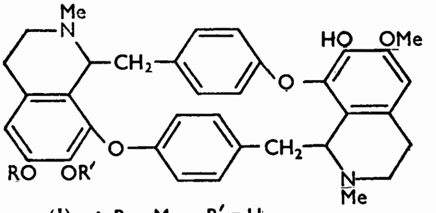
856. *Curare and Related Topics. Part II.* The Structure and Anomalous Optical Rotation of* iso*Chondrodendrine.*

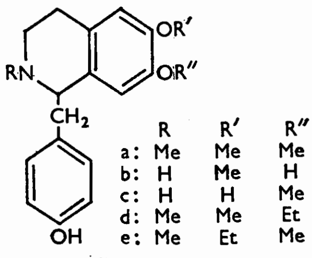
By John A. D. Jeffreys.

Fission of *iso*chondrodendrine diethyl ether with sodium in liquid ammonia gave only (—)-1 : 2 : 3 : 4-tetrahydro-7-ethoxy-1-4′-hydroxybenzyl-6-methoxy-2-methyl*iso*quinoline (IId), proving the structure of *iso*chondrodendrine to be (Ia). The specific rotation of *iso*chondrodendrine in excess of acid varies markedly with the concentrations of acid and base.

*iso*Chondrodendrine, one of the chief alkaloids of the South American *Chondrodendron* species, was shown to have structure (Ia or b) by Faltis [1] and by King; [2] fission of the dimethyl ether (cycleanine) with sodium in liquid ammonia [3, 4, 5] to give (—)-armepavine (IIa) as the product showed that both optically active centres had the same sign of rotation. The position of one of the hydroxyl groups remained uncertain. King [2] had shown, using the Millon reaction, that one of the hydroxyl groups had a vicinal substituent on each side of it, and Faltis [1] had assumed that the molecule was symmetrical since it could then arise from two molecules of coclaurine (IIb). This is not a conclusive argument; *iso*chondrodendrine occurs in both *Chondrodendron tomentosum* and *Ch. platyphyllum*: the former yields also chondrocurine (IVa),[6] and the latter chondrofoline (IVb),[2] each of which contains an *iso*coclaurine (IIc) nucleus.

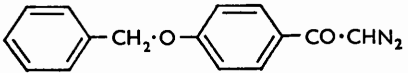


(I) a: R = Me, R′ = H
b: R = H, R′ = Me

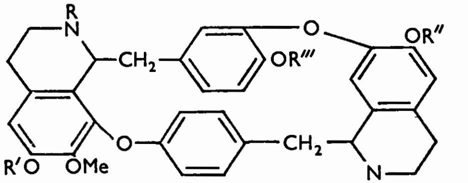


(II)

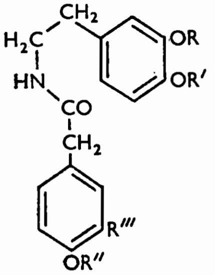
	R	R′	R″
a:	Me	Me	Me
b:	H	Me	H
c:	H	H	Me
d:	Me	Me	Et
e:	Me	Et	Me



(III)



	R	R′	R″	R‴
(IV) a:	Me	H	Me	H
(IV) b:	H	{H or Me}	{Me or H}	Me



	R	R′	R″	R‴
(V)	{Me or Et}	{Et or Me}	CH₂Ph	H
(VI)	Me	Me	Me	OMe

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* Part I, *J.*, 1954, 159.

[1] Review: Kulka, "The Alkaloids," Ed. Manske and Holmes, Academic Press Inc., New York, 1954, Vol. IV, pp. 224 *et seq.*

[2] King, *J.*, 1940, 737.

[3] Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 301; *Chem. Abs.*, 1952, **46**, 4555.

[4] Fujita and Murai, *ibid.*, p. 1043; *Chem. Abs.*, 1952, **46**, 5061.

[5] Kidd and Walker, *J.*, 1954, 669.

[6] Dutcher, *J. Amer. Chem. Soc.*, 1946, **68**, 419.

Accordingly, *iso*chondrodendrine was treated with diazoethane, and the resulting diethyl ether split with sodium in liquid ammonia. The sole phenolic product was identical with a synthetic sample of (—)-7-ethoxy-1 : 2 : 3 : 4-tetrahydro-1-4′-hydroxybenzyl-6-methoxy-2-methyl*iso*quinoline (IId), proving the truth of Faltis's original assumption that *iso*chondrodendrine has structure (Ia).

The synthesis of the two possible fission products (IId and e) followed in general a standard route. Schlittler's method [7] for converting *O*-ethylvanillin and *O*-ethyl*iso*vanillin into the corresponding phenethylamines has been improved, and these bases were converted into the required amides (V) by heating them with the diazo-ketone (III) in an inert solvent. The amide (VI) has been synthesised by Eistert [8] in this way, though no experimental details are available, and similarly some anilides have been prepared by Baddeley, Holt, and Kenner.[9] In the examples described in the Experimental section, the water produced in the reaction presumably arose by condensation of the amine with the carbonyl group of the diazo-ketone, before the latter had had time to become the keten.

Resolution of the two bases (IId and e) presented no difficulty, malic acid being successful with the former, and quinic acid with the latter; in the second case, only the (—)-isomer was obtained pure. The two (—)-bases had different melting points and optical rotations in chloroform; their infrared spectra differed but did not permit a clear distinction between the possibilities that *iso*chondrodendrine diethyl ether would give two molecules of (IId), or one each of (IId) and (IIe); paper chromatography did not separate the two isomers. Both the lævorotatory ethers gave a lævorotatory product on de-*O*-alkylation, showing that interchange of methoxy- and ethoxy-groups at positions 6 and 7 did not change the sign of the active centre.

The Optical Rotation of iso*Chondrodendrine.*—A new base with $[\alpha]_D$ +127° (*c* 0·2 in N-sulphuric acid) was found in the mother-liquors of the *iso*chondrodendrine isolated for this work. As this value for [α] is within the range recorded for *iso*chondrodendrine,[5, 10, 11] the specific rotation of the latter was examined. It was found to be anomalous.

The specific rotation of *iso*chondrodendrine in excess of acid varied markedly with the temperature and with the concentrations of acid and base. Over the concentration range $c = 0{\cdot}2$—$1{\cdot}3$, at 20°, the specific rotation in N-sulphuric acid is given by the equation $[\alpha]_D^{20} = 203° - 12°/c$, where c is the concentration in g./100 c.c. (see Table), the temperature variation being described roughly by the equation $d[\alpha]/dT = [\alpha]/70 - 4{\cdot}2$. After readings 2—5, 9, and 10 had been taken, the base was recovered and recycled, then giving readings 1, 6, 8, and 11, showing that this variation is not due to decomposition of the base.

No.:	1	2	3	4	5	6	7	8	9	10	11
c	1·293	1·088	0·817	0·546	0·273	0·215	0·137	0·108	0·068	0·034	0·0108
[α] (found) ...	+194°	+192°	+189°	+178°	+160°	+148°	+128°	+116°	+95°	+50°	(0)
[α] (calc.)	+194°	+192°	+188°	+181°	+159°	+147°	+115°				
Found in 0·1N-H_2SO_4:		*c*	0·841	0·084							
		[α]	+164°	+73°							

Ionic association seems the probable cause of this variation and, by making simplifying assumptions, it is possible to obtain a measure of the degree of association, as follows. Assume the solution to contain $(1 - x)c_1$ mole of monomer, with specific rotation $[\alpha_1]$, in equilibrium with x/nc_1 mole of polymer containing n units and having specific rotation $[\alpha_2]$, c_1 being in mole per l. Then,

$$\frac{xc_1}{n} \cdot \frac{1}{(1 - x)^n} \cdot c_1{}^n = K_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Changing c_1 into c, expressed in g. per 100 c.c., changing the constant, and rearranging the equation gives :

$$c^{n-1} = (x/n) \, . \, [1/(1 - x)^n] \, . \, (1/K) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

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[7] Schlittler, *Ber.*, 1933, **66**, 992.

[8] Eistert, *Angew. Chem.*, 1941, **54**, 124; Bachmann and Struve, "Organic Reactions," Ed. Adams, John Wiley and Sons Inc., New York, 1942, Vol. I, p. 44.

[9] Baddeley, Holt, and Kenner, *Nature*, 1949, **163**, 766.

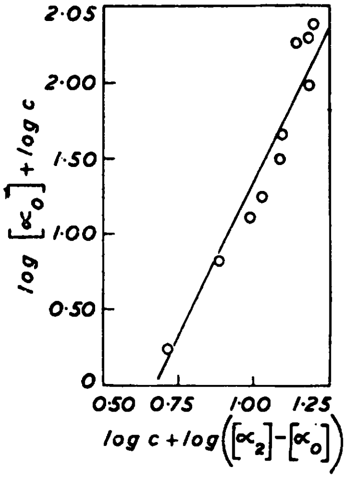
[10] King, *J.*, 1948, 1945.

[11] McKennis, Hearst, Drisko, Roe, and Alumbaugh, *J. Amer. Chem. Soc.*, 1956, **78**, 248.

If $[\alpha_1]$ is taken as the zero for specific rotations, $x = [\alpha_0]/[\alpha_2]$, where $[\alpha_0]$ is the observed specific rotation. Substituting this value for x into equation (1*a*), taking logarithms, and rearranging gives :

$$n\{\log c + \log([\alpha_2] - [\alpha_0])\} = \log[\alpha_0] + \log c + \text{Constant} \quad . \quad . \quad . \quad (2)$$

A plot of $\{\log[\alpha_0] + \log c\}$ against $\{\log([\alpha_2] - [\alpha_0]) + \log c\}$ should give a straight line of slope n. If $[\alpha_1]$ is taken as 0°, and $[\alpha_2]$ as +206°, the points fit fairly well on a straight line of slope 4 (see Figure), but, as $[\alpha_1]$ is rather uncertain, this should be taken as an order of magnitude only.



The equation $[\alpha]_D^{20} = +203° - 12°/c$ (see above) implies that $[\alpha_2] = +203°$; however, this equation was intended to hold over as great a concentration range as possible. Extrapolation for $[\alpha_2]$ based on the values of $[\alpha_0]$ in the four most concentrated solutions gives +206° as a better value.

(I am grateful to one of my referees for suggesting the development, quoted above, to give n by a graphical in place of a computational method.)

Compounds (IId and e) have been examined by Mr. J. J. Lewis, of the Department of Materia Medica, Glasgow University, who reports that they have a very weak curare-like activity on isolated tissues, but are convulsant poisons for intact animals. Details will be reported elsewhere.

EXPERIMENTAL

iso*Chondrodendrine*.—This base was isolated as described in Part I. A moving-film evaporator was used to concentrate the intensely foaming extract of the wood; without this apparatus, the isolation becomes tedious. *Chondrodendron limaciifolium* (1100 g.) gave *ca.* 2 g. of crude base which was recrystallised, first by adding methanol to its solution in chloroform, then from methanol alone. The alkaloid then appeared as needles, m. p. 288° (decomp.), $[\alpha]_D^{20}$ (in $CHCl_3$) −29° (*c* 1·3), −31° (*c* 0·33). With diazomethane it gave the dimethyl ether, m. p. 270—271° (decomp.; rapid heating), $[\alpha]_D^{19}$ −34° (*c* 0·3 in MeOH). Evaporation to dryness of solutions of this sample of *iso*chondrodendrine in dilute sulphuric acid disclosed traces of another base (probably base A, cf. Part I) whose sulphate crystallised in long thin plates (cf. Part I).

3-*Ethoxy*-4-*methoxy- and* 4-*Ethoxy*-3-*methoxy-phenethylamine*.—These were prepared from *O*-ethyl*iso*vanillin and *O*-ethylvanillin respectively by Schlittler's method,[7] the required amides being made by heating the corresponding acids with 1 mol. of urea at 200—220° for 4 hr.[12] The product was dissolved in chloroform and washed with sodium carbonate solution. After removal of the chloroform, the residue was recrystallised from benzene, in which the amides were sparingly soluble (yield 70—80%).

p-*Benzyloxyphenyl Diazomethyl Ketone* (III).—*p*-Benzyloxybenzoyl chloride (5·2 g., 1 mol.) in dry benzene (50 c.c.) was added to ether (200 c.c.) containing diazomethane (2·6 g., 3 mols.). After 24 hr. at room temperature the liquid was decanted from the crystals that had separated, and concentrated to *ca.* 50 c.c. Several hours later a second crop of crystals was collected. The *diazo-ketone* (3·96 g., 74%) formed pale yellow plates, m. p. 117° (decomp.), very soluble in benzene. For analysis a sample was precipitated from benzene solution with light petroleum (b. p. 60—80°) (Found : C, 71·7; H, 4·5; N, 10·9. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·7; N, 11·2%).

p-*Benzyloxy*-N-(3-*ethoxy*-4-*methoxyphenethyl*)*phenylacetamide*.—A solution of the above ketone (9·8 g., 1 mol.) and 3-ethoxy-4-methoxyphenethylamine (7·4 g., 1 mol.) in warm dry dichlorotoluene (b. p. 192—200°) (100 c.c.) was added dropwise during 30 min. to boiling dichlorotoluene (20 c.c.). The solution became deep red, and water collected in the condenser. Refluxing was continued for 10 min. after the addition, and the solution left for 24 hr. at room temperature. The crude product that had separated was collected (10·8 g.), and a further 0·5 g. was obtained by removal of the solvent in steam and repeated extraction of the dried residue with boiling light petroleum (b. p. 80—100°); recrystallisation of the crude product (73%)

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[12] Cherbuliez and Landolt, *Helv. Chim. Acta*, 1946, **29**, 3509.

from benzene gave the *amide* as needles, m. p. 125° after sintering from 121° (Found: C, 74·6; H, 7·0; N, 3·6. $C_{26}H_{29}O_4N$ requires C, 74·5; H, 6·9; N, 3·3%).

p-*Benzyloxy*-N-(4-*ethoxy*-3-*methoxyphenethyl*)*phenylacetamide*.—The diazoketone (15·4 g.) and 4-ethoxy-3-methoxyphenethylamine (11·4 g.) in dichlorotoluene (120 c.c.) gave, as above, the *amide* (16·8 g., 69%) as needles, m. p. 113° (from benzene) (Found: C, 74·7; H, 6·9; N, 3·3%). In some runs of the two experiments described above, the solid diazo-ketone (1 mol.) was added at *ca.* 0·2 g./min., to a solution of the amine (1 mol.) in boiling decalin. The yield was the same, and was not improved by the presence of suspended silver oxide. Increasing the rate of addition of the diazo-ketone reduced the yield.

1-4′-*Benzyloxybenzyl*-6-*ethoxy*-3 : 4-*dihydro*-7-*methoxy*iso*quinolinium Chloride*.—A solution of the amide (V; R = Me, R′ = Et) (11·3 g.) in chloroform (100 c.c.) and phosphorus oxychloride (20 c.c.) was refluxed for 4 hr. After cooling, the chloroform was extracted with sodium carbonate solution till the washings remained alkaline to litmus, then with dilute hydrochloric acid. To remove excess of water the chloroform solution was filtered, and the solvent evaporated. The residue was extracted with boiling benzene, which removed some colouring matter, leaving the *hydrochloride* (10·1 g., 93%), m. p. 214° (decomp., varies with rate of heating). Addition of ethyl acetate to its solution in chloroform gave minute needles, m. p. 213—215° (decomp. from 200°) (Found: C, 71·1; H, 6·6; N, 3·4; Cl, 8·3. $C_{26}H_{27}O_3N,HCl$ requires C, 71·3; H, 6·4; N, 3·2; Cl, 8·1%).

1-4′-*Benzyloxybenzyl*-7-*ethoxy*-3 : 4-*dihydro*-6-*methoxy*iso*quinolinium Chloride*.—Treated in the manner described above, the amide (V; R = Me, R′ = Et) (16·8 g.) gave the crude *amine hydrochloride* (17·0 g., 97%), m. p. 203° (effervescence, shrinking from 140°) (Found: C, 71·4; H, 6·6; N, 3·7; Cl, 8·4%). This salt, and the isomer, were readily soluble in methanol and in chloroform, but not in cold water. Each possessed in the solid state a vivid blue fluorescence, visible in daylight, which was similar in colour to that of pure anthracene; in solution the fluorescence was visible only under ultraviolet illumination.

1-4′-*Benzyloxybenzyl*-6-*ethoxy*-3 : 4-*dihydro*-7-*methoxy*-2-*methyl*iso*quinolinium Iodide*.—To a solution of the corresponding tertiary amine hydrochloride (6·97 g.) in methanol (80 c.c.) under nitrogen, a solution of sodium methoxide (from 0·4 g. of the metal) in methanol (20 c.c.) was added, followed by methyl iodide (13 c.c.), and the solution was refluxed for 6 hr. Evaporation left yellow crystals which were taken up in chloroform and washed with water, and the solvent was evaporated. Recrystallisation from methanol gave the quaternary *salt* (6·2 g., 71%) as yellow prisms, m. p. 209—211° (decomp. from 170°), with a golden-yellow fluorescence under ultraviolet light. A further recrystallisation from methanol did not alter the m. p. (Found: C, 59·5; H, 5·8; N, 3·1; I, 23·2. $C_{27}H_{30}O_3NI$ requires C, 59·7; H, 5·5; N, 2·6; I, 23·4%). In solution this salt was very readily oxidised.

1-4′-*Hydroxybenzyl*-6-*ethoxy*-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-2-*methyl*iso*quinoline*.—The methiodide described above was debenzylated and reduced as described by Kidd and Walker,[5] giving the tertiary *amine* (IIe) (42%). Recrystallisation from toluene gave prisms, m.p. 124—125° (Found: C, 73·5; H, 7·4; N, 4·6. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7; N, 4·2%). In a later run without isolation of the intermediate compounds, the dihydro*iso*quinoline hydrochloride (10·1 g.) gave this base (6·3 g., 84%).

1-4′-*Hydroxybenzyl*-7-*ethoxy*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-2-*methyl*iso*quinoline*.—The corresponding dihydro*iso*quinoline hydrochloride (6·94 g.) was converted, as in the preceding experiment, *via* the methiodide (which did not crystallise) into the tertiary *amine* (2·48 g., 48%), m. p. 154—162°. Recrystallisation gave needles from methanol, or prisms and thick plates from toluene, m. p. in each case 163—164° (slight decomp., with sintering from 160°) (Found: C, 73·4; H, 7·5; N, 4·5%). In a later run, the yield based on the dihydro*iso*quinoline hydrochloride was 75%.

Resolution of the Bases (IId *and* e).—The 6-ethoxy-7-methoxy-isomer (IIe) was resolved as the neutral quinate, a solution of the salt in hot acetone containing 10% of methanol rapidly depositing the salt of the (−)-base, which after a further crystallisation was decomposed, to give the pure (−)-base as prisms [from light petroleum (b. p. 100—120°)], m. p. 146° (shrinking from 120°), $[\alpha]_D^{20}$ −102° (*c* 2·24 in $CHCl_3$), unchanged by further recrystallisation of the quinate. The mother-liquors from the resolution slowly deposited the quinate of the impure (+)-base, which on liberation had $[\alpha]_D^{20}$ +77° (*c* 1·07 in $CHCl_3$), unchanged by further recrystallisation of the quinate. Neither the hydrogen tartrate nor the hydrogen malate was obtained crystalline.

The 7-ethoxy-6-methoxy-isomer (IId) was resolved as the hydrogen malate by crystallisation from acetone. In nearly every case the salt that separated (square plates or prisms) gave an inactive base, but on rare occasions the salt of the (−)-base separated as thick rhombs. Once seeds were available, the first crop of crystals could always be obtained as the salt of the (−)-base. The mother-liquors very slowly deposited the salt of the impure (+)-base as needles. The pure bases had m. p. 130—131°, $[\alpha]_D^{17}$ +83° (*c* 0·72 in $CHCl_3$), and $[\alpha]_D^{19}$ −82° (*c* 0·66 in $CHCl_3$), decreasing *ca.* 1° per degree rise in temperature.

*OO'-Diethyl*iso*chondrodendrine*.—Ether (30 c.c.) containing diazoethane (0·114 g.) was added to a suspension of *iso*chondrodendrine (0·11 g.) in 1 : 1 benzene–methanol (40 c.c.), and the solution kept (several days) until all the diazoethane had decomposed. Isolation of the non-phenolic product gave 0·10 g. (80%). Addition of light petroleum (b. p. 60—80°) to a solution of this product in benzene gave the *ether* as square plates, m. p. 216°, $[\alpha]_D^{20}$ −9° (*c* 0·735 in EtOH) [Found: C, 73·5; H, 6·9; N, 4·4%; no. of *O*-alkyl groups, 4·0. $C_{34}H_{30}O_2N_2(OMe)_2(OEt)_2$ requires C, 73·8; H, 7·1; N, 4·3%]. The base was much more soluble in the common solvents than was cycleanine.

*Fission of OO'-Diethyl*iso*chondrodendrine*.—To a solution of sodium (*ca.* 60 mg.) in liquid ammonia (100 c.c.) a solution of *OO'*-diethyl*iso*chondrodendrine (92·6 mg.) in dry toluene (20 c.c.) was added, and the solution left for an hour. It was still blue, and the ammonia was allowed to evaporate, some undissolved sodium collected, and the residue separated into a non-phenolic portion (23·2 mg.), presumably starting material, and a crude brown phenolic resin (58·1 mg.). Extraction of the latter with ether left a small part undissolved, and the ether-soluble portion was recrystallised from light petroleum (b. p. 60—80°) to give two crops of crystals, each with m. p. 128° (51·3 mg. in all). A second crystallisation, from light petroleum (b. p. 100—120°), gave a product of m. p. 129—129·5°; a mixture with (−)-1 : 2 : 3 : 4-tetrahydro-1-4'-hydroxybenzyl-7-ethoxy-6-methoxy-2-methyl*iso*quinoline (IId) had m. p. 129—130°; a mixture with the 6-ethoxy-7-methoxy-isomer (IIe) had no definite m. p., but after softening from *ca.* 80° about half of the mixture melted suddenly at 116—117°. This second crop had $[\alpha]_D^{20.5}$ −80° (*c* 0·336 in $CHCl_3$); pure (IId) had $[\alpha]_D^{20}$ −82°, and an equimolecular mixture of (IId) and (IIe) would have $[\alpha]_D^{20} = -92°$.

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THE UNIVERSITIES OF GLASGOW AND LEEDS.

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