as above in 100% yield by heating **2** and **1b** for 9 h: $^1$H NMR $\delta$ 1.67 (6 H, s, $CH_3$), 6.80 (2 H, s, CH), 7.40 (5 H, m, aromatic); $^{13}$C NMR $\delta$ 16.00 ($CH_3$), 78.44 (C-1 and C-4), 121.76, (q, $J$ = 273.0 Hz, $CF_3$), 128.49, 129.24, 132.39, 137.28, (aromatic carbons), 148 (C-5 and C-6), 150.90, (m, C-2 and C-3), 174.7 (C=O); mass spectrum (CI, $CH_4$), $m/e$ 362 ($M^+ + 1$); IR (neat) 3300, 3000, 1660, 1450, 1325, 1250, 1150, 700 cm$^{-1}$.

***N*-Benzoyl-2,3-bis(trifluoromethyl)-7-azabicyclo[2.2.1]heptane (4).** A solution of **3a** (0.50 g, 1.5 mmol) in EtOH (20 mL) was hydrogenated in a Parr apparatus at 75 lbs/in.$^2$ of $H_2$ for 2 h in the presence of 10% palladium on activated carbon (10 mg). The solution was filtered and concentrated in vacuo. The resulting solid was crystallized from hexane, yielding 0.49 g (97%) of **4** as colorless crystals: mp 114–115 °C; $^1$H NMR $\delta$ 2.00 (4 H, m, $CH_2$), 3.06 (2 H, m, CH), 4.60 (2 H, m, CH), 7.40 (5 H, m, aromatic); $^{13}$C NMR $\delta$ 24.05 (C-5 and C-6), 44.88 (C-2 and C-3), 58.86 (C-1 and C-4), 124.65 (q, $J$ = 280.5 Hz, $CF_3$), 128.13, 128.84, 131.92 134.08 (aromatic carbons), 169.98 (C=O); mass spectrum, $m/e$ (relative intensity) 337 ($M^+$, 21), 105 (100), 77 (33), 51 (8); IR (Nujol) 3300, 1630, 1410, 1305, 1275, 1230, 725 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{13}NOF_6$: C, 53.41; H, 3.86. Found C, 53.42; H, 3.99.

***N*-Benzoyl-2,3-bis(trifluoromethyl)-7-azabicyclo[2.2.1]-2-heptene (5a).** A solution of **3a** (2.65 g, 7.96 mmol) in EtOH (20 mL) was hydrogenated at 1 atm of $H_2$ in the presence of 10% palladium on activated carbon (30 mg). The uptake of hydrogen dropped sharply after 1 equiv (180 mL), and the solution was filtered and concentrated in vacuo, yielding 2.58 g (97%) of **5a** as a yellow oil. The product appeared pure by NMR and TLC and was used directly in the preparation of **6a**: $^1$H NMR $\delta$ 1.47 (2 H, m, $CH_2$), 2.13 (2 H, m, $CH_2$), 5.13 (2 H, m, CH), 7.36 (5 H, br s, aromatic); $^{13}$C NMR $\delta$ 24.15 (C-5 and C-6), 61.41 (C-1 and C-4), 120.2 (q, $J$ = 271.3 Hz, $CF_3$), 128.86, 128.88, 131.95, 133.30 (aromatic carbons), 139.44 (C-2 and C-3), 169.47 (C=O); mass spectrum (CI, $CH_4$), $m/e$ 336 ($M^+ + 1$); IR (neat) 3250, 3050, 2960, 1670, 1370, 1300, 1180, 1150, 1040, 730, 710 cm$^{-1}$.

***N*-Benzoyl-2,3-bis(trifluoromethyl)-1,4-dimethyl-7-azabicyclo[2.2.1]-2-heptene (5b).** Hydrogenation of **3b** as above gave **5b** (95% yield) as a yellow oil: $^1$H NMR $\delta$ 1.53 (6 H, s, $CH_3$), 1.58 (2 H, m, $CH_2$), 2.03 (2 H, m, $CH_2$), 7.40 (5 H, m, aromatic); $^{13}$C NMR 18.41 ($CH_3$), 34.39 (C-5 and C-6), 72.79 (C-1 and C-4), 121.24 (q, $J$ = 273.7 Hz, $CF_3$), 128.43, 129.52, 132.47, 138.00 (aromatic carbons), 140.90 (m, C-2 and C-3), 176.43 (C=O); mass spectrum (CI, $CH_4$), $m/e$ 364 ($M^+ + 1$); IR (neat) 3260, 2950, 1675, 1450, 1335, 1270, 1170, 945, 840, 760, 710 cm$^{-1}$.

***N*-Benozyl-3,4-bis(trifluoromethyl)pyrrole (6a).** A solution of **5a** (2.20 g, 6.57 mmol) in benzene (100 mL) was passed dropwise in a slow stream of nitrogen through a tube packed with glass beads and heated to 300 °C. The product was collected in a flask cooled to −78 °C. The column was washed with additional benzene (20 mL), and the solution was concentrated in vacuo. Distillation (0.15 mm, 84 °C) gave 1.90 g (94%) of **6a** as a colorless oil: $^1$H NMR $\delta$ 7.56 (7 H, m, aromatic and $\alpha$-pyrrole); $^{13}$C NMR $\delta$ 115.70 (q, $J$ = 37.7 Hz, $\beta$-pyrrole carbons), 121.75, (q, $J$ = 270.5 Hz, $CF_3$), 123.5 ($\alpha$-pyrrole carbons), 129.40, 130.00, 130.70, 134.20 (aromatic carbons), 166.50 (C=O); mass spectrum (CI, $CH_4$), $m/e$ 308 ($M^+ + 1$); IR (neat) 3360, 3160, 1730, 1560, 1320, 1250, 1150, 980, 900, 725 cm$^{-1}$.

***N*-Benzoyl-3,4-bis(trifluoromethyl)-2,5-dimethylpyrrole (6b).** Pyrolysis of **5b** as above gave **6b** (95% yield) as colorless crystals from hexane: mp 69.5–70.5 °C; $^1$H NMR $\delta$ 2.17 (6 H, s, $CH_3$), 7.60 (5 H, m, aromatic); $^{13}$C NMR $\delta$ 12.00 ($CH_3$), 110.09 (q, $J$ = 38.8 Hz, $\beta$-pyrrole carbons), 116.92 ($\alpha$-pyrrole carbons), 123.35, (q, $J$ = 269.1 Hz, $CF_3$), 129.78, 130.81, 133.16, 135.85 (aromatic carbons), 169.98 (C=O); mass spectrum, $m/e$ (relative intensity) 335 ($M^+ + 1$), 105 (100) 77 (57), 51 (11); IR (Nujol) 3350, 1725, 1370, 1260, 1200, 1150, 1110, 925, 725 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{11}NOF_6$: C, 53.73; H, 3.28. Found C, 53.73; H, 3.31.

**3,4-Bis(trifluoromethyl)pyrrole (7a).** A solution of **6a** (1.30 g, 4.23 mmol) and KOH (0.24 g, 1 equiv) in diethyl ether (60 mL) and water (3 mL) was stirred at room temperature for 6 h. The reaction was monitored by TLC (silica, $CH_2Cl_2$), and additional KOH was added in small amounts as needed. Water (200 mL) was added, and the solution was extracted with $CH_2Cl_2$. The combined organic fractions were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. Recrystallization from hexane–$CHCl_3$ (3:1) gave 0.77 g (90%) of **7a** as volatile, colorless crystals: mp 36.5–37.5 °C; $^1$H NMR $\delta$ 7.16 (2 H, d, $J$ = 3 Hz), 8.53 (1 H, br s, NH); $^{13}$C NMR $\delta$ 112.75 (q, $J$ = 39.0 Hz, $\beta$-pyrrole carbons), 121.18 ($\alpha$-pyrrole carbons), 122.96 (q, $J$ = 266.7 Hz, $CF_3$); mass spectrum, $m/e$ (relative intensity) 203 ($M^+$, 38), 184 (100), 153 (8), 134 (3); IR (neat) 3475, 3300, 1560, 1450, 1370, 1330, 1230, 1130, 980.

Anal. Calcd for $C_6H_3NF_6$: C, 35.47; H, 1.48. Found: C, 35.00; H, 1.51.

**3,4-Bis(trifluoromethyl)-2,5-dimethylpyrrole (7b).** A solution of **6b** (2.00 g, 5.97 mmol) and KOH (0.34 g, 1 equiv) in THF (130 mL) and water (7 mL) was stirred at room temperature for 6 h. The reaction was monitored by TLC (silica, hexane–$CH_2Cl_2$), and additional KOH was added in small amounts as needed. Water (300 mL) was added, and the solution was extracted with $CH_2Cl_2$. The combined organic fractions were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. Recrystallization from hexane gave 1.27 g (92%) of **7b** as colorless crystals: mp 95.5–96.5 °C; $^1$H NMR $\delta$ 2.27 (6 H, s, $CH_3$). 7.87 (1 H, br, s, NH); $^{13}$C NMR $\delta$ 12.04 ($CH_3$), 108.23 (q, $J$ = 39.7 Hz, $\beta$-pyrrole carbon), 123.89 (q, $J$ = 267.3 Hz, $CF_3$), 128.94 ($\alpha$-pyrrole carbon); mass spectrum, $m/e$ (relative intensity) 231 ($M^+$, 62), 230 (80), 212 (46), 162 (100), 69 (19), 42 (30); IR (Nujol) 3450, 3250, 1330, 1220, 1150, 1110, 1055 cm$^{-1}$.

Anal. Calcd for $C_8H_7NF_6$: C, 41.56; H, 3.03. Found: C, 41.37; H, 3.16.

**Registry No.** **1a**, 5145-65-3; **1b**, 5044-32-6; **2**, 692-50-2; **3a**, 83248-91-3; **3b**, 83248-92-4; **4**, 83248-93-5; **5a**, 83248-94-6; **5b**, 83248-95-7; **6a**, 83248-96-8; **6b**, 83248-97-9; **7a**, 82912-41-2; **7b**, 83248-98-0.

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## Nitrogen Bridgehead Compounds. 26.[1] Synthesis and Stereochemistry of 3-Phenylperhydropyrido[1,2-*a*]pyrimidin-4-ones

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*Received April 8, 1982*

4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones possess advantageous pharmacological properties;[2] therefore this class is being extensively investigated.[3] Hitherto, only a few representatives of the perhydro derivatives have been synthesized,[4] and the stereochemistry of these compounds has not been studied. In this paper catalytic hydrogenation of the tetrahydropyridopyrimidines (**1**)[5] and the conformational analysis of the resulting perhydro derivatives are reported.

**Synthesis.** The hydrogenation was performed in acetic acid solution, in the presence of platinum oxide at 30 °C and under a pressure of 62 atm. Hydrogenation of both **1a** and the 6-methyl derivative **1b** led to mixtures of two diastereoisomeric perhydro derivatives (**2** and **3**, Scheme I). Further diastereoisomers could not be detected by the GC/MS method. The ratio of the diastereoisomers **2** and **3** was 47:53 from **1a** and 40:60 from **1b**, as determined by GC analysis. The diastereomers **2** and **3** were separated

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0022-3263/82/1947-4780$01.25/0 

Table I. $^1$H NMR Data of Perhydropyrido[1,2-*a*]pyrimidin-4-ones 2-4

| | chemical shift,[b] δ | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | 2-H$_e$ | 2-H$_a$ | 3-H$_e$ | 3-H$_a$ | 6-H$_e$ | 6-H$_a$ | 7-H$_2$ | 8-H$_2$ | 9-H$_e$ | 9-H$_a$ | 10-H$_a$ | 3-Ph | 6-Me |
| 2a | 3.36 dd | 3.04 dd | | 3.57 dd | 4.83 dt | 2.52 dt | | 1.2-2.2 | 2.10[a] | 1.49[a] | 4.25 dd | 7.1-7.4 m | |
| 2b | 3.35 dd | 2.96 dd | | 3.58 dd | 5.09 m | | 1.69[a] | 1.2-2.15 | 2.00[a] | 1.35[a] | 4.44 dd | 7.0-7.4 m | 1.24 d |
| 3a | 3.33 dd | 3.09 dd | 3.70 dd | | 4.88 dt | 2.49 dt | | 1.1-2.15 | 1.93[a] | 1.22[a] | 4.13 dd | 7.05-7.45 m | |
| 3b | 3.23 dd | 3.03 dd | 3.68 dd | | 5.15 m | | 1.75[a] | 1.2-2.2 | 2.05[a] | 1.3[a] | 4.35 ddd | 7.05-7.45 m | 1.20 d |
| 4 | 2.7-3.3 m | | 2.25-2.45 m | | 4.98 m | | | 1.1-2.1 m | | | 4.24 dd | | 1.15 d |

| | coupling constants,[b] Hz | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| compd | $J_{2,2}$ | $J_{2e,3e}$ | $J_{2e,3a}$ | $J_{2a,3e}$ | $J_{2a,3a}$ | $J_{6,6}$ | $J_{6e,7a}$ | $J_{6e,7e}$ | $J_{6a,7e}$ | $J_{6a,7a}$ | $J_{9e,10a}$ | $J_{9a,10a}$ | $J_{10,NH}$ |
| 2a | 13.5 | | 5.5 | | 10 | 13 | 3 | 3 | 3 | 12 | 2.5 | 10 | |
| 2b | 13.5 | | 6 | | 10 | | 3 | 3 | | | 2.5 | 10 | |
| 3a | 14 | 4 | | 2 | | 12 | 3 | 3 | 3 | 12 | 2.5 | 10 | |
| 3b | 13.5 | 3.5 | | 1.5 | | | 3 | 3 | | | 2.5 | 10.5 | 9 |
| 4 | | | | | | | 3 | 3 | | | 2.5 | 11 | |

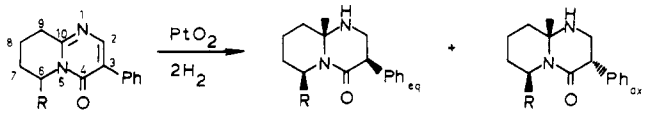
[a] Determined by selective coupling. [b] a = axial and e = equatorial.

Table II. Carbon-13 Chemical Shifts of Perhydropyrido[1,2-*a*]pyrimidin-4-ones (2-4)

| | chemical shift, δ | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Ph | | | |
| compd | C-2 | C-3 | C-4 | C-6 | C-7 | C-8 | C-9 | C-9a | Me | C-1 | C-2 | C-3 | C-4 |
| 2a | 48.0 t | 50.3 d | 168.7 s | 40.7 t | 25.0 t | 23.7 t | 33.5 t | 71.1 d | | 138.9 s | 128.4 d | 128.5 d | 126.6 d |
| 2b | 48.5 t | 50.4 d | 168.8 s | 43.9 d | 29.5 t | 18.4 t | 33.8 t | 67.1 d | 16.9 q | 139.5 s | 128.5 d | 128.5 d | 126.6 d |
| 3a | 47.5 t | 48.6 d | 167.6 s | 40.4 t | 25.4 t | 23.7 t | 33.6 t | 71.5 d | | 139.9 s | 127.9 d | 128.5 d | 126.6 d |
| 3b | 47.5 t | 48.6 d | 167.5 s | 43.6 d | 29.9 t | 18.4 t | 33.7 t | 67.0 d | 16.1 q | 140.3 s | 127.7 d | 128.5 d | 126.6 d |
| 4 | 40.3 t | 34.1 t[a] | 167.6 s | 43.6 d | 29.7 t | 18.2 t | 33.8 t | 66.8 d | 16.4 q | | | | |

[a] Assignment was proved by selective $^{13}$C{$^1$H} decoupling.

Scheme I




1a R = H
1b R = Me

2a R = H
2b R = Me

3a R = H
3b R = Me

by fractional crystallization (see Experimental Section), and structural assignment was made by $^1$H, $^{13}$C, and $^{15}$N NMR spectroscopy. The perhydro compounds **3**, with the lower melting points, contain the phenyl group in a pseudoaxial position, while diastereoisomers **2**, with the higher melting points, contain it in a pseudoequatorial position.

Table III. $^{15}$N Chemical Shifts

| compd | δ(N-1) | δ(N-5) |
|---|---|---|
| 2b | 337.3 | 237.3 |
| 3b | 346.9 | 237.1 |
| 4 | 338.0 | 239.2 |

**NMR Spectra and Conformational Analysis.** Characteristic $^1$H and $^{13}$C NMR data of compounds **2-4** are summarized in Tables I and II.

The coupling constants between H-10 and the methylene protons at C-9 are 10 and 2.5 Hz, indicating that H-10 is in an axial position in all of the isomers (**2** and **3**). In the spectrum of **3b** coupling between H-10 and NH was also observed. The magnitude of this coupling constant (9 Hz) suggests that predominantly the conformer containing the NH proton in an axial position is present.

The 6-methyl group is in an axial position in both **2b** and **3b**, similar to the structure of the starting tetrahydropyridopyrimidine **1b**.[6] This is supported by $^1$H and $^{13}$C NMR spectra. In the $^1$H NMR spectra the H-6 proton of **2b** and **3b** appears at relatively low field at 5.15 and 5.09 ppm, respectively, due to the deshielding effect resulting from the diamagnetic anisotropy of the neighboring carbonyl group. The coupling constants between H-6 and the methylene protons at C-7 (3 Hz) indicate the gauche position of these protons, i.e., to the axial position of the 6-methyl group. In the $^{13}$C NMR spectra the axial position of the 6-methyl group in **2b** and **3b** is supported by its γ

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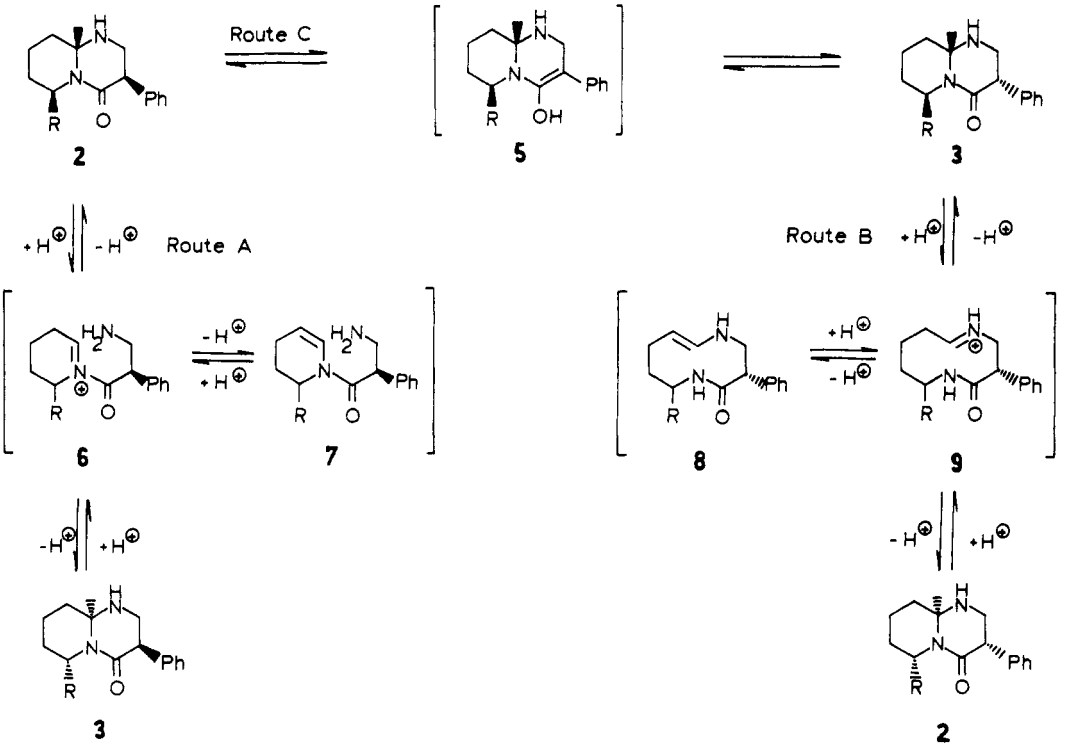
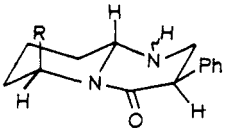
Scheme II




steric effect which results in a 5.3-ppm upfield shift at C-8 and 4.0- and 4.5-ppm upfield shifts at C-10, respectively, compared with the chemical shifts of the corresponding carbon atoms of the 6-demethyl derivatives **2a** and **3a**.

The perhydropyridopyrimidines **2a,b** contain an equa-

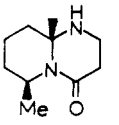


2

torial phenyl substituent on C-3. This is supported by the coupling constants between H-3 and the C-2 methylene protons, which are 5.5 and 10 Hz for **2a** and 6 and 10 Hz for **2b**. These coupling constants in **3a** and **3b** have values of 2 and 4 Hz and of 3.5 and 1.5 Hz, indicating that H-3 is in an equatorial and the phenyl group in an axial position.

In an previous case[8] the determination of the steric position of the substituent in position 3 of perhydropyrido[1,2-*a*]pyrimidin-4-ones by $^1$H NMR spectroscopy was difficult because of higher order couplings. $^{15}$N NMR spectroscopy offers an efficient method for determination of the steric position of this substituent. It is well-known that an upfield shift of about 10 ppm is caused by a substituent in $\gamma$ gauche position in relation to the nitrogen atom.[9] The effect of the substituent in $\gamma_{anti}$ position is significantly smaller. In our case an upfield shift was expected for the N-1 signal when the 3-phenyl group assumed an axial position. Steric interaction between the 3-substituent and the N-5 amide nitrogen was not expected, as the latter is nearly planar.[10]

The $^{15}$N chemical shifts of compounds **2b**, **3b**, and **4** are



4

listed in Table III. Not only at N-1 but at N-5 a nearly full NOE was measured. In **3b** the axial phenyl substituent caused an 8.9-ppm upfield shift for the N-1 signal compared with that of **4**, while the equatorial phenyl group of **2b** causes no significant effect. The presence of the phenyl group in **2b** and **3b** causes a downfield shift for N-5 of about 2 ppm, independently of its steric position.

**Epimerization of Diastereomers 2 and 3.** A slow epimerization of the separated perhydropyridopyrimidines **2** and **3** was observed. For example, in boiling ethanolic solution **3a** was 29% isomerized to **2a** within 1 h, the hydrochloride salt of **3a** was 69% isomerized to **2a** within 6 min, and the hydrochloride salt of **2b** was 15% isomerized to **3b** within 24 h. For the epimerization three possible routes were considered: route A, through ring opening and reclosure between the C-10 and N-5 atoms;[11] route B, through ring opening and reclosure between the C-10 and N-1 atoms;[12] route C, through oxo–enol tautomerism of the carbonyl group in position 4 (see Scheme II).

If the epimerization followed route A or B, then it would be expected not to occur in the case of the 6-methyl-substituted **2b** and **3b**. In these cases the reclosure of the ring-opening *N*-acyliminium and iminium salts **6** and **9** would be highly stereospecific[13] due to an $A^{1,3}$ strain, ap-

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pearing between the 6-methyl and 4-carbonyl groups. The epimerization through routes A or B should furthermore be accompanied by deuteration of the C-9 methylene, in deuteration experiments, because of the imine–enamine tautomerism.[12] In fact, epimerization does occur also with the 6-methyl derivatives **2b** and **3b**, and deuteration takes place at C-3 but not at C-9 on addition of trifluoroacetic acid in the presence of deuterium oxide. We therefore conclude that the epimerization of these derivatives (**2** and **3**) proceeds via oxo–enol tautomerism (route C).

## Experimental Section

Infrared (IR) spectra were obtained with KBr disks on a Zeiss UR-20 spectrophotometer. The $^1H$, $^{13}C$, and $^{15}N$ NMR spectra were recorded of samples in $CDCl_3$ in the PFT mode (16K data points for the FID) at ambient temperature with an internal deuterium lock at 99.6, 25.0, and 10.04 MHz by using a JEOL FX-100 multinuclear spectrometer. The $^1H$ and $^{13}C$ chemical shifts were determined on the $\delta$ scale by using tetramethylsilane ($\delta$ 0) as an internal standard. The concentration of $^1H$ NMR samples was about 0.1 mol/L, and that of the $^{13}C$ and $^{15}N$ samples was about 0.5–1.0 mol/L. $^{15}N$ chemical shifts were measured at natural abundance levels, were determined relative to the signal of external aqueous $K^{15}NO_3$, and then were converted to external neat nitromethane ($\delta_{CH_3NO_2} = 0$). Typical acquisition parameters included a spectral width of 5000 Hz, a flip angle of 30°, and pulse delays up to 5 s.

All GLC analyses were accomplished with a Hewlett-Packard 5830 A instrument on SP 2100 in a glass capillary column (10 m) with argon (2 mL/min) as the carrier gas and a temperature program (10 °C/min) from 150 to 250 °C. Mass spectral analyses were carried out with a JEOL B-300 spectrometer fitted with a JMA 2000 $\beta$ system.

The epimerization experiments were carried out in 0.1 M ethanolic solution, the product ratio was determined by GLC analysis in base form.

Melting points were measured in capillaries and are uncorrected.

**Hydrogenation.** Tetrahydropyridopyrimidine (10 mmol) in acetic acid (10 mL) was hydrogenated over $PtO_2$ (60 mg) at 30 °C under a pressure of 62 atm (about 24 h). After the catalyst was filtered out, the acetic acid was removed under reduced pressure. The residue was dissolved in methylene chloride (5 mL) and washed with 3% $NaHCO_3$ solution (50 mL). The aqueous phase was extracted three times with methylene chloride (1 mL each), and the combined organic solutions were dried ($Na_2SO_4$) and evaporated.

**Separation of the Diastereomers.** The product of the hydrogenation of **1a** (2.08 g, mixture of **2a** and **3a**) was recrystallized first from 5 volumes and then twice from 10 volumes of toluene at 50 °C to yield **2a**: 0.29 g; mp 146 °C; IR $\nu_{CO}$ 1614 cm$^{-1}$.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.37; H, 7.95; N, 12.11.

The toluene mother liquor was concentrated to give a crystalline fraction (mp 80–86 °C) which was recrystallized twice from an equal volume of toluene to yield **3a**: 0.6 g; mp 87 °C; IR $\nu_{CO}$ 1625 cm$^{-1}$.

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.12; H, 7.83; N, 12.35.

The product of the hydrogenation of **1b** (2.34 g, mixture of **2b** and **3b**) was dissolved in ethyl acetate (14 mL) and left for 2 days at 15 °C to crystallize. The crystals (0.8 g; mp 161 °C) were treated with dry hydrochloric acid in ethanol to give the hydrochloride salt. The latter was recrystallized twice from ethanol to give the hydrochloride of **2b**: 0.5 g; mp 234–237 °C; IR $\nu_{CO}$ 1632 cm$^{-1}$. The base was liberated ($NaHCO_3$, $CH_2Cl_2$) and recrystallized from toluene (6 mL) at 60 °C to yield **2b**: 0.37 g; mp 176 °C; IR $\nu_{CO}$ 1629 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 63.88; H, 7.54; N, 10.21.

The ethyl acetate filtrate was evaporated, and the oil was dissolved in an ethanolic solution of hydrogen chloride. The solution was seeded with the hydrochloride of **2b** and the separated **2b** hydrochloride salt filtered off after 1 day. The mother liquor was evaporated to half of its volume and diluted with an equal volume of ethyl acetate, and the precipitated crystals were filtered off to yield the hydrochloride of **3b**: 0.7 g; mp 183–187 °C; purity 95% (on the basis of GC analysis); IR $\nu_{CO}$ 1657 cm$^{-1}$. The base was liberated as above and dissolved in toluene (1.7 mL) at 30 °C, and the solution was diluted with hexane (2 mL) and left to crystallize at 10 °C to give **3b**: 0.41 g; mp 98 °C; IR $\nu_{CO}$ 1624 cm$^{-1}$.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 64.16; H, 7.54; N, 9.98. Found: C, 63.90; H, 7.70; N, 10.18.

**6-Methylperhydropyrido[1,2-*a*]pyrimidin-4-one (4).** To 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one[4d] (1.69 g) in water (20 mL) was added dropwise at 10 °C a solution of $NaBH_4$ (1.2 g) in water (10 mL) over 20 min. The solution was stirred for 2 h at 10 °C, and it was made acidic (pH 2–3) with 1:1 HCl. The pH was then adjusted to 8 with 10% aqueous $Na_2CO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the organic layer was dried ($MgSO_4$) and evaporated. The residue was distillated to give perhydropyridopyrimidinone **4**: 0.9 g; bp 135–140 °C (1 mmHg); HCl salt, mp 210 °C (EtOH).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 63.97; H, 9.71; N, 16.82.

**Acknowledgment.** We are indebted to Mr. B. Podányi for technical assistance.

**Registry No. 1a**, 39080-63-2; **1b**, 54672-35-4; **2a**, 83077-47-8; **2b**, 83077-48-9; **2b**·HCl, 83148-38-3; **3a**, 83077-49-0; **3b**, 83148-37-2; **3b**·HCl, 83198-16-7; **4**, 83077-50-3; **4**·HCl, 83077-51-4; 6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 32092-29-8.

(13) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

# Conformational Analysis. 44. 1,1,2-Trimethylcyclohexane[1]

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*Received April 2, 1982*

In a previous joint study with a group of Soviet investigators,[2,3] we had pointed out that the position of conformational equilibrium in 1-X-2,2-dimethylcyclohexanes (Scheme I, A ⇄ B) was almost the same as the position of the corresponding equilibrium for cyclohexyl-X (Scheme I, C ⇄ D). In essence, this means that, surprisingly, the extra $CH_3$/X gauche interaction in B (compared to A) does not seem to affect the conformational equilibrium of X to any palpable degree (<0.1 kcal/mol).

The substituents X in the previous[2] investigation were $OCH_3$, $OCOCH_3$, $OSi(CH_3)_3$, and OH, and the position of conformational equilibrium was based on the magnitude of the coupling constant of the C*H*X proton with vicinal protons of the ring or on the half-width of the C*H*X signal. This is not a highly accurate means of assessing $\Delta G°$; in addition the substituents investigated have rotational conformational inhomogeneity, are polar ($\Delta G°$ is somewhat dependent on solvent[2]), and, in the case of OH, are subject to hydrogen bonding.[4] We felt it would be worthwhile to investigate the case where X = $CH_3$, a nonpolar group, and

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(3) See also Mursakulov, I. G.; Guseinov, M. M.; Kasumov, N. K.; Zefirov, N. S.; Samoshin, V. V.; Chalenko, E. G. *Tetrahedron*, in press.

(4) Cf. Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487.

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