determined with a model DU Beckman spectrophotometer in 1-cm. quartz cells, point by point absorbance measurements being made at 2-mμ intervals or less. Concentrations were 1×10^{-3} to 1×10^{-5} mole per liter in methanol which was 0.1 *N* in hydrochloric acid except in the case of *p*-dimethylamino-β-nitrostyrene. In the latter case pure methanol was used in determining the spectrum of the free base. A methanolic solution 5 *N* in hydrochloric acid gave the spectrum of the conjugate acid, but the large amount of water in the methanol shifted the absorption maximum from 294 to 300 mμ (ε 18,000) presumably due to a solvent effect.[11] In the 0.1 *N* solution in methanol, peaks appeared for the free base at 436 mμ and for the conjugate acid at 294 mμ. The concentration of free base under these circumstances was calculated and a correction applied in calculating the molar absorptivity of the conjugate acid.

(11) D. J. Drain and W. Wilson, ref. *j*, Table I, report λ_{max} 305-308, ε 18,500 in 5 *N* aqueous HCl.

It was necessary to carry out all dilution operations in "low actinic" glassware and to avoid light wherever possible. Otherwise the nitrostyrenes in dilute solutions showed fading absorbancies at the $\lambda_{max.}$. This phenomenon, probably due to a light-catalyzed reaction,[12] led to absorbancy readings which differed by as much as 30% in the morning and afternoon or on a cloudy or sunny day, and depended to a great extent on the speed with which the operations were carried out. The use of protective "low actinic" glassware eliminated these difficulties and gave reproducible spectra.

(12) Dr. Harold Shechter has pointed out that β-nitrostyrene undergoes a light-catalyzed dimerization [see B. Priebs, *Ann.*, **225**, 339 (1884); J. Meisenheimer and F. Heim, *ibid.*, **335**, 260 (1907)]. The structure of the dimer is presently being investigated at the Ohio State University by Dr. Shechter and D. Miller.

SILVER SPRING, MARYLAND

[CONTRIBUTION FROM ROHM & HAAS CO.]

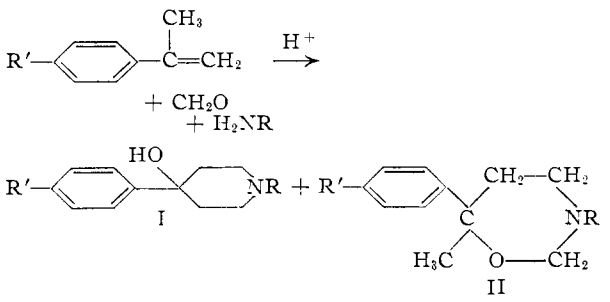
The Aminomethylation of Olefins. II. A New Synthesis of 1-Alkyl-4-aryl-4-piperidinols

BY CLAUDE J. SCHMIDLE AND RICHARD C. MANSFIELD

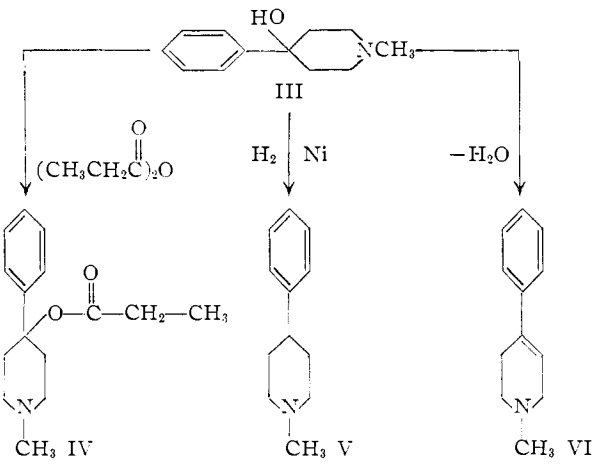
RECEIVED APRIL 16, 1955

A new and relatively simple synthesis of 1-alkyl-4-aryl-4-piperidinols from α-methylstyrenes, formaldehyde and primary amine salts is reported.

It has been reported[1] that esters of 1-alkyl-4-aryl-4-piperidinols (I) are potent analgesics. Previously these piperidinols have been prepared[2-4] by the reaction of arylmagnesium halides or lithium aryls with 1-alkyl-4-piperidones. We have found that 1-alkyl-4-aryl-4-piperidinols (I) are formed along with 3-alkyl-6-methyl-6-aryltetrahydro-1,3-oxazines (II) by the reaction of α-methylstyrenes, formaldehyde and primary amine salts.



While this work was in progress, Hartough, *et al.*,[5] reported that the reaction of α-methylstyrene, formaldehyde and methylamine hydrochloride gave 3,6-dimethyl-6-phenyltetrahydro-1,3-oxazine, but they did not identify 1-methyl-4-phenyl-4-piperidinol (III) as one of the products. The physical properties of the latter material III and those of its derivatives were found to agree with values reported in the literature.[2-4] Esterification with propionic anhydride gave 1-methyl-4-phenyl-4-propionoxypiperidine (IV), hydrogenolysis gave 1-methyl-4-phenylpiperidine (V) and dehydration gave 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (VI).



It therefore is the purpose of this paper to report on the 1-alkyl-4-aryl-4-piperidinols (I) which we have prepared by this new synthesis. These are summarized in Table I.

The reaction proceeds well in an aqueous medium thus making it possible to use aqueous formaldehyde, aqueous amine solutions and concentrated hydrochloric acid if desired. The formation of 1-methyl-4-phenyl-4-piperidinol (III) may be shown

(1) R. H. K. Foster and A. J. Carman, *J. Pharmacol. Exptl. Therap.*, **91**, 195 (1947).

(2) K. A. Jensen and F. Lundquist, *Dansk. Tids. Farm.*, **17**, 173 (1943); *C. A.*, **39**, 2506 (1945).

(3) K. A. Jensen, U. S. Patent 2,589,943 (March 18, 1952); *C. A.*, **46**, 11249 (1952).

(4) A. Ziering, L. Berger, S. D. Heineman and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

(5) H. D. Hartough, J. J. Dickert and S. L. Meisel, U. S. Patent 2,647,117 (July 28, 1953); *C. A.*, **48**, 8265 (1954).

TABLE I

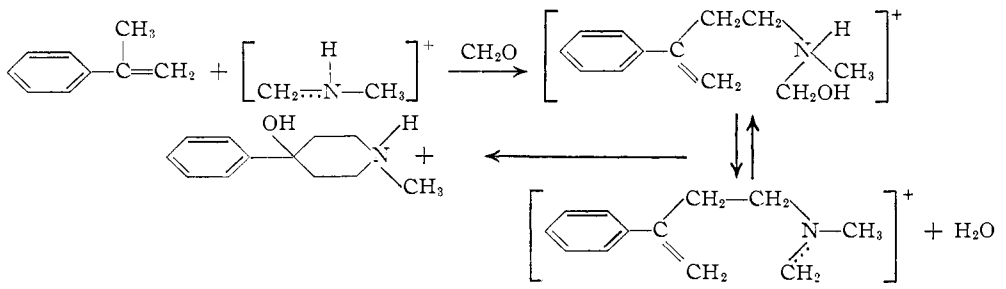
1-ALKYL-4-ARYL-4-PIPERIDINOLS, R—N(OH)—R′

R	R′	Yield,[a] %	B.p., °C.	Mm.	M.p., °C. uncor.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3-	H	29.8	125–150	2.0	114–116[c,d]	$C_{12}H_{17}NO$	75.35	75.05	8.96	8.83	7.33	7.18
C_2H_5-	H	11.7	120–140	0.8	88–90[e]	$C_{13}H_{19}NO$	76.05	75.92	9.33	9.52	6.82	6.81
$(CH_3)_2CH-$	H	26.9	120–160	.7	84–86[f,g]	$C_{14}H_{21}NO$	76.66	74.62	9.65	9.68	6.39	6.51
n-C_4H_9-	H	10.3	145–165	.7	87–88[h]	$C_{15}H_{23}NO$	77.21	77.34	9.93	9.99	6.00	5.96
n-$C_6H_{13}-$	H	18.4	155–185	.7	98–100	$C_{17}H_{27}NO$	78.11	78.27	10.41	10.47	5.36	5.43
$CH_2(CH_2)_4CH-$	H	33.3	160–200	2.0	144–145	$C_{17}H_{25}NO$	78.71	78.91	9.72	9.74	5.40	5.20
$CH_2{=}CHCH_2-$	H	27.2	120–160	0.7	86–87[i]	$C_{14}H_{19}NO$	77.38	77.47	8.81	9.11	6.45	6.65
$C_6H_5CH_2-$	H	7.1	185–195	.9	107–108[j]	$C_{18}H_{21}NO$	80.86	80.89	7.92	7.85	5.24	5.22
$CH_3O(CH_2)_3-$	H	18.2	145–170	.8	71–73	$C_{15}H_{23}NO_2$	72.25	72.33	9.30	9.24	5.62	5.40
$C_9H_{19}-$[k]	H	17.5	170–190	1.0	92–94	$C_{20}H_{33}NO$	79.15	79.23	10.96	10.97	4.62	4.75
CH_3-	CH_3	29.9[l]			124–126	$C_{13}H_{19}NO$	76.05	76.17	9.33	9.40	6.82	6.63
C_2H_5-	CH_3	26.5	125–140	0.8	113–114	$C_{14}H_{21}NO$	76.66	76.48	9.65	9.65	6.39	6.24
n-C_4H_9-	CH_3	26.8	140–165	.8	84–85[m]	$C_{16}H_{25}NO$	77.68	77.81	10.19	10.40	5.66	5.70
n-$C_6H_{13}-$	CH_3	29.8	160–176	.8	105–107	$C_{18}H_{29}NO$	78.49	78.43	10.61	10.88	5.09	5.10
$CH_2(CH_2)_4CH-$	CH_3	25.0	165–185	.8	138–139	$C_{18}H_{27}NO$	79.07	79.00	9.96	9.90	5.12	5.12
$CH_2{=}CHCH_2-$	CH_3	25.1	135–160	.8	[n]	$C_{15}H_{21}NO$	77.88	77.56	9.15	9.16	6.06	6.20

[a] Yields based on material of boiling range indicated. [b] Recrystallized from heptane unless otherwise stated. [c] Recrystallized from benzene. [d] Ref. 2 reported m.p. 114–115°. Ref. 4 reported m.p. 111°. [e] Ref. 4 reported m.p. 87°. [f] Recrystallized from Skellysolve B. [g] Ref. 4. reported m.p. 81°. [h] Ref. 4 reported m.p. 86–88°. [i] Ref. 4 reported m.p. 86°. [j] Ref. 4 reported m.p. 103°. [k] 3,5,5-Trimethylhexyl. [l] Crude base crystallized. [m] Ref. 4 reported m.p. 87.° [n] Did not crystallize. Redistilled; b.p. 135–140° (0.7 mm.).

as two consecutive aminomethylation reactions, the second being intramolecular.

$$CH_2O + H_2NCH_3 \overset{H^+}{\rightleftharpoons} \left[CH_2{=}\overset{\displaystyle H}{\overset{|}{N}}{-}CH_3\right]^+ + H_2O$$



The 1-alkyl-4-aryl-4-piperidinols thus formed may be esterified[4] with acid anhydrides using conventional methods. A future communication will describe the conversion of 3-alkyl-6-methyl-6-aryltetrahydro-1,3-oxazines (II) to 1-alkyl-4-aryl-1,2,-3,6-tetrahydropyridines and 1-alkyl-4-aryl-4-piperidinols (I).

Acknowledgment.—To Mr. C. W. Nash and his staff for analytical data reported.

Experimental

The following example illustrates the general procedure employed for the preparation of the 1-alkyl-4-aryl-4-piperidinols.

1-Methyl-4-phenyl-4-piperidinol (III).—A mixture of 67.5 g. (1 mole) of methylamine hydrochloride, 200 g. (2.5 moles) of 37% formaldehyde and 118 g. (1.0 mole) of α-methylstyrene was stirred vigorously and heated to 80°. It was maintained at 80–90° for one hour, during which time the α-methylstyrene went into solution. The mixture was heated for 4 hr. on a steam-bath, cooled and diluted with 250 ml. of water. It was extracted with benzene and the aqueous solution was made basic with excess 50% sodium hydroxide solution. The amine was taken up in benzene, dried and distilled to give 89 g., b.p. 93–125° (2 mm.), consisting largely of 3,6-dimethyl-6-phenyltetrahydro-1,3-oxazine, and 57 g. (30%) of 1-methyl-4-phenyl-4-piperidinol (III), b.p. 125–150° (2 mm.), which crystallized upon cooling. The piperidinol was recrystallized twice from benzene to give 29 g. (15%), m.p. 114–116°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.33. Found: C, 75.05; H, 8.83; N, 7.18.

The hydrochloride melted at 163–164° after recrystallization from acetone (lit.[2] m.p. 159–160°).

Anal. Calcd. for $C_{12}H_{18}NOCl$: Cl, 15.6. Found: Cl, 16.0.

1-Methyl-4-phenyl-4-propionoxypiperidine (IV).—A mixture of 48 g. (0.25 mole) of 1-methyl-4-phenyl-4-piperidinol (III), 320 ml. (2.5 moles) of propionic anhydride and 1 g. (0.01 mole) of concentrated sulfuric acid was stirred and heated on a steam-bath for 3 hr. Excess propionic anhydride was removed by distillation under reduced pressure (15 mm.). The residual liquid (100 ml.) was poured into 200 ml. of cold water and made basic with sodium carbonate. The amine was taken up in ether, dried and distilled to give 48 g. (85%) of 1-methyl-4-phenyl-4-propionoxypiperidine (IV), b.p. 115–117° (0.75 mm.), $n^{25}D$ 1.5170.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.16; H, 8.58; N, 5.80.

The hydrochloride melted at 185–187° after recrystallization from acetone (lit.[3] m.p. 183–184°).

Anal. Calcd. for $C_{15}H_{22}NO_2Cl$: Cl, 12.5. Found: Cl, 12.2.

1-Methyl-4-phenylpiperidine (V).—Hydrogenolysis of 57 g. (0.30 mole) of 1-methyl-4-phenyl-4-piperidinol (III) in

175 ml. of heptane and 20 ml. of ethanol at 150° and 1900 p.s.i. using 10 g. of Raney nickel gave 23 g. (44%) of 1-methyl-4-phenylpiperidine (V), b.p. 114–119° (8 mm.) (lit.[6] b.p. 120–122° (10 mm.)); picrate, m.p. 239–240° (lit.[6] m.p. 239–240°).

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.46; H, 5.34; N, 13.90.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (VI).—A mixture of 191 g. (1.0 mole) of 1-methyl-4-phenyl-4-piperidinol (III), 144 g. (8.0 moles) of water and 150 g. (1.5 moles) of concentrated hydrochloric acid was stirred at 95° for 7 hr., allowed to stand overnight, poured into 500 ml. of water and made basic with excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried and distilled to give 142 g. (82%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (VI), b.p. 85–105° (0.6 mm.). Redistillation gave a center cut of 56 g., b.p. 99–100° (1.3 mm.), which crystallized and melted at 40–42° after recrystallization from heptane.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.64; H, 8.64; N, 7.76.

The hydrochloride melted at 247–249° after recrystallization from acetone (lit.[7] m.p. 248–250°).

Anal. Calcd. for $C_{12}H_{16}NCl$: Cl, 16.9. Found: Cl, 16.8.

(6) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 261 (1944).

(7) S. M. McElvain and J. C. Safranski, Jr., THIS JOURNAL, **72**, 3134 (1950).

PHILADELPHIA, PENNSYLVANIA

[FROM THE BIOCHEMICAL INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Synthesis of 7-Indolecarboxylic Acid[1]

BY HERBERT SINGER[2] AND WILLIAM SHIVE

RECEIVED MAY 31, 1955

3-Chloro-2-nitrotoluene (VI) was condensed with diethyl oxalate in the presence of potassium ethoxide, and the product was hydrolyzed to form 3-chloro-2-nitrophenylpyruvic acid (VIII). Reductive cyclization of this compound with ferrous sulfate in dilute ammonium hydroxide yielded 7-chloro-2-indolecarboxylic acid (IX). Conversion of IX to 7-cyanoindole (X) was accomplished by means of cuprous cyanide in quinoline. Hydrolysis of the nitrile led to the desired product, 7-indolecarboxylic acid (XI). 7-Indolecarboxylic acid is inactive in replacing anthranilic acid in supporting growth of *Lactobacillus arabinosus* 17-5 and mutant strains of *Neurospora* requiring anthranilic acid or indole for growth.

The inhibitory effect of 5-methyltryptophan on growth of *Lactobacillus plantarum* 8293 is prevented competitively by anthranilic acid, but both indole and tryptophan at relatively low concentrations reverse the toxicity of the methyltryptophan non-competitively.[3] Among possible explanations for these results, including the possibility that 5-methyltryptophan inhibits the conversion of anthranilic acid to indole, one alternative explanation was considered in which the biological conversion of anthranilic acid to tryptophan might have been preceded by intermediate formation of 7-indolecarboxylic acid and 7-carboxytryptophan, the decarboxylation of which might have been inhibited by 5-methyltryptophan. The carboxyl group of anthranilic acid is known to be lost during its biological conversion to tryptophan.[4] Accordingly, 7-indolecarboxylic acid was synthesized in the present investigation but was found to be inactive in replacing anthranilic acid or indole in supporting growth of several organisms.

Several procedures including the Fischer method were unsuccessful in preparation of indoles from *o*-substituted anilines such as anthranilonitrile; however, the Reissert method of cyclization was successful with 3-chloro-2-nitrophenylpyruvic acid which could be converted to 7-chloro-2-indolecarboxylic acid and finally to 7-cyanoindole and 7-indolecarboxylic acid by a sequence of reactions analogous to the steps used in the synthesis of 4-indolecarboxylic acid by Uhle[5] and 6-indolecarboxylic acid by Kermack.[6] The various reactions including the preparation of 3-chloro-2-nitrophenylpyruvic acid as well as its conversion to 7-indolecarboxylic acid were carried out in the sequence as indicated.

To prepare the appropriate intermediates, sodium 4-amino-*m*-toluenesulfonate (I) was converted to the 2-amino-3-chlorotoluene (V) by acetylation, chlorination and hydrolysis of the acetylsulfonic acid groups as indicated by the sequence of compounds I to V[7]; and the aminochlorotoluene was converted by diazotization and replacement reactions to 3-chloro-2-nitrotoluene (VI) as previously reported.[8]

The condensation of 3-chloro-2-nitrotoluene (VI) with diethyl oxalate to form 3-chloro-2-nitrophenylpyruvic acid (VII) was effected by a procedure similar to that reported for the conversion of 2-nitro-4-(1-pentenyl)-toluene to 2-nitro-4-(1-pentenyl)-phenylpyruvic acid.[9] Ring closure of the chloronitrophenylpyruvate (VII) was accomplished by the standard procedure of reductive cyclization with ferrous sulfate in dilute ammonium hydroxide, and the resulting 7-chloro-2-indolecarboxylic acid

(1) From part of a thesis submitted by Herbert Singer to the Graduate School, The University of Texas, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1955.

(2) Rosalie B. Hite Fellow, 1954–1955.

(3) E. Beerstecher, Jr., and W. Shive, unpublished work; E. Beerstecher, Jr., Ph.D. Thesis, University of Texas, June, 1948.

(4) J. F. Nyc, *J. Biol. Chem.*, **179**, 783 (1949).

(5) F. C. Uhle, THIS JOURNAL, **71**, 761 (1949).

(6) W. O. Kermack, *J. Chem. Soc.*, **125**, 2285 (1924).

(7) An indication that 2-amino-3-chlorotoluene could be prepared as indicated appeared in early patent literature but preparative procedures and properties of the compounds were not reported (German Patent 217,370, Jan. 10, 1911; *Frdl.*, **10**, 932 (1910)).

(8) This conversion has been previously reported in patent literature (A. Sieglitz and K. Steger (to I. G. Farbenind. A-G) German Patent 638,486, Oct. 26, 1936; *Frdl.*, **23**, 191 (1940)), but the product was characterized only by boiling point under reduced pressure and no analytical data was reported. Other methods of synthesis of 3-chloro-2-nitrotoluene have been reported (K. Brand and H. Zoller, *Ber.*, **40**, 3324 (1907); J. B. Cohen and H. J. Hodsman, *J. Chem. Soc.*, **91**, 970 (1907); L. A. Elson, C. S. Gibson and J. D. A. Johnson, *ibid.*, 2735 (1929); J. P. Wibaut, *Rec. trav. chim.*, **32**, 292 (1913); H. Burton and J. Kenner, *J. Chem. Soc.*, **119**, 1052 (1921)).

(9) H. R. Snyder and H. R. Beilfuss, THIS JOURNAL, **75**, 4921 (1953).