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THE CHEMISTRY OF FLAVANS AND RELATED COMPOUNDS—I

SOME HYDROXYFLAVANS

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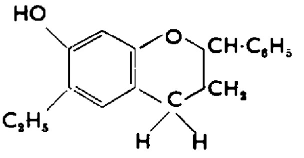
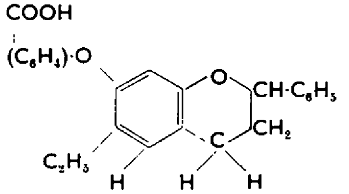
Abstract—Starting from 7-hydroxy-6-ethylflavan (I) and its formyl derivative (IV), 6-ethyl-(7,8,2′,3′)-chromonoflavan (III) of the draconal type and α-pyronoflavans have been synthesized.

IN reviewing further possible routes for the synthesis of Dracorubin-type compounds, the flavan system already formed seems to offer better advantages in the building up of the xanthone residues and the flavilium units. As a preliminary to the synthesis of the dracorubin system or the draconol type,[1] starting from simple flavan structures α-, and γ-pyrono units have been built up. 7-Hydroxy-6-ethylflavan (I) obtained by the Clemmensen reduction of 7-hydroxy-6-ethylflavanone[2] was employed as simple 7-hydroxyflavan[3] was found to be unstable under tropical conditions. When



I



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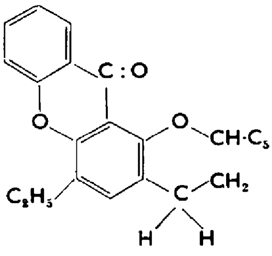

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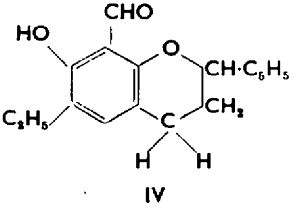

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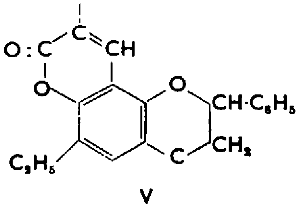

V

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[1] A. Robertson, W. B. Whalley and J. Yates, *J. Chem. Soc.* 3117 (1950).

[2] T. E. Ellison, *J. Chem. Soc.* 1722 (1927).

[3] A. Robertson, V. Venkateswarlu and W. B. Whalley, *J. Chem. Soc.* 3137 (1954).

I was condensed with *o*-bromo-benzoic acid following the Ullmann reaction, 7-O-(2′-carboxyphenyl)-6-ethylflavan (II) was obtained which underwent smooth cyclization to 6-ethyl-(7,8,2′,3′)chromonoflavan (III).

Formylation of I by the Gattermann method gave the 8-formyl derivative (IV) from which stable α-pyronoflavans (V) have been synthesized.

As a result of these experiments, the following observations which are of interest in building up units of the dracarubin type may be noted: (I) an ethyl group in the sixth position of 7-hydroxyflavan has a stabilizing effect, (2) simple flavans undergo decomposition and resinification due to temperature effects, (3) formylated flavan systems would give stable α-pyronoflavans and (4) it is possible to build up units of the dracanol type. These observations are supported by results published earlier.[3]

EXPERIMENTAL

7-Hydroxy-6-ethylflavanone. This was prepared by an improved procedure (cf. Ellison). 4-Ethylresacetophenone (20 g) was condensed with benzaldehyde (15 ml) in KOH aq. (40 g in 40 ml) by boiling under reflux for 3½ hr. After dilution with water, the unreacted benzaldehyde was ether extracted and the deep coloured solution acidified with excess HCl. The solid residue was treated with glacial acetic acid to dissolve the 2,4-dihydroxy-5-ethylphenyl styryl ketone and the residue thus obtained washed with benzene. The flavanone appeared as colourless rectangular plates (acetic acid), m.p. 240–241°, yield 4 g. (Found: C, 76·00; H, 6·21; $C_{17}H_{16}O_3$ requires: C, 76·12; H, 5·97%).

The pure *chalkone* was obtained as orange red prisms from benzene, m.p. 97–98°. (Found: C, 76·31; H, 6·14; $C_{17}H_{16}O_3$ requires: C, 76·12; H, 5·97%). The chalkone is more soluble in benzene than the flavanone, the solubility of the latter being 0·5% at 30°. The chalkone was cyclized to the flavanone by boiling under reflux for 30 hr using 50% ethanol containing 3% H_2SO_4.

7-Hydroxy-6-ethylflavan (I). Clemmensen reduction of 7-hydroxy-6-ethylflavanone (1 g) using amalgamated Zn (10 g) in glacial acetic acid (40 ml) and conc HCl (5 ml) during 24 hr in the cold gave the flavan as colourless needles (from pet ether 40–60° containing a few drops methanol) m.p. 114–115°. (Found: C, 80·50; H, 7·21; $C_{17}H_{18}O_2$ requires: C, 80·32; H, 7·09%). It dissolved in alkali giving a pale yellow solution and gives no colour with alcoholic $FeCl_3$.

8-Formyl-7-hydroxy-6-ethylflavan (IV). Interaction of 7-hydroxy-6-ethylflavan (1 g) and $Zn(CN)_2$ (5 g) in presence of anhydrous $ZnCl_2$ (0·5 g) in dry ether (100 ml) saturated with dry HCl gas (0°; 24 hr) gave a crystalline aldimine hydrochloride. Hydrolysis of the residue using water (75 ml) by warming on a water-bath for 5 min, gave a solid which crystallized from methanol or pet ether, as colourless rectangular plates, m.p. 80–81°, giving an olive green ferric reaction in alcoholic solution. (Found: C, 76·72; H, 6·50; $C_{18}H_{18}O_3$ requires: C, 76·61; H, 6·38%). The 2,4-dinitrophenylhydrazone, crystallized as deep red prisms (from excess ethyl acetate), m.p. 259–60° (dec). (Found: N, 12·31; $C_{24}H_{22}O_6N_4$ requires: N, 12·13%).

Reduction of 8-formyl-7-hydroxy-6-ethylflavan in acetic acid using Zn amalgam and conc HCl in the cold gave *8-methyl-6-ethyl-7-hydroxyflavan* as colourless stout rectangular plates and prisms, m.p. 110–112° (dec. during storage). (Found: C, 80·52; H, 7·67; $C_{18}H_{20}O_2$ requires: C, 80·61; H, 7·46%). It dissolves in alkali giving a pale yellow solution and does not give any colour with alcoholic $FeCl_3$.

6-Ethyl-3′-carbethoxy-α-pyrono(6′,5′,7,8)flavan (V). 6-Ethyl-7-hydroxyflavan-8-aldehyde (0·5 g) was treated with diethyl malonate (0·5 g) followed by piperidine (5 drops) while cooling and the clear reddish brown solution left overnight out of contact with air and then decomposed using dil HCl. The α-pyronoflavan crystallized as colourless shining rectangular plates (alcohol), m.p. 201–202°. (Found: C, 73·20; H, 5·91; $C_{22}H_{22}O_6$ requires: C, 73·02; H, 5·82%). In neutral alcoholic solution, it exhibits a bright bluish violet fluorescence and a deep violet fluorescence in conc H_2SO_4, the solutions being coloured pale yellow.

6-Ethyl-α-pyrono(6′,5′,7,8)flavan (V). The above carbethoxy-α-pyronoflavan was boiled under reflux for 1 hr using alcoholic KOH (20%, 20 ml). The product obtained on acidification was crystallized from ethyl acetate when the flavan appeared as colourless rectangular prisms m.p. 151–152°. (Found: C, 78·61; H, 6·01; $C_{20}H_{18}O_3$ requires: C, 78·43; H, 5·88%). It is insoluble in $NaHCO_3$ and NaOH in the cold and does not show the characteristic properties of a free hydroxyl group. The flavan dissolves in alcohol giving a violet fluorescence, the solution being colourless and in conc H_2SO_4 solution (pale yellow) it exhibited a weak violet fluorescence.

6-Ethyl-3′-acetyl-α-pyrono-(6′,5′,7,8)flavan (V). Condensation of 6-ethyl-7-hydroxy-flavan-8-aldehyde (1 g) with ethyl acetoacetate (0·8 g) in presence of piperidine (5 drops) yielded V which on crsytallization from methanol appeared as colourless lustrous plates, m.p. 90–91°. (Found: C, 75·72; H, 5·64; $C_{22}H_{20}O_4$ requires: C, 75·86; H, 5·75%). In neutral alcohol it dissolves to give a colourless solution which develops a weak violet fluorescence only after some time. In conc H_2SO_4 a weak violet fluorescence develops only on standing, from the yellow solution.

6-Ethyl-3′-cyano-α-pyrono(6′,5′,7,8)flavan (V). Condensation of 6-ethyl-7-hydroxy-flavan-8-aldehyde (0·5 g) with cyanoacetic ester (0·5 g) in presence of piperidine (5 drops) yielded V which crystallized as colourless rectangular plates (acetone–pet ether, b.p. 40–60°), m.p. 195–196°. (Found: C, 76·21; H, 5·24; N, 4·07; $C_{21}H_{17}O_3N$ requires: C, 76·14; H, 5·14; N, 4·23%).

8-Formyl-7-acetoxy-6-ethyflavan. Acetylation of 8-formyl-7-hydroxy-6-ethylflavan in the cold using acetic anhydride and pyridine gave 7-O-acetyl derivative which crystallized as colourless long needles and plates (methanol), m.p. 157–159° having a negative ferric reaction in alcoholic solution. (Found: C, 74·21; H, 6·23; $C_{20}H_{20}O_4$ requires : C, 74·08: H, 6·17%). The *2,4-dinitrophenylhydrazone* crystallized as scarlet red needles (ethyl acetate), m.p. 195–196°. (Found: N, 11·14; $C_{26}H_{24}O_7N_4$ requires: N, 11·11%).

6-Ethyl-7-hydroxyflavan-8-carboxylic acid. 6-Ethyl-7-acetoxy-flavan-8-aldehyde (2 g) dissolved in acetone (20 ml) was mechanically stirred (1 hr) during the addition of a hot solution of $KMnO_4$ (3·2 g in 80 ml water). After standing overnight, the solution was saturated with SO_2, and the acetone removed under red. press. It was then acidified and the product obtained hydrolysed on a steambath for 10 min using aqueous KOH (2N, 2 ml). 6-Ethyl-7-hydroxyflavan-8-carboxylic acid crystallized as colourless needles (methanol) m.p. 260–261° giving a deep brown ferric reaction in alcoholic solution. (Found: C, 72·58; H, 6·21; $C_{18}H_{18}O_4$ requires: C, 72·49; H, 6·04%).

7-O-(2′-Carboxyphenyl)-6-ethylflavan (II). An intimate mixture of 6-ethyl-7-hydroxyflavan (1 g), *o*-bromobenzoic acid (1·5 g) and KOH (1·2 g in abs ethanol, 5 ml) was treated with Cu bronze (0·2 g) and the mixture heated at 160° for 30 min. The cooled reaction mixture was taken up in alkali, filtered and the filtrate saturated with CO_2 to remove unreacted 6-ethyl-7-hydroxyflavan (0·3 g), the clear solution was then acidified with dil H_2SO_4. The product obtained crystallized as colourless prisms and plates from pet ether (b.p. 40–60°), m.p. 131–132° giving no positive ferric reaction. (Found: C, 77·21; H, 6·00; $C_{24}H_{22}O_4$ requires: C, 77·00; H, 5·88%).

6-Ethyl-(7,8,2′,3′-chromono)flavan (III). The above acid (0·5 g) was cyclized using HI (5 ml *d.* 1·7) in acetic anhydride (5 ml) by warming on a steam bath during 1 hr. On working up, III crystallized as pale yellow prisms (benzene), m.p. 179–180°. It is insoluble in $NaHCO_3$, Na_2CO_3 and NaOH solutions. (Found: C, 80·72; H, 5·81; $C_{24}H_{20}O_3$ requires: C, 80·91; H, 5·62%).