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PYRAZOLO-4-AZAPHENANTHRENES

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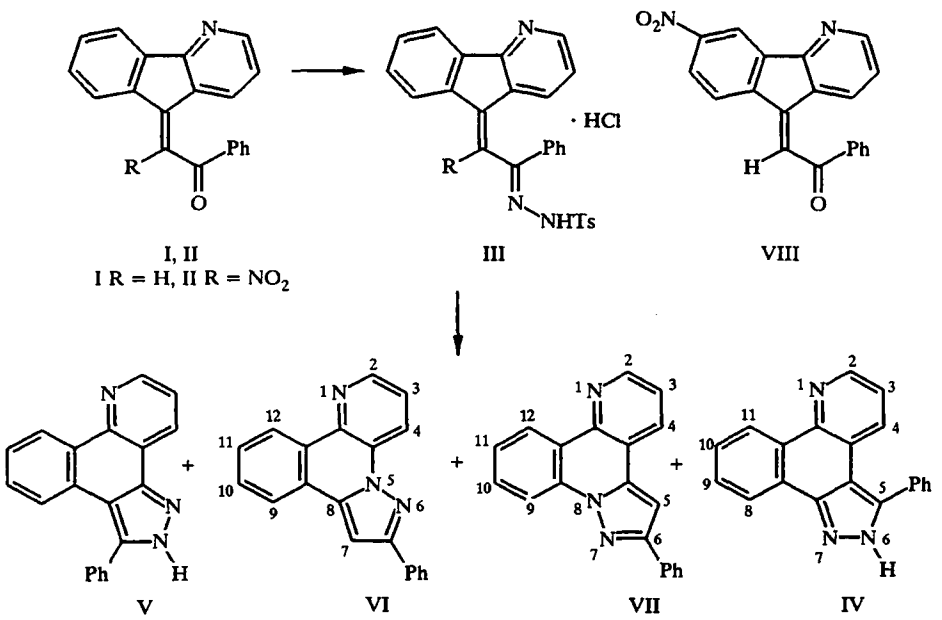
A mixture of phenyl substituted pyrazolo-4-azaphenanthrenes with different closure of the heterocyclic units was obtained by alkaline scission of 9-phenacylidene-4-azafluorene tosylhydrazone. Elimination of the nitro group occurs when 9-(α-nitrophenacylidene)-4-azafluorene is condensed with tosylhydrazine.

1,3-Dipolar cycloaddition of diazocompounds with alkenes and alkynes is widely used for the synthesis of pyrazolines and pyrazoles [1]. In general the initial cycloaddition adduct undergoes rearrangement to give, most commonly, 1H-pyrazoles [2]. This type of rearrangement is most characteristic for adducts with spiro structures [3, 4]. However 4'- and 5'-phenyl(4',5'-dimethoxycarbonyl)spiro[4-azafluoren-9,3'-pyrazolenines], prepared from 9-diazo-4-azafluorene and phenylacetylene or ethyl acetylenedicarboxylate [5], appear to be stable compounds. Their thermal rearrangement into isomers of pyrazolo[3,4-*l*]- and -[4,3-*l*]4-azaphenanthrenes occurs only at 140-150°C. 5'-Phenylspiro(10,10-dimethyl-9,10-dihydro-10-sila-2-azaanthracene-9,3'-pyrazolenine), synthesized by scission of the tosylhydrazone of 9-phenacyliden-10,10-dihydro-10-sila-2-azaanthracene with sodium isopropoxide in boiling benzene, also appears to be stable [6].

In order to determine the synthetic limits of this method for the preparation of the corresponding tosylhydrazones and their conversions we have used 9-phenacyliden- and 9-(α-nitrophenacyliden)-4-azafluorenes (I and II) as starting materials.



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Compounds I and II condensed with tosylhydrazine in acid media. The tosylhydrazones were isolated from the reaction mixture as hydrochlorides in 84 and 57% yields respectively.

Reaction of ketone II with tosylhydrazine occurred with loss of the nitro group as indicated by the absence of intensive absorption bands at 1555-1510 and 1365-1335 cm^{-1} in the IR spectrum of the condensation product. Evidently the product isolated is the hydrochloride of the tosylhydrazone of an isomer of compound I (III). Its IR spectrum has a band at 2700-2450 cm^{-1}, ascribed to the NH^+ stretch, and in its ^1H NMR spectrum (DMSO-d_6) there is a singlet for the 10-H proton at 7.49 ppm and a single doublet of doublets for the 3-H proton with a chemical shift of 8.56 ppm and coupling constants $J_{2,3}$ = 5.2, $J_{1,2}$ = 1.2 Hz. In the spectrum of the hydrochloride of the tosylhydrazone III, obtained from compound I, there are two doublets of doublets for proton 3-H at 8.60 and 8.78 ppm ($J_{2,3}$ = 5.2, $J_{1,2}$ = 1.2 Hz) with an intensity ratio of ~2:1.

The free bases were obtained by treating the hydrochloride III with soda. Both hydrochlorides of the tosylhydrazones underwent alkaline scission with sodium isopropoxide in boiling absolute benzene. In both cases complex reaction mixtures were formed and the expected cycloaddition products – spiro(4-azafluoren-pyrazolenines) – were absent. 5-Phenylpyrazolo[3,4-*l*]- (IV), 7-phenylpyrazolo[4,3-*l*]-4-azaphenanthrene (V), 7-phenylpyrazolo[5,1-*l*]- (VI), and 6-phenylpyrazolo[5,1-*l*]-4-azaphenanthrene (VII) were isolated from the reaction mixture by chromatography.

Compounds IV and V are identical in physico-chemical and spectroscopic characteristics with samples prepared previously [7]. The relative positions of the ^1H NMR signals of compounds IV and V (Table 1) coincide completely with spectra published previously. Systematic differences in the chemical shifts of no more than 0.1 ppm may be linked with concentration effects and difference in temperatures when the spectra were recorded.

The pyrazoloazaphenanthrenes VI and VII have been obtained for the first time. Note that the pyrazolo-azaphenanthrene VII was not obtained from the scission of the tosylhydrazone obtained from α-nitrophenacyliden-4-azafluorene. However in this case the *E*-isomer of 6-nitro-9-phenacyliden-4-azafluorene (VIII) was isolated from the reaction mixture (1.3% yield). Evidently this compound is a byproduct of the nitration of 9-phenacyliden-4-azafluorene which was not observed in the ^1H NMR spectrum of the nitration products because of its small concentration.

The structures of the pyrazoloazaphenanthrenes VI and VII were established from the ^1H NMR spectra by pair-wise comparison of the chemical shifts for the 4-H and 9-H protons in the azaphenanthrene fragment of the molecules [5]. If $N_{(6)}$ or $N_{(7)}$ is close to these protons the signals of the 4-H and 9-H protons should shift to weak field under the influence of the unshared electron pairs of the pyrazole rings nitrogen atoms. On this basis the pyrazolo[5,1-*l*]-4-azaphenanthrene structure was proposed for compound VI which has the weaker field signal for 4-H at 8.90 ppm (8.35 ppm for compound VII), while the pyrazolo[1,5-*l*]-4-azaphenanthrene structure was proposed for compound VII with the weaker field signal for 9-H at 8.65 ppm (8.11 ppm for compound VI).

The ^1H NMR spectrum of compound VIII contains six sharp signals, three of which can be assigned to protons 1-H, 2-H, and 3-H of the pyridine fragment of the molecule from their chemical shifts – 7.52, 7.23, and 8.67 ppm – and their characteristic coupling constants (J_{12} = 7.9, J_{23} = 4.9, and J_{13} = 1.5 Hz) (confirmed by {3-H} double resonance). The singlet of proton 10-H occurred at 7.49 ppm. A comparison of the chemical shifts of protons 1-H and 10-H with those of the analogous protons for the *E*- (7.99 and 7.55 ppm) and *Z*-isomers (8.72 and 7.77 ppm) of 9-phenacylidene-4-azafluorene permits the conclusion that compound VIII has the *E*-configuration. The presence in the spectrum of compound VIII of a doublet with ^4J = 2.1 Hz (9.05 ppm) and a doublet with ^3J = 8.5 and ^4J = 2.1 Hz (8.23 ppm) shows that the nitro group can only be on either $C_{(6)}$ or $C_{(7)}$. Considering that the increment on chemical shifts caused by the nitro group for *ortho*-protons in the aromatic system Δ(*ortho*) = 0.95 ppm [8], it may be assumed that the nitro group in compound VIII is at $C_{(6)}$. Thus the chemical shifts, δ_5 = 8.93 and δ_7 = 8.28 ppm, calculated from the known values of the chemical shifts for 5-H (7.98 ppm) and 7-H (7.33 ppm) of the *E*-isomer of 9-phenacylidene-4-azafluorene and the Δ(*ortho*) shift, are close to the observed values (Table 1). If the nitro group were at $C_{(7)}$, the doublet for proton 8-H and the doublet of doublets of 6-H would be shifted to 9.24 and 8.43 ppm respectively, i.e., considerably different from those measured in the spectrum of compound VIII. We note that the corresponding calculation of the chemical shift of proton 8-H *via* the incremental effect of the nitro group on the *meta* proton, Δ(*meta*) = 0.26 ppm [8], gave a value of 8.55 ppm, whereas in the actual spectrum the

TABLE 1. ^{1}H NMR Spectra of the Pyrazolo-4-azaphenanthrenes IV–VI and 6-Nitro-9-phenacylidene-4-azafluorene VIII

Compound	Chemical shifts, ppm, and coupling constants, Hz									
	2-H, dd	3-H, dd	4-H, dd	5-H, s	8-H	9-H	10-H	11-H	12-H	Ph, m
IV	8.82 J_{23} = 4.6 J_{24} = 1.8	7.29 J_{23} = 4.6 J_{34} = 8.2	8.31 J_{34} = 8.2 J_{24} = 1.8	—	8.25 (m)	7.65-7.80 (m)		9.27 (m)	—	7.50-7.65
V	8.90 J_{23} = 4.6 J_{24} = 1.8	7.38 J_{23} = 4.6 J_{34} = 8.2	8.52 J_{34} = 8.2 J_{24} = 1.8	—	7.94 (dd) J_{89} = 8.2 J_{810} = 1.2	7.40-7.60 (m)		9.18 (dd) J_{1011} = 7.9 J_{911} = 1.2	—	7.40-7.60
VI	8.78 J_{23} = 4.6 J_{24} = 1.5	7.57 J_{23} = 4.6 J_{34} = 8.5	8.90 J_{34} = 8.5 J_{24} = 1.5	—	7.30 (s)	8.11 (m)	7.65-7.75 (m)		8.98 (m)	8.07 (*o*-Ph) 7.30-7.60 (*m*-, *p*-Ph)
VII	8.89 J_{23} = 4.6 J_{24} = 1.8	7.50 J_{23} = 4.6 J_{34} = 7.9	8.35 J_{34} = 7.9 J_{24} = 1.8	7.31	—	8.31 (dd) J_{910} = 8.5 J_{911} = 1.2	7.75 (m) J_{910} = 8.5 J_{1011} = 7.6 J_{1012} = 1.5	7.56 (m) J_{1011} = 7.6 J_{1112} = 8.2 J_{911} = 1.2	8.98 (dd) J_{1112} = 8.2 J_{1012} = 1.5	8.07 (*o*-Ph) 7.35-7.50 (*m*-, *p*-Ph)
	1-H, dd	2-H, dd	3-H, dd	5-H, d	7-H, dd	8-H, m	10-H, s	—	—	Ph, m
VIII	7.52 J_{12} = 7.9 J_{13} = 1.5	7.23 J_{12} = 7.9 J_{23} = 4.9	8.67 J_{23} = 4.9 J_{13} = 1.5	9.05 J_{57} = 2.1	8.23 J_{78} = 8.5 J_{57} = 2.1	7.30-7.40	7.49			7.25-7.40

signal of this proton appears at stronger field, in the 7.3-7.4 ppm region. This disagreement may be connected to the magnetic anisotropy of the phenyl substituent when the 8-H proton lies above the plane of this ring.

EXPERIMENTAL

IR spectra of KBr disks were recorded with a UR-20 spectrometer and mass spectra with a Varian MAT-112 instrument with direct inlet of the sample into the ionizing chamber and an ionizing voltage of 70 eV. ^{1}H NMR spectra of 1–2% $CDCl_3$ solutions with TMS as internal standard were recorded at 30°C with a Bruker WP-200 instrument at a working frequency of 200 MHz. Assignment of signals to particular protons of molecules I–VII was confirmed by double resonance experiments. A silica gel (L100/400) was used for the column chromatography. The course of reactions and the purity of products was monitored by TLC on Alufol and Silufol UV-254 plates, with a solvent system of hexane–ethyl acetate, 2:1, and visualization with iodine vapor. Extracts were dried over magnesium sulfate.

Hydrochloride of 9-Phenacylidene-4-azafluorene Tosylhydrazone (III). A. Tosylhydrazine (4.24 g, 22.8 mmol) and concentrated HCl (5 ml) were added to a solution of compound I (2.4 g, 8.48 mmol) in ethanol (70 ml). The solution was stirred for 2 h at 60°C. The precipitate was filtered of and washed successively with ethanol and aqueous ethanol to give light yellow crystals of the hydrochloride of the tosylhydrazone III (3.5 g, 84%); mp 184-188°C (ethanol). IR spectrum: 1560 (C=N) and 3150-3300 cm^{-1} (NH). Found, %: C 66.3, H 4.8, N 8.5. $C_{27}H_{21}N_3O_2S \cdot HCl$. Calculated, %: C 66.5, H 4.5, N 8.6.

The free base, which was formed by treating the tosylhydrazone hydrochloride (1.15 g, 2.36 mmol) with 20% aqueous soda, was extracted with chloroform, and the extract was dried. The tosylhydrazone III was isolated (0.59 g, 56%) as light yellow crystals; mp 168-170°C (dec.) (1:1 hexane–ethyl acetate). IR spectrum: 1570 (C=N), 3150-3300 cm^{-1}. Found, %: C 71.8; H 4.7; N 9.2. $C_{27}H_{21}N_3O_2S$. Calculated, %: C 71.8; H 4.7; N 9.3.

B. A solution of compound II (2.5 g, 7.62 mmol), tosylhydrazine (3.97 g, 21.3 mmol), and concentrated hydrochloric acid (5 ml) in ethanol (90 ml) was heated for 4 h at 60°C (TLC monitoring). The precipitate was filtered off and washed successively with ethanol and aqueous ethanol to give the hydrochloride of tosylhydrazone III (2.3 g, 62%). A melting point of sample mixed from methods A and B showed no depression.

5-Phenylpyrazolo[3,4-*l*]- and 7-Phenylpyrazolo[4,3-*l*]-4-azaphenanthrene (IV and V), and 7-Phenylpyrazolo[5,1-*l*]- and 6-Phenylpyrazolo[1,5-*l*]-4-azaphenanthrenes (VI and VII). A. A solution the tosylhydrazone III (2.4 g, 4.9 mmol) and sodium isopropoxide (2.09 g, 26 mmol) in absolute benzene (150 ml) was heated for 6 h at 60°C (TLC monitoring). The reaction mixture was poured into water, the benzene layer was separated, and the aqueous layer was extracted with chloroform. The combined extracts were dried and the residue after removal of the solvents was chromatographed on a silica gel column (L 40/100, 40 × 1.5 cm) with hexane–ethyl acetate, 2:1, as eluent. The following were eluted successively.

Compound VI: (0.01 g, 0.7%), pink crystals; mp 99-102°C (hexane–ethyl acetate, 2:1), R_f 0.67 (ethyl acetate–hexane, 1:2). IR spectrum: 1691 cm^{-1}. Found, %: C 81.6; H 4.2; N 14.3. M^+ 295. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

Compound VII: (0.027 g, 1.9%), rosy crystals; mp 155-159°C (hexane–ethyl acetate, 2:1), R_f 0.58 (ethyl acetate–hexane, 1:2). IR spectrum: 1545-1605 cm^{-1} (C=N). Found, %: C 81.3; H 4.6; N 14.1. M^+ 295. $C_{20}H_{13}N_3$. Calculated %: C 81.4; H 4.4; N 14.2. M 295.

Compound IV: (0.2 g, 13.8%), colorless crystals; mp 226-228°C (hexane–ethyl acetate, 2:1), R_f 0.25 (ethyl acetate–hexane, 1:2, (Lit. [6], mp 232-234°C). IR spectrum: 3100-3300 cm^{-1} (NH). Mass spectrum, *m/z* (I_{rel}, %): 295 (M^+ 18), 267 (55). Found, %: C 81.1; H 4.5; N 14.0. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

Compound V: (0.16 g, 11.1%), light yellow crystals; mp 188-191°C (hexane–ethyl acetate, 2:1), R_f 0.15 (ethyl acetate–hexane 1:2). (Lit. [6], mp 188-190°C). IR spectrum: 3100-3350 cm^{-1} (NH). Found, %: C 81.7; H 4.2; N 14.3. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

B. Sodium isopropoxide (1.9 g, 23.6 mmol) was added to a solution of the tosylhydrazone hydrochloride (2.3 g, 4.72 mmol), obtained from compound II, in absolute benzene (150 ml) and the mixture was heated at 60°C for 1.5 h (monitored by TLC). The mixture was poured into water, the benzene layer was separated, and the aqueous

layer was extracted with chloroform (3 × 20 ml). The combined extracts were dried and the residue after evaporation of the solvents was chromatographed on a silica gel L40/100 (40 × 1.5 cm) with 2:1 hexane-ethyl acetate as eluant. The following compounds were eluted successively:

Compound VI: (0.063 g, 0.9%), rosy crystals; mp 106-109°C (hexane–ethyl acetate, 2:1), R_f 0.63 (ethyl acetate–hexane, 1:2). IR spectrum: 1560 cm^{-1} (C=N). M^+ 295. Found, %: 81.7; H 4.5; N 14.4. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

Compound VII: (0.009 g, 1.3%), colorless crystals; mp 152-155°C (dec), R_f 0.5 (ethyl acetate–hexane, 1:2). IR spectrum: 1751 (C=O) and 1517 cm^{-1} (NO_2).Mass spectrum, *m/z* (I_{rel}, %): 328 (55), 311 (5), 282 (9), 281 (7), 254 (21), 226 (25), 180 (15), 152 (20), 122 (31), 105 (96), 77 (100).

Compound IV: (0.04 g, 3.1%), white crystals; mp 230-232°C (hexane–ethyl acetate, 2:1) (Lit. [6], mp 232-234°C). IR spectrum: 3100-3250 cm^{-1} (NH). Found, %: C 81.4; H 4.2; N 14.4. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

Compound V: (0.055 g, 4.3%), pale yellow crystals; mp 192-194°C (hexane–ethyl acetate, 2:1), R_f 0.2 (ethyl acetate–hexane, 1:2). (Lit. [6], mp 188-190°C). IR spectrum: 3100-3350 cm^{-1} (NH). Found, %: C 81.6; H 4.1; N 14.4. $C_{20}H_{13}N_3$. Calculated, %: C 81.4; H 4.4; N 14.2.

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