3β-Acetoxy-5-androstene[17,16-*d*]isoxazole (VIII).—The iodo compound IV (5 g) was dissolved in 100 ml of glacial acetic acid and 5 g of silver acetate was added. The mixture was heated under reflux for 1 hr. After separating the insoluble silver salts by filtration, the product was precipitated with water and extracted with ether. The ether solution was washed with water and sodium bicarbonate solution until neutrality and concentrated to dryness. Crystallization of the solid residue from methanol yielded pure VIII (3.2 g): prisms; mp 189–190° [lit.[7] mp 184–186°]; $[\alpha]_D$ −47.7°; λ_{max} 230 mμ ($E^{1\%}_{1cm}$ 152); ν_{max} 1015, 1030, 1053, 1086, 1134, 1250, 1310, 1355, 1375, 1418, 1449, 1455, 1470, 1608 and 1725 cm^{-1}; nmr 1.00 (19-H), 1.09 (18-H), 2.02 (OAc) and 2.21 ppm (21-H).

Registry No.—Lead Tetraacetate, 546-67-8; I, 2174-13-2; II, 19471-38-6; III, 19459-14-4; IV, 19459-15-5; V, 19459-16-6; VI, 19459-17-7; VII, 19459-18-8.

Mechanism and Stereochemical Considerations in the Reaction of Some Arylserine Derivatives with Thionyl Chloride

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The reaction of esters of N-acylphenyl- and *p*-nitrophenylserinates with thionyl chloride has been studied by nmr. The *erythro* isomers rapidly cyclize to *trans*-oxazolines which open (more slowly) to *erythro*-β-chloro-β-arylalaninates. *threo*-Phenylserinates give *threo*-β-chloro derivatives without the intervention of oxazolines, while the *threo*-*p*-nitrophenyl analogs slowly form *cis*-oxazolines which do not open under the same conditions. Reasons for the different mechanisms based on both steric and electronic factors are offered. Hydrolytic studies help reconcile present results with some prior reports which, by themselves, seem inconsistent.

Although the reaction of thionyl chloride with vicinal amido alcohols has been known and used both widely and advantageously for more than 45 years,[1] our understanding of it is still far from complete. We wish to describe new studies which clarify and correct some of the considerable ambiguity, uncertainty, and contradiction found in the literature.

A very brief review is in order. Fry,[2] in summarizing the state of knowledge in 1949 pointed out that ". . .in no case has a β-chloro alkylamide been recovered when the reaction mixture is kept cold. . ." Elliott's[3] concurrent work with threonine derivatives supported this view. Not much later, however, Holland, Jenkins, and Nayler[4] synthesized methyl α-acetamido-β-chloro-β-phenylproprionate *via* reaction of the corresponding *threo*-phenylserine derivative with thionyl chloride at 0°.

Bolhofer[5] cited some distincions attributed to stereoisomerism and suggested a generalization: the *erythro*-"β-phenyl-β-hydroxyethylamine" derivatives undergo facile inversion (*via* oxazolines) while the *threo* isomers react with marked difference. Wagner[6] later reported the inversion of ethyl *threo*-N-benzoyl-β-(*p*-nitrophenyl)serinate while the *erythro* isomer was converted into a chloro compound of the same configuration. Some studies of the isomeric 1,2-diaryl-2-acylamido-1-ethanols are also contradictory.[7]

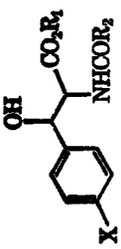
Most recently, experiments with 3-aryl-2-methylserines[8] showed that both *erythro* and *threo* isomers reacted similarly, in accord with the threonine–allothreonine interconversions,[3,9] but contrary to the (desmethyl) arylserine results.

We have examined the reactions of several phenylserine derivatives with thionyl chloride. The starting materials, *erythro* and *threo* pairs of both N-acetyl- and N-benzoylphenylserinates and *p*-nitrophenylserinates, include compounds previously investigated. The reactions were performed initially in an nmr probe, some in deuteriochloroform, others in neat thionyl chloride. Temperatures were adjusted where appropriate in order to "observe" unisolated intermediates, to modify reaction rates, or to minimize secondary reactions. Spectral assignments were verified after isolation and characterization of the products, some of which have been previously reported with or without stereochemical assignments.

The eight starting compounds (Table I), chromatographically free of their diastereomers, were made from the known amino acids by Fischer esterification followed by acylation with benzoyl chloride or acetic anhydride. It was also of interest to apply the oxidation–reduction procedure[8] to phenylserinates *threo* **1** and **2** in order to provide *erythro* **1** and **2** (Scheme I). In connection with the second step of this sequence, we did not experience the stereospecificity which Bolhofer[5,10] reported for the hydrogenation of **5** (ethyl ester). It seems likely to us that the lesser *threo* isomer either escaped his detection or was lost in crystallization mother liquors. Hydrogenation of other very similar

(1) M. Bergmann and E. Brand, *Ber.*, **56**, 1280 (1923).
(2) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).
(3) D. F. Elliott, *J. Chem. Soc.*, 589 (1949).
(4) D. O. Holland, P. A. Jenkins, and J. H. C. Nayler, *ibid.*, 273 (1953).
(5) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **74**, 5459 (1952).
(6) A. F. Wagner, *ibid.*, **79**, 3240 (1957).
(7) T. Ishimaru [*Nippon Kagaku Zasshi*, **81**, 1424 (1960); *Chem. Abstr.*, **56**, 3386 (1962)] claimed inversion of the *threo* isomer in contrast to these reports: J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Amer. Chem., Soc.*, **73**, 1216 (1951); G. G. Lyle and M. L. Durand, *J. Org. Chem.*, **32**, 3295 (1967).
(8) S. H. Pines, S. Karady, M. A. Kozlowski, and M. Sletzinger, *ibid.*, **33**, 1762 (1968).
(9) K. Pfister, 3rd, C. A. Robinson, A. C. Shabica, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 2297 (1948); **71**, 1101 (1949); J. Attenburrow, D. F. Elliott, and G. F. Penny, *J. Chem. Soc.*, 310 (1948); D. F. Elliott, *ibid.*, 62 (1950).
(10) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **75**, 4469 (1963).

TABLE I
AMIDO ALCOHOLS

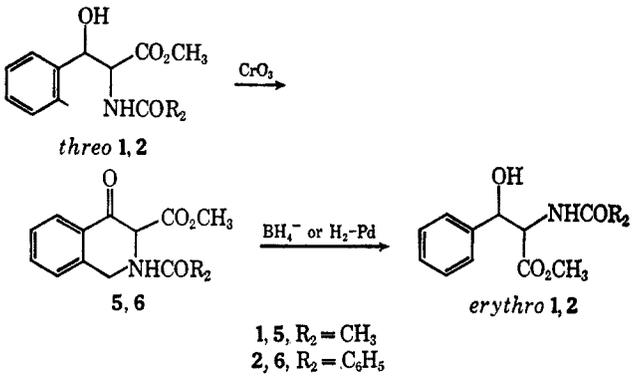


Compd	R_1	R_2	X	Mp, °C	Solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
erythro **1**	CH_3	CH_3	H	120–122	EA	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	61.09	6.50	5.96
2	CH_3	C_6H_5	H	127–130	EA–H	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.25	5.67	4.77
3	CH_3	CH_3	NO_2	181–184	An	$C_{12}H_{14}N_2O_6$	51.06	5.00	9.93	51.55	5.19	10.10
4	C_2H_5	C_6H_5	NO_2	159–161	E	*b*						
threo **1**	CH_3	CH_3	H	180–184	An	*c*						
2	CH_3	C_6H_5	H	110–112	M–Et	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.45	5.80	4.45
3	CH_3	CH_3	NO_2	198–200	M–EA	$C_{12}H_{14}N_2O_6$	51.06	5.00	9.93	51.14	5.01	10.00
4	C_2H_5	C_6H_5	NO_2	140–141	EA	*b*						

[a] Solvent used for recrystallization. EA = ethylacetate, H = hexane, An = acetonitrile, E = ethanol, M = methanol, Et = ether. [b] Reference 6. [c] References 4 and 20.

structures[10,11] have been reported. In many cases single (*erythro*) isomers have been claimed.

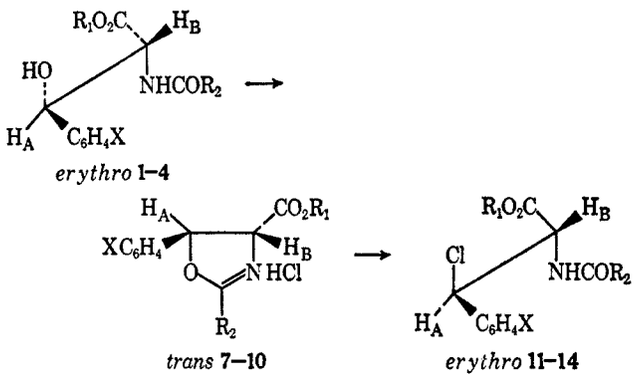
SCHEME I



Results and Discussion

Primary Reactions.—The *erythro* isomers of **1–4** underwent the same[12] basic reaction sequence (Scheme II): at ambient temperature in the nmr, the "instantaneous" products were oxazolines (hydrochloride), *trans* **7–10**. The nmr (Figure 1) showed that the O-alkyl protons of the ester group moved downfield, reflecting the formation of a rigid ring structure in which aromatic shielding was no longer possible. At the same time, the H_A–H_B pattern evolved to a pair of doublets with J_{AB} = 7–8 Hz. Much more slowly, the oxazolines opened to β-chloro compounds of the original stereochemistry, *erythro* **11–14**. The spectral data and specificity of reaction support the stereochemical assignments.

SCHEME II
REACTION OF *erythro* ISOMERS



For the sake of additional substantiation, *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*trans* **8**) was synthesized[13] from *threo*-β-phenylserine methyl ester and benziminoethyl ether hydrochloride and converted into *erythro* **12** in thionyl chloride containing hydrogen chloride. The nmr spectra of this latter sequence were identical with those from the reaction of *erythro* **2** and thionyl chloride.

(11) (a) Y. Chang and W. H. Hartung, *J. Amer. Chem. Soc.*, **75**, 89 (1953); (b) I. Elphimoff-Felkin and H. Felkin, *Compt. Rend.*, **232**, 241 (1951); (c) M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 1 (1953); (d) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(12) We hesitate to generalize at this stage. See further concerning the *threo* compounds.

(13) By the method of ref 11c.

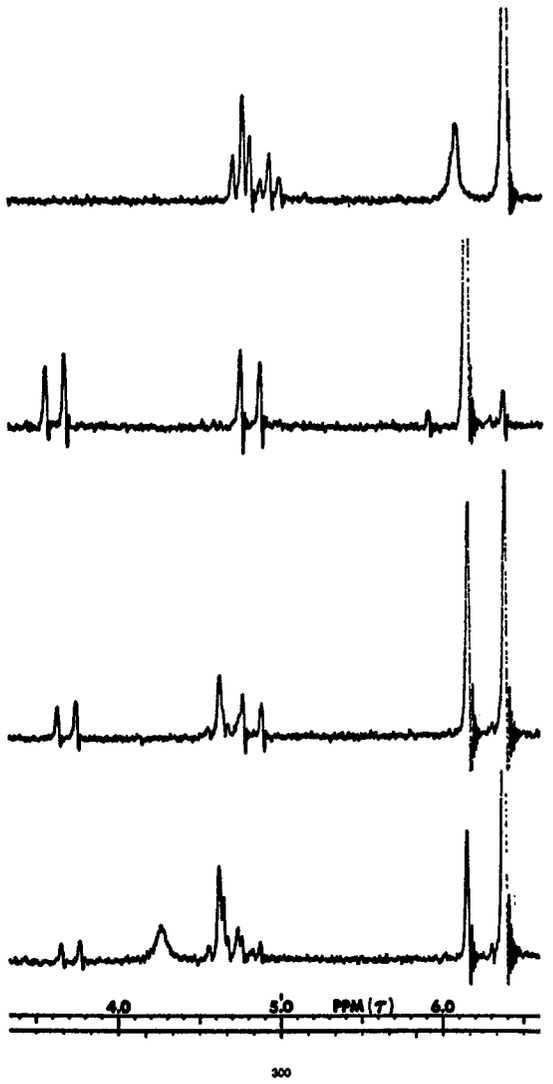
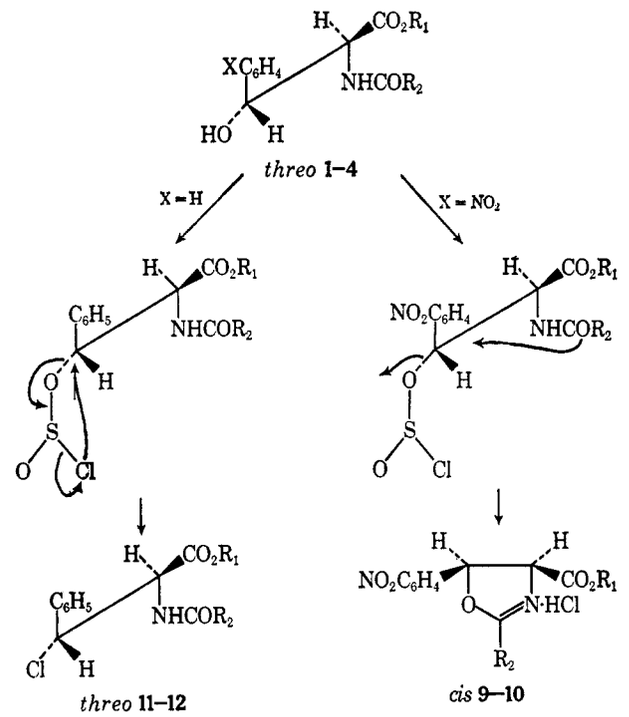


Figure 1.—Main features of typical nmr spectra for the reaction of *erythro* amido esters with thionyl chloride. Top: *erythro*-N-benzoyl-β-phenylserine methyl ester (*erythro* **2**) in $CDCl_3$ (broad resonance at *ca.* 235 cps in OH). Second: one minute after addition of thionyl chloride, *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline hydrochloride (*trans* **8**). Third: one hour; about 50% conversion of *trans* **8** into *erythro*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*erythro* **12**). Bottom: conversion into *erythro* **12** is 75%; broad "mobile" peak at *ca.* 345 cps moves upfield throughout reaction.

To our knowledge, Wagner[6] alone has reported formation of a chloro compound (*erythro* **14**) by reaction of an *erythro*-arylserine derivative with thionyl chloride.[14] He did not observe the oxazoline intermediate and could not verify the reaction mechanism. In our case, the nmr spectra provide compelling evidence for the reaction pathway as described. In one case in which thionyl chloride was added at −20° the chlorosulfite ester was initially evident (H_A shifted downfield) prior to the appearance of the oxazoline spectrum.

threo-Phenylserinates did not react with thionyl chloride like their *erythro* counterparts, nor did the *threo*-*p*-nitro analogs behave like the parent (unsubstituted) compounds. *threo* **1** and **2** underwent rapid SNi (or ion pair)[15] reaction exclusively *via* their chlorosulfite esters to provide chloro compounds *threo* **11** and **12** (Scheme III, X = H). Even at lower temperatures (−20°) where the reaction was reasonably slow, no hint of oxazoline formation could be seen in the nmr. In fact, *cis*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*cis* **8**), synthesized by an alternative route,[13] failed to give a chloro compound [and was, in fact, unchanged (nmr) by anhydrous hydrogen chloride] in over 24 hr at 37°.

SCHEME III
REACTION OF *threo* ISOMERS



The *p*-nitro analogs *threo* **3** and **4**, however, behaved differently. Their chlorosulfite esters (Scheme III, X = NO_2) slowly underwent internal displacement with the formation of oxazolines *cis* **9** and **10** which, over an extended period of time, did not open to chloro compounds.

Two questions arise from the experimental findings. First, why is there a difference in mechanism between the *threo*-phenyl- and -*p*-nitrophenyl compounds (Scheme III)? Second, why are the thermodynamically less stable *cis*-oxazolines resistant to the ring opening observed with the *trans*-oxazolines?

It has long been recognized that increased participation of a neighboring group accompanies the decreased stability of a developing carbonium ion.[16] The destabilizing influence of the *p*-nitro group provides, we believe,[17] the answer to the first question. The

(14) Physical constants reported by E. D. Bergmann, H. Bendas, and W. Taub [*J. Chem. Soc.*, 2673 (1951)] for methyl α-benzamido-β-chloro-β-phenylpropionate and its immediate precursor suggest that these were *erythro* compounds, contrary to implications. The homogeneity of his *threo* starting phenylserine has been questioned before; see also E. D. Bergmann, H. Bendas, and E. Krakauer, *ibid.*, 1064 (1954).

(15) Whether this is an SNi or an ion-pair reaction is not the point. More important, only one reaction pathway was followed to give a sterically pure product.

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

(17) It could be instructive to examine the reaction with an arylserine containing a ring substituent of the "right" intermediate Hammett σ value. Conceivably, both mechanisms might operate.

recently described radical-anion substitution[18] of *p*-nitrobenzylic substantces does not fit the case. For it to pertain, one would expect both the *erythro* and *threo* isomers to form the same *p*-nitrobenzylic radical (losing steric integrity) and to give, ultimately, the same product.

As for the second question, we suggest that the distinction in reactivity between the *cis*- and *trans*-oxazolines resides in the geometrical requirement of the transition state. It is entirely plausible that the aromatic ring should assume coplanarity[19] with the bond making–bond breaking center in order to assist in charge delocalization. Molecular models show that to do so in the *cis* case creates severe steric interaction with the ester group. No such interference occurs for the *trans* isomer.

Hydrolysis.—At this point, it is important to recognize that many of the prior workers included hydrolytic work-up of their gross reaction mixtures in evaluating the thionyl chloride reaction. In order to reconcile their reports with ours, we must examine the stereochemical consequences of hydrolysis of both the oxazolines and the chloro compounds.

As is well known, mild hydrolysis of a 2-oxazoline occurs without steric change; ring opening proceeds *via* hydration of the C=N linkage. The 2-methyloxazoline hydrochlorides were, in fact, hard to isolate; adventitious moisture frequently converted them into O-acetate amino ester hydrochlorides.

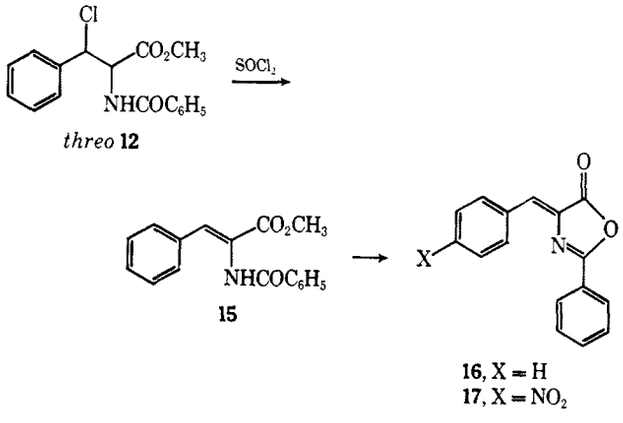
We have shown that acid hydrolysis of *erythro*-β-chloro-β-phenylalaninates occurs with a high degree of inversion to give mostly, but not exclusively, *threo*-β-phenylserine.[20] The *threo*-chloro compounds give rise to a mixture of both *erythro*- and *threo*-phenylserines, the latter predominating.[20]

Thus, it can be seen that with hydrolytic work-up, *erythro* compounds would have given products of net inversion irrespective of whether the *trans*-oxazoline or the *erythro*-chloro compound was the true substrate.

Wagner's[6] inversion of the *threo*-*p*-nitrophenylserinate (*threo* **4**) follows readily from hydrolysis of the *cis*-oxazoline (*cis* **10**) now that its formation has been shown. The inversion of *threo*-N-acetyl-β-phenylserine ethyl ester claimed by Fones[21] was in all probability the consequence of his isolation procedure. We believe that, in fact, he hydrolyzed the *threo*-β-chloro-β-phenylalaninate to a mixture of *erythro*- and *threo*-phenylserines and isolated the former. He also describes a second crop of ". . . 23 g (40%) of material of mp 115–150° which presumably was a mixture. . ."

Finally we have observed a novel decomposition pathway of *threo* **12** (Scheme IV). On extended storage in thionyl chloride, both hydrogen chloride and methyl chloride[22] were eliminated with the formation of the azlactone **16** in good yield. Control experiments showed that methyl 2-(benzoylamido)cinnamate (**15**) was converted into **16** faster than was the starting β-chloro-β-phenylalaninate *threo* **12.** Small amounts of **15** were isolated from 4-day reaction mixtures, along with good yields of **16.** When the reaction of ethyl *erythro*-N-benzoyl-β-(*p*-nitrophenyl)serinate (**4**) was allowed to continue well beyond the formation of the *erythro*-chloroalaninat **14** (1 week, 37°), the azlactone **17** crystallized directly from the thionyl chloride.[23]

SCHEME IV



Experimental Section[25]

Amido Esters. a.—The amino acids were converted into ester hydrochlorides by Fischer esterification. For benzoylation, the ester hydrochloride was treated in ethyl acetate with 2.2 equiv of triethylamine and 1.2 equiv of benzoyl chloride. N-Acetates were prepared by adding 1.1 equiv of acetic anhydride to the free amino esters in ethyl acetate. Acylations were conveniently carried out overnight at ambient temperature. The compounds are listed in Table I.

b.—Oxidation–Reduction Method.—*threo* **1** and **2** were oxidized with Jones reagent as previously described[8] to give **methyl α-acetamidobenzoylacetate** (**5**), mp 75–77.5° (ether–hexane). *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.39; H, 5.54; N, 5.87.

Methyl α-Benzamidobenzoylacetate (**6**) was prepared by the

(18) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 725 (1967), and references contained therein.

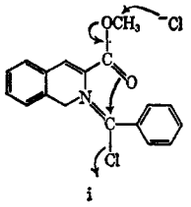
(19) Analogous to the situation discussed by P. D. Bartlett and E. N. Trachtenberg, *ibid.*, **80**, 5808 (1958). In the *cis* compound the aromatic ring occupies a more perpendicular position; *cf.* the shielding effect on the ester alkyl protons (Table IV).

(20) Unpublished observations, estimated from paper chromatograms.

(21) W. S. Fones, *J. Org. Chem.*, **17**, 1534 (1952). Bolhofer[5] simultaneously recorded the same experimental results, but expressed doubt as to whether an actual "oxazoline-type" of inversion had occurred or whether some other series of reactions had taken place. Others[4] reported isolation of a *threo*-β-phenylserine from HCl hydrolysis of *threo* **11.**

(22) This was shown by nmr. CH_3OSOCl is sufficiently stable to have been visible in the spectrum if it had been formed by carbonyl–oxygen cleavage.

(23) We did not look for this reaction in any other case. It is reasonable to suspect that all of the chloro compounds should ultimately eliminate HCl, and that at least the N-benzoylamides should form stable azlactones. Ester cleavage *via* thionyl chloride[24] normally requires more vigorous conditions. For these compounds, however, a mechanism can be written invoking an intermediate imino chloride structure, i, that could assist and at the same time provide extended conjugation.



i

(24) M. Green and D. M. Thorp, *J. Chem. Soc., B*, 1067 (1967).

(25) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and associates of these laboratories. Ir spectra were obtained with a Perkin-Elmer Model 137 Infracord, uv with a Perkin-Elmer Model 202 spectrophotometer, and nmr with a Varian A-60A. In the interests of brevity, ir and uv data are not routinely reported. Those physical constants and analyses found in Tables I–III are not repeated in the Experimental Section. Characteristic nmr resonances are found in Table IV for most compounds. Unless otherwise stated, it may be assumed that all organic solutions were dried over sodium sulfate; solvent was removed by vacuum evaporation in a rotating evaporator. Preparative chromatographies were run on silica gel H (E. Merck) with the solvent systems reported parenthetically, unless otherwise specified. Commercially available tlc plates (Analtech or Brinkmann) were used without pretreatment.

TABLE II

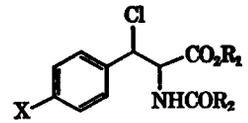
OXAZOLINES

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
trans-4-Carbomethoxy-2-methyl-5-phenyl-2-oxazoline hydrochloride (**7**)	91–94	$C_{12}H_{14}NO_3Cl$	56.36	5.52	5.48	55.89	6.15	5.42
trans-4-Carbomethoxy-2,5-diphenyl-2-oxazoline (**8**)	80–85[a]	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.27	5.16	5.21
trans-4-Carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (**9**)	101–104	$C_{12}H_{13}N_2O_5Cl$	47.93	4.36	9.34	47.89	4.61	9.32
trans-4-Carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (**10**)	86–88	[b]						
cis **8**	142–144	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.68	5.57	5.08
cis **9**	140–141	$C_{12}H_{13}N_2O_5Cl$	47.93	4.36	9.34	48.91	4.36	9.42
cis **10**	140–141	$C_{18}H_{16}N_2O_5$	63.51	4.74	8.23	63.90	4.49	8.22

[a] Bath temperature at which sample was slowly distilled (short path) *trans* **8** was obtained as an oil. [b] Reference 6.

TABLE III

β-CHLOROALANINATES



Compd	R_1	R_2	X	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
erythro **11**	CH_3	CH_3	H	123.5–125.5	$C_{12}H_{14}ClNO_3$	56.36	5.52	5.48	56.53	5.65	5.42
12	CH_3	C_6H_5	H	136–138	$C_{17}H_{16}ClNO_3$	64.26	5.08	4.41	64.56	5.25	4.46
13	CH_3	CH_3	NO_2	99–100	$C_{12}H_{13}ClN_2O_5$	48.00	4.36	9.32	48.03	4.46	9.38
14	C_2H_5	C_6H_5	NO_2	120–121	[a]						
threo **11**	CH_3	CH_3	H	128–130	[b]						
12	CH_3	C_6H_5	H	132–133	$C_{17}H_{16}ClNO_3$	64.26	5.08	4.41	64.49	5.02	4.51

[a] Reference 6. [b] Reference 4.

TABLE IV
NMR DATA[a]

Compd	H_A[b]	H_B[b]	J_{AB}	OCH_3
erythro **1**	313	299	3.5	221
2	321	311	4	224
3	319	302	4.5	219
4	332	313	3.5	...
threo **1**	309	278	3.5	219
2	319	300	3.5	220
3	333	307	3	229
4	331	309	3.5	...
erythro **11**	318	306	4.5	220
12	332	323	5	224
13	329	313	4.5	223
14	338	322	4	...
threo **11**	333	315	4	227
12	341	327	4	229
cis **8**	358	319	11	194
9	406	338	10.5	199
10	363	322	10.5	...
trans **7**	383	313	8	235
8	355	291	7.5	231
9	388	312	8	235
10	312	286	7.5	...

[a] All values are in cycles per second downfield from internal TMS = 0. Solutions are in $CDCl_3$ except *erythro and threo* **2**, after dilute DCl exchange; *erythro* and *threo* **3**, in CD_3CO_2D; *threo* **1**, in DMSO-d_6; *erythro* **11** and *trans* **7** *in situ* $CDCl_3$ + $SOCl_2$ + HCl; *cis* and *trans* **9**, *in situ* $SOCl_2$ + HCl. [b] H_A and H_B as shown in Scheme II.

same method, mp 132–134° (ethyl acetate). *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.96; H, 5.12; N, 4.85.

Catalytic hydrogenation of **5** and **6** in either methanol or acetic acid over 5% Pd–C gave *erythro* **1** and **2** which were freed of minor amounts of *threo* isomer by chromatography (*erythro* **1**, benzene–methanol, 9:1 on alumina; *erythro* **2**, chloroform–acetone, 23:2). Reduction *via* sodium borohydride gave very similar results.

Reactions with Thionyl Chloride.—All reactions were initially followed in an nmr tube to determine the appropriate reaction conditions for product isolation.

a. **With *erythro*-N-Acetyl-β-phenylserine Methyl Ester.**—Thionyl chloride (0.2 ml) was added to 150 mg of *erythro* **1** in 3 ml of chloroform. After 2 min, the stirred solution was cooled in ice and crystals separated. After 5 min they were filtered and washed with anhydrous tetrahydrofuran. Because the product, *trans*-4-carbomethoxy-2-methyl-5-phenyl-2-oxazoline hydrochloride (*trans* **7**) was deliquescent, these operations were best accomplished in a dry box.

When a sample of *trans* **7** was dissolved in wet acetone it was rapidly converted into *threo*-O-acetyl-β-phenylserine methyl ester hydrochloride, mp 146.5–148° dec (from acetone–ether). *Anal.* Calcd for $C_{12}H_{16}ClNO_4$: C, 52.65; H, 5.89; N, 5.12. Found: C, 52.30; H, 5.98; N, 5.13. The ir readily differentiated *trans* **7** from the O-acetate.

When the thionyl chloride reaction was continued overnight at room temperature, chromatography of the residue (methylene chloride–ethyl acetate, 5:1) gave *erythro*-N-acetyl-β-chloro-β-phenylalanine methyl ester (*erythro* **11**), crystallized from ethyl acetate–ether.

b. **With *erythro*-N-Benzoyl-β-phenylserine Methyl Ester.**—A solution of 250 mg of *erythro* **2** in 3 ml of chloroform through which nitrogen was bubbled was treated with 0.5 ml of thionyl chloride. After 5 min, the solvent was removed *in vacuo* without heat. Chromatography (chloroform) gave 178 mg of *trans*-4-carbomethoxy-2,5-diphenyl-2-oxazoline (*trans* **8**), an oil. When the reaction was allowed to stand overnight, evaporation of the solvent gave crystalline *erythro*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*erythro* **12**) which was recrystallized from tetrahydrofuran–ether for analysis.

c. **With *erythro*-N-Acetyl-β-(*p*-nitrophenyl)serine Methyl Ester.**—After standing 20 min in 5 ml of thionyl chloride, 200 mg of *erythro* **3** was converted into *trans*-4-carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (*trans* **9**). Removal of the solvent and trituration with anhydrous tetrahydrofuran gave analytically pure material. When an identical reaction was allowed to proceed over the weekend, the residue gave (chromatography, ethyl acetate–chloroform–tetrahydrofuran 10:10:2.5) *erythro*-N-acetyl-β-chloro-β-(*p*-nitrophenyl)alanine methyl ester (*erythro* **13**). The analytical sample was recrystallized from methylene chloride–cyclohexane.

d. **With *erythro*-N-Benzoyl-β-(*p*-nitrophenyl)serine Ethyl Ester.**—The residue from reaction of 700 mg of *erythro* **4** in 15 ml of thionyl chloride for 20 min was chromatographed (chloroform) to give both *trans*-4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (*trans* **10**) (crystallized from ether–hexane) and *erythro*-N-benzoyl-β-chloro-β-(*p*-nitrophenyl)alanine ethyl ester (*erythro* **14**) (crystallized from ether).

When a solution of *erythro* **4** in thionyl chloride was stored at 37° for 1 week, there deposited bright yellow crystals, mp 237–240°. Spectral (ir, uv, nmr) and elemental analyses confirmed the structure as 4-*p*-nitrobenzal-2-phenyl-5-oxazolone (**17**).[26]

e. **With *threo*-N-Acetyl-β-phenylserine Methyl Ester.**—Cold (0°) thionyl chloride (5 ml) was added to 500 mg of *threo* **1** and the solution was stored at 0° for 36 hr. Removal of the solvent and crystallization from ethyl acetate gave 380 mg of *threo*-N-acetyl-β-chloro-β-phenylalanine methyl ester (*threo* **11**).

f. **With *threo*-N-Benzoyl-β-phenylserine Methyl Ester.**—Removal of the thionyl chloride with heating after 1 hr of reaction of *threo* **2** at room temperature gave a quantitative yield of crystalline *threo*-N-benzoyl-β-chloro-β-phenylalanine methyl ester (*threo* **12**), mp 126–128°. The analytical sample was crystallized from ethyl acetate–hexane.

When a thionyl chloride solution was stored, two new nmr peaks became clearly evident after a day; one, 179 cps, was shown to be due to methyl chloride, and the other, 435 cps, was vinylic. After 4 days at 38°, a reaction was evaporated *in vacuo* without heat, taken up in cold chloroform, and washed quickly with cold salt and bicarbonate solution. The residue crystallized from ethanol to give 1.24 g (50%) of 4-benzal-2-phenyl-5-oxazolone (**16**), mp 158–159°, which exhibited the proper uv[27] absorption. From the mother liquor was deposited 575 mg (17.5%) of *threo* **12**, mp 126–128°. Chromatography (chloroform, then 1% acetone in chloroform) gave an additional 10% **16**, more *threo* **12**, and 370 mg (13%) of a crystalline substance, mp 130–131°, which was identified by its spectral properties[28] as methyl 2-(benzoylamido)cinnamate (**15**).

g. **With *threo*-N-Acetyl-β-(*p*-nitrophenyl)serine Methyl Ester.**—After standing 2 days, a solution of 200 mg of *threo* **3** in 2 ml of thionyl chloride was blown free of solvent with dry nitrogen. Trituration with anhydrous tetrahydrofuran gave *cis*-4-carbomethoxy-2-methyl-5-*p*-nitrophenyl-2-oxazoline hydrochloride (*cis* **9**). Recrystallization of *cis* **9** from water–acetone gave *erythro*-O-acetyl-β-*p*-nitrophenyl)serine methyl ester hydrochloride, mp 188–190° dec. The ir spectrum (Nujol) showed broad ester carbonyl 1760 cm^{-1}; no amide C=O or oxazoline C=N was present. *Anal.* Calcd for $C_{12}H_{15}ClN_2O_6$: C, 45.22; H, 4.74; N, 8.79. Found: C, 45.43; H, 4.92; N, 8.92.

Stirring for 30 min with aqueous bicarbonate converted the product to *erythro* **3** in quantitative yield.

h. **With *threo*-N-Benzoyl-β-(*p*-nitrophenyl)serine Ethyl Ester.**—The reaction run as in g gave a crystalline residue which was dissolved in chloroform and washed with saturated bicarbonated solution. After removal of the chloroform, crystallization from ethyl acetate gave *cis*-4-carbethoxy-5-*p*-nitrophenyl-2-phenyl-2-oxazoline (*cis* **10**).

***cis*-4-Carbomethoxy-2,5-diphenyl-2-oxazoline (*cis* 8).**—*erythro*-β-Phenylserine methyl ester was heated on a steam bath [13] with a 20% excess of benziminoethyl ether hydrochloride for 40 min. The melt was dissolved in chloroform, washed with water, dried, and concentrated. The crystalline residue was recrystallized for analysis from tetrahydrofuran–hexane.

***trans*-4-Carbomethoxy-2,5-diphenyl-2-oxazoline (*trans* 8)** was made as above from *threo*-β-phenylserine methyl ester. The product was indistinguishable from that made *via* the thionyl

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chloride reaction b, above. Treatment of *trans* **8** in thionyl chloride with hydrogen chloride opened the oxazoline to give chloro compound *erythro* **12**.

Attempted Opening of *cis* 8 with Hydrogen Chloride.—A cold $CDCl_3$ solution of *cis* **8** in an nmr probe was saturated with hydrogen chloride. The only observable change was a downfield shift of the H_A and H_B doublets (J = 11 cps) as a result of protonation. The spectrum remained essentially unchanged after 24 hr at 37°.

Registry No.—**1** (*erythro*), 19185-82-1; **1** (*threo*), 19185-83-2; **2** (*erythro*), 19185-84-3; **2** (*threo*), 19185-85-4; **3** (*erythro*), 19185-86-5; **3** (*threo*), 19202-70-1; **4** (*erythro*), 19185-38-7; **4** (*threo*), 19185-39-8; **5**, 19185-44-5; **6**, 19185-45-6; **7** (*trans*), 19185-46-7, **8** (*cis*), 19185-47-8; **8** (*trans*), 19185-48-9; **9** (*cis*;) 19185-49-0; **9** (*trans*), 19185-50-3; **10** (*cis*), 19185-51-4; **10** (*trans*), 19185-52-5; **11** (*erythro*), 19185-40-1; **11** (*threo*), 19185-41-2; **12** (*erythro*), 19185-42-3; **12** (*threo*), 19185-43-4; **13** (*erythro*), 19191-01-6; **14** (*erythro*), 19191-02-7; *threo*-O-acetyl-β-phenylserine methyl ester hydrochloride, 19191-04-9; *erythro*-O-acetyl-β-(*p*-nitrophenyl)serine methyl ester hydrochloride, 19191-05-0; thionyl chloride, 7719-09-7.

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The Reaction of Arsenic Trihalides with Nucleosides. Halomethylene Dimethylammonium Halide. A New Halogenating Agent for Nucleosides[1]

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The reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro(bromo)uridine (**7a** and **b**) when carried out in N,N-dimethylformamide (DMF). Arsenic triiodide gave poor results. Specificity for the 5′ position was found in the case of uridine. Two new nucleoside halogenating agents, chloromethylenedimethylammonium chloride (**2a**) and bromomethylenedimethylammonium bromide (**2b**), were found to be the actual halogenating agents. These agents gave excellent halogenation at the 5′ position of both **1** and **6**. Comparison was made of the facility by which these chloro and bromo derivatives cyclized to 5′-O²-cyclo nucleosides **4** and **8**. Attempts at the synthesis of nucleoside 5′-arsenate **5** indicated that these compounds may be too unstable to be isolated.

In attempts at the synthesis of arseno nucleosides we have studied the reactions of arsenic trihalides with nucleosides. In our study it was found that the reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide in anhydrous N,N-dimethylformamide (DMF) gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro(bromo)-uridine (**7a** and **b**) (Scheme I). Arsenic triiodide gave poor results. Surprisingly the reaction of uridine with the arsenic trihalides gave a high degree of specificity for the 5′ position. However when N,N-dimethylacetamide (DMA) was used as the solvent in the reaction of $AsCl_3$ with uridine, 3′-deoxy-3′-chlorouridine (**9**) was formed in addition to **7a**.

Arsenic trihalides have not been known to serve as halogenating agents for alcohols. Instead they have been reported[4,5] to react with alcohols to form dichloroarsenite derivatives. However, DMF has been reported[6-8] to react with inorganic acid halides ($COCl_2$, $POCl_3$, PCl_3, and $SOCl_2$) to form an active intermediate chloromethylenedimethylammonium chloride (**2a**). Initially **2a** found use as a formylating agent for aromatic, heterocyclic, and ethylenic compounds. Nonetheless compound **2a** and its bromide analog (**2b**) have been reported[9] to be highly effective in replacing hydroxyl and related groups with halogen. A mechanism for the formation of **2a** from $SOCl_2$ and DMF has been reported.[10] The applicability of this mechanism to the reaction of arsenic trihalides and DMF has been indicated by the report[11] of the chloromethylation of naphthalene by $AsCl_3$ and paraformaldehyde. Thus it is proposed that arsenic trihalides react with DMF in a manner similar to $SOCl_2$.

On the basis of this information we have synthesized both **2a** and **2b** by the method of Bosshard, *et al.*,[10] and used them for the halogenation of **1** and **6**. In all cases paper chromatography and thin layer chromatography indicated a quantitative conversion into the corresponding 5′-deoxy-5′-halogeno nucleoside. Isolation and purification gave yields in the range of 80–90%. (See Table I.)

In the reactions of **2a** and **2b** with uridine, fast moving (R_f 0.80–0.85, paper chromatography) uv absorbing substances were found when the reaction mixture was not refluxed with NH_4OH. These rather unstable compounds gave a negative *cis*-glycol test,[12]

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