deuterium isotope effect, k_{H_2O}/k_{D_2O}, is, therefore, 0.45, a value similar to those found for related reactions[14] and nearly identical with the value found by DeWolfe and Jensen for the hydrolysis of ethyl orthobenzoate.[10] This solvent deuterium isotope effect is consistent with either pre-equilibrium substrate protonation or with general acid catalysis by the hydrated proton, provided that, in the transition state, the proton is largely transferred to the substrate.[15] This condition appears to be met in the present case since Kwart and Price have observed a Brønsted α value of 0.74 for general acid catalysis of methyl orthobenzoate hydrolysis.[9] The observation that methyl orthobenzoate hydrolysis is subject to general acid catalysis[9,10] suggests, but does not prove, that the specific acid-catalyzed reaction is, in fact, general acid catalysis by the hydrated proton.

Experimental

Materials.—Methyl orthobenzoate was prepared from benzotrichloride as previously described.[16] Other reagents were recrystallized or redistilled before use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder as previously described.[17,18] At the conclusion of several runs involving the hydrolysis of methyl orthobenzoate in the presence of hydroxylamine or semicarbazide, the amount of methyl benzoate produced was determined by the ferric chloride–hydroxylamine method of Lipmann and Tuttle.[19] Ionic strength was adjusted to 0.50 with potassium chloride in all kinetic runs.

Measurements of pH were made with the glass electrode and a Radiometer Model PHM 4c pH meter. Values of pD were obtained from measured pH values and the relationship pD = pH + 0.40.[20] This relationship was verified for our pH meter using carefully neutralized acetate buffers.

Activation parameters were obtained from second-order rate constants measured at several temperatures and the Eyring equation, $\ln k = \ln ekT/h + \Delta S^*/R - E_a/RT$.[21]

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The Reaction of Guanazole and Diformylhydrazine[1]

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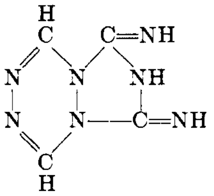
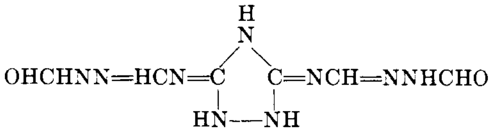
Papini and Checchi[2] treated equimolar quantities of guanazole (3,5-diamino-1,2,4-triazole) and diformylhydrazine and obtained a compound, $C_4H_5N_7$, to which they assigned the structure 7,8-dihydro-6,8-diimino-6*H*-*s*-triazolo[1,2-*a*]-*s*-tetrazine (I). Wiley and Hart[3] treated 1 mole of guanazole with 2 moles of diformylhydrazine and obtained a product to which they tentatively assigned the empirical formula $C_6H_9N_9O_2$[4] and the structure 3,5-bis{[(2-formylhydrazono)methyl]-imino}-1,2,4-triazolidine (II).

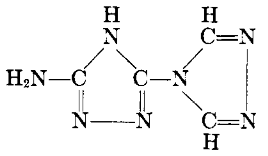


I



II

In the present work, we have found that the material obtained by Wiley and Hart is not $C_6H_9N_9O_2$ but a tetarto hydrate, $C_4H_5N_7 \cdot 1/4H_2O$,[5] of the material obtained by Papini and Checchi. Further, the product of the equimolar reaction, postulated as I, is in fact the isomeric 5-amino-3,4′-bi-1,2,4-triazole (III).



III

The reaction of 2 moles of diformylhydrazine and 1 mole of guanazole by the procedure of Wiley and Hart[3] gave two distinct products. The first of these (A-1) was obtained on rapid cooling of the water used to extract the reaction melt. The elementary analysis of A-1 fitted the empirical formula $C_4H_5N_7$. On standing, the aqueous extract deposited a second solid (A-2) whose carbon–hydrogen analysis was substantially the same as that given by Wiley and Hart. However, the nitrogen analysis of A-2 did not fit the empirical formula $C_6H_9N_9O_2$.

The formula $C_6H_9N_9O_2$ had been assigned on the basis of carbon–hydrogen analysis and the fact that the material did not appear to lose water on drying. When a sample of A-2 was dried for 24 hr. at 60° (1 mm.), there was no detectable weight loss and no change in microanalysis. When the same sample was dried for 24 hr. at 150° (1 mm.) water was given off and the resulting material was identical with A-1. In addition, A-2 could be converted to A-1 by solution in the minimum amount of boiling water, followed by quick cooling.

This unusual dehydration was repeatedly confirmed and, in fact, samples of A-1 prepared from A-2 in this manner could be air-dried without retaining or regaining water. Similarly, A-1 gave A-2 on solution in excess boiling water and very slow cooling.

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(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, and was monitored by the Bureau of Naval Weapons, RMMP, under Contract NOrd 18728. Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

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(4) Based on the remainder of their paper, it is assumed that the formula $C_6H_9N_4O_2$ in the Experimental section of the paper by Wiley and Hart is a typographical error.

(5) Based on X-ray powder patterns this material may be $2(C_4H_5N_7) \cdot {}^1/_2H_2O$ or $4(C_4H_5N_7) \cdot H_2O$, but the evidence is not conclusive.

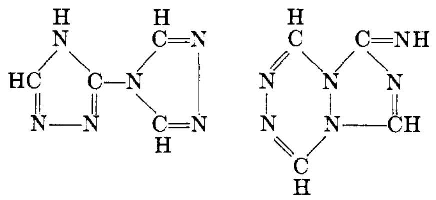
The ultraviolet spectra of A-1 and A-2 were identical in aqueous solution. In the infrared region, A-1 and A-2 had similar but slightly shifted spectra. Karl Fischer analysis of A-2 showed the presence of water and that this water remained after drying at 60° (1 mm.).[6] On the basis of these data plus elemental analysis, the formula $C_4H_5N_7 \cdot 1/4H_2O$, rather than $C_6H_9N_9O_2$, was assigned to compound A-2. That A-2 is a true quarter-hydrate was further demonstrated by the fact that microanalyses on five separate preparations of A-2 were identical for carbon, hydrogen, nitrogen, and oxygen within analytical limits. Additionally, weight loss of samples predried at 60° (1 mm.) and then heated at 150° (1 mm.) was constant.

Both the existence of a tetarto hydrate and the dehydration of a hydrate by recrystallization from water are known but rare phenomena in organic chemistry.[7] It would seem likely that this unusual and unexpected combination of circumstances led to the assignment of structure II.

The equimolar reaction of diformylhydrazine and guanazole by the procedure of Papini and Checchi[2] gave results similar to those above. Two products, B-1 and B-2, were obtained and these were identical with A-1 and A-2, respectively. It was, therefore, concluded that the reaction of guanazole with either 1 or 2 moles of diformylhydrazine gave a compound, $C_4H_5N_7$, or its *tetarto-hydrate*, $C_4H_5N_7 \cdot 1/4H_2O$, as the only product.

Structure I had been proposed on the basis that, working with a large excess of diformylhydrazine over guanazole, only a one to one reaction occurred. However, it subsequently has been noted in these laboratories[8] that reaction of only one amino group is a characteristic of many reactions of guanazole. Since the condensation of diformylhydrazine with aromatic and heteroaromatic amines to give triazoles is a known process,[3,9–11] we were led to believe that the structure represented by $C_4H_5N_7$ might be III, rather than I.

Reductive deamination of III gave a compound, $C_4H_4N_6$, identical with that prepared by Wiley and Hart[3] by the reaction of 3-amino-1,2,4-triazole and diformylhydrazine. They correctly had assigned the structure 3,4′-bi-1,2,4-triazole (IV) to this material, but the possibility remained that this compound might be the isomeric triazole (V) arising from reductive deamination of a tautomer of I and by condensation of diformylhydrazine with a tautomer of 3-aminotriazole. The nuclear magnetic resonance spectrum of this material showed only two peaks in a 2 (τ 0.79) to 1 (τ 1.17) ratio in the C–H region. These are assigned to the two equivalent C–H bonds in one triazole ring of IV and one C–H bond in the second triazole ring. V would be expected to show three peaks of equal intensity in this region. In addition, the infrared spectrum of this material showed no bands in the 1600–1700-cm.$^{-1}$ region (=NH) and a broad band at 2700–2900 cm.$^{-1}$ (triazole ring N–H). These data confirmed IV as the correct structure of the reaction product obtained from 3-amino-1,2,4-triazole and diformylhydrazine and this, in turn, confirmed III as the structure of the guanazole–diformylhydrazine reaction product.



IV V

Experimental[12]

Reaction of Guanazole and Diformylhydrazine at a 1 to 2 Mole Ratio (Method of Wiley and Hart[3]). Compound A-1.—A mixture of guanazole (3.96 g., 0.040 mole) and diformylhydrazine (7.04 g., 0.080 mole) was heated at 180° for 1 hr. The cooled, solidified melt was then dissolved in boiling water. Rapid cooling of the aqueous solution gave 4.2 g. of white, crystalline solid, m.p. >350°. An analytical sample was prepared by several rapid recrystallizations from the minimum amount of water.

Anal. Calcd. for $C_4H_5N_7$: C, 31.79; H, 3.31; N, 64.90. Found: C, 32.03; H, 3.19; N, 64.97.

Compound A-2.—Prolonged cooling of the reaction mixture gave an additional 1.1 g. of white, crystalline solid, m.p. >350°. An analytical sample was prepared by several slow recrystallizations from excess water.

Anal. Calcd. for $C_4H_5N_7 \cdot 1/4H_2O$: C, 30.87; H, 3.54; N, 63.02. Found: C, 30.58; H, 3.68; N, 62.63.

The reaction filtrate was evaporated to dryness at reduced pressure. The semisolid residue was triturated with 100 ml. of absolute methanol to give an additional 0.6 g. of compound A-5 as insoluble material. The reaction yield based on a one to one reaction and the anhydrous A-1 was 96%.

Interconversion of A-1 and A-2.—A sample of A-1, dissolved in excess boiling water and the solution then allowed to cool slowly, gave a precipitate whose infrared spectrum was identical with that of A-2. A sample of A-2, dissolved in the minimum amount of boiling water and the solution then rapidly cooled, gave a precipitate whose infrared spectrum was identical with that of A-1. A finely ground sample of A-2 was heated for 24 hr. at 150° (1 mm.). The resultant material was identical with A-1 (infrared, ultraviolet).

Anal. Calcd. for $C_4H_5N_7$: C, 31.79; H, 3.31; N, 64.90. Found: C, 31.94; H, 3.47; N, 65.14.

Equimolar Reaction of Guanazole and Diformylhydrazine (Method of Papini and Checchi).—This procedure gave products, B-1 and B-2, which were identical (analysis, infrared and ultraviolet) with A-1 and A-2. The interconversions described for compounds A-1 and A-2 also were performed with compounds B-1 and B-2.

3,4′-Bi-1,2,4-triazole (IV). A. Reaction of 3-Amino-1,2,4-triazole and Diformylhydrazine (Method of Wiley and Hart[3]).—Diformylhydrazine (0.40 g., 0.0046 mole) and 3-amino-1,2,4-triazole (0.39 g , 0.0046 mole) were mixed and heated at 160° for 0.5 hr. The cooled, solidified melt was dissolved in 25 ml. of boiling water. The precipitate which formed on chilling the aqueous solution was recrystallized from water to give 0.30 g. (48%) of small, colorless needles, m.p. 304–306° sl. dec. (lit. m.p.[3] 300–302° dec.).

B. Reductive Deamination of 5-Amino-3,4′-bi-1,2,4-triazole (III).—A slurry of 2.0 g. (0.013 mole) of the hydrated form of III in 25 ml. of 10% hydrochloric acid, cooled to 5°, was treated with a solution of 1.8 g. (0.026 mole) of sodium nitrite in 5 ml. of water at 5°. Solution of III was rapid and complete. After 0.25 hr., 12 g. (0.091 mole) of cold 50% aqueous hypophosphorous acid was added. The resulting solution evolved a considerable

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[6] The insolubility of A-2 in solvents necessary for water determination precluded an accurate water analysis, but approximate values of 2–4% corresponded well with the theoretical 2.89%.

[7] *Cf.* Discussion of R. S. Tipson in "Technique of Organic Chemistry," Vol. III, part I, 2nd Ed., A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp. 551, 552.

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[10] G. Pellizzari and M. Bruzzo, *Atti. accad. Lincei*, [5]**10**, i, 414 (1901); *Chem. Zentr.*, **II**, 125 (1901).

[11] G. Pellizzari and A. Alciatore, *Atti. accad. Lincei*, [5]**10**, i, 444 (1901); *Chem. Zentr.*, **II**, 353 (1901).

[12] All melting points are uncorrected and were taken on a capillary melting apparatus.

amount of gas. The reaction flask was then loosely stoppered and refrigerated for 24 hr. The solution was neutralized with 2 *N* potassium hydroxide and concentrated to 20 ml. by boiling. On cooling, a white precipitate formed. Recrystallization from water gave 0.82 g. (44%) of small, colorless needles, m.p. 306–308° sl. dec.

Anal. Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.94; N, 61.77. Found: C, 35.34; H, 3.07; N, 61.73.

The materials in A and B had identical infrared and ultraviolet spectra, and a mixture melting point showed no depression.

Acknowledgment.—The authors are indebted to the Research Service Department, Stamford Research Laboratories, American Cyanamid Company, for microanalyses and aid in the interpretation of infrared, ultraviolet, and nuclear magnetic resonance spectra.

Direction of Ring Opening in the Reaction of Episulfides with Amines[1]

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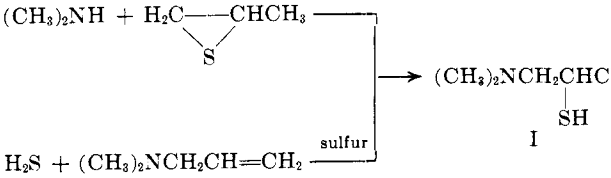
Received October 14, 1963

The reaction of isobutylene sulfide with amines has been investigated by Snyder and co-workers[2] who found that displacement occurred at the primary carbon to give tertiary mercaptans as products. Propylene sulfide was used in one instance in their work, but the structure of the product was not investigated. It has also been shown that cleavage of the styrene sulfide ring with secondary amines takes place at the primary carbon atom.[3] In a study of the reaction of propylene sulfide with dimethylamine, however, Hansen[4] concluded that the episulfide ring is opened at the secondary carbon to give 2-dimethylamino-1-propanethiol. Since ring opening reactions of episulfides are of interest in the synthesis of amino mercaptans for evaluation as radioprotectants, we have investigated this reported difference in reactivity of propylene sulfide. Our finding, contrary to that of Hansen's, is that the direction of ring opening in the propylene sulfide–dimethylamine reaction is the same as in the isobutylene sulfide–amine reaction, *i.e.*, the product is 1-dimethylamino-2-propanethiol.

Our approach to establishing the direction of ring opening consisted of comparing the products obtained by the reactions shown in eq. 1, 2, and 4.



(1)

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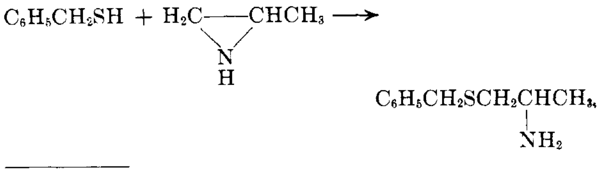

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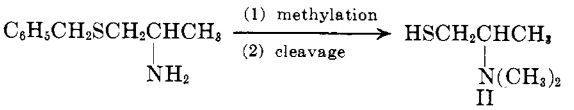

$$C_6H_5CH_2SCH_2\underset{NH_2}{CH}CH_3 \xrightarrow[\text{(2) cleavage}]{\text{(1) methylation}} \underset{\text{II}}{HSCH_2\underset{N(CH_3)_2}{CH}CH_3} \quad (4)$$

Thiolation of dimethylallylamine, in the presence of sulfur to suppress free-radical type addition, gave authentic 1-dimethylamino-2-propanethiol (I). The isomeric addition product, 1-dimethylamino-3-propanethiol, was prepared previously[5] by ultraviolet light-promoted addition of hydrogen sulfide to the hydrochloride of dimethylallylamine. Authentic 2-dimethylamino-1-propanethiol (II) was obtained by opening propylenimine with benzyl mercaptan, methylating the resulting 2-aminopropyl benzyl sulfide, and removing the benzyl group with sodium in liquid ammonia. Meguerian and Clapp[6] have shown that thiophenol opens unsymmetrical ethylenimines in the manner shown in eq. 3. The hydrochloride melting points, the refractive indices, and the boiling points of the products from reactions 1 and 2 were the same. The corresponding properties of II differ significantly from I. These properties, for all three of the dimethylaminopropanethiol isomers, are listed in Table I.

TABLE I

Compound	B.p., °C. (mm.)	n^{20}_{D}	Hydrochloride m.p., °C.
$(CH_3)_2NCH_2\underset{SH}{CH}CH_3$ (I)	70 (88)	1.4557	166–167
$HSCH_2\underset{N(CH_3)_2}{CH}CH_3$ (II)	70 (70)	1.4704	120–121
$HSCH_2CH_2CH_2N(CH_3)_2$[a]	73.5–74.5 (50)	1.4658	105–107

[a] See ref. 5.

The n.m.r. spectra[7] of I obtained by reactions 1 and 2 were identical. A doublet at 1.23 p.p.m. (equivalent to three protons) was characteristic of CH_3 protons in CH_3–CH–SH structures. In the n.m.r. spectrum of II the corresponding doublet was at 1.00 p.p.m., consistent with our observation that nitrogen raises the frequency of nearby protons a smaller degree than does sulfur. Both spectra were dominated by the single strong resonance from the CH_3–N protons at 2.20 p.p.m.

In the earlier work[2] on reaction of amines with isobutylene sulfide the products were shown to be tertiary mercaptans by a color test and by the ease of formation of sulfenyl iodides. In our investigation the isobutylene sulfide–piperidine reaction was repeated, and the n.m.r. spectrum of the product was consistent with that expected for 1-(1-piperidyl)-2-methyl-2-propanethiol. A single sharp peak, equivalent to six CH_3 protons, was observed at 1.27 p.p.m. The two methylene protons between the quaternary carbon and tertiary nitrogen gave a single sharp peak at 2.28 p.p.m. During the course of the work 1-*n*-octylamino-2-methyl-2-propanethiol and 1-*n*-decylamino-2-methyl-2-propanethiol were

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[1] This work was done, in part, under Contract DA-49-193-MD-2069 with the U. S. Army Medical Research and Development Command.

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[5] S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **27**, 2846 (1962).

[6] G. Meguerian and L. B. Clapp, *J. Am. Chem. Soc.*, **73**, 2121 (1951).

[7] The n.m.r. spectra were determined with a Varian A-60 console using a 12-in. magnet. Chemical shifts are given in parts per million from tetramethylsilane.