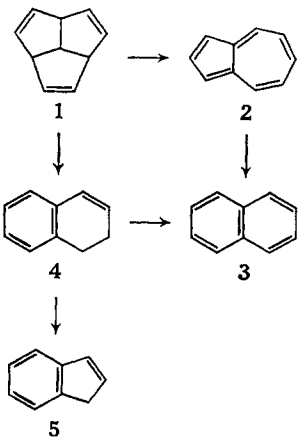
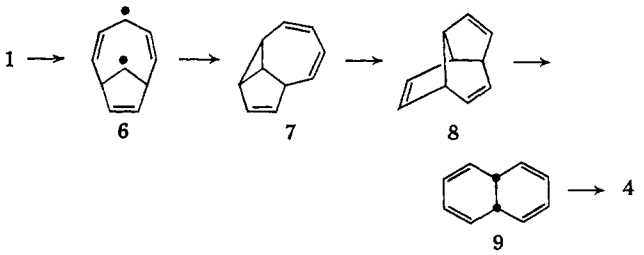
Scheme I



yields increasing amounts of both naphthalene and indene at the expense of **1**, **2**, and **4**. In the limit (735°, 20 sec, 100% conversion) the ratio of **3** to **5** reaches 7:1.

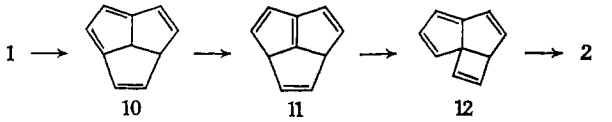
Carbon–carbon bond rupture to produce **6** represents one of the more plausible molecular changes which triquinacene might suffer at elevated temperatures. This diradical could collapse to "isobullvalene" (**7**),[8] a $(CH)_{10}$ isomer which has been reported[8] to rearrange quantitatively at room temperature to "lumibullvalene" (**8**).[9] Above 280° the latter compound is known[9] to isomerize further to *cis*-9,10-dihydronaphthalene (**9**). We have found that **9** fails to survive under our pyrolysis conditions (700°, 0.5 sec), giving **3**, **4**, and **5** as the principal products.[10] Thus the reaction pathway outlined in Scheme II could readily account for the formation of **4** from triquinacene; since **7**, **8**, and **9** all isomerize faster than **1** itself, they should not be expected among the pyrolysis products.

Scheme II



The mechanistic details for the lower energy thermal conversion of triquinacene to azulene, on the other hand, appear less obvious. In particular most known $(CH)_{10}$ hydrocarbons, including **7**, must be excluded as possible reaction intermediates, for none yields azulene on heating;[3] in fact most rearrange ultimately to **9**, another thermal sink on the $(CH)_{10}$ energy surface.[3] Concerted loss of molecular hydrogen from triquinacene[11] to give **10** would remove the molecule from the $(CH)_{10}$ energy surface and thereby preclude isomerization to **9**. We wish to suggest that **10** could suffer sequential [1,5]-sigmatropic shifts of hydrogen and carbon, respectively, to produce **12**, which should open to azulene above 600° (Scheme III). This mechanistic hypothesis predicts an

Scheme III



exclusive loss of allylic hydrogens from triquinacene, and labeling studies designed to test this proposition have been initiated in our laboratory.

Acknowledgments. We are indebted to Professor P. Deslongchamps for generously supplying details of his efficient new triquinacene synthesis in advance of publication.[1e] Financial support from the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, and the Research Committee of the University of California, Los Angeles, is gratefully acknowledged.

Lawrence T. Scott,* Garabed K. Agopian
Contribution No. 3324, Department of Chemistry
University of California
Los Angeles, California 90024
Received April 4, 1974

Synthesis of Coformycin

Sir:

Coformycin (**1**) is a unique nucleoside, having a moiety of 3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8(*R*)-ol as the base moiety, and has an interesting biological property.[1] We now wish to report the total synthesis of coformycin starting from a purine ribonucleoside (Scheme I).

9-β-D-Ribofuranosylpurine (**2**) was taken as the starting material, since it is a naturally occurring nucleoside antibiotic called nebularine[2] and was already synthesized,[3] and even coformycin might be biologically formed by ring expansion from such a purine riboside. Treatment of **2** with acetic anhydride in pyridine at 5° for 2 days afforded 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**3**) in 98% yield [M^+ 378, $[\alpha]^{26}D$ −10.8 (*c* 1.5, CH_3OH)].[4] The introduction of a C_1-unit, which can be used for the ring expansion of purine moiety, was achieved by the application of the method of Linschitz and Connolly.[5] Thus, the photoaddition of methanol to **3** was carried out under argone atmosphere and irradiation (10-W low-pressure mercury lamp) at 5° for 3.5 hr, affording 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-hydroxymethyl-1,6-dihydropurine (**4**) in 96% yield [M^+ 410, mp 84–86°, uv_{max} (CH_3OH)

(1) H. Nakamura, G. Koyama, Y. Iitaka, M. Ohno, N. Yagisawa, S. Kondo, K. Maeda, and H. Umezawa, *J. Amer. Chem. Soc.*, **96**, 4327 (1974).

(2) L. Ehrenberg, H. Hedström, N. Löfgren, and B. Takman, *Sv. Kem. Tidskr.*, **58**, 269 (1946); R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 261.

(3) (a) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953); (b) J. J. Fox, I. Wempen, A. Hampton, and I. L. Doerr, *J. Amer. Chem. Soc.*, **80**, 1669 (1958).

(4) H. Iwamura and T. Hashizume, *J. Org. Chem.*, **33**, 1796 (1968).

(5) H. Linschitz and J. S. Connolly, *J. Amer. Chem. Soc.*, **90**, 2980 (1968).

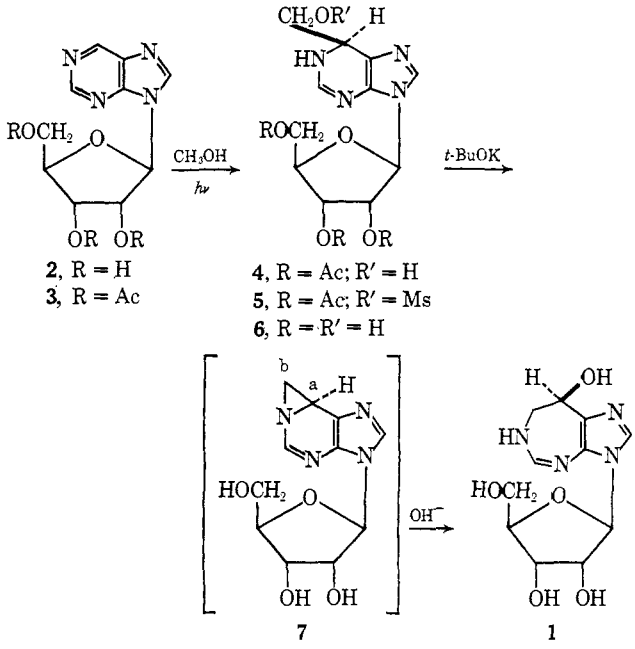
(8) K. Hojo, R. T. Seidner, and S. Masamune, *J. Amer. Chem. Soc.*, **92**, 6641 (1970); T. J. Katz, J. J. Cheung, and N. Acton, *ibid.*, **92**, 6643 (1970).

(9) M. Jones, Jr., *J. Amer. Chem. Soc.*, **89**, 4236 (1967); S. Masamune, H. Zenda, M. Wiesel, N. Nakatsuka, and G. Bigam, *ibid.*, **90**, 2727 (1968); M. Jones, Jr., S. D. Reich, and L. T. Scott, *ibid.*, **92**, 3118 (1970); L. A. Paquette and M. J. Kukla, *ibid.*, **94**, 6874 (1972).

(10) *Cf.* W. von E. Doering and J. W. Rosenthal, *J. Amer. Chem. Soc.*, **89**, 4534 (1967); W. von E. Doering, B. M. Ferrier, E. T. Fossel, T. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967).

(11) The thermal interconversion of cyclopentene with cyclopentadiene and molecular hydrogen has been thoroughly studied: D. A. Knecht, *J. Amer. Chem. Soc.*, **95**, 7933 (1973); F. A. L. Anet and F. Leyendecker, *ibid.*, **95**, 156 (1973), and references cited therein.

Scheme I



296 nm (ε 9000), 244 (5500)]. This photoadduct was considered to be free of isomeric impurities[6] as determined by thin-layer chromatography[7] and the careful analysis of the hydrolysis product **6**.[8] The photoadduct **4** was treated with mesyl chloride in the presence of sodium hydride[9] in anhydrous dimethoxyethane at 0° for 17 hr to afford a pale yellow oil [M^+ 488, uv_{max} (CH_3OH) 293 nm (ε 7600), 246 (sh) (5400)] in 91% yield. The mesylate **5**[10] was immediately treated with potassium *tert*-butoxide in dimethoxyethane at 0° for 18 hr to afford a brown precipitate. The precipitate was dissolved in water at room temperature (30 min) and treated with active charcoal to adsorb the reaction product.[11] The extract of the charcoal with 50% aqueous acetone gave a pale yellow glassy material which was treated with Dowex 1-X2 (OH^-) and adjusted to pH 8–8.5 at room temperature for 17 hr. The product was subjected to preparative thin-layer chromatography, affording coformycin (**1**) in 38% yield.[12]

(6) This result was markedly different from that of the photoaddition of methanol to **2**: B. Evans and R. Wolfenden, *J. Amer. Chem. Soc.*, **92**, 4751 (1970).

(7) This was carried out using three solvent systems with benzene–methanol (5:1, R_f = 0.22), chloroform–methanol (7:3, R_f = 0.25), and ethyl acetate–methanol (3:1, R_f = 0.15).

(8) **4** was treated with Dowex 1-X2 (OH^-) in water at room temperature overnight, and the product was analyzed according to the procedure of Evans and Wolfenden.[6]

(9) The hydroxyl group in alcohol **4** is very strongly hydrogen bonded by the N-7, judging from the ir spectrum, which is the reason why attempted sulfonylation with tosyl chloride–pyridine or mesyl chloride–pyridine was completely unsuccessful in our case and for a similar preparation of benzyl tosylates using sodium hydride; see K. I. H. Williams, S. E. Cremer, F. W. Kent, E. J. Sehm, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **82**, 3982 (1960).

(10) The mesylate **5** was very unstable, giving three spots by tlc after dissolving it in chloroform at room temperature for 2–3 hr.

(11) During the synthetic experiment, it was found that a complex salt was formed from coformycin and potassium methanesulfonate and easily adsorbed by active charcoal and coformycin was easily recovered by the treatment of the salt with a strong anion-exchange resin.

(12) The synthetic coformycin was confirmed to be free of the diastereomer by tlc using different solvent systems such as benzene–methanol (1:1, R_f = 0.31) and butanol–ethanol–chloroform–17% NH_3 in H_2O (4:5:2:4, R_f = 0.39). Besides **1**, there was obtained another product of higher mobility in 20% yield which was considered to be a compound with aromatic purine nucleus[6] based on the uv spectrum (263 nm, ε 6550). The characterization of the compound will be published in a full paper.

The identity of the synthetic coformycin (**1**) with the natural one was confirmed by mixture melting point, tlc, spectroscopic data including ir, uv, and nmr, $[\alpha]_D$, and ORD.

The successful ring expansion of the mesylate **5** strongly suggests that the product **1** was formed exclusively through fission at a of aziridine intermediate **7**, although an attempt to isolate **7** was unsuccessful.[13] Since the stereochemistry of the hydroxyl group of the base moiety of **1** is *R* configuration,[1] the stereochemistry of the hydroxymethyl group of **4** must also be *R* configuration based on SN2 character of the solvolysis of the intermediate **7**.[14] Therefore, the photoaddition of methanol to **2** is stereospecific.

(13) The fission at b of the aziridine intermediate **7** will give original **4** unstable and easily oxidized. On the other hand, the vinylic bond (C_4–C_5 bond) of **4** is also properly disposed for a 1,2 shift, but such rearrangement will require an unfavorable intermediate highly strained. For ring expansion of dihydro heterocycles, see G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 2968 (1971).

(14) The cleavage reaction of such an aziridine intermediate is considered to be stereospecific with retention of configuration for **7** to **1**. See, for instance, D. R. Crist and N. J. Leonard, *Angew. Chem., Int. Ed. Engl.*, **8**, 965 (1969).

(15) Address correspondence to this author at Basic Research Laboratories, Toray Industries, Inc., Kamakura, Japan.

Masaji Ohno,*[15] Naomasa Yagisawa, Seiji Shibahara
Shinichi Kondo, Kenji Maeda, Hamao Umezawa
Institute of Microbial Chemistry
Shinagawa-ku, Tokyo, Japan
Received December 21, 1973

Structure of Coformycin, an Unusual Nucleoside of Microbial Origin

Sir:

Coformycin was discovered in culture filtrates of *Nocardia interforma* and *Streptomyces kaniharaensis* SF-557[1] which produced formycin. Coformycin showed a strong synergistic activity with formycin[2] in inhibiting the growth of bacteria,[1] although coformycin alone did not exhibit antibacterial activity. It was also confirmed to be the strongest inhibitor of adenosine deaminase which deaminates adenosine and formycin.[3] We would like to report the structure of coformycin (**1**), an unusual nucleoside of microbial origin with dihydrohomopurine nucleus.

Coformycin (**1**) has the formula $C_{11}H_{16}N_4O_5$ (M^+ 284.110): mp 182–184°; $[\alpha]^{24}D$ +34 (*c* 1.0, H_2O); pK_a 5.3; uv_{max} (H_2O) 282 nm (ε 8250); ORD Cotton effect (H_2O), negative at 270 nm and positive at 307 nm. As D-ribose was obtained by acid hydrolysis, **1** was considered to be a ribonucleoside linked by the usual C–N glycosyl bond.[4] A close structural relationship[5] with a purine riboside was strongly considered based on the spectroscopic and chemical evidences mentioned above and the competitive nature of inhibition to enzymatic deamination of substrate such as adenosine.[3]

(1) A preliminary report of the isolation and characterization of coformycin was given: T. Niida, *et al.*, 153rd Scientific Meeting of Japan Antibiotics Research Association, Tokyo, Jan 27, 1967. See also R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970, p 366.

(2) G. Koyama, K. Maeda, H. Umezawa, and Y. Iitaka, *Tetrahedron Lett.*, 597 (1966).

(3) T. Sawa, Y. Fukagawa, H. Homma, T. Takeuchi, and H. Umezawa, *J. Antibiot., Ser. A*, **20**, 227 (1967), and reference contained therein.

(4) T. Tsuruoka, T. Ito, and T. Niida, unpublished result.

(5) The detailed spectral interpretation will be reported in a full paper.