The Total Synthesis of (±)-Guaiol

By G. L. BUCHANAN* and G. A. R. YOUNG

(*Department of Chemistry, The University of Glasgow, Glasgow* W.2.)

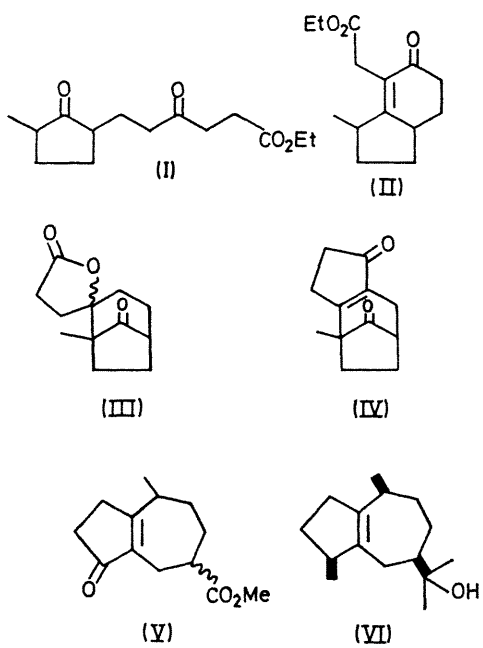
Summary (±)-Guaiol has been synthesised from 2-methylcyclopentanone and 4-oxovaleric acid *via* a bicyclo[3,2,1]-octanone intermediate.

BRIDGE scission of bridged bicyclic compounds provides a useful route to particularly substituted medium-sized rings,[1] although the reaction has been little used as a synthetic method. We report here its application to the total synthesis of (±)-guaiol.†

The Mannich base of 4-oxovaleric ester[2] condensed with 2-methylcyclopentanone under thermal Michael conditions[3] to give (I) (68%), free from the 2,2-disubstituted isomer. Under a variety of conditions (NaOMe; BF_3; toluene-*p*-sulphonic acid), cyclisation of this diketone afforded the $\alpha\beta$-enone (II) [λ_{max} 243 nm (ϵ 12,100), ν_{max} (CCl_4) 1732 and 1664 (C=O) cm^{-1}]. However, stirring at room temperature with 10N-HCl brought about ester hydrolysis and aldol cyclisation, the product being trapped by lactonisation to (III) (80%) as a mixture of two isomers [ν_{max} (CCl_4) 1780 and 1750 (C=O) cm^{-1} and 1772 and 1758 (C=O) cm^{-1}].

The principal factor governing the cyclisation of 1,5-diketones of this type to bridged rather than fused bicycles appears to be the presence of substituents at the developing ring-junction.[4] However, the foregoing results indicate that the bridged product is the *first* formed in a rapid reversible step and justifies our tentative suggestion[5] that the bridged bicycles are kinetically favoured whereas the fused $\alpha\beta$-enones are the products of thermodymamic control.

The spiro-lactones (III), separately or as a mixture, were converted into (IV) [λ_{max} 247 nm (ϵ 9000), ν_{max} (CCl_4) 1760 and 1705 (C=O) cm^{-1}] and then (V) [λ_{max} 237 nm (ϵ 11,900), ν_{max} (CCl_4) 1735 and 1704 (C=O) cm^{-1}] by successive treatment with polyphosphoric acid and NaOMe. The final product was a 1:1 mixture of stereoisomers, inseparable by t.l.c. or g.l.c., but discernible by n.m.r. This mixture was treated with methyl-lithium and on mild dehydration followed by reduction (H_2/5% Pd–C) of the crude product yielded a mixture of isomers, separable by g.l.c. One of these was identical (g.l.c. and mass spectrum) with natural guaiol (VI).



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† Since this manuscript was submitted, a more stereoselective but more arduous synthesis has been published (J. A. Marshall, A. E. Greene, and R. Ruden, *Tetrahedron Letters*, 1971, 855; J. A. Marshall and A. E. Greene, *ibid.*, p. 859).

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[5] Ref. 1, p. 207.