STEREOCHEMISTRY OF NITROGEN-CONTAINING HETEROCYCLES

XV. Stereoisomerism of 2-Methyloctahydro-1-pyridin-4-ol*

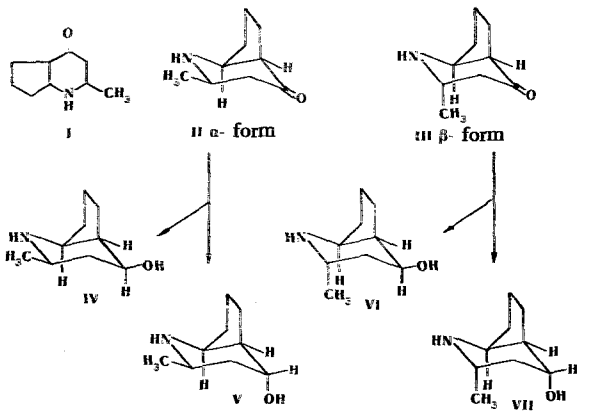
Zh. I. Isin, B. T. Sydykov, A. A. Andrusenko, and D. V. Sokolov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 3, pp. 494–498, 1968

UDC 547.759.4'822.3:543.422.4:542.941.7

The reduction of the α- and β-isomers of 2-methyl-4-oxooctahydro-1-pyrindine in the presence of Raney nickel and sodium in ethanol has been studied, and four isomers of 2-methyloctahydro-1-pyrindin-4-ol have been obtained. On the basis of an analysis of IR spectra, basicity constants, and the conditions for the reduction of the ketones, the most probable spatial structures have been assigned to all four piperidols.

In a previous communication [1] it was shown that 2-methyl-4-oxooctahydro-1-pyrindine (I), obtained by Nazarov's method, consists of two isomers which were isolated in the pure state by column chromatography on alumina. A consideration of the physicochemical constants of the isomeric ketones permitted them to be assigned the configurations II and III with the identical cis-linkage of the piperidine and cyclopentane rings but with different orientations of the methyl group at C-2. The high values of the dipole moments [3] of the isomers II and III (3.16 and 2.9 D, respectively) in comparison with the racemic ketones of the decahydroquinoline series (2.6 D) [4] shows that the piperidine chair in both piperidones is in the state of an unusual degree of flattening.



The present investigation is devoted to a study of the isomerism of 2-methyloctahydro-1-pyrindin-4-ol, using as the starting materials the individual bicyclic piperidones described above. From a careful study of the composition of the products of the reduction of the ketones II and III, we have obtained, in agreement with theory, all four racemic 2-methyloctahydro-1-pyrindin-4-ol IV-VII; their properties are given in the table. The racemic alcohol IV was obtained with a yield of about 90% by the hydrogenation of the α-form II in the presence of a nickel catalyst. When the same ketone was reduced with sodium in isopropanol and the reduction products were chromatographed on alumina, in addition to the racemate IV (60%) we obtained the epimeric piperidinol V in a yield of 26%. The column chromatography on alumina of the second pair of epimeric alcohols obtained in the form of a mixture by the hydrogenation of the β-ketone III in the presence of Raney nickel gave 2% of the piperidinol VI and 78% of the piperidinol VII in the pure state. When this ketone was reduced with sodium in ethanol, the epimeric piperidinols VI and VII were formed in approximately equal amounts; the first of them was most readily isolated in the form of the base and the second in the form of the picrate, with yields of 34 and 28%, respectively.

We have established the most probable spatial configurations of all four piperidinols on the basis of an analysis of the chemical and physicochemical data obtained in studying both the alcohols themselves and the isomeric ketones corresponding to them. Thanks to the equatorial position of the methyl radical, the carbonyl group of the ketone II must belong to the category of "unhindered" groups and, because of this, on catalytic hydrogenation and on reduction with sodium in ethanol, as was also to be expected on the basis of Barton's rules [5, 6], it forms predominantly the alcohol IV with an equatorial hydroxy group. In the ketone III, conversely, the carbonyl group is strongly screened by the methyl at C-2 and therefore it hydrogenates considerably more slowly giving, in accordance with the same rules, the alcohol VII with the axial orientation of the hydroxyl as the main isomer. This arrangement of the hydroxy groups is supported by the features of the IR spectra [7].

Equatorial C—O bonds have (see table) a greater frequency of their stretching vibrations than axial bonds [8]. At the same time, a higher frequency of the stretching vibrations of the O—H* bond corresponds to a lower frequency of the C—O vibrations, and conversely [9]. These rules, derived by the study of a large number of steroid alcohols, are therefore followed also by the hydroxy derivatives of octahydropyrindine that we are studying (see also [7]).

We explain the high frequency of the stretching vibrations of the C—O bond of the alcohol VII by the specific structure of its bicyclic system. In particular, we assume that the flattened chair conformation of the piperidine ring in the octahydropyrindine system

*For part XIV, see [1].

*The IR spectra were measured by O. V. Agashkin and S. S. Chasnikov.

Characteristics of the 2-Methyloctahydro-1-pyridin-4-ols

Compound	Mp, °C	Yield of alcohols under the conditions of reducing the ketones II and III, %		R_f	Frequency of the vibrations, cm^{-1}				Dissociation constants		Configuration*	
					C—O		O—H					
		H_2, Ni	Na, ethanol		CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	pK_a	$K \cdot 10^5$	OH	CH_3
IV	128—129	89.13	60.7	0.57	1040	1035	3625	3618	9.11	1.29	e	e
V	160—161	10	26.4	0.27	—	996	3628	3620	9.50	3.16	a	e
VI	141—142	2	34.6	0.20	1050	1042	3610	3630	9.41	2.58	e	a
VII	109—110	78	28.3	0.10	1040	1033	3630	3620	9.62	4.17	a	a

* e—equatorial, a—axial

[1] is enhanced in this case by the presence of an oblique interaction between the methyl and hydroxy groups present in the 1,3 positions (metadiaxial interaction), as a result of which the hydroxy group departs from its true axial position.

The results of column and thin-layer chromatography enable us to draw a preliminary conclusion on the inapplicability of the known chromatographic rules [5,13] to the geometric isomers of the bases of the secondary alcohols of 2-methyloctahydropyrindine, the R_f values of which have the reverse magnitudes.

Similar results have been obtained in our laboratory in a study of the adsorption capacity in a thin layer of alumina of seven diastereoisomeric forms of 4-hydroxy-2-methyldecahydroquinoline. It has been shown that alcohols with an equatorial orientation of the hydroxyl possess a lower absorption capacity and, consequently, have a higher R_f value than their axial epimers; the adsorption capacity of the N-benzoyl derivatives in some cases proves to be opposite to that of the epimeric bases. The results of these investigations are being prepared for the press.

In conclusion, we must consider the basicity constants and their dependence on the spatial structure of the amino alcohols. It has been convincingly shown previously in our laboratory in the case of numerous isomers of the decahydroquinoline and piperidine series [10] that alcohols with an axial hydroxy group have greater dissociation constants than their equatorial epimers and that this rule can be used as the basis of the simplest method of distinguishing the configuration of the hydroxy groups of amino alcohols of analogous structure. The same rule has been established for the 4-piperidinols having substituents in the α-position. In particular, it has been shown that an axial methyl group at C-2 in the trans-decahydroquinoline series increases the basicity of the epimeric alcohols, while an equatorial group decreases it.

The values of the dissociation constants of the amino alcohols IV-VII given in the table are in full agreement with the rules described above and thus serve as an important confirmation of the correctness of the spatial configuration assumed for these compounds.

EXPERIMENTAL

The α- and β-isomers of 2-methyl-4-oxooctahydro-1-pyrindine II and III were obtained as described previously [1]. The Raney nickel catalyst was prepared from nickel-aluminum alloy by a published method [11].

Hydrogenation of the α-form of 2-methyl-4-oxooctahydro-1-pyrindine (II) in the presence of Raney nickel catalyst. Preparation of 2-methyloctahydro-1-pyrindin-4-ol(IV). Ten grams (~0.15 mole) of the α-ketone II with bp 82° C (2 mm), d_4^{20} 1.0289, n_D^{20} 1.4940, in 80 ml of anhydrous ethanol was hydrogenated in the presence of the nickel catalyst prepared from 10 g of alloy. The calculated amount of hydrogen (1.46 *l*) had been absorbed in 2 hr. The catalyst was filtered off and washed with hot ethanol, and after the ethanol had been distilled off to dryness in a moderate vacuum, the solid residue was repeatedly recrystallized from ether. This gave 9.1 g (89.13%) of the racemate IV in the form of a white powder with mp 128°-129° C, R_f 0.57 (alumina—ether system). Found, %: C 70.13, 70.25; H 11.24, 11.21; N 9.25, 9.30. Calculated for $C_9H_{17}NO$, % C 69.63; H 11.04; N 9.02. The **hydrochloride** was obtained by neutralizing an ethanolic solution of the piperidinol IV with the calculated amount of an alcoholic solution of hydrogen chloride; silvery plates with mp 253°-254° C (from ethanol). Found, %: N 7.58, 7.48. Calculated for $C_9H_{17}NO \cdot HCl$, %: N 7.30. **Picrate**—small yellow crystals with mp 158°-159° C (from methanol). Found, %: N 14.16, 13.82. Calculated for $C_9H_{17}NO \cdot C_6H_3N_3O_7$, %: N 14.57.

Reduction of the α-form of 2-methyl-4-oxooctahydro-1-pyrindine (II) with metallic sodium in isopropanol. Racemates of 2-methyloctahydro-1-pyrindin-4-ol IV and V. In a current of argon, 10 g (~0.15 mole) of the α-ketone II in solution in 15 ml of dry toluene and 12 ml of anhydrous isopropanol were added dropwise over 20 min to a suspension of 5 g of metallic sodium in 38 ml of dry toluene [12]. The mixture was boiled for 2 hr 30 min, after which 7.5 ml of isopropanol was added and it was heated for another hour. The cooled solution was treated with 25 ml of water and the reaction products were extracted with benzene and dried. The dry crystalline residue, amounting to 10.2 g obtained after the distillation of the solvent, was studied in two ways.

a) Fractional crystallization of the mixture of isomers from ether gave 0.91 g (9%) of the racemate of 2-methyloctahydro-1-pyrindin-4-ol (V) in the form of coarse bars with mp 160°-161° C, R_f 0.27 (alumina, ether). A mixture with the piperidinol IV gave a depression; mp about 117°-119° C. Found, %: C 70.49, 70.17; H 11.68, 11.27; N 9.16, 9.46. Calculated for $C_9H_{17}NO$, %: C 69.63; H 11.04; N 9.02. Hydrochloride of the piperidinol V — small colorless crystals with mp 207°-208° C (by reprecipitation from ethanol with ether); a mixture with the hydrochloride of the piperidinol IV gave a depression, mp about 191°-198° C. Found, %: N 7.28, 7.35. Calculated for $C_9H_{17}NO \cdot HCl$, %: N 7.30. **Picrate** — yellow crystalline powder with mp 185°-186° C (by reprecipitation from methanol with ether); a mixture with the picrate of the piperidol IV melted at 152°-154° C. Found, %; N 15.13, 15.11. Calculated for $C_9H_{17}NO \cdot C_6H_3N_3O_7$, %: N 14.57. The remainder of the mixture of isomers was converted into the hydrochlorides by the usual method, and the fractional crystallization of these from ethanol gave 3.07 g (25%) of the hydrochloride of the alcohol IV, showing no depression of the melting point (252°-253° C) in admixture with the specimen described above.

b) 1.5 g of the mixture of piperidinols IV and V in 2 ml of ethanol was transferred to a chromatographic column (70 cm × 3 cm) filled with 600 g of alumina of activity grade II moistened with ether. After elution with ether for 4 hr, thirteen fractions (of 25 ml each) of the pure piperidol IV were collected (the individuality of the

isomers was checked by thin-layer chromatography on alumina, the substances being revealed with iodine vapor), and then 25 fractions of a mixture of isomers, after which the piperidol V began to be eluted. After the solvent had been distilled off, 0.91 g (60.7%) of the piperidinol IV with mp 128°-129° C (R_f 0.57), 0.39 g (26.4%) of the piperidinol V with mp 160°-161° C (R_f 0.27), and 0.27 of an unresolved mixture of isomers were obtained.

Hydrogenation of the β-form of 2-methyl-4-oxooctahydro-1-pyridine (III) in the presence of a nickel catalyst. Racemates of 2-methyloctahydro-1-pyrindin-4-ol VI and VII. The hydrogenation of 10.36 g (0.15 mole) of the β-ketone III with bp 105° C (5 mm), d_4^{20} 1.0463, n_D^{20} 1.4985 in 80 ml of ethanol was carried out in the presence of the nickel catalyst prepared from 10 g of alloy. The calculated amount of hydrogen (1.51 *l*) had been absorbed after 3 hr. The reaction products were isolated in the usual way. The mixture of piperidinols (2 g) was chromatographed on alumina in a column as described in the preceding experiment. After the elimination of the ether from the identical fractions, 0.04 g (2%) of the racemic alcohol VI with mp 141°-142° C, R_f 0.20; 0.31 g (15.5%) of a mixture of isomers VI and VII; and 1.5 g (78%) of the alcohol VII with mp 109°-110° C, R_f 0.1, were obtained.

The racemate of 2-methyloctahydro-1-pyrindin-4-ol (VII) with mp 109°-110° C consisted of small colorless crystals, and mixtures of it with the other alcohols IV, V, and VI gave marked depressions. Found, %: C 69.50, 69.87; H 10.40, 10.90; N 8.32, 8.44. Calculated for $C_9H_{17}NO$, %: C 69.63; H 11.04; N 9.02. **Hydrochloride** — microcrystalline powder with mp 189°-190° C (by reprecipitation from ethanol with ether). Found, %; N 6.82, 6.84. Calculated for $C_9H_{17}NO \cdot HCl$, %: N 7.30. **Picrate** — small yellow crystals with mp 181°-182° C (from ethanol). Found, %: N 14.63, 14.71. Calculated for $C_9H_{17}NO \cdot C_6H_3N_3O_7$, %: N 14.57.

Reduction of the β-form of 2-methyl-4-oxooctahydro-1-pyrindine (III) with metallic sodium in isopropanol. The β-ketone III (4.6 g; ~0.3 mole) was reduced in isopropanol as described above. This gave 4.65 g of a mixture of isomeric alcohols from which by fractional crystallization from petroleum ether (bp 60°-70° C) we obtained 1.3 g (28.3%) of the piperidol VII with mp 109°-110° C, giving no depression of the melting point in admixture with the specimen described in the preceding experiment. The residual isomers were converted into the picrates, and the fractional crystallization of these from ethanol gave 3.95 g (34.6%) of the picrate of the piperidinol VI with mp 201°-202° C (from ethanol by precipitation with ether). Found, %: N 14.09, 14.23. Calculated for $C_9H_{17}NO \cdot C_6H_3N_3O_7$, %: N 14.57.

Decomposition of the picrate with mp 201°-202° C. 3.5 g of the picrate was treated with dilute hydrochloric acid (1:1), the picric acid was extracted with benzene, the aqueous solution of the hydrochloride was saturated with potassium carbonate, the liberated base was extracted with ether, and the ethereal solution was dried with calcined potassium carbonate. Distillation of the ether yielded 1.29 g (90.2%) of the piperidinol VI with mp 141°-142° C (from gasoline with bp 80°-90° C), R_f 0.2. Found, %: C 69.94, 69.80; H 11.43, 11.53; N 9.44, 9.23. Calculated for $C_9H_{17}NO$, %: C 69.63; H 11.04; N 9.02. **Hydrochloride** — small colorless crystals with mp 213°-214° C (reprecipitated from ethanol with ether). Found, %: N 6.91, 7.03. Calculated for $C_9H_{17}NO \cdot HCl$, %: N 7.3.

The basicity constants of the isomers of 2-methyloctahydro-1-pyrindin-4-ol (IV-VII) were determined from the pH value at the semineutralization point in the potentiometric titration of 0.01 N solutions of the bases with 0.5 N hydrochloric acid at 25° C. The accuracy of the measurements was ±0.03 pH. The titration was carried out in a thermostated cell in an atmosphere of argon.

REFERENCES

1. Zh. I. Isin, B. T. Sydykov, and D. V. Sokolov, Izv. AN Kazakhsk. SSR, ser. khim., 4, 60, 1966.

2. I. N. Nazarov and V. A. Rudenko, Izv. AN SSSR, OKhN, 6, 610, 1948.

3. I. Yu. Kokoreva, ZhSKh, 5, 314, 1964.

4. A. N. Shidlovskaya, Ya. K. Syrkin, I. N. Nazarov, and D. V. Sokolov, Izv. AN SSSR, OKhN, 241, 1958.

5. D. H. R. Barton, J. Chem. Soc., 1027, 1953.

6. W. Hückel and M. Maier, Ann., 616, 46, 1958.

7. O. V. Agashkin, G. S. Litvinenko, D. V. Sokolov, and S. S. Chasnikova, ZhOKh, 31, 861, 1961.

8. H. Rosenkrantz, A. T. Milhorad, and M. Farber, J. Biol. Chem., 195, 509, 1952.

9. M. I. Batuev, A. A. Akhrem, A. D. Matveeva, A. V. Kamernitskii, and I. N. Nazarov, DAN, 120, 779, 1958.

10. D. V. Sokolov, G. S. Litvinenko, V. I. Artyukhin, and A. A. Andrusenko, Izv. AN Kazakhsk, SSR, ser. khim. nauk, no. 4, 73, 1965.

11. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, ZhOKh, 29, 3204, 1959.

12. E. A. Mistryukov and V. F. Kucherov, Izv. AN SSSR, OKhN, 10, 1816, 1961.

13. D. H. R. Barton, Experientia, 6, 316, 1950.

4 June 1966

Institute of Chemical Sciences
AS Kazakh SSR, Alma-Ata