The major product, the compound melting at 128°, was assigned the structure of 2,2,3-triphenyl-*p*-dioxane on the basis of its analysis, molecular weight, and method of synthesis. The compound, m.p. 201°, has not been positively identified, but it is probably a tetraphenyl-*p*-dioxanyl-*p*-dioxane (VIII).

Compound, m.p. 201°. Yield: 0.3 g. *Anal.* Calcd. for $C_{32}H_{30}O_4$: C, 80.5; H, 6.3. Found: C, 80.86, 80.26; H, 6.30, 6.30. Compound, m.p. 128°. Yield: 2 g. Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.51; H, 6.09. Molecular weight: Calcd.: 316. Found: 306 (Rast camphor).

## The Structure of the Thiocytosine Analog of Nitrogen Mustard[1]

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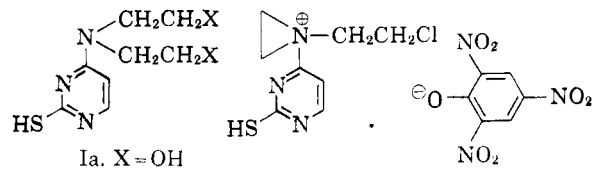
Recently the synthesis of 4-[bis(2-chloroethyl)-amino]-2-pyrimidinethiol (Ib, the thiocytosine analog of nitrogen mustard) by the chlorination of 2,2′-[(2-mercapto-4-pyrimidinyl)imino]diethanol (Ia) with thionyl chloride has been claimed[2] but no evidence was offered that both chlorine atoms of this compound are in fact covalent. Further, the conversion of Ib to 1-(2-chloroethyl)-1-(2-mercapto-4-pyrimidinyl)aziridinium picrate (II) by treatment with hot ethanolic picric acid is described. Since the true structure of a nitrogen mustard such as Ib is important to the evaluation of biological data obtained with it, and since it has been established that attempts to prepare the purin-6-yl analog of nitrogen mustard by thionyl chloride chlorination of the corresponding iminodiethanol gave only the tricyclic purine III,[3] we have studied the chlorination of Ia as recently described.[2] We have obtained conclusive evidence that the product of this reaction is actually the hydrochloride of the bicyclic 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]-pyrimidine-5(1*H*)-thione (IV)[4] and, therefore, that the reported picrate is the picrate of the dihydromidazopyrimidine IV and not of the ethyleneimonium form of the nitrogen mustard.

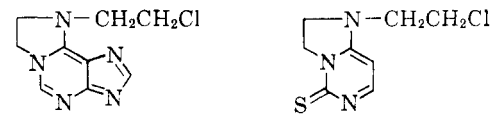
Chlorination of Ia gave a material which resembled the reported compound,[2] but about half of its chlorine content was ionic. This material could, by careful neutralization, be converted to its free base whose ultraviolet spectrum is practically identical with that of the chloride and quite different from that of Ia (whose spectrum should be very similar to a structure such as Ib). The free base, which must have the structure IV, was then converted back to its hydrochloride by treatment with dry hydrogen chloride in chloroform. An anhydrous sample of the hydrochloride was thus obtained.

The rather low toxicity reported[2] for the chlorination product of Ia is more in keeping with the imidazo[1,2-*c*]pyrimidine (IV) than the nitrogen mustard (Ib) structure.



Ia. X = OH
Ib. X = Cl

II



III IV

### Experimental[5]

**2-(2-Chloroethyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV).** (a) **Free Base.**[6]—2,2′-[(2-Mercapto-4-pyrimidinyl)imino]diethanol (Ia)[2] (2.0 g., 9.3 mmoles) was added to a well stirred solution of 0.3 ml. of thionyl chloride and 0.5 ml. of ethyl alcohol in 22 ml. of bis(2-methoxyethyl) ether. Additional thionyl chloride (4.0 ml.) was slowly added to the mixture and the resulting white suspension stirred at room temperature overnight. The reaction mixture was then evaporated to dryness under reduced pressure to give a tan residue, which was dissolved in hot ethyl alcohol (100 ml.), treated with charcoal, and filtered. The clear filtrate was evaporated to dryness under reduced pressure to give the crude hydrochloride of IV; $\lambda_{max}$ in m$\mu$ ($\epsilon \times 10^{-3}$): pH 1—247 (11.4), 273 (16.9), 320 (4.07); pH 7—232 (12.2), 266 (9.44), 336 (7.10); pH 13–232 (14.5), 266 (9.15), 338 (7.90); EtOH—245 (10.5), 278 (16.8), 326 (3.65).

*Anal.* Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: Cl (total), 28.12; Cl (ionic), 14.06. Found: Cl (total), 27.0; Cl (ionic), 13.1 (by acid-base titration at 0°).

After several unsuccessful attempts to recrystallize the crude hydrochloride, it was dissolved in cold water and the pH carefully brought to 8 by the dropwise addition of 0.1 *N* sodium hydroxide solution. The free base precipitated as a yellow solid, which was recrystallized from methyl alcohol

(1) This work was carried out at the suggestion of Dr. H. W. Bond and was supported by funds from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) H. Segal and C. G. Skinner, *J. Org. Chem.*, **27**, 199 (1962).

(3) T. P. Johnston, A. L. Fikes, and J. A. Montgomery, *ibid.*, **27**, 973 (1962).

(4) Many examples have been reported in which the chlorination of a 2-(4-pyrimidinylamino)ethanol has resulted in the formation of an imidazo[1,2-*c*]pyrimidine [G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4410 (1952); R. H. Martin and J. Mathieu, *Tetrahedron*, **1**, 75 (1957); J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958); J. H. Lister, *ibid.*, 899 (1960); P. R. Brook and G. R. Ramage, *ibid.*, 896 (1955)].

(5) Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in alcoholic and aqueous solutions with a Cary Model 14 spectrophotometer. Paper chromatography was done by the descending technique on Whatman No. 1 paper; spots were viewed in ultraviolet light. $R_{Ad}$ values were determined by locating spots relative to adenine arbitrarily assigned an $R_f$ value of 1.00. Solvent systems: A, water-saturated butyl alcohol; B, butyl alcohol–acetic acid–water (5:2:3 by vol.); C, isopropyl alcohol–concentrated ammonium hydroxide–water (14:1:5 by vol.); D, acetate buffer (pH 6.1).

(6) The first part of this procedure is practically identical with that described by Segal and Skinner.[2]

and dried *in vacuo* over phosphorus pentoxide at 60° for 8 hr.; yield 1.05 g. (53%); m.p. 178–180°, the melt solidifying and remelting > 260° dec.; $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): pH 1—248 (15.5), 274 (23.6), 320 (6.55); pH 7—234 (17.5), 268 (13.2), 338 (12.5); pH 13—232 (17.9), 267 (12.7), 338 (12.6); $R_{Ad}$: A—1.23; B—0.94 and 1.16; C—1.48; D—2.26.

*Anal.* Calcd. for $C_8H_{10}ClN_3S$: C, 44.54; H, 4.68; N, 19.49. Found: C, 44.66; H, 4.72; N, 19.47.

(b) **Hydrochloride.**—A well stirred suspension of 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV) (500 mg., 2.33 mmoles) in 20 ml. of chloroform was cooled in an ice bath to 0° and anhydrous hydrogen chloride slowly bubbled through the suspension for 2 hr. The volatiles were removed under reduced pressure to give a thick syrup, which formed a white crystalline residue on repeated *in vacuo* evaporations with additions of ethyl alcohol. The residue was recrystallized from a small volume of ethyl alcohol and dried over phosphorus pentoxide *in vacuo* at 60° for 18 hr.; yield 450 mg. (76%); m.p. 196–198°; $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): pH 1—247 (14.3), 273 (21.9), 320 (6.00); pH 7—233 (16.4), 267 (12.3), 338 (12.0); pH 13—233 (16.4), 267 (11.9), 338 (12.0); EtOH—244 (13.4), 277 (23.4), 329 (5.56); $R_{Ad}$: A—1.34; B—1.03 and 1.17; C—1.50; D—2.14.

*Anal.* Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: C, 38.10; H, 4.40; N, 16.67. Found: C, 38.34; H, 4.52; N, 16.60.

The picrate was prepared in ethyl alcohol and recrystallized from methyl alcohol; m.p. 176–178° dec.; $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): pH 1—245 (16.0), 274 (15.7), 335 (9.06); pH 7—232 (17.4), 260 (10.9), 344 (14.7); pH 13—232 (17.7),; 260 (10.9), 345 (15.0); $R_{Ad}$: A—1.47; B—1.22; C—1.59 and 1.94; D—1.49.

*Anal.* Calcd. for $C_{14}H_{13}ClN_6O_7S$: C, 37.80; H, 2.94; N, 18.90. Found: C, 38.02; H, 3.21; N, 18.59.

**Acknowledgment.**—The authors are indebted to the members of the Analytical Section of Southern Research Institute who, under the direction of Dr. W. J. Barrett, performed the spectral and microanalytical determinations reported and to Miss Mary Broadaway for the chromatographic work reported.

## Methylaminomethylsuccinic Acid

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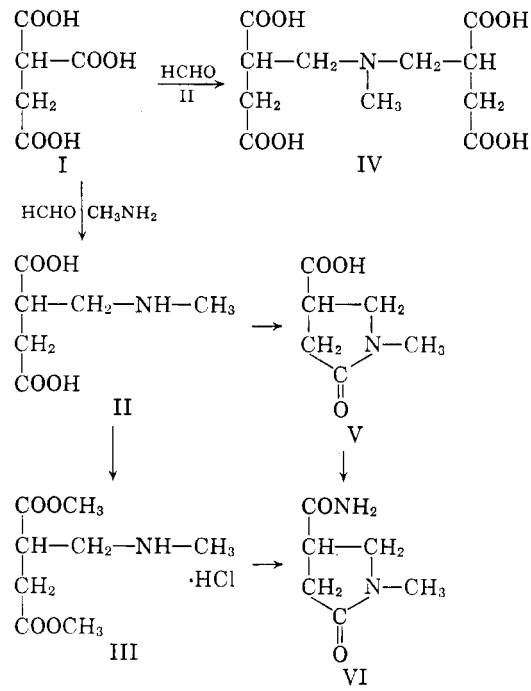
Some years ago the preparation of a methylaminodicarboxylic acid designed as an intermediate for a projected synthesis of lysergic acid was mentioned in a preliminary communication.[1] Experimental details, together with newer results, are given in the present report.

Carboxysuccinic acid (I) was allowed to react with aqueous methylamine and formaldehyde under Mannich conditions[2] to afford methylaminomethylsuccinic acid (II). Esterification of II with methanolic hydrogen chloride in the presence of 2,2-dimethoxypropane,[3] or with methanol and thionyl chloride,[4] gave 85% of nicely crystalline, nonhydroscopic dimethyl methylaminomethylsuccinate hydrochloride (III). Esterification of II with ethanolic hydrogen chloride furnished the less stable diethyl methylaminomethylsuccinate hydrochloride. The methylamino acid and its dimethyl and diethyl esters were characterized as *N*-p-toluenesulfonyl derivatives.




Brief pyrolysis of II at the melting point, or prolonged boiling of its aqueous solution, gave 1-methyl-5-oxo-3-pyrrolidinecarboxylic acid (V).[5] Treatment of dimethyl methylaminomethylsuccinate hydrochloride (III) with concentrated aqueous ammonia at 0° afforded 1-methyl-5-oxo-3-pyrrolidinecarboxamide (VI). Reaction of diethyl bromomethylsuccinate with ethanolic methylamine provided the ethyl ester of V. Hydrogen chloride ethanolysis of the ethyl ester at reflux temperature opened the pyrrolidone ring to give the diethyl ester hydrochloride of II.

Condensation of methylaminomethylsuccinic acid (II) with carboxysuccinic acid (I) and formaldehyde gave the methylamino tetracarboxylic acid IV. Esterification of IV with methanol and thionyl chloride afforded the tetramethyl ester hydrochloride.

(1) F. C. Uhle, *J. Am. Chem. Soc.*, **73**, 2402 (1951).

(2) C. A. Mannich and E. Ganz, *Ber.*, **55**, 3486 (1922).

(3) For introduction of this excellent general procedure see N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(4) For other examples of this method see M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953); F. C. Uhle and L. S. Harris, *J. Am. Chem. Soc.*, **78**, 381 (1956).

(5) This compound has also been prepared (70%) from itaconic acid with 25% aqueous methylamine at reflux temperature during forty minutes: P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1092 (1956).