REINVESTIGATION OF A CYCLIZATION REACTION OF 2-HYDRAZINO-3-(1H-PYRROL-1-YL)PYRIDINE

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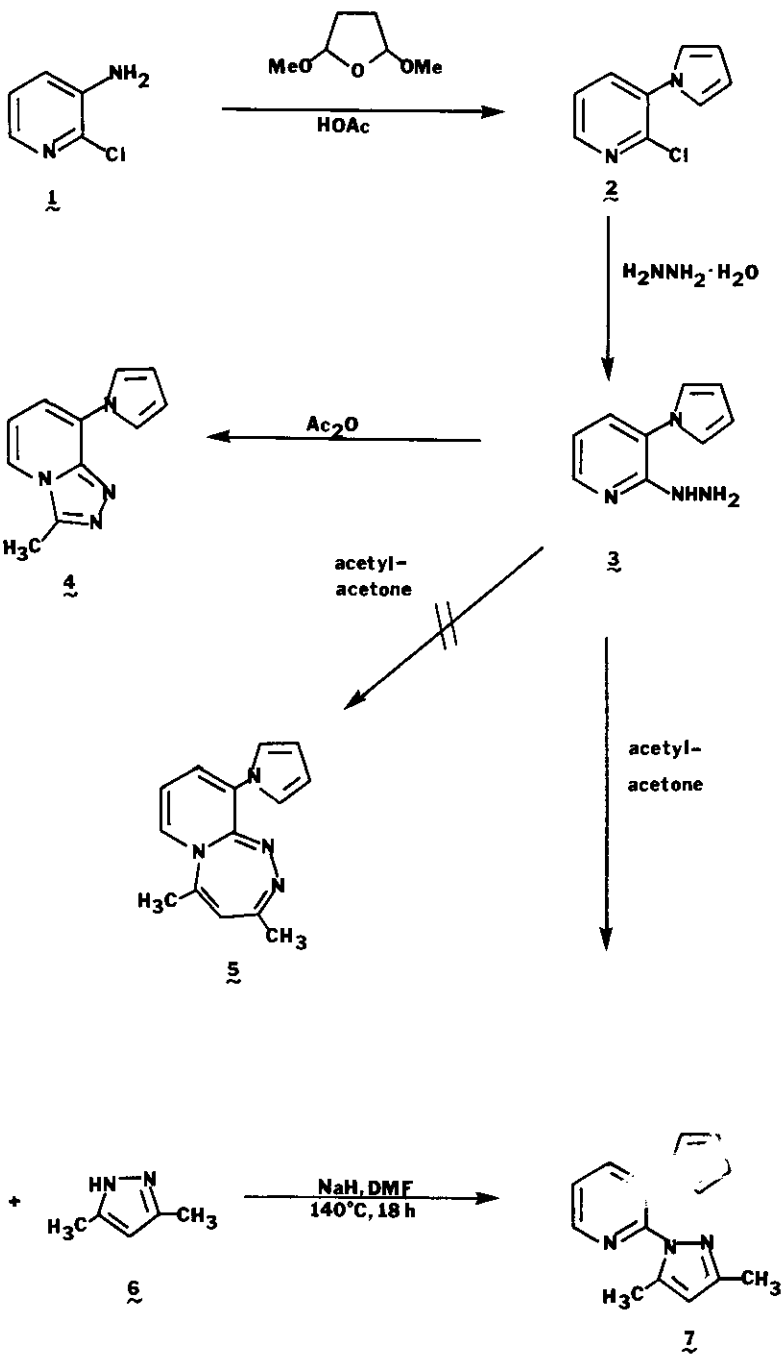
Abstract - The reaction of 2-hydrazino-3-(1H-pyrrol-1-yl)pyridine (3) with acetylacetone affords 2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-(1H-pyrrol-1-yl)pyridine (7) rather than 3,5-dimethyl-10-(1H-pyrrol-1-yl)pyrido[2,1-c][1,2,4]triazepine (5), as previously reported.

A recent report by Lancelot, et al.[1] decribes the synthesis of 2-hydrazino-3-(1H-pyrrol-1-yl)-pyridine (3) from 2-chloro-3-aminopyridine, as shown in Scheme I, and its cyclization with acetic anhydride to give triazolopyridine 4. Also reported was the cyclization of 3 with acetylacetone to afford 3,5-dimethyl-10-(1H-pyrrol-1-yl)pyrido[2,1-c][1,2,4]triazepine (5). We have reinvestigated this latter transformation and found it to be in error. The product of this cyclization is, instead, 2-(3,5-dimethyl-1H-pyrazol-1-yl)-3-(1H-pyrrol-1-yl)pyridine (7).

The reported[1] synthesis of 3 was repeated as shown in Scheme I. We found that the condensation product of 3 and acetylacetone was identical to the displacement product obtained by treating 2-chloro-3-(1H-pyrrol-1-yl)pyridine (2) with the anion derived from 1H-3,5-dimethylpyrazole (6). Thus, the product of both of these reactions is pyrazolylpyridine 7. The steric interaction of the two ortho aromatic substituents in 7 must be considerable.

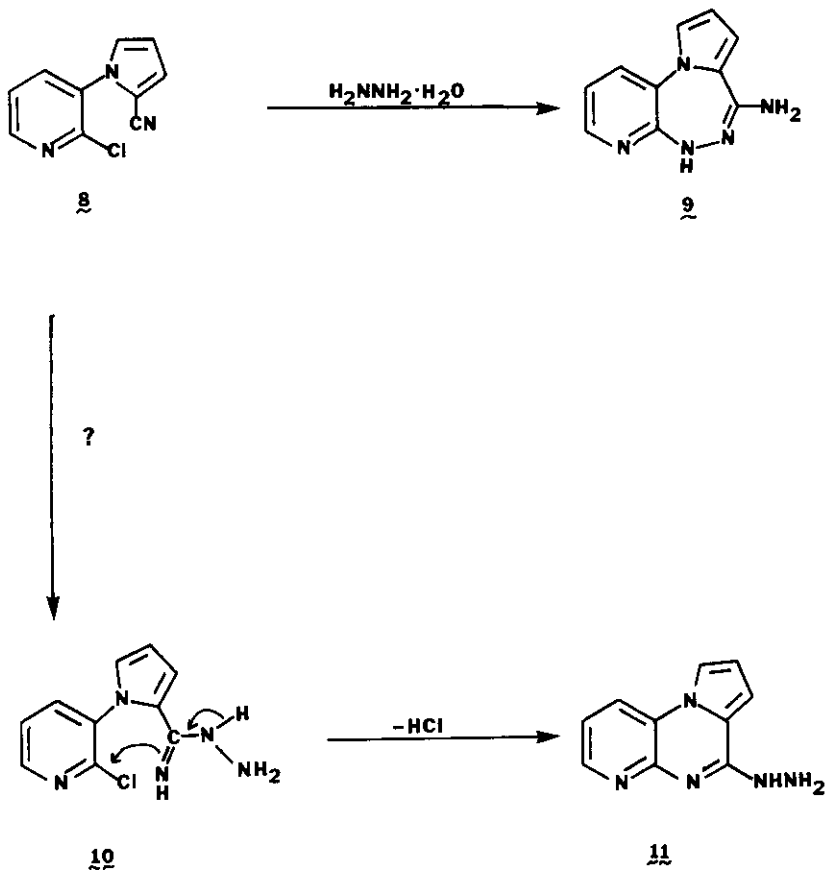
We have recently shown that 2-hydrazino-4-(4-nitrophenyl)thiazole reacts with 1,3-diketones to give 2-pyrazolylthiazoles,[2] rather than thiazolotriazepines as previously reported.[3] A very recent article, describing the cyclization of 4-hydrazino[1]benzothieno[2,3-e]pyrrolo[1,2-a]-pyrazine to 1,3-dimethyl[1]benzothieno[2',3':5,6]pyrrolo[1',2':1,2]pyrazino[3,4-c]-1,2,4-triazepine,[4] must also be in error. This cyclization must produce a pyrazolylpyrazine, instead.

Scheme I


NH2
Cl
1
MeO
OMe
HOAc
2
H2NNH2·H2O
NHNH2
3
Ac2O
H3C
4
acetyl-
acetone
acetyl-
acetone
5
2
+
HN
N
H3C
CH3
6
NaH, DMF
140°C, 18 h
7

An additional transformation described by Lancelot, et al.[1] is shown in Scheme II. Cyclization of 2-chloro-3-(2-cyano-1H-pyrrol-1-yl)pyridine (8) with hydrazine hydrate reportedly gave fused triazepine 9. Since triazepine syntheses often fail when the potential for the formation of smaller ring sizes exists,[5] we envisioned fused pyrazine 11 as a possible product of the reaction

Scheme II



8 9 10 11

of 8 with hydrazine hydrate. Pyrazine 11 could result from intermediate 10, which would, in turn, derive from initial interaction of hydrazine hydrate with the cyano group rather than the 2-position of pyridine. Compound 11 is isomeric with 9 and would be difficult to spectroscopically distinguish from triazepine 9. Thus, we set out to prepare hydrazinopyrazine 11 in order to compare its properties with those reported for aminotriazepine 9.

A precursor to 11, chloro compound 18, has previously been prepared by several routes.[6] One of these routes involved aminolysis of 2 in an autoclave (methanolic ammonia, 100 °C, 5 h) to produce 2-amino-3-(1H-pyrrol-1-yl)pyridine (16). Amino compound 16 was then cyclized to 17 with phosgene, and 17 was converted to 18 with phosphorous oxychloride and pyridine.

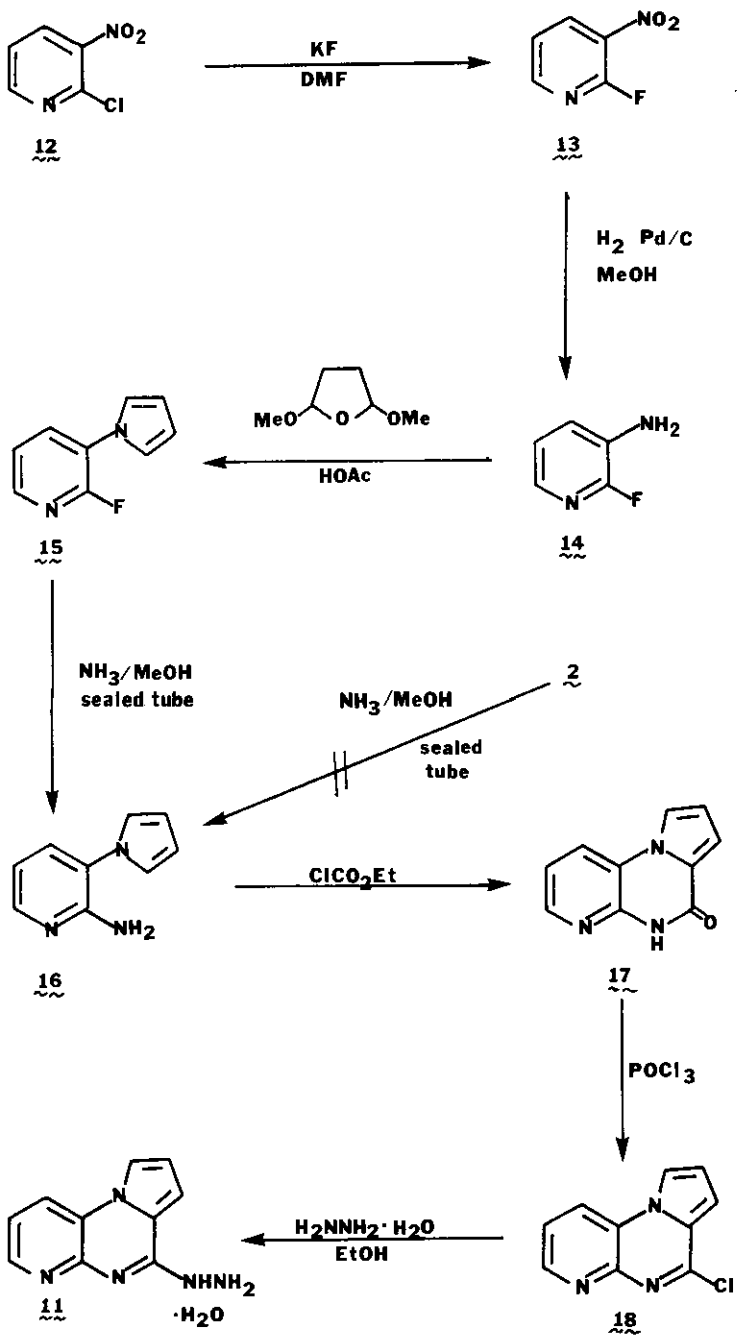
When we treated chloro compound 2 with methanolic ammonia in a sealed tube (260 °C, 4 h), only a negligible amount of 16 was produced. Thus, we prepared 16 by the alternate route shown in Scheme III, in which we prepared the fluoro analog of 2 (15), which was more susceptible to aminolysis. Treatment of 2-chloro-3-nitropyridine (12) with potassium fluoride in dimethylformamide gave 2-fluoro-3-nitropyridine (13), which was hydrogenated to the corresponding amino compound 14. 2-Fluoro-3-(1H-pyrrol-1-yl)pyridine (15) was then elaborated from 14 with 2,5-dimethoxytetrahydrofuran. Aminolysis of 15 in a sealed tube gave 16. In our hands, cyclization of 16 to 17 was most efficiently accomplished with neat ethyl chloroformate. Chloro compound 18, which was prepared from 17 and phosphorous oxychloride, was converted to hydrazino compound 11 with hydrazine hydrate.

The melting point reported for 9 is 215 °C,[1] while 11 does not melt up to 300 °C. ^{1}H nmr spectral data reported for 9[1] are quite different from that which we recorded for 11. Thus, we conclude that structure 9 must be correct, and that initial interaction of hydrazine with 8 occurs at the 2-position.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

Scheme III


NO2
Cl
12
KF
DMF
NO2
F
13
H2 Pd/C
MeOH
NH2
F
14
MeO
OMe
HOAc
F
15
NH3/MeOH
sealed tube
2
NH3/MeOH
sealed
tube
NH2
16
ClCO2Et
O
17
POCl3
Cl
18
H2NNH2·H2O
EtOH
NHNH2
·H2O
11

2-Chloro-3-(1H-pyrrol-1-yl)pyridine (2). A solution of 24.5 g (0.190 mol) of 3-amino-2-chloropyridine (1) and 33.0 g (0.250 mol) of 2,5-dimethoxytetrahydrofuran in 100 ml of acetic acid was heated at reflux for 1 h. The solution was diluted with water and extracted with methylene chloride. The combined extracts were washed twice with water, dried (sodium sulfate) and concentrated. The resulting viscous liquid was purified by Kugelrohr distillation [lit.[1] bp 154 °C (0.05 mm)] to give 17.0 g (50%) of 2; ^{1}H nmr (DMSO-d_6) δ 8.40 (dd, 1H, C6-H), 7.87 (dd, 1H, C4-H), 7.50 (dd, 1H, C5-H), 7.02 (dd, 2H, C2'-H and C5'-H), 6.27 (dd, 2H, C3'-H and C4'-H); ms (100 eV, chemical ionization, methane) 179 (M^+ +1), 207 (M^+ +29), 219 (M^+ +41).

2-Hydrazino-3-(1H-pyrrol-1-yl)pyridine (3). A solution of 7.60 g (42.6 mmol) of 2 in 50 ml of hydrazine hydrate was heated at reflux for 4 h. The solution was concentrated and partitioned between water and chloroform. The organic layer was dried (sodium sulfate) and concentrated, and the resulting viscous liquid was purified by Kugelrohr distillation (lit.[1] mp 74 °C) to give 6.11 g (82%) of 3; ^{1}H nmr ($CDCl_3$) δ 8.10 (dd, 1H, C6-H), 7.36 (dd, 1H, C4-H), 6.90 (dd, 2H, C2'-H and C5'-H), 6.70 (dd, 1H, C5-H), 6.47 (br s, 1H, NH), 6.23 (dd, 2H, C3'-H and C4'-H), 4.12 (br s, 2H, NH_2); ms (100 eV, chemical inonization, methane) 175 (M^+ +1).

2-(2,4-Dimethyl-1H-pyrazol-1-yl)-3-(1H-pyrrol-1-yl)pyridine (7). A. From 2. To 1.0 g (45 mmol) of sodium hydride, prepared from 1.8 g of 60% sodium hydride dispersed in mineral oil by washing with hexane, was added a solution of 2.88 g (30.0 mmol) of 2,4-dimethyl-1H-pyrazole in 30 ml of dimethylformamide. After 5 min of stirring, 4.47 g (25.0 mmol) of 2 was added and the solution was heated at 140 °C for 18 h. Evaporation of the dimethylformamide left 5.20 g of viscous liquid which was purified by distillation to provide 4.20 g (70%) of 7, bp 145 °C at 0.3 mm; ir (neat) 1570, 1555, 1490, 1330 and 720 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 8.48 (dd, 1H, C6-H), 8.08 (dd, 1H, C4-H), 7.63 (dd, 1H, C5-H), 6.55 (dd, 2H, pyrrolyl C2-H and C5-H), 6.10 (dd, 2H, pyrrolyl C3-H and C4-H), 5.91 (s, 1H, pyrazolyl C3-H), 2.13 (s, 3H, CH_3), 1.80 (s, 3H, CH_3); ms (100 eV, chemical ionization, methane) 239 (M^+ +1), 267 (M^+ +29), 279 (M^+ +41); Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51. Found: C, 70.26; H, 5.85; N, 23.10.

B. From 3. A solution of 3.07 g (17.6 mmol) of 3 and 2.00 g (19.9 mmol) of acetylacetone in 30 ml of acetic acid was heated at reflux for 1.5 h. The acetic acid and excess acetylacetone were removed by distillation and the residue was partitioned between water and methylene chloride. The organic layer was dried (sodium sulfate) and concentrated, and the residual oil was further concentrated under vacuum at 80 °C to leave 4.01 g (94%) of 7, whose ir and ^{1}H nmr spectra were identical to those of 7 prepared in Part A.

2-Fluoro-3-nitropyridine (13). To a solution of 12.3 g (77.6 mmol) of 2-chloro-3-nitropyridine (12) in 30 ml of dimethylformamide at 120 °C was added 9 g of anhydrous potassium fluoride. After 6 h at 150 °C the mixture was poured onto ice. The aqueous solution was saturated with sodium chloride and steam-distilled. The distillate was extracted with ether and the combined extracts were dried (sodium sulfate) and concentrated to a yellow oil. Kugelrohr distillation at 85 °C (ca. 1 mm) gave 8.01 g (73%) of 13 [lit.[7] bp 109-109.5 °C (10 mm)]; ^{1}H nmr ($CDCl_3$) δ 8.70-8.30 (m, 2H, C4-H and C6-H), 7.43 (dd, 1H, C5-H).

3-Amino-2-fluoropyridine (14). A solution of 6.00 g (42.2 mmol) of 13 was hydrogenated in a Parr apparatus at ca. 50 p.s.i. for 0.5 h in the presence of 10% Pd/C. The catalyst was removed by filtration and the concentrated filtrate was purified by flash chromatography (600 ml dry volume silica gel; 9:1::$CHCl_3$:CH_3OH) to give 4.08 g (86%) of 14 as a clear, colorless oil [lit.[8] bp 116-117 °C (24 mm)]; ^{1}H nmr ($CDCl_3$) δ 7.52-7.48 (m, 1H, C6-H), 7.17-7.09 (m, 1H, C4-H), 6.99-6.93 (m, 1H, C5-H), 4.10 (s, 2H, NH_2); ms (100 eV, chemical ionization, methane) 113 (M^+ +1), 141 (M^+ +29), 153 (M^+ +41).

2-Fluoro-3-(1H-pyrrol-1-yl)pyridine (15). A solution of 11.0 g (97.8 mmol) of 14 and 13.2 g (0.100 mol) of 2,5-dimethoxytetrahydrofuran in 30 ml of acetic acid was heated at reflux for 1 h. The solution was concentrated and the residue was partitioned between methylene chloride and water. A black, insoluble solid was removed by filtration and the organic layer was dried (sodium sulfate) and concentrated. Kugelrohr distillation at 85 °C (ca. 1 mm) gave 7.68 g (48%) of 15 as a yellow oil; ^{1}H nmr ($CDCl_3$) δ 8.00-7.80 (m, 1H, C6-H), 7.80-7.43 (m, 1H, C4-H), 7.23-7.03 (m, 1H, C5-H), 7.03-6.83 (m, 2H, C2'-H and C5'-H), 6.33-6.17 (m, 2H, C3'-H and C4'-H); ms (70 eV, electron impact) m/z 162 (molecular ion); Anal. Calcd. for $C_9H_7FN_2$: C, 66.66; H, 4.35; N, 17.27. Found: C, 66.66; H, 4.39; N, 17.19.

2-Amino-3-(1H-pyrrol-1-yl)pyridine (16). Two solutions each of 3.8 g (23.4 mmol) of 15 in 100 ml of methanol saturated with ammonia in sealed glass tubes were heated at 260 °C for 23 h. The contents of the tubes were filtered to remove a small amount of particulate matter and the filtrate was concentrated to a small volume and cooled. The resulting crystalline solid was collected and recrystallized from ethanol to give 4.70 g (63%) of 16, mp 104-105 °C (lit.[6] mp 72 °C); ir (Nujol) 3460 and 3280 (NH_2), 1630 (C=N) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 7.98 (dd, 1H, C6-H), 7.39 (dd, 1H, C4-H), 6.94 (dd, 2H, C2'-H and C5'-H), 6.67 (dd, 1H, C5-H), 6.26 (dd, 2H, C3'-H and C4'-H);[9] ms (100 eV, chemical ionization, methane) 160 (M^+ +1), 188 (M^+ +29), 200 (M^+ +41); Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.75; H, 5.72; N, 26.43.

5,6-Dihydro-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazine (17). A mixture of 500 mg (3.14 mmol) of 16 and 10 ml of ethyl chloroformate was heated at reflux for 1 h. The mixture was cooled and the yellow solid was collected, washed with ether and dried to give 410 mg (70%) of crude 17. Recrystallization from methanol afforded pure 17 as a white solid, mp > 300 °C (lit.[6] mp 275 °C); ir (Nujol) 1680 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6) δ 11.7 (s, 1H, NH), 8.48 (dd, 1H, C1-H), 8.28 (dd, 1H, C3-H), 8.25 (dd, 1H, C9-H), 7.29 (dd, 1H, C2-H), 7.07 (dd, 1H, C7-H), 6.74 (dd, 1H, C8-H); ms (70 eV, electron impact) m/z 185 (molecular ion); Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.60; H, 3.86; N,22.52.

6-Chloropyrido[2,3-e]pyrrolo[1,2-a]pyrazine (18). A mixture of 460 mg (2.48 mmol) of 17 and 25 ml of phosphorous oxychloride was heated at reflux for 1.5 h. The solution was concentrated to dryness and the residue was partitioned between water and methylene chloride. The organic layer was washed with sodium hydrogen carbonate, dried (sodium sulfate) and concentrated to give 500 mg (99%) of 18, mp 254-255 °C (dec) (ethanol); ^1H nmr (DMSO-d_6) δ 8.92 (dd, 1H, C1-H), 8.80-8.72 (m, 2H, C3-H and C9-H), 7.77 (dd, 1H, C2-H), 7.22 (dd, 1H, C7-H), 7.11 (dd, 1H, C8-H); ms (100 eV, chemical ionization, methane) 204 (M^+ +1), 232 (M^+ +29), 244 (M^+ +41); Anal. Calcd. for $C_{10}H_6ClN_3$: C, 58.98; H, 2.97; N, 20.63. Found: C, 58.76; H, 3.00; N, 20.63.

6-Hydrazinopyrido[2,3-e]pyrrolo[1,2-a]pyrazine Monohydrate (11). A mixture of 230 mg (1.13 mmol) of 18, 130 mg (2.59 mmol) of hydrazine monohydrate and 25 ml of ethanol was heated at reflux for 2 h. The mixture was cooled and the solid was collected, washed with ether and dried to give 194 mg (79%) of 11, mp > 300 °C; ^1H nmr (DMSO-d_6) δ 8.45 (dd, 1H, C1-H), 8.37 (dd, 1H, C3-H), 8.27 (dd, 1H, C9-H), 7.22 (dd, 1H, C2-H), 7.09 (dd, 1H, C7-H), ca. 6.8 (very broad signal, 1H, NH), 6.76 (dd, 1H, C8-H), ca. 3.6 (very broad signal, 4H, NH_2 and H_2O); ms (100 eV, chemical ionization, methane) 200 (M^+ +1), 228 (M^+ +29), 240 (M^+ +41). Anal. Calcd. for $C_{10}H_9N_5\ H_2O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 54.91; H, 4.55; N, 31.97.

REFFERENCES AND NOTES

1. J.-C. Lancelot, D. Laduree, H. E. Kashef and M. Robba, Heterocycles, 1985, 23, 909.
2. N. P. Peet and S. Sunder, J. Heterocyclic Chem., 1986, 23, 593.
3. B. V. Alaka, D. Patnaik and M. K. Rout, J. Indian Chem. Soc., 1982, 59, 1168.
4. H. E. Kashef, S. Rault, J.-C. Lancelot and M. Robba, J. Heterocyclic Chem., 1986, 23, 161.
5. J. W. H. Watthey, J. Stanton and N. P. Peet, Heterocyclic Compounds, 1984, 43, Pt. 2, 719.
6. J.-C. Lancelot, D. Laduree and M. Robba, Chem. Pharm. Bull., 1985, 33, 3122.

7. G. C. Finger and L. D. Starr, J. Am. Chem. Soc., 1959, 81, 2674.

8. G. C. Finger, L. D. Starr, A. Roe and W. J. Link, J. Org. Chem., 1962, 27, 3965.

9. The ^{1}H nmr spectrum we report for 16 differs substantially from that reported for 16 by Lancelot, Laduree and Robba.[6]

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