BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. IV.*

AMINES DERIVED FROM 4-PHENYL-8-CHLORO-2,3,4,5-TETRAHYDRO-1-BENZOXEPIN

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2-Phenyl-4-(3-chlorophenoxy)butyric acid (*V*) is cyclized in the presence of polyphosphoric acid to 4-phenyl-8-chloro-4*H*-2,3-dihydro-1-benzoxepin-5-one (*VI*) from which four approaches were used to obtain various amines: *1. via* the oxime *VII* and its aminoalkylation (*VIII* as the product); *2.* by reduction both stereoisomeric alcohols *Xa* and *Xb* were prepared which were then converted to 2-dimethylaminoethyl ethers (*XIa*, *XIb*); *3. via* the olefin *XII*, the dibromide *XIII* and reaction with amines — dehydrobromination took then place and a substitution reaction connected with allyl rearrangement, giving rise to amines *XIV* and *XV*; *4.* reaction with 3-dimethylaminopropylmagnesium chloride and subsequent transformation of the product yielded amines *IX* and *XVI*—*XVIII*. The pharmacodynamic effects of the compounds are weak; amines *IX*, *XIa* and *XIb* showed anticonvulsant activity in the pentetrazol test.

While the basically substituted derivatives of dibenz[*b,f*]oxepin of type *I* (particularly if R is a substituted piperazino group) showed a high degree of central depressant and neuroleptic activity[1], the monobenzoanalogues of type *II* were rather uninteresting in this respect[2]. The attaining a higher degree of central neurotropic activity apparently requires the presence of both aromatic rings in the molecule of this type of compound[3]. For this reason, in the present study we are dealing with type *III*, *i.e.* derivatives of 4-phenyl-1-benzoxepin.

Similarly to our previous study on the derivatives of 1-benzoxepin[2], we used here 3-chlorophenol as the starting compound[4] which reacted with sodium hydroxide and 2-phenyl-4-butyrolactone[5,6] (*IV*) at 160°C to produce 2-phenyl-4-(3-chlorophenoxy)butyric acid (*V*). Its reaction with polyphosphoric acid at 130°C gives rise satisfactorily to 4-phenyl-8-chloro-4*H*-2,3-dihydro-1-benzoxepin-5-one (*VI*) (*cf.* the completely negative results of a similar experiment in the series of carba-analogues[7]). Only in a small extent the cleavage of the ether bond took place and 2-phenylbutyrolactone (*IV*) was formed. The ketone *VI* yields the oxime *VII* in the usual way. This oxime reacts with sodium ethoxide and 2-dimethylaminoethyl chloride to the cor-

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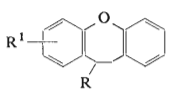
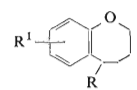
responding O-(2-dimethylaminoethyl) derivative *VIII*, the structure of which was confirmed by its IR spectrum.

Reduction of ketone *VI* with sodium borohydride in ethanol gives rise to a mixture of stereoisomeric alcohols *X* which was separated by chromatography on alumina or by crystallization. Using NMR spectra, the higher melting product (fragment $R^1R^2CH—CHR^3R^4$ in the cycle is characterized by a doublet at 5·00 p.p.m., J = = 9·0 Hz) was identified as the *trans*-isomer *Xa* while the lower melting one (singlet at 4·68 p.p.m.) is the *cis*-isomer *Xb*. In an experiment in a different context the *cis*-isomer *Xb* was isomerized to the *trans*-isomer *Xa*. The alcohol *Xb* was treated in pyridine with methanesulfonyl chloride and then with 1-methylpiperazine. The intended nucleophilic substitution did not take place at all and hydrolysis of the reaction mixture, *i.e.* of the methanesulfonic ester of alcohol *Xb*, gave rise to alcohol *Xa*. Reaction of alcohols *Xa* and *Xb* with sodium amide and 2-dimethylaminoethyl chloride in benzene yielded the corresponding 2-dimethylaminoethyl ethers *XIa* and *XIb*. In view of the fact that a contamination of these products with the stereoisomer



I



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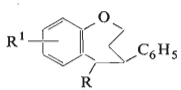
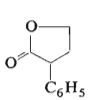
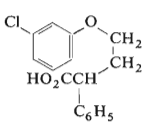


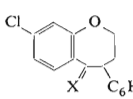
III



IV

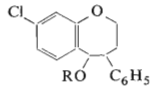


V

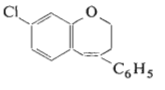


VI, X = O
VII, X = NOH
VIII, X = $NO(CH_2)_2N(CH_3)_2$
IX, X = $CH(CH_2)_2N(CH_3)_2$

was possible, this being possibly due to a partial inversion at the centre in position 4 in the presence of sodium amide[8], the two products were purified by a partial crystallization of the picrates and the melting points of the hydrochlorides prepared from pure picrates were compared with those of hydrochlorides prepared from crude bases. While in the *trans*-series (*XIa*) a completely homogeneous product was formed (the crude hydrochloride has the same melting point as the hydrochloride after purification *via* picrate), in the *cis*-series (*XIb*) apparently the above centre was partly attacked and an inhomogeneous product was formed which was manifested by a considerable increase of the melting point of the hydrochloride after purifying the product by picrate crystallization.



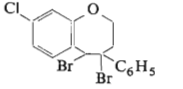
Xa, *Xb*, R = H
XIa, *XIb*, R = $CH_2CH_2N(CH_3)_2$



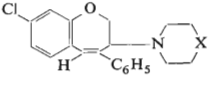
XII

When the alcohols *Xa* and *Xb* were treated with hydrogen chloride in benzene at room temperature the same product was formed in both cases and was identified as 4-phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XII*). This olefinic derivative adds a molecule of bromine giving rise to the dibromide *XIII* which was subjected to a reaction with 1-methylpiperazine in boiling benzene. A bromine-free basic product was obtained, which yielded a stable dihydrochloride. This fact excluded the possibility of formulating the product as an enamine. The NMR spectrum then identified the product as the base *XIV* which was formed by dehydrobromination to the 5-bromo-3(4)-dehydro compound which, in a further step, reacted with methylpiperazine in a substitution reaction accompanied by an allylic rearrangement. Reaction of the dibromide *XIII* with piperidine resulted in a similar base which, by analogy, should have the structure of *XV*. In both cases an important neutral by-product was the olefin *XII*.

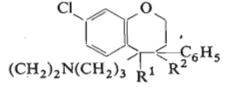
Reaction of the ketone *VI* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gives rise to the desired tertiary alcohol *XVI*. In this case, too, there is the possibility of formation of two stereoisomers but only one was isolated in the crystalline state. Chromatography of the mother liquors yielded another product but it corresponded to the empirical formula of $C_{26}H_{37}ClN_2O_2$. Its molecule apparently contains two dimethylaminopropyl residues which leads to the formulation of the product as the diamine *XVII*. Grignard's reagent which was used in considerable excess apparently contains a part of the nonreacted 3-dimethylaminopropyl chloride which has an alkylating effect. Formation of the required carbonium anion at the carbon in position 4 was accomplished by the Grignard reagent. Dehydration of alcohol *XVI* by heating with 3N-H_2SO_4 resulted in an oily olefinic base which, on the basis of its UV spectrum, has the structure of *IX* with an exocyclic double bond (*cf.* the spectrum of *XII*). Reduction of alcohol *XVI* with hydroiodic acid gave rise to a saturated amine *XVIII* the configuration of which has not been examined.



XIII



XIV, X = NCH_3
XV, X = CH_2



XVI, R^1 = OH, R^2 = H
XVII, R^1 = OH, R^2 = $(CH_2)_3N(CH_3)_2$
XVIII, $R^1 = R^2$ = H

The following compounds were tested pharmacologically, using intravenous (or intraperitoneal) administration with the particular aim of assumed neurotropic and psychotropic effects and in a wider spectrum of tests of general screening (values of acute toxicity to mice LD_{50} in mg/kg are shown): *IX*-hydrogen maleate (36), *XIa*-HCl—H_2O (47), *XIb*-HCl (32), *XVI*-hydrogen maleate (35), *XVII*-2 HCl—C_2H_6O (25).

Compounds *IX*, *XIa* and *XIb* are inactive as central depressants (the rotating-rod test and potentiation of thiopental narcosis in mice), do not affect the reserpine ptosis of mice in a dose of 10 mg/kg (*i.p.*), they are inactive as antiserotonins in the *in vivo* test in rats and inactive as antihistamines in the aerosol test in guinea-pigs at a dose of 5 mg/kg (*i.p.*). Compound *IX* is inactive in the catalepsy test in rats while *XIa* and *XIb* at a dose of 10 mg/kg (*i.p.*) bring about a sign of the cataleptic state. All the three compounds have anticonvulsant effect in mice in the pentetrazol test (with compound *XIa* the mean effective dose ED_{50} is 5 mg/kg). Compound *XVI* at a dose of 7 mg/kg *i.v.* showed only a slight adrenolytic effect on rats. Compound *XVII* at a dose of 5 mg/kg *i.v.* brings about a mild and protracted rise of blood pressure in rats and has a pronounced diuretic effect in mice. Compounds *IX* and *XIa* at concentrations of 25—100 μg/ml were bacteriostatic *in vitro* agaist *Streptococcus β-haemolyticus*, *Staphylococcus pyogenes aureus* and *Mycobacterium tuberculosis* H37Rv.

In general, one may state a complete dissimilarity between the pharmacodynamic effects of compounds of type *III* and the neurotropically highly active tricyclic compounds of type *I*. It appears that for obtaining this high degree of activity it is necessary that both aromatic rings are included in the tricyclic system.

EXPERIMENTAL

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

2-Phenyl-4-(3-chlorophenoxy)butyric Acid (*V*)

Reaction of 26·3 g 3-chlorophenol[4] with 8·2 g sodium hydroxide in boiling 1-butanol yielded the corresponding phenoxide solution from which the solvent was removed by distillation at 150°C. At this temperature, 33·2 g 2-phenyl-4-butyrolactone (*IV*) (b.p. 138—140°C/0·6 Torr)[5,6] was added and the mixture was heated for 4 h under a reflux condenser at 160°C. After cooling it was dissolved in 200 ml water and the volatile fractions were removed by steam-distillation, the remaining aqueous solution was filtered with charcoal and made acid with hydrochloric acid. On the following day it was filtered to yield 43 g of a crude product which was crystallized from aqueous ethanol; m.p. 115—116°C. For $C_{16}H_{15}ClO_3$ (290·7) calculated: 66·09% C, 5·20% H, 12·20% Cl; found: 66·17% C, 5·20% H, 12·23% Cl.

4-Phenyl-8-chloro-4*H*-2,3-dihydro-1-benzoxepin-5-one (*VI*)

Polyphosphoric acid was prepared in the usual way from 318 g phosphorus pentoxide and 182 ml phosphoric acid. Then at 130°C 91 g acid *V* was added and the mixture was maintained at that temperature under stirring for 2 h. After partial cooling it was decomposed by pouring into 2 kg of a mixture of ice and water and the oily product was isolated by extraction with benzene. The extract was washed with 15% sodium carbonate and water, dried with $MgSO_4$ and evaporated. The residue after mixing with light petroleum and standing in the refrigerator overnight partly

crystallized. 43·5 g (53%), m.p. 92—94°C (benzene–light petroleum). UV spectrum: λ_{max} 217 nm (log ε 4·44), 256 nm (4·17), 302 nm (3·53); IR spectrum: 703, 734 (C_6H_5), 820, 889 (1,2,4-C_6H_3), 1198 (Ar—O—R), 1598 (Ar), 1695 cm^{-1} (CO conjug.). For $C_{16}H_{13}ClO_2$ (272·4) calculated: 70·46% C, 4·80% H, 13·00% Cl; found: 70·89% C, 4·88% H, 12·89% Cl.

Oxime VII, m.p. 152°C (aqueous ethanol). UV spectrum: λ_{max} 214 nm (log ε 4·45), 246 nm (4·03), 290 nm (3·48). IR spectrum: 700, 724, 740 (C_6H_5), 809, 821, 869 (1,2,4-C_6H_3), 1011, 1219 (Ar—O—R), 1563 (Ar), 1600 (C=N), 3270 cm^{-1} (OH). For $C_{16}H_{14}ClNO_2$ (287·8) calculated: 66·79% C, 4·90% H, 12·32% Cl, 4·87% N; found: 66·49% C, 5·05% H, 12·58% Cl, 5·06% N.

Distillation of the mother liquor after crystalline ketone *VI* yielded 15 g of a fraction boiling at 150—170°C/1·2 Torr. This fraction was dissolved in benzene and chromatographed on a column of 130 g alumina (activity II). Redistillation of the eluate yielded 9·0 g of a product boiling at 135—140°C/0·6 Torr, which was identified as *IV*. IR spectrum: 700 and 756 (C_6H_5), 1027 and 1154 (C—O—C), 1500 and 1604 (Ar), 1772 cm^{-1} (five-membered lactone). For $C_{10}H_{10}O_2$ (162·2) calculated: 74·05% C, 6·22% H; found: 74·27% C, 6·00% H.

4-Phenyl-5-[O-(2-dimethylaminoethyl)]oximino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*VIII*)

Oxime *VII* (3·5 g) was added to a solution of 1·7 g sodium in 20 ml ethanol and after refluxing for 20 min a solution of 2·1 g 2-dimethylaminoethyl chloride hydrochloride in 11 ml ethanol was added. The mixture was refluxed for 4 h, the ethanol was then evaporated and the residue separated between benzene and water. The benzene solution was dried and evaporated and the residue was mixed with 10 ml cyclohexane and 15 ml light petroleum to precipitate 1·1 g nonreacted oxime *VII* (m.p. 151°C). The filtrate was again evaporated and the residue dissolved in 10% hydrochloric acid. The insoluble residue was removed by extraction with benzene, the acid-aqueous solution was made alkaline with 10% sodium hydroxide and the base was isolated by extraction with benzene; 0·8 g oil. By means of an ethereal solution of hydrogen chloride it yielded a hydrochloride which crystallized from a mixture of ethanol and ether as a hemihydrate; m.p. 155—158°C. UV spectrum: λ_{max} 251 nm (log ε 4·05), 290 nm (3·60); IR spectrum: 700, 720, 750 (C_6H_5), 819, 830, 894 (1,2,4-C_6H_3), 1032, 1043, 1061 (Ar—O—R), 1596 (C=N), 2430 and 2560 (N···HCl), 3400, 3470 cm^{-1} (H_2O). For $C_{20}H_{24}Cl_2N_2O_2.1/2\,H_2O$ (404·4) calculated: 59·41% C, 6·23% H, 17·54% Cl, 6·93% N; found: 59·73% C, 6·23% H, 18·18% Cl, 6·85% N.

trans- and *cis*-4-Phenyl-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*Xa*, *Xb*)

A) *Using chromatographic separation*: Sodium borohydride (1·0 g) was added to a solution of 6·25 g ketone *VI* in 50 ml ethanol and the mixture was refluxed for 30 min. Ethanol was then evaporated and the residue separated between water and chloroform. By evaporating the chloroform solution a total of 6·25 g of a mixture of alcohols *X* was obtained. The mixture was dissolved in benzene and chromatographed on 180 g alumina (activity II). By elution with benzene a total of 0·5 g homogeneous substance melting at 109·5—110·5°C light petroleum was obtained. According to its NMR spectrum we are dealing here with the *trans*-isomer *Xa*: δ 5·00 (doublet, 2 H *trans* $R^1R^2CH—CHR^3R^4$ in the ring, J = 9·0 Hz). IR spectrum: 702, 708 and 753 (C_6H_5), 810, 882 (1,2,4-C_6H_3), 1043 (Ar—O—R), 1568 and 1595 (Ar), 3390 and 3538 cm^{-1} (OH). For $C_{16}H_{15}ClO_2$ (274·8) calculated: 69·94% C, 5·50% H, 12·90% Cl; found: 70·16% C, 5·49% H, 13·04% Cl.

By continuing with the chromatography and applying elution with ether a total of 1·g g of a homogeneous substance melting at 75·5°C (cyclohexane–light petroleum) was obtained. According

to the NMR spectrum the substance represents the *cis*-isomer *Xb*: ϑ 4·68 (singlet, 2 H in *cis*-$R^1R^2CH{-}CHR^3R^4$ in the ring). UV spectrum: λ_{max} 215·5 nm (log ε 4·17), 225 nm (4·05), 273 nm (3·09), 278 nm (3·10); IR spectrum: 700, 743 and 749 (C_6H_5), 832, 854 and 876 (1,2,4-C_6H_3), 1076 and 1213 (Ar—O—R), 1567 and 1595 (Ar), 3484 cm^{-1} (OH). For $C_{16}H_{15}ClO_2$ (274·8) calculated: 69·94% C, 5·50% H, 12·90% Cl; found: 70·10% C, 5·57% H, 13·04% Cl.

B) *Using separation of isomers by crystallization*: Similarly to the preceding case, reduction of 43·4 g ketone *VI* yielded 43·4 g (almost the theoretical yield) of a mixture of stereoisomeric alcohols *X*. The mixture was dissolved in 50 ml cyclohexane and 10 ml light petroleum was added. A total of 11·1 g compound precipitated which was twice crystallized from cyclohexane to 8·8 g (20%) pure *trans*-isomer *Xa*, m.p. 108·5—110°C. The combined mother liquors were mixed with further light petroleum whereby a pure *cis*-isomer *Xb* crystallized in a yield of 37·7 g (61%), m.p. 67·5—70°C. Two further crystallizations from a mixture of cyclohexane and light petroleum resulted in a pure compound, m.p. 75·5°C.

C) *Conversion of the* cis-*isomer* Xb *to the* trans-*isomer* Xa: Methanesulfonyl chloride (1·3 g) was added under cooling to a solution of 3·0 g alcohol *Xb* in 10 ml pyridine, the mixture was left to stand for an hour at room temperature and then 5 ml 1-methylpiperazine were added. The mixture was briefly (10 min) heated on a water bath and left overnight at room temperature. Then it was diluted with 200 ml water and extracted with benzene and chloroform. The combined organic phases were then washed with water and 10% hydrochloric acid, dried and evaporated. A total of 2·85 g oily neutral product was obtained which yielded the *trans*-alcohol *Xa* after mixing with light petroleum; m.p. 108·5—109·5°C (cyclohexane). UV spectrum: λ_{max} 216 nm (inflex) (log ε 4·23), inflex 224·5 nm (4·13). The IR spectrum is identical with the spectrum of the product prepared according to *A*. From the mother liquor there were regenerated 0·9 g of the starting *cis*-alcohol, m.p. 69·5—76°C (light petroleum).

trans-4-Phenyl-5-(2-dimethylaminoethoxy)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIa*)

Alcohol *Xa* (5·65 g) was added to a suspension of 1·5 g sodium amide in 30 ml benzene and after 30 min of stirring this was followed by 2·75 g 2-dimethylaminoethyl chloride. The mixture was refluxed under stirring for 8 h. After cooling it was decomposed with water, the benzene layer was washed with water, dried with $MgSO_4$ and evaporated. An almost theoretical yield (7·0 g) of a crude base was obtained; this was treated with hydrogen chloride in ether to produce 5·8 g hydrochloride, m.p. 189—191°C. Recrystallization from ethanol–ether led to the analytical product which was identified as the monohydrate, m.p. 194°C. UV spectrum: λ_{max} 221 nm (log ε 4·11); IR spectrum: 707 and 759 (C_6H_5), 839 and 890 (1,2,4-C_6H_3), 1036, 1057 and 1108 (Ar—O—R), 1566 and 1580 (Ar), 2480, 2515 and 2620 (N···HCl), 3415 cm^{-1} (H_2O). For $C_{20}H_{27}Cl_2NO_3$ (400·4) calculated: 60·00% C, 6·79% H, 17·71% Cl, 3·50% N; found: 59·95% C, 6·71% H, 17·33% Cl, 3·45% N. A part of the product was converted to the picrate in the usual way; this, after two crystallizations from a mixture of acetone and ethanol melts, with a constant m.p. of 168—171°C. For $C_{26}H_{27}ClN_4O_9$ (575·0) calculated: 54·31% C, 4·73% H, 6·17% Cl, 9·75% N; found: 54·46% C, 4·88% H, 6·36% Cl, 9·77% N. This picrate was decomposed to a base from which a hydrochloride was prepared, m.p. 190—193°C (ethanol–ether).

cis-4-Phenyl-5-(2-dimethylaminoethoxy)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIb*)

Similarly to the preceding case, reaction of 11·5 g alcohol *Xb* with 3·0 g sodium amide and 5·5 g 2-dimethylaminoethyl chloride in 60 ml benzene yielded 14·5 g crude base which yielded with an ether solution of hydrogen chloride 11·4 g (72%) hydrochloride with an unsharp m.p. 202 to

206°C (it softens from 184°C up). The whole amount of the product was converted in the usual way to picrate which after repeated crystallization from a mixture of ethanol and acetone melts at 172—174°C. In a mixture with picrate of the base *XIa* it melts with a depression of 10°C. For $C_{26}H_{27}ClN_4O_9$ (575·0) calculated: 54·31% C, 4·73% H, 6·17% Cl, 9·75% N; found: 54·30% C, 4·80% H, 6·22% Cl, 9·67% N. By decomposition of the picrate one obtains a base which yields a hydrochloride, melting sharply after crystallization from a mixture of ethanol and ether at 218—219°C. For $C_{20}H_{25}Cl_2NO_2$ (382·3) calculated: 62·83% C, 6·59% H, 18·55% Cl, 3·66% N; found: 63·17% C, 6·72% H, 18·78% Cl, 3·68% N.

4-Phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XII*)

A) *From* cis-*alcohol* Xb: Anhydrous calcium chloride (8·7 g) was suspended in a solution of alcohol *Xb* in 75 ml benzene and the suspension was saturated for 3·5 h with anhydrous hydrogen chloride at room temperature. After standing overnight it was filtered and the filtrate was gently evaporated at reduced pressure. The residue crystallized on standing: 9·3 g (100%), m.p. 68·5 to 70·5°C (cyclohexane–light petroleum). UV spectrum: λ_{max} 231 nm (log ε 4·21), 293 nm (4·47); IR spectrum: 696, 723 and 750 (C_6H_5), 804 (1,2,4-C_6H_4), 1 092, (Ar—O—R), 1 557, 1 561 and 1 591 cm^{-1} (Ar). NMR spectrum: δ 3·01 (triplet, 2 H in =C—CH_2), 4·30 (triplet, 2 H in —O—CH_2—), 6·54 (singlet, 1 H in —CH=C—), 6·75—7·40 (multiplet, 8 H of the aromatic protons, from this a singlet at 7·35 corresponding to unsubstituted phenyl). For $C_{16}H_{13}ClO$ (256·7) calculated: 74·85% C, 5·10% H, 13·81% Cl; found: 74·81% C, 4·96% H, 13·96% Cl.

B) *From* trans-*alcohol* Xa: Similarly to the preceding case, 9·1 g alcohol *Xa* yielded practically the theoretical amount of the olefinic derivative *XII* (8·5 g) melting at 68·5° (light petroleum). The product was identical with that of the preceding experiment and showed no depression of the melting point when mixed with it.

4-Phenyl-4,5-dibromo-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XIII*)

A solution of 16·7 g bromine in 30 ml chloroform was added dropwise under stirring to a solution of 26·75 g olefine *XII* in 300 ml ether and the mixture was stirred for 2 h at room temperature. By filtering the crystalline product and by processing the mother liquor a total of 34·0 g (78%) product melting at 150—152°C was obtained (benzene–light petroleum). NMR spectrum: δ 3·35—4·25 (multiplet, 2 H in CBr—CH_2), 4·25—4·90 (multiplet, 2 H in —OCH_2—), 5·68 (singlet, 1 H in Ar—CHBr), 6·95—7·90 (multiplet, 8 H, aromatic protons). For $C_{16}H_{13}Br_2ClO$ (416·6) calculated: 46·13% C, 3·15% H, 38·37% Br, 8·51% Cl; found: 46·28% C, 3·12% H, 38·08% Br, 8·93% Cl.

3-(4-Methylpiperazino)-4-phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XIV*)

A mixture of 20·0 g dibromide *XIII*, 60 ml benzene and 23·0 g 1-methylpiperazine was refluxed for 1 h. After cooling, it was diluted with 100 ml benzene and washed several times with water, the benzene solution was dried with solid potassium hydroxide and benzene was evaporated. A total of 14·3 g crude product was obtained and this was dissolved in ether and treated with an ether solution of hydrogen chloride to obtain the hygroscopic dihydrochloride: 4·35 g (20%), m.p. 146—157°C (ethanol–acetone–ether). According to analysis it is a dihydrate. UV spectrum: λ_{max} 225·5 nm (log ε 4·29), 290 nm (4·13), 310 nm (4·04); IR spectrum: 701 and 759 (C_6H_5), 817 and 900 (1,2,4-C_6H_3), 1 600 (Ar), 2 340 and 2 420 (N···HCl), 3 430 and 3 520 cm^{-1} (H_2O). For $C_{21}H_{29}Cl_3N_2O_3$ (463·9) calculated: 54·38% C, 6·30% H, 22·93% Cl, 6·04% N; found: 54·47% C, 6·15% H, 23·08% Cl, 6·08% N.

The hydrochloride yielded in the usual way the oily base whose NMR spectrum was recorded: δ 2·16 (singlet, 3 H in NCH_3), 2·20—2·90 (8 H multiplet, CH_2 groups of the piperazine ring), 3·80—4·20 (multiplet, 2 H in —OCH_2—), 4·60—4·90 (twin doublet, 1 H in =CCH), 6·65—7·75 (multiplet, 9 H, aromatic protons and the olefinic proton). The ether mother liquor after filtration of the hydrochloride was evaporated to obtain an appreciable amount (8·6 g) of a neutral by-product which was identified as olefin *XII*, m.p. 66—67°C.

3-Piperidino-4-phenyl-8-chloro-2,3-dihydro-1-benzoxepin (*XV*)

Similarly to the preceding case, the dibromide *XIII* (4·16 g) reacted with 10 ml piperidine in 12 ml benzene. After diluting the reaction mixture with 100 ml benzene it was washed with water and shaken with 10% hydrochloric acid. The precipitated hydrochloride was filtered and combined with the acid aqueous solution, treatment with sodium hydroxide liberated the base which was extracted with benzene. After evaporation of the extract the base was converted by means of the ether solution of hydrogen chloride to the hydrochloride, m.p. 220—223°C (ethanol–ether–acetone). It is a solvate containing one-half of an ethanol molecule. UV spectrum: λ_{max} 226 nm (log ε 4·28), 290 nm (4·35), 311 nm (4·24); IR spectrum: 703 and 757 (C_6H_5), 820 and 898 (1,2,4-C_6H_3), 1090 (Ar—O—R), 1559 and 1593 (Ar), 2480 cm^{-1} (N···HCl). For $C_{21}H_{23}Cl_2NO.1/2\,C_2H_6O$ (399·4) calculated: 66·16% C, 6·56% H, 17·76% Cl; found: 66·13% C, 6·65% H, 17·50% Cl.

The benzene layer after extraction with hydrochloric acid yielded on evaporation 1·5 g olefin *XII*, m.p. 68·5—70°C (light petroleum).

4-Phenyl-5-(3-dimethylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XVI*)

A solution of 26·5 g ketone *VI* in 80 ml tetrahydrofuran was added dropwise to a solution of Grignard's reagent prepared from 4·7 g magnesium and 23·8 g 3-dimethylaminopropyl chloride in 60 ml tetrahydrofuran (initiated with iodine and 0·5 g ethyl bromide) and the mixture was refluxed for 4 h. After cooling it was decomposed with a saturated solution of ammonium chloride and extracted with chloroform. The organic layer was evaporated, the residue dissolved in 250 ml benzene, the solution washed with water and shaken with excess 10% hydrochloric acid. Upon standing of the acid aqueous solution obtained, a total of 15·7 g hydrochloride (monohydrate) precipitated; this was recrystallized from a mixture of ethanol and ether and then melted at 237—240°C. For $C_{21}H_{29}Cl_2NO_3$ (414·4) calculated: 60·87% C, 7·05% H, 17·11% Cl, 3·38% N; found: 61·35% C, 6·97% H, 17·36% Cl, 3·42% N.

Decomposition of the hydrochloride with 20% sodium hydroxide and extraction with ether yielded a base melting at 93·5—94·5°C (light petroleum). UV spectrum: λ_{max} 223·5 nm (log ε 4·03), 269 nm (3·02), 277 nm (3·00); IR spectrum: 699 and 754 (C_6H_5), 834 and 874 (1,2,4-C_6H_3), 1028, 1202 (Ar—O—R), 1561 and 1591 (Ar), 3120 cm^{-1} (OH). For $C_{21}H_{26}ClNO_2$ (359·9) calculated: 70·08% C, 7·28% H, 9·85% Cl, 3·89% N; found: 69·99% C, 7·15% H, 9·99% Cl, 3·85% N.

Hydrogen maleate, m.p. 147—148°C (ethanol–ether). For $C_{25}H_{30}ClNO_6$ (476·0) calculated: 63·09% C, 6·35% H, 7·45% Cl, 2·94% N; found: 63·00% C, 6·47% H, 7·54% Cl, 2·96% N. Treatment of the benzene solution from which the basic product was extracted with dilute hydrochloric acid, recovered 4·5 g ketone *VI*, m.p. 91—92°C (ethanol).

4-Phenyl-4,5-bis(3-dimethylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (*XVII*)

The acid aqueous filtrate after crystallization of the hydrochloride from the preceding experiment was made alkaline with 20% sodium hydroxide and the released base was extracted with

benzene; 21·5 g oily mixture of basic compounds. The mixture was chromatographed on a column of 600 g alumina (activity II) using consecutive elution with light petroleum, benzene, ether and finally ethanol. The combined most polar fractions gave on treatment with an ether solution of hydrogen chloride 6·0 g homogeneous dihydrochloride, m.p. 161—164°C (ethanol–acetone–water), which was shown to be a solvate with one molecule of ethanol. For $C_{28}H_{45}Cl_3N_2O_3$ (564·1) calculated: 59·62% C, 7·99% H, 18·86% Cl, 4·97% N; found: 59·26% C, 8·18% H, 19·46% Cl, 5·22% N.

The base was liberated from the hydrochloride in the usual way and isolated by extraction with ether; m.p. 119—121°C (ether–light petroleum); UV spectrum: λ_{max} 220 nm (log ε 4·25); IR spectrum: 700 and 758 (C_6H_5), 829 and 878 (1,2,4-C_6H_3), 1066 (Ar—O—R), 1557, 1590 and 1601 (Ar), 3160 cm^{-1} (OH). For $C_{26}H_{37}ClN_2O_2$ (445·1) calculated: 70·17% C, 8·38% H, 7·97% Cl, 6·29% N; found: 69·80% C, 8·82% H, 7·95% Cl, 6·18% N.

Dipicrate, m.p. 213—215°C (aqueous acetone). For $C_{38}H_{43}ClN_8O_{16}$ (903·3) calculated: 50·53% C, 4·80% H, 3·92% Cl, 12·41% N; found: 50·44% C, 5·02% H, 4·23% Cl, 12·34% N.

4-Phenyl-5-(3-dimethylaminopropylidene)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*I X*)

A solution of 4·9 g base *XVI* in 80 ml 3N-H_2SO_4 was refluxed for 4 h (bath at 150°C). After cooling, it was made alkaline with 20% sodium hydroxide and extracted with ether. Drying the extract with K_2CO_3, evaporating the ether and distilling the residue yielded 4·25 g (92%) oily base boiling at 170°C/0·9 Torr. The UV spectrum indicates an exocyclic double bond: λ_{max} 250·5 nm (log ε 4·12). IR spectrum: 701 and 763 (C_6H_5), 822 and 877 (1,2,4-C_6H_3), 1046, 1217 (Ar—O—R), 1559 and 1593 cm^{-1} (Ar). For $C_{21}H_{24}ClNO$ (341·9) calculated: 73·77% C, 7·08% H, 10·37% Cl, 4·10% N; found: 73·80% C, 7·16% H, 10·23% Cl, 4·02% N. *Hydrochloride hemihydrate*, m.p. 151—154°C (acetone–ether). For $C_{21}H_{25}Cl_2NO.1/2\,H_2O$ (387·4) calculated: 65·12% C, 6·77% H, 18·31% Cl, 3·61% N; found: 64·92% C, 6·65% H, 18·42% Cl, 3·61% N. *Hydrogen maleate*, m.p. 179·5—181°C (acetone–ether). For $C_{25}H_{28}ClNO_5$ (458·0) calculated: 65·57% C, 6·16% H, 7·74% Cl, 3·06% N; found: 65·50% C, 6·20% H, 7·97% Cl, 2·98% N.

4-Phenyl-5-(3-dimethylaminopropyl)-8-chloro-2,3,4,5-tetrahydro-1-benzoxepin (*XVIII*)

Alcohol *XVI* (4·6 g) was added to a mixture of 15 ml 56% hydroiodic acid (decolourized by heating with 3·5 g sodium hypophosphite) and 12·5 ml acetic acid and the mixture was refluxed under stirring for 4 h at 130—140°C. After cooling it was diluted with water, made alkaline with 50% sodium hydroxide and extracted with benzene. The benzene solution was extracted with excess 15% hydrochloric acid, the acid aqueous solution was again made alkaline and the base was isolated by extraction with ether. Distillation yielded 2·1 g (48%) product boiling at 180—200°C/1 Torr. Neutralization of the distillate with 0·7 g maleic acid in a mixture of 50 ml ether and 15 ml acetone yielded 0·9 g hydrogen maleate, m.p. 162—165°C (acetone–ether). For $C_{25}H_{30}ClNO_5$ (460·0) calculated: 65·28% C, 6·57% H, 7·71% Cl, 3·04% N; found: 65·21% C, 6·30% H, 7·88% Cl, 3·09% N.

Pharmacological evaluation of compounds IX, XIa *and* XIb *for neurotropic effects was done by Dr J. Metyšová and Dr J. Metyš at the pharmacological department of this Institute. Compounds* XVI *and* XVII *were subjected to pharmacological screening in the unit of this institute at Rosice n./L. under the direction of Dr F. Hradil and Dr J. Němec. The antimicrobial activity was examined by Dr J. Turinová at the bacteriological department of this Institute (headed by Dr A. Šimek). The analytical estimations were done at the analytical department (headed by Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs A. Slavíková. Mrs M. Hrubantová assisted with the preparatory part.*

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