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1, 2, 4-TRIAZOL-3-ONE AND ITS NITRO AND AMINO DERIVATIVES

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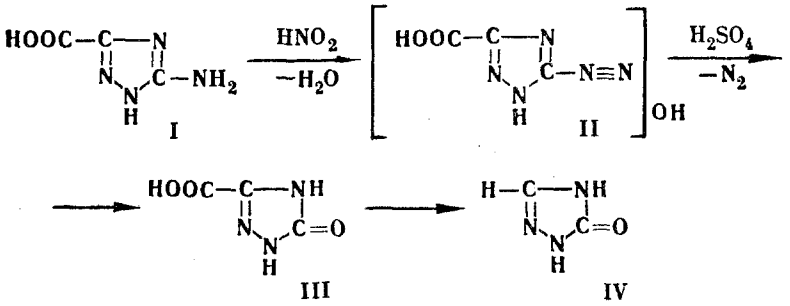
Some possible methods of preparation of 1, 2, 4-triazol-3-one are explored. A new method of preparing it from semicarbazide hydrochloride and formic acid is worked out. Nitration of the triazolone gives 5-nitro-1,2,3-triazol-3-one, whose structure is proved.

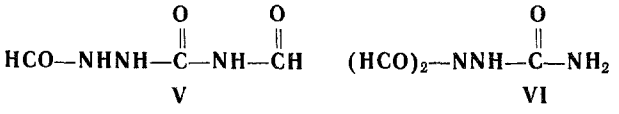
The present work aimed to explore some possible routes to 1, 2, 4-triazol-3-one, and derivatives with nitro and amino groups.

The literature describes a few methods of preparing 1, 2, 4-triazol-3-one: decarboxylation of 1,2,4-triazol-3-one-5-carboxylic acid [1]; from acetone semicarbazone and formic acid; from diformylsemicarbazide and formic acid [2]; and by deaminating 4-amino-1, 2, 4-triazol-3-one [3].

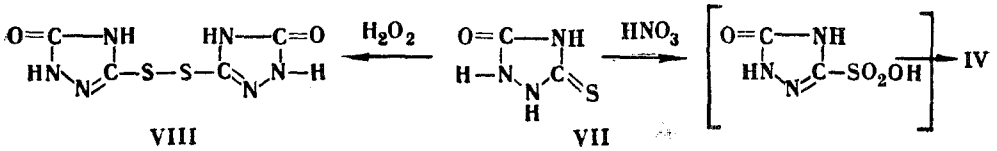
Thermal decarboxylation of 1,2,4-triazol-3-one carboxylic acid (III) gives triazolone (IV) in good yield [1]. Synthesis of the acid III is most readily effected via 3-diazo-1,2,4-triazole-5-carboxylic acid (II) [4-6]. We studied the decomposition reaction of diazo compound II in sulfuric acid at different concentrations (15, 25, and 35%). Optimum yields of III are obtained with the 25% acid. We have also improved the method of preparing the diazotriazolecarboxylic acid II.



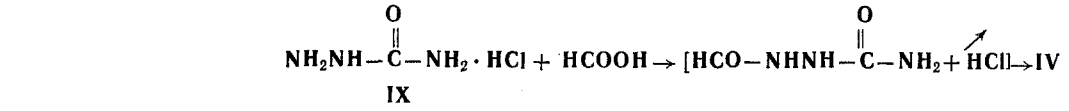
When acetone semicarbazone is acylated with formic acid, the primary reaction product is diformylsemicarbazide (V or VI), which on prolonged heating gives the triazolone (IV). However, according to our results, using 85% formic acid, the yield of IV in this reaction does not exceed 10% (a paper [2] does not give yields).



Heterocyclic compounds containing the group $-N{=}C(SH)-N{=}$, are readily oxidized to the corresponding sulfo acids, which, for this class of compound, are unstable, and decompose with splitting out of SO_3. For example, nitric acid oxidation of 1, 2, 4-triazole-3-thione gives 1, 2, 4-triazole in 58% yield [7]. But with monothiourazole (VII) the main oxidation product is the corresponding disulfide VIII. The triazolone IV is formed only in insignificant amount. When we used H_2O_2 in acetic acid as the oxidizing agent (for the method of oxidation see [8]), only the disulfide VIII was isolated.



Our method of preparing 1, 2, 4-triazol-3-one by acylating semicarbazide hydrochloride (IX) with 85% formic acid was the most suitable. When IX is boiled with excess formic acid, the semicarbazide is acylated with simultaneous splitting out of hydrogen chloride and cyclization, 1, 2, 4-triazol-3-one (IV) being formed in 64% yield.



IX

Nitration of 1, 2, 4-triazolone with fuming nitric acid as described in [4], gives 5-nitro-1, 2, 4-triazol-3-one (X). However, in our experiments, use of fuming nitric acid (d 1.495) resulted in complete carbonization of the starting material. The table gives the effect of empirical change in nitric acid concentration on yield of nitration product. The fuming nitric acid was diluted with water immediately before the nitration.

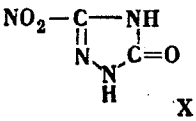
Results Obtained in Nitrating the Triazolone IV

Experiment number	Triazolone, g	Nitrating mixture		Yield X	
		HNO_3 (d 1.495), ml	H_2O, ml	g	%
1	4	4	—	—*	—
2	4	2	2	—*	—
3	4	5	3	3.06	50.0
4	4	6	3	3.50	57.2
5	10	15	8	10.4	67.5
6	4	6	4	2.65	43.4

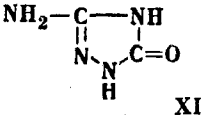
*Under the experimental conditions, IV carbonizes.

The nitrotriazolone X is a white crystalline substance, melting point 265-268°, soluble in water to give yellow solutions, becoming colorless on acidification. It is readily soluble in solutions of alkalies, to give orange red solutions. It is stable towards concentrated aqueous solutions of alkalies, but is decomposed by boiling with mineral acids. Nitrotriazolone is rather a strong acid (pH 2.35 for a 0.1 M solution), and readily forms salts with both organic and inorganic bases. These salts readily crystallize, and some of them have low solubilities in water, which is of preparative and analytical interest. Neutralization of aqueous solutions of nitrothiazolone with potassium or sodium hydroxide solution gives salts which are sparingly soluble in cold water; fine long needles, reminiscent of cotton wool in the case of the sodium salt, and minute prisms, in the case of the potassium one. The lithium salt is readily soluble in cold water. Nitrotriazolone also forms sparingly soluble salts with ions of uni- and di-valent metals (Ba^{2+}, Hg^{2+}, Ag^+, and others).

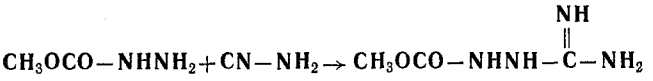
The literature describes two forms of 5-amino-1, 2, 4-triazol-3-one (XI). One compound is a white substance, melting point 285° (picrate melting point 210-212°), prepared by reacting dicyanodiamidine with hydrazine hydrochloride, or by melting together urea and aminoguanidine hydrochloride [9]. It forms a white silver salt. The second compound is a pale yellow substance (hydrochloride melting point 196°, picrate 204°) prepared by reducing nitrotriazolone with zinc and hydrochloric acid; it forms a red silver salt [4].



X



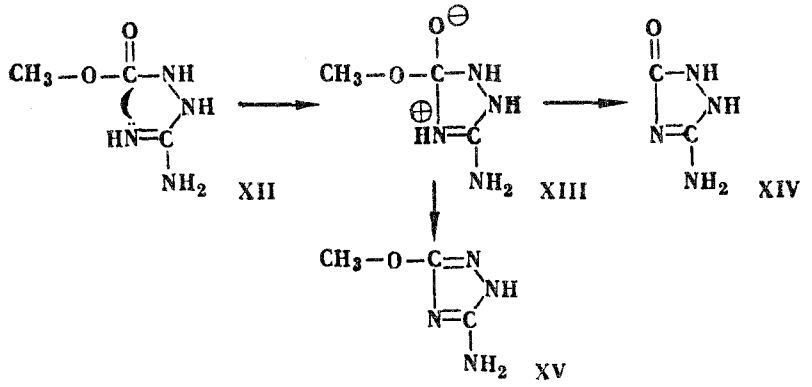
XI



XII

Recently XI with melting point 286-290° (picrate melting point 210-212°) has been prepared by hydrolyzing 1-isopropylideneamidino-3-phenylurea with hydrochloric acid [10].

We also obtained aminotriazolone mp 290° in an attempted synthesis of 3-methoxy-5-amino-1, 2, 4-triazolone (XV) by cyclizing 1-carbomethoxyaminoguanidine (XII) in alkaline medium. Compound XII was synthesized from the methyl ester of hydrazine carboxylic acid and cyanamide. However it appeared that alkaline cyclization of XII gave, instead of the expected methoxyaminotriazole XV, the aminotriazole XIV. As our previous research showed [11], the first stage in the cyclization of acylaminoguanidines is nucleophilic attack on the carbonyl carbon atom by the imine nitrogen atom of the guanidine group. With carbomethoxyaminoguanidine, nucleophilic attack gives structure XIII, which can undergo further transformation in two ways: either there is an overall splitting out of methanol to give the aminotriazolone XIV, or water splits out to give the methoxyaminotriazole XV. Obviously in this case anionoid splitting with migration of a lone electron pair proceeds more readily. Though the MeO^- anion is more basic than the OH^- one, obviously such a splitting out promotes possible neutralization of the MeO^- anion insofar as it is formed by proton bonding [12].



The aminotriazolone XIV which we obtained was wholly identical with preparations, prepared by the methods of [9, 10]. It is natural to raise the question of the structures of the compound, obtained by nitrating the triazolone, and those of its reduction products.

We did not suceed in isolating an aminotriazolone by reducing the nitrotriazolone X with zinc and hydrochloric acid by the method of [4]. The reaction proceeds in a number of directions, and is evidently bound up with partial splitting of the triazole ring. Reactions of that kind are well known, e.g., in the nitroimidazole series [13, 14].

Actually we succeed in obtaining the aminotriazolone XI by catalytic reduction in the presence of Adam's catalyst, and this also proved structure X. It should be mentioned that here reduction of the nitrotriazolone evidently proceeds via azo- and hydrazotriazolones, since contact of the post-reduction solutions with air led to their quickly becoming yellow. With Ag^+ ions such a solution gives an orange-red precipitate; obviously traces of nitrotriazolone incomplete reduction products also gave rise to a colored silver salt with aminotriazolone in another paper [4]. For complete reduction of the nitrotriazolone the reduction time must be multiplied somewhat.

Experimental

3. -diazo-1, 2, 4-triazole-5-carboxylic acid (II). A solution of 180 ml concentrated HCl in 300 ml water was prepared in a 2 *l* flask, 68.5 g (0.54 mole) 3-amino-1, 2, 4-triazole-5-carboxylic acid (I) added, and the whole heated until it dissolved. After cooling to room temperature, 500 g ice was added to the solution (part of the aminotriazolecarboxylic acid separated out as a precipitate in a fine state of division), then 40 g (0.58 mole) $NaNO_2$ in 100 ml water was added in 2-3 mins, with mechanical stirring, after which stirring was continued for half an hour more, the temperature being kept at 0-4° (external cooling). The diazotriazolecarboxylic acid precipitated was filtered off on a Buchner funnel, and used damp for the following synthesis (the dry diazotriazolecarboxylic acid is liable to explode).

1, 2, 4-Triazol-3-one-5-carboxylic acid (III). The diazotriazolecarboxylic acid II was put in a 2 *l* flask, with 640 ml 25% H_2SO_4, and the whole slowly heated. The diazocompound began to decompose with evolution on N_2, at 40-50°. Further, the reaction was exothermic. The course of the reaction could be controlled by applying the necessary cooling with ice water. To bring the reaction to completion the solution was rapidly heated to 95-100°, and immediately cooled. The triazolonecarboxylic acid III precipitated was filtered off, washed with water, and air-dried. Yield 41.0 g (56%, based on II), mp 196° (decomp). After recrystallizing from water (1 g from 40 ml) it had mp 205° (decomp), yield after recrystallization 61%. The literature gives for 1, 2, 4-triazol-3-one-5-carboxylic acid mp (decomp) 205° [4], 218° [5], 210° [7].

When the diazotriazolecarboxylic acid decomposition was run in 15% and 35% H_2SO_4, the yields of impure triazolonecarboxylic acid were 53% and 59% respectively.

Diformylsemicarbazide (V or VI). 3.7 g (0.03 mole) acetone semicarbazone and 7 ml 85% formic acid were refluxed together for 4 hr, the formic acid distilled off under reduced pressure, the residue dissolved in 5 ml EtOH, and left to crystallize. Yield of diformylsemicarbazide 1.37 g (32%), mp 157° (ex EtOH) (158° [2]). Found: N 31.75%. Calculated for $C_3H_5N_3O_3$: N 32.04%.

1, 2, 4-Triazol-3-one (IV). a) From 1, 2, 4-triazol-3-one-5-carboxylic acid. 14.7 g (0.11 mole) acid III was decarboxylated at 205-210°, and the residue recrystallized from 20 ml water. Yield, 6.1 g (75%), mp 233-234° (234° [4]). Found: C 28.26; H 3.67; N 49.26%. Calculated for $C_2H_3N_3O$: C 28.24; H 3.55; N 49.38%.

b) From acetone semicarbazone. 5 g (43 mmole) acetone semicarbazone and 10 ml 85% formic acid were refluxed for 30 hr. The formic acid was distilled off under reduced pressure, and the oily residue left for 24 hr at −5°, then diluted with 4 ml EtOH, and filtered, to give 0.37 g (10%) 1, 2, 4-triazolone on the filter, mp 220°. After recrystallizing from water mp 233-234°, undepressed mixed mp with an analyzed specimen.

c) Oxidation of monothiourazole. 4.2 g (36 mmole) monothiourazole VII was introduced in small portions into a solution comprising 24 ml water, 12 ml concentrated HNO_3, and 0.1 g $NaNO_2$, the solution being held at 35-40°. After cooling the precipitate was filtered off, yield of disulfide VIII, 2.35 g (56%), mp 243°(decomp, ex EtOH)(245° [15]). Found: N 36.20%. Calculated for $C_4H_4N_6S_2O_3$: N 36.68%.

After separating off the disulfide, the filtrate was neutralized with NaOAc, and evaporated to dryness on a water bath. The dry residue was extracted three times with 50 ml dry EtOH each time. The alcoholic solution was evaporated to dryness, and the residue recrystallized from 5 ml hot water. On cooling 0.1 g triazolone IV separated, mp 231-233°, undepressed mixed mp with a specimen prepared by decarboxylating the triazolonecarboxylic acid.

d) By acylating semicarbazide hydrochloride. 223 g (2 mole) semicarbazide hydrochloride and 230 ml 85% formic acid were placed in a 1 *l* round-bottomed flask fitted with a reflux condenser, and boiled for 8 hr. During reaction the semicarbazide hydrochloride slowly dissolved, and split off HCl which passed out through the condenser. After boiling, the solution was kept for 12 hr at 0°, and the precipitated triazolone filtered off, yield 110 g(64.5%), mp 200-207°. Recrystallized from 220 ml water it gave 80 g (72.5%) IV, mp 228°. For analysis it was recrystallized once more from water, mp 233°. Found: C 28.76; H 3.44; N 49.42%. Calculated for $C_2H_3N_3O$: C 28.24; H 3.55; N 49.38%.

A diacetyl derivative mp 136°(ex EtOH) was prepared by boiling the triazolone with Ac_2O [4].

5-Nitro-1,2,4-triazolone (X). The appropriate quantities of triazolone (see table) and nitric acid were heated in a beaker till reaction commenced (violent evolution of nitrogen oxides), after which heat was removed. Depending on the acid concentration, the reaction was complete in 2-4 min. The reaction product which crystallized after half an hour was diluted with 10-15 ml ice water, filtered, and dried in a vacuum desiccator over KOH. Recrystallization from water gave X mp 265-268°(decomp, capillary put in a block at 250°). When the compound was slowly heated to 320°, it did not melt. A specimen from experiment 5 was analyzed. Found: C 18.95; H 1.74; N 43.44%. Calculated for $C_2H_2N_4O_3$ C 18.47; H 1.55; N 43.07%.

Potassium salt of the nitrotriazolone. 26 g (0.2 mole) nitrotriazolone was dissolved in 100 ml water, and 11.2 g (0.2 mole) KOH added. On cooling the K salt of the nitrotriazolone crystallized out as a hydrate, yield 27 g(80%), mp 228-230°(decomp). Found: C 13.47, 13.46; H 1.73, 1.83; N 30.14, 30.40%. Calculated for $C_2HN_4O_3K \cdot H_2O$: C 13.15; H 1.62; N 30.65%.

A mercury salt of the nitrotriazolone is precipitated on reacting equinormal solutions of nitroazolone and $Hg(OAc)_2$. Found: N 24.04%. Calculated for $C_4H_2N_8O_6Hg$: N 24.41%.

1-Carbomethoxyaminoguanidine (XII) hydrochloride. A solution of 12.65 g (0.1 mole) methyl hydrazine carboxylate hydrochloride and 6.3 g (0.15 mole) cyanamide in 50 ml EtOH were heated together for 1 hr, and on cooling there crystallized out 7.9 g (47%) 1-carbomethoxyaminoguanidine, mp 201°(decomp, ex EtOH). Found: N 33.72%. Calculated for $C_3H_8N_4O_2 \cdot HCl$: N 33.22% .

5-Amino-1,2,4-triazol-3-one (XI ⇄ XIV). a) From 1-carbomethoxyaminoguanidine (XII). A solution of 7.9 g (49 mmole) XII hydrochloride and 5.6 g (53 mmole) NaOAc in 20 ml water was refluxed for half an hour, cooled, and neutralized with AcOH. 3.55 g(75.7%) aminotriazolone XIV separated. After recrystallizing from water it had mp 290° (decomp, block)(286-290° [10]. Found: C 23.75; H 3.93; N 55.17%. Calculated for $C_2H_4N_4O$: C 24.00; H 4.02; N 55.96%.

b) Reduction of nitrotriazolone. A solution of 0.65 g nitrotriazolone X and 80 ml water was reduced with H_2, using Adam's catalyst (0.1 g). The theoretical quantity of H_2 was absorbed in 4 hr, but reduction was continued for another 4 hr. On evaporating the solution there crystallized 0.37 g (74%) aminotriazolone, mp 290°(decomp, block). Found: C 24.32; H 4.66; N 55.63%. Calculated for $C_2H_2N_4O$: C 24.00; H 4.02; N 55.96%.

Aminotriazolone picrate, mp 200-210° (ex water) (210-212° [10]).

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