121. *The Active Principles of Leguminous Fish-poison Plants. Part VIII. The Synthesis of Dehydrotetrahydroelliptone and of Dehydrotetrahydromalaccol.*

By STANLEY H. HARPER.

Condensation of methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate with 2-ethylresorcinol by the Hoesch method and subsequent hydrolysis gave rise to tetrahydroelliptic acid. Cyclisation of this acid with hot acetic anhydride and sodium acetate furnished through the acetate dehydrotetrahydroelliptone, identical with that prepared from elliptone. The formula established for elliptone by degradative experiments (J., 1939, 1424) has therefore been fully substantiated.

By an analogous condensation with ethylphloroglucinol, tetrahydromalaccolic acid was prepared. This acid on cyclisation gave dehydrotetrahydromalaccol, for which an angular and a linear formula are possible. It has not proved possible, however, to compare this product with that derived from natural sources.

FROM the results of degradative experiments it was concluded in Part III (J., 1939, 1424) that elliptone had structure (I).* This formulation could be conclusively established by synthesis of dehydrotetrahydroelliptone (VI), a degradation product obtained recently (preceding paper). An attempt was therefore made to use the Hoesch method already successfully employed by Robertson *et al.* in the synthesis of dehydrotetrahydrorotenone (J., 1933, 1163) and of dehydrotetrahydrosumatrol (J., 1939, 1601).

Condensation of 2-ethylresorcinol with methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate by the method of Hoesch and subsequent hydrolysis of the crude ketimine gave *methyl tetrahydroelliptate*. Hydrolysis of this ester gave tetrahydroelliptic acid (IX), identical with that prepared from the reduction of elliptone (preceding paper). Cyclisation of this acid with boiling acetic anhydride and sodium acetate gave a small yield of O-*acetyldehydrotetrahydroelliptone*, which on deacetylation with hot aqueous alcoholic hydrochloric acid gave rise to dehydrotetrahydroelliptone (VI), identical with a specimen prepared from elliptone. As the cyclisation of tetrahydroelliptic acid can only occur in one direction, the structure previously assigned to elliptone and its degradation products is established conclusively.

In Part IV (J., 1940, 309) an angular formula (XIX*a*) was postulated for malaccol, although the corresponding linear form (XIX*b*) could not be excluded. An attempt was therefore made to confirm this formulation by the synthesis of dehydrotetrahydromalaccol by the Hoesch method. Ethylphloroglucinol was substituted for 2-ethylresorcinol in the preceding condensation and *methyl tetrahydromalaccolate, tetrahydromalaccolic acid,*

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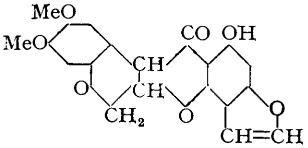
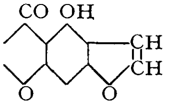
* Formulæ are numbered consecutively from the preceding paper.

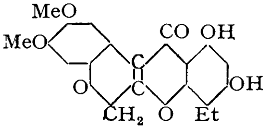
O-*diacetyldehydrotetrahydromalaccol*, and *dehydrotetrahydromalaccol* were successively prepared. The last compound gave a negative Durham test and a deep green colour with ferric chloride, reactions similar to those of dehydromalaccol. The cyclisation of tetrahydromalaccolic acid can, however, occur in two ways to give the angular (XX*a*) or the linear (XX*b*) form of dehydrotetrahydromalaccol. There is no evidence to decide for or against either formula for this synthetic product. In the analogous case of tetrahydrosumatrolic acid Kenny, Robertson, and George (J., 1939, 1601) regarded their cyclised product as having the angular formula. It has not proved possible to prepare natural dehydrotetrahydromalaccol for comparison with this synthetic specimen. Several experiments on the oxidation of tetrahydromalaccol with iodine and subsequent reduction of the iodo-compound with zinc in acetic acid in no case led to crystalline material. Hence it has not been possible to confirm either structure postulated previously for malaccol, but the angular formula (XIX*a*) is still regarded as the more probable.



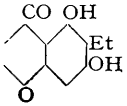
(XIX*a*.)



(XIX*b*.)



(XX*a*).



(XX*b*.)

EXPERIMENTAL.

Veratrole.—No convenient method for the preparation of veratrole could be found in the literature. Practically no yield was obtained from pyrocatechol by the method of Perkin and Weizman (J., 1906, **89**, 1649), which may be due to the fact that the stated quantity of methyl sulphate is only one quarter of the theoretical requirement. By a modification, however, of the method for veratraldehyde (*Organic Syntheses*, **16**, 91) veratrole was prepared in 83—86% yield from both guaiacol and pyrocatechol.

Veratrole was nitrated in 100 g. lots by Clark's method (*J. Amer. Chem. Soc.*, 1931, **53**, 3434), the temperature being kept below 5° during the addition; the product, 4-nitroveratrole, without recrystallisation was suitable for reduction (97% yield, m. p. 95°). 4-Nitroveratrole was reduced to 4-aminoveratrole in 93% yield, allowing for recovered nitro-compound (Fargher, J., 1920, **117**, 869). The amine was purified by distillation, b. p. 170°/16 mm. The method of Baker and Evans for the preparation of 4-hydroxyveratrole was used (J., 1938, 375), and the yield (45%) consistently obtained. The remaining seven stages to methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate were covered by the methods of Robertson *et al.* (J., 1930, 2440; 1932, 1386; 1933, 1164).

2-Ethylresorcinol was prepared substantially as described by Russell, Frye, and Mauldin (*J., Amer. Chem., Soc.*, 1940, **62**, 1442). The high yield, however, recorded by these authors in the preparation of 7-hydroxy-4-methylcoumarin could not be duplicated (yield, 60%).

Methyl Tetrahydroelliptate.—Through methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate (2 g.), 2-ethylresorcinol (2 g.), and zinc chloride (2 g., fused and powdered) in dry ether (50 c.c.), dry hydrogen chloride was passed until the reactants had dissolved (1 hour), the whole being cooled in ice and salt. On keeping at 0° a brown oil separated which slowly crystallised. After 7 days the ether was decanted, and the solid washed with ether (3 × 50 c.c.) and hydrolysed by heating on the steam-bath with water (100 c.c.) for 2 hours. The precipitate was collected and stirred with sodium bicarbonate solution. After drying, the insoluble portion (1·78 g.) was repeatedly crystallised from methyl alcohol to give *methyl tetrahydroelliptate* in feathery needles, m. p. 185° (Found : C, 61·8; H, 5·75; OMe, 22·4. $C_{21}H_{24}O_8$ requires C, 62·35; H, 5·95; 3OMe, 23·0%). The ester gave a red colour with alcoholic ferric chloride. Acidification of the sodium bicarbonate filtrate gave crude tetrahydroelliptic acid (22 mg.), m. p. 185—190°.

Tetrahydroelliptic Acid.—Methyl tetrahydroelliptate was quantitatively hydrolysed to tetrahydroelliptic acid by warm 0·1N-sodium hydroxide (30 mins.). The acid crystallised on acidification and could be recrystallised from aqueous alcohol, m. p. 202° (Found : C, 60·9; H, 5·6; OMe, 15·9. Calc. for $C_{20}H_{22}O_8$: C, 61·5; H, 5·65; 2OMe, 15·9%), not depressed by tetrahydroelliptic acid prepared from elliptone (preceding paper). The acid gave a deep wine-red colour with alcoholic ferric chloride.

Dehydrotetrahydroelliptone.—Tetrahydroelliptic acid (500 mg.) and sodium acetate (250 mg.) were refluxed in acetic anhydride (10 c.c.) and acetic acid (0·5 c.c.) for 10 mins. Dilution with methyl alcohol (25 c.c.) caused the separation of O-*acetyldehydrotetrahydroelliptone* (203 mg.), which crystallised from chloroform–alcohol in pale yellow plates, m. p. 253° (Found : C, 66·3; H, 5·05; OMe, 15·2. $C_{22}H_{20}O_7$ requires C, 66·6; H, 5·1; 2OMe, 15·6%). The substance was insoluble in alkali and gave no ferric chloride colour. No secondary products could be isolated in a crystalline state.

The acetyl compound (200 mg.) was deacetylated by refluxing with 20% alcoholic hydrochloric acid for 2 hours Dehydrotetrahydroelliptone (150 mg.) crystallised from alcohol in yellow plates, m. p. 255—260° (decomp.) (Found : C, 67·6; H, 5·3; OMe, 17·4. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1; 2OMe, 17·5%), not depressed by dehydrotetrahydroelliptone prepared from elliptone (preceding paper). The dehydro-compound was soluble in aqueous alkali, but gave no colour with alcoholic ferric chloride.

Attempted Synthesis of Elliptic Acid.—The above nitrile (1 g.), 4-hydroxycoumarone (Reichstein and Hirt, *Helv. Chim. Acta*, 1933, **16**, 121) (1 g.) and fused zinc chloride (1 g.) in dry ether (35 c.c.), cooled in ice and salt, were saturated with dry hydrogen chloride. From the hydrolysed product, however, no acid was extracted by sodium bicarbonate.

Methyl Tetrahydromalaccolate.—Methyl 2-cyanomethyl-4 : 5-dimethoxyphenoxyacetate (1·2 g.) and ethylphloroglucinol (2 g.) (prepared by Clemmensen reduction of phloroacetophenone, b. p. 195°/1 mm., m. p. 120°) were condensed together in the presence of zinc chloride (1 g.) as described above for methyl tetrahydroelliptate. The portion of the hydrolysed product insoluble in aqueous sodium bicarbonate was crystallised from aqueous methyl alcohol to give *methyl tetrahydromalaccolate* (690 mg.) in plates, tenaciously retaining solvent, m. p. 184° (Found : C, 59·4; H, 5·75; OMe, 20·6. $C_{21}H_{24}O_9$ requires C, 60·0; H, 5·75; 3OMe, 21·1%). The ester gave a brownish-purple colour with alcoholic ferric chloride. Acidification of the sodium bicarbonate filtrate gave crude tetrahydromalaccolic acid (270 mg.).

Tetrahydromalaccolic Acid.—Methyl tetrahydromalaccolate was hydrolysed to *tetrahydromalaccolic acid* by warm 0·1N-sodium hydroxide (30 mins.). The acid crystallised on acidification, and from 25% aqueous acetone it separated as a dihydrate in plates [Found (after drying over phosphoric oxide in a vacuum desiccator at room temperature) : OMe, 14·0. $C_{20}H_{22}O_9,2H_2O$ requires OMe, 14·0%]. The acid had m. p. 225° and gave a brownish-purple colour with alcoholic ferric chloride (Found : C, 57·0; H, 5·6; OMe, 15·1. $C_{20}H_{22}O_9,H_2O$ requires C, 56·6; H, 5·7; OMe, 14·6. $C_{20}H_{22}O_9$ requires C, 59·1; H, 5·5; OMe, 15·3%).

Dehydrotetrahydromalaccol.—Tetrahydromalaccolic acid (250 mg.) and sodium acetate (125 mg.) were refluxed in acetic anhydride (5 c.c.) and acetic acid (0·25 c.c.) for 10 mins. The reaction mixture was decomposed with water (dilution with methyl alcohol at this stage did not cause the separation of diacetyldehydrotetrahydromalaccol), and the residue treated with warm aqueous sodium bicarbonate. The insoluble portion was crystallised from a small volume of methyl alcohol to give O-*diacetyldehydrotetrahydromalaccol* (30 mg.) in pale yellow needles, m. p. 194—196° (Found : C, 63·0; H, 4·9. $C_{24}H_{22}O_9$ requires C, 63·4; H, 4·9%). The ferric chloride reaction was negative. No other crystalline product could be isolated.

The diacetyl compound (25 mg.) was deacetylated by refluxing with 20% alcoholic hydrochloric acid (3 c.c.) for 2 hours. *Dehydrotetrahydromalaccol* (18 mg.) separated in yellow needles on dilution, m. p. 240° (decomp.) (Found : C, 63·5; H, 4·75. $C_{20}H_{18}O_7,H_2O$ requires C, 63·3; H, 5·0%).

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