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RESEARCHES ON IMIDAZOLES

XX. Aminonitroimidazoles and Diaminoimidazoles*

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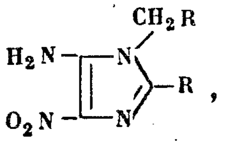
A number of 1-alkyl(1,2-dialkyl)-4-nitro-5-amino-and 1-alkyl(1,2-dialkyl)-4-amino-5-nitroimidazoles are prepared by ammonolysis of 1-alkyl- or 1,2-dialkyl-4-nitro-5-chloroimidazoles or their 4-chloro-5-nitro isomers. Hydrogenation of 1-ethyl-2-methyl-4-nitro-5-aminoimidazole in acetic anhydride gives 1-ethyl-2-methyl-4,5-diaminoimidazole di- and tetra-acetates.

4(5)-Amino-5(4)-nitro- and 4,5-diaminoimidazoles have been but little investigated. When the present work was begun, three compounds of the aminonitroimidazole series had been described: 4(5)-nitro-5(4)-carbomethoxy(carboethoxy) aminoimidazoles and 1-methyl-4-nitro-5-aminoimidazoles [1]. Diaminoimidazoles were unknown. A recent publication [2] described the preparation of 1-methyl-4-nitro-5-alkyl (dialkyl) aminoimidazoles and some of their acylation and reduction products.

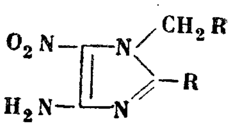
The present syntheses of aminonitroimidazoles and diaminoimidazoles were undertaken with a view to a more detailed study of their properties and their possible use for preparing new derivatives of various heterocyclic systems condensed with the imidazole ring.

Aminonitroimidazoles

Formula of Compounds I-VII



Formula of Compounds VII-XII



Compound No.	R	Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
I	H	302—303* (decomp).	$C_4H_6N_4O_2$	33.94	4.15	39.28	33.80	4.25	39.42	89
II	CH_3	214—215	$C_6H_{10}N_4O_2$	42.45	5.81	32.82	42.34	5.92	32.92	62.3
III	C_2H_5	146—147	$C_8H_{14}N_4O_2$	48.40	7.28	27.96	48.50	7.07	28.25	61.4
IV	n-C_3H_7	127—128	$C_{10}H_{18}N_4O_2$	53.24	7.69	24.45	53.07	8.02	24.76	61.7
V	i-C_3H_7	187—188	$C_{10}H_{18}N_4O_2$	52.79	7.80	25.10	53.07	8.02	24.76	15
VI	n-C_4H_9	131—131.5	$C_{12}H_{22}N_4O_2$	56.92	8.54	21.87	56.67	8.72	22.03	15—20
VII	i-C_4H_9	108—110	$C_{12}H_{22}N_4O_2$	56.50	8.65	22.00	56.67	8.72	22.03	15
VIII	H	222.5—223	$C_4H_6N_4O_2$	34.02	4.45	39.23	33.80	4.25	39.42	30.5
IX	CH_3	198—199	$C_6H_{10}N_4O_2$	42.65	6.06	32.62	42.34	5.92	32.92	39.5
X	C_2H_5	160—161	$C_8H_{14}N_4O_2$	48.37	6.96	28.36	48.50	7.07	28.25	58
XI	n-C_3H_7	130—131	$C_{10}H_{18}N_4O_2$	53.27	8.05	24.85	53.07	8.02	24.76	32
XII	i-C_4H_9	129—130	$C_{12}H_{22}N_4O_2$	56.73	8.54	22.11	56.67	8.72	22.03	21.5

*The literature [1, 2] gives mp 303° (decomp). Using an ordinary thermometer the compound is found to melt at 290-293° (decomp).

The starting compounds used were nitrochloroimidazoles [3], whose halogen atom, like that of nitrochlorobenzoles, is rather mobile, and readily replaced by an amino group. Ammonolysis of 4-nitro-5-chloro- and 4-chloro-5-nitroimidazoles gives a series of 1-alkyl(1,2-dialkyl)4-nitro-5-amino- and 1-alkyl(1,2-dialkyl)-4-amino-5-nitroimidazoles (I-XII); yields, constants, and analyses of these are given in the Table.

Heating 1-methyl-4-nitro-5-chloro- and 1-ethyl-2-methyl-4-nitro-5-chloroimidazoles with 3.5% alcoholic ammonia under the conditions given in the literature (4 hr at 140° [1]) led to the isolation, along with compounds I and II (yields 55% and 20% respectively) of unreacted starting materials. So a more concentrated alcoholic solution of ammonia (8-15%) was used to prepare the aminonitroimidazoles, and the reaction carried out at 120-150° for 5-10 hr.

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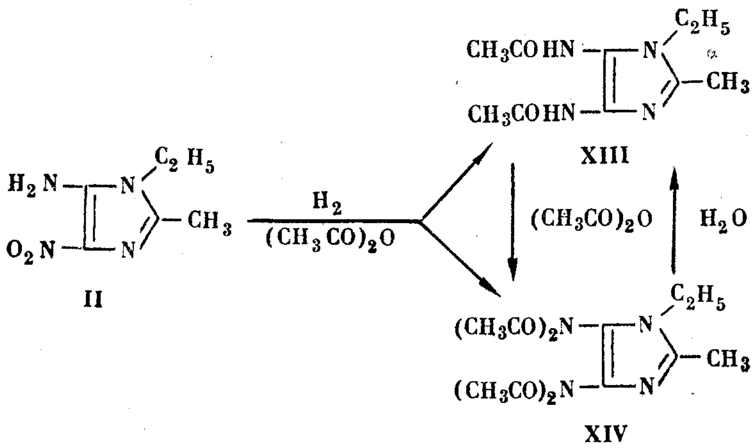
*For Part XIX see [3]. Paper presented at the All-Union Conference on the Chemistry of Five-membered Heterocyclic Ring Nitrogen Compounds, Rostov-on Don, 1962 [5].

In a number of experiments ammonolysis was effected in the presence of copper sulfate, which resulted in a higher yield of certain aminonitroimidazoles. For example, compound I was obtained in 89% yield, as compared with the 75.6% under the same conditions but without the catalyst. It was observed that as the alkyl groups as positions 1 and 2 in the nitrochloroimidazoles increased and branched, the replacement of chlorine by an amino group takes place less smoothly. For example, because of considerable resinification of the reaction products, compounds V-VII and XII were obtained in yields of 15-22%.

The chemical properties of 4(5)-amino-5(4) nitroimidazoles (I-XII) were markedly different to those of 4(5)-aminoimidazoles. The latter are strong bases, and are unstable in the free state [4]. Only their acyl derivatives, picrates, hydrochlorides or other salts are stable. 4(5)-Nitro-5(4)-aminoimidazoles are stable crystalline compounds, undecomposed by boiling with water, but readily decomposed by heating with acids and alkalies. Due to the presence of the electron-accepting nitro group, aminonitroimidazoles exhibit very feeble basic properties. They are acylated with great difficulty, and do not form hydrochlorides or picrates.

Reduction of some aminonitroimidazoles was investigated with a view to preparing 4,5-diaminoimidazoles. The usual reduction methods were unsuccessful, as the diaminoimidazoles formed are very unstable. However, reduction in acetic anhydride facilitated formation of more stable acetyl derivatives of the diaminoimidazoles, some of which were isolated and characterized. Thus, depending on reaction temperature conditions, hydrogenation of the imidazole II in acetic anhydride using Raney nickel catalyst gives the diacetate XIII (isolated as its picrate) and tetra-acetate XIV of 1-ethyl-2-methyl-4,5-diaminoimidazole. The picrate of diacetate XIII is unchanged on prolonged boiling with water, while heating with acetic anhydride converts it to the picrate of the tetraacetate XIV. Prolonged boiling of tetraacetate XIV with acetic anhydride leaves it unchanged, boiling it with water converts it to the diacetate XIII, and when heated for a short time with dilute hydrochloric acid it decomposes, with formation of ammonium chloride.



Experimental

A previous paper [3] has described the synthesis of the starting nitrochloroimidazoles. The latter were ammonolyzed in sealed glass tubes, holding 80-100 ml, and heated in an electric rocking furnace.

Aminonitroimidazoles (I-XII). A mixture of 4-5 g nitrochloroimidazole and 40-50 ml of an 8.2-15.2% solution of ammonia in absolute alcohol was heated for 7-10 hr at 135-150°. After cooling the tubes were opened, and the reaction products cooled to between 0° and −5°, the precipitate filtered off, washed with a small amount of cold alcohol, then with water (to remove ammonium chloride), dried, and recrystallized (first using activated charcoal) from a suitable solvent. A further quantity of aminonitroimidazole was obtained by evaporating the alcoholic mother liquor to dryness. Compound V was isolated by evaporating the solution of reaction products to dryness, washing the residue with ether, dissolving it in ethyl acetate, and precipitating with ether. In preparing compound VII, the residue after distilling off the alcohol was washed with carbon tetrachloride and then with ether. For analysis, compounds I-III were recrystallized from water, compound IV from ethyl acetate, V-VII, XII from aqueous alcohol, VIII from nitrobenzene, IX and X from alcohol.

In preparing compounds I-IV a 15.2% alcoholic solution of ammonia was used (8.5 hr heating at 140-150°); for compounds V, VI, IX, and XI, a 12% ammonia solution (10 hr at 140-145°), for compounds VII, X, and XII, an 8.2% ammonia solution (7 hr at 138-140°); for compound VIII, a 12% ammonia solution (4 hr at 120°). Compounds I, VII, and XII were prepared in the presence of copper sulfate catalyst (0.1-0.5 g per 5 g nitrochloroimidazoles).

Aminonitroimidazoles are yellow crystalline compounds, which are stable when stored. Compounds I and VIII are almost insoluble in organic solvents and in water (cold), and easily soluble only in dimethylformamide (hot). The other compounds are soluble in most organic solvents and hot water, insoluble in cold water and petrol ether. They decompose on heating with acids or alkalies.

1-Ethyl-2-methyl-4, 5-diaminoimidazole diacetate (XIII) picrate. a) 5.1 g 1-ethyl-2-methyl-4-nitro-5-aminoimidazole (II) in 300 ml acetic anhydride was hydrogenated in the presence of Raney nickel (2.6 g), at 30-45°, under an initial hydrogen pressure of 10 atm. Reduction was complete after 4.5 hr, almost the theoretical quantity of hydrogen being taken up (2.16 g). The catalyst was filtered off, and the filtrate distilled under reduced pressure to remove acetic anhydride. The viscous residue was dissolved in acetone, hydrogen sulfide passed in, the solution filtered, and the acetone distilled off under reduced pressure. The dark brown residue was heated with ethyl acetate (using charcoal), filtered, and the solvent distilled off under reduced pressure. The uncrystallized oil was dissolved in 50-60 ml 6% picric acid in alcohol, the precipitate filtered off, and dried. Yield 1.7 g diacetate (XIII) picrate, mp 199-199.5°. A further amount of this picrate, mp 195-196°, was isolated from the alcoholic mother liquor by precipitation with ether. Yellow prisms mp 201.5-202.5° (vaporizes, from alcohol), soluble in water, alcohol and acetone. Found: C 42.54; H 4.13; N 21.71%. Calculated for $C_{10}H_{16}N_4O_2 \cdot C_6H_3N_3O_7$: C 42.39; H 4.22; N 21.63%. Five hrs drying at 135° did not affect either the melting point or the elementary composition of the picrate.

b) A solution of 0.1 g of the picrate of compound XIV, prepared as described below, was refluxed for 5 hr with 3 ml water, the water distilled off under reduced pressure, the residue washed with ether, and dried. Yellow crystals mp 199-200° were obtained, mixed mp with a specimen of XIII picrate prepared as described in (a) above, undepressed. Mixed mp with starting picrate (mp 158-159°), 150-153°.

1-Ethyl-2-methyl-4, 5-diaminoimidazole tetraacetate (XIV). a) 2.4 g II in 150 ml acetic anhydride was hydrogenated in the presence of 2.4 g Raney nickel, under a hydrogen pressure of 100 atm, and at 50-80°. Hydrogenation was complete in 5 hr. The reaction product was heated to 100° (on a bath), filtered, and the acetic anhydride taken off under-reduced pressure. The dark brown residue was warmed up with a mixture of ethyl acetate and ether (using charcoal), filtered, and the filtrate evaporated to dryness. Yield 1.15 g material mp 97-104°. A specimen for analysis was prepared by 3 precipitations from ethyl acetate with petrol ether. Colorless crystals mp 109.5-112.5°, readily soluble in water and most organic solvent, insoluble in petrol ether. Found: C 54.79; H 6.48; N 18.34%. Calculated for $C_{14}H_{20}N_4O_4$: C 54.54; H 6.54; N 18.17%.

Picrate, yellow prisms mp 158-159° (from alcohol), readily dissolves when heated with water or alcohol, sparingly soluble in the cold in the solvents listed above. Found: C 44.45; H 4.42; N 18.29%. Calculated for $C_{14}H_{20}N_4O_4 \times$ $\times C_6H_3N_3O_7$: C 44.69; H 4.31; N 18.24%.

b) A solution of 0.3 g picrate XIII in 5 ml acetic anhydride was refluxed for 5 hr, the acetic anhydride distilled off under reduced pressure, the residue washed with ether, and dried. Yellow crystals mp 154-156°. Mixed mp 154-157° with the picrate prepared as described in (a) above. Mixed mp 144-145° with the starting picrate.

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