*Pharmacology.* All of the compounds were evaluated for hypotensive response following procedures previously described.[5] A 3+ response was noted on administration of compounds 14, 15, 20 and 25, while compounds 3, 24 and 26 showed 2+ hypotension. Each of the 3+ compounds also showed a potentiating effect on adrenalin and complete ganglionic block. Compound 26 inhibited adrenalin and showed a ganglionic block, compound 3 resembled the 3+ responders, and compound 24 was without effect on adrenalin.

In the carbamido series (compounds 15–26) it is of interest that hypotensive activity was associated with the compounds $R_1$, $R_2$ = H, and $R_1$ = aralkyl or aryl and $R_2$ = H. Other structural modifications such as those found in compounds 16, 17, 18, 19, 22 and 23 were associated with loss of hypotensive activity.

### EXPERIMENTAL[6]

*N-(Iodomethyl) tropinium iodide* (Compound 6, Table I). Tropine (5.6 g., 0.04 mole) and 5.3 g. (0.02 mole) of diiodomethane were dissolved in 30 ml. of acetonitrile and maintained at 20° for 5 days.

The formed crystals were separated to give 5.0 g. (62%), m.p. 198–202°.

The same compound was obtained from 1:1 molar ratios of the reactants at 20°, or when the reaction mixture above was heated for 0.5 hour under reflux. The reaction of tropine with penta-erythrityl tetrabromide failed with no evidence of quaternization after 50 hr. under reflux in acetonitrile.

*N-(Carbamidomethyl)tropinium chloride* (Compound 15, Table I). A solution of 4.2 g. (0.03 mole) of tropine, 5.6 g. (0.06 mole) of α-chloroacetamide and 60 ml. of acetonitrile was maintained at 20° for 5 days. Filtration yielded 4.7 g. of product, m.p. 232–237°. An additional 1.4 g. was obtained by addition of ether to the filtrate.

*N-Methyl-α-chloroacetanilide.*[7] The following preparation is typical of the synthesis of compounds of the α-haloacetamides.

A solution of 11.8 g. (0.11 mole) of *N*-methylaniline in 75 ml. of acetonitrile was slowly added to a cooled solution of 5.7 g. (0.05 mole) of chloroacetyl chloride in 25 ml. of acetonitrile. After 48 hr. at 20°, the *N*-methylaniline hydrochloride was separated and the filtrate evaporated. Trituration of the residue with ether gave 8.8 g. (96%) of crude product, which recrystallized (hexane) melted 69–70°.

The constants of most of the α-haloacetamides were in substantial agreement with values reported in the literature. The following amides have not been previously reported: *N*-benzyl-*N*-*i*-propyl-bromacetamide, b.p. 124–136° (0.2 mm.); *N*-α-phenethyl-bromacetamide, m.p. 82–83° (hexane); *N*-(2,5-endomethylenecyclohexyl)methyl-bromacetamide, b.p. 104–130° (0.04 mm.).

Analyses were N Calcd./N Found, respectively, 5.2/5.1, 5.8/6.0, 5.7/5.6.

(5) (a) For evaluation of hypotensive effect see Ref. 1; (b) for evaluation of effect on adrenalin and ganglionic block see S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, *J. Am. Chem. Soc.*, **81**, 203 (1959).

(6) Data given in the tables are not reproduced in this section. Representative examples of the synthetic work are given.

(7) Reported by W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 105 (1915), m.p. 70°.

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## Bis(5-hydroxymethyl-1-naphthyl)disulfide

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Although preparations of bis(hydroxyalkyl-aryl) disulfides, including those of bis(2-hydroxymethylphenyl)disulfide,[1a,b,c] bis(4-hydroxylmethyl phenyl) disulfide,[1c] and bis(4-β-hydroxyethyl-1-naphthyl) disulfide[2] have been reported previously, an example of a bis(hydroxymethyl-naphthyl)disulfide was hitherto unknown. Since the aforementioned known disulfides have been evaluated as chain transfer agents for free radical polymerization systems,[1b,1c,2] it seemed worthwhile to evaluate a compound of the latter type in such a system.

This paper reports the preparation of such a disulfide, namely bis(5-hydroxymethyl-1-naphthyl)-disulfide (VI) by the following procedure: A sample of 5-acetoxymethyl-1-nitronaphthalene (II) was prepared in two steps from 1-nitronaphthalene by the method of Short and Wang[3] *via* chloromethylation and acetolysis, and hydrolyzed to the known carbinol (III) (99%) with alcoholic alkali. The overall yield of III obtained from 5-chloromethyl-1-nitronaphthalene (I) by this two step method was much greater (65%) than that which we obtained by hydrolyzing the chloride directly to the carbinol with aqueous sodium carbonate by Short's procedure[3] (12%). Compound III was catalytically reduced to 5-hydroxymethyl-1-naphthylamine (IV), an orange compound, m.p. 107.2–108.4° (94%) with Raney nickel, converted to a crude form of 5-hydroxymethyl-1-thionaphthol (V) *via* the xanthate method, and oxidized to the corresponding disulfide (VI), a tan compound, m.p. 196.1–197.1°.

### EXPERIMENTAL[4]

*5-Hydroxymethyl-1-nitronaphthalene* (III). This compound was prepared by alkaline hydrolysis of 5-acetoxymethyl-

(1) (a) A. Reichert and K. Crämer, *Ber.*, **61**, 2555 (1928); (b) A. J. Costanza, R. J. Coleman, R. M. Pierson, C. S. Marvel, and C. King, *J. Polymer Sci.*, **17**, 319 (1955); (c) R. M. Pierson, A. J. Costanza, and A. H. Weinstein, *J. Polymer Sci.*, **17**, 221 (1955).

(2) A. H. Weinstein, R. M. Pierson, B. Wargotz, and T. F. Yen, *J. Org. Chem.*, **23**, 363 (1958).

(3) W. F. Short and H. Wang, *J. Chem. Soc.*, 991 (1950).

(4) All melting points are corrected.

1-nitronaphthalene (II), m.p. 90.2–91.2°, which was prepared in turn (70%) from 5-chloromethyl-1-nitronaphthalene (I)[3] by an acetolysis procedure described by Short and Wang.[3]

A 4.90 g. (0.0200 mole) portion of II was suspended in 45 ml. of 0.44*N* alcoholic potassium hydroxide, and the mixture refluxed for 3 hr. By concentrating the resultant solution *in vacuo*, and adding water to it, a brown precipitate was formed. By collecting this precipitate, washing it with water, then with *n*-hexane, and desiccating it, 4.02 g. (99%) of III, m.p. 128–129°, was obtained. The product was recrystallized from hot 1:1 chloroform/cyclohexane to pale yellow needles, m.p. 130.4–131.2°. (Compare with m.p. 128–129° reported for III by Short and Wang[3] as prepared by hydrolysis of I with aqueous sodium carbonate.)

*Anal.* Calcd. for $C_{11}H_9NO_3$: C, 65.01; H, 4.46; N, 6.89. Found: C, 65.27; H, 4.37; N, 6.79, 6.83.

*5-Hydroxymethyl-1-naphthylamine* (IV). A 10.16 g. (0.0500 mole) quantity of III, m.p. 128–129°, was dissolved in 200 ml. of warm absolute ethanol, and the solution poured into a 375 ml. Parr hydrogenation pressure bottle, and allowed to cool. Water-wet, active Raney nickel catalyst (2.9 g.) was added to the bottle, which was connected to a Parr low pressure hydrogenation apparatus. The system was swept with hydrogen and reduced with hydrogen at an initial pressure of three atmospheres, at 25° with mechanical shaking, for 4 hr. (to constant pressure value of gas reservoir). Then the solution was exposed to the system for another hour at 75° (during which time no further drop in hydrogen pressure occurred). After filtering the catalyst from the hot solution (quickly flushing the pyrophoric residue into the sink), the ethanol solution was evaporated *in vacuo*. In this way, 8.13 g. (93.6%) of fairly pure IV was obtained as a brown solid m.p. 106.4–107.4°. On recrystallizing the product from hot 7:1 toluene/ethanol solution, orange-brown crystals, m.p. 107.2–108.4°, with an equivalent weight of amine of 175 (on basis of titration with perchloric acid in acetic acid with methyl violet indicator), as compared with a theoretical equivalent weight of 173 for $C_{11}H_{11}NO$, were obtained.

*Bis(5-hydroxymethyl-1-naphthyl) disulfide* (VI). (A) Formation of crude 5-hydroxymethyl-1-thionaphthol (V). A 3.98 g. (0.0230 mole) quantity of IV was mixed with 5.76 ml. of concentrated hydrochloric acid and 15 ml. of water. To this yellow-green slurry, cooled to −5°, was added an ice-chilled solution of 1.59 g. of sodium nitrite in 5 ml. of water, gradually with stirring, along with some ice. This brown diazonium salt suspension was added, dropwise, with stirring to a solution of 5.60 g. (0.0350 mole) of potassium ethyl xanthate in 10 ml. of water, maintaining the latter system at 50°, and the former at 0°. After mixing, the system was maintained at 50° for an additional hour, with continued stirring, and allowed to cool. After acidification with 1:1 concentrated sulfuric acid/water in the hood, the system was extracted with ether and the solvent removed. The resultant 5.30 g. of crude 5-hydroxymethyl-1-naphthyl ethyl xanthate was hydrolyzed by treating with a solution containing 3.46 g. potassium hydroxide, 1 ml. of water, and 5 ml. of ethanol at reflux for 1 hr. After removal of ethanol *in vacuo*, the residue was extracted with 100 ml. of water, and the aqueous extract acidified with 6*N* sulfuric acid. The brown precipitate which formed was collected, washed with water, then with hexane, and air dried. This crude 2.68 g. of thiol (V), m.p. 73–76°, was obtained in 61% yield of product of 58% thiol activity (on the basis of potentiometric titration of an ammoniacal solution of V in isopropanol with standardized silver nitrate).

(B) Disulfide formation. A 1.96 g. quantity of V (containing 0.00600 mole of active V) was dissolved in 30 ml. of ethanol, and treated with a solution of 0.76 g. (0.0060 gram atoms) of iodine in aqueous potassium iodide solution. By collecting, washing, and drying the resultant yellow precipitate, 1.34 g. of solid, m.p. 178–185°, was obtained. On recrystallizing this product from 60 ml. of 4:2:1 toluene/ethanol/nitrobenzene solution, 0.56 g. of VI, m.p. 193–194°, was isolated. This was recrystallized from 5:1 ethanol/nitrobenzene to tan crystals, m.p. 196–197°. The latter substance gave a negative test for mercaptan with silver nitrate reagent, but did form the silver mercaptide after being reduced with aqueous sodium sulfite (the latter test confirms presence of the disulfide function).

*Anal.* Calcd. for $(C_{11}H_9OS)_2$: C, 69.85; H, 4.80; S, 16.95. Found: C, 69.18, 69.30; H, 4.57, 4.68; S, 17.38, 17.46.

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## Resolution of DL-β-Hydroxybutyric Acid

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The resolution of racemic β-hydroxybutyric acid, described in 1902 by McKenzie[2] and repeated by Levene and Haller,[3] depends primarily on inoculation of an aqueous solution of the quinine salts with a crystalline sample of the salt of the L acid obtained from diabetic urine.

In the procedure here described advantage is taken of the hitherto unrecorded great difference in the solubility in acetone of the two quinine salts, the D variety of which requires nearly ten times as much of the solvent as the L isomer for solution. The relationships are illustrated in Table I.

TABLE I

APPROXIMATE PERCENTAGE CONCENTRATION OF SATURATED SOLUTIONS OF THE QUININE SALTS OF D- AND L-β-HYDROXYBUTYRIC ACIDS IN ACETONE AND IN WATER AT VARIOUS TEMPERATURES

| Acetone | | Water | |
|---|---|---|---|
| D | L | D | L |
| 0.49/1° | 4.4/1° | 3.5/0° | 2.6/0° |
| 1.33/21° | 13.2/25° | 4.0/25° | 5.8/25° |
| | | 10/60° | 10/36° |

### EXPERIMENTAL

To a hot solution of 200 meq. of DL-β-hydroxybutyric acid (91.3% by titration) in 500 ml. of acetone, 65 g. (200 mmoles) of anhydrous quinine base was gradually added. When solution was complete the mixture was chilled at 0–1° for 24 hr.; the crystalline salt was collected with suction, washed with 50 ml. of ice cold acetone, and then digested with 300 ml. of boiling acetone for 30 min. The suspension was cooled, held at 0–1° overnight, and filtered with suction; the crystals were washed with 30 ml. of cold acetone, digested as before with 150 ml. of boiling acetone, and dried in air. The yield was 36 g. (81 mmoles, calculated as monohydrate) of quinine D-β-hydroxybutyrate.

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(2) A. McKenzie, *J. Chem. Soc.*, **81**, 1402 (1902).

(3) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **65**, 49 (1925).