Studies in Restricted Rotation. Part I. Barrier to Rotation in Some 3-Arylcyclohexenone Derivatives

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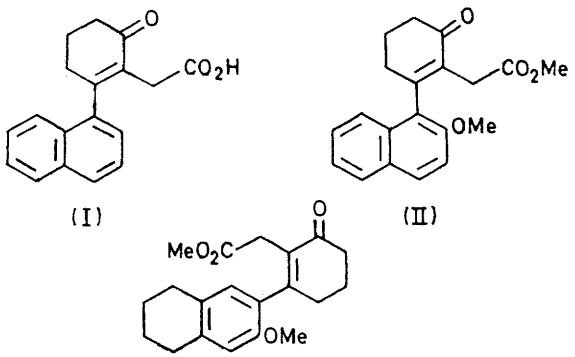
Temperature dependence of the n.m.r. spectra of three 2-aryl-6-oxocyclohex-1-enylacetic acid derivatives (I)—(III) has been studied and the free energy of activation of internal rotation about the aryl–cyclohexenone bond in each determined from the coalescence temperature. The 1-naphthyl derivative (I) possesses an appreciable energy barrier (*ca.* 22 kcal mol^{-1}) which is lowered considerably by the introduction of a methoxy-group adjacent to the pivot bond [as in (II)]. Some plausible explanations are suggested.

DYNAMIC n.m.r. provides an excellent tool for determining energy barriers in restricted rotation about single bonds in different molecules.[1] Of late, this has been extensively used in biphenyl derivatives, *o,o'*-bridged [2] or otherwise,[3] and valuable information has been obtained regarding the effect of substituents on the rotational barrier.[4] When the internal rotation is slow on the n.m.r. time scale, appropriately placed methylene protons or geminal methyls in the molecule become non-equivalent (diastereoisotopic) giving rise to an AB spectrum. Study of the change in line shapes of these signals with temperature furnishes kinetic data involving the internal rotation. During our recent study of some 3-arylcyclohexenone derivatives,[5] it was noted that 2-(1-naphthyl)-6-oxocyclohex-1-enylacetic acid (I) showed an AB quartet in the n.m.r. spectrum for the side chain methylene protons which did not coalesce up to 155°. It appeared to be a case of hindered rotation about an aryl–cyclohexenone bond with a high energy barrier. We decided to investigate some of



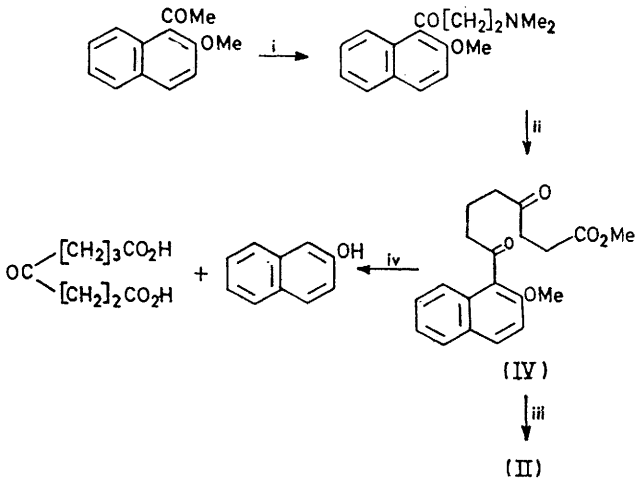
(I) (II)

(III)

these ketones (I)—(III) by dynamic n.m.r. in order to see whether rotation in any of them could be sufficiently restricted to permit resolution into enantiomers. Our other objective was to study the effect of a methoxy-substituent adjacent to the pivot bond on the barrier height.

RESULTS AND DISCUSSION

2-(1-Naphthyl)-6-oxocyclohex-1-enylacetic acid (I) and methyl 2-(5,6,7,8-tetrahydro-3-methoxy-2-naphthyl)-6-oxocyclohex-1-enylacetate (III) have been previously reported.[5] Methyl 2-(2-methoxy-1-naphthyl)-6-oxocyclohex-1-enylacetate (II) was synthesised by a slight variation of the general method.[6] In this con-



SCHEME Reagents and conditions: i, heating with dimethylamine hydrochloride and paraformaldehyde in ethanol; ii, treatment with methyl iodide, heating with ethyl β-oxoadipate and potassium ethoxide, and esterification with methanolic 3% hydrogen chloride; iii, potassium t-pentoxide in benzene; iv, heating with HCl–AcOH.

[1] G. Binch, ' Topics in Stereochemistry,' eds. E. L. Eliel and N. L. Allinger, Interscience, New York, 1968, vol. 3, p. 97.

[2] R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, 1964, **40**, 2426; K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, *J. Amer. Chem. Soc.*, 1964, **86**, 1710; M. Oki, H. Iwamura, and N. Hayakawa, *Bull. Chem. Soc. Japan*, 1963, **36**, 1542; 1964, **37**, 1865; M. Oki and H. Iwamura, *Tetrahedron*, 1968, **24**, 2377; I. O. Sutherland and M. V. J. Ramsay, *ibid.*, 1965, **21**, 3401.

[3] W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, 1963, **85**, 2170; for other similar systems see H. O. House, W. J. Campbell, and M. Gall, *J. Org. Chem.*, 1970, **35**, 1815; H. O. House, D. G. Koepsell, and W. J. Campbell, *ibid.*, 1972, **37**, 1003; R. M. Acheson and I. A. Selby, *J. Chem. Soc.* (*C*), 1971, 691; J. J. Bergman and W. D. Chandler, *Canad. J. Chem.*, 1970, **50**, 353.

[4] M. Oki, H. Iwamura, and G. Yamamoto, *Bull. Chem. Soc. Japan*, 1971, **44**, 262, 266; M. Oki. K. Akashi, G. Yamamoto, and H. Iwamura, *ibid.*, 1971, **44**, 1683.

[5] D. Nasipuri and A. Bhattacharya, *Indian J. Chem.*, 1972, **10**, 799.

[6] D. Nasipuri, A. C. Chaudhuri, and J. Roy, *J. Chem. Soc.*, 1958, 2734; D. Nasipuri and J. Roy, *ibid.*, 1960, 1571.

nection, an unusual deacylation reaction of the dioxo-ester (IV) under acidic condition was also recorded (Scheme). The methyl esters (II) and (III) were easily crystallisable and hence were used in dynamic n.m.r. experiments instead of the acids.

The two methylene protons of the acetate side chain in each of the compounds (I)—(III) appeared as an AB quartet at τ *ca.* 7·0 at ambient temperatures. J_{AB} and $\Delta\nu_{AB}$ were calculated in the usual way [7] from the first three peaks which were clearly discernible in all the spectra and which were more or less unchanged in different solvents. The approximate exchange rate, k_c, and the free energy barrier to configurational inversion, $\Delta G^{\ddagger}$, at the coalescence temperature, T_c, were calculated using the equations (1) and (2).[8] The n.m.r.

$$k_c = \pi[(\Delta\nu_{AB}^2 + 6J_{AB}^2)/2]^{\frac{1}{2}} \quad (1)$$

$$\Delta G^{\ddagger} = 4{\cdot}57\ T_c\ (10{\cdot}32 + \log T_c/k_c) \quad (2)$$

data and free energy of activation are given in the Table. Spectra of two compounds [(I) and (III)] at different temperatures are shown in Figures 1 and 2.

In the absence of full line shape analysis of the spectra, the measurements are at present confined to the calculation of free energy barriers to conformational inversion at the coalescence temperatures. The significance of the values is limited by the fact that their temperature dependence is not known. On the other hand, the enthalpy and entropy of activation derived from n.m.r. line shape analysis using approximate equations are subject to large systematic errors.[9] For comparison purposes, therefore, $\Delta G^{\ddagger}$ values may be considered as a good approximation to the energy barrier to inversion assuming that $\Delta S^{\ddagger}$ is negligible.

N.m.r. parameters * and free energies of activation of rotation in compounds (I)—(III)

Compound	Frequency (MHz)	Solvent	$\Delta\nu_{AB}$/Hz	J_{AB}/Hz	T_c/°C	k_c/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
(I)	60	$PhNO_2$	17·0	17·0	165	100·0	21·9 ± 0·2
		Ph_2O	16·0	18·0			
		$CDCl_3$	17·0	17·0			
		CCl_3CHCl_2	19·0	16·5			
		$CHBr_3$	20·0	16·5			
(I)	100	$CDCl_3$	29·0	17·0			
(II)	60	$CDCl_3$	10·5	17·0	45	95·5	15·8 ± 0·2
(III)	100	$CDCl_3$	24·0	17·0			
		CCl_3CHCl_2	27·0	17·0	50	110·0	15·9 ± 0·2

* The spectral changes are reversible with temperature.

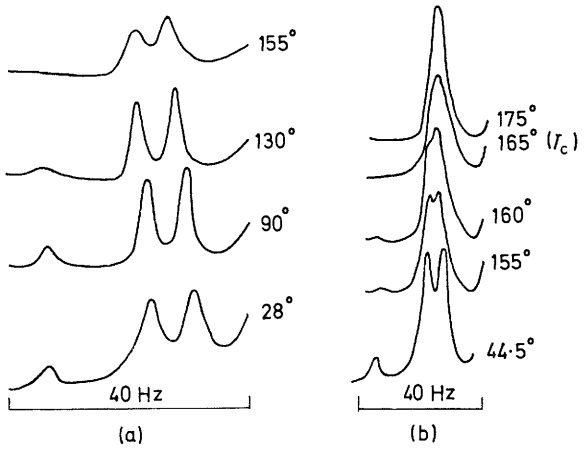


FIGURE 1 60 MHz Variable-temperature n.m.r. spectra of the keto-acid (I) in CCl_3CHCl_2 (a) and in $PhNO_2$ (b)

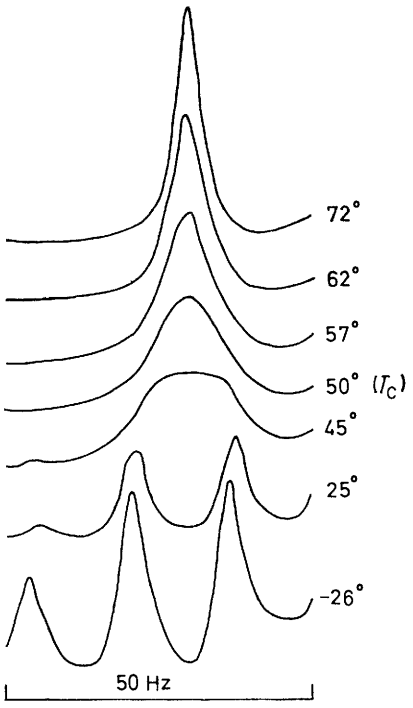


FIGURE 2 100 MHz Variable temperature n.m.r. spectra of compound (III) in CCl_3CHCl_2

The data in the Table show that compound (I) has an appreciable energy barrier (*ca.* 22 kcal mol^{-1}) consistent

[7] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 129.

[8] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959; also see refs. 2 and 4.

[9] A. Allerhand, H. S. Gutowsky, J. Jones, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 1966, **88**, 3185.

with the behaviour of other sterically hindered 1-naphthyl derivatives [10] and is possibly capable of resolution into stable enantiomeric forms.[11] The comparatively low barrier (*ca.* 16 kcal mol^{-1}) for compound (III) is also expected; the methoxy-group adjacent to the pivot bond apparently creates sufficient steric interference in an otherwise unhindered molecule to slow down the inversion on the n.m.r. time scale. The case of the 2-methoxy-1-naphthyl derivative (II) is, however, atypical. The adjacent methoxy-group instead of increasing the energy barrier, as normally expected, decreases it considerably (from 22 to 16 kcal mol^{-1}). *A priori*, at least three factors may be considered to be responsible for lowering the activation energy in the compound (II): (i) stabilisation of the planar transition state by interannular resonance through the methoxy-group, (ii) out-of-plane bending of the axis leading to a distorted transition state [12] in which the usual steric interactions are minimised, an operation made easy in this case by the increased electron density at the 1,1'-positions [13] on account of the methoxy-group, and (iii) an increase of ground state energy in the normal non-planar molecule due to steric and/or electronic reasons. The significance of the first two factors has already been demonstrated by Oki *et al.*[4] in biphenyl systems studied by dynamic n.m.r. But the difference in the activation energy due to them is not as high as in the present case. The major contribution in lowering the barrier energy may therefore be looked for elsewhere, perhaps in the raising of the ground state energy of compound (II) by some obscure structural features. More data are necessary before any definite conclusion can be drawn.

EXPERIMENTAL

^1H N.m.r. spectra were measured with Varian A-60, T-60, and HR-100 spectrometers for [^2H]chloroform solutions unless otherwise stated; chemical shifts (τ) are reported relative to tetramethylsilane as internal standard. Light petroleum refers to the fraction b.p. 40—60°. Organic solutions were dried over anhydrous sodium sulphate.

1-*Acetyl*-2-*methoxynaphthalene*.— 1-Acetyl-2-methoxynaphthalene was prepared according to the method of Fries.[14] It crystallised from light petroleum in light yellow plates, m.p. 58°.

2-*Dimethylaminoethyl* 2-*Methoxy*-1-*naphthyl Ketone*.—A mixture of 1-acetyl-2-methoxynaphthalene (15·6 g, 0·078 mol), dimethylamine hydrochloride (6·4 g, 0·078 mol), paraformaldehyde (3·6 g), absolute ethanol (22 ml), and concentrated hydrochloric acid (0·3 ml) was refluxed for 6 h. The amino-ketone was worked up in the usual way [6] and obtained as an oil which was used in the next operation without further purification.

Methyl 8-(2-*Methoxy*-1-*naphthyl*)-4,8-*dioxo-octanoate* (IV).—To an ice-cold solution of the foregoing amino-ketone (12·8 g, 0·05 mol) in dry benzene (60 ml), methyl iodide (3·4 ml, 0·05 mol) was added dropwise with stirring and the mixture left overnight. To the methiodide so formed, a solution of ethyl β-oxoadipate [15] (12·0 g, 0·056 mol) in benzene (30 ml) was added dropwise followed by a solution of potassium (3·25 g, 0·081 mol) in ethanol (40 ml). The mixture was stirred at room temperature for 4 h and then refluxed for 1 h. The product was worked up in the usual way and hydrolysed with a refluxing solution of potassium hydroxide (9·0 g) in water (100 ml) under nitrogen for 4 h. The crude dioxo-acid (11·3 g) was heated with methanolic 3% hydrogen chloride to furnish the *dioxo-ester* (IV) (10·2 g, 60%) as an oil, b.p. 210—220° at 0·2 mmHg (Found: C, 70·4; H, 6·7. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%). It afforded a *monodinitrophenylhydrazone*, m.p. 165—166° (Found: C, 59·4; H, 5·1; N, 10·7. $C_{26}H_{26}N_4O_8$ requires C, 59·8; H, 5·0; N, 10·7%); τ (100 MHz) −1·22 (1H, s, ArNH), 0·94 (1H, d, J 3 Hz, 3-ArH), 1·72 (1H, 2d, J 9 and 3 Hz, 5-ArH), 2·00—2·78 (7H, m, ArH), 6·02 (3H, s, OMe), 6·29 (3H, s, CO_2Me), 6·91 (2H, t, J 7 Hz, 2-H_2), 7·05—7·55 (6H, m, 3 × CH_2), and 7·70—8·00 (2H, m, 6-H_2).

The formation of the dioxo-acid in the above reaction is rather unusual, the normal product in similar reactions being the cyclised cyclohexenone derivative.[6] The failure of the condensation product to undergo aldol condensation is conceivably due to a steric factor.

The derived *dioxo-acid* [as (IV)] was chromatographed on a silica gel column and obtained as a transparent gum (Found: C, 69·45; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%); τ (100 MHz) 1·28br (1H, s, CO_2H, exchangeable with D_2O), 2·14—2·84 (6H, m, ArH), 6·12 (3H, s, OMe), 7·09 (2H, t, J 7 Hz, 2-H_2), 7·42 (6H, m, 3 × CH_2CO), and 7·97 (2H, m, 6-H_2).

Methyl 2-(2-*Methoxy*-1-*naphthyl*)-6-*oxocyclohex*-1-*enyl-acetate* (II).—The foregoing dioxo-ester (2·8 g, 8·2 mmol) was added to a solution of alcohol-free potassium t-pentoxide, prepared from potassium (0·32 g, 8·2 mmol), in benzene (55 ml). The solution was refluxed under nitrogen for 6 h, cooled, and decomposed with 1N-hydrochloric acid. The product was worked up in the usual way and sublimed at 150—160° and 0·4 mmHg to afford a gum (1·2 g). On chromatography over a column of silica gel (60—100 mesh), the *keto-ester* (II) was obtained as a crystalline solid (from benzene–light petroleum) (0·7 g), m.p. 101—102° (Found: C, 74·3; H, 6·5. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%); $\nu_{max.}$ (Nujol) 1723, 1665, and 1615 cm^{-1}; $\lambda_{max.}$ (EtOH) 275, 285, 295, and 305 nm (log ε 3·72, 3·81, 3·65, and 2·67); τ (100 MHz) 2·07—2·80 (7H, m, ArH), 6·12 (3H, s, OMe), 6·58 (3H, s, CO_2Me), 7·05 (2H, m, CH_2CO_2Me), 7·35 (4H, m, 3- and 5-H_2), and 7·75 (2H, m, 4-H_2). The 2,4-*dinitrophenylhydrazone* formed red needles (from benzene–methanol), m.p. 216—217° (Found: C, 62·0; H, 5·05; N, 11·2. $C_{26}H_{24}N_4O_7$ requires C, 61·9; H, 4·8; N, 11·1%).

Attempted Cyclisation of the Dioxo-acid [*as* (IV)] *with Acetic and Hydrochloric Acids*.—The dioxo-acid [as (IV)] (2·5 g) was refluxed with a mixture of glacial acetic acid (20 ml), hydrochloric acid (10 ml), and water (2 ml) under nitrogen for 4 h. Acetic acid was removed under reduced pressure and the residue taken up in ether. The ethereal solution was washed with aqueous sodium hydrogen

[10] R. Adams and L. O. Binder, *J. Amer. Chem. Soc.*, 1941, **63**, 2773.
[11] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 156.
[12] M. M. Harris and C. Cheung King Ling, *J. Chem. Soc.*, 1964, 1825.
[13] R. D. Kross, V. A. Fassel, and M. Margoshes, *J. Amer. Chem. Soc.*, 1956, **78**, 1332.
[14] K. Fries, *Ber.*, 1921, **54B**, 709.
[15] *Cf.* M. Guha and D. Nasipuri, *Org. Synth.*, 1962, **42**, 41.

carbonate solution. The solid residue after evaporation of ether was chromatographed on a silica gel column and afforded methyl 2-naphthyl ether (0·1 g) and 2-naphthol (0·80 g) which were identified by mixed m.p. determination. The sodium hydrogen carbonate extract was acidified and evaporated to dryness. A sticky semisolid was obtained which was taken up in chloroform and finally crystallised from ethyl acetate–light petroleum to give 4-oxo-octanoic acid as plates (0·6 g), m.p. 132—133° (Found: C, 50·8; H, 6·7. Calc. for $C_8H_{12}O_5$: C, 51·1; H, 6·4%) (lit.,[16] m.p. 132·5—134·6°). The methyl ester obtained by treatment with diazomethane showed the following n.m.r. peaks: τ (100 MHz, CCl_4) 6·36 (6H, s, 2 × CO_2Me), 7·25—7·58 (6H, m, 2-, 3-, and 7-H_2), 7·70 (2H, t, J 7 Hz, 5-H_2), and 8·12 (2H, m, J 7 Hz, 6-H_2).

[16] R. C. Cope and W. R. Schmitz, *J. Amer. Chem. Soc.*, 1960, **72**, 3056.

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