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SYNTHESIS OF OPTICALLY ACTIVE 1,2,5-TRIMETHYL-4-ETHYNYL-4-PIPERIDOLS AND THE CORRESPONDING DIACETYLENIC GLYCOLS

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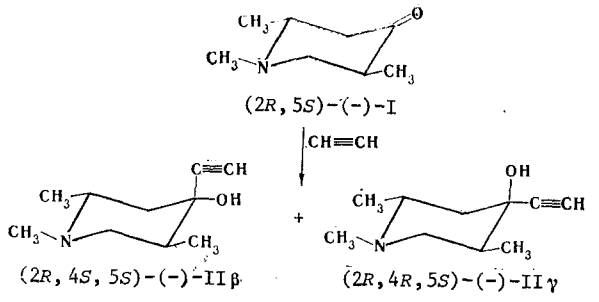
The following optically active enantiomeric pairs were synthesized by the Favorskii reaction from (+)-(2S,5R)- and (−)-(2R,5S)-trans-1,2,5-trimethyl-4-piperidones: (+)-(2S,4R,5R)- and (−)-(2R,4S,5S)-trans-1,2,5-trimethyl-4-ethynyl-4-piperidol and (+)-(2S,4S,5R)- and (−)-(2R,4R,5S)-trans-1,2,5-trimethyl-4-ethynyl-4-piperidol. Optically active 1,4-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)buta-1,3-diynes were obtained by Glaser oxidative dimerization of the enantiomeric pairs of ethynylpiperidols. The antagonistic action of the dihydrochlorides of (+)-(2S,4R,5R)- and (−)-1,4-bis[(2R,4S,5S)-1,2,5-trimethyl-4-hydroxy-4-piperidyl]buta-1,3-diyne on cell respiration was established from the results of biological tests on cultures of tobacco and chlorella cells.

It has been previously shown that racemic diacetylenic glycols of the piperidone series obtained from trans-1,2,5-trimethyl-4a-ethynyl-4-piperidol (isomer IIβ) and trans-1,2,5-trimethyl-4e-ethynyl-4-piperidol (isomer IIγ) stimulate plant growth and that 1,4-bis(trans-1,2,5-trimethyl-4a-hydroxy-4-piperidyl)buta-1,2-diyne (IIIγ) has greater activity than glycol IIIβ [1].



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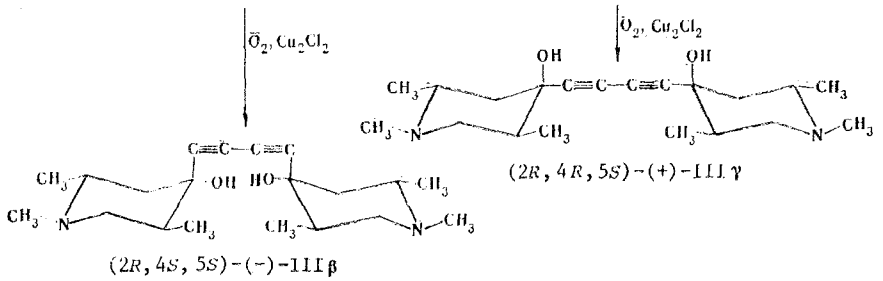

The aim of the present research was to ascertain a relationship between the biological activity and the chiral character of the asymmetric centers of diacetylenic glycols IIIβ, γ. Enantiomeric pairs of β and γ isomers of 1,2,5-trimethyl-4-ethynylpiperidol were obtained by the Favorskii reaction by reaction of (−)-(2R,5S)-trans-1,2,5-trimethyl-4-piperidone with acetylene in the presence of powdered potassium hydroxide in absolute ether. Two diastereomers, viz., (−)-trans-1,2,5-trimethyl-4a-ethynyl-4-piperidol [(−)-IIβ] and (−)-trans-1,2,5-trimethyl-4e-ethynyl-4-piperidol [(−)-IIγ], in a ratio of 2.4:1 were isolated in 54% overall yield. Similarly, (+)-IIβ and (+)-IIγ diastereomers in a ratio of 2.2:1 were isolated in 75% overall yield in the reaction with (+)-(2S,5R)-trans-1,2,5-trimethyl-4-piperidone.

The properties of the (+)- and (−)-IIβ and (+)- and (−)-IIγ pairs of enantiomers of 1,2,5-trimethyl-4-ethynyl-4-piperidol are presented in Table 1. We found that the melting points of mixed samples of enantiomers (+)- and (−)-IIβ and (+)- and (−)-IIγ are in agreement with the literature data for the melting points of the racemates of IIβ and IIγ [2, 3]. The optical rotatory dispersion (ORD) curves of the enantiomeric pairs of ethynylpiperidols IIβ and IIγ are presented in Fig. 1. The (+)-IIβ and (−)-IIβ enantiomers are characterized by ORD curves that have antipodal character and virtually equal intensities, and this confirms their identical enantiomeric purity. A similar principle is also observed for the IIγ enantiomeric pair; however, this pair has higher molecular rotation values. Since the hydroxy group in the IIβ enantiomers is equatorially oriented but is axially oriented in the IIγ enantiomers, it may be assumed that the increase in the molecular rotation of the IIγ isomers may be associated with the greater contribution of the axial OH groups to rotation. We carried out additional studies to ascertain the generality of this assumption.

Chromatographically individual stereoisomers of each of the 4-ethynylpiperidols were subjected to Glaser oxidative dimerization [4]. In each case we obtained the antipodal forms of 1,4-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)buta-1,3-diyne in up to 96% yields. The IR and PMR spectra of the diacetylenic glycols obtained from the enantiomeric (+)- and (−)-trans-1,2,5-trimethyl-4-ethynyl-4-piperidols (IIβ) and ethynylpiperidols (+)- and (−)-IIγ were identical taken in pairs. The ORD curves of the (+) and (−) enantiomers of diacetylenic glycols IIIβ and starting (+)- and (−)-ethynylpiperidols IIβ were similar (Figs. 1 and 2). The trend of the ORD curves for the (+)- and (−)-IIIγ enantiomeric pair is just the opposite of the trend of the curves of the starting (−)- and (+)-ethynylpiperidols IIγ.

Biological tests of the dihydrochlorides of IIIβ and IIIγ on cultures of tobacco and chlorella cells showed that the (+) and (−) enantiomers of IIIβ have an antagonistic effect on the respiration of tobacco and chlorella cells. The (+)- and (−)-IIIγ enantiomers displayed identical positive biological activity.

EXPERIMENTAL

The IR spectra of mineral oil suspensions and CCl_4 solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in pyridine were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The optical rotatory dispersion (ORD) spectra of solutions in methanol were recorded with a Jasco J-20 spectropolarimeter. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionization energy of 50 eV and a temperature of 200°C.

(+)-(2S,4R,5R)-Trimethyl-4-ethynyl-4-piperidol [(+)-IIβ] and (+)-(2S,4S,5R)-1,2,5-Trimethyl-4-ethynyl-4-piperidol [(+)-IIγ]. A solution of 1.3 g (10 mmole) of (+)-trans-

TABLE 1. Properties of the β and γ Isomers of 1,2,5-Trimethyl-4-ethynyl-4-piperidols

Isomer	mp, °C	R_f[a]	$[\alpha]_D^{20}$, deg (c, methanol)	IR spectrum, cm^{-1}: CCl_4, saturated solution		mineral oil	PMR spectrum, ppm (J, Hz)			M^+
				C—H	C≡CH	C≡C	≡C—H	N—CH_3	2-CH_3; 5-CH_3	
(+)-IIβ	136—137[b] (236—237)[c]	0,2	(+)—15 (14,7)	3620	3320	2115	3,3 s	2,2 s	1,27 d (6); 1,05 d (6)	167
(—)-IIβ	137—138[b] (239—240)[c]	0,2	(—)—16,7 (16,7)	3620	3320	2115	3,3 s	2,2 s	1,26 d (6); 1,05 d (6)	167
(±)-IIβ	112—114[d]	0,2	—	3620	3320	2115	—	—	—	—
(+)-IIγ	147—149[e] (219—220)[c]	0,5	(+)—34 (14,1)	3625	3320	—	3,17 s	2,2 s	1,27 d (6); 1,05 d (6)	167
(—)-IIγ	146—148[f] (219—220)[c]	0,5	(—)—27 (21,5)	3620	3320	—	3,17 s	2,2 s	1,25 d (6); 1,05 d (6)	167
(±)-IIγ	177—178[g]	0,5	—	3615	3315	—	—	—	—	—

[a]Silufol and chloroform saturated with ammonia. [b]Crystallized from acetone. [c]Melting point of the dihydrochloride, from ethanol—ether. [d]The melting point of a mixed sample is presented; the racemate had mp 113-114°C [3]. [e]Crystallized from hexane—ether. [f]Crystallized from petroleum ether—ether. [g]The melting point of a mixed sample is presented; the racemate had mp 177-178°C [3].

1,2,5-trimethyl-4-piperidone (I) in 10 ml of absolute ether was added to potassium acetylide obtained by passing acetylene through a suspension of 1.3 g (23 mmole) of powdered potassium hydroxide in 60 ml of absolute ether at —5 to —10°C. Acetylene was passed through the reaction mixture for another 6 h, after which it was allowed to stand at room temperature for 20 h. It was then decomposed with water, and the ether layer was separated. The aqueous layer was saturated with KOH and extracted with ether (five 40-ml portions). The combined ether extracts were neutralized by bubbling carbon dioxide through them, after which they were dried with Na_2SO_4. The ether was removed to give 1.63 g of a partially crystallized substance, from which 0.3 g of the (+) isomer of IIβ was obtained after successive crystallization from ether and acetone. The residual 1.3 g of a mixture of IIβ, γ isomers was applied to a column packed with neutral Al_2O_3 and eluted with chloroform. The chromatographically homogeneous fractions were combined to give an additional 0.56 g of the (+) isomer of IIβ, as well as 0.39 g of the (+) isomer of 1,2,5-trimethyl-4-ethynyl-4-piperidol IIγ. The overall yield of (+)-IIβ and (+)-IIγ isomers was 75%. Found for the (+) of IIγ: C 71.1; H 10.1; N 8.9%. $C_{10}H_{17}NO$. Calculated: C 71.9; H 10.3; N 8.4%.

(—)-(2R,4S,5S)-1,2,5-Trimethyl-4-ethynyl-4-piperidol [(—)-IIβ] and (—)-(2R,4R,5S)-1,2,5-Trimethyl-4-ethynyl-4-piperidol [(—)-IIγ]. Similarly, 1.08 g of the (—) isomer of IIβ and 0.41 g of the (—) isomer of 1,2,5-trimethyl-4-ethynyl-4-piperidol IIγ were obtained from 2.4 g (17 mmole) of (—)-trans-1,2,5-trimethyl-4-piperidone (I). The overall yield was 54%.

(+)-1,4-Bis[(2S,4R,5R)-1,2,5-trimethyl-4-hydroxy-4-piperidyl]buta-1,3-diyne[(+)-IIIβ]. A flask equipped with a gas inlet tube was charged with 0.31 g (1.9 mmole) of (+)-ethynyl-piperidol IIβ, 0.02 g of cuprous chloride, and 15 ml of dry pyridine, and oxygen was then bubbled in with stirring at room temperature until the starting compound had vanished completely (according to chromatographic monitoring). The pyridine was removed by vacuum distillation, and the crystalline residue was washed with ammonium hydroxide (until the wash liquid was no longer blue) and water and dried to give 0.25 g (80%) of the (+) isomer of IIIβ with mp 219-220°C (dec., from acetone—methanol—ether). PMR spectrum: 0.88 (3H, d, J = 6 Hz, CH_3), 1.1 (3H, d, J = 6 Hz, CH_3), 2.0 (3H, s, N—CH_3), and 1.73-2.63 ppm (m). IR spectrum: 3560 cm^{-1} (OH). The dihydrochloride had mp 273-275°C (dec., from ethanol—ether).

(—)-1,4-Bis[(2R,4S,5S)-1,2,5-trimethyl-4-hydroxy-4-piperidyl]buta-1,3-diyne[(—)-IIIβ]. Similarly, 0.2 g (60%) of the (—) isomer of IIIβ, with mp 218-220°C (dec., from acetone—

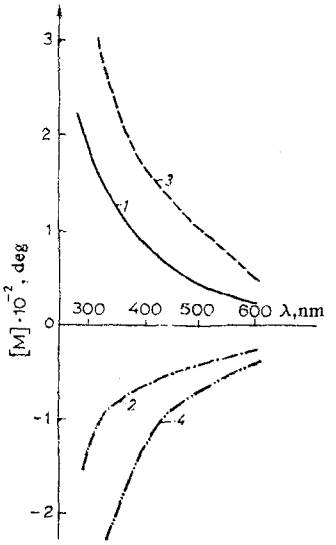

Fig. 1

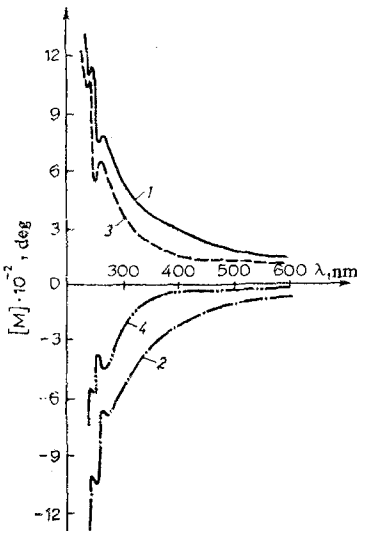

Fig. 2

Fig. 1. Optical rotatory dispersion of 1,2,5-trimethyl-4-ethynyl-4-piperidols: 1) (+)-(2S,4R,5R)-IIβ; 2) (−)-(2R,4S,5S)-IIβ; 3) (+)-(2S,4S,5R)-IIγ; 4) (−)-(2R,4R,5S)-IIγ.

Fig. 2. Optical rotatory dispersion of 1,4-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)buta-1,3,diynes: 1) (+)-(2S, 4R, 5R)-IIIβ; 2) (−)-(2R,4S,5S)-IIIβ; 3) (+)-(2R,4R,5S)-IIIγ; 4) (−)-(2S,4S, 5R)-IIIγ.

—methanol—ether), was obtained from 0.338 g (2 mmole) of (−)-ethynylpiperidol IIβ, 0.02 g of cuprous chloride, and 15 ml of dry pyridine. PMR spectrum: 0.85 (3H, d, J = 6 Hz, CH_3), 1.1 (3H, d, J = 6 Hz, CH_3), 2.0 (3H, s, N—CH_3), and 1.73-2.63 ppm (m). IR spectrum: 3565 cm^{-1} (OH). The dihydrochloride had mp 276-278°C (dec., from ethanol—ether).

(−)-1,4-Bis[(2S,4S,5R)-1,2,5-trimethyl-4-hydroxy-4-piperidyl]buta-1,3-diyne[(−)-IIIγ]. Similarly, 0.076 g (87%) of (−)-diyne IIIγ, with mp 231-232°C (dec., from pyridine), was obtained from 0.086 g (0.5 mmole) of ethynylpiperidol (+)-IIγ, 0.01 g of cuprous chloride, and 10 ml of dry pyridine. PMR spectrum: 0.95 (3H, J = 6 Hz, CH_3), 1.15 (3H, d, J = 6 Hz, CH_3), and 2.13 ppm (3H, s, N—CH_3). IR spectrum: 3100-3200 cm^{-1} (OH). The dihydrochloride had mp 274-275°C (dec., from ethanol—ether).

(+)-1,4-Bis[(2R,4R,5S)-1,2,5-trimethyl-4-hydroxy-4-piperidyl]buta-1,3-diyne[(+)-IIIγ]. Similarly, 0.1 g (96%) of (+)-diyne IIIγ, with mp 231-232°C (dec., from pyridine), was obtained from 0.104 g (0.6 mmole) of ethynylpiperidol (−)-IIγ, 0.01 g of cuprous chloride, and 10 ml of dry pyridine. PMR spectrum: 0.87 (3H, d, J = 6 Hz, CH_3), 1.08 (3H, d, J = 6 Hz, CH_3), and 2.07 ppm (3H, s, N—CH_3). IR spectrum: 3100-3200 cm^{-1} (OH). The dihydrochloride had mp 274-275°C (dec., from ethanol—ether).

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