BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. V.*

2-(2-AMINOETHYL)-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENE AND DERIVATIVES

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2-Cyanomethyl and 2-acetonyl derivatives of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*, *IV*) were used to synthesize analogues of phenethylamine, amphetamine and phentermine *VI*, *VII*, and *XII*, and their N-methyl derivatives *IX*, *XIII* and *XIV*. Reaction of 2-chloromethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene with the acetamidomalonic ester anf further treatment yielded the alanine derivative *XVI*. Compounds *VI*, *VII* and *IX* at high doses cause symptoms of excitation and show an antireserpine activity; with substances *XII*–*XIV* this effect is lacking and hypotensive activity appears. The whole group is characterized by a local-anaesthetic and an antiarrhythmic activity.

In connection with a systematic investigation of benzocycloheptene derivatives as potential drugs[1] we thought it useful to prepare 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl analogues of phenethylamine as the basic representative of sympathomimetic amines[2], further analogues of amphetamine as a prototype of central stimulants[3] and of "phentermine" as a typical anorectic[4]. In these analogues, the benzene ring of the basic compounds is substituted in the typical positions 3,4 by condensation with a seven-membered alicycle.

Similarly to preceding work[1] we used 6,7,8,9-tetrahydrobenzocycloheptene-5-one as the starting compound which can be reduced[5–7] to 6,7,8,9-tetrahydro-5*H*-benzocycloheptene, most suitably by the Wolff-Kižněr method[7,8]. This can be chloromethylated[9–11] to the 2-chloromethyl derivative *I* which is converted[9] to the 2-cyanomethyl derivative *II*. Claisen's reaction of nitrile *II* with ethyl acetate[12] yielded the acetylacetonitrile derivative *III*, the IR spectrum of which lacks the keto group band and, instead, exhibits a band of the hydroxyl group in a hydrogen bond (3110 cm^{-1}). The compound is apparently fully enolized, the enol being stabilized by a hydrogen bond with the nitrogen atom of the nitrile group. Acid hydrolysis of this compound[13] gives rise to 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl-acetone (*IV*).

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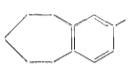
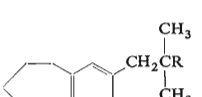
Reduction of the nitrile *II* with lithium aluminium hydride in ether produced 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl) ethylamine (*VI*) *i.e.* the desired analogue of phenethylamine.

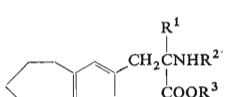


I, R = CH_2Cl *IV*, R = CH_2COCH_3
II, R = CH_2CN *V*, R = $CH_2C(=NOH)CH_3$
III, R = $CH(CN)COCH_3$ *VI*, R = $CH_2CH_2NH_2$
VII, R = $CH_2CH(CH_3)NH_2$
VIII, R = $CH_2CH(NHCHO)CH_3$
IX, R = $CH_2CH(NHCH_3)CH_3$

The oily oxime *V*, prepared from ketone *IV* was reduced with sodium and ethanol, giving rise to 1-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-2-aminopropane (*VII*), *i.e.* the desired analogue of amphetamine. Heating of this primary amine with ethyl formate in an autoclave to 105–115°C yielded the formamide derivative *VIII* which is reduced with lithium aluminium hydride to the secondary amine *IX*. Reaction of the ketone *IV* with methylmagnesium iodide gave rise to the tertiary alcohol *X* which underwent Ritter's reaction (sodium cyanide and sulfuric acid in acetic acid) to yield the formamide derivative *XI*. Its alkaline hydrolysis yielded the primary amine *XII* (analogue of phentermine) while reduction with lithium aluminium hydride resulted in the secondary amine *XIII*. Methylation of this amine with formaldehyde and formic acid gave rise to the dimethylamino derivative *XIV*.



X, R = OH
XI, R = NHCHO
XII, R = NH_2
XIII, R = $NHCH_3$
XIV, R = $N(CH_3)_2$



XV, $R^1 = COOC_2H_5$, $R^2 = COCH_3$, $R^3 = C_2H_5$
XVI, $R^1 = R^2 = R^3 = H$

Alkylation of ethyl acetamidomalonate[14] with the chloromethyl derivative[14] *I* yielded the amidodiester *XV* and this was hydrolyzed under acid conditions to β-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)-α-alanine (*XVI*) which can be considered as an analogue of phenylalanine as well as of 3,4-dihydroxyphenylalanine.

Compounds *VI*, *VII*, *IX*, *XII*–*XIV* and *XVI* were evaluated pharmacologically in the form of hydrochlorides by methods of pharmacological screening and with special emphasis on the suggested central or circulatory effects. The results are shown below (the mode of application

during basic testing, acute toxicity for mice LD_{50} and the dose D at which the substance was used in *in vivo* tests). Table I shows the antimicrobial activity of the compounds in *in vitro* tests.

Compound *VI* (*i.v.*, LD_{50} 40 mg/kg, D 8 mg/kg) at doses greater than D in mice brings about signs of central excitation which are only suggested at dose D. Subcutaneous doses of 40—100 mg/kg cause slight excitation in mice but depress the locomotor activity. Disturbance of motor coordination in 50% mice (the rotating-rod test) is caused by subcutaneous dose of 28 mg/kg (maximum effect was observed 15 min after application). The dose D antagonizes the reserpine ptosis of mice but not reserpine hypothermis. In rats, an oral dose of 50 mg/kg inhibits the reserpine ulcerogenic effect. At 0·5 mg/kg *i.v.* it brings about a short-term rise in blood pressure in narcotized rats. In the mouse pupil there is a myotic effect, the substance depresses the sugar blood level in rats, acts as an analgesic in two tests in mice and has an antiarrhythmic effect in mice (toward chloroform).

Compound *VII* (*i.v.*, LD_{50} 44 mg/kg, D 8 mg/kg) has certain central stimulatory effects but of a substantially lower degree than d-amphetamine. The locomotor activity of mice is increased at a dose of 5 mg/kg *s.c.* (c. 20%). A higher dose (10 mg/kg) has no more intensive stimulatory effect. Disturbances of motor coordination in mice (with some 50% animals) take place only after doses greater than 40 mg/kg *s.c.* The compound depresses in mice their reactivity to nociceptive stimulation (heat stimulus): D_{50} = 1·8 mg/kg *s.c.* (a similar type of "analgesic" effect is observed after amphetamine). A double dose D antagonizes pronouncedly the reserpine ptosis of mice. Hypothermia is not affected. It causes a protracted rise in blood pressure of narcotized rats. Similarly to *VI* it has a pronounced myotic effect (comparable with that of pilocarpine), an antiarrhythmic and also a pronounced localy-anaesthetic effect (in the test of infiltration anaesthesia of guinea pigs like procaine, in rabbit cornea like cocaine, but it irritates).

Compound *IX* (*i.v.*, LD_{50} 50 mg/kg, D 10 mg/kg) at high doses brings about signs of central excitation. At dose D it increases the motility of mice and has an antireserpine effect in the ptosis test of mice. It depresses briefly rat blood pressure. It depresses the blood sugar level in rats (the

TABLE I

Antimicrobial Activity (Minimum Inhibitory Concentration in μg/ml of the Compounds Prepared Here *in vitro*[a]

Microorganism	*VI*	*VII*	*IX*	*XII*	*XIII*	*XIV*
Streptococcus β-haemolyticus	25	100	50	25	50	50
Streptococcus β-haemolyticus WARD	25	100	50	25	50	50
Staphylococcus pyogenes aureus[b])	50	100	50	12·5	50	50
Klebsiella pneumoniae	100	100	100	50	50	50
Pseudomonas aeruginosa	100	100		100	100	100
Escherichia coli	100	100	100	100	100	100
Salmonella typhi abdominalis	100	50	100	100	100	100
Proteus vulgaris	100	100	100	100	100	
Mycobacterium tuberculosis H 37 Rv	50	50	100	50	50	100

[a] All the compounds were inactive against *Saccharomyces pasteurianus*, *Trichophyton mentagrophytes*, *Candida albicans* and *Aspergillus niger*. [b] The same values were obtained also with the penicillin-resistant strain.

same with oral application of 30 mg/kg). The local anaesthetic effect is apparent only in the rabbit corneal test.

Compound *XII* (*i.v.*, LD_{50} 50 mg/kg, D 10 mg/kg) has no stimulatory effect. On the contrary, it inhibits searching activity and motility in known surroundings. In the test of infiltration anaesthesia it has the same effect as procaine. In mouse cornea it shows signs of myotic effect. It depresses briefly but substantially rat blood pressure. It depresses protractedly rat blood pressure in the case of mild experimental hypertension (DOCA). Also, an oral dose of 25 mg/kg depresses the blood pressure of rats with normal tension. On the other hand, in monkeys the effect was negative. It has further an antiarrhythmic effect (chloroform), prolongs the survival of an asphyctic mouse myocard and has a negatively chronotropic effect in an isolated rabbit auricle. Compound *XIII* (*i.v.*, LD_{50} 40 mg/kg, D 8 mg/kg) does not affect the central nervous system or blood pressure of rats with normal tension. On the other hand, at dose D it depresses protractedly the blood pressure of rats with experimental hypertension (DOCA). It has a local anaesthetic effect (irritating), further a slight antiarrhythmic effect (toward chloroform and aconitine), a sign of myotropic spasmolytic effect (toward $BaCl_2$) in an isolated rat intestine *in vitro*. Compound *XIV* (*i.v.*, LD_{50} 38 mg/kg, D 7 mg/kg) has a slight central depresant activity: it inhibits motility and searching activity of mice in known surroundings. It is not interesting from the point of view of blood pressure effects. It has a slight local anaesthetic effect of procaine type, it irritates rabbit cornea. It shows signs of antiarrhythmic activity (toward chloroform) and has negative inotropic and chronotropic effect. Compound *XVI* (*p.o.*, LD_{50} 2 500 mg/kg, D 300 mg/kg) slightly prolongs thiopental sleep of mice. Otherwise it has no pronounced effects.

EXPERIMENTAL

The melting points 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) in a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform) in a ZKR 60 spectrometer (Zeiss, Jena).

2-Acetyl-2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)acetonitrile (*III*)

A mixture of 92·5 g nitrile *II*[9] (b.p. 146—152°C/2 Torr) and 66 g ethyl acetate was added over 10 min to warm sodium methoxide (from 175 ml methanol and 15 g sodium) and the mixture formed was refluxed under stirring for 4 h. After 48 h of standing at 0°C filtration yielded 68 g of a sodium salt of the product. Processing of the filtrate and decomposition of the salt with dilute acetic acid yielded 90 g (80%) crude product which was purified by crystallization from methanol, m.p. 101—102°C. UV spectrum: λ_{max} 212 nm (log ε 4·16), 217 nm (4·15), 269 nm (4·10). IR spectrum: 770 (OH), 815 and 891 (1,2,4-C_6H_3), 1 370 (C—O), 1 502 (Ar), 1 634 (C=C), 2 215 (CN) and 3 110 cm^{-1} (OH in hydrogen bond). For $C_{15}H_{17}NO$ (227·3) calculated: 79·25% C, 7·54% H, 6·16% N; found: 79·53% C, 7·49% H, 6·11% N.

(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)acetone (*IV*)

Ketonitrile *III* (90 g) was added slowly to 120 ml sulfuric acid in 45 ml water and heated on a boiling-water bath until a homogeneous solution was formed. After cooling it was diluted with 580 ml water and refluxed for 11 h in a 120—130°C bath. After cooling, the oily product was extracted with ether, the extract was washed with 10% sodium carbonate (acidification of the alkaline washings recovered 19 g of the starting *III*, m.p. 101—102°C, identity of the IR spectrum), dried and distilled: 43 g (54%), b.p. 138°C/1 Torr, n_D^{22} 1·5415. UV spectrum: λ_{max} 217 nm inflex. (log ε 4·02), 266 nm (2·86), 275 nm (2·81). IR spectrum: 821, 885 (1,2,4-C_6H_3), 1 713 cm^{-1} (CO). NMR spectrum: δ 6·80—7·20 (multiplet, 3 H of the aromatic ring), 3·63 (singlet, 2 H of the acetone

CH_2 group), 2·80 (multiplet, 4 H of the CH_2 groups in the seven-membered ring adjacent to the aromatic ring), 2·15 (singlet, 3 H in CH_3), 1·75 (multiplet, 6 H of the remaining CH_2 groups in the seven-membered ring). For $C_{14}H_{18}O$ (202·3) calculated: 83·12% C, 8·97% H; found: 83·13% C, 8·93% H.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)ethylamine (*VI*)

Nitrile *II* (15 g) in 100 ml ether was added dropwise under stirring to a suspension of 5·0 g lithium aluminium hydride in 100 ml ether and the mixture was refluxed for 5 h. After standing overnight, it was decomposed with 20 ml 20% NaOH, the solid components were filtered and washed with ether and the filtrate was dried with solid KOH. Distillation yielded 9·8 g, b.p. 122°C/0·5 Torr, n_D^{21} 1·5475. For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H; found: 82·56% C, 10·12% H. *Hydrochloride*, m.p. 203—204°C (ethanol). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·02% C, 8·83% H, 15·44% Cl, 6·16% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-aminopropane (*VII*)

Oily oxime *V* (19·0 g) (obtained in a 93% yield by the reaction of ketone *IV* with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol) in 150 ml ethanol was added dropwise to 65 g sodium and the mixture was refluxed in a 120—130°C bath until all sodium dissolved, during which time 380 ml ethanol was gradually added. After cooling, the mixture was decomposed with 150 ml water and steam-distilled; the distillate was trapped in a solution of 15 ml HCl in 100 ml water. The distillate (2 l) was evaporated *in vacuo* to dryness and the theoretical yield (21 g) of *hydrochloride* was obtained. This was recrystallized from a mixture of ethanol and ether, m.p. 219—220°C. For $C_{14}H_{22}ClN$ (239·8) calculated: 70·12% C, 9·25% H, 14·79% Cl, 5·84% N; found: 70·33% C, 9·27% H, 14·76% Cl, 5·81% N. The *base* was obtained by decomposition of the hydrochloride with 20% NaOH, extraction with ether and distillation: b.p. 155°C/10 Torr. For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 82·35% C, 10·64% H, 6·84% N.

N-[1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-propyl]formamide (*VIII*)

A mixture of 6·2 g amine *VII* and 5 ml ethyl formate was heated in an autoclave for 6 h to 110 to 115°C. After cooling it was diluted with ether, the solution was washed with dilute hydrochloric acid, dried and evaporated. The residue (7·1 g, 100%) is an oil, a part of which was distilled: b.p. 186°C/0·5 Torr. UV spectrum: λ_{max} 211·5 nm (log ε 4·02), 215·5 nm (4·00), 266 nm (3·59), 274·5 nm (3·58). IR spectrum: 819 and 890 (1,2,4-C_6H_3), 1 502, 1 540 and 1 680 (CONH), 3 280 cm^{-1} (NH). For $C_{15}H_{21}NO$ (231·3) calculated: 77·88% C, 9·15% H, 6·05% N; found: 78·41% C, 9·36% H, 6·00% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-methylaminopropane (*IX*)

A solution of 7·0 g crude amide *VIII* in 50 ml ether was added to a solution of 2·5 g lithium aluminium hydride in 50 ml ether and the mixture was refluxed for 2 h. After cooling it was decomposed with 10 ml 20% NaOH, the precipitated solid was filtered and the filtrate distilled: 5·85 g (91%), b.p. 158°C/10 Torr, n_D^{23} 1·5340. NMR spectrum: δ 6·70—7·10 (multiplet, 3 H of the benzene ring) *c.* 2·70 (multiplet, 7 H of the CH_2 groups adjacent to the benzene ring and a CH group adjacent to the amino group), 2·38 (singlet, 3 H in NCH_3), 1·75 (multiplet, 6 H of the remaining CH_2 groups in the seven-membered ring), 1·35 (singlet, 1 H in NH, disappears on deuteriation), 1·05 (doublet, 3 H in C—CH_3, J = 6·0 Hz). For $C_{15}H_{23}N$ (217·3) calculated: 82·89% C, 10·67% H, 6·44% N; found: 82·64% C, 10·88% H, 6·40% N. *Hydrochloride*, m.p.

166—167°C (ethanol–ether). For $C_{15}H_{24}ClN$ (253·8) calculated: 70·98% C, 9·53% H, 13·97% Cl, 5·52% N; found: 70·99% C, 9·62% H, 13·82% Cl, 5·49% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-methyl-2-propanol (*X*)

A solution of 30 g ketone *IV* in 100 ml ether was added dropwise to a solution of methyl magnesium 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 20 g NH_4Cl in 100 ml water, the ether phase was washed with 10% sodium thiosulfate, dried and evaporated. The residue (33 g, 100%) solidified on cooling; sample for analysis was recrystallized from hexane, m.p. 74—75°C. NMR spectrum: ϑ 7·45—6·85 (multiplet, 3 H of the benzene ring), 2·76 (deformed singlet, 6 H of the CH_2 groups adjacent to the benzene ring), 1·83 (deformed singlet, 6 H of the remaining CH_2 groups in the seven-membered ring), 1·60 (singlet, 1 H in OH), 1·30 (singlet, 6 H in CH_3-C-CH_3). For $C_{15}H_{22}O$ (218·3) calculated: 82·50% C, 10·16% H; found: 82·98% C, 10·02% H.

N-[1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-methyl-2-propyl]formamide (*XI*)

Sodium cyanide (20 g) was added slowly under stirring at 10°C to 10 ml acetic acid and 10 ml sulfuric acid with 33 g alcohol *X* in 50 ml acetic acid. After further 15 min of stirring, a mixture of 20 ml acetic acid and 30 ml sulfuric acid was added under stirring at the same temperature, the mixture was stirred for 3 h and left to stand for 48 h at room temperature. It was then decomposed by pouring into a mixture of 400 g ice and 250 ml water, the mixture was roughly neutralized with 450 ml 20% NaOH (to pH 8), diluted with 200 ml lukewarm water and the product isolated by extraction with ether. An oily product was obtained (35 g) which was dissolved in 30 ml warm hexane and the solution combined with 60 ml light petroleum (fraction between 40 and 60°C). On standing overnight in a refrigerator, 18 g of a product crystallized, m.p. 84—85°C (hexane). NMR spectrum: ϑ 8·15 (multiplet, 1 H in CHO, disappears on deuteriation), 6·70—7·05 (multiplet, 3 H, protons of the benzene ring), 5·0—6·20 (broad doublet, 1 H in NH, disappears on deuteration), 2·50—3·05 (multiplet, 6 H of CH_2 groups adjacent to the benzene ring), 1·45—2·00 (multiplet, 6 H of the remaining CH_2 groups in the seven-membered ring), 1·34 (doublet, 6 H in CH_3-C-CH_3). For $C_{16}H_{23}NO$ (245·4) calculated: 78·31% C, 9·45% H, 5·71% N; found: 78·47% C, 9·58% H, 5·70% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-amino-2-methylpropane (*XII*)

A solution of 6·0 g NaOH in 45 ml water was added to a solution of 15 g formamide *XI* in 65 ml ethanol and the mixture was refluxed for 48 h. Ethanol was evaporated at reduced pressure and the product was extracted from the residue with ether. By shaking the extract with 70 ml dilute HCl (1 : 4) the base was brought to the aqueous solution in the form of hydrochloride. The solution was made alkaline with 20% NaOH and the base was isolated by extraction with ether and by distillation of the extract: 10·5 g (81%), b.p. 168°C/10 Torr, n_D^{21} 1·5401. For $C_{15}H_{23}N$ (217·3) calculated: 82·89% C, 10·67% H, 6·45% N; found: 82·61% C, 10·56% H, 6·12% N. *Hydrochloride*, m.p. 207—208°C, (ethanol–ether). For $C_{15}H_{24}ClN$ (253·8) calculated: 70·98% C, 9·53% H, 13·97% Cl, 5·52% N; found: 71·10% C, 9·60% H, 13·69% Cl, 5·51% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-methylamino-2-methylpropane (*XIII*)

Reduction of 18 g formamide *XI* with 5·0 g lithium aluminium hydride in 370 ml ether was done as with compound *IX*. A total of 15·4 g (91%) base was obtained boiling at 168°C/10 Torr, n_D^{21} 1·5338. NMR spectrum: ϑ 6·70—7·10 (multiplet, 3 H of the benzene ring), 2·75 (multiplet, 4 H of the CH_2 groups in the seven-membered ring adjacent to the benzene ring), 2·61 (singlet, 2 H

of CH_2 of the side chain), 2·36 (singlet, 3 H in NCH_3), 1·73 (multiplet, 6 H of the remaining CH_2 groups in the seven-membered ring), 1·33 (singlet, 1 H in NH, disappears on deuteriation), 1·02 (singlet, 6 H in CH_3-C-CH_3). For $C_{16}H_{25}N$ calculated: 83·05% C, 10·89% H, 6·05% N; found: 82·90% C, 10·90% H, 6·05% N. *Hydrochloride*, m.p. 170–171°C (ethanol–ether). For $C_{16}H_{26}ClN$ (267·8) calculated: 71·74% C, 9·79% H, 13·24% Cl, 5·23% N; found: 71·42% C, 9·68% H, 13·17% Cl, 5·26% N.

1-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-dimethylamino-2-methylpropane (*XIV*)

A mixture of 9·6 g amine *XIII*, 8·5 ml 85% formic acid, 12 ml water and 12 ml 36% formaldehyde was refluxed for 5 h in a 120–130°C bath. After cooling it was combined with 45 ml concentrated HCl and the mixture was evaporated at reduced pressure practically to dryness. The residue was made alkaline with 20% NaOH and the product isolated by extraction with ether and by distillation: 9·7 g, b.p. 132°C/0·5 Torr, n_D^{22} 1·5332. For $C_{17}H_{27}N$ (245·4) calculated: 83·18% C, 11·10% H, 5·72% N; found: 83·35% C, 11·10% H, 5·64% N. *Hydrochloride*, m.p. 204–205°C (ethanol–ether). For $C_{17}H_{28}ClN$ (281·9) calculated: 72·44% C, 10·01% H, 12·58% Cl, 4·97% N; found: 72·28% C, 10·02% H, 12·34% Cl, 4·92% N.

Diethyl α-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)methyl-α-acetamidomalonate (*XV*)

Diethyl acetamidomalonate (14·8 g) was added to 1·57 g sodium in 100 ml ethanol, the mixture was stirred for 30 min, combined with 15 g 2-chloromethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[9] (*I*) (b.p. 125–127°C/1 Torr) and the mixture was refluxed for 13 h. It was then evaporated *in vacuo* to dryness, the residue was mixed with 50 ml water and extracted with benzene. By evaporation of the extract a total of 16 g crude product was obtained which was chromatographed on a column of 290 g alumina. Elution with benzene produced 10·5 g product, m.p. 118–120°C (benzene–hexane). UV spectrum: λ_{max} 265·5 nm (log ε 3·60), 274 nm (3·58). IR spectrum: 809, 891 (1,2,4-C_6H_3), 1189 and 1201 (C—O), 1517 and 1648 (CONH), 1745 (COOR), 3280 cm^{-1} (NH). For $C_{21}H_{29}NO_5$ (375·5) calculated: 67·18% C, 7·79% H, 3·73% N; found: 67·45% C, 7·98% H, 3·91% N.

β-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-α-alanine (*XVI*)

A mixture of 60 ml concentrated hydrochloric acid and 10·0 g ester *XV* was refluxed for 8 h. After cooling, the precipitated hydrochloride was filtered: 6·60 g (93%), m.p. 247–248°C (ethanol–ether). For $C_{14}H_{20}ClNO_2$ (269·8) calculated: 62·33% C, 7·48% H, 13·14% Cl, 5·19% N; found: 62·47% C, 7·43% H, 13·09% Cl, 5·33% N. The free amino acid was obtained by adding the theoretical amount of pyridine to an ethanolic solution of the hydrochloride; m.p. 211–212°C. For $C_{14}H_{19}NO_2$ (233·3) calculated: 72·06% C, 8·21% H, 6·00% N; found: 71·40% C, 8·13% H, 5·63% N.

The pharmacological evaluation of the compounds was done by the general screening methods at the affiliated unit of this institute at Rosice n/L under the direction of Dr J. Němec. The cardiovascular effects were evaluated at the pharmacological department under the direction of Dr V. Trčka and Dr M. Vaněček. The antimicrobial activity was evaluated by Dr J. Turinová of the bacteriological department (headed by Dr A. Šimek). The analytical determinations were done at the analytical department (headed by Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Dr M. Čech and Mrs A. Slaviková. The spectra were recorded and interpreted by Dr B. Kakáč, Dr J. Holubek and Dr E. Svátek. Technical assistance of Mr L. Tůma with the preparatory part of the work is acknowledged.

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