STUDIES IN THE FIELD OF SULFANILIDES

XXIV. 2-(N-Arylsulfonyl-N-phenylaminoethyl)benzimidazoles

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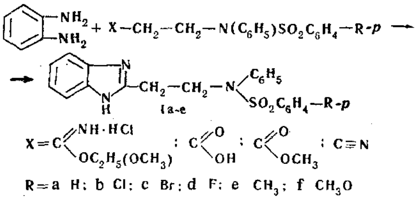
2-(N-Arylsulfonyl-N-phenylaminoethyl)benzimidazoles and some of their derivatives have been synthesized.

Benzimidazole derivatives include plant growth stimulators [1], fungicides [2, 3], chemotherapeutic substances [4, 5], and also a number of substances suppressing the growth of tumors [6, 7]. The object of the present investigation was the synthesis of derivatives of aminoethylbenzimidazole containing arysulfonyl groups in the side chain.

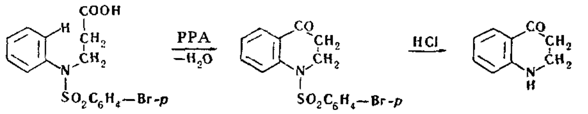
We have synthesized 2-(N-arylsulfonyl-N-phenylaminoethyl)benzimidazoles by the condensation of o-phenylenediamine with N-arylsulfonyl-N-phenyl-β-alanines, their esters, their nitriles, and their hydrochlorides by the following



Compounds I were formed in high yield by the reaction of the hydrochlorides of the methyl and ethyl iminoethers of N-arylsulfonyl-N-phenyl-β-alanines with o-phenylenediamine.

N-p-Bromobenzenesulfonyl-N-phenyl-β-alanine and its ester form different substances with o-phenylenediamine according to the reaction conditions. On condensation in the presence of 4 N hydrochloric acid [8, 9], the main reaction products are benzimidazole derivatives.

If the reaction is carried out in the presence of polyphosphoric acid, intramolecular condensation takes place with the formation of 1-N-p-bromobenzenesulfonyl-1,2,3,4-tetrahydro-4-oxoquinoline, the structure of which was shown by its conversion into 1,2,3,4-tetrahydro-4-oxoquinoline and its p-nitrophenylhydrazone, which are described in the literature [10].



Compound **Ic** was also obtained from the ester and nitrile of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine by fusion with the dihydrochloride of o-phenylenediamine in a sealed tube.

The compounds I obtained were white crystalline substances readily soluble in acetone and chloroform, soluble on heating in ethanol, nitromethane, and dioxane, and insoluble in water, ether, and benzene. The picrates and hydrochlorides of I were synthesized. The properties of the compounds obtained are given in the table.

Some chemical reactions of I have been studied: alkylation, acylation, and the reaction with 1-chloro-2,4-dinitrobenzene [11, 12].

EXPERIMENTAL

2-(N-Arylsulfonyl-N-phenylaminoethyl)benzimidazoles. A solution of 0.02 mole of o-phenylenediamine in 50 ml of absolute ethanol was prepared in a three-necked flask fitted with a mechanical stirrer, reflux condenser, and thermometer, and then 0.02 mole of the hydrochloride of the ethyl iminoether of a N-arylsulfonyl-N-phenyl-β-alanine was added in one portion. The temperature of the reaction mixture rose by 8°-12° C. The mixture was heated in the water bath at 70°-80° C for 3 hr and was left overnight. The precipitate was filtered off, washed with water, and crystallized from aqueous ethanol.

Hydrochlorides of the 2-(N-arylsulfonyl-N-phenylaminoethyl)benzimidazoles. a) A compound I (0.0025 mole) was boiled with dilute hydrochloric acid for 15 min. After cooling, the oily substance was dissolved in ethanol and precipitated with ether.

b) A solution of 0.005 mole of a compound I in chloroform was saturated with dry hydrogen chloride for 1 hr. After the solvent had been driven off, the residue was crystallized from ethanol and ether.

The picrates of I were synthesized by the usual method.

2-(N-p-Bromobenzenesulfonyl-N-phenylaminoethyl)benzimidazole (Ic). a) A mixture of 1.92 g (0.005 mole) of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine, 0.54 g (0.005 mole) of o-phenylenediamine, and 50 ml of 4 N hydrochloric acid was heated at 180° C for 12 hr. After cooling, the hydrochloric acid was distilled off in the vacuum of a water pump. This gave 1.18 g (48%) of the hydrochloride of Ic with mp 178.5°-179° C (ethanol—ether). By the action of aqueous ammonia, the hydrochloride was converted into the base with mp 161°-162° C.

A mixture with the Ic obtained from the iminoether gave no depression of the melting point.

b) A mixture of 0.99 g (0.0025 mole) of the methyl ester of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine, 0.27 g (0.0025 mole) of o-phenylenediamine, and 25 ml of 4 N hydrochloric acid was heated in a sealed tube at 180° to 200° C for 7 hr. After cooling, 0.59 g (48%) of the hydrochloride of Ic with mp 178.5°-179° C separated out. The base was obtained by treating the solvent with ammonia with subsequent crystallization from ethanol. Mp 161°-162° C.

c) A carefully ground mixture of 0.91 g (0.005 mole) of o-phenylenediamine dihydrochloride and 1.99 g (0.005 mole) of the methyl ester of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine was heated in a sealed tube at 190° C for 2 hr 30 min and at 200°-210° C for 30 min. After cooling, the contents of the tube were heated with 150 ml of 5% hydrochloric acid. This gave 1 g (40.7%) of Ic in the form of the hydrochloride, mp 178°-179° C. The base had mp 160.7°-162° C. A mixture with Ic synthesized by the method described above gave no depression of the melting point.

2-(N-Arylsulfonyl-N-phenylaminoethyl)benzimidazoles

Compound	R	Mp, °C	Empirical formula	N, %		Yield, %	Hydrochlorides					Picrates				
				found	calculated		mp, °C	empirical formula	N, %		yield, %	mp, °C	empirical formula	N, %		yield, %
									found	calculated				found	calculated	
Ia	H	171—172	$C_{21}H_{19}N_3O_2S$	10.73	11.13	89	177—178	$C_{21}H_{19}N_3O_2S \cdot HCl$	10.28	10.15	87	187—188	$C_{21}H_{19}N_3O_2S \cdot C_6H_3N_3O_7$	14.02	13.84	86
Ib	Cl	167—168	$C_{21}H_{18}ClN_3O_2S$	10.45	10.20	84.2	195—196	$C_{21}H_{18}ClN_3O_2S \cdot HCl$	9.94	9.38	85	189—190	$C_{21}H_{18}ClN_3O_2S \cdot C_6H_3N_3O_7$	12.77	13.11	84
Ic	Br	162—163	$C_{21}H_{18}BrN_3O_2S$	9.56	9.21	84	178—179	$C_{21}H_{18}BrN_3O_2S \cdot HCl$	8.50	8.53	82	186—187	$C_{21}H_{18}BrN_3O_2S \cdot C_6H_3N_3O_7$	11.92	12.26	76
Id	F	167.5—168.7	$C_{21}H_{18}FN_3O_2S$	10.68	10.63	82	195.8—197	$C_{21}H_{18}FN_3O_2S \cdot HCl$	9.75	9.72	88	198—199	$C_{21}H_{18}FN_3O_2S \cdot C_6H_3N_3O_7$	13.51	13.45	80
Ie	CH_3	179—180	$C_{22}H_{21}N_3O_2S$	10.96	10.74	81	209—210	$C_{22}H_{21}N_3O_2S \cdot HCl$	9.89	9.81	86	202—203	$C_{22}H_{21}N_3O_2S \cdot C_6H_3N_3O_7$	13.26	13.54	73
If	CH_3O	168—169	$C_{22}H_{21}N_3O_3S$	10.28	10.32	81	198—199	$C_{22}H_{21}N_3O_3S \cdot HCl$	9.40	9.46	85	200 (decomp.)	$C_{22}H_{21}N_3O_3S \cdot C_6H_3N_3O_7$	13.32	13.20	73

d) A mixture of 7.30 g (0.02 mole) of the nitrile of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine and 3.62 g (0.02 mole) of the dihydrochloride of o-phenylenediamine was heated in a sealed tube at 200° C for 1 hr 30 min at 210°-215° C [sic]. The dark gray melt was ground and was boiled with 200 ml of 5% HCl for 1 hr. The solid hydrochloride of Ic so obtained was separated off and crystallized from ethanol and ether. Mp 178.5° C. The base had mp 161° C. Yield 4.83 g (53%). A mixture with the Ic synthesized from the iminoether gave no depression of the melting point.

1-N-p-Bromobenzenesulfonyl-1, 2, 3, 4-tetrahydro-4-oxoquinoline. a) A mixture of 1.92 g (0.005 mole) of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine, 0.54 g (0.005 mole) of o-phenylenediamine, and 20 g of PPA was heated at 160°-170° C for 2 hr. The cooled mixture was poured into ice water; the precipitate that deposited was separated off and washed with 10% sodium carbonate solution and then with water, and was crystallized from aqueous methanol. This gave 1.09 g (60%) of the reaction product in the form of colorless needles with mp 169.5°-170° C. Found, %: N 3.80. Calculated for $C_{15}H_{12}BrNO_3S$, %: N 3.82. The o-phenylenediamine was recovered quantitatively (0.53 g).

b) A mixture of 0.99 g (0.0025 mole) of the methyl ester of N-p-bromobenzenesulfonyl-N-phenyl-β-alanine and 10 g of polyphosphoric acid in the form of a paste was heated at 160°-170° C for 2 hr. This gave 0.55 g (60%) of a substance with mp 169.5°-170° C which showed no depression in the mixed melting point test with the substance obtained in experiment (a).

2, 4-Dinitrophenylhydrazone —red crystalline powder with mp 186.5°-187.5° C. Found, %: N 12.80. Calculated for $C_{21}H_{16}BrN_5O_6S$, %: N 12.81.

1, 2, 3, 4-Tetrahydro-4-oxoquinoline. A mixture of 3.66 g (0.01 mole) of 1-N-p-bromobenzenesulfonyl-1, 2, 3, 4-tetrahydro-4-oxoquinoline, 6 ml of concentrated HCl, 4 ml of 80% acetic acid, and 3 ml of water was heated at 85° C for 2 hr. On cooling, the clear solution deposited the crystalline hydrochloride of 1, 2, 3, 4-tetrahydro-4-oxoquinoline. Treatment of the hydrochloride with ammonia gave the base, which was extracted with benzene. The benzene solution was dried with sodium sulfate and after the benzene had been driven off the residue was distilled in vacuum. Yield 2 g (89%). Bp 167° C (8 mm).

p-Nitrophenylhydrazone—red crystalline powder with mp 189°—190° C (from ethanol). According to the literature [13], bp of oxoquinoline 195° C (20 mm); mp of the p-nitrophenylhydrazone 189°-190° C.

2-(N-Benzenesulfonyl-N-phenylaminoethyl)-1-methylbenzimidazole. With cooling and stirring, 1.7 g (0.012 mole) of methyl iodide was added over 15 min to a solution of 0.5 g (0.009 mole) of caustic potash and 2.27 g (0.006 mole) of Ia in 20 ml of ethanol. After the end of the addition, the reaction mixture was stirred for 3 hr. The precipitate formed was filtered off, and the filtrate was evaporated in vacuum on the water bath. The oily substance obtained was crystallized from chloroform for three days. Yield 1.54 g (65%). Mp 129°-130° C. Found, %: N 11.34. Calculated for $C_{22}H_{21}N_3O_2S$, %: N 10.72.

Picrate—mp 175°—176° C (from ethanol), yield 86%. Found, %: N 14.00. Calculated for $C_{22}H_{21}N_3O_2S \cdot C_6H_3N_3O_7$, %: N 13.73.

2-(N-benzenesulfonyl-N-phenylaminoethyl)-1-benzoylbenzimidazole. With stirring and cooling, 1.4 g (0.010 mole) of benzoyl chloride was added to 1.89 g (0.005 mole) of Ia in 10 ml of pyridine. The mixture was stirred for 2 hr. The pyridine hydrochloride filtered off and the solvent was driven off in the vacuum of a water pump. The oily product crystallized in five days. Yield 1.79 g (75%). Mp 168.7°-169.2° C (from ethanol). Found, %: N. 8.79. Calculated for $C_{28}H_{23}N_3O_3S$, %: N 8.73.

2-(N-Benzenesulfonyl-N-phenylaminoethyl)-1-(2', 4'-dinitrophenyl)benzimidazole. A mixture of 1.88 g (0.005 mole) of Ia, 1.013 g (0.005 mole) of 1-chloro-2, 4-dinitrobenzene, and 0.68 g (0.005 mole) of crystalline sodium acetate was dissolved in 10 ml of ethanol, and the solution was boiled in the water bath for 3 hr 30 min and was then left overnight. The precipitate formed was crystallized twice from ethanol. Yield 1.12 g (42%). Mp 166°-166.5° C. Found, %: N 13.07. Calculated for $C_{27}H_{21}N_5O_6S$, %: N 12.87.

REFERENCES

1. A. M. Efros and M. P. Fedoseeva, DAN, 146, 236, 1962.
2. I. D. Neklesova and N. V. Egorova, DAN, 154, 155, 1964.
3. G. I. Braz, G. G. Rozantsev, A. Ya. Yakubovich, and V. P. Bazov, ZhOKh, 35, 305, 1965.
4. S. Clifford, U.S. patent no. 3080282, 1963; RZhKh, 3N194, 1965.
5. The Dow Chemical Co., U. S. patent no. 3075-991, 1963; RZhKh, 6N249, 1965.
6. T. Osdene, U.S. patent no. 3133923; RZhKh, 22N159, 1965.
7. K. Dietrich, W. Ozegowski, and M. Wunderwald, German Democratic Republic patent no. 28929, 1964; RZhKhim, 8N239, 1965.
8. M. A. Phillips, J. Chem. Soc., 2393, 1928.
9. B. A. Porai-Koshits, L. S. Efros, and O. F. Ginzburg, ZhOKh, 19, 1545, 1949.
10. G. R. Clemo and W. H. Perkin, J. Chem. Soc., 1608, 1924.
11. B. A. Porai-Koshits and Kh. L. Muravich, ZhOKh, 23, 1583, 1953.
12. A. M. Simonov and N. D. Vitkevich, ZhOKh, 29, 2404, 1959.

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