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.

(16) T. H. Applewhite, R. G. Binder, and W. Gaffield, *Chem. Commun.*, 255 (1965).

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

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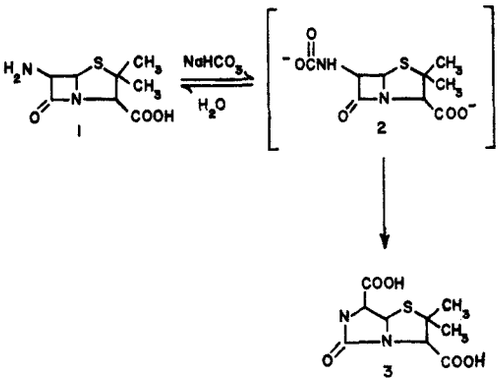
The penicillin nucleus, 6-APA (**1**), is transformed into 8-hydroxypenillic acid (**3**) by the action of carbon dioxide under a variety of conditions[2–5] which include solution of the 6-APA in aqueous bicarbonate at room temperature.[2,3] The suggested mechanism[4] for this conversion postulates the 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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(3) A. Ballio, *et al.*, *ibid.*, **191**, 909 (1961).
(4) D. A. Johnson and G. A. Hardcastle, Jr., *J. Am. Chem. Soc.*, **83**, 3534 (1961).
(5) P. L. Tardrew and M. J. Johnson, *J. Biol. Chem.*, **234**, 1850 (1959).
(6) "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 453.
(7) G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1595 (1965).

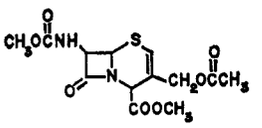
tions of bicarbonate, signals at both δ 5.46 and 4.75 are observed.[8]

The postulation of an equilibrium between **4** and **5**, with **5** predominating at high concentrations of bicarbonate and **4** at low concentrations, clearly explains the observed nmr behavior. Any alternative explanation would have to consider either rearrangements of **4** in aqueous bicarbonate or epimerization at H-7.

Epimerization at position 7 is unlikely since (a) solutions of **4** at differing bicarbonate concentrations exhibit the same specific rotation and (b) there is no deuterium incorporation at C-7 in D_2O–bicarbonate solutions of **4**.

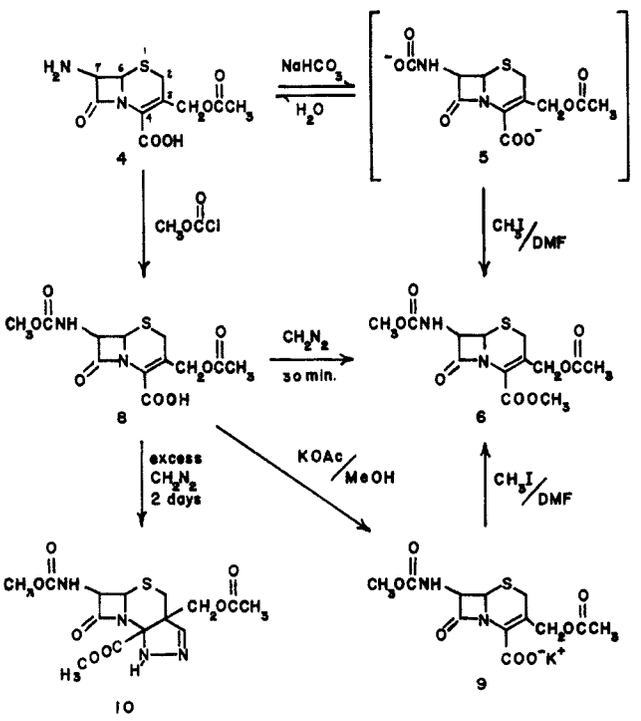
Direct chemical verification of carbamate (**5**) formation in aqueous bicarbonate solutions of **4** involved the preparation of the methylcarbamate methyl ester (**6**) by treatment of the solid obtained from a lyophilized bicarbonate solution of **4** with methyl iodide in dimethylformamide. Chromatography of the reaction product on silica gel gave the Δ^2 isomer (**7**) although nmr and ultraviolet spectra of the crude product showed none of the Δ^2 isomer (**7**) present and were consistent with the Δ^3 isomer (**6**). Thus, isomerization of **6** to **7** has occurred during silica gel chromatography.

SCHEME II



7

The structure of **6**, although consistent with all physical data including high-resolution mass spectrometry, was demonstrated by its preparation from the action of diazomethane on the corresponding acid (**8**) obtained from **4** by acylation with methylchloroformate. Alternatively, the potassium salt (**9**), obtained from **8** by the action of potassium acetate in methanol, upon methylation with methyl iodide in dimethylformamide gave the desired methyl ester methylcarbamate (**6**). This material upon chromatography on silica gel gave the Δ^2 isomer (**7**).



10

When the free acid (**8**) was permitted to stand for 2 days in a solution containing excess diazomethane, a crystalline compound assigned the pyrazoline structure **10** was formed and isolated by Florisil chromatography. (See Scheme II.) An nmr spectrum of this derivative showed the same general patterns as **6** with three notable exceptions: (a) the AB pattern assigned to the hydrogens adjacent to sulfur occurred at δ 3.05 *vs.* δ 3.50 for **6**; (b) the AB pattern assigned to the methylene group attached to C-3 occurred at δ 4.32 *vs.* δ 4.99 for **6**; and (c) two additional singlets at δ 5.70 and 6.90 were present, the lower field singlet being exchangeable with D_2O. This nmr evidence coupled with an ultraviolet absorption maximum of 285 mμ (ϵ 9030) is inconsistent with the spectral properties of Δ^1-pyrazolines.[9] Furthermore, high-resolution mass spectrometry with elemental mapping of fragments confirmed the molecular weight and empirical formula of $C_{14}H_{18}N_4O_7S$ and showed no peak at M − 28 which would be expected from loss of nitrogen from the Δ^1-pyrazoline isomer.

Experimental Section[10]

7-ACA Carbamate Formation in Aqueous Bicarbonate.—An aqueous solution of 5.0 g (18 mmoles) of 7-ACA (**4**) and 6.0 g (72 mmoles) of sodium bicarbonate was lyophilized. The resulting white powder containing **5** was suspended in 200 ml of dimethylformamide and stirred for 1 hr at room temperature with 23.0 g (160 mmoles) of methyl iodide. After removal of most of the solvent under reduced pressure, the mixture was diluted with water and extracted twice with ethyl acetate. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 1.9 g of a brown oil. Chromatography of the oil on 50 g of Florisil (60–100 mesh) with ethyl acetate–methylene chloride yielded 1.4 g of **6** as a yellow oil: R_f 0.5 (silica gel, ethyl acetate); λ_{max}^{EtOH} 261 mμ (ϵ 7000). Further chromatography of 477 mg on 10 g of silica gel (E. Merck) with 10% ethyl acetate–benzene gave 248 mg of **7** as a clear oil which crystallized from methanol–ether–hexane: mp 120–121°; R_f 0.35 (20% ethyl acetate–benzene on silica gel); λ_{max}^{EtOH} 230 mμ (ϵ 7060) and 247 mμ (ϵ 7400); nmr peaks ($CDCl_3$) at δ 2.06 (3 H singlet, CH_3COO), at 3.72 and 3.80 (two singlets, 3 H each, CH_3OCONH and $COOCH_3$), at 4.65 (2 H singlet, CH_2OAc), at 5.03 (1 H doublet, J = 2 cps, H-3), at 5.25 (1 H doublet, J = 4.5 cps, H-6), at 5.58 (1 H quartet and 1 H doublet overlapping, H-7 and NH), and at 6.45 (1 H doublet, J = 2 cps, H-2); mol wt 344 and empirical formula established by high-resolution mass spectrometry; infrared absorption at 5.61 (β lactam C=O) and 5.72 μ (ester C=O).

Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 45.34; H, 4.69. Found: C, 45.37; H, 4.80.

(8) Such anomalous nmr behavior has been noted for sodium 7-aminocephalosporanate.[7] No explanation for this behavior was advanced by these authors.

(9) T. V. Van Auken and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **84**, 3736 (1962).

(10) Melting points were taken on a Mel-Temp apparatus. A Perkin-Elmer Infracord was used to obtain the infrared spectra. Ultraviolet spectra were determined by W. Halcomb on a Cary recording spectrometer (Model 15). Nmr spectra were obtained by L. Spangle on a Varian HA-60 nmr spectrometer. The chemical shifts are reported as δ values in ppm relative to TMS = 0 for deuteriochloroform solutions and sodium 2,2-dimethyl-2-silapentane 5-sulfonate (DSS) = 0 for D_2O solutions. High-resolution mass spectra were determined by Dr. W. Hargrove and G. Maciak on a CEC (Model 21-110A-1) high-resolution mass spectrometer. Microanalyses were performed by W. L. Brown, C. Ashbrook, H. Hunter, and R. Meister.

7-Methoxycarbamidocephalosporanic Acid (8).—To a solution of 4.0 g (15 mmoles) of 7-ACA (4), 70 ml of water, 70 ml of acetone, and 1.5 g (16 mmoles) of triethylamine at −10° was added dropwise with stirring 1.4 g (15 mmoles) of methyl chloroformate. The mixture was stirred for 2 hr at room temperature with dropwise addition of triethylamine to maintain a clear solution. After removal of most of the acetone under reduced pressure, the aqueous portion was layered with ethyl acetate, chilled to 15°, and the pH adjusted to 2.3 with 2 *N* hydrochloric acid. The layers were separated; the organic layer was filtered, dried (Na_2SO_4), and evaporated under reduced pressure to give 3.3 g (69%) of 8 as a light yellow solid which was used without further purification: nmr peaks ($CDCl_3$) at δ 2.10 (3 H singlet, CH_3COO), at 3.52 (2 H AB pattern, J_{AB} = 19 cps, CH_2S), at 3.75 (3 H singlet, CH_3OCONH), at 5.02 (1 H doublet, J = 4.5 cps, H-6), at 5.04 (2 H AB pattern, J_{AB} = 14 cps, CH_2OAc), at 5.80 (2 H unresolved, H-7 and NH), and at 9.17 (1 H singlet, COOH).

Methyl-7 Methoxycarbamidocephalosporanate (6). A.—To a solution of 1.0 g (3.0 mmoles) of 8 in methylene chloride was added excess diazomethane (prepared from N-nitroso-N-methylurea and distilled) in ether at −10°. After 30 min at room temperature the solvents were removed under reduced pressure to give 850 mg of 6 as a yellow solid. The crude product was dissolved in methylene chloride and washed three times with 5% bicarbonate, dried (Na_2SO_4), and evaporated under reduced pressure to afford 533 mg of a yellow solid. This solid was chromatographed on 10 g of Florisil (60–100 mesh) with 10% ethyl acetate–benzene to give 399 mg of 6 as a pale yellow glass which was crystallized from ethyl acetate–ether to give 108 mg of 6 as white needles: mp 126–127°; λ_{max}^{EtOH} 261 mμ (ε 7500); infrared absorption at 5.59 (β-lactam C=O) and 5.78 μ (ester C=O); nmr peaks ($CDCl_3$) at δ 2.08 (3 H singlet, CH_3COO), at 3.50 (2 H AB pattern, J_{AB} = 18 cps, SCH_2), at 3.75 and 3.86 (two singlets, 3 H each, CH_3OCONH and $COOCH_3$), at 4.96 (1 H doublet, J = 4.5 cps, H-6), at 4.99 (2 H AB pattern, J_{AB} = 14 cps, CH_2OCONH), and at 5.64 (2 H unresolved pattern, H-7 and NH); mol wt 344 and empirical formula established by high-resolution mass spectrometry.

Anal. Calcd for $C_{13}H_{16}N_2O_4S$: C, 45.35; H, 4.69. Found: C, 45.54; H, 4.81.

B.—To 625 mg (1.9 mmoles) of 8 in methanol was added a solution of 186 mg (1.9 mmoles) of potassium acetate in methanol. Cooling to −10° followed by addition of isopropyl alcohol gave 450 mg (72%) of 9 as an off-white powder: nmr peaks (D_2O) at δ 2.10 (3 H singlet, CH_3COO), at 3.53 (2 H AB pattern, J_{AB} = 19 cps, CH_2S), at 3.72 (3 H singlet, CH_3OCONH), at 4.82 (2 H AB pattern, J_{AB} = 13 cps, CH_2OAc), at 5.12 (1 H doublet, J = 4.5 cps, H-6), and at 5.54 (1 H doublet, J = 4.5 cps, H-7); Treatment of this powder with methyl iodide in dimethylformamide as described above gave the methyl ester 6. Chromatography of 6 as prepared above on Merck silica gel gave the Δ^2 isomer (7).

3a-Acetoxymethyl-8a-carbomethoxy-6-methoxycarbamidopyrazolino[4,5-*c*]cepham (10).—To a solution of 2.0 g (6.1 mmoles) of 8 in methylene chloride was added excess diazomethane in ether at −10°. After standing at room temperature for 2 days, the solution was evaporated under reduced pressure to give 512 mg of a yellow solid which was chromatographed on silica gel to give 260 mg of 10: mp 91–120° dec; λ_{max}^{EtOH} 285 mμ (ε 9030); infrared absorption at 5.61 (β-lactam C=O) and 5.71 μ (ester C=O); nmr peaks ($CDCl_3$) at δ 2.08 (3 H singlet, CH_3COO), at 3.05 (2 H AB pattern, J_{AB} = 14 cps, SCH_2), at 3.73 and 3.89 (two singlets, 3 H each, CH_3OCONH and $COOCH_3$), at 4.32 (2 H singlet, CH_2OAc), at 4.86 (1 H doublet, J = 4.5 cps, H-6), at 5.20 (1 H quartet, J = 4.5 cps and 9.0 cps, H-7), at 5.70 (1 H singlet, pyrazoline CH=N), at 5.88 (1 H doublet, J = 9.0 cps, NH) and at 6.90 (1 H singlet, pyrazoline NH); mol wt 386 and empirical formula confirmed by high-resolution mass spectrometry.

Anal. Calcd for $C_{14}H_{18}N_4O_7S$: C, 43.40; H, 4.67; N, 14.50. Found: C, 43.51; H, 4.82; N, 14.05.

Acknowledgment.—The authors wish to express their appreciation to Drs. Robert B. Morin and Edwin H. Flynn for their interest and encouragement during the course of this investigation.

Steroids. CCXCVIII.[1] Solvolytic Reactions with 19-Tosyloxy Δ^5-Steroids. Stereochemistry of a Cyclopropylcarbinol Solvolysis Product

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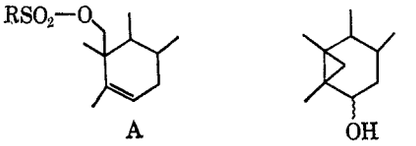
The 19-sulfonate esters of various 19-hydroxy Δ^5-steroids undergo buffered solvolysis with participation of the π electrons of the 5,6 double bond to afford 6-hydroxy-5β-19-cyclo steroids (A → B).[3–5] The stereochemistry of the 6-hydroxyl group of the latter system has never been established by unequivocal chemical methods. Earlier reports concerning the rearrangement assigned the 6α configuration to the hydroxyl group.[3–5] Tadanier reassessed the stereoelectronic factors operative during this rearrangement and concluded that the substituent introduced at C-6 is probably β oriented.[6,7] The availability in these laboratories of suitable reference compounds of assured stereochemistry[8] prompted an attept to resolve this equivocal situation on a chemial basis. Results presented below establish the 6β configuration.



A B

As previously reported, chromic acid oxidation of 3β,6ξ-dihydroxy-5β-19-cycloandrostan-17-one 3-acetate[3] (a solvolysis product derived from 3β,19-dihydroxyandrost-5-en-17-one 3-acetate 19-tosylate) yielded 3β-hydroxy-5β-19-cycloandrostane-6,17-dione 3-acetate (**1a**).[9] When this diketone **1a** was reduced with lithium aluminum hydride a triol, mp 203–204°, was obtained in good yield. Direct lithium aluminum hydride reduction of the solvolysis product afforded a second triol, mp 184–185°, presumably differing from the higher melting triol only in the configuration of the 6-hydroxyl group.

Identification of the foregoing triols was achieved by comparison with an authentic sample of 5β-19-cycloandrostane-3β,6β,17β-triol (**1b**), which was prepared by a three-step sequence from 3β,6β-dihydroxy-5β-19-cycloandrostan-17-one 3-tetrahydropyranyl ether (**1c**).[8] The synthetic route to the latter employs lead tetraacetate oxidation of a 19-hydroxy Δ^5-steroid to the

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(2) Syntex Postdoctoral Fellow, 1965–1966.

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(7) Published nmr data[3,4] permit only the definition of the 6 substituent as being axially or pseudoaxially oriented. Then, according to whether ring B is a boat or half-chair, this substituent must have the 6α or 6β configuration, respectively.

(8) R. Ginsig and A. D. Cross, *J. Org. Chem.*, in press.

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