Restricted Rotation. Part 3.[1] Barrier to Rotation in Methyl 2-(8-Quinolyl)-6-oxocyclohex-1-enylacetate: Comparative Study of the Effective Bulk of a Nitrogen Lone Pair in Quinoline and of a Naphthalene Hydrogen

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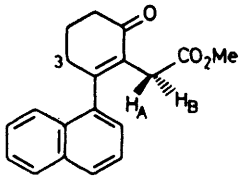
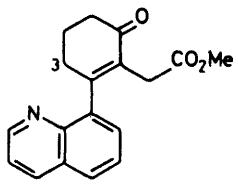
The rotational free energy barrier of methyl 2-(8-quinolyl)-6-oxocyclohex-1-enylacetate (2) about the aryl–cyclohexenone bond is found to be 75.7 kJ mol^{-1} by dynamic n.m.r. The value is lower than that (95.4 kJ mol^{-1}) for the corresponding 1-naphthyl derivative (1) indicating that the effective bulk of the nitrogen lone pair in quinoline is less than that of a naphthalene hydrogen. A similar study with methyl 2-(1-naphthyl)-5-oxocyclopent-1-enylacetate (4) shows that the energy barrier in this case is lower than 37.0 kJ mol^{-1}.

In previous papers,[1,2] the free energy of activation of restricted rotation about the aryl–cyclohexenone bond in a number of substituted arylcyclohexenones [*e.g.* (1)] was determined by dynamic n.m.r. from the coalescence temperature of the AB quartet of the side-chain methylene protons. The values in general correlated well with the size of aromatic substituents adjacent to the pivotal bond. The highest barrier (95.4 kJ mol^{-1}) was encountered in the 1-naphthyl-derivative (1) originating from a *peri*-interaction between 8-H of naphthalene and 3-H of the cyclohexenone moiety. The study has now been extended to a 8-quinolyl derivative (2) in which 8-H is replaced by a nitrogen lone pair with the idea that it will permit direct correlation of their effective bulks. The variable temperature n.m.r. spectra of methyl 2-(1-naphthyl)-5-oxocyclopent-1-enylacetate (4), a cyclopentenyl analogue, have also been examined to compare the steric situation between cyclopentenone and cyclohexenone systems.



(1)



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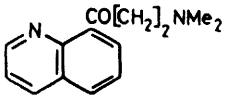

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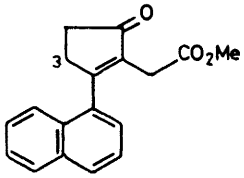

(4)

RESULTS AND DISCUSSION

Methyl 2-(8-quinolyl)-6-oxocyclohex-1-enylacetate (2) was synthesised from 8-acetylquinoline [3] employing the general method [4] which consisted of the condensation of its Mannich base methoiodide [as (3)] with ethyl β-oxoadipate,[5] and subsequent hydrolysis and esterification of the product. The conventional Mannich procedure,[2] however, did not work in this case, the product being entirely a tar. The quinoline nitrogen in the Mannich base presumably abstracts an α-proton intramolecularly from the side chain and the resulting vinyl ketone polymerises readily. The procedure of Back [6] in which the reaction is carried out in an aldehyde-free solution proved equally abortive. Finally, by using an excess of hydrochloric acid in boiling ethanol or 3-methylbutan-1-ol,[7] the desired Mannich base (3) was obtained in 30% yield. The subsequent steps went smoothly and the methyl ester (2) and the free acid were both obtained in pure crystalline form.

The methylene protons of the acetate side chain in the ester (2) and in the acid appeared as a quartet at δ *ca.* 3.05 at ambient temperature from which J_{AB} and $\Delta\nu_{AB}$ were calculated in the usual way.[2,8] The n.m.r. parameters in different solvents and for different frequencies (MHz) are shown in the Table. The approximate exchange rate k_c and the free energy of con-

N.m.r. parameters and free energies of activation of rotation in compounds (1) and (2)

Compound	Frequency (MHz)	Solvent	$\Delta\nu_{AB}$/Hz	$\Delta\delta_{AB}$/p.p.m.	J_{AB}/Hz	k_c/s^{-1}	T_c/°C	$\Delta G^{\ddagger}$/kJ (kcal) mol^{-1}
(1) [a]	100	$C_6D_5NO_2$	23.0	0.23	16.5	103.5	183	95.4 (22.80)
(2) [b]	100	$C_6D_5NO_2$	45.0	0.45	16.5	134.5	95	75.8 (18.1) [c]
	100	$CDCl_3$	53.5	0.54	16.5	149.0		
	90	$CDCl_3$	48.2	0.54	16.5	139.5		
	90	CD_2Cl_2	37.5	0.42	16.5	122.5		
(1) [a] as acid	60	$C_6D_5NO_2$	17.0	0.28	17.0	100.0	165	91.5 (21.90)
(2) as acid	100	$CDCl_3$	53.0	0.53	16.5	148.0		
	90	CD_3COCD_3	48.2	0.54	16.5	139.5		

[a] Data taken from ref. 1. [b] The spectral data were reversible with temperature. [c] The maximum errors are estimated to be ±0.8 kJ mol^{-1}.

figurational inversion $\Delta G^{\ddagger}$ at the coalescence temperature T_c for the methyl ester (2) were determined using equations as in the previous cases.[2] The free energy of activation of restricted rotation for the compound (2) is found to be 75.7 kJ (18.1 kcal) mol^{-1} appreciably lower than that (95.4 kJ mol^{-1}) for the 1-naphthyl analogue (1). The effective bulk of the nitrogen lone pair in quinoline is thus considerably less than that of an aromatic hydrogen. Sutherland *et al.*[9] and Boekelheide *et al.*[10] came to similar conclusions from the study of the conformational mobility of [2,2]metacyclophanes and [2,2]metaparacyclophanes.

One or two points may be noted in this connection. A marked variation is observed in the chemical shift difference ($\Delta\delta_{AB}$) between the two diastereoisotopic protons in compounds (1) and (2) (also in the acids) in a particular solvent (see Table). One of the protons has shifted upfield (*ca.* 0.12 p.p.m.) and the other downfield (*ca.* 0.10 p.p.m.) in the ester (2) compared with the ester (1), the centre of the quartet remaining unchanged at δ 3.05 [3.09 for (1)]. Such differences have previously been observed [1] for other compounds in this series with the phenyl or naphthyl ring differently substituted near the pivotal bond and are conceivably due to the difference in the magnitude of aromatic ring currents and/or slight changes in the preferred conformation of the molecules. Another interesting phenomenon was noted for the acid [as (2)] which showed the two methylene protons as an AB quartet in [^{2}H]chloroform and [$^2H_6$]-acetone (see Table) but as a sharp singlet (δ 3.15) in [$^2H_5$]nitrobenzene between 20 and 100 °C. This chance isochronism may be attributed to some obscure factor associated with the formation of a zwitterion since the ester in the same solvent showed the usual quartet. The possibility of the formation of an enol-lactone was considered because of the presence of a weak lactone band at 1 750 cm^{-1} but was effectively ruled out by the recovery of the original acid from the solution.

The variable temperature n.m.r. spectra of the analogous 1-naphthylcyclopentenyl derivative (4) * were likewise studied but the methylene protons did not show any sign of splitting in [$^2H_6$]benzene at 20, in [$^2H_6$]chloroform at −50, and in [$^2H_2$]dichloromethane at −90 °C. There was, however, considerable broadening of the peak at −90 °C. Assuming this as near coalescence temperature and accepting a value of 100 for k_c (a fair average of this series [1]), the free energy of activation was calculated roughly as <37.0 kJ (9.0 kcal) mol^{-1} which is much lower than that for the corresponding cyclohexenone derivative (1). Previously, the energy barrier about an N–N bond has been reported for hindered substituted hydrazones of cyclic and acyclic ketones and that for cyclopentanone derivative was found to be comparatively low.[11] Apparently, the methylene protons in cyclopentane are further removed from the pivotal bond than those in cyclohexane. Thus an examination of the Dreiding models revealed that during a complete rotation about the aryl–cycloalkenyl bond, the minimum distance between 3- and 8-H in compounds (1) and (4) is 0.70 and 1.25 Å, respectively, which explains why rotation about the aryl–cyclopentenone ring is so much easier. Of course in the transition states, these distances may not be real, the models being suitably deformed to avoid the high van der Waals interaction but never the less, they give a measure of the energy of activation of the rotational process.

* Synthesis of this and some analogous compounds is reported elsewhere.[12]

We would like to rectify an inaccuracy in one of our earlier publications.[1] It was stated that the singlets due to two methoxy groups (OMe and CO_2Me) in methyl 2-(4-methoxy-1-naphthyl)-6-oxocyclohex-1-enylacetate [as (1) with 4-OMe in the naphthyl ring] showed signs of splitting above 155 °C. The experiments have been repeated and no such splitting is now observed. The earlier finding was possibly due to an instrumental artefact since scrutiny of the spectra showed similar splitting for the tetramethylsilane protons.

EXPERIMENTAL

Variable temperature ^{1}H n.m.r. spectra were taken on a Varian XL-100 100 MHz machine as reported earlier.[1] A few spectra were also taken on a Perkin-Elmer 90 MHz machine. Chemical shifts (δ) in [^{2}H]chloroform are reported relative to tetramethylsilane as internal standard.

8-*Acetylquinoline*.—8-Acetylquinoline was prepared from ethyl quinoline-8-carboxylate following the method of Campbell *et al.*[3] Attempts to prepare it from quinoline-8-carboxylic acid by treatment with methyl-lithium led to extensive nuclear methylation as well.

2-*Dimethylaminoethyl* 8-*Quinolyl Ketone* (3).—(*a*) A mixture of the preceding ketone (7.6 g, 0.045 mol), dimethylamine hydrochloride (4.1 g, 0.05 mol), paraformaldehyde (2.1 g, 0.07 mol), concentrated hydrochloric acid (4.5 ml), and ethanol (25 ml) was refluxed for 8 h on a steam-bath. The product was made alkaline and the organic matter extracted with ether. The dark brown liquid (5.4 g) left on evaporation of the solvent was a mixture of the original ketone (80%) and the *Mannich base* (3) (20%), the ratio being determined by the methyl peak at δ 2.92 in the ketone and NMe_2 peak at δ 2.28 of the Mannich base. The latter was preferentially extracted with calculated quantity of 0.5N-sulphuric acid and obtained as a red oil (1.1 g), δ (100 MHz) 8.92 (1 H, 2 × d, *J* 2 and 4 Hz, 2-H), 8.16 (1 H, 2 × d, *J* 2 and 9 Hz, 7-H), 7.96—7.81 (2 H, m, 2 ArH), 7.62—7.22 (2 H, m, 2 ArH), 3.55 (2 H, t, *J* 7 Hz, CH_2), 2.80 (2 H, t, *J* 7 Hz, CH_2N), and 2.28 (6 H, s, NMe_2). The residue after isolation of the Mannich base was distilled to furnish unchanged 8-acetylquinoline (3.5 g).

(*b*) A mixture of the ketone (12.0 g, 0.07 mol), paraformaldehyde (4.0 g, 0.13 mol), dimethylamine hydrochloride (8.15 g, 0.1 mol), concentrated hydrochloric acid (7 ml), and 3-methylbutan-1-ol (100 ml) was heated under gentle reflux for 1.5 h. Paraformaldehyde was added into the hot reactants in three equal instalments. The resultant dark liquid was basified and worked up as before to give a deep brown oil (7.9 g). N.m.r. showed it to be a mixture of the unchanged ketone (65%) and the Mannich base (3) (30—35%).

Methyl 2-(8-*Quinolyl*)-6-*oxocyclohex*-1-*enylacetate* (2).—The foregoing Mannich base was converted into its methiodide and was condensed with ethyl β-oxoadipate in the

usual way [4] to furnish a gum (3.85 g). This was hydrolysed and re-esterified with diazomethane to afford the crude methyl ester (2) (2.06 g), m.p. 65—70°. It was absorbed on silica gel (80—200 mesh) and eluted with ether–petroleum. After some initial gum, the *methyl ester* (2) (2.0 g, 34%) was obtained which was recrystallised as plates, m.p. 88° (Found: C, 73.3; H, 5.8; N, 4.8%; M^+, 295. $C_{18}H_{17}NO_3$ requires C, 73.3; H, 5.8; N, 4.7%; M^+, 295); $\nu_{max.}$ ($CHCl_3$) 1 735 and 1 670 cm^{-1}; δ (100 MHz) 8.90 (1 H, 2 × d, *J* 2 and 4 Hz, ArH), 8.17 (1 H, 2 × d, *J* 2 and 9 Hz, ArH), 7.80 (1 H, m, ArH), 7.60—7.30 (3 H, m, 3 ArH), 3.58 (3 H, s, CO_2Me), 3.03 (2 H, q, CH_2CO_2Me), 2.75—2.45 (4 H, m, 2 CH_2), and 2.40—2.10 (2 H, m, CH_2). 2-(8-*Quinolyl*)-6-*oxocyclohex*-1-*enylacetic acid* was obtained as plates, m.p. 208—210° (from methanol) (Found: C, 72.35; H, 5.5; N, 5.1. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.3; N, 5.0%); $\nu_{max.}$ (KBr) 1 720 and 1 680 cm^{-1}; δ (90 MHz) 9.80 (1 H, s, CO_2H), 8.90 (1 H, 2 × d, *J* 2 and 4 Hz, ArH), 8.20 (1 H, 2 × d, *J* 2 and 9 Hz, ArH), 7.80 (1 H, m, ArH), 7.70—7.32 (3 H, m, 3 ArH), 3.04 (2 H, q, CH_2CO_2H), 2.65 (4 H, m, 2 CH_2), and 2.30—2.02 (2 H, m, CH_2).

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