BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. X.*

DERIVATIVES OF 2-AMINO AND 2-HYDROXY--6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENE

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Hydrolysis of 2-acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*) yielded the aniline analogue *II* which was then converted to phenol *III*. From this compound and from dimethylaminoalkyl chlorides, the basic ethers *IV* and *V* were prepared. Reaction of phenol *III* with epichlorhydrin and reaction of the product *VI* with isopropylamine yielded the 3-isopropylamino--2-hydroxypropyl ether *VII*. Sandmeyer's reaction starting from aniline *II* yielded the bromo derivative *VIII*. Heating of the hydrochlorides of amine *II* and of diethanolamine led to 2-piperazino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IX*) which underwent alkylation, addition and acylation reactions to the 1,4-disubstituted piperazines *X*—*XVI*. The products were found to possess central depressant (*X*), excitatory and antireserpine (*XII*), anticonvulsant (*X*—*XII*, *XIV*, *XV*), antiarrhythmic (*IX*, *X*, *XIII*) and negatively inotropic and chronotropic effects (*IV*, *V*, *IX*, *XIII*). Compound *VII* showed no β-adrenolytic activity.

When continuing with the systematic pharmacochemical studies in the group of benzocycloheptene derivatives we proceeded here from 2-acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[1] (*I*). Its acid hydrolysis yielded the novel 2-amino--6,7,8,9-tetrahydro-5*H*-benzocycloheptene(*II*) which was diazotized and the diazonium salt decomposed to 2-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene(*III*) which had been described before but prepared by different methods[2-5]. Amine *II* and phenol *III* represent the basis of the present study.

Reaction of phenol *III* with an equivalent of sodium ethoxide in ethanol yielded a solution of phenoxide which reacted with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride to the aminoethers *IV* and *V*. Reaction of phenol *III* with epichlorhydrin in an aqueous solution of sodium hydroxide yielded the epoxypropyl ether *VI*, which was treated with isopropylamine in a mixture of ethanol and ether at room temperature to yield the aminoether *VII*, a structural analogue of the well-known β-adrenolytic "propranolol"[6].

The Sandmeyer reaction of the diazonium salt prepared from amine *II* resulted in a poor yield of 2-bromo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VIII*). Heating

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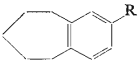
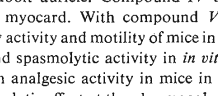


I, R = $NHCOCH_3$
II, R = NH_2
III, R = OH
IV, R = $O(CH_2)_2N(CH_3)_2$
V, R = $O(CH_2)_3N(CH_3)_2$

VI, R = $OCH_2CH{-}CH_2$ (O)
VII, R = $OCH_2CHCH_2NHCH(CH_3)_2$ (OH)
VIII, R = Br

of the mixture of hydrochlorides of amine *II* and of diethanolamine to 220–240°C yielded 2-piperazino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IX*) (for analogy see[7]). Its alkylation with propargyl bromide, benzyl chloride and 3-phenylpropyl bromide[8] in 1-butanol in the presence of potassium carbonate resulted in 1,4-disubstituted piperazines *X*–*XII*. Reaction of the secondary amine *IX* with 1,2-epoxypropane in methanol yielded the N-(2-hydroxypropyl) derivative *XIII*. Addition of acrylonitrile to amine *IX* led to the cyanoethyl derivative *XIV*. Finally, acylation of amine *IX* with acetic anhydride and methanesulfonyl chloride led to amide *XV* and sulfonamide *XVI*.

Most of the products prepared were tested in the form of salts (see Experimental) by methods of general screening (at the unit of this institute at Rosice n/L), the results being shown below (for each compound, the way of application *in vivo* is shown, followed by the mean lethal dose LD_{50} in mice and the dose D at which the compound was applied in most of the tests; both values in mg/kg). The basic ethers *IV* (*i.v.*, 60, 12) and *V* (*i.v.*, 60, 12) in high doses bring about signs of excitation of the central nervous system, in rats with normal blood pressure the dose D decreases the pressure and a concentration of 50 μg/ml displays a negatively inotropic and chronotropic effect in isolated rabbit auricle. Compound *IV* at dose D prolongs significantly the survival of asphyctic mouse myocard. With compound *V*, dose D brings about signs of central depression (the exploratory activity and motility of mice in known surroundings is depressed) and a clear locally anaesthetic and spasmolytic activity in *in vitro* tests (against barium chloride and acetylcholine spasms) and an analgesic activity in mice in the hot-plate test. The ether *VII* was tested for its expected β-adrenolytic effect at the pharmacological department of this institute (Dr M. Vaněček); in the test of interaction with isoprenaline during a histamine bronchospasm of guinea-pigs it is ineffective in intraperitoneal doses of 2·5–4·5 mg/kg, similarly to the test of adrenaline arrhythmia in rats.



IX, R = H
X, R = $CH_2C{\equiv}CH$
XI, R = $CH_2C_6H_5$
XII, R = $(CH_2)_3C_6H_5$

XIII, R = CH_2CHCH_3 (OH)
XIV, R = CH_2CH_2CN
XV, R = $COCH_3$
XVI, R = SO_2CH_3

The piperazine derivative *IX* (*i.v.*, 62·5, 12·0) decreases briefly the blood pressure, it has a pronounced antiarrhythmic effect toward chloroform arrhythmias in mice, at a concentration of 50 μg/ml it decreases the heart inotropy and frequency. It depresses slightly the temperature of rats and decreases the blood sugar levels of rats. With other piperazine derivatives the central neurotropic effects are more pronounced. Thus, the propargyl derivative *X* (*p.o.*, 2000, 300) potentiates the thiopental sleep of mice, depresses clearly the body temperature of rats and has an anticonvulsant effect in mice, both against pentetrazol and against the electro-shock. It resembles the preceding compound in its antiarrhythmic and hypoglycemic effect. Compound *XI* (*p.o.*, > 2500, 300) retains its anticonvulsant effect toward pentetrazol and its hypoglycemic activity. With compound *XII* (*p.o.*, 2000, 300) the central depressant activity is replaced with a slight stimulant effect (it increases slightly the motility of mice); at the same time, a slight prolongation of thiopental sleep was observed while the anticonvulsant activity was maintained. The most interesting effect of the compound is the antireserpine one in mice, both against reserpine hypothermia and against ptosis. With compound *XIII* (*i.v.*, 85, 17) the cardiovascular effects predominate: it brings about a pronounced brief drop of blood pressure, it has a clear antiarrhythmic effect and in the *in vitro* test (50 μg/ml) it diminishes heart inotropy. It antagonizes slightly the reserpine hypothermia. With compound *XIV* (*p.o.*, 1500, 300) a certain neurotropic and cardiovascular activity is encountered. Even at a dose of D/4 it potentiates clearly the thiopental sleep, at a dose of D/2 it has a clear anticonvulsant activity against pentetrazol and electro-shock, it decreases the blood pressure, prolongs the survival of an asphyctic myocard; it depresses further the blood sugar level and shows signs of antiinflammatory activity (the kaolin arthritis in rats). The amide *XV* (*p.o.* 500, 100) and the sulfonamide *XVI* (*p.o.*, 1000, 200) display at high doses signs of central depression and they retain the anticonvulsant activity toward pentetrazol.

Some of the compounds were tested for their antimicrobial activity in *in vitro* tests at the bacteriological department of this institute (Dr A. Šimek and Dr J. Turinová). Some of them inhibited the growth of *Mycobacterium tuberculosis* H 37 Rv (the inhibitory concentration in μg/ml is shown): *VII* 50; *IX*, 25; *XI*, 100; *XIII*, 50. Others show an antifugal activity; thus, *XI*, *XII*, *XIV* and *XV* inhibit the growth of *Trichophyton mentagrophytes* at concentrations of 125 μg/ml. Generally, the activity of the compounds prepared was never so pronounced as to warrant further detailed investigation.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected. The sample were dried in the usual way. The UV spectrum (in methanol) was recorded on a Unicam SP 700 spectrophotometer, the IR spectrum (in Nujol) on a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform) in a ZKR 60 (Zeiss, Jena) spectrometer.

2-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*)

A mixture of 136 g 2-acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[1] (*I*), 610 ml water and 410 ml concentrated hydrochloric acid was refluxed for 2 h and then evaporated at reduced pressure to about one-half. On cooling, 130 g (98%) hydrochloride of the product precipitated and was recrystallized for analysis from a mixture of ethanol and ether (needles, which undergo sublimation at about 200°C); m.p. 209—210°C (in capillary). For $C_{11}H_{16}ClN$ (197·7) calculated: 66·82% C, 8·16% H, 17·93% Cl, 7·09% N; found: 67·15% C, 8·27% H, 18·05% Cl, 7·04% N.

Decomposition of the hydrochloride with 20% NaOH and extraction with ether led to the base, b.p. 140—142°C/14 Torr, n_D^{22} 1·5830; m.p. 34—35°C. For $C_{11}H_{15}N$ (161·2) calculated: 81·93% C, 9·38% H, 8·69% N; found: 81·69% C, 9·25% H, 8·92% N.

Picrate, m.p. 214—215°C under decomposition (ethanol). For $C_{17}H_{18}N_4O_7$ (390·4) calculated: 52·30% C, 4·65% H, 14·35% N; found: 52·22% C, 4·72% H, 14·28% N.

2-Hydroxy-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*III*)

A suspension of 27·0 g hydrochloride of amine *II* in a mixture of 135 ml water and 85 ml concentrated hydrochloric acid was diazotized with a solution of 12·0 g $NaNO_2$ in 110 ml water at below 6°C. The solution formed was poured under stirring into a mixture of 580 ml water and 90 ml sulfuric acid heated on a boiling-water bath to nearly 100°C. After 5 min of heating, the mixture was cooled and the product was extracted with ether. The extract was dried with Na_2SO_4, filtered with charcoal and the filtrate distilled: 14·6 g (65%), b.p. 110—120°C/3 Torr, or 106 to 108°C/1 Torr, m.p. 69—70°C (hexane), Ref.[2,4,5] give m.p. of 72°C. UV spectrum: λ_{max} 218 nm (log ε 3·77), 224 nm (3·76), 276 nm (3·29). IR spectrum: 816 (2 vicinal aromatic C—H), 860 (isolated aromatic C—H), 1252 (Ar—OH), 1500, 1590 (Ar), 3310 cm^{-1} (OH). NMR spectrum: ϑ 6·93 (d, J = 8·5 Hz, 1 H, aromatic proton in position 4), 6·56 (s, 1 H, aromatic proton in position 1), 6·50 (dd, 1 H, aromatic proton in position 3), 4·95 (s, disappears on deuterization, 1 H, OH), 2·85 (d, 4 H, CH_2ArCH_2), 1·74 (s, 6 H, remaining CH_2 groups). For $C_{11}H_{14}O$ (162·2) calculated: 81·44% C, 8·70% H; found: 81·12% C, 8·59% H.

2-(2-Dimethylaminoethoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IV*)

Phenol *III* (5·40 g) was added to a solution of sodium ethoxide (0·8 g Na in 30 ml ethanol) and the solution formed was combined with a solution of 3·60 g 2-dimethylaminoethyl chloride in 20 ml ethanol. The mixture was refluxed for 4 h, cooled, filtered, the filtrate was evaporated at reduced pressure. The residue was divided between water and ether, the organic solution was washed with 10% NaOH, dried with solid KOH and distilled. A total of 5·8 g crude base was obtained: b.p. 134—136°C/1 Torr. The base was converted in the usual way to the hydrochloride (5·2 g), m.p. 179—180°C (ethanol–ether). For $C_{15}H_{24}ClNO$ (269·8) calculated: 66·76% C, 8·97% H, 13·15% Cl, 5·19% N; found: 66·87% C, 9·05% H, 12·90% Cl, 5·05% N.

2-(3-Dimethylaminopropoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*V*)

Similarly to the preceding case, 4·6 g phenol *III* and 4·0 g 3-dimethylaminopropyl chloride yielded 5·70 g (85%) crude base boiling at 147—148°C/1 Torr which led to 4·4 g hydrochloride, m.p. 159—160°C (ethanol–ether). For $C_{16}H_{26}ClNO$ (283·8) calculated: 67·70% C, 9·23% H, 12·50% Cl, 4·93% N; found: 68·02% C, 9·31% H, 12·14% Cl, 4·95% N.

2-(2,3-Epoxypropoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VI*)

Phenol *III* (16·2 g) was dissolved in a solution of 5·0 g NaOH in 100 ml water, combined with 9·3 g epichlorhydrin and the mixture was stirred for 1 h at room temperature. After standing overnight, the product was isolated by extraction with ether. The extract was washed with 10% NaOH, dried with $MgSO_4$ and distilled: 7·3 g, b.p. 144—146°C/1 Torr. NMR spectrum: ϑ 7·04 (d, J = 8·0 Hz, 1 H, aromatic proton in position 4), 6·70 (s, 1 H, aromatic proton in position 1), 6·65 (d, 1 H, aromatic proton in position 3), 4·06 (m, 2 H, $ArOCH_2$), 3·36 (m, 1 H, CH—O), 2·60—3·00 (m, 6 H, CH_2ArCH_2 and CH_2O in the ring), 1·75 (bs, 6 H, remaining CH_2 groups). For $C_{14}H_{18}O_2$ (218·3) calculated: 77·03% C, 8·31% H; found: 76·72% C, 8·27% H.

2-(3-Isopropylamino-2-hydroxypropoxy)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VII*)

Oxide *VI* (7·3 g) in 30 ml ether was added to a solution of 6·0 g isopropylamine in 8 ml ethanol, the mixture was stirred for 2 h at room temperature and left to stand overnight. After evaporation, the remaining oil was converted with an ether solution of hydrogen chloride to the hydrochloride: 5·60 g (52%), m.p. 164—165°C in a capillary (ethanol–ether). For $C_{17}H_{28}ClNO_2$ (313·9) calculated: 65·05% C, 8·99% H, 11·30% Cl, 4·46% N; found: 65·11% C, 9·03% H, 11·03% Cl, 4·33% N.

2-Bromo-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VIII*)

A solution obtained by diazotation of 105 g amine *II* in a mixture of 650 ml water and 70 ml concentrated H_2SO_4 with the aid of 46 g $NaNO_2$ in 85 ml water was added dropwise over a period of 90 min to a hot solution of cuprous bromide (prepared by heating 41 g crystalline $CuSO_4$, 13 g copper, 87 g KBr, 650 ml water and 19·6 g H_2SO_4). Already during the addition of the solution the mixture was steam-distilled. A total of 2·5 liters liquid was thus obtained and this was made alkaline with 20% NaOH and the crude product was isolated by extraction with ether and by distillation: 18·3 g (13%), b.p. 135°C/10 Torr. This product was thoroughly washed with sulfuric acid, was shaken for 12 h with 20% NaOH, dissolved in ether, dried with $CaCl_2$ and redistilled: b.p. 140°C/12 Torr. For $C_{11}H_{13}Br$ (225·1) calculated: 58·68% C, 5·82% H, 35·50% Br; found: 58·61% C, 5·83% H, 35·25% Br.

2-Piperazino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*IX*)

The volatile components were evaporated from a mixture of 8·7 g amine *II*, 6·2 g diethanolamine, 20 ml water, 6 ml ethanol and 10 ml concentrated hydrochloric acid, and the residue was heated for 8 h to 220—240°C. After a partial cooling, the melt was dissolved in 100 ml water, the solution was made alkaline with 20% NaOH and the product was extracted with ether; 10·2 g (83%) oil which was distilled to 8·2 g fraction boiling at 185°C/1 Torr; m.p. 59—60°C (hexane). NMR spectrum: ϑ 6·94 (d, 1 H, aromatic proton in position 4), 6·64 (s, 1 H, aromatic proton in position 1), 6·54 (d, 1 H, aromatic proton in position 3), 3·04 (bs, 8 H, CH_2 groups of piperazine), c. 2·70 (m, 4 H, CH_2ArCH_2), 2·64 (s, disappears on deuterization, 1 H, NH), 1·70 (m, 6 H, remaining CH_2 groups). For $C_{15}H_{22}N_2$ (230·3) calculated: 78·20% C, 9·63% H, 12·17% N; found: 78·15% C, 9·79% H, 12·05% N.

Maleate, m.p. 165—166°C in a capillary (ethanol). For $C_{19}H_{26}N_2O_4$ (346·4) calculated: 65·87% C, 7·56% H, 8·09% N; found: 65·87% C, 7·52% H, 7·87% N.

2-(4-Propargylpiperazino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*X*)

Propargyl bromide (4·8 g) and 5·7 g K_2CO_3 was added to a solution of 7·70 g base *IX* in 50 ml 1-butanol and the mixture was refluxed under stirring for 12 h in a 110°C bath. After cooling, it was filtered, the filtrate was made acid, the residue dissolved in a mixture of benzene and ether and the solution was shaken with 300 ml dilute (1 : 2) hydrochloric acid. The hydrochloride solution was filtered and the base released from the filtrate by treatment with 20% NaOH and isolated by extraction with a mixture of benzene and ether; 6·8 g, b.p. 182—184°C/0·3 Torr, m.p. 85—86°C (hexane). NMR spectrum: ϑ 6·96 (d, J = 8·0 Hz, 1 H, aromatic proton in position 4), 6·66 (s, 1 H, aromatic proton in position 1), 6·58 (q, J = 8·0; 2·5 Hz, 1 H, aromatic proton in position 3), 3·32 (d, J = 2·5 Hz, 2 H, $NCH_2C\equiv$), 3·15 (m, 4 H, $CH_2N^1CH_2$), 2·70 (m, 8 H, CH_2ArCH_2 and $CH_2N^4CH_2$), 2·25 (t, J = 2·5 Hz, 1 H, $CH\equiv$), 1·70 (bs, 6 H, CH_2 groups in positions 6,7,8). For $C_{18}H_{24}N_2$ (268·4) calculated: 80·55% C, 9·01% H, 10·44% N; found: 80·56% C, 9·03% H, 10·37% N.

Maleate, m.p. in crude state without recrystallization 105—106°C (ethanol–ether). For $C_{22}H_{28}N_2O_4$ (384·5) calculated: 68·72% C, 7·34% H, 7·29% N; found: 68·36% C, 7·47% H, 7·36% N. On recrystallization from a mixture of ethanol and ether a compound is formed (m.p. 157—158°C) with analytical composition corresponding to maleate of the secondary amine *IX*. For $C_{19}H_{26}N_2O_4$ (346·4) calculated: 65·87% C, 7·56% H, 8·09% N; found: 66·31% C, 7·53% H, 7·99% N. Thus, the propargyl group is split off even under very mild conditions.

2-(4-Benzylpiperazino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XI*)

Similarly to the preceding case, alkylation of 6·8 g base *IX* with the aid of 4·4 g benzyl chloride yielded 6·2 g base, m.p. 67—68°C (hexane). NMR spectrum: δ 7·32 (s, 5 H, aromatic protons of phenyl), 6·98 (d, $J = 8{\cdot}0$ Hz, 1 H, aromatic proton in position 4), 6·66 (s, 1 H, aromatic proton in position 1), 6·58 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, aromatic proton in position 3), 3·52 (s, 2 H, $ArCH_2N$), 3·10 (m, 4 H, $CH_2N^1CH_2$), c. 2·65 (m, 8 H, CH_2ArCH_2 and $CH_2N^4CH_2$), 1·68 (bs, 6 H, CH_2 groups in positions 6,7,8). For $C_{22}H_{28}N_2$ (320·5) calculated: 82·44% C, 8·81% H, 8·75% N; found: 82·52% C, 8·90% H, 8·64% N.

Maleate, m.p. 192—193°C (ethanol). For $C_{26}H_{32}N_2O_4$ (436·5) calculated: 71·53% C, 7·39% H, 6·42% N; found: 71·17% C, 7·37% H, 6·38% N.

2-[4-(3-Phenylpropyl)piperazino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XII*)

Similarly to the preceding cases, alkylation of 6·8 g base *IX* with the aid of 7·0 g 3-phenylpropyl bromide[8] yielded 8·68 g base, b.p. 248°C/1 Torr. For $C_{24}H_{32}N_2$ (348·5) calculated: 82·70% C, 9·26% H, 8·04% N; found: 82·63% C, 9·28% H, 7·78% N.

Maleate, m.p. 148—149°C (ethanol–ether). For $C_{28}H_{36}N_2O_4$ (464·6) calculated: 72·37% C, 7·81% H, 6·03% N; found: 72·46% C, 7·75% H, 5·88% N.

2-[4-(2-Hydroxypropyl)piperazino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIII*)

1,2-Epoxypropane (3·0 g) was added dropwise under stirring to a solution of 7·70 g amine *IX* in 15 ml methanol. The mixture was stirred for 2 h at room temperature, whereafter 2·0 g 1,2-epoxypropane was added and the mixture was left to stand overnight. Filtration of the precipitate yielded 7·1 g product which was recrystallized for analysis from hexane, m.p. 109—110°C. NMR spectrum: δ 6·96 (d, $J = 8{\cdot}0$ Hz, 1 H, aromatic proton in pošition 4), 6·66 (s, 1 H, aromatic proton in position 1), 6·58 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, aromatic proton in position 3), 3·75 (d, $J = 7{\cdot}5$ Hz, 1 H, CH—O), 3·43 (s, 1 H, OH), 3·10 (m, 4 H, $CH_2N^1CH_2$), 2·65 (m, 8 H, CH_2ArCH_2 and $CH_2N^4CH_2$), 2·30 (m, 2 H, NCH_2—C—O), 1·71 (bs, 6 H, CH_2 groups in positions 6,7,8), 1·12 (d, $J = 7{\cdot}5$ Hz, 3 H, CH_3). For $C_{18}H_{28}N_2O$ (288·4) calculated: 74·95% C, 9·79% H, 9·71% N; found: 75·18% C, 10·09% H, 9·80% N.

Maleate, m.p. 151—152°C (ethanol–ether). For $C_{22}H_{34}N_2O_5$ (406·5) calculated: 65·00% C, 8·43% H, 6·89% N; found: 65·43% C, 8·08% H, 6·83% N.

2-[4-(2-Cyanoethyl)piperazino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIV*)

Acrylonitrile (3.0 g) was added to a solution of 7·0 g amine *IX* in 50 ml benzene and the mixture was refluxed for 7 h, left to stand overnight and then 2·0 g acrylonitrile was added and refluxing continued for 5 h. Benzene was evaporated and the residue distilled; 7·2 g product boiling at

215—218°C/0·5 Torr, m.p. 46—47°C (hexane). NMR spectrum: ϑ 6·98 (d, $J = 8{\cdot}0$ Hz, 1 H, aromatic proton in position 4), 6·65 (s, 1 H, aromatic proton in position 1), 6·58 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, aromatic proton in position 3), 3·10 (m, 4 H, $CH_2N^1CH_2$), c. 2·65 (m, 12 H, CH_2ArCH_2, $CH_2N^4CH_2$ and CH_2CH_2CN), 1·68 (bs, 6 H, CH_2 groups in positions 6,7,8). For $C_{18}H_{25}N_3$ (283·4) calculated: 76·27% C, 8·90% H, 14·83% N; found: 76·16% C, 9·00% H, 14·64% N.

Maleate, m.p. 128—129°C (ethanol–hexane). For $C_{22}H_{29}N_3O_4$ (399·6) calculated: 10·52% N; found: 10·29% N.

2-(4-Acetylpiperazino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XV*)

A mixture of 8·0 g base *IX* and 20 ml acetic anhydride was refluxed for 5 h and, after partial cooling, decomposed with water. The crystalline product precipitating on standing was filtered; 8·5 g (90%), m.p. 85—86°C (hexane). NMR spectrum: ϑ 7·00 (d, $J = 8{\cdot}0$ Hz, 1 H, aromatic proton in position 4), 6·66 (s, 1 H, aromatic proton in position 1), 6·58 (q, $J = 8{\cdot}0$; 2·0 Hz, 1 H, aromatic proton in position 3), 3·64 (m, 4 H, $CH_2N^4CH_2$), 3·10 (m, 4 H, $CH_2N^1CH_2$), 2·72 (m, 4 H, CH_2ArCH_2), 3·10 (s, 3 H, CH_3), 1·70 (bs, 6 H, CH_2 groups in positions 6,7,8). For $C_{17}H_{24}N_2O$ (272·4) calculated: 74·94% C, 8·88% H, 10·30% N; found: 74·90% C, 9·00% H, 10·33% N.

2-(4-Methanesulfonylpiperazino)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XVI*)

Pyridine (3 ml) and 4.0 g methanesulfonyl chloride were added to a solution of 8·0 g base *IX* in 60 ml benzene. The mixture was refluxed for 6 h, after cooling it was decomposed with water and the partly precipitating product was extracted with a larger amount of benzene at 50°C. The extract was washed with warm water, dried briefly with Na_2SO_4 and evaporated: 8·5 g product, m.p. 168—169°C (benzene–hexane). NMR spectrum: ϑ 6·98 (d, $J = 8{\cdot}0$ Hz, 1 H, aromatic proton in position 4), 6·66 (s, 1 H, aromatic proton in position 1), 6·58 (q, $J = 8{\cdot}0$; 2·5 Hz, 1 H, aromatic proton in position 3), 3·25 (m, 8 H, CH_2 groups of piperazine), 2·78 (s, 3 H, CH_3), c. 2·70 (m, 4 H, CH_2ArCH_2), 1·69 (bs, 6 H, CH_2 groups in positions 6,7,8). For $C_{16}H_{24}N_2O_2S$ (308·4) calculated: 62·29% C, 7·84% H, 9·09% N, 10·40% S; found: 62·38% C, 7·86% H, 10·25% N, 10·44% S.

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