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티오인산이수소 S-2-(ω-아미노알킬아미노)에틸들의 간편합성법 연구

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Study on the Facile Preparation of S-2-(ω-aminoalkylamino)ethyl Dihydrogen Phosphorothioates

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요 약. 방사선장해를 예방할 수 있는 특성을 지닌 티오인산 이수소 S-2-(ω-아미노알킬아미노)에틸들의 간편한 합성법을 연구하였다. 중간체인 3-(2-프탈이미도에틸)-2-옥사졸리디논을 프탈이미드 칼륨염과 3-(2-브로모에틸)-2-옥사졸리디논을 반응시켜 만들었으며, 이 브로모에틸의 옥사졸리디논 유도체는 디에탄올아민으로부터 만들어진 2,2-디브로모 디에틸아민과 탄산염 혼합물의 알카리성 고리닫기 반응으로 합성할수 있었다. 이 중간체는 30% 브롬화수소(가스)-초산용액으로 반응시켜 브롬화수소 N-(2-(2-브로모에틸아미노)에틸)프탈이미드로 유도되었고 이것을 다시 브롬화수소-초산용액으로 반응시켜 이브롬화수소 N-(2-브롬화에틸)-1, 2-에탄디아민을 얻을 수 있었다. 1, 3-디아미노프로판과 2-클로로에탄올로부터 2-(3-아미노프로필아미노)에탄올을 합성하고 이것을 Cortese씨법으로 처리하여 이브롬화수소 N-(2-브로모에틸)-1, 3-프로판아민을 얻었다. 이들 이브롬화수소들을 DMF 용매에서 티오인산 나트륨으로 처리하여 티오인산 이수소 S-2-(ω-아미노알킬아미노)에틸들을 합성하였다. 각각의 합성과정의 특징을 반응조건 및 총수율과 관련시켜 논의하였으며 티오인산 유도체를 합성하는 간편한 방법을 제의하였다.

ABSTRACT. The facile route of preparing S-2-(ω-aminoalkylamino) ethyl dihydrogen phosphorothioates, potential chemical radioprotectants, have been studied. Intermediate 3-(2-phthalimidoethyl)-2-oxazolidinone was prepared by a reaction of potassium phthalimide and 3-(2-bromoethyl)-2-oxazolidinone, which was obtained through the alkaline ring closure of a mixture of carbonate and 2,2′-dibromo diethylamine prepared from diethanolamine. This was converted to N-[2-(2-bromoethylamino) ethyl] phthalimide hydrobromide by 30% HBr (gas) in acetic acid and N-(2-bromoethyl)-1,2-ethanediamine dihydrobromide was obtained by reacting the hydrobromide with a solution of HBr-HOAc. N-(2-bromoethyl)-1,3-propanediamine dihydrobromide could be prepared through the Cortese treatment of 2-(3-aminopropylamino)ethanol, which was prepared by a reaction of 1,3-diaminopropane and 2-chloroethanol. These dihydrobromides were treated by sodium thiophosphate in DMF to result S-2-(ω-aminoalkylamino) ethyl dihydrogen phosphorothioates. The characteristics of each reaction path were discussed in regards to reaction conditions and overall yields and a facile route of preparing each derivative was proposed.

1. INTRODUCTION

In the literature[1], S-2-(ω-aminoalkylamino) ethyl dihydrogen phosphorothioates had been known as potent chemical radioprotectants, which have recently been subjected to clinical applications at major hospitals in the world. Preparative procedures for these compounds had already been reported in the literature[2] as shown in *Fig.* 1. However, preparative procedures described for each synthetic step of the scheme in *Fig.* 1 were rather unclear and they should be reevaluated to perform the preparation of compounds in accordance with the reported scheme. Thus, compound (E) could not be obtained through the chemical process, (C)+(D)→(E). Where n was 2 in compounds (E), the product could only be obtainable through the process (A)+(B)→(E), and the preparative process or industrial origins of compounds (B) were quite uncertain except rough descriptions on (B) in the patent[3]. Where n was 3 in compounds (E), the product could, in some cases, be obtainable through the process (C)+(D)→(E), but the reaction conditions reported were rather inconsistent to form (E) and gave various side products other than (E)[4] under the ordinary reaction conditions reported. An alternative route to prepare compound G(n=3) by the processes (I)→(J)→(G) coule be considered but the source of the compound (J) is unclear and its laboratory preparation required the reaction between diamine and ethylene oxide[9], which need a special handling technique and apparatus for toxic ethylene oxide gas. In the final step, (G)→(H), special separation schemes for isolating the pure product (n=3) are reported in a patent[5] and there are no particular mentionings on the isolation of the products in the original literature, which warranted further studies on these aspects of the process.

In this paper, authors have intended to clarify those uncertain aspects of the synthetic scheme reported in the existing literature and hoped to develope a simple and convenient route of preparing the compounds concerned. The route developed would be practical and may easily be applicable at an ordinary research laboratory. The results are presented and advantages of the developed route for the preparation are discussed herein.

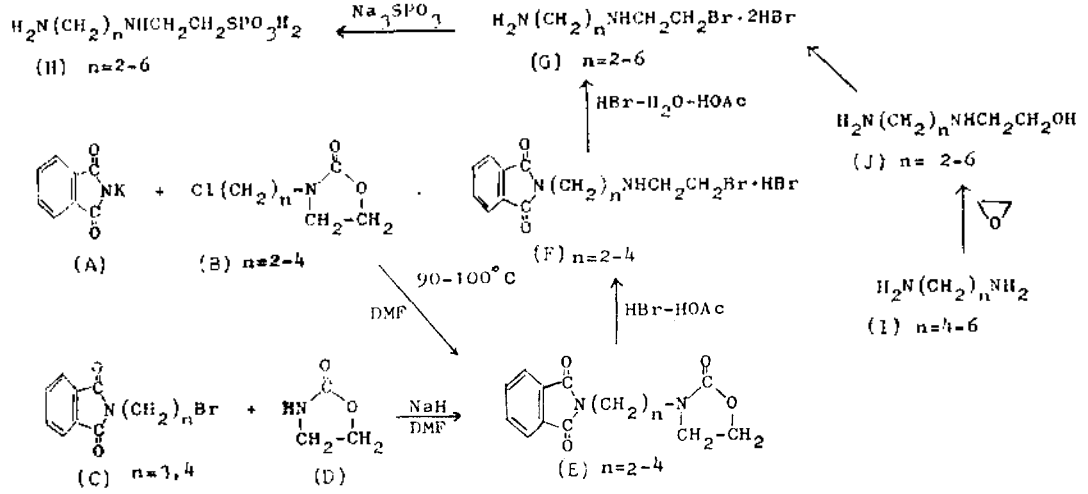

Fig. 1. Preparation of phosphorothioate derivatives.[2]

2. EXPERIMENTAL*

2.1 Reagents

The reagents for syntheses, which were Diethanolamine (Junsei Chemical Co., Ltd., extra pure reagent, mp 28°C), 1,3-Diaminopropane(Alpha Products, for chemical purposes, b.p. 128~9°C), Hydrobromic acid(47%, sp. gr. 1.50, Merck Art. 304), Hydrogen bromide(99.8%, Takachiho Commercial Co., Japan), Sodium thiophosphate(Alpha Chemical, for chemical purposes), Sodium hydride(50% in oil dispersion, Alpha Products), Thiourea (Merck Art. 7978, m.p. 178°C), and *etc.*, were used without purification. The solvents used for reactions were purified through the distillation

2.2 Preparation of *S*-2-(ω-Aminoethylamino)ethyl Dihydrogen Phosphorothioate (Fig. 2) 2,2'-Dibromodiethylamine Hydrobromide (II).

In a 1L, 3-necked round bottomed flask fitted with a distillation adjustor connected with a downward distillation condenser, a stirrer, and a dropping funnel were placed 500 m*l* of hydrobromic acid, which was cooled with stirring and 41.6g (0.4mole) of diethanolamine was added dropwise through the dropping funnel. The falsk was heated until 130cc of distilate has been collected. The rate of heating was then diminished to a point at which the liquid ceases to distil and merely refluxes. The heating under reflux was continued for one hour. At the end of this time, 50cc more was distilled, and the solution was again heated under reflux for one hour. This procedure was followed with 60, 50, 25, and 10cc portions of distillate. The total volume of distillate must not be less than 400cc. The dark brown residue was cooled to about 70°C, and 230cc of abs. acetone was added and stirred in order to be dissolved. After standing in the refrigerator overnight, the formed deposit was filtered on aspirator, washed with abs. acetone, discolored with active carbon, and air dried for 15 minutes. The TLC(silica gel, developing solvent; 95% EtOH : 33% NH_3 water= 3 : 1(v/v)) of the product showed spots at R_f 0.33, 0.55 & 0.60 which were colored by a ninhydrin solution. By recrystallization from abs. acetone the pure product, 26g, melted at 198~200°C was obtained. The TLC of the pure product showed one spot at Rf. 0.6. The yield of the product(II) was increased to 63g (50.4%) when the rate of HBr distillation was adjusted slowly(16hrs.). IR(KBr) cm^{-1} ; $\nu_{NH_2}{}^+$ 2720, ν_{C-N} 1230, ν_{C-Br} 570.

3-(2-Bromoethyl)-2-oxazolidinone (III).

The method of preparation reported in the patent[3] was partly applied for the present case. In a 100m*l*, 3-neck flask fitted with a magnetic stirrer, a thermometer and a reflux condenser was placed 12g(0.04mole) of the compound(II), and 16g of sodium hydrogen carbonate mixed with 40cc of H_2O was added under the cooling. The reactants were heated with stirring at 37~40°C for 1h. After then, it was cooled and filtered to remove the residue(35g). The filtrate was extracted with three 50m*l*, portions of 1,2-dichloroethane, and the extracts were dried over anhydrous $MgSO_4$ and the solvent was distilled to obtain the yellowish sticky residue. The yield was 5.0g(65%). By means of repeated extractions the yield was increased to maximum 80%. This crude product was used for the next reaction without further purification.

3-(ω-Phthalimidoethyl)-2-oxazolidinone (IV).

Reported procedure[2] was partly applied for the case. In a 50m*l* flask fitted with a conde-

*Melting points were determined by the Fisher-John's Melting Point Apparatus of which the thermometer was uncorrected.

nser, a thermometer and a magnetic stirrer were placed 10.0g(0.052mole) of compound (III), 10.0g of potassium phthalimide and 20 ml of DMF. The reactants were heated with stirring to 95~105°C for 2hrs., and cooled to room temperature. The reaction mixture were transferred to a 200m*l* beaker, and 100m*l* of distilled water was added with stirring to isolate white crystalline mass. After filtering and drying under the reduced pressure 14.0g of the product(IV) (a quantitative yield)melted at 153~4°C(ref.[2] 158°C) was obtained. Recrystallizing from abs. acetone the pure product was obtained melting at 155~6°C. The TLC (silica gel, developing solvent; EtOH : H_2O= 2 : 1(v/v)) showed one spot at R_f 0.8. IR (KBr) m^{-1} ; $\nu_{C=O}$ 1770, 1710, ν_{C-N} 1280.

N-(ω-(ω-Bromoethylamino) ethyl) phthalimide Hydrobromide(V). In a 100m*l*, 3-neck flask fitted with a thermometer, a reflux condenser and a magnetic stirrer were placed 10g(0.038mole) of compound(IV). and 50m*l* of 30 % HBr-HOAc solution. The reactants were heated with stirring at 25~30°C for 21hrs. It was cooled and transferred to a 300m*l* beaker, in which 170m*l* of abs. ethyl ether was added with stirring and cooling to deposit the white crystalline mass. The crystalline mass was filtered and dried under the reduced pressure, which amounted to 11.2g. By washing with abs. acetone, the pure compound(V) was obtained, which melted at 190~ 2°C(ref.[2] 190~3°C). The yield was 80 %. The TLC(silica gel, developing solvent; EtOH : H_2O=2 : 1(v/v)) showed one spot at R_f 0.65. IR(KBr)cm^{-1} ; $\nu_{NH_2^+}$ 2800(s), $\nu_{C=O}$ 1780(s), 1720(m), ν_{C-N} 1230(m), ν_{C-Br} 570.

N-(3-Bromoethyl)-α, ω-ethylenediamine dihydrobromides(VI). In a 100m*l*, 3-neck flask fitted with a reflux condenser, a stirrer and a thermometer were placed 6.0g(0.016 mole) of compound(V), 30 m*l* of 48 % hydrobromide and 30m*l* of acetic acid, after which the reactants were heated to reflux with stirring for 17hrs. It was then stirred with cooling, and phthalic acid deposited was filtered off. The filtrate was distilled under the reduced pressure in order to remove the solvent and the excess hydrobromide. The distilled residue was dissolved in abs. EtOH, and the impurity was removed by filteration. To the filtrate, its 4-times volume of abs. ethyl ether was then added to deposit white crystalline mass. The crystalline mass was filtered and recrystallized from abs. EtOH to obtain the pure product(VI), 41g, melted at 172°C(ref.[2] 174~6°C). The yield was 88 %. IR(KBr)cm^{-1} ; $\nu_{NH_3^+}$ 3080(m), $\nu_{NH_2^+}$ 2720, ν_{C-N} 1280(m).

S-2-(2-aminoethylamino)ethyl Dihydrogen Phosphorothioate(VII). In a 20m*l* flask fitted with a reflux condenser, a thermometer and a magnetic stirrer was placed 0.5g(0.0028 mole) of sodium thiophosphate with 3m*l* of distilled water, and when it was partly dissolved by stirring, 1.0g (0.003mole) of compound(VI) was added under cooling. With continuous stirring, 1.5m*l* of DMF was added. After 30mins, the reactants were warmed to 30°C with stirring and it was kept at 25~ 30°C until the $AgNO_3$ test for unchanged SPO_3^{3-} was negative. At the end of the reaction, the reactants were cooled and then oil-phase liquor was deposited, which was decanted for separation. Its 4-times volume of abs. MeOH was added to deposit the precipitate. It was separated by filtering and a little amount of distilled water was added to the filtered solid for dissolution, in which abs. MeOH was added to deposit the white mass. The oil-phase liquor from the reaction mixture was purified by repeating the above method

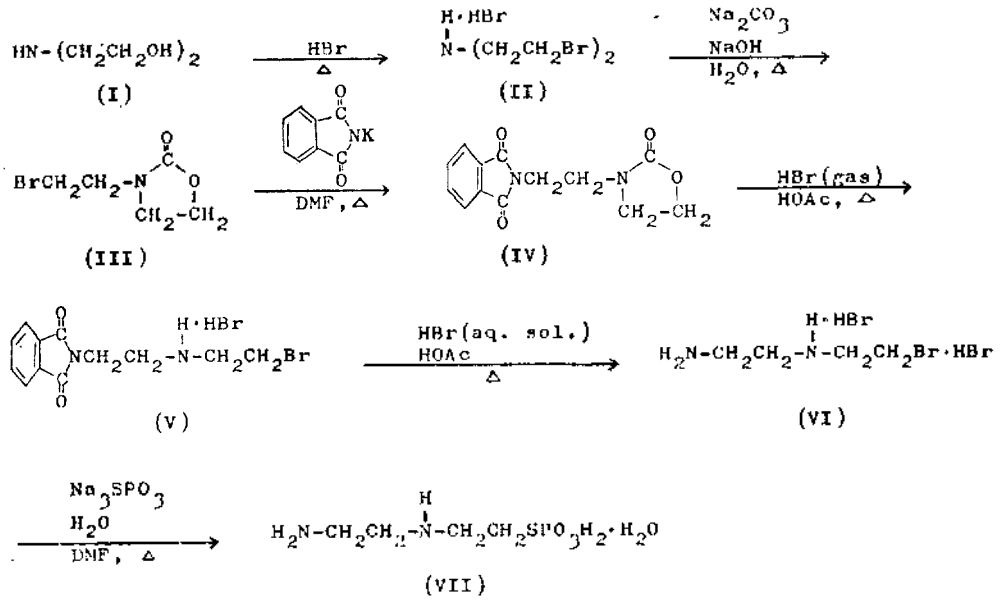

Fig. 2. A convenient route for the preparation of S-2-(ω-aminoethylamino) ethyl dihydrogen phosphorothioate.

until the solid was separated. By filtering and drying the solid under reduced pressure, the white crystalline(VII), melted at 136~140°C (ref.[2] 139~141°C) 0.4g was obtained. The yield was 61.0 %. The TLC(silica gel, developing solvent; EtOH : H_2O=1 : 1(v/v)) showed one spot at R_f 0.05. IR(KBr)cm^{-1} ; ν_{NH_2} 3400, ν_{NH} 3240, ν_{C-N} 1235, ν_{S-CH_2} 1465, $\nu_{P=O}$ 1110. The yield could be increased to 80% by purifying sodium thiophosphate used.

2.3 Preparation of *S*-2-(ω-aminopropylamino) ethyl dihydrogen Phosphorothioate

2-(3-Aminopropylamino) ethanol(IX). In a 100m*l*, 3-neck flask fitted with a dropping funnel, a thermometer, a reflux condenser and a magnetic stirrer was placed 37g(0.5mole) of 1,3-diaminopropane and the mixture was heated with stirring to 135~140°C of the inner temp., in which 8.1g(0.1mole) of 2-chloroethanol was dropped slowly. The reactants were heated further with stirring at 130~5°C for 15hrs. At the end of the reaction, the reactants were cooled with stirring and 4.0g of sodium hydroxide dissolved in 7m*l* of distilled water was added at once and 8m*l* of distilled water was added at once and 8m*l* of distilled water was added more with stirring. The deposit, sodium chloride, was filtered for separation and in the filtrate was added a solution of 20m*l* of benzene in 20m*l* of EtOH with stirring, and then sodium chloride was deposited again, which was filtered off. The filtrate was simple distilled for removing benzene, ethanol, and water, and the residue from the distillation was distilled under the reduced pressure for removing water and unreacted reagents. Again, 20m*l* of ethanol and 20m*l* of benzene were added to the residue of the distillation with stirring to precipitate sodium chloride, which was filtered off. The filtrate was distilled for removing benzene and ethanol and the residue weighed 9.0g. The TLC(silica gel; developing solvent; 95 % EtOH : 45 % NH_3 water=2 : 1 (v/v)) showed a distinct spot at R_f 0.43 and a faint one at R_f 0.61. The distillation residue was considered to be the crude product, and

therefore, it was used for the next synthesis without further purifications.* The yield was 76.3%. (*This type of compound was known[6] to be decomposed during the distillation, and hence the crude product was not subjetced to further purifications through distillation processes.)

N-(2-bromoethyl)-1,3-propanediamine Dihydrobromide(X). The Corteses method[7] was applied for this synthesis. In a 100m*l*, 3-neck flask fitted with a dropping funnel, a magnetic stirrer and a distillation adaptor connected with a downward distillation condenser, was placed 9.3g(0.079mole) of the crude compound(IX). Through the dropping funnel, 35m*l* of 47 % HBr aqueous solution was slowly added dropwise with stirring under cooling, and heated to reflux for 16hrs. After elapsing 8hrs from startup, the flask was kept warm by covering it with glass-wools in order to distil the excess HBr solution through the downward distilling condenser, and the heating temperature was so adjusted that the distilled solution was reached to 25m*l* for 8hrs interval. At the end of the reaction, the excess HBr solution was further distilled under the reduced pressure, and the hot residue was treated with abs. acetone to precipitate the crystalline mass. It was filtered and redissolved in abs. MeOH, and decolorized with active carbon. The solution was mixed with its 4-times volume of ethyl ether to precipitate white crystalline product. It was filtered and the solid was repeatedly recrystallized from ethanol or the mixture of ethanol and ethyl acetate(1 : 1 w/w) to obtain 21g of the pure product, melted at 188~191°C(ref.[2] 205~6°C). Because of the strong hygroscopic property of this compound, a partial melting due to the moisture was observed during the course of the melting point determination. The TLC(silica gel, developing solvent; 95% EtOH : 45 % NH_3 water=2 : 1(v/v)) showed one spot at R_f 0.69. The yield was 78 %. IR (KBr)cm^{-1} ; $\nu_{NH_3^+}$ 3000(m), $\nu_{NH_2^+}$ 2760, ν_{C-N} 1270, ν_{C-Br} 570.

S-2-(3-Aminopropylamino)ethyl Dihydrogen Phosphorothioate(XI). 1.0g(0.003mole) of compound(X), 0.5g of phosphorothioate, 3m*l* of distilled water and 1.5m*l* of DMF were reacted under the same reaction conditions with those of Exp. B(6). The white crystalline which formed from abs. MeOH was amounted 0.4g, melted at 138~141°C(ref.[2] 160~1°C). Because it was strongly hygroscopic, some melting phenomena were observed during the course of the melting point determination. The TLC's(silicagel, developing solvent; 95 % EtOH : 45 % NH_3 water =2 : 1(v/v)) of this product and YM-08310[8] (mp 140~2°C), the authentic sample, were all showed the same main spot at R_f 0.00 and the faint one at R_f 0.18. Therefore, the difference of melting point from those of reported was considered to be due to the method of the melting point determination adopted. The yield was 60 %. IR(KBr)cm^{-1} ; ν_{NH_2} 3420, ν_{NH} 3310, ν_{S-CH_2} 1420, ν_{C-N} 1280, $\nu_{P=O}$ 1120. The product could show the equivalent radioprotective effects as compared to those of reported.[1,2] The yield could be increased to

$$H_2N(CH_2)_3NH_2 \xrightarrow[\text{② NaOH, } \triangle]{\text{① } ClCH_2CH_2OH} \underset{\text{(VIII)}}{}$$

$$H_2N(CH_2)_3NHCH_2CH_2OH \xrightarrow[H_2O,\ \triangle]{HBr} \underset{\text{(IX)}}{}$$

$$H_2N(CH_2)_3NHCH_2CH_2Br\cdot 2HBr \xrightarrow[DMF,\ H_2O]{Na_3SPO_3} \underset{\text{(X)}}{}$$

$$H_2N(CH_2)_3NHCH_2CH_2SPO_3H_2\cdot H_2O$$
(XI)

Fig. 3. A convenient route for the preparation of S-2-(ω-aminopropylamino) ethyl dihydrogen phosphorothioate.

80 % by purifying sodium thiophosphate used.

3. RESULTS AND DISCUSSION

Preparative schemes shown in *Fig.* 2 and *Fig.* 3 were experimented to improve the existing synthetic routes shown in *Fig.* 1 with regards to the reaction condition, the availability of the intermediates involved, and other relevant factors. Both schemes were able to afford the final products through relatively simple and convenient processes with reasonable yields as follows.

3.1 Preparation of *S*-2-(ω-Aminoethylamino) ethyl Dihydrogen Phosphorothioate In *Fig.* 2, the process(I)→(II) is not found in the existing literatures and authors intended to apply the Cortese's procedure[7] for this system to obtain the compound (II). The process has proceeded smoothly with 50.4 % conversion of the (II). The remainings of materials used were composed of the unreacted starting material and the monosubstituted product, which were identified through TLC. This material could further be recycled in the original reaction system to obtain the product (II). The net yield of the (II) was, therefore, said to be quantitative. The process (II)→(III) was reported in the patent[3] for the case of the chloro derivative of the (II). The present approach using the bromo derivative of (II) could proceed effectively to result a high yield of the (III). The compound (III), a viscous oil, was liable to be decomposed during the course of the distillation even under a high vacuum, and hence the crude product was used to the next step without further purifications. The process (III)→(IV) could provide the quantitative yield of the product (IV) even after being reacted for less than 2hrs. This procedure had reported[2] in the case of the chloro derivative of the(III) to provide 94 % yield of the (IV). The product (IV) was quite stable to be recrystallized from ethanol or the mixture of ethanol and ethyl acetate. The processes (IV)→(V) and (V)→(VI) could proceed smoothly in accordance with the reported procedures.[2] There were none to be mentioned with respects of yields and reaction conditions adopted. In the process (VI)→(VII), a special consideration on the isolation of the product (VII) was required, which was not mentioned in details in the literature. By means of repeating the isolation of the product from the solution of methanol and water, the white crystalline product could be obtained, which was proved to be the pure product both by its melting point and TLC. The yield of the product (VII) was depended on the purity of sodium thiophosphate used. Thus, 80 % yield of the product could be achieved when sodium thiophosphate was completely dehydrated and recrystallized from absolute ethanol. Overall yield of the product (VII) starting from (I) was around 45%. This procedure of preparing the compound (VII) was limited to the case of the ethyl derivative as shown in *Fig.* 2, but it may further be extended to the case of the propyl derivative when the corresponding propyl intermediates involved are available or prepared. Generally, this route of preparing the compound (VII) was of simple and convenient, which did not require any of special reagents or apparatus as compared to those of the route shown in *Fig.* 1. The starting compound, diethanolamine, and other reagents involved may easily be available from industrial sources.

3.2 Preparation of *S*-2-(ω-Aminoprodylamino)ethyl Dihydrogen Phosphorothioate. In *Fig.* 3, the process (VIII)→(IX) was author's modifications of the existing ethylene oxide procedure[9] utilizing 2-haloethanol. In case of reacting 2-bromoethanol with 1, 3-diaminopropane,

the reaction was proceeded faster than that of 2-chloroethanol. However, 2-chloroethanol, which was known to be available easily from industrial sources, was adopted in the present preparation. The reaction could result the product (IX) without forming any siginificant amount of the disubstituted product when the molar ratio of the diamine to the chloroethanol was maintained as 4. If the molar ratio of two reagents are below than 4, a siginificant amount of the disubstituted product was formed with decreasing the yield of the product (IX). The product (IX) was a dense paste which was decomposed during the course of the distillation process even under a high vacuum. According to the literature[6], this type of compounds is known to decompose during the course of the distillation process even under a high vacuum, and therefore, the crude product was immediately used to the next step of the preparation. The process (X)→(XI), the application of the Cortese's procedure[7], could proceed without any difficulties. The final step, the process (X)→(IX), gave serious difficulties of isolating the syruppy paste resulted from the reaction. The special solvent system appeared in the patent[5] was applied to isolate a solid product, but the isolated product has usually been contaminated by impure inorganics which were confirmed by means of TLC. By means of several recrystallizations from the solution of methanol and water, pure product could be obtained as described in Exp. 2.3(4) The yield of the product (IX) was in creased to 80 % when sodium thiophosphate was dehydrated and purified as the case of A. The overall yield of the product (XI) was around 47.61 %. The prepared product was subjected to the animal testing to confirm its' radioprotective effect. It was found that the radioprotective effect of the prepared compound was quite in accordance with that of the reported data.[1] The results were, however, reported elsewhere.[10] Generally, this route of preparing the compound (XI) could also be extended to the corresponding ethyl derivative, if the ethylene diamine is adopted as the starting compound. The route was of simple and convenient and did not require difficult reagents such as ethylene oxide and others. Overall yield of this route was slightly higher than that of the route described in A, even though the numbers of the step involved are less than those of the latter.

In conclusion, two convenient routes of preparing S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates were developed starting from easily available material and conveniencies of these routes for the preparative works were ascertained and discussed.

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