

A NEW REACTION OF PATULIN

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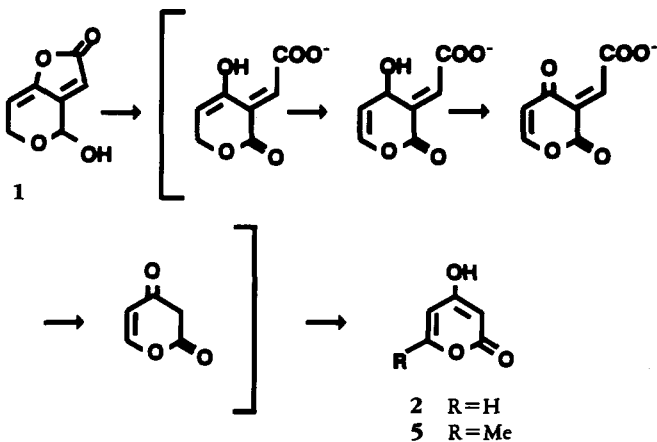
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ABSTRACT.—Treatment of patulin with sodium hypiodite gave a product that on methylation with CH_2N_2 gave two isomeric monomethyl ethers. Based on spectroscopic evidence, the unusual reaction product has been identified as 4-hydroxy(2*H*)pyran-2-one, formed by the loss of the two carbons that were part of the lactone ring.

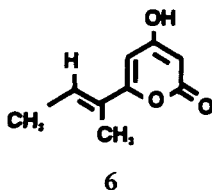
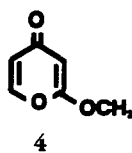
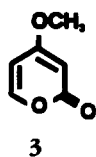
Patulin [**1**] (1,2), a commonly occurring mycotoxin, has been isolated by us during a screening program as a phytotoxic agent. Because patulin is a known carcinogen (3), attempts were made to modify the structure in order to generate active analogues possibly devoid of this property. Oxidation was attempted with sodium hypiodite at room temperature for the purpose of generating the corresponding lactone. The reaction proceeded smoothly and gave a homogeneous product that showed a uv absorption maximum at 278 nm and a carbonyl absorption band at 1740 cm^{-1} , somewhat similar to those seen in patulin. Its ^1H -nmr spectrum was different, however, with a one-proton doublet at δ 5.31 (typical of a 1-3 coupling), another one-proton doublet of doublets at δ 6.09 (1-2 cis and a 1-3 coupling) and a third one-proton doublet at δ 7.61 (1-2 cis coupling). These observations along with the mass spec-

tral evidence indicated structure **2** for the compound. A possible mechanism for the formation of **2** is also presented. Following the opening of the γ -lactone system and shift of the double bond, oxidation of the doubly allylic hydroxyl to the ketone is proposed. The loss of the two-carbon chain that was part of the γ -lactone system can be explained as a consequence of a reverse aldol reaction (Scheme 1).

In support of structure **2**, methylation of **2** with CH_2N_2 gave a mixture of two isomeric monomethyl ethers which are assigned structures **3** and **4**. Compound **3** showed λ max of 273 nm and a carbonyl absorption band at 1740 cm^{-1} , while compound **4** showed λ max of 246 nm and a carbonyl absorption band of 1640 cm^{-1} , which were in agreement with their proposed structures. Although compounds **2**, **3**, and **4** have not been described in the literature, the methyl homologue **5** is well known (4).



SCHEME 1.



Formation of two isomeric methyl ethers from 4-hydroxy-2-pyrones is well documented (5, 6), as for example, in the synthesis of nectriapyrone [6], an antibiotic substance (7).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points are uncorrected and were obtained using a Fisher-Johns apparatus. ^1H -nmr spectra were measured with a Varian EM-390 spectrometer at 90 MHz using TMS as an internal reference. Mass spectra were obtained with a Kratos MS 80RFA instrument. Ir spectra were recorded with a Beckman model Acculab 3 spectrophotometer. Uv spectra were recorded on a Perkin-Elmer (Lambda 3B) instrument using EtOH as the solvent.

PATULIN.—*Penicillium patulum*, NRRL 994, was cultivated in a medium containing potatoes (20%) and glucose (2%). After the potatoes were cooked and homogenized and glucose added, 2-liter portions of the medium were distributed into 4-liter glass jars and sterilized (1 h). The jars were connected to sterile air (one volume per volume of liquid) and to an agitator (160 rpm). The fermentation proceeded at 26–28° for 96 h, and the culture was harvested. The filtered broth (10 liters) was extracted with *n*-BuOH (4 liters) at pH 3 and the extract concentrated azeotropically to near dryness. The crude material was subjected to chromatography on Si gel (200 g) in CHCl_3 . Elution with 5% Me_2CO in CHCl_3 gave the major band, which was recovered by concentration and crystallization from C_6H_6 : yield 1.2 g, mp 108–110°. It was identical with an authentic sample of patulin purchased from Sigma.

OXIDATION.—To a solution of **1** (0.2 g) in 1 M phosphate buffer (pH 7, 40 ml) was added sodium hypiodite solution (10 ml, prepared by adding 2.5 g of iodine to 10 ml of 2 N NaOH) over 1 h, and the mixture was stirred for 14 h. Sodium bisulfite was added in portions until the

solution became colorless. The resulting solution (pH 4) was extracted with EtOAc (3 × 50 ml). The washed, dried (Na_2SO_4) extract was concentrated to dryness. The product was crystallized from EtOAc-hexane (4:1) to yield **2** (0.1 g): mp 182–184°; hrms 112.0149 (calcd for $\text{C}_5\text{H}_4\text{O}_3$, 112.0160); uv λ max (log ϵ) 278 nm (3.77); ir 1740, 1650, 1605, 1440, 1200, 830 cm^{-1} ; ^1H nmr (DMSO- d_6) δ 5.31 (d, $J = 1.8$ Hz, H-3); 6.09 (dd, $J = 1.8$ and 5.4 Hz, H-5); 7.61 (d, $J = 5.4$ Hz, H-6); ^{13}C -nmr (DMSO- d_6) δ 91.43, 103.66, 153.94, 164.02, 170.07; ms 112 (96%), 84 (100), 69 (98), 55 (90).

METHYLATION OF 2.—A solution of **2** (0.1 g) in MeOH (5 ml) was treated with ethereal CH_2N_2 until there was a slight excess. After 30 min, the mixture was concentrated to dryness and subjected to preparative plate chromatography (silica, 10% MeOH in CHCl_3). The compound with R_f 0.6, **3**, was crystallized from CHCl_3 /hexane: yield 55 mg; mp 82–83°; hrms 126.0288 (calcd for $\text{C}_6\text{H}_6\text{O}_3$, 126.0306); uv λ max (log ϵ) 273 nm (3.72); ir 1740, 1640, 1555, 1500, 1230, 1000, 830 cm^{-1} ; ^1H nmr δ 3.83 (s, OMe), 5.88 (d, $J = 2$ Hz, H-3), 6.05 (dd, $J = 2$ and 6 Hz, H-5), 7.4 (d, $J = 6$ Hz, H-6); ms 126 (78%), 98 (84), 83 (50), 69 (100), 53 (64).

The compound with R_f 0.4, **4**, was crystallized from CHCl_3 /hexane: yield 20 mg; mp 100–101°; hrms 126.0312 (calcd for $\text{C}_6\text{H}_6\text{O}_3$, 126.0316); uv λ max (log ϵ) 246 nm (4.00); ir 1640, 1540, 1370, 1230, 990, 820 cm^{-1} ; ^1H nmr δ 3.56 (s, OMe), 5.62 (d, $J = 2$ Hz, H-3), 6.28 (dd, $J = 2$ and 6 Hz, H-5), 7.52 (d, $J = 6$ Hz, H-6); ms 126 (92%), 98 (26), 83 (50), 69 (100), 59 (22).

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