NEUROTROPIC AND PSYCHOTROPIC AGENTS. LVII.*

ESTERS OF ALCOHOLS OF THE 10-PIPERAZINODIBENZO[*b,f*]THIEPIN SERIES AND OF THEIR ANALOGUES WITH FATTY ACIDS

J.O.JÍLEK, K.ŠINDELÁŘ, A.DLABAČ, E.KAZDOVÁ, J.POMYKÁČEK, Z.ŠEDIVÝ and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, Prague 3

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Esterification of amino alcohols *Ia*—*VIIIa* with free fatty acids or their chlorides, in particular oenanthic, caprylic, capric, lauric and palmitic, resulted in the corresponding esters. In two tests (using dogs and rats) with single doses of intramuscular injection of an oil solution of the base, the esters display a pharmacodynamic effect persisting for up to 3 weeks.

One of the important present trends of research of antipsychotic neuroleptics consists in the development of depot preparations. The chemical basis of the hitherto used preparations of this type are esters of amino alcohols of the phenothiazine or thioxanthene series with fatty acids containing a longer chain, especially fluphenazine oenanthate[1–6], fluphenazine decanoate[7–9], perphenazine oenanthate[10], pipothiazine undecylenate[11–13], pipothiazine palmitate[14] and flupenthixol decanoate[15–16]. In the form of base solutions in vegetable oils the substances are applied intramuscularly. After slow resorption in the blood-stream, blood plasma esterases bring about a rapid hydrolysis of the ester and release of the neuroleptic amino alcohol. This assures the relatively constant essential level of the agent in blood and tissues.

Likewise, in the group of neuroleptics of the type of 10-piperazinodibenzo[*b,f*]-thiepins and their analogues there are possibilities of developing depot antipsychotic preparations; in our past work[17–20] we described several neuroleptically highly effective amino alcohols, *i.e.* hydroxyalkylpiperazine derivatives, which are suitable as starting compounds for the preparation of esters. For the given purpose the most suitable appear to be amino alcohols[18] *Ia*–*IVa*, of which oxyprothepin (*IVa*) has been studied in some detail as a potential antipsychotic[21–25]. In the present study we used two other amino alcohols, a derivative of 10,11-dihydrodibenz[*b,f*]oxepin[19] *Va* and a derivative of benzo[*b*]thieno[3,2-*f*]thiepin[20] *VIIIa*. Amino alcohols *VIa* and *VIIa* which have the character of enamines had not been described and were prepared here from the corresponding ketones[26,27] and from 1-(3-hydroxypropyl)-piperazine[28] using the titanium tetrachloride technique[29–31].

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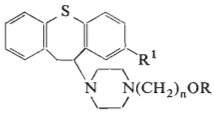
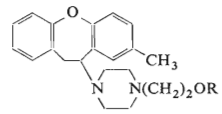
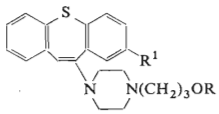
In our previous work[17,18,32–34] we took up the preparation of esters of aminoalcohols *Ia*, *IIa*, *IVa* and of some others, but only with lower aliphatic acids (acetic, propionic) and with 3,4,5-trimethoxybenzoic acid; the products were then evaluated only from the viewpoint of acute effects and it was found that on increasing the acyl residue the activity in the acute tests decreases; while acetates and propionates are still rather active. trimethoxybenzoate is practically inactive[18].



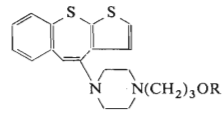
I, $R^1 = Cl$, $n = 2$
II, $R^1 = Cl$, $n = 3$
III, $R^1 = OCH_3$, $n = 3$
IV, $R^1 = SCH_3$, $n = 3$



V



VI, $R^1 = Cl$
VII, $R^1 = OCH_3$



VIII

For compounds of the series *a*, R = H; *b*, R = $COCH_3$; *c*, R = $CO(CH_2)_2CH_3$; *d*, R = = $CO(CH_2)_5CH_3$; *e*, R = $CO(CH_2)_6CH_3$; *f*, R = $CO(CH_2)_8CH_3$; *g*, R = $CO(CH_2)_{10}CH_3$; *h*, R = $CO(CH_2)_{12}CH_3$; *i*, R = $CO(CH_2)_{14}CH_3$

We prepared now a series of esters of amino alcohols *Ia*–*VIIIa* with saturated fatty acids with a linear chain, with oenanthic, caprylic, capric, lauric, myristic and palmitic acids[35–37]. As a general method, a reaction of the above amino alcohols with the acyl chlorides[38–40] was effected in chloroform, benzene or a mixture of the two solvents at room temperature or at a slightly raised temperature. Crude ester bases were converted to di(hydrogen maleates), the crystallization of which represented the main purification procedure. Pure ester bases were obtained by decomposition of these salts and were characterized by their IR and NMR spectra (Table I). In the experimental section we describe also the preparation of ester *IIIc* through the reaction of amino alcohol *IIIa* with butyric anhydride, and of acetate *IVb* which was obtained by a conventional procedure. Preparation of the esters studied by heating the amino alcohols with a free fatty acid in xylene with continuous azeotropic removal of water also appears to be feasible. The procedure was described using the preparation of ester *IIf* by the reaction of amino alcohol *IIa* with capric acid[41].

TABLE 1
Esters of Tricyclic Piperazino Alcohols

Compound[a] M.p., °C[b]	Formula (M.w.)	Calculated/Found				
		% C	% H	% N	% Cl	% S
Id-2 HM	$C_{35}H_{43}ClN_2O_{10}S$	58·44	6·03	3·89	4·93	4·46
148—149	(719·2)	57·85	6·12	3·89	5·05	4·52
If-2 HM[c]	$C_{38}H_{49}ClN_2O_{10}S$	59·95	6·48	3·68	4·66	4·21
150—151	(761·3)	60·16	6·57	3·33	4·89	4·45
Ig-2 HM[d]	$C_{40}H_{53}ClN_2O_{10}S$	60·86	6·77	3·55	4·49	4·06
149—150	(789·3)	60·88	6·93	3·47	4·57	4·16
IId-2 HM	$C_{36}H_{45}ClN_2O_{10}S$	58·96	6·19	3·82	4·83	4·37
149—150	(733·3)	58·93	6·08	3·75	5·05	4·48
IIf-2 HM	$C_{39}H_{51}ClN_2O_{10}S$	60·41	6·63	3·61	4·57	4·14
147—148	(775·3)	60·04	6·74	3·63	4·78	4·40
IIIc-2 HM[e]	$C_{34}H_{42}N_2O_{11}S$	59·46	6·16	4·08	—	4·67
148—149	(686·8)	59·61	6·24	4·10	—	4·89
IIIe-2 HM	$C_{38}H_{50}N_2O_{11}S$	61·44	6·78	3·77	—	4·32
130	(742·9)	61·86	6·86	3·83	—	4·69
IIIg-2 HM	$C_{42}H_{58}N_2O_{11}S$	63·13	7·32	3·51	—	4·01
126—129	(799·0)	63·43	7·86	3·52	—	4·20
IVb-M	$C_{28}H_{34}N_2O_6S_2$	60·20	6·14	5·02	—	11·48
162—164[f]	(558·6)	59·83	6·24	4·96	—	11·34
IVd-2 HM[g]	$C_{37}H_{48}N_2O_{10}S_2$	59·66	6·49	3·76	—	8·61
126—128	(744·9)	59·66	6·52	3·73	—	8·63
IVe-2 HM[e]	$C_{38}H_{50}N_2O_{10}S_2$	60·14	6·64	3·69	—	8·45
122—123	(758·9)	60·14	6·70	3·61	—	8·32
IVf-2 HM[h]	$C_{40}H_{54}N_2O_{10}S_2$	61·04	6·91	3·56	—	8·15
120—121	(787·0)	61·02	7·11	3·40	—	8·20
IVg-2 HM	$C_{42}H_{58}N_2O_{10}S_2$	61·89	7·17	3·44	—	7·87
121—122	(815·0)	61·93	7·15	3·58	—	8·05
IVi-2 HM	$C_{46}H_{66}N_2O_{10}S_2$	63·42	7·63	3·22	—	7·36
126—127	(871·1)	63·73	7·79	3·31	—	7·57
Vf-2 HM	$C_{39}H_{52}N_2O_{11}$	64·62	7·23	3·86	—	—
135—137	(724·8)	64·88	7·37	3·96	—	—
Vh-2 HM	$C_{43}H_{60}N_2O_{11}$	66·13	7·74	3·59	—	—
139—141	(780·9)	66·33	7·71	3·69	—	—
VId-2 HM[i]	$C_{36}H_{44}ClN_2O_{10,5}S$	61·57	6·46	4·49	5·68	5·14
141—142[j]	(740·2)	61·69	6·59	3·93	5·44	5·12
VIIe-M	$C_{34}H_{44}N_2O_7S$	65·36	7·10	4·48	—	5·13
125—126[k]	(624·8)	65·14	7·08	4·86	—	5·44
VIIIe-M	$C_{31}H_{40}N_2O_6S_2$	61·97	6·71	4·66	—	10·68
147—148·5[k]	(600·8)	61·99	6·72	4·81	—	10·50

In the preparation of esters *IIIe* and *IIIg* where dilute aqueous ammonia was used for the decomposition of the crude reaction mixture, the by-products isolated were caprylamide[42,43] or lauramide[44]. During synthesis of ester *IVe*, a detected by-product was 8-methylthio-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin[27]. Its origin is explained by cleavage of the piperazine residue from position 10 of the skeleton through the action of the acyl chloride.

Table II shows the pharmacological properties of most of the used amino alcohols and of five esters in acute tests. All the compounds were applied intravenously (in the catalepsy test intraperitoneally) or per os in the form of salts (methanesulfonates, maleates), the values shown representing effects per base. In addition to acute toxicity for white mice (LD_{50}) the table shows the mean effective doses (ED_{50}) in the rotating-rod test in mice which detects disturbances of motor coordination and hence a central depressant activity, and further the mean effective doses in the catalepsy test in rats (ED_{50}). Table II shows that all the amino alcohols tested represent highly effective neuroleptics which exceed chlorpromazine in the rotating-rod test 3–10 times, and in the catalepsy test usually more than 10 times. Especially, the enamines *VIa* and *VIIa* are compounds of enormous activity and belong to the most effective products of our systematic studies in this group. Oxymethothepin butyrate (*IIIc*), also included in the table, is still quite active in acute tests and exceeds chlorproma-

Footnote to Table I.

[a] 2 HM = di(hydrogen maleate), M = maleate. [b] Crystallized from acetone. [c] Spectra of the base: IR 755 (1,2-C_6H_4), 815, 832 and 891 (1,2,4-C_6H_3), 1165 (OC—O—C), 1579 (Ar), 1738 (ester CO), 2810 and 2896 cm^{-1} (N—CH_2); NMR: δ 7·66 (mcs, J = 2·5 Hz, 1 H, aromatic proton in position 9), 6·85–7·60 (m, 6 H, other aromatic protons), 4·15 (t, J = 6·0 Hz, 2 H in CH_2O), 3·00–4·00 (m, 3 H in $ArCH_2CHAr$), 2·10–2·80 (m, 10 H of the NCH_2 groups), 1·24 (bs, 16 H, CH_2 groups of the alkyl), 0·85 (t, 3 H, C—CH_3). [d] Spectra of the base: IR 750 (1,2-C_6H_4), 810, 830 and 885 (1,2,4-C_6H_3), 1155 and 1168 (OC—O—C), 1517 and 1575 (Ar), 1735 (ester CO), 2810 and 2845 cm^{-1} (NCH_2); NMR: δ 7·68 (mcs, J = 2·5 Hz, 1 H, aromatic proton in position 9), 7·15–7·60 (m, 5 H, aromatic protons in positions 1,2,3,4 and 6), 7·00 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 7), 4·17 (t, J = 7·0 Hz, 2 H in CH_2O), 3·00–4·00 (m, 3 H in $ArCH_2CHAr$), 2·60 (m, 10 H in CH_2N), 2·30 (t, J = 7·0 Hz, 2 H in CH_2CO) about 1·70 (m, 2 H, CH_2 adjacent to the methyl), 1·25 (bs, 16 H, remaining CH_2 groups), 0·85 (t, 3 H in C—CH_3). [e] See the experimental section. [f] Crystallized from aqueous ethanol. [g] Spectra of the base: IR: 752 (1,2-C_6H_4), 812 (1,2,4-C_6H_3), 1155 and 1170 (OC—O—C), 1575 (Ar), 1730 cm^{-1} (ester CO); NMR: δ 6·85–7·65 (m, 7 H, aromatic protons), 4·09 (t, J = 7·0 Hz, 2 H in CH_2O), 3·00–3·95 (m, 3 H in $ArCH_2$—CHAr), 2·49 and 2·60 (m, 10 H in NCH_2), 2·40 (s, 3 H in S—CH_3), 2·28 (t, J = 7·0 Hz, 2 H in CH_2CO), about 1·80 (m, 2 H, CH_2 adjacent to the methyl), 1·30 (m, 8 H, remaining CH_2), 0·89 (t, 3 H in C—CH_3). [h] Spectra of the base: IR: 750 (1,2-C_6H_4), 810, 829, 883 (1,2,4-C_6H_3), 1155 (OC—O--C), 1570 (Ar), 1730 cm^{-1} (ester CO); NMR: δ 7·55 (mcs, J = 2·5 Hz, 1 H, aromatic proton in position 9), 6·80–7·50 (m, 6 H, other aromatic protons), 4·05 (t, J = 6·0 Hz, 2 H in CH_2O), 3·00–4·00 (m, 3 H in $ArCH_2CHAr$), 2·60 and 2·48 (m, 8 H of piperazine), 2·36 (s, 3 H in S—CH_3), 2·26 (t, 2 H, CH_2 adjacent to the piperazine N), 1·70 (m) and 1·24 (bs, 18 H, other CH_2 groups), 0·85 (t, 3 H in C—CH_3). [i] Hemihydrate. [j] Crystallized from dioxane. [k] Crystallized from a mixture of ethyl acetate and ether.

TABLE II

Pharmacological Properties of Amino Alcohols *Ia*—*VIIIa* and Esters *IId* and *IIIc* in Acute Tests

Compound	Application	Acute toxicity LD_{50} mg/kg	Rotating rod ED_{50} mg/kg	Catalepsy[a] ED_{50} mg/kg
Ia	*i.v.*	30·0	0·21	0·85
IIa	*i.v.*	49	0·18	1·0
IIIa	*i.v.*	37	0·052	0·5
IVa	*i.v.*	44	0·11	0·62
IVa	*p.o.*	68	4·6	3·3
VIa	*i.v.*	28	0·034	0·33
VIIa	*i.v.*	90[b]	0·032	0·2
VIIIa	*i.v.*	[c]	0·078	2·1
IId	*p.o.*	310	15·5	16·5
IIIc	*p.o.*	82	1·5	8·6
CPZ[d]	*i.v.*	52·2	0·585	8·6
CPZ[d]	*p.o.*	198	8·2	16·0

[a] If *i.v.* application is shown for the whole line, *i.p.* was actually used for the catalepsy test. [b] *Per os.* [c] Toxicity not determined. [d] Chlorpromazine.

TABLE III

Persistence of Pharmacodynamic Effects of Some Esters after a Single Application of Solution in Oil

Compound (% solution)	Blockade of emesis[a], days	Disturbance of avoidance reaction[b], days
If (2·5)	14	16—20
IIf (2·5)	19	16—20
IVd (1)	19	21
IVd (2·5)	19	21
IVe (1)	10—14	7
IVf (2·5)	19	16—20
IVi (1)	7—14	21
FFE[c] (2·5)	10—14	>21

[a] Dogs were administered 5 mg/kg of the tested compound and complete blockade of emesis was followed as caused by subcutaneous application of 0·31 mg apomorphine hydrochloride/kg (the application was repeated 1—2 times per week). [b] Significant disturbance of the avoidance reaction in rats following application of 30 mg/kg. [c] Fluphenazine oenanthate (Moditen^{R} — Squibb).

zine in both tests 2–3 times. On the other hand, oenanthate of oxyclothepin (*IId*) is much weaker in the acute tests and only in the catalepsy test retains the activity of chlorpromazine.

For evaluating the depot neuroleptic effect of some of the prepared esters we used 1% or 2·5% solutions of the bases in refined sunflower oil which were applied to the animals intramuscularly. Two tests were employed: *1.* Persistance of the blockade of apomorphine emesis in dogs[45]; *2.* persistence of disturbances (alteration) of a conditioned avoidance reaction in rats following a single dose of the substance tested (for methods see ref.[23,46]). Preliminary results are summarized in Table III. As a reference compound, fluphenazine oenanthate[1-6] was used. It follows from the results that the esters exceed the reference compound in the persistence of the blockade of the apomorphine emesis while they do not match it as to influencing the conditioned avoidance reaction in rats. In both tests, the effects persisted for 2–3 weeks.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectrum (in methanol) was recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in substance or in Nujol) using the Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform) using the ZKR 60 (Zeiss, Jena) spectrometer.

8-Chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

Using an earlier procedure[18] we prepared the base in a 73% yield, m.p. 104–108°C (benzene); the base was previously characterized as a hemihydrate melting at 103–105°C, crystallizing from aqueous ethanol[18]. Now the water-soluble methanesulfonate was prepared which crystallizes as hemihydrate, m.p. 161–162°C (ethanol–ether). For $C_{21}H_{27}ClN_2O_4S_2.^1/_2\,H_2O$ (480·0) calculated: 52·54% C, 5·88% H, 7·28% Cl, 5·84% N, 13·36% S; found: 52·52% C, 5·84% H, 7·23% Cl, 5·79% N, 13·70% S.

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

The base prepared as described previously[18] in a 57% yield crystallized on further standing: m.p. 80–82°C in a capillary (cyclohexane). According to the spectrum and analysis we are dealing here with a solvate with one-half molecule cyclohexane. NMR spectrum: δ 7·00–7·75 (m, 6 H, aromatic protons in positions 1,2,3,4,6 and 9), 6·65 (d, $J = 8{\cdot}0; 3{\cdot}0$ Hz, 1 H, aromatic proton in position 7), 4·95 (bs, 1 H in OH), 3·71 (s, 3 H in OCH_3), 3·60–4·00 (m, 4 H in CH_2O and ArCH–CHAr), 3·10 (d, $J = 9{\cdot}0$ Hz, 1 H, remaining benzyl proton), about 2·60 (m, 10 H of the CH_2N groups), 1·72 (m, 2 H of the middle CH_2 group of the side chain), 1·30 (s, 6 H of cyclohexane). For $C_{25}H_{34}N_2O_2S$ (426·5) calculated: 70·39% C, 8·03% H, 6·57% N, 7·50% S; found: 70·64% C, 8·11% H, 6·22% N, 7·59% S.

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

The base[18] crystallized from benzene as a solvate with 1 benzene molecule: m.p. 68–70°C. For $C_{28}H_{34}N_2OS_2$ (478·7) calculated: 70·25% C, 7·16% H, 5·85% N; found: 69·66% C, 7·29% H, 5·85% N. *Embonate*(1 : 1)-*monohydrate* was obtained by precipitation of the methanesulfonate

of base *IVa* with an aqueous solution of the sodium salt of 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid, m.p. 180–185°C. For $C_{45}H_{46}N_2O_8S_2$ (807·0) calculated: 66·98% C, 5·74% H, 3·47% N, 7·94% S; found: 67·01% C, 5·42% H, 3·30% N, 7·42% S.

8-Methyl-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenz[*b,f*]oxepin (*Va*)

The base was obtained in a 75% yield by the substitution reaction of 8-methyl-10-chloro-10,11-dihydrodibenz[*b,f*]oxepin[19] with 1-(2-hydroxyethyl)piperazine in boiling chloroform; in contrast with our previous work[19] it was now obtained free of the crystal solvent; m.p. 58–61°C (benzene–light petroleum). For $C_{21}H_{26}N_2O_2$ (338·4) calculated: 74·52% C, 7·74% H, 8·28% N; found: 74·30% C, 7·94% H, 8·08% N. Di(hydrogen maleate), m.p. 164–166°C (aqueous ethanol). For $C_{29}H_{34}N_2O_{10}$ (570·6) calculated: 61·04% C, 6·00% H, 4·91% N; found: 60·68% C, 6·10% H, 5·15% N.

8-Chloro-10-[4-(3-hydroxypropyl)piperazino]dibenzo[*b,f*]thiepin (*VIa*)

1-(3-Hydroxypropyl)piperazine[28] (36·0 g) was added to a solution of 13·0 g 8-chloro-11*H*-dibenzo[*b,f*]thiepin-10-one[26] in 100 ml benzene. The mixture was stirred and over a period of 10 min, a solution of 4·74 g titanium(IV) chloride in 30 ml benzene was added dropwise. The mixture was refluxed under stirring for 32 h, cooled and decomposed by adding 140 ml water. The precipitate was removed by filtration, the filtrate separated and the benzene phase was evaporated. A total of 13·4 g (70%) crude base was obtained. This was neutralized with 4·0 g maleic acid in 50 ml ethanol to convert it to the maleate, m.p. 193–194°C (ethanol). For $C_{25}H_{27}ClN_2 \cdot O_5S$ (503·0) calculated: 59·70% C, 5·41% H, 7·05% Cl, 5·57% N, 6·37% S; found: 60·05% C, 5·52% H, 7·30% Cl, 5·52% N, 6·46% S.

Decomposition of the pure maleate with aqueous ammonia and extraction with benzene led to the pure base, m.p. 151–152°C (ethanol). IR spectrum: 762 (1,2-C_6H_4), 818 and 868 (1,2,4-C_6H_3), 1055 (CH_2OH), 1545 and 1602 (Ar), 2770 (CH_2N), 3150 cm^{-1} (OH). NMR spectrum: δ 7·00–7·70 (m, 7 H, aromatic protons), 6·34 (s, 1 H in ArCH=CAr), 4·75 (s, disappears on deuteration, 1 H in OH), 3·78 (t, J = 5·0 Hz, 2 H in CH_2O), 2·95 (m, 4 H, CH_2 groups in the vicinity of the enamine N), 2·65 (m, 6 H, CH_2 groups in the vicinity of the amine N), 1·72 (m, 2 H of the middle CH_2 group of the side chain). For $C_{21}H_{23}ClN_2OS$ (386·9) calculated: 65·19% C, 5·99% H, 9·16% Cl, 7·24% N, 8·28% S; found: 65·27% C, 5·93% H, 9·22% Cl, 7·13% N, 8·47% S.

8-Methoxy-10-[4-(3-hydroxypropyl)piperazino]dibenzo[*b,f*]thiepin (*VIIa*)

In analogy to the preceding case, a total of 6·6 g (63%) maleate of base *VIIa* was obtained from 5·4 g 8-methoxy-11*H*-dibenzo[*b,f*]thiepin-10-one[27] and 17·5 g 1-(3-hydroxypropyl)piperazine[28]; m.p. 194–195°C (ethanol). For $C_{26}H_{30}N_2O_6S$ (498·5) calculated: 62·64% C, 6·07% H, 5·62% N, 6·42% S; found: 62·93% C, 6·16% H, 5·40% N, 6·61% S.

Fatty acid chlorides were obtained by the reaction of free acids with excess thionyl chloride according to described procedures; the yields and the boiling points are shown. Oenanthyl chloride[38], 90%, 170–174°/740 Torr; capryloyl chloride[38], 87%, 80–83°C/13 Torr; decanoyl chloride[38], 93%, 106–108°C/8 Torr; lauroyl chloride[38,39], 74%, 145–150°C/15 Torr; myristoyl chloride[38,39], 88%, 158–165°C/12–14 Torr; palmitoyl chloride[38,39], 76%, 190–192°C/12 Torr.

8-Chloro-10-[4-(2-oenanthoyloxyethyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

Oenanthoyl chloride (7·1 g) was added to a solution of 9·0 g substance *Ia* in 70 ml chloroform and the mixture was left for 24 h at room temperature. Then 100 ml chloroform and 100 ml

water were added and the mixture was agitated for 2 h. The layers were separated, the chloroform layer was extracted with 70 ml 15% NaOH and 70 ml water, dried with K_2CO_3 and evaporated *in vacuo*. A total of 11·7 g (100%) ester was obtained which, on chromatography on a thin layer of alumina, appears homogeneous. After dissolving in 20 ml acetone, a solution of 5·57 g maleic acid in 20 ml acetone was added. On standing, 13·7 g (79%) di(hydrogen maleate) precipitated, m.p. 148—149°C (acetone); see Table I. This salt (12·6 g) was suspended in 200 ml water, 20 ml ammonium hydroxide was added, followed with 150 ml ether and the mixture was shaken. After separation, the ether layer was dried with K_2CO_3 and evaporated. A total of 8·3 g base was obtained and this was used for the pharmacological tests. IR spectrum: 752 (1,2-C_6H_4), 812, 830 and 889 (1,2,4-C_6H_3), 1168 (OC—O—C), 1578 (Ar), 1732 (ester CO), 2815 and 2855 cm^{-1} (N—CH_2). NMR spectrum: δ 7·68 (mcs, J = 2·5 Hz, 1 H, aromatic proton in position 9), 7·15—7·63 (m, 5 H, aromatic protons in positions 1,2,3,4 and 6), 7·00 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 7), 4·18 (t, J = 7·0 Hz, 2 H in CH_2O), 3·00—4·00 (m, 3 H in $ArCH_2CHAr$), 2·64 (m, 10 H in NCH_2 groups), 2·32 (t, J = 7·0 Hz, 2 H in $COCH_2$), about 1·70 (m, 2 H, CH_2 in the vicinity of methyl), 1·30 (bs, 6 H of CH_2 groups in the middle of the terminal alkyl), 0·89 (t, 3 H in C—CH_3). Most of the esters shown in Table I were prepared in a similar way. During preparation of ester *IIIe*, the mother liquor after preparation of maleate was made alkaline with ammonia and extracted with benzene to isolate caprylamide: m.p. 105 to 107°C (benzene–light petroleum), in agreement with the literature[43]. Similarly, during preparation of ester *IIIg*, lauramide was isolated, m.p. 97—99°C; ref.[44] gives 102°C.

8-Methylthio-10-[4-(3-capryloyloxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IVe*)

Capryloyl chloride (12·2 g) was added to a solution of 14·0 g base *IVa* in 20 ml chloroform and 60 ml benzene, the mixture was left for 4 days at room temperature and then heated for 1 h to 60°C. After cooling, it was decomposed with 100 ml water, 20 ml ammonium hydroxide was added and it was extracted with 100 ml benzene. Evaporation of the benzene phase yielded 21·6 g oil, from which 2·1 g crystalline substance precipitated after a week's standing. The substance was isolated by filtration after adding 50 ml light petroleum. Since it was not homogeneous even after several crystallizations from benzene, it was purified by chromatography on alumina, using elution with benzene; m.p. 120°C (benzene). According to spectrum and analyses we are dealing here with 8-methylthio-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin for which a m.p. of 117 to 118°C (aqueous ethanol) had been reported in this laboratory[27]. NMR spectrum: δ 7·10—7·60 (m, 6 H, aromatic protons in positions 1,2,3,4,6 and 9), 6·98 (mcd, J = 8·0; 2·5 Hz, 1 H, aromatic proton in position 7), 5·30 (dd, J = 9·0; 4·5 Hz, 1 H in ArCH), 3·00—3·90 (m, 2 H in $ArCH_2$), 2·39 (s, 3 H in S—CH_3), 2·22 (s, 1 H in OH). For $C_{15}H_{14}OS_2$ (274·3) calculated: 65·69% C, 5·15% H, 23·33% S; found: 65·80% C, 5·22% H, 23·28% S.

From the light petroleum fraction, di(hydrogen maleate) was prepared as previously: 13·7 g, m.p. 122—123°C (acetone); the analysis is shown in Table I. On decomposition of this salt (12·0 g), similarly as with preparation of ester *Id*, a total of 6·7 g oily base was obtained; this was used for pharmacological purposes. UV spectrum: λ_{max} 276 nm ($\log \varepsilon$ 4·11). IR spectrum: 751 (1,2-C_6H_4), 810, 830 (1,2,4-C_6H_3), 1152 (OC—O—C), 1572 (Ar), 1732 cm^{-1} (ester CO). NMR spectrum: δ 7·60 (mcs, J = 2·0 Hz, 1 H, aromatic proton in position 9), 6·98 (mcd, J = 9·0; 2·0 Hz, 1 H, aromatic proton in position 7), 7·10—7·55 (m, 5 H, aromatic protons in positions 1,2,3,4 and 6), 4·10 (t, J = 7·0 Hz, 2 H in CH_2O), 3·00—4·00 (m, 3 H in $ArCH_2CHAr$), 2·40 to 2·70 (m, 8 H of piperazine), 2·40 (s, 3 H in S—CH_3), 1·00—2·40 (m, remaining CH_2 groups), 0·86 (t, 3 H in C—CH_3).

8-Methoxy-10-[4-(3-butyryloxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIc*)

Solution of 2·95 g base *IIIa* and 2·43 g butyric anhydride in 20 ml benzene was refluxed for 7 h. After cooling, it was diluted with 60 ml benzene, and 60 ml water and 10 ml ammonium hydroxide were added. After shaking, the benzene layer was processed as in the foregoing examples and the crude base was converted to di(hydrogen maleate): 4·45 g (85%), m.p. 148–149°C (acetone). The analytical data are shown in Table I.

8-Chloro-10-[4-(3-decanoyloxypropyl)piperazino]-10,11-dihydrodibenzo[*b,f*]thiepin (*IIf*)

From a solution of 5·0 g base *IIa* and 4·5 g decanoic acid[41] in 100 ml xylene, the solvent was distilled off over a period of 12 h at normal pressure and was continually replaced in the reaction mixture with anhydrous xylene. After this procedure, the reaction mixture contains less than 10% of the nonreacted amino alcohol *IIa* (thin-layer chromatography). After cooling, it was diluted with 100 ml xylene, the solution was washed with 150 ml 5% NaOH, dried with K_3CO_3 and evaporated. The residue was dissolved in 15 ml acetone and the solution was neutralized with 2·7 g maleic acid. A total of 8·00 g (80%) di(hydrogen maleate) was obtained, m.p. 146–147°C. It melts without depression in a mixture with the product prepared by esterification as during preparation of ester *Id*. The analysis of the salt is shown in Table I. Similarly to the preparation of *Id*, the base was liberated. IR spectrum: 750 (1,2-C_6H_4), 810 and 883 (1,2,4-C_6H_3), 1150 (OC—O—C), 1572 (Ar), 1730 (ester CO), 2810 and 2850 cm^{-1} (N—CH_2). NMR spectrum: δ 7·68 (mcs, J = 2·5 Hz, 1 H, aromatic proton in position 9), 7·15–7·60 (m, 5 H, aromatic protons in positions 1,2,3,4 and 6), 7·00 (mcd, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 7), 4·08 (t, J = 7·0 Hz, 2 H in CH_2O), 3·00–3·90 (m, 3 H in ArCH_2CHAr), 2·10–2·80 (m, 12 H of the NCH_2 groups), 1·70 (m) and 1·24 (bs, other CH_2 groups of the aliphatic chains), 0·86 (t, 3 H in C—CH_3).

The evaluation of some of the compounds in acute tests (Table II) was done under the direction of Dr J. Metyšová at the pharmacological department of this institute. The NMR *and* IR *spectra were registered and interpreted by Dr E. Svátek, Dr B. Kakáč and Dr J. Holubek at the physicochemical department of this institute. The analytical estimations were done at the analytical department (headed by Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová and Dr M. Čech. Technical assistance with the preparation of some of the starting compounds by Mrs M. Hrubantová is also acknowledged.*

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