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Studies in the Pyrazole Series. III. Substituted Guanidines[1,2]

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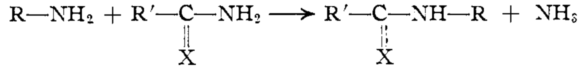
RECEIVED MARCH 17, 1953

The reaction of a number of hydrazines and amines with 3,5-dimethyl-1-guanylpyrazole nitrate gives the corresponding guanidines and aminoguanidines. The mode of aminolysis of this type of pyrazole is exceptional amongst the amidines and guanidines.

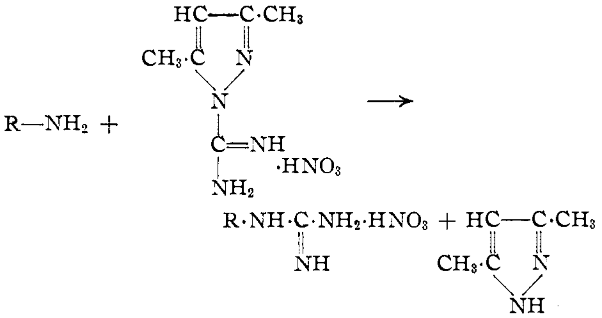
The reaction of an amine[3] with an amidine[4] or a guanidine[5] occurs *via* an addition–elimination mechanism[6] (or, possibly, by an S_N2 type displacement), the amine or hydrazine fragment is incorporated into the molecule and a relatively simple molecule such as ammonia is evolved.

The reactions of amines with related compounds such as semicarbazones,[7] thiosemicarbazones,[8] amides[9] and sulphonamides[10] also follow this pattern. The process may be written in general as



$$R{-}NH_2 + R'{-}\underset{\underset{X}{\|}}{C}{-}NH_2 \longrightarrow R'{-}\underset{\underset{X}{\|}}{C}{-}NH{-}R + NH_3$$

With 3,5-dimethyl-1-guanylpyrazole nitrate (A), however, reaction is abnormal, thus



e.g., with hydrazine hydrate (1 mole), A affords aminoguanidine nitrate and 3,5-dimethylpyrazole. The reactions of the other amines and hydrazines described below confirm this abnormality of reaction, all giving the corresponding substituted guanidines and 3,5-dimethylpyrazole.

These results could be due to a different mode of scission of the intermediary adduct, or of the S_N2 transition complex, or due to other factors specific to the pyrazoles amongst these compounds, such as ring opening, etc. However, if this latter mechanism had been operative, in a manner analogous to the comparable isoxazole ring,[11] the reaction products from phenylhydrazine and A would have been 3,5-dimethyl-1-phenylpyrazole and aminoguanidine nitrate. The isolated products are a mixture of 1-anilinoguanidine and 1-phenyl-1-aminoguanidine nitrates and 3,5-dimethylpyrazole. Thus the abnormal mode of aminolysis adopted by A must be[12] due to an abnormal scission direction of the intermediary adduct (or complex), this resulting from symmetry considerations.

No simple correlation between yield and *pK* was established but the experiments provided easy routes to a number of valuable synthetical intermediates.

Experimental[13,14]

The 3,5-dimethyl-1-guanylpyrazole nitrate used in these experiments was prepared by the method of Scott and Reilly.[15]

The following reactions with aniline illustrate the two general methods employed. Those of hydrazine hydrate and phenylhydrazine further illustrate method A.

(I) **Reaction with Aniline. Method A.**—Two grams (0.01 mole) of 3,5-dimethyl-1-guanylpyrazole nitrate was dissolved in 10 cc. of aniline (0.1 mole) and the solution refluxed for 2 hours. The solution darkens on heating, finally becoming black. On addition of ether to the reflux solution, a violet oil separated which on standing solidified to give 1.55 g. (79%) of a violet solid of m.p. 112–116°, which on recrystallization from alcohol melted at 125–126°. This compound was converted to the picrate, m.p. 225–226° and analyzed as such. The result showed that this was phenylguanidine picrate.

Anal. Calcd. for $C_{13}H_{12}N_6O_7$: C, 42.8; H, 3.3; N, 23.1. Found: C, 42.9; H, 3.6; N, 23.6.

The ethereal aniline solution was evaporated *in vacuo* when 0.65 g. (68%) of 3,5-dimethylpyrazole was isolated.

Method B.—Two grams (0.01 mole) of 3,5-dimethyl-1-guanylpyrazole nitrate was dissolved in 40 cc. of water and 5 cc. of aniline (0.05 mole) was added. The solution was refluxed for 24 hours, allowed to cool and extracted with 10-cc. portions of ether and the ether solution on evaporation gave 0.87 g. (91%) of 3,5-dimethylpyrazole, identified by mixed melting point with an authentic sample. The aqueous solution was evaporated to dryness *in vacuo* to give 1.8 g. (96%) of a solid, m.p. 125–126°. This solid was again identified in the form of its picrate as phenylguanidine picrate, m.p. 225–226°.

(II) **Reaction with Hydrazine Hydrate.**—To 2 g. (0.01 mole) of 3,5-dimethyl-1-guanylpyrazole nitrate dissolved

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(1) For Part II of this series see F. L. Scott, M. T. Kennedy and J. Reilly, THIS JOURNAL, **75**, 1294 (1953).

(2) For a preliminary communication see F. L. Scott, M. T. Kennedy and J. Reilly, *Nature*, **169**, 72 (1952).

(3) Hydrazines behave similarly.

(4) R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 351 (1944).

(5) "Nitrogen Chemicals Digest—IV. The Chemistry of Guanidine," American Cyanamid Co., New York 20, N. Y., 1950, p. 17, *et seq.*

(6) A. F. McKay, *Chem. Revs.*, **51**, 301 (1952).

(7) F. J. Wilson and co-workers, *J. Chem. Soc.*, **125**, 2145 (1924); *ibid.*, 2367 (1926); 2114 (1927); A. B. Crawford and J. Primrose, *J. Roy. Tech. Coll.* (Glasgow), **4**, 28 (1937); A. B. Crawford, *ibid.*, **4**, 607 (1940); I. Matsurevich, *Univ. etat. Kiev. Bull. Sci. Rec. chim.*, No. 4, 21 (1939); *C. A.*, **35**, 1385^5 (1941).

(8) W. Baird, R. Burns and F. J. Wilson, *J. Chem. Soc.*, 2527 (1927).

(9) A. Galat and G. Elion, THIS JOURNAL, **65**, 1566 (1943); M. J. Schlatter, *ibid.*, **64**, 2722 (1942).

(10) I. M. Kogan and V. M. Dzimomko, *Zhur. obschei Khim.*, **21**, 1891 (1952); *C. A.*, **46**, 6608f (1952).

(11) See C. Musante, *Gazz. chim. ital.*, **72**, 537 (1942), for a summarizing paper. His observation, *viz.*, that hydrazine hydrate and phenylhydrazine afford the corresponding nitropyrazoles with 4-nitro-3,5-dimethylisoxazole is of limited application. Under the reaction conditions described or in more strongly basic solutions, *e.g.* aminoguanidine, nitroaminoguanidine or *p*-nitrophenylhydrazine do not form nitropyrazoles. For a fuller description of these reactions see F. L. Scott, M. T. Kennedy and J. Reilly (forthcoming publication).

(12) It is possible that the abnormal result is due to preliminary dearrangement to cyanamide and 3,5-dimethylpyrazole. On McKay's (ref. 6) arguments this mechanism was discounted.

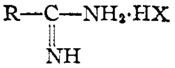
(13) M.p.'s are uncorrected.

(14) Analyses by Drs. Weiler and Strauss, Oxford.

(15) F. L. Scott and J. Reilly, THIS JOURNAL, **74**, 3456 (1952).

TABLE I

SUBSTITUTED GUANIDINES



$R-\underset{\underset{\textstyle NH}{\|}}{C}-NH_2\cdot HX$

Amine (or hydrazine)	R	Formula of product	M.p., °C.	Yield, %	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
Benzhydrazide[a]	$C_6H_5\cdot CO\cdot NH\cdot NH$	$C_{14}H_{13}N_7O_8$[c]	243	66	41.3	41.6	3.2	3.1
Benzylamine[a]	$C_6H_5\cdot CH_2\cdot NH$	$C_8H_{12}N_4O_3$[d]	150–153	63	45.3	45.8	5.7	6.0
Benzylamine	$C_6H_5\cdot CH_2\cdot NH$	$C_{14}H_{14}N_6O_7$[c]	186–189	..	44.4	44.9	3.7	3.9
2-Benzylthiazolylhydrazine[a]	$C_7H_4NS\cdot NH\cdot NH$	$C_{14}H_{12}N_8SO_7$[c]	220	85	38.5	39.0	2.8	2.5
Morpholine[b]	$C_4H_8O\cdot N$	$C_{11}H_{14}N_6O_8$[c]	230	50	36.9	37.4	3.9	3.9
β-Phenylethylamine[a]	$C_6H_5\cdot CH_2\cdot CH_2\cdot NH$	$C_9H_{14}N_4O_3$[d]	135–137	75	47.8	47.6	6.2	5.9
β-Phenylethylamine	$C_6H_5\cdot CH_2\cdot CH_2\cdot NH$	$C_{15}H_{16}N_6O_7$[c]	176	..	45.9	46.2	4.1	4.3
Piperidine[a]	$C_5H_{10}\cdot N$	$C_{12}H_{16}N_6O_7$[c]	244	68	40.4	40.7	4.4	4.1
Pyrrolidine[b]	$C_4H_8\cdot N$	$C_{11}H_{14}N_6O_7$[c]	220	92	38.6	38.7	4.1	3.8
2-Quinolylhydrazine[a]	$C_9H_6N\cdot NH\cdot NH$	$C_{22}H_{17}N_{11}O_{14}$[c,e]	241	67	40.1	39.9	2.5	2.3
p-Toluenesulfonhydrazide[a]	*p*-$CH_3\cdot C_6H_4\cdot SO_2\cdot NH\cdot NH$	$C_{14}H_{15}N_7SO_9$[c]	223	16	36.8	37.6	3.3	3.5

[a] Reacting by method B. [b] Reacting by method A. [c] Analysis and other data correspond to that of picrate. [d] Analysis, etc., is that for nitrate. [e] Substance is a dipicrate.

in 40 cc. of absolute alcohol was added 0.6 cc. (0.01 mole) of hydrazine hydrate and refluxed for 2 hours, when the solution turned pink. The reflux solution on cooling deposited 1.29 g. of a white solid of m.p. 141–144°, which on recrystallization from alcohol melted at 145°. This compound was identified as aminoguanidine nitrate (yield 100%) by mixed m.p. determination with authentic samples, and by analysis, and by means of its benzaldehyde hydrazone, m.p. 156–158°.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.6; H, 4.8; N, 31.1. Found: C, 42.0; H, 4.7; N, 31.8.

The filtrate was evaporated at room temperature when 0.95 g. (90%) of a white compound was obtained, m.p. 104–106°. This compound was identified as 3,5-dimethylpyrazole by mixed m.p. with an authentic sample.

A similar experiment was performed using three molecular quantities of hydrazine hydrate to 1 of guanylpyrazole. The solution again turned pink and deposited 1.14 g. (69%) of a white solid of m.p. 210–212° on cooling. This compound was identified as triaminoguanidine nitrate. *Anal.* Calcd. for $CH_{10}N_7O_3$: N, 58.3. Found: N, 58.2, 58.11. 0.65 g. (68%) of 3,5-dimethylpyrazole was isolated from the alcoholic filtrate.

(III) Reaction with Phenylhydrazine.—Three grams of 3,5-dimethyl-1-guanylpyrazole nitrate was dissolved in 15 cc. (0.14 mole) of phenylhydrazine and the solution was refluxed for 2.5 hours, when it became almost black. On adding ether to the refluxed solution, 3 g. of a pink solid separated, m.p. 147–152°. The ethereal solution on evaporation at room temperature yielded 1.25 g. (85%) of 3,5-dimethylpyrazole, identified by a mixed m.p. with an authentic sample. The pink solid on repeated recrystallization yielded a compound of m.p. 178° which was identified, on analysis, as 1-phenylaminoguanidine nitrate.

Anal. Calcd. for $C_7H_{11}N_5O_3$: C, 39.4; H, 5.1; N, 32.9. Found: C, 39.9; H, 5.1; N, 33.0.

When a quantity of the original pink solid, in ethanol, was treated with picric acid, a mixture of two picrates was precipitated, one yellow and one red. These were separated by their different solubilities in absolute ethanol. Picrate I melted at 193° and was identified as the 1-phenylaminoguanidine salt by analysis and by mixed m.p. with an authentic sample.[16]

Anal. Calcd. for $C_{13}H_{13}N_7O_7$: C, 41.2; H, 3.4; N, 25.8. Found: C, 41.5; H, 3.5; N, 25.8.

Picrate II melted at 178° and was identified as the 1-phenyl-1-aminoguanidine salt by analysis and by mixed m.p. with an authentic sample.[16]

Anal. Calcd. for $C_{13}H_{13}N_7O_7$: C, 41.2; H, 3.4; N, 25.8. Found: C, 40.4; H, 3.6; N, 25.3.

The two picrates were isolated in approx. 50% proportions, respectively.

The reactions between the dimethylguanylpyrazole nitrate and other amines and hydrazines are summarized in Table I.

3,5-Dimethyl-1-guanylpyrazole nitrate was recovered unchanged from refluxing in aqueous ethanolic solution for 2-hour periods with semicarbazide, thiosemicarbazide, nitroaminoguanidine, maleic hydrazide, phenylhydrazine-*p*-sulfonic acid and methylhydrazine sulfate, respectively. Its reaction with 4-phenylthiosemicarbazide was anomalous and is therefore described more fully.

Three grams of 3,5-dimethyl-1-guanylpyrazole nitrate was dissolved in the minimum quantity of 95% ethanol and to it was added 2.4 g. of 4-phenylthiosemicarbazide, dissolved in the minimum quantity of the same solvent. The solution was refluxed for 2 hours during which time it assumed a yellow color and evolved a small quantity of hydrogen sulfide. To the cooled solution was added ether and 2.4 g. of a white solid of m.p. 174–180° was deposited. By fractional crystallization from aqueous ethanol, white crystals of m.p. 186° were separated. *Anal.* Calcd. for $C_7H_7N_2S$: C, 55.6; H, 4.6; N, 18.6; S, 21.2. Found: C, 55.8; H, 4.4; N, 18.6; S, 21.4.

The other solid, isolated as its picrate, proved to be unchanged 3,5-dimethyl-1-guanylpyrazole.

Anal. Calcd. for $C_{12}H_{13}N_7O_7$: C, 39.2; H, 3.5. Found: C, 39.8; H, 3.6.

A solid of m.p. 186° also was isolated from the reaction of acetylacetone and 4-phenylthiosemicarbazide in aqueous ethanolic solution, and is most probably a rearrangement product of the carbazide, perhaps of the guanyl disulfide type.[17]

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[16] Prepared by the method of G. Pellizzari, *Gazz. chim. ital.*, **26**, II, 179 (1896).

[17] *Cf.* ref. 15 where the isolation of a structurally analogous pyrazolylguanyl disulfide is described.