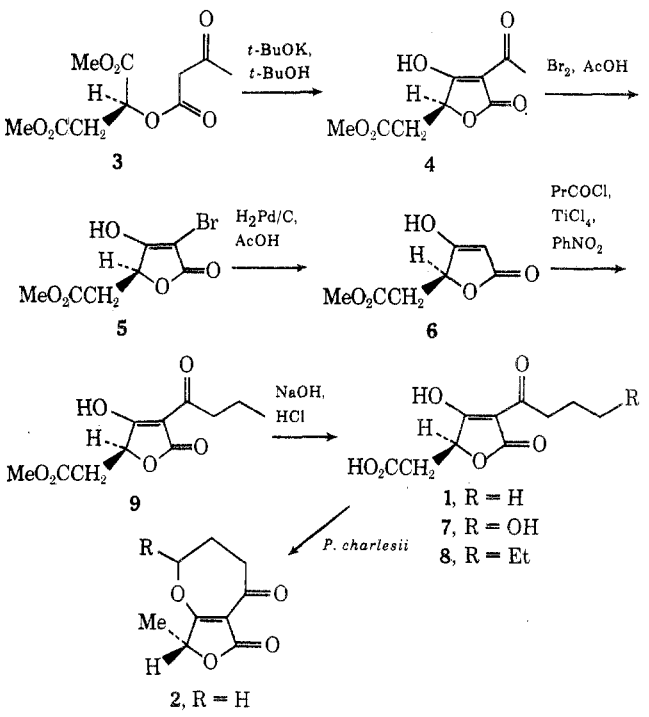
Total Synthesis of a γ-Carboxymethyltetronic Acid. (S)-Carlosic Acid

Summary: The first total synthesis of a naturally occurring mold tetronic acid with correct absolute configuration is described, as well as a possible biogenetic precursor for the entire family.

Sir: In recent biosynthetic studies,[1] we demonstrated that carlosic acid (**1**) was the major precursor of (*R*)-carolic acid (**2**) in *Penicillium charlesii*. We noted that no synthetic work had been done on any of the mold tetronic acids bearing the γ-carboxymethyl substituent. Furthermore, the reported total syntheses in the γ-methyl series, *viz.*, (±)-carolic acid[2] and (±)-carolinic acid,[3] were not applicable to either work with chiral compounds or isotopic labeling.[4] This communication describes the first example of a total synthesis of a mold tetronic acid in its correct absolute configuration and incorporates all of the desirable features described above.

The key step in the synthesis involved the cyclization of **3**, which was formed in 80% yield from dimethyl (*S*)-malate and diketene (Et_3N catalyst, PhH). The nmr spectrum of **3** was similar to the starting ester. In addition to the malate moiety [δ 3.67 (3 H, s, ester), 3.72 (3 H, s, ester), 2.90 (2 H, d, J = 6 Hz, methylene), and 5.47 (1 H, t, J = 6 Hz, methine)], new signals appeared at δ 2.25 (3 H, s, acetyl) and 3.50 (2 H, s, methylene) ($CDCl_3$) for the acetoacetyl group. Compound **3** was very thermolabile, and had to be purified by chromatographic means (alumina). The cyclization of **3** to **4** had to be carried out at a low temperature; otherwise mainly dimethyl fumarate was obtained (with concomitant loss of CO_2 and acetone). Treatment of **3** with *t*-BuOK in *t*-BuOH at the freezing point effected a 39% yield of **4** in which the acetoacetyl methylene signal and the ester signal at δ 3.72 were no longer present. In addition to nmr signals at δ 2.38 (3 H, s, acetyl), 3.67 (3 H, s, ester), 2.72 (2 H, m, methylene), and 4.57–4.75 (1 H, m, methine), a new signal appeared at δ 8.42 (1 H, s, enol) ($CDCl_3$). The bromination of **4** to **5** had to be carried out rapidly owing to the sensitivity of the ester function to HBr liberated by the reaction. Compound **5** had a similar nmr spectrum to **4** except for loss of the acetyl signal (δ 2.38) (DMSO-d_6). Its structure was confirmed by conversion to the free carboxylic acid which had been obtained from carlosic acid by degradation.[5] The catalytic reduction of **5** to **6** [which had a nmr similar to **5** except for the appearance of a new signal at δ 4.99 (1 H, s, vinylic) ($CDCl_3$ + 5% DMSO-d_6)] was carried out similarly to that for α-bromo-(*S*)-γ-methyltetronic acid.[6]



Excepting the cyclization, all synthetic yields were in the 70–80% range. Elementary analyses and spectral data for all of the above compounds were in agreement with the assigned structures.

Since our biosynthetic studies[1] seemed to indicate that *P. charlesii* contained a relatively nonspecific biological acylation system, the compound **6** represents a potential intermediate in both the biosynthesis (as the free acid) and synthesis of carlosic acid (**1**), carlic acid (**7**), and viridicatic acid (**8**). In the specific instance of carlosic acid (**1**), treatment of **6** with butyryl chloride, $TiCl_4$, and $PhNO_2$ gave the ester **9**, which was converted by gentle saponification to **1**. The **1** thus obtained was identical in all respects with the natural product. The application of intermediate **6** to the synthesis of **7** and especially **8** should be straightforward. Our present work allows specific isotopic labeling of **9** or **1** *via* use of PrC*OCl, which is available with either ^{14}C or ^{13}C label as shown.

A full account will be given of this work upon completion.

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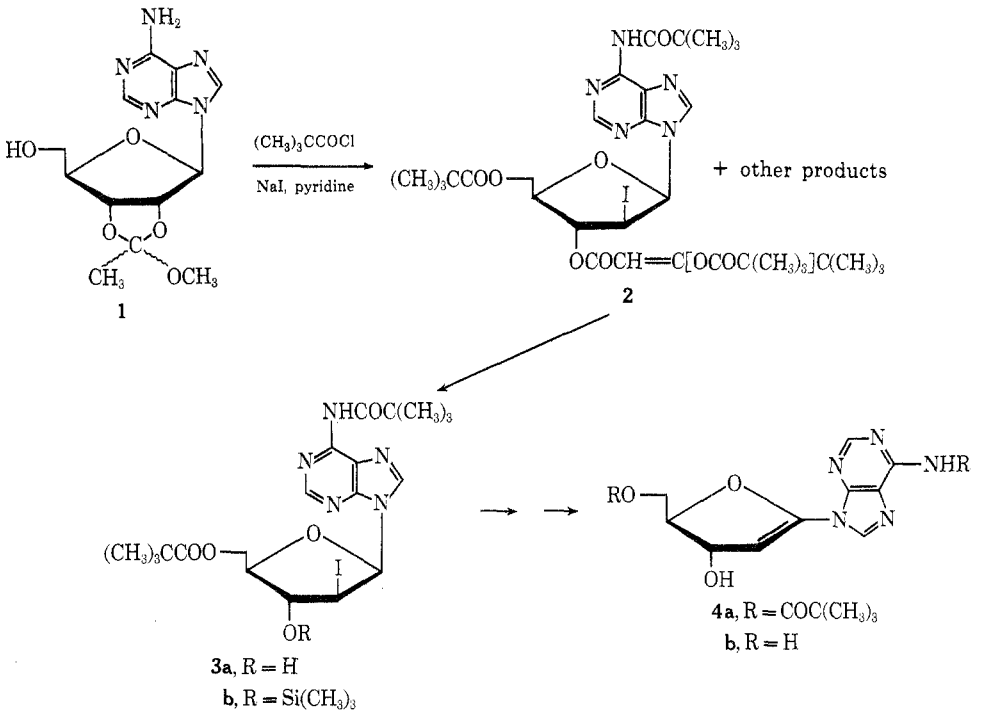
Nucleic Acid Related Compounds. 9. The Synthesis of 6-Amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)-purine, the First 1′,2′-Unsaturated Purine Nucleoside[1,2]

Summary: Adenosine has been transformed into 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (**4b**) by elimination of hydrogen iodide from a suitably blocked 2′-iodo derivative, and hydrogenation of **4b** completes the conversion to α- and β-2′-deoxyadenosines.

Sir: Access into unsaturated pentofuranosyl nucleosides including the 2′,3′,[3] 3′,4′,[4] and 4′,5′[5] olefinic systems has been reported. However, no authenticated 1′,2′-unsaturated purine nucleoside has been described, although the antibiotic augustmycin A (decoyinine)[6] was originally assigned this structural feature.[7] It has been considered that biological transformation of ribo nucleosides to their 2′-



deoxy counterparts might involve 1′-ene intermediates.[8] The finding that only one deuterium is incorporated completely stereoselectively into the 2′-ribo configuration of the 2′-deoxy nucleotides upon reductase action[9] argues against any unsaturated intermediate unless an unusual abstraction–addition mechanism within a specific, nonexchangable enzymatic cage surrounding the 1′ position occurred. The present example provides access to such a 1′-ene for biochemical evaluation.

It has been reported that treatment of 2′-bromo-2′-deoxyuridine [1-(2-bromo-2-deoxy-β-D-ribofuranosyl)uracil] with reduced hydroxycobalamin gave 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)uracil.[10] However, only uv spectral data and qualitative color tests in conjunction with paper chromatography were given as supporting evidence and neither the proposed unsaturated nucleoside nor derived sugar was isolated and characterized.

A refluxing solution of 0.002 mol of 2′,3′-*O*-methoxyethylideneadenosine[11] (**1**) and a 20-fold molar excess of dried NaI in 40 ml of dry pyridine was treated with a 10-fold molar excess of pivalic acid chloride and heating was continued for ~6 min. After cooling, MeOH was added and, after stirring for 2 hr, the mixture was poured into aqueous $NaHCO_3$–$Na_2S_2O_3$ solution and extracted with Et_2O. The washed organic phase was evaporated and the residue chromatographed on activated carbon using EtOAc to elute the 3′-iodo isomer and 3′,4′-unsaturated products.[4a] EtOAc–$CHCl_3$ (1:1) eluted the 2′-iodo isomer (**2**). Rechromatography of intermediate fractions containing 60 mg of both isomers on an analogous smaller column gave effective separation and combination of appropriate fractions gave 6-*N*-pivalamido-9-[2-iodo-2-deoxy-5-*O*-pivalyl-3-*O*-(4,4-dimethyl-3-pivalyloxypent-2-enoyl)-β-D-arabinofuranosyl]purine[12] (**2**) in 15% yield: uv (MeOH) max 272, 213 nm (ε 18,600, 29,100), min 243 nm (ε 9700); uv (0.1 *N* NaOH) 275–295, 216 nm (ε 11,900, 30,600), min 248 nm (ε 7800); uv (0.1 *N* HCl) 282, 218 nm (ε 16,700, 23,500), min 249 nm (ε 7200); nmr ($CDCl_3$, TMS internal) δ 1.18 [s, 9, CH=C[C(CH_3)$_3$](*O*-pivalyl)], 1.26 and 1.34 [s and s, 9 and 9, 5′-OCOC(CH_3)$_3$ and CH=C(*t*-Bu)[OCOC(CH_3)$_3$], 1.41 [s, 9, 6-NHCOC(CH_3)$_3$], 4.17–4.61 (m, 3, $H_{4'}$, $H_{5',5''}$), 4.87 ("q," $J_{2'-1'}$ = 4.5 Hz, $J_{2'-3'}$ = 2.0 Hz, 1, $H_{2'}$), 5.64 ("t," $J_{3'-2'}$ = 2.0 Hz, $J_{3'-4'}$ = 3.0 Hz, 1, $H_{3'}$), 5.75 [s, 1, CH=C(*t*-Bu)(*O*-pivalyl)], 5.95 (d, $J_{1'-2'}$ = 4.5 Hz, 1, $H_{1'}$), 8.31 (s, 1, H_8), 8.60 (br, 1, 6-NH-pivalyl), 8.76 (s, 1, H_2). Treatment of **2** with $KMnO_4$ in pyridine–water (2:1) at 2° effected selective removal of the 3′-enol ester group to give 6-*N*-pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-β-D-arabinofuranosyl)purine[12] (**3a**) in 75% yield: mp 216–217° dec.; uv (MeOH) max 272, 211 nm (ε 17,400, 19,000), min 231 nm (ε 3600); uv (0.1 *N* NaOH) 280–300, 215 nm (ε 10,600, 16,100), min 244 nm (ε 5700); uv (0.1 *N* HCl) 282, 213 nm (ε 18,900, 17,800), min 238 nm (ε 4100); nmr ($CDCl_3$, TMS internal) δ 1.18 [s, 9, 5′-OCOC(CH_3)$_3$], 1.31 [s, 9, 6-NHCOC(CH_3)$_3$], 3.95 (br m, 1, $H_{4'}$), 4.43 (m, 2, $H_{5',5''}$), 4.78 (m, 2, $H_{2'}$, $H_{3'}$), 6.16 (m, 1, 3′-OH), 6.45 (d, $J_{1'-2'}$ = 4.8 Hz, 1, $H_{1'}$), 8.55 (s, 1, H_8), 8.60 (br, 1, 6-NH-pivalyl), 8.72 (s, 1, H_2).

To avoid the concomitant epoxide formation otherwise observed during the elimination step, **3a** was treated with *N*,*O*-bis(trimethylsilyl)acetamide in pyridine to give the 3′-*O*-trimethylsilyl derivative **3b**: uv (CH_3CN) max 272, 212 nm (ε 272/212 = 0.88), min 237 nm (ε 272/237 = 4.92); nmr ($CDCl_3$, TMS internal) δ 0.24 [s, 9, Si(CH_3)$_3$], 1.27 [s, 9, 5′-OCOC(CH_3)$_3$], 1.41 [s, 9, 6-NHCOC(CH_3)$_3$], 4.11 (m, 1, $H_{4'}$), 4.47 ("d," $J_{apparent}$ = 4.5 Hz, 2, $H_{5',5''}$), 4.66 ("q," $J_{2'-1'}$ = 5.5 Hz, $J_{2'-3'}$ = 4.5 Hz, 1, $H_{2'}$), 4.84 ("t," $J_{3'-2'}$ = $J_{3'-4'}$ = 4.5 Hz, 1, $H_{3'}$), 6.11 (d, $J_{1'-2'}$ = 5.5 Hz, 1, $H_{1'}$), 8.25 (s, 1, H_8), 8.35 (s, 1, 6-NH-pivalyl), 8.78 (s, 1, H_2); mass spectrum calcd for $C_{23}H_{36}IN_5O_5Si$ 617.1531, found 617.1506. To the silylation reaction mixture was added 1,5-diazabicyclo[4.3.0]nonene-5 (DBN) and the solution was stirred for 90 min at room temperature. After methanolysis of the trimethylsilyl blocking group and column chromatographic purification, a 98% yield (overall from **3a**) of 6-*N*-pivalamido-9-(2-deoxy-5-*O*-pivalyl-D-erythro-pent-1-enofuranosyl)purine[12] (**4a**) was obtained: uv (MeOH) max 264, 248 nm (ε 18,600, 19,200), sh 216 nm (ε 15,900), min 257, 227 nm (ε 18,500, 13,200); uv (0.1 *N* NaOH) max 288, 232 nm (ε 12,700, 17,100), min 267 nm (ε 10,700); nmr ($CDCl_3$, TMS internal) δ 1.21 [s, 9, 5′-OCOC(CH_3)$_3$], 1.31 [s, 9, 6-NHCOC(CH_3)$_3$], 4.32 (m, 2, $H_{5',5''}$), 4.69 (m, 1, $H_{4'}$), 4.92 (m, 1, $H_{3'}$), 5.57 (d, *J* = 6.0 Hz, 1, 3′-OH), 5.82 (d,

$J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 8.60 (br, 1, 6-NH-pivalyl), 8.56 and 8.86 (s and s, 1 and 1, H_8 and H_2); mass spectrum (of the 3′-*O*-trimethylsilyl derivative of **4a**) calcd for $C_{23}H_{35}N_5O_5Si$ 489.2407, found 489.2425. Deblocking of **4a** with methanolic sodium methoxide gave (in 84% yield from **3a**) 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (**4b**): mp 196–198°, resolidifies at ~202–210°, and melts with decomposition at 224–235°; $[\alpha]^{27}D$ 100.5° (*c* 0.96, DMF); uv (MeOH) max 250 nm (ϵ 16,500), sh 281, 290 nm (ϵ 7200, 4700), min 222 nm (ϵ 10,700); uv (0.1 *N* NaOH) max 251 nm (ϵ 16,400), sh 279, 290 nm (ϵ 6200, 3300), min 221 nm (ϵ 10,600); nmr (DMSO-d_6, TMS internal) δ 3.59 ("t," $J_{apparent}$ = 6 Hz, 2, $H_{5',5''}$), 4.43 ("sextet," $J_{4'-5',5''}$ = 5.0 Hz, $J_{4'-3'}$ = 3.0 Hz, 1, $H_{4'}$), 4.84 ("quintet," $J_{3'-4'}$ = 3.0 Hz, $J_{3'-3'-OH}$ = 6.0 Hz, 1, $H_{3'}$), 5.03 (t, $J_{5'-OH-5',5''}$ = 6.0 Hz, 1, 5′-OH); 5.35 (d, $J_{3'-OH-3'}$ = 6.0 Hz, 1, 3′-OH), 5.69 (d, $J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 7.47 (s, 2, 6-NH_2), 8.30 and 8.34 (s and s, 1 and 1, H_2 and H_8); mass spectrum calcd for $C_{10}H_9N_5O_2$ ($M^+ - H_2O$) 231.0756, found 231.0752; mass spectrum [of the tris(trimethylsilyl) derivative of **4b**] calcd for $C_{19}H_{35}N_5O_3Si_3$ 465.2047, found 465.2062; spectrophotometrically determined $pK_a \sim 3.31$.

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.28; H, 4.74; N, 27.92.

It is interesting to note that conjugation of the adenine ring with the 1′–2′ double bond shifts the uv spectrum hypsochromically as found with 9-(5-methyl-2-furyl)adenine.[3a] Heating **4b** gives 9-(5-methyl-2-furyl)adenine[3a] and attempted determination of the uv spectrum at pH 1 results in rapid cleavage to adenine. Blue fluorescence is observed when **4b** is visualized under 2537-Å light, which could be useful if this presumably base-sugar planar 2′-deoxyadenosine derivative can be incorporated into DNA and/or oligonucleotides.

Hydrogenation of **4b** at 3 psi over palladium/charcoal in alcohol–water containing sodium bicarbonate gave 2′-deoxyadenosine and 6-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine[13] in yields of 60 and 12%. It is interesting that the β:α stereoselectivity (5:1) is so high. A preliminary attempt at reduction of **4a** appeared to give no detectable α anomer, although accompanying hydrogenolysis of the glycosidic linkage to give 6-*N*-pivalyladenine made evaluation difficult.

The present study provides a possible route for the conversion of an intact ribo nucleoside to its 2′-deoxy-α anomer. As well, the new nucleoside 1-ene system is now available for biochemical, fluorescence, and synthetic studies.

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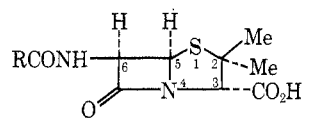
An Exocyclic Thio Analog of the Penicillin System[1]

Summary: A number of 3-arylidene-2-thioalkyl-1-pyrrolines were synthesized from 2-pyrrolidone *via* a three-step sequence and condensation of these thioimidates with phenoxyacetyl chloride in presence of triethylamine led to novel penicillin analogs in which substituents at C-5 have been interchanged to give an exocyclic alkylthio substituent and a carbocyclic five-membered ring; the stereochemistry of these fused β-lactams was established from a study of their nmr spectra.

Sir: An important structural feature of penicillins (**1**) in clinical use is a fused thiazolidine β-lactam system. In the course of research directed toward the synthesis of penicillin and cephalosporin analogs we became interested in the possibility of interchanging the substituents at C-5 to obtain derivatives of a novel fused β-lactam system (**2**) with an exocyclic alkylthio substituent. We describe here the preparation of some derivatives of this previously unknown class of compounds.



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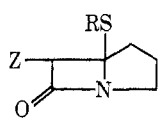

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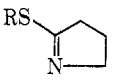

3

In recent years we[2] have synthesized diverse types of mono- and polycyclic β-lactams by the reaction of appropriate acid chlorides with imines in the presence of triethylamine. To take advantage of this approach we sought thioimidates of type **3** as intermediates for **1**. The reaction of phenoxyacetyl chloride and triethylamine with 2-methylthio-1-pyrroline (**3**, R = Me), however, led to the pyrroline derivative **5** instead of the desired β-lactam **6**. Evidently the initial reaction intermediate was **4** which underwent an elimination reaction in preference to cyclization.

To preclude the elimination pathway and thereby favor cyclization to a β-lactam, thioimidates of type **9** were examined next as imine components in the reaction with acid chlorides and triethylamine. Following the method of Zimmer[3] a series of pyrrolidone derivatives of type **7** were prepared by treating *N*-acetylpyrrolidone with aromatic aldehydes in the presence of sodium hydride. A suspen-