547. *Alkaloids from Greenheart. Part I. The Isolation of the Alkaloids, and the Structure of Sepeerine.*

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Two new alkaloids, sepeerine and ocotine, have been isolated from greenheart bark (*Nectandra rodiei* R. Schomb). Rodiasine, previously obtained only as its dimethiodide, has also been isolated. Sepeerine is shown to be a de-*N*-methyloxyacanthine of structure (I; R^1 = Me, R^2 = H; R^3 = H and R^4 = Me or *vice versa*).

Maclagen [1] separated the alkaloids of greenheart (*Nectandra rodiei* R. Schomb) into two amorphous fractions. The portion soluble in ether was named bebeerine, but this name has since been applied to the crystalline bisbenzylisoquinoline alkaloid from *Chondrodendron platyphyllum*; [2] the alternative name, curine, seems preferable. There is no proof that crystalline bebeerine is identical with the greenheart alkaloid, although the formula $C_{35}H_{40}N_2O_6$ assigned [3] to the latter suggested a close relation between the two bases.

In a re-investigation, already reported briefly,[4] we obtained the alkaloids (1·2%) by extraction of greenheart bark with aqueous tartaric acid. Curine was not detected. Fractionation with ether gave a crystalline sparingly soluble alkaloid (0·06%), named sepeerine. The ether-soluble bases gave a crystalline alkaloid, ocotine (0·03%), and

[1] Maclagen, *Annalen*, 1843, **48**, 106.
[2] Faltis and Neumann, *Monatsh.*, 1921, **42**, 311.
[3] Maclagen and Tilley, *J. prakt. Chem.*, 1846, **37**, 247.
[4] Grundon, *Chem. and Ind.*, 1955, 1772.

afforded an insoluble methiodide isolated recently [5] from the ether-soluble greenheart alkaloids.

Extraction of approximately 100 kg. of a new sample of bark gave the alkaloids in 2·2% yield, but no crystalline alkaloids were isolated by fractionation with ether. Chromatography of the bases soluble in benzene gave sepeerine in reduced yield (0·013%). No ocotine was obtained, but a new crystalline alkaloid (0·033%) was isolated. This, apparently, was rodiasine, since it afforded the insoluble methiodide in high yield.

The formula, $C_{36}H_{38}N_2O_6$, for sepeerine suggested that it was of the bisbenzylisoquinoline type. The alkaloid formed a series of hydrates which retained water of crystallisation tenaciously; the anhydrous compound was obtained from the benzene adduct. Sepeerine was characterised as its dihydrochloride, di(hydrogen sulphate), sulphate, and dipicrate.

The alkaloid contained three methoxyl groups and one methylimino-group, and one phenolic and one secondary amino-group were indicated by acetylation and methylation.

Acetic anhydride at room temperature gave an *NO*-diacetate [$\nu_{max.}$ 1767, 1195 (phenolic OAc), 1645 cm.$^{-1}$ (>NAc)], hydrolysed with sodium hydroxide to an *N*-monoacetate ($\nu_{max.}$ 1642 cm.$^{-1}$). The acetylation might be interpreted as the cleavage of a tetrahydro-*N*-methylisoquinoline derivative, although this reaction normally requires more vigorous conditions.[6,7] Indeed, laudanosine was unaffected by acetic anhydride at room temperature. Curine gave an amorphous compound which was, apparently, an *OO*-diacetate, as reported previously,[7] since it absorbed at 1762 and 1190 cm.$^{-1}$, but not in the hydroxyl or amide-carbonyl region.

Sepeerine behaved as a secondary amine with nitrous acid, giving a brown amorphous *N*-nitroso-derivative, which showed a positive Liebermann reaction.

Sepeerine was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride. With diazomethane it afforded *O*-methylsepeerine, characterised as its dihydrochloride. The secondary amino-group was unaffected in this reaction, since the methylation product gave an acetate with an infrared maximum at 1640 cm.$^{-1}$ (>NAc). This interpretation was confirmed by a comparison of the infrared absorption of sepeerine at 3570 (OH) and at 3440—3260 cm.$^{-1}$ (OH and NH) with that of *O*-methylsepeerine at 3330 cm.$^{-1}$ (NH).

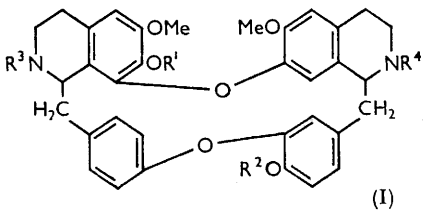
Sepeerine was converted by methyl iodide into *N*-methylsepeerine dimethiodide. This was not a monomethiodide hydriodide as it was unaffected by ammonia.

NO-Dimethylsepeerine dimethiodide, $[\alpha]_D^{19}$ +31°, obtained with methyl iodide and sodium methoxide, was identical with the dimethiodide, $[\alpha]_D^{20}$ +40°, of *NO*-dimethyldaphnandrine [8] (I; $R^1 = R^2 = R^3 = R^4 =$ Me) (*O*-methyloxyacanthine). The optical rotations, although not identical, were sufficiently close to indicate that sepeerine belonged to the oxyacanthine series rather than to the diastereoisomeric repandine series (*O*-methylrepandine dimethiodide,[9] $[\alpha]_D^{15}$ −95°). *NO*-Dimethylsepeerine dimethiodide, after Hofmann degradation and methylation, gave *NO*-dimethylsepeerinemethine dimethiodide, identical with *NO*-dimethyldaphnandrinemethine dimethiodide.[8]

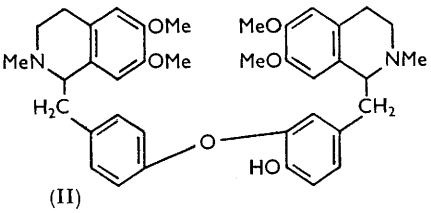
Since sepeerine gave a positive Millon reaction, it was probable that the phenolic group was at position 7 of an isoquinoline residue or at position 4 of a benzyl residue.[8,10] The phenolic group was located by conversion of *N*-methylsepeerine dimethiodide with ethyl iodide and sodium ethoxide into *O*-ethyl-*N*-methylsepeerine dimethiodide, which was submitted to a Hofmann degradation. The methine base was oxidised by potassium permanganate to 4',5-dicarboxy-2-ethoxydiphenyl ether, identical with a sample prepared [11]

[5] McKennis, Hearst, Drisko, Roe, and Alumbaugh, *J. Amer. Chem. Soc.*, 1956, **78**, 245.
[6] Gadamer and von Bruchhausen, *Arch. Pharm.*, 1926, **264**, 193.
[7] Scholtz, *Ber.*, 1896, **29**, 2054.
[8] Bick, Ewen, and Todd, *J.*, 1949, 2767.
[9] Bick and Todd, *J.*, 1948, 2170.
[10] King, *J.*, 1937, 1472; 1940, 737.
[11] Kondo and Narita, *Ber.*, 1930, **63**, 2422.

from 4′,5-dicarboxy-2-methoxydiphenyl ether. The latter compound was conveniently obtained by oxidation of 5-formyl-2-methoxy-4′-methyldiphenyl ether. Thus, the phenolic group is in a benzyl residue, and sepeerine is a de-*N*-methyloxyacanthine of structure (I; R^1 = Me, R^2 = H; of R^3 and R^4 one is H and the other is Me).



(I)



(II)

In the early stages of this work it was important to show that sepeerine was not a 3,4-dihydroisoquinoline derivative. Accordingly, the ultraviolet and infrared spectra of sepeerine were compared with those of analogous compounds. We confirmed the observation [12] that 3,4-dihydroisoquinolines absorb at 250—280 and 290—310 mμ, and that there is a bathochromic shift in the hydrochlorides (see Table). Sepeerine, like other

Infrared absorption maxima (KBr *disc*) *in the region* 1700—1550 *cm.*$^{-1}$ *and ultraviolet absorption maxima in the region* 250—360 *mμ.*

	Infrared (cm.$^{-1}$)			Ultraviolet			
				mμ	ε	mμ	ε
1-Benzyl-3,4-dihydroisoquinoline	1622	1603	1574	254	6170	290	1250 [a]
hydrochloride	1643	1615	1590	271	2920	325	3735
1-(3,4-Dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline	1620	1606	1583 } 1573 }	280	8360	308	6560
hydrochloride	1654	1615	1568	300	8790	350	8690
Laudanosine	1614	1597	—	282	6030	—	—
Laudanosine hydrochloride	1618	1598	—	280	3255	—	—
Sepeerine	1613	1590	—	284	6150	—	—
Sepeerine hydrochloride	1614	1592	—	283	6680	—	—
Rodiasine	1613	1587	—	287	9010	—	—
Rodiasine hydrochloride	1617	1592	—	284	6940	—	—
Ocotine	1604	1574	—	285	4800	—	—

[a] Inflexion.

tetrahydroisoquinolines, gave a single peak in this region, which was unchanged in acid solution (see Table). 3,4-Dihydroisoquinolines show an infrared triplet in the 1550—1630 cm.$^{-1}$ region.[13] A more striking characteristic is shown in the spectra of the salts, in which the peak at 1620—1630 cm.$^{-1}$ for the bases is shifted to higher frequency. A similar change has been noted with myosmine.[14] Like other tetrahydroisoquinolines, sepeerine showed a doublet in the 1550—1630 cm.$^{-1}$ region, unchanged in the hydrochloride.

Rodiasine contained two methylimino-groups, probably present in tetrahydro-*N*-methylisoquinoline systems, since the ultraviolet and infrared spectra of rodiasine and its dihydrochloride were very similar to those of sepeerine and its dihydrochloride. Rodiasine contained four methoxyl groups, and the presence of a phenolic group was indicated by its absorption at 3410 cm.$^{-1}$, and by the formation, with diazomethane, of *O*-methylrodiasine (5OMe), which did not absorb in the 3000—3500 cm.$^{-1}$ region. Thus, rodiasine is probably a bisbenzylisoquinoline containing one diphenyl ether linkage. If its biogenesis involves two molecules of norcoclaurine, it would be expected to be an isomer of

[12] Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 957; Openshaw and Wood, *J.*, 1952, 391; Battersby and Binks, *J.*, 1958, 4333.
[13] Battersby, Davidson, and Harper, *J.*, 1959, 1744.
[14] Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.

dauricine (II), with the molecular formula $C_{38}H_{44}N_2O_6$. Analyses of rodiasine dimethiodide and *O*-methylrodiasine dimethiodide reported by McKennis *et al.*[5] support this formula for the alkaloid, but our analytical data can also be reconciled with the formula $C_{36}H_{40}N_2O_6$. This question is unlikely to be resolved until more is known of the structure of rodiasine. There is, apparently, no simple relation between rodiasine and dauricine, as the properties of *O*-methylrodiasine dimethiodide (m. p. 294—298°, $[\alpha]_D$ +47°), obtained from *O*-methylrodiasine with methyl iodide or from rodiasine dimethiodide with methyl iodide and sodium methoxide, differ from those reported[15] for *O*-methyldauricine dimethiodide (m. p. 181—182°, $[\alpha]_D$ −151°).

As ocotine was not isolated in the large-scale extraction, an insufficient quantity was available for structural studies. Ocotine can be assigned tentatively the molecular formula $C_{35}H_{38}N_2O_6$ (with 4OMe and 1NMe). The ultraviolet and infrared spectra of ocotine are closely related to those of sepeerine and rodiasine. Ocotine probably contained one phenolic group and one secondary amino-group, as with acetic anhydride at room temperature it gave an *NO*-diacetate [$\nu_{max.}$ 1766, 1193 (phenolic OAc), 1643 cm.$^{-1}$ (>NAc)]. Furthermore, methylation with methyl iodide and sodium methoxide gave *NO*-dimethylocotine dimethiodide (5OMe). As this compound was not identical with *NO*-dimethylrodiasine dimethiodide, ocotine is not a de-*N*-methylrodiasine.

Experimental

Isolation of the Alkaloids.—(*a*) Finely powdered bark (1 kg.) was extracted with 1% aqueous tartaric acid (3 × 2 l.). The solution was concentrated to 1 l. at 50°, made alkaline with aqueous sodium hydroxide, and extracted with chloroform (4 × 300 c.c.). Evaporation of the chloroform gave the non-phenolic and cryptophenolic bases as a brown powder (9·5 g.).

The alkaline solution was acidified with hydrochloric acid and then made alkaline with aqueous sodium hydrogen carbonate. Extraction with chloroform gave the phenolic alkaloids as a brown powder (2·12 g.).

The alkali-insoluble bases (9·3 g.) were shaken with ether (2 × 700 c.c.). Trituration of the residue (2·35 g.) with ethanol (50 c.c.) gave a brown powder (0·75 g.), which was extracted with chloroform. Evaporation of the chloroform solution gave sepeerine, crystallising from ethanol in prisms (0·35 g.). The two ethanol solutions were combined and evaporated, and the residue was extracted with ether (2 × 200 c.c.). The ether solution, together with that obtained earlier, was concentrated to 300 c.c. and kept at 0° for 12 hr. The white precipitate with ethanol gave sepeerine (0·25 g.; total yield 0·6 g.).

The residue, obtained by evaporation of the ether solution, was triturated with light petroleum (b. p. 60—80°). The residual solid in ethanol (50 c.c.) slowly deposited ocotine (0·33 g.).

The ethanol solution, obtained after removal of ocotine, was evaporated. The residue in methanol with methyl iodide gave rodiasine dimethiodide (0·62 g.).

(*b*) The bark (97 kg.) was extracted as in (*a*) except that ammonia was used for precipitation, giving the total alkaloids as a brown powder (2151 g., 2·2%).

The finely powdered alkaloid mixture (100 g.) was extracted with boiling benzene (4 × 500 c.c.), leaving a residue (38·7 g.). The benzene solution, after concentration to 150 c.c. and removal of solid (5·9 g.), was chromatographed on alumina (300 g.). Elution with benzene gave a fraction (24·3 g.), which was dissolved in chloroform. The solution was shaken with 1% sulphuric acid (3 × 350 c.c.), and the acid solution was made alkaline with aqueous sodium hydroxide. The alkaloids, recovered by extraction with chloroform (4 × 300 c.c.), were converted into their hydrochlorides by dissolving them in methanol (150 c.c.), adding concentrated hydrochloric acid (20 c.c.), and precipitating the salts with ether. The resultant gum with 15% hydrochloric acid (100 c.c.) afforded rodiasine dihydrochloride (1·50 g., 0·033%).

Elution with benzene–chloroform and finally with chloroform gave ten fractions. Each, on evaporation and treatment with ethanol, gave sepeerine (total yield, 0·57 g., 0·013%).

Sepeerine. *Sepeerine* separated from methanol in colourless rods, m. p. 197—199°, $[\alpha]_D^{20}$

[15] Tomita, Ito, and Yamaguchi, *Pharm. Bull.* (*Japan*), 1955, **3**, 449.

+391° (Found: C, 66·7; H, 6·5; after drying at 110° *in vacuo*, C, 68·9; H, 6·6; N, 4·7; OMe, 15·2. $C_{36}H_{38}N_2O_6,3H_2O$ requires C, 66·7; H, 6·8. $C_{36}H_{38}N_2O_6,2H_2O$ requires C, 68·6; H, 6·7; N, 4·4; 3OMe, 14·8%). Crystallisation from benzene gave plates, m. p. 164—166° (Found, after drying at 135° *in vacuo*: C, 72·4; H, 6·1; N, 4·9; OMe, 15·7; *N*-Me, 2·1. $C_{36}H_{38}N_2O_6$ requires C, 72·7; H, 6·4; N, 4·7; 3OMe, 15·7; 1*N*-Me, 2·5%), and then from ethanol in prisms, m. p. 194—196° (Found: C, 70·8; H, 6·5; N, 5·0; OMe, 15·1. $C_{36}H_{38}N_2O_6,1H_2O$ requires C, 70·6; H, 6·6; N, 4·6; 3OMe, 15·2%).

Sepeerine was insoluble in 2N-sodium hydroxide and gave no colour with ferric chloride. When sepeerine was warmed with Millon's reagent a pink colour developed.

A solution of sepeerine in dilute hydrochloric acid, treated with sodium nitrite, gave an orange precipitate of an amorphous *N*-nitroso-derivative, m. p. 254—256° (decomp.), which, when mixed with phenol and sulphuric acid, diluted with water, and neutralised with sodium hydroxide, gave a blue colour.

The *dihydrochloride*, prepared in methanol with concentrated hydrochloric acid, separated from methanol–ether in prisms, m. p. 254—256° (decomp.) (Found: C, 60·2; H, 6·4; N, 4·3; Cl, 9·8; OMe, 12·0. $C_{36}H_{40}Cl_2N_2O_6,3H_2O$ requires C, 59·9; H, 6·4; N, 3·9; Cl, 9·8; 3OMe, 12·9%).

Sepeerine in ethanol with concentrated sulphuric acid afforded a *di*(*hydrogen sulphate*), crystallising from ethanol as a powder, m. p. >300° (Found: C, 53·3; H, 5·3; N, 3·2; S, 6·2. $C_{36}H_{42}N_2O_{14}S_2,H_2O$ requires C, 53·5; H, 5·4; N, 3·5; S, 7·9%). Crystallisation of the salt from water gave the *sulphate* in prisms, m. p >300° (Found: C, 56·0; H, 6·3; N, 4·2; S, 4·8. $C_{36}H_{40}N_2O_{10}S,4H_2O$ requires C, 56·5; H, 6·3; N, 3·7; S, 4·2%).

The *picrate*, prepared in benzene, separated from aqueous ethanol as a yellow powder, m. p. 178—180° (decomp.) (Found: C, 54·2; H, 4·1; N, 10·4. $C_{48}H_{44}N_8O_{20}$ requires C, 54·8; H, 4·2; N, 10·6%).

ON-*Diacetylsepeerine*. A solution of sepeerine (100 mg.) in acetic anhydride (10 c.c.) was kept for 24 hr., water (20 c.c.) was added, and the solution was made alkaline with sodium hydrogen carbonate and extracted with ether. Evaporation of the ether solution gave the *acetate* (93 mg.), crystallising from ether in cubes, m. p. 156—158° (Found: C, 69·0; H, 6·3; Ac, 10·2. $C_{40}H_{42}N_2O_8,1H_2O$ requires C, 69·0; H, 6·4; 2Ac, 12·4%).

N-*Acetylsepeerine*. A solution of *ON*-diacetylsepeerine (70 mg.) in methanol (20 c.c.) and 2N-aqueous sodium hydroxide (2 c.c.) was kept for 44 hr. After evaporation of the methanol, the aqueous solution was saturated with carbon dioxide and extracted with chloroform. Evaporation of the chloroform gave the *acetate* (49 mg.), crystallising from ether, and then from acetone–light petroleum (b. p. 40—60°), as a powder, m. p. 174—176° (Found: C, 68·7; H, 6·0; Ac, 4·8. $C_{38}H_{40}N_2O_7,1\frac{1}{2}H_2O$ requires C, 68·7; H, 6·5; 1Ac, 6·5%).

Acetylation of Curine.—Curine with acetic anhydride at room temperature gave the acetate as a white powder, m. p. 156—160° (lit.,[7] m. p. 147—148°).

N-*Methylsepeerine Dimethiodide*.—(*a*) A solution of sepeerine (189 mg.) in methanol (20 c.c.) containing methyl iodide (1 c.c.) was refluxed for 1 hr. and evaporated. The *methiodide* separated from water as a white powder, decomp. 253—258° (Found: C, 49·2; H, 5·1. $C_{39}H_{46}I_2N_2O_6,3H_2O$ requires C, 49·5; H, 5·5%).

(*b*) Sepeerine (250 mg.) was refluxed in methanol and methyl iodide for 1·5 hr., the methyl iodide removed, aqueous ammonia added, and the methanol evaporated. The precipitate (270 mg.) in water was boiled with copper powder for 10 min., and the solution was concentrated to 10 c.c. The methiodide separated as a buff powder, decomp. 243—251° (Found: I, 29·4. $C_{39}H_{46}I_2N_2O_6,3H_2O$ requires I, 26·8%), identical with the sample prepared as in (*a*).

O-*Methylsepeerine Dihydrochloride*.—Excess of ethereal diazomethane was added to a solution of sepeerine (500 mg.) in methanol (100 c.c.). After 48 hr. the solution was evaporated to give *O*-methylsepeerine as a brown amorphous powder (509 mg.), m. p. 118—122°, $[\alpha]_D$ +191°, which with acetic anhydride at room temperature gave an amorphous acetate, m. p. 85—89°.

A solution of *O*-methylsepeerine (385 mg.) in methanol was acidified with concentrated hydrochloric acid. Addition of excess of ether gave the *dihydrochloride* as a gum, crystallising from dilute hydrochloric acid as a powder (164 mg.), and then from ethanol in prisms, decomp. 230—235° (Found: C, 62·2; H, 6·6; OMe, 17·1. $C_{37}H_{42}Cl_2N_2O_6,2H_2O$ requires C, 61·9; H, 6·5; 4OMe, 17·3%).

ON-*Dimethylsepeerine Dimethiodide*.—Sepeerine (2 g.), methanolic sodium methoxide

[12 c.c. of a solution of sodium (7·5 g.) in methanol (200 c.c.)], and methyl iodide (6 c.c.) were refluxed for 48 hr., additions of the same quantities of the reagents being made every 6 hr. The solution was evaporated and the residue, after trituration with water, was dissolved in hot water and boiled with copper powder for 10 min. After filtration, the solution was concentrated, to give the methiodide (1·22 g.), $[\alpha]_D^{19}$ +31° (*c* 0·41 in 50% aqueous ethanol), crystallising from ethanol in prisms, decomp. 249—255° (Found: C, 49·6; H, 5·4; N, 3·2; OMe, 12·8. Calc. for $C_{40}H_{48}I_2N_2O_6,3H_2O$: C, 50·0; H, 5·7; N, 2·9; 4OMe, 12·9%), shown by a comparison of infrared spectra to be *ON*-dimethyldaphnandrine dimethiodide.[8]

ON-*Dimethylsepeerinemethine Dimethiodide.*—A solution of *ON*-dimethylsepeerine dimethiodide (0·94 g.) in water (100 c.c.) was passed over an ion-exchange column (Amberlite IRA-400, OH^- form), and the column was washed with water. The eluate was concentrated to 100 c.c., potassium hydroxide (20 g.) was added, and the solution was heated on a steam-bath for 30 min. The precipitated gum was removed with ether, and the alkaline solution was heated for 1 hr., and a further quantity of gum obtained with ether. Evaporation of the combined ether solutions gave the methine as a brown powder (0·636 g.), m. p. 79—87°, $[\alpha]_D^{20}$ +3·5° (*c* 0·40 in $CHCl_3$).

The crude methine (90 mg.) in methanol and methyl iodide was refluxed for 1 hr., and the solution evaporated. Crystallisation of the residue from ethanol gave the dimethiodide in needles (86 mg.), m. p. 250—258° (decomp.) (Found: C, 50·5; H, 6·0; N, 2·9. Calc. for $C_{42}H_{52}I_2N_2O_6,4H_2O$: C, 50·1; H, 6·0; N, 2·8%), identical (infrared) with *ON*-dimethyldaphnandrinemethine dimethiodide, m. p. 256—258° (decomp.).[8]

O-*Ethyl*-N-*methylsepeerine Dimethiodide.*—A solution of sepeerine (1·16 g.) in methanol (150 c.c.) and methyl iodide (2 c.c.) was refluxed for 7 hr., and evaporated. The residue in ethanolic sodium ethoxide [5 c.c. of a solution of sodium (0·8 g.) in ethanol (50 c.c.)] and ethyl iodide (3 c.c.) was refluxed for 48 hr., the same quantity of reagents being added every 6 hr. The residue, obtained by evaporation, was triturated with water (50 c.c.), and the solid in water (100 c.c.) was heated with copper powder for 10 min. After filtration and concentration of the solution, the *methiodide* (1·21 g.) separated, and crystallised from ethanol as a fine powder, m. p. 232—235° (decomp.) (Found: C, 50·4; H, 5·7. $C_{41}H_{50}I_2N_2O_6,3H_2O$ requires C, 50·5; H, 5·8%).

5,4′-*Dicarboxy*-2-*ethoxydiphenyl Ether.*—*O*-Ethyl-*N*-methylsepeerine dimethiodide (1·13 g.) was converted into its methohydroxide which was degraded by Hofmann's method as described for *ON*-dimethylsepeerine dimethiodide. The methine was obtained as a brown powder (0·69 g.), m. p. 112—122°, $[\alpha]_D^{17}$ −9·5° (*c* 0·21 in $CHCl_3$).

1% Aqueous potassium permanganate (250 c.c.) was added in portions with stirring to a solution of the methine (0·45 g.) in water (100 c.c.). The solution was clarified with sulphur dioxide; 5,4′-dicarboxy-2-ethoxydiphenyl ether slowly separated (57 mg.); it crystallised from acetic acid in prisms, m. p. 285—287°, identical (mixed m. p. and infrared) with a sample, m. p. 288—290°, prepared by the method of Kondo and Narita.[11]

5,4′-*Dicarboxy*-2-*methoxydiphenyl Ether.*—A solution of potassium permanganate (5 g.) in hot water (100 c.c.) was added during 1 hr., to a boiling solution of 5-formyl-2-methoxy-4′-methyldiphenyl ether[16] (8·4 g.) in acetone (500 c.c.) and water (100 c.c.). Four similar additions of aqueous potassium permanganate were made during 6 hr. The solution was clarified with sulphur dioxide, the acetone was removed, and the solution was added to water (1 l.).

The precipitate, m. p. 205—207°, probably consisted of 5′-carboxy-2-methoxy-4′-methyldiphenyl ether. A solution of the acid in 10% aqueous sodium hydroxide (200 c.c.) was treated with a solution of potassium permanganate (20 g.) in water (600 c.c.) during 2 hr., and then kept for 6 hr. After removal of manganese dioxide with sulphur dioxide, 5,4′-dicarboxy-2-methoxy-diphenyl ether crystallised from the aqueous solution, and recrystallised from acetic acid in prismatic needles (7·5 g., 76%), m. p. 312—315° (lit.,[17] m. p. 313—314°).

The dimethyl ester crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 94—96° (lit.,[17] m. p. 96—97°).

Rodiasine.—An aqueous solution of crude rodiasine hydrochloride (2·05 g.) was made alkaline with 2N-sodium hydroxide and extracted with chloroform. Evaporation of the chloroform and crystallisation of the residue from ethanol gave *rodiasine* in cubes, m. p. 195°,

[16] Glover and Grundon, unpublished work.
[17] Späth and Pikl, *Ber.*, 1929, **62**, 2251.

$[\alpha]_D^{18}$ +134° (*c* 0·63 in $CHCl_3$) (Found: C, 72·3, 72·1; H, 6·7, 6·9; N, 4·8; OMe, 20·6; *N*-Me, 4·1. $C_{36}H_{40}N_2O_6$ requires C, 72·5; H, 6·8; N, 4·7; 4OMe, 20·8; 2*N*-Me, 5·0. $C_{38}H_{44}N_2O_6,\frac{1}{2}H_2O$ requires C, 72·0; H, 7·2; N, 4·4; 4OMe, 19·6; 2*N*-Me, 4·7%).

The *hydrochloride* separated from ethanol in cubes, decomp. 255—259° (Found: C, 61·5; H, 6·4; N, 3·8; OMe, 16·4. $C_{36}H_{42}Cl_2N_2O_6,2H_2O$ requires C, 61·3; H, 6·6; N, 4·0; 4OMe, 17·6. $C_{38}H_{46}Cl_2N_2O_6,2H_2O$ requires C, 62·2; H, 6·9; N, 3·8; 4OMe, 16·9%).

Rodiasine Dimethiodide.—A solution of rodiasine (159 mg.) in methanol and methyl iodide gave, after 10 min. at room temperature, a precipitate (158 mg.) of the dimethiodide, separating from methanol in cubes, decomp. 291—295°, $[\alpha]_D$ +73° (*c* 0·21 in H_2O) {lit.,[5] m. p. 321° (decomp.), $[\alpha]_D$ +68°} (Found: C, 51·9; H, 5·2; OMe, 13·8; I, 28·7. Calc. for $C_{38}H_{46}I_2N_2O_6$: C, 51·9; H, 5·3; 4OMe, 14·1; I, 28·9. Calc. for $C_{40}H_{50}I_2N_2O_6,H_2O$: C, 51·8; H, 5·7; 4OMe, 13·4; I, 27·4%). The compound was identical (infrared) with the methiodide obtained from the mixture of ether-soluble bases.

O-*Methylrodiasine.*—A solution of rodiasine (763 mg.) in methanol (100 c.c.) containing excess of ethereal diazomethane was kept for 60 hr., then evaporated. Crystallisation of the residue from ether gave O-*methylrodiasine* (272 mg.), m. p. 172—173°, $[\alpha]_D$ +85° (*c* 0·57 in $CHCl_3$) (Found: C, 69·9; H, 6·5; N, 4·4; OMe, 24·2. $C_{37}H_{42}N_2O_6,H_2O$ requires C, 70·7; H, 7·0; N, 4·5; 5OMe, 24·7. $C_{39}H_{46}N_2O_6,2H_2O$ requires C, 69·4; H, 7·5; N, 4·2; 5OMe, 23·0%).

The *hydrochloride*, crystallised from methanol–ether, had m. p. 232—236° (decomp.) (Found: C, 60·1; H, 7·2; OMe, 21·6. $C_{37}H_{44}Cl_2N_2O_6,3H_2O$ requires C, 60·2; H, 6·8; 5OMe, 21·0. $C_{39}H_{48}Cl_2N_2O_6,4H_2O$ requires C, 59·8; H, 7·2; 5OMe, 19·8%).

O-*Methylrodiasine Dimethiodide.*—(*a*) Rodiasine dimethiodide (1·78 g.) was methylated with methyl iodide and sodium methoxide as described in the preparation of *ON*-dimethylsepeerine dimethiodide, and gave the methiodide (1·59 g.), crystallising from methanol in plates, m. p. 294—298° (decomp.), $[\alpha]_D$ +47° {lit.,[5] m. p. 304° (decomp.), $[\alpha]_D^{20}$ +50°} (Found: C, 52·6; H, 5·7; OMe, 16·8. Calc. for $C_{39}H_{48}I_2N_2O_6$: C, 52·4; H, 5·4; 5OMe, 17·4. Calc. for $C_{41}H_{52}I_2N_2O_6,1H_2O$: C, 52·4; H, 5·8; 5OMe, 16·5%).

(*b*) A solution of *O*-methylrodiasine in methanol and methyl iodide gave the methiodide, separating from methanol in plates, m. p. 289—291° (decomp.), identical (infrared) with the compound prepared as in (*a*).

Ocotine.—*Ocotine* crystallised from ethanol in needles, m. p. 162—164°, $[\alpha]_D^{18}$ +32° (Found: C, 72·3; H, 6·1; N, 4·8; OMe, 21·5; *N*-Me, 2·1. $C_{35}H_{38}N_2O_6$ requires C, 72·1; H, 6·6; N, 4·8; 4OMe, 21·3; 1*N*-Me, 2·6%).

The *hydrochloride*, prepared in methanol with concentrated hydrochloric acid, separated from ethanol–ether in prisms, decomp. 240° (Found: C, 62·5; H, 6·3; Cl, 10·0; OMe, 18·6. $C_{35}H_{40}Cl_2N_2O_6,1H_2O$ requires C, 62·4; H, 6·3; Cl, 10·5; 4OMe, 18·4%). The *picrate* crystallised from ethanol in yellow prisms, m. p. 178—180° (decomp.) (Found: C, 54·2; H, 4·7; N, 10·2. $C_{47}H_{44}N_8O_{20}$ requires C, 54·2; H, 4·3; N, 10·8%).

A solution of ocotine (48 mg.) in methanol (20 c.c.) containing methyl iodide (1 c.c.) was refluxed for 1 hr. and evaporated. Crystallisation of the residue from ethanol gave N-*methylocotine dimethiodide* as prisms (47 mg.), decomp. *ca.* 250° (Found: C, 51·8; H, 4·8; I, 29·1. $C_{38}H_{46}I_2N_2O_6$ requires C, 51·9; H, 5·3; I, 28·9%).

A solution of ocotine (53 mg.) in acetic anhydride (2 c.c.) was kept for 12 hr. Addition of water and excess of sodium hydrogen carbonate gave a precipitate which was obtained with chloroform. Extraction of the gum with ether and evaporation of the ether solution gave ON-*diacetylocotine*, crystallising from ether–light petroleum (b. p. 40—60°) as a powder, m. p. 159—161° (Found: C, 68·1; H, 6·9. $C_{39}H_{42}N_2O_8,1H_2O$ requires C, 68·4; H, 6·5%).

Reaction of ocotine (70 mg.) with methyl iodide and sodium methoxide, as described for rodiasine, gave ON-*dimethylocotine dimethiodide* (55 mg.), $[\alpha]_D^{18}$ +100°, separating from water in needles, m. p. 240—244° (decomp.) (Found: C, 50·3; H, 6·0; OMe, 17·1. $C_{39}H_{48}I_2N_2O_6,2H_2O$ requires C, 50·3; H, 5·6; 5OMe, 16·7%).

We are indebted to Drs. F. R. Smith and W. W. Easton, of Messrs. T. and H. Smith Ltd., for carrying out the large-scale extraction, to the Colonial Products Council for supplying the bark, to Professor Sir Alexander Todd for samples of daphnandrine derivatives, and to the Ministry of Education for Northern Ireland for a postgraduate studentship (to J. E. B. McG.).

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