HETEROCYCLIC NITRO COMPOUNDS.

28.* 1-(OXOALKYL)-3-NITRO-5-R-1,2,4-TRIAZOLES IN REACTIONS WITH HYDRAZINE AND HYDROXYLAMINE

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UDC 547.792.1.9'873'892.07:543.422

The reaction of 1-(oxoalkyl)-3-nitro-5-R-1,2,4-triazoles with hydroxylamine and hydrazine takes place at the keto group to give azines and oximes (R = H, CH_3), with reduction of the nitro group (R = NO_2, hydroxylamine), or with participation of both reaction centers with annelation and conversion to triazolo[3,2-c]-1,2,4-triazines and -1,2,4-triazepines, depending on the character of the substituent in the 5 position of the triazole ring and the type of reagent.

We have established that the reaction of ketones that are derivatives of 3-nitro-5-R-1,2,4-triazole (I-VI) with hydrazine and hydroxylamine is determined by the character of the substituent in the 5 position of the heteroring. Depending on the ability of the substituent to undergo substitution or reduction by these reagents, these transformations in the structure of the ketone take place at the keto group, at the ring C_5 atom, or at both reaction centers simultaneously.

Reactions exclusively at the keto group occur only when the substituent attached to C_5 is absolutely inert to the action of nucleophilic reagents and reducing agents (R = H, CH_3). Thus when ketones I, IV, and V are treated with hydrazine, they give azines VII-IX both in the case of catalysis by mineral acids or when they are absent. Azines are the only reaction products, regardless of the molar ratio of the reagents (N_2H_4/ketone = 1-20). We were unable to isolate the intermediate hydrazones (A), although their presence in the reaction mixture in the presence of a 20-fold excess of hydrazine was recorded in the PMR spectrum [1.73, s, 3H (CH_3); 5.00, s, 2H (CH_2), 6.10, s, 2H (NH_2), and 8.8, s, 1H (CH) for ketone I] in addition to an azine. The absence of hydrazones in the final reaction products can be explained by their high reactivities and their consumption in situ.

In structures II, III, and VI, which have a substituent in the 5 position that is capable of nucleophilic substitution (R = Br, NO_2), the intermediate hydrazone is stabilized due to intramolecular cyclization with the elimination of the substituent and the formation of annelated systems (X-XIII). The reactions proceed similarly for hydrazine and methylhydrazine. Varying the solvent (water, alcohols, dioxane), the temperature (10-90°C), and the reagent ratio (N_2H_4/ketone = 0.5-20) and the introduction of acids in the reaction did not lead to the formation of other compounds in the reaction of ketones II and III with hydrazines. Changes in the conditions affected only the yields of 1,2,4-triazolo[3,2-c]-1,2,4-triazines X and XI. An increase in the percentage of hydrazine in the reaction mixture led to the formation of 1-(3-nitro-5-amino-1,2,4-triazol-1-yl)-butan-3-one hydrazone (XIV) along with two-ring system XII only in the case of butanone VI. Compound XIV predominates in the reaction products (more than 70%) when a tenfold (or greater) excess of hydrazine is used. It is the only product of the reaction of ketone VI at 25-30°C in 25% aqueous hydrazine in the presence of a 20-fold excess of the latter (the yield was 75-80%).

The reaction in a homogeneous medium (ethanol, dioxane) and at increased temperature leads to a decrease in the yield of hydrazone XIV due to the realization of a reverse Michael reaction for starting ketone VI, which is unstable in an alkaline medium; this is

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*See [1] for Communication 27.

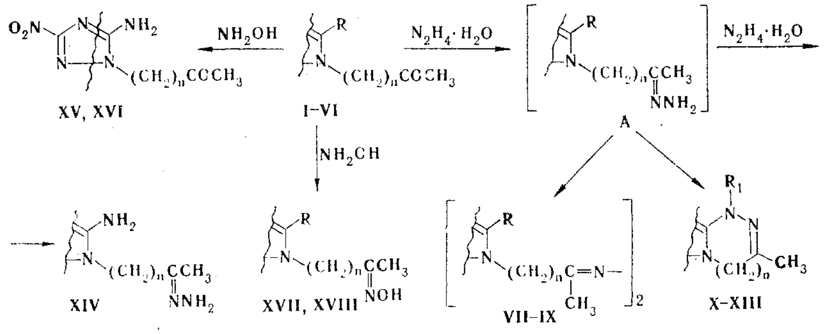
Lensovet Leningrad Technological Institute, Leningrad 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1113-1117, August, 1982. Original article submitted December 9, 1981.

0009-3122/82/1808-0854$07.50

confirmed by the presence of 3,5-dinitro-1,2,4-triazole in the reaction products [determined by thin-layer chromatography (TLC)].

The formation of XII and XIV from ketone VI can be explained by the initial synthesis of hydrazone A (R = NO_2;, the nitro group of which then undergoes reduction or intramolecular substitution, according to the conditions (the hydrazine concentration). The nucleophilic properties of hydrazine in this case are not manifested, and the formation of 5-hydrazino derivatives of triazole, as noted in [2], is not observed. The introduction into the formation of only two-ring compounds (XI, XIII), i.e., intramolecular substitution proves to be preferable.

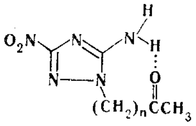
Reduction of the nitro group with hydrazine occurs only in the case of butanone VI. The similarly constructed propanone III under the conditions presented above also gives triazolo[3,2-c]-1,2,4-triazine X. The greater lability of the nitro group attached to C_5, which is associated with the approach of the electron-acceptor oxo group to the reaction center, probably plays the deciding role in the direction of the reaction in this case.



I—III, VII, X, XI, XV, XVII n=1; IV—VI, VIII, IX, XII, XIII, XVI, XVIII n=2; I, IV, VII, VIII, XVII, XVIII R=H; V, IX R=CH_3; II R=Br; III, VI R=NO_2; X, XII R_1=H; XI, XIII R_1=CH_3

We were able to carry out the reduction of the nitro group in ketones VI and III by treatment with a milder reducing agent, viz., hydroxylamine, which is simultaneously less basic. The selective course of the process with retention of the ketone structure (XV, XVI) is characteristic. We were also unable to obtain the oximes and hydrazones of 1-(oxoalkyl)-3-nitro-5-amino-1,2,4-triazoles XV and XVI in directed synthesis under the conditions that are standard for these reactions.

At the same time ketones I and IV, which do not have an amino group in the 5 position, gives oximes XVII and XVIII in ∿70% yields when they are treated with a methanol solution of hydroxylamine. This fact can hardly be interpreted as being the result of a sharp decrease in the electrophilicity of the carbonyl carbon atom when an amino group is introduced into the triazole ring. A comparison of the pK_a values of 3-nitro-5-amino- and 3-nitro-5-methyl-1,2,4-triazoles (7.05* and 6.75 [3]) shows that their donor effects on the N_1 atom and, consequently, on the alkyl substituent are comparable. The decreased reactivity of the keto group is possibly explained by the formation of an intramolecular hydrogen bond with the introduction of an amino group.



One should also note the anomalous stability of butanone XVI with respect to the action of bases — the formation of 3-nitro-5-amino-1,2,4-triazole is recorded in the UV spectra only when it is allowed to stand for a long time in 5 N sodium hydroxide solution.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in hexadeuteroacetone were recorded with a Perkin-Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The IR spectra of films of the compounds were recorded with a UR-20 spectrometer. The spectrophotometric determination of the pK_a values was carried out with an SF-16 spectrophotom-

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*Determined by potentiometry and spectrophotometry.

TABLE 1. Derivatives of 1-(Oxoalkyl)-3-nitro-5-R-1,2,4-triazoles

Compound	mp,[a] °C	IR spectrum, cm⁻¹	PMR spectrum, ppm (J, Hz)			Found, %			Empirical formula	Calculated, %			*M* b		Yield, %
			CH_3	CH_2	other	C	H	N		C	H	N	found	calc.	
VII	121—122	800 w., 860 s, 930 w, 1060 m 1190 w., 1215 s, 1320 s 1335 s, 1430 s, 1520 s, 1570 s, 1650 m	3,6 s (3H)	5,3 s (2H)	—	36,0	3,7	41,7	$C_{10}H_{12}N_{10}O_4$	35,7	3,6	41,7	331	336	77
VIII	124—125	710 m, 755 w., 785 w, 855 o, 895 w, 930 w, 1030 w, 1065 s, 1175 w., 1220 s, 1285 w., 1325 s, 1400 m, 1420 m, 1440 w, 1520 s, 1585 s, 1660 m	1,7 s (3H)	3,00 s (2H), 4,70 t (2H), (10)	—	39,4	4,4	38,7	$C_{12}H_{16}N_{10}O_4$	39,6	4,4	38,5	359	364	50
IX	109—110	750 m, 770 w, 850 s, 1140 m, 1215 m, 1315 m, 1420 m 1490 m, 1530 w., 1550 s, 1650 m	1,7 s (3H), 2,6 s (3H)	3,00 s (2H), 4,60 t (3H)	—	42,6	5,3	35,4	$C_{14}H_{20}N_{10}O_4$	42,8	5,1	35,7	404	392	40
X	236—237	730 w, 780 w, 820 w., 875 m, 915 m, 960 w, 1130 m, 1230 w, 1275 m, 1320 s, 1430 w, 1445 w, 1490 m, 1550 s, 1565 s, 1620 s., 3340 m	2,05 s (3H)	4,95 s (2H)	NH: 11,4 уш (1H)	33,5	3,3	46,4	$C_5H_6N_6O_2$	33,0	3,3	46,1	186	182	95
XI	123—124	760 m, 810 w., 855 s, 925 w, 980 w, 1040 m, 1080 w, 1125 w, 1160 m, 1250 w., 1325 s, 1410 s, 1475 m, 1515 m. 1560 s	2,10 s (3H), 2,48 s (3H)	4,95 s (2H)	—	36,7	4,3	42,7	$C_6H_8N_6O_2$	36,7	4,1	42,9	190	196	73
XII	237—238	740 m, 775 w, 860 s, 870 s. 1035 w, 1075 w, 1140 w, 1160 w, 1180 m, 1270 w, 1330 s, 1370 m, 1445 m, 1480 w, 1500 s, 1550 s., 1590 s, 3350 m	2,12 s (3H)	3,05 m (2H), 4,40 m (2H)	NH: 10,6 уш (1H)	36,8	4,1	43,0	$C_6H_8N_6O_2$	36,7	4,1	42,9	192	196	70
XIII	138—139	730 m, 770 m, 810 w, 860 s, 930 w, 980 w, 1050 w, 1120 w, 1170 m, 1260 w, 1325 s, 1370 m, 1420 m, 1425 m, 1445 m, 1520 s, 1570 s	2,15 s (3H), 3,33 s (3H)	3,00 m (2H), 4,40 m (2H)	—	39,7	4,9	40,3	$C_7H_{10}N_6O_2$	40,0	4,8	40,0	205	210	60

XIV	149—150	750 w, 800 w, 870 s, 930 w, 970 w, 1045 m, 1110 m, 1145 m, 1225 w, 1260 m, 1325 s, 1380 w, 1425 w, 1535 s, 1670 s, 3180 w, 3330 w	1,80 s (3H)	4,30 t (2H), 2,80 t (2H) (10)	NH_2: 6,9 br (2H)	29,0	4,6	47,5	$C_5H_9N_7O_3$	28,9	4,2	47,6	207	215	70
XV	220—221	750 m, 760 s, 820 s, 855 m, 890 s, 960 w, 1045 w, 1055 w, 1110 w, 1150 m, 1200 s, 1280 m, 1330 s, 1360 w, 1380 w, 1425 s, 1460 w, 1530 s, 1590 w, 1665 s, 1745 s, 3190 w, 3465 w	2,15 s (3H)	5,05 c (2H)	NH_2: 7,05 br (2H)	32,5	4,0	37,9	$C_5H_7N_5O_3$	32,4	3,8	37,8	191	185	70
XVI	169—170	755 m 770 m, 805 w, 820 w, 865 w, 930 w, 960 w, 990 m, 1022 m, 1070 w, 1140 w, 1170 w, 1225 w, 1290 w, 1300 m, 1355 w, 1385 s, 1395 s, 1450 w, 1500 w, 1555 s, 1595 w, 1635 w, 1685 w, 1725 vs, 3240 s, 3475 m	2,10 s (3H)	4,10 t (2H), 2,65 t (2H) (13)	NH_2: 6,4 br (2H)	33,4	4,3	33,0	$C_5H_8N_5O_3 \cdot H_2O^c$	33,2	5,1	33,2	218	217	75
XVII	210—211	770 m, 830 w, 860 s, 920 m, 950 m, 960 m, 990 m, 1050 m, 1060 s, 1070 m, 1220 m, 1290 m, 1320 s, 1340 w, 1360 w, 1370 m, 1420 m, 1430 m, 1450 w, 1460 w, 1490 w, 1505 s, 1550 s, 1560 s, 3250 m	1,80 s (3H)	5,15 s (2H)	CH_{tr}, 9,00 s (H), NOH: 11,25 s (1H)	32,3	4,0	38,1	$C_5H_7N_5O_3$	32,4	3,8	37,8	191	185	70
XVIII	115—116	700 w, 740 w, 845 s, 890 m, 910 m, 935 s, 975 w, 1010 m, 1035 s, 1060 s, 1080 w, 1200 m, 1220 w, 1270 w, 1315 s, 1360 w, 1420 m, 1450 m, 1515 m, 1560 m, 3330 m	1,90 s (3H)	2,85 t (2H), 4,65 t (2H) (12)	CH_{tr}, 8,8 s (1H), NOH: 10,5 s (1H)	36,0	4,6	35,5	$C_6H_9N_5O_3$	36,2	4,5	35,9	218	199	69

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[a] The compounds were crystallized: VII, X, XII, XVII, and XVIII from ethanol, VIII, IX, XIII, XIV, and XV from propanol, and XI from CCl_4. Compound XVI was reprecipitated from methanol by the addition of CCl_4. [b] Inverse ebullioscopy from acetone. [c] The presence of crystallization water was confirmed by derivatography. Found: H_2O 7.5%. Calculated: H_2O 8.2%.

eter at 20°C, and potentiometric titration was carried out with an LPM-60M pH meter; the pK_a values were calculated by the method in [4]. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 (with development of the chromatograms by UV illumination) in an ethyl acetate—petroleum ether—dioxane system (4:2:1). Starting ketones I-VI were obtained by the method in [5]. The derivatographic studies were accomplished with the system of F. Paulik, J. Paulik, and L. Erdey.

1-(Oxoalkyl)-3-nitro-5-R-1,2,4-triazole Azines (VII-IX). A 0.3-ml (8.8 mmole) sample of hydrazine hydrate was added at 20°C to a solution of 4.4 mmole of ketone I, IV, or V in 20 ml of dioxane (ethanol), and the mixture was stirred for 0.5-1 (monitoring by TLC with the exception of the ketone). The solvent was then evaporated, and the residue was crystallized.

2-Nitro-7-methyl-1,2,4-triazolo[3,2-c]-5,6-dihydro-1,2,4-triazepine (XII) and 2-Nitro-6-methyl-1,2,4-triazolo[3,2-c]-5,6-dihydro-1,2,4-triazine (X). These compounds were synthesized from ketones VI, II, and III, respectively, by a method similar to the preceding procedure.

2-Nitro-7,9-dimethyl-1,2,4-triazolo[3,2-c]-5,6-dihydro-1,2,4-triazepine (XIII) and 2-Nitro-6,8-dimethyl-1,2,4-triazolo[3,2-c]-5,6-dihydro-1,2,4-triazine (XI). A 44-mmole sample of ketone III or VI was added in portions at 20°C to a solution of 4 g (88 mmole) of methylhydrazine in 20 ml of dioxane (water), and the mixture was allowed to stand for 1-1.5 h (monitoring by TLC). The precipitate was removed by filtration, and the filtrate was evaporated. The residue was washed with water, added to the principal amount of product, and crystallized.

1-(3'-Oxobutyl)-3-nitro-5-amino-1,2,4-triazole Hydrazone (XIV). Ketone VI was added in portions with stirring at 20°C to 18 ml (88 mmole) of 25% aqueous hydrazine solution, and the mixture was allowed to stand for 1 h (monitoring by TLC). The hydrazone was removed by filtration, washed with water, and crystallized.

1-(Oxoalkyl)-3-nitro-5-amino-1,2,4-triazoles (XV, XVI). A suspension of 5 mmole of ketone III or VI in 10 ml of methanol was added with stirring at 20°C to a solution of 25 mmole of hydroxylamine, prepared by neutralization of a solution of 1.9 g (25 mmole) of hydroxylamine hydrochloride in 10 ml of methanol with a solution of 1.3 g (25 mmole) of potassium hydroxide in 10 ml of methanol, and the mixture was allowed to stand (monitoring by TLC). The solvent was evaporated, and the residue was crystallized.

1-(Oxoalkyl)-3-nitro-1,2,4-triazole Oximes (XVII, XVIII). A solution of 25 mmole of hydroxylamine prepared as in the preceding experiment was added to a solution of 12.5 mmole of ketone I or IV in 20 ml of methanol, and the mixture was stirred for 2 h. The solvent was evaporated, and the residue was crystallized.

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