[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

CERTAIN N-MONOSUBSTITUTED DERIVATIVES OF BIS(*p*-AMINOPHENYL) SULFONE

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Certain derivatives (1) of bis(*p*-aminophenyl) sulfone (I) having an alkyl type of substituent in one amino group are active in experimental tuberculosis, and possess the advantages of stability and only moderate toxicity. *p*-Aminophenyl-*p'*-*n*-propylaminophenyl sulfone was rated high in guinea-pig tuberculosis, but the compound is only slightly absorbed by man. Inasmuch as hydroxylation of the alkyl group appears to improve absorption, *p*-aminophenyl-*p'*-γ-hydroxypropylaminophenyl sulfone (III) has been synthesized through reaction of 3-bromo-1-propanol with *p*-nitrophenyl-*p'*-aminophenyl sulfone and subsequent reduction of the resulting *p*-nitrophenyl-*p'*-γ-hydroxypropylaminophenyl sulfone (II) with hydrogen and a Raney nickel catalyst. The hydroxypropylation reaction produced a less satisfactory yield than was obtained previously in the hydroxyethylation (2) of *p*-nitrophenyl-*p'*-aminophenyl sulfone by reaction with 2-bromoethanol.

p-Aminophenyl-*p'*-β-ethylthioethylaminophenyl sulfone (IV) resulted in high yield from the reaction of ethanethiol and sodium ethoxide with *p*-aminophenyl-*p'*-β-bromoethylaminophenyl sulfone (V) (2). The reaction of sodium methoxide in methanol with V yielded a crystalline compound which, by analogy with established structures (3) of the products of the reaction of alkaline reagents with β-haloethylamines, is designated *p*-aminophenyl-*p'*-ethyleneiminophenyl sulfone (VI) in preference to *p*-aminophenyl-*p'*-vinylaminophenyl sulfone. Compound VI reacts with hydrogen chloride in methanol solution to yield *p*-aminophenyl-*p'*-β-chloroethylaminophenyl sulfone (VII). The latter compound is produced in high yield through substitution of a chlorine atom for the bromine atom of compound V in boiling ethanol solution containing 1.7% hydrogen chloride. It was prepared also by the reduction of the nitro group of *p*-nitrophenyl-*p'*-β-chloroethylaminophenyl sulfone with stannous chloride. Acetylation of V in aqueous suspension with acetic anhydride yielded *p*-acetylaminophenyl-*p'*-β-bromoethylaminophenyl sulfone (VIII).

Unsuccessful attempts were made to prepare a crystalline ether by substitution of the oxy-L-phenylalanine group for the bromine atom of V through refluxing methanol solutions of equimolecular amounts of sodium methoxide, compound V, and the methyl ester of L-tyrosine or of N-acetyl-L-tyrosine. Some of the ethyleneimino derivative (VI) was identified as one product of these reactions. β-[3-(*p*-Sulfanilylphenylazo)-4-hydroxyphenyl]-L-alanine (IX) was prepared by diazotization of I with one equivalent of nitrous acid and subsequent coupling of the resulting diazonium salt with L-tyrosine at the minimum *p*H 8.0. With the use of D-tyrosine similar reactions yielded β-[3-(*p*-sulfanilylphenylazo)-4-hydroxyphenyl]-D-alanine (X).

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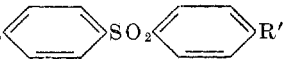
TABLE I

DERIVATIVES OF PHENYL SULFONE R  R′

NO.	R	R′
I	NH_2	NH_2
II	NO_2	$NHCH_2CH_2CH_2OH$
III	NH_2	$NHCH_2CH_2CH_2OH$
IV	NH_2	$NHCH_2CH_2SC_2H_5$
V	NH_2	$NHCH_2CH_2Br$
VI	NH_2	
VII	NH_2	$NHCH_2CH_2Cl$
VIII	$NHCOCH_3$	$NHCH_2CH_2Br$
IX and X	NH_2	$N{=}N{-}(3)C_6H_3(OH{-}4)CH_2CH(NH_2)CO_2H$

EXPERIMENTAL[1]

p-Nitrophenyl-p′-γ-hydroxypropylaminophenyl sulfone (II). To a hot solution of 100 g. of *p*-nitrophenyl-*p*′-aminophenyl sulfone in 500 cc. of Cellosolve (2-ethoxyethanol) were added in succession 50 cc. of water, 50 g. of 3-bromo-1-propanol, and 30 g. of powdered calcium carbonate. The mixture was kept on the steam-bath under reflux for 80 hours with shaking twice daily; 25 g. of 3-bromo-1-propanol and 15 g. of calcium carbonate were added and the heating continued for an additional 75 hours. Excess calcium carbonate was filtered off and the solvent was removed by distillation *in vacuo*. The sirup was mixed with some water, which was then evaporated *in vacuo*. The thick brown sirup, after being mixed with 600 cc. of water, crystallized for the most part during several days. Compound II was purified by fractional crystallization from ethanol or in later stages from methanol. Crystallization of II from ethanol solutions of the crude substance usually was preceded by separation of another, as yet unidentified, compound melting above 200°. Pure, orange colored prisms of II melted at 156–157°; yield 22 g.; more II probably was a constituent of a considerable amount of accompanying sirup.

Anal. Calc'd for $C_{15}H_{16}N_2O_5S$: C, 53.56; H, 4.80; N, 8.33; S, 9.53.
Found: C, 53.44; H, 4.92; N, 8.48; S, 9.44.

p-Aminophenyl-p′-γ-hydroxypropylaminophenyl sulfone (III). A suspension of 3.5 g. of powdered II in 90 cc. of absolute ethanol was shaken for six hours with hydrogen and a Raney nickel catalyst at room temperature and atmospheric pressure, 3 molecular-equivalents of hydrogen being absorbed. The filtered solution was concentrated to 10 cc. and diluted with sufficient water to precipitate most of the product as a sirup, which soon crystallized. Purification was completed by recrystallization as colorless, rod-shaped prisms from a mixture of ethanol and water; yield 2.4 g. or 75%; m.p. 150–151°. It is readily soluble

[1] Melting points are uncorrected.

in acetone, soluble in ethanol and methanol, somewhat soluble in hot water, and only slightly soluble in cold water.

Anal. Calc'd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.15; S, 10.46.
Found: C, 58.60; H, 5.67; N, 9.07; S, 10.55.

p-Aminophenyl-p'-β-ethylthioethylaminophenyl sulfone (IV). To a solution of sodium ethoxide, prepared from 0.6 g. of sodium and 75 cc. of absolute ethanol, were added 1.5 g. of ethanethiol and 3 g. of V. After being refluxed for two hours the solution was neutralized with hydrochloric acid, filtered, and the solvent evaporated *in vacuo*. Extraction of the residue with hot absolute ethanol and filtration removed sodium salts. Crude IV was washed with cold water and recrystallized from ethanol as slightly yellow prisms; yield 2.3 g. or 82%; m.p. 100–101°.

Anal. Calc'd for $C_{16}H_{20}N_2O_2S_2$: C, 57.11; H, 5.99; N, 8.33; S, 19.06.
Found: C, 57.04; H, 6.16; N, 8.12; S, 18.96.

p-Aminophenyl-p'-ethyleneiminophenyl sulfone (VI). To a hot solution of 2 g. of V in 120 cc. of methanol was added 53.6 cc. of 0.1034 *N* sodium methoxide, prepared from sodium and methanol. The solution was refluxed for 21 hours, the solvent was removed, and the crystalline residue washed with cold water. Recrystallized from ethanol as colorless plates, it melted at 186–187°; yield 1.2 g. In 30% dioxane solution it showed diazotization and coupling with the Bratton-Marshall (4) reagents.

Anal. Calc'd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.69.
Found: C, 61.12; H, 5.20; N, 9.92; S, 11.91.

The compound reacts with hydrogen chloride to produce VII. A solution of 0.25 g. in 30 cc. of methanol, cooled in ice-water, was saturated with dry hydrogen chloride and left stoppered at room temperature for 22 hours. The solvent was evaporated at room temperature, and the residue mixed with 5 cc. of water, and neutralized with sodium hydroxide. Crystals melting at 157–158° in a yield of *ca.* 60% were obtained readily by recrystallization of the crude product from methanol. Several additional recrystallizations from methanol and from mixtures of methanol and petroleum ether yielded slightly brown prisms melting at 160–161°. A mixture with pure authentic crystals of VII melted at 161–162°. The reaction of ethyleneimine derivatives with halogen acids is known (5) to produce dimerization or polymerization in some instances, and it is possible that the presence of such a product may have rendered purification of VII difficult with the small quantity of material available.

p-Aminophenyl-p'-β-chloroethylaminophenyl sulfone (VII). To a hot solution of 1 g. of V in 150 cc. of 95% ethanol was added 7 cc. of 38% HCl. After the solution had been refluxed for 3½ hours, it was neutralized with sodium hydroxide solution and filtered to remove crystals of sodium chloride. The solvent was evaporated *in vacuo*, the residue extracted with 10 cc. of cold water, and then purified by recrystallization from ethanol and from methanol as slightly brown prisms; yield 0.8 g. or 90%; m.p. 162–163°. The same product, m.p. 162–163° alone or mixed with the crystals just described, was obtained under reducing conditions (2), 3 g. of 40-mesh iron filings being added to the above reaction mixture.

Anal. Calc'd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.87; Cl, 11.41; N, 9.02; S, 10.32.
Found: C, 53.83; H, 5.01; Cl, 11.71; N, 9.06; S, 10.25.

Reduction of the nitro group of *p*-nitrophenyl-*p'*-β-chloroethylaminophenyl sulfone (2) with stannous chloride produced VII. A solution of 0.2 g. of stannous chloride dihydrate in 2 cc. of 38% hydrochloric acid was mixed with a hot solution of 0.1 g. of the nitro compound in 25 cc. of absolute ethanol. The solution was refluxed for two hours, then nearly neutralized with aqueous sodium hydroxide solution and treated with hydrogen sulfide to remove tin. After a suspension of the product in water had been neutralized with sodium hydroxide it was collected and washed with water. Recrystallized from methanol, it melted at 162–163°. Found: C, 54.23; H, 4.88.

p-Acetylaminophenyl-p'-β-bromoethylaminophenyl sulfone (VIII). To a suspension of 5 g. of V in 25 cc. of water was added 25 cc. of acetic anhydride. The crystals dissolved when the mixture was stirred and the solution was cooled to prevent the temperature from increasing above 70°. After three hours the crystals were filtered and washed with cold water.

Additional product was precipitated upon mixing the filtrate with a large volume of ice-water, followed by the addition of 10 g. of sodium carbonate. It was purified by recrystallization from methanol as slightly brown, boat-shaped prisms; yield 4.6 g.; m.p. 175–176°.

Anal. Calc'd for $C_{16}H_{17}BrN_2O_3S$: C, 48.37; H, 4.31; Br, 20.12; N, 7.05; S, 8.07.

Found: C, 48.64; H, 4.66; Br, 19.85; N, 6.92; S, 8.21.

β-[3-(p-Sulfanilylphenylazo)-4-hydroxyphenyl]-L-alanine (IX). A solution of 1.4 g. of sodium nitrite in 25 cc. of water was added during 30 minutes to a stirred suspension of 5 g. of I in 150 cc. of 13% hydrochloric acid at 0–5°. The diazonium salt solution was mixed gradually with a stirred solution of the sodium salt of L-tyrosine, prepared by mixing 3.7 g. of L-tyrosine, 55 g. of anhydrous sodium carbonate, 20.4 cc. of *N* sodium hydroxide, and 200 cc. of water. During the coupling process the mixture was kept cold by addition of cracked ice and at the minimum *p*H 8.0 (glass electrode). After separation of solid was complete at 5°, it was filtered and extracted twice with hot water, first with 200 cc. and then with 800 cc. to which 2 cc. of *N* sodium hydroxide solution was added. The two dark-red solutions were kept overnight at 5°, a little solid was removed by filtration and the combined filtrates were concentrated *in vacuo* to *ca.* 150 cc. Acidification of the solution to *p*H 4.5 with acetic acid precipitated the brown, gelatinous acid. A filtered solution of the freshly precipitated, wet acid in 70 cc. of pyridine was mixed with 300 cc. of methanol. The precipitated amorphous solid was collected and again precipitated from its pyridine solution in a similar way. After the black solid had been extracted with 20 cc. of cold acetone and dried at 80°, it weighed 1.6 g.; it softened somewhat but did not melt at 320°. The acid is only slightly soluble in water, dilute hydrochloric acid, and the common organic solvents; it is soluble in pyridine and in water as its sodium salt. The analytical sample, which was dried at 100° *in vacuo*, left 4.4% ash upon combustion.

Anal. Calc'd for $C_{21}H_{20}N_4O_5S$: C, 57.26; H, 4.58; N, 12.72; S, 7.28.

Found: C, 56.13; H, 4.49; N, 12.62; S, 7.42.

The color of solutions of IX precluded the determination of its optical rotation. Since a comparison of its tuberculostatic activity with that of compound X from D-tyrosine was planned, evidence of optical activity was obtained after reduction. A mixture of 0.2 g. of IX, 0.4 g. of stannous chloride dihydrate, and 10 cc. of 38% hydrochloric acid was kept at 100° under reflux for three hours, then diluted with 5 cc. of glacial acetic acid and the heating continued for 30 minutes. After concentration *in vacuo* to *ca.* 7 cc., the mixture was heated on the steam-bath and clarified by addition of hydrochloric acid. The warm solution was diluted with water and treated with hydrogen sulfide. The filtered solution, after concentration to 7 cc., showed α_D −0.17° in a 4-dm. tube.

β-[3-(p-Sulfanilylphenylazo)-4-hydroxyphenyl]-D-alanine (X) was prepared by the procedure described for IX, using 1.25 g. of I, 0.35 g. of sodium nitrite, and 0.93 g. of D-tyrosine which showed $[\alpha]_D^{25}$ +11.5° in *N*-hydrochloric acid (c, 4.0). The product softened somewhat but did not melt at 320°; it resembled the L-isomer in appearance and solubility. Found: N, 13.27; S, 7.66.

SUMMARY

Hydroxypropylation of *p*-nitrophenyl-*p'*-aminophenyl sulfone by reaction with 3-bromo-1-propanol and catalytic reduction of the product has yielded *p*-aminophenyl-*p'*-γ-hydroxypropylaminophenyl sulfone. *p*-Aminophenyl-*p'*-β-bromoethylaminophenyl sulfone (V) reacts with ethanethiol and sodium ethoxide to produce *p*-aminophenyl-*p'*-β-ethylthioethylaminophenyl sulfone and with sodium methoxide to form *p*-aminophenyl-*p'*-ethyleneiminophenyl sulfone. *p*-Amino phenyl-*p'*-β-chloroethylaminophenyl sulfone results in high yield through replacement of the bromine atom of V by a chlorine atom in hot ethanolic hydrogen chloride solution. The reaction of *p*-sulfanilylbenzenediazonium chloride with

D- and L-tyrosine under selected conditions afforded the two optical isomers of β-[3-(*p*-sulfanilylphenylazo)-4-hydroxyphenyl]alanine.

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