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Stereoelective Conversion of Ethyl Pipecolinate into (±)-α- and (±)-β-Conhydrins

I. L. Lysenko, A. V. Bekish, and O. G. Kulinkovich

Belorussian State University, Minsk, 220050, Belarus

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Abstract–Reaction of ethyl *N*-benzhydrylpipecolinate with ethylmagnesium bromide in the presence of catalytic amount of titanium(IV) isopropoxide furnished in a high yield the corresponding hydroxypropyl-substituted piperidine that by treating with alcoholic alkali was quantitatively converted into 1-benzhydryl-2-propionylpiperidine. The reduction in the latter of carbonyl group with lithium aluminum hydride or sodium borohydride in methanol gave rise prevailingly to threo-aminoalcohol. With sodium borohydride in the presence of cerium chloride an erythro-aminoalcohol was the main product. Deprotection of the nitrogen atom from the benzhydryl group of the aminoalcohols obtained provided racemic α- and β-conhydrines.

We established recently that an ester moiety in the esters of N-benzyl-substituted amino acids cleanly underwent cyclopropanation when treated with ethylmagnesium bromide in the presence of catalytic amount of titanium(IV) isopropoxide [1]. The removal of one or two protection benzhydryl groups by catalytic hydrogenolysis occurred without opening of the three-membered ring thus providing a possibility of preparation of a wide range of 1-aminoalkyl-substituted cyclopropanols [1, 2]. Esposito and Taddei [3] also successfully applied these reagents for cyclopropanation of N-acyl-substituted α-amino acids. Taking into account the simplicity of preparation of 1-aminoalkylcyclopropanols the development of conditions for the opening of the three-membered ring would ensure their efficient application as intermediates in the synthesis of nitrogen-containing compounds of other classes.

We report here on conversion of cyclopropanation product obtained from ethyl *N*-benzhydrylpipecolinate (**I**) into erythro-2-(1-hydroxypropyl)piperidine (**IIa**), racemic form of (+)-α-conhydrin that was isolated from poison hemlock (Conium maculatum) [4]. This compound is a representative of biologically active alkaloids widely occurring in nature possessing in their structure 2-(1-hydroxyalkyl)piperidine fragment [5]. We also prepared the corresponding threo-isomer, (±)-β-conhydrin (**IIb**) [6, 7]. The key stages of synthesis of compounds **IIa, b** were cyclopropanation of ester **I**, isomerization of the arising alcohol **III** catalyzed by base [8] providing ethyl ketone **IV**, and reduction of the carbonyl group in the latter by complex metal hydrides. The building up of the hydroxypropyl moiety of conhydrines by reduction of the carbonyl group was previously performed by hydrogenation of 2-propionylpyridine on platinum catalyst [6, 9].

Compound **I** was prepared from ethyl pipecolinate by a standard procedure [10]. Its reaction with ethylmagnesium bromide in the presence of catalytic amount of titanium(IV) isopropoxide in contrast to the process with ethyl *N*-benzylpipecolinate [1] occurred cleanly in diethyl ether providing in good yield a crystalline cyclopropanol **III** that was easily separated from the reaction mixture. The three-membered carbocycle in compound **III** activated by the presence of a hydroxy group underwent heterolytic cleavage by potassium hydroxide in ethanol [8] affording 1-benzhydryl-2-propionylpiperidine (**IV**) in quantitative yield. The reduction of carbonyl group in ketone **IV** by lithium aluminum hydride in ethyl ether at room temperature occurred with low selectivity yielding virtually equimolar mixture of diastereomers of 1-benzhydryl-2-hydroxypropylpiperidines **Va, b** (see table, run no. 1).

The mixture of compound **Va, b** obtained was separated by fractional crystallization of their hydrochlorides, and thereafter the protective benzhydryl group was removed by hydrogenation on palladium hydroxide on carbon [1, 11]. Therewith compounds **Va** and **Vb** were converted into (±)-α-conhydrin **IIa** and (±)-β-conhydrin **IIb** respectively. Basing on these

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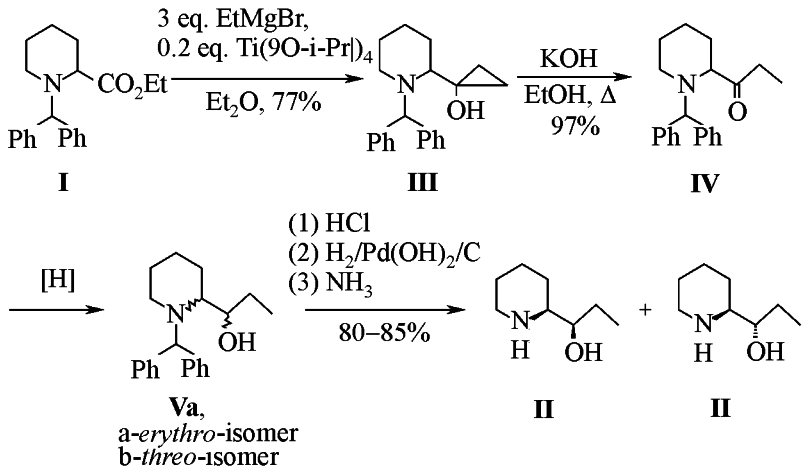

data to compound **Va** was ascribed *erythro* structure, and to compound **Vb** *threo* structure.

The signals of methine protons from the benzhydryl groups of compounds **IV, Va**, and **Vb** in the ^{1}H NMR spectra of reaction mixtures were easily distinguishable and possessed considerably different chemical shifts (see EXPERIMENTAL). Therefore this analysis was applied to evaluation of products composition in the reaction mixture after reduction of ketone **IV**. The results obtained showing the effect of the reducing reagent and solvent on the ratio of *erythro*-, **Va**, and *threo*-, **Vb**, aminoalcohols are listed in the table. The reduction of ketone **IV** with $LiAlH_4$, $LiAlH(OBu\text{-}t)_3$ and $LiAlH(OPh)_3$ in ethyl ether or benzene was of low stereoselectivity (runs nos. 1–4). In tetrahydrofuran the reduction of ketone **IV** was more stereoselective, and as the main product threo-aminoalcohol **Vb** was obtained (run no. 5). The latter was also formed in larger amount at reduction of ketone **IV** with $LiAlH_4$ in ethyl ether in the presence of $MgBr_2$ (runs nos. 6, 7). Similar stereoselectivity was attained by reducing ketone **IV** with sodium borohydride in methanol, but the yield of alcohols was low even at large excess of the reductant (run no. 8). Note that reduction of aminoketone **IV** with $NaBH_4$ in the presence of $MgBr_2$ afforded in low yield predominantly *erythro*-aminoalcohol **Va** (run no. 9). Replacing $CeCl_3$ for $MgBr_2$ significantly increased the yield of reduction product retaining prevailing formation of *erythro*-aminoalcohol **Va**; therewith at increased relative amount of metal halide the stereoselectivity of reaction grew (cf. runs no. 6, 7, and 10–13).

Within a framework of the developed stereochemical model of nucleophilic addition to a carbonyl group in α-dialkylaminoaldehydes and ketones [12, 13] the formation of *erythro*-isomer **Va** should by stereochemically controlled at the stage of reduction of a chelate complex formed by metal halide with the substrate molecule, whereas *threo*-isomer **Vb** should arise from nonchelated aminoketone **IV**. However the assumption of better chelate complex formation between compound **IV** and metal halides in methanol than in ethyl ether seems dubious. The reversion of hydride addition direction to the carbonyl group of aminoketone **IV** is caused presumably by complexing of magnesium or cerium halides with the solvent thus increasing the acidity of the latter and favoring more efficient protonation of the nitrogen atom in the substrate. The formation of an internal hydrogen bond with the carbonyl group of the protonated aminoketone **IV** would increase the reactivity of the carbonyl group in reduction with the borohydride [14]. Therewith the reduction stereochemistry is also controlled by the molecule conformation in the chelate form; however the chelating agent here is the proton.

Thus in the present study the building up of *erythro*- and *threo*-2-(1-hydroxypropyl)-piperidine moieties was efficiently performed by a succession of reactions of cyclopropanation of the ester function in ethyl *N*-benzhydrylpipecolinate, base-catalyzed isomerization of the arising 1-piperidyl-substituted cyclopropanol into the corresponding aminoketone, and stereoselective reduction in the latter of the carbonyl group by complex metal hydrides.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Bruker AC 200 (200 MHz) from solutions of compounds **I**–**IV** in deuterochloroform. IR spectra were recorded on spectrophotometer Specord 75IR from solutions in carbon tetrachloride or chloroform. Ethyl

Stereochemistry of reduction of benzhydryl-2-propionylpiperidine (**IV**) by complex metal hydrides

Run no.	Reducing agent	Molar ratio of reagents: (**IV**)-complex hydride-metal halide	Solvent	Ratio **Va : Vb**[a]	Yield[b] (V a+b), %
1	$LiAlH_4$	1/0.75/0	Et_2O	40 : 60	97
2	$LiAlH(OBu\text{-}t)_3$	1/2/0	Et_2O	55 : 45	96
3	$LiAlH(OPh)_3$	1/2/0	Et_2O	40 : 60	94
4	$LiAlH_4$	1/0.5/0	C_6H_6	50 : 50	98
5	$LiAlH_4$	1/0.75/0	THF	25 : 75	97
6	$LiAlH_4/MgBr_2$	1/0.5/1.5	Et_2O	25 : 75	94
7	$LiAlH_4/MgBr_2$	1/0.75/4	Et_2O	10 : 90	97
8	$NaBH_4$	1/3/0	MeOH	15 : 85	24
9	$NaBH_4/MgBr_2$	1/3/6	MeOH	75 : 25	26
10	$NaBH_4/CeCl_3$	1/1/1	MeOH	60 : 40	45
11	$NaBH_4/CeCl_3$	1/1.5/4	MeOH	70 : 30	55
12	$NaBH_4/CeCl_3$	1/3/6	MeOH	80 : 20	85

[a] Isomer ratio **Va** : **Vb** was estimated from integral intensity of methine protons of benzhydryl groups in the ^1H NMR spectra of reaction mixtures.

[b] Yield of the crude product according to ^1H NMR data.

ether and benzene were dried and distilled from sodium metal, tetrahydrofuran was distilled from lithium aluminum hydride. Ethyl *N*-benzhydrylpipecolinate (**I**) was prepared from ethyl pipecolinate and benzhydryl bromide [10].

Ethyl *N*-benzhydrylpipecolinate (I). IR spectrum (CCl_4): 1710 cm^{-1} ($\nu C{=}O$). ^1H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 1.20 t (3H, *J* 7 Hz), 1.20–2.06 m (6H), 2.52–2.68 m (1H), 2.84–3.02 m (1H), 3.43 t (1H, *J* 4 Hz) 4.10 q (2H, *J* 7 Hz) 5.10 s (1H), 7.10–7.40 m (8H), 7.42–7.56 (2H). Found, %: C 80.03; H 7.82. $C_{21}H_{25}NO_2$. Calculated, %: C 77.99; H 7.79.

1-(Benzhydryl-2-(1-hydroxycyclopropyl)piperidine (III). To a solution of 5.65 g (16.7 mmol) of ethyl 1-benzhydrylpipecolinate (**I**) and 0.95 ml (3.3 mmol) of titanium(IV) isopropoxide in 50 ml of ether was added within 1.5–2 h at room temperature while stirring a solution of 50 mmol of ethylmagnesium bromide in 30 ml of ether. The stirring was continued for 3 h, the reaction mixture was cooled to 0°C and treated with 40 ml of 2 N hydrochloric acid. The mixture was stirred for 2 h, and the formed precipitate of compound **II** hydrochloride was filtered off, washed with 2 N hydrochloric acid, then with water and ether. Then the precipitate was treated with 50 ml of 20% aqueous ammonia and 70 ml of dichloromethane. The organic layer was separated and dried with sodium sulfate. The solvent was distilled off, the residue was recrystallized from 95% ethanol. Yield of compound **II** 4.0 g (77%), mp 109–110°C. IR spectrum ($CHCl_3$): 3490 cm^{-1} ($\nu_{O\text{-}H}$). ^1H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 0.32–0.48 m (1H), 0.70–0.88 m (2H), 0.94–1.06 m (2H), 1.06–1.24 m (1H), 1.40–2.02 m (6H), 2.22 d.d (1H, *J* 8, 4 Hz), 2.82–2.98 m (1H), 3.06 br.s (1H), 5.98 s (1H), 7.08–7.44 m (10H). Found, %: C 81.94; H 8.21. $C_{21}H_{25}NO$. Calculated, %: C 82.04; H 8.20.

1-Benzhydryl-2-propionylpiperidine (IV). A solution of 3.7 g (12 mmol) of compound **III** and 1.8 g of potassium hydroxide in 30 ml of ethanol was boiled for 15 min. On removing the solvent under reduced pressure to the residue was added 50 ml of water, the reaction product was extracted into dichloromethane (2 × 25 ml), and the extract was dried with sodium sulfate. The solvent was distilled off in a vacuum, the residue was dissolved in benzene, and the solution was passed through 1.5 g of silica gel. On removing the solvent we obtained 3.6 g (97%) of ketone **IV**, mp 67.5–68°C (from petroleum ether). IR spectrum (CCl_4): 1705 cm^{-1} ($\nu_{C=O}$). ^1H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 0.96 t (3H, *J* 7 Hz), 1.34–1.66 m (4H), 1.68–1.88 m (2H), 2.24–2.44 m

(3H), 2.96 d.d.d (1H, *J* 12, 9, 3.5 Hz), 3.30 t (1H, *J* 5 Hz), 4.98 s (1H), 7.12–7.36 m (8H), 7.42–7.54 m (2H). Found, %: C 82.07; H 8.23. $C_{21}H_{25}NO$. Calculated, %: C 82.00; H 8.18.

***erythro*-1-Benzhydryl-2-hydroxypropylpiperidine (Va).** In 30 ml of methanol at heating was dissolved 1.5 g (4.9 mmol) of ketone **IV** and 11.0 g (29.4 mmol) of cerium chloride heptahydrate. The mixture was cooled to –20°C and while stirring 0.56 g (14.7 mmol) of sodium borohydride was added by portions within 20–30 min. After the mixture was stirred for 1 h it was slowly warmed to room temperature, stirred for 5 h and boiled for 2 h. The solvent was distilled off, to the residue 30 ml of 2 N hydrochloric acid was added, and the reaction product was extracted into dichloromethane (2 × 15 ml). The organic solution was washed with 10 ml of 20% aqueous ammonia, dried with sodium sulfate, and the solvent was distilled off in a vacuum. The residue was subjected to chromatography on a column charged with 10 g of silica gel (eluent benzene). We obtained 1.28 g (85%) of a mixture containing diastereomeric alcohols **Va** and **Vb** in 4 : 1 ratio (according to ^{1}H NMR spectrum). A single fractional crystallization of the mixture of alcohols **Va, b** hydrochlorides from chloroform with ether as additive afforded a mixture with **Va** to **Vb** ratio of 7 : 1. IR spectrum (CCl_4): 3320 cm^{-1} (ν_{O-H}). ^{1}H NMR spectrum ($CDCl_3$, TMS) δ, ppm: 1.00 t (3H, *J* 7.5 Hz), 1.10–1.80 m (8H), 2.00–2.20 m (1H), 2.34–2.64 m (2H), 2.80–2.96 m (1H), 4.16–4.28 m (1H), 5.52 s (1H), 7.04–7.50 m (10H). Found, %: C 81.60; H 8.68. $C_{21}H_{27}NO$. Calculated, %: C 81.51; H 8.79

***threo*-1-Benzhydryl-2-hydroxypropylpiperidine (Vb).** To a solution of 29.2 mmol of magnesium bromide in 10 ml of ether obtained from 0.71 g (29.2 mmol) of magnesium and 5,5 g (29.3 mmol) of 1,2-dibromoethane was added in one portion 0.14 g (3.68 mmol) of lithium aluminum hydride. After 5 min the mixture was cooled to –20°C and while stirring was added dropwise within 5–10 min 1.5 g (4.9 mmol) of ketone **IV** in 10 ml of ether. The mixture was warmed to room temperature within 30 min, and the solvent was removed under reduced pressure. To the residue was slowly added at 0°C 25 ml of 2 N hydrochloric acid, and the reaction product was extracted into dichloromethane (2 × 25 ml). The organic solution was washed with 10 ml of 20% aqueous ammonia and dried with sodium sulfate. Then the solvent was distilled off in a vacuum to afford 1.43 g (95%) of a mixture of **Va** and **Vb** alcohols in 1 : 9 ratio (according to ^{1}H NMR spectrum). After recrystallization of the alcohols mixture in hydrochloride form from chloroform containing 4–5% of ethyl ether we isolated 1.22 g (85%) of alcohol **Vb**. IR spectrum (CCl_4): 3320 cm^{-1} (ν_{O-H}). ^{1}H NMR spectrum ($CDCl_3$, TMS) δ, ppm: 0.90 t (3H, *J* 7 Hz), 0.96–1.36 m (3H), 1.40–1.90 m (5H), 2.54 d.d (1H, *J* 10, 5 Hz), 2.66–2.96 m (2H), 3.90 d.d.d (1H, *J* 11, 8, 2.5 Hz), 4.82 br.s (1H), 5.20 s (1H), 7.04– 7.34 m (6H), 7.34–7.54 m (4H). Found, %: C 81.45; H 8.82. $C_{21}H_{27}NO$. Calculated, %: C 81.51; H 8.79

***erythro*-2-(1-Hydroxypropyl)piperidine (IIa) [(±)-α-conhydrin].** A mixture of 1 g of aminoalcohol **Va** hydrochloride and 80 mg of 20% $Pd(OH)_2$ on carbon in 10 ml of methanol was stirred under hydrogen atmosphere at 1 at pressure. After the hydrogen absorption ceased the catalyst was filtered off, and the filtrate was evaporated. The residue was washed with anhydrous ether, then dissolved in 10 ml of anhydrous dichloromethane, and the solution was treated with gaseous ammonia. The precipitate was filtered off, the solvent was removed in a vacuum, and the residue was recrystallized. We obtained 0.35 g (85%) of (±)-α-conhydrin IIa, mp 98–99°C (from ether). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 0.96 t (3H, *J* 7.5 Hz), 1.20–1.90 m (8H), 2.44–2.76 m (2H), 3.02–3.30 m (3H), 3.36–3.50 m (1H). Published data [7, 9]: mp 98–100°C (from ether).

***threo*-2-(1-Hydroxypropyl)piperidine (IIb) [(±)-β-conhydrin]** was prepared by hydrogenation of threo-1-benzhydryl-2-hydroxypropylpiperidine (Vb) as described for compound **IIa**. Yield 88%. mp 86–88°C (from hexane). ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm: 1.00 t (3H, *J* 7.5 Hz).[(±)-α-conhydrin]. 1.08–1.92 m (8H), 2.28–2.46 m (1H), 2.48–2.68 m (1H), 3.04–3.18 m (1H), 3.22 t.d (1H, *J* 7.5, 2 Hz), 3.62 br.s (2H). Published data [6, 7]: mp 87–88°C (from hexane).

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