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Agents Acting on the Central Nervous System: Part IX—5,6-Disubstituted 6,7,8,9-Tetrahydro-5H-benzocycloheptenes & 8,9-Dihydro-7H-benzocycloheptadienes

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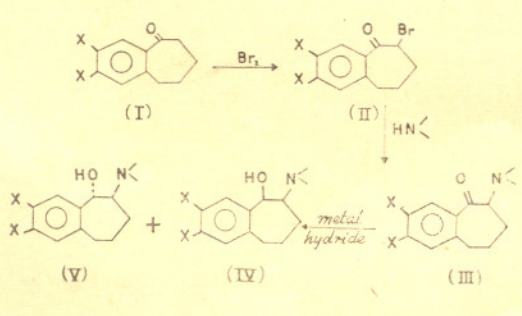
A series of 6-tertiaryamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ones and their corresponding heptenols, 8,9-dihydro-7H-benzocyloheptadiene[6,5-d]pyrazoles, and isoxazoles has been prepared and tested for their pharmacological activity. It has been shown that in reduction of 6-tertiaryamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ones both the *cis*- and *trans*-isomers are formed, the structure of which have been assigned on the basis of NMR studies. 6-(4-N-methylpiperazinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one has been found to possess marked adrenolytic activity, while 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one and the corresponding heptenol shows central depressant action.

CONDENSATION of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ones (II) with the appropriate amines afforded 6-tertiaryamino - 6,7,8,9 - tetrahydro -5H - benzocyclohepten - 5-ones (III). These ketones on reduction with metal hydrides gave the corresponding 6-tertiaryamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ols (IV and V). TLC of the reduction products showed them to be a mixture of two compounds, which were separated in the case of 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol and its 2,3-dimethyl analogue. The NMR spectra of the pair of isomers of the latter are given in Fig. 1. Both the isomers showed a doublet centred at τ 5·1 and τ 5·4 for the 5-methine proton; J = 3-4 cps for the isomer (Sl No. 24) m.p. 156-7° and J = 8·5 cps for the isomer (Sl No. 25) melting at 150°. The former has, therefore, been assigned the *cis*- and the latter the *trans*-configuration. In the *cis*-compound the aromatic proton peri to the benzylic CHOH was shifted up field compared to its location in the *trans*-isomer. This has been found to be so in some other 6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ols studied by us. This appears to be a general phenomenon and will be discussed elsewhere. In the IR spectrum there was greater shift of the OH-frequency in the *cis*-isomer than in the *trans*-isomer: *cis*-isomer $\nu_{max.}^{KBr}$ 3150, 1010 cm.$^{-1}$; *trans*-isomer $\nu_{max.}^{KBr}$ 3275, 1050 cm.$^{-1}$ (OH-band). The two compounds obtained in the case of 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol had m.p.s. 150-52° (Sl No. 17) and 112-15° (Sl No. 18). The NMR of the former again gave a doublet centred at τ 5·1 (J = 4 cps) and is, therefore, the *cis*-isomer, the other isomer (Sl No. 18) has J = 8·5 cps and is, therefore, the *trans*-isomer. No attempt was made to isolate the isomers



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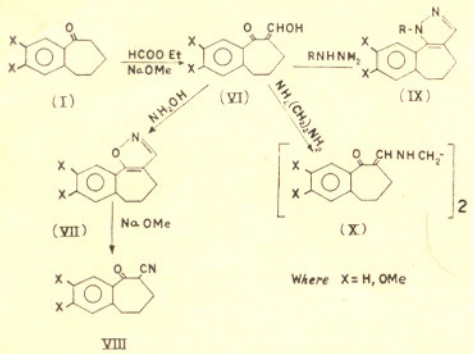
in other cases. It has been observed by us that in the reduction of 2,3-disubstituted 6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (unpublished work) only the *trans*-isomer was formed and appeared to be a case of steric control reduction. The formation of both the isomers in the present case is obviously due to the large bulk on the 6-amino group. A similar difference in the control reduction has been noticed earlier in the case of analogous acyclic compounds.

8,9-Dihydro-7H-benzocycloheptadiene [6,5-*d*]pyrazoles and Isoxazoles

The 6-hydroxymethylene-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (VI), on condensation with hydroxylamine, gave the isoxazoles (VII) and with hydrazines the pyrazoles (IX). Although two products can concievably be formed in these condensations, only one product was obtained in each case. In the case of steroidal pyrazoles NMR studies have shown that these compounds are formed by an initial attack of the more nucleophilic amino group (the amino group β- to phenyl residue in phenylhydrazine) on the aldehyde carbonyl (the hydroxymethylene group). The 8,9-dihydro-7H-benzocycloheptadiene [6,5-*d*]isoxazoles synthesized above have, therefore, been assigned the structure (VII) and the pyrazoles the structure (IX). The structure of the isoxazoles (VII) was confirmed by its conversion to the nitrile (VIII) by treatment with $NaOCH_3$. Further confirmation of these structures was obtained from their UV spectra. The log ε values of isoxazoles (VII) and pyrazoles (IX) are in agreement with the data previously reported on steroidal pyrazoles[1].



Condensation of the hydroxymethylene ketone (VI) with ethylenediamine gave the N,N′-bis(6,7,8,9-tetrahydro-5-oxo-5H-benzocyclohepten-6-yl)methylene ethylenediamine (X); this bis-adduct was obtained even when excess of ethylenediamine or 'high dilution' of the reactants was used which would normally favour intramolecular cyclization. From the fact that the product was insoluble in alkali, thus indicating the absence of the enolic hydroxyl, and the fact that aldehyde carbonyl in hydroxymethylene ketones is the first centre to be attacked by nucleophilic agents, structure (X) was assigned to this product. It gave a violet colour with ferric chloride which would be due to its ability to undergo keto-enol tautomerism[2]. The adduct (X) formed a 2,4-DNP which would support the assigned structure (X).

Experimental Procedure

The homogeneity of the compounds was checked by thin layer chromatography on silica gel G plates using iodine vapours for the detection of the compounds. The UV spectra were measured with Unicam spectrophotometer. The IR spectra were recorded as a routine to check the structure of all the reaction products on Perkin-Elmer infracord, and only such IR spectra are mentioned which require special discussion. Melting points were determined in a sulphuric acid-bath.

The methods of synthesis described below is typical of the general method followed for the preparation of the various compounds listed in Tables 1-3. All the compounds (Tables 1-3) gave satisfactory C, H analyses.

6-Bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 1) — Bromine (1·60 g.; 0·01 mole) in dry ether (25 ml.) was added dropwise to a solution of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1·60 g.; 0·01 mole) in ether (25 ml.) kept at 0°. After the addition was complete, the solvent was removed and the residue distilled to give the product as a pale yellow oil.

6-(1-Piperidyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 4) — 6-Bromo-6,7,8,9-tetrahydro-

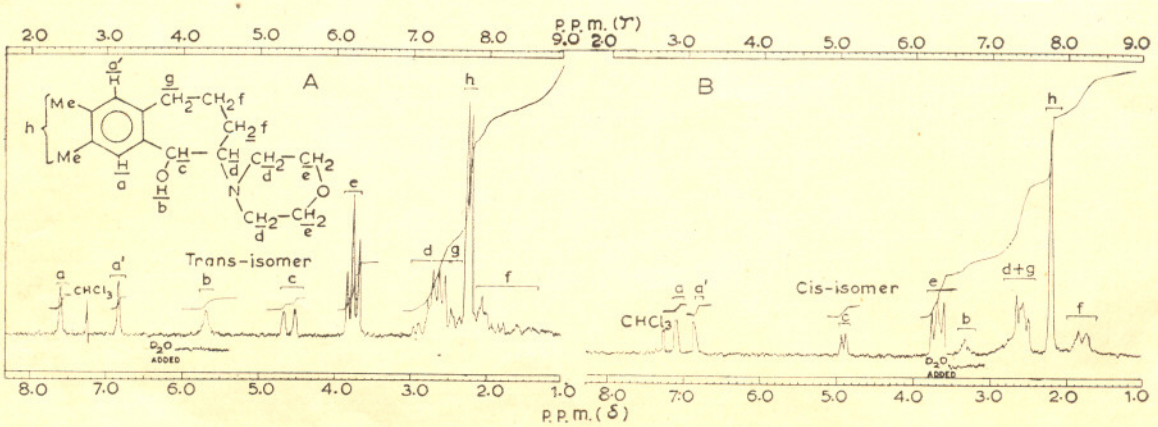


Fig. 1 — NMR spectra of (A) *trans*-2,3-dimethyl-6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol and (B) the corresponding *cis*-isomer

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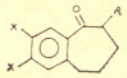
TABLE 1 — 6-TERTIARYAMINO-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-ONES



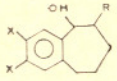
Sl No.	X	R	Yield %	Salt	S	m.p./b.p. °C.	Mol. formula	N (%) Found	N (%) Reqd
1	H	Br	90	—	—	180-82/5-6 mm. (lit.[4], 140-42°/ 1 mm.	$C_{11}H_{11}BrO$	—	—
2	OCH_3	Br	85	—	a	125-6	$C_{13}H_{15}BrO_3$	—	—
3	CH_3	Br	82	—	—	180-82/5-6 mm.	$C_{13}H_{15}BrO$	—	—
4	H	1-Piperidyl	72	Base (unstable)	—	—	$C_{16}H_{21}NO$	5·76	5·76
				HCl	b	237	$C_{16}H_{21}NO.HCl$	5·27	5·00
5	H	4-Morpholinyl	73	HCl	b	209	$C_{15}H_{19}NO_2.HCl$	5·35	4·97
6	H	4-N-Methylpiperazinyl	63	HCl	b	200 (d)	$C_{16}H_{22}N_2O.2HCl$	8·30	8·55
7	H	4-N-Phenylpiperazinyl	15	HCl* (hygro-scopic)	b	178-80	$C_{21}H_{24}N_2O.2HCl$	7·32	7·12
8	H	$-N(CH_3)-CH_2C_6H_5$	63	Base†	—	—	$C_{19}H_{21}NO$	5·34	5·01
9	H	$-NHCH_3$	92	Base	—	125-8/5-6 mm.	$C_{12}H_{15}NO$	7·23	7·40
10	OCH_3	1-Piperidyl	45	Base	a	85-86	$C_{18}H_{25}NO_3$	4·75	4·62
				HCl	b	130-32	$C_{18}H_{25}NO_3.HCl.H_2O$	3·93	3·91
11	OCH_3	4-Morpholinyl	40	Base	a	116-18	$C_{17}H_{23}NO_4$	4·42	4·59
				HCl	b	225-8	$C_{17}H_{23}NO_4.HCl$	4·32	4·09
12	OCH_3	4-N-Methylpiperazinyl	45	Base	a	103-5	$C_{18}H_{26}N_2O_3$	8·80	8·80
				HCl	b	238-40	$C_{18}H_{26}N_2O_3.2HCl$	7·32	7·16
13	CH_3	1-Piperidyl	73	Base	—	—	$C_{18}H_{25}NO$	5·32	5·16
				HCl	b	205-6	$C_{18}H_{25}NO.HCl$	4·75	4·55
14	CH_3	4-Morpholinyl	75	HCl	b	218-20	$C_{17}H_{23}NO_2.HCl$	4·87	4·52
15	CH_3	4-N-Methylpiperazinyl	78	Base	—	—	$C_{18}H_{26}N_2O$	9·68	9·79
				Oxalate	d	215	$C_{18}H_{26}N_2O.(CO\text{-}OH)_2$	7·23	7·44

S = solvent of crystallization; (a) benzene-pet. ether; (b) ethanol-ether, (c) aq. ethanol; and (d) ethanol.

*Free base decomposes very rapidly at room temperature, only 10-15% of the product was obtained which was reduced immediately with $NaBH_3$ to the corresponding heptenol.

†The product decomposes on distillation; therefore, the product was separated from the unreacted benzylmethylamine by chromatography on basic alumina (Grade I) using benzene as the eluant.

TABLE 2 — 6-TERTIARYAMINO-6,7,8,9-TETRAHYDRO-5H-BENZOCYCLOHEPTEN-5-OLS



Sl No.	X	R	Yield %	Salt	S	m.p./b.p. °C.	Mol. formula	N (%) Found	N (%) Reqd
16	H	1-Piperidyl	83	HCl	a	198-200	$C_{16}H_{23}NO.HCl$	4·94	4·97
17	H	*cis*-4-Morpholinyl	85	Base	c	150-2	$C_{15}H_{21}NO_2$	5·78	5·66
18	H	*trans*-Isomer	—	do	e	112-15	$C_{15}H_{21}NO_2$	5·66	5·66
19	H	4-N-Methylpiperazinyl	78	do	b	185-7	$C_{16}H_{24}N_2O$	10·77	10·76
				HCl	a	257-8	$C_{16}H_{24}N_2O.HCl$	9·09	9·44
20	H	$NHCH_3$	67	Base	c	128-30	$C_{12}H_{17}NO$	7·00	7·32
21	H	4-N-phenylpiperazinyl	85	do	d	148-50	$C_{21}H_{26}N_2O$	8·88	8·69
				HCl	a	95-97	$C_{21}H_{26}N_2O.2HCl$	7·27	7·08
22	CH_3	1-Piperidyl	85	Base	d	110-12	$C_{18}H_{27}NO$	5·31	5·12
23	CH_3	4-N-Methylpiperazinyl	78	do	d	130-31	$C_{18}H_{28}N_2O$	9·51	9·72
24	CH_3	*cis*-4-Morpholinyl	85	do	b	157	$C_{17}H_{25}NO_2$	5·22	5·09
25	CH_3	*trans*-Isomer	—	do	d	150-51	$C_{17}H_{25}NO_2$	5·15	5·09
26	OCH_3	1-Piperidyl	82	do	b	127-8	$C_{18}H_{27}NO_3$	4·69	4·59
				HCl	a	178-80	$C_{18}H_{27}NO_3.HCl$	4·21	4·09
27	OCH_3	4-Morpholinyl	68	Base	b	154-6	$C_{17}H_{25}NO_4$	4·82	4·56
28	OCH_3	4-N-Methylpiperazinyl	68	do	b	163-5	$C_{18}H_{28}N_2O_3$	8·45	8·75
				HCl	a	203-5	$C_{18}H_{28}N_2O_3.2HCl$	7·91	7·85

S = solvent of crystallization; (a) ethanol-ether; (b) benzene-pet. ether; (c) benzene; (d) aq. ethanol; and (e) pet. ether.

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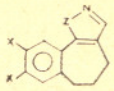
TABLE 3 — VARIOUS PYRAZOLES AND ISOXAZOLES



Sl No.	X	Z	Yield %	Salt	S	m.p. °C.	Mol. formula	N (%) Found	N (%) Reqd
29	H	NH	82	Base	a	108-10 (lit.[3] 114-15)	$C_{12}H_{12}N_2$	15·00	15·21
				HCl	b	204	$C_{12}H_{12}N_2.HCl$	12·92	12·69
30	H	N-C_6H_5	78	Base	a	112-14	$C_{18}H_{16}N_2$	10·73	10·76
				HCl	b	168	$C_{18}H_{16}N_2.HCl$	9·61	9·50
31	H	*p*-F.C_6H_4-N	82	do	b	183-4	$C_{18}H_{15}N_2F.HCl$	8·80	8·90
32	H	O	68	Base	a	82-83	$C_{12}H_{11}NO$	7·38	7·56
33	OCH_3	NH	85	do	a	142-4	$C_{14}H_{16}N_2O_2$	11·23	11·47
				HCl	b	235-7	$C_{14}G_{16}N_2O_2.HCl$	10·21	9·98
34	OCH_3	N-C_6H_5	85	do	b	158-60	$C_{20}H_{20}N_2O_2.HCl$	7·62	7·85
35	OCH_3	p-F.C_6H_4-N	78	HCl (hygroscopic)	b	145-6	$C_{20}H_{19}N_2O_2F.HCl$	7·73	7·47
36	OCH_3	O	85	Base*	a	154-6	$C_{14}H_{15}NO_3$	6·01	5·71

S = solvent of crystallization; (a) benzene-pet. ether; and (b) ethanol-ether *$\lambda_{max.}^{C_2H_5OH}$ 282 mμ (log ε 4·17).

5H-benzocyclohepten-5-one (2·39 g.; 0·01 mole) and piperidine (1·75 g.; 0·02 mole) in dry benzene (50 ml.) were refluxed for 24 hr. The reaction mixture was cooled and the precipitated piperidine hydrobromide removed by filtration. The filtrate was extracted with 2*N* HCl, the combined acid extracts made alkaline and extracted with ether, the ether extract dried (Na_2SO_4) and the solvent removed to give the product as a pale yellow oil.

trans- and cis-6-(4-Morpholinyl)-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (Sl Nos. 24 and 25) — $NaBH_4$ (1·9 g.; 0·05 mole) was added in portions to a stirred solution of 6-(4-morpholinyl)-2,3-dimethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 14) (or its hydrochloride) (0·01 mole) in absolute methanol (30 ml.) kept in an ice-bath and stirring was continued for 12 hr. The solvent was then removed under reduced pressure and the residue extracted repeatedly with ether. The ether extract was dried (Na_2SO_4), the solvent removed and the product crystallized on trituration with petroleum ether; m.p. 130-32°; yield 85 per cent. The two isomers were separated by thick layer chromatography on silica gel G plates using benzene-methanol (19: 1) (S 1) as the solvent system. *cis*-Isomer (Sl No. 24) was obtained in 60 per cent yield of the total product as colourless crystals from benzene; m.p. 156-7°; IR $\nu_{max.}^{KBr}$ 3150, 1010 cm.$^{-1}$ (OH band); R_f 0·25 (S1). In NMR spectrum *J* value of 5-methine proton is 3·5 cps. *trans*-Isomer (Sl No. 25) was obtained in 40 per cent of the total mixture as colourless crystals from benzene-petroleum ether; m.p. 150-51°; *J* value for 5-methine proton is 8·5 cps; $\nu_{max.}^{KBr}$ 3230, 1050 cm.$^{-1}$ (OH band); R_f 0·75 (S 1). When the reduction was carried out with $LiAlH_4$, the percentage of the *cis*-isomer increased. The ratio of the two products is 3·5: 1.

6-Methylamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 9) — Compound (Sl No. 8) (2·79 g.; 0·01 mole) in methanol (50 ml.) containing conc. HCl (3 ml.) was hydrogenated over Pd/C (10 per cent, 500 mg.) at room temperature and atmospheric pressure for 24 hr. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in water, the solution made alkaline with 2*N* NaOH and the free base extracted with ether. The ether extract was dried (Na_2SO_4), the solvent removed and the residue chromatographed on basic alumina (grade I) using benzene as the eluant, to give a pale yellow oil.

8,9-Dihydro-7H-benzocycloheptadiene[6,5-d]pyrazole (Sl No. 29) — A solution of 6-hydroxymethylene-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one [3,4] (1·88 g.; 0·01 mole) and hydrazine hydrate (0·60 g.; 0·012 mole of 99-100 per cent) in absolute ethanol (25 ml.) was refluxed for 3 hr, the solution evaporated to dryness under reduced pressure. The pyrazole was obtained from the residue on crystallization from hexane as pale yellow crystals; $\lambda_{max.}^{C_2H_5OH}$ 258 mμ (log ε 4·10).

8,9-Dihydro-7H-benzocycloheptadiene[6,5-d]-1'-phenylpyrazole (Sl No. 30) — A mixture of 6-hydroxymethylene-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (0·01 mole), phenylhydrazine hydrochloride (0·012 mole) and CH_3COONa (0·012 mole) in absolute ethanol (50 ml.) was refluxed for 4 hr, and the solution concentrated under reduced pressure. The residue was taken up in ether and was washed successively with NaOH solution (10 per cent), HCl (10 per cent) and water. The ether layer was dried (Na_2SO_4) and the solvent removed. The residue on crystallization gave the required pyrazole (Sl No. 30) as pale yellow crystals; $\lambda_{max.}^{C_2H_5OH}$ 252 mμ (log ε 4·24). The other pyrazoles were prepared in a similar manner and are described in Table 3.

8,9-Dihydro-7H-benzocycloheptadiene[6,5-d]isoxazole (Sl No. 32) — 6-Hydroxymethylene-6,7,8,9-tetra-

hydro-5H-benzocyclohepten-5-one (1·88 g.; 0·01 mole) was added to a solution of hydroxylamine hydrochloride (1·39 g.; 0·02 mole) in acetic acid (30 ml.) and the mixture heated in an oil-bath at 160-70° for 10-15 min. The solution was cooled and poured on to water (300 ml.) when the isoxazole separated as a crystalline product and collected on a filter. The other isoxazoles prepared in a similar manner are described in Table 3.

6-Cyano-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one — The compound (Sl No. 36) (245 mg.; 0·001 mole) was dissolved in dry ether (25 ml.) and treated with a solution of $NaOCH_3$ (prepared from 0·23 g. of sodium) in dry methanol (25 ml.). After 1 hr, water was added, the ether layer separated and washed thoroughly with KOH solution (5 per cent). The combined alkaline extracts were acidified and the liberated 6-cyano-2,3-dimethoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one was filtered and crystallized from benzene-petroleum ether; m.p. 165-6°; yield 220 mg. (90 per cent) (Found: C, 68·43; H, 6·40; N, 5·52. $C_{14}H_{15}NO_3$ requires C, 68·57; H, 6·12; N, 5·71%).

N,N'-bis(6,7,8,9-tetrahydro-5-oxo-5H-benzocyclohepten-6-yl)methylene ethylenediamine — Ethylenediamine (0·60 g.; 0·01 mole) was added to a solution of 6-hydroxymethylene-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1·88 g.; 0·01 mole) in ethanol (30 ml.) and the reaction mixture refluxed for 3 hr, concentrated and the residue crystallized from benzene; m.p. 208-9°; yield 1·8 g. (90 per cent) (Found: C, 78·30; H, 7·15; N, 6·83. $C_{26}H_{28}N_2O_2$ requires C, 78·00; H, 7·00; N, 7·00%). Dihydrochloride, crystallized from ethanol-ether; m.p. 245-7° (Found: C, 65·82; H, 6·37; N, 5·85. $C_{26}H_{28}N_2O_2.2HCl$ requires C, 65·96; H, 6·34; N, 5·91%); 2,4-dinitrophenylhydrazone, m.p. 155°.

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 were recorded. Some of the other pharmacological actions investigated include the diuretic and hypoglycemic activity in rats, electrogenesis in rabbits, and locomotor, anti-electroshock, antiamphetamine, anti-reserpine, analgesic and anti-barbiturate activities in mice. None of the compounds showed diuretic, hypoglycemic or anticonvulsant activities. The anti-acetylcholine, anti-5-hydroxytryptamine, ganglion blocking and antihistaminic activities were studied in isolated guinea pig ileum preparation.

Some selected compounds were also screened for their anti-viral, anti-bacterial, anti-fungal and anti-fertility activities. None of the compounds was found to possess any activity in these tests.

Structure activity relationship — The most prominent activity shown by these compounds was the sedative, ganglion blocking, anti-acetylcholine and antihistaminic actions. The sedative action was most prominent in 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 5), while the adrenergic blocking and anti-histaminic action was most marked in the 6-(4-N-methylpiperazinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 6). In the case of 6-(1-piperidyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 4), the 2,3-dimethoxy derivative (Sl No. 10) had greater ganglion blocking activity than the unsubstituted compound, while in the case of 6-(4-N-methylpiperazinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one, the introduction of 2,3-dimethoxy groups (Sl No. 12) reduced the adrenergic blocking and anti-histamine actions. In the case of 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one, also the introduction of 2,3-dimethoxy groups (Sl No. 11) or 2,3-dimethyl groups (Sl No. 14) reduced the sedative action.

In general the substituents in the benzene ring tended to decrease the activity, as shown by the reduction in the respective activity of compounds (Sl Nos. 6 and 5) by the introduction of 2,3-dimethoxy or 2,3-dimethyl groups. The 6-tertiary-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ones and the corresponding heptenols had the same pattern of activity, although the ketones seemed more active than the alcohols.

The nature of the depressant activity of 6-(4-morpholinyl)-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (Sl No. 5) was studied in detail. It was found that it reduced amphetamine induced motor activity, potentiated hexobarbital sleep time, but did not block the CAR. It, therefore, appears that 5 is more of a hypnotic and sedative than a tranquilizer (neuroleptic).

The 8,9-dihydro-7H-benzocycloheptadiene[6,5-*d*]pyrazole (Sl No. 29) showed a significant anticonvulsant action.

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