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THE FUSED QUINUCLIDINE-VALEROLACTONE SYSTEM

SYNTHESIS AND CONFORMATION OF 4-ALKYL OR 4-ARYL-6-OXA-1-AZATRICYCLO (4.2.2.0^{2,7}) DODECAN-5-ONE

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Abstract—Michael addition of ethyl malonate, alkylmalonate and phenylacetate to 2-methylene-quinuclidin-3-one, followed by $NaBH_4$ reduction of the 3-oxo group in the resulting adduct, then acid hydrolysis and decarboxylation (in the case of malonates) gave 6-oxa-1-azatricyclo-(4.2.2.0^{2,7})dodecan-5-one, its 4-alkyl and 4-aryl derivatives. A minor byproduct is 2-(*trans*-3-hydroxyquinuclidin-2-yl)-α-alkyl-propanoic acid which is unable to undergo cyclization to δ-lactone.

The present study deals with the synthesis and conformation of compounds in the rigid system, 6-oxa-1-azatricyclo[4.2.2.0^{2,7}]-dodecan-5-one (**4**). These bear structural analogy to the potent cholinergic agents acetylcholine and 3-acetoxyquinuclidine[1] and our interest in them stems from a desire to insert the cholinergic pharmacophore[2] in a framework of utmost rigidity. Their pharmacology will be reported elsewhere.

The synthetic procedure used is shown in Scheme 1. Michael addition of 2-methylene-quinuclidin-3-one[3] (**1**) to diethyl malonate[4] has been extended to alkyl substituted malonates and phenyl acetate to yield the adduct **2** (*ca* 70%). Reduction of **2** with sodium borohydride afforded a mixture of two isomeric carbinols **3** and **5** with preponderance of the former. The mixture of **3** and **5** was finally converted, after acid hydrolysis and decarboxylation (in the case of malonate), into the desired δ-lactone **4** and the acid **6** which were readily separable from each other.

That the C_2 and C_3 hydrogens in **6** are indeed *trans* follows from the NMR spectrum. This is exemplified in Table 1 for **6B** (hydrochloride). H_a appears as a broad double doublet with $J_{ab} = 3{\cdot}75$ Hz, $J_{ad} = 0$ and $J_{ae'} \simeq 1{\cdot}5$ Hz. H_a is coupled in a long range coupling with $H_{e'}$, because these protons are capable of forming a planar *W* conformation.[5]

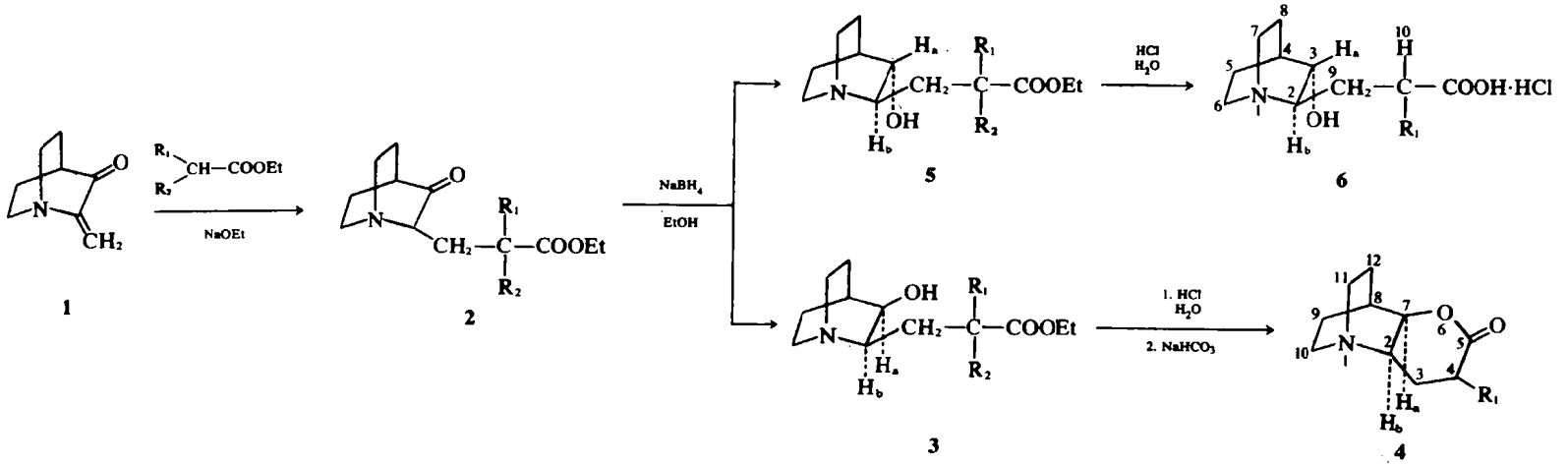
Assuming a 10° rotation[1b] about the N–C_4 axis in quinuclidine to relieve steric interaction of the ethylene bridge C_7–C_8 with the carboxyalkyl moiety, the values of dihedral angles measured from Dreiding models are: $\theta_{ab} = 130°$, $\theta_{ad} = 80°$. The corresponding coupling constants from the original Karplus equation[6a,b] would then be: $J_{ab} = 3{\cdot}6$ Hz, $J_{ad} = 0$, and from Abraham's modification,[6c] 4·1 Hz and 0, respectively. The observed values are 3·75 Hz and 0 (Table 1). At this point we recall that the Karplus equation was successfully used in a closely related system: *trans*-3-dimethylamino-bicyclo(2,2,2)octan-2-ol[7] or *trans*-3-trimethylammonium-2-acetoxybicyclo(2,2,2)octane.[8]

The structure of **4** follows from its NMR and IR spectra. A key feature in the conformation of **4** is the δ-lactone C–O–CO–C group which, being planar,[9] imposes a boat or a half-chair conformation in unhindered 6-membered rings.[9] In the case of **4**, however, the rigid boat conformation of the quinuclidine moiety is expected to impose a twist-boat conformation on the δ-lactone part of the molecule. This is borne out by Dreiding and CPK models and by analysis of the NMR spectra.

Use of low and high-resolution NMR spectroscopy with spin-spin decoupling and deuterium labelling has permitted the assignment of all informative proton signals and coupling constants in these spectra (Table 2).

In all members of series **4**, H_a appears as a double doublet at $\delta = 4{\cdot}95$–$4{\cdot}55$ ppm. In the free base, H_b is obscured by the $4H_f$ multiplet but is induced to shift downfield by protonation or alkylation at N_1 and appears then as broad quartet with hidden splittings ($W_{1/2} = 5$ Hz). The coupling constants, resolved from decoupling experiments, are: $J_{ab} = 8$ Hz, $J_{ad} = 5$ Hz. H_a collapses to a narrow triplet on irradiation of H_b at 4·2 ppm, indicating that it is coupled with H_d and further with $H_{e'}$, in long range coupling because the pair is capable of forming a planar *W* conformation.

The chemical shift and shape of H_e was demonstrated by spin-decoupling and comparison with the spectrum of the C_4-deuterated analogue of **4B** (henceforth referred to as **4F**, Fig 2). H_e appears as an eleven-line multiplet ($\delta = 2{\cdot}8$ ppm) in the spectrum of **4B** (hydrochloride, Fig 1). On irradiation at this frequency, the Me doublet at $\delta = 1{\cdot}23$ ppm ($J_{xe} = 6{\cdot}5$ Hz) collapses to a singlet. Conversely, on irradiation at the Me signal ($\delta = 1{\cdot}23$ ppm) H_e collapses to a broad double doublet ($W_{1/2} = 10$ Hz) with $J_{g'e} = 14$ Hz and $J_{ge} = 4$ Hz, in the range expected for axial-axial and equatorial-axial vicinal couplings.[10] Hence, H_e is axial whilst the Me group is equatorial. Indeed, Dreiding models of the twist-boat conformation preclude a Me group in the axial position because of extensive overlap of the van der Waals radii of H_x of the Me group and H_a. The conformation which requires a 15° rotation about the N_1–C_8 axis would also relieve the van der Waals



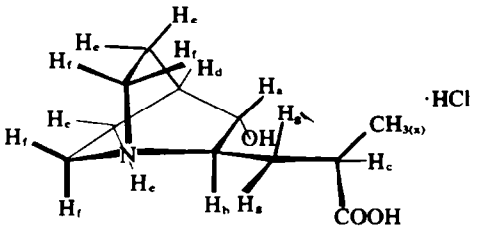
SCHEME 1

Compd. denomination

R_1	R_2
A: H	COOEt
B: Me	COOEt
C: Et	COOEt
D: i-Pr	COOEt
E: Ph	H

F: C_4-deuterated B
G: C_4,C_7-dideuterated B

Table 1. NMR data for 2 - (*trans* - 3 - hydroxyquinuclidin - 2 - yl) - α - methylpropanoic acid hydrochloride (**6B**)



Chemical Shift (δ)	Dihedral angles, θ*	Coupling constants, (Hz) J exp.	J calcd.†
H_a, 3·9(*dd*)	θ_{ab} = 130°	J_{ab} = 3·75	J_{ab} = 3·6[a]; 4·1[b]
H_b, H_f, 3·7–3(*m*)	θ_{ad} = 80°	J_{ad} = 0	J_{ad} = 0[a,b]
H_c, 3–2·5(*m*)		$J_{ae'}$ ≃ 1·5	
H_g, H_e, H_d, 2·5–1·6(*m*)		J_{cx} = 7·5	
H_x, 1·3(*d*)			

The NMR spectrum was taken in D_2O.

*Measured from Dreiding models.

†J calculated from the Karplus equation (*a*); from Abraham's modification (*b*).

Code: *d*: doublet; *dd*: doublet of doublets; *m*: multiplet.

interaction of the geminal C_3 protons with the ethylenic bridge C_{11}–C_{12}.

The protons at C_3 being adjacent to a chiral center (C_4) are anisochronous and display an AB-type spectrum.[11]

In the specific case of **4B** (hydrochloride), one of the H_g's appears as a 4-line multiplet at 2·3 ppm but collapses to a narrow doublet with J_{gc} = 4 Hz on irradiation at H_b, δ = 4·2 ppm. In **4F**, **4G** (deuterochlorides) or upon irradiation of H_a, (Fig 1) H_b appears as a 3-line multiplet with a splitting of 18 Hz between the two outermost lines. Assuming again the twist-boat conformation, and H_g equatorial, the measured dihedral angles are: θ_{gb} = 25°, θ_{gc} = 55°. That H_g is indeed equatorial we also know from its appearance at lower field than the geminal $H_{g'}$.[12] Unfortunately, the latter is obscured by the 4H_e multiplet. H_b, which appears as a broad quartet ($W_{1/2}$ = 5 Hz for the inner lines, $W_{1/2}$ = 4*Hz* for the outer lines collapses to a broad triplet ($W_{1/2}$ = 5 Hz for the inner line, $W_{1/2}$ = 4 Hz for the outer lines) when irradiated at H_a, δ = 4·55 ppm in the **4B** hydrochloride and the 4-deuterated compound **4F**, deuterochloride.

This indicates that H_b and the geminal H_g's form an *ABX* spectrum. The same *ABX* spectrum appears also in the 4,7-dideuterated analog of **4B**. (**4G**, deuterochloride, where the *X* part (H_b) is a triplet, as expected. The *X* part appears as a triplet because either of two conditions is fulfilled:[13]

$$\nu_0\delta_{AB} \quad \text{or} \quad \tfrac{1}{2}(J_{AX} - J_{BX}) = 0; \tag{1}$$

$$\nu_0\delta_{AB} = 0 \quad \text{and} \quad \frac{1}{2}\left(\frac{J_{AX} - J_{BX}}{J_{AB}}\right) \to 0 \tag{2}$$

The spacing between the triplet lines corresponds to

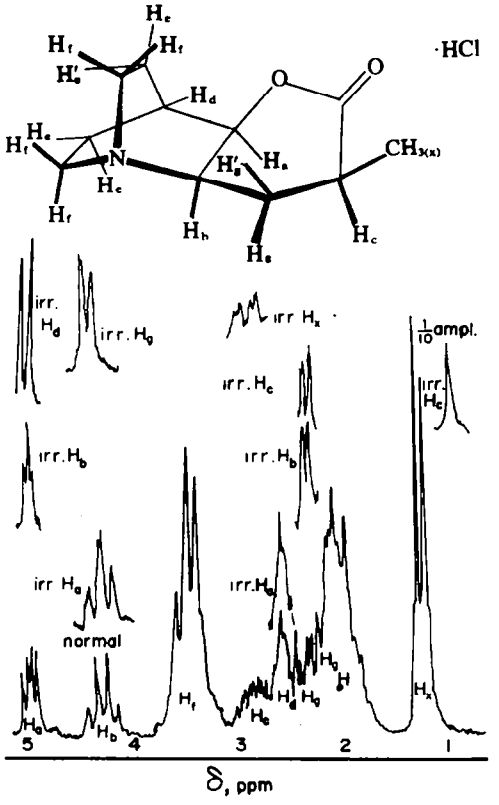


Fig. 1.

$J = \frac{1}{2}(J_{AX} + J_{BX}) = 9$ Hz (where $A = H_{g'}$; $B = H_g$; $X = H_b$). Obviously, this is a case of a deceptively simple *ABX* spectrum[13,14] and will be discussed further below. Unfortunately, J_{AB} could not be measured because $H_{g'}$ is obscured by the 4H_e multiplet. *J* values for the dihedral angles, θ_{ab}, θ_{ad}, θ_{bg}, $\theta_{bg'}$, θ_{cg}, $\theta_{cg'}$, calculated by the original Karplus equation proved to be much lower than the observed ones (Table 3), the deviation being unaccountable by the known tendency of this equation to low results[15,16] or to the effect of electronegative oxygen on coupling constants.[6b,17]

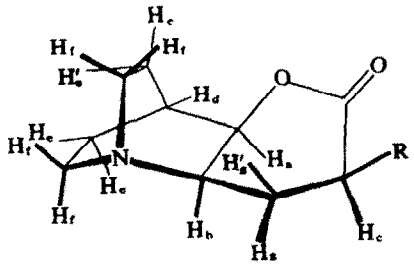
We attribute this to a departure from ideal boat conformation of the δ-lactone and that arises from an exaggerated torsion on the C_2–C_3 and C_3–C_4 bonds imposed by planarity of the C–O–CO–C group on the one hand and van der Waals repulsion between H_g and a proximal H_f on the other. More satisfactory results were obtained by use of a modified Karplus equation:

$$J_{HH'}\begin{cases} 10\cos^2\theta & 0° \le \theta \le 90° \\ 16\cos^2\theta & 90° \le \theta \le 180° \end{cases}$$

initially proposed by Williamson and Johnson for 2-acetoxy-3-cholestanones[16a] and subsequently applied successfully to γ-lactones.[16b] The *J* values thus obtained are in reasonable agreement with the observed ones (Table 3).

The coupling constants obtained by the modified equation may explain in part the deceptively simple *ABX*

Table 2. NMR data for 4-alkyl and aryl derivatives of 6-oxa-1-azatricyclo(4.2.2.0^{2,7})dodecan-5-one (4)

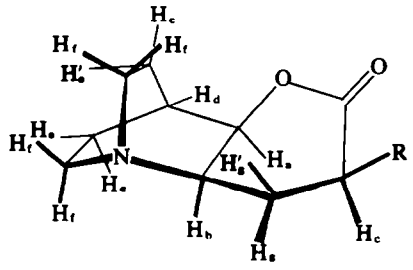


Compound (Hz)	Solvent	Chemical Shift (δ), ppm									
		R		H_a	H_b	H_b, $4H_f$	H_c	H_d	H_g	$H_{g'}$, $4H_e$	J(H_2)
4A (Base)	$CDCl_3$	H_x,	3·0–2·4* (*m*)	4·5 (*dd*)	—	3·7–2·6* (*m*)	3·0–2·4* (*m*)	3·0–2·4* (*m*)	3·0–2·4* (*m*)	2·4–1·4 (*m*)	*ab* = 5 *ad* = 5
4B (Base)	$CDCl_3$	$CH_{3(x)}$	1·29(*d*)	4·55 (*dd*)	—	3·7–2·8 (*m*)	2·5 (*m*)	2·3–2·2* (*m*)	2·3–2·2* (*m*)	2·2–1·6 (*m*)	*ab* = 8 *ad* = 5 *xc* = 6·75
4B (HCl)	DCl/D_2O, 2–5%	$CH_{3(x)}$	1·23(*d*)	4·87 (*dd*)	4·3(*q*)	–, 3·6–3·2 (*m*)	*2·8 (*m*)	2·6 (*m*)	2·3 (*m*)	2·2–1·8 (*m*)	*ab* = 8 *ad* = 5 *bg'* + *bg* = 18 *xc* = 6·75 *cg'* = 14 *cg* = 4
4B (Methiodide)[a]	DCl/D_2O, 2–5%	$CH_{3(x)}$	1·23(*d*)	4·95 (*dd*)	4·3(*q*)	–, 3·8–3·25 (*m*)	2·8** (*m*)	2·6 (*m*)	2·3 (*m*)	2·2–1·8 (*m*)	*ab* = 8 *ad* = 5 *bg'* + *bg* = 18 *xc* = 6·5 *cg'* = 14 *cg* = 4
4C (Base)	$CDCl_3$	$CH_{2(x)}CH_{3(z)}$ H_x: 2·1–1·4† (*m*) H_z: 1·0(*t*)		4·53 (*dd*)	—	3·7–2·7 (*m*)	2·5 (*m*)	2·3–2·1* (*m*)	2·3–2·1* (*m*)	2·1–1·4 (*m*)	*ab* = 8 *ad* = 5 *xz* = 7·5
4C (HCl)	DCl/D_2O, 2–5%	$CH_{2(x)}CH_{3(z)}$ H_x: 2·2–1·4† (*m*) H_z: 1·0(*t*)		4·93 (*dd*)	4·28(*q*)	–, 3·7–3·1 (*m*)	2·75 (*m*)	2·6–2·3* (*m*)	2·6–2·3* (*m*)	2·1–1·4 (*m*)	*ab* = 8 *ad* = 5 *xz* = 7·5
4D (Base)	$CDCl_3$	$CH_{3(z)}$ $CH_{(x)}$ $CH_{3(z')}$	H_x: 2·1–1·6† (*m*) H_z: 1·13(*d*) $H_{z'}$: 1·03(*d*)	4·55 (*dd*)	—	3·7–2·8 (*m*)	2·5 (*m*)	2·3–2·2* (*m*)	2·3–2·2* (*m*)	2·2–1·6 (*m*)	*ab* = 8 *ad* = 5 *xz* = *xz'* = 8

4D (HCl)	DCl/D_2O, 2–5%	$CH_{3(x)}$ $CH_{(x)}$ $CH_{3(x')}$	H_x: 2·3(*m*) $H_{x'}$: 0·95(*d*) $H_{x'}$: 1·05(*d*)	4·86 (*dd*)	4·2(*q*)	–, 3·65–3·1 (*m*)	2·72 (*m*)	2·55 (*m*)	2·4⁺ (*m*)	2·2–1·6 (*m*)		*ab* = 8 *ad* = 5 *bg'* + *bg* = 18 *xz* = *xz'* = 9 *xc* = 5
4E (Base)	$CDCl_3$	C_6H_5	7·35(*s*)	4·45 (*dd*)	3·4–3·02 (*m*)	–, 3·02–2·63 (*m*)	3·5* (*dd*)	2·47–2·02† (*m*)	2·47–2·02† (*m*)	2·47–2·02, (*m*)	2·0–1·13 (*m*)	*ab* = 7·5 *ad* = 5
4E (Base)	C_5D_5N:$CDCl_3$ (1:1)	C_6H_5	7·35(*s*)	4·42 (*dd*)	3·4–2·86 (*m*)	–, 2·86–2·44 (*m*)	3·68 (*m*)	2·25–1·86† (*m*)	2·25–1·86† (*m*)	2·25–1·86, (*m*)	1·86–1·0 (*m*)	*ab* = 8 *ad* = 5 *cg'* = 13 *cg* = 5
4E (HCl)	DCl/D_2O 2–5%	C_6H_5	7·35(*s*)	5·0 (*dd*)	4·6–3·8* (*m*)	–, 3·7–3·1 (*m*)	4·6–3·8* (*m*)	2·8–2·3† (*m*)	2·8–2·3† (*m*)	2·8–2·3, (*m*)	2·3–1·4 (*m*)	*ab* = 8 *ad* = 5
4F (DCl)	DCl/D_2O, 2–5%	$CH_{3(x)}$	1·23(*s*)	4·95 (*dd*)	4·23(*q*)	–, 3·7–3·1 (*m*)	—	2·7–2·4 (*m*)	2·4–2·2* (*m*)	2·2–1·7 (*m*)		*ab* = 8 *ad* = 5 *bg'* + *bg* = 18
4G (DCl)	D_2O	$CH_{3(x)}$	1·23(*s*)	—	4·23(*t*)	–, 3·7–3·1 (*m*)	—	2·7–2·4 (*m*)	2·4–2·2* (*m*)	2·2–1·7 (*m*)		*ad* = 8 *ad* = 5 *bg'* + *bg* = 18

Code: *s*; singlet; *d*: doublet; *dd*: doublet of doublets; *m*: multiplet; *t*: triplet; *q*: quartet.
*Inclusive the other indicated protons.
**Obscured by the N-Me signal.
†Obscured by $H_{g'} + 4H_e$.
⁺Obscured by H_x.
ˣPartially obscured by $H_{g'}$ and H_d.
^N-Me, $\delta = 3(s)$.

Table 3. Dihedral angles and coupling constants of lactones of type 4 (HCl)



	H_a, H_d	H_a, H_b	H_b, H_g	H_b, H_g	H_g, H_c	H_g, H_c
θ obsd.[a] (deg.)	45	25	135	25	175	55
J obsd.[b] (Hz)	5	8	*d*	*d*	14	4
J calcd.[c] (Hz)	4·0	6·7	4	6·7	9·2	2·5
J calcd.[c] (Hz)	5	8·2	8	8·2	16	3·3

[a] Approximate values measured on Dreiding models assuming the conformation of the lactone ring is a twist-boat and the group C–O–CO–C is planar.

[b] J observed from spin decoupling and deuterium labelling experiments at 27°C.

[c] J calculated from θ observed using the original Karplus equation[16]:

$$J\begin{cases}8{\cdot}5\cos^2\theta - 0{\cdot}28 & 0 \le \theta \le 90^\circ \\ 9{\cdot}5\cos^2\theta - 0{\cdot}28 & 90 \le \theta \le 180^\circ\end{cases}$$

[d] $J_{bg'} + J_{bg} = 18$ Hz.

[e] J calculated from θ observed using the modified Karplus equation[16]:

$$J\begin{cases}10\cos^2\theta & 0 \le \theta \le 90^\circ \\ 16\cos^2\theta & 90 \le \theta \le 180^\circ\end{cases}$$

spectrum due to H_b, H_g and $H_{g'}$: now one may see that $J_{AX} \simeq J_{BX}$ so that $\frac{1}{2}(J_{AX} - J_{BX}) \simeq 0$ which is enough for such a spectrum to arise. The two large couplings J_{bg} and $J_{bg'}$, require that H_b should lie outside the dihedral angle enclosed by the *AB* protons. In view of this and other coupling constants (Table 3), the likelihood of a half-chair conformation is inadmissible.

Further information on the conformation of **4** was obtained by studying solvent effect on the NMR spectrum. Interactions between polar solutes and aromatic solvents have been used successfully to identify the conformation of γ-and-δ-lactones[15,18] and coumarins.[19]

In the case of **4E**, upon dilution of its $CDCl_3$ solution with C_5D_5N (1:1), H_c shifts downfield and appears as a clear double doublet at $\delta = 3{\cdot}68$ ppm with $J_{g'c} = 13{\cdot}0$ Hz and $J_{gc} = 5$ Hz. This is further proof that H_c is axial since it forms an axial-axial coupling with one of the H_g's. This and the observed solvent shifts for the Me analog, **4B**, **4F** and **4H** (free base) on dilution from $CDCl_3$ to C_6D_6 ($\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$) are given in Table 4; the values obtained are uniformly positive. The results are consistent with the formation of a collision complex in which the aromatic solvent molecule is oriented towards the

Table 4. Solvent shifts for **4B**, **4E**, **4F** and **4G** upon dilution with C_6D_6

Compound	$\Delta(\delta_{CDCl_3} - \delta_{C_6D_6})$, ppm[a,b,c]			
	H_a	H_c	H_d	$CH_3(x)$
4B (Base)	0·53	0·5	0·25	0·13
4E (Base)[d]	0·85	0·5	0·25	—
4F (Base)	0·53	—	0·25	0·13
4G (Base)	—	—	0·25	0·14

[a] 10% (W/v) solutions with TMS as internal reference.

[b] The compounds are slightly soluble in C_6D_6, so the $CDCl_3$ solutions were diluted 1:1 with C_6D_6.

[c] The change is taken as positive when the resonance moves upfield in going from $CDCl_3$ to C_6D_6.

[d] The spectra were run in $CDCl_3$ and in C_6D_6 solutions.

electron deficient ring-oxygen and away from the negative dipole of the lactone group and the nitrogen lone pair.[18,10]

In such orientation the axial protons H_a and H_c and to a lesser extent H_d and H_x lie within the shielding range of the aromatic solvent molecule, and, therefore, shift to higher field.

Possible change in the twist-boat conformation due to a rise in temperature was studied for **4B**, **4D**, **4F** and **4G** (hydrochlorides). No significant spectral changes could be observed throughout the range +20° to +80°, with the sum $J_{bg} + J_{bg'}$, remaining essentially constant. Measurements at lower temperatures were not possible because solutions of the hydrochlorides of these compounds in D_2O became viscous and resolution spoiled. In the case of **4D** (hydrochloride), non-equivalence of the two Me's of the isopropyl group due to intrinsic anisotropy at an environment of low symmetry[20] persists throughout this range of temperature ($\delta = 1{\cdot}13$ and $1{\cdot}03$ ppm).

The proposed structure of **4** finds also support in the work of Cheung *et al*[21] and Lindsay and Overton[22] on the IR absorption frequencies of δ-lactones. According to these authors, $\nu_{C=O}$ (in CCl_4) associated with a half-chair conformation lies within the range 1730–1750 cm^{-1}, whilst that associated with a boat conformation lies in the range 1750–1765 cm^{-1}, in the same solvent. All lactones of type **4** absorb near 1740 cm^{-1} ($CHCl_3$). This figure, if increased by +10 to +15 cm^{-1} to account for the solvent shift $CHCl_3 \rightarrow CCl_4$ for δ-lactones[21] lends further support to the proposed structure of **4**, any departure from the ideal boat geometry being reflected partially by the actual values found in each case.

EXPERIMENTAL

M.ps were determined with a Thomas-Hoover apparatus or a Mettler FP-1 and FP-11 melting and boiling point apparatus. IR spectra were measured with a Perkin-Elmer Infracord 457 grating instrument; NMR spectra were recorded on a Jeol C-60HL (60 MHz), Bruker HFX-10NMR (90 MHz) or a Varian HA 100 (100 MHz) spectrometers. Samples were run as 10% solns in D_2O, DCl in D_2O (2–5%) using DSS[2,2,3,3 Tetradeutero-(3-trimethylsilyl) propanoic acid sodium salt] as internal reference

and in $CDCl_3$, C_6D_6, $CDCl_3$:C_6D_6(1:1) or C_5D_5N:$CDCl_3$(1:1) using TMS as an internal standard. The δ values reported are those obtained from the 60 MHz or the 90 MHz spectrum. Decoupling experiments were run on the Bruker HFX-10NMR (90 MHz) Spectrometer with the frequency sweep technique.

Elemental analysis were performed by the Weizman Institute Micro-analytical Laboratory, Rehovot. Wöelm silica gel F, aluminium oxide neutral, basic or acidic were used for analytical TLC. Solns in organic solvents were dried over $MgSO_4$. Methoiodide salts were prepared by reflux of the free base in solution of acetone and excess MeI, separation of the solid salts, washing with acetone and recrystallization from abs EtOH.

Proton coding in NMR signals for compounds of structure **2** is identical with that for compounds **4** except that $R_2 = -COOCH_{2_{(m)}}CH_{3_{(n)}}$.

Diethyl (3-oxoquinuclidin-2-yl)methylmalonate (**2A**). This was prepared by the method of Oppenheimer and Bergmann[4] with slight modifications: the product, obtained as a crude oil, was purified by chromatography on Merck Kieselgel G with $CHCl_3$ as eluent, then distilled, b.p. 160–163° (1·5–2 mm Hg); R_f, 0·8 (silica, EtOAc); ν_{max}C=O, 1735, 1720 cm^{-1} (neat); NMR ($CDCl_3$) δ 4·2(*q*, $4H_m$), 3·65 (*dd*, H_x), 3·4–2·7 (*m*, $H_b + 4H_f$), 2·6–1·8 (*m*, $H_d + H_g + H_{g'} + 4H_e$), 1·4 (*t*, $6H_n$).

Diethyl (3-oxoquinuclidin-2-yl)methyl-methylmalonate (**2B**). Ethanolic NaOEt (from 2·9 g, 0·126 mole Na and 100 ml EtOH) and diethyl methylmalonate (50 g, 0·29 mole) were refluxed for 30 min then cooled to 5° and a soln of **1**[3] (39·4 g, 0·29 mole) in EtOH (50 ml) was added dropwise. After 16 hr, the soln was neutralised with AcOH, EtOH removed by flash distillation, water (100 ml) added and the mixture extracted with $CHCl_3$. Drying, evaporation of solvent and recrystallization (P.E. 40–60°) gave **2B** (72 g, 81%), m.p. 58·4°. (Found: C, 61·9; H, 8·1; N, 4·4; $C_{16}H_{25}NO_5$ requires: C, 61·7; H, 8·1; N, 4·5%). R_f, 0·8 (silica, EtOAc); ν_{max}C=O, 1740, 1720(Nujol), 1735 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·2 (*q*, $4H_m$), 3·4–2·8 (*m*, $H_b + 4H_f$), 2·55–2·2 (*m*, $H_d + H_g$), 2·2–1·75 (*m*, $H_{g'} + 4H_e$), 1·5 (*s*, $3H_x$), 1·3 (*t*, $6H_n$).

Diethyl (3-oxoquinuclidin-2-yl)methyl-ethylmalonate (**2C**). This was prepared likewise from Na (3 g, 0·13 mole), EtOH (100 ml), diethyl ethylmalonate (56·4 g, 0·3 mole) and **1** (41·1 g, 0·3 mole); yield, 64 g (66%), m.p. (P.E. 40–60°), 60–61·1°. (Found: C, 63·1; H, 7·8; N, 4·6; $C_{17}H_{25}NO_5$ requires: C, 63·1; H, 7·8; N, 4·3%); R_f, 0·8 (silica, EtOAc), ν_{max}C=O, 1740, 1730 (Nujol), 1750, 1730 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·2 (*q*, $4H_m$), 3·45–2·7 (*m*, $H_b + 4H_g$), 2·6–2·4 (*m*, $H_d + H_g$), 2·3–1·9 (*m*, $H_g + 4H_e + 2H_x$), 1·3 (*t*, $6H_n$), 0·9 (*t*, $3Hz$).

Diethyl (3-oxoquinuclidin-2-yl)methyl-isopropylmalonate (**2D**). This was prepared from the same quantities of Na, EtOH and **1** as given for **2B** and diethyl isopropylmalonate (60·6 g, 0·3 mole); yield, 62·9 g (62%), m.p. (P.E. 40–60°), 43·3–44·1°. (Found: C, 63·9; H, 8·8; N, 4·4; $C_{18}H_{28}NO_5$ requires: C, 63·7; H, 8·6; N, 4·1%); $M^+ = 339$; R_f, 0·7–0·8 (silica, EtOAc); ν_{max}C=O, 1740 (Nujol), 1735 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·35 (*q*, $4H_m$), 3·5 (*dd*, H_b) 3·2–2·7 (*m*, $4H_f$), 2·55 (*m*, $H_d + H_g$), 2·3–1·8 (*m*, $H_x + H_g + 4H_e$), 1·35 (*t*, $6H_n$), 1·1 (*dd*, $3H_z + 3H_{z'}$).

Ethyl (3-oxoquinuclidin-2-yl)methyl-phenylacetate (**2E**). This was prepared from Na, EtOH and **1** as given for **2B** and ethyl phenylacetate (49·2 g, 0·3 mole). The product, obtained as a brown oil, was first distilled at 195–200° (1 mm Hg), then chromatographed on Merck Kieselgel G with $CHCl_3$ as eluent, Yield, 54 g (60%), $M^+ = 301$; R_f, 0·5–0·4 (silica, EtOAc); ν_{max}C=O, 1710 cm^{-1} (neat). Methiodide salt, m.p. 194·7–195·6°. (Found: C, 51·4, H, 5·3; N, 3·4. $C_{19}H_{26}INO_5$ requires: C, 51·5; H, 5·3; N, 3·2%); NMR of the base ($CDCl_3$) δ7·3 (*s*, Ph), 4·25 (*q*, $2H_m$), 3·92 (*dd*, H_c), 3·4–2·55 (*m*, $H_b + 4H_e$), 2·55–2·2 (*m*, $H_d + H_g$), 2·2–1·7 (*m*, $H_{g'} + 4H_e$), 1·2 (*t*, $3H_n$).

Diethyl (3-hydroxyquinuclidin-2-yl)methylmalonate (mixture of isomers **3A** *and* **5A**). A soln of **2A** (43·3 g, 0·15 mole) in EtOH (50 ml) was treated at 5° with $NaBH_4$ (2·2 g, 0·06 mole) in EtOH (350 ml) in small increments. The progress of reduction was monitored by TLC on silica and EtOAc. Upon disappearance of **2A** (20 hr), the mixture was neutralised with conc HCl, EtOH removed by evaporation. The residue, taken up in water and extracted with $CHCl_3$, gave 27 g (60%) of viscous oil, ν_{max}C=O 1735 cm^{-1}; ν_{max}O–H, 3400 cm^{-1} ($CHCl_3$).

Diethyl (3-hydroxyquinuclidin-2-yl)methyl-methylmalonate (mixture of isomers **3B** *and* **5B**). This was prepared likewise from **2B** (72 g, 0·23 mole) in EtOH (43 ml) and $NaBH_4$ (3·55 g, 0·093 mole) in EtOH (600 ml), Yield, 55 g (74%) of viscous oil; ν_{max}O–H, 3400 cm^{-1}, ν_{max}C=O, 1735 cm^{-1} ($CHCl_3$). Methiodide salt, m.p. 228·2° (Found: C, 44·8; H, 6·3; N, 2·8. $C_{17}H_{30}INO_5$ requires: C, 44·8; H, 6·6; N, 3·1%).

Diethyl (3-hydroxyquinuclidin-2-yl)methyl-ethylmalonate (mixture of isomers **3C** *and* **5C**). This was prepared likewise from **2C** (55·5 g, 0·17 mole) in EtOH (660 ml) and $NaBH_4$ (2·9 g, 0·076 mole) in EtOH (400 ml), Yield, 50 g (87%) of viscous oil, ν_{max}O–H, 3500–3200 cm^{-1}, ν_{max}C=O, 1730 cm^{-1} (neat). Methiodide salt, m.p. (EtOH), 190·8–191·4° (hygroscopic). (Found: C, 45·2; H, 6·3; N, 2·6. $C_{18}H_{32}INO_5 \cdot \frac{1}{2}H_2O$ requires: C, 45·2; H, 6·9; N, 2·9%).

Diethyl (3-hydroxyquinuclidin-2-yl)methyl-isopropylmalonate (mixture of **3D** *and* **5D**). This was prepared likewise from **2D** (9·2 g, 0·077 mole) in EtOH (100 ml) and $NaBH_2$ 0·5 g, 0·013 mole) in EtOH (150 ml), Yield, 9·6 g (86%) of viscous oil, ν_{max}O–H, 3550–3300, ν_{max}C=O, 1730 cm^{-1} ($CHCl_3$). Methiodide salt, m.p. (EtOH), 213·3–213·5° (hygroscopic). (Found: C, 46·5; H, 6·7; N, 2·9. $C_{19}H_{34}INO_5 \cdot \frac{1}{2}H_2O$ requires: C, 46·3; H, 7·1; N, 2·8%).

Ethyl (3-hydroxyquinuclidin-2-yl)methyl-phenylacetate (mixture of isomers **3E** *and* **5E**). This was prepared likewise from **2E** (22·4 g, 0·74 mole) in EtOH (100 ml) and $NaBH_4$ (1·2 g, 0·031 mole) in EtOH (200 ml), Yield, 19·5 g (80%); m.p. (acetone) 147·7–148·2°; ν_{max}O–H, 3200–3100 cm^{-1}, ν_{max}C=O, 1710 cm^{-1} ($CHCl_3$). (Found: C, 70·9; H, 8·1; N, 4·2. $C_{18}H_{25}NO_3$ requires: C, 71·3; H, 8·3; N, 4·6%).

Diethyl (3-hydroxy-3-deuteroquinuclidin-2-yl)methyl-methylmalonate mixture of **3H** *and* **5H**). This was prepared likewise from **2B** (17·6 g, 0·06 mole) in EtOH (50 ml) and $NaBD_4$ (1 g, 0·026 mole) in EtOH (150 ml), Yield, 15 g (79·9%) of viscous oil; ν_{max}O–H, 3400 cm^{-1}, ν_{max}C=O, 1735 cm^{-1} ($CHCl_3$). The crude oil was used further without purification.

6-Oxa-1-azatricyclo(4.2.2.0^{2,7})dodecan-5-one (**4A**). A soln of the mixture **3A** and **5A**, (26·1 g, 0·087 mole), conc HCl (150 ml) and water (40 ml) was refluxed for 22 h then flash-evaporated. The residual glass, dissolved in water (50 ml), neutralised with $NaHCO_3$, extracted with $CHCl_3$, dried, evaporated and triturated with light petroleum (b. 40–60°) gave **4A** (1 g), m.p. 86·7° (extremely hygroscopic). (Found: C, 64·7; H, 8·4; N, 7·7. $C_{10}H_{15}NO_2 \cdot H_2O$ requires: C, 64·7; H, 8·4; N, 7·6). $M^+ = 181$; ν_{max}C=O, 1745 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·5 (*dd*, H_a), 3·7–2·6 (*m*, $H_b + 4H_f$), 2·6–2·4 (*m*, $2H_c + H_d + H_g$), 2·4–1·4 (*m*, $H_{g'} + 4H_e$).

2-(trans-3-Hydroxyquinuclidin-2-yl)-α-methyl propanoic acid hydrochloride (**6B**). Reflux of the mixture **3B**, **5B** (54·8 g, 0·176 mole) with conc HCl (200 ml) and water (100 ml) followed by partial evaporation and cooling gave **6B** which crystallized spontaneously (8 g, 18%); m.p. 268·8–269·4°. (Found: C, 53·0; H, 7·9; N, 5·5. $C_{11}H_{20}NO_3$ requires: C, 52·9; H, 8·1; N, 5·6%); ν_{max}O–H, 3300 (br), $\nu_{max}NH^+$, 2500 (br) ν_{max}C=O, 1720 cm^{-1} (Nujol); NMR (D_2O) δ 3·9 (*dd*, H_a), 3·7–3 (*m*, $H_b + 4H_f$), 3–2·5 (*m*, H_c), 2·5–1·6 (*m*, $H_d + H_g + H_{g'} + H_e$), 1·3 (*d*, $3H_x$).

4-Methyl - 6 - oxa - 1 - azatricyclo(4.2.2.0^{2,7})dodecan - 5 - one hydrochloride (**4B**). The mother liquor from the previous preparation was further evaporated to dryness and **4B** was recrystallized from the crude solid with EtOH (27·5 g, 66%); m.p. = 267·2° (dec); (Found: C, 56·5; H, 8·0; N, 6·2. $C_{11}C_{18}ClNO_2$ requires: C, 57·0; H, 7·8; N, 6·1%); R_f, 0·4 (acidic alumina,

$CHCl_3$). ν_{max}C=O, 1755 cm^{-1} (Nujol); NMR (DCl in D_2O 2–5%) δ 4·87 (*dd*, H_a), 4·2 (*bq*, H_b), 3·6–3·2 (*m*, $4H_f$), 2·8 (*m*, H_c), 2·6 (*m*, H_d), 2·3 (*m*, H_g), 2·21–1·8 (*m*, $H_{g'}+4H_e$), 1·23 (*d*, $3H_x$).

4 - *Methyl* - 6 - *oxa* - 1 - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one* (**4B**-*Base*). 5 g of **4B**-(HCl) was dissolved in 50 ml of water; the soln was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. Usual work-up yielded 3·5 g of a white solid which was triturated with and recrystallized from light petroleum, m.p. = 100–102° (Found: C, 67·5; H, 8·8; N, 7·4. $C_{11}H_{17}NO_2$ requires: C, 67·7; H, 8·8; N, 7·2); R_f, 0·7 (alumina, $CHCl_3$; M^+ = 195; ν_{max}C=O, 1745 cm^{-1} (Nujol), 1740 cm^{-1} ($CHCl_3$); NMR ($CHCl_3$) δ 4·55 (*dd*, H_a), 3·7–2·8 (*m*, H_b+4H_g), 2·5 (*m*, H_c), 2·3–2·2 (*m*, H_d+H_g), 2·2–1·6 (*m*, $H_{g'}+4H_e$), 1·29 (*d*, $3H_x$). Methiodide salt (6*B*-Methiodide), m.p. (EtOH) 191·2°; (Found: C, 42·6; H, 5·9; N, 4·2. $C_{12}H_{20}INO_2$ requires: C, 42·7; H, 6·0; N, 4·2%); ν_{max}C=O, 1755 cm^{-1} (Nujol); NMR (DCl in D_2O 2–5%) δ 4·95 (*dd*, H_a), 4·3 (*q*, H_b), 3·8–3·15 (*m*, $4H_f$), 3(*s*, *N*-M_e), 2·8 (*m*, H_c), 2·6 (*m*, H_d), 2·3 (*m*, H_g), 2·2–1·8 (*m*, $H_{g'}+4H_e$), 1·23 (*d*, $3H_x$).

4 - *Ethyl* - 6 - *oxa* - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one* (**4C**). Reflux of the mixture **3C**, **5C** (12·3 g, 0·038 mole) with conc HCl (64·8 ml) and water (32·4 ml) for 20 hr then evaporation gave a glassy residue which, redissolved in water (50 ml), neutralized with $NaHCO_3$, extracted with $CHCl_3$, dried and evaporated, gave crystalline **4C** (2 g, 25%) upon trituration with light petroleum (b. 40–60°), m.p. 63–65°. (Found: C, 69·0; H, 9·0; N, 6·7. $C_{12}H_{13}NO_2$ requires: C, 68·9; H, 9·2; N, 6·7%); M^+ = 209; ν_{max}C=O, 1755 (Nujol) or 1745 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·53 (*dd*, H_a), 3·7–2·7 (*m*, H_b+4H_f), 2·5 (*m*, H_c), 2·3–2·1 (*m*, H_d+H_g), 2·1–1·4 (*m*, $H_{g'}+2H_x+4H_e$), 1·0 (*t*, $3H_x$). Hydrochloride salt, prepared from **4C** in dry ether and gaseous HCl, m.p. (EtOH) 255·1–256·1° (Hygroscopic); R_f, 0·3 (acidic alumina, $CHCl_3$) (Found: C, 56·3; H, 8·5; Cl, 14·4; N, 5·5. $C_{12}H_{20}ClNO_2\cdot\frac{1}{2}H_2O$ requires: C, 56·6; H, 8·3; N, 5·5; Cl, 14·0) ν_{max}C=O, 1755 cm^{-1} (Nujol). NMR (DCl in D_2O, 2–5%) δ 4·93 (*dd*, H_a), 4·28 (*q*, H_b), 3·7–3·1 (*m*, $4H_f$), 2·75 (*m*, H_c), 2·6–2·3 (*m*, H_d+H_g), 2·1–1·4 (*m*, $H_{g'}+2H_x+4H_e$), 1·0 (*t*, $3H_x$). Methiodide salt of **4C**, m.p. (EtOH) 158·1° (Found: C, 44·3; H, 6·4; N, 4·0. $C_{13}H_{22}INO_2$ requires: C, 44·5; H, 6·3; N, 4·0%).

4 - *Isopropyl* - 6 - *oxa* - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one* (**4D**). This was prepared from the mixture **3D**, **5D** (9 g, 0·026 mole), conc HCl (70 ml) and water (30 ml) as described for **4C**, yield, 1 g (17·2%); m.p. (P.E. 40–60°) 128–130°. (Found: C, 69·6; H, 9·4; N, 6·4. $C_{13}H_{21}NO_2$ requires: C, 69·9; H, 9·5; N, 6·3%); M^+ = 223; R_f 0·7 (neutral alumina, chloroform); ν_{max}C=O, 1740 (Nujol) or 1745 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·55 (*dd*, H_a), 3·7–2·8 (*m*, H_b+4H_f), 2·5 (*m*, H_c), 2·3–2·2 (*m*, H_d+H_g), 2·2–1·6 (*m*, $H_{g'}+4H_e+H_x$), 1·13 (*d*, $3H_z$), 1·03 (*d*, $3H_{z'}$). The hydrochloride of **4D** prepared from **4D** in dry ether and gaseous HCl, m.p. (EtOH) 259·6–260·1°. (Found: C, 59·7; H, 8·7; N, 5·0. $C_{13}H_{22}ClNO_2$ requires: C, 60·1; H, 8·5; N, 5·3%); R_f 0·4 (acidic alumina, $CHCl_3$); ν_{max}C=O, 1760 cm^{-1} (Nujol); NMR (DCl in D_2O 2–5%) δ 4·86 (*dd*, H_a), 4·2 (*q*, H_b), 3·65–3·1 (*m*, $4H_f$), 2·72 (*m*, H_c), 2·55 (*m*, H_d), 2·4 (*m*, H_g), 2·3 (*m*, H_x), 2·2–1·6 (*m*, $H_{g'}+4H_e$), 1·05 (*d*, $3H_z$), 0·95 (*d*, $3H_{z'}$).

4 - *Phenyl* - 6 - *oxa* - 1 - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one* (**4E**). This was prepared by reflux of the mixture **3F**, **5F** (16·9 g, 0·056 mole) in conc HCl (100 ml) and water (40 ml) as described for **4C**, yield, 2·7 g (18%); m.p. (P.E. 40–60° + EtOH, 2:1) 162–163°. (Found: C, 74·4; H, 7·5; N, 6·6. $C_{16}H_{13}NO_2$ requires: C, 74·4; H, 7·4; N, 6·4%); R_f 0·6 (neutral alumina, $CHCl_3$); M^+ = 257; ν_{max}C=O, 1740 cm^{-1} (Nujol or $CHCl_3$); NMR ($CDCl_3$) δ 7·35 (s, 5H), 4·45 (*dd*, H_a), 3·5 (*dd*, H_c), 3·4–3·02 (*m*, H_b), 3·02–2·63 (*M*, $4H_f$), 2·47–2·02 (*m*, $H_d+H_g+H_{g'}$), 2·0–1·3 (*m*, $4H_e$). The hydrochloride was prepared from **4F** in anhyd ether and gaseous HCl, m.p. (EtOH) 300°. (Found: C, 65·3; H, 6·8; N, 4·9. $C_{16}H_{20}ClNO_2$ requires: C, 65·4; H, 6·9; N, 4·8%); R_f 0·8 (acidic alumina, $CHCl_3$): ν_{max}C=O, 1765 cm^{-1} (Nujol); NMR (DCl in D_2O, 2–5%) δ 7·35 (*s*, 5*H*), 5·0 (*dd*, H_a), 4·6–3·8 (*m*, H_c+H_b), 3·7–3·1 (*m*, $4H_f$), 2·8–2·3 (*m*, $H_d+H_g+H_{g'}$), 2·3–1·4 (*m*, $4H_e$).

2 - (3 - trans - *Hydroxyquinuclidin* - 2 - *yl*) - α - *methyl* - α - *deutero*, *deuteropropanoic acid* (**6F**–DCl). This was prepared as described for **6B**, from mixture of **3B**, **5B** (13·7 g, 0·043 mole), and DCl in D_2O (20%, 20 ml); partial evaporation and cooling gave **6F** (DCl) which crystallized out spontaneously, yield, 1·7 g (15·5%), m.p. (EtOH) 273·2–273·9° dec. (Found: C, 52·1; H + D, 8·7; N, 5·9; Cl, 14·2. $C_{11}D_3H_{17}ClNO_3$ requires: C, 52·3; H + D, 9·1; N, 5·5; Cl, 14·1%). ν_{max}O–H, 3300 (br), $\nu_{max}NH^+$, 2500 (br), ν_{max}C=O, 1720 cm^{-1} (Nujol); NMR (D_2O) 3·9 (*dd*, H_a), 3·7–3 (*m*, H_b+4H_f), 2·5–1·6 (*m*, $H_d+H_g+H_{g'}+4H_e$), 1·3 (*s*, $3H_x$).

4 - *Methyl* - 4 - *deutero* - 6 - *oxa* - 1 - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one deuterochloride* (**4F**). This was obtained from the mother liquor of the previous preparation by complete evaporation and trituration with acetone, yield, 7·6 g (74%), m.p. (EtOH), 263·3–263·9° (Hygroscopic). (Found: C, 52·8; H, 8·3; N, 5·8; Cl, 14·1. $C_{11}H_{16}D_2NO_2Cl\cdot H_2O$ requires: C, 52·5; H, 8·7; N, 5·6; Cl, 14·1%); ν_{max}C=O, 1755 cm^{-1} (Nujol); NMR (DCl in D_2O, 2–5%) δ 4·55 (*dd*, H_a), 4·23 (*q*, H_b), 3·7–3·1 (*m*, $4H_f$), 2·7–2·4 (*m*, H_d), 2·4–2·2 (*m*, H_g), 2·2–1·7 (*m*, $H_{g'}+4H_e$), 1·2 (*s*, $3H_x$).

4 - *Methyl* - 4 - *deutero* - 6 - *oxa* - 1 - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one* (**4F**-*Base*). This was prepared from **4F**-(DCl) as described for **4B**-(Base). M.p. (P.E. 40–60°), 97·8–98·1; (Found: C, 66·9; H + D, 8·8; N, 6·9. $C_{11}DH_{16}NO_2$ requires: C, 67·3; H + D, 9·2; N, 7·1%); M^+ = 196; ν_{max}C=O, 1740 cm^{-1} ($CHCl_3$); NMR ($CDCl_3$) δ 4·55 (*dd*, H_a), 3·7–2·8 (*m*, H_b+4H_f), 2·3–2·2 (*m*, H_d+H_g), 2·2–1·6 (*m*, $H_{g'}+4H_e$), 1·29 (*s*, $3H_x$).

2 - (3 - trans - *Deuterohydroxyquinuclidin* - 2 - *yl*) - α - *methyl* - α - *deutero* - *deuteropropanoic acid* (**6H**-DCl). This was prepared as described for **6B**, from mixture of **3H**, **5H** (14·1 g, 0·045 mole), and DCl in D_2O (20%, 25 ml); partial evaporation and cooling gave **6H** (DCl) which crystallized out spontaneously, yield, 3 g (11·8%), m.p. (EtOH) 272·5°–273·1° (dec). (Found: C, 51·7; H + D, 9·7; N, 5·1; Cl, 13·9. $C_{11}D_4H_{16}ClNO_3$ requires: C, 52·1; H + D, 9·5; N, 5·5; Cl, 14·0%); ν_{max}O–H, 3300(br), ν_{max}C=O, 1720 cm^{-1} (Nujol); NMR (D_2O) 3·7–3(m, H_b+4H_f), 2·5–1·6(*m*, $H_d+H_g+H_{g'}+4H_e$), 1·3(*s*, $3H_x$).

4 - *Methyl* - 4,7 - *dideutero* - 6 - *oxa* - 1 - *azatricyclo*(4.2.2.$0^{2,7}$)*dodecan* - 5 - *one deuterochloride* (**4G**). The compound was obtained as **4F**(DCl) from the mother liquor of the previous preparation, yield, 8 g (70%); m.p. (EtOH), 269·1° (dec), (Hygroscopic). (Found: C, 52·7; H + D, 9·5; N, 5·2; Cl, 14·0. $C_{11}H_{15}D_3NO_2Cl\cdot H_2O$ requires: C, 52·3; H + D, 9·1; N, 5·5; Cl, 14·1%); R_f, 0·3 (acidic alumina, $CHCl_3$); ν_{max}C=O, 1755 cm^{-1} (Nujol); NMR (D_2O) δ 4·23 (*t*, H_b), 3·7–3·1 (*m*, $4H_f$), 2·7–2·4 (*m*, H_d), 2·4–2·2 (*m*, H_g), 2·2–1·7 (*m*, $H_{g'}+4H_e$), 1·23 (*s*, $3H_x$).

4 - Methyl - 4,7 - dideutero - 6 - oxa - 1 - azatricyclo(4.2.2.$0^{2,7}$)dodecan - 5 - one (**4G**. *Base*). This was prepared from **4H** (DCl) as described for (**4B**. Base). M.p. (P.E. 40–60°), 96·8; (Found: C, 66·6; H + D, 9·2; N, 6·8; $C_{11}D_2H_{15}NO_2$ requires: C, 67·0; H + D, 9·6; N, 7·1%); M^+ = 197; ν_{max}C=O, 1740 ($CHCl_3$); NMR ($CDCl_3$) δ 3·7–2·8 (*m*, H_b+4H_f), 2·3–2·2 (*m*, H_d+H_g), 2·2–1·6 (*m*, $H_{g'}+4H_e$), 1·29 (*s*, $3H_x$).

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REFERENCES

[1a] R. W. Baker, C. H. Chotia, P. Pauling and T. J. Petcher, *Nature Lond.* **230**, 439 (1971); [b] R. W. Baker and P. J. Pauling, *J.C.S.* Perkin II, 2340 (1972); [c] W. H. Beers and E. Reich, *Nature Lond.* **228**, 917 (1970)

[2] B. Belleau, *J. Med. Chem.* **7**, 776 (1964)

[3] A. Hansen and H. Bader, *J. Het. Chem.* **3**, 109 (1966)

[4] E. Oppenheimer and E. D. Bergmann, *Synthesis* (5), 269 (1972)

[5] M. Barfield and B. Chakrabarti, *Chem. Rev.* **69**, 757 (1969); B. Sternhell, Rev. *Pure and Appl. Chem.* **14**, 15 (1964)

[6a]M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); [b]M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963); [c]R. J. Abraham, *Nuclear Magnetic Resonance for Organic Chemists* (Edited by D. W. Mathieson) Academic Press, New York (1967)
[7]A. H. Beckett and R. E. Reid, *Tetrahedron* **28**, 5555 1972)
[8]W. L. Nelson and R. S. Wilson, *J. Med. Chem.* **14**, 169 (1971)
[9a]A. McL Mathieson and J. C. Taylor, *Tetrahedron Letters* 1590 (1961); [b]A. McL Mathieson, *Ibid.* 81 (1963); [c]J. F. McConnell, A. McL Mathieson and B. P. Shoenborn, *Ibid.* 445 (1962); [d]B. P. Shoenborn and J. F. McConnell, *Acta. Cryst.* **15**, 779 (1962); [e]G. G. Overberger and H. Kaye, *J. Am. Chem. Soc.* **89**, 5646 (1967); [f]R. C. Shepphard and S. Turner, *Chem. Comm.* 77 (1968); [g]F. I. Carroll and J. T. Blackwell, *Ibid.* 4173 (1970)
[10]R. Cahill and T. A. Crabb, *Org. Mag. Res.* **4**, 509 (1972)
[11]G. M. Whitesides, D. Holtz and J. D. Roberts, *J. Am. Chem. Soc.* **86**, 2628 (1964)
[12]J. A. Pople, *High Resolution NMR*, pp. 389–399. McGraw-Hill, New York (1959)
[13]R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **39**, 216 (1961)
[14]E. O. Bishop, *Ann. Rev. NMR Spect.* **1**, 91 (1968)
[15]K. Sisido, K. Inomata, K. Kogeyema and K. Utimoto, *J. Org. Chem.* 3149 (1968)
[16a]K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.* **83**, 4623 (1961); [b]D. Savostianoff and M. Pfau, *Bull. Soc. Chim. Fr.* 4162 (1967)
[17]H. Booth, *Tetrahedron Letters* 411 (1963) and refs cited
[18]K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal and H. G. Welsh, *J. Am. Chem. Soc.* **89**, 2401 (1967) and refs cited
[20a]G. H. Whitesides and J. D. Roberts, *Ibid.* **87**, 4878 (1965); [b]H. L. Martin and G. J. Martin, *Bull. Soc. Chim. Fr.*, 2117 (1966) and refs cited
[21]K. K. Cheung, K. H. Overton and G. A. Sim, *Chem. Comm.* 634 (1965)
[22]G. A. Lindsay and K. H. Overton, *J.C.S.* Perkin I, 385 (1973) and refs cited