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30. (late) Hikoichi Hagiwara, Mitsuo Numata, Kazuo Konishi, and Yoshikazu Oka : Synthesis of Nereistoxin and Related Compounds.[*1] I.

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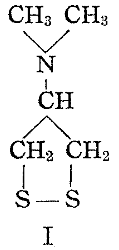
Nereistoxin, a compound neurotoxic to various species of animals, was first isolated by Nitta from marine annelid (*Lumbriconereis heteropoda* MARENZ).[1] Okaichi and Hashimoto, on the basis of ultraviolet, nuclear magnetic resonance spectra and chemical degradation studies of nereistoxin, proposed the structure (I)——4-dimethylamino-1,3-dithiolane——to the compound.[2]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The unusual activity of the compound as well as its interesting structure, which might be related to that of lipoic acid, prompted us to totally synthesize this novel compound. After many attempts to synthesize the compound in vain we finally came up with some synthetic routes to I to substantiate the proposed structure.

This report deals with the synthesis of nereistoxin starting with 1,3-bis(benzylthio)-2-propanol (III).

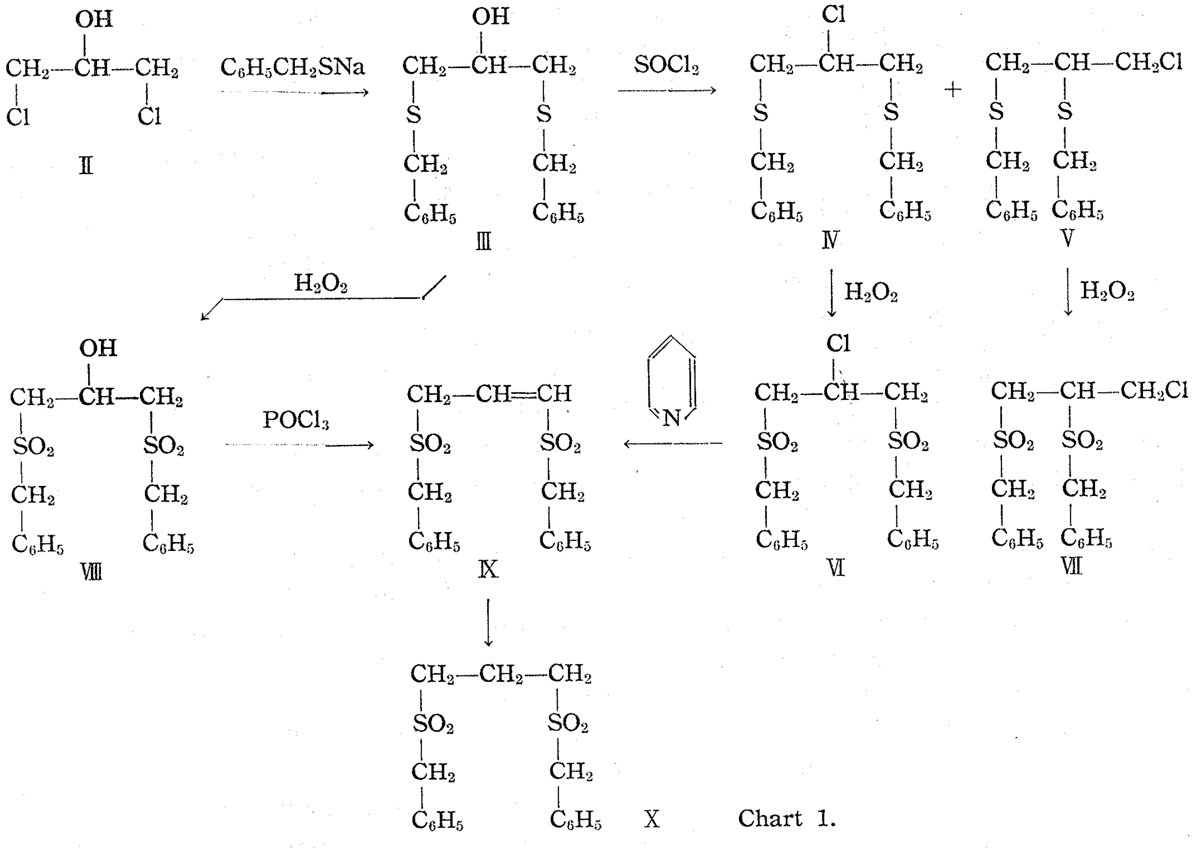

Chart 1.

[*1] A part of the results was presented by Dr. Yasuo Abe, Chairman of the synthetic organic chemical department of our laboratories, at the Gordon Research Conference (section of steroids and other natural products), New Hampton, U. S. A., July (1962) and also presented by one of us at the 6th Symposium on the Chemistry of Natural Products, Sapporo, July (1962) : Abstracts p. 88.

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1) S. Nitta : Yakugaku Zasshi, **54**, 648 (1934).

2) T. Okaichi, Y. Hashimoto : Agr. Biol. Chem., **26**, 224 (1962).

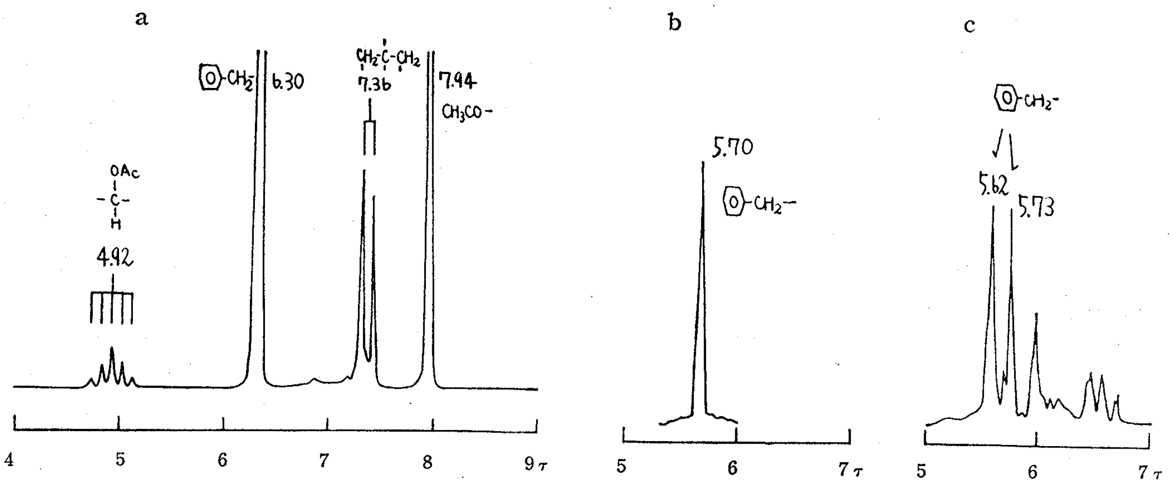

Fig. 1. Nuclear Magnetic Resonance Spectra measured at 60 Mc.

a : Acetate of 1,3-bis(benzylthio)-2-propanol (Ⅲ) in $CDCl_3$
b : 2-Chloro-1,3-bis(benzylsulfonyl)propane (Ⅵ) in DMF
c : 1-Chloro-2,3-bis(benzylsulfonyl)propane (Ⅶ) in $CHCl_3$

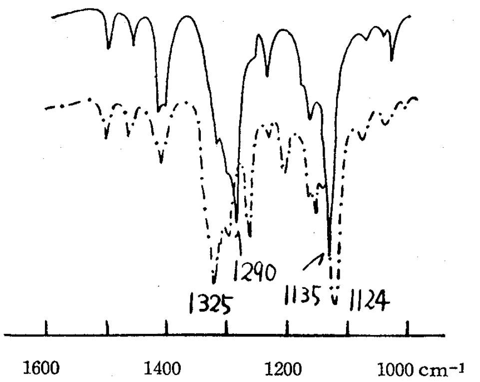

Fig. 2. Infrared Spectra of the Chlorosulfones (Ⅵ and Ⅶ) in Potassium Bromide Disks
——— Ⅵ —·—·— Ⅶ

1,3-Bis(benzylthio)-2-propanol (Ⅲ)[3] was prepared from 1,3-dichloro-2-propanol (Ⅱ) and sodium benzylmercaptide, and the structure was confirmed by the elemental analysis and the nuclear magnetic resonance of its acetate, in which the band at 4.92 τ due to the tertiary hydrogen was splitted into five (Fig. 1-a). Treatment of Ⅲ with thionyl chloride gave an oily substance. When the oily substance was oxidized with hydrogen peroxide there were obtained two crystalline products, one was insoluble in chloroform, m.p. 201~202°, and the other soluble in chloroform, m.p. 135~137°. Both products showed a correct analysis for the chlorosulfone $C_{17}H_{19}O_4ClS_2$ (Ⅵ and Ⅶ), but their infrared and nuclear magnetic resonance spectra were completely different (Fig. 1-b, c, and Fig. 2). These results indicate that these are isomers to each other and that, therefore, the structures (Ⅵ and Ⅶ) have to be assigned to the compounds.

In the nuclear magnetic resonance spectrum of the chlorosulfone, m.p. 201~202°, the band ascribable to the hydrogens of methylene adjacent to benzene ring is singlet at 5.70 τ showing that these four hydrogens are all equivalent (Fig. 1-b), while in the nuclear magnetic resonance spectrum of the other chlorosulfone, m.p. 135~137°, this band is splitted into two at 5.62 τ and 5.73 τ (Fig. 1-c). These results strongly suggest that the sulfone, m.p. 201~202°, should have the symmetrical structure (Ⅵ) and the other, m.p. 135~137°, the asymmetrical structure (Ⅶ).

Fitt and Owen,[4] on the contrary to our conclusion, erroneously assigned the asymmetrical structure (Ⅶ) to the chlorosulfone of m.p. 204~205°, which was obtained by treatment of 2,3-bis(benzylthio)-1-propanol (Ⅺ) with hydrochloric acid. Their experiment was repeated by present authors to give the sulfone, m.p. 201~202°, which was shown to be identical with the specimen obtained by our synthesis.

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3) N. S. Johary, L. N. Owen : J. Chem. Soc., **1955**, 1302.
4) P. S. Fitt, L. N. Owen : *Ibid.*, **1957**, 2251.

Since it became apparent that the same compound was assigned two different structures by English workers and by us, the following experiments were undertaken to clarify the problem.

The chlorosulfone of m.p. 201～202° on treatment with aqueous pyridine gave the dehydrochlorinated product, $C_{17}H_{18}O_4S_2$, m.p. 177～179° which was identical with 1,3-bis-(benzylsulfonyl)propene (IX) prepared by the dehydration of 1,3-bis(benzylsulfonyl)-2-propanol (VIII). On catalytic reduction this sulfone gave the known 1,3-bis(benzylsulfonyl)propane (X). These experiments indicate that the chlorosulfone of m.p. 201～202° is 2-chloro-1,3-bis(benzylsulfonyl)propane (VI), and that the chlorosulfone of m.p. 135～137° is accordingly 1-chloro-2,3-bis(benzylsulfonyl)propane (VII).

It follows from these results that III on treatment with thionyl chloride should give rise to a mixture of 2-chloro-1,3-bis(benzylthio)propane (IV) and 1-chloro-2,3-bis(benzylthio)propane (V), and that XI on treatment with hydrochloric acid to IV as a main product.

The mechanism of the rearrangement of benzylthio group during the chlorination reactions would be interpreted by the intervention of a cyclic sulfonium intermediate (XII):

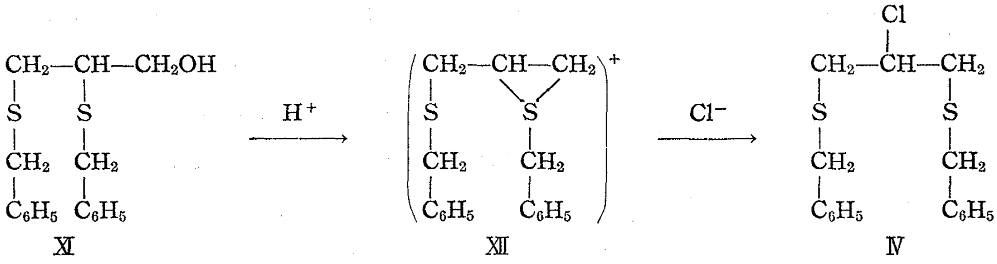

Chart 2.

When the mixture of IV and V was treated with dimethylamine under pressure a reddish brown amine was obtained, the hydrogen oxalate being analyzed for $C_{22}H_{27}O_4NS_2$. That the amine was a mixture of isomers, XIII and XIV, was demonstrated by two distinct spots on the thin-layer chromatogram. Judging from the intensity of the spots it was evident that the fast moving isomer was a minor and the slow moving isomer was a major component. The latter was isolated and recrystallized as the hydrogen oxalate salt, which melted at 145～147°. The nuclear magnetic resonance spectrum of the free base showed two peaks at 6.37 τ and 6.42 τ, which were assigned to the hydrogens of methylene adjacent to benzene ring (Fig. 3-b). These results indicate that the slow moving isomer should have the asymmetrical structure (XIV), and the fast moving isomer the symmetrical structure (XIII), although the latter was not isolated owing its poor yield.

However, 2-dimethylamino-1,3-bis (benzylthio) propane (XIII) was synthesized from benzyl chloride and dihydronereistoxin (XV), which was prepared by reduction of nereistoxin (I), and the comparison was made by thin-layer chromatography between two amines synthesized by two different methods. The result demonstrated that the fast moving amine was identical with XIII. Moreover XIII showed a single peak at 6.40 τ due to the hydrogens of methylene adjacent to benzene ring (Fig. 3-a).

It was evident by these results that the fast moving amine was XIII and the slow moving one N,N-dimethyl-2,3-bis(benzylthio)propylamine (XIV).

The mixture of XIII and XIV was reduced by the Birch reduction with sodium in liquid ammonia. Paper partition chromatography of the reaction product indicated that the resulting amine was a mixture of two, one of which of Rf 0.28 was a major, and the other of Rf 0.57 was a minor. Such constitution of the amines in the reduction

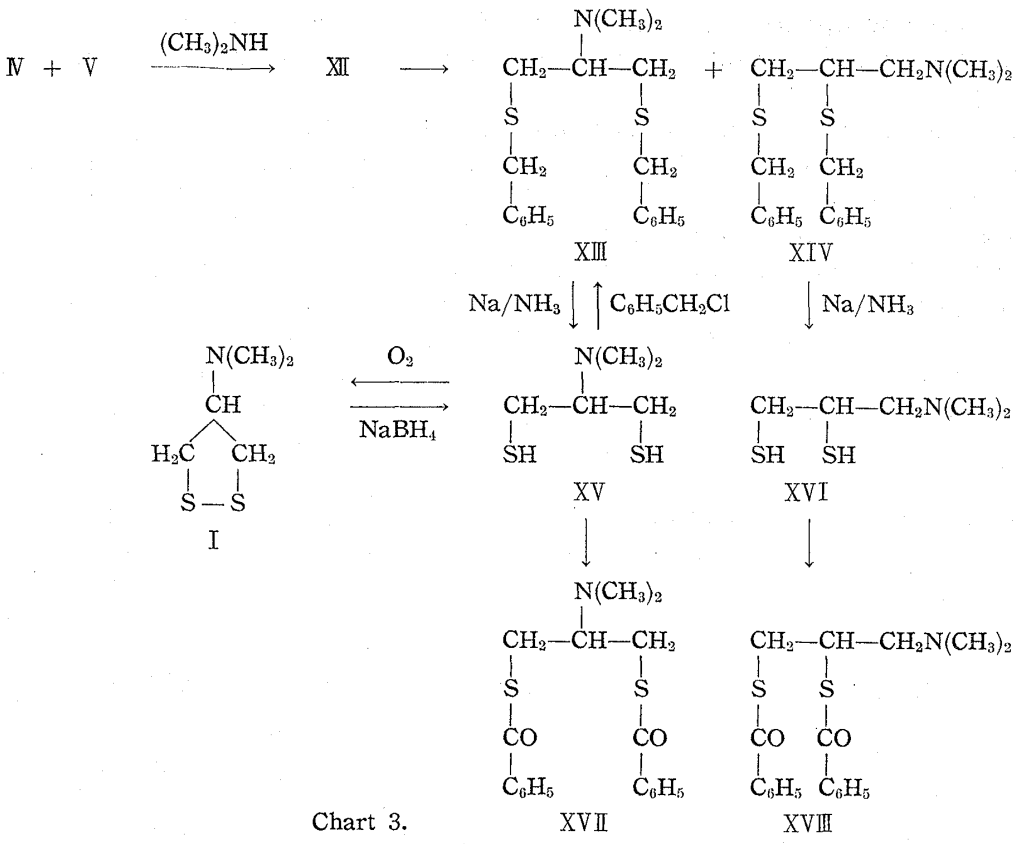

Chart 3.

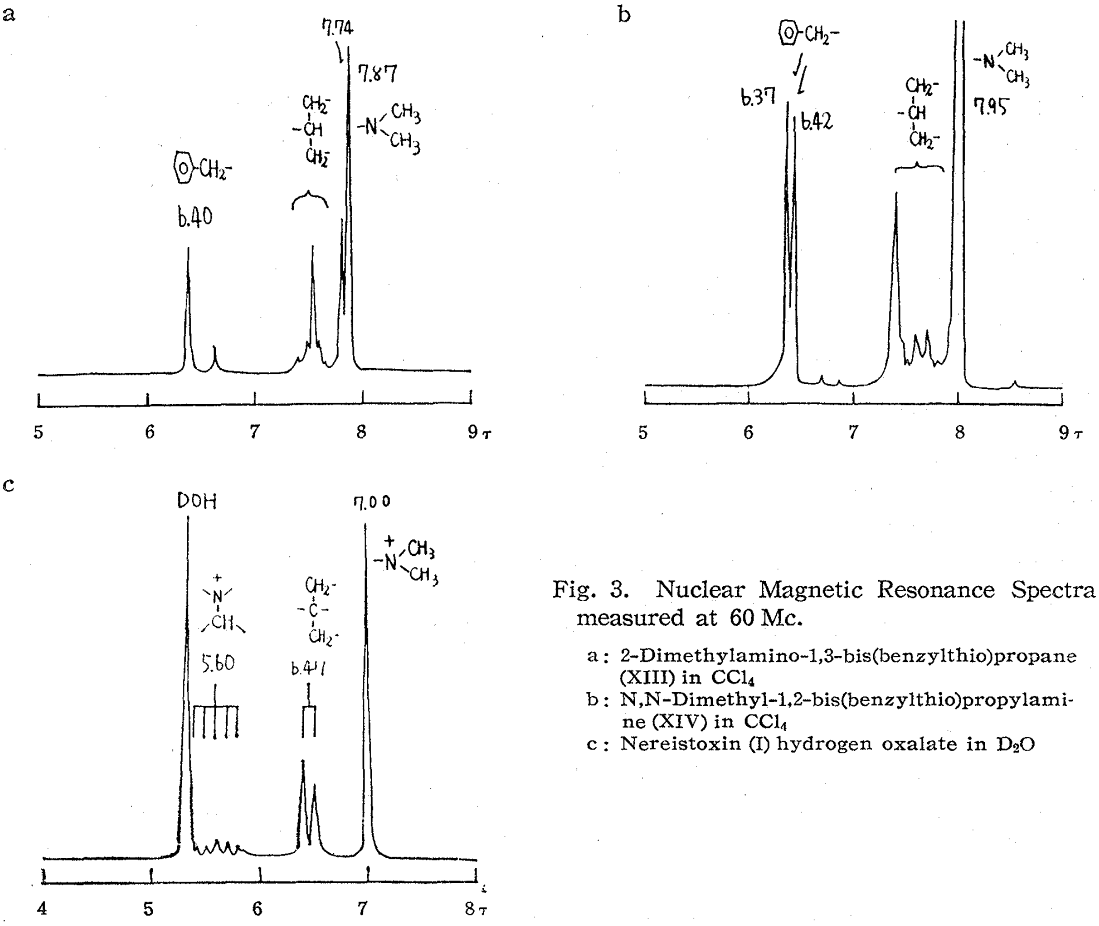

Fig. 3. Nuclear Magnetic Resonance Spectra measured at 60 Mc.

a : 2-Dimethylamino-1,3-bis(benzylthio)propane (XIII) in CCl_4
b : N,N-Dimethyl-1,2-bis(benzylthio)propylamine (XIV) in CCl_4
c : Nereistoxin (I) hydrogen oxalate in D_2O

mixture indicated that the amine of Rf 0.28 was derived from XIV, and the other of Rf 0.57 from XIII, provided no rearrangement was operative during the reduction.

These amines were easily separable from each other when an alkaline solution of the product was extracted with ether, thus the amine of Rf 0.57 was extracted with ether, while the amine of Rf 0.28 remained in the mother liquor. Upon treatment with benzoylchloride the mother liquor furnished 3-dimethylamino-1,2-propanedithiol dibenzoate (XVIII) in fairly good yield. From these results it is evident that the amine of Rf 0.28 is 3-dimethylamino-1,2-propanedithiol (XVI). This receives further support by the experiment descrived below.

Treatment of the alkaline solution of XVI with carbon disulfide gave 4-dimethylaminomethyl-1,3-dithiolane-2-thione (XIX). The presence of a five membered 1,3-dithiolane-2-thione ring in this compound was apparent from comparison of its ultraviolet spectrum with that of model compounds (Fig. 4).

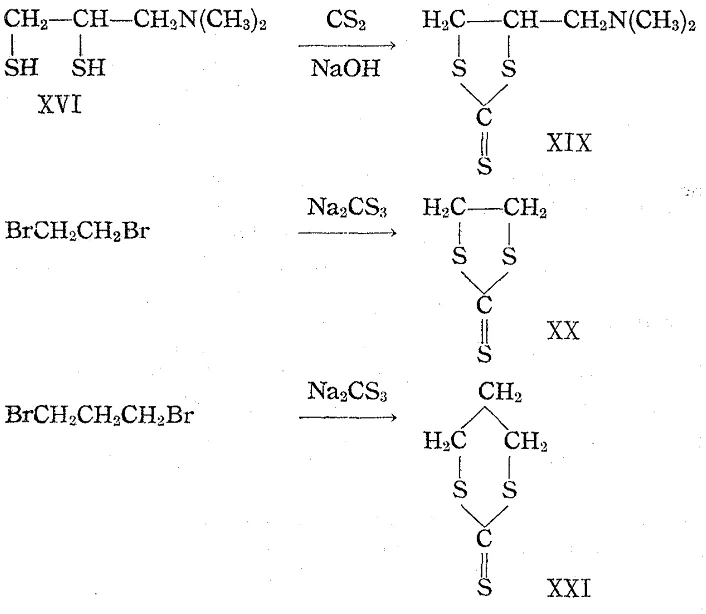

Chart 4.

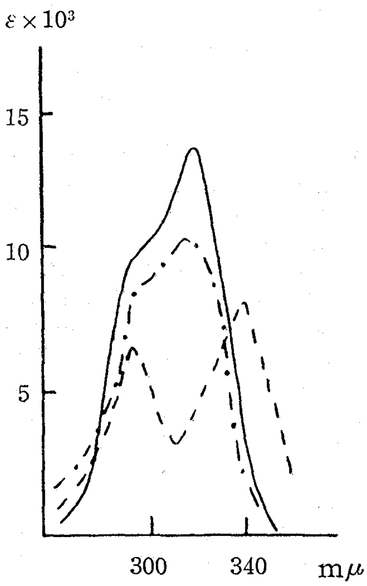

Fig. 4. Ultraviolet Spectra of Some Cyclic Trithiocarbonates

——— XIX hydrogen oxalate in H_2O
—·—·— XX } in EtOH
– – – – – XXI

It was pertinent to assume, at this stage, that the amine of Rf 0.57 was dihydronereistoxin (XV). As a matter of fact pale yellow crystals of m.p. 173~174° was obtained from the ether extract as a hydrogen oxalate, which somewhat surprisingly was shown to be identical with natural nereistoxin hydrogen oxalate by comparison of their ultraviolet, infrared, nuclear magnetic resonance (Fig. 3-c) spectra and their chromatograms. Moreover no depression in melting point was observed when the synthetic and the natural nereistoxin hydrogen oxalates were admixed. It would reasonably be interpreted that the intermediate dihydronereistoxin (XV) underwent air oxidation to nereistoxin (I) during the experimental procedures.

However the yield of nereistoxin calculated from the mixed amine (XIII and XIV) was only 6%. A better yield could not be attained, even where the mixed chloride (IV and V) containing much the symmetrical isomer IV more than the asymmetrical V was subjected to the amination with dimethylamine followed by the Birch reduction. Since there was no evidence of appreciable rearrangement during the reduction, these results strongly point out that the amination reaction should have proceeded through a cyclic sulfonium intermediate (Ⅻ) and that the nucleophil, dimethylamine, should have favored an attack on a far end carbon of Ⅻ owing to steric factors to afford predominantly XIV rather than objective ⅩⅢ.

Experimental[*3]

1,3-Bis(benzylthio)-2-propanol (III)——A solution of 1,3-dichloro-2-propanol (Ⅱ, 64.5 g.) in EtOH (200 ml.) was added to a solution of benzylmercaptan (124 g.) and sodium (23 g.) in EtOH (400 ml.) under ice cooling. The mixture was allowed to stand overnight and filtered to remove NaCl. The filtrate was evaporated, the residual oil was dissolved in benzene. The mixture was washed with H_2O and 10% NaOH, dried, evaporated to dryness. The yellow residual oil (132.5 g.) was used substantially as Ⅲ. The oil became crystalline solid after standing for three months or more. The resulting solid was recrystallized from ligroin-cyclohexane to give white leaflets (82.8 g.), m.p. 41~45°. *Anal.* Calcd. for $C_{17}H_{20}OS_2$: C, 67.07; H, 6.62; S, 21.05. Found : C, 67.05; H, 6.52; S, 21.02.

Ⅲ was acetylated as usual with acetic anhydride and pyridine to give pale yellowish oil. Its NMR spectrum was shown in Fig. 1-a.

2-Chloro-1,3-bis(benzylthio)propane (IV), 1-Chloro-2,3-bis(benzylthio)propane (V)——To a stirred solution of Ⅲ (28.3 g.) in benzene (100 ml.) $SOCl_2$ (12 g.) was added dropwise. Following the addition the mixture was refluxed for half an hour, and condensed under reduced pressure. The residue was dissolved in benzene and the mixture was washed with H_2O and 10% $NaHCO_3$, and dried. The solvent was removed to give yellowish oil (28 g.), which was shown to be a mixture of Ⅳ and Ⅴ by the results of next experiment.

2-Chloro-1,3-bis(benzylsulfonyl)propane (VI), 1-Chloro-2,3-bis(benzylsulfonyl)propane (VII)——To a suspension of above obtained oil (8.2 g.) in HCOOH (100 ml.), 30% H_2O_2 (14 g.) was added under violent stirring. After a while exothermic reaction set in, the temperature rised to about 80° and the mixture became homogeneous. After the reaction had subsided, stirring was continued for 3 hr., and the solvent was removed under reduced pressure. The residue was poured into ice-H_2O and the precipitated solid was collected by filtration. The solid material was suspended in $CHCl_3$ (400 ml.) overnight, the insoluble material (1.7 g.) was collected by filtration and was recrystallized from dioxane to give white needles, m.p. 201~202° of Ⅵ. From the filtrate the solvent was removed to dryness, the residual solid (4.6 g.) was recrystallized from EtOH to give white powders, m.p. 135~137° of Ⅶ. Their NMR and IR spectra were shown in Fig. 1-b, c and Fig. 2. *Anal.* Calcd. for $C_{17}H_{19}O_4ClS_2$: C, 52.77; H, 4.95; O, 16.54. Found (Ⅵ, m.p. 201~202°) : C, 52.50; H, 5.00; O, 16.28. Found (Ⅶ, m.p. 135~137°) : C, 52.77; H, 5.07; O, 16.69.

1,3-Bis(benzylsulfonyl)propene (IX)——a) A mixture of Ⅵ (600 mg.), pyridine (20 ml.) and H_2O (5 ml.) was refluxed for 6 hr., evaporated to dryness. To the residual solid H_2O was added, the solid was collected by filtration and recrystallized from EtOH to afford white leaflets (320 mg.), m.p. 177~179°. IR ν_{max}^{Nujol} cm^{-1} : $\nu_{C=C}$ 1642, 964; ν_{SO_2} 1311, 1130. *Anal.* Calcd. for $C_{17}H_{18}O_4S_2$: C, 58.26; H, 5.18; O, 18.26; S, 18.32. Found : C, 58.58; H, 5.13; O, 18.01; S, 18.38.

b) A mixture of 1,3-bis(benzylsulfonyl)-2-propanol (Ⅷ, 500 mg.), $POCl_3$ (1 g.), and pyridine (20 ml.) was heated at 80° for an hour. The mixture was poured into ice-H_2O, the precipitated solid was collected by filtration and recrystallized from EtOH to afford white leaflets, m.p. 177~179°. This was identical with the sample obtained from the method of (a) by comparison of IR spectra. *Anal.* Found : C, 58.13; H, 5.34.

1,3-Bis(benzylsulfonyl)propane (X)——In the pressure bottle of an apparatus for catalytic reduction were placed Ⅸ (0.6 g.), 5% Pd-C (5 g.) and dioxane (100 ml.), and an initial hydrogen pressure of 3 atm. was applied. After 7 hr. the reduction was completed and the contents were transferred to a flask, boiled and filtered. The filtrate was evaporated to dryness and the residual solid was recrystallized from EtOH to give colourless needles, m.p. 207~209°. *Anal.* Calcd. for $C_{17}H_{20}O_4S_2$: C, 57.93; H, 5.72. Found : C, 57.94; H, 5.87.

2-Dimethylamino-1,3-bis(benzylthio)propane (XIII), N,N-Dimethyl-2,3-bis(benzylthio)propylamine (XIV)——The mixed oil of Ⅳ and Ⅴ (15 g.) was heated with 30% dimethylamine-benzene solution (45 g.) in an autoclave at 160° for 16 hr. The mixture was evaporated under reduced pressure, the residual oil was dissolved in ether. The ethereal solution was washed with H_2O, dried, and condensed to give reddish brown oily mixed amine (13.7 g.). By thin-layer chromatography this was shown to consist of ⅩⅢ and XIV, among them the former was a minor component and the latter was a major one (two spots were brought out with Kraut-Dragendorff reagent after elution with CH_3CN and cyclohexane-benzene-CH_3CN on Merck silicagel G, a spot of fast moving ⅩⅢ was weak and another one of slow moving XIV was strong in intensity).

[*3] All melting points are uncorrected. Paper partition chromatography, Toyo Roshi No. 50 BuOH-AcOH-H_2O (4:1:5), ascending method.

Hydrogen Oxalate Salt——To a solution of the oily mixed amine (4.5 g.) in ether (100 ml.), a saturated ether solution of oxalic acid (40 ml.) was added, the precipitated solid (5.9 g.) was collected by filtration and recrystallized from dioxane-ether. There was obtained white leaflets, m.p. 136~142° of hydrogen oxalate salt of mixed amine. (On thin-layer chromatography, two spots were brought out with Kraut-Dragendorff reagent after elution with MeOH-CH_3CN on Merck silicagel G). *Anal.* Calcd. for $C_{21}H_{27}O_4NS_2$: C, 59.82; H, 6.46; N, 3.32. Found: C, 59.61; H, 6.58; N, 3.35.

N,N-Dimethyl-2,3-bis(benzylthio)propylamine (XIV) Hydrogen Oxalate——The hydrogen oxalate salt of mixed amine (XIII and XIV, 5 g.) above mentioned was suspended in boiling $CHCl_3$ (100 ml.), the insoluble material was removed by filtration, the filtrate was evaporated to dryness. The residual solid (1.9 g.) was recrystallized from MeOH-ether to give white leaflets, m.p. 145~147°. This was shown to be homogeneous by thin-layer chromatography. (Only one spot, which corresponded to the spot of slow moving component amine in the above experiment, was brought out with Kraut-Dragendorff reagent after elution with MeOH-CH_3CN on Merck silicagel G). *Anal.* Calcd. for $C_{21}H_{27}O_4NS_2$: C, 59.82; H, 6.46; N, 3.32. Found: C, 59.54; H, 6.48; N, 3.25. The NMR spectrum of the free base was shown in Fig. 3-b.

2-Dimethylamino-1,3-bis(benzylthio)propane (XIII) Hydrogen Oxalate——To a stirred solution of nereistoxin (I, 740 mg.) in MeOH (20 ml.) and EtOH (10 ml.), $NaBH_4$ (1 g.) was added under ice cooling. After 30 min. stirring, benzylchloride (8 g.) was added dropwise to the solution, and the resulted mixture was refluxed for an hour. The solvent was removed, the residual oil was dissolved in ether. To the ethereal solution, a saturated ether solution of oxalic acid was added until no more deposit was appeared. After standing for 3 hr., upper ether solution was decanted off. To the residual oily deposit, 10% K_2CO_3 (20 ml.) was added, the mixture was shaken with ether, and the organic layer was separated. To the ethereal solution, a saturated ether solution of oxalic acid was added and the mixture allowed to stand overnight. The deposit was collected by filtration and recrystallized from EtOH-ether to give white powders, m.p. 90~93° (decomp.). This was shown to be homogeneous and identical with the fast moving component of the mixed amine (XIII and XIV) by thin-layer chromatography. The NMR spectrum of the free base was shown in Fig. 3-a. *Anal.* Calcd. for $C_{21}H_{27}O_4NS_2$: C, 59.82; H, 6.46; N, 3.32. Found: C, 59.40; H, 6.83; N, 3.02.

3-Dimethylamino-1,2-propanedithiol (XVI)——Sodium (1.9 g.) and a solution of the mixed amine (XIII and XIV, 4.6 g.) in EtOH (40 ml.) were added simultaneously to a stirred mixture of liquid NH_3 (80 ml.) and EtOH (40 ml.) under dry ice-acetone cooling. After stirring for 30 min., NH_3 was evaporated off at room temperature, EtOH was removed under reduced pressure, and the residue was poured into H_2O. The resulted solution was shown to contain XVI as a main component and nereistoxin (I) as a minor component by paper partition chromatography, which showed a strong spot of XVI at Rf 0.28 and a weak spot of I at Rf 0.57 with Kraut-Dragendorff reagent. The solution was shaken with ether, two layers were separated. The paper partition chromatograms of each layer showed that I was extracted completely with ether and XVI remained in mother liquor. Further attempt to obtain XVI in purer form was not allowed because of its unstable nature. Therefore thus obtained alkaline aqueous solution was used substantially as XVI in the following experiments. From the ethereal layer nereistoxin (I) was isolated, about this procedure see next column.

Nereistoxin (I) Hydrogen Oxalate——a) To the above obtained ether extract, a saturated ether solution of oxalic acid was added, precipitated solid (360 mg.) was collected by filtration and recrystallized from 95% EtOH. There was thus obtained faintly yellowish needles, m.p. 173~174° (decomp.). Its NMR spectrum was shown in Fig. 3-c. UV: $\lambda_{max}^{H_2O}$ 320 mμ (ε 150). Reduction potential of S-S bond at pH 6.8, $E\frac{1}{2}$-0.57 volt. This was identical with natural nereistoxine hydrogen oxalate by comparison of these data and IR spectra, and no depression in melting point was observed in admixture. *Anal.* Calcd. for $C_7H_{13}O_4NS_2$: C, 35.13; H, 5.46; N, 5.85. Found: C, 35.16; H, 5.72; N, 6.08.

2-Dimethylamino-1,3-propanedithiol Dibenzoate (XVII)——To a stirred solution of I-hydrogen oxalate (120 mg.) in pH 7 buffer solution (30 ml.), $NaBH_4$ (120 mg.) was added under ice cooling. The mixture was extracted with ether, the organic layer was separated and was shaken vigorously with 10% NaOH (20 ml.). To the aqueous layer benzoylchloride (200 mg.) was added dropwise under ice cooling and stirring. After stirring for 40 min., the mixture was extracted with ether. To the ethereal solution, a saturated ether solution of oxalic acid was added, the precipitated solid was collected by filtration and recrystallized from EtOH to afford white needles, m.p. 144~144.5° (decomp.) of XVII-hydrogen oxalate. *Anal.* Calcd. for $C_{21}H_{23}O_6NS_2$: C, 56.12; H, 5.16; N, 3.12. Found: C, 55.73; H, 5.46; N, 3.34.

XVII-Hydroperchlorate (from EtOH), white needles, m.p. 170~174°. *Anal.* Calcd. for $C_{19}H_{22}O_6ClNS_2$: C, 49.62; H, 4.82; N, 3.05. Found: C, 49.55; H, 4.82; N, 3.14.

3-Dimethylamino-1,2-propanedithiol Dibenzoate (XVIII)——To a stirred alkaline aqueous solution of XVI derived from the mixed amine (XIII and XIV, 4.6 g.), benzoylchloride (4 g.) was added dropwise under ice cooling. After stirring for 30 min., the solution was extracted with ether. The organic layer was washed with H_2O, and then shaken with 7% oxalic acid solution (50 ml.), the aqueous layer was separated and allowed to stand overnight. The crystalline deposit (2.1 g.) was collected by filtration and recrystallized from EtOH to give white leaflets, m.p. 154~156° (decomp.) of XVIII-hydrogen oxalate. *Anal.* Calcd. for

$C_{21}H_{23}O_6NS_2$: C, 56.10; H, 5.16; N, 3.12. Found : C, 54.68; H, 5.62; N, 3.16.

XVIII-Hydroperchlorate (from MeOH–ether), colourless needles, m.p. 160～163°. *Anal.* Calcd. for $C_{19}H_{22}O_6ClNS_2$: C, 49.62; H, 4.82; N, 3.05. Found : C, 49.66; H, 4.97; N, 3.32.

4-Dimethylaminomethyl-1,3-dithiolane-2-thione (XIX) Hydrogen Oxalate——To a stirred alkaline aqueous solution of XVI derived from the mixed amine (XIII and XIV, 2.6 g.), CS_2 (30 g.) was added in one portion. After 30 min., the mixture was extracted with ether three times, the organic layers were combined, dried, and to the ethereal solution a saturated ether solution of oxalic acid was added. The yellow crystalline deposit was collected by filtration and recrystallized from 50% EtOH to afford yellow leaflets (0.5 g.), m.p. 187～189° (decomp.). UV : $\lambda_{\max}^{H_2O}$ 318 mμ (ε 14,000). *Anal.* Calcd. for $C_8H_{13}O_4NS_3$: C, 33.93; H, 4.63; N, 4.94; S, 33.94. Found : C, 33.95; H, 4.95; N, 4.94; S, 34.03.

1,3-Dithiane-2-thione (XXI)——A solution of sodium trithiocarbonate in EtOH was prepared by the general method; a solution of Na (2.3 g.) in EtOH (50 ml.) was saturated with H_2S, CS_2 (5 g.) was added to the solution, and the resulted mixture was refluxed for an half hour. To the solution of sodium trithiocarbonate, a solution of trimethylenedibromide (10 g.) in EtOH (50 ml.) was added, and the mixture was allowed to stand overnight. H_2O (500 ml.) was added to the mixture, and the mixture was extracted with ether. The solvent was removed and the residual oil became crystalline solid after standing in an ice box. The solid was recrystallized from EtOH to afford yellow needles, m.p. 80°. UV $\lambda_{\max}^{EtOH}$ mμ (ε) : 292 (6,990), 338 (8,550). *Anal.* Calcd. for $C_4H_6S_3$: C, 31.96; H, 4.03; S, 64.00. Found : C, 32.27; H, 4.19; S, 63.55.

1,3-Dithiolane-2-thione (XX)——To a stirred solution of trithiocarbonate in EtOH, which was prepared by the same procedure as above mentioned, ethylenedibromide (9.5 g.) was added, and the mixture was treated same as above to afford yellow oil. UV : $\lambda_{\max}^{EtOH}$ 318 mμ (ε 10,600).

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Summary

Nereistoxin (I) was synthesized from 1,3-bis(benzylthio)-2-propanol (III) *via* the intermediates (VI), (XIII), and (XV). The structures of some synthetic isomers were also discussed.

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