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Synthesis and Conformational Analysis of Substituted (Dimethylamino)oxanes and the Corresponding Quaternary Ammonium Iodides

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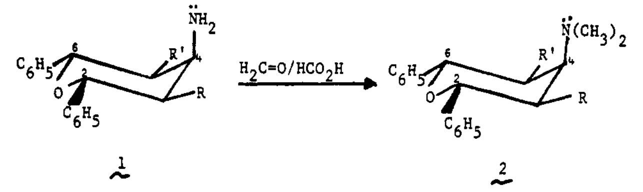
Reaction of substituted 4-aminooxanes with a mixture of formaldehyde and formic acid gave 4-(dimethylamino)oxanes in good yields. The methiodides of these (dimethylamino)oxanes were also prepared. The conformations of these tertiary amines as well as those of the corresponding quaternary ammonium iodides were analyzed via ^{1}H and ^{13}C NMR analysis. The spectral data suggest that the methiodides with an axial C–N bond exist in twist conformations. The rates of methylation of epimeric pairs of (dimethylamino)oxanes with methyl iodide have been measured at 30 ± 0.05 °C in acetonitrile. The kinetic data are used, in part, to evaluate the steric environment of the dimethylamino group in this system. A possible twist conformation for *trans*-2,6-diphenyl-*cis*-3,5-dimethyl-*r*-4-(dimethylamino)oxane and its C(4) epimer is suggested from the kinetic results. The examples of oxanes in a nonchair arrangement (the data support a possible twist form) are the first recorded in the family.

Simple six-membered oxygen heterocyclics are known to exist in the chair conformation.[2-6] In contrast, a few six-membered nitrogen heterocycles with a preferred boat conformation are recorded.[7-9] The synthesis and ^{1}H NMR and ^{13}C NMR analysis of a large number of heterocyclic compounds were reported recently from this laboratory.[6,10-14] The synthesis and stereochemistry of substituted 4-aminooxanes have also been published.[13]

The synthesis, stereochemistry, and conformational analysis of (dimethylamino)oxanes and their corresponding quaternary ammonium iodides are heretofore unknown. In continuation of our interest in tetrahydropyran derivatives,[6,11,13] we now report our synthetic efforts and conformational analysis of substituted 4-(dimethylamino)oxanes and the corresponding methiodides which are the first to be recorded in this family of heterocycles.

Synthesis of (Dimethylamino)oxanes and the Corresponding Quaternary Ammonium Iodides. Reaction of 4-aminooxanes **1a–d**[13] and **3a–d**[13] with formaldehyde and formic acid gave the tertiary amines **2a–d** and **4a–d**,[15] the details of which are given in Table I. Treatment of the (dimethylamino)oxanes **2a–d** and **4a–d** with methyl iodide gave the quaternary ammonium iodides **5a–d** and **6a–d**, respectively. The relevant data for the methiodides are given in Table II.



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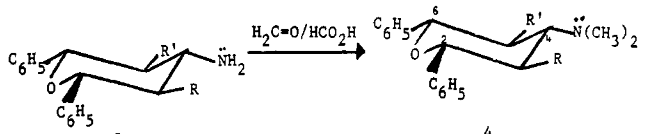
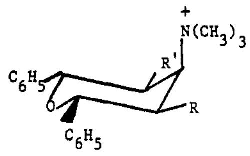


3 **4**

	R	R'
a	H	H
b	CH_3	H
c	C_2H_5	H
d	CH_3	CH_3



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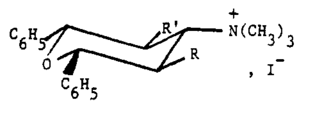

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	R	R'
a	H	H
b	CH_3	H
c	C_2H_5	H
d	CH_3	CH_3

^{1}H NMR Analysis of the (Dimethylamino)oxanes. ^{1}H NMR data on the (dimethylamino)oxanes **2a–d** and

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Table I. Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes

compd	yield, %	mp, °C	formula	analysis, %					
				found			calcd		
				C	H	N	C	H	N
2a	65	94-95[a]	$C_{19}H_{23}NO$	80.98	8.20	4.95	81.10	8.24	4.98
2b	82	66-67[a]	$C_{20}H_{25}NO$	81.40	8.50	4.71	81.31	8.53	4.74
2c	74	171[b] (1.7 mm)	$C_{21}H_{27}NO$	81.39	8.86	4.56	81.51	8.80	4.53
2d	83	93-94[a]	$C_{21}H_{27}NO$	81.59	8.76	4.50	81.51	8.80	4.53
4a	66	74-75[a]	$C_{19}H_{23}NO$	81.00	8.27	5.01	81.10	8.24	4.98
4b	83	105-106[a]	$C_{20}H_{25}NO$	81.16	8.58	4.76	81.31	8.53	4.74
4c	81	65-66[a]	$C_{21}H_{27}NO$	81.42	8.84	4.55	81.51	8.80	4.53
4d	60	111-112[a]	$C_{21}H_{27}NO$	81.61	8.75	4.51	81.51	8.80	4.53

[a] Recrystallized from petroleum ether (bp 60-80 °C). [b] Boiling point with pressure in parentheses.

Table II. Methiodides of Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes

compd	yield, %	mp,[a] °C	formula	analysis, %					
				found			calcd		
				C	H	N	C	H	N
5a	66	236-237	$C_{20}H_{26}NOI$	56.64	6.16	3.33	56.74	6.19	3.31
5b	68	186-188	$C_{21}H_{28}NOI$	57.74	6.48	3.18	57.67	6.45	3.20
5c	69	192-194	$C_{22}H_{30}NOI$	58.44	6.66	3.09	58.54	6.70	3.10
5d	69	230-232	$C_{22}H_{30}NOI$	58.66	6.67	3.08	58.54	6.70	3.10
6a	66	149-151	$C_{20}H_{26}NOI$	56.82	6.23	3.29	56.74	6.19	3.31
6b	68	155-157	$C_{21}H_{28}NOI$	57.59	6.42	3.22	57.67	6.45	3.20
6c	55	143-145	$C_{22}H_{30}NOI$	58.63	6.74	3.12	58.54	6.70	3.10
6d	15	232-235	$C_{22}H_{30}NOI$	58.42	6.73	3.11	58.54	6.70	3.10

[a] Recrystallized from methanol/ether.

Table III. ^1H NMR Data for Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes[d]

compd	chemical shift, δ					
	H(2)	H(3)	H(4)	H(5)	H(6)	others
2a	5.01 [d,[a] J = 12.0 Hz, 2 H, H(2), H(6)]	1.48-2.18 [m, 4 H, H(3), H(5)]	2.45[b] [merged with $N(CH_3)_2$]			2.36 [s, 6 H, $N(CH_3)_2$], 7.08-7.49 [m, 10 H, Ar H]
2b	4.67 [d, J = 9.0 Hz]	1.78-2.32 [m, 3 H, H(3), H(5)]	2.64[b] [$w_{1/2}$ = 17.0 Hz]		4.92 [dd, J = 4.0 Hz, J = 11.0 Hz]	0.85 [d, 3 H, CH_3, J = 7.0 Hz], 2.42 [s, 6 H, $N(CH_3)_2$], 7.06-7.60 [m, 10 H, Ar H]
2c	4.75 [d, J = 9.0 Hz]	2.12-2.27 [m]	2.79[b] [$w_{1/2}$ = 16.0 Hz]	1.02-1.94 [m, 4 H, CH_2CH_3, H(5)]	4.91 [dd, J = 3.0 Hz, J = 11.0 Hz]	0.75 [t, 3 H, CH_2CH_3, J = 7.0 Hz], 2.40 [s, 6 H, $N(CH_3)_2$], 7.08-7.46 [m, 10 H, Ar H]
2d	4.71 [d, J = 9.0 Hz, 2 H, H(2), H(6)]	2.02-2.36 [m]	2.78[b] [merged with $N(CH_3)_2$]			0.90 [d, 6 H, CH_3, J = 8.0 Hz], 2.64 [s, 6 H, $N(CH_3)_2$], 7.10-7.48 [m, 10 H, Ar H]
4a	4.53 [d,[a] J = 12.0 Hz, 2 H, H(2), H(6)]	1.98-2.21 [m, 2 H, $H(3)_e$, $H(5)_e$]	2.72[b] [$w_{1/2}$ = 24.0 Hz]	1.29-1.73 [m, 2 H, $H(3)_a$, $H(5)_a$]		2.28 [s, 6 H, $N(CH_3)_2$], 7.16-7.52 [m, 10 H, Ar H]
4b	4.11 [d, J = 9.0 Hz]	1.92-2.16 [m]	2.57[c] [$w_{1/2}$ = 27.0 Hz, J = 3.0 Hz, J = 11.0 Hz]	1.38-1.82 [m]	4.52 [dd, J = 3.0 Hz, J = 11.0 Hz]	0.77 [d, 3 H, CH_3, J = 7.0 Hz], 2.25 [s, 6 H, $N(CH_3)_2$], 7.04-7.62 [m, 10 H, Ar H]
4c	4.31 [d, J = 10.0 Hz]	1.90-2.16 [m]	2.78[c] [$w_{1/2}$ = 27.0 Hz, J = 3.0 Hz, J = 11.0 Hz]	1.16-1.82 [m, 4 H, CH_2CH_3, H(5)]	4.48 [d,[a] J = 12.0 Hz]	0.68 [t, 3 H, CH_2CH_3, J = 7.0 Hz], 2.25 [s, 6 H, $N(CH_3)_2$], 7.12-7.49 [m, 10 H, Ar H]
4d	4.07 [d, J = 9.5 Hz]	1.80-2.20 [m, 3 H, H(3), H(5), H(4)]	2.00 [merged with H(3) and H(5)] H(5)]			0.72 [d, 6 H, CH_3, J = 7.0 Hz], 2.48 [s, 6 H, $N(CH_3)_2$], 7.06-7.42 [m, 10 H, Ar H]

[a] Poorly resolved doublet of doublet. [b] Center of multiplet. [c] Center of doublet of triplet. [d] Shifts for $CDCl_3$ solutions of compounds. Abbreviations used: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet.

4a–d are provided in Table III. The H(4) proton signals in the tertiary amines are generally shielded by about 0.1–0.5 ppm in comparison with the corresponding signal in the primary amines.[13] Similar shieldings were observed in the case of 4 *tert*-butylcyclohexylamine and its *N*,*N*-dimethyl derivative.[16] In the case of *trans*-2,*trans*-6-di-

Table IV. ^{13}C Chemical Shifts for Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes[a]

	chemical shift, ppm						
compd	C(2)	C(3)	C(4)	C(5)	C(6)	C(6)	others
2a	74.07	43.80	59.50				$N(CH_3)_2$, 37.27; Ar, 143.20, 127.97, 126.91, 125.62
2b	81.88	45.20	61.19	41.33	75.61		CH_3, 15.69; $N(CH_3)_2$, 35.34; Ar, 143.48, 142.20, 127.97, 127.28, 126.96, 126.76, 125.42
2c	81.09	47.62	57.19	44.54	78.18		CH_2CH_3, 12.20; CH_2CH_3; 21.07; $N(CH_3)_2$, 34.22; Ar, 143.52, 142.49, 127.82, 127.08, 126.70, 125.19
2d	82.23	45.67	64.27				CH_3, 15.36; $N(CH_3)_2$, 42.58; Ar, 142.70, 127.96, 127.24, 126.57
4a	78.67	41.29	61.72				$N(CH_3)_2$, 36.85; Ar, 142.58, 128.02, 127.08, 127 125.57
4b	86.35	40.41	66.62	39.93	79.06		CH_3, 13.54; $N(CH_3)_2$, 30.75; Ar, 142.90, 141.30, 127.96, 127.37, 127.05, 125.54
4c	83.63	45.08	62.50	40.01	78.99		CH_2CH_3, 9.42; CH_2CH_3, 19.02; $N(CH_3)_2$, 30.64; Ar, 142.90, 141.23, 128.02, 127.52, 127.29, 127.03, 125.53
4d	86.23	41.47[b]	72.43				CH_3, 15.10; $N(CH_3)_2$, 41.47; Ar, 141.36, 127.88, 127.32

[a] All data are given in parts per million downfield from Me_4Si; solutions used were 0.3 M in $DCCl_3$. [b] Overlapped with signals for the carbons in $N(CH_3)_2$.

phenyl-*r*-4-(dimethylamino)oxane (**2a**), the result of this effect was that the signal for the H(4) proton was hidden beneath the absorption for the H(3) and H(5) protons. The spectra of **2d** and **4d** showed similar features for H(4) protons. However, the 3-alkyl derivatives **2b**, **4b**, **2c**, and **4c** gave spectra in which H(4) signals were visible and well resolved. Conversion of **4a** to **4b**, i.e., replacement of the equatorial hydrogen at C(3) by a methyl group, caused a shielding on the axial hydrogen H(4). On the contrary, conversion of **2a** to **2b**, i.e., replacement of an equatorial hydrogen at C(3) by a methyl group, caused a *deshielding* effect on the equatorial hydrogen H(4). Thus, the H(4) resonances for **2a** and **2b** were found at δ 2.45 and 2.64, respectively. Similar alkyl substituent effects on the chemical shifts of ring protons in 2-alkylcyclohexylamines[16] and neomenthols[17] have been noted.

In the spectra of conformationally biased tertiary amines **2b** and **4b**, the equatorial H(4) in **2b** resonates at δ 2.64, while its counterpart in **4b** resonates at δ 2.57. The H(4) signal in **4b** at δ 2.57 ($w_{1/2}$ = 27.0 Hz) was a 1:2:1 triplet (J = 11.0 Hz) due to coupling with two axial hydrogens H(3a) and H(5a) and suggested that the C–N bond was equatorial. Each component of the triplet was a doublet (J = 3.0 Hz), due to further coupling with the equatorial hydrogen H(5e). Similar well-resolved spectra were obtained for the all-equatorial tertiary aminooxane **4c**. In the tertiary amines **2b** and **2c**, the H(4) signals were found at δ 2.64 and 2.79, respectively, with a narrow bandwidth ($w_{1/2}$ = 17.0 Hz). The H(2) signals in **2b**, **4b**, **2c**, and **4c** were doublets ($J_{2a,3a}$ = 9.0 Hz), and the H(6) signals were a doublet of doublets ($J_{6a,5a}$ = 11.0 Hz and $J_{6a,5e}$ = 4.0 Hz). From the data in Table III, it is evident that introduction of 3-alkyl substituent leads to a *decrease* in $J_{2a,3a}$ of 3.0 Hz. For example, the H(2) proton signal in **2a** appears as a doublet ($J_{2a,3a}$ = 12.0 Hz), and the H(2) proton signal of **2b** is a doublet ($J_{2a,3a}$ = 9.0 Hz). The ^1H NMR spectra of **2d** and **4d** were examined carefully in order to extract further information on the effect of steric crowding on the coupling constant. Interestingly, in both **2d** and **4d** the values of the axial/axial coupling constant ($J_{2a,3a} = J_{6a,5a}$ = 9.0 Hz) were identical with the coupling constant ($J_{2a,3a}$ = 9.0 Hz) observed for the tertiary amines **2b** and **4b**. The Karplus equation ($J = K \cos^2 \phi$)[18,19] relates the vicinal coupling constant (J) to the dihedral angle (ϕ) and indicates that $J_{a,e}$ and $J_{e,e}$ ($\phi \approx 60°$) are highly sensitive to small changes in ϕ whereas $J_{a,a}$ ($\phi \approx 180°$) is relatively insensitive to small changes in ϕ. The marked changes of $J_{2a,3a}$ in amines **2b–d** and **4b–d** could provide information of the change in the dihedral angle. The significant changes observed in the coupling constants in tertiary amines **2b–d** and **4b–d** upon alkyl substitution might be attributed to a combination of an alteration in the dihedral angle[18-20] and the electronegativity of the alkyl substituent.[21-24] To avoid steric crowding between the dimethylamino group and the alkyl group, the amines **2b–d** and **4b–d** may exist in an equilibrium with deformed chair conformations, possibly flattened chairs.

^{13}C NMR Analysis. The carbon-13 chemical shifts of the epimeric tertiary amines **2a–d** and **4a–d** are summarized in Table IV. In general, it was noted that the C(4) carbon shielding was controlled by the orientation of the dimethylamino group. An axial dimethylamino group shields C(4) by about ~5 ppm as illustrated with the compounds **2b** and **4b** given below. Such chemical shift differences for epimeric heterocyclic alcohols[6,11,14] and 4-aminooxanes[13] have only recently been established.

The ^{13}C resonance for the equatorial methyl carbon at C(3) in **2b** is shifted upfield by ~2.15 ppm compared to the corresponding signal found for the equatorial methyl carbon in **4b**. In both epimers, the dimethylamino group and the equatorial 3-methy groups are gauche, and the upfield shift of 2.15 ppm found for the equatorial methyl carbon, relative to its shielding in **2b**, may be attributed to the γ-antiperiplanar effect.[25] In general, the methyl carbons in the equatorial dimethylamino group are shielded compared to corresponding signal found in the axial epimers. The most striking feature of the data,

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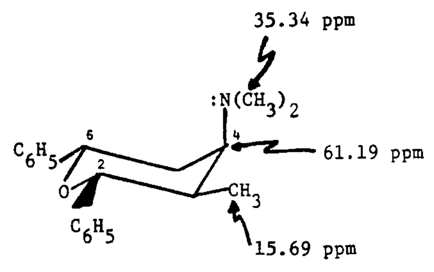
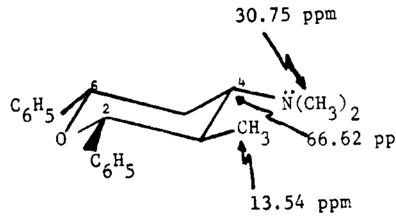
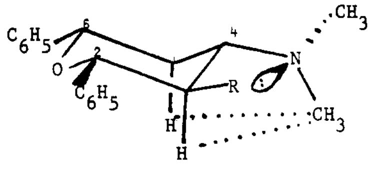


2b



4b

however, is the pronounced upfield shift (~6 ppm) of the methyl carbon in the equatorial dimethylamino groups in **4b** and **4c** in comparison to the corresponding signal found in **4a**. This observation appears to confirm the steric origin of the effect. An examination of molecular models indicates that in the all-equatorial tertiary amines **4b** and **4c** the dimethylamino group may preferentially exist in a rotamer in which the lone pair points toward the alkyl group. In the preferred conformation **4b′**, there will be severe nonbonded interactions between one of the methyl groups and the axial hydrogens H(3) and H(5) as shown. Presumably the interaction between the methyl group and the axial hydrogens H(3) and H(5) is sufficient to perturb the electron distribution about these carbons such that their shielding is increased. The upfield shift for the methyl carbons in **4b** and **4c** strongly suggests that the equatorial dimethylamino groups in these compounds are sterically more crowded than the axial dimethylamino groups in **2b** and **2c**. Such a view is also supported by the kinetics of quaternization of the tertiary aminooxanes with methyl iodide (given later in the discussion) and ^{15}N NMR spectral studies.[26]



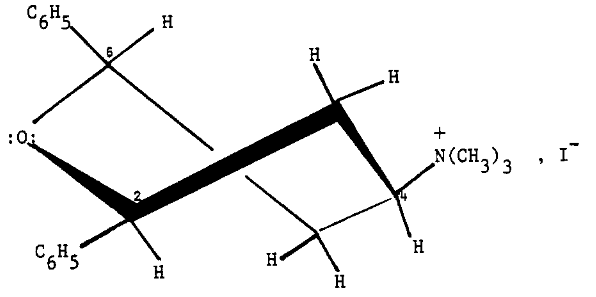
4b′ R = CH_3

4c′ R = C_2H_5

^1H NMR Analysis of Quaternary Ammonium Iodides. Chemical shifts and coupling constants of quaternary ammonium iodides **5a–d** and **6a–d**, deduced by a first-order approach, assisted by ^1H spin-decoupling experiments, are summarized in Table V. The ^1H spectrum of quaternary ammonium salt **5a** was recorded at 100 MHz in Me_2SO-d_6 and the spectra of **5b–d** and **6a–d** were recorded at 270 MHz in Me_2MO-d_6.

For compounds listed in Table V, the proton signals from the trimethylammonium group were singlets in the range of δ 3.07–3.17. In general, the methyl protons of the axial ammonium function occurred at a slightly lower field than those of equatorial trimethylammonium protons. As expected, quaternary ammonium salt formation caused the H(4) proton resonance to be shifted *downfield*. Thus, the H(4) signals of **5b** and **6b** occurred at δ 4.05 and 3.92, respectively, whereas the corresponding signals in the tertiary amines **2b** and **4b** were found at δ 2.64 and 2.57. The chemical shifts of the H(2) and H(6) protons of the epimeric quaternary ammonium iodides (Table V illustrate clearly that they are *deshielded* by an axial trimethylammonium group as a result of 1,3-diaxial spatial proximity, and this served to confirm our configurational and conformational assignments.

The spectrum of **6a**, at 270 MHz, showed the following features: (i) the H(4) proton at δ 3.98 appeared as a triplet with separations of 11.0 Hz; (ii) the benzylic protons H(2) and H(6) were at δ 4.67 and appeared as a doublet (separation 10.66 Hz). The ^1H NMR spectrum thus indicates that compound **6a** has a six-membered tetrahydropyran ring in a chair conformation with the trimethylammonium group in the equatorial position. The H(4) signal in the spectrum of methiodide **5a** appeared at δ 3.87 as a triplet, the spacings between the somewhat broadened lines being 7.0 Hz. The values of 8.0 and 5.0 Hz for $J_{2a,3a} = J_{6a,5a}$ and $J_{2a,oe} = J_{6a,5e}$, respectively, suggest that **5a** exists to an appreciable extent in a twist conformation, possibly **5a′**. This avoids the severe 1,3-interactions which the bulky $^+N(CH_3)_3$ group experiences in the chair conformation **5a**.



5a′

The spectrum of **6b** showed a triplet (J = 10.14 Hz) at δ 3.92 for H(4). Moreover, the spectrum clearly reveals the H(2) and H(6) protons as two doublets at δ 4.32 (J = 9.5 Hz) and 4.63 (J = 9.0 Hz), respectively. The value of the coupling constant $J_{2a,3a}$ suggests that replacement of an equatorial hydrogen in **6a** by a methyl group, i.e., conversion of **6a** to **6b**, causes a *decrease* in $J_{2a,3a}$. It is evident that conversion of **6a** to **6c** does lead to a decrease in $J_{2a,3a}$ of 1.10 Hz and in $J_{6a,5a}$ of 0.73 Hz (Table V). The small changes in coupling constants upon alkyl substitution may be attributed to the substituent electronegativity effect.[20–23]

In the spectrum of **5b** in Me_2SO-d_6 the H(2) proton resonance appeared at δ 4.38 as a doublet (separation 5.88 Hz) due to coupling with axial H(3). The spectrum of **5b** showed a doublet of doublets at δ 5.06 ($J_{6a,5a}$ = 8.09 Hz, $J_{6a,5e}$ = 4.05 Hz) for H(6). These values are presumably due to ring distortions because of the size of the axial substituent or, alternatively, the effective size of the $^+N(CH_3)_3$ in the solvent conditions used. The $^+N(CH_3)_3$ group is sterically identical (isosteric) with the *tert*-butyl group. For the methiodide **5b**, the H(4) signal was clearly observed at a lower field as a broad, well-resolved multiplet with a half-bandwidth of 24.75 Hz. The value found for the H(4) resonance in **5b** is identical with the half-bandwidth (24.75 Hz) found for the H(4) resonance in **6b**. This suggests that the compound **5b** exists in a twist confor-

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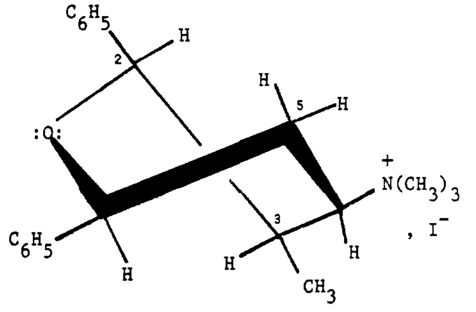
Table V. ^{1}H NMR Data for Methiodides of Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes

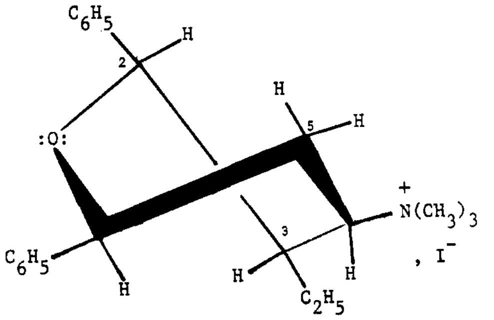
	H(2)		H(6)		H(4)		
compd	δ^a	J^b	δ^a	J^b	δ^a	J^b	$w_{1/2}{}^c$
5a	$5.16^{d,j}$	5.0, 8.0			3.87^e	7.0	18.0
5b	4.38^f	5.88	5.06^d	4.05, 8.09	4.05^g	13.24, 4.78	24.75
5c	4.76^f	2.94	5.01^h	7.35	3.98^g	11.40, 4.68	24.75
5d	$4.61^{f,j}$	5.15			4.03^h	4.8	11.25
6a	$4.67^{f,j}$	10.66			3.98^e	11.68	27.0
6b	4.32^f	9.56	4.63^f	9.0	3.92^e	10.14	24.75
6c	4.54^f	9.56	4.61^f	9.93	4.23^i	11.00, 3.93	24.75
6d	$4.40^{f,j}$	8.60			3.73^h	3.68	7.87

[a] Values are expressed in δ values downfield from Me_4Si. [b] J values are expressed in hertz. [c] $w_{1/2}$ values expressed in hertz. [d] Center of doublet of doublet; J values are for the separation between lines 1 and 3 and lines 3 and 4. [e] Center of unresolved triplet. [f] Center of doublet. [g] Center of triplet of doublet; J values are for the separations between lines 2 and 5 and lines 5 and 6. [h] Center of 1:2:1 triplet. [i] Center of doublet of triplet; J values are for the separations between lines 1 and 3 and lines 3 and 4. [j] Includes the values of both H(2) and H(6).

mation, **5b′**, with the $^+N(CH_3)_3$ group perhaps in a pseudoequatorial arrangement.



5b′



5c′

In the spectrum of **5c**, the H(2) signal appeared at δ 4.76 as a doublet ($J_{2a,3a}$ = 2.94 Hz) while the H(6) signal appeared at δ 5.01 as a 1:2:1 triplet (J = 7.35 Hz). The observed values of $J_{2a,3a}$ and $J_{6a,5a}$ in **5c** are much smaller than the coupling constants found in other related oxane derivatives which exist in the rigid chair conformations.[13] This indicates a highly distorted tetrahydropyran ring system in **5c**. The coupling constants observed are once more reconcilable with a molecule existing mainly as **5c′**. The H(4) signal at δ 3.98 is a well-resolved multiplet with a half-bandwidth of 24.75 Hz. The larger half-bandwidth for the H(4) proton in **5c** further supports a compound which could mainly exist as a mixture of rapidly interconverting twist conformations. A significant decrease in $J_{2a,3a}$ occurs when an alkyl group is substituted for an equatorial hydrogen at C(3) as in **5b** and **5c**; the decrease in value is greater for the ethyl derivative than for a methyl derivative.

Table VI. Pseudo-First-Order Rate Constants (k_1) for the Reaction between Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes and Methyl Iodide in Acetonitrile at 30 °C

compd	10^5k_1, s^{-1}	compd	10^5k_1, s^{-1}
2a	62.11 ± 0.04	**4a**	too fast to measure
2b	80.12 ± 0.07	**4b**	31.72 ± 0.01
2c	22.47 ± 0.03	**4c**	10.28 ± 0.04
2d	1.71 ± 0.01	**4d**	0.31 ± 0.00

The spectra of epimeric methiodides **5d** and **6d** appear to be complex. At 270 MHz, the ^{1}H NMR spectrum of **6d** has the H(4) proton at δ 3.73 as a narrow triplet (J = 3.68 Hz). The H(4) resonance has a half-bandwidth of only 7.87 Hz. The observed half-bandwidth of the signal for H(4) in **6d** is much less than for a molecule existing entirely in chair conformation.[13] For comparison, the H(4) signal in *cis*-2-6-diphenyl-*trans*-3,5-dimethyl-*r*-4-aminooxane had a half-intensity width of 20.0 Hz.[13] In the chair conformation of **6d** there exist gauche interactions [two $C_6H_5 \cdots CH_3$ and two $CH_3 \cdots {}^+N(CH_3)_3$]. The observed spectra thus suggest that the methiodide spends most of its time in rapidly interconverting twist conformations. Iodide **5d** with the axial trimethylammonium group is another compound which is expected to evade the chair conformation. Interestingly, the H(4) signal at δ 4.03 in the ^{1}H NMR spectrum was a resolved triplet (J = 4.8 Hz), but its half-intensity bandwidth (11.25 Hz) is much higher than that of the corresponding signal (7.87 Hz) in its equatorial epimer **6d**. In the ^{1}H NMR spectrum of **5d** in Me_2SO-d_6, the diaxial protons H(2) and H(6) appear at δ 4.61 as a doublet (J = 5.15 Hz) due to coupling with H(3a) and H(5a). Ring flattening is, however, likely in the case of **5d**, which results in a decrease in dihedral angle for $J_{2a,3a}$ = $J_{6a,5a}$. The most probable explanation for the observed H(2) and H(4) signals is that the methiodide eliminates most of the steric strain involved in the chair conformation **5d** [bulky $^+N(CH_3)_3$ axial] by existing in twist conformations of comparable energy which are undergoing rapid interconversions.

Kinetics of Quaternization of (Dimethylamino)oxanes. In order to gain further insight into the conformations of the (dimethylamino)oxanes **2a–d** and **4a–d**, a study of the rates of methylation with methyl iodide was carried out at 30 °C in acetonitrile. The pseudo-first-order rate constants for methiodide formation are given in Table VI. The kinetic runs were normally followed to about 80% completion, and no difficulties due to reversibility of the reaction were encountered.

The rate of methylation of *cis*-2,*cis*-6-diphenyl-*r*-4-(dimethylamino)oxane (**4a**; equatorial amino group) was found to be too fast to measure under the experimental conditions of our study. The axial isomer **2a**, with two 1,3-diaxial interactions, reacted with methyl iodide at a slower rate. This is in accordance with the general principles of conformational analysis.[27]

Consideration of the rates of methylation of **2b** and **4b** in conjunction with those of **2a** and **4a** permits an evaluation of the effect of the methyl group on the rate of methylation. The rate data in Table VI indicate that the tertiary amine **2b** with an equatorial methyl group at C(3) and α to the dimethylamino group reacts at a slightly faster rate than the "parent" amine **2a**. However, introduction of an equatorial methyl group at C(3) greatly reduces the rate of methylation of tertiary amine **4b**. Examination of the data in Table VI indicates that in the pair **2b** and **4b** the rate of methylation of **2b**, with an axial dimethylamino group, is 2.5 times faster than that of **4b**, which has an equatorial dimethylamino group. The 3-ethyl derivatives **2c** and **4c** react significantly slower than 3-methyl derivatives **2b** and **4b**, respectively. Tertiary aminooxane **2c** with an axial dimethylamino group reacts with methyl iodide 2.2 times faster than its equatorial epimer **4c**. Indeed, there is a similar trend in the pK_a values of the tertiary amines[28] as that of the methylation rates, with the latter values showing much larger differences between epimers. The rate of methylation depends upon the availability of the nitrogen lone pair to undergo a nucleophilic substitution reaction. As discussed earlier, amines **4b** and **4c** may well prefer the conformations **4b′** and **4c′** in which the lone pair of electrons is pointing toward the alkyl group. In such rotational conformations, the free electron pair is sterically shielded, and hence amines **4b** and **4c** react at a slower rate than the axial epimers **2b** and **2c**. A similar reversal in order of reactivity for (2-alkylcyclohexyl)dimethylamines has been reported.[29,30]

Both **2d** and **4d** undergo methylation much more slowly than the other tertiary amines, indicating that the former amines possess the most hindered nitrogen atom with the methyl groups attached to C(3) and C(5) as in **2d** and **4d**; severe gauche interactions likely exist between dimethylamino and methyl groups. The actual magnitude of the rate of retardation of methylation is expected, however, to differ greatly according to the mutual position of the nitrogen lone pair and the methyl groups. It is reasonable that in the transition state for the methylation of **4d** the six-membered tetrahydropyran ring will be considerably deformed. The deformation may to some extent exist in the ground state, particularly for the all-equatorial isomer **4d**. The higher k_a/k_e ratio (5.8) for this epimeric pair, **2d** and **4d**, in comparison with the k_a/k_e ratio (2.5) observed for epimeric amines **2b** and **4b** is probably indicative of the significant difference in the conformation of **2d** and **4d**. Examination of molecular models of **2d** and **4d** and the spectral data suggests that these two bases exist in twist conformations presumably to minimize nonbonded interactions.

Experimental Section

General Data. Melting points were taken on a BOETIUS micro heating table and are uncorrected. Proton magnetic resonance spectra for tertiary amines were obtained on a Varian XL-100(15) high-resolution NMR spectrometer (with a time-averaging computor accessory, C-1024) operating at 100.0 Hz and are expressed in δ values relative to an Me_4Si internal standard. ^1H NMR spectra for methiodides were recorded at 270 MHz on a Bruker WH270 NMR spectrometer (with a Bruker Model B-NC 12 data system, a Nicolet NIC Model 294 disk memory coupler, and a Type 602 display unit) and are also expressed in δ values relative to an Me_4Si internal standard in Me_2MO-d_6. Proton-noise-decoupled ^{13}C NMR spectra were recorded at 25.2 MHz on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 accessory. Chemical shift data encompassing a 5000-Hz spectral region were collected into 8K data points. Single frequency, off-resonance ^{13}C NMR spectra were obtained by irradiation with a CW frequency at about δ –5 compared to Me_4Si in the proton spectrum. The samples were run as 0.3 M solutions in $DCCl_3$ and recorded at 37 °C. Assignments have been made on the basis of signal multiplicity found in the off-resonance decoupled spectra and from the magnitude of the $^1J_{^{13}C-H}$ couplings.

Preparation of Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes. 4-Aminooxane[13] (0.2 mol) was added slowly with cooling to a mixture of formic acid[15] (85%; 1 mol) and aqueous formaldehyde (37%; 0.6 mol). The mixture was heated in an oil bath at 90–100 °C. A vigorous evolution of carbon dioxide began after 3–5 min, and the flask was removed from the oil bath and allowed to stand at room temperature until the evolution of the gas subsided (20–25 min). It was then returned to the bath, and heating was continued for 8–10 h. Evaporation of the reaction mixture under reduced pressure left a pale yellow, syrupy residue which was treated with dry acetic anhydride and heated on a water bath for 5–6 h. The reaction mixture was cooled and diluted with ice-cold water followed by the addition of dilute HCl (1:2 HCl/water). Extraction with ether (4 × 55 mL) gave two layers, and the aqueous layer was saved and basified with aqueous ammonia (1:1 ammonia/water). The solid which separated was filtered, washed with water, dried (Na_2SO_4), and recrystallized from a suitable solvent. If the isolated base was a liquid, it was taken up in ether, and the ethereal solution was dried (Na_2SO_4). Evaporation of the ether and distillation of the residual oil under reduced pressure gave product. Details are given in Table I.

Preparation of Methiodides of Substituted 2,6-Diphenyl-4-(dimethylamino)oxanes. Addition of excess methyl iodide to an ether solution of the tertiary amine (0.003 mol) gave, after standing for some time, the methiodide. The salt was crystallized from a methanol–ether mixture (see Table II)

Kinetic Procedure. Acetonitrile was purified by a known procedure.[31] Methyl iodide was successively washed with an aqueous solution of sodium thiosulfate, water, and an aqueous solution of sodium carbonate, dried over $CaCl_2$, and distilled.[32] The liquid distilling at 42.7 °C was collected and stored over mercury in an amber bottle.

The kinetics of alkyl iodide formation were followed conductometrically[33] by taking the conductance of the reaction mixture as a measure of the amount of the salt formed. The apparatus consisted of a conductivity cell with black platinized electrodes connected to a conductivity bridge to measure the conductance of the solution in the cell.

A solution of the tertiary amine in acetonitrile (approximately 10^{-3} M, 10 mg in 10 mL of acetonitrile) was introduced into the cell at 30 ± 0.05 °C. Nitrogen was bubbled through the system. A solution of methyl iodide in acetonitrile was then added in approximately 500-fold excess. Conductance values were measured at appropriate time intervals until the reaction had reached completion, at which time the conductance remained constant. The alkyl iodide was used in large excess so that the second-order reaction would follow a pseudo-first-order kinetic law. The pseudo-first-order rate constant k is given by the eq 1, where C_∞

$$k = \frac{2.303}{t}\left[\log \frac{C_\infty}{C_\infty - C_t}\right] \qquad (1)$$

is the conductance at the end of the reaction and C_t is the conductance at time t.

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Registry No. **2a**, 81158-62-5; **2b**, 81158-63-6; **2c**, 81158-64-7; **2d**, 81158-65-8; **4a**, 81158-68-1; **4b**, 81158-69-2; **4c**, 81158-70-5; **4d**, 81158-71-6; **5a**, 85318-63-4; **5b**, 85318-64-5; **5c**, 85318-65-6; **5d**, 85318-66-7; **6a**, 85318-67-8; **6b**, 85318-68-9; **6c**, 85318-69-0; **6d**, 85318-70-3.

Base Strengths of 4-Aminooxanes (Tetrahydropyrans), (Methylamino)oxanes, (Dimethylamino)oxanes, (Methylamino)thianes, and (Dimethylamino)thianes

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The pK_a values of a series of epimeric 4-aminooxanes (tetrahydropyrans), (methylamino)oxanes, (dimethylamino)oxanes, (methylamino)thianes and (dimethylamino)thianes have been determined in 80% 2-methoxyethanol at 27 ± 0.1 °C. Alkyl groups on the carbon α to the C–N group reduce the basicity of the nitrogen in the 4-aminooxanes, apparently due to reduced stability of the conjugate acid because of steric factors. Possible twist conformations are suggested for *trans*-2,6-diphenyl-*cis*-3-methyl-*r*-4-(dimethylamino)oxane (**1l**), *trans*-2,6-diphenyl-*cis*-3-ethyl-*r*-4-(dimethylamino)oxane (**1m**), *trans*-2,6-diphenyl-*cis*-3,5-dimethyl-*r*-4-(dimethylamino)oxane (**1n**), *cis*-2,6-diphenyl-*trans*-3,5-dimethyl-*r*-4-(dimethylamino)oxane (**2n**), *trans*-2,6-diphenyl-*cis*-3-methyl-*r*-4-(dimethylamino)thiane (**4e**), 2,2-dimethyl-*trans*-6-phenyl-*r*-4-(methylamino)thiane (**6a**), 2,2-dimethyl-*trans*-6-phenyl-*r*-4-(dimethylamino)thiane (**6b**), and 2,2-dimethyl-*trans*-6-(4-chlorophenyl)-*r*-4-(dimethylamino)thiane (**6c**). Such a twist form avoids severe nonbonded interactions between the C–N bond(s) and axial C(2,6)–H or C(2,6)–C bonds or between C–N bond(s) and equatorial C(3,5)–C bonds, depending upon the system involved. Solvation of the free amine is suggested to be favored over solvation of the protonated amine since the latter may experience rather strong nonbonded interactions in the ground state with concomitant retardation of solvation compared to that with the free amine. ^1H NMR data are also presented which support a nonchair form for several of the molecules. The study is the first in which a systematic investigation is described concerning the basicity of the amine group in 4-aminooxanes and 4-aminothianes and the configuration at the carbon bonded to the nitrogen atom.

Although assignments of configurations of carbons bonded to amino groups in six-membered cyclic systems[4–7] and alicyclic systems[8] have been made via analysis of pK_a determinations, such a study on six-membered heterocycles has apparently not been recorded. Certain aminooxanes[9] appear to exist in biased chair conformations. We report herein the first systematic study of the relationship of the basicity of selected 4-aminooxanes and 4-aminothianes to the configuration at carbon bonded to nitrogen. Systems 1–8 were those investigated at 27 ± 0.1 °C in 80% 2-methoxyethanol. All values are the average of at least two independent measurements for each compound. Both the synthesis and ^1H and ^{13}C NMR analysis have been described.[10]

Table I. pK_a Values for the Aminooxanes in 80% 2-Methoxyethanol (v/v) at 27 ± 0.1 °C[a]

compd	pK_a (axial amines)	compd	pK_a (equatorial amines)
1a	7.96	2a	8.40
1b	7.60	2b	8.09
1c	7.70	2c	8.15
1d	7.38	2d	7.98
1e	7.11	2e	7.71
1f	7.10	2f	7.72
1g	6.84	2g	7.49
1h	7.81	2h	8.27
1i	7.40	2i	8.03
1j	7.08	2j	8.00
1k	6.54	2k	7.40
1l	6.88	2l	7.18
1m	6.65	2m	6.85
1n	6.55	2n	5.85
		3	8.33

[a] The values were reproducible to within ±0.01 of a pK_a unit.

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(1) Taken in part from the Ph.D. dissertation of N.C., submitted to the University of Madras, India.

(2) Taken in part from the Ph.D. dissertation of P.K.S., submitted to the University of Madras, India.

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