

# THE $^1\text{H}$ NMR SPECTRA AND CONFORMATIONS OF SOME SUBSTITUTED MORPHOLIN-2-ONES

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**Abstract**—A series of substituted morpholin-2-ones has been synthesized, and their  $^1\text{H}$  NMR spectra interpreted in terms of a half-chair conformation. The effect of different solvents on the spectra is discussed.

WORK aimed at establishing the conformation of  $\delta$ -lactones has been described in several recent communications. The results<sup>1,2</sup> of crystal structure analyses are in accord with a planar  $\text{C}=\text{CO}-\text{O}-\text{C}$  group, and Mathieson<sup>3</sup> inferred that the presence of this group in a 6-membered ring produced a boat conformation. Later work<sup>4</sup> indicates that  $\delta$ -lactones normally adopt the half-chair conformation, and a correlation between the carbonyl stretching frequency in solution and the presence of the half-chair and half-boat conformations in the crystal has been made. ORD data have been interpreted<sup>5</sup> as supporting a boat conformation for  $\delta$ -lactone ring. More recently,<sup>6,7</sup> the PMR spectra of some substituted valerolactones and of some steroidal ketones have been reported, and the vicinal coupling constants obtained are consistent with half-chair or slightly flattened half-chair conformations.

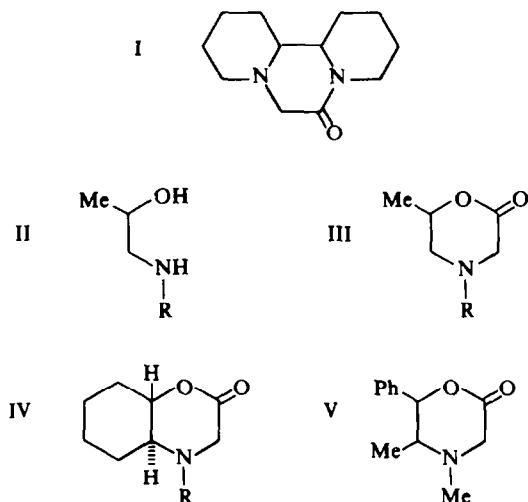
Our interest<sup>8</sup> in geminal coupling constants in methylene groups prompted us to prepare a series of N-substituted morpholin-2-ones, since in our original survey of coupling constants we had no values for the  $\text{N}-\text{CH}_2-\text{CO}-\text{O}$  system. The very negative value of  $J_{gem} = -16$  Hz has recently been observed<sup>9</sup> for the related  $\text{N}-\text{CH}_2-\text{CO}-\text{N}$  system in the two diastereoisomers of I.

Accordingly, propylene oxide was reacted with a series of primary amines to give aminoalcohols (II), and these on treatment with ethyl chloroacetate gave N-substituted 6-methyl morpholin-2-ones (III). In a similar manner, the perhydrobenzomorpholin-

TABLE 1. PMR SPECTRA OF SUBSTITUTED MORPHOLIN-2-ONES  
COUPLING CONSTANTS (Hz) IN  $\text{CCl}_4$

Compound	$J_{3ax' 3eq'}$	$J_{5ax' 5eq'}$	$J_{5ax' 6ax'}$	$J_{5eq' 6ax'}$	$J_{3eq' 5eq'}$
III R = cyclohexyl	-17.4	-12.0	8.3	3.7	1.5
III R = benzyl	-17.1	-12.0	8.5	3.4	1.4
III R = phenyl	-18.0	-12.4	9.2	3.0	0
III R = o-OMe	-17.5	-12.5	8.6	3.4	1.5
III R = iso-Pr	-17.1	-12.2	8.5	3.0	1.4
III R = t-Bu	-17.5	-12.2	8.2	3.4	1.5
IV R = benzyl	-17.6	—	—	—	—
IV R = cyclohexyl	-17.5	—	—	—	—
IV R = phenyl	Singlet	—	—	—	—
V	Singlet	—	—	3.1	—

2-ones (IV) were prepared from cyclohexene oxide and 4,5 dimethyl 6-phenyl morpholin-2-one (V) from ephedrine and ethyl chloroacetate. Table 1 shows the observed coupling constants for all the compounds prepared.

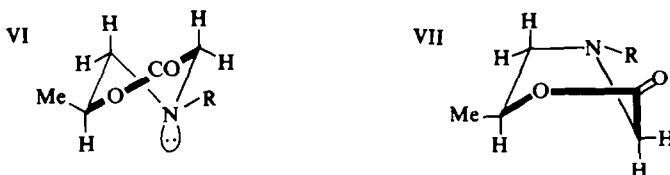


In the series of compounds III prepared from propylene oxide,  $J_{gem}^*$  for the  $N-CH_2-C=O$  protons varies between  $-17$  and  $-18$  Hz, a much more negative value than that observed for methylene protons adjacent to nitrogen in piperidine derivatives for which the range is  $-11$  to  $-14$  Hz.<sup>8</sup> Lambert *et al.*<sup>10</sup> report that  $J_{gem}$  for the  $\alpha$ -methylene group varies with solvents between  $-10.2$  and  $-12.3$  Hz in piperidine, and between  $-11.0$  to  $-11.4$  Hz in *N*-methylpiperidine. Assuming a Barfield-Grant  $J^{\pi}-\phi$  type of relationship<sup>11</sup> to exist for the effect of the lactone carbonyl on the  $J_{gem}$  of an adjacent methylene group, the observed  $J_{gem}$  of  $-17$  to  $-18$  Hz can only be reconciled with a conformation in which the  $C=O$  group bisects the C3 methylene. To achieve this stereochemistry and simultaneously to maintain the planarity of the lactone grouping, the half-chair conformation (VI) is necessary. In support of this, the vicinal couplings between the C5 methylene protons and the C6 proton are ca. 8.3 and 3.4 Hz. The analogous couplings in valerolactones have been reported<sup>6</sup> as 12.7 and 3.1 Hz. However, the former value is somewhat large for this type of vicinal coupling since the dihedral angle in question is less than  $180^\circ$  in a half-chair conformation.

In all the compounds except III ( $R = Ph$ ) long range coupling (ca. 1.5 Hz) was observed between  $H_{3eq'}$  and  $H_{5eq'}$ . Although long range couplings involving various types of stereochemistry have been reported recently, the maximum effect seems to occur when the planar W configuration is present.<sup>12</sup> This geometry is present in the half-chair conformation (VI). The values of  $J_{vic}$ ,  $J_{gem}$  and  $^4J$  are all consistent with a fixed conformation with the 6-Me and the N-substituent equatorially orientated, rather than a rapidly equilibrating system. The value of  $J_{gem}$  for the C5 methylene protons is ca.  $-12.5$  Hz, consistent with conformation (VI) in which the nitrogen

\*  $J_{gem}$  is assumed to be negative.

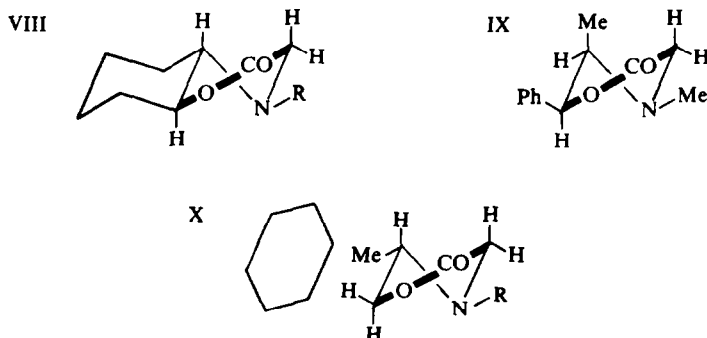
lone pair is axially orientated. A more negative value of  $J_{gem}$  would be expected<sup>13</sup> for conformation VI with an equatorial nitrogen lone pair.



Alternative boat and half-boat conformations may be ruled out from a consideration of the values of the coupling constants, particularly of  $J_{3eq'3ax}$ . For example, in the boat conformation (VII) the lactone plane makes a dihedral angle of  $0^\circ$  with the C3H and a value of ca.  $-12$  Hz would be expected for  $J_{3eq'3ax}$ . In addition the geometry of VII is not the favourable one for the observation of a large  $J_{3eq'5eq}$ . Models of half-boat conformations possessing a planar C—O—CO—C arrangement suggest dihedral angles of ca.  $30^\circ$  between the C=O plane and C3H which should give rise to values of  $J_{3eq'3ax}$  in the region of  $-13$  to  $-14$  Hz.

The perhydrobenzomorpholines IV prepared from cyclohexene oxide were obtained as stable crystalline solids, a fact difficult to reconcile with results described in a recent note<sup>14</sup> stating that morpholones, including the N—Ph compound (IV) were sensitive to humidity and oxidation, and extremely unstable, decomposing within a few hours.

Compound IV (R = Ph) showed a singlet for the N—CH<sub>2</sub>—C=O methylene protons at  $6.05 \tau$  in CCl<sub>4</sub>, whereas IV (R = benzyl) and IV (R = cyclohexyl) exhibited the expected quartet.  $J_{gem}$  for these latter compounds was within the range  $-17$  to  $-18$  Hz, as for series III, and again can only be reconciled with a half-chair conformation (VIII). The value of  $J_{gem}$  ( $-4$  to  $-6$  Hz) quoted<sup>14</sup> for the CH<sub>2</sub>—C=O protons in a number of perhydrobenzo morpholin-2-ones is inconsistent with a geminal coupling in this type of system.<sup>8</sup> Also the observed value of  $\nu_{max}$  for IV (R = Ph) of  $1760 \text{ cm}^{-1}$  (C=O) does not agree with the quoted value<sup>14</sup> of  $1715 \text{ cm}^{-1}$ .



Compound V was assigned the half-chair conformation IX on the basis of the value of  $3.1$  Hz for the vicinal coupling constant between the C5 and C6 protons, and the the known configuration of ephedrine. A singlet was observed for the C3 methylene protons in this compound.

In both compound V and the series of compounds III prepared from propylene oxide, the C6 proton appears at very low field, presumably a result of deshielding by the O—C=O group. Large deshieldings over an analogous amide plane have been observed.<sup>15</sup>

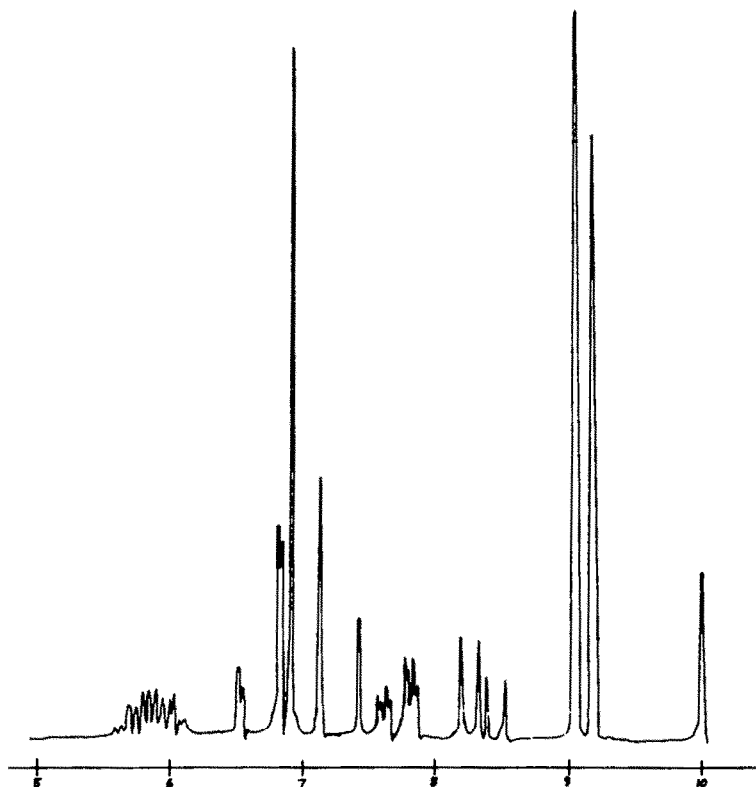


FIG. 1. The PMR spectrum of N-benzyl 6-methyl morpholin-2-one (III, R = benzyl).

Most of the morpholinones described in this paper exhibit the carbonyl absorption in the IR in the region of  $1750\text{ cm}^{-1}$  in accord with a half-chair conformation.<sup>4</sup> Two compounds, III (R = Ph) and IV (R = Ph) show the carbonyl absorption at  $1760\text{ cm}^{-1}$  which might be interpreted<sup>4</sup> as indicating a boat conformation were it not for the observed values of the coupling constants for the C3 methylene protons (Table 1). For III (R = Ph)  $J_{3ax'3eq'}$  is only ca. 0.5 Hz more negative than for the other compounds in the series but evidence of a long range coupling between H3eq' and H5eq' disappears. However, III (R = OMePh) has very similar coupling constants, including the  $^4J$ , to all the other compounds III. This suggests that in III (R = Ph) the N lone pair and the phenyl ring are coplanar leading to a redistribution of electrons with a resultant flattening around the N atom and it is this change in geometry which gives rise to the small variations in the coupling constants and in the higher value of  $\nu(\text{C=O})$ . In III (R = OMe) presumably the presence of the ortho MeO group hinders coplanarity of the N lone pair and the aromatic ring, preventing significant distortion of the half chair;  $\nu_{\text{max}}$  for this compound is  $1750\text{ cm}^{-1}$ .

PMR solvent induced shifts have been the subject of a number of recent papers.<sup>16</sup> For a particular proton, these shifts are dependent on the relative positions in the molecule of that proton, and any polar sites present. Hence such shifts have potential utility in assigning configuration and conformation. However, owing to the immense complexity of the subject comparatively little progress has been made in this direction in the last few years.

TABLE 2. PMR SPECTRA OF SUBSTITUTED MORPHOLIN-2-ONES  
CHEMICAL SHIFTS ( $\tau$  VALUES) IN  $\text{CCl}_4$ ,  $\text{CDCl}_3$  AND BENZENE

Compound	Solvent	$\tau_{3\text{eq}}$	$\tau_{3\text{ax}}$	$\tau_{5\text{ax}}$	$\tau_{5\text{eq}}$	$\tau_{6\text{ax}}$	$\tau_{\text{Me}}$
III R = cyclohexyl	$\text{CCl}_4$	6.60	6.90	7.73	7.09	5.60	8.69
	$\text{CDCl}_3$	6.46	6.79	7.70	7.00	5.46	8.66
	benzene	6.61	7.07	8.18	7.59	5.84	8.96
III R = benzyl	$\text{CCl}_4$	6.69	7.07	7.84	7.25	5.52	8.74
	$\text{CDCl}_3$	6.54	7.00	7.80	7.18	5.44	8.72
	benzene	6.71	7.21	8.35	7.70	5.85	9.10
III R = phenyl	$\text{CCl}_4$	6.05	6.23	7.08	6.51	5.40	8.60
	$\text{CDCl}_3$	5.85	6.09	6.99	6.40	5.28	8.54
	benzene	6.31	6.47	7.73	7.21	6.05	9.10
III R = o-OMePh	$\text{CCl}_4$	6.10	6.52	7.20	6.65	5.40	8.67
	$\text{CDCl}_3$	5.86	6.34	7.11	6.52	5.24	8.59
	benzene	5.95	6.49	7.53	6.99	5.63	8.85
III R = isoPr	$\text{CCl}_4$	6.66	6.98	7.79	7.14	5.50	8.70
	$\text{CDCl}_3$	6.52	6.88	7.75	7.10	5.44	8.66
	benzene	6.71	7.09	8.18	7.58	5.75	8.96
III R = t-Bu	$\text{CCl}_4$	6.60	6.92	7.80	7.10	5.58	8.70
	$\text{CDCl}_3$	6.44	6.78	7.75	7.20	5.47	8.65
	benzene	6.63	6.99	8.18	7.50	5.80	8.95
IV R = benzyl	$\text{CCl}_4$	6.63	7.19	—	—	—	—
	$\text{CDCl}_3$	6.48	7.06	—	—	—	—
	benzene	6.53	7.18	—	—	—	—
IV R = cyclohexyl	$\text{CCl}_4$	6.55	6.83	—	—	—	—
	$\text{CDCl}_3$	6.38	6.68	—	—	—	—
	benzene	6.51	6.84	—	—	—	—
IV R = phenyl		singlet at					
	$\text{CCl}_4$		6.05 $\tau$	—	—	—	—
	$\text{CDCl}_3$		5.93 $\tau$	—	—	—	—
	benzene		6.16 $\tau$	—	—	—	—
V		$\tau_{\text{CH}_2}$	$\tau_{\text{Ph}}$	$\tau_{\text{CSMe}}$	$\tau_{\text{H5eq}}$	$\tau_{6\text{ax}}$	$\tau_{\text{N-Me}}$
	$\text{CCl}_4$	6.71	2.75	9.33	7.05	4.54	7.72
	$\text{CDCl}_3$	6.61	2.70	9.33	6.97	4.43	7.72
	benzene	6.81	3.85	9.59	7.40	4.68	8.10

For aromatic solvents, the observed shifts depend on:

1. attraction of aromatic solvent to positive dipole(s) in the polar solute molecule, associated with mutual orientation of the solute and aromatic solvent, probably in a transient 1:1 complex.

2. The diamagnetic anisotropy of the aromatic solvent, which implies shielding or deshielding of solute protons, depending on the geometry of the solvent-solute association.

Bhacca and Williams<sup>17</sup> originally suggested that the positive centre of the solute molecule interacted with the  $\pi$ -electron system of the aromatic ring in such a way that the negative end of the solute dipole was as far from the ring as possible, consistent with a planar association. Later work<sup>18</sup> showed that observed shifts could only be accounted for in terms of a non-planar collision complex.

PMR solvent shifts in  $\delta$ -lactones have been very briefly studied;<sup>19</sup> however, in the series of compounds III much more striking solvent shifts are observed. The signals arising from the C5 methylene protons appear to move most,  $\delta$   $\text{CDCl}_3$ — $\text{C}_6\text{H}_6$  being as much as 0.74 (Table 2). The C6H and C6—Me signals both move upfield in benzene, relative to  $\text{CDCl}_3$  or  $\text{CCl}_4$ . In contrast, the C3 methylene protons are least affected. This is consistent with a collision complex in which the benzene ring is orientated away from the negative dipole of the lactone group so that it lies in the vicinity of the C5—C6 bond, thus shielding the C5 methylene protons, the C6 methyl and hydrogen, but hardly affecting the C3 methylene. (See X).

In addition, the PMR spectra of compounds III were run in a variety of aromatic solvents and certain regularities can be observed in the results obtained (Table 3). A particularly striking shift is produced by pyrrole on both the C5 protons ( $\delta_{\text{CCl}_4\text{--pyrrole}} \approx 0.5$  ppm), and while realising the number of factors influencing the change of chemical shift with solvent, particularly when employing polar solvents, it is tempting to correlate this with the electrophilic nature of the pyrrole nucleus. This should lead to a close association of the ring with the positive dipole of the  $\text{O—C=O}$  group, resulting in a greater shielding than is produced by benzene. Thiophene produces similar solvent shifts to those produced by benzene whereas  $\delta_{\text{CCl}_4\text{--C}_5\text{H}_5\text{N}}$  values are smaller than  $\delta_{\text{CCl}_4\text{--C}_6\text{H}_6}$  values in accord with the repulsion expected between the pyridine nucleus and the positive end of the  $\text{O—C=O}$  dipole.

#### EXPERIMENTAL

All elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Micro-analytical Laboratory, Bonn, Germany and the Microanalytical Section, University of Reading. M.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 grating instrument, and measured as 0.2 M solns in  $\text{CCl}_4$  using 0.2 mm matched cells. The NMR spectra were determined on a Perkin-Elmer R-10 60 MHz spectrometer as 10% solns in different solvents, with TMS as internal reference.

Preparation of N-substituted 6-Me morpholin-2-ones.

**General procedure.** Propylene oxide (29 g, 0.5M) was heated with the appropriate amine (0.5M) in an autoclave at 150° for 6 hr. The resulting aminalcohol was distilled *in vacuo*, and heated under reflux with ethyl chloroacetate (0.5M) for 2½ hr. The mixture was cooled, basified with  $\text{Na}_2\text{CO}_3$  aq, and  $\text{CHCl}_3$  extracted 3 times. The dried ( $\text{Na}_2\text{SO}_4$ )  $\text{CHCl}_3$  extract was evaporated and the residue distilled. Where necessary the crude lactones were purified by picrate formation, and subsequent recovery of the pure lactone by passing the picrate down a short alumina column (Woelm neutral, activity 1), with acetone as eluent.

**N-Cyclohexyl-6-methylmorpholin-2-one** (III, R = cyclohexyl). The aminalcohol (38 g) b.p. 82°/0.1 mm was obtained from propylene oxide (29 g) and cyclohexylamine (49.5 g). N-cyclohexyl-6-methylmorpholin-

TABLE 3. PMR SPECTRA OF SUBSTITUTED MORPHOLIN-2-ONES  
CHEMICAL SHIFTS ( $\tau$  VALUES) IN OTHER SOLVENTS

Compound	Solvent	$\tau_{3\text{eq}}$	$\tau_{3\text{ax}}$	$\tau_{5\text{ax}}$	$\tau_{5\text{eq}}$	$\tau_{6\text{ax}}$	$\tau_{\text{Me}}$
III R = cyclohexyl	pyrrole	6.77	7.16	8.24	7.65	5.85	9.05
	thiophene	6.66	7.03	8.11	7.25	5.74	8.94
	furan	6.56	6.86	7.92	7.33	5.60	8.82
	$\text{CD}_3\text{CN}$	6.52	6.85	7.75	7.11	5.50	8.74
	pyridine	6.43	6.75	7.83	7.18	5.50	8.78
	nitrobenzene	6.50	6.75	7.78	7.14	5.47	8.89
III R = benzyl	pyrrole	6.82	7.41	8.38	7.73	5.84	9.12
	thiophene	6.72	7.20	8.28	7.63	5.78	9.05
	furan	6.62	7.08	8.12	7.56	5.65	8.95
	pyridine	6.46	6.90	7.91	7.32	5.48	8.85
III R = phenyl	pyrrole	6.35	6.62	7.74	7.13	6.00	9.06
	thiophene	6.14	6.43	7.58	7.06	5.91	9.01
	furan	6.02	6.30	7.38	6.78	5.68	8.87
	pyridine	5.67	5.98	7.08	6.44	5.38	8.74
III R = o-OMePh	pyrrole	6.07	6.70	7.64	7.08	5.75	9.02
	thiophene	5.93	6.49	7.48	6.92	5.60	8.93
	furan	5.92	6.43	7.33	6.78	5.48	8.82
	pyridine	5.73	6.19	7.15	6.60	5.30	8.75
III R = isoPr	pyrrole	6.79	7.22	8.29	7.79	5.85	9.04
	thiophene	6.67	7.07	8.13	7.63	5.71	8.92
	furan	6.61	6.98	7.97	7.32	5.60	8.83
	pyridine	6.47	6.85	7.88	7.23	5.50	8.78
III R = t-Bu	pyrrole	6.66	7.08	8.25	7.57	5.84	9.02
	thiophene	6.56	6.95	8.08	7.40	5.72	8.91
	furan	6.50	6.88	7.98	7.26	5.65	8.84
	pyridine	6.36	6.74	7.86	7.16	5.50	8.77
IV R = benzyl	pyrrole	6.69	7.33	—	—	—	—
	thiophene	6.47	7.11	—	—	—	—
	furan	6.54	7.20	—	—	—	—
	$\text{CD}_3\text{CN}$	6.63	7.05	—	—	—	—
	pyridine	6.34	6.94	—	—	—	—
IV R = cyclohexyl	pyrrole	6.65	6.95	—	—	—	—
	thiophene	6.49	6.83	—	—	—	—
	furan	6.44	6.74	—	—	—	—
	$\text{CD}_3\text{CN}$	6.47	6.75	—	—	—	—
	pyridine	6.27	6.63	—	—	—	—
V		$\tau_{3\text{ax}}, 3\text{eq}$	$\tau_{5\text{Me}}$	$\tau_{5\text{ax}}$	$\tau_{6\text{eq}}$	$\tau_{\text{NMe}}$	
	pyrrole	6.93	9.64	7.42	4.81	8.15	
	thiophene	6.82	9.59	7.37	4.66	8.09	
	furan	6.70	9.45	7.18	4.53	7.91	

2-one was obtained pure by distillation, b.p.  $104^{\circ}/0.1$  mm, yield 17.4 g  $\nu_{\text{max}}^{\text{CCl}_4}$   $1750\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $n_D^{25} = 1.49225$ . The picrate m.p.  $191\text{--}193^{\circ}$  (dec) from EtOH was prepared for analysis. (Found: C, 48.03; H, 5.03; N, 13.11.  $\text{C}_{17}\text{H}_{22}\text{O}_9\text{N}_4$  requires: C, 47.88; H, 5.20; N, 13.14%.)

*N*-Benzyl-6-methylmorpholin-2-one (III, R = benzyl). The aminoalcohol (53 g) b.p.  $110\text{--}126^{\circ}/0.2$  mm was obtained from propylene oxide (29 g) and benzylamine (53.5 g). Distillation of the final mixture yielded a product b.p.  $132\text{--}134^{\circ}/0.15$  mm, yield 40.5 g, which the NMR spectrum proved to be a mixture of the required lactone, and possibly unreacted aminoalcohol, present in approximately equal proportions. The calculated amount of picric acid in EtOH was added to a soln of the mixture (21.5 g) in EtOH. The resultant oil solidified within 24 hr, and was recrystallized twice from EtOH to give pure picrate, m.p.  $170\text{--}171^{\circ}$ , yield 21.6 g. (Found: C, 49.86; H, 4.54; N, 12.63.  $\text{C}_{18}\text{H}_{18}\text{O}_9\text{N}_4$  requires: C, 49.77; H, 4.18; N, 12.90%). A slurry of the picrate (13 g) in acetone was passed down an alumina column. After removal of acetone, the soln was distilled to give *N*-benzyl-6-methylmorpholin-2-one as a clear liquid, b.p.  $130^{\circ}/0.05$  mm, yield 3.4 g;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1750\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ );  $n_D^{25} = 1.52893$ .

*N*-Phenyl-6-methylmorpholin-2-one (III, R = phenyl). The aminoalcohol (33 g) b.p.  $108\text{--}114^{\circ}/0.2$  mm was obtained from propylene oxide (29 g) and aniline (46.5 g). After heating with ethyl chloroacetate, and working up as before, the mixture was distilled. The highest boiling fraction, b.p.  $130\text{--}138^{\circ}/0.09$  mm gave white crystals m.p.  $67^{\circ}$  from EtOH, yield 15 g;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1760\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). (Found: C, 69.06; H, 6.82; N, 7.29.  $\text{C}_{11}\text{H}_{11}\text{O}_2\text{N}$  requires: C, 69.09; H, 6.85; N, 7.33%.)

*N*-Orthomethoxyphenyl-6-methylmorpholin-2-one (III, R = *o*-OMe phenyl). The aminoalcohol (47.5 g) b.p.  $110\text{--}130^{\circ}/0.7$  mm was obtained from propylene oxide (29 g) and *o*-anisidine (61.5 g). After heating with ethyl chloroacetate and working up, the mixture was distilled. The highest boiling fraction, b.p.  $140\text{--}150^{\circ}/0.125$  mm gave white crystals m.p.  $83^{\circ}$  from EtOH, yield 16 g. (Found: C, 65.01; H, 7.06; N, 6.14.  $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}$  requires: C, 65.14; H, 6.83; N, 6.33%);  $\nu_{\text{max}}^{\text{CCl}_4}$   $1750\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ).

*N*-Isopropyl-6-methylmorpholin-2-one (III, R = isopropyl). The aminoalcohol (37 g) b.p.  $50\text{--}96^{\circ}/0.5$  mm was obtained from propylene oxide (29 g) and isopropylamine (29.5 g). The crude lactone (21 g) b.p.  $90\text{--}120^{\circ}/0.2$  mm formed picrate (16 g) m.p.  $145^{\circ}$  from EtOH. (Found: C, 43.59; H, 4.70; N, 14.51.  $\text{C}_{14}\text{H}_{16}\text{O}_9\text{N}_4$  requires: C, 43.52; H, 4.70; N, 14.50%). A slurry of the picrate (20 g) in acetone was passed down an alumina column as before, and *N*-isopropyl-6-methylmorpholin-2-one b.p.  $74\text{--}76^{\circ}/0.05$  mm obtained by distillation, yield 4.5 g;  $n_D^{25} = 1.46124$ ;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1750\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ).

*N*-*t*-Butyl-6-methylmorpholin-2-one (III, R = *t*-Bu). The aminoalcohol (38 g) b.p.  $60\text{--}90^{\circ}/0.4$  mm was obtained from propylene oxide (29 g) and *t*-butylamine (36.5 g). The crude lactone b.p.  $92\text{--}100^{\circ}/0.5$  mm gave picrate (44.8 g) m.p.  $196^{\circ}$  (dec) from EtOH. (Found: C, 45.15; H, 4.91; N, 14.14.  $\text{C}_{15}\text{H}_{20}\text{O}_9\text{N}_4$  requires: C, 45.00; H, 5.04; N, 14.00%). *N*-*t*-butyl 6-methylmorpholin-2-one (4.6 g) b.p.  $73^{\circ}/0.5$  mm was obtained from the picrate (20 g) as before;  $n_D^{25} = 1.46401$   $\nu_{\text{max}}^{\text{CCl}_4}$   $1745\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ).

#### Preparation of *N*-substituted perhydro-1,4-benzomorpholin-2-ones

*N*-Benzylperhydrobenzomorpholin-2-one (IV, R = benzyl). A mixture of benzylamine (21.4 g, 0.2M) and cyclohexene oxide (19.6 g, 0.2M) was boiled under reflux for 16 hr, cooled and ethyl chloroacetate (30.6 g, 0.25M) added. The mixture was refluxed for a further 2 hr, cooled, basified with  $\text{Na}_2\text{CO}_3$  aq, and  $\text{CHCl}_3$  extracted 3 times. The dried ( $\text{Na}_2\text{SO}_4$ )  $\text{CHCl}_3$  extract was evaporated, and the residue distilled. The fraction b.p.  $137\text{--}140^{\circ}/0.2$  mm gave white needles m.p.  $91^{\circ}$  from EtOH, yield 20 g;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1753\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). (Found: C, 73.51; H, 7.71; N, 5.69.  $\text{C}_{15}\text{H}_{19}\text{O}_2\text{N}$  requires: C, 73.44; H, 7.81; N, 5.71%).  $J_{\text{gem}}$  for benzyl protons  $\sim 13.8$  Hz ( $\text{CCl}_4$ );  $\tau$  values for benzyl protons in  $\text{CCl}_4$ : 6.02, 6.94.

*N*-Cyclohexylperhydrobenzomorpholin-2-one (IV, R = cyclohexyl). This was prepared as above from a mixture of cyclohexylamine (19.8 g, 0.2M) and cyclohexene oxide (19.6 g, 0.2M). After evaporation of the  $\text{CHCl}_3$  extract, the mixture was filtered to remove the solid present. The filtrate was distilled and the fraction b.p.  $158\text{--}160^{\circ}/1$  mm gave white crystals m.p.  $62^{\circ}$  from EtOH, yield 15 g;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1753\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). (Found: C, 70.83; H, 9.62; N, 5.76.  $\text{C}_{14}\text{H}_{23}\text{O}_2\text{N}$  requires: C, 70.85; H, 9.77; N, 5.90%).

*N*-Phenylperhydrobenzomorpholin-2-one (IV, R = Ph). Aniline (18.8 g, 0.2M) and cyclohexene oxide (19.6 g, 0.2M) were heated under reflux for 3 days. The resulting aminoalcohol was distilled *in vacuo*, b.p.  $130^{\circ}/0.7$  mm, yield 31 g. This was refluxed for 2 hr with ethyl chloroacetate (41 g) and the mixture worked up as before. The highest boiling fraction  $160\text{--}164^{\circ}/0.8$  mm, gave white crystals m.p.  $66\text{--}67^{\circ}$  from EtOH, yield 4 g;  $\nu_{\text{max}}^{\text{CCl}_4}$   $1760\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). (Found: C, 72.71; H, 7.27; N, 6.08.  $\text{C}_{14}\text{H}_{17}\text{O}_2\text{N}$  requires: C, 72.70; H, 7.41; N, 6.06%).

4,5-Dimethyl-6-phenylmorpholin-2-one (V). Ephedrine (10 g) and ethyl chloroacetate (15 g) were heated under reflux for 4 hr; soln cooled, filtered, basified with  $\text{Na}_2\text{CO}_3$  aq,  $\text{CHCl}_3$  extracted; dried ( $\text{Na}_2\text{SO}_4$ )



and distilled after removal of  $\text{CHCl}_3$ ; fraction boiling  $131^\circ/0.4$  mm collected. (Found: C, 70.23; H, 7.72; N, 6.84.  $\text{C}_{12}\text{H}_{15}\text{NO}_2$  requires: C, 70.22; H, 7.37; N, 6.82%);  $n_D^{16} = 1.53848$ ;  $\nu_{\text{max}}^{\text{CCl}_4} = 1755 \text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ).

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