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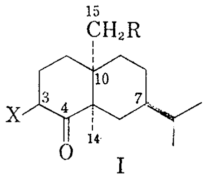
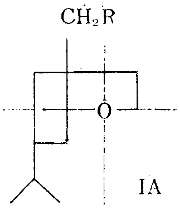
Conformation of Valeranone and Derivatives

The structure and absolute stereochemistry of valeranone (I; R=H, X=H) and kanokonol (I; R=OH, X=H) were first correctly deduced by the authors[1,2] who have taken an interest in the conformational analysis of the compounds in the valeranone series. The conformation of valeranone has been discussed in relation to the interpretation of its optical rotatory dispersion curve[3~6]; however, no definite conclusion has hitherto been drawn. This communication is concerned with the conformation of valeranone and its derivatives.

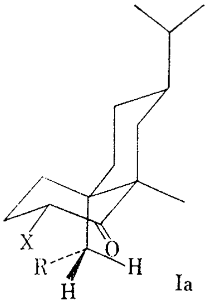
Due to the flexible nature of a *cis*-decalone, besides some possible conformations with a twist form, at least the two interchangable all-chair conformations, Ia (X=H) and Ib (X=H), need to be considered for this series. In these two conformations, however, the latter (Ib) can be excluded by the following evidence. Coprostan-4-one, in which the carbonyl group is situated in the same relative environment but without an α-axial methyl as that of the conformer (Ib), gives a weak positive Cotton effect (a, +3).[7] Because the contribution of an adjacent axial methyl group to the amplitude is fairly strong,[8] the Cotton effect of the conformer (Ib) is expected to be positive. In contrast, however, these ketones are found to exhibit a large negative Cotton effect*[1] (a, −141 for valeranone, a, −149 for kanokonol, and a −124 for kanokonyl acetate). Further, in the nuclear magnetic resonance spectra,*[2] the differences in the C-14 methyl proton signals are observed to be 0.13 p.p.m.[1] between valeranone and valerane



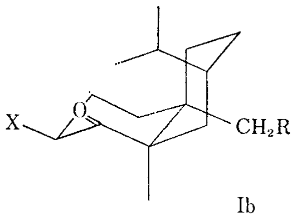
I



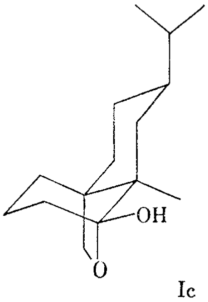
IA



Ia



Ib



Ic

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*[1] ORD curves were measured in MeOH solution.

*[2] NMR spectra were determined at 60 Mc. in CCl_4 solution.

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(deoxovaleranone), 0.19 p.p.m. between kanokonol and deoxokanokonol, and 0.13 p.p.m. between kanokonyl acetate and deoxokanokonyl acetate. These values also eliminate the conformer (Ib) in which the difference should fall in the range of 0.35~0.40 p.p.m. by analogy with the differences in the C-19 methyl proton signals between 1-oxo- and 1-deoxo-steroids.[9]

Since the Cotton curves of valeranone, kanokonol, and its acetate are essentially the same, this is good evidence that all these compounds are in the same conformation.

If the ketones have the conformation Ia, an intramolecular hydrogen-bond may be expected to exist between the C-15 hydroxyl and the C-4 carbonyl group in kanokonol. Precise measurement of the infrared spectrum*[3] of kanokonol (0.2~0.001M), however, showed the absence of such a hydrogen-bond (*vide infra*).

The monobromo-derivatives were, therefore, prepared: *viz.* monobromovaleranone (I; R=H, X=Br),[3] $C_{15}H_{25}OBr$,*[4] m.p. 99~99.5°, $[\alpha]_D$ $-26.6°$ ($CHCl_3$), and monobromokanonyl acetate (I; R=OAc, X=Br), $C_{17}H_{27}O_3Br$, m.p. 86~87°, $[\alpha]_D$ $-81.8°$ ($CHCl_3$). Essentially the same optical rotatory dispersion curves (a, −121 and a, −109, respectively) also indicate that both the monobromoketones are in the same conformation. The equatorial nature of the bromine atom in these bromoketones is shown by the shift of the carbonyl absorption in their infrared spectra to lower wave-length (1724 and 1726 cm^{-1}, respectively) with respect to the parent ketones (1704 cm^{-1}), and by the coupling constants of the C-3 hydrogen signals in their nuclear magnetic resonance spectra (J_1=12, J_2=6 and J_1=11, J_2=8 c.p.s., respectively).

As a negative Cotton effect excludes the conformation Ib (X=Br), the monobromoketones must exist in the conformation Ia (X=Br). Comparison of the rotatory dispersion curves of the bromo-ketones with those of the parent ketones reveals that both series have the same conformation because the former with wave-length for Cotton effect unchanged fit well for equatorially brominated ketones and the differences in amplitude are of the kind that might be expected in terms of the Octant rule.[6] Therefore, it follows that the conformation of valeranone, kanokonol, and its acetate is expressed by projection Ia.

Although no evidence about the conformation of the non-oxygenated ring is available, the above conclusions are based on the assumption that this ring will be in the chair form so as to keep the C-7 isopropyl group equatorial. However, this is not unreasonable since there are no grounds why this ring should be twisted.

The large negative Cotton effect of valeranone, kanokonol, and kanokonyl acetate has then to be accounted for by the contribution related to the conformation Ia (octant diagram IA). This conclusion is confirmed by the close similarity of the optical rotatory dispersion curves with that of methyl 1-oxo-5β-etianate (a, −136),[10] the environment of the carbonyl groups being the same.

The presence of an appreciable amount of the hemiketal form (Ic) in kanokonol is excluded by measurement of its nuclear magnetic resonance spectrum which shows this compound to be homogenous. Furthermore, the C-15 methylene protons appear as an AB quadruplet[2] which indicates that rotation about the C(10)-C(15) bond is restricted. Due to this steric hindrance, therefore, all or almost all of the C-15 hydroxyl group may be oriented in the energetically most advantageous position, as shown in projection Ia (R=OH, X=H). This is probably the reason for the absence of chelation between the C-15 hydroxyl and the C-4 carbonyl group (*vide supra*).

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*[3] IR spectra were measured in 0.1M CCl_4 solution with a Beckman IR-7 spectrophotometer unless otherwise stated.

*[4] Analytical values are in good accord with the molecular formulae shown.

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Recently, Hartshern, *et al.*,[11] on comparing the optical rotatory dispersion curve of valeranone with those of 5-methylcoprostan-4-one (a, -75) and methyl 1-oxo-5β-etianate (a, -136),[10] suggested that the preferred conformation of valeranone is related to projection Ia (R=H, X=H); an assumption which is in agreement with the present conclusion.

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Structure of Cyperotundone

From the tuber of nutgrass (*Cyperus rotundus* LINNÉ) of Japanese origin, a new sesquiterpenoid ketone has been isolated for which the name cyperotundone is proposed.*1 The present communication provides evidence that cyperotundone is represented by formula I.

Cyperotundone (I), $C_{15}H_{22}O$, m.p. 46~47.5°, $[\alpha]_D$ $+40.4°$,*2 was characterized as the 2,4-dinitrophenylhydrazone, $C_{21}H_{26}O_4N_4$, m.p. 224~225°. The spectral properties [$\lambda_{\max}^{\text{EtOH}}$ 245 mμ (log ε 3.96), $\nu_{\max}$ 1706, 1667 cm^{-1}, no vinyl proton signal in the ketone (I) and $\lambda_{\max}^{\text{EtOH}}$ 396 mμ (log ε 4.76) in its 2,4-dinitrophenylhydrazone] are those of a fully-substituted α,β-unsaturated ketone in a five-membered ring. The presence of a methyl group at the α-position on the double bond in cyperotundone is indicated by a vinyl methyl signal at 8.33 τ in the nuclear magnetic resonance spectrum. A band at 1412 cm^{-1} in the infrared spectrum of the ketone (I) suggests the presence of a methylene grouping adjacent to carbonyl. This is confirmed by the following evidence. Lithium aluminum hydride reduction of the ketone (I) gave the alcohol (II; R=H), $C_{15}H_{24}O$, m.p. 136°, $[\alpha]_D$ $-37.7°$, $\nu_{\max}$ 3205 cm^{-1} (hydroxyl), which on manganese dioxide oxidation regenerated the ketone (I). The nuclear magnetic resonance spectra of the alcohol (II; R=H) and its acetate (II; R=Ac), $C_{17}H_{26}O_2$, n_D^{25} 1.508, $[\alpha]_D$ $-28.3°$, show that the proton in the -C$\underline{H}$(OR)-moiety is coupled with a pair of the adjacent methylenic protons.

Hydrogenation of the ketone (I) over palladized carbon in ethanol yielded the saturated dihydro-derivative (III), mol. wt. 220 (mass spec.), $C_{15}H_{24}O$, m.p. 83~84°, $[\alpha]_D$ $-9.9°$. The infrared spectrum shows the presence of a cyclopentanone (1736 cm^{-1}) and a methylene adjacent to carbonyl (1412 cm^{-1}). Base-catalyzed deuteration of the ketone (III)

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*1 Details of the isolation will be published elsewhere.

*2 All compounds analyzed correctly. Rotations were measured in $CHCl_3$ solution and IR spectra in KBr disk unless noted otherwise. NMR spectra were determined in CCl_4 solution with $(CH_3)_4Si$ as internal standard.