NEUROTROPIC AND PSYCHOTROPIC AGENTS. LXII.*

SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 8-SULFAMOYL-10-PIPERAZINODIBENZO[*b,f*]THIEPINS

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The diazonium salt prepared from 8-amino-11*H*-dibenzo[*b,f*]thiepin-10-one reacts with sulfur dioxide and cuprous chloride giving rise to the sulfonyl chloride *VIII* which is converted by amines to sulfonamides *IX*—*XI*. Compounds *IX* and *X* were converted in two steps to the chlorides *XIV* and *XV* which underwent substitution reactions with 1-methylpiperazine, piperazine and 1-(3-hydroxypropyl)piperazine to yield the corresponding 8-sulfamoyl-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins *III*— *V* and *XVI*. Titanium tetrachloride method applied to the ketone *IX* yielded the enamine *XIX*. Compounds *III*, *V* and *XIX* are very powerful neuroleptics, enamine *XIX* exceeding octoclothepin and perphenazine in the intensity of cataleptic and antiapomorphine effects.

The high degree of neuroleptic activity of thioproperazine[1] (*I*) and thiothixene[2,3] (*II*), *i.e.* of psychotropic sulfonamides of the phenothiazine and thioxanthene series indicated the usefulness of investigating the analogous sulfonamides of the dibenzo[*b,f*]thiepin series of neuroleptics, first of all of 8-(dimethylsulfamoyl)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*III*). Some time ago[4] we described synthetic experiments in this line which did not go beyond the stage of acid *VI*. Attempts at cyclization of this acid to the ketone *IX* by various procedures, particularly using polyphosphoric acid under various conditions, led to complex mixtures of neutral products where ketone *IX* apparently was present[5] but, from the preparative point of view, the method appeared unsatisfactory. Certain information on the character of the participation of side reactions is provided by the identification of one of the crystalline products as the dimethylamide *VII*. When seeking new procedures leading to ketone *IX* we used Meerwein's modification[6] of the Sandmeyer reaction which allows to replace a diazo group by a sulfonyl chloride one, through a reaction of a solution of diazonium chloride with a solution of sulfur dioxide in acetic acid in the presence of cuprous chloride. Application of this method to 8-amino-11*H*-dibenzo[*b,f*]thiepin-10-one[7,8], *i.e.* to a solution of diazonium chloride prepared therefrom, led to the crude 8-chlorosulfonyl-11*H*-dibenzo[*b,f*]thiepin-10-one (*VIII*).

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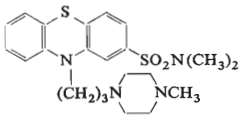
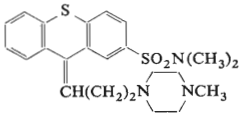
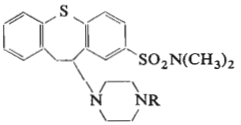
Reaction of this sulfonyl chloride with dimethylamine, pyrrolidine or N-methylpiperazine, resulted smoothly in sulfonamides *IX*–*XI*. The first two (*IX* and *X*)



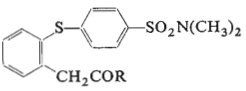
I



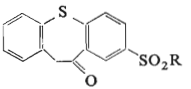
II



III, R = CH_3
IV, R = H
V, R = $(CH_2)_3OH$



VI, R = OH
VII, R = $N(CH_3)_2$

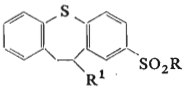


VIII, R = Cl

IX, R = $N(CH_3)_2$

X, R = 

XI, R = 



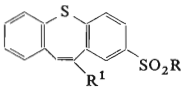
XII, R = $N(CH_3)_2$, R^1 = OH

XIII, R =  , R^1 = OH

XIV, R = $N(CH_3)_2$, R^1 = Cl

XV, R =  , R^1 = Cl

XVI, R =  , R^1 = 



XVII, R = $N(CH_3)_2$, R^1 = H

XVIII, R =  , R^1 = H

XIX, R = $N(CH_3)_2$, R^1 = 

were converted in three steps to methylpiperazine derivatives *III* and *XVI* using the methods described earlier[4,5]. Reduction with sodium borohydride led to alcohols *XII*

and *XIII* which, through the action of hydrogen chloride in chloroform, yielded the chloro derivatives *XIV* and *XV*. The final step was represented by substitution reactions of these compounds with 1-methylpiperazine in boiling chloroform; besides the desired bases *III* and *XVI*, the corresponding elimination products were obtained, *viz*. *XVII* and *XVIII*. Analogous substitution reactions of chloride *XIV* with piperazine, or with 1-(3-hydroxypropyl)piperazine[9], resulted in bases *IV* and *V*. Reaction of ketone *IX* with 1-methylpiperazine and titanium tetrachloride in benzene[10–12] yielded the enamine *XIX*.

The piperazine derivatives *III*—*V*, *XVI* and *XIX* were tested pharmacologically with a view to the assumed central depressant and neuroleptic activities, always using parenteral application. They were applied in the form of the corresponding salts (see Experimental) dissolved in 0·9% sodium chloride. The results obtained are shown in Table I, the values referring to bases. As standards we used octoclothepin[13] as a neuroleptic of the 10-piperazinodibenzo[*b*,*f*]thiepin series (applied in the form of methanesulfonate solution in 5% glucose), and perphenazine[14] as a potent neuroleptic of the phenothiazine series (applied in the form of hydrochloride solution in 0·9% NaCl).

First of all, the acute toxicity of the compounds for mice was tested after intravenous application. Females in groups of ten were used and their survival was followed for 48 h after application. The results are shown in Table I in the form of the usual mean lethal dose (LD_{50}). It may be seen that the highest toxicity is shown by the secondary amine *IV*; within two h of application, clonic convulsions and death appeared; after the highest dose some animals died even on the following day. The lowest toxicity was displayed by the amino alcohol *V*. The toxicity of the other compounds is similar to that of the standards used. The compounds always brought about depression, paresis of limbs, ptosis and, in higher doses excitation and clonic convulsions; the animals died mostly on the day of application, occasionally on the following day.

For evaluation of depressant activity two tests with mice were used. The effect of compounds on the locomotor activity of mice was investigated by the photo-cell method of Dews[15]. Male mice were placed in groups of three into glass cylinders for 15 min in the dark. For each dose 5 animals were used. The interval between the intravenous application of the compound and the examination for activity was 30 min. The dose inhibiting locomotor activity by 50% of the mean control value (D_{50}) was calculated statistically. It follows from Table I that the most active compound in this test was the enamine *XIX* which is practically equally active as the standards used. The least active was the secondary amine *IV* while the other compounds are approximately three times less active than octoclothepin.

The effect on the motor coordination in mice was examined in the rotating rod test[16]. The ability of female mice to maintain their balance for 1 min on a horizontally rotating rod was evaluated in groups of ten animals. The intervals between intravenous application of the compound and the examination of coordination were 5, 10, 15, 30, 45 and 60 min. The values shown in Table I are the mean effective doses (ED_{50}) causing a disturbance of coordination at the time of maximum effect of the compounds tested. Here, too, the most active compound was the enamine *XIX* but it did not reach the activity of octoclothepin. The other compounds are similarly active as perphenazine, with the exception of the secondary amine *IV* where a discoordinating effect sets in only in subtoxic doses.

To evaluate the neuroleptic activity, two tests in rats were used. First of all, the cataleptic effect[17] was examined in female rats (weighing 100—140 g); an animal was classified as cataleptic when it remained for 5 s in a cross-pawed position. The individual doses were applied intra-

peritoneally to groups of 10 animals and catalepsy was examined in half-hour intervals for 4 h. The optimal values obtained in the course of the experiment were used for determining the mean effective dose (ED_{50}) bringing about catalepsy in 50% animals and these are shown in the table. The highest cataleptic activity was again exhibited by the enamine *XIX*. The standards in this test are surpassed also by the basic compound *III*. The aminoalcohol *V* is still as good as octoclothepin while the pyrrolidine derivative *XVI* is substantially weaker and the secondary amine *IV* shows only weak activity.

Finally, the antiapomorphine effect was examined in a test according to Janssen and coworkers[18-19]. Male rats (190—270 g) were placed isolated in glass jars and their chewing and agitation caused by an intravenous injection of apomorphine (1·25 mg/kg) were followed. The individual doses of the compounds were applied subcutaneously always to 10 animals 60 min before administering the apomorphine. The intensity of chewing and agitation was evaluated in four degrees (0—3) at five-min intervals for 15 min after application of apomorphine. Doses decreasing the average control value by 50% (D_{50}) were determined and are shown in the table. The substances tested affected both parameters (chewing, agitation) caused by apomorphine, approximately in the same range of doses. The sequence of activity in this test is the same as in the catalepsy test.

Generally, one can describe the 8-sulfamoyl-10-piperazinodibenzo[*b,f*]thiepins *III*, *V* and *XIX* as highly effective neuroleptics, the enamine *XIX* displaying an extreme activity in all the tests, while the 10,11-saturated compounds *III* and *V* exhibit, in comparison with octoclothepin, a shift of the equilibrium between depressant and neuroleptic activity in favour of the latter.

TABLE I

Pharmacological Properties (Doses in mg/kg) of 8-Sulfamoyl-10-piperazinodibenzo[*b,f*]thiepins

Compound	Acute toxicity	Locomotor activity	Motor coordination	Cataleptic activity	Antiapomorphine activity	
					chewing	agitation
	i.v. LD_{50}	*i.v.* D_{50}	*i.v.* ED_{50}	*i.p.* ED_{50}	*s.c.* D_{50}	*s.c.* D_{50}
III	40·5	0·32	0·42	1·2	0·20	0·23
IV	16·5	0·93	[a]	[b]	[c]	[c]
V	58·0	0·38	1·0	2·6	0·51	0·58
XVI	42·5	0·33	0·88	10·5	9·10	11·7
XIX	49·0	0·07	0·18	0·55	0·10	0·12
Octoclothepin[13]	46·3	0·09	0·06	2·4	0·40	0·40
Perphenazine[14]	46·0	0·06	0·60	1·3	0·25	0·38

[a] The discoordinating effect sets in only in subtoxic doses. [b] The highest dose applied (10 mg/kg) brings about catalepsy in only 20% animals. [c] The highest dose applied (10 mg/kg) does not affect chewing or agitation brought about by apomorphine.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol, unless stated otherwise) in a Unicam SP 200 G spectrophotometer, and the NMR spectra ($CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer.

N,N-Dimethyl-2-(4-dimethylsulfamoylphenylthio)phenylacetamide (*VII*)*

2-(4-Dimethylsulfamoylphenylthio)phenylacetic acid[4] (*VI*) (4·0 g) was added to polyphosphoric acid (from 16 ml 85% phosphoric acid and 24 g P_2O_5); this was followed with 20 ml toluene and the mixture was then stirred and heated for 1 h to 120°C. After standing overnight it was decomposed with water, extracted with chloroform and the organic phase was washed with a dilute solution of NaOH. After drying (K_2CO_3), evaporation led to 1·5 g product which was dissolved in 2·5 ml benzene. Addition of 1·5 ml light petroleum resulted in crystallization of 1·15 g *VII*. After recrystallization from a mixture of benzene and light petroleum the m.p. was 137 to 139°C. UV spectrum: λ_{max} 270 nm (log ε 4·23), 277 nm (4·23). IR spectrum: 766 (1,2-C_6H_4), 830 (1,4-C_6H_4), 1143, 1166 and 1341 (SO_2NR_2), 1581 (Ar), 1649 cm^{-1} ($CONR_2$). For $C_{18}H_{22}N_2O_3S_2$ (378·5) calculated: 57·11% C, 5·86% H, 7·40% N, 16·94% S; found: 57·62% C, 5·88% H, 7·38% N, 16·69% S.

8-(Dimethylsulfamoyl)-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*IX*)

Heating of a mixture of 13·5 g 8-amino-11*H*-dibenzo[*b*,*f*]thiepin-10-one[7,8] with 30 ml concentrated hydrochloric acid and subsequent cooling to 5°C led to a suspension of the hydrochloride which was diazotized by adding dropwise 5·1 g $NaNO_2$ in 9 ml water. The mixture was stirred for 1 h at 5°C and then was added to a solution of 45 g sulfur dioxide and 4·5 g cupric chloride in 90 ml acetic acid and 30 ml benzene at 10°C. The mixture formed was heated to 40°C, stirred for 3 h at room temperature and, after standing overnight, separated between water and benzene. The benzene phase was washed with 10% Na_2CO_3 and with water and evaporated. A total of 17·0 g oily sulfonyl chloride *VIII* was obtained. The product was dissolved in 120 ml dioxane and, at 25–30°C, 60 ml of a 40% aqueous solution of dimethylamine was added dropwise over 5 min. On standing at room temperature, a solid product precipitated and was filtered after 48 h; 9·4 g (50%), m.p. 207–208°C (benzene–ethanol). UV spectrum: λ_{max} 229 nm (log ε 4·30), 241 nm (4·27), 281 nm (4·01), 332 nm (3·64). IR spectrum (KBr): 756, 770 (1,2-C_6H_4), 840, 882 (1,2,4-C_6H_3), 1169, 1342 (SO_2NR_2), 1580 (Ar), 1683 cm^{-1} (Ar—CO). NMR spectrum: ϑ 8·59 (s, 1 H, aromatic proton in position 9), 7·83 (s, 2 H, aromatic protons in positions 6 and 7), 7·10–7·70 (m, 4 H, other aromatic protons), 4·36 (s, 2 H, CH_2CO), 2·69 (s, 6 H, CH_3—N—CH_3). For $C_{16}H_{15}NO_3S_2$ (333·3) calculated: 57·66% C, 4·54% H, 4·20% N, 19·20% S; found: 57·88% C, 4·68% H, 4·20% N, 19·19% S. In patents[5] an erroneous value of the m.p. of *IX* was given due to an oversight.

8-(Pyrrolidinosulfonyl)-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*X*)

Similarly to the preceding case, 9·0 g aminoketone was used to prepare the crude sulfonyl chloride *VIII* (11·4 g). It was dissolved in 60 ml dioxane and, at 25–30°C, 18 ml pyrrolidine was added dropwise to the solution. The mixture was stirred for 3 h at room temperature, diluted with 20 ml

* This experiment was done in this laboratory by Dr K. Pelz.

water and, after 24 h of standing, the precipitated product was filtered; 6·95g (52%), m.p. 205·5 to 206·5°C (benzene–ethanol). UV spectrum: λ_{max} 231 nm (log ε 4·30), 245 nm (4·30), 283·5 nm (4·05), 335 nm (3·72). IR spectrum: 600 (SO_2N), 750 and 769 (1,2-C_6H_4), 840 and 880 (1,2,4-C_6H_3), 1151, 1168 and 1340 (SO_2N), 1580 (Ar), 1685 cm^{-1} (Ar—CO). NMR spectrum: ϑ 8·60 (s, 1 H, aromatic proton in position 9), 7·15—8·00 (m, 6 H, other aromatic protons), 4·34 (s, 2 H, CH_2CO), 3·20 (t, 4 H, CH_2NCH_2), 1·71 (t, 4 H, remaining CH_2 of pyrrolidine). For $C_{18}H_{17}NO_3S_2$ (359·5) calculated: 60·14% C, 4·77% H, 3·90% N, 17·84% S; found: 60·07% C, 4·74% H, 4·13% N, 17·92% S.

8-(4-Methylpiperazinosulfonyl)-11*H*-dibenzo[*b,f*]thiepin-10-one (*XI*)

As in the above cases, 9·8 g crude sulfonyl chloride *VIII* was prepared, dissolved in 60 ml dioxane, and 17 ml 1-methylpiperazine was added dropwise to the solution under stirring. The mixture was stirred for 4 h at room temperature, diluted with water and extracted with benzene. The extract was washed with water and the product was extracted with excess 5% hydrochloric acid. The solution of the hydrochloride thus obtained was made alkaline with aqueous ammonia and the base was isolated by extraction with chloroform; 9·23 g oil. Neutralization with maleic acid in ethanol and crystallization of the product from ethanol yielded 5·9 g hydrogen maleate which crystallized with a molecule of ethanol; m.p. 120—121°C. For $C_{25}H_{30}N_2O_8S_2$ (550·7) calculated: 54·53% C, 5·49% H, 5·09% N, 11·65% S; found: 54·23% C, 5·31% H, 5·09% N, 11·94% S.

8-(Dimethylsulfamoyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XII*)

A solution of 1·27 g $NaBH_4$ in 5 ml water with two drops of 15% NaOH was added dropwise to a solution of 11·15 g ketone *IX* in 100 ml dioxane, 100 ml ethanol and 80 ml tetrahydrofuran at 50°C. The mixture was refluxed for 5 h, left to stand overnight, evaporated and the residue separated between water and chloroform. The chloroform solution was washed with 100 ml 5% hydrochloric acid, dried with $MgSO_4$ and evaporated; 11·1 g (99%), m.p. 156—157°C (benzene). IR spectrum (KBr): 1051, 3440 and 3478 (OH), 1160 and 1340 cm^{-1} (SO_2NR_2). NMR spectrum: ϑ 7·99 (s, 1 H, aromatic proton in position 9), 7·10—7·60 (m, 6 H, other aromatic protons), 5·35 (m, 1 H, CH—O), 3·20—3·80 (m, 2 H, $ArCH_2$), 2·63 (s, 6 H, CH_3—N—CH_3), 2·50 (bs, 1 H, OH). For $C_{16}H_{17}NO_3S_2$ (335·5) calculated: 57·29% C, 5·11% H, 4·17% N, 19·12% S; found: 57·14% C, 5·12% H, 4·15% N, 19·08% S.

8-(Pyrrolidinosulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIII*)

In analogy with the preceding case, reduction of 6·7 g ketone *X* yielded 6·7 g crude product which was recrystallized from a mixture of benzene and ethanol and melted at 186·5—187·5°C. IR spectrum: 750 and 760 (1,2-C_6H_4), 830 and 860 (1,2,4-C_6H_3), 1012 (CHOH), 1160 and 1330 (SO_2NR_2), 3490 cm^{-1} (OH). For $C_{18}H_{19}NO_3S_2$ (361·5) calculated: 59·81% C, 5·30% H, 3·87% N, 17·74% S; found: 59·82% C, 5·24% H, 4·27% N, 17·55% S.

8-(Dimethylsulfamoyl)-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIV*)

Powdery $CaCl_2$ (5·0 g) was added to a solution of 10·6 g alcohol *XII* in 200 ml chloroform and the suspension was stirred while being saturated with anhydrous hydrogen chloride for 4 h. After standing overnight it was filtered and the filtrate was evaporated at reduced pressure.

A total of 11·0 g (98%) crude product was obtained which was recrystallized from a mixture of chloroform and benzene; m.p. 203—206°C. For $C_{16}H_{16}ClNO_2S_2$ (353·9) calculated: 54·30% C, 4·56% H, 10·02% Cl, 3·96% N, 18·12% S; found: 54·30% C, 4·66% H, 10·03% Cl, 3·85% N, 17·90% S.

8-(Pyrrolidinosulfonyl)-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XV*)

This was prepared as the preceding compound in a 90% yield from alcohol *XIII*; m.p. 198—200°C (benzene–chloroform). For $C_{18}H_{18}ClNO_2S_2$ (379·9) calculated: 56·81% C, 4·77% H, 9·33% Cl, 3·69% N, 16·88% S; found: 57·12% C, 4·87% H, 9·67% Cl, 3·24% N, 16·95% S.

8-(Dimethylsulfamoyl)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A mixture of 10·0 g chloride *XIV*, 20 ml 1-methylpiperazine and 20 ml chloroform was refluxed for 7 h. After 48 h of standing at room temperature chloroform was evaporated at reduced pressure and the residue was separated between 100 ml water and 100 ml benzene. The benzene solution was washed with water and extracted with 200 ml 5% hydrochloric acid. The suspension of the hydrochloride thus formed was filtered, the solid was suspended in the aqueous phase of the filtrate and the mixture was made alkaline with 15% NaOH. Extraction with benzene resulted in the base; 8·1 g (69%), m.p. 162—163°C (methanol). IR spectrum: 760 (1,2-C_6H_4), 838 (1,2,4-C_6H_3), 1155 and 1340 (SO_2NR_2), 2740, 2760, 2795, 2805 cm^{-1} (NCH_3 and NCH_2—). NMR spectrum: δ 8·25 (d, 1 H, aromatic proton in position 9), 7·05—7·70 (m, 6 H, other aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·65 (m, 4 H, Ar—C—$N(CH_2)_2$), 2·65 (s, 6 H, $SO_2N(CH_3)_2$), c. 2·40 (m, 4 H, remaining CH_2), 2·25 (s, 3 H, NCH_3). For $C_{21}H_{27}N_3O_2S_2$ (417·5) calculated: 60·42% C, 6·52% H, 10·07% N, 15·34% S; found: 60·45% C, 6·67% H, 9·89% N, 15·03% S. *Methanesulfonate* (*monohydrate*), m.p. 139—140°C (ethanol–ether). For $C_{22}H_{33}N_3O_6S_3$ (531·7) calculated: 49·70% C, 6·26% H, 7·90% N, 18·09% S; found: 49·81% C, 6·03% H, 7·73% N, 17·91% S.

Evaporation of the benzene solution from which the base had been removed with 5% hydrochloric acid, yielded 2·62 g elimination product, *i.e.* 2-(*dimethylsulfamoyl*)*dibenzo*(b,f)*thiepin* (XVII), m.p. 156—158°C (ethanol). UV spectrum: λ_{max} 232 nm (log ε 4·42), 272 nm (4·39), 296 nm (3·79). NMR spectrum: δ 7·00—7·80 (m, 9 H, aromatic and olefinic protons), 2·67 (s, 6 H, CH_3—NCH_3). For $C_{16}H_{15}NO_2S_2$ (317·3) calculated: 60·56% C, 4·77% H, 4·41% N, 20·20% S; found: 60·72% C, 4·87% H, 4·22% N, 20·31% S.

8-(Pyrrolidinosulfonyl)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XVI*)

In analogy with the preceding case, 4·9 g chloride *XV* reacted with 10 ml 1-methylpiperazine. A total of 4·46 g (78%) base was obtained: m.p. 167—168°C (ethanol–methanol). IR spectrum (KBr): 698 ($ArSO_2N$), 750 (1,2-C_6H_4), 838 and 848 (1,2,4-C_6H_3), 1162 and 1344 cm^{-1} (SO_2N). NMR spectrum: δ 8·32 (s, 1 H, aromatic proton in position 9), 7·05—7·80 (m, 6 H, other aromatic protons), 3·00—3·95 (m, 3 H, $ArCH_2CHAr$), 3·19 (m, 4 H, CH_2NCH_2 in pyrrolidine), 2·60 (m, 4 H, $CH_2N^1CH_2$ in piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ in piperazine), 2·23 (s, 3 H, NCH_3), 1·70 (m, 4 H, C—CH_2CH_2—C of pyrrolidine). For $C_{23}H_{29}N_3O_2S_2$ (443·6) calculated: 62·27% C, 6·59% H, 9·47% N, 14·45% S; found: 62·29% C, 6·67% H, 8·93% N, 14·24% S. *Dimethanesulfonate* (*monohydrate*), m.p. 137—138°C (aqueous ethanol–ether). For $C_{25}H_{39}N_3O_9S_4$ (653·9) calculated: 45·92% C, 6·01% H, 6·43% N, 19·62% S; found: 45·67% C, 5·94% H, 6·05% N, 19·35% S.

As in the preceding case, the elimination product was isolated, *viz.* 2-(*pyrrolidinosulfonyl*)*dibenzo*[b,f]*thiepin* (XVIII) (1·04 g), m.p. 206—207°C (benzene–ethanol). IR spectrum (KBr): 692 ($ArSO_2N$), 750 (1,2-C_6H_4), 798 (CH=CH), 830 and 885 (1,2,4-C_6H_3), 1 168 and 1 342 cm^{-1} (SO_2NR_2). For $C_{18}H_{17}NO_2S_2$ (343.5) calculated: 62·94% C, 4·99% H, 4·08% N, 18·67% S; found: 62·77% C, 5·06% H, 3·80% N, 18·58% S.

8-(Dimethylsulfamoyl)-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*)

A mixture of 2·95 g chloride *XIV*, 16·5 g anhydrous piperazine and 15 ml chloroform was refluxed for 10 h and treated in analogy to the preparation of base *III*. A total of 1·4 g (42%) *base* was obtained: m.p. 178—180°C (aqueous ethanol). For $C_{20}H_{25}N_3O_2S_2$ (403·4) calculated: 59·54% C, 6·25% H, 10·42% N, 15·86% S; found: 59,74% C, 6·31% H, 9·82% N, 16·09% S. *Dimethanesulfonate* (solvate with ethanol), m.p. 168°C (ethanol). For $C_{24}H_{39}N_3O_9S_4$ (641·9) calculated: 44·91% C, 6·12% H, 6·55% N, 19·98% S; found: 44·46% C, 5·96% H, 6·32% N, 19·87% S.

8-(Dimethylsulfamoyl)-10-[4-(3-hydroxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*V*)

A mixture of 2·05 g chloride *XIV*, 10 g 1-(3-hydroxypropyl)piperazine[9] and 10 ml chloroform was refluxed for 9 h and treated as during preparation of base *III*. A total of 2·38 g (89%) crude base *V* was obtained and this was converted by 1·0 g methanesulfonic acid in a mixture of ethanol and ether to *dimethanesulfonate(hemihydrate)*, m.p. 191—192°C (ethanol–ether). For $C_{25}H_{40}$·$.N_3O_{9\cdot5}S_4$ (662·9) calculated: 45·30% C, 6·08% H, 6·34% N, 19·35% S; found: 45·63% C, 6·10% H, 6·06% N, 19·50% S.

8-(Dimethylsulfamoyl)-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*XIX*)

A solution of 0·7 g $TiCl_4$ in 10 ml benzene was added dropwise to a mixture of 2·0 g ketone *IX*, 10·0 g 1-methylpiperazine and 40 ml benzene and the mixture was refluxed for 32 h. After cooling, it was diluted with 100 ml benzene and decomposed by an addition of 50 ml water. The precipitated solid was filtered, the filtrate was separated between water and benzene, the benzene phase was washed with water, dried with $MgSO_4$ and evaporated. The base was obtained in a theoretical yield and was dissolved in 10 ml ethanol whereupon it crystallized; 1·4 g (56%), m.p. 173—174°C (aqueous ethanol). UV spectrum: λ_{max} 279·5 nm (log ε 4·40), 305 nm (4·21), 226 nm (4·48). IR spectrum: 753 (1,2-C_6H_4), 830 and 860 (1,2,4-C_6H_3), 1 148 and 1 340 (SO_2NR_2), 1 611 (Ar), 1 650 (C=C), 2 760 and 2 785 cm^{-1} (N—CH_3). NMR spectrum: ϑ 8·05 (s, 1 H, aromatic proton in position 9), 7·00—7·80 (m, 6 H, remaining aromatic protons), 6·40 (s, 1 H, ArCH=CAr), 2·95 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·62 (s, 6 H, $SO_2N(CH_3)_2$), 2·55 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{21}H_{25}N_3O_2S_2$ (415·4) calculated: 60·71% C, 6·07% H, 10·12% N, 15·42% S; found: 61·07% C, 6·22% H, 9·90% N, 15·50% S. *Methanesulfonate*, m.p. 239°C (ethanol–ether). For $C_{22}H_{29}N_3O_5S_3$ (511·7) calculated: 51·64% C, 5·71% H, 8·21% N, 18·80% S; found: 51·26% C, 5·84% H, 7·78% N, 18·98% S.

The UV, IR and NMR spectra were recorded and interpreted by Dr B. Kakáč, Dr E. Svátek and Dr J. Holubek of the physicochemical laboratory of this institute. The analytical estimations were done by Mr M. Čech, Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Miss J. Hrdá and Miss I. Vitová.

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