SYNTHESIS OF 4-HYDROXY-1,2,5-TRIMETHYL-4-PIPERIDYL CARBINOLS

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Spatial directivity of reactions of the geometrical isomers of 4-acetyl-, 4-propionyl-, and 4-benzoyl-1,2,5-trimethyl-4-piperidols with Grignard reagents and lithium aluminum hydride has been studied. Stereospecific synthesis of some stereoisomeric 4-hydroxy-1,2,5-trimethyl-4-piperidyl carbinols has been effected and their probable spatial configurations have been discussed.

Stereospecificity of the addition of arylmagnesium halides and aryllithiums to the carbonyl group of geometrical isomers of 4-acetyl-1,2,5-trimethyl-4-piperidol [2] has been established and the spatially-directed synthesis of the stereoisomers of some aryl 4-hydroxy-1,2,5-trimethyl-4-piperidyl methyl carbinols has been described previously [1]. It appeared of interest to study in more detail the stereochemical laws of reactions of this type and to determine the spatial structure of the heterocyclic α-glycols formed.

In the present communication, we describe reactions of the geometric isomers of 4-acetyl-, 4-propionyl- and 4-benzoyl-1,2,5-trimethyl-4-piperidols with Grignard reagents and lithium aluminum hydride, leading to the stereoisomeric synthesis of new representatives of the stereoisomeric 4-hydroxy-1,2,5-trimethyl-4-piperidyl carbinols, and we discuss their probable spatial configurations.

As the starting materials for the preparation of di-secondary and secondary-tertiary α-glycols of this type, we used the previously-described [2,3] geometrical isomers of 4-acetyl-, 4-propionyl- and 4-benzoyl-1,2,5-trimethyl-4-piperidol, Iβ, γ[2], IIβ, γ[3], and IIIβ, γ[3], respectively. The spatial structure of the ketones Iβ, γ—IIIβ, γ has been established previously [3–5].

Reactions of compounds Iβ, γ and IIβ, γ with phenylmagnesium bromide or phenyllithium and of IIIβ, γ with methylmagnesium iodide and ethylmagnesium bromide led to the stereospecific synthesis of the stereoisomers of the di-tertiary glycols IV-XI (scheme). Reactions of the ketols Iβ, γ with phenylmagnesium bromide, just like their reactions with phenyllithium described previously [1], proved to be stereospecific and instead of a mixture of the erythro and threo isomers* of the methyl 4-hydroxy-1,2,

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*Configuration of the substituents on the asymmetric carbon atom in the side chain given in the Scheme of the glycols has been shown arbitrarily and is provisional.

Stereoisomeric 4-Hydroxy-1,2,5-trimethyl-4-piperidyl Carbinols

Compound No.	Probable spatial configuration	Starting material	Mp, °C	Solvent for crystallization	Empirical formula	Found, %			Calculated, %			Yield,* %
						C	H	N	C	H	N	
IV	Erythro	IIIγ	181—182	Benzene	$C_{16}H_{25}NO_2$	73.14	9.58	5.48	73.00	9.50	5.32	93.8
VII	Threo	IIIβ	87—88	Petroleum ether		73.00	9.87	5.38				86.7
IX	Threo	IIγ	130—130.5	Gasoline		74.01	9.68	4.87				56.1
VIII	Erythro	IIIγ	152—153	Benzene-acetone	$C_{17}H_{27}NO_2$	73.81	9.71	5.18	73.64	9.74	5.05	75.8
X	Erythro	IIβ	109—110	Gasoline		73.42	9.96	4.80				77.9
XI	Threo	IIIβ	97—98	Gasoline		73.69	9.99	5.14				82.0
XIII	Erythro	Iγ	82—82.5	Dichloroethane	$C_{10}H_{21}NO_2$	64.28	11.35	7.72	64.17	11.23	7.48	93.6
XIV	Threo	Iβ	121—122	Dichloroethane		64.01	11.40	7.40				95.0
XVII	Erythro	IIIγ	122—123	Dichloroethane	$C_{15}H_{23}NO_2 \cdot H_2O$	67.74	9.34	5.20	67.41	9.36	5.24	96.0
XVIII	Threo	IIIβ	146—147	Dichloroethane	$C_{15}H_{23}NO_2$	71.74	9.29	5.34	72.29	9.23	5.62	96.3
XXI	—	XXγ	92—93	Benzene-acetone	$C_9H_{19}NO_2$	62.70	11.30	8.11	62.42	10.98	8.09	82.8
XXII	—	XXβ	89—90	Benzene-acetone		62.62	11.12	7.87				85.8

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*Yields of the glycols after recrystallization.

5-trimethyl-4-piperidyl phenyl carbinols IV, V (from Iγ) and VI, VII (from Iβ) they permitted the preparation of the diastereomers V and VI exclusively*. Because of well-marked spatial directivity, the reactions of the ketols IIβ, γ with phenylmagnesium bromide and phenyllithium that have been described also lead to the formation not of a mixture of the erythro and threo isomers of the ethyl 4-hydroxy-1,2,5-trimethyl-4-piperidyl phenyl carbinols VIII and IX (from IIγ) and X and XI (from IIβ) but of only the isomers IX and X.

and VI and VII (from IIIβ), the diastereomers IV and VII as the sole products, and the reactions of IIIβ, γ with ethylmagnesium bromide gave, instead of a mixture of VIII and IX (from IIIγ) and of X and XI (from IIIβ), only the diastereomers VIII and XI, respectively (scheme). The addition of ethylmagnesium bromide to the carbinol groups of the ketols IIIβ, γ is accompanied by their partial reduction, as a result of which the products of these reactions contain, in addition to the di-tertiary glycols VIII and XI, about 1% of the corresponding secondary-tertiary glycols.
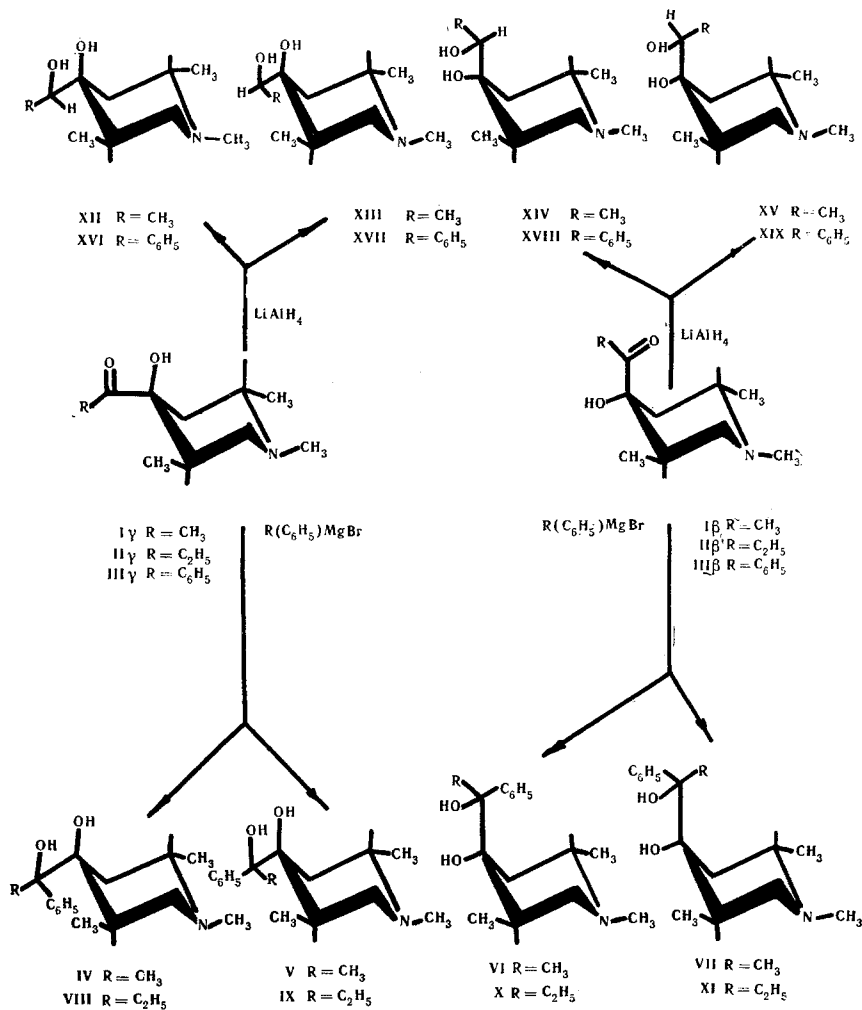

In agreement with data in the literature [7–10] and the rule of asymmetric induction [11–15], it was possible to perform the stereo-directed synthesis of the geometrical isomers of the glycols V, VII, IX, and XI not accessible by the above route from the ketols IIβ, γ. The reactions of IIIβ, γ with methylmagnesium iodide or methyllithium gave, instead of a mixture of the erythro-and threo-glycols IV and V (from IIIγ)

The stereospecific synthesis of secondary-tertiary glycols is readily effected by the reduction of the ketols Iβ, γ–IIIβ, γ with lithium aluminum hydride [16–18]. Compounds Iβ, γ form a mixture of the erythro and threo isomers of the methyl 4-hydroxy-1,2,5-trimethyl-4-piperidyl carbinols XII and XIII (from Iγ) and XIV and XV (from Iβ), with a marked predominance of compounds XIII and XIV. In their turn, under the action of lithium aluminum hydride, the ketols IIIβ, γ form mixtures of the erytho and threo isomers of 4-hydroxy-1,2,5-trimethyl-4-piperidyl phenyl carbinols XVI and XVII (from IIIγ) and XVIII and XIX (from IIIβ) with a marked predominance of the glycols XVII and XVIII (scheme). The identity of the glycols XVII and XVIII so obtained, with the products of the

*In accordance with later work [4, 5], the provisional spatial arrangement of the substituents at C_4 of the piperidine ring in the glycols IV and VI given previously [6] has been changed to the opposite arrangement.
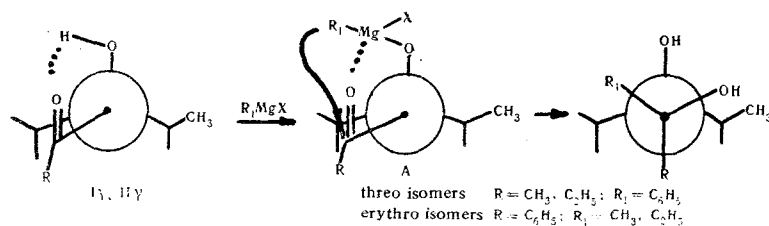
reduction of the ketols with ethylmagnesium bromide, was established.

By the lithium aluminum hydride reduction of the geometrical isomers of the 4-methoxycarbonyl-1,2, 5-trimethyl-4-piperidols XXβ, γ, which are configuratively related to the ketols Iβ, γ [2], primary-tertiary glycols—the stereoisomeric 4-hydroxy-1,2,5-trimethyl-4-piperidyl carbinols XXI and XXII—have also been synthesized.
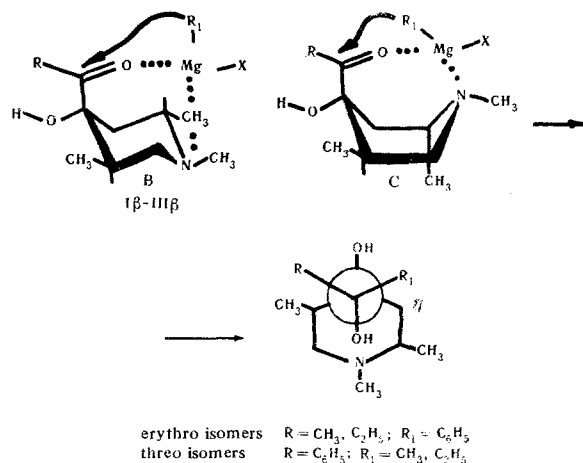

XXI R = OH, R$_1$ = CH$_2$OH;
XXII R = CH$_2$OH, R$_1$ = OH
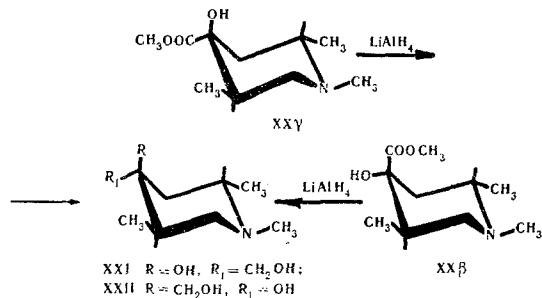
The properties and yields of the α-glycols are given in the table.

The well-marked stereospecificity of the reactions of the piperidinic α-ketols Iβ, γ–IIIβ, γ with Grignard reagents and lithium aluminum hydride is a consequence of the presence in their molecules of geminal acyl and hydroxy groups, on the one hand, and the specific role of the nitrogen of the piperidine ring, on the other hand. According to the literature [11–18], the reaction of the ketols Iβ, γ–IIIβ, γ with Grignard reagents and complex metal hydrides takes place through cyclic transition states of the chelate complex type. Under these conditions, the attack of the entering substituents on the carbonyl groups of Iβ, γ–IIIβ, γ takes place exclusively or predominantly from the less sterically hindered sides of the planes of the complexes formed [11–18], namely from the side of the C$_2$ of the piperidine ring. Starting from these assumptions, it follows that the ketols Iγ, IIγ react with Grignard reagents through the cyclic transition state A [12–15] and are converted into the glycols V and IX, which have the threo configuration*. In their turn, the compounds IV, VIII, and XVII obtained from IIIγ and the glycol XII obtained from Iγ via an analogous cyclic complex are the erythro isomers (intermediate stages of the reaction omitted) [16–18].

In contrast to the ketols Iγ–IIIγ, their geometric isomers Iβ–IIIβ probably react with Grignard reagents and lithium aluminum hydride exclusively in the less sterically hindered rotameric form with transoid hydroxy and carbonyl groups through the cyclic transition state B or C.

B
Iβ–IIIβ

C

erythro isomers   R = CH$_3$, C$_2$H$_5$; R$_1$ = C$_6$H$_5$
threo isomers   R = C$_6$H$_5$; R$_1$ = CH$_3$, C$_2$H$_5$

In this case, the glycols VI and X formed from the ketols Iβ and IIβ have the erythro configuration, and their diastereomers obtained from IIIβ, and the glycol XVIII, have the threo configuration. The glycol XVI formed from Iβ has the same configuration.

Considerably less likely is occurrence of the reactions of ketols Iβ–IIIβ via the transition state D in the rotameric form with the cisoid orientation of the hydroxy and carbonyl groups or with the participation of both rotamers simultaneously through the transition states B, C, and D.

Iβ, IIβ

Iγ, IIγ

A

threo isomers   R = CH$_3$, C$_2$H$_5$; R$_1$ = C$_2$H$_5$
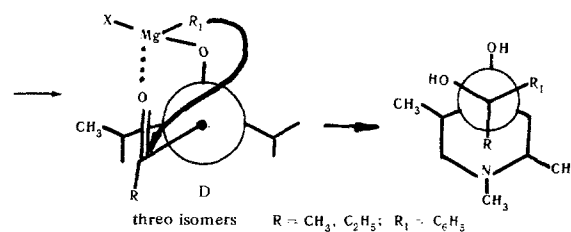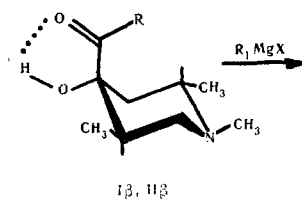erythro isomers R = C$_6$H$_5$; R$_1$ = CH$_3$, C$_2$H$_5$

*To define the erythro and threo configurations we considered Newman projection formulas and as the "similar" substituents on the carbonyl asymmetric centers we provisionally took the substituents in the asymmetric centers in the side chains with the largest effective volumes and the projections of the substituents at C$_5$ of the piperidine ring ("pseudoethyl groups").

D

threo isomers   R = CH$_3$, C$_2$H$_5$; R$_1$ = C$_6$H$_5$

Transition of IIIβ into the cisoid rotamer and the formation from it of the cyclic chelate complex D proves to be absolutely impossible because of the steric hindrance created by the meta-axial hydrogen atoms at C_2 and C_6 of the pyridine ring. Occurrence of the reactions of Iβ and IIβ only through transition state D and of those of IIIβ exclusively through the cyclic complexes B and C contradicts the experimental results. In this case, for example, the identical glycols with the threo configuration should be obtained strictly stereospecifically both from Iβ and phenylmagnesium bromide and from IIIβ and methylmagnesium iodide.

Study of the spatial configurations and conformations of the glycols synthesized by IR-spectroscopic methods will be the subject of one of our subsequent communications.

EXPERIMENTAL

Ethyl 4-hydroxy-1,2,5-trimethyl-4-piperidyl phenyl carbinol (IX). A solution of 4.6 g of 4-propionyl-1,2,5-trimethyl-4-piperidol IIγ [3] in 50 ml of ether was added over 20 min with stirring and cooling to 0-5° C to an ethereal solution of phenyllithium obtained from 1.2 g of lithium and 13.5 g of bromobenzene in 100 ml of dry ether, after which the reaction mixture was heated to a gentle boil for 4 hr, cooled, and hydrolyzed with 30 ml of water. The ethereal layer was separated off and the aqueous layer was extracted with ether (5 × × 50 ml). The combined ethereal extracts were dried with calcined magnesium sulfate, the ether was evaporated off, and the crystalline residue was recrystallized to give 3.32 g of the glycol IX with R_f 0.40 [alumina of activity grade II, benzene-acetone (1:1)].

In a similar manner, the ketol IIβ and phenyllithium or phenylmagnesium bromide gave X.

Ethyl 4-hydroxy-1,2,5-trimethyl-4-piperidyl ethyl carbinol (VIII). To an ethereal solution of ethylmagnesium bromide prepared from 6.7 g of magnesium and 30 g of ethyl bromide in 400 ml of dry ether was added 17 g of 4-benzoyl-1,2,5-trimethyl-4-piperidol IIIγ [3] over 3 hr by gradual extraction with boiling ether using a Soxhlet apparatus, after which the reaction mixture was cooled and hydrolyzed with a saturated solution of ammonium chloride. The ethereal layer was separated off, and the aqueous layer was extracted with ether (5 × 30 ml). The combined ethereal extracts were dried with calcined magnesium sulfate, the ether was distilled off, and crystallization of the solid residue yielded 14.4 g of the carbinol VIII with R_f 0.45. The small amount of the glycol XVII with R_f 0.10 in the reaction product passed into the mother liquor completely on recrystallization. To isolate the XVII, the mother liquor was evaporated and the crystalline mixture of the glycols VIII and XVII was chromatographed on a column of alumina using as eluant mixtures of petroleum ether and ether with gradually increasing proportions of the latter. The glycol XVII isolated has R_f 0.10 and gave no depression of the melting point in admixture with a sample of the glycol XVII obtained by the reduction of the ketol IIIγ with lithium aluminum hydride.

In a similar manner, IV was obtained from IIIγ, and VII and XI from IIIβ (see table).

4-Hydroxy-1, 2, 5-trimethyl-4-piperidyl phenyl carbinol (XVII). A solution of 20 g of 4-benzoyl-1,2,5-trimethyl-4-piperidol IIIγ [3] in 20 ml of dry ether was added over 40 min with stirring to a suspension of 3.4 g of lithium aluminum hydride in 50 ml of dry ether, after which the reaction mixture was stirred at room temperature for 3 hr and with the ether gently boiling for 30 min, and was cooled and hydrolyzed with 3 ml of 15% NaOH. The precipitate that deposited was filtered off and the aqueous filtrate was extracted with ether (5 × 40 ml). The combined ethereal extract was dried with calcined magnesium

sulfate, the ether was distilled off, and the residue was crystallized to give 18.92 g of the glycol XVII with R_f 0.10 [alumina of activity grade II, benzene-acetone (1:1)].

In a similar manner, XIII, XIV, and XVIII were obtained from Iγ, Iβ, and IIIβ (see table).

4-Hydroxy-1,2,5-trimethyl-4-piperidyl carbinol (XXI). Over 3 hr, 7.8 g of 4-methoxycarbonyl-1,2,5-trimethyl-4-piperidol XXγ [2] was added to a suspension of 2.4 g of lithium aluminum hydride in 50 ml of dry ether. After cooling and hydrolysis of the reaction mixture with 6 ml of 15% NaOH solution, the ethereal layer was separated off and the aqueous layer was extracted with ether using a Soxhlet extractor. The ethereal extracts were combined and dried with calcined magnesium sulfate. Elimination of the solvent gave 5.75 g of 4-hydroxy-1,2,5-trimethyl-4-piperidyl carbinol XXI in the form of a viscous rapidly-crystallizing substance with R_f 0.09. The glycol XXII was obtained from the hydroxy ester XXβ by a similar method.

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