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STUDIES IN THE ABSOLUTE CONFIGURATION OF OPTICALLY ACTIVE AMINES RELATED TO AMPHETAMINE AND EPHEDRINE[1]

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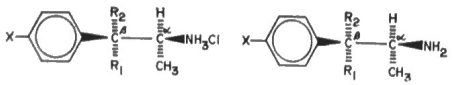
ABSTRACT

(*S*)-(+)-Amphetamine hydrochloride [(*S*)-*1a*], (*R*)-(-)-*p*-chloroamphetamine hydrochloride [(*R*)-*2a*], (*aR*)-(+)-norphedrine hydrochloride [*aR*-*3a*], (*aS*)-(+)-norpseudoephedrine hydrochloride [*aS*)-*4a*] are used as model compounds to establish the validity of the N-salicylidene sector rule for determining the absolute configuration of β-phenylalkylamines with an asymmetric center adjacent to the one bearing the nitrogen atom and a substituent in the *para* position of the ring. Application of this sector rule to (-)-*p*-chloronorephedrine hydrochloride [(-)-*5a*] and (+)-*p*-chloronorpseudoephedrine hydrochloride [(+)-*6a*] leads to the assignment of the *S* configuration to the α-carbon of both (-)-*5a* and (+)-*6a*. The proton magnetic resonance (pmr) spectra of (±)-*5a* and (±)-*6a* are compared with the spectra of (±)-*3a* and (+)-*4a*. The erythro configuration is assigned to (±)-*5a*, and the threo configuration to (±)-*6a* based on the coupling constant of the β-C proton absorption. Therefore, (-)-*5a* has the absolute configuration *aS*, *βR;* and (+)-*6a* has the absolute configuration *aS*, *βS*.

INTRODUCTION

The administration of (±)-*p*-chloroamphetamine hydrochloride [(±)-*2a*]



(*S*)-*1a*—R_1= H; R_2= H; X=H —(*S*)-*1b*
(*S*)-*2a*—R_1= H; R_2= H; X=Cl—(*S*)-*2b*
(*aS*)-*3a*—R_1= H; R_2=OH; X=H —(*aS*)-*3b*
(*aS*)-*4a*—R_1=OH; R_2= H; X=H —(*aS*)-*4b*
(*aS*)-*5a*—R_1= H; R_2=OH; X=Cl—(*aS*)-*5b*
(*aS*)-*6a*—R_1=OH; R_2= H; X=Cl—(*aS*)-*6b*

to rats leads to a marked and long-lasting reduction of the levels of 5-hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid (5-HIAA) and the activity of tryptophan hydroxylase in the brain. The activity of tryptophan hydroxylase was inhibited *in vivo* but not *in vitro* (Sanders-Bush, et al., 1972).

The lack of activity *in vitro* suggests that the active compound is not *2a* but a metabolite of *2a*. The metabolic pattern of (*S*)-(+)-amphetamine (*1b*) suggests either *p*-chlorononephedrine (*5b*) or *p*-chloronorpseudoephedrine (*6b*) as this active metabolite of (±)-*2a*.

In rats, (*S*)-(+)-amphetamine (S)-*1b* is metabolised to (*S*)-*p*-hydroxyamphetamine which is subsequently converted by dopamine-β-hydroxylase to a metabolite identified as *p*-hydroxynorephedrine. This metabolite has been implicated in the persistent reduction of brain norepinephrine after amphetamine administration to rats (Freeman and Sulser, 1972; Groppetti and Eosta, 1969; Lewander, 1971). The absolute configuration of this metabolite at the α-carbon follows from the absolute configuration of its precursor which is known (Karrer and Ehrhardt, 1951). However the absolute configuration at the β-carbon has not been established. This means that the metabolite may be either ($_a$*S*)-p-hydroxynorephedrine or ($_a$*S*)-p-hydroxynorpseudophedrine.

In view of the fact that the optical isomers of a drug can produce dramatically different pharmacological effects (Downes, et al., 1970) and can in fact be antagonistic when administered together (Dubnick and Rucki, 1970) it seemed necessary to have both optically active isomers of *p*-chloronorephedrine hydrochloride (*5a*) and *p*-chloronorpseudoephedrine hydrochloride (*6a*) for testing and to establish the absolute configuration of all four isomers.

In the present paper the preparation of (±)-*5a* and (±)-*6a*, which have been reported earlier as racemates (Müller, 1956; Zenitz and Hartung, 1946), their resolution and establishment of the absolute configuration of the four optical isomers are discussed. The action of (*aS*)-(-)-and (*aR*)-(+)-*p*-chloronorephedrine and (*aS*)-(+)-and (*aR*)-(-)-p-chloronorpseudoephedrine hydrochlorides on the level of 5-hydroxytryptamine and the activity of tryptophan hydroxylase in rat brain have been discussed elsewhere (Smith, et al., 1974).

[1] Based wholly on the M.S. Thesis of Charles D. Mount, Tennessee State University, May 1973.

METHODS AND MATERIALS

A. (±)-*p*-Chloronorephedrine Hydrochloride [(±)-*5a*].

Nitrosation of 4'-chloropropiophenone (Zenitz and Hartung, 1946) followed by hydrogenation in MeOH-HCl over 10% Pd-C at 30 psi until two equivalents of H_2 had reacted gave, after recrystallation from EtOH-Et_2O, 2-amino-4'-chloropropiophenone hydrochloride (42% overall): m.p. 218-222° dec (lit. m.p. 220-222° dec (Müller, 1956)). Treatment of this ketone (11.0 g, 50.0 mmol) with sodium borohydride (2.0 g, 53 mmol) in MeOH (100 ml) gave after recrystalization from EtOH-Et_2O (±)-*5a* (8.55 g, 77%): m.p. 244-246° dec (lit. m.p. 244-245° dec (Zenitz and Hartung, 1946) and 245-246° dec (Müller, 1956)), pmr (methanol-d4) δ1.12 ppm (d[2], 3, J=7.0 Hz, C-CH_3), 360 (m, 1, d,αC-H), 5.10 (d, 1, —=3.5 Hz, βC-H), 7.45 (s, 4, C_6H_4Cl).

B. (*aR*)-(+)-*p*-Chloronorephedrine Hydrochloride [(*aR*)-*5a*] and (*aS*)-(—)-*p*-Chloronorephedrine Hydrochloride [(*aS*)-*5a*].

A solution of N-acetyl-L-leucine (4.33 g, 25.0 mmol) and sodium hydroxide (1.00 g, 25.0 mmol) in water (50 ml) was added to a solution of (±)-*5a* (11.1 g, 50.0 mmol) in water (100 ml). The resulting precipitate was collected and recrystallized three times from water to give the salt as white needles (1.50 g): m.p. 224-225°, $(\alpha)^{25}_D$ + 4° (c 1.02, water). The salt was decomposed with sodium hydroxide solution and the amine was extracted with ether. The ether solution was extracted with 2N HCl. The water solution was evaporated to dryness at reduced pressure. Recrystallation from ethanol-ether gave (*aR*)-*5a* (0.56 g, 36%): m.p. 224-232°, $(\alpha)^{25}_D$ + 35° (c 1.92, water).

Analysis.[3] Calculated for $C_9H_{13}Cl_2NO$: Cl=31.92 (found Cl=32.12). From the mother liquor from the preparation of (*aR*)-*5a*, partially resolved amine hydrochloride (6.01 g) was recovered: $(\alpha)^{25}_D$-11.18° (c 2.66, water). This partially resolved salt (4.00 g, 18 mmol) was dissolved in water (75 ml) and a solution of N-acetyl-*D*-leucine (3.12 g, 18.0 mmol) and sodium hydroxide (0.75 g, 19 mmol) in water (35 ml) was added. The precipitate was treated as in the preparation of (*aR*)-*5a* to give (*aS*)-*5a* (0.63 g, 42%): m.p. 223-235°, $(\alpha)^{25}_D$-35° (c 3.07, water).

C. (±)-*p*-Chloronorpseudoephedrine Hydrochloride [(±-*6a*)].

(±)-N-Acetyl-*p*-chloronorephedrine (10.5 g, 46.1 mmol) m.p. 202-204° (lit. m.p. 207° (Müller, 1956)) was prepared from (±)-*5a* and added in small portions to excess $SOCl_2$ (25 ml, 0.35 mmol), stirred and ice-cooled. Stirring was continued for 45 minutes, 25% aqueous NaOH (45 ml) was added, and the mixture extracted with three portions of ether. The combined ether extracts were evaporated to dryness at reduced pressure. Recrystallization from ethanol-ether gave (±)-*6a* (6.30 g, 60%): m.p. 236-238° dec (lit. m.p. 238-238.5° (Müller, 1956)), pmr (methanol-d4) 1.12 ppm (d, 3, J=7.0 Hz, C-CH_3), 4.57 (d, 1, J=8.0 Hz, C-H), 7.45 (s, 4, C_6H_4Cl).

D. (S)-(+)- and (R)-(-)-p-Chloronaorpseudoephedrine Hydrochloride (S)- and (R)-6a.

M.p. 277-278° dec and 275-276° dec, respectively, $(\alpha)^{25}_D$ + 39° (c. 2.00, water) and $(\alpha)^{25}_D$-35° (c 2.02, water), respectively, were furnished through Dr. J. Lafferty of Smith, Kline and French Laboratories.

E. (*R*)-*p*-Chloroamphetamine Hydrochloride [*R*-*2a*]

Prepared according to a modified procedure (Smith, et al., 1974) had a m.p. 198-199°, $(\alpha)^{26}_D$-21.5° (c 1.98, water).[4] Feit and Brunn (1967) recorded m.p. 199-199.5°, $(\alpha)^{20}_D$-19.5° (c 5.0, water).

F. (±)-Norephedrine Hydrochloride [(±)-*3a*].

Purchased from Eastman Organic Chemicals, Rochester, New York, and used without further purification. M.p. 194-195° (lit. m.p. 194° (Nagai and Kanao, 1929)), pmr (methanol-d4) δ1.15 ppm (d, 3, J=7.0 Hz, C-CH_3), 3.55 (m, 1, αC-H), 5.11 (d, 1, J=4.0 Hz, βC-H), 7.45 (s, 5, C_6H_5).

[2] s=singlet, d=doublet, m=multiplet)
[3] Performed by Galbraith Laboratories, Knoxville, Tenn.
[4] Sample from Dr. Smith, Vanderbilt University, Nashville, Tenn.

G. (αR)-(+)-Norephedrine Hydrochloride [(αR)-*3a*].
Prepared by resolution of (±)-*3a* with tartaric acid: m.p. 169-171° (lit m.p. 171-172° (Nagai and Kanao, 1929)), $(\alpha)^{25}_D$ + 32° (c 1.07, water) $(\alpha)^{27}_D$ + 33.40° (c 6.45, water) recorded by Zenitz and Hartung (1946).

H. (αS)-(+)-Norpseudoephedrine Hydrochloride [(αS)-*4a*].
M.p. 180-182° (lit. m.p. 180-181° (Nagai and Kanao, 1929)), $(\alpha)^{25}_D$ + 43° (c 6.16, water) $(\alpha^{20}_D$ + 42.53° (c 7.01, water) after Nagai and Kanao (1929), pmr (methanol-d4) δ1.12 (d, 3, J=7.0) Hz, C-CH_3), 4.65 (d, 1, J=9.0 Hz, βC-H), 7.45 ppm (s, 5, C_6H_5) was purchased from K and L Laboratories, Inc.

N-5-Bromosalicylidene and N-Salicylidene Derivatives
Each amine hydrochloride was decomposed with aqueous sodium hydroxide, and the amine was extracted with ether. The solution was dried (Na_2SO_4) and the ether evaporated under reduced pressure. The amine thus obtained was dissolved in nine times its weight of MeOH. An equimolar solution of 5-bromosalicylaldehyde or a 10% molar excess of salicylaldehyde was added. The resulting precipitate was collected and recrystallized from and appropriate solvent. They were yellow or orange crystalline solids.
The properties of the optically pure N-5-Bromosalicylidene and N-Salicylidene derivatives are given under the appropriate heading below.

I. (*S*)-(+)-N-(5-Bromosalicylidene) amphetamine [(*S*)-*1c*].
absolute ethanol) (lit. b.p. 87-88°, $(\alpha)^{25}_D$ + absolute ethanol) (lit. m.p. 87-88°, $(\alpha^{25}_D$ + 186° (c 0.9, absolute ethanol) (Smith, et al., 1964)).

J. (*S*)-(+)-N-Salicylideneamphetamine [(*S*)-*1d*].
M.p. 56-57°, $(\alpha)^{25}_D$ + 348° (c. 1.34, absolute ethanol) (lit. m.p. 58-60°, $(\alpha)^{24}_D$ + 346° (c 1.0, absolute ethanol) (Smith, et al., 1964)).

K. (*R*)-(-)-N-(5-Bromosalicyledene)-*p*-Chloroamphetamine [(*R*)-*2c*].
M.p. 116-117°, $(\alpha)^{25}_D$-209° (c 0.972, absolute ethanol) after recrystallization from 2-propanol.

Analysis. Calculated for $C_{16}H_{15}BrClNO$: C, 54.49; H, 4.28; N, 3.97. Found: C, 54.64; H, 4.04; N, 4.00.

L. (*R*)-(-)-N-(5-Bromosalicylidene) norephedrine [(αR)-*3c*].
M.p. 99-100°, $(\alpha)^{26}_D$-118° (c 1.02, absolute ethanol) after recrystallization from 2-propanol-hexanes.

Analysis. Calculated for $C_{16}H_{16}BrNO_2$: C 57,53; H, 4.83; N, 4.19; Br, 23.91. Found: C, 57.65; H, 4.14; N, 4.14; Br, 23.85.

M. (αS)-(+)-N-(5-Bromosalicylidene) norpseudoephedrine [(αS)-*4c*].
M.p. 100-101.5°, $(\alpha)^{25}_D$+179° (c 1.10, absolute ethanol) after recrystallization from cyclohexane.

Analysis. Calculated for $C_{16}H_{16}BrNO_2$: C, 57.53; H, 4.83. Found: C, 57.39; H, 4.68.

N. (αS)-(+)-N-Sylicylidenenorpseudoephedrine [(αS)-*4d*].
M.p. 97-98°, $(\alpha)^{25}_D$+226° (c 1.09, absolute ethanol) after recrystallization from cyclohexane.

Analysis. Calculated for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.19; H, 6.99; N, 5.32.

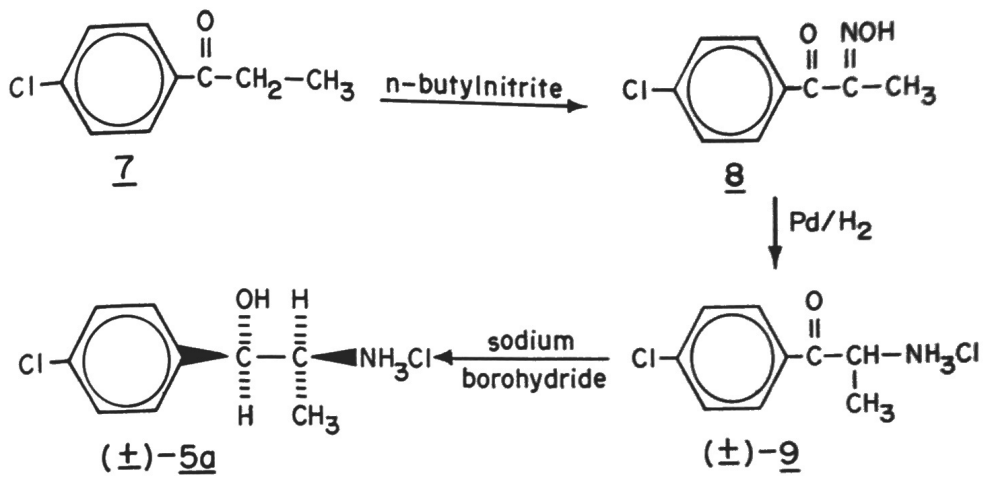
O. (αS)-(+)-(5-Bromosalicylidene)-*p*-Chloronorephedrine [(αS)-*4d*].
M.p. 100-101°, $(\alpha)^{25}_D$+70.3° (c 1.00, absolute ethanol) after recrystallization from 2-propanol-hexanes.

Analysis. Calculated for $C_{16}H_{15}BrClNO_2$: C, 52.13; H, 4.10; N, 3.72. Found: C, 51.90; H, 3.98; N, 3.80.

P. (αS)-(+)-N-(5-Bromosalicylidene) - p - chloronorpseudoephedrine [αS)-*6c*].
M.p. 109-110°, $(\alpha)^{25}_D$+140° (c 1.02, absolute ethanol). Furnished by Dr. Barrows, Vanderbilt University.

RESULTS

Synthesis.
(±)-*p*-Chloronorephedrine hydrochloride (±)-*5a* (Müller, 1956; Zenitz and Hartung, 1946) was synthesized in three steps, nitrosation of 4'-chloro-propiophenone (7) to give 4'-chloro-2-oximinopropiophenone (*8*), catalytic hydrogenation of the oximino group of (*8*) to give (±)-*9* followed by sodium borohydride reduction (Müller, et al., 1971) of the carbonyl group of (±)-*9* to give (±)-*5a*.
The sodium borohydride reduction proceeds according to Cram's rule leading to two isomers instead of the four possible. Cram's rule predicts that the major product will have the erythro configuration (Cram and Elfahez, 1952).
Conversion of (±)-*5a* to is diastereomer (±)-*6a* was accomplished by a Walden inversion on the N-acetyl derivative of (±)-*5a* with thionyl chloride fol-



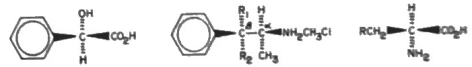
lowed by aqueous alkali (Müller, 1956). The reaction with thionyl chloride proceeds by an S_Ni (substitution nucleophilic internal) mechanism to replace the hydroxyl group with a chloride with retention of configuration. Reaction of this intermediate with sodium hydroxide replaced the chloride with a hydroxy group through an S_N2 mechanism leading to an inversion of configuration. The inverted amide was decomposed to give (±)-*6a*.
Resolution of (±)-*5a* was accomplished using N-acetyl-L-leucine while the enantiomers of (±)-*6a* were supplied by Dr. J. Lafferty, Smith, Kline and French Laboratories.

Configurational Studies.
In the determination of absolute configurations, it was necessary to have model compounds of known absolute configuration for comparison. The model compounds chosen were:

i) (*S*)-(+)-amphetamine hydrochloride [(*S*)-*1a*],
ii) (*R*)-(-)-p-chloroamphetamine hydrochloride [(*R*)-*2a*],
iii) (-)-norephedrine hydrochloride [-*3a*],
iv) (+)-norpseudoephedrine hydrochloride [+ *4a*].

The absolute configuration of (*S*)-*1a* was established by Karrer and Ehrhardt (1951). (*S*)-*1a* was prepared from (*S*)-*2a* by Feit and Bruun (1967) to establish the absolute configuration of (*S*)-*2a*, from which follows the configuration of (*R*)-*2a*.
(—)-Norephedrine hydrochloride has the same configuration as (—)-ephedrine hydrochloride [(αS)-*11a*] (Nagi and Kano, 1929) and (+)-norpseudoephedrine hydrochloride has the same configuration as (+)-pseudoephedrine hydrochloride [(αS)-*12*] (Smith, 1928).

Both (-)-ephedrine hydrochloride [αS)-*11a*] and (+)-pseudoephedrine hydrochloride [(αS)-*12a*], can be converted to (+)-desoxyephedrine (Emde, 1929) hydrochloride [(*S*)-13] which in turn can be prepared from (*S*)-(+)-amphetamine hydrochloride [*S*)-*1a* (Leithe, 1932). This established the configuration of the α-carbon of (-)-3a and (+)-*4a* as *S*.
The original correlation was made by Freudenberg and Nikolai (1934) who related (-)-ephedrine hydrochloride to (*S*)-(+)-alanine [(*S*)-14] to establish the α-carbon configuration. More recently, Koga and coworkers (1966) prepared (-)-norephedrine hydrochloride from (*S*)-(-)-phenylalanine [(*S*)-*15*].



(*R*)-*10* (αS)-*11a* R_1=OH; R_2= H (*S*)-*14*, R=H
(αS)-*12a*, R_1= H; R_2=OH (*S*)-*15*, R=C_6H_5
(*S*)-*13* R_1= H; R_2= H

Freudenberg and coworkers (1932) synthesized (αS)-*11a* from R-mandelic acid (R)-*10*. Leithe and coworkers (1932) synthesized (αS)-*12a* from (*S*)-*10*. These two independent methods are in agreement and lead us to assign *R* configuration for the β-carbon of (-)-norephedrine hydrochloride (αS)-*3a* and the *S* configuration to the β-carbon of (+)-norpseudoephedrine hydrochloride (αS)-*4a*.

PMR Data.

Hyne (1961) has reported that in the case of the diastereomeric ephedrines (αS)-*11b* and (αS)-*12b* the *erythro* configuration produces a coupling constant for the interaction of the α- and β-protons about one-half as great as does the *threo* configuration. Comparison of the pmr spectra for norephedrine hydrochloride [(+)-*3a*] (J =4.0 Hz), norpseudoephedrine hydrochloride [(αS-*4a*] (J =9.0 Hz), *p*-chloronorephedrine hydrochloride [(+)-*5a*] (J =3.5 Hz), and *p*-chloronorpseudoephedrine hydrochloride [(±-*6a*] (J=8.0 Hz) led to the assignment of the erythro configuration for (±)-*5a* and the threo configuration for (±)-*6a*.

These results are summarized in Table 1.

TABLE 1: *Summary of PMR Coupling Constants*

Erythro configuration		*Threo configuration*	
Compound	(J, Hz)	*Compound*	(J, Hz)
(αS)-*11b*	(4.0)[10]	(αS)-*12b*	(8.2)
(±)-*3a*	(4.0)	(αS)-*4a*	(9.0)
(±)-*5a*	(3.5)	(±)-*6a*	(8.0)

Circular Dichroism (CD) spectra of N-salicyidene Derivatives.

Smith nad coworkers (1964; 1965; 1968; 1969; 1971; 1974) have studied the optical rotatory dispersion and circular dichroism spectra of N-salicylidene derivatives of a number of optically active amines. These studies have shown that the sign of the Cotton effects near 255 and 315 nm gave the absolute confiuration at the nirogen bearing carbon, the *S* configuration giving the positive Cotton effect and the *R* configuration giving negative Cotton effects. It was also shown that the 5-bromosalicyledene derivates have similar spectra.

In the present work, since some of the desired N-salicyledene derivatives were oils, the N-5-bromosalicylidene derivatives were used. In order to show that the chloride in the 4′-position on the amine had no effect on the spectra, the derivative was made from (*R*)-*2a* (Fgures 1, 2 and 3). The effect of the hydroxy group in the β-position was shown to be negligible by studying the derivatives of (αR)-*3a* (Figure 4) and (αS)-*4a* (Figure 5). The 5-bromosalicylidene derivatives were then made from (—)-*p*-chloronorephedrine hydrochloride [(—)-*5a*] (Figure 7) and (+)-*p*-chloronorpseudoephedrine hydrochloride [(+)-*6a*] (Figure 8): both gave positive Cotton effects near 255 and 315 nm indicative of the *S* configuration. These results are summarized in Table 2.

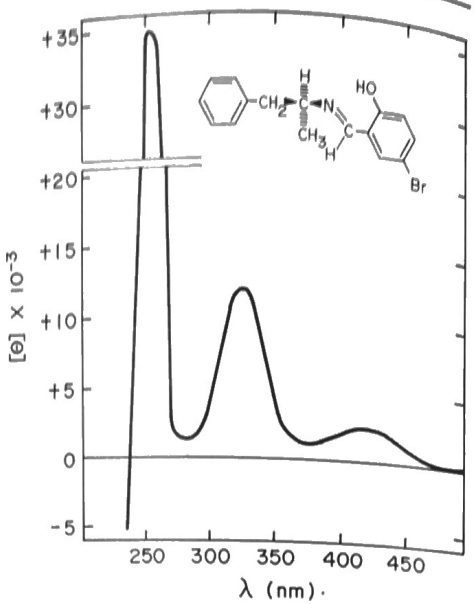


FIG. 1: *CD spectra of (S)-N-(5-bromosalicylidene)-amphetamine [(S)-1c]*

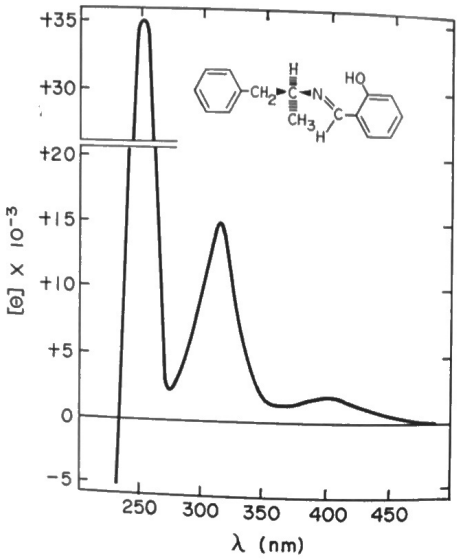


FIG. 2: *CD spectra of (S)-N-salicyledeneamphetamine [(S)-1d]*

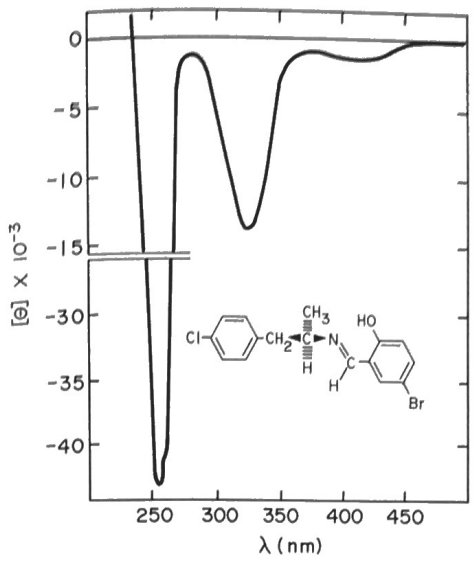


FIG. 3: *CD spectra of (R)-N-(5-bromosalicyledene) -p-chloroamphetamine [(R)-2c]*

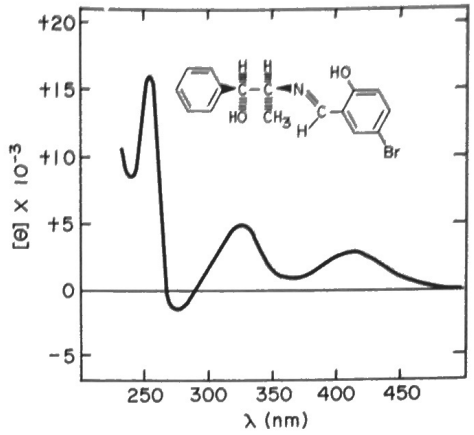


FIG. 5: *CD spectra of (αS)-N-(5-bromosalicylidene) norpseudoephedrine [(αS)-4c]*

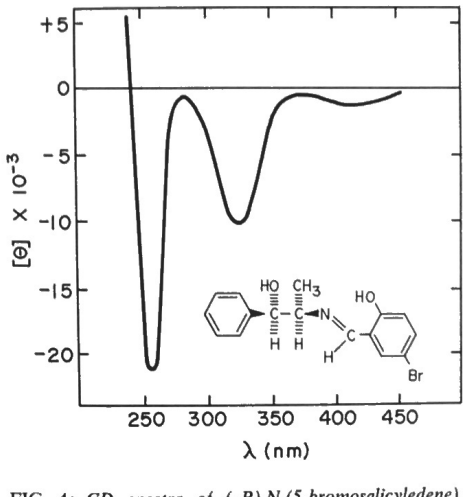


FIG. 4: *CD spectra of (αR)-N-(5-bromosalicyledene) norephedrine [(αR)-3c]*

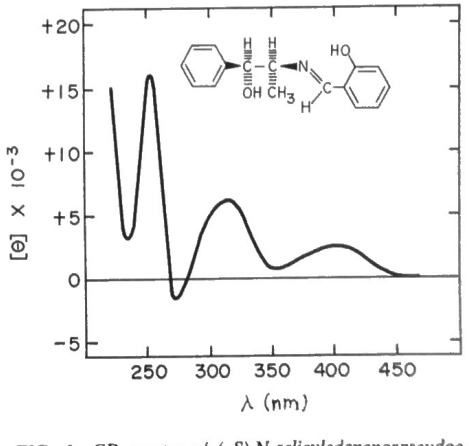


FIG. 6: *CD spectra of (αS)-N-salicyledenenorpseudoephedrine [(αS)-4d]*

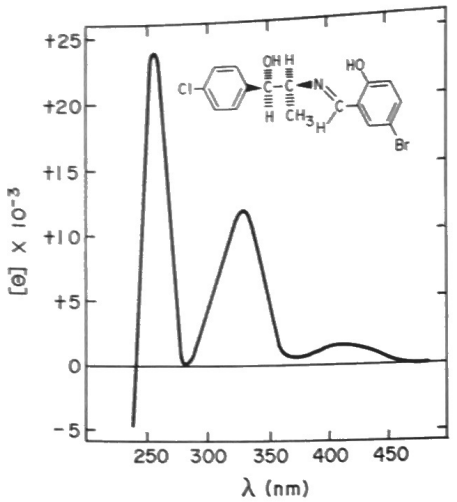


FIG. 7: *CD spectra of (αS)-N-(5-bromosalicyledene)-p-chlorononorephedrine [(αS-5c]*

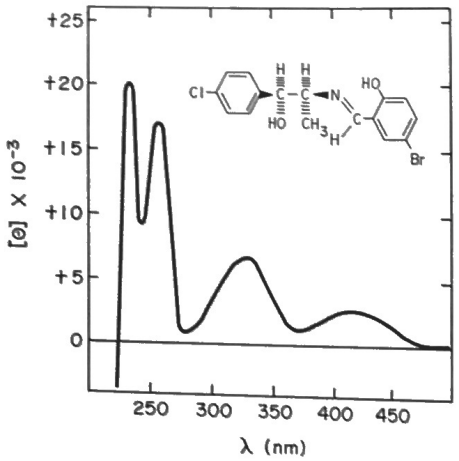


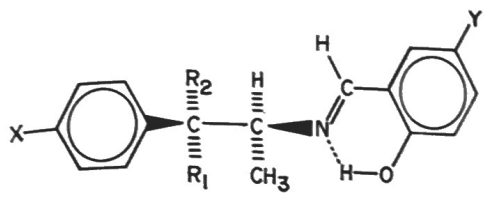
FIG. 8: *CD spectra of (αS)-N-(5-bromosalicyledene)-p-chloronorpseudoephedrine [(αS)-6c]*

On the basis of this evidence, (−)-*5a* is assigned the configuration *αS, βR*, its enantiomer αR, βS, (+)-*6a* is assigned *αS, βS* and its enantionmer *αR, βR*.

TABLE 2: *EA and CD spectra of N-Salicylidene and N-5-bromosalicylidene derivatives in absolute ethanol*

Compound	EA Maxima, λ, nm (ε)	CD Maxima, λ, nm ([θ])
(*S*)-(+)-N-(5-Bromosalicylidene)amphetamine		
(*S*)-*1c*	415 (740)	411 (+2200)
	327 (3600)	327 (+12,000)
	276 (sh) (1600)	
	254 (sh) (10,000)	254 (+35,000)
	220 (31,000)	234* (-7800)
(*S*)-(+)-N-Salicylideneamphetamine		
(*S*)-*1d*	403 (630)	399 (+1700)
	311 (4000)	314 (+15,000)
	282 (sh) (2100)	
	255 (12,000)	254 (+35,000)
	214 (27,000)	225* (-3700)
(*R*)-(-)-N-(5-Bromosalicylidene)-p-chloroamphetamine		
(*R*)-*2c*	415 (600)	415 (-1500)
	328 (3700)	326 (-14,000)
	276 (sh) (1700)	
	254 (sh) (10,000)	255 (-43,000)
	225* (36,000)	233* (+10,000)
(αR)-(-)-N-(5-Bromosolicylidene) norephedrine		
(αR)-*3c*	415 (1300)	417 (-1300)
	327 (3400)	327 (-10,000)
	276 (sh) (2500)	
	252 (sh) (10,000)	256 (-21,000)
	222 (31,000)	230* (+38,000)
(αS)-(+)-N-(5-Bromosalicylidene) norpseudoephedrine		
(αS)-*4c*	415 (1400)	412 (+2700)
	327 (3500)	327 (+5000)
	277 (sh) (2400)	
	253 (sh) (11,000)	255 (+16,000)
	230* (20,000	234* (+12,000)
(αS)-(+)-N-Salicylidenenorpseudoephedrine		
(αS)-*4d*	402 (1100)	400 (+2400)
	316 (3900)	315 (+6200)
	278 (sh) (3300)	
	255 (14,000)	253 (+16,000)
	215* (25,000)	223* (+15,000)
(αS)-(+)-N-(5-Bromosalicylidene) -p-chlorononorephedrine		
(αS)-*5c*	417 (1200	417 (+1400)
	328 (3500)	328 (+12,000)
	277 (sh) (2400)	
	255 (sh) (10,000)	256 (+24,000)
	230* (25,000)	240 (-11,000)
(αS)-(+)-N-(5-Bromosalicylidene)-p-chloronor-pseudoephedrine		
(αS)-*6c*	417 (1100)	417 (+2600)
	327 (3000)	328 (+6900)
	280 (sh) (2100)	
	253 (sh) (10,000)	256 (+17,000)
	223 (34,000)	220* (-14,000)

*cut-off



(*S*)-*1c*	R_1 = H	R_2 = H	X = H	Y = Br
(*S*)-*1d*	R_1 = H	R_2 = H	X = H	Y = H
(*S*)-*2c*	R_1 = H	R_2 = H	X = Cl	Y = Br
(αS)-*3c*	R_1 = H	R_2 = OH	X = H	Y = Br
(αS)-*4c*	R_1 = OH	R_2 = H	X = H	Y = Br
(αS)-*4d*	R_1 = OH	R_2 = H	X = H	Y = H
(αS)-*5c*	R_1 = H	R_2 = OH	X = C	Y = Br
(αS)-*6c*	R_1 = OH	R_2 = H	X = Cl	Y = Br

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