Phosphorus Mustards. I. A New Class of Potential Antineoplastic Agents[1]

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The marked cytotoxic action of a wide variety of nitrogen and sulfur mustards and the known chemical properties of phosphorus as well as its position in the periodic table would indicate that the bis(2-haloethyl)phosphines may be useful compounds for cancer chemotherapy. This is the first attempted preparation of such compounds for this purpose. As a model compound bis(2-chloroethyl)phenylphosphine was synthesized and converted to the more stable bis(2-chloroethyl)phenylphosphine oxide. The instability of the former compound may be due to the high nucleophilic properties of the trivalent phosphorus atom. There are good indications that this is one of the more potent neighboring groups. The biological properties of the above phosphine oxide have been evaluated and there appears to be no "mustard-like" activity and no deleterious effect upon a subcutaneously transplanted brain tumor. This is in contrast to the nitrogen mustards where such oxides are biologically active. Apparently the phosphine oxides are stable under *in vivo* conditions, whereas their nitrogen counterparts are reduced to the parent bis(2-haloethyl)amine.

The marked cytotoxic action of the sulfur and nitrogen mustards and the dramatic effect of several of these compounds upon established tumors has resulted in considerable chemical, pharmacological, and clinical study of these compounds over the past two decades. Regression of tumors by such agents, although normally of a temporary nature, has provoked the synthesis of a multitude of sulfur and nitrogen mustards.[3] The known chemical properties of phosphorus and its position in the periodic table suggest that bis(2-haloethyl)phosphines should also show "mustard" activity, and might therefore prove useful in the treatment of neoplasms. There are few data on the toxicity of phosphines, but the reports available suggest that tertiary phosphines, their quaternary salts, and oxides can be administered at moderate dose rates,[4,5] and several have shown activity against various tumors.[4,6,7] This is corroborative evidence that the bis(2-chloroethyl)phosphines may have useful biological properties.

Discussion and Results

The present work relates to the synthesis of a phosphorus mustard, information regarding its chemical properties, and the attempts made toward a general synthetic method applicable to the preparation of bis(2-substituted ethyl)phosphines. Although the preparation of 2-hydroxy- and 2-haloethylphosphines has been reported,[8-11] only one compound which may be classified as a phosphorus mustard has been synthesized. This was prepared[12] by the cleavage of bis(2-ethoxyethyl)phenylphosphine with hydrogen bromide to give bis(2-bromoethyl)phenylphosphine hydrobromide as an impure gum. This cleavage of an ether to give either a hydroxy or a halo compound would seem to be a promising approach, but the compound used[12] required severe conditions to promote cleavage. However, Beyerman, *et al.*, have successfully developed the *t*-butyl group as a protective moiety for hydroxyl groups on amino acids[13] and steroids,[14] and this group can be removed readily under acidic conditions to give the free hydroxy compound in high yield.

The necessary intermediate for preparing such ethers is 2-*t*-butoxyethyl chloride (I), which can be synthesized readily by allowing isobutylene to react with 2-hydroxyethyl chloride. Interaction of phenylphosphine in liquid ammonia with sodium, followed by the addition of an equivalent of the chloro ether I, and repetition of this whole process, gave bis(2-*t*-butoxyethyl)-phenylphosphine (II) in 70% yield. Treatment of II with concentrated hydrochloric acid gave bis(2-hydroxyethyl)phenylphosphine hydrochloride (III) in essentially theoretical yield, as determined by its conversion to the dibenzoate of bis(2-hydroxyethyl)-phenylphosphine oxide (VI). The hydrochloride (III) itself was a gum which could not be induced to crystallize. It served, however, as the starting material for the synthesis of bis(2-chloroethyl)phenylphosphine oxide (VII) *via* two routes. The first was by chlorination of the alcohol with thionyl chloride followed by oxidation to VII. The second method was to oxidize the free base (IV) and to convert it to VII with thionyl chloride. Addition of alkali to a concentrated solution of the salt (III) followed by ether extraction, gave the free phosphine (IV) in quantitative yield, as a colorless, dense oil. The bis-alcohol, especially in ethereal solution, was readily oxidized by air, corroborating the observation of Knunyants and Sterlin[15] that 2-hydroxyalkylphosphines and their acyl derivatives undergo facile oxidation. This free phosphine (IV) decomposed at elevated temperatures (120–140° at 0.1 mm.) with the elimination of water and the formation of a solid residue. This is in contrast to the

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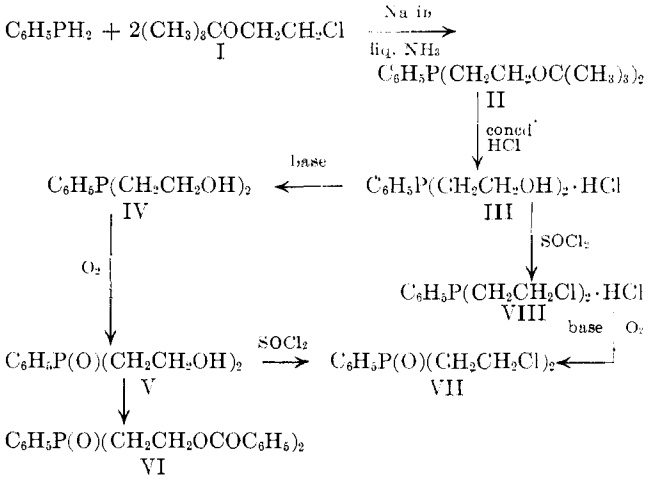
(15) I. L. Knunyants and R. N. Sterlin, *Compt. rend. Acad. sci. URSS*, **56**, 49 (1947).

temperature stability of the bis- and tris(2-hydroxyethyl)phosphines[15] and bis(1-hydroxyethyl)phenylphosphine.[16]

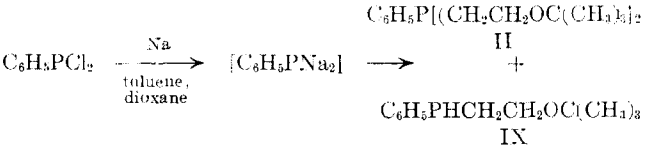
Treatment of a chloroform solution of bis(2-hydroxyethyl)phenylphosphine oxide (V) with thionyl chloride gave bis(2-chloroethyl)phenylphosphine oxide (VII). Reaction between the bis-alcohol hydrochloride (III) and thionyl chloride was exothermic and required cooling to minimize the production of impurities. The product (VIII), a partially crystalline paste, was characterized by conversion to the oxide (VII) in high yield, indicating a moderate degree of purity for bis(2-chloroethyl)phenylphosphine hydrochloride (VIII).



(2-Bromoethyl)ethylphenylphosphine undergoes spontaneous dimerization at room temperature,[12] and, as has been stated, bis(2-bromoethyl)phenylphosphine hydrobromide has only been obtained in impure form.[12,17] Similarly, the purification of the hydrochloride VIII has not as yet been possible, and although the free base can be formed by reaction of the salt with cold sodium bicarbonate solution, no crystalline derivative such as a methiodide has been obtained. This apparent instability of halogens β to the trivalent phosphorus and the recent observation[18] that dialkyl-2-acetoxyethylphosphines self-quaternize spontaneously at temperatures in excess of 80°, while di-*n*-butyl-3-acetoxypropylphosphine remains unchanged at temperatures up to 300°, indicates a possible common mechanism. The high nucleophilicity of phosphines, shown by their ready quaternization and the high stability of their oxides, points to the probable effectiveness of trivalent phosphorus as a neighboring group in eliminating substituents β to it. It would appear that this entity would be more effective than those considered and listed by Capon[19] and by Winstein and Grunwald.[20] This hypothesis is supported by the fact that these β-substituted phosphines are stabilized by their conversion to the phosphine oxides.

N,N-Bis(2-chloroethyl)aniline has only mild activity as a tumor growth inhibitor,[21] and so for direct biological comparison of phosphorus and nitrogen mustards it would be preferable to examine the phosphorus analog of bis(2-chloroethyl)methylamine (HN2) stabilized as the hydrochloride. In order to avoid the synthesis and use of the highly reactive lower monoalkylphosphines, other methods of preparation of the bis-ether (II) were investigated using the phenyl compound as a model. The purpose of the following work was to serve ultimately as a basis for synthesizing bis(2-chloroethyl)methylphosphine.

Preliminary experiments to form either 2-*t*-butoxyethylmagnesium chloride or the corresponding lithium compound were unsuccessful, with very little reaction occurring between the chloro ether (I) and the metal. In view of the low reactivity of 2-alkoxyalkyl halides in the Grignard reaction[22] it was decided not to investigate this reaction further but to consider the preparation and use of metallo derivatives of the phosphines.



The synthesis of phenyldisodiophosphine has been reported,[23,24] and such compounds present a general method for the preparation of tertiary phosphines using the less reactive and higher boiling phosphonous halides. However, considerable difficulty was experienced before a reliable procedure was developed for the preparation of phenyldisodiophosphine.[25] Commercial dispersions of sodium were not suitable. Dioxane was found to be a better solvent than toluene in the preparation of such suspensions since initiation of the reaction was easier and more reliable, and the disodio compound was obtained in an appreciably shorter time. Reaction of this compound with the chloro ether (I), however, gave low and variable yields of bis(2-*t*-butoxyethyl)phenylphosphine (II) as well as comparable amounts of the monoether, 2-*t*-butoxyethylphenylphosphine (IX). Variation of the reaction conditions, including a change of solvent after production of the disodio compound, and addition of gaseous and liquid ammonia to the system did not significantly improve the yield of the bis-ether (II). Increasing the time of the reaction or addition of an excess of the chloro ether (I) were likewise without effect upon the proportions or over-all yields of the mono- (IX) and the bis-ether (II). Using toluene in place of dioxane as the solvent for the preparation of phenyldisodiophosphine and its reaction with the chloro ether (I), no bis-ether (II) was isolated and only low yields of 2-*t*-butoxyethylphenylphosphine (IX) were obtained.

In view of these singularly unsuccessful results using phenyldisodiophosphine for the preparation of the bis-ether (II), further efforts along these lines have not been contemplated. However, additonal work is underway toward a general synthetic method for the preparation of such phosphorus mustards.

The oxide (VII) was devoid of any "mustard-like" activity as assessed by its lack of effect upon bone

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(25) We are greatly indebted to Professor L. Horner for his advice on this problem.

marrow in C_3H mice[26] at doses of 500 mg./kg. At these levels and above, definite toxic symptoms to the CNS were observed. At comparable doses there was no alteration in the growth pattern of transplanted murine ependymoblastomas[27] compared with untreated controls. The lack of useful biological activity of such phosphorus compounds is in marked contrast to that of their nitrogen counterparts. This is undoubtedly due to the fact that compounds as bis(2-chloroethyl)methylamine oxide (Nitromin) are reduced under *in vivo* conditions to the corresponding tertiary amines, whereas the high stability of the phosphine oxides probably preclude their biological reduction to trivalent phosphorus. The impurity of the mustard hydrochloride (VIII) to date has prevented its biological evaluation. Further studies are now underway to synthesize other trivalent phosphorus compounds with a variety of different leaving groups to determine whether such compounds are biologically active.

Experimental[28]

Phenylphosphine was prepared from phenylphosphonous chloride according to the method of Pass and Schindlbauer[23] and had b.p. 40–42° (10 mm.).

2-*t*-Butoxyethyl Chloride (I).—This compound was prepared by suitable modification of the procedure of Beyerman and Bontekoe.[13] 2-Chloroethanol (32.2 g., 0.4 mole) was placed in a pressure bottle (tested to 8.79 kg./cm.^{2}), and the bottle was flushed with nitrogen, stoppered, and cooled to −20°. Isobutylene (200 ml., 2.1 moles) and concentrated H_2SO_4 (1 ml.) were then added and the mixture was shaken overnight at room temperature. The pressure was then slowly decreased *via* a release valve, and nitrogen was bubbled throughout the remaining liquid until it had attained a constant level. The crude product was washed with five 100-ml. portions of 5% $NaHCO_3$ solution and dried over K_2CO_3. Distillation through a 20-cm. Vigreux column gave I (33.8 g., 62%), b.p. 135–137° (lit. 135–138°).[29]

Bis(2-*t*-butoxyethyl)phenylphosphine (II).—Phenylphosphine (5.0 g., 0.045 mole) was added to liquid ammonia (*ca.* 100 ml.), and to the stirred mixture sodium (1.05 g., 0.045 g.-atom) was added in portions to give a permanent blue-black color. After stirring for 15 min. the chloro ether (I) (6.2 g., 0.045 mole) in ethyl ether (6 ml.) was added over 10 min. and the yellow mixture was stirred for an additional 30 min. A further quantity of sodium (*ca.* 1 g.) was then added until the blue-black coloration produced was again permanent. The suspension was then stirred for 1 hr. and to this mixture was added over a 15-min. interval 6.2 g. of the chloro ether in 6 ml. of ethyl ether. The mixture was again stirred for another hour. Ethyl ether (100 ml.) was added, the ammonia was permitted to boil off, and 25 ml. of ice-cold, oxygen-free water was added carefully. The ether layer was separated and dried (Na_2SO_4). Upon removal of the solvent and distillation of the product, 10.3 g. of the bis-ether II (73%), b.p. 113–115° (0.2 mm.), was obtained as a colorless, viscous, liquid which oxidized moderately slowly in air; n_D^{25}, 1.508.

Anal. Calcd. for $C_{18}H_{31}O_2P$: C, 69.6; H, 10.1. Found: C, 69.7; H, 10.1.

The bis-ether was characterized as the **methiodide** which was prepared in methanolic solution and separated by adding this mixture to an excess of ethyl ether. The product had m.p. 146–147° (ether–ethanol).

Anal. Calcd. for $C_{19}H_{34}IO_2P$: C, 50.4; H, 7.6; P, 6.8; I, 28.0. Found: C, 50.6; H, 7.8, P, 6.9; I, 27.9.

Bis(2-hydroxyethyl)phenylphosphine (IV).—The bis-ether II (6.2 g., 0.02 mole) was placed in a separatory funnel previously flushed with nitrogen, and 23 ml. of concentrated HCl (*ca.* 0.2 mole) was added with shaking.[30] The mixture became warm with the formation of a white emulsion. Hydrolysis was essentially complete when two clear layers had formed (within 4–6 hr.), but normally it was more convenient to have the reaction mixture stand overnight. The top layer was *t*-butyl chloride (3.7 g., 0.04 mole), b.p. 50–51°. The bottom acid layer was concentrated to constant weight on a rotary evaporator in a water bath at 45–50°. The residue, bis(2-hydroxyethyl)-phenylphosphine hydrochloride (III) (4.65 g., 99% by weight), was a viscous, slightly cloudy gum which could not be induced to crystallize. It was soluble in water, methanol, ethanol, and dioxane; less soluble in acetone; and insoluble in chloroform, benzene, and ether.

The bis-alcohol hydrochloride (7.0 g., 0.03 mole) was dissolved in oxygen-free water and, upon basification with 16% NaOH, the free phosphine separated out as an oil. The mixture was extracted with three 80-ml. portions of ethyl ether, and the combined extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure to give IV (5.6 g., 95% by weight) as a viscous oil which was oxidized readily by air especially in an ethereal solution.

Distillation of the phosphine (IV) at 0.1 mm. was unsuccessful. Vigorous decomposition occurred at a temperature of 120–140° and only a small amount of liquid distilled. The distillation temperature was entirely dependent upon the bath temperature, and no homogeneous fraction was obtained. The residue was a brittle, pale brown glass, and represented, by weight, *ca.* 60% of the total phosphine taken.

The alcohol IV was characterized by conversion, in ethereal solution, to the oxide followed by its esterification with benzoyl chloride in an aqueous sodium hydroxide solution. The crude **dibenzoate** (VI), after trituration with ether and recrystallization from ethyl acetate, had m.p. 141–142° (preliminary shrinking).

Anal. Calcd. for $C_{24}H_{23}O_5P$: C, 68.2; H, 5.5; P, 7.3. Found: C, 68.1; H, 5.8; P, 7.6.

Bis(2-chloroethyl)phenylphosphine Oxide (VII).—The bis-alcohol IV (5.6 g., 0.028 mole) was dissolved in chloroform (160 ml.) and a slow stream of air was bubbled through for 1.5 hr. The clear and colorless solution was then cooled in ice–water, and thionyl chloride (13.3 g., 0.112 mole) in chloroform (60 ml.) was added dropwise with stirring. An emulsion was formed on mixing and HCl was evolved immediately. After standing overnight at room temperature, the clear, yellow solution was taken down to dryness under reduced pressure and this procedure was repeated with successive portions of chloroform until no thionyl chloride remained. The yellow solid residue was extracted with three 120-ml. portions of boiling ether, and the combined extracts were taken to dryness to give the crude bischloroethyl oxide (VII) (6.4 g., 90%). This was dissolved in a minimum volume of boiling cyclohexane and the hot solution was decanted from a yellow oil. This process was repeated until a white, crystalline product was obtained, m.p. 94°. Further extraction of the oil gave more oxide, but complete separation of the two components required several crystallizations.

Anal. Calcd. for $C_{10}H_{13}Cl_2OP$: C, 47.8, H, 5.2; Cl, 28.2; P, 12.3. Found: C, 48.0; H, 5.5; Cl, 28.1; P, 12.1.

The bischloroethyl oxide was also purified by sublimation at 75–80° (0.1–0.2 mm.); the white, microcrystalline product had m.p. 94–95°.

Anal. Found: Cl, 28.6.

Bis(2-chloroethyl)phenylphosphine Hydrochloride (VIII).—The bis-alcohol hydrochloride (III) (3.4 g., 0.0145 mole) was suspended in chloroform (100 ml.) and cooled in an ice bath. Thionyl chloride (6.9 g., 0.058 mole) in chloroform was added dropwise at such a rate that the temperature did not rise more than 2°. After completion of the addition, stirring was continued for 2 hr. and then the reaction mixture was refrigerated overnight. The clear yellow solution was taken to dryness under reduced pressure without heating and this procedure, using additional chloroform, was repeated twice more to remove the last traces of thionyl chloride. The residue after this treatment was a yellow, semicrystalline paste, which could not be induced to

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(28) All analyses were performed by Schwarzkopf Microanalytical Laboratories, New York, N. Y. All of the phosphines, tertiary, secondary, and primary, were handled under nitrogen. Only the phosphine oxides were treated and purified in the normal atmosphere.

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(30) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932).

solidify. It was soluble in chloroform and dioxane, and insoluble in ether, ethyl acetate, and benzene. A cold chloroform solution of this product was neutralized with cold sodium hydroxide (16%). The chloroform layer was separated, and a stream of air was passed through this solution. The solvent was removed and (2-chloroethyl)phenylphosphine oxide (VII), m.p. 92°, was isolated in 72% yield.

Anal. Found: Cl, 28.1.

Phenyldisodiophosphine.—This compound was prepared essentially according to the procedure given by Horner[23,24] with certain modifications. A 500-ml. three-necked flask was fitted with a reflux condenser, high-speed stirrer [rated at a maximum speed of 20,000 r.p.m. (Labline, Inc., Model 1285)] and equal-pressure dropping funnel. The entire system was thoroughly flushed with nitrogen. Into the flask was added 100 ml. of solvent (dioxane or toluene) and 5.1 g. (0.22 g.-atom) of sodium; into the dropping funnel was placed 8.95 g., (0.05 mole) of phenyl phosphonous chloride. The solvent was brought to reflux and the dispersion was prepared by stirring at maximum speed for 1–2 min. Stirring was then discontinued, the heating mantle removed, and 15–20 drops of the chlorophosphine was added immediately. When the initial effervescence had subsided, the stirrer was restarted at a moderate rate and heating was resumed such that a gentle reflux was maintained. After 1–5 min., the dispersion had a definite yellow color and the remaining chlorophosphine, now diluted with 10 ml. of solvent, was added over 45 min. If dioxane was the solvent media, the reaction mixture was boiled under reflux for an additional 4 hr., and a thick suspension of a yellow solid in a red solution was obtained. With toluene as the solvent, the reflux time required for the reaction to go to completion, as shown by the absence of metallic sodium and the formation of a thick, pale green mixture, was 7–9 hr. If no yellow coloration was produced after the initial addition of the chlorophosphine, it was found to be unlikely that the reaction would go to completion. Under such conditions it is essential to redry the solvent and/or redistil the chlorophosphine prior to attempting the reaction again.

Bis(2-*t*-butoxyethyl)phenylphosphine (II) and Mono-2-*t*-butoxyethylphenylphosphine (IX).—The suspension containing phenyldisodiophosphine (0.05 mole) was cooled to room temperature with a water bath and diluted with solvent (50 ml.). A slightly exothermic reaction occurred during the 1-hr. interval required for the addition of 13.7 g. of the chloro ether I (0.1 mole) in 50 ml. of solvent. The water bath was removed and the suspension was stirred for an additional hour at room temperature prior to refluxing the stirred mixture for a further hour. At the end of this interval, the reaction mixture was cooled in an ice bath and 35 ml. of oxygen-free water was added cautiously. The solvent layer was separated, dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. With dioxane as the solvent, distillation of the residue gave two fractions, b.p. 55–70° (0.2 mm.), and 110–115° (0.2 mm.). Redistillation of the higher boiling fraction gave the bis-ether II, b.p. 113–115° (0.2 mm.), in 10–20% yields. The lower boiling fraction was shown to be mono-2-*t*-butoxyethylphenylphosphine (IX) (12–25%). Treatment of this fraction in liquid ammonia with sodium and then the chloro ether I gave the bis-ether II (50%), b.p. 112–115° (0.2 mm.). With toluene as the solvent, only the lower boiling fraction was obtained, b.p. 65–66° (0.15 mm.).

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α-Amidinium Thiosulfates (Bunte Salts) as Antiradiation Drugs

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The synthesis of a number of α-amidinium thiosulfates is described and their protective action against ionizing radiation is reported.

In our search for radiation-protective agents, we turned our attention to the synthesis of functional analogs of cysteamine, $HSCH_2CH_2NH_2$. α-Mercaptoamidines, $HSCHRC(=NH)NH_2$, and their derivatives were considered to fall into this category and their synthesis[2] became the object of our attention.[3] Although α-mercaptoamidines themselves are yet unknown, a number of their thiol esters and Bunte salts have been prepared.[2] Initial biological data revealed that some of the then reported[2] α-amidinium thiosulfates (Bunte salts), $RCH(S_2O_3^-)C(=NH_2^+)NR'R''$ (I) afforded protectivity and hence additional members of this series were synthesized in the hope of learning which molecular modification would bring about increased activity. Biological data of all of the α-amidinium thiosulfates which have been tested to date are compiled in Table I. Several features are apparent from these data. Derivatives of acetamidine (I, R = H), on the whole, showed considerably more activity than their homologs I (R = CH_3 and C_6H_5). On the other hand when the N-alkyl side chain of the acetamidine series is increased (R = R′ = H; R″ from H to *n*-C_5H_{11}), considerable activity is maintained. Although no optimum chain length was determined, the long-chain *n*-nonyl and *n*-decyl derivatives were devoid of activity. The synthesis of additional members of this series is planned in an effort to explore the potential of α-amidinium thiosulfates as radiation protective agents.

The synthesis of the α-amidinium thiosulfates reported here followed essentially that developed previously.[2] α-Halonitriles were converted to the corresponding α-chloramidine hydrochlorides, which were treated with sodium thiosulfate to yield I. In one instance, when a water-soluble product was obtained, the α-amidinium Bunte salt could be isolated when thallous thiosulfate was used instead of the sodium salt. The new members of the series are listed in Table II.

(1) Taken from the M.S. Thesis submitted by Karen Rover Sandberg to the University of Illinois at the Medical Center, Chicago, Ill., June, 1964.

(2) L. Bauer and T. L. Welsh, *J. Org. Chem.*, **27**, 4382 (1962).

(3) During the course of this investigation the synthesis of β-mercaptopropionamidine was reported by T. P. Johnston and A. Gallagher [*J. Org. Chem.*, **28**, 1436 (1963)] and that of β-amidinium thiosulfates, $RC(=NH_2^+)NH(CH_2)_nS_2O_3^-$ (n = 2 and 3) was described by G. Sosnovsky and P. Schneider [*Tetrahedron*, **19**, 1313 (1963)].