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

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Reduction of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one oxime with sodium and ethanol yielded 6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*) which was converted *via* the acyl derivatives *II* and *III* to the secondary amines *IV* and *V*. Alkylation reactions produced amines *VI* and *VII* from *I*. Reaction of the above ketone with methylmagnesium iodide gives rise to alcohol *VIII* together with a small amount of the olefin *XIII*. Ritter's reactions of alcohol *VIII* produced the formamide *IX* which was hydrolyzed to the primary amine *X* or reduced to the secondary amine *XI*. Methylation of amine *X* yielded the tertiary amine *XII*. Pharmacologically most interesting is the primary amine *I* which shows a pronounced anorectic, antireserpine and mydriatic effect, a stimulating effect being observed only after high doses.

6-Amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*I*) is a cyclic analogue of amphetamine[1] and hence one could expect it to possess some features of the pharmacodynamic profile of the amphetamine prototype of psychostimulants and anorectics. Synthesis of amine *I* was described[2] using reductive amination of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one on Raney nickel but the authors of the procedure did not take up the pharmacodynamic aspects of the product. In connection with our systematic studies of amines derived from the benzocycloheptene skeleton[3-9] we investigated compound *I* and some of its derivatives.

As in previous studies the parent compound was 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[10] which was transformed *via* the corresponding alcohol[11] to 6,7-dihydro-5*H*-benzocycloheptene[3]; this was hydroxylated with hydrogen peroxide in acetic acid to 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5,6-diol which underwent acid-catalyzed dehydration to yield 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one[12-14]. The oxime prepared in the usual way[2] was reduced with sodium and ethanol to amine *I* which was isolated directly in the form of a new hydrochloride.

Heating of amine *I* with ethyl formate in an autoclave to 120°C yielded the formamide *II* while refluxing of amine *I* with acetic anhydride yielded the acetamide *III*. Reduction of the two amides with lithium aluminium hydride yielded the secondary amines *IV* and *V*. The ethylamino derivative *V* was pre-

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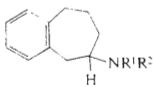
pared in a less suitable way by alkylation of amine *I* with ethyl iodide in boiling acetone in the presence of potassium carbonate. Alkylation of amine *I* with formaldehyde and formic acid resulted in the dimethylamino derivative *VI*. Finally, a reaction of 3,3-diphenylpropyl bromide[15] with excess amine *I* yielded the secondary amine *III* which is an analogue of the vasodilating agent "prenylamine"[16].



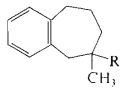
I, $R^1 = R^2 = H$ *IV*, $R^1 = H$, $R^2 = CH_3$
II, $R^1 = H$, $R^2 = CHO$ *V*, $R^1 = H$, $R^2 = CH_2CH_3$
III, $R^1 = H$, $R^2 = COCH_3$ *VI*, $R^1 = R^2 = CH_3$
VII, $R^1 = H$, $R^2 = CH_2CH_2CH(C_6H_5)_2$

Reaction of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one[12-14] with methylmagnesium iodide in ether gave rise to a not completely homogeneous product from which chromatography separated a highly nonpolar product, apparently the corresponding olefin. The predominating product was characterized as the tertiary alcohol *VIII*. Ritter's reaction of the crude product of Grignard's reaction (sodium cyanide and sulfuric acid in acetic acid) yielded the oily formamide *IX*. As a lower-boiling product there appeared a considerable amount of the hydrocarbon $C_{12}H_{14}$, which, on the basis of the NMR spectrum, has the structure of 8-methyl-6,7-dihydro-5*H*-benzocycloheptene (*XIII*). Hydrolysis of formamide *IX* with a boiling mixture of hydrochloric acid and ethanol yielded the primary amine *X*. Reduction of *IX* with lithium aluminium hydride yielded the methylamino derivative *XI*. The dimethylamino derivative *XII* was formed by methylation of amine *X* with formaldehyde and formic acid.

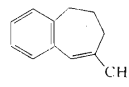
All the amines prepared were evaluated pharmacologically in the form of hydrochlorides with special emphasis on the assumed amphetamine-type activity. Of greatest interest here was the amine *I* ("amizoptene"). The acute toxicity of amizoptene in mice was estimated after intravenous administration in aggregated animals as well as in isolated animals, further for oral and intraperitoneal administration; the corresponding LD_{50} values were 36·0 (for amphetamine 8·4), 42·0 (for amphetamine 14·0), 210, and 55 mg/kg. The character of toxic symptoms is the same with all modes of administration. The compound has an excitatory effect; restlessness, increased salivation and piloerection are observed. Death takes place under clonic convulsions. The LD_{50} for rats after *p.o.* administration is 270 mg/kg; the toxic symptoms are similar to those in mice. In the rotating-rod test in mice after *i.p.*

application the compound shows greatest incoordinating effect 30–60 min following application. The mean effective dose ED_{50} is 39 mg/kg. The incoordinating effect is due to central excitation. The spotaneous motor activity in mice during *i.p.* application is increased by two-fold by a dose of 13 mg/kg amizoptene, or by 1 mg amphetamine/kg. Using the Animex apparatus which records the total motor activity of male rats after a *p.o.* application, amizoptene was found 45 min after application of 10 and 25 mg/kg to decrease somewhat the activity of the animals; a slight increase of activity took place only after 90 or 180 min following application. On the other hand, amphetamine[1] as well as phenmetrazine[17] in doses of 1 and 5 mg/kg increase the activity of the animals by 3–8-fold of the controls as early as 45 min after application. Similarly, phentermine[18] in a dose of 1 mg/kg stimulates the overall activity more than amizoptene does in a dose of 25 mg/kg. The anorectic effect of amine *I* was evaluated in a test on rats after *p.o.* application[19]. A dose of 30 mg/kg decreased with statistical significance the food consumption; a dose of 60 mg/kg showed an even greater effect. In the same test, amphetamine showed an effect from a dose of 5 mg/kg, phenmetrazine from 20 mg/kg and phentermine from a dose of 10 mg/kg. All the three standards show a strong central stimulation at the doses shown. Amizoptene thus appears to be an anorectic which is active in doses not causing significant excitation.

Amizoptene antagonizes with statistical significance the effect of reserpine in mice in the test of eyelid ptosis in doses of 10 and 40 mg/kg *i.p.* This antireserpine effect is comparable with the effect of imipramine[20]; in contrast with imipramine, effective doses of amizoptene also antagonize the sedative effect of reserpine. In the test of ulcerogenic effect of reserpine in rats, the antireserpine effect of amizoptene is significant at a dose of 50 mg/kg *p.o.* In doses of 20, 40 and 60 mg/kg *i.p.*,amizoptene prolongs significantly the hypnotic effect of thiopental: no dose-response relationship was observed since after all the three doses shown the thiopental sleep was extended by nearly five-fold. Amizoptene potentiates the convulsant effect of pentatrazol and strychnine in mice at doses about five times greater than amphetamine. Amizoptene displayed a relatively pronounced mydriatic effect on mice; at a dose of 6·7 mg/kg *i.v.* the pupil diameter was increased to the two-fold of the value before



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



XIII

administration (for amphetamine this dose is 3·5 mg/kg). In the test of effect on methacholine lachrimation it was found to display no effect of peripheral cholinolytic character. In the hot-plate test amizoptene showed an analgesic effect on mice, the mean effective dose being 3·0 mg/kg *s.c.* Since in preliminary test with normotensive rats a slight hypotensive effect of amizoptene could be observed after a dose of 30 mg/kg *i.v.*, its effect on the blood pressure of normotensive nonanaesthesized monkeys (*Macacus mulatta*) was examined, after oral doses of 40 and 100 mg/kg. It was found that amizoptene has no unequivocal effect on the height of systolic pressure (even at a higher dose); similarly, the heart rate was generally unaffected. With monkeys, the interaction of the compound with reserpine was examined; amizoptene was used at a dose of 40 mg/kg *p.o.*, reserpine at a dose of 2·5 mg/kg *i.v.* If amizoptene was administered before reserpine, the general sedative effects of reserpine were weakened and their duration reduced. The drop of blood pressure was not affected as to its depth; only its duration was shorter. If the compound was administered after reserpine, a transient pressor phase occurred (a rise by 50 mm Hg), followed by rather substantial drop which took place earlier than after reserpine alone.

In experiments with rats, the levels of serotonin and dopamine in the brain are raised after an oral dose of 20 mg amizoptene/kg; changes in the level of noradrenaline are not significant. If the application of the drug was preceded by that of serotonin or dopamine precursors, the increase in the levels of the corresponding amines was much more pronounced and a clear excitation and piloerection was observed. On the other hand, amizoptene does not affect the changes in the levels of monoamines caused by apomorphine. In an orientation experiment it potentiated somewhat the general excitation and aggressiveness after apomorphine. At a dose of 20 mg/kg *s.c.*, amizoptene blocks the aggressiveness of rats by mesorgydine[21]. On the other hand, at a dose of 2 mg/kg *s.c.*, amphetamine potentiates the effect of mesorgydine. Like amphetamine, amizoptene increases the occurrence of tryptamine convulsions in rats only at relatively high doses, after which some of the animals perish. Hence amizoptene does not act as an inhibitor of monoamine oxidase. At a dose of 10 mg/kg *p.o.*, amizoptene shows no antiserotonin effect in the test of rat paw oedema. At doses of 15 and 30 mg i.p., amizoptene inhibits the cataleptic and the central depressant effect of octoclothepin[22]. An electroencephalographic study of rabbits with implanted brain electrodes showed no specific effect of amizoptene on the CNS. In a subacute experiment with dogs which were given for 10 days daily doses of 30 mg amizoptene/kg *p.o.*, no toxic effects on hematopoiesis, the erythrocyte and leukocyte counts, principal biochemical parameters or organ morphology were found. During the experiment, the animals showed symptoms of excitation (but also of depression), their intensity decreasing after the third or fourth dose of amizoptene (a trend toward tachyphylaxy). In experiments with rats, the effect of amizoptene on the course of gravidity and embryonic development was followed; amizoptene was applied at a daily dose of 20 or 80 mg/kg *p.o.*, from the 1st to the 19th

day of gravidity. The compound was found to interfere with the normal course of gravidity; although no malformations of the embryos occur, the percentage of their resorption increases significantly.

The other amines prepared here were not of such interest as amine *I* and they were tested only in an orientative way. Methylated amines *IV, VI, X, XI,* and *XII* display an acute toxicity for mice with a LD_{50} of 30—50 mg/kg *i.v.* In the rotating-rod test in mice, they were applied in doses from 10 to 60 mg/kg *i.p.*, their mean effective dose ED_{50} being about 30 mg/kg. The maximum of the effect occurs 15—30 min after application. All the compounds showed an expressed mydriatic effect in doses of 10 and 20 mg/kg *i.v.* in mice. At a dose of 30 mg/kg *p.o.* they did not affect the consumption of food by rats in an acute experiment. The effect on mouse motility was tested in an orientative way after a dose of 20 mg/kg *i.p.*; it was found that within 60 min, a slight depression of motility occurs. None of the compounds showed an antireserpine effect in the ptosis test in mice at a dose of 30 mg/kg *p.o.*

The ethylamine derivative *V*, on the other hand, showed an antireserpine effect in the above test at a dose of 5 mg/kg *i.p.*, the effect being weaker than that of imipramine[20]. In the rotating-rod test in mice, one may observe the maximum incoordinating effect 15 min after application, the mean effective dose being 22·5 mg/kg *i.p.*. The prenylamine analogue *VII* was evaluated from the point of view of cardiovascular effects. Its acute intravenous toxicity for mice showed a LD_{50} of 24 mg/kg. Compound *VII* showed no vasodilating effect on an isolated rat heart and no antiarrhythmic effect on rats after *p.o.* or *i.v.* administration. Using an intravenous application to monkeys in a dose of 5 mg/kg, it brings about no obvious changes. Of all the compounds tested, only *VII* showed some antimicrobial activity in *in vitro* tests: the minimum inhibitory concentrations in μg/ml are shown: *Streptococcus β-haemolyticus*, 25; *Staphylococcus pyogenes aureus*, 25; *Klebsiella pneumonia*, 50; *Mycobacterium tuberculosis* H37Rv, 12·5; *Saccharomyces pasterianus*, 125; *Trichophyton mentagrophytes*, 125.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried in the usual way. The NMR spectra in CDCl3 were recorded in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of compounds was tested by thin-layer chromatography on silica gel. All the compounds prepared are racemic mixtures.

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

A solution of 29·5 g 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-one oxime[2] (m.p. 87—89°C, ref.[2]; the higher melting form m.p. 100—103°C) in 150 ml ethanol was added dropwise to 104 g metallic sodium; this was followed by 850 ml ethanol and the mixture was refluxed for 5 h. The solution was then combined with 160 ml water and the mixture was steam-distilled into a receiver containing 25 ml hydrochloric acid and 85 ml water. A total of 3 liters distillate was collected. The distillate was filtered and evaporated at reduced pressure. The residue was crystallised from a mixture of 200 ml ethanol and 100 ml ether to yield 28·2 g (85%) hydrochloride of amine *I*, m.p. 237—238°C. For $C_{11}H_{16}ClN$ (197·7) calculated: 66·82% C, 8·15% H, 17·95% Cl, 7·08% N; found: 66·46% C, 8·20% H, 18·05% Cl, 7·05% N. The base liberated in the usual way boils at 106°C/2 Torr and solidifies on standing in a refrigerator to a crystalline compound. Ref.[2] reports a b.p. of 132—133°C/11 Torr and a m.p. of 53—54°C for amine *I* prepared in a different way.

N-(6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-6-yl)formamide (*II*)

A mixture of 7·5 g amine *I* and 15 ml ethyl formate was heated for 6 h in an autoclave to 120°C. After diluting with hot benzene, the solution was evaporated at reduced pressure; 8·5 g (96%) homogeneous product, m.p. 111–112°C (benzene–hexane). IR spectrum (Nujol): 756 (4 adjacent Ar—H), 1254 (C—N), 1560 and 1658 (CONH), 3200 cm^{-1} (NH). NMR spectrum: δ 8·00 (bs, 1 H, CHO), 7·10 (s, 4 H, aromatic protons), 5·60 (d, 1 H, NH), 4·30 (m, 1 H, CH—N—CO), c. 2·80 (m, 4 H, CH_2—Ar—CH_2), c. 1·85 (m, 4 H, remaining CH_2CH_2 in the ring). For $C_{12}H_{15}$·NO (189·3) calculated: 76·15% C, 8·00% H, 7·40% N; found: 75·85% C, 7·97% H, 7·23% N.

N-(6,7,8,9-Tetrahydro-5*H*-benzocycloheptene-6-yl)acetamide (*III*)

A mixture of 10·0 g amine *I* in 40 ml acetic anhydride was refluxed for 2 h, decomposed with 400 ml water and stirred to cool. Filtration of the solid and extraction of the filtrate with benzene yielded a total of 10·3 g (82%) product which was recrystallized for analysis from benzene; m.p. 144–145°C. NMR spectrum: δ 7·17 (s, 4 H, aromatic protons), 5·42 (bs, 1 H, NH), 4·15 (bs, 1 H, CH—N—CO), c. 2·85 (m, 4 H, CH_2—Ar—CH_2), 1·86 (s, 3 H, CH_3), 1·40–2·20 (m, 4 H, remaining CH_2CH_2 in the ring). For $C_{13}H_{17}NO$ (203·3) calculated: 76·81% C, 8·43% H, 6·89% N; found: 77·31% C, 8·59% H, 6·88% N.

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

A warm solution of 8·2 g formamide *II* in 80 ml benzene was added dropwise to a solution of 4·0 g $LiAlH_4$ in 150 ml ether and the mixture was refluxed for 5 h. Under cooling, it was decomposed adding dropwise 16 ml 20% NaOH, the mixture was filtered, the filtrate was dried with solid KOH and distilled; 7·4 g (97%), b.p. 128°C/10 Torr, n_D^{22} 1·5472. For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H; found: 81·78% C, 9·86% H.

Hydrochloride, m.p. 146–147°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: 68·18% C, 8·73% H, 17·03% Cl, 6·48% N.

6-Ethylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*V*)

A. A warm solution of 10·0 g acetamide *III* in 200 ml tetrahydrofuran was added dropwise under stirring to a solution of 5·0 g $LiAlH_4$ in 150 ml ether and the mixture was refluxed for 6 h. After cooling, it was decomposed with 20 ml 20% NaOH, the precipitate was filtered and washed with ether and the filtrate was distilled; 7·40 g (80%), b.p. 95°C/0·2 Torr, n_D^{21} 1·5346. NMR spectrum: δ 7·20 (s, 4 H, aromatic protons), 2·70 (q, J = 7·0 Hz, 2 H, N—CH_2), c. 2·80 and 1·80 (2 m, 9 H, 4 CH_2 and 1 CH in a seven-membered ring), 1·55 (bs, 1 H, NH), 1·06 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H, 7·40% N; found: 82·60% C, 10·25% H, 7·21% N.

Hydrochloride, m.p. 179–180°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·28% C, 9·09% H, 15·49% Cl, 5·90% N.

B. A mixture of 7·4 g amine *I*, 130 ml acetone, 6·4 g K_2CO_3 and 7·2 g ethyl iodide was refluxed under stirring for 7 h. After cooling, it was filtered and the filtrate was distilled; 4·10 g (47%), b.p. 106°C/1 Torr. For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H; found: 82·60% C, 10·25% H.

6-Dimethylamino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VI*)

A solution of 7·5 g amine *I* in mixture with 9 ml 85% formic acid and 12 ml water was combined with 17 ml 28% aqueous solution of formaldehyde and the mixture was refluxed for 5 h in a 110 to 120°C bath. After cooling, 35 ml hydrochloric acid were added and the mixture was evaporated at reduced pressure. The residue was dissolved in 60 ml water with an addition of 2 ml hydrochloric acid, the solution was washed with ether, made alkaline with 20% NaOH and the base was isolated by extraction with ether; 7·6 g (87%), b.p. 136°C/10 Torr, n_D^{19} 1·5390. NMR spectrum: δ 7·05 (s, 4 H, aromatic protons), 2·5—3·0 (m, 4 H, CH_2—Ar—CH_2), 2·26 (s, 6 H, CH^3—N—CH_3), 1·0—2·15 (m, 5 H, in positions 6,7,8). For $C_{13}H_{19}N$ (189·3) calculated: 82·46% C, 10·13% H; found: 82·36% C, 10·29% H.

Hydrochloride, m.p. 208—209°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·27% C, 8·94% H, 15·90% Cl, 6·00% N.

6-[N-(3,3-Diphenylpropyl)amino]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VII*)

A mixture of 12·0 g amine *I*, 12·0 g 3,3-diphenylpropyl bromide[15] and 80 ml benzene was refluxed for 15 h. After cooling, the precipitated hydrobromide of amine *I* was filtered and the filtrate was extracted by excess dilute hydrochloric acid. The precipitated hydrochloride of the product (7·5 g, 52%) was filtered and purified by crystallization from ethanol; m.p. 218—219°C. For $C_{26}H_{30}ClN$ (392·0) calculated: 79·68% C, 7·71% H, 9·04% Cl, 3·57% N; found: 79·54% C, 7·85% H, 9·11% Cl, 3·53% N.

6-Methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-ol (*VIII*)

Reaction of 37·5 g methyl iodide with 5·9 g Mg in 100 ml ether yielded the corresponding Grignard reagent. After cooling, it was combined dropwise under stirring over a period of 90 min with a solution of 35·2 g 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one[12] (b.p. 117—120°C/2·5 Torr, n_D^{20} 1·5568) in 80 ml ether, the mixture was refluxed for 90 min and, after standing overnight, it was decomposed by adding a solution of 26 g NH_4Cl in 130 ml water. After diluting with ether, the ether phase was separated, dried with Na_2SO_4 and evaporated. A total of 32 g (83%) crude product was obtained. Chromatography of a sample (2·0 g) on a column of 50 g alumina (activity II) and elution with hexane yielded 0·41 g fraction of nonpolar character, probably the dehydration product of alcohol *VIII*. The remainder of the substance was homogeneous and, before analysis, the sample was purified by distillation; b.p. 80°C/0·1 Torr, n_D^{20} 1·5507. NMR spectrum: δ 7·08 (s, 4 H, aromatic protons), 2·92 (s, 2 H, $ArCH_2$—C—O), 2·75 (m, 2 H, second $ArCH_2$), 1·75 (bs, 4 H, remaining CH_2CH_2 in the ring), 1·57 (s, 1 H, OH), 1·15 (s, 3 H, CH_3). For $C_{12}H_{16}O$ (176·2) calculated: 81·77% C, 9·15% H; found: 82·01% C, 9·19% H.

N-(6-Methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-yl)formamide (*IX*)

Crude alcohol *VIII* (30 g) was added to a mixture of 120 ml acetic acid and 15 ml H_2SO_4, followed, under stirring, at 5°C, with 28 g NaCN, the mixture was stirred for 20 min at room temperature; a mixture of 20 ml acetic acid and 30 ml sulfuric acid was then added dropwise. The mixture was stirred for 5 h, left to stand overnight, poured into a mixture of 400 ml water and 500 g ice, neutralized under cooling with 20% NaOH. The precipitated product was extracted with ether, the extract was dried with Na_2SO_4 and fractionated by distillation. A total of 10·2 g fraction boiling at 75—90°C/0·5 Torr was obtained, followed by an intermediate fraction (3·8 g)

and by 16·0 g (47%) of the desired product boiling at 168—172°C/1 Torr. NMR spectrum: δ 8·35 and 7·90 (2 d, J = 12·0; 2·0 Hz, after deuteration 2 s, 1 H, CHO), 7·10 (s, 4 H, aromatic protons), 3·04 and 2·76 (s and m, 4 H, CH_2—Ar—CH_2), 1·50—2·10 (m, 4 H, remaining CH_2CH_2 in the ring), 1·50 and 1·40 (2 s, 3 H, CH_3). For $C_{13}H_{17}NO$ (203·3) calculated: 76·80% C, 8·43% H; found: 77·27% C, 8·46% H.

The low boiling fraction was redistilled in a column; b.p. 75°C/1 Torr, n_D^{20} 1·5822. According to the NMR spectrum and analysis we are dealing here with 8-methyl-6,7-dihydro-5*H*-benzocycloheptene (*XIII*) with an endocyclic double bond in conjugation with the ring. NMR spectrum: δ 7·05 (s, 4 H, aromatic protons), 6·24 (m, 1 H, Ar—CH=), 2·55—3·05 (m, 2 H, $ArCH_2$), 1·60 to 2·55 (m, 4 H, remaining CH_2CH_2 in the ring), 1·91 (s, 3 H, CH_3). For $C_{12}H_{14}$ (158·2) calculated: 91·08% C, 8·92% H; found: 91·29% C, 9·02% H.

6-Amino-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*X*)

A mixture of 9·0 g formamide *IX*, 5 ml ethanol and 30 ml concentrated hydrochloric acid was refluxed for 3 h, diluted with 50 ml water and washed with warm benzene. Cooling of the aqueous solution caused precipitation of the hydrochloride (5·5 g, 59%) which was crystallized from a mixture of ethanol and ether; m.p. 249—250°C. For $C_{12}H_{18}ClN$ (211·7) calculated: 68·08% C, 8·57% H, 16·74% Cl, 6·61% N; found: 68·30% C, 8·67% H, 16.94% Cl, 6·53% N. The mother liquors after the hydrochloride were combined, evaporated *in vacuo* and made alkaline with a 20% solution of NaOH. This liberated the base which was isolated by extraction with ether and distilled; b.p. 150°C/20 Torr, n_D^{23} 1·5458. NMR spectrum: δ 7·10 (s, 4 H, aromatic protons), 2·94 and 2·86 (ABq, J = 14·0 Hz, 2 H, $ArCH_2$—C—N), c. 2·70 (m, 2 H, second $ArCH_2$), 1·70 (m, 4 H, remaining CH_2CH_2 in the ring), 1·15 (s, 2 H, NH_2), 1·07 (s, 3 H, CH_3). For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·06% C, 9·94% H, 7·73% N.

6-Methylamino-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XI*)

Formamide *IX* (7·2 g) was reduced with 4·0 g $LiAlH_4$ in a mixture of ether and benzene similarly to the preparation of *IV*. A total of 6·0 g (86%) base was obtained: b.p. 155°C/20 Torr, n_D^{20} 1·5443. For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H; found: 82·66% C, 10·12% H.

Hydrochloride, m.p. 204—205°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·34% C, 9·16% H, 15·67% Cl, 5·99% N.

6-Dimethylamino-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XII*)

The primary amine *X* (4·0 g) was methylated by 6 ml 85% formic acid and 12 ml 28% formaldehyde in the presence of 6 ml water, like in the preparation of *VI*. Analogously, 3·80 g (83%) base was obtained: b.p. 160°C/20 Torr, n_D^{22} 1·5398. NMR spectrum: δ 7.08 (s, 4 H, aromatic protons), 3·04 and 2·64 (ABq, J = 14·0 Hz, 2 H, $ArCH_2$—C—N), c. 2·70 (m, 2 H, remaining $ArCH_2$), 2·25 (s, 6 H, CH_3—N—CH_3), 1·75 (m, 4 H, remaining CH_2CH_2 in the ring), 0·81 (s, 3 H, C—CH_3). For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 82·68% C,10·65% H, 6·81% N.

Hydrochloride, m.p. 204—205°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: 70·18% C, 9·51% H, 14·96% Cl, 5·72% N.

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