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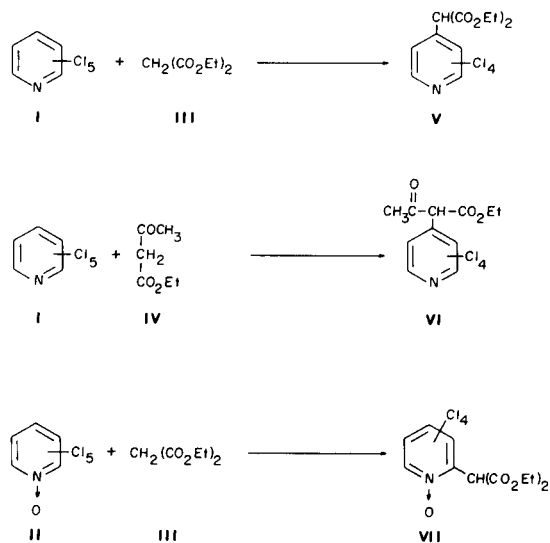
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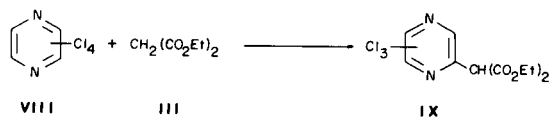
When tetrachloropyrazine was allowed to react with the anions formed from diethyl malonate and malononitrile, the normal alkylation took place. When the anions from ethyl acetoacetate and *N,N*-diethylacetoacetamide were used, alkylation was followed by enolization and ring formation to give furo[2,3-*b*]pyrazines. The structure proof and reactions of the furo[2,3-*b*]pyrazines are discussed.

J. Heterocyclic Chem., **20**, 365 (1983).

Highly chlorinated nitrogen heterocycles are very reactive toward nucleophilic agents. When an anion from a reactive methylene compound is used as the nucleophile, a carbon-carbon bond is formed. Moshchitskii, *et al.* (2), reported the reaction of pentachloropyridine (I) and its *N*-oxide (II) with diethyl malonate (III) and ethyl acetoacetate (IV) to give products V-VII.



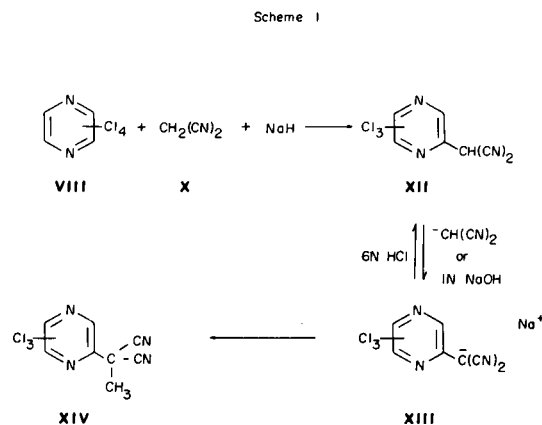
A previous observation in our laboratory by Nasutavicus (3) was the reaction of tetrachloropyrazine VIII and diethyl malonate (III) to give IX.



We repeated and expanded the reaction of tetrachloropyrazine with diethyl malonate to include other reactive methylene compounds. *e.g.* malononitrile (X), ethyl acetoacetate (IV) and *N,N*-diethyl acetoacetamide (XI).

The product (XII), from the reaction of tetrachloropyrazine (VIII) with malononitrile (X), has a very acidic proton which reacts with a second mole of anion to form a

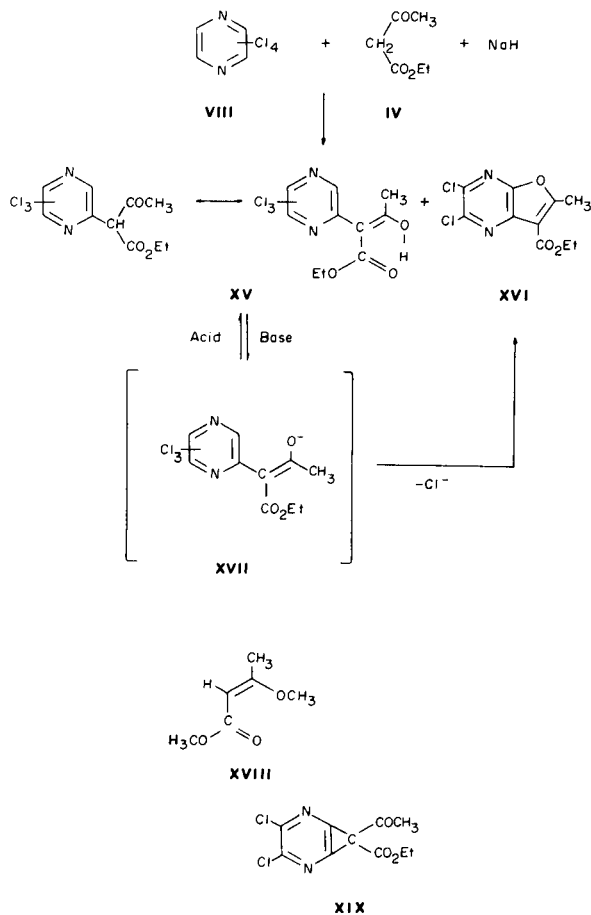
stable salt XIII. The salt can be isolated or methylated to give XIV, or acidified to give XII as summarized in Scheme I. The yield of XII varied with the ratio of reactants. When a 1:1:1 ratio of tetrachloropyrazine, malononitrile and sodium hydride was used, 31% of XII was obtained. When the ratio was 1:2:2.2, yield of XII increased to 84%. A ratio of 1:1:2 did not improve the yield from 30%.



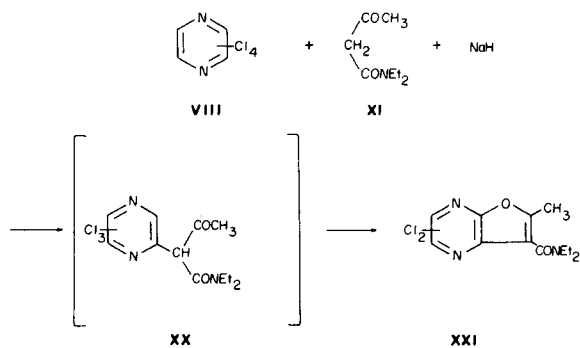
Reaction of VIII with ethyl acetoacetate (IV) gave two products XV and XVI in yields of 10% and 54% respectively. The reaction conditions can be varied to favor XV or XVI as summarized in Scheme II. Compound XV most likely exists as the enol form. Its ir (Nujol) ν CO 1650, 1610 indicated the lack of normal keto and ester carbonyl. C^{13} nmr (deuteriochloroform) showed carbons at δ 170.2 and 99.5 corresponded to the β and α carbons of methyl 3-methoxy-2-butenate (XVIII) at δ 172.5 and 90.2.

The structure of XVI was assigned by means of elemental analysis, and C^{13} nmr. One of the carbons of the pyrazine ring shifted down field to δ 150.5 indicating the presence of the oxygen-carbon bond, thus excluded the alternative structure XIX.

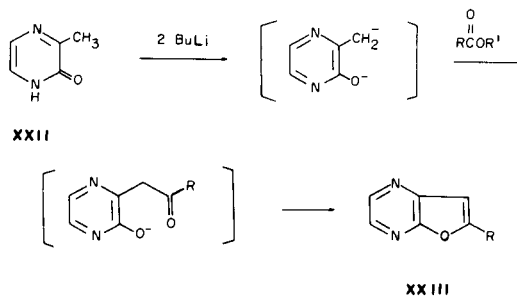
Scheme II



N,N-Diethyl acetoacetamide (XI) reacted with VIII to give the cyclized amide XXI without any detectable amount of XX.

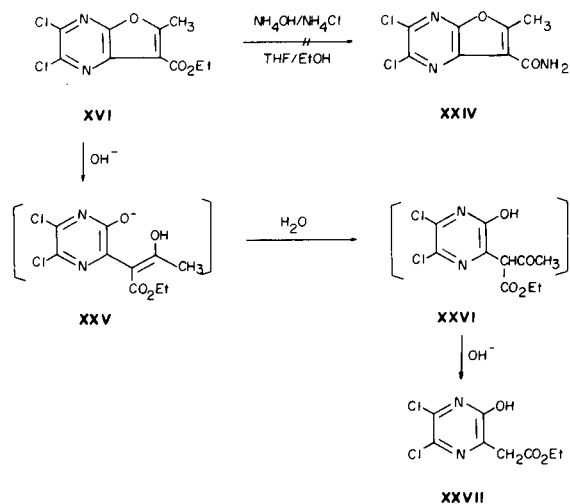


A 6-substituted furo[2,3-*b*]pyrazine XXIII was prepared by van der Gen, *et al.* (4) by way of 3-methyl-2-pyrazone (XXII). Our procedure offers a simple alternative route to this ring system with a functional group at position 7.

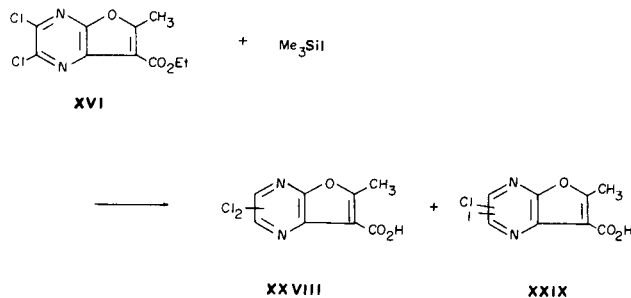


Attempts to convert the ester to amide (XXIV) with ammonium hydroxide/ammonium chloride gave the ring opened product XXVII. A probable path is given in Scheme III.

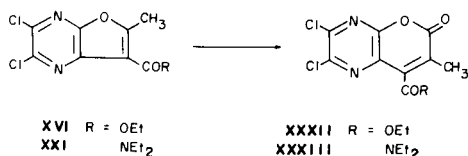
Scheme III



Attempted acid hydrolysis gave starting material. The ester was hydrolyzed with iodotrimethylsilane (5). Unfortunately, iodine-chlorine exchange also took place, and iodine was detected in the product, probably XXIX.



Castle, *et al.* (6) reported ring expansion of furo[2,3-*d*]pyridazine (XXX) with potassium cyanide. Under similar condition, the same reaction was observed with furo[2,3-*b*]pyrazines (XXVI and XXI) to give the pyrano[2,3-*b*]pyrazines XXXII and XXXIII.



Tetrachloropyrazine, with reactive adjacent chloro groups, is an ideal starting point for fused ring systems. The furo[2,3-*b*]pyrazines and 6*H*-pyrano[2,3-*b*]pyrazines reported here add to an expanding list which includes 10*H*-pyrazino[2,3-*b*][1,4]benzothiazine (7), 1*H*-imidazo[4,5-*b*]pyrazine (8), 1,2,5-thiadiazolo[3,4-*b*]pyrazine (9), 1,3-thiazolo[4,5-*b*]pyrazine (10), 3,4-dihydro-2*H*-pyracino[2,3-*b*][1,4]oxazine (11) and 7,8-dihydro-6*H*-[1,2,5]thiadiazolo[3',4'-5,6]pyrazino[2,3-*b*][1,4]oxazine (12) to date. Others will be added in the future.

EXPERIMENTAL

Melting points were taken with Thomas-Hoover Capillary Melting point Apparatus and were not corrected. Infrared spectra were recorded with a Perkin-Elmer Infrared Spectrophotometer Model 297. Proton magnetic resonance spectra were recorded with a Varian T-60 Spectrometer. Carbon¹³ magnetic resonance spectra were recorded with Jeol JNM-FX60 Spectrometer. Preparative liquid chromatography separation was run with Waters Associates Prep LC System 500 with silica gel. Microanalysis were done by M. Gade.

Ethyl α -(Carboethoxy)-3,5,6-trichloropyrazineacetate (IX).

Into a reaction flask was weighed 5.2 g (0.11 mole) of 50% sodium hydride. It was washed with hexane twice then covered with 150 ml of tetrahydrofuran. Diethyl malonate, 16.0 g (0.1 mole), was added and the reaction mixture was stirred at room temperature for 1 hour. A solution of 21.8 g (0.1 mole) of VIII in 100 ml of tetrahydrofuran was added through a dropping funnel. The reaction mixture was heated at boiling under reflux for 20 hours. Tetrahydrofuran was removed under reduced pressure and the residue partitioned between water and dichloromethane. The dichloromethane solution was dried, concentrated and distilled with a Kugelrohr apparatus to give 13.6 g (40%) of product, bp 125°/0.5 mm; ir (Nujol): ν CO 1755, 1740 cm^{-1} ; pmr (deuteriochloroform): δ 1.32 (t, 6H), 4.34 (q, 4H), 5.10 (s, 1H).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}_4$: C, 38.68; H, 3.24; N, 8.20. Found: C, 38.60; H, 3.17; N, 7.98.

α -Cyano-3,5,6-trichloropyrazineacetonitrile (XII).

Sodium hydride, 10.4 g (0.22mole) of 50% suspension, was weighed into a reaction flask and washed twice with hexane. Tetrahydrofuran, 300 ml, was followed by 12.0 g (0.1 mole) of X in 100 ml of tetrahydrofuran and 21.8 g (0.1 mole) of VIII in 100 ml of tetrahydrofuran. The reaction mixture was refluxed for 20 hours. The solvent was removed under reduced pressure and the residue was stirred in dichloromethane and filtered. The solid was suspended in 150 ml of water and acidified with 50 ml of concentrated hydrochloric acid and extracted with dichloromethane. The

organic solution was dried and concentrated to 200 ml, diluted with 200 ml of hexane and filtered through silica gel. The filtrate was further concentrated to 175 ml, cooled to give 20.9 g (84.5%) of product XII, mp 124-125°; ir (potassium bromide): ν CN 2260 cm^{-1} ; pmr (deuteriochloroform): δ 5.46 (s, 1H); cmr (deuteriochloroform and deuterioacetone): δ 28.6, 109.1, 138.7, 143.9, 146.2, 148.4.

Anal. Calcd. for $\text{C}_7\text{HCl}_3\text{N}_4$: C, 33.97; H, 0.41; N, 22.64. Found: C, 33.82; H, 0.40; N, 22.43.

α -Cyano- α -methyl-3,5,6-trichloropyrazineacetonitrile (XIV).

In 20 ml of tetrahydrofuran was added 9.9 g (0.04 mole) of XII. To this solution was added 2 g (0.05 eq) of sodium hydroxide in 20 ml of water, followed by 7.1 g (0.05 mole) of iodomethane. The mixture was stirred at room temperature for 1 hour then heated to reflux for 20 hours. After removal of the solvents the residue was diluted with water and extracted with dichloromethane. The organic solution was dried, concentrated and distilled with a Kugelrohr apparatus to give 5.8 g (56%) of an oil which solidified, mp 103-105°; ir (neat): ν CN 2255 cm^{-1} ; pmr (deuteriochloroform): δ 2.31 (s, 3H).

Anal. Calcd. for $\text{C}_8\text{H}_2\text{Cl}_3\text{N}_4$: C, 36.74; H, 1.15; N, 21.43. Found: C, 36.57; H, 1.36; N, 20.73.

Ethyl α -(1-Hydroxyethylidene)-3,5,6-trichloropyrazineacetate (XV).

In a reaction flask were placed 250 ml of tetrahydrofuran, 21.8 g (0.1 mole) of VIII, 13.0 g (0.1 mole) of IV. To this mixture was added 10.4 g (0.22 mole) of 50% sodium hydride in small portions as fast as foaming would allow and with the temperature maintained below 50°. After the addition was complete, the reaction mixture was stirred at room temperature overnight. Ten ml of water was added and then evaporated to dryness. The residue was diluted with water and filtered. The alkaline aqueous filtrate was neutralized with acetic acid and extracted with dichloromethane. The organic solution was dried, concentrated, and purified by liquid chromatography (silica gel 1% acetone in hexane). Recrystallization from hexane gave 3.2 g (10%) of product, mp 47-48°; ir (Nujol): ν CO 1650, 1610 cm^{-1} ; pmr (deuteriochloroform): δ 1.20 (t, 3H), 1.95 (s, 3H), 4.25 (q, 2H); cmr (deuteriochloroform): 14.0, 19.6, 61.3, 99.5, 144.1, 144.3, 146.9, 147.4, 170.2, 177.3.

Anal. Calcd. for $\text{C}_{10}\text{H}_5\text{Cl}_3\text{N}_2\text{O}_3$: C, 38.55; H, 2.90; N, 8.99. Found: C, 38.66; H, 2.95; N, 8.82.

Ethyl 2,3-Dichloro-6-methylfuro[2,3-*b*]pyrazine-7-carboxylate (XVI).

Sodium hydride, 20.8 g (0.44 mole) of 50% suspension, was weighed into a reaction flask, washed twice with hexane and covered with 700 ml of tetrahydrofuran. A solution of 52.1 g (0.4 mole) of IV in 100 ml of tetrahydrofuran was added and the mixture heated to 60°. A solution of 43.6 g (0.2 mole) of VIII in 200 ml of tetrahydrofuran was added over a 2 hour period. Heating was continued for another 6 hours. The reaction mixture was evaporated to dryness, diluted with 500 ml of dichloromethane and filtered. The dichloromethane solution was concentrated and residue distilled with a Kugelrohr apparatus. The material that came over at 80-145°/0.5 mm was recrystallized from dichloromethane/hexane mixture to give 29.8 g (54%) of XVI, mp 99-101°; ir (Nujol): ν CO 1712 cm^{-1} ; pmr (deuteriochloroform): δ 1.45 (t, 3H), 2.92 (s, 3H), 4.50 (q, 2H); cmr (deuteriochloroform): 14.0, 14.9, 61.0, 109.2, 136.1, 139.9, 143.9, 150.5, 161.1, 169.0.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{Cl}_2\text{N}_2\text{O}_3$: C, 43.66; H, 2.93; N, 10.18. Found: C, 43.70; H, 2.96; N, 10.25.

2,3-Dichloro-*N,N*-diethyl-6-methylfuro[2,3-*b*]pyrazine-7-carboxamide (XXI).

Using the same procedure for XVI, 21.8 g (0.1 mole) of VIII, 31.4 g (0.2 mole) of XI and 10.4 g (0.22 mole) of 50% sodium hydride in 600 ml of tetrahydrofuran gave 15.4 g (51%) of product XXI, mp 112-113°; ir (Nujol): ν CO 1632 cm^{-1} ; pmr (deuteriochloroform): δ 1.23 (t, 3H), 1.30 (t, 3H), 2.68 (s, 3H), 3.40 (q, 2H), 3.62 (q, 2H); cmr (deuteriochloroform): δ 12.5, 13.8, 14.1, 39.3, 42.9, 113.5, 136.2, 138.9, 142.6, 150.3, 160.7, 163.1.

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_2$: C, 47.70; H, 4.34; N, 13.91. Found: C, 47.32; H, 4.32; N, 13.69.

Ethyl 5,6-Dichloro-3-hydroxypyrazineacetate (XXVII).

In a reaction flask were placed 120 ml of concentrated ammonium hydroxide and 12 g of ammonium chloride, 16.5 g (0.06 mole) of XVI, 10 ml of ethanol and 20 ml of tetrahydrofuran. The reaction mixture was heated at 50° overnight, then evaporated to a semisolid under reduced pressure. The residue was washed with water, dissolved in dichloromethanol, dried and concentrated on a steambath. The brown oily residue was extracted with 5:95 (V/V) mixture of acetone-hexane. The acetone-hexane solution was concentrated and extracted again with a mixed solvent. This process was repeated three times until upon concentration, a yellow solid came out. Recrystallization from 1,1,1-trichloroethane-hexane gave 4.4 g (29%) of product XXVII, mp 109-111°; ir (Nujol): ν CO 1737 cm^{-1} ; pmr (deuteriochloroform): δ 1.25 (t, 3H), 3.88 (s, 2H), 4.22 (q, 2H); cmr (deuteriochloroform): δ 13.8, 37.8, 61.6, 135.3, 138.3, 140.3, 156.5, 169.5.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{Cl}_2\text{N}_2\text{O}_3$: C, 38.27; H, 3.21; N, 11.16. Found: C, 38.47; H, 3.25; N, 11.5.

Ethyl 2,3-Dichloro-7-methyl-6-oxo-6H-pyrano[2,3-b]pyrazine-8-carboxylate (XXXII).

To a mixture of 50 ml of tetrahydrofuran and 50 ml of water were added 13.8 g (0.05 mole) of XVI and 6.5 g (0.1 mole) of potassium cyanide. The reaction mixture was stirred at room temperature for 3 days, then concentrated under reduced pressure. The residue was diluted with water and acidified with 20 ml of concentrated hydrochloric acid. A red precipitate formed was collected by filtration, washed with water and dissolved in dichloromethane. After drying over magnesium sulfate, the dichloromethane solution was concentrated to 100 ml, diluted with 100 ml of hexane and decolorized with silica gel. Further concentration to 100 ml upon cooling, gave 4.9 g (33%) of product XXXII, mp 123-124°; ir (Nujol): ν CO 1765, 1736 cm^{-1} ; pmr (deuteriochloroform): δ 1.42 (t, 3H), 2.25 (s, 3H), 4.52 (q, 2H); cmr (deuteriochloroform): δ 13.9, 14.9, 62.7, 128.8, 129.5, 140.7, 142.7, 145.5, 150.8, 158.4, 162.4.

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{Cl}_2\text{N}_2\text{O}_4$: C, 43.59; H, 2.66; N, 9.24. Found: C, 43.51; H, 2.74; N, 9.14.

2,3-Dichloro-N,N-diethyl-7-methyl-6-oxo-6H-pyrano[2,3-b]pyrazine-8-carboxamide (XXXIII).

Using the same procedure as XXXII, 15.1 g (0.05 mole) of XXI, 6.5 g (0.1 mole) of potassium cyanide in 50 ml of tetrahydrofuran and 50 ml of water reacted to give 4.9 g (30%) of XXXIII, mp 150-151°; ir (Nujol): ν CO 1740, 1640 cm^{-1} ; pmr (deuteriochloroform): δ 1.10 (t, 3H), 1.30 (t, 3H), 2.23 (s, 3H), 3.23 (q, 2H), 3.63 (q, 2H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_3$: C, 47.29; H, 3.97; N, 12.73. Found: C, 47.49; H, 4.11; N, 12.73.

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