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BISULFITE-CATALYZED FACILE DECARBOXYLATION REACTION OF 5-CARBOXYURACIL DERIVATIVES AND TRANSFORMATION OF POLYOXINS*

Kiyoshi Isono and Saburo Suzuki
The Institute of Physical and Chemical Research
Yamato-machi, Saitama, Japan
Mutsuo Tanaka, Takeo Nanbata and Kunitoyo Shibuya
Kaken Chemical Company Ltd.
Jujodai, Kita-ku, Tokyo, Japan

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Because C-6 of uracil is known to be susceptible to the nucleophilic addition, the same carbon of 5-carboxyuracil should be expected to be more reactive. Indeed, when polyoxin C acid [1-(5'-amino-5'-deoxy-β-D-allofuranuronosyl)uracil-5-carboxylic acid][1] (1a) was treated with 2~3 equiv of $NaHSO_3$ at 50° for 16 hrs (initial pH 4.0), considerable hypsochromic shift (from 275mμ to 261mμ) and hypochromicity (one-third in extinction coeficient) were observed. Paper-electrophoresis of the reaction solution at pH 5.0 showed an uv-absorbing ninhydrin positive spot near the base line and an anode-migrating ninhydrin positive spot which lacked uv absorption.

After separation on a Dowex 50W column, crystalline uracil-polyoxin C [1-(5'-amino-5'-deoxy-β-D-allofuranuronosyl)uracil][1] (3a) (75mg from 510mg of 1a) and the C-6 epimeric mixture of the sulfonate intermediate (2a) (120mg from 510mg of 1a) were obtained. 2a was white powder with the formula, $C_{10}H_{15}N_3O_{12}S$, uv max (0.05N HCl, H_2O) end-absorption, (0.05N NaOH) 261mμ (ε 7360), ir 1245, 1050 and 625 cm^{-1} ($-SO_3^-$). The C-6 epimers were partially separated by cellulose chromatography (BuOH-AcOH-H_2O) to afford fast-eluting epimer A, $[\alpha]_D^{20}$ -32.8°

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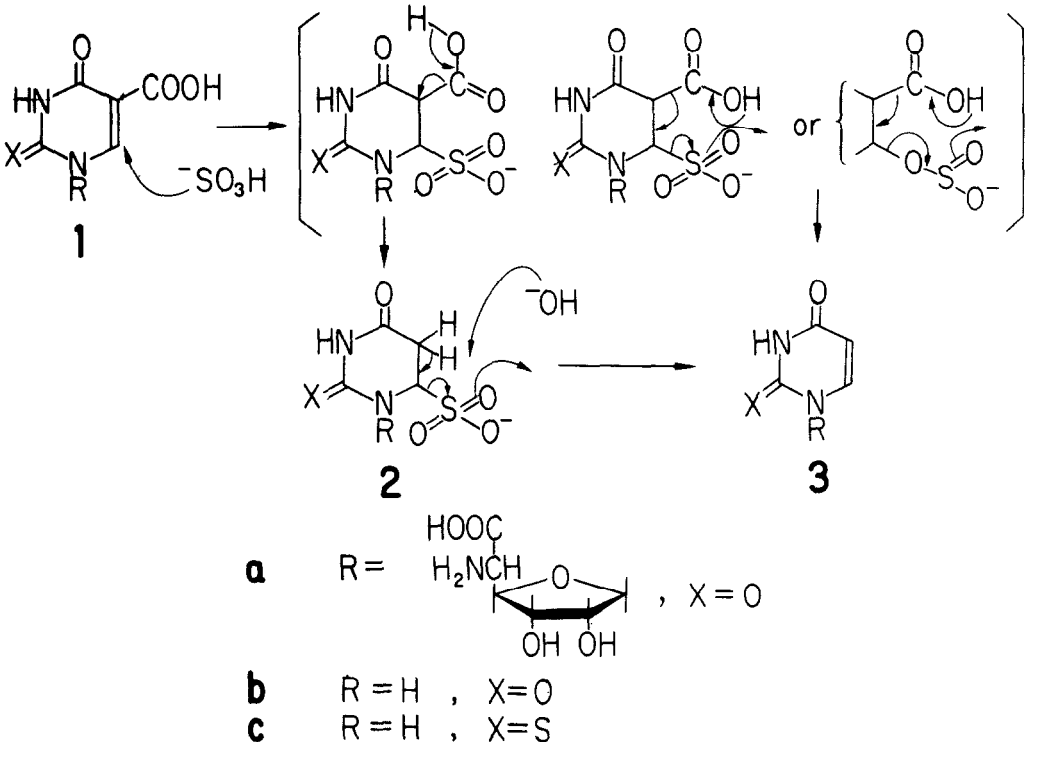
* Studies on polyoxins, antifungal antibiotics, part XIV. The preceding paper, part XIII; K. Isono, K.Asahi and S. Suzuki, J. Amer. Chem. Soc., 91, 7490 (1969). This reaction was suggested briefly in the footnote 52 of that paper.

Scheme 1



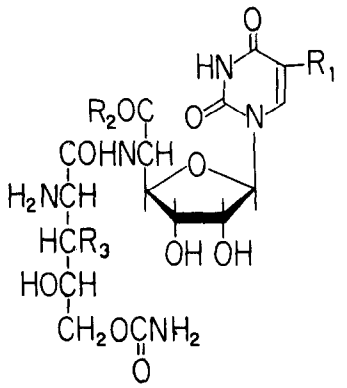
(c 0.5, H_2O) and slow-eluting epimer B, $[\alpha]_D^{20}$ +11.0° (c 0.5, H_2O). Each compound showed an ABX system on 100 MHz nmr in D_2O attributed to C-5 methylene and C-6 methine (epimer A: H-5,5 δ3.07, 3.31; H-6 4.86, $J_{5,6}$= 2.4, 6.5, $J_{5,5}$= 17.4 Hz. epimer B: H-5,5 δ3.06, 3.34; H-6 4.88, $J_{5,6}$= 1.9, 7.0, $J_{5,5}$= 18.0 Hz). Considerable high-field shift of the anomeric protons (δ 5.35 for epimer A and 5.28 for epimer B) should be ascribed to the anisotropy of the C-6 sulfonate group.

2a easily underwent quantitative elimination of the sulfonate group to give 3a in alkaline media (pH 11~12) at room temperature. The possible reaction mechanism is illustrated in Scheme 1. The reaction intermediate formed by the nucleophilic addition of bisulfite on C-6 would undergo either decarboxylation to yield 2 or to afford 3 directly by the concerted decarboxylation and desulfonation. The sulfite ester intermediate is also possible in the latter case.

5-Carboxyuracil (1b), 5-carboxy-2-thiouracil (1c) reacted similarly,

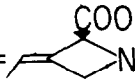
affording uracil (3b) and 2-thiouracil (3c), respectively. The sulfonate intermediates, 2b and 2c were obtained as sodium salt monohydrate, $C_4H_7N_2O_6SNa$ and $C_4H_7N_2O_5S_2Na$, respectively. The nmr of the pyridinium salts of 2b and 2c in DMSO-d_6 showed a coupling between H-6 (multiplet centered at δ 3.91 for 2b and 4.00 for 2c) and N^1-H (δ 7.87 for 2b, 9.71 for 2c, broad doublet, J≃ 4 Hz), supporting the C-6 sulfonate structure.

This newly discovered mild decarboxylation reaction was applied successfully to the transformation of polyoxins D[1](4), E[1](5) and F[1](6). The reaction yield was nearly quantitative on the basis of uv and biological activity. Polyoxins L[1](7), M[2](8) and K[1](9) thus obtained were identified with authentic samples by optical rotation, uv, ir, nmr, pKa', tlc and hydrolytic data. Details of these transformation will be the subject of the following paper.



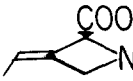
4 R_1=COOH , R_2=OH , R_3=OH

5 R_1=COOH , R_2=OH , R_3=H

6 R_1=COOH , R_2=  , R_3=OH

7 R_1=H , R_2=OH , R_3=OH

8 R_1=H , R_2=OH , R_3=H

9 R_1=H , R_2=  , R_3=OH

This reaction constitutes a novel bisulfite-catalyzed facile decarboxylation reaction and wide-range of applicability is expected. Indeed, decarboxylation of 1-hydroxy-2-naphthoic acid[3] with $NaHSO_3$ or the displacement (probably misassignment for the sulfonate position[4]) of the carboxyl group of 3-carboxycoumarin[5] by bisulfite was reported, although no right explanation given to the structure of the bisulfite adduct and the reaction mechanism. This reaction also provides further interest to the reaction of 4-thiouridine with Na_2SO_3 and O_2[6] and the bisulfite addition to uridine and cytidine[7].

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References and Notes

(1) K. Isono and S. Suzuki, Agr. Biol. Chem., 32, 1193 (1968).
K. Isono, K. Asahi and S. Suzuki, J. Amer. Chem. Soc., 91 7490 (1969).

(2) Although the presence of polyoxin M in the polyoxin complex has not yet been described, 8 obtained by transformation of 5 was identical with the minor component isolated from polyoxin complex on the basis of tlc, paper-electrophoresis and alkaline hydrolysis data. This is to prove the structure of polyoxin M present in the polyoxin complex in minor amount. Analytical data; $C_{16}H_{23}N_5O_{11}$; $[\alpha]_D^{20}$ +49.9° (c 1, H_2O); pKa' 3.0, 7.4, 9.5; uv max (0.05N HCl) 259mμ(ε 8650), (0.05N NaOH) 261mμ(ε 6430); ir 3380, 1690, 1612, 1470, 1400, 1345, 1277, 1120, 1064, 823, 775 and 570 cm^{-1}.

(3) N. N. Karandasheva and S. V. Bogdanov, Zhur. Obshchei Khim., 25, 1152 (1955); C. A. 50, 3355f.

(4) Coumarin-3-sulfonate structure was given to the bisulfite-reaction product. This may be misassignment and may be corrected to the 4-sulfonate structure. It is hard to understand this reaction as a displacement reaction.

(5) W. Daniewski, Roczniki Chemii, 32, 667 (1958); C. A., 53, 3201c.

(6) H. Hayatsu, J. Amer. Chem. Soc., 91, 5693 (1969).

(7) H. Hayatsu, M. Yano, A. Wataya and K. Kai, 2nd Symposium on Heterocyclic Chemistry (Japan), Nagasaki, Nov. 11, 1969.