Table III. Enzymic Analysis of Dipeptide Hydrolysates

Solution	Area	Enzyme blank	Corr. area	Concn. of alanine[a] Total[b]	Free[c]	Bound[d]
I–G	21.1[e]		21.1	1.08	0.003	1.08
I–H	18.4[e]	1.3	17.1	0.88	0.003	0.88
II–G	19.9[f]		19.9	1.02	0.006	1.01
II–H	17.0[g]	1.3	15.7	0.81	0.006	0.80
III–G	21.2[h]		21.2	1.09	0.007	1.08
III–H	21.4[h]	1.3	20.1	1.03	0.007	1.02

[a] In μmoles/ml. [b] Calculated. [c] Taken from Table II; converted to concentration units and corrected for dilution by a factor of 10^{-2}. [d] Alanine present in some form other than the free amino acid. [e] Average of 2 runs. [f] Average of 8 runs. [g] Average of 4 runs. [h] Average of 3 runs.

lactic acid obtained from a standard curve was 4.2 μmoles/ml.

Preparation of N-Carbobenzoxy-D-alanyl-L-alanine Benzyl Ester. N-Carbobenzoxy-D-alanine *p*-nitrophenyl ester[19] (3.66 g., 0.0106 mole) and L-alanine benzyl ester *p*-toluenesulfonate (3.73 g., 0.0106 mole) were dissolved in 15 ml. of N,N-dimethylformamide. Triethylamine (1.48 ml., 0.0106 mole) was added and the solution was kept at room temperature for 38 hr. The reaction mixture was diluted with 40 ml. of ethyl acetate and washed twice with 1 *N* hydrochloric acid, once with water, five times with 5% sodium bicarbonate solution, and three times with water. The organic layer was dried and concentrated to a white solid. Recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) provided 3.14 g. (77%) of the protected dipeptide, m.p. 123.5–124.5, $[\alpha]^{25}D$ +9.8° (*c* 3.7, $CHCl_3$) (lit.[20] m.p. 114°, $[\alpha]^{25}D$ −2.9° (*c* 1, $CHCl_3$)).

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.47; H, 6.24; N, 7.28.

Preparation of D-Alanyl-L-alanine (XIV). N-Carbobenzoxy-D-alanyl-L-alanine benzyl ester (2.77 g., 7.22 mmoles) was suspended in 30 ml. of methanol and treated with ethyl acetate until solution was complete. After addition of a few milliliters of dilute acetic acid, the solution was hydrogenated at 50 p.s.i. in the presence of 300 mg. of palladium hydroxide-on-charcoal catalyst. The reduction was complete in 5 min. Removal of the solvent afforded a sirup which crystallized on addition of ethanol. Recrystallization was accomplished by dissolving the dipeptide in a few milliliters of water, adding 10 ml. of ethanol, seeding, and adding 1 drop of ethyl acetate. In this manner 1.00 g. (87%) of XIV was obtained, $[\alpha]^{25}D$ −71.0° (*c* 1.9, H_2O) (lit.[21] $[\alpha]^{25}D$ −71.1°).

The D-alanyl-L-alanine exhibited a purple ninhydrin spot and the same R_f (0.39) in the 1-butanol–water–acetic acid system (4:5:1) as an authentic sample of L-alanyl-L-alanine. The two dipeptides had slightly different retention times by ion-exchange chromatography.

Reductive Amination of α-Ketoglutaric Acid. Hydrogenation of α-ketoglutaric acid and 3 equiv. of L-α-methylbenzylamine in the manner previously described[4] provided a clear gum. The material was dissolved in a few milliliters of water and cooled. The crystalline solid amounted to 29% of theoretical.

The mother liquor was evaporated to a sirup and triturated with ether to provide a solid which was combined with the crystals obtained from water, total yield 79%, $[\alpha]^{25}D$ +11.1° (*c* 2, *N* HCl) (lit.[22] $[\alpha]^{25}D$ +31.8°).

The combined solids exhibited a single peak identical with pure glutamic acid when analyzed by ion-exchange chromatography.

Acknowledgment. The amino acid analyses were performed by Mrs. Mary Pendergraft. It is also a pleasure to acknowledge Dr. Carol Kepler who kindly performed the enzymic determinations of L-(+)-lactic acid.

(19) M. Goodman and K. C. Stuben, *J. Am. Chem. Soc.*, **81**, 3190 (1959).
(20) N. C. Li, G. W. Miller, N. Solony, and B. T. Gillis, *ibid.*, **82**, 3737 (1960).
(21) S. C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *ibid.*, **76**, 6054 (1954).
(22) J. P. Greenstein, S. M. Birnbaum, and M. C. Otey, *J. Biol. Chem.*, **204**, 307 (1953).

Optically Active Amines. III. The Optical Rotatory Dispersion Curves of the N-Salicylidene Derivatives of Some Open-Chain Primary Amines[1]

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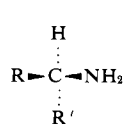
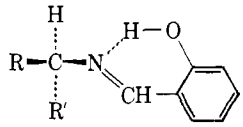
The optical rotatory dispersion curves and electronic absorption spectra of the N-salicylidene derivatives of a series of optically active amines and amino acid esters were measured. The Schiff bases having an aryl group α or β to the salicylidenimino group display anomalous rotatory dispersion curves with a Cotton effect near 315 mμ of high amplitude, similar to some of those associated with inherently dissymmetric chromophores. The correlation of the absolute configuration of an α-arylalkylamine Schiff base with the shape of its dispersion curve is discussed.

(1) Paper II: H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2265 (1964).
(2) This work is taken from the Ph.D. thesis of M. E. W., Jr., Vanderbilt University, June 1963; National Defense Education Act Fellow, 1959–1962.
(3) To whom inquiries should be sent.

Table I. Rotatory Powers of Some Optically Active Primary Amines and Their N-Salicylidene Derivatives

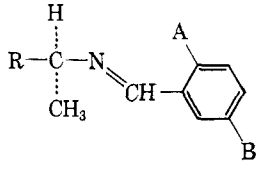




R	R′	Amine: Compound	Amine: $[\phi]_D$,[a] deg.	N-Salicylidene derivative: Compound	N-Salicylidene derivative: $[\phi]_D$,[a] deg.	Cotton effects[b] or plain dispersion curve[c]: 95% Ethanol	Dioxane	Hexane	Configuration ref.
$C_{10}H_7$-1	CH_3	(*S*)-IIa	−88.4	(*S*)-IIb	+856	+250 (414)	+32,000 (314)	+48,000 (316)	+49,000 (316)	10
C_6H_5	CH_3	(*S*)-IIIa[d]	−36[e]	(*S*)-IIIb[d]	+424[f]	+400 (412)	+21,000 (314)	+26,000 (315)	+33,000 (313)	8
C_6H_5	CH_2CH_3	(*S*)-IVa[g]	−11	(*S*)-IVb[g]	+385	+500 (412)	+21,000 (314)	+30,000 (314)	+28,000 (312)	*h*
C_6H_5	$CH_2CO_2C_2H_5$	(*S*)-Va[g]	−13	(*S*)-Vb[g]	+251	Infl. (430)	+19,000 (316)	+23,000 (316)		9
C_6H_5	$C(CH_3)_3$	(*S*)-VIa[g]	−4.1[f]	(*S*)-VIb[g]	+671[f]	+600 (413)	+25,000 (315)	+26,000 (313)	+33,000 (311)	*h*
$CH_2C_6H_5$	CH_3	(*S*)-VIIa[d]	+44.8[i]	(*S*)-VIIb[d]	+828	+1000 (406)	+14,800 (314)	+18,000 (314)	+23,000 (316)	17
$CH_2C_6H_4OH$-*p*	CO_2CH_3	D-VIIIa[g]	−55[f]	D-VIIIb[g]	+808[f]	Infl. (430)[f]	+20,000 (318)[f]	+19,000 (316)		16
C_2H_5	CH_3	(*S*)-IXa[d]	+2[i]	(*S*)-IXb[d]	+104	Extremum with $[\phi]_{437}$ +370			Plain pos., $[\phi]_{375}$ +474	19
CH_3	$CO_2C_2H_5$	D-Xa[g]	−2	D-Xb[g]	+11	Plain neg., $[\phi]_{450}$ −13[k]				16
$CH_2CH_2SCH_3$	$CO_2C_2H_5$	D-XIa[g]	−13	D-XIb[g]	+318	Plain pos., $[\phi]_{370}$ +1550[k]				16
$CH_2CH(CH_3)_2$	$CO_2C_2H_5$	D-XIIa[g]	−33	D-XIIb[g]	+202	Plain pos., $[\phi]_{360}$ +890[k]				16
$CH(CH_3)C_2H_5$	$CO_2C_2H_5$	D-XIIIa[g]	−61	D-XIIIb[g]	+135	Plain pos., $[\phi]_{450}$ +255[k]				16
$CH(CH_3)C_2H_5$-*allo*	$CO_2C_2H_5$	D-XIVa	−61	D-XIVb	+140	Plain pos., $[\phi]_{440}$ +350[k]				16
C_6H_5	$CH_2C_6H_5$	(*S*)-XVa	+83	(*S*)-XVb	−270	Plain neg., $[\phi]_{275}$ −8400		Plain neg., $[\phi]_{270}$ −7700	Plain neg., $[\phi]_{275}$ −7900	18

[a] Molecular rotation, absolute ethanol as the solvent or as otherwise noted. [b] Described by the amplitude expressed in degrees of molecular rotation, and in parentheses, the wave length in mμ about which the Cotton effect is centered. [c] Molecular rotation, degrees, at the last reliable measurement. [d] For complete characterization, see ref. 1. [e] (*R*)-IIIa had $[\alpha]^{24}D$ +30° (*c* 2.0) and $[\alpha]^{23}D$ +39.9° (neat.) [f] Methanol as the solvent. [g] Enantiomorph used. [h] This work. [i] This amine had $[\alpha]^{27}D$ +33.1° (*c* 6.2) and $[\alpha]^{25}D$ +34.1° (neat). [j] This amine had $[\alpha]^{21}D$ + 3° (*c* 2.1) and $[\alpha]^{25}D$ +8.1° (neat). [k] Absolute ethanol as the solvent.

Recently, the electronic absorption spectra and the optical rotatory dispersion curves[4] of a number of Schiff bases (I) derived from three optically active



I

R = C_6H_5, $C_6H_5CH_2$, or C_2H_5
A = H, CH_3O, or OH
B = H, NO_2, Cl, or Br

primary amines and a series of aromatic aldehydes were reported.[1] Positive Cotton effects[4] were observed near 410 and 315 mμ in the dispersion curves of the N-salicylidene and the N-(5-chloro)- and N-(5-bromo)salicylidene derivatives of (*S*)-(−)-α-phenyl- and (*S*)-(+)-α-benzylethylamine.[5] A comparison of these curves with that displayed by (*S*)-(+)-N-salicylidene-*sec*-butylamine, for which no complete Cotton effect could be observed, suggested that for the α- and β-phenylalkylamine derivatives, the most rotationally significant interactions are those of the π-electron systems of the phenyl and benzyl groups and the salicylidenimino moiety. The interactions may be analogous to that between the carbon–carbon π-electrons and the carbonyl group in optically active β,γ-unsaturated and α-phenyl ketones,[6] which sometimes results in a Cotton effect near 300 mμ of much greater amplitude than those displayed by saturated analogs. While this marked increase in the rotational strength of an unsaturated ketone is also accompanied by an intensity enhancement of the absorption band near 300 mμ,[6] no such enhancements are observed in the electronic absorption spectra of the N-salicylidene derivatives of the α- and β-phenylalkylamines.

Continuing this work, the N-salicylidene Schiff bases of an extended series of optically active open-chain primary amines have now been prepared, and their absorption spectra and optical rotatory dispersion curves measured.

Results

The optically active amines are listed in Table I,[7] together with the important features of the rotatory dispersion curves of the N-salicylidene derivatives.

Absolute configurations have not been assigned previously to (−)-α-phenyl-*n*-propylamine (IVa) and (−)-α-phenylneopentylamine (VIa). The (*S*)-configuration is now assigned to the former by reason of the similarity of the rotatory dispersion curve of its N-salicylidene derivative to those of (*S*)-(+)-N-salicylidene-α-phenylethylamine[8] (IIb) and (*S*)-(+)-ethyl N-salicylidene-β-aminohydrocinnamate[9] (Vb). On this same basis, the assignment of the (*S*)-configuration to (−)-α-(1-naphthyl)ethylamine (IIa) is also confirmed, the latter assignment having been made recently by Wolf, Bunnenberg, and Djerassi,[10] using the rotatory dispersion curve of its N-phthaloyl derivative. Al-

(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(5) Designation of configurations according to R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(6) (a) R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962); (b) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1945 (1962); (c) K. Mislow and J. G. Berger, *ibid.*, **84**, 1956 (1962); (d) K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962); (e) S. F. Mason, *J. Chem. Soc.*, 3285 (1962); *Mol. Phys.*, **5**, 343 (1962).

(7) For ease of presentation and discussion, the amines and α-amino acid esters are listed as the (*S*)- and D-absolute configurations, respectively, regardless of which isomer was actually used.

(8) Absolute configuration: W. Leithe, *Ber.*, **64**, 2827 (1931).

(9) Absolute configuration: R. Lukes, J. Kovar, J. Kloubek, and K. Blaha, *Collection Czech Chem. Commun.*, **23**, 1367 (1958).

(10) H. Wolf, E. Bunnenberg, and C. Djerassi, *Ber.*, **97**, 533 (1964).

though no completely suitable model compounds were available for comparison, (−)-α-phenylneopentylamine (VIa) is also assigned the (*S*)-configuration on the basis of the rotatory dispersion curve of its N-salicylidene derivative. These assignments are considered further in the Discussion.

The sign of the rotatory power of α-phenylneopentylamine and that of α-(1-naphthyl)ethylamine can be predicted correctly using Brewster's rules,[11] assuming their absolute configurations to be as given in Table I. The attachment atom of the 1-naphthyl group[12] must be assumed to have the same relative ranking in polarizability as that of the phenyl group in α-phenylalkylamines.[11b]

Although the N-salicylidene derivatives of all of the amines in Table I are optically stable at room temperature, the derivatives of α-amino acid esters are racemized or epimerized at the α-carbon atom when distilled.[13] This optical instability is primarily dependent on the presence of the carboalkoxy group attached to the asymmetric center. Those N-salicylidene derivatives not possessing this structural feature are optically stable during distillation at moderate temperatures or during recrystallization.[14]

The sodium D-line rotatory powers in absolute ethanol of the heat-sensitive Schiff bases were measured in the following way. A weighed amount of the α-amino acid ester was mixed with a slight excess of salicylaldehyde in a measured volume of solvent, and the formation of the derivative was observed polarimetrically. Since increasing the relative amount of salicylaldehyde did not increase the maximum rotatory power reached, the formation of the Schiff base was assumed to be essentially quantitative. Solutions prepared in this way were also used for rotatory dispersion measurements, during which their specific rotations at the sodium D-line remained constant.

The N-salicylidene derivatives in absolute ethanol display multiple electronic absorption bands above 225 mμ with those at the longest wave lengths being near 405 mμ (log ε 2.1–3.0) and 316 (3.6–3.7). For other solvents, the spectra show the same changes noted earlier[1] and reported[15] by others for similar Schiff bases. The band in ethanol near 405 mμ is replaced in dioxane by a broad shoulder centered near 404 mμ (log ε 1.0–1.5), and is absent or extremely weak in hexane. In dioxane or hexane the other band is not appreciably changed in wave length (0–5 mμ) but is usually slightly enhanced in intensity. All of the Schiff bases display very similar spectra in a given solvent.

As reported previously[1] the N-salicylidene derivatives of the (*S*)-α- and (*S*)-β-arylalkylamines (IIa–IVa, VIa, and VIIa) in ethanol display above 270 mμ optical rotatory dispersion curves each with two positive

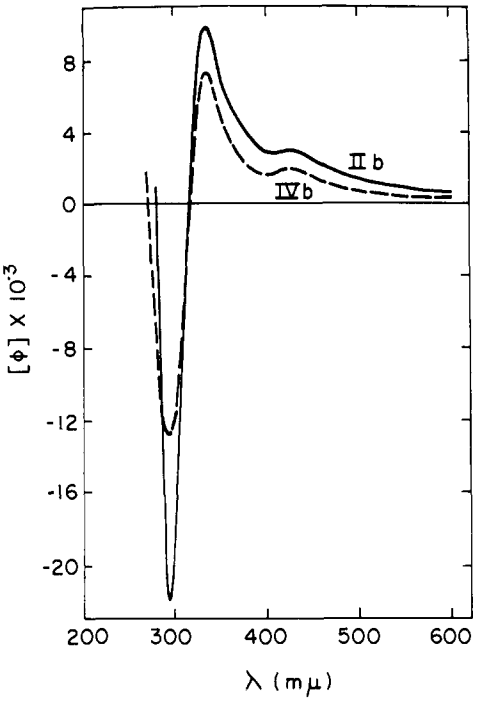


Figure 1. Optical rotatory dispersion curves of (*S*)-N-salicylidene-α-(1-naphthyl)ethylamine (IIb) and (*S*)-N-salicylidene-α-phenyl-*n*-propylamine (IVb) in 95% ethanol.

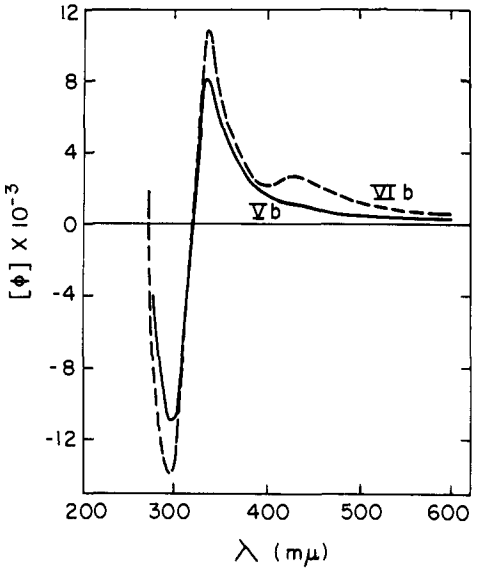


Figure 2. Optical rotatory dispersion curves of (*S*)-ethyl N-salicylidene-β-aminohydrocinnamate (Vb) and (*S*)-N-salicylidene-α-phenylneopentylamine (VIb) in 95% ethanol.

Cotton effects (Figures 1 and 2), a weak effect centered near 410 mμ, and a stronger one near 315 mμ. With dioxane or hexane as the solvent, only one positive Cotton effect, centered near 315 mμ, is observed (Figure 3), enhanced in amplitude but similar to that observed in ethanol near 315 mμ.

The dispersion curve for the N-salicylidene derivative of methyl D-tyrosinate[16] (VIIIa) in methanol displays

(11) (a) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959); (b) *Tetrahedron Letters*, **No. 20**, 23 (1959).

(12) The attachment atom of the 1-naphthyl group has been assigned a polarizability greater than that of the phenyl group on the basis of the absolute configuration and rotatory powers of (*R*)-(+)-methyl(1-naphthyl)phenylsilane [A. G. Brook and W. W. Limburg, *J. Am. Chem. Soc.*, **85**, 832 (1963)] and (*R*)-(+)-methyl(1-naphthyl)phenylgermane [A. G. Brook and G. J. D. Peddle, *ibid.*, **85**, 1869 (1963)].

(13) T. Taguchi and T. Ishida, *Pharm. Bull.* (Tokyo), **5**, 181 (1957).

(14) S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 1778 (1935).

(15) (a) J. Hires and L. Hackl, *Acta Univ. Szeged, Acta Phys. Chem.*, **5**, 19 (1955); (b) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **85**, 183, 188 (1963); (c) J. Charette, G. Faltlhansl, and Ph. Teyssie, *Spectrochim. Acta*, 20, 597 (1964).

(16) The absolute configurations of the Schiff bases of the α-amino acid esters follow from those of the respective amino acids. For the latter, see J. P. Mathieu, P. Desnuelle, and J. Roche, "Tables of Constants and Numerical Data," part 10, Pergamon Press, New York, N. Y., 1959; and J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 2.

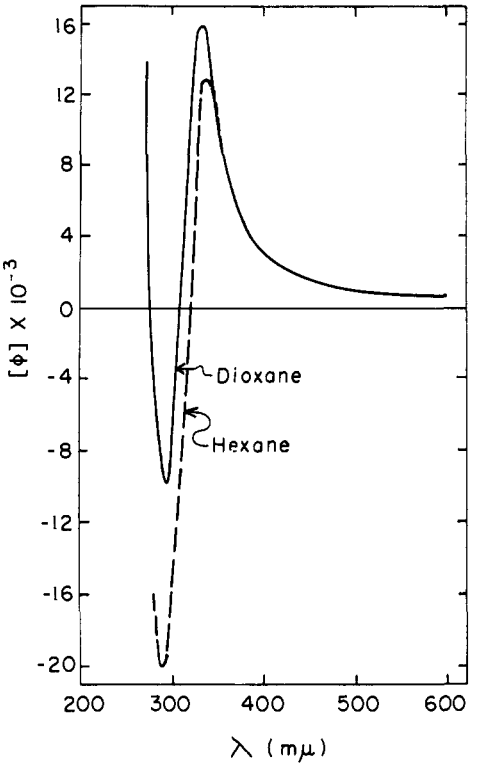


Figure 3. Optical rotatory dispersion curves of (*S*)-N-salicylidene-α-phenylneopentylamine (VIb) in dioxane and hexane.

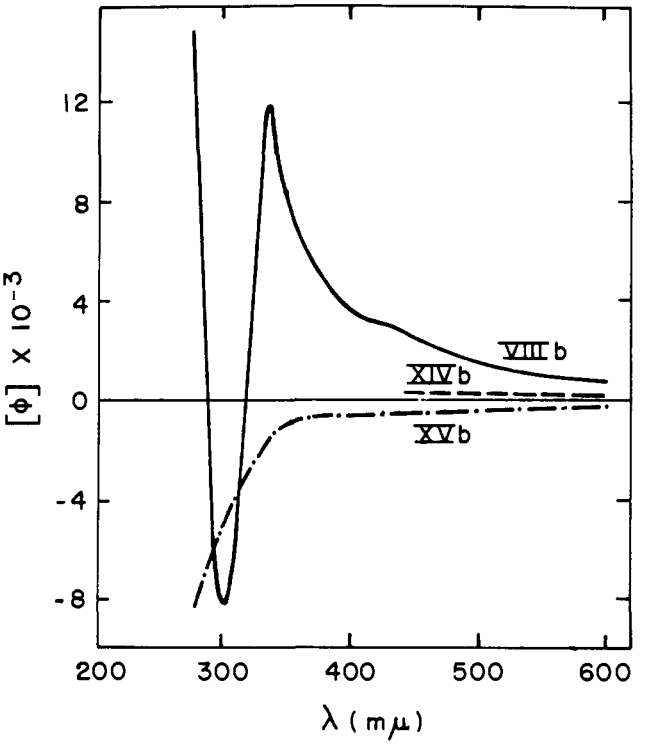


Figure 4. Optical rotatory dispersion curves of methyl N-salicylidene-D-tyrosinate (VIIIb) in methanol, ethyl N-salicylidene-D-alloisoleucinate (XIVb) in absolute ethanol, and (*S*)-N-salicylidene-α,β-diphenylethylamine (XVb) in 95% ethanol.

only an inflection at 430 mμ, but at 318 mμ a strong positive Cotton effect is found (Figure 4). The latter is of the same sign as that observed at 314 mμ for the N-salicylidene derivative of (*S*)-(+)-α-benzylethylamine[17] (VIIa) in ethanol. In dioxane the dispersion curves of these two Schiff bases are similar, each displaying a single Cotton effect near 315 mμ.

With (*S*)-(+)-ethyl N-salicylidene-β-aminohydrocinnamate (Vb) in ethanol the rotatory dispersion curve also shows only an inflection at 430 mμ (Figure 2). In both ethanol and dioxane, each dispersion curve exhibits a strong positive Cotton effect centered at 316 mμ.

For the N-salicylidene derivatives of the D-aliphatic amino acid esters[16] (Xa–XIVa) in ethanol and of (*S*)-(+)-α,β-diphenylethylamine[18] (XVa) in ethanol, dioxane, and hexane, only plain dispersion curves (Figure 4) were observed. These curves are similar to those previously reported[1] for the N-salicylidene derivative of (*S*)-(+)-*sec*-butylamine[19] (IXa). With the amino acid derivatives in ethanol, low rotatory powers prevented precise measurements of the dispersion curves in the region of strong absorption beyond 400 mμ.[20] The rotatory power of the α,β-diphenylethylamine derivative is substantially higher, and rotatory dispersion measurements were reliable to about 275 mμ. In ethanol, dioxane, or hexane, however, this Schiff base displayed only a plain negative curve.

Discussion

The strong Cotton effects observed for the N-salicylidene derivatives of the α- and β-arylalkylamines and the aromatic amino acid esters provide a striking contrast to the curves displayed by the corresponding Schiff bases of the alkylamines and the aliphatic amino acid esters. This supports the suggestion made earlier[1] that the difference is not solely the result of steric effects. A comparison of the rotatory dispersion curves of (+)-ethyl N-salicylidene-D-alaninate (Xb) and of (+)-ethyl N-salicylidene-D-isoleucinate (XIIIb) or (+)-ethyl N-salicylidene-D-alloisoleucinate (XIVb) shows that an increase in the effective size of a substituent from methyl to *sec*-butyl, except for sign, makes comparatively only a small difference in the rotatory dispersion curve. On the other hand, for the derivatives of (*S*)-(−)-ethyl β-aminohydrocinnamate (Va) and (−)-methyl D-tyrosinate (VIIIa) in which the phenyl group is assumed to be somewhat larger than the *sec*-butyl group while the *p*-hydroxybenzyl

(17) Absolute configuration: P. Karrer and E. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

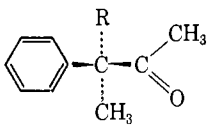
(18) Absolute configuration: P. Pratesi, A. La Manna, and G. Vitali, *Farmaco* (Pavia), *Ed. Sci.*, **15**, 387 (1960). This assignment is opposite to that deduced by G. G. Lyle [*J. Org. Chem.*, **25**, 1779 (1960)] on the basis of the optical rotatory dispersion curves of the free base and of the hydrochloride salt. It is to be noted also that A. La Manna and V. Ghislandi [*Farmaco* (Pavia), *Ed. Sci.*, **17**, 355 (1962)] have found the optical rotatory dispersion curve of (*R*)-(+)-N-nitroso-N-acetyl-α,β-diphenylethylamine to be enantiomeric in comparison to those of the corresponding derivatives of (*S*)-(−)-α-phenylethylamine and (*S*)-(+)-α-benzylethylamine.

(19) Absolute configuration: (a) for references see J. A. Mills and W. Klyne in "Progress in Stereochemistry," Vol. 1, W. Klyne, Ed., Academic Press, Inc., New York, N. Y., 1954, p. 195; (b) A. Kjaer and S. H. Hansen, *Acta Chem. Scand.*, **11**, 898 (1957).

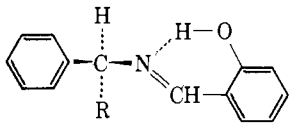
(20) However, D. Bertin and M. Legrand [*Compt. rend.*, **256**, 960 (1963)] have observed a positive maximum [C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963)] at 315 mμ in the positive circular dichroism curves of the N-salicylidene derivatives of some 20α-amino steriods [(20*S*)-configuration] in dioxane. For those with the 20β-configuration the curves are negative with one negative maximum also at 315 mμ.

group is smaller,[21] strong Cotton effects are observed. The Cotton effects near 315 mμ, and near 410 mμ as well, may be due to the presence of a dissymmetric chromophore,[24] arising from an interaction of the benzyl or phenyl group and the salicylidenimino moiety.

The presence of a dissymmetric chromophore in certain β,γ-unsaturated and α-phenyl ketones is well documented.[6] The rotatory power depends chiefly on the spatial arrangement of the interacting π-electrons of the carbon–carbon double bond or the aromatic ring and the carbonyl group. The conformational arrangements for which the interaction is most important have been discussed in detail.[6b] For (*S*)-(+)-3-phenyl-2-butanone (XVI), the Cotton effect near 300 mμ is positive, whereas for (*R*)-(−)-3-phenyl-3-methyl-2-pentanone (XVII), the effect is negative, the sign depending only on the relative effective size of the R group in XVI and XVII with respect to that of the methyl group.



(*S*)-XVI, R = H
(*R*)-XVII, R = C_2H_5



(*S*)-IIIb, R = CH_3
(*S*)-Vb, R = $CH_2CO_2C_2H_5$

It now appears that for the N-salicylidene derivative of an optically active α-arylalkylamine such as (*S*)-IIIb, a similar analysis may allow a correlation between its absolute configuration and its optical rotatory dispersion curve, the sign of the Cotton effect near 315 mμ[25] being independent of the relative size of the R group with respect to that of the phenyl group. For (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIb) and (*S*)-(+)-ethyl N-salicylidene-β-aminohydrocinnamate (Vb), the Cotton effect is positive. Since the effect for the derivative of (−)-α-phenylneopentylamine (VIa) is also positive, the (*S*)-configuration is also assigned to this amine, even though an assessment of the effective sizes of the groups attached to the respective asymmetric centers suggests that the preferred conformation of the latter derivative is different from that of the other two. In support of this hypothesis of a dissymmetric chromophore, degradative experiments are now in progress for an alternate establishment of the absolute configuration of (−)-α-phenylneopentylamine.

By the same considerations, the (*S*)-configuration may also be assigned to (−)-α-phenyl-*n*-propylamine (IVa) and to (−)-α-(1-naphthyl)ethylamine (IIa). These latter assignments, however, can be made without consideration of a dissymmetric chromophore. The effective sizes[22,23] of the groups attached to the asymmetric center in the N-salicylidene derivatives of α-(1-naphthyl)ethylamine, α-phenylethylamine, α-phenyl-*n*-propylamine, and ethyl β-aminohydrocinnamate indicate that for each the conformer composition is similar. It is also reasonable to expect that, for the same configuration, the derivatives should display similar optical rotatory dispersion curves with Cotton effects of the same sign.

It is remarkable that the N-salicylidene derivatives of (*S*)-(+)-α-benzylethylamine (VIIa) and methyl D-tyrosinate (VIIIa) display curves with a Cotton effect near 315 mμ of nearly the same amplitude as that of the α-arylalkylamine derivatives. It is interesting also that in (*S*)-(−)-N-salicylidene-α,β-diphenylethylamine (XVb) the effects of the α- and β-phenyl groups cancel each other. The dispersion curve of this compound shows no anomaly from 600 to 270 mμ.

Experimental[26]

Preparation of Amino Acid Esters. In general, each ester was prepared by heating the respective amino acid in 3 *N* ethanolic hydrogen chloride. The one exception was ethyl L-alaninate which was prepared at room temperature by bubbling dry hydrogen chloride through a suspension of the amino acid in absolute ethanol. After a reaction time of 3 to 4 hr., the alcoholic solution was evaporated and the residue suspended in ether. Treatment of this mixture with an excess of sodium bicarbonate in a minimum amount of water decomposed the salt, and the ester was collected by extraction with portions of ether. After drying over sodium sulfate, complete removal of the ether at reduced pressure on a rotary evaporator with the temperature below 25° gave the ester as a residue.

Preparation of N-Salicylidene Derivatives. These derivatives were formed and purified as outlined previously.[1] Those which are oils were shown by infrared absorption measurements to be free of salicylaldehyde.

Optical Rotatory Dispersion (R.D.) Measurements. Most of these measurements were obtained as described previously,[1] using a Rudolph automatic recording spectropolarimeter, Model 260/658/850/810-614, equipped with a double monochromator, measurements beginning at 600 mμ. The remainder were obtained using another Rudolph automatic recording instrument, Model 260/655/850/810-614, equipped with a single monochromator, measurements beginning at 700 mμ. For all measurements with this instrument, cut-off was indicated when the voltage on the photo-

(21) In the equilibrium between the axial and equatorial conformers in substituted cyclohexanes, the conformational free energy difference at 25°, $-\Delta G°$ (a–e), for the isopropyl group, similar to the *sec*-butyl group, has been reported[22a] to be 2.1 kcal./mole. The benzyl group certainly has a smaller effective size than phenyl for which $-\Delta G°$(a–e) values of 2.0,[23a] *ca.* 2.6 (35°),[23b] and 3.0[23c] kcal./mole have been reported.

(22) (a) N. L. Allinger, L. A. Freiberg, and S-E. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962); N. L. Allinger and S-E. Hu, *J. Org. Chem.*, **27**, 3417 (1962). For other values, see (b) E. L. Eliel and T. J. Brett, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 19Q; (c) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964), and references therein.

(23) (a) N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **27**, 4603 (1962); (b) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960); (c) E. W. Garbisch, Jr., and D. B. Patterson, *ibid.*, **85**, 3228 (1963).

(24) A. Moscowitz, *Tetrahedron*, **13**, 48 (1961).

(25) The band near 315 mμ in the electronic absorption spectra of the N-salicylidene derivative of an amine or α-amino acid salt in ethanol, dioxane, or hexane is attributed to an intramolecularly hydrogen bonded form such as (*S*)-IIIb.[15] In ethanol or dioxane, the band at longer wave length has been attributed to a tautomeric form[15b] or to intermolecularly hydrogen bonded complexes between the derivative and the solvent.[15a,c]

(26) All melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn. Electronic absorption spectra were obtained using an Applied Physics Corp. Cary Model 14 spectrophotometer employing 1-cm. quartz cells and purified solvents, and measurements were made from 700 mμ at initial concentrations of 0.001 *M*. Optical rotatory power measurements at the sodium D-line were obtained with a visual polarimeter, using absolute ethanol as the solvent and a 1-dm. sample tube or as otherwise noted. Molecular rotations, [φ], were calculated as [α] × mol. wt./100.

multiplier tube (RCA 7200) reached 600 v.[27] All other conditions were the same as those with the other instrument.

The rotatory dispersion curves are recorded by indicating for each concentration the molecular rotation $[\phi]$ at the longest wave length, 700 or 600 mμ, or at the wave length at which cut-off occurred at the next higher concentration, at 589 mμ if included, at the shortest wave length before cut-off, and at each extremum and inflection.

(S)-(−)-α-(1-Naphthyl)ethylamine (IIa). This amine was provided through the kindness of Dr. George E. Hulse, Chemical Products Division, Chemetron Corp., Newport, Tenn.; a colorless oil, b.p. 125° (3 mm.), $n^{25}D$ 1.6179, d^{20}_4 1.064, $[\alpha]^{24}D$ −75.4° (neat), $[\alpha]^{24}D$ −51.6° (*c* 2.1, 2 dm.); lit.[28] b.p. 153° (11 mm.), d^{25} 1.055, $[\alpha]^{25}D$ −80.8° (neat), $[\alpha]^{25}D$ −60.8° (*c* 1.9, ethanol).

(S)-(+)-N-Salicylidene-α-(1-naphthyl)ethylamine (IIb). Addition of (*S*)-IIa to a 10% excess of salicylaldehyde in ethanol gave (*S*)-IIb (80% yield), yellow prisms, m.p. 91–92° (absolute ethanol), $[\alpha]^{24}D$ +311° (*c* 2.0); electronic absorption in absolute ethanol: log $\epsilon^{max}_{406\,m\mu}$ 2.65, log $\epsilon^{max}_{314\,m\mu}$ 3.71, log $\epsilon^{sh}_{290\,m\mu}$ 3.90, log $\epsilon^{max}_{283\,m\mu}$ 4.02, log $\epsilon^{sh}_{272\,m\mu}$ 4.03, log $\epsilon^{max}_{250\,m\mu}$ 4.32, log $\epsilon^{max}_{225\,m\mu}$ 5.09; electronic absorption in dioxane: log $\epsilon^{sh}_{410\,m\mu}$ 1.32, log $\epsilon^{max}_{315\,m\mu}$ 3.73, log $\epsilon^{sh}_{292\,m\mu}$ 3.89, log $\epsilon^{max}_{285\,m\mu}$ 4.01, log $\epsilon^{sh}_{272\,m\mu}$ 4.03, log $\epsilon^{max}_{258\,m\mu}$ 4.23, log $\epsilon^{max}_{226\,m\mu}$ 4.99; electronic absorption in hexane: log $\epsilon^{max}_{314\,m\mu}$ 3.80, log $\epsilon^{max}_{294\,m\mu}$ 3.94, log $\epsilon^{max}_{288\,m\mu}$ 3.94, log $\epsilon^{max}_{281\,m\mu}$ 4.05, log $\epsilon^{max}_{270\,m\mu}$ 4.07, log $\epsilon^{max}_{257\,m\mu}$ 4.24, log $\epsilon^{max}_{224\,m\mu}$ 5.03; R.D. (Figure 1) in 95% ethanol, 22°: (*c* 0.14) $[\phi]_{600}$ +760°, $[\phi]_{589}$ +800°, $[\phi]_{423}$ +2980°, $[\phi]_{405}$ +2730°, $[\phi]_{355}$ +6340°; (*c* 0.0040) $[\phi]_{355}$ +4000°, $[\phi]_{335}$ +10,000°, $[\phi]_{294}$ −22,000°, $[\phi]_{280}$ +1000°; R.D. in dioxane, 21–22°: (*c* 0.99) $[\phi]_{600}$ +963°, $[\phi]_{589}$ +1050°, $[\phi]_{380}$ +5840°; (*c* 0.0050) $[\phi]_{380}$ +6100°, $[\phi]_{336}$ +20,000°, $[\phi]_{297}$ −28,000°, $[\phi]_{275}$ +34,000°; R.D. in hexane, 22°: (*c* 0.25) $[\phi]_{600}$ +1140°, $[\phi]_{589}$ +1180°, $[\phi]_{355}$ +10,800°; (*c* 0.0050) $[\phi]_{355}$ +9400°, $[\phi]_{337}$ +16,000°, $[\phi]_{296}$ −33,000°, $[\phi]_{270}$ +33,000°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 82.72; H, 5.99.

(R)-(+)-α-Phenyl-n-propylamine (IVa). Racemic α-phenyl-*n*-propylamine was resolved as previously described[29] using (−)-malic acid. The optically active free base was a colorless oil, b.p. 98° (23 mm.), $n^{25}D$ 1.5157, d^{20}_4 0.936, $[\alpha]^{24}D$ +21.2° (neat), $[\alpha]^{27}D$ +8.1° (*c* 7.9); lit.[29] $[\alpha]^{17}D$ +20.15° (neat).

(R)-(−)-N-Salicylidene-α-phenyl-n-propylamine (IVb). Addition of (*R*)-IVa to a 91% excess of salicylaldehyde in absolute ethanol gave (*R*)-IVb (78% yield), yellow prisms, m.p. 45–47° (methanol), $[\alpha]^{24}D$ −161° (*c* 2.0); electronic absorption in absolute ethanol: log $\epsilon^{max}_{405\,m\mu}$ 2.57, log $\epsilon^{max}_{317\,m\mu}$ 3.60, log $\epsilon^{max}_{254\,m\mu}$ 4.12, log $\epsilon^{max}_{213\,m\mu}$ 4.43; electronic absorption in dioxane: log $\epsilon^{sh}_{410\,m\mu}$ 1.31, log $\epsilon^{max}_{317\,m\mu}$ 3.73, log $\epsilon^{max}_{262\,m\mu}$ 4.22, log $\epsilon^{max}_{255\,m\mu}$ 4.28, log $\epsilon^{sh}_{250\,m\mu}$ 4.16, log $\epsilon^{sh}_{227\,m\mu}$ 4.09, log $\epsilon^{max}_{212\,m\mu}$ 4.36; electronic absorption in hexane: log $\epsilon^{max}_{320\,m\mu}$ 3.70, log $\epsilon^{sh}_{261\,m\mu}$ 4.13, log $\epsilon^{max}_{256\,m\mu}$ 4.18, log $\epsilon^{sh}_{228\,m\mu}$ 4.35, log $\epsilon^{max}_{216\,m\mu}$ 4.50; R.D. (Figure 1) in 95% ethanol, 22°: (*c* 0.090) $[\phi]_{600}$ −350°, $[\phi]_{589}$ −380°, $[\phi]_{428}$ −2100°, $[\phi]_{396}$ −1600°, $[\phi]_{350}$ −5260°; (*c* 0.0090) $[\phi]_{350}$ −5300°, $[\phi]_{336}$ −7500°, $[\phi]_{292}$ +13,000°, $[\phi]_{270}$ −2000°; R.D. in dioxane, 24°: (*c* 1.7) $[\phi]_{700}$ −234°, $[\phi]_{589}$ −409°, $[\phi]_{400}$ −2230°; (*c* 0.0084) $[\phi]_{400}$ −2000°, $[\phi]_{334}$ −16,000°, $[\phi]_{293}$ +14,000°, $[\phi]_{280}$ + 10,000°; R.D. in hexane, 22°: (*c* 0.25) $[\phi]_{600}$ −400°, $[\phi]_{589}$ −420°, $[\phi]_{360}$ −5700°; (*c* 0.010) $[\phi]_{360}$ −6200°, $[\phi]_{334}$ −12,000°, $[\phi]_{289}$ +16,000° $[\phi]_{265}$ −4300°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.22; H, 6.96.

(R)-(+)-Ethyl β-Aminohydrocinnamate (Va). Racemic N-formyl-β-aminohydrocinnamic acid was resolved as previously described[30] using quinidine. The optically active N-formyl acid, m.p. 136–140°, $[\alpha]^{22}D$ +100° (*c* 0.5, 95% ethanol), was hydrolyzed and by the usual method of esterification converted to (*R*)-Va (36% yield). The ester, a colorless oil, was further purified by distillation, b.p. 99° (0.75 mm.), $n^{25}D$ 1.5101, d^{20}_4 1.077, $[\alpha]^{22}D$ +13.9° (neat), $[\alpha]^{24}D$ +6.6° (*c* 2.0); lit.[30] d^{24}_4 1.063, $[\alpha]^{24}D$ +13.74° (neat).

(R)-(−)-Ethyl N-Salicylidene-β-aminohydrocinnamate (Vb). Addition of distilled (*R*)-Va to an 18% excess of salicylaldehyde in absolute ethanol gave (*R*)-Vb (71% yield), a yellow oil, b.p. 190–200° (1.7 mm.), $n^{25}D$ 1.5729, $[\alpha]^{24}D$ −84.3° (*c* 1.5); electronic absorption in absolute ethanol: log $\epsilon^{max}_{404\,m\mu}$ 2.11, log $\epsilon^{max}_{317\,m\mu}$ 3.66, log $\epsilon^{max}_{250\,m\mu}$ 4.17, log $\epsilon^{max}_{214\,m\mu}$ 4.48; electronic absorption in dioxane: log $\epsilon^{sh}_{420\,m\mu}$ 0.82, log $\epsilon^{max}_{318\,m\mu}$ 3.70, log $\epsilon^{max}_{255\,m\mu}$ 4.19; R.D. (Figure 2) in 95% ethanol, 23°: (*c* 0.52) $[\phi]_{600}$ −260°, $[\phi]_{589}$ −260°, $[\phi]_{430}$ −1040° (infl.), $[\phi]_{380}$ −2220°; (*c* 0.013) $[\phi]_{380}$ −2400°, $[\phi]_{337}$ −8000°, $[\phi]_{294}$ +11,000°, $[\phi]_{275}$ +4000°; R.D. in dioxane, 22°: (*c* 1.0) $[\phi]_{600}$ −270°, $[\phi]_{589}$ −290°, $[\phi]_{370}$ −3300°; (*c* 0.016) $[\phi]_{370}$ −2600°, $[\phi]_{336}$ −8700°, $[\phi]_{295}$ +14,000°, $[\phi]_{275}$ +7200°.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44. Found: C, 73.25; H, 6.29.

(R)-(+)-α-Phenylneopentylamine (VIa). To 72.2 g. (0.417 mole) of N-acetyl-L-leucine[31] in 1250 ml. of hot water was added 72.7 g. (0.445 mole) of racemic α-phenylneopentylamine, a colorless oil, b.p. 102–105° (16 mm.), obtained from pivalophenone by the Leuckart reaction.[32] The hot solution was clarified with Norit and crystals were allowed to form overnight at room temperature. The crystals, 53.7 g., were collected by filtration. After one recrystallization of this material from 850 ml. of water there was obtained 29.8 g. of one diastereoisomeric salt (42% yield), $[\alpha]^{21}D$ −7.2° (*c* 4.0, methanol), the rotatory power of which remained unchanged on further recrystallization from water. Decomposition of this salt with an excess of aqueous sodium hydroxide in the usual way gave (*R*)-VIa (73% yield), a colorless oil, b.p. 99–101° (14 mm.), $n^{25}D$ 1.5111, d^{20}_4 0.926, $[\alpha]^{21}D$ + 5.6° (neat), $[\alpha]^{21}D$ +2.5° (*c* 4.0, methanol); lit.[33] $[\alpha]D$ +0.26° (absolute ethanol).

(27) For a discussion of the stray-light problem encountered in the use of this particular model of spectropolarimeter and of its limit of reliability, see C. Djerassi, E. Lund, E. Bunnenberg, and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961). For similar difficulties with other instruments, see V. M. Potapov and A. P. Terent'ev, *Zh. Obshch. Khim.*, 31, 1003 (1961).

(28) E. Samuelsson, Thesis, University of Lund, 1923; *Chem. Abstr.*, **18**, 1833 (1924).

(29) A. J. Little, J. M'Lean, and F. J. Wilson, *J. Chem. Soc.*, 336 (1940).

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(31) H. D. DeWitt and A. W. Ingersoll, *J. Am. Chem. Soc.*, **73**, 3359 (1951).

(32) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, and G. Jennings, *ibid.*, **58**, 1808 (1936); A. W. Ingersoll and H. D. DeWitt, *ibid.*, **73**, 3360 (1951).

(R)-(−)-N-Salicylidene-α-phenylneopentylamine (VIb). Addition of (*R*)-VIa to a 14% excess of salicylaldehyde in methanol gave (*R*)-VIb (44% yield), yellow plates, m.p. 123–124° (methanol), $[\alpha]^{20}D$ −251° (*c* 0.99, methanol); electronic absorption in absolute ethanol: log $\epsilon^{max}_{403\,m\mu}$ 2.60, log $\epsilon^{max}_{317\,m\mu}$ 3.61, log $\epsilon^{sh}_{263\,m\mu}$ 4.08, log $\epsilon^{max}_{256\,m\mu}$ 4.13, log $\epsilon^{max}_{215\,m\mu}$ 4.46; electronic absorption in dioxane: log $\epsilon^{sh}_{410\,m\mu}$ 1.26, log $\epsilon^{max}_{318\,m\mu}$ 3.64, log $\epsilon^{sh}_{262\,m\mu}$ 4.06, log $\epsilon^{max}_{257\,m\mu}$ 4.12, log $\epsilon^{max}_{215\,m\mu}$ 4.45; electronic absorption in hexane: log $\epsilon^{max}_{321\,m\mu}$ 3.72, log $\epsilon^{max}_{263\,m\mu}$ 4.15, log $\epsilon^{max}_{256\,m\mu}$ 4.18, log $\epsilon^{sh}_{223\,m\mu}$ 4.44; R.D. (Figure 2) in 95% ethanol, 22°: (*c* 0.090) $[\phi]_{600}$ −570°, $[\phi]_{589}$ −630°, $[\phi]_{426}$ −2700°, $[\phi]_{400}$ −2100°, $[\phi]_{345}$ −7350°; (*c* 0.0090) $[\phi]_{345}$ −7600°, $[\phi]_{336}$ −11,000°, $[\phi]_{294}$ +14,000°, $[\phi]_{270}$ −2000°; R.D. (Figure 3) in dioxane, 24°: (*c* 2.0) $[\phi]_{700}$ −395°, $[\phi]_{589}$ −602°, $[\phi]_{400}$ −2810°; (*c* 0.010) $[\phi]_{400}$ −2700°, $[\phi]_{332}$ −16,000°, $[\phi]_{294}$ +10,000°, $[\phi]_{270}$ −14,000°; R.D. (Figure 3) in hexane, 24°: (*c* 2.0) $[\phi]_{700}$ −372°, $[\phi]_{589}$ −582°, $[\phi]_{390}$ −3460°; (*c* 0.20) $[\phi]_{390}$ −3300°, $[\phi]_{360}$ −7000°; (*c* 0.010) $[\phi]_{360}$ −7300°, $[\phi]_{334}$ −13,000°, $[\phi]_{288}$ +20,000°, $[\phi]_{280}$ +16,000°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.83; H, 7.83.

The solubility behavior of the N-salicylidene derivative of optically active and of racemic α-phenylneopentylamine provide a method of increasing the optical purity of a partially racemic sample of the amine. For example, 1.9 g. (0.012 mole) of optically impure α-phenylneopentylamine obtained from a foot fraction of the resolution was combined with an equivalent amount of salicylaldehyde in 25 ml. of methanol, and there was obtained 1.7 g. of a solid N-salicylidene derivative, $[\alpha]^{22}D$ +134° (*c* 1.6, methanol). Two recrystallizations of this material from methanol gave pure (*S*)-VIb, 0.6 g. (19% yield), $[\alpha]^{21}D$ +251° (*c* 1.7, methanol).

(+)-Methyl L-Tyrosinate (VIIIa). The hydrochloride salt of methyl L-tyrosinate, from Mann Research Laboratories, Inc., was decomposed with an excess of aqueous sodium bicarbonate and the ester was collected in ether. After drying over sodium sulfate and removal of the ether at reduced pressure, recrystallization of the solid residue from methyl acetate gave L-VIIIa (23% yield), white prisms, m.p. 135–136°, $[\alpha]^{24}D$ +28° (*c* 1.0, methanol); lit.[34] m.p. 135–136°, $[\alpha]^{20}D$ +25.97° (*c* 5.1, methanol).

(−)-Methyl N-Salicylidene-L-tyrosinate (VIIIb). Addition of L-VIIIa to a 10% excess of salicylaldehyde in methyl acetate gave L-VIIIb (66% yield), thin, yellow prisms, m.p. 166–167° (methyl acetate), $[\alpha]^{22}D$ −270° (*c* 2.0, methanol); electronic absorption in methanol: log $\epsilon^{max}_{405\,m\mu}$ 2.41, log $\epsilon^{max}_{319\,m\mu}$ 3.58, log $\epsilon^{sh}_{286\,m\mu}$ 3.46, log $\epsilon^{max}_{256\,m\mu}$ 4.07, log $\epsilon^{sh}_{220\,m\mu}$ 4.53; electronic absorption in dioxane: log $\epsilon^{sh}_{420\,m\mu}$ 0.96, log $\epsilon^{max}_{319\,m\mu}$ 3.71, log $\epsilon^{sh}_{285\,m\mu}$ 3.50, log $\epsilon^{max}_{258\,m\mu}$ 4.14, log $\epsilon^{sh}_{222\,m\mu}$ 4.45, log $\epsilon^{max}_{216\,m\mu}$ 4.48; R.D. (Figure 4) in methanol, 22°: (*c* 0.22) $[\phi]_{600}$ −820°, $[\phi]_{589}$ −890°, $[\phi]_{430}$ −3120° (infl.), $[\phi]_{355}$ −7600°; (*c* 0.011) $[\phi]_{355}$ −7100°, $[\phi]_{337}$ −12,000°, $[\phi]_{300}$ +8200°, $[\phi]_{275}$ −15,000°; R.D. in dioxane, 22°: (*c* 1.2) $[\phi]_{700}$ −570°, $[\phi]_{589}$ −840°, $[\phi]_{375}$ −5140°; (*c* 0.012) $[\phi]_{375}$ −4100°; $[\phi]_{334}$ −13,000°, $[\phi]_{297}$ +6200°, $[\phi]_{280}$ −8000°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: C, 68.10, 68.20; H, 5.56, 5.69.

To demonstrate that the crystalline derivative described above was optically pure, a solution of L-VIIIb was prepared by combining 0.0804 g. (0.412 mmole) of L-VIIIa with 0.0578 g. (0.467 mmole) of salicylaldehyde and diluting the mixture to 25.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{24}D$ −267° (*c* 0.49).

(+)-Ethyl L-Alaninate (Xa). Esterification of L-alanine, $[\alpha]^{21}D$ +13° (*c* 2.0, 1 *N* HCl), gave L-Xa (41% yield), a viscous, colorless oil, $n^{25}D$ 1.3911, $[\alpha]^{22}D$ +2° (*c* 4.0); lit.[35] $[\alpha]^{22}D$ +3° (*c* 3.9, ethanol).

(−)-Ethyl N-Salicylidene-L-alaninate (Xb). Addition of L-Xa to a 10% excess of salicylaldehyde in absolute ethanol gave, after distillation, mostly racemized L-Xb (21% yield), a yellow oil, b.p. 97–101° (0.08 mm.), $n^{25}D$ 1.5364, $[\alpha]^{26}D$ −0.4° (*c* 3.0); electronic absorption in absolute ethanol: log $\epsilon^{max}_{407\,m\mu}$ 2.21, log $\epsilon^{max}_{318\,m\mu}$ 3.62, log $\epsilon^{max}_{256\,m\mu}$ 4.09, log $\epsilon^{max}_{214\,m\mu}$ 4.35.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.34; H, 6.98.

For observation of the rotatory dispersion curve, a solution of L-Xb was prepared by combining 0.2006 g. (1.712 mmoles) of L-Xa with 0.2435 g. (1.994 mmoles) of salicylaldehyde and diluting the mixture to 10.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{23}D$ −5.1° (*c* 3.8); R.D., 24–25°: (*c* 3.8) $[\phi]_{700}$ −17°, $[\phi]_{589}$ −12°, $[\phi]_{450}$ +13°. At lower concentrations measurements were made from 450 to 370 mμ. These were of only qualitative significance, but in this spectral region the dispersion curve was also plain positive.

(+)-Ethyl L-Methioninate (XIa). Esterification of L-methionine, $[\alpha]^{27}D$ +24.6° (*c* 4.2, 1 *N* HCl), gave L-XIa, a viscous colorless oil, $n^{25}D$ 1.4780, $\alpha^{24}D$ −4.4° (neat, 1 dm.). The ester was purified by distillation (73% yield over-all), b.p. 148° (31 mm.), $n^{25}D$ 1.4787, $\alpha^{27}D$ −5.9° (neat, 1 dm.), $[\alpha]^{28}D$ +7.6° (*c* 3.1); lit.[13] for the D-isomer, $[\alpha]^{30}D$ −9.1° (solvent not specified).

Anal. Calcd. for $C_7H_{15}NO_2S$: C, 47.43; H, 8.53. Found: C, 47.47; H, 8.70.

(−)-Ethyl N-Salicylidene-L-methioninate (XIb). Addition of distilled L-XIa to a 10% excess of salicylaldehyde in absolute ethanol gave, after distillation, racemic ethyl N-salicylidenemethioninate (67% yield), a viscous, yellow oil, b.p. 170° (0.75 mm), $n^{25}D$ 1.5550, d^{20}_4 1.133, $[\alpha]^{20}D$ ±0° (neat); electron absorption in absolute ethanol: log $\epsilon^{max}_{408\,m\mu}$ 2.05, log $\epsilon^{max}_{320\,m\mu}$ 3.65, log $\epsilon^{max}_{258\,m\mu}$ 4.13, log $\epsilon^{sh}_{221\,m\mu}$ 4.32, log $\epsilon^{max}_{214\,m\mu}$ 4.35.

Anal. Calcd. for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81. Found: C, 60.07; H, 6.79.

For observation of the rotatory dispersion curve, a solution of L-XIb was prepared by combining 0.2897 g. (1.634 mmoles) of distilled L-XIa with 0.2132 g. (1.746 mmoles) of salicylaldehyde and diluting the mixture to 10.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{27}D$ −113° (*c* 4.6); R.D., 24°: (*c* 1.0) $[\phi]_{700}$ −247°, $[\phi]_{589}$ −334°, $[\phi]_{370}$ −1550°.

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(+)-*Ethyl* L-*Leucinate* (*XIIa*). Esterification of L-leucine, $[\alpha]^{27}D$ +12° (*c* 4.0, 1 *N* HCl), gave L-XIIa, a viscous, colorless oil, $n^{25}D$ 1.4264, $\alpha^{24}D$ +8.5° (neat, 1 dm.). The ester was purified by distillation (72% yield over-all), b.p. 99–100° (27 mm.), $n^{25}D$ 1.4256, d^{25}_4 0.9094, $[\alpha]^{27}D$ +10.0° (neat), $[\alpha]^{27}D$ +21° (*c* 2.9); lit.[36] $[\alpha]^{20}D$ +13.1° (neat).

(−)-*Ethyl N-Salicylidene*-L-*leucinate* (*XIIb*). Addition of distilled L-XIIa to a 48% excess of salicylaldehyde in absolute ethanol gave, after distillation, mostly racemized L-XIIb (82% yield), a viscous, yellow oil, b.p. 138° (0.7 mm.), $n^{25}D$ 1.5221, $[\alpha]^{28}D$ −13° (*c* 3.0); electronic absorption in absolute ethanol: log $\epsilon^{max}_{408\,m\mu}$ 2.27, log $\epsilon^{max}_{321\,m\mu}$ 3.63, log $\epsilon^{max}_{257\,m\mu}$ 4.12, log $\epsilon^{sh}_{223\,m\mu}$ 4.31, log $\epsilon^{max}_{216\,m\mu}$ 4.33.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04. Found: C, 68.11; H, 7.87.

For observation of the rotatory dispersion curve, a solution of L-XIIb was prepared by combining 0.7461 g. (4.686 mmoles) of distilled L-XIIa with 0.6038 g. (4.944 mmoles) of salicylaldehyde and diluting to 25.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{28}D$ −76.8° (*c* 4.9, 2 dm.); R.D., 24°: (*c* 0.74) $[\phi]_{700}$ −200°, $[\phi]_{589}$ −250°, $[\phi]_{460}$ −444°; (*c* 0.20) $[\phi]_{460}$ −400°, $[\phi]_{360}$ −890°.

(+)-*Ethyl* L-*Isoleucinate* (*XIIIa*). Decomposition in the usual way of the hydrochloride salt of ethyl L-isoleucinate, from Mann Research Laboratories, Inc., gave L-XIIIa, a viscous, colorless oil, $\alpha^{24}D$ +22.9° (neat, 1 dm.), $[\alpha]^{25}D$ +31° (*c* 2.0). The ester was further purified by distillation, b.p. 99° (21 mm.), $n^{25}D$ 1.4294, $\alpha^{24}D$ +27.8° (neat, 1 dm.), $[\alpha]^{24}D$ +38° (*c* 2.0); lit.[37] b.p. 75–76° (10 mm.), $n^{20}D$ 1.4328, no rotational data reported.

(−)-*Ethyl N-Salicylidene*-L-*isoleucinate* (*XIIIb*). Addition of distilled L-XIIIa to a 34% excess of salicylaldehyde in absolute ethanol gave, after distillation, a mixture of 92% L-XIIIb and 8% D-XIVb (77% yield), a viscous, yellow oil, b.p. 107–111° (0.07 mm.), $n^{25}D$ 1.5259, $[\alpha]^{23}D$ −43.6° (*c* 3.2); electronic absorption in absolute ethanol: log $\epsilon^{max}_{407\,m\mu}$ 2.36, log $\epsilon^{max}_{319\,m\mu}$ 3.63, log $\epsilon^{max}_{257\,m\mu}$ 4.12, log $\epsilon^{sh}_{221\,m\mu}$ 4.30, log $\epsilon^{max}_{216\,m\mu}$ 4.33.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04. Found: C, 68.50; H, 8.38.

For observation of the rotatory dispersion curve, a solution of L-XIIIb was prepared by combining 1.0100 g. (6.343 mmoles) of distilled L-XIIIa with 0.8146 g. (6.670 mmoles) of salicylaldehyde and diluting to 50.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{23}D$ −51.3° (*c* 3.3); R.D., 25°; (*c* 2.0) $[\phi]_{700}$ −94°, $[\phi]_{589}$ −132°, $[\phi]_{450}$ −255°.

(−)-*Ethyl* D-*Alloisoleucinate* (*XIVa*). Esterification of D-alloisoleucine, $[\alpha]^{21}D$ −39° (*c* 0.65, 6 *N* HCl), lit.[38] $[\alpha]^{20}D$ −38.4° (*c* 4, 6 *N* HCl), gave D-XIVa, a viscous, colorless oil, $n^{27}D$ 1.4243, $[\alpha]^{25}D$ −34° (*c* 2.0). The ester was purified by distillation (49% yield over-all), b.p. 47° (0.3 mm.), $n^{21}D$ 1.4297, d^{20}_4 0.934, $[\alpha]^{21}D$ −32.7° (neat), $[\alpha]^{25}D$ −38° (*c* 2.1).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76. Found: C, 60.26; H, 10.65.

(+)-*Ethyl N-Salicylidene*-D-*alloisoleucinate* (*XIVb*). Addition of distilled D-XIVa to a 13% excess of salicylaldehyde in absolute ethanol gave, after distillation, a mixture of 91% D-XIVb and 9% L-XIIIb (81% yield), b.p. 106° (0.03 mm.), $n^{25}D$ 1.5263, $[\alpha]^{23}D$ +44.2° (*c* 3.1); electronic absorption in absolute ethanol: log $\epsilon^{max}_{406\,m\mu}$ 2.40, log $\epsilon^{max}_{319\,m\mu}$ 3.63, log $\epsilon^{max}_{257\,m\mu}$ 4.13, log $\epsilon^{sh}_{221\,m\mu}$ 4.31, log $\epsilon^{max}_{216\,m\mu}$ 4.34.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04. Found: C, 68.58; H, 8.10.

For observation of the rotatory dispersion curve, a solution of D-XIVb was prepared by combining 0.4995 g. (3.137 mmoles) of distilled D-XIVa with 0.4053 g. (3.319 mmoles) of salicylaldehyde and diluting to 25.00 ml. with absolute ethanol. This solution exhibited a maximum rotatory power of $[\alpha]^{22}D$ +53.3° (*c* 3.3); R.D. (Figure 4), 25°: (*c* 0.60) $[\phi]_{700}$ +87°, $[\phi]_{589}$ +150°, $[\phi]_{440}$ +350°.

(*S*)-(+)-α,β-*Diphenylethylamine* (*XVa*). This amine was provided through the kindness of Professor Gloria G. Lyle, Department of Chemistry, University of New Hampshire; $[\alpha]^{27}D$ +42° (*c* 2.0); lit.[39] *d* 1.039, $[\alpha]^{18}D$ +12.2° (neat).

(*S*)-(−)-*N-Salicylidene-α,β-diphenylethylamine* (*XVb*). Addition of (*S*)-XVa to an excess of salicylaldehyde without solvent gave (*S*)-XVb (79% yield), yellow prisms, m.p. 89–90° (methanol), $[\alpha]^{23}D$ −89° (*c* 0.88); electronic absorption in absolute ethanol: log $\epsilon^{max}_{407\,m\mu}$ 2.45, log $\epsilon^{max}_{317\,m\mu}$ 3.66, log $\epsilon^{sh}_{264\,m\mu}$ 4.12, log $\epsilon^{max}_{258\,m\mu}$ 4.19, log $\epsilon^{max}_{213\,m\mu}$ 4.59; electronic absorption in dioxane: log $\epsilon^{sh}_{410\,m\mu}$ 1.29, log $\epsilon^{max}_{317\,m\mu}$ 3.70, log $\epsilon^{sh}_{262\,m\mu}$ 4.17, log $\epsilon^{max}_{257\,m\mu}$ 4.21, electronic absorption in hexane: log $\epsilon^{max}_{320\,m\mu}$ 3.72, log $\epsilon^{sh}_{263\,m\mu}$ 4.12, log $\epsilon^{max}_{257\,m\mu}$ 4.18, log $\epsilon^{max}_{213\,m\mu}$ 4.57; R.D. in 95% ethanol (Figure 4), 22°: (*c* 0.80) $[\phi]_{600}$ −300°, $[\phi]_{589}$ −310°, $[\phi]_{445}$ −521°; (*c* 0.020) $[\phi]_{445}$ −500°, $[\phi]_{275}$ −8400°; R.D. in dioxane, 22°: (*c* 1.0) $[\phi]_{600}$ −220°, $[\phi]_{589}$ −230°, $[\phi]_{380}$ −717°; (*c* 0.020) $[\phi]_{380}$ −500°, $[\phi]_{270}$ −7700°; R.D. in hexane, 22°: (*c* 0.26) $[\phi]_{600}$ −210°, $[\phi]_{589}$ −220°, $[\phi]_{360}$ −1200°; (*c* 0.026) $[\phi]_{360}$ −1000°, $[\phi]_{275}$ −7900°.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35. Found: C, 83.80; H, 6.26.

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