Synthesis of Some Tetrahydro-2- and 3-benzazepines, and of Hexahydro-3-benzazocine

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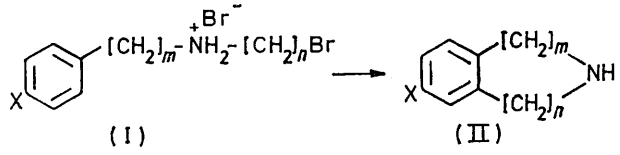
Hydrobromide salts of the compounds $Ar[CH_2]_m{\cdot}NH{\cdot}[CH_2]_nBr$ (I) have been readily cyclised by reaction with anhydrous aluminium chloride in decalin. In this way 2,3,4,5-tetrahydro-1*H*-2-benzazepine [from (I; $m = 1$, $n = 3$)] and its 7-methyl and 7-chloro-derivatives, 2,3,4,5-tetrahydro-1H-3-benzazepine [from (I; $m = n = 2$)] and its 7-chloro-derivative, and 1,2,3,4,5,6-hexahydro-3-benzazocine [from (I; $m = 2$, $n = 3$) have been prepared.

We have previously reported [1] that the readily prepared hydrobromide salts of *N*-(3-bromopropyl)arylamines (I; $m = 0$, $n = 3$) are smoothly decomposed by anhydrous aluminium chloride in decalin at 140° to give high yields of the corresponding tetrahydroquinolines. A variation of this reaction has subsequently been applied to the synthesis of tetrahydroisoquinolines from the appropriate intermediates derived from benzylamines (I; $m = 1$, $n = 2$).[2] We now report an extension of this reaction to the synthesis of pharmacologically interesting seven- and eight-membered ring compounds (tetrahydrobenzazepine and hexahydrobenzazocine).



(I) (II)

Numerous methods have been employed previously for the synthesis of the 2-benzazepine (II; $m = 1$, $n = 3$),[3,4] 3-benzazepine (II; $m = n = 2$),[5] and 3-benzazocine (II; $m = 2$, $n = 3$) [6] systems. In general, however, the compounds needed for the various cyclisation steps (especially where *o*-disubstituted benzenes are involved) require more involved syntheses than do the intermediates (I) reported here. There is a report [7] of a synthesis of some 3-benzazepines by a closely related cyclisation of *N*-(2-chloroethyl)phenethylammonium chloride, and derivatives, though the intermediates were prepared by a different method from that which we employed.

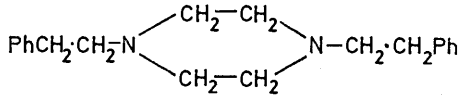
RESULTS AND DISCUSSION

The required intermediates were readily prepared [8] and the decompositions were carried out [1] by the general methods outlined previously.

2-Benzazepines.—Cyclisation of the intermediates (I; $m = 1$, $n = 3$) proceeded smoothly at 130°. The unsubstituted (85%), and the previously unreported 7-methyl (90%), and 7-chloro- (56%) tetrahydro-2-benzazepines were isolated by distillation and characterised by preparation of standard derivatives.

3-Benzazepines.—Decomposition of the intermediates (I; $m = n = 2$) proceeded readily, though the yields of unsubstituted (15%) and 7-chloro- (30%) tetrahydro-3-benzazepines were lower than for the corresponding 2-benzazepines, or the benzazocine (see later). The decompositions were carried out at 110°. Reaction at 130° resulted in a lower yield and more high boiling point material; reaction at 175° gave complete breakdown to phenethylamine.

In the decomposition of both intermediates, the major product consisted of a fraction of much higher boiling point. This was investigated in the unsubstituted case and, from i.r. spectral data (no N–H stretching band and peaks characteristic of aromatic monosubstitution) and analysis of derivatives, the compound was assigned the dimeric structure (III). It seems reasonable that the



(III)

six-membered ring in this compound is more likely to form than the eight-membered ring compounds which would be produced by the same reaction from the other two classes of intermediates studied [where $n = 3$ in (I)]. In the 3-benzazepine case, this dimerisation is more favourable than is formation of the seven-membered ring in the heterocycle, while in the synthesis of tetrahydroisoquinolines [2] [from (I; $m = 1$, $n = 2$)] such dimerisation did not effectively compete with the six-membered heterocyclic ring formation.

3-Benzazocine.—A reaction was observed at room temperature when aluminium chloride was added to the appropriate intermediate (I; $m = 2$, $n = 3$) in decalin. The decomposition was subsequently completed at 100—110° as it was found that here, too, higher temperature reaction resulted in a lower yield. The

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benzazocine was isolated in an almost pure state by distillation (55%) and was characterised by preparation of the trifluoroacetate and the known hydrochloride. The trifluoroacetate was easier to prepare and handle than the hydrochloride, and afforded the pure base on treatment with alkali.

It is evident from our work that the success of this type of ring closure depends on a fine balance between the ease of alternative cyclisations. The marked decrease in yield in passing from the 2-benzazepines to the 3-benzazepines illustrates this. As a further example, cyclisations are not successful from intermediates with $n = 4$. Reaction of compound (I; $m = 1$, $n = 4$) occurs rapidly to give *N*-benzylpyrrolidine in high yield. Thus, the 1-benzazepine and 2-benzazocine systems are not accessible by this route.

EXPERIMENTAL

Analyses were performed by the Australian Microanalytical Service, Melbourne. I.r. spectra were recorded for liquid films on a Perkin-Elmer 257 spectrophotomer.

Intermediates (I).—The general method of synthesis [8] involved reaction of the appropriate amine with a bromoalcohol, and conversion of the resulting ω-hydroxyalkylamino-compound into the hydrobromide salt of the corresponding ω-bromo-derivative. The following compounds were prepared in this way; the yields quoted refer to the overall conversion from the starting amine. *N-Benzyl-3-bromopropylammonium bromide* (70%), m.p. 190—191° (ethanol) (Found: C, 39·2; H, 4·7; Br, 51·5. $C_{10}H_{15}Br_2N$ requires C, 38·8; H, 4·85; Br, 51·8%); *N-(3-bromopropyl)-p-methylbenzylammonium bromide* (80%), m.p. 176—177° (ethanol) (Found: C, 41·1; H, 5·2; Br, 49·7. $C_{11}H_{17}Br_2N$ requires C, 40·9; H, 5·3; Br, 49·5%); *N-(3-bromopropyl)-p-chlorobenzylammonium bromide* (70%), m.p. 205—206° (ethanol) (Found: C, 34·85; H, 4·1; Br, 46·9. $C_{10}H_{14}Br_2ClN$ requires C, 34·9; H, 4·1; Br, 46·6%); *N-(2-bromoethyl)phenethylammonium bromide* (50%), m.p. 174—175° (ethanol) (Found: C, 38·9; H, 4·9; Br, 51·4. $C_{10}H_{15}Br_2N$ requires C, 38·8; H, 4·85; Br, 51·8%); *N-(2-bromoethyl)-p-chlorophenethylammonium bromide* (60%), m.p. 169—170° (ethanol–acetone) (Found: C, 35·25; H, 4·1; Br, 46·4. $C_{10}H_{14}Br_2ClN$ requires C, 34·9; H, 4·1; Br, 46·6%); *N-(3-Bromopropyl)phenethylammonium bromide* (60%), m.p. 186—187° (ethanol) (Found: C, 41·2; H, 5·4; Br, 49·6. $C_{11}H_{17}Br_2N$ requires C, 40·9; H, 5·3; Br, 49·5%).

Cyclisations.—These were carried out by heating and stirring the hydrobromide salts with a three molar excess of anhydrous aluminium chloride for 1 h in decalin as solvent. The optimum temperature for the reaction depended on the starting material; these temperatures are given below. In the case of *N*-(3-bromopropyl)phenethylammonium bromide, a slow reaction occurred at room temperature on addition of the aluminium chloride. After 0·5 h, more aluminium chloride was added and the temperature was then raised to 100—110° for 1 h.

At the end of the heating period, ice and hydrochloric acid were added to the reaction mixture and this was extracted with ether. In most cases, the oily reaction products were insoluble in the decalin, which was decanted off before the ice was added. The aqueous layer was made basic with aqueous sodium hydroxide and extracted with ether (× 2) and benzene (× 2). After being dried and concentrated, the residue was distilled (except in the one case noted).

2-Benzazepines. Reaction temp. 130°. 2,3,4,5-Tetrahydro-1*H*-2-benzazepine (85%), b.p. 130° at 3 mmHg, $\nu_{max.}$ 3300br, 1500s, 1460s, 1449m, 1140s, 1110m, 1030m, 885m, 855m, and 760vs cm^{-1}; *hydrobromide*, m.p. 200—201° (ethanol) (Found: C, 52·75; H, 6·4; Br, 35·3. $C_{10}H_{14}BrN$ requires C, 52·6; H, 6·1; Br, 35·1%), methiodide, m.p 180—181° (lit.,[9] 182°). *2,3,4,5-Tetrahydro-7-methyl-1H-2-benzazepine* (90%), b.p. 86—88° at 1 mmHg, m.p. 71—72° [light petroleum (b.p. 40—60°)] (Found: C, 81·9; H, 9·3. $C_{11}H_{15}N$ requires C, 82·0; H, 9·3%), $\nu_{max.}$ 3200vs, 1610m, 1500s, 1445m, 1250m, 1240m, 1130s, 1110s, 960s, 940m, 880 m, 860m, 820vs, and 800m cm^{-1}; *picrate*, m.p. 211—212° (ethanol) (Found: C, 52·0; H, 4·7; N, 14·6. $C_{17}H_{18}N_4O_7$ requires C, 52·3; H, 4·6; N, 14·35%). *7-Chloro-2,3,4,5-tetrahydro-1H-2-benzazepine* (54%), b.p. 145—148° at 3 mmHg (Found: C, 66·3; H, 6·5; N, 7·4. $C_{10}H_{12}ClN$ requires C, 66·1; H, 6·6; N, 7·5%), $\nu_{max.}$ 3300br, 1610m, 1500s, 1460m, 1145m, 1100s, 905s, 885m, and 815s cm^{-1}; *picrate*, m.p. 174—175° (methanol) (Found: C, 46·8; H, 3·6; N, 13·7. $C_{16}H_{15}ClN_4O_7$ requires C, 46·8; H, 3·65; N, 13·6%).

3-Benzazepines. Reaction temp. 100—110°. 2,3,4,5-Tetrahydro-1*H*-3-benzazepine (15%), b.p. 120—122° at 12 mmHg, $\nu_{max.}$ 3300br, 1495s, 1450s, 1325m, 1150m, 1050m, 960s, and 750vs cm^{-1}; hydrochloride, m.p. 249—250° (ethanol) (lit.,[10] 250°); picrate, m.p. 218—219° (ethanol) (lit.,[10] 220°). From the same reaction, *NN'*-diphenethylpiperazine (III), b.p. 195—200° at 1 mmHg, was obtained in 50% yield; *dipicrate*, m.p. 252—253° (ethanol) (Found: C, 51·0; H, 4·5. $C_{32}H_{32}N_8O_{14}$ requires C, 51·1; H, 4·25%); *bistrifluoroacetate*, m.p. 171—172° (ethanol) (Found: C, 55·2; H, 5·3; N, 5·0. $C_{24}H_{28}F_6N_2O_4$ requires C, 55·2; H, 5·4; N, 5·35%).

7-Chloro-2,3,4,5-tetrahydro-1H-3-benzazepine was isolated as the hydrochloride (30%), m.p. 175—176° (ethanol–acetone) (lit.,[11] 177—178·5°), directly from the crude, concentrated product by a literature method.[11] The free base was liberated by treatment with alkali; $\nu_{max.}$ 3300br, 1495vs, 1460m, 1130s, 1090s, 1015s, and 815s cm^{-1}.

3-Benzazocine. Reaction temp. 100—110°. 1,2,3,4,5,6-Hexahydro-3-benzazocine (50%), b.p. 80—84° at 1 mmHg, $\nu_{max.}$ 3300br, 1485m, 1450vs, 1125s, 815m, and 750vs cm^{-1}; hydrochloride, m.p. 227—230° (lit.,[6] 230—233°); *picrate*, m.p. 220—222° (ethanol) (Found: C, 52·35; H, 4·8; N, 14·3. $C_{17}H_{18}N_4O_7$ requires C, 52·3; H, 4·6; N, 14·35%); *trifluoroacetate*, m.p. 159—160° (ethanol) (Found: C, 54·9; H, 5·8; N, 5·0. $C_{12}H_{16}F_3NO_2$ requires C, 54·75; H, 6·0; N, 5·3%).

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