BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 1975—1977 (1971)

The Absolute Configurations of 2-Phenylaziridine and Its Derivatives

Shinsaku FUJITA, Kazuo IMAMURA, and Hitosi NOZAKI

Department of Industrial Chemistry, Kyoto University, Yosida, Sakyo-ku, Kyoto

(Received December 31, 1970)

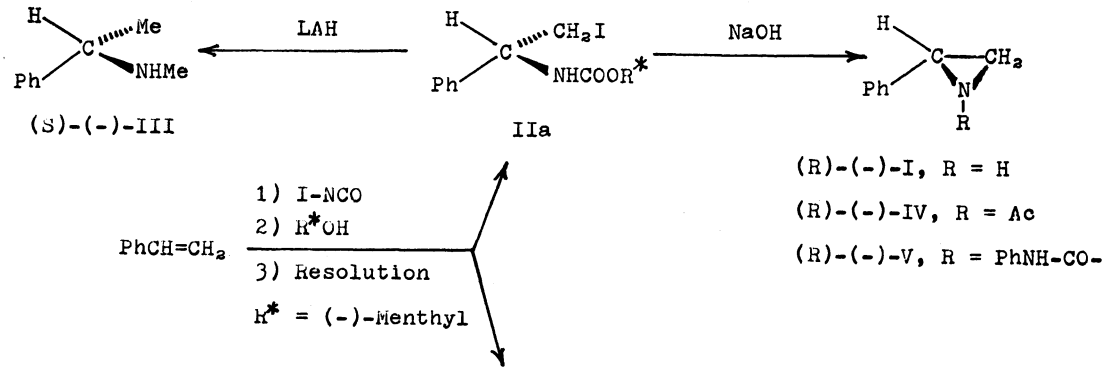
As the optical resolution of aziridines is rarely feasible because of their acid-sensitivity, optically-active aziridines have been obtained by the stereospecific ring-closure of suitable precursors, mainly of natural origin.[1] The present report will describe a novel synthesis of optically active 2-phenylaziridine (I) and its derivatives, and the determination of their absolute configulations.

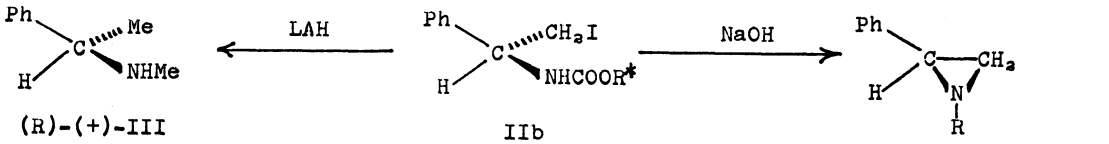
The addition of iodine isocyanate[2] to styrene and subsequent treatment with (−)-menthol gave a mixture of the diastereomers of α-(iodomethyl)benzylcarbamic acid (−)-methyl ester (II), which was fractionally recrystallized from methanol. The less soluble diastereomer ($[\alpha]_D$ −73.0°) was treated with methanolic sodium hydroxide, and the resulting aziridine was separated from (−)-menthol by preparative thin-layer chromatography. The optically-active 2-phenylaziridine ((−)-I) thus obtained had an optical rotation of $[\alpha]_D$ −45.5° (75% optically pure, *vide infra*). Similarly, the ring-closure of the more soluble one (IIb) gave another enantiomer (+)-I. which was obtained only in a lower optical purity.

The absolute configuration of I was correlated to that of known α-methylbenzylamine, with the results illustrated in Schemes 1 and 2. The reduction of IIa ($[\alpha]_D$ −70.5°)and IIb with lithium aluminum hydride afforded (−)-N-methyl-α-methyl-benzylamine ((−)-III $[\alpha]_D$ −58.2°) and (+)-enantiomer respectively. On the other hand, the reaction of (R)-(+)-α-methylbenzylamine with ethyl chloroformate yielded (R)-(+)-ethyl α-methylbenzylcarbamate (VII), which in turn afforded (R)-(+)-III on LAH reduction. Therefore, the absolute configuratoins of enantiomers of I were

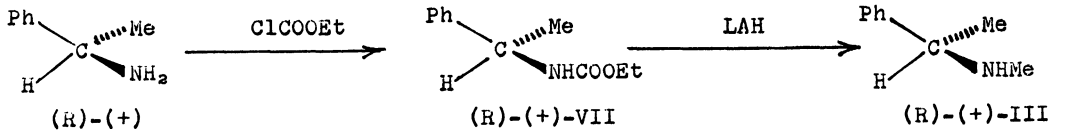
1) a) S. J. Brois and G. P. Geardsley, *Tetrahedron Lett.*, **1966, 5113.** b) T. Taguchi and M. Kojima, *Chem. Pharm. Bull. Japan*, **7**, 103 (1959). c) P. G. Gassman and A. Fentiman, *J. Org. Chem.*, **32**, 2388 (1967). c) P. G. Gassman and A. Fentiman, *J. Org. Chem.*, **32**, 2388 (1967). d) P. G. Kostyanovsky, Z. E. Samojlova, and I. I. Tchervin, *Tetrahedron Lett.*, **1969,** 719. e) Y. Sugi and S. Mitsui, This Bulletin, **43**, 564 (1790).

2) a) S. Fujita, T. Hiyama, and H. Nozaki, *Tetahedron*, **26**, 4347 (1979). b) H. Nozaki, Y. Okuyama, and S. Fujita, *Can. J. Chem.*, **46**, 3333 (1968)





Scheme 1



Scheme 2

concluded to be (R)-(−) and (S)-(+).

The following derivatives of (R)-(−)-I were prepared: (R)-(−)-1-acetyl-2-phenylaziridine (IV) and (R)-(−)-1-phenylcarbamoyl-2-phenylaziridine (V). (S)-(+)-1-Methyl-2-phenylaziridine (VI) was also prepared from (S)-(+)-I.

Experimental

All the melting points are uncorrected. Unless otherwise stated, each optical rotation was determined in chloroform at room temperature. The optically-active aziridines were identified by comparing the spectral data with those of racemic samples.

Addition of Iodine Isocyanate to Styrene. Iodine (50.8 g, 0.20 mol) was added in one portion to a cooled mixture of silver isocyanate (40.0 g, 0.26 mol), styrene (20.8 g, 0.20 mol), and dry ether (400 m*l*). Stirring was continued for 1 hr over an ice-salt bath and then for 4 more hr at room temperature. The silver salt then precipitated was filtered off. (−)-Menthol (31.3 g, 0.20 mol) was added to the filtrate, and the solution was allowed to stand in the dark for 4 days. The mixture was poured into ice water (700 m*l*) containing 20 g sodium sulfite and extracted with ether. The combined extracts were dried over sodium sulfate. Concentration gave a mixture of IIa and IIb (81.0 g, 94%). Fractional recrystallization (4 times) of the mixture from methanol yielded a IIa-rich mixture as white crystals (4.53 g); mp 149°C; $[\alpha]_D$ −73.0° (c=1.21 g/100 m*l*).

Found: C, 53.4; H, 6.5; I, 29.9; N, 3.2%. Calcd for $C_{19}H_{28}INO_2$: C, 53.1; H, 6.6; I, 29.6; N, 3.3%.

A IIb-rich mixture was obtained from the mother liquor. Mp 115°C; $[\alpha]_D$ −12.9° (c=0.64 g/100 m*l*).

(R)-(−)-2-Phenylaziridine (I). A mixture of IIa (8.95 g, 20.9 mmol, $[\alpha]_D$ −73.0°) and methanolic sodium hydroxide (10 N, 50 m*l*) was heated at reflux for 1.5 hr under a nitrogen atmosphere. After the evaporation of the solvent, the residue was extracted with ether and dried over sodium sulfate. Concentration and distillation gave a mixture of (R)-(−)-I, menthol, and acetophenone. Preparative-scale TLC (silica-gel G, using ether as a solvent and chloroform as a eluent) and subsequent distillation afforded pure (R)-(−)-I (0.64 g, 27%); bp 56°C/2.5 mmHg; $[\alpha]_D$ −45.5° (c=1.72 g/100 m*l*). Calculation indicated that the optically-pure sample has the optical rotation of $[\alpha]_D$ −60.3°.

(S)-(+)-2-Phenylaziridine (I). ($[\alpha]_D$ +29.4°, c=1,53 g/100 m*l*) was obtained similarly from IIb ($[\alpha]_D$ −12.9°).

(S)-(−)-N-Methyl-α-methylbenzylamine (III) from IIa. A solution of IIa (2.00 g, 4.7 mmol, $[\alpha]_D$ −73.0°) in ether was added, drop by drop at room temperature, to a suspension of lithium aluminum hydride (1.5 g) in ether (30 m*l*). The mixture was then heated at 50°C for 20 hr. The excess hydride was quenched with water and extracted with ether. Then combined ethereal solutions were then extracted with 15% hydrochloric acid. The aqueous layer was neutralized with 25 N aqueous sodium hydroxide, extracted with ether, and dried over sodium sulfate. Distillation afforded (S)-(−)-III (0.044 g, 6%, $[\alpha]_D$ −58.2°, c=0.88 g/100 m*l*). The optical purity was calculated to be 75.4%.

(R)-(+)-N-Methyl-α-methylbenzylamine (III). ($[\alpha]_D$ +45.8°, c=0.57 g/100 m*l*) was obtained from IIb ($[\alpha]_D$ −8.05°).

(R)-(+)-ethyl α-methylbenzylcarbamate (VII). A solution of ethyl chloroformate (0.56 g, 5.2 mmol) in ether (30 m*l*) was added at 0°C to a mixture of (R)-(+)-α-methylbenzylamine (1.24 g, 10 mmol, $[\alpha]_D$ +36.4° (neat), 91.7% optically pure), ether (20 m*l*), and water (30 m*l*). Then another solution of ethyl chloroformate (0.56 g, 5.2 mmol) and aqueous sodium hydroxide (NaOH 0.48 g in water 10 m*l*) were

added to the reaction mixture at the same time. Work-up gave (R)-(+)-VII (1.70 g, 88%); $[\alpha]_D$+64.4° (c=1.99 g/100 ml); bp 97—101°C/1 mmHg.

Found: C, 68.6; H, 7.9; N, 7.2%. Calcd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.3%.

*(R)-(+)*N-*Methyl-α-methylbenzylamine (III).* The reduction of (R)-(+)-VII (0.58 g, 3.0 mmol, $[\alpha]_D$+64.4°, 91.7% optically pure) with lithium aluminum hydride gave (R)-(+)-III (0.34 g, 85%); bp 74°C/14 mmHg; $[\alpha]_D$+70.8° (c=1.92 g/100 m*l*). The optical rotation of pure (R)-(+)-III was calculated to be $[\alpha]_D$+77.2°.

(R)-(−)-1-Acetyl-2-Phenylaziridine (IV). A solution of acetyl chloride (0.10 g, 1.3 mmol) in ether (5 m*l*) was added at 0°C to a solution of (R)-(−)-I (0.23 g, 1.5 mmol, $[\alpha]_D$ −45.5°, optical purity 75.4%) and triethylamine (0.18 g) in ether (10 m*l*). The reaction mixture was stirred for 1 hr. The triethylamine hydrochloride thus precipitated was filtered off and washed well with ether. After the evaporation of the solvent, the oily residue was distilled to give (R)-(−)-IV (0.10 g, 31%); bp 56°C/0.2 mmHg; $[\alpha]_D$ −106° (c=1.28 g/100 m*l*). The optically pure sample was calculated to have the rotation of $[\alpha]_D$ −141°.

(R)-(−)-1-phenylcarbamoyl-2-phenylaziridine (V). Phenyl isocyanate (0.090 g) was added to a solution of (R)-(−)-I (0.090 g, $[\alpha]_D$ −45.5°, 75.4% optically pure) in ether (10 m*l*). After it had been stirred for 1.5 hr, the ether was evaporated *in vacuo* to give (R)-(−)-V (0.17 g, 94%); mp 97—99°C (lit. mp for racemic sample[3] 96.5—97.5°C); $[\alpha]_D$ −262° (c=1.56 g/100 m*l*). The optical rotation of pure (R)-(−)-V was calculated to be $[\alpha]_D$ −348°.

(S)-(+)-1-Methyl-2-phenylaziridine (VI). A 1.30 M solution (1.0 m*l*) of *n*-butyllithium in *n*-hexane was added, drop by drop under a nitrogen atmosphere, to a solution of (S)-(+)-I (0.15 g, 1.3 mmol, $[\alpha]_D$ +8.08°, 13.4% optically pure) in tetrahydrofuran (20 m*l*), and the mixture was stirred for 30 min at room temperature. To the reaction mixture we then added drop by drop methyl iodide (0.18 g); the mixture was stirred for 1 hr, poured into saturated aqueous ammonium chloride (20 m*l*), and extracted with ether. The combined etheral extracts were dried over sodium sulfate and concentrated *in vacuo*. The distillation of the oily residue afforded (S)-(+)-VI (0.076 g, 45%); bp 39°C/1 mmHg; $[\alpha]_D$ +32.1° (c=1.51 g/100m*l*). The optical rotation of pure (S)-(+)-VI was calculated to be $[\alpha]_D$ +241°.

The authors are grateful to Professor Keiiti Sisido for his generous help. Financial support from the Ministry of Education, the Japanese Government, and from the Toray Science Foundation is acknowledged with pleasure.

3) K. Kotera, S. Miyazaki, H. Takahashi, T. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 3681 (1968).