A NEW OXIDATIVE REACTION IN THE

2-AMINOIMIDAZOLE SERIES

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2-Aminoimidazoles in liquid ammonia display the properties of polybasic NH acids, forming mono-, di-, and possibly trianions according to the conditions. The following methods have been developed for the generation of these N anions: the action of bases on 2-aminoimidazoles; debenzylation of their N-benzyl derivatives; and reductive fission of 2-azidoimidazoles by sodium in liquid ammonia. The polyanions have been shown to be oxidized by atmospheric oxygen to 2, 2'-azo- and 2-nitroimidazoles.

The acidic properties of the amino group have hardly been investigated. Although both hydrogen atoms in aromatic amides are replaceable by alkali metals in aprotic solvents [1], it is not clear at the present time whether dianions of aromatic amines exist in liquid ammonia [2]. Urea and guanidine are known to form dianions with potassium amide in liquid ammonia, and cyanourea gives the trianion [3].

N anions are apparently formed during the unique oxidative conversion, discovered by us, of 1-benzyl-2-aminobenzimidazole (I), which may formally be considered as a cyclic guanidine [4]. During our attempts to obtain 2-aminobenzimidazole (II) by debenzylation of I with 2 g-atoms of sodium in liquid ammonia, we observed the formation of 2, 2'-azobenzimidazole (III, 32%) together with II (45%).



Treatment of I with 4g-atoms of sodium increases the yield of III to 55%, 2-nitrobenzimidazole (IV, 43%) also being formed. The compounds listed in Table 1 react similarly.

8-Aminopurine, 2-aminopyridine, and N-alkyl-2-aminoimidazoles afford at best only traces of the azo derivatives.

	Yield, %			
Compound	Azo-compound	Nitro compound		
1-Benzyl-2-aminobenzimidazole 1-Benzyl-2-amino-5-methylbenzimidazole[5] 1-Benzyl-2-amino-5-methoxybenzimidazole[5] 1-Benzyl-2-amino-5,6-dimethylbenzimidazole[6] 1(3)-Benzyl-2-aminonapht[1,2]imidazole [7] 1-Benzyl-2-amino-4,5-diphenylimidazole [8] 7-Benzyl-8-aminotheophyllin	55 61 61 81 74,6 90,4 4,2	43 35 35 17 20,7 —		

TABLE 1. Results of the Reaction of N-Benzyl-2-aminoimidazoles with Sodium (4 g-atom) in Liquid Ammonia

Rostov-on-Don State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1267-1272, September, 1970. Original article submitted June 23, 1969.

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UDC 547.781.1

The whole process occurs under mild conditions, with quantitative yields of isolated compounds. It appears that highly reactive ions are formed during the course of the reaction, and that these are oxidized by atmospheric oxygen. Under strongly basic reaction conditions, these ions can only be N anions. In fact, if the reaction is carried out in the absence of air, and the reaction mixture after addition of the sodium is treated with a source of protons (NH_4Cl , C_2H_5OH , etc.), the sole reaction product is the 2-aminoimidazole. The first stage of the reaction involves debenzylation of Ia to give the N anion (V) and the benzyl anion (for the theory of reductive debenzylation with solutions of alkali metals in liquid ammonia, see [9]):



The monoanions V and VI are oxidized very slowly by air. Similarly inert towards oxygen are also the dianions VIIb, which are formed by reaction of 1-alkyl-2-azidobenzimidazoles (Xb) with sodium in liquid ammonia [10]. The experimental facts may be explained on the assumption that 2, 2'-azo- and 2-nitroimidazoles are formed by oxidation of the di- and trianions VIII and IX, which are produced by the action of a strong base B⁻ on V:



Theoretically, sodium itself, the benzyl anion, and the amide ion formed by ammonolysis of the latter (the acidity constants pK_a of ammonia and toluene are respectively 34 and 37 [3]) may function as the base B⁻. The roles of the sodium and the sodium (or potassium) amide have not, however, been elucidated. In fact, reaction of 2-aminobenzimidazole with 3-4g-atoms of sodium gives 2, 2'-azo- and 2-nitrobenzimidazole in yields of only 18 and 10%, respectively.

It will be seen from Table 2 that the reaction of II with potassium amide results in almost all the amine being converted into the di- and triionized forms, but in this case, also, the yield of 2-nitrobenzimidazole is much lower than the 40-45% obtained by debenzylation of I. Similar behavior is observed with 8-aminotheophyllin and 2-amino-4, 5-diphenylimidazole. This indicates that the main contributor to the formation of the trianion IX is the benzyl anion, the amination of which in liquid ammonia appears to proceed slowly. The important role of the benzyl anion was demonstrated by our experiments on the "cross generation" of polyanions, involving debenzylation of 1-benzylbenzimidazole (a donor of benzyl anions) with sodium (6 g-atom) in liquid ammonia, in the presence of 2-aminobenzimidazole. Standard yields of the azo and nitro compounds were obtained (52 and 44%, respectively), as in the debenzylation of I.

The formation of both the azo and nitro compounds could, in principle, result from oxidation of the di- and trianions.



The results given in Table 3, however, show that it is more probable that 2, 2'-azoimidazoles are formed from the dianion, and 2-nitroimidazoles from the trianion. In fact, the yield of IV increases when the quantity of alkali metal is increased from 2 to 4 g-atom, possibly as a result of an increase in the concentration of the trianion in the reaction mixture. Debenzylation of I with 2 g-atom of sodium can only result in the formation of the dianion, and accordingly 32% of III is obtained, with only traces of IV.

TABLE 2. Results of the Reaction of 2-Aminobenzimidazole with Potassium Amide in Liquid Ammonia

Molar ratio,	Yield,	%		
II:KNH2	III	IV		
1:1	Trace	-		
1:2	36	10		
1:3	81	15		
1:4	84	14		

TABLE 3. Dependence of the Yields of 2, 2'-Azo- (III) and 2-Nitrobenzimidazole (IV) on the Amount of Alkali Metal in the Debenzylation of 1-Benzyl-2-aminobenzimidazole (I)

Molar ratio,	1	Yield, %			
II: KNH ₂	Metal	111	IV		
1:2	Na	32	1-2		
1:3	Na	61	35		
1:4	Na	55	43		
1:6	Na	52	35		
1:3	K	53	45		

The trianions X may be obtained by the method developed by us [10], involving reduction of 2-azidobenzimidazole Xa and its 1-benzyl derivative Xc with sodium in liquid ammonia:



In this reaction, the yield of IV exceeds that of III, but the overall yield of both compounds is not high owing to the difficulty in converting the dianion VII into the trianion IX. It cannot be said with certainty in this case, whether the azobenzimidazole is formed from the trianion, or from the dianion which results from ammonolysis of the trianion. Irrespective of this, experiments with the 2-azidobenzimidazoles Xa-c showed that the preferred source of 2-nitrobenzimidazole is the trianion. The results support the occurrence of slow acid-base conversion at high pK_{α} values. This explains why anions of the type of IX, and probably benzyl anions, can exist in liquid ammonia for prolonged periods without undergoing appreciable ammonolysis. The ratio of the polyanions is apparently determined by the equilibrium VIII \Rightarrow IX. It may be assumed that electron-donating substituents will reduce the acidity of the NH group in 2-aminoimidazoles. and will shift this equilibrium to the left, in the direction of the dianion. The yield of 2-nitro derivative should correspondingly be reduced. This is fact occurred with 5-methyl, 5-methoxy, and 5, 6-dimethyl-2aminobenzimidazole. It is not entirely clear why, in the case of the more acidic 2-aminonaphthimidazoles. the yields of the 2-nitro derivatives are reduced, while in the cases of 8-aminotheophyllin and 8-aminopurine, the reaction proceeds either poorly, or not at all. The probable reason is a reduction in the reactivity of the N anions caused by the stronger electron-acceptor character of the naphthalene, and especially the pyrimidine. rings. It appears that the greater the electron density at the exocyclic nitrogen atom, the more readily does the oxidation of the N anions take place. With 2-amino-4, 5-diphenylimidazole, even the monoanion, on oxidation under the standard conditions, gives about 40% of of the azo compound. However, generation of N polyanions will become increasingly difficult with increasing electron density in the imidazole ring. It is probably as a result of this that the action of sodium or potassium amide in liquid ammonia on 2-aminoimidazole gives hardly any oxidation products (starting material being recovered quantitatively). In similar experiments, both 2-aminoimidazole-4, 5-dicarboxylic acid (XIa) and its di-(N.N'-n-butyl) amide (XIb) were also recovered unchanged, probably owing to the more ready ionization of the carboxyl and amide groups as compared with the amino group. In the case of the dimethyl ester of this acid (XIC). generation of N polyanions becomes possible, and the formation of azo-compounds has been observed.

EXPERIMENTAL

Reaction of 1-Benzyl-2-aminobenzimidazole (I) with Sodium. A. To liquid ammonia (~ 50 ml) was added 2.23 g (0.01 mole) of I, and 0.5 g (0.02 g-atom) of sodium. A stable blue color appeared. The rest of the experiment was carried out under standard conditions, as described below: the reaction mixture was stirred for 1 h at -70° to -80°, then for a further h at -33°. The ammonia was allowed to evaporate, and the residue was kept in air to oxidize it for 15-20 h. An intense orange coloration appeared during the evaporation of the ammonia, and this deepened on standing. To the dry, red residue was added 50 ml of water, and I (0.4-0.56 g; 18-25%) was filtered off. On shaking the filtrate with 10-15 ml of ethyl acetate. there was obtained 32% (~0.4 g) of 2, 2'-azobenzimidazole (III) [4]; acidification of the solution with conc. HCl or acetic acid gave 1-2% of 2-nitrobenzimidazole (IV) [4]. Extraction of the neutral solution with ethyl acetate afforded 2-aminobenzimidazole (II) after removal of the solvent, washing the residue with chloroform, and drying (yield 0.53-0.65 g; 40-50%), mp 225.5-226.5° [11] (from water, with activated charcoal). If, in this experiment, the evaporation of the ammonia is carried out in a stream of ammonia or nitrogen, and the residue is treated immediately with water, the yield of II rises to 80%, and no III or IV are formed. The same results were obtained if ammonium chloride (0.02 mole) was added on completion of the debenzylation.

<u>B.</u> To a suspension of 4.46 g (0.02 mole) of I in 50-70 ml of liquid ammonia was added in small pieces 1.4 g (0.06 g-atom) of sodium. A stable blue coloration was produced after about 1 g (0.04 g-atom) of sodium had been added. The reaction was carried out under the standard conditions. To the dry residue was added 30 ml of water, filtered, and water added to 50 ml in a calibrated flask. One ml of this solution was taken for spectrophotometric analysis (SF-4a spectrophotometer). The analysis was carried out in all the experiments in which simultaneous formation of III and IV was observed. The results were generally in agreement with those obtained by preparative separation. Ethyl acetate extracted from the filtrate 1.6 g (61%) of III, the treatment with conc. HCl gave 1.11 g (34%) of IV.

<u>7-Benzyl-8-aminotheophyllin</u>. A solution of 2 g (0.04 mole) of sodium hydroxide, 3.9 g (0.02 mole) of 8-aminotheophyllin [12], and 10 g (0.04 mole) of Leucotrone "0" in 30 ml of water were boiled for 1 h, and the dimethylaniline was removed in a current of steam. The hot solution was separated from the oil, which was triturated with acetone to give 0.7 g of colorless solid. The solution on cooling gave a further 1.1 g of 7-benzyl-8-aminotheophyllin, overall yield 31.5%, mp 235-236' (from alcohol). Found: C 58.9; H 5.5%; $C_{14}H_{15}N_5O_2$. Calculated: C 58.9; H 5.3%.

<u>Reactions of 2-Aminobenzimidazole (II)</u>. <u>A</u>. 0.67 g (0.005 mole) of II was reacted with 0.35 g (0.015 g-atom) of sodium in liquid ammonia at -70 to -80° . After 45-60 min, the blue color disappeared. The ammonia was evaporated, and the residue was kept in air for 15-20 h, and worked up by the method described above to give 0.12 g (18.2%) of III and 0.08 g (10%) of IV. Extraction of the neutral filtrate with ethyl acetate yielded 0.4 g (~60%) of II. Under similar conditions, using 2 g-atom of sodium, only 2% of III and 1% of IV were formed.

<u>B.</u> A solution of potassium amide was obtained from liquid ammonia (~50 ml) and 0.78 g (0.02 g-atom) of potassium in the presence of ferric nitrate and platinum black, and to this solution was added rapidly 1.33 g (0.01 mole) of II. The conditions were standard. There was obtained 0.48 g (36%) of III and 0.17 g (10%) of IV. The residual solution gave 0.68 g (51%) of II.

<u>C.</u> To a suspension of 6.24 g (0.03 mole) of 1-benzylbenzimidazole and 1.33 g (0.01 mole) of II in 50 ml of liquid ammonia was added 1.61 g (0.07 g-atom) of sodium. The reaction was carried out under the standard conditions, giving 0.68 g (52%) of III and 0.72 g (44.2%) of IV. These products were freed from accompanying benzimidazole by washing with 5% hydrochloric acid.

<u>2-Aminoimidazole</u>. This was obtained by the sodium hydrosulfite reduction of 2-p-sulfobenzeneazoimidazole [14]. It was characterized as the picrate, mp 236-237° [15].

Dimethyl 2-Aminoimidazole-4, 5-dicarboxylate (Xc). To 30 ml of methanol which had been saturated with dry hydrogen chloride was added at -10 to 0° 8.55 g (0.05 mole) of 2-aminoimidazole-4, 5-dicarboxylic acid [15], and the suspension was boiled with stirring for 1 h. The mixture was cooled, treated with a further 30 ml of saturated methanolic hydrogen chloride, and boiled for a further hour. This procedure was repeated once more, and the resulting transparent solution was neutralized with sodium carbonate solution On cooling, 6.4 g (64.3%) of Xc was filtered off, colorless needles, mp 185° (decomp., from methanol). Found: C 42.0; H 4.7; N 21.0%. C₇H₉N₃O₄. Calculated: C 42.2; H 4.6; N 21.1%.

 $\frac{2-\text{Aminoimidazole-4, 5-dicarboxylic Acid Di-(N,N'-butyl)amide}}{\text{of Xc and 4.38 g (0.06 mole) of n-butylamine was heated in a glycerine bath at 150° for 1 h, whereupon the reaction mixture solidified. The mass was triturated with water to give a quantitative yield of Xb, colorless leaflets, mp 166-167° (from ethanol). Found: C 56.0; H 8.3; N 24.4%. C₁₃H₂₃N₅O₂. Calculated: C 55.5: H 8.2; N 24.9%.$

Compound	Мр, ℃	Molecular formula	Found, %			Calculated,		
			с	н	N	с	н	N
2,2'-Azo-(5-methylben- zimidazole) *	277 (ethyl acetate)	C ₁₆ H ₁₄ N ₆ ·	64,5	5,2	27,8	64,2	5,1	28,1
2,2'-Azo-(5-methoxybenzi- midazole	251,5 (dioxane)	$C_{16}H_{14}N_6O$	59,4	4,3	26,0	59,6	4,4	26,1
2,2'-Azo-(5,6-dimethyl- benzimidazole)	276277 (aqueous	$C_{18}H_{18}N_6$	67,9	õ ,9	26,1	67,9	5,7	26,4
2,2'-Azonaphth[1,2]- imidazole	³⁴⁰ (dimethylforma-	$C_{22}H_{14}N_6$	72,6	4,1		72,9	3,9	
2,2'-Azo-(4,5-diphenyl- imidazole)	³⁰⁵¹³ (pyridine)	C ₃₀ H ₂₂ N ₆	-		-	-	-	
2,2'-Azo(4,5-dimethoxy- carbonylimidazole	199 (water)	$C_{14}H_{14}N_6O_8$	42,7	3,7	21,8	42,6	3,6	21,3
8,8°-Azotheophyllin	320 (precipitated	$C_{14}H_{14}N_{10}O_4$	43,5	3,9		43,95	3,7	
1	from alkali		1	ļ]		1	

TABLE 4. Azoimidazoles

* λ_{max} (in 0.1 N NaOH) 475 nm, log ε 4.49.

TABLE 5. 2-Nitroimidazoles

Compound	Мр, °С (decomp.)	Method of purification	Molecular formula	Found, %			Calculated,%			
				с	н	N	С	н	N	
2-Nitro-5- methylbenzimidazole * 2-Nitro-5- methoxybenzimidazole 2-Nitro-5; 6-dimethyl- benzimidazole	235-36 254 213-14	Distill. (175°, 3 mm) Distill. (180– 185°, 5 mm) Distill. (160– 165°. 1 mm)	$C_8H_7N_3O_2$ $C_8H_7N_3O_3$ $C_9H_9N_3O_2$	54,3 50,0 56,6	4,0 3,8 4,7	23,3 21,2 22,0	54,2 49,7 56,5	4,0 3,7 4,8	23,7 21,8 22,0	
2-Nitronaphth[1, 2] imidazole †	170	ammoniacal solution	C11H7N3O2	61,4	3,7		61,9	3,3		

* λ_{max} : 363 nm, log ε 4.04 (in methanol); 380 nm, log ε 4.07 (in 0.1

N NaOH); $\nu_{\rm NO_2}$ 1345; 1560 cm $^{-1}$.

† λ_{max} : 400 nm, log ε 3.56 (in methanol).

<u>Reaction of 2-Aminoimidazoles with Potassium Amide (3 moles) in Liquid Ammonia.</u> The reactions were carried out under the standard conditions. A) From 2-amino-4, 5-diphenylimidazole [16], there was obtained 93% of the azo compound [13]. B) Dimethyl 1-aminoimidazole-4, 5-dicarboxylate (XIc) afforded 58% of the azo compound (see Table 4). From 8-aminotheophyllin there was obtained only 7.45 of the azo compound (Table 4); other unidentified products were isolated from the solution.

Reaction of 2-Azidobenzimidazole (Xa) [17] with Sodium. 0.8 g (0.005 mole) of Xa was reacted with 0.35 g (0.015 g-atom) of sodium in 50 ml of liquid ammonia under the standard conditions. There was obtained 0.04 g (6.1%) of III and 0.15 g (18.3%) of IV. Extraction of the solution with ethyl acetate afforded 0.28 g of a mixture of II and Xa.

Reaction of 1-Benzyl-2-Azidobenzimidazole (Xc) with Sodium. 1.25 g (0.005 mole) of Xc was reacted with 0.46 g (0.02 g-atom) of sodium in 50 ml of liquid ammonia, under the standard conditions. After adding water, 0.03 g of I was filtered off (part remained in solution). There were also isolated 0.036 g (5.54%) of III and 0.135 g (16.7%) of IV.

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