ethyl acetate and ether yielded approximately 50% of white crystals of VII, m.p. 119–121°.

*Anal.* Calcd. for $C_{15}H_{20}Cl_2N_2O_2$: C, 54.39; H, 6.09; N, 8.45. Found: C, 54.15; H, 6.21; N, 8.33.

Recovery procedure A yielded the same quality and quantity of product. However, in some instances only the washed solutions yielded crystalline products.

**Antitumor Tests.**—Procedures for determination of antitumor effects are described elsewhere for the Crocker sarcoma 180[12] and other mouse tumors.[13] Treatment was begun in mice bearing S180, sarcoma T241, or Ehrlich ascites 24 hr. after implantation of tumor, and in mice with C1025 or Ridgway osteogenic sarcoma 5 days after implantation. Each animal received 0.5 ml. of preparation intraperitoneally once daily for 7 consecutive days. Control tumor-bearing animals were similarly treated with 0.5% carboxymethylcellulose in 0.85% aqueous NaCl. Effects, evaluated 1 week after initiation of treatment (24 hr. after the last injection), were based on relative diameters of the solid tumors or on relative volumes of ascitic fluid for the Ehrlich carcinoma. Each experimental group contained five mice. In those instances in which a compound was retested at the same dose, the results of individual trials did not differ significantly and were averaged. A ratio between the average diameter of tumors in treated groups and that in controls ($T/C$) of $\leq 0.75$ for S180, $\leq 0.60$ for C1025 and Ridgway osteogenic sarcoma, $\leq 0.50$ for E0771, and $\leq 0.70$ for T241 are considered to be valid indications of inhibition of the growth of the tumors. In the Ehrlich ascites system a $T/C \leq 0.40$ is considered acceptable. Mortalities among mice in treated groups may be attributed to toxicity of the compounds; no deaths occurred in tumor-bearing control groups during the period of observation.

For injection the compounds were suspended by grinding in 0.5% carboxymethylcellulose in 0.85% aqueous NaCl. Suspensions were prepared daily just prior to injection.

**Acknowledgments.**—We wish to thank Miss Valentina Fetzer, Mr. William Robinson, Mrs. Miyono Schmid, Miss Barbara Smol, and Mrs. Beverly Stern for assistance with the antitumor tests.

(12) C. C. Stock, *Am. J. Med.*, **8**, 658 (1950).

(13) (a) F. A. Schmid, J. G. Cappuccino, P. C. Merker, and G. S. Tarnowski, *Cancer Res.*, in press; (b) G. S. Tarnowski, F. A. Schmid, and J. G. Cappuccino, *ibid.*, in press.

TABLE I

SCREENING DATA AGAINST WALKER 256 (SUBCUTANEOUS)[a]

| Compd. | Dose, mg./kg. | Survivors | Animal wt. diff. ($T-C$) | Tumor wt. $T/C$ | $T/C$, % |
|---|---|---|---|---|---|
| I | 200 | 6/6 | −20 | 5.8/5.4 | 107 |
| | 100 | 6/6 | −10 | 6.4/5.4 | 118 |
| | 50 | 6/6 | 6 | 6.9/5.4 | 127 |
| | 25 | 6/6 | 4 | 5.3/5.4 | 98 |
| II[b] | 50 | 6/6 | | 16.0/16.0 | 100 |
| | 10 | 6/6 | | 15.5/16.0 | 97 |
| III | 200 | 6/6 | 0 | 7.3/5.4 | 135 |
| | 100 | 6/6 | −1 | 6.2/5.4 | 114 |
| | 50 | 6/6 | 8 | 7.1/5.4 | 131 |
| | 25 | 6/6 | 9 | 5.9/5.4 | 109 |
| IV | 200 | 6/6 | −11 | 6.0/5.4 | 111 |
| | 100 | 6/6 | 4 | 7.0/5.4 | 129 |
| | 50 | 6/6 | −1 | 2.4/4.5 | 53 |
| | 25 | 6/6 | −2 | 3.5/4.5 | 77 |
| | 12.5 | 6/6 | −2 | 5.1/4.5 | 113 |
| V | 200 | 6/6 | 3 | 5.8/5.4 | 107 |
| | 100 | 6/6 | 6 | 6.5/5.4 | 120 |
| | 50 | 6/6 | 1 | 6.9/5.4 | 127 |
| | 25 | 6/6 | 3 | 5.7/5.4 | 105 |
| VI | 200 | 6/6 | 4 | 5.7/5.4 | 105 |
| | 100 | 6/6 | 3 | 5.8/5.4 | 107 |
| | 50 | 6/6 | −2 | 3.3/4.5 | 73 |
| | 25 | 6/6 | −5 | 4.1/4.5 | 91 |
| | 12.5 | 6/6 | −5 | 3.8/4.5 | 84 |

[a] The biological testing was performed by the screening contractors of the Cancer Chemotherapy National Service Center. The authors are also indebted to the Sloan-Kettering Institute for preliminary screening of compound I. [b] These data are from tests with Dunning leukemia (solid).

## Chloroalkyl-N-sulfinylamines[1]

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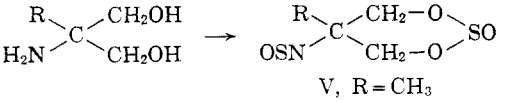
Chloroalkyl-N-sulfinylamines may be considered to be analogs of nitrogen mustards. In the course of studying the preparation of N-sulfinylamines we have prepared some of these chloroalkyl compounds for testing as antitumor agents (Table I). Their preparation can be readily accomplished by treating primary hydroxyalkylamines with thionyl chloride.

$$HO(CH_2)_nNH_2 + 2SOCl_2 \xrightarrow{\text{pyridine}} Cl(CH_2)_nNSO + \text{pyridine}\cdot HCl + SO_2$$

This method worked satisfactorily for the preparation of 2-chloro-N-sulfinylethylamine (I), 3-chloro-N-sulfinylpropylamine (II), 2-chloro-N-sulfinylpropylamine (III), and 2-chloro-1,1-dimethyl-N-sulfinylethylamine (IV). When 2-methyl- and 2-ethyl-2-amino-1,3-propanediol were treated with excess thionyl chloride, the amino groups were converted to sulfinylamino groups and the diols were converted to the cyclic sulfite ester.



V, R = $CH_3$
VI, R = $C_2H_5$

### Experimental

**2-Chloro-N-sulfinylethylamine (I).**—To a stirred, cooled solution of redistilled ethanolamine (61.1 g., 1.0 mole), pyridine (237 g., 3.0 moles), and chloroform (500 ml.) was added $SOCl_2$ (357 g., 3.0 moles) in $CHCl_3$ (250 ml.) over a period of 2 hr. The dark, viscous mixture was stored overnight in a refrigerator and then filtered to remove a small amount of insoluble material. The filtrate was divided into two equal parts and each part was extracted with three 200-ml. portions of Skellysolve A. The extracts were combined and evaporated under reduced pressure. The red oil thus obtained was distilled to give 27.4 g. (22%), b.p. 50–53° (6 mm.).

*Anal.* Calcd. for $C_2H_4ClNOS$: N, 11.15; S, 25.53. Found: N, 10.9; S, 25.1.

**3-Chloro-N-sulfinylpropylamine (II).**—Starting with 75.1 g. (1.0 mole) of 2-amino-1-propanol, the above procedure gave 84.2 g. (60%), b.p. 59–62° (4 mm.). Redistillation gave 67.1 g. (48%) of II, b.p. 61–63° (4 mm.).

*Anal.* Calcd. for $C_3H_6ClNOS$: N, 10.04; S, 22.97. Found: N, 9.67; S, 23.4.

**2-Chloro-N-sulfinylpropylamine (III).**—Starting with 75.1 g. (1.0 mole) of 1-amino-2-propanol, the above procedure gave 50 g. (36%) of III, b.p. 44–46° (2 mm.).

(1) This research was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research, under Contract No. AF-49(638)-49. Reproduction in whole or in part is permitted for any purpose of the U. S. Government.

*Anal.* Calcd. for $C_3H_6ClNOS$: S, 22.97. Found: S, 23.0.

**2-Chloro-1,1-dimethyl-N-sulfinylethylamine (IV).**—Starting with 45 g. (0.5 mole) of 2-amino-2-methyl-1-propanol, the above procedure gave 19 g. (25%) of IV, b.p. 42–43° (2 mm.).

*Anal.* Calcd. for $C_4H_8ClNOS$: S, 20.9. Found: S, 20.9.

**Cyclic Sulfite Ester of 2-Methyl-2-sulfinylamino-1,3-propanediol (V).**—Starting with 52.5 g. (0.5 mole) of 2-amino-2-methyl-1,3-propanediol, the above procedure gave after two distillations 25 g. (25%) of V, b.p. 65–70° (2 mm.).

*Anal.* Calcd. for $C_4H_7NO_4S_2$: S, 32.5. Found: S, 32.5.

**Cyclic Sulfite Ester of 2-Ethyl-2-sulfinylamino-1,3-propanediol (VI).**—Starting with 50 g. (0.42 mole) of 2-amino-2-ethyl-1,3-propanediol, the above procedure gave after two distillations 35 g. (39%) of VI, b.p. 82–85° (2 mm.).

*Anal.* Calcd. for $C_5H_9NO_4S_2$: S, 30.4. Found: S, 30.5.

## Anticholinergic Agents. Esters of 4-Dialkyl- (or 4-Polymethylene-) amino-2-butynols

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During the study of a series of diphenylacetate, benzilate, and related esters of N,N-disubstituted 4-amino-2-butynyl alcohols[1] in this laboratory which were found to have potentially useful anticholinergic activities, the preparation and some biological properties of the diphenylacetates and some of the benzilates were reported elsewhere by Dahlbom, *et al.*[2,3] We wish to report the preparation of other novel acetylenic amino esters listed in Tables I and II.

Initially, the Mannich reaction was employed (method A) in our preparation of 4-amino-2-butynyl esters. The intermediate propargyl esters were readily obtained by the usual esterification procedures, and these esters were treated with paraformaldehyde and a secondary amine according to the procedure of Jones, *et al.*[4]

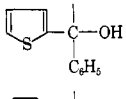
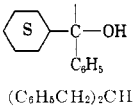
Most of the esters, however, were synthesized more conveniently (B) through a base-catalyzed ester–alcohol interchange involving the 4-amino-2-butynyl alcohols and various methyl esters. A few of them were also prepared (Ca) by the treatment of the aminobutynyl alcohols with the appropriate acid chlorides. Esterification of two of the aminobutynyl alcohols with α-chlorodiphenylacetyl chloride followed by treatment with ethanol furnished two α-ethoxydiphenylacetate esters (Cb).

Another procedure (D), employed specifically for the preparation of kilogram quantities of 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride (**19**) for clinical study, involved a base-catalyzed ester–ester transesterification of methyl phenylcyclohexylglycolate and 4-diethylamino-2-butynyl acetate.

The principle pharmacologic properties exhibited by the compounds listed in Tables I and II were smooth muscle depressant, local anesthetic, and/or anticholinergic actions. 4-Piperidino-2-butynyl α-methylmercaptodiphenylacetate hydrochloride (**23**) was found to have local anesthetic activity equivalent to lidocaine hydrochloride when tested by instillation in the rabbit eye and by infiltration in guinea pig skin. This compound was also similar to lidocaine hydrochloride in a well-known test[5] allowing quantitative appraisal of irritancy.

TABLE I

$R_1COOCH_2C{\equiv}CCH_2R_2 \cdot HCl$

| No. | $R_1$ | $R_2$ | Method | Yield, % | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Chloride, % Calcd. | Chloride, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4-$CH_3OC_6H_4$ | $N(CH_3)_2$ | A[a] | 58 | 153–154[b] | $C_{14}H_{17}NO_3 \cdot HCl$ | 59.26 | 59.94 | 6.39 | 6.56 | 12.52 | 12.45 | 4.94 | 4.95 |
| 2 | 4-$CH_3OC_6H_4$ | $C_5H_{10}N$[c] | A[d] | 35 | 156.5–157.5[b] | $C_{17}H_{21}NO_3 \cdot HCl$ | 63.07 | 63.30 | 6.85 | 6.78 | 10.95 | 10.85 | 4.33 | 4.27 |
| 3 | 3,4,5-$(CH_3O)_3C_6H_2$ | $N(CH_3)_2$ | A[e] | 43 | 152–153[b] | $C_{16}H_{21}NO_5 \cdot HCl$ | 55.89 | 55.94 | 6.46 | 6.86 | 10.31 | 10.50 | 4.07 | 4.10 |
| 4 | 3,4,5-$(CH_3O)_3C_6H_2$ | $C_4H_8N$[f] | C(a) | 11 | 171.5–173.5[g] | $C_{18}H_{23}NO_5 \cdot HCl$ | 58.46 | 58.60 | 6.54 | 6.65 | 9.59 | 9.94 | 3.79 | 3.56 |
| 5 | 3,4,5-$(CH_3O)_3C_6H_2$ | $C_5H_{10}N$[c] | C(a) | 35 | 185.5–187.5d.[g] | $C_{19}H_{25}NO_5 \cdot HCl$ | 59.44 | 59.71 | 6.84 | 6.84 | 9.24 | 9.21 | 3.65 | 3.46 |
| 6 | 4-$ClC_6H_4$ | $C_5H_{10}N$[c] | C(a) | 42 | 171–173[h] | $C_{16}H_{18}NO_2Cl \cdot HCl$ | 58.50 | 58.48 | 5.84 | 6.05 | | | 4.27 | 4.20 |
| 7 | 2-$ClC_6H_4$ | $C_5H_{10}N$[c] | C(a) | 31 | 171.5–173.5[h] | $C_{16}H_{18}NO_2Cl \cdot HCl$ | 58.50 | 58.30 | 5.84 | 6.01 | | | 4.27 | 4.29 |
| 8 | 4-$NH_2C_6H_4$ | $C_5H_{10}N$[c] | B[i] | 26 | 100.0–102.5[j] | $C_{16}H_{20}N_2O_2$ | 70.56 | 70.93 | 7.40 | 7.08 | | | 10.29 | 10.15 |
| 9 | 1-Naphthyl | $N(CH_3)_2$ | B[k] | 27 | 165.5–168.5[h] | $C_{17}H_{17}NO_2 \cdot HCl$ | 67.25 | 66.98 | 5.97 | 6.21 | | | 4.61 | 4.43 |
| 10 | 1-Naphthyl | $C_5H_{10}N$[c] | B[i] | 57 | 189.5–191.5[h] | $C_{20}H_{21}NO_2 \cdot HCl$ | 69.86 | 70.36 | 6.46 | 6.57 | | | 4.07 | 3.84 |
| 11 | 1-Naphthyl | $C_4H_8NO$[l] | B[i] | 39 | 194–197d.[m] | $C_{19}H_{19}NO_3 \cdot HCl$ | 66.00 | 65.70 | 5.83 | 5.82 | | | 4.05 | 3.64 |
| 12 | 2-Naphthyl | $C_5H_{10}N$[c] | B[k] | 40 | 160–163[h] | $C_{20}N_{21}NO_2 \cdot HCl$ | 69.86 | 69.89 | 6.46 | 6.06 | 10.33 | 10.06 | 4.07 | 4.08 |
| 13 | 2-Naphthyl | $C_4H_8NO$[l] | B[i] | 30 | 199–201.5[h] | $C_{19}H_{19}NO_3 \cdot HCl$ | 66.00 | 66.26 | 5.84 | 6.04 | 10.25 | 10.00 | 4.05 | 4.49 |
| 14 | 4,4′-Biphenyl | $C_5H_{10}N$[c] | B[i] | 68 | 161.5–166.5[h] | $C_{22}H_{23}NO_2 \cdot HCl$ | 71.44 | 71.11 | 6.55 | 6.61 | | | 3.79 | 3.78 |
| 15 | 9-Fluorenyl | $C_5H_{10}N$[c] | B[i] | 43 | 172–173[h] | $C_{23}H_{23}NO_2 \cdot HCl$ | 72.33 | 72.07 | 6.33 | 6.18 | | | 3.66 | 3.47 |
| 16 | 9-Fluorenyl | $N(C_2H_5)_2$ | B[k] | 21 | 143–144[h] | $C_{22}H_{23}NO_2 \cdot HCl$ | | | | | 9.58 | 9.10 | | |
| | | | D | 0 | | | | | | | | | | |
| 17 | 2-Phenyl-2-styryl | $C_5H_{10}N$[c] | B[i] | 28 | 170–171.5[h] | $C_{24}H_{25}NO_2 \cdot HCl$ | 72.78 | 73.09 | 6.62 | 6.73 | | | 3.54 | 3.62 |
| 18 |  | $N(C_2H_5)_2$ | B[k] | 59 | 81.5–83.5[h] | $C_{20}H_{23}NO_3S \cdot HCl$ | 60.98 | 61.39 | 6.14 | 6.86 | 9.00 | 8.69 | 3.56 | 3.70 |
| 19 |  | $N(C_2H_5)_2$ | D | 60 | 125–128[h] | $C_{22}H_{31}NO_3 \cdot HCl$ | 67.06 | 66.88 | 8.19 | 8.25 | 9.00 | 8.68 | 3.56 | 3.50 |
| 20 | $(C_6H_5CH_2)_2CH$ | $C_5H_{10}N$[c] | C(a) | 39 | 156.5–158.5[n] | $C_{25}H_{29}NO_2 \cdot HCl$ | 72.89 | 72.51 | 7.34 | 6.94 | | | 3.40 | 3.17 |

[a] Heated reaction mixture on steam bath 96 hr. [b] Recrystallized from propanol. [c] $C_5H_{10}N$ = piperidino. [d] Heated reaction mixture on steam bath 120 hr. [e] Heated reaction mixture on steam bath 85 hr. [f] $C_4H_8N$ = pyrrolidino. [g] Recrystallized from ethyl acetate. [h] Recrystallized from ethyl acetate–ethanol. [i] Used sodium methoxide catalyst. [j] Free base melting point; recrystallized from ethanol–petroleum ether. [k] Used sodium metal catalyst. [l] $C_4H_8NO$ = morpholino. [m] Recrystallized from ethanol. [n] Recrystallized from benzene.

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(2) R. Dahlbom and R. Mollberg, *Acta Chem. Scand.*, **17**, 916 (1963).
(3) R. Dahlbom, B. Hansson, and R. Mollberg, *ibid.*, **17**, 2354 (1963).
(4) E. R. H. Jones, I. Marszak, and H. Bader, *J. Chem. Soc.*, 1578 (2947).