DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF β-PHENYLHOMOTAURINE

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Investigations into the synthesis of sulfoanalogs of γ-aminobutyric acid (GABA) are related to the search for new biologically active compounds. A comparative study of the sedative (calming) effects of GABA and homotaurine showed that the latter compound is more active [1]. As is known, introduction of an aryl substituent at the β position with respect to the acid group can significantly modify the biological activity of the compound. This was recently confirmed for suclofen – 3-amino-2-(4-chlorophenyl)propanesulfonic acid – an active specific GABA antagonist [2 – 4]. However, no readily accessible pathways for the synthesis of β-substituted γ-aminosulfonic acids were reported. Suclofen was obtained by two multistage synthetic pathways, proceeding from 4-chlorophenylacetonitrile [4] and α-methyl-4-chlorostyrene [2]. 2-Hydroxysuclofen and 2-hydroxy-2-phenylsuclofen were synthesized by radical addiction of ammonium bisulfite to the corresponding 3-amino-2-arylpropenes [3].

Below, we propose a convenient pathway for the synthesis of β-phenylhomotaurine, a sulfoanalog of the drug fenibut, proceeding from compound I obtained by adding a nitromethane salt to a phenyl ester of styrylsulfonic acid. No such reactions of α,β-alkenesulfonic acids were reported previously. The use of a phenyl ester instead of alkyl esters is explained by easy dealkylation of the latter in the presence of bases. For example, under similar conditions, the ethyl ester of styrylsulfonic acid fully converts into an inactive salt of this acid. Using the catalytic hydrogenation of nitroester I, we have obtained an aminosulfonic acid ester (II) and its hydrochloride (III) (depending on the reaction conditions). Similarly to the γ-aminocarboxylic esters, which readily form pyrrolidones upon cyclization in an alkaline medium, compounds II and III converted under analogous conditions into sultam (IV).

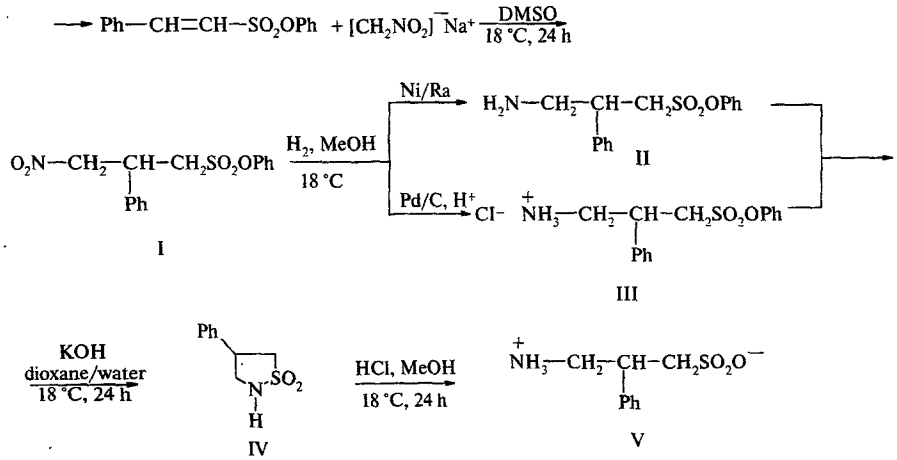

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TABLE 1. Yields and Physicochemical Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., C°	Empirical formula	^{1}H NMR spectrum: δ, ppm						IR spectrum: ν, cm^{-1}
				Solvent	CH_2N	CH	CH_2S	C_6H_5	$NH(NH_3^+)$	
I	70	39 – 41	$C_{15}H_{15}NO_5S$	$CDCl_3$	4.91 m	4.15 m	3.6 m	7.25 m	–	1350, 1320 (SO_3) 1570, 1320 (NO_2)
II	62	82 – 84	$C_{15}H_{17}NO_3S$	$(CD_3)_2SO$	3.34 m	4.06 m	3.79 m	7.50 m	6.95	1340, 1150(SO_3) 3380, 3300 (NH_2)
III	86	198 – 201	$C_{15}H_{17}NO_3S \cdot HCl$	$(CD_3)_2SO$	3.77 m	4.29 m	4.01 m	7.54 m	7.36 s	1350, 1140(SO_3) 3100 – 2600 (NH_3^+)
IV	63	101 – 103	$C_9H_{11}NO_2S$	$(CD_3)_2SO$	3.55 m	3.70 m	4.00 m	7.53 s	8.24 s	1320, 1155 (SO_3) 3300 (NH)
V	99	350(decomp.)	$C_9H_{13}NO_3S$	D_2O	3.65 m	...	3.75 m	7.70 s	...	1240, 1030 (SO_3) 3200 – 2500 (NH_3^+)

This is the first example of sultam synthesis from an aminosulfonic acid ester. Previously (see [2, 4]), the initial compounds in the synthesis of this drug were sulfochlorides or sulfamides subjected to cyclization under rather severe conditions.

The passage of gaseous hydrogen chloride through a methanol solution of sultam led to opening of the ring and the formation of γ-phenylhomotaurine (V) occurring in water in the form of a bipolar ion. The proposed structures of all products were confirmed by spectroscopic data (see Table 1).

Thus, we have obtained β-phenylhomotaurine (V) and its derivatives II and III, cyclization of which leads to the formation of sultam (IV).

EXPERIMENTAL PART

The IR spectra were measured on an UR-20 spectrophotometer in chloroform solutions. The ^{1}H NMR spectra were recorded on a Tesla BS487C (80 MHz) spectrometer using HMDS as the internal standard. TLC was performed on Silufol UV-254 plates eluted in a hexane – acetone (2 : 1) mixture; the spots were visualized under UV illumination.

The characteristics of the synthesized compounds are given in Table 1.

Styrylsulfonic acid was obtained by sulfidation of styrene with dioxane sulfotrioxide as described in [5].

Styrylsulfonic acid phenyl ester was synthesized by reacting the corresponding chloroanhydride [5] with sodium phenolate as described in [6].

3-Nitro-2-phenylpropane-1-sulfonic acid phenyl ester (I). To 1.26 g (15 mmole) of a nitromethane sodium salt (obtained by interaction between equimolar amounts of nitromethane and sodium methylate) in 15 ml DMSO was added with stirring 2 g (7.6 mmole) of β-styrylsulfonic acid in 15 ml DMSO. The reaction mixture was kept for 24 h at room temperature, with the course of the reaction monitored by TLC. Then the solution was poured into 300 g of finely crushed ice and hydrochloric acid was added to pH 3 – 4. The precipitate was filtered and washed with water to obtain 1.75 g of compound I. Finally, the target product was recrystallized from CCl_4 and dried in vacuum.

3-Amino-2-phenylpropane-1-sulfonic acid phenyl ester (II). Compound II was obtained by reduction of compound I (2 g, 6 mmole) on Raney nickel catalyst in methanol (15 ml) for 24 h at room temperature and atmospheric pressure (hydrogen uptake, 0.42 liter). Then the catalyst was separated by filtration and washed with hot methanol. The filtrate and washing methanol were combined and evaporated in vacuum to dryness. This yielded 1.12 g of a white crystalline product II, which was purified by recrystallization from CCl_4.

3-Amino-2-phenylpropane-1-sulfonic acid phenyl ester hydrochloride (III). A mixture of 0.15 g $PdCl_2$, 1.6 g charcoal, 1.6 ml hydrochloric acid, and 16 ml methanol in a hydrogenation vessel was saturated with hydrogen (0.2 – 0.24 liter). Then a solution of 2 g (6 mmole) of compound I in 4 ml of methanol was added and the reduction process was continued until a preset amount of hydrogen (0.42 liter) was absorbed. Then the catalyst was separated and the solvent (methanol) evaporated to obtain 1.72 g of compound III, which was purified by repeated precipitation with ether from methanol.

4-Phenylsultam (IV). A solution of 0.84 g (2.9 mmole) of compound II and 0.33 g (5.8 mole) of KOH in 10 ml of a 70 % aqueous dioxane was kept for 24 h, with the course of the reaction monitored by TLC. Then the solution was acidified with hydrochloric acid to pH 3.0 and the product was extracted with ether. The ether fraction yielded 0.36 g of compound IV, which was purified by recrystallization from benzene.

3-Amino-2-phenylpropane-1-sulfonic acid (V). A solution of 0.2 g (1 mmole) of 4-phenylsultam in 10 ml of methanol was bubbled for 1 h with gaseous hydrogen chloride, with the course of the reaction monitored by TLC. Then the reaction solution was evaporated to dryness and the

syrup-like residue was mixed with 2 – 3 ml of water and allowed to stand for 5 – 10 min. The resulting colorless crystalline product V was recrystallized from 80 % aqueous methanol.

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