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SYNTHESIS OF OXADEAZAFLAVINES FROM BARBITURIC ACID AND AROMATIC ALDEHYDES

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Abstract: 2*H*-Chromeno[2,3-*d*]-pyrimidine-2,4(3*H*)-diones were prepared directly from barbituric acid and salicylaldehydes or by thermal cyclization of the condensation product of barbituric acid and 6-bromopiperonal.

The 2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones or 10-oxa-5-deaza-flavines are known as potential organic oxidizers[1-4]. Up to 1990 the works of Yoneda *et al.* [1] and Blythin *et al.*[3] were the only known general procedures for the preparation of oxadeazaflavines. All the reported attempts to prepare this heterocyclic system by the direct condensation of barbituric acid with salicylaldehydes have been unsuccessful[3-7]. We have been able to obtain oxadeazaflavines in reasonable to good yields by reacting barbituric acid with salicylaldehydes at room temperature. Thus, the reaction of barbituric acid (**1**) with salicylaldehyde (**2a**) in water at 25°C gives an orange crystalline product which is converted into 2*H*-chromeno[2,3-*d*]pyrimidine-

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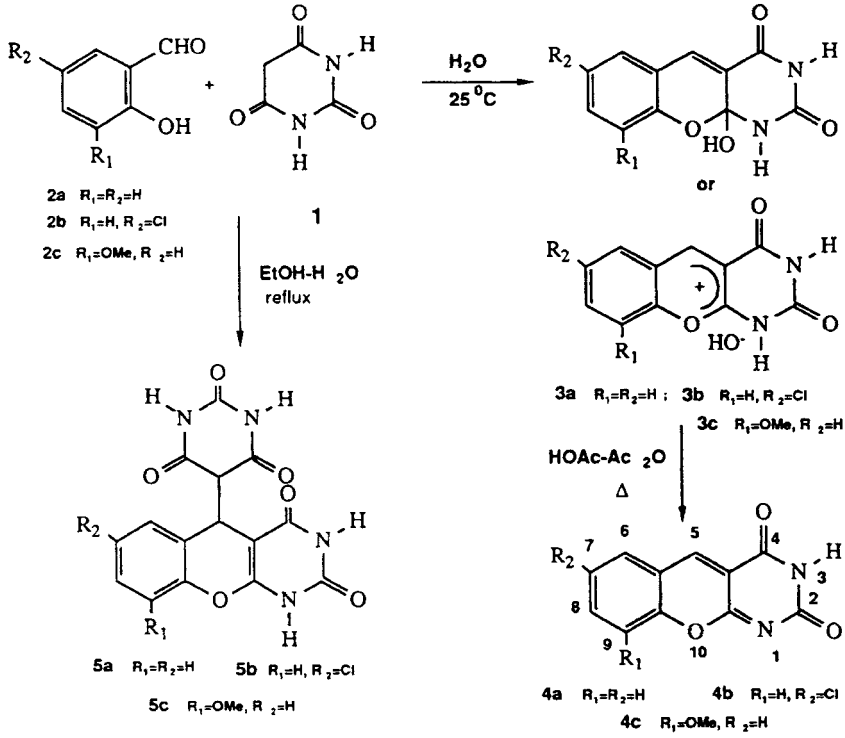
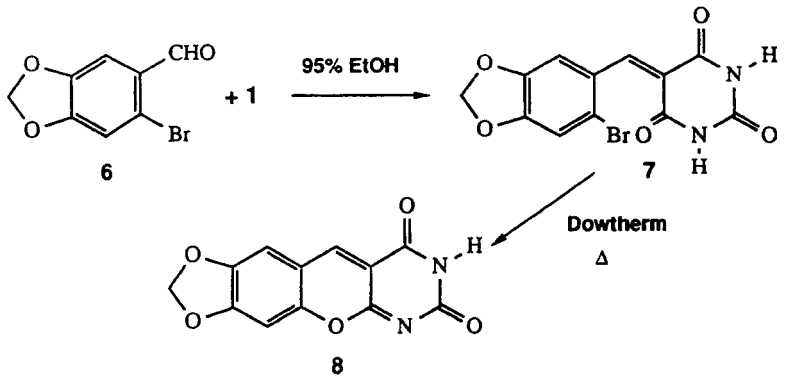
Scheme 1 - Reaction of barbituric acid and salicylaldehydes.



2,4(3*H*)-dione (**4a**) by recrystallization from an HOAc-Ac_2O 9:1 mixture, in 50% overall yield. When the same reaction is performed at 100°C, the reaction product is the 1,5-dihydro-5-[5-pyrimidine-2,4(1*H*,3*H*)-dionyl]-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (**5a**). The reaction of **1** with the aldehydes **2b** and **2c** at room temperature gave the oxadeazaflavines **4b** and **4c** in 50% and 56% yields respectively. At 100°C the tetracyclic products **5b** and **5c** were obtained in almost quantitative yield (Scheme 1). Both types of reaction failed when nitrosalicylaldehydes were used.

The chemical nature of the orange crystalline intermediates isolated in the reactions at room temperature has not been determined, but they seem to be either a

Scheme 2 - Reaction of barbituric acid and 6-bromopiperonal.



stable hydrated form of the respective oxadeazaflavines or the anthocyanidin-like compounds **3a-3c**.

The reaction of 6-bromopiperonal (**6**)[8] with barbituric acid in 95% ethanol, at room temperature, affords the corresponding 5-[5-bromo-1,3-benzodioxol-6-yl]-methylenepyrimidin-2,4,6(1*H*,3*H*)-trione (**7**) in 98% yield. When **7** was boiled in Dowtherm-A for 1 hour, a solid was formed which, after recrystallization from acetic acid, gave the oxadeazaflavine **8** as a light brown amorphous solid in 50% overall yield (Scheme 2). We are currently investigating the use of these two new methodologies for the synthesis of other oxadeazaflavines.

Experimental

High resolution electron impact mass spectra (hreims) were recorded on an AEI MS-50 mass spectrometer. Fourier transform infrared (Ftir) 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, CFT-20, or Bruker

Table 1 - Spectroscopic data of the oxadeazaflavines

Comp.	m.p. (°C)	UV ($CHCl_3$)* λ_{max} (nm)	IR (KBr) ν_{max} (cm^{-1})	HREIMS m/z
4a	320-322	328,368,386,408	3180,1710,1676	214.0370 $C_{11}H_6N_2O_3$
4b	310-312	316,378,396,418	3200,1710,1675	247.9986 $C_{11}H_5N_2O_3Cl$
4c	>350	260,358,395 (sh)	3210,1710,1688	244.0484 $C_{12}H_8N_2O_4$
8	>350	213,261,326,437	3210,1706,1696	260.0383 $C_{12}H_6N_2O_5$

*Low solubility in this solvent.

Table 2 - ^1H nmr data of the oxadezaflavines

Comp.	^1H nmr (360 MHz, DMSO-d_6) δ (Int., multipl., J,assignment)
4a	11.45 (1H, s, H3), 8.93 (1H, s, H5), 8.07 (1H, d, J=8.0 Hz, H9), 7.89 (1H, t, J=8.0 Hz, H7), 7.70 (1H, d, J=8.0 Hz, H6), 7.54 (1H, t, J=8.0 Hz, H8)
4b	11.53 (1H, s, H3), 8.85 (1H, s, H5), 8.19 (1H, s, H6), 7.91 (1H, d, J=9.0 Hz, H8), 7.74 (1H, d, J=9.0 Hz, H9)
4c	11.45 (1H, s, H3), 8.90 (1H, s, H5), 7.59 (1H, d, J=8.0 Hz, H8), 7.57 (1H, d, J=8.0 Hz, H6), 7.48 (1H, t, J=8.0 Hz, H7), 3.97 (3H, s, OMe)
8	11.23 (1H, s, H3), 8.72 (1H, s, H5), 7.44 (1H, s, H6), 7.43 (1H, s, H9), 6.22 (2H, s, -O-CH_2-O)

Table 3 - ^{13}C nmr data of the oxadeazaflavines

Comp.	^{13}C nmr δ (Assignment)
4a	163.6 (C4), 157.8 (C2), 156.9 (C10a), 153.4 (C9a), 146.9 (C5), 142.4 (C6), 132.5 (C8), 129.9 (C7), 120.1 (C4a), 117.3 (C9), 108.5 (C5a)
4b	164.1 (C4), 157.8 (C2), 155.0 (C10a), 151.6 (C9a), 147.6 (C5), 141.5 (C6), 136.5 (C7), 130.6 (C8), 120.6 (C4a), 118.6 (C9), 109.8 (C5a)
4c	163.2 (C4), 157.9 (C2), 157.0 (C10a), 147.8 (C9), 146.8 (C5), 142.9 (C9a), 130.1 (C7), 122.7 (C6), 122.5 (C8), 121.0 (C4a), 108.6 (C5a), 55.3 (OMe)
8	159.8 (C4), 154.7 (C8, C10a), 150.2 (C2), 150.1 (C5), 144.6 (C9a), 140.4 (C7), 110.7 (C6), 107.1 (C5a), 102.3 (OCH_2O), 98.6 (C4a), 97.2 (C9)

4a TFA - DMSO-d_6, 20 MHz; **4b** TFA - DMSO-d_6, 20 MHz; **4c** TFA - DMSO-d_6, 20 MHz; **8** H_2SO_4 - DMSO-d_6, 20 MHz.

WM-360 spectrometers. 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. Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Purity of the compounds was verified by TLC. All solvents were distilled prior to use.

General procedure for the reaction of 1 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.

Reaction of **1** *with the aldehydes at room temperature.*

A solution of **1** (1.28 g, 10 mmol) in 50 ml of 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.

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

One gram of the desired condensation product of **1** with the corresponding aldehyde at room temperature 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).

Tables 1 to 3 show the characterization of the oxadeazaflavines.

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