[Contribution from the Chemical Corps, U. S. Army]

ACYLATION OF 3,6-PYRIDAZINEDIONES

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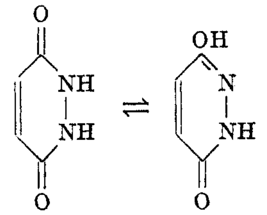
Received July 21, 1953

A study of the reactions undergone by cyclic hydrazides led Arndt (1) in conjunction with the work of others (2–4) to postulate the following tautomerism for maleic hydrazide (1,2-dihydro-3,6-pyridazinedione) (I):



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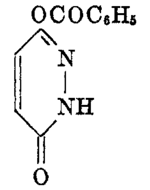

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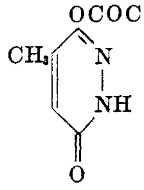

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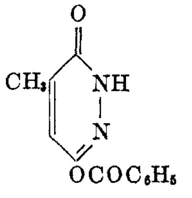

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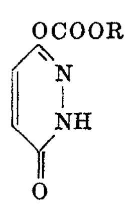

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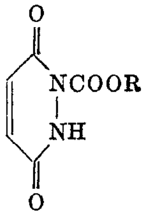

VI

Cyclic hydrazides are known to yield O-methyl derivatives with diazomethane (1), O-acetyl derivatives with acetic anhydride (5), and monometallic salts with bases, but unstable dimetallic salts are prepared only with difficulty (6), or not at all (1, 5). Since these reactions resemble those of phenols to a great extent, it was thought probable that acylation of these compounds might proceed quite easily. Consequently, the action of some acyl chlorides upon the 3,6-pyridazinedione ring system was investigated.

Acylation was attempted by various means, using alkyl chlorocarbonates and benzoyl chloride. These compounds were chosen because of the ease with which they enter a Schotten-Baumann reaction. Attempts to react I with chlorocarbonates using sodium ethoxide or potassium carbonate as a condensing agent, or by the use of the sodium salt of I in a solvent all failed, and only tarry products of undetermined composition were obtained.

Using alkyl chlorocarbonates and I in pyridine at room temperature resulted in the decomposition of the chlorocarbonate. At 0°, no decomposition was apparent as evidenced by effervescence, but no identifiable products other than I and pyridine hydrochloride could be isolated upon evaporating the pyridine *in vacuo*. Under the same conditions, benzoyl chloride and I in pyridine gave 2,3-dihydro-3-oxo-6-pyridazinyl benzoate (II).

The Schotten-Baumann reaction in dilute sodium hydroxide solution gave excellent results with both benzoyl chloride and chlorocarbonates. With the former, II was obtained as with pyridine. When hydrazides containing a subsituent in the 4 position were used, apparently only one isomer was obtained in each case (either III or IV), since the melting point was not appreciably changed upon recrystallization; but its structure was not determined. The reaction failed however, with succinic hydrazide, which has been claimed not to enolize (1). With chlorocarbonates there were formed alkyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonates (V). The evidence for this type of structure instead of VI has been presented by Thiele (7), Arndt (1), Ruggli (6), and others (3, 4, 8) and will not be discussed here.

3,6-Pyridazinediones in pyridine with these acylating agents gave rise to intense colors when the reactants were poured together. This coloration was intensified upon heating. An attempt was made to isolate the pigment, but with no success. If used as a test, the production of the color seemed to require at least 50 mg. of I. Succinic hydrazide gave an intense red color under these conditions.

In general, cyclic hydrazides derived from maleic acid reacted with benzoyl chloride and alkyl chlorocarbonates to give substituted 2,3-dihydro-3-oxo-6-pyridazinyl esters.

Acknowledgement. The authors wish to express their thanks to Dr. B. Warshowsky for the nitrogen analyses.

EXPERIMENTAL PART

All melting points were taken on a Fisher-Johns apparatus and are corrected. Nitrogen analyses were done by the Dumas method.

General method for the preparation of 2,3-dihydro-3-oxo-6-pyridazinyl carbonates. Maleic hydrazide (Naugatuck Chemicals, Naugatuck, Conn.) (11.2 g., 0.1 mole) and 5.6 g. (0.1 mole) of potassium hydroxide were dissolved in 75 ml. of water, with slight heating on the steam-bath to aid dissolution. Chlorocarbonate (0.1 mole) was added after cooling, and the resulting mixture intermittently was shaken until it solidified. This usually took about an hour. The resulting white mass was filtered with suction and washed with about 200 ml. of ligroin to free it from unreacted chlorocarbonate. Crystallization was accomplished from a suitable solvent, yielding the product, which was washed several times with petroleum ether (30–60°) and air-dried.

Ethyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate gave colorless crystals from benzene, yield 6.9 g. (33%), m.p. 106–108°. It was soluble in water, ethanol, and chloroform; insoluble in ether, benzene, and carbon tetrachloride.

Anal. Calc'd for $C_7H_8N_2O_4$: N, 15.20. Found: N, 15.37.

β-Chloroethyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate gave colorless crystals from benzene, yield 14.0 g. (56%), m.p. 103.3–104.8°. The compound was soluble in acetic acid, insoluble in ether and carbon tetrachloride. It was slightly soluble in benzene, ethanol, and chloroform.

Anal. Calc'd for $C_7H_7ClN_2O_4$: N, 12.83. Found: N, 12.77.

γ-Chloropropyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate gave colorless lustrous plates and needles from benzene-ligroin (*d.* 0.67–0.69); yield 11.2 g. (43%), m.p. 99.2–100.7°. It was soluble in benzene, acetic acid, and chloroform; slightly soluble in ether, and carbon tetrachloride.

Anal. Calc'd for $C_8H_9ClN_2O_4$: N, 12.01. Found: N, 11.96.

n-Propyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate. Crystallization from benzene-ligroin gave an oil which solidified on cooling, with a further deposition of well-defined crystals from the mother liquor. A better crystallization was accomplished by dissolving the crude material in hot benzene, filtering off the insoluble material, and cooling the resultant solution below 10°. Cold ligroin (*d.* 0.67–0.69) was added portionwise with further lowering of the temperature until a turbidity was evident. The resulting mixture was allowed to stand in a refrigerator for 30 minutes, then was filtered and washed with petroleum ether (30–60°) to give small colorless crystals, which were air-dried. Yield, 8.0 g. (41%); m.p. 79.7–81°. It was soluble in the usual organic solvents, but was insoluble in carbon tetrachloride, ligroin, and water.

Anal. Calc'd for $C_8H_9N_2O_4$: N, 14.20. Found: N, 14.21.

n-Butyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate was crystallized as above, giving a fine crystalline powder, yield 8.0 g. (38%); m.p. 84–85°. This was soluble in organic solvents and slightly soluble in carbon tetrachloride. It was insoluble in water and ligroin.

Anal. Calc'd for $C_9H_{12}N_2O_4$: N, 13.25. Found: N, 13.32.

Isobutyl 2,3-dihydro-3-oxo-6-pyridazinyl carbonate was crystallized as above, giving fine lustrous plates. Yield, 8.0 g. (38%), m.p. 76–77°. The compound was soluble in organic solvents but was insoluble in water and ligroin.

Anal. Calc'd for $C_9H_{12}N_2O_4$: N, 13.25. Found: N, 13.00.

1,2-Dihydro-4-methyl-3,6-pyridazinedione (citraconic hydrazide). To 11.2 g. (0.1 mole) of citraconic anhydride in 50 ml. of absolute ethanol was added 6.0 g. (0.1 mole) of 85% hydrazine hydrate. An immediate yellow coloration was produced with the evolution of heat. The resulting solution was refluxed on the steam-bath for several hours, whereupon a yellow solid precipitated. This was filtered with suction, washed well with absolute alcohol to decolorize it, and dried in an oven at 100° for 2 hours. A white crystalline powder was obtained, yield 7.5 g. (67%); m.p. 289–290° with decomposition. Freri (9) reported this compound to be pink with m.p. 277°.

Anal. Calc'd for $C_5H_6N_2O_2$: N, 22.28. Found: N, 22.33.

1,2-Dihydro-4-chloro-3,6-pyridazinedione (chloromaleic hydrazide). To 13.3 g. (0.1 mole) of chloromaleic anhydride (Eastman Kodak Co.) in 50 ml. of glacial acetic acid was added 6.0 g. (0.1 mole) of 85% hydrazine hydrate. A yellow precipitate was formed almost at once. The mixture was refluxed for 30 minutes in an oil-bath, cooled, and the resulting yellow powder was collected. This was washed well with absolute ethanol and was taken up in boiling water. Decolorization was accomplished by boiling the resulting solution with Norit for 15 minutes. The resulting mixture was filtered and cooled, yielding fine white crystals, which were collected and air-dried. Yield, 9.4 g. (64%), m.p. 285–288°, with decomposition.

Anal. Calc'd for $C_4H_3ClN_2O_2$: N, 19.15. Found: N, 20.15.

General method for the preparation of 2,3-dihydro-3-oxo-6-pyridazinyl benzoates. The cyclic hydrazide (0.01 mole) was added to 10 ml. of pyridine in a large test tube, followed by 0.01 mole of benzoyl chloride, and the mixture was shaken, causing formation of a red or violet color. This mixture was then allowed to stand for 1–2 hours, until solidification was complete. About 200 ml. of water was added, and the mixture was filtered with suction, yielding slightly colored crystals, which were recrystallized from a suitable solvent to give the product.

2,3-Dihydro-3-oxo-6-pyridazinyl benzoate formed colorless needles from ethanol. Yield, 1.0 g. (47%), m.p. 162.5–164.5°. The compound was soluble in acetic acid and chloroform; insoluble in water and other organic solvents.

Anal. Calc'd for $C_{11}H_8N_2O_3$: N, 12.96. Found: N, 12.87.

2,3-Dihydro-4-(or 5)-methyl-3-oxo-6-pyridazinyl benzoate gave colorless needles from absolute ethanol. Yield, 0.83 g. (36%), m.p. 182.5–183.5°. It was soluble in acetic acid and chloroform; insoluble in water, ether, and carbon tetrachloride.

Anal. Calc'd for $C_{12}H_{10}N_2O_3$: N, 12.08. Found: 12.22.

4(or 5)-Chloro-2,3-dihydro-3-oxo-6-pyridazinyl benzoate gave fine white crystals from absolute ethanol, yield 0.4 g. (16%); m.p. 205–207°. The ester was insoluble in benzene, water, ether, carbon tetrachloride, and chloroform, and was slightly soluble in ethanol and acetic acid.

Anal. Calc'd for $C_{11}H_7ClN_2O_3$: N, 11.09. Found: N, 11.20.

1,2,4,5-Tetrahydro-3,6-pyridazinedione (succinic hydrazide). This compound is claimed by Sernagiotto (10) but the work should be reevaluated, since no melting points or analyses are given. Succinic anhydride (10.0 g., 0.1 mole) and 6.0 g. (0.1 mole) of 85% hydrazine hydrate were added to 50 ml. of absolute ethanol, and the mixture was refluxed for 2 hours. A white mass settled out, which was pulverized after cooling, washed several times with hot ethanol, and dried in an oven at 100°. Yield, 6.5 g. (58%), m.p. 266–268°.

Anal. Calc'd for $C_4H_6N_2O_2$: N, 24.60. Found: N, 24.00.

SUMMARY

3,6-Pyridazinediones react with benzoyl chloride in the presence of pyridine or of a dilute sodium hydroxide solution to yield 2,3-dihydro-3-oxo-6-pyridazinyl benzoates. Similarly the action of alkyl chlorocarbonates in a Schotten-Baumann reaction gives alkyl 2,3-dihydro-3-oxo-6-pyridazinylcarbonates. These reactions go at room temperature with great ease, giving further evidence for the monoenolic character of the 3,6-pyridazinedione ring system. A new series of esters of carbonic and benzoic acid has been prepared.

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