Preparation of Some *N*-Benzylpiperidines

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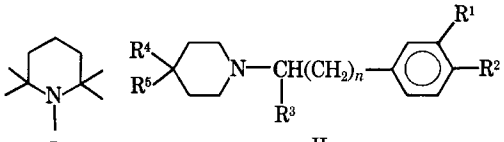
A number of *N*-(*p*-substituted benzoyl)piperidines was prepared. The reduction of the amides with lithium aluminum hydride provided the corresponding *N*-(*p*-substituted benzyl)piperidines. Isobutyric anhydride and 3,4,5-trimethoxybenzoyl chloride were used to prepare several esters of *N*-(*p*-hydroxybenzyl)piperidines. Several of the compounds were tested in mice for their general behavioral effects and in dogs for pharmacodynamic activity.

EXTENSIVE INVESTIGATIONS have been conducted in a search for hypotensive agents and a number of useful compounds have been produced (1).

The need for agents with greater safety characteristics and different limits of tolerance prompted an investigation into the preparation of some *N*-benzylpiperidines (III). The hypotensive properties exhibited by 1,2,2,6,6-pentamethylpiperidine (I) and related compounds (2), and the observations of Somers and Handley (3) that 1-aralkyl-4,4-dialkylpiperidines (II) possess substantial hypotensive activity, added impetus to this work.



I

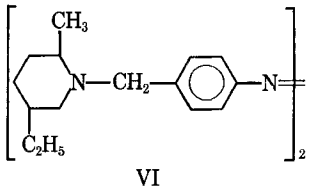
II

DISCUSSION

The synthesis of *N*-(*p*-substituted benzyl)piperidines (III) was accomplished primarily *via* reduction of the corresponding benzoylpiperidines (IV). (Scheme I.)

The intermediate *N*-(*p*-substituted benzoyl)-piperidines (IV) (Table I) were prepared by the reaction of a substituted benzoyl chloride with a substituted piperidine.

The reduction of IV with lithium aluminum hydride, with one exception, provided the corresponding benzyl derivatives (III) (Table II). The reduction of *N*-(*p*-nitrobenzoyl)-2-methyl-5-ethylpiperidine yielded the azo derivative (VI). The formation of azo compounds *via* lithium aluminum hydride reduction of nitro groups is not uncommon (4). The *N*-(*p*-aminobenzyl)-2-methyl-5-ethylpiperidine is obtained if, preceding lithium hydride reduction, the nitro group is reduced with palladium-carbon.



VI

The synthesis of *N*-(*p*-hydroxybenzyl)piperidines (Table II) ultimately was effected by the following methods: (*a*) demethylation of *N*-(*p*-methoxybenzyl)piperidines, (*b*) debenzylation of *N*-(*p*-benzyloxybenzyl)piperidines, (*c*) utilization of a modified Wallach reaction, and (*d*) reduction of *N*-(*p*-acetoxybenzoyl)piperidines.

Demethylation was accomplished using refluxing hydriodic acid in glacial acetic acid (5) and debenzylation was performed by hydrogenolysis with palladium-carbon.

A modified Wallach reaction (6) was utilized for the preparation of *N*-(*p*-hydroxybenzyl)piperidine. The maximum yield, however, never exceeded 10%. Increasing the length of reaction time did not increase the yield.

The *N*-(*p*-acetoxybenzoyl)piperidines were prepared by condensing *p*-acetoxybenzoyl chloride with an appropriately substituted piperidine and were employed without purification in subsequent lithium aluminum hydride reductions.

The esterification of the *N*-(*p*-hydroxybenzyl)-piperidines to V was accomplished using isobutyric anhydride and 3,4,5-trimethoxybenzoyl chloride. The esters of both of these acids are prevalent in the veratrum series (7). Table III lists the esters prepared.

Preliminary studies in mice indicated that the amides (Table I) in general exhibit weak central nervous system (CNS) depressant properties. Cheymol and associates (8) noted hypnotic properties of *o*-(piperidinothiocarbonyl)phenol. The amines (Table II) in general exhibited weak CNS stimulant activity. Preliminary studies of the esters (Table III) in dogs showed transient depressor responses.

EXPERIMENTAL[1]

p-Benzyloxybenzoyl chloride (9), *p*-acetoxybenzoyl chloride (10), and *p*-nitrobenzoyl chloride (11) were prepared according to reported procedures. Commercially available anisoyl chloride was utilized.

N-(p-Substituted Benzoyl)piperidines (Table I)—*Method A*—A cooled solution of 0.07 mole of the

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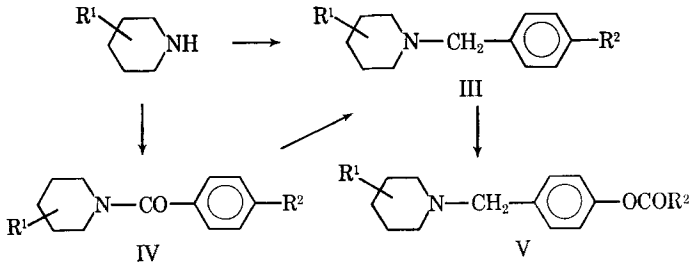
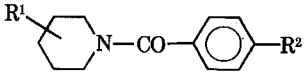
[1] All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infrared data were obtained on all compounds with a Perkin-Elmer model 137 G Infracord spectrophotometer using KBr pellets.



Scheme I

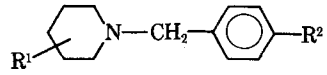
TABLE I—*N*-(*p*-SUBSTITUTED BENZOYL)PIPERIDINES



R_1	R_2	Method	M.p., °C. or B.p., °C./mm.	Yield, %	Molecular Formula	Anal., % Calcd. C	H	N	Found C	H	N
2-CH_3-5-C_2H_5	OCH_3	*A*	140–142/0.05	86	$C_{16}H_{23}NO_2$	74.0	8.7	5.3	73.9	8.9	5.7
2,6-di-CH_3	OCH_3	*A*	140–142/0.05	62	$C_{15}H_{21}NO_2$	72.9	8.5	5.7	72.7	8.5	5.5
2-CH_3	OCH_3	*A*	53–54[a]	24	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	72.3	8.3	6.1
3-CH_3	OCH_3	*A*	52–53[a]	60	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	72.0	8.0	6.0
4-CH_3	OCH_3	*A*	54–55.5[a]	90	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	72.4	8.1	6.2
4-CH_3	$OCH_2C_6H_5$	*A*	105–107[b]	50	$C_{20}H_{23}NO_2$	77.7	7.4	4.5	77.8	7.4	4.6
2-CH_3-5-C_2H_5	NO_2	*B*	185/0.75	86	$C_{15}H_{20}N_2O_3$	65.2	7.3	10.1	65.3	7.3	11.0
2-CH_3-5-C_2H_5	NH_2	*C*	183–184.5[b]	96	$C_{15}H_{22}N_2O$	73.2	8.9	11.4	73.1	8.8	11.4
2-CH_3	OH	*D*	213–213.5[c]	60	$C_{13}H_{17}NO_2$	71.2	7.8	6.4	71.4	7.7	6.3

[a] Recrystallized from petroleum ether (30–60°). [b] Recrystallized from ethanol–water. [c] Recrystallized from ethanol.

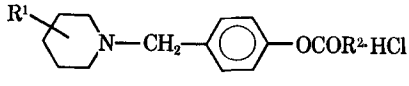
TABLE II—*N*-(*p*-SUBSTITUTED BENZYL)PIPERIDINES



R_1	R_2	Method	M.p., °C.	Recrystn. Solvent[a]	Yield, %	Molecular Formula	Anal., % Calcd. C	H	N	Found C	H	N
H	OH	*H, I*	254–255	Et–W	98, 5	$C_{12}H_{18}ClNO$[b]	63.3	8.0	6.1	63.2	8.3	6.2
2-CH_3	OH	*F, I*	191–193	Et–E	60, 67	$C_{13}H_{20}ClNO$[b]	64.7	8.3	5.8	64.5	8.3	5.8
3-CH_3	OH	*I*	163–165	A–E	53	$C_{13}H_{20}ClNO$[b]	64.6	8.3	5.8	64.5	8.4	5.8
4-CH_3	OH	*I, G*	171–172	A–M	75, 42	$C_{13}H_{20}ClNO$[b]	64.6	8.3	5.8	64.3	8.4	6.0
2-CH_3-5-C_2H_5	OH	*I*	191–193.5	A–M	75	$C_{15}H_{24}ClNO$[b]	66.9	9.0	5.2	66.1	8.8	5.5
2,6-diCH_3	OH	*I*	173–174	B	60	$C_{14}H_{22}ClNO$[b]	65.9	8.6	5.4	65.7	8.8	5.6
2-CH_3-5-C_2H_5	OCH_3	[c]	141/0.75 mm.[d]		23	$C_{16}H_{25}NO$	77.7	10.1	5.6	77.9	9.8	5.7
2-CH_3-5-C_2H_5	NH_2	[c]	113–114.5	Et–W	86	$C_{15}H_{24}N_2$	77.6	10.3	12.1	77.2	10.2	12.7
2-CH_3-5-C_2H_5	N=NC$_6$H$_4$-*p*-CH_2—R^3[e]	*E*[f]	82–84	M	33	$C_{30}H_{44}N_4$	78.3	9.6	12.2	78.2	9.6	12.2

[a] Et, ethanol; W, water; A, acetone; E, ether; M, methanol; B, 2-butanone. [b] Hydrochloride. [c] Prepared from the corresponding amide utilizing the procedure described by Sommers (12). [d] Boiling point. [e] R^3 = 2-ethyl-6-methylpiperidine. [f] From *N*-(*p*-nitrobenzoyl)-2-methyl-5-ethylpiperidine.

TABLE III—*N*-(*p*-ACYLOXYBENZYL)PIPERIDINES



R_1	R_2	Method	M.p., °C.	Recryst. Solvent[a]	Yield, %	Molecular Formula	Anal., % Calcd. C	H	N	Found C	H	N
H	$(CH_3)_2CH$	*J*	227–228.5	A–E	58	$C_{16}H_{24}ClNO_2$	64.6	8.1	4.7	64.5	8.1	4.7
2-Me	$(CH_3)_2CH$	*J*	179.5–180	B–E	95	$C_{17}H_{26}ClNO_2$	65.6	8.4	4.5	65.4	8.2	4.5
3-Me	$(CH_3)_2CH$	*J*	176–177	Ea	66	$C_{17}H_{26}ClNO_2$	65.6	8.4	4.5	65.6	8.5	4.6
4-Me	$(CH_3)_2CH$	*J*	202.5–203	Ea	93	$C_{17}H_{26}ClNO_2$	65.6	8.4	4.5	65.4	8.4	4.3
4-Me	3,4,5-triCH_3OC$_6$H$_2$	*K*	217–218	A–E	91	$C_{23}H_{30}ClNO_5$	63.4	6.9	3.2	62.8	6.6	3.4

[a] A, acetone; E, ether; B, benzene; Ea, ethyl acetate.

appropriate piperidine in 50 ml. of anhydrous ether was treated dropwise with 0.03 mole of anisoyl or *p*-benzyloxybenzoyl chloride. The reaction mixture was allowed to stand 15 min. and then treated with 25 ml. of ice water. The ether solution was washed with two 50-ml. portions of 10% sodium bicarbonate and two 50-ml. portions of 10% hydrochloric acid, respectively. The ether was evaporated and the residual material either distilled or recrystallized from a suitable solvent.

In the case of the *N*-(*p*-acetoxybenzoyl)piperidines, the final ethereal layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The residual product was used in subsequent reduction reactions.

Method B—To a solution of 38 Gm. (0.3 mole) of 2-methyl-5-ethyl piperidine in 150 ml. of pyridine was added slowly 28 Gm. (0.18 mole) of *p*-nitrobenzoyl chloride. The reaction mixture was heated 45 min. on a steam bath. The solution was cooled and then washed with two 50-ml. portions of 10% sodium bicarbonate and two 50-ml. portions of 10% hydrochloric acid, respectively. The residual oil was extracted with ether, dried, and then distilled.

Method C—A solution of 18.6 Gm. (0.07 mole) of *N*-(*p*-nitrobenzoyl)-2-methyl-5-ethyl piperidine in 50 ml. of ethanol was hydrogenated with 10% palladium-carbon at 40 p.s.i. for 2 hr. The product was isolated in the usual manner.

Method D—To 7 Gm. (0.03 mole) of *N*-(*p*-methoxybenzoyl)-2-methyl piperidine was added 100 ml. of glacial acetic acid and 100 ml. of 57% hydriodic acid. The mixture was refluxed 6 hr., cooled, and treated with 100 ml. of water. The solution was decolorized with sodium bisulfite and extracted with two 50-ml. portions of ether. The ether was extracted with 50 ml. of 10% sodium hydroxide. The aqueous layer was separated and acidified with 10% hydrochloric acid. The acid solution was extracted with 50 ml. of ether. Evaporation of the ether yielded the product.

N-(p-Substituted Benzyl)piperidines (Table II)—*Method E*—The procedure outlined by Sommers (12) for lithium aluminum hydride reductions was modified and used. A stirred slurry of 18.2 Gm. (0.4 mole) of lithium aluminum hydride and 100 ml. of anhydrous tetrahydrofuran was treated dropwise with 0.1 mole of the amide in 50 ml. of anhydrous tetrahydrofuran. The mixture was stirred and refluxed 24 hr., cooled, and cautiously decomposed with 200 ml. of ethyl acetate. The reaction mixture was filtered and the solvent distilled. The residual oil was converted to the hydrochloride in the usual manner and recrystallized from the appropriate solvent.

Method F—To a solution of 20 ml. of 57% hydriodic acid in 20 ml. of glacial acetic acid was added 4.3 Gm. (0.02 mole) of *N*-(*p*-methoxybenzyl)-2-methylpiperidine and the whole refluxed 6 hr. The cooled solution was treated with 100 ml. of water, made alkaline with solid sodium bicarbonate, and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate. The hydrochloride was prepared in the usual manner.

Method G—A solution of 29.5 Gm. (0.1 mole) of *N*-(*p*-benzyloxybenzyl)-4-methylpiperidine in 90% ethanol was hydrogenated with 10% palladium-carbon catalyst at 42 p.s.i. for 12 hr. The catalyst was removed by filtration and the ethanol distilled under reduced pressure. The oil was extracted with 50 ml. of 10% sodium hydroxide; the latter was washed with ether and then neutralized with solid carbon dioxide. The product was extracted with ether and converted to the hydrochloride in the usual manner.

Method H—Following a modified procedure of Staple and Wagner (6), 16 Gm. (0.2 mole) of piperidine and 4.6 Gm. (0.1 mole) of formic acid (90%) were heated on a steam bath for 30 min. The mixture was cooled, treated with 12.2 Gm. (0.1 mole) of *p*-hydroxybenzaldehyde, and thereafter heated in an oil bath at 110–120° for 14 hr. The mixture was cooled, treated with 100 ml. of 10% sodium bicarbonate, and extracted with ether. The hydrochloride was prepared in the usual manner.

Method I—The *N*-(*p*-acetoxybenzoyl)piperidines (prepared according to method *A*) were reduced with lithium aluminum hydride according to the procedure outlined in method *E* to *N*-(*p*-hydroxybenzyl)piperidines.

Esters of N-(p-Hydroxybenzyl)piperidine (Table III)—*Method J*—The procedure outlined by Behrend (13) and Hudson and Dale (14) was followed. A solution of 0.004 mole of the requisite *N*-(*p*-hydroxybenzyl)piperidine hydrochloride in 20 ml. of pyridine was treated with 3.2 Gm. (0.02 mole) of isobutyric anhydride and stirred 12 hr. The pyridine was distilled under reduced pressure and the residue was recrystallized from an appropriate solvent.

Method K—A modified procedure of Counsell and Soine (15) was employed. A solution of 1 Gm. (0.005 mole) of *N*-(*p*-hydroxybenzyl)-4-methylpiperidine in 25 ml. of anhydrous benzene was treated with 2.3 Gm. (0.01 mole) of commercial 3,4,5-trimethoxybenzoyl chloride and 2 Gm. (0.02 mole) of triethylamine. The mixture was refluxed 12 hr., cooled, and washed with 10% sodium hydroxide and water, respectively. The product was isolated in the usual manner and converted to a hydrochloride.

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