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Self-condensation of 2-(ethoxalylmethyl)chromones into new derivatives of isotetronic acid

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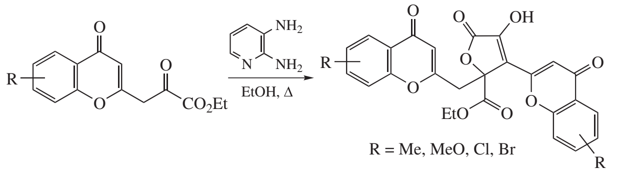
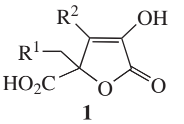
2-(Ethoxalylmethyl)chromones undergo dimerization to dichromonyl derivatives of isotetronic acid in 62–89% yields on refluxing with 2,3-diaminopyridine in ethanol for 1–2 h.



Isotetronic acid derivatives with general formula **1** can be obtained by self-condensation of monosubstituted pyruvic acids and their esters in the presence of bases such as triethylamine or sodium ethoxide.[1] Some of them are metabolic products isolated from various natural sources.[2] Zymonic acid (**1**, $R^1 = R^2 = H$), a metabolic dimer of pyruvic acid,[3] was recently recommended as a biosensor to determine the pH values in living organisms that can be used in MRT diagnostics of cancer diseases.[4] Butyrolactone I [**1**, R^1 = 4-HO-3-($Me_2C=CHCH_2$)C_6H_3, R^2 = 4-HOC_6H_4, Me-ester] isolated from *Aspergillus terreus* mold fungus along with other metabolites[5] exercises antitumor activity by inhibiting the cell cycle in the G1/S and G2/M transitions and is a selective inhibitor of cyclin dependent kinases and an important biosensor for understanding the role of CDKs in cells.[6] On the other hand, chromones are more widely distributed in nature, especially in the plant kingdom, and exhibit low toxicity along with a wide spectrum of useful properties, including synthetic valuable.[7] The combination of a chromone system with butyrolactone derivatives would allow one to develop of a new class of biologically active molecules and useful synthetic building blocks in organic and medicinal chemistry.



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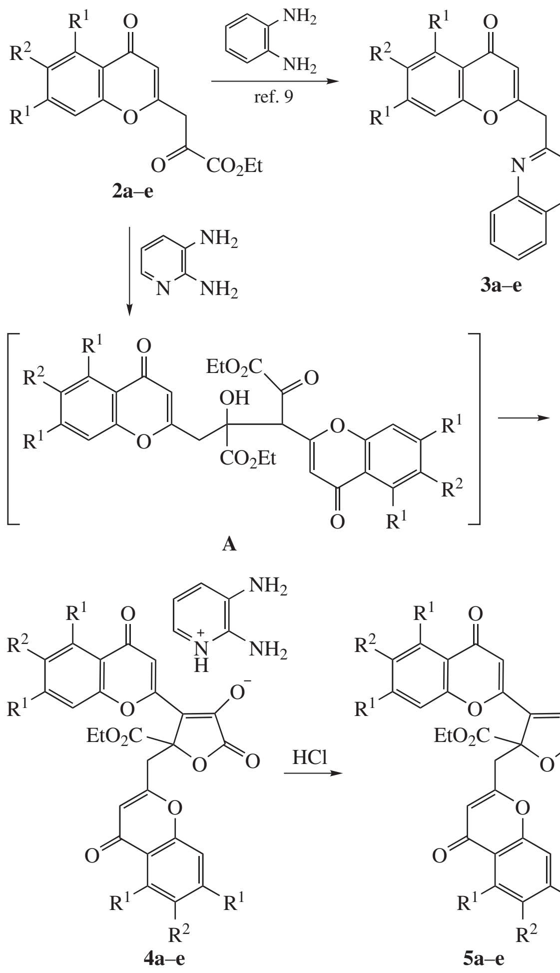
It is known that 2-methylchromones react with diethyl oxalate at the vinylogous methyl group to give 2-(ethoxalylmethyl)chromones **2**.[8,9] The reaction of the latter with *o*-phenylenediamine occurs only by the ethoxalyl group to afford chromones **3** with a quinoxalinone moiety.[9] Our attempt to expand this reaction to 2,3-diaminopyridine showed that it gave quite different products. Unlike *o*-phenylenediamine that reacts as a 1,4-dinucleophile, 2,3-diaminopyridine behaves as a base and catalyzes the dimerization of chromonylpyruvates **2**. In fact, refluxing chromones **2a–e** with 2,3-diaminopyridine (1.25 equiv.) in ethanol for 1–2 h followed by addition of water resulted in 2,3-diaminopyridinium salts of bis(4-oxochromen-2-yl)zymonic acid **4a–e** (Scheme 1). Of these, salts **4a**,**c** (79–83% yields) were characterized comprehensively.[†] Acids **5a–e** can be obtained in pure form in 62–89% yields on treatment of the reaction mixture with hydrochloric acid.[‡] Self-condensation of pyruvates also occurs in the presence of pyridine, *N*-aminoguanidine or triethylamine, but yields of such products are lower. In view of the easy functionalization of the chromone ring at the 2-position with nucleophilic reagents, compounds **5** can serve as promising building blocks for novel three-dimensional molecules of structural and physicochemical interest.

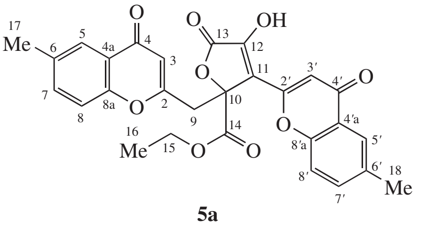
[†] *2,3-Diaminopyridinium 5-(ethoxycarbonyl)-4-(6-methyl-4-oxo-4*H*-chromen-2-yl)-5-[(6-methyl-4-oxo-4*H*-chromen-2-yl)methyl]-2-oxo-2,5-dihydrofuran-3-olate* **4a**. A mixture of 6-methyl-2-(ethoxalylmethyl)chromone **2a** (150 mg, 0.55 mmol) and 2,3-diaminopyridine (74 mg, 0.68 mmol) was refluxed in EtOH (8 ml) for 1 h. The reaction mixture was cooled and diluted with water (100 ml). The resulting precipitate was filtered, washed with water (20 ml) and recrystallized from EtOH. Yield 83%, green powder, mp 198–200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (t, 3H, 16-Me, *J* 7.1 Hz), 2.35 (s, 3H, 17-Me), 2.40 (s, 3H, 18-Me), 3.65 (d, 1H, C^9*H*H, *J* 14.8 Hz), 3.80 (d, 1H, C^9H*H*, *J* 14.8 Hz), 4.16 (dq, 1H, C^{15}*H*H, *J* 10.8 Hz, *J* 7.1 Hz), 4.21 (dq, 1H, C^{15}H*H*, *J* 10.8 Hz, 7.1 Hz), 5.75 (br. s, 2H, NH_2), 6.03 (s, 1H, H-3), 6.72 (dd, 1H, H-5 Py, *J* 7.7 Hz, *J* 6.2 Hz), 6.94 (d, 1H, H-8, *J* 8.5 Hz), 6.99 (s, 1H, H-3′), 7.04 (dd, 1H, H-4 Py, *J* 7.7 Hz, *J* 1.3 Hz), 7.26 (dd, 1H, H-6 Py, *J* 6.2 Hz, *J* 1.3 Hz), 7.34 (d, 1H, H-8′, *J* 8.5 Hz), 7.35 (br. s, 2H, NH_2), 7.49 (dd, 2H, H-7, H-7′, *J* 8.8 Hz, *J* 1.4 Hz), 7.70 (d, 1H, H-5, *J* 1.4 Hz), 7.74 (d, 1H, H-5′, *J* 1.4 Hz), 13.10 (br. s, 1H, N^+H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.8, 20.3, 20.4, 61.7, 82.1, 100.8, 101.6, 107.9, 112.0, 113.5, 116.6, 117.4, 119.7, 122.5, 122.6, 123.7, 124.0, 124.0, 133.2, 133.4, 133.5, 134.7, 135.0, 144.7, 152.8, 153.9, 159.6, 162.0, 164.3, 169.0, 169.7, 175.0, 176.3. IR (ν/cm^{-1}): 3437, 3408, 3384, 3365, 3268, 3238, 3215, 3202, 1759, 1738, 1693, 1614, 1573, 1521. Found (%): C, 62.64; H, 4.71; N, 7.04. Calc. for $C_{33}H_{29}N_3O_9 \cdot H_2O$ (%): C, 62.95; H, 4.96; N, 6.67.

[‡] *General procedure for the synthesis of compounds* **5**. A mixture of the corresponding 2-(ethoxalylmethyl)chromone **2** (0.55 mmol) and 2,3-diaminopyridine (0.55 mmol, 60 mg) was refluxed in EtOH (8 ml) for 2 h. The reaction mixture was cooled and treated with dilute HCl (1 : 10, 50 ml). The precipitate that formed was collected by filtration and washed with water (5 ml) and EtOH (3 ml). Finally, the material was refluxed in water (0.5 ml) and EtOH (2 ml) for 0.5 h, filtered off and dried at 60 °C.



a R^1 = H, R^2 = Me
b R^1 = H, R^2 = MeO
c R^1 = H, R^2 = Cl
d R^1 = H, R^2 = Br
e R^1 = Me, R^2 = H

Scheme 1



5a

$C^9H_2 \leftrightarrow C^{10}$
$C^9H_2 \leftrightarrow C^3$
$C^9H_2 \leftrightarrow C^{11}$
$C^9H_2 \leftrightarrow C^2$
$C^9H_2 \leftrightarrow C^{14}$
$C^{3'}H \leftrightarrow C^{11}$
$C^{3'}H \leftrightarrow C^{4'a}$
$C^{3'}H \leftrightarrow C^{2'}$
$C^{3'}H \leftrightarrow C^{4'}$
$C^{5'}H \leftrightarrow C^{4'}$
$C^3H \leftrightarrow C^{4a}$
$C^3H \leftrightarrow C^2$
$C^3H \leftrightarrow C^4$
$C^8H \leftrightarrow C^4$
$C^5H \leftrightarrow C^4$

Figure 1 Selected 2D ^1H–^{13}C HMBS cross-peaks for dimer **5a**.

The structures of dimers **5** were confirmed by ^1H and ^{13}C NMR spectroscopy. Complete assignment of all signals was based on the results of 2D ^1H–^1H COSY, ^1H–^{13}C HSQC and HMBC experiments (see Online Supplementary Materials). The most informative cross-peaks of the 2D HMBC spectrum of compound **5a** in DMSO-d_6 are provided in Figure 1. In the ^1H NMR spectra, attention should be paid to the considerable difference in the chemical shifts of the H-3 and H-8 protons of the non-conjugated chromone moiety and the H-3′ and H-8′ protons of the conjugated chromone (Figure 2). The upfield shift of the H-8 proton by 0.5 ppm in comparison with the similar signal in chromones **3** can be rationalized by the assumption that in DMSO-d_6 solution, a molecule of dimer **5** adopts a conformation in which this atom is shielded by the benzene ring of conjugated chromone. On the other hand, the H-3′ proton is shifted downfield by the same value, which is apparently due to the deshielding effect of the oxygen atom at C^{12}.

According to single crystal X-ray diffraction data (Figure 3),[§] compound **5b** crystallizes as a solvate in a centrosymmetric space group of the rhombic system. Due to the strong disordering of solvent molecules, the solvent was excluded from the structural model by means of the SQEEZE procedure available in the PLATON program.

An interesting feature of the structure is that it contains two chromone rings that differ by the presence or absence of a system of conjugation with the dihydrofuran moiety. A direct relationship is observed between the geometric parameters of the chromone ring and the existence of conjugation with the furandione ring. The non-conjugated chromone ring has the expected bond lengths and bond angles. The tentatively double and single bonds of the pyrone moiety are well distinguishable based on their lengths.

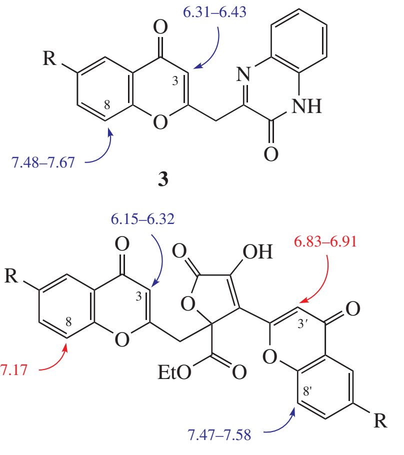


Figure 2 Selected chemical shifts (DMSO-d_6, δ, ppm) for compounds **3** and **5**.

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*Ethyl 4-hydroxy-3-(6-methyl-4-oxo-4*H*-chromen-2-yl)-2-[(6-methyl-4-oxo-4*H*-chromen-2-yl)methyl]-5-oxo-2,5-dihydrofuran-2-carboxylate* **5a**. Yield 89%, light green powder, mp 239–241 °C. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.14 (t, 3H, 16-Me, *J* 7.0 Hz), 2.35 (s, 3H, 17-Me), 2.43 (s, 3H, 18-Me), 3.84 (d, 1H, C^9HH, *J* 15.1 Hz), 3.90 (d, 1H, C^9HH, *J* 15.1 Hz), 4.25 (dq, 1H, $C^{15}HH$, *J* 10.9 Hz, *J* 7.1 Hz), 4.32 (dq, 1H, $C^{15}HH$, *J* 10.9 Hz, *J* 7.1 Hz), 6.22 (s, 1H, H-3), 6.83 (s, 1H, H-3′), 6.98 (d, 1H, H-8, *J* 8.5 Hz), 7.50 (d, 1H, H-8′, *J* 8.5 Hz), 7.52 (dd, 1H, H-7, *J* 8.3 Hz, *J* 2.0 Hz), 7.65 (dd, 1H, H-7′, *J* 8.5 Hz, *J* 1.7 Hz), 7.70 (s, 1H, H-5), 7.82 (s, 1H, H-5′), OH was not observed. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.8 (C^{16}), 20.3 (C^{17}), 20.4 (C^{18}), 38.2 (C^9), 63.0 (C^{15}), 82.8 (C^{10}), 109.4 ($C^{3'}$), 112.7 (C^3), 116.4 (C^{11}), 117.3 (C^8), 117.9 ($C^{8'}$), 122.5 (C^{4a}), 122.7 ($C^{4'a}$), 124.1 ($C^{5'}$), 124.2 (C^5), 135.2 (C^7), 135.3 (C^6), 135.6 ($C^{6'}$, $C^{7'}$), 147.5 (C^{12}), 153.1 ($C^{8'a}$), 153.8 (C^{8a}), 156.5 ($C^{2'}$), 162.6 (C^2), 165.9 (C^{13}), 166.7 (C^{14}), 175.6 ($C^{4'}$), 176.3 (C^4). IR (ν/cm^{-1}): 3097, 2982, 2929, 1783, 1749, 1653, 1612, 1548. HRMS (ESI), *m/z*: 503.1350 $[M+H]^+$ (calc. for $C_{28}H_{23}O_9$, *m/z*: 503.1337). Found (%): C, 66.04; H, 4.35. Calc. for $C_{28}H_{22}O_9 \cdot 0.33H_2O$ (%): C, 66.14; H, 4.49.

[§] *Crystal data for* **5b**: $C_{28}H_{22}O_{11}$ (M = 534.46). The crystals are orthorhombic, space group *Pbca*, a = 24.5265(18), b = 9.0278(7) and c = = 25.1989(14) Å, V = 5579.5(7) Å^3, absorption coefficient μ(MoKα) = = 0.099 mm^{-1}, Z = 8. On the angles $5.6 < 2\theta < 56.6°$ the intensities of 19685 reflections were measured, from which 6334 independent reflections were measured (R_{int} = 0.0647). The final factors of the refinement wR_2 = 0.1180 (all fata) and R_1 = 0.0569 $[I > 2\sigma(I)]$, $\Delta\rho_e$ = 0.24–0.22 eÅ^{-3}.

CCDC 1818432 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

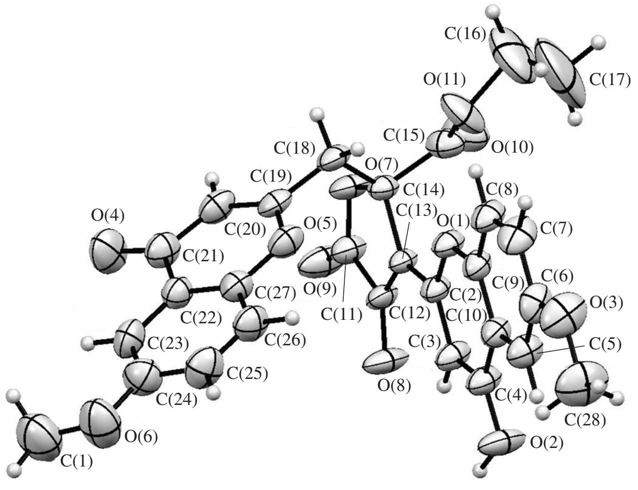

Figure 3 Molecular structure of compound **5b** (thermal ellipsoids at 50% probability level).

In particular, the lengths of the C=O, C(19)=C(20), C(20)–C(21) and C(18)–C(19) bonds are 1.228(3), 1.334(4), 1.415(4) and 1.483 Å, respectively, which is typical of chromones. Conjugation with a five-membered heterocycle results in considerable reorganization of the pyrone ring. In this case, the length of the C=O bond increases to 1.276(3) Å, while those of carbon–carbon bonds in the ring equalize to reach 1.373(4) Å for C(2)=C(3) and 1.388(4) Å for C(3)–C(4).

An important structural element in the crystal packing is the presence of intermolecular hydrogen bonds that bind two molecules of **5b** into centrosymmetric dimers **A** and **B** (Figures 4 and S1, see Online Supplementary Materials). These dimers, in which the conjugation system combines two chromone and two furandione rings, are macrocycles that are planar within 0.15 Å with *trans*-orientation of two ethoxycarbonyl groups and two chromon-2-ylmethyl substituents relative to each other. The parameters of the hydrogen bond with H···A < r(A) + 2.000 Å and ∠DHA > 110° are as follows: d[O(8)–H(8)] 1.35(5) Å, d[H(8)···O(2)] 1.16(5) Å, ∠O(8)H(8)O(2) 169.8(15)°, d[O(8)···O(2)] 2.501(3) Å, [1 – x, 1 – y, 1 – z]. The distribution of bond lengths does not allow one to make unambiguous conclusions concerning the character of binding in this system. In fact, the distribution of bond lengths, C(4)–O(2) 1.276(3) Å and C(12)–O(8) 1.290(3) Å, indicates that the proton is preferably located at the five-membered ring oxygen, whereas the measured O–H bond lengths show the opposite. The contradiction can be resolved if we assume that proton exchange in the crystal exists between the oxygen atoms in the six- and five-membered rings, perhaps with a considerable contribution of bipolar structure **B**. Otherwise, the measured position of the hydrogen bond proton should be recognized as wrong. This seems not unlikely, taking into account the rather complicated structural model and the existence of the disordered solvent factor.

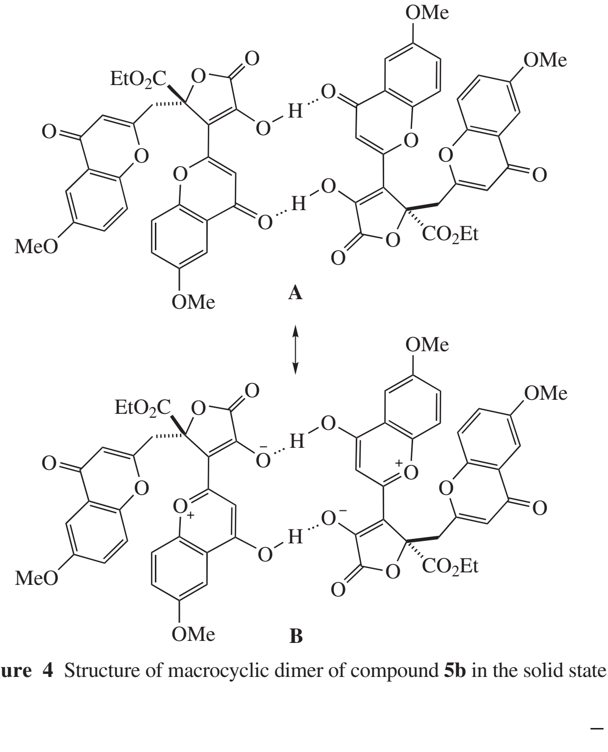

Figure 4 Structure of macrocyclic dimer of compound **5b** in the solid state.

In summary, we were the first to describe a series of isotetronic acids containing two chromone moieties. They can be of interest for medicinal chemistry as compounds with potential biological activity and as templates for further modification.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.032.

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