Synthesis of the Basic Nucleoside Skeleton of the Polyoxin Complex[1]

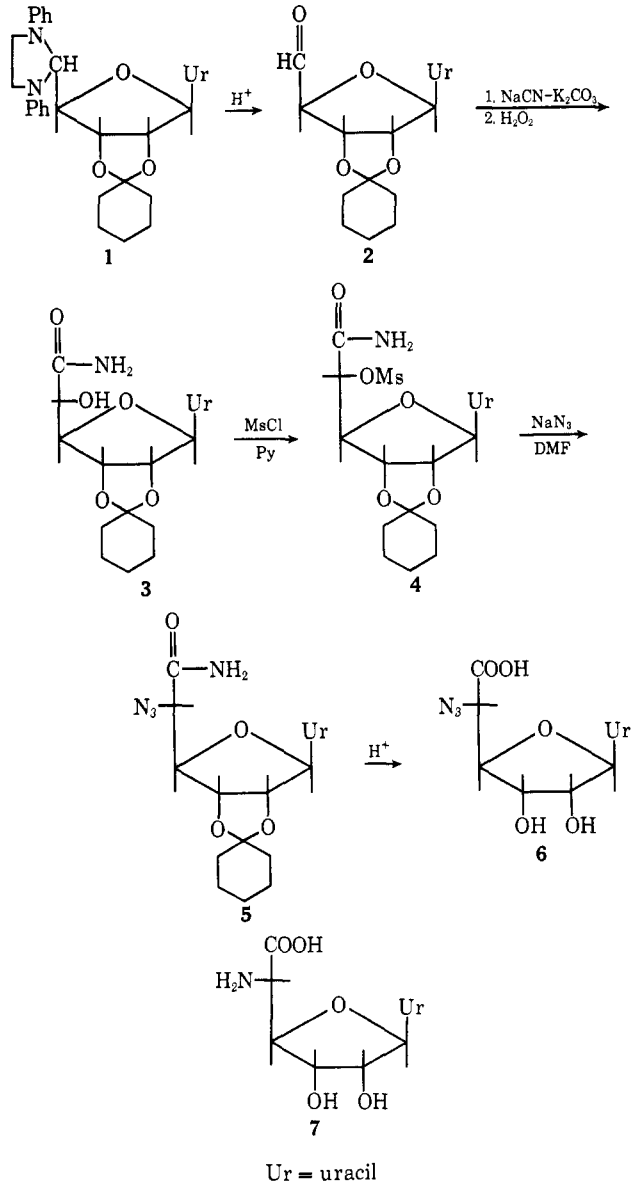
Sir:

In recent years the structures of a number of members of the Polyoxin complex of antifungal agents have been elucidated through the exhaustive efforts of Isono, *et al.*[2] These compounds are interrelated in that they are all derivatives of the unusual nucleoside amino acid 1-(5-amino-5-deoxy-β-D-allofuranosyluronic acid)-uracil (**7a**). Naka, *et al.*,[3] have very recently reported the synthesis of a fully protected derivative of the sugar component of **7a** and we now describe the synthesis of the basic nucleoside skeleton **7a** as well as of its α-L-talo isomer, **7b**.

Oxidation of 2′,3′-*O*-cyclohexylideneuridine[4] with dimethyl sulfoxide and diisopropylcarbodiimide in the presence of dichloroacetic acid[5] gave the 5′-aldehyde **2** which was isolated in 78% yield as its crystalline 1,3-diphenylimidazolidine derivative **1** (mp 224–225°)[6] upon reaction with *N*,*N*′-diphenylethylenediamine.[7] Subsequent treatment of **1** with 2.5 equiv of *p*-toluenesulfonic acid monohydrate in methylene chloride–acetone at 23° for 30 min followed by filtration of the amine salt gave analytically pure 2′,3′-*O*-cyclohexylideneuridine 5′-aldehyde in essentially quantitative yield:[8] nmr ($CDCl_3$) 9.45 ppm (s, 1, CHO).

The reaction of **2** (or its hydrate) with sodium cyanide in aqueous methanolic potassium carbonate gave a mixture of epimeric cyanohydrins, but purification of these compounds was difficult due to their facile reversion to **2**. If, however, **2** was treated briefly at 0° with sodium cyanide as above and an excess of 15% hydrogen peroxide was then added, the epimeric hydroxyamides **3a** and **3b** were formed in a rapid, irreversible reaction. Separation of **3a** and **3b** was achieved by fractional crystallization from ethanol giving the α-L-taluronamide **3a** (25%) with mp 280–282° ($[\alpha]^{23}D$ 46.1° (*c* 0.11, MeOH); nmr (DMSO-d_6) 5.93 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 4.41 (t, 1, $J_{3',4'}$ = 2.5 Hz, $J_{4',5'}$ = 2.5 Hz, $C_{4'}H$), 7.94 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H)) and the β-D-alluronamide isomer **3b** (23%) as the ethanol solvate with mp 145–148° ($[\alpha]^{23}D$ −50.4° (*c* 0.15, MeOH), nmr (DMSO-d_6) 5.93 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}H$), 4.28 (t, 1, $J_{3',4'}$ = 2 Hz, $J_{4',5'}$ = 2 Hz, $C_{4'}H$), 7.76 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H)).

The structures of **3a** and **3b** were assigned by hydrogenation of the uracil rings using a rhodium catalyst[9] followed by vigorous acidic hydrolysis of the glycosidic and amide functions. In this way **3a** was converted into L-taluronic acid[10] while **3b** gave D-alluronic acid,[2] the acids being distinguished and characterized by paper chromatography and by the formation of their crystalline brucine salts.[2,10]



a, series as above
b, series as above but with inverted configuration at $C_{5'}$ of the sugar moiety

Reaction of **3a** with methanesulfonyl chloride in pyridine gave the 5-mesyl derivative **4a** isolated in 81% yield as the acetone solvate with mp 148–149°. Subsequent reaction of **4a** with sodium azide in dimethylformamide at 60° for 6 hr gave an 86% yield of homogeneous 1-(5-azido-2,3-*O*-cyclohexylidene-5-deoxy-β-D-allofuranosyluronamide)uracil (**5a**) with mp 156–159°: $[\alpha]^{23}D$ 30.3° (*c* 0.11, MeOH); nmr (acetone-d_6) 5.93 (d, 1, $J_{1',2'}$ = 1.5 Hz, $C_{1'}H$), 7.76 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H). Vigorous hydrolysis of **5a** in aqueous dioxane at 90° for 18 hr in the presence of Dowex-50 (H^+) resin gave the 5-azido-D-alluronic acid derivative **6a** which was isolated in 50% yield by ion exchange chromatography on a column of Bio-Rad AG 1 × 8 (OAc^-) resin using triethylammonium bicarbonate as eluent. Palladium-catalyzed reduction of the azido function

(1) This work was presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., 1971, Abstract C-4.
(2) K. Isono, K. Asahi, and S. Suzuki, *J. Amer. Chem. Soc.*, **91**, 7490 (1969), and references therein.
(3) T. Naka, T. Hashizume, and M. Nishimura, *Tetrahedron Lett.*, 95 (1971).
(4) S. Chládek and J. Smrt, *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).
(5) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).
(6) All crystalline products gave satisfactory elemental analyses and nmr spectra.
(7) H. W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).
(8) Subsequent work in this laboratory by Dr. G. B. Howarth has shown that treatment of **1** with Dowex-50 (H^+) resin in aqueous tetrahydrofuran readily gives **2** as its crystalline hydrate with mp 189–190°. Subsequent azeotropic dehydration of this hydrate then gives the crystalline free aldehyde **2** with 165–166 mp°.
(9) W. E. Cohn and D. G. Doherty, *J. Amer. Chem. Soc.*, **78**, 2863 (1956).
(10) J. R. Siddiqui and C. B. Purves, *Can. J. Chem.*, **41**, 382 (1963).

of **6a** afforded 1-(5-amino-5-deoxy-β-D-allofuranosyluronic acid)uracil (**7a**) with mp 238–243° dec from ethanol ($[\alpha]^{23}D$ 17.6° (*c* 0.49, H_2O); nmr (TFA) 5.72 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{1'}H$), 6.17 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_5H)) in agreement with the properties of "uracil polyoxin C" described by Isono, *et al.*[2]

In a similar series of reactions the β-D-alluronamide derivative **3b** was converted in 94% yield into the 5-*O*-mesyl derivative **4b** ($[\alpha]^{23}D$ −11.7° (*c* 0.46, MeOH); nmr (acetone-d_6) 6.05 ppm (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}$ H)) and thence to the 5-azido-α-L-taluronamide **5b** (75%) ($[\alpha]^{23}D$, 25.2° (*c* 0.1, MeOH); nmr (acetone-d_6) 5.94 (d, 1, $J_{1',2'}$ = 0.5 Hz, $C_{1'}$ H), 7.84 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_6H)), both of which were isolated as analytically pure foams by chromatography on silicic acid. Acidic hydrolysis of **5b** with Dowex-50 (H^+) as above gave the 5-azido-α-L-taluronic acid **6b** (38% with mp 200–202°) and subsequent reduction gave 1-(5-amino-5-deoxy-α-L-talofuranosyluronic acid)uracil (**7b**) with mp 215–217° dec from ethanol: $[\alpha]^{23}D$ 9.9° (*c* 0.45, H_2O); nmr (TFA) 5.67 (d, 1, $J_{1',2'}$ = 1 Hz, $C_{1'}H$), 6.15 ppm (d, 1, $J_{5,6}$ = 8 Hz, C_5H). The amino acids **7a** and **7b** could not be separated by paper chromatography in several solvents. They can, however, be distinguished by their nmr spectra which are very similar but show distinctly different signals for their $C_{1'}$ and C_5 protons either alone or as mixtures.

Deamination of α-amino acids is recognized to occur with retention of configuration[11] and treatment of **7a** and **7b** with nitrous acid gave a pair of chromatographically distinguishable α-hydroxy acids. The acid arising from **7a** was shown to correspond to that obtained by acidic hydrolysis of the amide and acetal functions of **3b**. Similarly, a common product resulted from deamination of **7b** or hydrolysis of **3a**, these results being consistent with the expected inversion of configuration during formation of the azido amides **5a** and **5b** and confirming the stereochemical assignments of the amino acids.

Other routes to both sugar and heterocyclic base analogs of polyoxin nucleosides have been concomitantly developed and will be reported shortly.

(11) P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature (London)*, **166**, 179 (1950).
(12) Syntex Postdoctoral Fellow, 1968–1970.

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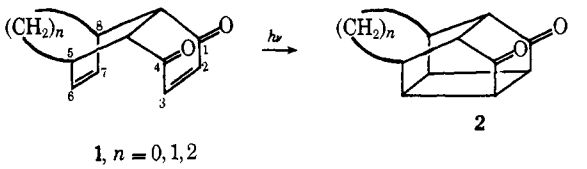
Solution Photochemistry. VI. Novel Photorearrangement of the Butadiene–Benzoquinone Diels–Alder Adduct[1,2]

Sir:

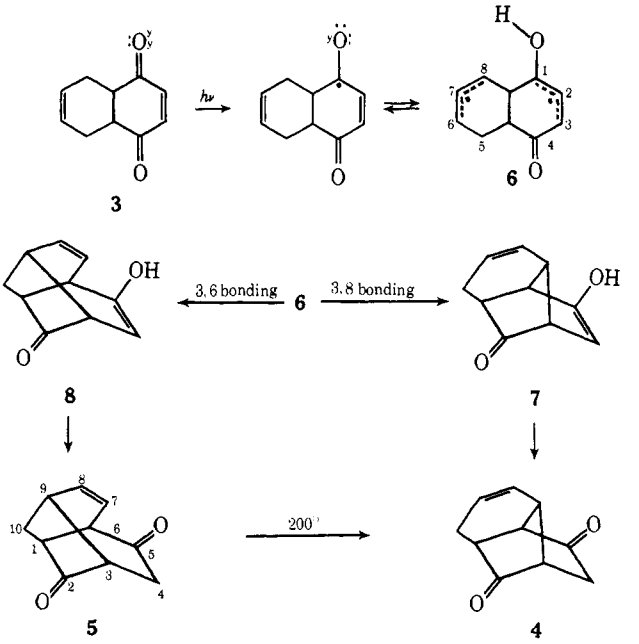
The photochemical cyclobutane ring-forming reaction between two remote double bonds in the same molecule has traditionally provided organic chemists with a method for the synthesis of highly strained and unusual polycyclic ring systems.[3] For example, the Diels–Alder adducts of *p*-benzoquinone with cyclobutadiene, cyclopentadiene, and cyclohexadiene (**1**, $n = 0, 1,$ and 2, respectively) undergo smooth photochemical closure to the corresponding cage compounds **2**.[4]



1, $n = 0, 1, 2$ **2**

Remarkably, the presence of a bridge or a bond between carbon atoms 5 and 8 seems to be a prerequisite for the success of this reaction; photolysis of the nonbridged butadiene–benzoquinone Diels–Alder adduct **3** (*cf.* Scheme I) has been reported[4a] to lead only to tar and ill-defined products postulated to arise from intermolecular α,β-unsaturated double bond dimerization.

Scheme I



Interest in this dichotomy has led us to a reinvestigation of the photochemistry of the butadiene–benzoquinone Diels–Alder adduct **3**. We report here that irradiation of this material under carefully controlled conditions does not lead to cage product formation but gives instead two novel tricyclic ene–diones in low but nevertheless useful yields; the first of these, **4**, represents a facile entry into the copaborneol,[5a] copacamphene,[5a] and sativene[5b] ring systems while the other, **5**, possesses a previously unknown carbon skeleton.

Conventional irradiation of **3**[6] (*i.e.*, 450-W Hanovia lamp, Pyrex filter, immersion well apparatus) at varying concentrations in a variety of solvents led, in agreement with literature reports,[4a] to amorphous, uncharacterizable material. However, selective n → π* ex-

(1) Part V: J. R. Scheffer and B. A. Boire, *J. Amer. Chem. Soc.*, in press.
(2) Support of this research by the National Research Council and the University of British Columbia is gratefully acknowledged.
(3) W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966).
(4) (a) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3062 (1964); (b) P. E. Eaton and S. A. Cerefice, *Chem. Commun.*, 1494 (1970).
(5) (a) M. Kolbe-Haugwitz and L. Westfelt, *Acta Chem. Scand.*, **24**, 1623 (1970), and references cited therein; (b) P. de Mayo and R. E. Williams, *J. Amer. Chem. Soc.*, **87**, 3275 (1965).
(6) Synthesized by the method of E. E. van Tamelen, *et al.*, *ibid.*, **91**, 7315 (1969).