Condensed Pyridazines. Part I. Synthesis of 2-Oxo-2*H*-pyrano[2,3-*d*]-pyridazine and 2-Oxo-2*H*-pyrano[2,3-*c*]pyridazine (1)

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The reaction of 4,7-dichlorofuro[2,3-*d*]pyridazine (I) with potassium cyanide in DMSO gave two products, (*E*)-3,6-dichloro-5-(2-cyanovinyl)-4-hydroxypyridazine (II) and 5,8-dichloro-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine (III) as a result of ring opening or ring expansion. A new ring system, 2-oxo-2*H*-pyrano[2,3-*c*]pyridazines (IX, XII, XIII) was obtained from 5,8-dichloro-3-methyl-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine (VI).

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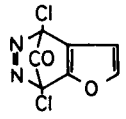
In a continuation of our search for biologically active furo[2,3-*d*]pyridazine derivatives (2), it became necessary to re-examine the structure of the carbonyl bridge compound **A** which was obtained by the reaction of 4,7-



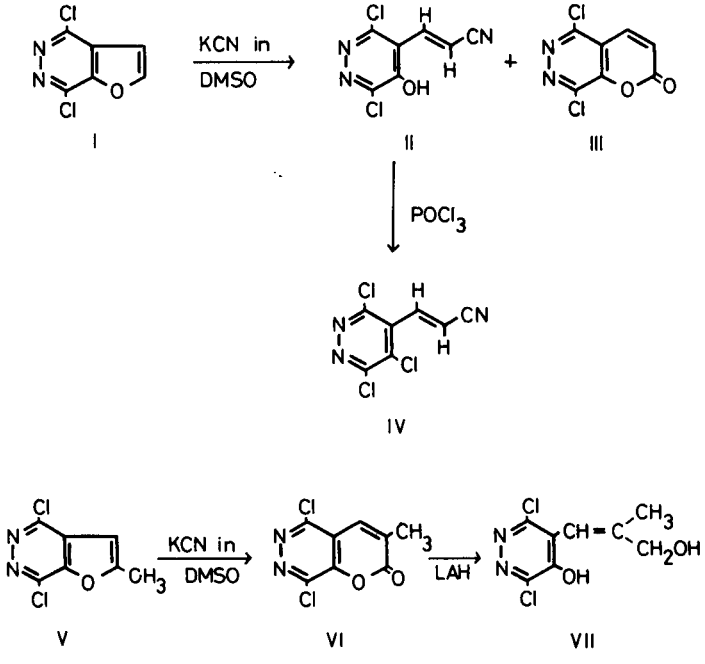
A

dichloro-2-methylfuro[2,3-*d*]pyridazine (V) with potassium cyanide in dimethylsulfoxide (DMSO) (3). This paper deals with the correct assignment of compound **A** as 5,8-dichloro-3-methyl-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine (VI).

Recently, the synthesis of pyrano[2,3-*c*]pyrazolone derivatives as useful cardiovascular agents were reported by Sato, *et al.* (4). This report prompted us to investigate the synthesis of pyrano[2,3-*c*]pyridazines, which appeared to have some biological activities. For the synthesis of pyrano[2,3-*c*]pyridazines, compound VI served as the starting material. The reaction proceeds with ring opening followed by cyclization. This apparently is the first reported example of the pyrano[2,3-*c*]pyridazine ring system.

2-Oxo-2*H*-pyrano[2,3-*d*]pyridazines.

Reaction of 4,7-dichlorofuro[2,3-*d*]pyridazine (I) (5) with potassium cyanide in DMSO at room temperature gave two products, colorless needles of m.p. 226-227° (II) and colorless needles of m.p. 142-143° (III), in yields of 35% and 9%, respectively. Elemental analysis and mass spectral data of II agreed with $C_7H_3Cl_2N_3O$ and its ir spectrum showed absorption bands at 2800-3200 cm^{-1} (OH) and 2250 cm^{-1} (CN). The nmr spectrum of II (measured in deuteriodimethylsulfoxide) showed an AB quartet at δ 7.24 and 7.43 (J = 16 Hz) due to the vinyl proton. From these spectral data and elemental analysis it seems reasonable to assume that II is 3,6-dichloro-5-(2-cyanovinyl)-4-hydroxypyridazine. The configuration of II can be assigned as the *E* form because of the J value. Chlorination of II with phosphorus oxychloride gave 3,4,6-trichloro-5-(2-cyanovinyl)pyridazine (IV) in 55% yield. Elemental analysis and mass spectral data of III agreed with $C_7H_2Cl_2N_2O_2$ and its ir spectrum showed an absorption band at 1780 cm^{-1} (CO). Its nmr spectrum (measured in deuteriodimethylsulfoxide) showed an AX pattern at δ 7.07 and 8.12 (J = 10 Hz) due to the vinyl proton on the pyrone ring (6). From these spectral data and elemental analysis it seems reasonable to assume that III is 5,8-dichloro-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine. This fact suggests that the structure of compound **A** belongs to the 2-oxo-2*H*-pyrano[2,3-*d*]pyridazine ring system. It is well known that coumarin forms *o*-hydroxycinnamyl

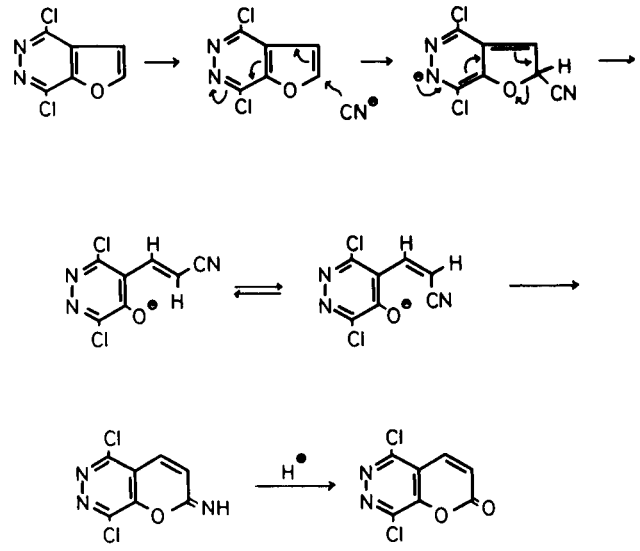


Scheme 1

0022-152X/79/020245-03$02.25

alcohol by reduction with lithium aluminium hydride (LAH) (7). It was expected that VI would react similarly with LAH to form 3,6-dichloro-4-hydroxy-5-(2-hydroxymethylprop-1-enyl)pyridazine (VII). In fact, treatment of VI with LAH gave VII in a yield of 32% (Scheme 1).

The above results indicate that cyanation of I and V would occur preferentially at the C-2 position under these conditions. The mechanism of this transformation is proposed as shown in Scheme 2.



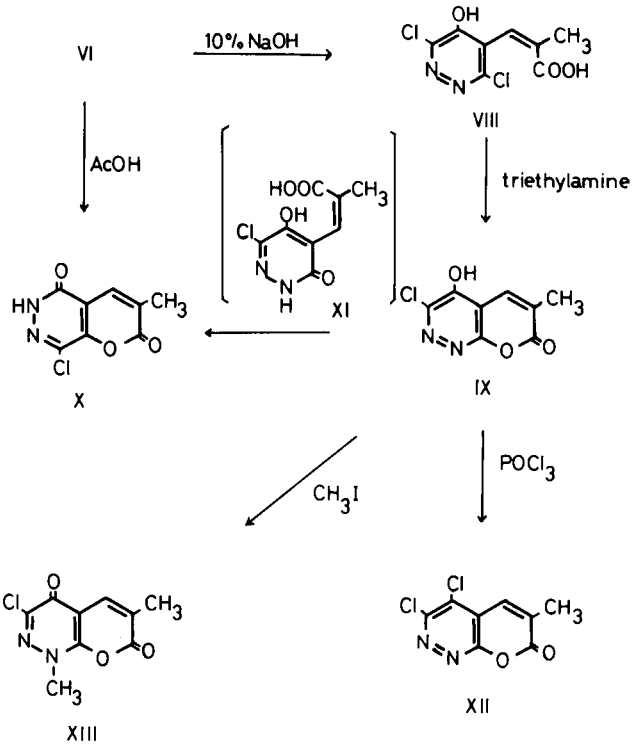
Scheme 2

2-Oxo-2*H*-pyrano[2,3-*c*]pyridazines.

When compound VI was treated with 10% sodium hydroxide solution at room temperature, (*Z*)-3-(3,6-dichloro-5-hydroxypyridazin-4-yl)-2-methylacrylic acid (VIII) was obtained in high yield. Attempted purification of VIII failed due to its thermal instability, however, the formation of VIII was proven by its ir and nmr spectral data. Intramolecular cyclization of VIII with triethylamine in methanol afforded 6-chloro-5-hydroxy-3-methyl-2-oxo-2*H*-pyrano[2,3-*c*]pyridazine (IX) in 82% yield. The structure of IX is based on the following evidence: the molecular ion in the mass spectrum of IX appears at m/e 212 and the nmr spectrum consists of a quartet at δ 7.80 (1H, J = 1 Hz) and a doublet at δ 2.08 (3H, J = 1 Hz).

Treatment of lactone IX with 10% sodium hydroxide solution followed by acidification with dilute hydrochloric acid afforded 3-chloro-3-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine (X), instead of the ring opened compound XI. Compound X was identical with the product which was obtained by the hydrolysis of VI with acetic acid.

Finally, in order to be able to expand the chemistry of pyrano[2,3-*c*]pyridazine, we attempted the chlorination



Scheme 3

and alkylation of IX (Scheme 3). Examination of the biological activities of these compounds are now under investigation.

EXPERIMENTAL

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

(*E*)-3,6-Dichloro-5-(2-cyanovinyl)-4-hydroxypyridazine (II) and 5,8-Dichloro-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine (III).

Compound I (1.0 g.), potassium cyanide (0.6 g.) and dimethylsulfoxide (20 ml.) were stirred for 6 hours at room temperature, and the resulting brown solution was allowed to stand for 3 days. After the reaction mixture was poured into ice water the solution was acidified with hydrochloric acid solution. The brown precipitate was filtered and purified by recrystallization from acetone to give II, 0.4 g. (35%), m.p. 226-227°; ms: m/e 215 (M^+).

Anal. Calcd. for $C_7H_3Cl_2N_3O$: C, 38.92; H, 1.40; N, 19.45. Found: C, 39.01; H, 1.11; N, 19.13.

The filtrate was extracted three times with chloroform, washed with water and dried with anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crystalline residue was recrystallized from methanol to give III, 0.1 g. (9%), m.p. 142-143°; ms: m/e 216 (M^+).

Anal. Calcd. for $C_7H_2Cl_2N_2O_2$: C, 38.74; H, 0.93; N, 12.91. Found: C, 38.63; H, 0.69; N, 12.71.

(*E*)-3,4,6-Trichloro-5-(2-cyanovinyl)pyridazine (IV).

Compound II (0.1 g.), phosphorus oxychloride (5 ml.) and

dimethylaniline (1 drop) were heated at 130° for 2 hours. The solvent was removed *in vacuo* and the residue was poured into ice water. The precipitate was filtered, washed with cold water and dried over anhydrous calcium chloride *in vacuo*. The precipitate was recrystallized from methanol to give colorless prisms of IV 60 mg. (55%), m.p. 136-137°; ms: m/e 233 (M^+); nmr (deuteriodimethylsulfoxide): δ 6.14 (d, 1H, J = 16 Hz), 7.65 (d, 1H, J = 16 Hz).

Anal. Calcd. for $C_7H_2Cl_3N_3$: C, 35.85; H, 0.86; N, 17.92. Found: C, 35.64; H, 1.03; N, 18.25.

3,6-Dichloro-4-hydroxy-5-(2-hydroxymethylprop-1-enyl)pyridazine (VII).

A solution of VI (2.0 g.) in dry tetrahydrofuran (100 ml.) was added at 0° over 20 minutes to a stirred mixture of lithium aluminium hydride (0.7 g.) and tetrahydrofuran (150 ml.) and set aside at room temperature for 1 hour. The complex was decomposed with water, acidified with 10% sulfuric acid and extracted three times with chloroform. The extract was dried with anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residue from water gave 0.7 g. (32%) of colorless needles of VII, m.p. 146-147°; ms: m/e 234 (M^+); nmr (deuteriopyridine): δ 2.15 (d, 3H, J = 1.0 Hz, CH_3), 4.48 (s, 2H, CH_2), 6.09 (q, 1H, J = 1.0 Hz, vinyl), 11.3 (very broad, 2H, OH, exchangeable with deuterium oxide); ir (potassium bromide): 3400-2800 cm^{-1} (OH).

Anal. Calcd. for $C_8H_8Cl_2N_2O_2$: C, 40.88; H, 3.43; N, 11.92. Found: C, 40.87; H, 3.25; N, 11.62.

(*Z*)-3-(3,6-Dichloro-5-hydroxypyridazin-4-yl)-2-methylacrylic acid (VIII).

A mixture of 5.0 g. (0.02 mole) of VI and 40 ml. of 10% sodium hydroxide solution was stirred for 1 hour at room temperature. The solution was acidified with concentrated hydrochloric acid and the resulting crystals were filtered, washed with water, and dried in air, giving a crude product (5.0 g., 95%) suitable for use in the next stage; ir (potassium bromide): 3150-2580 cm^{-1} (broad, OH), 1680 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.08 (d, 3H, J = 1.5 Hz, CH_3), 6.23 (q, 1H, J = 1.5 Hz, vinyl).

6-Chloro-5-hydroxy-3-methyl-2-oxo-2*H*-pyrano[2,3-*c*]pyridazine (IX).

A mixture of 1.0 g. (0.0047 mole) of VIII, 1 ml. of triethylamine and 10 ml. of methanol was refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was added to water. The solution was acidified with concentrated hydrochloric acid and the resulting crystals were filtered, washed with water, and recrystallized from methanol to give colorless prisms of IX, 750 mg. (82%), m.p. 289-290°; ms: m/e 212 (M^+); ir (potassium bromide): 1750 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.08 (d, 3H, J = 1.0 Hz, CH_3), 7.80 (q, 1H, J = 1.0 Hz, ring proton 4 position).

Anal. Calcd. for $C_8H_5ClN_2O_3$: C, 45.20; H, 2.37; N, 13.18. Found: C, 45.24; H, 2.17; N, 13.06.

8-Chloro-3-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine (X).

A mixture of 100 mg. (0.0005 mole) of I and 5 ml. of acetic acid was heated at 120° for 3 hours. The solvent was removed under reduced pressure and the residue was poured into ice. The precipitate was filtered, washed with water and recrystallized from methanol to give 700 mg. (75%) of colorless needles, of X, m.p. 245-246°; ms: m/e 212 (M^+); ir (potassium bromide): 1740 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 13.8 (broad, 1H, OH), 7.85 (q, 1H, J = 1.5 Hz, ring proton 4 position), 2.18 (d, 3H, J = 1.5 Hz, CH_3).

Anal. Calcd. for $C_8H_5ClN_2O_3$: C, 45.20; H, 2.37; N, 13.18. 0.22.58. Found: C, 45.63; H, 2.21; N, 13.22; O, 23.09.

Conversion of IX into X.

The procedure described for the preparation of VIII was repeated with IX giving a 90% yield of X. Identity was confirmed by comparing the ir spectra and a mixed melting point determination.

5,6-Dichloro-3-methyl-2-oxo-2*H*-pyrano[2,3-*c*]pyridazine (XII).

A mixture of 100 mg. (0.0005 mole) of IX and 3 ml. of phosphorus oxychloride was heated for 1 hour at 120°. The reaction mixture was poured into ice water. The solution was extracted with three 10 ml. portions of chloroform and dried with anhydrous magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residue from methanol gave 55 mg. (50%) of colorless prisms of XI, m.p. 181-182°; ms: *m/e* 230 (M^+); nmr (deuteriodimethylsulfoxide): 2.26 (d, 3H, J = 1.0 Hz, CH_3), 8.00 (q, 1H, J = 1.0 Hz, ring proton 4 position).

Anal. Calcd. for $C_8H_4Cl_2N_2O_2$: C, 41.59; H, 1.75; N, 12.13. Found: C, 41.66; H, 1.59; N, 12.10.

6-Chloro-3,8-dimethyl-2,5-dioxo-5,8-dihydro-2*H*-pyrano[2,3-*c*]-pyridazine (XIII).

A mixture of 210 mg. (0.001 mole) of IX, 150 mg. of anhydrous potassium carbonate, 500 mg. of methyl iodide and 3 ml. of hexamethylphosphoric triamide was stirred for 1 hour at room temperature. The excess of methyl iodide was removed under reduced pressure and the residue was added to water. The solution was extracted with three 10 ml. portions of ethyl acetate and dried with anhydrous magnesium sulfate and evaporated. Recrystallization of the residue from methanol gave 200 mg. (89%) of colorless needles (XIII), m.p. 243-244°; ms: *m/e* 226 (M^+); nmr (deuteriochloroform): 2.28 (d, 3H, J = 1.0 Hz, 3-CH_3), 7.80 (q, 1H, J = 1.0 Hz, ring proton 4 position); ir (potassium bromide): 1740 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_7ClN_2O_3$: C, 47.70; H, 3.11; N, 12.36. Found: C, 47.76; H, 2.93; N, 12.30.

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