and the homogeneous yellow solution (violet fluorescence) allowed to stand at ambient temperatures for two days. The tube was then frozen, opened, and the ammonia and solvents evaporated. Recrystallization of the residual yellow powder from methanol gave 1.41 g. (77%) of crude diamide, m.p. 300–302°. An analytical sample was prepared by a second recrystallization from methanol and desiccation overnight at 60° (0.4 mm.) to give XXI as fine yellow needles, m.p. 310–315° dec.

Anal. Calcd. for $C_{20}H_{20}O_2N_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.69; H, 6.95; N, 8.31.

9,10-Anthracene-bis-(3′-propanol) (XXII).—A solution of 1.0 g. of lithium aluminum hydride (70%) in dry tetrahydrofuran was stirred while a solution of 1.0 g. (0.003 mole) of XIX, m.p. 142–145°, in 50 ml. of dry tetrahydrofuran was added dropwise. The mixture was stirred at reflux for three hours after addition was complete. After cooling, water was added cautiously, then enough dilute hydrochloric acid to acidify. A small quantity of insoluble material was removed by filtration, and the layers separated. The aqueous layer was extracted twice with ethyl acetate, and the combined organic solutions (deep indigo fluorescence) dried over anhydrous sodium sulfate. Concentration to 20-ml. volume and cooling gave 0.85 g. (100%) of pale tan crystals, m.p. 174–176°. Recrystallization from 95% ethanol with charcoal treatment followed by one sublimation at 200–210° (0.9 mm.) gave straw-colored crystals of XXII, m.p. 173.5–175°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.76; H, 7.19.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXVII. The Condensation of 4-Piperidones and Piperidinols with Phenols

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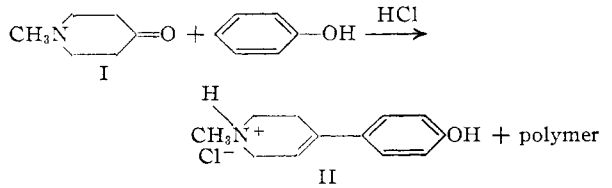
1-Methyl-4-piperidone is condensed by hydrogen chloride with phenol and 2,4-dimethylphenol to yield a 4-aryl-tetrahydropyridine (II and IV), but with 2,6-dimethylphenol the diphenol IIIa is formed. Considerable amphoteric polymeric material is formed with the piperidone and phenol; similar polymers are the only reaction products where resorcinol or its monomethyl ether is used instead of phenol. 3-Substituted-4-piperidones do not condense with phenol. 1-Methyl-4-phenyl-4-hydroxypiperidine condenses with phenols in 60% sulfuric acid to yield 4,4-diarylpiperidines (VI and VIa), but the corresponding 4-alkyl-4-hydroxypiperidines are only dehydrated under these conditions.

The condensation of phenols with 4-piperidones and piperidinols, extensions of reactions that have been successfully carried out with simple ketones[2] and tertiary alcohols,[3] seemed to offer an attractive preparative route to certain 4,4-disubstituted piperidines. The results of a study of these reactions are now reported.

1-Methyl-4-piperidone (I) condensed with phenol in an acetic acid solution of hydrogen chloride to yield the tetrahydropyridine II (50%) and an amphoteric polymer. This latter material resists purification by crystallization and gradually darkens on standing. Inasmuch as the crystalline condensation product (II) is unchanged on further treatment with the acetic acid–hydrogen chloride solution, it is not the precursor of the polymer.



The *p*-orientation of II was shown by its conversion by hydrogenation to 1-methyl-4-(*p*-hydroxyphenyl)-piperidine, the hydrobromide of which has been described.[4]

The tetrahydropyridine (II) could not be made to add acetic acid, water or acetonitrile[5] across the double bond in the presence of a variety of acidic catalysts. However, it did add phenol in a 60% sulfuric acid solution to yield the diphenol III. It appears from these results that such groups as $-OCHOCH_3$, $-OH$ and $-NHCOCH_3$ are as easily removed from, as they are attached to, the 4-position of protonated II, and that the establishment of a carbon to carbon bond is necessary to produce a stable 4,4-disubstituted piperidine under these acidic conditions.

In contrast to I, 3-ethyl(or benzyl)-4-piperidone[6] failed to condense with phenol under a variety of acidic conditions; in each case the piperidone was recovered unchanged. When resorcinol and its monomethyl ether were substituted for phenol in the reaction with I only the amphoteric polymeric material was obtained. These latter results and the failure of II to be converted into the polymer suggest that the intermediate carbinol, 1-methyl-4-(*p*-hydroxyphenyl)-4-hydroxypiperidine, or the carbonium ion derived from it, undergoes self-condensation to give the polymer before it decomposes into the stable tetrahydropyridine (II).

Such a conclusion concerning the origin of the polymeric material indicated that a phenol with a single reactive ring position would not produce any of the polymer. Indeed, it was found that the condensation of 2,6-dimethylphenol with I in an acetic acid solution of hydrogen chloride gave the diphenol IIIa in 86% yield, while the condensation with 2,4-

(1) Monsanto Chemical Company Fellow, 1952–1953; Sinclair Oil Company Fellow, 1953–1954.

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(3) (a) R. C. Huston and G. W. Herrick, *ibid.*, **59**, 2001 (1937); (b) Ng. Ph. Buu Hoï, *J. Org. Chem.*, **18**, 4 (1953).

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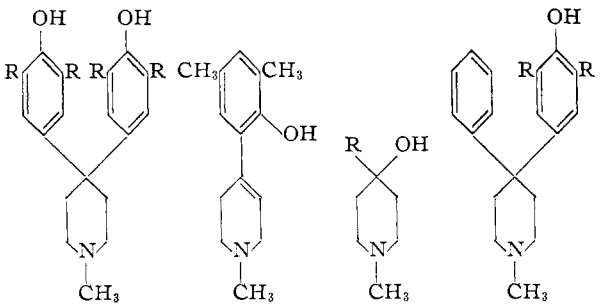

III, R = H
IIIa, R = CH_3

IV V, R = CH_3
Va, R = n-C_4H_9
Vb, R = C_6H_5

VI, R = H
VIa, R = CH_3

dimethylphenol stopped at the tetrahydropyridine structure IV. There was no evidence of the formation of any polymeric material from either of these phenols. It appears that the hydroxyl group *ortho* to the reaction site of 2,4-dimethylphenol blocks the attachment of a secondary aryl group to the 4-position of the piperidine ring.

The 4-piperidinols V, Va and Vb were prepared in 27, 43 and 76% yields, respectively, by the interaction of the corresponding organolithium compounds with 1-methyl-4-piperidone. The main cause of the lower yields of the 4-alkylpiperidinols was the enolization of the piperidone by the lithium alkyls.

Of these piperidinols only Vb could be successfully condensed with phenols. Both VI and VIa were obtained in 28–30% yields from the condensation of the appropriate phenol with Vb in the presence of 60% sulfuric acid. Both hydrogen chloride in acetic acid, the best reagent found for the condensation of 1-methyl-4-piperidone with phenols, and 85% phosphoric acid, which has been found[3b] to alkylate phenols with such tertiary alcohols as methyldiethylcarbinol, only dehydrated Vb to the 4-phenyltetrahydropyridine in the presence of phenol. Neither of the 4-alkyl-4-piperidinols, V and Va, were condensed with phenol by the 60% sulfuric acid or a variety of other acidic catalysts; either the carbinol or a mixture of the carbinol and its dehydration product was obtained.

Experimental

1,4-Dimethyl-4-hydroxypiperidine.—Into a dry 500-ml. three-necked round-bottom flask equipped with a dropping funnel, mechanical stirrer and reflux condenser was placed 150 ml. of diethyl ether. The system was flushed with dry nitrogen and 1.39 g. (0.2 mole) of lithium wire cut into small pieces was added to the flask. The stirrer was started, and 14.2 g. (0.1 mole) of methyl iodide dissolved in ether was added dropwise from the separatory funnel. After all the halide had been added, the mixture was warmed on the steam-bath for about one-half hour to complete the reaction.

Into a 1-l. three-necked round-bottom flask, equipped as in the methyllithium preparation just described, was placed a solution of 11.3 g. (0.1 mole) of 1-methyl-4-piperidone[7] in 150 ml. of diethyl ether. While this solution was stirred and cooled with a Dry Ice–acetone bath, the ethereal solution of methyllithium was added dropwise from the separatory funnel. After this addition was complete, the complex was decomposed with a solution of 18 ml. of concentrated hydrochloric acid in 7 ml. of water. The ether layer was separated and washed with 10 ml. of water and then with a solution of 5 ml. of concentrated hydrochloric acid in 10 ml. of water, after which it was discarded.

The aqueous layers were combined and made basic with 30 g. of potassium carbonate. The slush of liquid and solid was centrifuged, and the liquid decanted and extracted several times with benzene and then ether, after which the salts were continuously extracted with ether in a Soxhlet extractor for 36 hours.

The extracts were combined, the solvents removed, and the residual oil distilled at 11 mm. to give 2.4 g. (21%) of 1-methyl-4-piperidone, b.p. 60–78° and 3.5 g. (27%) of 1,4-dimethyl-4-hydroxypiperidine, b.p. 83–86°. This latter fraction crystallized in the receiver as white prisms. Recrystallization several times from 60–68° petroleum ether followed by sublimation gave an analytical sample, m.p. 66.4–68°.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; neut. equiv., 129.2. Found: C, 65.25; H, 11.58; neut. equiv., 130.

Further distillation at 0.6 mm. of the residue from the distillation above gave 2.0 g. (18%), b.p. 130–133°, $n^{25}D$ 1.5026, of a mixture of self-condensation products of 1-methyl-4-piperidone.[8] A residue of 1.0 g. (9%) was obtained to make the total recovery 75%.

The picrate of 1,4-dimethyl-4-hydroxypiperidine, after recrystallization from absolute ethanol as fine yellow needles, melted at 188–189°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06. Found: C, 43.71; H, 5.32.

1-Methyl-4-*n*-butyl-4-hydroxypiperidine.—A solution of 22.5 g. (0.199 mole) of 1-methyl-4-piperidone in ether was added dropwise from the dropping funnel to the stirred solution of 0.25 mole of *n*-butyllithium[9] in ether cooled to 0° to −10° by a Dry Ice–acetone bath. After all the ketone was added, the lithium complex was decomposed with a solution of 30 ml. of concentrated hydrochloric acid in 60 ml. of water. The layers were separated, and the ether layer extracted with a solution of 10 ml. of concentrated hydrochloric acid in 20 ml. of water. This extract was combined with the separated aqueous layer.

To this aqueous solution was added 60 g. of potassium carbonate. The slush of solid and liquid was centrifuged, the centrifuged liquid decanted and extracted once with ether, and then subjected to continuous extraction with ether for 36 hours. The inorganic salts remaining were similarly continuously extracted with ether in a Soxhlet extractor.

The combined ether extracts were dried and distilled at 13 mm. to give 4.0 g. (18%) of 1-methyl-4-piperidone, b.p. 57–59°, and 14.7 g. (43%) of 1-methyl-4-*n*-butyl-4-hydroxypiperidine, b.p. 110–120°, $n^{25}D$ 1.4709. This base had a neut. equiv. of 169 (calcd. 171).

1-Methyl-4-*n*-butyl-4-hydroxypiperidine picrate was prepared in ethanol, and after two recrystallizations from absolute ethanol was obtained as fine yellow needles, m.p. 196–196.5°.

Anal. Calcd. for $C_{16}H_{24}N_4O_8$: C, 47.99; H, 6.04. Found: C, 47.98; H, 6.04.

Condensation of 1-Methyl-4-piperidone with Phenol. 1-Methyl-4-(*p*-hydroxyphenyl)-1,2,5,6-tetrahydropyridine Hydrochloride (II).—Hydrogen chloride was passed into a solution of 1.13 g. (0.01 mole) of 1-methyl-4-piperidone and 0.94 g. (0.01 mole) of phenol in 5 ml. of glacial acetic acid for 15 seconds. The solution then was warmed on the steam-bath for ten minutes, and hydrogen chloride again passed into it for about 30 seconds. The resulting solution was allowed to cool and stand at room temperature for ten days. During this time 1.1 g. (50%) of crystalline II separated from the solution.

The acetic acid was removed from the filtrate under diminished pressure on the steam-bath. The residue was dissolved in water, extracted with ether, and the aqueous layer neutralized to yield 0.31 g. (16%) of amphoteric, noncrystalline, polymeric material.

Recrystallization of II from absolute alcohol gave an analytical sample, m.p. 264–265°.

Anal. Calcd. for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.15. Found: C, 63.79; H, 7.11.

The free base of II, obtained by carefully neutralizing a solution of II with dilute sodium hydroxide, melted at 205–208° after recrystallization from an ethanol–water mixture.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99. Found: C, 76.18; H, 7.95.

(7) S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820 (1948).

(8) S. M. McElvain and R. E. Lyle, Jr., *ibid.*, **72**, 386 (1950).

(9) H. Gilman, *et al.*, *ibid.*, **71**, 1499 (1949).

This free base (0.9 g.) in 75 ml. of methanol was hydrogenated in about 12 minutes over W-1 Raney nickel catalyst (1.5 g.) under 30 p.s.i. of hydrogen. The product after removal of the catalyst and evaporation of the solvent melted at 168–174°; recrystallization from an ethanol–water mixture gave an analytical sample of **1-methyl-4-(*p*-hydroxyphenyl)-piperidine**, m.p. 179–180°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.70; H, 9.05.

The hydrobromide salt of this base, after recrystallization from acetone, melted at 210–211°, lit.[4] 210°.

A mixture of 0.225 g. of II, 5 ml. of acetic acid and 5 ml. of acetic anhydride was warmed for 3 hr. on a steam-bath, after which all volatile material was removed under diminished pressure. The residue was treated with 5 ml. of acetone and the undissolved crystals separated, m.p. 191–197°; concentration of the acetone gave an additional 0.06 g. of this product. Recrystallization of this material from absolute ethanol gave small white buds of **1-methyl-4-(*p*-acetoxyphenyl)-1,2,5,6-tetrahydropyridine hydrochloride**, m.p. 200–202°.

Anal. Calcd. for $C_{14}H_{18}ClNO_2$: C, 62.79; H, 6.77. Found: C, 62.49; H, 6.86.

1-Methyl-4,4-di-(*p*-hydroxyphenyl)-piperidine (III).—A solution of 0.272 g. of phenol and 0.225 g. of II in 3.5 g. of 60% sulfuric acid was heated on the steam-bath for 2.5 hr. and then poured onto ice. The resulting solution was exactly neutralized with 10% sodium hydroxide and the precipitated III collected. Recrystallization from water and ethanol gave 43% yield of crystals, m.p. 255–258°. Further recrystallization gave an analytical sample, m.p. 262.5–263°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.14; H, 7.49; N, 5.23.

1-Methyl-4,4-di-di-(3,5methyl-4-hydroxyphenyl)-piperidine (IIIa) Hydrochloride.—Dry hydrogen chloride was passed into a solution of 2.44 g. (0.02 mole) of 2,6-dimethylphenol and 1.13 g. (0.01 mole) of 1-methyl-4-piperidone in 20 ml. of acetic acid for 2.5 hours while it was heated on the steam-bath. The resulting solution was allowed to stand at room temperature for three days, after which time 3.0 g. (78%) of the salt of IIIa was filtered off. This salt melted at 281–283° (vac.). After two additional weeks of standing at room temperature, another 0.1 g. (3%) was obtained from the acetic acid filtrate. Removal of the acetic acid from the filtrate gave an additional 0.19 g. (5%) of product. Several recrystallizations of the product from ethanol gave analytical sample, m.p. 322–323° dec. Analyses showed that this product held 0.5 mole of water of crystallization.

Anal. Calcd. for $C_{22}H_{30}ClNO_2 \cdot 0.5H_2O$: C, 68.64; H, 8.12; Cl, 9.21; N, 3.64. Found: C, 68.38, 68.64; H, 8.05, 7.82; Cl, 8.99, 9.64; N, 3.49.

The free base IIIa was prepared from this hydrochloride by suspending the latter in water (the hydrochloride is not soluble in cold water) and adding aqueous sodium bicarbonate to the mixture. The insoluble IIIa was filtered and recrystallized from absolute alcohol. An analytical sample melted at 235–237°.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13; neut. equiv., 339.5. Found: C, 77.45; H, 8.59; N, 3.66; neut. equiv., 338.

1-Methyl-4-(2-hydroxy-3,5-dimethylphenyl)-1,2,5,6-tetrahydropyridine (IV) Hydrochloride.—Dry hydrogen chloride was passed into a solution of 2.26 g. (0.02 mole) of 1-methyl-4-piperidone and 2.44 g. (0.02 mole) of 2,4-dimethylphenol in 20 ml. of glacial acetic acid for four hours at steam-bath temperature. After three days of standing at room temperature the glacial acetic acid was removed under diminished pressure and the resultant sirup triturated with acetone. The solid IV hydrochloride obtained weighed 1.95 g. (38.5%); a second crop obtained from the acetone amounted to 0.55 g. (11%). Recrystallization from absolute ethanol gave white crystals, m.p. 224–225.5°.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94. Found: C, 66.36; H, 8.14.

1-Methyl-4-phenyl-4-(*p*-hydroxyphenyl)-piperidine (VI).—A solution of 1.92 g. (0.010 mole) of 1-methyl-4-phenyl-4-hydroxypiperidine (Vb),[10] 1.30 g. (0.014 mole) of phenol and 4.8 g. (0.030 mole) of 60% sulfuric acid was warmed on the steam-bath for 2.5 hours. After cooling, it was exactly neutralized with 10% sodium hydroxide. The resultant gummy amphoteric solid was recrystallized to give 0.80 g. (30%) of VI, which after further recrystallization from absolute ethanol gave an analytical sample, m.p. 203–204.5°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.85; H, 7.93. Found: C, 81.03; H, 7.76.

The acetate of VI was prepared in a similar manner to that of II; yield, 0.33 g. (85%); m.p. 274–274.5°.

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 69.45; H, 6.99. Found: C, 69.01; H, 7.18.

When this condensation was attempted in acetic acid with hydrogen chloride, the product was 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine hydrochloride,[10] m.p. 250–251°, which was isolated in 62% yield.

1-Methyl-4-phenyl-4-(3,5-dimethyl-4-hydroxyphenyl)-piperidine (VIa).—A solution of 0.96 g. (0.005 mole) of Vb and 0.61 g. (0.005 mole) of 2,6-dimethylphenol in 2.4 g. of 60% sulfuric acid was heated for 30 minutes on the steam-bath and then allowed to stand overnight at room temperature. The mixture then was neutralized with 10% sodium hydroxide to give 0.7 g. of amphoteric solid which included some starting phenol. One recrystallization from acetone gave 0.42 g. (28.5%) of solid; two additional recrystallizations from acetone gave an analytical sample, m.p. 190.3–191.8°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. Found: C, 81.11; H, 8.52.

In contrast with the 4-phenyl-4-hydroxypiperidine (Vb), the corresponding 4-alkyl derivatives, V and Va failed to condense with phenol. The reaction was studied with Va using a variety of acidic catalysts, *e.g.*, 85% phosphoric acid, sulfuric acid of varying concentrations, and boron trifluoride. In no case was any amphoteric condensation product found. The phenol always contaminated the basic products that were separated from the reaction mixture and made them difficult to purify.

In order to determine the effect of the acids on these carbinols, Va was treated with 60% sulfuric acid in the absence of phenol. After heating a solution of 7.2 g. of Va in 14 g. of 60% sulfuric acid at 100° for 1.7 hr., it was cooled, diluted with water and made basic with 10% sodium hydroxide solution. The liberated amine was taken up in ether, and the ether extract dried and distilled at 10 mm. pressure. Fractions were collected as follows: (1) 0.81 g. (14%), b.p. 80–84°, $n^{25}D$ 1.4637; (2) 1.35 g. (23%), b.p. 84–87.5°, $n^{25}D$ 1.4634; (3) 0.64 g. (11%), b.p. 87.5–91°, $n^{25}D$ 1.4635; (4) 1.97 g. (27%), b.p. 91–120°, $n^{25}D$ 1.4680. There was a residue of 1.0 g. (16%) giving a total recovery of 91% of the amine. Fraction (2) showed unsaturation when tested with 2% aqueous potassium permanganate. A similar test on the starting carbinol showed no unsaturation. Fraction (4) partly solidified and is doubtless a mixture of the lower boiling material and the starting material (b.p. 110–120° at 13 mm., $n^{25}D$ 1.4709). The first three fractions were combined and redistilled. A center cut of this distillate had a neut. equiv. of 156; calcd. for 1-methyl-4-*n*-butyl-1,2,5,6-tetrahydropyridine, 153.

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(10) S. M. McElvain and J. C. Safranski, This Journal, **72**, 3134 (1950).