ϵ 4.83), 272 (5.21), 297 (4.27), 308 (4.28), 324 (4.22), 347 (3.49), 364 (3.29) ir 743, 778, 801, 860 (w), 1255 (w), 2898 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 94.11; H, 6.13.

The remainder of the product was recovered directly from the reaction mixture by vacuum sublimation, giving 42 mg (42%) of **13** as a white powder, mp 256–261°.

Registry No.—**3**, 35639-14-6; **6**, 35639-15-7; **7**, 35639-16-8; **8**, 35639-17-9; **9**, 35639-18-0; **10**, 35639-19-1; **11**, 35639-20-4; **13**, 35639-21-5; ethyl benzoylacetate, 94-02-0.

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Studies of the Synthesis of Cephalotaxine. I

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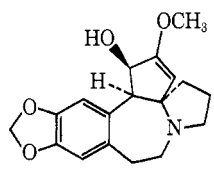
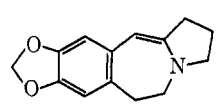
An attempted synthesis of cephalotaxine is described. The key intermediate, 8,9-methylenedioxy-1,2,3,6-tetrahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (**1**) was obtained by a six-step sequence from *N*,*N*-dimethylpiperonylamide and pyrrole. Annelation of **1** with ethyl γ-bromoacetoacetate afforded a rearrangement product, 11,12-methylenedioxy-2-oxo-3-carboethoxy-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (**10**), rather than the expected product **8** bearing the cephalotaxine skeleton. Hydrolysis of **10** yielded 11,12-methylenedioxy-2-oxo-2,3,3a,4,5,6,8,8-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (**11**), which was reduced to yield 11,12-methylenedioxy-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine which was identical with authentic material.

Cephalotaxine and several closely related compounds have been isolated from several species of the *Cephalotaxacea* family.[1] The structure of cephalotaxine was deduced from its spectroscopic properties[2] and an X-ray crystallographic study.[3] In particular, the harringtonines which are naturally occurring esters of cephalotaxine have shown promising antileukemic activity.[4] Neither the acid portion of the harringtonines nor cephalotaxine show antileukemic activity alone. However, cephalotaxine presents the more difficult synthetic problem.



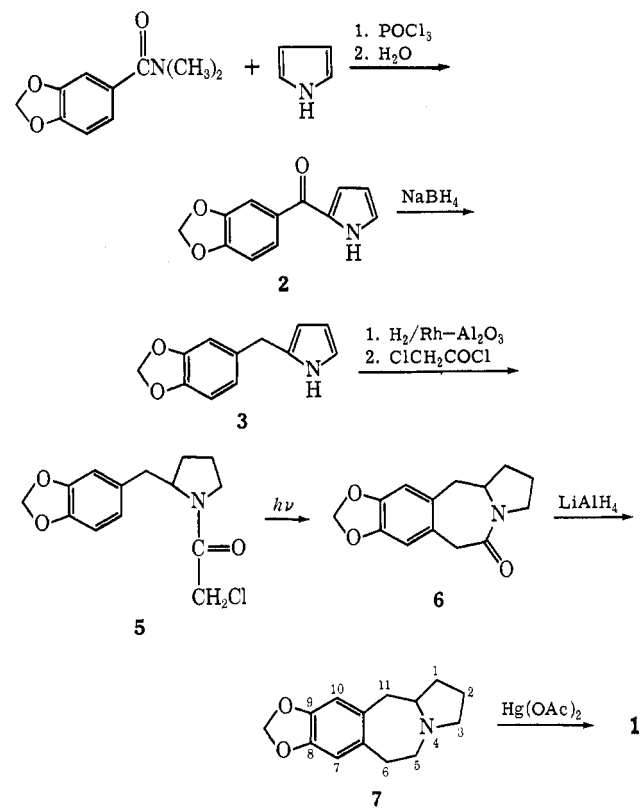
cephalotaxine

An attractive approach to the synthesis of cephalotaxine involves the annelation of the tricyclic enamine **1**, which was obtained by the sequence outlined in Scheme I.



1

SCHEME I



The sequence leading to the enamine **1** proceeds smoothly and none of the steps is exceptional. The Vilsmeier–Haack condensation[5] between *N*,*N*-dimethylpiperonylamide and pyrrole affords the 2-acylpyrrole **2** in 80% yield. Removal of the ketonic oxygen by treatment with sodium borohydride gives the benzylpyrrole **3** in 60% yield. Hydrogenation of the pyrrole ring and acetylation with chloroacetyl chloride give good yields of the chloroacetamide **5**. Photolytic cyclization of the chloroamide affords the benzazepine derivative **6** in 25% yield.[6] The structure of this material is supported by its spectroscopic properties.

(1) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963).

(2) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969).

(3) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *ibid.*, 4085 (1969).

(4) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *ibid.*, 815 (1970).

(5) G. H. Cooper, *J. Org. Chem.*, **36**, 2897 (1971).

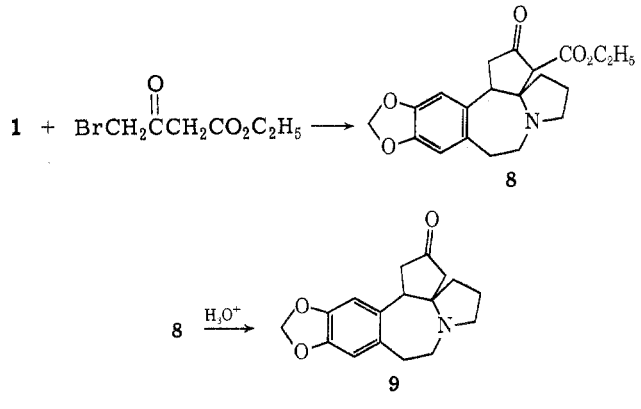
(6) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 5686 (1970).

The infrared spectrum shows carbonyl absorption at 1640 cm^{-1}, whereas the proton magnetic resonance spectrum exhibits two singlets, one proton each, at δ 6.25 and 6.60 ascribed to the remaining hydrogens on the aromatic ring. The methylenedioxy graoup appears as a singlet at δ 5.87. Decoupling experiments were useful in analyzing the remainder of the spectrum; the benzylic protons at C-11 appear as a broad doublet at 2.97 ppm, the benzylic protons at C-6 are found as an AB quartet at 3.45 and 3.98 ppm, the methine proton adjacent to nitrogen is found as a multiplet at 4.10 ppm, and the methylene protons adjacent to nitrogen are found at 3.55 ppm. The remaining protons of the pyrrolidine ring absorb as a complex multiplet at 1.52–2.22 ppm.

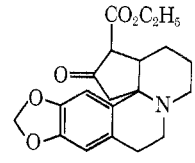
Lithium aluminum hydride reduction of the lactam affords the tricyclic base **7** in 65% yield. Oxidation of **7** with mercuric acetate in dilute acetic acid gave the enamine **1** on isolation.[7] Use of a chelating ion exchange resin to remove the excess mercuric acetate proved superior to precipitation of mercuric sulfide by treatment with hydrogen sulfide. The enamine was isolated by basifying the eluates from the ion exchange resin and extracting with methylene chloride. The enamine **1** proved to be unstable and very unpleasant to handle. However, the mass spectrum showed the expected parent ion and the pmr spectrum showed the single vinyl proton at C-11 as a broad singlet at 4.90 ppm. Four triplets of two protons each are assigned to the methylene groups of carbons 1, 3, 5, and 6. The C-2 protons appear as a multiplet at 1.60–2.2 ppm. The ultraviolet spectrum of **1** shows a single broad and intense maximum at 322 nm in alkaline solution, whereas in dilute acid three maxima are observed: absorptions of about equal intensity at 235 and 291 nm characteristic of the methylenedioxyphenyl chromophore are shown along with a weaker absorption at 321 nm.

The desired annelation of enamine **1** to produce the cephalotaxine skeleton is outlined in Scheme II.

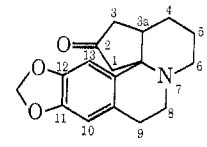
SCHEME II



In fact, treatment of the enamine **1** with ethyl γ-bromoacetoacetate in acetonitrile did produce a tetracyclic β-keto ester of the expected molecular formula. The infrared spectrum of this material showed absorptions at 1755 and 1720 cm^{-1}, indicating formation of a 2-carboethoxycyclopentanone. Treatment of this material with dilute acid effected removal of the carboethoxy group to give a tetracyclic cyclopentanone, as indicated by its infrared absorption at 1745 cm^{-1}. However, careful inspection of the mass spectra and the proton magnetic resonance spectra of these two materials indicated that they have structures **10** and **11**, respectively.



10



11

Treatment of the cyclopentanone **11** with deuterium oxide–dioxane in the presence of potassium carbonate produced a tetradeuterio compound which did not exhibit a signal in its pmr spectrum in the region δ 3.5–3.8 as expected for the benzylic methine proton of structure **9**.[2] Moreover, by comparing the spectra of the deuterated and undeuterated materials, and AB quartet (J_{AB} = 17.0 Hz) could be discerned, which is assigned to the protons adjacent to the carbonyl group at C-1. The same AB quartet appears in the spectrum of the β-keto ester **10** along with a one-proton doublet at δ 3.80, which is ascribed to the proton attached to the carbon bearing the carboethoxy group. These observations are consistent with structures **10** and **11** but rule out structures **8** and **9**. The fragmentation mass spectrum pattern of the ketone **11** shows the most prominent peaks arising from loss of C_2H_3O and C_3H_5O from the parent ion, a pattern which is difficult to rationalize on the basis of structure **9**.

Firm chemical evidence for the structure **11** was obtained by removal of the ketonic oxygen to give the parent base, which has been prepared independently by Taylor and Robinson.[8] Treatment of **11** with 1,3-propanedithiol gave the thioketal, which was reduced with Raney nickel to the parent tetracyclic base. The material thus obtained was identical with an authentic sample prepared by Taylor and Robinson and kindly furnished to us by Dr. Neville Finch of the CIBA-GEIGY Corp.

We would propose that β-keto ester **10** is formed by rearrangement of the desired isomer **8** as outlined in Scheme III.

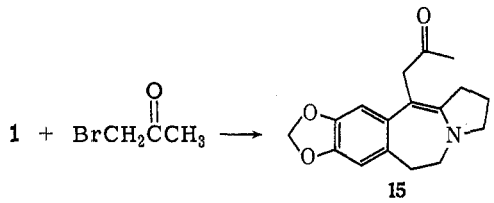
The mechanistic details of the formation of **10** are obscure, but the rearrangement is undoubtedly initiated by elimination of **8**, probably *via* the enol, to give tricyclic intermediate **12** containing a ten-membered ring. Double bond isomerization would be expected to be facile in such a system and would lead to intermediates **13** and/or **14**, both of which could cyclize to the observed product.

Since the formation of **10** is initiated by elimination from a β-keto ester system, changes which inhibit the elimination might be expected to lead to the desired product. Accordingly, enamine **1** was alkylated with bromoacetone in the hope that cyclopentanone **9** would be formed directly and survive the reaction conditions. The condensation of enamine **1** and bromo-

(7) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, **77**, 439 (1955).

(8) W. I. Taylor and M. M. Robinson, U. S. Patent 3,210,357 (1966); *Chem. Abstr.*, **65**, 2234e (1966).

acetone instead gave the simple alkylation product **15**, which was subsequently cyclized.



15

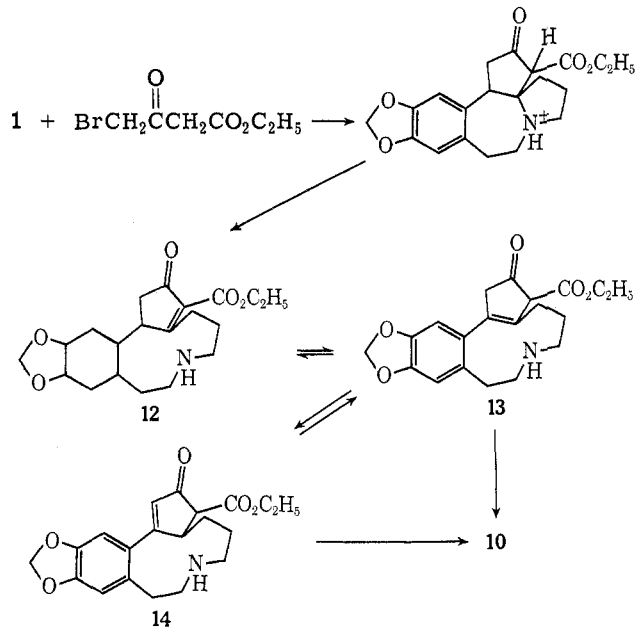
Acetic acid–sodium acetate solutions did not effect the cyclization of **15**. At room temperature no reaction was observed, and on warming some new products were formed but they did not possess a cyclopentanone ring. It appears that the enamine double bond moves into conjugation with the carbonyl group in acetic acid–sodium acetate solution, but the products were not characterized. Trifluoroacetic acid–methylene chloride solutions also failed to effect cyclization, but treatment with pyrrolidine and *p*-toluenesulfonic acid under enamine-forming conditions did effect cyclization with the formation of a cyclopentanone. Isolation of the cyclopentanone revealed that ketone **11** was the product once again. We would propose that ketone **11** is obtained from this reaction *via* its isomer **9** by a sequence similar to that outlined in Scheme III. In view of the difficulty encountered in cyclizing the enamino ketone **15**, it appears that the desired cyclopentanone **9** will not be isolated although it is formed as an intermediate. Moreover, this type of rearrangement is disastrous to the final stages of the synthesis, in which we planned to make the enol ether of ketone **9** as the next step, since enol ether forming conditions would surely cause rearrangement.

Experimental Section[9]

N,*N*-**Dimethylpiperonylamide.**—Piperonylic acid (63.8 g, 0.384 mol) was added in portions with stirring to thionyl chloride (270 ml) over 20 min. The slurry was heated under reflux for 1 hr, during which time the acid gradually dissolved. Excess thionyl chloride was removed under reduced pressure and the residue was evaporated with dry benzene. The crude acid chloride was added to 40% aqueous dimethylamine in portions with stirring and cooling over 15 min. The mixture was stirred for 2 hr at room temperature and then made strongly alkaline with 4 *N* sodium hydroxide and saturated with sodium chloride. The aqueous solution was extracted with methylene chloride, and the organic phases were filtered through paper and concentrated under reduced pressure to give the crude amide (57.1 g, 77%) as a dark oil. Distillation gave the amide as a hygroscopic, viscous liquid (53 g, 71%): bp 122–125° (0.01 mm); ir $\nu_{max}^{CCl_4}$ 2980, 1620, 1498, 1455, 1392, 1340, 1250, 1145, 1100, 1058, 1045, 932, 875, and 818 cm^{-1}; pmr (CCl_4) δ 2.90 (s, 6), 5.91 (s, 2), and 6.62–6.9 (m, 3). A satisfactory combustion analysis was not obtained.

(9) All melting points and boiling points are uncorrected. Infrared spectra were measured with Beckman IR-5A or IR-7 infrared spectrophotometers. Proton magnetic resonance spectra were determined at either 60 or 100 MHz with Varian Models A-60 and HA-100 pmr spectrometers. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the pmr spectra the following notations are used: b, broad; u, unsymmetrical; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; and m, multiplet. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer. The mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110 double-focus mass spectrometer equipped with a direct inlet system. Thin layer chromatographic analyses were carried out on silica gel plates. A 3% ceric sulfate–10% sulfuric acid solution or a 5% phosphomolybdic acid solution was used to visualize the spots. Combustion analyses were performed either by Chemalytics, Inc., Tempe, Ariz., or by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon, Eugene, Oregon. Unless otherwise specified, all organic solutions were dried with anhydrous magnesium sulfate.

SCHEME III



2-(3,4-Methylenedioxybenzoyl)pyrrole (**2**).—To a cooled solution of *N*,*N*-dimethylpiperonylamide (58.5 g, 0.303 mol) in ethylene dichloride (60 ml) was added dropwise over 15 min freshly distilled phosphorus oxychloride (46.5 g, 0.303 mol) with stirring. The mixture was stirred in the cold for 10 min and then at room temperature for 1.5 hr. Additional ethylene dichloride was added (60 ml) followed by addition of a solution of freshly distilled pyrrole (20.3 g, 0.303 mol) in ethylene dichloride (60 ml) over 10 min. The mixture was stirred at room temperature for 10 min and then brought to reflux for 1 hr. The dark red mixture was cooled and sodium acetate trihydrate (300 g) in water (600 ml) was added, slowly at first, then as rapidly as possible with vigorous stirring. The mixture was brought to reflux for 15 min, after which the phases were separated while still warm. The aqueous phase was extracted with chloroform and the combined organic solutions were washed with brine, dried, and concentrated under reduced pressure. The dark solid residue was washed with a small amount of cold methanol, then ether, and dried to give the acylpyrrole (51.7 g, 80%) as a yellow solid. An analytical sample, recrystallized twice from ethanol and then ethyl acetate–hexane, had mp 146–147°; ir $\nu_{max}^{CHCl_3}$ 3460, 1625, 1595, 1442, 1405, 1328, 1255, 1100, and 1045 cm^{-1}; pmr ($CDCl_3$) δ 6.05 (s, 2), 6.30 (q, 1, J_{4-3} = 6.0, J_{4-2} = 1.7 Hz), 6.90 (m, 2), 7.13 (m, 1), 7.39 (ud, 1, J = 1.5 Hz), and 7.53 (q, 1, J_{2-3} = 8.0, J_{2-4} = 1.7 Hz).

Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.80; H, 4.13; N, 6.45.

2-(3,4-Methylenedioxybenzyl)pyrrole (**3**).—A mixture of the acylpyrrole **2** (37.8 g, 0.175 mol), sodium borohydride (19 g, 0.50 mol), and dioxane (500 ml) was refluxed under nitrogen for 4 hr. The solution was concentrated under reduced pressure, diluted with water (500 ml), and extracted with ether–methylene chloride (2:1, 300 ml). The organic solution was washed with water, dried, and concentrated under reduced pressure to leave a dark viscous oil. Distillation under reduced pressure gave the benzylpyrrole **3** as a colorless liquid (20.8 g, 59%), bp 125–130° (0.03 mm). An analytical sample was obtained by preparative vpc, 20% SE-30 on Chromosorb W, 5 ft × 0.375 in. column at 209°. The infrared spectrum showed $\nu_{max}^{CCl_4}$ 3455, 2845, 2770, 1500, 1490, 1445, 1245, 1042, and 710 cm^{-1}; pmr δ ($CDCl_3$ 3.77 (s, 2), 5.70 (s, 2), 5.80 (bs, 1), 5.93 (q, 1, J_{4-2} = 7.2, J_{4-3} = 2.6 Hz), 6.35 (m, 1), and 6.52 (m, 3).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.28; H, 5.45; N, 6.95.

2-(3,4-Methylenedioxybenzyl)pyrrolidine (**4**).—A solution of the benzylpyrrole **3** (28.9 g, 0.144 mol) in glacial acetic acid (100 ml) was hydrogenated at an initial pressure of 50 psi in a Parr apparatus over 5% rhodium on alumina (3 g) for 8 hr. The catalyst was filtered and the filtrate was diluted to 500 ml with

water. The aqueous solution was extracted with ether and then made strongly alkaline with 50% sodium hydroxide and extracted with methylene chloride. The organic solution was dried and concentrated under reduced pressure and the dark oil was distilled under reduced pressure to give the benzylpyrrolidine **4** (18.3 g, 75%) as a hygroscopic, colorless liquid: bp 125–130° (0.01 mm); ir $\nu_{max}^{CHCl_3}$ 3200–3400 (b), 1505, 1492, 1445, 1205, 1045, 942, and 865 cm^{-1}; pmr (CCl_4) δ 1.1–1.9 (m, 4), 2.52 (d, 2, J = 7.0 Hz), 2.62–3.75 (m, 3 H), 5.80 (s, 2), and 6.45–6.70 (m, 3). A hydrochloride salt was prepared by the addition of saturated ethanolic hydrogen chloride to an ether solution of the pyrrolidine **4**. Recrystallization from ethyl acetate–ethanol provided an analytical sample, mp 164–165°.

Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.51; H, 6.66; N, 5.79.

***N*-Chloroacetyl-2-(3,4-methylenedioxybenzyl)pyrrolidine (5).**—A solution of chloroacetyl chloride (21.2 g, 0.189 mol) in dry methylene chloride (50 ml) was added with vigorous stirring to an ice-cold mixture of the benzylpyrrolidine **4**, methylene chloride (200 ml), water (200 ml), and K_2CO_3 (35 g, 0.25 mol), over 20 min. Vigorous stirring was continued for 2 hr, during which time the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic solutions were washed with bicarbonate solution, filtered, and concentrated under reduced pressure. Trituration of the oily residue with ether gave the chloroacetamide **5** (29.0 g, 82%) as a cream-colored powder. Recrystallization from ether gave colorless blocks: mp 81–2°, ir $\nu_{max}^{CHCl_3}$ 1650, 1505, 1490, 1230, 1045, and 930 cm^{-1}; pmr (CCl_4) δ 1.65–2.08 (m, 4), 2.48 (q, J_{AB} = 12.5, J_{AX} = 9.0 Hz), 3.35–3.75 (m, 2), 3.90 (s, 2), 4.15 (bs, 1), 5.78 (s, 2), and 6.45–6.75 (m, 3).

Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.51; H, 5.73; N, 4.83.

5-Oxo-8,9-methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (6).—A 0.04 M solution of the chloroacetamide **5** (14 g, 49 mmol) in 40% aqueous ethanol was purged with nitrogen for 30 min. The solution was irradiated with a Hanovia 450-(high-pressure mercury lamp in a quartz immersion well with a Corex filter for 44 hr. After 24 hr the immersion well was cleaned to remove a gummy deposit. The clear yellow solution was concentrated under reduced pressure to remove the ethanol and the turbid concentrate was extracted with methylene chloride. The organic solution was filtered through paper and concentrated under reduced pressure to leave a dark oil (6.05 g). The combined material from two identical experiments was filtered through 300 g of Florisil eluting with chloroform to give 12.1 g of pale yellow oil. Trituration of the oil with ether and standing overnight in the cold gave the amide **6** (6.9 g, 27%) as a colorless powder. Recrystallization from benzene–hexane gave colorless blocks: mp 153–155°; ir $\nu_{max}^{CHCl_3}$ 1640, 1508, 1485, 1230, 1042, and 930 cm^{-1}; pmr ($CDCl_3$) δ 1.52–2.22 (m, 4), 2.97 (ud, 2), 3.45 (d, 1, J = 14 Hz), 3.55 (m, 2), 3.98 (d, 1, J = 14 Hz), 4.10 (m, 1), 5.87 (s, 2), 6.52 (s, 1), and 6.60 (s, 1).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.62, H, 6.18; N, 5.60.

8,9-Methylenedioxy-1,2,3,6,11,11a-hexahydro-5*H*-pyrrolo-[2,1-*b*][3]benzazepine (7).—A solution of the amide **6** (6.88 g, 28.0 mmol) in dry tetrahydrofuran (75 ml) was added rapidly to a slurry of lithium aluminum hydride (3.6 g, 95 mmol) in tetrahydrofuran (110 ml) and the mixture was brought to reflux for 12 hr. The mixture was cooled and water (3.6 ml) was carefully added followed by 4 N sodium hydroxide (3.6 ml) and an additional amount of water (10 ml). The salts were filtered and washed with tetrahydrofuran and the combined filtrates were concentrated under reduced pressure. The residue was hydrogenated over Adams catalyst (0.5 g) in 100 ml of 0.5 N hydrochloric acid at 50 psi for 14 hr to reduce any enamine which had formed. The catalyst was filtered and the filtrate was made strongly alkaline with solid potassium carbonate followed by 50% sodium hydroxide. The aqueous mixture was extracted with methylene chloride, which was concentrated to leave a pale yellow oil (4.5 g). Bulb-to-bulb distillation (125°, 0.07 mm) provided a colorless, hygroscopic oil (4.22 g, 65%) which on standing solidified. The infrared spectrum showed absorption at $\nu_{max}^{CHCl_3}$ 1500, 1485, 1260, 1209, 1165, 1040, 938, and 858 cm^{-1}; pmr ($CDCl_3$) δ 1.40–3.35 (m, 13), 5.82 (s, 2), and 6.58 (bs, 2). A hydrochloride salt was prepared for analysis by passing dry hydrogen chloride into an ether solution of the amine. Recrystallization from ethanol gave colorless needles, mp 265–266° dec.

Anal. Calcd for $C_{14}H_{18}NO_2Cl$: C, 62.80; H, 6.78; Ni, 5.23. Found: C, 62.45; H, 6.82; N, 5.02.

8,9-Methylenedioxy-1,2,3,6-tetrahydro-5*H*-pyrrolo[2,1*b*][3]-benzazepine (1).—A solution of the amine **7** (513 mg, 2.24 mmol) in 2% acetic acid (3 ml) was stirred under nitrogen at 80° (oil bath) for 100 min, during which time a precipitate of mercurous acetate had formed and the solution had darkened. The precipitated salts were filtered and the filtrate was passed through Dowex chelating resin A-1 (40 ml wet volume) eluting with 0.2 N hydrochloric acid. The eluents were made strongly basic with 50% sodium hydroxide and extracted with methylene chloride. The organic solution was filtered and concentrated to leave the enamine **1** (301 mg, 59%) as a dark oil. Tlc (5% triethylamine in benzene) indicated that the material was homogeneous. A portion was filtered through a small amount of alumina (Woelm neutral) to give a pale yellow oil which on standing partially crystallized. Solutions of the purified material rapidly turned dark even when protected by nitrogen atmosphere.[10] The infrared spectrum showed absorptions at $\nu_{max}^{CHCl_3}$ 1640, 1605, 1500, 1580, 1230, 1045, and 795 cm^{-1}; pmr ($CDCl_3$) δ 1.60–2.02 (m, 2), 2.65 (t, 2, J = 8.0 Hz), 2.90 (ut, 2, J = 4.5 Hz), 3.25 (t, 2, J = 8.0 Hz), 3.42 (ut, 2, J = 4.5 Hz), 4.90 (bs, 1), 5.75 (s, 2), 6.42 (bs, 2); uv $\lambda_{max}^{EtOH-OH^-}$ 322 nm; $\lambda_{max}^{EtOH,\ H^+}$ 322, 291, and 235 nm; mass spectrum m/e 229.110 (calcd for $C_{14}H_{16}NO_2$, 229.110).

11,12-Methylenedioxy-2-oxo-3-carboethoxy-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (10).—A mixture of enamine **1** (57.6 mg, 0.250 mmol) and ethyl γ-bromoacetoacetate was refluxed in acetonitrile (2 ml) for 17 hr. Ether (10 ml) was added and the precipitated salt was washed by decantation with two small portions of ether. The material was taken up in water and the aqueous solution was made alkaline with potassium carbonate (pH 10) and extracted with methylene chloride. The organic solution was filtered and concentrated under reduced pressure to leave the keto ester **10** as a yellow, gummy solid (45.6 mg, 51%). Recrystallization from ethyl acetate provided the analytical sample as colorless needles: mp 171–173°; ir $\nu_{max}^{CHCl_3}$ 1755, 1720, 1505, 1485, 1370, 1145, 1045, 945, and 860 cm^{-1}; pmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz), 1.45–2.05 (m, 4), 2.30 (d, 1, J = 18 Hz), 2.92 (d, 1, J = 18 Hz), 2.20–3.62 (m, 6), 3.80 (d, 1, J = 11 Hz), 4.22 (p, 2), 5.85 (s, 2), 6.50 (s, 1), and 6.82 (s, 1); uv λ_{max}^{EtOH} 292 nm (ϵ 6050), 234 (5880); $\lambda_{max}^{EtOH-OH^-}$ 288 nm (ϵ 22,200); mass spectrum m/e 357 (M^+), 314, 228 (100), and 156.

11,12-Methylenedioxy-2-oxo-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine (11). A. By Hydrolysis of 10.—A solution of the keto ester **10** (21.8 mg, 0.061 mmol) in 5% sulfuric acid (3 ml) was heated under gentle reflux for 14 hr. The mixture was cooled, made alkaline with 50% sodium hydroxide, and extracted with methylene chloride. The organic solution was filtered and concentrated under reduced pressure to leave a crystalline residue (15.6 mg, 90%). Sublimation (130–150°, 0.01 mm) and recrystallization from ethyl acetate–hexane gave colorless needles, mp 173–174°. The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1745, 1505, 1485, 1255, 1045, 945, and 865 cm^{-1}; pmr ($CDCl_3$) δ 1.20–1.95 (m, 4), 2.22 (d, 1, J = 18.0 Hz), 2.24–3.85 (d, 1, J = 18.0 Hz), 5.88 (s, 2), 6.52 (s, 1), and 6.79 (s, 1); mass spectrum m/e 285 (M^+), 242 (100), and 228.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found, C, 71.56; H, 6.82; N, 4.80.

B. By Annelation of Enamine 1 with Bromoacetone.—A solution of enamine **1** (350 mg) and bromoacetone (260 mg) was heated for 10 hr under reflux in *ca.* 15 ml of acetonitrile. The mixture was diluted with 5% sulfuric acid and extracted with ether. The aqueous solution was basified and extracted with methylene chloride to yield 170 mg (40%) of enamino ketone **15**. The material showed carbonyl absorption at 1700 cm^{-1} but no absorption at 1745 cm^{-1} in its infrared spectrum. Treatment of **15** with 1 M sodium acetate in acetic acid at room temperature effected no change, but warming on the steam bath for 8 hr produced a mixture showing new carbonyl absorption at 1690 cm^{-1} and peaks at 1635 and 1620 cm^{-1} but no maxima in the 1745-cm^{-1} region. Treatment of **15** with 2% trifluoroacetic acid in methylene chloride had effected no change after 32 hr at room temperature. A solution of **15** (150 mg), *p*-toluenesulfonic acid

(10) After this paper had been submitted, Professor Steven Weinreb of Fordham University kindly informed us of the synthesis of crystalline enamine **1** in his laboratory. The ir and pmr spectra of our preparation were identical with those of a sample provided by Dr. Weinreb. He noted that contact with chlorinated solvents as we used in our work greatly accelerates the decomposition of the enamine.

(103 mg), and pyrrolidine (110 mg) was heated under reflux in a Soxhlet extraction apparatus containing molecular sieves (5A) for 2 days. The cooled reaction mixture was stirred for 20 min in 5% sulfuric acid, after which the layers were separated and the benzene layer was extracted twice with 20-ml portions of 5% sulfuric acid. The sulfuric acid solution was basified and extracted with methylene chloride. The methylene chloride was evaporated and the residue was subjected to preparative tlc (silica gel, 10% methanol–chloroform) to yield 28 mg (19%) of ketone 11 identical in all respects with the material obtained above. The other materials from preparative tlc showed no maxima at 1745 cm^{-1} in their infrared spectra.

Deuterium Exchange of Ketone 11.—A solution of the tetracyclic ketone 11 (12.0 mg, 0.045 mmol) in 1:1 deuterium oxide–dioxane (0.5 ml) containing a small amount of anhydrous potassium carbonate was heated at 80° (oil bath) for 5 hr. Additional deuterium oxide was added (0.25 ml) and the solution was allowed to stand at room temperature for 24 hr. The solution was extracted with dry methylene chloride and the organic phase was washed with a small volume of deuterium oxide. The organic solution was concentrated under reduced pressure and the residue was dried under high vacuum for 15 hr to give the deuterated ketone (11.6 mg, 95%) as a colorless, crystalline solid. The pmr spectrum showed a disappearance of the AB quartet assigned to the methylene protons of C-1 in the protio compound. The mass spectrum showed *m/e* 289, 244, and 228.

11,12-Methylenedioxy-2,3,3a,4,5,6,8,9-octahydro-1*H*-benzo[*a*]cyclopenta[*i*]quinolizine.—A solution of ketone 11 (18 mg), 1,3-propanedithiol (180 mg), and *p*-toluenesulfonic acid hydrate (25 mg) in benzene (15 ml) was placed in a Soxhlet extractor containing molecular sieve (5A) and heated under reflux for 4.5 hr. The reaction mixture was extracted with 5% sulfuric acid and the aqueous extracts were basified and extracted with methylene chloride to yield the crude thioketal, which showed no carbonyl absorption in its infrared spectrum. The crude thioketal was dissolved in 10 ml of 95% ethanol and heated under reflux overnight with *ca.* 100 mg of Raney nickel. The reaction mixture was filtered, concentrated, and subjected to preparative tlc (5% methanol–chloroform on silica gel) to afford 10 mg of the title compound. The mass spectrum of this material was identical with that of an authentic sample[8] obtained from the hydrochloride in the usual manner. The picrates[8] of the two samples were identical by melting point behavior and their pmr spectra were identical.

Registry No.—**1**, 35667-11-9; **2**, 35667-12-0; **3**, 35667-13-1; **4**, 35667-14-2; **4** (HCl), 35667-15-3; **5**, 35667-16-4; **6**, 35667-17-5; **7**, 35667-18-6; **7** (HCl), 35667-19-7; **10**, 35667-20-0; **11**, 35667-21-1.

The Direct Utilization of Unsaturated Sugars in Nucleoside Syntheses. The Synthesis, Configuration, and Conformation of Certain Hex-1-enitol-3-yl-, Hex-2-enopyranosyl-, and Hexopyranosylpurines. The Preparation of 9-(1,5-Anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)adenine and 9-(2,3-Dideoxy-β-D-*erythro*-hex-2-enopyranosyl)adenine from D-Glucal[1]

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The acid-catalyzed fusion of 3,4,6-tri-*O*-acetyl-D-glucal (I) and 2-acetamido-6-chloropurine has furnished the α and β anomers of 2-acetamido-6-chloro-9-(4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine (III) and 2-acetamido-6-chloro-9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol-3-yl)-9*H*-purine (IX). A facile conversion of III to 2-amino-9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)-9*H*-purine-6-thiol (VI) and 9-(2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine (VII) was effected by the appropriate functional group transformation. Cis dihydroxylation of VII furnished the 2′,3′-dihydroxyhexopyranoside, which hydrolyzed to give D-mannose, D-allose, and guanine and firmly established the position of the endocyclic double bond of III as C-2′–C-3′. The direct fusion of I with either 6-chloro-2-methylthiopurine or 6-benzamidopurine furnished a mixture of the corresponding diastereoisomeric 9-(1,5-anhydro-2,3-dideoxy-D-*erythro*-hex-1-enitol-3-yl)-9*H*-purines and 9-(2,3-dideoxy-D-*erythro*-2-enopyranosyl)-9*H*-purines. The conformation and anomeric configuration of these nucleosides was assigned with the aid of pmr spectroscopy. 9-(2,3-Dideoxy-β-D-*erythro*-hexopyranosyl)-adenine (XXIII) and 9-(1,5-anhydro-2,3-dideoxy-D-*arabino*-hexitol-3-yl)adenine (XXII) were obtained by hydrogenation of XIX and XX, respectively. Compound XXIII has a 2′,3′-dideoxypyranosyl structure similar to that found in amicetin.

The direct utilization of glycals in the "acid-catalyzed" fusion reaction has been the subject of preliminary reports from our laboratories[3,4,5] as a new and general synthetic approach to the preparation of 2′,3′-unsaturated pyranosyl nucleosides structurally related to Blasticidin S.[6] The structural elucidation[7,8] of Blasticidin S has established this nucleoside antibiotic to be a pyranosyl derivative of cytosine possessing an endocyclic double bond in the 2,3 position of the carbohydrate moiety. Blasticidin S has been shown to inhibit several transplantable animal tumors[9] and to inhibit protein synthesis.[10]

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