SOME NITRO- AND AMINO-COMPOUNDS PREPARED FROM NATURALLY OCCURRING 2,2-DIMETHYLCHROMENES

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Summary

The preparation of some nitro-compounds of *allo*evodionol and dihydromethylevodionol is described. Aminodihydromethylevodionol has also been prepared and found to be too toxic for pharmacological use and devoid of antibiotic activity.

I. Introduction

The volatile oils of several Australian plants contain derivatives of 2,2-dimethylchromene, for example, evodionol (Lahey 1942), evodione (Wright 1948) and *allo*evodionol (Sutherland 1949). These substances were tested for pharmacological activity (Burgison, personal communication) and were found to have some vasodilator activity, but their sparing solubility in aqueous solvents makes their pharmacological study difficult. Therefore, it was decided to attempt to prepare some nitro-compounds of these substances in order to convert them to the corresponding amines, at the same time reducing the chromene nucleus to the saturated chromane.

*allo*Evodionol (I) has been shown (Sutherland 1949) to be 2,2-dimethyl-7-hydroxy-5-methoxy-8-acetylchromene. Nitration, using nitric acid in boiling ethanol, gave a bright yellow solid dinitro*allo*evodionol, m.p. 157 °C. When fuming nitric acid was used a white solid, m.p. 264 °C, possibly a nitro-dimer of *allo*evodionol was isolated. *allo*Evodionol undergoes dimerization when heated with dimethyl sulphate (Sutherland 1949), so that a nitro-dimer is not unexpected. When the nitration was carried out in ice-cold glacial acetic acid, using nitric acid, the same dimer was obtained together with a smaller amount of yellow coloured nitro*allo*evodionol, m.p. 130–131 °C. Dinitro*allo*evodionol was methylated to give a yellow solid methyldinitro*allo*evodionol, m.p. 119 °C, but attempts to reduce this compound to the diamine of the corresponding chromane with hydrogen and Raney nickel at atmospheric pressure and room temperature were unsuccessful. Bachman and Levine (1948) found that catalytic reduction of 2-methyl-3-nitrochroman with hydrogen and Raney nickel proved very difficult, requiring extreme conditions. Similar difficulty might also be expected with dinitro*allo*evodionol, since one of the nitro-groups enters the aromatic nucleus at position 6, and the other most probably at position 3, as the effect of the *p*-orientating phenolic group is likely to be transferred to position 3 in the chromene nucleus by the unsaturated linkage conjugated with the benzene nucleus.

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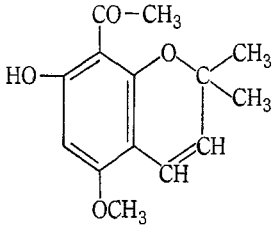
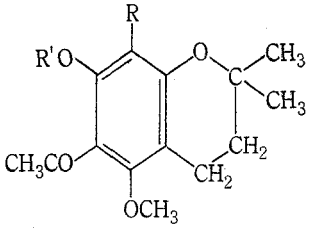
The preparation of a monoamine was then attempted, using as a starting material evodionol, 2,2-dimethyl-7-hydroxy-5-methoxy-6-acetylchromene (Lahey 1942). This compound was first reduced catalytically (Lahey 1940) to the corresponding chromane, dihydroevodionol (II, R,R′=H) which was nitrated (Lahey 1942), using nitric acid in ethanol to give 8-nitrodihydroevodionol (II, R=NO_2; R′=H). This compound was methylated with diazomethane to give 8-nitrodihydromethylevodionol, m.p. 104 °C (II, R=NO_2; R′=CH_3), which on reduction with hydrogen and Raney nickel at atmospheric pressure gave good yields of 8-aminodihydromethylevodionol (II, R=NH_2; R′=CH_3), m.p. 87 °C. This amine and its dimethyl derivative were tested for toxicity by Professor R. H. Thorp, and were found to have an LD_{50} of 200 and of 75 mg/kg respectively. These values are too high to warrant further pharmacological tests. Both compounds were also tested for antibiotic properties against several bacteria but were found to be inactive.



(I)



(II)

Diazotization of 8-aminodihydromethylevodionol, followed by treatment with hot saturated copper sulphate solution, was attempted in order to prepare the corresponding phenol. This phenol on methylation should give dihydroevodione (Wright 1948) but the reaction was unsuccessful, as the chromane nucleus appeared to undergo fission, giving a mixture of unidentified liquid phenols.

II. Experimental

All melting points are uncorrected. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory.

(*a*) *Nitration of* allo*Evodionol.*—(i) *With Concentrated Nitric Acid.* Nitric acid (sp. gr. 1·4; 20 ml) added to *allo*evodionol (1 g) in ethanol (180 ml) was boiled gently in an open flask for 20 min. After cooling, the solution was poured into ice-cold saturated brine (250 ml), a *reddish solid* separated, which was recrystallized from ethanol in yellow needles, m.p. 157 °C. Yield 0·2 g (Found: C, 50·0; H, 4·3; N, 7·9%. Calc. for $C_{14}H_{14}O_8N_2$: C, 49·7; H, 4·1; N, 8·2%).

(ii) *With Fuming Nitric Acid.* *allo*Evodionol (1 g) in ethanol (20 ml) was treated with fuming nitric acid (2 ml), added slowly while shaking. The shaking was continued without heating until a *yellowish solid* separated; a further small amount was recovered by ether extraction of the nitration liquid. The solid was crystallized from acetone as a pale yellow solid, m.p. 264 °C (decomp.) (Found: C, 62·5; H, 5·8; N, 2·3%. Calc. for $C_{28}H_{29}O_{10}N$: C, 62·2; H, 5·5; N, 2·5%).

(iii) *With Concentrated Nitric Acid and Glacial Acetic Acid.* *allo*Evodionol (0·5 g) in a mixture of glacial acetic acid (8 ml) and acetic anhydride (1 ml) was treated with nitric acid (sp. gr. 1·4; 2 ml) at 0 °C. After 2–3 min the mixture was poured into water (50 ml) when a yellow solid separated (0·06 g) recrystallized from ethanol, m.p. 264 °C (decomp.), it was identical with the nitro-dimer described previously. The nitration mixture was extracted with ether and the ether removed after washing with bicarbonate, a small amount of dimer separated. The ether extract, on standing, deposited crystals which on recrystallization from ethanol yielded 0·02 g of a pale *yellow mononitro-compound*, m.p. 130–131 °C (Found: N, 4·5%. Calc. for $C_{14}H_{15}O_6N$: N, 4·8%).

(*b*) *Methyldinitro*allo*evodionol.*—A suspension of dinitro*allo*evodionol (0·2 g) in ether (25 ml) was treated with excess of diazomethane (prepared from nitrosomethylurea) in ether. On standing overnight all the solid dissolved. After standing a further 24 hr, the ether was removed, leaving an *orange-yellow solid*, recrystallized from ethanol, m.p. 119 °C (Found: C, 51·3; H, 4·7; N, 7·5%. Calc. for $C_{15}H_{16}O_8N_2$: C, 51·2; H, 4·5; N, 8%).

(*c*) *Nitrodihydromethylevodionol.*—Nitrodihydroevodionol (0·5 g) in ether (10 ml) was methylated overnight with excess of diazomethane. The ether was removed and a *colourless solid* obtained, recrystallized from ethanol, m.p. 104 °C (Found: C, 58·7; H, 6·1; N, 4·7%. Calc. for $C_{15}H_{19}O_6N$: C, 58·2; H, 6·2; N, 4·5%).

(*d*) *Aminodihydromethylevodionol.*—Nitrodihydromethylevodionol (0·5 g) in ethanol (30 ml) was hydrogenated in the presence of freshly prepared Raney nickel (0·5 g) for 4–6 hr at room temperature and atmospheric pressure. On removal of the ethanol, a white solid separated, recrystallized from ethanol, m.p. 86–87 °C. Yield 0·4 g (Found: C, 64·7; H, 7·8; N, 5·1%. Calc. for $C_{15}H_{21}O_4N$: C, 64·5; H, 7·5; N, 5·0%).

(*e*) *Dimethylaminodihydromethylevodionol.*—Aminodihydromethylevodionol (0·4 g) in acetone (50 ml) was methylated with dimethyl sulphate by refluxing in the presence of excess of anhydrous potassium carbonate. A white crystalline solid was isolated, recrystallized from acqueous ethanol, m.p. 62 °C (Found: C, 66·7; H, 8·2; N, 4·8%. Calc. for $C_{17}H_{25}O_4N$: C, 66·5; H, 8·2; N, 4·6%).

III. Acknowledgments

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IV. References

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