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Bicyclic Mannich Bases. 1. Psychotropic Activity of 2-(4-Aryl-1-piperazinyl)bicyclo[3.3.1]nonan-9-ones and Derivatives

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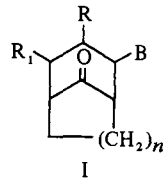
A series of 2-(4-aryl-1-piperazinyl)bicyclo[3.3.1]nonan-9-ones were synthesized and some of them were converted to the 9-phenyl-9-hydroxy derivatives. In most CNS models, 2-(4-phenyl-1-piperazinyl)-9-phenylbicyclo[3.3.1]nonan-9-ol (**17**) was found to exhibit an activity pattern similar to chlordiazepoxide.

It has been reported that 2-substituted-4-phenyl-1-piperazinylmethyl cycloalkanones possess analgetic and antiinflammatory activity in laboratory animals.[1] These findings prompted the synthesis of a number of analogous bicyclic Mannich bases having the general structure I where



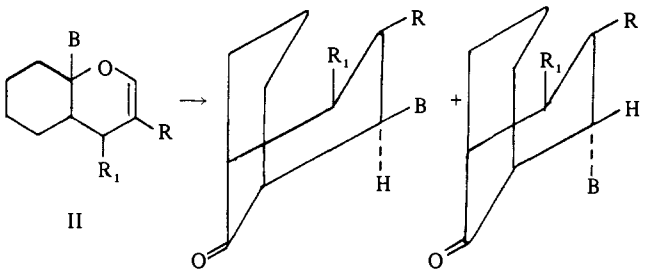
I

R = H or lower alkyl, R_1 = H or Ph, n = 1-3, and B = tertiary amino.

In initial general studies it was noted that 2-(4-phenyl-1-piperazinyl)bicyclo[3.3.1]nonan-9-one (**4**) had the property of inducing catalepsy in the rat. Since this effect is an indicator of potential tranquilizing activity, it was decided to further investigate this bicyclic structure where the 2-(4-aryl-1-piperazinyl) moiety is an integral part of the ring system. This paper is primarily concerned with the synthesis and CNS pharmacological properties of 2-(4-aryl-1-piperazinyl)-bicyclo[3.3.1]nonan-9-ones and derivatives thereof.

The compounds in Table I were prepared by the method of Stork and Landesman.[2] The fact that enamines derived from cyclohexanone and higher molecular weight amines reacted with acrolein in inert solvents to give crystalline 8a-amino-4a,5,6,7,8,8a-hexahydro-4*H*-1-benzopyrans (II) has been reported previously.[3] These intermediates could be isomerized to the bicyclic ketones by heating in DMF-Et_3N; it was later found that heating in 2-PrOH-Et_3N resulted in cleaner isomerization of the intermediate.

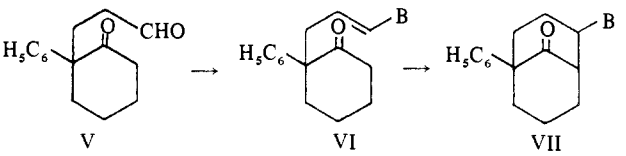
In the case of the isomerization of II (B = 4-phenyl-1-piperazinyl; R = R_1 = H), we showed that the stereochemical results were formation of III and IV in a ratio of approximately 4:1.[3] These results are consistent with those reported by Dean, *et al.*,[4] who determined the stereochemistry of the amino ketones formed in the reaction of 1-morpholinocyclohexene with acrolein.



II III IV

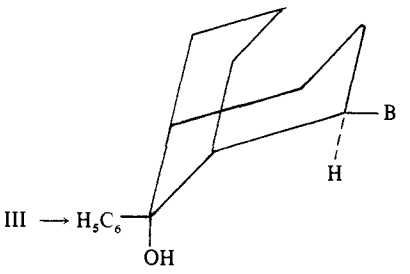
Bicyclic amino ketones having a Ph group at the bridgehead 5 position (type VII) could not be synthesized by the general method described above because 2-phenylcyclohexanone forms mainly the enamine with the double bond in the 1,6 position.[5] Instead a base-catalyzed condensation of acrolein with 2-phenylcyclohexanone was carried out. The ketoaldehyde V was converted into enamine VI which was isomerized in low yield to the desired bicyclic amino ketone.

The derivatives which seemed to enhance and prolong tranquilizing activity as judged by the conditioned avoidance response in rats were the tertiary alcohols formed by the reaction of the bicyclic amino ketones with Grignard and similar reagents (*cf.* Table II). The reaction of PhMgBr with



V VI VII

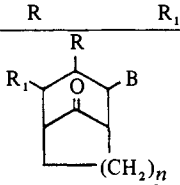
III (B = 4-phenyl-1-piperazinyl) gave almost exclusively one of the 2 possible amino alcohols. We were not able to prove the stereochemistry of the product by any unequivocal experiment, but assigned structure VIII on the basis of analogy with the stereochemistry of X which was the predominant



VIII

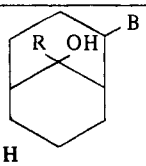
product of the $LiAlH_4$ reduction of the helminthosporal intermediate IX.[7] We also found that the predominant

Table I. 2-Aminobicycloalkanones

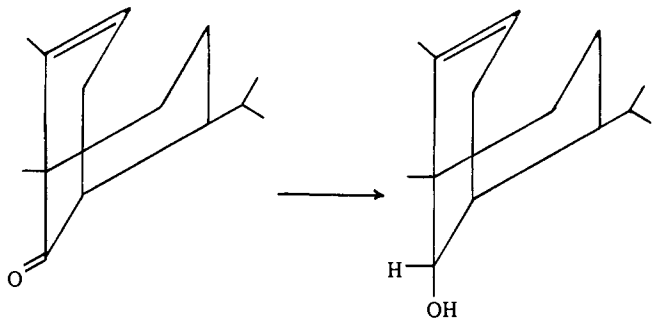
No.	B	R	R_1	*n*	Mp, °C	Formula[c]
						
1[a]	4-Phenyl-1-piperazinyl	H	C_6H_5	2	167-168	$C_{25}H_{30}N_2O$
2	4-Phenyl-1-piperazinyl	CH_3	H	2	145-146	$C_{20}H_{28}N_2O$
3	4-Phenyl-1-piperazinyl	H	H	1	137-138	$C_{18}H_{24}N_2O$
4	4-Phenyl-1-piperazinyl (eq amine)	H	H	2	133-134	$C_{19}H_{26}N_2O$
5	4-Phenyl-1-piperazinyl (axial amine)	H	H	2	100-101	$C_{19}H_{26}N_2O$
6	4-Phenyl-1-piperazinyl	H	H	3	136-137	$C_{20}H_{28}N_2O$
7	4-*m*-Chlorophenyl-1-piperazinyl	H	H	2	94-96	$C_{19}H_{25}ClN_2O$
					195-196	$C_{19}H_{25}ClN_2O \cdot HCl$
8	4-*m*-Trifluoromethylphenyl-1-piperazinyl	H	H	2	209-210	$C_{20}H_{25}F_3N_2O \cdot HCl$
9	4-*p*-Fluorophenyl-1-piperazinyl	H	H	2	194-195	$C_{19}H_{25}FN_2O \cdot HCl$
10[b]	Pyrrolidino	H	H	2		$C_{13}H_{21}NO$
11	4-Phenyl-1-piperazinyl (6,7-benzo, eq amine)	H	H	2	136-138	$C_{23}H_{26}N_2O$
12	4-Phenyl-1-piperazinyl (6,7-benzo, axial amine)	H	H	2	200-202	$C_{23}H_{26}N_2O$
13	4-Phenyl-4-hydroxy-1-piperidyl	H	H	2	155-156	$C_{20}H_{27}NO_2$
14	4-Phenyl-4-carbethoxy-1-piperidyl	H	H	2	170-171	$C_{23}H_{31}NO_3 \cdot C_4H_4O_4$
15	4-Phenyl-1-piperazinyl (Bridgehead 5-phenyl)	H	H	2	198-200	$C_{25}H_{30}N_2O \cdot HCl$

[a]Compounds 1-6 have been disclosed by us previously (ref 3). [b]Disclosed in reference 2. [c]All compds were analyzed for C, H, N; compd 7, N analysis only.

Table II. 2-Aminobicyclo[3.3.1]nonan-9-ols

No.	B	R	Mp, °C	Formula[a]
				
16	4-Phenyl-1-piperazinyl	H	128-130	$C_{19}H_{28}N_2O$
17	4-Phenyl-1-piperazinyl	C_6H_5	149-150	$C_{25}H_{32}N_2O$
			257	$C_{25}H_{32}N_2O \cdot HCl$
18	4-*p*-Fluorophenyl-1-piperazinyl	C_6H_5	227-228	$C_{25}H_{31}FN_2O \cdot HCl$[b]
19	4-Phenyl-1-piperazinyl	4-FC_6H_4	182-185	$C_{25}H_{31}FN_2O$
20	4-Phenyl-1-piperazinyl	CH_3	300	$C_{20}H_{30}N_2O \cdot HCl$
21[c]	Pyrrolidino	C_6H_5		$C_{19}H_{27}NO$
22	4-Phenyl-1-piperazinyl	$C_6H_5CH_2$	201-203	$C_{26}H_{34}N_2O \cdot C_4H_4O_4$
23	4-Phenyl-4-acetyl-1-piperidyl	CH_3	254-256	$C_{23}H_{33}NO_2 \cdot HCl$

[a]All compds were analyzed for C, H, N. [b]Calcd: C, 69.66. Found: C, 69.10. [c]See ref 6.



IX X

alcohol from the $NaBH_4$ reduction of III showed a signal in the nmr spectrum at δ 3.16 assignable to the CHO proton. This is the expected location for an equatorial carbinyl proton; the axial proton generally occurs at *ca.* 0.5 ppm higher field.[8,9]

Pharmacology. CNS activity of listed compounds was first evaluated as described by Irwin.[10] Graded doses of each drug were given ip to groups of mice and the animals were observed continuously over a period of 6 hr. Lethality and delayed effects were noted 24 hr after drug administration. Selected compounds were further evaluated for effects on conditioned avoidance behavior of rats,[11] on pentylenetetrazole-induced convulsions in mice,[12] and on electrically induced fighting behavior of mice.[13] For all tests, compounds were dissolved or suspended in 0.2% methylcellulose and administered ip.

A number of compounds in both series caused marked sedation in mice as judged by their ability to reduce spontaneous motor activity. This effect could be regarded as specific since it was observed at doses not affecting muscular coordination or decreasing exploratory activity. As shown in Table III, the 2-aminobicyclo[3.3.1]nonan-9-ols were in general more potent than the corresponding ketone derivatives. In both series the presence of the 4-phenyl-1-piperazinyl moiety was essential for activity; replacement by other groups (**10**, **13**, **14**, **21**, **23**) led to considerable decrease in activity. Compound **17** was found to be the most effective in the alcohol series. Structural changes led to no improvement in sedative activity. For example, removal of the 9-Ph group (**16**) or substitution by 9-Me (**20**) or 9-benzyl (**22**) led to lowering of activity. Halogen substitution on the 9-Ph group (**19**) or in the phenylpiperazine moiety (**18**) also tended to decrease depressant effects. In the ketone series, optimal activity was found with the unsubstituted bicyclic ring (**4**). *m*-Chloro (**7**), *p*-fluoro (**9**), or *m*-trifluoromethyl (**8**) substitutions in the amine moiety provided less or equally active drugs. Compound **11** and its geometrical isomer **12** with a benzene ring fused to the bicyclic system showed diminished activity. Finally, changes in the ring size did not alter (**3**) or decrease activity (**6**). The isomeric compound **5** with an axial (exo) amine function was somewhat less active than 4.

Compounds **1**, **3**, **4**, **9**, **16**, **17**, **18**, and **20**, selected for further testing, were found to block conditioned avoidance behavior of rats at doses that did not affect escape responses. In this test, **16** appeared to be the most active (see Table III). Only **9** and **17** suppressed fighting behavior in mice in doses below those producing motor incoordination,[14] whereas none of them exhibited interesting anticonvulsant properties in the antipentylenetetrazole test. Other pharmacological properties of **17** were also investigated. In the unanesthetized chronically implanted cat **17**, at doses of 3.1 mg/kg, synchronized electrical brain activity and significantly reduced EEG arousal induced by auditory stimulation. It was found to be a moderate antagonist of electrically induced seizures in mice.[15] The ED_{50} of **17** was 13.2 mg/kg, while those of phenobarbital and diphenylhydantoin were 2.9 mg/kg and 1.0 mg/kg, respectively. Significant reduction of fighting behavior of mice with isolation-induced aggressiveness[16] was observed with doses as low as 10 mg/kg. At doses up to 68.1 mg/kg, **17** did not antagonize chewing behavior

Table III. Pharmacological Activity

Compd	Decreased spontaneous activity[a]	Decreased exploratory activity[a]	Catatonia[a]	Decreased muscular tone[a]	Ataxia	Death[a]	Anti-avoidance[a]	Antipentylene-tetrazole[a]	Antifighting[a]
1	10	100	*d*	300	300	>1000	23.0	>100	>20
2	100	300	300	*d*	100	>1000	*e*	*e*	*e*
3	10	100	100	300	100	1000	9.9	>100	>20
4	10	30	100	300	300	1000	18.7	>100	>20
5	30	100	*d*	300	300	1000	*e*	*e*	*e*
6	30	100	*d*	100	100	>1000	*e*	*e*	*e*
7	300	300	*d*	1000	1000	>1000	*e*	*e*	*e*
8	100	300	*d*	1000	1000	>1000	*e*	*e*	*e*
9	10	30	100	300	30	300	10.9	>100	ED_{50} = 8.2
10[b]	100	100	*d*	*d*	300	300	*e*	*e*	*e*
11	100	1000	*d*	100	*d*	>1000	*e*	*e*	*e*
12	30	300	*d*	1000	1000	>1000	*e*	*e*	*e*
13	100	100	*d*	*d*	*d*	300	*e*	*e*	*e*
14[b]	300	300	300	*d*	300	1000	*e*	*e*	*e*
15	30	100	100	300	1000	>1000	*e*	*e*	*e*
16	10	10	30	100	30	1000	3.4	>100	>20
17	3	100	10	100	100	1000	12.8	ED_{50} = 88.0	ED_{50} = 8.0
18	10	100	*d*	300	300	>1000	13.4	>100	>20
19	30	100	*d*	300	300	>1000	*e*	*e*	*e*
20	10	100	*d*	100	100	1000	9.7	>100	>20
21[c]	100	100	*d*	*d*	100	300	*e*	*e*	*e*
22	30	100	*d*	300	100	1000	*e*	*e*	*e*
23[c]	*d*	*d*	*d*	*d*	*d*	300	*e*	*e*	*e*
CDP	10	100	*d*	100	100	300	9.2	ED_{50} = 2.1	ED_{50} = 11.6
CPZ	3	10	10	30	10	1000	3.5	*d*	ED_{50} = 3.6[f]

[a]Lowest dose producing effect. Doses are ip in mg/kg. [b]Signs of CNS stimulation at doses of 300 mg/kg. [c]Signs of CNS stimulation at 100 mg/kg. [d]Not observed. [e]Not tested. [f]Not selective.

induced by apomorphine in rats.[17] It did not elicit significant autonomic or cardiovascular effects in cats and dogs. In all the experimental procedures described, except for the antipentylenetetrazole test, **17** was found to be either similar to or slightly more potent than chlordiazepoxide.

Experimental Section†

Preparation of 2-Aminobicycloalkanones. The following general procedure using the synthesis of **2-(4-phenyl-1-piperazinyl)bicyclo[3.3.1]nonan-9-one (4)** as an example, was adopted. A soln of 162 g (1.00 mole) of *N*-phenylpiperazine, 98.0 g (1.00 mole) of cyclohexanone, and 1.0 g of TsOH in 250 ml of xylene was heated under reflux for 1 day while the liberated H_2O was collected in a Dean–Stark trap. The xylene was distd *in vacuo* and the residue dissolved in 1 l. of hot 2-PrOH. The cryst enamine which formed on cooling was collected, washed with a little cold MeOH, and dissolved immediately in 500 ml of dry C_6H_6. To the cooled solution was added 78.0 g (1.20 moles) of acrolein over a 15-min period. The reaction mixt was stirred at room temp for 1 hr after which the intermediate aminopyran (II, R = R_1 = H; B = 4-phenyl-1-piperazinyl) was collected and washed with cold EtOAc; yield 156 g, mp 119–120°. A second crop of the same mp was isolated from the filtrate, total yield 186 g (62%).

The aminopyran was dissolved in 475 ml of Et_3N and 95 ml of 2-PrOH and heated under reflux for 1 day. The reaction mixt was cooled in an ice bath and the product collected and washed with 2-PrOH; yield 130 g, mp 123–126°. At this point the axial and equatorial amino ketones may be separated by column chromatog according to the procedure reported in reference 3. Otherwise the predominant equatorial isomer **4** can be obtained by recrystn from EtOAc, yield 112 g (60%).

2-(4-Phenyl-1-piperazinyl)-9-phenylbicyclo[3.3.1]nonan-9-ol (17). A solution of 157 g (0.97 mole) of C_6H_5Br in 300 ml of THF was slowly added to 25 g (1.0 g-atom) of Mg turnings in 50 ml of THF at such a rate as to maintain gentle refluxing. After the Mg had reacted, 112 g (0.38 mole) of the amino ketone **4** in 300 ml of THF was added. The mixt was stirred under reflux for 18 hr, then 600 ml of 10% NH_4Cl was added. Solvent was removed and the org material extracted into $CHCl_3$. Drying and concentration of the ext *in vacuo* followed by crystn of the residue from 2-PrOH gave 102 g (73%) of product, mp 144–145°. For purification this material was stirred in 400 ml of 20% HCl for 2 hr. The hydrochloride was collected and converted back to the free base using K_2CO_3 soln. Final recrystn from C_6H_5–hexane gave analytically pure material showing 1 spot on tlc.

2-(4-Phenyl-1-piperazinyl)-9-methylbicyclo[3.3.1]nonan-9-ol Hydrochloride (20). To a soln of 7.00 g (0.023 mole) of **4** in dry THF was added 5 equiv of MeLi in Et_2O. The soln was stirred at room temp under N_2 for 4 hr, then poured on ice water and allowed to stand for 1 hr. The product was isolated by extn with $CHCl_3$, converted to the hydrochloride and purified by recrystn from aq EtOH.

2-(4-Phenyl-4-acetyl-1-piperidyl)-9-methylbicyclo[3.3.1]nonan-9-ol Hydrochloride (23). To a cold stirred soln of 10.9 g (0.041 mole) of 1-(4-cyano-4-phenyl-1-piperidyl)cyclohexene in 100 ml of dry C_6H_6 was added 2.40 g (0.043 mole) of acrolein in 50 ml of C_6H_6 at 10°. After 2 days the solvent was removed *in vacuo* and the residue was heated in 100 ml of DMF containing 4 g of Et_3N. After removal of solvent the crude material was purified by chromatog on Silicar cc 7 (Mallinckrodt). Elution with Et_2O gave 4.40 g of cyanoketone, $\nu_{max}^{CHCl_3}$ 2235 (CN), 1710 (C=O) cm^{-1}. This intermediate was dissolved in 500 ml of Et_2O and treated with MeLi (100 ml of a 2.3 *M* soln in Et_2O). The mixt was heated under reflux for 12 hr under N_2. Excess MeLi was decompd with 2-PrOH, then 150 ml of 5% HCl was added and the mixt heated for 1 hr to effect hydrolysis of the imine function. The organic solvents were removed *in vacuo* and the hydrochloride was separated from the aq mixt by extn with $CHCl_3$. The crude salt was converted to the free base in aq K_2CO_3 which was then extd into EtOAc. Addition of HCl-2-PrOH gave the purified hydrochloride, yield 2.30 g, $\nu_{max}^{CHCl_3}$ 3300 (OH), 1700 (C=O) cm^{-1}.

2-(4-Phenyl-1-piperazyl)-5-phenylbicyclo[3.3.1]nonane-9-one Hydrochloride (15). To a soln of 38.0 g (0.21 mole) of 2-phenylcyclohexanone in 200 ml of Et_2O at 10° under N_2 was added 3 drops of Triton B (40% in MeOH) followed by dropwise addn of 16.8 g (0.30 mole) of acrolein in 50 ml of Et_2O. The reaction temp was not allowed to rise above 35° during the addn. After 2 hr stirring, the solvent was removed *in vacuo* and the residue distd. A fraction (9.4 g) with bp 135–140° (0.1 mm) was a mixt of the desired aldehyde and the isomeric 2-hydroxy-5-phenylbicyclo[3.3.1]nonan-9-one; ir ($CHCl_3$) 3400 (OH), 2720 (CHO), 1725 (C=O, aldehyde) and 1710 (C=O, ketone) cm^{-1}; nmr ($CDCl_3$) 8.75 (t, 0.5, CHO); the benzylic proton signal at 3.5 for 2-phenylcyclohexanone was absent.

A soln of 8.0 g (0.034 mole) of the product described above and 6.5 g (0.040 mole) of 1-phenylpiperazine in 100 ml of $PhCH_3$ was heated under reflux for 3 hr during which time the theoretical amt of H_2O was collected in a Dean–Stark trap. Removal of the solvent *in vacuo* gave 12.5 g of the enamine as a red-brown oil; ir ($CHCl_3$) 1715 (C=O, ketone), 1650 (NC=C) cm^{-1}.

The crude enamine in 40 ml of DMF and 10 ml of Et_3N was stirred at 80° for 1 day. After removal of solvent, the residue was stirred in 150 ml of Et_2O–5% aq HCl (2:1) for 18 hr. The hydrochloride was collected and recrystd from MeOH, yield 0.6 g; ir (KCl) 1715 cm^{-1}.

†Melting points were taken on a Büchi melting point determination apparatus and are uncorrected. Ir spectra were determined with a Perkin-Elmer Model 237 spectrophotometer and nmr spectra were obtained with a Varian Model A-60 spectrometer (resonance peaks given in δ units relative to Me_4Si). Where analyses are indicated only by symbols the elements are within 0.4% of the theoretical values.

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