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SYNTHESIS OF 1-ARYLSULFONYL-4-ARYLPIPERAZINES WITH A STERICALLY HINDERED NITROGEN ATOM

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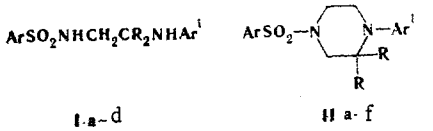
UDC 547.861.3.07

The corresponding piperazines are formed in high yields by alkylation of 1-arenesulfamido-2-arylaminoethanes with dichloroethane in an aqueous alkaline solution of triethylbenzylammonium chloride. Some properties of the synthesized compounds were investigated.

We have previously shown [1] that arylsulfonylarylamides are alkylated at the nitrogen atom by 1,2-dihaloethanes in the presence of small amounts of a triethylbenzylammonium salt, the addition of which raises the yield and increases the reaction rate. We have carried out the reaction of dichloroethane with a number of 1-arenesulfamido-2-arylaminoethanes (Ia-d), and in this case, both the amine and amide nitrogen atoms are alkylated in an aqueous alkaline solution of triethylbenzylammonium chloride to give high yields of the corresponding piperazines (IIa-f).



I a-d II a-f

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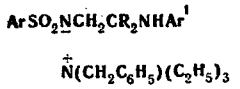
TABLE 1. Physical Constants of the Synthesized Compounds

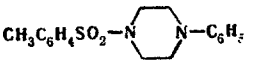
Compound	Ar	Ar′	R	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	S	C	H	N	S	
Ib	C_6H_5	o-$CH_3C_6H_4$	CH_3	110—111 (toluene)	$C_{17}H_{22}N_2O_2S$	63,7	7,1	8,7	10,0	64,1	7,0	8,8	10,1	91
Ic	C_6H_5	m-$CH_3C_6H_4$	CH_3	75—76 (octane—toluene)	$C_{17}H_{22}N_2O_2S$	64,4	6,9	8,8	10,2	64,1	7,0	8,8	10,1	90
Id	C_6H_5	p-$CH_3C_6H_4$	CH_3	71,5—72,5 (toluene)	$C_{17}H_{22}N_2O_2S$	64,6	6,7	8,6	10,4	64,1	7,0	8,8	10,1	95
IIa	C_6H_5	C_6H_5	CH_3	134—135 (alcohol)	$C_{18}H_{22}N_2O_2S$	66,7	6,7	8,7	9,6	65,4	6,7	8,5	9,7	90
IIb	C_6H_5	o-$CH_3C_6H_4$	CH_3	120—121 (alcohol)	$C_{19}H_{24}N_2O_2S$	65,8	6,7	7,9	9,3	66,2	7,0	8,1	9,3	91
IIc	C_6H_5	m-$CH_3C_6H_4$	CH_3	134—135 (alcohol)	$C_{19}H_{24}N_2O_2S$	66,2	6,9	8,2	9,3	66,2	7,0	8,1	9,3	88
IId	C_6H_5	p-$CH_3C_6H_4$	CH_3	155—156 (alcohol)	$C_{19}H_{24}N_2O_2S$	66,9	6,7	8,3	9,4	66,2	7,0	8,1	9,3	96
IIe	p-$CH_3C_6H_4$	p-NOC_6H_4	H	155—156 (benzene)	$C_{17}H_{19}N_3O_3S$	58,7	6,4	12,4	9,6	59,1	5,5	12,1	9,3	60
IIf	p-$CH_3C_6H_4$	p-$C_6H_4N_2C_6H_4NO_2$	H	250 (DMF)	$C_{23}H_{23}N_5O_4S$	60,9	4,4	15,2	6,9	59,3	5,0	15,0	6,9	91

The presence of methyl groups adjacent to the amine nitrogen atom does not substantially hinder alkylation even in the case of ortho substitution in the phenyl ring. The role of the quaternary ammonium base apparently consists in the fact that it promotes homogeneity of the medium by forming an intermediate complex salt of the III type, which is soluble in dichloroethane. In compounds of the II type the presence of considerable branching adjacent to the nitrogen atom evidently leads to disruption of the coplanarity of the carbon–nitrogen bond with the bonds of the aromatic ring. Compound IV (without methyl groups) is readily nitrosated and undergoes diazocoupling in the para position of the phenyl ring, whereas IIa does not undergo these reactions under normal conditions.

Correspondingly, the UV spectrum of IV has an absorption maximum at 234 nm (ε 18,400); insofar as the spectra of II are concerned, a considerable decrease in the absorption intensity (ε 10,700) and a hypsochromic shift of the absorption band (λ 226 nm) are observed because of the presence of methyl groups in the 2 position of the piperazine ring.



III



IV

The presence of a methyl group in the ortho position of the phenyl ring (IIb) leads to an even greater hypsochromic shift of the absorption bands; the spectrum of this compound at 220-400 nm does not have an absorption maximum.

EXPERIMENTAL

The IR spectra of KBr pellets of the compound were recorded with a UR-20 spectrometer. The UV spectra of isooctane solutions were recorded with an SF-4A spectrophotometer.

Starting **Ia-d** were obtained by ring opening of the appropriate aziridines by means of aromatic amines by the methods in [2-4].

3,3-Dimethyl-1-phenylsulfonyl-4-phenylpiperazine (IIa). A 1.85-g (0.01 mole) sample of triethylbenzylammonium chloride was added to 20 ml of dichloroethane, after which 3 ml (0.03 mole) of 40% sodium hydroxide and 3.02 g (0.01 mole) of 2-methyl-2-phenylamino-3-benzenesulfamidopropane were added. The mixture was refluxed for 20-25 h, after which the excess dichloroethane was removed by steam distillation, and the oil in the residue crystallized rapidly on cooling to give 3 g (90%) of a product with mp 134-135° (from alcohol). IR spectrum: 1320 s, 1145 s, 1120 s, 1030 m, 930 m, and 910 m cm^{-1} (piperazine ring vibrations). Substituted piperazines (IIb-d), which were similarly obtained, are presented in Table 1.

1-(p-Tolylsulfonyl)-4-(p-nitrosophenyl)piperazine (IIe). A 1.6-g (0.005 mole) sample of 1-(p-tolylsulfonyl)-4-phenylpiperazine was dissolved in 150 ml of acetic acid, 10 ml of concentrated HCl was added, and the mixture was cooled to 18°. A solution of 0.7 g (0.01 mole) of sodium nitrate in 15 ml of water was then added all at once with continuous stirring. After 1 h, the solution was poured into 200 ml of ice water, and the resulting bright-green precipitate was removed by filtration to give 1 g (60%) of a product with mp 155-156° (from benzene). IR spectrum: 1310-1360 s (NO, broad band), 1300 s, 1160 s, 1020 w, and 950 s cm^{-1} (piperazine ring vibrations).

1-(p-Tolylsulfonyl)-4-(p-nitrobenzeneazophenyl)piperazine (IIf). A solution of a p-nitrobenzenediazonium salt obtained by diazotization of 0.69 g (0.05 mole) of p-nitroaniline was added gradually with stirring to a solution of 1.6 g (0.006 mole) of 1-(p-tolylsulfonyl)-4-phenylpiperazine in 100 ml of glacial acetic acid, during which the color of the solution changed to crimson. The mixture was allowed to stand, during which shiny orange-red leaflets precipitated from the solution. The yield was 1.2 g. A Beilstein test for chlorine was negative. The filtrate was diluted with 500 ml of ice water and neutralized with ammonia to give an additional 0.9 g of IIf. The overall yield of a product with mp 250° (from DMF) was 2.2 g (91%). IR spectrum: 1430 m (N=N); 1300 m, 13.30s, 1160 s, 1140 s, and 950 s cm^{-1} (piperazine ring vibrations).

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CONDENSATION OF o-DIAMINO DERIVATIVES OF ANTHRAQUINONE AND NAPHTHOQUINONE WITH MESITYL OXIDE

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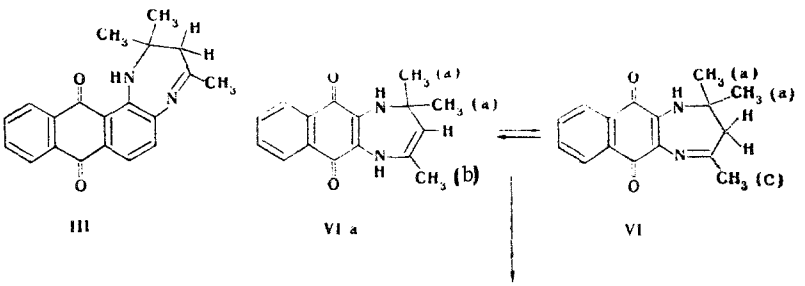
Anthraquinone- and naphthoquinonediazepines are formed by the reaction of 1,2- and 2,3-diamino-9,10-anthraquinones and 2,3-diamino-1,4-naphthoquinones with mesityl oxide. It was shown by spectral methods that naphthoquinonediazepine exists in two tautomeric forms.

It is known that 2,2,4-trimethyl-1,5-benzodiazepine is formed in the reaction of o-phenylenediamine with mesityl oxide [1, 2] or with acetone in acidic media [3, 4]. In order to synthesize heterocyclic derivatives of quinones we carried out the condensation of mesityl oxide with o-diamino derivatives of anthra- and naphthoquinones.

At room temperature 1,2- and 2,3-diaminoanthraquinones (I and II) react with mesityl oxide to give diazepines III and IV (in 60-70% yields), the structures of which were confirmed by spectral data. Thus, in addition to the signals of six aromatic protons (7.37, 7.66, 7.70, and 8.17 ppm), the PMR spectrum of III contains singlets of nine protons of methyl groups (1.44 and 2.29 ppm, intensity ratio 6:3) and two protons of a methylene group (2.52 ppm). The shift of the signal of the proton of the NH group to weak field (9.15 ppm) as compared with the position of the same protons in the spectrum of diazepine IV (4.34 ppm) is in agreement with the presence in the IR spectrum of III of two frequencies corresponding to $\nu_{C=O}$ vibrations (1665 and 1630 cm^{-1}) and also with the position of the frequency of the stretching vibrations of the N–N bond and its independence of dilution; this constitutes evidence for linkage of the NH group by an intramolecular hydrogen bond with the carbonyl group and confirms the structure of diazepine III.

2,3-Diamino-1,4-naphthoquinone (V) reacts with mesityl oxide to give diazepine VI, which can be isolated from the reaction mixture in the form of a salt or the free base. The formation of diazepines is also observed in the reaction of diamines I, II, and V with acetone in acidic media (acetone forms mesityl oxide under these conditions), but this method is less convenient because of the low yields of reaction products.



III VI a VI

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