[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE UNIVERSITY]

Synthesis and Characterization of Nitraminotetrazoles[1]

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The preparation of several 1-alkyl-5-nitramino- and 5-alkyl-nitraminotetrazoles is described. Comparison of the apparent dissociation constants and ultraviolet absorption spectra of these compounds and of 5-nitraminotetrazole indicates that the strong first dissociation of the latter is associated with the hydrogen of the nitramino group.

Recently 5-nitraminotetrazole was characterized as a dibasic acid with *p*K values of 2.5 and 6.1.[3] Since the two hydrogens in the structure do not necessarily occupy equivalent positions, it became of interest to determine whether the hydrogen attached to the tetrazole ring or the hydrogen of the nitramino group was responsible for the relatively strongly acidic character of the compound. Lieber *et al.*[4,5] have assigned the stronger acid function to the hydrogen of the nitramino group, a conclusion based on comparison of ultraviolet absorption spectra of 5-nitraminotetrazole and several of its salts with the spectra of nitramide and N-nitro-N′-aminoguanidine. Since corresponding data for other tetrazole derivatives were not available, it was thought that a more direct approach was needed to establish definitely which hydrogen was involved in the first dissociation of 5-nitraminotetrazole.

An analogy has been developed between the apparent acidity of 5-substituted tetrazoles, R—CN_4H, and carboxylic acids, R—COOH, and it has been shown that the nature of the group R affects the apparent acidic dissociation constant of the 5-substituted tetrazoles in much the same way as it affects the dissociation constant of the carboxylic acid.[6,7,8] Due to the instability of carbamic acid and most of its N-substituted derivatives, a direct comparison with the 5-aminotetrazoles is not feasible. Baur[9] has shown that 5-aminotetrazole behaves as a weak acid ($K_a = 5.73 \times 10^{-7}$; $pK_a = 6.24$). Acetylation of 5-aminotetrazole causes a marked increase in the acidic dissociation of the tetrazole group ($pK = 4.53$).[10] It would hardly be expected that the electron withdrawing effect of the acetyl group would be sufficiently great to endow the amidic hydrogen with strongly acidic character, and 5-acetylaminotetrazole behaves as a monobasic acid in aqueous media.

The introduction of a nitro group in place of one of the amino hydrogens of 5-aminotetrazole may be considered as acylation with a strongly electron withdrawing group. The resulting 5-nitraminotetrazole is capable of existing in a number of tautomeric forms (Fig. 1). It will be noted that forms D and E are identical, also, in form C, due to certain elements of symmetry in the 5-tetrazolyl system, the two hydrogens occupy equivalent positions on the ring and cannot be distinguished. The first dissociation of 5-nitraminotetrazole as a strong acid may involve either of two resonance hybrids of the tetrazole anion that can be developed from contributing forms (*a*) of the anion obtained by dissociation of the nuclear hydrogen or (*b*) resulting from dissociation of the nitramino hydrogen (Fig. 2).

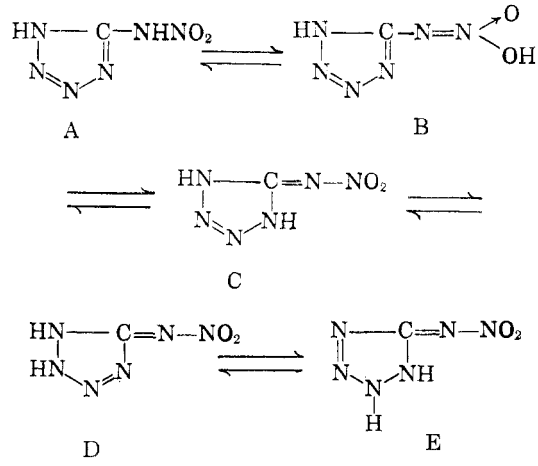

FIG. 1

In order to determine which type of resonance, Fig. 2 (*a*) or (*b*), predominated, two groups of monoalkyl nitraminotetrazoles were prepared and their physical properties studied. The first included 1-methyl-5-nitraminotetrazole (I) and 1-ethyl-5-nitraminotetrazole (II) in both of which only dis-

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(3) Herbst and Garrison, *J. Org. Chem.*, **18**, 941 (1953).

(4) Lieber, Patinkin, and Tao, *J. Am. Chem. Soc.*, **73**, 1792 (1951).

(5) Lieber, Sherman, and Patinkin, *J. Am. Chem. Soc.*, **73**, 2329 (1951).

(6) Mihina and Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(7) Garbrecht and Herbst, *J. Org. Chem.*, **18**, 1022 (1953).

(8) Herbst, in Graff, *Essays in Biochemistry*, John Wiley & Sons, Inc., New York, 1956, pp. 141–155.

(9) Baur, *Z. physik. Chem.*, **23**, 409 (1897).

(10) Herbst and Garbrecht, *J. Org. Chem.*, **18**, 1283 (1953).

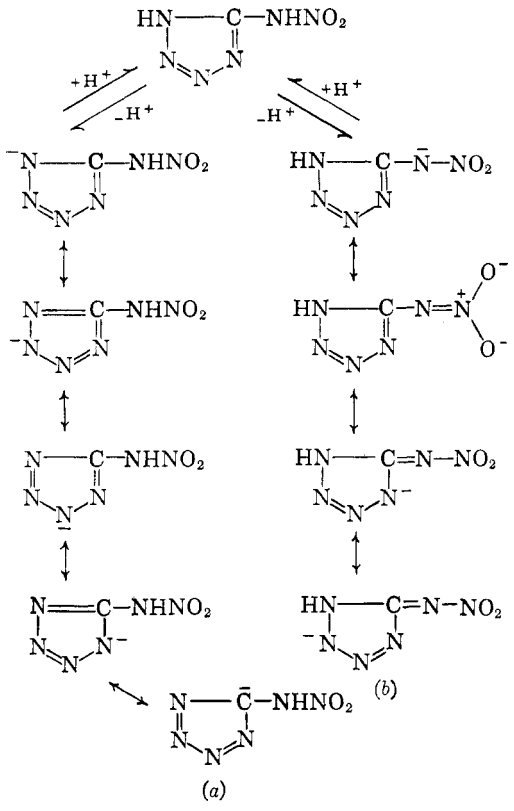
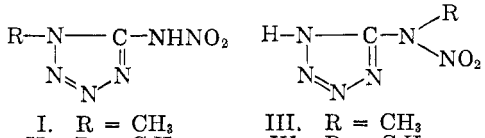


FIG. 2

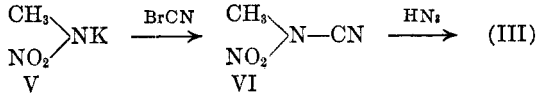
sociation and resonance of type (*b*) is expected; the second consisted of 5-methylnitraminotetrazole (III) and 5-ethylnitraminotetrazole (IV) in both of which only dissociation and resonance of type (*a*) is probable.



I. R = CH_3 III. R = CH_3
II. R = C_2H_5 IV. R = C_2H_5

1-Methyl- and 1-ethyl-5-aminotetrazole and 5-methylamino- and 5-ethylaminotetrazole were prepared by the methods of Garbrecht and Herbst.[7,11] The corresponding alkyl nitraminotetrazoles were prepared by dehydration of the appropriate alkyl 5-aminotetrazole nitrates by adaptations of the procedure of Herbst and Garrison.[3] No attempt was made to find the optimum conditions for the preparation and isolation of the alkyl nitraminotetrazoles.

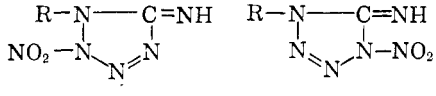
Since nitration of the 5-alkylaminotetrazoles could have taken place on the tetrazole ring in positions 1 or 2 with formation of 1-nitro- or 2-nitro-5-alkylaminotetrazoles, an independent synthesis of 5-methylnitraminotetrazole was carried out as follows: potassium methylnitramine (V), prepared according to Franchimont,[12] was treated with cyanogen bromide to form methylnitrocyanamide (VI). After interaction of VI and hydrazoic acid, III was isolated. The product was identical with the compound obtained by nitration of 5-methylaminotetrazole as shown by melting point, mixture melting point, infrared absorption spectrum and characterization as the 2-aminopyridine salt.



V VI

An attempt to characterize the product of nitration of 5-methylaminotetrazole by reduction to the corresponding hydrazino compound was unsuccessful. After hydrogenation of (III) only methylaminotetrazole, presumably formed by hydrogenolysis of the hydrazino compound, could be isolated.

The structure of 5-ethylnitraminotetrazole is assigned on the basis of analogy of method of preparation and similarity of properties with those of III. Although the structure of the 1-alkyl-5-nitraaminotetrazoles is not supported by independent synthesis, it seems reasonable to assume that nitration of the 1-alkyl-5-aminotetrazoles follows a similar course, an assumption supported by the properties of the products, particularly their dissociation constants and ultraviolet absorption spectra. The 1-alkyl-5-nitraminotetrazoles are moderately strong acids (*p*K 2.7–2.8). Had nitration taken place on one of the ring nitrogens, a 1-alkyl-2-(or 4)-nitro-5-iminotetrazoline (VII) would have resulted. It is doubtful that ring nitration would have resulted in such strongly acidic compounds.



VIIa VIIb

The apparent dissociation constants of the alkyl nitraminotetrazoles are given in Table I. Both the 1-alkyl-5-nitramino- and the 5-alkylnitraminotetrazoles have *p*K values in the range 2.7–2.9. On the basis of dissociation constants resonance of either type (*a*) or (*b*) could explain the strong first dissociation of 5-nitraminotetrazole.

TABLE I

APPARENT DISSOCIATION CONSTANTS OF ALKYL 5-NITRAMINOTETRAZOLES

Compound	Apparent	
	pK_1	$K_1 \times 10^3$
5-Nitraminotetrazole	2.55[a]	2.8[a]
I	2.72	1.9
II	2.74	1.8
III	2.88	1.3
IV	2.86	1.4

[a] The values for the second apparent dissociation constant are $pK = 6.04$, $K = 9.1 \times 10^{-7}$.

(11) Garbrecht and Herbst, *J. Org. Chem.*, **18**, 1014 (1953).

(12) Umbgrove and Franchimont, *Rec. trav. chim.*, **15**, 195 (1895).

Since both the nuclear and the nitramino hydrogen dissociate with equal ease, methods other than measurement of the dissociation constants were needed to differentiate between dissociations and resonance of type (*a*) and (*b*). 5-Nitraminotetrazole exhibits strong absorption in the ultraviolet with a maximum at 277–278 mμ and a minimum at 237 mμ.[3,5] The 5-alkylnitraminotetrazoles should be almost completely dissociated in aqueous solution to a tetrazole anion of type (*a*), while the 1-alkyl-5-nitraminotetrazoles should be almost completely dissociated to a tetrazole anion of type (*b*). Resonance hybrids of types (*a*) and (*b*) should show differences in their ultraviolet absorption. Furthermore, since both tetrazole anions are formed from relatively strong acids, conversion to the sodium or potassium salts should cause little, if any, change in the ultraviolet absorption. These considerations were realized. Both I and II and their potassium salts exhibited a maximum at 277–278 mμ and a minimum at 237 mμ. On the other hand, III and IV and their potassium salts exhibited a maximum at 246 mμ; the minimum was out of the range of the instrument. Since the maxima and minima of 5-nitraminotetrazole, I and II, both as such and as potassium salts, are identical, it may be concluded that the hydrogen of the nitramino group of 5-nitraminotetrazole is responsible for the first dissociation of this compound with a tetrazole anion of type (*b*) forming. The ultraviolet absorption of 5-nitraminotetrazole in a large excess of potassium hydroxide solution, in which it should exist as a doubly charged anion, is very similar to the spectra in aqueous solution of both itself and the 1-alkyl-5-nitraminotetrazoles. The maximum is shifted toward shorter wave lengths, 271–272 mμ for the doubly charged anion as compared with 277–278 mμ for the singly charged anion; the minima are 232 mμ and 237 mμ, respectively. The results indicate that resonance of type *b* is modified by the second negative charge but still predominates.

The four alkyl nitraminotetrazoles were further characterized as potassium salts, 2-aminopyridine salts, and by infrared absorption spectra (Fig. 3).

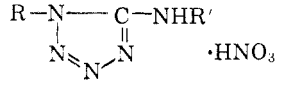
EXPERIMENTAL[13]

Alkyl 5-aminotetrazoles. 1-Methyl- and 1-ethyl-5-aminotetrazole were prepared from the appropriate alkyl cyanamides by interaction with hydrazoic acid.[11] 5-Methylamino- and 5-ethylamino-tetrazole were prepared by hydrogenolysis of 5-benzylmethylamino- and 5-benzylethylaminotetrazole.[7,14]

Alkyl 5-aminotetrazole nitrates. The appropriate alkyl 5-aminotetrazole was added with cooling to concentrated nitric acid (sp. gr. 1.419) in 1:1.5 molar proportion. The mixture was warmed gently, avoiding overheating, until all the tetrazole had dissolved. The nitric acid salt which separated on cooling was filtered, washed with ethyl ether and used without crystallization. Melting points and analyses are given in Table II.

TABLE II

ALKYL 5-AMINOTETRAZOLE NITRATES



R	R′	M.P., °C.	Formula	Analysis: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
CH_3	H	158–160	$C_2H_6N_6O_3$	14.8	3.7	51.8	15.2	3.6	51.9
C_2H_5	H	125–127	$C_3H_8N_6O_3$	20.5	4.6	47.7	20.7	4.5	47.6
H	CH_3	70–72	$C_2H_6N_6O_3$	14.8	3.7	51.8	14.6	3.6	51.9
H	C_2H_5	68–70	$C_3H_8N_6O_3$	20.5	4.6	47.7	20.8	4.8	47.2

1-Methyl-5-nitraminotetrazole (I). To 8 ml. of ice cold concentrated sulfuric acid was added 6.9 g. (0.023 mole) of 1-methyl-5-aminotetrazole nitrate. The mixture was allowed to warm slowly to 20° and then poured slowly onto 50 g. of ice. After about 90% of the sulfuric acid had been neutralized by addition of the calculated amount of potassium hydroxide, the aqueous solution was extracted with ether in a continuous extractor for three days. The ether solution was separated, dried over sodium sulfate, and evaporated to about 100 ml. on a steam bath. The remaining ether was removed at room temperature in a current of dry air. The solid residue was recrystallized by dissolving in a small amount of ethyl acetate and adding four volumes of petroleum ether. Yield, 1.9 g. (31%), m.p. 129–130°.

Anal. Calcd. for $C_2H_4N_6O_2$: C, 16.7; H, 2.8; N, 58.3. Found: C, 16.8; H, 2.7; N, 58.1.

1-Ethyl-5-nitraminotetrazole (II). Five grams of 1-ethyl-5-aminotetrazole nitrate was dissolved in 100 ml. of cold concentrated sulfuric acid by addition in small portions so that the temperature did not rise above 10°. The mixture was allowed to warm slowly to 20° and then poured into 150 ml. of ice cold ether. The sulfuric acid was further extracted with two 150-ml. and four 50-ml. portions of ether. The combined extracts were evaporated to dryness at room temperature. The crude product was recrystallized from benzene. Yield, 1.15 g. (26%), m.p. 102–103°.

Anal. Calcd. for $C_3H_6N_6O_2$: C, 22.8; H, 3.8; N, 53.1. Found: C, 23.1; H, 3.7; N, 53.0.

5-Methylnitraminotetrazole (III). (*a*) 5-Methylaminotetrazole nitrate (6.5 g., 0.04 mole) was added slowly with cooling and stirring to 5.5 ml. of ice cold concentrated sulfuric acid. The mixture was allowed to stand in an ice

(13) All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(14) Finnegan, Henry, and Lieber, *J. Org. Chem.*, **18**, 779 (1953); Garbrecht and Herbst, *J. Org. Chem.*, **18**, 1269 (1953).

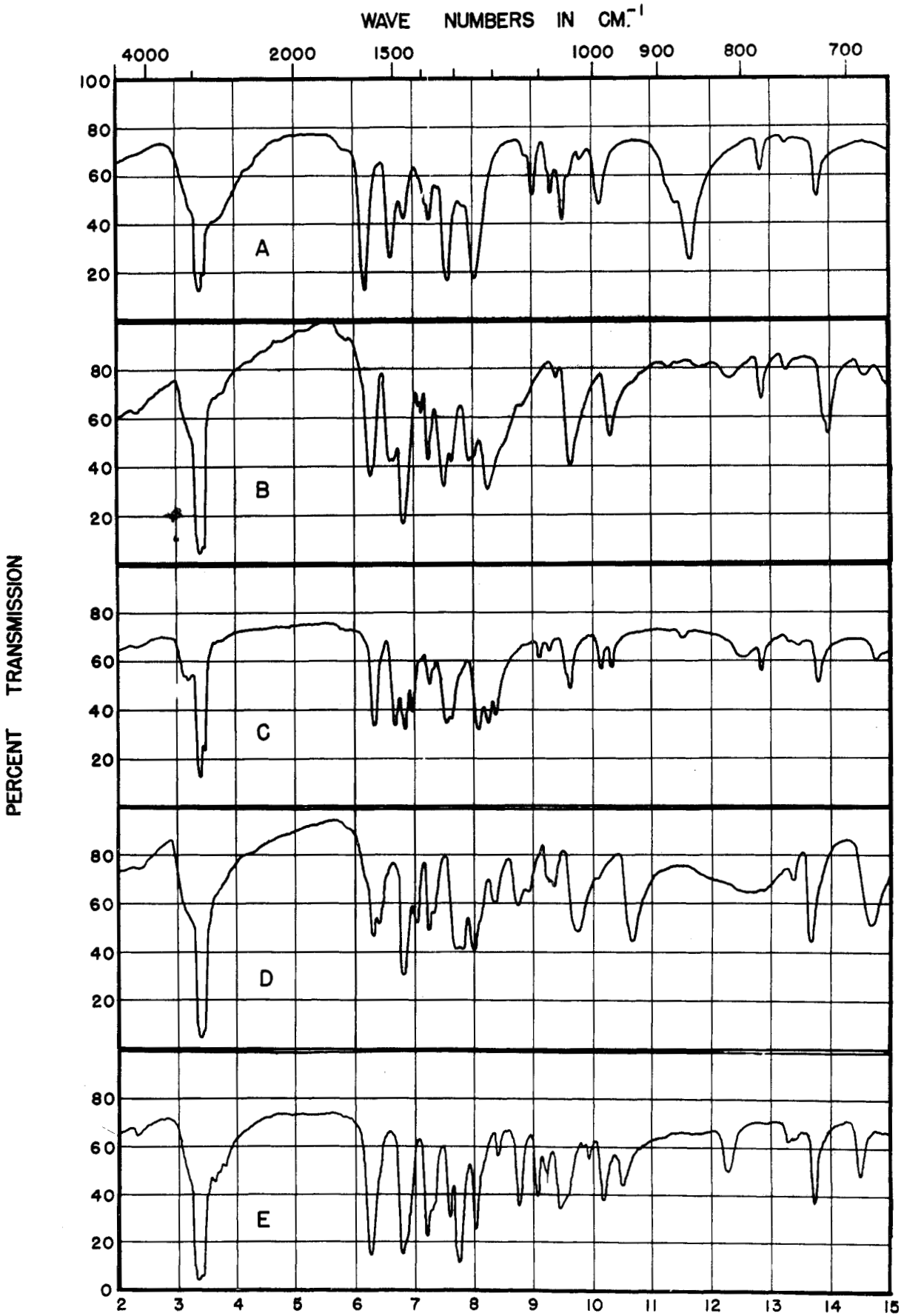


FIG. 3.—INFRARED ABSORPTION SPECTRA IN WHITE MINERAL OIL MULLS OF (A) 5-Nitraminotetrazole; (B) 1-Methyl-5-Nitraminotetrazole; (C) 1-Ethyl-5-nitraminotetrazole; (D) 5-Methylnitraminotetrazole; (E) 5-Ethylnitraminotetrazole.

bath for 15 min. and then poured onto 30 g. of ice. (On one occasion the product crystallized from the aqueous acid solution but this could not be repeated.) The aqueous solution was extracted with two 150-ml. and three 50-ml. portions of ether. The combined ethereal extracts were dried over sodium sulfate and evaporated to dryness at room temperature. The residue was recrystallized by dissolving in the minimum volume of ethyl acetate and adding three volumes of petroleum ether. Yield, 2.0 g. (35%), m.p. 112–113°.

Anal. Calcd. for $C_2H_4N_6O_2$: C, 16.7; H, 2.8; N, 58.3. Found: C, 16.7; H, 3.0; N, 58.0.

(*b*) Forty grams of N,N'-dinitrodimethyloxamide[12] was treated with 160 ml. of concentrated aqueous ammonia (sp. gr. 0.899). The mixture warmed spontaneously to about 40°. After cooling to room temperature the mixture was made slightly acid to Congo red with 10% sulfuric acid. The colorless precipitate of oxamide was removed by filtration and the filtrate was extracted with three 100-ml. portions of ether. An equivalent amount of potassium hydroxide dissolved in 100 ml. of methanol was added to the ethereal extracts. Upon evaporation of the solution to a small volume potassium methylnitramine separated as a colorless powder. Yield, 18 g., m.p. 220°.[12]

One-tenth mole (11.4 g.) of potassium methylnitramine suspended in 50 ml. of methanol was treated with 10.6 g. (0.1 mole) of cyanogen bromide in 100 ml. of ether. The solution was filtered to remove potassium bromide and the filtrate evaporated to a small volume at room temperature. At this point the mixture separated into two layers. The upper, water-insoluble layer was assumed to be methylnitrocyanamide. The product was not purified.

Four grams of crude methylnitrocyanamide was dissolved in 25 ml. of a 13% solution of hydrazoic acid in benzene and allowed to stand at room temperature for two days when an additional 25 ml. of hydrazoic acid solution was added and the mixture boiled under reflux for 2 hr. After cooling and evaporating to a small volume at room temperature, 100 ml. of petroleum ether was added. The mixture separated into two layers, the upper, petroleum ether layer, was decanted and the lower layer was dissolved in ethyl acetate. After dilution of the ethyl acetate solution with four volumes of petroleum ether, the product separated slowly as long, colorless needles, m.p. 113–114°. The material was identical with III as prepared in (*a*) as shown by mixture melting point, infrared spectrum, and identity of the 2-aminopyridine salts.

5-Ethylnitraminotetrazole (IV). 5-Ethylaminotetrazole nitrate (2.0 g.) was dissolved in 2.0 ml. of cold concentrated sulfuric acid. The cold solution was poured over 20 g. of ice, the aqueous solution was then extracted twice with 100-ml. portions of ether, the ethereal extracts dried over sodium sulfate and evaporated to dryness at room temperature. The residue was dissolved in the minimum volume of cold ethyl acetate and the clear solution diluted with a large volume of petroleum ether. IV separated as colorless plates, yield 0.7 g. (25%), m.p. 88–89°.

Anal. Calcd. for $C_3H_6N_6O_2$: C, 22.8; H, 3.8; N, 53.1. Found: C, 22.7; H, 4.0; N, 53.2.

Reduction of 5-methylnitraminotetrazole. 5-Methylnitraminotetrazole (1.44 g., 0.01 mole) was dissolved in 50 ml. of absolute ethanol and reduced with hydrogen at 50 p.s.i. using palladium oxide catalyst. When three molar equivalents of hydrogen had been absorbed, the reduction was stopped and the catalyst removed by filtration. The alcoholic solution was treated with 1.06 g. of benzaldehyde and evaporated to dryness. The residue was recrystallized twice from 1,4-dioxane. Elemental analysis and mixture melting point indicated that the product was 5-methylaminotetrazole. Yield 0.5 g. (50%), m.p. 185–187°. (The product resolidified on further heating and remelted at 224–225°.)[14]

Anal. Calcd. for $C_2H_5N_5$: C, 24.2; H, 5.1; N, 70.7. Found. C, 24.4; H, 5.1; N, 70.4.

Potassium salts of alkyl nitraminotetrazoles. The potassium salts were prepared by dissolving the alkyl nitraminotetrazole in ether and adding methanolic potassium hydrox-

TABLE III

2-AMINOPYRIDINE SALTS OF ALKYL NITRAMINOTETRAZOLES

2-Aminopyridine Salt of	M.P., °C.	Formula	Analysis					
			Calculated			Found		
			C	H	N	C	H	N
I	177–178	$C_7H_{10}N_8O_2$	35.3	4.2	47.0	35.5	4.4	46.8
II	131–132	$C_8H_{12}N_8O_2$	38.1	4.8	44.4	38.2	4.7	44.2
III	165–167	$C_7H_{10}N_8O_2$	35.3	4.2	47.0	35.1	4.2	47.1
IV	139–140	$C_8H_{12}N_8O_2$	38.1	4.8	44.4	38.5	5.1	44.1

TABLE IV

ULTRAVIOLET ABSORPTION OF ALKYL NITRAMINOTETRAZOLES AND THEIR POTASSIUM SALTS IN 1×10^{-4} AQUEOUS SOLUTION

Compound	Ultraviolet Absorption			
	Maximum		Minimum	
	mμ	$\epsilon \times 10^{-3}$	mμ	$\epsilon \times 10^{-3}$
5-Nitraminotetrazole	277	(1.285)[a]	237	(0.131)[a]
I	277	9.77	237	2.9
II	277	9.90	237	2.72
III	246	4.70	—	—
IV	246	4.95	—	—
Potassium 5-nitraminotetrazole	277[b]		237[b]	
Potassium I	277	8.10	236	2.42
Potassium II	277	7.93	236	2.51
Potassium III	246	5.29	—	—
Potassium IV	246	5.09	—	—
Dipotassium 5-nitraminotetrazole	272	6.09	230	2.64

[a] $\epsilon \times 10^{-4}$. [b] Reference 5.

ide until precipitation was complete. The salts were filtered off and recrystallized from ethyl acetate. Yields were quantitative. The potassium salts decompose explosively at, or near, their melting points which are as follows: potassium I, 170–171°; potassium II, 205–206°; potassium III, 191–192°; potassium IV, 174–175°. Due to the explosive nature of these salts they were not subjected to elemental analysis. Ultraviolet spectra of the salts were identical with those of the free alkyl nitraminotetrazoles in water or in an equivalent amount of dilute potassium hydroxide solution.

2-Aminopyridine salts of alkyl nitraminotetrazoles were prepared by treating an ethereal solution of the appropriate alkyl nitraminotetrazole with an equivalent amount of 2-aminopyridine dissolved in ether and recrystallizing from 1:1 isopropyl alcohol-ethyl alcohol. Yields were quantitative. Melting points and analyses are given in Table III.

Potentiometric titrations were done using a Beckman Model G *p*H meter. Approximately 0.01 molar solutions of the alkyl nitraminotetrazoles in water were titrated with standard 0.1*N* aqueous potassium hydroxide at 25 ± 0.02°. The results are summarized in Table I.

Ultraviolet absorption spectra were determined with a Beckman model DU spectrophotometer with approximately 1×10^{-4} molar aqueous solutions of the alkyl nitraminotetrazoles or their potassium salts. Spectra of the alkyl nitraminotetrazoles in an equivalent amount of aqueous potassium hydroxide and of 5-nitraminotetrazole with two equivalents of aqueous potassium hydroxide were also determined. The location of maxima and minima and extinction coefficients is given in Table IV.

EAST LANSING, MICH.

[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY]

Vibrational Frequencies of Isatin Oximes

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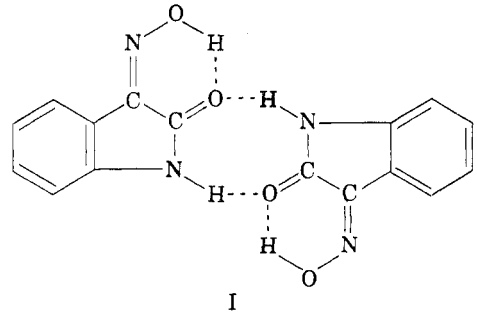
The infrared spectra of a set of substituted isatin-β-oximes and related compounds indicate that the former contain both intra- and intermolecular hydrogen bonding. Comparatively large shifts in the α-carbonyl group stretching frequencies occur with variation in ring substituents similar to the shifts observed with substituted oxindoles and with substituted acetanilides in the solid state. These shifts increase with the appropriate σ values of the substituents. Frequencies associated with the oxime group occur near 1660, 1200, and 1000 cm.$^{-1}$ and are referred to C=N stretching, N—O—H deformation and N—OH stretching modes, respectively. The 1660 cm.$^{-1}$ band is of variable intensity. The medium intensity deformation mode decreases in frequency with increase in the σ value of the substituent, while the 1000 cm.$^{-1}$ band is the strongest in the spectrum and increases in frequency with the σ value. Lower frequency ring vibrations are correlated with the substitution pattern.

Few systematic data are available on the infrared spectra of oximes. Palm and Werbin[1] found that α- and β-oximes in nujol mulls possessed associated OH stretching frequencies near 3250 and 3150 cm.$^{-1}$, respectively, and bands near 1650, 1300, and 920 cm.$^{-1}$ which were ascribed to C=N stretching, OH deformation and N—OH stretching vibrations. Duyckwerts[2] provided further data in a study of some oximes and their metal coordination complexes. Substituted isatin-β-oximes were examined for information on their structure, on the position of bands characteristic of the oxime group and for the effect of substituents on these frequencies. A number of possible isomeric structures exist for these compounds, together with a considerable variety of hydrogen-bonded association complexes. Infrared results obtained with isatin-β-oximes substituted in the benzene ring are consistent with the assumption that formula I represents the structure and mode of association of compounds of this type. Other association forms appear less likely.



I

Free OH and NH stretching absorptions, to be expected near 3650 and 3450 cm.$^{-1}$, respectively, are absent from all oximes in Table I. Intense absorption near 1720 cm.$^{-1}$, produced by the stretching vibrations of the carbonyl group, and the presence, in some cases, of a C=N stretching frequency near 1660 cm.$^{-1}$ confirm the usually ascribed molecular structures, but the existence of an intense and broad band between 3200 and 2600 cm.$^{-1}$ indicates that the structures are involved in extensive hydrogen bonding. N-Methylindoxyl oxime II, which can associate only through the oxime groups, possesses a broad band of medium intensity with a fairly sharp maximum at 3210 cm.$^{-1}$ in accordance with the behavior of simpler oximes.[1] The sharp and lower intensity band at 2922 cm.$^{-1}$ in both N-methylindoxyl oxime and isatin is produced by CH stretching vibration. Remaining compounds in Table I possess an intense broad band near 3200

(1) A. Palm and H. Werbin, *Can. J. Chem.*, **31**, 1004 (1953).

(2) G. Duyckwerts, *Bull. soc. roy. sci. Liège*, **21**, 196 (1952).