HETARYLATION OF 1-METHYLPYRROLE BY ISOQUINOLINE IN THE PRESENCE OF AROMATIC OR ALIPHATIC SULFONYL CHLORIDES

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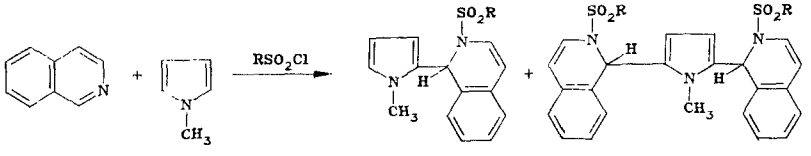
When N-alkyl(or aryl) sulfonylisoquinolinium salts are reacted *in situ* with 1-methylpyrrole, 2-aryl(or alkyl)sulfonyl-1-(pyrrole-2-yl)-1,2-dihydroixoquinolines and 2,5-di[2-aryl(or alkyl)-sulfonyl-1,2-dihydroisoquinolin-1-yl]-1-methylpyrroles form with high yields.

The reactivity of isoquinolinium and other benzopyridinium and pyridinium cation in reactions with nucleophiles depends on the nature of the substituent at the nitrogen heteroatom [1, 2]: The stronger are the electron-acceptor properties of the substituent, the more reactive is the cation. N-alkyl cations, which form very unstable salt-like adducts with many nucleophiles, are least active in these reactions [3, 4], the N—H and N—aryl cations are more active, and the N-acyl heteroaromatic cations, which are often used in *in situ* reactions with nucleophiles (so-called hetarylation reactions [3]), are the most reactive. We recently showed that N-arylsulfonylbenzimidoylisoquinolinium salts are even more active in these reactions and that with their aid it is possible to introduce an isoquinoline residue into a ferrocene molecule, which does not react with N-acyl cations [6]. It seemed to be of interest to evaluate the activity of the scarcely studied N-alkyl- and N-arylsulfonylisoquinolinium salts in hetarylation reactions. These salts can be obtained as a result of the aromatization of 1-substituted N-arylsulfonyl-1,2-dihydroisoquinolines under the action of N-acylisoquinolinium cations [7], this being evidence of the great electrophilicity of the latter.

A convenient object for comparing the activities of various cations in hetarylation reactions is 1-methylpyrrole. It is known that N-acylisoquinolinium salts react with pyrrole to form mono (in an α or β position of the pyrrole ring) and dihetarylation (in both α positions) products [8]. The salts of the less electrophilic N-acylpyridinium cations form only monohetarylation products in these reactions [9, 10], and the reactions of the even less electrophilic N-alkylpyridinium cations give unstable adducts, rather than hetarylation products. These adducts are essentially ion pairs, which readily decompose into the original reactants, as was recently observed in reactions with indole in [4].

It was found that the reaction of isoquinoline with 1-methylpyrrole in the presence of various sulfonyl chlorides results in the formation of both mono- and dihetarylpyrroles I and II with high yields (Table 1). Monohetarylation products I can be used to obtain bishetaryl derivatives II in a similar reaction with isoquinoline and the appropriate sulfonyl chloride:



Ia–i IIa–g

The structures of compounds Ia and IIa synthesized were established with the aid of their PMR and mass spectra, while the remaining compounds of types I and II have similar UV spectra, and were consequently assigned similar structures. The PMR spectrum of compound IIa (R = C_6H_5) showed signals for the following protons: The singlet at 4.09 ppm (3H) was assigned to the methyl group of the pyrrole ring. The singlet of the C—H proton in position

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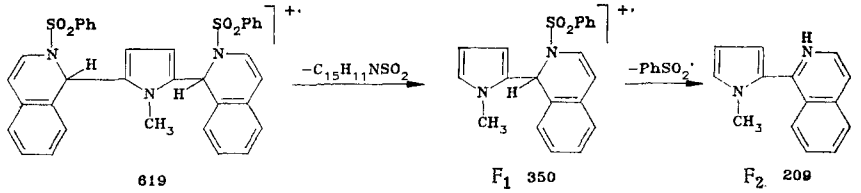
TABLE 1. Characteristics of the Compounds Synthesized

Compound	R	mp, °C	R_f	Found, %				Empirical formula	Calculated, %				Yield, %
				C	H	N(Br)	S		C	H	N(Br)	S	
Ia	C_6H_5—	99—100	0,6	68,3	5,3	8,2	8,9	$C_{20}H_{18}N_2O_2S$	68,5	5,2	8,0	9,1	74
Ib	NO_2—C_6H_4—	127—128	0,6	60,5	4,3	10,7	7,9	$C_{20}H_{17}N_3O_4S$	60,7	4,3	10,6	8,1	52
Ic	CH_3—C_6H_4—	117—118	0,6	68,8	5,7	7,9	8,6	$C_{21}H_{20}N_2O_2S$	69,3	5,5	7,7	8,8	59
Id	Br—C_6H_4—	178—180	0,6	55,7	4,1	6,3 (18,8)	7,7	$C_{20}H_{17}BrN_2O_2S$	55,9	4,0	6,5 (18,6)	7,5	68
Ie	2,4-$(NO_2)_2C_6H_3$	177—179	0,6	54,7	3,5	12,7	7,3	$C_{20}H_{16}N_4O_6S$	54,5	3,7	12,7	7,3	44
If	2-Naphthyl-	106—107	0,6	72,0	5,3	6,9	8,0	$C_{24}H_{20}N_2O_2S$	72,0	5,0	7,0	8,0	62
Ig	CH_3—	93—94	0,6	62,9	5,9	9,8	11,4	$C_{15}H_{16}N_2O_2S$	62,5	5,6	9,7	11,1	60
Ih	C_2H_5—	87—88	0,6	63,7	5,8	9,3	10,7	$C_{16}H_{18}N_2O_2S$	63,6	6,0	9,3	10,6	42
Ii	*i*-C_3H_7—	62—63	0,5	64,8	6,4	8,8	10,2	$C_{17}H_{20}N_2O_2S$	64,6	6,3	8,9	10,2	39
IIa	C_6H_5—	160	0,3	67,9	4,9	6,9	10,1	$C_{35}H_{29}N_3O_4S_2$	67,8	4,7	6,8	10,4	63
IIb	NO_2—C_6H_4—	164—165	0,4	59,6	3,8	9,6	8,9	$C_{35}H_{27}N_5O_4S_2$	59,2	3,8	9,9	9,0	60
IIc	CH_3—C_6H_4—	199—200	0,5	68,7	5,2	6,3	9,7	$C_{37}H_{33}N_3O_4S_2$	68,6	5,0	6,4	9,8	65
IId	2-Naphthyl-	170—172	0,4	71,9	4,6	5,9	8,9	$C_{43}H_{33}N_3O_4S_2$	71,7	4,6	5,8	8,9	60
IIe	*n*-Br—C_6H_4—	206—208	0,4	54,4	3,5	5,5(20,0)	8,0	$C_{35}H_{27}Br_2N_3O_4S$	54,1	3,5	5,4 (20,6)	8,2	52
IIf	2,4-$(NO_2)_2C_5H_3$	195—196	0,5	52,8	3,1	12,0	8,1	$C_{35}H_{25}N_7O_{12}S_2$	52,6	3,2	12,2	8,0	40
IIg	CH_3—	110—111	0,4	60,9	5,0	8,6	12,8	$C_{25}H_{25}N_3O_4S_2$	60,6	5,0	8,4	12,9	63

1 of the isoquinoline fragment has δ = 4.94 ppm (2H), and the singlet of the β protons of the pyrrole ring is detected at 6.52 ppm (2H). The aromatic protons of the isoquinoline ring and the phenyl protons are displayed in the form of a complicated multiplet at 6.2-7.7 ppm (22H).

In the mass spectrum of this compound, which was obtained with an energy of the ionizing electrons equal to 70 eV, there is no peak for the molecular ino (M^+), and in the region of high m/z values there is a peak at 350,* which corresponds to the $[M - C_{15}H_{11}NSO_2]^+$ fragment (F_1).



The further fragmentation of the pseudomolecular F_1 ion follows a known scheme [6]: Splitting of the internuclear bond with the formation of ions 80 and 270 occurs to a lesser extent, and the splitting of the N—S bond with the formation of the $PhSO_2^+$ (141) and F_2 (209) ions occurs to a greater extent. The fragmentation of the F_2 ion, which has the structure of the 1-(1-methylpyrrol-2-yl)isoquinolinium cation, follows the paths characteristic of bishetaryls [7, 8]: dehydrogenation with the formation of ions 208 and 207, which results in the cyclization of hetaryl residues with the simultaneous splitting of the pyrrole ring to a pyridine ring and the elimination of a neutral HCN particle (ion 182) with the subsequent elimination of the methyl radical (ion 167).

When the energy of the ionizing electrons was lowered to 15 eV, were were able to detect a peak for M^+ (619). In this case, ion 478, which corresponds to the $[M - SO_2Ph]^+$ fragment, was detected along with the others already cited.

The mass spectrum of compound Ia contains both M^+ (350) and all the fragment ions described above.

The PMR spectra of compounds Ia and IIa are identical: the singlet of the protons of the methyl group on the pyrrole ring has δ = 3.78 ppm (3H), and the aromatic 3-H, 4-H, and 5-H protons in this ring produce a complex multiplet owing to the long-range spin—spin interaction with centers at 6.32, 5.24, and 5.72 ppm. The aromatic protons of the isoquinoline fragment (H_{5-8}) produce a signal in the form of a complex multiplet at 7.01-7.53 ppm (4H). The 3-H and 4-H protons form a quartet for an AB system with a center at 7.64 ppm (2H) ($J_{3,4}$ = 2 Hz), the 1-H proton is detected at 4.78 ppm (1H), and a multiplet for the phenyl grouping is detected at 6.15-6.67 ppm. The UV spectra of compounds I and II are characterized by the following absorption bands: λ_{max} = 225 nm (ε = $1.8 \cdot 10^{-4}$) and 263 nm (ε = $1.5 \cdot 10^4$).

EXPERIMENTAL

The mass spectra† were obtained on a Finnigan 4021 spectrometer, the ionizing voltage corresponds to 70 eV, the temperature of the source was 170°C, and the accelerating voltage was equal to 2.5 kV. The PMR spectra were recorded on a Tesla-80 spectrometer in $CDCl_3$ with HMDS as an internal reference.

The thin-layer chromatograph in Al_2O_3 was carried out with elution by a 6:1:30 benzene—hexane—chloroform solvent mixture.

2-Benzenesulfonyl-1-(1-methylpyrrol-2-yl)-1,2-dihydroisoquinoline (Ia). A mixture of 6.4 g (50 mmole) of anhydrous isoquinoline and 4.4 g (25 mmole) of freshly distilled benzenesulfonyl chloride in 30 ml of absolute benzene is given an addition of 4.06 g (50 mmole) of N-methylpyrrole, and the resultant mixture is held for 4-6 h at 18-20°C with intense stirring. Then the reaction mass is dissolved in 50 ml of chloroform, and the chloroform solution is washed with dilute (1:1) HCl and then dried with magnesium sulfate. The residue remaining after evaporation is crystallized from methanol. The yield is 6.42 g (74%) (see Table 1).

*The numbers characterizing an ion define the value of m/z.

†We sincerely thank N. A. Klyuev for recording and interpreting the mass spectra.

IR spectrum (KBr tablets): 1625 ($\nu_{C=C}$), 1338 ($\nu_{as}SO_2$), 1172 cm^{-1} (V_s, SO_2). Mass spectrum (70 eV), m/z, %: 39 (17.4), 42 (15.7), 51 (16.1), 53 (16.9), 77 (32.2), 80 (45.5), 81 (51.7), 189 (21), 167 (17.8), 182 (100), 207 (16.1), 209 (46.9), 350 (35.7).

All the compounds Ia-i (Table 1) were obtained in a similar manner.

Compounds IIa-g were obtained by reacting 50 mmole of isoquinoline, 50 mmole of a sulfonyl chloride, and 25 mmole of 1-methylpyrrole (Table 1). Mass spectrum of compound IIa (15 eV, the ions with an intensity $\geq$ 15% are given), m/z, %: 77 (35.6), 129 (80.0), 182 (32.5), 209 (37.2), 350 (100), 352 (25.1), 619 (17.3).

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