Synthesis and Absolute Configuration of 3-Ethyl and 3-*n*-Propylpyrrolidine

Giancarlo Bettoni, Carla Cellucci and Francesco Berardi

Istituto di Chimica Farmaceutica e Tossicologica dell'Università,
Via G. Amendola 173, 70126 Bari, Italy

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Optically active 3-ethyl and 3-*n*-propylpyrrolidine were prepared by two independent routes from their corresponding succinic acids and the absolute configurations were assigned. Maximum optical rotation was also established through evaluation of the degree of racemization of the products obtained *via* both synthetic routes.

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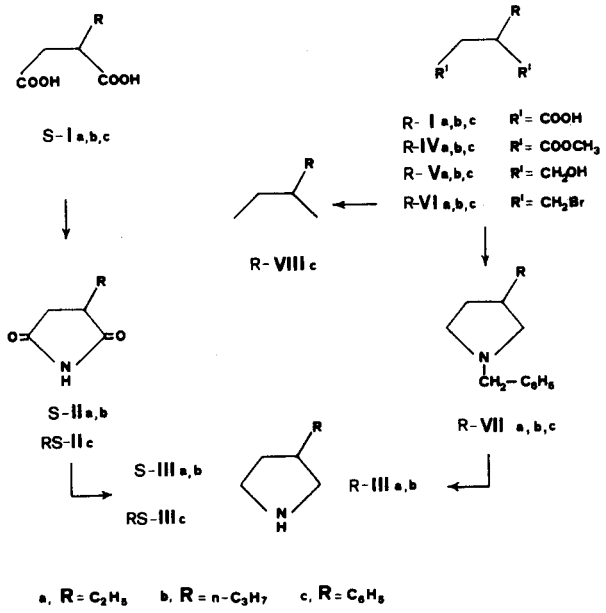
In continuation of our studies concerned with the relationships between the absolute configuration, conformation, the presence of chromophoric groups in open-chain (1) or in cyclic (2) amino compounds, and the shape of the CD curves, we now report the synthesis of 3-ethyl and 3-*n*-propylpyrrolidine. The absolute configurations for these compounds have been determined through chemical correlations with the corresponding succinic acids of known chirality (3).

According to the method reported (4), ethyl fumarate and the appropriate nitroalkane were reacted to give 2-ethyl and 2-*n*-propylsuccinic acid which were resolved by the fractional crystallization of their salts with D-(-)-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol. This latter compound was found to be a better resolving agent than strychnine, which has previously been used (5) for both acids. By melting the ammonium salts of *S*-(-)-Ia and *S*-(-)-Ib, we obtained the imides *S*-(+)-IIa and *S*-(+)-IIb, which gave *S*-(-)-IIIa and *S*-(-)-IIIb, respectively upon reduction with lithium aluminum hydride.

In a previous paper (6) we reported the synthesis and the absolute configuration of 3-phenylpyrrolidine; however we were not able to use this same chemical sequence for the synthesis of *R*-IIc, since *R*-(-)-2-phenylsuccinic acid gave the racemic imide IIc. This result agrees with that reported by other authors (7), who found that phenylsuccinic acid racemizes when heated at 150° for two hours in an alkaline medium. These authors attributed this behaviour to heat rather than to alkaline medium.

In order to evaluate if and to what degree racemization occurs during the imide cyclization reaction when the starting material bears an alkylic group at the chiral center, compounds IIIa and IIIb were prepared in optically active form, using the same preparative route used for the synthesis of 3-phenylpyrrolidine. Thus, we were able to establish the maximum optical rotation without resolving the racemic compounds.

The acids *R*-(+)-Ia and *R*-(+)-Ib having been recovered from the mother liquors of the fractional crystallizations, were converted into the corresponding



methyl esters *R*-(+)-IVa and *R*-(+)-IVb (8), which upon reduction with lithium aluminum hydride gave the diols *R*-(+)-Va and *R*-(+)-Vb (8). These latter compounds were first converted into the corresponding dibromides *R*-(-)-VIa and *R*-(-)-VIb (8), which were reacted with benzylamine to give R-(-)-VIIa and *R*-(-)-VIIb, respectively. The amines *R*-(+)-IIIa and *R*-(+)-IIIb were finally obtained by catalytic hydrogenation. This synthesis confirms the previously assigned chiralities and the optical rotation proves the reality of a loss of optical activity during the formation of imides IIa,b,c. This loss is probably due to the possibility that the intermediate carbanion might be stabilized by resonance as well as to the vigorous conditions used during the cyclization reaction. Total racemization occurs when a phenyl group is found at the chiral center, whereas in the case of alkyl substituted compounds, the loss of optical activity is incomplete.

During the course of the synthetic route which converts succinic acids into the corresponding *N*-benzyl derivatives, the loss of optical activity is found to be less than 10%.

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This finding is based firstly on the fact that the optical rotations of the *N*-benzyl derivative of 3-phenylpyrrolidine derived from the resolution of its racemate and of the *N*-benzyl-derivative obtained from optically pure 2-phenylsuccinic acid are in agreement, and secondly on the fact that *R*-(-)-2-phenyl-1,4-dibromobutane VIc gives *R*-(-)-VIIIc with an optical purity of 91% with respect to the reported maximum optical rotation (9).

Therefore, the *S* absolute configuration can be assigned to the levorotatory isomers of 3-ethyl and 3-*n*-propylpyrrolidine. The specific rotations of the optically pure amines are -19.5° and -19°, respectively.

EXPERIMENTAL

Microanalyses were conducted by Dr. A. Reho, Ist. Chimica Farmaceutica, Bari, with a Hewlett-Packard Model 185 Analyzer. The melting points, determined with a Tottoli apparatus, are not corrected. Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. Nmr spectra were recorded with a Varian HA 100 spectrometer in deuteriochloroform using TMS as internal standard; chemical shifts are expressed in τ.

S-(-)-2-Ethylsuccinic Acid (*S*-Ia).

Compound *RS*-Ia, prepared according to the method reported by Cloetzel (4), was resolved by fractional crystallization of its D-(-)-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol salt from ethanol. After four crystallizations *S*-Ia was obtained; $[\alpha]_D$ -24° (c = 3%, acetone) [lit. (5a) $[\alpha]_D$ +20.65°, (acetone) for the antipode].

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.49; H, 7.01.

S-(+)-2-Ethylsuccinimide (*S*-IIa).

The ammonium salt of *S*-Ia, obtained by repeated evaporation of the acid (4 g.) in a solution of ethanol (50 ml.) and ammonium hydroxide (32%, 10 ml.), was distilled under reduced pressure. A low melting solid (*S*-IIa) was obtained (2.5 g.); $[\alpha]_D$ +1.2° (c = 20%, methanol) [lit. (10) m.p. 77° for the racemic compound].

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.91; H, 7.02; N, 11.10.

S-(-)-3-Ethylpyrrolidine (*S*-IIIa) from *S*-IIa.

Compound *S*-IIa (2.5 g.) dissolved in dry tetrahydrofuran (20 ml.) was added to a suspension of lithium aluminum hydride (3 g.) in dry tetrahydrofuran. After refluxing 12 hours, the reaction was worked-up in the usual way. Compound *S*-IIIa was obtained (0.9 g.), b.p. 100° [lit. (11) b.p. 131°, d 0.8579]; $[\alpha]_D$ -2.5° (neat); nmr: 7.53 (s, 1H, NH), 9.10 (t, 3H, CH_3).

The picrate was crystallized from ethanol, m.p. 100° [lit. (11) m.p. 102° for the racemic compound].

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 43.91; H, 4.91; N, 17.07. Found: C, 43.58; H, 4.86; N, 16.82.

R-(+)-2-Ethyldimethylsuccinate (*R*-IVa).

Compound *R*-(+)-Ia (13 g.), obtained from the mother liquors of the racemic acid resolution ($[\alpha]_D$ +8.1°, c = 3%, acetone, optical purity 39%), was esterified with diazomethane. Compound *R*-IVa was obtained (15.3 g.), b.p. 95°/10 mm; $[\alpha]_D$ +5.3° (neat) [lit. (12) b.p. 91-94°/13 mm; $[\alpha]_D$ -14.89° (neat), d = 1.053 for the pure antipode]; nmr: 6.33 (s, 3H, OCH_3), 6.36 (s, 3H, OCH_3), 7.20-7.70 (m, 3H, CH,CH_2CH), 8.25-8.50 (m, 2H, CH_2CH_3), 9.07 (t, 3H, CH_3CH_2).

R-(+)-2-Ethyl-1,4-butanediol (*R*-Va).

Compound *R*-IVa (15 g.) was reacted with lithium aluminum hydride (12 g.) in dry ether with 2 hours of refluxing. Compound *R*-Va was obtained (10.5 g.), b.p. 116°/8 mm; $[\alpha]_D$ +7.7° (neat) [lit. (13) b.p. 129-131°/10 mm, d = 0.9825 for the racemic compound]; nmr: 5.30-5.60 (broad, 2H, 2OH), 6.20-6.70 (m, 4H, $2CH_2OH$), 8.25-8.90 (m, 5H, CH_2CH_3, $CHCH_2$), 9.07 (t, 3H, CH_3).

R-(-)-2-Ethyl-1,4-dibromobutane (*R*-VIa).

To a solution of *R*-Va (10.2 g.) in dry pyridine (10 ml.), phosphorus tribromide (10.2 ml.) was added stirring at 0°. After heating at 100° for one hour, the reaction mixture was treated with water (50 ml.) and the resulting suspension was extracted with petroleum ether. The organic layer was successively washed with 5% sodium hydroxide, concentrated sulfuric acid and water. After evaporation of the solvent and distillation of the residue, *R*-VIa was obtained (13.2 g.), b.p. 74°/6 mm; $[\alpha]_D$ -5.1° (neat) [lit. (14) b.p. 84°/12 mm, d = 1.6510 for the racemic compound]; nmr: 6.50-6.70 (m, 4H, $2CH_2Br$), 7.90-8.40 (m, 3H, $CHCH_2$), 8.45-8.70 (m, 2H, CH_2CH_3), 9.05 (t, 3H, CH_3).

R-(-)-*N*-Benzyl-3-ethylpyrrolidine (*R*-VIIa).

Compound *R*-VIa (13 g.) was dissolved in ethanol (50 ml.) and refluxed for 7 hours with benzyl amine (17.1 g., molar ratio of dibromide-amine 1:3). After cooling, concentrated hydrochloric acid (5 ml.) was added and the resulting solution was concentrated under vacuum. The residue was then dissolved in water and the aqueous solution was extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with ether. From the solvent, by distillation, *R*-VIIa was obtained (7.1 g.), b.p. 110°/6 mm; $[\alpha]_D$ -1.24° (neat), d = 0.9358; nmr: 2.70-2.90 (m, 5H, aromatic), 6.44 (s, 2H, benzylic CH_2), 7.20-8.20 (m, 6H), 8.50-8.80 (m, 2H), 9.12 (t, 3H, CH_3). The picrolonate was crystallized from ethanol, m.p. 138°.

Anal. Calcd. for $C_{23}H_{27}N_5O_5$: C, 60.92; H, 6.00; N, 15.44. Found: C, 61.24; H, 5.90; N, 15.53.

R-(+)-3-Ethylpyrrolidine (*R*-IIIa) from *R*-VIIa.

Compound *R*-VIIa (2 g.), dissolved in glacial acetic acid, was hydrogenated in a Gallenkamp glass apparatus in the presence of 10% palladium on charcoal under one atmosphere pressure. After 24 hours the absorption of hydrogen was complete. The solvent was evaporated and the residue dissolved in water, made alkaline with sodium hydroxide and extracted with ether. Compound *R*-IIIa was obtained (0.8 g.), b.p. 100°; $[\alpha]_D$ +7.5° (neat); the nmr spectrum of the base and physical constants of the picrate were identical with those of *S*-IIIa synthesized from *S*-IIa.

S-(-)-2-*n*-Propylsuccinic Acid (*S*-Ib).

Compound *RS*-Ib, prepared by the known method (4), was resolved by four crystallizations of its salt with D-(-)-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol in ethanol. Upon hydrolysis of the salt with 2*N* hydrochloric acid, *S*-Ib was obtained, m.p. 88°; $[\alpha]_D$ -23° (c = 2%, water) [lit. (5b) m.p. 94° $[\alpha]_D$ +22.5° (water) for the antipode].

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.52; H, 7.80.

S-(+)-2-*n*-Propylsuccinimide (*S*-IIb).

Compound *S*-Ib (8 g.) was reacted as described above for the preparation of *R*-IIa. In this manner *S*-IIb was obtained (6.5 g.), m.p. 55°; $[\alpha]_D$ +3° (c = 10%, methanol).

Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.88; H, 7.71; N, 10.03.

S-(-)-3-*n*-Propylpyrrolidine (*S*-IIIb) from *S*-IIb.

Compound *S*-IIb (5 g.) was reacted with lithium aluminum hydride (5.5 g.) in the usual way. Compound *S*-IIIb was obtained (2.1 g.), b.p. 90°/15 mm; $[\alpha]_D$ -7° (neat); nmr: 6.96 (s, 1H, NH), 8.95-9.20 (m, 3H, CH_3) [lit. (10) b.p. 158/746 mm, d = 0.8535]. The picrate had m.p. 101-102° [lit. (10) m.p. 101° for the racemic compound].

R-(-)-*N*-Benzyl-3-*n*-propylpyrrolidine (*R*-VIIb).

Compound *R*-VIb was prepared starting from *R*-(+)-Ib ($[\alpha]_D$ +16.5°, water, optical purity 73%) according to the method reported (8). Compound *R*-VIb had $[\alpha]_D$ -7° (neat) and was reacted as described above giving *R*-VIIb, b.p. 110°/2 mm; $[\alpha]_D$ -5.2° (neat); nmr: 2.64-2.94 (m, 5H, aromatic), 6.44 (s, 2H, benzylic CH_2), 7.10-8.20 (m, 7H), 8.50-8.90 (m, 4H) 9.00-9.20 (m, 3H, CH_3). The picrate was crystallized from ethanol, m.p. 138°.

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.84; H, 5.67; N, 13.22.

R-(+)-3-*n*-Propylpyrrolidine (*R*-IIIb) from *R*-VIIb.

The hydrogenation of *R*-VIIb (2 g.) gave *R*-IIIb (0.9 g.), b.p. 90°/15 mm; $[\alpha]_D$ +13.9° (neat). The nmr spectrum of the base and the physical constants of the picrate were identical with those of the isomer synthesized from *S*-IIb.

R-(-)-2-Phenylbutane (*R*-VIIIc).

Compound *R*-(-)-VIc (4.5 g.), prepared as previously described (6) and having $[\alpha]_D$ -36° (c = 2.5%, methanol, optical purity 70%) was refluxed with lithium aluminum hydride (1.35 g.) in dry ether for 10 hours. The reaction mixture was worked-up in the usual way and *R*-VIIIc was obtained (1.5 g.), b.p. 125°/200 mm; $[\alpha]_D$ -15.4° (neat) [lit. (8) $[\alpha]_D$ -24.3° (neat) for the optically pure compound]; nmr: 2.65-3.00 (m, 5H, aromatic), 7.46 (m, 1H, CH), 8.30-8.60 (m, 2H, CH_2), 8.78 (d, 3H, $CHCH_3$), 9.20 (t, 3H, CH_2CH_3).

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