BENZOFURAN DERIVATIVES

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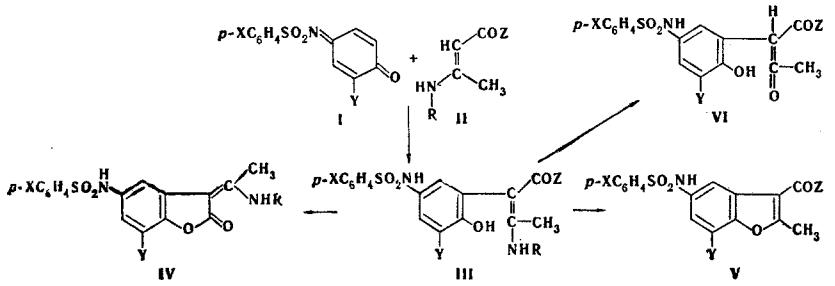
The condensation of 1,4-benzoquinone arylsulfonylimines with esters and arylamides of 3-alkyl- and 3-cycloalkylaminocrotonic acids has been studied and the conditions for the cyclization of the resulting products into benzofuran derivatives are discussed.

With the aim of a further study of the transformations of the substituted 3-aminocrotonates that we synthesized previously [1, 2], in the present work we have investigated the reaction of 1,4-benzoquinone arylsulfonylimines (I) with derivatives of 3-alkyl- and 3-cycloalkylaminocrotonic acids (II) and have considered methods of cyclizing the resulting esters and arylamides of 3-alkylamino- and 3-cycloalkylamino-2-(2-hydroxyarene-5-sulfonamidophenyl)crotonic acids (III). The synthesis of benzofuran derivatives was performed by the following route:



The production of (III) was confirmed by the presence in the IR spectra not only of absorption bands at (cm^{-1}) 3400 (ν_{OH}), 3330-3250 (ν_{NH}), and 1390 and 1180 (ν_{SO_2}) but also of a band at 1650 ($\nu_{C=O}$), which shows the conjugation of the carbonyl group with the vinylamine residue [3]. In the PMR spectra of (IIIb, g,j) splitting of the signal of the protons of the CH_3-N group (in the 2.2-ppm region; J = 5 Hz) under the action of the NH proton is observed, and there is also a singlet signal with a chemical shift of 1.3 ppm corresponding to the resonance of the protons of a CH_3 group on a double bond.

The treatment of compounds (IIIa-e and i-q) with 70% sulfuric acid in the cold formed the 3-(1-alkyl-[or cycloalkyl]aminoethylidene)-5-arenesulfonamido-2-oxocoumarans (IVa-i), the structure of which was confirmed by a study of their IR, PMR, and mass spectra, and also by the preparation of (IVg) from (IIIj, r) and (IVh) from (IIIl, q). The IR spectra of (IV) lack the bands of a hydroxy group but they have a band at 1710 cm^{-1} ($\nu_{C=O}$) that is characteristic for derivatives of 3-(1-aminoethylidene)-2-oxocoumaran [4]. Signals of the protons of an ethyl group are lacking in the PMR spectra of (IVb, g), and the singlet (1.82 ppm) of the protons of a CH_3 group on a C = C bond and also the splitting of the signal of the protons of another methyl group (2.51 ppm, J = Hz), confirming the presence of the CH_3-NH fragment, are observed.

In the mass spectrum of (IVg) in the region of high values of m/e there is a strong (52.8% of the maximum) peak of ions with m/e 344 corresponding to the molecular weight of the proposed structure. The relatively high intensity of the peak of the $(M+2)^+$ ions (4.2% of the molecular ion) shows the presence of a

*Deceased.

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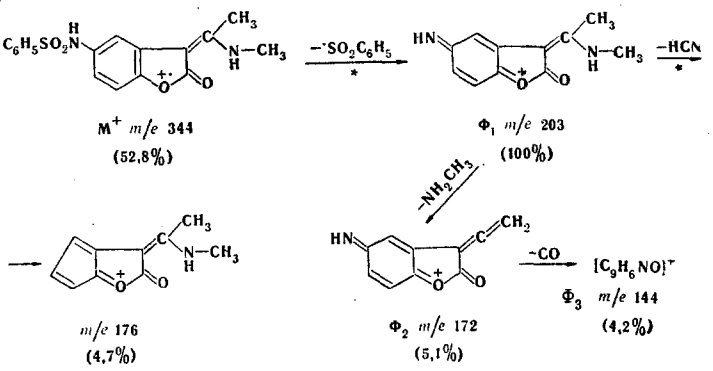
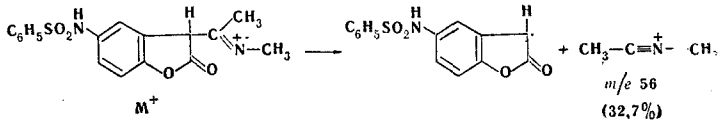
sulfur atom in the molecule and is due to its isotope ^{34}S. The main process of the decomposition of the molecular ions (M^+) is the successive elimination of a $\cdot SO_2C_6H_5$ radical and a HCN molecule with the formation of ions with m/e 203 (Φ_1, maximum peak) and 176. The occurrence of both processes is confirmed by the corresponding metastable transitions. The Φ_1 ions then eliminate a fragment with mass 32, apparently a H_2N-CH_3 molecule, with the formation of the Φ_2 ions with m/e 172 which then split out a molecule CO with the formation of the Φ_3 ions with m/e 144. Thus, the fragmentation of compound (IVg) can be represented by the following scheme:



The presence in the mass spectrum of an intense (32.7% of the maximum) peak of ions with m/e 56 shows the existence of M^+ in two tautomeric forms and the occurrence of the following process:



The direction of the transformations of (III) depends on the nature of Y and the experimental conditions. If Y = Cl, boiling (III) in ethylene glycol or aqueous acetic acid leads to 5-benzenesulfonamido-7-chloro-3-ethoxycarbonyl-2-methylbenzofuran (Vc, X = H, Y = Cl), while when Y = H heating the compound in ethylene glycol forms a mixture of (IV) and (V), and in acetic acid compounds (III) are converted into (V) and are partially hydrolyzed to ethyl 2-(5-arenesulfonamido-2-hydroxyphenyl)acetoacetates (VI).

EXPERIMENTAL

The PMR spectra were taken in pyridine on an RS-60 instrument with hexamethyldisiloxane as internal standard, and the IR spectra were taken on a UR-20 spectrophotometer using KBr, NaCl, and LiF prisms with the samples in KBr tablets. To evaluate the individuality of the substances obtained, thin-layer chromatography on LS_{250} 5/40 (chloroform; spots revealed with iodine vapor) was used. The mass spectrum was obtained on an MKh-1303 instrument with an ionizing voltage of 50 eV, an emission current of 150 mA, and a temperature of 170°C. The initial quinone arylsulfonylimines and 3-alkylamino- and 3-cycloalkylaminocrotonates were obtained by known methods [5, 6].

TABLE 1. Ethyl 3-Alkylamino- and 3-Cycloalkylamino-2-(2-hydroxy-5-arenesulfonamidophenyl)crotonates

Compound	X	Y	R	mp, °C*	Solvent for treating the oil	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	Cl	N	C	H	Cl	N	
IIIa	Cl	H	H	160—162	Diethyl ether	$C_{18}H_{19}ClN_2O_5S$	53,4	4,7	8,4	6,7	52,6	4,7	8,6	6,8	71,3
IIIb	Cl	H	CH_3	168—170 (dec.)	Same	$C_{19}H_{21}ClN_2O_5S$	54,5	5,4	8,3	6,3	53,7	5,0	8,3	6,6	70,6
IIIc	Cl	H	C_2H_5	145—147	Benzene	$C_{20}H_{23}ClN_2O_5S$	54,7	5,5	8,1	6,4	54,7	5,3	8,1	6,4	
IIId	Cl	H	n-C_4H_9	153,5	Diethyl ether – benzene	$C_{22}H_{27}ClN_2O_5S$	57,4	6,7	7,6	5,8	56,6	5,8	7,6	6,0	74,9
IIIe	Cl	H	Cyclohexyl	166	Diethyl ether	$C_{24}H_{29}ClN_2O_5S$	58,9	6,2	7,1	5,5	58,5	5,9	7,2	5,7	77,1
IIIf	H	Cl	H	79—81	Methanol	$C_{18}H_{19}ClN_2O_5S$	52,6	4,7	8,7	6,8	52,6	4,7	8,6	6,8	49
IIIg	H	Cl	CH_3	166,5 (dec.)	Same	$C_{19}H_{21}ClN_2O_5S$	53,5	4,5	8,3	6,6	53,7	5,0	8,3	6,6	64,5
IIIh	H	Cl	C_2H_5	151—152	"	$C_{20}H_{23}ClN_2O_5S$	54,4	5,4	7,9		54,7	5,3	8,1	6,4	56

*Solvents for crystallization: for (IIIa and d) – a mixture of benzene and methanol; for (IIIb, e, f, and g) – methanol; for (IIIc) – dichloroethane; for (IIIh) – benzene.

TABLE 2. N-Aryl-3-alkylamino-2-(2-hydroxy-5-arenesulfonamidophenyl)crotonamides

Compound	R	X	Z	mp, °C*	Empirical formula	Found, %		Calc., %		Yield, %
						N	S	N	S	
IIIi	H	H	NHC_6H_5	193—194	$C_{22}H_{21}N_3O_4S$	9,9	7,8	9,9	7,6	75,6
IIIj	CH_3	H	NHC_6H_5	178—179	$C_{23}H_{23}N_3O_4S$	9,8	7,3	9,6	7,3	66,3
IIIk	C_2H_5	H	NHC_6H_5	175—175,5	$C_{24}H_{25}N_3O_4S$	9,3	7,0	9,3	7,1	90
IIIl	$CH_2C_6H_5$	H	NHC_6H_5	168—168,5	$C_{29}H_{27}N_3O_4S$	8,1	6,1	8,1	6,2	65
IIIm	H	CH_3	NHC_6H_5	208—209	$C_{23}H_{23}N_3O_4S$	9,6	7,6	9,6	7,3	73
IIIn	CH_3	CH_3	NHC_6H_5	188—189	$C_{24}H_{25}N_3O_4S$	9,6	6,9	9,3	7,1	59
IIIo	C_2H_5	CH_3	NHC_6H_5	188—189	$C_{25}H_{27}N_3O_4S$	9,0	6,9	9,0	6,9	65
IIIp	$CH_2C_6H_5$	CH_3	NHC_6H_5	166—166,5	$C_{30}H_{29}N_3O_4S$	8,3	6,3	8,1	6,2	55
IIIq	$CH_2C_6H_5$	H	o-ClC_6H_5NH	181—182	$C_{29}H_{26}ClN_3O_4S$	7,8	6,4	7,7	6,4	56,5

*Solvents for crystallization: for (IIIi, j, l, n, and q) ethanol; for (IIIk, o, and p) methanol; for (IIIm) a mixture of ethanol and acetone.

TABLE 3. 3-(1-Alkyl[or cycloalkyl]aminoethylidene)-5-arenesulfonamido-2-oxocoumarans

Compound	R	X	mp, °C*	Empirical formula	Found, %		Calc., %		Yield, %
					Cl	N	Cl	N	
IVa	H	Cl	242—243	$C_{16}H_{13}ClN_2O_4S$	9,5	7,6	9,7	7,7	89
IVb	CH_3	Cl	265—266	$C_{17}H_{15}ClN_2O_4S$	9,2	7,3	9,4	7,4	65
IVc	C_2H_5	Cl	220—221	$C_{18}H_{17}ClN_2O_4S$	8,9	6,8	9,1	7,1	58,3
IVd	p-C_4H_9	Cl	197—198,5	$C_{20}H_{21}ClN_2O_4S$	8,2	6,6	8,5	6,7	58,5
IVe	Cyclohexyl	Cl	201,5—202,5	$C_{22}H_{23}ClN_2O_4S$	7,6	6,4	7,9	6,3	90
IVf	H	H	203—203,5	$C_{16}H_{14}N_2O_4S$		8,3		8,5	85
IVg	CH_3	H	247—248,5	$C_{17}H_{16}N_2O_4S$		8,1		8,1	66,7
IVh	$CH_2C_6H_5$	H	192,5—193	$C_{23}H_{20}N_2O_4S$		6,8		6,7	83
IVi	H	CH_3	230—231	$C_{17}H_{16}N_2O_4S$		8,0		8,1	78

*Solvents for crystallization: for (IVa and b) dioxane; for (IVc) a mixture of methanol and dioxane; for (IVd) methanol; for (IVe-i) ethanol.

3-Methylamino-2-(2-hydroxy-5-benzenesulfonamidophenyl)crotonanilide (IIIj). At room temperature with mechanical stirring 2.1 g (0.001 mole) of 3-methylaminocrotonanilide in 10 ml of acetone was added to a suspension of 2.48 g (0.01 mole) of 1,4-benzoquinone phenylsulfonylimine (Ia). A sample of the reaction taken after 5 min no longer showed the indophenol reaction with phenol and aqueous ammonia that is characteristic for the initial quinone imine [6]. The acetone was evaporated in a current of air, and the oily residue was left to crystallize. In the case of the isolation of (IV) the oily residue was treated with ethanol or other organic solvents. Compounds (IIIa-q), information on which is given in Tables 1 and 2, were synthesized similarly.

5-Benzenesulfonamido-3-(1-methylaminoethylidene)-2-oxocoumaran (IVb). At room temperature with stirring, 2 g of finely ground (IIIb) was added to 100 ml of 70% sulfuric acid. The mixture was stirred for 5 h and was poured onto finely crushed ice. The white precipitate that separated out was filtered off, washed with water, and dried in the air. Information on the compounds (IVa-i) obtained is given in Table 3. Compounds (IV) are resistant to being heated in 15% hydrochloric acid for an hour, but boiling in a mixture of hydrochloric and acetic acids is accompanied by the formation of primary amine, detected by the color reaction with p-dimethylaminobenzaldehyde [7]. A solution of 2.5 g (0.0064 mole) of (IIIr) (X = H, Y = H, R = CH_3, Z = OC_2H_5) [2] in 20 ml of propylene glycol, ethylene glycol, or diethyleneglycol was heated to the boil (an intense odor of methylamine was detected), cooled to room temperature, and diluted with an equal volume of methanol. From the solution 0.6 g (26%) of (IVg) identical with that obtained in sulfuric acid from (IIIj, r) crystallized out. After dilution of the filtrate with water, 1.5 g (65%) of 5-benzenesulfonamido-3-ethoxycarbonyl-2-methylbenzofuran (Va), identical with that described in the literature [8], separated out. Similarly, (IIIs) (X = H, Y = H, Z = OC_2H_5, R = n-C_4H_9) and (IIIt) (X = CH_3, Y = H, Z = OC_2H_5, R = CH_3), which have been described previously [1], gave (IVj) (X = H, Y = H, R = n-C_4H_9) and (IVk) (X = CH_3, Y = H, R = CH_3), identical with substances described previously [2], and also (Va) and 3-ethoxycarbonyl-2-methyl-5-(p-toluenesulfonamido)benzofuran (Vb). Yield 0.3 g (32%). mp 132-133°C (from aqueous acetic acid). Found: N 3.8; S 8.4%. $C_{19}H_{19}NO_5S$. Calculated: N 3.7; S 8.6%.

When compounds (IIIg and h) were heated in ethylene glycol or aqueous acetic acid (1:1), only (Vc) was obtained, while (IIIr) gave a mixture of (Va) and (VIa). The use of a mixture of acetic acid and water (1:5) led to the formation of (VIa) as the sole product. On being heated in ethylene glycol and aqueous acetic acid, and also when an alkylamine was added to these solvents, no cyclization of (VIa) into (Va) was observed. The closure of the ring was effected by the method of Adams and Whitaker [8].

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