NITROAZINES.

9.* CHARACTERISTIC FEATURES OF NUCLEOPHILIC SUBSTITUTION OF THE NITRO GROUP IN DIHYDROAZOLO[5,1-c][1,2,4]TRIAZINES

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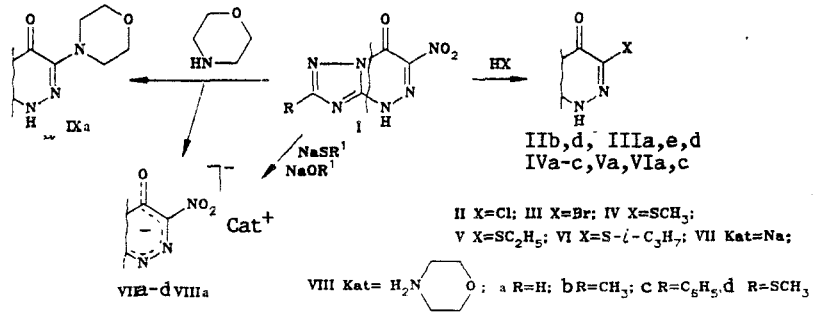
The reaction of 6-nitro-7-oxo-4,7-dihydroazolo[5,1-c]-1,2,4-triazines with O-, N-, and S-nucleophiles leads to the corresponding 6-substituted compounds. In the reaction of 2,4-dimethyl-6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazine with hydrazine hydrate, 3-methyl-5-(N-methylamino)-1,2,4-triazole is formed.

The nucleophilic substitution of the nitro group in the series of nitroarenes has been studied quite extensively (see, for example, review [2]). Much less information is available on transformations of this type among the heterocyclic compounds. A substitution of the nitro group by a halogen, alkoxy, alkylthio, or amino fragment has been described for nitropyridine derivatives [3-7]. Individual examples of these reactions are also known in the diazine series, pyrazines [8, 9] and pyriridazines [10-13]. We have given a brief report on the substitution of the nitro group by a halogen in condensed nitro-1,2,4-triazine derivatives — 6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazines [14]. In continuation of the investigations in this field in order to develop effective methods of synthesis of the azolo[5,1-c]-[1,2,4]triazone derivatives (among the compounds of this class, compounds exhibiting high cardiovascular, [5, 16], antiviral [17, 18] and psychotropic activity [19,20] were found), we have examined the behavior of 2-R-6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazines Ia-d in reactions with a number of N-, O-, and S-nucleophiles.

It was found that the nitro compounds studied react readily with nucleophiles having an acid character. On being treated with hydrogen halides in alcohol, the nitro group is substituted by halogen with the formation of chloro- or bromo derivatives IIa-d, IIIa, c, d, which previously have not been obtainable by other methods. It is probable that in such cases, the replacement of the nitro group proceeds as a nucleophilic substitution with the participation of a Hal^- ion.



When compound Ia was boiled in benzene with KCl and 18-crown-6 ether, despite the very low solubility of potassium chloride in this system, the formation of a choride could be detected by the TLC method [20]. Heating azolotriazine Id with KBr and dibenzo-18-crown-6 ether in DMFA leads to the formation of bromide IIId in a quantitative yield.

*Article 8, see [1].

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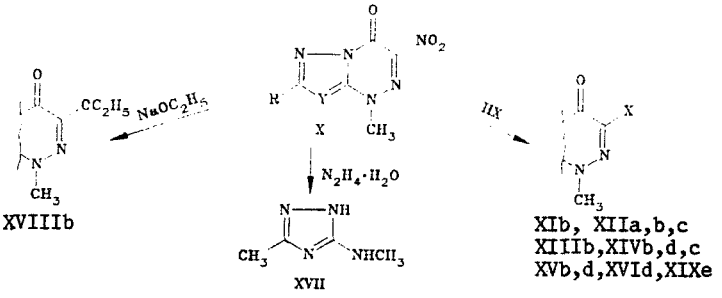
6-Alkylthio-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]-triazines IV-VI are formed in the reaction of compounds Ia,c with alkyl mercaptans. A similar substitution of the nitro group in the benzene [2], pyridine [4, 5], or pyridazine [10, 12] ring occurs by the action of an anionic form of the reagent – a thiolate ion. In this case, the reaction proceeds with a nonionized form of the thiol, which indicates the high mobility of the nitro group bound to an as-triazine ring.

The reaction of compounds Ia-c with nucleophilic bases leads to deprotonation with the formation of anions stable towards nucleophilic attack. Thus, when sodium thiolates are used in the reaction, only sodium salts of triazolotriazine VII are formed, the physical constants of which coincide with those previously described in [20]. Substitution also can not be carried out with nucleophilic reagents such as alcoholates: when nitrotriazines Ia-c were heated with sodium ethylate, sodium salts VIIa-c were also obtained.

In the reaction with morpholine under mild conditions, ammonium salts VIII are formed, and only under conditions of prolonged boiling in an excess of morpholine, was it possible to obtain the substitution product of the nitro group (compound IXa).

The 4-methyl analogs Xa-e, which are not capable of forming anions, react more readily with nucleophile bases. Thus, in DMFA, on passing ammonia through at 90-100°C, a substitution of the nitro group by an amino group is observed (compound (XI). Primary amines (benzylamine, ethanolamine, cyclohexylamine) also react redily with alkylated azolotriazines, as a result of which 6-aminoderivatives XII–XIV are formed in high yields.



XI X=NH_2; XII X=$NHCH_2C_6H_5$; XIII X=NHC_6H_{11}; XIV X=$NH(CH_2)_2OH$; XV X=morpholyl XVI X=piperidyl XIX X=SC_4H_9; a R=H, Y=N; b R=CH_3, Y=N; d R=SCH_3, Y=N; e R=H, Y=$CCO_2C_2H_5$

The reaction with cycloalkylimines – morpholine or piperidine – proceeds under more rigorous conditions. Only on prolonged boiling can a good yield of compounds XV and XVI be obtained. At the same time, diethylamine was found under such conditions to be incapable of substituting the nitro group in several of the compounds studied. Primary aromatic amines, such as for example aniline, p-toluidine, p-anisidine, also do not react with alkylated azolotriazines because of insufficient nucleophilicity.

In reaction with the substrates studied, the reducing properties of hydrazine predominate over the nucleophilic properties. On heating nitroazolotriazine Xb with hydrazine hydrate in ethanol, a reductive decomposition of the triazine ring takes place, and 3-methyl-5-(N-methylamino)-1,2,4-triazole (XVII) is formed. The nitro compound Xb can react with sodium ethylate with the formation of 6-ethoxytriazolotriazine XVIII. However, the same azolotriazine does not react with potassium tert-butylate even after prolonged treatment in DMFA, which is possibly the result of a steric hindrance of the reagent. Prolonged boiling of the substrate in an alcoholic alkali leads to the decomposition of the heterocyclic system with the formation of a complex mixture of compounds. Thiols and thiolates are capable of substituting the nitro groups in compounds X under extraordinarily mild conditions, which leads to the formation of the corresponding derivatives XIX. No difference was observed between the thioalcohols and their anions in their substituting ability.

In the IR spectra of all the compounds obtained there is a stretching vibration band of carbonyl in the region of 1710...1740 and bands are present in the 1320...1350 and 1520... 1550 cm^{-1} regions, belonging to the nitro group [20] (Table 1). In the PMR spectra proton signals are recorded of the azole fragment, the N-methyl group (compounds XI–XIX) and the corresponding substituting groups – amino-, alkylamino (compounds XI–XVI), alkylthio (compounds IV–VI, XIX), and ethoxy groups. It should be noted that when the acceptor nitro group is replaced by halogen, amino, alkylamino, alkylthio or an alkoxy fragment, the chemical shifts of signals belonging to the azolotriazine protons undergo shift of a strong field. Thus,

TABLE 1. Characteristics of Synthesized Azolo[5,1-c][1,2,4]-triazines

Compound	Empirical formula	Mp, °C (from ethanol)	R_f*	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm	Yield, %
				C=O	NH		
IIb	$C_5H_4ClN_5O$	273...275	—	1727	3260	2,42 (3H, s, 2-CH_3); 13,00 (1H, s, NH)	83
IIc	$C_{10}H_6ClN_5O$	300	—	1735	3260	7,80...8,00, 8,50...8,65 (5H, m, C_6H_5); 13,20 (1H, br. s, NH)	92
IId	$C_5H_4ClN_5OS$	300†	—	1730	3250	2,50 (3H, s, SCH_3); 13,20 (1H, br.s, NH)	75
IIIa	$C_4H_2BrN_5O$	280...282	—	1730	3250	8,40 (1H, s, 2-H); 13,60 (1H, s, NH)	85
IIIc	$C_{10}H_6BrN_5O$	300	—	1740	3260	7,80...8,00, 8,50...8,70 (5H, m, C_6H_5); 13,25 (1H, br.s, NH)	90
IIId	$C_5H_4BrN_5OS$	300	—	1730	3250	2,55 (3H, s, SCH_3); 13,20 (1H, br.s, NH)	82
IVa	$C_5H_5N_5OS$	252...255†	—	1715	3260	2,45 (3H, s, SCH_3); 8,52 (1H, s, 2-H)	84
IVb	$C_6H_7N_5OS$	267...270	—	1720	3265	2,25 (3H, s, 2-CH_3); 2,50 (3H, s, SCH_3)	75
IVc	$C_{11}H_9N_5OS$	270	—	1722	3280	2,55 (3H, s, SCH_3); 7,70...7,90, 8,30...8,55 (5H, m, C_6H_5)	80
Va	$C_6H_7N_5OS$	270...272	—	1720	3260	1,45 (3H, t, CH_3); 3,55 (2H, q, SCH_2); 8,50 (1H, s, 2-H)	70
VIa	$C_7H_9N_5OS$	260...263	—	1715	3275	1,40 (6H, d, $(CH_3)_2$); 3,80 (1H, m, SCH); 8,68 (1H, s, 2-H)	74
VIc	$C_{13}H_{13}N_5OS$	270	—	1720	3280	1,42 (6H, d, $(CH_3)_2$); 3,85 (1H, m, SCH); 7,75...7,90, 8,35...8,60 (5H, m, C_6H_5)	65
XIb	$C_6H_6N_6O$	174	0,47	1720	3320	2,28 (3H, s, 2-CH_3); 3,69 (3H, s, N—CH_3); 6,20 (2H, br.s, NH_2)	85
XIIa	$C_{12}H_{12}N_6O$	182	0,33	1720	3400	3,90 (3H, s, N—CH_3); 4,50 (2H, d, N—CH_2); 5,85 (1H, t, NH); 7,29 (5H, s, C_6H_5); 7,98 (1H, s, 2-H)	75
XIIb	$C_{13}H_{14}N_6O$	175	0,32	1700	3380	2,45 (3H, s, 2-CH_3); 3,86 (3H, s, N—CH_3); 4,48 (2H, d, N—CH_2); 5,80 (1H, br. t, NH); 7,29 (5H, s, C_6H_5)	84
XIIe	$C_{16}H_{18}N_6O_3$	148	0,39	1700	3400	1,36 (3H, t, CH_3); 4,25 (2H, q, O—CH_2); 4,30 (3H, s, N—CH_3); 4,49 (2H, d, N—CH_2); 5,82 (1H, br.t, NH); 7,30 (5H, s, C_6H_5); 8,20 (1H, s, 2-H)	70
XIIIb	$C_{12}H_{18}N_6O$	172	0,51	1700	3380	1,20...2,22 (11H, m, C_6H_{11}); 2,40 (3H, s, 2-CH_3); 3,84 (3H, s, N—CH_3); 5,37 (1H, br. s, NH)	81
XIVb‡	$C_8H_{12}N_6O_2$	217	0,40	1710	3320	2,35 (3H, s, 2-CH_3); 3,32 (2H, m, N—CH_2); 3,59 (2H, m, O—CH_2); 3,80 (3H, s, N—CH_3); 4,75 (1H, br. s, OH); 6,70 (1H, br. t, NH)	76
XIVd‡	$C_8H_{12}N_6O_2S$	202	0,42	1710	3380	2,65 (3H, s, SCH_3); 3,34 (2H, m, N—CH_2); 3,67 (2H, m, O—CH_2); 3,80 (3H, s, N—CH_3); 4,50 (1H, br.t, OH); 6,75 (1H, br. t, NH)	65
XIVe‡	$C_{11}H_{15}N_5O_4$	208	0,41	1700	3390	1,35 (3H, t, CH_3); 3,42 (2H, m, N—CH_2); 3,72 (2H, m, O—CH_2); 4,20 (2H, q, O—CH_2); 4,24 (3H, s, N—CH_3); 4,76 (1H, br. t, OH); 6,70 (1H, br. t, NH); 8,23 (1H, s, 2-H)	60
XVb	$C_{10}H_{14}N_6O_2$	191	0,53	1740	—	2,33 (3H, s, 2-CH_3); 3,31 (4H, m, N—CH_2); 3,62 (4H, m, O—CH_2); 3,78 (3H, s, N—CH_3)	42
XVd	$C_{10}H_{14}N_6O_2S$	167	0,48	1740	—	2,62 (3H, s, SCH_3); 3,31 (4H, m, N—CH_2); 3,60 (4H, m, O—CH_2); 3,80 (3H, s, N—CH_3)	46
XVId	$C_{11}H_{16}N_6OS$	167	0,44	1740	—	1,65 (10H, m, C_5H_{10}); 2,65 (3H, s, SCH_3); 3,83 (3H, s, N—CH_3)	62
XVIIIb	$C_8H_{11}N_5O_2$	153	0,52	1720	—	1,37 (3H, t, CH_3); 2,35 (3H, s, 2-CH_3); 3,80 (3H, s, N—CH_3); 4,26 (2H, q, O—CH_2)	68
XIXe	$C_{13}H_{18}N_4O_3S$	175	0,44	1700	—	0,92 (3H, t, CH_3); 1,32 (3H, t, CH_3); 1,40...1,80 (4H, m, $(CH_2)_2$); 3,12 (2H, t, CH_2S); 4,30 (2H, q, O—CH_2); 4,40 (3H, s, N—CH_3); 8,30 (1H, s, 2-H)	62

*In ethyl acetate.

†From water.

‡In the IR spectrum ν_{OH} for compound XIVb 3450, XIVd 3470, XIVe 3490 cm^{-1}.

introduction of halogen into a triazolotriazine molecule (compounds IIa, IIIa) leads to a 0.3 ppm shift of the azole proton signal to the strong field. Replacement of the nitro group in the alkylated azolotriazines X by any of the above fragments causes a 0.2...0.3 ppm shift of the three-proton singlet of the N–CH_3 group to the strong field. The signal of the 2-H proton in the spectra of compounds XIIa,e, XIVe is also shifted by 0.4 ppm to the strong field, compared with the similar signals of the starting compounds.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in mineral oil. The PMR spectra were run on a Perkin-Elmer R-12B spectrophotometer (60 MHz) in DMSO-D_6, using TMS as internal standard. The TLC was carried out on Silufol UV-254 plates in ethyl acetate, with development by iodine vapors. The data of the elemental analysis for C, H, and N correspond to the calculated values.

2-R-6-Halo-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]-triazines (IIa-d, IIa,c,d). A. A 0.01 mole portion of compound I is suspended in 20 ml of absolute ethanol and a moderate current of the hydrogen halide is passed through for 2 h with ice-cooling of the reaction flask. The precipitate is filtered, washed with cold water, and crystallized.

B. A 0.02 mole portion of KBr and 0.5 g of (0.001 mole) of dibenzo-18-crown-6 ether are added to a solution of 0.01 mole of Id in 1 ml of DMFA. The mixture is boiled for 1 h, cooled, and the solvent is distilled in vacuo. The dry residue is extracted with $CHCl_3$ (2 × 5 ml), and bromide IIId is crystallized.

C. Synthesis of azolotriazine IIa, see in [20].

The physicochemical and spectral characteristics of the compounds synthesized are given in Table 1.

2-R-6-Alkylthio-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]-triazines (IVa-c, Va, VIa, c). A 0.01 mole portion of azolotriazine I is suspended in 20 ml of ethanol, 0.05 mole of alkyl mercaptan is added, and the mixture is heated for 7 h at 130...140°C in an autoclave. The reaction mixture is evaporated to dryness, and the residue is crystallized with the addition of carbon.

Sodium salts of 2-R-6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo-[5,1-c][1,2,4]triazines (VIIa-c). A 20 ml portion of 10% sodium ethylate or mercaptide is added to a solution of 0.01 mole of compound Ia-d in 30 ml of absolute ethanol, and the mixture is boiled for 6 h. The reaction mixture is cooled and salts VIIa-c are filtered.

Morpholinium salt of 6-nitro-7-oxo-4,7-dihydro-1,2,4-triazolo-[5,1-c][1,2,4]triazines (VIIIa, $C_8H_{11}N_7O_4$). A 1.8 ml portion (0.02 mole) of morpholine is added to a solution of 0.01 mole of Ia in 50 ml of ethanol, and the mixture is boiled for 15 min. The reaction mixture is evaporated to 2/3 of its volume, the residue is cooled with ice, the precipitate that separates is filtered, and crystallized from ethanol. Yield 1.2 g (50%), mp 163°C, R_f 0.6. IR spectrum: 1340, 1520 (NO_2), 1710 cm^{-1} (C=O). PMR spectrum (DMSO-D_6): 3.0...3.2 (4H, m, CH_2–N); 3.6...3.9 (4H, m, CH_2–O), 8.3 ppm (1H, s, 2–H).

6-Morpholyl-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]-triazine (IXa, $C_8H_{10}N_6O_2$). A 0.01 mole portion of azolotriazine Ia is suspended in 20 ml of morpholine and the mixture is boiled for 3 h. The reaction mixture is evaporated in vacuo, the residue is ground with 15 ml of acetone, and crystallized from ethanol. Yield 0.4 g (20%). R_f 0.7. IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum (DMSO-D_6): 2.80...3.10 (4H, m, N-CH_2); 3.60...3.90 (4H, m, O-OCH_2); 7.97 ppm (1H, s, 2H).

2,4-Dimethyl-6-amino-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazine (XIb). A solution of 0.01 mole of triazolotriazine Xb in 1 ml of DMFA is heated to 100...120°C and ammonia is passed through for 3 h. The reaction mixture is cooled, the precipitate is filtered and crystallized.

2-R-4-methyl-6-alkylamino-7-oxo-4,7-dihydro-1,2,4-triazolo-[5,1-c][1,2,4]triazines (XIIa,b,e. XIIIb, XIVb,d,e). A solution of 0.1 mole of compound X in 2 ml of DMFA is held for 2 h at 100°C. After cooling, the precipitate is filtered and crystallized.

2-R-4-methyl-6-cycloalkylamino-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c][1,2,4]triazines (XVb,d, XVId). A 0.06 mole portion of morpholine or piperidine is added to a solution of 0.01 mole of triazolotriazine X in 2 ml of DMFA, and the mixture is boiled for 10 h. The reaction

mixture is cooled, 4 ml of ethanol are added, the precipitate is filtered and crystallized.

2,4-Dimethyl-6-ethoxy-7-oxo-4,7-dihydro-1,2,4-triazolo[5,1-c]-[1,2,4] triazine (XVIIIb). A 0.01 mole portion comopund Xb is added to 20 ml of a 10% solution of sodium ethylate in ethanol and the mixture is boiled for 1 h. It is then cooled, the precipitate is filtered and crystallized.

3-Carbethoxy-4-methyl-6-(n-butylthio)-7-oxo-4,7-dihydropyrazolo-[5,1-c][1,2,4]triazine (XIXe). A 0.02 mole portion of n-butyl mercaptan is added to a solution of 0.01 mole of pyrazolotriazine Xe in 1 ml of DMFA and the mixture is boiled for 2 h. After cooling, the precipitate is filtered and crystallized.

3-Methyl-5-(N-methylamino)-1,2,4-triazole (XVII, $C_3H_6N_4$). A 0.03 mole portion of hydrazine hydrate is added to a solution of 0.01 mole of compound Xb in 10 ml of ethanol, and the mixture is boiled for 15 min. After cooling, the precipitate is filtered and crystallized from ethanol. Yield 0.72 g (70%). PMR spectrum (DMSO-D_6): 2.05 (3H, s, 3-CH_3); 2.68 (3H, d, J = 5 Hz, N-CH_3); 5.80 (1H, br.m, NH); 11.80 ppm (1H, br. s, NH).

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