NITROAZINES.

10.* ADDITION OF POLYATOMIC PHENOLS TO 6-NITROAZOLO[1,5-a]PYRIMIDINES

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Products of addition of polyphenols to 6-nitroazolo[1,5-a] pyrimidines without activation of the reagent and the substrate were obtained. The effect of substitution in the polyphenols and azolopyrimidines on the course of the process was examined.

Depending on the number and orientation of electron-donor substituents in them, phenols and polyphenols react with π-deficient hetarenes and arenes. The hetarylation of phenols with acridinium salts has been investigated in detail [2, 3]. Instances of the introduction of the residue of an N-acyl salt of isoquinoline into the ring of resorcinol dimethyl ether and of 2,6-di-tert-butylphenol [4] and the proton salt of quinoline into the phenol ring [5] are known. Pyrimidine and quinazoline readily replace hydrogen in resorcinol when the reaction is carried out in benzene—trifluoroacetic acid [6]. In the reaction of 1,3,5-trinitrobenzene with the phenoxide anion the latter displays ambident properties, depending on the experimental conditions, to give O- or C-σ complexes [7-11]. In all of the examples presented a necessary condition for the hetarylation of phenols is either activation of the substrate via the formation of N-acyl, N-alkyl, or proton salts or the use of a nucleophile in the anionic form.

We have established that 6-nitroazolo[1,5-a]pyrimidines can add indoles [12] and pyrroles [13] without prior activation of the reagents. The reaction of 6-nitro-1,2,4-triaxolo[1,5-a]pyrimidine and 6-nitro-1,2,4-triazolo[5,1-c]triazine with resorcinol, as a result of which C adducts were obtained, has been briefly reported [14]. In order to ascertain the boundaries of the applicability of this reaction we investigated the reaction of 6-nitroazolo[1,5-a] pyrimidines that contain various substituents in the azole part of the molecule with phenol and its derivatives in the present research.

It was established that R-6-nitro-7-hydroxyaryl-4,7-di-hydroazolo[1,5-a]pyrimidines Ia-e, IIa, IIIa, IVa, b, Va, VIa, f, VIIa, and VIIIa (Table 1), which are stable crystalline yellow substances, are formed smoothly when 6-nitroazolo[1,5-a]pyrimidines and the corresponding phenol derivatives are refluxed in butanol.

An analysis of the results obtained shows that the ability of phenols to participate in the reaction with 6-nitroazolo[1,5-a]pyrimidines depends on their nucleophilicities. Phenol itself and sodium phenoxide do not undergo the reaction. The more nucleophilic resorcinol reacts with 6-nitroazolo[1,5-a]pyrimidines to give addition products Ia-VIIIa. The presence of acceptor groupings such as bromo or acetyl in the resorcinol molecule does not prevent the formation of adducts Ie and VIf. At the same time, compounds such a 2,4-dihydroxybenzoic acid or its Na salt proved to be unreactive.

In contrast to resorcinol, the reaction of 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine with pyrocatechol leads to the formation of two isomers that we were unable to separate. An analysis of the reaction mass by means of PMR spectroscopy made it possible to establish that the addition of the azolopyrimidine fragment in the 3 and 4 positions of pyrocatechol takes place in a ratio of 3:4. Hydroquinone does not form adducts with 6-nitroazolopyrimidines under similar conditions.

Polyphenols that contain three hydroxy groups — phloroglucinol and pyrogallol — react successfully with 6-nitro-azolopyrimidines (see Ib,d and IVb). However, gallic acid, like 2,4-dihydroxybenzoic acid, does not react with them.

*See [1] for Communication 9.

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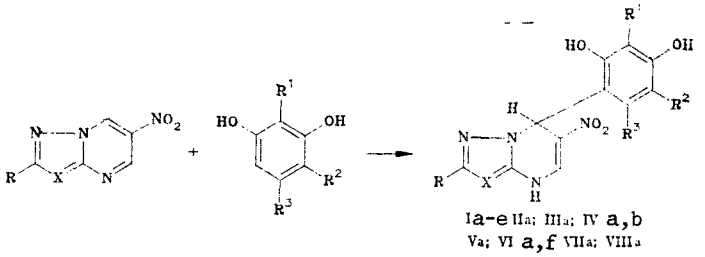


Ia-e IIa; IIIa; IV a,b
Va; VI a,f VIIa; VIIIa

In all cases, despite the ambident character [7-11] of the nucleophile, products of C addition of the phenol were obtained. The alternative O adducts were not detected under the experimental conditions, even when the phenoxides were used.

The π-deficient character of 6-nitroazolo[1,5-a]pyrimidines plays an important role in the transformations under consideration. In the triazolopyrimidine series the introduction of donor substituents such as CH_3 and C_2H_5 into the azole part does not hinder the reaction, but groups that have a + M effect [NH_2, $N(CH_3)_2$] deactivate the substrate, and the corresponding adducts are not formed with polyphenols.

The deaza analogs of triazolo[1,5-a]pyrimidines — pyrazolo[1,5-a]pyrimidines — have much lower electrophilicity. The possibility of their participation in the reaction is ensured only after the introduction of acceptor substituents — $COOC_2H_5$, NO_2, CN — into the pyrazole fragment. 6-Nitropyrazolo[1,5-a]pyrimidine and especially 2-methyl-6-nitropyrazolo-[1,5-a]pyrimidine are not capable of adding polyphenols.

The spectral characteristics of the compounds obtained correspond to the assigned structures.

Absorption band of the stretching vibrations of nitro (1590-1610, 1320-1330 cm^{-1}), hydroxy (3400-3500 cm^{-1}), and amino (3070-3280 cm^{-1}) groups are observed in the IR spectra (Table 1). Absorption at 1680-1740 cm^{-1} is observed in the spectra of IVa,b and VIa,f, which contain carbonyl fragments. An M^+ peak is recorded in the mass spectra of all of the synthesized substances. The PMR spectra of the compounds obtained are superimpositions of the signals of the protons of the heterocyclic and aryl parts of the molecule (Table 1). The assignment of the signals of the 5-H proton of the pyrimidine ring — singlet at 8.15-8.40 ppm — and the 7-H proton — signal at 6.60-6.65 ppm — was made with the aid of the PMR spectra of the previously described 6-nitro-7-indolyl-4,7-dihydroazolo[1,5-a]pyrimidines [12]. The characteristic PMR spectrum of the polyphenol part of the molecule for the products of the addition of resorcinol (Ia-VIIIa) is typical for ABX systems and indicates unequivocally attack in the 4 position of resorcinol. An AB spectral pattern is characteristic for pyrogallol derivatives Ib and IVb; this indicates $C(_4)$ hetarylation of pyrogallol by nitroazolopyrimidine. In the spectra of Id, which contains a phloroglucinol residue, there is a singlet of 3'-H and 5'-H protons at 5.90 ppm. The presence in the PMR spectra of a broad singlet of protons of an OH group at 8.20-10.15 ppm, which vanishes when CD_3COOD is added, is common for the various polyphenol systems.

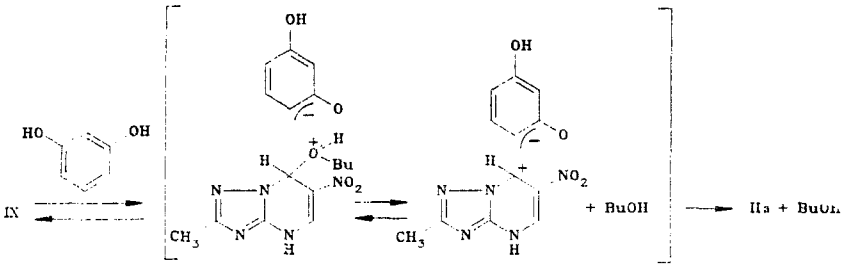
An analysis by PMR spectroscopy of the reaction mass obtained in the reaction of 2-methyl-6-nitrotriazolo[1,5-a]pyrimidine with resorcinol in butanol shows that the transformation after 30 min proceeds in quantitative yield, and only signals of the final compound IIa are recorded in the spectrum. Signals corresponding to the resonance of the protons of the starting compound or the products of adition to the $C(_5)$ atom, like those observed in the reaction of 6-nitroazolo[1,5-a]pyrimidines with pyrrole [13], and other signals are not observed. When the reaction time is shortened to 15 min, yet another two substances, viz., unchanged resorcinol and the product of addition of butanol to the starting pyrimidine — 2-methyl-6-nitro-7-butoxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IX) — are present in addition to the desired product. When butanol is replaced by absolute dioxane, the reaction between the substrate and resorcinol is only 30% complete after 30 min, but the addition of butanol makes it possible, under the same conditions, to obtain adduct IIa in 98% yield. The genuine butoxytriazolopyrimidine IX obtained reacts with resorcinol when they are refluxed in absolute dioxane also in virtually quantitative yield, while carrying out the reaction in tert-butyl alcohol, which, because of steric hindrance, does not form σ adducts with 2-methyl-6-nitrotriazolo[1,5-a]pyrimidine, makes it possible to obtain an adduct with resorcinol as in dioxane, in only 25-30% yield.

TABLE 1. Characteristics of 6-Nitro-7-hydroxyaryl-4,7-dihydroazolo[1,5-a]pyrimidines Ia-e, IIa, IIIa, IVa, b, Va, VIa, b, VIIa, and VIIIa

Compound	X	R	R^1	R^2	R^3	Empirical formula	M	mp, °C*	R_f	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
Ia	N	H	H	H	H	$C_{11}H_9N_5O_4$	275	280	0,24	1590, 1330 (NO_2) 3450 (OH) 3130 (NH)	6,20 (1H, s, 3′-H); 6,20 (1H, d, 5′-H); 6,60 (1H, s, 7-H); 7,10 (1H, d, 6′-H); 7,70 (1H, s, 2-H); 8,30 (1H, s, 5-H); 9,30 (1H, s, OH); 9,45 (1H, s, OH); 11,80 (1H, br.s NH); $J_{5',6'}$=9 Hz	60
Ib	N	H	OH	H	H	$C_{11}H_9N_5O_5$	291	300	0,32	1590, 1320 (NO_2) 3500 (OH) 3140 (NH)	6,25 (1H, d, 5′-H); 6,60 (1H, s, 7-H); 6,64 (1H, d, 6′-H); 7,65 (1H, s, 2-H); 8,20 (2H, br. s, OH); 8,30 (1H, s, 5-H); 8,40 (1H, s, OH); 9,10 (1H, br. s, NH); $J_{5',6'}$=8,4 Hz	77
Ic	N	H	H	C_6H_{13}	H	$C_{17}H_{21}N_5O_4$	359	261	0,22	1600, 1330 (NO_2) 3440 (OH) 3250 (NH)	0,70...1,50 (13H, m, hexyl); 6,20 (1H, s, 6′-H); 6,65 (1H, s, 3′-H); 6,85 (1H, s, 7-H); 7,65 (1H, s, 2-H); 8,30 (1H, s, 5-H); 9,10 (2H, s, OH); 11,80 (1H, br.s NH)	70
Id	N	H	H	H	OH	$C_{11}H_9N_5O_5$	291	245 dec.	0,30	1610, 1330 (NO_2) 3390 (OH) 3130 (NH)	5,90 (2H, s, 3′-H); 7,30 (1H, s, 7-H); 7,60 (1H, s, 2-H); 8,30 (1H, s, 5-H); 8,80 (1H, br. s, OH); 9,15 (2H, br. s, OH); 11,30 (1H, br.s, NH)	55
Ie	N	H	H	Br	H	$C_{11}H_8BrN_5O_4$	354	>300	0,12	1590, 1320 (NO_2) 3430 (OH) 3080 (NH)	6,40 (1H, s, 6′-H); 6,60 (1H, s, 3′-H); 7,30 (1H, s, 7-H); 7,70 (1H, s, 2-H); 8,35 (1H, s, 5-H); 9,75 (1H, s, OH); 9,90 (1H, br. s, NH); 10,15 (1H, br. s, OH)	47
IIa	N	CH_3	H	H	H	$C_{12}H_{11}N_5O_4$	289	256 dec.	0,20	1595, 1320 (NO_2) 3450 (OH) 3120 (NH)	2,09 (3H, s, CH_3); 6,17 (1H, s, 3′-H); 6,18 (1H, d 5′-H); 6,48 (1H, s, 7-H); 6,97 (1H, d, 6′-H); 8,30 (1H, s, 5-H); 9,30 (1H, s, OH); 9,43 (1H, s, OH); 11,80 (1H, br. s, NH); $J_{5',6'}$=9 Hz	46
IIIa	N	C_2H_5	H	H	H	$C_{13}H_{13}N_5O_4$	304	>300	0,23	1600, 1320 (NO_2) 3460 (OH) 3120 (NH)	1,10 (3H, t, CH_3); 2,50 (2H, q, CH_2); 6,15 (1H, s, 3′-H); 6,60 (1H, s, 7-H); 7,00 (1H, d, 6′-H); 8,30 (1H, s, 5-H); 9,25 (1H, br. s, OH); 6,15 (1H, d, 5′-H); 9,40 (1H, s, OH); $J_{5',6'}$=9 Hz	61
IVa	N	$COOC_2H_5$	H	H	H	$C_{14}H_{13}N_5O_6$	347	232	0,16	1590, 1320 (NO_2) 1740 (CO) 3390 (OH) 3100 (NH)	1,20 (3H, t, CH_3); 4,25 (2H, q, OCH_2); 6,15 (1H, s, 3′-H); 6,20 (1H, d, 5′-H); 6,65 (1H, s, 7-H); 7,10 (1H, d, 6′-H); 8,40 (1H, s, 5-H); 9,60 (2H, br. s, OH); 11,85 (1H, br.s, NH); $J_{5',6'}$=9 Hz	57
IVb	N	$COOC_2H_5$	OH	H	H	$C_{14}H_{13}N_5O_7$	363	279	0,12	1590, 1320 (NO_2) 1745 (CO) 3420 (OH) 3120 (NH)	1,28 (3H, t, CH_3); 4,28 (2H, q, OCH_2); 6,30 (1H, d, 5′-H); 6,65 (1H, d, 6′-H); 6,68 (1H, s, 7-H); 8,40 (1H, s, 5-H); 8,30 (2H, br. s, OH); 8,50 (1H, s, OH); 8,10 (1H, br. s, NH); $J_{5',6'}$=8,4 Hz	94
Va	N	CF_3	H	H	H	$C_{12}H_8F_3N_5O_4$	343	255	0,14	1590, 1320 (NO_2) 3370 (OH) 3090 (NH)	6,17 (1H, s, 3′-H); 6,18 (1H, d, 5′-H); 6,64 (1H, s, 7-H); 7,10 (1H, d, 6′-H); 8,37 (1H, s, 5-H); 9,32 (1H, s, OH); 9,51 (1H, s, OH); $J_{5',6'}$=9 Hz	50
VIa	$CCOOC_2H_5$	H	H	H	H	$C_{15}H_{14}N_4O_6$	346	265	0,25	1590, 1330 (NO_2) 1690 (CO) 3470 (OH) 3270 (NH)	1,30 (3H, t, CH_3); 4,35 (2H, q, OCH_2); 6,20 (1H, s, 3′-H); 6,20 (1H, d, 5′-H); 6,55 (1H, s, 7-H); 7,05 (1H, d, 6′-H); 7,70 (1H, s, 2-H); 8,20 (1H, s, 5-H); 9,30 (1H, s OH); 9,50 (1H, s, OH); $J_{5',6'}$=8.9 Hz	43
VIb	$CCOOC_2H_5$	H	H	$COCH_3$	H	$C_{17}H_{16}N_4O_7$	388	272	0,16	1600, 1330 (NO_2) 1720 (CO) 3340 (OH) 3070 (NH)	1,32 (3H, t, CH_3); 4,38 (2H, q, OCH_2); 3,68 (3H, s, $COCH_3$); 6,25 (1H, s, 6′-H); 6,62 (1H, s, 3′-H); 7,00 (1H, s, 7-H); 7,70 (1H, s, 2-H); 8,25 (1H, s, 5-H); 9,10 (2H, s, OH); 10,80 (1H, br.s, NH)	39
VIIa	CCN	H	H	H	H	$C_{13}H_9N_5O_4$	299	274	0,20	1590, 1320 (NO_2) 3460 (OH) 3170 (NH)	6,28 (1H, s, 3′-H); 6,30 (1H, d, 5′-H); 6,65 (1H, s, 7-H); 6,75 (1H, d, 6′-H); 7,70 (1H, s, 2-H); 8,35 (1H, s, 5-H); 9,0...10,0 (2H, br.s, OH); $J_{5',6'}$=9 Hz	43
VIIIa	CNO_2	H	H	H	H	$C_{12}H_9N_5O_6$	319	>300	0,15	1590, 1320 (NO_2) 3420 (OH) 3100 (NH)	6,20 (1H, d, 5′-H); 6,20 (1H, s, 3′-H); 6,60 (1H, s, 7-H); 7,10 (1H, d, 6′-H); 8,10 (1H, s, 2-H); 8,15 (1H, s, 5-H); 9,40 (1H, br. s, OH); 9,60 (1H, s, OH); 11,30 (1H, br. s, NH); $J_{5',6'}$=9 Hz	48

*The compounds were crystallized: Ia, Ib, IIa, IVb, and Va from butanol, Ic,e, VIa, VIb, VIIa, and VIIIa from dioxane, and IVa from water.

The facts presented above make it possible to propose the participation in the reaction of polyphenols with 6-nitroazolo[1,5-a]pyrimidines of an adduct of the latter with butanol. At the same time, drawing analogies with the well-studied reaction of trinitrobenzene with nucleophile [15-18], including phenols [7-11], makes a substitution mechanism extremely problematic. The acceleration of the reaction in the pesence of alcohol can evidently be explained by preprotonation of adduct IX, which facilitates the subsequent transformation via a dissociative scheme.



EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Perkin—Elmer R-12B spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the purity of the compounds obtained were monitored by means of TLC on Silufol UV-254 plates in a chloroform—ethanol system (10:1) with development in UV light. The results of elementary analysis of I-IX for C, H, and N were in agreement with the calculated values.

6- Nitroazolo[1,5-a]pyrimidines were obtained by the method in [19].

6-Nitro-7-hydroxyaryl-4,7-dihydroazolo[1,5-a]pyrimidines (Ia-e, IIa, IIIa, IVa-b, Va, VIa-b, VIIa, and VIIIa. A 2-mmole sample of azolo[1,5-a]pyrimidine and 2 mmole of the polyphenol were refluxed in 8 ml of butanol for 30 min, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed with ether (30 ml), dried, and crystallized. The characteristics are presented in Table 1.

2-Methyl-6-nitro-7-n-butoxy-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IX, $C_{11}H_{17}N_5O_3$). A 0.36-g (2 mmole) sample of 2-methyl-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine was refluxed in 8 ml of butyl alcohol for 10 min, after which the solution was filtered hot. The filtrate was cooled, and the precipitate was removed by filtration, washed with ether, and dried at room temperature to give 0.49 g (98%) of a product with mp 144°C (from butanol). IR spectrum: 1590, 1320 (NO_2); 3120 cm^{-1} (NH). PMR spectrum: 0.90 (3H, t, CH_3), 1.07-1.30 (4H, m, $2CH_2$), 2.60 (3H, s, CH_3), 3.75 (2H, t, OCH_2), 6.80 (1H, s, 7-H), 8.48 ppm (1H, s, 5-H).

Reaction of 2-Methyl-6-nitro-1,2,4-triazolo[1,5-a] pyrimidine with Resorcinol in Dioxane. A 0.36-g (2 mmole) sample of 2-methyl-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine and 0.22 g (2 mmole) of resorcinol were refluxed in 8 ml of dioxane for 30 min, after which the mixture was evaporated to dryness in vacuo, and the residue was washed with ether. According to the PMR spectral data, the sample obtained contained 30% IIa and 70% starting substrate.

2-Methyl-6-nitro-7-(2,4-dihydroxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IIa). A) A 0.72-g (4 mmole) sample of 2-methyl-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine and 0.44 g (4 mmole) of resorcinol were refluxed in 16 ml of butyl alcohol for 30 min, after which the reaction mass was evaporated to dryness in vacuo, and the residue was washed with ether and dried to give 0.99 g (99%) of a product with mp 256°C.

B) A 0.72-g (4 mmole) sample of 2-methyl-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine and 0.44 g (4 mmole) of resorcinol were refluxed in a mixture of 8 ml of dioxane and 2 ml of butyl alcohol for 30 min, after which the mixture was evaporated to dryness in vacuo, and the residue was washed with ether and dried. The yield was 0.97 g (97%).

C) A 1.02-g (4 mmole) sample of 2-methyl-6-nitro-7-n-butoxy-4,7-dihydro-1,2,4-triazolo-[1,5-a]pyrimidine (IX) and 0.44 g (4 mmole) of resorcinol were refluxed in 16 ml of dioxane for 30 min, after which the mixture was evaporated to dryness in vacuo, and the residue was washed with ether and dried. The yield was 0.97 g (97%).

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