POTENTIAL DEPOT NEUROLEPTICS IN THE 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN SERIES; ESTERS OF NOROXYCLOTHEPIN AND RELATED AMINO ALCOHOLS WITH UNSATURATED, BRANCHED-CHAIN ALIPHATIC, ALICYCLIC, ARALIPHATIC AND DICARBOXYLIC ACIDS*

I.ČERVENÁ, J.O.JÍLEK, A.DLABAČ and M.PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

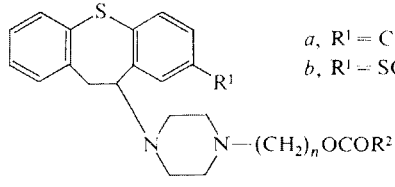
Received March 5th, 1976

Esterification of 8-chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (noroxyclothepin) (*XIVa*) and of two similar amino alcohols with chlorides of undecylenic, 2-ethylcaproic, 2-(n-butyl)caproic, 2-(isobutyl)isocaproic, cyclopentylacetic, 3-cyclopentylpropionic, adamantane-1-carboxylic, 3-phenylpropionic and phenylcyclohexylacetic acids resulted in esters *IVa*, *Va*, *VIb* and *VIIa*—*XIIIa*. Reactions of amino alcohol *XIVa* with pimelic, suberic and azelaic acids yielded esters *XVI*—*XVIII*. On a single intramuscular application to rats, some of these esters block for 2—3 weeks the effects of apomorphine and bring about protracted disturbances of fixed conditioned reflexes. In the reaction of oxyprothepin (*XVb*) with decanoyl chloride, chloride *XIXb* and ester-amide *XXVII* are formed. Octoclothepin (*XXIII*) is similarly cleaved by treatment with ethyl chloroformate, giving rise to chloride *XIXa* and 1-(ethoxycarbonyl)-4-methylpiperazine. Ether *XXIa*, a by-product of octoclothepin synthesis, was prepared in both stereoisomeric forms by heating alcohol *XXa* with dilute sulfuric acid. Compounds *XXX* and *XXVI* were synthesized as potential metabolites of oxyprothepin decanoate (*IIIb*) and of octoclothepin (*XXIII*).

All the therapeutically used depot ester neuroleptics are esters of the neuroleptic amino alcohols of the phenothiazine or thioxanthene series with straight-chain saturated fatty acids: fluphenazine oenanthate, fluphenazine decanoate, perphenazine oenanthate, pipothiazine palmitate and flupenthixol decanoate[1]. The only exception is formed by pipothiazine undecylenate[2] which contains an unsaturated aliphatic acid residue. Our previous work dealing with the development of a depot ester neuroleptic in the series of 10-piperazinodibenzo[*b*,*f*]thiepin derivatives, also went along these lines at first: neuroleptic amino alcohol esters with saturated fatty acids with a straight chain were synthesized[1,3—13], particularly of the general formula *I*. Of the compounds prepared, a certain interest was aroused first by noroxyclothepin decanoate[14,15] (*IIa*) and then especially by oxyprothepin decanoate

* Part CIV in the series Neurotropic and Psychotropic Agents; Part CIII: This Journal *41*, 3420 (1976).

(VÚFB-9977) (*IIIb*) (refs[16–22]). The interesting properties of pipothiazine 2,2-dimethylpalmitate[23] with a sterically hindered ester group showed that other types of esters might play a role in the therapy as depot antipsychotics. For this reason, we began to study esters of amino alcohols *XIV* and *XV* with unsaturated and branched aliphatic acids, further with alicyclic, araliphatic and dicarboxylic acids[24], as described in the present communication.



a, $R^1 = Cl$
b, $R^1 = SCH_3$

I, $R^2 = (CH_2)_mCH_3$
II, $n = 2$, $R^2 = (CH_2)_8CH_3$
III, $n = 3$, $R^2 = (CH_2)_8CH_3$
IV, $n = 2$, $R^2 = (CH_2)_8CH{=}CH_2$
V, $n = 3$, $R^2 = (CH_2)_8CH{=}CH_2$
VI, $n = 3$, $R^2 = CH(CH_2)_3CH_3$ | CH_2CH_3
VII, $n = 2$, $R^2 = CH(CH_2)_3CH_3$ | $(CH_2)_3CH_3$

VIII, $n = 2$, $R^2 = CHCH_2CH(CH_3)_2$ | $CH_2CH(CH_3)_2$

IX, $n = 2$, $R^2 = CH_2$– 

X, $n = 2$, $R^2 = CH_2CH_2$– 

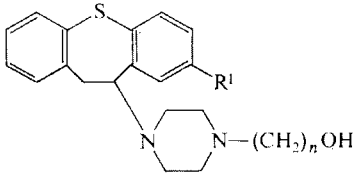
XI, $n = 2$, $R^2 =$ 

XII, $n = 2$, $R^2 = CH_2CH_2C_6H_5$

XIII, $n = 2$, $R^2 = CH(C_6H_5)$– 

The starting amino alcohol in most of the work was 8-chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin (noroxyclothepin)[1,25] (*XIVa*), in some cases also oxyclothepin[25] (*XVa*) and oxyprothepin (*XVb*) (refs[1,12,25]). The esterifications were done by treatment with acyl chlorides in chloroform at room temperature (method *A*); chlorides of undecylenic[26], 2-ethylcaproic[27], 2-(n-butyl)-caproic[27–29], 2-(isobutyl)isocaproic[30,31], cyclopentylacetic[32,33], 3-cyclopentylpropionic[34,35], adamantane-1-carboxylic[36], 3-phenylpropionic[37] and phenylcyclohexylacetic[38] acids were used. The resulting esters were *IVa*, *Va*, *VIb* and *VIIa*–*XIIIa*. With the exception of *XIa* which was crystalline as the base, the esters were purified as crystalline di(hydrogen maleates); only ester *XIIIa* was obtained as normal maleate. By treatment with alkali released pure bases were all oily (except for *VIIIa*) and were used for measuring the spectra and for preparation of solutions in sunflower oil for pharmacological evaluation. In the preparation of the diesters *XVI*–*XVIII*

method *A* was not successful. In these cases, esterification of pimelic, suberic and azelaic acids was done with amino alcohol *XIVa* in distilling xylene in the presence of a small amount of *p*-toluenesulfonic acid (method *B*); the esters were also purified in the form of crystalline maleates. Table I shows the characterized forms of the esters prepared together with the usual experimental data.



XIV, $n = 2$
XV, $n = 3$

While preparing larger amounts of *IIIb* by method *A* it was found that the method is not suited for technical preparations since, together with the formation of an ester, there is a cleavage reaction yielding a basic and a neutral product. This side reaction plays a role even when using equivalent amounts of amino alcohol *XVb* and of decanoyl chloride[39] (the reaction mixture contains then also the starting *XVb*) and further when working in the presence of triethylamine. When using an excess of decanoyl chloride the role of the cleavage side reaction increases and if the excess of decanoyl chloride is more than 100% and if the reaction is conducted at boiling temperature, no ester *IIIb* is formed and the above cleavage reaction proceeds quantitatively. Its neutral product was identified as 10-chloro-8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIXb*) and the basic product as 1-decanoyl-4-(3-decanoyloxypropyl)piperazine (*XXVII*). The structure of *XXVII* was checked by its synthesis from 1-(3-hydroxypropyl)piperazine[40] and decanoyl chloride[39]. *XXVII* is also formed during esterification of 1-(3-hydroxypropyl)piperazine with excess decanoic acid in distilling xylene. The esterification is accompanied here by an N-acylation. For technical preparation of *IIIb* the best method available was *B*, *i.e.* esterification of amino-alcohol *XVb* with decanoic acid in distilling xylene. The presence of *p*-toluenesulfonic acid is not necessary and the crude product may be purified by chromatography (filtration) through a column of alumina when amino alcohol *XVb* is selectively separated. Purification of the crude ester by crystallization of salts (maleate[1], oxalate) is not essential. When using excess decanoic acid, the esterification proceeds faster and the product does not contain the starting *XVb* which facilitates the purification. Excess decanoic acid can be recovered.

In connection with the cleavage reaction described here 1-decanoyl-4-(2-decanoyloxyethyl)piperazine (*XXVIII*) and further 8-chloro-10-(4-decanoylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXII*) were prepared for comparison. The first of these

TABLE I

Esters of Noroxyclothepin and Related Amino Alcohols

Compound[a] (Method[b])	M.p., °C (Solvent[c])	Formula (m.w.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
IVa-2M (*A*)	144—146	$C_{39}H_{49}ClN_2O_{10}S$ (773·3)	60·57 60·47	6·39 6·53	4·58 4·83	3·62 3·64	4·14 4·14
Va-2M (*A*)	143—144	$C_{40}H_{51}ClN_2O_{10}S$ (787·3)	61·02 60·99	6·53 6·65	4·50 4·80	3·56 3·74	4·07 4·28
VIb-2M (*A*)	145—146	$C_{38}H_{50}N_2O_{10}S_2$ (758·9)	60·14 60·17	6·64 6·83	— —	3·69 3·57	8·45 8·40
VIIa-2M (*A*[d])	148—150 (ethyl acetate)	$C_{38}H_{49}ClN_2O_{10}S$ (761·3)	59·95 59·19	6·49 6·50	4·65 4·97	3·68 3·84	4·21 4·53
VIIIa (*A*)	73—74[e]	$C_{30}H_{41}ClN_2O_2S$ (529·2)	68·09 68·46	7·81 8·14	6·70 6·98	5·29 5·28	6·06 6·26
VIIIa-2M	153—154	$C_{38}H_{49}ClN_2O_{10}S$ (761·3)	59·94 60·10	6·49 6·87	4·66 4·78	3·68 3·70	4·21 4·61
IXa-2M (*A*)	141—145[f]	$C_{35}H_{41}ClN_2O_{10}S$ (717·2)	58·61 58·30	5·76 5·86	4·94 5·21	3·91 4·13	— —
Xa-2M (*A*)	152—155[g]	$C_{36}H_{43}ClN_2O_{10}S$ (731·2)	59·13 59·97	5·93 6·05	4·85 4·65	3·83 3·73	4·38 4·66
XIa (*A*)	138—139[h]	$C_{31}H_{37}ClN_2O_2S$ (537·1)	69·31 69·86	6·94 7·12	— —	5·22 4·90	— —
XIIa-2M[i] (*A*)	138—139	$C_{37}H_{41}ClN_2O_{11}S$ (757·2)	58·68 58·89	5·46 5·41	4·68 5·09	3·70 3·89	4·24 4·68
XIIIa-M (*A*)	127—130	$C_{38}H_{43}ClN_2O_6S$ (691·3)	66·02 65·85	6·27 6·56	5·13 5·13	4·05 3·94	4·64 4·70
XVI-3M (*B*)	144—147[j]	$C_{59}H_{66}Cl_2N_4O_{16}S_2$ (1 222·2)	57·98 57·57	5·44 5·52	5·80 5·53	4·58 4·47	5·25 5·16
XVII-4M (*B*)	143—146[k]	$C_{64}H_{72}Cl_2N_4O_{20}S_2$ (1 352·3)	56·84 57·02	5·37 5·85	5·24 5·13	4·14 4·41	4·74 4·62
XVIII-4M (*B*[d])	149—150	$C_{65}H_{74}Cl_2N_4O_{20}S_2$ (1 366·3)	57·14 56·87	5·46 5·71	5·19 5·08	4·10 4·21	4·69 4·71

[a] M maleate. [b] The yields of method *A* could not be estimated and are mostly rather low, the yields of method *B* are 75—90%. [c] Acetone unless stated otherwise. [d] See Experimental. [e] ^{1}H-NMR spectrum: δ 7·77 (mcs, J = 3·0 Hz, 1 H, 9-H), 6·90—7·70 (m, 6 H, remaining Ar—H), 4·21 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), c. 3·00 (m, 1 H, COCH), 2·61 (m, 10 H, 5 NCH_2), 1·00—2·00 (m, 6 H, 2 CH_2CH in isobutyls), 0·89 (d, J = 6·0 Hz, 12 H, 4 CH_3). [f] For measuring spectra, the base was set free; IR spectrum (film): 750, 810, 830 (Ar—H), 1 142, 1 171 (C—O), 1 580 (Ar), 1 730 cm^{-1} (COOR); ^{1}H-NMR spectrum: δ 7·68 (mcs, 1 H, 9-H),

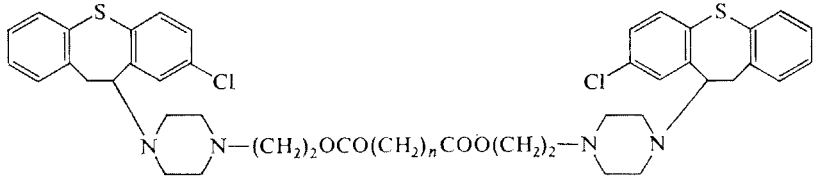
was prepared by acylation of 1-(2-hydroxyethyl)piperazine with decanoyl chloride, the second by acylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[25] (*XXIV*) in pyridine. In further work, octoclothepin[41,42] (*XXIII*) was left to react with a slight excess of ethyl chloroformate in boiling benzene; a quantitative N-dealkylation cleavage takes place, the products of which were identified as chloride[41] *XIXa* and 1-(ethoxycarbonyl)-4-methylpiperazine (isolated as hydrochloride[43,44]).

In further work we tried to identify the by-product occurring in some batches of octoclothepin (*XXIII*) prepared by a substitution reaction of chloride[41] *XIXa* with 1-methylpiperazine in boiling chloroform[42]. This minor product was separated from base *XXIII* on the basis of its insolubility in ethanol and purified by crystallization. With the aid of analysis and of ^{1}H-NMR spectra it was identified as ether *XXIa*. When attempting to prepare this ether by heating alcohol[41] *XXa* with concentrated hydrochloric acid (for analogy see[45]) chloride *XIXa* was obtained in a fine yield. For transformation of alcohol *XXa* to chloride *XIXa* one thus does not need anhydrous medium[41]. The required ether *XXIa* is formed during heating of alcohol *XXa* with about 20% sulfuric acid as a mixture of two stereoisomers. The lower-melting stereoisomer is identical with the product isolated from the technical base *XXIII*. Both stereoisomers were subjected to a mass spectrometric analysis. The spectra of both isomers are practically identical. Both compounds yield ionized molecules at *m/e* 506 (18%) with isotopically conjugated forms corresponding to the presence of two atoms of chlorine and sulfur. The most abundant spectrum ions are at *m/e* 245 (100%) containing chlorine atom. The IR spectra of both stereoisomers are in agree-

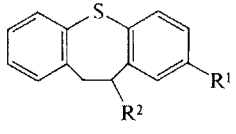
---

6·90—7·55 (m, 6 H, remaining Ar—H), 4·12 (t, 2 H, OCH_2), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·30—2·90 (m, 12 H, 5 NCH_2 and $COCH_2$), 1·00—2·30 (m, 9 H, 4 CH_2 and CH of cyclopentyl). [g] For measuring the ^{1}H-NMR spectrum, the pure base was prepared: δ 7·74 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·90—7·60 (m, 6 H, remaining Ar—H), 4·19 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·15—2·90 (m, 12 H, 5 NCH_2 and $COCH_2$), 1·30—2·00 (m, 11 H, 4 CH_2 and CH of cyclopentyl and the adjacent CH_2). [h] IR spectrum (Nujol): 756, 810, 885 (4 and 2 adjacent and solitary Ar—H), 1 235 (C—O), 1 550, 1 580 (Ar), 1 714 (COOR), 2 760 and 3 065 cm^{-1} (CH_2—N); ^{1}H-NMR spectrum: δ 7·75 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·95—7·65 (m, 6 H, remaining Ar—H), 4·19 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·62 (m, 10 H, 5 NCH_2), 1·40—2·00 (m, 15 H, 6 CH_2 and 3 CH of adamantyl). [i] Monohydrate. [j] For measuring spectra, the free base was prepared from the salt; IR spectrum: 815, 830, 890 (Ar—H), 1155, 1172 (C—O), 1578 (Ar), 1730 (COOR), 2700 cm^{-1} (N—CH_2); ^{1}H-NMR spectrum: δ 7·63 (mcs, J = 3·0 Hz, 2 H, 9,9′-H_2), 6·80—7·50 (m, 12 H, remaining Ar—H), 4·13 (t, J = 6·0 Hz, 4 H, 2 CH_2O), 3·00—4·00 (m, 6 H, 2 $ArCH_2CHAr$), c. 2·55 (m, 24 H, 10 NCH_2 and 2 CH_2O), c. 1·50 (m, 6 H, remaining 3 CH_2). [k] For measuring spectra, the free base was prepared from the maleate; IR spectrum ($CHCl_3$): 815, 830 (Ar—H), 1155, 1170 (C—O), 1728 (COOR), 2700 cm^{-1} (N—CH_2); ^{1}H-NMR spectrum: δ 6·64 (mcs, J = 3·0 Hz, 2 H, 9,9′-H_2), 6·80—7·50 (m, 12 H, remaining Ar—H), 4·12 (t, J = 6·0 Hz, 4 H, 2 CH_2O), 3·00—4·00 (m, 6 H, 2 $ArCH_2CHAr$), c. 2·55 (m, 24 H, 10 NCH_2 and 2 CH_2CO), c. 1·50 (m, 8 H, remaining 4 CH_2).

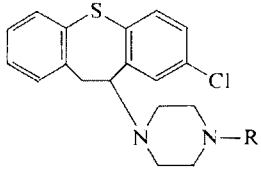
ment with structure *XXIa*; while there are some differences between the two stereoisomers when recording the spectrum in KBr, they are identical when using a chloroform solution.



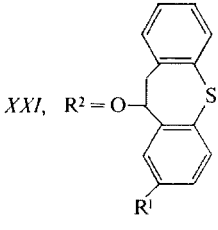
XVI, $n = 5$
XVII, $n = 6$
XVIII, $n = 7$



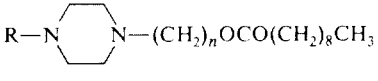
XIX, $R^2 = Cl$
XX, $R^2 = OH$



XXII, $R = CO(CH_2)_8CH_3$
XXIII, $R = CH_3$
XXIV, $R = H$
XXV, $R = OCOC_6H_5$
XXVI, $R = OH$



XXI, $R^2 = O$



XXVII, $R = CO(CH_2)_8CH_3$, $n = 3$
XXVIII, $R = CO(CH_2)_8CH_3$, $n = 2$
XXIX, $R = CH_2C_6H_5$, $n = 3$
XXX, $R = H$, $n = 3$

The final part of the present communication deals with two potential metabolites of neuroleptics of this series. Firstly, it was the hydroxylamine derivative *XXVI*. Our interest in substances of this type was aroused by the work of Beckett and coworkers[46-50] who identified similar hydroxylamine derivatives as important metabolites of psychotropic primary, secondary and tertiary amines (in the last-named case there is an N-hydroxylation after previous metabolic demethylation): chlorpromazine, fenfluramine, amphetamine, amitriptyline, nortriptyline, imipramine and

desipramine. According to this, *XXVI* may be considered as a potential metabolite of octoclothepin (*XXIII*). For its preparation we used the known sequence of reactions (for analogy see refs[51-55]), proceeding from the secondary amine[25] *XXIV*. Treatment with benzoyl peroxide in a mixture of ether and chloroform at 5°C yielded a mixture of benzoate of amine *XXIV* and of the N-(benzoyloxy) derivative *XXV* which was separated by crystallization. Hydrolysis of *XXV* with ethanolic sodium hydroxide yielded the desired hydroxylamine *XXVI*. 1-(3-Decanoyloxypropyl)piperazine (*XXX*) was considered as a potential metabolite of oxyprothepin decanoate (*IIIb*). When it was found to be impossible to prepare this compound by esterification of 1-(3-hydroxypropyl)piperazine[40] with decanoic acid we proceeded from 1-benzylpiperazine[56] which was converted by alkylation with 3-chloropropanol in boiling 1-butanol in the presence of potassium carbonate to 1-benzyl-4-(3-hydroxypropyl)-piperazine (see also[57,58]). Esterification with decanoic acid in distilling xylene led to ester *XXIX* which was debenzylated to *XXX* by hydrogenolysis on a palladium catalyst.

Some of the esters prepared were evaluated pharmacologically as potential depot neuroleptics on rats in a test of antiapomorphine effect and further from the point of view of affecting a fixed defense reaction. They were applied in a single intramuscular dose as a 2·5% solution in sunflower oil and the duration of effect in the above tests was recorded. In general it may be stated that they did not reach the duration of effect of analogous esters with linear saturated fatty acids[1]. Thus *e.g.* ester *VIIa* (VÚFB-10 088) was applied to rats in a single dose of 25 mg/kg *i.m.* and the duration of its antiapomorphine effect with respect to chewing and agitation was followed. The effect lasts 2 weeks, disappearing during the third week while the effect of the same dose of fluphenazine oenanthate was still present after three weeks. The antiapomorphine effect of the same dose of ester *Xa* (VÚFB-10 033) is more intense but it also disappears between the 14th and the 21st day after application. Ester *XIa* (VÚFB — 9979) was evaluated from the point of view of affecting a fixed defense reflex in rats (Dr E. Kazdová), applying a single dose of 30 mg/kg *i.m.* The maximum effect (*i.e.* a disturbance of the conditioned reflex) was observed 24 h after administration (with all eight animals in the group). A significant effect was observed still two weeks after application (a disturbance of the reflex with four out of eight rats); the effect disappeared again during the third week.

Three other substances were evaluated by methods of general screening at the affiliated unit of this institute at Rosice n/L (Dr M. Bartošová) using oral application throughout. The number of the compound is followed by its code number, the approximate value of acute toxicity (LD_{50}) in mg/kg and further dose D at which the substance was applied for the first orientation: *XXII*-maleate, VÚFB-10 110, >2500, 300; *XXVII*-methanesulfonate, VÚFB-10 583, >2500, 300; *XXVIII*--methanesulfonate, VÚFB-10582, >2500, 300. Substance *XXII* showed only a potentiation of thiopental sleep (doses 50—100 mg/kg *p.o.* extend sleep in mice treated with thiopental to about twice the control value). Compounds *XXVII* and *XXVIII* bring about a slight hypothermic effect in rats (measuring the rectal temperature). These two compounds displayed a slight antimicrobial activity in tests *in vitro* against several species (the minimum inhibitory concentrations in μg/ml of *XXVII* and *XXVIII*, respectively, are shown): *Streptococcus β-haemolyticus*, —, 100; *Pseudomonas aeruginosa*, 100, 100; *Proteus vulgaris*, 100, 100; *Mycobacterium tuberculosis* H37Rv, 50, 50; *Saccharomyces pasterianus*, 100, 100; *Trichophyton mentagrophytes*, 50, 50; *Candida albicans*, 100, 100; *Aspergillus niger*, 100, 100 (Dr J. Turinová and Dr A. Čapek of the bacteriological department of this institute).

EXPERIMENTAL

The melting points of analytical preparations were determined partly in Kofler's block and are not corrected, partly in an automatic Mettler FP 5 melting point recorder. The samples were dried at about 0·5 Torr over P_2O_5 at room temperature or at 77°C. IR spectra (in KBr unless stated otherwise) were recorded in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer, the mass spectra in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of alumina. Analyses of esters *IV*—*XIII* and *XVI*—*XVIII* are shown in Table I.

10-(4-[2-(2-n-Butylcaproyloxy)ethyl]piperazino)-8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VIIa*) (Method *A*)

2-(n-Butyl)caproyl chloride[27] (b.p. 128°C/30 Torr) (4·58 g) was added to a solution of 3·75 g *XIVa* (refs[1,25]) in 30 ml chloroform. The mixture was left to stand for 24 h at room temperature, diluted with 50 ml chloroform and decomposed with 100 ml 5% NaOH. The chloroform solution was washed with 5% NaOH, dried with Na_2SO_4 and evaporated. The nonhomogeneous residue was chromatographed on a column of 200 g alumina (activity II). Benzene eluted 5·1 g (96%) of a not quite homogeneous base. This was neutralized with 2 equivalents of maleic acid in acetone and converted to di(hydrogen maleate) (4·0 g) which was purified by crystallization from ethyl acetate; m.p. 148—150°C. Decomposition of a sample of this salt with 10% NaOH and isolation of the product by extraction with ether yielded a homogeneous oily base. IR spectrum ($CHCl_3$): 812, 827 (Ar—H), 1168 (C—O—C), 1575, 1600 (Ar), 1720 (COOR), 2680 and 2740 cm^{-1} (N—CH_2). ^{1}H-NMR spectrum: δ 7·84 (mcs, J = 3·0 Hz, 1 H, 9-H), 7·00—7·70 (m, 6 H, remaining Ar—H), 4·26 (t, J = 6·0 Hz, 2 H, CH_2O), 3·00—4·00 (m, 3 H, $ArCH_2$. .CHAr), 2·00—3·00 (m, 11 H, 5 NCH_2 and CHCO), *c.* 1·32 (m, 12 H, 6 CH_2 in acyl), 0·88 (t, 6 H, 2 CH_3).

Bis(2-[4-(8-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-piperazino]-ethyl)azelaate (*XVIII*) (Method *B*)

From a mixture of 11·25 g *XIVa* (ref.[1,25]), 3·01 g azelaic acid, 1·0 g *p*-toluenesulfonic acid and 100 ml xylene the solvent slowly distilled off together with water formed in the reaction and was replaced with anhydrous xylene. Within 13 h 700 ml solvent was removed by distillation. After cooling, the solution was washed with 5% NaOH, dried with K_2CO_3 and evaporated at reduced pressure. The practically homogeneous residue (13·5 g) was dissolved in 40 ml acetone and the solution was neutralized with 7·6 g maleic acid in 30 ml acetone. The poorly soluble tetra(hydrogen maleate) was obtained in a yield of 19·5 g (48%), m.p. 149—150°C. The pure oily base was released from the sample. IR spectrum ($CHCl_3$): 815, 830 (Ar—H), 1155 (C—O—C), 1730 (COOR), 2700 cm^{-1} (N—CH_2). ^{1}H-NMR spectrum: δ 7·65 (mcs, J = 3·0 Hz, 2 H, 9,9′-H_2), 6·85—7·50 (m, 12 H, remaining Ar—H), 4·15 (t, J = 6·0 Hz, 4 H, 2 CH_2O), 3·00—4·00 (m, 6 H, 2 $ArCH_2CHAr$), c. 2·56 (m, 24 H, 10 NCH_2 and 2 CH_2CO), c. 1·50 (10 H, remaining 5 CH_2).

10-[4-(3-Decanoyloxypropyl)piperazino]-8-(methylthio)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IIIb*)

A. Like with method *A* and as described before[1], *XVb* (ref.[25]) (30 g) was left to react with 28·0 g decanoyl chloride[39] (a two-fold excess) in 90 ml chloroform by a 24 h standing at room

temperature. After dilution with 100 ml chloroform, 140 ml 4% solution of NaOH was added and the mixture was stirred for 3 h at room temperature (ester *IIIb* is stable under these conditions). After separation, the chloroform solution was dried and evaporated. A total of 56·7 g nonhomogeneous residue was obtained, which, according to thin-layer chromatography, contains together with ester *IIIb* a small amount of the starting *XVb*, and a further basic substance (its identification as *XXVII* see in the following paragraph under *C*). It contains also neutral constituents including the non-hydrolyzed decanoyl chloride (its relative stability in the presence of diluted NaOH was checked in a separate experiment) and very probably decanoic anhydride (see ref.[59,60]). On further standing of the residue, 6·2 g substance precipitated and was crystallized from cyclohexane and identified as 10-chloro-8-(methylthio)-10,11-dihydrodibenzo[*b,f*]-thiepin[61] (*XIXb*), m.p. 108—109°C. ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 7 H, Ar—H), 5·69 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·56 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·35 (s, 3 H, SCH_3). For $C_{15}H_{13}ClS_2$ (292·8) calculated: 61·52% C, 4·47% H, 12·11% Cl, 21·90% S; found: 61·81% C, 4·47% H, 12·07% Cl, 21·67% S.

Combined mother liquors after *XIXb* were evaporated and the residue (50 g) was chromatographed on a column of 1·2 kg neutral alumina (activity II). Light petroleum and a mixture of light petroleum with benzene eluted 2·1 g of little polar oily fractions. Benzene then eluted 19·0 g (46%) of a practically homogeneous ester *IIIb*, a sample of which was neutralized with oxalic acid in acetone to prepare the new di(hydrogen oxalate), m.p. 173—175°C (75% ethanol). For $C_{36}H_{50}N_2O_{10}S_2$ (734·9) calculated: 58·83% C, 6·86% H, 3·81% N, 8·72% S; found: 58·96% C, 7·00% H, 4·06% N, 8·79% S.

B. Wet xylene was slowly distilled off for 6 h and substituted with dry solvent from a mixture of 10·0 g *XVb* (ref.[25]), 13·8 g decanoic acid and 150 ml xylene. Then it was distilled off completely, the residue was dissolved in 150 ml benzene and the solution was shaken for 20 min with 180 ml 5% NaOH. After drying with K_2CO_3 it was evaporated. The residue (13·5 g) was dissolved in benzene and the solution was filtered through a column of 150 g neutral alumina (activity II). Benzene eluted a total of 12·6 g (91%) ester *IIIb* which, according to thin-layer chromatography on alumina, is homogeneous. Neutralization with oxalic acid in acetone yields directly di(hydrogen oxalate) with the m.p. of the analytical preparation, 173·5—175°C. 90% of the excess decanoic acid (b.p. 170—175°C/20—25 Torr) was recovered from the alkaline aqueous solution by acidification with hydrochloric acid and extraction with toluene.

1-Decanoyl-4-(3-decanoyloxypropyl)piperazine (*XXVII*)

A. A solution of 9·5 g decanoyl chloride[39] in 20 ml chloroform was added dropwise to a solution of 2·9 g 1-(3-hydroxypropyl)piperazine[40] in 15 ml chloroform and the solution mixed with 5·0 g K_2CO_3. Then it was refluxed for 3 h. After cooling, it was diluted with 50 ml chloroform and the mixture was stirred for 1 h with 50 ml 2% NaOH. After separation, the chloroform layer was dried and evaporated. The yield was 8·7 g (96%) of an almost homogeneous oily product which, according to R_F on a thin layer of alumina, is identical with the basic by-product of synthesis of ester *IIIb* according to *A*. It crystallizes on standing, m.p. 42—43° (pentane). IR spectrum: 1180 (C—O—C), 1660 (CON), 1740 (COOR), 2860 cm^{-1} (N—CH_2). ^{1}H-NMR spectrum: δ 4·05 (t, J = 6·0 Hz, 2 H, CH_2O), 3·47 (m, 4 H, $\begin{matrix}CH_2\\CH_2\end{matrix}\!\!>$NCO), c. 2·30 (m, 6 H, remaining 3 NCH_2), 1·00—2·00 (m and bs, remaining 17 CH_2), 0·85 (def. t, 6 H, 2 CH_3). For $C_{27}H_{52}N_2O_3$ (452·7) calculated: 71·63% C, 11·58% H, 6·19% N; found: 71·96% C, 11·45% H, 6·28% N.

Hydrogen oxalate, m.p. 137°C (75% ethanol). For $C_{29}H_{54}N_2O_7$ (542·7) calculated: 64·17% C, 10·03% H, 5·16% N; found: 64·06% C, 9·84% H, 5·49% N.

Hydrogen maleate, m.p. 106–107·5°C (acetone). For $C_{31}H_{56}N_2O_7$ (568·8) calculated: 65·46% C, 9·92% H, 4·93% N; found: 65·83% C, 9·52% H, 5·03% N.

Methanesulfonate, m.p. 109–110°C (acetone). For $C_{28}H_{56}N_2O_6S$ (548·8) calculated: 61·27% C, 10·29% H, 5·10% N, 5·84% S; found: 61·11% C, 10·40% H, 5·31% N, 5·85% S.

B. Wet xylene was slowly distilled off from a mixture of 7·2 g 1-(3-hydroxypropyl)piperazine[40], 30·0 g decanoic acid and 80 ml xylene and was continually replaced with anhydrous xylene. After complete evaporation of the xylene, the residue was dissolved in 100 ml benzene, the solution was washed several times with a 5% solution of NaOH, dried with K_2CO_3 and evaporated. Residue (17·2 g, 76%), m.p. 42°C; during TLC on alumina it has the same R_F as the product according to *A*.

C. A mixture of 2·0 g *XVb* (ref.[25]), 4·0 g decanoyl chloride[39] and 20 ml chloroform was refluxed under stirring for 7 h, cooled, diluted with chloroform and stirred for 1 h with 60 ml 3% NaOH. The chloroform layer was dried and evaporated. The residue (5·2 g, nonhomogeneous oil) yielded with the aid of 1·0 g oxalic acid in 20 ml acetone 1·6 g hydrogen oxalate of *XXVII*, m.p. 135–136°C (75% ethanol). For $C_{29}H_{54}N_2O_7$ (542·7) calculated: 64·17% C, 10·03% H, 5·16% N; found: 64·02% C, 10·02% H, 5·24% N. The mother liquor after this salt was evaporated, the residue was dissolved in 50 ml benzene and the solution was washed with dilute NH_4OH and shaken with 50 ml 3M-HCl. After filtration, the neutral benzene solution was evaporated and the residue (1·2 g) was recrystallized from cyclohexane, m.p. 103–106°C. We are dealing here with chloride *XIXb*; in mixture with this authentic product[61] it melts without depression (for a substance obtained from *XXb* by treatment with HCl we reported previously[61] a m.p. of 106–108°C).

1-Decanoyl-4-(2-decanoyloxyethyl)piperazine (*XXVIII*)

Like in the preceding case according to *A*, reaction of 3·9 g 1-(2-hydroxyethyl)piperazine with 13·5 g decanoyl chloride[39] and 7·5 g K_2CO_3 in 40 ml chloroform yielded 12·7 g (97%) product melting at 39–42°C. The analytical product melts at 45–46°C (n-pentane). IR spectrum (Nujol): 1159, 1172 (C—O—C), 1655 (CON), 1737 cm^{-1} (COOR). For $C_{26}H_{50}N_2O_3$ (438·7) calculated: 71·18% C, 11·49% H, 6·39% N; found: 71·13% C, 11·13% H, 6·23% N.

Methanesulfonate, m.p. 97–99°C (acetone). For $C_{27}H_{54}N_2O_6S$ (534·8) calculated: 60·67% C, 10·18% H, 5·24% N, 5·99% S; found: 60·71% C, 10·26% H, 5·36% N, 6·03% S.

8-Chloro-10-(4-decanoylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXII*)

Decanoyl chloride[39] (3·0 g) was added to a solution of 3·0 g *XXIV* (ref.[25]) in 10 ml pyridine and the mixture was heated for 1·5 h to 90–95°C. After cooling, it was diluted with 100 ml benzene and the solution was washed with 100 ml 5% NaOH and with water. After drying with K_2CO_3 the solution was evaporated; 4·1 g (93%) oily product which was purified by chromatography on a column of 130 g alumina (activity II). Benzene eluted 3·14 g base which was converted with maleic acid in ethanol containing some ether, to the hydrogen maleate, m.p. 142–143°C (ethanol). IR spectrum: 740, 750, 765, 784, 830, 880 (4 and 2 adjacent and solitary Ar—H), 1360 (COOH), 1585 (Ar), 1665 (CON), 1705 and 2968 (COOH), 2480 cm^{-1} (NH^+). ^{1}H-NMR spectrum: δ 13·31 (bs, disappears after D_2O, 2 H, 2 COOH), 6·90–7·55 (m, 7 H, Ar—H), 6·26 (s, 2 H, CH=CH of maleic acid), 4·65 (t, 1 H, Ar—CH—N), 2·60–4·20 (m, 10 H, $ArCH_2$ and 4 CH_2 of piperazine), 2·30 (t, J = 7·0 Hz, 2 H, $COCH_2$), 1·24 (bs, 14 H, remaining 7 CH_2 in acyl), 0·86 (def. t, 3 H, CH_3). For $C_{32}H_{41}ClN_2O_5S$ (601·2) calculated: 63·93% C, 6·87% H, 4·66% N, 5·33% S; found: 63·97% C, 7·05% H, 4·68% N, 5·64% S.

Cleavage of Octoclothepin (*XXIII*) with Ethyl Chloroformate

Ethyl chloroformate (1·3 g) was added dropwise to a solution of 3·45 g base[41,42] *XXIII* in 30 ml benzene and the mixture was refluxed for 6 h. Then it was cooled, diluted with 20 ml benzene, washed with water and shaken with 50 ml 3M-HCl. The precipitated hydrochloride of base *XXIII* (0·2 g) was filtered. The filtrate separated into an aqueous and a benzene layer. Evaporation of the benzene phase yielded 2·60 g (93%) 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIXa*), m.p. 105—107°C (cyclohexane). In mixture with the authentic product[41] (m.p. 106 to 107°C) it melts without depression. The acid aqueous phase was evaporated *in vacuo*. Yield 1·68 g (80%) hydrochloride of 1-(ethoxycarbonyl)-4-methylpiperazine, m.p. 170—171°C (ethanol–ether). For the compound prepared differently ref.[43,44] report m.p. of 168—169 and 170—171°C, respectively.

8,10-Dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIXa*)

A mixture of 2·0 g *XXa* (ref.[41]) and 10 ml concentrated hydrochloric acid was refluxed for 15 h. After cooling, the product was extracted with chloroform; processing of the extract and recrystallization from cyclohexane yielded *XIXa* practically pure, m.p. 103—104°C (1·30 g, 62%). In mixture with the authentic product[41] it melts without depression.

Bis(8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl) Ether (*XXIa*)

A. A mixture of 10·0 g alcohol[41] *XXa*, 120 ml water and 12 ml H_2SO_4 was refluxed under stirring for 16 h (a 150°C bath). After cooling, the product was extracted with 200 ml benzene, the extract was dried and placed on a column of 250 g alumina (activity II). A mixture of light petroleum and benzene (5 : 1) was used for the elution. A total of 4·04 g little polar compounds was eluted. Directly from the first fraction and after crystallization from further fractions (benzene and light petroleum) a total of 0·62 g homogeneous stereoisomer *A* was obtained, m.p. 180°C (needles from the above solvent mixture or from cyclohexane). Mass spectrum: *m/e* 506 (M^+; 13·9%), 261 (22·6), 246 (31·5), 245 (100), 231 (10·8), 210 (63·0), 197 (13·9), 178 (13·0), 165 (28·9). IR spectrum: 752, 770, 810, 842, 860, *892* (4 and 2 adjacent and solitary Ar—H), 1110 (R—O—R), 1466, 3045 cm^{-1} (Ar). For $C_{28}H_{20}Cl_2OS_2$ (507·5) calculated: 66·26% C, 3·97% H, 13·97% Cl, 12·64% S; found: 66·32% C, 3·95% H, 13·61% Cl, 12·50% S.

Besides needles, the mother liquors separate on standing to large prisms. Mechanical separation of these yielded 0·17 g of a substance which is homogeneous after a single crystallization from cyclohexane and represents the stereoisomer B, m.p. 167—168°C. Mass spectrum: *m/e* 506 (M^+; 18·8%), 261 (19·1), 246 (28·8), 245 (100), 231 (6·8), 210 (61·2), 197 (15·5), 178 (12·4), 165 (28·9). IR spectrum: 751, 773, 815, 848, 880 (4 and 2 adjacent and solitary Ar—H), 1070, 1115 (R—O—R), 1471, 3050 cm^{-1} (Ar). For $C_{28}H_{20}Cl_2OS_2$ (507·5) calculated: 66·26% C, 3·97% H, 13·97% Cl, 12·64% S; found: 66·32% C, 4·01% H, 13·97% Cl, 12·67% S.

B. A batch of octoclothepin base (*XXIII*) (67 g) prepared by the substitution reaction of *XIXa* (ref.[41]) with 1-methylpiperazine in boiling chloroform[42] which did not meet the standard requirements because it did not dissolve to a clear 5% solution in ethanol, was heated with 750 ml ethanol and the insoluble fraction was isolated by filtration. A total of 0·41 g compound melting at 164—167°C which, after crystallization from a mixture of cyclohexane and light petroleum, melts at 168°C and is homogeneous. It is identical with the stereoisomer *B*, prepared according to *A*. ^{1}H-NMR spectrum: δ 6·80—7·50 (m, 14 H, Ar—H), 5·68 (dd, J = 9·5; 4·0 Hz, 2 H, 2 Ar—CH—O), 3·52 and 3·12 (2 dd, J = 15·0; 4·0 and 15·0; 9·5 Hz, 4 H, 2 $ArCH_2$).

10-(4-Benzoyloxypiperazino)-8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXV*)

A solution of 1·70 g 87% benzoyl peroxide in a mixture of 30 ml ether and 10 ml chloroform was added dropwise under stirring at 5°C to a solution of 3·30 g *XXIV* (ref.[25]) in 80 ml ether and 20 ml chloroform. The mixture was stirred for 3 h at 5°C and left to stand for 12 h in the refrigerator at 0°C. The precipitated compound was filtered (2·45 g) and crystallized from aqueous ethanol, m.p. 203—205°C. It is the benzoate of 8-chloro-10-piperazino-10,11-dihydrodibenzo-[*b,f*]thiepin (*XXIV*). For $C_{25}H_{25}ClN_2O_2S$ (453·0) calculated: 66·29% C, 5·56% H, 7·82% Cl, 6·18% N, 7·08% S; found: 65·94% C, 5·57% H, 8·06% Cl, 6·12% N, 7·29% S.

After filtration of *XXIV*, the filtrate was washed with 10% solution of Na_2CO_3 and water, dried with Na_2SO_4 and evaporated *in vacuo* at below 50°C. The residue crystallized after mixing with ethanol; 1·40 g (31%), m.p. 130—137°C. After a single crystallization from a mixture of chloroform and ethanol compound *XXV* is homogeneous; m.p. 146—147°C. IR spectrum: 725, 765, 842, 901 (5, 4 and 2 adjacent and solitary Ar—H), 1262 (C—O), 1590, 1607 (Ar), 1745 cm^{-1} (ArCOO). ^{1}H-NMR spectrum: δ 8·10 (m, 2 H, 2,6-H_2 of benzoyl), 6·90—7·80 (m, 10 H, remaining Ar—H), 2·50—4·00 (m, 11 H, $ArCH_2CHAr$ and 4 CH_2 of piperazine). For $C_{25}H_{23}ClN_2O_2S$ (451·0) calculated: 66·58% C, 5·14% H, 7·86% Cl, 6·21% N, 7·11% S; found: 67·10% C, 5·25% H, 7·55% Cl, 6·19% N, 7·19% S.

8-Chloro-10-(4-hydroxypiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XXVI*)

A suspension of 1·0 g *XXV* in a mixture of 30 ml ethanol and 2 ml water was combined with 3 ml 10% KOH and the mixture was refluxed for 90 min. On cooling and standing overnight, 0·30 g (38%) product crystallized; from ethanol it crystallizes as hemihydrate, m.p. 193—196°C. For $C_{18}H_{20}ClN_2O_{1.5}S$ (366·9) calculated: 60·75% C, 5·66% H, 9·96% Cl, 7·87% N, 9·01% S; found: 60·94% C, 5·72% H, 9·99% Cl, 7·99% N, 8·83% S.

Di(hydrogen maleate), m.p. 126—128°C (ethanol). For $C_{26}H_{27}ClN_2O_9S$ (579·0) calculated: 53·93% C, 4·70% H, 6·12% Cl, 4·84% N, 5·54% S; found: 53·70% C, 5·38% H, 6·35% Cl, 4·85% N, 5·39% S.

1-Benzyl-4-(3-hydroxypropyl)piperazine

A mixture of 17·6 g 1-benzylpiperazine[56], 13·0 g 3-chloropropanol, 16·0 g K_2CO_3 and 80 ml 1-butanol was refluxed under stirring for 9 h (a 140°C bath). After cooling, the solid fractions were filtered and washed with 1-butanol, the solvent was distilled off from the filtrate at reduced pressure; 20·0 g (85%), b.p. 148—150°C/0·1 Torr. Ref.[58] described the preparation of the compound using 3-bromopropanol and reports a b.p. of 144—146°C/2 Torr.

1-Benzyl-4-(3-decanoyloxypropyl)piperazine (*XXIX*)

Wet xylene was slowly distilled for 8 h from a mixture of 16·5 g of the preceding aminoalcohol, 36·0 g decanoic acid and 150 ml xylene and continually replaced with anhydrous xylene (a 170 to 180°C bath). A total of 350 ml distillate was collected. Xylene was then evaporated completely at reduced pressure, the residue was diluted with 100 ml benzene, the solution was washed three times with 150 ml 5% NaOH, dried with K_2CO_3 and evaporated. The residue is 26·5 g (97%) homogeneous oil (TLC). For characterization, the di(hydrogen oxalate) was prepared; m.p. 218—220°C under decomposition (aqueous ethanol). For $C_{28}H_{44}N_2O_{10}$ (568·7) calculated: 59·14% C, 7·80% H, 4·93% N; found: 59·45% C, 8·13% H, 5·03% N.

1-(3-Decanoyloxypropyl)piperazine (*XXX*)

The preceding crude product (24·0 g) was dissolved in 150 ml 90% ethanol and, after adding palladium catalyst on charcoal (prepared from 1·5 g $PdCl_2.2\,H_2O$ and 4·0 g charcoal), it was hydrogenated on a shaker at room temperature. Theoretical consumption of hydrogen was attained after 21 h of shaking (equal amounts of catalyst were added every 7 h). After filtration, the filtrate was evaporated *in vacuo*; 15·0 g (81%) oil.

Di(hydrogen oxalate), m.p. 198—200°C under decomposition (85% ethanol). For $C_{21}H_{38}N_2.O_{10}$ (478·6) calculated: 5·86% N; found: 5·90% N.

Dipicrate, m.p. 213—217° (90% ethanol). For $C_{29}H_{40}N_8O_{16}$ (756·7) calculated: 46·03% C, 5·33% H, 14·81% N; found: 45·83% C, 5·32% H, 15·18% N.

The authors are indebted to Dr V. Hanuš, J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, Prague, Drs B. Kakáč, J. Holubek and E. Svátek (department of physical chemistry of this institute) for recording and interpretation od the spectra, further to Mr J. Pomykáček and Mrs M. Hrubantová for technical cooperation during the synthesis of various compounds, and finally to Mrs J. Komancová, Mrs V. Šmídová, Mr K. Havel, Mr M. Čech, Mrs A. Slavíková, Mrs J. Hrdá and Mrs Z. Volková (analytical department of this institute) for carrying out the analyses.

REFERENCES

1. Jílek J. O. Šindelář K., Dlabač A., Kazdová E., Pomykáček J., Šedivý Z., Protiva M.: This Journal *38*, 1190 (1973).
2. Anonym: Medicamentos de Actualidad (Drugs of Today, Barcelona) *10*, 174 (1974).
3. Jílek J. O., Dlabač A., Protiva M.: 4th Symp. Chemie Ústí 74, Psychotrop. Agents, May 1974; Abstr., p. 16.
4. Jílek J. O., Červená I., Šindelář K.: RGW-Symposium Psychopharmaka, Sofia, Nov. 1973; Proc., p. 158 (Published 1975).
5. Protiva M., Jílek J., Šindelář K., Metyšová J.: Czech. 149 351 (Appl. 30. VII. 1970).
6. Protiva M., Jílek J., Šindelář K., Metyšová J.: Czech. 152 024 (Appl. 30. IV. 1971).
7. Protiva M., Jílek J., Šindelář J., Metyšová J.: Czech. 152 136 (Appl. 10. V. 1971).
8. Protiva M., Jílek J., Šindelář K., Metyšová J. (Spofa): Ger. Offen. 2 138 039; Belg. 770 643; Brit. 1 364 082; Australian 466 449; Austrian 309 438; Swiss 554 362; Chem. Abstr. *76*, 140 881 (1972).
9. Protiva M., Jílek J., Dlabač A., Kazdová E.: Czech. 157 341 (Appl. 15. V. 1972).
10. Valenta V., Metyšová J., Šedivý Z., Protiva M.: This Journal *39*, 783 (1974).
11. Jílek J. O., Šindelář K., Rajšner M., Dlabač A., Metyšová J., Votava Z., Pomykáček J., Protiva M.: This Journal *40*, 2887 (1975).
12. Jílek J. O., Červená I., Kopicová Z., Šindelář K., Svátek E., Metyšová J., Dlabač A., Pomykáček J., Protiva M.: This Journal *41*, 443 (1976).
13. Červená I., Metyšová J., Svátek E., Kakáč B., Holubek J., Hrubantová M., Protiva M. This Journal *41*, 881 (1976).
14. Kazdová E., Dlabač A.: Activ. Nerv. Super. *15*, 81 (1973).
15. Votava Z., Likovský Z., Dlabač A.: Activ. Nerv. Super. *15*, 82 (1973).
16. Dlabač A.: Psychopharmacologia *26*, Suppl. (8th Congr. CINP), 106 (1972).
17. Dlabač A.: Česk. Fysiol. *22*, 356 (1973).
18. Dlabač A., Kazdová E.: Activ. Nerv. Super. *16*, 166 (1974).
19. Dlabač A., Kazdová E.: Česk. Fysiol. *23*, 336 (1974).

20. Dlabač A.: J. Pharmacol. (Paris) *5*, Suppl. 2 (9th Congr. CINP), 26 (1974).
21. Dlabač A.: RGW-Symposium Psychopharmaka, Sofia, Nov. 1973; Proc., p. 165 (Published 1975).
22. Queisnerová M., Roubal Z., Dlabač Z.: 4th Xenobiochem. Symp., Pezinok—Lipiny, May 1975; Pharmazie *30*, 757 (1975).
23. Julou L., Bourat G., Ducrot R., Fournel J., Garret C., Mottet F.: Thérapie *28*, 475 (1973).
24. Protiva M., Jílek J., Červená I., Dlabač A.: Czech. 159 044 (Appl. 26. VI. 1972).
25. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
26. Kapp R., Knoll A.: J. Amer. Chem. Soc. *65*, 2062 (1943).
27. Tiffeneau M., Bull. Soc. Chim. Fr. (4) *33*, 183 (1923).
28. Levene P. A., Cretcher L. H. jr: J. Biol. Chem. *33*, 505 (1918).
29. Speck S. B.: J. Amer. Chem. Soc. *74*, 2876 (1952).
30. Bentley W. H., Perkin W. H. jr: J. Chem. Soc. *73*, 45 (1898).
31. Freylon G.: Ann. Chim. Phys. (8) *20*, 71 (1910).
32. Burschkies K., Scholl J.: Arch. Pharm. (Weinheim) *281*, 328 (1943); Chem. Abstr. *38*, 5801 (1944).
33. Goryaev M. I., Sharipova F. S., Tikhonova L. K., El'chibekova L. A., Kushnikov Yu. A., Orlova Z. F.: Tr. Inst. Khim. Nauk, Akad. Nauk Kaz. SSR *19*, 77 (1967); Chem. Abstr. *69*, 18 646 (1968).
34. Shepard E. R., Noth J. F.: J. Org. Chem. *19*, 415 (1954).
35. Barrett J. W., Cook A. H., Linstead R. P.: J. Chem. Soc. *1935*, 1065; Chem. Zentralbl. *1936* I, 757.
36. Stetter H., Rauscher E.: Chem. Ber. *93*, 1161 (1960).
37. Ingold C. K., Thorpe J. F.: J. Chem. Soc. *115*, 143 (1919).
38. Venus-Danilowa E. D., Bolschukin A. I.: Zh. Obshch. Khim. *7* (69), 2823 (1937); Chem. Zentralbl. *1938* II, 3391.
39. Fierz-David H. E., Kuster W.: Helv. Chim. Acta *22*, 82 (1939).
40. Zawisza T., Machoń Z., Kuczyński L.: Acta Polon. Pharm. *22*, 477 (1965).
41. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
42. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
43. Stewart H. W., Turner R. J., Denton J. J., Kushner S., Brancone L. M., McEwen W. L., Hewitt R. I., Subbarow Y.: J. Org. Chem. *13*, 134 (1948).
44. Protiva M., Seidlová V., Svátek E., Hradil F.: This Journal *37*, 868 (1972).
45. Ward A. M.: J. Chem. Soc. *1927*, 2290.
46. Beckett A. H., Essien E. E.: J. Pharm. Pharmacol. *25*, 188 (1973).
47. Beckett A. H., Coutts R. T., Ogunbona F. A.: J. Pharm. Pharmacol. *25*, 190 (1973).
48. Beckett A. H., Al-Sarraj S.: J. Pharm. Pharmacol. *25*, 328 (1973).
49. Beckett A. H., Al-Sarraj S.: J. Pharm. Pharmacol. *25*, 335 (1973).
50. Beckett A. H.: Biochem. Pharmacol. *1974*, Suppl., Pt. 1, 91; Chem. Abstr. *82*, 38 359 (1975).
51. Zeeh B., Metzger H. in the book: *Houben-Weyl Methoden der Organischen Chemie* (Müller E., Ed.), 4th. Ed., Vol. X/1 *Stickstoffverbindungen*, p. 1091. G. Thieme, Stuttgart 1971.
52. Challis B. C., Butler A. R. in the book: *The Chemistry of the Amino Group* (S. Patai, Ed.), p. 277. Interscience, New York 1968.
53. Feldman A. M., Hoffmann K. (American Cyanamid Co.): Fr. 1 360 030 (U.S. Appl. 13. VI. 1962); Chem. Abstr. *61*, 13 289 (1964).
54. Schröter H. Prins D. A. (J. R. Geigy AG.): Swiss 439 322 (Appl. 6. V. 1964); Czech. 124 361; Fr. 4.649 M; Ger. (GDR) 50 621; Neth. Appl. 65/5680; Chem. Abstr. *64*, 12 621 (1966).

55. Schröter H., Prins D. A. (J. R. Geigy AG.): Swiss 451 141 (Appl. 27. IV. 1965); Brit. 1 111 733; Chem. Abstr. *69*, 67 224 (1968).
56. Cymerman-Craig J., Young R.: Org. Syn., Coll. Vol. *5*, 88 (1973).
57. Friedman O. M., Bien S., Chakrabarti J. K.: J. Amer. Chem. Soc. *87*, 4978 (1965).
58. Ikeda Y., Nitta Y., Yamada K.: Yakugaku Zasshi *89*, 669 (1969).
59. Holde D., Gentner R.: Ber. Deut. Chem. Ges. *58*, 1418 (1925).
60. Holde D., Gentner R.: Ber. Deut. Chem. Ges. *58*, 1424 (1925).
61. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1895 (1968).

Translated by A. Kotyk.