333. *Alkaloids of* Daphnandra *Species. Part III. Micranthine.*

By I. R. C. Bick and A. R. Todd.

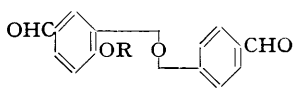
Micranthine, obtained as the sole alkaloidal constituent of a specimen of the bark of *D. micrantha* grown in Queensland, has a molecular formula $C_{34}H_{32}O_6N_2$ and contains one methoxy- and one methylimino-group. By a combination of degradative studies and consideration of biogenetic possibilities, it is concluded that the alkaloid has structure (VI) in which R_5 = H, of R_1 and R_2 one is H and the other Me, and of R_3 and R_4 one is H and the other Me. Micranthine is thus to be regarded as one of the small group of bisbenzyl*iso*quinoline alkaloids containing a phenodioxin system, the other members being trilobine and *iso*trilobine [(VII) and (VIII)], menisarine, for which structure [(X) or (XI)] is preferred, and normenisarine. In agreement with the structures proposed for micranthine and menisarine, *N*-methyldihydromenisarinemethine and *OON*-trimethylmicranthinemethine (XII) appear to be identical, whilst *N*-methyldihydromenisarine is the enantiomorph of *OON*-trimethylmicranthine.

The alkaloid micranthine was first described by Pyman (*J.*, 1914, 1619) as a minor constituent of the bark of the Australian tree *Daphnandra micrantha*, where it was accompanied by much larger amounts of the alkaloids daphnandrine and daphnoline. As reported in Part II of this series (Bick, Ewen, and Todd, *J.*, 1949, 2767), we were unable to detect either of the last two alkaloids in a sample of *D. micrantha* bark collected in southern Queensland; this bark, however, contained micranthine in much larger quantity than Pyman's material. The bark used by Pyman appears to have been collected in New South Wales and there is some reason to believe that local botanical variation occurs within the species; this matter will be discussed in a later report.

Using an improved isolation procedure, micranthine, identical with the alkaloid described by Pyman (*loc. cit.*), was obtained in a yield of *ca.* 2%. Analysis showed that it contained one

methoxy- and one methylimino-group, and indicated a formula $C_{34}H_{32}O_6N_2$ rather than the $C_{36}H_{32}O_6N_2$ proposed by Pyman (*loc. cit.*). Tests for methylenedioxy-groups gave negative results, but with a mixture of nitric and sulphuric acids the alkaloid gave a blue coloration. Parallel tests showed that the colour was apparently identical with that given under similar conditions by trilobine (Tomita and Tani, *J. Pharm. Soc. Japan*, 1942, **62**, 94; Tani, *ibid.*, p. 146) and menisarine (Kondo and Tomita, *Arch. Pharm.*, 1936, **274**, 73), alkaloids of the Far Eastern menispermaceous plants *Cocculus sarmentosus* and *Cocculus trilobus*; this test is usually considered specific for the phenodioxin (diphenylene dioxide) system present in these latter alkaloids (Kondo and Tomita, *J. Pharm. Soc. Japan*, 1932, **52**, 139; Tomita, *ibid.*, p. 147; 1933, **53**, 138). The usual tests for phenolic groups gave negative or indecisive results, but the alkaloid appeared to contain two active hydrogen atoms (Zerewitinoff) and, although it was insoluble in aqueous alkali, it dissolved in Claisen's cryptophenol reagent (*Annalen*, 1919, **418**, 96) and was recovered unchanged on neutralisation. It seemed therefore probable that micranthine contained two phenolic hydroxyl groups. Moreover, from its molecular formula and its occurrence (Pyman, *loc. cit.*) in the same plant source as the bisbenzyl*iso*quinoline alkaloids, daphnandrine and daphnoline (Bick, Ewen and Todd, *loc. cit.*), it was likely that it belonged to the same series, or, more specifically, to the sub-group of the series represented by trilobine and menisarine. These considerations dictated the methods of degradation employed in the present studies.

Heated with methyl iodide in methanolic sodium methoxide, micranthine yielded *OON*-trimethylmicranthine dimethiodide, and this on Hofmann degradation gave the optically-inactive base *OON*-trimethylmicranthinemethine which contained three methoxy-groups. Since the original alkaloid contained only one methoxy-group, it is evident that the others must have been introduced at the initial methylation step, and hence the view expressed above that micranthine contains two phenolic hydroxyl groups is confirmed. A portion of the methine base was treated with methyl iodide and the crystalline dimethiodide submitted to Hofmann degradation, yielding *OO*-dimethylde-*N*-micranthine. Ozonolysis of a second portion of the methine base gave two products, one of which was identified as 5 : 4′-diformyl-2-methoxydiphenyl ether (I; R = Me), previously obtained as a degradation product from a number of bisbenzyl*iso*quinoline alkaloids. The second product, an amino-aldehyde, was converted into its dimethiodide and again degraded by the Hofmann procedure, giving a crystalline substance which, from its analysis and properties, appeared to be a diformyldimethoxydivinylphenodioxin.



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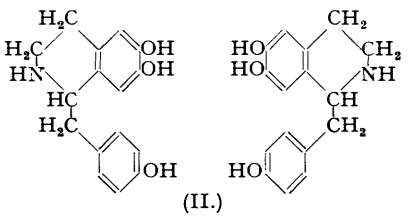

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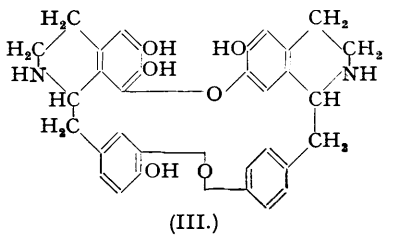

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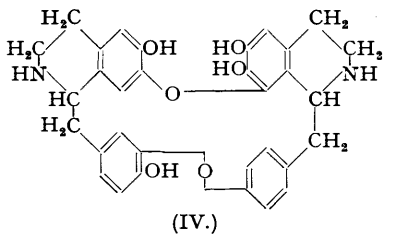

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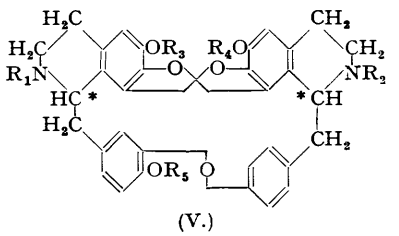

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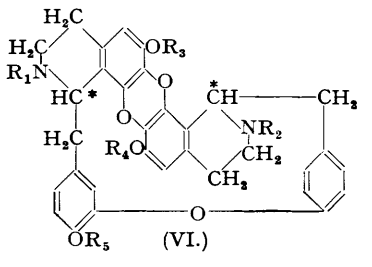


(VI.)

It is clear that a knowledge of the detailed structure of the phenodioxin derivative obtained by the above procedure would go far towards establishing the structure of micranthine. In endeavouring to deduce the structure of these two substances some assistance can be derived from suggestions put forward by Faltis and his co-workers (*Ber.*, 1930, **63**, 806; 1941, **74**, 79; *Annalen*, 1932, **497**, 69; **499**, 301) and by Kondo and Tomita (*Arch. Pharm.*, 1936, **271**, 65) regarding the biogenesis of the biscoclaurine alkaloids. According to their views, these alkaloids are considered to be derived from two molecules of norcoclaurine (II) joined together by a variable number of ether linkages formed as a result of dehydrogenation or dehydration. Thus daphnoline (Bick, Ewen, and Todd, *loc. cit.*) could be derived from the hypothetical bis(norcoclaurine), structures (III) or (IV), by methylation of one imino-group and the two hydroxy-groups at position 6 in each of the *iso*quinoline nuclei; daphnandrine (Bick, Ewen, and Todd, *loc. cit.*) could be formed from daphnoline by methylation of the free hydroxyl group in the benzyl nucleus. Condensation processes of this nature must yield bisbenzyl*iso*quinoline alkaloids which are *O*-substituted at positions 6 and 7 of the *iso*quinoline nuclei, and which may also be substituted at position 8, but only by oxygen in an ether cross-linkage with the other norcoclaurine residue. These conditions hold good for all the biscoclaurine alkaloids so far examined; moreover, no known alkaloid of the group is substituted at position 5 in an *iso*quinoline nucleus. When alkaloids of this group containing a phenodioxin system are considered, only the structural types (V) [which is more conveniently represented as (VI)], (VII), and (VIII) meet the necessary requirements as regards substituents. Of these, only an alkaloid based on (VI) could, by the process of repeated Hofmann degradation, yield a diformyldimethoxydivinylphenodioxin such as was obtained from micranthine. Of the other two structures, (VII) and (VIII), one has been shown to represent trilobine (R = Me) and the other *iso*trilobine (R = Me) (Tomita and Tani, *loc. cit.*) and both yield by the same series of degradations a monomethoxy-phenodioxin derivative. Our conclusion is therefore that micranthine must have a structure of type (VI) and that the aldehyde obtained as final degradation product has structure (IX) (4 : 9-diformyl-1 : 6-dimethoxy-3 : 8-divinylphenodioxin). A space model of (VI) shows that there is no undue strain within the molecule only if there is the same stereochemical configuration about each of the asymmetric centres (marked with asterisks). It will be observed that (VI) can readily be derived from (III) or (IV), the hypothetical precursor of daphnoline, which may well be itself the precursor of micranthine in the plant.

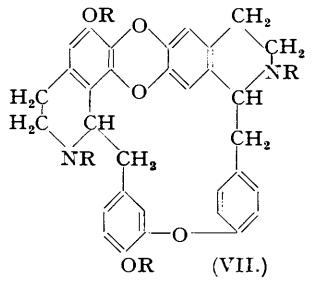
If these arguments and conclusions be accepted, then in micranthine (VI) two of the groups R_3, R_4, and R_5 must be H and one Me. *N*-Methylmicranthine dimethiodide was ethylated and the resulting *N*-methyl-*OO*-diethylmicranthine dimethiodide submitted to Hofmann degradation. The *N*-methyl-*OO*-diethylmicranthinemethine so obtained was ozonised and the neutral product obtained from it was identified as 5 : 4′-diformyl-2-ethoxydiphenyl ether (I; R = Et) by direct comparison with a specimen prepared by a similar route from repandine (Bick and Todd, *J.*, 1948, 2170). Since the ethoxy-group in this compound must correspond to a hydroxyl group in the starting material, R_5 must be H in micranthine. We are therefore justified in ascribing to micranthine structure (VI), in which R_5 = H, of R_1 and R_2 one is H and the other Me, and of R_3 and R_4 one is H and the other Me.

A structure closely related to (VI) was originally considered, among a number of others, for the alkaloid menisarine by Kondo and Tomita (*loc. cit.*, 1936) but was rejected in favour of two alternative structures more in keeping with the then current formulæ of trilobine and *iso*trilobine (Faltis, *loc. cit.*, 1932). The now accepted structures for trilobine and *iso*trilobine, (VII) and (VIII), were finally proposed by Faltis, Holzinger, Ita, and Schwarz (*loc. cit.*, 1941) and their validity was established by Tomita and Tani (*loc. cit.*), who synthesised the methoxydimethyldiethylphenodioxin obtained from them by reduction of the aldehyde end product of Hofmann degradation. The Japanese workers suggested at the same time that structures (X) and (XI), which correspond to type (V), should again be considered for menisarine. If Kondo and Tomita's earlier experimental evidence (*J. Pharm. Soc. Japan*, 1935, **55**, 100) is re-interpreted in terms of (X) or (XI) for this alkaloid, then it is evident that dihydromenisarine must be represented by (VI; R_1 = H and R_2 = Me or *vice versa*; R_3 = R_4 = R_5 = Me) and *N*-methyldihydromenisarinemethine by (XII). If the formulæ proposed for micranthine (VI; R_1 = H and R_2 = Me or *vice versa*; R_3 = H and R_4 = Me or *vice versa*; R_5 = H) and menisarine (X) or (XI) are correct, then (XII) should also represent *OON*-trimethylmicranthinemethine. The melting points of the two methine bases, together with those of certain of their derivatives and degradation products are compared in Table I, the values for the menisarine derivatives being those given by Kondo and Tomita (*loc. cit.*, 1935); the comparison supports our view that *OON*-trimethylmicranthinemethine and *N*-methyldihydromenisarinemethine are identical.

TABLE I.

	M. p.
N-Methyldihydromenisarinemethine	112°
OON-Trimethylmicranthinemethine	115
N-Methyldihydromenisarinemethine dimethiodide	265 (decomp.)
OON-Trimethylmicranthinemethine dimethiodide	255—260 (decomp.)
De-*N*-dihydromenisarine	208
OO-Dimethylde-*N*-micranthine	210
Aminoaldehyde dimethiodide from menisarine	224 (decomp.)
Aminoaldehyde dimethiodide from micranthine	225—230 (decomp.)
Diformyldimethoxydivinylphenodioxin from menisarine	>300
Diformyldimethoxydivinylphenodioxin from micranthine	no m. p. below 300° >300° gradually decomposes

The dimethiodides (XIII), from which these methine bases (XII) were obtained by Hofmann degradation, each have two asymmetric centres and *a priori* might be identical, enantiomorphic,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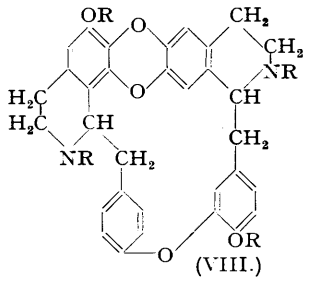
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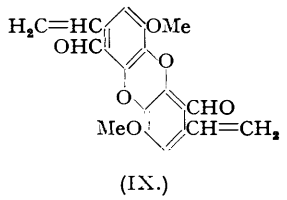
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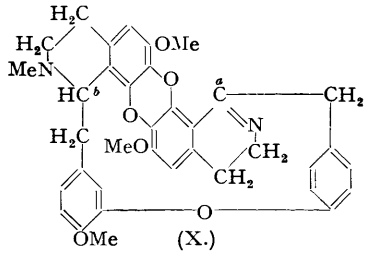
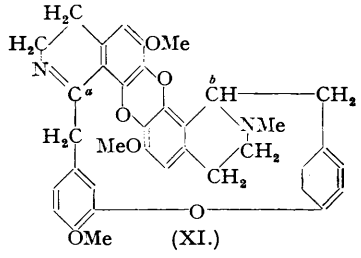

(X.)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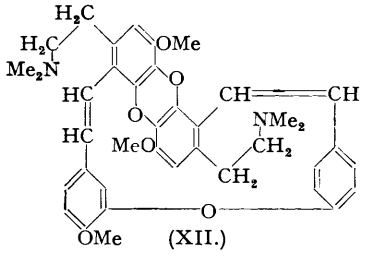
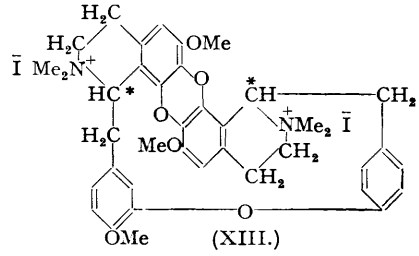
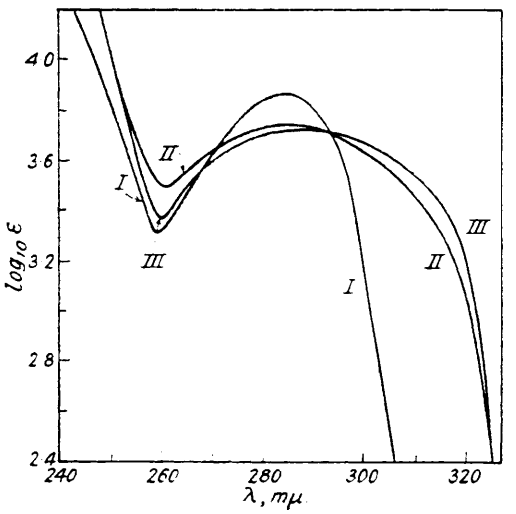

(XII.)


(XIII.)

or diastereoisomeric. As has been mentioned above, however, space models indicate that a molecule such as (XIII), containing asymmetric centres with dissimilar configuration, if it existed at all, would be under great internal strain; the possibility that the two compounds are diastereoisomers can therefore be virtually excluded. To distinguish between the other possibilities, *N*-methyldihydromenisarine dimethiodide was prepared as described by Kondo and Tomita (*loc. cit.*, 1935) from a small sample of menisarine generously provided by Prof. Kondo; it had m. p. 265° (decomp.) and $[\alpha]_D^{19}$ +150° (*c*, 0·1 in water). *OON*-Trimethylmicranthine dimethiodide had m. p. 255—260° (decomp.) and $[\alpha]_D^{20}$ −158° (*c*, 0·4 in water). The quantity of *N*-methyldihydromenisarine dimethiodide was too small to permit of further comparisons, but we feel justified in concluding that it is the enantiomorph of *OON*-trimethylmicranthine dimethiodide. In connection with the formulation of menisarine as (X) or (XI), it is of interest to note that its reduction to dihydromenisarine involves an asymmetric synthesis at carbon atom *a*, the new asymmetric centre formed at this point having the same configuration

as that at carbon atom *b*. This is in accord with the recorded specific rotations of menisarine (+149·4°) and dihydromenisarine (+265·8°); the latter value may be compared with the value −231° found for micranthine.

The absorption spectrum of micranthine is shown in the figure, together with those of trilobine and oxyacanthine. The close similarity between the micranthine ($\lambda_{max.}$ 2860; $\lambda_{min.}$ 2610 A.) and trilobine ($\lambda_{max.}$ 2880; $\lambda_{min.}$ 2610 A.) spectra is presumably due to the common phenodioxin system. A corresponding similarity between the spectra of trilobine, *iso*trilobine, and dihydromenisarine ($\lambda_{max.}$ 2860; $\lambda_{min.}$ 2630 A.) has already been noted by Kondo and Tomita (*loc. cit.*, 1935).



Absorption spectra of oxyacanthine (I), micranthine (II), and trilobine (III) in methanol.

Experimental.

Extraction of Daphnandra micrantha *Bark.*—Finely ground bark (100 g.) was extracted by being stirred overnight with aqueous tartaric acid (500 c.c.; 1%) and filtered. The process was repeated until the extract gave only a weak positive reaction with Meyer's reagent. The combined extracts (4 l.) were concentrated *in vacuo*, and after filtration the solution (500 c.c.) was made strongly alkaline (pH >11) with aqueous sodium hydroxide to precipitate non-phenolic alkaloids. The precipitate was removed by centrifugation, redissolved in aqueous tartaric acid (500 c.c.; 1%), and reprecipitated as before, then washed with water by centrifugation. The washing was repeated until the centrifugate was only slightly alkaline. After being dried, first in a vacuum desiccator over calcium chloride, and finally at 50°/0·1 mm. over phosphoric oxide, this precipitate (5 g.) was extracted in a Soxhlet apparatus with ether. Crude micranthine separated gradually from the ethereal extract and was removed at intervals as a yellowish amorphous solid. Extraction was complete after 5 days; the extract was evaporated and the residue so obtained added to the main bulk of crude micranthine (total yield, 2·3 g.). The residue from the extraction gave weak alkaloid tests with Meyer's reagent; a portion was extracted with chloroform, but the residue left after evaporation of the chloroform extract gave no Millon test, indicating that daphnoline and daphnandrine were absent (Bick, Ewen, and Todd, *loc. cit.*); it could not be crystallised.

The combined alkaline centrifugates and washings obtained after the non-phenolic alkaloids in the original extract had been precipitated were saturated with carbon dioxide and the precipitate separated by centrifugation. After being washed and dried as described above, the precipitate (0·7 g.) was exhaustively extracted with ether in a Soxhlet apparatus. After removal of the ether, the residue (0·2 g.), which could not be crystallised, gave a weakly positive Meyer reaction but the Millon test and the diphenylene dioxide (phenodioxin) test (Kondo and Tomita, *loc. cit.*, 1932) were negative.

The yield of crude micranthine from a large-scale extraction of bark (2·2 kg.) by the same procedure was 45 g.

Micranthine.—A sample of crude micranthine (5·0 g.) was dissolved in dry benzene (500 c.c.) and poured on a column of neutral alumina (*ca.* 150 g.). The column was washed with chloroform, the washings evaporated to dryness *in vacuo*, and the residue (4·4 g.) moistened with methanol, whereupon it set to a mass of colourless needles. Recrystallised from ethyl acetate and then from methanol, and finally dried at 100°/0·1 mm., micranthine formed colourless needles which on being heated softened at 185° and melted at 194—196° (Pyman, *loc. cit.*, records sintering from about 190° and gradual melting and decomposition at 196°). Admixture with a sample of micranthine isolated by Pyman did not depress the m. p. Micranthine is sparingly soluble in methanol, ethyl acetate and benzene, rather more soluble in chloroform and ethanol, and very slightly soluble in ether. In chloroform it had $[\alpha]_D^{22}$ −231° (*c*, 0·7). With Fröhde's reagent it gave an indigo solution, becoming emerald green. With concentrated sulphuric

acid containing a trace of nitric acid, micranthine gave a deep-blue colour, identical with that produced by trilobine and menisarine in parallel tests. No coloration was produced with ferric chloride or with Millon's reagent in the cold, but when warmed with Millon's reagent micranthine gave a faint pink colour. Micranthine was insoluble in aqueous alkali, but dissolved in Claisen's cryptophenol reagent (*loc. cit.*). On carbon dioxide being passed through this solution a white precipitate was formed which was removed by centrifugation; recrystallisation yielded micranthine, m. p. and mixed m. p. 194—196° (Found: C, 72·1; H, 5·9; N, 4·9; MeO, 6·4; MeN, 3·9, 5·2; active H, 0·42. Calc. for $C_{34}H_{32}O_6N_2$: C, 72·3; H, 5·7; N, 5·0; MeO, 5·5; MeN, 5·2; active H, 0·35%).

Micranthine Sulphate.—A solution of micranthine (1·0 g.) in hot aqueous sulphuric acid (100 c.c.; 0·5%) gave a micro-crystalline precipitate of micranthine sulphate (1·0 g.) on cooling. Recrystallised from hot water, micranthine sulphate formed colourless needles, m. p. 305—310° (decomp.), $[\alpha]_D^{12}$ −127° (*c*, 0·5 for anhydrous salt in water) (Found: C, 57·7; H, 5·4; N, 4·2; loss at 110°/0·1 mm., 6·6. Calc. for $C_{34}H_{32}O_6N_2,H_2SO_4,2\frac{1}{2}H_2O$: C, 57·3; H, 5·2; N, 4·0; H_2O, 6·4%).

OON-*Trimethylmicranthine Dimethiodide.*—Micranthine (5·0 g.) was suspended in dry methanol (300 c.c.) and methyl iodide (10 c.c.) was added, followed by methanolic sodium methoxide (0·5 g. of sodium dissolved in 15 c.c. of methanol). The mixture was heated under reflux for 6 hours, a similar amount of sodium methoxide was added, and heating continued for a further 6 hour period; the process was repeated until in all 5 such additions had been made. The solvent was removed *in vacuo*, and the residue taken up in hot water. The yellow amorphous solid which was deposited on cooling the aqueous solution was collected and redissolved in boiling water, and the solution boiled with a little copper powder during 10 minutes. The filtered solution on being set aside deposited a cream-coloured precipitate which was filtered off and dissolved in hot methanol. From the solution colourless needles (4·9 g.) of the *dimethiodide* separated; m. p. 255—260° (decomp.), $[\alpha]_D^{20}$ −158° (*c*, 0·4 for anhydrous salt in water) (Found: C, 48·4; H, 5·6; N, 2·9; loss at 110°/0·1 mm., 8·9. $C_{39}H_{44}O_6N_2I_2,4\frac{1}{2}H_2O$ requires C, 48·2; H, 5·5; N, 2·9; H_2O, 8·3%).

OON-*Trimethylmicranthinemethine.*—*OON*-Trimethylmicranthine dimethiodide (3 g.) was dissolved in water (1 l.) and shaken with freshly prepared silver oxide (from 3·0 g. of silver nitrate) until the solution was free from iodide ions (2 hours). The filtered solution was concentrated to 100 c.c. under reduced pressure and heated on the steam-bath with aqueous potassium hydroxide (25 c.c.; 50%). The yellowish resin, which slowly separated, was extracted from the cooled solution with ether from time to time. Heating and extraction were continued until no more resin was formed (about 2 hours). The combined ether extracts were dried (Na_2SO_4) and evaporated; the resinous residue (1·5 g.), when moistened with methanol, crystallised in colourless needles. Recrystallised from methanol it had m. p. 115°, $[\alpha]_D^{17}$ 0·0° (*c*, 0·8 in chloroform). It gave no coloration with ferric chloride, was Millon negative, and was insoluble in Claisen's cryptophenol reagent (Found: C, 73·7; H, 6·6; N, 4·5; MeO, 12·7. Calc. for $C_{39}H_{42}O_6N_2$: C, 73·8; H, 6·7; N, 4·4; MeO, 14·7%).

OON-*Trimethylmicranthinemethine Dimethiodide.*—*OON*-Trimethylmicranthinemethine (0·5 g.) was dissolved in warm methanol (50 c.c.) and boiled under reflux during 15 minutes with methyl iodide (0·5 c.c.). The solution was evaporated to about half its original volume and set aside. Colourless needles (0·5 g.) of *OON*-trimethylmicranthinemethine dimethiodide separated, and after recrystallisation from methanol had m. p. 255—260° (decomp.) (Found: C, 50·4; H, 5·9; N, 3·4; loss at 110°/0·1 mm., 6·3. Calc. for $C_{41}H_{48}O_6N_2I_2,3\frac{1}{2}H_2O$: C, 50·2; H, 5·6; N, 2·9; H_2O, 6·4%).

OO-*Dimethylde*-N-*micranthine.*—*OON*-Trimethylmicranthinemethine dimethiodide (0·2 g.) was dissolved in water (50 c.c.) and heated on the steam-bath with sodium hydroxide solution (5 c.c.; 30%). Trimethylamine was evolved, and a resin slowly separated. The latter was extracted from the cooled solution with chloroform, and the heating and extraction repeated until no more resin separated (30 minutes). The chloroform solutions were combined, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue, moistened with ethanol, crystallised in colourless needles; recrystallised from ethanol, it had m. p. 210° (Found: C, 75·3; H, 5·8. Calc. for $C_{35}H_{28}O_6,C_2H_6O$: C, 75·2; H, 5·8%).

Ozonolysis of OON-*Trimethylmicranthinemethine.*—*OON*-Trimethylmicranthinemethine (5 g.) was dissolved in aqueous acetic acid (200 c.c.; 1%), the solution cooled in ice, and a stream of ozone (5%) passed through it. The sticky yellowish mass which slowly separated was extracted from time to time with ether. Ozonolysis was continued until no further cloudiness appeared in the liquid and a test portion of the solution gave no precipitate with ammonia solution (1½ hours). The ether extracts were washed with sodium carbonate solution until free from acid, dried (Na_2SO_4), and evaporated. The residue (1·1 g.) was recrystallised from light petroleum and had m. p. 77—78° undepressed in admixture with a sample of 5 : 4′-diformyl-2-methoxydiphenyl ether prepared from repandine (Bick and Todd, *loc. cit.*) (Found: C, 70·3; H, 5·2. Calc. for $C_{15}H_{12}O_4$: C, 70·3; H, 4·7%).

The aqueous solution from the ozonolysis was freed from peroxides by shaking it with palladised charcoal, and from amine oxides by shaking it with hydrogen for 15 minutes. The solution was now filtered, made strongly alkaline with sodium hydroxide, and thoroughly extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue (1·1 g.) was dissolved in methanol (20 c.c.) and heated under reflux with methyl iodide (2 c.c.) for 30 minutes. The solvent was now removed and the residue dissolved in hot methanol and set aside. The amorphous amino-aldehyde dimethiodide which separated was further purified by the same process and was finally obtained as yellowish micro-prisms, m. p. 225—230° (decomp.) (Found: C, 43·2; H, 5·2; N, 4·4. Calc. for $C_{26}H_{36}O_6N_2I_2$: C, 43·0; H, 5·0; N, 3·9%).

4 : 9-*Diformyl*-1 : 6-*dimethoxy*-3 : 8-*divinylphenodioxin* (IX).—The above amino-aldehyde dimethiodide (0·5 g.) was dissolved in water (100 c.c.), and the solution made alkaline with potassium hydroxide solution (5 c.c.; 50%) and heated on the steam-bath. Trimethylamine was evolved and the yellowish precipitate which formed was extracted from time to time with chloroform. Heating was continued until no further precipitate appeared and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue so obtained (0·2 g.) was dissolved in benzene (20 c.c.) and chromatographed on a column of neutral alumina (about 10 g.). Elution with

chloroform gave a fraction which on evaporation yielded a yellowish crystalline powder (50 mg.). Recrystallised from chloroform, the product on being heated gradually decomposed above 300° without melting. It gave a positive Schiff's test and a blue colour with concentrated sulphuric acid containing a trace of nitric acid, indicating the presence of a diphenylene dioxide (phenodioxin) system. A solution in glacial acetic acid gave a blue colour on addition of concentrated sulphuric acid, indicating the presence of an *O*-vinylaldehyde grouping. On catalytic hydrogenation, the substance took up 2 mols. of hydrogen rapidly and a further 2 mols. more slowly (Found: C, 68·4; H, 4·9; MeO, 16·9. Calc. for $C_{20}H_{16}O_6$: C, 68·2; H, 4·6; MeO, 17·6%).

N-*Methyl*-OO-*diethylmicranthine Dimethiodide*.—Micranthine (1 g.) was dissolved in boiling methanol (100 c.c.) and heated under reflux with methyl iodide (2·5 c.c.) for 6 hours. The solvent was removed *in vacuo*, and the yellowish resinous residue dissolved in boiling ethanol (250 c.c.). The solution was boiled under reflux with ethyl iodide (3 c.c.) and ethanolic sodium ethoxide (0·08 g. of sodium in 5 c.c. of ethanol). A further four additions of similar quantities of sodium ethoxide were made at intervals of 6 hours to the boiling solution, then the solvent was removed *in vacuo*, and the residue dissolved in boiling water. The yellowish resin which separated on cooling was redissolved in hot water, and the solution boiled with a a little copper powder for 10 minutes then filtered and allowed to cool. The amorphous product which separated was redissolved in hot methanol, and the solution on being kept deposited colourless needles (0·8 g.), m. p. 250—255° (decomp.) (Found: C, 49·8; H, 5·5; N, 2·9; loss at 110°/0·1 mm., 7·8. $C_{41}H_{48}O_6N_2I_2,4H_2O$ requires C, 49·7; H, 5·7; N, 2·8; H_2O, 7·3%).

N-*Methyl*-OO-*diethylmicranthinemethine*.—An aqueous solution of *N*-methyl-*OO*-diethylmicranthine dimethiodide (1 g. in 100 c.c.) was heated on the steam-bath with aqueous potassium hydroxide (5 c.c.; 50%). The yellowish resin which separated was removed from time to time and heating was continued until no further resin was formed. The solution was cooled and thoroughly extracted with ether, and the extracts were combined with an ethereal solution of the resin. After the ether solution had been washed with water and dried (Na_2SO_4), the ether was removed and the residue moistened with methanol. The product crystallised in colourless needles (0·6 g.) which, after recrystallisation from methanol, had m. p. 121°. A mixed-m. p. with *OON*-trimethylmicranthine gave a depression of about 20° (Found: C, 73·9; H, 7·0; N, 4·5. $C_{41}H_{46}O_6N_2$ requires, C, 74·3; H, 6·9; N, 4·2%).

Ozonolysis of N-*Methyl*-OO-*diethylmicranthinemethine*.—*N*-Methyl-*OO*-diethylmicranthinemethine (0·5 g.) was ozonised in dilute acetic acid solution as described above for *OON*-trimethylmicranthinemethine. The resin which separated was extracted with ether and the extract washed first with aqueous sodium carbonate and then with water, dried (Na_2SO_4), and evaporated. The residue, recrystallised from light petroleum, formed colourless needles (0·1 g.), m. p. 60°, identical (mixed m. p.) with 5 : 4′-diformyl-2-ethoxydiphenyl ether obtained by an analogous procedure from repandine (Bick and Todd, *loc. cit.*) (Found: C, 71·5; H, 5·4. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%).

N-*Methyldihydromenisarine Dimethiodide*.—Menisarine (8 mg.) was dissolved in acetic acid (2 c.c.; 10%) and the yellowish solution heated on the steam-bath with powdered zinc (20 mg.) with occasional stirring, until colourless. The residue left on filtration was washed with small quantities of hot water, and the combined filtrate and washings were made alkaline with ammonia solution and thoroughly extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (7 mg.) was dissolved in methanol (1 c.c.) and heated under reflux with methyl iodide (0·01 c.c.) for 30 minutes. After removal of the solvent under reduced pressure, the residue was dissolved in water (2 c.c.) and boiled with a small amount of charcoal. The solution was filtered, the residue washed with hot water, and the combined filtrate and washings evaporated to a small bulk under reduced pressure and set aside. *N*-Methyldihydromenisarine dimethiodide (4·70 mg.; dried at 110°/0·1 mm.), $[\alpha]_D^{19}$ +150° (*c*, 0·1 in water) separated from solution; it could not be obtained crystalline.

Absorption Spectra of Micranthine, Trilobine, and Oxyacanthine.—The absorption spectra of the above alkaloids was determined in methanol solution (about M/10,000) by using a Beckman quartz spectrophotometer. The curves are shown in the figure. The values obtained for wave-length and, in parentheses, extinction coefficients at the minima and maxima, respectively, were: micranthine, 2610 (3020), 2860 (5310); trilobine, 2610 (2240), 2880 (5250); and oxyacanthine 2600 (2040), 2850 A. (7090).

We express our gratitude to Mr. C. J. Trist of the Queensland Forestry Department and Mr. L. J. Webb of the Commonwealth Scientific and Industrial Research Organisation, Australia, for supplies of bark used in this investigation, to Prof. H. Kondo for gifts of menisarine and trilobine, and to the British Council and the Australian National University for scholarships held by one of us (I. R. C. B.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 28th,* 1950.]