optimum acids in all cases. It is obvious from Fig. 1, for instance, that in the analysis of cyclizine it would be logical to substitute 0.5 *N* HCl for the 2 *N* acid specified. The latter acid was entirely suitable, however, for effecting quantitative recoveries. A simple screening, as described above, with the three acids was effective in the selection of a suitable acid for the assay of a wide variety of alkoids in addition to those discussed, including methapyrilene, codeine, pheniramine, antazoline, thonzylamine, methorphan, hexylcaine, narcotine, and others. Thus, the need to explore the behavior of each alkoid vis-à-vis a variety of acids over a wide range of concentrations is obviated. It is to be expected, of course, that acids other than these three will be required for some individual alkoids; the screening will indicate this situation.

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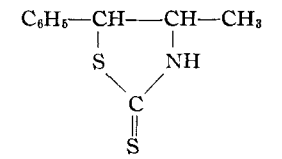
Potential Radiation Protective Agents IV. Sulfur Analogs Related to Norephedrine

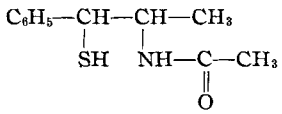
By K. VENKATRAMANA BHAT and WALTER C. McCARTHY

Condensation of 2-amino-1-chloro-1-phenylpropane with potassium ethyl xanthate gave 4-methyl-5-phenylthiazolidine-2-thione. Reaction of 2-amino-1-chloro-1-phenylpropane with sodium thioacetate gave 2-acetamido-1-mercapto-1-phenylpropane, which oxidized in air to the corresponding disulfide. The amide group of the latter compound, bis-(2-acetamido-1-phenyl-1-propyl) disulfide, was cleaved by refluxing with acid.

IN A CONTINUATION of work reported previously on mercapto analogs related to ephedrine (1, 2), similar analogs corresponding to norephedrine were investigated also. *dl*-Norephedrine reacted with thionyl chloride to produce 2-amino-1-chloro-1-phenylpropane hydrochloride (3). This salt was converted to the free base, and its reaction with two different sulfur nucleophiles was studied. Upon reaction of the free base with potassium ethyl xanthate, cyclization occurred to produce 4-methyl-5-phenylthiazolidine-2-thione (I). Upon condensation of the free base with sodium thioacetate, migration of



I



II

the acetyl group from sulfur to nitrogen occurred to produce 2-acetamido-1-mercapto-1-phenylpropane (II). During isolation, the mercaptan was partly air-oxidized to the corresponding disulfide.

Hydrolysis of the acetyl group of bis-(2-acetamido-1-phenyl-1-propyl) disulfide was hindered, but it could be forced under drastic conditions. The amide was recovered unchanged after refluxing for 6 hr. in a mixture of 30 ml. of ethanol and 20 ml. of concentrated hydrochloric acid. The amide group was cleaved, however, by refluxing for 48 hr. in concentrated hydrochloric acid. Originally, bis-(2-amino-1-phenyl-1-propyl) disulfide dihydrochloride was obtained, but because solvent of crystallization gave difficulty in securing a satisfactory analytical sample, this compound was converted through the free base to the hydrobromide salt.

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EXPERIMENTAL

4-Methyl-5-phenylthiazolidine-2-thione (I).—To a solution of 20.6 Gm. (0.1 mole) of 2-amino-1-chloro-1-phenylpropane hydrochloride, m.p. 201–202° (3), in 200 ml. of anhydrous methanol was added 23 ml. of methanolic sodium methoxide (10% w/v sodium) to liberate the free base. Potassium ethyl xanthate (16 Gm., 0.1 mole) was added, and the mixture was refluxed for 4 hr. After cooling, the mixture was filtered, and the solvent was evaporated under reduced pressure in a rotary evaporator. The white gum which remained was crystallized from isopropyl alcohol and cyclohexane to give, after several recrystallizations from the same mixture, a yield of 5.6 Gm. (27%), m.p. 97–98°.

Anal.—Calcd. for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69; S, 30.64. Found: C, 57.44; H, 5.27; N, 6.73; S, 30.94.

2-Acetamido-1-mercapto-1-phenylpropane (II).—To a solution of 35.5 Gm. (0.172 mole) of 2-amino-1-chloro-1-phenylpropane hydrochloride (3) in 200 ml. of absolute methanol was added 39.5 ml. of methanolic sodium methoxide (10% w/v sodium) to liberate the free base. A solution of sodium thioacetate, prepared from 12.5 ml. (0.172 mole) of thioacetic acid in 39.5 ml. of methanolic sodium methoxide (10% w/v sodium), was added; the mixture was refluxed for 3 hr. with stirring. After

cooling, the precipitated sodium chloride was removed by filtration, and the residue was washed with absolute methanol. The filtrate was evaporated under reduced pressure in a rotary evaporator, then crystallized from dilute alcohol to give 21 Gm. of crude material, m.p. 130–145°. This was dissolved in the least amount of hot alcohol and allowed to crystallize. After cooling in an ice bath, 12 Gm. of crystals was collected, m.p. 205–210°. Water was added to the mother liquor until cloudy; after further cooling in an ice bath, a second crop of crystals of another compound was collected (6 Gm.), m.p. 143–147°. This latter material was recrystallized several times from dilute alcohol to give 3 Gm. (8.5%) of product, m.p. 151–152°.

The infrared absorption spectrum of this compound showed a weak absorption peak at 2565 cm.$^{-1}$, indicating the presence of a mercapto group, and a peak at 1635–1640 cm.$^{-1}$, indicating a secondary amide carbonyl group. The mercaptan content of this compound was determined by dissolving in alcohol, adding excess standard iodine solution, and titrating the excess with standard sodium thiosulfate. Three samples of the compound were found to consume 101.1, 100.3, and 101.4% of the amount of iodine theoretically required to oxidize the mercaptan to the corresponding disulfide.

Bis-(2-acetamido-1-phenyl-1-propyl) Disulfide.—The first fraction isolated in the above preparation, m.p. 205–210°, was recrystallized from dilute alcohol to give 8 Gm. (22%) of the disulfide, m.p. 215–216°. The analytical sample was recrystallized further from acetone with no change in melting point. The infrared spectrum showed no absorption in the region of 2550–2600 cm.$^{-1}$, an indication of the absence of a mercapto group. A strong absorption band for the secondary amide carbonyl group was observed at 1635–1640 cm.$^{-1}$.

Anal.—Calcd. for $C_{22}H_{28}N_2O_2S_2$: C, 63.44; H, 6.78; N, 6.73; O, 7.68; S, 15.37. Found: C, 63.01; H, 6.82; N, 6.75; O, 7.82; S, 15.67.

Bis-(2-amino-1-phenyl-1-propyl) Disulfide Dihydrobromide.—*Preparation A.*—A solution of 1 Gm. of bis-(2-acetamido-1-phenyl-1-propyl) disulfide in 30 ml. of ethanol and 20 ml. of concentrated hydrochloric acid was refluxed for 6 hr. The mixture was evaporated under reduced pressure in a rotary evaporator, and the residue was recrystallized from dilute alcohol to give 0.8 Gm. of starting material, m.p. 214–216°, with no depression of melting point upon admixture with the starting material.

Preparation B.—A mixture of 4.2 Gm. (0.01 mole) of bis-(2-acetamido-1-phenyl-1-propyl) disulfide and 25 ml. of concentrated hydrochloric acid was refluxed for 48 hr. After evaporation under reduced pressure in a rotary evaporator, the residue was recrystallized several times from isopropyl alcohol to give 1.5 Gm. (37%) of the hydrochloride salt, m.p. 242–243°. Because of difficulty with solvent of crystallization with this salt, it was converted to the free base, extracted into ether, treated with hydrobromic acid to convert it to the hydrobromide salt, evaporated to dryness, and recrystallized from isopropyl alcohol, m.p. 265–267°.

Anal.—Calcd. for $C_{18}H_{26}Br_2N_2S_2$: C, 43.73; H, 5.29; Br, 32.32; N, 5.67; S, 12.97. Found: C, 43.93; H, 5.25; Br, 32.46; N, 5.50; S, 12.70.

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Synthesis of Some Diamides of 2-Chlorobenzaldehyde, 2,4-Dichlorobenzaldehyde, and 3,4-Dichlorobenzaldehyde

By JOSEPH P. LAROCCA and WILLIAM C. CULPEPPER*

The synthesis of some *N,N'*-bis-(amido) chlorotoluenes is described. These compounds are prepared by the condensation of various amides with the appropriate chlorinated benzaldehyde.

THE IDEAL antiepileptic drug should be long acting, nonsedating, well tolerated, and effective against the various types of seizures, including mixed types, and devoid of unwanted side effects (1). None of the drugs available meet all the requirements of an ideal antiepileptic drug completely.

Although most antiepileptic drugs currently in use contain a carbonyl-nitrogen-carbonyl grouping, anticonvulsant activity also is found in other compounds, such as simple amides, *N*-substituted amides, aldehydes, and alcohols. *N*-Benzyl-β-chloropropionamide has anticonvulsant activity and is an example of a compound which has a methylene-nitrogen-carbonyl grouping instead of the typical carbonyl-nitrogen-carbonyl group (2). Numerous *N*-substituted amides have been reported in the literature (3, 4). LaRocca and his associates have prepared some chloral and 2,2,3-trichlorobutyraldehyde amides, and LaRocca and Byrum reported the potentiality of the compounds as sedative-hypnotics and anticonvulsants (3, 4). LaRocca reported the synthesis and pharmacological activity of some *N*-(2,2,3-trichloro-1-hydroxypropyl)-amides, of which the acetamide derivative has shown a high degree of anticonvulsant activity (5). These compounds have a hydroxyl-nitrogen-carbonyl instead of the carbonyl-nitrogen-carbonyl group usually found in

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