

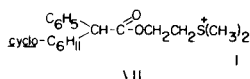
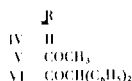
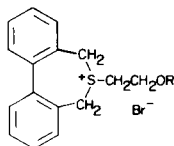
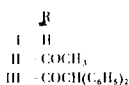
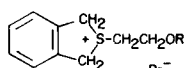
Some Cyclic Sulfonium Salts

Edgar A. Steck (1) and Evelyn H. Wilson

Johnson & Johnson Research Center, New Brunswick, New Jersey 08902
and McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034

Received June 23, 1975

Sulfonium salts derived from the 1,3-dihydroisothianaphthene and the 2,7-dihydrodibenzo[*c,e*]thiepine ring systems were of interest for trial as anticholinergic agents. To this end, there were prepared 2-(2-hydroxyethyl)-1,3-dihydroisothianaphthenium bromide (I) and 6-(2-(2-hydroxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium bromide (IV), and each was converted into the respective acetate and diphenylacetate esters (i.e., II, III, and V, VI). None of the compounds had anticholinergic activity approaching that of Thiospasmin (cf. 24) - VII - and the work was discontinued.



In the present work, it was advantageous to employ a procedure which had been used (5) in converting δ - and ϵ -halogenated sulfides into cyclic sulfonium halides. By this method, interaction of α,α' -dibromo-*o*-xylene with 2-mercaptoethanol readily gave the desired 2-(2-hydroxyethyl)-1,3-dihydroisothianaphthenium bromide, I. In similar manner, 2,2'-bis-bromomethylbiphenyl was converted into 6-(2-(2-hydroxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium bromide, IV. Each of the hydroxy compounds was used to prepare the respective acetate and diphenylacetate esters. The esters derived from IV were consider-

ably more stable and less hygroscopic than those prepared from I.

EXPERIMENTAL (6)

2-(2-Hydroxyethyl)-1,3-dihydroisothianaphthenium Bromide (I).

A solution of 26.4 g. (0.1 mole) of α,α' -dibromo-*o*-xylene in 400 ml. of refluxing tetrahydrofuran was stirred well and 16.8 g. (0.21 mole) of 2-mercaptoethanol in 200 ml. of tetrahydrofuran was added during a 24 hour reflux period. Thereafter, refluxing was continued for an additional 8 hours, and the solvent removed by distillation until ca. 100 ml. remained. While the mixture was hot, absolute ether (500 ml.) was added slowly, and the sulfonium bromide separated as a dense oil. Upon considerable chilling and rubbing, the hygroscopic intermediate solidified and could be crystallized either from methanol-ether or from 2-propanol. It was expedient to crystallize it at least once from each of the solvents, with minimal exposure to light. A yield of 16.5 g. (63%) of white leaflets resulted, m.p. 134-136°.

Anal. Calcd. for C₁₀H₁₃BrOS: C, 45.98; H, 5.02; Br, 30.60; S, 12.27. Found: C, 46.42; H, 5.31; Br, 30.28; S, 12.26.

2-(2-Acetoxyethyl)-1,3-dihydroisothianaphthenium Bromide (II).

Prior to use, the 2-(2-hydroxyethyl)-1,3-dihydroisothianaphthenium bromide was dried *in vacuo*, in the dark, over phosphorus pentoxide, then 20.0 g. (0.0765 mole) of I was added rapidly to a mixture of 100 ml. of acetic anhydride with 1 ml. of a 30% solution of anhydrous hydrogen bromide in glacial acetic acid. The mixture was stirred (under drying tube, protected from light) at ambient temperature for 2 days, even though there was essentially complete solution after 22 hours. To the clear solution there was added a total of 0.5 liter of anhydrous ether, then the oil allowed to separate at room temperature. The supernatant liquid was decanted, and twice replaced with a like amount of fresh ether, each time triturating well in the cold. In such manner, it was possible to obtain material which became crystalline when rubbed with a little anhydrous acetone. It was recrystallized from 2-propanol and ether to give 12.4 g. (53% yield) of shiny white microcrystals of II, m.p. 91-92°. This compound was very hygroscopic and somewhat sensitive to light. It was unstable even when stored in a desiccator at room temperature, and the odor of acetic acid was noted after less than a week. Satisfactory analyses were obtainable only immediately following crystallization.

Anal. Calcd. for C₁₂H₁₅BrO₂S: C, 46.71; H, 5.10. Found: C, 46.75; H, 5.21.

2-(2-Diphenylacetoxyethyl)-1,3-dihydroisothianaphthenium Bromide (III).

Six-hundredth mole (15.7 g.) of freshly dried hydroxy com-

ound (I) was mixed with 14.6 g. (0.063 mole) of pulverized diphenylacetyl chloride in a flask protected from moisture, and warmed gently on the steam bath until molten. The mixture was swirled, heated 0.5 hour longer, then set aside overnight. The yellowish vitreous mass was triturated repeatedly with absolute ether, and the resultant crystalline solid collected. It was crystallized from 2-propanol to give 13.0 g. (48% yield) of creamy blades, m.p. 104-106°. This compound (III) was hygroscopic, but considerably more stable and less photosensitive than either of the two described above.

Anal. Calcd. for $C_{24}H_{23}BrO_2S$: C, 62.97; H, 5.09; S, 7.04. Found: C, 62.91; H, 5.60; S, 6.90.

6-(2-Hydroxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium Bromide (IV).

Seventeen g. (0.05 mole) of 2,2'-bis-bromomethylbiphenyl (7) and 8.2 g. (0.105 mole) of 2-mercaptoethanol in 375 ml. of tetrahydrofuran was stirred, and 1 ml. of 30% solution of anhydrous hydrogen bromide in glacial acetic acid was added. The mixture was kept at room temperature for 3 days, refluxed for 1 day, and then the solvent removed. The residues (*ca.* 75 ml.) were triturated with anhydrous ether; a creamy crystalline solid resulted readily. The crude product (IV) crystallized well from 2-propanol to give 11.5 g. (67% yield) of shiny cubic crystals, m.p. 143-145°.

Anal. Calcd. for $C_{16}H_{17}BrOS$: C, 56.97; H, 5.08. Found: C, 56.80; H, 5.36.

6-(2-Acetoxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium Bromide (V).

6-(2-Hydroxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium bromide (IV) was converted into its acetate, V, after the procedure described for II. In this case, the reaction mixture was finally heated at 70° for 8 hours prior to work-up. The white microcrystalline product was obtained in 88% yield following crystallization from methanol-ether, m.p. 158-160°. In contrast to II, this sulfonium salt was not hygroscopic and was stable for a prolonged

time interval.

Anal. Calcd. for $C_{18}H_{19}BrO_2S$: C, 57.00; H, 5.05. Found: C, 56.69; H, 5.36.

6-(2-Diphenylacetoxyethyl)-5,7-dihydrodibenzo[*c,e*]thiepinium Bromide (VI).

The method used for preparing the diphenylacetate III was applied to IV. A 74% yield of white microcrystalline solid (m.p. 154-155°) resulted after crystallization of the crude product from methanol-ether. This compound was slightly hygroscopic.

Anal. Calcd. for $C_{30}H_{27}BrO_2S$: C, 65.91; H, 5.29. Found: C, 65.84; H, 5.63.

Acknowledgments.

The authors are indebted to Mr. J. Weinberger for the analyses, and to Dr. W. M. Govier and staff we are grateful for biological testing of the compounds here reported.

REFERENCES

- (1) Present address: Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. 20012.
- (2) This work was done during 1959; publication was delayed by diverse circumstances which intervened. Subject compounds have not been reported hitherto in the literature, despite the long interval since this was done.
- (3) Z. Votava, Ya. Metysh, I. Shramkova, and M. Vanecek, *Farmakol. Toksikol.*, **20**, #4 35 (1957).
- (4) O. Piták and J. Zikmund, *Collect. Czech, Chem. Commun.*, **24**, 4053 (1959).
- (5) G. M. Bennett, F. Heathcoat, and A. N. Mosses, *J. Chem. Soc.*, 2567 (1929).
- (6) Melting points are uncorrected.
- (7) D. M. Hall, M. S. Leslie, and E. E. Turner, *J. Chem. Soc.*, 711 (1950).