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# Synthesis of 1,5-Benzothiazepine Derivatives. III[1]

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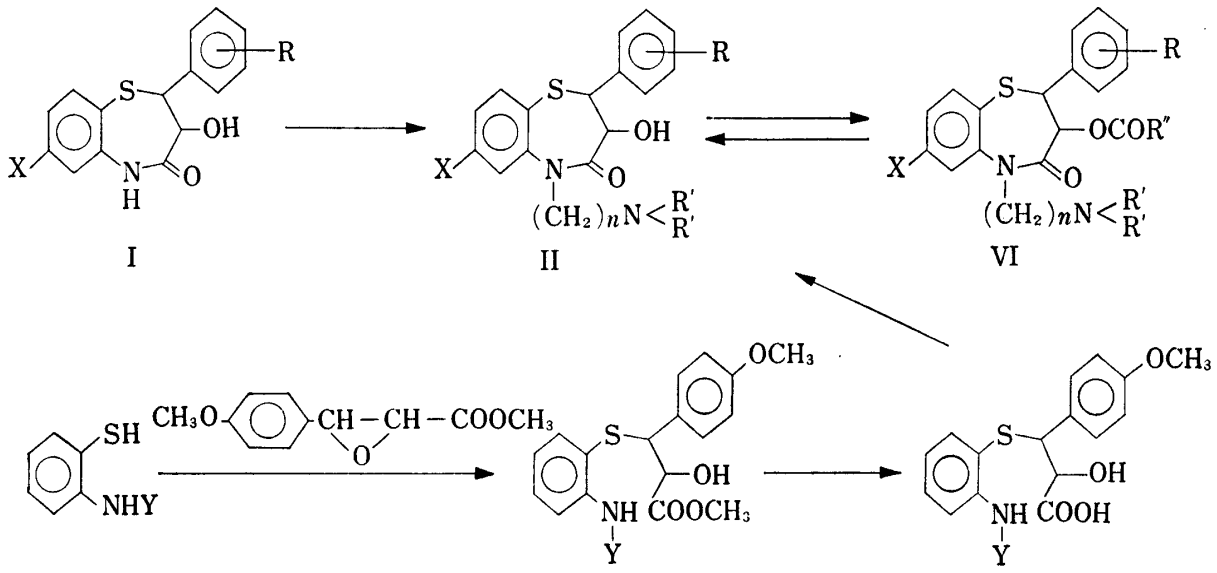
Various derivatives of 2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (I) were synthesized. Alternative routes to 2-aryl-3-hydroxy-5-alkyl-*trans*-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (II-$\beta$) and 2-aryl-3-acetoxy-5-dimethylaminoethyl-*cis*-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (VI-$\alpha$) 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.



IIIa : Y = $CH_2CH_2N<^{Et}_{Et}$
IIIb : Y = Me

IVa : Y = $CH_2CH_2N<^{Et}_{Et}$
IVb : Y = Me

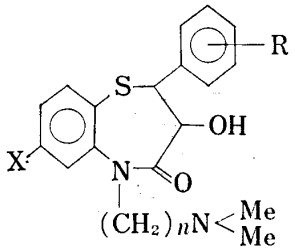
Va : Y = $CH_2CH_2N<^{Et}_{Et}$
Vb : Y = Me

Chart 1

Reaction of 2-aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones (I) with dialkylaminoethyl 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).

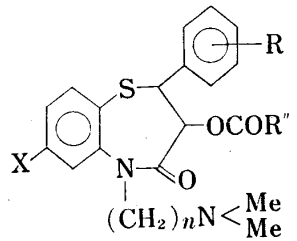
TABLE I. 2-Aryl-3-hydroxy-5-alkyl-2,3-1,5-benzothiazepin-4(5H)-one




| α,β | X | R | n | Salt | mp (°C) | Yield (%) | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N | IR $\nu_{max}^{Nujol}$ cm$^{-1}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α | H | H | 2 | HCl | 215—218 (EtOH) | 28.5[a] | $C_{19}H_{23}O_2N_2SCl$ | 60.22 | 6.12 | 7.39 | 59.69 | 5.92 | 7.27 | 1650 | |
| | H | H | 3 | HCl | 198—199 (EtOH) | 76 | $C_{20}H_{25}O_2N_2SCl\cdot\frac{1}{2}H_2O$ | 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] | $C_{20}H_{25}O_3N_2SBr$ | 52.99 | 5.56 | 6.18 | 53.36 | 5.79 | 6.06 | 1660 | |
| | H | 4-MeO | 3 | HCl | 151—156 (EtOH–eter) | 54.5 | $C_{21}H_{27}O_3N_2SCl\cdot H_2O$ | 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] | $C_{21}H_{27}O_4N_2SCl\cdot H_2O$ | 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] | $C_{22}H_{29}O_5N_2SBr$ | 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 | $C_{29}H_{31}O_5N_2SCl$ | 57.19 | 6.47 | 5.80 | 57.22 | 6.58 | 5.80 | 3450 | 1662 |
| | H | 4-Me | 2 | HCl | 238—241 (MeOH) | 60 | $C_{20}H_{25}O_2NSCl$ | 61.13 | 6.41 | 7.13 | 61.29 | 6.53 | 7.12 | 3400 | 1642 |
| | H | 4-Me | 3 | HCl | 212—213 (EtOH) | 68.3 | $C_{21}H_{27}O_2N_2SCl$ | 61.97 | 6.69 | 6.88 | 61.92 | 6.64 | 6.73 | 3400 | 1662 |
| | H | 4-Cl | 2 | HCl | 215—217 (EtOH) | 58.5 | $C_{19}H_{22}O_2N_2SCl_2$ | 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] | $C_{19}H_{21}O_2N_2SCl_2$ | 50.95 | 4.73 | 6.26 | 51.22 | 4.72 | 6.33 | 1660 | |
| | H | 4-MeO | 3[b] | $(CO_2H)_2$ | 189—190 (EtOH) | 38.5 | $C_{23}H_{28}O_7N_2S$ | 57.97 | 5.92 | 5.88 | 58.12 | 5.73 | 5.88 | 1750 | 1670 |
| | Cl | H | 2 | HCl | 228—230 (MeOH) | 29.1[a] | $C_{19}H_{22}O_2N_2SCl\cdot\frac{1}{2}H_2O$ | 54.03 | 5.49 | 6.63 | 53.74 | 5.38 | 6.53 | 3440 | 1675 |
| | Cl | H | 3 | $(CO_2H)_2$ | 126—128 (MeOH–EtOH) | 52 | $C_{22}H_{25}O_6N_2SCl\cdot\frac{1}{2}H_2O$ | 53.93 | 5.34 | 5.71 | 53.90 | 5.74 | 5.39 | 1710 | 1660 |
| | Cl | 4-MeO | 2 | HCl | 217—220 (EtOH) | 56.8 | $C_{20}H_{24}O_3N_2SCl_2$ | 54.17 | 5.45 | 6.32 | 54.46 | 5.56 | 6.61 | 3540 | 1642 |
| | Cl | 4-MeO | 3 | HCl | 221—225 (EtOH–ether) | 61 | $C_{21}H_{26}O_3N_2SCl_2$ | 54.78 | 5.69 | 6.08 | 55.02 | 5.83 | 5.90 | 3540 | 1640 |
| | Cl | 3,4-diMeO | 2 | HCl | 154—156 (EtOH) | 25.2[a] | $C_{21}H_{26}O_4N_2SCl_2\cdot H_2O$ | 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 | $C_{22}H_{28}O_9N_2SCl_2\cdot\frac{1}{2}H_2O$ | 45.83 | 5.07 | 4.86 | 45.98 | 5.04 | 4.96 | 3360 | 1668 |
| | Cl | 4-Me | 2 | HCl | 178—180 (EtOH) | 62.5 | $C_{20}H_{24}O_2N_2SCl_2$ | 56.20 | 5.66 | 6.56 | 55.93 | 5.44 | 6.27 | 3400 | 1643 |
| | Cl | 4-Cl | 2 | HCl | 194—197 (EtOH–ether) | 63 | $C_{19}H_{21}O_2N_2SCl_3$ | 50.95 | 4.74 | 6.33 | 50.98 | 4.65 | 6.30 | 1640 | |
| | Cl | 4-Cl | 3 | HCl | 230—231 (EtOH) | 43 | $C_{20}H_{23}O_2N_2SCl_3$ | 52.01 | 5.02 | 6.07 | 52.19 | 5.21 | 6.00 | 1645 | |
| | Cl | 2,4-diCl | 2 | HCl | 217—219 (EtOH) | 56.8 | $C_{19}H_{20}O_2N_2SCl_4$ | 47.31 | 4.18 | 5.81 | 47.17 | 4.45 | 5.70 | 1660 | |
| β | H | H | 2 | $(CO_2H)_2$ | 237—238 (MeOH) | 77.8 | $C_{20}H_{23}O_4N_2S$ | 61.99 | 5.98 | 7.23 | 61.67 | 6.07 | 7.06 | 1690 | 1625 |
| | H | H | 3 | $(CO_2H)_2$ | 198—199 (EtOH) | 73.7 | $C_{22}H_{26}O_6N_2S$ | 59.17 | 5.87 | 6.50 | 58.71 | 5.94 | 6.10 | 3440 | 1660 |
| | H | 4-MeO | 2 | HCl | 201—202 (EtOH) | 80.6 | $C_{20}H_{25}O_3N_2SCl$ | 58.74 | 6.12 | 6.85 | 58.94 | 6.18 | 6.81 | 3140 | 1678 |
| | H | 4-MeO | 3 | $(CO_2H)_2$ | 166—169 (EtOH) | 57 | $C_{23}H_{28}O_7N_2S$ | 57.96 | 5.92 | 5.89 | 57.80 | 5.95 | 5.90 | 3400 | 1658 |
| | Cl | 4-MeO | 2 | HCl | 180—183 (EtOH) | 65 | $C_{20}H_{24}O_3N_2SCl_2$ | 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 | $C_{21}H_{26}O_3N_2SCl_2$ | 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 (%) Calcd. C | H | N | Found C | H | N | IR $\nu_{max}^{Nujol}$ cm$^{-1}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α | H | H | Me | 2 | HBr | 215—217 (EtOH–acetone) | 86.5 | $C_{21}H_{25}O_3N_2SBr$ | 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 | $C_{22}H_{27}O_3N_2SCl$ | 60.75 | 6.26 | 6.44 | 60.34 | 6.13 | 6.44 | 1738 | 1659 |
| | H | H | $n$-$C_5H_{11}$ | 2 | $HClO_4$ | 137—139 (EtOH) | 80.5 | $C_{25}H_{33}O_7N_2SCl$ | 55.49 | 6.14 | 5.17 | 55.36 | 6.23 | 4.91 | 1740 | 1680 |
| | H | H | Et | 3 | $MeSO_3H$ | 132—133 (AcOEt–acetone) | 26 | $C_{24}H_{32}O_6N_2S_2$ | 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 | $C_{22}H_{27}O_4N_2SCl$ | 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 | $C_{23}H_{29}O_8N_2SCl$ | 52.22 | 5.52 | 5.30 | 52.02 | 5.50 | 5.52 | 1740 | 1680 |
| | H | 4-MeO | $n$-$C_3H_7$ | 2 | $HClO_4$ | 161—162 (EtOH) | 80 | $C_{24}H_{31}O_8N_2SCl$ | 53.08 | 5.75 | 5.16 | 53.35 | 5.72 | 5.09 | 1740 | 1680 |
| | H | 4-MeO | $n$-$C_4H_9$ | 2 | $HClO_4$ | 133—135 (EtOH) | 86.2 | $C_{25}H_{33}O_8N_2SCl$ | 53.90 | 5.97 | 5.03 | 54.18 | 6.00 | 5.06 | 1740 | 1680 |
| | H | 4-MeO | $i$-$C_4H_9$ | 2 | | 125—128 (isopro$_2$-O) | 81 | $C_{25}H_{32}O_4N_2S$ | 65.76 | 7.06 | 6.14 | 66.42 | 7.12 | 6.17 | 1740 | 1678 |
| | H | 4-MeO | $n$-$C_5H_{11}$ | 2 | $HClO_4$ | 200—201 (EtOH–ether) | 62 | $C_{26}H_{35}O_8N_2SCl\cdot\frac{1}{2}H_2O$ | 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 | $C_{23}H_{29}O_5N_2SBr$ | 52.47 | 5.56 | 5.33 | 52.65 | 5.60 | 5.35 | 1745 | 1682 |
| | H | 4-MeO | $C_6H_5$ | 2 | HCl | 203—204 (EtOH–ether) | 86.5 | $C_{27}H_{29}O_4N_2SCl$ | 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 | $C_{22}H_{27}O_3N_2SCl$ | 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 | $C_{23}H_{29}O_3N_2S$ | 61.52 | 6.53 | 6.24 | 61.21 | 6.43 | 5.90 | 1750 | 1690 |
| | H | $(MeO)_3$ | Me | 2 | $(CO_2H)_2$ | 117—119 (EtOH–ether) | 66.7 | $C_{26}H_{32}O_{10}N_2S\cdot\frac{1}{2}H_2O$ | 54.44 | 5.80 | 4.89 | 54.15 | 5.70 | 4.79 | 1740 | 1680 |
| | H | $(MeO)_3$ | Me | 3 | HCl | 136—139 ($Me_2CO$–ether) | 82.5 | $C_{25}H_{33}O_6N_2SCl$ | 57.18 | 6.33 | 5.34 | 57.16 | 6.57 | 4.78 | 1740 | 1675 |
| | Cl | 4-MeO | Me | 2 | HCl | 162—167 (EtOH–ether) | 66 | $C_{22}H_{26}O_4N_2SCl_2$ | 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 | $C_{23}H_{28}O_4N_2SCl$ | 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 | $C_{21}H_{24}O_3N_2SCl_2$ | 55.38 | 5.31 | 6.15 | 55.39 | 5.04 | 6.07 | 1740 | 1663 |
| | Cl | H | Me | 3 | HCl | 159—161 (MeOH–ether) | 75 | $C_{22}H_{26}O_3N_2SCl_2\cdot H_2O$ | 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 | $C_{21}H_{23}O_3N_2SCl_2$ | 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 | $C_{22}H_{25}O_3N_2SCl_3$ | 52.44 | 5.00 | 5.56 | 52.57 | 5.47 | 5.12 | 1740 | 1680 |
| β | H | H | Me | 2 | HCl | 211—214 (EtOH–ether) | 79.3 | $C_{22}H_{25}O_3N_2SCl$ | 59.91 | 5.99 | 6.65 | 59.72 | 6.09 | 6.59 | 1745 | 1670 |
| | H | H | Me | 3 | HCl | 246—248 (EtOH) | 80 | $C_{22}H_{27}O_3N_2SCl$ | 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 | $C_{22}H_{27}O_4N_2SCl\cdot H_2O$ | 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 | $C_{23}H_{29}O_4N_2SCl$ | 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 | $C_{22}H_{26}O_4N_2SBrCl\cdot H_2O$ | 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 | $C_{23}H_{28}O_4N_2SCl_2$ | 55.09 | 5.63 | 5.59 | 55.14 | 5.84 | 5.58 | 1733 | 1666 |

a) measured in $CCl_4$

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 ($\beta$-series) as indicated by the nuclear magnetic resonance (NMR) spectrum (11 cps: $C_2$-H-$C_3$-H).[6]

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

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

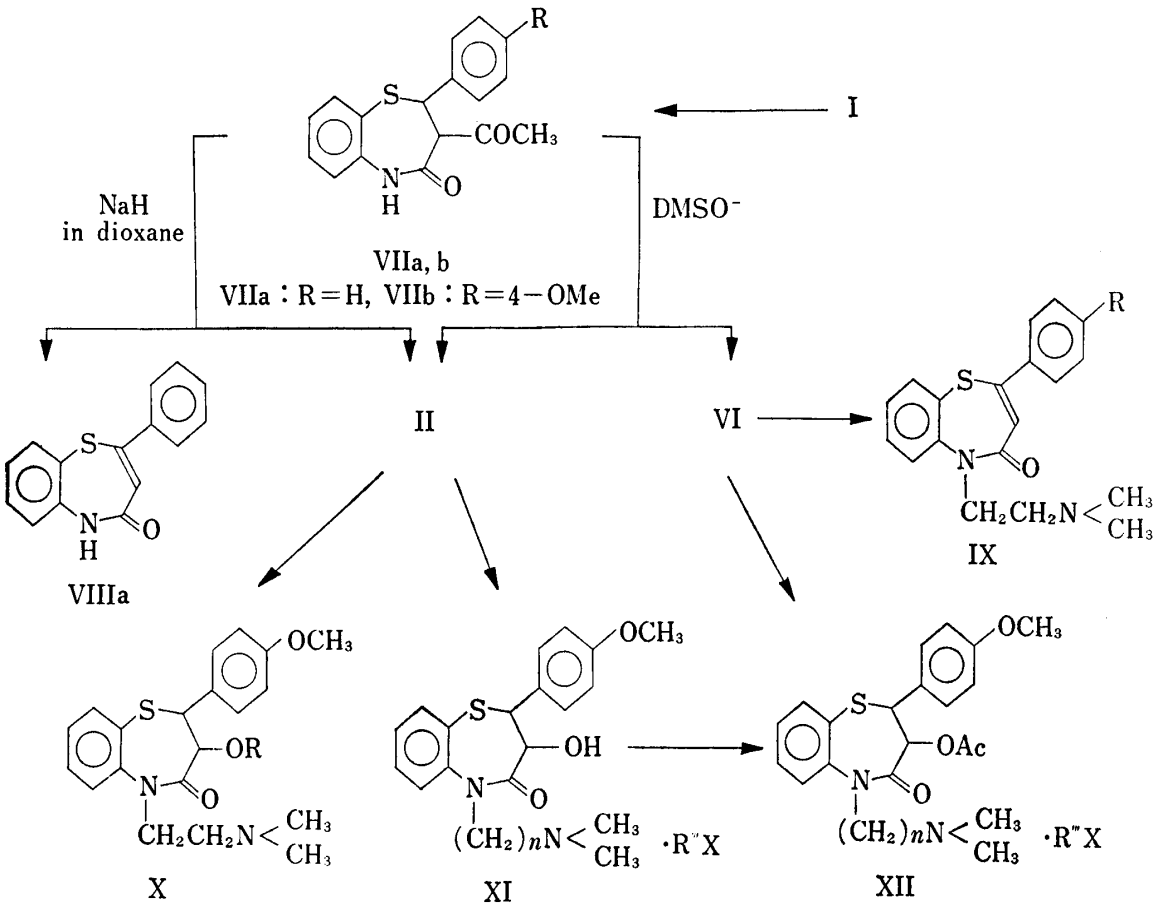
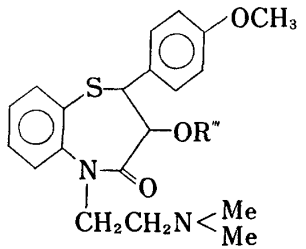



Chart 2

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-$\alpha$ 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-$\alpha$) was not obtained in this case. A similar elimination of acetic acid occured

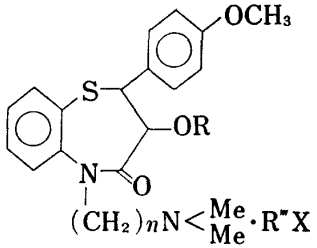
4) *o*-Aminothiophenols are generally unstable in the air, and give disulfides readily. While, *o*-dialkylaminothiophenols are comparatively stable under these conditions.
5) K. Fujii, *Yakugaku Zasshi*, **77**, 3 (1957).
6) The coupling constant between $C_2$-H and $C_3$-H shows 7 cps in the *cis* compounds ($\alpha$-series) and 11 cps in the *trans* ones ($\beta$-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 (%) Calcd. C | H | N | Found C | H | N | IR $\nu_{max}^{Nujol}$ $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Me | | 1 | 38 | 128—129 (isopro$_2$-O) | | | | | | | | 1672 |
| | $HClO_4$ | 2 | 18 | 175—176 (EtOH) | $C_{21}H_{27}O_7N_2SCl$ | 51.79 | 5.59 | 5.75 | 51.46 | 5.67 | 5.59 | |
| Et | $HClO_4$ | 1 | 54 | 202 (EtOH) | $C_{22}H_{29}O_7N_2SCl \cdot \frac{1}{2}H_2O$ | 51.88 | 5.88 | 5.49 | 51.86 | 5.77 | 5.45 | 1674 |
| | $HClO_4$ | 2 | 26 | | | | | | | | | |
| *n*-Pr | $HClO_4$ | 2 | 20 | 162 (EtOH) | $C_{23}H_{31}O_7N_2SCl \cdot H_2O$ | 51.83 | 6.24 | 5.25 | 52.27 | 5.96 | 5.18 | 1660 |
| Bz | | 2 | 64 | 134—135 (EtOH) | $C_{27}H_{30}O_3N_2S$ | 70.11 | 6.54 | 6.06 | 69.91 | 6.61 | 6.02 | 1678 |

TABLE IV. The Quarternary Salts




| R | *n* | Salt | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N | IR $\nu_{max}^{Nujol}$ $cm^{-1}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 2 | MeI | 81.6 | 162—167 (acetone–ether) | $C_{21}H_{27}O_3N_2SI \cdot \frac{1}{2}H_2O$ | 48.18 | 5.39 | 5.35 | 48.27 | 5.49 | 4.90 | 1660 | |
| Ac | 2 | MeI | 80.0 | 178—181 (EtOH) | $C_{23}H_{29}O_4N_2SI \cdot \frac{1}{2}H_2O$ | 48.85 | 5.39 | 4.95 | 48.98 | 5.12 | 4.74 | 1735 | 1680 |
| Ac | 2 | EtBr | 92.3 | 143—145 (acetone–ether) | $C_{24}H_{31}O_4N_2SBr \cdot \frac{1}{2}H_2O$ | 54.13 | 6.06 | 5.26 | 54.29 | 6.12 | 5.08 | 1738 | 1682 |
| Ac | 2 | *n*-PrBr | 44.3 | 137—139 (acetone–ether) | $C_{25}H_{33}O_4N_2SBr \cdot \frac{1}{2}H_2O$ | 54.94 | 6.27 | 5.13 | 55.12 | 6.29 | 5.05 | 1740 | 1680 |
| H | 3 | MeI | 92.0 | 237—238 (EtOH–ether) | $C_{22}H_{29}O_3N_2SI$ | 50.00 | 5.33 | 5.30 | 49.92 | 5.65 | 5.01 | 3290 | 1680 |
| Ac | 3 | MeI | 87.0 | 148—154 (acetone–ether) | $C_{24}H_{31}O_4N_2SI \cdot \frac{3}{2}H_2O$ | 48.29 | 5.74 | 4.69 | 48.77 | 5.54 | 4.44 | 1738 | 1678 |
| H | 3 | EtBr | 84.5 | 225—226 (acetone–ether) | $C_{23}H_{31}O_3N_2SBr$ | 55.62 | 6.47 | 5.40 | 55.75 | 6.31 | 5.65 | 3160 | 1680 |
| Ac | 3 | EtBr | 88.5 | 209—210 (EtOH) | $C_{25}H_{33}O_4N_2SBr$ | 55.86 | 6.19 | 5.21 | 55.74 | 6.23 | 4.99 | 1730 | 1680 |

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.

## Experimental[7]

**N-Alkylation of 2-Aryl-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (I)**——1) Alkyl ation 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 $CHCl_3$–ether and extracted with 10% HCl. The aquous layer was made alkaline with $K_2CO_3$ and extracted with ether. The extract was washed with water, dried over $Na_2SO_4$ 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 Dimethylsulinyl 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 $Na_2CO_3$ and extracted with $CHCl_3$. 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-benzothiazolinone[5] (8.0 g), KOH (8.0 g), EtOH (60 ml) and $H_2O$ was refluxed for 2 hours. After removal of EtOH, 15 ml of water was added to the reaction mixture. Neutralization of the aquous 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)amino-thiophenol (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 aquous layer was neutralized with $K_2CO_3$ and extracted with ether. The extract was washed wtih water and dried over $Na_2SO_4$. Evaporation of the solvent gave an oily product (6.5 g), which was chromatographed on $Al_2O_3$. IVa (1.73 g; 12.5%), mp 84—85° (MeOH), was obtained from the first portion of benzene eluate. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3320, 1740. *Anal.* Calcd. for $C_{23}H_{32}O_4N_2S$: 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 ($CDCl_3$) $\tau$ :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 $\nu_{max}^{Nujol}$ $cm^{-1}$: 1658. NMR ($CDCl_3$) $\tau$: 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 $C_{20}H_{23}O_8N_5S$ (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=$CH_3$) was obtained in 12.8% yield by the same procedure as that described above. IR $\nu_{max}^{liquid}$ $cm^{-1}$: 3480, 3370, 1732.

**2-Hydroxy-3-(4-methoxyphenyl)-3-(2-diethylaminoethyl)aminophenylthiopropionicacid(Va)**—Amixture of IVa (1.0 g), 1N NaOH (15ml) 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 $\nu_{max}^{Nujol}$ $cm^{-1}$: 3305, 1610, 1585. Oily Vb (Y=$CH_3$) was obtained in 77.1% yield by the same procedure as that described above. IR $\nu_{max}^{liquid}$ $cm^{-1}$: 3355, 1712.

**2-(4-Methoxyphenyl)-3-hydroxy-5-(2-diethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4-(5H)-one (IIc-β[6])**——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.

$\nu_{max}^{Nujol}$ cm $^{-1}$: 1660. NMR ($CDCl_3$) $\tau$: 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 $C_{22}H_{28}O_3N_2S$: 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-$\beta$ (R=$OCH_3$, $N_5$—Me) was obtained in 30.4% yield by the same procedure as that described above, mp 142—144° (EtOH). IId-$\beta$ 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 equivalnts) 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.[8] Reaction of 2-(4-methoxyphenyl)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-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(5*H*)-one hydrochloride (IXb·HCl), mp 219—221° (EtOH–ether) was obtained in 35% yield from the first portion of ether eluate. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1620. *Anal.* Calcd. for $C_{20}H_{23}O_2N_2SCl$: 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.

IIb (R=4-MeO, R'=$CH_3$, X=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 IIb (R=4-MeO, R'=Me, X=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, whtch was crystallized by trituration with isopropyl ether to afford Xb (R'''=Me) (0.47 g; 38%), mp 126—128°. Recrystallization from isopropylether gave a pure product, mp 128.5—129.5°. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1672. NMR ($CDCl_3$)$\tau$: 7.78 (6H, singlet), 6.83 (3H, singllet), 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 IIb (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 X·$HClO_4$. Recystallization from EtOH gave 700 mg of pure X·$HClO_4$, mp 202.5°. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 1670. Other products were shown in Table III.

**Formation of the Quarternary Salts (Representatives)**——1) A mixture of IIb (0.80 g) and $CH_3I$ (1 ml) in 10 ml of acetone was left overnight in a refrigerator. The crystals were collected by filteration. Recrystallization from acetone–ether gave 0.90 g of 2-(4-methoxyphenyl)-3-hydroxy-5-(2-dimethylaminoethyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one methyliodide (XIb) (R'''X=$CH_3I$,$n$=2), mp 162—167°. IR $\nu_{max}^{Nujol}$ 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(5)H-one ethylbromide (XIId) (2.61 g; 92.3%),

8) J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).

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

3) A solution of XIb (0.67 g) in 10 ml of $Ac_2O$ was refluxed for 3 hours. Removal of excess $Ac_2O$ under diminished pressure gave 0.63 g (87%) of VIIb. All the quarternary 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 $\nu_{max}^{Nujol}$ $cm^{-1}$: 1745, 1695. *Anal.* Calcd. for $C_{17}H_{15}O_3NS \cdot \frac{1}{3}C_6H_6$: 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 describerd above. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1745, 1695. *Anal.* Calcd. for $C_{18}H_{17}O_4NS$: 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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