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Agents Acting on the Central Nervous System: Part VIII — 5-Substituted-6,7,8,9-tetrahydro-5H-benzocycloheptenes

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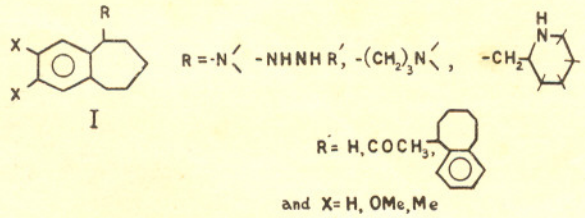
The synthesis and pharmacological evaluation of certain 5-substituted amino-6,7,8,9-tetrahydro-5H-benzocycloheptenes, 1-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazines, 5-(γ-diethylamino) propyl-6,7,8,9-tetrahydro-5H-benzocycloheptene and 5-(2-piperidylmethyl)-6,7,8,9-tetrahydro-5H-benzocycloheptene have been carried out. 5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene shows a strong antipyretic effect and a weak anti-inflammatory action, while 5-hydroxy-5-(2-pyridylmethyl)-6,7,8,9-tetrahydro-5H-benzocycloheptene shows anti-amphetamine action.

IN a continued study of the structure-activity relationship of 5,6-substituted 6,7,8,9-tetrahydro-5H-benzocycloheptenes the synthesis of 5-substituted 6,7,8,9-tetrahydro-5H-benzocycloheptenes of the type (I) has been carried out.

The 5-N-alkylamino derivatives were prepared by reductive alkylation of 5-amino-6,7,8,9-tetrahydro-5H-benzocycloheptenes (Sl Nos. 1-32, Tables 1-4). The 5-dimethylamino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 5) and the corresponding 2,3-dimethyl derivative (Sl No. 18) were prepared by Eschweiler-Clark dimethylation of the 5-amino derivatives by heating with HCHO-HCOOH. Attempted dimethylation of 5-amino-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzocycloheptene by this method was not successful and resulted in the formation of 2,3-dimethoxy-8,9-dihydro-7H-benzocycloheptadiene. This facile elimination of the 5-amino group under acidic conditions in the case of 2,3-dimethoxy compound is obviously due to the ability of the 2-methoxy group to donate its lone pair of electrons, resulting in deamination and the formation of benzocycloheptadiene. The rest of the 5-tertiaryamino-6,7,8,9-tetrahydro-5H-benzocycloheptenes were synthesized by the condensation of 5-chloro-6,7,8,9-tetrahydro-5H-benzocycloheptene[1,2] with the appropriate amines.

5-(γ-Diethylamino)propyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 28) was synthesized by the addition of γ-diethylaminopropyl magnesium chloride to 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one followed by dehydration with acetic anhydride and catalytic reduction. 5-(2-Pyridylmethylene)-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 26) was synthesized in a similar manner by the reaction of 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one with picolyl lithium followed by dehydration. Reduction of compound (Sl No. 26) using 10 per cent Pd-C in methanol gave the corresponding 5-pyridylmethyl compound (Sl No. 29); when the reduction was carried out in acetic acid, the corresponding piperidyl methyl derivative (Sl No. 30) was obtained.



For the preparation of 1-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine (Sl No. 20), condensation of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (II, X = H) with hydrazine hydrate was investigated. With 1 mole of hydrazine hydrate the corresponding azine (VIII, X = H) was obtained. This azine was very unstable and readily regenerated the original ketone. The azine was, therefore, used for further reaction without any purification. On reduction with sodium-ethanol it gave 5-amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 2), while on catalytic reduction it yielded 1,2-bis(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine (IX, X = H) (Sl No. 10). Condensation of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one with acetyl hydrazine gave the 5-acetylhydrazone (III) (Sl No. 8), which on catalytic reduction gave 1-acetyl-2-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine (IV, X = H) (Sl No. 9). It was not found possible to remove the acetyl group from (IV, X = H). Treatment of (IV, X = H) with 3*N* HCl gave 8,9-dihydro-7H-benzocycloheptadiene (VI, X = H), identified by comparison with an authentic sample prepared by the method of Fujita *et al.*[3] while treatment with 20 per cent ethanolic NaOH solution gave the unreacted 1-acetyl-2-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine. The 1-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine (V, X = H) (Sl No. 20) was ultimately prepared by condensing 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one with excess of hydrazine to form the hydrazone (VII, X = H) (Sl No. 19) followed by catalytic reduction. These reactions are described in Chart 1.

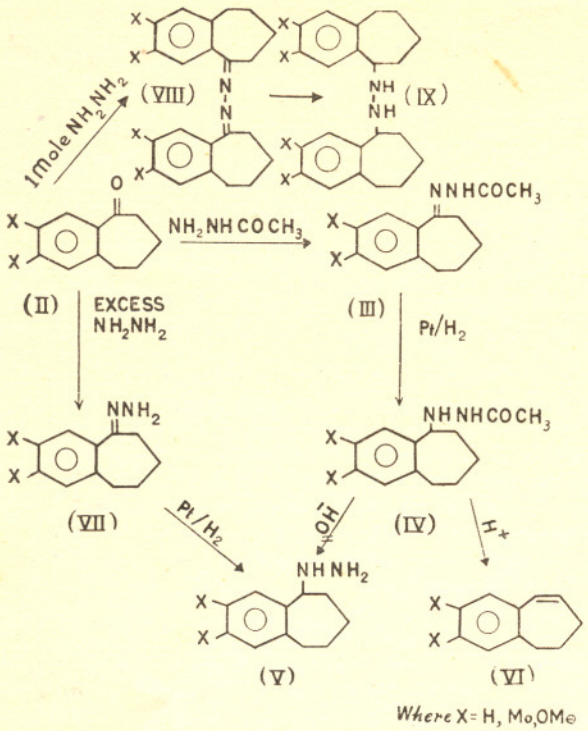


Chart 1

Biological Activity

The compounds were screened for their gross effects in mice by i.p. administration, and cardiovascular effects (interactions with acetylcholine, histamine and adrenaline on blood pressure) in anaesthetized cats by i.v. administration. Some of the other pharmacological actions investigated include the diuretic and hypoglycemic activity in rats, electrogenesis in rabbits, and locomotor, antielectroshock, antiamphetamine, antireserpine, analgesic and antibarbiturate activities in mice. None of the compounds showed diuretic, hypoglycemic or anticonvulsant activities. The antiacetylcholine, anti-5-hydroxytryptamine, ganglion blocking and antihistaminic activities were studied in isolated guinea pig ileum preparation.

Some selected compounds were also screened for their antiviral, antibacterial, antifungal and antifertility activities. None of the compounds was found to possess any activity in these tests.

The compounds of this group did not show any prominent effects on the CNS or the cardiovascular systems. 5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 2) showed a strong antipyretic effect and a weak antiinflammatory action, while the corresponding N-methyl derivative (Sl No. 4) showed a strong analgesic activity which disappeared in the corresponding N-dimethyl derivative (Sl No. 5). 5-Isopropylamino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 6) showed strong antispasmodic action but this was non-specific being equally strong against different spasmogens; no such effects were observed in the corresponding 2,3-dimethoxy derivative (Sl No. 15). 1,2-bis-(6,7,8,9-Tetrahydro-5H-benzocycloheptenyl) hydrazine (Sl No. 10) showed antireserpine action, while 5-hydroxy-5-(2-pyridylmethyl) 6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 23) showed antiamphetamine action, but this action was rather weak.

Experimental Procedure

The UV and IR spectra were recorded on Unicam spectrophotometer and Perkin-Elmer infracord respectively. Melting points were determined in a sulphuric acid-bath and are uncorrected.

5-Substituted amino-6,7,8,9-tetrahydrobenzocycloheptenes — The experimental conditions as described below for 5-substituted amino-6,7,8,9-tetrahydro-5H-benzocycloheptenes are typical of the method followed for the preparation of the corresponding 2,3-disubstituted benzocycloheptenes. Any variations from these conditions are specially mentioned.

5-Oximino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 1) — A mixture of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (3·2 g., 0·02 mole), hydroxylamine hydrochloride (4·17 g., 0·06 mole) and potassium hydroxide (3·36 g., 0·06 mole) in aq. ethanol (30 ml., 50 per cent) was refluxed for 4 hr, cooled and diluted with water. The product which separated out was filtered and washed with water; yield 2·9 g.

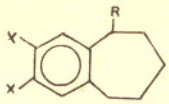
5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 2) — A solution of the above oximino derivative (1·75 g., 0·01 mole) in absolute ethanol (30 ml.) was added rapidly to a fine suspension of sodium (2·3 g., 0·10 g. atoms) in dry toluene (25 ml.). Sufficient absolute ethanol was added to dissolve the unreacted sodium and the mixture was refluxed for 30 min. The solvent was then removed under reduced pressure and the residue triturated with water and extracted with ether. The ether layer was extracted with 5 per cent HCl, the acid extract made alkaline with 20 per cent NaOH solution and the liberated amine taken up in ether. The ether extract was washed with water, dried (Na_2SO_4), the solvent removed and the residue distilled; yield 1·1 g.

5-Formamido-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 3) — Freshly distilled chloral (1·47 g., 0·01 mole) was added to the above amino compound (1·61 g., 0·01 mole) under cooling and the mixture was heated on a steam-bath for 1·5 hr. Removal of excess of chloral under reduced pressure gave the formamido compound which was crystallized from chloroform-petroleum ether (40-60)°; yield 1·41 g.

5-Methylamino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 4) — A solution of the above 5-formamido derivative (1·89 g., 0·01 mole) in dry tetrahydrofuran (25 ml.) was added dropwise to a stirred suspension of $LiAlH_4$ (1·14 g., 0·03 mole) in dry ether (50 ml.) and the mixture refluxed for 6 hr. The excess of $LiAlH_4$ was then decomposed with ethyl acetate (25 ml.) and the metal complex with water (50 ml.). The organic layer was decanted off and the residue extracted with ethyl acetate. The latter extract was combined with the organic layer, dried (Na_2SO_4), the solvent removed, and the residue chromatographed over basic alumina (Grade I) using benzene as the eluant, when a colourless oil was obtained; yield 1·4 g.

5-Dimethylamino-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 5) — 5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (3·22 g., 0·02 mole) was added

TABLE 1— 5-SUBSTITUTED 6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENES



Sl No.	X	R	Yield %	Salt	Solvent of crystallization	m.p./b.p. °C.	Formula	N(%) Found	N(%) Reqd
1	H	=NOH	83	—	Aq. ethanol	108	$C_{11}H_{13}NO$	7·82	8·00
2	H	$-NH_2$	70	Base	—	114-16/5-6 mm.	$C_{11}H_{15}N$	—	—
				HCl	Ethanol-ether	280 (decomp.)	$C_{11}H_{15}N.HCl$	6·79	7·08
3	H	−NHCHO	75	—	Chloroform pet. ether	165	$C_{12}H_{15}NO$	7·44	7·40
4	H	$-NHCH_3$	80	HCl	Ethanol-ether	199-200	$C_{12}H_{17}N.HCl$	6·98	6·61
5	H	$-N(CH_3)_2$	72	Base	—	98-100/5 mm.	$C_{13}H_{19}N$	7·21	7·40
				HCl	Ethanol-ether	218 (Hygroscopic)	$C_{13}H_{19}N.HCl$	6·52	6·20
6	H	$-NH.CH(CH_3)_2$	85	Base	—	128-30/5-6 mm.	$C_{14}H_{21}N$	6·56	6·40
				HCl	Ethanol-ether	199-200	$C_{14}H_{21}N.HCl$	5·72	5·84
7	H	$-NH.CH(CH_3).CH_2.C_6H_5$	80	Base	—	160-5/5-6 mm.	$C_{20}H_{25}N$	5·31	5·01
8	H	$=NNH.COCH_3$	72	Base	Ethanol	160-1	$C_{13}H_{16}N_2O$	13·24	12·96
9	H	$-NHNHCOCH_3$	90	Base	Benzene-pet. ether	100-2	$C_{13}H_{18}N_2O$	12·72	12·84
				HCl	Ethanol-ether	162-5	$C_{13}H_{18}N_2O.HCl$	10·87	11·00
10	H	−(NH)$_2$-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl)	95	HCl	Ethanol-ether	270-2	$C_{22}H_{28}N_2.2HCl$	7·06	7·12
11	H	1-Piperidyl	70	Base	—	100-102/2 mm.	$C_{16}H_{23}N$	5·98	6·11
12	H	4-Morpholinyl	65	Base	—	—	$C_{15}H_{21}NO$	6·29	6·06
				Picrate	Ethanol	202-5	$C_{15}H_{21}NO.C_6H_3N_3O_7$	11·78	12·17
13	H	4-Methylpiperazinyl	40	Base	—	—	$C_{16}H_{24}N_2$	11·67	11·47
				Picrate	Ethanol	270(decomp.)	$C_{16}H_{24}N_2.C_6H_3N_3O_7$	14·76	14·79
14	OCH_3	$-NH_2$	85	Base	Benzene-pet. ether	55-56	$C_{13}H_{19}NO_2$	—	—
				HCl	Ethanol-ether	230-4	$C_{13}H_{19}NO_2.HCl$	5·74	5·43
15	OCH_3	$-NH.CH(CH_3)_2$	70	HCl	Ethanol-ether	215-16	$C_{16}H_{25}NO_2.HCl.\frac{1}{2}H_2O$	4·71	4·53
16	OCH_3	$-NHNHCOCH_3$	78	Base	Benzene-pet. ether	125-8	$C_{15}H_{22}N_2O_3$	10·23	10·07
				HCl	Ethanol-ether	163-4	$C_{15}H_{22}N_2O_3.HCl$	8·94	8·90
17	CH_3	$-NH_2$	66	HCl	Ethanol-ether	215-17	$C_{13}H_{19}N.HCl$	6·32	6·20
18	CH_3	$-N(CH_3)_2$	72	Base	—	120-5/8 mm.	$C_{15}H_{23}N$	6·69	6·45
19	H	$=NNH_2$	92	Base	Aq. ethanol	83	$C_{11}H_{14}N_2$	16·24	16·09
20	H	$-NHNH_2$	90	HCl	Ethanol-ether	270	$C_{11}H_{16}N_2.2HCl$	11·55	11·24
21	CH_3	$=NNH_2$	82	Base	Aq. ethanol	95-96	$C_{13}H_{18}N$	13·48	13·86

Sl. No. 1, lit.[1,9] m.p. 107-8°; Sl. No. 2, lit.[10] b.p. (base) 100-6°/3-5 mm.; Sl. No. 2 $[n]_D^{33}$ 1·584; Sl. No. 5 (base) $[n]_D^{33}$ 1·587; Sl. No. 6 (base) $[n]_D^{33}$ 1·585; Satisfactory C,H analysis have been obtained for all the compounds.

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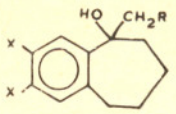
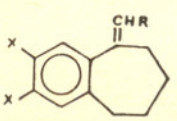
TABLE 2 — 5-HYDROXY-5-SUBSTITUTED AMINO-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENES



Sl No.	X	R	Yield %	Salt	Solvent of crystallization	m.p./b.p. °C.	Formula	N(%) Found	N(%) Reqd
22	H	$-(CH_2)_2N(Et)_2$	40	Base	—	172-4/6 mm.	$C_{18}H_{29}NO$	5·06	5·01
				HCl	Ethanol-ether	120 (Hygroscopic)	$C_{18}H_{29}NO.HCl$	4·31	4·49
23	H	2-Pyridyl	62	Base	*n*-Hexane	76	$C_{17}H_{19}NO$	5·24	5·53
				HCl	Ethanol-ether	178	$C_{17}H_{19}NO.HCl$	4·57	4·83
24	OCH_3	2-Pyridyl	55	Base	*n*-Hexane	76-78	$C_{19}H_{23}NO_3$	4·62	4·47
				HCl	Ethanol-ether	160-1	$C_{19}H_{23}NO_3.HCl$	4·24	4·00

Sl. No. 22, $[n]_D^{25}$ 1·521

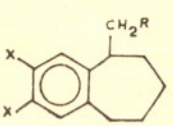
TABLE 3 — 5-SUBSTITUTED AMINOMETHYLENE-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENES



Sl No.	X	R	Yield %	Salt	m.p./b.p. °C.	Formula	N(%) Found	N(%) Reqd
25	H	$-(CH_2)_2N(Et)_2$	82	Base	160-5/6 mm.	$C_{18}H_{27}N$	4·99	5·44
26	H	2-Pyridyl	85	Base	166-8/5-6 mm.	$C_{17}H_{17}N$	5·92	5·95
27	OCH_3	2-Pyridyl	60	HCl	208-10	$C_{19}H_{21}NO_2.HCl$	4·25	4·22

Sl. No. 27 crystallized from ethanol ether. Satisfactory C,H analysis have been obtained.

TABLE 4 — 5-SUBSTITUTED AMINOMETHYL-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTENES



Sl No.	X	R	Yield %	Salt	m.p./b.p. °C.	Formula	N(%) Found	N(%) Reqd
28	H	$-(CH_2)_2N(Et)_2$	95	Base	150/6 mm.	$C_{18}H_{29}N$	5·33	5·40
29	H	2-Pyridyl	90	Base	160-2/6 mm.	$C_{17}H_{19}N$	6·12	5·90
				HCl	113-14	$C_{17}H_{19}N.HCl$	4·90	5·11
30	H	2-Piperidyl	82	Base	130-2/5-6 mm.	$C_{17}H_{25}N$	5·80	5·76
				HCl	185-6	$C_{17}H_{25}N.HCl$	5·23	5·00
31	OCH_3	2-Pyridyl	90	Base	175-8/5 mm.	$C_{19}H_{23}NO_2$	4·52	4·71
				HCl	120-2	$C_{19}H_{23}NO_2.HCl$	4·32	4·20
32	OCH_3	2-Piperidyl	92	Base	—	$C_{19}H_{29}NO_2$	4·30	4·29
				HCl	65-67 (Hygroscopic)	$C_{19}H_{29}NO_2.HCl.H_2O$	3·67	3·99

Sl. Nos. 29-32 (hydrochlorides) crystallized from ethanol-ether. Sl. No. 29 $[n]_D^{30}$ 1·572.

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dropwise to a cooled mixture of formic acid (4·6 g., 0·1 mole, 99-100 per cent) and formaldehyde (4·5 ml., 40 per cent). The resulting solution was heated on a steam-bath for 8 hr, cooled, 4*N* HCl (10 ml.) added to it and the solution evaporated to dryness under reduced pressure. The residue was made alkaline with 70 per cent NaOH solution and extracted with ether, the ether extract dried (Na_2SO_4) and the solvent removed to give the product as a colourless oil; yield 2·7 g.

5-*Isopropylamino*-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene* (Sl No. 6) — 5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (1·61 g., 0·01 mole) was kept for 2 hr at 32° with Raney nickel (1·0 g.), acetone (5 ml.) and absolute ethanol (15 ml.) and then hydrogenated at 60 lb. p.s.i. for 24 hr at room temperature. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to give the product as a colourless oil; yield 1·71 g.

5-(α-*Methyl*-β-*phenyl*)*ethylamino*-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene* (Sl No. 7) — 5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene (1·61 g., 0·01 mole), phenyl acetone (1·34 g., 0·01 mole) and Raney nickel catalyst (1 g.) in absolute ethanol (40 ml.) was hydrogenated as described above. The product was obtained as a colourless oil; yield 2·24 g.

Acetylhydrazone of 6,7,8,9-*tetrahydro*-5*H*-*benzocyclohepten*-5-*one* (Sl No. 8) — A mixture of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (3·20 g., 0·02 mole) and acetyl hydrazine (1·48 g., 0·02 mole) in absolute ethanol (50 ml.) was refluxed for 2 hr, cooled and the solvent removed under reduced pressure; yield 3·1 g.

1-*Acetyl*-2-(6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptanyl*) *hydrazine* (Sl No. 9) — The above acetylhydrazone (1·08 g., 0·005 mole) in glacial acetic acid (20 ml.) was hydrogenated for 24 hr at 50 lb. p.s.i. using Adam's platinum catalyst. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to give a colourless crystalline solid; yield 1·0 g.

Hydrolysis of 1-*acetyl*-2-(6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptenyl*) *hydrazine* — 1-Acetyl-2-(6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine hydrochloride (2·44 g., 0·01 mole) was refluxed for 6 hr with 3*N* HCl (50 ml.). The oily product which separated on cooling was extracted with ether. Evaporation of the aqueous layer under reduced pressure gave a residue of hydrazine hydrochloride, identified by m.p. and m.m.p. with authentic sample. The residue from the ether extract was found to be 8,9-dihydro-7H-benzocycloheptadiene; b.p. 105-10°/5-6 mm. (lit.[3] b.p. 82-4°/3 mm.); $\lambda_{max.}^{EtOH}$ 252 mμ (ε 11,720) (Found: C, 91·46; H, 8·21. $C_{11}H_{12}$ requires C, 91·66; H, 8·33%).

1-Acetyl-2-(2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzocycloheptenyl) hydrazine similarly on treatment with 3*N* HCl gave 2,3-dimethoxy-8,9-dihydro-7H-benzocycloheptadiene; $\nu_{max.}^{liq.\ film}$ 1620 cm.$^{-1}$.

bis-(6,7,8,9-*Tetrahydro*-5*H*-*benzocyclohepten*-5-*one*) *azine* (VIII, X = H) — A solution of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1·60 g., 0·01 mole) and hydrazine hydrate (0·5 g., 0·01 mole, 99-100 per cent) in ethanol (25 ml.) was refluxed for 1·5 hr. The reaction mixture was evaporated to dryness under reduced pressure when the product was obtained as a colourless solid. The product was very unstable and readily hydrolysed to give back 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one. It was, therefore, reduced without any further purification.

1,2-*bis*-(6,7,8,9-*Tetrahydro*-5*H*-*benzocycloheptenyl*) *hydrazine* (IX, X = H) (Sl No. 10) — The above azine (3·16 g., 0·01 mole) in glacial acetic acid (40 ml.) solution was hydrogenated for 24 hr at 40 lb. p.s.i. and room temperature using Adam's platinum catalyst (25 mg.). The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The residue was taken up in ether and extracted with 5 per cent HCl and the acid extract evaporated to dryness under reduced pressure to give a colourless crystalline solid; yield 3·1 g.

1-(6,7,8,9-*Tetrahydro*-5*H*-*benzocycloheptenyl*) *hydrazine* (V, X = H) (Sl No. 20) — 6,7,8,9-Tetrahydro-5H-benzocyclohepten-5-one (1·60 g., 0·01 mole) and hydrazine hydrate (2·0 g., 0·04 mole) were refluxed in absolute ethanol (25 ml.) for 2 hr. The solution was cooled, evaporated under reduced pressure and the residue of the hydrazone crystallized from aq. ethanol. Catalytic reduction of the hydrazone, as described for Sl No. 9, gave the corresponding hydrazine.

5-(1-*Piperidyl*)-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene* (Sl No. 11) — 5-Chloro-6,7,8,9-tetrahydro-5H-benzocycloheptene was obtained by refluxing 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol[4,5] with thionyl chloride in benzene; b.p. 95°/0·4 mm. (lit.[1,2], b.p. 95°/0·5 mm., 112·5-14°/8 mm.).

A mixture of the 5-chloro compound (1·80 g., 0·01 mole) and piperidine (10 ml.) was refluxed for 8 hr, water was added and the mixture extracted with ether. The ether extract was washed with water and then extracted with 5 per cent HCl. The acid extract was made alkaline, extracted with ether, the extract dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the product as a colourless oil; yield 1·60 g.

5-*Amino*-2,3-*dimethoxy*-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene* (Sl No. 14) — This was prepared according to the method of Caunt *et al.*[6] by reduction of 5-oximino-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzocycloheptene with 4 per cent sodium amalgam.

Attempted methylation of 5-*amino*-2,3-*dimethoxy*-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene by Eschweiler-Clark's method* — The above amino compound (Sl No. 14) (4·42 g., 0·02 mole) was heated with formic acid (4·6 g., 0·1 mole, 99-100 per cent) and formaldehyde (4·5 ml., 40 per cent) on a steam-bath for 8 hr, and the reaction mixture worked up in the usual manner. A pale yellow oil was obtained which proved to be 2,3-dimethoxy-8,9-dihydro-7H-benzocycloheptadiene; b.p. 138-40°/0·1 mm. (lit.[6,7], b.p. 150°/0·2 mm., 129-31°/0·1 mm.); $\nu_{max.}^{liq.\ film}$ 1620 cm.$^{-1}$ (Found: C, 76·64; H, 7·83. $C_{13}H_{16}O_2$ requires C, 76·47; H, 7·84%).

5-*Amino*-2,3-*dimethyl*-6,7,8,9-*tetrahydro*-5*H*-*benzocycloheptene* (Sl No. 17) — 5-Oximino-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene[8] (2·03 g., 0·01 mole) was reduced with $LiAlH_4$ (1·90 g.; 0·05 mole) as described for the compound (Sl. No. 4). The reaction mixture was extracted with ether, the ether extract dried (Na_2SO_4) and solvent removed under reduced pressure. The residual mixture of the

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amino derivative and unreacted oximino compound was taken up in ether and the former compound precipitated as hydrochloride by addition of ethereal HCl. The hydrochloride was filtered and the unreacted oximino derivative was recovered from the filtrate.

5-Dimethylamino-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 18) — This was prepared from 5-amino-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 17) (1·89 g., 0·01 mole), by treatment with formic acid (1·84 g., 0·04 mole, 99-100 per cent) and formaldehyde (2·4 ml., 40 per cent) as described for Sl No. 5 and was obtained as a colourless oil; yield 1·56 g.

5-Hydroxy-5-(γ-diethylamino) propyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 22) — A solution of γ-diethylaminopropyl chloride (2·99 g., 0·02 mole) in dry tetrahydrofuran (15 ml.) was added dropwise to freshly activated magnesium turnings (0·48 g., 0·02 g. atoms) kept under dry tetrahydrofuran (5 ml.). A few crystals of iodine or ethyl bromide (50 mg.) were added to initiate the reaction. After the addition the mixture was allowed to reflux for 2 hr, when most of the magnesium turnings had reacted. A solution of 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-one (1·6 g., 0·01 mole) in dry tetrahydrofuran (25 ml.) was then added dropwise and the mixture kept refluxing for 24 hr, cooled and 10 per cent NH_4Cl solution added. The solution was extracted several times with ether, the combined ether layer extracted with 2*N* HCl, the acid extract made alkaline, the product which separated was again taken up in ether, the ether extract dried (Na_2SO_4), and the solvent removed to give the product as a colourless thick liquid; yield 1·1 g.

5-(γ-Diethylamino)Δ$^{\alpha}$ propylene-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 25) — A solution of 22 (2·75 g.; 0·01 mole) in acetic anhydride (50 ml.) was refluxed for 6 hr., concentrated under reduced pressure; the residue triturated with 40 per cent NaOH solution extracted with ether, the ether extract dried (Na_2SO_4), the solvent removed and the residue distilled to give the product as a colourless liquid; yield 2·1 g.

5-(γ-Diethylamino) propyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 28) — The above compound (Sl No. 25) (2·57 g., 0·01 mole) was dissolved in methanol, 10 per cent Pd-C (0·5 g.) added and the solution hydrogenated at room temperature and atmospheric pressure for 24 hr. The catalyst was removed by filtration, the filtrate concentrated under reduced pressure and the residue distilled to give the product as a colourless liquid; yield 2·5 g.

5-Hydroxy-5-(2-pyridylmethyl)-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 23) — A solution of bromobenzene (1·57 g., 0·01 mole) in dry ether (20 ml.) was added dropwise to a vigorously stirred suspension of lithium ribbon (0·14 g., 0·02 g. atoms) in dry ether (25 ml.). The mixture was allowed to reflux for 1 hr, when most of the lithium metal had reacted, α-picoline (0·93 g., 0·01 mole) was added dropwise and the mixture stirred for 1 hr. To this mixture a solution of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1·60 g., 0·01 mole) in dry ether (25 ml.) was added drop by drop and the solution allowed to reflux for 6 hr. It was cooled, water added, the ether layer separated and extracted with 3*N* HCl. The ether layer on concentration gave the unreacted ketone. The acid layer was made alkaline with NaOH solution and the oily product which separated extracted with ether, the ether extract washed with water, dried (Na_2SO_4) and the solvent removed. The product was obtained as a colourless crystalline solid; yield 1·5 g.

5-(2-Pyridylmethylene)-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 26) — A solution of compound (Sl No. 23) (2·53 g., 0·01 mole) in acetic anhydride (25 ml.) was refluxed for 6 hr, the product worked up as described for the compound (Sl No. 25). It was obtained as a pale yellow liquid; yield 1·9 g.

5-(2-Pyridylmethyl)-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 29) — A mixture of 26 (2·35 g., 0·01 mole) and 10 per cent Pd-C (500 mg.) in methanol (50 ml.) was hydrogenated at room temperature and atmospheric pressure till the absorption of hydrogen ceased and the product worked up in the usual manner; yield 2·1 g.

5-(2-Piperidyl)methyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (Sl No. 30) — A mixture of 26 (2·35 g., 0·01 mole) and Adam's platinum catalyst (100 mg.) in acetic acid (25 ml.) was hydrogenated at 50 lb. p.s.i. at 23°. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure and the residue chromatographed over basic alumina (Grade I) using benzene as the eluant, when the product was obtained as a viscous liquid; yield 2·0 g.

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