*The Action of Sodium in Liquid Ammonia on Phaeanthine, OO′-Dimethylcurine, and OO′-Dimethyl*isochondrodendrine.

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[Reprint Order No. 4757.]

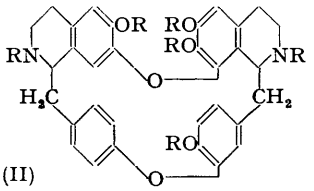
The sodium–liquid ammonia fission process has been applied to phaeanthine (II; R = Me), *OO′*-dimethylcurine (IV; R = Me), and *OO′*-dimethyl-*iso*chondrodendrine (V; R = Me), as typical representatives of three groups of bisbenzyl*iso*quinoline alkaloids, particular regard being paid to the homogeneity of the direction of cleavage of the diaryl ether linkages. In benzene–toluene solution fission of phaeanthine and of *OO′*-dimethylcurine gave only (−)-*O*-methylarmepavine (VIII) as non-phenolic product and (−)-*N*-methylcoclaurine (IX) as sole phenolic product. In dioxan solution, however, evidence of other modes of fission was obtained, but only the phenolic products of the alternative modes of cleavage have been isolated; that from phaeanthine has not been identified with certainty but it was neither corpaverine (XI) nor laudanidine (XII), while that from *OO′*-dimethylcurine was identified as laudanidine [(−)-laudanine] (XII). Cleavage of *OO′*-dimethyl*iso*chondrodendrine in dioxan solution gave (−)-armepavine (XVII) as the only product that could be characterised, but evidence for the formation of two others was obtained.

A synthesis of (±)-*N*-methylcoclaurine (IX) is described.

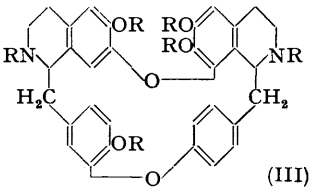
The bisbenzyl*iso*quinoline (biscoclaurine) alkaloids are derived formally by linking together two 1-benzyl*iso*quinoline units by one, more often two, or even three, diaryl ether linkages, and Faltis has suggested (Faltis and Frauendorfer, *Ber.*, 1930, **63**, 808; Faltis, Holzinger, Ita, and Schwarz, *ibid.*, 1941, **74**, 79) that they may arise in the plant by enzymic dehydrogenation and condensation of coclaurine (I). Considering only those alkaloids with two diaryl ether linkages, four distinct groups are known: (II), which includes berbamine, phaeanthine, tetrandrine, *iso*tetrandrine, menisine, fangchinoline, and cepharanthine; (III), which includes oxyacanthine, repandine, aromoline, trilobamine, daphnandrine, epistephanine, and hypoepistephanine; (IV), which includes curine, bebeerine, tubocurarine (quaternary), chondrofoline, and chondrocurine; and (V), which includes *iso*chondrodendrine, cycleanine, protocuridine, and *neo*protocuridine. In addition to this structural isomerism, the alkaloids of these four groups vary with regard to the degree of *O*- or *N*-methylation (R = H or Me in II—V), and in configurations at the asymmetric centres; apart from the incidental circumstances that cepharanthine contains a methylenedioxy-group, and epistephanine and hypoepistephanine have each one dihydro*iso*quinoline nucleus, all are seen to be derivable theoretically from two molecules of the coclaurine type by similar means. Attack by the 7- and 4′-hydroxyl groups of one coclaurine-type molecule on the unsubstituted 8- and 3′-positions of another leads to type (II), and on the 3′- and 8-positions of the other respectively to type (IV); or the 7-hydroxyl group of one molecule may attack the 8-position of another, while the 3′-position of the first is attacked by the 4′-hydroxyl group of the second, leading to type (III); or the 4′-hydroxyl groups of two coclaurine type molecules may simultaneously attack the 8-positions of each other leading to type (V).

It has recently been shown that when certain bisbenzyl*iso*quinoline alkaloids are reduced with sodium (or potassium) in liquid ammonia in toluene or benzene solution, cleavage of the diaryl ether linkages occurs in such a way as to yield, apparently exclusively, products of the coclaurine type (I), thus reversing formally what may possibly be the biogenetic mode of synthesis. For the first time also the differentiation of alkaloids of type (II) from those of type (III) has been made possible. At the outset of the work described in the present communication, part of which has been the subject of a preliminary note (*Chem. and Ind.*, 1953, 243), this technique had been applied to *iso*tetrandrine (Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 226, 1035; Tomita, Inubushi, and Niwa, *ibid.*,

1952, **72**, 211), tetrandrine (Tomita, Fujita, and Murai, *ibid.*, 1951, **71**, 301; Fujita and Murai, *ibid.*, p. 1039) and berbamine (Inubushi, *ibid.*, 1952, **72**, 220) belonging to group (II), to *O*-methyloxyacanthine (Fujita, *ibid.*, 1952, **72**, 213, 217) belonging to group (III), and to cycleanine (Tomita, Fujita, and Murai, *ibid.*, 1951, **71**, 301; Fujita and Murai, *ibid.*, p. 1043) belonging to group (V); while, in the interval, it has also been applied to *O*-methylrepandine (Fujita and Saijoh, *ibid.*, 1952, **72**, 1232) and to dauricine (Inubushi and Niwa,



(II)



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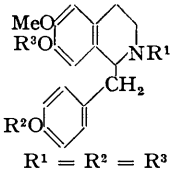
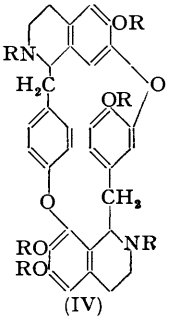
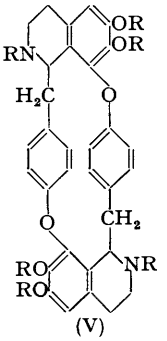


(I) $R^1 = R^2 = R^3 = H$
(VIII) $R^1 = R^2 = R^3 = Me$
(IX) $R^1 = Me$, $R^2 = R^3 = H$
(XVII) $R^1 = R^3 = Me$, $R^2 = H$



(IV)

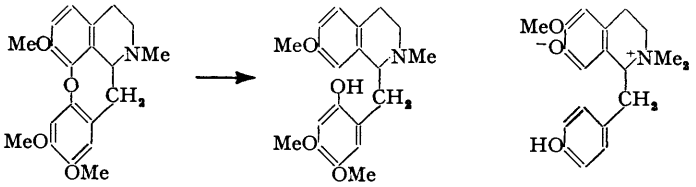


(V)

ibid., p. 762), which contains only one diaryl ether linkage. In every case only substances of the coclaurine type have been reported as the products of complete fission of the diaryl ether linkages. This apparent homogeneity of the fission process is surprising, as one would expect, on the basis of the sodium–liquid ammonia fission of model diaryl ethers (Sartoretto and Sowa, *J. Amer. Chem. Soc.*, 1937, **59**, 603; Kranzfelder, Verbanc, and Sowa, *ibid.*, p. 1488; Weber and Sowa, *ibid.*, 1938, **60**, 94), to obtain mixtures resulting from fission of the diaryl ether linkages at *either* side of the oxygen atoms to varying extents. The sodium–liquid ammonia cleavage of cularine (VI) to give (VII) as apparently sole product (Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55) is feasible when one notes that the reductions of 2-methoxy-, 2 : 3′-dimethoxy-, and 2 : 4′-dimethoxy-diphenyl ether give respectively 45, 24, and 1% of guaiacol (Sowa *et al.*, *locc. cit.*). In general, however, and particularly with unsymmetrical diaryl ethers with 2 : 2′-dimethoxy-substitution, one would expect detectable amounts of other products to be formed. We have therefore examined carefully the sodium–liquid ammonia fission products from phaeanthine (II; R = Me), *OO*′-dimethylcurine (IV; R = Me), and *OO*′-dimethyl*iso*chondrodendrine (cycleanine) (V; R = Me), as typical representatives of three distinct groups, with the object of finding out if, and to what extent, alternative modes of cleavage may occur. The starting materials were shown to be chromatographically homogeneous and paper chromatography was used in the examination of fission products.

In benzene–toluene solution the cleavage of phaeanthine (II; R = Me) went smoothly to completion and gave a syrupy non-phenolic product and a crystalline phenolic substance. The non-phenolic material was shown to be homogeneous by paper chromatography and, apart from the fact that it was not obtained crystalline in this instance, its properties agreed in detail with those recorded for (—)-*O*-methylarmepavine (VIII). Similarly, the phenolic product of fission was shown to be homogeneous, and although its physical constants (m. p. 176°, $[\alpha]_D^{23}$ −69·6°) were, apart from the sign rotation, markedly different from those (m. p. 137—138·5°, $[\alpha]_D^{16}$ +88·51°) recorded for the enantiomorph (Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 1035), it could only have been (—)-*N*-

methylcoclaurine (IX), since it gave a product identical with the non-phenolic fraction on treatment with diazomethane and afforded (—)-magnocurarine (X) on quaternisation. Incidentally, the isolation of (—)-*N*-methylcoclaurine (IX) and of (—)-*O*-methylarmepavine (VIII) from the cleavage of phaeanthine (II; R = Me) completes confirmation of the formulation of the latter alkaloid as the enantiomorph of tetrandrine (Kondo and Keimatsu, *Ber.*, 1935, **68**, 1503). It is also of interest to note that phaeanthine (II; R = Me) and (+)-magnocurarine (X) are found together in the bark of *Gyrocarpus americanus* Jacq. (McKenzie and Price, *Austral. J. Chem.*, 1953, **6**, 180), and it may well be, if the Faltis scheme of biogenesis is correct, that the plant makes both enantiomorphs of *N*-methylcoclaurine (IX) and converts the (—)-form into phaeanthine (II; R = Me) and quaternises the (+)-form to (+)-magnocurarine (X). The cleavage of *OO'*-dimethylcurine (IV;

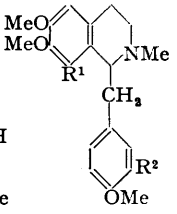


R = Me) in benzene–toluene proceeded rather less smoothly and the presence of some unchanged starting material was noted in the product. The products of fission, however, consisted of a single non-phenolic substance, (—)-*O*-methylarmepavine (VIII), and a single phenolic substance, (—)-*N*-methylcoclaurine (IX), identical with the fission products obtained from phaeanthine (II; R = Me) in the same circumstances. The isolation of these two lævorotatory fragments from *OO'*-dimethylcurine (IV; R = Me) also confirms the fact that both asymmetric centres in *dextro*bebeerine are dextrorotatory (King., *J.*, 1948, 265).

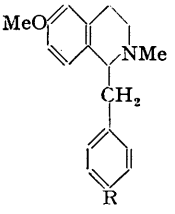
When cleavage was effected in dioxan solution, phaeanthine (II; R = Me) gave, as before, (—)-*O*-methylarmepavine (VIII), which was now obtained in a crystalline condition, but no other non-phenolic product was detected. The phenolic fraction yielded again (—)-*N* methylcoclaurine (IX), but, in addition, a small amount of a second phenolic component, m. p. 125—127°, was isolated. As it gave a strong Gibbs reaction (*J. Biol. Chem.*, 1927, **72**, 649) it was obviously not a demethylation product and it must have arisen by an alternative mode of fission from that giving (VIII) and (IX). The amount of material available was too small for extensive examination but it was shown to be distinct from corpaverine (XI) (Manske, *J. Amer. Chem. Soc.*, 1952, **74**, 2864), although the melting points were not far apart, and it was also shown not to contain laudanidine (XII). By exclusion it must have been the dihydric phenol (XIII), although no trace of the complementary non-phenolic fragment (XIV) was found; alternatively, it might conceivably have been produced by cleavage of only one of the two diaryl ether linkages but, in any event, no intermediate of such a type giving a positive Gibbs reaction could ultimately give rise to (VIII) and (IX).

When *OO'*-dimethylcurine (IV; R = Me) was similarly reduced in dioxan solution the reaction appeared to go to completion; the non-phenolic fraction again appeared to be homogeneous (VIII) and it was characterised as the methiodide. The phenolic fraction was, however, clearly a mixture and pure (—)-*N*-methylcoclaurine (IX) was isolated with some difficulty. In addition, a fraction was isolated having properties agreeing closely with those recorded for laudanidine [(—)-laudanine] (XII), and identity was confirmed by paper chromatography in comparison with (±)-laudanine (XII), and, after methylation with diazomethane, with (±)-laudanosine (XV). The phenolic fragment (XVI), complementary to (XII) from (IV; R = Me), was not isolated, and, although it would not have given a Gibbs reaction it could, in favourable circumstances, have been detected by paper chromatography. With both phaeanthine (II; R = Me) and *OO'*-dimethylcurine (IV; R = Me), therefore, sodium–liquid ammonia cleavage may, under appropriate condi-

tions, give products other than those (VIII) and (IX) of the coclaurine type; such a mode of fission is not detectable if reduction is carried out in benzene–toluene solution, and the extent to which it occurs is only small if cleavage takes place in dioxan solution.



(XI) $R^1 = OH$, $R^2 = H$
(XII) $R^1 = H$, $R^2 = OH$
(XIII) $R^1 = R^2 = OH$
(XV) $R^1 = H$, $R^2 = OMe$



(XIV) R = H
(XVI) R = OH

When *OO'*-dimethyl*iso*chondrodendrine (cycleanine) (V; R = Me) was reduced in dioxan solution with sodium and liquid ammonia, the product, in agreement with Fujita and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1043), consisted essentially of (—)-armepavine (XVII), agreeing well in its properties with those recorded in the literature. In addition however, two further substances must have been produced to account for two spots observed on paper chromatograms, but, curiously, no satisfactory positive Gibbs reaction was observed although the product of any other mode of cleavage than that giving (XVII) would have been unsubstituted in the *p*-position to a phenolic hydroxyl group. Predominantly, therefore, sodium–liquid ammonia cleavage of all three of these typical bisbenzyl*iso*quinoline alkaloids leads to substances of the coclaurine type, and fission in alternative directions occurs to a slight extent only.

As the properties of our (—)-*N*-methylcoclaurine (IX) were markedly different, apart from the sign of rotation, from those recorded for the enantiomorph, (±)-*N*-methylcoclaurine was synthesised, but numerous attempts to effect its resolution were unsuccessful. The (±)-substance was not distinguishable chromatographically from the optically active material from phaeanthine or from *OO'*-dimethylcurine, and the same applied to the derived methiodides [(±)- and (—)-magnocurarine iodide]. The synthesis followed conventional lines but several stages constitute improvements over previously known methods.

Experimental

Paper Chromatography.—Whatman's No. 1 paper was immersed in aqueous 0·2M-potassium dihydrogen phosphate, pressed between filter papers to remove excess of liquid, dried at 100°, and allowed to equilibrate against atmospheric moisture for several hours before use. Development was effected by the downward technique in sealed tanks, with, as routine solvent systems, the upper layers of the following mixtures, which gave the best results of a range examined: solvent A, amyl alcohol (110 c.c.), pyridine (110 c.c.), and water (sufficient to saturate, about 90 c.c.); solvent B, *n*-butanol (63 c.c.), acetic acid (10 c.c.), and water (27 c.c.). In some runs a second solvent front was observed but this did not interfere with the formation of spots which usually preceded it; it could be avoided by substituting the phosphate solution, used for impregnating the paper, for water in the above solvent mixtures, and R_F values were not noticeably affected by this substitution. For the detection of alkaloidal spots, the Dragendorff reagent (Munier and Macheboeuf, *Bull. Soc. Chim. biol.*, 1949, **31**, 1144) was used for non-phenolic substances; with phenolic alkaloids, however, the red spots obtained with this reagent were too transient, and the Folin–Denis reagent followed by alcoholic ammonia (Dalgliesh, *J.*, 1952, 3943) was more satisfactory. R_F values were usually reproducible within narrow limits but occasional variations occurred; comparisons between substances were always made directly by running samples, reference specimens, and mixtures of the two side by side.

Phaeanthine, *OO'*-dimethylcurine, and *OO'*-dimethyl*iso*chondrodendrine used in the following experiments were shown to be chromatographically homogeneous.

Reductive Cleavage of Phaeanthine (II; R = Me) *in Toluene–Benzene.*—A solution of phaeanthine (0·5 g.) in toluene (20 c.c.) and benzene (20 c.c.) was added dropwise to stirred liquid ammonia (500 c.c.) containing a small piece of sodium, and more sodium (total, 0·5 g.) was added whenever the blue colour faded until the reaction was at an end (blue colour relatively stable; time, 1½ hr.). After spontaneous evaporation of the ammonia, water was added, and the layers

were separated. The organic phase was washed with aqueous sodium hydroxide and water, then dried and evaporated, yielding a yellow syrup (Ph_1) (0·27 g.). The combined alkaline solutions were carbonated with solid carbon dioxide, and the phenolic product was obtained as a tan-coloured solid (Ph_2) (0·23 g.).

The readily-soluble non-phenolic syrup (Ph_1) did not crystallise and no seed was at the time available. It was, however, homogeneous as shown by paper chromatography since it gave single compact spots with both solvent systems A and B, and it had $[\alpha]_D^{23}$ −82·3° (*c*, 1·78 in $CHCl_3$). On treatment with methyl iodide (0·2 c.c.) in boiling methanol (10 c.c.) it afforded a crystalline methiodide, which separated from methanol in small cream-coloured prisms, m. p. 136—137°, sintering at 127—128° (Found: C, 51·8; H, 6·4; N, 2·9. Calc. for $C_{21}H_{28}O_3NI,H_2O$: C, 51·7; H, 6·2; N, 2·9%). Apart from the fact that it was not obtained crystalline in this instance, these properties are consistent with those of (−)-*O*-methylarmepavine (VIII), for which Tomita, Fujita, and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1035) record m. p. 62°, $[\alpha]_D^{16}$ −83·26° (methiodide, m. p. 135—136°), and Yunnussoff, Konowalowa, and Orechoff (*J. Gen. Chem., U.S.S.R.*, 1940, **10**, 641; *Chem. Zentr.*, 1941, I, 2530) record m. p. 64°, $[\alpha]_D$ −84·48° (methiodide, m. p. 135—136°).

The phenolic fraction (Ph_2) was also shown to be homogeneous by paper chromatography, and recrystallisation from benzene or toluene gave well-defined prisms of (−)-N-*methylcoclaurine* (IX), m. p. 176—177°, $[\alpha]_D^{23}$ −69·6° (*c*, 0·85 in $CHCl_3$) (Found: C, 72·4; H, 7·1; N, 4·4; OMe, 10·0. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1; N, 4·7; OMe, 10·4%). Tomita, Fujita, and Murai (*loc. cit.*) record m. p. 137—138·5°, $[\alpha]_D^{16}$ +88·51° (*c*, 0·14 in $CHCl_3$) for the hemihydrate (from methanol) of (+)-*N*-methylcoclaurine obtained by fission of *iso*tetrandrine, and Fujita and Murai (*ibid.*, p. 1039) record m. p. 138—139·5°, $[\alpha]_D^{16}$ +87·33° (*c*, 0·11 in $CHCl_3$) for the same base obtained from tetrandrine.

Reductive Cleavage of Phaeanthine in Dioxan.—Phaeanthine (1·5 g.), dissolved in anhydrous dioxan (35 c.c.), was reduced under conditions similar to those described above and the products were separated into a syrupy non-phenolic fraction (0·56 g.) and a phenolic fraction (0·9 g.). From the non-phenolic fraction *O*-methylarmepavine (Ph_1) was now obtained crystalline by slow evaporation of an ethereal solution, which afforded hard prisms, m. p. 60—61° (lit., m. p. 62—64°); all attempts at recrystallisation were, however, unsuccessful. The methiodide, prepared as before, was recrystallised twice from methanol, and both the pure substance and the mother-liquor residues were examined by paper chromatography; single spots were obtained in all cases, of R_F 0·52 in solvent A and R_F 0·64 in solvent B.

The phenolic product, obtained this time as a glass, was triturated with light petroleum, and the resulting solid was recrystallised twice from toluene, giving (−)-*N*-methylcoclaurine (Ph_2) (0·45 g.), m. p. 176—177°, $[\alpha]_D^{23}$ −69·2° (*c*, 0·98 in $CHCl_3$). The partly purified substance, the pure material, and the mother-liquor residues were examined by paper chromatography in solvent B. The impure solid gave two distinct spots of R_F 0·71 and 0·85; the pure substance (Ph_2) gave one spot of R_F 0·75, while the mother-liquor residues gave one spot of R_F 0·87. Evaporation of the mother-liquors gave a syrup which solidified under light petroleum, and recrystallisation from toluene gave a minute amount of a microcrystalline solid (Ph_3), m. p. 125—127°, giving a strong Gibbs reaction.

Methylation of (−)-N-*Methylcoclaurine* (*Ph*$_2$) *to* (−)-O-*Methylarmepavine* (*Ph*$_1$).—A solution of (−)-*N*-methylcoclaurine (Ph_2) (0·3 g.) in benzene (10 c.c.) and methanol (20 c.c.) was slowly added to ethereal diazomethane (from 5 g. of methylnitrosourea) during 1½ hr. After 1 hr. a further (equal) quantity of ethereal diazomethane was added, and the excess of diazomethane was allowed to evaporate. The solution was washed with aqueous sodium hydroxide and water, dried, and evaporated, yielding methylated Ph_2 as a yellow syrup (0·24 g.), $[\alpha]_D^{21}$ −77·7° (*c*, 1·61 in $CHCl_3$); this solidified spontaneously but the substance, m. p. 42—47°, could not be recrystallised. On comparison with substance Ph_1 by paper chromatography the two substances gave identical spots of R_F 0·75 in solvent A and 0·83 in solvent B. The methiodide from methylated Ph_2 formed yellowish prisms, m. p. 136—137° (sintering at 127—128°), and could not be distinguished from the methiodide of substance Ph_1 either by mixed m. p. or by infra-red spectrum (Nujol mull).

Attempted Identification of Substance Ph$_3$.—(*a*) Corpaverine, m. p. 140—141°, and substance Ph_3 were compared by paper chromatography and shown to be distinct, the former running somewhat faster than the latter in both solvents A and B; mixtures of the two gave linked spots. *X*-Ray powder photographs of the two substances were superficially similar in general pattern but showed significant differences in detail.

(*b*) A small quantity of substance Ph_3 was methylated with diazomethane in the usual way

and the product, a yellow syrup, was compared with (±)-laudanosine by paper chromatography. The latter ran rather more slowly than methylated Ph_3 in both solvents, and mixtures of the two substances gave elongated dumb-bell spots with both solvents, indicating non-identity.

Reductive Cleavage of OO′-*Dimethylcurine* (IV; R = Me) *in Toluene–Benzene.*—The curine used had been isolated by Dr. Harold King. It was methylated with diazomethane essentially as described by Späth, Leithe, and Ladeck (*Ber.*, 1928, **61**, 1698), and the product was chromatographed on alumina in benzene–light petroleum and eluted with benzene containing 1% of methanol. Evaporation of the various fractions gave amorphous (*X*-ray) material, and fractions of m. p. 116—121° were bulked for subsequent use.

OO′-Dimethylcurine (1 g.), dissolved in benzene (20 c.c.) and toluene (20 c.c.), was treated with sodium (approx. 1 g. required) in liquid ammonia as described above for phaeanthine, reaction being complete in about 2 hr. The product was separated, as before, into a non-phenolic syrup (0·59 g.) and a semi-solid phenolic fraction (0·34 g.).

The presence of unchanged *OO′*-dimethylcurine in the crude non-phenolic product was shown by paper chromatography, and the other component (Cu_1) and substance Ph_1 from phaeanthine, run side by side, had R_F values of 0·79 and 0·81 in solvent A and 0·88 and 0·90 in solvent B. The crude product was treated with methyl iodide (0·3 c.c.) in boiling methanol and one recrystallisation from methanol gave the methiodide of substance Cu_1 in the form of cream-coloured prisms, m. p. 137—138°, sintering at 123—125°, $[\alpha]_D^{23}$ −98·6° (*c*, 2·43 in $CHCl_3$) (Found: C, 51·5; H, 6·2; N, 3·4%). No depression of the m. p. was observed on admixture with the methiodide of substance Ph_1, and the two methiodides also gave identical infra-red spectra (Nujol mulls) and *X*-ray powder photographs.

The phenolic fraction was shown to be homogeneous by paper chromatography, and recrystallisation from benzene, toluene, or acetone gave substance Cu_2 in colourless lances or rectangular prisms, m. p. 173—175° (not depressed on admixture with substance Ph_2), $[\alpha]_D^{23}$ −67·0° (*c*, 0·28 in $CHCl_3$) (Found: C, 72·3; H, 6·8; N, 5·0%). The analytical data and physical properties, including infra-red spectra, of substances Cu_2 and Ph_2 showed them to be identical [(−)-*N*-methylcoclaurine]; in solvents A and B substance Cu_2 had R_F values of 0·73 and 0·77 respectively, while substance Ph_2 had an R_F value of 0·75 in both solvents.

Reductive Cleavage of OO′-*Dimethylcurine in Dioxan.*—A solution of *OO′*-dimethylcurine (1·5 g.) in anhydrous dioxan (30 c.c.) was gradually added to liquid ammonia and reduced with sodium under the conditions described above. Reaction took 2 hr. and the product, when partitioned in the usual way, gave a non-phenolic syrup (0·25 g.) and a phenolic glass (1·03 g.). The former was converted into the methiodide in the usual way and recrystallisation from methanol gave substance Cu_1 methiodide, m. p. 138—139°.

The phenolic material was shown by paper chromatography to be inhomogeneous, and it was recrystallised three times from toluene, giving substance Cu_2, m. p. 166°, which was still not quite pure. Evaporation of the mother-liquors from the first two recrystallisations gave gummy residues, in each case giving a positive Gibbs reaction, whereas the residue from the mother-liquors of the third recrystallisation and substance Cu_2 itself gave no reaction. The combined residues from the first two mother-liquors were dissolved in benzene containing 2% of methanol and chromatographed on a column of alumina (12 g.) made up in the same solvent. The first three fractions to be eluted were evaporated and the residues were taken up together in a little methanol from which large colourless prisms (substance Cu_3) (40 mg.) crystallised overnight; these had m. p. 182—183° (micro) (depressed to 163—164° on admixture with pure substance Cu_2, m. p. 173—175°), $[\alpha]_D^{20}$ −99·2° (*c*, 5·06 in $CHCl_3$), and gave a strong Gibbs reaction.

Methylation of (−)-N-*Methylcoclaurine* (*Cu*$_2$) *to* (−)-O-*Methylarmepavine* (*Cu*$_1$).—A solution of substance Cu_2 (0·1 g.) in methanol (20 c.c.) and benzene (10 c.c.) was methylated with diazomethane (from 3 g. of methylnitrosourea) in the manner described for substance Ph_2, and the product was converted in the usual way into the methiodide, m. p. 138—139°, shown by mixed m. p. and infra-red spectrum (Nujol mull) to be identical with the methiodide of substance Cu_1.

Identification of Substance Cu$_3$ *as Laudanidine* (XII).—The properties of substance Cu_3 (m. p. 182—183°, $[\alpha]_D^{20}$ −99·2°) were in close agreement with those of laudanidine [(−)-laudanine], for which Späth and Bernhauer (*Ber.*, 1925, **58**, 200) record m. p. 184—185°, $[\alpha]_D^{18}$ −100·6°. The colour reactions tallied with those described for laudanine; with concentrated sulphuric acid substance Cu_3 gave a faint pink colour darkening rapidly to purple-red on heating (cf. Hesse, *Annalen, Suppl.*, 1872, **8**, 273), and a methanolic solution was rendered pale green by a drop of aqueous ferric chloride (cf. Hesse, *Annalen*, 1870, **153**, 54; 1894, **286**, 208). On comparison by paper chromatography of substance Cu_3 with (±)-laudanine, obtained by demethylation of (±)-laudanosine with hydrochloric acid (Späth and Burger, *Monatsh.*, 1926, **47**, 733), both sub-

stances had identical R_F values in both solvent systems (0·70 in A, and 0·57 in B), and mixtures of the two afforded single spots with both solvents.

Substance Cu_3 (9·2 mg.) was treated in methanol (2 c.c.) with diazomethane (from 1·5 g. of methylnitrosourea) in ether (15 c.c.). After 16 hr. the excess of diazomethane was destroyed with acetic acid, and the mixture was basified with ammonia, the ethereal layer being washed with aqueous sodium hydroxide, then with water, then dried, and evaporated. The residue (9 mg.) was crystalline, m. p. 76—77°; for optically active laudanosine, Pictet and Athanasescu (*Ber.*, 1900, **33**, 2346) record m. p. 89°. When run in solvents A and B the substance had R_F values of 0·72 and 0·66 respectively, while (±)-laudanosine had R_F values of 0·73 and 0·64; mixtures of methylated Cu_3 and (±)-laudanosine gave single spots of R_F 0·73 and 0·64 in solvents A and B respectively.

Conversion of (−)-N-*Methylcoclaurine* (IX) *into* (−)-*Magnocurarine* (X).—(−)-*N*-Methylcoclaurine (0·7 g.), derived from phaeanthine, was refluxed in methanol (30 c.c.) with methyl iodide (1 c.c.) for 1 hr. Crystals (0·83 g.) separated during concentration of the solution, and recrystallisation from methanol afforded (−)-N-*methylcoclaurine methiodide* [(−)-*magnocurarine iodide*] in fine cream-coloured leaflets or flat prisms, m. p. 194—197°, sintering at 149° (Found: C, 49·6; H, 5·8; N, 2·9. $C_{19}H_{24}O_3NI,H_2O$ requires C, 49·7; H, 5·7; N, 3·1%).

The major part of the methiodide was converted into the methochloride (cf. Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 5231) by refluxing for 1 hr. with methanol (50 c.c.) of which part (30 c.c.) had been saturated with hydrogen chloride. Evaporation to dryness left a brown syrup which was taken up in a little methanol and brought to pH 7—8 with methanolic 0·5N-potassium hydroxide. A portion of the neutralised solution was diluted with water, and the methanol was evaporated; saturated aqueous sodium picrate was added and the precipitated picrate crystallised from acetone in yellow needles, m. p. 172—173°: Tomita, Inubushi, and Yamagata (*J. Pharm. Soc. Japan*, 1951, **71**, 1069) record m. p. 169—172°, and Tomita and Nakano (*ibid.*, 1952, **72**, 197) record m. p. 177—178° for (−)-magnocurarine picrate. The bulk of the neutralised methochloride solution deposited crystals of the phenol-betaine when set aside at pH 8; the colourless prisms which separated on recrystallisation from water containing a little methanol had m. p. 198—200°, $[\alpha]_D^{23}$ −89·6° (*c*, 1·2 in H_2O): Tomita, Inubushi, and Yamagata (*loc. cit.*) record m. p. 200°, $[\alpha]_D^{29}$ −91° (in H_2O) for (−)-magnocurarine, and McKenzie and Price (*loc. cit.*) record m. p. 198—199°, $[\alpha]_D^{22}$ +106° (in H_2O) for the enantiomorph.

Reductive Cleavage of OO'-*Dimethyliso*chondrodendrine (V; R = Me) *in Dioxan.*—(*a*) Powdered stems (1700 g.) of *Chondrodendron candicans* were extracted with 1% tartaric acid as described by King (*J.*, 1940, 737) and the crude chloroform-soluble bases (46 g.) were crystallised from methanol. *iso*Chondrodendrine was isolated from the resulting mixture as the sulphate, m. p. 305—309° (decomp.) $[\alpha]_D^{19}$ +107° (*c*, 0·58 in H_2O; on material dried *in vacuo* at room temperature). The homogeneity of the specimen was demonstrated by paper chromatography on phosphate-treated paper in solvent A, which is capable of effecting separation of *iso*chondrodendrine and bebeerine, the major alkaloids found in this species.

(*b*) A suspension of *iso*chondrodendrine (1·5 g.) in benzene (70 c.c.) and methanol (25 c.c.) was stirred during the addition during 2 hr. of a benzene solution (50 c.c.) of diazomethane (from 10 g. of methylnitrosourea). The mixture, which rapidly cleared, was stirred for a further ½ hr. and kept overnight before destruction of excess of diazomethane with acetic acid. Evaporation of the washed organic phase gave a crystalline residue (1·2 g.), from which pure *OO'*-dimethyl*iso*chondrodendrine was obtained by recrystallisation from acetone as clusters of long, flat prisms, m. p. 273—275°, $[\alpha]_D^{19}$ −30·3° (*c*, 2·6 in EtOH); the substance gave single spots in both solvent systems. Faltis and Neumann (*Monatsh.*, 1921, **42**, 311) record m. p. 256—257°, $[\alpha]_D^{19}$ −36·8° (in EtOH), and Kondo, Tomita, and Uyeo (*Ber.*, 1937, **70**, 1890) record m. p. 272—273°, $[\alpha]_D^{31}$ −28·7°.

(*c*) *OO'*-Dimethyl*iso*chondrodendrine (0·5 g.) in dioxan (25 c.c.) was reduced with sodium (0·6 g.) in liquid ammonia (500 c.c.) as described above in the case of phaeanthine. The product was partitioned in the usual way, giving a syrupy non-phenolic fraction (0·1 g.) and a solid phenolic fraction (0·4 g.). The latter was taken up in warm ethanol (10 c.c.) and treated with oxalic acid (0·5 g.) in ethanol. The crystalline hydrogen oxalate (0·45 g.; m. p. 210—211°) which rapidly separated was recrystallised from ethanol giving colourless needles, m. p. 211—212°. Basification of the purified oxalate afforded (−)-armepavine (0·34 g.), which separated from a small volume of acetone–ether (5 : 1) as a crust of small needles, m. p. 149—150°, $[\alpha]_D^{21}$ −105° (*c*, 1·25 in $CHCl_3$). Fujita and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1043) record m. p. 145—146°, $[\alpha]_D^{12}$ −109·1° (in $CHCl_3$) (oxalate, m. p. 211—212°), and Konowalowa, Yunussoff, and Orechoff (*Ber.*, 1935, **68**, 2158) record m. p. 148—149°, $[\alpha]_D$ −118·7° (oxalate, m. p. 211—212°).

The oxalate mother-liquors were basified and the liberated base (50 mg.) was isolated by extraction with chloroform. This crude residue, which gave no typical reaction with Gibbs's reagent, was compared with pure (−)-armepavine by paper chromatography; in solvent A, the latter gave a single compact spot of R_F 0·69, whereas the mother-liquor residues showed a corresponding spot of R_F 0·68 and two additional spots of R_F 0·57 and 0·76 respectively; in solvent B a similar result was obtained, the observed R_F values being 0·65 for armepavine, and 0·52, 0·63, and 0·74 for the mother-liquor residues.

The original crude non-phenolic fraction was dissolved in acetone and set aside for a week at 2°; no *OO'*-dimethyl*iso*chondrodendrine had separated at the end of this period, and none could be detected by paper chromatography. Chromatography on a column of alumina failed to yield any crystalline material.

*7-Benzyloxy-1-4'-benzyloxybenzyl-3 : 4-dihydro-6-methoxy*isoquinoline *Hydrochloride.*—The undernoted stages in this synthesis constitute improvements on previously described methods.

(*a*) A suspension of 4-nitrobenzyl cyanide (Pschorr, Wolfes, and Buckow, *Ber.*, 1900, **33**, 162) (100 g.) in a mixutre of ethyl acetate (450 c.c.) and ethanol (150 c.c.) was hydrogenated over 2% palladised strontium carbonate (1 g.) at an initial pressure of 10 atm. and room temperature until the theoretical amount of hydrogen was absorbed. Two such reaction mixtures were bulked, filtered, and taken to dryness. The residue was treated in chloroform (500 c.c.) with 5N-hydrochloric acid (350 c.c.). The precipitated hydrochloride was collected and the free base was liberated and taken up in ether, yielding, on evaporation, 4-aminobenzyl cyanide (133 g., 85%).

(*b*) 4-Hydroxybenzyl cyanide (77 g.), prepared from the amino-compound by the method of Koessler and Hanke (*J. Biol. Chem.*, 1919, **39**, 585), dissolved in the minimum amount of ethanol, was added to ethanolic potassium hydroxide (38·5 g. in 385 c.c.), and benzyl chloride (84 g.) was run in. After refluxing for 3 hr. the mixture was cooled, and the crystalline solid was collected and washed with ethanol. The solid was partitioned between ether and water, the organic phase was washed with 2N-sodium hydroxide and water, and the ether was evaporated; 4-benzyloxybenzyl cyanide, m. p. 68—70°, was thus obtained; Tomita, Nakaguchi, and Takagi (*J. Pharm. Soc. Japan*, 1951, **71**, 1046) record m. p. 68·5—69°. A further small quantity was isolated from the ethanolic mother-liquors, and, after recrystallisation from methanol, had m. p. 64—65° (total yield, 115·3 g.; 90%).

(*c*) The preceding nitrile (115·3 g.) was refluxed with potassium hydroxide (40 g.) in a mixture of water (800 c.c.) and ethanol (240 c.c.) for 5 hr. A further amount of aqueous potassium hydroxide (40 g. in 800 c.c.) was added and refluxing was continued for a further 8 hr. to complete the hydrolysis. When cold, the mixture was extracted with ether, and the aqueous phase was acidified, precipitating 4-benzyloxyphenylacetic acid (125 g., 99%), m. p. 120—122°; Mozingo and Folkers ("Chemistry of Penicillin," Oxford Univ. Press, 1949, p. 535) record m. p. 122°.

(*d*) The preceding acid (25 g.) was heated at 65—70° with thionyl chloride (5 c.c.) in ligroin (40 c.c.) until reaction ceased, leaving a clear solution. On cooling in ice, the acid chloride crystallised in quantitative yield, and was washed well with ligroin and dried *in vacuo*.

(*e*) A solution of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine hydrochloride (7 g.), prepared by Finkelstein's method (*J. Amer. Chem. Soc.*, 1951, **73**, 550), in chloroform (100 c.c.) was stirred with ice-cooling during the addition of triethylamine (4 c.c.) in chloroform (50 c.c.). After 30 min., a further similar quantity of triethylamine in chloroform and a solution of 4-benzyloxyphenylacetyl chloride (6·2 g.) in chloroform were added in portions alternately with continued stirring and cooling. An hour after addition was complete, water was added and the chloroform layer was separated and washed; evaporation then gave pure *N*-2'-(4-benzyloxy-3-methoxyphenyl)ethyl-4-benzyloxyphenylacetamide (10·9 g., 95%), m. p. 114—116°; Tomita, Nakaguchi, and Takagi (*loc. cit.*) record m. p. 115—117°.

(*f*) Phosphoryl chloride (26·7 c.c.) was added to a solution of the above amide (18·3 g.) in chloroform (43 c.c.), and the mixture was refluxed for 3½ hr. On dilution with several volumes of light petroleum and storage at 2° for 16 hr., a solid was obtained; this was well washed with light petroleum and dissolved in methanol (charcoal); addition of ether to the filtrate precipitated the hydrochloride of the required dihydro*iso*quinoline; the crystals (14·8 g., 86%), which separated, were sufficiently pure [m. p. 196—198° (decomp.)] for the next stage. Recrystallisation from alcohol raised the m. p. to 198—199° (decomp.); Tomita *et al.* (*loc. cit.*) record m. p. 197° (decomp.).

*7-Benzyloxy-1-4'-benzyloxybenzyl-3 : 4-dihydro-6-methoxy*isoquinoline *Methiodide.*—The above hydrochloride (10 g.) was dissolved in boiling ethanol (130 c.c.) and maintained at 65—70° while air was displaced with a stream of nitrogen. After 30 min., a solution of sodium ethoxide (from

0·5 g. of sodium) in ethanol (20 c.c.) was added, followed in a few minutes by methyl iodide (15 c.c.). Gentle boiling under nitrogen was continued for 5½ hr. The product, which crystallised from the cooled solution, was thoroughly ground with water, collected, washed with water, and dried (yield, 11·7 g., 96%; m. p. 188—190°). Recrystallisation from methanol–ether, or acetone–ether, gave light yellow platelets of the *methiodide*, m. p. 191—193° (Found: C, 63·7; H, 5·4; N, 2·0. $C_{32}H_{32}O_3NI$ requires C, 63·6; H, 5·3; N, 2·3%).

(±)-N-*Methylcoclaurine* (IX).—(*a*) The above methiodide (1·83 g.) was hydrogenated over Raney nickel in ethanol (500 c.c.) containing diethylamine (2·5 c.c.) for 3 hr. at 160° and an initial pressure of 60 atm. (cf. Barltrop and Taylor, *J.*, 1951, 108). Evaporation of the filtered solution gave a yellow solid residue (1·13 g.), which was extracted with successive portions of boiling toluene. On concentration to small bulk the toluene extracts gave a cream-coloured solid (0·2 g.; m. p. 152—156°), and a further crop (0·24 g.; m. p. 160—162°) was obtained from the mother-liquors. Recrystallisation from toluene, or from a small volume of acetone, gave small colourless prisms of (±)-*N*-methylcoclaurine, m. p. 161—162° (Found: C, 70·4; H, 7·5; N, 4·7. Calc. for $C_{18}H_{21}O_3N,\frac{1}{2}H_2O$: C, 70·1; H, 7·2; N, 4·5%); Tomita and Kusuda (*J. Pharm. Soc. Japan*, 1952, **72**, 280) record m. p. 161—162° for material prepared by *N*-methylation of natural (±)-coclaurine.

The synthetic (±)-material was indistinguishable by paper chromatography in both solvents A and B from (−)-*N*-methylcoclaurine obtained (above) by degradation of phaeanthine.

(*b*) The following procedure, though rather more tedious, gave a much better yield. The methiodide (5·9 g.) was converted into the methochloride with methanolic hydrogen chloride (cf. Phillips and Baltzly, *loc. cit.*). The crude methochloride (4·2 g.) was debenzylated by slow distillation at atmospheric pressure of its solution in 20% hydrochloric acid (175 c.c.) until no more benzyl chloride distilled over; the remaining solvent was then removed *in vacuo*. The residue was next reduced by being stirred for 3 hr. under reflux with zinc powder (7 g.) in boiling 30% acetic acid (50 c.c.) (cf. Schöpf, Jäckh, and Perrey, *Annalen*, 1932, **497**, 59). The cooled solution was filtered and the zinc was washed with 30% acetic acid. The acidic filtrates were basified with ammonia, and the product was recovered in ether, a further quantity being obtained by a subsequent extraction with chloroform. Recrystallisation from acetone then gave (±)-*N*-methylcoclaurine (2·1 g., 72%), m. p. 161—163°.

Unsuccessful attempts were made to resolve the (±)-substance using camphorsulphonic acid, α-bromocamphorsulphonic acid, camphoric acid, tartaric acid, dibenzoyltartaric acid, quinic acid, menthoxyacetyl chloride, and oleanolic acid.

(±)-N-*Methylcoclaurine Methiodide* [(±)-*Magnocurarine Iodide*].—(±)-*N*-Methylcoclaurine (0·3 g.) was treated with methyl iodide (0·5 c.c.) in boiling methanol (20 c.c.) for 1½ hr. Recrystallisation of the residue, left on evaporation, from a small volume of methanol gave the (±)-*methiodide* in the form of heavy cream-coloured prisms (0·28 g.), m. p. 155—156° (decomp.) (Found: C, 49·8; H, 5·8; N, 2·9. $C_{19}H_{24}O_3NI,H_2O$ requires C, 49·7; H, 5·7; N, 3·1%). The infra-red spectrum of the (±)-methiodide and that of the (−)-form showed very close correspondence but not complete identity (Nujol mulls), as could be expected. When compared by paper chromatography under standard conditions, the (±)- and (−)-methiodides had identical R_F values (0·72 in solvent A, and 0·48 in solvent B), and mixtures of the two gave single spots with both solvents.

The authors are indebted to Dr. J. R. Price for a generous gift of phaeanthine and to Dr. R. H. F. Manske for a specimen of corpaverine; they also thank Mrs. O. Kennard for providing *X*-ray powder photographs and Mr. R. J. Clark for technical assistance.

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[*Received, October 28th*, 1953.]