HETARYLATION OF N-ARYLSULFONYLPYRIDINIUM AND BENZOPYRIDINIUM SALTS IN SITU

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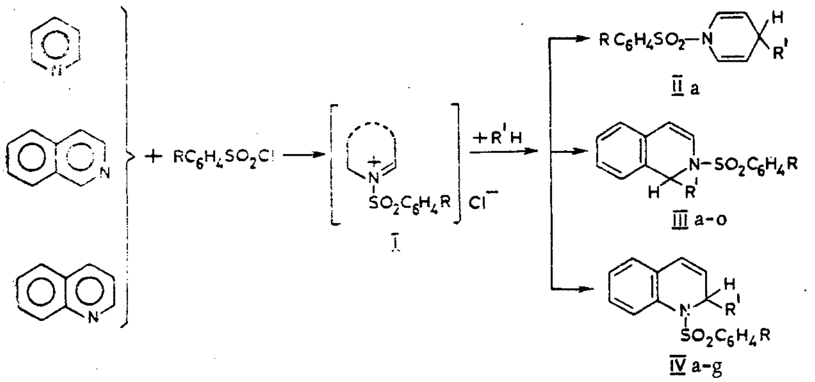
Indoles and dimethylaniline were subjected to direct hetarylation with pyridine, quinoline, and isoquinoline in the presence of arenesulfonyl chlorides. The arenesulfonamide heterocyclic derivatives of indoles and dimethylaniline were obtained and characterized.

The heterarylation of organic CH acids is accomplished by the simultaneous action on them of N-heteroaromatic compounds and acylating agents; carboxylic acid chlorides are usually employed as the acylating agents [1]. It was recently found that it is also possible to carry out this reaction in the presence of the chlorides of tri- and pentavalent phosphorous acids [2]. It was natural to assume that the same sort of reaction may also occur in the presence of sulfonyl chlorides with the intermediate formation of N-heteroaromatic sulfonyl salts of the I type as hetarylating agents. In fact, the formation of salts of this type in the reaction of N-heterocycles with sulfonyl chlorides has been observed by many investigators [3]. It has also been shown that isoquinoline salts of this type readily react with KCN at the instant of their formation [4], whereas quinoline hetarylates indole in the presence of p-toluenesulfonyl chloride [5]. In the present research in the case of dimethylaniline and indole we were able to show that hetarylation of sufficiently nucleophilic aromatic and heteroaromatic compounds is possible in the case of the simultaneous action on them of pyridine, quinoline, or isoquinoline and various arenesulfonyl chlorides:



II a R=H, R′= 3-indolyl; III a R=H, R′= 3-indolvl; b R=p-CH_3, R′= 3-indolvl; c R= =o-CH_3, R′=3-indolyl; d R=p-Br, R′= 3-indolyl; e R=H, R′=2-methvl-3-indolyl; f R= =p-CH_3, R′=2-methyl-3-indolyl; g R=p-Br, R′=2-methyl-3-indolyl; h R=p-Br, R′=1-methyl-3-indolyl; i R=H, R′=1-methyl-3-indolyl; j R=o-NO_2, R′= 3-indolvl; k R=p-Cl, R′=3-indolyl; *l* R=p-CH_3CONH, R′=3-indolyl; m R=H, R′=p-$(CH_3)_2NC_6H_4$-; n R= =p-Br, R′=p-$(CH_3)_2NC_6H_4$-; o R=p-CH_3, R′=p-$(CH_3)_2NC_6H_4$-; IV a R=H, R′=3-indolyl; b R=p-CH_3, R′=2 methyl-3-indolyl; c R=p-Br, R′= 3-indolyl; d R=p-Br, R′= =2-methyl-3-indolyl; e R=p-Br, R′=1-methyl-3-indolyl; f R=H, R′=2-methyl-3-indolyl g R=H, R′=p-$(CH_3)_2NC_6H_4$-

The most active salts in this reaction were found to be N-arylsulfonylisoquinolinium salts, which at room temperature hetarylate indoles and dimethylaniline to give compounds of the III type in high yields.

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TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	N	S		C	H	N	S	
IIa	165	68,0	4,7	8.2	9,4	$C_{19}H_{16}N_2SO_2$	67,8	4,7	8,3	9,5	15
IIIa	160	71,4	4,6	7,2	8,3	$C_{23}H_{18}N_2SO_2$	71,9	5,0	6,7	8,0	93
IIIb	140	71,8	5,1	6,8	8,1	$C_{24}H_{20}N_2SO_2$	71,9	5,0	6,7	8,0	90
IIIc	76	71,9	4,8	6,7	8,0	$C_{24}H_{20}N_2SO_2$	71,9	5,0	6,7	8,0	23
IIId	148	59,9	3,7	6.0	6,8	$C_{23}H_{17}BrN_2SO_2$[a]	60,0	3,8	5,9	6,8	68
IIIe	215	71,8	5,0	6.5	8,0	$C_{24}H_{20}N_2SO_2$	71,9	5,0	6,7	8,0	58
IIIf	164	72,3	5,3	6,6	7,8	$C_{25}H_{22}N_2SO_2$	72,4	5,3	6,7	7,7	87
IIIg	147	60,1	3,9	5,9	6,7	$C_{24}H_{19}BrN_2SO_2$[b]	60,1	4,0	5,8	6,7	53
IIIh	190	59,9	4,0	6,0	6,8	$C_{24}H_{19}BrN_2SO_2$[c]	60,1	4,0	5,8	6,7	55
IIIi	136	71,8	4,9	6,8	7,9	$C_{24}H_{20}N_2SO_2$	71,9	5,0	6,7	8,0	80
IIIj	159	64,1	4,0	9,7	7,3	$C_{23}H_{17}N_3SO_4$	64,0	3,9	9,7	7,4	73
IIIk	149	65,5	4,0	6,7	7,7	$C_{23}H_{17}ClN_2SO_2$[d]	65,6	4,1	6,6	7,6	60
IIIl	141	67,2	5,0	9,5	7,1	$C_{25}H_{21}N_3SO_3$	67,7	4,8	9,5	7,2	52
IIIm	112	70,2	5,7	6,9	8,0	$C_{23}H_{22}N_2SO_2$	70,1	5,6	7,0	8,0	72
IIIn	156	58,8	4,5	6,0	6,8	$C_{23}H_{21}BrN_2SO_2$	58,8	4,5	5,9	6,8	52
IIIo	166	71,5	6,1	7,0	7,9	$C_{24}H_{24}N_2SO_2$	71,3	6,0	6,9	7,9	66
IVa	170	71,4	4,8	7,1	8,2	$C_{23}H_{18}N_2SO_2$	71,5	4,8	7,1	8,3	48
IVb	226	72,0	5,4	6,8	7,8	$C_{25}H_{22}N_2SO_2$	72,4	5,3	6,7	7,7	50
IVc	218	59,9	4,0	6,0	6,7	$C_{23}H_{17}BrN_2SO_2$[e]	60,0	3,8	5,9	6,8	31
IVd	208	60,1	3,9	5,8	6,6	$C_{24}H_{19}BrN_2SO_2$[f]	60,1	4,0	5,8	6,7	15
IVe	150	60,2	4,1	5,8	6,8	$C_{24}H_{19}BrN_2SO_2$[g]	60,1	4,0	5,8	6,7	70
IVf	178	70,9	4,9	6,8	7,9	$C_{24}H_{20}N_2SO_2$	71,0	5,0	6,7	8,0	38
IVg	96	70,1	5,8	6,9	8,0	$C_{23}H_{22}N_2SO_2$	70,1	5,6	7,0	8,0	31

[a] Found: Br 17.1%. Calculated: Br 17.2%. [b] Found: Br 16.7%. Calculated: Br 16.6%. [c] Found: Br 16.6%. Calculated: 16.6%. [d] Found: Cl 8.2%. Calculated: Cl 8.4%. [e] Found: Br 17.1%. Calculated: Br 17.2%. [f] Found: Br 16.5%. Calculated: Br 16.6%. [g] Found: 16.7%. Calculated: Br 16.6%.

Quinoline and, particularly, pyridine were found to be less active. We were unable to realize reaction with these heterocycles with all of the arenesulfonyl chlorides (Table 1). An increase in the temperature in these cases does not lead to the desired effect, since oxidative side processes develop at 50-80°, and products of the oxidation of indole and dimethylaniline are formed along with the hetarylation products. As in the case of hetarylation of dimethylaniline with pyridine and benzoyl chloride in the presence of cupric chloride [6] or by the action of pyridine N-oxide on dimethylaniline [7], we isolated a crystalline violet dye in the reaction with dimethylaniline at elevated temperatures in all cases.

As a result of the acid hydrolysis of II-IV their molecules undergo complete fragmentation to give the starting heterocycles, indole or dimethylaniline, and arenesulfonic acids.

The IR spectra of II-IV contain characteristic bands of stretching vibrations of indole ν_{N-H}(3445-3465), $\nu_{as\,SO_2}$ (1348), $\nu_{s\,SO_2}$ (1170), and $\nu_{C=C}$ (1610-1625 cm^{-1}) groups (III and IV).

Ion peaks corresponding to each fragment of the molecule are observed in the mass spectra of synthesized II-IV; this completely confirms their structures. We will examine the mechanism of fragmentation of molecules of this type under the influence of electron impact in the case of IIIa and IIIm.

The molecular ions of IIIa and IIIm undergo fragmentation via two pathways: 1) elimination of a $C_6H_5SO_2$ particle; 2) detachment of hetaryl residues – indole or N-dimethylaniline, respectively. The first pathway is the predominant route (by a factor of ~10). The result of this process is the stable I-substituted isoquinolinium cation, which, because of destruction of the interannular bond, forms the corresponding hetaryl or aryl fragment ions or else undergoes dehydrogenation. The latter gives rise to the formation of a multiring system; the interpretation of the fragmentation of similar models [8-10] does not present any difficulties. The scheme presented below illustrates the above (in the case of IIIa).*

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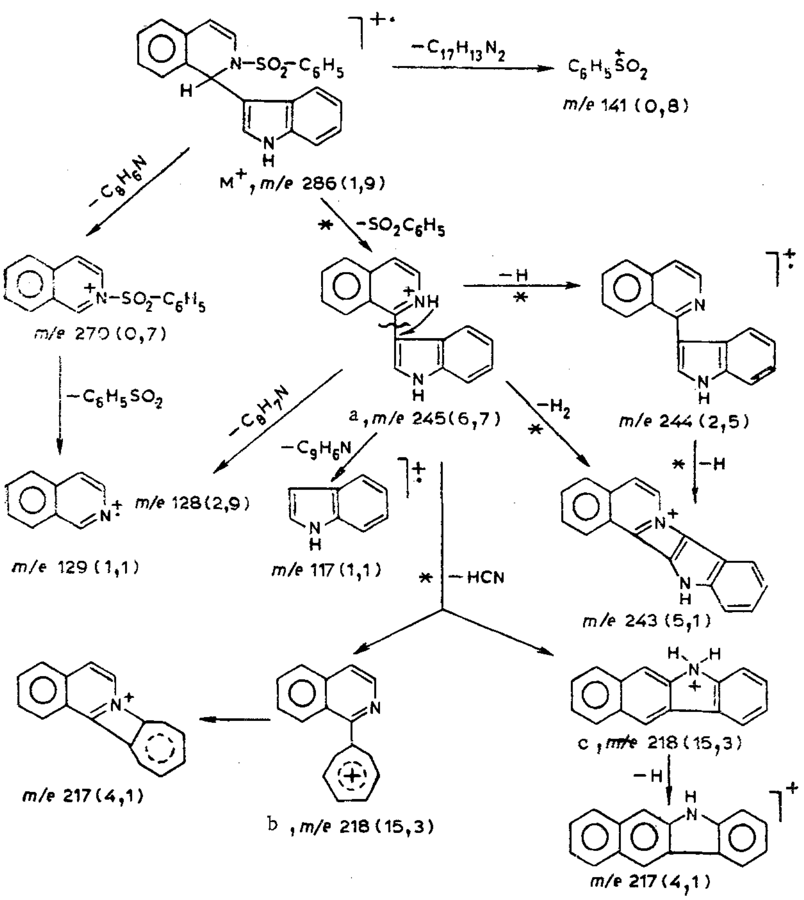
* The numbers under the formulas designate the mass numbers of the ions, the numbers in parentheses denote the intensities expressed in percent of the total ion current, and the asterisks indicate the presence of the corresponding metastable transition.

Scheme 1



Elimination of an HCN particle (together with the processes indicated above) is characteristic for the fragment ion with structure a. In this case two alternative pathways in the formation of an ion with m/e 218 are possible — from the isoquinoline or indole fragment of the system (structures b and c).

In the case of IIIm dehydrogenation takes place to a greater extent (up to six H atoms are lost) in the formation of the ion with structure a. $[M^{+\cdot} \xrightarrow{-C_6H_5SO_2} (M-C_6H_5SO_2)^{+\cdot}]$. A methyl group is also detached from the $(a-H)^+$ ion (m/e 248) with subsequent ejection of an HCN particle. Both fragmentation pathways are characteristic for N-dimethyl-substituted anilines [11]. Thus the mass spectra of the synthesized IIIa and IIIm completely confirm their structures.

EXPERIMENTAL

The mass spectra were obtained with a Varian Math-311 spectrometer. The samples were introduced directly into the ion source at an ionizing voltage of 70 eV, a cathode emission current of 1 mA, a source temperature of 110°, and an accelerating voltage of 3 kV (the intensities of the peaks in the mass spectra were 5% of the maximum peak in the spectra). The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. Thin-layer chromatography was carried out on activity II aluminum oxide with elution with benzene–hexane–chloroform (6:1:30) and development by iodine vapors.

2-Phenylsulfonyl-1-(3'-indolyl)-1,2-dihydroisoquinoline. A 1.45-g (12.5 mmole) sample of indole was added to a mixture of 3.2 g (25 mmole) of anhydrous isoquinoline and 2.2 g (12.5 mmole) of freshly distilled benzenesulfonyl chloride in 15 ml of absolute benzene, and the mixture was stirred vigorously at 18-20° for 1-2 h. It was then dissolved in 50 ml of chloroform, and the chloroform solution was washed with water, dilute HCl (1:1), and water and dried over potassium carbonate. The chloroform was evaporated, and the residual resin was crystallized from isopropyl alcohol to give 4.5 g (93%) with R_f 0.34 and mp 160-161°. IR spectrum (KBr pellet): ν_{NH} 3465, $\nu_{C=C}$ 1625, $\nu_{as\,SO_2}$ 1338, and $\nu_{s\,SO_2}$ 1172 cm^{-1}. Mass spectrum (m/e): 44 (5.2); 51 (11.8); 77 (29.7); 78 (10.4); 89 (8.0); 101 (5.8); 103 (5.9); 116 (17.9); 117 (6.9); 128 (19.4); 129 (7.3); 130 (5.4); 141 (5.4); 216 (11.5); 217 (26.8); 218 (100.0); 219 (18.7); 242 (11.5); 243 (36.1); 244 (16.4); 245 (43.7);

246 (7.8); 270 (5.2); 386 (12.6). Found: C 71.4; H 4.6; N 7.2; S 8.3%. $C_{23}H_{18}N_2SO_2$. Calculated: C 71.5; H 4.8; N 7.1; S 8.3%.

All of the remaining III were similarly obtained (Table 1). The reaction times for the preparation of II and IV were 12-25 h (monitoring by TLC). The products were isolated as described above. The physical constants are presented in Table 1.

Mass spectrum of IIIi (m/e): 44 (6.8); (16.6); 55 (11.6). 57 (52.6); 77 (58.2); 78 (18.9); 85 (17.5); 89 (8.8); 91 (6.7); 102 (9.0); 103 (8.3); 116 (16.1); 121 (8.3); 128 (23.8); 129 (9.9); 141 (11.6); 204 (14.9); 205 (16.2); 216 (13.0); 217 (24.5); 218 (100.0); 219 (17.7); 233 (23.9); 234 (5.8); 243 (32.8); 244 (15.8); 245 (15.8); 246 (9.9); 247 (15.5); 248 (14.3); 249 (57.4); 250 (12.5); 270 (9.4) 390 (12.0).

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RESEARCH ON HETEROCYCLIC QUINONES.

XXVIII.* CATALYTIC ACTIVITY OF METAL IONS IN THE AMINATION OF QUINOXALINE-5,8-QUINONES

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The catalytic activity of metal ions in the amination of quinoxaline-5-8-quinones was studied. It is shown that it changes in conformity with the Irving–Williams order. Proof in favor of the participation of complexes with mixed ligands in the amination is presented. It was observed that two competitive reactions – amination and hydroxylation in the 2 position – are observed in the presence of Cd^{2+} or Zn^{2+}.

In a previous communication [1] we showed that copper ions catalyze the amination of quinoxaline-5,8-quinones at 2-C. This was explained by the formation of a copper chelate complex of the starting quinone. Reactions of quinoline-5,8-quinones that are catalyzed by copper [2] or cerium [3] ions are known. The authors of these papers postulate the formation of chelates, which leads to a decrease in the electron density at 6-C. However, complexing should also increase the sensitivity of the heteroring to nucleophilic attack; in the case of quinoxalinequinones this leads to amination at 2-C. One should have expected that this reaction would not only be catalyzed by copper ions. The aim of the present research was to verify this assumption.

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