

The Absolute Configuration of 3-Phenylpyrrolidine

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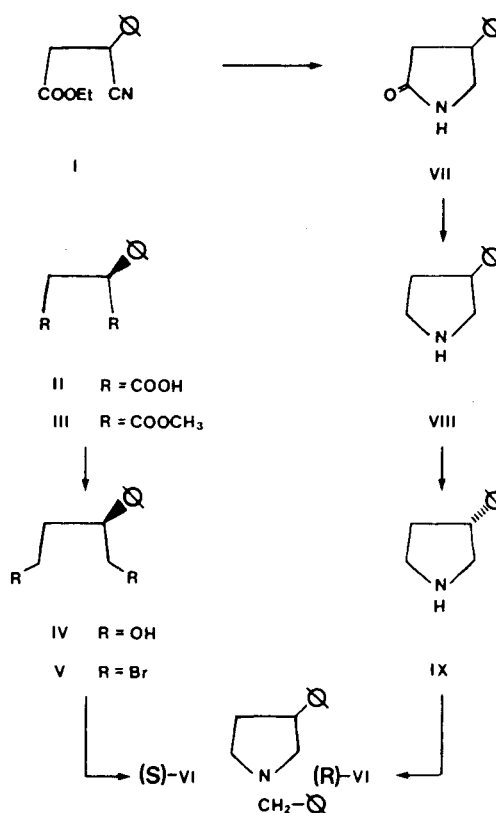
(+)-3-Phenylpyrrolidine and (+)-phenylsuccinic acid have been chemically correlated through (-)-*N*-benzyl-3-phenylpyrrolidine. All these compounds have an *S* absolute configuration.

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Some of our earlier investigations on stereochemistry (1) have led us to establish a general rule which permits the absolute configuration of amines containing an asymmetric carbon atom in the position α to the amine nitrogen to be deduced from the sign of the C.E. of the pyridine *N*-oxide derivatives. We also demonstrated the influence exerted by additional chromophore groups present in the amine on the sign and the magnitude of the C.E. The extension of these investigations to amines in which the nitrogen atom is incorporated in a ring structure requires a certain number of compounds for which both the optical purity and the absolute configuration determined by chemical methods are known.

Recently our group has established the optical properties of some piperidines and pyrrolidines substituted in positions 2 and 3 (2-6).

In the present paper we consider the absolute configuration of 3-phenylpyrrolidine. By fractional crystallization from ethanol of the brucine salt of *R,S*-phenylsuccinic acid we isolated the dextrorotatory isomer (II), to which the absolute configuration *S* has been assigned (7). On treatment with methyl iodide and calcium oxide this acid was converted into the corresponding liquid dimethyl ester (III). When the dimethyl ester is obtained from an acid that is not optically pure, a solid racemate separates out which is identical with that obtained from racemic phenylsuccinic acid. On reduction with lithium aluminum hydride, the ester (III) gave *S*-(+)-2-phenylbutane-1,4-diol (IV) which, by reaction with phosphorus tribromide in pyridine, was converted into the corresponding dibromide (V). The latter, by cyclization with benzylamine, yielded the *S*-(*-*)-*N*-benzyl-3-phenylpyrrolidine (VI) having the opposite optical rotation to that of the product obtained by treating with benzyl chloride the (*-*)-3-phenylpyrrolidine (IX) obtained by resolution of the racemic amine (VIII) with *D*-(*-*)-dibenzoyltartaric acid.



The racemic amine (VIII) was prepared by a lithium aluminum hydride reduction of the corresponding pyrrolidone (VII) obtained, in turn, by reductive cyclization of ethyl β -cyano- β -phenylpropionate (I) in the presence of Raney nickel. This series of transformations permits the absolute configuration *R* to be assigned to (*-*)-3-phenylpyrrolidine.

EXPERIMENTAL

The microanalyses were performed by Dr. R. De Leonardis of the Institute of Pharmaceutical Chemistry in Bari with the aid of a

Hewlett-Packard Model 185 CHN analyser. The melting points were determined with a Tottoli apparatus and have not been corrected. The rotatory powers were measured with a Hilger and Watts M 412 polarimeter and with a Roussel-Jouan electronic micropolarimeter. The nmr spectra were recorded with a Varian HA 100 spectrometer and with a Minimar 60 MHz in deuteriochloroform, using TMS as the internal standard; the chemical shifts are expressed in τ .

4-Phenyl-2-pyrrolidone (VII).

Compound I (8) (30 g.) was hydrogenated in an autoclave in the presence of Raney nickel (10 ml. of settled suspension) in absolute ethanol (300 ml.) containing 3-4% of ammonia, over 24 hours at 100 atmospheres and 100°. The catalyst was then filtered off and the solution was evaporated. Compound VII (23 g.) was obtained, and was purified by recrystallization from a benzene-n-hexane mixture, m.p. 70-72°.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.58; H, 7.06; N, 8.55.

R,S-3-Phenylpyrrolidine (VIII).

A solution of compound VII (15 g.) in ether (150 ml.) was added to a suspension of lithium aluminum hydride (4.3 g.) in ether (50 ml.). The mixture was boiled under reflux for 4 hours, the excess hydride was destroyed, the mixture was filtered, and the residue was washed with ether. Evaporation of the solvent and distillation of the residue (110°/1 mm Hg) gave compound VIII (12.2 g.); picrate, m.p. 155°.

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.07; H, 4.29; N, 14.89. Found: C, 50.95; H, 4.10; N, 15.10.

R(-)-3-Phenylpyrrolidine (IX).

Compound RS-VIII (21.3 g.) was converted into its salt with D(-)-dibenzoyltartaric acid (54 g.) in methanol. By recrystallization of the salt from methanol (about 10 recrystallizations), a fraction was obtained from which (by hydrolysis with carbonate, extraction with ether, and distillation) (-)-IX was obtained; $[\alpha]_D^{24}$ -24° (methanol; $c = 4.7\%$), -40° (pure substance; $d = 1.013$). From the crystallization mother liquors was similarly obtained (+)-IX; $[\alpha]_D^{27}$ + 27° (pure substance); nmr (on the R(-) compound): 2.81 (5H, s, aromatic), 7.93 (1H, s, NH), 6.64-7.36 and 7.70-8.40 (7H, m, aliphatic).

R(+)-N-Benzyl-3-phenylpyrrolidine [(VI) from (IX)].

A solution of benzyl chloride (1.93 ml.) in benzene (6 ml.) was added to a solution of R(-)-3-phenylpyrrolidine, $[\alpha]_D^{38}$ -38° (pure substance) (2.46 g.) and triethylamine (2.36 ml.) in anhydrous benzene (4 ml.). The mixture was boiled under reflux for 2 hours, cooled, and diluted with benzene; the organic phase was washed three times with water and 2N hydrochloric acid. The combined acidic solutions were then made alkaline with sodium hydroxide pellets and were extracted with ether. Evaporation of the ether yielded a residue which was purified by distillation through a bulb tube, (VI) (0.6 g.); $[\alpha]_D^{37}$ + 37.33° (methanol, $c = 4\%$) and was then transformed into the picrate with m.p. 172-173°.

Anal. Calcd. for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.35; H, 4.46; N, 12.03.

Hydrolysis of the picrate reformed the base; $[\alpha]_D^{36.2}$ (pure substance, $d = 1.01$); $[\alpha]_D^{40.0}$ (methanol, $c = 3\%$); nmr: 2.65-2.90 (10H, m, aromatic), 6.40 (2H, s, benzyl CH_2), 6.50-8.40 (7H, m, aliphatic).

S(+)-Phenylsuccinic Acid (II).

The R,S-phenylsuccinic acid (20 g.) was resolved by fractional

recrystallization of its brucine salt (88.6 g. of brucine) from ethanol. Decomposition of the salt gave an acid with $[\alpha]_D^{167}$ (acetone); after crystallization from water, S-(+)-II was obtained, with $[\alpha]_D^{172}$ (acetone).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.95; H, 5.25.

Dimethyl Ester of S-(+)-Phenylsuccinic Acid (III).

A solution of S-(+)-II (6.3 g.) in dimethyl sulphoxide (distilled over calcium chloride) (40 ml.) was treated with methyl iodide (19.5 ml.), calcium oxide (12.6 g.), and calcium sulfate (6.3 g.). The mixture was allowed to stand for 8 hours at room temperature, with stirring, and was then filtered. The residue was subjected to prolonged washing with benzene and petroleum ether. The filtrate was treated with water (100 ml.), and this was then extracted several times with petroleum ether. The combined organic solutions were washed twice with a 10% solution of sodium thiosulfate), once with a solution of sodium carbonate, and once with a solution of sodium chloride. The residue after evaporation of the solvent was distilled to give S-(+)-III, b.p. 119°/2 mm Hg, $[\alpha]_D^{124}$ (methanol, $c = 0.5\%$); $[\alpha]_D$ about +156° (pure substance, $d = 1.137$).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.72; H, 6.17.

[Starting from an acid with $[\alpha]_D^{-99.5}$, an ester was obtained which, in the crude state, had $[\alpha]_D^{-61}$ (methanol), but which on recrystallization from methanol led to the separation of a less soluble racemate].

S(+)-2-Phenylbutane-1,4-diol (IV).

A solution of S-(+)-III (5.3 g.) in anhydrous ether was added to a suspension of lithium aluminum hydride (2.8 g.) in anhydrous ether. The mixture was boiled under reflux for 1 hour and filtered, after the excess of the hydride had been destroyed. The residue was washed with ether. The ether was driven off under vacuum, and the residue was distilled to give S-(+)-IV (3.16 g.), b.p. 51°/0.2 mm Hg; $[\alpha]_D^{29}$ (methanol, $c = 2\%$).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.47; H, 8.40.

S(+)-1,4-Dibromo-2-phenylbutane (V).

A solution of S-(+)-IV (3.13 g.) in anhydrous pyridine (1.5 ml.) was treated with phosphorus tribromide (2.8 ml.). The mixture was heated with stirring for 1 hour, poured into ice and water, and extracted with hexane. The organic solution was washed successively with 5% sodium hydroxide, water, 10% sulfuric acid, concentrated sulfuric acid (5 times), and water. The solvent was evaporated off and the residue was distilled in a bulb tube, giving S-(+)-V (3.58 g.); $[\alpha]_D^{53}$ (methanol, $c = 2\%$), $[\alpha]_D^{57.5}$ (pure substance, $d = 1.57$).

Anal. Calcd. for $C_{10}H_{12}Br_2$: C, 41.13; H, 4.14. Found: C, 41.09; H, 4.35.

S(-)-N-Benzyl-3-phenylpyrrolidine [(VI) from (V)].

Benzylamine (4.3 g.) was added to a solution of S-(+)-V (3.23 g.) in absolute ethanol (25 ml.). The mixture was boiled under reflux for 7 hours. The alcohol was then distilled off, the residue was taken up in water, and the solution was made distinctly acid with 6N hydrochloric acid and washed with ether. The aqueous phase was next made alkaline and extracted with ether. Distillation of this last organic phase gave two fractions: a) b.p. 50°/1 mm Hg, which consisted of benzylamine; b) b.p. 155°/1 mm Hg, which was S(-)-VI (2.3 g.) $[\alpha]_D^{-40.8}$ (methanol).

Anal. Calcd. for $C_{23}H_{22}N_4O_7$: C, 59.22; H, 4.75; N, 12.01.

Found: C, 58.98; H, 5.02; N, 11.78 (picrate).

Nmr (60 MHz): 2.55-2.90 (10H, m, aromatic H), 6.36 (2H, s, benzyl CH₂), 6.40-8.40 (7H, m, aliphatic).

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