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Synthesis of 1,5-Benzothiazepine Derivatives. II[1]

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Threo-2-hydroxy-3-aryl-(2-nitroarylthio)propionates (III-β) were obtained by the reaction of 2-nitrothiophenols (I) and arylglycidic esters (II) in the presence of catalytic amount of $NaHCO_3$. Conversion of III-β to 1,5-benzothiazepine derivatives (VI-β), the configuration of which was 2,3-*trans*, was satisfied by the similer method as that in our previous paper.

Synthesis of 2-hydroxy-3-aryl-(2-nitroarylthio)-propionates (III-α) by the reaction of 2-nitrothiophenols (I) and arylglycidic esters (II), and conversion of III-α to 1,5-benzothiazepine structure (VI-α) were described in our previous paper.[1] In this paper we wish to report the synthesis and stereochemstry of the diastereoisomeric nitro-ester (III-β) and the corresponding 1,5-benzothiazepine derivatives (VI-β) derived from III-β.

Reaction of I with II in the presence of catalytic amount of $NaHCO_3$ or BF_3 gave the nitro-ester derivative (III-β), which was different from III-α previously obtained.[1,5] From infrared (IR) spectrum and elemental analysis, III-β was found to be an isomer of III-α.

In order to prove the structure, III-β was reduced following the procedure previously employed[1] to give the amino ester (IV—β). Desulfurization of the amino ester by Raney-Ni gave VII, identical with a sample previously obtained from IV-α[1] III-β was thus ascertained to be a diastereoisomer of III-α.

The amino-ester (IV-β) gave the corresponding 1,5-benzothiazepine structure (VI-β) through the same synthetic route as that employed for VI-α.[1]

Stereochemistry of these two diastereoisomers was investigated.

The lactams VI_a-α and VI_a-β were methylated with CH_3I and then acetylated to give IX_a-α and IX_a-β respectively. When treated with NaH in dioxane at 50—55°, α-system IX_a-α gave a compound of mp 84°. The spectral data, IR ν_{max}^{Nujol} cm^{-1} : 1642, 1580. NMR in $CDCl_3$ τ: 6.43 (3H, singlet), 3.47 (1H, singlet), 3.0—2.0 (5H, multiplet), suggested the structure X_a. Comparison with an authentic sample prepared according to Krapcho's method,[3] followed by methylation confirmed the structure. Benzothiazine derivative (XII_a) was also prepared from $XIII_a$ (synthesized by Baliah's method[4]) and proved to be different from X_a.

On the other hand IX_a-β gave the hydrolyzed product ($VIII_a$) as only an isolable product by the similar reaction in 81.7% yield.

As it is ordinary that trans elimination occurs by base catalyzed reaction, stereochemical relation between 2-H and 3-OH of the α-system compound would be trans and that between 2-Ph and 3-OH *cis*, and *vice versa* for the β-system compound which never caused the elimination.

Stereochemistry of the two series lactams was also investigated by spectral data.

Two conformation, A and A', are possible for the trans (2-aryl and 3-hydroxy) form of the 1,5-benzothiazepine ($VIII_a$-β) and likewise B and B' for the cis form ($VIII_a$-α). In a high

1) Part I: H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2028 (1970).
2) Location: *Shimotoda 2-2-50, Toda-shi, Saitama.*
3) J. Krapcho and C.F. Turk, *J. Med. Chem.*, **9**, 191 (1966).
4) V. Baliah and T. Rangarajan, *J. Chem. Soc.*, **1960**, 4703.
5) III_a-α could not be obtained.

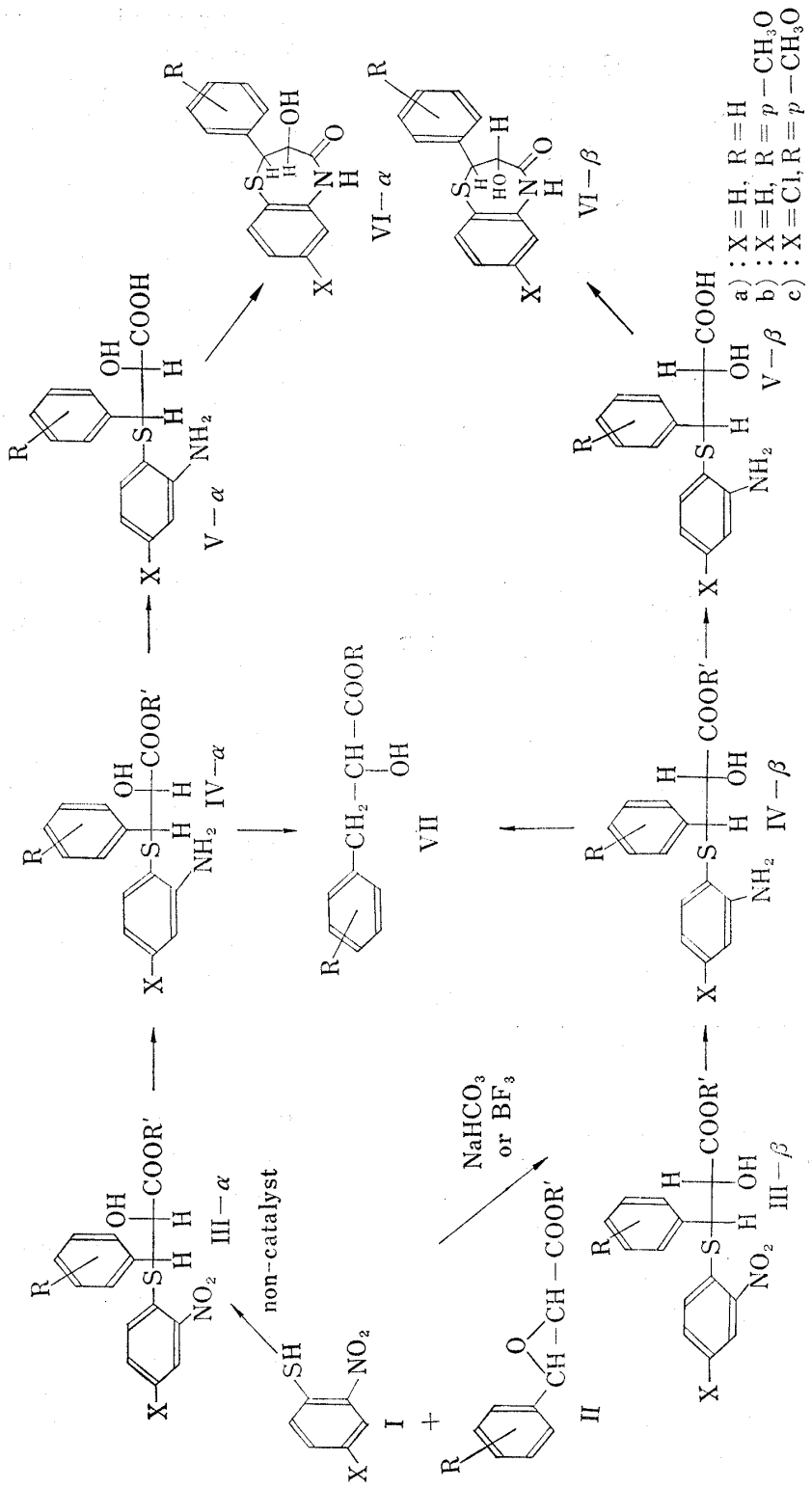
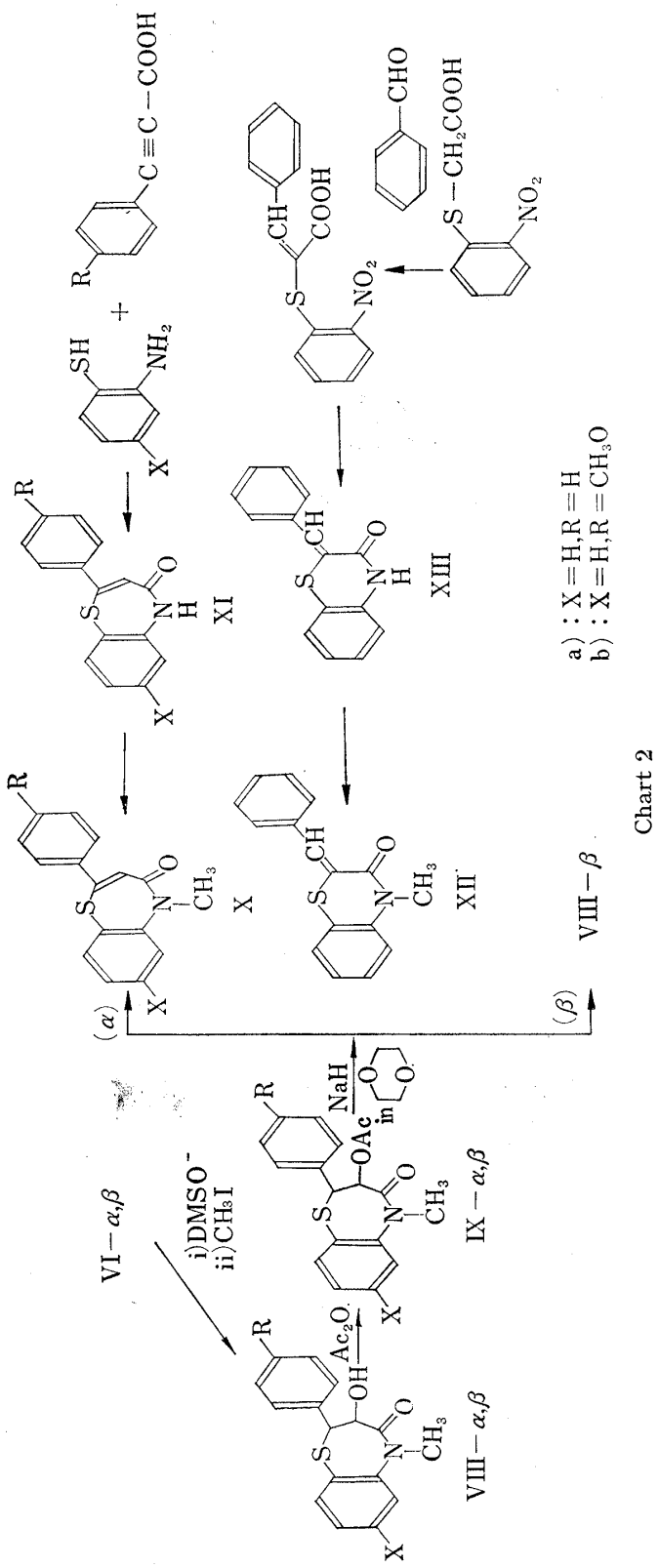


Chart 1

dilution IR spectrum a weak intramolecular hydrogen bond of OH---O=C< could be observed at 3460 cm^{-1} in $VIII_a$-α and 3440 cm^{-1} in $VIII_a$-β respectively.

It may be that A and B are the probable conformations of the two respectively. In NMR spectrum ($CDCl_3$) signals of C_2-H (H_a) and C_3-H (H_b) were shown as a doublet respectively; $J_{2,3}$=7 cps in $VIII_a$-α and IX_a-α, 11 cps in $VIII_a$-β and IX_a-β. The larger coupling constant is only possible with the conformation A, which is taken by 2,3-*trans* compound. The elimination reaction of the α-compound as described previously could be possible only when



the compound took the conformation B′, namely the α-compound should be 2,3-*cis*. On the other hand, the *trans* compound can never take a conformation so as to make anti-coplaner the leaving groups (H_a and acetoxy group). This coinsides with the fact that IX_a-β never produced elimination product. Thus stereochemical relationship of the two isomeric compounds was established.

The stereochemical relationship was also investigated likewise for the (b) and (c) series benzothiazepines respectively following method described above to give similar results.

It is well-known that glycidic esters synthesized by Darzens's reaction are *trans*.[6] Nucleophilic reaction of an anion to the glycidic ester ordinarily occurs with inversion.[7] As to the reaction mechanism producing the α-system compound, it may be that the SH group reacts with the epoxide through a four-center mechanism, and consequently the arylthio group enters into the glycidate molecule from the side of the epoxy ring.

On the other hand a mechanism producing the β-system compound may involve a back side attack of the S-anion produced by catalytic alkali.

Experimental[8]

Condensation in the Presence of $NaHCO_3$——A mixture of 0.50 g of 2-nitrothiophenol (I_a), 0.75 g of ethyl 3-phenylglycidate (II_a) and 50 mg of $NaHCO_3$ in 5 ml of EtOH was refluxed for 5—8 hr. After cooling, precipitated 2-nitrophenyldisulfide, mp 189—191°, was filtered off. The solvent was evaporated and the residue was dissolved in iso-propylether. On standing the solution, 0.67 g (55.6%) of yellow precipitate (III_a-β) was obtained, mp 122—123°. Recrystallization from iso-propylether gave pure III_a-β, mp 124—125°. IR ν_{max}^{Nujol} cm^{-1}: 3440, 1722, 1512, 1335. *Anal.* Calcd. for $C_{17}H_{17}O_5NS$: C, 58.77; H, 4.79; N, 4.03. Found: C, 58.73; H, 4.77; N, 4.01.

6) M. Ballester, *Chem. Revs.*, **55**, 283 (1955).
7) R.E. Parker and N.S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).
8) All melting points were uncorrected.

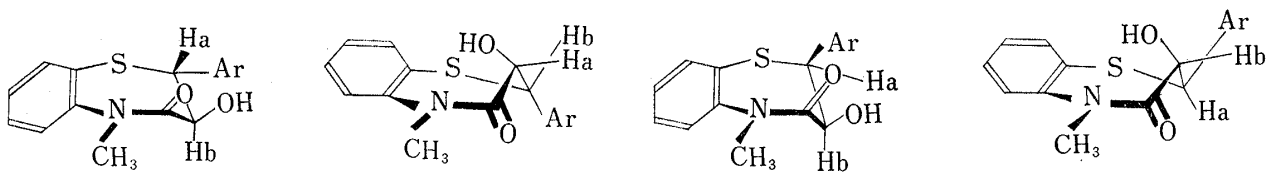


Fig. 1

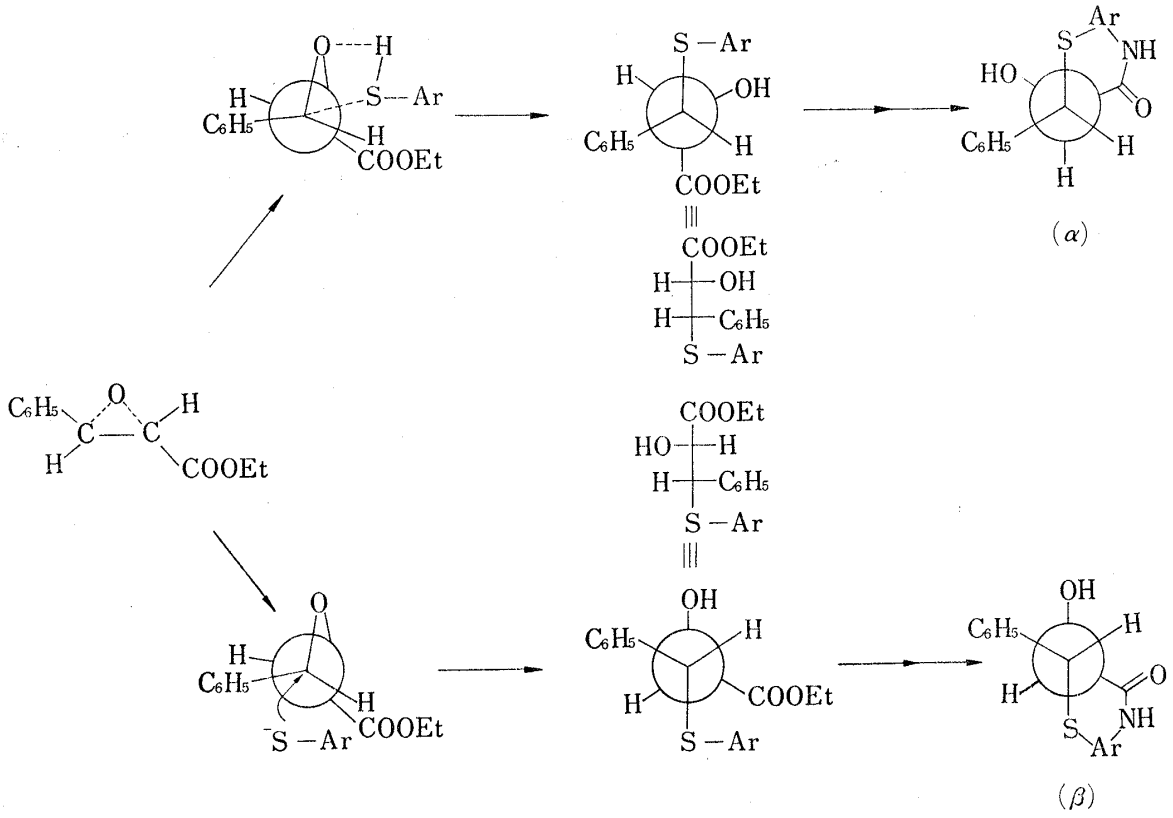


Fig. 2

III_b-β: mp 134—136° (EtOH). Yield 68.5%. IR ν_{max}^{Nujol} cm^{-1}: 3460, 1730, 1514, 1342. *Anal.* Calcd. for $C_{17}H_{17}O_6NS$: C, 56.19; H, 4.72; N, 3.85. Found: C, 56.00; H, 4.77; N, 3.64.

III_c-β: mp 98—99° (EtOH). Yield 50.5%. IR ν_{max}^{Nujol} cm^{-1}: 3470, 1728, 1510, 1340. NMR ($CDCl_3$) τ: 8.75 (3H, triplet, J=7.5 cps, $-CH_2-\underline{Me}$), 7.00 (1H, singlet, OH), 6.27 (3H, singlet, OCH_3), 5.84 (2H, quartet, J=7.5 cps, $-\underline{CH_2}-CH_3$), 5.32 and 5.23 (2H, doublets, J=3 cps, C_α–H and C_β–H), 3.22 (1H, doublet, J=9 cps), 2.68 (2H, multiplet), 2.65 (2H, doublet, J=9 cps), 2.00 (1H, multiplet). *Anal.* Calcd. for $C_{18}H_{18}O_6NSCl$: C, 52.49; H, 4.40; N, 3.40. Found: C, 52.36; H, 4.42; N, 3.30.

Condensation in the Presence of BF_3——A mixture of 5.0 g of I_a, 8.5 g of II_a and 0.2 ml of BF_3–ether in 50 ml of abs. ether was stirred for 10 hr at room temperature, then refluxed for 7 hr. The reaction mixture was washed with 10% Na_2CO_3 and the solvent was evaporated. The residual oil was mixed with 25 ml of EtOH and 25 ml of 10% Na_2CO_3 and stirred for 30 min at room temperature. The mixture was extracted with ether. The extract was washed with water, dried and evaporated. The residual oil was dissolved in iso-propylether. On standing the solution 1.05 g of III_a-β solidified, mp 122.5—124°.

Reduction of β-System Compounds——A mixture of 1.0 g of ethyl 2-hydroxy-3-phenyl-(2-nitrophenylthio)-propionate (III_a-β) and 6.65 g of $FeSO_4 \cdot 7H_2O$ in 30 ml of 50% (v/v) EtOH was refluxed for 30 min. To the vigourously stirred mixture 6 ml of conc. NH_4OH was added dropwise under refluxing during 15 min. The reaction mixture was refluxed for 10 min, then was cooled immediately, and extracted with AcOEt. The solvent was evaporated to give 0.45 g of oily IV_a-β. IR ν_{max}^{Liquid} cm^{-1}: 3440, 1725.

IV_b-β and IV_c-β were obtained by the same manner. IV_b-β: IR ν_{max}^{Liquid} cm^{-1}: 3430, 3420, 1739. Yield 87%. IV_c-β: IR ν_{max}^{Liquid} cm^{-1}: 3440, 3360, 1728. Yield 43.5%.

Desulfurization of IV-β——A mixture of IVa-β and 3.5 ml of Raney-Ni (w-7) in 15 ml of abs. EtOH was refluxed for 3 hr. The catalyst was filtered off, the solvent was evaporated and the residue was dissolved in ether. The ether layer was washed with 10% HCl and then with water, and dried. Evaporation of the solvent gave 0.23 g of oily product, which was distilled to give 0.16 g (31.2% from IV$_a$-β) of VII$_a$, bp 145—150° (7—8 mmHg) (at oil bath temperature). IR ν_{max}^{Liquid} cm^{-1}: 3480, 1745. Desulfurization of IV$_b$-β and IV$_c$-β by the some manner gave IIV$_b$ in about 80% yield respectively.

2-Hydroxy-3-phenyl-3-(2-aminophenylthio)propionic Acid (V$_a$-β) and 2-Phenyl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VI$_a$-β)——These compounds were obtained from IV$_a$-β according to the same method as in the corresponding α-system compounds in our previous paper.[1] Physical constants and spectral data are shown below.

V$_a$-β: mp 177—178° (decomp.) (70% EtOH). Crude yield 68.5%. IR ν_{max}^{Nujol} cm^{-1}: 3490, 3350, 1720. *Anal.* Calcd. for $C_{15}H_{15}O_3NS$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.88; H, 5.29; N, 4.65.

V$_b$-β: mp 179° (decomp.) (EtOH). Yield 68%. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3360, 1710. *Anal.* Calcd. for $C_{16}H_{17}O_4NS$: C, 60.17; H, 5.37; N, 4.39. Found: C, 59.81; H, 5.46; N, 4.21.

V$_c$-β: mp 174—175° (aquous EtOH). Yield 92%. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3340, 1735. *Anal.* Calcd. for $C_{16}H_{16}O_4NSCl$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.56; H, 4.69; N, 4.00.

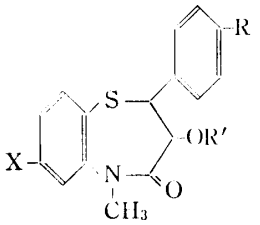
VI$_a$-β: mp 201—204° (EtOH). Yield 49.5% from III$_a$-β. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1690. *Anal.* Calcd. for $C_{15}H_{13}O_2NS$: C, 66.36; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.50; H, 4.93; N, 5.05; S, 11.67.

VI$_b$-β: mp 202—202.5° (EtOH). Yield 67.4% from III$_b$-β. IR ν_{max}^{Nujol} cm^{-1}: 3490, 1680. *Anal.* Calcd. for $C_{16}H_{15}O_3NS$: C, 63.78; H, 4.20; N, 4.17. Found: C, 57.10; H, 4.50; N, 3.99.

2-Phenyl-3-hydroxy-5-methyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIII$_a$-α)——Sixty milliliters of dimethylsulfoxide was added dropwise to 0.83 g of NaH (contents; 43.9%) and heated at 70° for 50 min with stirring. After cooling to room temperature, 4.50 g of VI$_a$-α was added to the mixture. The mixture was stirred for 40 min at room temperature, then for 40 min at 50° and cooled. 2.78 g of CH_3I in 3 ml of dimethylsulfoxide was added dropwise to it. The mixture was stirred for 6 hr at room temperature and poured into 500 ml of ice water. The resulting oily substance was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The residual oil solidified with a small amount of EtOH. Physical data of VIII$_a$-α and those of other benzothiazepine derivatives are shown in Table I and II.

2-Phenyl-3-acetoxy-5-methyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (IX)——A solution of 1.24 g of VIII in 15 ml of Ac_2O was heated for 4 hr on a water bath. Ac_2O was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with $NaHCO_3$ solution, water and dried.

Table I. 2-Aryl-3-hydroxy-5-methyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one



α,β	X	R	R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
α	H	H	H	132—133[a]	73.5	$C_{16}H_{15}O_2NS$	67.36	5.30	4.91	67.19	5.18	5.00
			Ac	158—159[a]	84.5	$C_{18}H_{17}O_3NS$	66.24	4.94	4.29	66.36	5.15	4.27
β			H	138—140[a]	77.3	$C_{16}H_{15}O_2NS$	67.36	5.30	4.91	67.25	5.38	4.76
			Ac	178[a]	95.0	$C_{18}H_{17}O_3NS$	66.24	4.94	4.29	65.90	5.03	4.26
α	H	OCH_3	H	134—135[a]	42.0	$C_{17}H_{17}O_3NS$	64.74	5.43	4.44	64.39	5.66	4.23
			Ac	214—216[b]	73.5	$C_{19}H_{19}O_4NS$	63.85	5.35	3.95	63.94	5.40	4.07
β			H	148[a]	59.2	$C_{17}H_{17}O_3NS$	64.74	5.43	4.44	65.00	5.52	4.32
			Ac	184—185[b]	73.3	$C_{19}H_{19}O_4NS$	63.85	5.35	3.95	64.03	5.29	3.78
α	Cl	OCH_3	H	158—161[a]	48.5	$C_{17}H_{16}O_3NSCl$	58.36	4.61	4.00	58.28	4.64	3.80
			Ac	182—184[a]	70.0	$C_{19}H_{18}O_4NSCl$	58.23	4.63	3.57	57.95	4.51	3.59
β			H	214—216[c]	64.5	$C_{17}H_{16}O_3NSCl$	58.36	4.61	4.00	58.22	4.60	3.83
			Ac	175—176[a]	90.0	$C_{19}H_{18}O_4NSCl$	58.23	4.63	3.57	58.74	4.46	3.75

recrystallization solvent; *a*) EtOH, *b*) AcOEt, *c*) MeOH

Evaporation of the solvent gave the residual oil, which solidified with a small amount of EtOH. See Table I and II.

Reaction of IX with NaH in Dioxane——1) α-System Compound: Fifty miligrams of NaH (contents; 43.9%) was added to a solution of 0.30 g of IX_a-α in 6 ml of abs. dioxane. The mixture was stirred for 1.5 hr at room temperature. After further addition of 50 mg of NaH the mixture was stirred for 3.5 hr at 50—55°. The solvent was evaporated under reduced pressure, the residue was dissolved in ether. The solution was washed with water, dried and evaporated. The residual oil solidified with a small amount of EtOH. Crude X_a, mp 80—83° was obtained in 72% yield. Recrystallization from isopropylether gave pure X_a, mp 84°. IR ν_{max}^{Nujol} cm^{-1}: 1641. NMR ($CDCl_3$) τ: 6.43 (3H, singlet, N–CH_3), 3.47 (1H, singlet C_3–H), 2.9—2.0 (8H, multiplet, arom-H). *Anal.* Calcd. for $C_{16}H_{13}ONS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.48; H, 4.81; N, 5.41. X_b; mp 116—117° (EtOH). Yield 25.8%. IR ν_{max}^{Nujol} cm^{-1}: 1617. NMR ($CDCl_3$) τ: 6.46 (3H, singlet, N–CH_3), 6.17 (3H, singlet, OCH_3), 3.26 (1H, singlet, C_3–H). *Anal.* Calcd. for $C_{17}H_{15}O_2NS$: C, 68.65; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.59; H, 5.08; N, 4.57; S, 10.58.

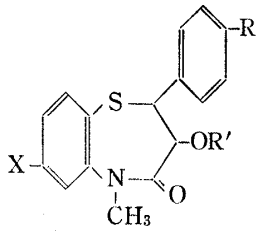
In the reaction of IX_b-α, $VIII_b$-α was obtained in 39% yield.

2) β-System Compound: A reaction was carried out in a similar manner, only to give the hydrolyzed product VII_a-β in 81.7% yield.

In the case of X_b-β the yield of the hydrolyzed product $VIII_b$-β was 87%.

Synthesis of Authentic Samples——X and XII for authentic samples were synthesized from XI and XIII respectively according to the DMSO-anion and CH_3I method previously described.[1] $XIII_a$; mp 85—86° (EtOH). Yield 63.5%. IR ν_{max}^{Nujol} cm^{-1}: 1645. *Anal.* Calcd. for $C_{16}H_{13}ONS$: C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 71.99; H, 4.96; N, 5.13; S, 12.26.

Table II. IR and NMR Data of 2-Aryl-3-hydroxy-5-methyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one



α,β	X	R	R′	IR ν_{max}^{Nujol} cm^{-1}	NMR in $CDCl_3$ (τ)						
					$COCH_3$	NCH_3	OCH_3	OH	Ha	Hb	J_{ab}(cps)
α	H	H	H	3460,[a] 1670		6.45(s)		7.00(s)	4.98(d)	5.57(d)	7
			Ac	1750, 1682	8.16(s)	6.50(s)			4.90(d)	4.66(d)	7
β			H	3440,[a] 1672		6.51(s)		6.34(s)	5.75(d)	5.72(d)	11
			Ac	1750, 1690	8.10(s)	6.53(s)			5.39(d)	4.75(d)	11
α	H	OCH_3	H	3400, 1656		6.50(s)	6.22(s)		5.08(d)[b]	5.67(m)[b]	7
			Ac	1735, 1660	8.11(s)	6.53(s)	6.23(s)		5.00(d)	4.76(d)	7
β			H	3440, 1669		6.48(s)	6.20(s)		5.78 (broad s)[c]		
			Ac	1732, 1658	8.08(s)	6.56(s)	6.24(s)		5.47(d)	4.85(d)	11
α	Cl	OCH_3	H	3400, 1645		6.52(s)	6.23(s)	7.20(m)	5.12(d)[d]	5.68(d)[d]	7
			Ac	1730, 1665	8.10(s)	6.53(s)	6.20(s)		4.98(d)	4.77(d)	7.5
β			H	3440, 1665		6.57(s)	6.28(s)		5.85 (broad s)[e]		
			Ac	1730, 1660	8.05(s)	6.55(s)	6.19(s)		5.43(d)	4.83(d)	11

a) measured in CCl_4; *b*), *c*), *d*), *e*) signals in $CDCl_3$+CF_3COOH; *b*) Ha 5.01 (d), Hb 5.44 (d), J_{ab} 7 cps; *c*) Ha 5.73(d), Hb 5.46(d), J_{ab} 10.5 cps; *d*) Ha 5.00(d), Hb 5.43(d), J_{ab} 7 cps; *e*) Ha 5.72(d), Hb 5.48(d), J_{ab} 11 cps

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