Optically Active Amines. XIX.[1] Circular Dichroism of Ortho-, Meta-, and Para-Substituted β-Phenylalkylamine Hydrochlorides. Further Applications of the Salicylidenimino Chirality Rule[2]

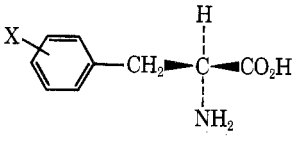
Howard E. Smith,*[3a] Elizabeth P. Burrows,[3a] and Fu-Ming Chen[3b]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, Tennessee Neuropsychiatric Institute, Nashville, Tennessee, and Department of Chemistry, Tennessee State University, Nashville, Tennessee 37203

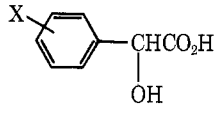
Received October 29, 1974

o- and *m*-chloroamphetamine have been resolved and the absolute configurations of the respective enantiomers determined by catalytic hydrogenolysis to amphetamine. The established absolute configurations of (*R*)-(−)-*o*-, (*S*)-(+)-*m*-, and (*S*)-(+)-*p*-chloroamphetamine are compared with predictions based on Snatzke's sector rule for the correlation of absolute configuration with the sign of the ^1L_b Cotton effect and with predictions based on the salicylidenimino chirality rule for the correlation of absolute configuration with the sign of the Cotton effects near 255 and 315 (325) nm in the CD spectrum of the *N*-salicylidene (*N*-5-bromosalicylidene) derivative. Snatzke's rule does not correctly predict the sign of the ^1L_b Cotton effect for the meta isomer. The salicylidenimino chirality rule, however, correctly predicts the sign of the Cotton effects near 255 and 325 nm observed for the *N*-5-bromosalicylidene derivatives, the *S* configuration in each case producing strong positive Cotton effects. These results confirm the configurational assignments for the nonstimulant anorectic agent (+)-fenfluramine and for the enantiomers of the psychotomimetic amine 1-(2,5-dimethoxy-4-methylbenzyl)ethylamine, made on the basis of the CD spectra of the respective *N*-salicylidene derivatives.

Few systematic studies have been made concerning the effect of ring substitution on the Cotton effects of chiral benzenoid compounds. The quadrant sector rules[4-6] for correlation of the sign of the ^1L_b Cotton effect with the absolute configuration of chiral 1-substituted indans[4] and α- and β-phenylalkylamines and their hydrochlorides[6] cannot be applied to ortho- and meta-substituted phenylalkyl compounds, since the symmetry of the chromophore is altered. Snatzke,[7] however, has proposed another sector rule based on the nodal planes of the benzene ring and Platt's spectroscopic moments[8,9] by which the direction of the overall spectroscopic moment vector is used to predict the sign of the ^1L_b Cotton effects of chiral ortho-, meta-, and para-disubstituted benzenes. If the spectroscopic moments of the two substituents are of the same sign and approximately the same magnitude, this rule predicts a ^1L_b Cotton effect for the ortho and meta compounds of opposite sign to that observed for the para compound. Experimental verification was found in the case of the substituted phenylalanines. Both L-phenylalanine (**1a**) and L-tyrosine (**1b**) show positive circular dichroism (CD) bands at about 260 nm[10-12] while the corresponding bands for L-*o*- and L-*m*-hydroxyphenylalanine (**1c** and **1d**) are negative.[12] Snatzke



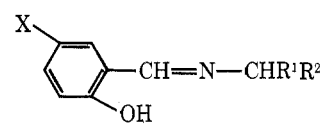
1a, X = H
b, X = *p*-OH
c, X = *o*-OH
d, X = *m*-OH



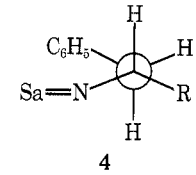
2, X = Br, Cl, F, or OCH_3

noted, however, that earlier data[13] for ring-substituted mandelic acids (**2**) did not agree with prediction. He attributed this failure to the presence of the chiral center adjacent to the benzene ring and a consequent change in the relative population of conformers resulting from rotation of the chiral center about its attachment bond on introduction of a substituent. The implication was strong that compounds having the chiral center separated from the ring by a methylene group should not be thus affected and should conform to the rule.

For the establishment of the absolute configurations of chiral α- and β-arylalkylamines, we have devised an alternate CD method, formulated as the salicylidenimino chirality rule.[14] This rule correlates the sign of the Cotton effects near 255 and 315 (325) nm in the CD spectra of *N*-salicylidene (**3a**) [*N*-5-bromosalicylidene (**3b**)] derivatives of the



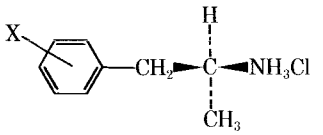
3a, X = H
b, X = Br



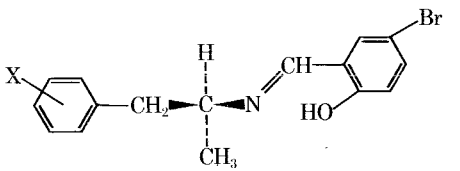
4

amines with their absolute configurations. For β-phenylalkylamine derivatives the sign of these Cotton effects is positive for a right-handed screw pattern as shown in **4**, the screw sense depending on both the absolute configuration and preferred conformation of the derivative. The Cotton effects arise by the coupled oscillator mechanism[15] and are the result of interaction of the electric dipole transition moments of the salicylidenimino chromophore, oriented approximately parallel to the attachment bond, with the ^1L_a and $^1B_{a,b}$ benzenoid transitions of the phenyl chromophore. The effective transition moment directions of the latter are along the phenyl group attachment bond. The transverse components of these moments are assumed to be cancelled by rotation of the phenyl group about its attachment bond. Substitution at various positions of the benzene ring of a particular chiral β-phenylalkylamine should have little effect on the Cotton effects near 255 and 315 (325) nm, except for possible minor variations in intensity reflecting changes in the magnitude of the effective transition moments along the phenyl group attachment bond due to the substituent.

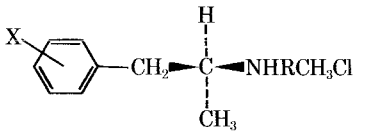
Our continuing interest in the determination of the absolute configuration of chiral amines by CD methods[14] and in the pharmacological effects of stereoisomeric chlorinated amphetamines[16] has prompted us to prepare enantiomers of *o*- and *m*-chloroamphetamine hydrochloride (**5a** and **6a**) and to use them to assess the validity of both Snatzke's sector rule and the salicylidenimino chirality rule. To this end we compare the CD spectra of (*R*)-**5a** and (*S*)-**6a** and the corresponding free bases (*R*)-**5b** and (*S*)-**6b** with those of (*S*)-(+)-*p*-chloroamphetamine hydrochloride[16,17] [(*S*)-**7a**]



(*S*)-**5a**, X = *o*-Cl
(*S*)-**6a**, X = *m*-Cl
(*S*)-**7a**, X = *p*-Cl
(*S*)-**8a**, X = H



(*S*)-**5c**, X = *o*-Cl
(*S*)-**6c**, X = *m*-Cl
(*S*)-**7c**, X = *p*-Cl
(*S*)-**8c**, X = H



(*S*)-**6d**, X = *m*-Cl; R = H
(*S*)-**6e**, X = *m*-Cl; R = CH_3
(*S*)-**7d**, X = *p*-Cl; R = H
(*S*)-**7e**, X = *p*-Cl; R = CH_3

Table I
Spectral Data for Amphetamine Hydrochlorides and Their *N*-Methyl Derivatives in Methanol[a]

Compd	Max	Wavelength, nm (ϵ^b or $[\theta]^c$)										
		^1L_b								^1L_a		
(*R*)-5a	EA	273 (160)		265 (200)	262 (190)[d,e]	258 (170)[d]	252 (120)[d]					212 (9200)
	CD	274 (+110)		267 (+100)							220 (+4100)	
(*S*)-6a	EA	274 (220)		267 (260)		260 (200)	253 (130)[d]	247 (80)[d]				213 (9200)
	CD	275 (+310)		268 (+350)		261 (+280)					222 (+8400)	
(*S*)-6d	EA	274 (220)		267 (270)		260 (200)	254 (140)[d]	247 (90)[d]				213 (9100)
	CD	275 (+240)		268 (+280)		261 (+180)					222 (+2300)	
(*S*)-6e	EA	274 (250)		267 (290)		260 (230)	254 (160)[d]	248 (120)[d]				213 (10,000)
	CD	275 (+270)		267 (+270)		261 (+180)					222 (+3200)	
(*S*)-7a	EA	276 (240)		268 (280)		261 (220)	255 (160)[d]	248 (110)[d]			224 (9500)[d]	220 (11,000)
	CD	277 (+160)		268 (+170)		262 (+140)				227 (+13,000)	223 (+9000)	
(*S*)-7d	EA	276 (230)		268 (280)		261 (220)	255 (160)[d]	249 (110)[d]			224 (9500)[d]	220 (11,000)
	CD	277 (+150)		268 (+180)		261 (+120)				227 (+8800)	222 (+4100)	
(*S*)-7e	EA	276 (230)		268 (380)		261 (220)	255 (160)[d]	248 (110)[d]			224 (9700)[d]	220 (11,000)
	CD	277 (+120)		268 (+180)		261 (+160)				227 (+10,000)	223 (+8200)	
(*S*)-8a	EA	267 (80)	264 (120)[e]	261 (120)[d]	258 (170)[e]		248 (100)	243 (60)[d]	237 (30)[d]			207 (7800)
	CD	268 (+210)		261 (+230)		254 (+160)	248 (+120)	243 (+110)	237 (+70)		215 (+8800)	

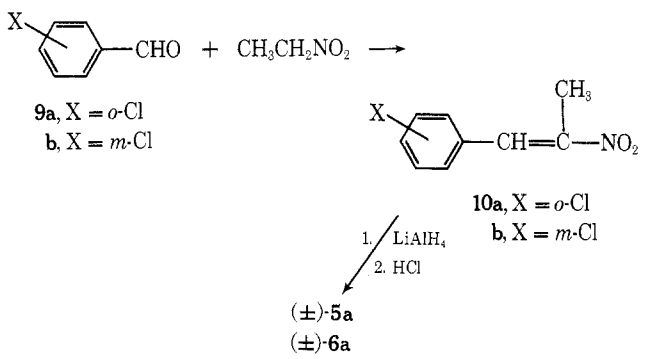
[a] c 1.38×10^{-3} to 8.29×10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder. [e] Transition to a non-totally symmetric vibrational mode.

and (*S*)-(+)-amphetamine hydrochloride [(*S*)-**8a**] and their free bases. The structural features of these amines are well suited for this purpose in that the chiral center is separated from the benzene ring by a methylene group, and the spectroscopic moments of a chlorine and a methyl substituent are nearly identical in sign and magnitude.[8,9] We also examine the effect of *N*-methyl substituents on the CD spectra of meta- and para-substituted β-phenylalkylamine hydrochlorides (**6d, 6e, 7d,** and **7e**). Finally, in extension of the salicylidenimino chirality rule to ortho- and meta-substituted β-phenylalkylamines, we compare the CD spectra of *N*-5-bromosalicylidene derivatives **5c–8c.**

Results and Discussion

Synthesis and Proof of Configuration. The most efficient synthesis of the racemic amines involved condensation of the requisite aldehyde (**9**) with nitroethane[19] followed by lithium aluminum hydride ($LiAlH_4$) reduction of the resulting chlorophenylnitropropene (**10**) (Scheme I).

Scheme I



An earlier paper[20] described the resolution of (±)-**5b** using (+)-tartaric acid, but we have found that the amine so obtained was 65% racemic (cf. Experimental Section). L-*N*-Acetylleucine had proven to be the acid of choice for the resolution of (±)-**7b**[16] and was equally successful with (±)-**5b.**

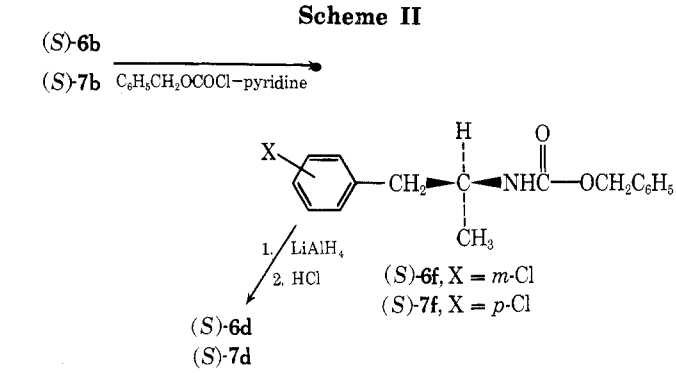
A recent patent[21] described a resolution of (±)-**6b** using (−)-dibenzoyltartaric acid to give a free base which we have found to be no more than 76% resolved. In our hands, this same resolving agent gave partially racemic (*R*)-**6a.** Optically pure (*S*)-**6a** was obtained, however, using (+)-dibenzoyltartaric acid and the partially resolved amine from the original resolution mother liquors.

The configurations of (*S*)-**7a** and (*S*)-**8a** are well known,[16] and the configurations of (*R*)-**5a** and (*R*)-**6a** were established by conversion of each to (*R*)-**8a** by catalytic hydrogenolysis. The samples of (*R*)-**8a** in each case were shown by gas–liquid chromatography (GLC) of the free base to be at least 99% pure. The enantiomers of **8a** are known to racemize on heating with Raney nickel,[22] and some racemization took place during hydrogenolysis of (*R*)-**6a** in hydrochloric acid. Hydrogenolysis of the free base (*R*)-**5b** over palladium on carbon in ethanolic acetic acid was not accompanied by racemization.

The *N*-methyl derivatives of **6a** and **7a** were prepared by $LiAlH_4$ reduction of the corresponding *N*-carbobenzoxy derivatives **6f** and **7f** (Scheme II). Thus (*S*)-**6d** and (±)-, (*S*)-, and (*R*)-**7d** were prepared from the respective amines. The *N,N*-dimethyl derivatives [(*S*)-**6e** and (±)-, (*S*)-, and (*R*)-**7e**] were prepared by reductive (Eschweiler–Clarke) methylation of **6b** and **7b** of the respective configurations with formaldehyde in aqueous formic acid.

Circular Dichroism of Amine Hydrochlorides and Amines. The electronic (isotropic) absorption (EA) and

Scheme II



CD data of the optically active amine hydrochlorides are summarized in Table I. The fine structure pattern in the ^1L_b band (ca. 235–275 nm) and the ^1L_a band (ca. 210–225 nm) in the CD spectra of **5a–8a** can be understood in terms of progressions dominated by the totally symmetric vibrational modes of 1050 cm^{-1} in *o*-chlorotoluene, 1000 cm^{-1} in *m*-chlorotoluene, 797 and 1092 cm^{-1} in *p*-chlorotoluene, and 1000 cm^{-1} in toluene.[23] The data in Table I also show that *N*-methyl substitution has little effect except to reduce the intensity of the ^1L_a Cotton effects shown by the methylated derivatives relative to the respective parent compounds.

As predicted by Snatzke's rule,[7] the ortho-substituted hydrochloride [(*R*)-**5a**] shows a ^1L_b Cotton effect of the same sign as those of the unsubstituted [(*S*)-**8a**] and the para-substituted hydrochlorides [(*S*)-**7a,** (*S*)-**7d,** and (*S*)-**7e**] of the opposite configuration. Contrary to prediction, however, those of the meta-substituted hydrochlorides [(*S*)-**6a,** (*S*)-**6d,** and (*S*)-**6e**] have the same sign as those of the unsubstituted and para-substituted hydrochlorides of the same configuration. The CD data for the amines (Table II), obtained by measurement with solutions prepared from the respective hydrochlorides in 0.1 *N* methanolic potassium hydroxide, show that the ^1L_b Cotton effect for an amine is not significantly different from that of its hydrochloride. It appears then that, aside from possible sign inversion due to transitions to non-totally symmetric vibrational modes,[11,24] caution should be exercised in correlation of the ^1L_b Cotton effect of an arylalkylamine with its absolute configuration, especially when the ring is polysubstituted.

It is noteworthy that, while hydrochlorides (*S*)-**6a,** (*S*)-**7a,** and (*S*)-**8a** all show optical rotations in water at the D

Table II
Circular Dichroism Data for Amphetamines in 0.1 *N* Methanolic Potassium Hydroxide[a]

Compd	λ, nm ([θ][b])	
	Max	Cutoff
(*R*)-**5b**	275 (+66)	
	267 (+74)	230 (−)
(*S*)-**6b**	276 (+170)	
	268 (+190)	
	261 (+130)	235 (+)
(*S*)-**7b**	277 (+260)	
	270 (+300)	
	263 (+190)	225 (+)
(*S*)-**8b**	269 (+140)	
	262 (+150)	
	255 (+110)	225 (+)

[a] Weighed amounts of hydrochlorides, *c* 8.01 × 10^{-2} to 8.62 × 10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molecular ellipticity.

Table III
Spectral Data for *N*-5-Bromosalicylidene Derivatives in Absolute Ethanol[a]

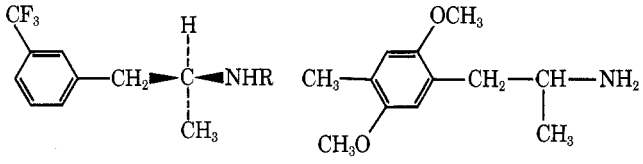
Compd	EA max, λ, nm (ε[c])	CD: Longest and shortest λ, nm ([θ][b])	CD: Max, λ, nm ([θ][b])	CD: Min, λ, nm ([θ][b])	CD: [θ][b] = ±0 λ, nm[d]
(*R*)-**5c**		500 (±0)			470
	416 (520)		416 (−1200)	376 (−800)	
	327 (3800)		327 (−12,000)	282 (−1500)	
	274 (1600)[e]				
	254 (10,000)		256 (−38,000)		232
		232 (±0)			
	219 (35,000)				
(*S*)-**6c**		500 (±0)			465
	417 (600)		417 (+1700)	380 (+1000)	
	328 (3900)		328 (+13,000)	285 (+1600)	
	275 (1800)[e]				
	254 (11,000)		255 (+38,000)		237
		233 (−5900)			
	220 (37,000)				
(*R*)-**7c**[f]		500 (±0)			455
	415 (600)		415 (−1500)	380 (−900)	
	328 (3700)		326 (−14,000)	280 (−900)	
	276 (1700)[e]				
	254 (10,000)[e,g]		255 (−43,000)		237
		233 (+2200)			
(*S*)-**8c**[f]		500 (±0)			470
	415 (740)		411 (+2200)	370 (+1100)	
	327 (3600)		327 (+12,000)	277 (+1000)	
	276 (1600)[e]				
	254 (10,000)[e]		254 (+35,000)		237
		233 (−8200)			
	220 (31,000)				

[a] *c* 2.65 × 10^{-3} to 6.78 × 10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molecular ellipticity. [c] Molar absorptivity. [d] Each first entry at a longer wavelength than a maximum indicates the interval from the longest wavelength examined for which [θ] = ±0. [e] Shoulder. [f] Data from ref 16. [g] Spectrum below 225 nm not determined.

line of the same sign as their ^1L_b and ^1L_a Cotton effects in methanol (positive), (*R*)-**5a** has a negative rotation at the D line and positive ^1L_b and ^1L_a Cotton effects. Thus it appears that the inaccessible (below 210 nm) $^1B_{a,b}$ Cotton effect for (*R*)-**5a** must be very strongly negative. In comparing CD spectra of the free bases (Table II), it is possibly significant that at cutoff (225–235 nm) (*R*)-**5b** is negative and the others positive.

Circular Dichroism of *N*-5-Salicylidene Derivatives. The EA and CD data for the *N*-5-bromosalicylidene derivatives are summarized in Table III. The signs of the Cotton effects near 255 and 325 nm are in accord with those predicted by the salicylidenimino chirality rule,[14] positive for all derivatives with the *S* configuration, negative for *R*. The more intense Cotton effects observed for (*R*)-**7a** result from reinforcement of the spectroscopic moments of the two para substituents on the benzene ring producing a larger transition moment along the attachment bond for the ^1L_a transition.

These results validate the application of the salicylidenimino chirality rule to polysubstituted arylalkylamines. Thus the assignment of the *S* configuration to the nonstimulant, anorectic agent (+)-fenfluramine [(+)-*N*-ethyl-α-(*m*-trifluoromethylbenzyl)ethylamine] [(*S*)-**11a**], made in part on the basis of the CD spectrum of the *N*-salicylidene derivative of (+)-norfenfluramine [(*S*)-**11b**],[25] is confirmed. The configurational assignment made on the same basis for the stereoisomers of the psychotomimetic amine α-(2,5-dimethoxy-4-methylbenzyl)ethylamine[26] (**12**) is also confirmed.



(*S*)-**11a**, R = C_2H_5
(*S*)-**11b**, R = H

12

Experimental Section

Hydrochlorides were prepared by treatment of potassium hydroxide dried ether solutions of the free bases with hydrogen chloride. Amines were obtained from the salts by treatment of the latter with 10% sodium hydroxide solution, extraction into ether, and drying over potassium hydroxide. Melting points were taken in sealed capillary tubes and are corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and a 1-dm tube. Proton magnetic resonance (^1H NMR) spectra were determined with a Jeol MH-100 spectrometer and chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Isotropic electronic absorption (EA) spectra were measured with a Cary Model 14 spectrometer with the normal variable slit. Circular dichroism (CD) spectra were measured with a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory, and the slit was programmed for a spectral band width of 1.5 nm. A Varian Aerograph Model 90-P instrument fitted with a 5 ft × 0.25 in. 5% SE-30 column was used for GLC analyses (140°). Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn.

(±)-*o*-Chloroamphetamine Hydrochloride [(±)-5a]. 1-(2-Chlorophenyl)-2-nitropropene[27] (**10a**, 65.1 g, 0.329 mol), prepared by the published procedure,[19] was reduced with excess $LiAlH_4$ in ether as described previously.[19] The resulting amine, (±)-**5b**, was

converted to the hydrochloride (±)-**5a** (46.1 g, 68%), recrystallized from acetone–ether, mp 182–183° (lit.[20] mp 175–176°).

(*R*)-(−)-*o*-Chloroamphetamine Hydrochloride [(*R*)-5a]. A solution of sodium L-*N*-acetylleucinate prepared from L-*N*-acetylleucine (7.35 g, 42.4 mmol) and sodium hydroxide (1.70 g, 42.5 mmol) in water (125 ml) was added dropwise to a stirred solution of (±)-**5a** (15 g, 73 mmol) in water (125 ml). It was necessary to concentrate the resulting solution to ca. 100 ml to obtain a crystalline salt (6 g) which was recrystallized twice from water to constant specific rotation, $[\alpha]^{25}D$ −31° (*c* 1.63, H_2O). Optically pure (*R*)-**5a** obtained therefrom had mp 171–172°; $[\alpha]^{25}D$ −26° (*c* 1.96, H_2O) [lit.[20] mp 175–176°; $[\alpha]^{25}D$ +9.0° (*c* 3.78, H_2O) for (*S*)-**5a**].

Hydrogenolysis of (*R*)-(−)-*o*-Chloroamphetamine Hydrochloride [(*R*)-5a]. A mixture of (*R*)-**5b** (0.32 g), absolute ethanol (12.5 ml), glacial acetic acid (2.5 ml), and 10% palladium on carbon (0.53 g) was stirred under hydrogen until uptake ceased (2.5 hr). The catalyst was removed by filtration, the filtrate was evaporated to near dryness and made strongly alkaline with 10% sodium hydroxide, and the amine was extracted into ether. GLC analysis showed in addition to ether a single peak identical in retention time (0.9 min) with authentic (*R*)-**8b** and no trace of (*R*)-**5b** (retention time 2.3 min). The hydrochloride had $[\alpha]^{25}D$ −24° (*c* 8.97, H_2O) [lit.[18] $[\alpha]^{25}D$ +21.6° (*c* 9.0, H_2O) for (*S*)-**8a**].

(*R*)-(−)-*N*-(5-Bromosalicylidene)-*o*-chloroamphetamine [(*R*)-5c] prepared from equimolar amounts of (*R*)-**5b** and 5-bromosalicylaldehyde was an oil which after drying for 48 hr at room temperature (0.05 mm) had $[\alpha]^{25}D$ −255° (*c* 1.06, absolute C_2H_5OH).

(±)-*m*-Chloroamphetamine Hydrochloride [(±)-6a]. 1-(3-Chlorophenyl)-2-nitropropene (**10b**), prepared in a similar manner to **10a**, had bp 98° (0.01 mm) [lit.[28] bp 101.5–102° (0.2 mm)]. Reduction of **10b** with excess $LiAlH_4$ in ether gave (±)-**6b**, bp 63–73° (0.5 mm). The hydrochloride (±)-**6a**, recrystallized from acetonitrile–methanol, had mp 158–160°.

Anal. Calcd for $C_9H_{13}Cl_2N$: C, 52.44; H, 6.36; Cl, 34.40. Found: C, 52.46; H, 6.39; Cl, 34.46.

(*S*)-(+)-*m*-Chloroamphetamine Hydrochloride [(*S*)-6a]. A solution of (−)-dibenzoyltartaric acid monohydrate (21.5 g, 0.057 mol) in 95% ethanol (120 ml) was added dropwise to a stirred solution of (±)-**6b** (18.2 g, 0.107 mol) in absolute ethanol (125 ml). The precipitated salt was collected, recrystallized twice from 80% aqueous ethanol, and treated with 10% sodium hydroxide to yield partially racemic (*R*)-**6b**, $[\alpha]^{25}D$ −18° (*c* 4.05, CH_3OH) [lit.[21] $[\alpha]^{20}D$ −17° (*c* 2, CH_3OH)]. Hydrochloride (*R*)-**6a** had $[\alpha]^{25}D$ −16° (*c* 1.98, H_2O).

Evaporation of the filtrate from the original precipitation of the dibenzoyltartrate salt above followed by treatment with 10% sodium hydroxide yielded partially racemic (*S*)-**6b** (3.86 g, 2.27 mmol). It was dissolved in absolute ethanol (20 ml) and treated as above with a solution of (+)-dibenzoyltartaric acid monohydrate (6.40 g, 1.70 mmol) in 95% ethanol (40 ml). The precipitated salt was collected, recrystallized from 80% aqueous ethanol, and treated with 10% sodium hydroxide to give (*S*)-**6b**. Hydrochloride (*S*)-**6a** had mp 165–166°, $[\alpha]^{25}D$ +21° (*c* 2.10, H_2O).

Hydrogenolysis of Partially Racemic (*R*)-(−)-*m*-Chloroamphetamine Hydrochloride [(*R*)-6a]. To a solution of partially resolved (*R*)-**6a** (219 mg), $[\alpha]^{25}D$ −16°, in water (9 ml) was added platinum oxide (110 mg) and concentrated hydrochloric acid (3 drops). The mixture was stirred under hydrogen until uptake ceased (20 hr). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The white, crystalline residue of partially racemic (*R*)-**8a** had, after drying for 12 hr at 60° (0.1 mm), $[\alpha]^{25}D$ −11° (*c* 9.03, H_2O) [lit.[18] $[\alpha]^{25}D$ +21.6° (*c* 9.0, H_2O) for (*S*)-**8a**]. GLC analysis of the amine obtained from this hydrochloride showed only **8b**.

(*S*)-(+)-*N*-(5-Bromosalicylidene)-*m*-chloroamphetamine [(*S*)-6c], prepared from equimolar amounts of (*S*)-**6b** and 5-bromosalicylaldehyde in methanol, had mp 92–93°, $[\alpha]^{25}D$ +228° (*c* 0.95, absolute C_2H_5OH).

Anal. Calcd for $C_{16}H_{15}BrClNO$: C, 54.49; H, 4.29. Found: C, 54.20; H, 4.15.

(*S*)-*N*-Methyl-*m*-chloroamphetamine Hydrochloride [(*S*)-6d]. (*S*)-*N*-Carbobenzoxy-*m*-chloroamphetamine [(*S*)-**6f**], prepared in 90% yield by the procedure described below for (±)-**7f**, was treated with excess $LiAlH_4$ in ether as described below for the preparation of (±)-**7d** to give crude (*S*)-**6d** (83%), recrystallized from acetone, mp 140–141°, $[\alpha]^{25}D$ +13° (*c* 1.90, H_2O).

Anal. Calcd for $C_{10}H_{15}Cl_2N$: C, 54.56; H, 6.87. Found: C, 54.78; H, 6.90.

(*S*)-*N,N*-Dimethyl-*m*-chloroamphetamine Hydrochloride [(*S*)-6e]. Optically pure (*S*)-**6b** was subjected to Eschweiler–Clarke methylation as described below for (±)-**7b** to give crude (*S*)-**6e**, recrystallized from acetone, mp 161–162°, $[\alpha]^{25}D$ +10° (*c* 2.02, H_2O).

Anal. Calcd for $C_{11}H_{17}Cl_2N$: C, 56.42; H, 7.32. Found: C, 56.34; H, 7.10.

(*S*)-(+)- and *R*-(−)-*p*-Chloroamphetamine hydrochloride [(*S*)- and (*R*)-7a] had $[\alpha]^{25}D$ +22° (*c* 2.01, H_2O) and $[\alpha]^{25}D$ −22° (*c* 2.16, H_2O), respectively [lit.[16] $[\alpha]^{25}D$ +21° (*c* 2.02, H_2O) and $[\alpha]^{25}D$ −22° (*c* 1.90, H_2O) for (*S*)- and (*R*)-**7a**, respectively]; (*S*)-**7a** had $[\alpha]^{25}D$ −8.6° (*c* 2.10, *i*-PrOH).

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N*-Carbobenzoxy-*p*-chloroamphetamine [(±)-, (*S*)-, and (*R*)-7f]. To a stirred, ice-cooled solution of (±)-**7b** (790 mg, 4.7 mmol) in pyridine (2 ml) was added dropwise during 30 min carbobenzoxy chloride (1.54 g, 9.03 mmol). The ice bath was removed and stirring was continued for 1.5 hr before water was added. The resulting mixture was extracted with ether, and the ether solution was washed with 2 *N* hydrochloric acid until the aqueous phase remained acidic, then with aqueous sodium bicarbonate and two portions of water. Removal of ether from the dried ($MgSO_4$) extract yielded crystalline (±)-**7f** (1.05 g, 74%). A sample recrystallized from carbon tetrachloride was homogeneous to TLC (silica gel HF-254, 9:1 benzene–ethyl acetate, R_f 0.7) and had mp 83–84°; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3, *J* = 7 Hz), 2.70 (m, 2), 3.94 (m, 1, $CHCH_3$), 4.58 (m, 1, NH), 5.00 (s, 2, $OCH_2C_6H_5$), 6.9–7.4 ppm (m, 9).

Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 66.73; H, 5.96; N, 4.81.

(*S*)-**7f** and (*R*)-**7f**, prepared in a similar manner from (*S*)-**7b** and (*R*)-**7b**, had mp 186–188°; $[\alpha]^{25}D$ +22° (*c* 2.20, CH_3OH) and $[\alpha]^{25}D$ −23° (*c* 2.00, CH_3OH), respectively.

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N*-Methyl-*p*-chloroamphetamine Hydrochloride [(±)-7d, (*S*)-7d, and (*R*)-7d]. A suspension of (±)-**7f** (602 mg, 1.98 mmol) in ether (15 ml) was ice cooled and stirred while excess $LiAlH_4$ was added in small portions. The mixture was stirred for 15 hr at room temperature, then cooled while water was added. The suspension was filtered, and the filtrate was extracted with 1 *N* hydrochloric acid (5 ml). Evaporation of the aqueous layer, trituration of the crystalline residue with acetone, and drying at 60° (0.1 mm) gave (±)-**7d** (345 mg, 79%): mp 136–138° (lit.[29] mp 133°); ^1H NMR (D_2O) δ 1.12 (d, 3, *J* = 7 Hz), 2.64 (s, 3), 2.84 (m, 2), 3.37 (m, 1], 7.0–7.3 ppm (m, 4).

Treatment of (*S*)-**7f** and (*R*)-**7f** in a similar manner gave (*S*)-**7d** and (*R*)-**7d**, which after recrystallization from acetone–methanol had mp 180–181°; $[\alpha]^{25}D$ +16° (*c* 1.22, H_2O) and $[\alpha]^{25}D$ −16° (*c* 1.20, H_2O), respectively.

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N,N*-Dimethyl-*p*-chloroamphetamine Hydrochloride [(±)-, (*S*)-, and (*R*)-7e]. A mixture of (±)-**7b** (370 mg, 2.18 mmol), 90% formic acid (0.8 g, 16 mmol), and 37% aqueous formaldehyde (0.7 ml) was heated for 14 hr at 90–95°. The mixture was cooled, mixed with 6 *N* hydrochloric acid (1 ml), and evaporated to dryness. The residue was washed with small portions of acetone and dried at 60° (0.1 mm), yielding (±)-**7e** (425 mg, 83%): mp 207–208° dec; ^1H NMR (D_2O) δ 1.18 (d, 3, *J* = 7 Hz), 2.84 (s, 3), 2.87 (s, 3), 2.92 (m, 2), 3.60 (m, 1), 7.1–7.4 ppm (m, 4).

Anal. Calcd for $C_{11}H_{17}Cl_2N$: C, 56.42; H, 7.32; N, 5.98. Found: C, 56.54; H, 7.32; N, 5.93.

Treatment of (*S*)-**7b** and (*R*)-**7b** in a similar manner gave (*S*)-**7e** and (*R*)-**7e**, mp 220–221° dec; $[\alpha]^{25}D$ +11° (*c* 2.09, H_2O) and $[\alpha]^{25}D$ −9.3° (*c* 2.05, H_2O), respectively.

Acknowledgment. We thank Mr. Charles D. Mount for the preparation of racemic **5a** and **6a**.

Registry No.—(±)-**5a**, 35334-29-3; (*R*)-**5a**, 54676-31-2; (*R*)-**5b**, 54676-32-3; (*R*)-**5c**, 54643-56-0; (±)-**6a**, 35378-15-5; (*R*)-**6a**, 54712-19-5; (*S*)-**6a**, 54676-33-4; (±)-**6b**, 2486-97-7; (*S*)-**6b**, 54676-34-5; (*S*)-**6c**, 54643-57-1; (*S*)-**6d**, 54643-58-2; (*S*)-**6e**, 54643-59-3; (*S*)-**6f**, 54643-60-6; (*R*)-**7a**, 16064-31-6; (*S*)-**7a**, 16064-30-5; (±)-**7b**, 2275-84-5; (*R*)-**7b**, 405-47-0; (*S*)-**7b**, 405-46-9; (*R*)-**7c**, 52372-24-4; (±)-**7d**, 30572-91-9; (*R*)-**7d**, 24359-23-7; (*S*)-**7d**, 156-11-6; (±)-**7e**, 54643-61-7; (*R*)-**7e**, 54712-53-7; (*S*)-**7e**, 54676-35-6; (±)-**7f**, 54643-62-8; (*R*)-**7f**, 54676-36-7; (*S*)-**7f**, 54676-37-8; (*R*)-**8a**, 41820-21-7; (*S*)-**8a**, 1462-73-3; (*S*)-**8b**, 51-64-9; (*S*)-**8c**, 52372-25-5; **10b**, 19394-34-4; sodium *N*-acetyl-L-leucinate, 54643-63-9; 5-bromosalicylaldehyde, 1761-61-1; (−)-dibenzoyltartaric acid, 2743-38-6; (+)-dibenzoyltartaric acid, 17026-42-5.

References and Notes

(1) Part XVIII: H. E. Smith, R. K. Orr, and F.-M. Chen, *J. Am. Chem. Soc.*, in press.

(2) Supported by U. S. Public Health Service Grant MH-11468 and U. S. Army Medical Research and Development Command Contract DADA 17-73-C-3130 and presented in part at the 26th Southeastern Regional Meeting of the American Chemical Society, Norfolk, Va., Oct 1974, Abstract 270.
(3) (a) Vanderbilt University; (b) Tennessee State University.
(4) J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966).
(5) G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969).
(6) H. E. Smith and T. C. Willis, *J. Am. Chem. Soc.*, **93**, 2282 (1971).
(7) G. Snatzke, M. Kajtár, and F. Werner-Zamojska, *Tetrahedron*, **28**, 281 (1972).
(8) J. R. Platt, *J. Chem. Phys.*, **19**, 263 (1951).
(9) J. Petruska, *J. Chem. Phys.*, **34**, 1120 (1961).
(10) M. Legrand and R. Viennet, *Bull. Soc. Chim. Fr.*, 2798 (1966).
(11) J. Horwitz, E. H. Strickland, and C. Billups, *J. Am. Chem. Soc.*, **91**, 184 (1969).
(12) T. M. Hooker, Jr., and J. A. Schellman, *Biopolymers*, **9**, 1319 (1970).
(13) O. Korver, *Tetrahedron*, **26**, 5507 (1970).
(14) H. E. Smith, J. R. Neergaard, E. P. Burrows, and F.-M. Chen, *J. Am. Chem. Soc.*, **96**, 2908 (1974).
(15) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).
(16) H. E. Smith, E. P. Burrows, J. D. Miano, C. D. Mount, E. Sanders-Bush, and F. Sulser, *J. Med. Chem.*, **17**, 416 (1974).
(17) Signs in parentheses refer to rotatory power observed at the D line for the amine hydrochlorides in water and for the Schiff bases in absolute ethanol. It was noted earlier[18] that (*S*)-(+)-amphetamine hydrochloride is dextrorotatory in water and levorotatory in isopropyl alcohol. (*S*)-(+)-*p*-Chloroamphetamine hydrochloride shows similar behavior (see Experimental Section).
(18) H. E. Smith, M. E. Warren, Jr., and L. I. Katzin, *Tetrahedron*, **24**, 1327 (1968); **25**, 4648 (1969).
(19) G. F. Holland, C. J. Buck, and A. Weissman, *J. Med. Chem.*, **6**, 519 (1963).
(20) I. B. Johns and J. M. Burch, *J. Am. Chem. Soc.*, **60**, 919 (1938).
(21) A. Ilvespaa, M. Wilhelm, and A. Marxer, German Offen. 1,900,576 (1969); *Chem. Abstr.*, **72**, 31477b (1970).
(22) T. C. Aschner, U. S. Patent 2608583 (1952); *Chem. Abstr.*, **48**, 1416*h* (1954).
(23) F. R. Dollish, W. G. Fateley, and F. F. Bentley, "Characteristic Raman Frequencies of Organic Compounds", Wiley, New York, N.Y., 1974, pp 171, 175, 363, 375, and 381.
(24) O. E. Weigang, Jr., *J. Chem. Phys.*, **43**, 3609 (1965).
(25) A. H. Beckett and L. G. Brookes, *Tetrahedron*, **24**, 1283 (1968).
(26) S. B. Matin, P. S. Callery, J. S. Zweig, A. O'Brien, R. Rapoport, and N. Castagnoli, Jr., *J. Med. Chem.*, **17**, 877 (1974).
(27) M. B. Neher, E. W. Goldberg, and R. W. Fairchild, *J. Org. Chem.*, **26**, 5220 (1961).
(28) M. Koremura, H. Oku, T. Shono, and T. Nakanishi, *Takamine Kenkyusho Nempo*, **13**, 212 (1961); *Chem. Abstr.*, **57**, 16451*b* (1962).
(29) T. M. Patrick, Jr., E. T. McBee, and H. B. Hass, *J. Am. Chem. Soc.*, **68**, 1009 (1946).

Photochemistry and Radiation Chemistry of Sulfur-Containing Amino Acids. A New Reaction of the 1-Propenylthiyl Radicals[1]

Hiroyuki Nishimura* and Junya Mizutani

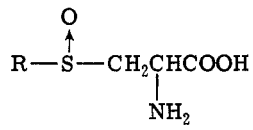
Department of Agricultural Chemistry, Hokkaido University, Sapporo, Japan

Received September 9, 1974

In connection with food-flavor deterioration caused by uv or γ irradiation, a new reaction of the 1-propenylthiyl radicals from *S*-(*cis*-1-propenyl)-L-cysteine irradiated by uv ray or γ-ray in oxygen-free aqueous solutions was investigated. The main products, formed via 1-propenylthiyl radicals, in uv photolysis were 1-propene-1-thiol, 2,4-dimethylthiophene, 3,4-dimethylthiophene, and 3-methylthiophene, while γ radiolysis yielded 1-propene-1-thiol, *n*-propyl 1-propenyl sulfide (cis and trans), and di-1-propenyl sulfide (cis,cis and cis,trans). Furthermore, cis–trans isomerization of 1-propenylthiyl radicals plays an important role in the formation of these products.

Sulfur-containing amino acids, such as *S*-alkyl-L-cysteine (alkyl: methyl, *n*-propyl, allyl, 1-propenyl), are found abundantly in *Allium*,[2] *Brassica*,[3] and *Phaseolus*[4] plants. These sulfoxides are also biologically active, i.e., they exhibit antihypercholesterolemic[5] and allithiamine effects.[6] Furthermore, since sulfur-containing amino acids are known to be highly sensitive to uv and γ irradiation, it is of interest to investigate the photolysis and radiolysis of these compounds.

We have studied the mechanism of formation of the major products when sulfoxide amino acids **1**, which are



1

$R = CH_3CH_2CH_2$, $CH_2{=}CHCH_2$, $CH_3CH{=}CH$

precursors of onion and garlic flavors, are irradiated by γ rays in an oxygen-free aqueous solution. This is of importance from the viewpoint of food irradiation.[7]

Recently, during studies on the uv photolysis and γ radiolysis of *S*-alkyl-L-cysteines (alkyl: *n*-propyl, allyl, 1-propenyl), we found that the major products formed from uv photolysis of *S*-*n*-propyl-L-cysteine (**2**) or *S*-allyl-L-cysteine (**3**) were approximately similar to those from γ radiolysis (Figure 1).[8] On the other hand, the uv photolysis of *S*-(*cis*-1-propenyl)-L-cysteine (**7**) proceeded quite differently from its γ radiolysis.

In this paper we report the identification of the products formed by uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine, one of the lachrymatory precursors in onions,[9] and suggest mechanistic schemes to rationalize the major products.

Results and Discussion

Identification of Products. Gas chromatograms of the volatile products from uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine are shown in Figure 2. Comparison of gas chromatographic retention time and mass spectrometric fragmentations with those of reference compounds permitted identification of the volatile compounds shown in Table I.

The major products of uv-irradiated *S*-(*cis*-1-propenyl)-L-cysteine were 1-propene-1-thiol, 2,4-dimethylthiophene, 3,4-dimethylthiophene, and 3-methylthiophene. Minor products were *n*-propyl 1-propenyl sulfides, di-1-propenyl sulfides, 2-methylthiophene, and 2,5- and 2,3-dimethylthiophenes.

The major products of γ radiolysis (10^4–10^6 rad) were 1-propene-1-thiol, *n*-propyl *cis*-1-propenyl sulfide, and *n*-propyl *trans*-di-1-propenyl sulfide. Minor products were *cis,cis*-di-1-propenyl sulfide and *cis,trans*-di-1-propenyl sulfide. No thiophene derivatives could be detected even by using a highly sensitive gas chromatograph and the combined GC–MS method.[10]

The mass spectral fragmentations of the main peaks in Figure 2 are summarized in Table II. Mass spectral fragmentations of 1-propene-1-thiol, *n*-propyl 1-propenyl sul-