Condensed Pyridazines. Part III. Rearrangement and Ring Cyclization during the Thermolysis of (*Z*)-Methyl 3-(6-Azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate

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The thermolysis of (*Z*)-methyl 3-(6-azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (II) provides a new synthetic route to pyrrolo[2,3-*c*-]pyridazines, specifically, methyl 3-chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carboxylate (III) in 91% yield. Treatment of III with ozone provides an entry into the novel pyridazino[3,4-*d*][1,3]oxazine ring system, specifically, 3-chloro-1,7-dimethylpyridazino[3,4-*d*][1,3]oxazine-4,5-dione (IV) in 73% yield. Compound IV is smoothly hydrolyzed into 6-acetylamino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (V) which is readily recyclized into IV by dehydration with acetic anhydride. Furthermore, IV undergoes a facile reductive ring opening reaction with sodium borohydride to give 3-chloro-6-ethylamino-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (VI) in 95% yield.

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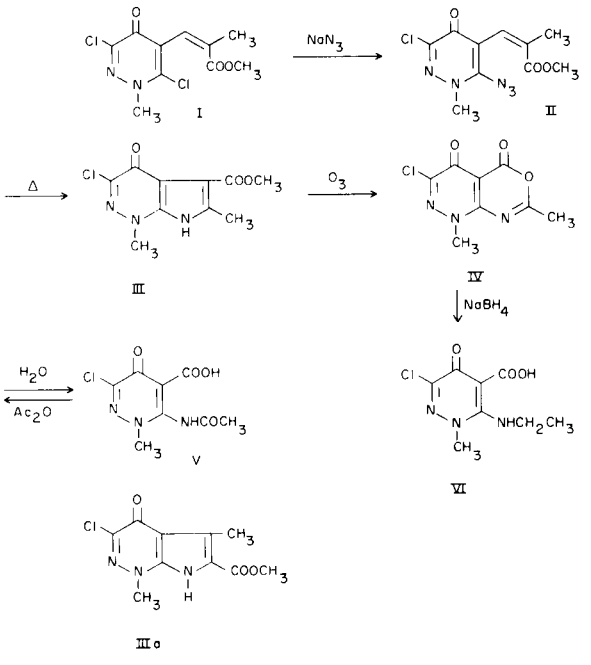
A number of pyrrolo[2,3-*d*]pyridazines (5,6-diazaindoles) have been prepared as potential antimetabolites of purine bases (1). However, pyrrolo[3,2-*c*]pyridazine and pyrrolo[2,3-*c*]pyridazine are members of a relatively unknown class of heterocyclic compounds (2). We, therefore, attempted to prepare a compound of these ring systems because of its structural relationship to the biologically important purines and indoles. A search of the literature revealed that the only representative of the synthesis of the pyrrolo[2,3-*c*]pyridazine ring system was reported by Lund and Gruhn which resulted from the reductive ring-opening of 8-chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c'*]dipyridazine (3). This method gave only a low yield of the desired product. There have been several reports describing the formation of 5-membered heterocycles *via* nitrene intermediates obtained by the thermal decomposition of aryl azides, and this type of synthesis appeared to be applicable to diazaindoles. We now describe applications of this type of reaction to the synthesis of pyrrolo[2,3-*c*]pyridazines (6,7-diazaindoles).

The starting azide II was prepared by nucleophilic displacement of the chlorine atom at C-6 of (*Z*)-methyl 3-(3,6-dichloro-1-methyl-4-oxo-1,4-dihydropyridazin-5--yl)-2-methylacrylate (I) (4) with sodium azide in dimethylsulfoxide. Compound II is somewhat unstable to light. Decomposition of the azide II in *o*-dichlorobenzene at 150-160° gave light yellow needles in a yield of 91%. The structure of this product was assigned as methyl 3-chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,-3-*c*]pyridazine-5-carboxylate (III) on the basis of the results described below. In the mass spectrum of the product, the parent peak was observed at m/e 255. The ir spectrum showed an absorption band at 3400 cm^{-1} and 1710 cm^{-1} attributed to a pyrrole ring NH and an ester carbonyl group, respectively. We have compared the nmr spectrum of the product with the nmr spectrum of the substrate, II. The substrate (II) showed signals at δ 2.17 (d, J = 1.5 Hz,

Scheme I



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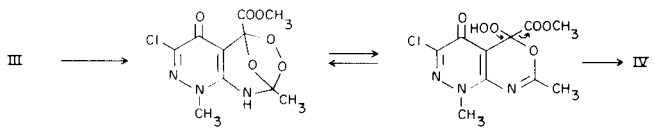
C-CH_3), 3.66 and 3.79 (s, N-CH_3 and O-CH_3) and 6.40 (q, J = 1.5 Hz, vinyl proton), while in the spectrum of the product, the vinyl proton signal disappeared and the C-CH_3 proton signal changed to a singlet. From these spectra, two probable structures (III and IIIa) suggest themselves as the reaction product; methyl 3-chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carboxylate (III) and methyl 3-chloro-1,5-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-6-carboxylate (IIIa) resulting from the migration of the ester group and the methyl group, respectively.

The confirmation of the structure was determined from the results of ozonolysis, decarbomethoxylation and reduction. It is well known that oxidative fissions of the indole 2-3 double bond have provided routes to 2-aminoarylketones. Other authors have used ozone in this oxidative fission (5). Thus we attempted the ozonolysis reaction in order to establish the structure of the reaction product.

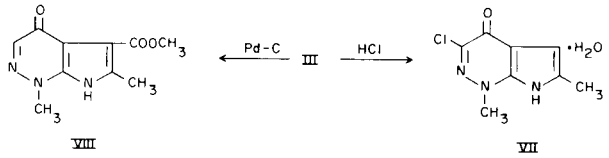
Treatment of the product in acetic acid with a large excess of ozone gave 3-chloro-1,7-dimethylpyridazino[3,4-*d*]-[1,3]oxazine-4,5-dione (IV) in 73% yield. The structure of this compound was established by elemental analysis, infrared, mass and nmr spectra (see Experimental). This ring structure is not listed in *Chemical Abstracts* and thus it appears to be a novel heterocyclic system. Compound IV was smoothly hydrolyzed providing the expected product, 6-acetylamino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (V), which was readily converted back into IV by dehydration with acetic anhydride. Reduction of IV with sodium borohydride in ethanol afforded 3-chloro-6-ethylamino-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic acid (VI) (Scheme 1). The proposed mechanism of this ozonolysis is that shown in Scheme 2.

Scheme 2



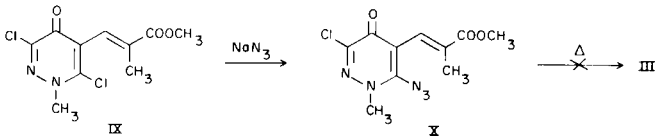
Moreover, the product was converted to 3-chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine (VII) by decarbomethoxylation with hydrochloric acid. The nmr spectrum of VII in DMSO-d_6 indicated a one proton singlet at δ 6.20 assigned as the C_5-proton. The use of hydrochloric acid for the decarbomethoxylation has been reported by Littell and Allen (6). Based on the above results, the position of the methyl and the ester group on the pyrrole ring on the product is effectively assigned as the methyl group to position 6 and the ester group to position 5. The product was catalytically dechlorinated with palladium on charcoal in acetic acid to give methyl 1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carboxylate (VIII) (Scheme 3).

Scheme 3



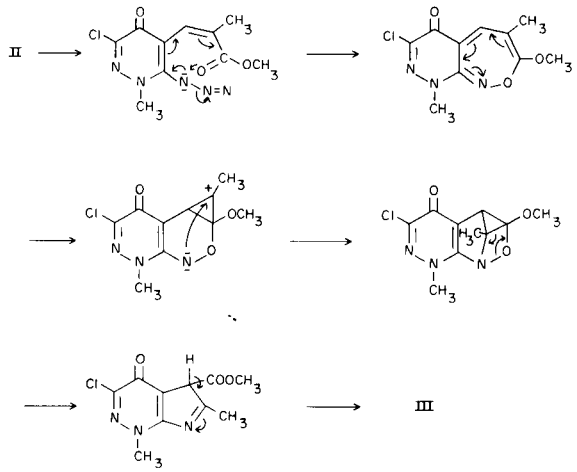
On the other hand, decomposition of (*E*)-methyl 3-(6-azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (X) under the same reaction conditions afforded an unidentified black mass (Scheme 4). These results indicate that the preference for ester

Scheme 4



migration may be determined by the stereochemical configuration of the azide. The rearranged product is best accounted for by a mechanism which involves cyclization by a concerted process (7) as illustrated in Scheme 5.

Scheme 5



EXPERIMENTAL

Melting points are uncorrected. The ir spectra were measured with a Jasco IRA-1 spectrometer and the nmr spectra were recorded on a JEOL-PS-100 spectrometer using TMS as an internal standard. Mass spectra were taken with a Hitachi M-52 spectrophotometer.

(*Z*)-Methyl 3-(6-Azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl) -2-methylacrylate (II).

Compound I (8.3 g.) and sodium azide (2.9 g.) in dimethylsulfoxide (90 ml.) were stirred for 2 hours at room temperature. The reaction mixture was poured into ice water and extracted wtih three 100 ml. portions of ethyl acetate and dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was triturated with ether to give II 8.0 g. (94%), m.p. 92-93°, suitable for use in the next

stage; ir (potassium bromide): 2110 cm^{-1} (N_3), 1715 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.17 (d, 3H, J = 1.5 Hz, C-CH_3), 3.66 (s, 3H, N-CH_3 or O-CH_3), 3.79 (s, 3H, N-CH_3 or O-CH_3), 6.40 (q, 1H, J = 1.5 Hz, vinyl proton).

Methyl 3-Chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo-[2,3-*c*]pyridazine-5-carboxylate (III).

Compound II (1.0 g.) was heated in *o*-dichlorobenzene (20 ml.) at 150-160° under a nitrogen atmosphere. Nitrogen was evolved at a moderate rate and the reaction was completed in 30 minutes. After being concentrated under reduced pressure, the brown precipitate was purified by recrystallization from water to give II 0.8 g. (91%), m.p. 254-255°; ms: m/e 255; ir (potassium bromide): 3400 cm^{-1} (NH), 1710 cm^{-1} (C=O); nmr (TFA): δ 2.88 (s, C-CH_3), 4.17 (s, N-CH_3), 4.43 (s, O-CH_3).

Anal. Calcd. for $C_{10}H_{10}ClN_3O_3$: C, 46.98; H, 3.94; N, 16.44. Found: C, 47.10; H, 3.88; N, 16.56.

3-Chloro-1,7-dimethylpyridazino[3,4-*d*][1,3]oxazine-4,5-dione (IV).

A current of ozonized oxygen was passed through a solution of 500 mg. of III in 50 ml. acetic acid for 1.5 hours. No cooling was applied. The solvent was removed under reduced pressure at 25°. The precipitate was recrystallized from acetone to colorless prisms of IV, 320 mg. (73%), m.p. 235-236°; ms: m/e 227; ir (potassium bromide): 1760 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.46 (s, C-CH_3), 3.87 (s, N-CH_3).

Anal. Calcd. for $C_8H_6ClN_3O_3$: C, 42.22; H, 2.66; N, 18.46. Found: C, 42.52; H, 2.51; N, 18.45.

6-Acetylamino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic Acid (V).

Compound IV (100 mg.) was added to 7 ml. of water and heated at 100° for 30 minutes. Water was removed under reduced pressure and the solid was recrystallized from chloroform-*n*-hexane to give colorless needles of V, 80 mg. (75%), m.p. 143-144°; ms: m/e 245; ir (potassium bromide): 3260 cm^{-1} (NH), 3000-2400 cm^{-1} (OH), 1720 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.38 (s, 3H, C-CH_3), 3.92 (s, 3H, N-CH_3), 11.12 (broad, 1H, NH), 15.00 (s, 1H, OH), 11.12 and 15.00 are deuterium oxide exchangeable.

Anal. Calcd. for $C_8H_8ClN_3O_4$: C, 39.12; H, 3.28; N, 17.11. Found: C, 39.27; H, 3.14; N, 17.07.

Dehydration of V into IV.

A mixture of 100 mg. of V and 5 ml. of acetic anhydride was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue was recrystallized from acetone to give IV. The identity was confirmed by comparing the ir spectra and by a mixed melting point.

3-Chloro-6-ethylamino-1-methyl-4-oxo-1,4-dihydropyridazine-5-carboxylic Acid (VI).

To a solution of 200 mg. of IV in ethanol was slowly added 150 mg. of sodium borohydride in 10 ml. of ethanol at room temperature. Mild effervescence was observed during the addition. Ten ml. of ethanol was then added and the mixture was stirred for 3 hours at room temperature. The reaction mixture was then cooled and decomposed with ice water. The solution was acidified with dilute sulfuric acid and extracted with chloroform and dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The solid was recrystallized from chloroform-*n*-hexane to give colorless needles of VI, 190 mg. (95%), 146-147°; ms: m/e 231; ir (potassium bromide): 2900-2800, 2550, 2220 cm^{-1} ($>\overset{+}{N}H_2$); nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_3), 3.52 (pentet-like multiplet, 2H, CH_2), 3.97 (s, 3H, N-CH_3), 9.63 (broad, 1H, NH), 15.50 (s, 1H, OH), 9.63 and 15.50 are deuterium oxide exchangeable.

Anal. Calcd. for $C_8H_{10}ClN_3O_3$: C, 41.48; H, 4.35; N, 18.14. Found: C, 41.54; H, 4.28; N, 18.13.

3-Chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine Hydrate (VII).

A mixture of 200 mg. of III and 20 ml. of concentrated hydrochloric acid was refluxed for 3 hours. After cooling, the precipitate was filtered off, washed with water, added to sodium bicarbonate solution and stirred for 5 hours at room temperature. The crystals were filtered off, washed with water and purified by recrystallization from water to give colorless needles of VII, 120 mg. (89%), m.p. > 300°; ms: m/e 197; ir (potassium bromide): 3400-2800 cm^{-1} (OH and NH), 1570 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.33 (s, 3H, C-CH_3), 3.30 (s, 3H, NH and H_2O), 3.92 (s, 3H, N-CH_3), 6.20 (s, 1H, C_5-H).

Anal. Calcd. for $C_8H_{10}ClN_3O_2$: C, 44.56; H, 4.67; N, 19.49. Found: C, 44.65; H, 4.53; N, 19.53.

Methyl 1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carboxylate (VIII).

A solution of III (1.0 g.) in acetic acid (10 ml.) was reduced catalytically using a palladium catalyst (Pd (5%) on carbon 200 mg.). After the uptake of an equimolar amount of hydrogen the catalyst was filtered off and the solvent removed under reduced pressure. The product was neutrallized by treatment with a sodium bicarbonate solution and extracted with chloroform which was dried and evaporated. The residue was recrystallized from chloroform-*n*-hexane to give colorless needles of VIII, 650 mg. (87%), m.p. 135-136°; ms: m/e 221; ir (potassium bromide): 3400 cm^{-1} (NH), 1700 cm^{-1}; nmr (deuteriochloroform): δ 2.77 (s, 3H, C-CH_3), 3.98 (s, 3H, N-CH_3), 4.37 (s, 3H, O-CH_3), 8.00 (s, 1H, C_3-H), 12.75 (broad, 1H, NH), 12.75 is deuterium oxide exchangeable.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 53.88; H, 4.84; N, 18.84.

(*E*)-Methyl 3-(6-Azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (X).

This compound was prepared from IX (4) as described above for II. The yield of X, m.p. 114-115°, was 85%; ir (potassium bromide); 2100 cm^{-1} (N_3), 1700 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.16 (d, 3H, J = 1.5 Hz, C-CH_3), 3.71 (s, 3H, N-CH_3 or O-CH_3), 3.93 (s, 3H, N-CH_3 or O-CH_3), 6.34 (q, 1H, J = 1.5 Hz, vinyl proton).

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