SYNTHESIS OF STEREOISOMERIC 1,3-DIMETHYL- AND 1,2,5-TRIMETHYL-4-ACYL(BENZOYL)-4-PIPERIDINOLS

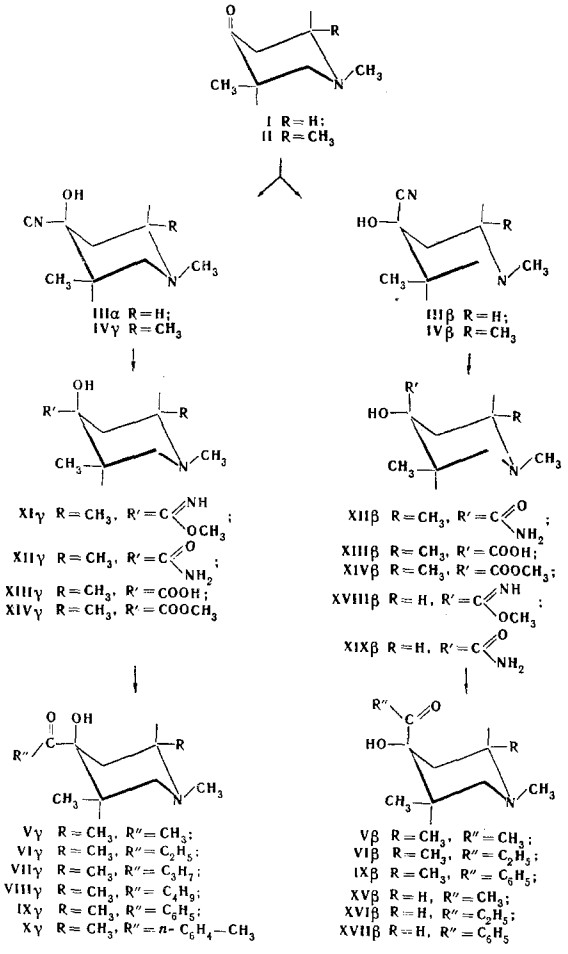
B. V. Unkovskii, N. P. Shulaev, Yu. F. Malina, and O. D. Saralidze

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 4, pp. 654–660, 1968

UDC 547.824.07:541.634

In order to synthesize stereoisometric 4-acyl(benzoyl)-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols, the reaction of the geometrical isomers of 4-cyano-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols and the amines and imidic esters corresponding to them with some alkyl- and arylmagnesium halides, leading to the corresponding isomeric piperidinic α-ketols, has been studied. The dependence of the reactivity of the geometrical isomers of the compounds studied on the spatial orientation of their functional groups has been shown.

In studying the stereochemistry of some derivatives of piperidine, we have come up against the necessity for obtaining stereoisomeric 4-acyl- and 4-benzoyl-4-piperidinols. Up to the present time, compounds of this type have been represented only by the geometrical isomers of 4-acetyl-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols, which are easily obtained by the hydration of the corresponding isomers of 4-ethynyl-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols [1,2], while stereoisomeric ketols with other acyl groups or with benzoyl groups have remained unknown.



In the present paper we describe the synthesis of some 4-acyl(aroyl)-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols by the reaction of Grignard reagents with the geometric isomers of 4-cyano-1,3-dimethyl- and -1,2,5-trimethyl-4-piperidinols IIIβ and IVβ and γ, obtained by the addition of hydrogen cyanide to the carbonyl groups of 1,3-dimethyl- and 1,2,5-trimethyl-4-piperidinones I and II [3–5].

In view of the possibility of the dissociative decomposition of the cyanohydrins and in order to find the optimum method of obtaining piperidinic ketols of this type, we have also investigated the analogous reactions of some derivatives of the cyanohydrins IIIβ and IVβ and γ (imidic esters, amides). It appeared of interest to study the different reactivities of these compounds as functions of the spatial orientation of their functional groups. A comparison of the methods of obtaining the 4-acyl- and 4-aroyl-1,2,5-trimethyl-4-piperidinols Vγ–Xγ (table) from the cyanohydrin IVγ, 4-hydroxy-1,2,5-trimethyl-4-piperidinecarbamidic ester (XIγ), and 4-carbamoyl-1,2,5-trimethyl-4-piperidinol (XIIγ) (see scheme) showed that the organomagnesium syntheses take place most smoothly and unambiguously when the amide IIγ is used. This compound is readily accessible and we have obtained them not only by the Pinner rearrangement of the imidic ester XIγ described previously [6] but also by the hydrolysis of the cyanohydrin IVγ at room temperature with concentrated hydrochloric acid saturated with hydrogen chloride [7–9] and by the ammonolysis of the previously-described [2,6] 4-methoxycarbonyl-1,2,5-trimethyl-4-piperidinol (XIVγ).

The reaction of XIIγ with methylmagnesium iodide takes place with particular difficulty, giving a 27% yield of 4-acetyl-1,2,5-trimethyl-4-piperidinol (Vγ), which has been obtained previously by a different method [2]. In accordance with the spatial structure of Vγ established previously [10] by IR-spectroscopic methods and on the basis of their common method of synthesis, the ketols VIγ–Xγ, like Vγ have the equatorial orientation of the acyl (aroyl) groupings.*

In combination with the previous spectroscopic data [10], the conversion of the cyanohydrin IVγ into the ketol Vγ once again confirms the previously-established [2] configurative connection between these compounds and

*A study of the spatial conformations of the stereoisomeric ketols described in the present paper and compounds related to them by the methods of IR and NMR spectroscopy will be published in subsequent communications.

Characteristics of the Compounds Synthesized

Compound	Mp, °C	Solvent for crystallization	Initial compound	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
XIIγ	223—224[6]	Ethanol	XIVγ	—	—	—	—	—	—	—	72.7
XIIβ	183—184	Acetone	XIVβ	$C_9H_{18}N_2O_2$	58.15 57.83	10.00 9.77	15.00; 15.05	58.03	9.74	15.04	50.8
XIXβ	187—188	Acetone	IIIβ XVIIIβ	$C_8H_{16}N_2O_2$	55.96 55.68	9.38 9.51	16.20; 16.30	55.79	9.36	16.26	79.7 15.0
Vγ	59—60[2]	Gasoline	XIIγ	—	—	—	—	—	—	—	27.0
VIγ	79—80	Gasoline	XIγ XIIγ IVγ	$C_{11}H_{21}NO_2$	65.96 65.86	10.65 10.64	6.89; 6.82	66.29	10.64	7.02	91.6 75.6 67.2
Picrate	221—222	Ethanol	—	$C_{11}H_{21}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	13.10; 13.37	—	—	13.08	
VIβ	123—124	Hexane	XIIβ IVβ, γ	$C_{11}H_{21}NO_2$	66.11 66.16	10.22 10.43	6.80; 6.81	66.29	10.64	7.02	39.7 17.5
VIIγ	55—56	Gasoline	XIIγ	$C_{12}H_{23}NO_2$	67.57 67.71	11.06 10.92	6.47; 6.57	67.56	10.86	6.56	50.0
Picrate	208—209	Ethanol		$C_{12}H_{23}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	12.34; 12.10	—	—	12.65	—
VIIIγ	33,5—35	Gasoline	XIIγ	$C_{13}H_{25}NO_2$	68.67 68.54	11.40 11.38	6.05; 6.24	68.68	11.08	6.16	79.7
Picrate	177—178	Ethanol		$C_{13}H_{25}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	12.16; 12.20	—	—	12.27	
IXγ	95—96	Gasoline	XIIγ IVγ	$C_{15}H_{21}NO_2$	72.60 72.54	8.71 8.64	5.54; 5.53	72.84	8.55	5.66	80.8 27.9
Picrate	193—194	Ethanol		$C_{15}H_{21}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	11.84; 11.77	—	—	11.76	
IXβ	129—130	Acetone	IVβ, γ	$C_{15}H_{21}NO_2$	73.10 72.80	8.45 8.58	5.63; 5.39	72.84	8.55	5.66	15,0
Xγ	77—78	Gasoline	XIIγ	$C_{16}H_{23}NO_2$	72.73 73.05	8.98 9.22	5.84; 6.26	73.52	8.87	5.36	67.0
Picrate	192—193	Ethanol		$C_{16}H_{23}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	11.59; 11.37	—	—	11.42	
XVβ	49—51[1]	Hexane	IIIβ	—	—	—	—	—	—	—	31.0
XVIβ	59—60	Gasoline	IIIβ	$C_{10}H_{19}NO_2$	64.30 64.58	10.60 10.49	7.51; 7.76	64.82	10.33	7.56	67.8 59.3
Picrate	155—156	Ethanol	XIXβ	$C_{10}H_{19}NO_2 \cdot C_6H_3(NO_2)_3OH$	—	—	13.65; 13.25	—	—	13.52	
XVIIβ	115—116	Gasoline	IIIβ XIXβ	$C_{14}H_{19}NO_2$	72.29 72.12	8.47 8.28	6.11; 5.98	72.07	8.21	6.00	56.6 36.7

shows that the cyano group in the cyanohydrin IVγ has the equatorial orientation*

The use of the cyanohydrin IVγ for the synthesis of the ketals Vγ-Xγ proved less suitable because of the lower yields of the desired products as a result of the partial dissociation of IVγ under the action of the Grignard reagents and the formation as by-products of the piperidinol II and the corresponding tertiary alcohols, the presence of which was detected on thin-layer chromatography of the products of the reaction of IVγ with ethylmagnesium and phenylmagnesium bromides. The use in the reaction with ethylmagnesium bromide of the imidic ester XIγ, obtained [6] from IVγ by Pinner's method, enables the ketol VIγ to be synthesized in higher yield (see table) but again with contamination by the piperidinol II and the tertiary alcohol formed from XIγ by the partial splitting off of methanol [15] and the formation of the cyanohydrin IVγ. The use of the imidic ester XIγ proved inconvenient because of its low stability, which prevented satisfactorily reproducible results from being obtained.

The reaction of methylmagnesium iodide and of ethylmagnesium and phenylmagnesium bromides with the cyanohydrin IIIβ takes place in full analogy with the reactions of IVγ and is accompanied by the formation of 4-acetyl-1,3-dimethyl-, 4-propionyl-1,3-dimethyl-, and 4-benzoyl-1,3-dimethyl-4-piperidinols XVβ, XVIβ, and XVIIβ, respectively (see table), of which XVβ has been obtained previously by a different method [1].

In agreement with the spatial structure of XVβ established previously [12] and the generality of the method of synthesis, the ketols XVIβ and XVIIβ have the cis-structure with axially-oriented propionyl and benzoyl groups (see scheme).

The reaction of ethylmagnesium and phenylmagnesium bromides with the stereoisomeric mixture of the cyanohydrins VIβ and γ obtained from the piperidinol II and acetone cyanohydrin at 0 to −5° C and enriched in the cyanohydrin IVβ (25–30%)** leads to mixtures of the ketols VIβ and γ and IXβ and γ. The separation of these mixtures and the isolation of pure samples of VIβ and IXβ can be done by fractional crystallization because of the different solubilities of the epimeric ketols.

In order to make a variation in the synthesis of the ketols VIβ, IXβ, XVIβ, and XVIIβ from the geometric isomers of amides with axially oriented carbamoyl groups and to study their reactivity, we have synthesized the previously-undescribed amide XIIβ and 4-carbamoyl-1,3-dimethyl-4-piperidinol (XIXβ) (see scheme and table). The conversion of the cyanohydrin IIIβ into the amide XIXβ via the hydrochloride of methyl 1,3-dimethyl-4-hydroxy-4-piperidinecarbamidate (XVIIIβ) by the Pinner rearrangement proved to be extremely laborious because of the low reactivity of XVIIIβ, as a result of which the amide XIXβ could not be obtained with a yield of more than 15%, in spite of variations in the reaction conditions. In contrast to this, the hydrolysis of the cyanohydrin IIIβ at room temperature with concentrated hydrochloric acid saturated with hydrogen chloride [7–9] enabled the amide XIXβ to be obtained with a yield of 80%. In the hydrolysis of the stereoisomeric mixture of cyanohydrins IVβ and γ under the same conditions, it was impossible clearly to fix the stage of the formation of the isomeric amides XIIβ and γ and to find the optimum reaction conditions since in all experiments these compounds were formed with yields of 35–40% in admixture with the 4-hydroxy-1,2,5-trimethyl-4-piperidinecarboxylic acids XIIIβ and γ. The most convenient method for the synthesis of the amide XIIβ proved to be the ammonolysis of the previously described [2] hydroxy ester XIVβ. In comparison with its epimer at C-4 of the piperidine ring XIVγ, the hydroxy ester XIVβ proved considerably less reactive under ammonolysis conditions and was converted into a mixture of the amide XIIβ and the hydroxy acid XIIIβ.

The reactivity of the axial amides XIIβ and XIXβ obtained in this way also proved to be considerably lower than that of the amide XIIγ.

These geometric isomers react with Grignard compounds with great difficulty and are converted into the ketols Vβ, VIβ, IXβ, XVβ, and XVIβ with yields of not more than 50% after taking the recovery of the initial amides into account.

The low reactivity of the amides XIIβ and XIXβ in Grignard reactions, of the imidic ester XIβ in the Pinner rearrangement, and of the hydroxy ester XIVβ in ammonolysis is due, in all probability, to steric hindrance caused by the 1,3-meta-axial interaction of the axial functional groups with the hydrogen atoms at C-2 and C-6 of the piperidine ring. At the same time, we have observed no appreciable differences in the reactivity of the cyanohydrins IIIβ and IVβ, on the one hand, and IVγ, on the other hand, which may be due to the small effective volume and linear structure of the cyano group [13,14].

EXPERIMENTAL

4-Propionyl-1,2,5-trimethyl-4-piperidinol (VIγ). a) Over an hour, an ethereal suspension of 5.3 g (~0.3 mole) of 4-cyano-1,2,5-trimethyl-4-piperidinol (IVγ) with mp 141–143° C was added to an

*The possible configurations of the geometric isomers of IVγ and Vα, β, γ have been discussed previously [11] on the basis of chemical data. In our most recent paper [10] it was shown by means of spectroscopic methods that the functional groups in the ketals Vβ and Vγ have the opposite spatial arrangement. In view of this, subsequently the spatial configurations at C-4 of the piperidine ring in the ketals Vβ and γ and in the compounds configuratively connected with them will be reversed.

**An investigation of the steric directivity of the addition of hydrogen cyanide to the carbonyl group of the piperidinols I and II and its dependence on the reaction temperature is the subject of the following communication, in which the quantitative ratios of the isomers in the stereoisomeric mixture of the cyanohydrins IIIα and β and IVβ and γ obtained under various conditions are established.

ethereal solution of the ethylmagnesium bromide prepared from 5.5 g (0.23 g-atom) of magnesium and 25 g (0.23 mole) of ethyl bromide in 150 ml of dry ether at such a rate that the ether boiled gently. After the whole of the cyanohydrin had been added, the mixture was boiled for 6 hr and was hydrolyzed with 150 ml of 18% hydrochloric acid; the ethereal layer was separated off and the acidic aqueous layer was heated in the water bath for 2 hr and was then cooled and neutralized with potassium carbonate. After extraction, the ethereal extract was dried with calcined magnesium sulfate, the ether was eliminated, and the residue was recrystallized to give 4.0 g of the ketol **VIγ**, R_f 0.76 (Al_2O_3, activity grade II, benzene—acetone, 1 : 1). Similarly, the cyanohydrin IVγ and phenylmagnesium bromide gave the ketol IXγ, and the stereoisomeric mixture IVβ, γ gave the ketols **VIβ** and γ and **IXβ** and γ.

b) Over an hour, 8 g (0.04 mole) of methyl 4-hydroxy-1, 2, 5-trimethyl-4-piperidinecarbamidate (XIγ) [6] was added to an ethereal solution of ethylmagnesium bromide prepared from 8.8 g (0.37 g-atom) of magnesium and 39.25 g (0.36 mole) of ethyl bromide in 200 ml of dry ether. After the reaction mixture had been heated to the boil for 3 hr and had been worked up in the usual way, 7.3 g of the ketol VIγ, giving no depression of the melting point in admixture with a sample of the material obtained in the previous experiment, was obtained.

c) Over an hour, an ethereal suspension of 5.6 g (~0.03 mole) of 4-carbamoyl-1, 2, 5-trimethyl-4-piperidinol (XIIγ) [6] was added to the ethylmagnesium bromide prepared from 5.5 g (0.23 g-atom) of magnesium and 25 g (0.23 mole) of ethyl bromide in 150 ml of dry ether. After 6 hours' heating and the usual working up, 4.5 g of the ketol VIγ, identical with the samples described above, was obtained.

In a similar manner, ketols Vγ, VIIγ, VIIIγ, IXγ, and Xγ were obtained from the amide XIIγ.

4-Carbamoyl-1, 2, 5-trimethyl-4-piperidinol (XIIβ). The sodium methoxide obtained by dissolving 1.5 g of sodium in 2.5 ml of methanol was added to a ammonia-saturated solution of 6.8 g (0.035 mole) of 4-methoxycarbonyl-1, 2, 5-trimethyl-4-piperidinol (XIVβ) [2] with mp 70–71° C in 100 ml of methanol. The mixture was heated for 12 hr at 100° C in a steel ampul; the methanol was distilled off and the residue was dissolved in water and neutralized with 18% hydrochloric acid. The resulting aqueous solution was saturated with potassium carbonate and extracted with ether. The ethereal extract was dried, the ether was driven off, and the residue was recrystallized to give 3.2 g of the amide XIIβ. Concentration of the aqueous solution yielded 2.5 g (39.7%) of 4-hydroxy-1, 2, 5-trimethyl-4-piperidinecarboxylic acid (XIIIβ) with mp 304° C (subl., from ethanol). Found, %: C 57.69, 57.56; H 9.36, 9.18; N 7.75, 7.73. Calculated for $C_9H_{17}NO_3$, %: C 57.75 H 9.09; N 7.48.

Similarly, the same amount of 4-methoxycarbonyl-1, 2, 5-trimethyl-4-piperidinol (XIVγ) with mp 118–119° C [2, 6] yielded 3.5 g of the amide XIIγ, identical with the sample of this compound synthesized [6] from the amino ester XIγ.

4-Propionyl-1, 2, 5-trimethyl-4-piperidinol (VIβ). Over an hour, an ethereal suspension of 4.7 g (~0.025 mole) of the amide XIIIβ was added to an ethereal solution of the ethylmagnesium bromide prepared from 4.6 g (~0.2 g-atom) of magnesium and 21 g (0.2 mole) of ethyl bromide in 200 ml of dry ether, after which the reaction mixture was heated to the boil for 10 hr. After the usual working up and recrystallization, 1.9 g of the ketol VIβ and 0.65 g (14%) of the initial amide XIIβ, sparingly soluble in gasoline, were obtained.

4-Carbamoyl-1, 3-dimethyl-4-piperidinol (XIXβ). A solution of 5 g (~0.03 mole) of 4-cyano-1, 3-dimethyl-4-piperidinol (IIIβ) with mp 97–98° C in 9 ml of concentrated hydrochloric acid was cooled with ice water and saturated with hydrogen chloride until the increase in weight was 4 g, and was then left at room temperature for 4 days. After the elimination of the excess of hydrochloric acid and neutralization of the solution with potassium carbonate, the crystalline amide XIXβ that had deposited was filtered off and the aqueous layer was saturated with potassium carbonate and extracted with ether. After the ether had been driven off, the crystalline residue was combined with the main substance and recrystallized to give 4.45 g of the amide **XIXβ**.

The hydrolysis of the stereoisomeric mixture of cyanohydrins **IVβ** and γ was carried out under the same conditions.

4-Propionyl-1,3-dimethyl-4-piperidinol (XVIβ). A suspension of 5 g of 4-cyano-1, 3-dimethyl-4-piperidinol (IIIβ) in 70 ml of ether was added to an ethereal solution of the ethylmagnesium bromide prepared from 5.5 g (0.23 g-atom) of magnesium and 25 g (0.23 mole) of ethyl bromide in 150 ml of dry ether at such a rate that the reaction mixture boiled gently. Boiling was continued for 5 hr and then the usual process of working up yielded 4.17 g of the ketol **XVIβ** with R_f 0.32 (Al_2O_3, activity grade II, benzene—acetone, 1 : 1).

The ketol XVIIβ was obtained similarly from the cyanohydrin IIIβ and phenylmagnesium bromide.

4-Benzoyl-1,3-dimethyl-4-piperidinol (XVIIβ). The reaction of 5.2 g (0.03 mole) of the amide **XIXβ** with the phenylmagnesium bromide prepared from 5.5 g (0.23 g-atom) of magnesium and 36.1 g (0.23 mole) of bromobenzene in 150 ml of ether gave, after the usual working up, 2.68 g of the ketol XVIIβ with R_f 0.53 (Al_2O_3, activity grade II, benzene—acetone, 1 : 1).

REFERENCES

1. B. V. Unkovskii, I. A. Mokhir, and E. M. Urinovich, ZhOKh, 33, 1808, 1963.

2. I. N. Nazarov, B. V. Unkovskii, I. A. Mokhir, and G. S. Gusakova, ZhOKh, 29, 2292, 1959.

3. I. N. Nazarov, A. A. Akhrem, and A. V. Kamernitskii, ZhOKh, 25, 1345, 1955.

4. B. V. Unkovskii, G. S. Gusakova, and I. A. Mokhir, ZhOKh, 30, 3926, 1960.

5. I. N. Nazarov and B. V. Unkovskii, ZhOKh, 26, 3181, 1956.

6. I. N. Nazarov and B. V. Unkovskii, ZhOKh, 26, 3186, 1956.

7. B. S. Rabinovitch and C. A. Winkler, Can. J. Res. 2013, 73, 1942.

8. E. L. Carpenter and H. S. Davis, J. Appl. Chem., 7, 671, 1957.

9. C. A. Weisgerber, U. S. patent no. 2535245, 1952; C. A., 46, 4220, 1952.

10. B. V. Unkovskii, V. B. Belyanin, I. A. Mokhir, and E. M. Urinovich, ZhOKh, 33, 2540, 1963.

11. N. I. Shvetsov, B. V. Unkovskii, I. A. Mokhir, and V. F. Kucherov, Izv. AN SSSR, OKhN, 843, 1961.

12. V. B. Belyanin, B. V. Unkovskii, and I. A. Mokhir, ZhOKh, 33, 2534, 1963.

13. R. I. Ouelette, J. Am. Chem. Soc., 86, 3089, 1964.

14. F. R. Iensen and B. Rickborn, J. Org. Chem., 27, 4606, 1962.

15. P. Reynaud and R. C. Moreau, Bull. Soc. chim. France, 2997, 1965.

8 January 1966

Lomonosov Moscow Institute of Precision Chemical Engineering