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Synthetic Studies on 2,4-Benzothiazepin-5(1H)-one and 2,4-Benzodiazepin-1-one Derivatives[1]

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2,4-Benzothiazepin-5(1H)-ones were usually the predominant products in reactions of *o*-chloromethylbenzoyl chloride with 1,3-disubstituted thioureas; but with methyl, benzyl or allyl substituted thioureas, 2,4-benzodiazepin-1-ones were obtained together with 2,4-benzothiazepin-5(1H)-ones. These structures were elucidated from infrared, ultraviolet and nuclear magnetic resonance spectra. We also found that nature of the base and solvent as well as thiourea substituents affected the course of the reactions affording 2,4-benzothiazepin-5(1H)-ones or 2,4-benzodiazepin-1-ones. Several 2,4-benzothiazepin-5(1H)-ones and 2,4-benzodiazepin-1-ones possessed weak pharmacological activities, such as coronary vasodilating and local anesthetic activity.

Although 1,4- and 1,5-benzodiazepines or benzothiazepines have been extensively investigated, few reports on the 2,4-analogs can be found in the literature.[3] This paper describes syntheses and pharmacological properties of 2,4-benzothiazepin-5(1H)-ones and 2,4-benzodiazepin-1-ones.

The only reported 3-imino-2,4-benzothiazepin-5(1H)-one derivative is 3,4-dihydro-4-phenyl-3-phenylimino-2,4-benzothiazepin-5(1H)-one, prepared from *o*-bromomethylbenzoyl bromide (IV_2) and 1,3-diphenylthiourea.[4] However, we observed that 2,4-dimethyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_1) was obtained as the major product together with 3,4-dihydro-4-methyl-3-methylimino-2,4-benzothiazepin-5(1H)-one (VI_1) in a reaction of *o*-chloromethylbenzoyl chloride (IV_1) with 1,3-dimethylthiourea. This difference as well as pharmacological interest in both 2,4-benzothiazepin-5(1H)-ones and 2,4-benzodiazepin-1-ones called our attention to the reaction of IV_1 with 1,3-disubstituted thioureas.

The initially attempted cyclization of S-[(*o*-ethoxycarbonyl)benzyl]isothiouronium chloride (II), prepared from ethyl *o*-chloromethylbenzoate (I) and thiourea afforded thiophthalide (III) instead of 2,4-benzothiazepin-5(1H)-one derivative. In the reaction of *o*-chloromethylbenzoyl chloride (IV_1) with thiourea, five-membered ring formation was also predominant yielding 2-thiocarbamoylphthalimidine (V).

1,3-Dimethylthiourea, however, reacted with IV_1 in the presence of sodium carbonate in acetone to furnish two isomeric ring closure products. The major one was assigned 2,4-dimethyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_1) on the basis of its infrared (IR) and ultraviolet (UV) spectra: namely in IR spectrum, neither the N–H nor S–H band was detected, the C=O and C=S band appeared at 1640 and 1500 cm^{-1}, respectively, and the UV maximum at 274.0 nm due to C=S was also measured. On the other hand, the minor component showed the absorption bands at 1645 (C=O) and 1605 (C=N) cm^{-1}, but no absorption band due to N–H nor S–H. There were no absorption maxima in the near ultraviolet region. The spectral evidence indicated that the minor component was 3,4-dihydro-4-methyl-3-methylimino-2,4-benzothiazepin-5(1H)-one (VI_1).

1) A part of this paper was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
2) Location: *1–2–58, Hiromachi, Shinagawa-ku, Tokyo.*
3) C.A. Archer and L.H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
4) D.N. Reinhaudt, *Rec. Trav. Chim.*, **92**, 20 (1973).

Similar results were observed in reactions of IV_1 with 1,3-dibenzylthiourea and 1,3-bis(*p*-substituted benzyl)thioureas. However, in the case of 1,3-diallylthiourea, the major product was 4-allyl-3-allylimino-3,4-dihydro-2,4-benzothiazepin-5(1H)-one (VI_5) and the minor one was 2,4-diallyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_5). The reactions of IV_1 with other thioureas, such as 1,3-diethyl, 1,3-diisopropyl, 1,3-dicyclohexyl, 1,3-di-*o*-tolyl, *etc.*, furnished 2,4-benzothiazepin-5(1H)-one derivatives ($VI_{2,3,4,6,8}$, *etc.*) as the only isolable products. Consequently, it was supposed that thioureas having active hydrogens on carbons ajacent to nitrogen would afford 2,4-benzodiazepin-1-ones. It was also presumed that partial double bond character would be endowed on the C–N bond in these thioureas because of the acidic property of the hydrogens and would increase polarizability of the nitrogen atoms. Thus, in these thioureas the nitrogen atoms might have competitive reactivity with the sulfur atom at the chloromethyl group in IV_1. This assumption was supported by the following result. In the reaction of *o*-bromomethylbenzoyl bromide (IV_2) with 1,3-dimethylthiourea or 1,3-bis(*p*-methylbenzyl)thiourea, 2,4-benzothiazepin-5(1H)-one was produced predominantly and 2,4-benzodiazepin-1-one could not be isolated contrary to the above results. It was assumed that the sulfur atom reacted more smoothly than the nitrogen atom with bromomethyl group, because the bromomethyl group and sulfur atom were softer than the chloromethyl group and nitrogen atom, respectively.

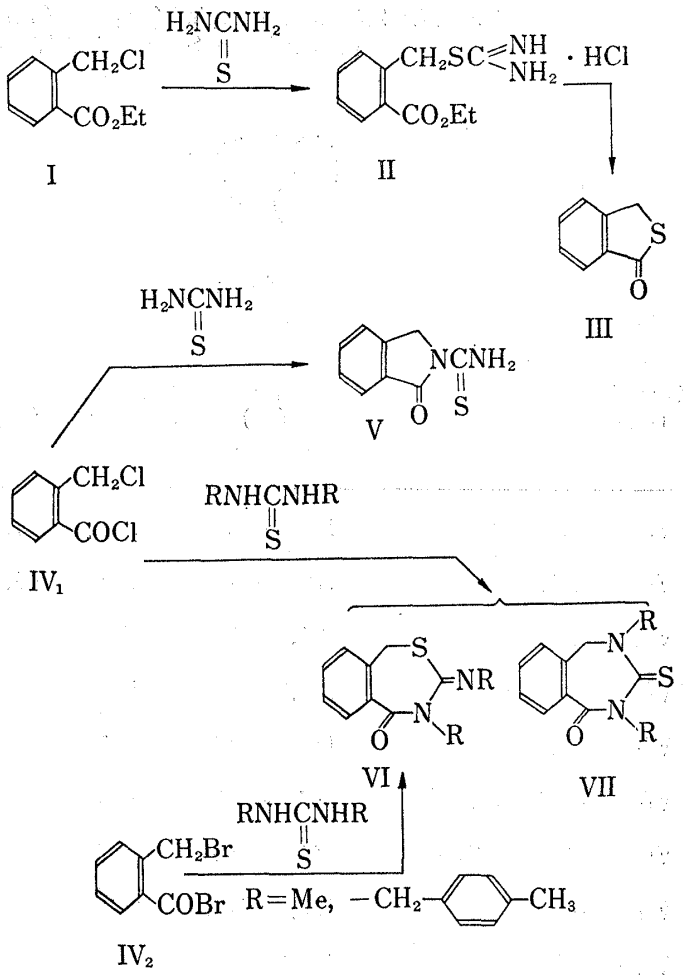
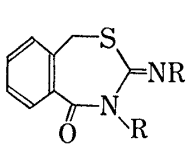


Chart 1

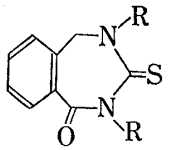
The nature of the base and solvent also affected the course of the reaction. In order to establish conditions to give specifically 2,4-benzothiazepin-5(1H)-ones or 2,4-benzodiazepin-1-ones, the base and solvent were varied in the reaction of IV_1 with 1,3-dimethylthiourea. Although a specific condition yielding only 2,4-benzodiazepin-1-one (VII_1) could not be found, it was observed that in the presence of a hard metal carbonate or base, such as sodium carbonate, potassium carbonate or triethylamine in acetone, compound VII_1 was mainly produced, and in the presence of a softer metal carbonate or base, for example basic lead carbonate or pyridine, 2,4-benzothiazepin-5(1H)-one (VI_1) was predominantly formed. Nevertheless, 2,4-benzothiazepin-5(1H)-one (VI_1) was the main isolable product in acetonitrile or benzene even in the presence of a hard metal carbonate. A similar result was observed in the case of 1,3-bis(*p*-methylbenzyl)thiourea.

Formation of the two isomeric 2,4-benzothiazepin-5(1H)-ones and two isomeric 2,4-benzodiazepin-1-ones was presumed in reactions of IV_1 with unsymmetrical 1,3-disubstituted thioureas. The results are shown in Table III. These structures were elucidated chiefly on the basis of spectral data, especially by a comparison of chemical shifts in the nuclear

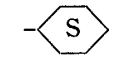
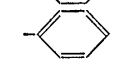
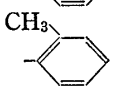
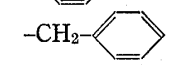
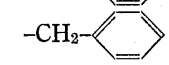
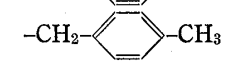
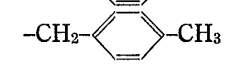
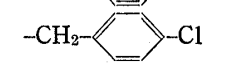
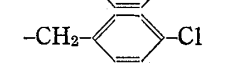
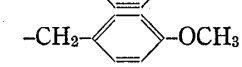
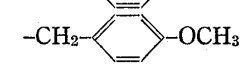
TABLE I. 2,4-Benzothiazepin-5(1H)-ones(VI) and 2,4-Benzodiazepin-1-ones(VII) prepared from Symmetrical 1,3-Disubstituted Thioureas



VI

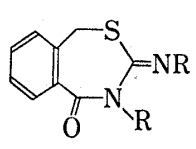


VII

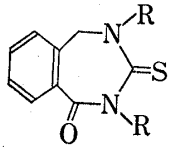
Compd. No.	R	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
VI$_1$	CH_3	150 —152	IPA	15.5	$C_{11}H_{12}ON_2S$	59.98 (60.03)	5.44 (5.24)	12.72 (12.74)	14.55 (14.60)
VII$_1$	CH_3	170 —171.5	IPA	45.5	$C_{11}H_{12}ON_2S$	59.98 (59.92)	5.44 (5.44)	12.72 (12.79)	14.55 (14.48)
VI$_2$	C_2H_5	94.5— 95	IPA	16.6	$C_{13}H_{16}ON_2S$	62.87 (62.89)	6.50 (6.50)	11.28 (11.49)	12.91 (13.26)
VI$_3$	iso-C_3H_7	118.5—120	IPA	53.0	$C_{15}H_{20}ON_2S$	65.18 (65.13)	7.29 (7.24)	10.13 (10.16)	11.60 (11.60)
VI$_4$	n-C_4H_9	112 —114	IPA	59.5	$C_{17}H_{24}ON_2S$	67.07 (67.04)	7.95 (7.95)	9.20 (9.14)	10.53 (10.61)
VI$_5$	$-CH_2CH=CH_2$	87 — 89	IPA	33.7	$C_{15}H_{16}ON_2S$	66.15 (66.02)	5.92 (5.96)	10.28 (10.30)	11.77 (12.08)
VII$_5$	$-CH_2CH=CH_2$	44 — 45	IPE	9.5	$C_{15}H_{16}ON_2S$	66.15 (65.84)	5.92 (5.83)	10.28 (10.42)	11.77 (11.79)
VI$_6$		177.5—178.5	IPA	60.6	$C_{21}H_{28}ON_2S$	70.75 (70.50)	7.92 (7.81)	7.86 (7.87)	8.99 (9.02)
VI$_7$[b]		158.5—159.5	IPA	45.0	$C_{21}H_{16}ON_2S$	73.23 (73.01)	4.68 (4.64)	8.13 (8.47)	9.31 (9.41)
VI$_8$		135 —137	IPA	21.4	$C_{23}H_{20}ON_2S$	74.17 (74.21)	5.41 (5.32)	7.52 (7.56)	8.61 (8.39)
VI$_9$		122 —124	IPA	30.0	$C_{23}H_{20}ON_2S$	74.17 (74.30)	5.41 (5.38)	7.52 (7.91)	8.61 (8.74)
VII$_9$		135 —136	IPA	50.0	$C_{23}H_{20}ON_2S$	74.17 (73.95)	5.41 (5.41)	7.52 (7.85)	8.61 (8.65)
VI$_{10}$		134.5—135	EA	11.2	$C_{25}H_{24}ON_2S$	74.97 (74.54)	6.04 (5.98)	6.99 (7.02)	8.00 (8.05)
VII$_{10}$		130 —131	EA	25.5	$C_{25}H_{24}ON_2S$	74.97 (75.15)	6.04 (6.06)	6.99 (7.14)	8.00 (7.98)
VI$_{11}$		122 —124	EA	17.2	$C_{23}H_{18}ON_2SCl_2$	62.59 (62.60)	4.11 (4.14)	6.35 (6.41)	7.26 (7.26)
VII$_{11}$		163 —164	EA	23.0	$C_{23}H_{18}ON_2SCl_2$	62.59 (62.45)	4.11 (4.12)	6.35 (6.38)	7.26 (7.30)
VI$_{12}$		78 — 84	H	9.4	$C_{25}H_{24}O_3N_2S$	69.42 (68.78)	5.59 (5.48)	6.48 (6.55)	7.41 (7.31)
VII$_{12}$		117.5	EA	18.3	$C_{25}H_{24}O_3N_2S$	69.42 (69.37)	5.59 (5.64)	6.48 (6.90)	7.41 (6.38)
XI	$-CH_2CH_2CH_2-$	142 —143	IPA	60.0	$C_{12}H_{12}ON_2S$	62.04 (61.92)	5.21 (4.99)	12.06 (12.06)	13.80 (13.91)
XII	$-CH_2CH_2CH_2-$ $\cdot CH_3I$	214 —216	EA		$C_{13}H_{15}ON_2SI$	41.72 (41.95)	4.04 (3.82)	7.48 (7.50)	8.57 (8.70)

a) EA: EtOH, IPA: isopropanol, IPE: isopropyl ether, H: n-hexane
b) Ref. 4

TABLE II. The Yield of 2,4-Benzothiazepin-5(1H)-one Derivatives (VI) and 2,4-Benzodiazepin-1-one Derivatives (VII) on the Reaction of *o*-Chloromethylbenzoyl Chloride with 1,3-Dimethyl-or 1,3-Bis(*p*-methylbenzyl)thiourea in Various Conditions



VI



VII

Expt. No.	R	Solvent[a]	Base (mole ratio to IV)	Reactn. temp. (°C)	Reactn. time (hr)	Yield (%) VI	Yield (%) VII
1	CH_3	A	Li_2CO_3 (2.0)	reflux	7.5	57.3	—
2	CH_3	A	Na_2CO_3 (2.0)	reflux	24.0	15.5	45.5
3	CH_3	A	K_2CO_3 (3.0)	reflux	5.5	12.0	50.0
4	CH_3	A	$BaCO_3$ (2.0)	reflux	6.5	57.5	—
5	CH_3	A	$(PbCO_3)_2$-$Pb(OH)_2$ (1.0)	reflux	6.5	61.4	—
6	CH_3	A	Et_3N (1.5)	reflux	7.0	14.5	32.7
7	CH_3	A	pyridine (3.0)	reflux	9.0	9.5	—
8	CH_3	AN	Na_2CO_3 (2.0)	70	5.5	74.6	—
9	CH_3	DME	Na_2CO_3 (2.0)	85	5.5	6.9	—
10	CH_3	DMF	Na_2CO_3 (2.0)	80—85	7.0	0.5	—
11	CH_3	B	K_2CO_3 (2.0)	reflux	24.0	53.6	—
12	$-CH_2-C_6H_4-CH_3$	A	Na_2CO_3 (2.0)	reflux	24.0	11.2	25.5
13	$-CH_2-C_6H_4-CH_3$	AN	Na_2CO_3 (2.0)	70	6.0	36.3	—

a) A: acetone, AN: acetonitrile, B: benzene, DME: dimethoxyethane DMF: dimethylformamide

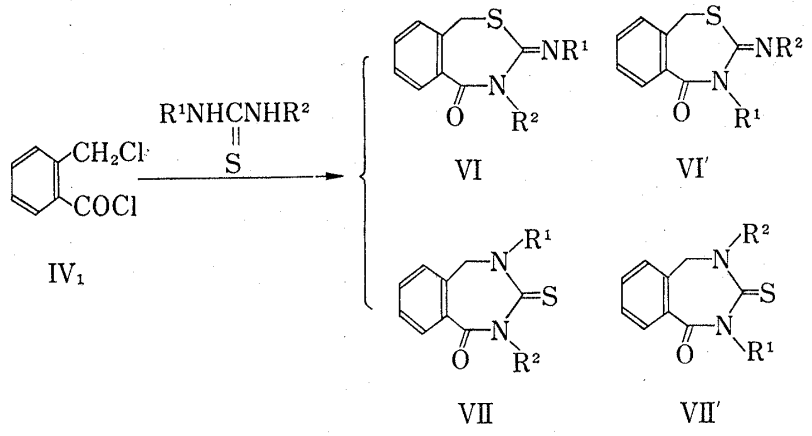


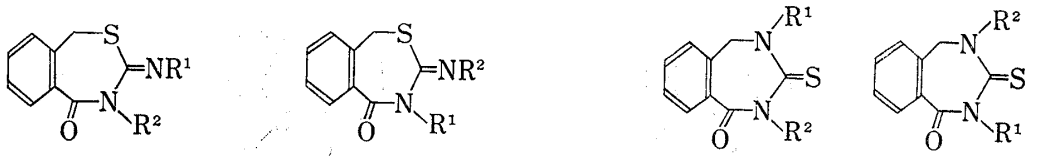
Chart 2

magnetic resonance (NMR) with those of the corresponding 2,4-benzothiazepin-5(1H)-one or 2,4-benzodiazepin-1-one derived from the symmetrical 1,3-disubstituted thiourea.

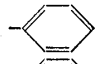
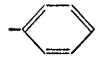
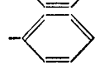
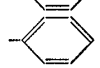
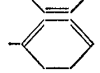
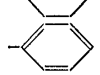
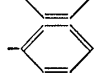
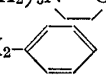
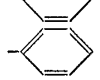
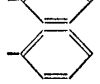
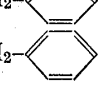
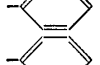
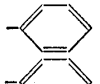
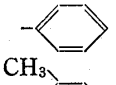
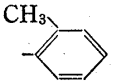
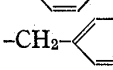
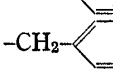
In cases of 2,4-benzothiazepin-5(1H)-ones having both phenyl and dialkylaminoalkyl substituents, it was difficult to establish their structures from only chemical shifts, owing to the anisotropic effect of benzene ring. Compound VI'_{18} was assigned the structure 3-(2-diethylaminoethylimino)-3,4-dihydro-4-phenyl-2,4-benzothiazepin-5(1H)-one, since acid hydrolysis of VI'_{18} gave 2-phenylphthalimidine (VIII). Others were assumed as 3-dialkylaminoalkylimino-4-phenyl-2,4-benzothiazepin-5(1H)-one derivatives by the NMR spectral com parison with VI'_{18}.

In the NMR spectra of 2,4-benzodiazepin-1-ones, ring methylene protons appeared as an AB quartet and any methylene protons bonded to the nitrogens, also exhibited an AB pattern

Table III. 2,4-Benzothiazepin-5(1H)-ones (VI and VI′) and 2,4-Benzodiazepin-1-ones (VII and VII′) prepared from Unsymmetrical 1,3-Disubstituted Thioureas

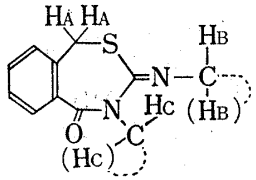


VI VI′ VII VII′

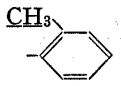
Compd. No.	R^1	R^2	mp (°C)	Recrystn.[a] solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
VII′$_{13}$	CH_3	$-(CH_2)_2N$	136—137	IPA	8.3	$C_{16}H_{21}ON_3S$	63.33 (63.42)	6.98 (7.22)	13.85 (13.88)	10.57 (10.99)
VII$_{14}$	CH_3	$-(CH_2)_3N$ O	117—118	IPA	8.9	$C_{17}H_{23}O_2N_3S$	61.23 (61.21)	6.95 (7.02)	12.60 (12.62)	9.62 (9.80)
VI$_{15}$	C_2H_5	$-(CH_2)_3N$ O	104—105	IPA	5.6	$C_{18}H_{25}O_2N_3S$	62.22 (62.22)	7.25 (7.14)	12.09 (12.12)	9.23 (9.45)
VI$_{16}$	iso-C_4H_9	$-(CH_2)_3N$ O	117.5—118.5	IPA-IPE	17.3	$C_{20}H_{29}O_2N_3S$	63.97 (64.04)	7.78 (7.77)	11.19 (11.28)	8.54 (8.64)
VI$_{17}$		$-(CH_2)_3N$	107—109	IPE	11.3	$C_{23}H_{33}ON_3S$	69.13 (69.20)	8.32 (7.96)	10.52 (10.64)	8.02 (8.27)
VI′$_{18}$		$-(CH_2)_2N(C_2H_5)_2$	77—79	IPA	55.7	$C_{21}H_{25}ON_3S$	68.63 (68.87)	6.86 (6.81)	11.43 (11.52)	8.72 (8.73)
VI′$_{19}$		$-(CH_2)_2N$	119—120	IPA	6.1	$C_{21}H_{23}ON_3S$	69.01 (69.17)	6.34 (6.36)	11.50 (11.54)	8.77 (8.97)
VII$_{19}$		$-(CH_2)_2N$	168—170	IPA	6.1	$C_{21}H_{23}ON_3S$	69.01 (69.39)	6.34 (6.30)	11.50 (11.51)	8.77 (9.05)
VI′$_{20}$		$-(CH_2)_2N$ O	107—110	IPA	18.0	$C_{21}H_{23}O_2N_3S$	66.12 (66.24)	6.08 (6.01)	11.01 (11.16)	8.40 (8.38)
VI′$_{21}$		$-(CH_2)_3N(CH_3)_2$	98.5—100.5	CT-H	9.8	$C_{20}H_{23}ON_3S$	67.96 (67.41)	6.56 (6.58)	11.89 (11.78)	9.07 (9.00)
VI′$_{22}$		$-(CH_2)_3N$	121—122	IPA	5.7	$C_{22}H_{25}ON_3S$	69.62 (69.53)	6.64 (6.70)	11.07 (11.05)	8.45 (8.72)
VI′$_{23}$		$-(CH_2)_3N$ O	124—126	IPA	23.0	$C_{22}H_{25}O_2N_3S \cdot 1/2H_2O$	66.97 (66.85)	6.64 (6.31)	10.65 (10.84)	8.13 (8.15)
VI$_{24}$		$-CH_2-$ 	159—160	IPA	9.6	$C_{22}H_{18}ON_2S$	73.72 (73.92)	5.06 (5.04)	7.81 (7.97)	8.94 (9.00)
VI′$_{24}$		$-CH_2-$ 	117—118.5	IPA	22.9	$C_{22}H_{18}ON_2S$	73.72 (73.54)	5.06 (4.98)	7.81 (7.86)	8.94 (9.02)
VII$_{24}$		$-CH_2-$ 	155—157	IPA	13.8	$C_{22}H_{18}ON_2S$	73.72 (73.54)	5.06 (4.98)	7.81 (7.86)	8.94 (9.02)
VI$_{25}$		$-CH_2CH=CH_2$	113	IPA	13.6	$C_{18}H_{16}ON_2S$	70.10 (69.90)	5.23 (5.12)	9.08 (9.13)	10.46 (10.44)
VI′$_{25}$		$-CH_2CH=CH_2$	139.5—140.5	IPA	21.2	$C_{18}H_{16}ON_2S$	70.10 (69.86)	5.23 (5.11)	9.08 (9.05)	10.46 (10.52)
VII$_{25}$		$-CH_2CH=CH_2$	137—138	IPA	13.5	$C_{18}H_{16}ON_2S$	70.10 (70.06)	5.23 (5.23)	9.08 (9.22)	10.46 (10.46)
VI′$_{26}$		iso-C_3H_7	132—133.5	IPA	41.0	$C_{19}H_{21}ON_2S$	70.12 (70.47)	6.50 (6.15)	8.61 (8.77)	9.85 (9.95)
VI$_{27}$ VI′$_{27}$	$-CH_2-$ 	iso-C_4H_9	70—73	IPA	16.8	$C_{20}H_{22}ON_2S$	70.97 (71.48)	6.55 (6.52)	8.28 (8.42)	9.47 (9.47)
VII$_{27}$	$-CH_2-$ 	iso-C_4H_9	91—93.5	IPA	7.5	$C_{20}H_{22}ON_2S$	70.97 (70.81)	6.55 (6.25)	8.28 (8.40)	9.47 (9.47)
VII′$_{27}$	$-CH_2-$ 	iso-C_4H_9	124—125	IPA	15.5	$C_{20}H_{22}ON_2S$	70.97 (71.11)	6.55 (6.37)	8.28 (8.50)	9.47 (9.50)

a) IPA: isopropanol, IPE: isopropyl ether, CT: carbon tetrachloride, H: *n*-hexane

TABLE IV. Spectral Data of 2,4-Benzothiazepin-5(1H)-one Derivatives (VI and VI')



Compd. No.	IR (Nujol), cm^{-1}		NMR ($CDCl_3$), δ		
	C=O	C=N	H_A	H_B	H_C
VI_1	1645	1605	4.05	3.10	3.45
VI_2	1630	1590	4.02	3.29(q, J=7Hz)	4.08(q, J=7Hz)
VI_3	1635	1585	3.99	3.62(septet, J=7Hz)	4.84(septet, J=7Hz)
VI_4	1635	1590	4.02	3.27(t, J=7Hz)	4.06(t, J=7Hz)
VI_5	1630	1590	4.03	3.85(m)	4.64(m)
VI_6	1640	1600	3.97	3.33(br)	4.47(br)
VI_7	1650	1580	4.16	—	—
VI_8	1660	1605	4.16	(1.53)[a]	(2.52)[a]
VI_9	1660	1580	3.92	4.17	5.30
VI_{10}	1625	1590	3.90	4.33	5.23
VI_{11}	1635	1595	3.95	4.31	5.21
VI_{12}	1640	1595	3.90	4.33	5.21
VI_{15}	1635	1590	4.00	3.27(q, J=7Hz)	4.07(t, J=7Hz)
VI_{16}	1645	1600	3.98	3.02(d, J=7Hz)	4.07(t, J=7Hz)
VI_{17}	1640	1600	3.96	3.25(m)	4.02(t, J=7Hz)
VI'_{18}	1640	1590	4.10	4.41(t, J=7Hz)	—
VI'_{19}	1650	1595	4.08	4.41(t, J=6Hz)	—
VI'_{20}	1640	1590	4.17	4.42(t, J=8Hz)	—
VI'_{21}	1650	1590	3.96	4.27(t, J=7Hz)	—
VI'_{22}	1650	1605	3.92	4.26(t, J=7Hz)	—
VI'_{23}	1655	1590	3.95	4.26(t, J=7Hz)	—
VI_{24}	1640	1590	3.87	—	5.42
VI'_{24}	1650	1590	4.24	4.50	—
VI_{25}	1660	1605	3.98	—	4.85(d, J=7Hz)
VI'_{25}	1645	1580	4.19	3.90(m)	—
VI'_{26}	1655	1590	4.23	3.53(septet, J=7Hz)	(2.50)[a]
VI_{27}	1645	1600	3.86	4.45	3.90(d, J=6Hz)
VI'_{27}			4.06	2.95(d, J=6Hz)	5.23

a) 

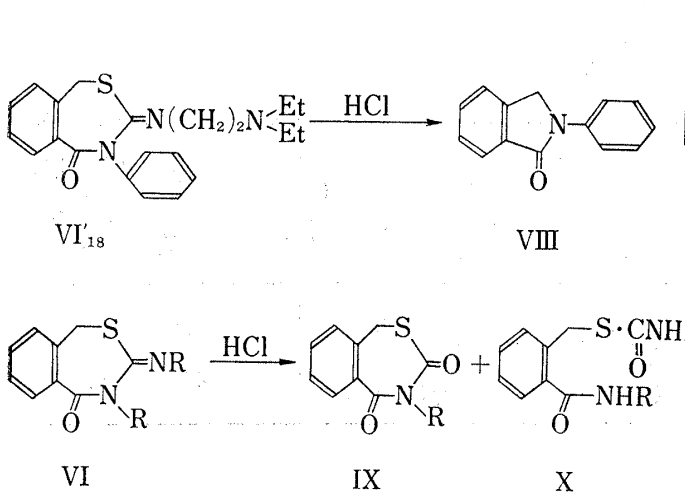


Chart 3

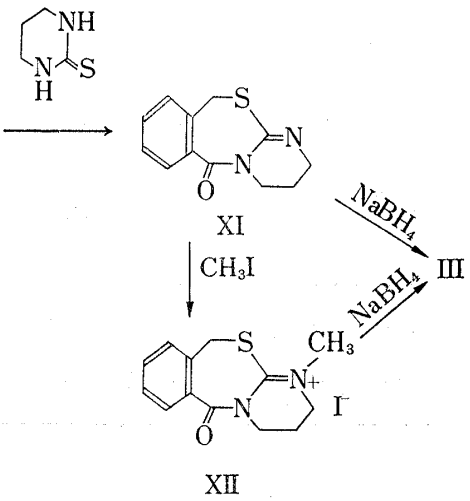
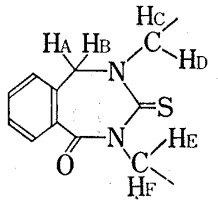


Chart 4

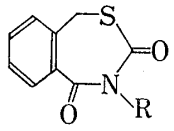
TABLE V. Spectral Data of 2,4-Benzodiazepin-1-one Derivatives (VII and VII')



Compd. No.	UV λ_{max}^{EtOH} nm (log ε)	IR (Nujol), cm^{-1}		NMR ($CDCl_3$), δ					
		C=O	C=S	H_A	H_B	H_C	H_D	H_E	H_F
VII$_1$	221.0(4.13) 274.0(4.19)	1640	1500	4.10 (d, J_{AB}=15Hz)	5.20	3.50		3.57	
VII$_5$	222.3(4.19) 281.0(4.15)	1655	1480	4.09 (d, J=15Hz)	a)	a)		a)	
VII$_9$	284.3(4.09)	1650	1440	3.83 (d, J_{AB}=15Hz)	4.95	4.55 (d, J_{CD}=15Hz)	5.82	5.45 (d, J_{EF}=15Hz)	5.98
VII$_{10}$	285.3(4.09)	1655	1485	3.85 (d, J_{AB}=15Hz)	4.90	4.45 (d, J_{CD}=15Hz)	5.77	5.40 (d, J_{EF}=15Hz)	5.90
VII$_{11}$	222.0(4.50) 283.6(4.06)	1645	1480	3.87 (d, J_{AB}=15Hz)	4.93	4.57 (d, J_{CD}=15Hz)	5.67	5.37 (d, J_{EF}=15Hz)	5.89
VII$_{12}$	224.8(4.50) 276.6(4.11)	1650	1480	3.83 (d, J_{AB}=15Hz)	4.83	4.45 (d, J_{CD}=15Hz)	5.67	5.33 (d, J_{EF}=15Hz)	5.85
VII'$_{13}$	277.0(4.15)	1640	1510	a) (d, J_{AB}=14Hz)	5.08	a)		3.54	
VII$_{14}$	277.5(4.15)	1650	1510	a) (d, J=12Hz)	5.17	3.46		4.40 (br. t, J=8Hz)	
VII$_{19}$		1645	1480	4.16 (d, J_{AB}=14Hz)	5.85	—		4.70(m)	
VII$_{24}$	285.3(4.02)	1650	1450	4.17 (d, J_{AB}=14Hz)	5.44	—		5.55 (d, J_{EF}=14Hz)	5.92
VII$_{25}$	221.0(4.29) 284.0(4.05)	1640	1450	a)		a)		a)	
VII$_{27}$	219.5(4.29) 284.0(4.13)	1660	1480	4.05 (d, J_{AB}=14Hz)	5.08	4.70 (d, J_{CD}=15Hz)	5.81	a)	
VII'$_{27}$	282.5(4.09)	1640	1495	3.91 (d, J_{AB}=14Hz)	5.04	3.19 (dd, J_{CD}=14Hz, J=8Hz)	4.20	5.39 (d, J_{EF}=15Hz)	5.88

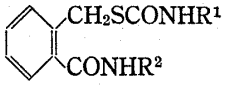
a) not assigned

TABLE VI. 2,4-Benzothiazepine-3,5(1H,4H)-diones (IX)



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found)				IR (Nujol) C=O, cm^{-1}	NMR, δ ($CDCl_3$)	
					C	H	N	S		O=N-CH	Ring-CH_2-
IX$_1$	iso-C_3H_7	23	88— 89	$C_{12}H_{13}O_2NS$	61.25 (61.76)	5.57 (5.45)	5.95 (6.19)	13.63 (13.70)	1660 1630	4.87	3.96
IX$_2$		20	122—123	$C_{15}H_{17}O_2NS$	65.43 (65.51)	6.22 (6.15)	5.09 (5.13)	11.64 (11.61)	1670 1630	4.50	4.01

Table VII. *o*-Carbamoylthiomethylbenzamides (X)



Compd. No.	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	S	IR (Nujol) cm^{-1} NH	C=O
X_1	iso-C_3H_7	iso-C_3H_7	24	142—143.5	$C_{15}H_{22}O_2N_2S$	61.20 (61.73)	7.53 (7.35)	9.51 (9.70)	10.89 (10.98)	3270 3180[a]	1660[a] 1630
X_2			22	147—148	$C_{21}H_{30}O_2N_2S$	67.34 (67.31)	8.07 (8.07)	7.48 (7.54)	8.56 (8.70)	3280 3200	1640[a] 1620
X_3			30	159.5—161.5	$C_{21}H_{18}O_2N_2S$	69.59 (69.64)	5.00 (4.92)	7.73 (7.85)	8.85 (8.93)	3260 3180	1660[a] 1640
X_4	-CH_2- 		55	157.5—159.5	$C_{22}H_{20}O_2N_2S$	70.19 (69.95)	5.36 (5.33)	7.44 (7.41)	8.52 (8.57)	3300 3270	1660[a] 1640
X_5	-$CH_2CH{=}CH_2$		47	149—150	$C_{18}H_{18}O_2N_2S$	66.24 (66.11)	5.56 (5.56)	8.58 (8.56)	9.82 (9.72)	3270 3250[a]	1660[a] 1645

a) shoulder

as shown in Table V. This fact indicated that ring inversion of 2,4-benzodiazepin-1-ones was slow at room temperature. A chair form in the seven-membered ring was assumed from consideration of a Dreiding model, but further examination of their conformation was not carried out.

Acid hydrolysis of 2,4-benzothiazepin-5(1H)-ones resulted mainly in ring opening to give *o*-carbamoylthiomethylbenzamide derivatives (X), along with the expected 2,4-benzothiazepine-3,5-dione derivatives (IX). These are listed in Table VI and VII.

Comparison of NMR spectra of 2,4-benzothiazepin-5(1H)-ones (VI) with corresponding 2,4-benzothiazepine-3,5 (1H,4H)-diones (IX) showed that methylene protons attached to an imino group of VI appeared at a higher field than those bonded to an amido group as shown in Table IV. Thus, the structural assignments of 2,4-benzothiazepin-5(1H)-one derivatives (VI) were made on the basis of this finding.

A reaction of IV_1 with tetrahydro-2(1H)-pyrimidinethione afforded tricyclic 1H-2,3-dihydropyrimido[2,1-*c*][2,4]benzothiazepin-11(6H)-one (XI) in a fair yield: XI was converted to its methiodide (XII). Sodium borohydride reduction of both XI and XII yielded thiophthalide (III).

Compounds synthesized in the present paper were tested for coronary vasodilating,[5] anti-hypertensive,[5] anesthetic and antiinflammatory activities. Compounds VI_{15}, VI_{16}, VI'_{19}, VI'_{22}, VII_5 showed weak coronary vasodilating activity in the canine heart. Mild anti-hypertensive activity in the spontaneously hypertensive rat was observed with compounds VI_{11}, VI'_{19} and VI'_{22}. Several 2,4-benzothiazepin-5(1H)-ones possessing alkylaminoalkyl substituents such as VI_{17}, VI'_{18}, VI'_{21} and VI'_{22}, exhibited local anesthetic activity. Compound XI had antiinflammatory activity.

Experimental[6]

S-[*o*-(Ethoxycarbonyl)benzyl]isothiouronium Chloride (II)——A mixture of I[7] (10 g) and thiourea (4.6 g) in EtOH (50 ml) was refluxed for 15 hr. After the solvent was removed, the residue was recrystallized from

5) Y. Sato, T. Tanaka, S. Kumakura, H. Koike, T. Oshima, K. Endo, and H. Takagi, *Chem. Pharm. Bull.* (Tokyo), **22**, 514 (1974).

6) Melting points were uncorrected. The UV spectra were measured in EtOH using Cary 14 spectrometer. The NMR spectra were taken with Varian A-60 spectrometer using tetramethylsilan as an internal standard. The IR spectra were determined with Hitachi EPI-G3 spectrometer.

iso-PrOH–isopropyl ether to afford II (8.75 g). Further recrystallization from EtOH–hexane gave an analytically pure sample as colorless needles. mp 179—180°. *Anal.* Calcd. for $C_{11}H_{15}O_2N_2SCl$: C, 48.09; H, 5.50; N, 10.19; S, 11.67; Cl, 12.90. Found: C, 47.73; H, 5.46; N, 10.24; S, 11.96; Cl, 12.98. IR ν_{max}^{Nujol} cm^{-1}: 3200 (N–H), 1710 (C=O), 1640 (C=N+).

Cyclization of II——a) In DMF: After 2.5 g of II in 20 ml of DMF was heated at 160—170° for 7 hr, the mixture was poured into ice-cooled dilute $NaHCO_3$ solution and extracted with AcOEt. The extract was chromatographed on silica gel with $CHCl_3$–EtOH (100: 1) and from the first fraction 0.42 g of thiophthalide (III) was obtained. Recrystallization from isopropyl ether yielded a pure sample as colorless needles. mp 56.5—58.5° (Lit.[8] mp 60°). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O).

b) With Na_2CO_3: A mixture of 548 mg of II and 213 mg of Na_2CO_3 in 8 ml of acetone was refluxed for 24 hr. After insoluble materials were filtered off, the filtrate was concentrated to give 0.4 g of a brown solid. Recrystallization from isopropyl ether furnished III, mp 54—55°.

2-Thiocarbamoylphthalimidine (V)——A mixture of 1.89 g of IV_1,[9] 0.76 g of thiourea and 2.12 g of Na_2CO_3 in 150 ml of dry acetone was refluxed for 29 hr, filtered and the filtrate was evaporated to dryness. The residue was recrystallized from DMF to give 1.14 g of crude V. Further recrystallization from the same solvent furnished a pure sample as pale yellow needles, mp 214—215.5°. *Anal.* Calcd. for $C_9H_8ON_2S$: C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 55.84; H, 4.04; N, 14.56; S, 16.56. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3220, 3140 (N–H), 1700 (C=O). NMR (δ in DMSO-d_6): 5.11 (2H, s, CH_2). Mass Spectrum *m/e*: 192 (M^+).

Reactions of IV_1 with 1,3-Disubstituted Thioureas——General Procedure: A mixture of 1,3-disubstituted thiourea (20 mmole), 3.8 g of IV_1 and 4.24 g of Na_2CO_3 in 250 ml of dry acetone was refluxed for 24 hr, inorganic salts were removed and acetone was evaporated to dryness. The residue was recrystallized from the appropriate solvent (usually iso-PrOH) immediately or after purification by column chromatography to give 2,4-benzothiazepin-5(1H)-one derivative (VI, VI′) and/or 2,4-benzodiazepin-1-one derivative (VII, VII′). When the products were soluble in dilute HCl solution, the residue was redissolved in AcOEt, extracted with 3N HCl. The aqueous layer was made alkaline with K_2CO_3 solution, precipitates or oil were collected by filtration or extraction. The resulting crude material was purified by recrystallization or column chromatography. 2,4-Benzothiazepin-5(1H)-one and 2,4-benzodiazepin-1-one derivatives are listed in Table I and III.

3,4-Dihydro-4-methyl-3-methylimino-2,4-benzothiazepin-5(1H)-one (VI_1) and 2,4-Dimethyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_1)——According to the general procedure, the reaction of IV_1 with 1,3-dimethylthiourea was carried out and then treated. The residue was recrystallized from iso-PrOH to give VII_1 as pale yellow needles. After concentration of mother liquor, the residue was redissolved in AcOEt, extracted with 3N HCl. The acidic aqueous layer was made alkaline with 3N K_2CO_3, the precipitates were separated out, filtered and recrystallized from iso-PrOH to afford VI_1 as colorless needles.

4-Allyl-3-allylimino-3,4-dihydro-2,4-benzothiazepin-5(1H)-one (VI_5) and 2,4-Diallyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_5)——The reaction of IV_1 with 1,3-diallylthiourea was carried out and then treated according to the general procedure, the residual mixture was submitted to silica gel column chromatography using benzene as an eluent. The first fraction was recrystallized from isopropyl ether to give colorless plates of VII_5. Recrystallization of the second fraction from iso-PrOH afforded colorless plates of VI_5.

4-Cyclohexyl-3-cyclohexylimino-3,4-dihydro-2,4-benzothiazepin-5(1H)-one (VI_6)——After the reaction and treatment were carried out according to the general procedure, the residue was recrystallized from iso-PrOH to give VI_6 as colorless needles.

4-Benzyl-3-benzylimino-3,4-dihydro-2,4-benzothiazepin-5(1H)-one (VI_9) and 2,4-Dibenzyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_9)——According to the general procedure, the reaction and treatment were carried out. The residue was separated by silica gel chromatography using benzene–$CHCl_3$ (1: 1) as an eluent. VII_9 was eluted first and then VI_9. Both were recrystallized from iso-PrOH to give colorless needles, respectively.

3-(2-Diethylaminoethylimino)-3,4-dihydro-4-phenyl-2,4-benzothiazepin-5(1H)-one (VI'_{18})——After the reaction and treatment were carried out according to the general procedure, the residue was redissolved in AcOEt and extracted with 3N HCl. The aqueous layer was made alkaline with 3N K_2CO_3 and extracted with AcOEt to give 6.17 g of oily material. The material was purified by silica gel column chromatography ($CHCl_3$–MeOH 5: 1) to afford 4.09 g of yellow oil which was crystallized on standing. Recrystallization from iso-PrOH furnished pale yellow prisms of VI'_{18}.

3,4-Dihydro-4-phenyl-3-[2-(1-pyrrolidinyl)ethylimino]-2,4-benzothiazepin-5(1H)-one (VI'_{19}) and 4-Phenyl-2-[2-(1-pyrrolidinyl)ethyl]-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_{19})——After the reaction and treatment were carried out according to the general procedure, the residue was chromatographed on alumina with benzene–EtOH (50: 1) as an eluent and the first fraction was recrystallized from iso-PrOH repeatedly to give VII_{19}. From the mother liquor, VI'_{19} was obtained.

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4-Benzyl-3,4-dihydro-3-phenylimino-2,4-benzothiazepin-5(1H)-one (VI_{24}), 3-Benzylimino-3,4-dihydro-4-phenyl-2,4-benzothiazepin-5(1H)-one (VI'_{24}) and 2-Benzyl-4-phenyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_{24})——According to the general procedure, the reaction and treatment were carried out. The residue was separated by silica gel column chromatography ($CHCl_3$–benzene 1: 1 and $CHCl_3$) into three fractions and all of three were recrystallized from iso-PrOH. The first fraction was colorless needles of VII_{24}, the second was colorless plates of VI_{24} and the third was colorless needles of VI'_{24}.

4-Allyl-3,4-dihydro-3-phenylimino-2,4-benzothiazepin-5(1H)-one (VI_{25}), 3-Allylimino-3,4-dihydro-4-phenyl-2,4-benzothiazepin-5(1H)-one (VI'_{25}) and 2-Allyl-4-phenyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_{25})——After the reaction and treatment were carried out according to the general procedure, VI_{25}, VI'_{25}, and VII_{25} were separated by silica gel chromatography with $CHCl_3$ as an eluent. VII_{25} was first eluted, followed by VI'_{25} and finally VI_{25}. All of three were recrystallized from iso-PrOH.

3-Benzylimino-3,4-dihydro-4-isobutyl-2,4-benzothiazepin-5(1H)-one (VI_{27}), 4-Benzyl-3,4-dihydro-3-isobutylimino-2,4-benzothiazepin-5(1H)-one (VI'_{27}), 4-Benzyl-2-isobutyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII_{27}) and 2-Benzyl-4-isobutyl-2,3,4,5-tetrahydro-3-thioxo-2,4-benzodiazepin-1-one (VII'_{27})——The reaction was carried out according to the general procedure and worked up as in the case of VI_{24}, VI'_{24}, and VII_{24}. Colorless prisms of VII_{27} was obtained from the first fraction and VII'_{27} was yielded from the second as colorless powders. The third fraction was crystallized from hexane and recrystallized from iso-PrOH to give colorless prisms. The NMR spectrum of the sample indicated VI_{27} and VI'_{27} were contained in the ratio of 6: 5.

Reaction of *o*-Bromomethylbenzoyl Bromide (IV_2)[10] with 1,3-Dimethylthiourea——A mixture of 1,3-dimethylthiourea (1.04 g), IV_2 (2.85 g) and Na_2CO_3 (2.12 g) in 250 ml of dry acetone was refluxed for 7 hr, filtered and the filtrate was concentrated. The residual solid was recrystallized from iso-PrOH to afford 1.02 g of VI_1 as colorless needles. From the mother liquor, additional crystals of VI_1 (0.24 g) were recovered as 3N–HCl soluble material.

Reaction of IV_2 with 1,3-Bis(*p*-methylbenzyl)thiourea——A mixture of IV_2 (2.78 g), the thiourea (2.84 g) and Na_2CO_3 (2.12 g) in 125 ml of dry acetone was refluxed for 7 hr, filtered and the filtrate was evaporated. The residue was crystallized from EtOH to afford 1.82 g of VI_{10}. Recrystallization from EtOH gave colorless prisms, mp 133—135°.

Reaction Conditions of 1,3-Dimethylthiourea with IV_1——1,3-Dimethylthiourea (1.04 g) was reacted with IV_1 (1.9 g) in the presence of base (10—30 mmole) in a solvent (125 ml) and usually worked up in the manner as described above. In the cases of $BaCO_3$, basic lead carbonate in acetone and Na_2CO_3 in acetonitrile, the residue was triturated with iso-PrOH to furnish VI_1·hydrochloride. Recrystallization from dioxane afforded colorless prisms, mp 198—200°. *Anal.* Calcd. for $C_{11}H_{13}ON_2SCl$: C, 51.46; H, 5.10; N, 10.91; S, 12.49; Cl, 13.81. Found: C, 50.93; H, 5.14; N, 10.94; S, 12.52; Cl, 13.68. The IR spectrum was identical with that of the hydrochloride derived from VI_1. The results are shown in Table II.

Reaction of 1,3-Bis(*p*-methylbenzyl)thiourea with IV_1 in Acetonitrile——A mixture of 1.9 g of IV_1, 2.84 g of the thiourea and 2.12 g of Na_2CO_3 in 125 ml of acetonitrile was heated at 70° for 6 hr, filtered and the filtrate was evaporated *in vacuo*. The residue was crystallized with EtOH to give 3,4-dihydro-4-(*p*-methylbenzyl)-3-(*p*-methylbenzylimino)-2,4-benzothiazepin-5(1H)-one (VI_{10}). mp 133—135°.

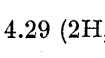
Hydrolysis of 3-(2-Diethylaminoethylimino)-3,4-dihydro-4-phenyl-2,4-benzothiazepin-5(1H)-one (VI'_{18})——VI'_{18} (0.5 g) in 4N HCl was heated at 95° for 24 hr, cooled and the precipitate was collected (0.12 g). Recrystallization from iso-PrOH gave 2-phenylphthalimidine (VIII). mp 160.5—161.5° (Lit.[8] mp 160°). *Anal.* Calcd. for $C_{14}H_{11}ON$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.40; H, 5.26; N, 7.11. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O).

4-Isopropyl-2,4-benzothiazepine-3,5(1H, 4H)-dione (IX_1) and N-Isopropyl-*o*-(isopropylcarbamoylthiomethyl)benzamide (X_1)——To 0.5 g of VI_8 in 5 ml of EtOH, 1 ml of hydrochloric acid was added, the mixture was heated at 60—80° for 4 hr and then refluxed for 4 hr. After concentration to dryness *in vacuo*, the residue was chromatographed on silica gel with $CHCl_3$–EtOH (50: 1) and the first fraction gave IX_1. Recrystallization from petroleum ether afforded 0.1 g of IX_1 as colorless needles. Mass Spectrum *m/e*: 235 (M^+).

The crystals obtained from the second fraction were recrystallized from benzene–petroleum ether to furnish 0.13 g of X_1 as colorless needles. NMR (δ in $CDCl_3$): 1.10 (6H, d, J=6 Hz, CH_3), 1.22 (6H, d, J=7 Hz, CH_3), *ca.* 4.10 (2H, br. m, CH), 4.25 (2H, s, CH_2), 5.60, 6.50 (each 1H, br, NH). Mass Spectrum *m/e*: 294 (M^+).

4-Cyclohexyl-2,4-benzothiazepine-3,5(1H, 4H)-dione (IX_2) and N-Cyclohexyl-*o*-(cyclohexylcarbamoylthiomethyl)benzamide (X_2)——1.5 g of VI_6 was hydrolyzed in a mixture of 12 ml of EtOH and 4 ml of hydrochloric acid at 95° for 11.5 hr. After EtOH was distilled off, the residue was extracted with AcOEt to give a yellow solid. The solid was treated with acetone and 0.18 g of X_2 was separated out. After acetone was removed, the residue was chromatographed on silica gel with $CHCl_3$, compound IX_2 was obtained from the first fraction and recrystallized from iso-PrOH to yield pale yellow needles (0.24 g). The second fraction was recrystallized from iso-PrOH–isopropyl ether to furnish additional X_2 (0.17 g) as colorless needles. NMR (δ in $CDCl_3$):

10) W. Davies and W.H. Perkin, Jr., *J. Chem. Soc.*, **121**, 2202 (1922).

ca. 3.80 (2H, br, ), 4.29 (2H, s, CH_2), 5.56, 6.44 (each 1H, br, NH).

***o*-(Phenylcarbamoylthiomethyl)benzanilide (X_3)**——A mixture of 0.3 g of VI_7 in 2.4 ml of EtOH and 0.8 ml of hydrochloric acid was refluxed for 13 hr, then EtOH was evaporated and the residue was extracted with AcOEt. The residue left after evaporation of the extract was recrystallized from iso-PrOH to afford 94 mg of X_3 as colorless needles. NMR (δ in DMSO-d_6): 4.38 (2H, s, CH_2), 10.12, 10.29 (each 1H, s, NH).

***o*-(Benzylcarbamoylthiomethyl)benzanilide (X_4)**——0.3 g of VI'_{24} was hydrolyzed and worked up in the manner as described above. Recrystallization from iso-PrOH–EtOH gave 0.17 g of colorless crystals. NMR (δ in DMSO-d_6): 4.28 (2H, d, J=6 Hz, CH_2), 4.30 (2H, s, CH_2), 8.62 (1H, br. t, NH), 10.38 (1H. s, NH).

***o*-(Allylcarbamoylthiomethyl)benzanilide (X_5)**——0.3 g of VI'_{25} was hydrolyzed and worked up in the manner as described above. Recrystallization from iso-PrOH afforded 0.15 g of X_5 as colorless crystalline powder. NMR (δ in DMSO-d_6): *ca.* 3.7 (2H, m, CH_2C=), 4.26 (2H, s, CH_2), 8.26 (1H, br. m, NH), 10.39 (1H, br. s, NH).

1H-2,3-Dihydropyrimido[2,1-*c*] [2,4]benzothiazepin-11 (6H)-one (XI)——A mixture of 3.8 g of IV_1, 2.32 g of tetrahydro-2(1H)-pyrimidinethione and 4.24 g of Na_2CO_3 in 230 ml of dry acetone was refluxed for 25 hr. Precipitates were collected, poured into water and 1.67 g of XI was obtained by filtration. The acetone solution was evaporated to dryness, the residue was dissolved in AcOEt and extracted with 3N HCl. The aqueous layer was made alkaline with K_2CO_3, precipitates were separated out and collected. Recrystallization from iso-PrOH afforded additional 1.06 g of XI. IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O), 1600 (C=N). NMR (δ in $CDCl_3$): 1.96 (2H, m, C–CH_2–C), 3.52 (2H, t, J=7 Hz, =N–CH_2), 3.96 (2H, s, S–CH_2), 3.99 (2H, t, J=6 Hz, –N–CH_2). Mass Spectrum *m/e*: 232 (M^+).

1H-2,3-Dihydro-4-methylpyrimidinium[2,1-c] [2,4]benzothiazepin-11(6H)-one Iodide (XII)——To a solution of 2.32 g of XI in 35 ml of $CHCl_3$, 5 ml of methyl iodide was added, the solution was refluxed for 5 hr and left overnight. Crystals (3.38 g) deposited were filtered and recrystallized from EtOH to give XII as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 1665 (C=O), 1590.

$NaBH_4$ Reduction of XI——1.15 g of XI was dissolved in 25 ml of MeOH–dioxane (3: 1), 0.4 g of $NaBH_4$ was added to the solution in an ice bath and the mixture was stirred at room temperature for 3 hr, then at 50—60° for 6 hr. After the reaction mixture was concentrated, the residue was dispersed in AcOEt and extracted with 3N HCl. Only a trace amount of materials was recovered from the 3N HCl extract. From the organic layer, 0.62 g of crude thiophthalide (III) was obtained. mp 54.5—56.5°. The structure was confirmed on the basis of its IR spectrum.

$NaBH_4$ Reduction of XII——To 0.37 g of XII in 10 ml of abs. MeOH, 0.15 g of $NaBH_4$ was added under ice cooling and the mixture was stirred at room temperature for 3 hr. After concentration, the residue was poured into dilute NaOH solution and 0.1g of thiophthalide (III) was obtained by filtration. mp 54—56°. Characterization was performed by the IR spectrum.

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