Marthasterone diacetate[16] and our diacetate IX show distinct differences in their nmr (δ 0.50–2.0 region) and mass spectra [characteristic *m/e* 98 peak ($(CH_3)_2C{=}CH\text{-}COHCH_2$) of marthasterone diacetate is relatively unimportant in IX].

The presence of the $\Delta^{20(22)}$ double bond in VIII suggests that it could be a precursor (either by hydration or through an intermediate epoxide) to (20*S*,22*R*)-monohydroxy or (20*S*,22*R*)-dihydroxy derivatives, believed to be involved[17] in the oxidative cleavage to pregnenolones (in the present case to genin I), or that the double bond arose from biodehydration of a 20*S* or 22*R* monohydroxy 23-ketone. Although labeling work is required to prove the bioorigin of the unique 23-oxo function in VIII and XV,[15] it can be speculated that it arises from the 22,23-olefinic linkage, so prevalent[18] in marine sterols, *via* an epoxide intermediate.

Work on other constituents of *A. planci* and a search for pregnanes from other echinoderms is currently in progress in our laboratory.

Acknowledgment. Financial assistance from the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged. Thanks are due to Dr. L. J. Durham, Dr. A. M. Duffield, and Mr. R. Ross for the spectral measurements.

(16) A. M. Mackie and A. B. Turner, *Biochem. J.*, **117**, 543 (1970).
(17) See S. Burstein and M. Gut, *Steroids*, **14**, 207 (1969), for experiments with adrenocortical preparations.
(18) J. Austin in "Advances in Steroid Biochemistry and Pharmacology," Vol. I, M. H. Briggs, Ed., Academic Press, New York, N. Y., 1970, pp 73–87.
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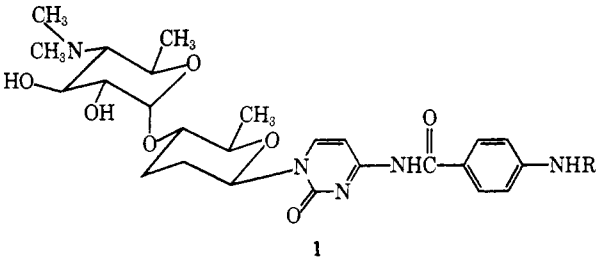
Total Synthesis of the Amino Sugar Nucleoside Antibiotic, Plicacetin

Sir:

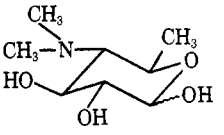
Amicetin, bamicetin, and plicacetin are three structurally similar amino sugar nucleoside antibiotics isolated from the filtrates of an actinomycete designated *Streptomyces plicatus*.[1,2] Members of this group of antibiotics are potent inhibitors of *in vitro* protein synthesis,[3] and are reported to inhibit the KB strain of human epidermoid carcinoma cells[4] and increase the survival time of mice[5] with leukemia-82. They also inhibit Gram positive and Gram negative bacteria as well as mycobacteria broth both *in vitro* and *in vivo*.[2])

We wish to report here the total synthesis of plicacetin (**1**). To our knowledge this is the first total synthesis of a disaccharide pyrimidine nucleoside antibiotic.

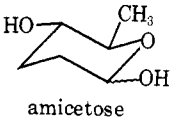


1

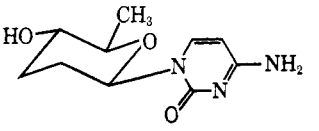
plicacetin, R = H
amicetin, R = L-α-methyl seryl



amosamine
2



amicetose
3



4

The gross structure and stereochemistry of amicetin and plicacetin have been determined[6–12] and several important fragments have been synthesized. Amosamine (**2**) has been shown to have the D-gluco configuration[13] and amicetose (**3**) is shown to have the 2,3,6-trideoxy-D-erythro structure[14] by synthesis.

The most difficult synthetic problem in the total synthesis of plicacetin was the stereospecific formation of the α-disaccharide linkage. The solution to this problem involved the synthesis of the stable crystalline β-chloro azido sugar derivative, **5**, which coupled without participation of the neighboring benzyloxy group to give excellent yields of derivatives with the required α configuration. The β-nucleoside linkage, in many cases easy to establish with the aid of a neighboring group, also represented a synthetic problem because of the lack of such groups. This problem had previously been solved during the synthesis[11] of the nucleosidic alcohol degradation fragment **4** of the antibiotic.

The chloro azido sugar **5** was prepared from the known α-methyl glycoside[15] **6** by the following series of reactions.

The methyl glycoside **6** was treated at 0° with acetic acid–acetic anhydride containing 0.5% sulfuric acid

(1) T. H. Haskell, *J. Amer. Chem. Soc.*, **80**, 747 (1958), and references cited therein.
(2) Amicetin was first isolated without bamicetin or plicacetin by C. DeBoer, E. L. Caron, and J. W. Hinman, *ibid.*, **75**, 499, 5864 (1953).
(3) T. D. Brock, *J. Bacteriol.*, **85**, 527 (1963).
(4) C. G. Smith, W. L. Lummis, and J. E. Grady, *Cancer Res.*, **19**, 847 (1959).
(5) J. H. Burchenal, M. Yuceloglu, M. K. Dagg, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, **86**, 891 (1954).
(6) E. H. Flynn, J. W. Hinman, E. L. Caron, and D. O. Woolf, *J. Amer. Chem. Soc.*, **75**, 5867 (1953).
(7) P. Sensi, A. M. Grecco, G. G. Gallo, and G. Rolland, *Antibiot. Chemother.*, **7**, 645 (1957).
(8) C. L. Stevens, R. J. Gasser, T. M. Mukherjee, and T. H. Haskell, *J. Amer. Chem. Soc.*, **78**, 6212 (1956).
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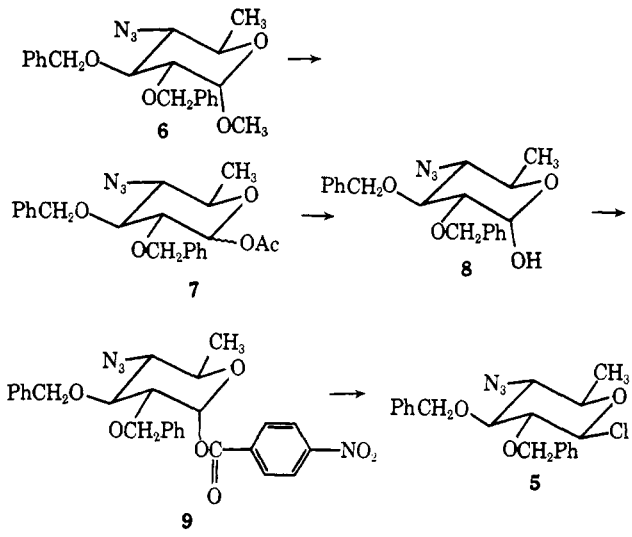
(10) C. L. Stevens, N. A. Nielsen, and P. Blumbergs, *J. Amer. Chem. Soc.*, **86**, 1894 (1964).
(11) C. L. Stevens, N. A. Nielsen, P. Blumbergs, and K. G. Taylor, *ibid.*, **86**, 5695 (1964).
(12) N. Takamura, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **15**, 1776 (1967).
(13) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Amer. Chem. Soc.*, **85**, 1552 (1963).
(14) C. L. Stevens, P. Blumbergs, and D. L. Wood, *ibid.*, **86**, 3592 (1964).
(15) C. L. Stevens, P. Blumbergs, F. A. Daniher, D. H. Otterbach, and K. Grant Taylor, *J. Org. Chem.*, **31**, 2822 (1966).



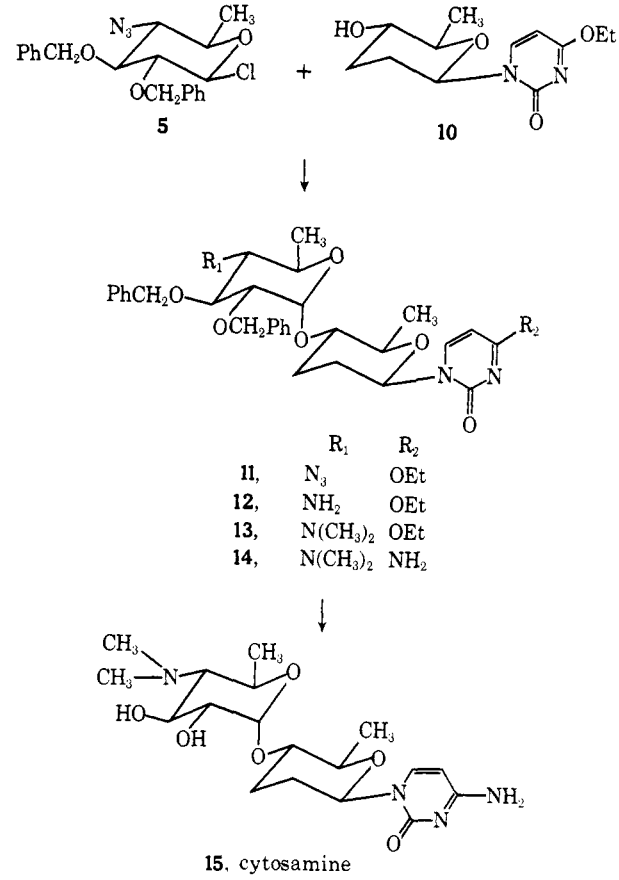
to give a 90% yield of the 1-O-acetyl derivative **7** as a syrup. Acetate **7** was deacetylated by means of sodium methoxide at room temperature for 45 min and the resulting free sugar **8** could be crystallized in the α form, mp 91–93°, in 72% yield.

Mutarotation studies in pyridine indicated that inversion to the β form occurred slowly, if at all, which allowed the free sugar to be converted to the 1-α-*p*-nitrobenzoate derivative, **9**, mp 66–67° in 58% yield. The *p*-nitrobenzoate reacted with dry hydrogen chloride to give clean inversion at the anomeric carbon and produced the crystalline β-chloro derivative, **5** (90%), mp 94.5–95.5°. The β configuration was confirmed by the rotation, $[\alpha]_D$ −155° (*c* 1.25, $CHCl_3$); the nmr spectrum (C_6D_6) showed the anomeric hydrogen as a doublet ($J_{1,2}$ = 8 Hz) at δ 4.85; and a coupling reaction with methanol in the presence of silver carbonate which cleanly gave the starting α-methyl glycoside.

The nucleosidic alcohol **10** was available in our laboratory from the previous synthesis of **4**.[11] Coupling to form the α-disaccharide linkage and the final chemical maneuvers to synthesize cytosamine and plicacetin are shown below.

The chloro sugar **5** was treated with the nucleosidic alcohol **10** in the molten state, under diminished pressure and in the presence of Dowex 1-X2 (OH^-), to give a 64% yield of crude **11**. Preparative thin-layer chromatography (2:1 $CHCl_3$–Et_2O) and two recrystallizations from ether gave 38% 1-[2,3,6-trideoxy-4-(4-azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-β-D-erythrohexapyranosyl]-4-ethoxy-2(1*H*)-pyrimidone (**11**), mp 106–108°; $[\alpha]_D$ −199° (*c* 1.2, $CHCl_3$). The α configuration of the disaccharide linkage was confirmed by nmr (CD_3COCD_3) which showed the anomeric proton as a doublet ($J_{1,2}$ = 3 Hz) at δ 5.08.

Reduction of the azido group in **11** was accomplished in a hydrogen atmosphere using 10% palladium/carbon as catalyst and gave the amine **12**, which after reductive methylation (HCHO, H_2, 10% Pd/C, EtOH) gave **13**, in 84% overall yield. Treatment of **13** with a liquid ammonia–ethanol mixture at 110° produced the cytosine derivative **14** in excellent yield (88%). Cytosamine **15** was obtained by reductive debenzylation in ethanol of **14** using hydrogen with 10% palladium/carbon and hydrochloric acid as catalysts. After recrystallization from isopropyl alcohol the synthetic cytosamine, mp 254–256° dec, was identical in all respects [ir(KBr), nmr (dihydrochloride in D_2O), $[\alpha]_D$ (0.1 *N* HCl), tlc (2:1 CH_3COCH_3–CH_3OH)] with natural product.[1] A mixture melting point was without depression. Conversion of **15** to its triacetate, mp 220.5–222° after recrystallization from benzene–hexane, was accomplished in 90% yield by treatment with acetic anhydride–pyridine (1:6) at room temperature overnight. A mixture melting point with the triacetate[1] of natural cytosamine was undepressed and ir (KBr) and nmr (CD_3CN) spectra were superimposable. The conversion of cytosamine to plicacetin has been recorded[1] previously.



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Bis(pentalenylnickel)

Sir:

Over the past 16 years two ideas have been formulated for making stable derivatives of unstable nonaromatic hydrocarbons. One was to make transition metal complexes, an extension of the explanation for the stability