off and extracted with chloroform and the chloroform solution treated with methyl orange as described. However, it was found that simply by adding sufficient droperidol (in lactic acid solution) to the sample during dilution to raise the ratio of droperidol to fentanyl to 50:1 in the final solution (0.02 mg./ml. fentanyl) complete precipitation of the droperidol was achieved.

The reineckate precipitate of droperidol can be used as a quantitative measure of droperidol. Once 4′-fluoro-4-(4-oxopiperidino)butyrophenone is removed by the addition of sodium bisulfite as directed in the proposed assay for droperidol, the chloroform solution of droperidol can be treated with the Reinecke solution and sulfuric acid. The droperidol-Reinecke precipitate is collected, dissolved in acetone, and the absorbance of the red colored solution read at about 525 mμ. The interference of 4-anilino-1-(2-phenylethyl)piperidine in the Reinecke precipitation of droperidol is small for the droperidol–fentanyl pharmaceutical preparations. The fentanyl would have to be completely hydrolyzed to affect the droperidol reineckate precipitate by 2%.

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Keyphrases

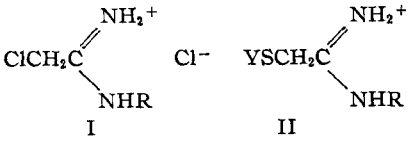
Droperidol, fentanyl citrate solution—analysis
Fentanyl citrate, droperidol—hydrolysis products
Chloroform extraction—droperidol
UV spectrophotometry—analysis
Methanol–chloroform extraction—fentanyl citrate
Colorimetric analysis—methyl orange reagent
TLC—identity

Synthesis of α-Mercaptoacetamidinium Chlorides *via* the Corresponding Phosphorothioates

By TERRY T. CONWAY, ABOO SHOEB, and LUDWIG BAUER

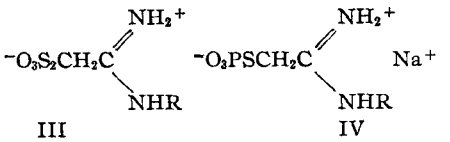
A facile synthesis of α-mercaptoacetamidinium chlorides is described. The procedure consists of treating α-chloroacetamidinium chlorides with trisodium phosphorothioate that formed the corresponding *S*-alkyl phosphorothioates. The latter were not isolated, but were hydrolyzed in the reaction medium by hot dilute acid to furnish the required products.

THE SYNTHESIS of α-mercapto amidines and derivatives as potential antiradiation agents has been under study in this laboratory for some time (1–3). The general approach consisted of treating an α-chloroacetamidinium chloride, I, with a sulfur bearing nucleophile, YS^-, to obtain a substituted acetamidinium cation, II. These



I II

reactions were successful since the substitution reaction of the halo group of the free α-chloroacetamidine was considerably faster than any reaction involving nucleophilic attack at the sp^2 amidine carbon. It was particularly important to exclude the latter type of reaction in an aqueous basic medium since displacement of the halo group by YS^- could easily be accompanied by hydrolysis of the amidine.[1] It was found that a relatively weakly basic, but excellent nucleophile like thiosulfate ion reacted quickly with I to form a series of α-amidinium Bunte salts, III. Due to the relatively easy preparation of



III IV

compounds of type III, it was of interest to explore the reaction of I with phosphorothioate ion, $^-O_3PS^-$, in the endeavor to synthesize a series of α-amidinium phosphorothioates, shown as the sodium salt, IV. It was intended to test a

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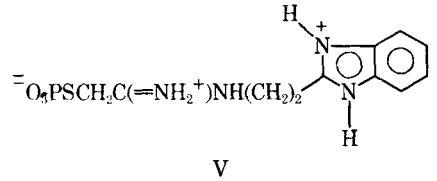
[1] The basic hydrolysis of amidines is a well-documented reaction. [For a recent reference see DeWolfe, R. D., and Keefe, J. R., *J. Org. Chem.*, **27**, 493(1962).]

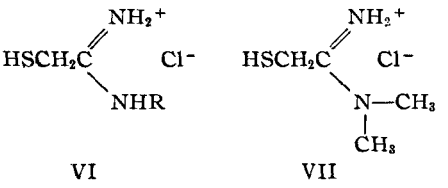
number of these salts, IV, as potential antiradiation agents since a number of analogous *S*-[β-aminoalkyl] phosphorothioates had been shown frequently to afford good protective action against ionizing radiation in mice (4, 5).

The reaction of a number of chloroacetamidinium chlorides with trisodium phosphorothioate in water was followed initially by the change in the NMR spectrum. For example, the proton magnetic resonance spectrum[2] of α-chloroacetamidinium chloride (I, R = H) in water showed a singlet for the CH_2 proton at δ 4.53 which disappeared quickly on the addition of trisodium phosphorothioate. There arose a doublet at δ 3.66 which was assigned to the CH_2—S—P resonance, coupling of the protons over three bonds with phosphorus being observed (J = 13.5 c.p.s.).[3] Addition of methanol to such an aqueous solution furnished the salt (as the trihydrate), IV (R = H). Analogous reactions of I (R = CH_3, $CH_2C_6H_5$, *cyclo*-C_6H_{11}) with Na_3SPO_3 invariably gave aqueous solutions whose NMR spectra showed a doublet (J = 13.5 c.p.s.) in the vicinity of δ 3.70 ± 0.1. Attempts to isolate these phosphorothioates by the addition of alcohols or *N,N*-dimethylformamide to the aqueous solution yielded solids which tenaciously clung to polar solvents. These solids were found to possess varying degrees of stability as was evident by their change in physical appearance and their NMR spectra.[4] One notable exception was the isolation of the relatively stable zwitterion, V. Apparently the basic β-(2-benzimidazole) ethyl group neutralized the second negative charge and V could be kept for months.



V

It was observed, however, that these phosphorothioates, IV, were hydrolyzed readily by hot dilute mineral acids to the corresponding thiols, VI. As a matter of expediency, it was found that the isolation of the intermediate phosphorothioates, IV, was not essential, but these could be hydrolyzed *in situ* and this proved to be a general method for the ready conversion of I to VI. It was possible to synthesize a number of derivatives of VI, where R was representative alkyl and aralkyl groups starting



VI VII

with the corresponding crystalline α-chloroacetamidinium chlorides, I, and without the isolation of IV. These solid α-mercaptoacetamidinium chlorides were stable in air. The only exception in the authors' experience was *N*-methyl-α-mercaptoacetamidinium chloride (VI, R = CH_3), which decomposed quickly. This particular salt began to smell badly of hydrogen sulfide, commenced to liquify within 24 hr. (*in vacuo* at 25°), and its NMR spectrum changed drastically. By contrast, the corresponding *N,N*-dimethyl analog, VII, was quite stable. This salt showed, as expected, two different N—CH_3 signals in the NMR. This restricted rotation about the CN bond is in keeping with that observed in other *N,N*-dimethyl amidinium salts (6).

An extension of this type of synthesis towards *N,N'*-disubstituted α-mercaptoacetamidinium chlorides led into the preparation of imidazole derivatives. For example, 2-(chloromethyl)-imidazoline was readily converted to 2-(mercaptomethyl)imidazoline by this method. An aromatic benzimidazole analog was prepared as shown in Scheme I. This involved originally the preparation of 1-methyl-2-(chloromethyl)-benzimidazole from the reaction of methyl chloroacetimidate (prepared *in situ* from the addition of methanol to chloroacetonitrile) (7) with *N*-methyl-*o*-phenylenediamine hydrochloride.[5] The chloro derivative was then readily converted to the corresponding mercaptan.

Attempts were made to utilize α-amidinium thiosulfates (Bunte salts), III, as suitable precursors to VI. On a preparative scale, the acid hydrolysis of the thiolsulfate group[6] in III was not nearly as satisfactory as that of the

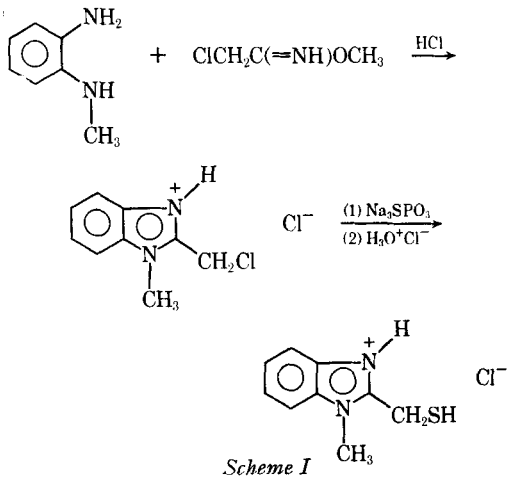
[2] The nuclear magnetic resonance (NMR) spectra were determined at 60 Mc. by means of a Varian A-60 spectrometer and chemical shifts are recorded in parts per million (δ) downfield from such internal standards as tetramethylsilane (TMS) in organic solvents and sodium 3-(trimethylsilyl)-propanesulfonate (TPS) in aqueous or D_2O solutions. Multiplicities are denoted as follows: singlet, s; doublet, d. Assignment of the signals is also based on correct integral information.

[3] Long-range coupling over three bonds, $J_{P\text{-}S\text{-}CH_2}$, has been reported for a number of similar systems: in a number of mercaptophosphazenes, J = 18.1 ± 0.5 c.p.s. [Boden, N., Emsley, J. W., Feeney, J., and Sutcliffe, L. H., *Chem. Ind.*, (London), 1909 (1962)]; in *S*-alkylphosphorothioates, J = 15 c.p.s. [Oswald, A. A., Griesbaum, K., and Hudson, B. E., Jr., *J. Org. Chem.*, **28**, 1262(1963)]; J = 12.7 – 17.5 c.p.s. [Mueller, W. H., Rubin, R. M., and Butler, P. E., *ibid.*, **31**, 3537(1966); Mueller, W. H., and Oswald, A. A., *ibid.*, **32**, 1730(1967)].

[4] Attempts to crystallize these salts with solvent of crystallization or to dry them *in vacuo* at 5° were unsuccessful in most instances and purification resulted in partial decomposition. Most of the *S*-(aminoalkyl)phosphorothioates were isolated with varying proportions of solvent of crystallization (see *References 4* and *5*).

[5] The synthesis of benzimidazoles from *o*-phenylenediamines and imidates was recently reinvestigated [see deSelms, R. C., *J. Org. Chem.*, **27**, 2163(1962)].

[6] For a recent study on the acid-catalyzed hydrolysis of Bunte salts, see Kice, J. L., Anderson, J. M. and Pawlowski, N. E., *J. Am. Chem. Soc.*, **88**, 5245(1966).



Scheme I

phosphorothioate moiety in IV to give VI. The acid hydrolysis of several α-amidinium thiolsulfates, III, was investigated in detail. For example, brief exposure of III (R = benzyl) to hot dilute hydrochloric acid yielded VI (R = benzyl) in poor yield. Prolonged acid treatment (even under nitrogen) produced predominantly the corresponding disulfides, $[-SCH_2C(=NH_2^+)NHCH_2C_6H_5\ Cl^-]_2$, VIII. Presumably, these disulfides are formed by the oxidation of the corresponding mercaptans, although the possibility of displacement of HSO_3^- in III by RSH of VI does exist.[7] This point was not investigated further.

In connection with the general study of nucleophilic displacement reactions of I, *N*-benzyl-α-chloroacetamidinium chloride was treated with sodium sulfite. There was formed the corresponding α-amidinium sulfonate, $^-O_3SCH_2C(=NH_2^+)HNCH_2C_6H_5$, IX. To prove that indeed this substitution reaction involved the formation of a C-S bond, the disulfide, VIII, was oxidized to give IX. The infrared spectrum of IX clearly showed it to be a zwitterion since the characteristic amidinium bands showed up, $-C(=N^+<$ stretching frequency in the vicinity of 1700 and the $>C=NH_2^+$ deformation mode around 1650 cm.$^{-1}$. These bands were also found in III and IV.

EXPERIMENTAL[8]

N-Cyclopentylchloroacetamidinium Chloride—The procedure developed previously (1–3) was used for this and related syntheses. Chloroacetonitrile (7.55 Gm., 0.1 mole) was added slowly to a stirred ice-cold solution of sodium (0.23 Gm., 0.01 Gm.-atom) in methanol (75 ml.). After 1 hr., cyclopentylammonium chloride (13.38 Gm., 0.11 mole) was then added and the mixture stirred for 1 hr. longer. The mixture was filtered and solvent removed at 20–30 mm. and at the lowest temperature. The purple residue was triturated with dry ether and the resultant solid (11.26 Gm., 55%) recrystallized from 2-propanol–ether, m.p. 142.5–143.5° dec.

Anal.—Calcd. for $C_7H_{14}Cl_2N_2$: C, 42.67; H, 7.16; N, 14.22. Found: C, 42.73; H, 7.53; N, 14.00.

N-Cyclohexylchloroacetamidinium Chloride—This salt was prepared in 80% yield in an analogous fashion, using cyclohexylammonium chloride, and recrystallized from 2-propanol, m.p. 181–182.5° dec.

Anal.—Calcd for $C_8H_{16}Cl_2N_2$: C, 45.40; H, 7.62; N, 13.24. Found: C, 45.55; H, 7.83; N, 12.95.

N - [β - (2 - Benzimidazolium)ethyl]chloroacetamidinium Dichloride—When 2-(β-aminoethyl)-benzimidazole dihydrochloride (8) was used as the ammonium salt, the title product commenced to precipitate, was filtered, and an additional quantity obtained when solvents were concentrated. The salt was obtained in 82% yield and was recrystallized from aqueous ethanol, m.p. 244–246°.

Anal.—Calcd. for $C_{11}H_{15}Cl_3N_2$: C, 42.65; H, 4.84; N, 18.09. Found: C, 42.50; H, 4.98; N, 17.98.

1-Methyl-2-(chloromethyl)benzimidazolium Chloride—This salt was obtained in 51% yield when *N*-methyl-*o*-phenylenediamine hydrochloride (Eastman Organic Chemicals) was substituted in the synthesis described above, m.p. 209° (from 2-propanol).

Anal.—Calcd. for $C_9H_{10}Cl_2N_2$: C, 49.77; H, 4.60; N, 12.90. Found: C, 49.49; H, 4.55; N, 12.97.

Sodium S-(Carboxamidiniummethyl)phosphorothioate Trihydrate—α-Chloroacetamidinium chloride (1) (2.58 Gm., 0.02 mole) was added to a solution of trisodium phosphorothioate[9] (3.6 Gm., 0.02 mole) in water (30 ml.) and the resultant solution stirred at 25° for 10 min. A small precipitate was filtered off and the filtrate diluted with methanol (50 ml.), and the mixture chilled for 10 min. The product (3.25 Gm., 66%) was collected, washed copiously with dry ether (two 40-ml. portions), and dried *in vacuo* (over H_2SO_4). On heating in an m.p. tube, it turned yellow and decomposed above 90°.

Anal.—Calcd. for $C_2H_6N_2NaO_3PS\cdot 3H_2O$: C, 9.75; H, 4.91; N, 11.38; S, 13.02. Found: C, 9.75; H, 5.02; N, 11.12; S, 13.11.

Sodium S-[N-(Benzyl)carboxamidiniummethyl]-phosphorothioate Hydrate—*N*-Benzyl-α-chloroacetamidinium chloride (1) (4.38 Gm., 0.02 mole) was added to a stirred aqueous solution of trisodium phosphorothioate (3.6 Gm., 0.02 mole in 35 ml.). After 10 min. at 25°, the mixture was filtered to remove a trace of insoluble material and the filtrate diluted with 2-propanol (50 ml.). The product was filtered, washed with 2-propanol. It was recrystallized by dissolving it in cold water

[7] In their review on Bunte salts, B. Milligan, and J. M. Swan [*Rev. Pure Appl. Chem.*, 12, 72(1962); *J. Chem. Soc.*, 6008 (1963)] state that the reaction of mercaptans with Bunte salts to give disulfides is favored at a high pH. Other relevant literature has been summarized by H. Distler [*Angew. Chem.*, 79, 520(1967)].

[8] All melting and boiling points are uncorrected. Infrared spectra were all determined in Nujol mull (unless otherwise specified) by means of the Perkin-Elmer model 337 spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. and Dr. Kurt Eder, Geneva, Switzerland. Most of the nitrogen analyses were obtained by Mr. Leo Horner in this department, using a Coleman model D-29.

[9] This salt was prepared from thiophosphoryl chloride (supplied by the Stauffer Chemical Co.) and sodium hydroxide solution at 60°. This modification of S. Akerfeldt's procedure [*Acta Chem. Scand.*, 14, 1980(1960)] was essential and was also reported by J. R. Piper, and T. P. Johnston, [*J. Org. Chem.*, 32, 1261(1967)].

and adding 2-propanol. It was dried at 5° at 20 mm. over concentrated H_2SO_4 until its NMR spectrum showed the absence of signals due to 2-propanol. In H_2O, the salt showed signals due to CH_2S at δ 3.75 (d, J_{CH_2SP} = 13.5 c.p.s.), CH_2N at δ 4.58 (d, J = 6.3 c.p.s.), and C_6H_5 at δ 7.54 (s).

Anal.—Calcd for $C_9H_{12}N_2NaO_3PS \cdot H_2O$: C, 36.01; H, 4.70; N, 9.33. Found: C, 36.46; H, 5.23; N, 8.83.

S - {N - [β - (2 - Benzimidazolium)ethyl]carboxamidiniummethyl}phosphorothioate, V—*N*-[β-(2-Benzimidazolium)ethyl]chloroacetamidinium dichloride (0.3 Gm., 0.001 mole) was added to an aqueous solution of trisodium phosphorothioate (0.18 Gm., 0.001 mole in 10 ml.) and the solution stirred at 25° for 10 min. The product (0.21 Gm., 70%) was collected, washed with hot water, boiling ethanol; m.p. 168–169°. It was dried *in vacuo* at 25° prior to analysis.

Anal.—Calcd. for $C_{11}H_{15}N_4O_3PS \cdot {}^1/_2H_2O$: C, 40.86; H, 4.95; N, 17.33; S, 9.90. Found: C, 41.19; H, 4.97; N, 17.29; S, 9.89.

α-Mercaptoacetamidinium Chloride—All stages of this and cognate experiments were conducted under a blanket of nitrogen. To an aqueous solution of trisodium phosphorothioate (3.66 Gm., 0.02 mole in 25 ml.) was added α-chloroacetamidinium chloride (2.58 Gm., 0.02 mole). The solution was stirred at ambient temperature until the test for phosphorothioate ion was negative [black precipitate with $AgNO_3$ (9), about 3–5 min.]. After 10 min., 6 *N* hydrochloric acid (20 ml.) was added and the solution heated at 90° for 10 min. and then evaporated *in vacuo*. The residue was extracted with 2-propanol (20 ml.) and filtered from inorganic salts. Addition of dry ether (150 ml.) yielded the salt (1.9 Gm., 75%), m.p. 120–122° dec.; infrared absorptions, 2540 (νSH), 1700 (νC=N), 1650 cm.$^{-1}$ (δ C=NH_2^+); NMR signal (D_2O) at δ 3.57 (s) for CH_2S.

Anal.—Calcd. for $C_2H_7ClN_2S$: C, 18.97; H, 5.57; N, 22.13; S, 25.32. Found: C, 18.97; H, 5.55; N, 21.99; S, 25.21.

This procedure was used to convert a number of crystalline α-chloroacetamidinium chlorides to the corresponding thiols.

N,N-Dimethyl-α-mercaptoacetamidinium chloride was prepared in this manner (64%); m.p. 160°; infrared, 2450 (νSH), 1690 (νC=N^+) and 1650 cm.$^{-1}$ (δ C=NH_2^+); NMR, δ (D_2O) 3.65, (s, CH_2S), 3.18, 3.26 (two s, NCH_3).

Anal.—Calcd. for $C_4H_{11}ClN_2S$: C, 31.06; H, 7.12; N, 18.12; S, 20.71. Found: C, 31.15; H, 7.10; N, 18.03; S, 20.64.

N-Cyclopentyl-α-mercaptoacetamidinium chloride was synthesized in this way (72%), m.p. 146–147.5° dec.

Anal.—Calcd. for $C_7H_{15}ClN_2S$: C, 43.17; H, 7.76; N, 14.39; S, 16.47. Found: C, 43.16; H, 7.78; N, 14.59; S, 16.39.

N-Cyclohexyl-α-mercaptoacetamidinium chloride was prepared (44%) as above, m.p. 163–165° dec.

Anal.—Calcd. for $C_8H_{17}ClN_2S$: C, 46.02; H, 8.21; N, 13.42; S, 15.36. Found: C, 45.77; H, 8.15; N, 13.36; S, 15.30.

N-Benzyl-α-mercaptoacetamidinium chloride was made from the corresponding α-chloro compound (1), in 44% yield, m.p. 115–117° dec.; infrared, 2570 (γSH), 1700 (νC=N^+), 1650 cm.$^{-1}$ (δ C=NH_2^+); NMR, δ (D_2O) 3.65 (s, CH_2S), 4.60 (s, CH_2N), 7.46 (s, C_6H_5).

Anal.—Calcd for $C_9H_{13}ClN_2S$: C, 49.87; H, 6.04; N, 12.93; S, 14.80. Found: C, 50.26; H, 5.88; N, 12.91; S, 14.80.

N-(2-Picolyl)-α-mercaptoacetamidinium chloride hydrochloride was produced from the chloro precursor (3) in 63% yield, m.p. 196–197°.

Anal.—Calcd. for $C_8H_{13}Cl_2N_3S$: C, 37.79; H, 5.11; N, 16.53; S, 12.60. Found: C, 37.55; H, 5.15; N, 16.44; S, 12.70.

N - (6 - Methyl - 2 - picolyl) - α - mercaptoacetamidinium chloride hydrochloride was prepared from the corresponding chloro derivative (3) in 48% yield, m.p. 179–181°.

Anal.—Calcd. for $C_9H_{15}Cl_2N_3S$: C, 40.30; H, 5.64; N, 15.64; S, 11.96. Found: C, 40.22; H, 5.53; N, 15.39; S, 11.79.

N - [β - (2 - Pyridyl)ethyl] - α - mercaptoacetamidinium chloride hydrochloride was obtained from the corresponding chloro compound (3) (60%), m.p. 180°.

Anal.—Calcd. for $C_9H_{15}Cl_2N_3S$: C, 40.30; H, 5.60; N, 15.67; S, 11.94. Found: C, 40.15; H, 5.63; N, 15.34; S, 11.91.

2-(Mercaptomethyl)imidazolinium chloride was synthesized in analogous fashion from 2-(chloromethyl)-imidazoline (3) (60%), m.p. 129–130°.

Anal.—Calcd. for $C_4H_9ClN_2S$: C, 31.47; H, 5.90; N, 18.35; S, 20.98. Found: C, 31.60; H, 6.17; N, 18.04; S, 20.40.

1 - Methyl - 2 - (mercaptomethyl) - benzimidazolium chloride hydrate was prepared (in 84% yield) from 1-methyl-2-(chloromethyl)benzimidazolium chloride as described above, m.p. 127°.

Anal.—Calcd. for $C_9H_{11}ClN_2S \cdot H_2O$: C, 46.45; H, 5.59; N, 12.04; S, 13.76; Cl, 15.26. Found: C, 46.53; H, 5.76; N, 12.14; S, 13.80; Cl, 15.30.

N - [β - (2 - Benzimidazolium)ethyl] - α - mercaptoacetamidinium Dichloride—*S*-{*N*-[β-(2-Benzimidazolium)ethyl]carboxamidiniummethyl}phosphorothioate (1.3 Gm., 0.004 mole, prepared above) was heated with 6 *N* HCl (10 ml.) on the steam bath for 10 min. (nitrogen atmosphere). Solvents were removed *in vacuo* to yield a solid (0.8 Gm., 66%), which was recrystallized from a mixture of ethanol–ether to give colorless crystals, m.p. 215–216°.

Anal.—Calcd. for $C_{11}H_{16}Cl_2N_4S$; C, 43.50; H, 5.21; N, 18.23; S, 10.42. Found: C, 43.07; H, 5.13; N, 18.08; S, 10.28.

N-Benzyl-α-mercaptoacetamidinium Chloride from the Hydrolysis of III (R = $CH_2C_6H_5$)—A solution of S-[*N*-(benzyl)-carboxamidinomethane]thiosulfuric acid (1.16 Gm., 0.004 mole) in 6 *N* hydrochloric acid (15 ml.) was heated at 96° for 1.5 hr. (N_2 atmosphere). After removing solvents *in vacuo*, the yellow oily residue crystallized and was recrystallized from ethanol–ether. It weighed 0.2 Gm., (24% yield), m.p. 115–116°, and was identical to the sample made *via* the phosphorothioate.

(N-Benzylcarboxamidinium)methyl Disulfide Dichloride—A solution of S-[*N*-(benzyl)carboxamidinomethane]thiosulfuric acid (1) (2.64 Gm., 0.01 mole) in 6 *N* hydrochloric acid (50 ml.) was heated at 96° for 15 hr. On cooling, the oil which separated solidified and was crystallized from water (1.6 Gm., 75%, m.p. 207–208.5° dec; infrared, 1680 (νC=N^+), 1635 cm.$^{-1}$ (δ C=NH_2^+); NMR in D_2O, δ 3.83 (s, CH_2S) 4.60 (s, CH_2N) 7.48 (s, C_6H_5), in (DMSO-d_6), δ 3.96 (s, CH_2S) 4.72 (d, CH_2N, J_{CH_2-NH} = 5 c.p.s.), 7.49 (s, C_6H_5), 9.95, 9.55, and 10.79 (broad s, NH).

Anal.—Calcd. for $C_{18}H_{24}Cl_2N_4S_2$: C, 50.11; H, 5.61; N, 12.91; S, 14.86. Found: C, 50.43; H, 5.86; N, 12.72; S, 15.21.

(Carboxamidinium)methyl Disulfide Sulfate—A solution of α-(carboxamidino)methanethiolsulfuric acid (1) (10.0 Gm., 0.059 mole) in 6 *N* hydrochloric acid (250 ml.) was heated at 96° for 17 hr. The reaction mixture was evaporated *in vacuo* and the yellow gummy residue recrystallized from 50% aqueous alcohol (4.5 Gm., 55%), m.p. 225–227° dec.; infrared,† 1700 cm.$^{-1}$ (ν C=N$^+$); NMR (D_2O), δ 3.82 (s, CH_2S–S–).

Anal.—Calcd. for $C_4H_{12}N_4O_4S_3$: C, 17.38; H, 4.38; N, 20.27; S, 34.81. Found: C, 17.62; H, 4.50; N, 20.00; S, 35.01.

(N-Benzylcarboxamidino)methanesulfonic Acid—(*a*) To an aqueous solution of *N*-benzyl-α-chloroacetamidinium chloride (1) (5 Gm., 0.019 mole) in 30 ml. was added an aqueous sodium sulfite solution (2.42 Gm. 0.019 mole in 22 ml.) and the mixture heated at the reflux for 0.5 hr. The crystals (1.2 Gm., 37%) which separated were recrystallized from methanol–ether to give the product (0.20 Gm., 47%), m.p. 245–246°; infrared, 1690 (ν C=N$^+$), 1645 cm.$^{-1}$ (δ C=NH_2^+); NMR (D_2O), δ 4.10 (s, CH_2S), 4.60 (*s*, CH_2N), 7.45 (s, C_6H_5).

Anal.—Calcd. for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.30; N, 12.27; S, 14.05. Found: C, 47.25; H, 5.52; N, 12.27; S, 13.90.

(*b*) A solution of (*N*-benzylcarboxamidinium)-methyl disulfide dichloride (0.40 Gm.), 30% hydrogen peroxide solution (5 ml.), and 6 *N* hydrochloric acid (10 ml.) were heated at 96° (17 hr.). Solvents were removed *in vacuo* and the residue crystallized and found to be identical to that described in *a*.

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Keyphrases

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Drug Standards

Selective Determination of Tolbutamide in Pharmaceutical Dosage Forms by Reaction with Ninhydrin

By K. K. KAISTHA and W. N. FRENCH

A colorimetric method is described for the quantitative determination of tolbutamide in pharmaceutical dosage forms. The procedure is based on the interaction of *n*-butylamine, liberated *in situ* from tolbutamide, and ninhydrin to form a blue complex which can be quantitated spectrophotometrically at 585 mμ. No color is produced by *p*-toluenesulfonamide or dibutylurea, two possible decomposition products of tolbutamide. Urea and its acyl derivatives, carbamates, amidines, guanidine, and common tablet excipients do not undergo the reaction. A modified procedure is described for the removal of *n*-butylamine, a major hydrolytic product of tolbutamide, from samples of the drug that have undergone decomposition. Results of the application of the assay procedure to a stability study of tolbutamide tablets are presented.

ALTHOUGH ULTRAVIOLET SPECTROPHOTOMETRIC analysis, as described in the USP XVII (1), is commonly used for tolbutamide preparations, this method is not satisfactory if ultraviolet-absorbing degradation products such as *p*-toluenesulfonamide or impurities such as *p*-toluenesulfonylurea are present in the sample. Similarly, a procedure involving total nitrogen determination, as described in the BP 1963 (2),

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