Heterocyclizations in the Pyrido[2,3-*b*]pyrazine Series

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In this paper, we report the results of heterocyclizations in the pyrido[2,3-*b*]pyrazine series to give the pyrido[2,3-*e*] or [3,2-*e*]pyrrolo[1,2-*a*]pyrazine. The Clauson-Kaas reaction on 2,3-diaminopyridine is investigated; regioselectivity on the 3-amino group is shown by ^{1}H- and ^{13}C-nmr. Synthesis and reactivity of the original pyrazino[2,3-*g*]indolizine series is also reported.

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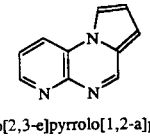
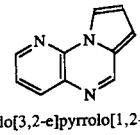
Introduction.

Several series of heterocyclic compounds possessing a bridgehead pyrrolic moiety have been shown to be of biological interest. Particulary, Bandurco showed that pyrrolo[1,2-*c*]quinazolines exhibit antihypertensive activity [1], and Neale reported anxyolitic activity of the pyrrolo-[1,2-*a*]quinoxaline series [2].

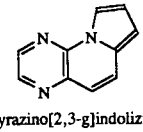
In continuation of our studies on bridgehead heterocyclic systems, we have investigated the synthesis of pyrido-[2,3-*e*]pyrrolo[1,2-*a*]pyrazine, pyrido[3,2-*e*]pyrrolo[1,2-*a*]-pyrazine, and pyrazino[2,3-*g*]indolizine series.



Pyrido[2,3-e]pyrrolo[1,2-a]pyrazine



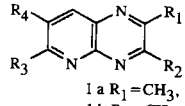
Pyrido[3,2-e]pyrrolo[1,2-a]pyrazine



Pyrazino[2,3-g]indolizine

Results and Discussion.

The starting pyrido[2,3-*b*]pyrazines **1a-e** used in this work were prepared from the corresponding 2,3-diamino-pyridines according to the reported methods [3].

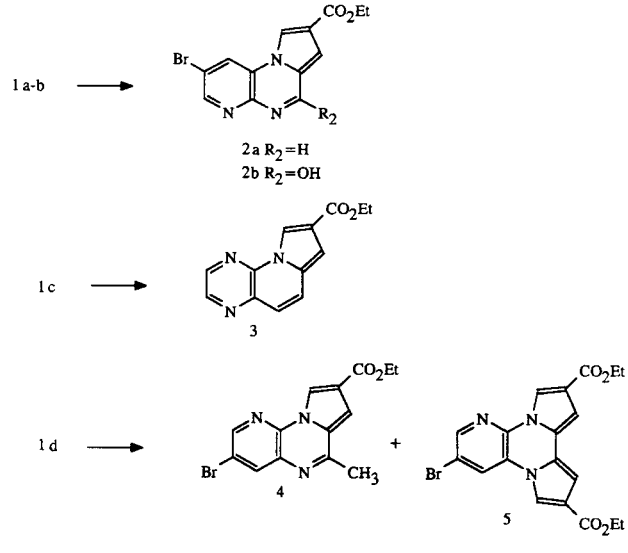


1 a R_1=CH_3, R_2=R_3=H, R_4=Br
1 b R_1=CH_3, R_2=OH, R_3=H, R_4=Br
1 c R_1=R_2=R_4=H, R_3=CH_3
1 d R_1=R_2=CH_3, R_3=H, R_4=Br
1 e R_1=CH_3, R_2=R_3=R_4=H

Treatment of **1a,b** with ethyl bromopyruvate led to the corresponding tricyclic systems **2a,b** in low yields. In a similar manner, 6-methylpyrido[2,3-*b*]pyrazine (**1c**) led to ethyl pyrazino[2,3-*g*]indolizine-2-carboxylate (**3**) in 26% yield. Structural determination of **3** was made by ms and nmr experiments. The ^{1}H-nmr spectra of **3** showed two doublets at δ 6.97 and δ 8.74 characteristic of the pyrrolic moiety ($J_{1,3}$ = 0.8 Hz) [4]. The signals of H-4,5 and H-7,8 could be discriminated on the basis of the LR-HETCOR experiment which showed the correlation between C-5a (δ 138.3) with the two signals at δ 7.47 and 8.62 (respectively H-4 and H-7), and between C-9a (δ 140.8) with H-5 and H-8.

Our attempts to prepare the required 3-methylpyrido-[2,3-*b*]pyrazine for the preparation of the pyrido[3,2-*e*]pyr-rolo[1,2-*a*]pyrazine series were unsuccessful under several experimental conditions used to obtain the trifluoromethylated derivatives [5].

Finally treatment of 2,3-dimethylpyrido[2,3-*b*]pyrazine (**1d**) with ethyl bromopyruvate affords a mixture of the two



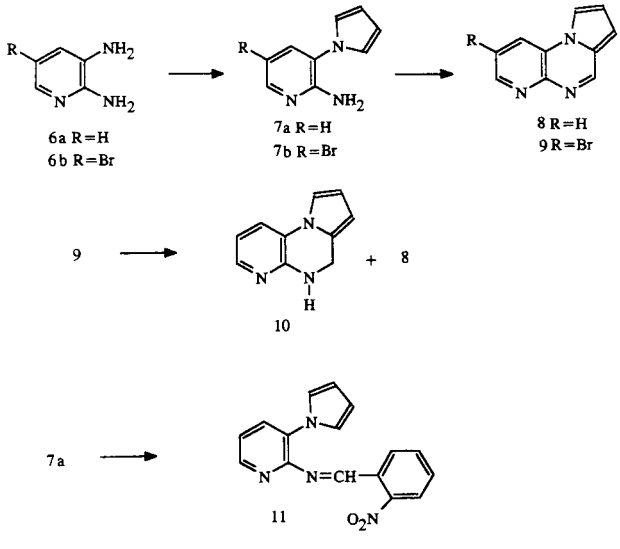
1 a-b → 2a R_2=H, 2b R_2=OH
1 c → 3
1 d → 4 + 5

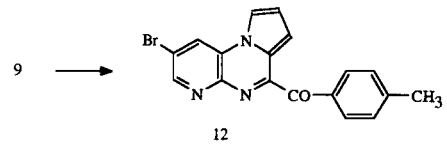
derivatives **4** and **5**. Structural determination of **5** was easily realized by ^{1}H-nmr. The determination of **4** was made by ^{13}C nmr experiment and by comparison with the unsubstituted pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine obtained according the reported method [6]. At this point, complete ^{13}C assignment of this structure by the LR-HETCOR experiment [7], and of **4** by ^{13}C-^{1}H HETCOR was necessary to confirm the proposed structure.

Our attempts to prepare the unsubstituted pyrido[2,3-*e*]-pyrrolo[1,2-*a*]pyrazine (**8**) by treatment of **1e** with bromoacetaldehyde failed. Treatment of 2,3-diaminopyridine (**6a**) with 2,5-dimethoxytetrahydrofuran according to the Clauson-Kaas procedure [8] led only to one product identified as the intermediary pyrrolic structure **7a**. This last product cyclizes in boiling formic acid to give the expected pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**8**) [9]. Similarly, (**6b**) gave the bromoderivative **9** which upon a catalytic dehalogenation (H_2/PdC) led to a mixture of **8** and **10**.

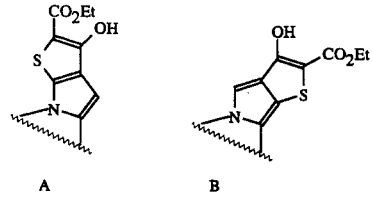
The regioselectivity of Clauson-Kaas reaction on the 3-amino group of **6a,b** to give **8,9** was confirmed by nmr. Proton assignment of **8,9** were made on the basis of a 2D COSY spectrum, and ^{13}C assignment by performing ^{13}C-^{1}H HETCOR experiments. Comparison of the ^{13}C spectrum of **8,9** with **4** and the unsubstituted structure pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine, showed that the tertiary carbon localized at the γ position of the nitrogen of the pyridinic ring (C-9 for (**8**), C-6 for pyrido[3,2-*e*]pyrrolo-[1,2-*a*]pyrazine), is well differenciated in the two series (δ 122.2 for **8**, and δ 137.2 for pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine).

Our attempts to prepare some 4-substituted derivatives directly from **7a,b** failed, and only the intermediary imine **11** was isolated when **7a** is treated by *o*-nitrobenzaldehyde [10]. Finally compound **12** was obtained from **9** following Higashino procedure using *p*-methylbenzaldehyde [11].

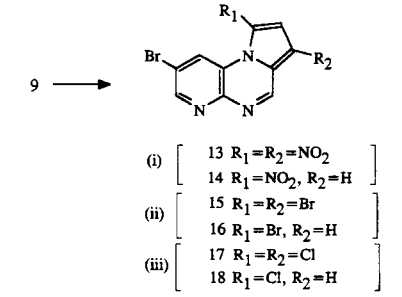




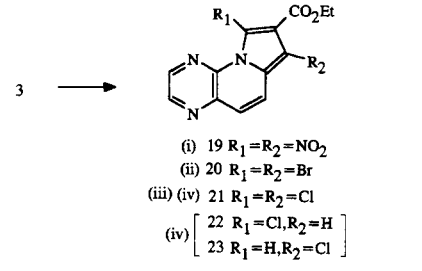
In order to prepare tetracyclic systems **A-B** for their potential immunostimulant activity [12], we have investigated the reactivity of compounds **3,9** toward electrophilic substitutions. Treatment of (**9**) by nitric acid in concentrated sulfuric acid led to a mixture of two products. Their determination to the 1,3-dinitro and the 1-nitro derivatives **13,14** is realized by ^{1}H-nmr who shows for **13** a singlet at δ 8.31 (H-2), and a peri effect for the chemical shift of H-4 at δ 10.16.



Bromination of **9** in acetic acid media gives in the same proportions 1,3,8-tribromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**15**) and 1,8-tribromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**16**). The ^{1}H-nmr spectra of **16** shows two doublets at δ 6.99 and 7.04. Their attribution to H-2 and H-3 respectively was made possible by performing the ^{13}C-^{1}H HETCOR experiment. This experiment also showed that the



(i) HNO_3/H_2SO_4, (ii) Br_2/CH_3CO_2H, (iii) $NOCl/CH_3CO_2H$



(i) HNO_3/H_2SO_4, (ii) Br_2/CH_3CO_2H, (iii) $NOCl/CH_3CO_2H$, (iv) NCS/CH_3CO_2H

doublet at δ 9.75 is attributable to H-9. This long range deshielding effect have previously been observed in the pyrrolo[1,2-*a*]quinoxaline series [13].

Our attempts to nitrosate structure **9** failed. Effectively, no reaction was found when carried out with sodium nitrite, and a treatment by nitrosyl chloride gave 1-chloropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**17**) admixed with the 1,3-dichloro derivative **18**. We have previously described this reactivity of nitrosyl chloride in the imidazo[1,2-*a*]-naphthyridine-[1,8] series [14].

Finally, we investigate the reactivity of **3** toward the same reagents. In this case, nitration, bromination, and treatment with nitrosyl chloride gave only the 1,3-disubstituted derivatives (respectively **19, 20, 21**), while the use of *N*-chlorosuccinimide gives a mixture of the three compounds **21, 22, 23**. From these results, further investigations are in progress to study the displacement of nitro and halogen groups of compounds **19-23**.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis were performed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-nmr spectra were taken on a Varian EM 360 (60 MHz) or a Brüker WM 90 or a Brüker MSL 300; ^{13}C-nmr spectra were obtained at 26° with proton noise decoupling at 75 MHz with a Brüker MSL 300 instrument. Chemical shifts are expressed relative to internal tetramethylsilane in deuteriochloroform at a concentration of *ca* 5%. Mass spectra were recorded on a LKB 2091 spectrometer at 70 eV [$(\theta_{source}) = 180°$]. Compounds were purified by high-performance liquid chromatography (hplc), Waters M 590, on a preparative alumina or silica gel column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (tlc) were performed on 0.25 mm E. Merck precoated neutral alumina plates.

7-Bromo-2-methylpyrido[2,3-*b*]pyrazine (**1a**).

To a solution of 2,3-diamino-5-bromopyridine [15] (5 g, 26 mmoles) in 50 ml of ethanol is added 2.5 g of methylglyoxal (35 mmoles). After being stirred for two hours at room temperature, the solvent is evaporated. The residue is diluted in water, made basic (sodium carbonate), and extracted with dichloromethane. After evaporation, the brown residue is chromatographed on neutral alumina to give **1a** in 78% yield, mp 166-168°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 2.90 (s, CH_3), 8.63 (d, J_{6-8} = 2.5 Hz, H-8), 8.90 (s, H-3), 9.20 (d, H-6).

Anal. Calcd. for $C_8H_6N_3Br$: C, 42.88; H, 2.70; N, 18.75. Found: C, 42.80; H, 2.72; N, 18.81.

7-Bromo-3-hydroxy-2-methylpyrido[2,3-*b*]pyrazine (**1b**).

To a solution of 2,3-diamino-5-bromopyridine (1 g, 5.3 mmoles) in 10 ml of ethanol is added 1.5 g of ethyl pyruvate (13 mmoles). After being stirred one hour at room temperature, the precipitate which formed is filtered to give 0.94 g (75%) of **1b**, mp >260°; ^{1}H-nmr (deuteriochloroform/perdeuteriomethanol, 60 MHz): δ 2.60 (s, CH_3), 8.30 (d, J_{6-8} = 3 Hz, H-8), 8.62 (d, H-6).

Anal. Calcd. for $C_8H_6N_3OBr$: C, 40.03; H, 2.52; N, 17.50. Found: C, 40.19; H, 2.58; N, 17.38.

6-Methylpyrido[2,3-*b*]pyrazine (**1c**).

This compound is obtained in 38% yield from 6-methyl-2,3-diaminopyridine and glyoxal sodium bisulfite using the same method employed for the preparation of **1a**, mp 94-96°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 2.86 (s, CH_3), 7.66 (d, J_{7-8} = 9 Hz, H-7), 8.40 (d, H-8), 8.96 (d, J_{2-3} = 1.5 Hz, H-2 or H-3), 9.13 (d, H-3 or H-2).

Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.10; H, 4.78; N, 29.12.

7-Bromo-2,3-dimethylpyrido[2,3-*b*]pyrazine (**1d**).

This compound is obtained in 69% yield from 5-bromo-2,3-diaminopyridine and 2,3-butanedione according the method described for **1a**, mp 140-142°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 2.79 (s, CH_3), 2.80 (s, CH_3), 8.53 (d, J_{6-8} = 2.5 Hz, H-8), 9.10 (d, H-6).

Anal. Calcd. for $C_9H_8N_3Br$: C, 45.40; H, 3.39; N, 17.65. Found: C, 44.51; H, 3.50; N, 17.79.

Pyrido[2,3-*b*]pyrazine (**1e**).

This compound is obtained according to the methods given in reference [3], mp 142-144°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 7.85 (dd, J_{7-8} = 8 Hz, J_{6-7} = 5 Hz, H-7), 8.60 (dd, J_{6-8} = 2 Hz, H-8), 9.09 (d, J_{2-3} = 1.5 Hz, H-2 or H-3), 9.20 (d, H-3 or H-2), 9.31 (dd, H-6).

Ethyl 8-Bromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine-2-carboxylate (**2a**).

To a solution of **1a** in ethanol (100 ml), was added 5.6 g (28 mmoles) of ethyl bromopyruvate, and the mixture is refluxed for 12 hours. After evaporation of the solvents, the residue is diluted with water, basified by sodium carbonate, and extracted three times with dichloromethane. Chromatography on neutral alumina eluted with dichloromethane gives **2a** in 3.5% yield, mp 172-174°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.41 (t, CH_3), 4.38 (q, CH_2), 7.32 (d, J_{1-3} = 1.4 Hz, H-3), 8.32 (d, J_{7-9} = 2.2 Hz, H-9), 8.52 (d, H-7), 8.72 (d, H-1), 8.73 (s, H-4).

Anal. Calcd. for $C_{13}H_{10}N_3O_2Br$: C, 48.77; H, 3.15; N, 13.13. Found: C, 48.85; H, 3.12; N, 13.26.

Ethyl 8-Bromo-4-hydroxypyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine-2-carboxylate (**2b**).

This compound is prepared from **1b** using the same method employed for the preparation of **2a** in 12% yield, mp >260°; ms: 337 ($M^{+\cdot}$ +2, 62%), 335 ($M^{+\cdot}$, 61%), 307 ($M^{+\cdot}$ $-C_2H_4$, 27%), 292 (M^+ +2 $-C_2H_5O$, 100%), 290 ($M^{+\cdot}$ $-C_2H_5O$, 94%), 263 ($M^{+\cdot}$ $-CO_2C_2H_5$ +H, 14%), 234 (8%); ^{1}H-nmr (DMSO-d_6, 90 MHz): δ 1.35 (t, CH_3), 4.45 (q, CH_2), 7.34 (d, J_{1-3} = 1.8 Hz, H-3), 7.82 (d, J_{7-9} = 2.5 Hz, H-9), 8.38 (d, H-7), 8.43 (d, H-1).

Anal. Calcd. for $C_{13}H_{10}N_3O_3Br$: C, 46.45; H, 3.00; N, 12.50. Found: C, 46.51; H, 2.91; N, 12.45.

Ethyl Pyrazino[2,3-*g*]indolizine-2-carboxylate (**3**).

This compound is prepared from **1c** in 26% yield, according to the method employed for the preparation of **2a,b**, mp 120-122°; ms: 241 ($M^{+\cdot}$, 68%), 213 ($M^{+\cdot}$ $-C_2H_4$, 36%), 196 ($M^{+\cdot}$ $-OC_2H_5$, 76%), 169 ($M^{+\cdot}$ $-CO_2C_2H_5$ +H, 100%), 168 ($M^{+\cdot}$ $-CO_2C_2H_5$, 40%), 141 (17%), 114 (24%); ^{1}H-nmr (deuteriochloroform, 300

MHz): δ 1.39 (t, CH_3), 4.39 (q, CH_2), 6.97 (d, J_{1-3} = 0.8 Hz, H-3), 7.14 (d, J_{4-5} = 9.5 Hz, H-5), 7.47 (d, H-4), 8.41 (d, J_{7-8} = 2.2 Hz, H-8), 8.62 (d, H-7), 8.74 (d, H-1); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ 14.5 (CH_3), 60.5 (CH_2), 106.4 (C-3), 118.4 (C-1), 120.1 (C-5), 121.0 (C-2), 124.6 (C-4), 131.1 (C-3a), 138.3 (C-5a), 140.7 (C-7), 140.8 (C-9a), 142.3 (C-8), 164.4 (CO).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.59; H, 4.71; N, 17.38.

Ethyl 7-Bromo-4-methylpyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine-2-carboxylate (**4**), and Diethyl 10-Bromopyrido[2,3-*e*]dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine-2,5-dicarboxylate (**5**).

These two derivatives are obtained from **1d** according to the procedure described for **2a,b**, **3**. Chromatography on neutral alumina eluted with dichloromethane gives first **4** in 9% yield, mp 224-226°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.41 (t, CH_3), 2.72 (s, CH_3), 4.39 (q, CH_2), 7.35 (s, H-3), 8.29 (s, H-6), 8.52 (s, H-8), 8.75 (s, H-1); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ 14.9 (CH_3), 21.9 (CH_3-4), 60.8 (CH_2), 109.5 (C-3), 117.4 (C-2), 118.8 (C-1), 121.3 (C-7), 127.7 (C-3a), 132.1 (C-5a), 137.7 (C-9a), 138.8 (C-6), 147.3 (C-8), 157.0 (C-4), 164.0 (CO).

Anal. Calcd. for $C_{14}H_{12}N_3O_2Br$: C, 50.32; H, 3.62; N, 12.57. Found: C, 50.11; H, 3.61; N, 12.59.

Further elution gave **5** (4%), mp 214-216°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 1.35 (t, 6H, CH_3), 4.33 (q, 4H, CH_2), 6.93 (m, H-3, H-4), 7.93 (d, J_{8-10} = 2 Hz, H-9), 8.13 (d, H-10), 8.37 (m, H-1, H-6).

Anal. Calcd. for $C_{19}H_{16}N_3O_4Br$: C, 53.04; H, 3.75; N, 9.77. Found: C, 52.95; H, 3.71; N, 9.62.

2-Amino-3-(1-pyrrolyl)pyridine (**7a**).

A solution of 8.9 g (68 mmoles) of 2,5-dimethoxytetrahydrofuran, 5 g (45.8 mmoles) of 2,3-diaminopyridine (**6a**) in 125 ml of acetic acid is refluxed for two hours. After evaporation of the acid under reduced pressure, the residual oil is diluted with water and stirred for one hour. After extraction with ether, the crude product is chromatographed on neutral alumina (eluent dichloromethane) to give **7a** (62%), mp 96-98° (lit [9] 72°); ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 4.90 (s, 2H, NH_2), 6.35 (t, J = 1.9 Hz, H-3', H-4'), 6.71 (dd, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz, H-5), 6.85 (t, H-2', H-5'), 7.41 (dd, J_{4-6} = 2 Hz, H-4), 8.10 (dd, H-6).

2-Amino-5-bromo-3-(1-pyrrolyl)pyridine (**7b**).

This product is prepared from **6b** in a 57% yield using the method employed for the preparation of **7a**, mp 98-100°; ^{1}H-nmr (deuteriochloroform, 60 MHz): δ 4.70 (s, NH_2), 6.15 (m, H-3', H-4'), 6.65 (m, H-2', H-5'), 7.35 (d, J_{4-6} = 2 Hz, H-4), 7.95 (d, H-6).

Anal. Calcd. for $C_9H_8N_3Br$: C, 45.40; H, 3.39; N, 17.65. Found: C, 45.29; H, 3.42; N, 17.64.

Pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**8**).

Method A.

Compound **8** is prepared according to the procedure given in reference [8] in 53% yield, mp 177-179° (lit [9] 172°); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 6.95 (dd, J_{1-2} = 3 Hz, J_{2-3} = 3.8 Hz, H-2), 6.98 (dd, J_{1-3} = 1.8 Hz, H-3), 7.46 (dd, J_{7-8} = 4 Hz, J_{8-9} = 8 Hz, H-8), 7.98 (dd, H-1), 8.29 (dd, J_{7-9} = 2 Hz, H-9), 9.02 (s, H-4); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ 108.2 (C-3), 114.9 (C-2), 115.5 (C-1), 122.1 (C-8), 122.2 (C-9), 123.6 (C-9a), 125.9 (C-3a), 146.6 (C-7), 147.1 (C-5a), 148.7 (C-4).

Method B.

Following the introduction of hydrogen gas into a solution of 100 mg (0.4 mmole) of **9** in 5 ml of ethanol in the presence of 50 mg of 5% Pd/C, the suspension was stirred for 2 hours at room temperature, and the Pd/C was filtered off. The filtrate was evaporated *in vacuo* and the residue submitted to a chromatography on neutral alumina eluted with dichloromethane to give **8** and 4,5-dihydropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**10**) (28%) as a brown oil; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 4.62 (s, 2H, H-4), 5.25 (s, NH), 6.03 (dd, J_{1-3} = 1.4 Hz, J_{2-3} = 5 Hz, H-3), 6.37 (dd, J_{1-2} = 2.2 Hz, H-2), 6.70 (dd, J_{8-9} = 8 Hz, J_{7-8} = 5 Hz, H-8), 7.10 (dd, H-1), 7.42 (dd, J_{7-9} = 1.5 Hz, H-9), 7.83 (dd, H-7); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 40.3 (C-4), 105.3 (C-3), 111.9 (C-2), 114.1 (C-1), 120.4 (C-9), 122.4 (C-8), 142.3 (C-7).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.18; H, 5.35; N, 24.47.

8-Bromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**9**).

This compound is prepared from **7b** in a 52% yield using method A given to obtain **8**, mp 254-256°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 6.97 (m, H-2), 7.02 (m, H-3), 7.95 (m, H-1), 8.37 (d, J_{7-9} = 1.8 Hz, H-9), 8.78 (d, H-7), 9.03 (s, H-4); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 109.3 (C-3), 116.0 (C-1 or C-2), 116.0 (C-2 or C-1), 125.0 (C-9), 148.0 (C-7), 148.3 (C-4).

Anal. Calcd. for $C_{10}H_6N_3Br$: C, 48.42; H, 2.44; N, 16.94. Found: C, 48.31; H, 2.50; N, 16.91.

3-(1-Pyrrolyl)-2-[(*N*-2-nitrobenzylidene)-amino]pyridine (**11**).

A solution of **7a** (1 g, 6.2 mmoles), 2-nitrobenzaldehyde (1.2 g, 9.4 mmoles), acetic acid (0.3 ml) in 20 ml of ethanol is refluxed for 3 hours. After being cooled, the solvents are removed under reduced pressure. The residue is diluted in water, basified with sodium carbonate, and extracted three times with dichloromethane. The crude product is submitted to chromatography on neutral alumina eluted with dichloromethane to give **11** as an oil (19%); ms: 292 ($M^{+\cdot}$, 3%), 157 (100%), 149 (31%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 6.37 (t, J = 2.1 Hz, H-3', H-4'), 7.12 (t, H-2', H-5'), 7.34 (dd, J_{4-5} = 7.9 Hz, J_{5-6} = 4.7 Hz, H-5), 7.62 (td, $J_{4''-5''}$ = 7.8 Hz, $J_{3''-5''}$ = 1.4 Hz, H-5''), 7.70 (td, $J_{3''-4''}$ = 7.8 Hz, $J_{4''-6''}$ = 1.1 Hz, H-4''), 7.75 (dd, J_{4-6} = 1.45 Hz, H-4), 8.04 (dd, H-6''), 8.29 (dd, H-3''), 8.44 (dd, H-6), 9.68 (s, -CH=CO).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.73; H, 4.28; N, 19.19.

8-Bromo-4-(4-methylbenzoyl)pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**12**).

Potassium cyanide (1 g, 15.3 mmoles) is added to a solution of **9** (1 g, 4 mmoles) and 4-methylbenzaldehyde (1 g, 8.3 mmoles) in 8 ml of DMSO, and the mixture is heated at 80° for 12 hours. After being cooled, the solution is acidified (1*N* hydrochloric acid) and stirred overnight. After extraction with dichloromethane, the crude product is chromatographed on silica gel to give **12** (11%), mp 184-186°; ^{1}H-nmr (deuteriochloroform, 90 MHz): δ 2.50 (s, CH_3), 7.11 (m, H-2), 7.32 (m, H-3), 7.36 (d, J = 8.5 Hz, H-3', H-5'), 8.11 (m, H-1), 8.16 (d, H-2', H-6'), 8.50 (d, J_{7-9} = 1.8 Hz, H-9), 8.90 (d, H-7).

Anal. Calcd. for $C_{18}H_{12}N_3OBr$: C, 59.04; H, 3.30; N, 11.47. Found: C, 59.13; H, 3.28; N, 11.39.

8-Bromo-1,3-dinitropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**13**) and 8-Bromo-1-nitropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**14**).

To a cooled solution of **9** (500 mg, 2 mmoles) in concentrated sulfuric acid, is added 1 ml of nitric acid (d = 1.38). After being stirred for one hour, the solution is crushed on ice to give a yellow precipitate which is chromatographed on neutral alumina eluted with dichloromethane to give **13** (34%), mp 218-220°; ms: 339 ($M^{+\cdot}$ +2, 58%), 337 ($M^{+\cdot}$, 65%), 321 ($M^{+\cdot}$ −O, 27%), 307 ($M^{+\cdot}$ −NO, 15%), 291 ($M^{+\cdot}$ −NO_2, 9%), 275 ($M^{+\cdot}$ −NO_2O, 10%), 261 ($M^{+\cdot}$ −NO_2NO, 18%), 260 (30%), 258 ($M^{+\cdot}$ −Br, 24%), 245 ($M^{+\cdot}$ −$2NO_2$, 15%), 234 (100%), 182 (48%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 8.50 (s, H-2), 8.92 (d, $J_{7\text{-}9}$ = 2.5 Hz, H-7), 9.33 (d, H-9), 9.57 (s, H-4); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 115.5 (C-2), 130.3 (C-9), 146.5 (C-7), 152.0 (C-4).

Anal. Calcd. for $C_{10}H_4N_5O_4Br$: C, 35.53; H, 1.19; N, 20.72. Found: C, 35.41; H, 1.14; N, 20.86.

Further elution gave **14** (24%), mp 217-219°; ms: 294 ($M^{+\cdot}$ +2, 100%), 292 ($M^{+\cdot}$, 99%), 276 ($M^{+\cdot}$ −O, 8%), 262 ($M^{+\cdot}$ −NO, 25%), 246 ($M^{+\cdot}$ −NO_2, 26%), 219 (16%), 208 (27%), 181 (18%), 167 ($M^{+\cdot}$ −NO_2Br, 22%), 140 (48%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 7.05 (d, $J_{2\text{-}3}$ = 4 Hz, H-3), 7.82 (d, H-2), 8.85 (d, $J_{7\text{-}9}$ = 1.4 Hz, H-7 or H-9), 8.95 (d, H-9 or H-7), 9.21 (s, H-4); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 108.3 (C-3), 120.7 (C-2), 130.1 (C-9), 148.8 (C-7), 150.2 (C-4).

Anal. Calcd. for $C_{10}H_5N_4O_2Br$: C, 40.98; H, 1.72; N, 19.12. Found: C, 41.10; H, 1.69; N, 18.87.

1,3,8-Tribromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**15**) and 1,8-Dibromopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**16**).

Bromine (0.2 ml) is added to a stirred solution of **12** (300 mg, 1.21 mmoles) in 8 ml of acetic acid. After 20 minutes, the mixture is filtered. The precipitate which was formed is diluted in water, basified (sodium carbonate), and extracted three times with dichloromethane. Chromatography on neutral alumina gave **15** (30%), mp 230-232°; ms: 409 ($M^{+\cdot}$ +6, 32%), 407 ($M^{+\cdot}$ +4, 99%), 405 ($M^{+\cdot}$ +2, 100%), 403 ($M^{+\cdot}$, 35%), 324 ($M^{+\cdot}$ −Br, 8%), 297 (10%), 245 ($M^{+\cdot}$ −2Br, 11%), 166 ($M^{+\cdot}$ −3Br, 7%), 139 (14%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 7.01 (s, H-2), 8.62 (d, $J_{7\text{-}9}$ = 2.5 Hz, H-7), 8.93 (s, H-4), 9.67 (d, H-9); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 122.1 (C-9), 126.0 (C-2), 147.0 (C-7), 148.8 (C-4).

Anal. Calcd. for $C_{10}H_4N_3Br_3$: C, 29.59; H, 0.99; N, 10.35. Found: C, 29.51; H, 1.10; N, 10.31.

Further elution gave **16** (19%), mp 228-230°; ms: 329 ($M^{+\cdot}$ +4, 54%), 327 ($M^{+\cdot}$ +2, 100%), 325 ($M^{+\cdot}$, 51%), 246 ($M^{+\cdot}$ −Br, 10%), 219 (31%), 167 ($M^{+\cdot}$ −2Br, 31%), 140 (32%); ^{1}H-nmr (deuteriochloroform, 300 Mz): δ 6.99 (d, $J_{2\text{-}3}$ = 4 Hz, H-2), 7.04 (d, H-3), 8.81 (d, $J_{7\text{-}9}$ = 1.8 Hz, H-7), 8.94 (s, H-4), 9.75 (d, H-9); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ 101.9 (C-1), 110.0 (C-3), 116.8 (C-8), 120.6 (C-2), 126.0 (C-9a), 126.2 (C-9), 128.9 (C-3a), 146.8 (C-5a), 148.2 (C-7), 148.4 (C-4).

Anal. Calcd. for $C_{10}H_5N_3Br_2$: C, 36.73; H, 1.54; N, 12.85. Found: C, 36.78; H, 1.43; N, 12.76.

8-Bromo-1,3-dichloropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**17**), and 8-Bromo-1-chloropyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (**18**).

To a cooled solution of acetic acid/acetic anhydride/potassium acetate (1.5 ml/0.75 ml/0.5 g) was added 300 mg (1.21 mmoles) of **9**. Nitrosyl chloride (1 ml) (0.37 g/ml in acetic anhydride) was then added at −15°. After being stirred 30 minutes at −15° and 30 minutes at room temperature, the mixture was crushed on ice. The precipitate was chromatographed on neutral alumina eluted with dichloromethane to give **17** (26%), mp 212-214°; ms: 321 ($M^{+\cdot}$ +6, 7.3%), 319 ($M^{+\cdot}$ +4, 35%), 317 ($M^{+\cdot}$ +2, 100%), 315 ($M^{+\cdot}$, 52%), 290 (10%), 280 ($M^{+\cdot}$ −Cl, 4%), 211 (16%), 209 (19%), 201 ($M^{+\cdot}$ −BrCl, 11%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 6.87 (s, 2-H), 8.83 (d, $J_{7\text{-}9}$ = 1.5 Hz, H-7), 9.02 (s, H-4), 9.43 (d, H-9); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 115.7 (C-2), 126.6 (C-9), 145.9 (C-7), 148.6 (C-4).

Anal. Calcd. for $C_{10}H_4N_3Cl_2Br$: C, 37.89; H, 1.27; N, 13.26. Found: C, 37.82; H, 1.32; N, 13.11.

Further elution gave **18** (13%), mp 252-254°; ms: 285 ($M^{+\cdot}$ +4, 24%), 283 ($M^{+\cdot}$ +2, 100%), 281 ($M^{+\cdot}$, 75%), 247 (36%), 175 (48%), 167 ($M^{+\cdot}$ −BrCl, 64%), 141 (25%): ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 6.89 (d, $J_{2\text{-}3}$ = 2 Hz, H-2), 7.02 (d, H-3), 8.80 (d, $J_{7\text{-}9}$ = 2 Hz, H-7), 8.96 (s, H-4), 9.48 (d, H-9); ^{13}C-nmr (deuteriochoroform, 75 MHz): δ_{CH} 109.0 (C-3), 116.3 (C-2), 126.5 (C-9), 148.2 (C-7), 148.6 (C-4).

Anal. Calcd. for $C_{10}H_5N_3ClBr$: C, 42.51; H, 1.78; N, 14.87. Found: C, 42.32; H, 1.78; N, 14.85.

Ethyl 1,3-Dinitropyrazino[2,3-*g*]indolizine-2-carboxylate (**19**).

This compound is obtained from **3** in 34% yield following the general procedure of nitration given for **13**, **14**, mp 166-168°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.44 (t, CH_3), 4.54 (q, CH_2), 8.11 (d, $J_{4\text{-}5}$ = 9.9 Hz, H-5), 8.67 (d, H-4), 8.71 (d, $J_{7\text{-}8}$ = 2 Hz, H-8), 9.03 (d, H-7); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 13.7 (CH_3), 63.6 (CH_2), 121.1 (C-5), 131.7 (C-4), 143.1 (C-7), 145.8 (C-8).

Anal. Calcd. for $C_{13}H_9N_5O_6$: C, 47.14; H, 2.74; N, 21.14. Found: C, 47.23; H, 2.76; N, 20.98.

Ethyl 1,3-Dibromopyrazino[2,3-*g*]indolizine-2-carboxylate (**20**).

This compound is obtained from **3** in 32% yield following the general procedure of bromination given for **15**, **16**, mp 160-162°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.47 (CH_3), 4.47 (CH_2), 7.34 (d, $J_{4\text{-}5}$ = 9 Hz, H-5), 7.67 (d, H-4), 8.55 (d, $J_{7\text{-}8}$ = 2.3 Hz, H-8), 8.72 (d, H-7); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ_{CH} 14.3 (CH_3), 61.5 (CH_2), 121.6 (C-5), 122.8 (C-4), 139.8 (C-7), 142.8 (C-8).

Anal. Calcd. for $C_{13}H_9N_3O_2Br_2$: C, 39.13; H, 2.27; N, 10.53. Found: C, 39.32; H, 2.28; N, 10.43.

Ethyl 1,3-Dichloropyrazino[2,3-*g*]indolizine-2-carboxylate (**21**).

This compound is obtained from **3** in 30% yield following the procedure given for the preparation of **17**, **18**, mp 144-146°; ms: 313 ($M^{+\cdot}$ = 4, 12%), 311 ($M^{+\cdot}$ +2, 61%), 309 ($M^{+\cdot}$, 100%), 281 ($M^{+\cdot}$ −C_2H_4, 98%), 264 ($M^{+\cdot}$ −C_2H_5O, 33%), 236 ($M^{+\cdot}$ −$CO_2C_2H_5$, 35%), 230 ($M^{+\cdot}$ −C_2H_5OCl+H, 30%), 201 ($M^{+\cdot}$ −$CO_2C_2H_5Cl$, 26%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.45 (s, CH_3), 4.46 (q, CH_2), 7.29 (d, $J_{4\text{-}5}$ = 9.6 Hz, H-5), 7.66 (d, H-4), 8.53 (d, $J_{7\text{-}8}$ = 2.4 Hz, H-8), 8.71 (d, H-7); ^{13}C-nmr (deuteriochloroform, 75 MHz): δ 14.3 (CH_3), 61.3 (CH_2), 108.6 (C-3), 116.0 (C-2 or C-1), 118.9 (C-1 or C-2), 121.2 (C-4 or C-5), 121.5 (C-5 or C-4), 127.9 (C-3a), 139.2 (C-5a), 139.5 (C-7), 142.5 (C-8), 142.8 (C-9a), 162.0 (CO).

Anal. Calcd. for $C_{13}H_9N_3O_2Cl_2$: C, 50.35; H, 2.92; N, 13.55. Found: C, 50.16; H, 2.98; N, 13.61.

Ethyl 1-Chloropyrazino[2,3-*g*]indolizine-2-carboxylate (**22**) and Ethyl 3-Chloropyrazino[2,3-*g*]indolizine-2-carboxylate (**23**).

To a solution of **3** (200 mg, 0.8 mmole) in 50% sulfuric acid was added NCS (108 mg, 0.81 mmole). After being stirred overnight at room temperature, the mixture was crushed on ice, basified with ammonium hydroxide, and extracted with dichloromethane. Chromatography on neutral alumina gave first **21** (11%). Further elution gave **22** (16%) as a brown oil; ^{1}H-nmr (deuteriochloro-

form, 300 MHz): δ 1.42 (t, CH_3), 4.41 (q, CH_2), 7.11 (s, H-3), 7.25 (d, J_{4-5} = 9.7 Hz, H-5), 7.52 (d, H-4), 8.55 (d, J_{7-8} = 2.5 Hz, H-8), 8.68 (d, H-7).

Anal. Calcd. for $C_{13}H_{10}N_3O_2Cl$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.52; H, 3.80; N, 15.21.

Further elution gave **23** (13%); ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.43 (t, CH_3), 4.43 (q, CH_2), 7.29 (d, J_{4-5} = 10 Hz, H-5), 7.65 (d, H-4), 8.49 (d, J_{7-8} = 2.5 Hz, H-8), 8.72 (d, H-7), 8.80 (s, H-1).

Anal. Calcd. for $C_{13}H_{10}N_3O_2Cl$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.62; H, 3.59; N, 15.26.

REFERENCES AND NOTES

[1] V. T. Bandurco, E. M. Wong, S. D. Levine and Z. G. Hajos, *J. Med. Chem.*, **24**, 1455 (1981).

[2] R. F. Neale, S. L. Fallon, W. C. Boyar, J. W. F. Wasley, L. L. Martin, G. A. Stone, B. S. Glaeser, C. M. Sinton and M. Williams, *Eur. J. Pharm.*, **1**, 136 (1987).

[3] B. A. Fox and T. L. Threlfull, *Org. Synth.*, **44**, 34 (1964); C. L. Leese and H. N. Rydon, *J. Chem. Soc.*, 303 (1955); V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948); L. N. Pino and W. S. Zehrung, *J. Org. Chem.*, **77**, 3155 (1955).

[4] M. L. Hefferman and G. M. Irvine, *Aust. J. Chem.*, **29**, 837 (1976).

[5] M. Cuschman and H. Patel, *J. Org. Chem.*, **53**, 5088 (1988).

[6] J. C. Lancelot, S. Rault, D. Ladurée and M. Robba, *Chem. Pharm. Bull.*, **33**, 2798 (1985).

[7] The ^{13}C-nmr of pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine (deuteriochloroform, 75 MHz) gives the following values: δ 108.6 (C-3), 114.3 (C-2), 115.4 (C-1), 121.3 (C-7), 127.7 (C-3a), 130.5 (C-5a), 137.2 (C-6), 139.7 (C-9a), 146.3 (C-4), 146.7 (C-8).

[8] N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 867 (1952); N. Clauson-Kaas and Z. Tyle, *ibid.*, **6**, 667 (1952).

[9] J. C. Lancelot, D. Ladurée and M. Robba, *Chem. Pharm. Bull.*, **33**, 3122 (1988).

[10] G. Stefanich, M. Artico, R. Silvestri, G. C. Pantaleoni, R. Giorgi and G. Palumbo, *Farmaco Ed. Sci.*, **45**, 7 (1990).

[11] T. Higashino, M. Goi and E. Hayashi, *Chem. Pharm. Bull.*, **24**, 238 (1976); S. Veeraghavan and F. D. Popp, *J. Heterocyclic Chem.*, **18**, 755 (1981).

[12] J. C. Teulade, G. Grassy, R. Escale and J. P. Chapat, *J. Org. Chem.*, **46**, 1026 (1981).

[13] Y. Blache, A. Elhakmaoui, A. Gueiffier, H. Viols, O. Chavignon, J. C. Teulade, G. Dauphin, A. Carpy, G. Grassy and J. P. Chapat, *Chem. Pharm. Bull.*, submitted; R. C. Fort, G. W. H. Cheeseman and E. C. Taylor, *J. Org. Chem.*, **29**, 2441 (1964).

[14] A. Gueiffier, Y. Blache, H. Viols, J. P. Chapat, O. Chavignon, J. C. Teulade, G. Dauphin, J. C. Debouzy and J. L. Chabard, *J. Heterocyclic Chem.*, **29**, 283 (1992).

[15] B. A. Fox and T. L. Threlfull, *Org. Synth.*, **44**, 34 (1964).