[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Preparation of 1-(3′,1′H,6′-Pyridazinone)-3,6-pyridazinedione. Attempts to Prepare Bicyclic Dimaleic Hydrazide[1,2]

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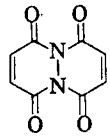
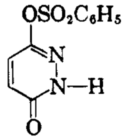
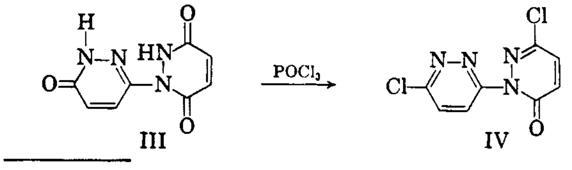
The reactions of maleic hydrazide (I) were found to be different from those of cyclic succinhydrazide (II). Under conditions such that II gave bicyclic disuccinhydrazide, I did not react. Compound I reacted with benzenesulfonyl chloride to give in addition to 3-(1′H,6′-pyridazinonyl)benzenesulfonate, 1-(3′,1′H,6′-pyridazinone)-3,6-pyridazinedione (III). Its structure was established by converting it to the known 1-(3′-chloro-6′-pyridazyl)-3-chloro-6-pyridazone (IV). The reaction of compound I and maleic anhydride with chlorine is discussed.

Cyclic succinhydrazide reacted readily with diethyl succinate, succinoyl chloride, or benzenesulfonyl chloride to give bicyclic disuccinhydrazide.[4] But attempts to synthesize bicyclic dimaleichydrazide (1,4,6,9-tetraketopyridazo[1,2-α]pyridazine) (V) by treating maleic hydrazide (I) with diethyl maleate or maleic anhydride in various solvents and under various conditions were fruitless.[5]


V


XIV

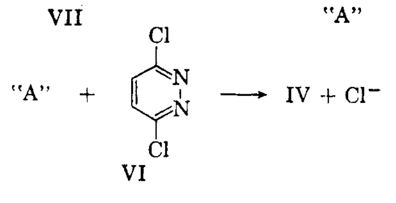
The reaction of compound I with benzenesulfonyl chloride gave 3-(1′H,6′-pyridazinonyl)benzenesulfonate as the major product.[6] The filtrate of the reaction mixture, on further heating, gave a new product which was not the expected compound V. On the basis of the empirical formula $C_8H_6N_4O_3$, calculated from the elemental analysis, and the infrared spectrum, which showed a carbonyl absorption maximum similar to that of compound I, the material was thought to be 1-(3′,1′H,6′-pyridazinone)-3,6-pyridazinedione (III). A search of the literature revealed that Druey and coworkers[7] had isolated in small amounts from the reaction of compound I with phosphorus oxychloride[8] a compound to which they assigned structure IV. The assignment of structure was made on the basis of elemental analysis, molecular weight, and infrared and ultraviolet spectra. It was therefore decided to synthesize compound IV and to prove the structure of compound III by relating it to compound IV.



Toward the preparation of compound IV we have found that the crude reaction product of compound I and phosphorus oxychloride[8] gave on fractional crystallization from carbon tetrachloride, 3,6-dichloropyridazine (VI), 3-chloro-6-pyridazinone (VII), and a third material which had a distinct melting point. By infrared anlaysis, molecular weight determination, and elemental analysis, the latter was shown to be an equimolar mixture of compounds VI and VII. The actual structure of this "complex" is not known; however, compound VI could be readily removed from compound VII by sublimation, indicating that actual compound formation had not occurred.

When the published procedure[7] for the preparation of compound IV was followed, that is, recrystallizing the above crude reaction mixture from cyclohexane and then from isopropyl ether followed by sublimation, compound IV could not be obtained. It was, however, obtained[9] after the crude reaction mixture was sublimed in vacuum *without prior purification*, and the residue subsequently recrystallized.

It is believed that compound IV formed during heating (sublimation) from compounds VI and VII in the following way:



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(1) Paper V in the series, "The Chemistry of Cyclic Hydrazides."

(2) Abstracted in part from the Ph.D. thesis of Harry Rubinstein (February 1958).

(3) Purdue Research Foundation Fellow 1956–1957.

(4) H. Feuer, G. B. Bachman, and E. White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).

(5) H. Rubinstein, Master's thesis, Purdue University, February 1956.

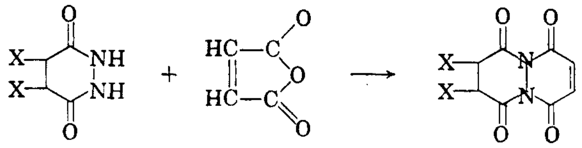
(6) H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

(7) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

The base (excess ammonium hydroxide), indicated in step (1) was introduced on neutralizing the crude reaction mixture[8] prior to sublimation.

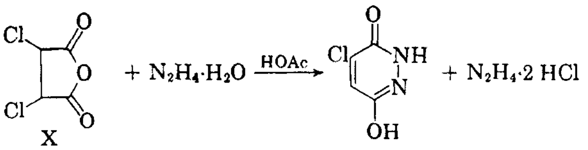
Efforts to convert compound IV into III by hydrolysis with aqueous base, resulted only in decomposition. Compound III was, however, readily converted into IV on refluxing with phosphorus oxychloride, and the structure of compound III was thereby established.

Reaction of maleic anhydride and maleic hydrazide with bromine and chlorine. In further efforts toward the synthesis of compound V, it was hoped that perhydro-4,5-dihalo-3,6-pyridazinedione (VIII) would react with maleic anhydride to give the bicyclic compound (IX) which then could be converted to V on treatment with zinc.



VIII IX

However, all efforts to prepare VIII by reacting I with either chlorine or bromine were fruitless. An alternate method for its preparation was then chosen by following the directions of Ligett, Closson, and Wolf,[10] who reported that the reaction of hydrazine hydrate and α,α'-dichlorosuccinic anhydride (X) gave compound VIII (X = Cl). Compound X was prepared from maleic anhydride and chlorine in carbon tetrachloride in the presence of ultraviolet light and treated with hydrazine hydrate in a mixture of benzene and ethanol.[10] This, however, gave only polymeric material. When acetic acid was used as a solvent, the reaction afforded monochloromaleic hydrazide[11] (XI), m.p. 263° dec., and hydrazine dihydrochloride instead of compound VIII. Since it was possible that dehydrohalogenation was caused by the basic hydrazine hydrate, it was substituted by hydrazine sulfate; but this also gave only compound XI.



X XI

The failure of compound I to add bromine or chlorine to its double bond, the failure encountered in the preparation of compound V from I, and the preferred dehydrohalogenation with the formation of compound XI rather than the expected compound VIII are believed to be due to resonance stabilization of compounds I and XI. This is supported by the work of Arndt *et al.*[12] who state that the double bond in compound I is not olefinic because of its failure to add diazomethane.[12] Furthermore, by comparing 2-methyl-6-methoxy-3-pyridazinone (XII) and 1,2-dimethyl-3,6-pyridazinedione (XIII) as to their reactivity to bromine, Eichenberger *et al.*[13] found that only compound XIII added bromine. This was explained by the fact that in order to become aromatic, compound XIII would have to form a structure which would violate the adjacent charge rule. On the other hand, compound XII can easily gain aromaticity without any such restriction.

It is also not surprising that compound I resists any chemical transformation which would lead to the loss of resonance stabilization. This would be the case in the conversion of compound I to V since the latter cannot have aromatic stabilization, due to the fact that it would involve two adjacent positive charges on the nitrogens.

EXPERIMENTAL

1-(1′,1′H′6′-Pyridazinone)-3,6-pyridazinedione (III). Five g. (0.044 mole) of maleic hydrazide and 25 g. of benzenesulfonyl chloride were heated in a beaker until a slight brown solution resulted. Then, 50 ml. of water was added with stirring and the mixture was left standing overnight on ice. The precipitated 3-(1′H′6′-pyridazonyl)benzenesulfonate was removed and the filtrate was then heated gently until a single layer had formed while more water was added to compensate for losses due to evaporation. Upon cooling, 1 g. (20%) of compound III deposited, m.p. >350° after two recrystallizations from water.

Anal. Calcd. for $C_8H_6O_3N_4$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.46; H, 2.75; N, 26.99.

Reaction of maleic hydrazide and phosphorus oxychloride. Maleic hydrazide (37.5 g., 0.29 mole) and 450 ml. of phosphorus oxychloride were refluxed for 5 hr. The solution was the concentrated *in vacuo* to a volume of 50 ml., poured into ice, and neutralized with concd. ammonium hydroxide until slightly basic. Filtration and drying gave 46 g. of crude reaction product, m.p. 150–190° dec. Boiling 5 g. of this material for 1 hr. with carbon tetrachloride and filtering gave the following products: (1) 0.8 g. of an insoluble material, m.p. 185–278° dec., which was not identified; (2) 1.3 g. of product which came out of the carbon tetrachloride solution on cooling to 25° in a Dewar containing warm water. This product consisted of a mixture which was separated manually to give needles, m.p. 140° and clusters, m.p. 116–117°; (3) 0.6 g. of crystals, m.p. 115–116° which deposited after placing the carbon tetrachloride filtrate from (2) on ice for several hours; (4) 1.7 g. of solid, m.p. 60–65° which was obtained on evaporating to dryness the filtrate from (3).

Mixture (2) was recrystallized from hot carbon tetrachloride by allowing it to cool to 25° overnight. This gave needles "A," m.p. 142–142.5°, the infrared spectrum of which was found to be identical with that of 3-chloro-6-

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(8) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1874 (1951).

(9) We are indebted to Dr. Druey for this advice and for an authentic sample of this compound.

(10) W. B. Ligett, R. D. Closson, and C. N. Wolf, U. S. Patent **2,640,005**, May 26, 1953.

(11) The patent[10] indicates an m.p. 260–263° for VIII (X = Cl), which agrees with our value of 263° for compound XI. Furthermore, the chlorine analysis indicated is 2% high for compound VIII.

(12) F. Arndt, L. Löwe, and L. Ergener, *Rev. Faculte Sci Univ. Istanbul*, **13**, 104 (1948).

(13) K. Eichenberger, H. Staehelin, and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954).

pyridazinone[14] (VII) and a mixture of authentic VII melted at 138–140°. The analytical data of "A" was as follows:

Anal. Calcd. for $C_4H_3ON_2Cl$: C, 36.80; H, 2.30; N, 21.4. Found: C, 36.90; H, 2.41; N, 21.26.

The above mother liquor gave after cooling on ice, clusters "B," m.p. 115–116°. Products "B" and (3) were identified as equimolar mixtures of 3,6-dichloropyridazine (VI) and compound VII. The infrared spectrum of a prepared equimolar mixture of compounds VI and VII was similar to "B" and (3) and a mixture of "B" and (3) melted at 115–116° after recrystallization from carbon tetrachloride.

Anal. Calcd. for (an equimolar mixture of VI and VII) $C_8H_5ON_4Cl_3/2$: N, 20.0; mol. wt. 139.7. Found: N, 19.95; mol. wt. 145 (Rast).

Subjecting mixtures "B" or (3) to heating *in vacuo* caused sublimation of compound VI and gave pure VII as the residue.

Anal. Calcd. for $C_4H_3ON_2Cl$ (VII): C, 36.8; H, 2.30; Cl, 27.21. Found: C, 36.95; H, 2.53; Cl, 27.22.

Product (4) on sublimation *in vacuo* gave pure VI, m.p. 69°, lit. value,[8] m.p. 68–69°, and no appreciable residue remained.

1-(3'-Chloro-6'-pyridazyl)-3-chloro-6-pyridazone (IV). A 7 g. sample of the crude reaction product resulting from the reaction of maleic hydrazide and phosphorus oxychloride was sublimed for 28 hr. at 70–80°. The residue was boiled with about 500 ml. of cyclohexane and after cooling, 1 g. of compound IV, m.p. 151–152° was obtained. This material gave no depression in a mixed melting point determination with authentic IV[9] and had a similar infrared spectrum.

Conversion of compound III to compound IV. In a 50-ml. flask fitted with an efficient condenser were placed 0.182 g. (0.88 mmole) of III and 15 ml. of phosphorus oxychloride. The mixture was refluxed 5.5 hr., filtered, and the filtrate concentrated *in vacuo* until 2 ml. of liquid remained. Addition of crushed ice, followed by sufficient concd. ammonium hydroxide to basify the solution, cooling on ice overnight, and filtering gave 0.12 g. (57% yield) of slightly tan product, m.p. 150–153°. Recrystallization from cyclohexane gave a m.p. 151–152°. A mixed melting point determination with authentic IV gave no depression.

α,α'-Dichlorosuccinic anhydride[15] (X). A three necked 1000-ml. flask was equipped with a coarse sintered glass gas dispersion tube and a condenser. Into this flask were placed 50 g. of maleic anhydride and 500 ml. of carbon tetrachloride. The mixture was heated to reflux and irradiated with an ultraviolet light while chlorine was introduced for about 14 hr. Upon cooling, light gray crystals deposited and evaporation of the solvent *in vacuo* gave additional material. Several recrystallizations from benzene gave a m.p. 91–92° which was raised to m.p. 95–97° (lit. value[15] m.p. 95°) after recrystallization from carbon tetrachloride.

It was found necessary to purify the crude reaction product immediately, since it discolorized readily on standing. The purified product (X) was converted very rapidly to the acid on standing in air and had to be kept dry.

Reaction of α,α,-dichlorosuccinic anhydride with hydrazine hydrate. To a mixture of 10 g. (0.059 mole) of α,α'-dichlorosuccinic anhydride and 100 ml. of acetic acid was added in 3 min. 3 g. (0.06 mole) of hydrazine hydrate with stirring. Refluxing for 1 hr., cooling, and filtering gave 4.4 g. of crystals, m.p. 225–240° dec. Concentrating the filtrate to 10 ml. gave an additional 2.5 g. of material, m.p. 256–257° dec. and evaporation to dryness afforded 3 g. of a dark residue. These solids were partially soluble in boiling ethanol. The residue was identified as hydrazine dihydrochloride, by a mixed melting point determination with an authentic sample which gave no depression, and by comparison of the infrared spectra which were identical.

On cooling, the filtrate gave 4.0 g. (50%) 4-chloromaleic hydrazide, m.p. 263° dec., lit. value,[16] 254° dec., after recrystallization from ethanol.

Anal. Calcd. for $C_4H_3O_2N_2Cl$: C, 32.8; H, 2.04; N, 19.13; neut. equiv. 146.5. Found: C, 33.12; H, 2.28; N, 19.36; neut. equiv. 147.

Acknowledgment. The authors are grateful to the Purdue Research Foundation for financial support of this investigation.

LAFAYETTE, IND.

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[14] This material has previously been reported, but was obtained with a half mole of water of hydration,[7] m.p. 138–140°.

[15] A. Michael and G. Tissot, *J. prakt. Chem.*, **46**, 392 (1892).

[16] Yu. A. Baskakov and N. N. Melnikov, *J. Gen. Chem. U.S.S.R.*, **24**, 1205 (1954).

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

Syntheses in the 1,2,4-Benzotriazine Series

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A series of 3-substituted-1,2,4-benzotriazine-1-oxides together with a few of the 3-substituted-1,2,4-benzotriazines have been synthesized for pharmacological evaluation.

The variety of structural modifications possible in substituted 1,2,4-benzotriazines and their kinship to existing chemotherapeutic agents prompted us to explore further derivatives for biological activity. Earlier work in this field, though limited, is well documented[1] and more recently claims for the utility of 1,2,4-benzotriazines have been registered;[2,3] as yet no member of this series has found widespread use.

A group of 1,2,4-benzotriazine-1-oxides together with a few of the corresponding 1,2,4-benzotriazines has been prepared by the general synthetic scheme I–VI.

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[1] J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 44.

[2] B. H. Shoemaker and C. M. Loane, U. S. Patent **2,160,293** (May 30, 1939).

[3] F. J. Wolf and K. Pfister III, U. S. Patents **2,489,351** to **2,489,359** (November 29, 1949), and *J. Am. Chem. Soc.*, **76**, 3551, 4611 (1954).