Rearrangement of Ketone Hydrazones Derived from 4-Hydrazino-1*H*-2,3-benzoxazines (1)

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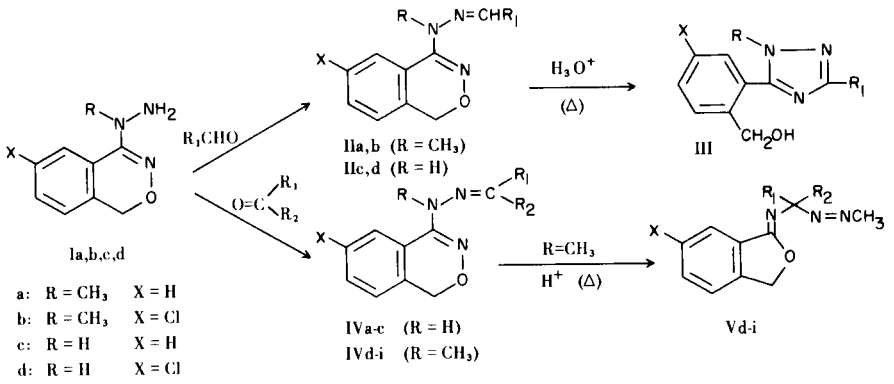
The ketone hydrazones IV, derived from 4-(1-methylhydrazino)-1*H*-2,3-benzoxazines and various ketones, rearrange by the action of anhydrous acids and/or heating to the phthalanylidene compounds V, which are the first reported examples of α-aminoazoaliphatic derivatives. The structure assignment was based on spectroscopic (ir, pmr, and uv) data and on the study of the hydrolysis products. A mechanism for the rearrangement is proposed and briefly discussed.

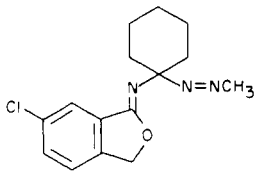
In a preceding paper (4) it was shown that aliphatic and aromatic aldehydes react with 4-hydrazino-1*H*-2,3-benzoxazines (Ia-d) (5,6) to give the corresponding hydrazones (II). When heated alone (IIc, d) or in an acidic medium (IIa-d), a rearrangement takes place and *s*-triazoles (III) form in very good yields. As an extension of this work, we wish to report the preparation and the chemical behavior of the ketone hydrazones (IV).

The condensation of compounds Ia-d with about one equivalent of a suitable ketone was carried out in anhydrous benzene at room temperature (Method A) and is favored by the presence of catalytic amounts of hydrogen chloride. In particular, to obtain isopropylidene hydrazones (IVa, b, d, e) (see Table I), an excess of acetone was used as solvent (Method B). Some ketones failed to give any condensation product; for example, benzophenone did not react with Ia using the conditions of both Methods A and B, even at a higher temperature. The analytical properties of nine derivative IVa-i prepared in this way from Ia-d and purified by rapid crystallization from isopropyl ether or hexane, are summarized in Table I. In general, the ketone hydrazones (IV) were obtained in poorer yields and are more heat- and moisture-sensitive than the aldehyde hydrazones II (4). Stability is greatly improved by the presence of a chlorine atom in position 6 and when R is a methyl instead of a hydrogen and R_1 is a phenyl group.

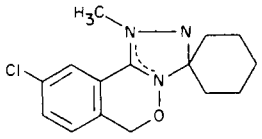
Treatment of compounds IV with warm diluted hydrochloric acid carried out as for the aldehyde hydrazones (II) yielded new products instead of the corresponding hydrazines (I). It was, therefore, desirable to investigate this reaction. 6-Chloro-4-(2-cyclohexylidene-1-methylhydrazino)-1*H*-2,3-benzoxazine (IVg) was chosen as representative. When IVg was treated for a short time at room temperature with a saturated solution of dry hydrogen chloride in chloroform a new product, melting at 103-104°, was isolated, with the elemental formula $C_{15}H_{18}ClN_3O$. The absence in the ir spectrum of O-H absorptions ruled out a possible rearrangement to an *s*-triazoline derivative (4). Consequently, the two structures below were considered to be the most probable ones for the new product and Vg was chosen on the basis of the



spectroscopic and chemical evidence reported here. A characteristic feature of the ir spectrum of Vg was the



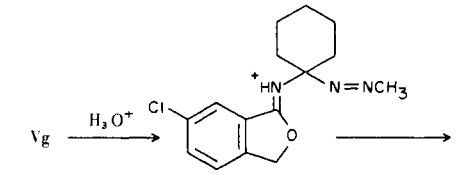
Vg



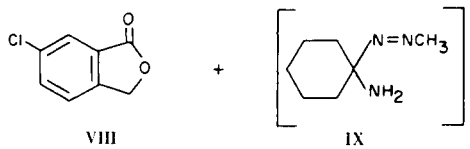
VI

appearance of a strong band at 1690 cm^{-1}, which had been observed for the C=N stretching vibration of some phthalanylideneimino compounds of type XI (7). Concerning the pmr spectrum of Vg, the resonances of the methyl (6.20 τ) and of the CH_2-O (4.76 τ) groups appear at somewhat low fields. In fact, the methylene group in position 1 of 2,3-benzoxazines does not absorb below 4.86 τ (8,9), while the same group in the five-membered ring compound XI is found at 4.69 τ. The signal of the methyl group of compounds IV is at about 7.0 τ, while the signal of a methyl attached to an aliphatic azo-group was reported at about 6.30 τ (10). The uv spectrum of Vg is similar to that of XIc. All these data favor the phthalanylidene structure Vg.

Hydrolysis of Vg with warm 5% hydrochloric acid for one hour gave 6-chlorophthalide (VIII) (approximately 1 equivalent), ammonium chloride (approximately 1.5 equivalent), a small amount of cyclohexanone and a fair amount of a basic compound, probably a hydrazino derivative. Evolution of formaldehyde was also observed during the hydrolysis, as expected (11). About 0.5 equivalent of formaldehyde was colorimetrically (12) determined in the distillate when Vg was heated with aqueous 10% sulfuric acid, thus confirming the presence of a methyl attached to an aliphatic azo group. The formation of one equivalent of VIII under rather mild conditions may be explained as arising from hydrolysis of the protonated form VII of Vg. The azoamine (IX) was not isolated. One could anticipate that it would not be very stable (13,14) and that it would generate the various products mentioned above.



VII



VIII IX

Moreover, some of the physical properties of Vg, such as the low melting point and the high solubility in nonpolar solvents, are contrary to those expected for the mesoionic structure VI. In addition, it might be anticipated that VI would give VIII only under more severe hydrolysis conditions (6,15). The above results, together with the spectroscopic data, clearly indicates structure Vg (16), which, to the best of our knowledge, is the first reported example of an α-aminoazoaliphatic derivative.

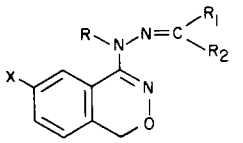
The rearrangement under the influence of acids for a short time (Method C) proved successful for the ketone hydrazones having R = CH_3 (IVd-i). However, the most stable hydrazone IVi reacted only at reflux temperature yielding, besides the rearranged product Vi, *s*-methylphenylketazine. The rearrangement to V could also be performed thermally by short heating of hydrazones IVd-h at 100-120° in a bulb under reduced pressure (Method D). In both Methods C and D, the reaction products consisted of mixtures of the rearranged materials V and the starting hydrazones (IV). Prolonging the reaction time did not increase the yields of Vd-h, which, owing to their instability under the reaction conditions, decomposed to the various products already mentioned. Thus, with the exception of Vg, purity was not improved beyond 90% as determined by pmr and ir spectroscopy.

The rearrangement to V is applicable to the derivatives of 1-methylhydrazine (IVd-i), but when the hydrazones (IVa-c) (in which R = H) were reacted with dry hydrogen chloride in chloroform, nitrogen was evolved immediately presumably from the corresponding intermediate X (see Chart 2). In the case of IVc, for example, it was found that *N*-phthalanylidene cyclohexylamine (XIc) was formed in good quantities.

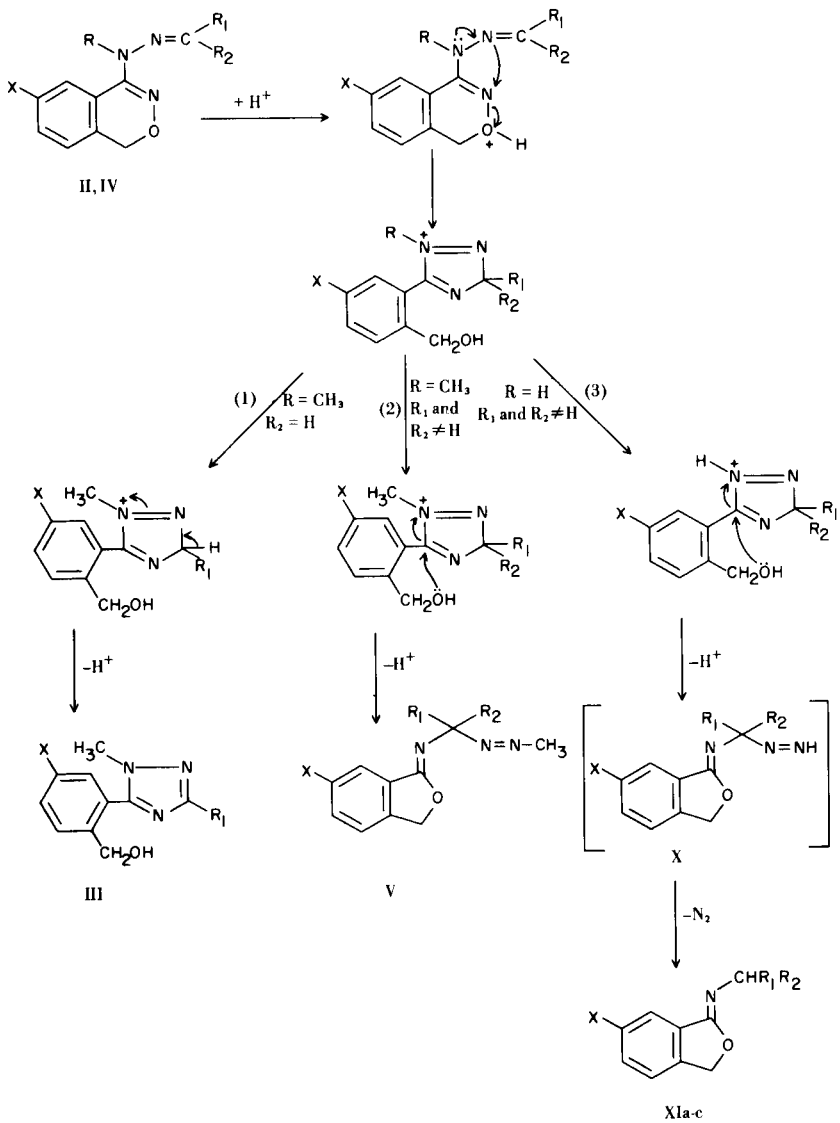
Finally, a discussion on the rearrangement mechanism of the aldehyde and ketone hydrazones II and IV is reported. The following sequence is proposed in which the first step is common for the rearrangement of the aldehyde hydrazones (II) to the *s*-triazoles (III) (4) and of the ketone hydrazones (IV) to the phthalanylidenes (V). A triazoline intermediate forms by cleavage of the weak N-O benzoxazine bond. At this point, if R_2 is equal to hydrogen, a proton abstraction is possible, leading to the *s*-triazole structure (III) (Path 1). When no hydrogen is available, a nucleophilic attack by the oxygen on carbon 5 occurs, accompanied by the cleavage of the C5-N1 bond to give the phthalanylidene derivatives V (Path 2). In the chart, a rearrangement mechanism is proposed also for the hydrazones (IVa-c) (in which R = H) (Path 3) which stems from the hypothesis that structure X is unstable.

TABLE I

1*H*-2,3-Benzoxazine Hydrazones (IV)



No.	R	=C(R1)(R2)	X	M.p., °C	Yield %	Formula	Analysis C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found
IVa	H	=C(CH3)(CH3)	H	76-77 (Hexane)	65	$C_{11}H_{13}N_3O$	65.00	65.05	6.45	6.54	20.68	20.78
IVb	H	=C(CH3)(CH3)	Cl	76-77 (Hexane)	56	$C_{11}H_{12}ClN_3O$	55.59	55.79	5.09	4.89	17.68	17.60
IVc	H	=cyclohexyl	H	53-55 (iProp.$_2$O)	67	$C_{14}H_{17}N_3O$	69.11	69.29	7.04	7.13	17.27	16.25
IVd	CH_3	=C(CH3)(CH3)	H	90-91 (iProp.$_2$O)	60	$C_{12}H_{15}N_3O$	66.34	66.00	6.96	7.01	19.34	19.70
IVe	CH_3	=C(CH3)(CH3)	Cl	105-106 (iProp.$_2$O)	55	$C_{12}H_{14}ClN_3O$	57.26	57.22	5.61	5.59	16.69	16.50
IVf	CH_3	=cyclohexyl	H	84-86 (iProp.$_2$O)	56	$C_{15}H_{19}N_3O$	70.00	69.62	7.44	7.74	16.33	16.26
IVg	CH_3	=cyclohexyl	Cl	128-130 (iProp.$_2$O)	65	$C_{15}H_{18}ClN_3O$	61.75	61.36	6.22	6.60	14.40	14.03
IVh	CH_3	=N-CH3-piperidyl	H	125-126 (iProp.$_2$O)	42	$C_{15}H_{20}N_4O$	66.15	65.88	7.40	7.50	20.57	20.03
IVi	CH_3	=C(CH3)(C6H5)	Cl	129-130 (iProp.$_2$O)	60	$C_{17}H_{16}ClN_3O$	65.08	65.12	5.14	5.18	13.39	13.60



EXPERIMENTAL (17)

General Procedure for the Preparation of 1*H*-2,3-Benzoxazine Hydrazones (IVa-i). Method A. Example: 4-(2-Cyclohexylidene-hydrazino)-1*H*-2,3-benzoxazine (IVc).

The reaction of 2.6 g. (0.016 mole) of 4-hydrazino-1*H*-2,3-benzoxazine (5) (Ic) and cyclohexanone (1.72 g., 0.017 mole) was carried out in anhydrous benzene in the presence of 0.1 ml. of a 3% solution of hydrogen chloride in ethanol. After ten minutes at room temperature, the solvent was removed *in vacuo* at low temperature (water-bath at 25°) and the residue was extracted three times with warm hexane and filtered to remove some insoluble material. The filtrate was concentrated to give 2.6 g. of crude IVc which was rapidly recrystallized from isopropyl ether, m.p. 53-55°; ir: 3100 (NH), 1630 (C=N), 1570 (cyclic C=N), 1070 (C-O) and 735 cm^{-1} (aromatic CH); pmr (deuteriochloroform): 8.5-8.1 (m, 6H, CH_2 in position 3,4,5 of the cyclohexane ring), 7.80-7.45 and 7.40-7.10 (two m, 4H, CH_2 in position 2,6 of the cyclohexane ring), 4.98 (s, 2H, CH_2O), 3.0-2.4 and 2.0-1.6 (m, 4H, aromatic hydrogens), 1.5-1.0 τ (broad s, 1H, NH).

Method B. Example: 6-Chloro-4-(2-isopropylidene-1-methyl-hydrazino)-1*H*-2,3-benzoxazine (IVe).

To a solution of 6-chloro-4-(1-methylhydrazino)-1*H*-2,3-benzoxazine (6) (Ib; 1 g., 4.7 mmoles) in 20 ml. of acetone, 0.05 ml. of a 3% solution of hydrogen chloride in ethanol was added and the mixture was worked up as for IVc. The hexane extracts were concentrated and the residue (1 g.) was quickly crystallized from isopropyl ether; m.p. 105-106°; ir: 1640 (C=N), 1530 (cyclic C=N), 1080 (C-O), 870 and 800 cm^{-1} (aromatic CH); pmr (deuteriochloroform): 7.93 and 7.80 (two s, 6H, CH_3-C=), 7.02 (s, 3H, CH_3-N ⊃), 5.15 (s, 2H, CH_2), 2.90-2.35 τ (m, 3H, aromatic hydrogens). The analytical properties of hydrazones (IVa-i), obtained from Ia-d according to the above procedures, are reported in Table I.

Rearrangement of Hydrazones (IVd-i) in an Anhydrous Protonating Medium. Method C. Example: *N*-(6-Chloro-1-phthalanylidene)-1-methylazocyclohexylamine (Vg).

A solution of 1.4 g. of 6-chloro-4-(2-cyclohexylidene-1-methyl-

hydrazino)-1*H*-2,3-benzoxazine (IVg) in 14 ml. of chloroform saturated with hydrogen chloride was left at room temperature with occasional stirring for twenty minutes. After washing with dilute sodium bicarbonate solution, the organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The residue was crystallized from 25 ml. of 70% methanol and immediately cooled in a refrigerator overnight, yield 0.8 g. (57%) of Vg, m.p. 103-104°; ir: 1690 (C=N), 1000 (C-O), 855 and 815 cm^{-1} (aromatic CH); uv (methanol): λ max = 237 mμ (log ϵ = 4.05), 245 (sh), 256 (sh), 278 (sh), 286 (3.66), 295 (3.69); pmr (deuteriochloroform): 8.6-7.8 (m, 10H, CH_2 of the cyclohexane ring), 6.20 (s, 3H, CH_3-N=), 4.76 (s, 2H, CH_2O), 2.70 (d, 1H, aromatic H in 4), 2.51 (two d, 1H, aromatic H in 5) and 2.10 (d, 1H, aromatic H in 7).

Anal. Calcd. for $C_{15}H_{18}ClN_3O$: C, 61.78; H, 6.22; N, 14.42; Cl, 12.15; O, 5.49. Found: C, 61.72; H, 6.49; N, 14.50; Cl, 11.98; O, 6.00.

Samples of IVd, e, f, and h underwent the rearrangement under the same conditions described above for IVg, while Vi reacted only at the reflux temperature. The crude oily products obtained are quite unstable in the presence of water and are heat sensitive. Despite numerous purifications by high-vacuum distillation and by chromatography, purity was not improved beyond 90%. The preparations of Vh and Ve are reported as an example.

1-Methyl-4-methylazo-4-(1-phthalanylidene)aminopiperidine (Vh).

A solution of 0.5 g. of 4-[2-(1-methyl-4-piperidylene)-1-methylhydrazino]-1*H*-2,3-benzoxazine (IVh) was rearranged according to the above procedure. The residue from the chloroform solution was shown to contain about 50% of Vh by ir and pmr spectroscopy. It was chromatographed on 3 plates (20 x 20 cm; 1 mm layer of silica gel HF) by using methanol/chloroform 5/95, then methanol/chloroform 10/90 as eluents. The silica gel of the spots with R_f = 0.23 (by uv light examination) was collected, combined and extracted with methanol. Evaporation of the solvent *in vacuo* gave 158 mg. of an oily residue consisting of Vh, with a purity of about 90% checked by ir and pmr. Phthalide according to ir examination was a possible impurity which was not present in the crude product; ir: 1690 (C=N), 1040 (C-O) and 730 cm^{-1} (aromatic CH); pmr (deuteriochloroform): 8.0-7.0 (m, 8H, CH_2 of the piperidine ring), 7.62 (s, 3H, CH_3-N<), 6.19 (s, 3H, CH_3-N=N-), 4.73 (s, 2H, CH_2-O), 2.8-1.9 τ (m, 4H, aromatic hydrogens).

Methylphenylketazine from the Rearrangement of IVi.

A solution of 0.31 g. (1 mmole) of 6-chloro-4-[1-methyl-2-(α-methylbenzylidene)hydrazino]-1*H*-2,3-benzoxazine (IVi) in 3 ml. of chloroform saturated with hydrogen chloride was refluxed for one hour. The solvent was then evaporated and the residue, taken up with water, was neutralized with aqueous sodium bicarbonate and extracted with ether. After being washed with water, the organic solution was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was crystallized from methanol, yielding 0.083 g. (0.35 mmole) of *s*-methylphenylketazine, m.p. 122-124°. The melting point was not depressed in admixture with an authentic sample, prepared from hydrazine and acetophenone (19). Ir examination of the residue from the methanolic mother liquor revealed the presence of a small quantity of rearranged product with the characteristic band at 1690 cm^{-1}.

Thermal Rearrangement of Hydrazones (IVd-h). Method D. Example: *N*-(6-Chloro-1-phthalanylidene)-1-methylazo-1-methylethylamine (Ve).

A sample of 0.4 g. of 6-chloro-4-(2-isopropyliden-1-methylhydrazino)-1*H*-2,3-benzoxazine (IVe) was heated for 90 minutes at 110-120° in a bulb (18) under reduced pressure (100 mm Hg). The melted product was then distilled at 130°/0.1 mm Hg, collecting a mixture of oily and crystalline material, which was taken up with 3 ml. of warm hexane and left in a refrigerator overnight. The crystalline precipitate weighed 0.25 g. (m.p. 105-106°) and was identified as the starting material IVe. The filtrate was evaporated *in vacuo* to give an oily residue (85 mg.) of crude Ve which, according to ir and pmr data, contained about 20% of the starting hydrazone (IVe). Purity was not greatly improved by chromatography of a sample on silica gel HF with benzene/acetone 4/1 as eluent; the ir spectrum indicated that under these conditions some 6-chlorophthalide was formed. The structure of Ve rests on the ir and pmr data since decomposition prevented good elemental analysis; ir (chloroform): 1690 (C=N) and 1045 cm^{-1} (C-O); pmr (deuteriochloroform): 8.47 (s, 6H, CH_3-C(=)), 6.14 (s, 3H, CH_3-N=), 4.67 (s, 2H, CH_2O), 2.69 (d, 1H, aromatic H in 7), 2.51 (two d, 1H, aromatic H in 6) and 2.01 τ (d, 1H, aromatic H in 4).

Cleavage of IVa-c in an Anhydrous Protonating Medium. Example: *N*-Phthalanylidenecyclohexylamine (XIc).

To a solution of 1 g. of 4-(2-cyclohexylidene)-1*H*-2,3-benzoxazine (IVc) in 5 ml. of anhydrous chloroform, 10 ml. of chloroform saturated with hydrogen chloride was added dropwise, while keeping the temperature at 20-25° by external cooling. When nitrogen evolution ceased (about 30 minutes), the solution was washed with a dilute sodium bicarbonate solution and dried over sodium sulfate. The solvent was distilled *in vacuo* and the residue was extracted twice with 10 ml. of hexane at 20° and any insoluble material was removed by filtration. On concentration, 0.3 g. of a crude product which consisted mainly of XIc was obtained. It was not purified, but its ir spectrum showed the characteristic bands at 1690 (C=N), 1020 (C-O), 770 and 725 cm^{-1} (aromatic CH), superimposable on those of a pure sample of *N*-phthalanylidenecyclohexylamine, m.p. 79-80°, prepared from 2-bromomethylbenzoyl bromide and cyclohexylamine (7); pmr (deuteriochloroform): 8.9-7.9 (m, 10H, CH_2 of the cyclohexane ring), 6.4-5.9 (m, 1H, CH of the cyclohexane ring), 4.69 (s, 2H, CH_2-O), 2.8-2.3 and 2.2-1.9 τ (m, 4H, aromatic hydrogens).

Hydrolysis of Vg to 6-Chlorophthalide (VIII).

A mixture of 2.91 g. (0.01 mmole) of *N*-(6-chloro-1-phthalanylidene)-1-methylazocyclohexylamine (Vg) and 20 ml. of 5% hydrochloric acid was heated on a steam bath for one hour. The solid was dissolved on heating and a precipitate was formed which, after cooling, was extracted four times with ether. The combined extracts were dried over anhydrous sodium sulfate, then the solvent was evaporated and the residue was scratched with 10 ml. of hexane to give 1.52 g. of 6-chlorophthalide (VIII), m.p. 111-112°. The melting point in admixture with an authentic sample (20) was not depressed. The hexane filtrate was evaporated yielding 0.15 g. of a mixture of an oil with some crystals. The ir spectrum clearly indicated the presence of 6-chlorophthalide and of cyclohexanone. The aqueous mother liquor was concentrated *in vacuo* and the residue was treated twice with ethanol and reconcentrated to dryness. The solid residue was taken up with 15 ml. of ethanol and 10 ml. of ether and left overnight in a refrigerator. The precipitate was collected (0.79 g.) and identified as ammonium chloride. The filtrate was evaporated, the residue was dissolved in 6 ml. of water and the solution was made basic with aqueous 10% sodium hydroxide. The oil which separated was thoroughly extracted with ether and dried over

potassium hydroxyde. Evaporation of the solvent left a crude product (0.82 g.) which was not examined further; its ir spectrum and its VPC suggested that a hydrazino base could be a major component.

Hydrolysis of Vg with Formaldehyde Determination.

Compound Vg (about 0.5 mmole) was suspended in 10 ml. of 10% sulphuric acid, diluted with 25 ml. of water and distilled at atmospheric pressure, collecting the formaldehyde in aqueous 5% sodium hydroxide. When a residual volume of 10 ml. was reached, another 25 ml. of water was added and distilled, repeating these operations twice. The distillate was diluted to 250 ml. with isopropyl alcohol and formaldehyde (approximately 0.25 mmole) was colorimetrically determined as described (12).

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