tory derivative, I, X = S, R = Bu, was about six times as toxic (intraperitoneally in mice; acute) as phenylbutazone.[10]

Experimental[11]

The preparation of I, X = S, R = Bu, is typical: To a stirred solution of 4.8 ml. of pyridine in 200 ml. of methylene chloride cooled to about −70° in a Dry Ice–acetone bath was added 5.3 g. of butylmalonyl dichloride followed by portionwise addition of a solution of 5.4 g. of II, X = S, in 100 ml. of methylene chloride, while maintaining the temperature below −50°. The solution was allowed to warm slowly to room temperature and to stand for 3 days. It was washed well with dil. hydrochloric acid, dried with anhydrous sodium sulfate, and evaporated *in vacuo*. The residue was dissolved in dilute potassium carbonate, washed once with ether, stirred with activated charcoal, filtered, and acidified to pH 4 with dil. hydrochloric acid. The oil was extracted in 4 l. of ether which was dried and condensed to 300 ml. After cooling to 0°, the white needles were filtered off and dried; yield, 4.0 g. (47%), m.p. 198–200°. Recrystallization of an analytical sample from ether raised the m.p. to 199–200°; the analysis is given in Table I.

(11) All melting points are corrected. Microanalysis were performed by the Microanalytical Department under Dr. R. T. Dillon, or by Microtech Laboratories, Skokie, Ill.

Methanesulfonates of Tertiary and Quaternary Amino Alcohols[1]

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Myers and Kemp[2] showed that methanesulfonyl fluoride is a reasonably potent inhibitor of cholinesterase. They suggested that its mechanism of inhibition and also that of dimethylcarbamyl fluoride might be similar to the action of dialkyl phosphorofluoridates which were known to produce phosphorylated enzyme derivatives. It has been shown recently[3] that dimethylcarbamyl fluoride and other carbamates do produce carbamyl enzyme derivatives with acetylcholinesterase. It was of interest therefore to synthesize a group of methanesulfonates in which the fluorine atom is replaced by groupings

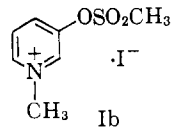
(1) This work was supported by the Division of Research Grants and Fellowships of the National Institutes of Health, Grant No. B-573 C13.

(2) D. K. Myers and A. Kemp, *Nature*, **173**, 33 (1954).

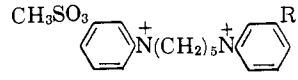
(3) I. B. Wilson, M. A. Hatch, and S. Ginsburg, *J. Biol. Chem.*, **235**, 2312 (1960); I. B. Wilson, M. A. Harrison, and S. Ginsburg, *ibid.*, **236**, 1498 (1961).

which in the case of organophosphates and/or carbamates had yielded active inhibitors.

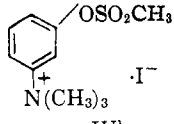
The syntheses of several potential inhibitors are described in this paper.



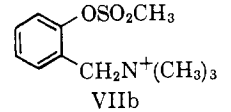
Ib



II, R = OSO_2CH_3 $\cdot 2I^-$
III, R = H



IVb



VIIb

$Br^-(CH_3)_3N^+CH_2CH_2XSO_2CH_3$
Vb, X = O
VI, X = S

The tertiary compounds were made from the corresponding hydroxyl compounds (except Vb and VI) by reaction with methanesulfonyl chloride and these in turn were quaternized with methyl iodide (Ib, IVb and VIIb). Compounds II and III were prepared from 3-hydroxypyridine methanesulfonate by reaction with 1,5-diiodopentane and 5-iodopentylpyridinium iodide, respectively. Compound Vb was synthesized by treating 2-bromoethanol with methanesulfonyl chloride and subsequently treating the bromoester with trimethylamine. Compound VI was prepared by reaction of bromocholine bromide with sodium methanethiosulfonate.

Studies of these compounds as inhibitors of acetylcholinesterase are reported separately.[4] Compounds I to IV are more potent inhibitors of acetylcholinesterase than methanesulfonyl fluoride. Compound I is the most potent and compounds V to VII do not produce irreversible inhibition. The active compounds form initial reversible complexes which progressively transfer a methanesulfonyl group to the enzyme surface in the neighborhood of the anionic site. The resulting methanesulfonyl enzyme derivative is the same in all cases. The inhibited enzyme cannot be reactivated by water, hydroxylamine, hydrazine or 1-methylpyridinium-2-aldoxime iodide. It is reactivated by 1-methylpyridinium-3-aldoxime iodide and at the same rate no matter which inhibitor is used. The formation of the methanesulfonyl enzyme can be prevented by tetramethylammonium ion and

(4) R. Kitz and I. B. Wilson, *J. Biol. Chem.*, **237**, 3245 (1962); J. Alexander, I. B. Wilson, and R. Kitz, *ibid.*, in press.

other reversible inhibitors and the reactivation can also be inhibited. The active compounds are clearly oxydiaphoric or acid transferring inhibitors.

Experimental[5]

3-Methanesulfonoxypyridine (Ia).—To a stirred solution of 9.5 g. (0.1 mole) of 3-pyridol in 12 ml. of 2,6-lutidine and 100 ml. of chloroform was added over a period of 1 hr. at room temperature 7.5 ml. (0.1 mole) of methanesulfonyl chloride in 25 ml. of chloroform. The reaction mixture was then refluxed for 20 min., cooled and extracted several times with water. The chloroform solution was dried over sodium sulfate, the solvent distilled off and the residue fractionated under vacuum, yielding colorless crystals (10.5 g., 61%), b.p. 103° (0.01 mm.), m.p. 60°.

1-Methyl-3-methanesulfonoxypyridinium Iodide (Ib).—Compound Ia was quaternized with an excess of methyl iodide in acetone at room temperature; recrystallization from methanol gave pale yellow crystals (62%), m.p. 173°.

Anal. Calcd. for $C_7H_{10}INO_3S$: C, 26.68; H, 3.20; N, 4.45; I, 40.27. Found: C, 27.08; H, 3.30; N, 4.16; I, 40.63.

1,5-Pentamethylene-bis-(3-methanesulfonoxypyridinium) Iodide (II).—A solution of 1.9 g. (0.011 mole) of Ia and 1.62 g. (0.005 mole) of 1,5-diiodopentane in 10 ml. of dimethylformamide was kept at room temperature for 2 days. The solvent was distilled off in vacuum; the hard dark residue was dissolved in boiling methanol, decolorized with Norit and cooled, yielding light beige crystals (54%), m.p. 172–173°; recrystallized from methanol, m.p. 174°.

Anal. Calcd. for $C_{17}H_{24}I_2N_2O_6S_2$: C, 30.46; H, 3.61; N, 4.18; I, 37.87. Found: C, 30.02; H, 3.61; N, 4.06; I, 37.32.

1-(3-Methanesulfonoxypyridinium)-5-(pyridinium)-pentane Diiodide (III).—A solution of 0.95 g. (0.0055 mmole) of compound Ia and 2.0 g. (0.05 mole) of 5-iodopentylpyridinium iodide[6] in 10 ml. of dimethylformamide was kept at room temperature for 1 day. The solvent was distilled off under vacuum and the sticky residue refluxed with acetone. Light yellow crystals formed (59%), m.p. 148°; recrystallized from methanol, m.p. 151°.

Anal. Calcd. for $C_{16}H_{22}I_2N_2O_3S$: C, 33.35; H, 3.85; N, 4.86; I, 44.05. Found: C, 33.19; H, 3.56; N, 4.91; I, 43.91.

3-Methanesulfonoxy-N,N-dimethylaniline (IVa).—The sulfonic ester was prepared in the same manner as Ia, but the crude oil was not distilled. It was extracted with boiling ether leaving a tar behind. The ether was evaporated off to yield a slightly yellow solid (55%) melting at 40–43°. A small sample recrystallized from ligroin gave colorless crystals, m.p. 43–46°.

3-Methanesulfonoxy-N,N,N-trimethylanilinium iodide (IVb) was prepared in the usual way (as Ib) from the crude ester IVa, yielding (56%) pale yellow crystals; recrystallized from methanol, m.p. 201°.

Anal. Calcd. for $C_{10}H_{16}INO_3S$: C, 33.62; H, 4.52; N, 3.92; I, 35.53. Found: C, 33.91; H, 4.34; N, 3.95; I, 35.00.

β-Bromoethyl methanesulfonate (Va) was prepared in the same manner as Ia, but methanesulfonyl chloride was added over 1.5 hr. at 10–15° and refluxing was omitted; colorless oil (40%), b.p. 96–98° (0.3 mm.).

(5) Melting points and boiling points are uncorrected.

(6) I. B. Wilson and S. Ginsburg, *Biochem. Pharmacol.*, **1**, 203 (1958).

Methanesulfonylcholine Bromide (Vb).—A solution of 5.1 g. (0.025 mole) of Va in 5 ml. of dimethylformamide was mixed with 20 ml. of a 25% solution of trimethylamine in methanol and allowed to stand at room temperature for 1 day. Colorless crystals formed (46%) which were recrystallized from methanol, m.p. 143°.

Anal. Calcd. for $C_6H_{16}BrNO_3S$: C, 27.48; H, 6.15; N, 5.34; Br, 30.48. Found: C, 27.65; H, 6.31; N, 5.19; Br, 30.71.

Methanesulfonyl Thiocholine Bromide (VI).—A solution of 2.5 g. (0.001 mole) of bromocholine bromide and 1.5 g. (0.0011 mole) of sodium methanethiosulfonate[7] in 20 ml. of methanol was refluxed for 2 days. When the clear solution was cooled below 0°, 1.02 g. of colorless crystals m.p. 154° separated out. Recrystallization from abs. ethanol gave the pure compound (26%), m.p. 160°.

Anal. Calcd. for $C_6H_{16}BrNO_2S_2$: C, 25.90; H, 5.80; N, 5.04; Br, 28.72. Found: C, 25.84; H, 5.87; N, 4.96; Br, 28.64.

2-Methanesulfonoxyphenylmethyl Dimethylamine (VIIa).—The sulfonic ester was prepared from crude commercial material following method Ia, but triethylamine was used instead of 2,6-lutidine. A colorless oil was obtained (39%), b.p. 127° (0.2 mm.).

2-Methanesulfonoxyphenylmethyltrimethylammonium iodide (VIIb) was prepared in the usual way (as Ib) from VIIa, yielding 60% of colorless crystals; recrystallized from abs. ethanol, m.p. 191–192°.

Anal. Calcd. for $C_{11}H_{18}INO_3S$: C, 35.59; H, 4.89; N, 3.77; I, 34.19. Found: C, 35.98; H, 5.16; N, 3.51; I, 33.90.

Acknowledgment.—The author wishes to thank Dr. I. B. Wilson for suggesting the problem.

(7) O. Foss, *Acta Chem. Scand.*, **10**, 868 (1956). Sodium methanethiosulfonate was prepared using Wahlsted's method for sodium *p*-toluenethiosulfonate, *Acta Univers. Lund*, **16** (2) II, 9 (1879–1880); Beilstein XI, 4th ed., Julius Springer, Berlin, 1928, p. 113.

Aldehyde Hydrazone Derivatives in Cancer Chemotherapy

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In previous studies[1a-b] it has been observed and reported that some substituted aldehyde hydrazone derivatives have borderline activity

(1) (a) Richard H. Wiley and G. Irick, *J. Med. Pharm. Chem.*, **5**, 49 (1962); (b) Richard H. Wiley, G. Irick, and H. K. White, *J. Org. Chem.*, **26**, 589 (1961); (c) Richard H. Wiley and G. Irick, *ibid.*, **26**, 593 (1961); (d) Richard H. Wiley and Y. Yamamoto, *ibid.*, **25**, 1906 (1960); (e) Richard H. Wiley and G. Irick, *ibid.*, **24**, 1925 (1959); (f) Richard H. Wiley, H. K. White, and G. Irick, *ibid.*, **24**, 1784 (1959).