contents becomes progressively slower as the caecum is approached." The effect of viscosity on gastric emptying is important for drug absorption, since the large surface area available for absorption makes the small intestine the optimum absorption site, even for weakly acidic drugs which show greater intrinsic absorption rates in the acidic stomach. This is evident from both human (25) and animal (8) absorption data.

In conclusion, increasing viscosity can decrease the absorption rate of drugs from the gastrointestinal tract by retarding the movement of drug molecules to the absorbing membranes and by slowing gastrointestinal transit. In addition, there may be specific effects due to complex formation, osmotic pressure, and other factors mentioned in preceding sections of this paper. The results of the present study have direct application to the use of viscous solutions or suspensions in pharmacologic studies on animals. The magnitude of effects encountered in humans with therapeutically realistic volumes of viscous solutions is presently under study and will be reported in a subsequent communication.

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Potential Radiation Protective Agents III

Mercapto Analogs Related to Ephedrine

By K. VENKATRAMANA BHAT and WALTER C. MCCARTHY

Reaction of chlorodeoxypseudoephedrine hydrochloride with sodium thioacetate gave 1-phenyl-1-mercapto-2-(*N*-methylacetamido) propane. This product was resistant to hydrolysis by aqueous acid or base, but the corresponding disulfide was reduced by lithium aluminum hydride to 1-phenyl-1-mercapto-2-(*N*-methyl-*N*-ethylamino) propane. Condensation of chlorodeoxypseudoephedrine hydrochloride with potassium ethyl xanthate gave 3,4-dimethyl-5-phenylthiazolidine-2-thione, which was also resistant to hydrolysis, but was reduced to 1-phenyl-1-mercapto-2-(*N,N*-dimethylamino) propane.

IN RECENT YEARS, there has been much interest in compounds containing mercapto and amino groups on adjacent carbon atoms as radiation protective agents. Mercapto analogs of known pharmaceutical agents that contain hydroxy and amino groups on adjacent carbon atoms would be of much interest for investigation as antiradiation compounds, not only because they possess a structural moiety associated with high radiation protective activity, but also because the parent hydroxy compounds are known to be absorbed and transported to many widely distributed tissue sites in the body. Since certain sympathomimetic amines have been demonstrated to possess radiation protective activity, the mercapto analogs related to ephedrine were selected early for investigation. In a previous paper (1), it was shown that chlorodeoxypseudoephedrine hydrochloride reacted with thiourea to give, instead of the expected isothiuronium salt, a cyclization product, 3,4-dimethyl-5-phenyl-2-iminothiazolidine hydrochloride. Because of the

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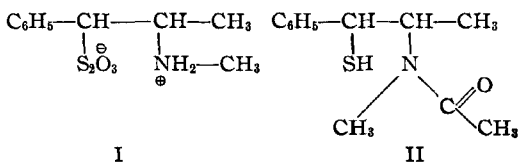
difficulty in isolating a crystalline mercapto amine from the hydrolysis of this compound, other routes were investigated for the synthesis of these mercapto analogs.

Reaction of (+)-chlorodeoxypseudoephedrine hydrochloride with sodium thiosulfate gave a Bunte salt (I), first reported by Bretschneider (2). The authors found that this compound required 12 to 20 recrystallizations to bring it to constant melting point and optical rotation. Because of the tedious recrystallization required, other methods for the introduction of the sulfur function were investigated. In view of the difficulty of hydrolysis of the other sulfur derivatives subsequently synthesized, it would now appear that the Bunte salt would be the route of choice to the mercaptan. Bretschneider (3) has reported the hydrolysis of this Bunte salt under oxidative conditions to the corresponding disulfide.

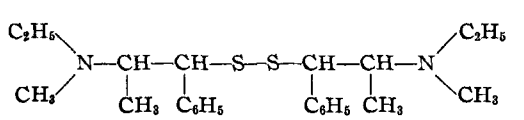
Reaction of (+)-chlorodeoxypseudoephedrine hydrochloride with sodium thioacetate gave a product in which the acetyl group migrated from sulfur to nitrogen, (+)-1-phenyl-1-mercapto-2-(*N*-methylacetamido)propane (II). Both this compound and the corresponding disulfide (III) are extremely resistant to hydrolysis by refluxing



I II

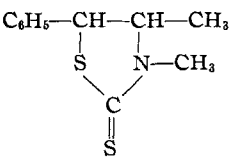
with aqueous acid or base. This was quite unexpected since the acyl derivatives of ephedrine, even though susceptible to acyl migrations under mild conditions, are readily amenable to hydrolysis. Even though these thio compounds are extremely hindered to hydrolysis, reduction proceeds readily with lithium aluminum hydride, with the conversion of the disulfide (III) to (+)-1-phenyl-1-mercapto-2-(*N*-methyl-*N*-ethylamino)propane. During the workup, air oxidation of the mercaptan occurred, and this product was isolated as the corresponding disulfide (IV).

Condensation of (+)-chlorodeoxypseudoephedrine hydrochloride with potassium ethyl xanthate gave (−)-3,4-dimethyl-5-phenyl-thiazolidine-2-thione (V). This compound was also

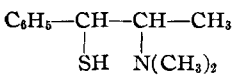


IV

unexpectedly resistant to hydrolysis. It could be recovered unchanged after refluxing for 2 days with concentrated hydrobromic acid. It was, however, readily reduced with lithium aluminum hydride to 1-phenyl-1-mercapto-2-(*N*,*N*-dimethylamino)propane (VI).



V



VI

Because of the extreme resistance to hydrolysis of derivatives of the mercapto analog of ephedrine, it was hoped that this difficulty might be circumvented by protecting the nitrogen with the easily cleaved formyl group. Upon reaction with *N*-formyl-(−)ephedrine, thionyl chloride failed to replace the hydroxy group by chloride, but gave instead (+)-pseudoephedrine. This inversion of the hydroxy group and cleavage of the *N*-acyl group is analogous to that reported in the reaction of thionyl chloride with *N*-formyl-D-*erythro*-2-amino-1,2-diphenylethanol (4). Apparently the oxazoline intermediate involved in the inversion can form even with a tertiary amide. Similarly, the authors found that *N*-acetylephedrine reacted with thionyl chloride to give *O*-acetyl-(+)-pseudoephedrine hydrochloride.

Synthetic routes utilizing chlorodeoxypseudoephedrine suffer from the drawback that they are readily amenable to the preparation of only one stereo configuration since the other isomer, chlorodeoxyephedrine, is obtainable only with difficulty using phosphorus pentachloride. Although (−)-ephedrine and (+)-pseudoephedrine possess opposite configurations of the hydroxyl group, Emde (5) has shown that both compounds give the identical product upon reaction with thionyl chloride. Apparently, ephedrine reacts by chloride ion displacement of the chlorosulfite ester to give the chloro compound with the inverted configuration, while pseudoephedrine reacts by internal return of the chlorosulfite ester to give the product with retained configuration. It was hoped that both sets of optical isomers could be synthesized through use of *O*-tosyl esters in the replacement reactions. Both (−)-ephedrine and (+)-pseudoephedrine could be monotosylated to produce the corresponding *N*-tosyl derivatives, but neither of these compounds could be further tosylated to produce the *N*,*O*-ditosyl derivatives. Neither could *N*-acetyl-(−)-ephedrine be tosylated to produce the *O*-tosyl derivative.

Dr. Thomas R. Sweeney, Department of Medicinal Chemistry, Walter Reed Army In-

stitute of Research, Washington, D. C., has reported that the Bunte salt (I), when administered to mice in the dosage range of 51 to 150 mg./Kg., showed no protective activity against an LD_{100} dose of radiation. Another ephedrine derivative, 3,4-dimethyl-5-phenyl-2-iminothiazolidine hydrochloride (1), administered to mice in the dosage range of 50 mg./Kg. or less, also showed no protective activity. This test and evaluation scale is described by Field *et al.* (6).

EXPERIMENTAL

(+) - 2 - Methylamino - 1 - phenyl - 1 - propylthiosulfuric Acid (I).—(+)-Chlorodeoxypseudo ephedrine hydrochloride (5) (19 Gm., 0.086 mole) and sodium thiosulfate pentahydrate (21.4 Gm., 0.086 mole) were dissolved in 40 ml. of hot water, allowed to stand for 1 hr., then heated on a water bath for 2 hr. On cooling, fine white crystals separated, 20.5 Gm., (91%), m.p. 158–162°. After repeated recrystallization from water, a constant melting point was reached at 186–187°, $[\alpha]_D^{25}$ +221°, c, 1, water. Bretschneider (2) reported m.p. 181°, $[\alpha]_D^{20}$ + 218°, c, 0.2292, water.

Anal.—Calcd. for $C_{10}H_{15}NO_3S_2$: C, 45.94; H, 5.79; N, 5.36; O, 18.36; S, 24.53. Found: C, 46.13; H, 5.85; N, 5.24; O, 18.67; S, 24.27.

(+) - 1 - Phenyl - 1 - mercapto - 2 - (N - methylacetamido)propane (II).—Methanolic sodium methoxide (23 ml., 10% w/v sodium) was added to a solution of 22 Gm. (0.1 mole) of (+)-chlorodeoxypseudoephedrine hydrochloride (5) in 150 ml. of anhydrous methanol. To this was added a solution of sodium thioacetate prepared from 7.5 ml. (0.1 mole) of thioacetic acid and 23 ml. of methanolic sodium methoxide (10% w/v sodium). The mixture was refluxed for 3 hr. It was then filtered, and the methanol was evaporated under reduced pressure in a rotary evaporator. The residue was recrystallized four times from dilute alcohol, 9.5 Gm. (43%), m.p. 112–113°, $[\alpha]_D^{25}$ + 190°, c, 1, ethanol.

Anal.—Calcd. for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.08; H, 7.70; N, 6.36; S, 14.59.

The mercaptan content was assayed by titration with 0.01 *N* iodine solution, in which 99% of the theoretical amount of iodine was consumed.

(+) - 1 - Phenyl - 2 - (N - methylacetamido) - 1-propyl Disulfide (III).—The disulfide was obtained from the mercaptan by oxidation with iodine and was recrystallized from dilute alcohol, m.p. 172–173°, $[\alpha]_D^{25}$ + 390°, c, 1, 95% ethanol.

Anal.—Calcd. for $C_{24}H_{32}N_2O_2S_2$: C, 64.83; H, 7.26; N, 6.30; S, 14.29. Found: C, 64.62, 64.50; H, 7.48, 7.40; N, 6.40; S, 14.10.

Attempted Hydrolysis of 1-Phenyl-1-mercapto-2-(N-methylacetamido)propane (II).—*Preparation A.*—1 - Phenyl - 1 - mercapto - 2 - (*N* - methylacetamido)propane (5.6 Gm., 0.025 mole) was dissolved in 50 ml. of ethanol and refluxed with 25 ml. of concentrated hydrochloric acid for 3 hr. The solvent was evaporated under reduced pressure in the rotary evaporator, and the residue was crystallized from dilute alcohol, to give 4.5 Gm. of starting material, m.p. 112–113°. A mixed melting point with the starting material showed no change.

Preparation B.—1 - Phenyl - 1 - mercapto - 2-(*N*-methylacetamido)propane (5.6 Gm., 0.025 mole) in 100 ml. of 20% sodium hydroxide solution was refluxed for 24 hours, then cooled and saturated with carbon dioxide. The precipitate was recrystallized three times from dilute alcohol to give 3.2 Gm. of the corresponding disulfide, m.p. 172–173°. Apparently during refluxing or during recrystallization, air oxidation of the mercaptan to the disulfide occurred. A mixed melting point with the disulfide prepared above showed no change.

(+) - 1 - Phenyl - 2 - (N - methyl - N - ethylamino)-1-propyl Disulfide (IV).—(+)-1-Phenyl-2-(*N*-methylacetamido)-1-propyl disulfide (4.5 Gm.) was placed in the thimble of a Soxhlet extractor and extracted with ether into a solution of 1.8 Gm. of lithium aluminum hydride in 275 ml. of ether in the boiling flask of the Soxhlet extractor. After 72 hr., all of the disulfide had been extracted into the reduction mixture. Water (0.9 ml.) was added dropwise with stirring, followed by 4.9 ml. of concentrated acid. The mixture was filtered, and the precipitate was further extracted with ether. The combined filtrates were dried over anhydrous sodium sulfate, and the ether was evaporated under reduced pressure in a rotary evaporator. The crude semisolid residue was recrystallized from hot alcohol, 2.0 Gm., m.p. 160–161°, $[\alpha]_D^{25}$ + 715°, c, 1, benzene.

Anal.—Calcd. for $C_{24}H_{36}N_2S_2$: C, 69.18; H, 8.71; N, 6.72; S, 15.39. Found: C, 69.03, 69.24; H, 8.61, 8.62; N, 6.89, 6.90; S, 15.23, 15.23.

The mercaptan content of the product was assayed by titration with 0.01 *N* iodine solution and required 7% of the theoretical iodine. Thus, the isolated product was the disulfide rather than the mercaptan.

(−) - 3,4 - Dimethyl - 5 - phenylthiazolidine - 2-thione (V).—A solution of 22 Gm. (0.1 mole) of (+)-chlorodeoxypseudoephedrine hydrochloride (5) in 200 ml. of absolute ethanol was converted to the free base by addition of 46 ml. of ethanolic sodium ethoxide (5% w/v sodium). Potassium ethyl xanthate (16 Gm., 0.1 mole) was added, and the mixture was refluxed for 3 hr. on the steam bath. After cooling and filtration, the solvent was evaporated under reduced pressure in a rotary evaporator to give a brownish-yellow gum. This was crystallized from isopropyl alcohol, 6 Gm. (25%), m.p. 65–66°, $[\alpha]_D^{25}$ − 155°, c, 1, alcohol.

Anal.—Calcd. for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.86; N, 6.27; S, 28.70. Found: C, 59.02; H, 5.84; N, 6.15; S, 28.28.

Attempted Hydrolysis of 3,4-Dimethyl-5-phenylthiazoladine-2-thione.—A solution of 5 Gm. of 3,4-dimethyl-5-phenylthiazoladine-2-thione in 25 ml. of concentrated (48%) hydrobromic acid was refluxed for 48 hr. The mixture was evaporated under reduced pressure in a rotary evaporator, and the residue was crystallized from isopropyl alcohol to give 4 Gm. of starting material, m.p. 64–66°.

1 - Phenyl - 1 - mercapto - 2 - (N,N - dimethylamino)propane (VI).—A solution of 8 Gm. (0.036 mole) of (−)-3,4-dimethyl-5-phenylthiazoladine-2-thione in 200 ml. of anhydrous ether was added dropwise to a solution of 3.79 Gm. (0.1 mole) of lithium aluminum hydride in 100 ml. of ether. This mixture was refluxed for 90 hr., after which the reduction complex was hydrolyzed by adding dropwise 7.2 ml. of water and 9.7 ml. of concentrated

hydrochloric acid. The mixture was filtered, the ether solution was dried over anhydrous sodium sulfate, and the ether was evaporated, leaving a white solid. After recrystallization from absolute alcohol, the yield was 4.5 Gm. (64%), m.p. 75–76°, $[\alpha]_D^{25}$ + 150°, c, 1, 0.1 *N* hydrochloric acid.

Anal.—Calcd. for $C_{11}H_{17}NS$: C, 67.64; H, 8.76; N, 7.17; S, 16.42; equivalent weight, 195.3. Found: C, 67.57; H, 8.67; N, 7.17; S, 16.25; equivalent weight by titration in acetic acid with acetous perchloric acid, 191.

The mercaptan content was assayed by titration with 0.01 *N* iodine solution, and required 103% of the theoretical iodine for oxidation of the mercaptan to disulfide.

1 - Phenyl - 2 - (N,N - dimethylamino) - 1-propyl Disulfide.—1-Phenyl-1-mercapto-2-(*N,N*-dimethylamino)propane was dissolved in ethanol and oxidized with a 1% solution of iodine. The excess iodine was decolorized by the addition of a few drops of sodium thiosulfate solution, and upon cooling the reaction mixture in ice, a white crystalline solid separated. This was recrystallized from alcohol, m.p. 196–197°, $[\alpha]_D^{25}$ + 300°, c, 1, 0.1 *N* hydrochloric acid.

Anal.—Calcd. for $C_{22}H_{32}N_2S_2$: C, 67.99; H, 8.30; N, 7.21; S, 16.50. Found: C, 67.85; H, 8.23; N, 7.21; S, 16.28.

N-Formylephedrine.—Chloral (15 Gm., 0.1 mole) (7) was added dropwise with stirring to 16.5 Gm. (0.1 mole) of (−)-ephedrine in an ice-cooled flask. After addition was complete, the mixture was stirred at room temperature for 2 hr. The mixture was evaporated in a rotary evaporator under reduced pressure to remove the chloroform generated during the reaction. An oily residue and a crystalline precipitate remained. Recrystallization of the solid product from absolute alcohol gave 1 Gm. of ephedrine hydrochloride, m.p. 217–218°. The oil was distilled under vacuum and gave 6 Gm. of formylephedrine collected at 168–174° (1 mm.). The infrared spectrum showed a strong carbonyl peak at 1665 cm.$^{-1}$.

(+)-Pseudoephedrine.—Excess thionyl chloride was added dropwise with stirring to *N*-formylephedrine, cooled in an ice bath. The mixture was stirred for 1.5 hr. at room temperature, and the excess thionyl chloride was evaporated under suction. Addition of acetone to the gummy residue gave a crystalline product. Recrystallization from absolute alcohol gave (+)-pseudoephedrine hydrochloride, m.p. 182–183°, $[\alpha]_D^{25}$ + 60°, c, 1, water.

O-Acetyl-(+)-pseudoephedrine Hydrochloride.—Thionyl chloride (1.13 ml., 0.15 mole) was added dropwise to an ice-cold solution of 2.07 Gm. (0.01 mole) of *N*-acetylephedrine (8) in 100 ml. of chloroform. The mixture was stirred for 30 min. at room temperature, then heated on a water bath for an additional 30 min. The solvent was evaporated under reduced pressure. The gummy residue was dissolved in hot acetone and gave a crystalline precipitate on cooling. After recrystallization from isopropyl alcohol, the yield was 1.5 Gm., m.p. 185–186°, $[\alpha]_D^{25}$ + 98°, c, 1, water. Mitchell (8, 9) prepared this compound by another method and reported m.p. 187°, $[\alpha]_D^{20}$ + 99.5°, c, 5, water.

N-p-Toluenesulfonyl-(−)-ephedrine.—A mixture of 10.7 Gm. (0.05 equivalent) of (−)-ephedrine sulfate and 12 Gm. (0.062 mole) of *p*-toluenesulfonyl chloride was shaken with 60 ml. of 10% sodium hydroxide solution. The reaction mixture was cooled in ice, and the precipitated product was collected by filtration. After three recrystallizations from 60% ethanol, the yield was 13 Gm. (81%), m.p. 117–118°, $[\alpha]_D^{25}$ − 27.5°, c, 1, 95% ethanol.

Anal.—Calcd. for $C_{17}H_{21}NO_3S$: C, 63.91; H, 6.63; N, 4.39; O, 15.03; S, 10.04. Found: C, 63.49; H, 6.52; N, 4.71; O, 15.18; S, 10.19.

The *N*-sulfonyl bond was confirmed by the presence of a sharp hydroxyl absorption band at 3570 cm.$^{-1}$ in the infrared spectrum.

N - p - Toluenesulfonyl - (+) - pseudoephedrine.—This was prepared in 84% yield from (+)-pseudoephedrine by a procedure similar to that in the above paragraph, m.p. 93–94.5°, $[\alpha]_D^{25}$ + 25°, c, 1, 95% ethanol.

Anal.—Calcd. for $C_{17}H_{21}NO_3S$: C, 63.91; H, 6.63; N, 4.39; O, 15.03; S, 10.04. Found: C, 63.48; H, 6.61; N, 4.67; O, 15.25; S, 10.13.

Attempted Tosylation of N-p-Toluenesulfonylephedrine.—A solution of 3.2 Gm. (0.01 mole) of *N-p*-toluenesulfonylephedrine and 2.5 Gm. (0.013 mole) of *p*-toluenesulfonyl chloride in 8 ml. of pyridine was stirred for 4 hr. at room temperature. Ether was added to the reaction mixture, and it was then extracted with 2 *N* hydrochloric acid and with water. The ether was evaporated, and the residue, after recrystallization from dilute ethanol, gave 94% of recovered *N-p*-toluenesulfonylephedrine, m.p. 117–118°.

Starting material was also recovered after heating the reaction mixture at 80°.

A similar reaction run at the reflux temperature of pyridine gave, after evaporation of the ether, an oil which could not be crystallized.

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