Scientific paper

Preparation and Reactivity of 5-benzylidenebarbituric and 5-benzylidene-2-thiobarbituric Acids

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Abstract

The reaction between barbituric acid or 2-thiobarbituric acid and different benzaldehydes, dependent upon the applied reaction conditions, selectively yields three different product types, *i.e.* 5-benzylidene(thio)barbituric acids **II**, symetric Michael adducts **III** or 5-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **IV**. The reaction mechanisms and reactivity of different benzaldehydes are discussed.

Keywords: 5-benzylidenebarbituric acid, 5-benzylidene-2-thiobarbituric acid, Knoevenagel condensation, Michael addition, hetero-Diels-Alder reaction, 5-aryl-pyrano[2,3-*d*]pyrimidine-2,4-diones

1. Introduction

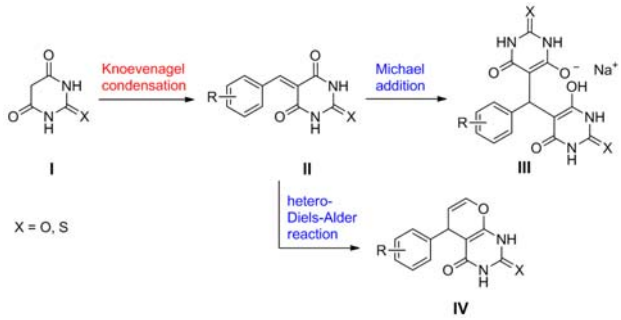
The diverse biological activity and coverage of a broad chemical space make barbituric acid derivatives excellent target compounds for organic and medicinal chemists.[1] Owing to their ready availability and various functionalization possibilities, the parent barbituric acid and 2-thiobarbituric acid are convenient starting compounds for the preparation of different fused heterocycles and 5-substituted derivatives which are pharmacologically the most important class of barbituric acid-based compounds.[1–10]

It is well-known that barbituric acid and 2-thiobarbituric acid **I** undergo Knoevenagel condensation with aldehydes to give 5-ylidene derivatives **II**[11–16] that can be further subjected to various chemical transformations. 5-Arylidene barbituric acids **II** contain a strongly polarized exocyclic double bond, with a positive partial charge on the methyne carbon atom.[17–19] They can thus form Michael adducts with nucleophiles such as alkoxides,[20] amines,[20–22] thiols,[23] water,[24] and *C*-nucleophiles derived from active methylene compounds.[19,25–28] The last reaction, resulting from Michael addition of a second barbituric acid molecule, gives rise to symmetric Michael adducts **III**. Furthermore, because their exocyclic double bond can be easily reduced,[29–31] 5-arylidene barbituric acids can be considered as models of redox coenzymes such as FAD and NAD and used as oxidants for mild oxidation of thiols[32,33] and alcohols.[34,35] 5-Arylidene barbituric acids can also react as dienes in a hetero-Diels-Alder reaction to give different 5-aryl-pyrano[2,3-*d*]pyrimidine-2,4-diones **IV**[36–41] which have received considerable attention due to the wide range of biological effects, including antiviral,[38] antibacterial,[39] antifungal,[39,40] and prostate-protective activity.[41] Owing to manifold reactivity of 5-arylidenebarbituric acids, reaction of (thio)barbituric acid with aromatic aldehydes usually results in complex mixtures of **II**, **III** and **IV**, which limits its synthetic applicability. Therefore, synthetic methods for efficient selective formation of compounds **II**, **III** or **IV** from (thio)barbitutic acids are highly desired.

2. Results and Discussion

During the synthesis of potential inhibitors of intracellular steps of peptidoglycan biosynthesis,[2,3] we have studied in detail the reaction between (2-thio)barbituric acid and different benzaldehydes and found, that the composition of products of this transformation depends strongly upon the applied conditions *i.e.* the solvent, temperature and catalyst. Depending on reaction conditions, the reaction does not necessarily stop with the formation of 5-benzylidene(thio)barbiturates **II**, but can proceed further to yield Michael adducts **III** or hetero-Diels-Alder

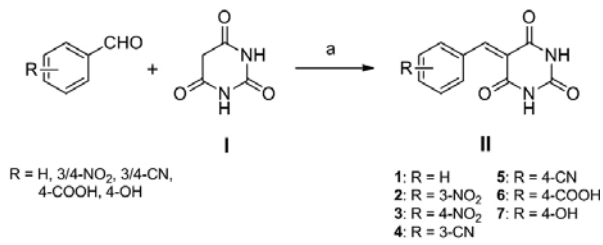
cycloaddition products **IV** (Scheme 1). In this paper, we report on selective transformations of barbituric and thiobarbituric acids to 5-arylidene derivatives **II**, Michael adducts **III** and 5-aryl-pyrano[2,3-*d*]pyrimidine-2,4-diones and their thio analogues **IV**, which makes compounds **II**, **III** and **IV** easily accessible in pure form.



Scheme 1. Three classes of products obtained from the reaction of (thio)barbituric acid with benzaldehydes.

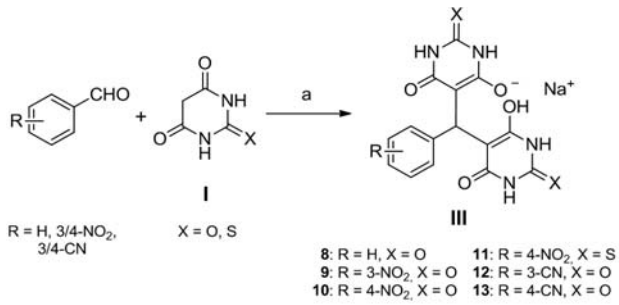
A common method for the preparation of Knoevenagel products **II** is (microwave) heating of active methylene compounds and different benzaldehydes in ethanol, with piperidine and glacial acetic acid as catalysts.[2,3,42] In our hands, starting from (thio)barbituric acid, this procedure gave the desired product only with 4-formylbenzoic acid, but not with 3- or 4-nitrobenzaldehyde. With 3-nitrobenzaldehyde, a mixture of products **9** and **15**, and with 4-nitrobenzaldehyde, a mixture of products **10** and **17** was obtained (Schemes 3 and 4). Retrosynthetic considerations suggested that these products originated (*i*) from Michael addition of a second molecule of barbituric acid and (*ii*) from a hetero-Diels-Alder reaction to 5-benzylidenebarbituric acid intermediates **2** and **3**. This observation stimulated us to investigate systematically the reaction of (thio)barbituric acid **I** with various benzaldehydes, in order to find specific reaction conditions that would drive the reaction exclusively towards the formation of product **II**.

After examining a number of different reaction conditions in which solvents and catalysts were varied, we found that the most convenient way for the preparation of 5-benzylidenebarbiturates **1**–**7**, is heating the reagents in water at 100 °C without a catalyst. The products were isolated simply by filtering off the crystals formed in the reaction mixture (Scheme 2).



Scheme 2. Reagents and conditions: (*a*) H_2O, reflux, 12 h.

On the contrary, when (thio)barbituric acid was reacted with 3-/4-nitro-, 3-/4-cyano-, or unsubstituted benzaldehyde in glacial acetic acid with one equivalent of sodium acetate, Michael adducts **8**–**13** were obtained (Scheme 3). These products result from Michael addition of a second molecule of (thio)barbituric acid to the exocyclic double bond of the initially formed Knoevenagel intermediates. Similar products were reported for the reaction in pyridine as solvent/base.[43] On the other hand, with 4-hydroxybenzaldehyde, 4-formylbenzoic acid and methyl 4-formylbenzoate, the reaction stopped almost exclusively at the Knoevenagel stage under conditions applied in Scheme 3. This can be explained by differences in the reactivity of the exocyclic double bond as a result of the electronic properties of substituents on the aromatic ring. It has been demonstrated that Lewis acidity, and hence reactivity of 5-arylidenebarbituric acids towards Michael addition, increases in the presence of electron-withdrawing substituents on the aromatic ring.[27,28] Thus, nitro and cyano groups enhance the Lewis acidity of benzylidene carbon, whereas the electron donating hydroxyl group stabilizes it and renders it less susceptible to nucleophilic attack. Although the carboxyl and methoxycarbonyl groups are moderately electron-withdrawing, they clearly do not activate the Knoevenagel product sufficiently to facilitate further reaction.

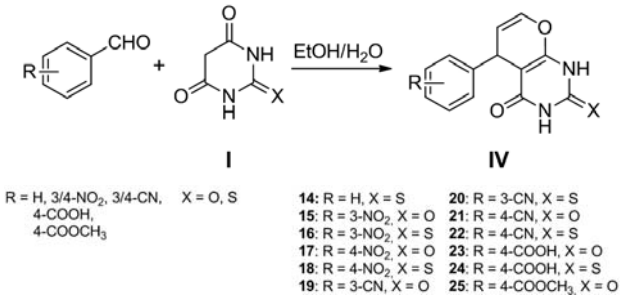


Scheme 3. Reagents and conditions: (*a*) NaOAc, AcOH, 65 °C, 12 h.

The infrared spectra of compounds **8**–**13** suggest, that they are present as mixed keto-enol tautomers. The Knoevenagel products **1**–**7** show C=O stretching bands only at frequencies 1780–1680 cm^{-1}, whereas Michael adducts **8**–**13** show additional absorption bands in the region 1600–1615 cm^{-1}. Moreover, the X-ray structure of a similar compound,[27] revealed that the distances between C and O atoms are intermediate between the ideal values for the keto and enol forms.

In addition to Knoevenagel products **II** (compounds **1**–**7**) and Michael adducts **III** (compounds **8**–**13**), (thio)barbituric acid and different benzaldehydes can, under slightly modified reaction conditions, also yield a third type of product. When the reaction was performed in ethanol/water (1:1) under conventional heating (reflux, 3

days) or microwave irradiation (120 °C, 1–2 hours), an unexpected series of 5-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones and 5-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-ones **IV** (compounds **14–25**) was obtained (Scheme 4). A detailed study of this reaction and its proposed mechanism was described recently.[36] The conversion comprises two interconnected domino reaction sequences (*i*) a domino Knoevenagel hetero-Diels-Alder reaction, and (*ii*) a domino oxidation hetero-Diels-Alder reaction. The reaction has an unique feature that both, diene and dienophile are formed *in situ*. First, Knoevenagel condensation of an aromatic aldehyde with barbituric or 2-thiobarbituric acid affords a 5-benzylidenebarbiturate. Due to the readily reducible exocyclic double bond, this is responsible for oxidation of ethanol to acetaldehyde.[34,35] Acetaldehyde enters the following reaction step in its enol form, and as a dienophile reacts with 5-benzylidenebarbiturate in a hetero-Diels-Alder reaction to give, after elimination of water from the intermediate, the annulated product (**14**–**25**). The reaction is successful with 4-formylbenzoic acid, nitro- and cyanobenzaldehydes, but not with 4-hydroxybenzaldehyde. This can be explained with differences in the oxidizing abilities of 5-benzylidenebarbiturates, which depend on the electron density in the C=C bond, and are enhanced with the growing number and strength of electron-withdrawing substituents on the aromatic ring.[34–36]



Scheme 4. Reagents and conditions: (*a*) reflux, 3 days (Method A), or microwave irradiation: 120 °C, 30 W, *ca.* 1–2 h (Method B).

3. Conclusion

In the present work, efficient and clean selective syntheses of 5-benzylidene(thio)barbiturates **II**, symmetric Michael adducts **III** as well as 5-aryl-pyrano[2,3-*d*]pyrimidine-2,4-diones and their thio analogues **IV** from (thio)barbituric acid and various benzaldehydes are described. Simple Knoevenagel products **II** (compounds **1**–**7**) are isolated in high yields when the reaction is performed in water, whereas in glacial acetic acid with one equivalent of sodium acetate, addition of a second molecule of barbituric acid to the exocyclic methyne carbon atom affords Michael products **III** (compounds **8**–**13**) in 81–97 percent yield. In ethanol/water as solvent, two interconnected reaction sequences, a domino Knoevenagel hetero-Diels-Alder reaction, and a domino oxidation hetero-Diels-Alder reaction, give annulated uracils **IV** (compounds **14**–**25**). Selective synthesis of all three classes of compounds is preparatively important and contributes to the understanding of reactivity of 5-benzylidenebarbituric acid derivatives.

4. Experimental

All reagents were used as received from commercial sources without further purification unless otherwise indicated. Analytical TLC was performed on Merck silica gel (60 F 254) plates (0.25 mm) and components visualized with ultraviolet light. Column chromatography was carried out on silica gel 60 (particle size 240–400 mesh). Microwave assisted reactions were conducted in a sealed glass vessel (capacity 10 mL) on a CEM Discover microwave synthesizer (CEM Corporation, USA) with a built-in pressure measurement sensor and operator-selectable power output from 0 to 300 W. The temperature was monitored using an infrared temperature sensor mounted under the reaction vessel. All experiments were performed using a high-speed stirring option. Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker AVANCE DPX300 spectrometer in DMSO-d_6 or D_2O solution with TMS as the internal standard at 25 °C. Spectra were assigned using gradient COSY, HSQC and DEPT experiments. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Mass spectra were obtained using a VGAnalytical Autospec Q mass spectrometer. Microanalyses were performed on a Perkin-Elmer C, H, N analyzer 2400 II. All reported yields are yields of purified products.

4. 1. General Procedure for the Preparation of 5-benzylidenebarbituric acids 1–7

A suspension of the corresponding benzaldehyde (1.00 mmol) and barbituric acid (128 mg, 1.00 mmol) in water (20 mL) was refluxed for 12 h, after which the mixture was cooled to rt, the product filtered off and washed with EtOH.

5-Benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1). Yield: 86 mg (40%); white crystals; mp 262–265 °C (lit.[44] 256–258 °C); IR (KBr) ν 3442, 3218, 3064, 2846, 1739, 1682, 1567, 1435, 1404, 1338, 1296, 1218, 1197, 1072, 1033, 801, 760, 680 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.44–7.57 (m, 3H, H-3,4,5), 8.06–8.09 (m, 2H, H-2,6), 8.29 (s, 1H, CH=C), 11.22 (s, 1H, NH), 11.38 (s, 1H, NH).

5-(3-Nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2). Yield: 157 mg (60%); white crystals; mp 245–247 °C (lit.[45] 242–244 °C); IR (KBr) ν 3443, 3241, 3120, 3096, 2824, 1779, 1756, 1738, 1698, 1681, 1595, 1538, 1434, 1397, 1336, 1354, 1301, 1212, 1109, 1031, 978, 844, 813, 795, 736 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.74 (t, 1H, *J* = 8.1 Hz, H-5), 8.23–8.25 (m, 1H, H-4/6), 8.30–8.34 (m, 1H, H-4/6), 8.35 (s, 1H, H-2), 8.91 (s, 1H, CH=C), 11.32 (s, 1H, NH), 11.47 (s, 1H, NH).

5-(4-Nitrobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3). Yield: 232 mg (89%); white crystals; mp 293–298 °C (lit.[45] 290–293 °C); IR (KBr) ν 3422, 3243, 3092, 2850, 2816, 1743, 1691, 1637, 1598, 1588, 1519, 1486, 1439, 1409, 1373, 1345, 1319, 1223, 1090, 1104, 1036, 1010, 928, 866, 855, 834, 792, 741, 713 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.03 (d, 2H, *J* = 8.7 Hz, H-2,6), 8.25 (d, 2H, *J* = 8.7 Hz, H-3,5), 8.33 (s, 1H, CH=C), 11.31 (s, 1H, NH), 11.48 (s, 1H, NH). MS for $C_{11}H_7N_3O_5$ (EI) *m*/*z* (%): 261 (M^+, 37), 244 (100), 214 (62), 172 (11), 101 (24).

3-((2,4,6-Trioxotetrahydropyrimidin-5(6*H*)-ylidene)methyl)benzonitrile (4). Yield: 207 mg (86%); white crystals; mp 290–294 °C (lit[46] 292–294 °C); IR (KBr) ν 3419, 3218, 3099, 2240 (CN), 1748, 1723, 1697, 1605, 1435, 1380, 1318, 1237, 1208, 1170, 1154, 957, 904, 806, 788, 754, 677 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.65 (t, 1H, *J* = 7.8 Hz, H-5), 7.94 (d, 1H, *J* = 7.8 Hz, H-4/6), 8.17 (d, 1H, *J* = 7.8 Hz, H-4/6), 8.27 (s, 1H, CH=C), 8.39 (s, 1H, H-2), 11.30 (s, 1H, NH), 11.46 (s, 1H, NH).

4-((2,4,6-Trioxotetrahydropyrimidin-5(6*H*)-ylidene)methyl)benzonitrile (5). Yield: 210 mg (87%); white crystals; mp 319–323 °C (lit.[46] 320 °C); IR (KBr) ν 3441, 3218, 3048, 2838, 2232 (CN), 1739, 1682, 1576, 1442, 1423, 1410, 1340, 1313, 1292, 1200, 1074, 848, 799 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.90 (d, 2H, *J* = 8.3 Hz, H-3,5), 8.00 (d, 2H, *J* = 8.3 Hz, H-2,6), 8.29 (s, 1H, CH=C), 11.29 (s, 1H, NH), 11.46 (s, 1H, NH).

4-((2,4,6-Trioxotetrahydropyrimidin-5(6*H*)-ylidene)methyl)benzoic Acid (6). Yield: 216 mg (83%); white crystals; mp 342–346 °C (lit.[47] >300 °C); IR (KBr) ν 3419, 3194, 3064, 2858, 2668, 2550, 1745, 1694, 1593, 1446, 1411, 1385, 1334, 1294, 1222, 1200, 1122, 1073, 1016, 961, 942, 863, 838, 796, 770, 706 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.96 (d, 2H, *J* = 8.7 Hz, H-3,5), 8.01 (d, 2H, *J* = 8.7 Hz, H-2,6), 8.30 (s, 1H, CH=C), 11.26 (s, 1H, NH), 11.43 (s, 1H, NH), 13.18 (s br, 1H, COOH).

5-(4-Hydroxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (7). Yield: 216 mg (93%); white crystals; mp >350 °C (lit.[48] >300 °C); IR (KBr) ν 3544, 3417, 3262, 3186, 2814, 1740, 1663, 1615, 1583, 1526, 1514, 1443, 1409, 1347, 1310, 1280, 1217, 1178, 1043, 886, 845, 834, 792, 771, 638 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.88 (d, 2H, *J* = 8.9 Hz, H-3,5), 8.21 (s, 1H, CH=C), 8.33 (d, 2H, *J* = 8.9 Hz, H-2,6), 10.78 (s, 1H, OH), 11.11 (s, 1H, NH), 11.23 (s, 1H, NH).

4. 2. General Procedure for the Preparation of Michael Adducts 8–13

A suspension of the corresponding benzaldehyde (1.00 mmol), sodium acetate (82 mg, 1.00 mmol) and barbituric (128 mg, 1.00 mmol) or 2-thiobarbituric acid (144 mg, 1.00 mmol) in glacial acetic acid (20 mL) was heated at 65 °C for 10 h, after which the mixture was cooled to rt, the product filtered off and washed with EtOH.

Sodium 5-((6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (8). Yield: 352 mg (96%); white crystals; mp >350 °C; IR (KBr) ν 3418, 3176, 2871, 1722, 1704, 1694, 1613, 1470, 1455, 1408, 1265, 1157, 909, 874, 812, 780 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.94 (s, 1H, CH), 6.99–7.16 (m, 5H, Ar-H), 9.98 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR → compound could not be dissolved in sufficient concentration in any known solvent. MS for $C_{15}H_{11}N_4NaO_6$ (ESI) *m*/*z*: 343 ([M–Na$^+$]$^-$, 12), 247 (100). Anal. calcd for $C_{15}H_{11}N_4NaO_6 \times 0.4\ H_2O \times 0.3\ CH_3COOH$: C, 47.86; H, 3.35; N, 14.31; found C, 48.03; H, 3.60; N, 14.15.

Sodium 5-((6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(3-nitrophenyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (9). Yield: 358 mg (87%); white crystals; mp >350 °C; IR (KBr) ν 3363, 3155, 2978, 2869, 1723, 1711, 1605, 1529, 1480, 1411, 1351, 1233, 1210, 1164, 1125, 1096, 902, 812, 795, 779, 732 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.02 (s, 1H, CH), 7.46–7.50 (m, 2H, H-5,6), 7.85 (s, 1H, H-2), 7.94–7.97 (m, 1H, H-4), 10.25 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR (D_2O + 10 μL 40% NaOD, 75 MHz) δ 36.38 (CH), 90.88 (CC=O), 120.40 (Ar-C), 122.67 (Ar-C), 128.84 (Ar-C), 134.94 (Ar-C), 148.11 (Ar-C), 148,43 (Ar-C), 154.43 (C=O), 166.70 (C=O). MS for $C_{15}H_{10}N_5NaO_8$ (ESI) *m*/*z* : 410 ([M–H$^+$]$^-$, 12), 388 ([M–Na$^+$]$^-$, 13), 127 (100). HRMS for $C_{15}H_9N_5NaO_8$ ([M–H$^+$]$^-$): calcd 410.0349; found 410.0341. Anal. calcd for $C_{15}H_{10}N_5NaO_8 \times 1.5\ H_2O$: C, 41.11; H, 2.99; N, 15.98; found C, 41.48; H, 2.93; N, 15.88.

Sodium 5-((6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-nitrophenyl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (10). Yield: 333 mg (81%); white crystals; mp >350 °C; IR (KBr) ν 3650, 3350, 3157, 2986, 2831, 1726, 1711, 1693, 1600, 1502, 1456, 1379, 1347, 1209, 1186, 1160, 1111, 1011, 857, 848, 779, 650 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.99 (s, 1H, CH), 7.31 (d, 2H, *J* = 8.6 Hz, H-2,6), 8.07 (d,

2H, *J* = 8.6 Hz, H-3,5), 10.32 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR (D_2O + 10 μL 40% NaOD, 75 MHz) δ 36.89 (CH), 91.04 (CC=O), 123.44 (Ar-C), 128.57 (Ar-C), 145.25 (Ar-C), 154.74 (Ar-C/C=O), 155.74 (Ar-C/C=O), 166.93 (C=O). MS for $C_{15}H_{10}N_5NaO_8$ (ESI) *m/z* (%): 388 ([M–Na$^+$]$^-$, 30), 113 (100). Anal. calcd for $C_{15}H_{10}N_5NaO_8 \times H_2O$: C, 41.97; H, 2.82; N, 16.31; found C, 42.18; H, 2.76; N, 16.24.

Sodium 5-((6-Hydroxy-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-nitrophenyl)methyl)-6-oxo-2-thioxo-1,2,3,6-tetrahydropyrimidin-4-olate (11). Yield: 372 mg (84%); white crystals; mp >350 °C; IR (KBr) ν 3353, 3291, 2950, 2563, 1671, 1622, 1547, 1537, 1514, 1435, 1347, 1321, 1218, 1196, 1178, 1129, 1111, 1011, 904, 844, 770, 730 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.07 (s, 1H, CH), 7.27 (d, 2H, *J* = 8.4 Hz, H-2,6), 8.07 (d, 2H, *J* = 8.4 Hz, H-3,5), 11.59 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR (D_2O + 10 μL 40% NaOD, 75 MHz) δ 36.77 (CH), 95.47 (CC=O), 123.54 (Ar-C), 128.63 (Ar-C), 145.54 (Ar-C), 153.90 (Ar-C), 164.76 (C=O), 171.58 (C=S). MS for $C_{15}H_{10}N_5NaO_6S_2$ (ESI) *m/z*: 420 ([M–Na$^+$]$^-$). HRMS for $C_{15}H_{10}N_5O_6S_2$ ([M–Na$^+$]$^-$): calcd 420.0073; found 420.0060. Anal. calcd for $C_{15}H_{10}N_5NaO_6S_2 \times CH_3COOH$: C, 40.56; H, 2.80; N, 13.91; found C, 40.34; H, 3.19; N, 14.02.

Sodium 5-((3-Cyanophenyl)(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (12). Yield: 376 mg (96%); white crystals; mp >350 °C; IR (KBr) ν 3527, 3360, 3209, 2869, 2813, 2238 (CN), 1704, 1694, 1608, 1482, 1413, 1362, 1352, 1312, 1252, 1180, 1130, 1053, 997, 903, 808, 782 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.98 (s, 1H, CH), 7.32–7.42 (m, 3H, H-2,5,6), 7.51–7.53 (m, 1H, H-4), 10.09 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR (D_2O + 10 μL 40% NaOD, 75 MHz) δ 36.69 (CH), 92.29 (CC=O), 110.25 (Ar-C), 121.30 (Ar-C/CN), 128.66 (Ar-C/CN), 128.83 (Ar-C/CN), 131.67 (Ar-C/CN), 133.15 (Ar-C/CN), 148.43 (Ar-C), 158.07 (C=O), 169.84 (C=O). MS for $C_{16}H_{10}N_5NaO_6$ (ESI) *m/z*: 368 ([M–Na$^+$]$^-$). HRMS for $C_{16}H_{10}N_5O_6$ ([M–Na$^+$]$^-$): calcd 368.0631; found 368.0627. Anal. calcd for $C_{16}H_{10}N_5NaO_6 \times 1.4\ H_2O$: C, 46.14; H, 3.10; N, 16.82; found C, 46.41; H, 3.39; N, 16.73.

Sodium 5-((4-Cyanophenyl)(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-olate (13). Yield: 380 mg (97%); white crystals; mp >350 °C; IR (KBr) ν 3361, 3207, 2236 (CN), 1722, 1710, 1694, 1613, 1470, 1455, 1409, 1360, 1230, 1155, 1124, 1018, 879, 848, 795, 781 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.00 (s, 1H, CH), 7.20 (d, 2H, *J* = 8.1 Hz, H-2,6), 7.61 (d, 2H, *J* = 8.1 Hz, H-3,5), 10.09 (s br, 4H, NH), proton from OH not seen. ^{13}C NMR (D_2O + 10 μL 40% NaOD, 75 MHz) δ 36.91 (CH), 91.21 (CC=O), 106.86 (Ar-C), 121.30 (Ar-C/CN), 128.55 (Ar-C/CN), 132.12 (Ar-C/CN), 153.14 (Ar-C/C=O), 155.19 (Ar-C/C=O), 167.34 (C=O). MS for $C_{16}H_{10}N_5NaO_6$ (ESI) *m/z*: 390 ([M–H$^+$]$^-$), 368 ([M–Na$^+$]$^-$). HRMS for $C_{16}H_9N_5NaO_6$ ([M–H$^+$]$^-$): calcd 390.0451; found 390.0458. Anal. calcd for $C_{16}H_{10}N_5NaO_6 \times 1.1\ H_2O$: C, 46.75; H, 2.99; N, 17.04; found C, 46.71; H, 2.99; N, 16.71.

4. 3. General Procedure for the Preparation of 5-phenyl-1*H*-pyrano[2,3-*d*]pyrimidine-4(3*H*,5*H*)-ones 14–25

Method A (Conventional heating). A suspension of the corresponding benzaldehyde (1.00 mmol) and barbituric or 2-thiobarbituric acid (1.00 mmol) in EtOH/H_2O 1:1 (20 mL) was refluxed for 3 days, then the mixture was cooled to rt, the product filtered off and washed with EtOH.

Method B (Microwave-assisted synthesis). A suspension of the corresponding benzaldehyde (1.00 mmol) and barbituric or 2-thiobarbituric acid (1.00 mmol) in EtOH/H_2O 1:1 (3 mL) was heated in a sealed 10 mL glass vessel in a microwave reactor for 1–2 h at 120 °C (power = 30 W, ramp time = 3 min). The mixture was cooled to rt, the product was filtered off and washed with EtOH.

For full experimental procedures and characterisation data of compounds **14**–**25** see Ref. 36.

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Povzetek

Reakcija med barbiturno kislino ali 2-tiobarbiturno kislino in derivati benzaldehida lahko, ob uporabi različnih reakcijskih pogojev, selektivno vodi do treh strukturnih tipov reakcijskih produktov, t.j. 5-benziliden(tio)barbiturnih kislin **II**, simetričnih Michaelovih aduktov **III** ali 5-fenil-1*H*-pirano[2,3-*d*]pirimidin-2,4(3*H*,5*H*)-dionov in 5-fenil-2-tiokso-2,3-dihidro-1*H*-pirano[2,3-*d*]pirimidin-4(5*H*)-onov **IV**. Članek obravnava tudi reakcijske mehanizme in razloge za opaženo reaktivnost izhodnih spojin.