217. *The Synthesis and Resolution of* (±)-*Corlumine.*

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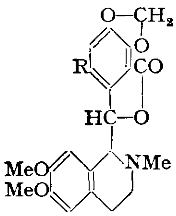
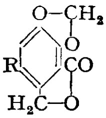
The synthesis of the 3-1′-*iso*quinolylphthalide alkaloid, corlumine (I; R = H) has been completed. Reduction of iodo-(±)-corlumine and deamination of amino-(±)-corlumine afforded (±)-corlumine which was readily resolved by crystallization of the (+)-(hydrogen tartrates) from methanol. The enantiomorphs were identified and compared with naturally occurring (+)-corlumine. No products having the adlumine configuration were encountered.

(±)-Adlumine (Manske, *Canadian J. Res.*, 1933, **8**, 210, 404; 1938, **16**, *B*, 81; 1939, **17**, *B*, 51) and (+)-corlumine (Manske, *ibid.*, 1936, **14**, *B*, 325, 347; 1938, 16, *B*, 81; 1940, **18**, *B*, 288) are two of the many alkaloids isolated from certain Fumariaceae. Their structural identity was placed beyond doubt (Manske, *ibid.*, 1933, **8**, 404; 1936, **14**, *B*, 325, 347; 1938, **16**, *B*, 81) by hydrolytic oxidation with dilute nitric acid, lodal and 6-formyl-2 : 3-methylenedioxybenzoic acid being obtained in each case and their identity established by a Cannizzaro rearrangement. No depressions in melting point occurred when the compounds obtained from (+)-corlumine were mixed with the corresponding ones obtained from (+)- and (−)-adlumine. Procedures used by Manske (*loc. cit.*) for the hydrolytic oxidation of adlumine were followed without modification for corlumine. It was obvious, therefore, that the two alkaloids differ only in the disposition of the substituents about the two asymmetric carbon atoms, formula (I; R = H) applying to both bases.

(I)





(II)

Groenewoud and Robinson (*J.*, 1936, 199) synthesized a base which they termed amino-*x*-adlumine *; conversion of the amino-compound into the free base, and resolution and identification of the enantiomorphs have now been accomplished. Their compound is actually amino-(±)-corlumine.

The synthesis followed the methods set forth by Hope and Robinson (*Proc.*, 1910, **26**, 228; *J.*, 1911, **99**, 1153) and Hope, Pyman, Remfry, and Robinson (*J.*, 1931, 236). 6 : 7-Methylenedioxyphthalide (II; R = H) was prepared from *o*-veratraldehyde as described by Perkin and Trikojus (*J.*, 1926, 2925). It was readily nitrated (Groenewoud and Robinson, *loc. cit.*) and the condensation of the 4-nitro-compound with lodal in boiling alcohol

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* The *x* signifies that the allocation to the stereoisomeric series α and β had not then been carried out.

followed the usual course. Lodal (Pyman, *J.*, 1909, **95**, 1266) was prepared from homoveratrylamine by a series of reactions involving methods employed by Späth and Polgar (*Monatsh.*, 1929, **51**, 195), Späth and Epstein (*Ber.*, 1926, **59**, 2796), Buck and Ide (*J. Amer. Chem. Soc.*, 1938, **60**, 2102), and Leonard and Leubner (*ibid.*, 1949, **71**, 3410).

It is noteworthy that no condensation occurred between lodal and 4-bromo-6 : 7-methylenedioxyphthalide (II; R = Br) even after extended periods under the usual conditions.

Whereas Groenewoud and Robinson (*loc. cit.*) reduced their nitrated base chemically, catalytic reduction is preferred as it permits easier isolation of the amino-base (I; R = NH_2). The latter was deaminated by two routes. One involved the conversion of the amino-base into the corresponding iodo-compound, followed by catalytic reduction of the latter, while the second method was a direct deamination of the diazotized amine with hypophosphorous acid. The two methods were equally efficacious, identical yields of identical products being obtained.

The (±)-corlumine so obtained has been completely resolved by crystallization of the (+)-(hydrogen tartrates) from methanol; one component is identical with natural (+)-corlumine.

The condensation of lodal with 6 : 7-methylenedioxy-4-nitrophthalide is apparently stereo-selective. Though a mixture of nitro-(±)-adlumine and nitro-(±)-corlumine is to be expected from the condensation, only the nitro-(±)-corlumine was isolated, and that in such a yield (85%) as to preclude a random reaction.

EXPERIMENTAL

M. p.s were determined with a calibrated apparatus. Microanalyses are by Galbraith Laboratories, Knoxville, Tennessee.

6 : 7-*Methylenedioxyphthalide* (II; R = H).—Prepared according to Perkin and Trikojus's method (*loc. cit.*) this compound had m. p. 230—232°. Perkin and Trikojus (*loc. cit.*) gave m. p. 227°, which was confirmed by Späth and Holter (*Ber.*, 1927, **60**, 1897) and Chakravarti (*J. Indian Chem. Soc.*, 1943, **20**, 384). Manske (*Canadian J. Res.*, 1933, **8**, 144) and Groenewoud and Robinson (*loc. cit.*) attributed m. p. 234° and m. p. 233—234°, respectively, to the phthalide.

6 : 7-*Methylenedioxy*-4-*nitrophthalide* (II; R = NO_2).—6 : 7-Methylenedioxyphthalide was nitrated according to Groenewoud and Robinson (*loc. cit.*), who reported m. p. 222—223°. The nitrophthalide obtained had m. p. 230—232°, depressed to 190—192° on admixture with 6 : 7-methylenedioxyphthalide.

4-*Bromo*-6 : 7-*methylenedioxyphthalide* (II; R = Br).—Groenewoud and Robinson (*loc. cit.*) prepared this compound from bromonormeconin, but we preferred to brominate 6 : 7-methylenedioxyphthalide directly. 6 : 7-Methylenedioxyphthalide (1 g.) was heated under reflux for 30 minutes with glacial acetic acid (35 c.c.) and bromine (1 g.). Dilution with ice–water (100 c.c.) induced immediate precipitation. The collected yellow solid was washed with cold alcohol (5 c.c.) and crystallized from ethyl acetate (charcoal). The bromo-compound (0·42 g., 30%) crystallized in long, flat, yellow needles, m. p. 198—199° (Found: C, 42·1; H, 2·0. Calc. for $C_9H_5O_4Br$: C, 42·1; H, 2·1%). Groenewoud and Robinson (*loc. cit.*) reported m. p. 196°.

Under the usual conditions, 4-bromo-6 : 7-methylenedioxyphthalide did not condense with lodal even after extended periods of heating, starting material being recovered in all cases.

4-*Iodo*-6 : 7-*methylenedioxyphthalide* (II; R = I).—A solution of 6 : 7-methylenedioxyphthalide (1 g.) in glacial acetic acid (30 c.c.) was refluxed for 2 hours with iodine monochloride (9·5 g.). After dilution of the solution with water (50 c.c.), the iodine liberated was reduced by sulphurous acid and 4-*iodo*-6 : 7-*methylenedioxyphthalide* collected (0·27 g., 15%) and washed with cold absolute alcohol (5 c.c.); it formed short, pale-yellow needles, m. p. 192—193° [from ethyl acetate (charcoal)] (Found: C, 35·7; H, 1·7. $C_9H_5O_4I$ requires C, 35·6; H, 1·7%). As a consequence of the low yield, condensation of the iodophthalide with lodal was not attempted.

Lodal.—Lodal was prepared by the treatment of 3 : 4-dihydro-6 : 7-dimethoxy-2-methyl*iso*quinolinium iodide with aqueous sodium hydroxide (Leonard and Leubner, *loc. cit.*) followed by extraction of the hydroxy-amine with chloroform. Removal of the chloroform in a stream of dry nitrogen afforded lodal. The substituted dihydro*iso*quinolinium iodide was prepared according to the following sequence of reactions:

(a) *N*-3 : 4-*Dimethoxyphenylethylformamide*. 2-(3 : 4-Dimethoxyphenyl)ethylamine (90 g.) and 90% formic acid (35 g.) were heated at 170° for 5 hours and the product (95 g., 91%) distilled; it had b. p. 208—210°/2—3 mm. Späth and Polgar (*loc. cit.*) reported b. p. 170°/0·01 mm.

(b) 3 : 4-*Dihydro*-6 : 7-*dimethoxy*iso*quinoline*. Cyclization of the formamide was accomplished by refluxing it (19·6 g.) with phosphorus oxychloride (143 g.) and dry toluene (370 c.c.) for 2 hours. The mixture was worked up in the usual manner (Whaley and Govindachari, "Organic Reactions," 1951, 6, 74); the orange residue distilled at 150—156°/2—3 mm., giving a colourless oil (10·8 g., 61%). Späth and Epstein (*loc. cit.*) used phosphoric oxide as the cyclizing agent and obtained a product, b. p. 155—160°/1 mm.

(c) 3 : 4-*Dihydro*-6 : 7-*dimethoxy*-2-*methyl*iso*quinolinium iodide*. The methiodide was prepared by Buck and Ide's general method (*loc. cit.*). Methyl iodide (24 g.) was added to the dihydro-base (10 g.), dissolved in benzene (40 c.c.), and the mixture set aside at room temperature for 30 minutes. The yellow solid was collected, pressed nearly dry, and crystallized from alcohol; it formed fine, yellow needles (15·6 g., 90%), m. p. 201—202°. Späth and Epstein (*loc. cit.*) reported m. p. 202°.

6 : 7-*Methylenedioxy*-4-*nitro*-3-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*-1-iso*quinolyl*)-*phthalide* [*Nitro*-(±)-*corlumine*] (I; R = NO_2).—Lodal (2·9 g.) and 6 : 7-methylenedioxy-4-nitrophthalide (1 g.) were refluxed in alcohol (100 c.c.) for 20 minutes and afforded orange, rectangular crystals (1·63 g., 85% of recrystallized product), m. p. 180—181° (decomp.) (Found : C, 58·9; H, 4·8; N, 6·7. Calc. for $C_{21}H_{20}O_8N_2$: C, 58·9; H, 4·7; N, 6·5%). The observed m. p. agrees with that recorded by Groenewoud and Robinson (*loc. cit.*). The base is phototropic and is easily cleaved by alcoholic hydrogen chloride.

Amino-(±)-*corlumine* (I; R = NH_2).—Several unsuccessful attempts were made to reduce nitro-(±)-corlumine, various solvents and catalysts being used. The following procedure was finally adopted. Nitro-(±)-corlumine (0·5 g.), dry benzene (150 c.c.), and Raney nickel were shaken with hydrogen at 500 lbs./sq. in. in a steel bomb (300 c.c.) at 50—60° for 1 hour. The bomb contents were filtered, and the bomb and the Raney-nickel sludge thoroughly washed with hot, dry benzene. The benzene was removed by distillation at reduced pressure under dry nitrogen. The amine crystallised from chloroform–methanol in clusters of short, pale-yellow needles (0·31 g., 66%), m. p. 221—223° (decomp.) (Found: C, 63·1; H, 5·5; N, 7·1. Calc. for $C_{21}H_{22}O_6N_2$: C, 63·3; H, 5·6; N, 7·0%). Groenewoud and Robinson (*loc. cit.*) recorded m. p. 218—219°.

Benzamido-(±)-*corlumine Hydrochloride* (as I; R = NHBz).—Prepared from amino-(±)-corlumine and benzoyl chloride in benzene and recrystallized from alcohol, *benzamido*-(±)-*corlumine hydrochloride* was obtained in short, white needles, m. p. 204—205° (decomp.) (Found : C, 62·3; H, 5·1; N, 5·3. $C_{28}H_{26}O_7N_2$,HCl requires C, 62·4; H, 5·1; N, 5·2%).

Iodo-(±)-*corlumine* (I; R = I).—The amino-compound was converted into iodo-(±)-corlumine by the method employed by Groenewoud and Robinson (*loc. cit.*) for converting amino- into iodo-*x*-bicuculline. The yellow iodo-base was extremely phototropic and was consequently employed, after being washed with cold water and cold alcohol, directly for reduction to (±)-corlumine.

(±)-*Corlumine* (I; R = H)—(a) *By reduction of iodo*-(±)-*corlumine*. The iodo-base obtained above was shaken in a steel bomb (300 c.c. capacity) with alcohol (125 c.c.), Raney nickel (one-half teaspoon), and hydrogen at 500 lbs./sq. in. at 50—60° for 2 hours. The mixture was filtered, the nickel residue extracted with hot alcohol, and the united filtrates made basic by addition of ammonia solution and concentrated. The concentrate was diluted with water (50 c.c.), aqueous sodium hydroxide (1 c.c.; 3N) added, and the basic solution thoroughly extracted with chloroform. The dried extracts were concentrated, methanol added (charcoal), and the whole concentrated. (±)-*Corlumine* [0·26 g., 27%; based on 1 g. of amino-(±)-corlumine] crystallized in short, stout prisms, m. p. 193·5—195° (decomp.) (Found: C, 65·7; H, 5·6; N, 3·7. $C_{21}H_{21}O_6N$ requires C, 65·8; H, 5·5; N, 3·7%).

(b) *By deamination of amino*-(±)-*corlumine*. Aqueous sodium nitrite (0·3 g. in 4 c.c. of water) was slowly added to a solution of amino-(±)-corlumine (1 g.) in dilute hydrochloric acid (5 c.c. of water and 3 c.c. of hydrochloric acid, *d* 1·18) at 0° during 30 minutes; this was followed by the addition of 50% hypophosphorous acid (5 c.c.) during 1 hour. The mixture was stirred for another hour, and after being kept at 0° for 24 hours, was poured into water (100 c.c.), made basic by addition of ammonia solution, and the free base (0·26 g., 27%) isolated as described above. The base obtained by deamination of amino-(±)-corlumine was identical in all respects with that obtained by catalytic reduction of iodo-(±)-corlumine. In admixture with a sample of natural (±)-adlumine, m. p. 190° (Manske, *Canadian J. Res.*, 1938, **16**, *B*, 89), the m. p. of our product was depressed 30°.

Resolution of (±)-*Corlumine.*—Methanolic solutions of (±)-corlumine (0·2 g. in 3 c.c.) and (+)-tartaric acid (0·08 g. in 4 c.c.) were mixed and heated to boiling; lustrous, white plates, m. p. 208—208·5° (decomp.) (with perceptible softening at 203°) of (−)-corlumine (+)-(hydrogen tartrate) then separated. The methanolic mother-liquors were treated with ether which precipitated the ill-defined (+)-corlumine (+)-(hydrogen tartrate); this began to swell at 110° and slowly fused to a viscous mass at 127—140°. (+)-Corlumine (+)-(hydrogen tartrate), prepared from naturally occurring (+)-corlumine (from Eastman Kodak Co., Rochester, N.Y.), exhibited the same ill-defined behaviour as the corresponding salt from synthetic (±)-corlumine.

The individual hydrogen tartrates, obtained from the resolution of (±)-corlumine, were decomposed by ammonia solution, and the free bases extracted with chloroform. The properties of the enantiomorphs and natural (+)-corlumine are listed in the Table.

	$[\alpha]_D^{26}$	M. p.
(−)-Corlumine (synthetic)	−73·0° (*c*, 1·32 in $CHCl_3$)	158—160° (decomp.)
(+)-Corlumine (synthetic)	+75·0° (*c*, 1·18 in $CHCl_3$)	154—158·5 (decomp.)
(+)-Corlumine (natural)	+77·3° (*c*, 1·13 in $CHCl_3$)	158—160 (decomp.)

In admixture, synthetic and natural (+)-corlumine had m. p. 156—159° (decomp.). To (+)-corlumine, its optical antipode as yet not having been found in Nature, Manske (*Canadian J. Res.*, 1936, **16**, *B*, 349) attributed m. p. 159° and $[\alpha]_D^{25}$ +77° (*c*, 0·8 in $CHCl_3$).

The racemic modification of corlumine was prepared by dissolving equal amounts of natural (+)-corlumine and synthetic (−)-corlumine in chloroform and concentrating the solution to a small volume. Methanol was then added and the remainder of the chloroform evaporated. When the solution cooled, short, stout prisms, m. p. 193·5—194·5° (decomp.), of (±)-corlumine separated. In admixture with completely synthetic (±)-corlumine, the m. p. of the half natural, half synthetic product was not depressed.

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