CONDENSATION OF 1,2,5-TRIMETHYL-4-PIPERIDONE WITH p-DIETHYNLBENZENE

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A mixture of stereoisomeric diacetylenic piperidols was obtained by the reaction of 1,2,5-trimethyl-4-piperidone with p-diethynylbenzene in liquid ammonia in the presence of sodium amide. Each of the two pure alcohol and glycol geometrical isomers were isolated by chromatography with columns filled with aluminum oxide. Assumptions relative to the three-dimensional structure of the synthesized compounds are expressed on the basis of the principles of conformational analysis, the chromatographic data, and a study of the IR and NMR spectra. Saturated piperidols were obtained by catalytic hydrogenation on a Raney nickel catalyst.

Di- and polyacetylenic compounds have recently attracted the attention of researchers because of their biochemical properties. Active bacteriocides and fungicides were found among such compounds [1, 2]. The condensation of diacetylene and its derivatives with various carbonyl compounds has been widely used to synthesize polyacetylenic compounds [3,4]. However, this method was investigated only for the simplest carbonyl compounds and has not been studied at all for heterocyclic ketones.

In continuing our investigations [5,6] of the synthesis of polyacetylenic alcohols of the heterocyclic series we studied the condensation of 1,2,5-trimethyl-4-piperidone (I) [7] with p-diethynylbenzene (II) [8]; the condensation was carried out in liquid ammonia in the presence of sodium amide. The reaction yielded mixtures of stereoisomeric alcohols – 1,2,5-trimethyl-4-[β-(p-diethynylphenyl]-4-piperidols (IIIβ, γ) and β, β'-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-p-diethynylbenzenes (IVβ, γ) – in the approximate ratios IIIβ: IIIγ = 2.5 : 1 and IVβ : IVγ = 2.3 : 1.

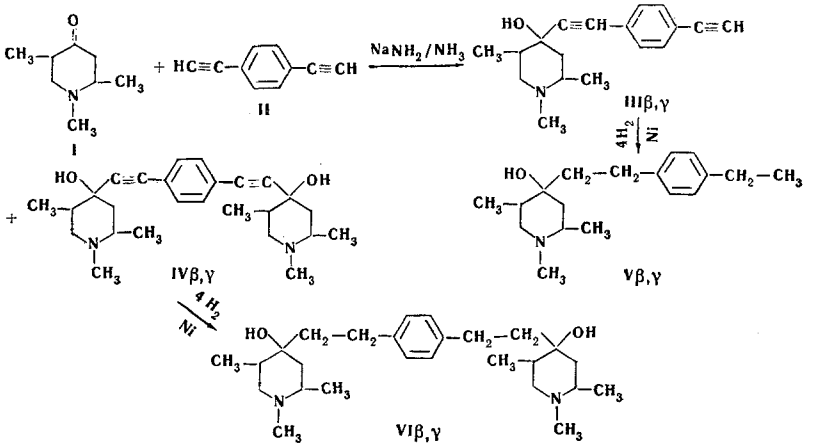

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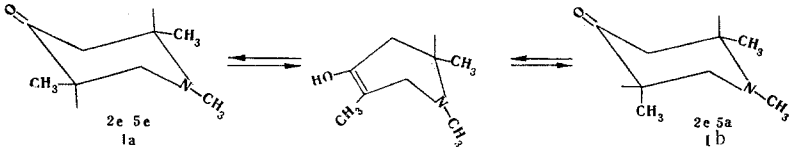
TABLE 1. Data of the IR and NMR Spectra of Stereoisomers IIIβ, γ and IVβ, γ*

Isomers		Vibrational frequencies (ν, cm^{-1}) and chemical shifts (τ, ppm)								
		O–H	≡C–H	C≡C	C–O	1,4-substitution	N–CH_3	3-H	6-H	2-and5-H
IIIβ	ν	3598	3230	2110	1030	828				
	τ	6,05	6,89			2,75	7,83	8,25—8,40	7,30—7,45	8,95—9,15
IIIγ	ν	3601	3245	2105	995	830				
	τ	7,05	6,93			2,60	7,80	8,25—8,35	7,35—7,45	8,95—9,05
IVβ	ν	3587			1031	842				
IVγ	ν	3589			1000	838				

*The IR spectra of alcohols IIIβ and IIIγ were obtained in CCl_4, while those of glycoles IVβ and IVγ were obtained in $CHCl_3$ (UR-10), c 0.01 M; the NMR spectra of alcohols IIIβ and IIIγ were obtained in $CHCl_3$ (JNM-3H, 100 MHz, hexamethyldisiloxane standard, c 0.1 M).

It is well known [9-13] that piperidone I enters into the majority of reactions at the carbonyl group in both of its stereoisomeric forms [trans (Ia) and cis (Ib)], which are in tautomeric equilibrium with the enol form:

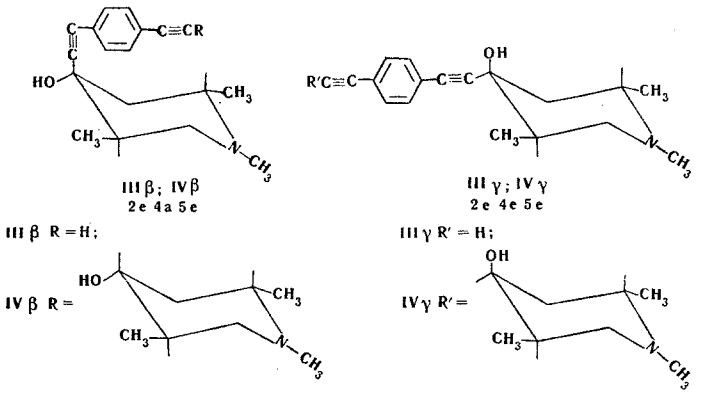


This equilibrium is markedly shifted to favor the trans isomer Ia with diequatorial methyl groups (2e5e conformation) [10-13]. Proceeding from these data, one can assume that the geometrical isomers of diacetylenic alcohol IIIβ and IIIγ and glycol IVβ, IVγ relate to derivatives of trans-piperidone Ia. Since they have the same trans-diequatorial conformation of the methyl groups, isomers IIIβ and IIIγ and IVβ and IVγ should be epimers with respect to C_4 of the piperidine ring and should differ only with respect to the spatial orientation of the hydroxyl and p-diethynylphenyl groups.

The stereoisomeric mixtures were separated into the individual isomers, and the approximate ratio of epimers was established by means of preparative adsorption chromatography with columns filled with aluminum oxide. In the process, it was found that chloroform elution occurs considerably more readily for IIIγ and IVγ than for their epimers, which have a high displacement volume. The R_f values were determined by chromatography of the individual isomers (IIIβ, IIIγ and IVβ, IVγ) in a loose, thin layer of aluminum oxide in a benzene–n–heptane–methanol(5 : 2 : 1) system: IIIγ 0.81, IIIβ 0.60, IVγ 0.45, and IVβ 0.30. It is well known [13-16] that geometrical isomers with an equatorial orientation of the polar groups are adsorbed more strongly than their axial epimers during adsorption chromatography. Consequently, isomers IIIγ and IVγ (which have larger R_f values have axial hydroxyl groups, while isomers IIIβ and IVβ (which have lower R_f values) have equatorial hydroxyl groups; this makes it possible to conclude that the C_5 p-diethynylphenyl and methyl groups of the piperidone rings of IIIγ and IVγ have a trans orientation, and that these substituents have the cis orientation in IIIβ and IVβ. Considering that piperidone I enters into nucleophilic addition at the carbonyl group primarily in the trans from (2e5e) [10-13], the chromatographic data and the principles of conformational analysis make it possible to conclude that IIIγ and IVγ have primarily the 2e4e5e conformation and that IIIβ and IVβ have primarily the 2e4e5e conformation with an equatorial hydroxyl group:

TABLE 2. Unsaturated Piperidols and Their Catalytic Hydrogenation Products

Compound	Mp, °C	R_f	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
IIIβ	135—136	0,60	$C_{18}H_{21}NO$	80,9	7,8	5,1	—	80,8	7,9	5,2	—	70
Hydrochloride of IIIβ	171 (dec.)	—	$C_{18}H_{22}NOCl$	71,3	7,2	4,5	11,5	71,1	7,2	4,6	11,6	
IIIγ	126—127	0,81	$C_{18}H_{21}NO$	80,7	7,8	5,1	—	80,8	7,9	5,2	—	28
Hydrochloride of IIIγ	159—160	—	$C_{18}H_{22}NOCl$	71,3	7,3	4,7	11,4	71,1	7,2	4,6	11,6	
IVβ	212 (dec)	0,30	$C_{26}H_{36}N_2O_2$	76,6	8,9	6,7	—	76,4	8,8	6,8	—	69
Dihydrochloride of IVβ	265—266	—	$C_{26}H_{38}N_2O_2Cl_2$	65,1	8,0	6,0	14,6	64,8	7,9	5,8	14,7	
IVγ	163 (dec)	0,45	$C_{26}H_{36}N_2O_2$	76,2	8,7	6,9	—	76,4	8,8	6,8	—	29
Dihydrochloride of IVγ	245 (dec)	—	$C_{26}H_{38}N_2O_2Cl_2$	64,7	7,8	5,7	14,6	64,8	7,9	5,8	14,7	
Vβ	101—102	0,78	$C_{18}H_{29}NO$	78,6	10,9	5,1	—	78,4	10,6	5,0	—	90
Vγ	83—84	0,93	$C_{18}H_{29}NO$	78,0	10,5	5,1	—	78,4	10,6	5,0	—	86
VIβ	184 (dec)	0,50	$C_{26}H_{44}N_2O_2$	75,4	10,5	6,8	—	74,9	10,6	6,7	—	89
VIγ	149 (dec)	0,66	$C_{26}H_{44}N_2O_2$	75,3	10,3	6,4	—	74,9	10,6	6,7	—	85



The IR spectra of the stereoisomeric alcohols and glycols (in KBr pellets and in dilute solutions) and the NMR spectra of isomers IIIβ and IIIγ (Table 1) were obtained to confirm the conclusions regarding the three-dimensional structure of the diacetylenic piperidols. The IR spectra of the isomers of glycols IVβ IVγ do not contain $-C \equiv C-$ absorption bands at 2260-2190 cm^{-1}; this is probably explained by the symmetry of the glycol molecule.

It was previously established [17-22] in the case of related cyclic compounds that an ethynyl group ($C \equiv C-H$) in the equatorial position has a large C–H frequency and that a hydroxyl group in the axial position has a large O–H frequency; the C–O frequency for isomers with an equatorial hydroxyl group occupies the 1020-1070 cm^{-1} region, while frequencies from 950-1010 cm^{-1} correspond to axial epimers. In the NMR spectrum, the greater acidic character of the proton causes a large shift in the resonance signal to the weak-field region. It is also well known that an equatorial hydroxyl group has a more acidic proton than an axial hydroxyl group. Consequently, on the basis of the IR and NMR data and in accordance with the literature data it can be concluded that the hydroxyl group in molecules of IIIβ and IVβ is in the equatorial position, while the p-diethynylphenyl group is in the axial position; in molecules of IIIγ and IVγ, on the the other hand, the hydroxyl group is in the axial position, while the p-diethynylphenyl group is in the equatorial position. In addition, the presence of two doublets at 9 ppm in the NMR spectra of IIIβ and IIIγ because of interaction of the methyl group protons with the C_2 and C_5 protons (the spin-spin splitting constant in both cases is found from 6 to 8 Hz) is evidence that the stereoisomers obtained are trans-piperidone derivatives.

Thus the data of adsorption chromatography and IR and NMR spectra make it possible to conclude that isomers IIIβ and IVβ, is formed by axial entry of the p-diethynylphenyl group into the cis position with respect to the C_5 methyl group of the piperidine ring (predominant 2e4a5e conformation), predominate in the stereoisomeric mixture of piperidole.

The IIIβ, IIIγ, IVβ, and IVγ isomers obtained were catalytically hydrogenated in the presence of Raney nickel to give the corresponding saturated compounds (Vβ, γ and VIβ, γ) (Table 2).

EXPERIMENTAL

1,2,5-Trimethyl-4-[β-(p-diethynylphenyl)]-4-piperidol (III) and β, β'-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-p-diethynylbenzene (IV). Liquid ammonia (250 ml) was added to a 500-ml three-necked equipped with a stirrer and a dropping funnel, the stirrer was switched on, and 0.05 g of thoroughly ground ferric nitrate (hydrated) was added. Sodium metal [1.63 g (0.71 g-atom)] was then added in the course of 10 min, the mixture was stirred for 1 h, and a solution of 9.0 g (0.071 mole) of II in 20 ml of dry ether was added dropwise. The resulting mixture was stirred for another 1 h. A solution of 10.02 g (0.071 mole) of I in 20 ml of dry ether was then added, and the reaction was stirred for 4 h and decomposed by the addition of 3.8 g (0.071 mole) of ammonium chloride. The reaction product was allowed to stand overnight under a layer of ether (200 ml) to evaporate the ammonia. The next day the precipitate of sodium chloride was filtered and and dissolved in water, and the aqueous solution was extracted with ether (five 50-ml portions). The combined ether extracts and the ether layer were dried with potassium carbonate. The ether was removed, the unchanged starting materials were removed by vacuum distillation [60-80 deg (3 mm)], and the solid residue

was crystallized from benzene (200 ml) to give 3.43 g (18%) of a mixture of isomers of the glycol (IVβ, γ); after filtration, the mother liquor was concentrated to 50 ml to give 13.56 g (71%) of a stereoisomeric mixture of alcohols (IIIβ, γ).

Chromatographic Separation of the Stereoisomeric Mixtures of Alcohols (IIIβ, γ) and Glycols (IVβ, γ). A. The Stereoisomeric mixture of alcohols (IIIβ, γ) (13.56 g) was dissolved in 250 ml of chloroform and chromatographed with a column (170 cm long and 3 cm in diameter) containing 1300 g of activity II aluminum oxide. The elution solvent was throughly dried chloroform. Eluate samples (20 ml) were selected, and the separation was monitored by thin-layer chromatography on aluminum oxide. The separation yielded 3.8 g (28% based on the mixture of IIIβ and γ) of isomer IIIγ with mp 126-127 deg (from n-heptane) and R_f 0.81 [in a benzene–n-heptane–methanol (5 : 2 : 1) system; the R_f values in all cases were determined in this solvent system]. The hydrochloride of IIIγ had mp 159-160 deg (from alcohol). High-melting isomer IIIβ [9.57 g (70% based on a mixture of IIIβ and IIIγ)] had mp 135-136 deg (from benzene) and R_f 0.60. The hydrochloride of IIIβ had mp 171 deg (dec., from alcohol).

B. The stereoisomeric mixture (3.43 g) of glycols IVβ and IVγ was similarly chromatographed with a column (120 cm long and 1.8 cm in diameter) containing 300 g of activity II aluminum oxide to give 1.01 g (29% based on a mixture of IVβ and IVγ) of isomer IVγ with mp 163 deg (dec., from benzene) and R_f 0.45. The dihydrochloride of IVγ had mp 245 deg (dec., from acetone). The high-melting isomer [2.37 g (69% based on a mixture of IVβ and IVγ)] had mp 212 deg (dec., from benzene) and R_f 0.30. The dihydrochloride of IVβ had mp 265 deg (dec., from acetone).

The yields, constants, and analytical data for the diacetylenic piperidols (IIIβ, γ and IVβ, γ) are presented in Table 2.

Catalytic Hydrogenation of Diacetylenic Piperidols IIIβ, IIIγ, IVβ, and IVγ. The diacetylenic piperidols (0.005 mole) were hydrogenated in the presence of Raney nickel (0.3 g) and 100 ml of ethanol at room temperature and normal pressure. After absorption of the volume of hydrogen calculated for two triple bonds, the catalyst was filtered, the ethanol was removed by distillation, and the solid residue of Vβ and Vγ was recrystallized from petroleum ether (40-70 deg fraction), while VIβ and VIγ were recrystallized from benzene. The yields, constants, and analytical data for the hydrogenation products are presented in Table 2.

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