

Studies on the Syntheses of Heterocyclic Compounds. Part DXXVII. (1).  
The Absolute Configuration of 1,2,3,4-Tetrahydro-1-phenylisoquinolines.

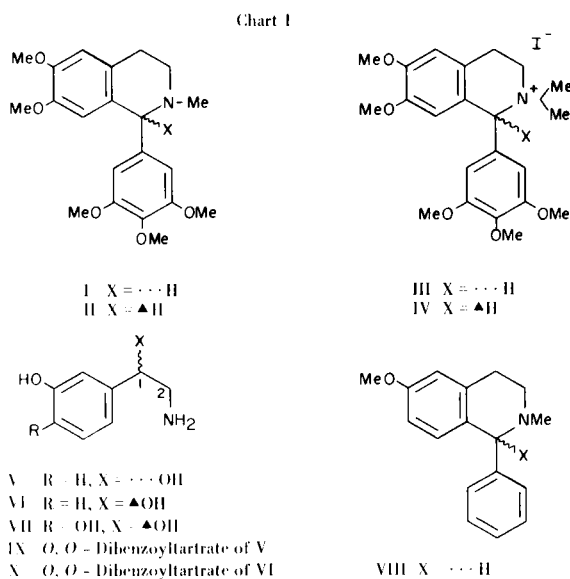
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The absolute configuration at the C<sub>1</sub>-position of 1,2,3,4-tetrahydro-1-phenylisoquinolines can be deduced from the CD curves of either the free base or its methiodide. Furthermore, the absolute configuration of (+)-2-amino-1-(3-hydroxyphenyl)ethanol (V) was revised and found to have R-configuration at the C<sub>1</sub>-position.

A comparison of the ORD and CD curves of 1-alkyl-1,2,3,4-tetrahydroisoquinolines has been known as one of the most useful methods for deduction of the absolute configuration at the 1-position. We have investigated a comparison of the CD curves of 1,2,3,4-tetrahydro-1(S)-phenylisoquinoline I (4,6) with those of its methiodide III. Herein, we wish to report these results.



(+)-1,2,3,4-Tetrahydro-1(S)-phenylisoquinoline (I) (4,6) gave three positive Cotton effects in its CD spectrum in the 200-300 nm region as shown in Fig. 1. 1(S)-Phenylisoquinoline methiodide III was found to give a CD curve similar to that of its tertiary base I in 200-225 nm, but gave a different mode of CD curves from that of I in the higher wave length region as shown in Fig. 1. Therefore, it is important to compare the CD curves of the free base of the tetrahydro-1-phenylisoquinoline with those of its quaternary salt in lower wave length region in order to deduce their absolute configuration at the C<sub>1</sub> position.

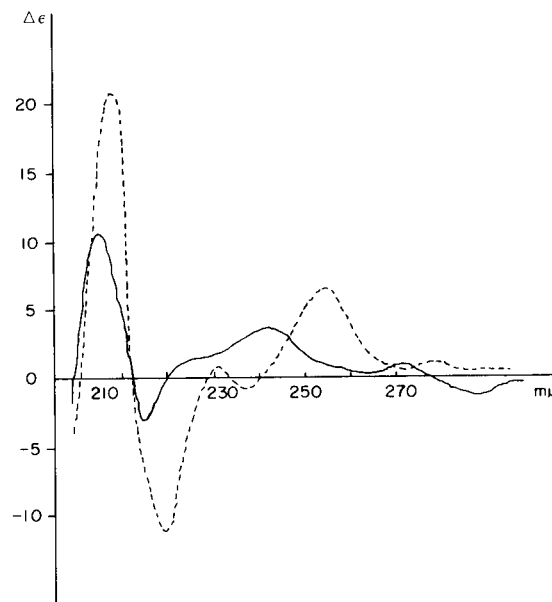


Fig. 1. CD curves of cryptostyline III (I) (—) and the methiodide (III) (-----).

In the previous papers (5,6), we determined the configuration of the 1,2,3,4-tetrahydro-4-hydroxy-6-methoxy-1-phenylisoquinoline derivative from (+)-2-amino-1-(3-hydroxyphenyl)ethanol (V) and then that of (+)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1-phenylisoquinoline (VIII) by a reductive removal of hydroxyl group at the C<sub>4</sub> position of the former compound. Moreover, the ORD and CD spectral comparisons of VIII with cryptostyline III (I) suggested both compounds to have the same configuration at the C<sub>1</sub>-position.

The absolute configuration of (+)- and (-)-2-amino-(3-hydroxyphenyl)ethanol (V and VI) (5,9), which were the phenolic amine used for the synthesis of 1-phenylisoquinoline, was confirmed by correlation of their CD

spectra with those of (-)-noradrenaline (VII), the absolute configuration of which was confirmed by Craig (10). (+)-2-Amino-1-(3-hydroxyphenyl)ethanol (V) and the (-)-isomer (VI) were prepared from the corresponding *O,O*-dibenzoyl(+)-tartrate (IX) and *O,O*-dibenzoyl(-)-tartrate (XI), respectively. As shown in Fig. 2, the (-)-isomer (VI) was found to give a pattern similar to (-)-noradrenaline (VII) in their CD spectra. Since the (+)-isomer (V) was used in the synthesis of (+)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-1(*S*)phenylisoquinoline (VIII), our previous assignment of *R*-configuration to the (+)-1-phenylisoquinoline (VIII) at the  $C_1$ -position (5) should be revised to the *S*-configuration (9). Therefore, the absolute configuration of cryptostyline (III) (4) (6) should possess the *S*-configuration at the  $C_1$ -position as Brossi reported (4).

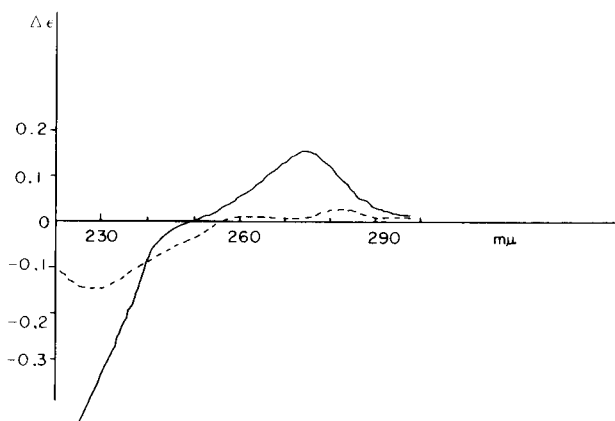


Fig. 2. CD curves of (-)-VI hydrochloride (—) and (-)-noradrenaline (VII) hydrochloride (-----).

#### EXPERIMENTAL (11)

(+)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-2-methylisoquinoline Methiodide (III).

A mixture of 30 mg. of (+)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-2-methylisoquinoline (I) (6), 5 ml. of methanol and 1.5 ml. of methyl iodide was refluxed for 3 hours. The solvent was evaporated and the resulting residue was recrystallized from methanol-ether to give 30 mg. of the methiodide (III) as pale yellowish needles, m.p. 154-156°,  $[\alpha]_D^{18} +68.19^\circ$  (c 0.40 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_{22}H_{30}INO_5$ : C, 52.90; H, 6.01; N, 2.80. Found: C, 52.65; H, 6.33; N, 2.75.

(-)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-2-methylisoquinoline Methiodide (IV).

A mixture of 30 mg. of (-)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-2-methylisoquinoline (II) (6), 10 ml. of methanol and 1.5 ml. of methyl iodide was refluxed for 3 hours.

The mixture was worked up as above to afford 32 mg. of the methiodide as yellowish needles, m.p. 154-156°  $[\alpha]_D^{18} -70^\circ$  (c 0.4 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_{22}H_{30}INO_5$ : C, 52.90; H, 6.01; N, 2.80. Found: C, 52.67; H, 5.95; N, 2.75.

(3)-2-Amino-1-(3-hydroxyphenyl)ethanol *O,O*-Dibenzoyl(+)-tartrate (IX).

A mixture of the free amine prepared from 3.78 g. of 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride, 7.16 g. of *O,O*-dibenzoyl(+)-tartaric acid and 20 ml. of methanol was heated on a water bath for 5 minutes. Evaporation and recrystallization of the residue from water afforded 1.5 g. of the tartrate IX as colorless needles, m.p. 188-190°,  $[\alpha]_D^{18} -70^\circ$  (c 0.497 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_{22}H_{24}NO_8$ : C, 61.05; H, 4.93; N, 2.74. Found: C, 61.10; H, 5.13; N, 2.92.

(+)-2-Amino-1-(3-hydroxyphenyl)ethanol (V) Hydrochloride.

To a solution of 0.2 g. of the above dibenzoyltartrate IX in 10 ml. of methanol was added an ethereal solution saturated with hydrogen chloride gas. After removal of the solvent, the remaining residue was washed with dry ether. The resulting solid was recrystallized from methanol-ether to yield 70 mg. of the hydrochloride of V (5) as colorless prisms, m.p. 128-130°,  $[\alpha]_D^{18} +49.81^\circ$  (c 0.4 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_8H_{11}NO_2 \cdot HCl$ : C, 50.66; H, 6.37; N, 7.38. Found: C, 50.39; H, 6.21; N, 7.49.

(-)-2-Amino-1-(3-hydroxyphenyl)ethanol *O,O*-Dibenzoyl(-)-tartrate (X).

The free base obtained from 3.78 g. of 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride was treated with 7.16 g. of *O,O*-dibenzoyl(-)-tartaric acid and the reaction mixture was worked up as above to give 1.5 g. of the tartrate X as colorless needles, m.p. 188-190°,  $[\alpha]_D^{18} +71.7^\circ$  (c 0.53 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_8H_{11}NO_2 \cdot C_{18}H_{14}O_8$ : C, 61.05; H, 4.93; N, 2.74. Found: C, 60.87; H, 5.12; N, 2.99.

(-)-2-Amino-1-(3-hydroxyphenyl)ethanol (VI) Hydrochloride.

To a solution of 150 mg. of the foregoing dibenzoyltartrate X in methanol was added an ethereal solution saturated with hydrogen chloride gas. The solvent was removed and the remaining residue was washed with dry ether. The resulting solid was recrystallized from methanol-ether to give 50 mg. of the hydrochloride of VI as colorless prisms, m.p. 128-130°,  $[\alpha]_D^{18} -44.98^\circ$  (c 0.4 in methanol; l, 0.2 dm).

*Anal.* Calcd. for  $C_8H_{11}NO_2 \cdot HCl$ : C, 50.66; H, 6.37; N, 7.38. Found: C, 50.97; H, 6.55; N, 7.58.

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- (11) Melting points are not corrected. Optical rotation was taken with a Jasco Model DIP-SL automatic polarimeter.