In summary, none of the compounds reported were as active as aminophylline.

Experimental Section[10]

8-Azatheophylline-7-acetic Acid Ethyl Ester (II).—To a soln of 0.69 g (0.03 mole) of Na in 50 ml of MeOH was added 5.43 g (0.03 mole) of I. The reaction mixt was refluxed for 0.5 hr and to it was added 5.0 g (0.03 mole) of $ClCH_2CO_2Et$. Refluxing was continued for 2 hr. The solvent was cooled to room temp, and the ppt was filtered and recrystd from MeOH–H_2O: yield 4.1 g (50%), mp 157–159°. *Anal.* ($C_{10}H_{13}N_5O_4$) C, H, N, O.

8-Azatheophylline-7-acetamide (III).—To a suspension of 9.2 g (0.1 mole) of chloroacetamide in 150 ml of H_2O was added 18.0 g (0.1 mole) of I, and the reaction mixt was heated to 50° for a few min. Heating was discontinued, and a soln of 4 g (0.1 mole) of NaOH and 0.1 g of NaI in 25 ml of H_2O was added. The reaction mixt was refluxed at 90° for 2 hr and cooled to room temp. The ppt was filtered and washed with cold H_2O. The product was recrystd (MeOH–DMF) to give 17.7 g (75%) of III, mp 228–230°. *Anal.* ($C_8H_{10}N_6O_3$) C, H, N.

8-Azatheophylline-7-acetamide derivatives (IV – VIII), listed in Table II, were prepd by the following procedure. A soln of 0.01 mole of II and 0.01 mole of an amine in EtOH was refluxed for 4 hr. The reaction mixt was cooled to room temp. The pptd solid was filtered and recrystd from an appropriate solvent with charcoal treatment.

8-Azatheophyllinamine salts (XIV-XIX), listed in Table II, were prepd by keeping a soln of 0.01 mole of I and 0.01 mole of an amine at room temp for 4 hr. The solvent was removed *in vacuo*, and the residue was heated with Et_2O and Me_2CO. The resultant solid was crystd from the appropriate solvent.

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(10) Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus. Ir spectra were determined in KBr disks with a Beckman IR-8. Microanalyses were provided by Orville Kolsto and Victor Rauschel and staff of the Abbott Microanalytical Laboratory, North Chicago, Ill.

Synthesis of 1-Amino-2-hydroxycyclopentanecarboxylic Acid

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In the search for effective chemotherapeutic agents, many amino acid analogs have been synthesized in recent years; several have been found to possess antitumor properties, and others inhibit the growth of certain bacteria and viruses.[1] 1-Aminocyclopentanecarboxylic acid[2] (cycloleucine) has, for example, shown promise as a chemotherapeutic agent in the treatment of such diverse problems as acne[3] and leukemia.[4]

Few specific antimetabolites of serine and threonine are known;[1] α-methylserine inhibits the growth of *Leuconostoc mesenteroides* P-60, but other bacterial strains are unaffected; the higher homologs of threonine, 2-amino-3-hydroxypentanoic acid and 2-amino-3-hydroxyhexanoic acid, are also reported to inhibit the growth of certain bacteria. The title compound possesses a cyclopentane ring which is present in cycloleucine and also contains the combination of α-amino and β-hydroxyl groups found in serine and threonine.

Several routes for the synthesis of 1-amino-2-hydroxycyclopentanecarboxylic acid were explored, for example, ammonolysis of a halohydrin produced from 1-cyclopentenecarboxylic acid. Procedures utilizing HOCl to form a halohydrin, which had proved useful in other systems,[5,6] failed to produce the desired intermediate; however, it was obtained by the action of monochlorourea (in AcOH) on 1-cyclopentenecarboxylic acid, utilizing a procedure which had been reported for the synthesis of *trans*-2-chlorocyclopentanol.[7] Upon ammonolysis of this chlorohydrin, the only amino acid isolated was 2-amino-1-hydroxycyclopentanecarboxylic acid.[8] This result is consistent with some previous studies where it was reported that several 2-chloro-3-hydroxy-substituted acids produced the corresponding 2-hydroxy-3-amino derivatives on ammonolysis[9–11] presumably through the mediation of an epoxide intermediate.

Ultimately, the synthesis of 1-amino-2-hydroxycyclopentanecarboxylic acid was accomplished by a route similar to the method for the preparation of serine and threonine.[12,13] 1-Cyclopentenecarboxylic acid was converted into an acetoxymercurimethoxy adduct which, upon bromination, yielded 1-bromo-2-methoxycyclopentanecarboxylic acid. Ammonolysis of this material gave the corresponding aminomethoxy derivative which was finally hydrolyzed with 49% HI to produce the desired amino acid analog. The ir spectrum of this compound was consistent with that of an α-amino-β-hydroxycarboxylic acid.

The nmr spectrum of 1-amino-2-hydroxycyclopentanecarboxylic acid indicated the absorption of CH (adjacent to OH) at δ 4.54; whereas, in the spectrum of 2-amino-1-hydroxycyclopentanecarboxylic acid, the CH (adjacent to NH_2) absorbs at δ 3.80. These data are comparable to those observed using model compounds, serine and isoserine, with absorptions at δ 4.18 and 3.48, respectively, and are consistent with the greater deshielding effect expected for the more electronegative OH. The CH of 1-amino-2-methoxycyclopentanecarboxylic acid was found to absorb at δ 4.20.

Gas chromatographic analysis of the trimethylsilyl derivatives of 1-amino-2-hydroxycyclopentanecarboxylic acid indicated that these compounds are present in approximately equimolar mixtures of cis and trans isomers. This would be anticipated since the replacement of the BrHg group with Br is known to proceed with

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racemization, even though the initial addition product is trans.[14]

Preliminary microbiological studies using 5 species of bacteria have been attempted; however, no significant inhibition of bacterial growth has been observed.

Experimental Section[15]

Intermediate Derivatives.—Cyclopentanone cyanohydrin was prepared from cyclopentanone in 86% yield,[16] converted into 1-cyanocyclopentene in 86% yield,[17] and finally, the latter compd was hydrolyzed to yield 1-cyclopentenecarboxylic acid in 50% yield.[18]

2-Amino-1-hydroxycyclopentanecarboxylic Acid.—Numerous attempts to prep the desired analog *via* a chlorohydrin reaction followed by ammonolysis failed, and the only amino acid isolated from these reactions was the isomeric product. For example, a soln of monochlorourea (40 ml), prepd from 5.5 g (0.77 mole) of Cl_2, 8 g (0.13 mole) of urea, and 6.7 g (0.067 mole) of $CaCO_3$,[7] was added to a mixt of 11.2 g (0.1 mole) of 1-cyclopentene-1-carboxylic acid in the presence of 5 ml of HOAc and 25 g of crushed ice, and the resulting mixt was stirred overnight with cooling in an ice bath. Attempts to isolate the chlorohydrin were unsuccessful, and the impure material was mixed with concd NH_4OH (350 ml) and allowed to stand at room temp for a 7-day period. The resulting soln was concd *in vacuo* and desalted by a modification of the procedure reported by Piez, *et al.*[19] The amino acid was crystd from H_2O–EtOH; mp 295–298° dec;[20] ir (KBr) 3.08, 3.37, 6.15, 9.0, and 12.6 μ; nmr δ 3.80 (t, 1 H, methine hydrogen), 1.60–2.64 (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_6H_{11}NO_3$): N.[21]

1-Amino-2-methoxycyclopentanecarbocylic Acid.—The synthesis of 1-bromo-2-methoxycyclopentanecarboxylic acid was patterned after a previously reported route for threonine[13] whereby a mixt of 56.2 g (0.5 mole) of 1-cyclopentene-1-carboxylic acid, 159.3 g (0.5 mole) of $Hg(OAc)_2$, and 750 ml of MeOH was stirred at room temp for 7 days to yield 149.2 g of adduct, mp 195–200° (presumably 1-acetoxymercuri-2-methoxycyclopentanecarboxylic acid). This material was added in small portions to a soln of 90 g (0.75 mole) of KBr in 500 ml of H_2O, cooled to 10°, and exposed to direct sunlight, and a soln of 80 g (0.5 mole) of Br_2 and 90 g (0.75 mole) of KBr in 150 ml of H_2O was added slowly with stirring. After extn with Et_2O and acidification with 47% HBr, there was recovered an amber oil (73.6 g, presumably 1-bromo-2-methoxycyclopentanecarboxylic acid) which failed to give a satisfactory elemental anal. *Anal.* (Calcd for $C_7H_{11}BrO_3$): C, 37.69; H, 4.97. Found: C, 38.51, 38.63; H, 5.25, 5.27.

A sample of this material (44.6 g) was added to 1350 ml of concd NH_4OH (cooled to 10–15°) and allowed to stand at room temp for 13 days. The resulting dark reaction mixt was filtered and reduced to near dryness *in vacuo*, and the residue was covered with Me_2CO to induce solidification. Ascending paper chromatograms indicated the presence of 2 ninhydrin-active components including a weak spot corresponding to 1-amino-2-hydroxycyclopentanecarboxylic acid (R_f 0.45, *n*-BuOH–HOAc–H_2O, 3:1:1); however, the major product was a ninhydrin-active compd with a different R_f value (R_f 0.68, *n*-BuOH–HOAc–H_2O, 3:1:1). This material was dissolved in H_2O, treated with decolorizing charcoal, and recrystd twice from H_2O–EtOH to yield white cryst free of the lower ninhydrin-active component which sublimes above 285°. *Anal.* ($C_7H_{13}NO_3 \cdot H_2O$): C, H, N.

An anhyd sample of 1-amino-2-methoxycyclopentanecarboxylic acid was obtained by vacuum sublimation at 124–140° (0.15 mm); ir (KBr) 3.38, 6.12, 7.20, 7.50, and 8.85 μ; nmr δ 4.20 (*t*, 1 H, CH), 3.52 (s, 3 H, OCH_3), 1.68–2.80 (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_7H_{13}NO_3$): C, H, N.

1-Amino-2-hydroxycyclopentanecarboxylic Acid.—A mixt 10.3 g of 49% HI and 0.7 g (0.0023 mole) of 1-amino-2-methoxycyclopentanecarboxylic monohydrate (0.70 g) was heated under reflux for 2 hr. The reaction mixt was concd to dryness *in vacuo*, and the resulting residue was dissolved in EtOH and reduced to dryness twice to remove excess HI. The clear, viscous residue was finally dissolved in a small vol of EtOH, adjusted to pH 8–9 with concd NH_4OH, and placed in the refrigerator. The pptd amino acid was filtered, and recrystd from H_2O–EtOH to yield 0.26 g (46% of theory) of 1-amino-2-hydroxycyclopentanecarboxylic acid: mp 288–290° dec; mmp with 2-amino-1-hydroxycyclopentanecarboxylic acid, 275–282°; ir (KBr) 3.35, 6.05–6.40, 7.20, 7.55, 9.15, 11.7, and 12.7 μ; nmr δ 4.54 (t, 1 H, CH), 1.60–2.80 (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_6H_{11}NO_3$): C, H, N.

Microbiological Assays.—Assays with *Escherichia coli* 9723 were carried out in a previously described inorganic salts medium[22] and incubated at 37° for 18 hr; assays using *Leuconostoc dextranicum* 8086, *Streptococcus lactis* 8039, *S. faecalis* 8043, and *Pediococcus cerevisiae* 8042 were determined in an acid-hydrolyzed casein medium.[23] For *P. cerevisiae*, the purine and pyrimidine supplement was increased to 1.2 ml/100 ml of basal media and the phosphate concn was increased fourfold. The phosphate concn was also increased fourfold with *L. dextranicum*, and 0.1 μg/tube of pantethine was added. The latter 4 microorganisms were incubated at 30° for about 16 hr. A previously reported amino acid medium[24] was utilized in the assay with *Lactobacillus arabinosus* 17-5 except that 1 μg/tube of calcium pantothenate was added, and the assays were incubated at 30° for 20 hr.

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Antiviral Agents. 1. Benzothiazole and Benzoxazole Analogs of 2-(α-Hydroxybenzyl)benzimidazole

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Since the discovery[2] of the antiviral activity of 2-(α-hydroxybenzyl)benzimidazole (HBB), many analogs have been synthesized in attempts to broaden and improve upon the antiviral effects.[3–6] The importance of the α-hydroxybenzyl group as well as a fused bicyclic ring[7] has been emphasized. Some evidence was found

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