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ACKNOWLEDGMENT

The research work was supported by FDA Contract 223-76-3009. The very capable technical assistance of Mr. Melford Henderson is gratefully acknowledged.

# Synthesis and Structural Study of *N*-Substituted Nortropane Spirohydantoins

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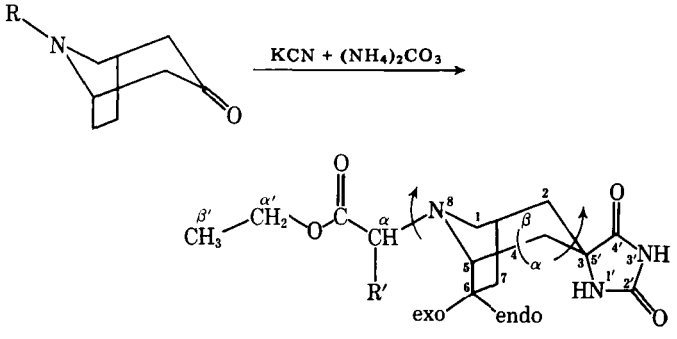
Received February 22, 1982, from the **Department of Organic and Pharmaceutical Chemistry, School of Pharmacy, Universidad Compultense, Madrid-3, Spain* and the ‡*Department of X-Ray, Rocasolano Institute of Physical Chemistry, C.S.I.C., Serrano 119, Madrid-6, Spain.* Accepted for publication June 29, 1982.

**Abstract** □ A series of $N^8$-alkyloxycarbonylalkyl-nortropane-3-spiro-5′-hydantoins has been synthesized and studied by spectral and crystallographic methods. The crystal and molecular structure of one [8(γ-ethoxycarbonylpropyl)nortropane-3-spiro-5′-hydantoin, VI] was determined by X-ray diffraction. The preferred conformations of these compounds and subsequent changes on protonation were determined from $^1$H-NMR and $^{13}$C-NMR data.

**Keyphrases** □ *N*-Substituted nortropane spirohydantoins—synthesis, structural studies using IR, NMR, and X-ray crystallography □ NMR spectroscopy—analysis of *N*-substituted nortropane spirohydantoins □ IR spectroscopy—analysis of *N*-substituted nortropane spirohydantoins □ X-Ray crystallography—analysis of *N*-substituted nortropane spirohydantoins

In a previous paper (1), $^1$H- and $^{13}$C-NMR studies of a pharmacologically interesting series of tropane- and *N*-substituted nortropane-3-spiro-5′-hydantoins were reported. The structure of tropane-3-spiro-5′-hydantoin (determined by X-ray methods) also has been described (2). In this study the synthesis and structural determination of a series of $N^8$-ethoxycarbonylalkyl-nortropane-3-spiro-5′-hydantoins and their corresponding hydrochlorides is reported (Scheme I). Treatment of the appropriate $N^8$-substituted nortropinone[1] with potassium cyanide and ammonium carbonate in aqueous ethanol gave the desired hydantoins.




I: R′ = H
II: R′ = $-CH_3$
III: R′ = $-CH_bH_cC_6H_5$
IV: R′ = $-CH_2CH_2CO_2CH_2CH_3$
V: R′ = $-CH(CH_3)_2$
VI: $>N^8-CH_2CH_2CH_2CO_2CH_2CH_3$
VII: $>N^8-C_6H_4$-*p*-$CO_2CH_2CH_3$

*Scheme I*

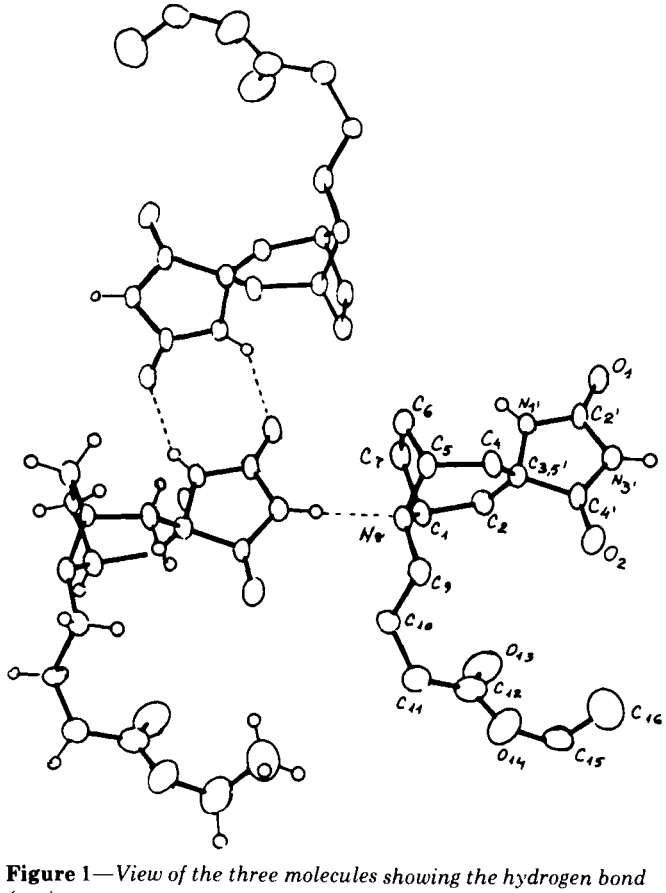


**Figure 1**—*View of the three molecules showing the hydrogen bond (---).*

[1] G. G. Trigo, M. Martinez and E. Galvez, unpublished results.

0022-3549/83/0800-0881$01.00/0

**Table I—Bond Distances and Angles of VI**

| Bond | Distance, Å | Bond | Angle, ° |
|---|---|---|---|
| C(1—C(2) | 1.533(3) | C(2)—C(1)—N(8) | 112.3(3) |
| C(1)—C(7) | 1.541(4) | C(2)—C(1)—C(7) | 112.4(3) |
| C(1)—N(8) | 1.487(4) | C(7)—C(1)—N(8) | 100.8(2) |
| C(2)—C(3,5′) | 1.545(4) | C(1)—C(8)—C(5) | 101.1(2) |
| C(3,5′)—C(4) | 1.544(4) | C(2)—C(3,5′)—C(4) | 111.6(2) |
| C(4)—C(5) | 1.529(4) | C(2)—C(3,5′)—N(1′) | 112.6(2) |
| C(5)—C(6) | 1.537(4) | C(2)—C(3,5′)—C(4′) | 109.0(2) |
| C(5)—N(8) | 1.487(4) | C(4)—C(3,5′)—N(1′) | 112.7(2) |
| N(8)—C(9) | 1.467(3) | C(4)—C(3,5′)—C(4′) | 109.9(2) |
| C(9)—C(10) | 1.528(5) | N(1′)—C(3,5′)—C(4′) | 100.4(2) |
| C(11)—C(12) | 1.504(6) | C(3,5′)—C(4)—C(5) | 112.6(3) |
| C(12)—O(13) | 1.198(5) | C(4)—C(5)—N(8) | 112.7(2) |
| C(12)—O(14) | 1.333(4) | C(4)—C(5)—C(6) | 113.4(3) |
| O(14)—C(15) | 1.457(6) | C(6)—C(5)—N(8) | 100.4(2) |
| C(15)—C(16) | 1.488(8) | C(5)—C(6)—C(7) | 104.7(3) |
| C(3,5′)—N(1′) | 1.468(3) | C(1)—C(7)—C(6) | 104.0(3) |
| N(1′)—C(2′) | 1.340(3) | C(1)—N(8)—C(5) | 101.1(2) |
| C(2′)—N(3′) | 1.400(3) | C(1)—N(8)—C(9) | 114.4(3) |
| C(2′)—O(1) | 1.223(3) | C(5)—N(8)—C(9) | 116.8(3) |
| N(3′)—C(4′) | 1.370(4) | N(8)—C(9)—C(10) | 111.8(3) |
| C(4′)—O(2) | 1.198(3) | C(9)—C(10)—C(11) | 110.8(3) |
| C(4′)—C(3,5′) | 1.536(3) | C(10)—C(11)—C(12) | 112.1(4) |
| | | C(11)—C(12)—O(13) | 124.7(4) |
| | | C(11)—C(12)—O(14) | 111.2(4) |
| | | O(13)—C(12)—O(14) | 124.1(4) |
| | | C(12)—O(14)—C(15) | 116.5(4) |
| | | C(14)—C(15)—C(16) | 110.3(5) |

## EXPERIMENTAL

IR spectra were recorded on a double-beam spectrophotometer[2] using indene and polystyrene for calibration. The $^1$H-NMR spectra were recorded at 60 MHz[3], 90 MHz[4], and 250 MHz[5]. The $^{13}$C-NMR spectra were determined at 20 MHz[6] in the Fourier transform mode at room temperature. Both broad-band decoupled and single-frequency off-resonance decoupled spectra were determined. Mass spectral determinations were made[7]. Elemental analyses were determined[8].

**$N^8$-Substituted Nortropane Spirohydantoins (I–VII)**—A solution of potassium cyanide (0.15 mole) and ammonium carbonate (0.3 mole) in water (115 ml) was added to a solution of the corresponding racemic *N*-substituted nortropinone[1] (0.1 mole) in ethanol (35 ml). The mixture was heated at 60° in a sealed flask for 24 hr. After cooling, the precipitated solid was removed by filtration. The mother liquors were concentrated (~50%) under reduced pressure and cooled, and the resulting solid was removed by filtration and added to the first material obtained.

**Hydrochlorides of I–VI**—Solutions of I–VI (0.01 mole) in ethanol (10 ml) were added to hydrogen chloride dissolved in ethanol (2 ml, 5 *N*). The resulting mixtures were heated at reflux for 10 min and then allowed to cool. The solvent was removed under reduced pressure, and each residue was recrystallized from ethanol.

## RESULTS AND DISCUSSION

**Structure Determination and Refinement of VI**—The cell parameters $a$ = 8.191 (1), $b$ = 9.380 (2), and $c$ = 10.752 Å (2) and $\alpha$ = 105.45 (2), $\beta$ = 98.68 (1), and $\gamma$ = 97.00° (1) were obtained from a least-squares calculation of the setting angles of 30 reflections measured on an automatic four-circle diffractometer[9]. The calculated density was 1.325 g/cm$^3$ with $Z$ = 2. The intensities were collected from a crystal of 0.30 × 0.40 × 0.25 mm in the range $2 \leq 2\theta \leq 60°$ in the $\theta/2\theta$ scan mode with MoK$_\alpha$ radiation monochromatized by a graphite crystal; 4478 independent reflections were measured of which 2598 had $I \geq 2\sigma$ (I), $\sigma$ being calculated from counting statistics. No systematic absences were observed; therefore, the possible space groups were P1 and P$\bar{1}$.

A centrosymmetric structure was suggested by normalized structure factor statistics. The structure was solved by direct methods [MULTAN 77 (3)]. The best E map revealed all the nonhydrogen atoms. Anisotropic full-matrix least-squares refinement with unit weights led to $R$ = 0.10.

[2] Perkin-Elmer 577.
[3] Hitachi/Perkin-Elmer R-24 B spectrometer.
[4] Varian EM 390 spectrometer.
[5] Bruker WM 250 SY spectrometer.
[6] Bruker WM 80 SY spectrometer.
[7] Hitachi/Perkin Elmer RMU-6M spectrometer.
[8] Carlo Erba Elemental Analyzer model 1104.
[9] Philips PW 1100.

**Table II—Atomic Parameters of VI**

| | x/a | y/b | z/c | Ueq |
|---|---|---|---|---|
| | | Nonhydrogen Atoms[a] | | |
| C(1) | 0.1901(3) | 0.8132(3) | 0.2776(3) | 318(9) |
| C(2) | 0.3822(3) | 0.8438(3) | 0.3078(3) | 294(8) |
| C(3,5′) | 0.4600(3) | 0.7014(3) | 0.3056(2) | 279(8) |
| C(4) | 0.3581(3) | 0.5954(3) | 0.3648(3) | 316(9) |
| C(5) | 0.1691(3) | 0.5894(3) | 0.3279(3) | 312(8) |
| C(6) | 0.1035(3) | 0.5451(3) | 0.1787(3) | 405(10) |
| C(7) | 0.1184(3) | 0.6941(4) | 0.1446(3) | 383(10) |
| N(8) | 0.1190(3) | 0.7395(3) | 0.3688(2) | 298(7) |
| C(9) | 0.1711(3) | 0.8245(3) | 0.5083(3) | 350(9) |
| C(10 | 0.0785(4) | 0.7524(4) | 0.5953(3) | 488(12) |
| C(11) | 0.1623(4) | 0.8191(5) | 0.7397(3) | 553(14) |
| C(12) | 0.3229(5) | 0.7624(4) | 0.7714(3) | 474(12) |
| O(13) | 0.3574(4) | 0.6479(4) | 0.7086(3) | 724(13) |
| O(14) | 0.4215(4) | 0.8548(3) | 0.8803(3) | 623(11) |
| C(15) | 0.5737(6) | 0.8048(5) | 0.9287(4) | 644(16) |
| C(16) | 0.7171(7) | 0.8660(7) | 0.8774(6) | 850(24) |
| O(1) | 0.7119(2) | 0.5600(3) | 0.0785(2) | 459(8) |
| O(2) | 0.6823(2) | 0.8149(3) | 0.4978(2) | 441(8) |
| N(1′) | 0.4891(2) | 0.6248(3) | 0.1749(2) | 313(7) |
| C(2′) | 0.6514(3) | 0.6202(3) | 0.1722(3) | 321(9) |
| N(3′) | 0.7441(2) | 0.7006(3) | 0.2971(2) | 342(8) |
| C(4′) | 0.6410(3) | 0.7480(3) | 0.3832(3) | 306(8) |
| | | Hydrogen Atoms | | |
| H(11) | 0.162(7) | 0.915(6) | 0.291(5) | |
| H(21) | 0.414(6) | 0.911(5) | 0.396(5) | |
| H(22) | 0.424(6) | 0.893(6) | 0.247(5) | |
| H(41) | 0.394(6) | 0.634(6) | 0.464(5) | |
| H(42) | 0.390(6) | 0.502(6) | 0.335(5) | |
| H(51) | 0.118(6) | 0.522(6) | 0.369(5) | |
| H(61) | 0.020(7) | 0.494(6) | 0.153(5) | |
| H(62) | 0.162(7) | 0.474(6) | 0.134(5) | |
| H(71) | 0.191(7) | 0.700(6) | 0.078(5) | |
| H(72) | 0.005(7) | 0.712(6) | 0.110(5) | |
| H(91) | 0.149(7) | 0.932(6) | 0.516(5) | |
| H(92) | 0.290(7) | 0.838(6) | 0.539(5) | |
| H(101) | 0.084(8) | 0.638(7) | 0.568(6) | |
| H(102) | 0.033(8) | 0.768(7) | 0.585(6) | |
| H(111) | 0.094(9) | 0.791(8) | 0.799(7) | |
| H(112) | 0.188(9) | 0.927(8) | 0.773(7) | |
| H(151) | 0.578(10) | 0.680(9) | 0.888(8) | |
| H(152) | 0.612(10) | 0.863(9) | 1.022(7) | |
| H(1′,1) | 0.426(6) | 0.580(5) | 0.109(5) | |
| H(3′,1) | 0.853(7) | 0.713(6) | 0.319(5) | |
| H(161) | 0.737(12) | 0.984(11) | 0.916(9) | |
| H(162) | 0.688(12) | 0.827(11) | 0.779(9) | |
| H(163) | 0.811(12) | 0.833(11) | 0.926(9) | |

[a] Coordinates and thermal parameters as Ueq = $(1/3)\cdot\Sigma[U_{ij} = a_i^* a_j^* a_i a_j \cos(a_i,a_j)]$ pm$^2$.

**Table III—Torsion Angles of VI**

| Bonds | Angle, ° |
|---|---|
| C(3,5′)—C(2)—C(1)—N(8) | 56.4(3) |
| C(2)—C(1)—N(8)—C(5) | −68.5(3) |
| C(1)—N(8)—C(5)—C(4) | 69.5(3) |
| N(8)—C(5)—C(4)—C(3,5′) | −57.5(3) |
| C(5)—C(4)—C(3,5′)—C(2) | 38.3(3) |
| C(4)—C(3,5′)—C(2)—C(1) | −38.1(3) |
| C(1)—N(8)—C(5)—C(6) | −51.5(3) |
| N(8)—C(5)—C(6)—C(7) | 31.3(3) |
| C(5)—C(6)—C(7)—C(1) | −0.5(3) |
| C(6)—C(7)—C(1)—N(8) | −30.4(3) |
| C(7)—C(1)—N(8)—C(5) | 51.3(3) |
| N(1′)—C(2′)—N(3′)—C(4′) | 4.4(3) |
| C(2′)—N(3′)—C(4′)—C(3,5′) | −3.3(3) |
| N(3′)—C(4′)—C(3,5′)—N(1′) | 1.1(3) |
| C(4′)—C(3,5′)—N(1′)—C(2′) | 1.7(3) |
| C(3,5′)—N(1′)—C(2′)—N(3′) | −3.7(3) |

A difference synthesis showed all hydrogen atoms. Final refinement, with the isotropic temperature factor for hydrogen, gave $R$ = 0.070 and $R_w = (\Sigma w \Delta^2/\Sigma w |F_0|^2)^{1/2}$ = 0.079. A final difference synthesis showed no significant electron density[10].

**Description of the Structure**—The molecular conformation of the

[10] The structure factor lists are deposited in the Division of Drug Chemistry, Food and Drug Administration, Washington, DC 20204; copies are available on request to the authors.

**Table IV—Physical Data and Spectral Properties of I–VII and the Corresponding Hydrochlorides**

| Compound | $R^1$ [a] | Yield, % | Melting Point[b], ° | IR[c] (KBr), $cm^{-1}$ | MS, *m/z* | Formula | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|---|---|
| I | —H | 47 | 225–226 | 3358 (m), 2720 (vw), 1765 (s), 1745 (s), 1710 (vs) 1760 (w), 1730 (s)[d] | 281 ($M^+$), 208, 181, 96, 80, 55, 44 | $C_{13}H_{19}N_3O_4$ | C 55.50<br>H 6.80<br>N 14.93 | 55.60<br>6.68<br>14.57 |
| I · HCl | | 95 | 185 | 1720, 1745, 1760 | | $C_{13}H_{20}ClN_3O_4$ | C 49.13<br>H 6.34<br>N 13.22 | 48.95<br>6.26<br>13.20 |
| II | $-CH_3$ | 58 | 239–240 | 3250 (m), 2720 (m), 1770 (s), 1740 (vs), 1720 (vs) 1760 (w), 1720 (s)[d] | 295 ($M^+$), 222, 168, 136, 70, 68, 56, 55, 44 | $C_{14}H_{21}N_3O_4$ | C 56.94<br>H 7.17<br>N 14.23 | 56.60<br>7.10<br>14.16 |
| II · HCl | | 83 | 199 | 1730, 1768 | | $C_{14}H_{22}ClN_3O_4$ | C 50.68<br>H 6.68<br>N 12.66 | 50.43<br>6.93<br>12.58 |
| III | $-CH_bH_cC_6H_5$ | 39 | 228–229 | 3240 (m), 2720 (w), 1765 (s), 1735 (sh), 1720 (vs) 1760 (w), 1720 (s)[d] | 342 ($M^+ - 29$), 299, 280, 159, 130, 103, 91, 89, 67, 55, 54, 44 | $C_{20}H_{25}N_3O_4$ | C 64.67<br>H 6.78<br>N 11.31 | 64.30<br>6.93<br>11.70 |
| III · HCl | | 72 | 248 | 1735, 1768 | | $C_{20}H_{26}ClN_3O_4$ | C 58.89<br>H 6.42<br>N 10.30 | 58.80<br>6.29<br>10.12 |
| IV | $-CH_2CH_2CO_2-CH_2CH_3$ | 72 | 135–136 | 3300 (w), 2712 (w), 1762 (m), 1750 (s), 1720 (vs) 1760 (w), 1730 (s)[d] | 281 ($M^+$), 336, 234, 151, 134, 63, 55, 54 | $C_{18}H_{27}N_3O_6 \cdot H_2O$ | C 54.12<br>H 7.31<br>N 10.51 | 54.37<br>7.45<br>10.82 |
| IV · HCl | | 96 | 198–199 | 1736, 1770 | | $C_{18}H_{28}ClN_3O_6$ | C 51.73<br>H 6.75<br>N 10.05 | 51.79<br>7.06<br>9.79 |
| V | $-CH(CH_3)_2$ | 57 | 206 | 3365 (m), 3190 (m), 1775 (s), 1728 (vs), 1710 (vs) 1760 (w), 1725 (s)[d] | 280 ($M^+ - 43$), 250, 138, 96, 83, 55, 54, 44 | $C_{16}H_{25}N_3O_4$ | C 59.61<br>H 7.50<br>N 13.03 | 60.00<br>7.85<br>12.75 |
| V · HCl | | 87 | 235–236 | 1730, 1767 | | $C_{16}H_{26}ClN_3O_4$ | C 53.40<br>H 7.28<br>N 11.67 | 53.32<br>7.26<br>11.77 |
| VI | $>NCH_2CH_2CH_2-CO_2CH_2CH_3$ | 37 | 180 | 3270 (m), 2710 (m), 1765 (m), 1730 (vs), 1715 (vs) 1765 (w) 1725 (s)[d] | 309 ($M^+$), 264, 208, 182, 124, 82, 64, 55, 54, 44 | $C_{15}H_{23}N_3O_4$ | C 58.23<br>H 7.49<br>N 13.58 | 58.26<br>7.80<br>14.00 |
| VI · HCl | | 82 | 250–252 | 1732, 1770 | | $C_{15}H_{24}ClN_3O_4$ | C 52.09<br>H 6.99<br>N 12.15 | 51.78<br>6.89<br>12.09 |
| VII | $>N-C_6H_4$-*p*-$CO_2-CH_2CH_3$ | 24 | 320–321 | 3400 (m), 3195 (m), 1770 (s), 1730 (vs), 1700 (vs) 1770 (w), 1732 (s)[d] | | $C_{18}H_{21}N_3O_4$ | C 62.96<br>H 6.16<br>N 12.23 | 62.65<br>6.10<br>12.57 |

[a] $R^1$ is the same in each compound for the free base and corresponding hydrochloride salt. [b] All compounds were recrystallized from ethanol except for III, which was recrystallized from methanol. [c] The N—H and C=O stretching frequencies are listed for the free bases. The C=O stretching frequencies are listed for the hydrochloride salts. Key: (s) strong; (w) weak; (sh) shoulder; (vs) very strong; (vw) very weak. [d] Spectra were run in dimethyl sulfoxide (DMSO) solution.

**Table V—Chemical Shifts of I–VII in Dimethyl Sulfoxide [a]**

| Group | I | II | III[b] | IV | V | VI | VII |
|---|---|---|---|---|---|---|---|
| $H_{2,4\alpha}$ | 1.50(a) | 1.40(a) | 1.43(a) | 1.40(a) | 1.40(a) | 1.40(a) | 1.53(a) |
| $H_{2,4\beta}$ | 2.20(a) | 2.30(a)<br>2.20(a) | 2.27(a)<br>2.21(a) | ~2.1(b)[c] | 2.18(a)<br>2.10(a) | 2.16(a) | 2.20(a) |
| $H_{1,5}$ | 3.31(c) | 3.40(c) | 3.35(c) | 3.26(c) | 3.15(c) | 3.20(c) | 4.4(c) |
| $H_{6,7}$ | 1.90(c) | 1.90(c) | 1.90(c) | 1.84(c) | 1.80(c) | 1.86(c) | 2.10(c) |
| $N^{1'}$—H | 8.25(d) | 8.30(d) | 8.22(d) | 8.0(d) | 8.0(d) | 8.14(d) | 8.36(d) |
| $N^{3'}$—H | 10.80(c) | 10.40(c) | 10.72(c) | 10.70(c) | 10.50(c) | 10.45(c) | 10.50(c) |
| $CH_\alpha$ | 3.30(d) | 3.40(e) | 3.52(a) | ~3.3(b)[c] | 3.05(f) | 2.36(g) | |
| $CH_\beta$ | | 1.18(f) | 2.73(a)<br>3.08(a) | ~2.2(b)[c] | ~1.8(b)[c] | 1.70(h) | |
| $CH_\gamma$ | | | | ~2.4(b)[c] | 0.88(f)<br>0.83(f) | 2.33(g) | |
| $CH_{\alpha'}$ | 4.15(e) | 4.15(e) | 3.88(e) | 4.06(e) | 4.0(e) | 4.10(e) | 4.20(e) |
| $CH_{\beta'}$ | 1.20(g) | 1.20(g) | 0.92(g) | 1.12(g) | 1.14(g) | 1.16(g) | 1.30(g) |
| $CH_{\alpha''}$ | | | | 4.04(e) | | | |
| $CH_{\beta''}$ | | | | 1.12(g) | | | |
| Aromatic $H_{2'(6')}$ | | | 7.1–7.3(b) | | | | 6.83(f) |
| Aromatic $H_{3'(5')}$ | | | | | | | 7.76(f) |

[a] Spectra recorded at 90 MHz unless otherwise indicated; tetramethylsilane was used as the internal standard. Key: (a) doublet of doublets; (b) multiplet; (c) wide singlet; (d) singlet; (e) quartet; (f) doublet; (g) triplet; (h) quintuplet. [b] Spectra recorded at 250 MHz. [c] Not resolved.

**Table VI—Coupling Constants of I–VII in Dimethyl Sulfoxide** [a]

| Identification | I | II | III | IV | V | VI | VII[b] |
|---|---|---|---|---|---|---|---|
| $JH_{2,4\alpha}$—$H_{2,4\beta}$ | 14 | 15 | 14 | 14 | 14 | 14 | 14 |
| $JH_{2,4\beta}$—$H_{1,5}$ | 3 | 3 | 3 | | 3 | 3 | 3 |
| $JH_{2,4\alpha}$—$H_{1,5}$ | <1 | 1 | <1 | ~1 | <1 | <1 | <1 |
| $JH_{1,5}(W_{1/2})$ | 8 | 9 | 10 | 10 | | 9 | 9 |
| $JH_{\alpha}$—$H_{\beta}$ | | 7 | [c] | | 6 | 6 | |
| $JH_{\beta}$—$H_{\gamma}$ | | | | | 6 | 6 | |
| $JH_{\alpha'}$—$H_{\beta'}$ | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| $JH_{\alpha''}$—$H_{\beta''}$ | | | | 7 | | | |

[a] Hertz values; tetramethylsilane was used as the internal reference. [b] Aromatic $^3J = 7$. [c] In the molecular fragment >N—$CH_a$—C(—$H_b$)(—$H_c$)—$\phi$; $JH_a$—$H_b$ = 10, $JH_a$—$H_c$ = 4, and $JH_b$—$H_c$ = 12.

compound reported here provides a comparison with some of the derivatives already studied (2, 4, 5). Figure 1 shows the structural formula. Table I lists the bond lengths and angles; Table II shows the final parameters for the atoms; Table III lists the torsion angles.

The molecule consists of a piperidine ring and a five-membered ring joined by a common C—N—C bridge, with an ethoxycarbonylpropyl group attached to the N-8 atom and a hydantoin ring substituted at the C-3,5′ atom. The piperidine ring adopts a distorted chair conformation. The asymmetry parameters (6) are $\Delta C_s^{(3,5')} = 0.9$, $\Delta C_2^{(2\text{-}3,5')} = 15.0$, and $\Delta C_2^{(1\text{-}2)} = 30.8$, showing that mirror symmetry is dominant with an approximate $C_s$-plane passing through C-3,5′ and N-8. The displacements of C-3,5′ and N-8 from the plane through the remaining atoms of the piperidine ring are 0.496 and −0.818 Å, respectively: larger than the corresponding deviations of the C-3,5′ and N-6 in $N^3$-ethyl-3-azabicyclo(3.2.1)octane-8-spiro-5′-hydantoin (4), −0.897 and 0.575 Å, respectively. The nonbonded distances C-7 · · · C-3,5′ and N-8 · · · C-3,5′ are 3.04 and 3.01 Å, respectively, similar to the corresponding distances found in $N^8$-methyl-nortropane-3-spiro-5′-hydantoin (2).

The five-membered ring adopts a puckering $N^8$-envelope conformation. This conformation has been studied in terms of the torsion angles (7). The pseudo-rotation parameters $\Delta$ and $\phi$ are −35.0 and 53.7°, respectively, and the deviation of N-8 atom from the plane through C-1, C- 5, C-6, and C-7 is −0.750 Å, similar to the value found previously (4) for the C-3,5′ atom.

The configuration of N-8 is pyramidal, as in other mentioned cases (2, 4), and the ethoxycarbonylpropyl radical is attached to the N-8 in an axial position as previously described (2). Two hydrogen bonds of the types N—H · · ·O and N—H · · ·N link the molecules together (Fig. 1). The geometry of these hydrogen bonds are N(1′) · · ·O(1)(−x + 1, −y + 1, −z) = 2.932 Å, N(3′) · · ·N(8)(x + 1, y,z) = 3.005 Å, N—H · · ·O = 163.0°, and N—H · · ·N = 178.3°.

**IR Spectra**—The IR data of I–VII (Table IV) were compared with analogous azabicyclospirohydantoins studied previously (8, 9). The IR spectrum of VI in the solid state shows a medium band at 3270 $cm^{-1}$ and a broad band at 2710 $cm^{-1}$. The band at 3270 $cm^{-1}$ is due to the stretching of the $N^{1'}$—H bond belonging to the intermolecular bonding system, $N^{1'}$—H · · ·O=$C^{2'}$ formed between pairs of molecules related by a center of symmetry. The band at 2710 $cm^{-1}$ is explained by the existence of a strong intermolecular hydrogen bond formed between the weak acid $N^{3'}$—H group and the basic piperidine nitrogen atom. Both structural facts are in good agreement with the results obtained by X-ray diffraction. The spectrum of VI in solid state shows a medium band at 1765 $cm^{-1}$ and two strong bands at 1730 and 1715 $cm^{-1}$ in the carbonyl region. The bands at 1765 and 1715 $cm^{-1}$ are attributed to the symmetrical and asymmetrical modes of the pseudo-ring system formed between molecules shown in Fig. 1. The band corresponding to the $C^{4'}$=O stretching vibration did not appear in the IR spectrum. As in related systems, this fact is explained by overlapping of the band corresponding to the $C^{2'}$=O asymmetric stretching mode of the dimer. The band at 1730 $cm^{-1}$ is attributed to the stretching of the ester carbonyl group. The spectra of II and III in solid state also showed bands similar to those found in VI.

The spectra of V and VII in solid state are different from those of II, III, and VI (in which the intermolecular hydrogen bonds deduced from IR data were confirmed by the X-ray study of VI). Therefore the intermolecular hydrogen bonds in V and VII are different; there is no $N^{3'}$—H · · ·N bond which can be attributed to the great size of the $N$-substituent in the case of V and to the low basicity of the piperidine nitrogen atom in the case of VII.

The carbonyl region shows the same pattern as those found in II, III, and VI. The spectra of I–VII showed the same absorption pattern in the carbonyl region in solid state as in solution in dimethyl sulfoxide; consequently, the $N^1$—· · ·O=$C^{2'}$ bonds remain in solution.

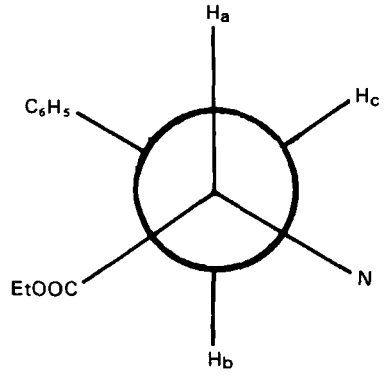



**Figure 2**—*Newman projection showing the conformation about $C_\alpha$—$C_\beta$ bond in III.*

**NMR Spectra**—The $^1$H- and $^{13}$C-NMR data of I–VII[11] are summarized in Tables V–XI. In all cases, broad-band decoupled and single-frequency off-resonance decoupling spectra were obtained. Assignments of the carbon resonances were made by the multiplicity of signals in the single-frequency off-resonance decoupled spectra, the peak intensity of the broad-band decoupled spectra, and the literature data (1, 10–18).

From the $^1$H- and $^{13}$C-NMR data of I–VII and the crystal structure of VI, the following general features were deduced: (*a*) the pyrrolidine and piperidine rings in these compounds all have a flattened $N^8$-envelope and distorted chair conformation puckered at N-8 and flattened at C-3,5′ similar to that observed in the crystal structure of VI; (*b*) the $C^{4'}$=O group is attached to the piperidine ring in an equatorial position (Scheme I), in good agreement with the X-ray results for VI; and (*c*) the radical attached to the piperidine nitrogen adopts an equatorial position; however, in the solid state (according to X-ray and IR data for II, III, and VI), the corresponding radical is attached in an axial position.

These conclusions are supported by the following. In the $^1$H-NMR spectra, the $W_{1/2}$ value (1) for the C-1 and C-5 hydrogen signals of ~10 Hz corresponds to a tropane system with the piperidine ring in a flattened chair conformation (1, 19). The $J$ $H_{2,4}$—$H_{1,5}$ values (Table VI) correspond to dihedral angles of ~60°. In all cases $J$ $H_{2,4\beta}$—$H_{1,5}$ is greater than $J$ $H_{2,4\alpha}$—$H_{1,5}$; consequently, the dihedral angle $H_{2,4\alpha}$—C—C—$H_{1,5}$ is greater than $H_{2,4\beta}$—C—C—$H_{1,5}$. The C-6 and C-7 hydrogen signal appears in all cases as a wide singlet; in an ideal chair, the C-6 and C-7 endo hydrogen atoms would be deshielded by the anisotropic effect due to the hydantoin ring. The C-2$\beta$ and C-4$\beta$ hydrogen signals are shifted to lower field, with respect to the C-2$\alpha$ and C-4$\alpha$ hydrogen signals, because of the anisotropic deshielding effect due to the equatorial $C^{4'}$=O group (1).

In the $^{13}$C-NMR spectra, the chair conformation adopted by the piperidine ring is confirmed by the C-2 and C-4$\delta$ values (Table IX). For a boat conformation, these carbon signals would be shifted to higher field because of the steric compressing effect due to the eclipsing between the C-2(4)$\beta$ and C-1(5) hydrogen atoms (16). The different radicals are attached to the piperidine nitrogen atom in an equatorial position. For an axial position of the radical, the $\gamma$-effect exerted on H-2$\alpha$ and H-4$\alpha$ would shift to higher field to the C-2 and C-4 carbon signals (16). The puckering of the piperidine ring at N-8 is deduced from the $\gamma$-shielding effect exerted by the equatorial $N$-group on H-6 exo and H-7 exo. This $\gamma$-effect is ~3 ppm[12], smaller than that expected for an ideal envelope conformation of the pyrrolidine ring.

The hydrochlorides of I–IV, which are the usual species in pharmacological studies, have also been studied. The main features found in the protonated forms are: (*a*) the puckering at N-8 is decreased, and (*b*) the proton attached to the $N$-piperidine atoms is in the axial position.

These results are supported by the following. In the $^{13}$C-NMR, the carbon signals corresponding to the C-2 and C-4 in the hydrochlorides of I–IV are shifted to higher fields with respect to the same carbon signals of the corresponding bases. This fact is due to the *syn*-diaxial effect of the $N^+$—H proton. The mentioned decreasing of the puckering is sup-

[11] Copies of the $^{13}$C-NMR spectra of II, II·HCl, III, III·HCl, V, and VI and the $^1$H-NMR spectrum of III are deposited in the Division of Drug Chemistry, Food and Drug Administration, Washington, DC 20204 and are available on request to the authors.

[12] This value is the difference between the C-6 and C-7$\delta$ values of compounds I–VII and the C-6 and C-7$\delta$ value of nortropane (10).

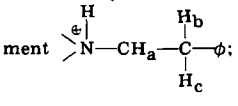
**Table VII—Chemical Shifts of the Hydrochlorides of I–VI [a]**

| Group | I[b,d] | I[c,e] | II[b,e] | II[c,e] | III[c,e] | IV[b,d] | IV[c,e] | V[b,d] | VI[c,e] |
|---|---|---|---|---|---|---|---|---|---|
| $H_{2,4\alpha}$ | 2.02(a) | 2.08(a) | 1.93(a) | 2.26(a) | 2.20(a) | 2.05(a) | 2.20(a) | 1.95(a) | 1.8–2.1(b)[f] |
| $H_{2,4\beta}$ | 2.60(a) | 2.60(a) | 2.5–2.8(b)[f] | 2.69(a) | 2.70(a) | ~2.7(b)[f] | ~2.7(b)[f] | 2.5–2.7(b)[f] | 2.55(a) |
| $H_{1,5}$ | 4.15(c) | 4.05(c) | 4.26(c) | 4.30(c) | 4.40(c) | 4.1(c) | 4.0(c) | 4.0(c) | 4.1(c) |
| $H_{6,7}$ | 2.25(c) | 2.27(c) | 2.26(c) | 2.35(c) | 2.35(c) | 2.30(c) | 2.34(c) | 2.30(c) | 2.20(c) |
| $N_{1'}$—H | 8.58(c) | | 8.63(c) | | | 8.60(c) | | 8.50(c) | |
| $CH_\alpha$ | 4.15(d) | 3.9(d) | ~4.2(b)[f] | 4.28(c) | 4.23(a) | ~4.2(b)[f] | ~4.0(b)[f] | 4.30(f) | 3.0(g) |
| $CH_\beta$ | | | 1.60(f) | 1.67(f) | 3.17(a) | 2–2.7(b)[f] | 2.60(c) | ~2.0(b)[f] | 2.0(h) |
| $CH_\gamma$ | | | | | | 2–2.7(b)[f] | 2.60(c) | 1.05(f)<br>1.06(f) | 2.4(g) |
| $CH_{\alpha'}$ | 4.30(e) | 4.27(e) | 4.26(e) | 4.35(e) | 4.10(e) | 4.33(e) | 4.36(e) | 4.30(e) | 4.05(e) |
| $CH_{\beta'}$ | 1.28(g) | 1.27(g) | 1.36(g) | 1.33(g) | 1.06(g) | 1.23(g) | 1.32(g) | 1.20(g) | 1.16(g) |
| $CH_{\alpha''}$ | | | | | | 4.02(e) | 4.20(e) | | |
| $CH_{\beta''}$ | | | | | | 1.12(g) | 1.31(e) | | |
| Aromatic | | | | | 7.2–7.4(b) | | | | |

[a] Key: (a) doublet of doublets; (b) multiplet; (c) wide singlet; (d) singlet; (e) quartet; (f) doublet; (g) triplet; (h) quintuplet. [b] In dimethyl sulfoxide. [c] In deuterium oxide. [d] Spectra recorded at 60 MHz. [e] Spectra recorded at 90 MHz. [f] Not resolved.

**Table VIII—Coupling Constants of the Hydrochlorides of I–VI [a]**

| Identification | I[b] | I[c] | II[b] | II[c] | III[c] | IV[b] | IV[c] | V[b] | VI[c] |
|---|---|---|---|---|---|---|---|---|---|
| $JH_{2,4\alpha}$—$H_{2,4\beta}$ | 16 | 16 | 15 | 16 | 15 | 14 | 16 | 14 | 14 |
| $JH_{2,4\beta}$—$H_{1,5}$ | ~3 | 3 | | 3 | 3 | | ~3 | | ~3 |
| $JH_{2,4\alpha}$—$H_{1,5}$ | <1 | <1 | <1 | <1 | <1 | ~1 | ~1 | <1 | |
| $JH_{1,5}(W_{1/2})$ | ~10 | ~10 | ~12 | | ~12 | | | ~12 | |
| $JH_\alpha$—$H_\beta$ | | | | 7 | [d] | | | 6 | 8 |
| $JH_\beta$—$H_\gamma$ | | | | | | | | 6 | 7 |
| $JH_{\alpha'}$—$H_{\beta'}$ | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| $JH_{\alpha''}$—$H_{\beta''}$ | | | | | | 7 | 7 | | |

[a] Hertz values; tetramethylsilane was used as the internal reference. [b] In dimethyl sulfoxide. [c] In deuterium oxide. [d] In the molecular fragment  ; $JH_a$—$H_b$ = 10, $JH_a$—$H_c$ = 5, and $JH_b$—$H_c$ = 15.

ported by the increased γ-effect exerted by the *N*-group on the C-6 and C-7 exo hydrogen atoms, so that the C-6 and C-7 carbon signals are shifted to higher fields.

To give a detailed account of the former results, several pairs of base–hydrochloride compounds were studied. For solubility reasons, it was not possible to run the spectra of the bases and the hydrochlorides in the same solvent; however, medium-induced shifts are often negligibly small in $^{13}C$-NMR because the nuclei studied are buried in the molecular framework.

*Compound I*—In this case, the decreasing of the puckering on protonation is noticeable $\Delta\delta$(C-6, C-7) = −4.5 ppm.

*Compound II*—In this case, the decreasing of the *N*-puckering is less than that observed in I, $\Delta\delta$(C-6, C-7) ≃ −2.5 ppm. The proton-coupled spectral data of II hydrochloride are in Table XI; from the $J$ $C^{4'}$—$H_{2,4\beta}$ value of 3 Hz, a value near 0° can be deduced for the dihedral angle $C^{4'}$—$C^3$—$C^2$—$H_{2,4\beta}$ in good agreement with values found in the literature (20, 21).

*Compounds III and IV*—For these compounds, the decreasing of N-8 puckering on protonation is remarkable, $\Delta\delta$(C-6,7) ≃ −5 ppm. From the $^1H$—NMR spectra of III resolved at 250 MHz, it can be deduced that the *N*-piperidine group adopts the preferred conformation represented in Fig. 2. This fact can be explained as:

1. The vicinal coupling constants (Table VI) of the $\phi$—$CH_2$—CH—N< fragment.
2. Hc resonates at a lower field with respect to Hb; this is due to the anisotropic effect exerted by the phenyl group.
3. The aromatic proton resonance is a complex multiplet, showing a distinct conformational preference about the aryl-Cβ bond.
4. In the proposed conformation, the ethyl ester protons resonate at a higher field position than those of related compounds (Table V) since they are shielded by the π-electron cloud of the phenyl group.

The deshielding of the C-1 and C-5 carbon signals on protonation (≈5 ppm, Tables IX and X) remains unexplained. It could be explained by the enhancement of the N-σ-effect on protonation, but it had been shown (22) that, in *N*-methyl piperidine, the *N*-protonation effect on the α-carbon is quite irregular (−1.7–26.1 ppm).

**Table IX—$^{13}C$-Chemical Shifts for I–VII in Dimethyl Sulfoxide**

| Carbon Position | Multiplicity[a] | I | II | III[b] | IV[b] | V | VI[b] | VII[b] |
|---|---|---|---|---|---|---|---|---|
| 1,5 | d | 57.09(d) | 55.70 | 54.43<br>54.82 | 54.34<br>54.70 | 53.87<br>55.70 | 56.70 | 51.90 |
| 2,4 | t | 38.58 | 37.41 | 37.50 | 38.01 | 38.47 | 38.92 | 35.41 |
| 3 | s | 59.28 | 59.24 | 59.55 | 59.01 | 59.75 | 59.70 | 60.15 |
| 6,7 | t | 24.97 | 25.48<br>25.01 | 25.87 | 25.60 | 25.88<br>26.03 | 25.14 | 26.43 |
| C—α | | 52.70(t) | 54.39(d) | 63.58(d) | 59.82(d) | 66.78(d) | 49.79(t) | |
| C—β | | | 16.28(q) | 37.50(t) | 25.60(t) | 28.14(d) | 23.65(t) | |
| C—γ | | | | | 29.14(t) | 16.79(q)<br>19.53(q) | 31.62(t) | |
| C—C=O | s | 170.73 | 172.63 | 171.83 | 172.13 | 171.72 | 172.80 | 165.55 |
| C—C=O | s | | | | 172.73 | | | |
| C—α′ | t | 59.68 | 60.41 | 59.76 | 60.13 | 59.53 | 59.52 | 59.49 |
| C—β′ | q | 13.91 | 13.98 | 13.75 | 13.87 | 13.98 | 14.02 | 14.17 |
| C—α″ | t | | | | 60.13 | | | |
| C—β″ | q | | | | 13.87 | | | |
| C—2′ | s | 156.68 | 156.79 | 156.84 | 156.84 | 156.72 | 156.81 | 156.81 |
| C—4′ | s | 178.84 | 178.70 | 178.92 | 178.77 | 178.80 | 178.95 | 177.82 |
| Aromatic | | | | | | | | |
| C—1 | s | | | 137.30 | | | | 149.02 |
| C—2,6 | d | | | 126.70 | | | | 130.92 |
| C—3,5 | d | | | 128.03 | | | | 117.01 |
| C—4 | d | | | 126.25 | | | | 113.36 |

[a] Signal multiplicity obtained from single-frequency off-resonance decoupling spectra. Key: (s) singlet; (d) doublet; (t) triplet; (q) quartet. [b] In 10% deuterated chloroform.

**Table X—$^{13}$C-Chemical Shifts for the Hydrochlorides of I–IV in Deuterium Oxide**

| Position | Carbon Multiplicity[a] | I | II | III[b] | IV |
|---|---|---|---|---|---|
| 1.5 | d | 59.09 | 57.60<br>61.20 | 58.10<br>60.16 | 57.70<br>58.16 |
| 2.4 | t | 35.41<br>36.25 | 37.50<br>37.71 | 34.32 | 34.28 |
| 3 | s | 55.85 | 58.46 | 55.43 | 55.61 |
| 6.7 | t | 20.44 | 22.96<br>23.55 | 20.50<br>20.80 | 20.39<br>20.93 |
| C—$\alpha$ | | 51.17(t) | 58.46(d) | 56.58(d) | 56.31(d) |
| C—$\beta$ | | | 13.92(q) | 31.68(t) | 20.93(t) |
| C—$\gamma$ | t | | | | 26.78 |
| $C_\alpha$—C=O | s | 167.34 | 169.45 | 165.41 | 165.50 |
| $C_\gamma$—C=O | s | | | | 171.13 |
| C—$\alpha'$ | t | 61.25 | 64.04 | 61.37 | 61.70 |
| C—$\beta'$ | q | 10.77 | 13.44 | 10.39 | 10.85 |
| C—$\alpha''$ | t | | | | 59.61 |
| C—$\beta''$ | q | | | | 10.69 |
| C—2′ | s | 155.80 | 158.30 | 155.66 | 155.63 |
| C—4′ | s | 176.06 | 178.44 | 176.01 | 175.90 |

[a] Signal multiplicity obtained from single-frequency off-resonance decoupling spectra. Key: (s) singlet; (d) doublet; (t) triplet; (q) quartet. [b] Aromatic: C-1, 130.70; C-2 and C-6[c], 126.70; C-3 and C-5[c], 126.58; C-4, 125.52. [c] Values may be interchanged.

**Table XI—$^{13}$C—H Coupling Constants of the Hydrochloride of II in Deuterium Oxide [a]**

$JC_1$—$H_1$: 154; $JC_5$—$H_5$: 150; $JC_2$—$H_2$ and $JC_4$—$H_4$: 130; $JC_6$—$H_6$ and $JC_7$—$H_7$: 138; $JC_\alpha$—$H_\alpha$: 150; $JC_\beta$—$H_\beta$: 126; $JC_\beta$—$H_\alpha$: 5; $JC_{\alpha'}$—$H_{\alpha'}$: 150; $JC_{\alpha'}$—$H_{\beta'}$: 4.5; $JC_{\beta'}$—$H_{\beta'}$: 126; $JC_{\beta'}$—$H_{\alpha'}$: 2.8; $JC_{4'}$—$H_{2,4_{ax}}$: 3

[a] Hertz values.

*Compounds V and VI*—The $^1$H- and $^{13}$C-NMR data for these compounds are analogous to those of I–IV.

*Compound VII*—Because of the $\pi$-releasing conjugative effect of the *N*-piperidine atom, the phenyl group is essentially located on a plane approximately parallel to the $C^1$—$C^2$—$C^4$—$C^5$ plane; consequently, a $\beta$-compressing effect on H-6 exo and H-7 exo is exerted, and the $^{13}$C-NMR signal of C-1 and C-5 carbon atoms are shifted to higher field ($\Delta \simeq -4$ ppm) with respect to the same C-signal of the parent compounds.

## CONCLUSIONS

In the crystalline state, the cyclohexane ring of VI adopts a deformed chair conformation with a flattening at C-3,5′. This deformation is probably due to the steric interaction between the ethylene bridge and the hydantoin group. The opposite puckering at N-8 and the axial position of the *N*-substituent make the formation of the intramolecular $N^{3'}$—H···$N^8$ bond easy. Compounds I–VII in dimethyl sulfoxide solution show the same deformation in the cyclohexane rings, but the N—H···N bond disappears, and the *N*-radical adopts the equatorial position to avoid the *syn*-diaxial effect on the C-2 and C-4 axial hydrogen atoms. In III and VII the $N^8$-group shows a distinct conformational preference. The $N^8$-puckering of I–VII in dimethylsulfoxide solution is governed by the steric effect of the $N^8$-group on the C-6 and C-7 exo hydrogen atoms. In deuterium oxide solution, the $N^8$-protonation of I–IV takes place in an axial position. An equatorial protonation would produce the aforementioned syn-diaxial effect. The decreasing of *N*-puckering on protonation would decrease the $N^+$—H *syn*-diaxial effect on the C-2 and C-4 axial hydrogen atoms and facilitate the $N^+$—H solvation.

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