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Absolute Configurations of 2-Methyl-2-phenylaziridine, 2-Phenylpropylamine, and Their Derivatives

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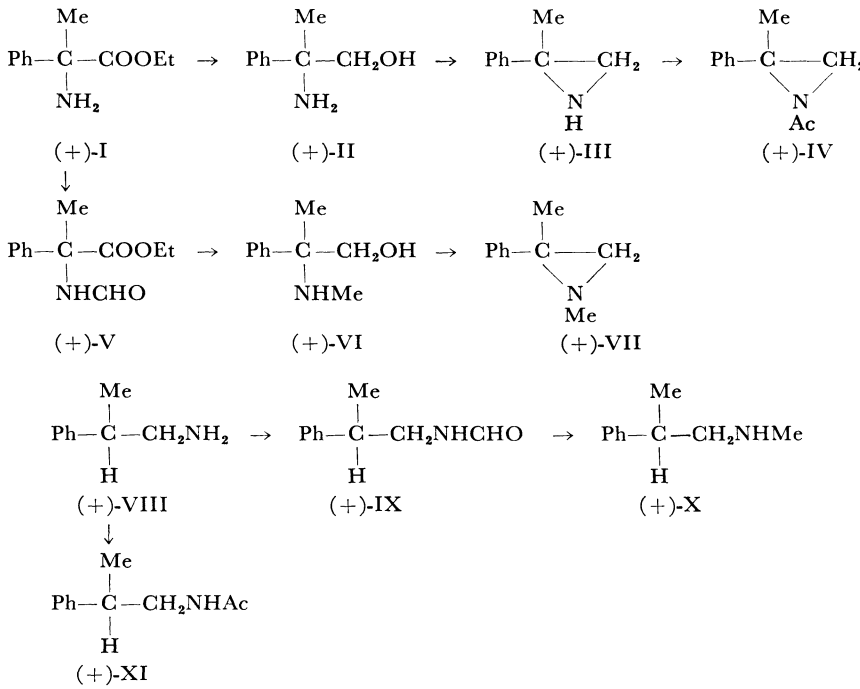
In previous publications,[1,2] we reported the stereoselectivity[1] and the effects of solvent and additive on the stereochemistry[2] of the catalytic hydrogenolysis of optically active 2-methyl-2-phenylaziridine derivatives. We now wish to describe the syntheses and the absolute configurations of 2-methyl-2-phenylaziridine, 2-phenylpropylamine, and their derivatives.

(+)-Ethyl 2-amino-2-phenylpropionate (I) was obtained by the resolution of (±)-I as its tartrate. The subsequent reduction of (+)-I with lithium aluminum hydride gave (+)-2-amino-2-phenylpropanol (II).[1] (+)-II was converted to (+)-2-methyl-2-phenylaziridine (III) *via* its sulfonate.[1] (−)-1-Acetyl-2-methyl-2-phenylaziridine (IV) was obtained by the acetylation of (−)-III. (+)-Ethyl 2-formylamino-2-phenylpropionate (V) was prepared by the formylation of (+)-I. The subsequent reduction of (+)-V with lithium aluminum hydride gave (+)-2-methylamino-2-phenylpropanol (VI). The cyclization of (+)-VI afforded (+)-1,2-dimethyl-2-phenylaziridine (VII). (+)-I has the S configuration.[3] Therefore, (+)-III, (+)-IV, and (+)-VII all have S configurations.

The formylation of (+)-2-phenylpropylamine (VIII) afforded (+)-*N*-2-phenylpropylformamide (IX). (+)-IX was reduced to (+)-*N*-methy-2-phenylpropylamine (X) with lithium aluminum hydride. (−)-*N*-2-Phenylpropylacetoamide (XI) was obtained by the acetylation of (−)-VIII. (+)-VIII has the R configuration.[4,5] Therefore, (+)-IX, (+)-X, and (+)-XI all have R configurations.



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Experimental

S(+)- and R(−)-Ethyl 2-Amino-2-phenylpropionates (I), S(+)- and R(−)-2-Methyl-2-phenylaziridines (III), and S(+)- and R(−)-2-phenylpropylamines (VIII). These substances were prepared by the procedure previously described.[1] The NMR spectrum of III had signals at 0.40 (broad singlet, >NH); 1.53 (singlet, $-CH_3$); 1.73 (singlet) and 1.78 (singlet), ($-CH_2-$); 7.25 (multiplet, aromatic protons).*1

R(−)-Acetyl-2-methyl-2-phenylaziridine (IV). Acetyl chloride (8.2 g) in ether (25 ml) was added at 0°C to a solution of R(−)-III (13.3 g, α_D^{22} −18.86 (neat), 37.3% optically pure) and triethylamine (15.0 g) in ether (75 ml). The reaction mixture was allowed to proceed to completion by being stirred for 1 hr at this temperature. The triethylamine hydrochloride thus precipitated was filtered off and washed well with ether. After the ether had been removed at room temperature *in vacuo*, the oily residue was distilled to give R(−)-IV; bp 45—47°C/0.01 mmHg, $[\alpha]_D^{24.5}$ −36.2 (*c* 8.98, ethanol), 7.5 g.

Found: C, 75.68; H, 7.67; N, 8.27%. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99%.

The NMR spectrum had signals at 1.59 (singlet, $-\overset{|}{C}-CH_3$); 1.94 (triplet, J=0.4 Hz, $-COCH_3$); 3.75 (quartet, J=0.4 Hz, $-CH_2-$); 7.25 (multiplet, aromatic protons).*1

S(+)-Ethyl 2-Formylamino-2-phenylpropionate (V). The procedure described by Tsuboyama[6] was used with slight modifications. To a solution of S(+)-I (39.6 g, $[\alpha]_D^{22}$ +26,6 (*c* 9.70, ethanol), 90.3% optically pure) in 88% formic acid (720 g), acetic anhydride (244 g) was added with stirring at 95°C. The reaction mixture was then allowed to stand at this temperature for 30 min. The excess of the reagents was removed *in vacuo*, and then water (500 ml) was added to the oily residue. The resulting precipitates were filtered and then recrystallized from benzene-*n*-hexane to give S(+)-V; mp 94—95°C, $[\alpha]_D^{23}$ +19.50 (*c* 5.18, ethanol), 25.3 g.

Found: C, 65.20; H, 6.88; N, 6.25%. Calcd for $C_{13}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33%.

The filtrate was treated with aqueous ammonia. S(+)-I (17.5 g, $[\alpha]_D^{20.5}$ +26.4 (*c* 9.88, ethanol)) was thus recovered.

For the check of the optical purity, S(+)-V (1.1 g, $[\alpha]_D^{23}$ +19.50 (*c* 5.18, ethanol)) was heated with hydrochloric acid in ethanol for 3 hr. S(+)-I was then isolated in the usual manner; $[\alpha]_D^{20.5}$ +27.8 (*c* 9.25, ethanol), 91.0% optically pure.

S(+)-2-Methylamino-2-phenylpropanol (VI). S(+)-V (24.2 g, $[\alpha]_D^{23}$ +19.50 (*c* 5.18, ethanol), 91.0% optically pure) in tetrahydrofuran (100 ml) was added to lithium aluminum hydride (8.0 g) in tetrahydrofuran (100 ml); the reaction mixture was then heated under reflux for 64 hr. After cooling, water (30 ml) was added with vigorous stirring; the organic layer was then decanted from the precipitates. The resulting precipitates were dissolved with aqueous sodium hydroxide, and the aqueous solution was extracted with ether. The combined extracts were dried over anhydrous sodium sulfate. After the evaporation of the solvents, the oily residue was distilled under a nitrogen stream to give S(+)-VI: bp 94—102°C/0.4 mmHg, $[\alpha]_D^{22.5}$ +21.2 (*c* 4.58, benzene), 16.0 g.

Found: C, 73.00; H, 9.15; N, 8.44%. Calcd for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48%.

S(+)-1, 2-Dimethyl-2-phenylaziridine (VII). S(+)-VII was obtained from S(+)-VI by a method similar to that used for the preparation of III.[1] S(+)-VI (16.0 g, $[\alpha]_D^{22.5}$ +21.2 (*c* 4.58, benzene), 91.0% optically pure) afforded S(+)-VII: bp 88—91°C/14 mmHg, $[\alpha]_D^{22}$ +45.0 (*c* 8.95, ethanol), 9.3 g.

Found: N, 9.41%. Calcd for $C_{10}H_{13}N$: N, 9.82%.

R(+)-*N*-2-Phenylpropylformamide (IX). R(+)-IX was prepared by a method similar to that used for the preparation of V. R(+)-VIII (4.0 g, $[\alpha]_D^{19.0}$ +9.84 (*c* 9.71, ethanol), 33.4% optically pure) gave R(+)-IX; bp 130—132°C/0.6 mmHg. $[\alpha]_D^{18.4}$ +8.26 (*c* 10.04, ethanol), 2.2 g.

Found: N, 8.37%. Calcd for $C_{10}H_{13}ON$: N, 8.58%.

R(+)-*N*-Methyl-2-phenylpropylamine (X). R(+)-X was obtained from R(+)-IX by refluxing it with lithium aluminum hydride in ether for 24 hr. R(+)-IX (2.0 g, $[\alpha]_D^{18.4}$ +8.26 (*c* 10.04, ethanol), 33.4% optically pure) afforded R(+)-X; bp 100—103°C/15 mmHg, $[\alpha]_D^{22}$ +8.45 (*c* 9.45, ethanol), 0.3 g (this substance was purified by preparative gas chromatography (10% PEG-10% KOH on fire-brick, 180°C, using helium-carrier gas), for two impurities were present in the crude product).

Found: N, 9.17%. Calcd for $C_{10}H_{15}N$: N, 9.39%.

S(−)-*N*-2-Phenylpropylacetoamide (XI). Acetic anhydride (3.50 g) was added at 0°C to a well-stirred suspension of S(−)-VIII (2.70 g, $[\alpha]_D^{20}$ −8.65 (*c* 9.37, ethanol), 29.3% optically pure) and sodium carbonate (4.2 g) in water (30 ml). The reaction mixture was then stirred for 1 hr at this temperature. The resulting suspension was extracted with ether. The etheral solution was washed with dilute hydrochloric acid, water, and saturated sodium bicarbonate, and was dried over anhydrous sodium sulfate. The evaporation of the ether and the subsequent distillation afforded S(−)-XI: bp 130—132°C/0.6 mmHg, $[\alpha]_D^{19.5}$ −13.83 (*c* 9.55, ethanol), 2.4 g.

Found: N, 7.81%. Calcd for $C_{11}H_{15}ON$: N, 7.90%.

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*1 The NMR spectra were determined with a Hitachi model H-6013 spectrometer for the carbon tetrachloride solution, using tetramethylsilane as the internal standard. The chemical shifts are expressed in δ-values.

6) S. Tsuboyama, This Bulletin, **35**, 1004 (1962).