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The Synthesis of 10-(4-Methylpiperazino)dibenzo[*b*,*f*]thiepin and Related Compounds.[1] Neurotropic and Psychotropic Agents

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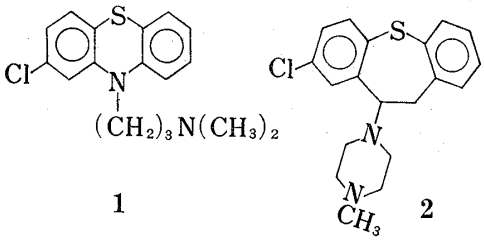
The preparation of 10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (**16a**) and related Compounds is described. The reduction of **16a** in an acidic medium yield the dihydro derivative (**21**) which was pharmacologically a valuable compound. Many of the compounds in this series showed marked neuroleptic effects similary to octoclotepine (**2**).

The tricyclic system has, during the past decade, been the object of intense investigation by medical chemist and organic chemist in search of compounds with useful neurotropic and psychotropic activity.[3]

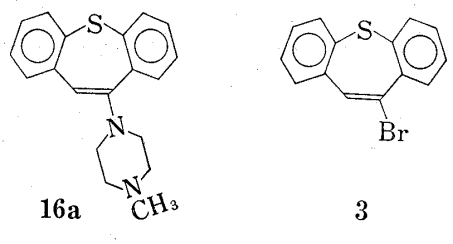
With the aim of discovering agents which show modified pharmacological properties compared to Chloropromazine (**1**), we have synthesized various derivatives of dibenzo[*b*,*f*]-thiepin, dibenz[*b*,*f*]oxepin and other tricyclic compounds.[4]

In 1965 Protiva, *et al.* reported the synthesis of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin, (Octoclotepine) (**2**) and its analogues.[5] Two years later Jílek, *et al.* reported an unsuccessful attempt to prepare 10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (**16a**) by the reaction of 10-bromodibenzo[*b*,*f*]thiepin (**3**) with 1-methylpiperazine.[6]



1 2

Chart 1



16a 3

Chart 2

In this manuscript we will describe a synthesis of the compound (**16a**) and related compounds which in our animal studies displayed marked neuroleptic effects similary to **1** and **2**.[7]

Our discovery of **16a** resulted from a comprehensive study of relationship between structure and activity of a series of tricyclic compounds.

The key intermediates for the synthesis of **16a** and related compounds are 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**6a—d**) and 10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (**6e—k**), ob-

1) *a*) S. Umio, I. Ueda, Y. Sato, and S. Maeno, Ger., Offen. 1801523 (1969) [*Chem. Abstr.*, **71**, 112976*v* (1969)]; *b*) J.O. Jílek, K. Šindelář, J. Metysová, J. Pomykáček, and M. Protiva, *Collection Czech, Chem. Commun.*, **35**, 3721 (1970).

2) Location: *Kashima, Yodogawa-ku, Osaka, 532, Japan*; *a*) Abstracted from a portion of the Ph. D. Dissertation submitted by I.U. in March 1974 at Osaka University.

3) *a*) Von Dr E. Jucker, *Angew. Chem.*, **75**, 524 (1963); *b*) M. Protiva, *Farmaco, Ed. Sci.*, **1973**, 58.

4) I. Ueda and S. Umio, *Bull. Chem. Soc. Japan*, **48**, 2323 (1975).

5) M. Protiva, J.O. Jílek, J. Metyšová, V. Seidlová, I. Jirkovský, J. Metyš, E. Adlerová, I. Ernest, K. Pelz, and J. Pomykáček, *Il. Farmaco. Ed. Sci.*, **20**, 721 (1965).

6) J.O. Jílek, E. Svátek, J. Metyšová, J. Pomykáček, and M. Protiva, *Collection Czech. Chem. Commun.*, **32**, 3186 (1967).

7) Unpublished data.

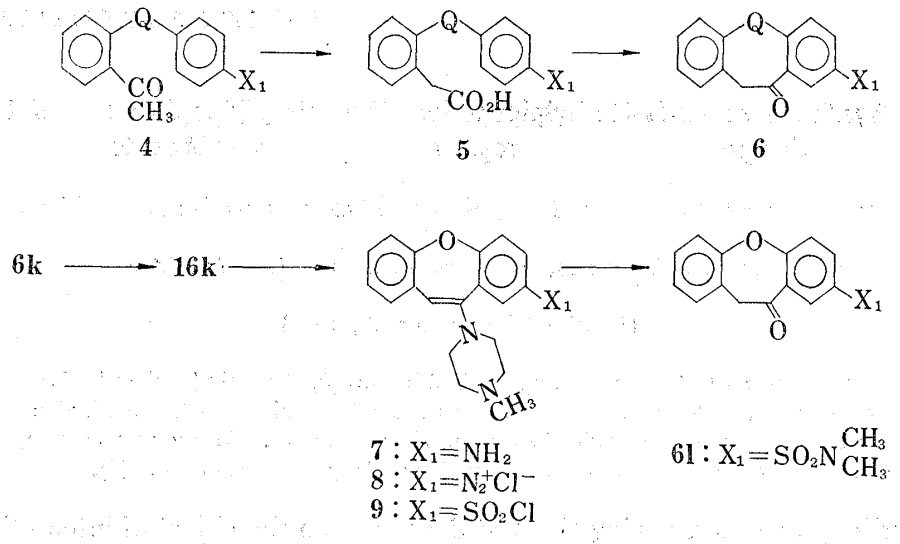


Chart 3

tained by the cyclization of homoacids (**5a—k**) using a large excess polyphosphoric acid. These homoacids were prepared by the Willgerodt reaction of acetophenones (**4a—j**).[8] The preparation of 8-dimethylaminosulfonyl-10,11-dihydrodibenz[*b*,*f*]oxepin (**61**) was prepared from 8-amino-10-(4-methylpiperazino)dibenz[*b*,*f*]oxepin (**7**) by modification of the patented procedure.[9] The reaction of 8-nitro-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (**6k**) with 1-methylpiperazine in the presence of titanium tetrachloride in refluxing toluene gave the compound (**16k**) which was reduced smoothly with catalytic reduction to 8-amino derivative (**7**). Diazotization and chlorosulfonation with $SO_2/CuCl_2$ gave sulfonylchloride (**9**) which was allowed to react with dimethylamine to give **61** in 10% yield from **7**.

Alkylation of 10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**6a**) with sodium hydride and methyliodide in toluene using the patented procedure,[10] substituted at the 11-position to yield 11-methyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**10**). Alkylation with benzyl chloride under similar condition produced the 11-benzyl derivative (**11**).

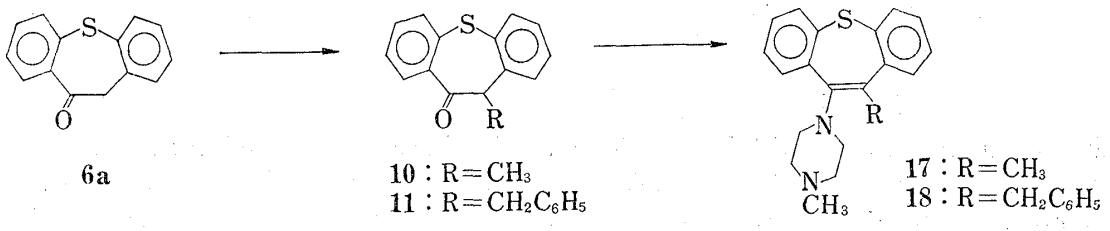
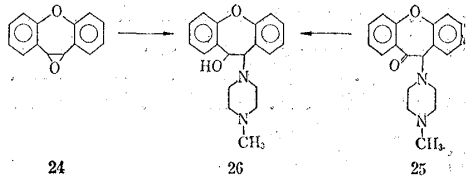


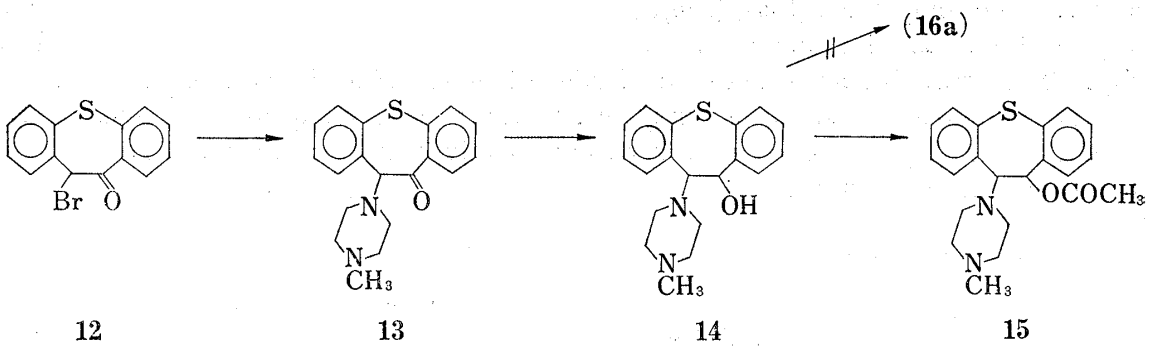
Chart 4

Synthesis of 10-(4-Methylpiperazino)dibenzo[*b*,*f*]thiepin and related Compounds

Attempt was made to prepare **16a** by the dehydration of 11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (**14**).[11] In this case using acetic anhydride (140°) the acetyl derivative (**15**) was isolated.

8) S. Kimoto, K. Kimura, and S. Muramatsu, *Yakugaku Zasshi*, **74**, 426 (1954).
9) J.R. Geigy A. -G, Swiss Patent 408927 [*Appl.*, **5**, 10 (1962)].
10) J.R. Geigy A. -G, Neth. Appl. 6404862 (1964) [*Chem. Abstr.*, **62**, 16215*a* (1965)].
11) *a*) See reference 6; *b*) The cleavage of epoxide (**24**) with 1-methylpiperazine gave 10-(4-methylpiperazino)-10,11-dihydrodibenz[*b*,*f*]oxepin-11-ol (**26**) which was assigned to the conformational isomer of the aminoalcohol, obtained by the reduction of the aminoketone (**25**) with $NaBH_4$ in methanol, on the basis of these NMR spectra.

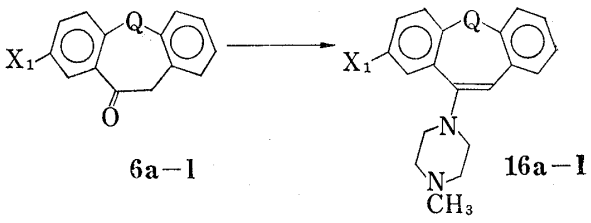




12 13 14 15

Chart 5

We employed for the preparation of enamine derivatives a new method described by White and Weingarten consisting in the presence of titanium tetrachloride in inert solvent such as ether and toluene.[12] In this method, the reaction of one mole of the ketone (**6a**) with eight moles of 1-methylpiperazine in the presence of one half mole of titanium tetrachloride in refluxing benzene or toluene gave **16a** in 72.4% yield.



6a–l 16a–l

Chart 6

If the condensation was carried out in the presence of *p*-toluenesulfonic acid as catalyst, the formation of **16a** was relative low yield and took as long as 2 to 3 days before termination of the reaction at about 110°.[13] In order to raise the efficiency of the reaction the condensation of **6a** with 1-methylpiperazine in refluxing toluene for 7 to 10 hours, using two moles of *p*-toluenesulfonic acid and eight moles of 1-methylpiperazine for **6a** gave **16a** in 64.7% yield.

The enamine derivatives listed in Table V were prepared by the use of titanium tetrachloride as a condensing agent.

The compound **16a** was subjected to chemical reduction and catalytic reduction in an acidic medium to give 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (**21**) in moderate yield. This is a novel way of preparing pharmacologically valuable compounds such as **2**. The catalytic reduction of **16a** in an alcoholic medium did not yield the dihydro derivative (**21**). The reaction of 10-(4-ethoxycarbonyl)dibenzo[*b*,*f*]thiepin (**23**) with lithium aluminum hydride (LAH) in refluxing tetrahydrofuran (THF) gave **6a** in high yield, but **21** was not formed.

The compound (**16a**) was readily hydrolyzed at pH of 3 or less into **6a** and 1-methylpiperazine, but relatively stable in pH near 4.5 in aqueous solution (half-life time; *ca.* 30 minute).

The treatment of **16a** with two equivalent of hydrochloric acid under anhydrous condition gave mono hydrochloride (**20**) in quantitative yield alone though **16a** has piperazine residue in molecule. The compound (**16a**) was treated with methyliodide in refluxing acetone at atmospheric pressure or in a sealed tube to give quarternary ammonium salt (**19**). Similar treatment of **22** did not produce a quarternary ammonium salt.

Pharmacological Results

All compounds prepared in this work were evaluated pharmacologically using the tests usual in search for neurotropic activity. The results of several typical compounds are shown

12) W.A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
13) *a*) K. Šindelář, J. Metyšová, J. Metyš, and M. Protiva, *Naturwissenshaften*, **556**, 374 (1969): see reference 1*b*; *b*) M. Mastivsi, S. Lembo, and R. Viterbo (Richerdson-Merrell S.p.A.) S. African Patent 68 01774 (1968) [*Chem. Abstr.*, **70**, 96823*g* (1969)].

in Table I. The compounds (**16a**), (**16b**), (**16e**) and (**16f**) displayed marked neuroleptic effects similary to **1** and **2**. The analogous amine (**17**) showed no pronounced pharmacological activity. The great difference between **17** and other enamine derivatives on the activity may be attributed to the steric factor regard to the methyl group at the 11-position.

The pharmacological properties and structure-activity relationships will be reported in detail elsewhere in near future.

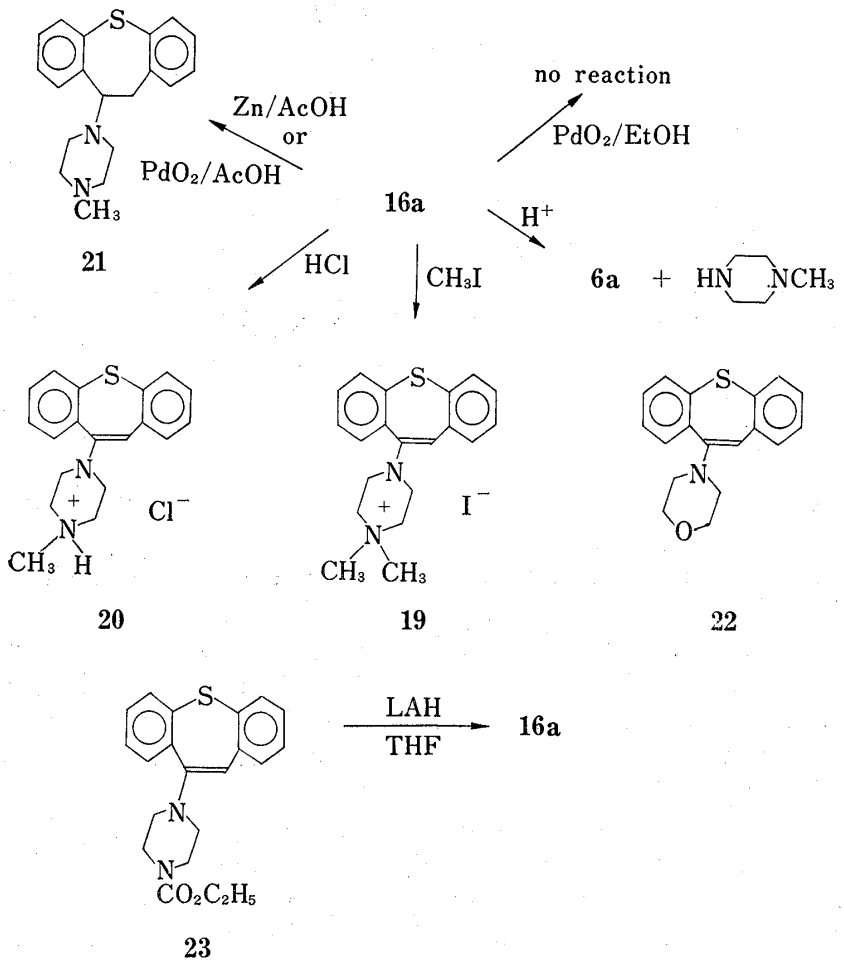


Chart 7

Table I. Neuroleptic Properties of the Dibenzo[*b*,*f*]thiepins, Related Compounds and Reference Compounds
Rats, *s.c.*

Compound	Antiapomorphine effect ED_{50} (mg/kg)	Potentiation of barbiturate sleep ED_{50} (mg/kg)
16a	0.1	0.2
16b	1.2	0.2
16e	0.06	0.4
16f	3.0	0.4
17	*a*)	*a*)
13	*a*)	*a*)
14	*a*)	*a*)
Chloropromazine	5.0	0.9
Octoclotepine	0.05	0.4

a) ineffective at the dose of 64 mg/kg

Experimental

2-(4-Methoxyphenyloxy)acetophenone (4h)——A mixture of 124 g of 2-chloroacetophenone, 130.5 g of 4-methoxyphenol, and 169 g of K_2CO_3 in 40 ml of AmOH was refluxed for 17 hr at 160—170° in the presence of cuprous acetate as the catalyst. After cooling, the reaction mixture was filtered to remove inorganic substances and the residue was washed with AcOEt. The filtrate and washings were combined. The organic layer combined was washed with 10% NaOH solution, dried over $MgSO_4$ and evaporated. The solvent was removed at 100°/5 mmHg and starting materials were distillated *in vacuo*. The residue was distillated under reduced pressure. A fraction boiling at 158—160°/0.8 mmHg was collected. The yield of **4h** was 43%.

In a similar manner as above, 2-(4-methoxyphenylthio) acetophenone (**4d**), (from benzene–cyclohexane) mp 94—96° was obtained in 68% yield by the reaction of 2-chloroacetophenone and 4-methoxythiophenol.

Table II. Preparation of o-Substituted Acetophenone Derivatives (4)

	Q	X_1	mp (bp) (°C)	Yield (%)	Analysis (%) Calcd. (Found) C	H	X
4a	S [a]	H	71—72.5	65.0			
4b	S [b]	Cl	93—95	37.0			
4c	S	CH_3	112	59.0	74.36	5.83	
4d	S [a]	OCH_3	94—96	68.0	(74.51	6.01)	
4e	O [c]	H	(132—8 /3)	60.0			
4f	O	Cl	(135—40 /0.35)	55.8	68.16	4.49	14.37
					(67.98	4.85	14.50)
4g	O	Br	(163—170 /0.7)	35.0	57.76	3.81	27.44
					(57.43	3.69	26.98)
4h	O	OCH_3	(146—150 /0.2)	43.0	65.69	5.15	
					(65.60	4.98)	
4i	O	SCH_3	(170—5 /3.3)	40.0	62.06	4.86	
					(62.31	4.39)	
4j	O	C_2H_5	(165—172 /0.5)	26.7	79.97	6.71	
					(80.01	6.83)	

a) S. Kimoto, M. Okamoto, K. Yabe, T. Uchida, and Y. Matsutaka, *Yakugaku Zasshi*, **88**, 1323 (1968)
b) J.O. Jílek, K. šindelář, J. Pomykáček, O. Horešovsky, K. Pelz, E. Svátek, B. Kakáč, J. Holubek, J. Metyšová, and M. Protiva, *Collection Czech. Chem. Commun.*, **38**, 115 (1973)
c) S. Kimoto, K. Kimura, and S. Muramatsu, *Yakugaku Zasshi*, **74**, 426 (1954)

2-(4-Methoxyphenyloxy)phenylacetic Acid (5h)——A mixture of 100 g of **4h**, 56.6 g of morpholine, and 20.8 g of sulfur was refluxed for 10 hr at 150° on an oil bath. The reaction mixture was dissolved in 300 ml of AcOH on heating and to this solution 20 ml of conc. HCl was added. The mixture was refluxed for 7 hr, and the reaction mixture was concentrated to one third the initial volume. To this solution 1.5 l of H_2O was added, and the mixture was extracted with ether. The aqueous layer was made acid with conc. HCl and the solid formed was extracted with ether and the ether layer was dried over $MgSO_4$ and evaporated. The oily residue crystallized on standing. **5h**, mp 72—73° was obtained in 59% yield.

In a similar manner as above, 2-(4-methoxyphenylthio)phenylacetic acid, a colorless needle, (from aq. EtOH) **5d** was obtained in 47% yield by the Willgerodt reaction of **4d**.

2-(4-Methanesulfonylphenyloxy)phenylacetic Acid (5k)——To a solution of 4.0 g of **5i** in 50 ml of AcOH dropwise 30 ml of 30% H_2O_2 was added over a period of 20 min. The reaction was continued for 5 hr at 100—105°. The AcOH was carefully concentrated to one half the initial amount, and the reaction mixture was cooled to 0°. The crystals were filtered, washed with H_2O, air-dried at room temperature, and recrystallized from 95% EtOH, and then from benzene–cyclohexane to give colorless needle crystals, mp 131°. Yield, 3.6 g (81%). *Anal.* Calcd. for $C_{15}H_{14}O_5S$: C, 58.85; H, 4.61; S, 10.44%. Found: C, 58.91; H, 4.60; S, 10.75%.

Synthesis of Derivatives of 10,11-Dihydrodibenzo[*b*,*f*]thiepin-10-one (6a—d) and 10,11-Dihydrodibenz-[*b*,*f*]oxepin-10-one (6e—k)——General Method: A solution of 10 g of a homoacid in 100 ml of PPA (prepared from 50 g of P_2O_5 and 50 g of H_3PO_4) was heated for 2 hr at 90—100°. After cooling, the reaction mixture was poured into 1.0 l of ice water and extracted with isopropylether. The organic layer was washed with H_2O and 10% NaOH solution and H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The solid obtained was purified by a recrystallization and the oil was purified by a distillation. The products obtained by this method are listed in Table IV.

8-Dimethylsulfamoyl-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (**61**) was prepared by a patented method from **7** in 10% yield. Infrared (IR) and nuclear magnetic resonance (NMR) spectra of **61**; IR ν_{max}^{Nujol} 1675 (CO), 1340 and 1160 (SO_2N) cm^{-1}. NMR ($CDCl_3$, ppm) 2.7 (6H, s, $SO_2N(CH_3)_2$) and 4.04 (2H, s, CH_2CO).

Table III. Preparation of o-Substituted-phenylacetic Acid Derivatives (5)

	Q	X_1	mp (bp) (°C)	Yield (%)	a) mp (bp) (°C)
5a	S	H	113—115	40.6	a) 123
5b	S	Cl	106—109	57.0	b) 115—116
5c	S	CH_3	112—113	30.0	c) 116—117
5d	S	OCH_3	100—102	47.0	c) 103—104
5e	O	H	89—91	40.0	d) 90—91
5f	O	Cl	115—118	62.0	e) 119—121
5g	O	Br	119—120.5	42.8	
5h	O	OCH_3	72—73	59.0	e) 79—80
5i	O	SCH_3	92—94	42.0	e) 96—99
5j	O	C_2H_5	oil	30.3	

a) M. Protiva, J.O. Jílek, V. Seidlová, E. Svákek, and, M. Protiva, *Mh. Chem.*, **96**, 182 (1965)
b) M. Protiva, J.O. Jílek, J. Metyšová, J. Pomykáček, and M. Protiva, *Collection Czech. Chem. Commun.*, **33**, 1831 (1968)
c) K. Pelz, I. Jirkovský, E. Adlerová, J. Metyšová, and M. Protiva, *Collection Czech. Chem. Commun.*, **33**, 1895 (1968)
d) S. Kimoto, K. Kimura, and S. Muramatsu, *Yakugaku Zasshi*, **74**, 426 (1954)
e) M. Protiva, V. Seidlová, K. Pelz, E. Adleová, I. Jirkovsky, J. Metyšová, and M. Protiva, *Collection Czech. Chem. Commun.*, **34**, 2258 (1969)

Table IV. Preparation of Dibenzo[*b*,*f*]thiepin-10-one and Dibenz[*b*,*f*]oxepin-10-one (6)

	Q	X_1	mp (bp) (°C)	Yield (%)	a)—e) mp (bp) (°C)
6a	S	H	72—73	77.2	a) 72—73
6b	S	Cl	121—122	73.0	b) 125
6c	S	CH_3	60.5—65	50.0	c) 68—69
6d	S	OCH_3	96—97	65.0	c) 97.5—98
6e	O	H	50(151—163 /0.4)	80.0	d) (142—145 /0.5)
6f	O	Cl	80—81	78.0	e) 83—84
6g	O f)	Br	100—101	85.0	
6h	O	OCH_3	(165—167/0.5)	24.5	e) (173 /0.4)
6i	O	SCH_3	60	29.0	e) 64—65
6j	O	C_2H_5	(170—178 /0.5)	78.8	
6k	O g)	NO_2	109—111.5	55.0	

a)—e) see references in Table III
f) IR ν_{max}^{nujol}; 1680 (CO) cm^{-1}
g) *Anal.* Found; C, 65.99; H, 3.48; N, 5.26%. Calcd. for $C_{14}H_9O_4N$; C, 65.88; H, 3.55; N, 5.45

11-Bromo-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (12)——A solution of 15 g of **6a** in 150 ml of $CHCl_3$ was warmed to 40°, and 9.4 g of Br_2 was added dropwise to this solution. The mixture was allowed to react for 2 hr at 40°. The $CHCl_3$ layer was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The crystalline residue was recrystallized from EtOH, mp 106—108° (lit, 109—110°).[6] Yield, 17.2 g (85%).

11-(4-Methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (13)[6]——A 5 g portion of **12** was added all at once to 1-methylpiperazine under ice-water cooling. After 10 min, the temperature was brought to room temperature. The reaction mixture was allowed to react for 2 hr at room temperature and 1 hr at 50°. The mixture was poured into ice-water and extracted with ether. The ether layer was extracted with 10% HCl. The aqueous layer was made alkaline with 10% NaOH solution. The oil suspended was extracted with ether. The ether layer was dried and evaporated to give a viscous oil, 4.7 g which was converted to hydrochloride of **13** in the usual manner. The hydrochloride was recrystallized from EtOH–ether, mp 183—185° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}OCl_2NS$: C, 54.91; H, 5.82; N, 6.79; S, 7.72; Cl, 17.06%. Found: C, 54.82; H, 5.82; N, 6.99; S, 7.98; Cl, 16.26%.

10-Hydroxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*] thiepin (14)——A solution of 3.8 g of **13** in a solvent consisting of 170 ml of MeOH and 11 ml of H_2O was warmed to 50°, and to this solution a small amount portions of 3.7 g of $NaBH_4$ was added over a period of 30 min. After 1 hr, the reaction mixture was cooled to room temperature and allowed to stand for 2 hr. After removal of the solvent, H_2O was added to the residue and the mixture was extracted with ether. The ether layer was extracted with 10% HCl and the aqueous layer was made alkaline with 10% NaOH solution. The oil formed was extracted with $CHCl_3$ and the $CHCl_3$ layer was dried over $MgSO_4$, and evaporated *in vacuo*. The residue was solidified by the addition of ethanol and recrystallized from EtOH, mp 152—154° (lit, 142—152°).[6] Yield, 1.3 g (41.5%).

10-Hydroxy-11-(4-methylpiperazino)-10,11-dihydrodibenz[*b*,*f*] oxepin (26)——In a similar manner described above, **26** was obtained in 42.6% yield from the reaction of 2.4 g of **25** and 2.5 g of $NaBH_4$ in 100 ml of MeOH, (from EtOH) mp 139—140°. *Anal.* Calcd. for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.14; N, 9.03%. Found: C, 73.27; H, 7.33; N, 9.02%.

10-Acetoxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*] thiepin (15)——A solution of 1.5 g of **14** in 15 ml of Ac_2O was refluxed for 6 hr and cooled. The reaction mixture was poured into sat. Na_2CO_3 solution, allowed to stand overnight, and extracted with ether. The ether layer was extracted with 10% HCl and the aqueous layer was made alkaline with 10% NaOH solution. The oil obtained was extracted with $CHCl_3$ and the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated *in vacuo*. A 1.6 g portion of the oil obtained was converted to the oxalate of **15** by the usual manner. The crude salt was recrystallized from EtOH–ether, mp 160—163°. *Anal.* Calcd. for $C_{21}H_{24}O_2N_2S \cdot C_2H_2O_4 \cdot 1/2H_2O$: C, 59.08; H, 5.82; N, 5.99; S, 6.86%. Found: C, 59.43; H, 5.82; N, 5.99; S, 7.17%.

10,11-Dihydrodibenz[*b*,*f*] oxepin-10,11-epoxide (24)——To a solution of 5.0 g of dibenz[*b*,*f*] oxepin in 50 ml of $CHCl_3$ a solution of perbenzoic acid in $CHCl_3$ (concentration; 65%)[14] was added and allowed to stand overnight in a refrigerator. The mixture was washed with a chilled 10% Na_2CO_3 solution, and H_2O, and dried over $MgSO_4$. The $CHCl_3$ was evaporated *in vacuo* and the solid obtained was recrystallized from benzene to give pale yellow needle, mp 110—112°. Yield, 3.5 g.

10-Hydroxy-11-(4-methylpiperazino)-10,11-dihydrodibenz[*b*,*f*] oxepin (26); Reaction of 24 with 1-Methylpiperazine——A mixture of 1.3 g of **24** and 5.0 g of 1-methylpiperazine was heated for 48 hr at 120—125° under stirring. The reaction mixture was dissolved in ether. The ether layer was washed with H_2O and extracted with 10% HCl. The aqueous layer was made alkaline with 10% NaOH solution. The oil was

Table V. Preparation of 10-(4-Methyl piperazino)-dibenzo[*b*,*f*]thiepin and related Compounds (**16**)

	Q	X_1	Salt[a]	mp (bp) (°C)	Yield (%)	Analysis (%) Calcd. (Found) C	H	N	S	Cl
16a	S[b,c]	H	FB	115—118	72.4	74.00	6.54	9.09	10.38	
						(74.21	6.65	8.91	10.20)	
16b	S[c,d,e]	Cl	MA	234	54.5	60.19	5.05	6.10	6.99	7.73
						(60.29	4.85	5.99	7.07	7.92)
16c	S[c]	CH_3	MA	227	62.0	65.75	5.98	6.39	7.31	
						(65.96	6.07	6.30	7.56)	
16d	S[c]	OCH_3	MA	221—222	65.0	63.43	5.77	6.16	7.04	
						(63.42	5.77	5.92	7.02)	
16e	O[b,c]	H	FB	109—110	53.5	78.05	6.90	9.58		
						(78.21	7.03	9.37)		
16f	O[b,c]	Cl	MA	178	54.5	62.37	5.23	6.38		8.01
						(62.14	5.18	6.58		7.95)
16g	O[c]	Br	FB	110—111	79.8	60.33	5.38	7.41		21.12
						(60.20	5.32	7.41		21.12)
16h	O[b,c]	OCH_3	MA	202—203	52.7	65.74	5.98	6.39		
						(65.97	5.96	6.45)		
16i	O	SCH_3	MA	198—199	44.5	63.42	5.77	6.16	7.06	
						(63.30	5.80	6.11	6.84)	
16j	O[c]	C_2H_5	MA	201—202	57.5	68.78	6.46	6.42		
						(68.77	6.59	6.46)		
16k	O[c]	NO_2	FB	163—164	22.9	67.64	5.68	12.45		
						(67.82	5.68	12.31)		
16l	O[c]	$SO_2N\begin{matrix}Me\\Me\end{matrix}$	MA	189—190	90.0	58.24	5.67	8.15	6.22	
						(57.96	5.74	8.17	5.95)	

a) FB; free base
MA; maleate
b) see reference **13b**
c) see reference **1a**
d) see reference **1b**
e) see reference **13a**

14) M. Kotake (Ed), "Jikken Kagaku Koza, Suppl," 17-I, Maruzen, Tokyo, 1963, p. 340.

extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated. The solid obtained was recrystallized from cyclohexane to give yellow prism crystals, mp 177—178 °C. *Anal.* Calcd. for $C_{19}H_{22}O_2N_2$: C, 73.52; H, 7.51; N, 9.03%. Found: C, 73.59; H, 7.42; N, 8.88%.

Synthesis of 10-(4-Methylpiperazino)dibenzo[*b*,*f*]thiepin (16a) and related Compounds (16b—1)——Method A; Use of $TiCl_4$: To a solution of 22.7 g of **6a** and 80 g of 1-methylpiperazine in 226 ml of absolute toluene a solution of 10 g of $TiCl_4$ in 50 ml of absolute toluene was added dropwise under cooling. The reaction mixture was stirred for 8 hr at 110°. After cooling, inorganic materials were removed, and washed with 50 ml of toluene. The toluene layer and washings were combined and washed with H_2O until the pH of the aqueous layer become 5 to 6. The toluene layer was dried over $MgSO_4$, and evaporated *in vacuo*. The oil obtained crystallized in cyclohexane. The crude crystals were recrystallized from cyclohexane, mp 115—118 °C. Yield, 22.3 g.

Method B; Use of *p*-TosOH: A solution of 45.3 g of **6a**, 160 g of 1-methylpiperazine and 34.4 g *p*-TosOH in 400 ml of xylene was refluxed for 7 hr under vigorous stirring. H_2O formed during the period of the reaction was removed by the Cope apparatus. The reaction mixture was poured into cold water containing 24 g of K_2CO_3. The aqueous layer was separated. The organic layer was washed with H_2O, dried, and evaporated to give 50 g of crude solid, which was recrystallized from cyclohexane, pale yellow crystals, mp 115—118°. Yield, 40.4 g (64.7%). Related compounds (**16b—1**) were prepared by Method A described above.

10-(4-Ethoxycarbonylpiperazino)dibenzo[*b*,*f*]thiepin (23)——mp 112—113° was obtained in 85% yield by the reaction of 2.3 g of **6a** with 8.0 g of 1-ethoxycarbonylpiperazine in the presence of 1.0 g of $TiCl_4$. *Anal.* Calcd. for $C_{21}H_{22}O_2N_2S$: C, 68.83; H, 6.65; N, 7.65; S, 8.73%. Found: C, 68.50; H, 6.13; N, 7.55; S, 8.47%.

8-Amino-10-(4-methylpiperazino) dibenz[*b*,*f*] oxepin (7)——A mixture of 3 g of Pd/C and 100 ml of MeOH was shaken with hydrogen gas under atmospheric pressure, and then 11.2 g of 8-nitro-10-(4-methylpiperazino)dibenz[*b*,*f*] oxepin (**16k**) was added subsequently. The mixture was shaken for 8 hr at room temperature while hydrogen gas was passed. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was recrystallized from a mixed solvent of EtOH and benzene to give **7**. mp 200.5—202°. Yield 4.0 g (32.2%). *Anal.* Calcd. for $C_{19}H_{21}ON_3$: C, 74.24; H, 6.89; N, 3.67%. Found: C, 74.35; H, 6.70; N, 3.96%.

11-Methyl-10-(4-methylpiperazino)dibenzo[*b*,*f*]thiepin (17)——To a solution of 4.8 g of 11-methyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (**10**)[10] and 8 g of 1-methylpiperazine in 48 ml of toluene a solution of 1.8 g of $TiCl_4$ in 18 ml of toluene was added. The mixture was refluxed for 15 hr under stirring. After cooling, inorganic materials were removed and washed with toluene. The toluene layer was washed with H_2O, dried over $MgSO_4$, and evaporated. The oil obtained was converted to the maleate, which was recrystallized from aq. EtOH to give 5.0 g of the maleate, mp 199—201°. Yield, 54.5%. *Anal.* Calcd. for $C_{20}H_{22}N_2S$ $C_4H_4O_4$: C, 65.73; H, 5.98; N, 6.39; S, 7.31%. Found: C, 66.12; H, 5.92; N, 6.28; S, 7.62%.

In a similar manner, 11-benzyl-10,11-(4-methylpiperazino) dibenzo [*b*,*f*] thiepin (**18**) was prepared from the reaction of 11-benzyl-10,11-dihydrobenzo [*b*,*f*] thiepin-10-one (**11**) and 1-methylpiperazine in 67.5% yield, mp 97—98°. *Anal.* Calcd. for $C_{26}H_{26}N_2S$: C, 78.36; H, 6.58; N, 7.03; S, 8.05%. Found: C, 77.16; H, 6.87; N, 6.87; S, 7.81%.

11-Benzyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-one (11)——Alkylation of 4.25 g of **6a** with 0.97 g of NaH(50% mineral oil dispersion) and 2.53 g of benzylchloride in dry benzene by the similar way of the patented procedure[10] gave 0.2 g of **11** in 3.6% yield. *Anal.* Calcd. for $C_{21}H_{16}OS$: C, 79.71; H, 5.10; S, 10.13 %. Found: C, 80.34; H, 4.86; S, 10.30%.

10-(4-Methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (21). Reduction of 10-(4-Methylpiperazino)-dibenzo[*b*,*f*]thiepin (16a)——A. To a solution of 100 mg of (**16a**) in 3 ml of AcOH 100 mg of zinc powder was added in one portion and the mixture was refluxed for 4 hr. After cooling, the solid was filtered and the filtrate was concentrated *in vacuo*. The residue was made alkaline with sat. Na_2CO_3 solution. The oil obtained was extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated. The solid obtained was recrystallized from MeOH, mp 132—133°. Yield 69.3%. *Anal.* Calcd. for $C_{19}H_{22}N_2S$: C, 73.52; H, 7.14; N, 9.03; S, 10.31%. Found: C, 73.31; H, 7.20; N, 8.97; S, 10.54%.

B. A mixture of PdO_2 and 5 ml of AcOH was shaken while hydrogen gas was passed for 30 min under atmospheric pressure and then 200 mg of **16a** was added subsequently. The mixture was shaken for 4 hr at room temperature while hydrogen gas was passed. The catalyst was removed by filtration and the filtrate was treated in a similar manner described (A) to give **21**, mp 132—133°, yield 160 mg (79%).

Reduction of 23 with LAH——To a suspension of 0.5 g of LAH in 5 ml of THF 1.0 g of **23** in 50 ml of THF was added over a period of 30 min under nitrogen gas. The mixture was stirred for 15 hr with refluxing. The excess LAH was decomposed by AcOEt, and water was added to the mixture. The mixture was then extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated. The solid obtained was recrystallized from *n*-hexane to give 0.8 g of the crystals, mp 115—118°, which agreed with the authentic sample (**16a**) for the spectrophotomeric data, *i.e.*, IR and NMR spectra and the melting point was not depressed by admixture with the authentic sample.

The reaction of 16a or 22 with Methyliodide Under Atmospheric Pressure——A solution of 0.2 g of (**22**) and 2.0 ml of MeI in 20 ml of purified acetone was refluxed vigorously for 3 hr. The reaction was followed by TLC (condition of TLC: Silica gel KF_{254}: developing solvent: benzene (6): cyclohexane (4). The reaction did not proceed.

A solution of 0.2 g of **16a** and 2 ml of MeI in 20 ml of purified acetone was refluxed for 3 hr. After removal of the solvent, the residue was recrystallized from 99% EtOH to give 0.28 g of **19**, mp 266—267°. Yield, 91%. *Anal.* Calcd. for $C_{20}H_{23}N_2SI$: C, 53.34; H, 5.15; N, 6.22; S, 7.12; I, 28.18%. Found: C, 53.05; H, 5.20; N, 6.00; S, 6.36; I, 28.93%.