HETEROCYCLIC NITRO COMPOUNDS

I. Synthesis Of Nitro Derivatives Of 1, 2, 4-Triazole, 1, 3, 4-Thiadiazole, Tetrazole, 1, 3, 4-Oxadiazole, And Pyrazole By The Noncatalytic Replacement Of The Diazo Group By The Nitro Group

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Replacement of the diazo group by the nitro group has given nitro derivatives of 1, 2, 4-triazole, 1, 3, 4-thiadiazole, tetrazole, 1, 3, 4-oxadiazole, and pyrazole. The reaction is a nucleophilic substitution, proceeding by a heterolytic mechanism. A similar reaction does not occur with 2-amino pyridine and 2-amino imidazole, possibly as a result of the low stability of the diazonium form of the corresponding diazo compounds.

Aromatic nitrogenous heterocycles bearing nitro groups attached directly to the heterocyclic nucleus are of potential interest as physiologically active compounds and as intermediates in organic synthesis.

Direct introduction of the nitro group is not possible in all heterocyclic compounds, since the accumulation of nitrogen hetero atoms in the ring deactivates it toward electrophilic substitution.

Attempts to introduce the nitro group directly into the nuclei of 1, 2, 4-triazole, 1, 3, 4-thiadiazole, tetrazole, and 1, 3, 4-oxadiazole by nitration were unsuccessful [1–4]. Until now, the only case known was the nitration of 3-hydroxy-1, 2, 4-triazole [5, 6], but it has been shown recently [6] that the nitration product has the triazolone structure, i. e., the aromatic nature of the ring was destroyed.

Nitro derivatives 1, 3, 4-thiadiazole and 1, 3, 4-oxadiazole with the nitro group in the 2(5)-position have not been synthesized. A communication [7] on the preparation of 2-nitro-5-amino-1, 3, 4-thiadiazole by the nitration of 2-amino-1, 3, 4-thiadiazole has been refuted [8], it having been shown that the product is 2-nitroamino-1, 3, 4-thiadiazole.

The representatives of nitro derivatives of 1,2,4-triazole, tetrazole, and imidazole were obtained by the Sandmeyer reaction, by treatment of the corresponding diazo compounds with sodium nitrite in presence of copper salts [9–13].

Derivatives of pyrazole with the nitro group in the 3-position are extremely difficult to obtain, and have, up to now, been prepared only by indirect methods [14, 15], since nitration of pyrazole affords the 4-nitro derivatives [16].

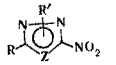
Isolated instances occur in the literature of the synthesis of nitro compounds of the benzene series [17], and of some 8-nitropurines from the corresponding diazonium salts by treatment with sodium nitrite in the absence of copper salts. The mechanism of this reaction apparently differs from that of the Sandmeyer reaction, but the available information does not permit more definite suggestions.

In order to accumulate more experimental data, and to investigate further the synthetic potential of this reaction, in particular for heterocyclic compounds, we undertook a more detailed examination of derivatives of 3(5)-amino-1, 2, 4-triazole, 2-amino-1, 3, 4-thiadiazole, 1- and 2-methyl-5-aminotetrazole, 2-amino-5-methyl-1, 3, 4-oxadiazole, 3-aminopyrazole, 2-aminoimidazole, and 2-aminopyridine.

Addition of the diazonium salts obtained from these amines to sodium nitrite solution results in evolution of nitrogen, and the formation in good yield of the corresponding nitro compounds. In several cases, it was not even necessary to isolate the diazonium salt, but simply to add a solution of the amine in dilute mineral acid to a solution of an excess of sodium nitrite.

The reaction proceeds according to the equation:

Table 1. Heterocyclic Nitro Compounds

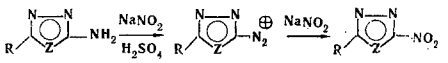


Compound	Z	R	R′	Method of prep.	Reaction time, min	Reaction temp, °C	Extraction solvent	Mp, °C (solvent for recrystallization)	Molecular formula	IR spectrum, cm^{-1}, ν_{NO_2}		Found					Calculated					Yield, %
										Asymmetric valency vibration	Symmetrical valency vibration	C, %	H, %	N, %	S, %	M	C, %	H, %	N, %	S, %	M	
I[1]*	N	H	H	a, b	60	45	Ethyl acetate	210 Methanol	$C_2H_2N_4O_2$	1570	1320	20.80	2.02	49.28	—	115	21.10	1.75	49.20	—	114	63
II	„	CH_3	H	b	60	45	„ „	194 Methanol	$C_3H_4N_4O_2$	1545	1310	28.00	2.97	43.92	—	126	28.10	3.13	43.75	—	128	54
III	„	C_2H_5	H	b	60	45	„ „	121 Chloroform-carbon tetrachloride	$C_4H_6N_4O_2$	1550	1310	33.50	4.59	39.80	—	137	33.80	4.23	39.50	—	142	55
IV	„	n-C_3H_7	H	b	60	45	„ „	92 Carbon tetrachloride	$C_5H_8N_4O_2$	1550	1320	38.90	5.60	35.56	—	149	38.50	5.15	35.90	—	156	44
V	„	C_6H_5	H	a	60	60	„ „	222—223 Ethanol	$C_8H_6N_4O_2$	1560	1310	49.90	3.09	29.47	—	188	50.55	3.16	29.45	—	190	26
VI	„	p-O_2N-C_6H_4	H	a	60	60	„ „	274—275 Methanol	$C_8H_5N_5O_4$	1560, 1520	1350, 1310	40.28	2.28	30.05	—	230	40.70	2.13	29.75	—	235	51
VII	„	m-O_2N-C_6H_4	H	a	60	60	„ „	189 Methanol	$C_8H_5N_5O_4$	1560, 1520	1350, 1310	40.60	2.30	29.71	—	233	40.70	2.13	29.75	—	235	34
VIII[1]*	„	COOH	H	a, b	60	45	„ „	102[2]*	$C_3H_2N_4O_4 \cdot 2H_2O$	1560	1320, 1720 (COOH)	18.55	3.04	29.00	—	191	18.55	3.09	28.90	—	194	67
IX[1]*	„	$COOCH_3$	H	a	60	45	„ „	134[2]*	$C_4H_4N_4O_4$	1560	1310, 1730 ($COOCH_3$)	27.80	2.30	32.75	—	172	27.90	2.33	32.55	—	172	81
X	„	H	2-CH_3	b	60	45	„ „	83 Ethanol	$C_3H_4N_4O_2$	1555	1320	28.30	3.21	43.67	—	132	28.10	3.13	43.75	—	128	69
XI	„	COOH	2-CH_3	a	60	45	„ „	166[2]*	$C_4H_4N_4O_4$	1555	1320, 1720 (COOH)	27.90	2.46	32.74	—	166	27.90	2.33	32.55	—	172	58
XII	„	H	4-CH_3	b	60	45	„ „	100 Ethanol	$C_3H_4N_4O_2$	1550	1335	28.00	3.35	43.78	—	130	28.10	3.13	43.75	—	128	51
XIII	„	NO_2	H		30	60	Ether	135 Benzene	$C_2HN_5O_4$	1560	1310	15.39	0.94	44.20	—	161	15.10	0.63	44.05	—	159	80[3]*
XVII	S	H	—	a, b	60	40	Ether, ethyl acetate	82 Carbon tetrachloride	$C_2HN_3O_2S$	1550	1360	18.03	—	31.88	24.33	135	18.30	0.76	32.08	24.45	131	76
XVIII	„	CH_3	—	b	60	40	Ethyl acetate	62 Ether, 70°	$C_3H_3N_3O_2S$	1555	1355	24.52	—	28.85	22.70	152	24.80	2.07	28.95	22.70	145	69
XIX	„	C_6H_5	—	b	40	40	Ether	141 Light petroleum	$C_8H_5N_3O_2S$	1550	1355	47.00	—	20.38	15.66	203	46.40	2.42	20.29	15.40	207	55
XX	„	o-O_2N-C_6H_4	—	a	60	40	Ethyl acetate	131 Carbon tetrachloride	$C_8H_4N_4O_4S$	1530, 1555	1345	37.90	—	22.30	12.88	243	38.10	1.59	22.11	12.70	252	23
XXI	„	n-O_2N-C_6H_4	—	a	60	40	Ethyl acetate	179 Benzene	$C_8H_4N_4O_4S$	1525, 1560	1350	37.98	—	22.15	12.90	259	38.10	1.59	22.11	12.70	252	26
XXII	O	CH_3	—		180	0	Ethyl acetate	75 Light petroleum	$C_3H_3N_3O_3$	1570, 1540	1305	27.70	2.37	32.57	—	125	27.90	2.33	32.55	—	129	25
XXV	CH	H	H	b	180	50	Ether	175 Benzene	$C_3H_3N_3O_2$	1525, 1560	1360	32.00	2.55	37.39	—	113	31.86	2.66	37.16	—	113	35

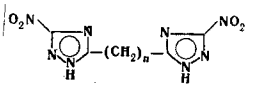
[1]*Identical with the compound obtained previously [11] (mixed mp, IR spectrum).

[2]*Precipitated from acetone or ethyl acetate with light petroleum.

[3]*Yield on the sodium salt of XIII.



The nitro compounds obtained are characterized in Table 1. Diamino-1, 2, 4-triazoles were also subjected to this reaction, giving the corresponding dinitro compounds (XIII–XVI, Table 2).

Table 2. Bicyclic Dinitrotriazoles 

Compound	n	Method of prep.	Mp, °C (solvent for cryst-allization)	IR spectrum, νNO_2		Molecular formula	Found				Calculated				Yield, %
				Asymmetrical valency vibrations	Symmetrical valency vibrations		C, %	H, %	N, %	M	C, %	H, %	N, %	M	
XIV	0	a	256—257*	1560	1315	$C_4H_2N_8O_4$	21.10	1.28	49.46	228	21.25	0.89	49.70	226	31
XV	1	a	280—282 (Ethanol)	1560	1320	$C_5H_4N_8O_4$	25.40	2.08	46.85	236	25.00	1.67	46.70	240	71
XVI	2	a	260—261 (Ethanol)	1555	1310	$C_6H_6N_8O_4$	28.50	2.62	43.63	266	28.40	2.36	44.00	254	79

*Precipitated from acetone with light petroleum.

The appropriate methyl-5-aminotetrazoles yielded 1-methyl (XXIII) and 2-methyl (XXIV)-5-nitrotetrazoles, and 3-aminopyrazole gave 3-nitropyrazole (XXV).*

Nitro derivatives were not obtained from 2-aminoimidazole or 2-aminopyridine by this method. This was not unexpected, since it is known that the diazonium forms of the diazo compounds from these amines are extremely unstable [19, 20], and the life of the diazocations in solution is apparently less than the time required for the formation of the transition state with the nitrite anion.

Results support the reaction mechanism for the replacement of the diazonium group by the nitro group derived from studies on the reaction kinetics in benzene compounds [22].

The nitro compounds are obtained as colorless crystalline solids, readily soluble in water, alcohols, ether, acetone, and ethyl acetate, and less soluble in benzene, chloroform, and carbon tetrachloride. 3, 5-Dinitrotriazole (XIII) has been described only in the form of salts and other derivatives [9, 10]. We have obtained it in the free state, as a very hygroscopic substance which deliquesces during the course of a few hours in air.

Comparison of the IR spectra of the nitro compounds with those of the unsubstituted heterocycles shows that a number of bands present in the parent compounds persist in the nitro derivatives, and new bands due to the vibration of the nitro group appear (Tables 1 and 2).

EXPERIMENTAL

3-Nitro-1, 2, 4-triazole (I). A) A solution of 1.68 g (0.02 mole) of 3-amino-1, 2, 4-triazole [23] in 16 ml of glacial acetic acid was added to 1.6 g (0.023 mole) of sodium nitrite in 7 ml of conc H_2SO_4 at 0 to −5° C. After 5 min, 50 ml of water was added dropwise at a temperature not exceeding 0° C, and the resulting solution was added to 200 ml of 10% sodium nitrite at 45–50° C.

After heating for 1 hr at 45° C, the solution was acidified with H_2SO_4 until oxides of nitrogen were no longer evolved, treated with urea to destroy dissolved oxides of nitrogen, and extracted with ethyl acetate. After removal of the ethyl acetate, the product was crystallized from methanol to give 1.3 g (57%) yield.

B) 1.68 g (0.02 mole) of the aminotriazole in 50 ml of 10% sodium nitrite at 45° C. The mixture was worked up as in method (A) above. Yield 63%.

*After this article went to press, a paper appeared describing a similar synthesis of 1-methyl-5-nitro-4-carboxypyrazole [21].

This method was typical for most of the nitro compounds.

3,5-Dinitro-1,2,4-triazole (XIII). To a solution of 80 g of sodium nitrite in 300 ml of water was added during 1.5 hr with stirring and cooling at 0 to −5° C a solution of 6 g (0.061 mole) of 3,5-diamino-1,2,4-triazole [24] in 214 ml of H_2SO_4. The mixture was heated to 60° C, kept for 30 min, cooled to 0° C, and 30% H_2SO_4 added until oxides of nitrogen were no longer evolved. Urea (4 g) was then added, and the mixture extracted with 6 × 200 ml of ether. The ether extract was dried over calcium chloride, and the ether distilled off until the volume had reached 15–20 ml. The residue was dissolved in 150 ml of acetone and treated with a solution of 15–20 g of sodium bicarbonate. The excess bicarbonate was filtered off and the acetone distilled to give the sodium salt of XIII as yellow crystals, mp 123° C (decomp.) (from alcohol), yield 8.9 g (80%). The sodium salt was identical in its properties with that described in [9]. In order to obtain the free compound XIII, the residue, after removal of the ether, was kept in a vacuum desiccator over H_2SO_4 until the material ceased losing weight, followed by extraction with boiling dry benzene. The benzene solution, on cooling, deposited XIII, which was filtered off and dried in a vacuum desiccator over phosphorus pentoxide. The compound was very hygroscopic, and on standing in air for 2–3 hr it began to deliquesce.

1- and 2-Methyl-5-nitrotetrazoles (XXIII, XXIV) were obtained by method (B). Compound XXIII was extracted from the reaction mixture with benzene, the extract dried over sodium sulfate, treated with alumina, the benzene removed, and the residue crystallized from ether with cooling to −70° C. Yield 57.5%, mp 55–56° C [12].

Compound XXIV, after isolation from the benzene extract, was crystallized from carbon tetrachloride. Yield 76.5%, mp 86–87° C [12].

2-Nitro-5-methyl-1,3,4-oxadiazole (XXII). Since derivatives of 1,3,4-oxadiazole are unstable in acid media [4], XXII was prepared in such a way as to avoid prolonged contact with acid. 2.1 g (0.023 mole) of 2-amino-5-methyl-1,3,4-oxadiazole [25] was suspended in 200 ml of a 20% solution of sodium nitrite, cooled to −5° C. During 3 hr, 100 ml of 7% H_2SO_4 was added slowly to the suspension, keeping the temperature below 0° C. The cooled solution was extracted with ethyl acetate, the extract evaporated, and the residue crystallized from light petroleum.

The IR spectra were taken on a UR-10 instrument in the form of films.

REFERENCES

1. K. T. Potts, Chem. Rev., **61**, 87, 1961.
2. R. Elderfield, ed., Heterocyclic Compounds [Russian translation], 7, 470, 1965.
3. R. Elderfield, ed., Heterocyclic Compounds [Russian translation], 8, 4, 1967.
4. E. P. Nesynov and A. P. Grekov, Usp. khim, **33**, 1184, 1964.
5. W. Manchot and R. Noll, Lieb. Ann., **343**, 1, 1905.
6. C. P. Chipen, R. P. Bokalder, and V. Ya. Grinshtein, KhGS [Chemistry of Heterocyclic Compounds], 110, 1966.
7. E. B. Towne and J. B. Dickey, US patent no. 2708671, 1954; C. A., **49**, 15252, 1955.
8. H. Saikati and M. Kanaoka, J. Pharm. Soc. Japan, **81**, 1333, 1961; RZhKh, 11, Zh 289, 1963.
9. R. H. Wiley and N. R. Smith, US patent No. 3111524, 1964; C. A., **60**, 2951, 1964.
10. H. Burchfield and D. K. Gullstrom, US patent no. 3054800, 1963; C. A., **58**, 10220, 1963.
11. L. I. Bagal, M. S. Pevzner, and V. A. Lopyrev, KhGS [Chemistry of Heterocyclic Compounds], collection 1, 180, 1967.
12. R. A. Henry and W. Finnegan, J. Am. Chem. Soc., **76**, 929, 1954.
13. A. Beaman, W. Tautz, T. Gabriel, and R. Duschinsky, J. Am. Chem. Soc., 87, 389, 1965.
14. H. Lund, J. Chem. Soc., 418, 1935.
15. R. Fusco and S. Rossi, 1-st. Lombardo Sci. Lettere, Sect. A, **93**, 334, 1959.
16. A. N. Kost and I. I. Grandberg, Advances in Heterocyclic Chemistry, 6, 347, 1966.
17. E. R. Ward, C. D. Johnson, and J. G. Hawkins, J. Chem. Soc., 894, 1960.
18. J. Jones and R. Robins, J. Am. Chem. Soc., 82, 3773, 1960.
19. K. Hoffmann, Imidazole and its Derivatives, N. Y., 141, 1953.
20. R. Elderfield, ed., Heterocyclic Compounds [Russian translation], **1**, 419, 1950.
21. C. C. Cheng, J. Heterocycl. Chem., **5**, 195, 1968.
22. L. I. Bagal, M. S. Pevzner, and A. N. Frolov, ZhOrKh, **5**, 1820, 1969.
23. C. Allen and A. Bell, The Synthesis of Organic Compounds [Russian translation], 4, 48, 1953.
24. R. Stolle and K. Krauch, J. prakt. Chem., 88, 306, 1913.

25. R. Stolle and K. Fehrenbach, J. prakt. Chem., **122**, 283, [2], 1929.

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