The Chemistry of Cyclic Hydrazides.[1] VII. The Course of the Michael-Type Addition with Cyclic Hydrazides[2]

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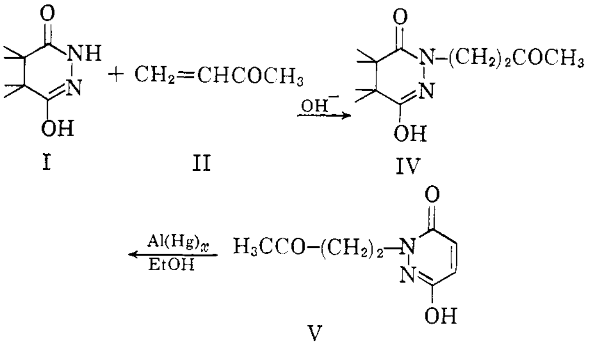
Cyclic succinhydrazide (4,5-dihydro-6-hydroxy-3-pyridazinone) (I) adds readily in the presence of base to compounds with activated double bonds, such as methyl vinyl ketone (II), methyl acrylate, and acrylonitrile to give high yields of diaddition products. A monoaddition product, 2-(3-ketobutyl)-4,5-dihydro-6-hydroxy-3-pyridazinone, results when I is treated with II in a 1:1 molar ratio. Phthalhydrazide (4-hydroxyphthalazinone) (XI) when treated with II affords only a monoaddition product. Structure proofs are presented which show that these Michael-type reactions lead to *N*-substituted derivatives of I and XI.

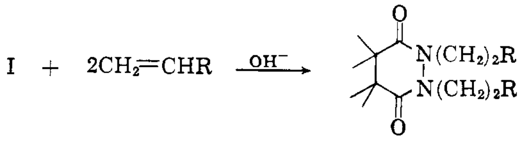
The reaction of succinic anhydride with symmetrically alkylated hydrazines affords *N,N'*-dialkylated cyclic succinhydrazides.

In 1958, we reported the course of the Michael-type addition of maleic hydrazide (III) to activated olefins. Since then, we have investigated these additions with cyclic succinhydrazide (I) and phthalhydrazide (XI), and have found that while XI reacts similarly to III, the reactions of I differ in some respects from those of III. While I yielded mono- and diaddition products, III and XI afforded only *N*-substituted monoadducts. This difference can be rationalized by comparing the expected stabilities of the anions of the monoaddition products IV, V, and XII formed from I, III, and XI. Anions from V and XII should be more stable than the anion from IV, because they represent highly stabilized resonating systems.[3] This correlates with the observed acidities of III (pK_a 5.5), XI (pK_a 7.0) and I (pK_a 8.0), a relationship which also was found to extend to their monoaddition products V (pK_a 5.6), XII (pK_a 6.9), and IV (pK_a 8.0).[4] Ingold[5] has pointed out that the Michael addition will be reversed if the starting anion is much more stable than the anion of the product. In any case, it can be concluded that the possibility of forming the adduct is closely related to the acidity of the starting compound.

When compound I[6] was treated with II in a 1:1 molar ratio, in the presence of a catalytic amount of base, the monoaddition product, 2-(3-ketobutyl)-4,5-dihydro-3-pyridazinone (IV) was obtained in 87% yield. The structure of IV was established by elemental analysis, neutral equivalent determination, and reduction of 2-(3-ketobutyl)-6-hydroxy-3-pyridazinone (V), a known compound,[1] to IV. The reduction product gave no depression in a mixture melting point determination with the Michael adduct IV, and their infrared spectra were superimposable.



The reaction of I with II, methyl acrylate or acrylonitrile, in a 1:2 molar ratio, in the presence of a catalytic amount of base afforded the diaddition products VI, VII, and VIII. Compound VI was also obtained from IV by further treatment with II in the presence of base. The structure of the diaddition products was established by a series of transformation reactions on compound VI, as shown in Chart I, which proved unambiguously that nitrogen substitution had taken place.



VI; VII; VIII

VI. $R = COCH_3$; VII, $R = CO_2CH_3$
VIII. $R = CN$

Compound VI was converted to the thioketal IX in 64% yield. It was anticipated that its reduction with Raney nickel would result in hydrogenolysis similar to that experienced with the thioketal of compound V, which gave *N*-butylsuccinamide. Instead, a liquid was obtained with correct analysis for 1,2-dibutyl-3,6-perhydropyridazinedione (X).

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(1) Previous partinent paper in this series H. Feuer and R. Harmetz, *J. Am. Chem. Soc.*, **80**, 5877 (1958).

(2) From the M.S. thesis of Gladys B. Silverman, Purdue University, August 1957.

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

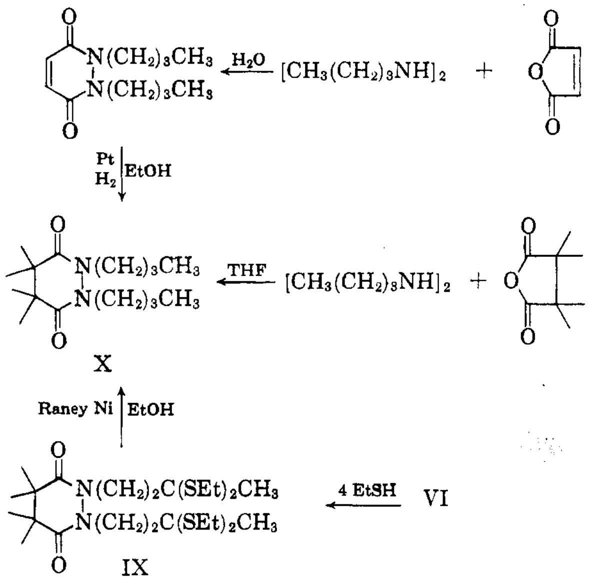
(4) The p*K*a's were determined in the usual manner by an aqueous acid-base titration.

(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., p. 692.

(6) Phthalhydrazide (XI) and compound V, a derivative of maleic hydrazide (III), are written in the mono-lactim form according to the evidence offered by J. U. N. Cheinker, T. V. Gortinskaia, and T. P. Sycheva, *J. Chim. Phys.*, **55**, 217 (1958). By analogy, succinhydrazide (I) is presented in the lactim structure.

CHART I

STRUCTURE DETERMINATION OF 1,2-[BIS(3-KETOBUTYL)]-3,6-PERHYDROPYRIDAZINEDIONE (VI)



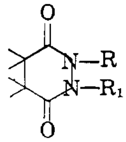
Its structure was established by two independent syntheses. Treatment of maleic anhydride with 1,2-dibutylhydrazine gave 1,2-dibutyl-3,6-pyridazinedione which on reduction with hydrogen over platinum oxide gave compound X. Subsequently it was found that X could be obtained directly by adding 1,2-dibutylhydrazine to a solution of succinic anhydride in tetrahydrofuran. To the best of our knowledge, this constitutes the first direct synthesis of a monocyclic 1,2-dialkyl perhydro-3,6-pyridazinedione without substituents in the 4 or in the 4- and 5-positions.[7] We are currently investigating the scope of this reaction and have found that 1,2-diisopropylhydrazine and succinic anhydride give 1,2-diisopropyl-3,6-perhydropyridazinedione. On the other hand the reaction between anhydrous hydrazine and succinic anhydride affords the acyclic 1,2-disuccinic acid hydrazine.[8]

Since the method of preparation of compounds VII and VIII is similar to that of VI and since their ultraviolet absorption spectra, as shown in Table I, are very similar, it is believed that they are also *N,N'*-disubstituted cyclic succinhydrazides.

When compound XI was treated with equivalent amounts, or excess, of II in the presence of a catalytic amount of base, only the monoaddition product, 2-(3-ketobutyl)-4-hydroxyphthalazinone (XII) was formed. The structure of XII was established by elemental analysis, neutral equivalent determination and by the transformations outlined in Chart II.

TABLE I

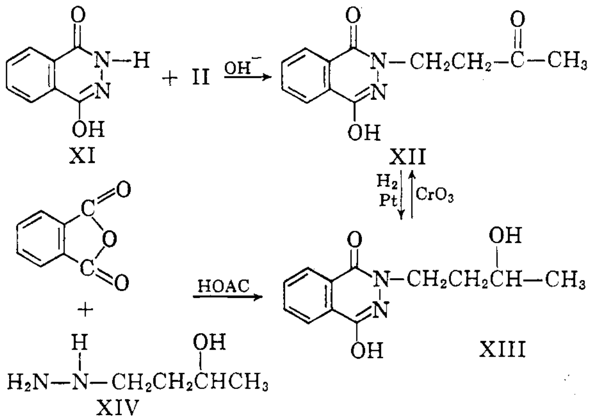
ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED SUCCINHYDRAZIDES



R	R_1	$\lambda_{max}^{95\%\ C_2H_5OH}$	log ε
H	H	243	4.75
$-(CH_2)_2COCH_3$	H	247.5	4.73
$-(CH_2)_2COCH_3$	$-(CH_2)_2COCH_3$	238–239	4.67
$-(CH_2)_2CO_2CH_3$	$-(CH_2)_2CO_2CH_3$	238–239	4.61
$-(CH_2)_2CN$	$-(CH_2)_2CN$	239	4.59
$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	238–239	4.70

CHART II

STRUCTURE DETERMINATION OF 2-(3-KETOBUTYL)-4-HYDROXYPHTHALAZINONE (XII)



The possibility that XII and XIII might represent derivatives of *N*-aminophthalimide was also considered. However, this was ruled out by the fact that XII and XIII were not basic but acidic. Moreover, the infrared ring carbonyl absorption maxima of compound XII and XIII occurred at 6.02 and 6.03 μ, respectively. These values agree well with that of the parent six-membered ring compound XI which occurs at 6.03 μ.

Compound XII was catalytically reduced to the alcohol XIII in 96% yield. Although this compound was resistant to the usual reagents used to form derivatives of alcohols, it could be reoxidized to ketone XII. The infrared spectrum of compound XIII, determined as a Nujol mull, did not show the characteristic absorption of alcohols around 3 μ, but a band did appear in this region when the spectrum was measured in a potassium bromide pellet. Recent reports[9,10] indicate that the absence of the OH absorption in the 3-μ region may be due to intramolecular hydrogen bonding such as is possible in XIII. Such bonding would be expected to render XIII a stronger acid than ketone XII. The observed acidities of XIII

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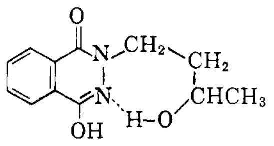
[7] Recently it was reported that 1,2-succinoylpiperidazine was synthesized from piperidazine and succinic anhydride by H. Stetter and H. Spangenberger, *Ber.*, **91**, 1982 (1958).

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

[9] E. W. Gill and E. D. Morgan, *Nature*, **183**, 248 (1959).

[10] H. E. Freedman, *J. Am. Chem. Soc.*, **83**, 2900 (1961).



XIII

(p*K*a 5.9) and XII (p*K*a 6.9) substantiate this prediction.

An independent synthesis of XIII was accomplished by treating phthalic anhydride with 4-hydrazino-2-butanol (XIV). XIII thus prepared gave no depression in a mixture melting point determination with the reduction product, and their infrared spectra were superimposable.

Experimental

1,2-(3-Ketobutyl)-4,5-dihydro-6-hydroxypyridazinone (IV). (a) From Cyclic Succinhydrazide.—Fifty milliliters of 95% ethanol, 4.56 g. (0.04 mole) of cyclic succinhydrazide[8] 2.8 g. (0.04 mole) of methyl vinyl ketone, and 3 drops of 20% aqueous sodium hydroxide were refluxed for 44 hr. Cooling at 0° gave, after 1 hr., 5.09 g. of white product, and an additional 1.34 g. was obtained after concentrating the filtrate *in vacuo* and cooling. Upon recrystallization from isopropyl alcohol, compound IV melted at 148–148.5°, (80% yield). The infrared spectrum showed a medium band at 5.85 μ characteristic of the carbonyl group in the side chain and a strong band at 6.05 μ (ring carbonyl).

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21; neut. equiv. 184. Found: C, 51.87; H, 6.69; N, 14.88; neut. equiv. 187.

(b) From 2-(3-Ketobutyl)-6-hydroxypyridazinone (V).—In a 600-ml. beaker were placed 8 g. of amalgamated aluminum, 5 g. of compound V, 33 ml. of ether, 28 ml. of water, and 150 ml. of 95% ethanol. After standing for 1 hr. at room temperature the mixture was filtered and the sludge washed with hot 95% ethanol. Combining the filtrates, concentrating to a sirup *in vacuo* and adding a small quantity of isopropyl alcohol afforded 4.4 g. (87% yield) of compound IV, m.p. 148°, after several recrystallizations from isopropyl alcohol. A mixture melting point determination with IV prepared by method (*a*) gave no depression and the infrared spectra were superimposable.

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.28; H, 6.53; N, 14.88.

1,2-[Bis(3-ketobutyl)]-3,6-perhydropyridazinedione (VI). (a) From Cyclic Succinhydrazide.—Employing conditions similar to those described in method (a) for the preparation of compound IV, 6.3 g. (0.09 mole) of methyl vinyl ketone, and 3.42 g. (0.03 mole) of cyclic succinhydrazide afforded 6.10 g. (80% yield) of compound VI, m.p. 101°, after recrystallization from isopropyl alcohol. The infrared spectrum showed strong bands at 5.87 μ (carbonyl group in the side chains) and at 6.0 μ (ring carbonyl).

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.57; H, 7.24; N, 10.93.

(b) From Compound IV.—A mixture of 5 g. (0.027 mole) compound IV, 1.92 g. (0.027 mole) of methyl vinyl ketone, 3 drops of 20% sodium hydroxide, and 50 ml. of 95% ethanol was refluxed overnight. Evaporation of the solvent gave 4.2 g. (61% yield) of compound VI, m.p. 101–102° after recrystallization from isopropyl alcohol. A mixture melting point determination with VI prepared by method (a) gave no depression.

1,2-[Bis(2-carbomethoxyethyl)]-3,6-perhydropyridazinedione (VII).—The procedure employed was similar to that used in method (a) for the preparation of compound IV except that the solvent was 90% methanol and that the reaction mixture was refluxed for 24 hr. The reaction afforded 7 g. (81.5% yield) of VII, m.p. 78–79° after recrystallization from absolute ethanol. The infrared spectrum showed strong bands at 5.75 μ and 5.92 μ for ester and ring carbonyl, respectively.

Anal. Calcd. for $C_{12}H_{18}O_6N_2$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.46; H, 6.49; N, 9.82.

1,2-[Bis(2-cyanoethyl)]-3,6-perhydropyridazinedione (VIII).—The procedure employed was similar to that used in method (a) for the preparation of compound IV except that the solvent was 90% methanol and the reaction mixture was refluxed for 15 hr. Concentrating the reaction mixture to 5 ml. *in vacuo* and cooling gave 7.53 g. (85% yield) of VIII, m.p. 112–113° after recrystallization from absolute ethanol. The infrared spectrum showed a medium band at 4.47 μ for C≡N and a strong band at 6.0 μ (ring carbonyl).

Anal. Calcd. for $C_{10}H_{12}O_2N_4$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.76; H, 5.72; N, 25.51.

1,2-(3,3,3',3'-Tetraethylmercaptobutyl)-3,6-perhydropyridazinedione (IX).—In a glass-stoppered bottle were placed 5 g. of sodium sulfate, 2.5 g. of freshly fused zinc chloride, and 108 ml. of ethyl mercaptan. After cooling the mixture to 0–5°, 10.03 g. (0.054 mole) of compound VI was added. The mixture was kept with shaking at 0–5° for 15 hr., allowed to warm to room temperature, and concentrated to 30 ml. *in vacuo*. Adding 100 ml. of ice cold water gave an oil which solidified when kept at 0°. After recrystallization from 70% ethanol, 11.9 g. (64% yield) of IX was secured, m.p. 57.5–58.5°. The infrared spectrum showed a strong band at 6.0 μ for the ring carbonyl.

Anal. Calcd. for $C_{20}H_{38}O_2N_2S_4$: C, 51.50; H, 8.15; N, 6.0. Found: C, 51.45; H, 8.06; N, 6.26.

1,2-Dibutylhydrazine.—To a solution of 76 g. (2 moles) of lithium aluminum hydride in 1200 ml. of ether was added dropwise 131 g. (0.94 mole) of butyraldazine.[11] The mixture was stirred overnight at room temperature and the complex decomposed by treating with 200 ml. of a 40% potassium hydroxide solution. Drying the ether layer over potassium hydroxide pellets, evaporating the solvent, and distilling the residue *in vacuo* gave 100 g. (74% yield) of colorless *1,2-dibutylhydrazine*, b.p. 85° at 15 mm.; $n^{20}D$ 1.4335.

Anal. Calcd. for $C_8H_{20}N_2$: C, 66.60; H, 13.88; N, 19.44. Found: C, 66.42; H, 14.14; N, 19.43.

1,2-Diisopropylhydrazine.—The procedure employed was similar to that used for the preparation of 1,2-dibutylhydrazine. The reaction afforded 77.5 g. (53% yield) of product, b.p. 124°; $n^{20}D$ 1.4142 (lit. value,[12] b.p. 124.5°, $n^{24}D$ 1.4125).

1,2-Dibutyl-3,6-pyridazinedione.—To a solution of 14.7 g. (0.15 mole) of maleic anhydride in 200 ml. of chloroform cooled in an ice bath was added dropwise 20 g. (0.14 mole) of freshly distilled 1,2-dibutylhydrazine. After 24 hours the solvent was evaporated *in vacuo* and the residue distilled to give 25 g. (80% yield) of yellow *1,2-dibutyl-3,6-pyridazinedione*, b.p. 108° (1 mm.); $n^{20}D$ 1.5141.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.26; H, 8.74; N, 12.73.

1,2-Dibutyl-3,6-perhydropyridazinedione (X). (a) By Reduction of Thioketal IX.—In a 500-ml. round bottom flask were placed 70 ml. of settled Raney nickel,[13] 250 ml. of 70% ethanol, and 4.64 g. (0.01 mole) of compound IX. The mixture was refluxed for 5 hr., centrifuged, and decanted while still hot. The Raney nickel was washed by decantation with hot 95% ethanol. The ethanolic solutions were combined and evaporated *in vacuo*. The remaining oil was distilled to give 2 g. (88.5% yield) of X, b.p. 115–116° (1 mm.), $n^{21}D$ 1.4820.

Anal. Calcd. for $C_{12}H_{22}O_2N_2$: C, 63.68; H, 9.80; N, 12.37. Found: C, 63.78; H, 9.70; N, 12.64.

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(11) H. C. Barany, E. A. Braude, and M. Pianka, *J. Chem. Soc.*, 1902 (1949).

(12) H. L. Lochte, W. A. Noyes, and J. R. Bailey, *J. Am. Chem. Soc.*, **44**, 2556 (1922).

(13) R. Mozingo *et al.*, *ibid.*, **65**, 1013 (1943).

(b) **By Reduction of 1,2-Dibutyl-3,6-pyridazinedione.**—A slurry of 10.1 g. (0.05 mole) of 1,2-dibutyl-3,6-pyridazinedione, 0.5 g. of platinum oxide, and 150 ml. of 95% ethanol was shaken in a Parr pressure reaction apparatus at an initial hydrogen pressure of 50 lb. Hydrogen uptake ceased after 20 hr. The slurry was filtered, the alcohol removed *in vacuo*, and the residue distilled to give 7 g. (64.5% yield) of X, b.p. 107° (0.01 mm.), n^{21}D 1.4824.

Anal. Found: C, 63.75; H, 9.85; N, 12.43.

(c) **From Succinic Anhydride.**—To an ice-cooled solution of 69.5 g. (0.69 mole) of succinic anhydride in 600 ml. of tetrahydrofuran was added dropwise 100 g. (0.69 mole) of freshly distilled 1,2-dibutylhydrazine. After allowing the mixture to stir overnight at room temperature, the solvent was evaporated *in vacuo* and the resulting oil distilled to give 65.5 g. (42% yield) of X, b.p. 133–135° (2 mm.), n^{20}D 1.4828.

Anal. Found: C, 63.76; H, 9.83; N, 12.12.

The infrared spectra of X prepared by procedures (a), (b), and (c) were superimposable and showed a strong band at 5.96 μ (ring carbonyl).

1,2-Diisopropyl-3,6-perhydropyridazinedione.—The procedure was similar to that used in method (c) for the preparation of compound X, except that the reaction was allowed to stir 8 hr. at room temperature. The reaction afforded 59 g. (45% yield) of product, m.p. 55°, after sublimation at 40° (0.5 mm.).

Anal. Calcd. for $C_{10}H_{18}O_2N_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.79; H, 9.25; N, 13.94.

1,2-Disuccinic Acid Hydrazine.—To a solution of 110 g. (1.1 moles) of succinic anhydride in 1500 ml. of dry tetrahydrofuran was added at room temperature 38 g. (1.19 mole) of anhydrous hydrazine[14] in 77 g of dry tetrahydrofuran. During the addition heat was evolved and a white precipitate formed. Stirring the reaction mixture at room temperature for 18 hr. and filtering gave 82 g. (80% yield) of 1,2-disuccinic acid hydrazine,[8] m.p. 218°. A mixture melting point determination with an authentic sample was undepressed.

Evaporation of the filtrate *in vacuo* gave 21 g. of unchanged succinic anhydride, m.p. 119°.

2-(3-Ketobutyl)-4-hydroxyphthalazinone (XII). (a) **From Phthalhydrazide and II.**—Phthalhydrazide, 8.1 g. (0.05 mole), was dissolved in 100 ml. of 95% ethanol and heated to reflux temperature. To this solution was added 3.5 g. (0.05 mole) of II and the mixture refluxed for 15 hours. Cooling, filtering, and recrystallizing from 95% ethanol gave 9.6 g. (82% yield) of XII, m.p. 153–154°.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.07; H, 5.17; N, 12.07; neut. equiv., 232. Found: C, 62.09; H, 5.20; N, 12.14; neut. equiv., 235.

The infrared spectrum showed strong bands at 5.8 μ (side chain carbonyl) and at 6.05 μ (ring carbonyl).

(b) **From Oxidation of XIII.**—To a solution of 5.3 g. XIII in 200 ml. of dry acetone cooled in an ice bath was added 5.62 ml. of chromium trioxide reagent (2.68 g. of chromium trioxide, 2.12 g. of concd. sulfuric acid, diluted with water to 10 ml.). After stirring for 15 min., the reaction was quenched with 10 ml. of isopropyl alcohol. The solvent was removed *in vacuo* to give a dark green oil. Compound XII, m.p. 152.5–154.0,° was isolated from this oil by extracting it with hot ethyl acetate and cooling. A mixture melting point determination with XII prepared by procedure (*a*) gave no depression, and the infrared spectra of XII prepared by the two methods were superimposable.

2-(3-Hydroxybutyl)-1-hydroxyphthalazinone (XIII). (a) **By Reduction of XII.**—A solution containing 7.2 g. (0.031 mole) of XII in 300 ml. of 95% ethanol and a catalytic amount of platinum oxide were shaken in a Parr hydrogenation apparatus at an initial pressure of 50 lb. After hydrogen uptake had ceased (3 hr.), the suspension was filtered and the solution concentrated *in vacuo* to one fifth its volume. On cooling, white needles, 4.1 g., separated and further concentration and cooling gave a second crop of crystals (2.9 g.). The total yield of XIII was 7.0 g. (96.5%), m.p. 154–155°, after recrystallization from 95% ethanol. The infrared spectrum showed only the ring carbonyl absorption at 6.03 μ.

Anal. Calcd. for $C_{12}H_{14}O_3N_2$: C, 61.54; H, 5.99; N, 11.97; neut. equiv., 234. Found: C, 61.80; H, 6.07; N, 11.81; neut. equiv., 235.

(b) **From Phthalic Anhydride and XIV.**—A solution of 1 g. of XIV in 10 ml. of glacial acetic acid was added slowly with stirring to 1.48 g. (0.01 mole) of phthalic anhydride dissolved in 30 ml. of hot glacial acetic acid. The mixture was stirred for 4 hr. and then the acetic acid was removed *in vacuo* leaving a dark orange oil which, upon treatment with a few drops of ether and cooling, solidied. Recrystallization of this solid from 95% ethanol gave a 36% yield of XIII. A mixture melting point determination with the product obtained in procedure (a) showed no depression and the infrared spectra of the two products were superimposable.

4-Hydrazino-2-butanol (XIV).—This compound was prepared according to the procedure outlined by G. Gever[15] for the preparation of 4-hydrazino-1-butanol.

To 80 g. (1.43 moles) of previously dried and freshly distilled acrolein was added dry hydrogen chloride until the weight of the reaction mixture became constant (86.5% of the theoretical amount of hydrogen chloride being absorbed). The chloroaldehyde was added slowly to a solution of methylmagnesium bromide in dry ether cooled in an ice bath. After the addition was complete, the mixture was poured slowly into a cold saturated ammonium chloride solution. This mixture was allowed to stand for 1 hr., then the ether layer was decanted. The residue was washed twice with ether, the extracts combined, dried, and the ether removed *in vacuo* to give a viscous oil. This oil was distilled to give 5.0 g. of 4-chloro-2-butanol, b.p. 65–75° at 13 mm. This alcohol was added dropwise to 12 g. of hydrazine hydrate at a rate which allowed the temperature of the mixture to remain below 30°. The reaction mixture was allowed to stand for 20 hours and then 12 ml. of methanol was added followed by a solution of 1.0 g. of sodium in 15 ml. of methanol. The precipitated sodium chloride was filtered, the excess solvent removed *in vacuo*, and the resulting oil distilled to give 2.7 g. of XIV, b.p. 97–104° (3–4 mm.), n^{20}D 1.4781.

Anal. Calcd. for $C_4H_{12}ON_2$: C, 46.15; H, 11.54; N, 26.92. Found: C, 46.42; H, 11.28; N, 26.94.

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[14] L. I. Smith and K. L. Howard, *Org. Syntheses*, Coll. Vol. II, 53 (1944).

[15] G. Gever, *J. Am. Chem. Soc.*, **76**, 1283 (1954).