Asymmetric Synthesis. I. Synthesis and Absolute Configuration of α-Aminoalkanesulfonates Derived from (−)-Ephedrine and Aromatic Aldehyde Bisulfites

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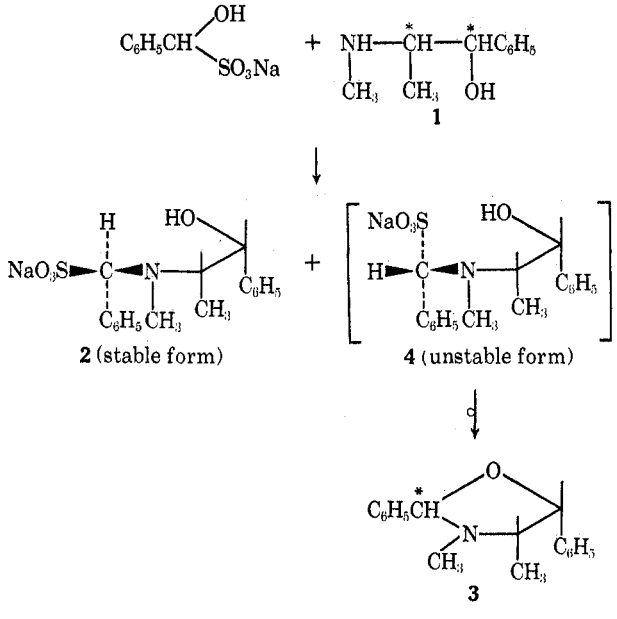
Equimolar amounts of aromatic aldehyde bisulfites and (−)-ephedrine in aqueous solution give equimolar amounts of each of an optically pure α-aminoalkanesulfonate and an oxazolidine. This is a stereospecific reaction. The induced asymmetric center in the α-aminoalkanesulfonate has the *R* configuration. In the presence of an excess of sodium bisulfite or in buffer pH 7, a diastereoisomeric mixture of the α-aminoalkanesulfonates is formed. Acetaldehyde, propionaldehyde, chloral, acetone, and other ketones also yield a mixture of diastereoisomers.

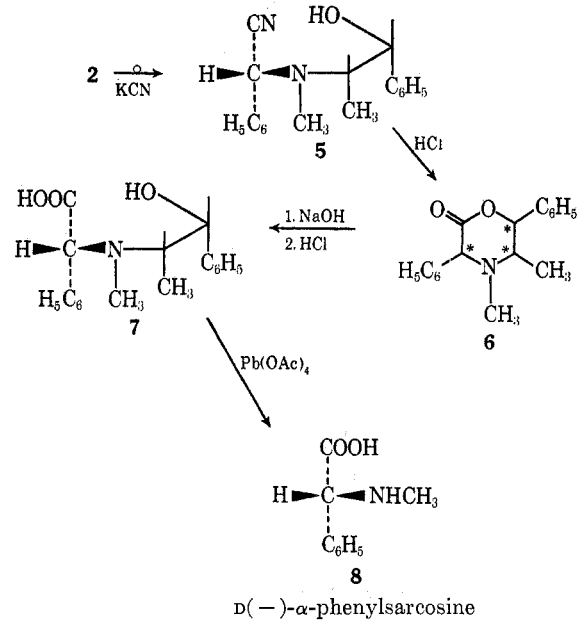
In a continuation of earlier studies[2] the reaction of aldehyde and ketone bisulfites with (−)-ephedrine (**1**) and (+)-pseudoephedrine was studied. Benzaldehyde bisulfite in aqueous solution reacts with an equimolar amount of (−)-ephedrine to yield an equimolar amount of an α-aminoalkanesulfonate (**2**) and an oxazolidine[3] (**3**). Initially, diastereoisomeric aminoalkanesulfonates are probably formed, one of which is unstable and gives the oxazolidine (**3**). Other aromatic aldehydes



such as *p*-chlorobenzaldehyde, *p*-tolualdehyde, and piperonal undergo the same reaction.

When (−)-ephedrine is added carefully with stirring and cooling to benzaldehyde bisulfite in the presence of excess sodium bisulfite, no oxazolidine formation takes place, and an almost quantitative yield of the mixture of diastereoisomeric α-aminoalkanesulfonates is obtained. Similarly, no oxazolidine is formed with equimolar quantities of benzaldehyde, sodium bisulfite, and (−)-ephedrine in phosphate buffer pH 7. The infrared spectrum of the diastereoisomeric mixture is very similar to that of the optically pure α-aminoalkanesulfonate. Partial separation of the diastereoisomers can be accomplished by fractional crystallization from absolute alcohol, but in the process some oxazolidine is always formed. Apparently one of the diastereoisomers easily cyclizes.

With potassium cyanide in methanol, sodium (−)-α-ephedrinophenylmethanesulfonate[4] (**2**) gives (+)-α-ephedrinophenylacetonitrile (**5**) which, with concentrated hydrochloric acid, gives the morpholone-2 (**6**). The morpholone, on hydrolysis with alkali, gives (+)-α-ephedrinophenylacetic acid (**7**) which, with lead tetraacetate, yields (−)-α-phenylsarcosine (**8**) identical with D(−)-α-phenylsarcosine of Sheehan.[5]



D(−)-α-phenylsarcosine

The conversion of the aminoalkanesulfonate to the aminonitrile is a base displacement reaction accompanied by an inversion. Lactone formation, hydrolysis, and the final degradation proceed without affecting the configuration of the induced asymmetric center. One can, therefore, ascribe the *R* configuration[6] to the induced asymmetric center in such (−)-α-ephedrinoarylmethanesulfonic acids.

Lead tetraacetate or periodate oxidation of the optically pure α-ephedrinoalkanesulfonates gave a variety

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(2) L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959).

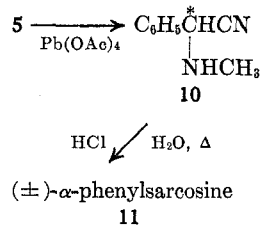
(3) L. Neelakantan, *ibid.*, **36**, 2256 (1971).

(4) The term "(−)-ephedrino" is used to denote the D-(−)-erythro-*N*,1-dimethyl-2-hydroxy-2-phenylethylamino group.

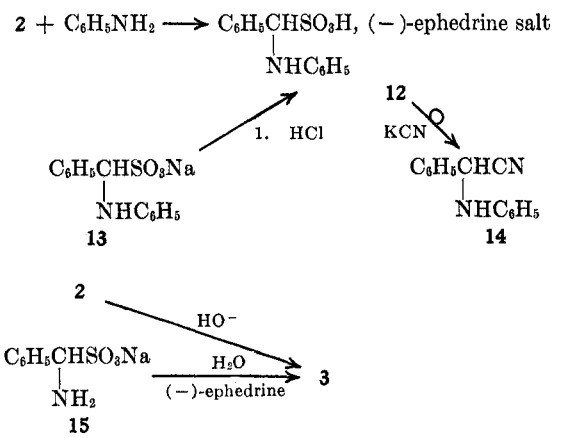
(5) J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Amer. Chem. Soc.*, **80**, 3349 (1950).

(6) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

of degradation products. Lead tetraacetate oxidation of α-ephedrinophenylacetonitrile (**5**) gave (−)-α-methylaminophenylacetonitrile (**10**). However, hydrolysis to the corresponding α-phenylsarcosine (**11**) results in an almost complete racemization.[4,7]

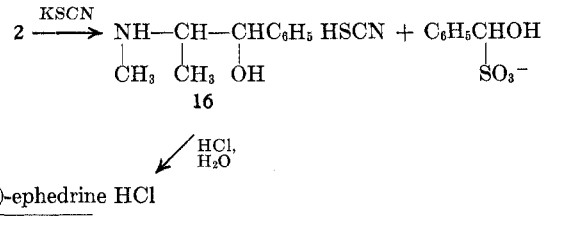


α-Ephedrinoalkanesulfonates (type **2**) undergo reactions typical of other α-aminoalkanesulfonates. With dilute alkali or hot water they form the corresponding oxazolidines. They react with aromatic amines to give α-arylaminoalkanesulfonic acids as the (−)-ephedrine salt (**12**). The same compound (**12**) is obtained from sodium α-anilinophenylmethanesulfonate (**13**) and ephedrine hydrochloride. Product **12** with potassium cyanide gives optically inactive α-anilinophenylacetonitrile (**14**). A simple amine displacement with a Walden inversion should give an optically pure compound. Complete breakdown of **2** to the starting materials and re-formation of an aminoalkanesulfonate would probably have yielded some oxazolidine. The possibility of a true amine exchange with subsequent racemization of the α-anilinoalkanesulfonate cannot be ruled out. Results from preliminary studies support this mechanism. When an aqueous



solution of sodium α-aminophenylmethanesulfonate (**15**) is treated with (−)-ephedrine, oxazolidine formation is the predominant reaction. Again, it is not quite clear whether amine exchange and cyclization or complete breakdown and recombination is the mechanism. Further study is in progress.

Sodium (−)-α-ephedrinophenylmethanesulfonate reacts with potassium or ammonium thiocyanate to give (−)-ephedrine thiocyanate (**16**). Compound **16**



(7) F. Ehrlich, *Biochem. Z.*, **8**, 446 (1908).

can also be prepared from ephedrine and ammonium thiocyanate.[8,9] Potassium thiocyanate and ephedrine give **16** only in the presence of sodium bisulfite or acids. Other α-ephedrinoarylalkanesulfonates undergo the same reaction.

When carbonyl compounds such as acetaldehyde, propionaldehyde, acetone, methyl ethyl ketone, chloral hydrate, cyclopentanone, 2-carbethoxycyclopentanone, and cyclohexanone reacted with (−)-ephedrine in the presence of sodium bisulfite, optically pure aminoalkanesulfonates were not obtained. Also, in those cases where oxazolidines were formed, they existed as a mixture of diastereoisomers.

(+)-Pseudoephedrine reacts with aromatic aldehyde bisulfites to give optically pure α-aminoalkanesulfonates and oxazolidines. This reaction is also stereospecific. The results will be published elsewhere.

Experimental Section

All melting points are uncorrected. Microanalyses were carried out by Messrs. Wiler and Strauss, Oxford, England, or by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

Sodium (−)-α-Ephedrinophenylmethanesulfonate (2).—Benzaldehyde (10.6 g, 0.1 mol) was stirred with sodium bisulfite (10.4 g, 0.1 mol) in water (60 ml) for 2 hr. To the cooled aldehyde bisulfite solution was added (−)-ephedrine (16.5 g, 0.1 mol) all at once, and the mixture was stirred at room temperature for 24 hr. The mass was cooled and the solid collected by filtration and dried in air. The dry powder was stirred with ether (100 ml) for 4 hr and the solid was separated, washed with ether, and air-dried (the ether extract A and washes were saved), yield 16.5 g (45%). The product was recrystallized from alcohol: mp 119–120° (dec); $[\alpha]^{20}D$ −23.1° (*c* 1, ethanol).

Anal. Calcd for $C_{17}H_{20}NO_4SNa$: C, 57.13; H, 5.64; N, 3.92; S, 8.97. Found: C, 57.03; H, 5.54; N, 4.03; S, 9.21.

The ether extract A and the washes were combined and evaporated to dryness when colorless crystals were obtained which were identified as 2,5-diphenyl-3,4-dimethyl-oxazolidine (**3**), yield 12.5 g (49%). The oxazolidine was crystallized from alcohol: mp 73–74°; $[\alpha]^{20}D$ −55.0° (*c* 1, ethanol).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.06; H, 7.51; N, 5.53. Found: C, 80.20; H, 7.58; N, 5.61.

Sodium (−)-α-Ephedrino-*p*-chlorophenylmethanesulfonate (18).—Similarly, *p*-chlorobenzaldehyde (14.0 g, 0.1 mol), sodium bisulfite (10.4 g, 0.1 mol), and (−)-ephedrine (16.5 g, 0.1 mol) reacted to give 18.6 g (47%) of the aminoalkanesulfonate. The product was crystallized from alcohol: mp 123–124° dec; $[\alpha]^{20}D$ −21.4° (*c* 1, ethanol).

Anal. Calcd for $C_{17}H_{19}ClNO_4SNa$: C, 52.05; H, 4.85; N, 3.54; S, 8.16. Found: C, 51.86; H, 5.09; N, 3.34; S, 8.05.

2-*p*-Chlorophenyl-5-phenyl-3,4-dimethyloxazolidine (**19**), 14.5 g (50%), was also isolated, which on crystallization from alcohol has mp 86–87°; $[\alpha]^{20}D$ −52.0° (*c* 1, ethanol).

Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.80; H, 6.25; N, 4.86. Found: C, 71.08; H, 6.52; N, 4.64.

Sodium (−)-α-Ephedrino-*p*-tolylmethanesulfonate (20).—Similarly, 0.1 mol (12.0 g) of *p*-tolualdehyde reacted to give an aminoalkanesulfonate, yield 17.1 g (45%). On recrystallization from alcohol the product has mp 118–119° dec; $[\alpha]^{20}D$ −21.2° (*c* 0.6, ethanol).

Anal. Calcd for $C_{18}H_{22}NO_4SNa$: 3, 57.25; H, 5.93; N, 3.77. Found: C, 56.95; H, 6.30; N, 3.75.

2-*p*-Tolyl-5-phenyl-3,4-dimethyloxazolidine (**21**), 31.1 g (49%), was also isolated which, on crystallization from alcohol, has mp 56–57°; $[\alpha]^{20}D$ −66.7° (*c* 0.5, ethanol).

Anal. Calcd for $C_{18}H_{21}NO$: C, 81.00; H, 7.86; N, 5.25. Found: C, 80.84; H, 7.94; N, 5.47.

Sodium (−)-α-Ephedrino-3,4-methylenedioxyphenylmethanesulfonate (22).—Piperonal (15.0 g, 0.1 mol) was similarly treated and the corresponding aminoalkanesulfonate was isolated, yield

(8) K. Koczka, *et al.*, *Acta Chim. Acad. Sci. Hung.*, **13**, 89 (1957).
(9) Japanese Patent 649 (1959); *Chem. Abstr.*, **54**, 6650 (1960).

18.5 g (45%). The product was recrystallized from alcohol: mp 121–122° dec; $[\alpha]^{20}D$ −20.0° (*c* 1, ethanol).

Anal. Calcd for $C_{18}H_{20}NO_6SNa$: C, 54.10; H, 5.02; N, 3.50; S, 8.00. Found: C, 54.30; H, 5.20; N, 3.48; S, 7.85.

The corresponding oxazolidine (**23**) was isolated in a yield of 14.8 g (50%) and on crystallization from alcohol has mp 82–83°; $[\alpha]^{20}D$ −64.3° (*c* 2, ethanol).

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found: C, 72.69; H, 6.28; N, 4.68.

Sodium α-Ephedrinophenylmethanesulfonate (Mixture of Diastereoisomers) (24).—Benzaldehyde (10.6 g, 0.1 mol) was stirred with sodium bisulfite (32.0 g, 0.3 mol) in water (160 ml). The solution was cooled and under good stirring was added (−)-ephedrine (16.5 g, 0.1 mol) in 50% alcohol (60 ml), dropwise. The pH was maintained close to 7.0 by controlling the rate of addition of ephedrine. The clear solution was allowed to stand at room temperature for 2 days and evaporated to dryness with a current of air, and the residue was extracted with absolute alcohol, concentrated, and diluted with ether. The product was collected and air-dried: yield 31.8 g (85%); mp 105–115° dec; $[\alpha]^{20}D$ −15.1° (*c* 1, ethanol).

Anal. Calcd for $C_{17}H_{20}NO_4SNa$: C, 57.13; H, 5.64; N, 3.92; S, 8.94. Found: C, 57.11; H, 6.00; N, 3.62; S, 8.84.

(+)-α-Ephedrinophenylacetonitrile (5).—**2** (7 g) and potassium cyanide (2.1 g) in methanol (50 ml) were stirred at room temperature for 48 hr. The methanol was evaporated by a current of air, the residue treated with water, and the oily product extracted with ether and concentrated. On dilution with petroleum ether (bp 30–60°) and cooling, large, colorless crystals were obtained: mp 94–95°; yield 4.8 g (85%); $[\alpha]^{20}D$ +9.3° (*c* 4, methanol).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.15; N, 10.01. Found: C, 77.30; H, 7.30; N, 9.80.

(+)-3,6-Diphenyl-4,5-dimethylmorpholone-2 (6).—The aminonitrile (**5**) (5 g) was dissolved in benzene (25 ml), cooled, and treated with ice-cold concentrated hydrochloric acid (30 ml). The mixture was stirred at room temperature for 2 days and cooled, and the crystalline solid was separated. It was then suspended in water and carefully neutralized with sodium carbonate. The product was collected, washed with a little water, and air-dried to give a yield of 4.7 g (92%). The product crystallizes from alcohol–water: mp 93–94°; $[\alpha]^{20}D$ +200.3° (*c* 0.6, ethanol).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 77.0; H, 6.80; N, 4.97. Found: C, 77.02; H, 6.84; N, 4.94.

(+)-α-Ephedrinophenylacetic Acid (7).—The morpholone **6** (5 g) was stirred with a solution of KOH (2.0 g) in water (25 ml) and methanol (10 ml) for 24 hr at room temperature. The solution was carefully neutralized with dilute hydrochloric acid, and the crystalline product was collected, washed with water, and air-dried, yield 4.8 g (90%). When recrystallized from alcohol–water, the amino acid has mp 206–208° dec; $[\alpha]^{20}D$ +198.2° (*c* 0.1, water).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.25; H, 7.12; N, 4.69. Found: C, 72.28; H, 7.30; N, 4.60.

Tosyl D(−)-α-Phenylsarcosine (9).—(+)-α-Ephedrinophenylacetic acid (**7**) (3 g) was stirred in benzene to obtain a fine suspension. To this was added a solution of lead tetraacetate (5 g, 85–90% pure) in chloroform (10 ml); the mixture was stirred at room temperature for 4 hr. It was then treated with dilute hydrochloric acid (excess) and stirred for another hour, the lead chloride filtered off, and the aqueous layer separated. This aqueous solution was made alkaline with sodium hydroxide, tosyl chloride (2.5 g) in ether (30 ml) was added, and the mixture was stirred for 5 hr after which it was made acid to congo red. The ether layer was separated, the solvent removed, and the residue washed repeatedly with petroleum ether and recrystallized from ethyl acetate–petroleum ether, when the pure tosyl derivative is obtained, which has mp 115–117°; yield 2.2 g (70%); $[\alpha]^{20}D$ −61.1° (*c* 0.5, ethanol) [reported[4] 115.5–117°; $[\alpha]^{20}D$ −63.0° (*c* 0.8, ethanol)].

(+)-α-Ephedrino-*p*-chlorophenylacetonitrile (25).—Sodium α-ephedrino-*p*-chlorophenylmethanesulfonate (**18**) reacted with potassium cyanide in methanol, as before, to yield the product, yield 90%. The aminonitrile crystallizes from benzene–petroleum ether to give colorless crystals with mp 97–98°; $[\alpha]^{20}D$ +13.1° (*c* 8, ethanol).

Anal. Calcd for $C_{18}H_{19}ClN_2O$: N, 8.90. Found: N, 8.79.

(+)-3-*p*-Chlorophenyl-6-phenyl-4,5-dimethylmorpholone-2 (26).—The aminonitrile (**25**) was treated with concentrated hydrochloric acid as before and the product worked up and finally recrystallized from alcohol: mp 153–154°; yield 90%; $[\alpha]^{20}D$ +201.2° (*c* 0.8, ethanol).

Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.50; H, 5.72; N, 4.44. Found: C, 68.62; H, 5.81; N, 4.40.

(+)-α-Ephedrino-*p*-chlorophenylacetic Acid (27).—The morpholone (**26**) was hydrolyzed with potassium hydroxide, and the product isolated and crystallized from water has mp 212–213° dec; $[\alpha]^{20}D$ +193.1° (*c* 0.1, water).

Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.89; H, 6.00; N, 4.21. Found: C, 64.73; H, 6.20; N, 4.10.

Tosyl D(−)-α-*p*-Chlorophenylsarcosine (28).—**27** (3.2 g) was oxidized with lead tetraacetate (5.0 g) and the amino acid directly converted to the tosyl derivative as before, yield 2.2 g (68%). The pure product crystallizes from ethyl acetate–petroleum ether and has mp 120–121°; $[\alpha]^{20}D$ −58.2° (*c* 1, ethanol).

Anal. Calcd for $C_{16}H_{16}ClNO_4S$: C, 54.50; H, 4.54; N, 3.97. Found: C, 54.62; H, 4.60; N, 3.82.

Tosyl α-Phenylsarcosine (29).—(+)-α-Ephedrinophenylacetonitrile (**5**) (2.8 g) was stirred with lead tetraacetate (5.0 g) in ether for 1 hr at room temperature. The lead salts were removed and the aminonitrile was taken up in ether (the ether solution is levorotatory). The ether was removed, the oil allowed to stand with concentrated hydrochloric acid for a day, the solution diluted with water and refluxed for 6 hr, most of the excess of hydrochloric acid removed under reduced pressure, and the residue tosylated as before. The product was isolated and recrystallized from ethyl acetate–petroleum ether, mp 144–145° [reported[4] mp (for the tosyl derivative) 145.5–146.5°]. The product obtained showed no optical rotation in alcohol solution.

α-Anilinophenylmethanesulfonic Acid (−)-Ephedrine Salt (12). Procedure A.—Compound **2** (3.5 g) in water (20 ml) was stirred with aniline (1.0 g) for 15 min. The crystalline precipitate was collected, washed with water and ether, and recrystallized from alcohol: mp 150–151° dec; $[\alpha]^{20}D$ −14.1° (*c* 0.5, ethanol); yield 3.2 g.

Procedure B.—α-Anilinophenylmethanesulfonate (**13**) (7.2 g) was added under stirring to a solution of (−)-ephedrine hydrochloride (5 g) in water (25 ml). The product was collected and crystallized from alcohol: mp 150–151° dec; yield 9.0 g; $[\alpha]^{20}D$ −13.9° (*c* 1, alcohol). The mixture melting point of the two products shows no depression. Their infrared spectra are identical.

Anal. Calcd for $C_{23}H_{25}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54; S, 7.48. Found: C, 64.20; H, 6.61; N, 6.62; S, 7.66.

α-Anilinophenylacetonitrile (14).—Compound **12** (3.0 g) was stirred with potassium cyanide (1.0 g) in water for 1 hr. The product was isolated and recrystallized from alcohol, mp 85–86° (reported[10] mp 85°). The product shows no optical rotation.

(−)-3,4-Dimethyl-2,5-diphenyloxazolidine (3). Procedure A.—**2** (7 g) was dissolved in water (30 ml) and the solution made alkaline with sodium hydroxide (pH 11) and stirred at room temperature for 4 hr. The product (4.7 g, 95%) was recrystallized from alcohol: mp 73–74°; $[\alpha]^{20}D$ −55.1° (*c* 1, ethanol).

Procedure B.—A solution of α-aminophenylmethanesulfonate (**15**) (0.05 mol) in water was stirred with (−)-ephedrine (0.05 mol) for 48 hr at room temperature. The product was collected and washed with water to give a yield of 11.0 g (90%). The product was recrystallized from alcohol: mp 73–74°; $[\alpha]^{20}D$ −55.0° (*c* 1, ethanol).

(−)-Ephedrine Thiocyanate (16). A.—An alcohol solution of 3.7 g of **2** was treated with a wwarm solution of potassium thiocyanate (1.5 g) in alcohol and allowed to stand for 1 hr and the bisulfite compound filtered off. The alcohol solution was concentrated and cooled, and the product was collected. The product was recrystallized from alcohol: mp 140–141°; $[\alpha]^{20}D$ −28.9° (*c* 1, water).

B.—Ammonium thiocyanate was used instead of potassium thiocyanate.

C.—A solution of (−)-ephedrine and ammonium thiocyanate in water also gives the same product.

D.—A solution of (−)-ephedrine and potassium thiocyanate in water does not give the product in 3 hr; on adding sodium bisulfite to the solution the product crystallizes out [reported[9] mp (for the product) 138–140°; $[\alpha]^{20}D$ −31.0°].

Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.75; H, 7.22; N, 12.48. Found: C, 58.68; H, 7.23; N, 12.26.

(10) E. Knoevenagel, *Ber.*, **37**, 4087 (1904).

Registry No.—1, 299-42-3; 2, 29843-08-1; 3, 29843-09-2; 5, 29843-10-5; 6, 29843-11-6; 7, 29843-12-7; 12, 29843-13-8; 16, 13900-17-9; 18, 29843-15-0; 19, 29843-16-1; 20, 29843-17-2; 21, 29843-18-3; 22, 29843-19-4; 23, 29843-20-7; 24, 29843-21-8; 25, 29843-22-9; 26, 29843-23-0; 27, 29843-24-1; 28, 29850-72-4.

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Asymmetric Synthesis. II. Synthesis and Absolute Configuration of Oxazolidines Derived from (−)-Ephedrine and Aromatic Aldehydes

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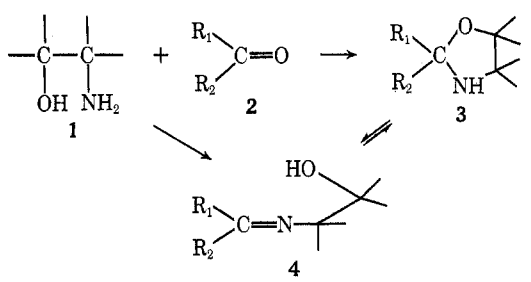
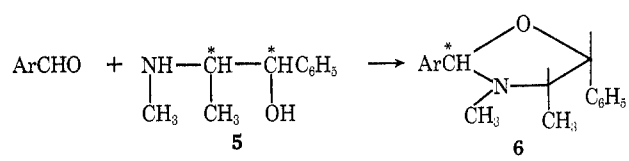
When D(−)-ephedrine reacts with aromatic aldehydes, oxazolidines are formed. This is a stereospecific reaction resulting in an asymmetric synthesis. The oxazolidines were cleaved by Grignard reagents to give tertiary amino alcohols which were further degraded with cyanogen bromide or lead tetraacetate or through the Hofmann elimination reaction to compounds of known absolute configuration. The oxazolidines thus prepared have the 2*R*:4*S*:5*R* configuration. These results have been confirmed by X-ray diffraction studies.

Though oxazolidines have been known for a number of years,[2,3] the structures of some of the compounds reported as oxazolidines have recently been questioned.[4] When primary β-amino alcohols are treated with carbonyl compounds, the products obtained (oxazolidines) may exist as a mobile tauomeric system with the corresponding Schiff bases. However, when a secondary

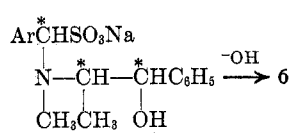


amino alcohol reacts with carbonyl compounds, true oxazolidines are formed.[5−13] Bergmann[14] in his comprehensive review has discussed their structure, syntheses, and reactions.

The present study is concerned with the reaction of (−)-ephedrine with aromatic aldehydes to form oxazolidines. When equimolar amounts of the amino alcohol and the carbonyl compounds are refluxed in benzene or ethanol or allowed to stand at room temperature, high yields of oxazolidines are formed. Similarly,



α-aminoalkanesulfonates derived from aromatic aldehydes, (−)-ephedrine, and sodium bisulfite[15] are easily converted into oxazolidines in the presnce of base.



The present author contends that, when D(−)-ephedrine or L(+)-pseudoephedrine is allowed to react with aromatic aldehydes, the reaction proceeds through a totally stereospecific mechanism. Under these conditions, the oxazolidine formed is optically pure. Though predominance of one of the diastereoisomers has been encountered in many asymmetric syntheses, due to the unusual steric features present here, formation of one of the diastereoisomers is not feasible. This results in an asymmetric synthesis.

The configuration of the asymmetric carbon at position 2 of the oxazolidine ring was established by the following sequence of reactions. The oxazolidine ring was cleaved by a Grignard[16,17] reagent to give a β-amino alcohol **9**. The tertiary amino alcohol was then degraded by the Hofmann elimination reaction to yield (*R*)-(+)-

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(3) L. Knorr and H. Mathes, *ibid.*, **34**, 3484 (1901).
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