# Anomeric Effects in Aziridin-1-yltetrahydropyrans

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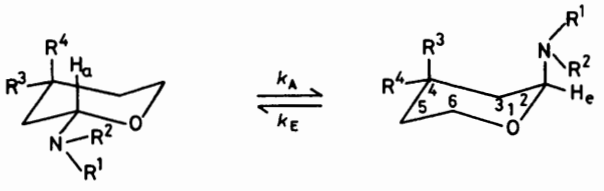
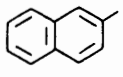
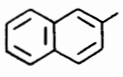
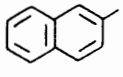
The stereochemistry of 2-aziridin-1-yltetrahydropyrans has been investigated by n.m.r. spectroscopic and dipole moment studies. Analysis of the 2-H signal, low-temperature n.m.r. data, and dipole moment measurements indicate that the aziridinyl ring is predominantly equatorial in the parent compound whereas the situation is reversed in *trans*-4-methyl-2-aziridin-1-yltetrahydropyran. Evidence was found for intense shielding above the aziridinyl ring.

ANOMERIC effects in 2-substituted tetrahydropyrans have been the subject of many investigations.[1] We report an n.m.r. and dipole moment study of the conformational equilibria of 2-aziridin-1-yltetrahydropyrans (1)—(3), (10), and (11) whose synthesis have recently been reported.[2a] Tetrahydropyranylamines (4)—(7) have previously been described.[2b,c] Compounds (8) and (9) are new.

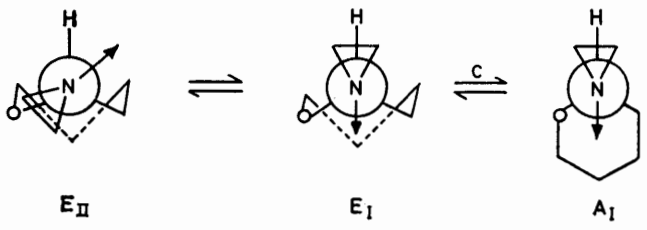


E $\rightleftharpoons$ A

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| (1) | $(CH_2)_2$ | | H | H |
| (2) | $(CH_2)_2$ | | H | $CH_3$ |
| (3) | $(CH_2)_2$ | | $CH_3$ | H |
| (4) | $CH_3$ | H | H | H |
| (5) | $CH_3$ | H | H | $CH_3$ |
| (6) | $CH_3$ | H | $CH_3$ | H |
| (7) |  | H | H | H |
| (8) |  | H | H | $CH_3$ |
| (9) |  | H | $CH_3$ | H |

## RESULTS AND DISCUSSION

Tetrahydropyranyl ring inversion, nitrogen inversion, and rotational isomerism can be expected in these compounds. The scheme shows the most likely conformers of aziridinyltetrahydropyrans (1)—(3) using a Newman projection along the exocyclic C–N bond.



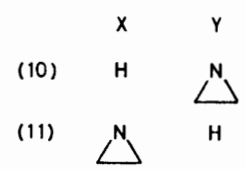
$E_{II}$ $E_I$ $A_I$

A *Proton Magnetic Resonance Studies* (*Table* 1).—A 2-monosubstituted tetrahydropyran usually undergoes ring inversion between two conformations, one in which 2-H is axial (2-$H_a$), and the other in which 2-H is equatorial (2-$H_e$) and, most of the time, more deshielded than 2-$H_a$.[1] (Exceptions have been noted for 1,3-dioxans and 1,3-dithians.[1i]) However, at room temperature, ring inversion is fast and an averaged signal is observed.

Three methods have been used to calculate the conformational free energy difference $\Delta G°$ between conformers A and E. (i) The exchange rate was lowered by cooling; below the coalescence temperature, two separated signals emerge whose areas allow the evaluation of the conformer ratio. (ii) The 2-H shift of 2-substituted tetrahydropyran was compared with those of two compounds expected to be conformationally homogeneous as in *cis*- and *trans*-4-alkyl-2-substituted tetrahydropyrans.[1e,3] (iii) The 2-H signal is analysed in terms of averaged coupling constants.[1d,e,4]

In general, two features of the $^1H$ n.m.r. spectra of 2-aminotetrahydropyrans are of interest,[2c,5] (i) the low field position and shape of the 2- and 6-H signals and (ii) the resonance of the protons of the 2-substituent. However, an amino-group does not exert a deshielding effect large enough to shift the 2-H signal to lower field than the 6-H lines.

(1) *Substituted compounds* (2) *and* (3). In each stereoisomer, 2-H is assumed to be the X part of an ABX system. At room temperature, the observed 2-H signal is an averaged resonance of this proton in the two conformations A and E, with $J^* = x_A J_A + (1 - x_A) J_E$ ($J^*$ is the separation between the outer lines of the 2-H multiplet and $x_A$ is the molar fraction of the tetrahydropyranyl compound in the conformation A). The accepted values for $J_A$ and $J_E$ in cyclohexylamines are *ca.* 6 and 15 Hz, respectively.[6] More accurate values can be obtained in 1-aziridin-1-yl-1,2-dideoxy-3,4,6-tri-*O*-acetyl-D-*arabino*-hexopyranoses (10) and (11); the outer lines of the anomeric proton signal are separated by 6.25 Hz for (10) and 12.25 Hz for (11).



| | X | Y |
|---|---|---|
| (10) | H | N |
| (11) | N | H |

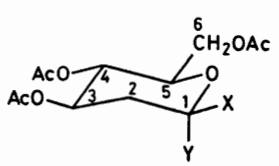


TABLE 1
$^1$H N.m.r. data

| Solvents | $D_2O$ | | $CH_3CN$ | DMSO | $CDCl_3$ | | | | $C_6H_6$ | $CS_2$ | | $CCl_4$ | | Neat | | | $CDCl_3$–Eu-(dmp)$_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T/K | 310 | 358 | 310 | 310 | 203 | 233 | 310 | 343 | 310 | 193 | 310 | 310 | 343 | 310 | 343 | 403 | 310 |
| (1) $\begin{bmatrix}(CH_2)_2\\ \vert\\ N\end{bmatrix}$ | 1.58 and 1.78 | | 1.43 1.52 | 1.49 1.55 | 1.52 1.82 | 1.49 1.71 | 1.51 1.65 | 1.55 | 1.50 | 1.37 1.49 | 1.42 | 1.42 | | 1.48 | | | $-\Delta$Eu-($10^{-6}$) |
| 2-H | 2.98 | | 3.10 | 3.15 | 2.96 | 3.09 (10) | 3.18 | 3.22 | 3.35 | 3.48 | 3.36 | 3.42 | | 3.40 | | | 24 |
| 6-$H_a$ | 3.52 | | 3.38 | 3.37 | 3.52 | 3.44 | 3.43 | 3.40 | 3.27 | 3.29 | 3.29 | 3.35 | | 3.26 | | | 7.8 |
| 6-$H_e$ | 4.04 | | 3.98 | 3.97 | 4.12 | 4.06 | 4.06 | 4.03 | 3.99 | 3.85 | 3.89 | 3.97 | | 3.98 | | | 4.3 |
| $x_a$ * | | | 0.24 | 0.23 | | | 0.32 | | 0.31 | 0.21 | 0.29 | 0.28 | | 0.31 | | | |
| (2) † 2-$H_e$ | | 3.07 | 2.97 | 2.98 (t) (5.75) | 2.97 | | 3.03 | 3.05 (6) | 2.97 | 2.77 | 2.87 (5.5) | 2.92 (t) (5.5) | | 2.96 (5.75) | 2.98 (6) | 3 | |
| (3) $CH_3$ | | | 0.96 | | | | 0.98 (d, *J* 5.75) | | | | 0.93 | 0.96 (d, *J* 5.75) | | | | | 2.8 |
| 2-$H_a$ | 2.97 | 3.07 | 3.14 (11.5) | 3.20 | 2.97 | | 3.25 | | 3.52 | 3.67 | 3.55 (q) (12) | 3.61 (q) (11.75) | | 3.6 | 3.58 | 3.52 | 30.2 |
| 6-$H_a$ | 3.43 *11.5* | 3.42 | 3.33 *11.5* | 3.30 | 3.48 | | 3.38 | | 3.28 | 3.27 | 3.23 *11.5* | 3.27 | | 3.3 | 3.28 | 3.27 | 8.4 |
| 6-$H_e$ | 4.02 | 4.01 | 3.93 | 3.91 | 4.11 | | 4.02 | | 3.85 | 3.85 | 3.83 | 3.90 | | 3.91 | 3.89 | 3.87 | 5.1 |
| $\begin{bmatrix}(CH_2)_2\\ \vert\\ N\end{bmatrix}$ | 1.53 and 1.80 | 1.67 | 1.50 | 1.50 | 1.53 1.87 | | 1.59 1.65 | 1.60 | | 1.32 1.60 | 1.37 1.53 | 1.42 1.60 | 1.52 | 1.62 1.43 | 1.55 | 1.50 | |
| (4) 2-H | | | | | | | 3.93 (11) | | | | | | | | | | |
| (5) 2-H | | | | | | | 4.35 (8.25) | | | | | | | | | | |
| (6) 2-$H_a$ | | | | | | | 3.87 (12) | | | | | | | | | | |
| (7) 2-H | | | | | 4.73 | | 4.81 | | | | | | | | | | |
| (8) 2-$H_e$ | | | | | 5.28 | | 5.27 (6.25) | | | | | | | | | | |
| (9) 2-$H_a$ | | | | | 4.70 | | 4.73 (12) | | | | | | | | | | |
| (10) 2-$H_e$ | | | | | | | 3.15 (6.25) | | | | | 3.08 | | | | | |
| (11) 2-$H_a$ | | | | | | | 3.73 (12.25) | | | | | 3.90 | | | | | |

$\delta$ in p.p.m. downfield from $Me_4Si$, $J$ in Hz. $J$* in parentheses, $|^2J|$ italicised.
* Molar fraction of conformer A. † $CH_3(CDCl_3$, 310 K): $\delta$ 0.95 (d, $^3J$ 6.5 Hz).

*cis*-4-Methyl-2-aziridin-1-yltetrahydropyran is expected to exist almost entirely in conformation (3E) with both substituents equatorial. This compound gives a sharply resolved quartet for 2-H with a value of $J$* of *ca.* 12 Hz. On cooling, the 2-H shift decreases in polar solvents and hardly increases in apolar solvents.

The 2-H signal of *trans*-4-methyl-2-aziridin-1-yltetrahydropyran is a fairly well resolved triplet in which the outer lines are separated by *ca.* 5.75—6 Hz. The shift and half-band width of this signal are nearly constant when temperature or solvent changes (in $CS_2$, $\delta$ 2.84 with $W_{\frac{1}{2}}$ *ca.* 7.5 Hz at 298 K and $\delta$ 2.75 with $W_{\frac{1}{2}}$ *ca.* 7.5 Hz at 173 K). Compound (2) is conformationally homogeneous with an axial–amino-group [(2A)] since its 2-H signal is not temperature dependent and shows a line separation $J$* close to that found in (10). In compounds (2), (3), (10), and (11), the equatorial anomeric proton gives rise to resonance upfield from its axial counterpart whereas the reverse is usually observed. This difference in shift indicates that aziridine strongly shields a proton situated above its ring.

(2) 2-*Aziridin*-1-*yltetrahydropyran* (1) (*parent compound*). In this compound, partial overlapping of the 2- and 6-H signals makes the evaluation of $J$* inaccurate but the 2-H shift can still be measured. Method (ii) (*vide supra*) is suitable for conformational analysis in this instance because of the slight effect of 4-methyl substitution:[7] using particular conditions of temperature and solvent, 2-$H_a$ in (3E), 2-$H_e$ in (2A), and 2-H in (1) appear at a similar shift (see Table 1, $CDCl_3$ at 203 K). The 2-H signal of (1) is shielded by increasing the polarity of the solvent and lowering the temperature. In apolar media, these effects are reversed and weaker. Inspection of the 2-H shift shows that (1) interconverts between conformers of different energy but the slow exchange limit cannot be reached by cooling at 173 K.

When the nitrogen inversion is slow in the n.m.r. time scale,[8] the aziridinyl protons appear as two ill

resolved bands, partly overlapped by 3-, 4-, and 5-H of the tetrahydropyranyl ring. The temperature at which ethyleneamino-group signals coalesce depends on the solvent used, which can also change the conformer and rotamer ratio. Thus, by 4-methylation of the oxygen-containing ring, the coalescence temperature is raised in apolar solvents, lowered in polar solvents, but remains unchanged in $D_2O$ or $CDCl_3$.

Induced shifts [9] caused by $Eu(dpm)_3$ in (1) and (3) clearly indicate that co-ordination takes place with the nitrogen atom, as previously reported.[2c,10] However, due to steric factors, an axially oriented nitrogen atom decreases the shift inducing power of the lanthanide.[2c] In *cis*-4-methylated complexes, the 2-H shift is the same for the 2-dimethylamino-group as well as for the 2-aziridinyl group, but in the parent complexes, the paramagnetic shift is lower for the aziridinyl substituent. This difference is thus ascribed to the contribution of the *N*-axial form.

(3) *2-Methylamino- and 2-naphthylamino-compounds* (4)—(9). 2-Methylaminotetrahydropyrans (4)—(6) have been previously studied.[2c] The *cis*-4-methyl compound (6), with $J^*$ 12 Hz, is conformationally homogeneous and exhibits two equatorial substituents (6E). The *trans*-4-methyl compound (5) and the parent compound (4) are present as a mixture of conformers whose ratio can be calculated with the reference values of $J^*$ in (10) and (11).

4-Methyl-2-naphthylaminotetrahydropyrans (8) and (9) are expected to exist almost entirely in one conformation in which 2-H is respectively equatorial (8A) and axial (9E): their spectra show no significant change at low temperature and the values of $J^*$ are close to those of (10) and (11) respectively. The 2-H multiplet of (7) is ill resolved and the population of the two interconverting forms (7A) and (7E) has been calculated by comparison of the shift of the anomeric proton with those of (8) and (9).

B *Carbon-13 Magnetic Resonance Studies* (*Table* 2).—The assignments of the spectra are based on signal multiplicities in off-resonance proton decoupled experiments and on comparison of observed shifts with 'calculated' ones. The $^1J$(C,H) one-bond coupling constant values provide important information, facilitating the interpretation of the spectra. The presence of electronegative heteroatoms increases the coupling constant, and $^1J$(C-2,H) is larger than $^1J$(C-6,H), both different from the coupling of the other carbons of the tetrahydropyranyl ring. In the aziridine part, the proton *trans* to the lone pair has the weaker coupling constant.[11]

The C-4 and C-6 signals appear in (2) at lower field than in (3). As the *γ-gauche*-effect is larger than the *γ-trans*-effect for nitrogen,[12] compound (2) is expected to exist in the form (2A) with axial nitrogen and equatorial methyl.

Variable-temperature $^{13}C$ n.m.r. spectroscopy has been used to determine conformational equilibria for (1) and to evaluate barriers to ring and nitrogen inversion.

TABLE 2

$^{13}C$ N.m.r. data

| Compounds | Solvent | T/K | Carbons: Chemical shifts δ (p.p.m.) C-2 | C-3 | C-4 | C-5 | C-6 | $CH_2N$ | | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|
| (1) | [$^2H_6$]Acetone | 273 | 93.9 | 31.8 | 22.4 | 26.3 | 66.0 | 23.0 | 21.9 | |
| | | 223 | 94.0 | 31.8 | 22.4 | 26.2 | 66.1 | 23.3 | 22.0 | |
| | | 183 | 94.3 | 31.7 | 23.1 | 26.0 | 66.4 | 23.1 | 21.8 | |
| | | 168 | 94.6 | 31.9 | 23.1 | 25.9 | 66.9 | 23.3 | 21.8 | |
| | | | | | 18.9 | | 61.2 | | | |
| | | 163 | 94.7 | 31.9 | 23.1 | | 66.9 | 23.5 | 21.8 | |
| | | | | | | | *0.84* | | | |
| | | | | | 18.8 | | 61.1 | | | |
| | | | | | | | *0.16* | | | |
| | | 158 | 94.9 | 31.9 | 23.0 | 25.8 | 66.9 | 23.4 | 21.8 | |
| | | | | | 18.6 | | 61.1 | | | |
| (1) | Neat | 300 | 92.3 | 31.8 | 22.4 | 26.3 | 65.6 | 22.1 | 21.6 | |
| | | | (151) | (128) | (129) | (128) | (141) | * | | |
| (2) | $CDCl_3$ | 308 | 95.5 | 39.0 | 27.2 | 35.3 | 62.7 | | | |
| (3) | $CDCl_3$ | 308 | 95.5 | 41.4 | 30.9 | 35.3 | 67.6 | 24.5 | 23.2 | 23.2 |

Intensities are italicised. $^1J$(C/H) Hz in parentheses.

* $^1J$(C/H*cis*) 164, $^1J$(C/H*trans*) 174 Hz (*cis* and *trans* with respect to tetrahydropyranyl group).

(1) *Conformational equilibria. Configurational inversion.* Slow nitrogen inversion in (1) at room temperature causes the methylene groups of the aziridine ring to be diastereotopic on the n.m.r. time scale; thus they give rise to distinct signals which coalesce at *ca.* 325 K in the pure liquid state. Cooling below 183 K results in splitting of the lines for C-4 and C-6: besides the strong peaks due to (1E), weaker lines due to (1A) appear at higher field, since the latter is expected to be less stable than its equatorial counterpart. No broadening has been observed for C-2 and C-5: this would involve weak differences in shifts and thus the same α- and δ-effects of the ethyleneamino-group in the axial and equatorial orientations. 4-Methyl compounds give identical information.

(2) *Determination of thermodynamic parameters.* $\Delta G^\circ$: Values were obtained from integration of the C-6 lines at 163 K in deuterioacetone. A value of +0.56 kcal $mol^{-1}$ has been found for E ⟶ A exchange for compound (1).

The study has been completed by variable-temperature $^1H$ n.m.r. in $CS_2$, involving the anomeric part of the spectra of (1). Observed shifts have been compared with those for (2) and (3) (in the same conditions) which are expected to be the 2-H shifts of pure (1A) and (1E) respectively. The equilibrium constant $K$ is related to the free energy $\Delta G°$ by $K_{E \rightarrow A} = x_A/(1 - x_A) = \exp(-\Delta G°/RT)$. The average chemical shift $\delta^{av.}$ of the 2-H shifts $\delta_E$ and $\delta_A$ in (1E) and (1A), respectively, is expressed by $\delta^{av.} = x_A\delta_A + (1 - x_A)\delta_E$. Two values of $\Delta G°$ have been obtained by measurement of $\delta^{av.}$ at different temperatures; insertion into the Helmholtz equation gives a value of 0.43 kcal mol$^{-1}$ for $\Delta H°_{E \rightarrow A}$ and a value of *ca.* −0.4 cal mol$^{-1}$ K$^{-1}$ for $\Delta S°_{E \rightarrow A}$. The equatorial form (1E) is statistically favoured as shown by $\Delta S°$. The amount of (1A) seems to be slightly increased in apolar solvents and $CDCl_3$.

(3) *Determination of kinetic parameters.* The determination of kinetic parameters in terms of rate constants and activation energies requires line-shape analysis, *i.e.* experiments have to be performed near the coalescence temperature.[13] The rate constant $k$ is related to the enthalpy of activation by the Eyring equation.

Nitrogen inversion in aziridine (1). For degenerate processes (exchanges between equally populated sites), the rate at the coalescence temperature is given by $k = \pi\Delta\nu/\sqrt{2}$ ($\Delta\nu$ denotes the frequency difference of the exchanging nucleus in the two sites).[13] The value of 17.05 kcal mol$^{-1}$ found for $\Delta G^{\ddagger}_{T_c}$ ($T_c$ *ca.* 325 K; $\Delta\nu$ *ca.* 10 Hz) agrees with literature data.[14]

Ring inversion in parent compound (1). For exchanges between unequally populated sites,[15] the population difference $\Delta P$ is related to the rate constant at coalescence by $[(X^2 - 2)/3]^3 = (\Delta P)^2X^2$ ($X$ refers to the parameter $\pi\Delta\nu/k$; the difference in population is derived from low-temperature $^1H$ experiments). For a first-order process, the individual rate constants $k_A$ and $k_E$ are deduced from $k = (k_A + k_E)/2$ through the equations $k_A = 2kx_A$ and $k_E = 2k(1 - x_A)$ so that the activation barriers can be calculated: $\Delta G^{\ddagger}_{E \rightarrow A}$ *ca.* 9.4, $\Delta G^{\ddagger}_{A \rightarrow E}$ *ca.* 8.9 kcal mol$^{-1}$ ($T_c$ *ca.* 183 K, $\Delta P$ *ca.* 0.6).

C *Nitrogen-15 Magnetic Resonance Studies.*—Nitrogen in (1) gives rise to a resonance (δ 26.5 p.p.m.) upfield from that in 2-dimethylaminotetrahydropyran (δ 35.4 p.p.m.). Moreover, *N*-(2-tetrahydropyranylation) has a deshielding effect of 37.9 p.p.m. on aziridine.[16,17]

D *Dipole Moment Study of* (1) (*Table* 3).—Dipole moments of 2-alkylaminotetrahydropyrans have been reported.[10] They have also been calculated by vector addition of alkylamine and tetrahydropyran and good agreement between experimental and calculated values has been observed. The same type of calculation was used here with 1-methylaziridine (μ 1.31 D[18]) and tetrahydropyran.

Of the rotamers of (1E), $E_I$ is sterically favoured but there is an orbital interaction which is relieved in $E_{II}$. Only form $A_I$ is expected for (1A), since other rotamers are strikingly hindered. A value of 1.82 D has been measured for the permanent moment of compound (1) in the pure liquid state. A dipole moment value of 1.86 D has been calculated for $E_{II} \rightleftarrows A_I$, using the relation $\mu = [x_A\mu^2_{A_I} + (1-x_A)\mu^2_{E_{II}}]^{\frac{1}{2}}$ and the conformer ratio found by $^1H$ n.m.r. So that, for pure (1), the nitrogen lone pair is expected to be antiperiplanar to the C-2–O bond in rotamer $E_{II}$ and nearly synclinal to both C-3 and oxygen in form $A_I$.

Hydrogen bonding of (1) in chloroform solution results in an increase of the apparent dipole moment, due to a lower orbital interaction with respect to pure (1), which involves the contribution of the less hindered rotamer $E_I$. This agrees with the shielding of the anomeric proton in polar solvents as shown by the $^1H$ n.m.r. data.

TABLE 3

Calculated dipole moments of different rotamers for compound (1) *

| | Conformer E | | | | Conformer A | | | |
|---|---|---|---|---|---|---|---|---|
| α(°) | 60 | 180 | 300 | Free rotation | 0 | 120 | 240 | Free rotation |
| Rotamer | | $E_{II}$ | $E_I$ | | | $A_I$ | | |
| Filled orbital interaction | 1 | 0 | 1 | | 1 | 0 | 0 | |
| μ/D | 2.64 | 2.11 | 2.64 | 2.48 | 1.94 | 1.13 | 1.13 | 1.45 |

* $\epsilon^{20}$ 5.55. μ(found) 1.8$_2$ D.

E *Interpretation.*—Mainly in conformation $E_I$, compounds (1), (3), (4), (6), (7), and (9) display an 'exo-anomeric-like' effect[19] while an anomeric effect is operative in compounds (2), (5), and (8), predominantly in the axial nitrogen form. Current interpretation[20] of the anomeric effect is based on dipole–dipole interactions, *gauche*-effects,[21] and overlap of the oxygen *p*-type lone pairs with adjacent antibonding orbitals.[1g] The interaction between an oxygen σ-type lone pair and the adjacent equatorial antibonding orbital is expected to stabilize the conformation with an equatorial 2-substituent.[20]

Thus the following interactions may be involved in any explanation of the conformational preference of 2-aminotetrahydropyrans.

(i) *Orbital interactions.* In the E form, overlap can occur between the oxygen σ-type lone-pair and the C-2–N σ* bond, between the oxygen *p*-type lone pair and the C-2–H σ* bond, and between the nitrogen lone pair and the C-2–O σ*; in the A form, it takes place between the oxygen *p*-type lone pair and the C-2–N σ* bond, between the oxygen σ-type lone pair and the C-2–H σ* bond, and between the nitrogen lone pair and the

C-2–O σ* bond. The last may be disregarded in aziridinyl compounds on steric grounds (one methylene group points into the oxygen-containing ring).

(ii) *Dipole–dipole interactions.* Repulsive effect due to the nitrogen and oxygen filled *p*-orbitals [22] results in the antiparallelism between the nitrogen lone pair and the C-2–O bond. By comparison, in 2-alkylthio-[1d] or 2-alkoxy-tetrahydropyrans,[1e] one lone pair of the equatorial substituent is necessarily *syn*-axial with regard to one doublet of the ring oxygen. For compounds (1) and (3), the dipolar effect is partially released in solvents of high dielectric constant or in protic solvents; conformer A is less favoured in acetonitrile or dimethyl sulphoxide but compound (2) is always in form (2A). Thus the above mentioned overlap between the nitrogen lone pair and the C-2–O σ* orbital is easily counterbalanced by interaction between the solute and a protic or polar solvent, and hence would not operate to the same extent.

(iii) *Steric effects of ring substituents.* Steric interactions in these heterocycles do not compare with those in substituted cyclohexanes. The spatial relationships between the σ- and *p*-atomic orbitals and the C–H and C–N bonds are different in the A and E conformers, so that energies, valence-bond angles, and bond lengths may be different in axial and equatorial isomers. This electronic perturbation from ideal electron-pair bonding would be greatest when the nitrogen lone-pair is less available (aziridine [23] or β-naphthylamine). Hence, in *trans*-4-methyl compounds, steric hindrance of the methyl group would be subject to the influence of the nitrogen substituents (Table 4).

TABLE 4

Equilibrium study E ⇌ A

| Compounds | (1) | (2) | (4) | (5) | (7) | (8) |
|---|---|---|---|---|---|---|
| $x_A$ | 0.3 | ⩾0.98 | 0.18 | 0.65 | 0.19 | ⩾0.95 |
| $\Delta G°_{E \rightarrow A}$ | $0.5_2$ | $\leqslant -2.3_4$ | $0.9_3$ | $-0.4_0$ | $0.8_9$ | $\leqslant -1.8_0$ |
| $(\Delta G°_N)_{E \rightarrow A}$ | $0.5_2$ | | $0.9_3$ | | $0.8_9$ | |
| $(\Delta G°_{CH_3})_{E \rightarrow A}$ | | $\geqslant 2.8_6$ | | $\sim 1.3_3$ | | $\geqslant 2.6_9$ |

ΔG° in kcal mol$^{-1}$.

*Conclusions.*—Good evidence has been obtained that in tetrahydropyrans, 2-amino-substituents are preferentially equatorial; on steric grounds an axial nitrogen may result. Thus 2-aminotetrahydropyrans do not display an anomeric effect.

## EXPERIMENTAL

Compounds (8) and (9) were obtained in nearly quantitative yields from 2-aminonaphthalene and 2-hydroxy-4-methyltetrahydropyran as described for (5) and (6).[2c] Other compounds were previously reported.[2] $^1$H N.m.r. spectra were performed on a Varian A60A or XL100 instrument in the continuous-wave mode or on a Bruker WP60 pulsed Fourier transform spectrometer. Solvents, concentrations, and temperatures are indicated in the Tables. Natural-abundance $^{13}$C n.m.r. spectra were obtained by Fourier transformation carried out on a Bruker WP60 spectrometer at 15.08 MHz or a Bruker WP80 instrument at 20.15 MHz. The products were examined in 10 mm tubes in the pure liquid state with an internal tube containing $D_2O$ used as an external deuterium lock, or as solutions in $CD_3COCD_3$ or $CDCl_3$ (30—50% v/v) as internal lock signal. We used a spectral width of 2—2.5 kHz with 8 K memory points and a flip angle of 30°. Tetramethylsilane was used as internal reference for chemical shifts for $^1$H and $^{13}$C spectra. Nitrogen chemical shifts were determined with a Bruker WP80 spectrometer operating at 8.12 MHz. The products were examined in the pure liquid state in 20 mm tubes with a concentric tube containing $^{15}$N-enriched nitric acid in $D_2O$, providing both the external reference and the field-frequency lock. The reference shift was calibrated by recording spectra of pure nitromethane and saturated aqueous ammonium nitrate. Chemical shifts are reported using the anhydrous ammonia scale. Proton-noise decoupling spectra were obtained with a spectral width of 4 kHz, 8 K memory points, a pulse angle of 30°, and a pulse interval of 10 s.

Dipole moments were determined by measuring dielectric constants and refractive indexes of compounds; values of 150° for angle $\phi$ and of 1.31 D for $\mu_{tma}$ have been inserted in the previously reported expression.[10]

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