Substituent Effects in the Reaction of *N*-Benzoyl-β-arylserinates with Thionyl Chloride

SEEMON H. PINES* AND MATTHEW A. KOZLOWSKI

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

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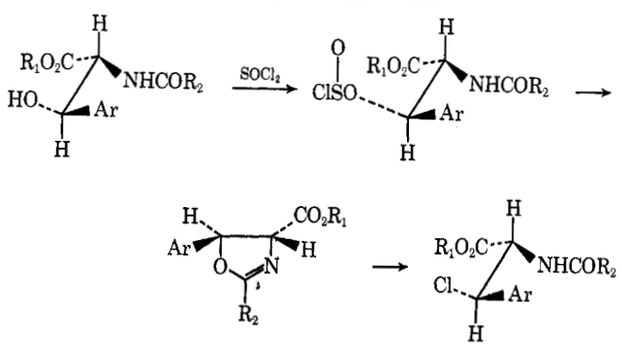
The reaction of several pairs of *N*-benzoyl-β-arylserine methyl esters with thionyl chloride has been studied by nmr and product isolation. The erythro isomers rapidly form trans oxazolines which react further to give *erythro*-β-chloro-β-arylalaninates. The reactions of the threo isomers depend upon the electrical effects of the aryl substituents. Thus, internal displacement of chlorosulfite is observed in the case of strongly deactivating groups (*m*-nitro and *p*-cyano) giving cis oxazolines which *do not* react further. SNi reaction occurs in the case of the *threo*-*p*-chlorophenyl analog yielding a *threo*-β-chloro-β-arylalaninate *without* intervention of an oxazoline. *threo*-*m*-Chlorophenylserinate undergoes both the above reactions as well as SN2 displacement. Both *erythro*- and *threo*-*p*-methoxyphenylserinates give evidence of an additional SN1 mechanism.

Previously, we reported on the reaction of some arylserine derivatives with thionyl chloride.[1] The *erythro*-*N*-acyl-phenylserinate and *p*-nitrophenylserinate esters were shown to undergo rapid ring closure to trans oxazolines, followed by a slower nucleophile initiated conversion to corresponding β-aryl-β-chloroalaninates of the same (erythro) configuration (Scheme I). Each of these steps occurred cleanly with inversion at the benzylic center.

SCHEME I

REACTION OF ERYTHRO ISOMERS



The threo isomers reacted differently, reflecting the steric interactions of two eclipsing bulky groups in the ensuing transition state which would lead to cis oxazolines. *threo*-*N*-Acylphenylserine esters underwent SNi reaction to give *threo*-β-chloro-β-phenylalaninates without intervention of an oxazoline (Scheme II, path a). On the other hand, *threo*-*p*-nitrophenylserinates slowly cyclized to cis oxazolines which did not open to β-chloro-β-(*p*-nitrophenyl)alaninates under the same reaction conditions (Scheme II, path b).

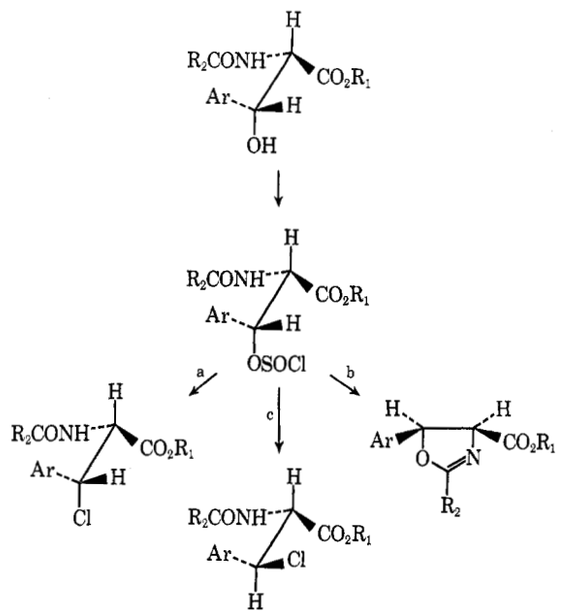
We suggested[1] that the marked difference in reactivity between *threo*-phenyl- and *threo*-*p*-nitrophenylserinates was attributable to the electron withdrawing effect of the ring substituent. In the case of the *p*-nitrophenylserinates, such an effect deters breaking of the benzylic C–O bond and invites participation of the neighboring amide group.[2] Participation of the amide group in the reaction of the erythro isomers is not unexpected, since a sterically favored conformer of the chlorosulfite ester would place the amide anticoplanar to the departing group.

(1) S. H. Pines, M. A. Kozlowski, and S. Karady, *J. Org. Chem.*, **34**, 1621 (1969).

(2) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952).

SCHEME II

REACTION OF THREO ISOMERS



The results summarized briefly above, and their rationalization prompted an extension of this research. Specifically, if the above attribution is correct, then there should exist *threo*-arylserinates which react with thionyl chloride by mechanisms of *both* path a and path b, Scheme II, to give both the cis oxazoline (participation) and the *threo*-β-chloroalaninate (SNi) products. Likely candidates would be those whose substituent(s) lie between H and NO_2 in electronegativity. A further aim was to extend the scope of the reaction beyond the "H" end of the scale with an electron-*donating* substituent, where the incipient benzylic ion would be more stabilized. For this latter goal, the *p*-methoxy substituent seemed ideal.

Starting amido esters were made by known methods. Each was chromotographically and spectroscopically (nmr) free of its diastereomer. We verified the stereochemistry on the basis of reaction with thionyl chloride in all cases except the *p*-methoxy derivative, (a special case, which is discussed separately, below.) Those isomers which rapidly and cleanly formed trans oxazolines (Scheme I) were the erythro isomers. Incidentally, the amino acids from which they derive all showed lower r_f vis-a-vis their diastereomers in the

chromatographic system of Shaw and Fox.[3] Assignment of stereochemistry on the basis of the presence or absence of ir absorption at 11.90–11.95 μ, first suggested by Bolhofer[4] and subsequently supported by Greenstein and Winitz,[5] is not a reliable criterion with some of the serines used in this work.

The stereochemistry of the two *p*-methoxyphenylserinates was provisionally assigned on the basis of tlc behavior[3] of the parent serines. Reaction of the methyl ester of the erythro isomer with benziminoethyl ether hydrochloride,[6] a procedure which does not affect the stereochemistry of the chiral centers, gave *cis*-4-carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline, as shown by its distinctive nmr spectrum. The threo ester gave the trans oxazoline as the major product in similar reaction with the imino ether. These results substantiated the original assignment.

Results

As indicated above, all erythro isomers of the derivatized serines, with the exception of *p*-methoxyphenylserine (*vide infra*), reacted with thionyl chloride according to Scheme I, cleanly and rapidly forming trans oxazolines which opened more slowly to form *erythro*-β-chloroalaninates. This behavior was expected from our previous study.

The threo isomers, on the other hand, showed an even greater variety of reactions than was previously encountered.[7] *threo-m*-Nitrophenyl- and *p*-cyanophenylserinates gave cis oxazolines slowly according to the mechanism of path b, Scheme II.

threo-p-Chlorophenylserinate was converted to the β-chloroalaninate (path a, Scheme II) *via* SNi reaction. As we had hoped,[8] *threo-m*-chlorophenylserinate gave products corresponding to both mechanisms. What was not anticipated, however, was that this substrate also gave a sizable amount of the isomeric *erythro*-β-chloroalaninate! Specifically, the three products, *threo*-β-chloroalaninate, cis oxazoline, and *erythro*-β-chloroalaninate, were formed in the approximate ratio[9] of 50:30:20 when the reaction was carried out in deuteriochloroform. Similar ratios (52:32:16) were measured when the reaction was run neat in thionyl chloride.

Both *erythro*- and *threo*-*N*-benzoyl-β-*p*-methoxyphenylserine methyl esters gave the *same* major reaction product, *threo*-*N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)alanine methyl ester. Other reaction products of these two starting materials were identified and their identity bears on the nature of the reaction mechanism(s) in this exceptional case.

Finally, the accumulated evidence of this and our previous work allows statement of some nmr spectral distinctions between the isomeric oxazolines, β-chloroalaninates, and amido alcohols. The cis oxazolines show the larger coupling constant of the C_4–C_5 protons 10.5–11 Hz *vs.* 7.5–8 for trans, and a markedly higher field signal for the ester methoxyl, δ ~3.2–3.3 *vs.* ~3.9 for trans. The threo linear compounds show the higher J_{HCNH}, 8.5–9 Hz *vs.* 7–7.5 Hz for the erythro isomers. Coupling constants between their vicinal aliphatic protons are too close to be definitive by themselves, but are slightly larger for the erythro member of a given pair.

Discussion

Reaction of erythro isomers with thionyl chloride according to Scheme I may now be accepted as general in view of the results reported here, our earlier report,[1] and some references cited therein. The exceptional case which is observed with the *p*-methoxy analog is discussed separately below. The conversions at each step were clean and essentially complete. The trans oxazolines, all but one of which are oils, were separated from traces of starting material or already formed β-chloro compounds by chromatography to obtain analytical samples, thus sacrificing isolation yield for purity. The latter *erythro*-β-chloroalaninates were obtained in near pure form (tlc, nmr) in quantitative yield. Simple recrystallization was sufficient for analysis.

Participation of the neighboring amide group in displacing the leaving group, –OSOCl, is reasonable in view of the sterically favored anticoplanar conformer of the intermediate chlorosulfite ester. Nucleophilic opening of the thus formed oxazoline in the anhydrous system is an unexceptional second step, and requires little elaboration. Fry, for example, used the nucleophilic opening of oxazoline-4-carboxylate with thiobenzoic acid as the key step in a synthesis of cystine. He also commented on the possibility of competition of Cl^- with the thiobenzoate under his reaction conditions.[10]

The results obtained with the threo isomers support our earlier views concerning the importance of the aryl substituent on the reaction mechanism. The *p*-cyano and *m*-nitro substituents, both strongly electronegative, destabilize the potential benzylic cation in the same way as did the *p*-nitro group,[1] and accordingly, could be expected to promote product formation *via* participation of the neighboring amide group.[2] Finding the cis oxazolines as the essential products in these instances (according to Scheme IIb) is consonant with this view. In the case of the *p*-chloro substituent, the stabilizing resonance effect apparently outweighs the negative inductive effect of Cl, and the product predicted by path a (Scheme II) (SNi reaction) is formed quantitatively.

The *m*-chloro substituent provides the first clear case for multiple reaction pathway. In this case,

(3) K. N. F. Shaw and Sidney W. Fox, *J. Amer. Chem. Soc.*, **75**, 3421 (1953). The relationship r_f (*threo*) > r_f (*erythro*) holds also for the unsubstituted phenylserines and *p*-nitrophenylserines. Our chromatograms were run on cellulose plates rather than paper. See also R. Wichert, *Ark. Kemi*, **25**, 231 (1966).

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

(5) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, New York, N. Y., 1961, p 2599.

(6) By the procedure of M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953); also ref 1.

(7) The discussion is restricted to the truly dominant products of reaction. Close examination of the various nmr spectra of the $SOCl_2$ reactions of threo isomers, including those of our previous work,[1] revealed small methoxy peaks which could be attributed to some of the "mechanistically excluded" products. In the case of the *threo-m*-nitrophenylserinate reaction, for example, the by-product was estimated at 5–8% of the total reaction. Its two major constituents were identified as *erythro*-*N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)-alanine methyl ester (by ir, melting point, and tlc), and *trans*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline (by ir and tlc). The *threo*-β-chloroalaninate was not found. Similar or lesser amounts of by-products were estimated for the phenyl,[1] *p*-nitrophenyl,[1] *p*-chlorophenyl, and *p*-cyanophenyl cases.

(8) See footnote 17, ref 1.

(9) Ratios from nmr integration.

(10) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).

the moderate $-I$ effect is not overly destabilizing, nor are there counteractive resonance contributions. Thus, about 30% conversion to a cis oxazoline is found. The remaining mixture of *threo-* and *erythro*-β-chloroalaninates can be accounted for by the usual SNi reaction for the former, and a heretofore unobserved SN2 displacement of -OSOCl by chloride (path c, Scheme II). An alternative carbonium ion mechanism is rejected on the basis of the findings with the *p*-methoxyphenyl analog (where SN1 reaction is suggested) which differ dramatically from these, especially with regard to formation of appreciable amounts of the trans oxazoline.

Both the erythro and threo isomers of *N*-benzoyl-β-*p*-methoxyphenylserine methyl ester react rapidly at ice temperature with thionyl chloride, giving *threo*-β-chloroalaninate, trans oxazoline, and *erythro*-β-chloroalaninate in that order of importance. Even though the conversion of trans oxazoline to erythro-β-chloroalaninate casts doubt on the meaningfulness of rigid yield figures, nevertheless, a crude estimate of yields from a rapid, cold reaction is instructive. Thus, after 10 min reaction at 0° with the erythro starting material, we find approximately 42, 35, and 15% of *threo*-β-chloroalaninate, trans oxazoline, and *erythro*-β-chloroalaninate, respectively. In the case of the threo starting material, the comparable numbers are ~70, 15, and 5%. In neither case is any intermediate chlorosulfite ester observed in the nmr. A trace of the cis oxazoline can be seen in the mother liquors remaining from isolation of the major product of the threo reaction.

The pattern and rate of product formation clearly distinguishes this pair of serinates from all the others we have studied, and suggests that a common ionic intermediate plays a role. Studies of the *p*-anisyl carbonium ion are all too familiar to require citation, and, in reactions such as these, its implication seems a foregone conclusion.

The ionic pathway to products might be an even more attractive explanation were the yields from both erythro and threo starting materials similar. The raw yield data suggest that reaction occurs not only through the carbonium ion intermediate, but also through some of the pathways cited previously. The strongest arguments for ionization are (a) formation of a *threo*-β-chloroalaninate from an erythro starting material, and (b) formation of a trans oxazoline from a threo starting material. One might argue that the former result could be explained by an SN2 reaction of Cl attacking the intermediate -OSOCl in a very rapid reaction. We suggest that, if this argument is valid, we should have seen some evidence for the same reaction with erythro starting materials. We did not.

Experimental Section[11]

threo-β-*p*-**Chlorophenylserine.**—Prepared from *p*-chlorobenzaldehyde and glycine according to the method of Holland and Nayler,[12] the crystals showed mp 186° dec (lit[12] 179° dec).

Anal. Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 49.47; H, 4.66; N, 6.44.

erythro-β-*p*-**Chlorophenylserine.**—Isolated from acid hydrolysis of the corresponding methyl ester (see below), this isomer appeared somewhat hygroscopic: mp 185° dec, unsharp; dta endotherms at 179 and 196° dec (lit.[12] 178° dec for "hemihydrate").

Anal. Found: C, 49.92; H, 4.55; N, 6.43.

threo-β-*p*-**Methoxyphenylserine.**—To 15 g (0.2 mol) of glycine and 54.5 g (0.4 mol) of anisaldehyde in 50% ethanol (160 ml) was added a solution of 28 g (0.7 mol) of sodium hydroxide in 80 ml of water. The reaction was stirred overnight, then acidified to pH 4 (HCl) and extracted with chloroform. The aqueous layer was taken to dryness, and the residue crystallized from 200 ml of water. The solids, after recrystallization from hot water, gave 1.7 g of almost pure (tlc) *threo*-*p*-methoxyphenylserine. The analytical sample, from water, showed (dta) an endotherm at 203° dec.[13]

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.50; H, 6.25; N, 6.57.

erythro-β-*p*-**Methoxyphenylserine.**—The original mother liquor from the isolation of the threo isomer (above) was allowed to stand several days. There was deposited 1.7 g of almost pure *erythro*-β-*p*-methoxyphenylserine. The analytical sample from water showed (dta) an endotherm at 198° dec.

Anal. Found: C, 56.67; H, 6.25; N, 6.87.

erythro-β-*p*-**Chlorophenylserine Methyl Ester Hydrochloride.**—A solution of 10.4 g (83 mmol) of glycine methyl ester hydrochloride, 23.2 g (166 mmol) of *p*-chlorobenzaldehyde and 11.7 ml (84 mmol) of triethylamine in 40 ml of methanol was stirred 2 days. The crystalline product separated after saturating the solution with anhydrous hydrogen chloride. Recrystallization of the crude (mp 177°) from ethanol, then methanol, gave an analytical sample, mp 188–189° dec.

Anal. Calcd for $C_{10}H_{13}Cl_2NO_3$: C, 45.13; H, 4.92; N, 5.26. Found: C, 45.05; H, 5.05; N, 5.38.

erythro-β-*m*-**Nitrophenylserine Methyl Ester Hydrochloride.**—This compound was prepared from *m*-nitrobenzaldehyde in the same way as reported directly above for the *p*-chlorophenyl analog. The analytical sample showed mp 184–185° dec (MeOH) (lit.[14] mp 190° dec.

Anal. Calcd for $C_{10}H_{13}N_2O_5Cl$: C, 43.4; H, 4.74; N, 10.13. Found: C, 43.36; H, 4.88; N, 10.10.

erythro-β-*p*-**Cyanophenylserine Methyl Ester Hydrochloride.**—A solution of 10 g (76 mmol) of *p*-cyanobenzaldehyde, 4.78 g (38 mmol) of glycine methyl ester hydrochloride, and 3.84 g (38 mmol) of triethylamine in 100 ml of methanol was stirred for 18 hr. The volatiles were removed, and the residue was warmed in dioxane to form a fluid slurry. After cooling, the crystalline triethylamine hydrochloride was removed, and the filtrate acidified with 6.5 ml of 6 *N* hydrochloric acid. The slurry was stirred in an ice bath for 2 hr and the product collected, 2.6 g of almost pure (nmr) *erythro*-β-*p*-cyanophenylserine methyl ester hydrochloride, mp 194–197° dec.

threo-β-*p*-**Cyanophenylserine Methyl Ester Hydrochloride.**—When the mother liquor solids from the previous experiment were stirred in tetrahydrofuran, a crude mixture (5.2 g), mp 153–157° dec, was isolated. This solid contained the title compound, contaminated with, *inter alia*, the erythro isomer, and glycine methyl ester. Nevertheless, it was satisfactory for benzoylation.

(11) (a) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and his associates of these laboratories. Infrared spectra were recorded using a Perkin-Elmer Model 137 spectrometer, and ultraviolet spectra were obtained by means of a Perkin-Elmer Model 202 spectrometer. Varian A-60A, T-60, and HA-100 spectrometers were used for nuclear magnetic resonance measurements.[11b] Thin layer chromatography was performed with commercially available plates. The solvent systems reported in the experimental section allowed separation of the specific compound from its diastereomer. Cellulose plates (Analtech) were used for the serines, and in each case the isomers were shown to be separable *via* the Shaw–Fox[3] solvent system. Where the free serines were not directly isolated, acid hydrolysates of the corresponding esters were examined. The "usual work-up" involves aqueous extractions, drying over sodium sulfate, and evaporation *in vacuo* to dryness. Preparative chromatography was carried out either in columns (silica gel H, E. Merck) or on purchased preparative plates. (b) The generatizations in the "Results" section of this paper taken in conjunction with the nmr data of Table IV, ref 1 (the entry for trans-**10**, however, should read H_A = 362) characterize the structural features of the compounds of this work. Presentation of further tables of nmr data seems unwarranted.

(12) D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, 273 (1953).

(13) K. W. Rosenmund and H. Dornsaft [*Ber.*, **52**, 1734 (1919)] reported mp 185–186°, as did S. Kanao and K. Shinozuka [*J. Pharm. Soc. Jap.*, **67**, 218 (1947); *Chem. Abstr.*, **45**, 9508*h* (1951)]. P. B. Mahajani and J. N. Ray [*Current Sci. (India)*, **22**, 146 (1953); *Chem. Abstr.*, **48**, 6964*g* (1954)] reported mp 155°.

(14) E. D. Bergmann, H. Bendas, and C. Resnick, *J. Chem. Soc.*, 2564 (1953).

TABLE I

N-BENZOYL-β-ARYLSERINE METHYL ESTERS

Phenyl substituent	Isomer[a]	Registry no.	Mp °C[b]	Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
p-Chloro	e	32721-54-3	151.1–154.5[c]	$C_{17}H_{16}ClNO_4$	61.17	4.83	4.20	61.34	4.95	4.23
	t	32721-55-4	142–144[c,d]					60.87	4.80	4.18
m-Chloro	e	32721-56-5	134–136.5[e]					60.95	4.69	4.12
	t	32721-57-6	99.5–101.5[c,d,f]					60.98	4.77	4.27
p-Cyano	e	32721-58-7	161–165[c]	$C_{18}H_{16}N_2O_4$	66.66	4.97	8.64	66.44	4.93	8.74
	t	32721-59-8	101–104[c,d,f]					66.71	5.05	8.73
p-Methoxy	e	32721-60-1	154–155.5[g]	$C_{18}H_{19}NO_5$	65.64	5.82	4.25	65.43	5.78	4.22
	t	32721-61-2	143.5–145[c]					65.44	5.65	4.23
m-Nitro	e	32721-62-3	138.5–140.5[c]	$C_{17}H_{16}N_2O_6$	59.30	4.68	8.14	59.20	4.70	7.99
	t	32721-64-5	117–120[c,f]					59.00	4.52	8.08

[a] e = erythro, t = threo. [b] Superscripts[c–g] denote recrystallization solvent or solvent combinations: *c* = ethyl acetate, *d* = ether, *e* = aqueous ethanol, *f* = hexane, *g* = acetonitrile.

TABLE II

4-CARBOMETHOXY-5-ARYL-2-PHENYL-2-OXAZOLINES

Phenyl substituent	Isomer	Registry no.	Mp °C[a,b]	Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
p-Chloro	Trans			$C_{17}H_{14}ClNO_3$	64.67	4.47	4.44	64.69	4.54	4.39
m-Chloro	Trans							64.64	4.40	4.69
	Cis	32721-64-5	86.5–89[d,f]					64.80	4.51	4.39
p-Cyano	Trans	32721-65-6	104.5–106.5[d]	$C_{18}H_{14}N_2O_3$	70.58	4.61	9.15	70.60	4.39	8.93
	Cis	32721-66-7	132–135[c]					70.38	4.70	9.05
p-Methoxy	Trans			$C_{18}H_{17}NO_4$	69.44	5.50	4.50	69.55	5.77	4.74
	Cis	32721-67-8	93–95[c,d]					69.20	5.57	4.42
m-Nitro	Trans			$C_{17}H_{14}N_2O_5$	62.57	4.32	8.59	62.97	4.45	8.50
	Cis	32721-68-9	103–105[c,f]					62.55	4.38	8.45

[a] Where no melting point is given, the compound was an oil. [b] Superscripts[c–f] denote recrystallization solvent or solvent combinations: *c* = ethyl acetate, *d* = ether, *f* = hexane.

erythro-β-*m*-**Chlorophenylserine Methyl Ester Hydrochloride.**—This compound was made from *m*-chlorobenzaldehyde in the same way described for the *erythro*-*p*-cyano ester. After recrystallization from ethanol, mp 183–185° dec, the product was pure (nmr).

Amido Esters.—The above compounds were all converted to their *N*-benzoyl derivatives by the previously mentioned procedure;[1] *i.e.*, Fischer esterification, where necessary, was followed by treatment of the ester hydrochloride in ethyl acetate with 2.2 equiv of triethylamine and 1.2 equiv of benzoyl chloride. In the case of the crude *threo*-β-*p*-cyanophenylserine methyl ester hydrochloride, some of the less soluble *erythro* amido ester was removed by crystallization (ether–ethyl acetate) before the threo isomer was obtained. The compounds are listed in Table I.

The two remaining amido esters were obtained *via* hydrolysis of the corresponding trans oxazolines. The procedure was the same in both cases, and is described only for the *threo*-*m*-nitro analog. The second one (*threo*-*m*-chloro) did not form a stable solvate. Characterization data are in Table I, also.

threo-*N*-**Benzoyl**-β-*m*-**nitrophenylserine Methyl Ester.**—A solution of 1.7 g (5.2 mmol) of *trans*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline in 20 ml of dioxane, 1 ml of water, and 2 ml (5 mmol) of 2.5 *N* HCl was stirred for 3 hr at room temperature. Sodium bicarbonate (500 mg) was added with a few milliliters of water and the mixture stirred overnight. After removal of the dioxane *in vacuo*, the residue was work up in the usual way with ethyl acetate. Crystallization from isopropyl alcohol gave 1.5 g of an isopropyl alcohol solvate of the title compound, mp 74–78°. The analytical sample showed two endotherms (dta) at 79 and 113°. Nmr showed a 1:1 mole ratio of the desired compound with isopropyl alcohol.

Anal. Calcd for $C_{17}H_{16}N_2O_6 \cdot C_3H_8O$: C, 59.40; H, 5.98; N, 6.93; volatiles, 14.85%. Found: C, 59.71; H, 5.48; N, 7.14; volatiles (by tga), 14.5%.

When the solvate was stirred overnight in water containing a few drops of *tert*-butyl alcohol (as surfactant), the unsolvated product was obtained.

Reactions with Thionyl Chloride.—All reactions were initially followed in an nmr tube to determine the reaction times most appropriate for isolation of the various products. Product identities for oxazolines could be made on the basis of these initial spectra. Thus, formation of a trans oxazoline was characterized by shift of the ester $-OCH_3$ signal downfield to $\delta \sim 3.9$ and the appearance of two doublets between 5 and 6.5 (J = 7.5–8 Hz) representing the C_4 and C_5 protons; a cis oxazoline showed an upfield shift of the ester $-OCH_3$ signal to 3.2–3.3 (aromatic shielding[1]) and more widely split C_4 and C_5 protons (J = 10.5–11 Hz). The stereochemistry of the β-chloro compounds was assigned after isolation of the pure product, and in conjunction with the mode of formation.[1] Preparative runs were made in chloroform, ~5–10% concentration, with about 5–10-fold excess thionyl chloride unless otherwise stated. Reaction times are listed in each case below. In some cases, the volatiles were removed *in vacuo* to provide the product (method A); in others, the reaction was quenched into ice–water, and the usual work-up (of footnote 11) was followed (method B). Physical constants and elemental analyses of the oxazolines and β-chloroalaninates which were formed are found in Tables II and III.

A. With *erythro*-*N*-**Benzoyl**-β-*p*-**chlorophenylserine Methyl Ester.**—After room temperature reaction for 10 min and work-up by method B, the pure *trans*-4-carbomethoxy-5-*p*-chlorophenyl-2-phenyl-2-oxazoline, an oil, was obtained by chromatography ($CHCl_3$ containing 1.5% ether).

When extended over the weekend, the same reaction gave (method A) crystalline *erythro*-*N*-benzoyl-β-chloro-β-(*p*-chlorophenyl)alanine methyl ester, which had been a very minor impurity of the 10-min reaction.

B. With *threo*-*N*-**Benzoyl**-β-*p*-**chlorophenylserine Methyl Ester.**—After 10 min at room temperature, method A work-up gave *threo*-*N*-benzoyl-β-chloro-β-(*p*-chlorophenyl)alanine methyl ester, mp 163–166°.

C. With *erythro*-*N*-**Benzoyl**-β-*m*-**chlorophenylserine Methyl Ester.**—Reaction for 1.5 min at room temperature and method B work-up gave almost complete reaction (tlc). Chromatography (9:1 benzene–ether) gave pure *trans*-4-carbomethoxy-5-*m*-chlorophenyl-2-phenyl-2-oxazoline, an oil.

Work-up of a 10-min reaction (method A) gave crystalline *erythro*-*N*-benzoyl-β-chloro-β-(*m*-chlorophenyl)alanine methyl ester.

D. With *threo*-*N*-**Benzoyl**-β-*m*-**chlorophenylserine Methyl Ester.**—A solution of 1.8 g of the title compound in 20 ml of chloroform was stirred for 20 hr with a 1 ml of thionyl chloride. The residue after removal of volatiles was chromatographed on 100 g of silica (benzene–ether 8:1). From the earlier fractions

TABLE III

N-BENZOYL-β-CHLORO-β-ARYLALANINE METHYL ESTERS

Phenyl substituent	Isomer[a]	Registry no.	Mp °C[b]	Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
p-Chloro	e	32721-69-0	110–112.5[d]	$C_{17}H_{15}Cl_2NO_3$	57.97	4.29	3.98	57.87	4.17	4.04
	t	32721-70-3	163.5–165.5[c]					58.24	4.45	3.92
m-Chloro	e	32721-71-4	148–151.5[c]					57.76	4.25	3.95
	t	32721-72-5	106–108[c,d]					58.05	4.19	3.99
p-Cyano	e	32721-73-6	119–121[c]	$C_{18}H_{15}ClN_2O_3$	63.07	4.41	8.17	62.81	4.43	8.07
p-Methoxy	t	32721-74-7	155–156[c]	$C_{18}H_{18}ClNO_4$	62.16	5.22	4.03	62.17	5.17	3.97
m-Nitro	e	32721-75-8	155–157[c]	$C_{17}H_{15}ClN_2O_5$	56.28	4.16	7.72	56.45	4.20	7.92

[a] e = erythro, t = threo. [b] Superscripts[c,d] denote recrystallization solvent or solvent combinations: *c* = ethyl acetate, *d* = ether.

was obtained *erythro*-*N*-benzoyl-β-chloro-β-(*m*-chlorophenyl)alanine methyl ester, mp 145–149°, undepressed on admixture with the product from the 10-min thionyl chloride reaction with the corresponding erythro amido ester C above). Nmr, ir, and tlc all support the assignment. Next in increasing polarity was *threo*-*N*-benzoyl-β-chloro-β-(*m*-chlorophenyl)alanine methyl ester.

The next fraction eluted, 500 mg, consisted mainly of methyl-α-benzamido-*m*-chlorocinnamate, an analytical sample of which showed mp 113.5–115.5° (EtOAc-Et_2O); uv max (EtOH) 278 nm (log ε 4.2), 221 (4.35).

Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.47; N, 4.44. Found: C, 64.77; H, 4.37; N, 4.60.

Close examination of the nmr spectrum of the original mixture revealed but a trace of this component. In all likelihood, and in conformity with the integration values determined on the reaction mixture prior to isolation, the cinnamate was generated during the chromatography.

More polar yet was *cis*-4-carbomethoxy-5-*m*-chlorophenyl-2-phenyl-2-oxazoline, which was eluted after the cinnamate.

E. With *erythro*-*N*-Benzoyl-β-*p*-cyanophenylserine Methyl Ester.—Reaction was for 3 min at room temperature. Chromatography ($CHCl_3$–1% acetone) after method B work-up gave the desired *trans*-4-carbomethoxy-5-*p*-cyanophenyl-2-phenyl-2-oxazoline.

The same reaction extended for 2 days gave directly (method A) crystalline *erythro*-*N*-benzoyl-β-chloro-β-(*p*-cyanophenyl)alanine methyl ester, mp 114–117°.

F. With *threo*-*N*-Benzoyl-β-*p*-cyanophenylserine Methyl Ester.—Two-day room temperature reaction, work-up by method B gave almost pure *cis*-4-carbomethoxy-5-*p*-cyanophenyl-2-phenyl-2-oxazoline, mp 125° from ether.

G. With *erythro*-*N*-Benzoyl-β-*p*-methoxyphenylserine Methyl Ester.—To a stirred suspension of 100 mg of the title compound in 1 ml of methylene chloride at 0–5° was added 0.2 ml of thionyl chloride. Solution was achieved in 2–3 min. After a total of 10 min, the reaction was quenched on ice and worked up by method B. Crystallization of the residue from ethyl acetate–ether gave 44.6 mg (42%) of single spot *threo*-*N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)alanine methyl ester, mp 152–153° dec.

The mother liquor solids, 60 mg, were examined by nmr. Two components accounted for essentially the entire spectrum, *trans*-4-carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline (~60%) and *erythro*-*N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)-alanine methyl ester (~30%). A small amount of the *threo*-β-chloro compound also remained.

A similar reaction extended for 1.5 hr at room temperature and worked up by method A gave a 47% yield of *threo*-β-chloro compound, mp 147–149° dec.

The mother liquors resulting from the isolation of the *threo*-β-chloro compound were chromatographed on preparative silica plates using 6:1 benzene–ether, then 2% methanol in benzene. The faster moving compound was *trans*-4-carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline, identical (ir, tlc, nmr) with that formed from the reaction of *threo*-β-*p*-methoxyphenylserine methyl ester and benziminoethyl ether hydrochloride (see below). The slower moving material was not the *erythro*-*N*-benzoyl-β-chloro-β-(*p*-methoxylphenyl)alanine methyl ester, but its dehydrochlorination product, methyl-α-benzamido-*p*-methoxycinnamate (characterization below).

When the reaction was run in an nmr probe ($CDCl_3$, $T \sim 5°$) the first spectrum obtained showed methoxyl signals equivalent to at least three species, two of which were clearly the trans oxazoline and the *threo*-β-chloro compound. The former amounted to approximately 40–45% of the total. It was not possible to quantify the others. After 90 min, the oxazoline had decayed to about 30%, and, after an additional hour (now at room temperature or slightly above), the signals for the oxazoline were considerably diminished. Observation over the following days showed a steadily increasing complexity of the methoxyl region and the growth of a signal attributable to methyl chloride. Ultimately, crystalline 4-*p*-methoxybenzylidene-2-phenyl-2-oxazolin-5-one deposited,[1] and was recovered: mp 156–157° (methanol) (lit.[15] mp 158–159°); uv max (methanol)[16] 252 nm (log ε 4.18) 259 (4.22), 383 (4.59).

H. With *threo*-*N*-Benzoyl-β-*p*-methoxyphenylserine Methyl Ester.—The identical 10-min reaction in the cold as described above (G) for the erythro isomer gave 75 mg (71%) of *threo*-*N*-benzoyl-β-chloro-β-(*p*-methoxyphenyl)alanine methyl ester, mp 152–153° dec from ethyl acetate–ether. The mother liquor residue when examined by nmr showed lines clearly attributable to trans oxazoline (~60%) and the *erythro*-β-chloro compound (~15–20%). Up to 10% of cis-oxazoline was present.

Extended reaction (1.5 hr at room temperature) gave 64% *threo*-β-chloro compound. From the mother liquors there was isolated (by thick plate chromatography) both the trans oxazoline (ir and tlc), and methyl α-benzamido-*p*-methoxycinnamate: mp 149–152° from aqueous methanol (lit.[17] mp 141–142°); uv max (CH_3OH) 311 nm (log ε 4.4), 228 (4.3).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.59; H, 5.59; N, 4.48.

This product, obtained in 14% yield was probably formed by dehydrochlorination of the *erythro*-β-chloroalaninate during the chromatography.

In the nmr probe ($CDCl_3$, $T \sim 3°$) the earliest spectra represented about 70% *threo*-β-chloro compound, with no evidence for the chlorosulfite ester of the starting material. A methoxyl signal attributable to the trans oxazoline ester could be seen, amounting to no more than 10–15% of the total. The signal corresponding to the cis oxazoline ester methyl group was not discernible.

I. With *erythro*-*N*-Benzoyl-β-*m*-nitrophenylserine Methyl Ester.—To 3.35 g of the title compound in 42 ml of chloroform was added 5 ml of thionyl chloride. After 5-min stirring, the reaction was quenched into ice water. After usual work-up, the residue was chromatographed (benzene–ether, 95:5). There was obtained 2.3 g of pure *trans*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline, an oil.

Overnight reaction at room temperature, followed by method A work-up, gave crystalline *erythro*-*N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)alanine methyl ester, mp 148–153°.

J. With *threo*-*N*-Benzoyl-β-*m*-nitrophenylserine Methyl Ester.—A mixture of 200 mg of the title compound in 5 ml of chloroform was stirred at 40° overnight with 1 ml of thionyl chloride. After method A work-up, the crystalline residue was triturated with ether containing ethyl acetate. Filtration gave 174 mg of solids (a) and mother liquors containing 37 mg of residue (b).

The mixture (a) consisted of *cis*-4-carbomethoxy-5-*m*-nitrophenyl-2-phenyl-2-oxazoline and its hydrochloride, as evidenced by its single spot tlc (6:1 C_6H_6–Et_2O, then 2% MeOH in C_6H_6). The ethyl acetate soluble portion gave an analytical sample.

When the hydrochloride-containing portion (+$AgNO_3$ test, ir) was dissolved in methanol and chromatographed on a prepara-

(15) H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

(16) D. A. Bassi, V. Deulofeu, and F. A. F. Ortega [*J. Amer. Chem. Soc.*, **75**, 171 (1953)] reported very similar values from ethanol.

(17) N. K. Kochetkov, E. I. Budovskii, R. M. Khomutov, and M. Ya. Karpeiskii, *J. Gen. Chem. U.S.S.R.*, **29**, 70 (1959).

tive plate (2% MeOH in C_6H_6), there was obtained, in addition to more cis oxazoline, a small amount of *erythro*-*N*-benzoyl-β-*m*-nitrophenylserine methyl ester, mp 135–137°, which arose from oxazoline hydrolysis (and O → N acyl migration) during work-up. This component was not present in the original crystalline precipitate (a).

The residue (b), which consisted of three major components was separated on thick plates (6:1 C_6H_6–Et_2O, then 2% MeOH in C_6H_6). The most polar of the three was cis oxazoline, the major reaction product. Next was the isomeric trans oxazoline (ir, tlc), and least polar was *erythro*-*N*-benzoyl-β-chloro-β-(*m*-nitrophenyl)alanine methyl ester (melting point, ir, tlc).

***cis*-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.**—An intimate mixture of 200 mg of *erythro*-*p*-methoxyphenylserine methyl ester, made by Fisher esterification of the more polar of the two *p*-methoxyphenylserines, and 200 mg of benziminoethyl ether hydrochloride was heated on the steam bath for 30 min.[6] Chromatography (3.5% MeOH in C_6H_6) gave 110 mg of crude product, the nmr of which clearly established the configuration as the cis oxazoline. The product was crystallized from ether–hexane. The same chromatography gave a vivid yellow fraction which was shown to be 4-*p*-methoxybenzylidene-2-phenyl-2-imidazolin-5-one: mp 295° dec from isopropyl alcohol (lit.[18] mp 289–290°); uv max (MeOH) 254 nm (log ε 4.39), 394 (4.54); M^+ 278, $C_{17}H_{14}N_2O_2$, mol wt 278.3.

***trans*-4-Carbomethoxy-5-*p*-methoxyphenyl-2-phenyl-2-oxazoline.**—When 400 mg of the threo isomer of *p*-methoxyphenylserine methyl ester underwent the same reaction as described directly above, there was obtained 124 mg of the title product, a light yellow oil, after chromatography on silica gel plates with 6·1 benzene–ether, then 2% methanol in benzene.

(18) A. R. Kidwai and G. M. Devasia, *J. Org. Chem.*, **27**, 4527 (1962).

Registry No.—Thionyl chloride, 7719-09-7; *threo*-β-*p*-methoxyphenylserine 32721-76-9; *erythro*-β-*p*-methoxyphenylserine, 32721-77-0; *erythro*-β-*p*-chlorophenylserine methyl ester hydrochloride, 32721-78-1; *erythro*-β-*p*-cyanophenylserine methyl ester hydrochloride, 32721-79-2; *threo*-β-*p*-cyanophenylserine methyl ester hydrochloride, 32721-80-5; *erythro*-β-*m*-chlorophenylserine methyl ester hydrochloride, 32721-81-6; methyl α-benzamido-*m*-chlorocinnamate, 32730-62-4; methyl α-benzamido-*p*-methoxycinnamate, 32730-63-5.

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(19) Deceased, May 10, 1971.

Synthetic Indole Alkaloids. I. Synthesis of a Pentacyclic Lactam[1]

FREDERICK V. BRUTCHER, JR.,* WILLIAM D. VANDERWERFF, AND BARRY DREIKORN

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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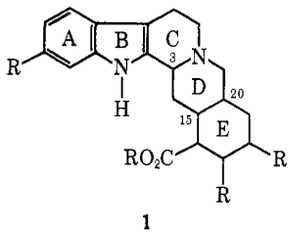
1,2,3,4,6,7,12,12b-Octahydro-2,4-diketoindolo[2,3-*a*]quinolizine (**3**), a tetracyclic keto lactam, has been prepared as an intermediate in the synthesis of pentacyclic indole alkaloids from tryptamine (**2a**) and citric acid. 6-Methoxytryptamine (**2b**) has also been used in place of **2a**. **3** has been reacted with carbethoxy methyl vinyl ketone (**15**) to produce the expected cyclized adduct, 1,2,3,4,5,7,8,13,13b,14-decahydrobenz[*g*]-1-carbethoxy-2,5-diketoindolo[2,3-*a*]quinolizine (**16**). **16** reduces smoothly with Pt and H_2 to produce the tetrahydro adduct **18**. Lithium aluminum hydride reduction of **18** produces a pentacyclic diol **21**. The stereochemistry of **21** is discussed.

Most of the total synthesis work in the reserpine[2] and the yohimbine[3] areas[4] (**1**) has involved preconstruction of the stereochemical relationships of the D/E rings before condensation with tryptamine (**2a**) or 6-methoxytryptamine (**2b**) to form the pentacyclic skeleton.



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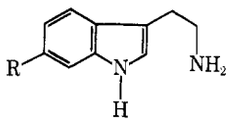


2a, R = H
b, R = OCH_3

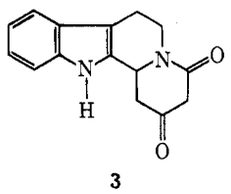
(1) (a) Supported in part by the National Institute of Mental Health. (b) Presented in part before the Division of Organic Chemistry, 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, Abstracts, No. ORGN 15.

(2) R. B. Woodward, F. Bader, H. Bickel, and R. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) E. Van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, *J. Amer. Chem. Soc.*, **80**, 5006 (1958); **91**, 7315 (1969).

(4) (a) J. Poisson, *Ann. Chim. (Paris)*, **9**, 99 (1964); (b) R. H. F. Manske in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1965, p 694; (c) E. Schlittler in "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1965, p 287; (d) I. Ernest and B. Kakac, *Chem. Ind. (London)*, 513 (1965); (e) for a different stepwise approach, see Cs. Szantay, L. Toke, and K. Honti, *Tetrahedron Lett.*, **No. 22**, 1665 (1965).

In this paper a stepwise construction of rings A through E is explored. In outline, it was envisaged that **2a** or **2b** might be combined with a modified β-oxoglutaric acid to yield a keto lactam of type **3** which then could be alkylated with a substituted methyl vinyl ketone and cyclized to yield a pentacyclic precursor of **1**.



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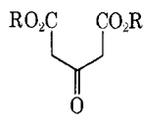

4a, R = H
b, R = C_2H_5

Synthesis Results.—Citric acid, an inexpensive starting material, was readily converted[5] to β-oxoglutaric acid (**4a**) which in turn was esterified[6] to yield **4b** as a preliminary to preparing the desired aldehydo ester **5**. To obtain **5**, **4b** was converted to the ketal ester **6a** which was converted to its disodium salt **6b**, and then cyclized with oxalyl chloride to give the anhydride **7**.[7] **7** was then transformed with ethanol to the acid es-

(5) R. Adams, H. M. Chiles, and C. F. Rassweiler, *Org. Syn.*, **5**, 5 (1925).

(6) R. Adams and H. M. Chiles, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1947, p 237.

(7) R. Adams, *J. Amer. Chem. Soc.*, **42**, 599 (1920).