CYCLIC ANALOGUES OF AMPHETAMINE: 1-(6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTEN-5-YL)ETHYLAMINE AND ANALOGUES*

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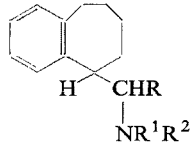
Degradation of amides *VII* and *VIII* led to (6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ylmethyl)amine (*II*) and 1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)ethylamine (*I*) which were converted to N-methylated amines *III*, *V* and *VI*. Amine *I* is a cyclic analogue of amphetamine; pharmacologically interesting is its N,N-dimethyl derivative *VI* which has an antireserpine activity almost equal to that of imipramine. Acid *XII* prepared as an intermediate has a clear antiinflammatory activity.

The interesting pharmacological properties of 6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[1] which is a cyclic analogue of amphetamine with a tetrahydrobenzocycloheptene skeleton led us to prepare for pharmacological testing another type of cyclic analogues of amphetamine with the same skeleton, represented by 1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)ethylamine (*I*).



I, R = CH_3, $R^1 = R^2 = H$
II, R = $R^1 = R^2 = H$
III, R = H, $R^1 = R^2 = CH_3$
IV, R = CH_3, R^1 = CHO, $R^2 = H$
V, R = $R^1 = CH_3$, $R^2 = H$
VI, R = $R^1 = R^2 = CH_3$

Synthesis of amine *I* was preceded by the preparation of the simpler amine *II* as a model experiment in which degradation of 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)acetamide[2] (*VII*) according to Hofmann[3] was employed. The starting amide was obtained in the usual way from 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)acetyl chloride[2], the acid having been prepared from 6,7,8,9-tetrahydro-

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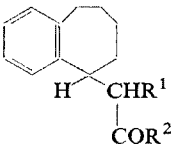
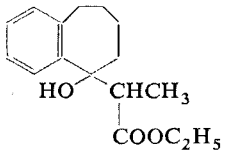
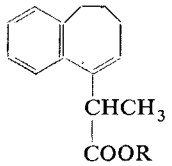
benzocyclohepten-5-one[4] in a Reformatsky reaction[2,5–8], subsequent dehydration, hydrolysis and reduction with Raney's Ni–Al alloy in an alkaline solution[2,6,7]. At the dehydration step, the formic acid reported in the literature[2,5–8] was replaced by boiling in benzene in the presence of a small amount of *p*-toluenesulfonic acid. Using the proton magnetic resonance spectrum of the product it was established that the method gives rise predominantly to a compound with an endocyclic double bond[8,9] which contributes to the correction of older reference[2,5]. Amine *II* was methylated with formaldehyde and formic acid to the N,N-dimethyl derivative *III*.



VII; $R^1 = H$, $R^2 = NH_2$
VIII; $R^1 = CH_3$, $R^2 = NH_2$
XII; $R^1 = CH_3$, $R^2 = OH$



IX



X; $R = C_2H_5$
XI; $R = H$

In the synthesis of amine *I* an analogous procedure was used. 6,7,8,9-Tetrahydrobenzocyclohepten-5-one[4] was processed by Reformatsky's reaction[10] with ethyl 2-bromopropionate[11] and the hydroxy ester *IX* was obtained. For its dehydration, it was boiled with benzene in the presence of *p*-toluenesulfonic acid. The resulting olefinic ester is not completely homogeneous but, according to the NMR spectrum, compound X with an endocyclic double bond clearly predominates. Alkaline hydrolysis and crystallization of the crude product yielded the pure acid *XI*. Reduction of the crude acid by heating in an alkaline solution with Raney's Ni–Al alloy gave rise to 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)propionic acid (*XII*) which was converted to amide *VIII via* the uncharacterized chloride.

As in the preceding case, degradation of amide *VIII* led to the desired amine *I* which was formylated with ethyl formate to the oily formamido derivative *IV* and this was then reduced with lithium aluminium hydride to the methylamino derivative *V*. In analogy to the preceding case, methylation of amine *I* led to the dimethylamino derivative *VI*. All the amines prepared were converted to crystalline hydrochlorides for characterization and for pharmacological testing. Compounds *I*, *IV*–*IX* and *XII* contain in their molecules two centres of asymmetry; the crude products are thus apparently mixtures of two racemates, the separation of which was not pursued. Some of the present compounds, in the form of analytical samples, behave as chemical individuals.

The prepared amines as hydrochlorides were subjected to an orientation psychopharmacological screening using intraperitoneal administration. The incoordinating effect in the rotating-rod test and the antireserpine effect in the eyelid ptosis test were determined in mice. Imipramine[12]

was used as standard, its ED_{50} in the rotating-rod test at the peak effect was 54 mg/kg; its minimum effective dose in the antireserpine test (suppresion of eyelid ptosis) is 2·5 mg/kg; a dose of 1·0 mg/kg is no more effective. The mean effective doses (mg/kg) of the present compounds in the rotating-rod test were as follows; *I*, 24·5; *II*, 31·0; *III*, 20·0; *V*, 23·0; *VI*, 31·0. For *I*, *II*, *III* and *V*, the minimum antireserpine-active dose is 40 mg/kg (for *I* the dose causes death of 20% animals). The most effective in this test is *VI* which has a significant antireserpine effect at 5 mg/kg; thus it has 50% of the activity of imipramine.

Acid *XII* was evaluated by Dr J. Grimová at the pharmacological department of this institute from the point of view of toxicity and antiinflammatory activity. Its mean lethal dose (LD_{50}) in mice on oral application is more than 1 g/kg. The dose causes no death in a group of ten mice. The antiinflammatory activity was followed in two models of acute inflammation (rat foot edema after injection of kaolin and the intrapleural fluid test) and in two models of subchronic inflammation (rat foot edema after injection of an adjuvant and the test of implanted pellets). The compound was administered per os in the form of an aqueous suspension with gum arabic at doses of 100 and 200 mg/kg. A statistically significant effect of the compound was demonstrated in all the models of inflammation with the exception of kaolin edema. The activity was much weaker than with phenylbutazone[13] used as standard in the same or a lower dose.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried in the usual way. NMR spectra (in $CDCl_3$) were recorded in a ZKR 60 (Zeiss, Jena) spectrometer, the IR spectra (Nujol) in a Unicam SP 200 G spectrophotometer.

Ethyl 2-(5-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)propionate (*IX*)

Iodine (0·4 g) was added to a boiling mixture of 400 ml benzene, 80 g 6,7,8,9-tetrahydrobenzocyclohepten-5-one[4], 100 g amalgamated zinc (washed with water, ethanol, ether and benzene) and 65 g ethyl 2-bromopropionate[11] (b.p. 72°C/25 Torr). The mixture was refluxed for 3 h during which period further 200 g ethyl 2-bromopropionate were gradually added as well as 30 g zinc (total amount) with a small amount of iodine, at hourly intervals. This was followed by 25 g ethyl 2-bromopropionate and the mixture was refluxed under stirring for further 4·5 h. After standing overnight, it was decompsoed under external cooling by gradually adding 1000 ml 3M-H_2SO_4 and, after separation, the aqueous layer was extracted with benzene. The combined benzene phases were washed with 3M-H_2SO_4, 2% NH_4OH, and water, dried with Na_2SO_4 and evaporated. Distillation of the residue yielded 85 g (65%) homogeneous product, boiling mainly at 158–162°C/5 Torr, m.p. 44–45°C (hexane). IR spectrum: 755 (4 adjacent Ar—H), 1185 (RCOOR'), 1600 (Ar), 1710 (RCOOR'), 3500 cm^{-1} (OH). NMR spectrum: δ 7·00–7·80 (m, 4 H, aromatic protons), 4·32 (s, 1 H, disappears after deuterization, OH), 3·75 (q, J = 7·5 Hz, 2 H, $COOCH_2$), 3·40 (q, J = 7·5 Hz, 1 H, CHCOO), 2·60–3·10 (m, 2 H, Ar—CH_2), 1·40–2·40 (m, 6 H, remaining 3 CH_2 in the ring), 1·28 (d, J = 7·5 Hz, 3 H, CH_3 of propionyl), 0·76 (t, J = 7·5 Hz, 3 H, CH_3 of ethyl). For $C_{16}H_{22}O_3$ (262·3) calculated: 73·25% C, 8·45% H; found: 73·20% C, 8·45% H.

Ethyl 2-(8,9-Dihydro-7*H*-benzocyclohepten-5-yl)propionate (*X*)

A solution of 90 g *IX* in 600 ml benzene containing 1·5 g *p*-toluenesulfonic acid was refluxed for 4 h using a water separator (6 ml water was separated). After cooling, the solution was washed

with 5% $NaHCO_3$, dried with Na_2SO_4 and evaporated. Distillation of the residue led to 61 g (73%) product boiling at 117–123°C/1 Torr, the mean (b.p. 120°C/1 Torr, n_D^{23} 1·5351) being used as analytical preparation. According to the NMR spectrum, the product contains about 80% of *X*, the remainder being probably an isomer with an exocyclic double bond: δ 7·00–7·60 (m, 4 H, aromatic protons), 6·10 (t, 0·8 H, Ar—C=CH), 4·05 (q, 2 H, $COOCH_2$), 3·60 (q, 0·8 H, CHCOO), 2·50–3·20 (m, 2 H, $ArCH_2$), 1·55–2·50 (m, 4·5 H, remaining CH_2 groups in the ring), 1·35 (d, 3 H, CH_3 of propionyl), 1·08 (t, 3 H, CH_3 of ethyl). For $C_{16}H_{20}O_2$ (244·3) calculated: 78·65% C, 8·25% H; found: 78·80% C, 8·21% H.

2-(8,9-Dihydro-7*H*-benzocyclohepten-5-yl)propionic Acid (*XI*)

A solution of 75 g *X* in 80 ml ethanol was added to a solution of 95 g NaOH in 750 ml water and the mixture was refluxed for 20 h. After cooling, 25 ml of the liquid was withdrawn (about 2·5% of the total amount), the ethanol was evaporated at reduced pressure, the residue was diluted with water to 50 ml, the solution was filtered with charcoal and the filtrate made acid with hydrochloric acid. The precipitated fraction (0·65 g) was crystallized from hexane to a constant melting point of 84–85°C. NMR spectrum: δ 10·35 (bs, 1 H, COOH), 7·00–7·50 (m, 4 H, aromatic protons), 6·18 (t, 1 H, Ar—C=CH), 3·65 (q, 1 H, CH—COO), 2·35–2·80 (m, 2 H, $ArCH_2$), 1·55–2·35 (m, 4 H, remaining 2 CH_2 in the ring), 1·35 (d, 3 H, C—CH_3). For $C_{14}H_{16}O_2$ (216·3) calculated: 77·75% C, 7·46% H; found: 77·72% C, 7·46% H.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-yl)propionic Acid (*XII*)

The total remainder of the reaction mixture from the preparation of *XI* was heated *in vacuo* to remove ethanol, the solution was made up with water to 1 litre and then 65 g Raney Ni–Al alloy was added under stirring over a period of 4 h at 65–75°C. After raising the temperature to 90°C, another 15 g of the alloy was added over an hour and the mixture was heated to 90°C for another hour. It was filtered while hot and washed with hot 2% NaOH. The filtrate was added dropwise (over a period of 20 min) to 1 litre boiling hydrochloric acid and the mixture was heated for 20 min. Then it was cooled with ice and water under stirring. After standing overnight, filtration yielded 50 g (77%) crude product, m.p. 115–117°C. A sample was crystallized from hexane to a constant melting point of 134–135°C; the compound probably represents an individual racemate. NMR spectrum: δ 10·60 (bs, 1 H, COOH), 7·16 (s, 4 H, aromatic protons), 3·00–3·35 (m, 2 H, Ar—CH—CH—COO), 2·60–3·00 (m, 2 H, Ar—CH_2), 1·50–2·30 (bs, 6 H, remaining 3 CH_2 in the ring), 1·01 (d, 3 H, CH_3). For $C_{14}H_{18}O_2$ (218·3) calculated: 77·03% C, 8·31% H; found: 77·16% C, 8·31% H. The product is apparently not identical with the compound reported in ref.[2], whose identity is doubtful.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-yl)propionamide (*VIII*)

Thionyl chloride (60 ml) was added dropwise under stirring to a solution of 50 g crude acid *XII* in 400 ml benzene, the mixture was refluxed for 5 h and the volatile components were removed by distillation *in vacuo*. The crude acyl chloride obtained was added slowly dropwise under cooling and stirring to 250 ml concentrated NH_4OH. The mixture was stirred for 30 min, the precipitated product was filtered and washed with water; 34·5 g, m.p. 168°C (benzene). IR spectrum: 750 (4 adjacent Ar—H), 1650 ($CONH_2$), 3200 and 3400 cm^{-1} (NH_2). NMR spectrum: δ 7·13 (bs, aromatic protons), 6·00 (d, 2 H, $CONH_2$), 2·50–3·30 (m, 4 H, Ar—CH_2, ArCH—CHCO), 1·50–2·15 (m, 6 H, remaining 3 CH_2 in the ring), 0·95 (d, 3 H, CH_3). For $C_{14}H_{19}NO$ (217·3) calculated: 77·38% C, 8·81% H, 6·45% N; found: 77·32% C, 8·84% H, 6·55% N.

(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-ylmethyl)amine (*II*)

By adding dropwise 16 ml bromine to a solution of 170 g KOH in 680 ml water (under stirring at below 5°C) a solution of hypobromite was prepared. This was combined with 50 g 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)acetamide[2] (*VII*). The mixture was stirred for 80 min under cooling, for further 80 min at 40–45°C and cooled. The separated oil was extracted with a total of 1 100 ml ether. The ether solution obtained was added dropwise (over a period of 40 min) to 150 ml concentrated hydrochloric acid and heated to 105–110°C using an efficient condenser. After the addition of the solution was terminated, the heating was continued until complete removal of the ether.The remaining liquid stood overnight whereupon the hydrochloride of the product precipitated; this was filtered, decomposed with 20% NaOH and the liberated base was extracted with a mixture of benzene and ether; 17·1 g (40%), b.p. 135°C/10 Torr, n_D^{24} 1·5580. NMR spectrum: δ 7·17 (s, 4 H, aromatic protons), 2·90 and 1·60 (2 m, 5 H, CH_2—Ar—CH—CH_2N), 1·72 (bs, 6 H, remaining 3 CH_2 in the ring), 1·20 (s, 2 H, NH_2). For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·05% C, 9·65% H, 7·86% N.

Hydrochloride, m.p. 208–209°C (ethanol–ether). For $C_{12}H_{18}ClN$ (211·7) calculated: 68·08% C, 8·57% H, 16·74% Cl, 6·61% N; found: 67·83% C, 8·68% H, 16·94% Cl, 6·57% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-yl)ethylamine (*I*)

Analogously, degradation of 33 g amide *VIII* yielded 15 g (44%) hydrochloride of base *I* which was recrystallized from a mixture of ethanol and ether; it does not melt below 290°C. For $C_{13}H_{20}$.ClN (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·00% C, 9·03% H, 15·52% Cl, 6·11% N.

N-Methyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)-ethylamine (*V*)

The base was liberated from 10·5 g hydrochloride of amine *I* with 20% NaOH and isolated by extraction with ether; 8·5 g of oil. The total amount was refluxed for 2 h with 25 ml ethyl formate, cooled, diluted with ether and washed with excess dilute hydrochlorid acid. A total of 4·8 g starting base was recovered from the acid aqueous solution. The organic phase was dried with Na_2SO_4 and evaporated. The residue, 4·4 g (95% with respect to conversion) of crude formamide *IV* was dissolved in 60 ml ether and the solution was added dropwise to a stirred solution of 3·0 g $LiAlH_4$ in 90 ml ether. The mixture was refluxed for 4 h, cooled, decomposed by adding dropwise 12 ml 20% NaOH, the solid was filtered and washed with benzene, the combined filtrates were dried with KOH and evaporated. Distillation of the residue yielded 3·70 g (90%) base *V*, b.p. 112°C/2 Torr, n_D^{20} 1·5420. NMR spectrum: δ *c.* 7·10 (m, 4 H, aromatic protons), 2·60–3·40 (m, 3 H, CH_2—Ar—CH), 2·44 (s, 3 H, N—CH_3), 1·74 (bs, 7 H, remaining 3 CH_2 in the ring and CH—N), 1·25 (bs, 1 H, NH), 0·88 (d, J = 6·0 Hz, 3 H, C—CH_3). For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 82·41% C, 10·20% H, 6·72% N.

Hydrochloride, m.p. 182–184°C (ethanol–ether). For $C_{14}H_{22}ClN$ (239·8) calculated: 70·12% C, 9·25% H, 14·79% Cl, 5·84% N; found: 69·87% C, 9·38% H, 15·08% Cl, 5·85% N.

N,N-Dimethyl-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl-methyl)amine (*III*)

Water (6 ml) and aqueous formaldehyde (8 ml) were added to a solution of 2·6 g *II* in 6 ml 85% formic acid and the mixture was refluxed for 5 h (in a 120–130°C bath). After cooling, 15 ml concentrated hydrochloric acid were added, the solution was evaporated to dryness *in vacuo*, the

residue was decomposed with excess 20% solution of NaOH and the released base was extracted with a mixture of ether and benzene; 2·9 g (96%), b.p. 114°C/2 Torr, n_D^{20} 1·5380. For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H; found: 82·47% C, 10·34% H.

Hydrochloride, m.p. 225—226°C (ethanol–ether). For $C_{14}H_{22}ClN$ (239·8) calculated: 70·12% C, 9·25% H, 14·79% Cl, 5·84% N; found: 69·91% C, 9·26% H, 14·70% Cl, 5·83% N.

N,N-Dimethyl-1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)-ethylamine (*VI*)

In analogy with the preceding case, 4·8 g amine *I* was methylated with 6 ml 85% formic acid and 12 ml concentrated aqueous solution of formaldehyde. A total of 4·6 g (84%) base was obtained, b.p. 118°C/2 Torr, n_D^{20} 1·5330, which reacts with hydrogen chloride in ether to the hydrochloride, which crystallizes from a mixture of 95% ethanol and ether as a monohydrate, m.p. 136—138°C (it softens at 110—115°C). For $C_{15}H_{26}ClNO$ (271·8) calculated: 66·27% C, 9·64% H, 13·05% Cl, 5·15% N; found: 66·27% C, 9·54% H, 13·22% Cl, 5·08% N.

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