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UDC 547.869.07 : 547.85.07

102. Akira Takamizawa and Yoshiro Sato: Studies on the Pyrimidine Derivatives and Related Compounds. XL.*1 Reaction of 3-Benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium Salts with Diethyl Benzoylphosphonate.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

In an earlier paper[1] dealing with the reaction between thiamine and diethyl benzoylphosphonate (VII), it was shown that the ring expansion of thiazole to 1,4-thiazine was carried out to give 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)-methyl-5-methyl-6-(2-benzoyloxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one (XV). Whether or not this novel reaction is applied on the other thiazolium salts derivatives besides thiamine was interested.

Although 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (V) has been synthesized by the condensation between benzyl chloride and 4-methyl-5-(2-hydroxyethyl)-thiazole,[2] but we were able to obtain conveniently *via* 3-benzyl-4-hydroxy-4-methyl-5-(2-acetoxyethyl)thiazolidine-2-thione (III) which was already reported by Yoshida and Ishizuka.[3]

Ammonium N-benzyldithiocarbamate (I) prepared from the reaction of benzylamine and carbon disulfide in ammonia-ethanol was allowed to react with 3-acetyl-3-chloropropyl acetate (II) to give III. III, withont separation from the mixture, was treated with hydrochloric acid to yield 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazoline-2-thione (IV), of which structural features were well illustrated by its ultraviolet spectrum (λ_{max}^{EtOH} 324 mμ, ε 14,500). Treatment of IV with hydrogen peroxide in hydrochloric acid gave 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (V) in good yield.

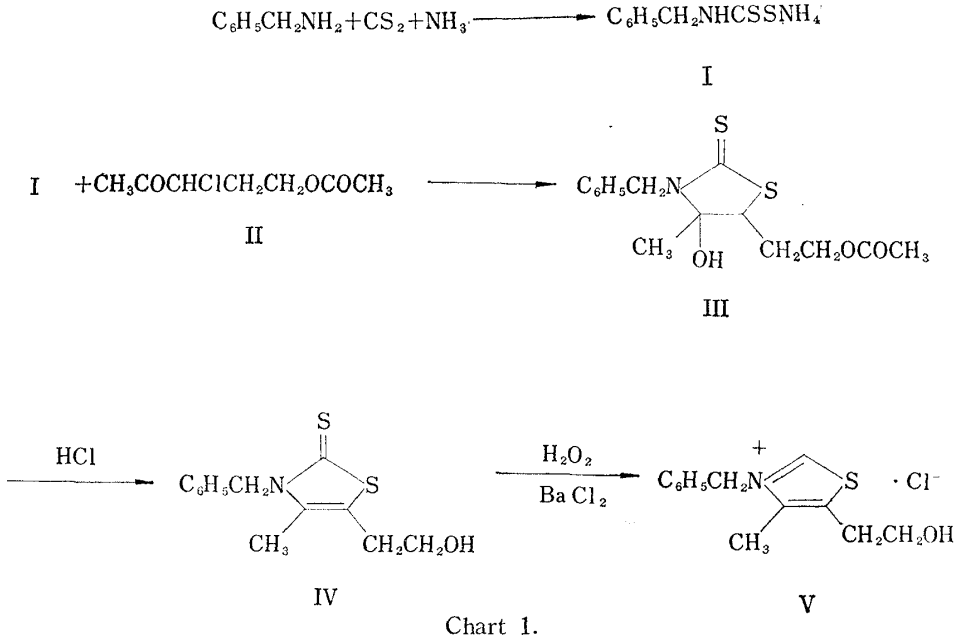

Chart 1.

*1 Part XXXIX. A. Takamizawa, Y. Sato, S. Tanaka: This Bulletin, **14**, 588 (1966).

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1) A. Takamizawa, Y. Sato, S. Tanaka, H. Itoh: This Bulletin, **14**, 407 (1966).
2) A. H. Livermore, R. R. Sealock: J. Biol. Chem., **167**, 699 (1947).
3) S. Yoshida, W. Ishizuka: Yakugaku Zasshi, **74**, 331 (1954).

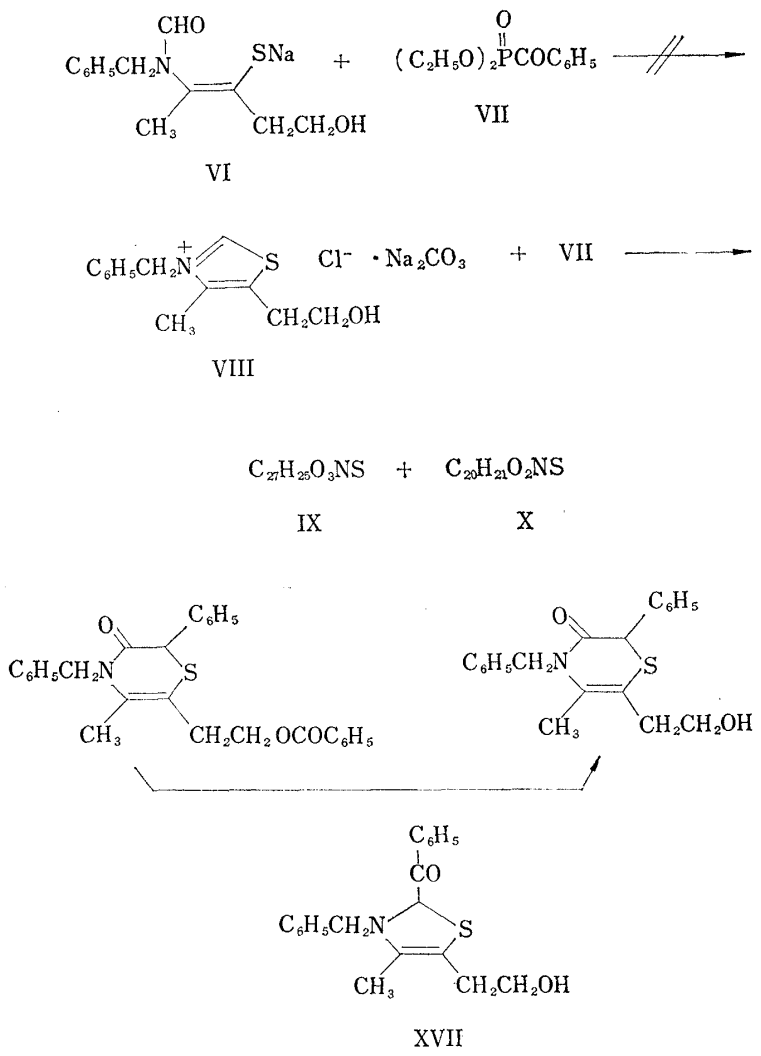

Chart 2.

Although a saturated aqueous solution of V was treated with two moles of sodium hydroxide and then acetone, correspondingly to the procedure of the "neutral form thiamine" making,[1] the crystalline solid which precipitated was not neutral form but sodium salt of thiol type (VI), because its infrared spectrum has a strong carbonyl absorption at 1661 cm^{-1} (N-CHO). This sodium salt (VI) on reaction with diethyl benzoylphosphonate (VII) gave a mixture consist of about ten spots on the thin-layer chromatography. Treatment of V with a saturated solution of an equimolar sodium carbonate and then acetone gave a crystalline solid (VIII). This product (VIII) was regarded as a mechanical mixture of V and sodium carbonate, since no carbonyl absorption band. When this product (VIII) was allowed to react with VII in toluene, two kinds of products were obtained; m.p. 104~106°, $C_{27}H_{25}O_3NS$ (IX), and m.p. 108~109°, $C_{20}H_{21}O_2NS$ (X), in 40% and 6% yields, respectively.

The infrared spectrum (in chloroform) of IX has two carbonyl absorptions at 1661 cm^{-1} and 1716 cm^{-1}, but no hydroxyl absorption. On hydrolysis IX was led to X, loosing one mole of benzoic acid. X has a carbonyl absorption band at 1661 cm^{-1} and a hydroxy band at 3557 cm^{-1} in its infrared spectrum in chloroform solution.

Probably, both substances (IX and X) may be the corresponding structures to 2-phenyl-4-(2-methyl-4-amino-5-pyrimidyl)-methyl-5-methyl-6-(2-benzoyloxy- or hydroxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one (XV or XVI) reported before.[1] The nuclear magnetic resonance spectrum (Fig. 1) of IX exhibited the following proton signals : CH_3 at 8.08τ

(singlet), $-CH_2-CH_2-$ at 7.45 and 5.85τ, $-CH_2-$ at 5.15 and 4.65τ (AB type quartet, J=16.0 c.p.s.), H at 5.38τ (singlet), and the three phenyl groups (ten proton signals were singlet at 2.78τ, and five proton signals were multiplet at 2.0~2.9τ). Since these signal patterns are closely parallel with that of XV, it is undoubtedly that IX has the same ring system with XV. Similarly, the nuclear magnetic resonance spectrum (Fig. 2) of X shows the same parallelism as that of XVI. Therefore the structures of IX and X may be presumed as 2-phenyl-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one and 2-phenyl-4-benzyl-5-methyl-6-(2-hydroxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one.

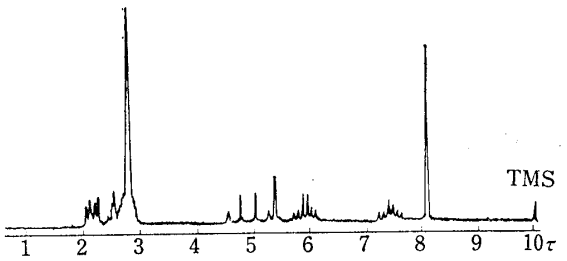

Fig. 1. Nuclear Magnetic Resonance Spectrum of 2-Phenyl-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-4*H*-1,4-thiazine-3-(2*H*)-one (IX) (in $CDCl_3$)

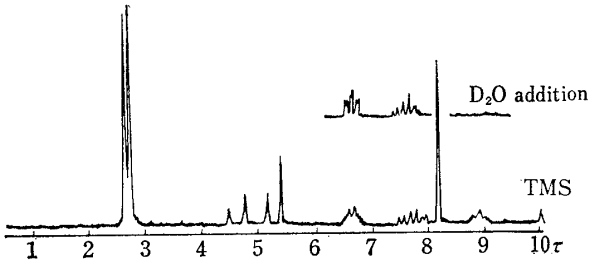

Fig. 2. Nuclear Magnetic Resonance Spectrum of 2-Phenyl-4-benzyl-5-methyl-6-(2-hydroxyethyl)-4*H*-1,4-thiazine-3(2*H*)-one (X) (in $CDCl_3$)

The ultraviolet spectrum of X in ethanol exhibited only weak absorption band (λ_{max}^{EtOH} 293 mμ, ε 2,300), and also X is a neutral substance. That is, it is unreasonable from these data that X would be 2-benzoyl-3-benzyl-4-methyl-5-(2-hydroxyethyl)-thiazoline (XVII).

On reduction with excess lithium aluminum hydride, X (or IX) afforded a product, m.p. 92~94.5°, $C_{20}H_{21}ONS$ (XI), in which loss of one oxygen atom was resulted from X. Its infrared spectrum has no carbonyl and hydroxyl absorption bands, however an enamine absorption band at 1623 cm^{-1} (in chloroform) appears characteristically.

Formation of the enamine indicates that reduction and dehydration took place on the carbonyl group of X. The ultraviolet absorption spectrum of XI in ethanol exhibited maxima at 229 mμ (ε 10,410) and 324 mμ (ε 13,050) due to the conjugated system. Further, formation of a styrene type system was concluded from the signal pattern of the phenyl protons and also chemical shift of singlet one proton (3.33τ) in its nuclear magnetic resonance spectrum (Fig. 3). On the other hand, signal groups of 2H (ca. 6.2τ), 1H (ca 6.8τ) and 2H (ca 7.7τ) indicate the existence of a substituted tetrahydrofuran ring, together with the absorption band at 932 and 1007 cm^{-1} in the infrared spectrum. From these data, XI may be formulated as 2-phenyl-4-benzyl 4*a*-methyl 4*a*,6,7,7*a*-tetrahydro-4*H*-furo[3,2-*b*]-1,4-thiazine.

Ozonolysis of XI gave a product, m.p. 116~118°, $C_{20}H_{21}O_3NS$ (XII), in which one atom of oxygen increased in comparison to XI. The infrared spectrum (in chloroform) of XII shows two absorptions of carbonyls at 1653 and 1667 cm^{-1}, and S-CO at 905 cm^{-1}, but no absorption of hydroxyl group. The ultraviolet spectrum exhibited maxima at 241 mμ (ε 10,670) and 268 mμ (ε 8,750) due to the formation of a benzoyl group. In its nuclear magnetic resonance spectrum (Fig. 4), the proton signal of one phenyl group is singlet and another one is benzoic acid like multiplet, and also the existence of N-CHO at 1.35τ is noticeable. Furthermore, the remain of the tetrahydrofuran ring is recognized from its infrared and nuclear magnetic resonance spectra. The structure of XII, therefore, can be estimated as 2-methyl-2-(benzylformyl)amino-3-benzoylthioxytetrahydrofuran.

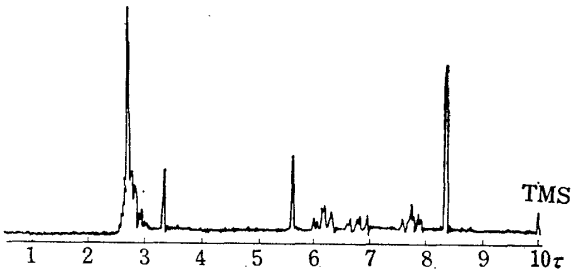

Fig. 3. Nuclear Magnetic Resonance Spectrum of 2-Phenyl-4-benzyl 4*a*-methyl-4*a*,6,7,7*a*-tetrahydro-4*H*-furo[3,2-*b*]-1,4-thiazine (XI) (in $CDCl_3$)

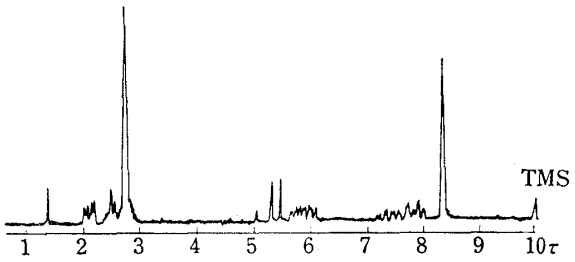

Fig. 4. Nuclear Magnetic Resonance Spectrum of 2-Methyl-2-(benzylformyl)amino-3-benzoylthioxytetrahydrofuran (XII) (in $CDCl_3$)

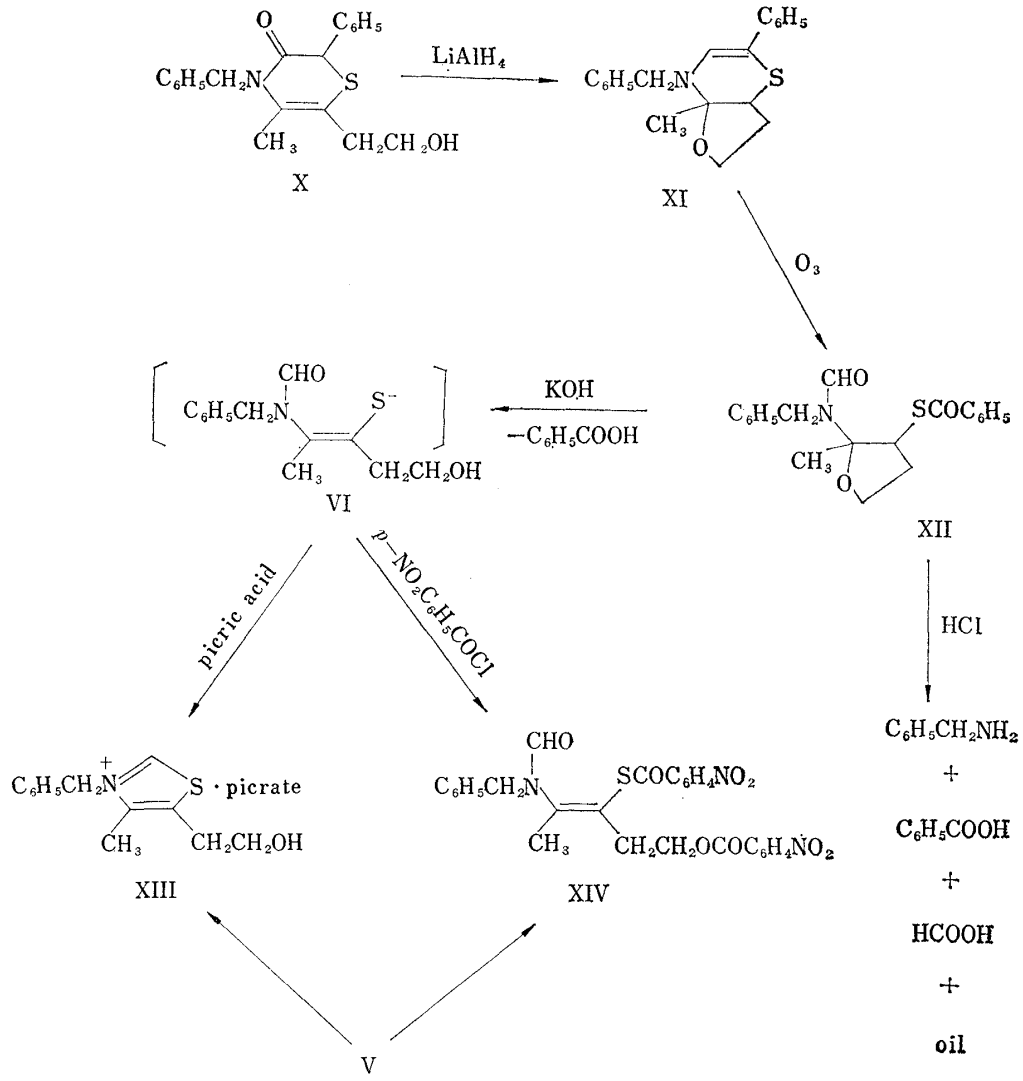

Chart 3.

When XII was treated with hydrochloric acid, benzylamine, benzoic acid, formic acid and neutral oil (containing mercapto group) were detected from the reaction mixture, respectively. Thus, all functional groups in the molecule presumed for XII were proved. Then XII was also treated with alcoholic potassium hydroxide at room temperature. Treatment of a part of the reaction mixture gave benzoic acid and a basic substance, of which pictrate was identified to 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium picrate (XIII). Therefore, in the reaction mixture, potassium salt of

N-formyl-N-(1-methyl-2-mercapto-4-hydroxy-1-butenyl)benzylamine (VI) should be formulated as the result of fission of the tetrahydrofuran ring followed dehydration, simultaneously with the selective hydrolysis of the benzoyl ester. Another part of the reaction mixture was then treated with *p*-nitrobenzoyl chloride to give colorless crystals, m.p. 167~168° (decomp.), which were identical with N-formyl-N-(1-methyl-2-*p*-nitrobenzoylthioxy-4-*p*-nitrobenzoyloxy-1-butenyl)benzylamine (XIV) derived from V by the ordinary method. Thus it is sure that XII on treatment with alkali afforded potassium salt of thiol (VI).

These results present synthetical supports on the structure of XII, therefore the structure of XI also confirmed. Accordingly, the structure of IX or X, as the anticipation, was decided as 2-phenyl-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-4*H*-1,4-thiazin-3-(2*H*)-one or 2-phenyl-4-benzyl-5-methyl-6-(2-hydroxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one having the same ring system with the case of thiamine.

Experimental*3

3-Benzyl-4-methyl-5-(2-hydroxyethyl)thiazoline-2-thione (IV)——To a mixture of 107 g. of benzylamine, 125 g. of 28% NH_4OH and 200 ml. of EtOH was added dropwise 84 g. of CS_2 at 20~25° with stirring, then stirred for 2 hr. at room temperature. After that 179 g. of 3-acetyl-3-chloropropyl acetate (III) was added at 20~25°, and stirred for 2 hr. at room temperature. And then 200 ml. of 35% HCl was added to the reaction mixture, and heated with reflux for 1 hr. After evaporation of the EtOH under reduced pressure the resulting aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 5% NaOH, H_2O and dried over Na_2SO_4. After removal of the solvent the residual black oil was dissolved in hot benzene and allowed to stand. The crystals which precipitated were recrystallized from benzene to give yellowish crystals, m.p. 90~91.5°. Yield, 178 g. (67.1%). *Anal.* Calcd. for $C_{13}H_{15}ONS_2$: C, 58.83; H, 5.70; S, 21.16. Found: C, 58.85; H, 5.87; S, 24.35.

3-Benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride (V)——To a suspension of 10.6 g. of IV in 100 ml. of 10% HCl was added dropwise 13.0 ml. of 34.5 w/v% H_2O_2 below 10° with stirring. After disappearance of an absorption at 324 mμ of the mixture, 9.8 g. of $BaCl_2 \cdot 2H_2O$ was added. $BaSO_4$ which precipitated was removed, the filtrate was concentrated *in vacuo*. The resulting oil was crystallized by addition of acetone, and recrystallized from a mixture of acetone-EtOH to yield colorless crystals, m.p. 141~143°. Yield, 8.9 g. (82.8%). *Anal.* Calcd. for $C_{13}H_{16}ONClS$: C, 57.87; H, 5.95; N, 5.19. Found: C, 57.70; H, 5.99; N, 5.29.

Treatment of 3-Benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride (V) with Sodium Carbonate-Acetone——To a solution of 21.2 g. of Na_2CO_3 in 90 ml. of H_2O was added 54.0 g. of V under ice cooling. Vigorous stirrings of the mixture gave a viscous yellow oil, then 3 L. of acetone was added, and stirred for 1 hr. under cooling. Colorless crystalline solid (VIII) which precipitated was collected and dried over P_2O_5 *in vacuo*. Yield, 47.0 g. (62.5%).

2-Phenyl-4-benzyl-5-methyl-6-(2-benzoyloxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one (IX)——To a suspension of 47.0 g. of VIII in 200 ml. of dry toluene was added 60.5 g. of diethyl benzoylphosphonate (VII) with stirring. The stirrings were continued under 30° until heat generation ceased, then the mixture was heated at reflux for 4 hr. The mixture was washed successively with 10% KOH, 10% HCl and H_2O, and dried over K_2CO_3. After evaporation of the solvent *in vacuo* the resulting oil was chromatographed on neutral alumina column. Elution with ether gave a solid residue which was recrystallized from MeOH to yield colorless prisms, m.p. 104~106°. Yield, 22.2 g. (40.0%). *Anal.* Calcd. for $C_{27}H_{25}O_3NS$: C, 73.10; H, 5.68; N, 3.15; S, 7.23. Found: C, 73.21; H, 5.75; N, 3.58; S, 7.25.

Continuous elution with AcOEt on the chromatography gave colorless crystals which were identified as X. Yield, 1.64 g. (6.3%).

2-Phenyl-4-benzyl-5-methyl-6-(2-hydroxyethyl)-4*H*-1,4-thiazin-3(2*H*)-one (X)——A solution of 10.0 g. of IX in 100 ml. of 10% NaOH in aq. EtOH was heated at reflux for 30 min. After removal of the solvent *in vacuo* the residue was extracted with $CHCl_3$, washed with H_2O, dried, and the solvent was evaporated. The resulting crystals ware recrystallized from aq. EtOH to yield colorless needles, m.p. 108~110°. Yield, 6.5 g. (85.0%). *Anal.* Calcd. for $C_{20}H_{21}O_2NS$: C, 70.75; H, 6.23; N, 4.12; S, 9.44. Found: C, 70.71; H, 6.52; N, 4.42; S, 9.81.

2-Phenyl-4-benzyl-4*a*-methyl-4*a*,6,7,7*a*-tetrahydro-4*H*-furo-[3,2-*b*]-1,4-thiazine (XI)——A solution of 10.0 g. of X in 50 ml. of tetrahydrofuran (THF) was added dropwise to a suspension of 10.0 g. of $LiAlH_4$ in

*3 All NMR spectra were taken on Varian Associates A-60 recording spectrometer with tetramethylsilane as an internal standard. All melting points are uncorrected.

250 ml. of THF at −5∼−6° with stirring. After the generation of heat ceased, the mixture was allowed to stand overnight about 10°. The excess of $LiAlH_4$ was decomposed by addition of H_2O under 0°, the precipitated solid was filtered off. The filtrate was saturated with CO_2, and then evaporated *in vacuo*. The resulting oil was dissolved in $CHCl_3$ and chromatographed on a silica gel (Davison, 60∼200 mesh) column. Elution with $CHCl_3$ gave colorless crystals which were recrystallized from MeOH as needles, 92∼94.5°. Yield, 1.68 g. (17.6%). *Anal.* Calcd. for $C_{20}H_{21}ONS$: C, 74.25; H, 6.54; N, 4.33; O, 4.94; S, 9.91. Found: C, 74.50; H, 6.70; N, 4.28; O, 5.46; S, 9.82.

2-Methyl-2-(benzylformyl)amino-3-benzoylthioxytetrahydrofuran (XII)——Small excess (1.2 mol. equiv.) of O_3 (6.85 mg. of O_3/100 ml. of O_2/70 sec.) was passed through a solution of 1.65 g. of XI in 150 ml. of $CHCl_3$ at −30°. Then the reaction mixture in which small amount of Zn powder and AcOH were added was stirred for 30 min. at room temperature. Filtrate of the mixture was washed successively with *N* HCl, *N* $NaHCO_3$ and H_2O, and dried over $MgSO_4$, then decolored with Norit. After removal of the solvent the resulting solid was recrystallized form aq. MeOH to yield colorless crystals, m.p. 112∼115°. Yield, 426 mg. (23.5%). *Anal.* Calcd. for $C_{20}H_{21}O_3NS$: C, 67.57; H, 5.96; N, 3.95; O, 13.50; S, 9.02. Found: C, 67.88; H, 5.97; N, 4.27; O, 13.64; S, 9.11.

Hydrolyses of 2-Methyl-2-(benzylformyl)amino-3-benzoylthioxytetrahydrofuran (XII)——i) A solution of 135 ml. of XII in 10 ml. of 10 w/v % HCl in EtOH was heated at reflux for 30 min. The reaction mixture in which H_2O was added was concentrated under reduced pressure. An aqueous distillate was reduced by addition of Mg ribbons, then the supernatant was mixed with H_2SO_4 and a little solid chromotropic acid was added, and the mixture was heated for 10 min. at 60°. A bright violet color appeared due to the presence of HCOOH.[4]

The concentrated acidic solution was extracted with $CHCl_3$. The $CHCl_3$ was also extracted with *N* $NaHCO_3$. The *N* $NaHCO_3$ extracts were then acidified with HCl, and extracted with ether, and dried over Na_2SO_4. Evaporation of the ether gave 6 mg. (13.0%) of benzoic acid.

The $CHCl_3$ layer was dried and evaporated to give an oil, of which alkaline solution colored deep red due to the presence of SH group by the addition of sodium nitroprusside solution.

On the other hand, the acidic solution which extracted with $CHCl_3$ was neutralized with NaOH and extracted with $CHCl_3$ to give a basic oil, of which picrate was identical with authentic sample of benzylamine picrate. Yield, 55 mg. (61.5%).

ii) A solution of 147 mg. of XII in 5 ml. of 5% KOH in aq. EtOH was stirred at 23° for 2 hr., then CO_2 gas was saturated under ice cooling. The EtOH was removed *in vacuo*, the remained aqueous solution was extracted with $CHCl_3$, which was then extracted with *N* HCl. To the HCl extracts after concentration *in vacuo* was added sodium picrate to yield viscous oil, which was crystallized from ether as needles, m.p. 106∼110°. Yield, 38 mg. (19.8%). *Anal.* Calcd. for $C_{19}H_{19}O_8N_4S$: C, 49.23; H, 4.13; N, 12.02; S, 6.92. Found: C, 49.28; H, 4.23; N, 12.03; S, 6.96. This picrate was identified as 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium picrate (XIII) prepared by the ordinary method from V.

The aqueous layer which was extracted with $CHCl_3$ was acidified with HCl, and extracted with ether to give 26 mg. (51.5%) of benzoic acid.

iii) A solution of 142 mg. of XII in 5 ml. of 5% KOH in aq. EtOH was stirred for 2 hr. at 20∼25°, and the EtOH was removed *in vacuo*, and then a solution of *p*-nitrobenzoyl chloride in $CHCl_3$ was added. The mixture was stirred during pH of the mixture was controlled at alkali by the addition of *N* KOH. Then the mixture was extracted with $CHCl_3$. The extracts were washed successively with *N* KOH, *N* HCl and H_2O, dried, and evaporated *in vacuo*. Recrystallization of the resulting crystals gave colorless crystals, m.p. 167∼168° (decomp.), which were identical to the specimen of N-formyl-N-(1-methyl-2-*p*-nitrobenzoylthioxy-4-*p*-nitrobenzoyloxy-1-butenyl)benzylamine (XIV). Yield, 4 mg. (1.8%).

N-Formyl-N-(1-methyl-2-*p*-nitrobenzoylthioxy-4-*p*-nitrobenzoyloxy-1-butenyl)benzylamine (XIV)——To a solution of 155 mg. of V and 46 mg. of NaOH in H_2O was added a solution of 213 mg. of *p*-nitrobenzoyl chloride in $CHCl_3$ under 10° with stirring. The mixture was stirred until pH did not change, and then extracted with $CHCl_3$. The extracts were washed with *N* KOH and H_2O, dried, and evaporated. The resulting solid was recrystallized from $CHCl_3$–EtOH to give O,S-bis(*p*-nitrobenzoyl) ester (XIV), m.p. 167∼168° (decomp.). Yield, 185 mg. (58.6%). *Anal.* Calcd. for $C_{27}H_{23}O_8N_3$: C, 59.00; H, 4.22; N, 7.64; O, 23.29. Found: C, 58.61; H, 4.26; N, 7.72; O, 22.48.

The authors are grateful to Emeritus Prof. E. Ochiai of Tokyo University, and Dr. K. Takeda, Director of this laboratory for their continuing encouragement.

Summary

Reaction of 3-benzyl-4-methyl-5-(2-hydroxyethyl)thiazolium chloride (V) with diethyl benzoylphosphonate (VII) was studied successively as an analogue of thiamine. It is

4) F. Feigl: "Spot Tests in Org. Analysis," 368 (1960), Maruzen.

also appeared in this case that a novel reaction took place accompanied by the ring expansion from thiazole to 1,4-thiazine ring.

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103. Yukio Ishida, Hideki Moritoki, and Michiko Onishi : Effects of Two Kinds of Oxytocin Antagonists on the Isolated Rat Uterus.

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On the way of our studies with drug receptors of acetylcholine (ACh), barium chloride and oxytocin on the isolated rat uterus, we found that the action of oxytocin was inhibited competitively by hydrogen ion[1] and simple phenolic compounds.[2] And then we found that carbobenzyloxylated peptides containing tyrosine inhibited competitively the action of oxytocin. Among these small peptides, carbobenzyloxy-L-tyrosyl-L-tyrosine ethylester (Cbz-Tyr-TyrOEt) showed the most active inhibition.[3] This compound showed competitive antagonism to oxytocin, but non-competitive to ACh and barium chloride from the shift of dose-responsecurve.

In this report, relative inhibitory activities of derivatives of tyrosyltyrosine were tested. These compounds are Cbz-Tyr-TyrOEt, Tyr-TyrOEt which is decarbobenzyloxylated, and Cbz-Tyr-TyrOH which has a carboxylic acid. Among these derivatives, original Cbz-Tyr-TyrOEt was the most active antagonist. Then, estrogens were also tested. They were estradiol and diethylstilbestrol. All these compounds showed competitive antagonism to oxytocin from the shift of dose-response curve. Furthermore, we have found that cystine diethylester (CySDE) had the competitive action to oxytocin. It is interesting that this is a new type of antagonist which has never been reported. This compound was not so strong inhibitor, but more active than thioglycollate which was reported to have the inhibitory action to oxytocin by Martin and Schild.[4] Parameters for these competitive antagonists were obtained by the method introduced by Schild.[5]

From their chemical structures, they may be divided into two types of antagonists : one of which has phenol group such as peptides containing tyrosine and estrogens and so on, and the other, CySDE and thioglycollate which may be concerned with -S-S- group of oxytocin. The compounds of two types showed the same competitive inhibition to oxytocin by means of their shifts of dose-response curve, but it is suggested that they may have different mechanisms of inhibition considering their chemical structures. So, we examined synergistic antagonism of both groups in combination.

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3) Y. Ishida, K. Hara : This Bulletin, **12**, 972 (1964).
4) P. J. Martin, H. O. Schild : Nature, **196**, 382 (1962).
5) H. O. Schild : Pharmacol. Rev., **9**, 242 (1957).