INVESTIGATIONS IN THE FIELD OF N-ARYL-β-AMINO ACIDS

III. HYDRAZINES OF N-ARYLSULFONYL-β-ALANINE

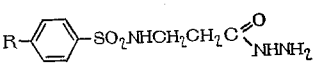
V. T. Braichenko, Z. F. Solomko,
M. S. Malinovskii, and R. F. Red'ko

UDC 615.31:547.466.23].012.1

Earlier we have studied some chemical transformations of N-aryl-β-alanine derivatives [1, 2]. In the continuation of the work on the synthesis of new biologically active compounds based on β-alanine derivatives, we have synthesized some hydrazides of N-arylsulfonyl-β-alanine and converted them to 2-(N-arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles. The latter are also interesting objects for biological tests, since substances having a wide spectrum of physiological action are found among them [3-6]. Intermediate products in the synthesis of 1,3,4-oxadiazole were: N_1-(N-arylsulfonyl-β-alanyl)-N_2-benzoylhydrazines, which were obtained by acylating hydrazides of N-arylsulfonyl-β-alanine with benzoyl chloride.

The structure of 2-(N-arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles was studied on the example of 2-(N-p-chlorobenzene-sulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazole. Hydrolysis in an acid and alkaline medium yielded benzoic and N-p-chlorobenzene-sulfonylaminopropionic acids. An IR spectrum of this oxadiazole recorded on IKS-22 in Vaseline oil shows two low-intensity bands in the 1580 cm^{-1} region, characterizing valence vibrations of oxadiazole ring, and three intense lines in the 790-720 cm^{-1} region, corresponding to deformation vibrations of the ring, in agreement with the literature data [7]. Inasmuch as the spectra of oxadiazole obtained by us may show a superposition of band vibrations of the oxadiazole ring and substituting groups, a comparison was made between the spectra of 2-(N-p-chlorobenzenesulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazole and starting N_1-(N-p-chlorobenzenesulfonyl-β-alanyl)-N-benzoylhydrazine. The absence of bands characterizing carbonyl group vibrations, as well as data on the thin-layer chromatography and hydrolysis, suggest that the compounds are 1,3,4-oxadiazoles.

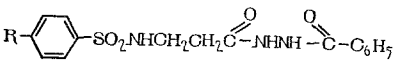
TABLE 1. Hydrazides of N-Arylsulfonyl-β-alanine.



R	Yield, %	Melting point, deg	Found, %	Empirical formula	Calculated, %
H	97,0	118,5—9	17,10 17,00	$C_9H_{13}N_3O_3S$	17,29
p-Cl	96,7	162—3	14,53 14,40	$C_9H_{12}ClN_3O_3S$	15,14
p-CH_3	97,7	96—7	15,91 15,63	$C_{10}H_{15}N_3O_3S$	16,40
p-I	91,0	157,5—8	11,86 11,70	$C_9H_{12}IN_3O_3S$	11,36
p-NO_2	84,0	181—1,5	20,04 19,80	$C_9H_{12}N_4O_5S$	19,44
p-CH_3CONH	92,5	138—9	19,10 19,00	$C_{11}H_{16}N_4O_4S$	18,66

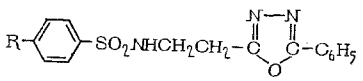
Dnepropetrovsk University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 8, pp. 6-8, August, 1972. Original article submitted October 20, 1970.

TABLE 2. N_1-(N-Arylsulfonyl-β-alanyl)-N_2-benzoylhydrazines



R	Yield, %	Melting point, deg	Found, %	Empirical formula	Calculated, %
H	72,0	144—5	11,78 11,96	$C_{16}H_{17}N_3O_4S$	12,10
p-Cl	70,0	188—9	11,38 11,00	$C_{16}H_{16}ClN_3O_4S$	11,01
p-CH_3	81,6	139—40	11,80 11,52	$C_{17}H_{19}N_3O_4S$	11,38
p-I	87,0	213—4	9,31 9,20	$C_{16}H_{16}IN_3O_4S$	8,90
p-NO_2	90,0	211—2	14,10 14,60	$C_{16}H_{16}N_4O_6S$	14,28
p-CH_3CONH	86,5	237—8	13,60 14,00	$C_{18}H_{20}N_4O_6S$	13,86

TABLE 3. 2-(N-Arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles



R	Yield, %	Melting point, deg	Found, %	Empirical formula	Calculated, %
H	92,0	121—2	13,35 13,20	$C_{16}H_{15}N_3O_3S$	13,15
p-CH_3	77,7	153—4	11,98 11,45	$C_{17}H_{17}N_3O_3S$	12,28
p-Cl	92,6	162—3	11,55 11,40	$C_{16}H_{14}ClN_3O_3S$	11,85
p-I	95,0	198—9	9,00 9,35	$C_{16}H_{14}IN_3O_3S$	9,23
p-NO_2	95,0	213—4	15,00 15,15	$C_{16}H_{14}N_4O_5S$	14,97
p-CH_3CONH	91,0	167—8	14,10 14,30	$C_{18}H_{18}N_4O_4S$	14,50

Tests of biological activity of hydrazides and their derivatives, carried out at the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, have shown that the hydrazides of N-p-chloro-, N-p-iodobenzenesulfonyl-β-alanine and of N-p-toluenesulfonyl-β-alanine possess weak activity with respect to acid-proof saprophyte B_5 and to tubercle bacilli in birds and man. 2-(N-Arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles have not shown such activity.

EXPERIMENTAL

Hydrazides of N-Arylsulfonyl-β-alanine. A mixture of 0.05 moles of methyl ester of N-arylsulfonyl-β-alanine, 0.1 mole of hydrazine hydrate, and 50 ml of ethyl alcohol was boiled on a water bath for 4 h. The alcohol was removed in vacuo. The resulting hydrazide was purified by recrystallization from alcohol (Table 1).

N_1-(N-Arylsulfonyl-β-alanyl)-N_2-benzoylhydrazines. To a solution of 0.01 mole of hydrazide of N-arylsulfonyl-β-alanine in a tenfold excess of dry pyridine was added with stirring 0.01 mole of benzoyl chloride. The temperature was maintained at 50-60°; after cooling, the mixture was poured into 200 ml of cold water. The precipitate was filtered off and washed with aqueous alcohol until the pyridine odor disappeared, and the product was then recrystallized from alcohol (Table 2).

2-(N-Arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles. A mixture of 0.005 mole of N_1-(N-arylsulfonyl-β-alanyl)-N_2-benzoylhydrazine, 0.05 mole of phosphorus oxychloride and 20 ml of dry benzene was boiled for 3.5 hours. To the cooled mixture was added 100 ml of cold water, and then it was cooled in an iced bath. The obtained precipitate was filtered off and recrystallized from alcohol (Table 3).

Hydrolysis of 2-(N-Arylsulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazoles. a. A mixture of 1 g of 2-(N-p-chlorobenzenesulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazole and 10 ml of concentrated hydrochloric acid was heated for five hours on a sand bath. Benzoic acid (0.1 g) sublimed in condenser. After cooling, the solution yielded 0.7 g of N-p-chlorobenzenesulfonylaminopropionic acid, the constants of which agree with the literature data [8]. Hydrazine was detected qualitatively (by the reduction of silver from an ammoniacal solution of silver oxide and decolorization of potassium permanganate solution).

b. A mixture of 1 g of 2-(N-p-chlorobenzenesulfonylaminoethyl)-5-phenyl-1,3,4-oxadiazole and 30 ml of 2% sodium hydroxide solution was heated to a complete disappearance of precipitate. The solution was cooled and neutralized with hydrochloric acid to pH 7.0. Yield, 0.82 g of precipitate representing a mixture of benzoic and N-p-chlorobenzenesulfonylaminopropionic acids. Benzoic acid was removed by sublimation.

LITERATURE CITED

1. Z. F. Solomko, M. S. Malinovskii, L. N. Polovina, et al., Khim. Geterotsiklich. Soed., 536 (1969).
2. Z. F. Solomko and G. A. Polinovskii, ibid., p 844.
3. H. Lehlen and W. Hildebrandt, GDR Pat. No. 30882 (1965); Ref. Zh. Khim., 1967, No. 14H295.
4. H. Wale and K. Losee, J. Med. Chem., 9, 1965 (1965).
5. French patent, No. 3573 (1965).
6. J. J. Piala and H. L. Vale, USA Pat. No. 3141022 (1964).
7. E. Müller and D. Ludsteak, Chem. Ber., 88, 921 (1955).
8. Z. F. Solomko, L. G. Gergel', S. A. Volkova, et al., Zh. Obshch. Khim., 34, 1964 (1964).