THE ALKALOIDS OF *CRYPTOCARYA BOWIEI* (HOOK.) DRUCE

By JEAN EWING,* G. K. HUGHES,* E. RITCHIE,* and W. C. TAYLOR*

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Summary

Two closely related water-soluble alkaloids cryptaustoline and cryptowoline iodides have been isolated from the bark of *Cryptocarya bowiei* (Hook.) Druce. Both have been shown to be derivatives of dibenzo[*b, g*]pyrrocoline. This constitutes the first isolation of substances containing this nucleus from natural sources.

I. INTRODUCTION

Bancroft (1887) reported the isolation of a crystalline alkaloid from the bark of *Cryptocarya australis* (Benth.), now known as *C. bowiei* (Hook.) Druce, which because of its paralytic action was thought to be related to curare. Maiden (1895) confirmed the presence of a respiratory poison and urged complete chemical investigation but this was not forthcoming until the present work was undertaken. A preliminary account of this investigation has been published (Ewing *et al.* 1952).

Stimulus was given to this project by de la Lande's (1948) isolation of the unusual vesicant alkaloid cryptopleurine from another of the Australian species, *C. pleurosperma*. Although *C. bowiei* varies in size from a small shrub in northern New South Wales and southern Queensland to a tree, about 30 ft. high, in northern Queensland it was surprising to find that the alkaloid from the southern bark samples was different from that of the northern bark samples but obviously closely related to it. Both were isolated as their sparingly soluble iodides and were optically active. Analyses indicated empirical formulae of $C_{20}H_{24}O_4NI$ (northern) and $C_{19}H_{20}O_4NI$ (southern); preliminary examination showed that these could be expanded to $C_{16}H_{11}(OH)(OCH_3)_3(NCH_3)^+I'$ and $C_{16}H_{11}(OH)(OCH_3)(O_2CH_2)(NCH_3)^+I'$ respectively. Neither gave Gibbs's reaction for phenols with a free *p*-position. It is proposed that they be called cryptaustoline and cryptowoline iodides, the latter being the one isolated from southern sources.

II. CRYPTAUSTOLINE IODIDE

By the action of methyl iodide and methanolic potassium hydroxide an *O*-methyl ether was formed in high yield and this with boiling sodium hydroxide solution gave optically active methine-I; molecular weight and analyses showed that the formula was $C_{21}H_{25}O_4N$. Catalytic hydrogenation gave dihydromethine-I, $C_{21}H_{27}O_4N$, which changed on exposure to air to a substance $C_{21}H_{25}O_4N$ referred to as dehydrodihydromethine-I, which gave a positive

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* Department of Organic Chemistry, University of Sydney.

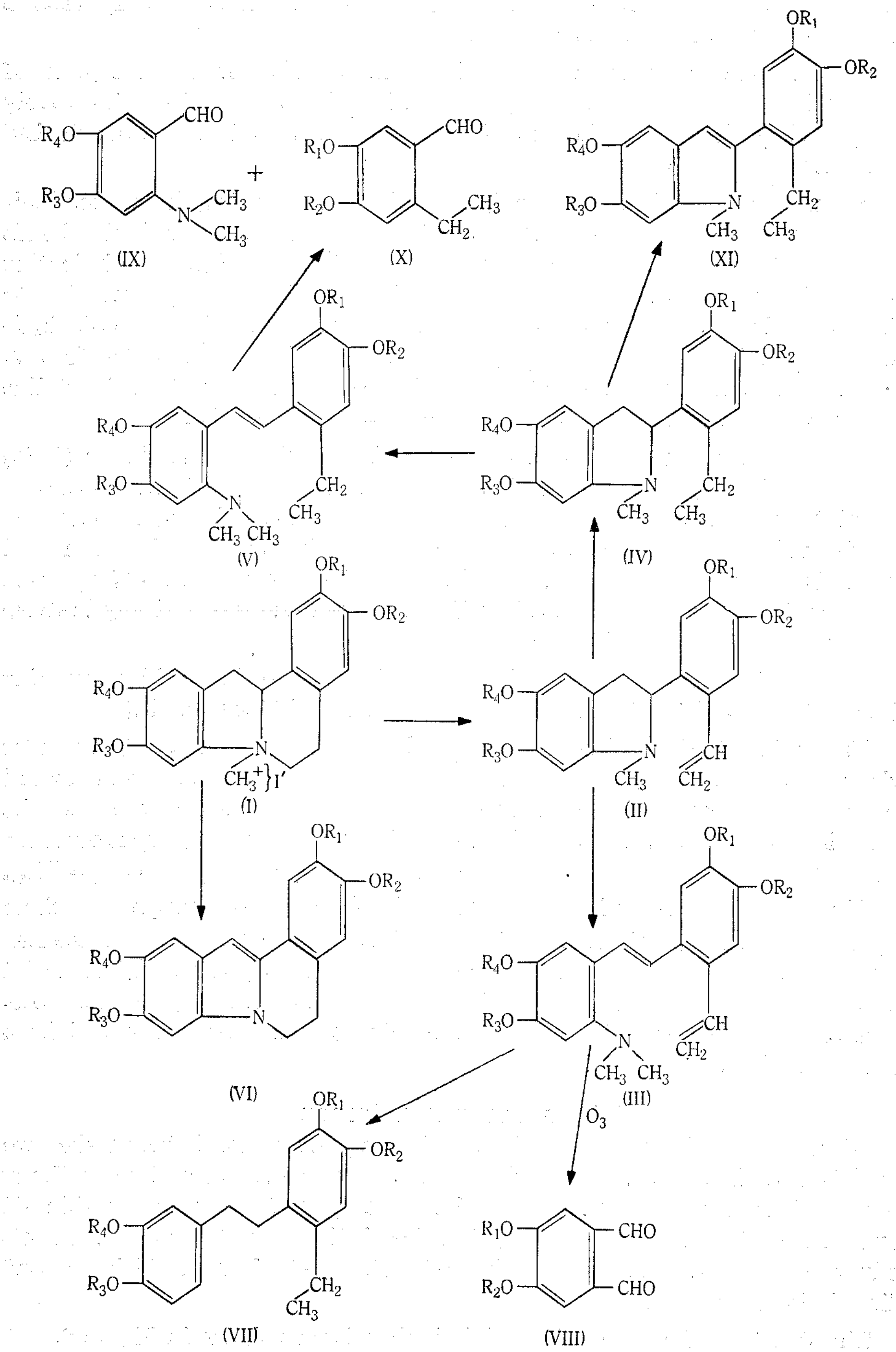
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Fig. 1

Ehrlich test. Ozonolysis of methine-I gave formaldehyde showing that a terminal methylene group was present.

A Hofmann degradation of methine-I methiodide gave a high yield of optically inactive methine-II, $C_{22}H_{27}O_4N$, which could not be further exhaustively methylated, the inference being that either the nitrogen was hindered or attached to a benzene nucleus.

Ozonolysis of methine-II gave 4,5-dimethoxyphthalaldehyde but the basic fraction could not be crystallized. As methine-II contained two double bonds it was thought desirable to reduce the complexity of the ozonolysis by eliminating part of the unsaturation. Consequently dihydromethine-I was converted to dihydromethine-II, which with ozone readily afforded 6-ethylveratric aldehyde and 6-dimethylaminoveratric aldehyde. Dihydromethine-II was therefore V, methine-II was III, methine-I was II, and the *O*-methyl ether of cryptaustoline iodide was I (see Fig. 1; in all cases $R_1=R_2=R_3=R_4=CH_3$).

Both Robinson and Sugasawa (1932) and Schöpf and Thierfelder (1932) had studied the dehydrogenation of laudanosoline hoping to obtain norglaucine, a possible morphine precursor. However, the resulting dehydrolaudanosoline was shown to be I ($R_1=R_2=R_3=R_4=H$) by exhaustive methylation and ozonolysis. The second methine obtained by them was identical (m.p. and mixed m.p.) with methine-II but since their first methine was optically inactive no comparison there could be made.

Confirmation of the structure of the methyl ether was obtained by preparing VI and VII by methods described by Schöpf and Thierfelder (loc. cit.).

It remained to determine the position of the hydroxyl group. By a similar series of reactions on the *O*-ethyl ether, 6-dimethylaminoveratric aldehyde and the previously unknown 3-ethoxy-6-ethyl-4-methoxybenzaldehyde (as its semicarbazone) were obtained. This showed that the hydroxyl group is attached to the 2-position and thus cryptaustoline iodide is I ($R_1=H$, $R_2=R_3=R_4=CH_3$).

The 3-ethoxy-6-ethyl-4-methoxybenzaldehyde was prepared from 4-hydroxy-3-methoxyacetophenone by ethylation followed by Clemmensen reduction and a Gattermann aldehyde synthesis. Permanganate oxidation of it gave an acid which had the same melting point as that found by Kondo, Noto, and Tanaka (1928) for 3-ethoxy-6-ethyl-4-methoxybenzoic acid prepared by a different method.

III. CRYPTOWOLINE IODIDE

At the outset it was believed that the only difference between the two alkaloids was that one had a methylenedioxy-group instead of two methoxy groups. Hence it was not unexpected that ozonolysis of the dihydromethine-II prepared from the ethyl ether of cryptowoline iodide gave the same non-basic product as above, that is, 3-ethoxy-4-methoxy-6-ethylbenzaldehyde and 6-dimethylaminopiperonal.

The structure of cryptowoline iodide is therefore as shown in Figure 2.

The 6-dimethylaminopiperonal was prepared by methylation of 6-aminopiperonylidene-*p*-toluidine.

Finally the isolation of these two alkaloids provides the first confirmation of the prediction of Schöpf and Thierfelder (1932) that alkaloids having the dibenzopyrrocolinium nucleus should occur in the plant cell. Folkers, Koniuszy, and Shavel (1951) suggested structures with this nucleus for the erythrina alkaloids but Carmack, McKusick, and Prelog (1951) have thrown doubt on this hypothesis.

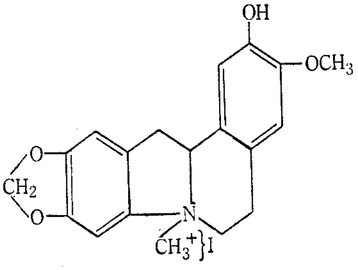

Fig. 2

IV. EXPERIMENTAL

All melting points are uncorrected. Analyses are by K. W. Zimmerman, C.S.I.R.O., and Mrs. E. Reichert, University of Sydney.

(*a*) *Isolation of Cryptaustoline Iodide.*—The ground bark (12 kg.), from trees growing at Mossman Gorge, north Queensland, was exhausted with cold methanol (6 × 5 l.). The combined extracts were concentrated to 1·5 l., thoroughly mixed with dilute acetic acid (3 l. of 2%), filtered, saturated with potassium iodide (300 g.), and set aside. The supernatant liquid was decanted and extracted with chloroform (9 × 2 l.). After removal of the solvent the residue was added to the gummy precipitate and dissolved in hot methanol (800 ml.). On standing *cryptaustoline iodide* was obtained as small prisms which after several recrystallizations from methanol had m.p. 214 °C. (decomp.), $[\alpha]_D^{20^\circ}$—151° (*c*, 0·4% in ethanol). Yield 80 g. (Found: C, 51·0; H, 5·3; N, 3·0; CH_3O, 19·5%. Calc. for $C_{20}H_{24}O_4NI$: C, 51·1; H, 5·4; N, 3·0; 3 × CH_3O, 19·8%).

(*b*) O-*Methylcryptaustoline Iodide.*—Cryptaustoline iodide (40 g.) dissolved in methanolic potassium hydroxide (400 ml. of 0·5N) and methyl iodide (25 ml.) were refluxed for 6 hr. and the mixture then concentrated to 100 ml. After removing the potassium iodide the solution was further concentrated, cooled, the methyl derivative collected and crystallized from water (300 ml.) as white rods (36 g., 85%), m.p. 80–90 °C. It was obviously a hydrate and no satisfactory analyses could be obtained even on carefully dried material of m.p. 153–155 °C., $[\alpha]_D^{20^\circ}$—175° (*c*, 0·4% in ethanol) (Found: C, 47·1; H, 5·6; N, 3·1; CH_3O, 23·0; H_2O, 8·2%. Calc. for $C_{21}H_{26}O_4NI.2H_2O$: C, 47·6; H, 5·0; N, 2·7; 4 × CH_3O, 23·6; H_2O, 8·5%).

(*c*) O-*Methyl Methine*-I.—A solution of *O*-methylcryptaustoline iodide (15 g.) and sodium hydroxide (90 g.) in water (700 ml.) was refluxed for 1·5 hr. by which time large oily drops had formed. These were transferred to ether, dried, and distilled under reduced pressure to produce a clear glass which crystallized from methanol as colourless needles (9 g., 90%), m.p. 101 °C., $[\alpha]_D^{20^\circ}$—221° (*c*, 0·4% in chloroform) (Found: C, 71·1; H, 7·1; CH_3O, 34·5%. Calc. for $C_{21}H_{25}O_4N$: C, 71·0; H, 7·0; 4 × CH_3O, 34·9%).

The *methiodide* was prepared by heating the base and methyl iodide in a sealed tube at 100 °C. for 3 hr. It was recrystallized from methanol-ether as colourless prisms (yield 84%), m.p. 195 °C. (Found: C, 53·0; H, 5·7; N, 3·0; CH_3O, 34·7%. Calc. for $C_{22}H_{28}O_4NI$: C, 53·1; H, 5·7; N, 2·8; 4 × CH_3O, 34·9%).

(*d*) O-*Methyl Methine*-II.—The above iodide (8 g.) and sodium hydroxide solution (300 ml. of 13%) were refluxed for 1·5 hr., cooled, and the lemon-yellow oil extracted with ether. The solvent was removed from the dried extract and the residue crystallized from methanol (30 ml.) as pale lemon needles (4·5 g.), m.p. 111 °C., $[\alpha]_D^{20°}0°$ (Found : C, 71·8 ; H, 7·5 ; N, 4·1 ; CH_3O, 33%. Calc. for $C_{22}H_{27}O_4N$: C, 71·7 ; H, 7·4 ; N, 3·8 ; 4×CH_3O, 33·6%).

The *methiodide*, the formation of which required a large excess of methyl iodide and prolonged heating, was obtained as microprisms, m.p. 188 °C. (Found : C, 54·0 ; H, 6·1 ; CH_3O, 24·6%. Calc. for $C_{23}H_{30}O_4NI$: C, 53·8 ; H, 6·1 ; 4×CH_3O, 24·4%). It was unaffected after heating with sodium hydroxide for 2 hr.

(*e*) O-*Methyl Tetrahydromethine*-II.—Prepared by catalytic hydrogenation of *O*-methyl methine-II in presence of Raney nickel. It crystallized from a small volume of ethanol as colourless needles, m.p. 64 °C. (Found : C, 70·5 ; H, 7·8 ; CH_3O, 33·1%. Calc. for $C_{22}H_{31}O_4N$: C, 70·7 ; H, 8·4 ; 4×CH_3O, 33·2%).

The *methosulphate* was prepared in benzene and crystallized from methanol-ether as microneedles, m.p. 197 °C. (Found : C, 57·9 ; H, 7·1 ; N, 2·8 ; CH_3O, 31·0%. Calc. for $C_{24}H_{37}O_8NS$: C, 57·7 ; H, 7·4 ; N, 2·8 ; 5×CH_3O, 31·0%).

(*f*) O-*Methyl Dihydromethine*-I.—The methine-I was hydrogenated at room temperature in presence of Raney nickel. The dihydro-derivative was recrystallized from aqueous ethanol as colourless needles, m.p. 67 °C. but was too unstable for analysis.

The *methiodide* prepared from freshly prepared base was recrystallized from methanol-ether as prisms, m.p. 201 °C. (Found : C, 52·1 ; H, 6·1 ; N, 2·8 ; CH_3O, 24·2%. Calc. for $C_{22}H_{30}O_4NI$: C, 52·4 ; H, 6·1 ; N, 2·8 ; 4×CH_3O, 24·8%). After long standing in solution the dihydromethine was converted to a less soluble compound which was finally crystallized from methanol as off-white prisms, m.p. 131 °C. This gave an intense indole reaction with Ehrlich's reagent and was evidently the dehydrodihydromethine (XI) (Found : C, 70·8 ; H, 6·9 ; CH_3O, 33·8%. Calc. for $C_{21}H_{25}O_4N$: C, 71·0 ; H, 7·1 ; 4×CH_3O, 34·9%).

(*g*) O-*Methyl Dihydromethine*-II.—Dihydromethine-I methiodide (3·2 g.), sodium hydroxide solution (150 ml. of 20%), and ethanol (10 ml.) were refluxed for 3 hr. The product, isolated as above, crystallized from ethanol (15 ml.) as needles (2·2 g.), m.p. 120 °C. (Found : C, 71·3 ; H, 7·2 ; N, 4·1 ; CH_3O, 33·3%. Calc. for $C_{22}H_{29}O_4N$: C, 71·1 ; H, 7·8 ; N, 3·8 ; 4×CH_3O, 33·4%).

(*h*) *Ozonolysis of* O-*Methyl Methine*-I.—The methine, dissolved in freshly distilled carbon tetrachloride, was ozonized at —20 °C. After removing the solvent *in vacuo* the residue was refluxed with water and then distilled into alcoholic dimedon. The precipitate (20% yield) was collected and recrystallized from ethanol, m.p. 188 °C. undepressed on admixture with formaldehyde dimedon.

(*i*) *Ozonolysis of* O-*Methyl Methine-II*.—An ethyl acetate solution of methine-II was ozonized at —20 °C. The solvent was removed *in vacuo* and the partially crystalline residue, which gave aldehyde reactions, was dissolved in ethanol. On cooling pale brown needles of 4,5-dimethoxyphthalaldehyde deposited and were recrystallized from water as straw coloured flakes (yield 38%), m.p. 170 °C. (Found : C, 61·6 ; H, 5·4 ; CH_3O, 31·4%. Calc. for $C_{10}H_{10}O_4$: C, 61·8 ; H, 5·2 ; 2×CH_3O, 31·8%). This aldehyde (0·15 g.) in water (40 ml.) was oxidized with potassium permanganate solution (1·5 ml. of 10%). The acid, isolated in the usual manner, crystallized from chloroform, m.p. 198–199 °C. (0·08 g., 57%). This was converted to the ethylimide, yellow needles from methanol, m.p. 228 °C. Perkin (1916) gave m.p. 228 °C. for the ethylimide of *m*-hemipinic acid (Found : C, 61·0 ; H, 5·3%. Calc. for $C_{12}H_{13}O_4N$: C, 61·2 ; H, 5·5%). The basic fraction from the ozonolysis was intractable.

(*j*) *Ozonolysis of* O-*Methyl Dihydromethine-II*.—A solution of the dihydromethine (1·0 g.) in water (130 ml.), sulphuric acid (10 ml. of 2N), and acetic acid (7 ml.) was ozonized for 40 min., the solution being extracted with ether (100 ml.) at 10-min. intervals (ether extract *A*).

The aqueous solution was shaken with palladized charcoal and hydrogen for 15 min., filtered, made strongly alkaline, and extracted with ether. The solvent was removed from the dried extract and the oily residue crystallized from light petroleum as yellow needles, m.p. 71 °C. (0·17 g., 30%) (Found : C, 63·2 ; H, 6·8 ; N, 7·0 ; CH_3O, 29·3%. Calc. for $C_{11}H_{15}O_3N$: C, 63·1 ; H, 7·2 ; N, 6·8 ; 2×CH_3O, 29·6%). Schöpf and Thierfelder (loc. cit.) report that 6-dimethylaminoveratric aldehyde has m.p. 71 °C.

The extract *A* was washed with dilute acid and alkali, dried, and distilled *in vacuo* to give a pale yellow oil, b.p. 170–180 °C./1 mm. (bath temp.) which solidified at 0 °C. and remelted at about 26 °C. It gave a semicarbazone, colourless needles from aqueous ethanol, m.p. 198 °C. (Found: C, 57·3; H, 6·5; N, 16·4; CH_3O, 24·7%. Calc. for $C_{12}H_{17}O_3N_3$: C, 57·3; H, 6·8; N, 16·8; 2×CH_3O, 24·7%). 6-Ethylveratric aldehyde semicarbazone has m.p. 198 °C. (Barger and Silberschmidt 1928).

(*k*) *Emde Degradation of* O-*Methyl Tetrahydromethine-II Methosulphate*.—The methosulphate (0·55 g.) in water (25 ml.) was heated on the steam-bath with sodium amalgam (20 g. of 5%) for 2 hr. The oil which separated was taken up in ether, washed with dilute hydrochloric acid to remove unchanged material (0·15 g.), and then dried. After removal of the solvent the oily residue was crystallized from aqueous ethanol as needles, m.p. 78 °C. (0·2 g., 52%) (Found: C, 73·0; H, 7·9; CH_3O, 37·1%. Calc. for $C_{20}H_{26}O_4$: C, 72·7; H, 7·9; 4×CH_3O, 37·6%). This substance was identical (m.p. and mixed m.p.) with tetrahydrolaudanosene, 6′-ethyl-3,4,3′,4′-tetramethoxy-αβ-diphenylethane, (VII) prepared from laudanosine after the method of Decker and Galatty (1909) using the methiodides instead of the methosulphates throughout (cf. Robinson and Sugasawa).

(*l*) *6-Dimethylamino-3,4,3′,4′-tetramethoxy-6-vinyl Stilbene*.—This was prepared from papaverine through tetramethyldehydrolaudanosoline by a combination of the methods of Robinson and Sugasawa (loc. cit) and Schöpf and Thierfelder. Its m.p. 110 °C. was undepressed on admixture with *O*-methyl methine-II.

(*m*) *Des*-N-*methyl*-O-*methyl Cryptaustoline*.—*O*-Methyl cryptaustoline chloride (from the iodide, 0·4 g.) was gradually heated to 200 °C. under vacuum (0·6 mm.) and then at 220 °C. for 3 min. The clear greenish yellow oil was recrystallized five times from methanol as grey-green flakes, m.p. 200 °C. Yield 0·08 g., 35% (Found: C, 70·8; H, 6·3; N, 4·4; CH_3O, 36·1%. Calc. for $C_{20}H_{21}O_4N$: C, 70·8; H, 6·3; N, 4·2; 4×CH_3O, 36·5%). It gave a royal blue colour with Ehrlich's reagent and was identical (m.p. and mixed m.p.) with 2,3,9,10-tetramethoxydihydrodibenzopyrrocoline prepared from tetramethyldehydrolaudanosoline (Schöpf and Thierfelder 1932).

(*n*) *The Ethyl Series*.—These compounds were prepared by essentially the same methods as for the corresponding methyl derivatives and are thus listed as briefly as possible.

(i) O-*Ethyl Cryptaustoline Iodide*. Colourless blades from water, m.p. 90–95 °C. Satisfactory analysis could not be obtained, the following is on material dried *in vacuo* at 60 °C. (Found: CH_3O, 24·7%. Calc. for $C_{22}H_{28}O_4NI$: 3×CH_3O, 1×C_2H_5O as CH_3O, 25·0%).

(ii) O-*Ethyl Methine-I*. Colourless prisms from methanol, m.p. 104 °C. (Found: C, 71·7; H, 7·2%. Calc. for $C_{22}H_{27}O_4N$: C, 71·8; H, 7·4%). The *methiodide* crystallized as prisms from methanol, m.p. 200 °C. (Found: N, 3·1%. Calc. for $C_{23}H_{30}O_4NI$: N, 2·8%).

(iii) O-*Ethyl Dihydromethine-I*. Colourless rectangular plates from methanol, m.p. 107 °C. (Found: C, 71·4; H, 7·8; N, 4·1%. Calc. for $C_{22}H_{29}O_4N$: C, 71·1; H, 7·8; N, 3·8%). The *methiodide* formed colourless plates, m.p. 203 °C. (Found: C, 53·9; H, 6·3; N, 2·6%. Calc. for $C_{23}H_{32}O_4NI$: C, 53·8; H, 6·3; N, 2·7%).

(iv) O-*Ethyl Methine-II*. Lemon-green fluorescent prisms from ethanol, m.p. 115–116 °C. (Found: C, 72·1; H, 7·5%. Calc. for $C_{23}H_{29}O_4N$: C, 72·0; H, 7·6%).

(v) O-*Ethyl Dihydromethine-II*. Rods with pale blue fluorescence from methanol, m.p. 109 °C. (Found: C, 71·5; N, 7·8%. Calc. for $C_{23}H_{31}O_4N$: C, 71·6; H, 8·1%).

(*o*) *Ozonolysis of* O-*Ethyl Dihydromethine-II*.—The basic product had m.p. 71 °C., undepressed on admixture with the compound obtained from the corresponding methyl derivative. The neutral aldehyde yielded a semicarbazone, fluffy needles from aqueous ethanol, m.p. 183 °C. (Found: C, 58·8; H, 7·4; N, 15·8%. Calc. for $C_{13}H_{19}O_3N_3$: C, 58·9; H, 7·2; N, 15·8%).

(*p*) *4-Ethoxy-3-methoxyethylbenzene*.—4-Ethoxy-3-methoxyacetophenone (6·5 g.) was added to a boiling mixture of amalgamated zinc turnings (32 g.), water (25 ml.), and concentrated hydrochloric acid (25 ml.) during 30 min. The mixture was refluxed for a further 4 hr. The product, isolated in the usual way, was a clear colourless liquid (4·5 g.), b.p. 92–94 °C./1 mm. Kondo, Noto, and Tanaka (1928) give b.p. 95 °C./5 mm.

(*q*) *3-Ethoxy-6-ethyl-4-methoxybenzaldehyde.*—A rapid stream of dry hydrogen chloride was passed into an ice-cooled and vigorously stirred mixture of 3-ethoxy-4-methoxyethylbenzene (3·7 g.), zinc cyanide (3·7 g.), and benzene (25 ml.) for 30 min. Powdered aluminium chloride (3·5 g.) was then added gradually and the stirring continued for 2 hr. After adding ice and dilute hydrochloric acid, the unchanged ether was removed in steam. The aldehyde, isolated by ether extraction and distillation (b.p. 140–142 °C./1 mm.) crystallized from light petroleum (40–60 °C.) as off-white needles, m.p. 80 °C. (0·8 g., 20%) (Found : C, 69·5 ; H, 7·6%. Calc. for $C_{12}H_{16}O_3$: C, 69·3 ; H, 7·7%). The semicarbazone was crystallized from aqueous ethanol as needles, m.p. 183 °C. undepressed by admixture with the semicarbazone described in Section IV (*o*) (Found: C, 59·2 ; H, 7·2 ; N, 15·7%. Calc. for $C_{13}H_{19}O_3N_3$: C, 58·9 ; H, 7·2 ; N, 15·8%). The aldehyde was oxidized by potassium permanganate in acetone to the acid, needles from water, m.p. 139 °C. Kondo, Noto, and Tanaka (1928) found m.p. 138 °C. for 3-ethoxy-6-ethyl-4-methoxybenzoic acid. This acid also obtained from the aldehyde described in Section IV (*o*) (Found : C, 64·3 ; H, 6·7%. Calc. for $C_{12}H_{16}O_4$: C, 64·3 ; H, 7·0%).

(*r*) *Isolation of Cryptowoline Iodide.*—The bark (4 kg.), obtained from trees growing at North Brookfield in southern Queensland, was extracted as in Section IV (*a*). The iodide after several recrystallizations from methanol was obtained as off-white prisms, m.p. 245–246 °C. (45 g., 1·1%), $[\alpha]_D^{20^\circ}$—186° (*c*, 0·4% in ethanol) (Found: C, 50·3 ; H, 4·5 ; N, 3·1 ; CH_3O, 7·8%. Calc. for $C_{19}H_{20}O_4NI$: C, 50·2 ; H, 4·5 ; N, 3·1 ; 1×CH_3O, 6·9%).

(*s*) O-*Methyl Cryptowoline Iodide.*—Colourless triangular prisms were crystallized from water, m.p. 227 °C., $[\alpha]_D^{20^\circ}$—179° (*c*, 0·4% in ethanol) (Found: C, 51·5 ; H, 4·9 ; N, 3·1 ; CH_3O, 13·4%. Calc. for $C_{20}H_{22}O_4NI$: C, 51·3 ; H, 5·0 ; N, 3·0 ; 2×CH_3O, 13·3%).

(*t*) O-*Methyl Methine-I.*—It formed a colourless glass, b.p. 238–240 °C./1 mm. which could not be crystallized, $[\alpha]_D^{25^\circ}$—172° (*c*, 0·85% in chloroform).

The *methiodide* crystallized from methanol-ether as rectangular plates, m.p. 185 °C. (Found : C, 52·2 ; H, 5·1 ; N, 2·9 ; CH_3O, 12·9%. Calc. for $C_{21}H_{24}O_4NI$: C, 52·3 ; H, 5·1 ; N, 2·9 ; 2×CH_3O, 12·9%).

The dihydro-derivative could not be crystallized but its methiodide formed colourless cubes, m.p. 198 °C. (Found: C, 52·2 ; H, 5·5 ; CH_3O, 13·1%. Calc. for $C_{21}H_{26}O_4NI$: C, 52·2 ; H, 5·4 ; 2×CH_3O, 12·9%).

(*u*) O-*Methyl Methine-II.*—Lemon-yellow plates formed from methanol, m.p. 114 °C. (Found : C, 71·7 ; H, 6·7 ; N, 4·2 ; CH_3O, 18·3%. Calc. for $C_{21}H_{23}O_4N$: C, 71·4 ; H, 6·6 ; N, 4·0 ; 2×CH_3O, 17·6%).

(*v*) O-*Ethyl Cryptowoline Iodide.*—Colourless prisms crystallized from methanol, m.p. 215 °C. (Found : C, 51·7 ; H, 5·1 ; N, 3·3 ; CH_3O, 13·5%. Calc. for $C_{21}H_{24}O_4NI$: C, 52·1 ; H, 5·1 ; N, 3·3 ; 1×CH_3O+1×C_2H_3O, 13·0%). This was converted to the methine which could not be crystallized.

(*w*) O-*Ethyl Dihydromethine-II.*—The product formed white needles, m.p. 102 °C. Its solution possessed a deep blue fluorescence (Found : C, 71·5 ; H, 7·4%. Calc. for $C_{22}H_{27}O_4N$: C, 71·5 ; H, 7·4%). Ozonolysis, as above, gave a non-basic aldehyde, the semicarbazone of which had m.p. 183 °C. undepressed on admixture with the semicarbazone prepared in Section IV (*q*). The basic fraction crystallized in yellow leaflets, m.p. 92 °C. (yield 30%). It gave a positive Labat methylenedioxy test (Found : C, 62·2 ; H, 5·9 ; N, 7·7%. Calc. for $C_{10}H_{11}O_3N$: C, 62·1 ; H, 5·7 ; N, 7·3%).

(*x*) *6-Dimethylaminopiperonal.*—This was prepared from 6-aminopiperonylidene-*p*-toluidine (Rilliet and Kreitmann 1921) using the methylation process of Schöpf and Thierfelder (loc. cit.). The crude product, dissolved in benzene, was run through a column of alumina. After several recrystallizations from light petroleum (40–60 °C.) it had m.p. 92 °C., undepressed by admixture with the substance described in the previous section (Found : N, 7·5%. Calc. for $C_{10}H_{11}O_3N$: N, 7·3%).

V. Acknowledgments

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VI. References

Bancroft, T. L. (1887).—*Proc. Roy. Soc. Qd.* **4**: 12.
Barger, G., and Silberschmidt, R. (1928).—*J. Chem. Soc.* **1928**: 2919.
Carmack, M., McKusick, B. C., and Prelog, V. (1951).—*Helv. Chim. Acta* **34**: 1601.
Decker, H., and Galatty, L. (1909).—*Ber. dtsch. chem. Ges.* **42**: 1179.
Ewing, Jean, Hughes, G. K., Ritchie, E., and Taylor, W. C. (1952).—*Nature* **169**: 618.
Folkers, K., Koniuszy, F., and Shavel, J. (1951).—*J. Amer. Chem. Soc.* **73**: 589.
Kondo, T., Noto, T., and Tanaka, S. (1928).—*J. Pharm. Soc. Japan* **48**: 1163.
de la Lande, I. S. (1948).—*Aust. J. Exp. Biol. Med. Sci.* **26**: 181.
Maiden, J. H. (1895).—Rep. Aust. Ass. Adv. Sci. p. 625.
Perkin, W. H. (1916).—*J. Chem. Soc.* **109**: 815.
Rilliet, A., and Kreitmann, L. (1921).—*Helv. Chim. Acta* **4**: 588.
Robinson, R., and Sugasawa, S. (1932).—*J. Chem. Soc.* **1932**: 789.
Schöpf., C., and Thierfelder, K. (1932).—*Liebigs Ann.* **497**: 22.