which was dissolved in ether and methylated with diazomethane in the usual way. The crude diester was crystallized from methanol–water, giving pure **11**, mp 120–21°. An analytical sample was prepared by recrystallization from aqueous methanol: mp 121–122°; ν_{max} 5.80 (acetate and methyl ester) and 8.00 μ; nmr δ 3.63 (1 H, multiplet, 3α-H), 3.60 (6 H, singlet, 15-COOCH$_3$ and 17-COOCH$_3$), 2.00 (3 H, singlet, 3β-OCOCH$_3$), 2.69 (1 H, doublet, J = 2.5 cps, 14β-H), 1.26 (3 H, singlet, 18-methyl) and 0.81 (3 H, singlet, 19-methyl); mass spectrum (70 eV) m/e 394 (M^+, strong), 362 [$(M - CH_3OH)^+$, weak].

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.78; H, 8.59.

15,17-Seco-D-nor-14-isoandrostane-3β,15,17-triol (12).—To the suspension of 500 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran was added 500 mg of **11**, dissolved in 5 ml of anhydrous tetrahydrofuran, over a period of 15 min. The mixture was then heated under reflux under nitrogen for 16 hr. Excess of reagent was decomposed following the procedure of Micovic and Mihailovic.[9] It was then filtered, washed with a small amount of tetrahydrofuran and the filtrate along with the washings were concentrated under vacuum, when a crystalline solid was obtained. The mixture was diluted with water, filtered and the residue was washed thoroughly with water and dried to give 300 mg (80%) of **12**. Recrystallization from methanol gave needles: mp 263–264° (transformation at 250°); ν_{max} 2.98, 3.42, 9.55, 9.71 and 10.9 μ; nmr[$CD_3(S\rightarrow O)CD_3$] δ 0.93 (3 H, singlet, 18-methyl) and 0.70 (3 H, singlet, 19-methyl), mass spectrum (70 eV) m/e 278 $(M - 18)^+$.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 72.98; H, 10.88. Found: C, 72.78, H, 10.68.

3β-Hydroxy-16-oxa-16-nor-5α-androstane (13).—The solution of 150 mg of **12** in 5 ml of anhydrous dimethyl sulfoxide was heated at 150° for 6 hr. It was then cooled, diluted with 15 ml of water and extracted with ether. The etheral extract was washed thoroughly with water and dried over sodium sulfate. On removal of solvent, an oil was obtained, which was purified through preparative thick layer chromatography using the system ethyl acetate–benzene 15:85. After elution a crystalline solid was obtained, which was recrystallized from aqueous methanol to give needles: mp 163–164°; ν_{max} 2.85 (OH) and 9.00 μ; mass spectrum (70 eV) m/e 278 (M^+), 260 $(M - 18)^+$.

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.36; H, 10.68.

3β-Hydroxy-16-oxa-5α,14β-androstan-15-one (14).—To the suspension of 300 mg of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran was added over a period of 15 min 300 mg of **8**, dissolved in 5 ml of anhydrous tetrahydrofuran. The mixture was refluxed overnight under nitrogen. It was then cooled and the excess of reagent was decomposed by following the procedure of Micovic and Mihailovic.[9] The mixture was then filtered, washed with a small amount of tetrahydrofuran and the filtrate along with its washings was concentrated under vacuum when a crystalline solid was obtained. More solids were precipitated when 10 ml of water was added to the filtrate. The solids were collected by filtration, washed repeatedly with water and dried. Recrystallization from methylene chloride–hexane gave needles: mp 208–210°; ν_{max} 2.85 (OH) and 5.40 μ (γ-lactone); nmr δ 3.78 (2 H, singlet, 17-H's), 2.10 (1 H, doublet, J = 3 cps, 14β-H), 1.29 (3 H, singlet 18-methyl), and 0.80 (3 H, singlet, 19-methyl); mass spectrum (70 eV) m/e at 292 (M^+).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.69; H, 9.55.

Registry No.—**3a**, 19018-69-0; **3b**, 19018-70-3; **4**, 19018-71-4; **5**, 19018-72-5; **6**, 19018-73-6; **9**, 19018-74-7; **10**, 19018-75-8; **11**, 19018-76-9; **12**, 19018-77-0; **13**, 19018-78-1; **14**, 19018-79-2.

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Lead Tetraacetate Oxidation of the Oxime of Pregna-5,16-dien-3β-acetoxy-20-one[1]

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Since the lead tetraacetate promoted free-radical reaction between a secondary hydroxyl group and an otherwise nonactivated hydrogen atom was first described in the steroid series by Jeger, *et al.*,[3] many similar reactions have been reported in the literature.[4]

A modification of the method was introduced by Heusler, *et al.*,[5] who added iodine to the reaction medium. Under these conditions both alternate products and a different reaction mechanism are often observed. It was of interest to determine if similar transformations could be achieved with a hydroxyl group attached to nitrogen. As an example we selected the oxime of 3β-acetoxypregna-5,16-dien-20-one (I) (Scheme I) which could possibly lead to heterocyclic products of biological interest. Treatment of oxime I with lead tetraacetate in dry benzene and also in the presence of iodine gave a high-melting crystalline compound as the major product. A dimeric structure II was assigned to this compound on the basis of the following spectroscopic evidence (Scheme I).

In the mass spectrum of II, there are peaks at m/e 680 and 620 clearly indicating the dimeric nature of the sample with a one degree higher oxidation state than the corresponding monomer (ion m/e 680 = 2 × monomer

(1) Contribution No. 346 from the Institute of Steroid Chemistry, Syntex Research, Palo Alto, Calif.

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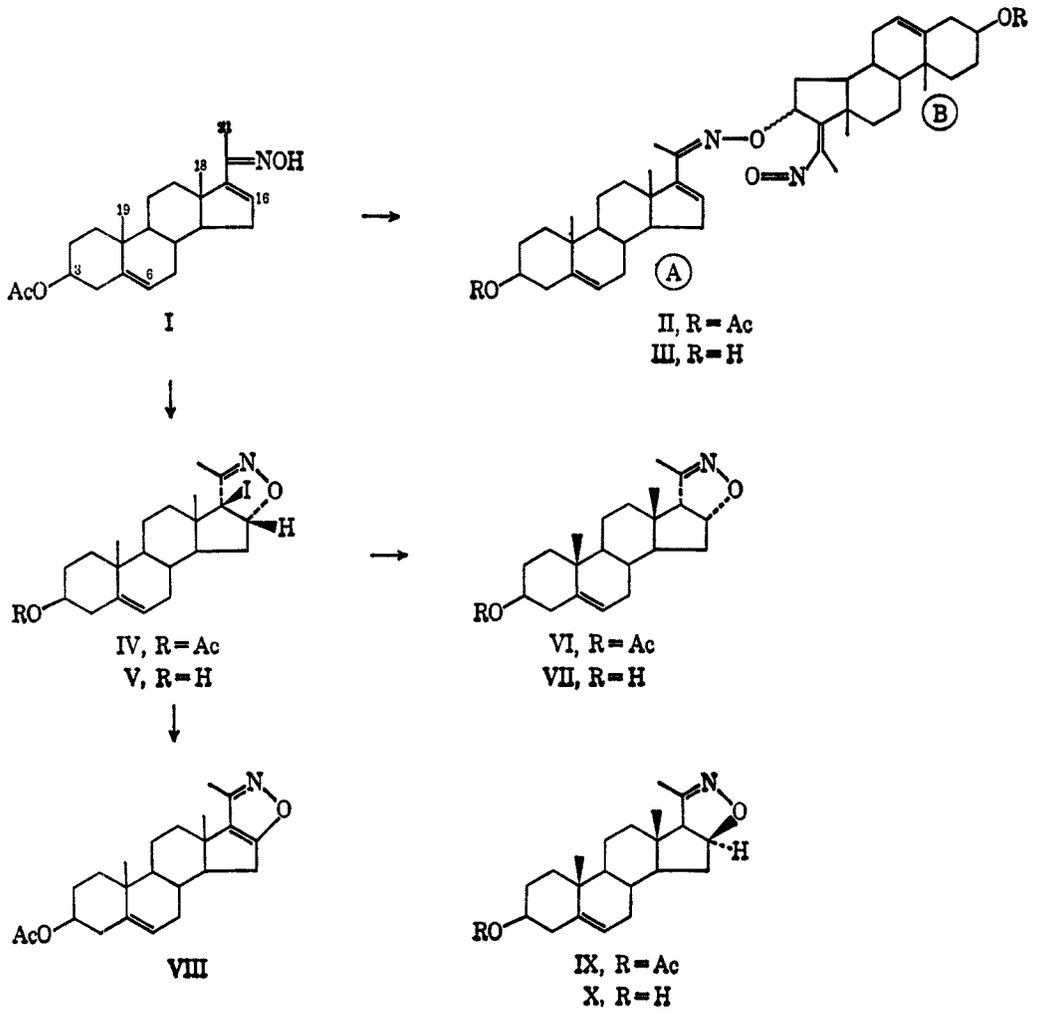
(3) G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(4) A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.* (London), 1299 (1960); A. Bowers and E. Denot, *J. Amer. Chem. Soc.*, **82**, 4956 (1960); A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(5) K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2161 (1962).

SCHEME I



I − HOAc − 2 H). As expected, a molecular ion (*m/e* 740) could not be detected due to the facile loss of acetic acid, but the presence of the two acetate groups was clearly established, *vide infra*, by nmr.

In addition to these dimeric ions, facile cleavage of the doubly activated O↔C-16 bond (a) provides ion b (*m/e* 370) irrespective of which side carries the charge, a fission which shed further light on the linkage between the two halves of the dimer. Ion b then undergoes further fragmentations, losing a methyl group (*m/e* 355), acetic acid (*m/e* 310), and the combination of the two (*m/e* 295).

The nmr spectrum of II showed two six-proton singlets at 1.03 (19-H) and 2.01 ppm (OAc) and four three-proton singlets at 0.91, 1.01, 1.97 and 1.89 ppm for the 18-H and 21-H of components A and B. The magnetic equivalence of the protons in rings A and B and of the substituents therein (3α-H, C_6-H, 3β-OAc and 19-H) and the nonequivalence of ring-D and side-chain proton resonances (16-H, 18-H and 21-H) confirmed that bonding between the two molecules had taken place in ring D, in the side chain, or in both.

Superimposing the nmr spectrum of I on the spectrum of II confirmed the assignment of the 18-H (0.91 ppm) and 21-H (1.97 ppm and 16-H (6.05 ppm) resonances of component A in structure II. The remaining two three-proton singlets at 1.01 and 1.89 ppm and the doublet at 4.81 ppm (J = 5 cps) may then be assigned to the 18-H, 21-H and 16-H resonances of component B in II, respectively. The low-field position (4.81 ppm) of the 16-H resonance of part B in II is consistent with a proton which is both allylic on a carbon atom bearing oxygen.

The stereochemistry at C-16 was not established but in view of the usual behavior of Δ^{16} steroids attack at C-16 would be expected to occur from the α side.

Formation of dimeric nitroso compounds by lead tetraacetate oxidation of aldoximes has been described previously by Kropf and Lambeck.[6] In the present case we can assume that bonding to C-16 is facilitated by the high reactivity of the Δ^{16} double bond of I.

Whereas the reactions in dry benzene gave compound II as the main product, the oxidation of oxime I with lead tetraacetate and iodine in the presence of small amounts of water led to a product (IV) which according to elemental analysis contained one atom of iodine. The mass spectrum of IV exhibited framgent ions corresponding to the loss of acetic acid (*m/e* 437) and hydrogen iodide (*m/e* 369) from an undetected molecular ion (*m/e* 497). These data suggest an empirical formula of $C_{23}H_{32}O_3NI$ for IV indicating that one hydrogen atom in I has been replaced by iodine. The absence of the vinylic 16-H resonance in the nmr spectrum (6.05 ppm in I) and the appearance of a pair of doublets (J = 6.5 and 1 cps) at 5.18 ppm indicated that cyclization has taken place at C-16.

(6) H. Kropf and R. Lambeck, *Ann.*, **700**, 1, 18 (1966); see also G. Just and K. Dahl, *Tetrahedron*, **24**, 5251 (1968).

The nature of the newly formed ring was established by dehydrohalogenation of IV with silver acetate in acetic acid yielding a known[7] isoxazole derivative VIII whose uv, nmr and mass spectral data were in good agreement with its structural assignment. It follows, therefore, that compound IV is an iodinated isoxazoline derivative. The iodine atom can be readily placed at C-17 in accordance with the chemical shift of the C-16 proton (5.18 ppm).

The assigned stereoconfiguration at positions 16 and 17 was based on the following evidence. Dehalogenation of compound IV with zinc in acetic acid gave rise to an isoxazoline derivative (VI) which was *not* identical with 3β-acetoxy-5-androstene[17ξ,6ξ-*d*]-3′-methylisoxazoline (IX), prepared by Sato and Kaneko,[8] for which the authors proposed the β configuration at C-16 and 17. The corresponding free alcohol (VII), obtained by alkaline hydrolysis of VI, was also different from compound X prepared by Sato and Kaneko.[8] Our isoxazoline VI exhibited a mass spectrum which was almost identical with that of compound IX[9] suggesting stereoisomeric relationship between the two.

The nmr spectrum of VI showed four three-proton singlets as 0.90. 1.03, 1.98 (broad, $J_{17\beta\text{-H},21\text{-H}} = 1$ cps) and 2.02 ppm for the 18-H, 19-H, 21-H, and OAc group, respectively. The 16β-H resonated at 5.05 ppm ($J_{16\beta\text{-H},17\beta\text{-H}} = 9$ cps; $J_{16\beta\text{-H},15\beta\text{-H}} = 4.5$ cps and $J_{16\beta\text{-H},15\alpha\text{-H}} = 0$ cps) and the 17β-H at 3.10 ppm ($J_{17\beta\text{-H},16\beta\text{-H}} = 9$ cps). The differences between the nmr data of compounds VI and IX were particularly noticeable for the chemical shifts or 16-H, 17-H and 18-H. The higher field resonance of the 18-H in IX (0.79 ppm) compared with that of VI (0.90 ppm) is explained by the presence of the adjacent 17β-substituent in IX.

Bis steroid II exhibits a strong positive Cotton effect ($a = +1350$), which corresponds to the summation of two chromophores, *in extenso* the unsaturated azomethine –C=CC=NO– and the –C=CN=O system.[10]

The iodoisoxazoline IV shows an intense positive Cotton effect ($a = +1353$). The 17β-iodine atom affects both the sign and the intensity of the optical properties associated with the isoxazoline VI ($a = -34$). The influence of the iodine on the Cotton effect of IV is in keeping with similar observations made with other chromophores (*e.g.*, carbonyl, etc.), in which cases it is known that an halogen atom situated next to the chromophore can affect its optical properties.

Finally, while the 16α,17α-isoxaline VI presents a weak negative Cotton effect, its β isomer IX exhibits a molecular amplitude which is much more intense ($a = -476$). Moreover, there seems to be a slight bathochromic shift in the position of the optically active transition of the isoxazoline VI, when compared with that of its isomer IX.

On the other hand, the uv spectrum of isoxazole VIII showed a bathochromic shift (λ_{max} 230 mμ) as compared with other steroidal isoxazoles.[11] This is probably due to the strain caused by the fusion of the isoxazole ring to ring D.

Experimental Section[12]

Oxidation of the Oxime of Pregna-5,16-dien-3β-acetoxy-20-one (I) with Lead Tetraacetate.—A solution of 30 g of oxime I and 40 g of lead tetraacetate in 1500 ml of dry benzene was heated under reflux for 5 hr. The reaction mixture was washed first with a concentrated solution of sodium bisulfite and then with water. After separation of the organic layer, the benzene solution was dried with anhydrous sodium sulfate and subsequently the solvent was distilled off to dryness. The dark residue (30 g) was dissolved in benzene and chromatographed on 600 g of aluminium oxide. After separation of less polar impurities, the crystalline fractions were combined and recrystallized from methylene chloride–methanol, whereby 12.5 g of the pure dimeric steroid (II) was obtained: plates; mp 260.5–262.5°; $[\alpha]_D$ +72.7°; λ_{max} 245 mμ ($E^{1\%}_{1cm}$ 265); ν_{max} 1038, 1100, 1132, 1160, 1242, 1378, 1439, 1470 and 1740 cm^{-1}. *Anal.* Calcd for $C_{46}H_{64}O_6N_2$: C, 74.55; H, 8.70; N, 3.77. Found: C, 74.41; H, 9.03; N, 3.95.

The same results are obtained if the reaction is carried out in dry benzene and in the presence of iodine.

Alkaline saponification of II leads to free alcohol III: prisms from methylene chloride; mp 282–283°; $[\alpha]_D$ +75.6°; ν_{max} 244 mμ ($E^{1\%}_{1cm}$ 292). *Anal.* Calcd for $C_{42}H_{60}O_4N_2$: C, 75.90; H, 9.55; N, 4.42. Found: C, 75.99; H, 8.83; N, 4.60.

3β-Acetoxy-17β-iodo-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (IV).—A solution of 10 g of the oxime of pregna-5,16-dien-3β-acetoxy-20-one (I), 10 g of lead tetraacetate and 10 g of iodine in 500 ml of benzene containing 1% water was heated under reflux for 5 hr. After the usual work-up, the dark oily reaction product was chromatographed on 200 g of aluminum oxide in benzene–hexane (1:1). Crystallization of the eluate in methanol yielded 3.5 g of pure 3β-acetoxy-17β-iodo-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (IV): plates; mp 164–166°; $[\alpha]_D$ +282°; λ_{max} 256 mμ ($E^{1\%}_{1cm}$ 75.5); ν_{max} 1020, 1032, 1078, 1138, 1155, 1250, 1365, 1372, 1440 and 1725 cm^{-1}. *Anal.* Calcd for $C_{23}H_{32}O_3NI$: C, 55.55; H, 6.48; N, 2.81; I, 25.51. Found: C, 56.09; H, 6.80; N, 3.41; I, 25.61.

Saponification of IV with potassium bicarbonate led to the free alcohol V: prisms from ethyl acetate; mp 194.5–196.5°; $[\alpha]_D$ +317.5°; λ_{max} 253 mμ ($E^{1\%}_{1cm}$ 75.5). *Anal.* Calcd for $C_{21}H_{30}O_2NI$: C, 55.37; H, 6.63; N, 3.07; I, 27.66. Found: C, 55.18; H, 6.60; H, 3.22; I, 28.00.

3β-Acetoxy-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (VI).—The iodo compound IV (6 g) was dissolved in 100 ml of glacial acetic acid and 10 g of pulverized zinc was added. The mixture was heated under reflux for 1 hr, filtered and then water was added. The reaction product was extracted with ether, washed with water and sodium bicarbonate solution and again with water. After drying with anhydrous sodium sulfate, the ether solution was concentrated until crystallization started. The crystals were harvested and recrystallized from methanol yielding 3.5 g of hexagonal prisms: mp 216–218°; $[\alpha]_D$ –72.90; ν_{max} 1020, 1032, 1136, 1153, 1250, 1320, 1365, 1375, 1440, 1620 and 1725 cm^{-1}. *Anal.* Calcd for $C_{23}H_{33}O_3N$: C, 79.37; H, 8.95; N, 3.76. Found: C, 79.38; H, 9.07; N, 3.90.

3β-Hydroxy-5-androstene[17α,16α-*d*]-3′-methylisoxazoline (VII).—A solution of 2 g of isoxazoline VI in 50 ml of alcohol was treated with a solution of 2 g of potassium hydroxide in 5 ml of water. The mixture was heated under reflux for 1 hr. The reaction product was precipitated in water, filtered and recrystallized from acetone–hexane giving 1.8 g of pure VII: plates; mp 239–242°; $[\alpha]_D$ –78.3°; ν_{max} 1015, 1020, 1044, 1103, 1135, 1153, 1234, 1296, 1324, 1383, 1440, 1622 and 3600 cm^{-1}. *Anal.* Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.66; H, 9.60; N, 4.33.

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(12) Melting points were recorded with a Thomas–Hoover melting point apparatus and are corrected. Rotations and infrared spectra were determined in chloroform solution and the ultraviolet spectra in ethanol solution. The nmr spectra were measured in deuteriochloroform solution with tetramethylsilane internal standard on a Varian HA-100 spectrometer and the mass spectra on an Atlas CH-4 mass spectrometer, equipped with a TO-4 ion source, at 70-eV ionizing potential. Microanalyses were performed by A. Bernhardt, Mülheim (Ruhr), Western Germany.

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

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