[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

Molecular Rearrangements. V. 4-Hydroxy-1-methylisonipecotonitrile as an Intermediate in the Synthesis of Substituted Piperidines[1]

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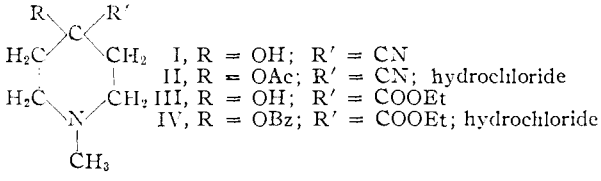
The preparation and reactions of 4-hydroxy-1-methylisonipecotonitrile (I) are described. The product of the pinacol rearrangement of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V), derived from I, is shown to depend on the reaction conditions. The anomalous reaction of bromine water with 1-methyl-4-piperidylidenediphenylmethane (XII) is discussed.

Because of the interest in substituted piperidines as pharmaceuticals and the availability of 1-methyl-4-piperidone,[2] the preparation and reactions of the cyanohydrin of 1-methyl-4-piperidone (4-hydroxy-1-methylisonipecotonitrile) (I) as a possible intermediate in the synthesis of more highly substituted piperidines have been studied.

Although the preparation and some of the reactions of I have been reported previously,[3] the reference is obscure and the details given in available periodicals are inadequate. For this reason 4-hydroxy-1-methylisonipecotonitrile (I) was prepared from 1-methyl-4-piperidone or its hydrochloride using the procedure of Tarboureich[4] for the synthesis of cyclohexanone cyanohydrin. With this method an 85% yield of I could be obtained; however, the isolation of I from the aqueous reaction mixture was complicated by its water solubility and ether insolubility indicating the polar nature of the compound.



I, R = OH; R′ = CN
II, R = OAc; R′ = CN; hydrochloride
III, R = OH; R′ = COOEt
IV, R = OBz; R′ = COOEt; hydrochloride

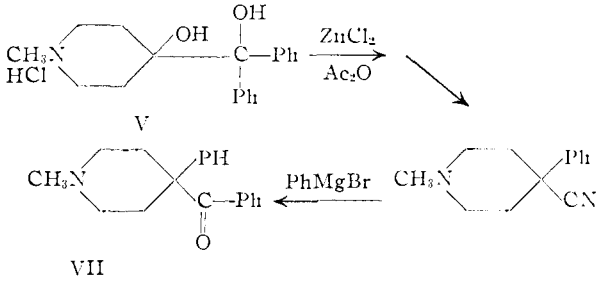
The cyanohydrin I on reaction with acetic anhydride gave a normal alcohol derivative, 4-acetoxy-1-methylisonipecotonitrile, characterized as the hydrochloride II. The free base of this ester, in contrast to many piperidine compounds, could be distilled at atmospheric pressure at a temperature of 250° with no apparent decomposition.

Hydrolysis of the nitrile I and esterification of the resulting acid gave a 70% yield of ethyl 4-hydroxy-1-methylisonipecotate (III). Comparable yields of the ester could be obtained directly from 1-methyl-4-piperidone hydrochloride without isolation of the intermediate compounds. The ester III readily formed a benzoate IV, isolated as a hydrochloride, on treatment with benzoyl chloride.

The reaction of phenylmagnesium bromide or phenyllithium with III gave 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V). The use of phenyl Grignard for the preparation of V was less satisfactory, however, for V is relatively insoluble in organic solvents and thus was not readily separated from the magnesium hydroxide produced in the basic reaction mixture.

By analogy to 1-hydroxy-1-cyclohexyldiphenylcarbinol,[5] V would be expected to undergo the pinacol rearrangement with ring expansion on treatment with sulfuric acid to form 1-methyl-5,5-diphenyl-1-aza-4-cycloheptanone (VI) and with migration of a phenyl group to give 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) with zinc chloride in acetic anhydride. The rearrangement of V under the former conditions gave a product to which the structure VI was assigned, for this product exhibited an ultraviolet spectum (λ_{max} 259 mμ, log ϵ_{max} 2.938 and λ_{max} 294.5 mμ, log ϵ_{max} 2.646) very closely related to that of 2,2-diphenylcycloheptanone,[5] formed an oxime, and was reduced to an alcohol, 1-methyl-5,5-diphenyl-1-aza-4-cycloheptanol (VIII), with lithium aluminum hydride.

The rearrangement of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V) with zinc chloride in acetic anhydride also was found to proceed in a manner analogous to that of 1-hydroxy-1-cyclohexyldiphenylcarbinol. If the free base of V were used in the rearrangement, however, a complex mixture of products was obtained from which only a small amount of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) could be isolated as the oxime. The use of the hydrochloride of V gave, with no complications, VII, identified by comparison with an authentic sample of VII prepared by the method of Eisleb.[6]



V

VII

In an effort to extend the information concerning these pinacol rearrangements, the synthesis of compounds related to V was attempted. In this alternate method isonicotinic acid was converted to methyl 1-methylisonipecotate (IX) by the method of Supniewski and Serafinowna.[7] The reaction of IX with phenyllithium gave 1-methyl-4-piperidyldi-

(1) Presented in part before the Division of Organic Chemistry at the 122nd Meeting of the American Chemical Society at Atlantic City, New Jersey, September 17, 1952.

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

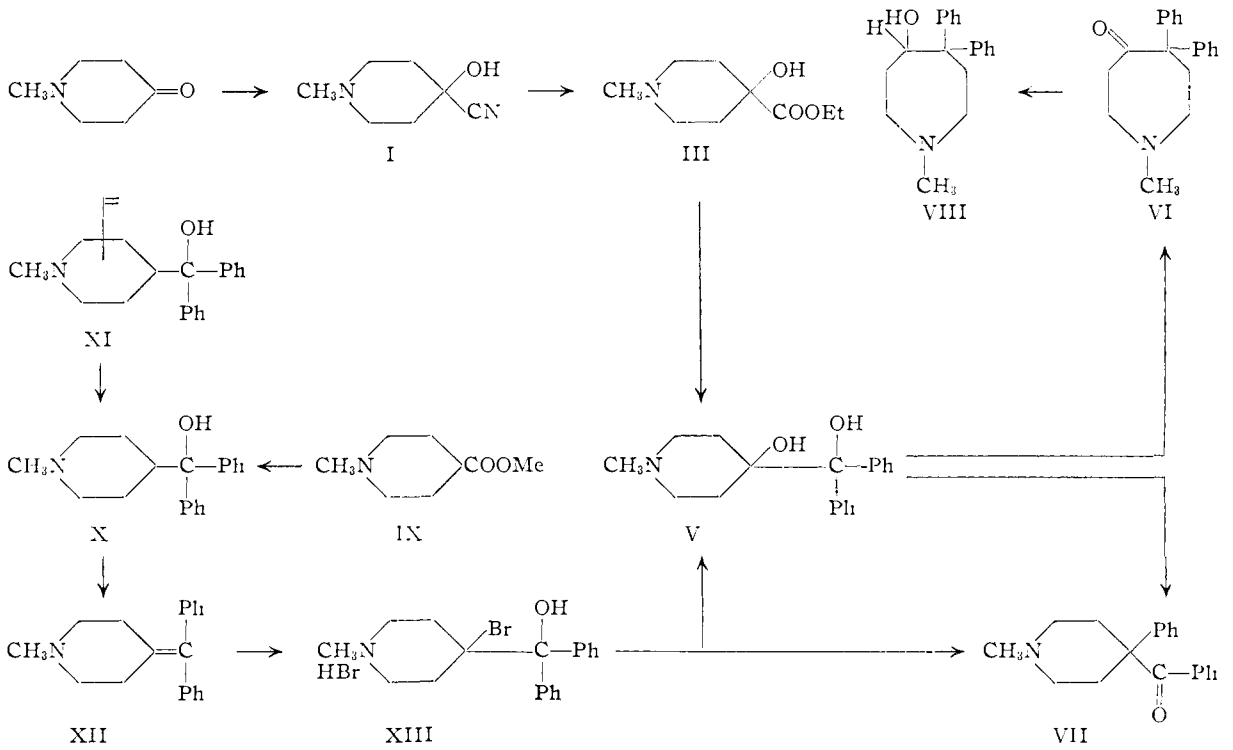
(3) Løven Kemiske Fabrik Vid A. Kongsted, Danish Patent 62,791 (Oct. 16, 1944); *C. A.*, **40**, 4181 (1946).

(4) P. J. Tarboureich, *Compt. rend.*, **149**, 604 (1909).

(5) R. E. Lyle and G. G. Lyle, THIS JOURNAL, **74**, 4059 (1952).

(6) O. Eisleb, U. S. Patent 2,248,018 (July 1, 1941).

(7) J. V. Supniewski and M. Serafinowna, *Arch. Chem. Farm.*, **3**, 109 (1936).



phenylcarbinol (X), previously reported as the product of a related reaction.[8]

From several preparations of X a second product, an ether insoluble solid, XI, was obtained. This compound XI could be prepared in good yield by the reaction of phenyllithium with the product of incomplete hydrogenation of methyl isonicotinate methiodide, believed to be methyl 1-methyltetrahydroisonicotinate.[7] Thus the IX prepared by the method of Supniewski and Serafinowna[7] apparently contained methyl 1-methyltetrahydroisonicotinate as impurity. The synthesis of X from IX prepared by the method of Sperber, *et al.*,[8b] never gave XI as a by-product. Reduction of XI produced X quantitatively.

The dehydration of 1-methyl-4-piperidyldiphenylcarbinol (X) with sulfuric acid gave 1-methyl-4-piperidylidenediphenylmethane (XII),[8] which, unlike previous reports, crystallized on standing. Attempts to convert XII to the corresponding epoxide or to the glycol V by peroxyacid oxidation failed giving either no reaction or a hygroscopic product, presumed to be an N-oxide. The reaction of XII with bromine water was more significant, however. On long heating of XII in hydrobromic acid solution with an excess of bromine water a mixture of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V) and 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII) was produced.

In an effort to obtain some information as to the course of this reaction a lower reaction temperature was used. From this reaction was obtained a complex mixture of compounds from which could be separated V, VII, and a new material which was stable only as the hydrobromide XIII. This latter compound contained two bromine atoms, one of which could be titrated directly by the Volhard method and both of which were detected by the Stepanow[9] modification. The most plausible structure for XIII on the basis of these data is 4-bromo-1-methyl-4-piperidyldiphenylcarbinol hydrobromide; the isomeric bromohydrin should not exist in aqueous solution. From this information it seems apparent that XIII is the intermediate in the formation of V and VII from XII, for hydrolysis of the tertiary bromine of XIII accompanied by rearrangement would produce VII, and hydrolysis without rearrangement would yield V.

(8) (a) N. Sperber, F. J. Villani, M. Sherlock and D. Papa, THIS JOURNAL, **73**, 5010 (1951); (b) F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1951).

Experimental

4-Hydroxy-1-methylisonipecotonitrile (I). (a) From 1-Methyl-4-piperidone.—To a cold, saturated solution of 12 g. of potassium cyanide in water was added 10 g. of 1-methyl-4-piperidone. After the mixture was stirred for about one minute, it became semi-solid, and dilute hydrochloric acid was added[10] with external cooling until the solution was slightly acidic. The solution was neutralized with potassium carbonate and 5 g. excess was added to salt out the cyanohydrin I. The reaction mixture was extracted with three 100-ml. portions of ether and an additional 5 g. of potassium carbonate was added. The solution was extracted again and the combined extracts were evaporated without drying, leaving 10.7 g. (87%) of 4-hydroxy-1-methylisonipecotonitrile (I), m.p. 135–138°. Recrystallization from ethyl acetate gave a colorless solid, m.p. 137–138°; lit.[8] 140–143°.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.64. Found: C, 59.97; H, 8.61.

(b) From 1-Methyl-4-piperidone Hydrochloride.—A solution of 20 g. of potassium cyanide in 35 ml. of water was added with cooling to 15 g. of 1-methyl-4-piperidone hydro-

(9) A. Stepanow, *Ber.*, **39**, 4056 (1906).

(10) The danger resulting from hydrogen cyanide formed from excess sodium or potassium cyanide and acid was lessened by using a suction flask as reaction vessel. During addition of acid the suction flask was attached to a water pump, thus removing hydrogen cyanide in water.

chloride in 15 ml. of water. Treatment of the resulting semi-solid with acid[10] and working up the reaction mixture as above yielded 12 g. (86%) of 4-hydroxy-1-methylisonipecotonitrile (I), m.p. 135–138°.

4-Acetoxy-1-methylisonipecotonitrile Hydrochloride (II).—After heating a solution of 1.0 g. of 4-hydroxy-1-methylisonipecotonitrile (I) in 10 ml. of acetic anhydride for 1.5 hr. on a steam-bath, the solvent was removed under reduced pressure. A solution of the residue in 10 ml. of water was treated with 1.0 g. of anhydrous potassium carbonate and extracted with ether. Anhydrous hydrogen chloride was added to the dried ether extracts and the insoluble gum which formed was recrystallized from acetone–ether to give 1.0 g. (70%) of II, m.p. 187–188°.

Anal. Calcd. for $C_9H_{15}ClN_2O_2$: C, 49.43; H, 6.91. Found: C, 49.46; H, 7.02.

Ethyl 4-Hydroxy-1-methylisonipecotate (III). (a) From 4-Hydroxy-1-methylisonipecotonitrile (I).—A solution of 7 g. of 4-hydroxy-1-methylisonipecotonitrile (I) in 16 ml. of concentrated hydrochloric acid was allowed to stand 60 hr. and then refluxed for 5 hr. The hydrochloric acid and water were removed under reduced pressure, and the remaining solid was dried by distilling benzene from it. To this solid was added 80 ml. of absolute ethanol and 8 ml. of concentrated sulfuric acid. After heating the solution under reflux for 5 hr., a portion of the ethanol was removed by distillation and the sulfuric acid neutralized by addition of moist sodium carbonate to the cooled mixture. The semi-solid mass was extracted 5 times with ether. After drying over sodium sulfate the ether was distilled and the residual oil fractionated yielding 6.5 g. (70%) of ethyl 4-hydroxy-1-methylisonipecotate (III), b.p. 142–147° at 26 mm., which solidified on cooling. An analytical sample was prepared by recrystallization from ether at Dry Ice (solid carbon dioxide)–acetone temperature and melted at 42–45°.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.70; H, 9.15. Found: C, 57.75; H, 9.46.

The picrate, after recrystallization from ethanol, melted 181.5–183.0°.

Anal. Calcd. for $C_{15}H_{20}N_4O_{10}$: C, 43.27; H, 4.84. Found: C, 43.08; H, 5.06.

(b) From 1-Methyl-4-piperidone Hydrochloride.—To a cooled solution of 7 g. of 1-methyl-4-piperidone hydrochloride in 5 ml. of water was added 10 g. of potassium cyanide in 18 ml. of water. After solidification, dilute hydrochloric acid was added[10] until the solution was acid. The water and hydrogen cyanide were removed under reduced pressure. The remaining oil was treated with 12 ml. of concentrated hydrochloric acid and the mixture heated under reflux for 14 hr. After removal of excess acid under reduced pressure, benzene was distilled from the solid. The solid was esterified and the product isolated as in (a) above to give 5.38 g. (61%) of ethyl 4-hydroxy-1-methylisonipecotate (III), b.p. 127–130° at 16 mm.

Ethyl 4-Benzoxy-1-methylisonipecotate Hydrochloride (IV).—Following the procedure for the preparation of 4-acetoxy-1-methylisonipecotonitrile hydrochloride (II), IV was prepared from III and benzoyl chloride. After recrystallization from ethyl acetate–ether, the solid melted at 164–165°.

Anal. Calcd. for $C_{16}H_{22}ClO_4$: Cl, 10.8. Found: Cl, 11.1.

4-Hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V).—A solution of 12.4 g. (0.06 mole) of ethyl 4-hydroxy-1-methylisonipecotate (III) in 35 ml. of dry ether was added very slowly to a solution of phenyllithium prepared from 3.5 g. (0.5 gram atom) of lithium and 39 g. (0.25 mole) of bromobenzene. After the addition of the ester was complete, the reaction mixture was heated under reflux and stirred for 4 hr. and allowed to stand 12 hr. The reaction mixture was poured into water giving 17.79 g. (94%) of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V) as a precipitated solid, m.p. 154–159°. An analytical sample melted at 160.0–160.5° after recrystallization from benzene.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.74; H, 7.71.

The hydrochloride melted at 207–208°.

Anal. Calcd. for $C_{19}H_{24}ClNO_2$: Cl, 10.6. Found: Cl, 10.8.

1-Methyl-4-phenyl-4-piperidyl Phenyl Ketone (VII).—After heating 1.6 g. (0.005 mole) of the hydrochloride of V with 1.5 g. of fused, pulverized zinc chloride in 8 ml. of acetic anhydride in an oil-bath at 100–110° for 1.5 hr., the solution was poured into ice containing sodium hydroxide. The strongly basic solution was extracted with three 25-ml. portions of ether and the extracts were dried over potassium carbonate and the ether removed. Distillation of the residue gave 0.53 g. (40%) of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII), b.p. 160–170° at 2 mm., lit.[6] b.p. 199° at 4 mm. After crystallization and recrystallization from petroleum ether at Dry Ice–acetone temperature the solid melted at 77–78°, lit.[6] m.p. 79–80°. This compound showed no depression of melting point on mixing with an authentic sample prepared by the method of Eisleb.[6] It is interesting to note that the solid, m.p. 77–78°, is not the hydrate of VII, as stated by Eisleb,[6] but is the anhydrous base.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.70; H, 7.64.

The oxime of VII, m.p. 184–186°, showed no depression of melting point when mixed with an authentic sample.[11]

1-Methyl-5,5-diphenyl-1-aza-4-cycloheptanone (VI).—To 20 ml. of concentrated sulfuric acid at 0° was added 5.0 g. (0.017 mole) of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V) in portions. After standing at 0° for 3 hr., the reaction mixture was poured into water and made basic with potassium carbonate. The solution was filtered, and the residue was washed with water and then triturated with ether. After drying, the ether extracts were distilled leaving a residue of 3.7 g. (79%) of 1-methyl-5,5-diphenyl-1-aza-4-cycloheptanone (VI), m.p. 87–88°. Recrystallization of VI from methanol–water gave an analytical sample melting at 91–92°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.21; H, 7.82.

The oxime of VI melted at 239.5–240.0° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53. Found: C, 77.09; H, 7.53.

1-Methyl-5,5-diphenyl-1-aza-4-cycloheptanol (VIII).—To a suspension of 1.9 g. of lithium aluminum hydride in 300 ml. of dry ether was added dropwise 4.0 g. (0.014 mole) of 1-methyl-5,5-diphenyl-1-aza-4-cycloheptanone (VII) in 100 ml. of ether. The reaction mixture was heated under reflux and stirred for 2 hr. and the excess reagent decomposed by the addition of water. The mixture was acidified with dilute hydrochloric acid and then made basic with excess potassium hydroxide. The organic layer was separated and the aqueous layer extracted with ether. The ether extracts were distilled leaving 3.5 g. (90%) of VIII, m.p. 125.5–128°. Recrystallization of VIII from ethanol or benzene raised the melting point to 128.2–129.8°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 81.02; H, 7.82.

Methyl 1-Methylisonipecotate (IX).—A solution of 21.0 g. of methyl isonicotinate methiodide[7] in 100 ml. of absolute methanol was subjected to 3 atm. pressure of hydrogen at room temperature with 0.30 g. of platinum oxide as catalyst. After the pressure of hydrogen had ceased to change, about 10 hr., the reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue, 21.0 g., m.p. 126.0–127.5°, appeared to be methyl 1-methyl-tetrahydroisonicotinate hydroiodide, lit.[7] m.p. 130–131°. The hydroiodide from several hydrogenations, 62.4 g., was converted to 27.8 g. of the base, b.p. 92–105° at 14 mm. Reduction of this material under 100 atm. pressure of hydrogen with platinum oxide catalyst gave, after removal of the catalyst and distillation, a quantitative yield of methyl 1-methylisonipecotate (IX), b.p. 73–80° at 8 mm., lit.[7] b.p. 138° at 32 mm.

1-Methyl-4-piperidyldiphenylcarbinol (X).—To an ethereal solution of 0.12 mole of phenyl lithium, prepared from 20.0 g. of bromobenzene and 1.8 g. of lithium, was added dropwise 8.2 g. (0.05 mole) of methyl 1-methylisonipecotate (IX) in ether. The mixture was heated under reflux for 3 hr., cooled and poured on ice. The ether layer was separated and the solvent removed by distillation. The residue solidified yielding 14.4 g. (98%) of crude X. Recrystallization from methanol gave 10.8 g. (74%) of X, m.p. 132.0–132.5°; lit.[6] m.p. 133–134°.

(11) R. Lyle and G. Lyle, *J. Org. Chem.*, **18**, 1058 (1953)

4-(1-Methyltetrahydropyridyl)-diphenylcarbinol (XI).—To an ethereal solution of 0.4 mole of phenyl lithium, prepared from 6.28 g. of bromobenzene and 0.56 g. of lithium, was added 3.17 g. of the mixture of methyl 1-methyltetrahydroisonicotinate and methyl 1-methylisonipecotate (IX) from the low pressure hydrogenation of methyl isonicotinate methiodide. The mixture was heated under reflux for 3 hr. and, after cooling, poured into ice and water. The water and ether insoluble solid was removed by filtration giving 1.58 g. of XI, m.p. 179.0–179.8, after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 80.93; H, 7.53.

The layers in the filtrate were separated and the water layer extracted with 50 ml. of ether. The dried extracts were distilled leaving 1.72 g. of X, m.p. 130–132°, as residue.

Catalytic Reduction of 4-(1-Methyltetrahydropyridyl)-diphenylcarbinol (XI).—A solution of 2.0 g. of XI in 100 ml. of absolute methanol was shaken for one hour at room temperature with 0.2 g. of platinum oxide catalyst under 60 atm. pressure of hydrogen. Removal of the catalyst and solvent gave 1.95 g. (96.5%) of 1-methyl-4-piperidyldiphenylcarbinol (X), m.p. 125–130°. After recrystallization from methanol, the solid melted at 127.5–130.0° and showed no depression of melting point on mixing with an authentic sample of X.

1-Methyl-4-piperidylidenediphenylmethane (XII).—A solution of 4.0 g. of 1-methyl-4-piperidyldiphenylcarbinol (X) in 30 ml. of 1:1 sulfuric acid–water was heated on a steam-bath for 1.5 hr., poured into water and neutralized. The basic solution was extracted with ether, and the combined, dried ether extracts were fractionally distilled. The fraction, b.p. 205–208° at 12 mm., lit.[8] b.p. 145–150° at 1 mm., unlike the previously reported cases, crystallized on standing or seeding to give 3.09 g. (82.6%) of 1-methyl-4-piperidylidenediphenylmethane (XII), m.p. 55.0–56.3°.

The hydrobromide of XII, after recrystallization from ethanol, melted at 264–266°. XII hydrobromide is only sparingly soluble in water.

Anal. Calcd. for $C_{19}H_{22}BrN$: Br, 23.2. Found: Br, 23.4.

The Reaction of 1-Methyl-4-piperidylidenediphenylmethane (XII) with Bromine Water. (a) At 100°.—To a suspension of 4.0 g. of XII hydrobromide in 50 ml. of water, heated on a steam-bath, was added in 5-ml. portions 62 ml. of saturated (0°) bromine water. Heating was continued for 0.5 hr. or until all the solid was in solution and the reaction mixture was allowed to stand for 2 hr. The precipitated solid redissolved on heating and the solution was neutralized with potassium hydroxide. The amines precipitated immediately and, after coagulation, were isolated by filtration to give 3.34 g. (air dried) of the mixture. Trituration of the amine mixture with petroleum ether (b.p. 30–60°) gave, as the soluble component, 1.53 g. of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII), m.p. 77.0–78.5°. The insoluble residue consisted of 1.44 g. of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V), m.p. 158.0–160.8°. These products account for 89% of the starting material.

(b) At 40–50°.—A suspension of 4.0 g. of 1-methyl-4-piperidylidenediphenylmethane (XII) in 250 ml. of water was treated with 7 ml. of 48% hydrobromic acid at 40–50° and 100 ml. of bromine water was added in portions. A large amount of undissolved solid remained even after the addition of 250 ml. of water. The mixture was cooled and the solid was removed by filtration and triturated with acetone. The acetone insoluble portion, 0.85 g., was found to be unreacted XII hydrobromide, m.p. 263–265°. Concentration of the acetone solution gave 1.51 g. of a hydrobromide, m.p. 150° dec., which gave evidence of being 4-bromo-1-methyl-4-piperidyldiphenylcarbinol hydrobromide (XIII).

Anal. Calcd. for $C_{19}H_{23}Br_2NO$: 1Br, 18.1; 2Br, 36.2. Found: Br (Volhard), 18.5; Br (Stepanow), 33.4.[12]

The acid filtrate from the removal of XIII and XII hydrobromide was neutralized with potassium hydroxide and the solid which separated was triturated with petroleum ether (b.p. 30–60°). From the petroleum ether 0.75 g. of 1-methyl-4-phenyl-4-piperidyl phenyl ketone (VII), m.p. 75–77°, was obtained. The petroleum ether-insoluble portion yielded only traces of 4-hydroxy-1-methyl-4-piperidyldiphenylcarbinol (V).

Acknowledgments.—The authors wish to express deep appreciation to Dr. S. M. McElvain for aid in initiating this problem and encouragement and suggestions which promoted the completion of the work. The authors also wish to express appreciation for a sample of 1-methyl-4-phenylisonipeconitrile furnished them by Sterling-Winthrop Research Institute of Rensselaer, N. Y.

(12) The total halogen analysis of XIII was consistently low as compared with the theoretical value; however, it is sufficiently high to indicate the presence of two bromine residues. The low value for the total halogen analysis undoubtedly results from the relative ease of elimination of the bromine on the 4-position. One recrystallization of XIII from acetone lowered the bromine content to 31.3%.

DURHAM, NEW HAMPSHIRE

[CONTRIBUTION FROM THE RADIOCHEMISTRY LABORATORY, DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Radioisotopic Dilution Analysis for D-Glucose and Gentiobiose in Hydrol

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The D-glucose and gentiobiose contents of a representative sample of hydrol have been determined by radioisotopic dilution analysis. The D-glucose content by this method agrees well with the corresponding value obtained elsewhere by direct isolation methods. In contrast, the gentiobiose content as determined by the present method is considerably greater than hitherto reported.

Hydrol is the residual sirup obtained after the commercial crystallization of D-glucose from acid hydrolysates of corn starch. Since mineral acids catalyze not only the hydrolysis of oligo- and polysaccharides but also the condensation of monosaccharides,[2] hydrol is a product both of the acid hydrolysis of starch and of the acid reversion of D-glucose. Oligosaccharides arising solely from the hydrolysis of starch are necessarily limited in structure to moieties of the original starch structure whereas no such limitations can be applied to the structures of those oligosaccharides resulting from acid reversion of D-glucose. Consequently, although D-glucose appears to be the only monosaccharide constituent of hydrol, the oligosaccharide fraction is complex and as yet has not been resolved completely into its component sugars.

The first disaccharide to be identified as a con-

(1) Corn Industries Research Foundation Fellow.

(2) A. Wohl, *Ber.*, **23**, 2084 (1890); E. Fischer, *ibid.*, **23**, 3687 (1890); H. Frahm, *Ann.*, **555**, 187 (1944); E. Pacsu and P. T. Mora, THIS JOURNAL, **72**, 1045 (1950); W. R. Fetzer, E. K. Crosby, C. E. Engel and L. C. Kirst, *Ind. Eng. Chem.*, **45**, 1075 (1953).