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Synthesis of 1,5-Benzothiazepine Derivatives. I

Hiroshi Kugita, Hirozumi Inoue, Muneyoshi Ikezaki and Satoshi Takeo

Organic Chemistry Research Laboratory of Tanabe Seiyaku Co., Ltd.[1]

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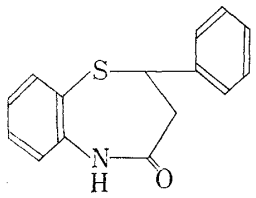
Reaction of 2-aminothiophenols and phenylglicidic esters gave 2-hydroxy-3-(2-aminophenylthio)-3-phenyl-propionic esters (VI) and 2-phenyl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (VII). Hydrolysis of the amino esters (VI) to the amino carboxylic acids (VIII) and cyclization of the amino acids gave satisfactory yield of the cyclic amides (VII).

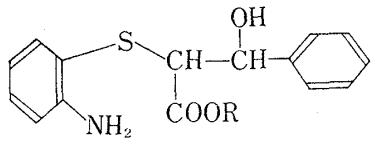
Reaction of 2-nitrothiophenols (XII) and phenylglicidic esters (V) was also studied.

Rearrangement of VIIa to 2-benzilidene-3-keto-benzothiazine (XV) was presented.

Mills and co-workers[2] synthesized 2-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (I) by the reaction of 2-aminothiophenol with cinnamic acid, and later Krapcho and co-workers[3] obtained 2-phenyl-1,5-benzothiazepin-4(5H)-one by similar reaction of 2-aminothiophenol with phenylpropiolic acid. The present authers have synthesized new 1,5-benzothiazepine derivatives which have hydroxy group at 3-position by employing novel reaction of phenylglycidic esters.

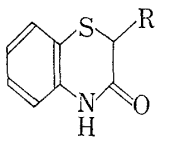


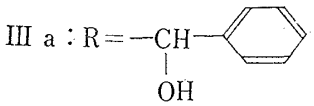
I



II a : R=K

II b : R=C_2H_5



III a : R= 

III b : R=H

Chart 1

Reaction of 2-Aminothiophenol with Phenylglycidic Esters

Culvenor and co-workers[4] reported that reaction of 2-aminothiophenol with ethyl 3-phenylglycidate (V: R=Et, R′=H) in the presence of potassium hydroxide in ethanol at an elevated temperature gave three products, potassium 2-(2-aminophenylthio)-3-hydroxy-3-phenylpropionate (IIa), 2-(α-hydroxybenzyl)-3-keto-dihydrobenzothiazine (IIIa) and 3-keto-dihydrobenzothiazine (IIIb). Further, Owen and co-workers[5] assigned ethyl 2-(2-aminophenylthio)-3-hydroxy-3-phenylpropionate (IIb) to the product obtained by similar reaction on the basis of infrared (IR) spectrum.

It was found, however, by the present authors that reaction of equimolar amounts of 2-aminothiophenol (IV: X=H) and ethyl 3-phenylglycidate (V: R=Et, R′=H) at 150—160°

1) Location: *Shimotoda 2-2-50, Toda, Saitama.*
2) W.H. Mills and J.B. Whitworth, *J. Chem. Soc.*, **1927**, 2738.
3) J. Krapcho and C.F. Turk, *J. Med. Chem.*, **9**, 191 (1966).
4) C.C.J. Culvenor, W. Davies and N.S. Heath, *J. Chem. Soc.*, **1949**, 278.
5) T.C. Owen, C.L. Gladys and L. Field, *J. Chem. Soc.*, **1962**, 656.

for 6 hours gave two products. Their melting points, 87—90° and 195—199° respectively, indicated that these two products should not be identical with any of the products reported by Culvenor. One of the two products, mp 87—90°, was soluble in diluted hydrochloric acid, and IR spectrum showed an absorption of ester-carbonyl at 1725 cm^{-1}. Hydrolysis of this amino ester with diluted sodium hydroxide and heating of the resultant acid in boiling xylene gave a product identical with the other product of higher melting point. The latter was assigned to a cyclic amide structure on the basis of its IR spectrum and elemental analysis. Hydrolysis of this cyclic amide with hot 5% NaOH[6] gave amino acid identical with that obtained by the hydrolysis of the amino ester.

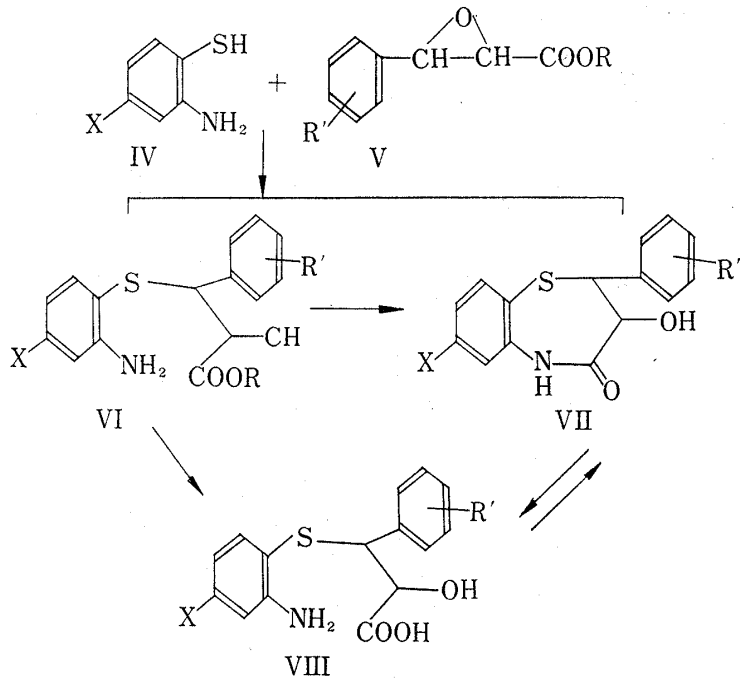


Chart 2

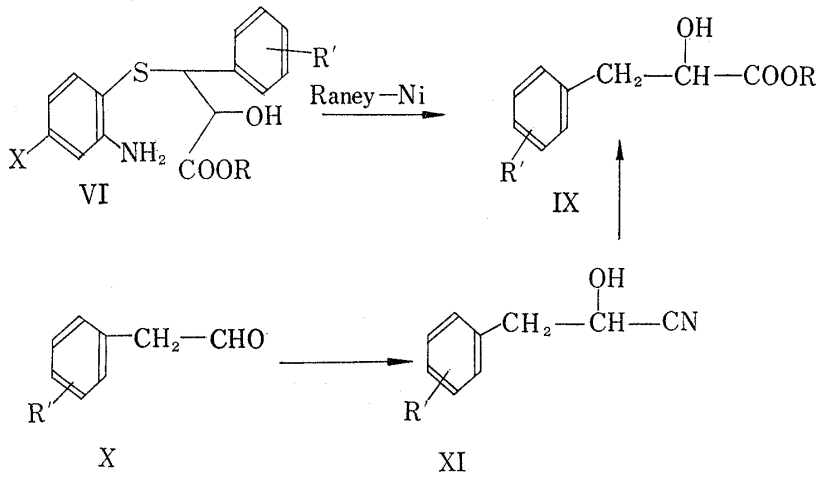


Chart 3

6) Such a treatment of 2-(α-hydroxybenzyl)-3-keto-dihydrobenzothiazine (IIIa) having six membered ring system gave benzaldehyde by the letro aldol condensation together with sodium 2-aminophenylthioacetic acid which was converted to 3-keto-dihydrobenzothiazine (IIIb) by acidification easily. See reference 4.

Table I. Condensation of 2-Aminothiophenol (IV) and Phenylglycidic Ester (V) at 160—165°

	X	R′	R	Amino ester (VI) Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Cyclic amide (VII) Yield (%)
a	H	H	Et	14.4[b]	87—88	$C_{17}H_{19}O_3NS$	64.33	6.03	4.41	64.45	5.80	4.71	13.2
b	H	4-methoxy	Et	5.4	91—92	$C_{18}H_{21}O_4NS$	62.24	6.10	4.03	61.85	5.73	4.00	10.1
c	H	3,4-dimethoxy	Et	35.8	101—102[c]	$C_{19}H_{23}O_5NS$	60.45	6.14	3.71	60.52	5.87	3.77	3.8
d	H	3,4,5-trimethoxy	Me	10.0	134—136	$C_{20}H_{25}O_6NS$	58.00	5.89	3.56	58.18	5.87	3.65	22.1
e	H	4-methyl	Et	35.6	85—87	$C_{18}H_{21}O_3NS$	65.24	6.39	4.23	65.48	6.10	4.08	4.8
f	H	2-chloro	Et	1.5	127—128	$C_{17}H_{18}O_3NSCl$	58.04	5.16	3.98	58.35	4.85	4.05	—
g	H	4-chloro	Et	—	—	—	—	—	—	—	—	—	5.1
h	H	2,4-dichloro	Et	9.5	128—129	$C_{17}H_{17}O_3NSCl_2$	52.85	4.44	3.63	53.14	4.11	3.75	6.0
i	Cl	H	Et	42.9	114—116	$C_{17}H_{18}O_3NSCl$	58.04	5.16	3.98	57.63	5.17	4.21	—
j	Cl	4-methoxy	Et	17.5	121—122	$C_{18}H_{20}O_4NSCl$	56.61	5.28	3.67	56.86	5.15	3.57	—
k	Cl	3,4-dimethoxy	Et	16.9	107—108	$C_{19}H_{20}O_4NSCl$	55.40	5.38	3.40	55.60	5.22	3.53	—
l	Cl	3,4,5-trimethoxy	Me	25.0[d]	117—119	$C_{19}H_{22}O_6NSCl$	53.33	5.18	3.27	53.68	5.00	3.41	—
m	Cl	4-methyl	Et	28.7	131—132	$C_{18}H_{20}O_3NSCl$	59.09	5.51	3.83	58.96	5.45	4.07	—
n	Cl	4-chloro	Et	41.0	120—121	$C_{17}H_{17}O_3NSCl_2$	52.85	4.44	3.63	52.77	4.12	3.65	—
o	Cl	2,4-dichloro	Et	20.6	137—138	$C_{17}H_{16}O_3NSCl_3$	48.53	3.83	3.33	48.45	3.42	3.35	—
p	H	4-methoxy	Me	3.2	93—94[e]	$C_{17}H_{19}O_4NS$	61.25	5.75	4.20	61.07	5.79	4.10	35.5

a) Recrystallized from EtOH.
b) Reaction at 130—140° for 3 and/or 6 hours gave amino ester (VIa) in 24.6% yield.
c) Recrystallized from EtOH–*n*-hexane.
d) Reaction at 160—175° for 5 hours gave amino ester (VIk) and cyclic amide (VIIk) in 24.3% and 6 1% yields respectively.
e) Recrystallized from 70% aq. EtOH.

Desulfurization of the amino ester with Raney-Ni gave ethyl 2-hydroxy-3-phenylpropionate (IXa: R=Et, R′=H) which was identical with an authentic specimen.[7]

From these observations, ethyl 2-hydroxy-3-(2-aminophenylthio)-3-phenylpropionate (VIa: R′=X=H, R=Et) was assigned to the amino ester and 2-phenyl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIIa: X=R′=H) to the cyclic amide.

Table II. Hydrolysis of Amino Ester (VI) to Amino Carboxylic Acid (VIII)

Compds.	X	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIIa	H	H	82.4	165—166[a]	$C_{15}H_{15}O_3NS$	62.28	5.23	4.84	62.60	5.04	4.84
VIIIb	H	4-methoxy	86.0	167—170[a]	$C_{16}H_{17}O_4NS$	60.18	5.39	4.39	59.94	5.13	4.35
VIIIc	H	3,4-dimethoxy	83.0	149—150[b]	$C_{17}H_{19}O_5NS$	58.42	5.48	4.01	58.01	5.14	3.96
VIIId	H	3,4,5-trimethoxy	78.0	195—197[c]	$C_{18}H_{21}O_6NS$	56.98	5.58	3.69	56.56	5.40	3.71
VIIIe	H	4-methyl	91.0	162—163[c]	$C_{16}H_{17}O_3NS$	63.36	5.65	4.62	63.51	5.40	4.49
VIIIh	H	2,4-dichloro	87.3	133—136[b]	$C_{15}H_{13}O_3NSCl \cdot \frac{1}{2}H_2O$	49.06	3.84	3.82	49.08	3.64	3.85
VIIIi	Cl	H	71.8	164—167[c]	$C_{15}H_{14}O_3NSCl$	55.64	4.36	4.33	55.94	4.39	4.80
VIIIj	Cl	4-methoxy	87.0	186—188[a]	$C_{16}H_{16}O_4NSCl$	54.31	4.56	3.96	53.97	4.76	3.81
VIIIk	Cl	3,4-dimethoxy	98.5	157—158[b]	$C_{17}H_{18}O_5NSCl$	53.18	4.73	3.65	53.09	4.62	3.63
VIIIl	Cl	3,4,5-trimethoxy	84.5	178—179[a]	$C_{18}H_{20}O_6NSCl$	52.24	4.87	3.35	52.36	4.69	3.63
VIIIm	Cl	4-methyl	95.0	187—190[a]	$C_{16}H_{16}O_3NSCl$	56.88	4.77	4.15	57.15	4.71	3.94
VIIIn	Cl	4-chloro	93.7	160—164[c]	$C_{15}H_{13}O_3NSCl_2$	50.29	3.66	3.91	50.37	3.67	3.93
VIIIo	Cl	2,4-dichloro	84.5	158—159[a]	$C_{15}H_{12}O_3NSCl_3$	45.87	3.08	3.57	45.69	2.88	3.74

a) Recrystallized from EtOH. *b*) Recrystallized from iso-PrOH. *c*) Recrystallized from aq. EtOH.

Table III. Ring Closure of Amino Carboxylic Acid (VIII) to Cyclic Amide (VII)

Compds.	X	R′	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	H	H	90	194—197	$C_{15}H_{13}O_2NS$	66.40	4.83	5.16	66.42	4.48	5.28
VIIb	H	4-methoxy	63	166—167	$C_{16}H_{15}O_3NS$	63.78	5.02	4.65	63.89	4.71	4.50
VIIc	H	3,4-dimethoxy	89	207—208	$C_{17}H_{17}O_4NS$	61.61	5.17	4.23	61.63	5.01	4.23
VIId	H	3,4,5-trimethoxy	70.3	171—172	$C_{18}H_{19}O_5NS$	59.82	5.30	3.88	59.88	5.19	3.86
VIIe	H	4-methyl	65	196—199	$C_{16}H_{15}O_2NS$	67.36	5.30	4.91	66.83	5.08	4.75
VIIg	H	4-chloro	—[b]	195—197	$C_{15}H_{12}O_2NSCl$	58.91	3.96	4.58	59.28	3.90	4.53
VIIh	H	2,4-dichloro	81.4	193—196	$C_{15}H_{11}O_2NSCl_2$	52.95	3.26	4.12	53.30	2.93	4.18
VIIi	Cl	H	77.3	204—208	$C_{15}H_{12}O_2NSCl$	58.91	3.96	4.58	59.16	4.08	5.10
VIIj	Cl	4-methoxy	61[c]	196—199	$C_{16}H_{14}O_3NSCl$	57.22	4.21	4.17	57.34	3.84	4.23
VIIk	Cl	3,4-dimethoxy	68.5	214—218[d]	$C_{17}H_{16}O_4NSCl$	55.81	4.41	3.83	55.87	4.30	3.82
VIIl	Cl	3,4,5-trimethoxy	57.4[c]	206—212[e]	$C_{18}H_{18}O_5NSCl$	54.60	4.58	3.54	54.58	4.36	3.68
VIIm	Cl	4-methyl	73[c]	195—198	$C_{16}H_{14}O_2NSCl$	60.09	4.41	4.38	60.28	4.20	4.45
VIIn	Cl	4-chloro	67	203—205	$C_{15}H_{11}O_2NSCl_2$	52.95	3.26	4.12	52.60	3.17	4.18
VIIo	Cl	2,4-dichloro	48.5[c]	213—217	$C_{15}H_{10}O_2NSCl_3$	48.08	2.69	3.74	48.24	2.51	3.87

a) Recrystallized from EtOH.
b) VIIg was obtained by condensation of 2-aminothiophenol (IV: X=H) and ethyl 3-(4-chlorophenyl)-glycidate (V: R=Et, R′=4-chloro) shown in Table I.
c) Starting material was recovered.
d) Recrystallized from DMF–EtOH.
e) Recrystallized from aq. EtOH.

7) F. Nerdel and H. Rachel, *Chem. Ber.*, **89**, 671 (1956).

A series of reactions of 2-aminothiophenol and 2-amino-4-chlorothiophenol with various kinds of ring-substituted 3-phenylglycidic esters were carried out under similar condition. The results were summarized in Table I.

Reaction of 2-aminothiophenol (IV: X=H) with ethyl 3-phenylglycidate (V: R=Et, R'=H) at 130—140° for 3 and/or 6 hours gave VIa (X=R'=H, R=Et) only in 24.6% yield. VIa (X=R'=H, R=Et) when heated at 160—165° gave VIIa (X=R'=H) in 32.2% yield together with 33% recovery of the starting material.

In a series of reactions of 2-amino-4-chlorothiophenol (IV: X=Cl) with phenylglycidic esters at 160—165°, amino ester (VI) was obtained as only isolable product or together with very small amount of the cyclic amide (VII) in all cases. The chlorinated amino ester VIi was cyclized to VIIi in 11.5% yield when heated at 170—180° for 3 hours. Thus, it appeared that the chlorinated amino ester is less liable to cyclize to the lactam than the unsubstituted amino ester under the reaction condition.

Cyclization of the amino ester was also effected by heating with acid (H_2SO_4 or HOAc). But hydrolysis of the amino ester (VI) to the amino carboxylic acid (VIII) and cyclization of the amino acid in boiling xylene gave more satisfactory yield of the cyclic amide (VII) (Table II and III).

1,5-Benzothiazepine structure of the cyclic amides listed in Table III was confirmed in each case: a) by the hydrolysis of the lactam (VII) to the corresponding amino carboxylic acid and b) by the desulfurization of the amino ester to respective 2-hydroxy-3-arylpropionic esters (IX), which were identified with authentic samples prepared as shown in Chart 3.

Reaction of 2-Nitrothiophenol with Phenylglycidic Ester

Reaction of 2-nitrothiophenols (XII: X=H, Cl) with ethyl 3-(4-methoxyphenyl)-glycidate (V: R=Et, R'=4-MeO) at 50—60° gave the nitro esters (XIIIb, XIIId). However, the reaction sometimes occured violently at 80—90°. Acetonitrile was found to be a suitable

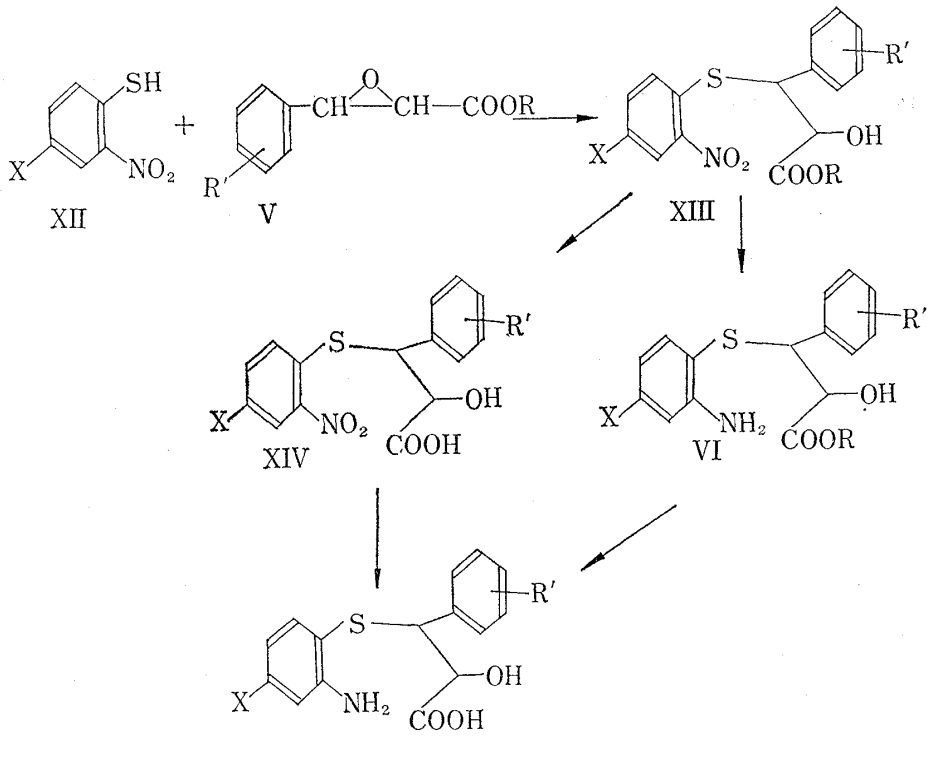


Chart 4

solvent for this reaction and similar yields of the nitro esters were obtained after five days at 20—50°.[8]

Table IV. Condensation of 2-Nitrothiophenol (XII) and Phenylglycidic Ester (V)

Compds.	X	R′	Reaction conditions	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIIIa	H	4-methoxy Me ester	CH_3CN, at 30° 5 days	56.4	157—158[a]	$C_{17}H_{17}O_6NS$	56.19	4.72	3.85	56.92	4.71	3.93
XIIIb	H	4-methoxy Et ester	—, at 50—60° 68 hours	38	101—103[b]	$C_{18}H_{19}O_6NS$	57.29	5.08	3.71	57.31	5.12	3.66
XIIIc	Cl	4-methoxy Me ester	CH_3CN, at 30° 5 days	38.4	118[a]	$C_{17}H_{16}O_6NSCl$	51.32	4.05	3.52	51.31	4.06	3.49
XIIId	Cl	4-methoxy Et ester	CH_3CN, at 30° 65 hours	40[c]	103—105[a]	$C_{18}H_{18}O_6NSCl$	52.49	4.40	3.40	52.34	4.46	3.31
XIIIe	H	3,4-dimethoxy Et ester	CH_3CN, at 45—50° 41 hours	65	gumm	$C_{19}H_{21}O_7NS$	56.02	5.20	3.44	56.29	5.29	3.25

a) Recrystallized from EtOH.
b) Recrystallized from 70% aq. EtOH.
c) In the absence of a solvent, XIIId was obtained in 41.5% yield (at 50—60°).

Table V. Reduction of Nitro Ester (XIII)

	X	R′	R	Yield of VI (%)
a	H	4-methoxy	Me	71 (VIp)
b	H	4-methoxy	Et	86 (VIb)
c	Cl	4-methoxy	Me	63 (VIq)[a]
d	Cl	4-methoxy	Et	85 (VIj)
e	H	3,4-dimethoxy	Et	43 (VIc)

a) Recrystallized from 70% *aq.* EtOH, *Anal.* Calcd. for $C_{17}H_{18}O_4NSCl$: C, 55.50; H, 4.92; N, 3.80. Found: C, 55.43; H, 4.85; N, 3.66.

Table VI. Hydrolysis of Nitro Ester (XIII)

Compds.	X	R′	R	Yield of XIV (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIIIa	H	4-methoxy	Me	87.5	157—159[a] (decomp.)	$C_{16}H_{15}O_6NS$	55.01	4.33	4.01	55.28	4.24	4.19
XIIIb	H	4-methoxy	Et	60								
XIIId	Cl	4-methoxy	Et	57	163—164.5[b] (decomp.)	$C_{16}H_{14}O_6NSCl$	50.07	3.68	3.65	50.17	3.71	3.46
XIIIe	Cl	3,4-dimethoxy	Et	20	163—165[c] (decomp.)	$C_{17}H_{17}O_7NS$	53.81	4.52	3.70	54.07	4.65	3.53

a) Recrystallized from 70% aq. EtOH.
b) Recrystallized from EtOH.
c) Recrystallized from AcOEt–*n*-hexane.

8) Use of other solvents resulted in lower yield (benzene, ether, methyl alcohol, acetone, DMF, DMSO).

The reaction was much dependent on the substituent of phenylglycidic esters. Phenylglycidic esters other than those substituted with methoxy group did not react with 2-nitrothiophenol under similar conditions.

Reduction of XIII with $FeSO_4$–NH_4OH gave the amino esters, identical with VI. Hydrolysis of XIII and reduction of the resultant acid (XIV) gave the amino carboxylic acid, identical with VIII.

The reaction of VIIa with pyridine–$SOCl_2$ afforded known 2-benzylidene-3-keto-benzothiazine (XV)[9] in 14% yield. A rearrangement involving migration of sulfur in three-membered sulfonium ion mechanism (XVI)[10] should be easier to occur than dehydration in this reaction.

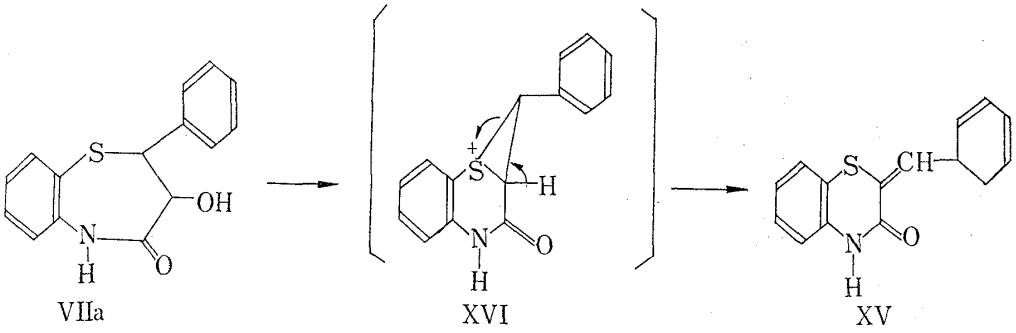


Chart 5

Experimental[11]

Reaction of 2-Aminothiophenol (IV: X=H) and Ethyl 3-Phenylglycidate (V: R′=H, R=Et)——1) A mixture of IV (X=H)[12] (13.6 g) and V (R′=H, R=Et)[13] (20.9 g) was heated with stirring at 120—140° for 1 hour under N_2 and then at 150—160° for 6 hours. The cooled mixture was dissolved in EtOH (20 ml) and allowed to stand at 5° overnight. The precipitated needles were filtered, washed with EtOH and recrystallized from EtOH to give 3.9 g (13.2%) of VIIa (X=R′=H), mp 194—197°, as colourless needles. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3200, 1680, 1640, 1110. UV λ_{max}^{EtOH} $m\mu$ (ε): 245 (14100), 273 (4380).

The mother liquor was evaporated. The solution of residual gumm in benzene was extracted with 10% HCl. The extract was basified with 10% NaOH, extracted with ether. The ether solution was washed with H_2O, dried (Na_2SO_4) and evaporated. The crystal was filtered and recrystallized from ether–*n*-hexane to give VIa (R′=H, X=H, R=Et) (4 g, 14.4%), mp 87—88°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3300—3000, 1725 (Table I).

2) A mixture of IV (X=H) (9.0 g) and V (R′=H, R=Et) (13.8 g) was heated at 130—140° for 3 and/or 6 hours under N_2 and worked up in above described manner to give VIa (R′=X=H, R=Et) (15.7 g, 24.6%). The related condensation was summarized in Table I.

3) The same reaction in diphenyl ether for 6 hours gave VIIa (2.5%) and VIa (10.1%).

Ring Closure of Amino Ester (VI)——1) A solution of VIi (R′=H, R=Et, X=Cl) (4.5 g) in 20% H_2SO_4 (360 ml) was refluxed for 4 hours. After cooling, crystal was collected on a filter and recrystallized from EtOH to give 2.3 g (58.8%) of VIIi (R′=H, X=Cl). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3180, 3100, 1682, 1640. The mother liquor was concentrated and neutralized with 10% NaOH to give 2-hydroxy-3-(2-amino-4-chloro-phenylthio)-3-phenylpropionic acid (VIIIi: R=H, X=Cl) (980 mg, 23.7%), mp 164—167°. IR ν_{max}^{Nujol} cm^{-1}: 3520, 3480, 3390, 1720. 1600.

9) V. Baliah and T. Rangarajan, *J. Chem. Soc.*, **1960**, 4703.
10) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, 1959, p. 561; H.L. Georing and K.L. Howe, *J. Am. Chem. Soc.*, **79**, 6542 (1957).
11) All melting points are uncorrected.
12) M. Onda, M. Kawanishi, S. Onishi, T. Tominaga, Y. Kunugi, M. Sasamoto and M. Susuki, *Yakugaku Zasshi*, **76**, 562 (1956).
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Reaction of VIa (R′=H, R=Et, X=H) gave 2-hydroxy-3-(2-aminophenylthio)-3-phenylpropionic acid (VIIIa: R=X=H) (54.9%), IR ν_{max}^{Nujol} cm^{-1}: 3400, 2600, 1620, 1560, 1590.

2) The solution of VIa (R′=X=H, R=Et) (200 mg) in HOAc (5 ml) was refluxed for 6 hours and worked up in usual manner to give VIIa (R′=X=H) (20 mg, 11.7%), IR ν_{max}^{Nujol} cm^{-1}: 3400, 3220, 1680, 1640, together with starting material (25%).

3) VIa (R′=X=H, R=Et) (1 g) was heated at 160—165° for 6 hours. The crystalline product was obtained from the solution of the resulting gumm in small amount of EtOH and recrystallized from EtOH to give VIIa (R′=X=H) (275 mg, 32.2%), mp 198—200°. Starting material was recovered from mother liquor (33%).

VIi (R′=H, X=Cl, R=Et) (1 g) was heated at 170—180° for 3 hours and worked up in similar manner to give VIIi (R′=H, X=Cl), (100 mg, 11.5%), mp 204—208°.

2-Hydroxy-3-(2-aminophenylthio)-3-arylpropionic Acid (VIII) (Hydrolysis of Amino Esters (VI))——A mixture of amino esters (1 g) and 5% NaOH (10—20 ml) was heated on steam bath until all of amino ester dissolved. The resultant clear solution was neutralized with 10% HCl. The precipitated crystal was collected and recrystallized to give amino carboxylic acid (VIII). This result was summarized in Table II.

2-Aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VII) (Ring Closure of Amino Carboxylic Acid)——The amino carboxylic acid (VIII) (1 g) was refluxed in xylene (20—30 ml) in a flask fitted with a Dean–Stark trap. After cooling, the crystalline product was collected on a filter and recrystallized to give VII. Starting material was recovered from mother liquor. The result was listed in Table III.

Hydrolysis of VII——The suspension of VIIa (X=R′=H) (180 mg) in 5% NaOH (12 ml) was heated on steam bath for 1.5 hours. The insoluble starting material was filtered off (10 mg). The mother liquor was neutralized to pH 5—6 with 1% HCl to give amino carboxylic acid VIIIa (R′=X=H) (140 mg, 72.7%), mp 158—161°, as colourless needles (from EtOH).

The others of VII were worked up in a similar manner to give corresponding amino carboxylic acids in satisfactory yields.

Desulfurization of Amino Ester (VI)——1) Ethyl 2-hydroxy-3-(2-aminophenylthio)-3-phenylpropionate (VIa: R′=X=H, R=Et) (1 g) and Raney–Ni (w-7) (7 ml) in EtOH (20 ml) were refluxed for 1.3 hours. After cooling, Raney–Ni was filtered off and washed with EtOH. The filtrate was evaporated, dissolved in ether, washed with 5% HCl and water, dried, evaporated and distillated to give ethyl 2-hydroxy-3-phenylpropionate (IXa: R′=H, R=Et), bp 145—149° (13 mmHg), (500 mg, 81.8%), identified with an authentic specimen.[7] IR ν_{max}^{nujol} cm^{-1}: 3540, 1730. Amide: mp 107—108° (benzene). Ethyl 2-hydroxy-3-(2-amino-4-chlorophenylthio)-3-phenylpropionate (VIi: R′=H, R=Et, X=Cl) was worked up in similar manner to give Xa (R′=H, R=Et) also in 80% yield.

2) Methyl 2-hydroxy-3-(2-aminophenylthio)-3-(3,4,5-trimethoxyphenyl)-propionate (VId: R′=3,4,5-tri-MeO, R=Me, X=H) (500 mg) was desulfurized in above described method. The resultant oil was chromatographed on Al_2O_3.

The first eluate with $CHCl_3$ gave methyl 3,4,5-trimethoxy-cinnamate (35 mg, 22%), mp 94—96° (from ether–*n*-hexane), as colourless pilars, identified with an authentic specimen. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1625.

The next eluate with $CHCl_3$–EtOH (9:1) gave the desulfurized product IXb (R=Me, R′=3,4,5-tri-MeO) (20 mg, 11.7%), mp 73.5—75° (from ligroin) as colourless needles. IR ν_{max}^{Nujol} cm^{-1}: 3400, 1720. *Anal.* Calcd. for $C_{13}H_{18}O_6$: C, 57.75; H, 6.71. Found: C, 57.52; H, 6.74.

VII (R′=3,4,5-tri-MeO, R=Me, X=Cl) gave similar result.

3) Ethyl 2-hydroxy-3-(2-aminophenylthio)-3-(2,4-dichlorophenyl)-propionate (VIh: R′=2,4-di-Cl, R=Et, X=H) (300 mg) gave ethyl 2-hydroxy-3-(2,4-dichlorophenyl)-propionate (IXc: R′=2,4-di-Cl, R=Et), bp 165—175° (8 mmHg), (135 mg, 66%). IR ν_{max}^{liquid} cm^{-1}: 3520, 1725. IXc was converted to the amide with NH_3–EtOH at room temperature, mp 161—163° (from iso-PrOH), colourless plates. IR ν_{max}^{Nujol} cm^{-1}: 3550, 1725. *Anal.* Calcd. for $C_9H_9ONCl_2$: C, 46.17; H, 3.88; N, 5.98. Found: C, 46.25; H, 3.87; N, 5.82. VIo (R′=2,4-di-Cl, R=Et, X=Cl) gave the same product (80%).

4) Methyl 2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate (VIp: R=Me, X=H, R′=4-MeO) (500 mg) was desulfurized in usual manner to give IXd (R′=4-MeO, R=Me), bp_5 140—145° (260 mg, 82.5%). IR ν_{max}^{liquid} cm^{-1}: 3450, 1728. IXd (250 mg) was hydrolyzed with EtOH (1.5 ml) and 5% NaOH (1.5 ml) at room temperature overnight to give 2-hydroxy-3-(4-methoxyphenyl)-propionic acid (from benzene), mp 102—103° as colourless prisms (200 mg, 82%). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1710. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.17; H, 6.18.

VIj (R′=4-MeO, X=Cl, R=Et) was converted to IXd (R′=4-MeO, R=Et) in 70% yield.

$NaHSO_3$-adduct of 2,4-Dichlorophenyl Acetaldehyde (Xc)——To the solution of ethyl 3-(2,4-dichlorophenyl)-glycidate (V: R′=2,4-di-Cl, R=Et) (11 g) in abs. benzene was added equimolar amounts of NaOEt and then equimolar amounts of water, and diluted with ether. The precipitated Na salt was filtered (10.3 g).

The suspension of Na salt (2.6 g) in benzene was shaken in a separate funnel and extracted with ether. The organic layer was washed with water, dried and evaporated. The solution of residue in HOAc (200 ml) was refluxed for 1.5 hours and evaporated. The residue in ether was washed with water and stirred vigorously with $NaHSO_3$ (2 g) in water (3 ml) for 40 hours at room temperature to give $NaHSO_3$-adduct of Xc (R′=2,4-di-Cl) (1.4 g, 46.9%), mp 170—175° (decomp.). 2,4-Dichlorophenylacetaldehyde semicarbazone; mp 181—

182° (from EtOH), colourless needles. *Anal.* Calcd. for $C_9H_9ON_3Cl_2$: C, 43.93; H, 3.69; N, 17.09. Found: C, 44.03; H, 3.71; N, 16.96.

Ethyl 2-Hydroxy-3-(2,4-dichlorophenyl)-propionate (IXc: R=Et, R′=2,4-di-Cl)——The $NaHSO_3$–adduct of Xc (R′=2,4-di-Cl) (1 g) was added to a solution of KCN (1 g) in water (1 ml) and ether (5 ml) at 0—5°, and stirred at room temperature for 2 hours. The ether layer was separated, dried and evaporated to give cyanohydrin (0.53 g, mp 108—112°), IR ν_{max}^{Nujol} cm^{-1}: 3360, 2280.

The cyanohydrin (160 mg) was stirred with 5% HCl–EtOH (1 ml) and abs. ether (5 ml) at room temperature overnight. To the resultant solution was added equimolar amounts of water and then neutralized with K_2CO_3 (1 g) and evaporated *in vacuo* and worked up in usual manner to give IXc (R=Et, R′=2,4-di-Cl) (70 mg, 36%).

Methyl 2-Hydroxy-3-(3,4,5-trimethoxyphenyl)-propionate (IXb: R=Me, R′=3,4,5-tri-MeO)——The $NaHSO_3$–adduct of 3,4,5-trimethoxyphenyl acetaldehyde (Xb: R′=3,4,5-tri-MeO)[14] (1 g) was worked up in above described manner to give cyanohydrin (320 mg, 42.4%). IR ν_{max}^{Nujol} cm^{-1}: 3180, 2260. The resultant cyanohydrin (150 mg) was hydrolyzed to give IXb (R=Me, R′=3,4,5-tri-MeO) (70 mg, 40.7%), mp 71—72°.

2-Hydroxy-3-(4-methoxyphenyl)-propionic Acid——To ethyl 3-(4-methoxyphenyl)-glycidate (V: R=Et, R′=4-MeO) (4 g) in benzene (20 ml) was added NaOMe (Na 0.415 g, MeOH 5 ml) and then water (0.36 ml) to give Na salt (3.3 g, 85%). The Na salt was heated in benzene (10 ml) and AcOH (0.96 g) for 2 hours. After cooling, the benzene solution was washed with water, dried and evaporated. The residue was stirred with $NaHSO_3$ (1.6 g), water (3.2 ml) and ether (7 ml) at room temperature for 5 hours to give $NaHSO_3$-adduct of Xd (R′=4-MeO) (2.16 g).

The adduct was stirred in a solution of KCN (2.16 g), water (3 ml) and ether (10 ml) at room temperature overnight. The obtained cyanohydrin (1.07 g) was hydrolyzed with 5% HCl–EtOH (10 ml) at room temperature overnight. The mixture was worked up in usual manner to give IXd (R′=4-MeO, R=Et), bp 135—140° (13 mmHg). IXd was converted with NaOH to 2-hydroxy-3-(4-methoxyphenyl)-propionic acid (0.6 g), mp 102—103°.

Condensation of 2-Nitrothiophenol (XII) and Glycidic Ester (V)——1) A mixture of 2-nitrothiophenol (XII: X=H)[15] (3 g) and ethyl 3-(4-methoxyphenyl)-glycidate (V: R=Et, R′=4-MeO) (4.3 g) was heated at 50—60° for 68 hours under N_2.

The resultant mixture was dissolved in EtOH. Insoluble disulfide was filtered off (0.07 g, mp 186—190°). The mother liquor was evaporated and dissolved in ether, washed with dil. $NaHCO_3$ and water, dried and evaporated. The residue was recrystallized from EtOH to give ethyl 2-hydroxy-3-(2-nitrophenylthio)-3-(4-methoxyphenyl)-propionate (XIIIb: R=Et, R′=4-MeO, X=H) (2.65 g, 38%), mp 97—99°, colourless needles. IR ν_{max}^{Nujol} cm^{-1}: 3480, 1725, 1510, 1340.

2) A mixture of 2-nitrothiophenol (XII, X=H) (787 mg), methyl 3-(4-methoxyphenyl)-glycidate (V: R=Me, R′=4-MeO) (1.21 g) and CH_3CN (2.5 ml) was stirred at 30° for five days. The precipitated crystal was collected and washed with di-isopropylether (2 ml), and recrystallized from EtOH to give methyl 2-hydroxy-3-(2-nitrophenylthio)-3-(4-methoxyphenyl)-propionate (XIIIa: R=Me, R′=4-MeO, X=H) (1.04 g, 56.4%), mp 154—156°. IR ν_{max}^{Nujol} cm^{-1}: 3510, 1730, 1513, 1345.

The result was summarized in Table IV.

Reduction of Nitro Ester (XIII)——A mixture of methyl 2-hydroxy-3-(2-nitrophenylthio)-3-(4-methoxyphenyl)-propionate (XIIIa: R=Me, R′=4-MeO, X=H) (1.25 g), $FeSO_4$–$7H_2O$ (8.60 g) and 50% MeOH–H_2O (v/v) (40 ml) was refluxed for 30 min. To the refluxing mixture was added dropwise conc. NH_4OH (5 ml) for 15 min. The mixture was refluxed for additional 10 min under stirring, extracted with AcOEt, dried and evaporated. The residue was recrystallized from 70% EtOH to give amino ester VIp (R=Me, R′=4-MeO, X=H) (842 mg, 73.6%), mp 93—94° (Table V).

Hydrolysis of Nitro Ester (XIII)——A suspension of methyl 2-hydroxy-3-(2-nitrophenylthio)-3-(4-methoxyphenyl)-propionate (XIIIa: R=Me, R′=4-MeO, X=H) (2.02 g) in 5% NaOH (10 ml) and EtOH (30 ml) was stirred at room temperature for 1 hour. After separating of insoluble starting material by filtration, the solution was diluted with water (160 ml), acidified with 10% HCl to give 2-hydroxy-3-(2-nitrophenylthio)-3-(4-methoxyphenyl)-propionic acid (XIVa: R′=4-MeO, X=H) (1.70 g, 875%). IR ν_{max}^{Nujol} cm^{-1}: 3400, 2600, 1710 (Table VI).

Reduction of Nitro Carboxylic Acid (XIV)——A solution of XIVa (R′=4-MeO, X=H) (200 mg) in HOAc (10 ml) was hydrogenated with 10% Pd–C (40 mg) at ordinary temprature and pressure, and worked up in usual manner to give VIIIb (R′=4-MeO, X=H) (113 mg, 61.8%), mp 172—175°.

Hydrogenation in HOAc or MeOH with PtO_2 or reduction with Zn-HOAc gave VIIIb (R′=4-MeO, X=H) in 22—55% yield. IR ν_{max}^{Nujol} cm^{-1}: 3250, 2600, 1620, 1585, 1560.

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Reduction of XIVb (R′=4-MeO, X=Cl) with $FeSO_4$-NH_4OH in above described method to give VIIIj (R′=4-MeO, X=Cl) in 10% yield.

Reaction of VIIa with $SOCl_2$-Pyridine——To a solution of 2-phenyl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIIa: X=R′=H) (540 mg) in pyridine (15 ml) was added $SOCl_2$ (240 mg) at 0—5°. The mixture was stirred at room temperature for 2 days, then at 50—55° for 4 hours and evaporated *in vacuo*. The precipitated crystal from a solution of the residue in a small amount of benzene was collected on a filter (mp 160—180°) and recrystallized from EtOH to give benzylidene-3-keto-benzothiazine (XV) (72 mg, 14%), mp 194—199° and starting material (180 mg, 33.3%), mp 194—199°. XV was identified with an authentic sample.[9]

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