795. *The Cleavage of Biscoclaurine Alkaloids with Sodium in Liquid Ammonia. Part I. Curine and Chondrocurine.*

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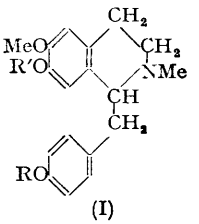
On fission with sodium in liquid ammonia, *OO*-dimethylcurine yields (−)-*O*-methylarmepavine and (−)-*N*-methylcoclaurine, while the diastereoisomeric *OO*-dimethylchondrocurine yields (−)-*O*-methylarmepavine and (+)-*N*-methylcoclaurine. The configurations of the two asymmetric centres in curine and chondrocurine are thereby proved.

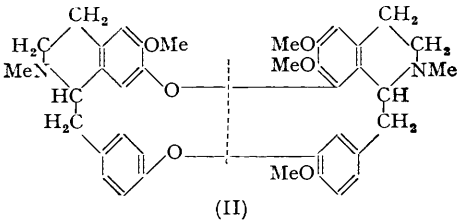
The biscoclaurine (bisbenzyl*iso*quinoline) alkaloids contain two benzyl*iso*quinoline units such as (I), joined together by ether linkages. The two units may be joined only by a single ether linkage between positions 3′ and 4′, or also by one or two 7 : 8-ether linkages, or by one 7 : 8- and one 6 : 7-ether linkage. However, in the biscoclaurine alkaloids, which occur in *Chondrodenron* species, the benzyl group of each coclaurine unit is connected to the *iso*quinoline group of the other, either by two 4′ : 8- or by one 4′ : 8- and one 3′ : 7-ether linkage. Further, structural and stereochemical isomerism, and variation in the degree of *N*- and *O*-methylation, occur in the thirty or so known biscoclaurine alkaloids.

The method generally used for structural investigation has been Hofmann degradation and oxidation of the resultant methine bases. This was not always decisive for structure and provided no evidence on the configuration of the asymmetric centres. More recently Tomita, Fujita, and Murai (*J. Pharm. Soc., Japan*, 1951, **71**, 226, 1036, 1039, 1043) introduced a method whereby the ether linkages are reduced with sodium in liquid ammonia, which gives almost quantitative yields of the single-unit, optically active coclaurine bases.

It is interesting that this reductive fission is a reversal of the probable biogenetic synthesis (Faltis and his co-workers, *Ber.*, 1930, **63**, 809; 1941, **74**, 79; *Annalen*, 1932, **497**, 69; **499**, 301).



(I)



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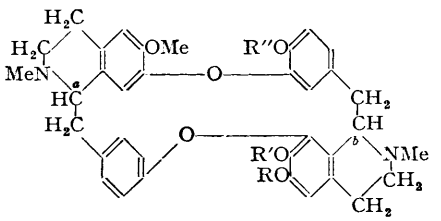
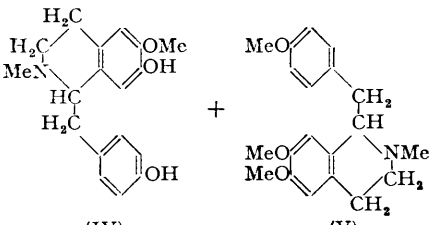


(III)



(IV) (V)

We are applying this fission to biscoclaurine alkaloids of incompletely known structure, and report now the cleavage of curine [(−)-bebeerine] and chondrocurine, two *Chondrodendron* alkaloids which have been isolated from tube curare and have been shown to be (III; R = Me, R′ = R″ = H; and R = R″ = H, R′ = Me, respectively) by King (*J.*, 1935, 1381; 1936, 1276; 1937, 1472; 1939, 1157; 1940, 737) and by Dutcher (*J. Amer. Chem. Soc.*, 1946, **68**, 419) respectively.

It was first necessary to methylate the phenolic groups with diazomethane. *OO*-Dimethylcurine and *OO*-dimethylchondrocurine so obtained are diastereoisomeric (Dutcher, *loc. cit.*), and from a comparison of the rotations of the two bases and their derivatives it seemed probable that *OO*-dimethylcurine, on fission, would yield two lævorotatory coclaurine-type units, while *OO*-dimethylchondrocurine would yield one dextrorotatory and one lævorotatory unit.

To secure samples of known constitution, the diastereoisomeric alkaloids *iso*tetrandrine and phæanthine (II) (Kondo and Keimatsu, *J. Pharm. Soc., Japan*, 1935, **55**, 63; *Ber.*, 1935, **68**, 1503) were cleaved with sodium in liquid ammonia. Fission of the former has been shown by Tomita, Fujita, and Murai (*loc. cit.*) to yield (−)-*O*-methylarmepavine (I; R = R′ = Me) and (+)-*N*-methylcoclaurine (I; R = R′ = H). In the case of phæanthine it was known from the same authors' study of the enantiomorphic alkaloid tetrandine (*loc. cit.*) that the products would be (−)-*O*-methylarmepavine and (−)-*N*-methylcoclaurine. These substances, isolated as described by the Japanese workers, corresponded in properties to the expected coclaurine derivatives.

Fission of *OO*-dimethylcurine (III; R = R′ = R″ = Me) with sodium in liquid ammonia yielded a phenolic and a non-phenolic base, both of which were lævorotatory. The non-phenolic product (V) gave a crystalline methiodide identical with (−)-*O*-methylarmepavine methiodide. The phenolic product (IV) proved difficult to crystallise, but when treated with diazomethane and then methyl iodide it gave crystalline (−)-*O*-methylarmepavine methiodide. Thus, both asymmetric centres are lævorotatory in curine. By similar methods, *OO*-dimethylchondrocurine gave a dextrorotatory phenolic and a lævorotatory non-phenolic base, and thence (+)-*O*-methylarmepavine methiodide and (−)-*O*-methylarmepavine methiodide respectively. Thus in *OO*-dimethylchondrocurine (III; R = R′ = R″ = Me) the asymmetric centres (*a*) and (*b*) are dextrorotatory and lævorotatory respectively.

Since this work began, Kidd and Walker (*Chem. and Ind.*, 1953, 243) have recorded the cleavage of phæanthine and (−)-*OO*-dimethylbebeerine (*OO*-dimethylcurine).

The products which they obtained from phæanthine differed as expected only in sign of rotation from those obtained by Tomita, Fujita, and Murai (*loc. cit.*) from the enantiomorphic alkaloid tetrandrine, and those from (−)-*OO*-dimethylbebeerine were in accord with ours.

Experimental

M. p.s are corrected. The microanalyses were carried out in the Microanalytical Laboratory of the C.S.I.R.O. by Dr. K. W. Zimmerman and his staff.

Fission of iso*Tetrandrine.*—*iso*Tetrandrine (0·8 g.) was dissolved in benzene (30 c.c.) and toluene (15 c.c.), and liquid ammonia (400 c.c.) was added. Sodium (2 g.) was then added gradually with vigorous stirring until the blue colour of the solution persisted for about an hour, whereafter the mixture was kept overnight to permit evaporation of the ammonia. Water and ether were added to the residue, and the ethereal phase was washed twice with 2% sodium hydroxide solution. The alkaline washings were combined with the aqueous phase (mixture A). The ether–benzene–toluene solution was exhaustively extracted with 5% hydrochloric acid, and the extract made alkaline with 2% aqueous sodium hydroxide. The non-phenolic base thus precipitated was re-extracted with ether, and the ethereal solution was dried (Na_2SO_4) and evaporated. The residue was chromatographed in benzene on alumina and yielded a pale oil which was warmed with methanolic methyl iodide (0·1 g. in 2 c.c.). The methiodide of the non-phenolic base separated as needles, and after recrystallisation from methanol had m. p. 135° (sinters at 128°), $[\alpha]_D^{20}$ −118·5° (*c*, 0·5 in MeOH) (Found: C, 51·4; H, 6·6; MeO, 21·1. Calc. for $C_{20}H_{25}O_3N,CH_3I,H_2O$: C, 51·7; H, 6·2; 3MeO, 19·1%). Tomita, Fujita, and Murai (*loc. cit.*) report m. p. 135° for *O*-methylarmepavine methiodide.

The phenolic base was recovered from mixture (A) by addition of ammonium chloride and extraction with ether. The ethereal solution was dried (Na_2SO_4) and evaporated to a yellow resin which was difficult to crystallise. It was methylated in methanol with ethereal diazomethane; after 1 day a further amount of ethereal diazomethane was added. After 2 days evaporation *in vacuo* and chromatography as above gave a yellow oil which was treated with excess of methanolic methyl iodide. The product, (+)-*O*-methylarmepavine methiodide, crystallised from methanol as needles (0·2 g.), m. p. 135° (sinters at 127°), $[\alpha]_D^{20}$ +125° (*c*, 0·2 in MeOH) (Found: C, 51·4; H, 6·6; I, 25·5%).

Fission of Phæanthine.—Phæanthine (1 g.), in benzene–toluene (15 c.c. each), was cleaved with sodium (2 g.) in liquid ammonia (500 c.c.). The non-phenolic product, purified as described above, gave a methiodide as needles (0·4 g.) (from methanol), $[\alpha]_D^{20}$ −118·1° (*c*, 0·5 in MeOH), m. p. 135° undepressed on admixture with (−)-*O*-methylarmepavine methiodide prepared from *iso*tetrandrine. A depression of *ca.* 10° was observed on admixture with (+)-*O*-methylarmepavine methiodide.

The phenolic base, treated as described above, gave (−)-*O*-methylarmepavine methiodide, $[\alpha]_D^{20}$ −114·1° (*c*, 0·5 in MeOH), m. p. and mixed m. p. 136° (from methanol). The m. p. was depressed on admixture of this product with the (+)-compound.

OO-*Dimethylcurine.*—To curine (1 g.) in methanol (300 c.c.), diazomethane (from 2 g. of methylnitrosourea) in ether was added and the mixture set aside for 2 days, after which a further similar quantity of diazomethane was added. After four such additions, the solvents were removed under reduced pressure and the residue dissolved in 1% hydrochloric acid. The solution was made alkaline with 1% aqueous sodium hydroxide, and the precipitated base was extracted with chloroform–ether (1 : 4). Chromatography on alumina of a benzene solution of the residue afforded a pale oil (0·9 g.) which did not crystallise. Attempts to crystallise the dimethiodide also failed, as found by previous workers.

Fission of OO-*Dimethylcurine.*—*OO*-Dimethylcurine (0·5 g.) in benzene–toluene (40 + 20 c.c.) was added to liquid ammonia (400 c.c.). Cleavage with sodium (1·5 g. in all) and isolation and purification of the products were carried out as for *iso*tetrandrine and phæanthine. The non-phenolic product (0·2 g.) gave (−)-*O*-methylarmepavine methiodide, m. p. and mixed m. p. 132° [depressed on admixture with the (+)-compound by *ca.* 10°], $[\alpha]_D^{14}$ −115·5° (*c*, 0·3 in MeOH).

The phenolic product, isolated as before and methylated with diazomethane, afforded a pale oil (0·13 g.) from which (−)-*O*-methylarmepavine methiodide, m. p. and mixed m. p. 132°, $[\alpha]_D^{14}$ −116·0° (*c*, 0·3 in MeOH), was formed as before.

Methylation of Chondrocurine.—Chondrocurine (1 g.) in methanol (100 c.c.) was methylated with diazomethane as described for curine. *OO*-Dimethylchondrocurine (1 g.) could not be

crystallised; with methanolic methyl iodide it gave the dimethiodide, m. p. 230—240° (decomp.) (from methanol), $[\alpha]_D^{18\cdot5}$ +153° (*c*, 0·3 in H_2O). Dutcher (*loc. cit.*) reported m. p. 266° and $[\alpha]_D^{24}$ +160° (in H_2O).

Fission of OO-*Dimethylchondrocurine.*—*OO*-Dimethylchondrocurine (0·85 g.) in benzene–toluene (1 : 1) was cleaved with sodium (1·7 g.) in liquid ammonia (500 c.c.) as previously described. The non-phenolic and the phenolic fraction were separated, purified, and treated as described for *OO*-dimethylcurine. The non-phenolic base gave (−)-*O*-methylarmepavine methiodide, needles (0·32 g.) (from methanol), m. p. 135°, $[\alpha]_D^{18}$ −118·3° (*c*, 0·3 in MeOH), and the phenolic base gave the *O*-methyl ether (purified by chromatography) and thence (+)-*O*-methylarmepavine methiodide, m. p. 134°, $[\alpha]_D^{18}$ +120·1° (*c*, 0·3 in MeOH). Both methiodides gave depressed and undepressed mixed m. p.s with authentic samples as appropriate.

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