SYNTHESIS OF DITERTIARY PHENYLENETETRAACETYLENIC GLYCOLS OF THE PIPERIDINE SERIES

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Stereoisomeric phenylenetetraacetylenic glycols of the piperidine series were synthesized by means of Glaser oxidative dimerization and the Chodkiewicz–Kadio condensation. The corresponding saturated piperidols were obtained by catalytic hydrogenation of these products on Raney nickel.

We previously described the syntheses of diacetylenic glycols of the heterocyclic series [1-3] which have high biological activity. It was of interest to work out methods for the synthesis of phenylenetetraacetylenic glycols of the piperidine series for a further investigation of the effect of the structure of the latter on the biological activity.

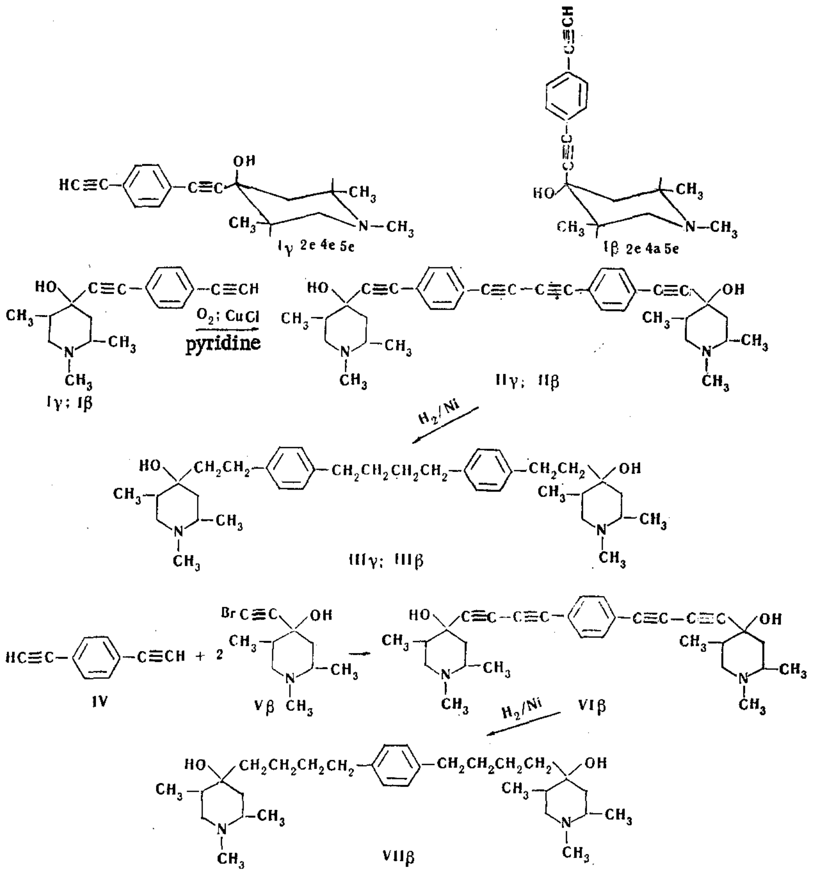

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TABLE 1. Physical Constants, Yields, and Analytical Data for the Synthesized Compounds

Compound	mp	R_f*	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
IIγ	204—205	0,56	$C_{36}H_{40}N_2O_2$	81,0	7,3	5,44	—	81,2	7,6	5,3	—	96
Dihydrochloride IIγ	212 (decomp)		$C_{36}H_{40}N_2O_2 \cdot 2HCl$	71,0	6,6	4,8	11,6	71,4	7,0	4,6	11,7	
IIβ	213—214	0,38	$C_{36}H_{40}N_2O_2$	81,5	7,9	5,1	—	81,9	7,6	5,3	—	93
Dihydrochloride IIβ	260 (decomp)		$C_{36}H_{40}N_2O_2 \cdot 2HCl$	71,1	6,8	4,7	11,6	71,4	7,0	4,6	11,7	
VIβ	201 (decomp)	0,44	$C_{30}H_{36}N_2O_2$	79,3	7,5	6,4	—	78,9	7,9	6,1	—	82
Dihydrochloride VIβ	233 (decomp)		$C_{30}H_{36}N_2O_2 \cdot 2HCl$	68,4	7,3	5,0	13,2	68,0	7,2	5,3	13,4	
IIIγ	132—133	0,70	$C_{36}H_{56}N_2O_2$	78,6	10,4	4,9	—	78,8	10,3	5,1	—	84
IIIβ	159 (decomp)	0,51	$C_{36}H_{56}N_2O_2$	79,1	10,3	5,5	—	78,8	10,3	5,1	—	92
VIIβ	161—162	0,52	$C_{30}H_{52}N_2O_2$	75,9	11,3	5,8	—	76,2	11,1	5,9	—	90

*Activity II Al_2O_3 with benzene–n-heptane–methanol (5 : 2 : 1).

The γ and β isomers of 1,4-bis[p-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)phenylethynyl]1,3-butadiyne (II) were synthesized by the Glaser oxidative dimerization [4] of the individual γ and β isomers of 1-[(1,2,5-trimethyl-4-hydroxy-4-piperidyl)ethynyl]-4-ethynylbenzene (I).

We previously obtained the starting Iγ and Iβ by the condensation of 1,2,5-trimethyl-4-piperidone with p-divinylbenzene (IV) in liquid ammonia in the presence of sodium amide. The three-dimensional structures of these compounds were established by various methods [5].

The Chodkiewicz–Kadio reaction [6] was used to synthesize the tetraacetylenic glycol, in which two conjugated diacetylenic systems are isolated from one another by one phenylene group. The β isomer of 1,4-bis[4-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-1-buta-1,3-diyinyl]benzene (VI) was obtained by the reaction of p-divinylbenzene (IV) with the β isomer of 1,2,5-trimethyl-4-(bromoethynyl)-4-piperidol (V). The absorption band characteristic for $\equiv C-H$ is absent in the IR spectra of IIγ, IIβ, and VIβ, and bands which are characteristic for 1,4-disubstituted aromatic systems (840 cm^{-1}) and associated OH groups (3400 cm^{-1}) appear. Because of the symmetry of the molecule, the $-C\equiv C-$ absorption bands do not appear.

The synthesized IIγ, IIβ, and VIβ were subjected to catalytic hydrogenation in the presence of Raney nickel to prove their structures. The corresponding saturated compounds (IIIγ, IIIβ, and VIIβ) were obtained as a result. The amount of hydrogen absorbed during the hydrogenation was in agreement with the calculated value and proved the presence of four acetylenic bonds.

EXPERIMENTAL

1,4-Bis[p-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)phenylethynyl]-1,3-butadiyne (II). A mixture of 5.35 g (0.02 mole) of the γ isomer of I and 0.3 g of CuCl in 30 ml of pyridine was shaken in an oxygen atmosphere at an initial temperature of 20°. The reaction proceeded smoothly with slight spontaneous heating and without additional cooling. The theoretical amount of oxygen was absorbed after 30 min. The complex was decomposed with water, and the precipitate was filtered, washed on the filter with water, concentrated ammonium hydroxide, and water until cupric ions were absent in the wash waters (absence of a blue coloration). Drying and recrystallization from ethyl acetate yielded 5.10 g (96%) of the γ isomer of II.

The β isomer of I was similarly oxidatively dimerized. The yields, constants, and analytical results for IIγ, IIβ, and their dihydrochlorides are presented in Table 1.

1,4-Bis[4-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-1-buta-1,3-diynyl]benzene (VI). A total of 0.04 g of CuCl, 0.05 g of hydroxylamine hydrochloride, and 18 ml of n-butylamine in 30 ml of methanol were added to a solution of 1.9 g (0.015 mole) of IV [7] in 15 ml of methanol. A solution of 7.4 g (0.03 mole) of the β-isomer of V [8] in 100 ml of methanol was then added slowly dropwise with vigorous stirring under argon while maintaining the temperature of the reaction mixture at 18-20°.

Several portions of hydroxylamine hydrochloride (2.0 g in all) were added to reduce the oxidized copper salt (appearance of a blue coloration in the reaction mixture). After adding Vβ, the mixture was stirred for 4 h at 20° and allowed to stand overnight. The precipitated crystals were filtered, and the mother liquor was diluted with water and extracted repeatedly with ether. The ether extracts were dried over $MgSO_4$ and concentrated. The material thus obtained was recrystallized from ethanol to give 5.69 g (82%) of the β isomer of VI. The constants and analytical data for VIβ and its dihydrochloride are presented in Table 1.

1,4-Bis{p-[2-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)ethylphenyl]}butane (IIIγ and IIIβ) and 1,4-Bis-[4-(1,2,5-trimethyl-4-hydroxy-4-piperidyl)butyl]benzene (VIIβ). Compounds IIγ, IIβ, or VIβ (0.0035 mole) were hydrogenated in the presence of a Raney nickel catalyst (0.3 g) in 100 ml of ethanol at room temperature and normal pressure. After the calculated volume of hydrogen (for four triple bonds) had been absorbed, the ethanol was removed, and the residue was recrystallized from benzene. The yields, constants, and analytical data for IIIγ, IIIβ, and VIIβ, are presented in Table 1.

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