The Isomeric Pyridopyrazines from the Reaction of Some Tetraaminopyridines with Pyruvaldehyde and Benzil[1]

ROBERT D. ELLIOTT, CARROLL TEMPLE, JR., AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received January 8, 1968

The major product obtained from the condensation of 2,3,4,6-tetraaminopyridine (**5**) with pyruvaldehyde under acidic conditions was identified as 6,8-diamino-3-methylpyrido[2,3-*b*]pyrazine (**1**). The condensation of ethyl 4,5,6-triamino-2-pyridinecarbamate (**18**) with benzil gave a 2:3 mixture of the pyrido[2,3-*b*]pyrazine (**19**) and pyrido[3,4-*b*]pyrazine (**20**) under neutral conditions, and mainly **20** containing a small amount of **19** under acidic conditions. These results were confirmed by the unambiguous synthesis of **19** and the ethoxy deamination of **20** to give ethyl 2,3-diphenyl-5-ethoxypyrido[3,4-*b*]pyrazine-7-carbamate (**24**). The isomeric carbamate (**23**) was obtained by a reaction sequence starting with 2,6-diamino-4-ethoxy-3-nitropyridine (**17**).

Previously the unambiguous syntheses of deaza analogs of methotrexate[2-4] was accomplished by modification of the multistep procedure of Boon and Leigh.[5] The successful preparation of 2,3,4,6-tetraaminopyridine (**5**), and availability of **2**[3] and **3**[4] for purposes of comparison, prompted the investigation of the more direct, one-step condensation of pyruvaldehyde with **5**. This reaction could theoretically give four isomeric deazapteridines (**1**–**4**) depending upon the relative nucleophilicities of the 2-, 3- and 4-amino groups of **5**. The condensation of **5** with pyruvaldehdye and of **18** with benzil under acidic conditions showed that the nucleophilicities of the amino groups are dependent on the pyridine substrate.

Reaction of diethyl 4-chloro-3-nitro-2,6-pyridinedicarbamate (**13**)[4] with methanolic ammonia in a bomb at 138° not only replaced the chloro group, but cleaved the urethan groups to give 3-nitro-2,4,6-triaminopyridine (**9**). The latter was reduced with Raney nickel to give 2,3,4,6-tetraaminopyridine (**5**), isolated as the dihydrochloride. A complex reaction mixture resulted from the reaction of the unstable free amine of **5** with pyruvaldehyde under neutral conditions. The condensation of the dihydrochloride of **5**, however, with 30% aqueous pyruvaldehyde in 0.1 *N* hydrochloric acid under nitrogen gave a 58% yield of crude product, which was purified to give a 49% yield of one of the four possible isomers (**1**–**4**). A second fraction, which was obtained from this reaction in 6% yield, was shown to be either **3** or **4** by thin layer chromatography (see below). The mother liquor from the second fraction appeared to contain only **5** or its decomposition products. The ultraviolet spectrum of the purified product was more similar to that of **2** than that of **3**, and was tentatively assigned structure **1**. This assignment was substantiated by preparation of the isomeric 5,7-diamino-2-methylpyrido[3,4-*b*]pyrazine (**4**). The (diphenylmethyl)amino compound **6**[3] was treated with 10% hydrogen bromide in acetic acid to give the hydrobromide of the 4-aminopyridine **7**, which was converted into the free base with sodium acetate. The nitro group of **7** was hydrogenated in the presence of Raney nickel, and the resulting 3,4-diaminopyridine was condensed *in situ* with 30% aqueous pyruvaldehyde to give **8** in 56% yield. The urethan groups of **8** were hydrolyzed with potassium hydroxide in ethanol to give the 2-methylpyrido[3,4-*b*]pyrazine **4** in 79% yield.

A comparison of the properties of the four isomers (**1**–**4**) is presented in Table I. The pair of pyrido[2,3-*b*]pyrazines **1** and **2** were easily distinguished from the pair of pyrido[3,4-*b*]pyrazines **3** and **4** by the differences in their ultraviolet spectra and R_f values. In addition, potentiometric titrations indicated that the ionization constants (pK_a) of **1** and **2** were near **7**, while those of **3** and **4** were less than **5**. By comparison the constant of 2,4-diaminopteridine is reported to be 5.32.[6] The isomers of each pair, however, have very similar physical and chemical properties. The pyrido[2,3-*b*]pyrazines **1** and **2** have identical R_f values on silica gel plates, and similar ultraviolet and infrared spectra. Proton magnetic resonance (pmr) spectroscopy was found to be the only unequivocal method for differentiating between **1** and **2**. Spectra of the two isomers were obtained both separately and in a mixture to ensure that displacements of absorption peaks were not due to concentration effects. The similarities and differences noted in **1** and **2** were also found in the pyrido[3,4-*b*]pyrazines **3** and **4**.

In the condensation of **5**, and the 3,4-diaminopyridine resulting from **7**, with pyruvaldehyde, it is reasonable to assume that the initial reaction occurred between the 3-amino group and the aldehyde moiety to give the corresponding pyridine anil. In the anil from **5** the direction of cyclization is determined by the relative nucleophilicities of the 2- and 4-amino groups in acidic media. Since **1** is the major isomer formed, the 2-amino group must be more nucleophilic than the 4-amino group under the conditions employed. This conclusion is supported by the reaction of 2,3,4-triaminopyridine with polyglyoxal to give the pyrido[3,4-*b*]pyrazine system under neutral conditions and the pyrido[2,3-*b*]pyrazine system under acidic conditions.[7]

The 3,4-diaminopyridine resulting from the reduction of **7** as described above was also condensed with benzil to give the 2,3-diphenyl derivative **11**. Hydrolysis of the urethan groups of this compound gave an 84% yield of 5,7-diamino-2,3-diphenylpyrido[3,4-*b*]pyrazine (**12**).

The isomeric 2,3-diphenylpyrido[2,3-*b*]pyrazine **16**

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Center Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 533 (1968).

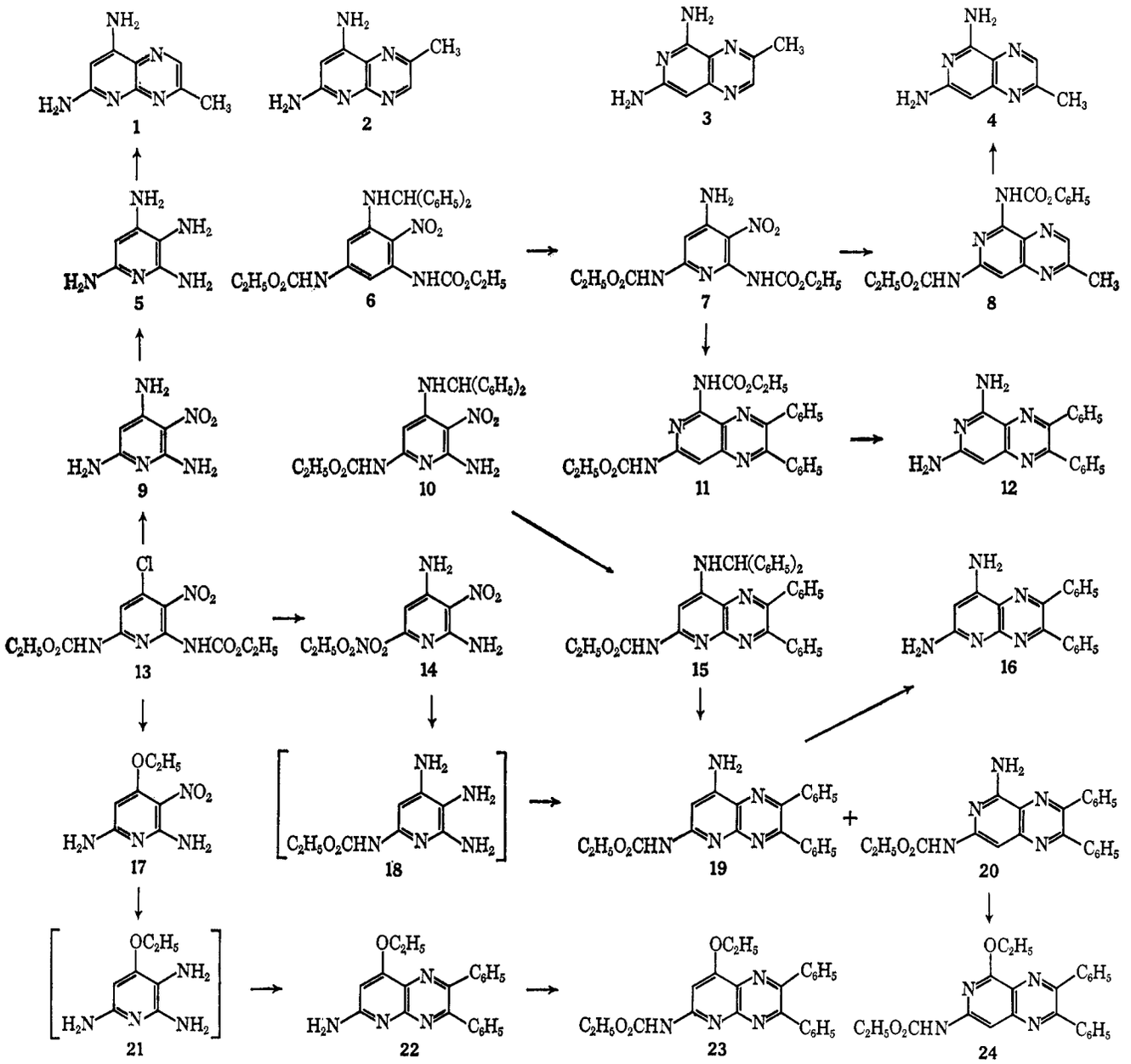
(3) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *ibid.*, **31**, 1890 (1966).

(4) J. A. Montgomery and N. F. Wood, *ibid.*, **29**, 734 (1964).

(5) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(6) A. Albert, D. J. Brown, and G. Cheeseman, *ibid.*, 4227 (1952).

(7) A. Albert and A. Hampton, *ibid.*, 4985 (1952).



was prepared in three steps from the pyridine **10**[3]. The nitro group of **10** was reduced in the presence of a 30% palladium-on-charcoal catalyst, and the resulting 2,3-diaminopyridine was condensed *in situ* with benzil to give **15**. The diphenylmethyl group of **15** was removed with 15% hydrogen bromide in acetic acid to give **19**, and the urethan group of the latter was cleaved with ethanolic potassium hydroxide to give **16**. A comparison of the properties of **12** and **16** is also included in Table I.

To examine the reaction of a 2,3,4-triaminopyridine with benzil, the nitro group of **14**[3] was reduced with Raney nickel to give the intermediate ethyl 4,5,6-triamino-2-pyridinecarbamate (**18**). In contrast to the reaction of **5** with pyruvaldehyde, which gave the pyrido[2,3-*b*]pyrazine ring system, the condensation of **18** *in situ* with benzil under acidic conditions gave **20** containing a small amount of **19**. The latter was identified by comparison of a thin layer chromatogram of the reaction product with a chromatogram of the unambiguously prepared sample of **19** described above. However, **19** was undetected in the pmr spectrum of the reaction product in deuterated DMSO indicating that this sample probably contained less than 10% **19**. Under neutral conditions the condensation of **18** with benzil gave a greater amount of **19**. The reaction product was estimated from its pmr spectrum to be a 2:3 mixture of **19** and **20**. The change in the direction of cyclization in the condensation of **18** with benzil, when compared with the reaction of **5** with pyruvaldehyde, is attributed to a change in the nucleophilicities of the 2- and 4-amino groups in the intermediate pyridine anil resulting from the ethoxycarbonyl group on the 2-amino group.

Although **20** was not completely freed of **19** by recrystallization, the ethoxy deamination[8] of **20** containing about 30% of **19** with ethanolic isoamyl nitrite and hydrogen chloride in a sealed tube at 100° gave **24**. The isomeric ethoxy compound **23** was prepared from 2,6-diamino-4-ethoxy-3-nitropyridine (**17**). The latter was obtained by treatment of **13** with ethanolic potassium hydroxide. Reduction of the nitro group of **17** with Raney nickel gave **21**, which was condensed

(8) N. C. Hindley and J. A. Low, British Patent 588,806 (1947).

TABLE I

Compd	Tlc,[a] R_f	Ultraviolet absorption spectra, λ_{max} in mμ (ε × 10⁻³) 0.1 N HCl	pH 7	0.1 N NaOH	Infrared absorption spectra, 1700–1500 cm⁻¹	Pmr spectra assignments,[b] chemical shift, τ (ppm) $CH_3(C_6H_5)$	CH	NH_2
1[c]	0.66	221 (37.0)	221 (36.5)	259 (14.3)	1645, 1600, 1555,	7.34	3.87	1.95
		246 (sh) (6.63)	246 (sh) (6.82)	351 (12.1)	1517		1.37	1.83
		331 (18.0)	332 (17.1)					
2[c,d]	0.66	221 (36.9)	220 (33.7)	259 (15.9)	1650, 1630 (sh),	7.31	3.73	1.97
		334 (15.9)	255 (9.32)	354 (9.56)	1600 (sh), 1545		1.25	1.66
			341 (12.1)					
3[e]	0.79	244 (17.9)	265 (22.6)	266 (23.3)	1650, 1600, 1575 (sh),	7.48	4.03	4.20
		314 (16.8)	312 (7.3)	312 (7.3)	1535		1.46	3.23
4	0.79	248 (17.7)	267 (27.2)	267 (27.2)	1650 (sh), 1608, 1590,	7.51	4.14	4.14
		256 (sh) (17.1)	314 (6.36)	314 (6.36)	1550		1.93	3.25
		320 (15.7)						
12		233 (25.3)	237 (21.0)	237 (20.7)	1650 (sh), 1605	2.65	3.97	*ca.* 4.3
		338 (30.2)	305 (24.5)	305 (24.5)	1580 (sh), 1555 (sh),			*ca.* 2.6
					1515			
16		222 (36.0)	277 (20.6)	229 (25.4)	1618, 1575 (sh),	2.61	3.72	1.90
		273 (17.2)	371 (18.6)	279 (24.7)	1540, 1525			1.60
		366 (22.6)		378 (16.9)				

[a] The compounds were spotted on silica gel H (Brinkmann) plates, exposed to ammonia, and developed with ethyl acetate–methanol (1:1). [b] Spectra were obtained on DMSO-d_6 solutions (2–11% w/v) with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. [c] Hydrochloride. [d] See ref 3. [e] See ref 4.

in situ with benzil to give **22**. Then, reaction of **22** with ethyl chloroformate and pyridine in dioxane gave the corresponding urethan **23**.

Experimental Section

Melting points, unless otherwise indicated, were determined on a Kofler Heizbank and are corrected. The ultraviolet absorption spectral were determined in aqueous solution with a Cary Model 14 spectrophotometer (sh designates shoulder), whereas the infrared absorption spectra were determined in pressed potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers.

6,8-Diamino-3-methylpyrido[2,3-*b*]pyrazine (1).—The dihydrochloride of **5** (500 mg, 2.36 mmol) was dissolved in a stirred solution of 30% aqueous pyruvaldehyde (622 mg, 2.59 mmol) and 0.1 *N* HCl (4.4 ml) at 0° under N_2. The resulting solution remained at room temperature for 2 hr and at 4° for 1 hr. The orange crystalline precipitate of crude **1** hydrochloride (290 mg) was collected by filtration, washed with cold water (0.5 ml), and recrystallized (charcoal) from hot 0.2 *N* HCl (4 ml). The light tan crystals of **1** hydrochloride were collected by filtration and dried *in vacuo* over P_2O_5 to yield 245 mg (49%), mp >330° (Mel-Temp).

Anal. Calcd for $C_8H_9N_5 \cdot HCl$: C, 45.40; H, 4.76; N, 33.09. Found: C, 45.45; H, 4.88; N, 32.82.

Concentration of the reaction filtrate gave 29 mg (6%) of a precipitate that was identified as either **3** or **4** by thin layer chromatography.

5,7-Diamino-2-methylpyrido[3,4-*b*]pyrazine (4).—A solution of **8** (319 mg, 1.00 mmol) and KOH (701 mg, 12.5 mmol) in EtOH (5 ml) was refluxed under N_2 for 7 hr. The reaction mixture was cooled to room temperature, and the resulting orange-yellow precipitate was collected by filtration. A suspension of the precipitate in H_2O (2 ml) was neutralized with 3 *N* HCl to give an orange precipitate of **4** which was collected by filtration, washed with cold H_2O, and dried at 78° *in vacuo* over P_2O_5 to yield 138 mg (79%), mp 237° dec (taken rapidly to melting point).

Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.80; H, 5.43; N, 40.09.

2,3,4,6-Tetraaminopyridine (5).—A solution of **9** (800 mg, 4.73 mmol) in EtOH (80 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1.4 g, weighed wet with EtOH). The reaction mixture absorbed the theoretical amount of H_2 in 80 min. The resulting solution was filtered under N_2, treated with 6.1 *N* anhydrous HCl in ethanol (1.64 ml, 10 mmol), and refrigerated. The crystalline precipitate of **5** dihydrochloride was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5 to yield 900 mg (90%): mp >220° with slow decomposition; λ_{max} in mμ (ε × 10⁻³), pH 1—224 (47.1) and 293 (11.5), pH 7 (unstable)—225 and 301, pH 13 (unstable)—288; $\bar{\nu}$ in cm⁻¹, 3320 and 3190 (NH), 2850 and 2560 (acidic H), 1670 and 1640 (NH_2), 1570 and 1500 (ring stretching).

Anal. Calcd for $C_5H_{11}Cl_2N_5$: C, 28.32; H, 5.23; N, 33.02. Found: C, 28.50; H, 5.12; N, 32.95.

Diethyl 4-Amino-3-nitro-2,6-pyridinedicarbamate (7).—A solution of **6**[3] (48.0 g, 0.100 mol) and phenol (5 g) in 10% HBr in AcOH (1.44 l.) was stirred at room temperature for 18 hr and diluted with ether (4.80 l.). The resulting yellow crystalline **7** hydrobromide was collected by filtration, washed with Et_2O, and dried *in vacuo* over P_2O_5 to yield 33.8 g (86%): mp 153–156° dec; λ_{max} in mμ (ε × 10⁻³), pH 1—221 (34.4), 244 (23.0), 273 (18.7), and 325 (10.9), pH 7—219 (33.0), 246 (20.3), and 343 (13.3), pH 13—224 (26.0), 263 (16.1), and 361 (8.03); $\bar{\nu}$ in cm⁻¹, 3430 and 3270 (NH), 2980 and 2930 (CH), 1728 (C=O), 1655 (NH_2), 1605 (ring stretching), 1230 (C–O–C).

Anal. Calcd for $C_{11}H_{13}N_5O_6 \cdot HBr$: C, 33.51; H, 4.09; N, 17.77. Found: C, 33.27; H, 4.33; N, 17.47.

A mixture of the hydrobromide (30.0 g, 76.1 mmol) and NaOAc (6.24 g, 76.1 mmol) in H_2O (400 ml) was stirred for 18 hr. The free base (**7**) was collected by filtration, washed with H_2O, air dried, recrystallized from boiling EtOH (2 l.), and dried *in vacuo* over P_2O_5 at 78° to yield 18.8 g (79%): mp *ca* 190°; λ_{max} in mμ (ε × 10⁻³), pH 1—221 (33.8), 244 (22.9), 273 (18.9), and 324 (10.8), pH 7—219 (32.5), 246 (20.8), and 343 (12.9), pH 13—226 (26.2), 263 (16.7), and 362 (6.92); $\bar{\nu}$ in cm⁻¹, 3460, 3435, 3340, 3315, and 3200 (NH), 3070, 2980, 2935, and 2905 (CH), 1745, 1735, and 1713 (C=O), 1620 (NH), 1590, 1530, and 1490 (ring stretching), 1200 (C–O–C).

Anal. Calcd for $C_{11}H_{15}N_5O_6$: C, 42.17; H, 4.83; N, 22.36. Found: C, 42.08; H, 4.80; N, 22.52.

Diethyl 2-Methylpyrido[3,4-*b*]pyrazine-5,7-dicarbamate (8).—A solution of **7** (1.00 g, 319 mmol) in Me_2CO (20 ml) and H_2O (1 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1 g weighed wet with EtOH). The H_2 uptake was complete in 2 hr. The resulting solution was filtered under N_2 and treated with a solution of 30% pyruvaldehyde (843 mg, 3.51 mmol) in H_2O (2 ml). The reaction mixture (under N_2) was allowed to stand at room temperature for 16 hr, then at 4° for 24 hr. The crystalline **8** that deposited was collected by filtration, washed with cold EtOH, and dried *in vacuo* over P_2O_5 at 78° to yield 570 mg (56%): mp 199°; λ_{max} in mμ (ε × 10⁻³), pH 1—219 (19.8), 240 (29.4), 257 (sh) (22.1), 263 (22.5), 304 (12.6), and 378 (3.16), pH 7—258 (36.5), 292 (4.88), and 366 (5.47), pH 13—262 (29.1) and 388 (3.11); $\bar{\nu}$ in cm⁻¹, 3385, 3255, and 3160 (NH), 3080, 2980, 2930, and 2910 (CH), 1762 (sh), 1750, 1732, and 1721 (sh) (C=O), 1610 (NH), 1588, 1540, and 1510 (ring stretching), 1220 and 1200 (C–O–C).

Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.73; H, 5.41; N, 21.94.

3-Nitro-2,4,6,triaminopyridine (9).—A solution of **13**[4] (3.00 g, 9.02 mmol) in MeOH (90 ml) saturated with NH_3 at 0° was heated in a Parr bomb at 138° for 23 hr. The residue that was obtained by evaporation of the reaction mixture was recrystallized from a boiling EtOH–H_2O mixture (1:3). The product which crystallized as long orange needles was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 to yield 1.26 g (83%): mp 261°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—216 (31.4), 274 (9.50), and 347 (8.95), pH 7—212 (26.2), 257 (11.0), and 349 (13.6), pH 13—256 (11.3) and 349 (13.9); $\bar{\nu}$ in cm^{-1}, 3475, 3440, 3395, and 3350 (NH), 3080 (CH), 1650 (NH_2), 1580 and 1550 (sh) (ring stretching).

Anal. Calcd for $C_5H_7N_5O_2$: C, 35.50; H, 4.17; N, 41.41. Found: C, 35.50; H, 4.18; N, 41.23.

Diethyl 2,3-Diphenylpyrido[3,4-*b*]pyrazine-5,7-dicarbamate (11).—A solution of **7** (2.00 g, 6.38 mmol) in Me_2CO (40 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of Raney nickel (1.7 g, weighed wet with EtOH). The theoretical quantity of H_2 was absorbed in 2 hr. The catalyst was removed by filtration and benzil (1.48 g, 7.02 mmol) was added to the filtrate. After 4 days at room temperature the solution was evaporated to dryness, and the resulting residue was recrystallized from EtOH (10 ml). The yellow crystalline product that deposited was collected by filtration, washed with EtOH, and dried at 100° *in vacuo* over P_2O_5 to yield 2.60 g (81%): mp 170° with softening from 100°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1 (unstable)—239 and 315, pH 7 (unstable)—257 and 312, pH 13—252 (24.9) and 307 (27.2); $\bar{\nu}$ in cm^{-1}, 3380 and 3250 (NH), 3060, 2977, 2930, and 2905 (CH), 1758 and 1730 (C=O), 1610 (NH), 1575, 1525, 1505, and 1496 (ring stretching), 1187 (C–O–C), 740 and 694 (monosubstituted phenyl).

Anal. Calcd for $C_{25}H_{23}N_5O_4$: C, 65.63; H, 5.07; N, 15.31. Found: C, 65.72; H, 5.13; N, 15.14.

5,7-Diamino-2,3-diphenylpyrido[3,4-*b*]pyrazine (12).—A mixture of **11** (458 mg, 1.00 mmol), KOH (1.40 g, 24.9 mmol), and EtOH (20 ml) was stirred at reflux under N_2 for 7 hr and cooled in an ice bath. The resulting orange crystalline precipitate was collected by filtration, suspended in H_2O (2 ml), and neutralized with 3 *N* HCl. The precipitate of orange product was collected by filtration, washed with cold H_2O, and dried *in vacuo* at 100° over P_2O_5 to yield 271 mg (84%), mp *ca.* 131° dec.

Anal. Calcd for $C_{19}H_{15}N_5 \cdot {}^1/_2H_2O$: C, 70.79; H, 5.00; N, 21.73. Found: C, 71.04; H, 4.93; N, 21.96.

Ethyl 2,3-Diphenyl-8-[(diphenylmethyl)amino]pyrido[2,3-*b*]pyrazine-6-carbamate (15).—A suspension of **10**[3] (1.00 g, 2.45 mmol) in EtOH (100 ml) was stirred with 30% palladium on charcoal (700 mg) in the presence of H_2 at atmospheric pressure and room temperature for 7 hr. The catalyst was removed by filtration and benzil (567 mg, 2.70 mmol) was added to the filtrate. After standing for 18 hr at room temperature, the resulting mixture containing white crystals was cooled at −25° for 1 hr, and the product was collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.24 g (92%), mp 205–215°. The analytical sample, mp *ca.* 225°, was obtained by recrystallization of a portion of the product from EtOH: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—243 (31.6), 273 (20.9), and 360 (22.4), pH 7 and 13 (cloudy)—242 (sh), 300, and 368; $\bar{\nu}$ in cm^{-1}, 3428 and 3400 (NH), 3062, 3030, 2980, 2928, and 2910 (CH), 1745 (C=O), 1595, 1569, 1540, 1510, and 1490 (ring stretching), 1193 (C–O–C), 740 and 690 (monosubstituted phenyl).

Anal. Calcd for $C_{35}N_5O_2$: C, 76.20; H, 5.30; N, 12.70. Found: C, 76.30; H- 5.23; N, 12.85.

6,8-Diamino-2,3-diphenylpyrido[2,3-*b*]pyrazine (16).—A solution of **19** (385 mg, 1.00 mmol) and KOH (2.00 g, 35.7 mmol) in EtOH (30 ml) was refluxed under N_2 for 7 hr. The solution was made slightly acidic with 6 *N* HCl and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH, and the extract was diluted with Et_2O to precipitate the hydrochloride of **16**. A mixture of the hydrochloride (270 mg, 0.772 mmol) and 1 *N* NaOH solution (0.772 ml, 0.772 mmol) in water (4 ml) was stirred for 1 hr and evaporated to dryness *in vacuo*. The residue was extracted with hot EtOH (10 ml), and the extract was refrigerated. The yellow needles that deposited were collected by filtration, washed with cold EtOH, and dried at 100° *in vacuo* over P_2O_5 to yield 173 mg (55%): mp *ca.* 148–153° (Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (36.0), 273 (17.2), and 366 (22.6), pH 7—277 (20.6) and 371 (18.6), pH 13—229 (25.4), 279 (24.7), and 378 (16.9); $\bar{\nu}$ in cm^{-1}, 3450, 3375, and 3160 (NH), 3050 (CH), 1618, 1575 (sh), 1540, 1525, and 1495 (NH_2, ring stretching), 739 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.82; H, 4.83; N, 22.35. Found: C, 72.37; H, 4.95; N, 22.55.

2,6-Diamino-4-ethoxy-3-nitropyridine (17).—A filtered solution of **13**[4] (5.00 g, 15.0 mmol) and KOH (15.0 g, 268 mmol) in EtOH (200 ml) was heated at reflux temperature for 3 hr. The yellow-orange precipitate was collected by filtration. Additional precipitate was obtained by concentration of the mother liquor *in vacuo*. The crops were combined, triturated with H_2O (5 ml), and dissolved in boiling water (380 ml). The hot solution after charcoal treatment and refrigeration deposited pure **17** as yellow needles which were collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.18 g (40%): mp 186–189°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—225 (sh) (10.3), 288 (3.29), and 360 (12.4), pH 7 and 13—222 (9.10), 257 (8.08), 311 (6.15), and 386 (13.3); $\bar{\nu}$ in cm^{-1}, 3441, 3419, 3348, 3230, and 3145 (NH), 2990, 2935, 2930, and 2885 (CH), 1650 and 1622 (NH_2), 1583 and 1550 (ring stretching), 1250 (C–O–C).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.46; H, 5.32; N, 28.39.

Ethyl 8-Amino-2,3-diphenylpyrido[2,3-*b*]pyrazine-6-carbamate (19).—A solution of **15** (500 mg, 0.907 mmol) in 15% HBr in AcOH (50 ml) was stirred for 18 hr at room temperature and evaporated to dryness at 40° (1 mm). The gummy residue was triturated with C_6H_6 (3 ml), collected by filtration under N_2, washed with C_6H_6 (3 ml), and dried *in vacuo* over P_2O_5 to yield 316 mg (68%): mp *ca.* 235–237° dec (Mel-Temp). The analytical sample, mp *ca.* 245–248° dec, was obtained by two recrystallizations of the crude hydrobromide from EtOH–Et_2O: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (30.4), 240 (sh), (26.1), 271 (20.5), and 360 (20.1), pH 7 (unstable)—221, 289, and 362, pH 13—221 (26.4), 288 (21.0), and 362 (11.6); $\bar{\nu}$ in cm^{-1}, 3600–2400 (NH, CH), 1740 (C=O), 1630 (NH_2), 1590, 1560, 1543, and 1505 (ring stretching), 1213 (C–O–C), 737 and 692 (monosubstituted phenyl).

Anal. Calcd for $C_{22}H_{19}N_5O_2 \cdot HBr$: C, 56.66; H, 4.32; N, 15.02. Found: C, 56.90; H, 4.52; N, 14.72.

A suspension of the crude hydrobromide (242 mg, 0.519 mmol) in 1.00 *N* NaOH solution (0.545 ml. 0.545 mmol) and H_2O (2 ml) was stirred at room temperature for 4 days. The free amine **19** was collected by filtration, washed with H_2O, dried *in vacuo* over P_2O_5, and recrystallized twice from EtOH–H_2O (3:1) to yield 140 mg (70%): mp >280°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—222 (31.9), 238 (sh) (28.3), 272 (22.1), and 362 (21.3), pH 7 (unstable)—222, 287 and 363, pH 13—289 (24.3) and 367 (14.4); $\bar{\nu}$ in cm^{-1}, 3470, 3430, 3280, and 3150 (NH), 3050 and 2975 (CH), 1720 (C=O), 1620 (NH_2), 1580, 1560, 1535, and 1510 (ring stretching), 1200 (C–O–C), 738 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.30; H, 4.89; N, 17.98.

The Preparation of 19 and 20. A.—A solution of **14**[3] (1.43 g, 5.93 mmol) in EtOH (35 ml) was stirred with Raney nickel (600 mg, weighed wet with EtOH) in the presence of H_2 at room temperature and atmospheric pressure for 4.5 hr to give **18**. The catalyst was removed by filtration and benzil (1.25 g, 5.93 mmol) was added to the filtrate. After standing for 18 hr at room temperature, the solution deposited yellow crystals, which were collected by filtration and dried *in vacuo* over P_2O_5 to yield 1.73 g (76%), mp 162° dec. A thin layer chromatogram and pmr spectrum showed that this solid was a 2:3 mixture of **19** and **20** (see discussion). Three recrystallizations of the mixture from EtOH afforded 650 mg (28%) of **20**, which was still contaminated with about 30% **19**, mp 255° dec.

Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 68.69; H, 4.89; N, 18.09.

B.—A solution of **14**[3] (500 mg, 2.07 mmol) in ethanol (15 ml) was hydrogenated as above and filtered under N_2 into 0.2 *N* HCl (15 ml). The resulting solution was treated with benzil (436 mg, 2.07 mmol) and stirred for 18 hr at room temperature and 15 min at reflux temperature. The yellow crystalline product which formed upon cooling the solution to room temperature was collected by filtration and dried *in vacuo* over P_2O_5 to yield 390 mg, mp 145–147° (Mel-Temp). A thin layer chromatogram of this crude product showed the presence of **20** and a trace of **19**. Only isomer **20** could be detected in a pmr spectrum of the product. Recrystallization of the solid from ethanol did not eliminate the trace of **19**.

6-Amino-2,3-diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine (22).—A solution of **17** (200 mg, 1.01 mmol) in EtOH (10 ml) was stirred with Raney nickel (300 mg, weighed wet with ethanol) in the presence of H_2 at atmospheric pressure and room temperature for 1.5 hr. The resulting colorless solution of **21** was carefully filtered under N_2 and treated with benzil (247 mg, 1.18 mmol). After standing for 18 hr under N_2 this solution deposited pale green crystals which were collected by filtration, washed with EtOH, and dried *in vacuo* over P_2O_5 to yield 318 mg (92%), mp 266–268° (Mel-Temp). The analytical sample, mp 268°, was obtained by recrystallization of a portion of the product from EtOH: λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—227 (32.1), 265 (sh) (17.6), and 370 (24.7), pH 7—228 (26.3), 266 (sh) (22.9), and 380 (20.6), pH 13—228 (27.7), 266 (23.8), and 380 (20.7); $\bar{\nu}$ in cm^{-1}, 3600–2800 (NH, CH), 1630 (NH_2), 1604, 1550, and 1533 (ring stretching), 1205 (C–O–C), 740 and 696 (monosubstituted phenyl).

Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.41; H, 5.40; N, 16.15.

Ethyl 2,3-Diphenyl-8-ethoxypyrido[2,3-*b*]pyrazine-6-carbamate (23).—Ethyl chloroformate (1 ml) was added dropwise to a stirred solution of **22** (100 mg, 0.292 mmol) in pyridine (2 ml) and dioxane (10 ml). After the exothermic reaction had ceased, the solution was refluxed for 30 min. The cooled reaction mixture was treated dropwise with additional ethyl chloroformate (1 ml), refluxed for 1.5 hr, and evaporated to dryness under reduced pressure. The residue was triturated with H_2O (5 ml), collected by filtration, air dried, and crystallized two times from EtOH–H_2O. The crystalline product was collected by filtration and dried at 100° *in vacuo* over P_2O_5 for 3 days to yield 63 mg (52%): mp 111–114° (soft at 108°, Mel-Temp); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—241 (34.2), 269 (23.8) and 373 (25.5), pH 7—223 (sh) (24.8), 254 (36.6), and 368 (22.9), pH 13—231 (27.2), 258 (30.0), 275 (sh) (27.8), and 382 (22.5); $\bar{\nu}$ in cm^{-1}, 3450 and 3120 (NH), 3055, 2975, and 2930 (CH), 1739 (C=O), 1604 (sh), 1596, 1539, and 1508 (ring stretching), 1195 (C–O–C), 740 and 693 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.46; H, 5.55; N, 13.67.

Ethyl 2,3-Diphenyl-5-ethoxypyrido[3,4-*b*]pyrazine-7-carbamate (24).—A sealed glass tube containing **20** (contaminated with **19**) (300 mg, 0.779 mmol), isoamyl nitrite (183 mg, 1.56 mmol), anhydrous HCl (28.4 mg, 0.779 mmol), and EtOH (20 ml) was refrigerated overnight and heated in a H_2O bath at 100° for 35 min. The solution was cooled to room temperature, filtered, and evaporated to dryness under reduced pressure. The residue was crystallized first from 1:1 EtOH–H_2O (3 ml) and then from propanol (5 ml) to give a yellow crystalline product which was collected by filtration and dried *in vacuo* over P_2O_5 to yield 70 mg (22%): mp 205°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—256 (18.0), 304 (25.2), and 390 (8.0), pH 7—256 (17.8), 304 (21.3), and 391 (10.4), pH 13—256 (18.6), 305 (23.2), and 390 (9.0); $\bar{\nu}$ in cm^{-1}, 3440 and 3230 (NH), 3057, 2980, 2930, 2900, and 2860 (CH), 1720 (C=O), 1608, 1570, 1530, and 1490 (ring stretching), 1218 and 1195 (C–O–C), 742 and 692 (monosubstituted phenyl).

Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.67; H, 5.41; N, 13.25.

Registry No.—Pyruvaldehyde, 78-98-8; benzil, 134-81-6; **1** HCl, 16335-89-0; **4**, 16335-90-3; **5**, 16335-91-4; **7**, 16335-92-5; **7** HBr, 16335-93-6; **8**, 16335-94-7; **9**, 16335-95-8; **11**, 16335-96-9; **12**, 16335-97-0; **15**, 16335-98-1; **16**, 16335-99-2; **17**, 16336-00-8; **19**, 16336-01-9; **19** HBr, 16336-02-0; **20**, 16336-03-1; **22**, 16336-04-2; **23**, 16336-05-3; **24**, 16336-06-4.

Acknowledgments.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical and Physical Chemistry Division of Southern Research Institute for the spectral and microanalytical determinations. Some of the analyses reported were performed by the Galbraith Laboratories, Knoxville, Tenn. The authors also wish to thank Dr. N. F. Wood for his work on the preparation of **5**.

The Quaternization of Isoxazoles with Alcohols and Perchloric Acid

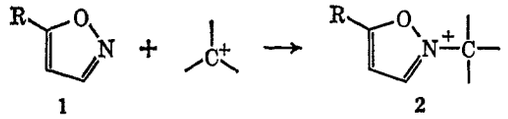
D. J. WOODMAN

Department of Chemistry, University of Washington, Seattle, Washington 98105

Received November 24, 1967

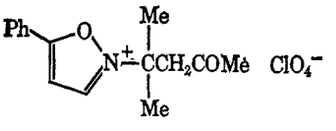
The reaction of isoxazoles and perchloric acid with alcohols which are efficient sources of carbonium ions has general utility as a method for the preparation of isoxazolium salts with branched quaternizing groups. The rate of reaction increases with the relative stability of the intermediate carbonium ion, while the equilibrium becomes less favorable for the formation of 3,5-dimethylisoxazolium cations as the bulk of the N-alkyl substituent is made greater.

In 1963, Eugster, Leichner, and Jenny, postulated[1] that combination of *t*-alkyl carbonium ions and unprotonated, 3-unsubstituted isoxazoles (**1**) gave isoxazolium salts (**2**) as reactive intermediates in sulfuric acid.



1 **2**

Subsequently, isolation of the perchlorate **3** from the reaction of 5-phenylisoxazole and mesityl oxide under the same conditions confirmed that this novel isoxazole quaternization had taken place, and it was found that 5-substituted N-*t*-butylisoxazolium salts (**4**) could conveniently be prepared simply by mixing *t*-butyl alcohol and the isoxazole with 70% perchloric acid.[2]



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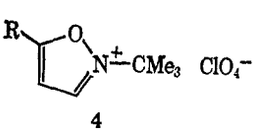

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A further study of the quaternization method was undertaken, because of the potential importance of the SN1 process as a general synthetic route to isoxazolium salts with branched groups on nitrogen. Such cations cannot be obtained with the normal SN2 alkylating agents,[3] and 3-unsubstituted isoxazolium salts with bulky nitrogen substituents have special significance as reagents for the preparation of stable enol ester acylating agents in peptide synthesis.[4–6] In addition it was

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