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NITRATION OF 2-AMINOTHIAZOLES

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When 2-aminothiazole is treated with two equivalents of nitric acid in 96% sulfuric acid the product is 2-nitramino-5-nitrothiazole (I), whereas the use of one equivalent of nitric acid leads to a good yield of 2-amino-5-nitrothiazole (II) (1). While we have been able to repeat these procedures successfully we have found also that another compound is isolable when the system contains 10–30% of water. This compound may be either 2-nitriminothiazoline or 2-nitraminothiazole (III). The latter structure is the more probable because the compound may be diazotized in the same manner as is 2-aminothiazole. This diazotization reaction seems to be characteristic of nitramines (2, 3) rather than nitrimines. Also III gives a strong Franchimont test (4). Furthermore the 2-nitraminothiazole (III) may be converted to 2-methylnitraminothiazole (IV) by use of diazomethane or by treatment of the solution in aqueous sodium bicarbonate with dimethyl sulfate. Nitration of IV by excess of absolute nitric acid leads to the same 2-methylnitramino-5-nitrothiazole (V) which is obtained by dimethyl sulfate methylation of a bicarbonate solution of I.

As might have been expected from the foregoing description, III acts like a nitramine when it is rearranged by use of absolute sulfuric acid to 2-amino-5-nitrothiazole (II). In order to ascertain the relationship of the nitramine (III) to II in the nitration system a series of experiments has been effected in which time and amount of water in the mixed acid have been varied. These experiments are listed in Table I. Since III is unstable and of poor melting point with decomposition, its yield and quality have in most cases been confirmed by conversion to IV.

It may be seen (Expts. 1 and 2) that the yield of 2-amino-5-nitrothiazole (II) in a mixed acid containing 96% sulfuric acid is time-dependent, since only a small amount of II is obtained after eight minutes; the principal product is the nitramine (III). This time differential is extended in 85% sulfuric acid so that only nitramine (III) is isolable after a reaction time of 70 minutes, but only II is found after 12 hours. None of the aminonitrothiazole (II) is found at any time in media containing more than 15% water, although the nitramine (III) may be isolated (in decreasing amount) as the water content is increased to 29%. Neither product is obtained when more than 30% of water is present.

Although the yield of 2-nitraminothiazole from a system containing 71% sulfuric acid seems to be constant at about 30% (Expts. 8 and 9, Table I), this amount should not be considered as representative of the equilibrium in this nitration system. Indeed when nitraminothiazole is added to the equivalent of the spent nitration mixture from which the 30% yield is obtainable, a recovery of 80% is obtained. Evidently the amine in the nitration system must be con-

TABLE I

NITRATION OF 1 MOLE OF 2-AMINOTHIAZOLE WITH 1 MOLE OF ABSOLUTE NITRIC ACID IN 6 MOLES OF SULFURIC ACID AND WATER AT 20°

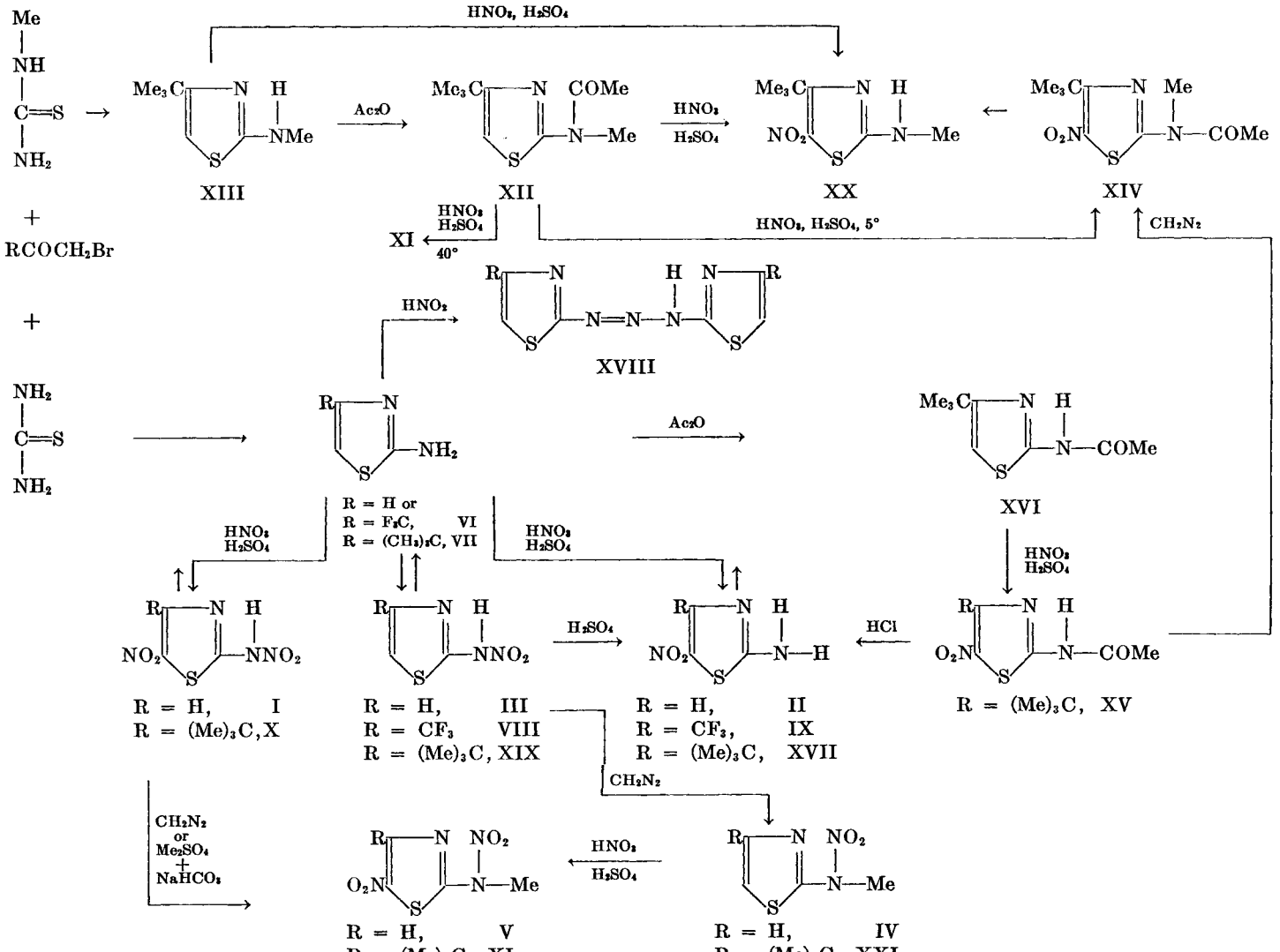
Expt. No.	Wt. % H_2SO_4	Time, mins.	Amino-nitro, II		Nitramine, III		Methylnitramine, IV, from III	
			Yield, %	m.p., °C.	Yield, %	m.p., °C.	Yield, %	m.p., °C.
1	96	8	6	170–190	31	188	0	
2	96	960	84	192	0		0	
3	85	70	0		31	196–198	87	270
4	85	455	4	185	55	low	62	267
5	85	820	32	192	0		0	
6	80	480	0		59	185	67	271
7	75	540	0		37	195	0	
8	71	480	0		27	185	83	270
9	71	1620	0		32	180	72	269
10	65	2160	0		0		0	

sumed partly in some manner not represented by the reaction products which have been isolated.

In order further to evaluate the significance of the nitramine in the nitration of aromatic amines as exemplified by aminothiazoles we have investigated three other amines. One of these, 2-amino-4-mesitylthiazole, could not be nitrated satisfactorily, for reasons which may be apparent after consideration of the other two compounds, 2-amino-4-trifluoromethylthiazole (VI) and 2-amino-4-*tert*-butylthiazole (VII).

The preparation of 2-amino-4-trifluoromethylthiazole (VI) is effected simply and in good yield from thiourea and either 3-bromo-1,1,1-trifluoroacetone or 3-chloro-1,1,1-trifluoroacetone. When the amine is treated with one equivalent of nitric acid in 6 equivalents of 96% sulfuric acid for more than a day the only isolable product is 2-nitramino-4-trifluoromethylthiazole (VIII), soluble in aqueous sodium bicarbonate and unaffected by treatment with absolute sulfuric acid at 25° for 13 hours. Only when it is heated to 60° for this time period is a partial conversion to 2-amino-5-nitro-4-trifluoromethylthiazole (IX) effected. Either IX or VIII can be diazotized in 65% sulfuric acid but only VIII gives a positive Franchimont test indicative for a primary nitramine.

The difficulty with which the nitro group is introduced into the 5-position of 2-amino-4-trifluoromethylthiazole might be attributed to steric (bulk) hindrance. However the trifluoromethyl group is no more bulky than the *tert*-butyl group. Experiments with 2-amino-4-*tert*-butylthiazole (VII) indicate the effect of polar distortion rather than bulk hindrance. The amine (VII), easily preparable from 1-bromo-3,3-dimethylbutanone-2, can be nitrated cleanly in 96% sulfuric acid with two equivalents of nitric acid. The product is evidently 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X) since it gives a positive Franchimont test, reacts readily with diazomethane, and is soluble in aqueous sodium bicarbonate. Interestingly, this alkaline solution does not yield the methylnitramine XI when


HNO3, H2SO4
Ac2O
HNO3 H2SO4
HNO3 H2SO4 40°
HNO3, H2SO4, 5°
CH2N2
HNO2
Ac2O
HNO3 H2SO4
HNO3 H2SO4
H2SO4
HCl
CH2N2
CH2N2 or Me2SO4 + NaHCO3
HNO3 H2SO4
RCOCH2Br
XIII
XII
XI
XX
XIV
XVIII
XVI
R = H or
R = F3C, VI
R = (CH3)3C, VII
R = H, I
R = (Me)3C, X
R = H, III
R = CF3 VIII
R = (Me)3C, XIX
R = H, II
R = CF3, IX
R = (Me)3C, XVII
R = (Me)3C, XV
R = H, V
R = (Me)3C, XI
R = H, IV
R = (Me)3C, XXI

treated with dimethyl sulfate. We attribute this failure to a high stability of the anion, which precludes coordination with the methylating agent.

The product of diazomethylation is indeed 4-*tert*-butyl-2-N-methylnitramino-5-nitrothiazole (XI) since it is obtained also by dinitration of 2-N-acetyl-N-methylamino-4-*tert*-butylthiazole (XII), the acetylation product of 4-*tert*-butyl-2-N-methylaminothiazole (XIII) which has been prepared from N-methylthiourea and 1-bromo-3,3-dimethylbutanone-2. The structure of XII has been established both by cold mononitration which yields 2-N-acetyl-N-methylamino-4-*tert*-butyl-5-nitrothiazole (XIV) with retention of the aceto group and by warm mononitration with elimination of aceto, 4-*tert*-butyl-2-N-methylamino-5-nitrothiazole (XX) being formed. The latter compound is also formed either by hydrolytic deacetylation of XIV or by mononitration of 4-*tert*-butyl-2-methylaminothiazole (XIII).

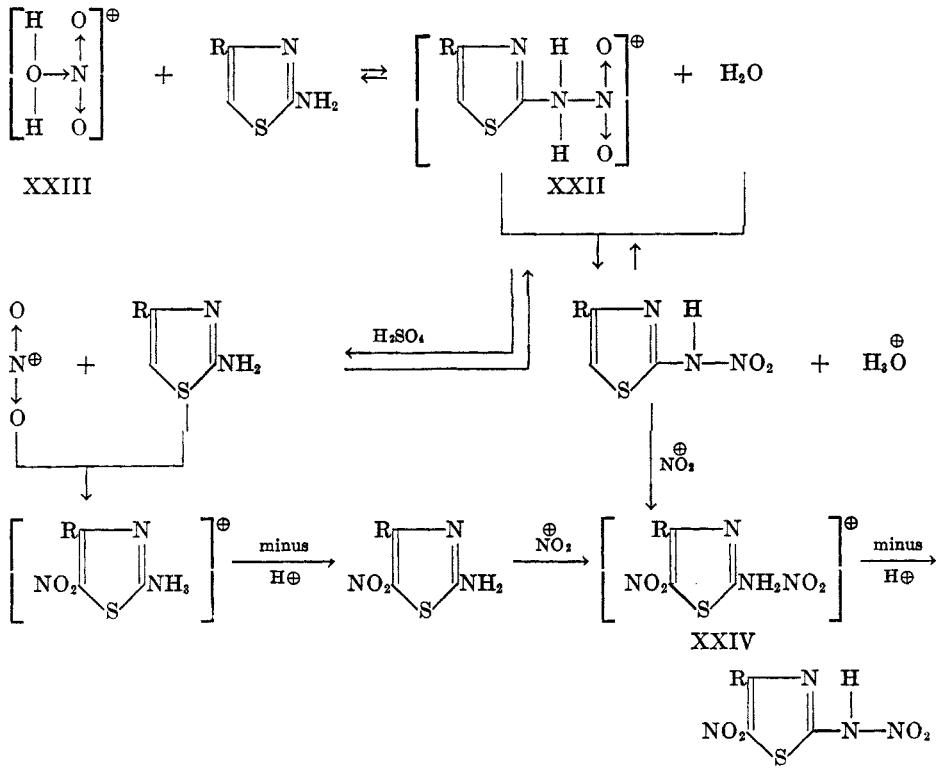
The high acidity of 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X) which is indicated by failure of methylation with dimethyl sulfate under our conditions has not been determined by measurement. However it seems probable that it is a strong acid in view of the behavior of 2-acetamino-4-*tert*-butyl-5-nitrothiazole (XV). This compound, prepared by nitration of 2-acetamino-4-*tert*-butylthiazole (XVI), has been found readily to undergo methylation either with diazomethane or with dimethyl sulfate in aqueous sodium bicarbonate suspension to yield XIV. Therefore it is evident that the 4-*tert*-butyl-5-nitrothiazolyl group is strongly electrophilic with respect to a substituent in its 2-position.

The dinitration of 2-amino-4-*tert*-butylthiazole (VII) has been shown to yield one product, X, in good yield. By contrast the mononitration in 96% sulfuric acid yields a complex mixture from which 2-amino-4-*tert*-butyl-5-nitrothiazole (XVII) can be isolated only with difficulty and in mediocre yield. The initial product obtained when the nitration system is drowned in ice is yellow, but this precipitate rapidly becomes very dark red before it can be filtered off. When this disagreeable product is separated by chromatography on alumina a deeply-red compound may be separated comprising 16% of the total weight. According to its elemental analysis and chemical behavior the compound is 4,4′-di-*tert*-butyldithiazolyltriazene (XVIII). This compound might be expected if an appreciable amount of 2-amino-4-*tert*-butylthiazole (VII) were remaining, in the presence of nitrous acid, after all of the nitric acid in the mixed acid were consumed. But this would imply that part of the single equivalent of nitric acid has partaken in a dinitration reaction.

This dinitration product has been found to be the 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X), which may be isolated in 8% yield by acidification of the basified reaction dilution liquors out of which a 60% yield of 2-amino-4-*tert*-butyl-5-nitrothiazole (XVII) has previously been removed by filtration. The amount of X is augmented to the detriment of the yield of XVII when the nitration is carried out in 80% sulfuric acid. Additionally some 4-*tert*-butyl-2-nitraminothiazole (XIX) is formed. This substance becomes easier to isolate and purify if the ratio of nitric acid to 4-*tert*-butyl-2-aminothiazole is reduced from 1:1 to 1:0.8.

The 4-*tert*-butyl-2-nitraminothiazole (XIX), as might be expected, rearranges rapidly to 2-amino-4-*tert*-butyl-5-nitrothiazole (XVII) in cold 96% sulfuric acid. It might then be inferred that XIX is the intermediate source of XVII from which, in turn, 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X) is formed. However such an inference probably misrepresents the nitramine-aminonitro (Orton) rearrangement. It is obvious that an intramolecular mechanism, especially if it involves bridging between 2- and 5-positions, is unrealistic because of the distance involved in this planar ring. A denitration-renitration mechanism is more reasonable. In this connection it is of interest to find that when 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X) is dissolved in absolute sulfuric acid it is converted to a mixture from which the denitration product, 2-amino-4-*tert*-butyl-5-nitrothiazole (XVII), can be isolated.

In summary it would appear that 2-aminothiazole is intermediate in behavior toward mixed nitration acid between 2-amino-4-trifluoromethylthiazole (VI), which is more weakly basic, and 2-amino-4-*tert*-butylthiazole (VII), which is more strongly basic than the unsubstituted amine. But all three amines are convertible under suitable conditions to nitramines. On the basis of a denitration-renitration mechanism it may be assumed that these conversions proceed through the organoammono analogs (XXII) of nitracidium sulfate (XXIII) and that these analogs are at least as stable as XXIII.



The cation XXII in which R is trifluoromethyl retains the nitro group even in media (95–100% sulfuric acid) wherein the nitronium ion seems to be a stable entity. However this cation is capable of the loss of a proton to give the nitramine VI. We attribute this retention of the nitro group to covalency in the N—N linkage in XXII (R = F_3C). This covalency is disrupted rapidly only when the temperature in sulfuric acid is raised to 60°.

When the R-group is hydrogen the cation XXII seems to be disposed to lose a proton and form the nitramine III in sulfuric acid containing 15–30% of water. In stronger sulfuric acid the nitro group is transferred to the 5-thiazolyl position. This transfer may of course be attributed to the stability of the nitronium ion in 85–100% sulfuric acid but it is equally reasonable to attribute the transfer to the instability of the ammononitracidium ion in this medium. A sufficiently precise analytical method has not yet been devised to test kinetically which ionic species is operative in this nitration. Otherwise the system seems to be amenable for study since the absence of 2-nitramino-5-nitrothiazole in the product of mononitration shows that its conjugate acid is not a significant species in the reaction system.

By contrast, competition of several ionic species (XXII and XXIV) seems to occur when R is the electron-repelling *tert*-butyl group. The resulting basicity seems to detract from N—N covalency in the postulated ion XXII since both 4-*tert*-butyl-2-nitraminothiazole (XIX) and 2-amino-4-*tert*-butyl-5-nitrothiazole (XVII) are obtained in 80% sulfuric acid. This indicated loss of both hydrogen to the system and nitro to the 5-thiazolyl position is of special interest since nitronium ion is not detectable in sulfuric acid containing 20% water. Furthermore the loss of the nitro group from XXII must involve the gain of nitro by the less basic XVII, ostensibly to form the cation XXIV [R = $(CH_3)_3C$] in which N—N may be expected to be more covalent than in XXII. This transfer is indicated by the occurrence of a third product, 4-*tert*-butyl-2-nitramino-5-nitrothiazole (X), the product of proton loss from XXIV, under conditions of mononitration in 80% sulfuric acid. The appearance of the three products under conditions of competition not only among themselves but also with nitracidium ion in 80% sulfuric acid medium seems most reasonably explained by postulation of ammono-nitracidium ions as intermediate species.

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EXPERIMENTAL[1]

2-Nitramino-5-nitrothiazole (I). A solution of 2.50 g. (0.025 mole) of 2-aminothiazole in 18.8 g. (0.15 mole) of 80 weight-percent aqueous sulfuric acid was chilled to below 0° and treated with 1.07 ml. (0.025 mole) of absolute nitric acid so as not to exceed 0° in temperature. Then after 20 hours at 20° the system was drowned in 70 g. of ice. The precipitate

[1] Melting points have been corrected against reliable standards. The five strongest lines of the x-ray diffraction patterns have been recorded as relative intensities [I/I_1] at d spacings in Å using Cu K_α (Ni filtered) radiation.

was filtered, re-slurried with cold water, re-filtered, and vacuum-dried at 25°; 2.13 g. (59%), m.p. 188–190° (decomp.). This product was purified by solution in a slurry of sodium bicarbonate; the aqueous suspension was filtered and acidified, m.p. 197–198° (decomp.). X-ray pattern: [10] 4.37, 3.20; [9] 7.62; [8] 4.21, 3.30; [4] 3.59.

Anal. Calc'd for $C_3H_3N_3O_2S$: C, 24.8; H, 2.08; S, 22.1.

Found: C, 24.7; H, 2.16; S, 22.0.

This compound gave a positive Franchimont test. Its elemental nitrogen analysis was low (Calc'd 29.0, found 27.6). This behavior is characteristic of many nitrated aminothiazoles.

2-Amino-5-nitrothiazole (II). *A. From 2-aminothiazole.* A solution of 25 g. (0.25 mole) of powdered 2-aminothiazole (free from sodium chloride) in 75 ml. (1.41 mole) of 96% sulfuric acid, prepared at 10–15°, was stirred while 11.6 ml. (0.25 mole) of nitric acid (*d.* 1.49–1.50) was added during 45 minutes so that the temperature did not exceed 12°. The system was maintained at 0° during three hours and at 25° for 12 hours, then drowned in ice-water to a volume of 1.5–2 l. The insoluble material (crude nitramine, insignificant) was filtered off and the filtrate was neutralized with 150 g. of powdered sodium carbonate. The product was filtered off, re-slurried in ice-water, re-filtered, and dried at 100°, 30.6 g. (84%), m.p. 189–192°. Crystallization from 2 l. of boiling water left 25 g. (70%), m.p. 192–195°, not raised by crystallization from hot ethanol (8 ml. per g.). Crystallization from hot acetic acid (16 ml. per g.) raised the melting point to 195–196°.

B. From 2-nitraminothiazole. A solution of 5 g. (0.034 mole) of 2-nitraminothiazole in 30 ml. of 96% sulfuric acid remained 12 hours before it was drowned in ice and filtered from a small insoluble contaminant. Neutralization of the filtrate with sodium carbonate precipitated 4.7 g. (94%) of 2-amino-5-nitrothiazole, m.p. 197° (decomp.); mixture melting point with the product by procedure *A* was not lowered. Acetylation with acetic anhydride gave the known 2-acetamino-5-nitrothiazole, m.p. 264–265°, identified by mixture melting point.

2-N-Methylnitraminothiazole (IV). A suspension of 1.17 g. (0.014 mole) of sodium bicarbonate and 1.01 g. (0.007 mole) of 2-nitraminothiazole in 25 ml. of water was stirred until solution was complete (or was finally filtered to remove 2-amino-5-nitrothiazole if any was present). Then 0.95 ml. (0.01 mole) of dimethyl sulfate was added. The stirring was continued for 130 minutes although the product began to precipitate after about one minute. The filtered product, water-washed and dried, weighed 0.97 g. (87%), m.p. 269°. A recovery of 85% was effected upon crystallization from hot acetic acid (110 ml. per g.), m.p. 268.5–269°. X-ray diffraction pattern: [10] 3.23; [4] 6.86; [3] 5.90, 4.59, 4.39, 4.07.

Anal. Calc'd for $C_4H_5N_3O_2S$: C, 30.2; H, 3.14; S, 20.1.

Found: C, 30.2; H, 3.33; S, 20.2.

This compound also may be prepared by treatment of 2-nitraminothiazole in acetone with etherous diazomethane. Evaporation of the solvent yields a very pure product, m.p. 271.5–272°.

2-Methylnitramino-5-nitrothiazole (V). *A. From N-methylnitraminothiazole.* To 8.6 ml. (0.1 mole) of absolute nitric acid at −70° was added 2.55 g. (0.016 mole) of methylnitraminothiazole during one minute. The deep red solution, warmed to 20°, was maintained for ten hours, then poured into ice. The product, filtered and vacuum-dried, weighed 1.4 g., m.p. 167°; m.p. 168.5° after crystallization from ethanol.

Anal. Calc'd for $C_4H_4N_4O_4S$: C, 23.5; H, 1.96; S, 15.7.

Found: C, 23.8; H, 2.10; S, 15.5.

B. From 5-nitro-2-nitraminothiazole. A solution consisting of 1.85 g. (0.022 mole) of sodium bicarbonate and 1.89 g. (0.01 mole) of nitronitraminothiazole in 50 ml. of water was stirred with 1.9 ml. (0.02 mole) of methyl sulfate. Precipitation did not commence before 13 minutes. After 140 minutes the product was filtered, 1.15 g. (56%), m.p. 166–167°. Crystallization from hot ethanol (43 ml. per g.) raised this m.p. to 169°. A mixture melting point with the product obtained by procedure *A* was not lowered.

2-Amino-4-trifluoromethylthiazole (VI). A mixture of 136 g. (0.712 mole) of 3-bromo-

1,1,1-trifluoroacetone [prepared in 68% yield (5)] and 54.2 g. (0.712 mole) of thiourea in 300 ml. of water was stirred under reflux during four hours. This system when chilled would yield 47 g. of the product as its hydrobromide. Alternatively the system at 25° was made basic with aqua ammonia. The precipitate, 2-amino-4-trifluoromethylthiazole, when dried weighed 60.2 g. (50%), m.p. 58–65°. A similar crude yield and melting point were obtained using 3-chloro-1,1,1-trifluoroacetone [obtained by acid hydrolysis of ethyl 2-chloro-4,4,4-trifluoro-3-ketobutanoate (6)] in the same procedure, though sodium carbonate was used for the neutralization. The crude product was purified by distillation, b.p. 125–128° (22 mm.) or 110–114° (9 mm.), m.p. 68–69.5°. X-ray diffraction pattern: [10] 3.80; [7] 5.15; [6] 3.53; [5] 2.37, 3.12, 6.10.

Anal. Calc'd for $C_4H_3F_3N_2S$: C, 28.6; H, 1.79; N, 16.6; S, 19.1.

Found: C, 28.6; H, 1.64; N, 16.7; S, 19.1.

2-Nitramino-4-trifluoromethylthiazole (VIII). A suspension of 16.8 g. (0.1 mole) of 2-amino-4-trifluoromethylthiazole (b.p. 125–128° at 22 mm., m.p. 68–69.5°) in 58.8 g. (0.6 mole) of 96% sulfuric acid was cautiously warmed to 60°, then cooled as solution became rapid. This solution, chilled to −20°, was treated with 4.97 ml. (0.115 mole) of absolute nitric acid, then warmed to 20° and maintained for 26 hours. The system, poured into 150 g. of ice yielded 12.8 g. (60%), m.p. 132°. Crystallization from hot water (10 ml. per g., using Norit) raised the m.p. to 150° but recovery was only 31%. Crystallization from hot dioxane (7 ml. per g.) raised this m.p. to 157° (decomp.), not raised by subsequent crystallization from hot water (30 ml. per g.).

Anal. Calc'd for $C_4H_2F_3N_3O_2S$: C, 22.5; H, 0.95; S, 15.0.

Found: C, 22.4; H, 1.29; S, 15.0.

2-Amino-5-nitro-4-trifluoromethylthiazole (IX). A solution of 10 g. (0.047 mole) of crude 2-nitramino-4-trifluoromethylthiazole in 25 ml. of 100% sulfuric acid was heated to 60° for 13 hours; then it was cooled and poured into 100 g. of ice. Filtration removed 5.04 g. (50%), m.p. 150–175°, which was washed with aqueous sodium bicarbonate solution and vacuum-dried. This product was crystallized from 400 ml. of water using Darco, 2.03 g., m.p. 188–190°. Recrystallization from water (with Darco, 110 ml. per g.) raised the m.p. to 189–190°, 1.44 g. X-ray diffraction pattern: [10] 3.68; [9] 10.84, 6.65; [3] 5.77, 5.55.

Anal. Calc'd for $C_4H_2F_3N_3O_2S$: C, 22.5; H, 0.95; S, 15.0.

Found: C, 22.5; H, 0.95; S, 14.8.

4-Mesityl-2-aminothiazole. A mixture of 153.4 g. (0.781 mole) of α-chloromethyl mesityl ketone and 59.7 g. (0.785 mole) of thiourea was heated at 90–100°. After 15 minutes a vigorous reaction occurred and the system solidified; it was heated for 12 hours longer, then poured into 8 l. of water and filtered. The precipitate was augmented slightly by neutralization of the filtrate with ammonia. The crude product (172 g.) was crystallized from aqueous ethanol, 132 g. (78%), m.p. 162°. Three crystallizations from aqueous ethanol raised this m.p. to 165.0°. X-ray diffraction pattern: [10] 2.48; [7] 3.80; [6] 11.40, 8.84, 5.14.

Anal. Calc'd for $C_{12}H_{14}N_2S$: C, 66.0; H, 6.42; N, 12.8; S, 14.7.

Found: C, 66.3; H, 6.47; N, 12.8; S, 14.6.

Acetylation of this product by acetic anhydride gave a derivative, m.p. 168°, which was purified by four crystallizations from 1:1 water-ethanol, m.p. 170°; mixture melting point with the amine was depressed. The compound was not analyzed. Attempted nitration of 4-mesityl-2-aminothiazole was unsuccessful.

2-Amino-4-tert-butylthiazole (VII). *A. In etherous medium.* A suspension of 24.5 g. (0.31 mole) of thiourea in 1000–1500 ml. of dry diethyl ether was stirred while 56 g. (0.31 mole) of 1-bromo-3,3-dimethylbutanone-2 (b.p. 78.5–79.5° at 14 mm.) was added during 30 minutes. After further stirring for three hours the system was filtered and the precipitate was washed with ether. Then it was dissolved in 800 ml. of water, reprecipitated by addition of solid sodium hydroxide, filtered, water-washed, and vacuum-dried, 47.7 g. (87%), m.p. 99–101°. This product was distilled (b.p. 134–135° at 18 mm. or 141–143° at 20 mm.) and then crystallized by solution in ethanol (2 ml. per g.) followed by addition of an equal volume of water (using Darco if necessary), m.p. 100–101°. X-ray diffraction pattern: [10] 2.87; [6] 4.61; [5] 10.84, 5.79; [4] 2.50, 1.76, 1.50.

Anal. Calc'd for $C_7H_{12}N_2S$: C, 53.8; H, 7.74; N, 17.9.
Found: C, 54.2; H, 8.05; N, 17.8.

B. In aqueous medium. A suspension of 14.2 g. (0.18 mole) of thiourea in 250 ml. of water was stirred while 33.5 g. (0.18 mole) of 1-bromo-3,3-dimethylbutanone-2 was added during 30 minutes. After three hours of reflux the system was cooled and extracted with ether to remove impurities; then the aqueous phase was treated with solid sodium hydroxide. The precipitated oil crystallized slowly, 23.3 g. (80%), m.p. 99.5–100.5°.

4-tert-Butyl-2-N-methylaminothiazole (XIII). A solution of 2 g. (0.22 mole) of N-methylthiourea in 80 ml. of water was stirred while 4 g. (0.22 mole) of 1-bromo-3,3-dimethylbutanone-2 was added during 30 minutes. Then the system was refluxed for two hours, cooled, washed with ether to remove impurities and finally precipitated with solid sodium carbonate, 3.3 g. (88%), m.p. 91–91.5°. Crystallization from petroleum ether (b.p. 60–70°) raised this m.p. 0.5°. X-ray diffraction pattern: [10] 4.12, 4.10; [9] 4.83; [8] 6.34, 6.23.

Anal. Calc'd for $C_8H_{14}N_2S$: C, 56.2; H, 8.25; N, 16.5; S, 18.8.
Found: C, 56.4; H, 8.14; N, 16.3; S, 18.8.

2-N-Acetyl-N-methylamino-4-tert-butylthiazole (XII). A solution of 0.5 g. (0.003 mole) of 4-*tert*-butyl-2-N-methylaminothiazole in 0.6 g. (0.006 mole) of acetic anhydride was refluxed for 30 minutes, then poured into 10 ml. of water. The oil was dissolved in ether, washed with alkali and with water, then dried with magnesium sulfate, and the ether was distilled. The melting point of the crystals (0.4 g., 63%) was unchanged by crystallization from 1:1 methanol-water (1 ml. per g.), 50.5–51°.

Anal. Calc'd for $C_{10}H_{16}N_2OS$: N, 13.2. Found: N, 13.15.

2-Acetamino-4-tert-butylthiazole (XVI). A solution of 4.5 g. (0.029 mole) of 2-amino-4-*tert*-butylthiazole in 5.9 g. (0.058 mole) of acetic anhydride was boiled for 30 minutes, then poured into water, 5.4 g. (quant.), m.p. 174.5–175.0°. When crystallized from 50% aqueous ethanol it melted at 175.6°. Acetyl chloride also could be used in this preparation.

Anal. Calc'd for $C_9H_{14}N_2OS$: C, 54.6; H, 7.1; N, 14.1.
Found: C, 54.8; H, 7.3; N, 13.9.

2-Acetamino-4-tert-butyl-5-nitrothiazole (XV). A solution of 3.12 g. (0.16 mole) of 2-acetamino-4-*tert*-butylthiazole in 13.4 g. (0.12 mole) of 85% sulfuric acid was cooled to −50° and treated with 0.86 ml. (0.02 mole) of absolute nitric acid. After 12 hours at 20° the system was poured into ice. The precipitate (2.26 g., m.p. 163–167°) was stirred with aqueous sodium bicarbonate for two hours and re-filtered, 2.06 g., m.p. 187.5–188° (54%). Crystallization from ethanol, or solution in 10% aqueous alkali followed by reprecipitation with dilute hydrochloric acid raised this melting point to 207.5–208.5°.

Anal. Calc'd for $C_9H_{13}N_3O_3S$: C, 44.4; H, 5.37; S, 13.2.
Found: C, 44.5; H, 5.53; S, 12.9.

This product was obtained in 26% yield when 80% sulfuric acid was used in an otherwise identical preparation. It was also obtained when 2-amino-4-*tert*-butyl-5-nitrothiazole was heated with five equivalents of acetyl chloride in acetic acid for ten hours. The product could be re-hydrolyzed to the amine by boiling 0.64 g. with 8 ml. of 22% hydrochloric acid for one hour.

2-N-Acetyl-N-methylamino-4-tert-butyl-5-nitrothiazole (XIV). A solution of 0.35 g. (0.0071 mole) of 2-N-acetyl-N-methylamino-4-*tert*-butylthiazole (XII) in 0.9 ml. (0.017 mole) of 95% sulfuric acid was cooled to 5° and treated with 0.10 ml. (0.0023 mole) of absolute nitric acid. After one hour the system, drowned in ice-water, precipitated 0.36 g. (79%, m.p. 140°) which was crystallized repeatedly from ethanol, m.p. 145.5–146°. X-ray diffraction pattern: [10] 3.55; [9] 7.38, 8.75, 9.93; [6] 3.30.

Anal. Calc'd for $C_{10}H_{15}N_3O_3S$: C, 46.7; H, 5.84; S, 12.4.
Found: C, 46.8; H, 5.88; S, 12.0.

This compound also could be obtained by treatment of 2 g. of 2-acetamino-4-*tert*-butyl-5-nitrothiazole (VI) with etherous diazomethane in 20 ml. of acetone. Evaporation left 1.7 g., m.p. 136–139°, which, crystallized from ethanol, chloroform, and methanol, melted at 145–146°. The melting point was not depressed on admixture with the product of nitration. Likewise the same product was obtained (mixture melting point and X-ray pattern)

by methylation with dimethyl sulfate as a suspension in aqueous sodium bicarbonate solution.

4-tert-Butyl-2-N-methylamino-5-nitrothiazole (XX). *A. By nitration.* A solution of 0.5 g. (0.003 mole) of 4-*tert*-butyl-2-methylaminothiazole in 1.77 g. (0.018 mole) of absolute sulfuric acid was cooled to +5° and treated with 0.18 g. (0.0029 mole) of absolute nitric acid, then maintained at 25° for six hours. Addition of the system to 20 ml. of ice-water precipitated 0.4 g. (62%), m.p. 173°. Three crystallizations from absolute ethanol raised this melting point to 191°. X-ray diffraction pattern: [10] 11.78; [8] 3.42; [7] 5.47, 3.30; [4] 6.80, 4.14, 3.88.

Anal. Calc'd for $C_8H_{13}N_3O_2S$: C, 44.6; H, 6.07.
Found: C, 44.9; H, 6.21.

B. By hydrolysis. A solution of 0.100 g. (0.0039 mole) of 2-N-acetyl-N-methylamino-4-*tert*-butyl-5-nitrothiazole (XIV) in 2 ml. of 60% sulfuric acid was refluxed during two hours, then diluted with water and partially neutralized with alkali. The precipitate (0.05 g., 60%), m.p. 182–183°, was thrice-crystallized from absolute ethanol, m.p. 191°, mixture melting point with material from procedure *A* not lowered.

4-tert-Butyl-2-nitramino-5-nitrothiazole (X). A yellow solution of 2.0 g. (0.0128 mole) of 4-*tert*-butyl-2-aminothiazole in 7.5 g. (0.077 mole) of 96% sulfuric acid was cooled to 0–10° and 1.51 g. (0.024 mole) of absolute nitric acid was added during a few minutes. After ten minutes subsequently at 0° and ten minutes at 0–25° the system was poured into 100 g. of ice. The yellow precipitate was filtered off, 2.59 g. (82%), m.p. 145° (decomp.). Three crystallizations from aqueous ethanol and two purifications by dilution of an acetone solution with water raised this melting point to 146° (decomp.). X-ray diffraction pattern: [10] 8.58; [7] 4.42; [6] 3.36, 4.82; [5] 3.12, 3.60, 3.95.

Anal. Calc'd for $C_7H_{10}N_4O_4S$: C, 34.1; H, 4.09; N, 22.8; S, 13.0.
Found: C, 34.0; H, 4.30; N, 23.1; S, 12.6.

This compound was also obtained by a comparable nitration of 2-amino-4-*tert*-butyl-5-nitrothiazole.

4-tert-Butyl-2-nitraminothiazole (XIX). A solution of 7.8 g. (0.05 mole) of 2-amino-4-*tert*-butylthiazole in 31.2 g. (0.125 mole) of 80% sulfuric acid was chilled to −30° and 2.15 ml. (0.05 mole) of absolute nitric acid was added. After ten hours at 20° the system was poured into an iced aqueous solution of 15.8 g. (0.175 mole) of sodium carbonate. The precipitate was filtered off and slurried with 600 ml. of 2% alkali, then filtered to remove 1.25 g. which, crystallized from 2:1 benzene-absolute ethanol (2.5 ml.), yielded 0.4 g. (4%) of 2-amino-4-*tert*-butyl-5-nitrothiazole, m.p. 192.5–193°. The combined alkaline filtrates were acidified, extracted with chloroform, and this extract was concentrated under reduced pressure to a volume of 25 ml. Addition of 25 ml. of carbon tetrachloride precipitated 1.13 g. of 4-*tert*-butyl-2-nitramino-5-nitrothiazole, m.p. 139°. Vacuum evaporation followed by addition of carbon tetrachloride then precipitated successive crops amounting to 1.63 g. (16%) of 4-*tert*-butyl-2-nitraminothiazole, m.p. 155–159° (decomp.). Solution in alkali followed by treatment with Darco and reprecipitation with acid raised this melting point to 167°. After crystallization from acetone (6 ml. per g.) the compound melted at 170–170.5°, decomp.

Anal. Calc'd for $C_7H_{11}N_3O_2S$: C, 41.7; H, 5.45.
Found: C, 41.8; H, 5.65.

From the residual chloroform-carbon tetrachloride liquors there could be isolated more *tert*-butylnitraminonitrothiazole because of the low solubility of its sodium salt in water. The chlorinated solvents were removed under reduced pressure and the residue was treated with 10% aqueous sodium hydroxide. The sodium salt (1.80 g.) was filtered off, washed with ether and dried, m.p. 144° without decomposition. The total yield of the dinitro compound is thus 21%. The sodium salt cannot be N-methylated by dimethyl sulfate either in water, acetone, or dioxane. Its water solution may be acidified to recover 80% of the dinitro compound, m.p. 143°.

When only 4-*tert*-butyl-2-nitraminothiazole (XIX) was desired the experiment was

carried out with 0.04 mole (1.72 ml.) rather than 0.05 mole of absolute nitric acid. After ten hours the system was poured into ice and water containing 26.5 g. (0.25 mole) of sodium carbonate and then extracted with ether to remove tar and some 2-amino-4-*tert*-butyl-5-nitrothiazole. The aqueous phase partially acidified with dilute hydrochloric acid, precipitated 2.21 g. (22%) of XIX, m.p. 167–168° (decomp.). Further acidification of the filtrate yielded a second crop, m.p. about 140°, containing principally X.

An experiment identical with the original one except for the use of 65% instead of 80% sulfuric acid yielded only the regenerated 2-amino-4-*tert*-butylthiazole, isolated as its relatively insoluble sulfate salt.

4-tert-Butyl-2-N-methylnitramino-5-nitrothiazole (XI). *A. By nitration.* A solution of 0.42 g. (0.002 mole) of 2-N-acetyl-N-methylamino-4-*tert*-butylthiazole (XII) in 1.06 ml. (0.02 mole) of 96% sulfuric acid was treated with 0.2 ml. (0.0046 mole) of absolute nitric acid at 0°. The reaction was allowed to proceed spontaneously until a temperature of 40° was attained. After one hour the system was drowned in ice, yielding 0.25 g. (52%), m.p. 85°. Crystallization from petroleum ether (b.p. 60–70°, 20 ml. per g.) raised the melting point to 107.5–108°. X-ray diffraction pattern: [10] 4.23, 7.08, 8.58; [7] 3.25; [6] 3.93, 5.34.

Anal. Calc'd for $C_8H_{12}N_4O_4S$: C, 36.8; H, 4.66; S, 12.3.

Found: C, 37.3; H, 4.80; S, 11.9.

B. By diazomethylation. Treatment of 4-*tert*-butyl-2-nitramino-5-nitrothiazole in dioxane with etherous diazomethane gave a 50% yield, m.p. 103°. This was crystallized from 95% ethanol (7 ml. per g.), m.p. 107–108°, and compared by mixture melting point.

2-Amino-4-tert-butyl-5-nitrothiazole (XVII). *A. By nitration.* A solution of 3.9 g. (0.025 mole) of 2-amino-4-*tert*-butylthiazole in 13.8 g. (0.141 mole) of 95% sulfuric acid, cooled to −15°, was treated with 1.50 g. (0.024 mole) of absolute nitric acid so that the temperature did not exceed −10°. After three hours subsequently at 0° and 12 hours at 20° the system was drowned in ice and the dirty red precipitate washed with 0.5% aqueous sodium carbonate solution. The remainder weighed 1.91 g., m.p. 176°, and was augmented by neutralization of the acid filtrate with solid sodium carbonate, 2.20 g., m.p. 170°. This combined yield was crystallized from 7:5 ethanol-water (12 ml. per g.) with Darco, m.p. 191–192°, 3 g. (60%). Recrystallization from acetic acid (10 ml. per g.) raised this melting point to 193°. The compound was recovered unchanged after treatment with diazomethane in ether and dioxane.

Anal. Calc'd for $C_7H_{11}N_3O_2S$: C, 41.8; H, 5.51.

Found: C, 41.3; H, 5.73.

The combined alkaline liquors were acidified to yield 0.5 g. (8%) of impure 4-*tert*-butyl-2-nitramino-5-nitrothiazole, m.p. 129°, identified after crystallization from ethanol by mixture melting point (144° decomp.).

The crude 2-amino-4-*tert*-butyl-5-nitrothiazole originally precipitated as a yellow solid but it rapidly became deep red in color when the ice-drowned mixture was warmed to room temperature. This red color was investigated by pouring a solution comprising 6 g. of crude product in 80 ml. of chloroform into a 980 × 25 mm. alumina column. Development with chloroform yielded five bands. The lower, red band was washed through, 0.85 g. (16%), m.p. 197–198°. After crystallization from benzene this substance melted at 209–209.5°.

Anal. Calc'd for $C_{14}H_{21}N_5S_2$: C, 52.0; H, 6.64.

Found: C, 51.9; H, 6.63.

The substance, which gave a derivative, m.p. 161–162° (crystallized from ethanol) with boiling acetic anhydride, was reducible with loss of color by aqueous stannous chloride. The color was restored by aqueous ferric chloride.

B. By denitration. When 0.5 g. (0.002 mole) of 4-*tert*-butyl-2-nitramino-5-nitrothiazole was maintained at 25° in 3 ml. of absolute sulfuric acid for ten hours and then drowned in ice, the filtered system yielded 0.12 g. (24%) of 2-amino-4-*tert*-butyl-5-nitrothiazole, m.p. 172°, authenticated by mixture melting point after crystallization from water-ethanol, m.p. 191°.

C. By hydrolysis. When 2-acetamino-4-*tert*-butyl-5-nitrothiazole (XV) was hydrolyzed

with hot 22% hydrochloric acid the liquors yielded 2-amino-4-*tert*-butyl-5-nitrothiazole upon neutralization with sodium carbonate. After crystallization from acetic acid the product was authenticated by mixture melting point.

2-Amino-4-tert-butyl-5-nitrothiazole and sulfate. A solution of the amine (2.01 g., 0.01 mole) in 25 ml. of acetic acid was treated with 0.98 g. of absolute sulfuric acid. The acid sulfate precipitated almost quantitatively, m.p. 216.7–217.5°. Crystallization from acetic acid or ethanol did not rise this melting point.

Anal. Calc'd for $C_7H_{13}N_3O_6S_2$: C, 28.1; H, 4.35; N, 14.1; S, 21.4.
Found: C, 28.2; H, 4.55; N, 14.0; S, 21.3.

SUMMARY

1. Mononitration of 2-aminothiazole in mixed acid of increasing water concentration tends toward formation of 2-nitraminothiazole rather than 2-amino-5-nitrothiazole. Neither compound is formed when more than 30% of water is present.

2. Mononitration of 2-amino-4-trifluoromethylthiazole at 25° leads exclusively to 2-nitramino-4-trifluoromethylthiazole even in mixed acid containing no water. Only at 60° in absolute sulfuric acid can the nitramine be "rearranged" to 2-amino-5-nitro-4-trifluoromethylthiazole.

3. Mononitration of 2-amino-4-*tert*-butylthiazole cannot occur exclusively since dinitration is favored. In consequence a complex reaction mixture is obtained.

4. These behaviors have been interpreted in terms of ammononitracidium ion mechanisms.

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REFERENCES

(1) GANAPATHI AND VENKATARAMEN, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945).
(2) BAMBERGER, *Ber.*, **30**, 1248 (1897).
(3) WIBAUT, OVERHOFF, AND GELDOF, *Rec. trav. chim.*, **54**, 807 (1935).
(4) FRANCHIMONT, *Rec. trav. chim.*, **16**, 226 (1897).
(5) MCBEE AND BURTON, *J. Am. Chem. Soc.*, **74**, 3902 (1952).
(6) HILL, TOWNE, AND DICKEY, *J. Am. Chem. Soc.*, **72**, 3289 (1950).