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Studies on Pyrimidine Derivatives and Related Compounds. LXXV.[1] Reactions of Thiazolium Salts with Diethyl Acylphosphonates and Hydroxylation of Some 3-Oxo-2,3-dihydro-4H-1,4-thiazine Derivatives

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Reaction of simple benzothiazolium salts (V) with diethyl acylphosphonates (II) afforded ring-expanded products, 1,4-benzothiazine derivatives (VII). In this reaction, it was found necessary to add II before triethylamine. VIIa-b were confirmed to be identical with authentic samples synthesized by the independent pathway shown in Chart 2. The reaction of 4-methylthiazolium salts (XIII) with II afforded 1:1 adducts (XIV), which were decomposed to corresponding 1,4-thiazine derivatives (XV) by alkaline treatment. Treatment of 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-acyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (IV) with hydrogen peroxide in acetic acid gave 2-hydroxy-2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-acyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (XIX).

In previous papers[3] we reported that thiamine and other thiazolium salts react with dialkyl acylphosphonates to give ring expanded-products, 1,4-thiazine derivatives, in good yields. The mechanism of this novel reaction was clarified using 3-benzyl-4-methyl-5-(2-benzoyloxy)ethylthiazolium halides (I) as model compounds.[4,5] The effect of substituents on the thiazolium ring on the reactivity was also demonstrated by the reactions of thiamine analogues with diethyl benzoylphosphonate (IIa).[1]

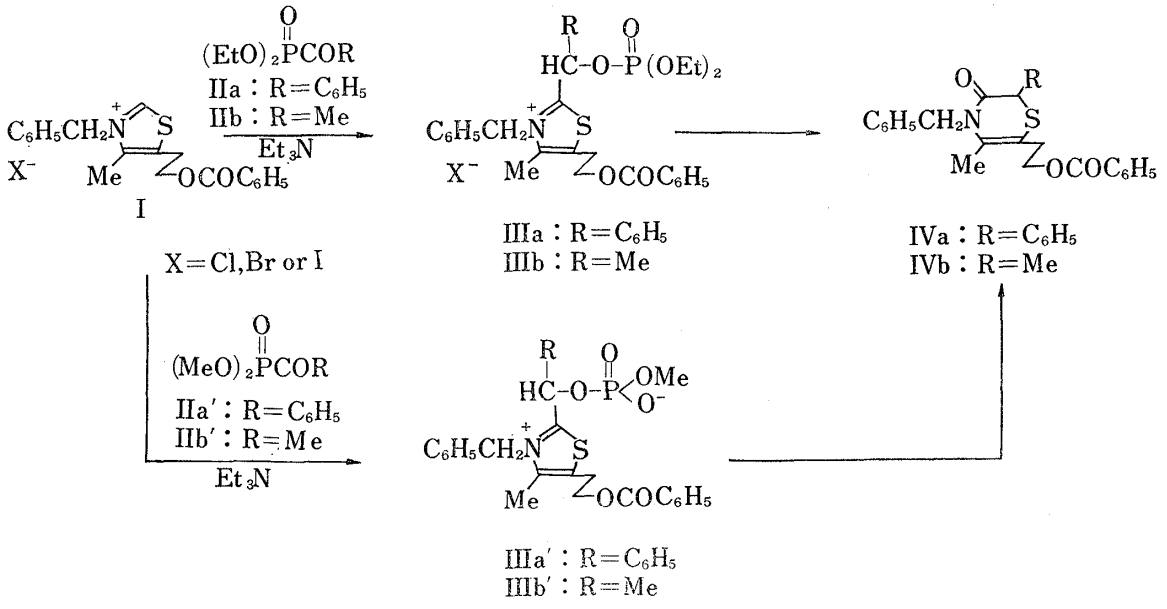
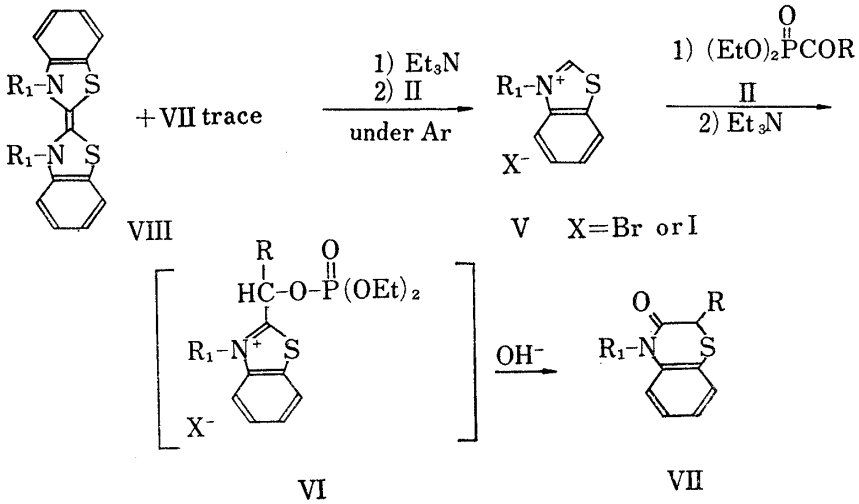
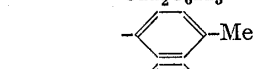
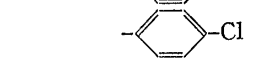


Chart 1

1) Part LXXIV: A. Takamizawa and H. Sato, *Yakugaku Zasshi*, **92**, 27 (1972).
2) Location: *Fukushima-ku, Osaka.*
3) *a*) A. Takamizawa, Y. Sato, S. Tanaka, and H. Itoh, *Chem. Pharm. Bull.* (Tokyo), **14**, 407 (1966); *b*) A. Takamizawa and Y. Sato, *ibid.*, **14**, 742 (1966); *c*) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Itoh, and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966).
4) A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968).
5) A. Takamizawa, Y. Hamashima, H. Sato, and S. Sakai, *Chem. Pharm. Bull.* (Tokyo), **17**, 1356 (1969).

TABLE I



Compd. No.	Substituents R_1	Substituents R	mp (°C)	IR (cm^{-1}) $\nu_{C=O}^{Nujol}$	NMR (in $CDCl_3$, τ, cps) CH-R	Yield (%)
VIIa	$C_6H_5CH_2$	C_6H_5	126—131	1664	5.23[s]	73.3
VIIb	Me	C_6H_5	153—156	1678	5.34[s]	36.5
VIIc	$C_6H_5CH_2$	Me	oil	1667[a)]	6.41[q] (7.0)	47.8
VIId	$C_6H_5CH_2$	$CH_2C_6H_5$	oil	1669[a)]		73.0
VIIe	$C_6H_5CH_2$		137—141	1665	5.26[s]	20.6
VIIf	$C_6H_5CH_2$		153—155	1658	5.27[s]	53.3
VIIg		C_6H_5	oil	1671[a)]	5.21[s]	85.3

a) in $CHCl_3$

Now, in order to determine the scope of the reaction, we have investigated its application to condensed-ring thiazolium salts.

An ice cooled mixture of 3-benzylbenzothiazolium bromide (Va) and diethyl benzoylphosphonate (IIa) was treated with two molar equivalents of triethylamine in N,N-dimethylformamide (DMF) to give a crystalline product (VIIa), mp 126—131°, the elementary analysis of which was in agreement with the composition $C_{21}H_{17}ONS$. The product VIIa showed a strong C=O band at 1664 cm^{-1} in the infrared (IR) spectrum, and its ultraviolet (UV) spectrum showed an absorption maximum at 240 mμ (log ε 3.03) in ethanol. Nuclear magnetic

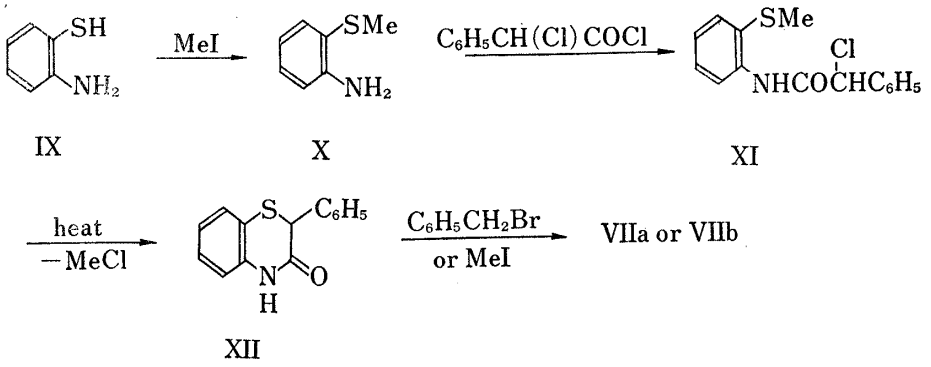


Chart 2

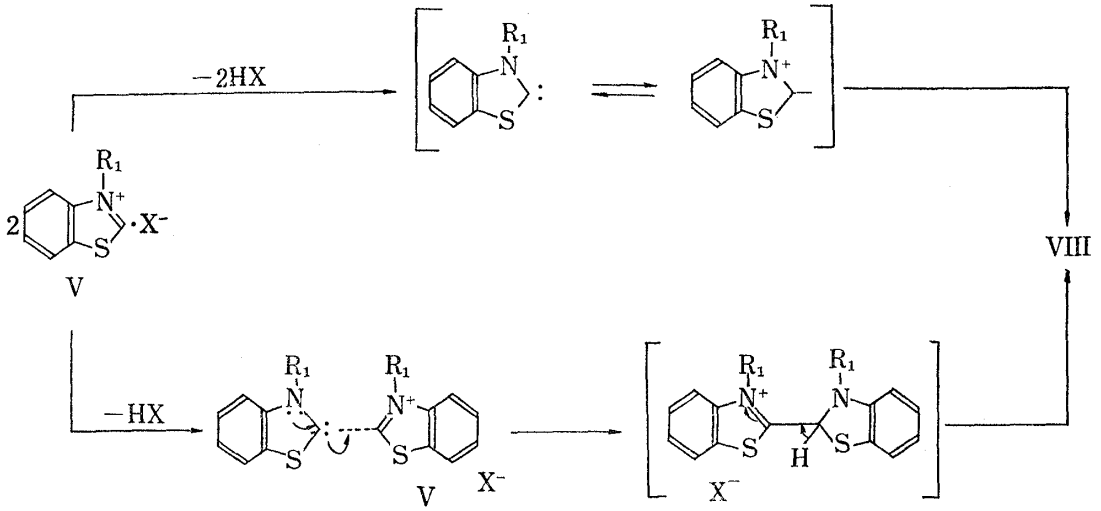


Chart 3

resonance[6] (NMR) exhibited proton signals as follows: τ 2.5—3.2 (aromatic multiplet, 14H), 4.67, 4.82 (AB-type quartet, 2H, J=16.3), 5.23 (singlet, 1H). Based on these data, the structure of VIIa could be assigned as 2-phenyl-3-oxo-4-benzyl-2,3-dihydro-4H-1,4-benzothiazine.

Chemical evidence for the structure of VIIa was obtained by synthesis *via* an alternative route as shown in Chart 2. The 2-phenyl-3-oxo-2,3-dihydro-4H-1,4-benzothiazine, XII (mp 208—209°), a new compound, was prepared according to the method of Davis, *et al.*[7] from 2-mercaptoaniline (IX). Treatment of XII with benzyl bromide[8] gave VIIa, which was identified with VIIa synthesized from Va and IIa, by comparison of IR and NMR spectra.

When in the reaction of Va with IIa triethylamine was added to the reaction mixture before IIa, the colourless crystalline product VIIIa (R=$C_6H_5CH_2$) was obtained in 52.2% yield accompanied by a trace of VIIa. The melting point of VIIIa was 151° and its elementary analysis was in agreement with the composition $C_{28}H_{22}N_2S_2$. The product VIIIa showed no absorption due to C=O group in the IR spectrum. The NMR spectrum taken at room temperature in d_6-DMSO containing a small amount of $CDCl_3$ showed two bridged methylene signals as AB-quartets (τ 4.90, 5.17, 5.39, 5.67, J=17.0 and 5.58, 5.81, 6.15, 6.37, J=13.0), respectively, and aromatic proton signals (multiplet, τ 1.87—4.05). The spectrum was taken at 82° and 115°, but differences between the chemical shifts, coupling constants, and intensities of two bridged methylene signals at the two temperatures were hardly discernible. These results suggest the structure 2,2′-bis(3-benzylbenzothiazolylidene) for compound VIIIa, and on the basis of the intensities of two methylene signals in the NMR spectrum it is probably a mixture of *cis*- and *trans*-isomers in about a 1:1 ratio.

The reaction took place similarly even in an argon atmosphere. This indicates that IIa reacts little to Va under the conditions described above.

The mechanism for formation of VIII may be considered as shown in Chart 3.[9]

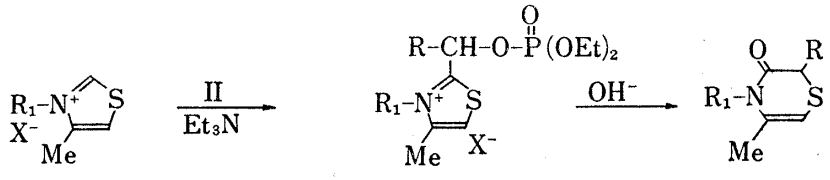
When 3-methylbenzothiazolium iodide (Vb) was treated with IIa before triethylamine, the corresponding 1,4-benzothiazine derivative VIIb, identified with the N-methylated derivative of XII, was obtained.

6) NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ solution containing TMS as an internal standard. Chemical shifts (τ), coupling constants (J, cps). Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), b (broad) and m (multiplet).
7) C.S. Davis, G.L. Jenkins, A.M. Knevel, and C. Paget, *J. Pharm. Sci.*, **51**, 840 (1962).
8) R.N. Prasad and K. Tietje, *Can. J. Chem.*, **44**, 1247 (1966).
9) H.W. Wanzlick, H.J. Kleiner, I. Lasch, H.U. Füldner, and H. Steinmaus, *Ann. Chem.*, **708**, 155 (1967).

Reactions of salts V with several diethyl acylphosphonates were similarly carried out; the results are listed in Table I. Isolation of the expected intermediates VIa—g corresponding to IIIa,b was not successful. This may be considered to be due to the fact that benzothiazolium compounds in general are more readily ring-opened than monocyclic thiazolium compounds,[10] so that VI will undergo nucleophilic attack by hydroxyl anion at the C_2 position of the thiazolium ring even without alkaline treatment to give VII by ring expansion.

The above results support the interpretation reported previously[1] for the effects of substituents at the C_4 and C_5 positions on the reactivity of the C_2 position in the thiazolium ring toward II. That is to say, in the case of I having alkyl groups at C_4 and C_5 positions, the thiazolium ylide (nucleophilic carbene[11]) produced by treatment of I with triethylamine is relatively stable and its C_2 position makes a nucleophilic attack on the carbonyl carbon of electrophiles II to give III. In the case of V, however, the benzothiazolium ylide produced by treatment of V with triethylamine is dimerized at its C_2 position to give VIII if II is absent from the reaction system, because the quasi-aromatic resonance stabilization[11] of the thia-

Table II



XIII X=Cl or I XIV XV

Compd. No.	Substituents R_1	Substituents R	mp (°C)	IR (cm^{-1}) $\nu_{C=O}$	NMR (in $CDCl_3$, τ, cps) CH–R	NMR (in $CDCl_3$, τ, cps) Me–C=CH	Yield (%)
XVa	$C_6H_5CH_2$	-Cl	113—116	1655[a]	5.48[d] (1.6)	4.53[m] (1.1)	54.6
XVb	$C_6H_5CH_2$	-Me	oil	1675[b]	5.46[d] (1.2)	4.54[m] (1.1)	59.0
XVc	Me	CH_2Ph	oil	1656[c]	7.2—6.4[m]	4.62[m] (1.1)	27.9

a) Nujol mull b) in CCl_4 c) film

zolium ring, attributable to π-electron participation[1] at C_8, C_9 positions in the benzothiazolium ring, is decreased by the fusion of a benzene ring onto the C_4, C_5 positions in the ring. However, when II is added to the reaction mixture before triethylamine, the benzothiazolium ylide is immediately consumed in the nucleophilic reaction with II, as in the case of I described above, affording the products VII *via* VI.

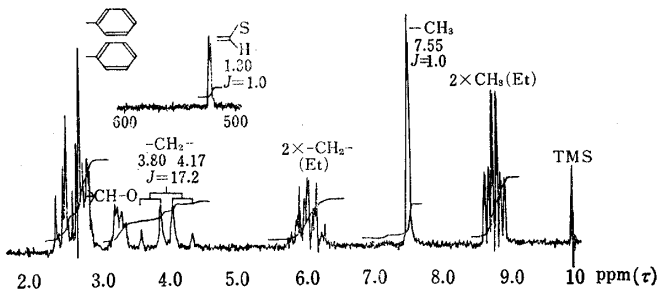
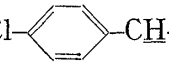


Fig. 1. NMR Spectrum of XIVa in $CDCl_3$

Simple 4-methylthiazolium salts (XIII) reacted with phosphonates (II) having acyl groups such as phenylacetyl or *p*-substituted benzoyl to give the corresponding 1,4-thiazine derivatives (XV) (Table II).

10) T. Matsukawa and T. Iwatsu, *Yakuguku Zasshi*, **69**, 550 (1949).
11) H.W. Wanzlick, *Angew. Chem.*, **74**, 129 (1962).

The 1:1 adduct XIVa, mp 143—146°, was obtained by reaction of 3-benzyl-4-methylthiazolium chloride (XIIIa) with diethyl *p*-chlorobenzoylphosphonate (IIc). The elemental analysis of the adduct was in agreement with the expected formula, $C_{22}H_{21}O_4NSPCl_2$, so it was assumed that the adduct has a structure analogous to those of IIIa,b. The IR spectrum showed a strong P=O band at 1274, and P-O-C bands at 1037 and 969 cm^{-1}, but no hydroxyl or carbonyl absorption band was observed. The NMR spectrum (Fig. 1) showed 2H AB-quartet signals at τ 4.17 and 3.80 (J=17.2), and a 1H multiplet signal at about 3.3 which did not disappear on the addition of deuterium oxide. The splitting of the latter 1H signal is probably due to coupling of the benzylic proton with the phosphorus nucleus.[4,5] Both the low chemical-shift values and other signal patterns indicate that XIVa still has the thiazolium moiety, and XIVa was assumed to be substituted at the thiazole C_2 position by the (1-diethylphosphoroyl)-*p*-chlorobenzyl group. These data are in accord with the structure 2-(1-diethylphosphoroyl)-*p*-chlorobenzyl-3-benzyl-4-methylthiazolium chloride for XIVa. Alkaline treatment of XIVa gave XVa ($C_{18}H_{16}ONSCl$), mp 113—116°, in good yield. The IR spectrum showed a C=O band at 1655 cm^{-1}. The NMR spectrum exhibited proton signals as follows: τ 8.12 (d, C$\underline{H}_3$, J=1.1), 5.48 (d, Cl-  -C$\underline{H}$-S, J=1.6), 5.12, 4.84 (AB-q, N-C$\underline{H}_2$, J=16.0), 4.53 (m, =  , J=1.1), 2.76 (m, -C$_6\underline{H}_4$-), 2.70 (s, C$_6\underline{H}_5$). These data indicate that XVa has a structure analogous to IVa,b, and it was concluded to be 2-*p*-chlorophenyl-3-oxo-4-benzyl-5-methyl-2,3-dihydro-4H-1,4-thiazine. Similarly, the reaction of XIIIa with IId (R=Me-  -) afforded 1,4-thiazine derivative XVb. The reaction of XIIIb (R_1=Me, X=I) with IIe (R=$C_6H_5CH_2$) afforded the 1:1 adduct XIVc, mp 122—124°, which gave XVc on alkaline treatment.

Considering the results of Table II together with that reported in a previous paper[5] with regard to the reaction of XIII with diethyl benzoylphosphonate (IIa), it is proved that the yield of XV is affected by the N-substituent of the thiazolium ring, which affects the stability of the thiazolium ylide produced by treatment of XIII with triethylamine or that of the precursor of the 1:1 adduct XIV, *i.e.*, zwitterion-type compounds,[4] rather than by the *p*-substituent of aroyl group in II.

In connection with our studies on 1,4-thiazine compound formation,[3] we have already reported[12,13] that treatment of 2-phenyl(or methyl)-3-oxo-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazines (XVIa or XVIb) with hydrogen peroxide in acetic acid gave pseudo-thamine analogues, 2-benzoyl(or acetyl)-2-hydroxy-3-(2-methyl-4-amino-5-pyrimidinyl)methyl-4-methyl-5-(2-hydroxy)ethylthiazolines (XVIIa or XVIIb) by ring contraction and hydroxylation reactions, and that the diacetates (XVIIIa,b) of these products gave O-acetylthiamine, which is a thiazolium salt, on acid treatment, and O-acetyl XVIa,b on $NaBH_4$ reduction (Chart 4).

In the present work, oxidation under the conditions described above was tried with 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-acyloxy)ethyl-2,3-dihydro-4H-1,4-thiazines (IVa, IV'a and IV"a), which are simple compounds corresponding to XVIa,b.

Treatment of IVa with hydrogen peroxide in acetic acid gave crystalline XIXa, mp 121—123°. The elemental analysis of this compound indicated a formula ($C_{27}H_{25}O_4NS$) containing one oxygen more than IVa. The IR spectrum ($CHCl_3$) showed an OH band at 3500, an O-C=O band at 1706, a COC band at 1273, and an N-C=O band at 1648 cm^{-1}. The NMR spectrum exhibited proton signals as follows: τ 8.16 (s, C$\underline{H}_3$), 7.55 (C$\underline{H}_2$), 5.96 (OC$\underline{H}_2$), 5.32, 4.43 (AB-q, N-C$\underline{H}_2$, J=16.2), 4.88 (s, O$\underline{H}$, disappeared on the addition of deuterium oxide), 2.78 (s, C$_6\underline{H}_5$CH$_2$), 3.0—2.0 (m, C$_6\underline{H}_5\times$2), but the methine proton signal observed

12) A. Takamizawa, Y. Sato, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **14**, 588 (1966).
13) A. Takamizawa, Y. Mori, H. Sato, and S. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **16**, 1773 (1968).

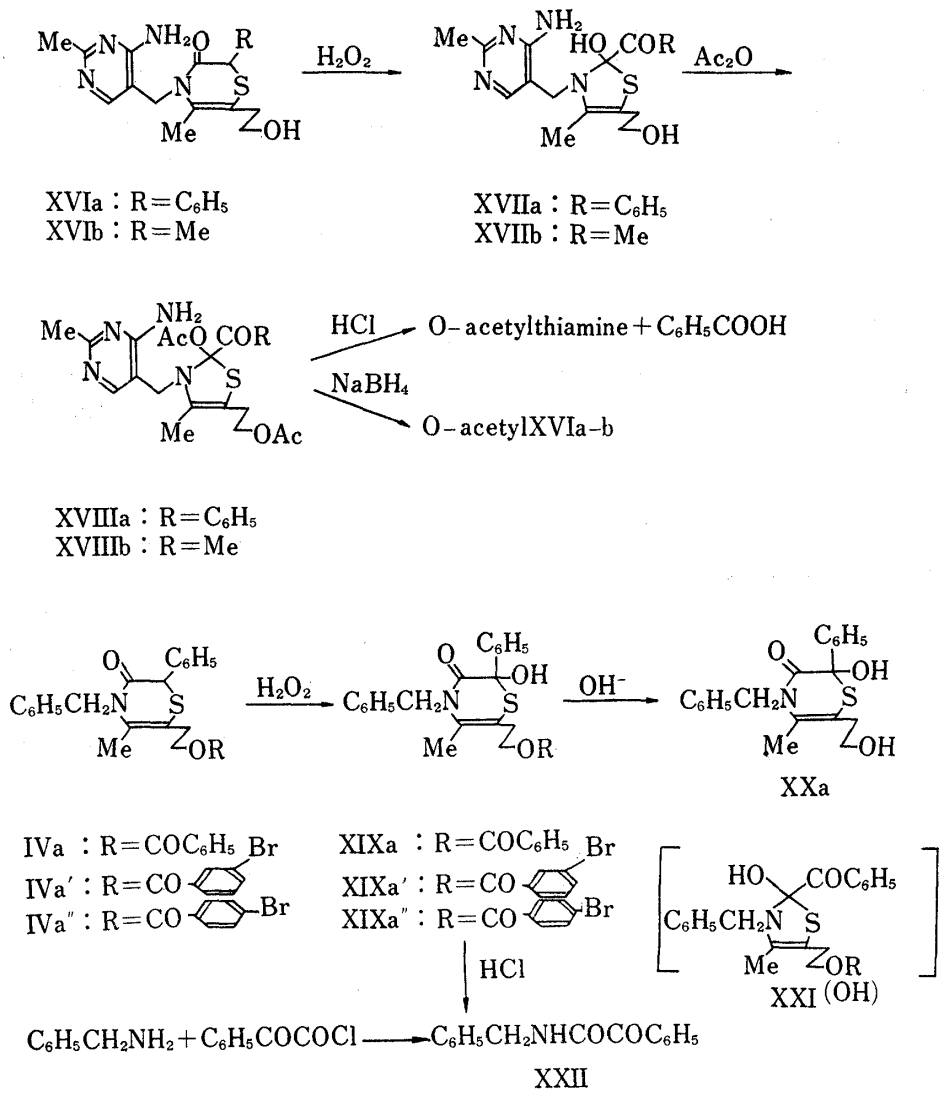


Chart 4

for IVa was not detected. Treatment of XIXa with alcoholic potassium hydroxide gave XXa ($C_{20}H_{21}O_3NS$), mp 75—78°. The IR spectrum ($CHCl_3$) showed no ester carbonyl band, but OH bands at 3584 and 3413, and a C=O band at 1654 cm^{-1} were seen. The NMR spectrum exhibited all of the proton signals observed for XIXa except that due to one of the phenyl groups. The UV spectrum pattern was similar to that of XIXa. Accordingly, XXa has the same fundamental structure as XIXa.

From these and the following results, it seemed highly probable that both XIXa and XXa have six-membered ring structures and not the five-membered ring structure XXI. The NMR spectrum of XXa in d_6-dimethyl sulfoxide showed two singlets at τ 2.75 and 2.62 due to two phenyl groups. The UV spectrum pattern [λ_{max}^{EtOH} mμ (log ε): 286 (3.39)] was similar to that [λ_{max}^{EtOH} mμ (log ε): 293 (3.38)] of 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-hydroxy)-ethyl-2,3-dihydro-4H-1,4-thiazine.[3b,14]

The structures of XIXa and XXa were then chemically confirmed to be 2-phenyl-2-hydroxy-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy and hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine. When XIXa was treated with aqueous hydrochloric acid, XXII, but not the thiazolium salt I (X=Cl), was obtained. Also, XIXa was not attacked by sodium boro-

14) UV spectral data: C_6H_5COOH, λ_{max}^{EtOH} mμ (log ε): 230 (4.00); C_6H_5COMe, λ_{max}^{EtOH} mμ (log ε): 240 (4.11).

hydride. If the structure of the hydroxylation product had been XXI ($R=COC_6H_5$), hydrogenation should have proceeded.[12] These results are thus contrary to those obtained for XVIIIa,b.

Oxidation of IV'a and IV"a afforded analogously the hydroxylation products XIX'a and XIX"a with retention of the 1,4-thiazine nucleus, respectively.

The X-ray analysis of XIX'a also supported the six-membered ring structure. Details of X-ray studies will be reported in the near future.

It should be point out here that the behavior of IV toward hydrogen peroxide is normal and that of XVI abnormal.

This is, therefore, interesting as an example showing dependence of the stability of the 2,3-dihydro-4H-1,4-thiazine nucleus on its ring substituents. At the present time, however, the difference of substituent effect between the pyrimidine ring and the benzene ring cannot be explained reasonably.

Experimental[15]

General Procedure for Preparation of VII——To a mixture of 10 mmole of V and 10 mmol of II in 20 ml of DMF, 20 mmol of Et_3N (dried over Na wire) was added dropwise under ice cooling and the mixture was stirred at 0—2° for 30 min then at 25° for 3 hr. After the reaction mixture had been allowed to stand overnight at room temperature, DMF was removed *in vacuo* at 50° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O successively, dried over Na_2SO_4, and evaporated. The residue was purified by recrystallization from EtOH or by Al_2O_3 column chromatography with AcOEt.

Table III. Elementary Analysis of VII

Compd No.	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
VIIa	$C_{21}H_{17}ONS$	76.11	5.17	4.23	9.68	75.76	5.17	4.26	9.19
VIIb	$C_{15}H_{13}ONS$	70.58	5.13	5.49	12.54	70.70	5.02	5.51	12.74
VIIe	$C_{22}H_{19}ONS$	76.50	5.55	4.06	9.26	76.33	5.85	3.93	9.37
VIIf	$C_{21}H_{16}ONSCl$	68.89	4.41	3.83	8.76	68.67	4.13	4.13	8.98

2,2'-Bis(3-benzylbenzothiazolylidene) (VIIIa)——To a suspension of 3.0 g (9.8 mmole) of Va ($R_1=C_6H_5CH_2$, X=Br) in 25 ml of DMF, 2.0 g (19.8 mmole) of Et_3N was added dropwise at 0.5—1.5° with stirring in dry argon atomosphere. The temperature of mixture was maintained below 2° for 20 min, after which 2.4 g (9.91 mmole) of IIa was added dropwise under ice cooling and the mixture was stirred at 1° for 5.5 hr. The mixture was then allowed to stand overnight at room temperature. The precipitated $Et_3N\cdot HBr$ was removed by filtration, the filtrate was concentrated *in vacuo* at 43°, then acetone was added to it. The mixture was allowd to stand overnight below 2°, then the colorless crystals which had former were collected [1.15 g (52.2%), mp 147—148°]. Recrystallization from acetone gave colorless crystals, mp 151°. *Anal.* Calcd. for $C_{28}H_{22}N_2S_2$ (VIIIa): C, 74.65; H, 4.92; N, 6.22; S, 14.21. Found: C, 74.86; H, 4.88; N, 6.04; S, 14.26. The filtrate of VIIIa showed the presence of a trace amount of VIIa on TLC[16] (SiO_2–C_6H_6).

2-(α-Chlorophenylacetamido)phenyl Methyl Sulfide (XI)——A solution consisting of 12.5 g (90 mmole) of X[9] and 8.9 g (112.4 mmole) of dry pyridine in 200 ml of dry ether was cooled to 0°. To this mixture was added an ethereal solution of 17.0 g (90 mmole) of chlorophenylacetyl chloride. After the mixture had been allowed to stand at room temperature for 3 days, the deposited crystals were collected and washed with H_2O to give 21.4 g (81.7%) of crystals, mp 100—106°. Recrystallization from aq. EtOH gave colorless crystals, mp 106—109°. *Anal.* Calcd. for $C_{15}H_{14}ONSCl$ (XI): C, 61.74; H, 4.83; N, 4.80; S, 10.99. Found: C, 61.47; H, 4.89; N, 4.80; S, 11.00. IR λ_{max}^{Nujol} cm^{-1}: 3286 (NH), 1675 (C=O).

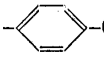
2-Phenyl-3-oxo-2,3-dihydro-4H-1,4-benzothiazine (XII)——XI (3.0 g) was heated in an oil-bath at 195° under 13 mmHg pressure for 30 min. Upon cooling, the mixture solidified and MeOH (50 ml) was

15) All melting points are uncorrected.
16) TLC: Thin-layer chromatography.

added. The colorless crystals were collected (2.3 g, 92.8%). Recrystallization from MeOH gave colorless sticks, mp 208—209°. *Anal.* Calcd. for $C_{14}H_{11}ONS$: C, 69.70; H, 4.59; N, 5.80; S, 13.27. Found: C, 69.67; H, 4.61; N, 5.90; S, 13.26. IR λ_{max}^{Nujol} cm^{-1}: 3192 (NH), 1678 (C=O). NMR τ: 5.27[m] ($C_6H_5CH\langle$).

N-Benzylation of XII——A solution of XII (1.7 g, 7.05 mmole) in DMF (40 ml) was added to a suspension of sodium hydride (0.34 g, 50% NaH, 7.05 mmole) in DMF (20 ml) without external cooling, and the mixture was stirred for 70 min. A solution of benzyl bromide (1.2 g, 7.02 mmole) in benzene (6 ml) was added, and the temperature was held at 100° for 1 hr. After evaporation of DMF, the residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The oily residue crystallized from ether to give the product (0.76 g, 32.5%), mp 115—121°. Recrystallization from 99% EtOH gave colorless sticks, mp 125—131°. *Anal.* Calcd. for $C_{21}H_{17}ONS$: C, 76.11; H, 5.17; N, 4.23; S, 9.68. Found: C, 76.48; H, 5.17; N, 4.34; S, 9.55. Identity with VIIa obtained above was shown by IR spectra comparison.

N-Methylation of XII——A solution of XII (5.5 g, 22.8 mmole), MeI (5.5 g, 38.7 mmole), and KOH (1.3 g, 23.15 mmole) in EtOH (300 ml) was refluxed for 5 hr. After evaporation of EtOH, the residue was extracted with $CHCl_3$, and the extract was washed with 10% aq. $Na_2S_2O_3$ and H_2O, dried and evaporated. Ether was added to the residue and the mixture was allowed to stand overnight at 2°. The precipitated starting material (XII) was removed by filtration and the filtrate was concentrated *in vacuo*. The residual crystals (0.5 g) were recrystallized from EtOH to give colorless sticks, mp 151—156°. *Anal.* Calcd. for $C_{15}H_{13}ONS$: C, 70.58; H, 5.13; N, 5.49; S, 12.54. Found: C, 70.30; H, 5.18; N, 5.51; S, 12.50. Identity with VIIb obtained above was shown by IR and NMR spectra comparison.

Reaction of XIIIa (R_1=$C_6H_5CH_2$, X=Cl) with IIc (R=-  -Cl)——To an ice cooled mixture of XIIIa (1.5 g, 6.64 mmole) and IIc (1.9 g, 6.87 mmole) in DMF (30 ml) Et_3N (1.4 g, 13.85 mmole) was added dropwise in nitrogen atmosphere and the mixture was stirred at 1—2° for 1.5 hr. After allowing the mixture to stand overnight at room temperature, DMF was removed *in vacuo* at 43°, and residual crystals were collected with ether and recrystallized from ether–EtOH–acetone affording XIVa (0.88 g) as colorless prisms, mp 143—146°. *Anal.* Calcd. for $C_{22}H_{21}O_4NSPCl_2$: C, 52.59; H, 5.22; N, 2.79; P, 6.17. Found: C, 52.41; H, 5.46; N, 2.69; P, 6.00. A mixture of XIVa (0.88 g) and the mother liquor from the recrystallization was concentrated *in vacuo*. The residue was dissolved in a mixture of EtOH (20 g) and 10% NaOH (15 g), and refluxed for 1 hr. EtOH was removed *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and concentrated leaving an oily residue. The residue was washed with petroleum ether and submitted to Al_2O_3 chromatography. Elution with ether gave XVa (1.2 g), 54.6% from XIIIa) as crystals, mp 111—115°. Recrystallization from EtOH gave colorless crystals, mp 113—116°. *Anal.* Calcd. for $C_{18}H_{16}ONSCl$: C, 65.53; H, 4.89; N, 4.24; S, 9.72. Found: C, 65.80; H, 4.94; N, 4.34; S, 9.07.

Reaction of XIIIa (R_1=$C_6H_5CH_2$, X=Cl) with IId (R=-  -Me)——To an ice cooled mixture of XIIIa (1.1 g, 5 mmole) and IId (1.3 g, 5.07 mmole) in DMF (30 ml) Et_3N (1.0 g, 9.9 mmole) was added dropwise and the mixture was stirred at 1—2° for 5 hr. After standing at 10° for 3 days, the reaction mixture was concentrated *in vacuo* to leave oily residue which was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and H_2O successively, dried, and concentrated leaving oily residue. The residue was chromatographed on aluminium oxide (AcOEt) yielding XVb (0.91 g, 59%) as yellowish brown oil. *Anal.* Calcd. for $C_{19}H_{19}ONS$: N, 4.53. Found: N, 4.41. IR $\lambda_{max}^{CCl_4}$ cm^{-1}: 1675 (C=O).

Reaction of XIIIb (R_1=Me, X=I) with IIe ($R=CH_2C_6H_5$)——To a mixture of XIIIb (2.0 g, 8.3 mmole) and IIe (2.15 g, 8.4 mmole) in DMF (30 ml), Et_3N (1.7 g, 16.8 mmole) was added dropwise at 1—2° for 2 hr. The mixture was allowed to stand overnight at room temperature, then DMF was removed *in vacuo* at 42° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O successively, dried over Na_2SO_4 and evaporated. The residual oil was crystallized from AcOEt slowly. The resulting light brown crystals were collected (1.15 g, 27.9%). Recrystallization from AcOEt–acetone yielded light brown plates, mp 122—124° (decomp.). *Anal.* Calcd. for $C_{17}H_{25}O_4NSPI$ (XVIc): C, 41.06; H, 5.07; N, 2.82; P, 6.24. Found: C, 41.35; H, 5.24; N, 2.46; P, 6.06. IR λ_{max}^{Nujol} cm^{-1}: 1270 (P=O), 1033, 965 (P-O-C). The mother liquors from the first and second crystallization of XIVc were mixed and the concentrated *in vacuo*. The residue was dissolved in a mixture of EtOH (6 g) and 10% NaOH (6 g) and stirred at room temperature for 1 hr. After evaporation, the residue was extractes with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. The oily residue was chromatographed over aluminium oxide and eluted with ether giving XVc (47 mg, 2.4%) as a pale yellow oil. IR λ_{max}^{film} cm^{-1}: 1660 (C=O).

2-Phenyl-3-oxo-4-benzyl-5-methyl-6-(2-*m*-bromobenzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine(IV'a)——To a solution of 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thaizine[3b] (10.0 g, 29.4 mmole) in pyridine (100 ml) was added *m*-bromobenzoyl chloride (10.0 g, 45.5 mmole) with stirring under cooling and the mixture was stirred for 1 hr at room temperature. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$ and washed with 1N $NaHCO_3$, 1N HCl, and H_2O successively, then dried over Na_2SO_4. The resulting oil after evaporation of $CHCl_3$ was crystallized from MeOH to give colorless crystals, mp 80—82°. Yield 13.1 g (85.3%). *Anal.* Calcd. for $C_{27}H_{24}O_3NSBr$: C, 62.06; H, 4.63; N, 2.68; Br, 15.28. Found: C, 61.94; H, 4.76; N, 2.72; Br, 15.52. IR λ_{max}^{Nujol} cm^{-1}: 1715, 1657 (C=O).

2-Phenyl-3-oxo-4-benzyl-5-methyl-6-(2-*p*-bromobenzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (IV''a)——Treatment as above using 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine[3b] (5.0 g, 14.7 mmole), *p*-bromobenzoyl chloride (6.4 g, 29.1 mmole) and pyridine (50 ml) gave IV''a (5.4 g, 73.1%), mp 93—95.5° (from MeOH). *Anal.* Calcd. for $C_{27}H_{24}O_3NSBr$: C, 62.06; H, 4.63; S, 6.14; Br, 15.28. Found: C, 61.99; H, 4.59; S, 6.09; Br, 15.00.

Oxidation of IVa, IV'a and IV''a with H_2O_2——To the solution of IV (20 mmole) in AcOH (90 ml) was added 30% H_2O_2 (20 mmole) at 20° with stirring, the stirring was continued for 2 hr, then the mixture was allowed to stand overnight at room temperature. After removal of the solvent the remaining oil was dissolved in $CHCl_3$ and the solution washed with 10% $KHCO_3$ and H_2O successively, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on aluminium oxide. After full elution with AcOEt and $CHCl_3$, the zone which still retained on the alumina column was eluted with $CHCl_3$ containing 5% MeOH to give yellowish brown oil, which was crystalliz ed from ether. The crude product was purified by recrystallization.

XIXa: mp 121—123° (MeOH), Yield 15.0%. *Anal.* Calcd. for $C_{27}H_{25}O_4NS$: C, 70.55; H, 5.48; N, 3.05; O, 13.92; S, 6.98. Found: C, 70.55; H, 5.63; N, 3.16; O, 13.94; S, 6.96.

XIX'a: mp 125—126° (MeOH), Yield 8.3%. *Anal.* Calcd. for $C_{27}H_{24}O_4NSBr$: C, 60.21; H, 4.49; N, 2.60; S, 5.95; Br, 14.94. Found: C, 60.14; H, 4.61; N, 2.61; S, 6.05; Br, 14.95. NMR τ: 8.17^s (CH_3), 7.55 (CH_2), 5.98 (OCH_2), 4.87^s (OH), 5.32, 4.40 (AB-q, J=16.0, NCH_2), 2.75^s ($C_6H_5CH_2$), 2—3^m (C_6H_5, C_6H_4).

XIX''a: mp 109—111° (aq. EtOH), Yield 17.9%. *Anal.* Calcd. for $C_{27}H_{24}O_4NSBr$: C, 60.21; H, 4.49; N, 2.60; O, 11.88; Br, 14.94. Found: C, 60.25; H, 4.59; N, 2.47; O, 11.92; Br, 14.95. IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 1721 (O–C=O), 1634 (C=O). NMR τ: 8.20^s (CH_3), 7.55 (CH_2), 5.95 (OCH_2), 5.33, 4.40 (AB-q, J=16.3, NCH_2), 4.88^s (OH), 2.77^s ($C_6H_5CH_2$), 2.3—3.0^m (C_6H_5, C_6H_4).

2-Hydroxy-2-phenyl-2-oxo-4-benzyl-5-methyl-6-(2-hydroxy)ethyl-2,3-dihydro-4H-1,4-thiazine (XXa)——A solution of XIXa (400 mg, 0.87 mmole) EtOH containing 5% KOH (10 ml) was heated at 50° for 2 hr. After addition of water, the reaction mixture was concentrated under reduced pressure. The remaining aqueous layer was saturated with CO_2 under cooling, and then extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated to give a colorless amorphous residue which was crystallized from ether, mp 75—78°. Yield 180 mg (58.2%). *Anal.* Calcd. for $C_{20}H_{21}O_3NS$: C, 67.56; H, 5.95; N, 3.94; S, 9.02. Found: C, 67.39; H, 6.15; N, 3.98; S, 8.95. NMR τ: 2.72 ($C_6H_5CH_2$), 5.28, 4.43 (AB-q, J=16.0, NCH_2), *ca.* 4.8^s (OH), 7.73 (CH_2), 6.63 (OCH_2), 8.17^s (CH_3), *ca.* 2.6^m (C_6H_5).

Treatment of 2-Hydroxy-2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (XIXa) with HCl——A solution of XIXa (500 mg, 1.088 mmole) in EtOH containing 10% HCl (75 ml) was heated at 30° for 3 days. After addition of H_2O, the reaction mixture was concentrated under reduced pressure. The aqueous layer remaining was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with 1N $NaHCO_3$. After evaporation of the $CHCl_3$ the residual oil was chromatographed on SiO_2 (Davison Chem. Co., 60—200 mesh). Elution with $CHCl_3$ gave colorless crystals, mp 98—100° (recrystallized from aq. EtOH), which were identical with N-phenylglyoxyloylbenzylamine (XXII). Yield 40 mg (15.4%).

N-Phenylglyoxyloylbenzylamine (XXII)——To a solution of benzylamine (1.0 g, 9.35 mmole) in pyridine (10 ml) phenylglyoxyloyl chloride (437 mg, 2.59 mmole) was added dropwise under cooling. The mixture was then stirred at room temperature for 1 hr and allowed to stand overnight. After removal of the pyridine, the residue was dissolved in $CHCl_3$, and the solution washed with 1N HCl, 1N $NaHCO_3$ and H_2O successively, then dried over Na_2SO_4. After evaporation of the solvent, the resulting crystals were recrystallized from aqueous EtOH. mp 98—100°, Yield 241 mg (39.0%). *Anal.* Calcd. for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.49; H, 5.56; N, 5.75.

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