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SPIRO[4-AZAFLUORENEPYRAZOLENINES] AND THEIR THERMAL REARRANGEMENT TO PYRAZOLOAZAPHENANTHRENES

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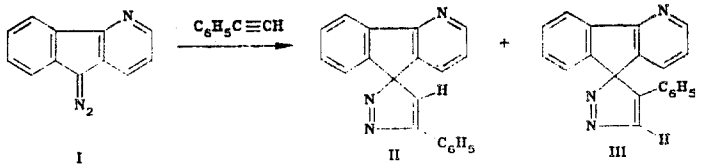
Reaction of 9-diazo-4-azafluorene with phenylacetylene gives spiro[4-azafluorene-9,3'-pyrazolenines], isomeric according to the position of the substituent in the pyrazolenine ring. Their thermal rearrangement to pyrazolo-4-azaphenanthrenes that are isomeric according to ring linkage and position of the substituent in the pyrazole ring has been studied.

The 1,3-dipolar cycloaddition of α,α-disubstituted diazo compounds to alkynes is a method for synthesizing pyrazolenines (3H-pyrazoles). However, in many cases it is not the initial adducts which are separated but products derived from subsequent rearrangement of them – 1H-pyrazoles [1]. The rearrangement of pyrazolenines with a spiro structure proceeds with particular ease [2]. Thus, when 9-diazofluorene is reacted with phenylacetylene, only the product from rearrangement of the initial spiro[fluorene-9,3'-pyrazolenine] is formed, namely, 2H-3-phenylphenanthro[9,10-d]pyrazole [3]. The presence of strong electron-withdrawing substituents at the 4- and 5-positions of the pyrazolenine fragment stabilizes spiropyrazolenines [4]. There is no information in the literature about the effect of substituents in the diazo compound on the stability of the spiropyrazolenines formed.

With the object of synthesizing new spiro compounds containing azafluorene and diazole fragments, we have studied the reaction of 9-diazo-4-azafluorene (1) [5] with phenylacetylene. We attempted to determine the effect of the nitrogen atom in the azafluorene fragment on the stability of the spiroazafluorenepyrazolenines formed and the direction of their thermal rearrangement to isomeric pyrazoloazaphenanthrenes.

The reaction of diazo compound I with phenylacetylene was carried out at 20°C. A 70% yield was obtained for a mixture of 5'- and 4'-phenylspiro[azafluorene-9,3'-pyrazolenines] (II and III), from which compounds II and III were obtained in the ratio 6:1 by chromatographic separation.



I II III

The position of the phenyl substituent in the pyrazolenine fragment of compounds II and III was established from the signal of the pyrazolenine proton in their PMR spectra (Table 1). The shift downfield by 1.38 ppm by the signal from this proton in compound III relative to compound II is due to the electron-withdrawing effect of the nitrogen atom in the pyrazolenine fragment. The predominant formation of isomer II is probably due to steric factors [6]. Rearrangement of compounds II and III to the tautomeric pyrazole form, as often occurs when similar reactions are carried out, does not take place during the reaction.

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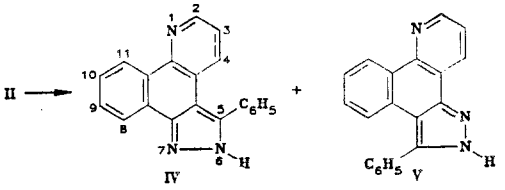
TABLE 1. PMR Spectra of Spiro[4-azafluorene-9,3'-pyrazolenines] II and III

Compound	Chemical shifts, δ, ppm (80 MHz, $CDCl_3$)								
	1-H	2-H	3-H	5-H	6-H	7-H	8-H	C—H*	C_6H_5
II	7,06	7,12	8,65	8,16	7,54	7,53	6,94	6,94	7,50...8,10
III	7,15	7,00	8,67	8,23	7,57	7,32	6,80	8,42	7,10...8,06

*Pyrazolenine.

The driving force of such [1,5]-sigmatropic rearrangements of pyrazolenines is the formation of energetically more favorable pyrazoles. The rearrangement of spiropyrazolenines proceeds as a 1,2-migration of the substituent from the 3-position either to the nitrogen atom or to the 4-position. In a number of cases both rearrangement routes occur at the same time. When the substituent migrates to the $N_{(2')}$ atom, pyrazolopyridines are formed. Migration of the radical to the 4-position is generally accompanied by the simultaneous shift of hydrogen or the substituent situated on $C_{(4)}$ to the nitrogen atom, which leads to the formation of annelated compounds with a 1H- or 1R-pyrazole fragment [2].

During thermal rearrangement of spiropyrazolenine II, two compounds are obtained, which have different melting points and chromatographic mobility.



In the IR spectra of compounds IV and V there are stretching vibrational bands at 3160 and 3200 cm^{-1} respectively due to hydrogen bonded N—H groups. The peak with maximum intensity in their mass spectra is that due to the molecular ion with m/z 295. In contrast to the fragmentation of the M^+ ion of compound II where the predominant decomposition route is expulsion of a nitrogen molecule to form an ion with m/z 267 (100%), the value of the peak from this ion in the mass spectra of rearrangement products IV and V does not exceed 3%. It can be assumed from these findings that compounds IV and V have the structure of pyrazolo-4-azaphenanthrene with phenyl substitution in the pyrazole ring. The position of the phenyl radical in the pyrazole fragment of rearrangement products IV and V was established with the help of the PMR spectra (Table 2) from the values of the chemical shifts of the 4-H and 8-H protons in the azaphenanthrene part of the molecule. When there is a cis configuration, the signals from these protons must be shifted upfield because of the magnetic anisotropy of the phenyl group. Therefore, compound IV, which has the signal from the 4-H proton at higher field can be assigned the structure of 5-phenylpyrazolo[3,4-ℓ]-4-azaphenanthrene, and compound V, with the 8-H proton signal at higher field, has the structure of 7-phenylpyrazolo-[4,3-ℓ]-4-azaphenanthrene. The formation of approximately equal quantities of compounds IV and V indicates that during thermal [1,5]-sigmatropic rearrangement of spiropyrazolenine II, migration of the phenyl or pyridine fragment of the 4-azafluorene molecule to the $C_{(4)}$ atom of the pyrazolenine ring occurs with equal probability.

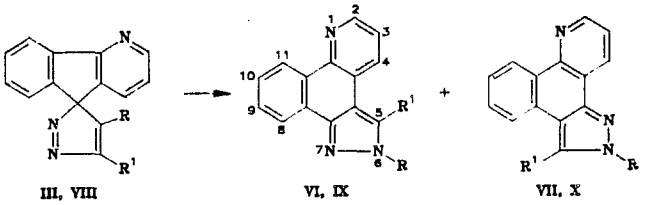
The rearrangement of 4'-phenylspiro[4-azafluorene-9,3'-pyrazolenine] (III) proceeds in a similar manner to give 6-phenylpyrazolo[3,4-ℓ]-4-azaphenanthrene (VI) and 6-phenylpyrazolo-[4,3-ℓ]-4-azaphenanthrene (VII), while that of the previously reported 4',5'-dimethoxycarbonylspiro[4-azafluorene-9,3'-pyrazolenine] (VIII) [5] goes to 5,6-dimethoxycarbonylpyrazolo[4,3-ℓ]-4-azaphenanthrene (IX). In the first case rearrangement is accompanied by migration of the phenyl group to nitrogen, while in the second case the methoxycarbonyl group migrates similarly. This is confirmed by the absence of a band due to stretching vibrations of the N—H bond in the IR spectra of a mixture of compounds VI and VII and by the appearance of a band at 1700 cm^{-1} due to vibrations of the C=O bond in the $N—COOCH_3$ group in the spectrum of compounds IX and X.

TABLE 2. PMR Spectra of Pyrazoloazaphenanthrenes IV-VII, IX, X

Compound	Chemical shifts, δ, ppm (400 MHz, $CDCl_3$)							
	2-H	3-H	4-H	8-H	9-H	10-H	11-H	others
IV	8,79	7,26	8,28	8,21	7,4...8,0		9,23	—
V	8,95	7,3...7,8	8,62	7,98	7,3...7,8		9,23	—
VI*	8,84	7,35	8,26	8,60	7,44...7,80		9,01	7,98 (5-H)
VII*	8,82	7,44...7,80	8,86	7,98	7,44...7,80		9,03	7,89 (5-H)
IX†	8,99	7,58	9,20	8,68	7,80	7,68	9,06	4,03; 4,056 ($COOCH_3$)
X	8,91	7,64	8,95	8,60	7,71	7,78	9,09	4,05; 4,062 ($COOCH_3$)

*Mixture of compounds VI and VII (2:1).
†Mixture of compounds IX and X (1.4:1).

It was not possible to separate the derived mixtures of compounds VI and VII and also IX and X into pure isomers. Their spectral properties (Table 2) confirm their structure and rearrangement route.



III, VI, VII R=C_6H_5, R¹=H; VIII, IX, X R=R¹=$COOCH_3$

In the mass spectra of the mixtures of pyrazoloazaphenanthrenes VI and VII, IX and X the peaks from the molecular ions with m/z 295 and 335 respectively occur with maximum intensity. There are no fragment ions that correspond to loss of nitrogen molecule from the M^+ ion as takes place in the mass spectra of the spiroazafluorenepyrazolenines.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrometer in the form of KBr pellets. PMR spectra (in $CDCl_3$) were recorded on Bruker WP-80 and Bruker WH-360 spectrometers with TMS as internal standard.

Mass spectra were recorded on an MX-1303 mass spectrometer using direct introduction of the sample into the ionization zone, with ionizing radiation of 70 eV. Column and thin layer chromatography were performed on silica gel L 100/160 μm and Silufol UV-254.

The PMR spectral data are given in Tables 1 and 2.

5'-Phenyl- and 4'-Phenylspiro[4-azafluorene-9,3'-pyrazolenines] (II, III). A solution of 0.4 g (2 mmoles) of diazo compound I in 3 ml of phenylacetylene was kept for 3 weeks at 20°C. The precipitate (0.3 g) of spiro compound II that formed was filtered off, yellowish crystals, mp 143-145°C (from heptane). Found, %: C 81.0; H 4.6; N 14.3; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295.

After the excess phenylacetylene had been distilled off under vacuum, the residue was chromatographed on a column of alumina (h = 40 cm, d = 1 cm), with a mixture of heptane and ethyl acetate (10:1) as elution agent. At first 0.03 g of spiro compound II was eluted, R_f 0.47 (hexane–ethyl acetate, 3:1), total yield 60%. Then 60 mg (10%) of spiro compound III was eluted, colorless crystals, mp 163-165°C (from heptane), R_f 0.25 (heptane–ethyl acetate, 3:1). Found, %: C 81.7; H 4.4; N 14.5; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295.

5-Phenylpyrazolo[3,4-ℓ]- and 7-Phenylpyrazolo[4,3-ℓ]-4-azaphenanthrenes (IV, V). Spiro compound II (0.5 g, 1.69 mmole) was heated for 30 min at 140-150°C in a current of nitrogen (monitored by TLC). The black reaction mixture was chromatographed on a column (h = 45 cm, d = 2 cm), with a mixture of heptane and ethyl acetate (10:1) as elution agent. At first 0.1 g (20%) of compound IV was eluted, white crystals, mp 233-235°C (from heptane), R_f 0.5

(ethyl acetate–heptane, 1:1). Found, %: C 81.3; H 4.6; N 14.5; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295. Then 0.1 g (20%) of compound V was eluted, yellowish crystals, mp 188-190°C, R_f 0.33 (ethyl acetate–heptane, 1:1). Found, %: C 81.2; H 4.5; N 13.9; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2; M 295.

6-Phenylpyrazolo[3,4-ℓ]- and -[4,3-ℓ]-4-azaphenanthrenes (VI, VII). Spiro compound III (40 mg, 0.14 mmole) was heated for 30 min at 160-165°C in a current of nitrogen (monitored by TLC). The black reaction mixture was chromatographed on a column of silica gel (h = 35 cm, d = 1.5 cm), with a mixture of hexane and ethyl acetate (5:1) as elution agent. A mixture (15 mg, 37%) of compounds VI and VII was isolated, mp 215-217°C (from heptane), R_f 0.4 (ethyl acetate–heptane, 1:1). Found, %: N 14.4; M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: N 14.2; M 295.

5,6-Dimethoxycarbonylpyrazolo[3,4-ℓ]- and 6,7-Dimethoxycarbonyl pyrazolo[4,3-ℓ]-4-azaphenanthrenes (IX, X). Spiro compound VIII (0.25 g, 7 mmoles) was heated for 30 min at 120-130°C in a current of nitrogen. Chromatography on a column of silica gel (h = 40 cm, d = 1.5 cm) with a mixture of heptane and ethyl acetate (3:1) as elution agent resulted in isolation of 50 mg (20%) of a mixture of compounds IX and X, yellowish crystals, mp 148-150°C (from heptane), R_f 0.36. Found, %: N 12.3; M^+ 335. $C_{18}N_{13}N_3O_4$. Calculated, %: N 12.5; M 335.

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ALKYLATION OF ALLOPURINOL AND INOSINE WITH DIMETHYLFORMAMIDE DIMETHYLACETAL OR DIETHYLACETAL

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The alkylation of allopurinol and inosine with dimethylformamide (DMF) dimethylacetal and diethylacetal was studied. Allopurinol is alkylated in both the pyrazole and pyrimidine rings. 1,5- and 2,5-Dimethyl derivatives are formed in the case of methylation. 1,5- and 2,5-Diethyl derivatives, as well as 1-ethyl-4-ethoxypyrazolo[3,4-d]pyrimidine, were obtained in the ethylation of allopurinol. The yields of the 1,5-substituted compounds are highest in both cases. The alkylation of inosine with DMF diethylacetal takes place in the 1 and 6 positions.

The N-alkylation of nitrogen heterocycles with acetals of amides in a number of cases is an effective and convenient method for obtaining the corresponding alkyl derivatives [1]. Recently we and a number of foreign authors described the use of DMF dialkylacetals for the alkylation of substituted pyrazoles [2], 1,2,3-triazoles [3], pyrazolo[3,4-d]pyrimidines [4], benzimidazoles and 1,2,4-triazoles [5], and uridine and its analogs [6]. The further development of this research seems of interest.

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