ANTISEPTICS AND ANTHELMINTHICS.

Part II. A Synthesis of 6-Benzyl-7-hydroxyflavone and 6-n-Hexyl-7-hydroxyflavone.

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In view of the therapeutic value of hexylresorcinol1 as an internal antiseptic2 extensive work on the alkyl derivatives of other phenols has been reported.3

Since the anthelmintic constituent of the leaves of Calycoceras floribunda has been identified as a dihydroxytetramethoxyflavone4 the examination of Indian plants with alleged vermicidal action for the presence of flavone derivatives, and of synthetic specimens of the latter for anthelmintic properties, has become relevant to the general attempt to prepare new antiseptics and anthelmintics5 Nakao and Tseng6 have isolated apigenin and its 7-methyl ether from the Chinese drug "Yuen-hua", believed from very early times to be a diuretic and anthelmintic, but the pharmacological action has not been correlated with the flavone content. The present work relates to the synthesis of the 6-benzyl and hexyl derivatives of 7-hydroxyflavone. The influence of a C-benzyl group on the bactericidal action of phenols and halogenated phenols has been demonstrated by Klarmann, Gates and Shternov.7

4-Benzylresorcinol (2:4-dihydroxydiphenylmethane) was prepared according to Klarmann8; the homogeneity of the product and the absence of

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1 Johnson and Lane, J. Amer. Chem. Soc., 1921, 43, 348.
5 Gulati, Seth and Venkataraman, Jour. pr. Chem., 1933, 137, 47.
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2: 4-dibenzylresorcinol were confirmed by comparison with the product of the Clemmensen reduction of resobenzophenone. The phenol was then converted into 5-benzylresacetophenone (I; R = CH₄Ph) by a Hoesch reaction with acetonitrile. Treatment of the ketone with benzoic anhydride led to a mixture of 6-benzyl-7-hydroxyflavone (II; R = CH₂Ph) and its 3-benzoyl derivative (III), the former being also prepared by the selenium dioxide oxidation of the chalkone (IV; R = CH₂Ph), followed by debenzylation.

By analogy with the Fries reaction on 7-acyloxycoumarins and chromones,⁹ which give rise to 8-substituted products, the Claisen change of 7-benzyloxyflavone was studied with the object of preparing 7-hydroxy-8-benzylflavone, but attempts at migration with zinc chloride or aluminium chloride resulted only in unchanged material or debenzylation to 7-hydroxyflavone. Difficulties were also encountered in efforts to prepare 7-hydroxy-8-benzoylflavone and reduce it to the desired substance.

By submitting 4-n-hexylresorcinol to the series of reactions outlined in the case of 4-benzylresorcinol, the ketone (I; R = n-hexyl), the chalkone (IV; R = n-hexyl) and the flavone (II; R = n-hexyl) were prepared.

Experimental.

C-Benzylresorcinol.—(a) Prepared according to Klarman (loc. cit.) the substance was obtained in a yield of 35%, the oil distilling at 198–200°/2 mms. The colourless needles from petroleum ether melted at 76–77°. (b) A mixture of resorcinol (25 g.), benzyl chloride (7.5 g.) and fused zinc chloride (2 g.) was warmed carefully on the water-bath until a vigorous reaction set in. More benzyl chloride (7.5 g.) was then added, the whole being finally heated for one hour on the water-bath. On cooling, water was added, the mixture

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⁹ Limaye, Ber., 1934, 67, 12; Wittig, Baugert and Richter, Ann., 1925, 446, 184.
extracted with ether, the ether extract washed with 2% sodium carbonate solution, dried and the solvent removed. Distillation of the residue in vacuo gave 15 g. of an oil boiling at 210-220°/12-13 mms., which was redistilled and collected at 198-200°/2 mms. (8 g.). (c) Resobenzophenone (20 g.), zinc amalgam (86 g.), aldehyde-free alcohol (60 g.) and 50% hydrochloric acid (140 g.) were boiled for 30 hours, when a drop of the oily product, taken up in alcohol and carefully neutralised, gave no colouration with ferric chloride. Ether extraction and distillation at 2 mms. pressure gave C-benzylresorcinol in 50% yield.

C-Benzy1resacetophenone (I; R = CH₂Ph).—After saturation of a mixture of C-benzylresorcinol (10 g.), acetonitrile (3·5 c.c.), ether (30 c.c.) and zinc chloride (4 g.) with hydrogen chloride, and 4 days in the ice-chest, the ether was decanted off, the residue boiled with water (250 c.c.) and filtered hot. The undissolved oil solidified on cooling and crystallised from benzene in very pale yellow leaflets (6 g.), m.p. 153° (Found: C, 74·1; H, 5·7. C₁₅H₁₁₀₃ requires C, 74·4; H, 5·8%). The alcoholic solution exhibited a deep violet colouration with ferric chloride. The di-nitrophenylhydrazone melted at 221° (Found: N, 13·0. C₂₁H₁₈O₃N₁₂ requires N, 13·3%). When the reaction was carried out with an impure C-benzylresorcinol, b.p. 210-220°/10-12 mms., the hot aqueous filtrate after removal of C-benzylresacetophenone, deposited colourless leaflets (0·4 g.) on cooling, which melted at 209° and gave an orange-red ferric chloride colouration (Found: C, 75·0; H, 5·9).

2-Hydroxy-4-benzyloxy-5-benzylacetophenone (V; R = CH₂Ph).—Benzylation in the known manner10 gave the ether, which crystallised from alcohol in colourless needles, m.p. 111° (Found: C, 79·4; H, 6·0. C₂₅H₂₈O₃ requires C, 79·5; H, 6·0%). The colour with ferric chloride was deep red.

2-Hydroxy-4-benzyloxy-5-benzylchalkone (IV; R = CH₂Ph).—To a warm solution of the above ketone (2·3 g.) and benzaldehyde (1·3 g.), 50% caustic soda solution (6 g.) was added. On leaving overnight, the chalkone was isolated as usual. The deep yellow needles (2·3 g.) from glacial acetic acid melted at 134° (Found: C, 82·8; H, 6·2. C₂₅H₂₄O₃ requires C, 82·9; H, 5·7%). The crystals were coloured orange-red by sulphuric acid.

6-Benzyl-7-benzyloxyflavone (VI; R = CH₂Ph).—From a mixture of the above chalkone (2 g.), selenium dioxide (2 g.) and amyl alcohol (12 c.c.), refluxed at 150° for 12 hours, the solvent was removed in steam, and the residue extracted with glacial acetic acid. The colourless needles (1 g.) separating from the filtrate melted at 222° (Found: C, 83·0; H, 5·4.

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C\textsubscript{22}H\textsubscript{22}O\textsubscript{3} requires C, 83·2; H, 5·3\%). The colourless solution in sulphuric acid exhibited a blue fluorescence.

6-Benzyl-7-hydroxyflavone (II; R = CH\textsubscript{3}Ph) — To the benzyl ether (1 g.) in glacial acetic acid (10 c.c.), hydrobromic acid saturated at 0° (10 g.) was added and the solution refluxed for an hour. Dilution with water and crystallisation of the precipitate from glacial acetic acid gave cream-coloured, elongated, triangular plates, m.p. 267° (Found: C, 80·6; H, 5·0. C\textsubscript{22}H\textsubscript{18}O\textsubscript{3} requires C, 80·5; H, 4·9\%). The acetyl derivative, colourless needles from alcohol, melted at 191° (Found: C, 78·1; H, 4·9. C\textsubscript{24}H\textsubscript{18}O\textsubscript{4} requires C, 77·8; H, 4·8\%).

3-Benzoyl-6-benzyl-7-hydroxyflavone (III).—The Robinson reaction with C-benzylresacetophenone (4 g.), benzoic anhydride (40 g.) and sodium benzoate (8 g.), hydrolysis with 10% alcoholic potash (210 c.c.) and saturation with carbon dioxide led to a yellow powder, crystallisation of which from glacial acetic acid gave colourless plates (1·5 g.), m.p. 267°, identical with the previously obtained flavone. Concentration of the mother-liquors and dilution gave thin, colourless plates, m.p. 229° (Found: C, 80·2; H, 4·6. C\textsubscript{26}H\textsubscript{20}O\textsubscript{4} requires C, 80·6; H, 4·6\%)

C-Hexylresacetophenone (I; R = n-hexyl).—The product, obtained by the Hoesch reaction between hexylresorcinol\textsuperscript{11} (30 g.) acetonitrile (12 g.) and zinc chloride (12 g.) in ether (50 c.c.), followed by aqueous hydrolysis, was an oil, which was taken up in ether. After removal of the ether from the dried extract and distillation of the residue in vacuo, the fraction coming over at 195-200°/3-4 mms. solidified in contact with light petroleum. The colourless plates (24 g.) from the same solvent melted at 85° (Found: C, 71·1; H, 8·7. C\textsubscript{14}H\textsubscript{16}O\textsubscript{3} requires C, 71·2; H, 8·5\%). The ferric chloride colouration was deep red. The dinitrophenylhydrazone melted at 183-184° (Found: N, 13·3. C\textsubscript{20}H\textsubscript{22}O\textsubscript{4}N\textsubscript{4} requires N, 13·4\%).

2-Hydroxy-4-benzyloxy-5-hexylacetophenone (V; R = n-hexyl).—The colourless needles from alcohol melted at 94° (Found: C, 77·6; H, 8·2. C\textsubscript{21}H\textsubscript{26}O\textsubscript{3} requires C, 77·3; H, 8·0\%).

2-Hydroxy-4-benzyloxy-5-hexylchalkone (IV; R = n-hexyl).—Yellow needles from alcohol, m.p. 92° (Found: C, 81·3; H, 7·4. C\textsubscript{25}H\textsubscript{30}O\textsubscript{3} requires C, 81·1; H, 7·2\%). The alcoholic solution turned dark brown with ferric chloride.

6-Hexyl-7-henzyloxyflavone (VI; R = n-hexyl).—The oxidation of the chalkone (16 g.) with selenium dioxide (18 g.) resulted in an oil, which

\textsuperscript{11} Dohme, Cox and Miller, Jour. Amer. Chem. Soc., 1926, 48, 1688.
solidified on cooling, and the colourless needles (4 g.) from glacial acetic acid melted at 120° (Found: C, 81·5; H, 6·9. $\text{C}_{28}\text{H}_{22}\text{O}_3$ requires C, 81·5; H, 6·7%)

6-Hexyl-7-hydroxyflavone (II; $R = n$-hexyl).—Colourless needles from alcohol, m.p. 191-192° (Found: C, 78·5; H, 6·9. $\text{C}_{21}\text{H}_{22}\text{O}_3$ requires C, 78·3; H, 6·8%). The alcoholic solution was unchanged in colour by the addition of ferric chloride and the colourless solution in sulphuric acid showed a blue fluorescence. The acetyl derivative, colourless needles from alcohol, melted at 104° (Found: C, 75·5; H, 6·6. $\text{C}_{23}\text{H}_{24}\text{O}_4$ requires C, 75·8; H, 6·6%).