[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Pyrrolopyridazines

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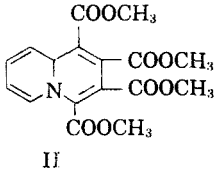
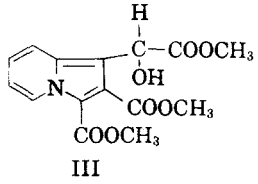
A new heterocyclic ring system, pyrrolo[1,2-*b*]pyridazine, is described. Carbomethoxy derivatives were prepared by the reaction of pyridazine and 3-methylpyridazine with methyl acetylenedicarboxylate.

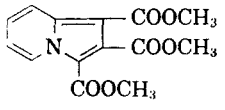
Diels and co-workers found that pyridine reacted with methyl acetylenedicarboxylate (I) to give a variety of heterocyclic condensation products.[1] From reactions carried out in ether they isolated quinolizines (such as II), and from reactions in methanol, pyrrocolines (III and IV).[2] More recently, Wiley and Knabeschuh[3] obtained a 20.4% yield of IV from a reaction in which pyridine and I were mixed initially at −78° in ether that contained traces of alcohol and peroxides.



II



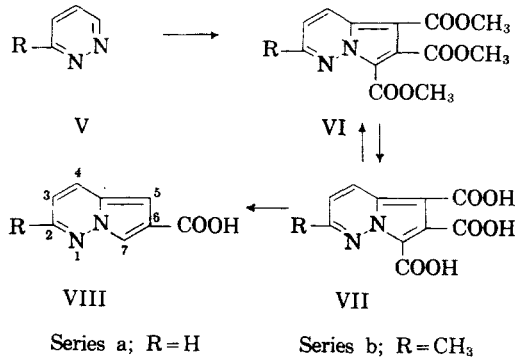
III



IV

This paper reports an extension of this unusual type of reaction to the pyridazine compounds (V). The work constitutes part of a more general program of study on this relatively unknown diazine. It was of special interest to determine whether condensation might occur at the second nitrogen atom as well as at the first, in which case a route would be opened to the synthesis of some unusual types of heterocyclic compounds.

Pyridazine reacted readily with methyl acetylenedicarboxylate in ether; however, the only products that could be isolated were high molecular weight and amorphorus. With methanol as a solvent, a white, crystalline product, which has been assigned structure VIa was obtained. This ester could be separated from a yellow contaminant by crystallization or chromatography; or, more conveniently, it could be isolated by treating the crude, solid reaction products with bromine in methanol, followed by crystallization from methanol. The yield of VIa thus obtained was 26%.



V VI VIII VII

Series a; R = H Series b; R = CH_3

As in the pyridine series, alkaline hydrolysis of VIa, followed by mild acidification, resulted in the precipitation of a slightly soluble potassium salt. With concentrated hydrochloric acid this salt yielded a tricarboxylic acid (VIIa) that could be reesterified to VIa with diazomethane, showing that no rearrangement had occurred during hydrolysis. When heated alone or in dilute hydrochloric acid, VIIa decarboxylated to give a monocarboxylic acid (VIIIa).

The parallelism of the empirical formulas and the properties of the compounds of this series and those of the pyrrocolines derived from pyridine constitutes good evidence for the pyrrolopyridazine structures (VIa–VIIIa). Nevertheless, it seemed desirable to gain additional support for this ring system by an independent synthesis. Borrows and Holland[2] prepared pyrrocoline-2-carboxylic acid (X) by a sequence of reactions which involved addition of ethyl bromopyruvate to α-picoline, ring closure of the quaternary salt (IX), and ester hydrolysis;[4] and showed that X was identical with the monocarboxylic acid which could be obtained by hydrolysis and decarboxylation of IV. Utilization of a similar synthesis for preparing VIIIa would be complicated by the fact that the wrong nitrogen in 3-methylpyridazine could, and probably would, quaternize. To obviate this difficulty, the

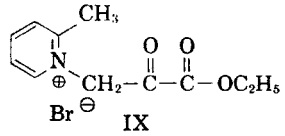
(1) Diels and Alder, *Ann.*, **498**, 16 (1932). Numerous other references are included in a review by Borrows and Holland, *Chem. Revs.*, **42**, 611 (1948).

(2) III was the product when the temperature was maintained at 0°, and IV, when the temperature was uncontrolled. In attempting to repeat the latter experiment, Borrows and Holland, *J. Chem. Soc.*, 672 (1947), isolated a substance that corresponded to III rather than IV.

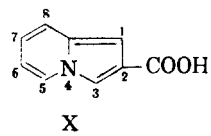
(3) Wiley and Knabeschuh, *J. Org. Chem.*, **18**, 836 (1953).

(4) This procedure has also been used by Clemo, Fox, and Raper, *J. Chem. Soc.*, 4173 (1953) for preparing 6-ethylpyrrocoline.

methyl substituted series (Vb–VIIIb) was selected for the comparison of products.



IX



X

Repetition of sequence V–VIII with 3-methylpyridazine as the starting material yielded VIb (37%), which was converted to VIIIb (82%). On the other hand, ethyl bromopyruvate was condensed with 3,6-dimethylpyridazine by the procedure of Borrows and Holland.[2] An acid and an ethyl ester were isolated from this reaction. The acid melted at the same temperature as that derived from the acetylenedicarboxylate reaction (VIIIb) and mixture melting points showed no depression. Furthermore, the ethyl ester was identical with that obtained by esterifying the acid from the acetylenedicarboxylate reaction. These data, in conjunction with the similar reactions of the pyridine compounds, confirm formulas VIb, VIIIb, and further support VIa–VIIIa. Throughout, the properties of the pyridine, pyridazine, and 3-methylpyridazine compounds showed marked similarities. This is illustrated by a tabulation of melting points of corresponding compounds (Table I).

TABLE I

A COMPARISON OF MELTING POINTS OF THE PYRROCOLINES, PYRROLOPYRIDAZINES, AND METHYLPYRROLOPYRIDAZINES

	Parent Compound		
Derivative	Pyridine	Pyridazine	Methyl-pyridazine
Triester (IV, VIa,b)	151–152[1] 146–147[3]	160–161	164.5–165
Monoacid (X, VIIIa,b)	240–242[1] 238–240[3]	243	225.5–226
Monomethyl ester	97–99[3]	93–94	84–85

The extra nitrogen atom in the pyrrolopyridazines proved to be relatively unreactive. Thus, neither the triester (VIa) nor the methyl ester of VIIIa showed any tendency to react with methyl acetylenedicarboxylate, methyl iodide, or phenacyl bromide under conditions that pyridine and pyridazine react readily.

EXPERIMENTAL

Preparation of dimethoxydihydrofurans. These compounds were prepared by methoxylation of the appropriate furan by the method of Fakstorp and co-workers.[5] 2,5-Dimethoxy-2,5-dihydrofuran, b.p. 48–53° (10 mm.), n_D^{25} 1.4324, was obtained in 74% yield; 2,5-dimethoxy-2,5-dihydrosylvan, b.p. 46° (10 mm.), n_D^{26} 1.4272, in 56% yield; 2,5-dimethoxy-2,5-dimethyl-2,5-dihydrofuran, b.p. 44–49° (7 mm.), n_D^{25} 1.4305, in 29.2% yield.

(5) Fakstorp, Raleigh, and Schneipp, *J. Am. Chem. Soc.*, 72, 872 (1950).

Preparation of pyridazine and substituted pyridazines. A solution of 116.6 g. (0.896 mole) of 2,5-dimethoxy-2,5-dihydrofuran in 800 ml. of 0.1 *N* sulfuric acid was allowed to stand one hour at room temperature, then heated for 15 minutes on a steam-bath, cooled to −5°, and mixed with 70 g. (1.4 moles) of cold hydrazine hydrate (the temperature rose to 15° after the mixing). After this solution had stood overnight at room temperature it was refluxed for 90 minutes, cooled, saturated with potassium carbonate, and extracted with two liters of benzene. Distillation yielded 57.0 g. (79.5%) of pyridazine, b.p. 62.5° (4 mm.), n_D^{27} 1.5193.[6] The *picrate* melted at 169–170° (reported value, 169°.[6a]

Methylpyridazinium iodide was prepared by the reaction of pyridazine with methyl iodide in ether; m.p. 90.0–90.5°.

Anal. Calc'd for $C_5H_7IN_2$: C, 27.04; H, 3.18. Found: C, 27.00, H, 3.29.

In the absence of a diluent such as ether, the reaction occurred with considerable violence.

Application of the method used for pyridazine to the preparation of alkylpyridazines yielded 3-methylpyridazine (55%), b.p. 73–76° (6 mm.), n_D^{27} 1.5060 from 2,5-dimethoxy-2,5-dihydrosylvan; and 3,6-dimethylpyridazine (32.4%), b.p. 55° (1 mm.) from 2,5-dimethoxy-2,5-dimethyl-2,5-dihydrofuran. 3,6-Dimethylpyridazine was also prepared in 20% yield from acetonylacetone and hydrazine by the time consuming method of Zimmerman and Lochte.[7] Its *methiodide* derivative melted at 118.5–119.5°.

Anal. Calc'd for $C_7H_{11}IN_2$: C, 33.61; H, 4.43. Found: C, 33.39; H, 4.39.

Reaction of pyridazine with methyl acetylenedicarboxylate. To a stirred solution of 59 ml. of methyl acetylenedicarboxylate in 150 ml. of dry methanol, cooled in an ice-salt bath to 0°, was added 29 ml. of pyridazine. This solution was stirred for an hour, then placed in a cold room. After several days, 26 g. (fraction A) of whitish-yellow crystals were removed by filtration. Over a period of six months several small additional crops of crystals were removed. These were combined as fraction B, and weighed 6.0 g. Recrystallization of A from methanol yielded 19.81 g. of light yellow crystals, m.p. 133–155°. Similarly, from B was obtained 5.44 g. of substance melting at 160–161°, which did not depress the melting point of recrystallized B. It was more convenient, however, to purify A as follows. A sample (8.43 g.) was dissolved in methanol and treated with a solution of bromine in methanol until the bromine color persisted. The crystalline material which separated on addition of water weighed 6.83 g. (81% recovery); m.p. 158–160°; and the melting point was not depressed by the 160–161° substance. The total recovery of purified A and B corresponds to a 26.1% yield of trimethyl pyrrolo[1,2-*b*]-pyridazine-5,6,7-tricarboxylate.

Anal. Calc'd for $C_{13}H_{12}N_2O_6$: C, 53.40; H, 4.11; N, 9.59. Found: C, 53.51; H, 4.29; N, 9.71; 9.85.

When the original yellow mixture was recrystallized very slowly, individual white and yellow crystals could be distinguished and separated mechanically. In this manner, enough yellow compound could be isolated for a melting point determination. It melted at the same temperature as the white compound, 160–161°, but depressed the melting point of the white compound (mixture melting point, 134–155°). The white compound could be separated from the yellow by

(6) Different values reported for the refractive index of pyridazine are: (a) $n_D^{23.5}$ 1.5231, Clauson-Kaas, Li, and Elming, *Acta Chem. Scand.*, 4, 1240 (1950); (b) $n_D^{23.5}$ 1.5231, Bruhl, *Z. physik. Chem.*, 22, 373 (1897); (c) n_D^{19} 1.5189, Marquis, *Ann. chim.* (8) 4, 245 (1905); (d) n_D^{20} 1.5170, Hufford, Tarbell, and Koszalka, *J. Am. Chem. Soc.*, 74, 3014 (1952); (e) n_D^{20} 1.5148, Evans and Wiselogle, *J. Am. Chem. Soc.*, 67, 60 (1945).

(7) Zimmerman and Lochte, *J. Am. Chem. Soc.*, 60, 2456 (1938).

chromatography, however, it was not possible to elute the more strongly adsorbed yellow compound satisfactorily from the column.

Pyrrolopyridazine-5,6,7-tricarboxylic acid (VIIa). The adduct (trimethyl pyrrolopyridazine-5,6,7-tricarboxylate) (3.35 g.) was shaken for one hour with a solution of 7 g. of potassium hydroxide and 15 ml. of water. During this time most of the material dissolved. The mixture then was heated on a steam-bath for an hour to complete the saponification, cooled, and acidified with dilute sulfuric acid. A white solid precipitated and was removed by filtration. After drying, it weighed 2.70 g. When heated, it did not melt, but charred at high temperature and left an alkaline residue. An analysis, while not checking as well as desired, suggests that the material is a monopotassium salt of the tricarboxylic acid. A similar salt was obtained by Diels and Alder by saponification of IV.

Anal. Calc'd for $C_{10}H_5KN_2O_6$: C, 41.66; H, 1.75; N, 9.72. Found: C, 39.81; H, 1.81; N, 9.94.

A portion (2.34 g.) of this salt was dissolved in just enough 10% potassium hydroxide to effect solution and then was acidified strongly with concentrated hydrochloric acid. A quantitative yield of pyrrolopyridazinetricarboxylic acid precipitated; m.p. 222°. An analytical sample, m.p. 223°, was obtained by recrystallization from water. This compound was colorless and decomposed with evolution of gas at the melting point.

Anal. Calc'd for $C_{10}H_6N_2O_6$: C, 48.01; H, 2.42; N, 11.20. Found: C, 48.51; H, 2.66; N, 11.21.

With diazomethane in benzene this compound yielded the trimethyl ester, m.p. 160–161°, which did not depress the melting point of the original white adduct.

Pyrrolopyridazine-6-carboxylic acid (VIIIa). This acid, m.p. 243°, was obtained in 92% yield by heating together 1.93 g. of the monopotassium salt (see the previous experiment) and 20 ml. of 6 *N* hydrochloric acid on a steam-bath for one hour. The yellow acid separated when the solution was cooled. It was also obtained as a sublimate when the tricarboxylic acid was heated above its melting point in a vacuum.

Anal. Calc'd for $C_8H_6N_2O_2$: C, 59.25; H, 3.73; N, 17.28; Neut. equiv., 162. Found: C, 59.32; H, 3.88; N, 17.60; Neut. equiv., 164.

The methyl ester was prepared by heating 0.330 g. of the acid with 50 ml. of methanol and 1 ml. of sulfuric acid. Most of the methanol was removed at reduced pressure; then 25 ml. of water was added. The methyl ester crystallized slowly from the solution; weight, 0.280 g. (78%), m.p. 93–94°. This ester was also prepared by treating the acid with diazomethane.

Anal. Calc'd for $C_9H_8N_2O_6$: C, 61.34; H, 4.58; N, 15.90. Found: C, 61.69; H, 4.73; N, 15.93.

Reaction of 3-methylpyridazine with methyl acetylenedicarboxylate. To a stirred solution of 22 ml. of methyl acetylenedicarboxylate in 60 ml. of dry methanol, cooled to −5°, was added 12.3 ml. of 3-methylpyridazine in four portions. The temperature did not rise above 5°. Within an hour a solid precipitate began to form. After a total of 90 minutes of stirring, the mixture was placed in a cold room, and then, the next day, the solid was removed by filtration; weight, 8.66 g., m.p. 153–159°. A single recrystallization from methanol yielded 6.13 g. of white needles, m.p. 163–164°. The addition of another milliliter of methyl acetylenedicarboxylate to the reaction mixture yielded, after three days, an additional 2.69 g. (after recrystallization from methanol) of adduct; m.p. 163.5–164.5°. Over the next three weeks, two more small portions of the ester were added. At the end of this time a total of 26 ml. of methyl acetylenedicarboxylate had been added and 12.12 g. (37.4%) of recrystallized adduct, m.p. 162–165°, had been isolated. Several additional recrystallizations yielded a sample which melted at 163.5–165°.

Anal. Calc'd for $C_{14}H_{14}N_2O_6$: C, 54.65; H, 4.61; N, 9.15. Found: C, 55.29; H, 4.44; N, 9.34.

A portion of this material was dissolved in methanol and a solution of bromine in methanol was added until a brown color persisted. Concentration, filtration, and recrystallization yielded a sample which melted at 164.5–165°, and analyzed more satisfactorily for carbon than the previous material.

Anal. Found: C, 54.72; H, 4.39.

2-Methylpyrrolopyridazine-6-carboxylic acid (VIIIb). The adduct (6 g.) was refluxed for 30 minutes with a solution of 14 g. of potassium hydroxide in 30 ml. of water. The homogeneous yellow solution then was cooled and acidified. A white potassium salt separated; weight, 4.74 g. A 3-g. portion of this substance was heated on a steam-bath for 90 minutes with 30 ml. of 6 *N* hydrochloric acid. On cooling, 1.8 g. (82% yield based on the adduct) of the yellow mono acid separated; m.p. 224–226°. This material was further purified for analysis by sublimation; m.p. 225.5–226°.

Anal. Calc'd for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; Neut. equiv., 176. Found: C, 61.47; H, 4.45; Neut. equiv., 175.

It was converted to the *methyl ester* with diazomethane; m.p. 84–85°.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: N, 14.73. Found: N, 15.37.

The *ethyl ester* was prepared by heating the acid in absolute ethanol in the presence of a small amount of sulfuric acid: m.p. 67.5–68°. It did not depress the melting point of ethyl 2-methylpyrrolo[1,2-*b*]pyridazine-6-carboxylate prepared as indicated below.

Condensation of ethyl bromopyruvate and 3,6-dimethylpyridazine. Ethyl bromopyruvate, b.p. 70–76° (2–3 mm.), n_D^{24} 1.4690, was prepared by bromination of ethyl pyruvate.[2] The *2,4-dinitrophenylhydrazone* derivative melted at 144–145°.

Anal. Calc'd for $C_{11}H_{11}BrN_4O_6$: N, 14.92. Found: N, 14.74.

In addition to the bromopyruvate a considerable quantity of unidentified material, b.p. 77–80°, $n_D^{23.5}$ 1.4919 was isolated which did not react with 2,4-dinitrophenylhydrazine under the conditions used to prepare carbonyl derivatives.

The condensation reaction was carried out with 8.31 g. (0.77 mole) of 3,6-dimethylpyridazine and 15 g. (0.77 mole) of ethyl bromopyruvate by the procedure used by Borrows and Holland[2] for the preparation of pyrrocoline-3-carboxylic acid. There was isolated 0.6 g. of brownish powder, which after sublimation, was yellow and melted at 223–225°. No depression was observed in the melting point of a mixture of this acid and the monocarboxylic acid isolated from the hydrolysis of the 3-methylpyridazine—methyl acetylenedicarboxylate reaction.

From the non-acidic products there was obtained 60 mg. of ethyl methylpyrrolopyridazinecarboxylate, m.p. 67.5–68.5°.

Anal. Calc'd[8] for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.93; N, 13.72. Found: C, 64.72; H, 5.89; N, 14.27.

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EVANSTON, ILLINOIS

(8) The carbon, hydrogen, and nitrogen analyses reported in this paper were performed by Miss H. Beck and Miss C. White.