[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY]

The Reaction of Amines with Nitro and Nitroso Derivatives of Cyclic Ureas and Cyclic Guanidines

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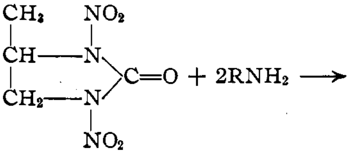
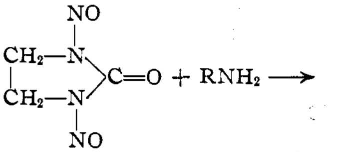
It has been shown[2] that dinitro cyclic ureas dissolve in ten per cent. sodium hydroxide solution and on acidification in the cold evolve carbon dioxide while the corresponding linear dinitramines are precipitated. If primary amines are used instead of sodium hydroxide solution then *sym.* disubstituted ureas are obtained along with the linear dinitramines.



$NO_2NH—CH_2—CH(CH_3)—NH—NO_2 + RNH—CO—NHR$

The following substituted ureas were prepared by this reaction, the yields are given in parentheses: 1,3-dicyclohexyl- (88.5), m. p. 227–228°; 1,3-dibenzyl- (98), m. p. 169–170°[3]; 1,3-diphenyl- (97.3), m. p. 235–236°[3,4]; 1,3-di-*o*-tolyl- (88.5), m. p. 245–246°[5]; 1,3-di-*m*-tolyl- (94.8), m. p. 216.5–217.8°[6]; 1,3-di-*m*-anisyl- (85.0), m. p. 170.8–171.9°; 1,3-di-*m*-phenetyl- (95.5), m. p. 156.2–157.5°; and 1,3-di-*p*-phenetylurea (95.4), m. p. 229–230°.[7-9]

sym-Disubstituted ureas were obtained also by treating 1,3-dinitroso-2-imidazolidone with amines.



RNH—CO—NHR + other products

Several of the 1,3-disubstituted ureas described above were prepared by this method along with 1,3-di-*p*-tolylurea, m. p. 261–262°,[4,5,10] and 1,3-di-*p*-anisylurea, m. p. 235–236°.[4,10]

Previously, in the studies[11,12] of the effect of primary amines on 1-alkyl-1-nitroso-3-nitroguanidines only the main reaction products were isolated. Therefore it appeared desirable to investigate the effect of primary amines on a cyclic nitrosamine derivative, *e. g.*, 1-nitroso-2-nitramino-2-imidazoline (I). This latter compound was expected to undergo ring opening with a retention of the alkyl residue which is eliminated with the linear 1-alkyl-1-nitroso-3-nitroguanidines. This was found to be the case and two new series of compounds were obtained.

The treatment of 1-nitroso-2-nitramino-2-imidazoline (I) with aromatic amines in aqueous ethanol at 30° gave 1-substituted-2-nitramino-2-imidazolines (II) and 1,2-disubstituted-3-nitroguanidines (III). Both 1-substituted-2-nitramino-2-imidazolines and 1,2-disubstituted-3-nitroguanidines on refluxing with the corresponding aromatic amines were recovered unchanged. Thus it must be considered that either one of these types of compounds is not an intermediate in the formation of the other under the conditions of the reaction.

The 1-substituted-2-nitramino-2-imidazolines (II) were converted into the corresponding 1-substituted-2-imidazolidones (IV) in good yield by hydrolysis in basic solutions. These imidazolidones (IV) also were prepared by treating oxazolidone-2 (V) with amines[13] as additional proof of the identity of these compounds. Oxazolidone-2 (V) was prepared by the method of Homeyer[14] from ethanolamine and ethyl carbonate.

All of the linear 1,2-disubstituted-3-nitroguanidines (III) were colored. Thus the double bonded nitrogen was assigned the position in conjugation with the aromatic substituent. In accordance with this assumption, the ureas (VI) produced by the alkaline hydrolysis of the 1,2-disubstituted-3-nitroguanidines were colorless. Alkaline hydrolysis of these latter compounds also produced a small amount of the corresponding 1-substituted-2-imidazolidones (IV). Since the 1,3-disubstituted ureas (VI) were found to be stable under these conditions, the small amounts of 1-substituted-2-imidazolidones formed must be derived from the 1,2-disubstituted-3-nitroguanidines by elimination of both an aromatic amino group and the nitramino group.

The results described above illustrate that 1-nitroso-2-nitramino-2-imidazoline in the presence of aromatic amines enters into both a substitution and an alkylation reaction. These two types of reactions would be expected to occur also when 1-substituted-1-nitroso-3-nitroguanidines are treated with primary amines.

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(13) S. Gabriel and G. Eschenbach, *Ber.*, **30**, 2495 (1897).

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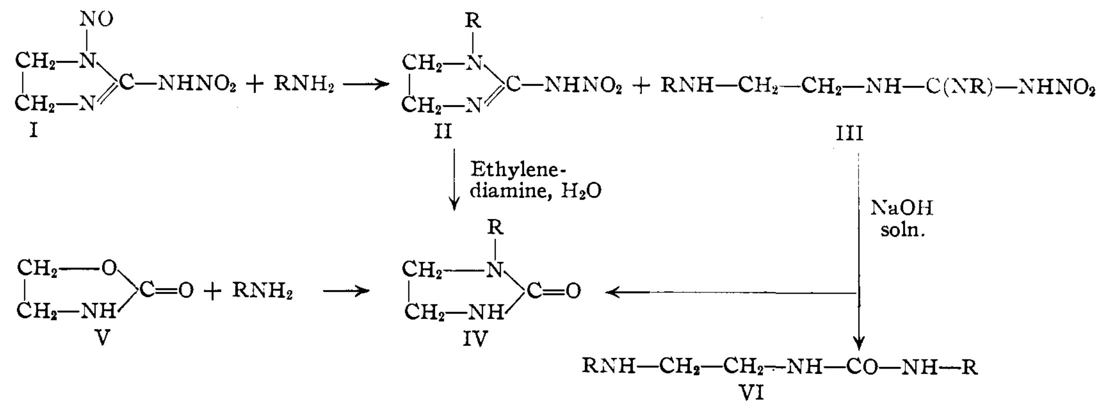

R = phenyl, *p*-tolyl, *p*-anisyl or *p*-phenetyl.

The compounds (represented by formulas II, III, IV and VI) prepared during the course of this work are described in Table I.

Table I

Compounds Derived from 1-Nitroso-2-nitramino-2-imidazoline

Compound	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1-Phenyl-2-nitramino-2-imidazoline	165.5–167	$C_9H_{10}N_4O_2$	52.4	52.6	4.85	4.93	27.2	27.0
1-*p*-Anisyl-2-nitramino-2-imidazoline	165.7–167	$C_{10}H_{12}N_4O_3$	50.8	51.0	5.08	5.08	23.7	23.6
1-*p*-Phenetyl-2-nitramino-2-imidazoline	166.4–167.5	$C_{11}H_{14}N_4O_3$	52.8	52.7	5.60	5.63	22.4	22.5
1-Phenyl-2-imidazolidone[13]	162–163	$C_9H_{10}N_2O$	66.6	66.8	6.18	6.43	17.2	17.1
1-*p*-Tolyl-2-imidazolidone	196.3–197.5	$C_{10}H_{12}N_2O$	68.2	68.0	6.82	6.71	15.9	15.7
1-*p*-Anisyl-2-imidazolidone	211–212	$C_{10}H_{12}N_2O_2$	62.5	62.4	6.25	6.23	14.5	14.8
1-*p*-Phenetyl-2-imidazolidone	211–212	$C_{11}H_{14}N_2O_2$	64.1	64.1	6.80	6.82	13.6	13.4
1-(2-Phenylaminoethyl)-2-phenyl-3-nitroguanidine	144.5–145.6, dec.	$C_{15}H_{17}N_5O_2$	60.2	60.2	5.68	5.67	23.4	23.6
1-(2-*p*-Tolylaminoethyl)-2-*p*-tolyl-3-nitroguanidine	162.5–163.5, dec.	$C_{17}H_{21}N_5O_2$	62.4	62.7	6.43	6.23	21.4	21.1
1-(2-*p*-Anisylaminoethyl)-2-*p*-anisyl-3-nitroguanidine	180–181.3, dec.	$C_{17}H_{21}N_5O_4$	56.8	56.9	5.85	5.82	19.5	19.7
1-(2-*p*-Phenetylaminoethyl)-2-*p*-phenetyl-3-nitroguanidine	170–171.4, dec.	$C_{19}H_{25}N_5O_4$	58.8	58.8	6.48	6.29	18.1	18.0
1-(2-Phenylaminoethyl)-3-phenylurea	105–106	$C_{16}H_{17}N_3O$	70.6	70.5	6.67	6.50	16.4	16.5
1-(2-*p*-Tolylaminoethyl)-3-*p*-tolylurea	146.3–147.3	$C_{17}H_{21}N_{13}O$	72.1	72.3	7.43	7.60	14.8	15.0
1-(2-*p*-Anisylaminoethyl)-3-*p*-anisylurea	136.2–137	$C_{17}H_{21}N_3O_3$	64.7	64.9	6.66	6.76	13.3	13.5
1-(2-*p*-Phenetylaminoethyl)-3-*p*-phenetylurea	142.6–143.4	$C_{19}H_{25}N_3O_3$	66.5	66.6	7.29	7.28	12.2	12.4

Experimental[15]

1,3-Dinitro-4-methyl-2-imidazolidone.—The 1,3-dinitro-4-methyl-2-imidazolidone (m.p. 101.8–102.9°) was prepared in 80% yield by the method of McKay and Manchester.[2] Final purification was effected by crystallization from toluene (2 cc./g.).

1,3-Dinitroso-2-imidazolidone.—Twenty grams (0.24 mole) of ethylene urea were dissolved in 500 cc. of 20% nitric acid solution in a 2 l. beaker. This solution was cooled to 15° in an ice–water-bath and maintained at 15–17° while 69 g. (1.0 mole) of sodium nitrite in 200 cc. of water was added under the surface of the reaction mixture during a period of forty-five minutes. Sodium chloride was then added to the ice–water bath and the reaction mixture mechanically stirred for a further period of fifteen minutes at a temperature below 0°. The product was filtered off and washed with water until acid free. The product was then washed with 95% ethanol (4 × 25 cc.) and toluene (2 × 25 cc.). If the toluene washing was omitted, it was found that occasionally the product decomposed spontaneously. The yield of yellow crystalline product (m.p. 143.4–145.2° with decomposition) was 27.9 g. (83.0%).

Anal. Calcd. for $C_3H_4N_4O_3$: C, 25:0; H, 2.77; N, 38.9. Found: C, 25.1; H, 2.90; N, 38.5.

1-Nitroso-2-nitramino-2-imidazoline.—One-half mole (65 g.) of 2-nitramino-2-imidazoline was dissolved in 105 cc. of 70% nitric acid. The mechanically stirred solution was held at 15–20° by means of an ice–water-bath while 104 g. (1.5 mole) of sodium nitrite in 160 cc. of water was added beneath the surface of the reaction mixture. Forty minutes were required for the addition of the sodium nitrite solution after which the reaction mixture was stirred for a further period of thirty minutes. The crystalline suspension was filtered and the crystals were washed with cold water (6 × 100 cc.) and ethanol (2 × 50 cc.) and allowed to air-dry. The crude product (69.9 g., 88%) melted at 136–140° with decomposition. After one crystallization from 95% ethanol (21.5 cc./g.) to which a small amount of glacial acetic acid had been added to decrease the tendency to denitrosate, the product melted at 141–142° with decomposition.

Anal. Calcd. for $C_3H_5N_5O_3$: C, 22.6; H, 3.14; N, 44.0. Found: C, 22.6; H, 3.12; N, 43.8.

Preparation of 1,3-Disubstituted Ureas: Method A.—To a solution of 0.0315 mole of amine in 20 cc. of 95% ethanol 2.0 g. (0.010 mole) of 1,3-dinitro-4-methyl-2-imidazolidone was added *en masse*. The solid dissolved

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(15) All melting points are uncorrected.

and within five minutes crystals formed. After the reaction mixture had remained at room temperature for two hours, it was filtered. In general a second crop of crystals was obtained by diluting the ethanolic filtrate with 100 cc. of water. Three new disubstituted ureas were prepared by this method along with several previously described ones. The analytical values of the hitherto undescribed ureas are given in Table II.

TABLE II

Sym. DISUBSTITUTED UREAS

Substituent	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
Cyclohexyl-	$C_{13}H_{24}N_2O$	69.7	69.7	10.7	10.58	12.5	12.8
m-Anisyl-	$C_{15}H_{16}N_2O_3$	66.1	66.2	5.90	5.94	10.3	10.5
m-Phenetyl-	$C_{17}H_{20}N_2O_3$	68.0	68.2	6.66	6.72	9.3	9.4

On concentrating the aqueous ethanolic filtrate from the second crop *in vacuo* to approximately 15 cc., a solid separated. The mixture was heated to reflux to dissolve the solid and the solution was transferred to an erlenmeyer flask. When this solution had cooled to 0° crystals were deposited. These crystals (m.p. 112.0–113.8°) were identified by a mixed melting point determination with an authentic sample of 1,2-dinitraminopropane.[2] The yields of 1,2-dinitraminopropane varied from 66.5–88.3%. When benzylamine and cyclohexylamine were employed in the above reaction, these amines formed salts with the 1,2-dinitraminopropane. Thus the reaction mixture had to be acidified before the desired products could be recovered.

Method B.—1,3-Dibenzylurea and 1,3-dicyclohexylurea were prepared by adding 5 mole equivalents of benzylamine and cyclohexylamine, respectively, to a suspension of 2 g. (0.013 mole) of 1,3-dinitroso-2-imidazolidone in 30 cc. of absolute ether. The temperature was maintained at 5–7° during the addition of the amine which required about forty-five minutes. The reaction mixture was allowed to stand overnight after which most of the ether had evaporated. The crystals were filtered off and washed with water. 1,3-Dibenzylurea was purified by one crystallization from glacial acetic acid (2 cc./g.) while 1,3-dicyclohexylurea was crystallized from ethanol (20 cc./g.).

Aniline, *o*-, *m*-, and *p*-toludine and *p*-anisidine would not react noticeably with 1,3-dinitroso-2-imidazolidone in absolute ether so a more polar solvent (95% ethanol) was used. The yields varied from 15–90.5% with the more basic amines giving the higher yields.

1-(2-Arylaminoethyl)-2-aryl-3-nitroguanidines and 1-Aryl-2-nitramino-2-imidazolines.—The procedure for the preparation of these compounds is very similar. Therefore only the preparation of 1-(2-phenylaminoethyl)-2-phenyl-3-nitroguanidine and 1-phenyl-2-nitramino-2-imidazoline is given in detail.

1-Nitroso-2-nitramino-2-imidazoline (15 g., 0.094 mole) and 52.7 g. (0.566 mole) of aniline were added to 105 cc. of 50% aqueous ethanol. An evolution of gas commenced almost immediately and the temperature rose to 30° where it was maintained by intermittent cooling. The evolution of gas continued for about fifty minutes and a reddish colored oil slowly separated. After standing for five hours part of the oil crystallized. The lemon yellow crystalline material was removed by filtration and washed with ether until free from excess amine. This crude product (8.4 g., 29.8%) gave pure 1-(2-phenylaminoethyl)-2-phenyl-3-nitroguanidine after one crystallization from 95% ethanol (18 cc./g.).

The filtrate, after acidification and cooling, gave long needle-like crystals of 1-phenyl-2-nitramino-2-imidazoline. A second crop of these crystals was obtained on dilution of the filtrate with several volumes of water. The two crops were combined and crystallized from 95% ethanol (30 cc./g.) to give 4.7 g. (24.6%) of product. Both compounds gave a positive primary nitramine test with α-naphthylamine in glacial acetic acid.[16]

1-(2-*p*-Tolylaminoethyl)-2-*p*-tolyl-3-nitroguanidine, 1-(2-*p*-anisylaminoethyl)-2-*p*-anisyl-3-nitroguanidine, 1-*p*-anisyl-2-nitramino-2-imidazoline, 1-(2-*p*-phenetylaminoethyl)-2-*p*-phenetyl-3-nitroguanidine and 1-*p*-phenetyl-2-nitramino-2-imidazoline were prepared by the above procedure in 32.8, 33.1, 14.4, 31.6 and 24.6% yields, respectively.

No crystalline 1-*p*-tolyl-2-nitramino-2-imidazoline was isolated from the reaction of *p*-toludine with the cyclic nitrosamine compound. However its presence was verified by hydrolyzing the gummy mass obtained in an aqueous ethylenediamine solution. The amount of 1-*p*-tolyl-2-imidazolidone obtained showed that the original gummy mass contained approximately 4.46 g. (21.5%) of 1-*p*-tolyl-2-nitramino-2-imidazoline.

1-(2-Arylaminoethyl)-3-arylureas.—1-(2-Phenylaminoethyl)-2-phenyl-, 1-(2-*p*-tolylaminoethyl)-2-*p*-tolyl-, 1-(2-*p*-anisylaminoethyl)-2-*p*-anisyl-, and 1-(2-*p*-phenetylaminoethyl)-2-*p*-phenetyl-3-nitroguanidine on hydrolysis in boiling 10% sodium hydroxide for a period of twelve hours gave 1-(2-phenylaminoethyl)-3-phenylurea (73.8), 1-*p*-tolyl-2-imidazolidone (8) and 1-(2-*p*-tolylaminoethyl)-3-tolylurea (77), 1-*p*-anisyl-2-imidazolidone (15.4) and 1-(2-*p*-anisylaminoethyl)-3-*p*-anisylurea (66), and 1-*p*-phenetyl-2-imidazolidone (6.3) and 1-(2-*p*-phenetylaminoethyl)-3-*p*-phenetylurea (75.5), respectively. The yields are given in brackets.

During the hydrolysis of 1-(2-*p*-tolylaminoethyl)-2-*p*-tolyl-3-nitroguanidine a white crystalline solid was deposited on the inside of the reflux condenser. This was recovered and identified as *p*-toludine by a mixed melting point determination.

1-Substituted-2-imidazolidones.—Two grams (0.009 mole) of 1-phenyl-2-nitramino-2-imidazoline were refluxed in a solution of 5 cc. of ethylenediamine in 120 cc. of water for one hour. On cooling a 89.9% yield of 1-phenyl-2-imidazolidone was obtained.

In a similar manner 1-*p*-anisyl- and 1-*p*-phenetyl-2-imidazolidone were prepared in 81.8 and 95.8% yield, respectively. The 1-substituted-2-imidazolidones were all identified by mixed melting point determinations with samples prepared from oxazolidone-2 and by analyses.

Preparation of 2-Substituted-2-imidazolidones from Oxazolidone-2.—1-Phenyl-, 1-*p*-anisyl-, 1-*p*-phenetyl- and 1-*p*-tolyl-2-imidazolidone were prepared by the method of Gabriel and Eschenbach[13] in 10.7, 16.3, 12.5 and 10.1% yield, respectively.

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Summary

sym-Disubstituted ureas have been prepared by the reaction of amines with 1,3-dinitro-4-methyl-2-imidazolidone and 1,3-dinitroso-2-imidazolidone.

1-(2-Arylaminoethyl)-2-aryl-3-nitroguanidines and 1-aryl-2-nitramino-2-imidazolines have been isolated from the products obtained when 1-nitroso-2-nitramino-2-imidazoline is treated with aromatic amines.

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