fide to obtain a similar yield. The product required more extensive purification, however, and the yields never exceeded those obtained by the use of carbon disulfide. Other catalysts, such as stannic chloride and ferric chloride, proved to be ineffective.

Conversion of Thioimides to Dicarboxylic Acids.—In a 100-ml., round-bottom, one-necked copper flask were placed 3 g. of a thioimide and 40 ml. of 25% aqueous potassium hydroxide. The mixture was refluxed until no evolution of ammonia was observed (24–72 hr.), followed by acidification, extraction with ether, and evaporation of the extracts under a stream of air. In this manner the acids listed in Table III were obtained. The melting points recorded were those observed with rapid heating or in a preheated bath; slow heating gave lower, less sharp, melting points. Melting was in all cases accompanied by gas evolution, presumably resulting from anhydride formation.

Reduction of 2-Thiohomophthalimides.—To 100 ml. of anhydrous ether containing 1.071 g. of lithium aluminum hydride (5 molar equiv.) was added 1 g. of 2a-thiohomophthalimide [1-thio-1,3(2H,4H)-isoquinolinedione] in two portions, over 2 min. The mixture was stirred under reflux for 15 hr., after which it was cooled. A mixture of 2 ml. of water and 2 ml. of 10% sodium hydroxide solution was added carefully and stirring was continued for another hour. After filtration and washing of the precipitate with anhydrous ether, the solvent was removed under the aspirator, and a saturated solution of picric acid in ethanol was added to the residue. The picrate of 1,2,3,4-tetrahydroisoquinoline formed in 47% yield on standing, m.p. 195°, lit.[18] m.p. 195–196°. Similarly, a 50% yield of 1,2,3,4-tetrahydroisoquinoline, isolated as its picrate, was obtained from the reduction of thio-3,4-dihydroisocarbostyril. A yield of 40% of 6-methyl-1,2,3,4-tetrahydroisoquinoline (as its picrate, m.p. 214°, lit.[19] m.p. 205°) was obtained by the reduction of 5-methyl-2a-thiohomophthalimide [1-thio-6-methyl-1,3(2H,4H)-isoquinolinedione].

Oxidation of Homophthalic Acids.—An aqueous solution of 0.5 g. of 5-methylhomophthalic acid and an excess of potassium permanganate was refluxed for 8 hr., filtered, and acidified. Evaporation to dryness in an air stream, extraction of the residue with boiling, glacial acetic acid, and cooling of the extract gave 0.3 g. (55%) of trimellitic acid, m.p. 225° dec. (lit. m.p. 226–227°,[20] 238°[21]). Refluxing this product with acetic anhydride for 2 hr., removal of reagent and acetic acid *in vacuo*, and sublimation of the residue at 200–220° (12 mm.) gave trimellitic anhydride, m.p. 160°, lit.[22] m.p. 162.5–163.5°.

Similar treatment of 5-methoxyhomophthalic acid gave 4-methoxyphthalic acid, m.p. 170°, lit.[23] m.p. 171–172°. Sublimation at 220° gave 4-methoxyphthalic anhydride, m.p. 95°, lit.[23] m.p. 94–95°.

Oxidation of Thiohomophthalimides to Phthalimides.—To a solution of 0.5 g. of 1-thio-1,3(2H,4H)-benzo[*d*]isoquinolinedione (the thiohomophthalimide from α-naphthylacetyl isothiocyanate) in 5 ml. of water containing 0.5 g. of potassium hydroxide was slowly added 2.8 ml. (10 molar equiv.) of 30% hydrogen peroxide. After 4 hr. at room temperature, the solution was acidified with concentrated hydrochloric acid and heated on the steam bath for 20 min. Upon chilling, there was obtained 0.35 g. (81%) of 1,2-naphthalimide as yellow needles, m.p. 223° after recrystallization from acetic acid, lit.[24] m.p. 224°.

Anal. Calcd. for $C_{12}H_7NO_2$: C, 72.42; H, 3.55; N, 7.04. Found: C, 72.25; H, 3.65; N, 7.00.

In a similar manner, 6-methyl-1-thio-1,3(2H,4H)-isoquinolinedione (the thiohomophthalimide from *m*-tolylacetyl isothiocyanate) was converted in 61% yield to 4-methylphthalimide, m.p. 196° (lit.[25] m.p. 196°, depressed by admixture with the known 3-methyl isomer).

Anal. Calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.70. Found: C, 67.39; H, 4.49; N, 8.91.

3-Methylphthalimide.—Sublimation at 110° (20 mm.) of the 3-methylphthalic acid obtained from *m*-tolulyl isothiocyanate by cyclization and hydrolysis gave 3-methylphthalic anhydride, m.p. 117–118°, lit.[26] m.p. 117–118°. Equal weights of 28% ammonium hydroxide and the 3-methylphthalic anhydride were heated for 2 hr. at 150–180°. Recrystallization of the crude product from hot water gave 3-methylphthalimide, m.p. 188–189° (lit.[27] m.p. 189–190°) in good yield.

(18) E. Bamberger and W. Dieckmann, *Ber.*, **26**, 1205 (1893).
(19) J. von Braun, G. Blessing, and R. S. Cahn, *ibid.*, **57**, 908 (1924).
(20) W. H. Perkin and J. F. S. Stone, *J. Chem. Soc.*, **127**, 2275 (1925).
(21) G. T. Morgan and E. A. Coulson, *ibid.*, 2551 (1929).
(22) W. Schultze, *Ann.*, **359**, 129 (1908).
(23) W. W. Prichard, *J. Am. Chem. Soc.*, **78**, 6137 (1956).
(24) E. F. Bradbrook and R. P. Linstead, *J. Chem. Soc.*, 1739 (1936).
(25) S. von Niementowski, *Monatsh.*, **12**, 620 (1891).
(26) F. Mayer and O. Stark, *Ber.*, **64**, 2003 (1931).
(27) S. Gabriel and A. Thieme, *ibid.*, **52**, 1079 (1919).

Optically Active Amines. II. The Optical Rotatory Dispersion Curves of the N-Benzylidene and Substituted N-Benzylidene Derivatives of Some Open-Chain Primary Amines[1,2]

HOWARD E. SMITH, SUSAN L. COOK,[3] AND MITCHUM E. WARREN, JR.[3,4]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee

Received December 4, 1963

Most of the optically active N-benzylidene, N-*o*-methoxybenzylidene, N-salicylidene, N-5-nitrosalicylidene, N-5-chlorosalicylidene, and N-5-bromosalicylidene derivatives of α-phenyl- and α-benzylethylamine and of *sec*-butylamine were prepared and their electronic absorption spectra and optical rotatory dispersion curves were measured. Cotton effects could be observed only in the rotatory dispersion curves of the N-salicylidenes and the N-5-chloro- and N-5-bromosalicylidenes of α-phenyl- and α-benzylethylamine. A comparison of these curves with that displayed by N-salicylidene-*sec*-butylamine suggests that, for the aralkylamine derivatives, there may be present rotationally significant interactions of the π-electron systems of the phenyl and benzyl groups with the N-salicylidene moiety which, for the derivatives with the (*S*)-configuration, result in strong positive Cotton effects near 410 and 315 mμ.

Many Schiff bases derived from aldehydes and ketones and optically active open-chain amines exhibit notably high rotatory powers at the sodium D-line. Betti[5] has recorded values for numerous derivatives of benzaldehyde and substituted benzaldehydes and (+)-1-(α-aminobenzyl)-2-naphthol ($[\phi]_D$ +147°) and observed marked differences, apparently related to the strengths of the acids corresponding to the aldehydes. For example, the derivative prepared from *p*-N,N-dimethylaminobenzaldehyde has an extremely high posi-

(1) Paper I: H. E. Smith, M. E. Warren, Jr., and A. W. Ingersoll, *J. Am. Chem. Soc.*, **84**, 1513 (1962).
(2) A preliminary report of some of this work was presented before the Combined Southeast and Southwest Regional Meeting of the American Chemical Society, New Orleans, La., 1961, Abstract 162.
(3) Part of this work is from the M.A. Thesis of S. L. Cook, Vanderbilt University, June, 1962, and part from the Ph.D. Thesis of M. E. Warren, Jr., Vanderbilt University, June, 1963.
(4) National Defense Education Act Fellow, 1959–1962.
(5) M. Betti, *Trans. Faraday Soc.*, **26**, 337 (1930).

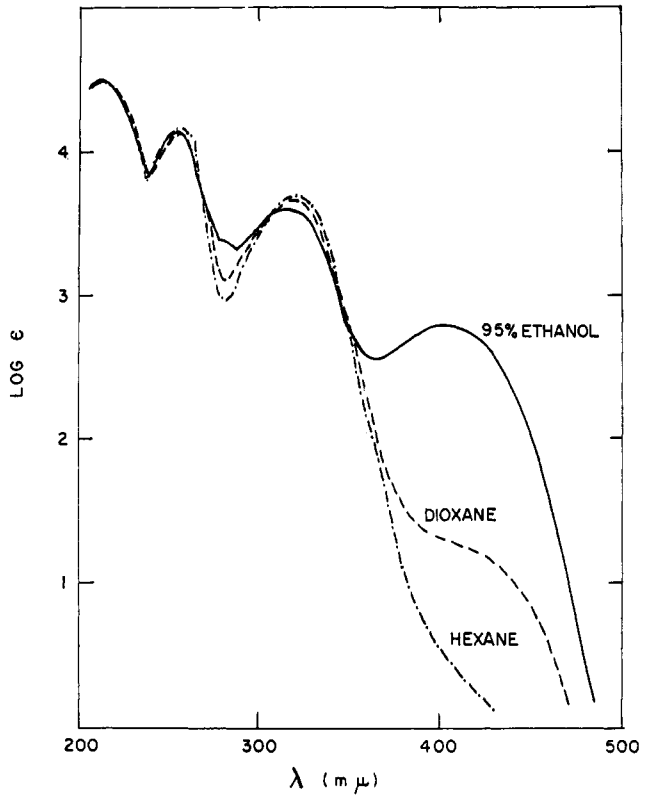


Fig. 1.—Electronic absorption spectra of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) in 95% ethanol, dioxane, and hexane.

tive rotation ([φ]D + 2676°), while that of *o*-nitrobenzaldehyde is negative ([φ]D −991°). Nerdel, Becker, and Kresze[6] have measured the optical rotatory dispersion curves[7] in a limited wave-length region, 656 to 486 mμ, of a number of Schiff bases prepared from (*S*)-(−)-α-phenylethylamine ([φ]D −48°) and various aromatic aldehydes including benzaldehyde and the three isomeric pyridylaldehydes. All of these derivatives in benzene, ethanol, chloroform, and dioxane display plain positive curves[7] in the spectral region studied and, with few exceptions, show molecular rotations at the sodium D-line of over 100°, with some over 300°. As an extension of these studies Terent'ev, Potapov, and co-workers[8] have examined the Schiff bases formed from a considerable number of aromatic aldehydes and a series of optically active aralkylamines, including α-phenylethylamine[8a] and α-benzylethylamine,[8b] and of *sec*-butylamine.[8e] All of these derivatives display much higher rotatory powers than the corresponding amines. Similarly, Taguchi and Ishida[9] have prepared the N-benzylidene, N-*p*-nitrobenzylidene, and N-isobutylidene derivatives of ethyl D-methioninate ([φ]D +16°), with sodium D-line molecular rotations of +332, +213, and +142°, respectively. Bergel and co-workers[10] have also reported high molecular rotations, some over 200°, for the Schiff bases of α- and β-amino acid esters and amides and of (*S*)-(+)-α-benzylethylamine.

Considering the phenomenon of optical activity,[11] one may assume that the presence in these Schiff bases of optically active azomethine chromophores[12] is associated with these high rotatory powers. This suggests that measurements of the optical rotatory dispersion curves for these compounds would be of some interest and perhaps of some utility in the establishment of the absolute configuration of optically active primary amines. In this connection, Klyne[13] has measured the rotatory dispersion curve for ethyl N-cyclopentylidene-L-tyrosinate. This compound, with an isolated azomethine group not expected to show absorption due to this chromophore above 200 mμ,[12a] is strongly levorotatory at 589 mμ and does display a strong negative plain rotatory dispersion curve from 600 to 300 mμ. Of more interest, however, would be similar measurements with Schiff bases derived from aromatic aldehydes, these bases displaying strong electronic absorption bands above 240 mμ,[12b,14-17] and some time ago we initiated[2] an extensive study of the optical rotatory dispersion curves of such compounds.[18]

We now wish to report such measurements using some Schiff bases prepared by the condensation of benzaldehyde and substituted benzaldehydes with (*S*)-(−)- and (*R*)-(+)-α-phenylethylamine,[19] (*S*)-(+)-α-benzylethylamine,[20] and (*S*)-(+)-*sec*-butylamine.[21]

Results

The N-benzylidene and substituted N-benzylidene derivatives prepared for this study and their respective rotatory powers and electronic absorption maxima occurring above 225 mμ are collected in Table I.[22] Eight of the compounds listed (Ia–IIIc) have been prepared previously.[8] Since similar Schiff bases of aralkyl- and alkylamines are reported[23] to be optically stable during distillation at moderate temperatures or during crystallization, it can be assumed on the basis of the rotatory powers of the respective amines used that the Schiff bases reported here are essentially optically pure.

It is to be noted in Table I that the spectra of the several derivatives prepared from a particular aldehyde

(6) F. Nerdel, K. Becker, and G. Kresze, *Ber.*, **89**, 2862 (1956).

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

(8) (a) A. P. Terent'ev and V. M. Potapov, *Zh. Obshch. Khim.*, **28**, 1161 (1958); (b) **28**, 3323 (1958); (c) V. M. Potapov, A. P. Terent'ev, and R. I. Sarybaeva, *ibid.*, **29**, 3139 (1959); (d) V. M. Potapov and A. P. Terent'ev, *ibid.*, **30**, 666 (1960); (e) V. M. Potapov, A. P. Terent'ev, and S. P. Spivak, *ibid.*, **31**, 2415 (1961).

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

(10) (a) F. Bergel and G. E. Lewis, *Chem. Ind.* (London), 774 (1955); (b) F. Bergel, G. E. Lewis, S. F. D. Orr, and J. Butler, *J. Chem. Soc.*, 1431 (1959); (c) F. Bergel and J. Butler, *ibid.*, 4047 (1961).

(11) A. Moscowitz; *cf.* ref. 7, Chapter 12.

(12) (a) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, Ltd., London, 1954, p. 56; (b) P. Brocklehurst, *Tetrahedron*, **18**, 299 (1962).

(13) W. Klyne; *cf.* ref. 10c.

(14) J. Hires and L. Hackl, *Acta Univ. Szeged. Acta Phys. Chem.*, **5**, 19 (1959).

(15) V. M. Potapov, V. M. Dem'yanovich, L. I. Lazutina, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **32**, 1187 (1962).

(16) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **85**, 183 (1963).

(17) D. Bertin and M. Legrand, *Compt. rend.*, **256**, 960 (1963).

(18) During the course of this investigation, Potapov, Dem'yanovich, Lazutina, and Terent'ev[15] have reported the optical rotatory dispersion curves of (*R*)-(−)-N-benzylidene-α-*p*-tolylethylamine in methanol and in benzene, measurements being reported to only 334 mμ. More recently Bertin and Legrand[17] have established the absolute configurations of a number of 20-amino steroids by observation of the circular dichroism of the corresponding N-salicylidene derivatives.

(19) W. Leithe, *Ber.*, **64**, 2827 (1931).

(20) P. Karrer and K. Ehrhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

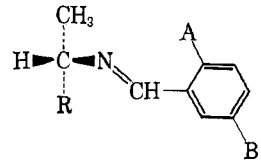
(21) J. A. Mills and W. Klyne, "Progress in Stereochemistry," Vol. 1, Academic Press, Inc., New York, N. Y., 1954, p. 195.

(22) For the sake of clarity, the rotatory powers of all of the Schiff bases in Table I and elsewhere in this section and in the Discussion are given for the (*S*)-isomer, although for some it was the (*R*)-isomer which was prepared and to which the Roman numerals refer in the Experimental.

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

TABLE I

ROTATORY POWERS AND ELECTRONIC ABSORPTION SPECTRA OF SOME OPTICALLY ACTIVE SCHIFF BASES IN ABSOLUTE ETHANOL



Compound	Substituents R	A	B	$[\phi]_D$,[a] degrees	Electronic absorption spectrum, max.[b]			
Ia	C_6H_5	H	H	+159				249 (4.31)
Ib	$C_6H_5CH_2$	H	H	+569				248 (3.84)
IIa	C_6H_5	CH_3O	H	−48		304 (3.80)		251 (4.21)
IIb	$C_6H_5CH_2$	CH_3O	H	+433		305 (3.75)		252 (4.20)
IIc	C_2H_5	CH_3O	H	+113		304 (4.00)		250 (4.40)
IIIa	C_6H_5	OH	H	+424[c]	404 (2.78)[d]	315 (3.61)	283 (3.35)[e]	256 (4.14)
IIIb	$C_6H_5CH_2$	OH	H	+828	402 (3.01)[d]	315 (3.58)	280 (3.44)[e]	253 (4.09)
IIIc	C_2H_5	OH	H	+104	401 (2.93)	312 (3.59)	278 (3.40)[e]	253 (4.09)
IVa	C_6H_5	OH	NO_2	+222	392 (3.99)[d]	348 (4.02)	253 (4.17)	233 (4.11)[e]
IVb	$C_6H_5CH_2$	OH	NO_2	+608	391 (4.01)[d]	354 (4.12)	248 (4.13)	228 (4.08)
IVc	C_2H_5	OH	NO_2	+151	390 (4.08)[d]	348 (4.11)	257 (4.27)	230 (4.07)[e]
Va	C_6H_5	OH	Cl	+239	415 (2.80)[d]	328 (3.55)	280 (3.21)[e]	254 (3.96)
Vb	$C_6H_5CH_2$	OH	Cl	+737	414 (3.01)[d]	327 (3.53)	278 (3.28)[e]	254 (3.98)
VIa	C_6H_5	OH	Br	+164	415 (2.68)	328 (3.60)	282 (3.12)[e]	253 (4.04)
VIb	$C_6H_5CH_2$	OH	Br	+592	413 (3.06)[d]	327 (3.55)	278 (3.36)[e]	254 (4.01)

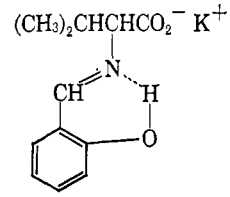
[a] Molecular rotation calculated as $[\alpha]_D \times$ mol. wt./100; c 0.4–1.3; temperature, 20–27°. [b] Wave lengths are given in mμ, numbers in parentheses are log ε. [c] Methanol as solvent. [d] 95% ethanol as solvent. [e] Shoulder.

are essentially identical. The presence of a phenyl group in the amine moiety apparently does not produce a significant effect in the spectrum.

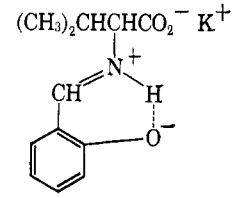
In complete agreement with the spectra reported for N-benzylidenemethylamine[12b] and N-benzylidene-α-*p*-tolylethylamine,[15] for each N-benzylidene derivative (Ia and Ib) in ethanol, only a band near 249 mμ was observed. A long wave-length band comparable with that for benzaldehyde at 280 mμ[24] was not observed.[25] On the other hand, for the derivatives of *o*-methoxybenzaldehyde (IIa–IIc), there appear, in addition to a strong band (log ε 4.5) near 211 mμ, two bands at nearly the same wave lengths as the two absorption bands displayed by *o*-methoxybenzaldehyde.[26] In contrast, the N-salicylidene derivatives (IIIa–IIIc, Fig. 1) and the substituted N-salicylidene derivatives (IVa–VIb) display in ethanol, in addition to bands at shorter wave lengths, multiple bands above 225 mμ, the presence of which has been interpreted in two ways.

Hires and Hackl[14] have found that the band near 410 mμ in the electronic absorption spectra of the N-salicylidene derivatives of benzylamine, *p*-toluidine, and isopropylamine and of N,N′-bis(salicylidene)ethylenediamine in ethanol changes in dioxane to a distinct shoulder and in hexane is absent. Based on this and other spectral data, Hires and Hackl suggest that the band is due to an intermolecular hydrogen bond complex of the salicylidene derivatives and solvents with an unshared pair of electrons.

An alternative explanation has been advanced by Heinert and Martell[16,27] who have observed a similar multiplicity of bands in the electronic absorption spectra of the α-amino acid potassium salt Schiff bases of 3-hydroxypyridine-4-aldehyde, 3-hydroxypyridine-2-aldehyde, and salicylaldehyde in dioxane and in methanol. From a careful study of both the infrared and electronic absorption spectra of these derivatives they have concluded that the multiplicity of bands in dioxane and in methanol is due to an equilibrium between tautomeric forms, for the potassium N-salicylidenevalinate represented as VIIa and VIIb, with an equilibrium constant in dioxane equal to unity and with band assignments as shown with VIIa and VIIb.



318 and 257 mμ
VIIa



411 and 278 mμ
VIIb

The electronic absorption spectra of the three N-salicylidene derivatives (IIIa–IIIc) in dioxane and in hexane reveal essentially the same solvent effects as reported by Hires and Hackl.[14] As seen in Fig. 1, for (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) the band in ethanol at 404 mμ is a broad shoulder in dioxane and is almost absent in hexane. The other band near near 315 mμ in both solvents is essentially identical in wave length but slightly higher in intensity. All three derivatives display almost identical spectra in a given solvent.

With respect to the optical rotatory dispersion measurements, the two N-benzylidene derivatives (Ia and Ib) in ethanol display positive plain curves to about 290 mμ (Fig. 2). Precise measurements of their rotatory powers were not possible at the dilutions necessary to penetrate further into the strong absorption band at 249 mμ.

(24) Ref. 12a, p. 126.

(25) For the classifications and recent discussions concerning the origin of the various bands in the electronic absorption spectra of aromatic compounds, see A. Burawoy, *Tetrahedron*, **2**, 122 (1958); S. F. Mason, *Quart. Rev.* (London), **15**, 287 (1961); and also footnote 8 in ref. 16.

(26) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952).

(27) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **84**, 3257 (1962); **85**, 188 (1963).

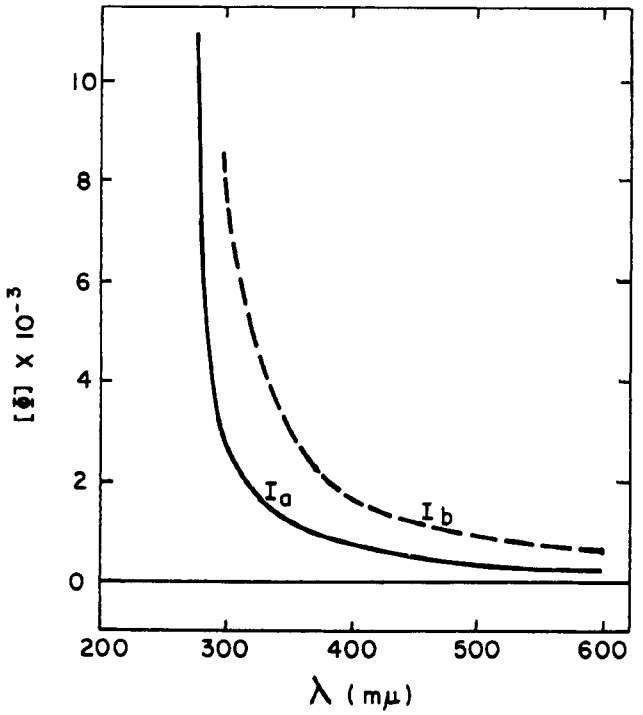


Fig. 2.—Optical rotatory dispersion curves of (*S*)-(+)-N-benzylidene-α-phenylethylamine (Ia) and (S)-(+)-N-benzylidene-α-benzylethylamine (Ib) in absolute ethanol.

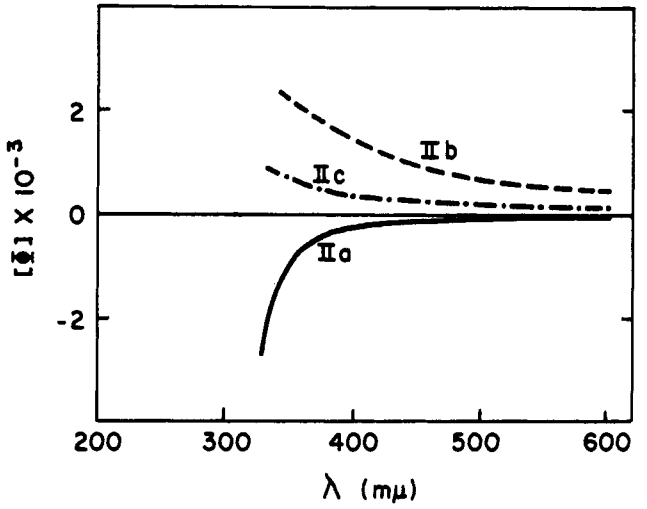


Fig. 3.—Optical rotatory dispersion curves of (*S*)-(−)-N-*o*-methoxybenzylidene-α-phenylethylamine (IIa), (*S*)-(+)-N-*o*-methoxybenzylidene-α-benzylethylamine (IIb), and (*S*)-(+)-*o*-methoxybenzylidene-*sec*-butylamine (IIc) in absolute ethanol.

For the N-*o*-methoxybenzylidene derivatives (IIa–IIc) in ethanol, plain rotatory dispersion curves were observed to about 330 mμ (Fig. 3), beyond which precise measurements were not possible. The curve for (*S*)-(−)-N-*o*-methoxybenzylidene-α-phenylethylamine (IIa) is negative while those for the other two derivatives, both with the same absolute configuration as IIa, are positive.

In contrast to these measurements, (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) and (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb) in ethanol display anomalous optical rotatory dispersion curves (Fig. 4) with two positive Cotton effects centered near 410 and 315 mμ and associated with the absorption bands

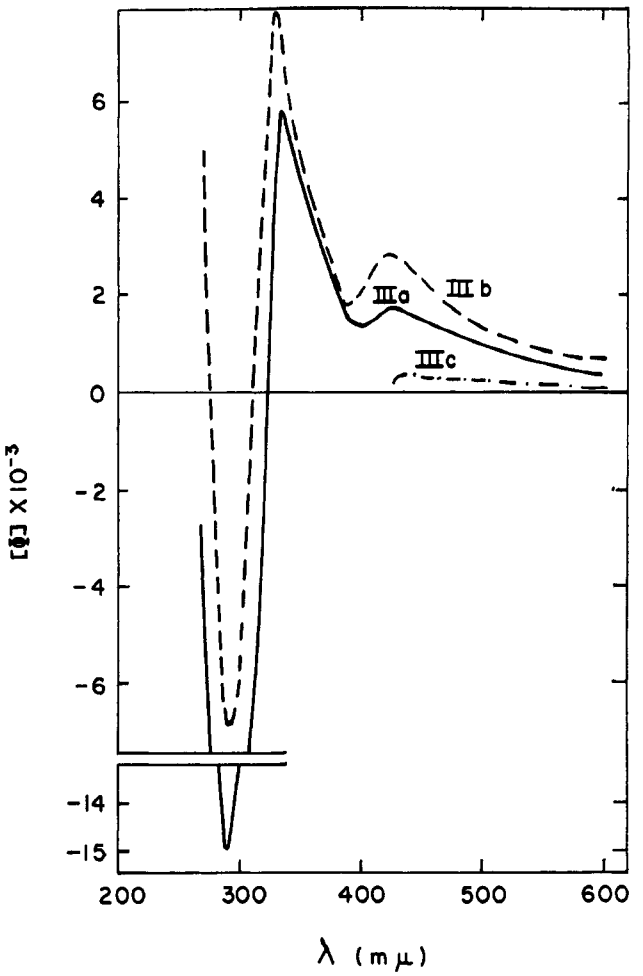


Fig. 4.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), (S)-(+)-N-salicylidene-α-benzylethylamine (IIIb), and (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) in 95% ethanol.

near 403 and 315 mμ. In each curve, the amplitude of the Cotton effect at the longer wave length is much smaller than that at the shorter. In comparison, (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) is much weaker in rotatory power above 437 mμ than the derivatives of the aralkylamines. With IIIc in ethanol only one rather weak extremum at 437 mμ was observed, and measurements of rotatory powers below 425 mμ were not possible.

The intense absorption of the (*S*)-N-5-nitrosalicylidene derivatives (IVa–IVc) in ethanol prevented reliable measurements of rotatory powers beyond about 440 mμ. Over this short spectral region, however, the three derivatives displayed plain positive curves.

The N-5-chlorosalicylidene and N-5-bromosalicylidene derivatives of (*S*)-(−)-α-phenylethylamine (Va and VIa) and of (*S*)-(+)-α-benzylethylamine (Vb and VIb) had essentially the same electronic absorption spectra and optical rotatory dispersion curves in ethanol as the corresponding N-salicylidene derivatives.

Some optical rotatory dispersion curves of the N-salicylidene derivatives were observed in dioxane and in hexane as well as in ethanol. In dioxane, each aralkylamine derivative (IIIa and IIIb) displayed only one Cotton effect (Fig. 5), centered near 315 mμ and associated with the absorption band near 318 mμ. No anomaly in the dispersion curve was observed to be as-

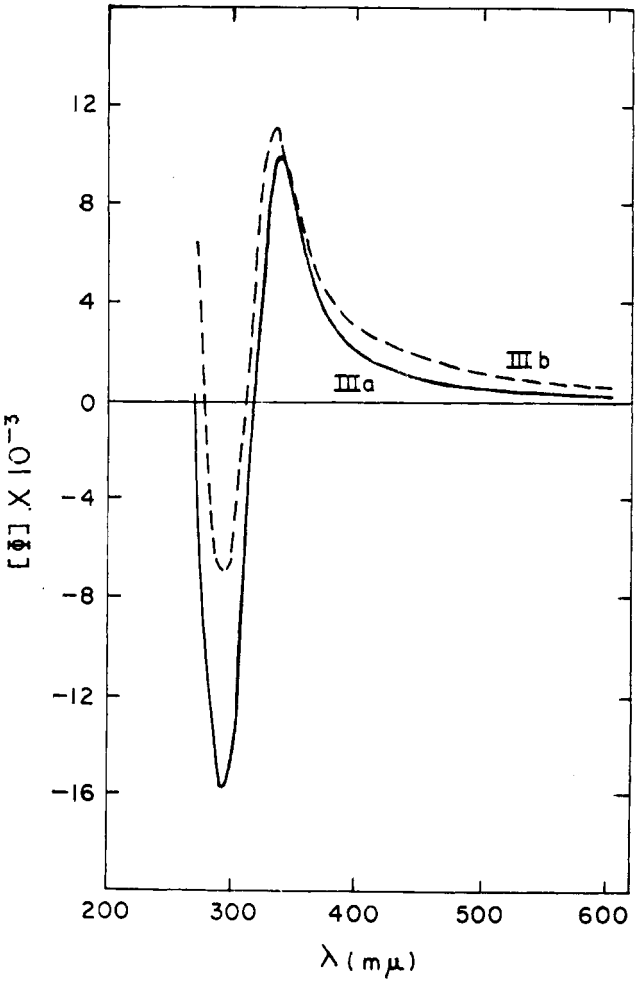


Fig. 5.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa) and (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb) in dioxane.

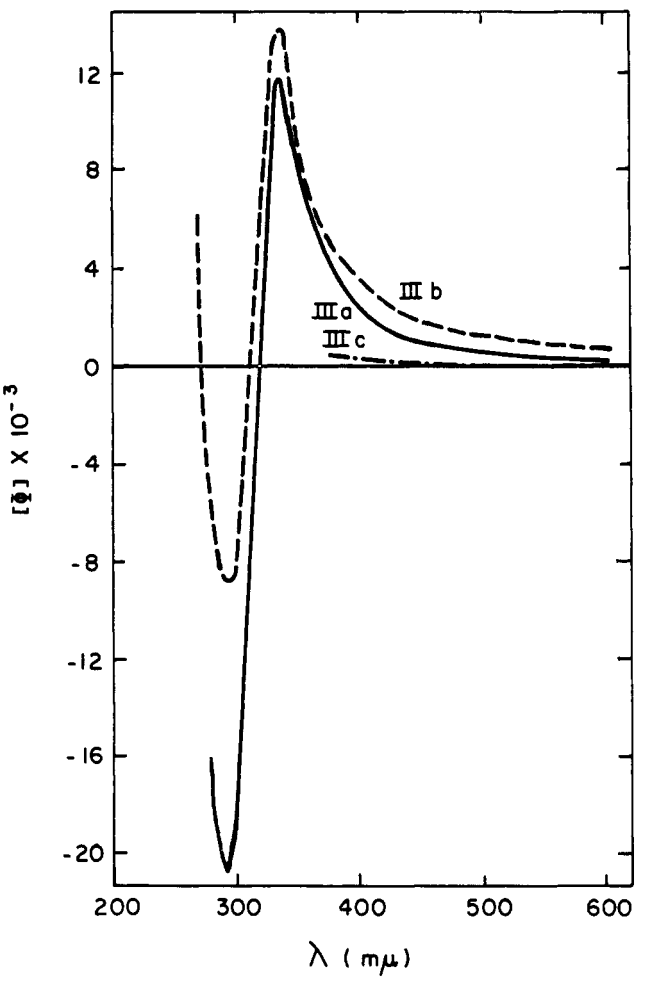


Fig. 6.—Optical rotatory dispersion curves of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), (*S*)-(+)-N-salicylidene-α-benzylethylamine (IIIb), and (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc) in hexane.

sociated with the shoulder in the absorption spectrum centered at 410 mμ, even when the concentration of each derivative during these measurements was increased enough to compensate for the decrease in the molecular extinction coefficient in this spectral region. These observations are in agreement with those recently reported by Bertin and Legrand[17] who have prepared the N-salicylidene derivatives of some 20-amino steroids. The derivatives with the 20α-configuration display in dioxane positive circular dichroism curves with a single positive maximum[28] at 315 mμ. For those with the 20β-configuration the curves are negative with one negative maximum[28] also at 315 mμ.

In hexane, the optical rotatory dispersion curves of the aralkylamine N-salicylidene derivatives (IIIa and IIIb) were found to be anomalous, both displaying one Cotton effect centered at about 315 mμ (Fig. 6), very similar to the effect seen in dioxane. With (*S*)-(+)-N-salicylidene-*sec*-butylamine (IIIc), however, the extremely low rotatory power prevented observation of the dispersion curve below 375 mμ, and above this wave length only a plain positive dispersion curve was observed.

Comparison of the amplitudes of the Cotton effects displayed by the N-salicylidene, N-5-chlorosalicylidene, and N-5-bromosalicylidene derivatives of the aralkylamines reveals that in ethanol the longer wave-length Cotton effects for the α-benzylethylamines are always greater than those for the corresponding α-phenylethylamines; the converse is true for those at the shorter wave lengths. In addition, for the two aralkylamine derivatives for which solvent effects were studied (IIIa and IIIb), the disappearance of the longer wavelength Cotton effects in changing the solvent from ethanol to dioxane, and then to hexane, is accompanied by successive increases in the amplitudes of the Cotton effects centered at about 315 mμ. In both dioxane and hexane, the larger amplitude for the effect is displayed by the α-phenylethylamine derivative.

Discussion

It is evident from the results outlined above that the optical rotatory dispersion curves of the N-salicylidene derivatives are of the most interest. Although the dispersion curves displayed by the N-benzylidene and N-*o*-methoxybenzylidene derivatives indicate that optically active absorption bands associated with the aldehyde moiety may be primarily responsible for the direction and magnitude of their rotatory powers at the sodium D-line, the present experimental difficulties in observing the relevant Cotton effects make these measurements of limited value.

(28) C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.*, 299 (1963).

With the N-salicylidene derivatives, however, some comment should be made concerning the interpretation of the changes which occur in their electronic spectra with changes in solvent. The conclusion drawn by Heinert and Martell[16,27] to explain similar changes in the spectra of α-amino acid potassium salt Schiff bases may also explain the changes observed in the absorption spectra of the N-salicylidene derivatives of α-phenyl- and α-benzylethylamine and *sec*-butylamine in going from ethanol to hexane as solvent (Fig. 1). Thus, for each derivative in ethanol there may exist an equilibrium between tautomers analogous to VIIa and VIIb, and for each aralkylamine derivative in ethanol two Cotton effects are observed in the rotatory dispersion curve. In hexane, the equilibrium is shifted so that only the tautomer analogous to VIIa is present in a significant enough concentration to be observed in the absorption spectrum and in the rotatory dispersion curve. In dioxane, however, the shoulder centered at about 410 mμ was found for the aralkylamines and 20-amino steroid[17] derivatives to be optically inactive. Thus, the presence of this shoulder in the electronic spectrum of each of these derivatives is not adequately explained by assuming that it merely represents a decreased but significant concentration of the tautomer analogous to VIIb.

As far as can be measured, the optical rotatory dispersion curves of the N-salicylidene derivatives, all with the (*S*)-configuration, are, at a particular wave length, of the same sign and all of the observed Cotton effects are positive. As seen in Fig. 4 and 6, however, the striking difference in the rotatory powers of the derivatives of the aralkylamines and that of *sec*-butylamine suggest that with the former the large amplitudes of the Cotton effects near 410 and 315 mμ may be due to rotationally significant interactions of the π-electron systems of the phenyl and benzyl groups and the salicylidene moiety, and not solely to the larger steric requirements of these groups. Thus the sign of the Cotton effects may be primarily dependent on the relative rotatory contributions of all conformers having the phenyl and N-salicylidene groups properly oriented for high optical activity.[29]

In some respects, the interactions may be analogous to that between the π-electrons and the carbonyl group in optically active β,γ-unsaturated and α-phenyl ketones,[30] which sometimes results in Cotton effects near 300 mμ of much greater amplitude than those displayed at the same wave length by optically active saturated ketones. It is to be noted, however, that, while the electric dipole transition moment responsible for the marked increase in the rotational strength of an unsaturated ketone also gives rise to an intensity enhancement of the associated absorption band near 300 mμ,[30] no such enhancements are observed in the electronic absorption spectra of the N-salicylidene aralkylamine derivatives.

For the other N-benzylidene and substituted N-benzylidene derivatives of the aralkylamines, similar rotationally significant interactions of the π-electron systems of the phenyl groups and the aldehyde moieties may be present, resulting in extremely high rotatory powers at the sodium D-line (Table I).

Further optical rotatory dispersion measurements with the Schiff base derivatives of other optically active amines are now in progress.

Experimental[31]

Preparation of Schiff Bases.—The amine was added to 0.01 to 0.03 mole of aldehyde in 10 ml. of solvent, warmed if necessary to effect solution of the aldehyde. The mixture was warmed on the steam plate for 15 min. and then allowed to stand at room temperature overnight, during which time the derivative separated as a crystalline solid or as an oil.

Solids were collected by filtration and recrystallized from appropriate solvents to constant melting points. The reported yields were calculated on the basis of materials with constant melting points. Samples for microanalysis were dried overnight at moderate temperatures and 0.1 mm.

For the oils, the reaction solvents were removed at reduced pressure and the derivatives were purified by distillation. All of the purified oils were shown by infrared absorption measurements to be free of the starting aldehydes.

Rotatory Dispersion (R.D.) Measurements.—All rotatory dispersion measurements were obtained using a Rudolph automatic recording spectropolarimeter, Model 260/658/850/810-614, equipped with a double monochromator. The voltage applied to the photomultiplier tube (RCA 7200) was monitored and, for all measurements, cut-off was indicated when this voltage reached 900 v. The slit width was 0.40 mm. with a scan speed of 20 mμ/min., a symmetrical angle of 7°, and a sample tube length of 10.00 mm. All solvents were purified.

Rotatory dispersion curves are reported by indicating for each concentration used the molecular rotation, [φ], at 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.

In one series of measurements, the optical rotatory dispersion curve of racemic N-5-bromosalicylidene-α-phenylethylamine was observed from 600 to 250 mμ at the same concentrations as used for the optically active form. Over this entire region the observed rotation of this compound was not greater than ±0.005°.

(*R*)-(+)-α-Phenylethylamine.—Racemic α-phenylethylamine was resolved as previously described[32] using N-acetyl-L-leucine. The optically active free base had b.p. 86° (22 mm.), $n^{25}D$ 1.5241, d^{20}_4 0.948, and $[\alpha]^{23}D$ +39.9° (neat); lit.[33] d^{15}_4 0.956, $[\alpha]^{15}D$ +40.7° (neat). Except for the preparation of (*S*)-(+)-N-salicylidene-α-phenylethylamine (IIIa), this sample of amine was used in the preparation of all optically active α-phenylethylamine Schiff base derivatives.

(S)-(+)-α-Benzylethylamine.—The amine was prepared by decomposition of the commercially available optically active hydrochloride salt. The free base had b.p. 96° (22 mm.), $n^{25}D$ 1.5159, d^{20}_4 0.930 and $[\alpha]^{25}D$ +34.1° (neat); lit.[34] d^{15}_4 0.940,

(29) In this connection it is interesting to note that application of th atomic and conformational asymmetry rules to the prediction of the rotatory powers of α-phenylalkylamines and alcohols [J. H. Brewster, *Tetrahedron Letters*, **No. 20**, 23 (1959)] requires that the amino and hydroxyl groups, usually with rotational ranks lower than that of the carbon sequence [J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959)], be assigned ranks higher than this sequence when they are α to a phenyl ring, suggesting the occurrence of rotationally significant interactions of these two substituents with phenyl groups.

(30) K. Mislow, M. A. W. Glass, A. Moscowitz, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 2771 (1961); A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *ibid.*, **84**, 1945 (1962); K. Mislow and J. G. Berger, *ibid.*, **84**, 1956 (1962); K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 457 (1962); S. F. Mason, *J. Chem. Soc.*, 3285 (1962); *Mol. Phys.*, **5**, 343 (1962).

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

(32) H. D. DeWitt and A. W. Ingersoll, *J. Am. Chem. Soc.*, **73**, 5782 (1951).

(33) W. Leithe, *Monatsh.*, **51**, 381 (1929).

(34) W. Leithe, *Ber.*, **65**, 660 (1932).

$[\alpha]^{15}D$ +35.6° (neat). This sample of amine was used in the preparation of all α-benzylethylamine Schiff base derivatives.

(*S*)-(+)-*sec*-**Butylamine.**—Racemic *sec*-butylamine was resolved as previously described[35] using (+)-tartaric acid. The optically active free base had b.p. 62.5–63.5°, $n^{25}D$ 1.3930, d^{20}_4 0.719, and $[\alpha]^{25}D$ +8.1° (neat); lit.[36] b.p. 63°, d^{20}_4 0.731, $[\alpha]^{20}D$ +7.8° (neat). Except for the preparation of (*S*)-(+)-*o*-methoxybenzylidene-*sec*-butylamine (IIc), this sample of amine was used to prepare all *sec*-butylamine Schiff base derivatives. For the preparation of IIc, another sample of (+)-*sec*-butylamine, resolved as above but partially racemic, was used. This latter material had b.p. 62.5–63.5°, $n^{25}D$ 1.3928, d^{20}_4 0.718, and $[\alpha]^{25}D$ +6.3° (neat).

(*R*)-(−)-**N-Benzylidene-α-phenylethylamine** (**Ia**).—Addition of (*R*)-(+)-α-phenylethylamine to a 10% excess of benzaldehyde in methanol gave Ia (88% yield), a light yellow oil, b.p. 119–120° (0.8 mm.), $n^{25}D$ 1.5857, $[\alpha]^{22}D$ −76°, $[\phi]^{22}D$ −159° (*c* 1.3, absolute ethanol); lit.[8a] $n^{20}D$ 1.5888, $[\phi]^{18}D$ −160° (*c* 5.0, methanol); R.D. (Fig. 2) in absolute ethanol, 26°: (*c* 1.1) $[\phi]_{600}$ −160°, $[\phi]_{589}$ −160°, $[\phi]_{338}$ −1350°; (*c* 0.011) $[\phi]_{338}$ −1300°, $[\phi]_{280}$ −11,000°.

(*S*)-(+)-**N-Benzylidene-α-benzylethylamine** (**Ib**).—Addition of (*S*)-(+)-α-benzylethylamine to a 9% excess of benzaldehyde in benzene gave Ib (86% yield), a light yellow oil, b.p. 118–120° (0.8 mm.), $n^{25}D$ 1.5715, $[\alpha]^{20}D$ +255°, $[\phi]^{20}D$ +569° (*c* 1.2, absolute ethanol); lit.[8b] for the (*R*)-isomer, $n^{20}D$ 1.5736, $[\phi]^{19}D$ −544° (*c* 4.0, methanol); R.D. (Fig. 2) in absolute ethanol, 26°: (*c* 1.2) $[\phi]_{600}$ +570°, $[\phi]_{589}$ +580°, $[\phi]_{460}$ +1120°; (*c* 0.12) $[\phi]_{460}$ +890°, $[\phi]_{320}$ +5220°; (*c* 0.012) $[\phi]_{320}$ +4900°, $[\phi]_{300}$ +8500°.

(*R*)-(+)-**N-*o*-Methoxybenzylidene-α-phenylethylamine** (**IIa**).—Addition of (*R*)-(+)-α-phenylethylamine to a 3% excess of *o*-methoxybenzaldehyde in benzene gave IIa (61% yield), a light yellow oil, b.p. 140–141° (0.5 mm.), $n^{25}D$ 1.5890, $[\alpha]^{26}D$ +20° $[\phi]^{26}D$ +48° (*c* 1.0, absolute ethanol); lit.[8a] $n^{20}D$ 1.5894, $[\phi]^{20}D$ +74°[37] (*c* 3.6, methanol); R.D. (Fig. 3) in absolute ethanol, 24–26°: (*c* 1.0) $[\phi]_{600}$ +47°, $[\phi]_{589}$ +47°, $[\phi]_{350}$ +1000°; (*c* 0.23) $[\phi]_{350}$ +1000°, $[\phi]_{340}$ +1300°; (*c* 0.023) $[\phi]_{340}$ +1400°, $[\phi]_{327}$ +2800°.

(*S*)-(+)-**N-*o*-Methoxybenzylidene-α-benzylethylamine** (**IIb**).—Addition of (*S*)-(+)-α-benzylethylamine to a 5% excess of *o*-methoxybenzaldehyde in benzene gave IIb (69% yield), a light yellow oil, b.p. 133° (0.3 mm.), $n^{25}D$ 1.5768, $[\alpha]^{24}D$ +171°, $[\phi]^{24}D$ +433° (*c* 1.2, absolute ethanol); lit.[8b] for the (*R*)-isomer $n^{20}D$ 1.5782, $[\phi]^{20}D$ −440° (*c* 2.3, methanol); R.D. (Fig. 3) in absolute ethanol, 26°: (*c* 1.1) $[\phi]_{600}$ +447°, $[\phi]_{589}$ +458°, $[\phi]_{345}$ +2334°; (*c* 0.11) $[\phi]_{345}$ +2000°, $[\phi]_{333}$ +2300°; (*c* 0.011) $[\phi]_{333}$ +2500°, $[\phi]_{315}$ +3600°.

(*S*)-(+)-**N-*o*-Methoxybenzylidene-*sec*-butylamine** (**IIc**).—Addition of a 25% excess of (*S*)-(+)-*sec*-butylamine[38] to *o*-methoxybenzaldehyde in methanol gave IIc (97% yield), a light yellow oil, b.p. 75–79° (0.5 mm.), $n^{25}D$ 1.5304, $[\alpha]^{21}D$ +59°, $[\phi]^{25}D$ +113° (*c* 1.3, absolute ethanol); lit.[8e] $n^{20}D$ 1.5350, $[\phi]D$ +98.7° (methanol); R.D. (Fig. 3) in absolute ethanol, 26°: (*c* 5.2) $[\phi]_{600}$ +108°, $[\phi]_{589}$ +112°, $[\phi]_{348}$ +660°; (*c* 0.52) $[\phi]_{348}$ +700°, $[\theta]_{334}$ +840°; (*c* 0.10) $[\phi]_{334}$ +780°, $[\phi]_{332}$ +840°; (*c* 0.010) no observable rotation to cut-off at 320 mμ.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.34, 75.50; H, 9.07, 9.19.

(*S*)-(+)-**N-Salicylidene-α-phenylethylamine** (**IIIa**).—A sample of IIIa provided by Dr. A. W. Ingersoll, Vanderbilt University, was after recrystallization yellow, flattened prismatic masses, m.p. 75–76° (methanol), $[\alpha]^{25}D$ +188°, $[\phi]^{25}D$ +424° (*c* 1.2, methanol); lit.[8a] m.p. 76°, $[\phi]^{20}D$ +433° (*c* 2.1, methanol); electronic spectrum (Fig. 1) in dioxane: log $\epsilon^{\text{shoulder}}_{410\ m\mu}$ 1.27, log $\epsilon^{\text{max}}_{318\ m\mu}$ 3.68, log $\epsilon^{\text{max}}_{257\ m\mu}$ 4.16; electronic spectrum (Fig. 1) in hexane: log $\epsilon^{\text{max}}_{320\ m\mu}$ 3.70, log $\epsilon^{\text{shoulder}}_{262\ m\mu}$ 4.13, log $\epsilon^{\text{max}}_{255\ m\mu}$ 4.18; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.10) $[\phi]_{600}$ +380°, $[\phi]_{589}$ +380°, $[\phi]_{428}$ +1800°, $[\phi]_{397}$ +1400°, $[\phi]_{350}$ +2600°; (*c* 0.010) $[\phi]_{350}$ +2700°, $[\phi]_{337}$ +5900°, $[\phi]_{291}$ −15,000°, $[\phi]_{270}$ −2700°; R.D. (Fig. 5) in dioxane, 22–23°: (*c* 1.65) $[\phi]_{600}$ +356°, $[\phi]_{589}$ +368°, $[\phi]_{385}$ +2550°; (*c* 0.010) $[\phi]_{385}$ +2700°, $[\phi]_{336}$ +10,000°, $[\phi]_{294}$ −16,000°, $[\phi]_{270}$ +200°; R.D. (Fig. 6) in hexane, 22°: (*c* 0.37) $[\phi]_{600}$ +270°, $[\phi]_{589}$ +280°, $[\phi]_{390}$ +2580°; (*c* 0.0073) $[\phi]_{390}$ +2200°, $[\phi]_{336}$ +12,000°, $[\phi]_{290}$ −21,000°, $[\phi]_{280}$ −16,000°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 79.79; H, 6.84.

(*S*)-(+)-**N-Salicylidene-α-benzylethylamine** (**IIIb**).—Addition of (*S*)-(+)-α-benzylethylamine to a 13% excess of salicylaldehyde in methanol gave IIIb (64% yield), flat yellow prisms, m.p. 58–60° (95% ethanol), $[\alpha]^{24}D$ +346°, $[\phi]^{24}D$ +828° (*c* 1.0, absolute ethanol); lit.[8b] m.p. 47–54°, $[\phi]^{20}D$ +1135°. (*c* 2.4, methanol); electronic spectrum in dioxane: log $\epsilon^{\text{shoulder}}_{410\ m\mu}$ 1.35, log $\epsilon^{\text{max}}_{317\ m\mu}$ 3.65, log $\epsilon^{\text{shoulder}}_{261\ m\mu}$ 4.08, log $\epsilon^{\text{max}}_{255\ m\mu}$ 4.13; electronic spectrum in hexane: log $\epsilon^{\text{max}}_{318\ m\mu}$ 3.67, log $\epsilon^{\text{shoulder}}_{262\ m\mu}$ 4.10, log $\epsilon^{\text{max}}_{255\ m\mu}$ 4.15; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.050) $[\phi]_{600}$ +810°, $[\phi]_{589}$ +810°, $[\phi]_{424}$ +2900°, $[\phi]_{387}$ +1900°, $[\phi]_{340}$ +6800°; (*c* 0.010) $[\phi]_{340}$ +6700°, $[\phi]_{333}$ +7900°, $[\phi]_{294}$ −6900°, $[\phi]_{270}$ +5000°; R.D. (Fig. 5) in dioxane, 22°: (*c* 1.00) $[\phi]_{600}$ +728°, $[\phi]_{589}$ +762°, $[\phi]_{375}$ +4470°; (*c* 0.010) $[\phi]_{375}$ +4600°, $[\phi]_{334}$ +11,000°, $[\phi]_{293}$ −7000°, $[\phi]_{270}$ +6500°; R.D. (Fig. 6) in hexane, 22°: (*c* 0.25) $[\phi]_{600}$ +840°, $[\phi]_{589}$ +870°, $[\phi]_{360}$ +6770°; (*c* 0.010) $[\phi]_{360}$ +6700°, $[\phi]_{336}$ +14,000°, $[\phi]_{295}$ −9000°, $[\phi]_{270}$ +6200°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.26; H, 7.10.

(*S*)-(+)-**N-Salicylidene-*sec*-butylamine** (**IIIc**).—Addition of (*S*)-(+)-*sec*-butylamine to an 11% excess of salicylaldehyde in methanol gave IIIc (84% yield), a yellow oil, b.p. 70–71° (0.3 mm.), $n^{25}D$ 1.5395, $[\alpha]^{27}D$ +59°, $[\phi]^{27}D$ +104° (*c* 1.1, absolute ethanol); lit.[8e] $n^{20}D$ 1.5435, $[\phi]D$ +145.2° (methanol); electronic spectrum in dioxane: log $\epsilon^{\text{shoulder}}_{392\ m\mu}$ 1.51, log $\epsilon^{\text{max}}_{316\ m\mu}$ 3.65, og $\epsilon^{\text{shoulder}}_{258\ m\mu}$ 4.06, log $\epsilon^{\text{max}}_{254\ m\mu}$ 4.09; electronic spectrum in hexane: log $\epsilon^{\text{max}}_{317\ m\mu}$ 3.67, log $\epsilon^{\text{shoulder}}_{260\ m\mu}$ 3.99, log $\epsilon^{\text{max}}_{254\ m\mu}$ 4.02; R.D. (Fig. 4) in 95% ethanol, 22°: (*c* 0.31) $[\phi]_{600}$ +130°, $[\phi]_{589}$ +130°, $[\phi]_{437}$ +370°, $[\phi]_{432}$ +320°; (*c* 0.077) $[\phi]_{432}$ +370°, $[\phi]_{425}$ +200°; (*c* 0.012) no observable rotation to cut-off at 265 mμ; R.D. (Fig. 6) in hexane, 22°: (*c* 2.0) $[\phi]_{600}$ +93°, $[\phi]_{589}$ +98°, $[\phi]_{375}$ +474°; (*c* 0.010) no observable rotation to cut-off at 325 mμ.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.86; H, 8.67.

(*R*)-(−)-**N-5-Nitrosalicylidene-α-phenylethylamine** (**IVa**).—Addition of (*R*)-(+)-α-phenylethylamine to a 41% excess of 5-nitrosalicylaldehyde in methanol gave IVa (74% yield), yellow needles, m.p. 102–103° (methanol), $[\alpha]^{25}D$ −82°, $[\phi]^{25}D$ −222° (*c* 0.4, absolute ethanol); R.D. in 95% ethanol, 23°: (*c* 0.23) $[\phi]_{600}$ −310°, $[\phi]_{589}$ −320°, $[\phi]_{450}$ −1550°; (*c* 0.058) $[\phi]_{450}$ −1500°, $[\phi]_{445}$ −1700°; (*c* 0.012) no observable rotation to cut-off at 430 mμ.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22. Found: C, 66.62, 66.78; H, 5.34, 5.14.

(*S*)-(+)-**N-5-Nitrosalicylidene-α-benzylethylamine** (**IVb**).—Addition of (*S*)-(+)-α-benzylethylamine to a 21% excess of 5-nitrosalicylaldehyde in methanol gave IVb (83% yield), yellow needles, m.p. 95–97° (heptane), $[\alpha]^{25}D$ +214°, $[\phi]^{25}D$ +608° (*c* 1.2, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.23) $[\phi]_{600}$ +756°, $[\phi]_{589}$ +820°, $[\phi]_{450}$ +2700°; (*c* 0.023) $[\phi]_{450}$ +2500°, $[\phi]_{432}$ +5500°; (*c* 0.0023) no observable rotation to cut-off at 280 mμ.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.56; H, 5.85.

(*S*)-(+)-**N-5-Nitrosalicylidene-*sec*-butylamine** (**IVc**).—Addition of a 3% excess of (*S*)-(+)-*sec*-butylamine to 5-nitrosalicylaldehyde in absolute ethanol gave IVc, collected in three crops of fine yellow prisms. A serial recrystallization of these crops from heptane indicated that the original amine contained a slight amount of the racemic form: head fraction (24%), m.p. 60–62°, $[\alpha]^{21}D$ +54° (*c* 1.0, absolute ethanol); middle fraction (27%), m.p. 60–62°; foot fraction (17%), m.p. 59–60°, $[\alpha]^{22}D$ +64° (*c* 1.0, absolute ethanol). After sublimation at 59° (1.5 mm.), the foot fraction, m.p. 59–60°, $[\alpha]^{22}D$ +68°, $[\phi]^{22}D$ +151° (*c* 1.0, absolute ethanol), was used for spectroscopic and rotatory dispersion measurements; R.D. in 95% ethanol, 26°: (*c* 0.74) $[\phi]_{600}$ +160°, $[\phi]_{589}$ +170°, $[\phi]_{458}$ +513°; (*c* 0.030) $[\phi]_{458}$ +200°, $[\phi]_{442}$ +750°; no measurements were made at greater dilutions.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35. Found: 59.43; H, 5.85.

(*R*)-(−)-**N-5-Chlorosalicylidene-α-phenylethylamine** (**Va**).—Addition of a 9% excess of (*R*)-(+)-α-phenylethylamine to 5-chlorosalicylaldehyde in heptane gave Va (55% yield), fine yellow prisms, m.p. 111–113° (heptane), $[\alpha]^{22}D$ −92°, $[\phi]^{22}D$ −239° (*c* 1.0, absolute ethanol); R.D. in 95% ethanol, 26°: (*c* 0.55) $[\phi]_{600}$ −317°, $[\phi]_{589}$ −331°, $[\phi]_{460}$ −1050°; (*c* 0.11) $[\phi]_{460}$

(35) A. Fleury-Larsonneau, *Bull. soc. chim. France*, **6**, 1576 (1939).

(36) W. Leithe, *Ber.*, **63**, 800 (1930).

(37) In ref. 8a, $[\alpha]^{20}D$ (*c* 3.6, methanol) is reported as +70°.

(38) This amine had $[\alpha]^{25}D$ +6.3° and was partially racemic. The rotatory powers for IIc have been corrected by multiplying all rotational values by the factor 8.1/6.3.

$-970°$, $[\phi]_{445}$ $-1110°$, $[\phi]_{408}$ $-470°$, $[\phi]_{354}$ $-3120°$; (c 0.011) $[\phi]_{354}$ $-3100°$, $[\phi]_{350}$ $-5400°$, $[\phi]_{305}$ $+11{,}000°$, $[\phi]_{270}$ $-3500°$.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43. Found: C, 69.41; H, 5.69.

(*S*)-(+)-**N-5-Chlorosalicylidene-α-benzylethylamine** (**Vb**).—Addition of (*S*)-(+)-α-benzylethylamine to a 1% excess of 5-chlorosalicylaldehyde in methanol gave Vb (63% yield), microscopic light yellow needles, m.p. 75–76° (heptane), $[\alpha]^{22}D$ $+264°$, $[\phi]^{22}D$ $+737°$ (c 1.0, absolute ethanol); R.D. in 95% ethanol, 26°: (c 1.0) $[\phi]_{600}$ $+829°$, $[\phi]_{589}$ $+869°$, $[\phi]_{470}$ $+1960°$; (c 0.051) $[\phi]_{470}$ $+2000°$, $[\phi]_{447}$ $+2300°$, $[\phi]_{403}$ $+850°$, $[\phi]_{360}$ $+4300°$; (c 0.021) $[\phi]_{360}$ $+4000°$, $[\phi]_{350}$ $+5000°$, $[\phi]_{308}$ $-6600°$, $[\phi]_{280}$ $+400°$.

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89. Found: C, 70.27; H, 6.13.

(*R*)-(−)-**N-5-Bromosalicylidene-α-phenylethylamine** (**VIa**).—Addition of (R)-(+)-α-phenylethylamine to a 13% excess of 5-bromosalicylaldehyde in methanol gave VIa (90% yield), yellow needles, m.p. 130–132° (95% ethanol), $[\alpha]^{25}D$ $-54°$, $[\phi]^{25}D$ $-164°$ (c 0.4, absolute ethanol); R.D. in 95% ethanol, 26°: (c 0.60) $[\phi]_{600}$ $-190°$, $[\phi]_{589}$ $-220°$, $[\phi]_{470}$ $-850°$; (c 0.096) $[\phi]_{470}$ $-1100°$, $[\phi]_{448}$ $-1400°$, $[\phi]_{409}$ $-760°$, $[\phi]_{370}$ $-2500°$; (c 0.0096) $[\phi]_{370}$ $-3200°$, $[\phi]_{351}$ $-6300°$, $[\phi]_{298}$ $+9500°$, $[\phi]_{275}$ $+1900°$.

Anal. Calcd. for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.64. Found: C, 59.03; H, 4.93.

(±)-**N-5-Bromosalicylidene-α-phenylethylamine**.—Addition of a 56% excess of (±)-α-phenylethylamine to 5-bromosalicylaldehyde in 95% ethanol gave the Schiff base (91% yield), yellow needles, m.p. 105–106° (95% ethanol).

Anal. Calcd. for $C_{15}H_{14}BrNO$: C, 59.22; H, 4.64. Found: C, 58.97; H, 4.63.

(*S*)-(+)-**N-5-Bromosalicylidene-α-benzylethylamine** (**VIb**).—Addition of (*S*)-(+)-α-benzylethylamine to an 18% excess of 5-bromosalicylaldehyde in methanol gave VIb (86% yield), microscopic light yellow needles, m.p. 87–88° (95% ethanol), $[\alpha]^{25}D$ $+186°$, $[\phi]^{25}D$ $+592°$ (c 0.9, absolute ethanol); R.D. in 95% ethanol, 26°: (c 0.30) $[\phi]_{600}$ $+640°$, $[\phi]_{589}$ $+680°$, $[\phi]_{470}$ $+1900°$; (c 0.061) $[\phi]_{470}$ $+2200°$, $[\phi]_{444}$ $+2900°$, $[\phi]_{403}$ $+900°$, $[\phi]_{360}$ $+4400°$; (c 0.012) $[\phi]_{360}$ $+3700°$, $[\phi]_{349}$ $+5300°$, $[\phi]_{306}$ $-5000°$, $[\phi]_{280}$ $+2600°$.

Anal. Calcd. for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07. Found: C, 60.31; H, 5.24.

Acknowledgment.—This work was supported by grants from the National Science Foundation (G-14524) and from the Committee on Natural Sciences of Vanderbilt University. We also wish to thank Dr. A. W. Ingersoll for his help and advice, and the Department of Microbiology, Vanderbilt University, for the use of its Rudolph spectropolarimeter, purchased with a grant from the U. S. Public Health Service (E-3125-03).

Peptide Synthesis. II. Convenient Synthesis of *p*-Nitrobenzyl Esters of Amino Acids and Peptides

D. THEODOROPOULOS[1] AND J. TSANGARIS

Laboratory of Organic Chemistry, Technical University of Athens, Athens, Greece

Received January 3, 1964

p-Nitrobenzyl tosylate undergoes ready nucleophilic attack with displacement of the $(-OSO_2C_6H_4CH_3)^-$ ion when it is treated with the sodium or trialkylammonium salt of carbobenzoxyamino acids and peptides. The yields of *p*-nitrobenzyl esters thus prepared are consistently better than 70%. Included are the *p*-nitrobenzyl esters of carbobenzoxyglycine, carbobenzoxy-L-phenylalanine, and carbobenzoxy-L-threonine, and the dipeptide esters of carbobenzoxyglycyl-L-leucine and carbobenzoxy-L-prolyl-L-phenylalanine. By use of this procedure, N-tritylglycine and N-trityl-L-tryptophan were converted into the corresponding *p*-nitrobenzyl esters. Detritylation of the latter by mild acid solvolysis afforded the respective *p*-nitrobenzyl esters of glycine and L-tryptophan, both isolated as the *p*-toluenesulfonates. Similarly, the tripeptide derivative, N(im)-benzyl-L-histidyl-L-prolyl-L-phenylalanine *p*-nitrobenzyl ester di-*p*-toluenesulfonate, was prepared. Esterification of the C-terminal carboxyl end proceeded, in all cases tested, with no detectable amount of racemization.

During the course of synthetic studies with angiotensin analogs [2] carried out in this laboratory, it was found preferable to cover the C-terminal carboxyl group of amino acids and peptides by the *p*-nitrobenzyl group. In contrast to benzyl esters which are labile to anhydrous hydrogen bromide, the *p*-nitrobenzyl esters exhibit a marked stability to acid cleavage.[3] This permits a selective splitting of the N-carbobenzoxy group of an intermediate peptide, while retaining the C-terminal carboxyl end protected by the *p*-nitrobenzyl group. The latter is readily removed by catalytic hydrogenation.

Reports on the syntheses of *p*-nitrobenzyl esters involve the carbon tetrachloride azeotropic method[3] and the alkylation of N-acylamino acids with *p*-nitrobenzyl bromide or chloride in the presence of a tertiary base.[4]

The azeotropic method affords high yields, but when applied in the case of peptides, with prolonged heating for 2–3 days in acidic medium, it is not free of complications. Furthermore, this method is not suitable in the case of complex peptides having polyfunctional groups protected by various labile groups, like trityl or other acid sensitive groups. On the other hand, the direct alkylation with *p*-nitrobenzyl bromide or chloride would involve undesirable side reactions in the case of N-acylpeptides.

In view of the importance of preparing *p*-nitrobenzyl esters of peptides at any stage during synthetic work on polypeptides, the potentialities of *p*-nitrobenzyl tosylate as the alkylating agent have been investigated.

p-Nitrobenzyl tosylate was prepared some years ago by Tipson,[5] and more recently by Kochi and Hammond,[6] during kinetic studies of the solvolysis rates of tosylates. The method consisted of the tosylation of *p*-nitrobenzyl alcohol in dry pyridine. We did not pursue this method, however, since we have found that reaction of the silver *p*-toluenesulfonate with *p*-nitrobenzyl bromide affords the desired ester in high and reproducible yield. By Tipson's method the partial solvation of the so-formed *p*-nitrobenzyl tosylate by

(1) This investigation was supported in part by the Royal Hellenic Research Foundation, to which we are indebted.

(2) D. Theodoropoulos and J. Gazopoulos, *J. Chem. Soc.*, 3861 (1960); D. Theodoropoulos, *Nature*, **194**, 283 (1962).

(3) J. E. Shields, W. H. McGregor, and F. H. Carpenter, *J. Org. Chem.*, **26**, 1491 (1961).

(4) (a) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **42**, 972 (1959); (b) H. Schwarz and K. Arakawa, *J. Am. Chem. Soc.*, **81**, 5691 (1959).

(5) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(6) J. K. Kochi and G. S. Hammond, *J. Am. Chem. Soc.*, **75**, 3443 (1953).