[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

STUDIES ON γ-PYRONES. II. SYNTHESIS OF 4-PIPERIDINOLS FROM PYRONES[1]

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4-Piperidinols, which are of considerable pharmacological interest, have usually been prepared from the corresponding 4-piperidones which, in turn, have been synthesized by various ring-closures such as the Dieckmann condensation (1, 2). Since many 4-pyrones are readily available, and are easily converted to pyridones by treatment with ammonia or primary amines, reduction of these pyridones might furnish a new route to 4-piperidinols, and permit the preparation of substituted piperidinols not accessible by other methods.

Some 4-pyridones have been reduced to 4-piperidinols by sodium in ethanol or amyl alcohol (3, 4), but in general they are resistant to chemical reducing agents (5). Armit and Nolan (5) found that 5-methoxy-1,2-dimethyl-4-pyridone was partially demethylated to the 5-hydroxy compound by sodium in amyl alcohol, but that the ring was unattacked. Emmert (6) claimed to have reduced some pyridones catalytically, at low pressures and temperatures over platinum black, but Armit and Nolan (5) and Ruzicka (7) were unable to hydrogenate these compounds over platinum or palladium catalysts.

In the present work it has been found that 4-pyridones are reducible to 4-piperidinols by sodium in liquid ammonia, but isolation of the product is difficult, and the yields are not high. No reduction occurred when 1,2,6-trimethyl-4-pyridone was treated with lithium aluminum hydride in ether, but this may have been due to the low solubility of the pyridone in ether.

In agreement with Armit and Nolan (5) we were unable to hydrogenate 1,2,6-trimethyl-4-pyridone catalytically at room temperature and 2–3 atmospheres pressure, using pre-reduced platinum oxide or palladium-charcoal catalysts in glacial acetic acid as solvent. When, however, 1,2,6-trimethyl-4-pyridone in ethanol was hydrogenated in the presence of Raney nickel at 125° and 1500 psi, 3 moles of hydrogen were taken up in four hours, and an 85% yield of 1,2,6-trimethyl-4-piperidinol was isolated. Nickel on silica catalyst gave similar results. Hydrogenation could also be brought about in the presence of copper chromite, but with this catalyst higher temperatures were required (140°) and occasionally the catalyst was converted to the "inactive red form", and only a small yield of piperidinol was obtained. It was possible to extend the reaction to methoxy-γ-pyridones, although in general these required somewhat higher temperatures (140–155°). No hydrogenolysis of the methoxyl groups was observed.

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The stereochemical course of hydrogenation of 4-pyridones is not clear. When 1,2,6-trimethyl-4-pyridone was hydrogenated over Raney nickel the product was identical with Mannich's *cis*-1,2,6-trimethyl-4-piperidinol (b.p. 105–107°/11, hydrochloride m.p. 267–268°) (8), but when nickel on silica was used the product was separable into two components, one of which was the *cis*-piperidinol and the other, m.p. 65°, hydrochloride m.p. 184–186°, corresponded to Mannich's *trans*-1,2,6-trimethyl-4-piperidinol.[4] With other pyridones only one product was isolated in each case; as this appeared homogeneous, it is concluded that reduction gave but one stereoisomer.

It was hoped to oxidize the 4-piperidonols to 4-piperidones and convert these to analogs of Demerol. Although the closely related tropine can be oxidized to tropinone (9), and 1,2,2,6-tetramethyl-4-piperidinol to the corresponding piperidone (10), by chromic acid in sulfuric acid, this method was unsuccessful with 1,2,6-trimethyl-4-piperidinol, and most of the piperidinol was recovered. Better results were obtained with aluminum *tert*-butoxide and acetone, and a 53% yield of 1,2,6-trimethyl-4-piperidone was isolated. Treatment of this compound with phenyllithium followed by propionic anhydride (11) gave the Demerol analog; 1,2,6-trimethyl-4-propionoxypiperidine, which was isolated as the oxalate.

Application of the Oppenhauer oxidation to 1,2,-dimethyl-5-methoxy-4-piperidinol was less successful, as the piperidone could not be separated from unreacted piperidinol by distillation through an efficient column. Infrared spectra indicated that the distillate contained about 50% of the piperidone (based on the carbonyl absorption at 5.83 mμ), but it could not be obtained in a pure state.

Two of the 4-piperidinols prepared in this work have been converted to esters for testing as spasmolytics.

EXPERIMENTAL[5, 6, 7]

4-Pyridones. Armit and Nolan (5) used alcoholic solutions of amines to convert 4-pyrones to 4-pyridones. We have obtained satisfactory results with aqueous solutions and found the procedure to be simpler. The following is a typical example: A solution of 70 g. (0.56 mole) of 2,6-dimethylpyrone (12) in 200 ml. of water was added with stirring to 150 ml. of 40% aqueous methylamine at such a rate that the temperature remained below 40°. Addition required one hour, and toward the end of this time the reaction mixture became very thick and difficult to stir. It was allowed to stand for 1–2 hours and was then cooled to 0° and filtered. The pyridone was recrystallized from hot water. The pyridones prepared in this work are recorded in Table I.

Reduction of 1,2,6-trimethyl-4-pyridone with sodium and alcohol in liquid ammonia. To a solution of 4 g. of 1,2,6-trimethyl-4-pyridone in 500 ml. of liquid ammonia there was added

[4] The terms *cis* and *trans* refer to the positions of the methyl groups only. The configuration of the hydroxyl group in the *cis*-piperidinol is not known.

[5] Analyses for C, H, and N were carried out by the Clark Microanalytical Laboratories, Urbana, Illinois.

[6] All melting points are uncorrected.

[7] We wish to thank the Northern Regional Laboratory and Corn Products Refining Company for the kojic acid used in this work, and the Cliff-Dow Company for a generous sample of maltol.

over a period of 1½ hours 27.5 g. (1.2 mole) of sodium metal in small pieces. A solution of 9.7 g. of the pyridone (total 13.7 g., 0.10 mole) in 50 ml. of dry ethanol was then added very slowly (several drops per minute). When the addition was complete, ethanol was added slowly until the blue color of sodium disappeared. The mixture became thick and more liquid ammonia was added occasionally to keep the mixture fluid. On completion of the reaction, concentrated ammonium hydroxide was added slowly to effect hydrolysis. Finally 200 ml. of water was added and the solution was extracted with 500 ml. of ether. The ether was removed by distillation and the residue was distilled to give 5.5 g. (40%) of a pale yellow oil, b.p. 105–111°/12 mm. (mainly 105–107°), n_D^{20} 1.4784–1.4801. Mannich (8) reported the same boiling point for 1,2,6-trimethyl-4-piperidinol.

The *hydrochloride* of the product was prepared in propanolic hydrogen chloride and recrystallized from ethanol, m.p. 266°. Mannich (8) reported m.p. 267–268° for the *cis*-piperidinol hydrochloride.

Anal. Calc'd for $C_8H_{18}ClNO$: Cl, 19.72. Found: Cl, 19.61, 19.62.

Catalytic hydrogenation of 1,2,6-trimethyl-4-pyridone. A mixture of 27.4 g. (0.20 mole) of 1,2,6-trimethyl-4-pyridone, 125 ml. of absolute ethanol, and about 4 g. of Raney nickel was shaken with hydrogen at 130 atmospheres and 125° for four hours. The alcohol was removed from the reaction mixture under reduced pressure and the residual oil was distilled *in vacuo* from a 100-ml. conical flask fitted with 30-cm. Vigreux side arm. The yield was 24.0

TABLE I

4-PYRIDONES FROM 4-PYRONES

PYRIDONE	YIELD, %	M.P., °C.	LIT. M.P., °C.	REF.
1,2,6-Trimethyl	88	245–246	245	5
1,2-Dimethyl-5-methoxy	70	98	95	5
1,2-Dimethyl-3-methoxy	67	79–80[a]	—	—
1-Methyl-2-hydroxymethyl-5-methoxy	71	205–206	203–204	5
2,6-Dimethyl-	55	225	225	16

[a] The compound was isolated as the monohydrate, which lost its water of crystallization on prolonged drying; the anhydrous material was analyzed. Calc'd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.4; H, 6.90; N, 9.00.

g. (85%) of colorless oil, b.p. 105–107°/11 mm., n_D^{20} 1.4734–1.4755. The *hydrochloride* had m.p. 265–266°. Mannich (8) reported m.p. 267–268° for the hydrochloride of the *cis*-isomer of 1,2,6-trimethyl-4-piperidinol.

When the Raney nickel was replaced by activated nickel on silica[8] the reduction occurred as above but the distillate of the product in each of three runs partially crystallized. The crystals were recrystallized from low-boiling petroleum ether, m.p. 65°. The hydrochloride from the material was separable into 2 fractions, one of which, m.p. 265–266°, was probably the *cis*-isomer; the other fraction had m.p. 184–186°.

Mannich (8) reported m.p. 70° for the *trans*-piperidinol, and m.p. 185° for its hydrochloride.

Catalytic hydrogenation of other 4-pyridones. These reactions were carried out essentially as described above, and the products isolated by distillation. The results are summarized in Tables II and III.

Oxidation of 1,2,6-trimethyl-4-piperidinol with acetone and aluminum tert-butoxide. A solution of 21 g. (0.14 mole) of 1,2,6-trimethyl-4-piperidinol in 200 ml. of dry acetone was added rapidly to 38 g. (0.15 mole) of aluminum *tert*-butoxide (13) in 300 ml. of dry benzene, and the mixture was heated with stirring at 55° for nine hours and allowed to stand at room temperature for twelve hours. It was then hydrolyzed by the addition of 200 g. of ice and

[8] Obtained from the Harshaw Chemical Company, Cleveland, Ohio.

acidified with 25% sulfuric acid. The benzene layer was extracted several times with 50-ml. portions of 25% sulfuric acid. The combined acid solutions were made strongly alkaline with 40% sodium hydroxide in an ice-bath and extracted with a liter of ether in portions. Distillation of the oil left after evaporation of the dried extract gave 8.5 g. of the piperidone, b.p. 95–106°/16 mm., n_D^{20} 1.4620–1.4662. Mannich (8) reported the b.p. to be 78–90°/14 mm. The yield was 53% based on piperidinol consumed (4 g. was recovered unchanged) or 42.5% on the amount of piperidinol originally used.

TABLE II

HYDROGENATION OF 4-PYRIDONES TO 4-PIPERIDINOLS

SUBSTITUENTS	CATALYST	MAX. TEMP., °C.	INITIAL PRESSURE, PSI.	TIME, HRS.	YIELD, %
1,2,6-Trimethyl	Raney Ni[a]	125	1500	4	85
1,2,6-Trimethyl	Ni–SiO_2	125	1500	4	83
1,2,6-Trimethyl	Cu chromite[b]	140	1600	4	80, 30[c]
1,2-Dimethyl-5-methoxy	Raney Ni	150	1500	4	87
1-Methyl-2-hydroxymethyl-5-methoxy	Raney Ni	155	1500	5	85
1-Methyl-2-hydroxymethyl-5-methoxy	Cu chromite	170	1500	4	49
1,2-Dimethyl-3-methoxy	Raney Ni	155	1900	5	50
2,6-Dimethyl	Raney Ni	155	1400	5	60

[a] Commercial Raney nickel and that prepared by Mozingo's method (17) gave essentially the same results. [b] Both commercial material and that prepared according to Adkins (18) were used. [c] Low yields were obtained when the catalyst was converted to the red form.

TABLE III

PHYSICAL CONSTANTS OF 4-PIPERIDINOLS

SUBSTITUENTS	B.P., °C./MM.	n^{20}	ANALYSES					
			Calculated			Found		
			C	H	N	C	H	N
1,2,6-Trimethyl	105–107	1.4734–1.4755	—	—	—	—	—	—
2,6-Dimethyl		m.p. 132.5°	65.05	11.60	10.80	64.83	11.42	10.72
1,2-Dimethyl-5-methoxy	104–107/11	1.4740	60.34	10.76	8.80	60.20	10.90	8.89
1,2-Dimethyl-3-methoxy	110–111/13	m.p. 86–88°	60.34	10.76	8.80	60.00	10.64	8.65
1-Methyl-2-hydroxymethyl-5-methoxy	143–147/4	—	54.84	9.78	8.00	54.73	9.92	8.33

The *oxime hydrochloride* was prepared and melted at 198–200° (dec.). Mannich (8) found the m.p. to be 198–200°. (dec.).

1,2,6-Trimethyl-4-phenyl-4-piperidinol. The method of Ziering, *et al.* (11) was used. Phenyllithium was prepared under helium in the usual manner (14) from 1.0 g. of lithium (0.14 mole) and after cooling the solution to −20°, 10 g. (0.07 mole) of 1,2,6-trimethyl-4-piperidone in 25 ml. of dry ether was added over a period of forty-five minutes. The cooling-bath was removed, stirring was continued for another 2½ hours, and the mixture was hy-

drolyzed by pouring on to cracked ice. The aqueous layer was extracted with two portions of ether and the combined ether layers were extracted with 200 ml. of 20% sulfuric acid. The acid layer was made strongly basic with potassium hydroxide and extracted with 250 ml. of ether. The ether extract was dried over potassium carbonate and evaporated. The oily residue was dissolved in 20 ml. of hexane, allowed to stand for twelve hours in the refrigerator, and the crystals which separated were recrystallized from hexane (25 ml. to the gram); the yield was 3.5 g. (22.5%), m.p. 120°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39.
Found: C, 76.26; H, 9.67; N, 6.36.

1,2,6-Trimethyl-4-phenyl-4-propionoxypiperidine monooxalate. To 20 ml. of propionic anhydride there was added two grams of 1,2,6-trimethyl-4-phenyl-4-piperidinol and the solution was heated at 90° for three hours. The excess propionic anhydride was then removed under reduced pressure. The residue was taken up in water, adjusted to *p*H 10 with sodium carbonate, and extracted with ether. The ether extract, after drying over magnesium sulfate, was evaporated and the residue was converted to the oxalate which was purified by slow recrystallization from an isopropanol-ether mixture. It had m.p. 192° and weighed 2.0 g. (60%).

Anal. Calc'd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83.
Found: C, 61.80; H, 7.52; N, 3.89.

The *hydrochloride* was too unstable to handle.

1,2,6-Trimethyl-4-mandeloxypiperidine meconate. The general procedure was similar to one described earlier (15). A solution of 10 g. (0.07 mole) of 1,2,6-trimethyl-4-piperidinol in 75 ml. of water was neutralized with concentrated hydrochloric acid and 27 g. (0.18 mole) of mandelic acid and two drops of concentrated hydrochloric acid were added. The solution was evaporated to dryness and the residue was taken up in 100 ml. of water containing two drops of hydrochloric acid. It was again evaporated to dryness and the procedure was repeated another time. After the third evaporation the residue was dissolved in dilute hydrochloric acid and extracted with ether to remove excess mandelic acid. The solution was made basic with sodium carbonate and the ester was extracted with ether. About 10 g. (52%) of an oily solid was obtained. This was converted to the meconate by treatment with one equivalent of meconic acid in warm ethanol. Addition of dry ether yielded an oil which solidified on repeated trituration with ether and vigorous stirring. It was recrystallized from ethanol-ether from which it first separated as an oil but crystallized upon trituration with dry ether. Yield 8 g., m.p. 138–140°.

Anal. Calc'd for $C_{23}H_{27}NO_{10}$: C, 57.85; H, 5.70; N, 2.93.
Found: C, 58.08; H, 5.94; N, 2.97.

1,2-Dimethyl-5-methoxy-4-diphenylacetoxypiperidine meconate. A two-fold excess of purified thionyl chloride was added to 10 g. (0.047 mole) of diphenylacetic acid and the mixture was refluxed for two hours. The excess thionyl chloride was removed by warming *in vacuo* and the residue was dissolved in 30 ml. of dry benzene. To this solution there was added 8.8 g. (0.055 mole) of 1,2-dimethyl-5-methoxy-4-piperidinol in 50 ml. of dry benzene. The mixture became warm and after standing for fifteen minutes was refluxed for two hours. The solvent was removed under reduced pressure, the residue was dissolved in 100 ml. of water, made basic with sodium carbonate, and extracted with ether. The ether extract after drying over magnesium sulfate yielded 9 g. (48%) of oil which was converted to the meconate salt as above, giving 6 g., m.p. 105–107°. The salt decarboxylated on drying for analysis.

Anal. Calc'd for $C_{28}H_{31}NO_8$: C, 65.99; H, 6.13; N, 2.75.
Found: C, 65.96; H, 5.70; N, 2.80.

SUMMARY

1. It has been found that 4-pyridones can be converted to 4-piperidinols by catalytic hydrogenation at high pressures and temperatures.

2. 1,2,6-trimethyl-4-piperidinol has been oxidized to 1,2,6-trimethylpiperi-

done by aluminum *tert*-butoxide and acetone, but this procedure failed with 1,2-dimethyl-5-methoxy-4-piperidinol.

3. Some derivatives of 4-piperidinols of pharmacological interest have been synthesized.

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