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SULFONES. III. 4-AMINOPHENYL ALKYL SULFONES

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Received October 27, 1949

It has been observed by Fourneau and co-workers (1) that 4-aminophenyl methyl sulfone has chemotherapeutic activity and that activity decreased as the length of the aliphatic side chain was increased. A number of 4-aminophenyl alkyl sulfones with functional groups in the alkyl residue have now been synthesized in order to determine their effect on activity.[1]

Condensation of sodium 4-acetaminobenzenesulfinate with ethylene chlorohydrin resulted in 4-acetaminophenyl β-hydroxyethyl sulfone. The hydroxyl group was converted to the *p*-toluenesulfonic ester with *p*-toluenesulfonyl chloride in pyridine. The tosylate group was very reactive and was readily replaced by such amines as diethylamine, piperidine or N-carbethoxypiperazine. The tosylate group also reacted smoothly with potassium phthalimide or sodium iodide to give 4-acetaminophenyl β-phthalimidoethyl sulfone and 4-acetaminophenyl β-iodoethyl sulfone, respectively. In all the above compounds the acetyl group was removed by short hydrolysis with boiling hydrochloric acid.

Similarly, by the condensation of sodium 4-acetaminobenzenesulfinate with propyl iodide, allyl bromide, octyl bromide, lauryl bromide, 4-nitrobenzyl chloride, 6-bromo-1-phthalimidohexane,β -bromopropionic acid, and ethyl α-bromocaproate followed by reduction and/or hydrolysis additional alkyl sulfones were synthesized.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

4-Acetaminophenyl β-hydroxyethyl sulfone. To a solution of 140 g. of 4-acetaminobenzenesulfinic acid in 540 cc. of water containing 36 g. of reagent sodium hydroxide was added 108 cc. of ethylene chlorohydrin. After being heated on the steam-bath for three hours, the solution was cooled in an ice-bath and the product collected on a filter. The filtrate and water washings were made just alkaline with 10% sodium hydroxide and heated on the steam-bath for three hours, 10% alkali being added at intervals to keep the solution barely alkaline; total yield, 118 g. (54%), m.p. 187–190°. Recrystallization of a sample from methanol-acetone gave white crystals, m.p. 192–193°.

Anal. Calc'd for $C_{10}H_{13}NO_4S$: C 49, 3; H, 5.4; N, 5.8.
Found: C, 49.0; H, 5.9; N, 6.0.

4-Acetaminophenyl β-(p-toluenesulfonyloxy)ethyl sulfone. To an ice-cold solution of 203 g. of *p*-toluenesulfonyl chloride in 950 cc. of reagent pyridine was added 225 g. of 4-acetaminophenyl β-hydroxyethyl sulfone. After two hours at 0°, the mixture was poured into a large volume of ice-water; yield, 290 g. (79%), m.p. 100–103°. Recrystallization from alcohol gave white crystals, m.p. 105–107°.

Anal. Calc'd for $C_{17}H_{19}NO_6S_2$: N, 3.5. Found: N, 3.4.

4-Acetaminophenyl β-piperidinoethyl sulfone. To 35 g. of the above tosyl sulfone was

[1] The biological studies will be reported elsewhere.

added 22 cc. of piperidine. Considerable heat was evolved. After being heated on the steam-bath for two hours, the oil was treated with water when it quickly solidified; yield, 28.7 g. (99%), of a hydrate, m.p. 110° (gas evolution). Recrystallization from benzene gave anhydrous white crystals, m.p. 121–123°.

Anal. Calc'd for $C_{15}H_{22}N_2O_3S$: N, 9.0. Found: N, 9.1.

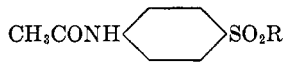
Similarly *4-acetaminophenyl β-diethylaminoethyl sulfone* was prepared in 99% yield, m.p. 100–102° from water.

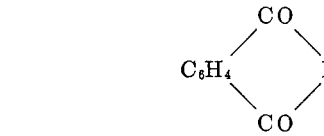
Anal. Calc'd for $C_{14}H_{22}N_2O_3S$: N, 9.4. Found: N, 9.3.

Walker (2) has synthesized this compound in a different manner and recorded that it formed a hydrate, m.p. 94–96°.

By condensation of the tosylate with N-carbethoxypiperazine in boiling alcohol for one hour a 92% yield of *4-acetaminophenyl β-(N-carbethoxypiperazinoethyl) sulfone* was ob-

TABLE I



R	REFLUX (hours)	YIELD %	M.P. °C.	ANALYSES					
				Calc'd			Found		
				C	H	N	C	H	N
n-C_3H_7-[f]	2	64	125–127[a]	54.8	6.3	5.8	54.5	6.5	6.1
CH_2=$CHCH_2$-[e]	½	67	113–115[a]			5.8			5.5
	20	87	175–177[c]			6.5			6.7
—CH_2CH_2COOH	17	42	182–183[d]	48.7	4.8	5.2	48.6	5.3	5.1
—$CH_2C_6H_4NO_2$	⅙	70	246–250[c]			8.4			8.2
$C_4H_9CHCO_2Et$ |	2.5	67	102–104[b]	56.3	6.8	4.1	55.7	6.8	4.4

[a] Recrystallized from ethyl acetate-petroleum ether. [b] Recrystallized from dilute alcohol. [c] Recrystallized from Methyl Cellosolve-water. [d] Reaction run in water, acidified, and product recrystallized from water. [e] This compound has been recently reported to melt at 98–100° (4). [f] Recently reported (6) to melt at 129°.

tained by evaporation of the solvent, solution in water and basification with 10% sodium hydroxide; white crystals from ethyl acetate-petroleum ether, m.p. 127–128°.

Anal. Calc'd for $C_{17}H_{25}N_3O_5S$: N, 11.0. Found: N, 11.0.

4-Acetaminophenyl β-phthalimidoethyl sulfone. A mixture of 5 g. of 4-acetaminophenyl β-(*p*-toluenesulfonyloxy)ethyl sulfone, 2.5 g. of potassium phthalimide, and 5 cc. of *n*-propyl alcohol was heated on the steam-bath for one hour. Dilution with water gave 4.5 g. (96%) of product, m.p. 216–221°.

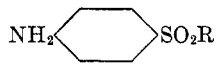
Goldberg (3) has recorded a m.p. of 228–230° for this compound prepared in a different manner.

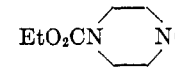
4-Acetaminophenyl β-iodoethyl sulfone. A mixture of 50 g. of 4-acetaminophenyl β-(*p*-toluenesulfonyloxy)ethyl sulfone, 38 g. of sodium iodide, and 380 cc. of acetone was refluxed for fifteen hours during which time sodium *p*-toluenesulfonate separated. The mixture was poured into about four volumes of water containing some sodium bisulfite. The product was collected; yield, 38.5 g. (87%), m.p. 188–190°. Recrystallization from acetone gave white crystals, m.p. 192–193°.

Anal. Calc'd for $C_{10}H_{12}INO_3S$: N, 4.0. Found: N, 3.9.

4-Acetaminophenyl n-propyl sulfone. To a solution of 2.0 g. of reagent sodium hydroxide in 2 cc. of water was added 50 cc. of alcohol and 10 g. of *p*-acetaminobenzenesulfinic acid. The solution was refluxed with 7.5 cc. of *n*-propyl iodide. Dilution with water gave an oil which was extracted with ethyl acetate. The extracts, washed with aqueous sodium bicarbonate and dried with magnesium sulfate, were evaporated to dryness *in vacuo* and the residue triturated with benzene. Other compounds prepared similarly are listed in Table I.

TABLE II



R	METHOD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
$HOCH_2CH_2$-	B	210–213 dec.[i]			5.9			6.0
$Et_2NCH_2CH_2$-[e]	C	102–104[j]	56.3	7.9	10.9	56.5	7.8	10.4
$C_5H_{10}NCH_2CH_2$-	C	127–129[j]	58.3	7.5	10.4	58.3	6.6	10.8
	C	96–98 dec.[a]	50.2	7.0	11.7	50.6	7.1	11.4
$NH_2CH_2CH_2$-	D	235–238 dec.[b]						
ICH_2CH_2-	A[c]	206–208 dec.[k]			4.0			4.4
$CH_3CH_2CH_2$-[f]	A	215–217 dec.[l]			6.0			6.3
CH_2=$CHCH_2$-[g]	A	212–213 dec.[l]	46.3	5.2	6.0	46.7	5.4	6.2
n-C_8H_{17}-[h]	E	96–98[k]	62.4	8.6	5.2	63.0	8.8	5.3
n-$C_{12}H_{25}$-	E	105–107[k]			4.3			4.5
$NH_2(CH_2)_6$-	D	217–220 dec.[l]			8.5			9.0
$-CH_2CH_2COOH$[f]	A	222–224 dec.[m]	40.7	4.6	5.5	41.1	4.7	5.3
$-CH_2C_6H_4NH_2$	[d]	215–216 dec.[n]	59.6	5.4	10.7	59.9	5.8	10.6
C_4H_9-$CHCOOEt$	F	148–150 dec.[o]	50.2	6.6	4.2	50.5	6.3	4.5
CH_3-	A	236–237 dec.[m]			6.8			6.9

[a] Monohydrate from water. [b] Obtained in 95% yield by modification of the procedure of Goldberg (3) who recorded a m.p. of 238–240°. [c] An equal volume of alcohol was used to aid solubility during the hydrolysis which required one hour. [d] The nitro group was reduced with simultaneous removal of the acetyl group using stannous chloride and the free base isolated as previously described for similar compounds in paper I of this series. [e] Walker (2) has described the dihydrochloride of this compound. [f] The free base has been synthesized in a different manner (5). [g] The free base has been described (4). [h] Smirnova (6) reported a m.p. of 197–198°, a probable misprint. [i] Methanol-ethyl acetate. [j] Benzene. [k] Methanol. [l] Methanol-ether. [m] 12 *N* Hydrochloric acid. [n] Aqueous Methyl Cellosolve. [o] Chloroform-ether.

4-Aminophenyl alkyl sulfones. The acetyl group was removed by boiling with 10 cc./g. of 6 *N* hydrochloric acid for fifteen minutes. The compounds obtained are listed in Table II. The yields were 80–95% with the following modifications in procedure.

A. The hydrochloride crystallized on cooling the reaction mixture.

B. The reaction mixture was evaporated to dryness *in vacuo* and the hydrochloride salt triturated with acetone.

C. The reaction mixture was evaporated to dryness *in vacuo*, the residue was dissolved in water and poured into an excess of ammonia water and ice. The free base was collected.

D. The acetyl and phthalyl groups were removed by boiling with 10 *N* hydrochloric acid for twelve hours. The phthalic acid was removed after cooling and the filtrate was worked up as in B.

E. The crude non-crystalline acetyl derivative was hydrolyzed by boiling with 10 cc. of 6 *N* hydrochloric acid and 5 cc. of alcohol per gram. The hydrochloride separated on cooling. It was dissolved in Methyl Cellosolve, made basic with ammonia water, and diluted with water.

F. The acetyl group was removed by refluxing with absolute ethanol saturated with hydrogen chloride for ninety minutes. Solvent was removed *in vacuo* and the residue crystallized from chloroform-ether.

SUMMARY

Fifteen 4-aminophenyl alkyl sulfones have been synthesized for chemotherapeutic testing.

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