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Note

Photosynthesis of New Heteropolycyclic Furolactones from *E,E*-2,5-di-(2-carboxystyryl)furan

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New heteropolycyclic furolactones; 2-(2-carboxystyryl)-6-phenyl-7a-methoxy-3a,7a-dihydrofurol[3,2-b]pyran-5-one (**3**) and 6-phenyl-2,3-epoxy-2,3-dihydrofuro[3,2-b]pyran-5-one (**4**) were prepared by photochemical dehydrocyclization reaction of *E,E*-2,5-di-(2-carboxystyryl)furan (**1**).

INTRODUCTION

Our continuing interest in the synthesis and photochemistry of substituted heterocyclic acrylic acids[1–5] prompted us to continue this examination.

Earlier results[1] showed that, after irradiation of the solution of substituted 2-phenyl-3-(2-furyl)acrylic acids in oxidative conditions products were present of two types of photochemical reactions: photodehydrocyclization, which gave the naphtho[3,2-b]furan derivatives, and photolactonization, which led to the furopyron derivatives.

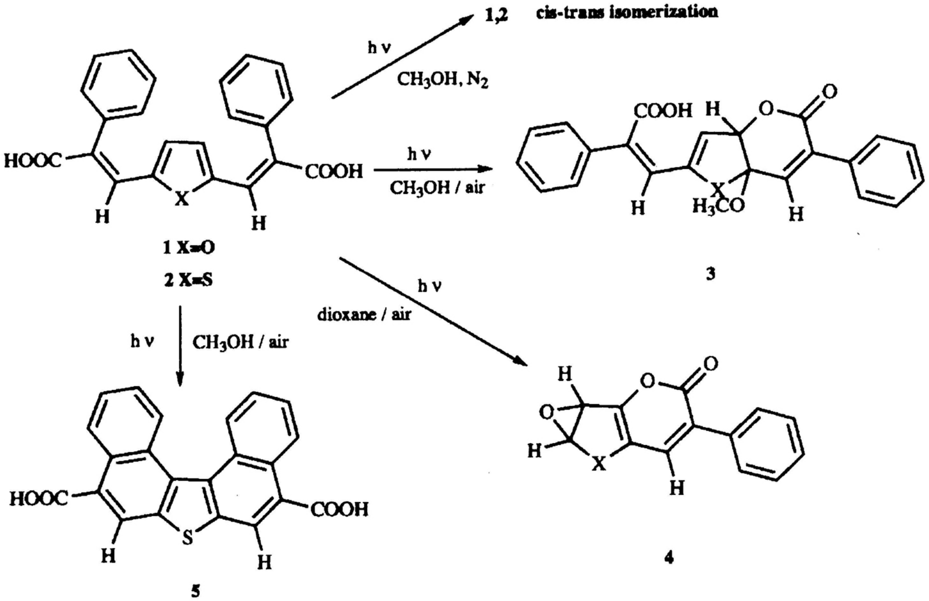
Photochemically prepared furopyrones are of interest because they can be used as $^1O_2$ traps, like simple furans[6] and psolarens.[7,8] Many furocoumarins (also called furanocoumarins) are natural plant products which have traditionally been used, some for over 2000 years, in combination with exposure to sunlight, to treat the vitiligo, a condition characterized by the absence of skin pigmentation. More recently, the drug has been administrated orally rather than topically, and artificial lamps have replaced exposure to sunlight.[6] 8-Methoxy-psoralen (MOP) (8-methoxy-furobenzo[1,2-b:4,5-c]-2-pyron) is a very efficient agent responsible for the inhibition of psoriasis. An epoxide on the furan ring is perhaps an intermediate, since a synthetic product known to be active was formally an addition product of methanol (solvent in the synthesis) to such an intermediate.[9]

RESULTS AND DISCUSSION

In our earlier papers,[4, 5] we prepared a number of derivatives of 2,5-distyrylfurans and 2,5-distyrylthiophenes.

Among others, 2,5-di-(*E*,*E*)-(2-carboxystyryl)furan (**1**) was prepared. By irradiation of methanolic solution of **1** under oxidative conditions (the air was bubbled through the reaction solution), the expected and more common product of twofold photochemical dehydrocyclization reaction; dinaphtho[2,1-b:1',2'-d]furan-5,9-dicarboxylic acid was not isolated but 2-(2-carboxystyryl)-7a-methoxy-6-phenyl-3a, 7a-dihydrofuro[3,2-b]pyran-5-one (**3**) in a 13% yield.

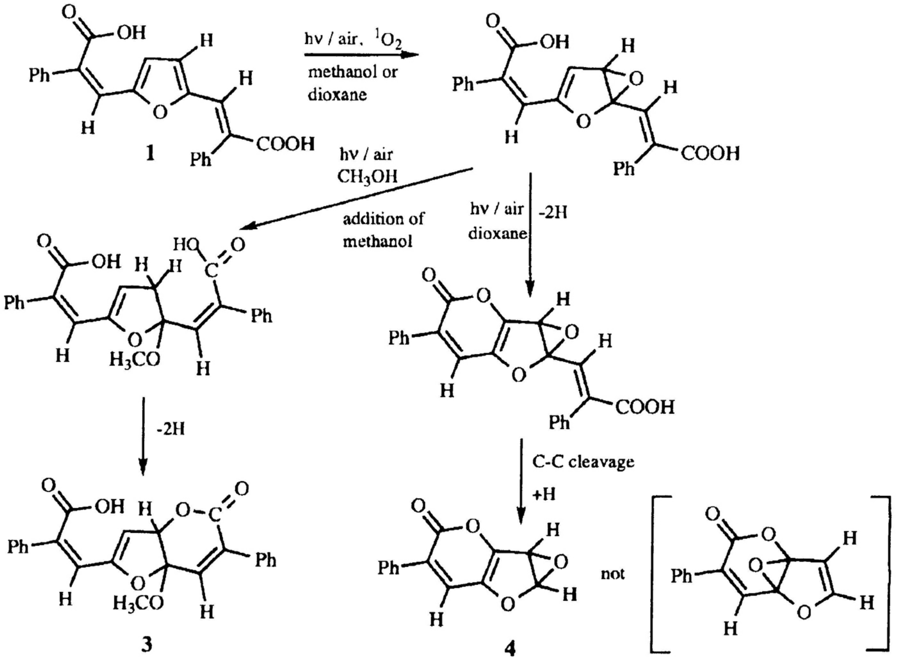
An unexpected fact is that, after prolonged irradiation in methanol, 2-carboxystyryl substituent in position 2 of compound **3** remained unchanged (except *cis-trans* isomerization). During the photochemical reaction, one molecule of methanol was added. Methoxy group was attached in position 7a rather than in position 3a, which was detected from ^{1}H NMR spectra. When the reaction was carried out in oxidative conditions in dioxane solution and in the presence of I_2, 6-phenyl-2,3-epoxy-2,3-dihydrofuro[3,2-b]pyran-5-one (**4**) was isolated in an 18% yield. Similar products were isolated when substituted 2-(2-carboxystyryl) furans were irradiated in methanolic solution.[1] Besides **4,** a lot



Scheme 1.

of unchanged compound **1** was isolated from the reaction mixture (only *cis-trans* isomerization) and dinaphtho[2,1-b:1',2'-d]furan-5,9-dicarboxylic acid only in traces. In contrast, (*E*,*E*)-2,5-di-(2-carboxystyryl)thiophene (**2**) gave, by oxidative photochemical irradiation in methanolic solution, the expected dinaphtho[2,1-b:1',2'-d]thiophene-5,9-dicarboxylic acid (**5**) in a 5% yield. After isolation of compound **5**, no product similar to **3** could be detected in the rest of the reaction mixture. A lot of unchanged material was left (except for the *cis-trans* isomerized compound **5**).

To confirm the reaction mechanism, we performed the photochemical reaction under anaerobic conditions. Nitrogen was bubbled through the methanolic solution of **1**. After prolonged irradiation (24 h), only the *cis-trans* isomerized product of **1** was present in the reaction mixture. When the methanolic solution of **2** was irradiated under anaerobic conditions (50 hrs), only *cis-trans* isomerized **2** was detected (in both cases IR spectra showed the unchanged CO frequency characteristic of acidic carbonyl group at 1670 cm^{-1}, but not at lactones, appearing between 1720 and 1760 cm^{-1}) although there is literature evidence of the photolactonization of substituted cinnamic acids under anaerobic conditions[10]. A large number of coumarines have been



Scheme 2.

isolated from plants, and their biosynthesis includes an (*E*) (*Z*) photoisomerization, which allows lactonization to procceed, like in biosynthesis, from dihydroxy coumarin from caffeic acid (2,4,6-tri-hydroxy cinnamic acid).[1]

The proposed mechanism reaction of photochemical lactonization in methanol is shown in Scheme 2. It seems that the reaction in the furan series includes addition of the singlet oxygen to the furan nuclei, while this is not the case in the thiophene series.

In the first reaction step, one atom of the singlet oxygen, probably generated by the influence of the molecule itself, was added to the furan nuclei to produce the unstable epoxy furan intermediate which, after addition of one molecule of methanol and elimination of hydrogen, resulted in compound **3** (like in the biosynthesis of dihydroxycoumarine from caffeic acid). Another double bond was only *cis-trans* isomerized and dilactone was not detected. When the reaction was performed in the dioxane solution, the first step was the same, namely the epoxy intermediate was formed. In the second reaction step, **3** hydrogen was eliminated but, in this case, not on the same side of the molecule, already on another carboxystyryl group. The last step, which includes elimination of one carboxystyryl group is not quite clear. After elimination of this group by C-C cleavage, one atom of hydrogen was added, probably from solvent. The mechanism was confirmed by carring out the reaction under anaerobic conditions where compound **1** did not change after 25 hours of irradiation and compound **2** after 50 hrs of irradiation, except for *cis-trans* isomerization.

EXPERIMENTAL DETAILS

M.ps. are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer in KBr discs. ^{1}H-NMR spectra were recorded on a Varian Gemini 300 spectrometer with TMS as internal standard in acetone-d_6. Irradiation was performed by water cooled immersion well equiped with an »Original Hanau« 400 W high pressure mercury arc lamp using a pyrex filter. All mass spectrometric measurements were performed using a Hewlett-Packard ('Palo Alto, CA:USA) 5890 G gas chromatograph and a 5989MS mass spectrometer operating in the electron ionization (EI) mode using 70 eV electrons.

Irradiation of E,E-2,5-di-(2-carboxystyryl)furan (1) in methanol

The starting compound **1** (500 mg, 1.4 mmole) in methanol (750 ml) was irradiated with a pyrex filtered 400W mercury arc lamp for 48 hours under air at room temperature. After evaporation of solvent, the oily photoproduct was first washed with 5% solution of sodium carbonate and then with water. The residue was recrystallized from methanol. White crystals were chromatographed on the preparative SiO_2 plates (petrolether: ether 9:1); 70 mg (13%) of white crystals m.p. 178–180 °C were obtained. IR (cm^{-1}): 1750 (C=O lactone), 1690 (COOH), 1620 (C=C). ^{1}H-NMR (acetone-d_6, δppm): 7.99–7.96 (m, 2H, arom.), 7.71 (s, 1H, lactone), 7.47–7.45 (m, 3H, arom.), 7.40–7.31 (m, 5H, arom.), 7.16 (s, 1H, ethylenic), 6.14 (d, 1H, $J_{3,3a}$=5.80 Hz), 5.65 (d, 1H, $J_{3,3a}$=5.7 Hz), 3.20 (s, 3H, OCH_3). MS: *m/z* 358 (50) (M-CH_3OH), 314(15), 212 (100), 156 (45), 126 (20). *Anal.* Calcd for $C_{23}H_{18}O_6$: C, 70.77; H, 4.61; O, 24.62; found: C, 70.49; H, 4.32.

To the alcaline solution, left after isolation of **3**, HCl (1:1) was added. The expected dinaphtho[2,1-b:1',2'-d]furan-5,9-dicarboxylic acid did not appear, but only the starting compound **1** with its *E*/*Z* isomers.

Irradiation of E,E-2,5-di-(2-carboxystyryl)furan (1) in dioxane

The starting compound **1** (360 mg, 1 mmole) was dissolved in dioxane (500 ml). A few drops of I_2 where added to the solution. The solution was irradiated for 10 hours. The air was bubbled through the solution at room temperature. After evaporation of solvent, the residue was washed with $NaHSO_3$ solution to remove I_2, the residue dissolved in chloroform and the solution extracted with 5% Na_2CO_3 solution. The aqueous layer was acidified with HCl (1:1), the obtained crystals were filtered off. The crystals are a mixture of »*E*« and »*Z*« isomers of compouns **1**. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on the SiO_2 preparative plates (chloroform: carbontetrachloride 1:1), and once again recrystallized from carbontetrachloride. The yield was 28 mg (18%), white crystals, m.p. 132–133 °C. IR (cm^{-1}) 1800, 1785 (C=O lactone). ^{1}H-NMR (acetone-d_6, δppm) 8.03–7.92 (m, 2H, arom.), 7.79 (s, 1H), 7.72 (d, 1H, J = 5.5 Hz), 7.55–7.44 (m, 3H, arom.), 6.60 (d, 1H, *J* = 5.57Hz). M^+ 228 (70), *m/z* 184 (50), 156 (20), 128 (30), 102 (50), 82 (100). *Anal.* Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.51; O, 28.07; found: C, 68.12, H, 3.37.

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SAŽETAK

Fotosinteza novih heteropolicikličkih furolaktona iz *E,E*-2,5-di-(2-karboksistiril)furana

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Pripređeni su novi heteropoliciklički furolaktoni reakcijom fotokemijske dehidrociklizacije: 2-(2-karboksistiril)-6-fenil-7a-metoksi-3a,7a-dihidrofuro[3,2-b]piran-5-on (**3**) i 6-fenil-2,3-epoksi-2,3-dihidrofuro[3,2-b]piran-5-on (**4**).