α-Ketol Rearrangements Involving Small Rings: the Formation and Rearrangement of 1-Hydroxy-6-isopropylbicyclo[3.2.0]heptan-7-one

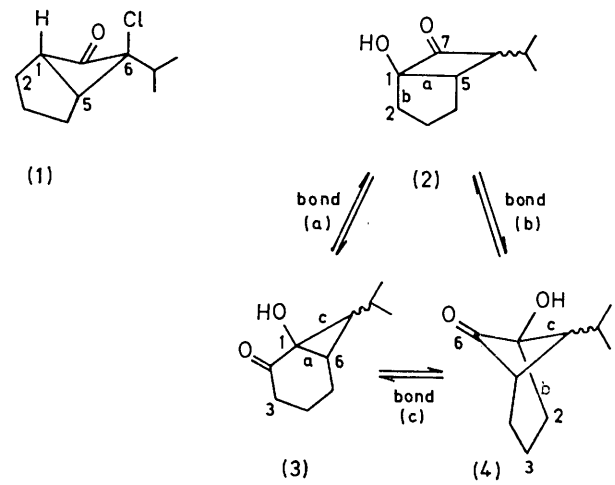
By PETER R. BROOK and DAVID E. KITSON
(*Department of Organic Chemistry, The University, Leeds* LS2 9JT)

Summary 1-Hydroxy-6-isopropylbicyclo[3.2.0]heptan-7-one (**2**) is formed by ciné-substitution of the corresponding 6-*exo*-chlorobicycloheptan-7-one (**1**), and is shown to be in equilibrium with 1-hydroxy-7-isopropylbicyclo[4.1.0]-heptan-2-one (**3**) by basic catalysis; ^{14}C-tracer studies show that 1-hydroxy-7-isopropylbicyclo[3.1.1]heptan-6-one (**4**) is to a lesser extent involved in the α-ketol rearrangements.

ALTHOUGH α-ketol rearrangements involving cyclobutane- and cyclopropane-derivatives are known,[1] there has been little investigation of their scope. We now report the steric course of such rearrangements within the bicyclo[3.2.0]-heptane system.

6-Chloro-6-*endo*-isopropylbicyclo[3.2.0]heptan-7-one (**1**), when shaken with 2M sodium hydroxide for 30 h gave mainly the 1-alcohol (**2**) (50%) and a little of the unrearranged 6-alcohol (2%). Ciné-substitution[2] giving (**2**) presumably involves near-concerted loss of the diaxially disposed H-1 and Cl-6 from (**1**) to give the zwitterionic Favorski intermediate which is then attacked by either solvent or hydroxide ion at C-1 to yield the most stable enolate ion (towards C-6). Structural proof for both the 1-alcohol (**2**) and the 6-alcohol was obtained by treatment of each with hydroxylamine (1 equiv.) at pH 5·9; each oxime underwent the abnormal Beckmann rearrangement with remarkable ease (overnight on steam-bath), to give respectively 2-(2-oxocyclopentyl)-3-methylbutyronitrile and 2-isobutyroylcyclopentanecarbonitrile, each synthesised by an unambiguous route.

The α-ketol (**2**), after chromatographic separation, appeared homogeneous by t.l.c. and g.l.c., but spectroscopic evidence suggested the presence of a second α-ketol, 1-hydroxy-7-isopropylbicyclo[4.1.0]heptan-2-one (**3**) (*ca.* 20%). Thus the i.r. spectrum of chromatographically pure (**2**) showed two carbonyl peaks (ν_{max} 1765 and 1670 cm^{-1}) and its ^{13}C n.m.r. spectrum showed double the ten peaks



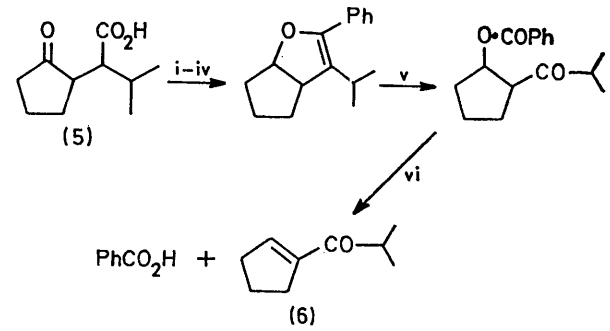
expected for (**2**). Also the α-ketol (**2**) isolated in this way gave a major and a minor 3,5-dinitrobenzoate (DNB) which after spectroscopic comparison were assigned as esters of (**2**) and (**3**) respectively.† Finally, preparation of (**2**) from the 6-chloro-derivative (**1**), using NaOD–D_2O gave 'chromatographically pure' (**2**) containing *three* deuterium atoms (after removal of labile-OD). This can be accounted for if a base-catalysed equilibration of the two α-ketols (**2**) and (**3**) occurs so that deuterium exchange replaces H-6 in (**2**) and 2 × H-3 in (**3**). This equilibrium must also be readily established during chromatography. The bond (a) which migrates in the conversion of the ketol (**2**) into the ketol (**3**) is not well placed to give good overlap stereoselectronically with the π-system of the carbonyl group, even when the cyclobutanone ring is in a non-planar conformation. Bond (b) of (**2**) is better placed for the α-ketol bond shift, yet the product of this alternative rearrangement, 1-hydroxy-7-isopropyl-

† major O-DNB ν_{CO} 1780 and 1730; minor O-DNB ν_{CO} 1745 and 1700 cm^{-1}. δ(^{13}C-1) major O-DNB 98·69; minor O-DNB 68·35 p.p.m. (cyclopropyl carbon).

bicyclo[3.1.1]heptan-6-one (**4**) was not detected either spectroscopically or as a 3,5-dinitrobenzoate. Possibly the greater ring-strain in the system (**4**) relative to isomers (**2**) and (**3**) precludes it as a major component of the equilibria. Starting from (**3**), migration of bond (c) which leads to (**4**) looks as likely as the observed shift of bond (a) to give (**2**).‡

One subtle consequence of such interconversions is that the ketol (**2**) after conversion first into (**4**) [shift of bond (b)] then (**3**) [shift of bond (c)] then back into the ketol (**2**) [shift of bond (a)] has interchanged the original C-1 and C-7. Any mixing of C-1 and C-7 of (**2**) can therefore be taken as strong support for the presence of three ketols (**2**), (**3**), and (**4**) in equilibria. We have demonstrated such mixing in the following way.

Labelled (±)-[1-^{14}C]valine was converted into 2-chloro-3-methylbutyroyl chloride and thence into the bicyclic chloro-ketone (**1**), labelled at C-7.[3] Ciné-substitution of this ketone with lithium benzyloxide—benzyl alcohol yielded the 1-benzyloxyketone[4] [(**2**) but with $PhCH_2O$ replacing OH]. Hydrogenolysis then gave the 1-hydroxy-ketone (**2**) [contaminated with isomer (**3**); $2\nu_{CO}$ i.r. absorptions]. Half of this hydrogenolysis product was immediately cleaved by metaperiodate into the keto-acid (**5**) (part A). The second half (part B) was cleaved in the same way, after equilibration with 2M sodium hydroxide for 18 h. Both samples of the keto-acid (**5**) were then degraded (see Scheme) allowing the original C-7 of the ketol (**2**) to be isolated as benzoic acid, with the remaining carbons intact in the $\alpha\beta$-unsaturated ketone (**6**). The activity of each sample was measured directly by liquid scintillation counting, with use of an internal standard, except for the ketone (**6**) which was isolated as its 2,4-dinitrophenylhydrazone (DNP), then burnt and counted as CO_2§ (*ca.* 90% efficiency). The values, reported as μCi mol^{-1}, were: (±) valine **92**; keto-acid (**5**), (A) **97**; (B) **94**; benzoic acid, (A) 85; (B) **47**; DNP of (**6**), (A) 6; (B) **47**.



SCHEME. Reagents: i, $NaBH_4$; ii, 10 M-HCl; iii, PhMgBr; iv, *p*-$MeC_6H_4SO_3H$–C_6H_6; v, H_2CrO_4, Jones' reagent; vi, 25% NaOH.

The base-catalysed equilibration of labelled (**2**) therefore shares the activity between C-7 and the remainder of the molecule, and the activity not found in the benzoic acid is assumed to be at the β-olefinic carbon of the $\alpha\beta$-unsaturated ketone (**6**) which was originally C-1 of the ketol (**2**) (see above). As mixing occurred to some extent in part (A) without basic catalysis, it is suggested that the equilibria are readily established, but, of the three ketols, (**4**) is thermodynamically less favoured than (**2**) or (**3**).

(*Received, 20th October* 1977; *Com.* 1092.)

‡ Stereoelectronically (in **3**), overlap the of migrating bonds (a) and (c) with the carbonyl π-system varies with the conformation of the cyclohexanone ring.

§ We thank Dr. E. R. Clark, Department of Pharmacology, Leeds University, for assistance in the combustion of these samples and trapping the CO_2.

[1] J. M. Conia and M. J. Robson, *Angew. Chem. Internat. Edn.*, 1975, **14**, 481.
[2] (a) P. D. Bartlett and T. Ando, *J. Amer. Chem. Soc.*, 1970, **92**, 7518; (b) D. L. Garin and K. L. Canmalk, *J.C.S. Chem. Comm.*, 1972, **333**; (c) P. R. Brook and J. M. Harrison, *ibid.*, p. 997; (d) W. T. Brady and J. P. Heeble, *J. Org. Chem.*, 1971, **36**, 2033.
[3] P. R. Brook, A. J. Duke, J. M. Harrison, and K. Hunt, *J.C.S. Perkin I*, 1974, 927.
[4] For related reactions, see ref. 2(b).

Printed by Heffers Printers Ltd Cambridge England