5,5-Dimethylol-6-hydroxyhexanoic Acid and Its Trinitrate Derivative

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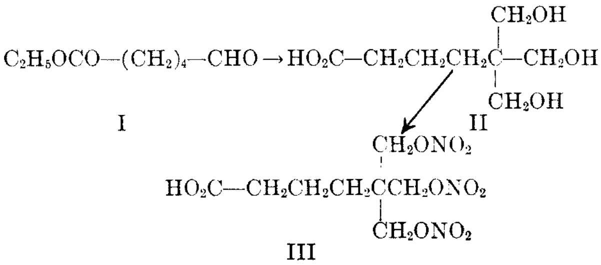
A previous communication described the preparation of several monoacid esters of pentaerythritol trinitrate.[1] These compounds, upon pharmacological examination, exhibited a very pronounced hypotensive action. One compound in particular, pentaerythritol trinitrate hydrogen succinate, proved to be quite interesting physiologically. In view of the pharmacological effects of this series of compounds, it was deemed desirable to prepare similar materials which lacked the internal ester grouping. It was hoped that the absence of this grouping would provide compounds which would be less subject to hydrolytic attack *in vivo*, and would consequently have a longer duration of action. We are therefore reporting the preparation of 5,5-dimethylol-6-hydroxyhexanoic acid (II) and the trinitrate ester (III) of this new polyalcohol.



$$C_2H_5OCO{-}(CH_2)_4{-}CHO \rightarrow HO_2C{-}CH_2CH_2CH_2\overset{CH_2OH}{\underset{CH_2OH}{C}}{-}CH_2OH$$

I II

$$HO_2C{-}CH_2CH_2CH_2\overset{CH_2ONO_2}{\underset{CH_2ONO_2}{C}}CH_2ONO_2$$

III

The Rosenmund reduction of ethyl 5-chloroformylvalerate afforded ethyl 5-formylvalerate[2] (I) as the starting material for this work. This aldehyde was chosen to preclude the possibility of lactone formation during the acidic conditions required for the subsequent nitration step. The reaction of ethyl 5-formylvalerate with formaldehyde did not lead to ethyl 5,5-dimethylol-6-hydroxyhexanoate. Instead, in the course of the reaction the ester grouping was hydrolyzed and the desired 5,5-dimethylol-6-hydroxyhexanoic acid (II) was formed directly in low yield. The product was accompanied by the formation of considerable polymeric material. Nitration of this polyalcohol, using 95% nitric acid, produced 5,5-dimethylol-6-hydroxyhexanoic acid trinitrate (III) in good yield.

The preliminary pharmacological examination of this new nitrate ester has shown it to have a very marked hypotensive action.

Acknowledgment. The microanalyses were performed by H. L. Hunter, G. Maciak, and Miss Gloria Beckmann. The author wishes to express his appreciation to Dr. F. G. Henderson for the preliminary pharmacological data.

EXPERIMENTAL[3]

5,5-Dimethylol-6-hydroxyhexanoic acid (II). A mixture of 79 g. (0.5 mole) of ethyl 5-formylvalerate, 210 g. (2.5 moles) of 37% formalin solution, and 300 ml. of water was stirred vigorously. A small volume (25 ml.) of ethanol was added to help effect solution of the aldehyde. Calcium oxide was added in small portions until a total of 74.1 g. (1.0 mole) had been added. This addition caused the temperature to rise to a high of 44°. After all of the calcium oxide had been added, the mixture was stirred at 50° for 3 hours. The mixture was cooled and made slightly acid with 10% sulfuric acid. Filter Aid was added and the precipitated calcium sulfate removed by vacuum filtration. After washing the filter cake with 500 ml. of boiling water, the aqueous filtrate and washings were concentrated *in vacuo* on the steam-bath to a viscous syrup. Upon trituration with 150 ml. of ethanol the syrup quickly changed to a white, amorphous powder. This was collected by filtration and air-dried. After recrystallization from hot water there was obtained 11.6 g. (16.6%) of a white solid; m.p. 157–160°. Several recrystallizations from water were necessary to prepare a pure sample; m.p. 165–166°. Infrared examination indicated the presence of a free carboxylic acid function. Titration data indicated a molecular weight of 200 as compared to the theoretical value of 192.

Anal. Calc'd for $C_8H_{16}O_5$: C, 50.00; H, 8.34. Found: C, 50.09; H, 8.43.

The filtrates from above were evaporated *in vacuo* to give a considerable amount of tacky polymeric material which appeared to lose formaldehyde slowly. This was not investigated further.

5,5-Dimethylol-6-hydroxyhexanoic acid trinitrate (III). To 125 ml. of 95% nitric acid was added 6.6 g. (0.03 mole) of the trihydroxy compound in small portions while keeping the temperature at 0–5°. After all was added, the mixture was stirred for one hour at 0–5°, and then was poured onto 300 g. of crushed ice. This caused the separation of a gummy material which quickly crystallized. The product was collected by filtration and washed on the filter with cold water. After air-drying, the product weighed 8.3 g. (85%); m.p. 109–112°. The sample for analysis was recrystallized twice from absolute ethanol; m.p. 115–116°.

Anal. Calc'd for $C_8H_{13}N_3O_{11}$: C, 29.36; H, 4.00; N, 12.84. Found: C, 29.61; H, 4.12; N, 12.46.

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[1] Cannon, *J. Am. Chem. Soc.*, **77**, 6369 (1955).

[2] Brown, Armstrong, Moyer, Anslow, Baker, Querry, Bernstein, and Safir, *J. Org. Chem.*, 12, 160 (1947).

[3] Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

Polynitrogen Systems from the Hydrazinocarbonic Acids. Part VI. Reactions of Some Amines with Guanyl Azide Nitrate and Nitroguanyl Azide[1]

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In two other papers[3] of this series, we have in-

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[1] See also F. L. Scott, A. J. Kocjarski, and J. Reilly, *Nature*, (*London*), **170**, 922 (1952).

[2] To whom inquiries concerning reprints are to be sent. Present address, Chemistry Department, University of California at Los Angeles, Los Angeles 24, California.

[3] (a) Part IV, F. L. Scott, A. J. Kocjarski, and J. Reilly, *J. Org. Chem.*, (being prepared for publication); (b) Part V, F. L. Scott, M. T. Scott, and J. Reilly, *J. Am. Chem. Soc.*, (in preparation); (c) See also, F. L. Scott, *Chemistry & Industry*, 959 (1954).

vestigated the influence of bases upon the reactions of some carbamyl azides, both those which readily undergo the Curtis rearrangement and those which do not. The present note appends some data on the effect bases have on the cyclizations of some imidyl azides (I). Figure 1 summarizes the possible modes of competition involved.

For the two azides chosen, *viz.* guanyl azide nitrate (IA) and nitroguanyl azide (IB), these cyclizations, (B, C, Fig. I), have been recently[4] placed on a quantitative basis. The excellent data of Henry, *et al.*,[4] disclose the rate of tetrazole formation of (IA), at *p*H 8.8–9.3, and at 266.8°K in water, was 2.1×10^{-3} sec.$^{-1}$ and that of (IB), at *p*H 7.9–8.2, at 266.6°K, again in water, was 9.6×10^{-4} sec.$^{-1}$ Despite these ready closures, however, some azide displacement reactions of (IA) and (IB) with nucleophiles have been effected previously, *e.g.*, with hydrazine hydrate, phenylhydrazine, etc.[5] We have now found that reaction, in refluxing aqueous ethanolic solution, of IA with thiosemicarbazide, semioxamazide, 1- or 4-phenylthiosemicarbazide, phenylhydrazine-*p*-sulfonic acid, asymmetric methylphenylhydrazine, methylhydrazine sulfate, or aniline, all resulted in the formation of 5-aminotetrazole[6] in 85–95% yield. Under these conditions therefore no interference (A, D, Fig. 1) was offered by the extraneous nucleophiles to the cyclization process. In order to better compete with the intramolecular closure, use of the nucleophiles themselves as joint solvent-reactants was next effected. Under these latter conditions, benzylamine, cyclohexylamine, di-*n*-butylamine, morpholine, piperidine, and pyrrolidine afforded with IA the corresponding amine salts (IVA) of 5-aminotetrazole.[7] To confirm their identification, these salts were also synthesized by an *ad hoc* technique.[7] Aniline alone, yielded a displacement reaction, resulting in a 70% yield of phenylguanidine nitrate (IIIA). All these undiluted amine reactions necessitated careful control of temperature, and rate of mixing, as without such precautions, some trials resulted in violent explosions.

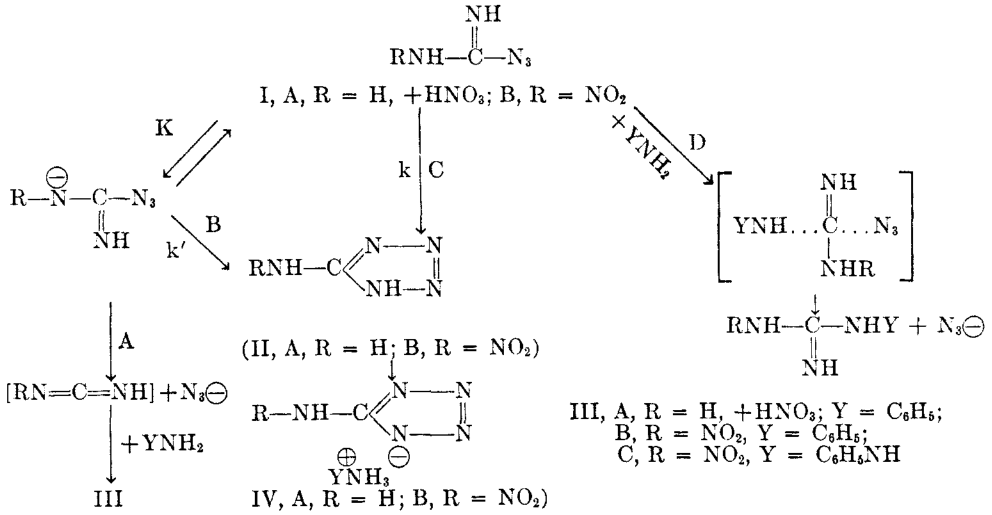

FIGURE 1.

With IB, as has been indicated elsewhere,[5b] reaction with bases in ethanolic or ethereal solution, results in ready formation of the appropriate 5-nitraminotetrazole (IVB) salts. We have now found that, without additional solvent, aniline formed with IB, at room temperature, 1-phenyl-3-nitroguanidine (IIIB) in 75% yield, and phenylhydrazine, similarly, gave 1-phenyl-4-nitroaminoguanidine (IIIC) in comparable quantity. Under analogous conditions, *viz.* IB plus undiluted amine, cyclohexylamine, morpholine, piperidine, and *n*-propylamine afforded high yields of the corresponding (IVB) salts. These reactions were again conducted under carefully controlled conditions, as an even higher explosion hazard (than with IA) exists, without such care.

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(4) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **77**, 2264 (1955).

(5) (a) For some earlier work on hydrazine, and hydrazide, displacement reactions see F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Appl. Chem.*, **2**, 368 (1952); (b) See also E. Lieber, E. Sherman, R. A. Henry, and J. Cohen, *J. Am. Chem. Soc.*, **73**, 2327 (1951) and E. Lieber, C. C. Herrick, and E. Sherman, *J. Am. Chem. Soc.*, **74**, 2684 (1952).

(6) To some extent these reactions may have resulted in the formation of salts of 5-aminotetrazole, initially, which then hydrolyzed during work-up, or otherwise. For example, apparently IA reacted, without additional solvent, with allylamine, methylamine, and isopropylamine, under our experimental conditions, to form IIA and not its expected salts (IVA). For our present purpose, *viz.* the competition of azide displacement *versus* tetrazole formation, whether IIA, or its salts, was isolated was essentially immaterial as tetrazole formation itself was the point sought. The extent that we isolated the salts of the tetrazoles (IIA) and (IIB) under our reaction conditions we have reported, otherwise no special effort was made to obtain the ammonium salts.

(7) At essentially the same time as we originally reported our isolation of some salts of (IIA), see F. L. Scott and J. Reilly, *Chemistry & Industry*, 907 (1952), R. A. Henry reported their *ad hoc* synthesis directly from IIA. see *J. Am Chem. Soc.*, **74**, 6303 (1952).

As suggested by the above, the tetrazole cyclizations of the two imidyl azides appear insensitive to change in dielectric constant, reaction occurring with comparable ease in ethanol (D = 24),[8] in ether (D = 4.3), or in a variety of amine solvents, wherein the dielectric constant varies from 3 to 6. This insensitivity is in accord with some qualitative observations of Henry, *et al.*,[9] and also is consistent with the solvent requirements of a purely intramolecular process. In the cyclizations effected in amines, the low dielectric constant of the solvent is undoubtedly compensated by its high basicity, (with the amines utilized the pK_a range ran from 8.7 to 11.2), so that the tetrazole closures therein appear undoubtedly to be base-catalyzed. This may,[10] or may not, be synomomous with postulating an intermediate anion (as in B, Fig. 1), in the cyclization. If such an anion were involved, then the over-all, or observed, rate of closure should be composite, ($k_{obs.} = Kk'$), and dependent upon both the population of such anion (as controlled by K), and its rate of closure (k′). For IB, K is undoubtedly many powers of ten greater[11] than the acidity constant for IA. One must therefore conclude from the observed, more rapid, base-induced, cyclization of IA relative to IB, that either k′ (for IA) >> k′ (for IB) and thus compensates for the large discrepancy in acidities, or that an anionic intermediate is not involved, at *p*H 8–9. If this latter holds, the role of the basic catalyst perhaps would then be, as suggested by Henry, *et al.*[4] to prevent the inhibiting action the acidic tetrazoles might exercise on the cyclizations. Furthermore, such an imidyl azide anion might be expected to undergo some, if not total, elimination[4] to substituted carbodiimide (A, Fig. I) and would then result in azide displacement. With the strong bases used, no such displacement was detected. On the basis of the data at hand at present, therefore, no unequivocal decision can be made as to the existence, or not, of an anionic intermediate in the tetrazole closures effected.

The azide displacement reactions encountered, without additional solvent, with aniline (D, 7.25; pK_a 4.6) and phenylhydrazine (D, 7.15; pK_a 5.2), amongst others,[5] would seem to correspond best to a reaction at the imidyl functions of IA and IB as indicated by (D, Fig. 1). The secondary amines, utilized in the present work, would accordingly have steric hindrance,[12] in addition to their basicities as a further reason to divert their reactions with IA and IB to tetrazole closures alone. The common characteristics of the bases that produce azide displacement would seem to be, preferably, both a low basicity towards proton and a high nucleophilicity towards carbonyl carbon.[13] While aniline and the substituted phenylhydrazines fulfill these criteria, hydrazine hydrate (D, 53; pK_a 8.0) possesses conflicting properties. Its reactions therefore with IA and IB, in ethanol, and otherwise, exemplify the competition between reasonably high basicity (with consequent tendency towards tetrazole closure) and high nucleophilicity (with thereby strong inclination towards azide displacement). The reaction products suggest that nucleophilicity is the more important quality. For, although some tetrazole formation has been detected[14] in the reaction of hydrazine hydrate with IA, and cannot be totally ruled out in its reaction with IB, the *major* products correspond to azide displacements, and thereby ensue from its strong affinity for carbonyl carbon.

EXPERIMENTAL[15]

Guanyl azide nitrate (IA) was prepared by the method of Thiele,[16] while nitroguanyl azide (IB) was obtained as by Lieber, *et. al.*[5b]

Reactions of IA with bases. *(1) In ethanol.* The following is typical of the procedure used. IA (2 g.) was refluxed with 1.25 g. (1 equivalent) of thiosemicarbazide in 30 ml. of a 60% aqueous ethanolic solution on a steam-bath for 1 hour. On cooling and subsequent work-up (concentration, etc.) 1.03 g. (91%) of 5-aminotetrazole separated. This was identified by mixture m.p. with a known sample. Use of three equivalents of thiosemicarbazide did not affect the result. The following appends the yields (%) of 5-aminotetrazole obtained with the bases concerned: aniline (88), diethylamine (90), *asym*-methylphenylhydrazine (85), methylhydrazine sulfate (90), 1-phenyl- (82) and 4-phenyl-(86)-thiosemicarbazides, phenylhydrazine *p*-sulfonic acid (82), and semioxamazide (89).

(2) Asolvently. *(a) With aniline.* A solution of 2.0 g. of IA in 10 ml. of aniline was heated at 100°, for 1 hour. An intense violet coloration developed in the reaction mixture during the heating and a strong evolution of hydrazoic acid was detectable. The solution was cooled, 5 ml. of absolute ethanol was added, the whole was concentrated to about 5 ml. in bulk and then 5 ml. of anhydrous ether was added. A greyish-white powder (1.79 g., 67%), m.p. 126°, separated. After recrystallization three times from water, it was obtained as white platelike crystals, m.p. 126–127°, and proved to be phenylguanidine nitrate (reported[17] m.p. 128°).

Anal. Calc'd for $C_7H_{10}N_4O_3$: C, 42.4; H, 5.0; N, 28.3. Found: C, 42.8; H, 4.9; N, 28.0.

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[8] Dielectric constant data, mentioned herein, are taken from *International Critical Tables*, McGraw-Hill and Co., New York, 1929, Vol. 6, page 83 *et seq.* The basicity data are taken from standard compilations in the literature.

[9] Compare reference, number **20**, in Ref. 4.

[10] We are indebted to one of the referees for the suggestion of a possible anionic intermediate.

[11] See *e.g.* (a) R. A. Henry, J. E. DeVries, and R. Boschan, *J. Am. Chem. Soc.*, **77**, 5693 (1955) and references therein; (b) Compare also A. H. Lamberton, *Quart. Revs.*, **5**, 75 (1951) and data therein.

[12] Amongst many references, see, *e.g.*, E. McC. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950).

[13] Compare C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953) and J. O. Edwards, *J. Am. Chem. Soc.*, **76**, 1540 (1954).

[14] T. E. O'Connor, K. Horgan, and J. Reilly, *J. Appl. Chem.*, **1**, 91 (1951).

[15] All melting points are uncorrected. All microanalyses are by Drs. Wieler and Strauss, Oxford, England.

[16] J. Thiele, *Ann.*, **270**, 46 (1892).

[17] I. Heilbronn and H. M. Bunbury, *Dictionary of Organic Compounds*, 3rd Edition, Eyre and Spottiswoode, London, 1953, Vol. 4, page 132.

Its *picrate* was obtained as orange-colored scintillating needles, m.p. 226–227°, (reported[17] m.p. 223°) from aqueous ethanol.

Anal. Calc'd for $C_{13}H_{12}N_6O_7$: C, 42.8; H, 3.8; N, 23.1. Found: C, 43.1; H, 3.5; N, 22.6.

(*b*) *With e.g., piperidine.* To 10 ml. of piperidine was added slowly 3.0 g. of IA. A vigorous exothermic reaction developed whose temperature was maintained below 10° by means of ice-water. The colorless solution obtained then was allowed to stand for 24 hours at 0°. This resulted in the precipitation of a white powder (2.50 g., 70% yield), m.p. 160–170°. This extremely hydroscopic solid was recrystallized 5 times from absolute ethanol and was ultimately obtained as long white plates, m.p. 165–172°.[18] It proved to be *piperidinium 5-aminotetrazole* (reported[7] m.p. 176–178°).

Anal. Calc'd for $C_6H_{14}N_5$: C, 42.3; H, 8.2; N, 49.4. Found: C, 42.1; H, 8.1; N, 49.5.

TABLE I

SOME AMINE SALTS OF 5-NITROAMINO- AND 5-AMINO-TETRAZOLES

Amine	Product M.P.°, C.	Yield, %	Carbon Calc'd	Carbon Found	Analyses Hydrogen Calc'd	Analyses Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
Benzylamine[a,b]	129–135[c]	60	50.2	50.1	6.25	6.2	43.7	43.7
Cyclohexylamine[a]	212–214	70	45.5	45.5	8.6	8.2	45.7	45.8
Di-*n*-butylamine[a,d]	82–90	72	46.6	47.4	9.5	9.8	36.2	36.8
β-Phenylethylamine[a]	75–85	75	52.4	52.7	6.8	6.8	40.7	40.5
Pyrrolidine[a]	138–141	87	38.4	38.3	7.6	7.9	53.8	53.5
Aniline[e,f]	152–154[f]	72	46.7	46.7	4.4	4.3	31.1	30.8
Cyclohexylamine[e,g]	197–198	51	47.5	47.5	8.5	8.4	34.1	34.7
Piperidine[e,h]	165–167	26	44.0	44.1	8.0	7.8	37.3	36.7
n-Propylamine[e,j]	153–156	53	33.9	34.1	8.1	8.0	45.4	44.8

[a] These represent reactions with IA, in undiluted amine. [b] Each salt reported was also prepared from the appropriate amine and substituted tetrazole. [c] Reported[7] m.p. 130.5–130.5°. [d] Compound is a monohydrate. [e] These represent reactions with IB, in undiluted amine. [f] Compound is 1-phenyl-3-nitroguanidine, reported [*e.g.*, by A. F. McKay, *J. Am. Chem. Soc.*, **71**, 1968 (1949)] m.p. 152–153° [g] The reported m.p.[5b] for this compound is 162°. That for 1-cyclohexyl-3-nitroguanidine has been reported by McKay (see *f* above) as 197–198°. To settle the identity of the IB-cyclohexylamine product, its preparation has been repeated and re-repeated both by Lieber's[5b] method and by the present technique. In both cases, the compounds obtained melt from 197–198°. When admixed, no m.p. depression results. In view of such facts and its analysis, the compound is oriented as being dicyclohexylammonium 5-nitroaminotetrazole. Incidentally we found such salts recrystallized best from a mixture of ethanol and acetone. [h] Reported m.p.[5b] 107°. In our hands, Lieber's work repeated, afforded a solid of m.p. 165–167°—this did not depress the m.p. of our material, which then is identified as the respective diamine salt of IIB. [j] Reported[5b] m.p. 161°

This compound was also prepared in 73% yield by refluxing 2 g. of 5-aminotetrazole in 10 ml. of piperidine for 1 hour. After many recrystallizations from ethanol and ethanol-ether mixtures, it too was found to melt from 165–172°.

Anal. Found: C, 42.2; H, 7.9; N, 49.8.

Within the limited significance the result possesses because of the m.p. ranges involved, samples of the piperidinium salt prepared by both of the above methods, when admixed did not result in a depression of the m.p. below the separately observed ranges.

Table I includes the further amine reactions effected with IA.

Reactions of IB with bases. (*1*) *With phenylhydrazine.* To 7.56 ml. (a 10-molar proportion) of phenylhydrazine was added 1.0 g. of pure nitroguanyl azide. The azide did not dissolve in the cold liquor, appreciably, and on heating under reflux it formed an orange solid. After about 3 minutes of such reflux, a violent explosion terminated the run. In a repeated reaction, the solution was heated on a steam-bath for 1 hour, after first cautiously and slowly raising the temperature of the mixture to the appropriate level stepwise. (Preheating the phenylhydrazine and then dropping in the azide portionwise with the resultant explosive-like but controlled reaction is also a successful technique.) No hydrazoic acid vapors were detected. The mixture then was cooled and allowed to stand at 0° for an hour. The orange solid obtained (1.07 g., 72%) was washed with absolute ethanol and filtered. After crystallization from aqueous ethanol it was obtained as fine white microcrystals, m.p. 165–165.4°. It was shown to be 1-phenyl-4-nitroaminoguanidine by mixture m.p. with an authentic sample.[19] A small quantity (*ca.* 0.08 g.) of a low m.p. solid, which was not further investigated was obtained together with a little (0.03 g.) further quantity of substituted nitroaminoguanidine in the ethanolic washings.

(*2*) *With morpholine.* To 6.7 ml. (a 10-molar equivalent) of morpholine, preheated to *ca.* 50°, was cautiously added 1.0 g. of IB. The temperature of the mixture was maintained at 50–70° for 90 minutes. On cooling, 1.9 g. of crude product (81%) of m.p. 160–162° was obtained. After recrystallization from aqueous ethanol this had m.p. 163–165° and did not depress the m.p. of an authentic sample of dimorpholinium-5-nitraminotetrazole (reported m.p. 166°), prepared as by Lieber, *et al.*[5b] The other amine reactions of IB are included in Table I.

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[18] The indefiniteness of m.p. of certain of these salts has been commented on elsewhere, see Henry, Ref. 7.

[19] Prepared in several ways, one being that of F. L. Scott, M. T. Kennedy, and J. Reilly, *J. Am. Chem. Soc.*, **75**, 1294 (1953).