BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. VIII.*

5-SUBSTITUTED 6,6-DIMETHYL-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENES

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6,6-Dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (*I*) reacts with 3-dimethylaminopropylmagnesium chloride to alcohol *II* which was dehydrated under acid catalysis to a mixture of *cis*- and *trans*-olefin *III*. Reduction of ketone *I* yielded alcohol *IV* which was converted by thionyl chloride to the chloro derivative *V* which does not readily undergo substitution reactions. In an attempt at a reaction with sodium cyanide in aqueous alcohols alcoholysis is the prevailing reaction. In an attempt at a reaction of the chloride *V* with sodium 2-diethylaminoethoxide a duplication to bi(6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl) (*VII*) takes place. The amine *III* showed no antireserpine activity.

In the first communication of this series[1] we described the preparation of several amines of the 6,7,8,9-tetrahydro-5*H*-benzocycloheptene series, their common parent compound being 6,7,8,9-tetrahydrobenzocyclohepten-5-one. For some reactions of this ketone, *e.g.* for the Grignard reaction, a complication arises from the possibility of enolization. For this reason the starting compound used in this work was 6,6-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one[2,3] (*I*) which has no possibility of enolization. This ketone is readily available through a repeated methylation of 6,7,8,9-tetrahydrobenzocyclohepten-5-one[4] with excess methyl iodide in the presence of sodium amide[2].

Reaction of ketone *I* with 3-dimethylaminopropylmagnesium chloride[1] in tetrahydrofuran yielded the relatively stable alcohol *II*. Heating with hydrochloric acid brings about its dehydration, the product of which is a mixture of geometric isomers of the olefinic amine *III*; no crystalline salt was prepared from the oily base so that attempts at separating the isomer mixture were not successful.

Reduction of ketone *I* with lithium aluminium hydride gave rise to alcohol *IV*. Its reaction with thionyl chloride in boiling benzene gave rise to the chloro derivative *V*. The chlorine atom in this compound shows low reactivity and resists substitution:

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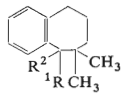
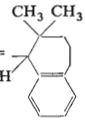
a 16-h heating with excess boiling 1-methylpiperazine resulted in a practically quantitative recovery of the unaltered starting compound. On heating the chloride *V* with sodium cyanide in aqueous ethanol (7 h) an oily mixture of compounds was formed, the chlorine content of which indicated that about 25% of the material underwent reaction. In an attempt to intensify the reaction conditions ethanol was replaced with boiling 2-butoxyethanol and the reaction was conducted at a much higher temperature. The reaction mixture was subjected to fractional distillation and a relatively high yield of a homogeneous product was obtained but it did not contain nitrogen and, according to spectra and analyses, it is the 5-(2-butoxyethoxy) derivative *VI*. Thus a reaction with the solvent used took place. This result brought us to an attempt at preparing the corresponding 2-diethylaminoethyl ether through a reaction of chloride *V* with a solution of sodium 2-diethylaminoethoxide in excess boiling 2-diethylaminoethanol. The main product of the reaction was a neutral oil from which a hydrocarbon crystallized (m.p. 203–204°C). According to analysis and NMR spectrum it is bi(6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten--5-yl) (*VII*). A similar duplication of a molecule was encountered some time ago[5,6] in attempts at a reaction of sodium 2-piperidinoethoxide with benzhydryl chloride.



I, $R^1R^2 = =O$
II, $R^1 = OH$, $R^2 = (CH_2)_3N(CH_3)_2$
III, $R^1R^2 = =CH(CH_2)_2N(CH_3)_2$

IV, $R^1 = H$, $R^2 = OH$
V, $R^1 = H$, $R^2 = Cl$
VI, $R^1 = H$, $R^2 = O(CH_2)_2O(CH_2)_3CH_3$

VII, $R^1 = H$, $R^2 =$



In view of the fact that amines *II* and *III* exhibit a certain structural relationship with the antidepressant amitriptyline[7], aqueous solutions of their salts (*II*-maleate, *III*-hydrochloride) were tested by Dr J. Metyšová at the pharmacological department of this institute for their antireserpine activity. It was found that at a dose of 50 mg/kg neither of the compounds antagonizes the ulcerogenic effect of reserpine in rats. Their acute toxicity for mice after intravenous administration was estimated: for *II* the LD_{50} is 42 mg/kg, for *III* it is 32 mg/kg.

EXPERIMENTAL

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

6,6-Dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (*I*)

A mixture of 80 g 6,7,8,9-tetrahydrobenzocyclohepten-5-one[4], 400 ml benzene and 60 g $NaNH_2$ was refluxed for 6 h. Over an hour, 212 g methyl iodide was then added under cooling, the mixture was refluxed for 6 h and processed[2]. A total of 79 g product boiling at 96—99°C/1·5 Torr was obtained. Its n_D^{20} was 1·5391 and its gas chromatography showed it to be a mixture of 65% dimethyl derivative *I*, 20% 6-monomethyl derivative and 15% starting ketone. This mixture was combined with 21 g 6,7,8,9-tetrahydrobenzocyclohepten-5-one and methylation in the presence of 60 g $NaNH_2$ and 212 g methyl iodide was repeated in the same fashion. Processing of the mixture yielded 103 g product boiling at 98—99°C/1·5 Torr, n_D^{20} 1·5340, which, according to gas chromatography, is the pure dimethyl ketone *I*. Ref.[2,3] give for this compound a b.p. of 140°C/16 Torr and 140°C/15 Torr, respectively.

5-(3-Dimethylaminopropyl)-6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (*II*)

A solution of 18·8 g ketone *I* in 80 ml tetrahydrofuran and 25 ml ether was added dropwise over an hour to a solution of Grignard's reagent[1] prepared from 13·0 g 3-dimethylaminopropyl chloride and 2·68 g magnesium in 150 ml tetrahydrofuran. The mixture was refluxed for 3 h and, after cooling, it was decomposed with a cold solution of 20 g NH_4Cl in 100 ml water. Extraction with ether and processing of the extract yielded a product which was distilled *in vacuo*; 16·1 g, b.p. 155—158°C/2 Torr, n_D^{24} 1·5290. IR spectrum: 760 (4 vicinal aromatic C—H), 1165 (OH), 965, 3140—3250 (OH in a hydrogen bond at N), 2780 cm^{-1} (dimethylamino). NMR spectrum: ϑ 7·90 (m, 1 H, aromatic proton in position 4), 6·95—7·40 (m, 3 H, other aromatic protons), 6·40 (bs, 1 H, OH), c. 2·80 (m, 2 H, $ArCH_2$), 3·15 (s, 6 H, CH_3—N—CH_3), 1·12 and 0·66 (2 s, 6 H, CH_3—C—CH_3). For $C_{18}H_{29}NO$ (275·4) calculated: 78·49% C, 10·61% H, 5·09% N; found: 78·43% C, 10·60% H, 4·86% N.

5-(3-Dimethylaminopropylidene)-6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*III*)

A mixture of 10·0 g alcohol *II*, 70 ml concentrated hydrochloric acid and 20 ml water was refluxed for 4 h and evaporated at reduced pressure. The residue was dissolved in a small amount of water, the solution was made alkaline with 20% NaOH and the product was isolated by extraction with a mixture of ether and benzene; 8·90 g (96%), b.p. 140°C/0·5 Torr, n_D^{22} 1·5355. The NMR spectrum indicates that the substance is a mixture of geometric isomers; only a part of it can be interpreted: ϑ 7·00—7·70 (m, 4 H, aromatic protons), 6·04 and 5·20 (2 t, together 1 H, C=CH). For $C_{18}H_{27}N$ (257·4) calculated: 83·99% C, 10·57% H, 5·44% N; found: 84·06% C, 10·70% H, 5·40% N.

6,6-Dimethyl-6, 7, 8, 9-tetrahydro-5*H*-benzocyclohepten-5-ol (*VI*)

Ketone *I* (30·0 g) was reduced by a 1 h refluxing with 3·0 g $LiAlH_4$ in a mixture of 50 ml ether and 100 ml benzene. After cooling, it was decomposed with 15 ml water and with excess hydrochloric acid. Processing of the organic phase yielded 30 g of a crude product which was redistilled for analysis: b.p. 105°C/1 Torr. NMR spectrum ϑ 7·00—7·50 (m, 4 H, aromatic protons), 4·40 (s, 1 H, Ar—CH—O), 2·25—2·35 (m, 2 H, $ArCH_2$), 1·90 (s, 1 H, OH), 1·45—2·00 (m, 4 H, Ar—C—CH_2CH_2), 1·00 and 0·81 (2 s, 6 H, CH_3—C—CH_3). For $C_{13}H_{18}O$ (190·3) calculated: 82·06% C, 9·54% H; found: 82·38% C, 9·52% H.

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

Thionyl chloride (20 ml) was added dropwise under stirring over 20 min to a solution of 29·0 g alcohol *IV* in 75 ml benzene and the mixture was refluxed for 4 h. The volatile fractions were then removed by evaporation at reduced pressure and the residue redistilled *in vacuo*: 30·0 g (97%), b.p. 102—105°C/1·5 Torr (after redistillation, 103°C/1 Torr), n_D^{19} 1·5490. NMR spectrum: ϑ 7·17 (s, 4 H, aromatic protons), 4·71 (s, 1 H, Ar—CH—Cl), 3·35 and 2·70 (2 m, 2 H, $ArCH_2$), 1·30—2·50 (m, 4 H, Ar—C—CH_2—CH_2), 1·18 and 0·80 (2 s, 6 H, CH_3—C—CH_3). For C_{13}·$H_{17}Cl$ (203·7) calculated: 74·80% C, 8·21% H, 16·99% Cl; found: 74·50% C, 8·21% H, 16·89% Cl.

5-(2-Butoxyethoxy)-6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*VI*)

A solution of 6·0 g NaCN in 6 ml water was added to a solution of 16·0 g chloride *V* in 60 ml 2-butoxyethanol and the mixture was refluxed for 16 h. After cooling, the solid was filtered and the filtrate evaporated *in vacuo*. The residue was distilled to yield as the main product 8·90 g liquid boiling at 135—138°C/1 Torr, n_D^{22} 1·5085. IR spectrum: 755 (4 vicinal aromatic C—H), 1100 (C—O—C), 1368 cm^{-1} [$C(CH_3)_2$]. NMR spectrum: ϑ 7·16 (s, 4 H, aromatic protons), 3·90 (s, 1 H, Ar—CH—O), 3·45 (m, 6 H, OCH_2CH_2—OCH_2), 2·00—3·00 (m, 2 H, $ArCH_2$), 1·04 and 0·71 (2 s, 6 H, CH_3—C—CH_3), 0·91 (t, 3 H, C—CH_3 at the chain end). For $C_{19}H_{30}O_2$ (290·4) calculated: 78·57% C, 10·41% H; found: 78·29% C, 10·10% H.

Bis-(6,6-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl) (*VII*)

Sodium (1·02 g) was dissolved in 20·0 g warm 2-diethylaminoethanol, 9·1 g chloride *V* was added and the mixture was refluxed for 8 h (160—170°C bath). After cooling, the mixture was diluted with 150 ml water and extracted with benzene. The extract was washed with dilute hydrochloric acid (only 1·2 g nonhomogeneous material passed over to the acid-aqueous phase and it was not processed further) and with water, dried with Na_2SO_4 and evaporated. From the residue (7·2 g), 1·0 g hydrocarbon crystallized which, after several crystallizations from a mixture of benzene and ethanol, melted at 203—204°C. NMR spectrum: ϑ c. 7·11 (m, 8 H, aromatic protons), 3·59 (s, 2 H, Ar—CH—CH—Ar), 3·40 and 2·70 (2 m, 4 H, 2 $ArCH_2$), 1·00—2·50 (m, 8 H, 2 Ar—C—CH_2CH_2), 0·50 and 0·11 (2 s, 12 H, 2 CH_3—C—CH_3). For $C_{26}H_{34}$ (346·5) calculated: 90·11% C, 9·89% H; found: 90·27% C, 10·07% H.

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