Synthesis of Some N-Substituted 3,5-Dimethyl-4-piperidinols and Their Derivatives as Potential Analgesics

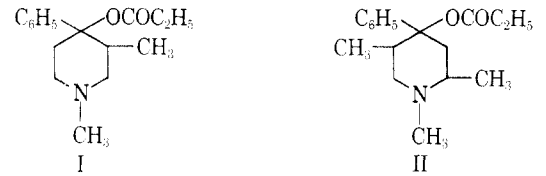
NORMAN J. HARPER, COLIN F. CHIGNELL,[1a,b] AND GEORGE KIRK

Chelsea School of Pharmacy, London S. W. 3, England

Received April 28, 1964

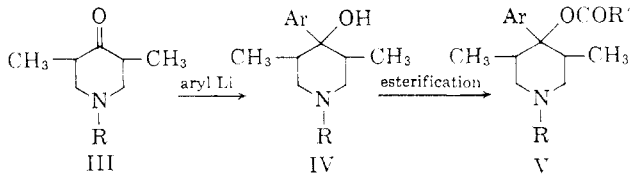
A series of N-substituted 3,5-dimethyl-4-piperidones has been prepared. Aryllithium addition gave piperidinols which were esterified and tested for analgesic activity.

The relatively high analgesic activity of α- and β-prodine (I) and trimeperidine (II)[2] prompted us to



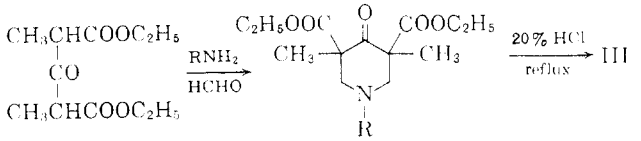
I II

undertake the synthesis of compounds of the type V, by the following well-established route.[3-5]



III IV V

An initial attempt to prepare N-phenethyl-3,5-dimethyl-4-piperidone from phenethylamine and two molecules of methyl methacrylate, according to previously reported procedures,[3-5] was unsuccessful; only (β-carbomethoxy-*n*-propyl)phenethylamine could be isolated in the initial condensation reaction. At length, a route previously described by Mannich and Schumann,[6] was successfully adapted for the preparation of several 3,5-dimethyl-4-piperidones.



R = $C_6H_5CH_2CH_2$, $C_6H_5CH_2$, CH_3

Reduction of N-phenethyl-3,5-dimethyl-4-piperidone (III, R = $C_6H_5CH_2CH_2$) with sodium and ethanol gave one 4-piperidinol, while reaction with aluminum isopropoxide in 2-propanol gave the isomeric compound; this result confirms Mannich's[6] original *cis* assignment to the methyl groups. An alternative procedure for the synthesis of 1,3,5-trimethyl-4-piperidone was reported after the completion of this work.[7]

Tertiary alcohols of the type IV were prepared, in 35–75% yields, by aryllithium additions to the corresponding piperidones, but in each case only one isomer was isolated. The infrared spectra of the noncrystalline residues showed carbonyl and hydroxyl absorption, indicating that they were mixtures of unreacted piperidone and piperidinol; the latter was possibly more of the isomer already isolated or perhaps the other isomer.[8] A consideration of steric and thermodynamic factors operating during the attack of an aryllithium on piperidones of the type III led us to assign a *trans* aryl–methyl configuration to the piperidinols reported in this paper (Fig. 1). This assignment has been confirmed, in the case of 4-phenyl-1,3,5-trimethyl-4-piperidinol, by Sorokin on the basis of esterification studies.[7] Debenzylation of N-benzyl-3,5-dimethyl-4-phenyl-4-piperidinol, in the presence of hydrogen and palladium on charcoal, gave 3,5-dimethyl-4-phenyl-4-piperidinol; alkylation of this compound with phenethyl bromide gave a product identical with that obtained by phenyllithium addition to N-phenethyl-3,5-dimethyl-4-piperidone.

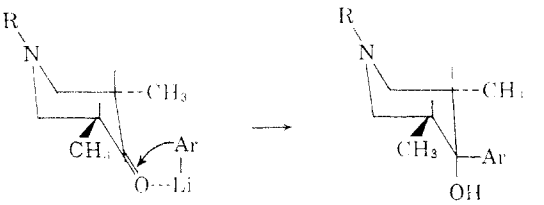


Figure 1.

The piperidinols were esterified by refluxing with an acid anhydride in pyridine; the low yields (<40%) obtained can be attributed to the highly hindered position occupied by the hydroxyl group. In an attempt to esterify 4-(2-furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol, using acetic anhydride in pyridine, only 4-(2-furyl)-3,5-dimethyl-N-phenethyl-1,2,3,6-tetrahydropyridine could be isolated. The facile elimination of water from 4-(2-furyl)-N-phenethyl-4-piperidinols under these conditions has been attributed to the electron-releasing properties of the furyl group.[9]

Although it has been found possible to eliminate one molecule of water from 4-aryl-4-piperidinols by refluxing with a mixture of acetic and aqueous hydrochloric acids,[10] those reported in this study, with one exception, prove refractory to this treatment. 4-(2-Furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol gave 4-(2-furyl)-3,5-dimethyl-N-phenethyl-1,2,3,6-tetra-

(1) (a) National Institutes of Health, Bethesda, Md. 20014. (b) This work was carried out during the tenure of a scholarship awarded by Department of Scientific and Industrial Research, London, England, and comprises a portion of the thesis presented by C. F. C. in partial fulfillment of the requirements for the Ph.D. degree at the University of London.

(2) Promedol®.

(3) S. M. McElvain and K. Rorig, *J. Am. Chem. Soc.*, **70**, 1820 (1948).

(4) A. H. Beckett, A. F. Casy, and G. Kirk, *J. Med. Pharm. Chem.*, **1**, 37 (1959).

(5) N. J. Harper, A. H. Beckett, and A. D. J. Balon, *J. Chem. Soc.*, 2704 (1960).

(6) Mannich and P. Schumann, *Chem. Ber.*, **69**, 2299 (1936).

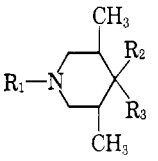
(7) O. I. Sorokin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 460 (1961).

(8) Since the completion of this work Sorokin[7] reported the isolation of three isomeric piperidinols, designated α, β, and γ, from the reaction of phenyllithium with 1,3,5-trimethyl-4-piperidone. The α-isomer, which accounted for 87% of the total yield, had the same melting point as that obtained in this investigation.

(9) A. F. Casy, A. H. Beckett, and N. A. Armstrong, *Tetrahedron*, **16**, 85 (1961).

(10) N. Sugimoto and S. Oshiro, Japanese Patent 4232 (June 5, 1956).

TABLE I
N-SUBSTITUTED 3,5-DIMETHYLPIPERIDINES



					Calcd., %				Found, %			
R_1	R_2	R_3	M.p., °C.	Formula	C	H	N	Neut. equiv.	C	H	N	Neut. equiv.
$C_6H_5CH_2CH_2$	OH	C_6H_5	277.5–278.5	$C_{21}H_{27}NO\cdot HCl$	72.9	8.2	4.0	346	72.4	8.1	3.9	346
$C_6H_5CH_2CH_2$	$OCOCH_3$	C_6H_5	222–223	$C_{23}H_{29}NO_2\cdot HCl$	71.2	7.8	3.5	388	70.7	7.4	3.5	392
$C_6H_5CH_2CH_2$	$OCOC_2H_5$	C_6H_5	235–236	$C_{24}H_{31}NO_2\cdot HCl$	71.7	8.0	3.5	402	71.4	7.8	3.7	408
$C_6H_5CH_2CH_2$	OH	o-$CH_3C_6H_4$	252–253	$C_{22}H_{29}NO\cdot HCl$	73.4	8.4	3.9	360	73.0	8.0	3.8	363
$C_6H_5CH_2CH_2$	$OCOCH_3$	o-$CH_3C_6H_4$	195.5–196.5	$C_{24}H_{31}NO_2\cdot HCl$	71.7	8.4	3.5	402	70.1	7.4	3.1	402
$C_6H_5CH_2CH_2$	OH	2-Furyl	244.5–245	$C_{19}H_{25}NO_2\cdot HCl$	67.9	7.6	4.2	336	67.4	7.6	4.0	339
$C_6H_5CH_2CH_2$ (isomer A)	OH	H	192–193	$C_{15}H_{23}NO_2\cdot HCl$	66.8	9.0	5.2	270	66.6	8.7	5.1	270
$C_6H_5CH_2CH_2$ (isomer B)	OH	H	200–200.5	$C_{15}H_{23}NO_2\cdot HCl$	66.8	9.0	5.2	270	66.6	8.7	5.3	269
$C_6H_5CH_2$	OH	C_6H_5	277–278	$C_{20}H_{25}NO\cdot HCl$	72.4	7.9	4.2	332	72.4	7.6	4.0	333
H	OH	C_6H_5	284–285	$C_{13}H_{19}NO\cdot HCl$	64.6	8.3	5.8	242	65.0	8.4	5.5	243
CH_3	OH	C_6H_5	129–130[a]	$C_{14}H_{21}NO$	76.7	9.7	6.4	219	76.8	9.9	6.3	220
CH_3	$OCOCH_3$	C_6H_5	225–226	$C_{16}H_{23}NO_2\cdot HCl$	64.5	8.1	4.7	298	64.1	8.0	4.5	300
CH_3	$OCOC_2H_5$	C_6H_5	172–173	$C_{17}H_{25}NO_2\cdot HCl$	65.5	8.4	4.5	312	64.9	8.4	4.4	316

[a] Lit.[7] m.p. 131.5–132.0°.

hydropyridine, identical with that isolated in the esterification experiments. Furthermore, despite the successful dehydration of 2,6-dimethyl-1-phenyl-1-cyclohexanol and 2,6-dimethyl-1-*o*-tolyl-1-cyclohexanol by heating with anhydrous oxalic acid,[11] 3,5-dimethyl-N-phenethyl-4-phenyl-4-piperidinol was unaffected by this reagent. Treatment of the same compound with 85% v./v. sulfuric acid for 30 min. resulted in degradation of the molecule, giving an unidentified neutral solid.

The 4-piperidinols and their esters were subjected to a pharmacological screening. Although 4-(2-furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol had an analgesic activity one-fifth that of pethidine when assayed by the hot plate method,[12] all other compounds were found to be inactive. This is in marked contrast to the high analgesic activities reported by Nazarov[13] for the 1,2,5- and 1,2,3-trimethyl-4-phenyl-4-propionoxypiperidines. However, Sorokin[7] also reported that the α- and β-isomers (*cis* Me–Me) of 1,3,5-trimethyl-4-phenyl-4-propionoxypiperidine were inactive, although the γ-isomer (*trans* Me–Me) was as potent as trimeperidine itself. The inactivity of these *cis* isomers may be due to the equatorial methyl groups hindering the formation of a drug–receptor complex.

Experimental

Melting points were taken in a glass capillary and are uncorrected for stem exposure. Equivalent weights of the bases, and their picrates, were determined by titration with 0.02 *N* perchloric acid in acetic acid, with oracet blue B as indicator. Titrations of the salts were carried out in the same solvent, in the presence of mercuric acetate.[14] Microanalyses were carried out by Mr. G. S. Crouch of the School of Pharmacy, University of London, and Drs. G. Weiler and F. B. Strauss of the Microanalytical Laboratory, Oxford, England. Ultraviolet absorption spectra were determined using the Beckman DK-2 spectrophotometer.

3,5-Dimethyl-N-phenethyl-4-piperidone Hydrobromide.—Diethyl α,α'-dimethylacetonedicarboxylate[15] (198.0 g.) was added, over a period of 10 min., to a mixture of phenethylamine (104.0 g.), concentrated HCl (73.0 ml.), and aqueous formaldehyde (40% w./v.) (160.0 ml.). The stirred reaction mixture was heated on an oil bath at 60° for 3 hr., allowed to stand at room temperature for 48 hr., and extracted with ether (200 ml.). The aqueous solution was made alkaline with solid KOH and extracted with three 200-ml. portions of ether. The combined ethereal extracts were dried (Na_2SO_4), and the solvent was removed by distillation under reduced pressure to give a viscous amber oil (205.0 g.). Hydrochloric acid (20% w./v.) (656 ml.) was added, the mixture refluxed for 24 hr., and then was concentrated to 300 ml. by distillation under reduced pressure. The acidic solution was made alkaline by the addition of solid NaOH and extracted with three 200-ml. portions of ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give a viscous dark brown oil (133.0 g.). After acidifying with aqueous HBr (60% w./v.) (76.0 ml.), the solution was evaporated to dryness and the residue was crystallized from ethanol–ether to give colorless needles (35.0 g.), m.p. 192–192.5°.

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.7; H, 7.1; N, 4.5; neut. equiv., 312. Found: C, 57.2; H, 6.9; N, 4.5; neut. equiv., 312.

1,3,5-Trimethyl-4-piperidone was prepared in a similar manner and was isolated as a mobile colorless oil, b.p. 79° (12 mm.).

Anal. Calcd. for $C_8H_{15}NO$: neut. equiv., 141. Found: neut. equiv., 141.

The hydrochloride (from ethanol–ether) had m.p. 230.5–231.5° (lit. m.p. 235°,[6] 219–220°[7]).

N-Benzyl-3,5-dimethyl-4-piperidone, also prepared in a similar manner, was isolated as a viscous pale yellow oil, b.p. 136–140° (0.3 mm.), $n^{25}D$ 1.5328.

Anal. Calcd. for $C_{14}H_{19}NO$: neut. equiv., 217. Found: neut. equiv., 220.

The **picrate** (from ethanol) had m.p. 206.5–207.5°.

Anal. Calcd. for $C_{20}H_{22}N_4O$: C, 53.8; H, 5.0; N, 12.6; neut. equiv., 446. Found: C, 53.8; H, 4.9; N, 12.2; neut. equiv., 446.

3,5-Dimethyl-N-phenethyl-4-piperidinol (Isomer A) Hydrochloride.—A solution of 3,5-dimethyl-N-phenethyl-4-piperidone (10.7 g.) in a mixture of toluene (20 ml.) and ethanol (13.3 ml.) was added over a period of 15 min. to sodium (5.3 g.) in toluene (10 ml.). The solution was refluxed for 17 hr., cooled, water (20 ml.) was added, and the aqueous layer was separated and extracted with toluene. The combined toluene solutions were dried (Na_2SO_4) and the solvent was removed by distillation under reduced pressure. The residue obtained was dissolved in ethanolic HCl (10% w./v.) and stored at −5°. The solid which separated was crystallized from ethanol–ether to give **isomer A hydrochloride** (6.7 g.), m.p. 192–193°. Exhaustive examination of the mother liquors failed to indicate the presence of another isomer.

(11) R. B. Carlin and H. P. Landerl, *J. Am. Chem. Soc.*, **75**, 3969 (1953).
(12) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).
(13) I. N. Nazarov, *Izbrannye Tr., I. N. Nazarov, Akad. Nauk SSSR*, 588 (1961); *Chem. Abstr.*, **56**, 8682 (1962).
(14) C. W. Pifer and E. G. Wollish, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 609 (1951).
(15) G. Schroeter, *Chem. Ber.*, **49**, 2697 (1916).

3,5-Dimethyl-N-phenethyl-4-piperidinol (Isomer B) Hydrochloride.—3,5-Dimethyl-N-phenethyl-4-piperidone (6.7 g.) was added dropwise to a suspension of aluminum isopropoxide (18.8 g.) in 2-propanol (134 ml.) and the reaction mixture was heated on a steam bath. During this time, slow distillation of the solvent and the acetone produced occurred. After 6 hr. the distillate gave no cloudiness with acetone test reagent.[16] The bulk of the solvent was removed by distillation under reduced pressure, and the residue was acidified with acetic acid (25 ml.). On making alkaline with concentrated NH_4OH solution, extraction with ether gave, after drying (Na_2SO_4), a residue (6.0 g.) which was dissolved in ethanolic HCl (10% w./v.). The solid which separated was fractionally crystallized to give **isomer B hydrochloride,** m.p. 200–200.5° (4.2 g.), as colorless prismatic crystals. No other isomeric products could be isolated from this reaction and a mixture melting point of isomers A and B showed a marked depression.

General Method for the Preparation of Tertiary Alcohols (IV).[17]—The piperidone (1 mole) was added dropwise, with stirring, to a cooled solution of the aryllithium in ether, prepared from lithium (3.0 g.-atoms) and an aryl bromide (1.5 moles).[18] The mixture was stirred for 5 hr. at room temperature and then added to crushed ice and excess acetic acid. The solid which separated on cooling to −5° was washed with ether, the base was liberated with strong aqueous ammonia and extracted with ether. After drying (Na_2SO_4), the solvent was removed and the residue was treated with ethanolic HCl (10% w./v.). The solid which separated on cooling to −5° was recrystallized from ethanol–ether. In no case was more than one isomeric product isolated.

3,5-Dimethyl-4-phenyl-4-piperidinol Hydrochloride.—A solution of N-benzyl-3,5-dimethyl-4-piperidinol hydrochloride (11.3 g.) in ethanol (100 ml.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (1.2 g.). After 8 hr. the theoretical amount of hydrogen had been absorbed, the mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residual solid (7.0 g.) was crystallized from ethanol–ether to give colorless prismatic crystals, m.p. 284–285° (4.5 g.).

3,5-Dimethyl-N-phenethyl-4-phenyl-4-piperidinol Hydrochloride.—A mixture of sodium bicarbonate (4.2 g.), phenethyl bromide (3.4 g.), 3,5-dimethyl-4-phenyl-4-piperidinol (3.4 g.), and chloroform (45 ml.) was stirred and refluxed for 43 hr. The solid was filtered off and washed with three 10-ml. portions of chloroform. The combined chloroform extracts were washed with three 10-ml. portions of water and added to crushed ice (5.0 g.) and concentrated HCl (1.5 ml.). On cooling the mixture, a solid (4.0 g.) separated and was crystallized from ethanol–ether to give colorless prismatic crystals, m.p. 277.5–278.5°, undepressed on admixture with the piperidinol prepared above.

General Method for the Preparation of Esters (V).[17]—A mixture of the piperidinol (1.0 g.), acid anhydride (1.5 ml.), and pyridine (1.5 ml.) was refluxed for 3 hr. and the solvent was removed by distillation under reduced pressure. The residue was dissolved in ethanolic HCl (10% w./v.) and the solid, which separated on cooling, was crystallized from ethanol–ether.

4-(2-Furyl)-3,5-dimethyl-N-phenethyl-1,2,3,6-tetrahydropyridine. A.—4-(2-Furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol (2.0 g.) was refluxed for 1 hr. with concentrated HCl (7.0 ml.) and acetic acid (17.0 ml.), the solvent was removed by distillation under reduced pressure, and the residue was dissolved in ethanol. No crystals separated on storage in the refrigerator. The free base (obtained by treatment with excess concentrated NH_4OH followed by extraction with ether) was purified by passage over alumina (50 g.) (Peter Spence Type H) in petroleum ether (b.p. 60–80°). The residue (0.5 g.), obtained from the first 40 ml. of eluent, was treated with ethanolic HCl and gave colorless prismatic crystals, m.p. 216–218°, λ_{max}^{EtOH} 257 mμ (ε 13,970).

Anal. Calcd. for $C_{19}H_{24}ClNO$: C, 71.9; H, 7.6; N, 4.4; neut. equiv., 318. Found: C, 72.3; H, 7.8; N, 4.5; neut. equiv., 326.

B.—4-(2-Furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol (2.0 g.) was refluxed for 3 hr. with pyridine (3 ml.) and acetic anhydride (3 ml.), the solvent was removed by distillation under reduced pressure, and the residue was dissolved in ethanolic HCl (10% w./v.). The solid which separated was recrystallized from ethanol–ether to give colorless prismatic crystals (1.1 g.), m.p. 218–219°, undepressed on admixture with a sample prepared by A.

With the exception of 4-(2-furyl)-3,5-dimethyl-N-phenethyl-4-piperidinol (*vide supra*), it was found impossible to effect the elimination of water from the 4-aryl-4-piperidinols described in this investigation by refluxing with acetic and hydrochloric acids.[10] In two further experiments 3,5-dimethyl-N-phenethyl-4-phenyl-4-piperidinol was heated with anhydrous oxalic[11] acid but was recovered unchanged, while refluxing with 85% v./v. H_2SO_4 for 30 min. resulted in degradation of the molecule.

Acknowledgment.—The biological screening of these compounds was carried out by Dr. D. K. Vallance of Smith Kline and French Laboratories, Welwyn Garden City, Herts., England.

(16) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1957, p. 884.

(17) The analytical data for these compounds will be found in Table I.

(18) 2-Furyllithium, which cannot be prepared by this method, was obtained by adding furan (redistilled) to an equimolar proportion of phenyllithium in ether, followed by refluxing for 2 hr.