The Synthesis of 11-(2′-Dimethylaminoethyl)-5-methyl-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin and Related Compounds. Neurotropic and Psychotropic Agents

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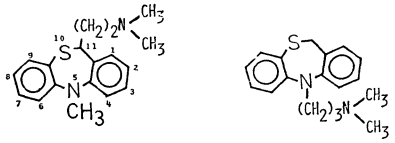
The synthesis of 11-(2′-dimethylaminoethyl)-5-methyl-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin and related compounds is described. 11-Lithiolated 5-methyl-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin (**18**) was employed as the key intermediate in the preparation of these compounds.

Morimoto had indicated, from his molecular orbital treatment using the Hückel approximation, that the dibenzo[*b*,*e*][1,4]thiazepin ring has approximately the same π-electron level as phenothiazine.[1] This result led the present authors to investigate the synthesis of 11-substituted dibenzo[*b*,*e*][1,4]thiazepin derivatives (**I**).



I **14e**

Chart 1.

In this paper, the authors will describe a synthesis of 11-substituted 5-methyl-5,11-dihydrodibenzo[*b*,*e*]-[1,4]thiazepin and related compounds which, in our animal studies, displayed an imipramine-like activity.[2]

Results and Discussion

The synthesis of Compound **I** was attempted by the following two methods. Method A involved the preparation of 11-substituted dihydrodibenzo[*b*,*e*][1,4]-thiazepins by the cyclization of α-substituted phenyl benzyl thioethers, while Method B involved the preparation of 5-methyl-11-substituted dibenzo[*b*,*e*][1,4]-thiazepins by the electrophilic substitution reaction of 5-methyl-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin lithiolated(**18**) with alkyl halides and other reagents (Chart 2).

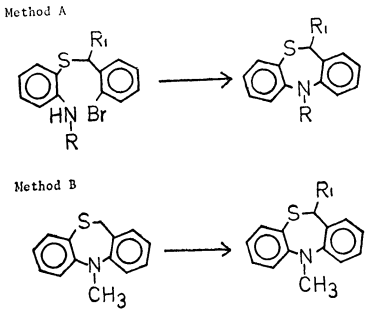
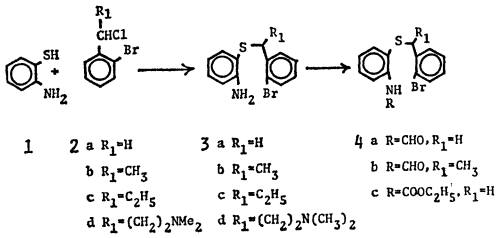


Chart 2.

The starting materials, α-substituted phenyl benzyl thioethers(**3**), were prepared by a patented procedure[3] or its modifications. The treatment of sodium thiophenolate with benzyl halides (**2**) in ethanol at room temperature or at the boiling point of the solvent used gave **3**, which was then allowed to react with 98% formic acid and with ethyl chloroformate to afford the **4** compounds in good yields. The catalytical hydrogenation of the Mannich base(**6**) with palladium carbon under atmospheric pressure gave an aminoalcohol(**9**). Compound **6** was reduced with sodium borohydride in methanol to give Compound **7**, which was then converted to benzyl chloride(**2d**) with thionyl chloride.



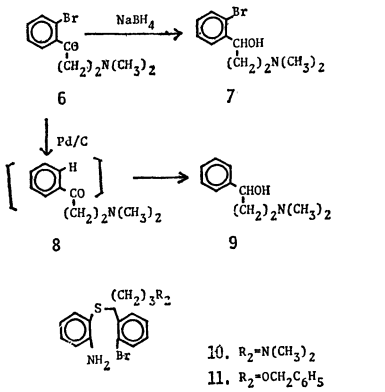


Chart 3.

The cyclization of **3a**, **b** and **4** at 120 to 140 °C in the presence of copper yielded 5,11-dihydrodibenzo-[*b*,*e*][1,4]thiazepins, **12** and **13**, in moderate yields, while the saponification of **13a**, **b** with an aqueous alcoholic sodium hydroxide solution gave Compound **12**. When R_1 in **3** was sterically bulky, such as a phenyl or dimethylaminoethyl group, either the starting material unchanged was recovered or resinous substances were formed. The alkylation of **12** with

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sodium hydride and methyl iodide, allyl bromide, and dimethylaminoalkyl chloride[4] in DMF gave the corresponding 5-substituted 5,11-dihydrodibenzo[*b*,*e*]-[1,4]thiazepins(**14**) in moderate yields.

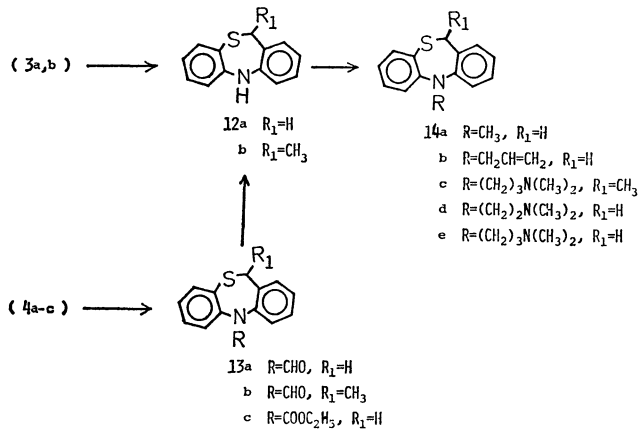

Chart 4.

It is known that compounds containing sulfur and/or nitrogen in the molecule are metalated at the carbon adjacent to the hetero atom by alkyl- or aryl-lithium to form organolithium compounds, which can then be used as synthetic intermediates.[5] The present authors employed this method for the preparation of 11-substituted dibenzo[*b*,*e*][1,4]thiazepin derivatives. In this case, the three sites shown by the a, b, and c arrows in Chart 5 are metalated with alkyl- or aryl-lithium.

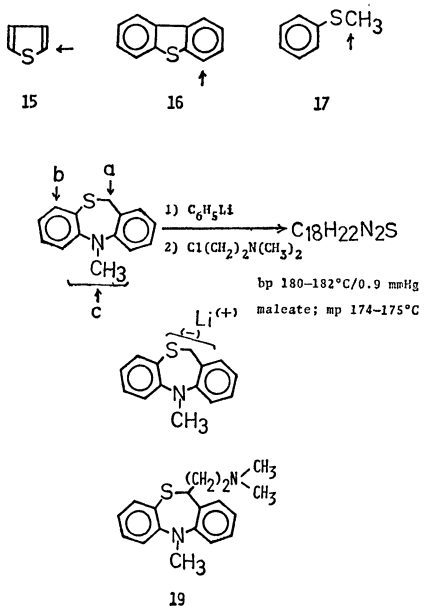

Chart 5.

The reaction of **14a** with phenyl lithium and dimethylaminoethyl chloride in ether afforded Compound **19** in a 62.4% yield. Evidence for the **19** structure was provided by the results of elementary analysis and by the spectral data. Compound **19** showed an emprical formula, $C_{18}H_{22}N_2S$, upon elementary analysis; its IR spectrum showed bands at 2800(tertiary amino group, NCH_3) and 700(condensed

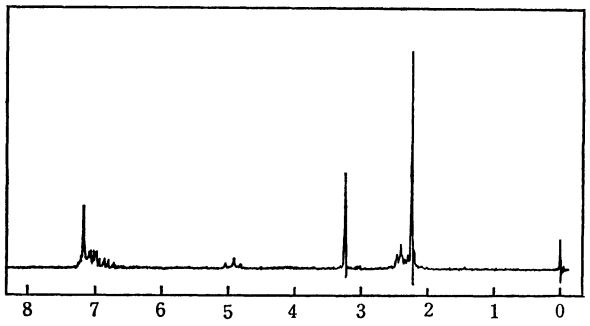

Fig. 1. NMR spectrum of **19** in $CDCl_3$.

aromatic)cm^{-1}, and the NMR spectrum in deuteriochloroform exhibited signals at δ 2.17—2.50(4H, m, CH_2CH_2) 2.28(6H, s, $N(CH_3)_2$) and 3.25(3H, s, $N-CH_3$)ppm. A signal due to methine proton was observed at δ 4.29(1H, t, J=7.0 Hz, $C_{11}-H$)ppm. These findings show that the electrophlic substitution reaction occurred on the 11-position of **14a**. The structure of this product was, therefore, identified as 5-methyl-11-(2'-dimethylaminoethyl)-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin (**19**).

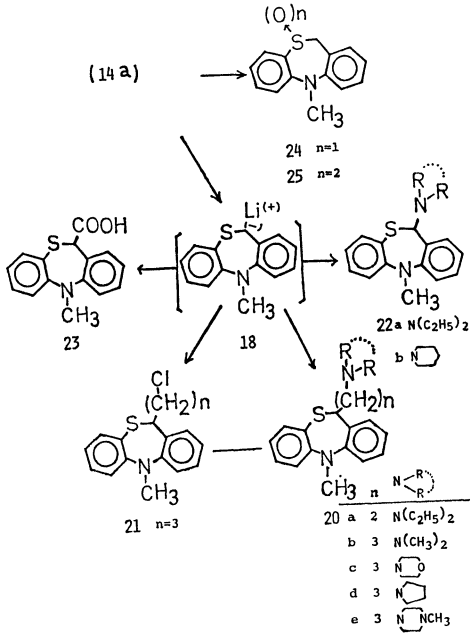

Chart 6.

The lithio derivative **18** was employed as a versatile intermediate for preparing 11-substituted 5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepins; almost all the derivatives shown in Chart 6 were successfully prepared by this method. Thus, the reaction of **18** with carbon dioxide yielded 11-(5-methyl-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepin)carboxylic acid (**23**). The treatment of **18** with 1-bromo-3-chloropropane yielded a haloalkyl derivative(**21**), which was then allowed to react with 1-methylpiperazine to give **20e** in a moderate yield. It is hard to synthesize 11-amino compounds (**22**) by the usual method. However, **22** was prepared by this method in about a 20% yield. The reaction of **14a** with hydrogen peroxide in a mixed solvent of acetone and acetic

acid at room temperature or in a solution of acetone with refluxing led to 5-methyl-5,11-dihydrodibenzo-[b,e][1,4]thiazepin-10-oxide(**24**) or 5-methyl-5,11-dihydrodibenzo[b,e][1,4]thiazepin-10,10-dioxide (**25**).

Compound **19** and related compounds were shown to have an imipramine-like activity in experimental animals; **19** is the most valuable among these compounds.

Our pharmacological findings will be reported elsewhere in the near future.

Experimental

All the melting points are uncorrected. The IR spectra were taken with a Hitachi EPI-2 spectrometer. The NMR spectra were recorded by means of a Varian A-60 spectrometer in $CDCl_3$, using TMS as the internal standard.

The *o*-bromobenzylbromide was prepared by the bromination of *o*-bromotoluene by a previously reported procedure.[6] The *o*-bromo-1-chloroethylbenzene(**2b**)[7] (bp 98—105 °C/13 mmHg) and *o*-bromo-1-chloropropylbenzene(**2c**) (bp 100—110 °C/10 mmHg) were prepared by the reduction of *o*-bromoacetophenone and *o*-bromopropiophenone, and by the subsequent chlorination of the resulting substances.

*o-Bromo-3-dimethylaminopropiophenone (**6**).*[8] A mixture of *o*-bromoacetophenone (1.94 g), dimethylamine (10.7 g), paraformaldehyde (3.9 g), and conc. HCl (0.2 ml) in 15 ml of EtOH was refluxed for 2 hr on an oil bath and then cooled. The solid thus precipitated was filtered, washed with acetone, and recrystallized from a mixed solvent of acetone and MeOH to give **6** (2.10 g); mp 185—189 °C. Found: C, 45.20; H, 5.27; N, 4.66%. Calcd for $C_{11}H_{14}BrON \cdot HCl$: C, 45.15; H, 5.17; N, 4.79%.

*1-(o-Bromophenyl)-3-dimethylaminopropyl Alcohol (**7**).* To a solution of **6** (1.8 g) in 30 ml of MeOH, we added 5 ml of a 10% NaOH solution; $NaBH_4$ (500 mg) was then added in small portions, and the mixture was stirred for 2 hr at 50 °C. The solvent was then evaporated *in vacuo*. H_2O was added to the residue, and the aqueous layer was extracted with benzene. The benzene layer was dried over $MgSO_4$ and evaporated. The solid was recrystallized from a mixed solvent of benzene/petr. benzine to give **7** (1.3 g); mp 74—75 °C.

*1-o-Bromophenyl-3-dimethylaminopropyl Chloride (**2d**).* To a solution of **7** (1.0 g) in 30 ml of $CHCl_3$, $SOCl_2$ in $CHCl_3$ was added, drop by drop under cooling. The reaction mixture was stirred first at the same temperature for 30 min, and then at 50 °C for 2 hr, and subsequently cooled. The $CHCl_3$ was removed *in vacuo*, and the residue was recrystallized from acetone to give **2d** (0.8 g); mp 180.5—181 °C.

*1-Methyl-o-bromobenzyl-o'-aminophenylthioether (**3b**).* To NaOEt in an EtOH solution (prepared from Na (3.5 g) and abs. EtOH (80 ml)), then *o*-aminothiophenol (16.6 g) was added all at once. The mixture was stirred for 30 min. 1-Chloro-*o*-bromoethylbenzene **2b** (19.4 g) was added to this solution, and the mixture was refluxed for 2 hr. After the removal of the solvent, H_2O was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated. The oil thus obtained was distilled under reduced pressure. The fraction boiling at 169—172 °C/0.9 mmHg was collected to give **3b** (16.6 g; 60.6%). Found: C, 54.53; H, 4.41; N, 4.56; S, 10.70; Br, 25.79%. Calcd for $C_{14}H_{14}BrNS$: C, 54.55; H, 4.58; N, 4.54; S, 10.40; Br, 25.92%.

*1-Ethyl-o-bromobenzyl-o'-aminophenylthioether (**3c**).* In a similar manner, **3c**, a yellow viscous oil, was obtained in a 50% yield; bp 178—182 °C/0.55 mmHg. Found: C, 55.20; H, 4.78; N, 4.06; S, 10.20%. Calcd for $C_{15}H_{16}BrNS$: C, 55.91; H, 5.00; N, 4.35; S, 9.95%.

*N,N-Dimethyl-3-(o-bromophenyl)-3-(o'-aminophenylthio)-propylamine (**3d**).* To a solution of NaOEt in EtOH (EtOH; 100 ml, Na; 600 mg), *o*-aminothiophenol(1.0 g) and then 3.0 g of **2d** were added. The mixture was refluxed for 3 hr. A small amount of H_2O was then added to the reaction mixture, and the solvent was removed *in vacuo*. H_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated. An oil (3.9 g) was thus obtained; IR: ν_{max} (neat); 3400 and 3300 (primary amine), and 2800 cm^{-1} (tertiary amine). This oil was converted to an oxalate in a usual manner. The oxalate melted completely at 180 °C after having decomposed at 138—140 °C. Found: C, 50.04; H, 5.24; N, 6.27; S, 7.18; Br, 17.39%. Calcd for $C_{17}H_{21}N_2SBr \cdot C_2H_2O_4$: C, 50.12; H, 5.09; N, 6.15; S, 7.04; Br, 17.55%.

*o'-(N-Formylamino)phenyl-o-bromobenzylthioether (**4a**).*[4] A solution of **3a** (70 g) in 420 ml of 98% HCOOH was refluxed for 2 hr. The reaction mixture was then poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with a 10% NaOH solution and H_2O, dried, and evaporated. The solid thus obtained was recrystallized from EtOH–cyclohexane to give 75 g of **4a**; mp 112—113 °C.

*o'-(N-Formylamino)phenyl-o-bromo-α-methylbenzyl thioether (**4b**)* was obtained in a 51.7% yield in a similar manner.

*o-Bromobenzyl-o'-(N-ethoxycarbonylamino)phenylthioether(**4c**).* To a solution of **3a** (2.9 g) in 5 ml of pyridine, we added $ClCOOC_2H_5$ (1.1 g) under cooling. Stirring was then continued for 2 hr. The mixture was allowed to stand overnight at room temperature, and then it was poured into water and extracted with ether; the ether layer was washed with H_2O and 10% HCl, dried over $MgSO_4$, and evaporated. The oil thus obtained was treated with EtOH to give a solid. The solid was recrystallized from aq. EtOH to give 1.5 g of **4c**, as colorless needles; mp 54–55 °C. Found: C, 52.72; H, 4.50; N, 3.97; S, 8.79; Br, 22.08%. Calcd for $C_{16}H_{16}NSO_2Br$: C, 52.47; H, 4.40; N, 3.82; S, 8.75; Br, 21.82%.

*5,11-Dihydrodibenzo[b,e][1,4]thiazepin (**12a**).* **3a** was prepared by Ullman reaction from *o*-bromophenyl-benzylthioether, which had itself been obtained by the reaction of *o*-aminothiophenol with *o*-bromobenzylbromide according to a patented procedure.[3]

A mixture of **3a** (100 g) and copper powder (10 g) in 1.0l of pyridine was stirred with refluxing at 110—115 °C in the presence of K_2CO_3(100 g) and then cooled. The solid was filtered off, and the filtrate was concentrated to one-third of the initial volume. The residue was poured into chilled 10% HCl, and the resulting semi-solid was extracted with ether. The ether layer was washed with H_2O, dried over $MgSO_4$, and evaporated. The residue was distilled under reduced pressure. The fraction boiling at 200—220 °C/0.4 mmHg was collected to give **12a** (80 g); mp 117—118 °C (lit, 121—122 °C).[3]

5-Formyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin (**13a**).*[4] A mixture of **4a** (70 g) and Cu powder (8.0 g) in 600 ml of pyridine was stirred with refluxing in the presence of K_2CO_3 (80 g). The solid was then filtered off, and the filtrate was concentrated *in vacuo*. The residue was poured into chilled dil. H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated to give **13a** (50 g); mp 123—124 °C.

5-Ethoxycarbonyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin (**13c**).* A mixture of **4c** (8.0 g), and K_2CO_3 (8.0 g) in 160 ml of pyridine was refluxed in the presence of Cu powder (0.8 g) for 4 hr. After the mixture had then been cooled, a solid was filtered off. The filtrate was poured into 20% H_2SO_4

Table 1. Preparation of 5-substituted dibenzo[*b,e*][1,4]thiazepin derivatives

	R	R_1	mp(bp)(°C)	Formula (Mol wt)	Analysis% Calcd (Found) C	H	N	S
14a	CH_3	H	93—94	$C_{14}H_{13}NS$ (227.25)	73.99 (78.91	5.77 5.73	6.16 6.05	14.08 14.15)
14b	$CH_2CH{=}CH_2$	H	104—104.5	$C_{16}H_{15}NS$ (253.29)	75.87 (75.77	5.97 6.17	5.53 5.43	12.67 12.44)
14c	$(CH_2)_3NMe_2$	CH_3	(187/0.6)[c]	$C_{19}H_{24}N_2S$ (312.40)			88.97 (88.87	10.24 10.24)
14d	$(CH_2)_2NMe_2$[a]	H	154—155[d]	$C_{17}H_{20}N_2S$ (284.32)	62.99 (63.03	6.04 6.11	7.00 7.01	7.99 8.61)[b]
14e	$(CH_2)_3NMe_2$[a]	H	133—134	$C_{18}H_{22}N_2S$ (298.32)	63.75 (63.65	6.32 6.53	6.67 6.53	7.72 7.76)[b]

a) P. Gailliot *et al.*, *Chem. Abstr.*, **55**, 19.972[d] (1961). b) Analysis of maleate is shown in Table 1. c) Maleate; mp. 153—155 °C (99% ethanol), Oxaleate; mp 139—143 °C (decomp.). d) Maleate.

and extracted with ether. The ether layer was washed with H_2O, dried, and evaporated. The solid thus obtained was recrystallized from 95% EtOH to give **13c** (4.2 g); mp 101.5—104 °C. NMR (δ); 1.23 (3H, t, J=7.0 Hz, $-CH_3$), 4.22 (2H, q, J=7.0 Hz, $-CH_2-$), 3.54 (1H, d, J=14 Hz, C_{11}–H), 4.88 (1H, d, J=14 Hz, C_{11}–H), 7.0—7.5 (8H, m, phenyl protons). Found: C, 65.46; H, 5.36; N, 5.17; S, 11.43%. Calcd for $C_{16}H_{15}NSO_2 \cdot 1/2H_2O$: C, 65.28: H, 5.49; N, 4.76; S, 10.89%.

Saponification of **13a** *with Alkaline Solution.* A solution of **13a** (50 g) and a 10% NaOH solution (110 ml) in 550 ml of 95% EtOH was refluxed for 2 hr. After the subsequent removal of the solvent *in vacuo*, the residue was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The solid thus obtained was recrystallized from 99% EtOH to give **12a** (48 g); mp 120—121 °C.[4]

N-Formyl-11-methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin* (***13b***): (mp 162—164 °C (from benzene-cyclohexane)) was obtained in a 75% yield by the Ullman reaction of **4b** at 110—115 °C. NMR (δ): 1.64 (3H, d, J=7.4 Hz, C_{11}–CH_3), 5.17 (1H, q, J=7.4 Hz, C_{11}–H), 7.0—8.0 (8H, m, phenyl protons). Found: C, 70.94; H, 5.04; N, 5.43; S, 12.74%. Calcd for $C_{15}H_{13}NSO$: C, 70.58; H, 5.13; N, 5.49; S, 12.80%.

11-Methyl-5,11-dihydrodibenzo[*b,e*][1,4]*thiazepin* (**12b**) (bp 190—200 °C (0.3 mmHg)) was obtained in a 50% yield by the saponification of **13b** with a 10% NaOH solution. NMR (δ): 1.51 (3H, d, J=7.5 Hz, C_{11}–CH_3), 4.33 (1H, q, J=7.5 Hz, C_{11}–H), 6.5—7.4 (8H, m, phenyl protons). Found: C, 73.71; H, 5.98; N, 6.09; S, 14.32%. Calcd for $C_{14}H_{13}NS$: C, 73.99; H, 5.77; N, 6.16; S, 14.08%.

5-Methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin* (***14a***). To a suspension of NaH (50% mineral oil dispersion; 65 g) in a mixed solvent of toluene (500 ml) and DMF (500 ml), a solution of **12a** (200 g) in a mixed solvent of toluene (200 ml) and DMF (200 ml) was added, drop by drop. The mixture was then stirred for 2 hr at 50 °C, and a solution of CH_3I (283 g) in 200 ml of DMF was added. Stirring was continued for another 2 hr at 50 °C. After cooling, MeOH (100 ml) was added, drop by drop, to the reaction mixture to decompose the excess NaH. The mixture was then poured into ice water (1.0 l). The oil thus obtained was extracted with toluene. The toluene layer was washed with H_2O, dried, and evaporated *in vacuo*. The solid thus formed was recrystallized from *n*-hexane (2.0 l) to give **14a**; 117 g (87%). NMR (δ): 3.67 (3H, s, N–CH_3), 4.41 (2H, s, C_{11}–H), 6.5—7.5 (8H, m, phenyl protons).

Compounds **14d** and **14c**, prepared in a manner similar to those described above, are summarized in Table 1.

5-Methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin-10-oxide* (***24***). To a solution of **14a** (22 g) in a mixed solvent of purified acetone (300 ml) and AcOH (300 ml), 30% H_2O_2 (20 g) was added, drop by drop, at a temperature below 25 °C; the reaction mixture was thereafter stirred for 25 hr at room temperature and poured into ice water (3.0 l). The solid thus precipitated was filtered off and recrystallized from MeOH to give **24**; 19.5 g (80%); mp 157 °C. NMR (δ): 3.44 (3H, s, N–CH_3), 4.30 and 4.55 (2H, d, J=12 Hz, C_{11}–H), 7.0—8.0 (8H, m, phenyl protons). Found: C, 69.69; H, 5.51; N, 5.78; S, 13.16%. Calcd for $C_{14}H_{13}NOS$: C, 69.13; H, 5.39; N, 5.76; S, 13.16%.

5-Methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin-10,10-dioxide* ***25***. To a solution of **14a** (3.5 g) in 30 ml of purified aceton 30% H_2O_2 (3.0 g) was added, drop by drop; the reaction mixture was then refluxed for 3 hr. After the subsequent removal of the solvent, the residue was recrystallized from 99% EtOH to give **25**; 1.5 g (43.9%); mp 230—233 °C. NMR (δ): 3.37 (3H, s, N–CH_3), 4.86 (2H, s, C_{11}–H), 6.9–7.9 (8H, m, phenyl protons). Found: C, 65.09; H, 5.09; N, 5.19; S, 12.46%. Calcd for $C_{14}H_{13}NO_2S$: C, 64.80; H, 5.06; N, 5.40; S, 12.34%.

Preparation of Phenyllithium.[9] To a solution of bromobenzene (32 g, 0.204 mol) in 100 ml of abs. ether, we added Li metal (3.0 g, 0.43 mol) under a flow of nitrogen. Stirring was slowly started at room temperature, and the reaction begin. (The reaction mixture was heated up to ether reflux when the reaction was hard to initiate.) The reaction mixture was then refluxed for 30 min.

11-(2'-Dimethylaminoethyl)-5-methyl-5,11-dihydrodibenzo[b,e]-[*1,4*]*thiazepin* (***19***). To a solution of phenyllithium (prepared from bromobenzene (4.7 g) and Li metal (410 mg)), a solution of **14a** (6.1 g) in 80 ml of abs. ether was added, drop by drop, after which the mixture was stirred for 2—3 hr at room temperature. The color of the solution changed from gray to red- or black-brown. To the resulting solution we then added freshly distilled dimethylaminoethyl chloride (60 g). The mixture was stirred with refluxing for 5 hr and then cooled. The unchanged Li metal was removed, and the ether solution was washed with H_2O and extracted with HCl. The extract was made alkaline with a 10% NaOH solution under cooling. The oil thus obtained was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with H_2O, dried, and evaporated *in vacuo*. The residue was distilled under reduced pressure. A fraction boiling at 180—182 °C

Table 2. Preparation of 11-substituted-5-methyl-10,11-dihydrodibenzo[*b,e*][1,4]thiazepin derivatives

	n	$N\langle^{R}_{R}$	mp(bp)(°C)	Yield (%)	Formula (Mol wt)	Analysis(%) Cald(Found) C	H	N	S
20a	2	$N(C_2H_5)_2$	oil	58.2	$C_{20}H_{26}N_2S$ (326.42)	73.58 (73.29	8.03 7.95	8.58 8.60	9.08 10.06)
20b	3	$N(CH_3)_2$	(200—230/0.5)	29.8	$C_{19}H_{24}N_2S$ (312.40)	73.04 (72.42	7.44 7.74	8.94 8.87	10.24 9.10)
20c	3		(230—240/0.4—0.5)	71.5	$C_{21}H_{26}ON_2S$ (354.43)	71.14 (71.40	7.39 7.45	7.90 3.15	9.05 9.10)
20d	3		(240—260/0.85)	26.6	$C_{21}H_{26}N_2S$ (338.43)	74.52 (74.34	7.74 7.88	8.28 8.14	9.46 8.86)

(0.9 mmHg) was collected to give **19** of 5.0 g (62.4%). IR (ν) Nujol: 2800 ($N-CH_3$) and 700 (condensed aromatic) cm^{-1}, NMR (δ): 2.17—2.50 (4H, m, $-CH_2CH_2-$), 2.28 (6H, s, $N(CH_3)_2$, 3.25 (3H, s, $N-CH_3$), 4.29 (1H, t, $J=7.0$ Hz, $C_{11}-H$), 6.7—7.3 (8H, m, phenyl protons). Found: C, 72.30; H, 7.24; N, 9.56; S, 10.74%. Calcd for $C_{18}H_{22}N_2S$: C, 72.42; H, 7.43; N, 9.39; S, 10.72%.

The oil thus obtained was converted to maleate in a usual manner; mp 174—175 °C (decomp.) (from EtOH). Found: C, 63.28; H, 6.28; N, 6.59; S, 7.59%. Calcd for $C_{18}H_{22}N_2S \cdot C_4H_4O_4$: C, 63.75; H, 6.32; N, 6.72; S, 7.72%.

Compounds **20a—d**, prepared in a manner similar to that described above, are summarized in Table 2.

11-(4'-Methylpiperazinopropyl)-5-methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin (20e).* To a reaction solution prepared by the reaction of **14a** (2.0 g) with phenyllithium, 1,3-propylene bromochloride (7.5 g) was added, after which the mixture was stirred with refluxing for 3 hr at 50 °C. After cooling, the ether layer was washed with H_2O, dried, and evaporated. Crude oil (2.0 g) was thus obtained.

A mixture of this crude oil and 1-methylpiperazine (20 ml) was heated at 120 °C for 7 hr with stirring. The reaction mixture was then poured into ice water and extracted with a 2 : 1 mixture of benzene and ether. The organic layer was extracted with 10% HCl, and the aqueous layer was made alkaline with a 10% NaOH solution. The oil thus obtained was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with H_2O, dried, and evaporated *in vacuo*. The oil in the AcOEt solution was chromatographed on alumina. The eluate was evaporated to give 1.1 g of a viscous oil which was distilled under reduced pressure. The fraction boiling at 240—260 °C (0.1—0.2 mmHg) was collected; 1.1 g of **20e**. The oil thus obtained was converted to maleate in a usual manner; mp 185—186 °C (decomp) (from 99% EtOH). Found: C, 60.05; H, 6.23; N, 7.05%. Calcd for $C_{22}H_{29}N_3S \cdot 2C_4H_4O_4$: C, 60.09; H, 6.21; N, 7.01%.

11-Diethylamino-5-methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin (22a).* **18** was prepared from **14a** (2.3 g) and phenyllithium (prepared from bromobenzene (1.6 g) and Li metal (150 mg)) in abs. ether. To the resulting solution, we added a solution of diethylaminobromide[10] in abs. ether, after which the mixture was refluxed for 5 hr. After the removal of the unchanged Li, the ether solution was extracted with 10% HCl and the extract was made alkaline with a 10% NaOH solution under cooling. The oil thus obtained was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The residue was distilled under reduced pressure. The fraction boiling at 200 °C (0.1 mmHg) was collected to give 0.5 g (16.8 %) of a yellow, viscous oil. Found: C, 71.94; H, 7.38; N, 9.28; S, 10.98%. Calcd for $C_{18}H_{22}N_2S$: C, 72.42; H, 7.43; N, 9.39; S, 10.73%.

11-Piperidino-5-methyl-5,11-dihydrodibenzo[*b,e*][*1,4*]*thiazepin (22b)* (bp 220—240 °C (0.3 mmHg)) was obtained in a 21.7% yield by the reaction of **14a** (6.1 g) lithiolated and *N*-chloropiperidine[10] in a manner similar to that described above. Found: C, 73.85; H, 7.23; N, 9.28; S, 10.43%. Calcd for $C_{19}H_{22}N_2S$: C, 73.51; H, 7.14; N, 9.02; S, 10.33%.

11-(5-Methyl-5,11-dihydrodibenzo[b,e][*1,4*]*thiazepin)-carboxylic Acid (23).* **18** was prepared by the reaction of **14a** with phenyllithium ((prepared from bromobenzene (3.0 g) and Li metal (300 mg)) in abs. ether. To the resulting solution we added, all at once, powdered dry ice (10 g) under cooling, after which the mixture was stirred with refluxing while CO_2 was passed through. The mixture was then poured into H_2O, and the ether layer was separated and extracted with a 10% $NaHCO_3$ solution. The aqueous layers were combined and made acid with 10% HCl. The oil obtained was extracted with $CHCl_3$ and the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated *in vacuo*. The solid obtained was recrystallized from a mixed solvent of benzene and *n*-hexane, and then from benzene, to give 1.0 g, of **23**; mp 193—194 °C (decomp.). Found: C, 66.40; H, 4.99; N, 4.92; S, 11.57%. Calcd for $C_{15}H_{13}O_2NS$: C, 66.41; H, 4.83; N, 5.16; S, 11.79%.

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