Reductive Cyclization of (*Z*)-Methyl 3-(6-Azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (I) to Pyrido[2,3-*c*]pyridazines and the Acid-Catalysed Cyclization of I to a Pyrano[2,3-*d*]pyridazine

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Reduction followed by cyclization of (*Z*)-methyl 3-(6-azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (I) to pyrido[2,3-*c*]pyridazines by treatment with triethyl phosphite or hydrazine hydrate as the reducing agents is described. Compound I was also reductively cyclized with sodium borohydride. Treatment of I with concentrated sulfuric acid gave 8-chloro-3,6-dimethyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine (VII) which also could be synthesized by another independent route. A mechanism for the cyclization is proposed.

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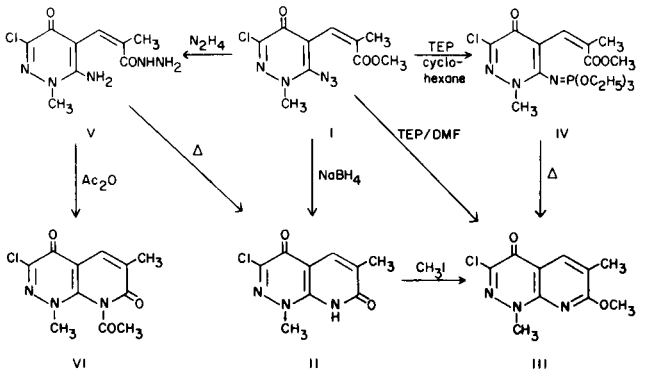
We have recently reported that the thermoylsis of (*Z*)-methyl 3(6-azido-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (I) gave the rearranged cyclization product, methyl 3-chloro-1,6-dimethyl-4-oxo-1,4-dihydro-7*H*-pyrrolo[2,3-*c*]pyridazine-5-carboxylate (1). Although the cyclization of azido derivatives leading to five-membered heterocycles are well known (2), less attention has been paid to the cyclization to six-membered rings (3). As our interest continues in cyclizations of the azido compound I, we now describe the simple reductive cyclization of I to pyrido[2,3-*c*]pyridazines, by treatment with sodium borohydride. Treatment of I with triethyl phosphite or hydrazine hydrate gave intermediates which could then be cyclized with appropriate reagents into pyrido[2,3-*c*]pyridazines. The acid-catalysed cyclization of I to a pyrano[2,3-*d*]pyridazine by sulfuric acid has also been observed.

Scheme I



Reductive Cyclization of I.

Treatment of I with sodium borohydride in methanol at room temperature afforded 3-chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido[2,3-*c*]pyridazine (II) in 93% yield. The structure of II was shown to be identical with an authentic sample prepared by the reaction of (*Z*)-methyl 3(3,6-dichloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate with 80% hydrazine hydrate followed by a deamination reaction (4). Compound II reacts with methyl iodide in dimethyl sulfoxide to afford the *O*-methylated compound III, m.p. 210-211°, in 88% yield. None of the *N*-methylated compound was obtained. Compound III was identical with the product which was obtained by the reaction of 3,7-dichloro-1,6-dimethyl-4-oxo-1,4-dihydropyrido[2,3-*c*]pyridazine (4) with sodium methoxide. To the best of our knowledge, this is the first example of the reductive cyclization of an azido compound by sodium borohydride.

On the other hand, Foster, *et al.*, (5) reported that irradiation of the phosphorimidate of 2-azidocinnamates gave 2-substituted quinolines. Therefore, another cyclization leading to the pyrido[2,3-*c*]pyridazine ring system was considered to be possible by thermolysis of the (*Z*)-form (I) with triethyl phosphite. Treatment of I with triethyl phosphite in dimethylformamide gave the expected product (III) in 59% yield. The phosphorimidate intermediate (IV) of this reaction was obtained by treatment of I with triethyl phosphite in cyclohexane. Compound IV was also cyclized to III in dimethylformamide. Attempts to prepare III from irradiation of IV with a 100 W high-pressure mercury arc lamp was unsuccessful.

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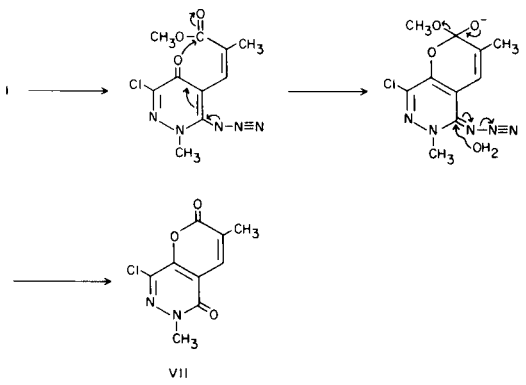
Scheme 2



VII

The formation of benzo[*f*]indazolin-3-one has been obtained by treating methyl 3-azido-2-naphthoate with hydrazine hydrate in ethanol (6). Recently, Paterson, *et al.*, (7) proposed the mechanism of this cyclization involving the tautomeric pentazene followed by loss of nitrogen and ammonia. We have also investigated the reaction of I with hydrazine hydrate in ethanol and the product was not the expected diazepine but the amino compound 3(6-amino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylhydrazide (V), m.p. > 310°, in 64% yield. Thermolysis of V in dimethylformamide gave the cyclization product II in 90% yield. Treatment of V with acetic anhydride gave the *N*-acetylated cyclization product VI. The structure of V and VI were assigned from the spectral data and elemental analyses. These cyclizations take place with extreme ease and the yields were high.

Acid-Catalysed Cyclization of I.

The acid-catalysed decomposition of aryl azides has been studied from a number of points of view, the objectives being mainly synthetic or mechanistic (8). These reports prompted us to investigate the decomposition of I by treatment with sulfuric acid. Treatment of the azide (I) with concentrated sulfuric acid at room temperature gave VII, as colorless needles m.p. 234-235°, in 79% yield. Elemental analysis and the mass spectral data of this compound agree with $C_9H_7ClN_2O_3$ and the ir spectrum showed an absorption band at 1730 cm^{-1} (C=O). The nmr spectrum (deuteriochloroform) exhibited signals at δ 2.28 (d, 3H, J = 1.5 Hz, C-CH_3), 3.79 (s, 3H, N-CH_3) and 7.83 (q, 1H, J = 1.5 Hz, ring proton). The nmr spectrum is very similar to that of 6-chloro-3,8-dimethyl-2,5-dioxo-5,8-dihydro-2*H*-pyrano[2,3-*c*]pyridazine (9). From these spectral findings and the elemental analysis, it seems reasonable to assume that VII is 8-chloro-3,6-dimethyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine. Compound VII was identical with the product which was obtained by methylation of 8-chloro-3-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine (9). A possible reaction mechanism for the formation of VII is suggested in Scheme 2.

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 tetramethylsilane as an internal standard. The mass spectra were taken with a Hitachi M-52 spectrophotometer.

Reaction of I with Sodium Borohydride.

To a solution of 850 mg. (2.69 mmoles) of I and 30 ml. of methanol was added in a small portions 240 mg. (3.08 mmoles) of sodium borohydride with stirring at room temperature. Stirring was continued for an additional one hour. The solvent was removed under reduced pressure and the residue was added to water and acidified with acetic acid. The precipitate was filtered, washed with water and recrystallized from methanol to give II, 630 mg. (93%), m.p. >310°. The identity of II was confirmed by comparing the ir spectra.

3-Chloro-7-methoxy-1,6-dimethyl-4-oxo-1,4-dihydropyrido[2,3-*c*]-pyridazine (III).

A mixture of 250 mg. (1.1 mmoles) of II, 200 mg. (1.45 mmoles) of anhydrous potassium carbonate, 0.5 ml. (2.9 mmoles) of methyl iodide and 5 ml. of dimethyl sulfoxide was stirred for two hours at room temperature. The excess 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 over anhydrous magnesium sulfate and evaporated. The solid was recrystallized from chloroform and *n*-hexane to give colorless needles of III, 210 mg. (88%), m.p. 210-211°; ms: m/e 239 (M^+); ir (potassium bromide): 1610 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.27 (d, 3H, J = 1.5 Hz, C-CH_3), 4.05 (s, 6H, O-CH_3 and N-CH_3), 8.14 (q, 1H, J = 1.5 Hz, ring proton, 5 position).

Anal. Calcd. for $C_{10}H_{10}ClN_3O_2$: C, 50.12; H, 4.21; N, 17.53. Found: C, 50.35; H, 4.17; N, 17.47.

Methylation of 3,7-dichloro-1,6-dimethyl-4-oxo-1,4-dihydropyrido[2,3-*c*]pyridazine with sodium methoxide in the usual manner gave III. The identity was confirmed by comparing the ir spectra and a mixed melting point determination.

Reaction of I with Triethyl Phosphite in Dimethylformamide.

A mixture of 100 mg. (0.32 mmole) of I, 0.5 ml. of triethyl phosphite and 3 ml. of dimethylformamide was refluxed for two hours. The solvent was removed under reduced pressure. Purification of the residue by preparative tlc (developing with chloroform) and crystallization from chloroform and *n*-hexane gave colorless needles of 3-chloro-1,6-dimethyl-7-methoxy-4-oxo-1,4-dihydropyrido[2,3-*c*]pyridazine (III), 50 mg. (59%), m.p. 210-211°. The identity was confirmed by comparing the ir spectra and by a mixed melting point determination.

Reaction of I with Triethyl Phosphite in Cyclohexane.

A solution of I (100 mg., 0.32 mmole) in 0.2 ml. of chloroform was added to a stirred mixture of 0.5 ml. of triethyl phosphite and cyclohexane (3 ml.) and allowed to stand at room temperature for three hours. The solvent was removed under reduced pressure and the solid was recrystallized from ether to give colorless needles of IV, 130 mg. (93%), m.p. 90-91°; nmr (deuteriochloroform): δ 1.33 (t, 9H, J = 7.5 Hz, -CH_2CH_3), 2.05 (d, 3H, J = 1.5 Hz, C-CH_3), 3.58 (s, 3H, N-CH_3 or O-CH_3),

3.70 (s, 3H, N-CH_3 or O-CH_3), 4.03 (q, 6H, J = 7.5 Hz, -CH_2CH_3), 6.17 (q, 1H, J = 1.5 Hz, vinyl H).

Anal. Calcd. for $C_{16}H_{25}ClN_3O_6P$: C, 45.56; H, 5.97; N, 9.96. Found: C, 45.49; H, 6.21; N, 9.74.

Cyclisation of Phosphorimidate (IV) to III.

The procedure described for the reaction of I with triethyl phosphite in dimethylformamide was repeated with IV giving a 60% yield of III. The identity was confirmed by comparing the ir spectra and by a mixed melting point determination.

Reaction of I with 80% Hydrazine Hydrate. Preparation of 3-(6-Amino-3-chloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylhydrazide (V).

A mixture of 500 mg. (1.58 mmoles) of I, 1 ml. of 80% hydrazine hydrate and 10 ml. of methanol was stirred at room temperature for three hours. The precipitate was filtered and recrystallized from methanol to give colorless needles of V, 310 mg. (64%), m.p. > 310°; ir (potassium bromide): 3260, 3170, 3000-2600 cm^{-1} (NH_2 and $NHNH_2$), 1600 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_{12}ClN_5O_2$: C, 41.95; H, 4.69; N, 27.18. Found: C, 42.18; H, 4.66; N, 26.95.

Cyclisation of V to II.

A mixture of 100 mg. (0.39 mmole) of V and 3 ml. of dimethylfofmamide was heated at 120° for two hours. The solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol to give colorless needles of II, 75 mg. (90%), m.p. >310°. Identity was confirmed by comparing the ir spectra.

Reaction of V with Acetic Anhydride. Preparation of 8-Acetyl-3-chloro-1,6-dimethyl-1,4,7,8-tetrahydropyrido[2,3-*c*]pyridazine-4,7-dione (VI).

A mixture of 270 mg. (1.05 mmoles) of V and 10 ml. of acetic anhydride was heated at 140° for one hour. The solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol to give colorless needles of VI, 260 mg. (97%), m.p. 169-170°; ms: m/e 267 (M^+); ir (potassium bromide): 1760, 1615 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.33 (d, 3H, J = 1 Hz, C-CH_3), 2.40 (s, 3H, $COCH_3$), 4.05 (s, 3H, N-CH_3), 8.47 (q, 1H, J = 1.0 Hz, ring proton, 5 position).

Anal. Calcd. for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.45; H, 3.61; N, 15.53.

Reaction of I with Concentrated Sulfuric Acid.

A mixture of 100 mg. (0.32 mmole) of I and 1 ml. of concentrated sulfuric acid was stirred at room temperature for two hours. The reaction mixture was poured into ice water and neutralized with sodium bicarbonate. The solution was extracted with three 10 ml. portions of chloroform and dried with anhydrous magnesium sulfate and evaporated. The solid was recrystallized from methanol to give colorless needles of VII, 60 mg. (75%), m.p. 234-235°. The identity was confirmed by comparing the ir spectra and by a mixed melting point determination.

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

This compound was prepared from 260 mg. (1.22 mmoles) of 8-chloro-3-methyl-2,5-dioxo-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine (9), 200 mg. (1.45 mmoles) of anhydrous potassium carbonate, 1 ml. (5.8 mmoles) of methyl iodide and 5 ml. of dimethyl sulfoxide as described for III above. The yield of VII, m.p. 234-235°, was 230 mg. (83%); ms: m/e 226 (M^+).

Anal. Calcd. for $C_9H_7ClN_2O_3$: C, 47.70; H, 3.11; N, 12.36. Found: C, 47.83; H, 3.05; N, 12.27.

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