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Conversion of Threonine Derivatives to Dehydroamino Acids by Elimination of β-Chloro and *O*-Tosyl Derivatives

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DL-Threonine methyl ester was converted by chlorination with phosphorus pentachloride followed by N-acylation to *erythro*-α-acylamino-β-chloro-DL-butyric acid methyl esters, which upon elimination with Dabco as base yielded 2-acylaminocrotonates as a mixture of *E* and *Z* isomers. Elimination with DBU as base furnished predominantly the *E* isomer. The *Z* isomers formed from the above erythro compounds were shown to arise by isomerization of the corresponding *E* isomer. In comparison, *N*-acyl-*O*-tosyl-DL-threonine methyl esters (threo configuration) yielded only the *Z* isomer upon elimination. *N*-Tosylthreonine derivatives, regardless of configuration, undergo elimination to give *N*-tosylaminocrotonates of *Z* configuration. Evidence is given that aziridines are intermediates in the formation of olefin from *N*-tosylthreonine derivatives.

Dehydroamino acids are constituents of certain peptide antibiotics.[1] Considerable attention[2] has been given recently to the preparation of dehydroamino acids, particularly of the dehydroalanine unit, which unit is generally derived from serine or cysteine derivatives. In this paper, we report studies on elimination reactions of threonine to give 2-acylaminocrotonate derivatives.

Threonine derivatives have been converted to 2-acylaminocrotonates by dehydration[3] and tosylate elimination.[4] Other methods not directly involving threonine for preparation of 2-acylaminocrotonates have been by elimination reactions of sulfonium salts,[2b] sulfoxides,[2c] *N*-chloro-α-amino acid esters,[2f] α-(*N*-acylhydroxyamino) acid esters,[2g] and by amide condensation with α-keto esters.[2h] We recently have prepared peptides containing dehydroalanine by conversion of serine to a β-chloroalanine unit with subsequent elimination.[2i] In this paper, we report application of this method, and also elimination reactions of tosylate derivatives, for preparation of dehydroamino acids from derivatives of threonine.

DL-Threonine methyl ester hydrochloride (**1**) was transformed to *erythro*-β-chloro-DL-α-aminobutyric acid methyl ester hydrochloride (**2**)[5] by chlorination with phosphorus pentachloride, a reaction known to occur with inversion of configuration.[5] Acylation of **2** gave the *N*-acyl-*erythro*-β-chloro-DL-α-aminobutyrates **4**.

Treatment of the *erythro*-β-chlorobutyrates **4** with 1,4-diazabicyclo[2.2.2]octane (Dabco) in ethyl acetate effected elimination to yield the 2-acylaminocrotonates **5**. In all cases, a mixture of geometrical isomers was obtained, though the relative amounts of the *E* and *Z* isomers varied depending upon the *N*-acyl group (Table I). The proportion of geometrical isomers formed and assignment of configuration were determined by NMR spectroscopy[6] (see Table IV). The *E* isomer would be the product expected to be formed from the *erythro*-β-chlorobutyrates if a trans E_2 elimination was occurring. The *Z* isomer formed in these reactions likely arises from isomerization of the *E* isomer. Evidence for this was obtained by treatment of an 87:13 *E*:*Z* mixture of **5a** under the conditions of elimination for an additional 16 h, whereupon NMR analysis showed the composition to be 75:25 *E*:*Z*. Likewise, **4c** and **4e** each gave predominantly the *Z* isomer upon elimination, a result consistent with enhanced *E* to *Z* isomerization due to the electron-withdrawing effects of the *N*-benzyloxycarbonyl and trifluoroacetyl groups, respectively. Poisel and Schmidt[2f] have reported that, under acidic conditions, the *Z* isomer of 2-acylaminocrotonates is the thermodynamically controlled product, a result consistent with our observations.

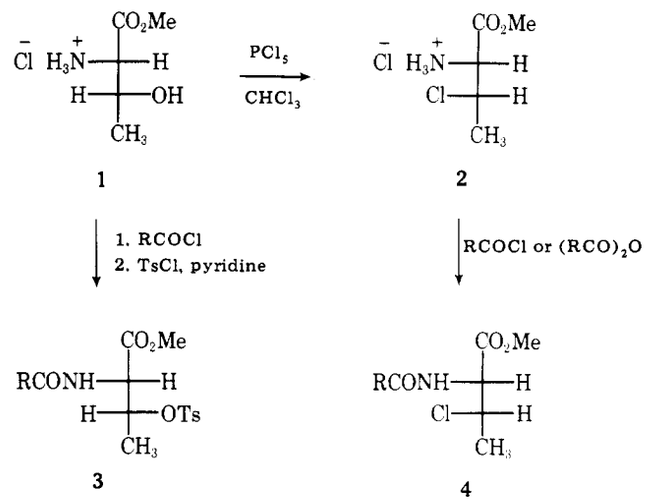
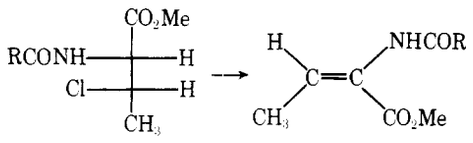


Table I. Elimination Reactions Using Dabco as Base

Reactant 4	R	Product 5 yield, %	Ratio E	Ratio Z
a	C_6H_5	90	66	33
b	$C_6H_5CH_2$	79	59	41
c	$C_6H_5CH_2O$	80	43	57
d	CH_3	46	77	23
e	CF_3	81	13	87
f	Z-$NHCH_2$	81	66	33



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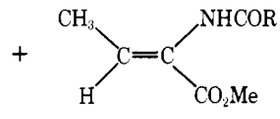
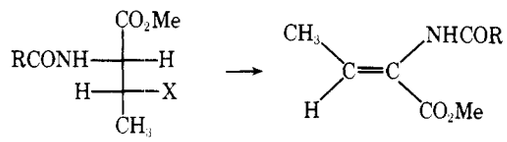
5-*E*



5-*Z*

Interestingly, treatment of the β-chlorobutyrate **4a** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) effected elimination to give, as measured from the NMR spectrum of the product mixture, a 95:5 *E*:*Z* ratio; similar results were obtained for **4c** (entries 3 and 5, Table II). Thus, use of DBU as base affords a synthetically useful method for preparation of 2-acylaminocrotonates of *E* configuration. The elimination reactions with DBU proceed at a much faster rate than with Dabco and were complete within 1 h. In comparison, reaction of **4a** with Dabco was only 75% complete after a reaction period of 6 h. Treatment of **4a** with DBU for 72 h led to a 64:36 mixture of *E* and *Z* isomers; this result again is consistent for isomerization of the *E* to the *Z* isomer.

N-Acyl-*O*-tosyl-DL-threonine methyl esters (**3a–d**) of natural threo configuration underwent elimination to yield only *N*-acylaminocrotonates **5** of *Z* configuration, as expected for a trans E_2 elimination leading directly to the more stable *Z* isomer. *N*-Benzyloxycarbonyl-*threo*-β-chloro-DL-α-aminobutyric acid methyl ester (**3e**), prepared by chlorination of *allo*-threonine methyl ester, also yielded only the *Z* isomer upon elimination. The tosylates **3a–d** were prepared by tosylation of the corresponding *N*-acyl-DL-threonine methyl ester. Yields of the *Z* crotonates **5** obtained in the elimination reactions are given in Table III.



3a, R = Ph; X = OTs
b, R = $PhCH_2$; X = OTs
c, R = $PhCH_2O$; X = OTs
d, R = Z-$NHCH_2$; X = OTs
e, R = $PhCH_2O$; X = Cl

5-*Z*a, R = Ph
b, R = $PhCH_2$
c, R = $PhCH_2O$
f, R = Z-$NHCH_2$

Oxazolines are known[7,8] to be formed from serine and threonine derivatives upon chlorination. The possibility exists, therefore, that tosylate **3** and β-chlorobutyrate **4** could form oxazolines as intermediates in the elimination reaction leading to olefin. The formation of olefin from oxazolines has been reported.[9] We prepared the oxazoline hydrochloride **7** from **6** according to the procedure of Tishler and co-workers;[8] however, when **7** was treated to the conditions for elimination, no elimination to yield crotonate occurred and only the neutralized oxazoline **8** was obtained.

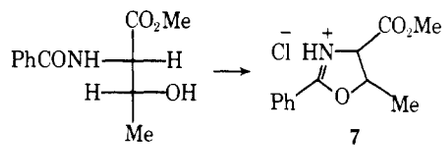
Table II. Variation of Isomer Distribution with Reaction Time and Base Used

Reactant	Base	Reaction time, h	Product 5, % E	Product 5, % Z
4a	Dabco	16	87	13
4a	Dabco	32	75	25
4a	DBU	1	95	5
4a	DBU	72	64	36
4c	DBU	1	85	15

Table III. Elimination Reactions of *N*-Acyl-*O*-tosylthreonine Derivatives

Reactant	Product Z isomer	Product Yield, %	Mp, °C	Solvent[a]
3a	5a	81	78–79	A
3b	5b	76	79–81	A
3c	5c	85	65.5–67	B
3d	5f	89	56–59	A
3e	5c	64	65.5–67	B

[a] A = ethyl acetate–petroleum ether, B = benzene–petroleum ether.



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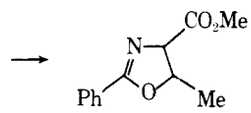

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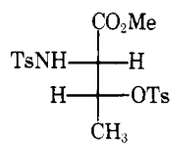
The elimination reaction of *N*-tosyl-DL-threonine methyl ester (**9**) appears to proceed by a diferent mechanism than the above elimination reactions, in that the aziridine **10** is implicated as an intermediate leading to at least a portion of the *Z* crotonate **11** formed in the reaction. Nakagawa et al.[4] have reported obtaining a mixture of **10** and **11**, as ethyl esters, when the ditosylate **9** was treated with *N*-ethylpiperidine in benzene. When a 40:60 mixture of **10** and **11**, which we prepared according to Nakagawa,[4] was treated with Dabco in ethyl acetate for 6 h, the only product obtained was the *Z* crotonate **11**, thus establishing that under these conditions the aziridine **10** is converted to crotonate **11**. The ring opening of the aziridine anion has been discussed.[10] When ditosylate **9** was caused to react with Dabco, only **11** was obtained. Treatment of *erythro*-*N*-tosyl-β-chloro-DL-α-aminobutyric



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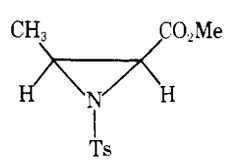

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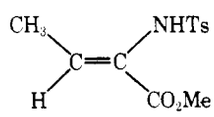

11

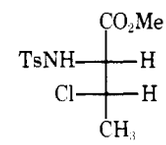

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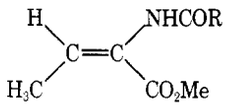
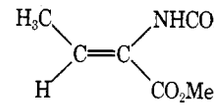
Table IV. NMR Data of 2-Acylaminocrotonates[a,b]



5-*E*



5-*Z*

Compd	Confign	R group: Ph	R group: CH_2	R group: CH_3	NH	Vinyl	β-Methyl	Methyl ester
5a	*E*	7.3–7.9			8.31	7.18	2.05	3.77
5a	*Z*	7.3–7.9			7.80	6.80	1.78	3.67
5b	*E*	7.32	3.57		7.10	7.03	1.97	3.62
5b	*Z*	7.32	3.65		6.90	6.68	1.65	3.66
5c	*E*	7.30	5.15		7.30	6.71	2.05	3.73
5c	*Z*	7.30	5.15		7.30	6.68	1.77	3.67
5d	*E*			2.00	7.62	6.90	2.02	3.75
5d	*Z*			2.00	7.40	6.72	1.71	3.68
5e	*E*				*c*	7.15	2.07	3.93
5e	*Z*				9.74	6.92	1.73	3.87
5f	*E*	7.32	5.12, 3.90[d]		8.12, 5.95	6.99	2.03	3.78
5f	*Z*	7.32	5.12, 3.85[d]		7.87, 5.95	6.83	1.71	3.70

[a] Spectra were recorded in $CDCl_3$ with shift values given in parts per million relative to Me_4Si. [b] Multiplicities for the various proton groupings in the order listed above are as follows: Ph (s or m), CH_2 (s), CH_3 (s), NH (brd), vinyl (q), β-methyl (d), methyl ester (s). [c] Intensity too weak to observe. [d] Shift values for glycine methylene.

acid methyl ester (**12**) with Dabco also furnished only *Z* crotonate **11**. Attempts to observe formation of an aziridine in these reactions with Dabco as the base were not successful; if an aziridine intermediate is formed, it must rapidly undergo ring opening to form olefin. We also did not observe formation of the *E* crotonate from **12**; however, if the *E* isomer were formed, either by direct elimination or via an aziridine, it may be rapidly isomerized to the *Z* isomer **11**, though this isomerization would have to occur at a much faster rate, as might be expected, than for isomerization of the less acidic *N*-acylcrotonates **5**.

The *Z* configuration was assigned to crotonate **11** on the basis that N-methylation of **11** with methyl iodide–sodium hydride in DMF gave a single product in which the vinyl proton showed a small downfield shift as compared to the vinyl proton position in **11**. This result is consistent for a *Z* isomer of an *N*-acylaminocrotonate; in contrast, the corresponding *E* isomer would be expected to have undergone a substantial upfield shift upon N-methylation.[6]

Experimental Section

All new compounds that were crystalline gave satisfactory analytical data for C, H, and N to within ±0.4% of the calculated values. NMR spectra were obtained for all compounds with a Varian XL-100-12 spectrometer. Recrystallized products and products obtained as oils were shown to be homogeneous by TLC on Brinkmann silica gel F_{254} plates developed in chloroform–methanol–acetic acid (85:10:5), ethyl acetate–ligroin, bp 60–90 °C (1:1), or chloroform. Evaporations in vacuo were carried out with a Buchler rotary evaporator. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

Preparation of *erythro*-α-Acylamino-β-chloro-DL-butyric Acid Methyl Esters 4a–e. For the preparation of **4a–c**, *erythro*-α-amino-β-chloro-DL-butyric acid methyl ester hydrochloride (**2**,[5] 5–10 mmol) in water–$NaHCO_3$ (2 equiv) was treated with the appropriate acid chloride (1 equiv) and the reaction mixture was stirred at room temperature for 4–6 h. The mixture was extracted with ethyl acetate, and the extracts were washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4). In the case of **4a**, the product precipitated during the reaction and was collected by filtration.

4a: mp 77–78 °C from ethyl acetate–petroleum ether (bp 60–90 °C); 91% yield; NMR ($CDCl_3$) δ 1.67 (d, 3 H, β-methyl), 3.80 (s, 3 H, methyl ester), 4.41 (m, 1 H, β hydrogen), 4.91 (m, 1 H, α hydrogen), 6.98 (brd, 1 H, NH), 6.30–6.81 (m, 5 H, phenyl).

4b: oil; 62% yield; NMR ($CDCl_3$) δ 1.47 (d, 3 H, β-methyl), 3.56 (s, 2 H, benzyl), 3.70 (s, 3 H, methyl ester), 4.22 (m, 1 H, β hydrogen), 4.81 (m, 1 H, α hydrogen), 6.71 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl).

4c: mp 53.5–55.5 °C from ether–petroleum ether; 74% yield; NMR ($CDCl_3$) δ 1.51 (d, 3 H, β-methyl), 3.70 (s, 3 H, methyl ester), 4.26 (m, 1 H, β hydrogen), 4.80 (m, 1 H, α hydrogen), 5.17 (s, 2 H, benzyl), 6.70 (brd, 1 H, NH), 7.31 (s, 5 H, phenyl).

Compounds **4d** and **4e** were prepared by treatment of **2** (5–10 mmol) with 1 equiv of triethylamine in ethyl acetate, followed by addition of 1.2 equiv of acetic anhydride and trifluoroacetic anhydride, respectively. The reaction mixture was stirred at room temperature for 6 h and filtered, and the filtrate was washed with saturated NaCl solution and dried over Na_2SO_4.

4d: oil; 56% yield; NMR ($CDCl_3$) δ 1.55 (d, 3 H, β-methyl), 2.00 (s, 3 H, acetyl), 3.72 (s, 3 H, methyl ester), 4.24 (m, 1 H, β hydrogen), 4.79 (m, 1 H, α hydrogen), 6.88 (brd, 1 H, NH).

4e: oil; 81% yield; NMR ($CDCl_3$) δ 1.70 (d, 3 H, β-methyl), 3.88 (s, 3 H, methyl ester), 4.37 (m, 1 H, β hydrogen), 4.91 (m, 1 H, α hydrogen), 7.55 (brd, 1 H, NH).

***N*-Benzyloxycarbonylglycyl-*erythro*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (4f).** To a solution of **2** (1.88 g, 0.01 mol) and Z-Gly-OH (2.09 g, 0.01 mol) in chloroform–dimethylformamide (2:1) were added equimolar amounts of triethylamine and *N,N*[1]-dicyclohexylcarbodiimide and the reaction mixture was stirred for 8 h. Following filtration, the filtrate was washed with 2 N HCl, 5% $NaHCO_3$, and water and dried over Na_2SO_4. Removal of the solvent in vacuo furnished **4f** as a viscous oil: 50% yield; NMR ($CDCl_3$) δ 1.54 (d, 3 H, β-methyl), 3.78 (s, 3 H, methyl ester), 3.95 (d, 2 H, glycyl methylene), 4.31 (m, 1 H, β hydrogen), 4.73 (m, 1 H, α hydrogen), 5.21 (s, 2 H, benzyl), 5.80 (brd, 1 H, NH), 7.21 (brd, 1 H, NH), 7.31 (s, 5 H, phenyl).

Preparation of *N*-Acyl-DL-threonine Methyl Esters. The *N*-acyl-DL-threonine methyl esters used in the tosylation reactions described in the following section were prepared from DL-threonine methyl ester hydrochloride (**1**)[5] by acylation using the procedure described above for preparation of **4a–c**. The following compounds were prepared: *N*-benzyloxycarbonyl-DL-threonine methyl ester, oil, 80%; *N*-benzoyl-DL-threonine methyl ester, mp 83–84 °C (lit.[8] mp 82–84 °C), 73%; *N*-phenylacetyl-DL-threonine methyl ester, oil, 61% yield.

N-Benzyloxycarbonylglycyl-DL-threonine methyl ester was prepared from *N*-benzyloxycarbonylglycine and DL-threonine methyl ester hydrochloride using the carbodiimide procedure described above for **4f**, mp 104–105 °C from benzene, 50% yield.

Preparation of *O*-Tosyl-DL-threonine Derivatives 3a–d. The appropriate *N*-acyl-DL-threonine methyl ester (2–5 mmol) was dissolved in dry pyridine and the resulting solution was cooled to −5 °C. *p*-Toluenesulfonyl chloride (2 equiv) in dry pyridine was added dropwise at a rate to maintain the temperature below −5 °C. The reaction mixture was kept at 0 °C for 2 h and then was allowed to stand overnight in the refrigerator. The reaction mixture was poured

into water and the product, which precipitated as a solid, was collected by filtration and air dried. **3d** was an oil, which was isolated by extraction of the aqueous phase with chloroform.

3a: mp 89–90 °C from benzene–petroleum ether; 51% yield; NMR ($CDCl_3$) δ 1.26 (d, 3 H, β-methyl), 2.33 (s, 3 H, tolyl methyl), 3.50 (s, 3 H, methyl ester), 4.86 (m, 1 H, α hydrogen), 5.09 (m, 1 H, β hydrogens), 6.70 (brd, 1 H, NH), 7.18–7.80 (m, 9 H, phenyl hydrogens).

3b: mp 74–75 °C from ethyl acetate–petroleum ether; 40% yield; NMR ($CDCl_3$) δ 1.21 (d, 3 H, β-methyl), 2.43 (s, 3 H, tolyl methyl), 3.53 (s, 3 H, methyl ester), 3.61 (s, 2 H, $PhCH_2$), 4.73 (m, 1 H, α hydrogen), 5.06 (m, 1 H, β hydrogen), 6.14 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl), 7.17–7.71 (A_2B_2, 4 H, tolyl).

3c: mp 74–75 °C from benzene–petroleum ether; 71% yield; NMR ($CDCl_3$) δ 1.33 (d, 3 H, β-methyl), 2.40 (s, 3 H, tolyl methyl), 3.55 (s, 3 H, methyl ester), 4.51 (m, 1 H, α hydrogen), 5.12 (s) superimposed upon m at 5.13 (3 H, benzyl and β hydrogen), 5.51 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl), 7.15–7.80 (A_2B_2, 4 H, tolyl).

3d: oil; 57%yield; NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 2.49 (s, 3 H, tolyl methyl), 3.66 (s, 3 H, methyl ester), 4.01 (d, 2 H, glycyl methylene), 4.81 (m, 1 H, α hydrogen), 5.19 (s) superimposed upon m at 5.20 (3 H, benzyl and β hydrogen), 5.71 (brd, 1 H, NH), 6.98 (brd, 1 H, NH), 7.40 (s, 5 H, phenyl), 7.20–7.78 (A_2B_2, 4 H, tolyl).

***N*-Benzyloxycarbonyl-*threo*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (3e).** *threo*-β-Chloro-DL-α-aminobutyric acid methyl ester hydrochloride[5] (0.75 g, 0.4 mmol) was treated with carbobenzoxy chloride as described above for **4c**. The product was obtained as a viscous oil in 57% yield: NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 3.65 (s, 3 H, methyl ester), 4.57 (m, 2 H, α and β hydrogens), 5.18 (s, 2 H, benzyl), 5.70 (brd, 1 H, NH), 7.32 (s, 5 H, phenyl).

General Procedure for Elimination Reaction of Threonine Derivatives. The respective *N*-acyl-*O*-tosylthreonine esters **3a–d** and *N*-acyl-*erythro*-β-chloro-α-aminobutyrates **4a–f** were dissolved in ethyl acetate and 2 equiv of 1,4-diazabicyclo[2.2.2]octane (Dabco) was added. The reaction mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the organic phase was separated, washed with water, and dried over Na_2SO_4. The solvent was removed in vacuo to yield the dehydroamino acid derivatives **5**. The erythro derivatives **4** yielded a mixture of *E* and *Z* isomers of **5** (see Table I); the product mixture of *E* and *Z* isomers was analyzed by use of reported NMR spectral data;[6] complete NMR data are given in Table IV. The threonine derivatives **3** gave only the *Z* isomers of **5** (see Table III).

For the elimination reactions using 1,5-diazabicyclo[5.5.0]undec-5-ene (DBU) as base, the *N*-acyl-*erythro*-β-chloro-α-aminobutyrates **4a** and **4c** were dissolved in chloroform, DBU was added, and the reaction mixture was stirred for 1 h. The mixture was washed with 2 N HCl, saturated $NaHCO_3$, and water. The solvent was dried over $MgSO_4$ and removed in vacuo to yield product (Table II).

Reaction of Oxazoline 7 with Dabco. The oxazoline hydrochloride **7** (1.27 g, 5 mmol), prepared according to Tishler,[8] was treated with Dabco according to the general procedure described above. After the usual workup, 1.0 g (90%) of the neutral oxazoline **8** was obtained as an oil: NMR ($CDCl_3$) δ 1.32 (d, 3 H, methyl), 3.73 (s, 3 H, methyl ester), 4.90 (m, 2 H, H-4 and H-5), 7.22–8.00 (m, 5 H, phenyl).

The oxazoline **8**, upon treatment with ethereal HCl, furnished the oxazoline hydrochloride **7**, mp 117–119 °C (lit. 117–119 °C),[8] mixture melting point undepressed.

***N,O*-Ditosyl-DL-threonine Methyl Ester (9).** DL-Threonine methyl ester hydrochloride (3.4 g, 0.02 mol) in 20 mL of dry pyridine cooled to −5 °C was treated with 15.2 g (0.08 mol) of tosyl chloride in 30 mL of pyridine at a rate to maintain the temperature below −5 °C. The reaction mixture was kept at 0 °C for 2 h, stored overnight in the refrigerator, and poured into water. The solid was collected by filtration and air dried to yield 7.0 g (79%) of **9**: mp 120.5–122 °C from benzene–petroleum ether; mp of L isomer[11] 146–149 °C; NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 2.50 (s, 6 H, tolyl methyl), 3.51 (s, 3 H, methyl ester), 4.02 (m, 1 H, α hydrogen), 5.06 (m, 1 H, β hydrogen), 5.46 (brd, 1 H, NH), 7.21–8.00 (m, 8 H, tolyl aromatic).

***N*-Tosyl-*erythro*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (12).** A solution of **2**[5] (3.4 g, 0.02 mol) in pyridine was treated with 1 equiv of tosyl chloride as described above. The reaction mixture was poured into crushed ice, and the solid was collected by filtration, washed with water, and air dried. Recrystallization from benzene–petroleum ether gave 4.9 g (81%) of **12**: mp 95–97 °C; NMR ($CDCl_3$) δ 1.49 (d, 3 H, β-methyl), 2.36 (s, 3 H, tolyl methyl), 3.48 (s, 3 H, methyl ester), 4.60 (m, 2 H, α and β hydrogens), 5.51 (brd, 1 H, NH), 7.18–7.62 (m, 4 H, tolyl aromatic).

Elimination Reactions for *N*-Tosyl Threonine Derivatives. The ditosyl derivative **9** (2.2 g, 5 mmol) was treated with *N*-ethylpiperidine according to the procedure of Nakagawa[4] to yield a mixture of aziridine **10** and (*Z*)-*N*-tosyl-α-aminodehydrobutyric acid methyl ester (**11**) in a ratio of 40:60. In other experiments, the percentage of aziridine **10** varied from 40 to 91%; similar erratic yields have been reported by Atherton and Meienhofer.[11] The above mixture of **10** and **11** was treated with Dabco (1 equiv according to the amount of aziridine) in ethyl acetate at room temperature for 6 h. Workup of the reaction mixture in the usual manner yielded 1.12 g (81%) of the dehydrobutyric acid **11**, mp 117–119 °C (lit.[4] mp 118–120 °C).

N,O-Ditosyl-DL-threonine (**9**) was treated with Dabco (2 equiv) in ethyl acetate and the reaction mixture stirred overnight at room temperature. Workup in the usual manner gave the *Z* isomer **11** in 85% yield.

Treatment of *N*-tosyl-*erythro*-β-chloro-α-aminobutyric acid methyl ester (**12**) with Dabco as above gave the *Z* isomer **11** in 79% yield. Reaction of **12** with *N*-ethylpiperidine also yielded only **11**; the aziridine **10** was not detected even when shorter reaction periods were used.

***N*-Methyl-*N*-tosyl-α-aminodehydrobutyric Acid Methyl Ester.** To a solution of **11** (270 mg, 1.0 mmol) in 2 mL of dimethylformamide was added 30 mg (1.2 mmol) of sodium hydride. After the evolution of hydrogen had ceased, 0.2 mL of methyl iodide was added. The mixture was stirred at room temperature for 2 h, poured into water, and extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent in vacuo gave an oil that solidified upon standing. Recrystallization from petroleum ether gave 170 mg (60%) of product: mp 54–55 °C; NMR ($CDCl_3$) δ 1.91 (d, 3 H, β-methyl), 2.36 (s, 3 H, tolyl methyl), 2.94 (s, 3 H, *N*-methyl), 3.46 (s, 3 H, methyl ester), 7.09 (s, 1 H, vinyl), 7.18–7.60 (m, 4 H, tolyl aromatic). The position of the vinyl proton in **11** (ethyl ester) occurs at δ 6.93.[4]

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Registry No.—**1**, 62076-66-8; **2**, 62076-67-9; **3a**, 62076-68-0; **3b**, 62076-69-1; **3c**, 62078-71-1; **3d**, 62076-70-4; **3e**, 62076-71-5; **4a**, 62076-72-6; **4b**, 62076-73-7; **4c**, 62076-74-8; **4d**, 62076-75-9; **4e**, 62076-76-0; **4f**, 62076-77-1; *Z*-**5a**, 60027-58-9; *E*-**5a**, 26927-54-8; *Z*-**5b**, 60027-60-3; *E*-**5b**, 60027-54-5; *Z*-**5c**, 60027-61-4; *E*-**5c**, 60027-55-6; *Z*-**5d**, 60027-59-0; *E*-**5d**, 60027-53-4; *Z*-**5e**, 60027-63-6; *E*-**5e**, 60027-57-8; *Z*-**5f**, 60027-62-5; *E*-**5f**, 60027-56-7; **7**, 62107-39-5; **8**, 62107-40-8; **9**, 62076-78-2; **11**, 62076-79-3; **12**, 62078-72-2; benzoyl chloride, 98-88-4; benzeneacetyl chloride, 103-80-0; carbonochloridic acid phenyl methyl ester, 501-53-1; trifluoroacetic anhydride, 407-25-0; Z-Gly-OH, 1138-80-3; *N*-benzyloxycarbonyl-DL-threonine methyl ester, 62076-80-6; *N*-benzoyl-DL-threonine methyl ester, 28415-16-9; *N*-phenylacetyl-DL-threonine methyl ester, 62078-73-3; *N*-benzyloxycarbonylglycyl-DL-threonine methyl ester, 19898-19-2; *p*-toluenesulfonyl chloride, 98-59-9; *threo*-β-chloro-DL-α-aminobutyric acid methyl ester HCl, 62076-81-7; *N*-methyl-*N*-tosyl-α-aminodehydrobutyric acid methyl ester, 62076-82-8.

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Displacement Reactions of Cyclic Sulfites and Phosphates by Salts of Weak Acids Applicable to the Synthesis of Phospholipids and Other Natural Substances

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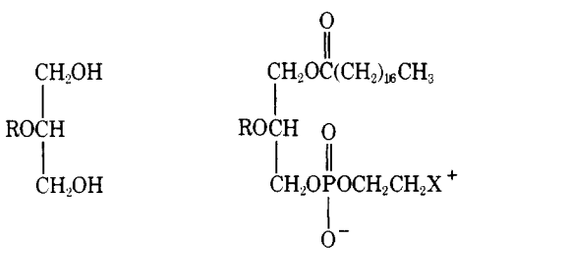
Six-membered ring cyclic sulfites **7a** derived from 2-*O*-benzylglycerol react in Me_2SO with salts of weak acids such as carboxylate and *p*-chlorophenoxide to yield 1-acyl- or 1-*O*-*p*-chlorophenoxy-2-*O*-benzylglycerols **8a**, **8b**, **8c**, and **8d** in good yields. In an analogous manner, the cyclic phenylphosphate **7b** reacts with carboxylate or phenylphosphate to yield the 1-acyl- or 1-phosphoryl-2-*O*-benzylglycerol 3-phosphates **8f** and **8h**. The potential applicability to the synthesis of glycerolphospholipids, e.g., the 2-arachidonoylphosphatidyldimethylethanolamine **2c**, and dinucleotides is demonstrated or discussed.

The structural feature present in glycerol (**1a**), i.e., the 1,3-diol system having at least one primary alcohol group, is present in natural products such as the glycerolphospholipids, sphingolipids, and also in carbohydrates that are found in oligosaccharides, glycolipids, and nucleotides. This paper describes a method which adds to other known and useful methods,[1] for the esterification and phosphorylation of the glycerol moiety.[2]

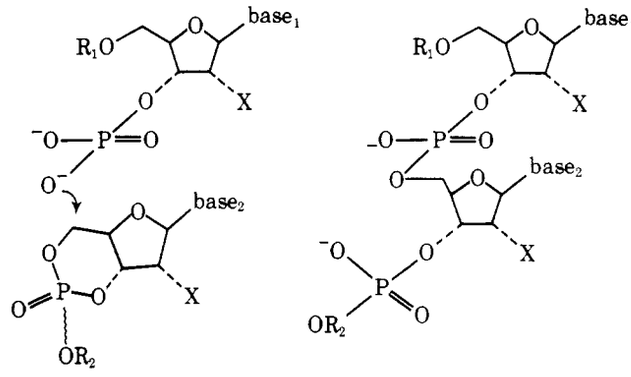
One of the purposes of this investigation was to facilitate the large-scale synthesis of glycerolphospholipids which would be esterified at C-1 and C-2 with a saturated and a polyunsaturated fatty acid, respectively. Such glycerolphospholipids play an important functional role in cell membranes in maximizing the activity of enzymes.[3] In addition, certain glycerolphospholipids, e.g., **2b**, esterified at C-2 with arachidonic acid, have been postulated as the immediate precursors of the fatty acids which are subsequently converted to prostaglandins.[4,5]



1 R	2 X	R
a H	a $N(CH_3)_3$	$CO(CH_2)_3(C{=}CCH_2)_4(CH_2)_3CH_3$
b CH_2Ph	b $NH(CH_3)_2$	H
	c $NH(CH_3)_2$	$CO(CH_2)_3(C{=}CCH_2)_4(CH_2)_3CH_3$

Another purpose of this study was to find a model reaction which may serve to indicate the potential that a nucleotide monophosphate ester may have in displacing a second cyclic 3′,5′-phenyltriphosphate ester to form a dinucleotide under relatively neutral conditions. This reaction which is under investigation may formally be represented by the general equations in Scheme I.

Scheme I



X = H or OH

R_1, R_2 = appropriate protecting group

The result of this investigation is a new method for the selective acylation or phosphorylation of the 1,3-diol system, typified by glycerol (**1a**). The method involves a new ring opening reaction of cyclic esters, which are derived from sulfurous and phenylphosphoric acid and 2-*O*-benzylglycerol (**1b**), by salts of weak acids, such as carboxylic acids, *p*-chlorophenol, and phenylphosphoric acid.

Synthesis and Stereochemistry of Cyclic Sulfite and Phosphate Esters from 2-*O*-Benzylglycerol. For the purpose of this study, 2-*O*-benzylglycerol (**1b**), which possesses a suitably protected secondary hydroxyl group, was utilized to study the formation of the corresponding cyclic esters derived from sulfurous, phenylphosphoric, and sulfuric acid.

When 2-*O*-benzylglycerol was heated with dimethyl sulfite it was converted to a mixture of diastereomeric cyclic sulfite esters which were separated by chromatography into the 1,3,2-dioxathiane 2-oxides **3** and **4**. A comparison of the NMR spectra of the isomers indicated that the predominant isomer and conformer, present as 67% of the mixture, was **3** in which the bulkier 5-benzyloxy group is in the axial position. In