# BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. IX.*

## AMINES DERIVED FROM 2-BENZYL-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENE

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6,7,8,9-Tetrahydro-5*H*-benzocycloheptene underwent the Friedel–Crafts reaction with benzoyl chloride to yield ketone *I*. Its oxime *II* was alkylated to the O-(dimethylaminoalkyl)oximes *III* and *IV*. Reduction of oxime *II* resulted in amine *V* which was converted to the dimethylamino derivative *VI*. Reduction of ketone *I* or its reaction with methylmagnesium iodide led to alcohols *VII* and *VIII* which were converted to amine ethers *IX*—*XII*. The chloride *XIII* prepared from alcohol *VII* with the aid of thionyl chloride reacted with 1-methyl and 1-ethoxycarbonyl-piperazine to *XIV* and *XV*. Reaction of the ketone *I* with 3-dimethylaminopropylmagnesium chloride yielded the tertiary alcohol *XVI* and the olefinic amine *XVII*. A partial demethylation of *XVII* yielded the secondary amine *XIX*. Compounds *III*—*VI*, *XV* and *XVII* displayed a central depressant activity while others showed only a local anaesthetic, spasmolytic and antiarrhythmic activities (*IX*—*XII*, *XIV*, *XIX*). Some of the compounds showed a rather pronounced antimicrobial activity *in vitro* and partly also *in vivo* (*X*, *XIV*-methiodide).

In the course of a systematic pharmacochemical investigation among the derivatives of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[1–4] we proceeded in preparing further amines from 2-benzoyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*) which was obtained in a high yield by the reaction of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[5] with benzoyl chloride and aluminium chloride in benzene. This ketone which is an analogue of benzophenone offers considerable possibilities as a starting compound for the synthesis of a large number of analogues of pharmacodynamically active diphenylmethane derivatives.

A conventionally prepared oxime *II* was converted in a reaction with sodium methoxide to a sodium salt and alkylated with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride. The O-(aminoalkyl)oximes *III* and *IV* were obtained in the form of crystalline hydrochlorides which can be considered as analogues of the thymoleptically active noxiptiline[6]. Reduction of oxime *II* with sodium and ethanol resulted in the primary amine *V* which was methylated with formaldehyde

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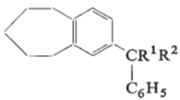
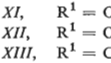
and formic acid to the tertiary amine *VI*. Reduction of ketone *I* with lithium aluminium hydride in ether led to the secondary alcohol *VII* whereas reaction of ketone *I* with methylmagnesium iodide produced the tertiary alcohol *VIII*. These alcohols were converted by a reaction with sodium amide in toluene and subsequent treatment with 2-dimethylaminoethyl chloride or 3-dimethylaminopropyl chloride to the corresponding aminoalkyl ethers *IX*–*XII* which are analogous to the antihistaminic benzhydryl ethers[7] and α-methylbenzhydryl ethers[8]. Reaction of alcohol *VII* with thionyl chloride yielded the crude chloride *XIII* which was subjected to substitution reactions with excess 1-methylpiperazine and 1-(ethoxycarbonyl)piperazine[9]; in the first case, amine *XIV* was formed, which was analogous to the antihistaminic cyclizine[10], in the second case the ethoxycarbonylpiperazine derivative *XV* was obtained.

Reaction of ketone *I* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran yielded an oily mixture of bases which was chromatographed on alumina to separate 24% of a crystalline product which was shown, by analysis and spectra, to be the expected tertiary alcohol *XVI*. The less polar oily residue contains the olefinic amine *XVII*. Dehydration of the original mixture was completed by heating with an aqueous–ethanolic solution of hydrochloric acid and olefin *XVII* was isolated by distillation. It yields a crystalline salt with maleic acid. The compound

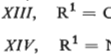


*I*, $R^1R^2 = =O$
*II*, $R^1R^2 = =NOH$
*III*, $R^1R^2 = =NO(CH_2)_2N(CH_3)_2$
*IV*, $R^1R^2 = =NO(CH_2)_3N(CH_3)_2$
*V*, $R^1 = NH_2$, $R^2 = H$
*VI*, $R^1 = N(CH_3)_2$, $R^2 = H$
*VII*, $R^1 = OH$, $R^2 = H$
*VIII*, $R^1 = OH$, $R^2 = CH_3$
*IX*, $R^1 = O(CH_2)_2N(CH_3)_2$, $R^2 = H$
*X*, $R^1 = O(CH_2)_3N(CH_3)_2$, $R^2 = H$

*XI*, $R^1 = O(CH_2)_2N(CH_3)_2$, $R^2 = CH_3$
*XII*, $R^1 = O(CH_2)_3N(CH_3)_2$, $R^2 = CH_3$
*XIII*, $R^1 = Cl$, $R^2 = H$



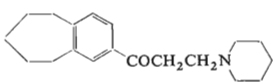
*XIV*, $R^1 =$ , $R^2 = H$



*XV*, $R^1 =$ , $R^2 = H$

*XVI*, $R^1 = (CH_2)_3N(CH_3)_2$, $R^2 = OH$
*XVII*, $R^1R^2 = =CH(CH_2)_2N(CH_3)_2$
*XVIII*, $R^1R^2 = =CH(CH_2)_2NCH_3$ (with $COOC_2H_5$)

*XIX*, $R^1R^2 = =CH(CH_2)_2NHCH_3$



*XX*

can be considered as an analogue of the thymoleptic amitriptyline[11]. Reaction with ethyl chloroformate results in partial demethylation and the formation of carbamate *XVIII*. Its hydrolysis by hydrobromic acid in acetic acid gives rise to the secondary olefinic amine *XIX* which is an analogue of nortriptyline[12]. As a possible intermediate for further work, the base *XX* was prepared by a Mannich reaction of 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[5,13] with piperidine.

Most of the bases prepared were evaluated pharmacologically in the form of salts by the methods of general screening (at the unit of this Institute at Rosice n/L), its results being reported below (for every substance the way of administration *in vivo* is shown, followed by the mean lethal dose for mice $LD_{50}$ and the dose D at which the compound was applied in most of the tests, both values being in mg/kg).

The basic oxime *III* (*p.o.*, 1 000, 200) was shown to be clearly anticonvulsant toward pentetrazol in mice, starting at 100 mg/kg; on the other hand, in the electro-shock test in mice a dose of 400 mg/kg was required to attain anticonvulsant activity. The compound slightly potentiates thiopental sleep in mice and brings about brief reduction of the blood pressure in rats with normal tension. With the homologue *IV* (*i.v.*, 31·75, 6·0) the anticolvulsant effect is not significant but the compound potentiates more pronouncedly the thiopental sleep (some 20% of the chlorpromazine effect) and a slight inhibition of motility of mice in familiar environment appears. A much more pronounced effect than with the lower homologue is found here on the reduction of blood pressure which sets in after 1·5—3·0 mg/kg and has a protracted character. The compound is a local anaesthetic for rabbit cornea (it irritates) and, in the isolated rat duodenum, it antagonizes slightly the acetylcholine contractions and more pronouncedly the barium chloride spasms (about as much as papaverine). In the isolated rabbit auricle it has a slight negative inotropic effect.

The primary amine *V* (*i. v.*, 20, 4) was shown to possess indications of anticonvulsant activity toward pentetrazol, an indication of hypothermic effect in rats, an indication of parasympathomimetic effect in the isolated mouse eye and a slight antiarrhythmic effect toward aconitine in rats. Likewise, the tertiary amine *VI* (*p.o.*, 1 000, 200) has an anticonvulsant effect (confirmed also by the electro-shock method), and a slight hypothermic and antiarrhythmic effect. In higher doses it shows a central stimulant activity (it increases mouse motility).

The basic ethers *IX* (*i.v.*, 30, 6), *X* (*i.v.*, 37·5, 8), *XI* (*i.v.*, 25, 5) and *XII* (*i.v.*, 30, 6) all bring about brief and profound drops of blood pressure in rats, have a spasmolytic effect on isolated rat duodenum toward acetylcholine and barium chloride spasms, they are locally anaesthetic (all of them irritant) and antiarrhythmic (toward chloroform and partly also aconitine arrhythmias). Effects on the CNS are completely absent and the expected antihistamine effect in the *in vitro* test was completely missing. The ethers *XI* and *XII* were tested for hypotensive activity in hypertensive rats (Dr V. Trčka); in an oral dose of 100, or 120 mg/kg, respectively, they did not alter the blood pressure throughout 4 h after administration by more than $\pm 15\%$ and hence they are considered as uninteresting in this context. They showed no β-adrenomimetic effect on isolated rat trachea (Dr M. Vaněček).

The piperazine derivative *XIV* (*i.v.*, 40, 8) depresses briefly the blood pressure of rats, it antagonizes slightly the hypothermic effect of reserpine in mice and has a myotropic spasmolytic effect *in vitro*. Its methiodide (*p.o.*, 1 500, 300) exhibits indications of central depressant activity (it depresses the motility of mice in familiar environment and has a pronounced hypothermic effect). With the ethoxycarbonylpiperazine derivative *XV* (*p.o.*, >2 500, 300) a slight anticonvulsant activity toward pentetrazol was found.

The olefinic amines *XVII* (*i.v.*, 50, 10) and *XIX* (*i.v.*, 30, 6) lack the predicted antireserpine

TABLE I

Antimicrobial Activity of the Compounds *in vitro*

Minimum inhibitory concentration in μg/ml. Where a minus sign is shown, no inhibition of microbial growth was observed even at 100 μg/ml or at 125 μg/ml (for the last four species).

| | *III* | *IV* | *X* | *XIV* | *XIV*-$CH_3I$ | *XVII* | *XIX* |
|---|---|---|---|---|---|---|---|
| *Streptococcus β-haemolyticus* | 6·25 | 6·25 | 12·5 | 50 | 12·5 | — | 6·25 |
| *Staphylococcus pyogenes aureus* | 6·25 | 6·25 | 12·5 | 50 | 12·5 | — | 6·25 |
| *Klebsiella pneumoniae* | — | 100 | 50 | 100 | 100 | — | 50 |
| *Pseudomonas aeruginosa* | — | — | 100 | — | 100 | — | — |
| *Escherichia coli* | — | 100 | — | — | 100 | — | — |
| *Salmonella typhi abdominalis* | — | 100 | 100 | 100 | 100 | — | 100 |
| *Proteus vulgaris* | — | — | 100 | — | 100 | — | — |
| *Mycobacterium tuberculosis* H37Rv | 12·5 | 12·5 | 6·25 | 12·5 | 100 | 25 | 12·5 |
| *Saccharomyces pasterianus* | 12·5 | 12·5 | — | — | — | 62·5 | 125 |
| *Trichophyton mentagrophytes* | 12·5 | 12·5 | — | 125 | — | 62·5 | 125 |
| *Candida albicans* | — | 12·5 | 12·5 | 125 | — | 125 | — |
| *Aspergillus niger* | — | — | — | — | — | 125 | — |

effect and their influence on the CNS is generally modest (a slight potentiation of thiopental sleep; at higher doses a slight increase in motility of mice). The structurally nonspecific effects are more pronounced: spasmolytic (particularly against barium chloride spasms *in vitro*), locally anaesthetic (effect of *XIX* on rabbit cornea is very pronounced) and antiarrhythmic. Both cause brief and profound drops of rat blood pressure.

The compounds were also examined for their antimicrobial effects in *in vitro* tests and, as shown in Table I, some of them were pronouncedly inhibitory (the minimum inhibitory concentrations in μg/ml are shown). Hydrogen maleate of *X* (daily dose 94 mg *p.o.*) and methiodide of *XIV* (daily dose 375 mg/kg *p.o.*) were also evaluated *in vivo* during experimental infection with *Escherichia coli* in mice (application twice a day with a 10-hour interval for 3 days). They were found to be clearly active, there being 50% surviving animals 12, 36, 60 and 84 h after the last administration of the compound. In mice infected with *Streptococcus β-haemolyticus* no chemotherapeutical activity of these compounds could be demonstrated (Dr A. Šimek, Dr J. Turinová).

In summary, it should be said that although the compounds displayed pharmacodynamic activities of different types, the efficacy was never such as to warrant further detailed study.

## EXPERIMENTAL

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

2-Benzoyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*)

Benzoyl chloride (72·0 g) was added to a solution of 73·0 g 6,7,8,9-tetrahydro-5*H*-benzocycloheptene[5] in 500 ml benzene (thiophene-free), the mixture was cooled to 0°C and, under stirring, 73 g $AlCl_3$ were added at temperatures not exceeding +8°C. The mixture was stirred for further 3 h under cooling and left to stand overnight at room temperature. It was decomposed by pouring into a mixture of 250 g ice and 80 ml concentrated hydrochloric acid, the benzene layer was washed with saturated $NaHCO_3$, dried with $MgSO_4$ and evaporated. The residue was distilled to yield 111·2 g (89%) product boiling at 230—235°C/10 Torr (after redistillation 205°C/3 Torr, or 190°C/1 Torr). UV spectrum: $\lambda_{max}$ 260 nm (log $\varepsilon$ 4·20); IR spectrum: 700, 722, 750 (5 vicinal aromatic C—H), 811 (2 vicinal aromatic C—H), 847, 907, 909 (isolated aromatic C—H), 1 569, 1 579, 1 603 (Ar), 1 660 $cm^{-1}$ (Ar—CO—Ar). For $C_{18}H_{18}O$ (250·3) calculated: 86·35% C, 7·25% H; found: 86·76% C, 7·32% H. *Oxime* (II), m.p. 147—148°C (ethanol). For $C_{18}H_{19}NO$ (265·4) calculated: 81·47% C, 7·22% H; found: 81·26% C, 7·54% H.

O-(2-Dimethylaminoethyl)-2-benzoyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptenoxime (*III*)

Oxime *II* (13·0 g) was dissolved in a boiling solution of 1·3 g sodium in 75 ml ethanol and the mixture was evaporated to dryness *in vacuo*. The remainder of ethanol was removed by adding 20 ml dimethylformamide and evaporation *in vacuo*. This operation was followed by the addition of 50 ml dimethylformamide and 7·3 ml 2-dimethylaminoethyl chloride whereafter the mixture was heated for 1 h to 100—110°C. The NaCl precipitated on cooling was removed by filtration, the filtrate was evaporated at reduced pressure, the residue was dissolved in 70 ml of a mixture of benzene and ether (2 : 1), the solution was washed with water, dried with $K_2CO_2$ and evaporated. A total of 14·5 g crude base was obtained which was dissolved in ether and treated with an ether solution of hydrogen chloride to yield 12·0 g hydrochloride; m.p. 147—148°C (ethanol–ether). UV spectrum: $\lambda_{max}$ 238 nm (log $\varepsilon$ 4·10), 260 nm (4·09). IR spectrum: 690, 698, 766 (5 vicinal aromatic C—H), 826 (2 vicinal aromatic C—H), 860, 896 (isolated aromatic C—H), 1 665 (C=N), 2 465, 2 510 and 2 585 $cm^{-1}$ ($NH^+$). For $C_{22}H_{29}ClN_2O$ (372·9) calculated: 70·85% C, 7·84% H, 9·51% Cl, 7·51% N; found: 70·18% C, 7·85% H, 9·70% Cl, 7·52% N.

O-(3-Dimethylaminopropyl)-2-benzoyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptenoxime (*IV*)

In analogy with the preceding case, alkylation of 12·0 g oxime *II* with the aid of 6·5 g 3-dimethylaminopropyl chloride yielded 14·3 g oily base which was converted to 14·5 g crystalline hydrochloride hemihydrate: m.p. 166—167°C (ethanol–ether). For $C_{23}H_{31}ClN_2O \cdot 1/2\ H_2O$ (396·0) calculated: 69·77% C, 8·14% H, 7·07% N; found: 70·02% C, 8·04% H, 7·13% N.

α-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzylamine (*V*)

A solution of 18·0 g oxime *II* in 400 ml ethanol was added dropwise to 42 g sodium and the mixture was refluxed to complete solution of the sodium. After cooling, it was decomposed by the addition of 100 ml water, ethanol was evaporated at reduced pressure and the base was isolated from the residue by extraction with ether; 15·4 g (90%), b.p. 174°C/1 Torr. For $C_{18}H_{21}N$ (251·4) calculated: 86·01% C, 8·42% H, 5·57% N; found: 86·47% C, 8·57% H, 5·30% N.

*Hydrochloride*, m.p. 231°C (ethanol–ether). For $C_{18}H_{22}ClN$ (287·8) calculated: 75·10% C, 7·71% H, 12·32% Cl; found: 74·80% C, 7·84% H, 12·14% Cl.

N,N-Dimethyl-α-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)benzylamine (*VI*)

A solution of 6·0 g amine *V* in 8·5 ml 85% formic acid and 12 ml water was treated with 12 ml of a 36% solution of formaldehyde and the mixture was refluxed for 6 h (on a 120—130°C bath). After cooling, 10 ml concentrated hydrochloric acid was added and the mixture was evaporated at reduced pressure to dryness. The crystalline residue was mixed with 25 ml ice-cold water and filtered: 7·5 g (theoretical amount) of hydrochloride, m.p. 248—249°C (needles from ethanol–ether). For $C_{20}H_{26}ClN$ (315·9) calculated: 76·05% C, 8·30% H, 11·22% Cl, 4·43% N; found: 75·48% C, 8·38% H, 10·73% Cl, 4·34% N. Decomposition of the hydrochloride with 20% NaOH and extraction with ether yielded the base, b.p. 186°C/1 Torr. NMR spectrum: $\delta$ 6·75—7·70 (m, 8 H, aromatic protons), 3·90 (s, 1 H, Ar—CH—Ar) 2·37—2·95 (m, 4 H, $CH_2$—Ar—$CH_2$), 2·14 (s, 6 H, $CH_3NCH_3$), 1·30—1·95 (m, 6 H, $CH_2$ groups in positions 6,7,8 of benzocycloheptene). For $C_{20}H_{25}N$ (279·4) calculated: 85·97% C, 9·02% H, 5·01% N; found: 85·50% C, 8·90% H, 4·89% N.

α-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzyl Alcohol (*VII*)

A solution of 25·0 g ketone *I* in 100 ml ether was added dropwise under stirring to 6·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 3 h. After cooling, it was decomposed with 24 ml of 20% solution of NaOH, filtered and the filtrate was dried with $Na_2SO_4$ and evaporated; 24·5 g (98%) crude product. After recrystallization from hexane it melts at 64—65°C (in a capillary). IR spectrum: 700, 730 (5 vicinal aromatic C—H), 805, 815 (2 vicinal aromatic C—H), 878 (isolated aromatic C—H), 1036 and 3360 $cm^{-1}$ (OH). For $C_{18}H_{20}O$ (252·3) calculated: 85·66% C, 8·00% H; found: 85·58% C, 7·92% H.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)ethanol (*VIII*)

A solution of 37·0 g ketone *I* in 100 ml ether was added dropwise to a solution of methylmagnesium iodide (from 26 g methyl iodide and 4·3 g magnesium in 80 ml ether) and the mixture was refluxed for 3 h. After cooling, it was decomposed with a solution of 20 g $NH_4Cl$ in 100 ml water, the ether solution was washed with 50 ml 5% solution of $Na_2S_2O_3$, dried with $Na_2SO_4$ and evaporated. A total of 39·3 g (98%) crude oily product was obtained. A 1·0 g sample was purified by chromatography on a column of 25 g alumina (activity II), using elution with hexane followed by benzene. The benzene eluate is homogeneous in thin-layer chromatography but it does not crystallize. After removing remainders of the solvent *in vacuo* it was used for determination of spectra and for analysis. UV spectrum: $\lambda_{max}$ 253 nm (log $\varepsilon$ 3·42), 258 nm (3·49), 264 nm (3·49), 274 nm (3·31). IR spectrum: 702 and 765 (5 vicinal aromatic C—H), 822 (2 vicinal aromatic C—H), 900 (isolated aromatic C—H), 1070 (tert C—OH), 1605 (Ar), 3450 and 3555 $cm^{-1}$ (OH). For $C_{19}H_{22}O$ (266·4) calculated: 85·67% C, 8·33% H; found: 85·42% C, 8·47% H.

α-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzyl 2-Dimethylaminoethyl Ether (*IX*)

A mixture of 8·0 g alcohol *VII*, 100 ml toluene and 2·5 g $NaNH_2$ was refluxed for 8 h, 5·0 g 2-dimethylaminoethyl chloride was then added and the mixture refluxed for 6 h under stirring. After cooling, it was decomposed by adding dropwise 50 ml water, the toluene layer was washed with water, dried with $Na_2SO_4$ and distilled; 6·1 g, b.p. 175°C/1 Torr. For $C_{22}H_{29}NO$ (323·5) calculated: 81·68% C, 9·04% H, 4·33% N; found: 81·54% C, 9·52% H, 4·56% N.

*Hydrogen maleate*, m.p. 77—78°C (ethanol–ether). For $C_{26}H_{33}NO_5$ (439·5) calculated: 71·04% C, 7·57% H, 3·19% N; found: 71·14% C, 7·99% H, 3·05% N.

α-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzyl 3-Dimethylaminopropyl Ether (*X*)

Similarly to the above case, 8·0 g alcohol *VII* and 5·7 g 3-dimethylaminopropyl chloride reacted to 6·5 g base, b.p. 186°C/1 Torr. For $C_{23}H_{31}NO$ (337·5) calculated: 81·85% C, 9·26% H, 4·15% N; found: 81·24% C, 9·38% H, 4·53% N.

*Hydrogen maleate (hemihydrate)*, m.p. 71—72°C (ethanol–ether). For $C_{27}H_{35}NO_5.1/2\ H_2O$ (462·6) calculated: 70·10% C, 7·84% H, 3·03% N; found: 69·67% C, 7·60% H, 3·45% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)ethyl 2'-Dimethylaminoethyl Ether (*XI*)

Similarly to the preceding cases, 10·0 g alcohol *VIII* reacted with 5·0 g 2-dimethylaminoethyl chloride; 11·2 g (90%), b.p. 182—183°C/1 Torr. For $C_{23}H_{31}NO$ (337·5) calculated: 81·85% C, 9·26% H, 4·15% N; found: 82·30% C, 9·20% H, 3·63% N.

*Hydrogen maleate*, m.p. 111—112°C (ethanol–ether). For $C_{27}H_{35}NO_5$ (453·6) calculated: 71·49% C, 7·78% H, 3·09% N; found: 71·64% C, 7·72% H, 3·03% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)ethyl 3'-Dimethylaminopropyl Ether (*XII*)

Similarly to the preceding cases, 10·0 g alcohol *VIII* reacted with 5·7 g 3-dimethylaminopropyl chloride to yield 11·7 g distilled base, b.p. 194°C/1 Torr. NMR spectrum: $\delta$ 7·05—7·50 (m, 5 H, aromatic protons of phenyl), 6·95—7·05 (m, 3 H, remaining aromatic protons), 3·19 (t, 2 H, $OCH_2$), 2·50—2·85 (m, 4 H, $CH_2$—Ar—$CH_2$), 2·18—2·50 (m, 2 H, $CH_2N$), 2·15 (s, 6 H, $CH_3$. .$NCH_3$), 1·76 (s, 3 H, C—$CH_3$), 1·1—2·0 (m, 8 H, aliphatic $CH_2$ groups in the ring and central in the chain). For $C_{24}H_{33}NO$ (451·5) calculated: 82·00% C, 9·47% H, 3·98% N; found: 82·74% C, 9·58% H, 3·94% N.

*Hydrogen maleate*, m.p. 76—77°C (ethanol–ether). For $C_{28}H_{37}NO_5$ (467·6) calculated: 71·92% C, 7·98% H, 3·00% N; found: 71·75% C, 8·02% H, 3·12% N.

1-[α-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzyl]-4-methylpiperazine (*XIV*)

A mixture of 10·0 g alcohol *VII* and 5 ml $SOCl_2$ was heated for 6 h to 80—100°C and the excess $SOCl_2$ was evaporated *in vacuo* at a temperature not exceeding 70°C. The residue (11·0 g crude chloride *XIII*) was combined with 8·2 g 1-methylpiperazine, the mixture was refluxed for 6 h in a 130—150°C bath. After cooling, it was divided between ether and water, the ether extract was washed with water, dried with KOH and evaporated. The remaining base (13·5 g oil) was converted in the usual way to di(hydrogen maleate), m.p. 155—156°C (ethanol–ether). For $C_{31}H_{38}$. .$N_2O_8$ (566·6) calculated: 65·71% C, 6·76% H, 4·94% N; found: 65·83% C, 6·77% H, 4·96% N.

*Monomethiodide* was prepared from a base that was liberated from purified maleate; m.p. 206—207°C (methanol–ether). For $C_{24}H_{33}IN_2$ (476·4) calculated: 60·50% C, 6·98% H, 26·64% I, 5·88% N; found: 60·03% C, 7·07% H, 26·67% I, 6·18% N.

1-[α(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)benzyl]-4-(ethoxycarbonyl)piperazine (*XV*)

A mixture of 7·0 g crude chloride *XIII* and 8·2 g 1-(ethoxycarbonyl)piperazine[9] was heated for 6 h to 130—150°C. After cooling, the mixture was divided between water and ether, the ether

solution was washed with water and then with excess hydrochloric acid. The acid aqueous layer with the precipitated hydrochloride was made alkaline and the base was isolated by extraction with ether; 8·20 g oil. It was converted in the usual way to hydrogen maleate (7·50 g), m.p. 138–139°C (ethanol–ether). For $C_{29}H_{36}N_2O_6$ (508·6) calculated: 68·47% C, 7·14% H, 5·51% N; found: 68·61% C, 7·15% H, 5·21% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-4-dimethylaminobutanol (*XVI*)

A solution of 21·8 g ketone *I* in 45 ml tetrahydrofuran was added dropwise over 10 min to a solution of reagent prepared from 18·8 g 3-dimethylaminopropyl chloride and 4·5 g magnesium in 150 ml tetrahydrofuran and the mixture was refluxed for 19 h. After cooling, it was decomposed with a solution of 25 g $NH_4Cl$ in 100 ml water and extracted with ether. Treatment of the extract gave rise to 29·0 g crude, noncrystalline product. A 1·0 g sample was chromatographed on a column of 30 g alumina (activity II), using elution with benzene. After removal of most of the less polar fractions, 0·24 g of a fraction was eluted which crystallised on standing: m.p. 65–66°C in a capillary (hexane). UV spectrum: $\lambda_{max}$ 258·5 nm (log $\varepsilon$ 2·75), 265 nm (2·77), 274 nm (2·64). IR spectrum: 702, 746, 770 (5 vicinal aromatic C—H), 821, 841 (2 vicinal aromatic C—H), 851, 889 (isolated aromatic C—H), 1100 (tert. C—OH), 1600 (Ar), 2660 and 3150 $cm^{-1}$ (OH in the hydrogen bond). For $C_{23}H_{31}NO$ (337·5) calculated: 81·85% C, 9·26% H, 4·15% N; found: 81·91% C, 9·21% H, 3·97% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-4-dimethylaminobutene (*XVII*)

The remainder of the crude product from the preceding experiment (28·0 g) was dissolved in 150 ml ethanol, the solution was neutralized with concentrated hydrochloric acid, another 6 ml concentrated hydrochloric acid was added and the mixture was refluxed for 6 h. After evaporation to dryness, the remaining hydrochloride was mixed with 120 ml water and, after treatment with a 20% solution of NaOH, the base was isolated by extraction with a mixture of benzene and ether. The extract was distilled. A total of 23·0 g product, boiling at 188–190°C/0·5 Torr was obtained. NMR spectrum: $\delta$ c. 7·17 (m, 5 H, $C_6H_5$), c. 6·87 (m, 3 H, remaining aromatic protons), 6·00 (m, 1 H, C=CH), 2·70 (m, 4 H, $CH_2$—Ar—$CH_2$), 2·35 (m, 4 H, $CH_2CH_2N$), 2·13 and 2·16 (2 s, 6 H, $CH_3NCH_3$), 1·70 (bs, 6 H, remaining $CH_2$ groups in the ring). For $C_{23}H_{29}N$ (319·5) calculated: 86·46% C, 9·15% H, 4·39% N; found: 86·29% C, 9·28% H, 4·48% N.

*Hydrogen maleate*, m.p. 120–121°C (ethanol–ether). For $C_{27}H_{33}NO_4$ (435·5) calculated: 74·44% C, 7·64% H, 3·22% N; found: 74·49% C, 7·64% H, 2·94% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-4-(N-ethoxycarbonylmethylamino)-butene (*XVIII*)

Ethyl chloroformate (15·0 g) was added dropwise under stirring to a solution of 12·2 g base *XVII* in 50 ml benzene and the mixture was refluxed for 6 h. After cooling, it was washed with dilute hydrochloric acid and with water and evaporated. A theoretical yield of an oily product (14·5 g) was obtained; a sample was redistilled for analysis; b.p. 225°C/0·5 Torr. UV spectrum: $\lambda_{max}$ 254 nm (log $\varepsilon$ 4·17). IR spectrum (film): 703 and 770 (5 vicinal aromatic C—H), 820 and 840 (2 vicinal aromatic C—H), 898 (isolated aromatic C—H), 1600 (Ar), 1700 $cm^{-1}$ (NCOOR). For $C_{25}H_{31}NO_2$ (377·5) calculated: 79·53% C, 8·28% H, 3·71% N; found: 80·27% C, 8·41% H, 3·72% N.

1-Phenyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-4-methylaminobutene (*XIX*)

A mixture of 14·0 g carbamate *XVIII*, 80 ml acetic acid and 35 ml 60% hydrobromic acid was refluxed for 3 h. After cooling, it was diluted with 400 ml water, made alkaline with 20% NaOH and extracted with ether. From the extract, the basic product was transferred by shaking with 150 ml dilute hydrochloric acid to the aqueous phase, after separation of ether the aqueous phase was again made alkaline and the basic fraction was reisolated by extraction with ether. Processing of the extract yielded 7·30 g base, boiling at 190°C/0·5 Torr. NMR spectrum: $\delta$ 7·20 (s) and 6·70—7·05 (m) (8 H, aromatic protons), 5·97 (t, 1 H, C=CH), 2·0—3·0 (m, 8 H, $CH_2ArCH_2$ and $CH_2CH_2N$), 2·35 (s, 3 H, N—$CH_3$), 1·70 (bs, 6 H, remaining $CH_2$ groups of the ring), 1·33 (s, disappears on deuterization, 1 H, NH). For $C_{22}H_{27}N$ (305·4) calculated: 86·50% C, 8·91% H, 4·59% N; found: 86·99% C, 8·29% H, 4·70% N.

*Hydrogen maleate*, m.p. 90—91°C (ethanol–ether). For $C_{26}H_{31}NO_4$ (421·5) calculated: 74·09% C, 7·41% H, 3·32% N; found 74·01% C, 7·37% H, 3·17% N.

2-(3-Piperidinopropionyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XX*)

A mixture of 17·9 g 2-acetyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[5,13], 11·6 g piperidine hydrochloride, 4·2 g paraformaldehyde, 42 ml ethanol and 14 drops of concentrated hydrochloric acid was refluxed for 1 h and, after adding 2·7 g paraformaldehyde, for further 3 h. The mixture was evaporated *in vacuo* to dryness, the residue was diluted with 250 ml water, washed with benzene and ether, made alkaline with 20% NaOH and extracted with a mixture of benzene and ether. The extract was washed with water, dried with potassium hydroxide and evaporated. The remaining oil (16·0 g) crystallized on standing: m.p. 44—45°C (light petroleum). UV spectrum: $\lambda_{max}$ 262 nm (log $\varepsilon$ 4·16). IR spectrum: 828 (2 vicinal aromatic C—H), 840 (isolated aromatic C—H), 1570 and 1600 (Ar), 1678 (Ar—CO), 2760 and 2800 $cm^{-1}$ ($NCH_2$). NMR spectrum: $\delta$ 7·75 (m, 2 H, aromatic protons in positions 1 and 3), 7·20 (d, $J$ = 9·0 Hz, 1 H, aromatic proton in position 4), 2·30—3·30 (m, 12 H, $CH_2ArCH_2$, $CH_2CH_2N$, $CH_2NCH_2$), 1·71 (bs, 6 H, remaining $CH_2$ in the cycloheptene ring), 1·48 (m, 6 H, remaining $CH_2$ in the piperidine ring). For $C_{19}H_{27}NO$ (285·4) calculated: 79·94% C, 9·54% H, 4·91% N; found: 79·96% C, 9·58% H, 5·03% N.

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REFERENCES

1. Vejdělek Z. J., Protiva M.: This Journal *36*, 1611 (1971).
2. Vejdělek Z. J., Hradil F., Metyš J., Protiva M.: This Journal *37*, 3136 (1972).
3. Vejdělek Z. J., Hradil F., Protiva M.: This Journal *37*, 3501 (1972).
4. Vejdělek Z. J., Kakáč B., Protiva M.: This Journal *38*, 2146 (1973).
5. Allinger N. L., Jones E. S.: J. Org. Chem. *27*, 70 (1972).
6. Aichinger G., Behner O., Hoffmeister F., Schütz S.: Arzneimittel-Forsch. *19*, 838 (1969).
7. Loew E. R., Kaiser M. E., Moore V.: J. Pharmacol. Exptl. Therap. *83*, 120 (1945).
8. Protiva M., Jílek J. O., Řeřicha V.: Chem. listy *43*, 257 (1949).
9. Moore T. S., Boyle M., Thorn V. M.: J. Chem. Soc. *1929*, 39.
10. Baltzly R., Du Breuil S., Ide W. S., Lorz E.: J. Org. Chem. *14*, 775 (1949).
11. Protiva M., Hněvsová-Seidlová V., Vejdělek Z. J., Jirkovský I., Votava Z., Metyšová J.: J. Med. Pharm. Chem. *4*, 411 (1961).
12. Peters L. R., Hennion G. F.: J. Med. Chem. *7*, 390 (1964).
13. Cagniant P.: Compt. Rend. *226*, 1623 (1948); Chem. Abstr. *43*, 2965 (1949).

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