Tetrahedron Vol. 49, No. 14, pp. 2855-2862, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

A Simple Approach towards the Synthesis of Oxadeazaflavines

José Daniel Figueroa-Villar* and Elizabete R. Cruz

Seção de Química, Instituto Militar de Engenharia, Pça Gal Tibúrcio 80, Rio de Janeiro, RJ, 22290 Brasil
FAX 55212759047

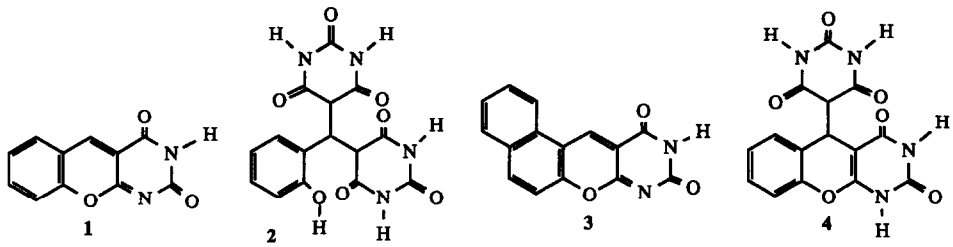
(*Received in USA* 4 *February* 1993)

Abstract: The synthesis of oxadeazaflavine (2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione) derivatives (**1a**, **1b** and **1c**) from barbituric acid and salicylaldehydes as starting materials was shown to be possible using water as solvent at room temperature. The orange intermediate formed, an anthocyanidin-like precursor of the desired products, gave reasonable yields of the oxadeazaflavines when treated with acetic acid-acetic anhydride mixture. When the reaction was carried out at 100°C the corresponding 1,5-dihydro-5(5'-barbituryl)-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (**4a**, **4b** and **4c**) were obtained. The reaction of barbituric acid with nitrosalicylaldehydes, at either 25 or 100°C, leads only to the corresponding arylidenebarbituric acids.

INTRODUCTION

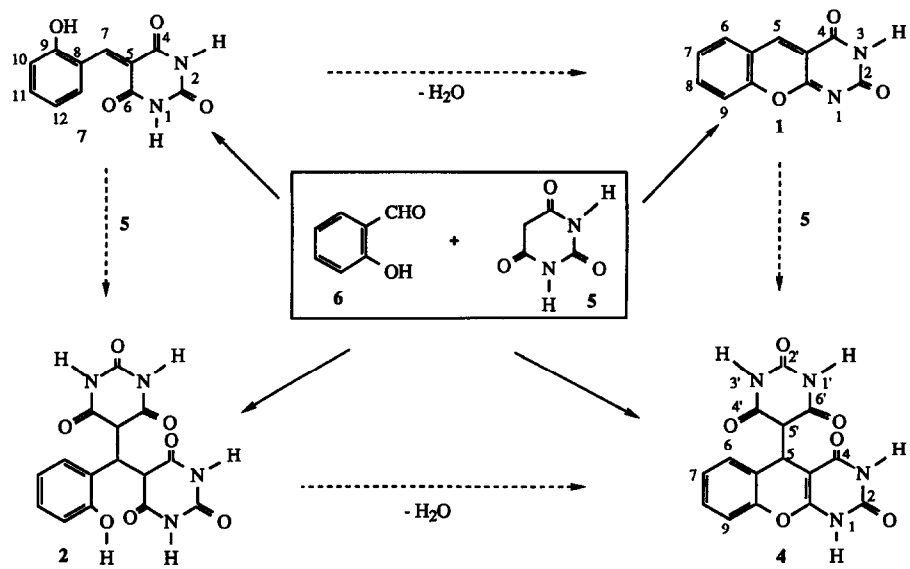
The 2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (oxadeazaflavines, **1**), which are biomimetic models of the 5-deazaflavine coenzyme, have been shown to possess strong redox properties in the conversion of alcohols to aldehydes or ketones[1-4].

Prior to this investigation only two synthetic routes that lead successfully to this type of compounds had been reported: a three step reaction from 3-alkyluracils and phenols[1,2] and a condensation reaction of N-cyanoacetylurethane with salicylaldehydes[4]. Two new alternative synthetic approaches to oxadeazaflavines have been recently reported[3]: the direct condensation of barbituric acid with *o*-halobenzaldehydes followed by dehydrohalogenation, and the condensation of 6-chlorouracil with *o*-hydroxybenzyl alcohol followed by oxidation. However, one of the simplest approaches to oxadeazaflavines, *i.e.* the direct condensation of barbituric acid with salicylaldehyde, has been investigated without success[3-7]. This condensation was first tried in 1901, when Conrad and Reinbach reacted barbituric acid with salicylaldehyde in boiling water. They obtained a compound to which the tricyclic structure **2** was attributed[5]. Later Pavolini[6] showed that the ratio barbituric acid:salicylaldehyde in this product was 2:1. In 1952, Ridi and Aldo[7] were able to prepare the benzooxadeazaflavine **3** from 2-hydroxy-1-naphtalaldehyde and barbituric acid, but the reaction with salicylaldehyde failed. More recently, Blythin *et al.*[4] and Chen *et al.*[3] reported that this approach to oxadeazaflavines was not successful. In this report we show that the 2:1 adduct of this reaction is actually the tetracyclic compound **4**, and not the tricyclic product described in previous works[3,5], and that it is possible to prepare either **1** or **4** in good yield by carrying out the reaction between barbituric acid and salicylaldehyde under controlled temperature conditions[8].



RESULTS AND DISCUSSION

The reaction of barbituric acid (**5**) and salicylaldehyde (**6**) could lead to four different compounds, as shown in Scheme 1.



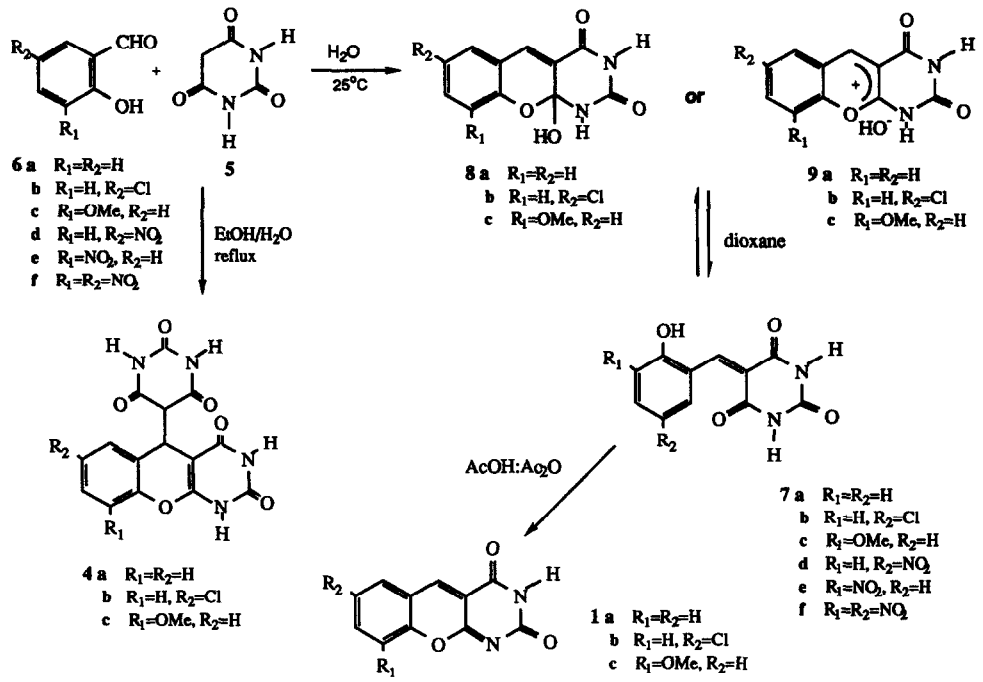
Scheme 1

Reaction in boiling water with equimolecular amounts of the starting materials results in a pale yellow crystalline solid precipitating from the reaction mixture[5]. The ultraviolet (UV) spectrum of this compound shows a single maximum at 258 nm, indicating that there is no conjugation between the phenyl and pyrimidine rings, thus excluding **1** and **7** as possible structures. The four bands observed in the carbonyl region of the infrared (IR) spectrum (1708, 1698, 1673 and 1650 cm^{-1}) suggest a more complex structure which could be either **2** or **4**. However, the ^1H nuclear magnetic resonance (NMR) spectrum shows four broad exchangeable singlets at δ 12.10, δ 11.41, δ 11.28 and δ 11.11 ppm, and only two hydrogens linked to sp^3

carbons. This result strongly favors the assignment of structure **4** to this product. The remaining peaks in the ^{1}H NMR correspond to the four aromatic hydrogens, at δ 7.20-7.60 ppm. The two broad doublets with a very small coupling constant at δ 3.96 and δ 4.85 ppm correspond to H5 and H5' respectively. The small coupling constant between them seems to indicate that the dihedral angle H5-H5' is close to 90°. Inspection of a molecular model of **4** shows that the barbituryl group is forced into a conformation where it is orthogonal to the 1,5-dihydrooxadeazaflavine due to steric interaction between the two carbonyl oxygens of the former, and the carbonyl oxygen at C4 and H6 of the latter. This steric interaction may hinder the free rotation of the barbituryl group, thus explaining the difference in the chemical shifts for the two hydrogens bonded to nitrogen in the barbituryl group. This structure also is confirmed by the 15 signals observed in the ^{13}C NMR spectrum.

The formation of **4** can occur *via* two different pathways shown by the dashed lines in Scheme 1. In both pathways the Michael-type addition reaction of **5** into **7** (or **1**) seems to be faster than the condensation between **5** and **6**. In this case the Michael-type addition may be disfavored either by increasing the steric hindrance at C7, using a C6-substituted salicylaldehyde as starting material, or by decreasing the temperature of the reaction so that the velocity of the Michael-type addition of barbituric acid is slowed down enough to make it unimportant. The first possibility seems to explain why compound **3** was easily obtained by Ridi and Aldo[7], and the second possibility was verified in this work.

Reaction temperatures in the range of 15 to 30°C were used. For this purpose, a diluted aqueous solution of barbituric acid was prepared and cooled to the desired temperature. A solution of salicylaldehyde in ethanol was then added. In this way a bright orange crystalline compound was obtained in 87% yield after recrystallization from dry dioxane. This orange compound gave yellow crystals of **1a** when recrystallized from an acetic acid-acetic anhydride (AcOH-Ac_2O) mixture (9:1) according to Yoneda's procedure[2]. The nature of the orange intermediate has not been completely defined, but we believe that it is the cyclized, but not dehydrated, intermediate **8a** or its ionic equivalent **9a** (Scheme 2). This coloration suggests the planar structure **9a**, which is similar to the well known anthocyanidin pigments[9]. The orange coloration is retained only in chloroform and ethyl acetate solutions. In dioxane and dimethyl sulfoxide (DMSO) it becomes yellow. Evaporation of dioxane yields yellow crystals which regain the original orange color when filtered and vacuum dried. The ^{1}H NMR spectrum recorded in deuterated DMSO shows that the yellow form of this compound corresponds to the uncyclized intermediate **7a**. Three exchangeable hydrogens are observed, two hydrogens bonded to the nitrogen atoms of the pyrimidine ring at δ 11.31 and δ 11.14 ppm, and one phenolic hydroxyl hydrogen at δ 10.61 ppm. The uncyclized character of this yellow intermediate was confirmed by the similarity of its ^{13}C NMR spectrum with that of the O-methylated derivative of **7a** (**10**). Compound **10** was prepared by Knoevenagel condensation of 2-methoxybenzaldehyde with **5**. Due to solubility limitations, the orange form was analyzed only by UV and IR spectroscopy. Its UV spectrum in chloroform indicates that the conjugated system is very similar to that of the oxadeazaflavine but, as expected, different from that of **10** in either methanol or chloroform and different from the uncyclized intermediate **7a** in methanol. By comparing IR spectra it can be seen that **7a** and **10** have three carbonyl absorptions in contrast to **8a-9a** and **1a** which have only two. These results support the cyclized nature of the orange intermediate (**8a-9a**), since it could be easily transformed into either the open form **7a** or the oxadeazaflavine **1a** under appropriate conditions. More thorough studies are being conducted on this orange compound in order to determine with certainty if it corresponds to **8a** or **9a**.



Scheme 2

The reactions of 4-chlorosalicylaldehyde (**6b**) and 2-methoxysalicylaldehyde (**6c**) with **5** at room temperature lead to the respective bright orange intermediates **8b-9b** and **8c-9c**, which afforded the oxadeazaflavines **1b** and **1c** in good yields upon recrystallization from AcOH-Ac_2O (9:1). As observed for **6a**, the salicylaldehydes **6b** and **6c** gave the corresponding tetracyclic compounds **4b** and **4c** when treated with **5** in ethanol-water under reflux. On the other hand, when the reaction was carried out with the nitrosalicylaldehydes **6d**, **6e**, and **6f**, either at room temperature or under reflux, only the uncyclized products **7d**, **7e**, and **7f** were obtained. We believe that the strong electron-withdrawing group present in the aromatic rings of the aldehydes **6d**, **6e**, and **6f** inhibits the conversion of the intermediates **7d**, **7e**, and **7f** into the corresponding orange intermediates, oxadeazaflavines, and tetracyclic products. This result suggests that the Michael type addition of **5** occurs only on the cyclized products, that is, on the oxadeazaflavines or on the orange intermediates, and not on the arylbarbiturylidenes **7**. This is supported by the fact that the methoxy derivative **10** does not undergo addition of barbituric acid when heated to reflux in an aqueous solution of **5**. The nitro group present in **7d**, **7e**, and **7f** decreases the nucleophilicity of the phenolic oxygen, thus making the pyran ring formation difficult. Without the pyran ring the aromatic ring would adopt a conformation with minimal conjugation with the exocyclic carbon-carbon double bond to the pyrimidine ring, possibly in a perpendicular relationship. The steric interference in this conformation would hinder the Michael type addition reaction of **5** on the exocyclic double bond.

EXPERIMENTAL

High resolution electron impact mass spectra (HREIMS) were recorded on an AEI MS-50 mass spectrometer. Fourier transform infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-171 spectrometer. Nuclear magnetic resonance (NMR) spectra (^{1}H and ^{13}C) were obtained on Varian VXR-300, XL-100, CFT-20, or Bruker ACE-200, WM-360 spectrometers. ^{1}H chemical shifts and coupling constants are reported as if they are first order. Tetramethylsilane was used as an internal standard and the solvents indicated in each case. Ultraviolet (UV) spectra were determined on a Varian DMS-80 spectrometer using the solvents and concentrations indicated in each case. Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Analytical thin-layer chromatography (TLC) was carried out on cut sections of E. Merck precoated aluminium sheets of silica gel 60 F-254 with visualization under a UV lamp (254nm). All solvents were distilled prior to use. The following starting materials were prepared according to literature procedures: barbituric acid (**5**)[10], 5-nitrosalicylaldehyde (**6d**)[11], 3,5-dinitrosalicylaldehyde (**6f**)[12], and 5-chlorosalicylaldehyde (**6b**)[13].

General procedure for the reaction of barbituric acid with aldehydes at 100°C

Barbituric acid (1.28 g, 10 mmol) was dissolved in boiling water and treated with the desired aldehyde (10 mmol) dissolved or suspended in 95% ethanol. After stirring under reflux for 30 min. the reaction mixture was cooled to room temperature and filtered. The solid products were recrystallized or washed with the appropriate solvents.

1,5-Dihydro-5-[5'-pyrimidine-2',4',6'(1'H,3'H,5'H)-trionyl]-2H-chromeno-[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4a**)

Yield: 100%; purified by washing with hot dioxane:acetic acid giving white crystals, m.p. 220-222°C (dec.); UV (MeOH) λ_{max} (ε): 204 (32900), 258 (14200) nm; IR (KBr) ν_{max}: 3487, 3278, 3222 (NH), 1708, 1698, 1673, 1650 (C=O) cm^{-1}; ^{1}H NMR (100 MHz, DMSO-d_6) δ: 12.10 (1H, s, NH), 11.41 (1H, s, NH), 11.28 (1H, s, NH), 11.11 (1H, s, NH), 7.60-7.20 (4H, m, aromatic H), 4.85 (1H, br d, J=0.5 Hz, H5'), 3.96 (1H, br d, J=0.5 Hz, H5); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 169.4 (C4'), 168.8 (C6'), 163.4 (C4), 155.3 (C10a), 150.4 (C2'), 149.4 (C2), 149.0 (C9a), 129.1 (C8), 127.9 (C6), 125.5 (C5a), 120.8 (C7), 116.4 (C9), 85.2 (C4a), 53.2 (C5'), 33.6 (C5); HREIMS, *m/z* calcd for $C_{11}H_6N_2O_3$ (M^+-barbituric acid): 214.0383; found: 214.0381 (84), 171.0323 (M^+-barbituric acid-CONH, 45), 143 0372 (56), 128.0223 (M^+-$C_{11}H_6N_2O_3$, 58), 85.0165 (20), 69.0006 (100).

1,5-Dihydro-7-chloro-5-[5'-pyrimidine-2',4',6'(1'H,3'H,5'H)-trionyl]-2H-chromeno[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4b**)

Yield: 84%, pale yellow solid, m.p. 281-282°C (dec.); UV (MeOH) λ_{max} (ε): 228 (19400), 259 (16800) nm; IR (KBr) ν_{max}: 3444, 3235 (NH), 1752, 1727, 1708, 1687, 1661 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.98 (1H, s, NH), 11.34 (1H, s, NH), 11.16 (1H, s, NH), 11.02 (1H, s, NH), 7.30 (1H, d, J=9 Hz, H8), 7.04 (1H, d, J=9 Hz, H9), 6.98 (1H, s, H6), 4.62 (1H, s, H5'), 3.94 (1H, s, H5); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 169.3 (C4'), 168.7 (C6'), 163.4 (C4), 155.1 (C10a), 150.5 (C2'), 149.5 (C2), 148.0 (C9a), 129.1 (C8 and C7), 127.7 (C6), 123.4 (C5a), 118.3 (C9), 84.8 (C4a), 53.5 (C5'), 33.1 (C5); HREIMS: *m/z* 249.9973 (24), 247.9966 (M^+-barbituric acid, 68), 191.1431 (40), 176.9983 (43), 149.0234 (31), 128.0223 (M^+- $C_{11}H_5N_2O_3Cl$, 43).

1,5-Dihydro-9-methoxy-5-[5'-pyrimidine-2',4',6'(1'H,3'H,5'H)-trionyl]-2H-chromeno[2,3-d]pyrimidine-2,4(1H,3H)-dione (**4c**)

Yield: 74%, pale yellow solid, m.p. 212-213°C (dec.); UV (MeOH) λ_{max} (ε): 259 (20100) nm; IR (KBr) ν_{max}: 3620, 3480, 3220, 3100 (NH), 1715 (br), 1652 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.70 (1H, s, NH), 11.04 (1H, s, NH), 10.88 (1H, s, NH), 10.68 (1H, s, NH), 7.05 (1H, t, J=8 Hz, H7), 6.95 (1H, d, J=8 Hz, H8), 6.64 (1H, d, J=8 Hz, H6), 4.64 (1H, s, H5'), 3.75 (4H, s, H5 and OMe); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 169.8 (C4'), 169.1 (C6'), 163.7 (C4), 155.6 (C10a), 150.7 (C2'), 149.6 (C2), 147.5 (C9), 138.8 (C9a), 125.6 (C5a), 121.7 (C7), 119.0 (C6), 112.1 (C8), 85.3 (C4a), 55.9 (OMe), 53.4 (C5'), 32.6 (C5); HREIMS: *m/z*

244.0484 (M^+-barbituric acid, 76), 211.0427 (M^+-barbituric acid-CONH, 41), 173.0476 (21), 128.0224 (M^+-$C_{12}H_8N_2O_4$, 59).

5-[(2-Methoxyphenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**10**)

Yield: 94%, yellow crystals from glacial AcOH, m.p. 265-266°C; UV (MeOH) λ_{max} (ε): 244 (10100), 258 (9300), 320 (5700), 375 (9000) nm; UV ($CHCl_3$) λ_{max} 242, 328, 393 nm; IR (KBr) ν_{max}: 3303, 3203 (NH), 1736, 1706, 1677 (C=O) cm^{-1}; ^1H NMR (100 MHz, DMSO-d_6) δ: 11.58 (1H, s, NH), 11.39 (1H, s, NH), 8.78 (1H, s, H7), 8.30 (1H, d, J=8 Hz, H13), 7.78 (1H, t, J=8 Hz, H11), 7.34 (1H, d, J=8 Hz, H10), 7.21 (1H, t, J=8 Hz, H12), 4.00 (3H, s, Me); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 163.3 (C4), 161.4 (C6), 159.0 (C9), 150.0 (C2 and C7), 134.0 (C11), 132.4 (C13), 121.5 (C8), 119.6 (C12), 118.5 (C5), 110.9 (C10), 55.9 (OMe); HREIMS *m/z* calcd for $C_{12}H_{10}N_2O_4$ (M^+): 246.0641; found: 246.0641 (20), 215.0457 (M^+-OMe, 100), 172.0399 (M^+-OMe-CONH, 56).

5-[(2-Hydroxy-5-nitrophenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7d**)

Yield: 95%, yellow crystals from dioxane, m.p. >350°C (dec.); UV (MeOH) λ_{max} (ε): 230 (7900), 258 (11600), 305 (7200) nm; IR (KBr) ν_{max}: 3200, 3070 (NH, OH), 1750, 1705, 1670 (C=O) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 11.20 (1H, s, NH), 11.05 (1H, s, NH), 8.98 (1H, d, J=2.5 Hz, H13), 8.38 (1H, s, H7), 8.14 (1H, br d, J=9 Hz, H11), 7.02 (1H, d, J=9 Hz, H10); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 163.6 (C4), 162.9 (C9), 161.4 (C6), 150.0 (C2),147.2 (C7), 138.6 (C12), 128.6 (C11), 128.4 (C13), 125.2 (C5), 119.4 (C8), 115.5 (C10); HREIMS: *m/z* calcd for $C_{11}H_7N_3O_6$ (M^+): 277.0336; found: 277.0336 (51), 260.0255 (M^+-OH, 55), 259.0228 (M^+-H_2O, 100), 234.0278 (M^+-CONH, 34), 218.0059 (32), 216.0141 (41), 114.0344 (29).

5-[(2-Hydroxy-3-nitrophenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7e**)

Yield: 80%, yellow crystals from dioxane, m.p. 236-237°C; UV (MeOH) λ_{max} (ε): 214 (13800), 258 (14100), 355 (3000) nm; IR (KBr) ν_{max}: 3458, 3203 (NH, OH), 1755, 1705, 1673 (C=O) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 11.45 (1H, s, NH), 11.26 (1H, s, NH), 8.36 (1H, s, H7), 8.11 (1H, d, J=8 Hz, H11), 8.10 (1H, d, J=8 Hz, H13), 7.06 (1H, t, J=8 Hz, H12); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 162.7 (C4), 161.1 (C6), 151.6 (C9), 150.1 (C2), 147.7 (C7), 138.4 (C11), 136.0 (C10), 127.8 (C13), 124.9 (C5), 121.0 (C8), 118.7 (C12).

5-[(2-Hydroxy-3,5-dinitrophenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7f**)

The reaction was carried out in 80% ethanol. Yield: 76%, yellow crystals from AcOH, m.p. 242-243°C; TLC: R_f 0.51 (15% AcOH - EtOAc); UV (MeOH) λ_{max}: (ε): 215 (17800), 262 (17100), 290 (sh), 366 (6600), 470 (6400) nm; IR (KBr) ν_{max}: 3195, 3140 (NH, OH), 1760, 1708, 1678 (C=O) cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6) δ: 11 78 (1H, s, NH), 11.62 (1H, s, NH), 9.78 (1H, s, H13), 9.22 (1H, s, H11), 9.00 (1H, s, H7); ^{13}C NMR (20 MHz, DMSO-d_6) δ: 162.9 (C4), 161.6 (C6), 160.6 (C9), 150.0 (C2),147.6 (C7), 137.6 (C12), 133.6 (C10), 132.5 (C11), 125.8 (C13), 124.2 (C5), 119.6 (C8); HREIMS, *m/z* calcd for $C_{11}H_6N_4O_8$ (M^+): 322.0189; found: 322.0187 (100)

Reaction of barbituric acid with the aldehydes at room temperature. Synthesis of the orange intermediates and their respective open forms

A solution of **5** (1.28 g, 10 mmol) in 50 mL boiling water was prepared and cooled to room temperature, then it was treated with a solution of the desired aldehyde (10 mmol) in an appropriate amount of ethanol or water. After 5 to 10 min. of stirring the formed precipitate was filtered off and washed with ethyl

acetate. These compounds exist as the open yellow form in solution, and as the orange form in the solid state. The reported data correspond to the form used to determine the spectra.

5-[(2-Hydroxyphenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7a**) *and its cyclized form* **8a-9a**

Yield: 87%, yellow crystals of **7a** from dry dioxane, m.p. 283-285°C (passing through the orange form, dec.); UV (MeOH) λ_{max}: 260, 324, 385 nm; IR (KBr) ν_{max}: 3203, 3152 (NH, OH), 1751, 1703, 1666 (C=O) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 11.31 (1H, s, NH), 11.14 (1H, s, NH), 10.61 (1H, br s, OH), 8.62 (1H, s, H7), 8.15 (1H, d, J=8 Hz, H13), 7.35 (1H, t, J=8 Hz, H11), 6.92 (1H, d, J=8 Hz, H10), 6.81 (1H, t, J=8 Hz, H12); ^{13}C NMR (50 MHz, DMSO-d_6) δ: 163.8 (C4), 161.9 (C6), 159.1 (C9), 150.5 (C2),150.4 (C7), 134.8 (C11), 132.9 (C13), 120.0 (C8), 118.3 (C12), 117.2 (C5), 115.5 (C10).

When **7a** was dried under vacuum for several hours it was transformed into its orange form **8a-9a** (100%); m.p. 283-285°C; UV ($CHCl_3$) λ_{max}: 332, 365, 387, 406 nm; IR (KBr) ν_{max}: 3409, 3184 (NH, OH), 1730, 1661 (C=O) cm^{-1}; HREIMS, *m/z* calc for $C_{11}H_8N_2O_4$ (M^+): 232.0486; found: 232.0485 (75), 215.0432 (M^+-OH, 98), 214.0378 (M^+-H_2O, 20), 173.0255 (48), 172.0397 (M^+-OH, -CONH, 34), 69.0004 (100).

5-[(5-Chloro-2-hydroxyphenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7b**) *and its cyclized form* **8b-9b**

The reaction was carried out in 80% ethanol. Yield: 78%, orange crystals upon concentration of the mixture to 10% volume or yellow solid precipitated after reaction is completed, m.p. 320°C (dec.); UV (MeOH) λ_{max} (ε): 226 (11500), 260 (9500), 366 (1700), 394 (2200) nm; IR (KBr) ν_{max}: 3200, 3110 (NH, OH), 1730, 1686, 1670 (C=O) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 11.37 (1H, s, NH), 11.21 (1H, s, NH), 10.89 (1H, br s, OH), 8.45 (1H, s, H7), 8.18 (1H, s, H13), 7.39 (1H, d, J=9 Hz, H11), 6.94 (1H, d, J=9 Hz, H10); ^{13}C NMR (50 MHz, DMSO-d_6) δ: 163.5 (C4), 161.9 (C6), 157 7 (C9), 150.4 (C2), 148.3 (C7), 133.8 (C11), 131.7 (C13), 121.9 (C12), 121.3 (C8), 118.7 (C5), 117.3 (C10); HREIMS *m/z* 266.0085 (M^+, $C_{11}H_7N_2O_4Cl$, 34), 248.9989 (M^+-OH, 46) 247.9982 (M^+-H_2O, 94), 223.0034 (M^+-CONH, 56), 206.9843 (M^+-OH-CONH, 100), 176.9985 (51).

5-[(2-hydroxy-3-methoxyphenyl)methylene]-2,4,6(1H,3H)pyrimidinetrione (**7c**) *and its cyclized form* **8c-9c**

Yield: 90%, orange crystals, m.p. >350°C (dec); UV (MeOH) λ_{max} (ε): 226 (11200), 262 (8300), 354 (4600) nm; IR (KBr) ν_{max}: 3510, 3340, 3130 (NH, OH), 1742, 1694, 1676 (C=O) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ: 11.31 (1H, s, NH), 11.14 (1H, s, NH), 9.83 (1H, br s, OH), 8.61 (1H, s, H7), 7.71 (1H, d, J=8 Hz, H13), 7.11 (1H, d, J=8 Hz, H11), 6.77 (1H, t, J=8 Hz, H12), 3.83 (3H, s, OMe); ^{13}C NMR (50 MHz, DMSO-d_6) δ: 163.7 (C4), 161.6 (C6), 150 3 (C2 and C7), 148.5 (C10), 147.3 (C9), 124.0 (C8), 120.3 (C12), 117.8 (C11), 117 5 (C13), 115.7 (C5), 56.0 (OMe).

Synthesis of the 2H-chromeno[2,3-d]pyrimidine-2,4(3H)-diones or oxa-deazaflavines

One gram of the desired condensation product of **5** with the corresponding aldehyde at room temperature (**8a-9a**, **8b-9b** or **8c-9c**), was added to a hot solution of acetic acid:acetic anhydride 9:1 (20 mL). The yellow crystals formed after cooling were filtered off, washed with ethyl acetate, and dried overnight at 70°C to afford the respective pure oxadeazaflavine (yellow crystals).

2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (**1a**)

Yield: 50%, m.p. 320-322°C (lit[2] 325°C); TLC: Rf 0.48 (EtOAc-MeOH-AcOH 90 5 5); UV (MeOH) λ_{max} 322, 360, 380, 400 nm; UV ($CHCl_3$) λ_{max}. 328, 368, 386, 408 nm; IR (KBr) ν_{max}: 3180 (NH), 1710, 1676 (C=O) cm^{-1}; ^1H nmr (360 MHz, DMSO-d_6) δ: 11.45 (1H, s, NH), 8.93 (1H, s, H5), 8.07 (1H, dd, J=8, 1.5Hz, H6), 7.89

(1H, td, J=8, 1.5Hz, H8), 7.70 (1H, d, J=8 Hz, H9), 7.54 (1H, t, J=8 Hz, H7); ^{13}C NMR APT (90 MHz, H_2SO_4-DMSO-d_6) δ: 161.7 (s, C4), 158.7 (d, C5), 158.4 (s, C10a), 153.4 (s, C9a), 146.0 (s, C2), 144.4 (d, C6), 133.2 (d, C8), 130.6 (d, C7), 120.6 (s, C4a), 117.6 (d, C9), 106.7 (s, C5a); HREIMS: *m/z* 214.0370 (M^+, $C_{11}H_6N_2O_3$, 100), 171.0318 (M^+-CONH, 56), 143.0369 (62).

7-Chloro-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (**1b**)

Yield: 50%, m.p. 310-312°C; TLC: R_f 0.61 (EtOAc-MeOH-AcOH 90:5:5); UV ($CHCl_3$) λ_{max}: 316, 378, 396, 418 nm; IR (KBr) ν_{max}: 3200 (NH), 1710, 1675 (C=O) cm^{-1}; ^{1}H nmr (360 MHz, DMSO-d_6) δ: 11.53 (1H, s, NH), 8.85 (1H, s, H5), 8.19 (1H, d, J=2.5 Hz, H6), 7.91 (1H, dd, J=9, 2.5Hz, H8), 7.74 (1H, d, J=9 Hz, H9); ^{13}C NMR APT (90 MHz, H_2SO_4-DMSO-d_6) δ: 161.9 (s, C4), 157.9 (s, C10a), 157.7 (d, C5), 151.7 (s, C9a), 145.8 (s, C2), 144.5 (d, C6), 136.5 (s, C7), 132.7 (d, C8), 120.6 (s, C4a), 118.6 (d, C9), 109.8 (s, C5a); HREIMS, *m/z* 249.9972 (M+2, 35)247.9986 (M^+, $C_{11}H_5N_2O_3Cl$, 100), 206.9879 (21).

9-Methoxy-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (**1c**)

Yield: 56%, m.p. >350°C; TLC: R_f 0.48 (EtOAc-MeOH-AcOH 90:5:5); UV ($CHCl_3$) λ_{max}: 260, 358, 395 (sh) nm; IR (KBr) ν_{max}: 3210 (NH), 1710, 1688 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, DMSO-d_6) δ: 11.45 (1H, s, NH), 8.90 (1H, s, H5), 7.59 (1H, t, J=8 Hz, H7), 7.57 (1H, d, J=8 Hz, H6), 7.48 (1H, d, J=8 Hz, H8), 3.97 (3H, s, OMe); ^{13}C NMR APT (90 MHz, H_2SO_4-DMSO-d_6) δ: 161.3 (s, C4), 159.0 (d, C5), 158.4 (s, C10a), 147.0 (s, C9), 146.2 (s, C2), 142.9 (s, C9a), 130.9 (d, C7), 125.2 (d, C6), 123.7 (d, C8), 121.1 (s, C4a), 107.0 (s, C5a), 56.4 (q, OMe); HREIMS, *m/z* 244.0484 (M^+, $C_{12}H_8N_2O_4$, 100), 201.0425 (M^+-CONH, 54), 173.0477 (25), 149.0238 (37).

ACKNOWLEDGEMENTS

The financial support of FINEP, CNPq and FAPERJ is gratefully acknowledged. We wish to thank Dr. Milan Ralitsch, Chemistry Department of the University of Alberta, for recording mass spectra, Dr. Vitor Rumjanek, Rural Federal University of Rio de Janeiro, and Dr. Sonia C. Menezes, of CENPES/PETROBRAS, for recording NMR spectra. The authors are grateful to Prof. William A. Ayer, Chemistry Department of the University of Alberta, for reviewing the manuscript of this paper.

REFERENCES AND NOTES

1. Yoneda, F ; Hirayama, R.; Yamashita, M. *Chem. Lett.* **1980**, (9), 1157-1160.
2. Yoneda, F.; Hirayama, R.; Yamashita, M. *J. Heterocycl. Chem.* **1982**, *19*, 301-304.
3. Chen, X.; Tanaka, K.; Yoneda, F. *Chem. Pharm. Bull.* **1990**, *38*, 307-311.
4 Blythin, D. J.; Domalski, M S.; Kim, Y. C.; Kuo, J ; Liu, J. H. *Heterocycles* **1981**, *16* , 203-207.
5. Conrad, M.; Reinback, H. *Ber* **1901**, *34*, 1339-1344.
6. Pavolini, T *Riv. Ital Essenze Profumi* **1933**, *15*, 171-173.
7. Ridi, M.; Aldo, G. *Gazz Chim. Ital.* **1952**, *82*, 13-22.
8. Part of this work appeared in a preliminary communication in *Synth. Commun.* **1992**, *22*, 1159-1164.
9. Britton, G. In *The Biochemistry of Natural Pigments;* Cambridge: London, 1983; pp. 102-129.
10. Dickey , J. B.; Gray, A. R. *Org. Syntheses,* Coll. Vol **2**, 1943, p. 60
11. Hach, C C.; Liggett, L. M , Diehl, H *J. Sci.* **1947**, *21*, 316-.
12. Icke, R. N.; Redemann, C. E.; Alles, G. A., Alles, W. B. B. *Organic Syntheses* , Coll. Vol. **3**, 1955, p.644
13 Durrans, T. H. *J Chem Soc.* **1923**, *123*, 1426-1429