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# Synthesis of Imidazo[4,5-*b*]pyridines and *v*-Triazolo[4,5-*b*]pyridines. Preparation of 1-Deaza-6-thioguanine Analogues[1]

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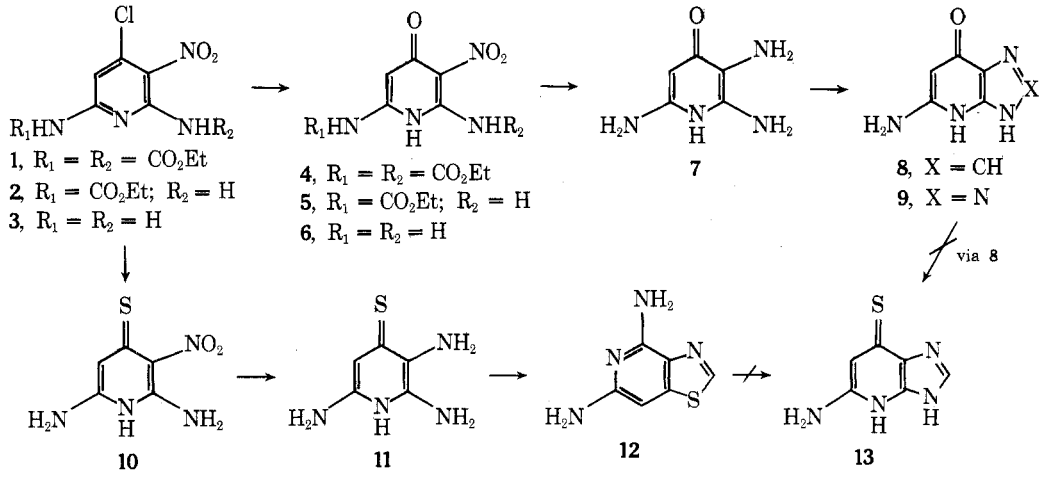
Improved methods for the preparation of 1-deazaguanine (8) and its 8-aza analogue are reported. The preparation of 1-deaza-6-thioguanine (13) either by the thiation of 8 or by the rearrangement of the isomeric 4,6-diaminothiazolo[4,5-*c*]pyridine was unsuccessful. The successful preparation of 13 was accomplished by the removal of the diphenylmethyl group of 2-amino-6-[(diphenylmethyl)thio]-1-deazapurine with refluxing trifluoroacetic acid. 8-Aza-1-deaza-6-thioguanine (26) was prepared by the reaction of the corresponding 6-chloro compound with sodium hydrosulfide. The reversible rearrangement between 26 and 4,6-diamino[1,2,3]thiadiazolo[4,5-*c*]pyridine was demonstrated. In addition, 2-amino-6-(methylthio)-1-deazapurine and its 8-aza analogue were prepared from 2,3,6-triamino-4-(methylthio)pyridine.

Previously we reported the development of synthetic methods for the preparation of the 5,7-diamino derivatives of imidazo[4,5-*b*]pyridine and *v*-triazolo[4,5-*b*]pyridine, the 1-deaza and 8-aza-1-deaza analogues of 2,6-diaminopurine.[2,3] Further work in this area has resulted in the development of procedures for the preparation of the 5-amino-7-thione derivatives of these ring systems, which are the 1-deaza and 8-aza-1-deaza analogues of 6-thioguanine.

The synthesis of the thione **13** from the corresponding chloro compound **24** was unsuccessful because of the unreactive nature of the chloro group toward nucleophilic displacement with sodium hydrosulfide.[2,4] In addition the direct preparation of **13** by the cyclization of a 2,3-diaminopyridine-4-thione precursor (**11**) was unlikely since analogous reactions in the pyrimidine series provided thiazolopyrimidines rather than purines.[5,6] However, the thiation of guanine with $P_4S_{10}$ in pyridine has been reported to give 6-thioguanine[7] and it was anticipated that thiation of the known 1-deaza analogues of guanine, **8** and **9**, might give the desired target compounds **13** and **26**, respectively. Also this route was attractive because both **8** and **9** can be prepared from the common intermediate **7**. In the original synthesis, **8** was obtained in 30% yield by hydrolysis of 2-amino-6-ethoxy-1-deazapurine with 48% HBr.[8] In addition, the triaminopyridine **7** was converted with formic acid to **8** in unspecified yield and with aqueous nitrous acid to **9** in 9% yield.[9,10] Modifications of these reactions gave higher yields of **8** and **9**. The chloropyridine **1**[11] was treated with refluxing 98% $HCO_2H$ to hydrolyze the chloro group. Reaction of the resulting crude pyridin-4-one **4** with ethanolic KOH hydrolyzed the urethane groups to give the intermediate 3-nitropyridine **6** in an overall yield of 75%. Also, the monourethane **2**[12] was converted to **5** with refluxing formic acid. When the crude product from this reaction was treated with ethanolic KOH, **6** was obtained in an overall yield of 82%. Catalytic hydrogenation of **6** to give **7** at atmospheric pressure and room temperature in the presence of Raney nickel was slow and required about 20 h for completion.[13] The resulting triaminopyridine **7** was isolated



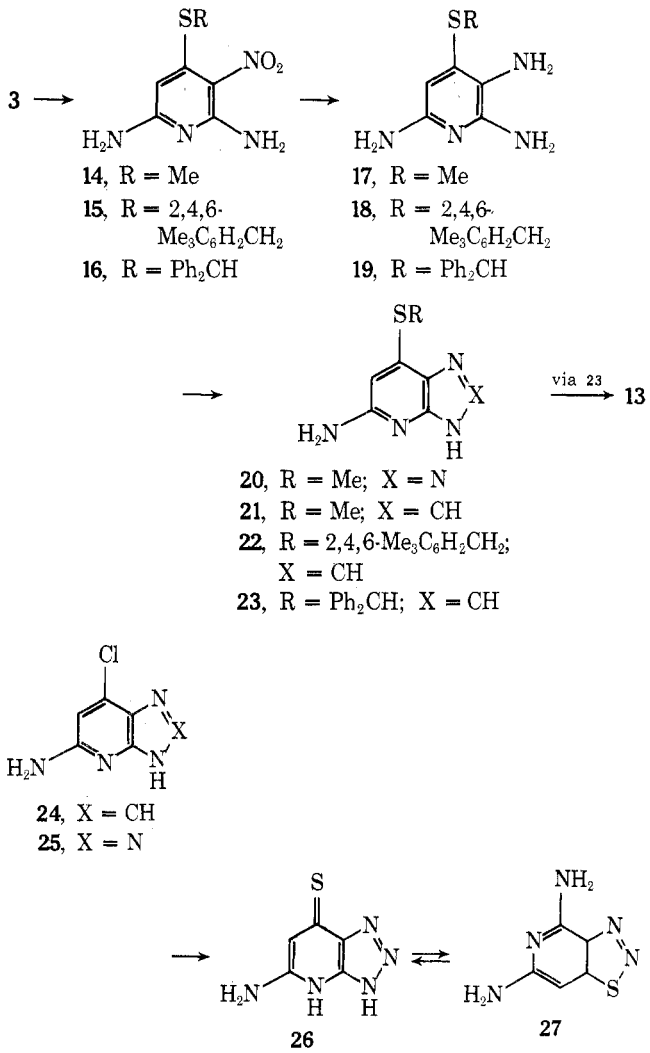
as its dihydrochloride, which was sensitive to air and rapidly changed from a white to a purple solid as has been noted for the free amino compound.[10] However, the dihydrochloride was cyclized to **8** with refluxing $HCO_2H$ in 43% yield and to **9** with aqueous $NaNO_2$ in DMF in 47% yield. Thiation of **8** with $P_4S_{10}$ in refluxing pyridine gave a product that was reprecipitated from a basic solution with acid. Although the ultraviolet spectrum of this product was dissimilar to that of **8**, treatment of the thiation product with hot base led to the recovery of the deazaguanine **8**, indicating that the thiation reaction gave a complex that resulted from the covalent addition of $P_4S_{10}$ to **8**. Because of these results, the preparation and rearrangement of the thiazolopyridine **12** to give **13** was considered.

Treatment of **2** with NaSH was expected to replace the chloro group with a mercapto group and possibly reduce the nitro group to give an amino group. However, purification of the resulting complex reaction mixture gave only a low yield of the nitropyridine **10**, which resulted from replacement of the chloro group and cleavage of the urethane moiety. To avoid the mixtures resulting from partial hydrolysis of the urethane group, **3** was prepared by treatment of **2** with methanolic NaOAc.[14] A crude sample of **3** was also obtained by the chlorodehydroxylation of **6** with $POCl_3$. In contrast to the conversion of **2** to give a low yield of **10**, the reaction of **3** with NaSH gave **11** directly in good yield. The cyclization of **11** with formic acid gave a formylated derivative of the thiazolopyridine **12**, which was readily converted to **12** by hydrolysis of the formyl groups with methanolic HCl. Also, the cyclization of **11** with ethyl orthoformate in the presence of $K_2CO_3$ was shown by TLC to give mainly **12**. The structure of **12** was supported by its $^1H$ NMR spectrum and was confirmed by its alkaline insolubility.

Although thiazolopyrimidines in base are rearranged via a ring-opened pyrimidine intermediate to give purines,[5] treatment of **12** either with excess aqueous NaOH at room temperature or with an equivalent amount of base at reflux gave little or no reaction; when **12** was treated with an excess amount of hot base, the ultraviolet spectrum of the product indicated that complete decomposition of the ring system had occurred. Apparently, opening of the thiazolo ring of **12** gave an extremely unstable pyridine intermediate, which was supported by the observation that **11** was unstable in base.

Simultaneously with the work described above, it was found that alkylation of MeSNa with **3** in DMF gave the 4-(methylthio)pyridine **14**. This compound was hydrogenated in the presence of Raney nickel to give **17**, which was converted to the 8-aza-1-deazapurine **20** with nitrous acid in low yield. The mass spectrum of the crude product of this reaction suggested that partial replacement of the amino group of **20** by a chloro group had occurred, indicating that diazotization of the amino group was a side reaction.

Treatment of **17** with refluxing formic acid gave a good yield of the 1-deazapurine **21**. This result indicated that the preparation of an intermediate similar to **21** but containing a removable S-blocking group might provide a route to 1-deaza-6-thioguanine (**13**). Since 2,4,6-trimethylbenzyl esters are cleaved with 2 N HBr in HOAc[15] at room temperature, this group was chosen as the S-blocking group. Alkylation of **3** with the potassium salt of 2,4,6-trimethyl-$\alpha$-toluenethiol gave **15**, which was hydrogenated in the presence of Raney nickel to give **18**. The cyclization of **18** was effected with formamide at 140 °C to give **22** (mass spectrum), which was not purified when it was found that only partial removal of the benzyl blocking group was obtained on treatment of **22** for a prolonged period of time with hot 30% HBr in HOAc. To obtain a less stable blocking group, **3** was alkylated with the sodium salt of diphenylmethylthiol to give **16**. Hydrogenation of **16** in the presence of Raney nickel gave **19**, which was isolated as the dihydrochloride in 34% yield. For this reduction to




proceed, the amount of Raney nickel used was twice the weight of **16**. Under these conditions, over-reduction occurred, suggesting that some of the diphenylmethyl group was reductively removed. In other runs, crude **19** was converted without purification to **23** with formamide at about 160 °C. The diphenylmethyl blocking group of **23** was removed in refluxing $CF_3CO_2H$ to give **13**.[16,17]

In earlier work it was demonstrated that the chloro group of **25** can be displaced with nucleophiles.[3] Treatment of **25** with NaSH in refluxing BuOH gave **26** contaminated with some of the rearrangement product **27**. This crude product was eluted from silica gel to give a pure sample of **26**. In addition, on heating **26** in DMAc, a pure sample of the rearrangement product **27** was obtained. The reverse rearrangement, **27** → **26**, was shown by TLC to be practically complete when **27** was heated in DMAc containing $K_2CO_3$ at 125 °C.[18]

The ultraviolet, infrared, and $^1H$ NMR spectral properties of the 1-deaza and 8-aza-1-deaza purines and related compounds are presented in Table I. Of interest is the similarity of the ultraviolet spectra in base of 1-deazaguanine (**8**) and 1-deaza-6-thioguanine (**13**) to those of the corresponding purines. In contrast, the anion of 8-aza-1-deaza-6-thioguanine has a maximum at a lower wavelength than that of 8-aza-6-thioguanine (328 nm).

## Experimental Section

Melting points were determined on a Mel-Temp or Kolfer-Heizbank apparatus.

**2,6-Diamino-4-chloro-3-nitropyridine (3).** A suspension of **2**[12] (10.0 g) and NaOAc (16.4 g) in absolute MeOH (700 ml) was refluxed

**Table I. Spectral Properties of 1-Deaza- and 8-Aza-1-deazapurines**

| Registry no. | Compd | Uv absorption[a] spectra, 0.1 N NaOH | Ir absorption[b] spectra, KBr, selected bands, $cm^{-1}$ | $^1H$ NMR spectral assignments,[c] chemical shifts, $\delta$ (rel area) |
|---|---|---|---|---|
| 60282-59-9 | 8 | 262 (10.6), 276 (9.41) | 1670, 1640, 1610 | 6.33 (1,6-CH), 8.30 (1,2-CH), ~10 br (6, NH) |
| 60282-60-2 | 9 | 282 (15.4), 326 (1.14) | 1645, 1595, 1515 | 5.72 (1,6-CH), 6.37, 9.88, (4, NH) |
| 60282-61-3 | 12 | 314 (10.4) | 1620, 1605, 1575 | 5.54 (2, $NH_2$), 6.14, 6.23 (3,7-CH, $NH_2$), 8.60 (1,2-CH) |
| 60282-62-4 | 13 | 280 (5.83), 317 (9.18) | 1640, 1525, 1500 | 6.98 (1,6-CH), 7.65 (4, NH), 8.84 (1,2-CH) |
| 60282-63-5 | 20 | 288 (14.7), 306 sh (11.5) | 1610 sh, 1590, 1550 | 2.59 ($CH_3$), 6.40 (6-CH), 6.57 ($NH_2$), ~12 br (NH) |
| 60282-64-6 | 21 | 233 sh (15.6), 271 sh (7.10), 277 (7.80), 312 (9.60) | 1650 br, 1555, 1520 | 2.65 (3, $CH_3$), 6.69 (1,6-CH), 7.42 br (NH), 8.50 (1,2-CH) |
| 60282-65-7 | 23 | 273 sh (8.22), 279 (9.20), 318 (10.1) | 1615 sh, 1600, 1555 | 5.68 (2, $NH_2$), 6.21, 6.43, (1,1,6-CH and $Ph_2CH$), 7.38 m (10, $C_6H_5$), 7.86 (1,2-CH) |
| 60282-66-8 | 26 | 217 (19.1), 308 (19.7) | 1640 br, 1570, 1545 | 6.46 (1,6-CH), 6.82 (2, $NH_2$) |
| 60306-33-4 | 27 | 241 sh (10.2), 256 (12.3), 310 (4.72), 360 (7.85) | 1640, 1610, 1565 | 6.18, 6.28 (3,7-CH, $NH_2$), 7.17 (2, $NH_2$) |

[a] Spectra were determined on a Cary Model 17 spectrophotometer. [b] Perkin-Elmer Model 621 spectrophotometer. [c] Spectra were determined on $Me_2SO$-$d_6$ solutions (3–7% w/v) on a Varian XL-100-15 spectrometer with $Me_4Si$ as an internal reference; the relative peak areas are given to the nearest whole number.

for 104 h, and evaporated to dryness in vacuo. The residue was washed with $H_2O$ and dried in vacuo over $P_2O_5$: yield 7.16 g (99%); mp 269–270 °C dec (lit.[14] mp 268 °C dec); $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 224 (10.8), 273 (6.95), 303 (4.17), 397 (14.3).

Also, treatment of **6** (1.0 g) with $POCl_3$ (25 ml) at reflux for 3 h gave crude **3** (0.76 g, 68%), which was identified by TLC.

**Ethyl 6-Amino-1,4-dihydro-5-nitro-4-oxo-2-pyridinecarbamate (5).** A solution of **2** (1.0 g) in 98% $HCO_2H$ (20 ml) was refluxed for 8 h, and evaporated to dryness in vacuo. The resulting residue was recrystallized from a mixture of EtOH–$H_2O$ and dried in vacuo over $P_2O_5$ at 78 °C: yield 0.25 g (27%); mp 239–240 °C dec; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 255 (11.8), 333 (9.87).

Anal. Calcd for $C_8H_{10}N_4O_5$: C, 39.67; H, 4.17; N, 23.13. Found: C, 39.88; H, 4.07; N, 23.24.

**2,6-Diamino-3-nitro-4(1*H*)-pyridinone (6). A.** The crude product of **5** obtained from **2** (12 g) as described above was suspended in a solution of KOH (24 g) in EtOH (220 ml), and the whole was heated in an oil bath at 100 °C for 72 h. The solid material was collected by filtration, dissolved in $H_2O$ (600 ml), and acidified to pH 1 (paper) with concentrated HCl to deposit unreacted crude **5,** yield 1.4 g (13% recovery). The filtrate was adjusted to pH 6 (paper) with 4 N NaOH to give a precipitate of **6,** yield 5.6 g (82%). For analyses a sample was dried in vacuo over $P_2O_5$ at 56 °C: mp 257–258 °C dec (lit.[10] mp 256–258 °C dec); $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 253 (8.62), 334 (8.66), 388 (8.89).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.29; H, 3.56; N, 32.93. Found: C, 35.35; H, 3.65; N, 32.71.

**B.** A solution of **1** (50 g) in 98% $HCO_2H$ (1300 ml) was refluxed for 8 h and evaporated to dryness in vacuo to give crude **4:** yield 46 g; mp 150–155 °C (lit.[10] mp 164–167 °C). A suspension of this material in a solution of KOH (79 g) in EtOH (1000 ml) was refluxed for 86 h. The solid was collected by filtration and treated as described above to give **6,** yield 19 g (75%).

**2,3,6-Triamino-4(1*H*)-pyridinone (7).**[13] A mixture of **6** (5.0 g) and Raney nickel (8 g, weighed wet, washed with EtOH) in EtOH (80 ml) was hydrogenated at room temperature and atmospheric pressure for 20 h and filtered (Celite) into a flask containing 2.3 N ethanolic HCl (40 ml). A white precipitate was obtained, which rapidly changed to a purple solid. Evaporation of the mixture to dryness under reduced pressure gave a solid that was dried in vacuo over $P_2O_5$ at 56 °C for 48 h, yield 6.1 g (93%). This sample decomposed from about 200 °C: $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 224 (9.15), 300 (8.52).

Anal. Calcd for $C_5H_8N_4O \cdot 2HCl \cdot 0.2C_2H_6O$: C, 29.15; H, 5.16; Cl, 31.87; N, 25.18. Found: C, 28.90; H, 4.96; Cl, 32.26; N, 25.20.

**5-Amino-3*H*-imidazo[4,5-*b*]pyridin-7(4*H*)-one (8).**[10] A solution of **7** $2HCl \cdot 0.2C_2H_6O$ (1.0 g) in 98% $HCO_2H$ (20 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The residue was heated at 160 °C (1 mm) for 3 h and extracted with hot $H_2O$ (450 ml). After filtration, the filtrate was evaporated to dryness and the resulting solid was refluxed in 6 N HCl for 1 h. This suspension was evaporated to dryness in vacuo to give an orange solid, which was dried in vacuo over $P_2O_5$: yield 0.43 g (43%); mp >300 °C.

Anal. Calcd for $C_6H_6N_4O \cdot 2HCl$: C, 32.30; H, 3.62; Cl, 31.79; N, 25.12. Found: C, 31.91; H, 3.83; Cl, 31.64; N, 25.30.

**5-Amino-3*H*-triazolo[4,5-*b*]pyridin-7(4*H*)-one (9).**[9] Solid $NaNO_2$ (0.33 g) was added with stirring and cooling to a solution of **7** $2HCl \cdot 0.2C_2H_6O$ (1.0 g) in a mixture of DMF (15 ml) and $H_2O$ (5 ml). After 15 min, the ice bath was removed; the solution was stirred at room temperature for 4 h, diluted with $H_2O$ (200 ml), and neutralized by the addition of solid $NaHCO_3$. The solid that deposited was collected by filtration and recrystallized from $H_2O$, yield 0.33 g (47%). This sample underwent decomposition from about 280 °C.

Anal. Calcd for $C_5H_5N_5O \cdot 0.2H_2O$: C, 38.81; H, 3.52; N, 45.26. Found: C, 38.91; H, 3.26; N, 45.52.

**2,6-Diamino-3-nitropyridine-4(1*H*)-thione (10).** A mixture of **2** (5.0 g) and hydrated NaSH (20 g) in EtOH (250 ml) was refluxed for 69 h and evaporated to dryness in vacuo. The residue was dissolved in water (170 ml) and acidified with concentrated HCl to pH 2 (paper) to deposit a crude mixture (1.3 g) of **10** and its urethane derivative, based on TLC and elemental analyses. The filtrate from this solid was adjusted to pH 6 with 1 N NaOH and evaporated to dryness. The resulting residue was extracted with boiling EtOH (3 × 300 ml) and evaporated to dryness, and the residue was washed with $C_6H_6$ to give crude **10,** yield 2.4 g. This sample was extracted with 1 N NaOH (50 ml), and the extract was acidified to pH 5 with 1 N HCl to give pure **10,** which was dried in vacuo at 78 °C for 4 h: yield 0.54 g (15%); mp >300 °C; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 234 (8.61), 267 (sh) (6.70), 338 (4.92).

Anal. Calcd for $C_5H_6N_4O_2S$: C, 32.26; H, 3.25; N, 30.11; S, 17.22. Found: C, 32.12; H, 3.18; N, 29.88; S, 17.46.

**2,3,6-Triaminopyridine-4(1*H*)-thione (11).** A mixture of **3** (5.0 g) and hydrated NaSH (10 g) in EtOH (250 ml) was refluxed for 24 h and evaporated to dryness in vacuo. The residue was dissolved in 1 N NaOH (40 ml), the solution was adjusted to pH 5 (paper) with concentrated HCl, and the sulfur (1.3 g) that deposited was removed by filtration. The filtrate was evaporated to dryness under reduced pressure, and the solid was washed by stirring in 3 N HCl for 1 h. The product was collected by filtration, washed with $C_6H_6$, and dried in vacuo over $P_2O_5$, yield 3.9 g (66%). This sample underwent decomposition from about 222 °C when taken from 200 °C: $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 293 (10.6), 342 (8.91).

Anal. Calcd for $C_5H_8N_4S \cdot 1.8HCl$: C, 27.07; H, 4.45; N, 25.26. Found: C, 27.44; H, 4.29; N, 24.96.

**4,6-Diaminothiazolo[4,5-*c*]pyridine (12). A.** A solution of **11** 1.8HCl (1.2 g) in 98% $HCO_2H$ (20 ml) was refluxed for 18 h, and evaporated to dryness in vacuo. The residue was suspended in 10% ethanolic HCl and stirred at room temperature for 18 h. The solid was collected by filtration, washed with $Et_2O$, and dried in vacuo over $P_2O_5$: yield 0.70 g (61%); mp 235–240 °C dec.

Anal. Calcd for $C_6H_6N_4S \cdot 1.25HCl$: C, 34.02; H, 3.45; Cl, 20.93; N, 26.46. Found: C, 34.23; H, 3.38; Cl, 20.88; N, 26.39.

A solution of the hydrochloride of **12** (200 mg) in $H_2O$ (6 ml) and 1 N NaOH (6 ml) was stirred at room temperature for 16 h to deposit **12:** yield 83 mg (53% recovery); mp 151–152 °C with decomposition from 145 °C when taken from 130 °C; $M^+$ *m/e* 166.

Anal. Calcd for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.10; H, 3.53; N, 33.96.

**B.** A powdered mixture of **11** 1.8HCl (222 mg) and $K_2CO_3$ (500 mg) in $(EtO)_3CH$ (10 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The resulting residue was suspended in $H_2O$ and acidified

to pH 5 (paper) with dilute HCl to give crude **12**, yield 159 mg (96%).

**5-Amino-1,4-dihydro-7*H*-imidazo[4,5-*b*]pyridine-7-thione (13).** A solution of **23** (500 mg) and phenol (500 mg) in $CF_3CO_2H$ (20 ml) was refluxed for 3 h and evaporated to dryness in vacuo. The resulting residue was stirred in 9% methanolic HCl (25 ml) for 2 h; the solid was collected by filtration (142 mg), and recrystallized from EtOH to give the HCl, yield 60 mg (20%), mp >265 °C (Mel-Temp).

Anal. Calcd for $C_6H_6N_4S$·HCl: C, 35.56; H, 3.48; N, 27.65. Found: C, 35.65; H, 3.43; N, 27.57.

The residue obtained from the methanolic HCl filtrate was recrystallized from EtOH to give an additional amount of **13** HCl, yield 17 mg (6%). The total yield was 77 mg (26%).

**2,6-Diamino-3-nitro-4-(methylthio)pyridine (14).** A solution of MeSNa was prepared from NaOMe (3.6 g) in MeOH (190 ml) by saturation of the solution with MeSH at 0 °C. A mixture of the solid obtained by evaporation of this solution to dryness in vacuo and **3** (6.3 g) in DMAC (150 ml) was heated at 50 °C for 24 h and diluted with $H_2O$ (2500 ml). The solid that precipitated was collected by filtration, washed with $H_2O$, and dried in vacuo over $P_2O_5$: yield 5.6 g (84%); mp 271–272 °C dec; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 272 (7.92), 347 (9.04), 398 (12.4).

Anal. Calcd for $C_6H_8N_4O_2S$: C, 35.99; H, 4.03; N, 27.98. Found: C, 36.36; H, 3.83; N, 28.01.

**2-(2,4,6-Trimethylbenzyl)-2-thiopseudourea Hydrochloride.** A solution of 2,4,6-trimethylbenzyl chloride (5.0 g) and thiourea (2.5 g) in EtOH (90 ml) was refluxed for 4 h and chilled. The white solid was collected by filtration and dried in vacuo over $P_2O_5$: yield 5.2 g (71.5%); mp 242–243 °C.

Anal. Calcd for $C_{11}H_{16}N_2S$·HCl: C, 53.97; H, 7.00; N, 11.44. Found: C, 54.16; H, 6.96; N, 11.60.

Concentration of the filtrate gave an additional amount of product: yield 1.0 g; mp 242–243 °C. The total yield was 6.3 g (86.5%).

**2,4,6-Trimethyl-α-toluenethiol.** A solution of 2-(2,4,6-trimethylbenzyl)-2-thiopseudourea hydrochloride (26 g) in 2.5 N NaOH (500 ml) was refluxed for 1 h and filtered. The filtrate was cooled in an ice bath and acidified with concentrated HCl. The white precipitate was collected by filtration, washed with $H_2O$, and dried in vacuo over $P_2O_5$: yield 15 g (85%): mp 44–45 °C.

Anal. Calcd for $C_{10}H_{14}S$: C, 72.23; H, 8.46. Found: C, 72.18; H, 8.43.

**2,6-Diamino-4-[(2,4,6-trimethylbenzyl)thio]-3-nitropyridine (15).** A solution of **3** (5.0 g) and 2,4,6-trimethyl-α-toluenethiol (4.6 g) in DMAC (100 ml) and anhydrous $K_2CO_3$ (3.7 g) was heated at 50 °C for 46 h. TLC of the reaction mixture showed the presence of unreacted **3**. After an additional amount of the thiol (1.2 g) was added, the reaction mixture was heated for 18 h and poured into cold $H_2O$ (3500 ml). The yellow solid was collected by filtration, washed with $Et_2O$ (800 ml), and dried in vacuo over $P_2O_5$: yield 5.2 g (61%); mp 290 °C dec. For analysis, a sample (100 mg) was recrystallized from propanol: yield 70 mg (70% recovery); mp 293 °C dec; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 224 (24.8), 296 (7.67), 375 (15.4).

Anal. Calcd for $C_{15}H_{18}N_4O_2S$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.46; H, 5.65; N, 17.47.

**2-(Diphenylmethyl)-2-thiopseudourea Hydrochloride.** A solution of thiourea (3.8 g) and diphenylmethyl chloride (8.7 ml) in EtOH (25 ml) was refluxed for 2.5 h and evaporated to dryness in vacuo. The residue was extracted in a hot Soxhlet apparatus with MeCN (1400 ml) for 20 h, and the solid that precipitated from the cooled extract was collected by filtration: yield 9.0 g (65%); mp 196–199 °C.

Anal. Clcd for $C_{14}H_{14}N_2S$·HCl: C, 60.31; H, 5.42; N, 10.05. Found: C, 60.08; H, 5.83; N, 10.27.

**2,6-Diamino-4-[(diphenylmethyl)thio]-3-nitropyridine (16).** A solution of 2-(diphenylmethyl)-2-thiopseudourea hydrochloride (6.8 g) in 1 N NaOH (122 ml) was heated in an oil bath at 77 °C for 0.5 h, acidified to pH 4 (paper) with dilute HCl, and extracted with $CHCl_3$ (3 × 300 ml). The combined extracts were evaporated to dryness in vacuo; the residue (4.7 g) of crude (diphenylmethyl)thiol[19] was dissolved in MeOH (125 ml) containing NaOMe (1.3 g), and the solution was evaporated to dryness in vacuo to give the crude sodium salt. A mixture of this salt and **3** (3.8 g) in DMAC (100 ml) was heated with stirring at 50 °C for 69 h and diluted with $H_2O$ (1000 ml). The solid was collected by filtration, washed with $H_2O$, and dried in vacuo over $P_2O_5$ to give crude **16**, yield 7.6 g. This sample was recrystallized from a large volume of $C_6H_6$: yield 4.6 g (65%); mp 230–233 °C; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 255 (27.2), 297 (9.93), 377 (19.5).

Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.04; H, 4.69; N, 15.86.

**2,3,6-Triamino-4-(methylthio)pyridine (17).** A suspension of **14** (2.0 g) in EtOH (1000 ml) containing Raney nickel (4 g, weighed wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure. After 3 h, the catalyst was removed by filtration (Celite). The filtrate was diluted with concentrated HCl (2 ml), and evaporated to dryness in vacuo: yield 2.2 g (90.5%); mp 248 °C dec; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 222 (sh) (14.4), 236 (18.2), 324 (6.04).

Anal. Calcd for $C_6H_{10}N_4S$·2HCl: C, 29.64; H, 4.97; N, 23.04. Found: C, 30.02; H, 4.82; N, 22.95.

**2,3,6-Triamino-4-[(2,4,6-trimethylbenzyl)thio]pyridine (18).** A solution of **15** (3.84 g) in a mixture of DMAC (40 ml) and EtOH (350 ml) was hydrogenated in the presence of Raney nickel (4 g, washed with EtOH, weighted wet) at 50 °C for 4.5 h. The catalyst was removed by filtration (Celite), the filtrate was evaporated to dryness in vacuo, and the resulting residue was washed with petroleum ether and dried under reduced pressure at 56 °C: yield 2.80 g (81%); mp 175 °C dec; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), 0.1 N HCl, 242 (22.9), 270 (15.3), 333 (9.52).

Anal. Calcd for $C_{15}H_{20}N_4S$: C, 62.47; H, 6.99; N, 19.42. Found: C, 62.21; H, 6.86; N, 19.54.

**2,3,6-Triamino-4-[(diphenylmethyl)thio]pyridine (19).** A solution of **16** (1.0 g) in EtOH (500 ml) containing Raney nickel (2 g, weighed wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure for 5 h. The mixture was filtered (Celite) into a flask containing 1 N HCl (6 ml), and the filtrate was evaporated to dryness in vacuo. The resulting residue was recrystallized from EtOH: yield 0.38 g (34%); mp 209–211 °C dec with presoftening; $\lambda_{max}$, nm ($\epsilon \times 10^{-3}$), pH 7, 337 (5.76).

Anal. Calcd for $C_{18}H_{18}N_4S$·2HCl: C, 54.69; H, 5.10; N, 14.17. Found: C, 54.53; H, 5.24; N, 13.71.

An additional amount of crude **19** (0.28 g) was obtained from the ethanol filtrate.

**5-Amino-7-(methylthio)-1*H*-*v*-triazolo[4,5-*b*]pyridine (20).** To a solution of **17** 2HCl (1.48 g) in $H_2O$ (58 ml) containing HOAc (3.05 ml) and NaOAc (1.00 g) was added solid $NaNO_2$ (0.50 g) with stirring. After 2 h the solid was collected by filtration, recrystallized from $H_2O$, and dried in vacuo over $P_2O_5$ at 78 °C: yield 0.29 g (20%); mp 279–280 °C with dec from 267 °C.

Anal. Calcd for $C_6H_7N_5S$·0.39$H_2O$: C, 38.28; H, 4.17; N, 37.20. Found: C, 38.54; H, 4.05; N, 36.86.

**5-Amino-7-(methylthio)-1*H*-imidazo[4,5-*b*]pyridine (21).** A solution of **17** 2HCl (100 mg) in 98% $HCO_2H$ (5 ml) was refluxed for 4 h and evaporated to dryness in vacuo. The resulting residue was suspended in 10% ethanolic HCl (5 ml), stirred at room temperature for 18 h, collected by filtration, washed with $Et_2O$, and dried in vacuo over $P_2O_5$ at 78 °C: yield 89 mg (88%); mp 254 °C dec with premelting from about 180 °C; $M^+$ *m/e* 180.

Anal. Calcd for $C_7H_8N_4S$·1.8HCl: C, 34.19; H, 4.02; N, 22.79. Found: C, 33.86; H, 3.96; N, 22.79.

**5-Amino-7-[(diphenylmethyl)thio]-1*H*-imidazo[4,5-*b*]pyridine (23).** A solution of **16** (3.68 g) in EtOH (2,000 ml) containing Raney nickel (8 g, weighted wet, washed with EtOH) was hydrogenated at room temperature and atmospheric pressure for 5.5 h. The $H_2$ absorbed was 17% in excess of the theoretical amount. The catalyst was removed by filtration under $N_2$; the filtrate was evaporated to dryness in vacuo, and the residue was heated in $HCONH_2$ (100 ml) at 160 °C for 18 h. The reaction mixture was evaporated to dryness in vacuo. The resulting solid was stirred in 1 N NaOH (64 ml) for 18 h, and the product was collected by filtration: yield 2.44 g (70%); mp ~195 °C dec. A portion (100 mg) of this sample was recrystallized from EtOH to give the analytical sample: yield 46 mg; mp 228–230 °C.

Anal. Calcd for $C_{19}H_{16}N_4S$: C, 68.65; H, 4.85; N, 16.86. Found: C, 68.30; H, 5.01; N, 16.59.

**5-Amino-1,4-dihydro-7*H*-*v*-triazolo[4,5-*b*]pyridine-7-thione (26).** A solution of **25** (1.50 g)[3] in butanol (75 ml) containing hydrated sodium hydrosulfide (7.50 g) was refluxed for 18 h, and the resulting suspension was evaporated to dryness in vacuo. The residue was dissolved in $H_2O$, and after acidification with HOAc, the solid was collected by filtration, washed with hot $C_6H_6$ (2 × 200 ml), and dried in vacuo over $P_2O_5$ at 110 °C, yield 1.15 g. This solid was dissolved in a minimum amount of 1 N $NH_4OH$ and poured into a fritted glass funnel containing silica gel H (23 g). The whole was washed with 8:2 $CHCl_3$–MeOH and the washings were evaporated to dryness in vacuo to give **26** contaminated with **27**, yield 0.44 g. Next the silica gel was washed with 1 N $NH_4OH$, and the washings were neutralized with HOAc to give a precipitate of **26**: yield 0.48 g; mp 236–237 °C with decomposition and presoftening from 220 °C.

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 35.71; H, 3.25; N, 41.62.

**4,6-Diamino[1,2,3]thiadiazolo[4,5-*c*]pyridine (27).** A solution of **26** (0.50 g) in DMAC (15 ml) was heated at 125 °C for 30 min, fil-

tered, and evaporated to dryness in vacuo. The residue was washed with $Et_2O$ and recrystallized from MeCN: yield 0.36 g (72%); mp 240 °C dec.

Anal. Calcd for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 36.18; H, 3.10; N, 41.81.

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**Registry No.**—**1**, 53995-21-4; **2**, 6506-86-1; **3**, 40497-64-1; **4**, 60282-67-9; **5**, 60282-68-0; **6**, 60282-69-1; **7** 2HCl, 60282-70-4; **8** 2HCl, 60282-71-5; **10**, 60282-72-6; **10** urethane derivative, 60282-73-7; **11** 1.8HCl, 60282-74-8; **12** 1.25HCl, 60282-75-9; **13** HCl, 60282-76-0; **14**, 60282-77-1; **15**, 60282-78-2; **16**, 60282-79-3; **17** 2HCl, 60282-80-6; **18**, 60282-81-7; **19** 2HCl, 60282-82-8; **21** 1.8HCl, 60282-83-9; **25**, 38359-74-9; 2-(2,4,6-trimethylbenzyl)-2-thiopseudourea HCl, 60282-84-0; 2,4,6-trimethylbenzyl chloride, 1585-16-6; thiourea, 62-56-6; 2,4,6-trimethyl-α-toluenethiol, 21411-42-7; 2-(diphenylmethyl)-2-thiopseudourea HCl, 60282-85-1; diphenylmethyl chloride, 90-99-3; (diphenylmethyl)thiol Na salt, 60282-86-2.

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# Stereochemistry in Trivalent Nitrogen Compounds. 31. Conformational Preferences and Torsional Barriers in *N*-Acylimidazoles[1]

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The low temperature $^1H$ NMR spectra of a series of *N*-acylimidazoles have been examined. All but one exhibited doubling of the resonances of H-2 and H-5 at low temperature reflecting the presence of two diastereomers which differ in configuration at the carbonyl to nitrogen (amide) bond. In all cases, the predominant diastereomer was assigned the *E* configuration. The configurational assignment involved the use of NMR chemical shifts and coupling constants, CNDO/2 calculations, solvent effects, and analogy to imides. Equilibrium constants and free energies of activation for isomerization were determined using variable temperature NMR spectroscopy in methylene chloride: *N*-formylimidazole, 4.6, 11.6 kcal/mol; *N*-acetylimidazole, 1.9, 10.5 kcal/mol; *N*-propionylimidazole, 1.5, 9.9 kcal/mol; *N*-(2-methylpropionyl)imidazole, 1.6, 9.9 kcal/mol; *N*-trifluoroacetylimidazole, 2.2, 10.2 kcal/mol; *N*-trimethylacetylimidazole, no splitting observed. The behavior of the first two of these compounds in three other solvents was also examined and the effects of solvent on NMR chemical shifts, the isomerization equilibrium constant, and the barrier to stereomutation are discussed. The relation between data for *N*-acylimidazoles and those for imides and *N,N*-dimethylamides is discussed.

Among the most informative amide torsional barriers are those for compounds in which the nitrogen lone pair forms part of an aromatic π system. The torsional barriers in such compounds are lower than in the corresponding *N,N*-dialkylamides, and the extent to which the barrier is lowered is related to the delocalization of the nitrogen lone pair and hence to the aromaticity of the heterocyclic ring. Although torsional barriers in amides have been intensively studied over the past 20 years,[3] only few studies have been made on amides of aromatic heterocyclic amines.[4-7] This paper reports our investigation of the variable temperature NMR spectra of a series of *N*-acylimidazoles, **1**, a system which had received no attention when our investigation was begun.

The *N*-acylimidazoles represented an interesting subject for study for another reason as well. The *N*-acylimidazoles can be considered as analogues of imides, a class of compounds whose torsional barriers and configurational preferences have been of interest in our laboratory.[8] Two labile configurational isomers are possible for *N*-acylimidazoles, *E*-**1** and *Z*-**1**, which can be interconverted by torsion about the carbon–nitrogen partial double bond. These two configurations are electronically related to the *E,E* and *E,Z* configurations of the imides **2**. Most imides prefer one of these two configurations when in solution in nonpolar solvents.[8,9] While the parent imide, diformamide, and its *N*-methyl derivative (**2a**, R′ = H, $CH_3$) prefer the *E,E* configuration, the higher homologues diacetamide and dipropionamide and their *N*-methyl derivatives (**2b**, R′ = H, $CH_3$ and **2c**, R′ = H, $CH_3$) adopt the *E,Z* configuration. The unsymmetrical imide *N*-acetylpropionamide