The **5-acetate** of V was prepared from 11.8 g of V and 6 g of anhydrous sodium acetate in 60 ml of acetic anhydride by heating for 2 hr at 95°. After standing at 25° with 400 ml of water, salt was added and the product was extracted with four 100-ml portions of ether. Distillation gave 2.3 g of 97% pure (by vpc) **5-*O*-acetyl-2,3-dideoxypentofuranose (VI)**, bp 102–103° (1 mm), $n^{20}D$ 1.4573.

Anal. Calcd for $C_7H_{12}O_4$: C, 52.54; H, 7.56. Found: C, 52.32; H, 7.60.

The infrared spectrum showed bands at 2.92 (74), 3.41 (65), 5.80 (89), 6.98 (61), 7.33 (81), 8.05 (91), 8.40 (65), 8.93 (62), 9.35 (83), 9.60 (88), 9.80 (84), 10.26 (84), 10.74 (57), 11.13 (57), 11.74 (42), and 12.20 (37) μ (per cent absorbance). The nmr spectrum (neat) showed a poorly defined peak at τ 4.7 (HOC*H*OR), a singlet at τ 5.4 (O*H*), a doublet at 6.0 (2 H, J = 4.5 cps, CH_2OAc), an irregular quintet at 6.5 (J = 4.5 cps), and a singlet at 8.0 (3 H) overlapping a multiplet at 7.9–8.3 (4 H).

The position of the acetyl group is established by a positive Benedict's test and the chemical shift of the proton in the 1 position, which would be expected to be much greater if adjacent to an acetyl group.[8] A furanose ring structure is suggested by the chemical shifts of the peaks corresponding to the protons in the 4 and 5 positions when these are compared to approximate theoretical values calculated using reference compounds of similar structure.[8] The calculated values for a pyranose structure are τ 4.8 for the 4 position and 6.5 for the 5 position, whereas a furanose structure was predicted to have values of 6.2 for the 4 position and 5.9 for the 5 position. The observed values were τ 6.5 for the 4 position and 6.0 for the 5 position. The complexity of the peaks for the 1 and 5 hydrogens is no doubt due to the presence of α and β isomers in the product.

(5-*O*-Acetyl-2,3-dideoxypentofuranosyl) 5-*O*-Acetyl-2,3-dideoxypentofuranoside.—This compound was isolated by continued fractional distillation of the residue from the distillation of 5-*O*-acetyl-2,3-dideoxypentofuranose above. A total of 2.4 g of crude material was obtained, bp 160–166° (0.8 mm), $n^{20}D$ 1.4637, undoubtedly a mixture of isomers.

Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34. Found: C, 55.96; H, 7.59.

The infrared spectrum showed bands at 3.41 (42), 5.78 (76), 6.97 (35), 7.32 (59), 8.09 (77), 8.90 (43), 9.10 (50), 9.57 (70), 10.23 (69), 11.13 (35), 11.70 (30), and 12.15 (20) μ (per cent absorbance).

Methyl 5-*O*-Acetyl-2,3-dideoxypentofuranoside.—This compound was isolated from the forerun of the distillation of crude VII. It was probably formed by acetylation of methyl 2,3-dideoxypentoside present in the crude 2,3-dideoxypentose used for the preparation of the diacetate. This suggests that methyl 2,3-dideoxypentoside is an intermediate in the hydrolysis of 1,1-dimethoxy-4,5-pentanediol to 2,3-dideoxypentose. This view is supported by the presence of sharp bands at τ 6.8 and 6.9 in the crude V, which might be due to the presence of some α- and β-methyl 2,3-dideoxypentosides. A pure sample of methyl 5-*O*-acetyl-2,3-dideoxypentofuranoside ($n^{20}D$ 1.4387) was obtained by vpc collection over the appropriate retention time range.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.78; H, 7.80.

The infrared spectrum showed bands at 3.51 (66), 5.81 (95), 6.99 (62), 7.37 (84), 8.14 (100), 8.89 (79), 9.22 (86), 9.61 (100), 10.40 (71), 11.01 (60), 11.40 (54), and 12.26 (26) μ (per cent absorbance).

1,5-*O*,*O*-Diacetyl-2,3-dideoxypentofuranose (VII).—A mixture of 10 ml of acetic anhydride and 20 ml of pyridine was cooled to 0° in an ice bath. To this was added gradually with swirling 6.7 g of crude 2,3-dideoxypentose. The resulting yellow solution was allowed to stand at room temperature for 36 hr. The pyridine, acetic acid, and excess acetic anhydride were removed by fractional distillation at 17 mm. The residual amber oil (9.3 g) was treated with 100 ml of anhydrous ether and a small amount of activated charcoal. The charcoal and a small amount of insoluble material were removed by filtration and the filtrate was warmed on a steam bath to evaporate the ether. The residual yellow oil (9.0 g) was distilled, and the three center cuts, bp 78–84° (0.17 mm), were found by vpc analysis to consist largely of 1,5-*O*,*O*-diacetyl-2,3-dideoxypentofuranose plus small amounts of 5-*O*-acetyl-2,3-dideoxypentofuranose. Attempts to obtain a pure sample of the former by vpc collection were unsuccessful owing to decomposition. The center cuts (5.8 g, 50%) were all colorless and had a strong, but not unpleasant odor, bp 79–80° (0.17 mm), $n^{21}D$ 1.4452.

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.15; H, 6.83.

The infrared spectrum showed bands at 3.46 (28), 5.82 (95), 7.00 (40), 7.35 (73), 8.13 (100), 8.85 (48), 9.11 (64), 9.57 (77), 9.93 (80), 10.42 (67), 10.72 (51), and 11.55 (46) μ (per cent absorbance). The nmr spectrum showed a poorly defined peak at τ 4.0, a doublet at 5.8 (J = 2.9 cps), a poorly defined multiplet at 6.3, and a singlet at 8.0 overlapping a multiplet at 8.2. The peak areas were in the approximate ratio 1:2:1:6:4. The values of the chemical shifts for the protons in the 4 position (τ 6.3) and the 5 position (τ 5.8) were in good agreement with the calculated values of 6.2 for the 4 position and 5.9 for the 5 position of a furanose structure.

Treatment of the diacetate VII with dry HBr in glacial acetic acid produced an amber syrup from which we did not succeed in obtaining the pure acetobromo sugar. The syrup gave a voluminous precipitate with methanolic silver nitrate and formed triethylamine hydrobromide when treated with triethylamine in toluene. Reaction with 2,4-diethoxy-5-methylpyrimidine cleaved one ethyl ether and dithyminyl mercury gave thymine as the only identified product.[9]

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12-Chloro-*cis*-9-octadecenyl Chloride

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In developing syntheses of hindered amides of ricinoleic (12-hydroxy-*cis*-9-octadecenoic) acid, we noted claims[2–4] regarding the preparation of ricinoleoyl chloride (presumably 12-hydroxy-*cis*-9-octadecenyl chloride) from this acid and thionyl chloride. We found, as expected from the known reactions of alcohols and thionyl chloride,[5] that the principal monomeric product in this case is a chloro acid chloride. If this reaction proceeded as expected, the product would be 12-chloro-*cis*-9-octadecenyl chloride (I). This chloro acid chloride, incompletely characterized, was described by Ulrich[6] who obtained it by reaction of ricinoleic acid with phosphorus pentachloride. The alcohol function also was converted to the related bromide with hydrogen bromide[7] or phosphorus pentabromide,[8] and Grigor, *et al.*,[9] reported that unstable 12-chloro esters

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were obtained from the reaction of thionyl chloride with methyl ricinoleate or its *trans* isomer.

It has been suggested that the rearrangements reported in the reactions of some C^{14}-labeled secondary aliphatic alcohols with thionyl chloride proceed *via* ion pairs.[10] Since the homoallylic structure of ricinoleic acid conceivably would stabilize such rearrangements in a reaction with thionyl chloride, and since the actual position and/or configuration of the chloro group in the products from this reaction were not unequivocally established,[6,9] we have sought to establish the structure (s) of the the chloro acid.

(+)-12-Hydroxy-*cis*-9-octadecenoic acid was treated with thionyl chloride as directed.[3,4] After excess thionyl chloride was removed, the crude, dark product was examined in the infrared and analyzed for chlorine. Both ester carbonyl (5.8 μ) and acid chloride carbonyl (5.6 μ) absorptions were observed, with the former estimated as about a 10% concentration of the latter. No hydroxyl absorption was noted. The chlorine content was about 2.5% lower than theory for monomeric chloro acid chloride. Simple distillation of the crude product at reduced pressure was accompanied by some decomposition as noted for the esters.[9] The distilled product had absorption only for acid chloride carbonyl (5.6 μ) and a chlorine content slightly below theoretical. The residue contained high-boiling material, which exhibited considerable infrared absorption in the ester carbonyl region, in addition to acid chloride carbonyl. No attempt was made to further characterize this residue. Small samples of the acid chloride were converted to amide or methyl ester. The derivatives contained chlorine in nearly the calculated amount, and had the spectral features expected.

On attempted hydrolysis with dilute carbonate solution of the distilled acid chloride dissolved in ether at room temperature, considerable symmetrical anhydride (typical infrared bands at 5.52, 5.75, and 9.68 μ) apparently formed, and some dehydrohalogenation occurred (increase in ultraviolet absorption at 231 mμ). Hydrolysis without these side reactions occurred slowly on exposure of the acid chloride to moist air. The hydrolysis products were ozonized and oxidized by Bailey's procedure[11] to yield oily mixtures of two major components plus several minor impurities. The solid compound (V) isolated from the mixtures was identified as azelaic acid by melting point and by glpc analysis after esterification. The oily component obtained from ozonolysis of the moist air hydrolysis product IIb was >95% 3-chlorononanoic acid (VIb) (glpc of methyl ester VII), but the product (VIa) was of somewhat lower purity (estimated as about 90%) when the partially dehydrohalogenated acid–anhydride mixture IIa was ozonized. Guest[12] has prepared (±)-3-chlorononanoic acid and some of its derivatives, but apparently the optically active isomer has not been described. If the reaction with thionyl chloride occurred by an SNi reaction,[5] a chloride with the same configuration as the parent alcohol would be expected. However, in view of the difficulties inherent in attaining optical purity of chlorides *via* the thionyl chloride route with active alcohols, it is unlikely that our sample is optically pure. Our methyl 3-chlorononanoate (VII) has $[\alpha]^{27}D$ +3.06° and the rotation increases with decreasing wavelength.

Nmr spectral analysis of the chloro acid IIb, its methyl ester IIIb, and of a crude chloro acid methyl ester[9] prepared in boiling thionyl chloride revealed that only unsaturated structures attributable to a β-chloro olefin grouping were present within experimental limits. Further, the methyl 3-chlorononanoate obtained on ozonolysis showed no detectable proton absorption for an α-chloro acid structure. Thus, under the conditions used here, no evidence was obtained suggesting that rearrangement occurred during reaction of the alcohol function with thionyl chloride. Some racemization probably occurred. Ord measurements on methyl 12-chloro-*cis*-9-octadecenoate led to $[\alpha]^{27}D$ +4.2° and the rotation steadily increased with decreasing wavelength. Under the same conditions methyl 12-hydroxy-*cis*-9-octadecenoate has $[\alpha]^{27}D$ +7.1° and its rotation increases at shorter wavelengths.

Experimental Section[13]

12-Chloro-*cis*-9-octadecenyl Chloride (I).—12-Hydroxy-*cis*-9-octadecanoic acid[14] (70 g, 0.23 mole), prepared from distilled methyl ester,[15] was introduced at *ca.* 2 g/min into a replicate of the apparatus[3,4] which contained a large excess of boiling thionyl chloride (Eastman, redistilled bp 76.2–76.5° uncor). The crude, dark product was reduced to constant weight on a rotary evaporator at 75° *in vacuo*. Yield was 77 g; theory is 78 g for chloro acid chloride. Principal infrared bands in CCl_4 were observed at 3.42 (s), 3.52 (s), 5.58 (s), 5.80 (m), 6.86 (m), and 14.8 (m) μ. Short-path distillation of 25 g gave *ca.* 12.5 ml of product bp 160–170° (0.4–0.6 mm). Gas evolution suggested that decomposition occurred. The pot residue contained material with nearly equivalent ester (5.8 μ) and acid chloride (5.6 μ) carbonyl absorptions. The distillate fractions had $n^{27}D$ 1.4720–1.4725; lit.[4] $n^{25}D$ 1.4759. Repetition of this synthesis resulted in 70.5 g of crude product with $n^{24}D$ 1.4757.

Anal. Calcd for $C_{18}H_{32}OCl_2$: Cl, 21.2. Found: Cl, 18.7. Distillation as above gave a fraction, bp 162–163° (0.25–0.27 mm), $n^{22}D$ 1.4742. Found: Cl, 20.4. Ultraviolet analysis (c ~0.001 g/ml; l = 0.011 cm) showed conjugated diene was <2% from a_{231} = 0.02 compared with monoene a_{185} = 0.39.

12-Chloro-*cis*-9-octadecenoic Acid (IIa).—A 2.2-g distilled sample of I was partially hydrolyzed by stirring for 2 hr at 25° in ether solution in the presence of excess 1 *M* potassium carbonate solution. Acidification, washing, drying, and evaporation of the solvent gave 1.75 g of mobile liquid. Infrared bands (CCl_4) were at 3.42 (s), 3.52 (s), 3.52 (m), 5.52 (m), 5.72–5.78 (m, doublet?), 5.88 (m), 9.68 (s), and 10.35 (w) μ. Ultraviolet absorption (c 0.00145 g/ml, l = 0.011 cm) was a_{231} = 0.075 and a_{185} = 0.627 indicating an estimated 4% conjugated diene content.

IIb.—Another distilled sample of I loosely stoppered in the refrigerator slowly hydrolyzed. Principal carbonyl absorption was at 5.88 μ. The nmr spectrum had the expected absorption bands including a multiplet for two olefinic protons at τ 4.58 and a quintet for one proton ($H_2CC\mathit{H}ClCH_2$) centered at 6.20.

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(13) Infrared spectra were measured on a Perkin-Elmer 137 in CS_2 or CCl_4 solutions or as thin films. Ultraviolet spectra were obtained in cyclohexane with an extended-range Beckman DK-2 spectrophotometer. Glpc were carried out with a F & M Model 700 dual thermal conductivity instrument on 3 ft × 1/4 in. columns of 10% ECNSS-S on 100–120 mesh Gaschrom-P with a He flow of *ca.* 50 ml/min and with various temperature programs. Nmr spectra referred to tetramethylsilane were obtained in CCl_4 with Varian A-60 or HR-60 instruments. Ord spectra were observed in methanol in a Cary Model 60 spectropolarimeter. Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

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No proton absorption was observed for ($CH_2CHClCH{=}CH$) which would be expected in the τ 5.5–6.0 region. No maximum for conjugated diene was observed in the ultraviolet and the concentration of this impurity was estimated as <2%.

Methyl 12-Chloro-*cis*-9-octadecenoate (IIIa).—Absolute methanol (5 ml) was mixed with 1 g of distilled I and, with ice cooling, 1 ml of dry pyridine was added dropwise. The mixture was heated under refluxing conditions for 30 min, cooled, dissolved in ether, and extracted with dilute hydrochloric acid, 1 *M* potassium carbonate, and water. An oily residue remained after evaporation of the solvent.

Anal. Calcd for $C_{19}H_{35}ClO_2$: C, 68.95; H, 10.66; Cl, 10.71. Found: C, 69.6; H, 10.7; Cl, 9.86.

Infrared bands (CCl_4) were typical for long-chain *cis*-unsaturated esters except for a slight *trans* band at 10.35 μ. Ultraviolet analysis permitted an estimate of *ca.* 3% conjugated diene. Evidence pointed toward dehydrohalogenation during esterification.

IIIb.—A 200-mg sample of IIb was esterified in ethyl ether–methanol with a slight excess of diazomethane. The product was of >98% purity by glpc analysis. The ORD spectrum at 27° (*c* 1.54, methanol) has the following features: $[\alpha]_{589}$ +4.5°, with a plain positive curve reaching $[\alpha]_{350}$ +21.4°. The parent methyl 12-hydroxy-*cis*-9-octadecenoate (*c* 1.68, methanol; *l* = 1 cm) has $[\alpha]^{27}_{589}$ +7.1° and has been reported to have a plain positive curve becoming levorotatory at low wavelength.[16]

IIIc.—Methyl 12-hydroxy-*cis*-9-octadecenoate (31 g, ~0.1 mole) was dropped into refluxing thionyl chloride (36 ml, ~0.5 mole) over a 30-min period. Essentially no hydroxy acid ester peak was detected on immediate glpc analysis; several impurities were formed that had shorter retention times than the principal product. Nmr analysis revealed that some addition of HCl to the olefin had apparently occurred, but no absorption for $CH_2CHClCH{=}CH$ was detected.

12-Chloro-*cis*-9-octadecenamide (IV).—Distilled I (0.3 g) in dry ether was cooled in ice as anhydrous ammonia was bubbled through for 30 min (white solid). The solution was held for 1 hr at room temperature, then repeatedly extracted with water and dried over magnesium sulfate, and the solvent was evaporated to yield 0.28 g of white wax. Recrystallization of the wax from petroluem ether (bp 60–70°) gave a white solid, mp 64.0–65.2°.

Anal. Calcd for $C_{18}H_{34}ClNO$: Cl, 11.22; N, 4.43. Found: Cl, 10.6; N, 4.43.

Infrared absorption ($CHCl_3$) bands were those expected for a long-chain unsubstituted amide.

Ozonolysis.—One gram of IIa was ozonized at −5° in 25 ml of 4:1 acetic acid–formic acid and oxidized with 2 ml of 30% hydrogen peroxide under refluxing conditions. Evaporation of the solvent *in vacuo* led to products that were washed repeatedly with commercial pentane leaving a residue of crude azelaic acid (Va), mp 99–103°. Evaporation of the washings and vacuum distillation of a portion of the residue (15-cm jacketed semimicro column) afforded a fraction, bp 79° (0.01 mm), $n^{23.5}D$ 1.4488.

Anal. Calcd for 3-chlorononanoic acid (VIa) $C_9H_{17}ClO_2$: C, 56.1; H, 8.90; Cl, 18.4. Found: C, 56.5; H, 8.92; Cl, 16.6.

Crude Va was washed with cold diethyl ether and recrystallized from the same solvent leading to product, mp 104.5–106.0° (authentic azelaic acid has mp 106.5°).

Ozonlysis of 1.5 g of IIb and separation as above gave 1.0 g of oily product and 0.78 g of solid azelaic acid (Vb). The oil, cooled to −10° in 10 ml of pentane, yielded an additional 0.09 g of solid. Evaporation of the filtrate afforded 0.92 g of acrid oil (VIb). Esterification of the solid Vb and glpc analysis revealed 95% dimethyl azelate, 3% VII, and *ca.* 2% other esters.

Methyl 3-Chlorononanoate (VII).—Crude VIb (0.2 g) was esterified (methanol–1% H_2SO_4). Analysis (glpc) of the crude product revealed *ca.* 92% VII, 4% dimethyl azelate and 4% shorter chained esters. The nmr spectrum was consistent with this analysis and no proton absorption for α-chloro acid ester was detected. The ord spectrum at 27° (*c* 0.85, methanol; *l* 1 cm) showed $[\alpha]_{589}$ +3.06°, $[\alpha]_{500}$ +5.29°, $[\alpha]_{400}$ +8.24°, $[\alpha]_{350}$ +11.2°, $[\alpha]_{300}$ +14.2°, and $[\alpha]_{275}$ +20.6°.

Acknowledgment.—The authors are indebted to R. G. Binder for glpc analyses, to W. Gaffield for ord measurements, and to G. Secor and L. White for microanalyses.

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Chemistry of Cephalosporin Antibiotics. VI.[1] Carbamate Formation in Aqueous Bicarbonate Solutions of 7-ACA

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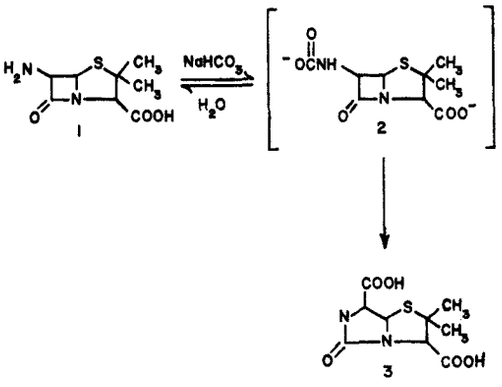
The penicillin nucleus, 6-APA (**1**), is transformed into 8-hydroxypenillic acid (**3**) by the action of carbon dioxide under a variety of conditions[2–5] which include solution of the 6-APA in aqueous bicarbonate at room temperature.[2,3] The suggested mechanism[4] for this conversion postulates the intermediacy of a carbamate (**2**) which subsequently undergoes a penillic acid type rearrangement.[6] (See Scheme I.)

SCHEME I



Although the analogous reaction of the cephalosporin nucleus, 7-ACA (**4**), with carbon dioxide has not been reported, nmr spectra of 7-ACA in D_2O with added sodium bicarbonate indicated formation of the carbamate (**5**).

With a fourfold molar excess of sodium bicarbonate, H-7 appears as a doublet at δ 5.46 coupled to H-6 at δ 5.06 (J = 4.5 cps). Both the H-6 and H-7 doublets integrate for one proton compared to the AB patterns for the methylene group attached to C-3 (δ 4.81) and the protons adjacent to sulfur at C-2 (δ 3.52), both of which integrate for two protons. The chemical shifts for H-6 and H-7 are comparable to those noted for cephalosporin derivatives where H-7 is α to an amide linkage.[7]

When only 1 molar equiv of sodium bicarbonate is present, the signal at δ 5.46 disappears and a new doublet is observed at δ 4.75 coupled to the H-6 proton at δ 5.06 (J = 4.5 cps). In intermediate concentra-

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