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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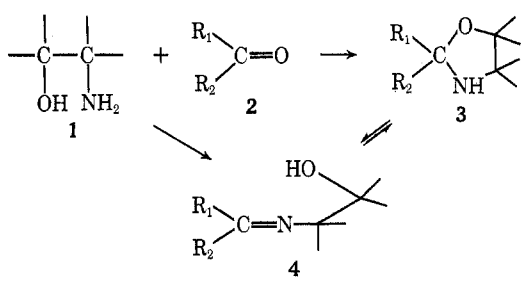
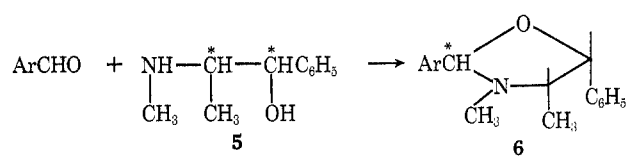
When D(−)-ephedrine reacts with aromatic aldehydes, oxazolidines are formed. This is a stereospecific reaction resulting in an asymmetric synthesis. The oxazolidines were cleaved by Grignard reagents to give tertiary amino alcohols which were further degraded with cyanogen bromide or lead tetraacetate 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

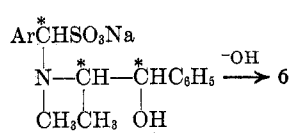


amino alcohol reacts with carbonyl compounds, true oxazolidines are formed.[5−13] Bergmann[14] in his comprehensive review has discussed their structure, syntheses, and reactions.

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*)-(+)-

(1) Division of Molecular Biophysics, Laboratory of Molecular Biology University of Alabama Medical Center, Birmingham, Ala. 35233.
(2) L. Knorr and P. Roessler, *Chem. Ber.*, **36**, 1278 (1903).
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(16) L. H. Goodson and H. Christopher, *J. Amer. Chem. Soc.*, **72**, 358 (1950).
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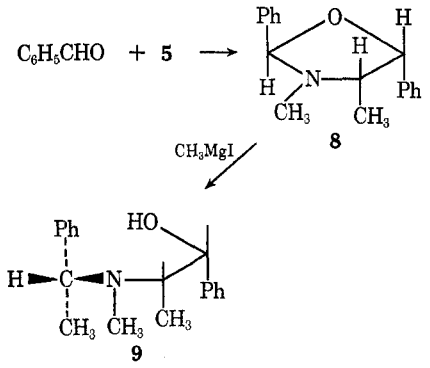
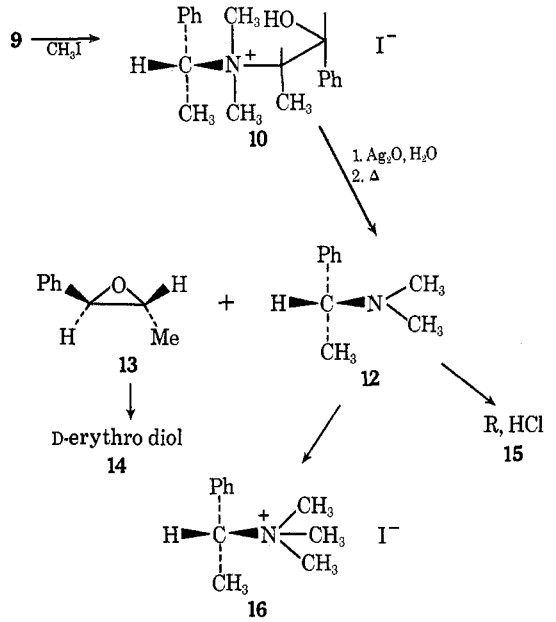
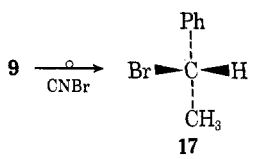


N,N-dimethyl-α-phenethylamine (**12**) and this was characterized[18-22] as the quaternary iodide **16**.

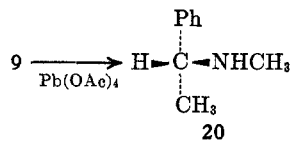


The tertiary amino alcohol **9** can be treated with cyanogen bromide to obtain L(−)-α-phenethyl bromide (**17**) of known configuration.[23-25] The alkyl bromide



was converted to the corresponding D(+)-α-phenethylisothiouronium bromide (**18**) or picrate for characterization.[26,27] The infrared spectra of the L(−)-α-phenethyl bromide and its derivatives are identical with those of the corresponding DL compound.

A third method of assigning the configuration of the induced asymmetric center was to cleave the tertiary amino alcohol with lead tetraacetate[28,29] to obtain D(+)-*N*-methyl-α-phenethylamine (**20**).[30-32] The secondary amine was characterized as the hydrochloride salt or the *p*-nitrobenzoyl derivative **21**. Their infrared spectra were identical with those of the corresponding DL compound.

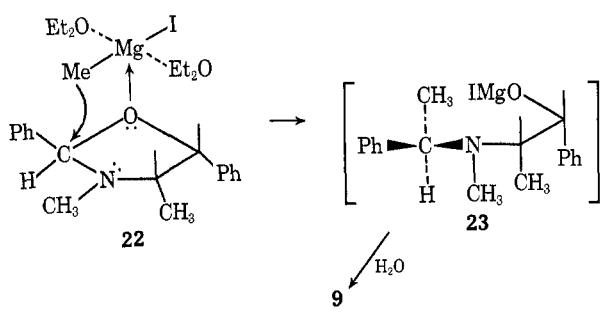


The oxazolidines derived from other aromatic aldehydes and D(−)-ephedrine are also optically pure products, and the configurations of the asymmetric centers at position 2 of the ring were determined by identical procedures. Further, such oxazolidines were also cleaved by EtMgI, $C_6H_5CH_2MgX$, ArMgX, and other Grignard reagents to obtain tertiary amino alcohols which, on degradation, yielded optically pure amines of known configuration.

Discussion

From the foregoing it is quite evident that the reaction of aromatic aldehydes with D(−)-ephedrine proceeds by a stereospecific mechanism. No fractional crystallization is involved, and the yields of the products are close to theoretical. These oxazolidines on degradation yield optically pure α-aryl ethylamines or α-aryl ethyl halides of known configuration. It is clear, therefore, that this is an asymmetric synthesis.

The first step in the degradation of these oxazolidines is the cleavage of the ring with Grignard reagents. The mechanism of this reaction is not fully understood. The exceptional steric features present in the oxazolidines under discussion, however, favor its reaction with Grignard reagents to proceed in a stereospecific manner. The following mechanism is proposed.



Let us consider the stereochemistry of these oxazolidines. It is obvious that the oxazolidine ring is fairly planar. Studies on boroxazolidines[33] and other oxazolidines[34,35] indicate that the conformation of ephedrine is retained in the ring structure. Molecular models show severe steric interaction between substituents in such oxazolidines when they are cis oriented. This interaction is relieved when the aryl group on C-2 lies

(18) W. Leithe, *Chem. Ber.*, **64**, 2827 (1931).
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(20) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *ibid.*, **82**, 4651 (1960).
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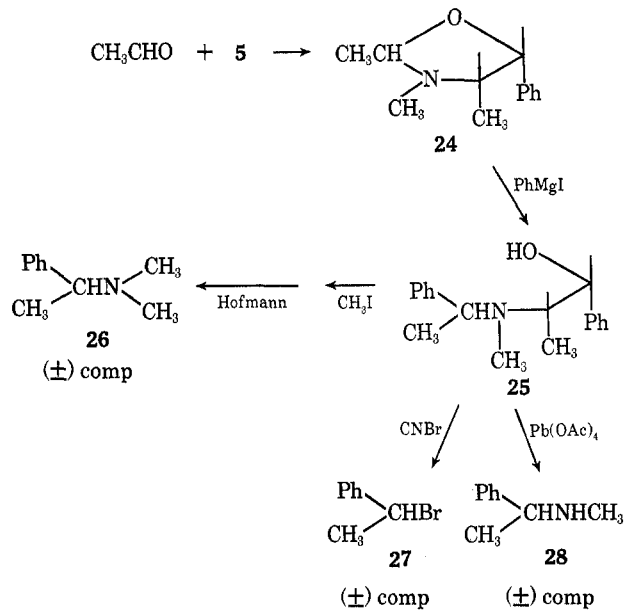
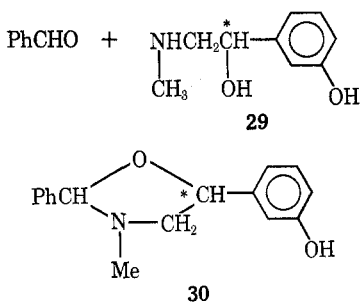
on the opposite side of the plane. In support of this hypothesis are the following observations.

(a) When acetaldehyde reacts with D(−)-ephedrine, the product obtained is a mixture of diastereoisomers.



(b) When benzaldehyde reacts with (+)- or (−)-phenylephrine, the product obtained is a mixture of diastereoisomers, as indicated by the preliminary studies. The absence of the methyl of position 4 is probably responsible for the nonstereospecific nature of the ring formation.



(c) Chloral and ketones as methyl ethyl ketone, acetophenone, cyclopentanone, and cyclohexanone failed to give the desired oxazolidines with D(−)-ephedrine. This again indicated the rigid steric requirements for the formation of such oxazolidines.

(d) It is noteworthy that ketones do form oxazolidines with norephedrine.[12] Hence, the steric interaction on the *N*-methyl group may be a contributing factor.

In conclusion, it can be stated that, when aromatic aldehydes are allowed to react with D(−)-ephedrine, optically pure oxazolidines are obtained. This is a stereospecific reaction and an asymmetric synthesis. In such oxazolidines the induced asymmetric center can be represented by the *R* configuration and hence named 2*R*:4*S*:5*R* oxazolidines. The results are confirmed by a three-dimensional structural analysis using the X-ray diffraction technique.[36]

Further study is in progress to find out the effects of (a) changing the bulk of the group at position 2, (b) changing the substitution on the nitrogen, and (c) changing the bulk of the groups on positions 4 and 5 on the oxazolidine ring system. Aromatic aldehydes react with L(+)-pseudoephedrine to give optically pure oxazolidines; this is also a stereospecific reaction and an asymmetric synthesis. These 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.

Preparation of Oxazolidines. Procedure A.—Ephedrine hydrate (alkaloid) (0.1 mol) and the aldehyde (0.1 mol) were heated under reflux in benzene (100 ml) for 1 hr. The calculated amount of water was then removed using a Dean-Stark column. The excess of benzene was distilled off under reduced pressure and the residue recrystallized from alcohol to give the pure product.

Procedure B.—The aldehyde (0.1 mol) and ephedrine alkaloid (0.1 mol) were refluxed in alcohol (100 ml) for 2 hr. Most of the alcohol was removed under reduced pressure and the residue recrystallized from alcohol.

Procedure C.—α-Ephedrinoalkanesulfonates were prepared from equimolar amounts of the aldehyde, sodium bisulfite, and ephedrine alkaloid in water at room temperature and working up the product as previously described. The pure aminoalkanesulfonates were dissolved in water and the solution made alkaline with sodium hydroxide (pH 9). After being stirred at room temperature for 1 day, the product was collected and recrystallized from alcohol. Table I lists the oxazolidines prepared.

Reaction of Oxazolidines with Grignard Reagents.—The Grignard reagent from magnesium (5 g, 0.2 g-atom), methyl iodide (28 g, 0.2 mol), and anhydrous ether (200 ml) was prepared in the usual way. To this was added **8** (13 g, 0.05 mol) in ether (150 ml) during 15 min with stirring. The solution was then heated under reflux for 8 hr and cooled, the complex decomposed with water, and the ether layer separated. The solution was dried over anhydrous sodium sulfate and the ether was removed under reduced pressure to leave the tertiary amino alcohol as a thick oil, yield 13 g (95%). The amine was converted to the quaternary iodide for characterization. The various tertiary amino alcohols prepared in this manner are listed in Table II.

Attempted Preparation of Tertiary Amino Alcohols.—When α-phenethyl bromide was treated with D(−)-ephedrine in benzene the only product isolated was ephedrine hydrobromide. Attempts to prepare the tertiary amino alcohol by hydrogenation of acetophenone and ephedrine in the presence of palladium-on-charcoal catalyst were also unsuccessful.

Hofmann Degradation of Tertiary Amino Alcohols.—*N*-(α-phenethyl)ephedrine methiodide (6.5 g, 0.016 mol) was suspended in water (50 ml). To this was added silver oxide from silver nitrate (3.4 g, 0.02 mol) and the mixture stirred for 24 hr at room temperature. The silver salts were removed by centrifugation and the aqueous solution was heated under reflux for 2 hr. The solution was cooled, acidified, and extracted with ether. (The ether extract was saved.) The aqueous acidic solution was concentrated under reduced pressure and made alkaline with sodium hydroxide, and the amine was extracted with ether. The amine was characterized as the methiodide or the hydrochloride salt. The results are listed in Table III.

The ether solution was concentrated to dispel the solvent and the residue hydrolyzed to give the diol which was benzoylated and the product characterized as D-*erythro*-1-phenyl-1,2-propanediol dibenzoate,[37] mp 95–96°, $[\alpha]^{20}D$ −60.45° (*c* 1, chloroform).

Reaction of Tertiary Amino Alcohols with Cyanogen Bromide.—A solution of the crude amino alcohol **9** (0.05 mol) in ether (30 ml) was treated with cyanogen bromide (0.15 mol) in ether (50 ml), allowed to stand at room temperature for 24 hr, heated under reflux for 4 hr, and then diluted with petroleum ether (bp 30–60°) (50 ml). The clear solution was separated from the syrupy part formed at the bottom of the flask, the solvent removed, and the residue distilled under reduced pressure. The fraction, bp 92–94° (18 mm), was collected, yield 3 g, αD −68.5°

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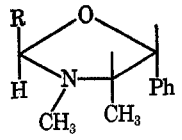
(37) B. Witkop and C. M. Foltz, *J. Amer. Chem. Soc.*, **79**, 197 (1957).

TABLE I

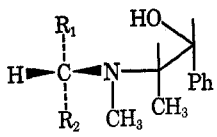
OXAZOLIDINES



No.	R	Mp, °C	Crystals from	$[\alpha]^{20}D$, deg	Yield, %	Procedure	Mol formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
					98	a							
8	C_6H_5	73–74	Alcohol	−55.0	96	b	$C_{17}H_{19}NO$	80.06	7.51	5.53	80.20	7.58	5.61
				(*c* 1, ethanol)	91	c							
8a	*p*-ClC_6H_4	86–87	Alcohol	−52.0	100	a	$C_{17}H_{18}ClNO$	70.80	6.25	4.86	71.08	6.52	4.64
				(*c* 1, ethanol)	98	b							
					97	c							
8b	*p*-$CH_3C_6H_4$	56–57	Alcohol	−66.7	95	a	$C_{18}H_{21}NO$	81.00	7.86	5.25	80.84	7.94	5.47
				(*c* 1, ethanol)	92	b							
					85	c							
8c	3,4-Methylene-dioxy-C_6H_3	82–83	Alcohol	−64.3	98	a							
				(*c* 2, ethanol)	97	b	$C_{18}H_{19}NO_3$	72.73	6.40	4.71	72.69	6.28	4.68
					92	c							
8d	*p*-$NO_2C_6H_4$	79–80	Alcohol	−62.5	98	a	$C_{17}H_{18}N_2O_3$	68.45	6.04	9.40	68.51	6.12	9.40
				(*c* 0.6, ethanol)	96	b							
24	CH_3	Oil			98	a							
					50	c							
31	*i*-C_5H_{11}	Oil			94	a							
					60	c							

TABLE II

TERTIARY AMINO ALCOHOLS FROM OXAZOLIDINES

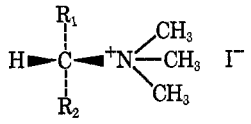


			Methiodide										
No.	R_1	R_2	Yield, %	Mp, °C (dec)	Crystals from	$[\alpha]^{20}D$, deg (ethanol)	Mol formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
9	C_6H_5	CH_3	95	183–184	Ethanol	+34.5	$C_{19}H_{26}INO$	55.58	6.32	3.41	56.04	6.37	3.33
9a	C_6H_5	C_2H_5	90	168–169	Ethyl acetate	+27.1	$C_{20}H_{28}INO$	56.46	6.65	3.29	56.40	6.42	3.19
9b	*p*-ClC_6H_4	CH_3	90	159–160	Ethyl acetate	+34.1	$C_{19}H_{25}ClINO$	51.19	5.66	3.14	51.33	5.61	3.10
9c	C_6H_5	$C_6H_5CH_2$	92	136–137	CH_3OH–ethyl acetate	−12.7	$C_{25}H_{30}INO$	61.60	6.22	2.87	61.48	6.11	2.80
9d	*p*-ClC_6H_4	$C_6H_5CH_2$	90	142–143	Ethyl acetate	−14.5	$C_{25}H_{29}ClINO$	57.41	5.60	2.68	57.26	5.62	2.59
25	CH_3	C_6H_5	95	168–170	Ethanol	−11.7	$C_{19}H_{26}INO$[a]			3.41			3.49

[a] Mixture of diastereoisomers.

TABLE III

METHIODIDE DERIVATIVES OF TERTIARY AMINES FROM HOFMANN ELIMINATION

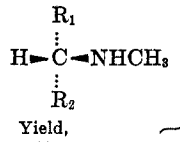


No.	R_1	R_2	Yield, %	Mp, °C	Crystals from	$[\alpha]^{20}D$, deg (methanol)	Mol formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
16	C_6H_5	CH_3	95	157–158 dec[a]	Alcohol–ethyl acetate	+19.8	$C_{11}H_{18}IN$	45.30	6.22	4.70	45.30	6.31	4.68
16a	*p*-ClC_6H_4	CH_3	92	161–162 dec	Alcohol–ethyl acetate	+17.9	$C_{11}H_{17}ClIN$	40.55	5.22	4.30	40.50	5.28	4.34
16b	C_6H_5	C_2H_5	95	163–164 dec	Ethyl acetate	+18.6	$C_{12}H_{20}IN$	47.25	6.70	4.48	47.30	6.79	4.45
16c	C_6H_5	$C_6H_5CH_2$		Mixture of products									
16d	*p*-ClC_6H_4	$C_6H_5CH_2$		Mixture of products									
26	CH_3	C_6H_5	95	144–145[b]	Alcohol–ethyl acetate	−0.5				4.70			4.66

[a] Reported mp 157°, $[\alpha]^{20}D$ +19.6°; see ref 20. [b] Reported mp 145–146°; see ref 21.

TABLE IV

SECOND AMINES BY LEAD TETRAACETATE OXIDATION



No.	R_1	R_2	Yield, %	Hydrochloride: Crystals from	Hydrochloride: Mp, °C (found)	Hydrochloride: $[\alpha]^{20}D$ (found)
20	C_6H_5	CH_3	88	EtOH–acetone	211–212[a]	+29.5
20a	C_6H_5	C_2H_5	85	EtOH–acetone	208–209[b]	+27.5
20b	*p*-ClC_6H_4	CH_3	90	EtOH–acetone	233–234[c]	+25.0
20c	C_6H_5	$C_6H_5CH_2$	92	EtOH–acetone	221–222[d]	−83.5
20d	*p*-ClC_6H_4	$C_6H_5CH_2$	90	EtOH–acetone	230–232[e]	−74.3
28	CH_3	C_6H_5	82	EtOH–acetone	177–178[f]	Nil

[a] Reported[29] mp 213°, $[\alpha]^{20}D$ +29.7°; *p*-nitrobenzoyl derivative, mp 75–76°, $[\alpha]^{20}D$ +180.0°. [b] *Anal.* Calcd for $C_{10}H_{16}ClN$: C, 64.69; H, 8.63; N, 7.55. Found: 64.60; H, 8.55; N, 7.62. [c] *Anal.* Calcd for $C_9H_{13}Cl_2N$: C, 52.43; H, 6.31; N, 6.80. Found: 52.55; H, 6.30; N, 6.75. [d] Reported [K. Oglu, H. Fujimura, and Y. Yamakawa, *Yakugaku Zasshi*, **80**, 283 (1960)] mp 221–222°, $[\alpha]^{20}D$ −84.5°; *p*-nitrobenzoyl derivative, mp 127–128°, $[\alpha]^{20}D$ +99.0°. [e] *Anal.* Calcd for $C_{15}H_{17}Cl_2N$: C, 63.82; H, 6.03; N, 4.96. Found: 63.68; H, 6.22; N, 5.07. [f] Reported[30] mp 178–179°. The compound is a DL mixture.

(neat). The infrared spectrum is identical with that of α-phenethyl bromide.

L(−)-α-phenethyl bromide (1.3 g) and thiourea (6.0 g) were refluxed in alcohol (40 ml) for 8 hr. The alcohol was removed under reduced pressure and the residue treated with dry benzene (40 ml). On being allowed to stand in the refrigerator for a day, the D(+)-α-phenethylisothiouronium bromide (**18**) separated, which was collected, washed with dry ether, and dried, mp 165–167°, $[\alpha]^{20}D$ +45.0° (*c* 2, water).

Part of the bromide **18** was treated with picric acid in alcohol to obtain the corresponding picrate which was crystallized from alcohol to give mp 167–168°, $[\alpha]^{20}D$ +28.2° (*c* 2, ethanol).

Anal. Calcd for $C_{15}H_{15}N_5SO_7$: C, 44.00; H, 3.68; N, 17.20. Found: C, 43.99; H, 3.63; N, 18.22.

The DL compound was made in a similar way, mp 156–157° (reported[26] mp 158–159°).

In the same way *p*-Cl-phenethylephedrine gave with cyanogen bromide L(−)-α-*p*-Cl-phenethyl bromide, bp 103–104° (15–20 mm), αD −55.0° (neat). This was converted to the corresponding isothiouronium picrate, mp 215–216°, $[\alpha]^{20}D$ +24.2° (*c* 1, ethanol).

Anal. Calcd for $C_{15}H_{14}N_5SO_7Cl$: C, 40.50; H, 3.16; N, 15.80. Found: C, 39.65; H, 3.28; N, 16.25.

Lead Tetraacetate Oxidation.—To a solution of 0.05 mol of the crude α-phenethylephedrine (**9**) in ether (100 ml) was added a solution of lead tetraacetate (0.05 mol) in ethyl acetate (50 ml). The mixture was stirred at 60° for 4 hr, cooled, treated with excess of dilute hydrochloric acid, and stirred at room temperature for 1 hr. The lead chloride was removed by filtration, the clear organic layer separated, and the aqueous phase evaporated to dryness. The residue was taken up in alcohol and diluted with acetone to yield D(+)-*N*-methyl-α-phenethylamine hydrochloride (**20**). The organic layer was carefully distilled to collect first acetaldehyde which was identified as the semicarbazone. The residue was worked up in order to isolate benzaldehyde as its phenylhydrazone.

The tertiary amino alcohol **9** in the form of its hydrochloride can also be cleaved by lead tetraacetate by heating the two in ethyl acetate at 60° for 6 hr and working up the product.

The secondary amines with their physical constants are listed in Table IV.

Registry No.—**5**, 299-42-3; **8**, 29843-09-2; **8a**, 29843-16-1; **8b**, 29843-18-3; **8c**, 29850-76-8; **8d**, 29850-77-9; **10**, 29936-54-7; **10a**, 29936-55-8; **10b**, 29850-78-0; **10c**, 29936-56-9; **10d**, 29936-57-0; **16a**, 29850-79-1; **16b**, 29850-81-5; **18**, 29850-82-6; **18** picrate, 29850-83-7; **20a** HCl, 29850-84-8; **20b** HCl, 29850-85-9; **20d** HCl, 29850-86-0; **21**, 29850-87-1; **21c**, 29850-88-2; **25** methiodide, 29936-59-2; L(−)-α-*p*-Cl-phenethyl bromide, 29850-89-3, 29850-90-6 (isothiouronium picrate).

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