

**Synthesis and Pharmacological Properties of 8-Chloro-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin and Related Compounds.<sup>1)</sup>  
Neurotropic and Psychotropic Agents. III**

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(Received April 13, 1978)

8-Chloro-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (**4**) and related compounds were prepared by various methods. The results from the pharmacological investigation suggest that many of these compounds will be a kind of neuroleptics and the clinical investigation of the compound **4** as a neuroleptic is underway.

**Keywords**—dibenzo[*b,f*]thiepin; dibenz[*b,f*]oxepin; dibenz[*b,f*]azepin; chlorpromazine; neurotropic effects; Willgerodt reaction; 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one

In the previous papers we reported on the preparation and central nervous system (CNS) activities of a number of derivatives of dibenzo[*b,f*]thiepin,<sup>3)</sup> dibenz[*b,f*]oxepin,<sup>3)</sup> and dibenzo[*b,f*][1,4]thiazepin (III).<sup>4)</sup> The typical compound, 8-chloro-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (I) contains an enamine bond (–C=C–N–) in the molecule. In spite of instability of the enamine bond in acidic media,<sup>3)</sup> I showed marked neurotropic activities in preliminary screening tests using laboratory animals. The observation that the enamine derivatives (I, II) showed very strong neurotropic activities prompted us to investigate the preparation of enol ether derivatives (IV).

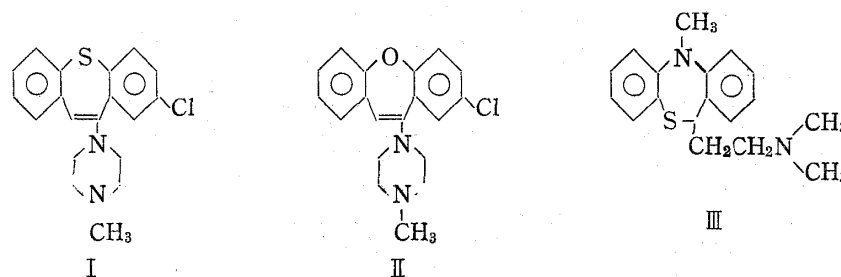


Fig. 1

Thus, many enol ether derivatives were prepared and pharmacologically tested. One of this series, 8-chloro-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (**4**) displayed marked neurotropic effects similar to chlorpromazine in laboratory animals.

In this communication, we describe the synthesis and CNS activities of tricyclic compounds shown in a formula of IV having the enol ether bond (–C=C–O–) and the preparation of an important intermediate, 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (Vb), which is required for the preparation of **4**.

- 1) a) S. Umio, I. Ueda, S. Maeno, Y. Sato, Ger. Offen. 1907670 (1969) [*Chem. Abstr.*, **72**, p55287r (1970);  
b) J.O. Jílek, K. Šindelář, J. Metyšová, J. Metyš, J. Pomykáček, and M. Protiva, *Collection Czech. Chem. Commun.*, **35**, 3721 (1970).
- 2) Location: *Kashima, Yodogawa-ku, Osaka, 532, Japan.*
- 3) I. Ueda, Y. Sato, S. Maeno, and S. Umio, *Chem. Pharm. Bull.* (Tokyo), **23**, 2223 (1975).
- 4) I. Ueda and S. Umio, *Bull. Chem. Soc. Japan*, **48**, 2323 (1975).

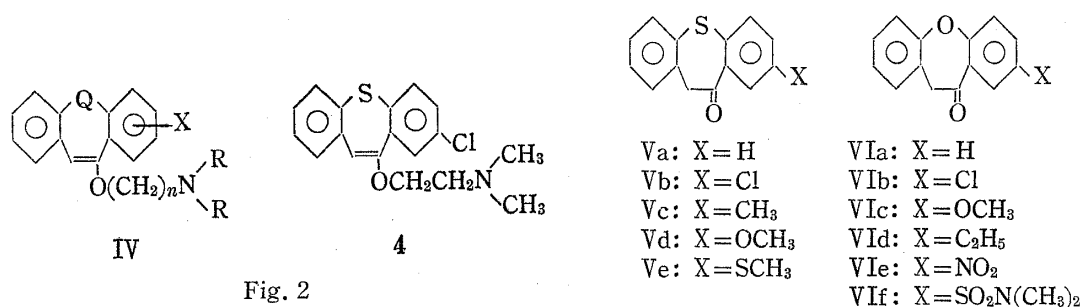


Fig. 2

Fig. 3

Starting materials, 10,11-dihydrodibenzo[*b,f*]thiepin-10-ones (Va—e) and 10,11-dihydrodibenzo[*b,f*]oxepin-10-ones (VIa—f) were prepared by the method described in the previous paper.<sup>3)</sup>

5-Methyl-10,11-dihydrodibenzo[*b,f*]azepin-10-one (VII) was synthesized as follows;<sup>5)</sup> *o*-(*N*-Methyl-*N*-phenylamino)phenylacetonitrile (VIII) upon treatment with dry hydrogen chloride below 0° afforded 5-methyl-10,11-dihydrodibenzo[*b,f*]azepin-10-imine hydrochloride (X), presumably *via* iminoether (IX). The imine X was then hydrolyzed under the same condition to give VII. Application of this procedure to 2-phenyloxy- and 2-phenylthiophenylacetonitrile (XI) was unsuccessful.

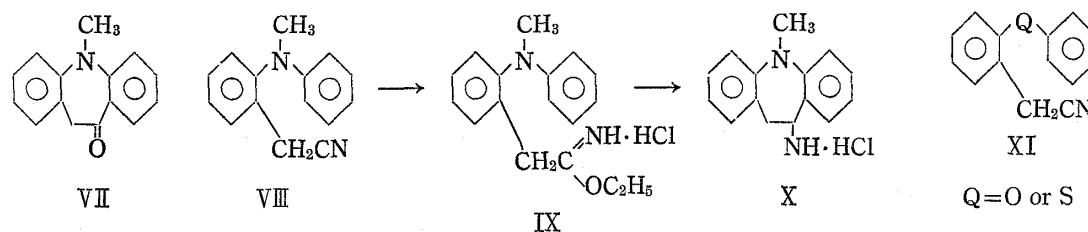


Chart 1

It has been reported in the patent literature that the reaction of 8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (Vb) with dimethylaminoethyl chloride (DMEC) and sodium amide in dry toluene gives 8-chloro-11-(2-dimethylaminoethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (XII) along with basic compounds.<sup>6)</sup> However, detail studies on this reaction were not carried out.

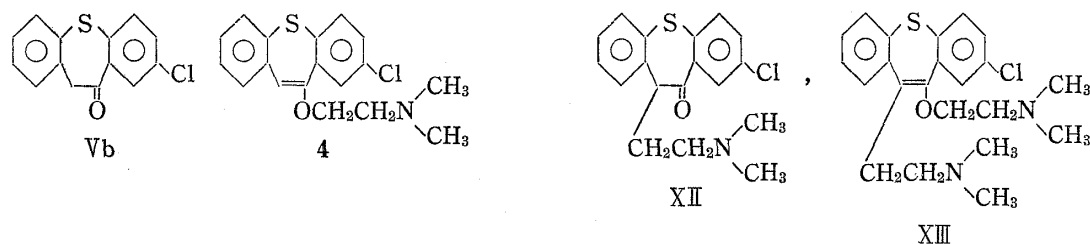


Fig. 4

Our reinvestigation of this reaction showed that the reaction of the ketone Vb with freshly distilled DMEC and sodium hydride in mixed solvent of dimethyl formamide (DMF) and toluene gave the considerable amount of 4 along with XII and 8-chloro-11-(2-dimethylaminoethyl)-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (XIII). These products were separated from the mixture by means of column chromatography on alumina. The structure of each

5) S. Umio and S. Maeno, Japanese Patent 71-09340 [*Chem. Abstr.*, **75**, p35814 (1971)].

6) W. Schindler and H. Blattner, Neth. Appl. 6414131 [*Chem. Abstr.*, **63**, 18130a (1965)].

compound isolated was assigned on the basis of elemental analysis and spectral data, *i.e.*, infrared (IR) and nuclear magnetic resonance (NMR) spectra. In order to obtain the compound **4** in high yield the further investigation of this reaction was carried out by changing bases and solvents employed. The reaction was followed up by the gas chromatography.

The reaction of Vb with sodium hydride and DMEC in the respective solvents of methanol, ethanol and isopropanol gave **4** in 18.3, 49.0, and 67.9% yields, respectively. The reaction of Vb and DMEC in the presence of respective bases of sodium methoxide, sodium hydride, and sodium amide in toluene afforded **4** in 21.9, 34.5, and 60.0% yields, respectively. The reaction in the presence of sodium methoxide gave uncharacterized side products in a yield of about 34.3% based on the ketone Vb. The reaction of Vb with sodium hydride and DMEC in respective solvents of DMF, mixed solvent of DMF and toluene, and tetrahydrofuran (THF) gave **4** in 80.9, 70.7, and 56.0% yields, respectively. In almost cases compound XII was formed.

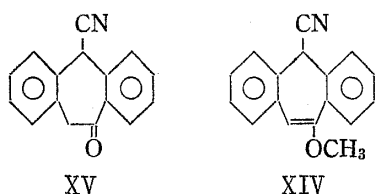


Fig. 5

A method for preparing selectively *O*-alkyl compound was studied. Generally ketones or aldehydes were reacted with alcohol in the presence of mineral acid to give the corresponding ketals or acetals. When these compounds have active methylene group adjacent to the carbonyl group the alcohol was eliminated to give the corresponding enol ethers. For example, it has been reported in the literature that the reaction of 5-cyano-5,11-dihydrodibenzo[*a,d*]cyclohepten-10-one (XV)

with methanol in the presence of hydrogen chloride gives 5-cyano-10-methoxy-5,11-dihydrodibenzo[*a,d*]cycloheptatriene (XIV) in a 86% yield.<sup>7)</sup>

When the compound Vb was allowed to react with 2-bromoethanol in the presence of *p*-TosOH under benzene refluxing 8-chloro-10-(2-bromoethoxy)dibenzo[*b,f*]thiepin (**23**) was obtained in a 56.7% yield. The structure of this compound was determined from elemental analysis and IR and NMR spectra. When 2-dimethylaminoethanol instead of 2-bromoethanol was employed for the preparation of the compound **4**, thin-layer chromatography (TLC) analysis of this reaction mixture indicated that the products consisted of two compounds, the starting material Vb and a small amount of **4** which was isolated in poor yield of 5% based on the ketone Vb.

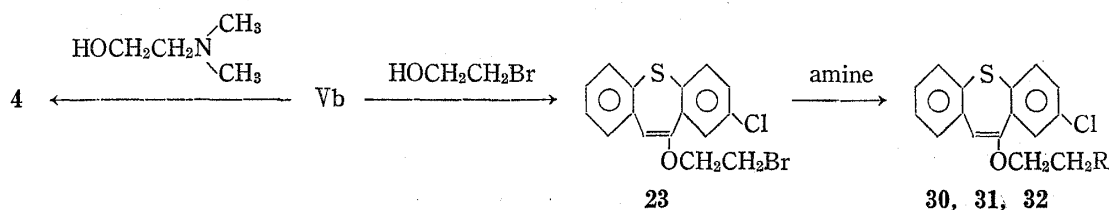


Fig. 6

Surprisingly, the alkylation of Vb with potassium carbonate and DMEC in methyl isobutyl ketone (MIBK) containing small amount of water gave **4** in 77.5% yield without the formation of C-alkyl derivatives XII and XIII.

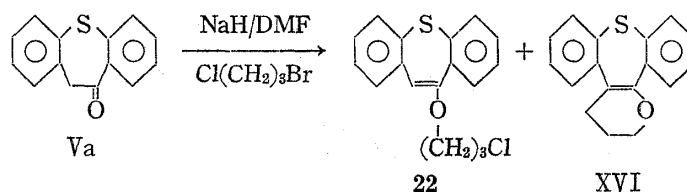


Fig. 7

7) M.A. Davis, T.A. Dobson, and J.M. Jordan, *Can. J. Chem.*, **47**, 2827 (1969).

The reaction of Va with sodium hydride and 3-bromopropyl chloride in DMF gave the mixture of **22** and XVI in 18.2 and 11.3% yields, respectively. The structures of these products were determined from elemental analysis and the spectral data. The treatment of **22** with dimethylamine or methylpiperazine in a sealed tube afforded the corresponding amino compound (**3** or **27**). The crude product (XVII) prepared by reacting Vb with sodium hydride and 2-bromoethyl chloride in DMF was treated with dimethylamine in a sealed tube to give **4** in poor yield, which was assigned by comparing spectral data of an authentic sample prepared by an independent method.

The methods investigated here are summarized in Chart 2 and most of compounds in this series were prepared by method A.

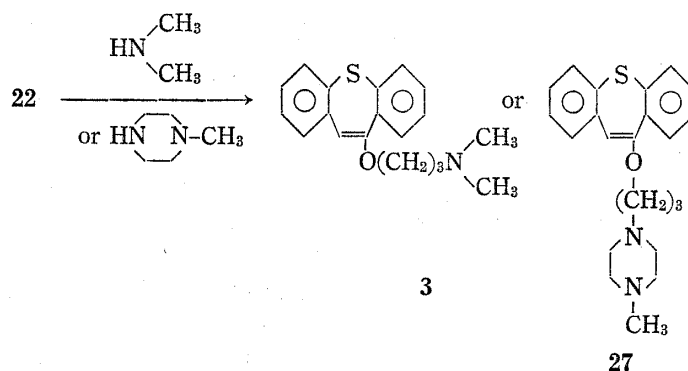


Fig. 8

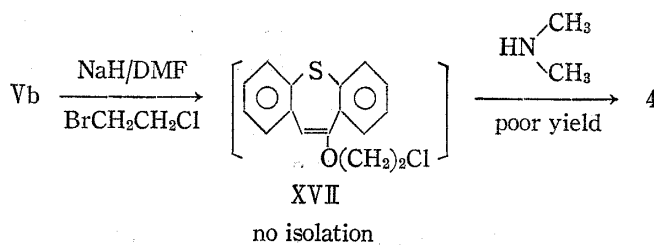
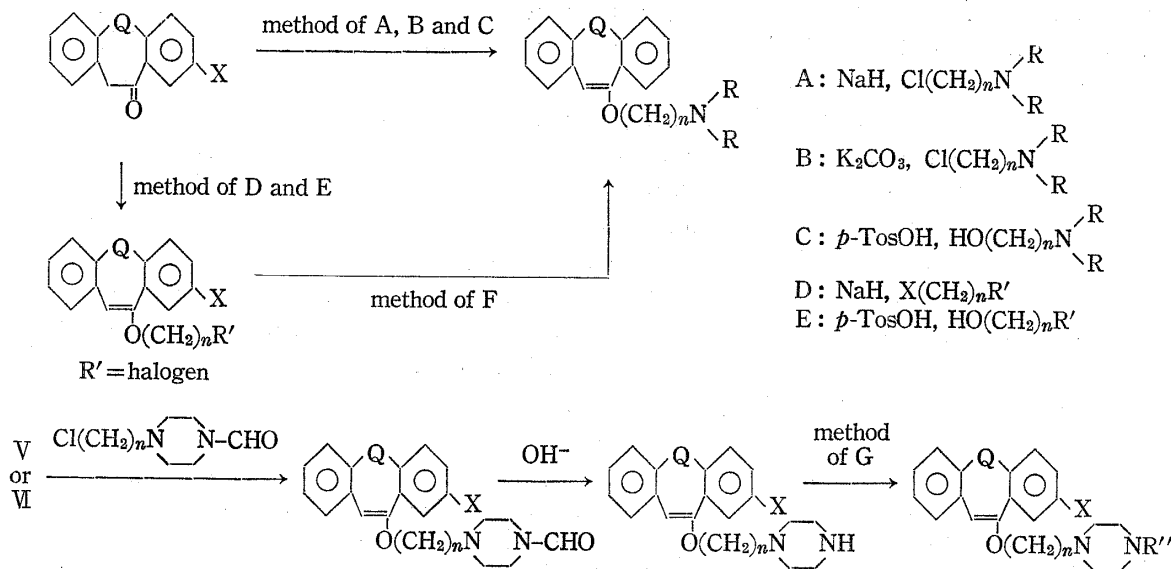
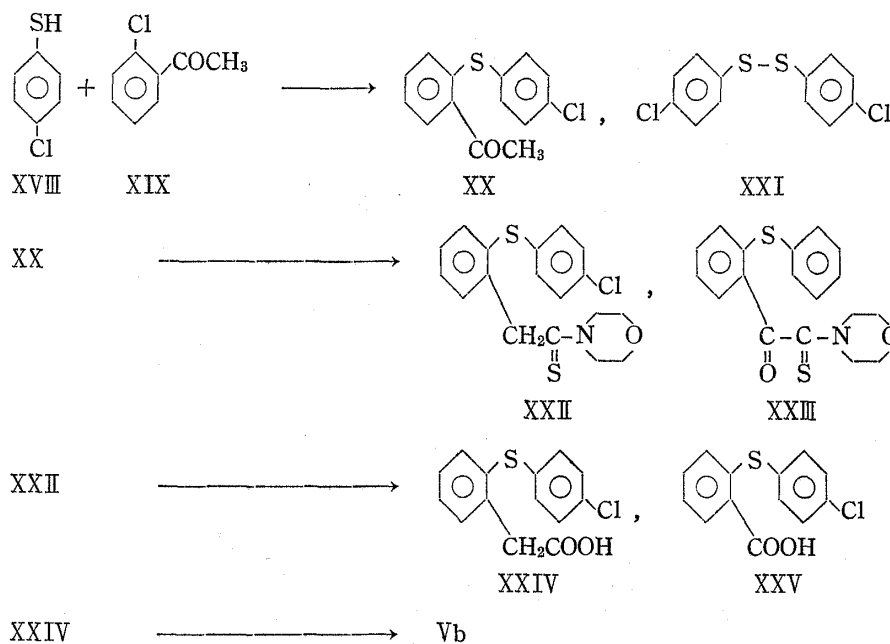


Fig. 9



We needed a large amount of the ketone Vb for the clinical evaluation of the compound 4. This led us to study the way for the preparation of Vb *via* 2-(4-chlorophenylthio)acetophenone (XX) as is depicted in Chart 3. It was reported in the previous paper that the condensation of 4-chlorothiophenol (XVIII) with 2-chloroacetophenone (XIX) gave XX in 37% yield<sup>1)</sup> along with a by-product, 4-chlorophenyldisulfide (XXI). In order to reduce the formation of XXI and to enhance the yield of XX this reaction was reinvestigation in details. When the reaction of freshly distilled XVIII with XIX keeping the mol ratio of 1 to 1.3 was carried out at the temperature of 150° for 8.5 hr under nitrogen atmosphere, the compound XX was obtained in 72.3% yield along with a small amount of the compound XXI.



The Willgerodt reaction of XX and related compounds in low yields was reported in the literatures.<sup>8)</sup> When the reaction of XX with sulfur and morpholine keeping a mol ratio of 1:3.0:1.5 to XX:sulfur:morpholine was carried out under nitrogen atmosphere, thiomorpholide (XXII) of 2-(4-chlorophenylthio)phenylacetic acid was obtained in 67% yield<sup>9)</sup> along with oxothiomorpholide (XXIII). The separation of XXII in pure stage from the reaction mixture was unsuccessful in a large scale.

The hydrolysis of the reaction mixture in acidic media by means of usual method produces the homoacid (XXIV) and undesired product, benzoic acid (XXV). It is very difficult to separate XXV from the hydrolysis products as is described by Protiva *et al.*<sup>10)</sup> Then, selective hydrolysis of either thioamide XXII or XXIII was investigated. From our experiment the hydrolysis of thiomorpholides XXII and XXIII in acetic acid media containing conc. HCl was found to be selectively accompanied affording the desired acid XXIV without the formation of XXV. The compound XXIV was converted into the compound Vb in 84% yield by using PPA. The overall yield of Vb was a 40% yield based on the compound XIX.

8) a) S. Kimoto, K. Kimura, and S. Muramatsu, *Yakugaku Zasshi*, **74**, 426 (1954); b) S. Kimoto, M. Okamoto, K. Yabe, T. Uchida, and Y. Matsutaka, *Yakugaku Zasshi*, **88**, 1323 (1968).

9) The yield was calculated from the amount of homoacid (XXIV) obtained.

10) J.O. Jílek, K. Šindelář, J. Pomykáček, O. Horešovský, K. Pelz, E. Svátek, B. Kakáč, J. Holubek, J. Metyšová, and M. Protiva, *Collection Czech. Chem. Commun.*, **38**, 115 (1973).

### Pharmacological Results

All compounds prepared in this work were evaluated pharmacologically using the test usual in search for neurotropic activity. The results of several typical compounds are shown in Table I. The compounds (4, 8, 12, and 32) displayed neurotropic activities which were weak comparing with those of the corresponding enamine compounds I, and II. These effects were similar to those of chlorpromazine. The analogous amine, 8-chloro-11-methyl-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (39) showed no pronounced pharmacological activity.

The clinical investigation of the compound 4 as a neuroleptic is underway. The pharmacological properties will be reported in detail elsewhere.

TABLE I. Neuroleptic Properties of the Dibenzo[*b,f*]thiepins, Related Compounds and Reference Compounds: Rats

Compound	Antiapomorphine effect ED <sub>50</sub> (mg/kg)		Potentiation of barbiturate sleep ED <sub>50</sub> (mg/kg)	
	<i>p.o.</i>	<i>s.c.</i>	<i>p.o.</i>	<i>s.c.</i>
4	17.4	7.7	27.6	6.5
8	101.0	—	8.5	1.1
12	19.5	9.0	—	33.1
32	15.0	—	33.0	—
39	<i>a)</i>	<i>a)</i>	<i>a)</i>	<i>a)</i>
I	—	0.1	—	0.4
II	—	0.06	—	0.7
Chlorpromazine	24.0	5.0	—	0.9
Octoclotepine	3.0	0.05	—	0.4

*a)* Ineffective at a dose of 500 mg/kg.

### Experimental<sup>11)</sup>

10,11-Dihydrodibenzo[*b,f*]thiepin-10-ones and 10,11-dihydrodibenz[*b,f*]oxepin-10-ones were prepared by the method described in the previous paper.<sup>9)</sup>

2-Phenyloxy- and 2-phenylthio-phenylacetone nitrile were prepared by the method described in the literatures.<sup>12,13)</sup>

**5-Methyl-10,11-dihydrodibenz[*b,f*]azepin-10-one (VII)**—Preparation of X: To a solution of 1.7 g of VIII and 0.4 g of abs. EtOH in 13 ml of dry toluene dry HCl gas was allowed to be absorbed below 5°. The hydrogen chloride gas-saturated solution obtained was allowed to stand overnight. The crystal precipitated was collected, and washed with benzene to give 1.5 g of X, green-yellow prism, mp 271—272° (dec.). *Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>·HCl: C, 69.63; H, 5.84; Cl, 13.70; N, 10.83. Found: C, 69.34; H, 5.77; Cl, 14.03; N, 10.79. NMR (*d*<sub>4</sub>-MeOH, ppm) 5.30 (2H, s, C<sub>11</sub>-CH<sub>2</sub>-), 6.17 (3H, s, CH<sub>3</sub>-) and 1.95—3.00 (8H, m, benzene protons).

**Preparation of VII Due to Hydrolysis of X**—The crystal X obtained was dissolved in water. The aqueous solution was warmed for several minutes on boiling water bath. The solution was allowed to stand overnight at room temperature. The crystals precipitated were filtered, and recrystallized from aqueous EtOH to give 1.05 g of VII, mp 102—103°. *Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.40; H, 5.73; N, 6.18.

- 11) 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 using tetramethyl silane (TMS) as the internal standard. The ultraviolet (UV) spectrum was taken with a Hitachi EPS-032 spectrophotometer in EtOH.
- 12) V. Seidlová, K. Pelz, E. Adlerová, I. Jirkovský, J. Metysšová, and M. Protiva, *Collection Czech. Chem. Commun.*, **34**, 2258 (1969).
- 13) J.O. Jílek, V. Seidlová, E. Svátek, and M. Protiva, *Mh. Chem.*, **96**, 182 (1965).

**Studies on the Alkylation of Vb under Various Reaction Conditions by Means of GLC**—The gas chromatograph<sup>14)</sup> was equipped with a flame ionization detector (FID). The column was 3% Dexsil 400 GC on high performance Chromosorb W, 80—100 mesh. Conditions used were oven 217°, nitrogen 1.1 kg/cm<sup>2</sup>, air 2.0 kg/cm<sup>2</sup>, and chart speed 10 mm/min.

Under chromatographic condition described the above compound 4, Vb, XII, and XIII had retention times of 7.7, 2.2, 4.5, and 9.6 min, respectively. Unchanged Vb, 4, XII, and XIII were measured by comparing the peak height of each compound of Vb, 4, XII, and XIII to the peak height obtained for standards.

A. Alkylation of Vb with Sodium Alkoxide in Alcohol Solution: Preparation of Sodium Alkoxide: To 13 ml of dry alcohol 0.25 g of 50% NaH as dispersion of gray powder in an industrial white oil [NaH (50% oil)] was carefully added under cooling. The mixture was stirred for 30 min at room temperature.

To this sodium alkoxide in alcohol 1.3 g of Vb was added. The mixture was stirred for 2 hr at 65°, and then to the mixture 1.5 g of freshly distilled DMEC was added. The mixture was allowed to react at 65° for 10 hr. The resulting reaction mixture was poured into 150 ml of ice-water and extracted twice with 50 ml of CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried over MgSO<sub>4</sub> and evaporated to dryness. The residue was dissolved into 10 ml of acetonitrile containing bis-trimethylsilyl acetamide (BSA) (25% w/v) and the solution was allowed to stand overnight at room temperature. This solution was injected into the gas chromatograph.

The results are shown in Table II.

TABLE II. Alkylation of Vb with Sodium Alkoxide in Alcohol Solution

Base	Solvent	Mol ratio of Vb: base: DMEC	Unchanged Vb	Products			
				4	XII	XIII	a)
NaOMe	MeOH	1 : 1.2 : 2	79.5	18.3	n.d. <sup>b)</sup>	n.d. <sup>b)</sup>	2.1
NaOEt	EtOH	1 : 1.2 : 2	41.0	49.0	1.4	n.d. <sup>b)</sup>	8.6
NaOCH <sub>2</sub> CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CHOH	1 : 1.2 : 2	11.1	67.9	2.7	5.4	12.2

a) The uncharacterized products; These were measured by comparing their peak height to that of the standard of Vb.

b) Not detected.

B. Alkylation of Vb with NaH, NaNH<sub>2</sub>, and NaOCH<sub>3</sub> in Toluene: The commercially available NaH (50% oil), NaNH<sub>2</sub>, and NaOCH<sub>3</sub> were used for this experiment.

To a suspension of base in 13 ml of dry toluene 1.3 g of Vb was added under cooling. The mixture was stirred for 2 hr at 65°. To the resulting mixture 1.5 g of freshly distilled DMEC was added and the mixture was allowed to react for 10 hr at 65°. The mixture was treated with 1 ml of MeOH for decomposition of excess of alkali metal. The reaction mixture was poured into 150 ml of ice-water. The organic layer and the aqueous phase were separated and the aqueous phase was extracted twice with 50 ml of CHCl<sub>3</sub>. The organic layer and the CHCl<sub>3</sub> extract were combined, dried over MgSO<sub>4</sub>, and evaporated to dryness. The residue was treated according to the procedure described in A.

The results are shown in Table III.

TABLE III. Alkylation of Vb with NaH, NaNH<sub>2</sub> or NaOCH<sub>3</sub> in Toluene

Base	Mol ratio of Vb: base: DMEC	Unchanged Vb	Products			
			4	XII	XIII	a)
NaOCH <sub>3</sub>	1 : 1.2 : 2	35.7	21.9	8.0	n.d. <sup>b)</sup>	34.3
NaH	1 : 1.2 : 2	32.0	34.5	10.3	n.d. <sup>b)</sup>	23.0
NaNH <sub>2</sub>	1 : 1.2 : 2	9.9	60.0	13.6	3.0	13.4

a) Uncharacterized products.

b) Not detected.

C. Alkylation of Vb with NaH in Various Solvents of DMF, Mixed Solvent of DMF and Toluene, or THF: The reaction was carried out according to the procedure described in A and B.

The results are summarized in Table IV.

14) Japan Electric, JEOL JGC-20K gas chromatograph.

TABLE IV. Alkylation of Vb with NaH in Various Solvents of DMF, Mixed Solvent of DMF and Toluene, or THF

Vb	Solvent	Mol ratio of Vb: NaH:DMEC	Unchanged Vb	Products			
				4	XII	XIII	a)
1.3g	DMF	1 : 1.2 : 2	7.3	80.9	n.d. <sup>b)</sup>	n.d. <sup>b)</sup>	11.4
1.3g	DMF-Toluene	1 : 1.2 : 2	4.0	70.7	1.5	n.d. <sup>b)</sup>	23.7
1.3g	THF	1 : 1.2 : 2	4.9	56.0	4.6	4.0	29.1

a) Uncharacterized products.

b) Not detected.

**8-Chloro-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (4)**—The Reaction of Vb with DMEC in the Presence of NaH (Method A): To a suspension of 15 g of NaH (50% oil) in 100 ml of dry DMF a solution of 52 g of Vb in 800 ml of dry DMF was added dropwise under nitrogen atmosphere. The mixture was stirred for 2 hr at 80° and cooled to room temperature. To the reaction mixture a solution of 43.6 g of freshly distilled DMEC in DMF was added. The resulting solution was stirred for 20 hr at 60°. After addition of 95% EtOH to decompose an excess of unchanged NaH, the mixture was poured into ice-water and extracted three times with ether. The ether layer was washed with water, and extracted with chilled 10% HCl. The aqueous layer was made alkaline with 10% NaOH, and the oil precipitated was extracted with AcOEt, which was washed with water and dried over MgSO<sub>4</sub>. After removal of the solvent, the residual oil was allowed to stand at room temperature to give crystal, which was recrystallized from cyclohexane to give 41 g of 4. IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 1618 (enol ether). NMR (CDCl<sub>3</sub>, ppm): 2.35 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 2.79 (2H, t, -NCH<sub>2</sub>-), 4.12 (2H, t, -OCH<sub>2</sub>-), 6.37 (1H, s, H<sub>A</sub> = <O-) and 7.0–7.7 (7H, m, benzene protons). UV  $\lambda_{\max}^{95\% \text{ EtOH}}$ : 266 nm.

The Reaction of Vb with DMEC in the Presence of K<sub>2</sub>CO<sub>3</sub> (Method B): A mixture of 52 g of Vb and 55 g of K<sub>2</sub>CO<sub>3</sub> in 260 ml of MIBK containing 25.5 ml of water was heated for 1 hr under MIBK refluxing. To the reaction mixture, 57.6 g of freshly distilled DMEC was added in one portion, and the mixture was allowed to react for 5.5 hr under MIBK refluxing. To the resulting solution 210 ml of water was added, and the organic and aqueous layers were separated. The aqueous layer was extracted with 120 ml of MIBK. The above organic layer and the MIBK extract were combined and dried over MgSO<sub>4</sub>. After removal of the solvent, oils obtained were treated with cyclohexane to give crystals, which were recrystallized from cyclohexane to give 51.3 g of 4 in 77.5% yield. The product was identified by elemental analysis and comparison of its IR and NMR spectra with those of a sample obtained by method A.

The Reaction of Vb with 2-Dimethylaminoethyl alcohol in the Presence of *p*-TosOH (Method C): A mixture of 2.2 g of Vb, 2.7 g of 2-dimethylaminoethyl alcohol and 3.3 g of *p*-TosOH in 100 ml dry benzene was refluxed for 48 hr. The reaction was washed with water, sat. NaHCO<sub>3</sub> aq. and brine and extracted with 10% HCl. The aqueous layer was made alkaline to litmus with 10% NaOH. The oil was extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried over MgSO<sub>4</sub> and evaporated. The residue was chromatographed on alumina using AcOEt as eluent. After removal of the AcOEt, the desired product 4 was obtained as oil in 5% yield. The product was identified by comparison of IR and NMR spectra with those of a sample obtained by method A.

Preparation of 4 via 8-Chloro-10-(2-chloroethoxy)dibenzo[*b,f*]thiepin (XVII) (Method D): To a suspension of 3.4 g of NaH (50% oil) in DMF a solution of 5.2 g of Vb in DMF was added under cooling. The mixture was heated at 80° for 2 hr with stirring, and cooled to room temperature. To the resulting mixture a solution of 14.2 g of an excess 2-bromoethyl chloride in DMF was added dropwise. The solution was allowed to react for 20 hr at 60°. After decomposition of an excess of NaH with 95% EtOH, the mixture was poured into ice-water, and extracted three times with ether. The ether was washed with water, and extracted with 15% HCl. The aqueous layer was made alkaline with 10% NaOH, and extracted with AcOEt. The AcOEt was dried over MgSO<sub>4</sub>. After removal of the solvent, 3.5 g of an oil was obtained.

The Oil was Confirmed by Derivatization to 4: The oil was allowed to react with dimethylamine in EtOH in a sealed tube. The product obtained was identified by comparison of its IR and NMR spectra with those of a sample obtained by method A.

**10-(3-Chloropropoxy)dibenzo[*b,f*]thiepin (22) and 10H-dihydropyrano[2,3-*d*]dibenzo[*b,f*]thiepin (XVI)**—To a suspension of 0.97 g of NaH (50% oil) in a mixed solvent of DMF and benzene 4.52 g of Va in DMF was added dropwise. The mixture was stirred for 1 hr at 50°. To the reaction mixture a solution of 3.2 g of 3-bromopropyl chloride in DMF was added. The mixture was stirred for 2 days at 50°. The resulting mixture was poured into ice-water, and extracted with benzene. The benzene layer was washed with water, and dried over MgSO<sub>4</sub>. After removal of the solvent, the reddish oil obtained was chromatographed on silicagel using benzene as eluent. The first elution was evaporated *in vacuo* to give 1.1 g of 22, yellow granule which was recrystallized from EtOH.



The second elution was evaporated and the crystal obtained was recrystallized from a mixed solvent of EtOH and benzene to give 0.6 g of XVI, yellow granule, mp 113—114°. *Anal.* Calcd. for C<sub>17</sub>H<sub>14</sub>OS: C, 76.66; H, 5.30; S, 12.04. Found: C, 76.35; H, 5.14; S, 12.33.

**8-Chloro-10-(2-bromoethoxy)dibenzo[*b,f*]thiepin (23)** (Method E): A mixture of 1.5 g of Vb, 2.0 g of bromoethanol, and 0.2 g of *p*-TosOH in 75 ml of dry benzene was refluxed for 17 hr, water produced being removed by azeotropic distillation. The reaction mixture was washed with 10% NaOH and water and dried over MgSO<sub>4</sub>. After removal of the solvent, the crystals obtained were purified by repeating 5 times recrystallizations to give 0.8 g of 23. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 1625 ( $\text{>C=O}$ ). NMR (CDCl<sub>3</sub>, ppm): 3.29 (2H, t, Br-CH<sub>2</sub>-), 4.32 (2H, t, O-CH<sub>2</sub>-), 6.38 (1H, s,  $\text{H}=\text{C}=\text{O}$ ) and 7.1—7.7 (7H, m, benzene protons).

Preparation of 4 by the Reaction of 23 with Dimethylamine (Method F): A solution of crude 23 and dimethylamine in ethanol was heated at 100° for 5.5 hr in a sealed tube. The resulting mixture was concentrated to dryness. The solid obtained was dissolved in benzene. The benzene layer was washed with water, and extracted with 10% HCl. The aqueous layer was made alkaline with 10% NaOH under cooling. The oil precipitated was extracted three times with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The residual oil was treated with cyclohexane to give crystal, which was recrystallized from cyclohexane to give 4. The product was identified by elemental analysis and comparison of IR and NMR spectra with those of a sample obtained by method A.

**10-(2-Dimethylaminoethoxy)dibenz[*b,f*]oxepin (11) via 10-(2-bromoethoxy)dibenz[*b,f*]oxepin (24)**—A solution of 15.0 g of VIa, 25 g of 2-bromoethanol, and 1.95 g of *p*-TosOH in benzene was refluxed for 17 hr, water produced being removed by azeotropic distillation. The reaction mixture was washed with 10% NaOH and water and dried over MgSO<sub>4</sub>. After removal of the solvent, the residual oils were dissolved in EtOH containing 7.52 g of dimethylamine. The mixture was heated at 100° for 5.5 hr in a sealed tube. After removal of the solvent, the residue was dissolved in benzene. The resulting solution was washed with water, and extracted with 10% HCl. The aqueous extract was made alkaline with 10% NaOH under cooling. The oil precipitated was extracted three times with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The obtained oil in AcOEt was chromatographed on alumina using AcOEt as eluent. The AcOEt elution was evaporated *in vacuo* and the oil obtained was converted into a maleate by a usual manner. The maleate was recrystallized from aqueous EtOH. A yield was 6.3% based on the ketone VIa.

**10-[3-(4-Methylpiperazinyl)propyloxy]dibenzo[*b,f*]thiepin (27)**—A mixture of 270 mg of 22 and 3.0 g of 1-methylpiperazine was stirred for 19 hr at the range of 120 to 125°. The reaction mixture was poured into water and extracted with ether which was extracted with chilled 10% HCl. The aqueous layer was washed with ether and made alkaline with 10% NaOH. The oil precipitated was extracted with ether. The ether was washed with water, dried over MgSO<sub>4</sub>, and evaporated *in vacuo* to give 0.3 g of oily 27, which was converted into a maleate by a usual manner. The maleate was recrystallized from aqueous EtOH to give 0.32 g.

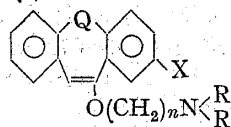
**10-[3-(4- $\beta$ -Hydroxyethylpiperazinyl)propyloxy]dibenzo[*b,f*]thiepin (28)**—Maleate, colorless needles, mp 169—170° (from aqueous EtOH), was obtained in 65% yield from 0.3 g of the chloride 22 and 3.0 g of 1- $\beta$ -hydroxyethylpiperazine by a similar method to that described above.

**8-Chloro-10-[2-(4-formylpiperazinyl)ethoxy]dibenzo[*b,f*]thiepin (40)**—2-(4-Formylpiperazinyl)ethyl chloride was prepared according to the method described in the literature.<sup>15)</sup>

To a suspension of 4.8 g of NaH (50% oil) in 30 ml of DMF a solution of 9.2 g of Vb in mixed solvent of 92 ml of DMF and 50 ml of THF was added. The mixture was allowed to react for 2 hr at 80°. After the reaction mixture was cooled to 30°, a solution of 10.5 g of 2-(4-formylpiperazinyl)ethyl chloride in 20 ml of ether was added (exothermic reaction). After stirring for 1 hr at room temperature, the mixture was warmed to 65° and stirred for 17 hr at this temperature. The reaction mixture was poured into ice-water and extracted with a mixed solvent of ether and benzene (1:1). The organic layer was washed with water and brine and extracted with 10% HCl, giving oily products. The oil was dissolved into water by adding a small amount of acetone. The aqueous layer was washed several times with ether and made alkaline to litmus with 10% NaOH. The oil was extracted with CHCl<sub>3</sub>, and the CHCl<sub>3</sub> was washed with water and brine, dried over MgSO<sub>4</sub> and evaporated to give 3.5 g of yellow brown oil. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 1650 (N-CHO) and 1620 (enol ether). NMR (CDCl<sub>3</sub>, ppm): 2.74—2.44 (4H, m, CH<sub>2</sub>-N $\begin{matrix} \text{CH}_2- \\ \text{CH}_2- \end{matrix}$ ), 3.74—3.34 (4H, m,  $\begin{matrix} -\text{CH}_2- \\ -\text{CH}_2- \end{matrix}$ N-CHO), 2.89 (2H, t, *J*=6.0 Hz, N-CH<sub>2</sub>-), 4.15 (2H, t, *J*=6.0 Hz, -OCH<sub>2</sub>-), 6.36 (1H, s,  $\text{O}=\text{C}=\text{H}$ ), and 7.96 (1H, s, CHO).

**8-Chloro-10-(2-piperazinylethoxy)dibenzo[*b,f*]thiepin (30)**—A mixture of 3.3 g of N-formyl 40 in 60 ml of 99% EtOH and 11 ml of 10% NaOH aq. was refluxed for 3.0 hr. After cooling the mixture was evaporated

15) a) P.N. Craig, M. Gordon, J.J. Lafferty, B.M. Lester, A.M. Pavloff, and C.L. Zirkle, *J. Org. Chem.*, **25**, 944 (1960); b) T. Fujii (Tanabe Pharmaceutical Co., Ltd.), Japan Patent 5527 (1954) [*Chem. Abstr.*, **49**, 15976f (1955)].

TABLE V. Preparation of 8-Chloro-10-(2-dimethylaminoethoxy)dibenzo[*d,f*]-thiepin (4) and Related Compounds

Q	X	n	R	Salt	Method	mp (°)	Solvent <sup>a)</sup> (Yield)	Analysis (%)					
								Calcd. (Found)					
								C	H	Cl	N	S	
1	S	H	CH <sub>3</sub>	HCl	A (F)	196—198	E-Ä	10.62 (10.35)					
2	S	H	C <sub>2</sub> H <sub>5</sub>	MA	A	129—130	99% E	65.29	6.16		3.17	7.25	
3	S	H	CH <sub>3</sub>	MA	A (F)	140—141	99% E	(65.09)	(6.10)		(3.12)	(7.20)	
4	S	Cl	CH <sub>3</sub>	F	A	90—91	Cy	64.62	5.90		3.28	7.48	
5	S	Cl	CH <sub>3</sub>	MA	A	198—	99% E	(64.33)	(5.76)		(3.07)	(7.73)	
6	S	Cl	CH(CH <sub>3</sub> )- CH <sub>2</sub> <sup>b)</sup>	CH <sub>3</sub>	MA	A	198.5(dec.)	95% E	65.15	5.47	10.68	4.22	9.66
7	S	CH <sub>3</sub>	CH <sub>3</sub>	MA	A	211—213	E	(65.00)	(5.44)	(10.68)	(4.16)	(9.68)	
8	S	OCH <sub>3</sub>	CH <sub>3</sub>	F	A	86—87	E-Ä	58.99	4.95		7.91	3.13	
9	S	SCH <sub>3</sub>	CH <sub>3</sub>	MA	A	190—191	E	(58.73)	(4.98)		(7.81)	(3.16)	
10	O	H	CH <sub>3</sub>	HCl	A (F)	230—231	E-Ä	59.80	5.24		7.68	3.03	
11	O	H	CH <sub>3</sub>	MA	A	172—173	E	(59.49)	(5.01)		(7.99)	(2.90)	
12	O	Cl	CH <sub>3</sub>	MA	A	161—	E-Ac	64.62	5.89		3.28	7.50	
13	O	Cl	C <sub>2</sub> H <sub>5</sub>	MA	A	115—116	E	(64.45)	(5.77)		(3.34)	(7.29)	
14	O	Cl	CH <sub>3</sub>	MA	A	153—	E	69.69	6.46		4.28	9.79	
15	O	Cl	CH(CH <sub>3</sub> )- CH <sub>2</sub> <sup>b)</sup>	CH <sub>3</sub>	MA	A	171—172	E	(70.01)	(6.24)		(3.95)	(9.61)
16	O	OCH <sub>3</sub>	CH <sub>3</sub>	MA	A	166—	E	60.11	5.48		3.05	13.95	
17	O	OCH <sub>3</sub>	CH(CH <sub>3</sub> )- CH <sub>2</sub> <sup>b)</sup>	CH <sub>3</sub>	MA	A	140—142	E-Ä	(59.84)	(5.01)		(3.43)	(14.09)
18	O	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	MA	A	172—173	E	68.02	6.34		4.41		
19	O	NO <sub>2</sub>	CH <sub>3</sub>	F	A	89—90	H	(67.85)	(6.62)		(4.05)		
20	O	SO <sub>2</sub>	CH <sub>3</sub>	MA	A	152—153	E	66.49	5.83		3.52		
21	-N-   CH <sub>3</sub>	H	CH <sub>3</sub>	MA	A (F)	150.5—	E-Ä	(66.35)	(5.65)		(3.52)		
22	S	H	(CH <sub>2</sub> ) <sub>3</sub> -Cl		D	125—126	Cy	61.19	5.13	8.21	3.24		
23	S	Cl	(CH <sub>2</sub> ) <sub>2</sub> -Br		D (E)	135—136	E	(61.09)	(5.08)	(8.41)	(3.48)		
24	O	H	(CH <sub>2</sub> ) <sub>2</sub> -Br		E	144—146	H	62.67	5.70		7.71	3.05	
25	-N-   CH <sub>3</sub>	H	(CH <sub>2</sub> ) <sub>2</sub> -Br		E	144—146	H	(62.36)	(5.51)		(7.71)	(3.15)	
								61.95	5.43		7.95	3.14	
								(61.67)	(5.39)		(8.20)	(2.99)	
								61.95	5.43		7.95	3.14	
								(62.13)	(5.50)		(8.01)	(3.52)	
								64.63	5.90		3.28		
								(64.50)	(5.98)		(3.36)		
								65.29	6.16		3.17		
								(65.58)	(5.97)		(3.01)		
								67.75	6.40		3.29		
								(68.01)	(5.95)		(3.61)		
								66.25	5.56		8.58		
								(66.41)	(5.79)		(8.08)		
								57.13	5.59		5.55	6.36	
								(56.91)	(6.11)		(5.79)	(6.05)	
								67.30	6.38		6.83		
								(66.99)	(6.16)		(6.78)		
								67.43	4.79	11.71		10.59	
								(51.3)	(4.74)	(12.02)		(10.68)	
								52.26	3.29			8.72	
								(56.7)	(3.11)			(8.66)	
								60.59	4.13				
								(52.8)	(4.51)				
								61.83	4.88		4.24		
								(19.7)	(4.59)		(3.97)		

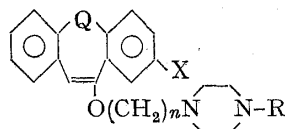
a) E: ethanol, Cy: cyclohexane, Ä: ether, Ac: acetone, H: *n*-hexane.b) Correspond to (CH<sub>2</sub>)<sub>n</sub>.c) Correspond to (CH<sub>2</sub>)<sub>n</sub>N<<sup>R</sup>/<sub>R</sub>.

to a volume of 1/2, poured into ice-water and extracted several times with AcOEt. The AcOEt was dried over  $\text{MgSO}_4$  and evaporated to give reddish oil which was converted to a maleate. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1627 (enol ether).

**N-Alkylation of 8-Chloro-10-(2-piperazinyloxy)dibenzo[*b,f*]thiepin (30) (Method G)**—General Method: To a solution of 30 in alcohol in the presence of  $\text{K}_2\text{CO}_3$  alkyl halide was added. The mixture was refluxed for 5 hr with stirring. The reaction was followed up by TLC (alumina, AcOEt developing). After the reaction was completed, the mixture was poured into ice-water and extracted with AcOEt. The AcOEt was washed with water and brine and dried over  $\text{MgSO}_4$ . A product in AcOEt was chromatographed on alumina using AcOEt as eluent. The elutions desired were collected and evaporated to give oily product which was converted into a maleate.

Compounds obtained in this work are summarized in Table V and VI.

TABLE VI. Preparation of 8-Chloro-10-(4'-hydroxyethylpiperazinyloxy)-dibenzo[*b,f*]thiepin (32) and Related Compounds



Q	X	n	R	Salt	Method	mp (°)	Solvent <sup>a)</sup> (Yield)	Analysis (%)					
								Calcd. (Found)					
								C	H	Cl	N	S	
26	S	H	2	CH <sub>3</sub>	2MA	A (F)	195—197 (dec.)	aq. E	59.58 (59.25)	5.52 (5.01)		4.79 (5.00)	5.48 (5.76)
27	S	H	3	CH <sub>3</sub>	2MF	A (F)	195—197 (dec.)	aq. E	60.19 (60.23)	5.72 (5.48)		4.68 (4.78)	5.36 (5.61)
28	S	H	3	C <sub>2</sub> H <sub>4</sub> OH	2MF	F	169—170	aq. E	59.22 (58.86)	5.77 (5.69)		4.46 (4.50)	5.10 (4.98)
29	S	Cl	2		MA	A	200.5— 202.0	E (30.9)	61.53 (61.31)	5.37 (5.40)	7.27 (7.50)	2.87 (2.56)	6.57 (6.70)
30	S	Cl	2	H	2MA	G (I)	153—156 (dec.)	E-Ä	55.58 (55.13)	4.83 (5.01)	5.86 (5.54)	4.63 (4.89)	5.30 (4.99)
31	S	Cl	2	CH <sub>3</sub>	2MA	A (F)	196 (dec.)	99% E	56.26 (56.53)	5.05 (5.14)	5.73 (5.58)	4.53 (4.32)	5.18 (5.35)
32	S	Cl	2	C <sub>2</sub> H <sub>4</sub> OH	2MA	A (F)	161 (dec.)	E-Ä	54.75 (54.92)	5.21 (4.99)	5.39 (5.63)	4.26 (4.26)	4.87 (4.88)
33	S	Cl	2		2MA	H	150—151 (dec.)	99% E (35.7)	56.15 (55.98)	5.32 (5.54)		4.22 (4.22)	4.84 (5.05)
34	S	Cl	2		2MA	H	189—190 (dec.)	E-Ä	56.15 (56.17)	5.32 (5.01)		4.22 (4.35)	4.84 (5.45)
35	S	Cl	2	CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	2MA	H	165—166	95% E	55.61 (55.47)	5.10 (5.04)	5.13 (5.35)	4.05 (3.98)	4.64 (4.68)
36	S	Cl	2	C <sub>2</sub> H <sub>4</sub> OCOCH <sub>3</sub>	2MA	H	174—176	E	55.61 (55.36)	5.10 (5.00)	5.13 (5.33)	4.05 (4.01)	4.64 (4.68)
37	S	Cl	2		2MA	H	153—154	95% E	56.21 (55.91)	5.29 (5.24)	5.03 (5.25)	3.97 (4.03)	4.55 (4.81)
38	O	Cl	2	CH <sub>3</sub>	2MA	A (F)	195—196 (dec.)	95% E	57.76 (57.53)	5.18 (5.29)	5.88 (5.69)	4.65 (4.75)	

a) E: ethanol, Ä: ether.

**8-Chloro-10-(2-diethylaminoethoxy)dibenz[*b,f*]oxepin (13)**—To a suspension of 1.4 g of NaH (50% oil) in 5 ml of dry DMF a solution of 2.45 g of VIb in 40 ml of dry DMF was added at room temperature during a period of 10 min. The mixture was stirred for 2 hr at 80° on an oil bath. To the reaction mixture 2.7 g of 2-diethylaminoethyl chloride was added at room temperature. The mixture was stirred for additional 17 hr at 50°. The resulting mixture was poured into ice-water, and extracted with ether. The ether was washed with water, and extracted with chilled 10% HCl. The aqueous layer was made alkaline with 10% NaOH under cooling. The oily product was extracted with ether and the ether was washed with water, dried over  $\text{MgSO}_4$ , and evaporated *in vacuo*. 2.6 g of oily products were chromatographed on alumina using AcOEt as eluent. The first eluate was evaporated *in vacuo* to give oil, which was converted

into a maleate by a usual manner. The maleate obtained was recrystallized from mixed solvent of EtOH and ether to give 1.2 g of colorless granule.

**10-(2-Dimethylaminoethoxy)-5-methyldibenz[*b,f*]azepin (21)**—To a suspension of 1.2 g of NaH (50% oil) in 10 ml of dry DMF a solution of 2.2 g of the ketone VII in 20 ml of dry DMF was added and the mixture was stirred for 1.5 hr at 50° on an oil bath. After the reaction mixture was cooled to room temperature, a solution of 2.2 g of DMEC in dry DMF was added to this reaction solution. The mixture was stirred for additional of 24 hr at 50°. The resulting solution was poured into ice-water, and extracted three times with AcOEt. The AcOEt was washed with chilled water, dried over MgSO<sub>4</sub>, and evaporated *in vacuo*. The oily products (3.1 g) obtained were chromatographed on 60 g of neutral alumina using AcOEt as eluent. The first elution was evaporated *in vacuo* to give 2.9 g of yellow oily products. The further purification by chromatography gave 1.8 g of a yellow oil, which was converted into a maleate by a usual manner. The maleate obtained was recrystallized from mixed solvent of EtOH and ether, to give pale yellow prisms. IR and NMR spectra of free base are shown as follows: IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 1638 (enol ether). NMR (CDCl<sub>3</sub>, ppm): 2.38 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 2.81 (2H, t, N-CH<sub>2</sub>-), 3.32 (3H, s, N<sup>5</sup>-CH<sub>3</sub>), 4.12 (2H, t, O-CH<sub>2</sub>-), 6.02 (1H, s, H) $\rangle\langle$ O-, and 6.8—7.6 (8H, m, benzene protons).

**8-Chloro-11-(2-dimethylaminoethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (XII)** was prepared according to the Method described in the Patent Literature: Concentration of the mother liquor after separation of 4 described in method A, gave a mixture of 4 and other basic compounds. The oily products obtained were refluxed for 2.5 hr with 300 ml of 10% HCl. The mixture was extracted with AcOEt. The acid aqueous layer was made alkaline to litmus with 10% NaOH. The oils obtained were extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was washed with water and brine and dried over MgSO<sub>4</sub>. After removal of the solvent, the oil was dissolved into MeOH. The methanol phase was allowed to stand overnight at room temperature to give 2.0 g of XII, prism, mp 104—105°. *Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>ClNOS: C, 65.14; H, 5.41; Cl, 10.69; N, 4.22; S, 9.66. Found: C, 64.99; H, 5.27; Cl, 10.98; N, 4.18; S, 9.51. IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 1675 (CO). NMR (CDCl<sub>3</sub>, ppm): 2.24 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 2.35 (2H, t, -CH<sub>2</sub>N-), 4.7—5.0 (3H, m, H) $\rangle\langle$ O-, 7.0—7.7 (7H, m, benzene protons), and 8.0—8.2 (1H, m, C<sub>9</sub>-H of benzene protons).

**8-Chloro-10-(2-dimethylaminoethoxy)-11-(2-dimethylaminoethyl)dibenzo[*b,f*]thiepin (XIII)** was prepared from the Reaction of XII with DMEC and NaH in DMF: To suspension of 0.5 g of NaH (50% oil) in 10 ml of DMF a solution of 3.3 g of XII in 15 ml of DMF was added dropwise at 10° with stirring. The mixture was stirred for 30 min at room temperature and for 60 min at 50°. To this reddish solution freshly distilled DMEC was added and the mixture was stirred for 5 hr at 60°. The resulting solution was poured into ice-water and extracted twice with AcOEt, which was extracted with 10% HCl. The aqueous phase was made alkaline to litmus with 10% NaOH. The oil was extracted with AcOEt. The AcOEt phase was washed with water and brine and dried over MgSO<sub>4</sub>. After removal of the solvent, the oil obtained was chromatographed on 50 g of alumina using benzene as eluent. First elution gave the less polar unchanged base XII and uncharacterized base, while the more polar base XIII was eluted with the following elution. The elution was evaporated to give 0.3 g of oily products which were converted to the corresponding maleate in the usual way; mp 190—192° (dec. from EtOH). *Anal.* Calcd. for C<sub>22</sub>H<sub>27</sub>ClN<sub>2</sub>SO·2C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>: C, 56.73; H, 5.55; Cl, 5.58; N, 4.41; S, 5.05. Found: C, 56.48; H, 5.53; Cl, 5.87; N, 4.31; S, 5.13. IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 2300—2700 (N<sup>+</sup>CH<sub>3</sub>), 1670 (COOH), 1620 (enol ether). NMR (DMSO-*d*<sub>6</sub>, ppm): 2.90 (12H, s, N<sup>+</sup>CH<sub>3</sub> group), 3.0—4.0

(8H, m, -CH<sub>2</sub>CH<sub>2</sub>- group), 6.15 (4H, s, H) $\rangle\langle$ H, and 7.3—7.8 (7H, m, benzene protons).

**8-Chloro-11-methyl-10-(2-dimethylaminoethoxy)dibenzo[*b,f*]thiepin (39)**—To a mixture of 0.4 g of NaH (50% oil) in 10 ml of dry DMF a solution of 4.9 g of 8-chloro-11-methyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-one was added dropwise with stirring at room temperature. The mixture was stirred for 60 min at 50°. Freshly distilled DMEC was added dropwise to the resulting solution. The mixture was stirred for 5 hr at 50° and poured into ice-water with careful and extracted with AcOEt. The AcOEt was extracted with 10% HCl and the aqueous layer was made alkaline to litmus with 10% NaOH. The oil was extracted with AcOEt. The products in AcOEt was chromatographed on alumina using AcOEt as eluent. After removal of the elution of starting material, the following elution were collected and evaporated. The oil obtained was converted into a corresponding hydrochloride, mp 114—116°, (from H<sub>2</sub>O-acetone). *Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>ClNS·HCl·H<sub>2</sub>O: C, 57.00; H, 5.79; Cl, 17.71; N, 3.50; S, 8.01. Found: C, 56.77; H, 5.62; Cl, 18.13; N, 3.83; S, 8.36. IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 1620 (enol ether). NMR (CDCl<sub>3</sub>, ppm): 2.33 (3H, s, CH<sub>3</sub>) $\rangle\langle$ , 3.02 (6H, d, -N(CH<sub>3</sub>)<sub>2</sub>), 3.30 (2H, t, -CH<sub>2</sub>-N), 4.05 (2H, t, -O-CH<sub>2</sub>-), and 7.05—7.65 (7H, m, benzene protons).

**Preparation of 8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-one (Vb) by an Improved Method**—*o*-(4-Chlorophenylthio)acetophenone (XX): A mixture of freshly distilled 365 g of XVIII and 300 g of XIX, 376 g of K<sub>2</sub>CO<sub>3</sub> (powdered) and 18 g of cupric acetate was stirred for 8.5 hr at 150° on an oil bath with bubbling nitrogen gas. The inorganic substances were filtered off and washed with 1000 ml of amylalcohol. The filtrates and the washing were combined and the amylalcohol was distilled at the range of 80 to 120° under reduced pressure of 8 mmHg. The fraction boiling at the range of 150 to 160° was collected. The distillate

obtained was dissolved in 800 ml of *n*-hexane at 60°. The resulting solution was cooled to 5°, with stirring to give the crystal of the acetophenone, which was collected on filter and air-dried at room temperature to afford 369 g of the acetophenone XX, mp 94—96° (lit.<sup>9</sup> 93—95°), in 72.3% yield.

**Preparation of Homoacid XXIV via the Willgerdt Reaction of Acetophenone XX:** A stirred mixture of 300 g of XX and 100.3 g of sulfur was dissolved in 139 g of morpholine at 150° on an oil bath. To the mixture 12.0 g of *p*-TosOH was added and the mixture was stirred for 10 hr at 150°. The reaction mixture was shaken with mixed solvent of 3 l of AcOEt and 3 l of water. The solution was filtered off to remove insoluble substances. The organic layer and water were separated. The organic layer obtained was washed with 10% NaOH, water and 10% HCl, and dried over MgSO<sub>4</sub>. After removal of the solvent, the residue was dissolved in mixed solvent of 3 kg of conc. HCl and 3 kg of acetic acid. The resulting solution was refluxed for 18 hr at 150°. The reaction mixture was poured into 10 l of ice-water and extracted twice with 10 l of benzene. The benzene layer was washed with water and extracted three times with 10 l of 10% sodium carbonate. The aqueous layer obtained was made acid with conc. HCl. The crystal precipitated was filtered and washed with water and air-dried to give 212.5 g of homoacid XXIV, mp 106—109°,<sup>3</sup> in 67% yield.

**Preparation of Vb:** To 280 g of PPA, prepared from 140 g of P<sub>2</sub>O<sub>5</sub> and 140 g of 85% H<sub>3</sub>PO<sub>4</sub>, 280 g of homoacid XXIV was added at 95° with stirring. The mixture was stirred for 1 hr at the range of 115 to 120°. The reaction mixture was poured into 15 l of ice-water and extracted with benzene. The benzene layer was washed with 10% NaOH and water, and dried over MgSO<sub>4</sub>. After removal of the solvent, 230 g of the residue was recrystallized from 4 l of EtOH to give 220 g of the ketone Vb, mp 123—124° (lit.<sup>10</sup> 125°), in 84% yield.

**Preparation and Identification of Thiomorpholide (XXII) and Oxothiomorpholide (XXIII)<sup>10</sup>**—A mixture of 10 g of XX, 4.64 g of morpholine, 3.42 g of sulfur (powder) and 0.04g of *p*-TosOH was heated at 105 to 110° for 15 hr with stirring. The mixture was shaken with a mixture of 100 ml of AcOEt and 100 ml of water to dissolve products. After the insoluble materials were filtered off, the AcOEt and the aqueous phase were separated. The AcOEt was washed with 10% NaOH, water and 10% HCl, and dried over MgSO<sub>4</sub>. The AcOEt was evaporated *in vacuo* to give 14.1 g of reddish oils. A solution of oils obtained in 50 ml of ether was allowed to stand overnight at 5° in a refrigerator to precipitate 2.0 g of crystal, mp 176—179°, which was recrystallized from AcOEt. This was assigned as the compound XXIII on the basis of elemental analysis and spectra data shown below. *Anal.* Calcd. for C<sub>18</sub>H<sub>16</sub>ClNO<sub>2</sub>S<sub>2</sub>: C, 57.21; H, 4.27; Cl, 9.38; N, 3.71; S, 16.79. Found: C, 57.34; H, 4.28; Cl, 9.19; N, 3.79; S, 16.82. IR  $\nu_{\max}^{\text{Nujol}}$  cm<sup>-1</sup>: 1640 (CO). NMR (CDCl<sub>3</sub>, ppm): 6.7—7.9 (8H, m, benzene protons), 3.70 (4H, s), 3.85 (2H, t), and 4.30 (2H, t).

The ether layer was evaporated to give 10.9 g of reddish oils. The TLC indicated to consist of one component. As this was impossible to purify with usual methods, the structure was confirmed by derivatization to the corresponding homoacid (XXIV); A solution of 10.9 g of the oil obtained the above in 100 g of conc. HCl and 100 g of AcOH was refluxed for 18 hr on an oil bath of 150°. The mixture was poured into 200 ml of water and extracted twice with 200 ml of benzene. The benzene was washed with water and extracted twice with 200 ml of sat. Na<sub>2</sub>CO<sub>3</sub> aq. The aqueous layer was made acid to litmus with conc. HCl to give crystals. The crystals were recrystallized from aqueous EtOH to give 6.3 g of XXIV, mp 111—113° (lit.<sup>3</sup>) 106—109°).

**Acknowledgement** The authors wish to express thanks to Mr. M. Matsuo for his kind discussion for the Willgerdt reaction and also are indebted to Mr. K. Otsuji, Mr. T. Kochi, and Mr. T. Kitaguchi for their skillful technical assistance.