NITROAZINES.

# 8.* REACTIONS OF 6-NITROAZOLO[1,5-*a*]PYRIMIDINES WITH PYRROLES

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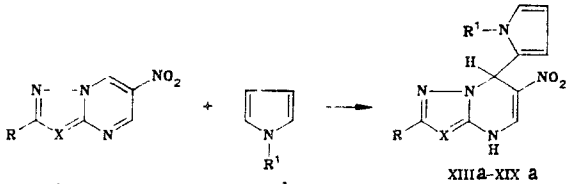
The reactions of 6-nitroazolo[1,5-*a*]pyrimidines with pyrroles have been examined, and the influence of substitution in the azole moiety of the substrate on the course of the reaction studied. The formation of two isomeric sigma-adducts has been established by spectroscopy.

We have previously reported [2] the direct introduction of the indole residue into 6-nitroazolo[1,5-*a*]pyrimidines to give stable sigma-adducts. Some of these compounds have hypotensive activity [3].

In order to establish the scope of this reaction, and in a search for biologically active compounds, we here report the reaction of pyrrole (Ia) and N-methylpyrrole (Ib) with 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines (II)-(VII) and 6-nitropyrazolo[1,5-*a*]pyrimidine (VIII)-(XII), which have a variety of substituents in the azole moiety of the molecule.

Pyrrole and N-methylpyrrole add readily to most of these 6-nitroazolo[1,5-*a*]pyrimidines. From the reaction mixtures there were isolated 6-nitro-7-(2'-pyrrolyl)-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidines (XIII) and (XIV a, b), (XV) and (XVIa), and 6-nitro-7-(2'-pyrrolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidines (XVII a, b), (XVIII), and (XIXa).



II–XII Ia,b XIIIa–XIX a XIIIb, XIVb, XVIIb

II—VII, XIII—XVI X=N; II, XIII R=H; III, XIV R=$CH_3$; IV, XV R=$SCH_3$; V, XVI R=*p*-$C_6H_4NO_2$; VI R=$NH_2$; VII R=$N(CH_3)_2$; VIII, XVII X=$CCOOC_2H_5$, R=H; IX, XI, XII, XVIII X=CH; IX, XVIII R=$C_6H_5$; XI R=H; XII R=$CH_3$; X, XIX X=CBr, R=$CH_3$; I, XIII—XIX a R¹=H; b R¹=$CH_3$

The maximum yields of (XIII)-(XIX) were obtained by boiling the reactants in ethanol for 15 minutes.

The reactivity of the nitropyrimidines (II)-(XII) towards pyrroles depends on the extent of π-deficiency in the system. 6-Nitropyrazolo[1,5-*a*]pyrimidines are capable of adding nucleophiles in the presence of acceptor substituents ($COOC_2H_5$, Br) or a phenyl group in the pyrazole moiety (compounds (VIII)-(X)). The formation of adducts of pyrrole with 6-nitro- or 2-methyl-6-nitropyrazolo[1,5-*a*]pyrimidines (XI) and (XII) could not be confirmed, even by chromatography.

The aza-analogs of 6-nitropyrazolo[1,5-*a*]pyrimidines, namely the 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines (II)-(V), are more reactive, the presence of donor substituents such as $SCH_3$ or $CH_3$ in the 2-position failing to prevent the reaction. However, groups with the +M-effect [$N(CH_3)_2$, $NH_2$] deactivate the system, since 2-amino- and 2-dimethylamino-1,2,4-triazolo[1,5-*a*]pyrimidines (VI) and (VII)) failed to react with pyrroles.

*For Communication 7, see [1].

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TABLE 1. 6-Nitro-7-(2'-pyrrolyl)-4,7-dihydroazolo[1,5-*a*]pyrimidines (XIII)-(XIX)

| Compound | mp, °C (ethanol) | Found, % | | | Empirical formula | Calculated, % | | | IR spectrum, $cm^{-1}$ | PMR spectrum, δ, ppm |
|---|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | | |
| XIIIa | 240 | 46,8 | 3,7 | 26,4 | $C_9H_8N_6O_2$ | 46,5 | 3,4 | 26,2 | 3110, 3300 (NH), 1590, 1325 ($NO_2$) | 5,89 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,58 (1H, m, $H_{(5')}$); 6,60 (1H, s, $H_{(7)}$); 7,68 (1H, s, $H_{(2)}$); 8,34 (1H, s, $H_{(5)}$); 11,00 (1H, s, $H_{(1')}$); 11,65 (1H, s, $H_{(4)}$) |
| XIVa | 226 | 48,6 | 4,1 | 34,2 | $C_{10}H_{10}N_6O_2$ | 48,8 | 4,1 | 34,1 | 3270, 3090 (NH), 1590, 1330 ($NO_2$) | 2,12 (3H, s, C—$CH_3$); 5,88 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,51 (1H, s, $H_{(7)}$); 6,55 (1H, m, $H_{(5')}$); 8,30 (1H, s, $H_{(5)}$); 10,95 (1H, s, $H_{(1')}$); 11,82 (1H, s, $H_{(4)}$) |
| XVa | 218...220* | 43,3 | 3,2 | 30,6 | $C_{10}H_{10}N_6O_2S$ | 43,2 | 3,6 | 30,2 | 3300, 3125 (NH), 1590, 1345 ($NO_2$) | 2,48 (3H, s, S—$CH_3$); 10,86 (1H, s, $H_{(1')}$); 5,90 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,70 (1H, m, $H_{(5')}$); 6,76 (1H, s, $H_{(7)}$); 8,45 (1H, s, $H_{(5)}$); 11,34 (1H, s, $H_{(1)}$) |
| XVIa | 265...267 | 51,4 | 3,5 | 27,5 | $C_{15}H_{11}N_7O_4$ | 51,0 | 3,1 | 27,8 | 3350, 3130 (NH), 1580, 1340 ($NO_2$), 1595, 1330 ($NO_2$) | 5,80 (2H, m $H_{(3')}$, $H_{(4')}$); 6,55 (1H, m, $H_{(5')}$); 6,58 (1H, s, $H_{(7)}$); 8,30 (4H, m, $C_6H_4$); 8,40 (1H, s, $H_{(5)}$); 10,95 (1H, s, $H_{(1')}$); 11,68 (1H, s, $H_{(4)}$) |
| XVIIa | 215...217 | 51,5 | 4,7 | 23,2 | $C_{13}H_{13}N_5O_4$ | 51,6 | 4,3 | 23,1 | 3345, 3140 (NH), 1590, 1330 ($NO_2$), 1710 (CO) | 1,28 (3H, t, C—$CH_3$); 4,23 (2H, q, $OCH_2$); 5,85 (2H, m, $H_{(3')}$ $H_{(4')}$); 6,50 (1H, m, $H_{(5')}$); 6,55 (1H, s, $H_{(7)}$); 7,62 (1H, s, $H_{(2)}$); 8,12 (1H, s, $H_{(5)}$); 10,65 (1H, s, $H_{(1')}$); 10,95 (1H, s, $H_{(4)}$) |
| XVIIIa | 252 | 63,0 | 4,5 | 22,4 | $C_{15}H_{13}N_5O_2$ | 62,6 | 4,2 | 22,8 | 3300, 3150 (NH), 1600, 1340 ($NO_2$) | 5,85 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,30 (1H, m, $H_{(5')}$); 6,60 (1H, s, $H_{(7)}$); 7,60 (5H, m, $C_6H_5$); 8,45 (1H, s, $H_{(5)}$); 11,00 (1H, s, $H_{(1')}$); 11,40 (1H, s, $H_{(4)}$) |
| XIXa | 200...202 | 40,6 | 3,6 | 21,1 | $C_{11}H_{10}N_5O_2Br$ | 40,7 | 3,1 | 21,6 | 3250, 3100 (NH), 1600, 1345 ($NO_2$) | 2,10 (3H, s, C—$CH_3$); 6,65 (1H, s, $H_{(7)}$); 5,80 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,50 (1H, m, $H_{(5')}$); 8,45 (1H, s, $H_{(5)}$); 10,95 (1H, s, $H_{(1')}$); 11,62 (1H, s, $H_{(4)}$) |
| XIIIb | 245...246* | 49,1 | 4,1 | 34,2 | $C_{10}H_{10}N_6O_2$ | 48,8 | 4,1 | 34,1 | 3140 (NH), 1590, 1320 ($NO_2$) | 3,80 (3H, s, N—$CH_3$); 5,85 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,63 (1H, m, $H_{(5')}$); 6,77 (1H, s, $H_{(7)}$); 7,70 (1H, s, $H_{(2)}$); 8,40 (1H, s, $H_{(5)}$); 11,80 (1H, s, $H_{(4)}$) |
| XIVb | 260...262* | 50,4 | 4,6 | 32,1 | $C_{11}H_{12}N_6O_2$ | 50,8 | 4,6 | 32,3 | 3200 (NH), 1595, 1335 ($NO_2$) | 2,15 (3H, s, C—$CH_3$); 3,86 (3H, s, N—$CH_3$); 6,70 (1H, s, $H_{(7)}$); 5,85 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,60 (1H, m, $H_{(5')}$); 8,40 (1H, s, $H_{(5)}$); 11,87 (1H, s, $H_{(4)}$) |
| XVIIb | 208...210* | 53,3 | 4,7 | 22,1 | $C_{14}H_{15}N_5O_4$ | 53,0 | 4,7 | 22,1 | 3400 (NH), 1600, 1340 ($NO_2$), 1670 (CO) | 1,28 (3H, t, C—$CH_3$); 3,81 (3H, s, N—$CH_3$); 4,25 (2H, q, $OCH_2$); 5,80 (2H, m, $H_{(3')}$, $H_{(4')}$); 6,60 (1H, m, $H_{(5')}$); 6,72 (1H, s, $H_{(7)}$); 7,70 (1H, s, $H_{(2)}$); 8,18 (1H, s, $H_{(5)}$); 11,55 (1H, s, $H_{(4)}$) |

*From aqueous DMSO.

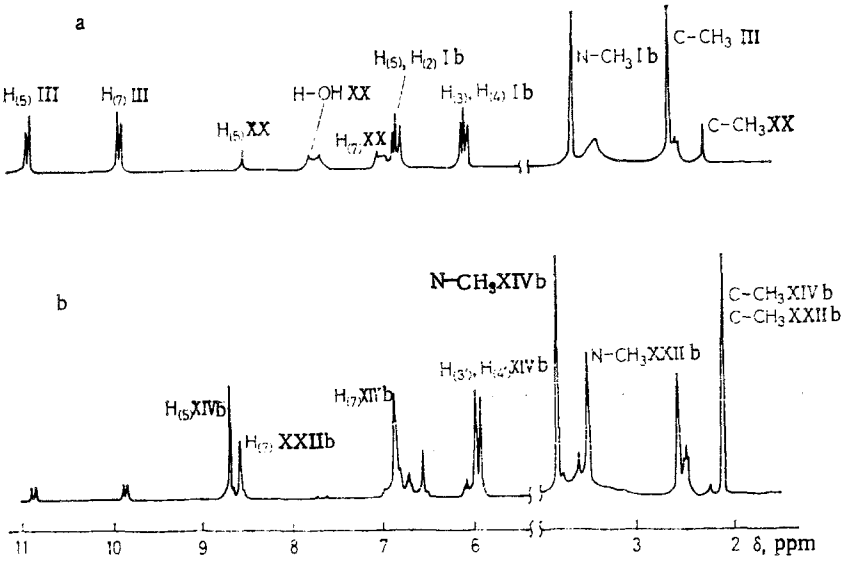


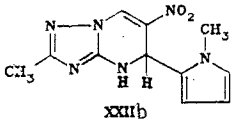

Fig. 1. PMR spectrum of a mixture of 2-methyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine with N-methylindole: a) at 35°C in DMSO-$D_6$; b) after heating for 15 min at 100°C.

The structures of the 2-R-6-nitro-7-(2'-pyrrolyl)-4,7-dihydroazolo[1,5-*a*]pyrimidines (XIII)-(XIX) were confirmed by their IR and PMR spectra.

The IR spectra of (XIII)-(XIX) (Table 1) showed absorption for stretching vibrations of the $NO_2$ group (1325-1345, 1600-1580 $cm^{-1}$) and of NH (3090-3400 $cm^{-1}$). In the spectra of (XVIIa, b), absorption was seen for the carbonyl group (1670-1710 $cm^{-1}$). The 4,7-dihydro-structure of (XIII)-(XIX) followed from a comparison of their PMR spectra with those of 6-nitro-7-indolyl-4,7-dihydroazolo[1,5-*a*]pyrimidines [2]. The signals for the protons of the pyrimidine moiety of the molecule were seen as two singlets at 8.30 ppm [$H_{(5)}$] and 6.60 ppm [$H_{(7)}$]. As reported in [4], the multiplet signals at 6.50 ppm were assigned to $H_{(5)}$ resonance, and those at 5.80 ppm to protons $H_{(3)}$ and $H_{(4)}$ of the pyrrole moiety, confirming the α-disposition of the pyrrole substituent in these compounds. The broadened singlet at 10.60-11.00 ppm in the spectra of (XIII)-(XIXa), and the absence of such a signal in the spectra of (XIII), (XIV), and (XVIIb), which contain the N-methylpyrrole residue, show that this signal corresponds to resonance for the pyrrole NH proton. In addition, the spectra of all the 6-nitro-7-pyrrolyl-4,7-dihydroazolo[1,5-*a*]pyrimidines show singlets for the NH protons of the dihydropyrimidine moiety at 11.30-11.87 ppm, together with signals corresponding to resonance of the substituents in the azole moiety of the molecule (Table 1).

Another site sensitive to nucleophilic attack in the 6-nitroazolo[1,5-*a*]pyrimidine system is $C_{(5)}$. Since pyrrole is a harder compound than indole [5], in this instance the formation of isomeric products would be expected.

PMR spectroscopy was used to examine the mixture obtained in the cell of the spectrometer by reacting 2-methyl-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine (III) with N-methylpyrrole in DMSO-$D_6$. The spectrum of these compounds (Fig. 1, a), taken in equimolar amounts at 35°C contained, in addition to the signals for the starting materials (Ib) and (III), signals for 2-methyl-6-nitro-7-hydroxy-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (XX), which is formed readily [3, 5] in the presence of water containing DMSO-$D_6$. After heating the reactants for 15 minutes at 100°C (Fig. 1, b), signals appeared corresponding to 2-methyl-6-nitro-7-(1-methyl-2'-pyrrolyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (XIVb), together with new signals, examination of the chemical shifts and integral intensities of which showed that they were attributable to the isomeric adduct 2-methyl-5-(1-methyl-2'-pyrrolyl)-6-nitro-4,5-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (XXIIb).




XXIIb

TABLE 2. Results of the Reaction of 6-Nitroazolo[1,5-*a*]pyrimidines with Pyrroles according to PMR Spectroscopy

| Reactants | Yields of adducts under reaction conditions | |
|---|---|---|
| | DMSO-$D_6$, 100°C, 15 min | ethanol, 78°C, 15 min |
| Ia+II | 50% XIIIa; 35% XXIa | 73% XIIIa; 23% XXIa |
| Ia+III | 56% XIVa; 24% XXIIa | 78% XIVa; 18% XXIIa |
| Ia+IV | 49% XVa; 26% XXIIIa | 76% XVa; 14% XXIIIa |
| Ia+V | 62% XVIa; 30% XXIVa | 80% XVIa; 17% XXIVa |
| Ia+VIII | 58% XVIIa; 27% XXVa | 70% XVIIa; 22% XXVa |
| Ia+IX | 48% XVIIIa; 21% XXVIa | 75% XVIIIa; 15% XXVIa |
| Ia+X | 59% XIXa; 34% XXVIIa | 78% XIXa; 21% XXVIIa |
| Ib+II | 47% XIIIb; 28% XXIb | 82% XIIIb; 10% XXIb |
| Ib+III | 53% XIVb; 37% XXIIb | 84% XIVb; 12% XXIIb |
| Ib+VIII | 65% XVIIb; 22% XXVb | 80% XVIIb; 18% XXVb |

The signals at 8.32 ppm [1H, s, $H_{(7)}$], 3.50 ppm (3H, s, N–$CH_3$), and 2.15 ppm (3H, s, C–$CH_3$) are attributed to resonance of the protons in (XXIIb). In view of the integral spectrum at 5.85-6.75 ppm, it may be assumed that in addition to the signals for $H_{(7)}$, $H_{(5')}$, $H_{(3')}$, and $H_{(4')}$, in (XIVb), the $H_{(5)}$, $H_{(5')}$, $H_{(3')}$, and $H_{(4')}$ protons of (XXIIb) also resonate in this region. The correctness of this assumption is confirmed as follows. The mixture obtained by carrying out the reaction in DMSO gives satisfactory elemental analyses for a reactant–substrate ratio of 1:1, and the PMR spectrum of this sample shows a set of signals for the two isomers (XIVb) and (XXIIb). It was not found possible to separate this mixture, either by chromatography or by fractional crystallization. Comparison of the integral intensities of the signals for $H_{(5)}$ and $H_{(7)}$ in the starting material (III) and the products (XIVb) and (XXIIb) enables the extent of reaction of (III) and the yields of the 5- and 7-isomers ((XIVb) and (XXIIb) respectively) to be found. Similarly, the yields of adducts obtained on reacting pyrroles with other azolopyrimidines in DMSO were found (Table 2). To determine the yields of the addition products of pyrroles (Ia) and (Ib) and 6-nitroazolo[1,5-*a*]pyrimidines (II-V) and (VIII-X) when the reaction was carried out in other solvents, the mixtures were evaporated to dryness, and their composition established by PMR analysis following washing with ether. It was found that in alcohol, almost complete reaction of the reactants occurred, with preferential formation of the 7-isomer (Table 2), whereas the reaction of (Ib) with (III) in dioxane gave a much lower yield of products (23% of (XIVb) and 11% of (XXIIb)).

On examining the reaction of 6-nitroazolo[1,5-*a*]pyrimidines with pyrroles, we have for the first time observed the formation of sigma-adducts not only in the 7-position, as reported previously for the reaction with indoles, but also in the 5-position of 6-nitroazolo[1,5-*a*]pyrimidines. The overall yields of isomers, and the preferred site of attack of the nucleophile are dependent on the solvent used.

## EXPERIMENTAL

IR spectra were obtained on a UR-20 in vaseline oil, and PMR spectra on a Bruker spectrometer (80 MHz) in DMSO-$D_6$, internal standard TMS.

6-Nitroazolo[1,5-*a*]pyrimidines (II-VII) and (VIII-XII) were obtained as described in [6].

6-Nitro-7-(2'-pyrrolyl)-4,7-dihydroazolo[1,5-*a*]pyrimidines (XIIIa-XIXa), (XIIIb), (XIVb), and (XVIIb) (Table 1). A mixture of 0.01 mole of the 6-nitroazolo[1,5-*a*]pyrimidine (II-V) or (VIII-X) with an equimolar amount of the pyrrole in 20 ml of ethanol was boiled for 15 minutes. The mixture was then cooled, washed with 20 ml of ether, dried, and thrice recrystallized from ethanol or aqueous DMSO.

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# DETERMINATION OF THE CONFORMATION OF MACROCYCLIC 1,8,9,20-TETRAHYDRO-3,6,9-TRIMETHYL-1,8-DIPHENYLDIBENZO[c,m]DIPYRAZOLO[3,4-f:4',3'-j]-[1,2,5,8,9,12]HEXAAZACYCLOTETRADECENE

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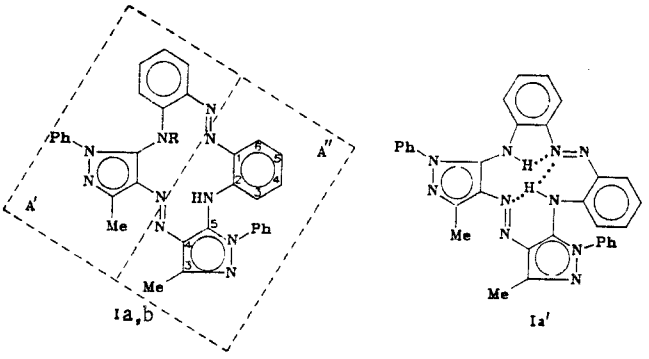
The conformation of the macrocyclic skeleton of 1,8,9,20-tetrahydro-3,6,9-trimethyl-1,8-diphenyldibenzo[c,m]dipyrazolo[3,4-f:4',3'-j][1,2,5,8,9,12]-hexaazacyclotetradecene was determined by means of the $^{13}C$ NMR spectra with respect to the known conformations of the macrocyclic skeleton in isomeric Ni(II) complexes of 1,8,9,20-tetrahydro-3,6-dimethyl-1,8-diphenyldibenzo[c,-m]dipyrazolo[3,4-f:4',3'-j][1,2,5,8,9,12]hexaazacyclotetradecene.

The molecular and crystal structure of 1,8,9,20-tetrahydro-3,6-dimethyl-1,8-diphenyl-dibenzo[c,m]dipyrazolo[3,4-f:4',3'-j][1,2,5,8,9,12]hexaazacyclotetradecene (Ia) has been previously established by various methods [1, 2].




I a R=H; b R=$CH_3$; Ia′ crystal structure

According to the IR spectral data, the conformations of the macrocyclic skeleton of Ia differ in the solid state and in solution. Only one of the three intramolecular hydrogen bonds (IMHB), viz., the one that forms a six-membered ring condensed with a pyrazole ring, that are observed in the crystal is retained in solution. However, the conformation of Ia in solution could not be investigated in greater detail because of exchange processes and the associated broadening of the resonance signals in the $^1H$ and $^{13}C$ NMR spectra. The NMR spectra of the mono-N-methyl derivative (Ib) of the ligand do not have this complication; this made it possible to make a more thorough study of the conformation of its macrocyclic skeleton in solution.

The signal of the proton of the NH group tied up by an IMHB in solution in $CDCl_3$ is observed at weaker field (12.10 ppm) for Ib than for Ia (11.78 ppm [1]); this constitutes evidence for a stronger NH...N IMHB in Ib. This is also confirmed by a comparison of the

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