Synthesis of 1,5-Benzothiazepine Derivatives. III¹⁾HIROSHI KUGITA, HIROZUMI INOUE, MUNEYOSHI IKEZAKI,
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Various derivatives of 2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (I) were synthesized. Alternative routes to 2-aryl-3-hydroxy-5-alkyl-*trans*-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (II- β) and 2-aryl-3-acetoxy-5-dimethylaminoethyl-*cis*-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VI- α) were also investigated respectively.

In 1963, Krapcho and co-workers reported the synthesis of 1,5-benzothiazepines, possessing antidepressant activity.³⁾ In continuation of our studies on 3-hydroxy-1,5-benzothiazepine derivatives,¹⁾ we have synthesized various compounds derived from the 3-hydroxy-1,5-benzothiazepine structure.

Chart 1

Reaction of 2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (I) with dialkyl-aminoethyl halides in dioxane using sodium hydride as a base afforded the N-dialkylaminoalkyl derivatives (II) in low yields. The reaction in the presence of dimethylsulfinyl carbanion in dimethylsulfoxide resulted in remarkable increase of the yields (Table I).

- 1) Part I: H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2028 (1970); Part II: H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2284 (1970).
- 2) Location: *Kawagishi 2-2-50 Toda-shi, Saitama.*
- 3) J. Krapcho, E.R. Spitzmiller and C.F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

TABLE I. 2-Aryl-3-hydroxy-5-alkyl-2,3,1,5-benzothiazepin-4(5H)-one

α, β	X	R	n	Salt	mp (°C)	Yield (%)	Formula	Analysis (%)						IR ν_{max} cm^{-1}
								Calcd.			Found			
								C	H	N	C	H	N	
α	H	H	2	HCl	215—218 (EtOH)	28.5 ^a	$\text{C}_{19}\text{H}_{23}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	60.22	6.12	7.39	59.69	5.92	7.27	1650
	H	H	3	HCl	198—199 (EtOH)	76	$\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}_2\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$	59.75	6.52	6.97	59.61	6.16	7.04	3420 1660
	H	4-MeO	2	HBr	225—228 (EtOH)	12.4 ^a	$\text{C}_{20}\text{H}_{25}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	52.99	5.56	6.18	53.36	5.79	6.06	1660
	H	4-MeO	3	HCl	151—156 (EtOH-ether)	54.5	$\text{C}_{21}\text{H}_{27}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	57.19	6.63	6.35	57.01	6.38	6.52	3500 1660
	H	3,4-diMeO	2	HCl	149—151 (EtOH)	12.5 ^a	$\text{C}_{21}\text{H}_{27}\text{O}_4\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	55.19	6.40	6.13	55.48	6.16	6.17	3360 1650
	H	3,4,5-triMeO	2	HBr	179—180 (EtOH-ether)	45 ^a	$\text{C}_{22}\text{H}_{29}\text{O}_5\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	51.45	5.69	5.46	51.44	5.69	5.40	3160 1650
	H	3,4,5-triMeO	3	HCl	187—188 (EtOH-acetone-ether)	56	$\text{C}_{23}\text{H}_{31}\text{O}_5\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	57.19	6.47	5.80	57.22	6.58	5.80	3450 1662
	H	4-Me	2	HCl	238—241 (MeOH)	60	$\text{C}_{20}\text{H}_{25}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	61.13	6.41	7.13	61.29	6.53	7.12	3400 1642
	H	4-Me	3	HCl	212—213 (EtOH)	68.3	$\text{C}_{21}\text{H}_{27}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	61.97	6.69	6.88	61.92	6.64	6.73	3400 1662
	H	4-Cl	2	HCl	215—217 (EtOH)	58.5	$\text{C}_{19}\text{H}_{22}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	55.20	5.37	6.78	54.84	5.19	6.77	1647
	H	2,4-diCl	2	HCl	215—217 (EtOH)	26.9 ^a	$\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	50.95	4.73	6.26	51.22	4.72	6.33	1660
	H	4-MeO	3 ^b	$(\text{CO}_2\text{H})_2$	189—190 (EtOH)	38.5	$\text{C}_{23}\text{H}_{28}\text{O}_2\text{N}_2\text{S}$	57.97	5.92	5.88	58.12	5.73	5.88	1750 1670
	Cl	H	2	HCl	228—230 (MeOH)	29.1 ^a	$\text{C}_{19}\text{H}_{22}\text{O}_2\text{N}_2\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$	54.03	5.49	6.63	53.74	5.38	6.53	3440 1675
	Cl	H	3	$(\text{CO}_2\text{H})_2$	126—128 (MeOH-EtOH)	52	$\text{C}_{22}\text{H}_{25}\text{O}_6\text{N}_2\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$	53.93	5.34	5.71	53.90	5.74	5.39	1710 1660
	Cl	4-MeO	2	HCl	217—220 (EtOH)	56.8	$\text{C}_{20}\text{H}_{24}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	54.17	5.45	6.32	54.46	5.56	6.61	3540 1642
	Cl	4-MeO	3	HCl	221—225 (EtOH-ether)	61	$\text{C}_{21}\text{H}_{26}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	54.78	5.69	6.08	55.02	5.83	5.90	3540 1640
β	Cl	3,4-diMeO	2	HCl	154—156 (EtOH)	25.2 ^a	$\text{C}_{21}\text{H}_{26}\text{O}_4\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	51.32	5.74	5.70	51.01	5.80	5.81	3480 1665
	Cl	3,4,5-triMeO	2	HClO_4	145—150 (EtOH)	69	$\text{C}_{22}\text{H}_{28}\text{O}_6\text{N}_2\text{S}\cdot\frac{1}{2}\text{H}_2\text{O}$	45.83	5.07	4.86	45.98	5.04	4.96	3360 1668
	Cl	4-Me	2	HCl	178—180 (EtOH)	62.5	$\text{C}_{20}\text{H}_{24}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	56.20	5.66	6.56	55.93	5.44	6.27	3400 1643
	Cl	4-Cl	2	HCl	194—197 (EtOH-ether)	63	$\text{C}_{19}\text{H}_{21}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	50.95	4.74	6.33	50.98	4.65	6.30	1640
	Cl	4-Cl	3	HCl	230—231 (EtOH)	43	$\text{C}_{20}\text{H}_{23}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	52.01	5.02	6.07	52.19	5.21	6.00	1645
	Cl	2,4-diCl	2	HCl	217—219 (EtOH)	56.8	$\text{C}_{19}\text{H}_{20}\text{O}_2\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	47.31	4.18	5.81	47.17	4.45	5.70	1660
	H	H	2	$(\text{CO}_2\text{H})_2$	237—238 (MeOH)	77.8	$\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}_2\text{S}$	61.99	5.98	7.23	61.67	6.07	7.06	1690 1625
	H	H	3	$(\text{CO}_2\text{H})_2$	198—199 (EtOH)	73.7	$\text{C}_{22}\text{H}_{26}\text{O}_6\text{N}_2\text{S}$	59.17	5.87	6.50	58.71	5.94	6.10	3440 1660
	H	4-MeO	2	HCl	201—202 (EtOH)	80.6	$\text{C}_{20}\text{H}_{25}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	58.74	6.12	6.85	58.94	6.18	6.81	3140 1678
	H	4-MeO	3	$(\text{CO}_2\text{H})_2$	166—169 (EtOH)	57	$\text{C}_{23}\text{H}_{28}\text{O}_7\text{N}_2\text{S}$	57.96	5.92	5.89	57.80	5.95	5.90	3400 1658
	Cl	4-MeO	2	HCl	180—183 (EtOH)	65	$\text{C}_{20}\text{H}_{24}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	54.17	5.45	6.32	54.17	5.47	6.32	3040 1663
	Cl	4-MeO	3	HCl	148—150 (EtOH-acetone-ether)	74	$\text{C}_{21}\text{H}_{26}\text{O}_3\text{N}_2\text{S}\cdot\text{H}_2\text{O}$	54.78	5.69	6.08	54.75	5.82	6.08	3180 1670

^a alkylation with NaH and alkylhalide in dioxane ^b 2-dimethylaminoisopropyl

TABLE II. 2-Aryl-3-acyloxy-5-alkyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one

α, β	X	R	R''	n	Salt	mp (°C)	Yield (%)	Formula	Analysis (%)						IR $\nu_{\max}^{\text{NaCl}}$ cm^{-1}
									Calcd.			Found			
									C	H	N	C	H	N	
α	H	H	Me	2	HBr	215—217 (EtOH-acetone)	86.5	$\text{C}_{21}\text{H}_{25}\text{O}_3\text{N}_2\text{SBr}$	54.19	5.41	6.02	54.32	5.28	6.16	1742 ^{a)} 1680
	H	H	Me	3	HCl	203—205 (EtOH-ether)	83.6	$\text{C}_{22}\text{H}_{27}\text{O}_3\text{N}_2\text{SCl}$	60.75	6.26	6.44	60.34	6.13	6.44	1738 1659
	H	H	<i>n</i> -C ₅ H ₁₁	2	HClO ₄	137—139 (EtOH)	80.5	$\text{C}_{25}\text{H}_{33}\text{O}_7\text{N}_2\text{SCl}$	55.49	6.14	5.17	55.36	6.23	4.91	1740 1680
	H	H	Et	3	MeSO ₃ H	132—133 (AcOEt-acetone)	26	$\text{C}_{24}\text{H}_{32}\text{O}_6\text{N}_2\text{S}_2$	56.67	6.34	5.58	57.06	6.35	5.57	1735 1663
	H	4-MeO	Me	2	HCl	187—188 (EtOH-ether)	84.5	$\text{C}_{22}\text{H}_{27}\text{O}_4\text{N}_2\text{SCl}$	57.48	6.03	6.21	57.26	6.09	6.02	1740 1680
	H	4-MeO	Et	2	HClO ₄	163—165 (EtOH)	91	$\text{C}_{23}\text{H}_{29}\text{O}_5\text{N}_2\text{SCl}$	52.22	5.52	5.30	52.02	5.50	5.52	1740 1680
	H	4-MeO	<i>n</i> -C ₃ H ₇	2	HClO ₄	161—162 (EtOH)	80	$\text{C}_{24}\text{H}_{31}\text{O}_5\text{N}_2\text{SCl}$	53.08	5.75	5.16	53.35	5.72	5.09	1740 1680
	H	4-MeO	<i>n</i> -C ₄ H ₉	2	HClO ₄	133—135 (EtOH)	86.2	$\text{C}_{25}\text{H}_{33}\text{O}_5\text{N}_2\text{SCl}$	53.90	5.97	5.03	54.18	6.00	5.06	1740 1680
	H	4-MeO	<i>i</i> -C ₄ H ₉	2		125—128 (isopropanol)	81	$\text{C}_{23}\text{H}_{29}\text{O}_4\text{N}_2\text{S}$	65.76	7.06	6.14	66.42	7.12	6.17	1740 1678
	H	4-MeO	<i>n</i> -C ₅ H ₁₁	2	HClO ₄	200—201 (EtOH-ether)	62	$\text{C}_{26}\text{H}_{35}\text{O}_5\text{N}_2\text{SCl} \cdot \frac{1}{2}\text{H}_2\text{O}$	53.83	6.32	4.83	53.93	6.24	4.72	1740 1683
	H	4-MeO	OEt	2	HBr	153—154 (EtOH-ether)	83.2	$\text{C}_{23}\text{H}_{29}\text{O}_5\text{N}_2\text{SBr}$	52.47	5.56	5.33	52.65	5.60	5.35	1745 1682
	H	4-MeO	C ₆ H ₅	2	HCl	203—204 (EtOH-ether)	86.5	$\text{C}_{27}\text{H}_{29}\text{O}_4\text{N}_2\text{SCl}$	63.21	5.70	5.46	63.68	5.81	5.31	1722 1682
	H	4-Me	Me	2	HCl	213—214 (EtOH-ether)	61.5	$\text{C}_{22}\text{H}_{27}\text{O}_3\text{N}_2\text{SCl}$	60.75	6.26	6.44	61.03	6.14	6.21	1745 1685
	H	4-Me	Me	3	HCl	203—205 (EtOH-ether)	61	$\text{C}_{23}\text{H}_{29}\text{O}_3\text{N}_2\text{S}$	61.52	6.53	6.24	61.21	6.43	5.90	1750 1690
	H	(MeO) ₃	Me	2	(CO ₂ H) ₂	117—119 (EtOH-ether)	66.7	$\text{C}_{26}\text{H}_{32}\text{O}_{10}\text{N}_2\text{S} \cdot \frac{1}{2}\text{H}_2\text{O}$	54.44	5.80	4.89	54.15	5.70	4.79	1740 1680
	H	(MeO) ₃	Me	3	HCl	136—139 (Me ₂ CO-ether)	82.5	$\text{C}_{25}\text{H}_{33}\text{O}_6\text{N}_2\text{SCl}$	57.18	6.33	5.34	57.16	6.57	4.78	1740 1675
β	Cl	4-MeO	Me	2	HCl	162—167 (EtOH-ether)	66	$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2\text{SCl}_2$	54.43	5.40	5.77	53.92	5.72	5.33	1740 1668
	Cl	4-MeO	Me	3	HCl	169—170 (MeOH-acetone-ether)	91	$\text{C}_{23}\text{H}_{28}\text{O}_4\text{N}_2\text{SCl}$	55.09	5.63	5.59	55.31	5.42	5.64	1738 1676
	Cl	H	Me	2	HCl	199—200 (EtOH-ether)	70.5	$\text{C}_{21}\text{H}_{24}\text{O}_3\text{N}_2\text{SCl}_2$	55.38	5.31	6.15	55.39	5.04	6.07	1740 1663
	Cl	H	Me	3	HCl	159—161 (MeOH-ether)	75	$\text{C}_{22}\text{H}_{26}\text{O}_3\text{N}_2\text{SCl}_2 \cdot \text{H}_2\text{O}$	54.21	5.79	5.75	54.55	5.72	5.84	1735 1668
	Cl	4-Cl	Me	2	HCl	156—158 (EtOH-ether)	57.6	$\text{C}_{21}\text{H}_{23}\text{O}_3\text{N}_2\text{SCl}_2$	51.49	4.73	5.72	51.09	4.94	5.71	1740 1680
	Cl	4-Cl	Me	3	HCl	155—156 (EtOH-acetone-ether)	75.5	$\text{C}_{22}\text{H}_{25}\text{O}_3\text{N}_2\text{SCl}_3$	52.44	5.00	5.56	52.57	5.47	5.12	1740 1680
	Cl	H	Me	2	HCl	211—214 (EtOH-ether)	79.3	$\text{C}_{22}\text{H}_{25}\text{O}_3\text{N}_2\text{SCl}$	59.91	5.99	6.65	59.72	6.09	6.59	1745 1670
	H	H	Me	3	HCl	246—248 (EtOH)	80	$\text{C}_{22}\text{H}_{27}\text{O}_3\text{N}_2\text{SCl}$	60.75	6.26	6.44	60.65	6.43	6.22	1741 1690
	H	4-MeO	Me	2	HCl	202—202 (EtOH-ether)	93.5	$\text{C}_{22}\text{H}_{27}\text{O}_4\text{N}_2\text{SCl} \cdot \text{H}_2\text{O}$	56.34	6.21	5.97	56.64	6.11	5.89	1741 1675
	H	4-MeO	Me	3	HCl	168—171 (EtOH-ether)	56.4	$\text{C}_{23}\text{H}_{29}\text{O}_4\text{N}_2\text{SCl}$	59.38	6.29	6.02	59.19	6.54	5.93	1742 1660
	Cl	4-MeO	Me	2	HBr	202—206 (EtOH-ether)	84	$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}_2\text{SBrCl} \cdot \text{H}_2\text{O}$	48.22	5.15	5.11	47.92	4.78	4.91	1730 1676
	Cl	4-MeO	Me	3	HCl	208—210 (EtOH-acetone-ether)	84	$\text{C}_{23}\text{H}_{28}\text{O}_4\text{N}_2\text{SCl}_2$	55.09	5.63	5.59	55.14	5.84	5.58	1733 1666

a) measured in CCl₄

As an alternative method for the preparation of the N-substituted benzothiazepine ring, the reaction of 2-(N-alkylamino)thiophenols (III)^{4,5} with methyl 4-methoxyphenylglycidate was carried out to give methyl 2-hydroxy-3-(4-methoxyphenyl)-3-(2-alkylaminophenylthio)propionates (IV). Hydrolysis of IV followed by cyclization of the resultant amino acid gave II. The N-substituted benzothiazepine thus prepared, however, proved to be 2,3-*trans* form (β -series) as indicated by the nuclear magnetic resonance (NMR) spectrum (11 cps: C₂-H-C₃-H).⁶

Acylation of II with acid anhydrides or acid chlorides in pyridine gave 2-ary-3-acyloxy-5-dialkylaminoalkyl-1,5-benzothiazepin-4(5H)-one (VI) (Table II).

Alkaline hydrolysis of VI gave the original alcohols (II).

For an alternative route to VI, reaction of VIIa which was obtainable from I by acetylation with acetyl chloride, with 2-dimethylaminoethyl chloride was carried out in dioxane in the presence of sodium hydride to give two products. One was identical with IIa- α described above, and the other was 2-phenyl-5-dimethylaminoethyl-1,5-benzothiazepin-4(5H)-one (VIIIa). The structure of VIIIa was confirmed from its analytical results and the similarity of its spectral data to that of an analogous product reported by us previously.¹⁾ The expected product (VIa- α) was not obtained in this case. A similar elimination of acetic acid occurred

4) *o*-Aminothiophenols are generally unstable in the air, and give disulfides readily. While, *o*-dialkylaminothiophenols are comparatively stable under these conditions.

5) K. Fujii, *Yakugaku Zasshi*, **77**, 3 (1957).

6) The coupling constant between C₂-H and C₃-H shows 7 cps in the *cis* compounds (α -series) and 11 cps in the *trans* ones (β -series).

TABLE III. 2-(4-Methoxyphenyl)-3-alkyloxy-5-(2-dimethylaminoethyl)-*cis*-2,3-dihydro-1,5-benzothiazepin-4(5H)-one

R'''	Salt	Method	Yield (%)	mp (°C)	Formula	Analysis (%)						IR $\nu_{\text{max}}^{\text{Nujol}}$ cm ⁻¹
						Calcd.			Found			
						C	H	N	C	H	N	
Me	HClO ₄	1	38	128—129 (isopropanol)	C ₂₁ H ₂₇ O ₇ N ₂ SCI	51.79	5.59	5.75	51.46	5.67	5.59	1672
	HClO ₄	2	18	175—176 (EtOH)		51.88	5.88	5.49	51.86	5.77	5.45	1674
Et	HClO ₄	1	54	202 (EtOH)	C ₂₂ H ₂₉ O ₇ N ₂ SCI·½H ₂ O	51.83	6.24	5.25	52.27	5.96	5.18	1660
	HClO ₄	2	26	162 (EtOH)		70.11	6.54	6.06	69.91	6.61	6.02	1678
<i>n</i> -Pr	HClO ₄	2	20	134—135 (EtOH)	C ₂₃ H ₃₁ O ₇ N ₂ SCI·H ₂ O							
	Bz	2	64	134—135 (EtOH)

TABLE IV. The Quaternary Salts

R	n	Salt	Yield (%)	mp (°C)	Formula	Analysis (%)									IR $\nu_{\text{max}}^{\text{Nujol}}$ cm ⁻¹
						Calcd.			Found						
						C	H	N	C	H	N	C	H	N	
H	2	MeI	81.6	162—167 (acetone—ether)	C ₂₁ H ₂₇ O ₄ N ₂ SI·½H ₂ O	48.18	5.39	5.35	48.27	5.49	4.90	1660			
Ac	2	MeI	80.0	178—181 (EtOH)	C ₂₃ H ₂₉ O ₄ N ₂ SI·½H ₂ O	48.85	5.39	4.95	48.98	5.12	4.74	1735			
Ac	2	EtBr	92.3	143—145 (acetone—ether)	C ₂₄ H ₃₁ O ₄ N ₂ SI·½H ₂ O	54.13	6.06	5.26	54.29	6.12	5.08	1738			
Ac	2	n-PrBr	44.3	137—139 (acetone—ether)	C ₂₅ H ₃₃ O ₄ N ₂ SI·½H ₂ O	54.94	6.27	5.13	55.12	6.29	5.05	1740			
H	3	MeI	92.0	237—238 (EtOH—ether)	C ₂₂ H ₂₉ O ₃ N ₂ SI	50.00	5.33	5.30	49.92	5.65	5.01	3290			
Ac	3	MeI	87.0	148—154 (acetone—ether)	C ₂₄ H ₃₁ O ₄ N ₂ SI·¾H ₂ O	48.29	5.74	4.69	48.77	5.54	4.44	1738			
H	3	EtBr	84.5	225—226 (acetone—ether)	C ₂₃ H ₃₁ O ₃ N ₂ SI	55.62	6.47	5.40	55.75	6.31	5.65	3160			
Ac	3	EtBr	88.5	209—210 (EtOH)	C ₂₅ H ₃₃ O ₄ N ₂ SI	55.86	6.19	5.21	55.74	6.23	4.99	1730			

also with VIa- α which gave IX by the similar reaction. On the other hand VIIb- α gave the desired product (VIb- α) in 25% yield together with a small amount of IIB- α . 3-Alkoxy derivatives (X) were prepared by alkylation of IIB with sodium hydride-alkyl halides or -alkyl sulfates (Table III).

Treating of II and VI with alkyl halides furnished the quarternary salts (XI) and (XII) respectively (Table IV).

The pharmacological data of the 1,5-benzothiazepine derivatives prepared by these methods will be presented in a latter communication.

Experimental⁷⁾

N-Alkylation of 2-Aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (I)—1) Alkylation with NaH and alkyl halide in dioxane (General Procedure). To a solution of I (0.10 mole) in 500 ml of dioxane was added 64% NaH in mineral oil (0.10 mole) at 25°. The mixture was stirred for 1 hour at 25°. A solution of an alkyl halide (0.15 mole) in 100 ml of dioxane was added dropwise to the mixture. The resultant mixture was heated with stirring at 60–65° for 6 hours. Evaporation of the solvent gave a crude solid, 10% which was suspended in CHCl₃-ether and extracted with 10% HCl. The aqueous layer was made alkaline with K₂CO₃ and extracted with ether. The extract was washed with water, dried over Na₂SO₄ and then evaporated. The residual crystals were isolated as an appropriate salt with a mineral acid to afford the salt of 2-aryl-3-hydroxy-5-dialkylaminoethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (II). The starting material was recovered from the insoluble portion in 10% HCl. Products were shown in Table I.

2) Alkylation with Dimethylsuliny anion (General Procedure). To 64% NaH in mineral oil (0.12 mole) was added 250 ml of DMSO under nitrogen. The mixture was heated with stirring at 70° for 1 hour. After cooling to room temperature, I (0.10 mole) was added to the mixture. The resultant mixture was stirred for 1 hour. An alkyl halide (0.12 mole) was added to the mixture. The reaction mixture was stirred overnight at room temperature, then poured into ice-water and extracted with benzene. The organic layer was extracted with 10% HCl. The HCl layer was basified with Na₂CO₃ and extracted with CHCl₃. Evaporation of the solvent gave II. Products were shown in Table I.

Methyl 2-Hydroxy-3-(4-methoxyphenyl)-3-(2-diethylaminoethyl)aminophenylthio-propionate (IVa)—A mixture of 3-(2-diethylaminoethyl)-2-benzothiazolinone⁵⁾ (8.0 g), KOH (8.0 g), EtOH (60 ml) and H₂O was refluxed for 2 hours. After removal of EtOH, 15 ml of water was added to the reaction mixture. Neutralization of the aqueous solution with AcOH gave crude precipitates, which were collected by filtration, washed with ether and dried overnight under reduced pressure to afford 2-N-(2-diethylaminoethyl)aminothiophenol (IIIa) (7.5 g), mp 104–108°.

A mixture of IIIa (7.5 g) and methyl 3-(4-methoxyphenyl) glycidate (6.7 g) was heated with stirring for 3 hours at 130–140° under nitrogen. The reaction mixture was cooled, dissolved in ether and extracted with 10% HCl. The aqueous layer was neutralized with K₂CO₃ and extracted with ether. The extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave an oily product (6.5 g), which was chromatographed on Al₂O₃. IVa (1.73 g; 12.5%), mp 84–85° (MeOH), was obtained from the first portion of benzene eluate. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3320, 1740. Anal. Calcd. for C₂₃H₃₂O₄N₂S: C, 63.86; H, 7.45; N, 6.48; S, 7.41. Found: C, 64.01; H, 7.49; N, 6.28; S, 7.28. NMR (CDCl₃) τ : 8.95 (6H, triplet, 7 cps), 7.40 (4H, quartet, 7 cps), 7.7–6.05 (8H, multiplet), 6.53 (3H, singlet), 6.28 (3H, singlet), 5.76 (1H, multiplet), 5.14 (1H, multiplet), 3.6–2.3 (8H, multiplet).

From the second portion of benzene eluate, oily 4-(2-diethylaminoethyl)-2H-1,4-benzothiazin-3(4H)-one was obtained, which was purified as a picrate, the structure of which confirmed by spectral data. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 1658. NMR (CDCl₃) τ : 8.98 (6H, triplet, 7 cps), 7.41 (4H, quartet, 7 cps), 6.67 (2H, singlet), 6.00 (2H, doublet, 9 cps), 5.90 (2H, doublet, 9 cps), 3.2–2.5 (4H, multiplet). Anal. Calcd. for C₂₀H₂₃O₈N₅S (picrate): C, 48.68; H, 4.70; N, 14.19; S, 6.50. Found: C, 48.65; H, 4.68; N, 13.90; S, 6.37.

Oily IVb (Y=CH₃) was obtained in 12.8% yield by the same procedure as that described above. IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 3480, 3370, 1732.

2-Hydroxy-3-(4-methoxyphenyl)-3-(2-diethylaminoethyl)aminophenylthiopropionic acid (Va)—A mixture of IVa (1.0 g), 1N NaOH (15 ml) and EtOH (3 ml) was heated for 3 hours on a steam bath. Evaporation of the solvent and then neutralization with AcOH gave 950 mg of Va, mp 184–187°. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3305, 1610, 1585. Oily Vb (Y=CH₃) was obtained in 77.1% yield by the same procedure as that described above. IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 3355, 1712.

2-(4-Methoxyphenyl)-3-hydroxy-5-(2-diethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4-(5H)-one (IIc- β)—A suspension of Va (800 mg) in 40 ml of xylene was refluxed for 20 hours. Evaporation of the solvent under reduced pressure gave IIc- β (260 mg; 34.2%), mp 142–143° (acetone-isopropyl ether). IR

7) All melting points were uncorrected.

$\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1660. NMR (CDCl_3) τ : 9.03 (6H, triplet, 7 cps), 7.46 (4H, quartet, 7 cps), 7.7—7.0 (4H, multiplet), 6.26 (3H, singlet) 5.82 (2H, multiplet), 3.3—2.2 (8H, multiplet). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_3\text{N}_2\text{S}$: C, 65.97; H, 7.05; N, 6.99; S, 8.01. Found: C, 66.02; H, 7.08; N, 6.76; S, 8.03.

IId- β ($\text{R}=\text{OCH}_3$, $\text{N}_5\text{—Me}$) was obtained in 30.4% yield by the same procedure as that described above, mp 142—144° (EtOH). IId- β was identified with the previous sample.¹⁾

O-Acylation of II—1) Acylation with Acid Anhydride (General Procedure): II was dissolved in three parts of Ac_2O and heated for 4—5 hours on a steam bath. Removal of excess Ac_2O under diminished pressure gave 2-aryl-3-acyloxy-5-dialkylaminoethyl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VI). Products were shown in Table II.

2) Acylation with Acyl Halide (General Procedure): To a solution of II (1.50 g) in 6 ml of pyridine was added an acyl halide (1.2—1.5 equivalents) at 5°. The mixture was left for 5—16 hours in a refrigerator then poured into ice-water. The resulting oily product was extracted with CHCl_3 , washed with NaHCO_3 solution and water, then dried over Na_2SO_4 . Evaporation of the solvent gave VI. Products were shown in Table II.

Hydrolysis of VI—A mixture of VI (1.0 g), 10% NaOH (1.5 equivalents) and EtOH (5 ml) was stirred for 30 min at room temperature. Neutralization of the reactant with 10% HCl gave crude II in almost quantitative yields.

Reaction of VI with NaH in Dioxane—A mixture of 2-phenyl-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIa) (290 mg) and 64% NaH in mineral oil (41 mg) in 7 ml of dioxane was stirred overnight at room temperature. After additional NaH in mineral oil (41 mg) was added, the mixture was heated with stirring at 60—65° for 6 hours. Evaporation of the solvent gave an oily product, which was dissolved in ether and extracted with 10% HCl. The HCl layer was basified with K_2CO_3 and extracted with ether. The extract was washed with water and dried over Na_2SO_4 . Evaporation of the solvent gave an oily product, which was isolated as a hydrobromide to afford 230 mg (75.5%) of 2-phenyl-5-(2-dimethylaminoethyl)-1,5-benzothiazepin-4(5H)-one hydrobromide (IXa·HBr), mp 223—225°. The hydrochloride of IXa was identified with an authentic sample.⁹⁾ Reaction of 2-(4-methoxyphenyl)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIb) was carried out by the same manner as that described above. The crude base, which was obtained by evaporation of the extract solvent, was chromatographed on Al_2O_3 to afford three products. 2-(4-Methoxyphenyl)-5-(2-dimethylaminoethyl)-1,5-benzothiazepin-4(5H)-one hydrochloride (IXb·HCl), mp 219—221° (EtOH-ether) was obtained in 35% yield from the first portion of ether eluate. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1620. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2\text{N}_2\text{S}\text{Cl}$: C, 61.43; H, 5.93; N, 7.16. Found: C, 61.30; H, 5.89; N, 6.93.

A product, mp 281—282° (EtOH), was obtained from the second portion of ether eluate. It was an isomer of IXb in view of its elementary analysis data.

IIf ($\text{R}=4\text{-MeO}$, $\text{R}'=\text{CH}_3$, $\text{X}=\text{H}$, $n=2$) was obtained in 40% yield from elution with ether-MeOH(9:1).

O-Alkylation of II—1) Alkylation with Alkylsulfate (Representatives): A mixture of IIf ($\text{R}=4\text{-MeO}$, $\text{R}'=\text{Me}$, $\text{X}=\text{H}$, $n=2$) (1.20 g) and 64% NaH in mineral oil (190 mg) in 30 ml of abs. benzene was refluxed for 1 hour under nitrogen. Me_2SO_4 (425 mg) in 5 ml of abs. benzene was added dropwise to the mixture at room temperature. The reaction mixture was stirred overnight at room temperature, and then washed with dil. NH_4OH and water. Evaporation of the solvent gave 0.83 g of an oily product, which was crystallized by trituration with isopropyl ether to afford Xb ($\text{R}''=\text{Me}$) (0.47 g; 38%), mp 126—128°. Recrystallization from isopropylether gave a pure product, mp 128.5—129.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1672. NMR (CDCl_3) τ : 7.78 (6H, singlet), 6.83 (3H, singlet), 6.23 (3H, singlet), 6.11 (1H, doublet, 7 cps), 5.04 (1H, doublet, 7 cps), 3.35—2.20 (8H, multiplet).

2) Alkylation with Alkyl Halide (Representatives): A mixture of IIf (2.0 g) and 63% NaH in mineral oil (250 ml) in 30 ml of dioxane was heated at 65° for 1 hour. EtBr (650 mg) in 2 ml of dioxane was added to the mixture at 40°. The reaction mixture was heated for 17 hours at 60°, and then poured into 100 ml of water and extracted with ether. Evaporation of the solvent gave a crude oily product (1.95 g), from the ether solution of which the starting material (0.53 g) was recovered. Treatment of the ether filtrate with 60% HClO_4 gave 850 mg of $\text{X}\cdot\text{HClO}_4$. Recrystallization from EtOH gave 700 mg of pure $\text{X}\cdot\text{HClO}_4$, mp 202.5°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1670. Other products were shown in Table III.

Formation of the Quarternary Salts (Representatives)—1) A mixture of IIf (0.80 g) and CH_3I (1 ml) in 10 ml of acetone was left overnight in a refrigerator. The crystals were collected by filtration. Recrystallization from acetone-ether gave 0.90 g of 2-(4-methoxyphenyl)-3-hydroxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one methylidide (XIb) ($\text{R}'''\text{X}=\text{CH}_3\text{I}$, $n=2$), mp 162—167°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3440, 1660.

2) A solution of VIb (2.2 g) in 20 ml of ethyl bromide was heated for 18 hours in a sealed tube at about 70°. Removal of the excess solvent under diminished pressure gave 2-(4-methoxyphenyl)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one ethylbromide (XIId) (2.61 g; 92.3%),

bp143—144° (acetone-ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3400, 1738, 1682.

3) A solution of XIb (0.67 g) in 10 ml of Ac₂O was refluxed for 3 hours. Removal of excess Ac₂O under diminished pressure gave 0.63 g (87%) of VIIb. All the quaternary salts were shown in Table IV.

Acetylation of I—To a solution of 2-phenyl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (Ia) (200 mg) in 4 ml of pyridine was added dropwise AcCl (58 mg) under ice-cooling. The mixture was left overnight in a refrigerator, then poured into ice-water. The resulting crude solid was collected by filtration and recrystallized from benzene to afford 120 mg (52%) of 2-phenyl-3-acetoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIIb). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1745, 1695. *Anal.* Calcd. for C₁₇H₁₅O₃NS· $\frac{1}{3}$ C₆H₆: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.16; H, 4.85; N, 4.41. 2-(4-Methoxyphenyl)-3-acetoxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VIIb), mp 200—202°, was obtained in 57% yield by the same procedure as that described above. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1745, 1695. *Anal.* Calcd. for C₁₈H₁₇O₄NS: C, 62.95; H, 4.99; N, 4.08; S, 9.34. Found: C, 62.63; H, 5.01; N, 4.16; S, 9.15.

N-Alkylation of VII—The same treatment of VIIa with NaH and dimethylaminoethyl chloride as that previously employed in the case of N-alkylation of I gave IIa-HBr, mp 225—227° (EtOH-ether) 21% yield and 2-phenyl-1,5-benzothiazepin-4(5H)-one(VIIIa), mp 209—214°, in 33% yield. The latter product was identified with an authentic sample.⁸⁾

The same treatment of VIIb with dimethylsulfinyl carbanion and dimethylaminoethyl chloride in DMSO as that previously employed in the case of N-alkylation of I gave IIb in 3% yield and VIb in 25% yield along with the starting material in 27% yield.

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