Concentrated Sulphuric Acid.*—(*a*) To concentrated sulphuric acid (70 ml) cooled below 5°, the dienone (4a) (340 mg) was added in portions with stirring during 15 min under a current of nitrogen, and stirring was continued for 2 h. The mixture was poured into ice–water (600 ml), and the resulting violet solution was basified with concentrated ammonia to give a green solution, which was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to yield a dark brown syrup (164 mg), t.l.c. of which (silica gel) showed seven spots [methanol–chloroform (1 : 10) as developer].

A solution of the syrup in methanol (5 ml) was treated with ethereal diazomethane (20 ml) [prepared from nitrosomethylurea (2 g)] and the mixture was set aside at 5° for 5 h and then at room temperature for 17 h. The solvent was then removed and residue was extracted with chloroform and worked up as usual. Separation by t.l.c. on silica gel in ether gave three compounds, R_F 0·3, 0·45, and 0·5.

The aporphine derivative (5) (main product, R_F 0·45) was obtained as an oil (60 mg), the oxalate of which crystallised from methanol as pale brown *needles*, m.p. 199—200° (decomp.) (Found: C, 63·2; H, 6·0; N, 3·3. $C_{20}H_{23}NO_3,C_2H_2O_4$ requires C, 63·6; H, 6·05; N, 3·53%), $\lambda_{max.}$ (EtOH) 223, 269sh, 277, 306, and 313sh nm (log ε 4·60, 3·96, 4·03, 4·15, and 4·12), τ ($CDCl_3$) (free base) 7·43 (3H, s, NMe), 6·13 (3H, s, OMe), 6·08 (6H, each s, 2 × OMe), 3·17 (1H, s, 8-H), 3·11 (1H, d, *J* 9 Hz, ArH), 2·93 (1H, d, *J* 9 Hz, ArH), and 2·0 (1H, s, 11-H), *m/e* 325 (M^+), 324 (M − 1), 310 (M − 15), 294 (M − 31), and 282 (M − 43).

The compounds (10 mg and 9 mg) of R_F values 0·3 and 0·5 were examined by g.l.c., but the presence of cularine was not observed.

(*b*) A mixture of the dienone (4b) (320 mg) and concentrated sulphuric acid (65 ml) was treated similarly to give a dark brown oil (209 mg), which was separated by t.l.c. on silica gel [chloroform–methanol (10 : 1)]. Spots were observed at R_F 0·44 (44 mg) (one spot), 0·28 (43 mg) (two spots), and 0·28—0·44 (28 mg) (three spots).

The compound of R_F 0·44 was obtained as a pale brown syrup, $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1} (OH), τ ($CDCl_3$) 7·47 (3H, s, NMe), 6·17 (3H, s, OMe), 6·15 (3H, s, OMe), 5·75br (1H, s, OH), 3·22 (1H, s, 8-H), 3·17 (1H, d, *J* 9 Hz, ArH), 2·98 (1H, d, *J* 9 Hz, ArH), and 2·08 (1H, s, 11-H), *m/e* 311 (M^+), 310 (M − 1), 296 (M − 15), 280 (M − 31), and 268 (M − 43).

Methylation of this syrup (24 mg) gave the same compound as that derived from dienone (4a) (comparison of spectroscopic data and of the derived oxalates).

N-(4-Methoxyphenethyl)-2-bromo-4,5-dimethoxyphenylacetamide (8).—A mixture of 4-methoxyphenethylamine (7) [13] (13 g) and 2-bromo-4,5-dimethoxyphenylacetic acid (6) [12] (26 g) was heated at 190—200° for 1 h, and then extracted with chloroform. The extract was washed with 10% hydrochloric acid, water, 5% sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to give the *amide* (8) (23·5 g, 66·9%) as pale brown needles (from chloroform–light petroleum), m.p. 153·5—154·4°

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(Found: C, 56·0; H, 5·4; Br, 19·95; N, 3·55. $C_{19}H_{22}BrNO_4$ requires C, 55·9; H, 5·45; Br, 19·6; N, 3·45%), $\nu_{max.}$ ($CHCl_3$) 3420 (NH) and 1660 cm^{-1} (CO), τ ($CDCl_3$) 7·29 (2H, t, *J* 6·5 Hz, $PhCH_2{\cdot}CH_2$), 6·57 (2H, t, *J* 6·5 Hz, $PhCH_2{\cdot}CH_2{\cdot}NH$), 6·38 (2H, s, $PhCH_2{\cdot}CO$), 6·20 (3H, s, OMe), 6·15 (3H, s, OMe), 6·10 (3H, s, OMe), 4·42br (1H, NH), 3·16 (2H, d, *J* 9 Hz, 3′-H and 5′-H), 3·14 (1H, s, 6-H), 2·91 (1H, s, 3-H), and 2·90 (2H, d, *J* 9 Hz, 2′-H and 6′-H).

1-(2-*Bromo*-4,5-*dimethoxybenzyl*)-3,4-*dihydro*-7-*methoxyisoquinoline* (9) *Methiodide*.—To a mixture of benzene (300 ml), Celite (30 g), and phosphorous pentoxide (60 g) under reflux, the amide (8) (16 g) in chloroform (100 ml) was added with stirring during 1 h, and the mixture was refluxed for 8 h. It was then cooled and poured into ice–water, and concentrated hydrochloric acid (40 ml) was added. The organic layer was separated, and the aqueous layer was basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown syrup, which was extracted with ether. Evaporation of the extract gave the 3,4-dihydroisoquinoline (9) (11·7 g) as a pale brown syrup. This syrup in methyl iodide (5 ml) and acetone (100 ml) was set aside overnight at room temperature to give the *methiodide* (10) (5·28 g, 25·1%) as pale yellow needles (from methanol), m.p. 207—210° (decomp.) (Found: C, 43·7; H, 4·56; N, 2·5. $C_{20}H_{23}BrINO_3,H_2O$ requires C, 43·65; H, 4·6; N, 2·55%).

1-(2-*Bromo*-4,5-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline* (11).—To a solution of the methiodide (10) (1·8 g) in methanol (60 ml), sodium borohydride (500 mg) was added with stirring at 5° during 10 min. The mixture was stirred for 1 h at 5° and then set aside at room temperature overnight. The methanol was evaporated off and the residue was extracted with ether; the extract was dried (Na_2SO_4) and evaporated to give the 1,2,3,4-*tetrahydroisoquinoline* (11), the *oxalate* (1·4 g, 81·2%) of which was recrystallised from methanol to give needles, m.p. 192—193·5° (decomp.) (Found: C, 52·95; H, 5·35; N, 2·85. $C_{20}H_{24}BrNO_3,C_2H_2O_4$ requires C, 53·35; H, 5·3; N, 2·8%), $\lambda_{max.}$ (in EtOH) 286sh and 289 nm (log ε 3·50 and 3·54), τ ($CDCl_3$) 7·78 (3H, s, NMe), 6·39 (3H, s, OMe), 6·29 (3H, s, OMe), 6·14 (3H, s, OMe), 3·76 (1H, d, *J* 3·0 Hz, 8-H), 3·46 (1H, s, 6′-H), 3·26 (1H, q, *J* 8·5 and 3·0 Hz, 6-H), 2·93 (1H, s, 3′-H), and 2·93 (1H, d, *J* 8·5 Hz, 5-H), *m/e* 405, 407 (isotope ion), and 176 (base peak).

1,9,10-*Trimethoxy*-6-*methylaporphine* (5).—A solution of the hydrochloride (1·2 g) of the isoquinoline (11) in 15% aqueous methanol (300 ml) was irradiated with a 200 W mercury lamp at 20° for 8 h under a current of argon gas. The methanol was evaporated off and the residue was basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown syrup (1 g), which was extracted with ether. Evaporation of the extract gave a pale brown syrup (650 mg), which was subjected to column chromatography on silica gel (20 g) with ether as eluant. Starting material (125 mg) was eluted first, and was followed by the crude aporphine (5) (58 mg), which was purified by thick-layer chromatography on silica gel. The i.r. and n.m.r. spectra of the product (38 mg) were identical with those of the samples from the dienones (4a and b).

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