11-(4-PIPERIDYLIDENE)-6,11-DIHYDRODIBENZO[*b*,*e*]THIEPINS AS POTENTIAL ANTIPSYCHOTIC AGENTS; SYNTHESIS AND PHARMACOLOGY

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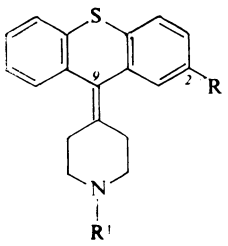
Received October 21st, 1983

The secondary amine *VIIIb*, prepared by demethylation of 2-chloro-11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IVb*), afforded by alkylation with 2-bromoethanol the amino alcohol *Vb* which was esterified to the decanoate *VIb*. A reaction of 5-fluorophthalide with the sodium salt of 4-chlorothiophenol in boiling 1-butanol gave the acid *X* which afforded by cyclization 2-chloro-8-fluorodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*XII*). Treatment with 1-methyl-4-piperidylmagnesium chloride resulted in the tertiary alcohol *IXc* which was transformed by an acid catalyzed dehydration to the desired unsaturated amine *IVc*. While compounds *Vb* and *IVc* showed properties of mild tranquillizers, the ester *VIb*, surprisingly, brought about a mild dopaminomimetic activity (it potentiates the action of apomorphine, has anticataleptic activity and lowers the homovanillic acid level in the striatum of rat brain.

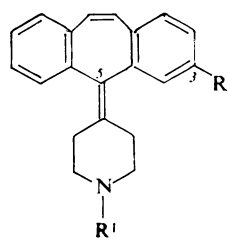
9-(1-Methyl-4-piperidylidene)thioxanthene (*I*, R = H, $R^1 = CH_3$; pimethixene) is a tranquillizer with significant antihistamine, antiserotonin, antiadrenaline and anticholinergic actions but it lacks the neuroleptic activity[1]. The introduction of a "neuroleptic substituent" (ref.[2,3]) to position 2 of the skeleton and substitution of the N-methyl by other groups (*I*, R = Cl, CF_3; R^1 = 2-hydroxyethyl, n-propyl cyclobutylmethyl) led to the design of relatively strong neuroleptics[4]. Similar relations between structure and activity exist in the series of analogous xanthenes[4–7]. 5-(1-Methyl-4-piperidylidene)dibenzo[*a*,*d*]cycloheptene (*II*, R = H, $R^1 = CH_3$) is the important antihistamine and antiserotonin agent cyproheptadine[8,9]. The introduction of a suitable substituent to position 3 combined eventually with a substitution of the N-methyl by another group (cyclopropylmethyl) leads in this case likewise to the appearing of a more or less intensive neuroleptic activity. As the substituents R (in compounds of formula *II*) the atoms of bromine[8] and iodine[10], methoxyl[11], the cyano[12,13], trifluoromethylthio[10,14–16] and trifluoromethylsulfonyl[17] groups were of use; compounds of this series are chiral and their neuroleptic activity is highly stereoselective. Finally, an indication of the neuroleptic activity was announced also for the dibenz[*b*,*e*]oxepin derivative *III* (ref.[4]).

In the series of 6,11-dihydrodibenzo[*b*,*e*]thiepin derivatives the corresponding 11-(1-methyl-4-piperidylidene) compound (*IVa*) has also been prepared[9,18] with

which central depressant, antireserpine, antihistamine and antiserotonin effects have been shown[19]. Its 2-chloro (*IVb*), 2-methyl, 2-methoxy and 2-methylthio derivatives were likewise prepared[18]. Antihistamine and antiacetylcholine activities were



I



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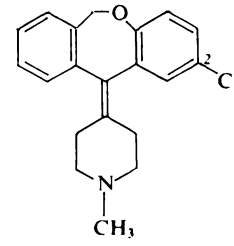
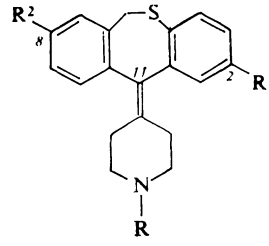


III

mentioned as their pharmacological properties; a possible neuroleptic activity was not considered. The purpose of the present paper was the synthesis of the amino alcohol *Vb* as a potential neuroleptic, of its decanoate *VIb* as a potential depot neuroleptic and finally of the 2-chloro-8-fluoro derivative *IVc* as a possible oral neuroleptic agent with a prolonged action[20]

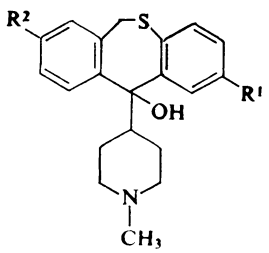


IV, R = CH_3
V, R = CH_2CH_2OH
VI, R = $(CH_2)_2OCO(CH_2)_8CH_3$
VII, R = $COOC_2H_5$
VIII, R = H

In formulae *IV*–*IX*: *a*, $R^1 = R^2 = H$; *b*, $R^1 = Cl$, $R^2 = H$; *c*, $R^1 = Cl$, $R^2 = F$

In the synthesis of compounds *Vb* and *VIb* 2-chloro-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*IXb*) (ref.[18]) was used as the starting substance. It was dehydrated by heating with a mixture of acetic acid and acetyl chloride and the obtained 2-chloro-11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]-thiepin (*IVb*) was found identical with the product described[18] and was characterized

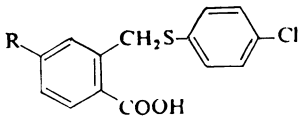
as hydrochloride. Treatment of compound *IVb* with ethyl chloroformate in boiling benzene effected demethylation and chromatography of the crude neutral product on aluminium oxide gave the carbamate *VIIb* in a high yield, which was characterized by spectra. Boiling this compound with an ethanolic potassium hydroxide solution led to the secondary amine *VIIIb* whose elemental composition was confirmed by the mass spectrum. This product was alkylated by heating with 2-bromoethanol in acetone in the presence of potassium carbonate. The oily amino alcohol *Vb* obtained was transformed to the hydrochloride which was used in pharmacological tests. The amino-alcohol *Vb* was esterified by treatment with decanoyl chloride[21]; the crude base *VIb* was chromatographed on alumina and the purified base was used in tests in the form of a solution in Miglyol^{R} (a mixture of triglycerides of vegetable fatty acids C_8-C_{12}). An alternative procedure consisted in the transformation of the crude base to the hydrochloride which was purified by crystallization, the pure base was released by dilute aqueous ammonia and used similarly like in the preceding case. Its identity was confirmed by means of the ^{1}H NMR spectrum.



IX

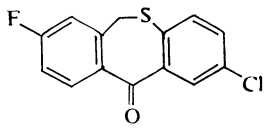
For the synthesis of the chloro fluoro derivative *IVc* we started from 5-fluorophthalide[22] which was reacted with the sodium salt of 4-chlorothiophenol in boiling 1-butanol and gave the acid *X* in an excellent yield. A reaction of 5-fluorophthalide with 4-chlorothiophenol (used in excess), which was carried out by heating with potassium carbonate to 100°C (without the use of a solvent), proceeded under a simultaneous nucleophilic substitution of the fluorine atom and crystallization of the crude acidic product afforded the acid *XI* whose structure was confirmed by the ^{1}H NMR spectrum. We met already with a similar case of a rather unexpected displacement of the fluorine atom, activated by the atom of sulfur in the *para*-position[23]. The acid *X* was cyclized by heating with polyphosphoric acid to 150–155°C; in a yield of 70% 2-chloro-8-fluorodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*XII*) was obtained (prepared on the one hand in the nonsolvated form, and as a cyclohexane solvate on the other). Its reaction with 1-methyl-4-piperidylmagnesium chloride[9] in a mixture of tetrahydrofuran and benzene gave the tertiary alcohol *IXc* which crystallized from a mixture of benzene and light petroleum in the form of two isomeric individuals

differing significantly by the melting points and IR spectra (in Nujol) but affording identical ^{1}H NMR spectra. Dehydration of the crude carbinol *IXc* by heating with a mixture of acetic acid and acetyl chloride gave the crude olefinic base *IVc* which was transformed to the crystalline maleate and purified in this form by crystallization. Decomposition of the pure salt with aqueous ammonia afforded the homogeneous base *IVc* whose ^{1}H NMR spectrum confirmed its structure. An attempt at dehydrating the carbinol *IXc* by heating with 6% sulfuric acid was unsuccessful and the starting compound *IXc* (the higher melting form) was recovered.



X, R = F

XI, R = S — Cl



XII

Compounds *Vb*, *VIb* and *IVc* were subjected to pharmacological screening (*Vb* and *IVc* in the form of salts, *VIb* in the form of a 5% solution in Miglyol^R) which was oriented mainly to the expected psychotropic effects (tranquillizing, neuroleptic, antidepressant), partly also to the general screening. The amino alcohol *Vb* was tested as hydrochloride on oral administration (the doses given were calculated for the base). Acute toxicity in mice, LD_{50} = 413 mg/kg; toxic doses elicit tremor and repeated convulsive seizures. In doses of 10–25 mg/kg the compound potentiates the thiopental effect in mice (prolongs the sleeping time to 200% in comparison with the control). In a dose of 50 mg/kg it shows antiamphetamine effect in mice (protects 100% animals from the lethal effect of a standard dose of amphetamine). In the same dose it is ineffective cataleptically in rats, does not influence the apomorphine stereotypies in rats and does not change the increased level of homovanillic acid in striatum of the rat brain (the increase was induced with probenecide, *i.e.* 4-[N,N-dipropylaminosulfonyl]benzoic acid). In a dose of 25 mg/kg it does not influence the reserpine ptosis in mice. In a dose of 100 mg/kg it brought about an antitussic effect in guinea-pigs in a test using the citric acid aerosol (the dose given decreased the number of cough attacks by 61% in comparison with the control group). In general, compound *Vb* exhibits properties neither of a neuroleptic agent, nor of a potential antidepressant; it may be characterized merely as a mild tranquillizer.

The ester *VIb* was administered intramuscularly. In a dose of 25 mg/kg it did not show the antiapomorphine effect in rats (neither stereotypies nor agitation) while fluphenazine decanoate in the same single dose significantly inhibited both parameters during the interval of 2 weeks. In a dose of 5 mg/kg compound *VIb* did not inhibit the emetic effects of apomorphine; on the contrary, in the interval of 1–2

weeks after the administration it potentiated significantly the emetic effect of apomorphine (maximum in the first week after the administration when the number of emetic attacks was increased to 270%). In a dose of 25 mg/kg it did not show any cataleptic action in rats; on the contrary, in interaction with perphenazine (4·5 mg/kg *i.p.*) it reduced its cataleptic activity by 20%. In a dose of 50 mg/kg it lowered the homovanillic acid (HVA) level in striatum of the rat brain; this effect is protracted because 2 days after the administration the decrease of homovanillic acid level reached the maximum (by 59%) but even after 5 days it was still by 58%. No change of the 5-hydroxyindoleacetic acid level was noted. In the same dose, however, the compound did not influence the increased dopamine turnover induced by perphenazine (0·5 and 1·5 mg/kg *s.c.*): the expected reduction of the increased homovanillic acid and 3,4-dihydroxyphenylacetic acid levels did not take place. In contradiction to the expectation, compound *VIb* does not show at all properties of a depot neuroleptic but rather of a dopaminomimetic with prolonged action. It is surprising from the point of view of structure *VIb* and we are not aware of any similar case.

Compound *IVc* was tested as hydrogen maleate (doses calculated for the base) on oral administration. It brought about a discoordinating effect in the rotarod test in mice, ED_{50} = 15·9 mg/kg (after 24 h the effect disappeared). In a dose of 40 mg/kg it had no antiapomorphine effect in rats in the interval of 4 h after the administration. In doses of 10, 25 and 50 mg/kg it did not influence the reserpine ptosis in mice. The compound has thus neither properties of a neuroleptic agent, nor of an antidepressant. The discoordinating effect manifests some central depressant action and the compound can be characterized as a mild tranquillizer. It should be noted that out of the fluoro derivatives of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (prothiadene, dosulepin) (2-fluoro[19,24–26], 9-fluoro[27], 2,9-difluoro[27] and 3,8-difluoro[22,27]) some showed significant antireserpine and anticataleptic activities, *i.e.* properties of potential antidepressants.

Compounds *IVc* and *Vb* were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml — unless they exceed 100 μg/ml — are given): *Streptococcus β-haemolyticus*, *IVc* 25, *Vb* 25; *Streptococcus faecalis*, *IVc* 25, *Vb* 50; *Staphylococcus pyogenes aureus*, *IVc* 25, *Vb* 12·5; *Proteus vulgaris*, *Vb* 50; *Escherichia coli*, *IVc* 25; *Trichophyton mentagrophytes*, *Vb* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C or at room temperature. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum with MCH-1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Chloro-11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IVb*)

A mixture of 20 g *IXb* (ref.[18]), 180 ml acetic acid and 60 ml acetyl chloride was refluxed for 4 h, the volatile components were evaporated *in vacuo*, the residue was made alkaline with 20% NaOH and the mixture was extracted with dichloromethane. The extract was evaporated, the residue dissolved in ether and the solution treated with an excess of HCl in ether. The solid hydrochloride was filtered, washed with ether and dried; 16·8 g (80%), m.p. 260–265°C. Analytical sample, m.p. 279–281°C (ethanol–ether). For $C_{20}H_{21}Cl_2NS$ (378·4) calculated: 63·49% C, 5·59% H, 18·74% Cl, 3·70% N, 8·47% S; found: 62·94% C, 5·62% H, 18·81% Cl, 3·58% N, 8·66% S.

The hydrochloride was decomposed with NH_4OH, the base was isolated by extraction with benzene, the extract was filtered through a column of 50 g neutral Al_2O_3 (activity II), the filtrate was evaporated and the residue crystallized from a mixture of cyclohexane and hexane; 9·0 g base, m.p. 162–163°C. Lit[18], m.p. 161–164°C.

2-Chloro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIIb*)

A warm solution of 5·6 g *IVb* in 12 ml benzene was added dropwise to a stirred solution of 2·5 g ethyl chloroformate in 6 ml benzene at 70°C. The mixture was refluxed for 2·5 h, cooled, decomposed with water and extracted with chloroform. The extract was washed with dilute hydrochloric acid and water, dried with $MgSO_4$ and evaporated. The residue was chromatographed on a column of 200 g neutral Al_2O_3 (activity II). Elution with chloroform gave 5·7 g (87%) *VIIb* which crystallized from cyclohexane, m.p. 125–126°C. UV spectrum: λ_{max} 210 nm (log ε 4·51), 233 nm (4·38), 271 nm (4·07), 313 nm (3·59). IR spectrum: 730, 742, 753, 768, 810, 817, 898 (4 and 2 adjacent and solitary Ar—H), 1 112, 1 226, **1 680**, **1 710** (NCOOR), 1 549, 1 578, 3 040, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·90–7·40 (m, 7 H, ArH), 4·88 and 3·42 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 4·18 (q, J = 7·0 Hz, 2 H, CH_2O), 3·00–4·00 and 2·00–2·60 (2 m, 8 H, 4 CH_2 of piperidine), 1·28 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{22}H_{22}ClNO_2S$ (399·9) calculated: 66·07% C, 5·54% H, 8·86% Cl, 3·50% N, 8·02% S; found: 65·88% C, 5·75% H, 8·98% Cl, 3·50% N, 7·95% S.

2-Chloro-11-(4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIIIb*)

A mixture of 25·0 g *VIIb*, 30 g KOH and 100 ml ethanol was stirred and heated for 1 h under reflux in a bath of 140°C. The solidified mixture (stirring discontinued after 30 min) was dissolved in 1 l water and the solid product was filtered after cooling, washed with water and dried *in vacuo*; 19 g (93%), m.p. 175–180°C. Analytical sample, m.p. 180–182°C (benzene–cyclohexane). Mass spectrum, *m*/*z* (%): 327 (M^+ corresponding to $C_{19}H_{18}ClNS$, 7·2%), 294 (42·8), 82 (16·8), 56 (100). For $C_{19}H_{18}ClNS$ (327·9) calculated: 69·60% C, 5·53% H, 10·81% Cl, 4·27% N, 9·78% S; found: 69·04% C, 5·74% H, 10·51% Cl, 3·97% N, 9·52% S.

2-Chloro-11-[1-(2-hydroxyethyl)-4-piperidylidene]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*Vb*)

A mixture of 12·1 g *VIIIb*, 6·75 g 2-bromoethanol, 6·75 g K_2CO_3 and 140 ml acetone was stirred and refluxed for 5 h. After cooling the salts were filtered off, washed with acetone and the filtrate was evaporated. The residue was dissolved in ether, the undissolved part was filtered off and the filtrate was treated with a slight excess of HCl in ether. The precipitated hydrochloride was filtered, washed with ether and dried; 11·7 g (76%), m.p. 278–281°C. Analytical sample, m.p. 265–267°C (aqueous methanol). For $C_{21}H_{23}Cl_2NOS$ (408·4) calculated: 61·76% C, 5·68% H, 17·36% Cl, 3·43% N, 7·85% S; found: 61·68% C, 5·81% H, 17·46% Cl, 3·19% N, 7·74% S.

2-Chloro-11-[1-(2-decanoyloxyethyl)-4-piperidylidene]-6,11-dihydrodibenzo[*b,e*]thiepin (*VIb*)

A) *Vb*.HCl (11·8 g) was suspended in 100 ml water and the suspension was treated with a slight excess of NH_4OH. The base *Vb* was isolated by extraction with benzene, the extract was dried and evaporated. The residue was dissolved in a mixture of 20 ml chloroform and 70 ml benzene, the solution was cooled to 0°C and treated with 13·8 g decanoyl chloride[21]. The mixture was allowed to stand overnight at room temperature, diluted with chloroform, washed with water and 5% NaOH, dried with $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in light petroleum, the solution was filtered and the filtrate was chromatographed on 150 g neutral Al_2O_3 (activity II). Elution with light petroleum and then with a 1 : 1 mixture of light petroleum and benzene gave 8·8 g (58%) homogeneous oily *VIb*. ^{1}H spectrum: δ 7·15 (m, 7 H, ArH), 4·90 and 3·38 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 4·19 (t, J = 6·0 Hz, 2 H, CH_2O), 2·00—3·00 (m, 12 H, 4 CH_2 of piperidine, CH_2N and CH_2CO), 1·60 (m, 2 H, CH_2 adjacent to methyl), 1·25 (bs, 12 H, remaining 6 CH_2 of decanoyl), 0·85 (def. t, 3 H, CH_3).

B) *Vb* (1·3 g) was esterified with 1·4 g decanoyl chloride[21] similarly like in the preceding case. The mixture was diluted with 20 ml chloroform, washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated. The residue was dissolved in acetone and neutralized by a slight excess of HCl in ether. The mixture was diluted with ether and allowed to crystallize; 1·8 g (92%) hydrochloride, m.p. 196—198°C (acetone–ether). For $C_{31}H_{41}Cl_2NO_2S$ (562·6) calculated: 66·18% C, 7·35% H, 12·60% Cl, 2·49% N, 5·70% S; found: 65·57% C, 7·65% H, 12·59% Cl, 2·55% N, 5·82% S. A careful decomposition of the hydrochloride with dilute NH_4OH and extraction with dichloromethane yielded the homogeneous oily base *VIb*, identical with the product prepared under *A*.

2-(4-Chlorophenylthiomethyl)-4-fluorobenzoic Acid (*X*)

Na (0·75 g) was dissolved in 15 ml 1-butanol, 4·7 g 4-chlorothiophenol were added and the mixture was stirred for 10 min. It was then treated with 5·0 g 5-fluorophthalide[22] and the mixture was stirred and refluxed for 4 h. The solvent was evaporated *in vacuo*, the residue was dissolved in water, the solution filtered with charcoal and the filtrate acidified with hydrochloric acid. After standing overnight the precipitated product was filtered, washed with water and dried; 8·3 g (96%), m.p. 100—105°C. Analytical sample, m.p. 144—146°C (cyclohexane). IR spectrum (KBr): 772, 820, 878, 890 (2 adjacent and solitary Ar—H), 928, 1 242, 1 287, **1 694** (ArCOOH), 1 477, 1 588, 1 608 (Ar), 2 680, infl. 3 100 cm^{-1} (COOH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·00 (dd, J_{H-H} = 8·0 Hz, J_{H-F} = 6·0 Hz, 1 H, 6-H), 7·40 (s, 4 H, 4 ArH of chlorophenylthio), 7·10—7·40 (m, 2 H, 3,5-H_2), 4·65 (s, 2 H, $ArCH_2S$). For $C_{14}H_{10}ClFO_2S$ (296·8) calculated: 56·67% C, 3·40 H, 11·95% Cl, 6·40% F, 10·81% S; found: 57·16% C, 3·57% H, 11·77% Cl, 5·97%F, 10·60% S.

4-(4-Chlorophenylthio)-2-(4 chlorophenylthiomethyl)benzoic Acid (*XI*)

A mixture of 5·0 g 5 fluorophthalide[22] and 6·1 g 4 chlorothiophenol was stirred and treated at 100°C slowly with 4·5 g K_2CO_3. It was then stirred for 2·5 h at 100°C. After standing overnight the solidified mixture was dissolved in 50 ml water, filtered with charcoal and the filtrate was acidified with hydrochloric acid. The semisolid product was extracted with chloroform, the extract was dried with $MgSO_4$, evaporated and the residue was crystallized from aqueous methanol; 2·6 g (19%), m.p. 155—162°C. Analytical sample, m.p. 161—162°C (aqueous methanol). UV spectrum: λ_{max} 223 nm (log ε 4·47), 261 nm (4·27), 289 nm (4·18). IR spectrum: 808, 826, 898 (2 adjacent and solitary Ar—H), 921, 1 266, **1 688**, 2 500, 2 630, infl. 3 100 (ArCOOH), 1 478, 1 550, 1 588 cm^{-1} (Ar). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·94 (d, J = 8·0 Hz, 1 H,

6 H), 7·55, 7·39 and 7·31 (d, d and s, 2 + 2 + 4 H, 8 ArH of two chlorophenylthio fragments), 7·25 (t, J = 8·0; 2·0 H, 1 H, 5 H), 7·12 (d, J = 2·0 Hz, 1 H, 3 H), 4·60 (s, 2 H, $ArCH_2S$). For $C_{24}H_{14}Cl_2O_2S_2$ (421·3) calculated: 57·01% C, 3·35% H, 16·83% Cl, 15·21% S; found: 56·89% C, 3·45% H, 16·64% Cl, 14·58% S.

2-Chloro-8-fluorodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*XII*)

A mixture of 21·9 g *X* and 250 g polyphosphoric acid was stirred for 8 h at 150—155°C. After cooling it was decomposed with ice and water and the product was extracted with benzene. The extract was washed with 5% NaOH and water, dried ($MgSO_4$) and evaporated. The residue was crystallized from ethanol; 14·5 g (71%), m.p. 169—172°C. Analytical sample, m.p. 172 to 174°C (acetone). UV spectrum: λ_{max} 250 nm (log ε 4·39), infl. at 270 nm (4·10). IR spectrum: 780, 796, 817, 829, 895 (2 adjacent and solitary Ar—H), 1 495, 1 580, 1 596, 1 608, 3 040, 3 060 (Ar), **1 652** cm^{-1} (ArCOAr'). For $C_{14}H_8ClFOS$ (278·7) calculated: 60·33% C, 2·89% H, 12·72% Cl, 6·82% F, 11·50% S; found: 60·55% C, 2·88% H, 12·90% Cl, 6·98% F, 11·71% S. Crystallization from cyclohexane gave a 2 : 1 solvate with cyclohexane, m.p. 126—130°C. For $C_{14}H_8ClFOS + 1/2\ C_6H_{12}$ (320·8) calculated: 11·05% Cl, 9·99% S; found: 10·96% Cl, 9·64% S.

2-Chloro-8-fluoro-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*IXc*)

Grignard reagent[9] was prepared from 5·0 g 4-chloro-1-methylpiperidine[9] and 0·9 g Mg in 20 ml tetrahydrofuran (initiation with *I* and 1,2-dibromoethane) and it was treated under stirring at room temperature with a solution of 7·0 g *XII* in 50 ml benzene, added dropwise. The mixture was refluxed for 2·5 h and allowed to stand overnight. It was then evaporated *in vacuo*, the residue was decomposed with a solution of NH_4Cl and extracted with benzene. The extract was washed with water, dried (K_2CO_3), filtered through a 3 cm layer of Al_2O_3 and the filtrate was evaporated *in vacuo*; 8·5 g (90%) almost homogeneous oily *IXc* which was used for dehydration in this state. A sample was chromatographed on a column of neutral Al_2O_3 (activity II). The benzene eluate crystallized from a mixture of benzene and light petroleum, m.p. 199—200°C (modification *A*). IR spectrum: 760, 775 (C—Cl), 817, 900 (2 adjacent and solitary Ar—H), 1 107 (R_3C—OH in the ring), 1 493, 1 586, 1 610 (Ar), 2 685, 2 740 (N—CH_3), 3 100 cm^{-1} (OH). ^1H NMR spectrum: δ 7·80 (m, 2 H, 1,3 H_2), 6·70—7·10 (m, 4 H, remaining ArH), 4·56 and 3·80 (ABq, J = 14·0 Hz, 1 + 1 H, $ArCH_2S$), 3·78 (bs, disappears after ^2H_2O, 1 H, OH), 3·30 (bm, 1 H, CH in position 4 of piperidine), 2·27 (s, 3 H, NCH_3). For $C_{20}H_{21}ClFNOS$ (377·9) calculated: 63·57% C, 5·60% H, 9·38% Cl, 5·03% F, 3·71% N, 8·48% S; found: 64·24% C, 5·61% H, 9·69% Cl, 5·20% F, 3·53% N, 7·96% S.

The mother liquor was evaporated and the residue was again crystallized from a mixture of benzene and light petroleum, m.p. 176—178°C (modification *B*). UV spectrum: λ_{max} 265 nm (log ε 3·99), inflexes at 232 nm (4·01), 295 nm (3·24) and 305 nm (3·01). IR spectrum: 730, 770 (C—Cl), 810, 868, 894 (2 adjacent and solitary Ar—H), 1 100, 1 110 (R_3C—OH in the ring), 1 460, 1 470, 1 488, 1 588, 1 608 (Ar), 2 700, 2 760 (N—CH_3), 3 210 cm^{-1} (OH). ^1H NMR spectrum is identical with that of modification *A*. For $C_{20}H_{21}ClFNOS$ (377·9) calculated: 63·57% C, 5·60% H, 9·38% Cl, 5·03% F, 3·71% N, 8·48% S; found: 63·78% C, 5·47% H, 9·21% Cl, 4·58% F, 3·52% N, 8·17% S.

2-Chloro-8-fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IVc*)

A mixture of 8·5 g crude *IXc*, 85 ml acetic acid and 25 ml acetyl chloride was stirred and heated for 3 h to 100°C. After standing overnight it was diluted with water, made alkaline with NH_4OH and extracted with dichloromethane. The extract was dried with K_2CO_3 and evaporated. The dark

residue was dissolved in benzene and chromatographed on a column of 250 g neutral Al_2O_3 (activity II). Benzene eluted 3·4 g (42%) homogeneous oily base *IVc* which was neutralized with 1·2 g maleic acid in ethanol and gave 4·0 g hydrogen maleate, m.p. 172—175°C (ethanol–ether). For $C_{24}H_{23}ClFNO_4S$ (476·0) calculated: 60·56% C, 4·87% H, 7·45% Cl, 3·99% F, 2·94% N, 6·74% S; found: 60·64% C, 4·94% H, 7·77% Cl, 3·78% F, 3·01% N, 6·81% S.

A sample of the maleate was decomposed with NH_4OH and the pure base was isolated by extraction with ether. ^{1}H NMR spectrum: δ 6·70—7·30 (m, 6 H, ArH), 4·80 and 3·28 (ABq, J = = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·00—2·70 (m, 8 H, 4 CH_2 of piperidine), 2·20 (s, 3 H, NCH_3).

The authors are indebted to Mr. V. Kmoníček and Mr M. Trampota for the preparation of intermediates and samples for pharmacological testing, to Drs J. Holubek, E. Svátek, M. Ryska and Mrs A. Hrádková (Physico-chemical department of this institute) for recording and interpretation of the spectra, to Dr J. Metyšová (Pharmacological department), Dr S. Wildt (Pharmacological screening) and Drs J. Turinová and V. Holá (Microbiological department) for the pharmacological and microbiological data, and finally to Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, Dr Z. Volková and Mr M. Čech (Analytical department) for carrying out the analyses.

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Translated by the author (M. P.).