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HETEROCYCLIC ANALOGS OF PLEIADIENE. 72.* SULFONES OF PERIMIDINE AND 2,3-DIHYDROPERIMIDINE. SYNTHESIS AND SOME PROPERTIES

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The arenesulfonation of perimidines has been carried out in polyphosphoric acid and found to occur at the 6(7) and 4(9) positions. Reduction then gave the first representatives of 2,3-dihydroperimidine sulfones. We report a comparative ^{1}H NMR spectroscopic analysis of the arenesulfonyl- and acylperimidines together with their annular prototropic tautomerism.

Keywords: perimidine, sulfones, annular prototropy.

The synthesis of the previously unknown perimidine series sulfones has been undertaken in connection with the recently reported slow annular prototropy of 6(7)-formyl- and 6(7)-acetyl-2-trifluoromethylperimidines on the ^{1}H NMR time scale [2]. The ^{1}H NMR spectra of these compounds in non-polar solvents at room temperature (and even upon heating) show signals for both NH-tautomers, while in polar solvents only averaged signals are present pointing to a rapid rate of their interconversion. In our view this hindrance to tautomerism is due to a combined electron-acceptor effect of the 2-CF_3 group and of the carbonyl which strongly reduces the basicity of the pyridine type nitrogen atom. We propose that, for 6(7)-sulfonyl derivatives of 2-trifluoromethylperimidine (and possibly perimidine itself) the slowing down of this prototropy should be even more marked since the electron acceptor effect of the 4-$MeC_6H_4SO_2$ group (σ_p = 0.67) is much higher than the CHO group (σ_p = 0.22).

Because perimidines readily participate in an electrophilic substitution reaction [3], for the synthesis of the sulfones we chose the method of direct arenesulfonation in polyphosphoric acid (PPA) [4]. By contrast with acylation [5, 6], the reactions of perimidine (**1a**) and 2-trifluoromethylperimidine (**1b**) with arenesulfonic acids or their salts in PPA occur under more rigid conditions and are initiated above 120°C. We have carried this out with a 1.5 molar excess of the sulfonic acid at 140-145°C over 1 h. The reaction results in a mixture of the corresponding 4(9)- and 6(7)-arenesulfonyl perimidines **2** and **3** respectively with the latter predominating. At higher temperatures the reaction is accompanied by tarring and this is becomes complete at 200-210°C.

* For Communication 71 see [1].

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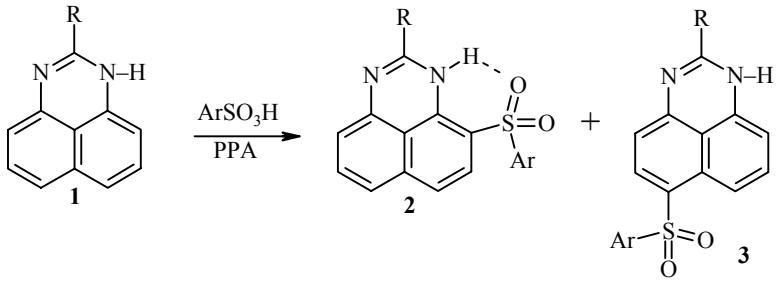
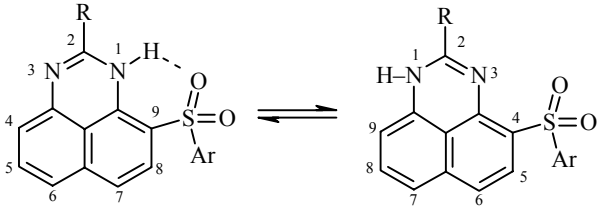


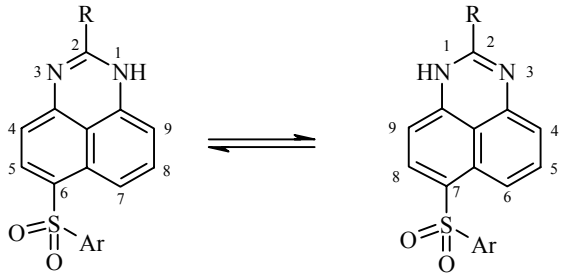
1 a R = H, **b** R = CF_3, **2**, **3 a** R = H, Ar = 4-MeC_6H_4, **b** R = H, Ar = 2-naphthyl, **c** R = CF_3, Ar = 4-MeC_6H_4

The separation of the sulfones **2** and **3** was based on their different chromatographic mobilities. The 4(9)-isomers, like the 4(9)-acylperimidines, are more mobile thanks to the intramolecular hydrogen bond and, in low-polarity solvents, exist virtually as the 9- tautomer. This is indicated, for example, in the ^{1}H NMR spectrum of compound **2a** where the strongly broadened NH proton signal in $CDCl_3$ is found at low field (δ = 10.3 ppm) (Table 1). The absence of a rapid tautomerism is also indicated by the sharp (narrow) signals for the aromatic protons. Since, however, sulfones form weaker hydrogen bonds when compared with sulfoxides [7], the spectra of compound **2** in DMSO-d_6 might be expected to show an averaging of signals due to rapid tautomeric exchange on the NMR time scale:



In fact, such an averaging is seen only as a slight broadening of the signal for the proton in position 4(9) and this is possibly connected with a significant shift of the equilibrium to the side of the 9-tautomer, even in the absence of intramolecular hydrogen bonding.

In the short communication [8] we have already mentioned that, in non-polar solvents ($CDCl_3$, $CDCl_2CDCl_2$), the ^{1}H NMR spectrum of sulfone **3c** is seen as a well resolved system of signals for two tautomers. As in the case of the 6(7)-formyl(acetyl)-analogs [2], the more basic 7-tautomer predominates (64:36 in $CDCl_2CDCl_2$) and this pattern is virtually unchanged upon heating the solution to 120°C. When a drop of water is added or upon solution in DMSO-d_6 coalescence is seen, even at room temperature.



By contrast, the ^{1}H NMR spectra of the sulfones **3a,b** point to a relatively rapid prototropic tautomerism, both in the polar DMSO-d_6 and in the low polarity $CDCl_3$. The most sensitive in similar examples are the protons in positions 4 and 9 and these appear as strongly broadened doublets. Thus the influence of a

TABLE 1. ^{1}H NMR Spectra of Compounds **2-5**

Com-pound	Solvent	Chemical shifts δ, ppm, *J* (Hz)								
		2-H	4-H	9-H	5-H	8-H	6-H	7-H	NH, br. s	Ar
1	2	3	4	5	6	7	8	9	10	11
2a	$CDCl_3$	7.5 (s)	7.2 (dd, *J* = 8.2)	—	7.5 (dd, *J* = 8.2, *J* = 7.2)	7.3 (m)	7.1 (dd, *J* = 7.2)	7.0 (d, *J* = 9.3)	10.3	2.4 (s, CH_3); 7.3 (m, 3'- and 5'-H); 7.8 (d, *J* = 8.3, 2'- and 6'-H)
3a	$CDCl_3$	7.4 (s)	6.5 (br. d, *J* = 8.3)	6.7 (br. d, *J* = 7.7)	8.2 (d, *J* = 8.3)	7.3 (dd, *J* = 8.8, *J* = 7.7)	—	7.8 (d, *J* = 8.8)	—	2.4 (s, CH_3); 7.2 (d, *J* = 8.3, 3'- and 5'-H); 7.8 (d, *J* = 8.3, 2'- and 6'-H)
	Me_2CO-d_6	7.6 (s)	6.6 (br. s)	6.8 (br. s)	8.2 (d, *J* = 8.3)	7.3-7.4 (m)	—	7.8 (d, *J* = 8.8)	—	2.4 (s, CH_3); 7.3-7.4 (m, 3'- and 5'-H); 7.8 (d, *J* = 8.8, 2'- and 6'-H)
2b	DMSO-d_6	7.7 (s)	6.7 (br. s)		7.4 (dd, *J* = 8.3, *J* = 7.7)	7.7 (m)	7.2 (d, *J* = 8.3)	7.2 (d, *J* = 8.2)	—	7.7 (m, 6'-H); 7.9-8.1 (m, 3'-4'-,7'-,8'-H); 8.1 (d, *J* = 7.7, 5'-H); 8.7 (s, 1'-H)
3b	DMSO-d_6	7.6 (s)	6.6 (br. d, *J* = 8.3)	6.7 (br. d, *J* = 7.2)	8.2 (d, *J* = 8.3)	7.3 (dd, *J* = 7.2, *J* = 8.3)	—	7.6-7.8 (m)	11.3	7.6-7.8 (m, 3-',6-',7'-H); 8.0 (d, *J* = 8.8, 4'-H); 8.2 (br. d, *J* = 8.3, 5'-H); 8.7 (s, 1'-H)
2c	DMSO-d_6	—	6.8 (br. d, *J* = 7.7)	—	7.4 (dd, *J* = 7.7, *J* = 7.7)	7.8 (d, *J* = 8.3)	7.3 (m)	7.3 (m)	12.3	2.4 (s, CH_3); 7.3 (m, 3'- and 5'-H); 7.9 (d, *J* = 8.3, 2'- and 6'-H)

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
3c	DMSO-d_6	—	6.8 (d, J = 8.3)	6.9 (d, J = 7.7)	8.1 (d, J = 8.3)	7.4 (dd, J = 7.7, J = 8.8)	—	7.8 (d, J = 8.8)	12.2	2.3 (s, CH_3); 7.4 (d, J = 8.3, 3-',5'-H); 7.8 (d, J = 8.3, 2'- and 6-'H)
3c (7-tautomer)	$CDCl_2CDCl_2$	—	7.1 (dd, J = 7.5)	6.4 (d, J = 8.1)	7.4 (dd, J = 7.5, J = 8.7)	8.1 (d, J = 8.1)	7.9 (dd, J = 8.7)	—	8.5	2.3 s (CH_3), 7.2 (d, J= 8.1, 3'-,5'-H), 7.7 (d, J = 8.1, 2'- and 6'-H)
3c (6-tautomer)	$CDCl_2CDCl_2$	—	7.0 (d, J = 8.1)	6.5 (dd, J = 7.3)	8.2 (d, J = 8.0)	7.3 (dd, J = 7.3, J = 8.9)	—	7.8 (dd, J = 8.9)	8.4	2.3 s (CH_3), 7.2 (d, J = 8.1, 3'-,5'-H), 7.7 (d, J = 8.1, 2'- and 6'-H)
4	$CDCl_3$	4.6 (br. s)	—	6.6 (d, J = 7.7)	7.6 (d, J = 9.4)	7.3 (dd, J = 7.7, J = 7.7)	7.1 (d, J = 9.4)	7.1 (d, J = 7.7)	7.5, 7.8	2.4 s (CH_3), 7.3 (d, J= 8.3, 3'-,5'-H), 7.8 (d, J = 8.3, 2'- and 6'-H)
	DMSO-d_6	4.5 (dd, J = 2.2, J = 1.7)	—	6.6 (d, J = 7.7)	7.3 (dd, J = 7.7, J = 8.3)	7.5 (d, J = 8.8)	7.0 (d, J = 8.3)	7.0 (d. J = 8.8)	6.7, 7.4	2.3 s (CH_3), 7.4 (d, J = 8.3, 3'-,5'-H), 7.8 (d, J = 8.3, 2'- and 6'-H)
5	DMSO-d_6	4.4 (dd, J = 2.0, J = 2.0)	6.5 (d, J = 8.3)	6.5 (d, J = 7.7)	8.1 (d, J = 8.3)	7.2 (dd, J = 7.7, J =8.3)	—	7.5 (d, J = 8.3)	6.8, 7.6	2.3 s (CH_3), 7.3 (d, J = 8.3 (3'-,5'-H), 7.7 (d, J = 8.3, 2'- and 6'-H)

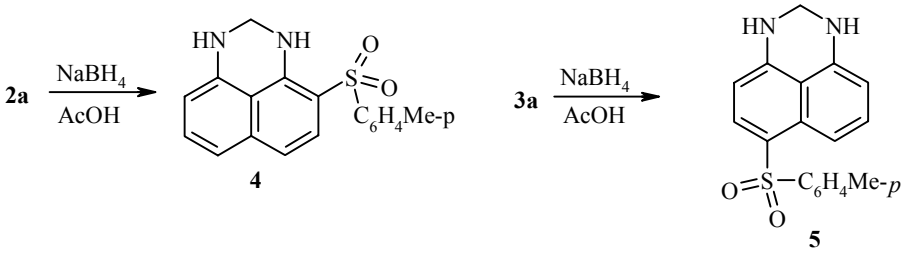
single acceptor substituent in the 6(7) position or the 2 position of the perimidine is insufficient for the existence of slow annular prototropy on the ^{1}H NMR time scale.

A characteristic feature of the ^{1}H NMR spectra of 6(7)-arenesulfonylperimidines is the fact that the lowest field signals prove not to be the *peri* protons, as in the case of 6(7)-acylperimidines [5, 6], but the protons found *ortho* to the $ArSO_2$ group. In our view this is explained by the difference in the steric structure of the sulfonyl and carbonyl group. A decrease in the C–S–O angle when compared with the carbonyl C–C–O angle leads to a more efficient transfer of the anisotropic effect of the S=O bond through a five and not six-membered ring. Evidence of a significant contribution of the SO bond anisotropy to the low-field shift of neighboring aromatic protons was found when comparing the spectra of the isomers **2** and **3**. In fact, the single *ortho* proton relative to the sulfonyl group (also including the protons of the aryl groups), whose shift to low field is significantly less (by ~ 0.5 ppm), is the proton at position 8 of the sulfone **2a** in $CDCl_3$. This result is a consequence of the conformational rigidity of the SO_2 group due to the intramolecular hydrogen bond and hence it does not lie within the cone of anisotropy of the S=O bond. When changing to the polar DMSO, this effect disappears.

In the IR spectra of the sulfones **2** and **3** the stretching vibrations of the SO_2 group appear at 1315-1305 and 1090-1105 cm^{-1}.

Attempts to carry out an intramolecular Smiles rearrangement [9] by refluxing 4(9)-*p*-toluenesulfonylperimidine (**2a**) in aqueous alcoholic base were unsuccessful. Evidently, this is a result both of the low nucleophilicity of the N-anion and the insufficient electrophilicity of the aryl radical. We were not able to prepare the alkylperimidinesulfones by treating perimidine with benzyl- or ethanesulfonic acid (used as their sodium salts) in PPA medium since it resulted in decomposition of the sulfonic acid with the evolution of SO_2. Treatment of the perimidine under the same conditions with *p*-toluenesulfonic acid gave only oligomeric, red colored crystals.

As was the case for the acylperimidines [10], the action of sodium borohydride in glacial acetic acid on compounds **2a** and **3a** caused reduction of the heterocyclic C=N bond to give the 4- and 6-*p*-toluenesulfonyl-2,3-dihydroperimidines **4** and **5** respectively.



In the ^{1}H NMR spectra of sulfones **4** and **5** in DMSO-d_6 (Table 1), the chemical exchange of the NH protons is slowed so much that a spin-spin interaction is observed between the protons of the CH_2 groups and the two NH protons (J = 1.7-2.0 Hz). By contrast with the starting **2a**, the intramolecular hydrogen bond in compound **4** is relatively weak (δ_{NH} = 7.5 and 7.8 ppm in $CDCl_3$).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WP-200 (200 MHz) instrument with TMS as internal standard. Signal assignments were made using a double resonance method. IR Spectra were taken on a UR-20 instrument. Monitoring of the course of the reaction and the purity of the compounds synthesized was carried out using Silufol UV-254 plates and column chromatography was performed on Chemapol L 40/100 grade silica gel.

General Method for the Arenesulfonylation of Perimidines. A mixture of perimidine or 2-trifluoromethylperimidine (4 mmol), p-toluenesulfonic acid monohydrate or the sodium salt of β-naphthalenesulfonic acid (6 mmol), and PPA (8-10 g) (containing 82% P_2O_5) was heated to 140-145°C and held at this temperature for 1 h with vigorous stirring. After cooling to 80-85°C, the reaction mixture was poured as a thin stream into vigorously stirred cold water (100 ml), basified with ammonia to pH ~ 8 (in the case of compounds **2c** and **3c** to pH ~ 4 to 5), and the precipitate was filtered off, washed with water, and dried. The dry product was treated with ethyl acetate (15 ml) (benzene in the preparation of compounds **2c** and **3c**) and, together with the precipitate, were transferred to a chromatography column with silica gel (~ 100 g). Elution of compounds **2a,b** was carried out with ethyl acetate and **2c** with benzene (the first fractions being pale yellow in color). The second fractions were bright yellow in color and were eluted with a mixture of ethyl acetate and ethanol (10:1) (compounds **3a,b**) or benzene and ethyl acetate (compound **3c**). Evaporation of solvent gave the corresponding sulfone.

4(9)-*p*-Toluenesulfonylperimidine (2a). Yield 0.2 g (15%). Pale yellow crystals; mp 187-188°C (benzene–petroleum ether). IR spectrum (vaseline oil), ν, cm^{-1}: 1095, 1305 (SO_2), 3240 (NH). Found, %: C 66.97; H 4.44; N 8.53. $C_{18}H_{14}N_2O_2S$. Calculated, %: C 67.06; H 4.38; N 8.69.

6(7)-*p*-Toluenesulfonylperimidine (3a). Yield 0.54 g (42%). Yellow green crystals; mp 220-222°C (benzene). IR spectrum ($CHCl_3$), ν, cm^{-1}: 1100, 1310 (SO_2), 3420 (NH). Found, %: C 67.21; H 4.23; N 8.59. $C_{18}H_{14}N_2O_2S$. Calculated, %: C 67.06, H 4.38; N 8.69.

4(9)-β-Naphthalenesulfonylperimidine (β-Naphthyl-4(9)-perimidinylsulfone) (2b). Yield 0.04 g (3%). Pale yellow crystals; mp 103-105°C (benzene–petroleum ether). Found, %: C 70.60; H 4.07; N 8.01. $C_{21}H_{14}N_2O_2S$. Calculated, %: C 70.37; H 3.94; N 7.82.

6(7)-β-Naphthalenesulfonylperimidine (β-Naphthyl-6(7)-perimidinylsulfone) (3b). Yield 0.6 g (42%). Yellow green crystals; mp 143-144°C (benzene–alcohol). Found, %: C 70.55; H 4.01; N 7.88. $C_{21}H_{14}N_2O_2S$. Calculated, %: C 70.37; H 3.94; N 7.82.

4(9)-*p*-Toluenesulfonyl-2-trifluoromethylperimidine (2c). Yield 0.22 g (14%). Yellow green crystals; mp 253-254°C (volatilized from benzene with petroleum ether). Found, %: C 58.56; H 3.07; N 7.28. $C_{19}H_{13}F_3N_2O_2S$. Calculated, %: 58.46; H 3.36; N 7.18.

6(7)-*p*-Toluenesulfonyl-2-trifluoromethylperimidine (3c). Yield 0.69 g (44%). Yellow green crystals; mp 259-260°C (benzene). IR spectrum (vaseline oil), ν, cm^{-1}: 1105, 1315 (SO_2), 3200-3300 (NH). Found, %: C 58.64; H 3.30; N 7.22. $C_{19}H_{13}F_3N_2O_2S$. Calculated, %: C 58.46; H 3.36; N 7.18.

General reduction method. Sodium borohydride (1.14 g, 30 mmol) was added portionwise over 30 min with vigorous stirring to a solution of the sulfone **2a** or **3a** (1.61 g, 5 mmol) in glacial acetic acid (10 ml) at room temperature. The mixture was stirred for a further 30 min, poured into cold water (50 ml), basified with a solution of ammonia to pH ~ 8, and the precipitate was filtered off, washed with water, and dried.

4-*p*-Toluenesulfonyl-2,3-dihydroperimidine (4). Yield 1.13 g (70%). Cream crystals; mp 78-80°C (aqueous alcohol). Found, %: C 66.58; H 5.05; N 8.49. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.65; H 4.97; N 8.64.

6-*p*-Toluenesulfonyl-2,3-dihydroperimidine (5). Yield 1.47 g (91%). Yellow green crystals; mp 209-210°C (benzene–alcohol). Found, %: C 66.77; H 4.98; N 8.70. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.65; H 4.97; N 8.64.

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