collected and recrystallized to give the corresponding salts as shown in Table II.

(3) Reaction of N-Benzyl Tertiary Amines with 3,3-Dimethylallyl Bromide.—A mixture of 1 molar equiv of tertiary amine and 3,3-dimethylallyl bromide in dry Me_2CO was refluxed on a water bath for 1–5 hr in the presence of dry $NaHCO_3$.[20] After completion of the reaction, the solvent was distilled, and the residue was extracted with EtOH in order to remove an inorganic reagent and filtered. Evaporation of the filtrate gave the corresponding salts as shown in Table II.

(4) 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-3-(3,3-dimethylallyl)-3-benzazocinium Iodide (III).—A mixture of 0.36 g of I, 0.54 g of MeI, and 20 ml of dry PhH was refluxed on a water bath for 3 hr. After cooling, the solvent was distilled and the residue was triturated and washed (Et_2O) to give 0.34 g (63.1%) of colorless needles, mp 105–107° dec, which were used in the following reaction.

(5) 3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6,11-dimethyl-3-(3,3-dimethylallyl)-3-benzazocinium Bromide (IV).—A mixture of 2 g of I, 20 ml of dry PhH, and 3 g of $PhCH_2Br$ was refluxed on a water bath for 40 min. After cooling, excess Et_2O was added to the reaction mixture, which was set aside to precipitate 3.1 g (97%) of a colorless powder. Recrystallization from EtOH–Et_2O afforded a colorless powder, mp 159–161° dec, identical with an authentic sample (VIII)[1] by mixture melting point and ir (KBr) spectral comparison.

Reaction of Quaternary Ammonium Salts with Thiophenol. (1) Reaction of N-Benzyl Quaternary Ammonium Salts with Thiophenol in Aqueous NaOH.—A mixture of N-benzyl derivatives (*cf.* reaction 1–8 in Table I), excess thiophenol, and aqueous NaOH solution was heated on a water bath with stirring. After cooling, the reaction mixture was extracted (Et_2O). The extract was washed (saturated NaCl solution) and then extracted with 5–10% HCl. In this case evaporation of the above Et_2O gave benzyl phenyl thioether as colorless plates (from EtOH), mp 41–42°.[13] The acidic solution was made basic with aqueous NaOH or concentrated NH_4OH and extracted with a large amount of Et_2O. The extract was washed (saturated NaCl solution), dried (Na_2SO_4), and evaporated to give the free bases, which were purified as such, and/or salts by recrystallization or distillation *in vacuo*.

(2) N-Allyl- and N-(3,3-Dimethylallyl)-N-benzyl Quaternary Ammonium Salts with Thiophenol in Alkaline Solution.—By the same conditions as above, reactions 9–13 in Table II were carried out to give a syrup, which showed two spots (except in case of 9) on its tlc (Wakogel B-5). Column chromatography on silicic acid using PhH, PhH–$CHCl_3$, $CHCl_3$, $CHCl_3$–MeOH, and finally MeOH as eluent, followed by purification, gave two compounds as shown in Table II, which were characterized by tlc and ir spectral comparisons with the authentic samples. Furthermore, benzyl phenyl thioether, mp 40–41°,[15] and allyl phenyl thioether, bp 83–87° (10 mm),[16] were obtained as insoluble substances in aqueous NaOH and aqueous HCl.

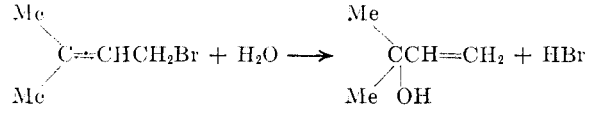
(3) Reaction of II and III with Thiophenol in Alkaline Solution.—A mixture of quaternary ammonium salts (II and III), thiophenol, and 5% aqueous NaOH was heated on a water bath at 40–50° with stirring for 5 hr. After cooling, the reaction mixture was mixed with Et_2O and extracted with 10% HCl. The acidic extract was made basic with concentrated NH_4OH and again extracted with $CHCl_3$ while salting out. The extract was washed (H_2O), dried (Na_2SO_4), and evaporated to give a colorless solid, whose recrystallization from EtOH gave V in 66.9–90.5% yields, identical with an authentic sample.[17]

(4) Reaction of IV with Thiophenol in Alkaline Solution.—A mixture of 3.9 g of IV, 9.4 g of C_6H_5SH, and 34 ml of 5% NaOH was heated with stirring on a water bath at 40–50° for 5 hr and treated as usual to give a colorless caramel-like substance, which was purified by chromatography using silicic acid. Removal of the Et_2O eluent gave 0.64 g (24.4%) of VI and evaporation of the Et_2O–$CHCl_3$ (95:5) eluent gave 1.24 (51%) of I, both of which were identical with the authentic samples.

(5) Reaction of IV with Sodium Thiophenoxide in Organic Solvents.—A mixture of 2 g of IV, 1.18 g of C_6H_5SNa,[21] and 50 ml of 2-butanone was heated on a water bath at 73–75° for 5 hr. After addition of 50 ml of H_2O to the reaction mixture, followed by extraction with $CHCl_3$, the $CHCl_3$ layer was evaporated to give a residue, which was extracted with 10% HCl. The resultant acidic solution was basified with saturated $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a brown caramel, which was purified by silicic acid chromatography using Et_2O, Et_2O–$CHCl_3$, $CHCl_3$, and MeOH as eluent. Removal of Et_2O gave 0.31 g (24.7%) of VI, whereas evaporation of ether–$CHCl_3$ afforded 0.79 g (58.7%) of I, both of which were identical with the authentic samples, respectively.

Acknowledgment. We thank Dr. K. Morita, Takeda Pharmaceutical Co. Ltd., and President A. Yanagisawa and Director O. Takagi of The Grelan Pharmaceutical Co. Ltd. for their encouragement. We also thank Miss R. Hasebe, Miss A. Kawakami, Miss Y. Tadano, Miss T. Yoshida, Miss K. Shima, and Miss R. Kato of Pharmaceutical Institute, Tohoku University, for ir and nmr spectral determinations and for microanalyses.

(20) Since 3,3-dimethylallyl bromide is decomposed in the presence of water, the HBr[14] formed seems to give the hydrobromide of the base. Therefore, this reagent was used.



(21) S. I. Miller, C. E. Orzech, C. A. Welch, G. R. Ziegler, and J. I. Dickstein, *J. Am. Chem. Soc.*, **84**, 2020 (1962).

Sulfamoylbenzoic Acid Ester Derivatives as Potential Local Anesthetics. I

N. SHARGHI, I. LALEZARI, G. NILOOFARI, AND H. GOLGOLAB

Department of Chemistry, Faculty of Pharmacy, University of Tehran, Iran

Received March 21, 1969

In view of the local anesthetic activity of the aromatic esters of the dialkylamino alcohols such as procaine, it was of interest to study the local anesthetic activity of sulfamoylbenzoic acid ester derivatives.

p-Dipropylsulfamoylbenzoic acid and *p*-dibutylsulfamoylbenzoic acid are widely used as uricosuric agents.[1] Some dialkylaminoethyl esters of *p*-dialkylsulfamoylbenzoic acids were reported to block the tubules in the kidneys, delaying secretion of therapeutic substances,[2,3] or forming crystalline salts with penicillin.[4] *p*-Dimethylsulfamoylbenzoic acid dimethylaminoethyl and diethylaminoethyl esters were found to be respiratory analeptics with low toxicity.[5]

In this work, aminoethyl esters of sulfamoylbenzoic acids were synthesized by the route outlined in Scheme I. The compounds prepared are tabulated in Table I and were subjected to local anesthetic screening. Rabbit's corneal application and subcutaneous injection in the guinea pig were used to determine their anesthetic activities.[6]

The preliminary assays showed that *p*-dipropylsulfamoylbenzoic acid dimethylaminoethyl ester hydrochloride (**9**), applied on the rabbits's cornea as a 1% solution, is as active as a 2% solution of cocaine hydro-

(1) C. S. Miller, U. S. Patent 2,608,507 (1952); *Chem. Abstr.*, **47**, 5440 (1953).

(2) Aktiebolaget Bofors, British Patent 797,794 (1958); *Chem. Abstr.*, **53**, 4218 (1959).

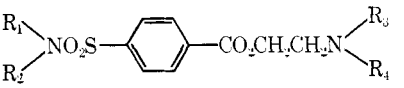
(3) Aktiebolaget Bofors, U. S. Patent 2,991,283 (1961); *Chem. Abstr.*, **56**, 4420 (1962).

(4) H. Sato, *J. Pharm. Soc. Japan*, **72**, 74 (1952).

(5) I. I. Krasil'nikov, *Farmakol. i. Toksikol.*, **29**, 163 (1966).

(6) The authors thank Dr. B. Djahanguiri, Faculty of Medicine, University of Tehran, for the local anesthetic activity testing.

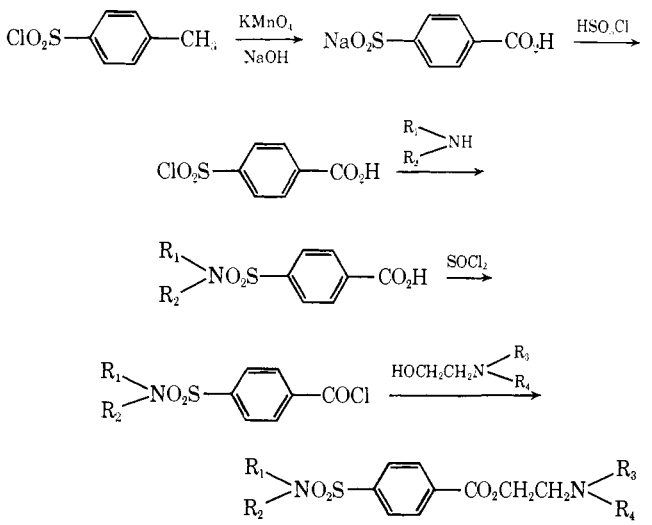
TABLE I



Compd	R_1	R_2	R_3	R_4	Yield, %	Mp, °C Base	Mp, °C HCl	$n^{18}D$ (base)	Formula[e]	Rel act.[f]
1	CH_3	CH_3	CH_3	CH_3	67	98	206[a]		$C_{13}H_{20}N_2O_4S$	—
2	CH_3	CH_3	C_2H_5	C_2H_5	72	57	177[a]		$C_{15}H_{24}N_2O_4S$	—
3	CH_3	CH_3	$-(CH_2)_5-$		81	103	200		$C_{16}H_{24}N_2O_4S$	0.3
4	CH_3	CH_3	$O(CH_2CH_2-)_2$		76	88	188		$C_{15}H_{22}N_2O_5S$	—
5	C_2H_5	C_2H_5	CH_3	CH_3	88	Oil	178[b]	1.5181	$C_{15}H_{24}N_2O_4S$	0.1
6	C_2H_5	C_2H_5	C_2H_5	C_2H_5	81	Oil	172[c]	1.5140	$C_{17}H_{28}N_2O_4S$	0.4
7	C_2H_5	C_2H_5	$-(CH_2)_5-$		69	Oil	178	1.5304	$C_{18}H_{28}N_2O_4S$	0.3
8	C_2H_5	C_2H_5	$O(CH_2CH_2-)_2$		77	Oil	188	1.5241	$C_{17}H_{26}N_2O_5S$	0.1
9	C_3H_7	C_3H_7	CH_3	CH_3	89	Oil	190	1.5165	$C_{17}H_{28}N_2O_4S$	0.5
10	C_3H_7	C_3H_7	C_2H_5	C_2H_5	86	Oil	171	1.5103	$C_{19}H_{32}N_2O_4S$	0.2
11	C_3H_7	C_3H_7	$-(CH_2)_5-$		81	Oil	207[d]	1.5239	$C_{20}H_{32}N_2O_4S$	0.5
12	C_3H_7	C_3H_7	$O(CH_2CH_2-)_2$		79	Oil	207	1.5165	$C_{19}H_{30}N_2O_5S$	—
13	$-(CH_2)_2-$		CH_3	CH_3	65	85	203		$C_{15}H_{22}N_2O_4S$	—
14	$-(CH_2)_4-$		C_2H_5	C_2H_5	68	50	175		$C_{17}H_{26}N_2O_4S$	0.4
15	$-(CH_2)_4-$		$-(CH_2)_5-$		73	133	160		$C_{18}H_{26}N_2O_4S$	—
16	$-(CH_2)_4-$		$O(CH_2CH_2-)_2$		69	140	195		$C_{17}H_{24}N_2O_5S$	—
17	$-(CH_2)_5-$		CH_3	CH_3	72	114	219		$C_{16}H_{24}N_2O_4S$	0.4
18	$-(CH_2)_5-$		C_2H_5	C_2H_5	65	62	123		$C_{18}H_{28}N_2O_4S$	0.2
19	$-(CH_2)_5-$		$-(CH_2)_5-$		61	101	130		$C_{19}H_{28}N_2O_4S$	0.2
20	$-(CH_2)_5-$		$O(CH_2CH_2-)_2$		95	102	207		$C_{18}H_{26}N_2O_5S$	0.1

[a] Reference 4; melting point was not given. [b] Reference 2; melting point was not given. [c] Lit.[5] mp 175–177°. [d] Reference 3; melting point was not given. [e] All compounds prepared were subjected to ir and nmr spectroscopy and showed the expected absorptions. Analytical data were within ±0.30% of theoretical values. [f] Procaine hydrochloride as a 1% solution by subcutaneous injection = 1; — = inactive.

SCHEME I



chloride. The corresponding piperidinoethyl ester (**11**) was as active as cocaine hydrochloride. Subcutaneous injections of 0.5 ml of 1% solutions of **9** or **11** showed an activity comparable with that of 0.5 ml of 0.5% of procaine hydrochloride. The local anesthetic activity of the compounds prepared are included in Table I.

Experimental Section[7]

***p*-Pyrrolidinosulfonylbenzoic Acid.**—To a solution of 7.1 g (0.1 mole) of pyrrolidine in 40 ml of 10% aqueous NaOH was added with stirring 11 g (0.05 mole) of *p*-chlorosulfonylbenzoic acid.[8] After 3 hr the clear solution was acidified with HCl and the precipitate was filtered and recrystallized from MeOH–Me_2CO to give 6 g (56%) of product, mp 239°, ir and nmr (CF_3COOH) as expected. *Anal.* ($C_{11}H_{13}NO_4S$) N.

***p*-Pyrrolidinosulfonylbenzoyl Chloride.**—*p*-Pyrrolidinosulfonylbenzoic acid (2.55 g 0.01 mole), and 5 ml of $SOCl_2$ were allowed to react 1 hr at room temperature, then excess $SOCl_2$ was distilled off and the residue was washed with ice–water and filtered until dry. The yield was almost quantitative, mp 154°. *Anal.* ($C_{11}H_{12}ClNO_3S$) Cl.

***p*-Pyrrolidinosulfonylbenzoic Acid Dimethylaminoethyl Ester (13).**—To *p*-pyrrolidinosulfonylbenzoyl chloride (2.7 g, 0.01 mole) in 20 ml of dry C_6H_6 was added 0.9 g (0.01 mole) of dimethylaminoethyl alcohol in 5 ml of dry C_6H_6. The mixture was allowed to stand overnight at room temperature and then the solvent was evaporated *in vacuo*. The crystalline mass was recrystallized (EtOAc–EtOH) to give 2.3 g (65%) of product, mp 203°. The free base was recrystallized from EtOH–H_2O; mp 85°, ir and nmr ($CDCl_3$) as expected. *Anal.* See Table I.

(7) Melting points were taken on a Kofler hot stage microscope. The ir spectra were determined with a Leitz Model III spectrograph (KBr). Nmr spectra were obtained on a Varian A60A instrument using Me_4Si as internal standard.

(8) S. Smiles and O. C. Harrison, *J. Chem. Soc.*, **121**, 2022 (1922).

Inhibition of Cholesterolgenesis *in Vitro* by Chlorophenoxyacetic Acids. Effect of α-Methyl Groups[1a]

DONALD T. WITIAK, ROBERT E. HACKNEY,[1b] AND MICHAEL W. WHITEHOUSE[1c]

Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received March 10, 1969

We recently reported that the two isomeric desmethyl analogs of ethyl α-(4-chlorophenoxy)-α-methylpropionate (**1**)[2] differ in their hypocholesterolemic activity in rats; only the L isomer **2** is equally as active as **1** *in vivo*.[3] The D isomer **2** is not significantly active. Experiments in this laboratory have shown that like **1**, which readily undergoes *in vivo* and *in vitro* hydrolysis to **3**, esters L-**2** and D-**2** are readily hydrolyzed to their respective acids L-**4** and D-**4** by rat liver, serum, and

(1) (a) Presented to the Division of Medicinal Chemistry, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 13–18, 1969. (b) American Foundation for Pharmaceutical Education Fellow. (c) National Science Foundation Senior Visiting Foreign Scientist 1967–1968.

(2) Clofibrate: chlorpenisate, ICI-28257, CPIB, Atromid-S, Regelan.

(3) D. T. Witiak, T. C.-L. Ho, R. E. Hackney, and W. E. Connor, *J. Med. Chem.*, **11**, 1086 (1968).