3-Aryl-2-methylserines. II. Inversions at Carbon 3

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The interconversion of both the *erythro* and *threo* isomers of derivatives of 3-aryl-2-methylserines can be accomplished readily by reaction with thionyl chloride. Prior studies of desmethyl homologs showed this reaction to be generally facile only in *erythro* to *threo* transformation. An oxidation–reduction route applicable primarily for *threo* to *erythro* conversion is described. Key resonances of nmr spectra are given and their diagnostic value in distinguishing the stereoisomers is noted. Some observations have been made concerning the conformation of a representative pair of isomers.

In an accompanying paper,[1] we have described a new synthesis of 3-aryl-2-methylserines. In addition to the potential biological value of these compounds,[2] it was of interest to us to examine some of the chemistry of these relatively unknown structures. Within this paper we wish to elaborate on these studies; in particular, this report describes (a) methods of interconversion of the *erythro* (E) and *threo* (T) isomers of several members of the series, (b) some of the more interesting features of the nmr spectra, and (c) observations on the conformational disposition of a representative isomeric pair.

Tristram, *et al.*,[3] synthesized two optically active isomers of 3-(3-hydroxyphenyl)-2-methylserine, and was able to assign their absolute stereochemistry, based on both physical and chemical studies. The major product, *threo*, was shown to be 2*S*:3*R* (*SR*-**3**), and the minor product, *erythro*, 2*R*:3*R* (*RR*-**3**).[4,5] This synthesis is shown in Scheme I (**1** → **3**).

Preparation of the remaining two isomers required inversion at C-3 of each of those already available. First, inversion of the configuration at C-3 of *SR*-**3** (to provide *SS*-**3**) was achieved by reactions outlined in Scheme I. The *threo*-amido alcohol *SR*-**5** was oxidized to a ketone **6**, then reduced with sodium borohydride (buffered with carbon dioxide in order to avoid retroaldolization). The resulting mixture (*SS*-**5** and *SR*-**5** in 4:1 ratio) was separated by dry column chromatography and the so-obtained *erythro*-amido alcohol (*SS*-**5**) was hydrolyzed to *SS*-**3**. The same amino acid was also obtained from *SR*-**5** by treatment with thionyl chloride, followed by acid hydrolysis (*vide infra*). This oxidation–reduction method would seem to be quite suitable for *threo* to *erythro* interconversions, which have not normally been achieved by reaction with thionyl chloride.[6] As expected, the *erythro* alcohols were the dominant products of reduction of analogous ketones, resulting from hydride attack on the less hindered side.[7] Thus, *erythro* alcohols E-**9a** and E-**15** were the major reduction products of their corresponding ketones.[1]

Of incidental interest, comparison of the ketones **6** derived from *SR*-**5** and *RR*-**5** presented additional proof that the two amino acids (*SR*-**3** and *RR*-**3**) obtained *via* Tristram's[3] oxazolidinone process differed only in the configuration at C-2. The two ketones were antipodes, possessing identical physical properties except rotations which were equal in magnitude, opposite in sign.

The fourth isomeric 3-(3-hydroxyphenyl)-2-methylserine, *RS*-**3**, was obtained *via* reaction of *RR*-**5** with thionyl chloride, followed by acid hydrolysis.

The reaction of thionyl chloride with amido alcohols has been frequently used in the past to accomplish inversions similar to that which we now desired. In the case of (desmethyl)-3-arylserine derivatives, it has become generally accepted that the sequence depicted in Scheme II applied facilely only in the *erythro* → *threo* transformation.[6] Wagner,[8] on the other hand, has reported inversion of the *threo*-N-benzoyl-*p*-nitrophenylserine derivative, but not the *erythro* by the same reaction. This is all the more exceptional since prior workers[9] had described the inversion of ethyl *erythro*-N-acetyl-3-*p*-nitrophenylserinate with thionyl chloride in 40 min at room temperature.

With this anomaly in mind, we have examined the reaction of thionyl chloride with isomeric amido alcohols derived from three different 3-aryl-2-methylserines. In addition to two of the isomers of **5** mentioned above, the phenyl[1] and *p*-nitrophenyl[10] analogs have also been studied.

When thionyl chloride was added to a chloroform solution of E-**9a** in an nmr probe, rapid reaction occurred to give a single product, which after hydrolytic work-up provided almost pure *threo*-amino acid T-**14a**.

With the *threo* isomer, T-**9a**, nmr spectroscopy again showed rapid reaction which gave two products in approximately a 4:1 ratio. While acid hydrolysis gave a mixture (80% E-**14a**, 15% an unknown, and 5% T-**14a**, by chromatographic analysis[11]), direct work-up permitted isolation of the oxazoline hydrochloride, E-**11a**, and a chloro compound, **13a**.

Thus, in the case of *each* isomer, inversion occurred

(1) S. H. Pines, S. Karady, and M. Sletzinger, *J. Org. Chem.*, **33**, 1758 (1968).

(2) The relationship, for example, of 3-(3,4-dihydroxyphenyl)-2-methylserine to nordefrin (*via* decarboxylation) and to α-methyl-DOPA (*via* reduction of the β-OH group) is obvious.

(3) E. W. Tristram, B. F. Powell, D. E. Williams, R. J. Tull, and J. M. Chemerda, presented at the meeting of the New York–New Jersey Section of the American Chemical Society, Jan 1962.

(4) Nomenclature according to the convention of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(5) For clarity in assignment of the *erythro* and *threo* prefixes, see footnote 8, ref 1.

(6) (a) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **74**, 5459 (1952). (b) K. Vogler, *Helv. Chim. Acta*, **33**, 2111 (1950); W. S. Fones, *J. Org. Chem.*, **17**, 1534 (1952); D. O. Holland, P. A. Jenkins, and J. H. C. Nayler, *J. Chem. Soc.*, 273 (1953), among others.

(7) In the desmethyl series, only *erythro* alcohols were obtained by catalytic hydrogenation of similar ketones. See ref 6a.

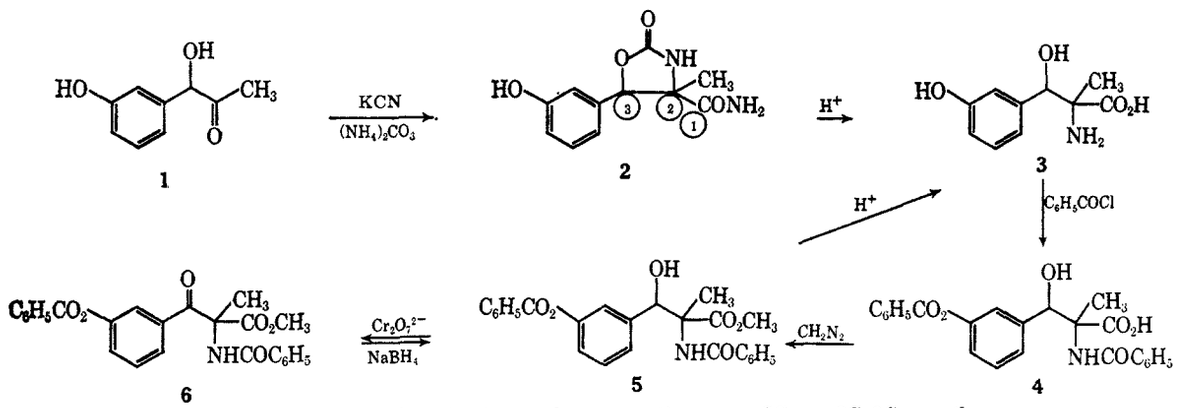
(8) A. F. Wagner, *J. Amer. Chem. Soc.*, **79**, 3240 (1957).

(9) G. W. Moersch, M. C. Rebstock, A. C. Moore, and D. P. Hylander, *ibid.*, **74**, 565 (1952).

(10) Y. Kameda and Y. Kimura, *Kanazawa Daigaku Yakugakubu Kenkyu Nempo*, **9**, 23 (1959); *Chem. Abstr.*, **54**, 3237 (1960).

(11) Spinco amino acid analyzer, Beckman Instruments, Inc., Palo Alto, Calif.

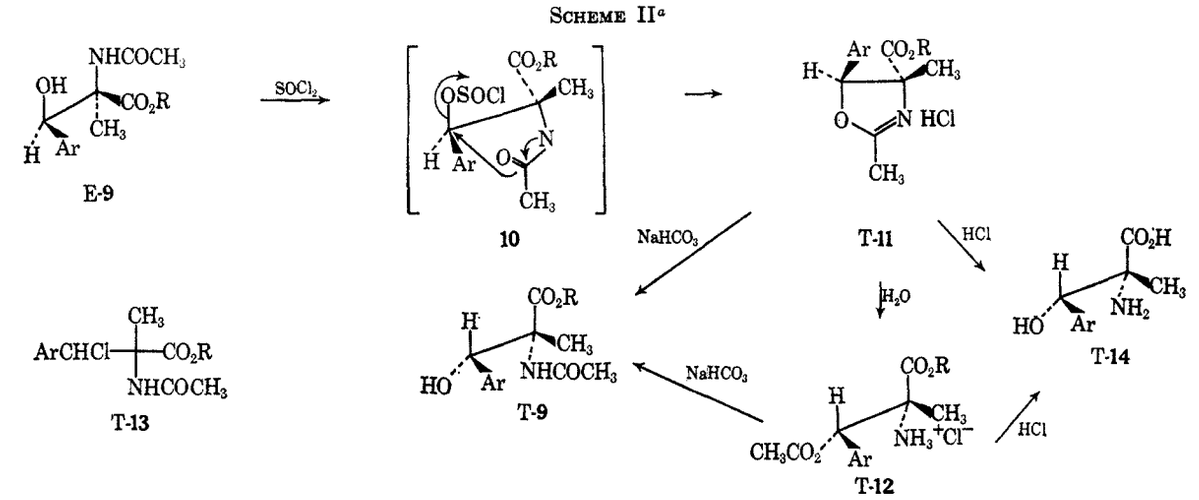
SCHEME I[a]



SR = 2*S*:3*R* *threo* (major product, 1 → 2) *SS* = 2*S*:3*S* *erythro*
RR = 2*R*:3*R* *erythro* (minor product, 1 → 2) *RS* = 2*R*:3*S* *threo*

[a] The numbering here is based on the derived serine.

SCHEME II[a]



a, Ar = C_6H_5; R = C_2H_5
b, Ar = *p*-$NO_2C_6H_4$; R = CH_3

[a] Shown for *erythro* to *threo* inversion.

to provide the predominant, if not total, product of reaction.[12]

When the same reactions were run with the *p*-nitro analogs, E-**9b** and T-**9b**, each gave (more slowly) a single reaction product, convertible by acid hydrolysis into the corresponding inverted amino acid, T-**14b** and E-**14b**, respectively.

All the oxazolines dissolved in water, opening to O-acetate hydrochlorides, **12**. Aqueous bicarbonate converted either **11** or **12** into acetamido alcohols, **9**.[13]

The roughly equal reactivity of both *erythro* and *threo* isomers (in contrast to prior experience with desmethyl analogs[6a,8]) can, perhaps, be explained qualitatively. In the desmethyl series, the cyclization reaction occurs from a much more favorable conformation of the *erythro* isomer than of the *threo*. The introduction of a methyl group at the 2 position decreases this steric distinction. Moreover, it exerts a generally activating effect on both isomers by virtue of increased crowding in the ground states. This crowding is relieved[14] in the cyclic transition (and product) states.

Nuclear magnetic resonance has proved most useful in these studies. By its use we have assigned the stereochemistry of the two 2-methyl-3-*p*-nitrophenylserines previously reported[10] without structural assignment.

In Table I are found the more characteristic chemical shifts of *erythro* and *threo* isomers. Comparisons with the 3-(3-hydroxyphenyl)-2-methylserines whose stereochemistry has already been documented[8] are clear.

The *threo* (aryl and methyl *cis*) heterocyclics show the higher field methyl resonance ($\Delta\tau$ 0.6–0.7), a consequence of shielding by the aromatic ring.[15] Likewise, the carboxyl substituents (–NH_2, –OCH_2CH_3, –OCH_3) of the *erythro* isomers are at higher field.

(12) In the absence of the other isomer, the stereochemistry of **13a** cannot be assigned with certainty. The nmr spectrum of the **13a** isolated suggests that it is an *erythro* compound.

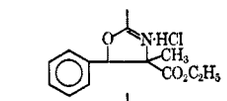
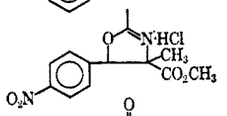
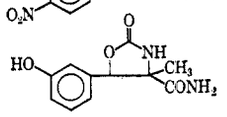
(13) Wagner[8] has reported the contrasting base stability of 4-carboethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline. We hope to discuss this and related studies later.

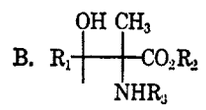
(14) See, for example, the discussion of G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman Ed., John Wiley and Sons, New York, N. Y., 1956, p 460 ff. L. Eberson [*Acta Chem. Scand.*, **13**, 40 (1959)] presents a specific example of the principle in showing the ease of cyclization of certain substituted succinic acids in aqueous media.

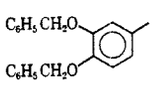
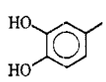
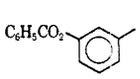
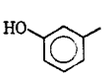
(15) J. B. Hyne, *J. Amer. Chem. Soc.*, **81**, 6058 (1959).

TABLE I
NMR SPECTRAL DATA

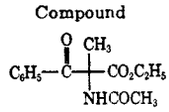
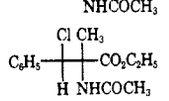
A. Heterocycles

Compound	Designation	Solvent	Resonance[a] —C—CH₃	Resonance[a] O—CH₂—CH₃		$\Delta\tau$[b]
	E-11a T-11a	$CDCl_3$ + $SOCl_2$	8.00 8.70	5.95 5.58	9.17 8.6	0.7
	E-11b T-11b	$CDCl_3$ + $SOCl_2$	7.92 8.65	6.60 6.0		0.73
	E-2 T-2	DMSO-d_6	8.48 9.10	3.0[c] 2.5[c]		0.62

B. 

R_1	R_2	R_3	Designation[d]	Solvent	Resonance[a] 2-Methyl	Resonance[a] O—CH₂	—CH₃	$\Delta\tau$[b]
C_6H_5	C_2H_5	CH_3CO	E-9a[e] T-9a[e]	$CDCl_3$	8.29 8.60	5.72 5.88	8.68 8.84	0.31
C_6H_{11}	C_2H_5	CH_3CO	E-19 T-19	$CDCl_3$	8.40 8.48	5.70 5.75	8.70 8.72	0.08
C_6H_5	H	H	E-14a T-14a	D_2O	8.38 8.72			0.34
p-$NO_2C_6H_5$	CH_3	CH_3CO	E-9b T-9b	$CDCl_3$	8.28 8.58	6.10 6.25		0.30
p-$NO_2C_6H_5$	H	H	E-14b T-14b	DCl + D_2O	8.29 8.50			0.21
	$CH_2C_6H_5$	CH_3CO	E-15 T-15	$CDCl_3$	8.35 8.70			0.35
	H	H	E-16 T-16	D_2O	8.39 8.70			0.31
	CH_3	COC_6H_5	E-5 T-5	$CDCl_3$	8.19 8.43	6.12 6.25		0.24
	H	H	E-3 T-3	D_2O	8.4 8.72			0.32

C. Miscellaneous

Compound	Designation	Solvent	Resonance[a] 2-Methyl	Resonance[a] O—CH₂	—CH₃
	18	$CDCl_3$	8.1	5.78	8.85
	13	$CDCl_3$	8.29	5.85	8.8

[a] τ values, with τ 10 for internal TMS standard. [b] $\Delta\tau$ = difference (*threo* − *erythro*) of 2-methyl resonance. [c] —C(=O)NH_2. [d] The *threo* and *erythro* isomers of **9a**, **14a**, **15**, and **16**, as well as compound **18**, are described in ref 1. [e] Spectra of E- and T-**9a** in tetrachloroethane at temperatures between −40 and 140° showed no significant changes in the chemical shifts.

The acyclic compounds show a smaller 2-methyl shift ($\Delta\tau$ ~0.3) as expected. The ester alkyl signals of *threo* compounds are also (to a lesser extent) shifted upfield. Proof of the aromatic anisotropic effect comes from the nmr spectra of the derived cyclohexyl amido alcohols E-**15** and T-**15**, wherein only minor differences appear in the 2-methyl and O-alkyl resonances.

Much has been written concerning the conformation of compounds similar in structure to those described herein.[16] Hyne[16a] has studied the ephedrines *via* nmr spectroscopy; Drefahl and Zimmermann[16b] have examined differences in the ir spectra with respect to hydrogen bonding of the phenylserines; and Verbit, Mitsui, and Senda[16c] have found from optical rotatory

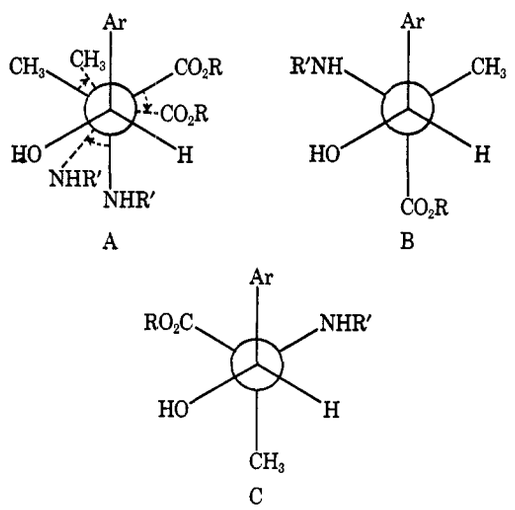
(16) See, for example, (a) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961); (b) G. Drefahl and H. Zimmermann, *Chem. Ber.*, **94**, 2011 (1961); (c) L. Verbit, S. Mitsui, and Y. Senda, *Tetrahedron*, **22**, 753 (1966), and references contained therein.

dispersion studies that the aromatic Cotton effect is conformation dependent.

In spite of the steric crowding of the amido alcohols, rotation about the C_2–C_3 axis is quite possible. Both isomers form oxazolines with thionyl chloride (requiring *trans* OH:NH geometry) and undergo N → O acyl migration (requiring *cis* OH:NH disposition) with hydrogen chloride. Thus, while each exists in a dynamic equilibrium of the various rotamers[16a,c] (Chart I), the observed chemical shifts indicate

CHART I

CONFORMATION of *threo* ISOMERS



that the *threo* isomer has a favored conformation in which the 2-methyl and carboalkoxy groups are shielded by the aromatic ring. Conformer A best satisfies these observations, but an "off-staggered" A (dotted lines)[17] can also be considered.

Finally, we note that, in the series of four different 3-aryl-2-methylserines and derivatives,[18] certain useful characteristic differences in the physical properties of the isomers were found.

threo-Amino acids showed the higher melting points. While they were inseparable from the *erythro* isomers by thin layer chromatography in all systems tried, they were distinguishable by virtue of their shorter retention time in ion exchange chromatography.[11] This latter analytical method was useful in establishing purity and estimating ratios in mixtures.

The derived amido esters were very cleanly separated by thin layer chromatography on silica gel. In all cases, the *threo* isomer was the less mobile.

The ir band at *ca.* 835 cm^{-1} of various *erythro*-3-alkyl- and -arylserines[19] does not seem to be a reliable characteristic of the 2-methyl homologs. While it is present in some of the *erythro*-3-aryl-2-methylserines, it is absent in others.

Experimental Section[20]

4-Carbamoyl-4-methyl-5-(3-hydroxyphenyl)-2-oxazolidinone[3] (2).—A solution of 80 g of L-(−)-acetyl-3-hydroxyphenylcarbinol, 40.7 g of potassium cyanide, and 407 g of ammonium carbonate in 490 ml of water was heated and stirred at 55° for 4 hr. The reaction was extracted three times with 300 ml of *n*-butyl alcohol, evaporated to dryness, and taken up in ethyl acetate. The dried and filtered solution gave 135 g of crude product as a glass.

Chromatographic Separation.—The crude reaction mixture (65 g) was chromatographed on 2 kg of silica gel H (dry column). Ethyl acetate saturated with water was used for elution. The first fractions were crystallized from ethanol–chloroform, yielding 26 g (50% over-all yield) of pure *threo*-oxazolidinone (*SR*-2), colorless sugarlike crystals. An analytical sample was prepared by recrystallization from acetonitrile and melted at 166–167°, $[\alpha]^{EtOH}_D$ −37°.

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.10; N, 11.86. Found: C, 55.80; H, 5.07; N, 11.91.

Later fractions of the chromatography containing the minor oxazolidinone were rechromatographed (same system) yielding, after recrystallization from acetonitrile, 6 g of pure *erythro*-oxazolidinone (*RR*-2) as an acetonitrile solvate. The analytical sample was obtained by further recrystallization from a large volume of acetonitrile, mp 125–127°, $[\alpha]^{EtOH}_D$ +15°.

Anal. Calcd for $C_{11}H_{12}N_2O_4 + C_2H_3N$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.18; H, 5.28; N, 15.20.

Thermogravimetric analysis showed 14.8% weight loss at 110–130° (0.4 mm) corresponding to 1 mol of acetonitrile.

After having obtained the two isomeric oxazolidinones in a crystalline form it was possible to effect this separation by *direct crystallization*. To an ethanolic solution of the crude mixture (65 g), chloroform was added to turbidity, and after seeding some of the major oxazolidinone (*SR*-2) crystallized. After the solvent was removed from the mother liquor, the residue was dissolved in acetonitrile and seeded with *RR*-2. The product deposited was the acetonitrile solvent of the minor oxazolidinone (*RR*-2). By repeating this procedure a total of 30 g (59%) pure *threo*- and 7.1 g (14%) of *erythro*-oxazolidinone was obtained. The homogeneity of the samples could be easily checked by tlc (silica gel plates, ethyl acetate saturated with water).

(2*S*:3*R*)-3-(3-Hydroxyphenyl)-2-methylserine (*threo*) (*SR*-3).—Acid hydrolysis of the *threo*-oxazolidinone (*SR*-2) gave *SR*-3 by the procedure of Tristram, *et al.*[3] After recrystallization from ethanol–water it melted at 222.5–223.5° dec, $[\alpha]_{546}$ 26.4°.[21]

(2*R*:3*R*)-3-(3-Hydroxyphenyl)-2-methylserine (*erythro*) (*RR*-3).—The identical procedure as above starting from the minor oxazolidinone (*RR*-2) yielded the title compound, mp 161.5–162.5° dec, $[\alpha]_{546}$ −344°.[21]

(2*S*:3*R*)-3-(3-Benzoyloxyphenyl)-N-benzoyl-2-methylserine (*SR*-4).—To a stirred, cooled solution of (2*S*:3*R*)-3-(3-hydroxyphenyl)-2-methylserine (*SR*-3, 4.2 g, 0.02 mol) in 100 ml of 0.5 *N* sodium hydroxide and ether (50 ml) was added simultaneously 7 ml of benzoyl chloride (0.06 mol) and 30 ml of 1 *N* sodium hydroxide over a period of 2 hr.

The mixture was allowed to warm to room temperature (30 min) and the layers were separated. The aqueous layer was acidified with dilute hydrochloric acid and the precipitated oil extracted with methylene chloride. After the dried solvent was removed, the residue (10 g) was crystallized from propionitrile to yield 7 g (83%) of product, contaminated with a small amount of benzoic acid. This material was suitable for use in the next step. In some cases the crude reaction product was used for the next step without any purification. An analytical sample was prepared by repeated recrystallization from ethyl acetate, mp 168°, $[\alpha]^{EtOH}_D$ −25°.

Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.76; H, 5.04; N, 3.48.

(2*R*:3*R*)-3-(3-Benzoyloxyphenyl)-N-benzoyl-2-methylserine (*RR*-4).—Amino acid *RR*-3 was benzoylated by the same procedure as above. The analytical sample, prepared by recrystallization from acetonitrile, melted at 60–65°, $[\alpha]^{EtOH}_D$ 38°.

Anal. Found: C, 68.86; H, 4.98; N, 3.78

(2*S*:3*R*)-3-(3-Benzoyloxyphenyl)-N-benzoyl-2-methylserine Methyl Ester (*SR*-5).—To the crude benzoylation product from 4.2 g of *SR*-3 (~10 g of oil) in dioxane (50 ml) was added a slight excess of diazomethane in ether. After the solvent was removed the residue was heated under vacuum to 80° to remove part of the methyl benzoate formed. The residue was crystallized

(17) Postulated as the dominant conformation of ψ-ephedrine by J. B. Hyne.[16a]

(18) Some of the examples are to be found in ref 1.

(19) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **76**, 1322 (1954).

(20) See general comments (footnote 16) in Experimental Section, ref 1.

(21) Obtained in buffered copper sulfate solution, prepared as follows: sodium acetate (20 g), acetic acid (50 ml), copper sulfate pentahydrate (62.5 g), diluted to 1 l. with water. Amino acid concentration was 0.5%. This solvent was used for rotation of all the amino acids reported herein.

from ethyl acetate yielding 7.4 g of methyl ester (*SR*-**5**). An analytical sample was prepared by recrystallization from ether, mp 160–161°, $[\alpha]^{EtOH}D$ −6.0°.

Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.29; H, 5.27; N, 3.03.

(2*R*:3*R*)-**3-(3-Benzoyloxyphenyl)-N-benzoyl-2-methylserine methyl ester** (*RR*-**5**) was prepared by diazomethane treatment of the corresponding acid (*RR*-**4**). Since it refused to crystallize it was characterized by showing that it had an ir spectrum and chromatographic mobility identical with those of its enantiomer (*SS*-**5**).

(2*S*)-**Methyl 2-(3-Benzoyloxybenzoyl)-N-benzoylalaninate** (**6**). —To an ice-cooled, stirred solution of *SR*-**5** (6.5 g, 0.015 mol) in acetone (200 ml) was added dropwise 9 ml of Jones reagent (0.072 equiv). The mixture was stirred at room temperature for 1 hr, when the bulk of the acetone was evaporated *in vacuo* (bath temperature 30–40°). The residue was partitioned between ether and water; the washed (saturated sodium bicarbonate and water) and dried ether layer was evaporated to dryness; and the residue was crystallized from ether, yielding the desired ketone (5.9 g, 90%) as colorless crystals. An analytical sample was obtained by recrystallization from ether: mp 55–60°; $[\alpha]^{EtOH}D$ −24°; λ_{max}^{EtOH} 233 mμ (ε 34,200).

Anal. Calcd for $C_{25}H_{21}NO_6$: C, 69.59; H, 4.91; N, 3.25. Found: C, 69.59; H, 4.70; N, 3.27.

(2*R*)-**Methyl 2-(3-benzoyloxyBenzoyl)-N-benzoylalaninate** (**6**) was obtained by Jones oxidation of *RR*-**5** as detailed above. A pure sample had the following physical constants: mp 55–63°; $[\alpha]^{EtOH}D$ +24°; λ_{max}^{EtOH} 233 mμ (ε 33,000); ir spectrum superimposable with that of the 2*S* isomer.

Anal. Found: C, 69.18; H, 4.82.

Reduction of (2*S*)-Methyl 2-(3-Benzoyloxybenzoyl)-N-benzoylalaninate.—To a stirred solution of keto ester *S*-**6** (1.15 g, 0.0026 mol) in dioxane (20 ml) was added 3 ml of 10% aqueous sodium borohydride solution, while carbon dioxide was bubbled through the mixture. The reaction was quenched with dilute hydrochloric acid and the product extracted with ether. The water-washed and dried extracts were evaporated to an oil. The thin layer chromatogram showed that two products formed. These were separated by dry column chromatography on silica gel H and elution with chloroform–acetone (20:1). The more mobile product was the *erythro* alcohol (*SS*-**5**), 860 mg, obtained as an oil. It exhibited an infrared spectrum and chromatographic mobility identical with those of its mirror image, *RR*-**5**. The less polar product (300 mg) was identical in all respects with *SR*-**5**.

(2*S*:3*S*)-**3-(3-Hydroxyphenyl)-2-methylserine** (*erythro*) (*SS*-**3**). —Amido ester *SS*-**5** (4 g) was allowed to stand in saturated methanolic hydrogen chloride at room temperature for 3 hr and then heated to reflux for the same length of time. After the solvent was evaporated, the residue was heated to reflux with acetic acid (10 ml) and 6 *N* hydrochloric acid (50 ml) overnight. The mixture was evaporated to dryness, and the residue triturated with ether to remove the benzoic acid formed. The insoluble part was decolorized by charcoal treatment in an acetone solution (20 ml) and the free amino acid was precipitated by the action of propylene oxide. This crude product was dissolved in ethanol (10 ml) and water (2 ml) and allowed to crystallize overnight, depositing 950 mg of pure amino acid. From the mother liquor, an additional 300 mg of pure product was obtained bringing the combined yield of the hydrolysis to 61%. This material had mp 158–159°, $[\alpha]_{546}$ 326°,[21] and showed some decomposition when dried at 100° *in vacuo* overnight.

When an analytical sample was prepared by recrystallization from methanol, the solvate of the amino acid was obtained as dense crystals, mp 161–162°, $[\alpha]_{546}$ 306°.[21]

Thermogravimetric analysis showed 11.2% weight loss at 100° (1 mol of methanol corresponds to 12.5%). This amino acid was indistinguishable from its enantiomer *RR*-**3** by Spinco analysis, but had longer retention time than the *threo* isomers. The infrared spectrum of the two *erythro*-amino acids were superimposable.

Anal. Calcd for $C_{10}H_{13}NO_4 + CH_4O$: C, 54.31; H, 7.04; N, 5.74. Found: C, 54.11; H, 6.90; N, 5.91.

(2*R*:3*S*)-**3-(3-Hydroxyphenyl)-2-methylserine** (*threo*) (*RS*-**3**). **Inversion *via* Oxazoline.**—*erythro* ester (*RS*-**5**, 500 mg) was dissolved in 2 ml of ice-cold thionyl chloride. After 10 min the reagent was removed *in vacuo* and the last traces were removed by trituration with dry ether. Without further characterization, this material was hydrolyzed by refluxing overnight in 6 *N* hydrochloric acid (5 ml). After the acid was removed by evaporation *in vacuo* the amino acid was liberated from an acetone solution of its hydrochloride with propylene oxide. Pure amino acid was obtained by recrystallization from ethanol–water, mp 225–226°, $[\alpha]_{546}$ +25°.[21] This amino acid was indistinguishable from the enantiomeric *SR*-**3** by Spinco analysis, but had shorter retention time than the *erythro* isomers.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.89; H, 6.35; N, 6.96.

erythro-**N-Acetyl-3-cyclohexyl-2-methylserine Ethyl Ester E-19.**—A solution of 100 mg of the corresponding aromatic E-**9a**,[1] in 10 ml of ethanol was hydrogenated at 150° and 200 psig for 3 hr in the presence of 10% Ru–C (100 mg). The residue obtained after filtration and evaporation of the solvent was crystallized from hexane to give 65 mg of the desired product. An analytical sample was obtained from ethyl acetate, mp 91–92°.

Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.46; N, 5.07.

threo-**N-Acetyl-3-cyclohexyl-2-methylserine Ethyl Ester (T-19).** —Reduction of T-**9a**[1] in the same manner as above provided the title compound, mp 106–108°.

Anal. Found: C, 62.39; H, 9.37; N, 5.37.

Reactions with Thionyl Chloride. With *erythro*-Amido Ester E-9a.—This reaction was first studied in an nmr tube. When 1 drop of thionyl chloride was added to a solution of E-**9a**[1] in deuteriochloroform, a rapid reaction occurred, as indicated by the shift of the methyl group resonance from τ 8.3 to 8.7. The solvent was evaporated, and the residue hydrolyzed with hydrochloric acid. The crude hydrolysis product contained the *threo*-amino acid T-**14a**, contaminated with less than 1% *erythro* isomer E-**14a**, as measured by nmr and Spinco analysis.

Preparatively, 2 g of E-**9a** was stirred in 8 ml of thionyl chloride in an ice bath. The solvent was removed after 5 min by vacuum evaporation at room temperature. The residue was hydrolyzed in 15 ml of boiling concentrated hydrochloric acid for 5 hr. After the usual work-up, there was obtained 960 mg (65%) of pure *threo*-amino acid T-**14a**, mp 243° dec. If the reaction product was treated with dilute sodium bicarbonate instead of acid hydrolysis, *threo*-amido ester T-**9a** was obtained.

With *threo*-Amido Ester T-9a.—The reaction with thionyl chloride was first tested in an nmr tube as in the previous case. The nmr spectrum showed the presence of two products. Evaporation and hydrolysis as before provided a mixture which, by analysis (Spinco), consisted of 80% *erythro*-amino acid E-**14a**, 5% *threo*-amino acid T-**14a**, and 15% an unknown amino acid.

From a larger run, two reaction products were isolated and identified. To 200 mg of T-**9a** in 2 ml of chloroform was added 0.5 ml of thionyl chloride. After standing at room temperature, the volatiles were removed and the residue triturated with boiling ether. The ether-soluble portion was chromatographed on a short bed of silica gel H (chloroform–acetone, 85:15) to provide, after recrystallization from ether, 45 mg of pure ethyl N-acetyl-3-chloro-2-methyl-3-phenylalaninate (**13a**), mp 120–121°.

Anal. Calcd for $C_{14}H_{18}NO_3Cl$: C, 59.40; H, 6.4; N, 4.94. Found: C, 59.40; H, 6.28; N, 5.02.

The ether-insoluble residue was recrystallized from ethyl acetate–ether to yield 65 mg of pure *erythro*-O-acetyl-2-methyl-3-phenylserine ethyl ester hydrochloride (E-**12a**), mp 149–150°.

Anal. Calcd for $C_{14}H_{20}NO_4Cl$: C, 55.8; H, 6.69; N, 4.65. Found: C, 55.23; H, 6.63.; N, 4.70.

Acid hydrolysis converted the above product into E-**14a**, while O → N acyl migration occurred in dilute bicarbonate to provide E-**9a**.

erythro-**2-Methyl-N-(*p*-nitrobenzylidene)-3-(*p*-nitrophenyl)-serine Methyl Ester.**—Equimolar portions of *p*-nitrobenzaldehyde and alanine methyl ester were stirred in methanol for several days at ambient temperature. There crystallized therefrom a total of 30% of the theoretical yield (two crops) of the title compound, mp 146–148° (lit.[10] mp 148–149°).

erythro-**2-Methyl-3-(*p*-nitrophenyl)serine Methyl Ester Hydrochloride.**—The above product (14 g) was refluxed in 75 ml of 5 *N* ethanolic hydrogen chloride until all was dissolved. The solvent was removed and the solids were stirred with chloroform to remove *p*-nitrobenzaldehyde. The separated product (10.65 g) was recrystallized from ethanol to provide 8.5 g (81%), mp 195–196° (lit.[10] mp 188°).

erythro-**2-Methyl-3-(*p*-nitrophenyl)serine** (**E-14b**).—Hydrolysis of the above ester hydrochloride in a boiling mixture of methanol–6 *N* hydrochloric acid provided, after neutralization of a water solution of the crystalline residue, the *erythro*-amino acid. Re-

crystallization from water gave a pure sample, mp 206–207° (lit.[10] mp 200–201°).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.04; N, 11.66. Found: C, 49.49; H, 5.17; N, 11.66.

erythro-**N-Acetyl-2-methyl-3-(*p*-nitrophenyl)serine Methyl Ester (E-9b).**—The amino ester hydrochloride (8 g) was dissolved in 50 ml of water and neutralized with sodium bicarbonate solution. Ethyl acetate extracts provided 5.8 g of crude residue which was slurried in 60 ml of ether to which an ether solution of 2.5 ml of acetic anhydride was added. After stirring overnight the crystals were filtered and washed with ether. The crude product was recrystallized from 50 ml of methanol to provide 3.25 g (40%) of amido ester, mp 180–185° (lit.[10] mp 179°).

threo-**4-Carbomethoxy-2,4-dimethyl-5-(*p*-nitrophenyl)oxazoline Hydrochloride (T-11b).**—An initial experiment in an nmr tube showed that more than 3 hr was required to approach complete reaction. To a solution of 1.5 g of amido alcohol E-**9b** in 40 ml of chloroform was added 4.5 ml of thionyl chloride. The crystals which deposited on stirring overnight (540 mg) were filtered and washed with chloroform, mp 178–181°.

Anal. Calcd for $C_{13}H_{15}N_2O_5Cl$: C, 49.61; H, 4.80; N, 8.91. Found: C, 50.15; H, 4.80; N, 8.75.

threo-**N-Acetyl-2-methyl-3-(*p*-nitrophenyl)serine Methyl Ester (T-9b).**—The product and mother liquor residue of the above thionyl chloride reaction was stirred with 15 ml of water and 4 ml of saturated sodium bicarbonate solution for 2 hr. The crude product was filtered and washed with water. Chromatography on silica gel H (dry column) using chloroform–acetone (85:15) provided pure T-**9b**, 0.8 g, mp 168–171° (from ethyl acetate–ether).

Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.53; H, 5.58; N, 9.18.

threo-**2-Methyl-3-(*p*-nitrophenyl)serine (T-14b).**—Hydrolysis of 500 mg of T-**9b** in methanol–6 *N* hydrochloric acid (as for the *erythro* isomer E-**14b**) provided after work-up 230 mg of the title amino acid, mp 202–203° (lit.[10] mp 195–196°). Recrystallization from water raised the melting point to 209–210°.

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.04; N, 11.66. Found: C, 49.44; H, 5.07; N, 11.53.

erythro-**4-Carbomethoxy-2,4-dimethyl-5-(*p*-nitrophenyl)oxazoline Hydrochloride (E-11b).**—To 100 mg of T-**9b**, the *threo*-amido alcohol, in 5 ml of chloroform was added 20 drops of thionyl chloride. After stirring overnight, the crystals which had deposited were filtered and washed with chloroform. The dry product, 54 mg, showed mp 194–196°.

Anal. Calcd for $C_{13}H_{15}N_2O_5Cl$: C, 49.61; H, 4.80; N, 8.91. Found: C, 49.40; H, 4.71; N, 9.14.

When a portion of E-**11b** was stirred in water and sodium bicarbonate solution added, E-**9b** was recovered, indistinguishable (ir and tlc) from the sample described above.

Registry No.—*SR*-**2**, 16062-32-1; *RR*-**2**, 16096-48-3; *SR*-**3**, 13020-48-9; *RR*-**3**, 16062-34-3; *SS*-**3**, 16062-35-4; *RS*-**3**, 16062-36-5; *SR*-**4**, 16062-37-6; *RR*-**4**, 16062-38-7; *SR*-**5**, 16062-39-8; E-**5**, 16062-40-1; T-**5**, 16062-41-2; 2*S*-**6**, 16062-42-3; 2*R*-**6**, 16096-49-4; E-**9a**, 16047-64-6; T-**9a**, 16047-66-8; E-**9b**, 16062-44-5; T-**9b**, 16062-45-6; E-**11a**, 16062-46-7; T-**11a**, 16096-51-8; E-**11b**, 16062-47-8; T-**11b**, 16062-53-6; E-**12a**, 16062-48-9; E-**13a**, 16062-49-0; E-**14a**, 16047-68-0; T-**14a**, 16047-69-1; E-**14b**, 16062-52-5; T-**14b**, 16065-52-4; E-**15**, 16047-65-7; T-**15**, 16047-67-9; E-**16**, 16047-71-5; T-**16**, 16047-72-6; **18**, 16065-59-1; E-**19**, 16065-57-9; T-**19**, 16065-58-0.

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Partial Asymmetric Synthesis in the Simmons–Smith Reaction. I[1]

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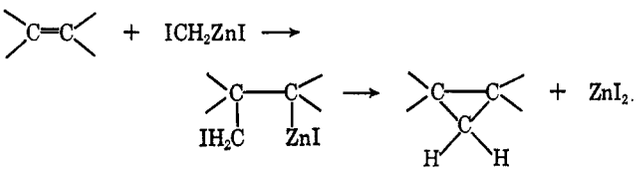
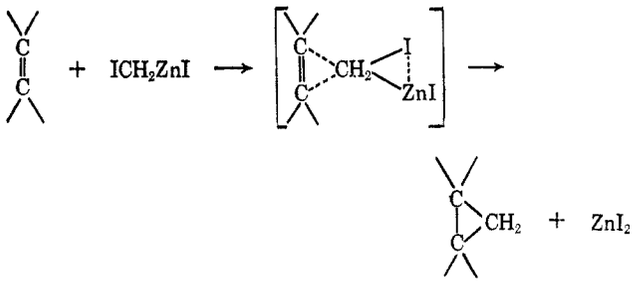
Partial asymmetric synthesis of cyclopropanes was obtained by reaction of the Simmons–Smith reagent with (−)-menthyl esters of α,β- and β,γ-unsaturated carboxylic acids. The steric course was interpreted as proceeding through an intermediate complex in which the Simmons–Smith reagent coordinates with ester carbonyl oxygen and the double bond in a twisted cisoidal conformation. Evidence for an effective coordination of the Simmons–Smith reagent with ester carbonyl oxygen was provided by the Simmons–Smith reaction with 2-cyclohexenyl acetate, leading exclusively to *cis*-2-bicyclo[4.1.0]heptanol.

A novel general stereospecific synthesis of cyclopropanes which involved the treatment of olefins with an active intermediate, iodomethylzinc iodide, prepared from methylene iodide and zinc–copper couple has been developed by Simmons and Smith[2a] and has been proved very useful in preparative applications.[2b-d]

As to the mechanism of the Simmons–Smith reaction, Hoberg[2c] postulated the cyclopropane formation as proceeding *via* addition of the active intermediate iodomethylzinc iodide to olefin and subsequent elimination of zinc iodide.



As an alternative, a three-center reaction involving a one-step displacement of zinc iodide from iodomethyl-



(1) (a) This work was supported by Grant 1240-A4 from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund. (b) A short communication of this subject has appeared in *Bull. Inst. Chem. Res. Kyoto Univ.*, **44**, 203 (1966).

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