207. *The Methylation of Alkyl* 3-*Alkyl*-2,4,6-*trihydroxyphenyl Ketones and the Structure of Xanthohumol.*

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With diazomethane 1-acetyl-2,4,6-trihydroxy-3-(3-methylbut-2-enyl)-benzene yields the 6-methoxy-, and not as stated the 4-methoxy-derivative. This can be used to prove our structure (I) for xanthohumol.

FOR xanthohumol, a chalcone found in hops, structure (I) was advanced[1] and confirmed[2] by us. Recently, however, Hübner and Riedl[3] proposed structure (II), their argumentation being that Robertson and Sandrock[4] proved methylation of 2,4,6-trihydroxy-1-isobutyryl-3-methylbenzene (VIII) with diazomethane to yield the 4-methoxy-derivative and that, by analogy, 1-acetyl-2,4,6-trihydroxy-3-(3-methylbut-2-enyl)benzene (III) should also give the 4-methoxy-compound (IVb). When the hydrolysis product of the substance obtained experimentally proved to be the hydrolysis product (Va) of xanthohumol they concluded that this degradation product had structure (Vb) and that the chalcone therefore

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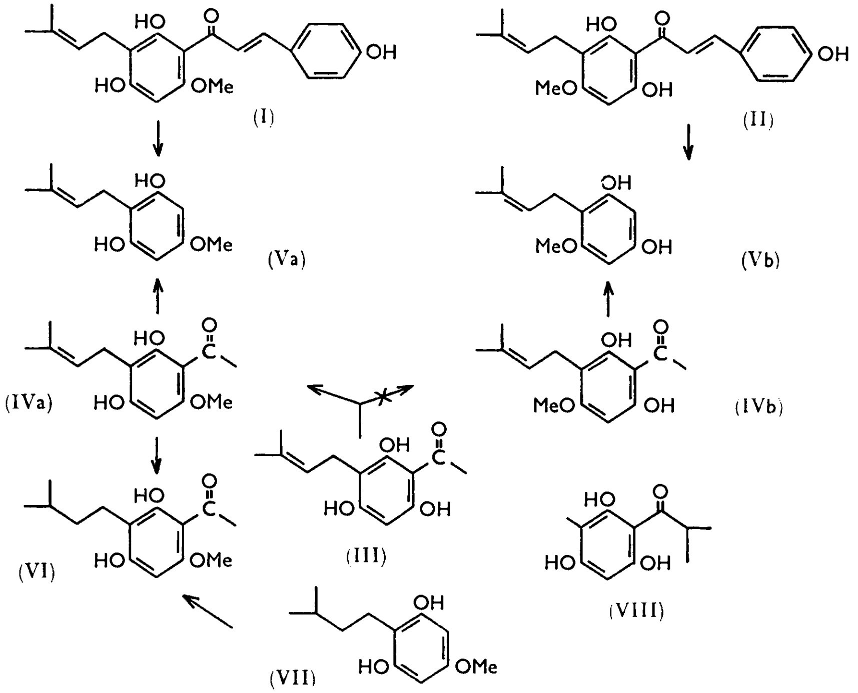
[1] Verzele, Stockx, Fontyn, and Anteunis, *Bull. Soc. chim. belges*, 1957, **66**, 452.

[2] Vandewalle and Verzele, *Bull. Soc. chim. belges*, 1959, **68**, 711.

[3] Hübner and Riedl, *Chem. Ber.*, 1960, **93**, 312.

[4] Robertson and Sandrock, *J.*, 1933, 819.

has structure (II). This particular methylation, however, produces the 6-methoxy-compound (IVa), as shown by the following facts.



Catalytic hydrogenation of the ether produces 1-acetyl-2,4-dihydroxy-3-isopentyl-6-methoxybenzene (VI) which is also obtained by a Hoesch synthesis with acetonitrile from 1,3-dihydroxy-2-isopentyl-5-methoxybenzene (VII), the identity being proved by m. p. and mixed m. p. and ultraviolet and infrared spectra. Proof of the structure of the starting material (VII) has been given earlier.[2] These facts support structure (I) for xanthohumol.

Additional proof that in this case the methylation produces the 6-methoxy-derivative comes from ultraviolet spectra. Aryl ketones with a free *p*-hydroxy-group have maximum absorption in alkaline solution at about 325 mμ, which they do not if the *p*-hydroxy-group is absent or blocked as methyl ether. This has been verified for (*a*) *p*-hydroxyacetophenone, phloracetophenone, 1-acetyl-2,4,6-trihydroxy-3-(3-methylbut-2-enyl)benzene, and the *o*-methyl ether of phloracetophenone,[5,6] and (*b*) *o*-hydroxyacetophenone, the *p*-methyl ether and the 2,4-dimethyl ether of phloracetophenone,[5,6] and 1-acetyl-2-hydroxy-4,6-dimethoxy-3-(3-methylbut-2-enyl)benzene. The monomethylation product of 1-acetyl-2,4,6-trihydroxy-3-(3-methylbut-2-enyl)benzene under discussion in this paper shows maximum absorption in an alkaline medium at 327 mμ.

There is a simple explanation for the differing methylation of phenols (III) and (VIII). The 3-methylbut-2-enyl-group in the former is large in comparison with the methyl group in the latter; and the acetyl group is small in comparison with the isobutyryl group. Orientation is therefore based on steric rather than inductive or mesomeric influences.

EXPERIMENTAL

1-*Acetyl*-2,4-*dihydroxy*-3-*isopentyl*-6-*methoxybenzene* (VI).—(1) On hydrogenation in presence of 5% platinum–charcoal in methanol the ether (IVa) (0·105 g.) absorbed 1 mol. of hydrogen

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[5] Sonn, *Ber.*, 1928, **61**, 2300.

[6] Sonn and Bülow, *Ber.*, 1925, **58**, 1691.

in 4 min. The catalyst was filtered off and water added to produce crystallization. Recrystallized from benzene, the product (VI) (65 mg.) melted at 184—185°.

(2) Dry hydrogen chloride was passed for 30 min. through a solution of 1,3-dihydroxy-2-isopentyl-5-methoxybenzene (VII) (0·32 g.), acetonitrile (0·06 g.), and anhydrous zinc chloride (0·21 g.) in dry ether (15 ml.). The mixture was left overnight at 0°. Hydrogen chloride was again passed through the solution for 30 min. and the whole kept for 24 hr. at 0°. After removal of the ether, the imine hydrochloride was boiled for 1 hr. with water (20 ml.). 2,4-*Dihydroxy*-3-*isopentyl*-6-*methoxyacetoph–one* was precipitated on cooling and, recrystallized from benzene, had m. p. 186° alone or mixed with the above product (yield, 0·17 g., 45%) (Found: C, 66·6, 67·4; H, 7·7, 7·9. $C_{14}H_{20}O_4$ requires C, 66·7; H, 7·9%).

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