An Efficient Synthesis of Chromeno[2,3-*d*]pyrimidine-2,4-diones with a Nitroketene-Aminal Moiety at C(5) by a One-Pot Four-Component Reaction

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An efficient and novel synthesis of chromeno[2,3-*d*]pyrimidine-2,4-dione derivatives with a nitroketene-aminal moiety at C(5) *via* four-component reaction of salicylaldehydes, barbituric acid, diamines, and 1,1-bis(methylsulfanyl)-2-nitroethene in EtOH and in the presence of AcOH is reported. Easy performance, good yields, and easy purification are the main advantages of this method. All structures were confirmed by IR, MS, and ^{1}H- and ^{13}C-NMR, and by X-ray crystal-structure analyses. A plausible mechanism for this type of reaction is proposed (*Scheme*).

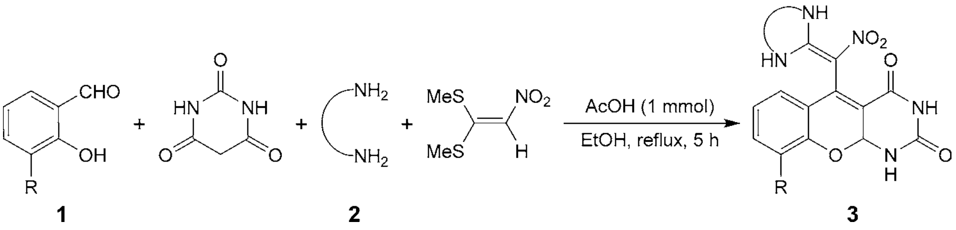
Introduction. – Chromeno[2,3-*d*]pyrimidine-2,4-diones ('oxadeazaflavins') are interesting organic compounds with various biological properties [1]. They are also biomimetic models of the deazaflavine coenzyme and have been shown to possess strong redox properties in the conversion of alcohols to aldehydes or ketones [2]. Due to the importance of oxadeazaflavins, various methods have been reported for their synthesis [3].

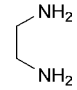
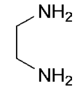
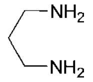
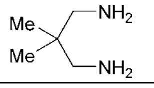
Heterocyclic ketene aminals are powerful and versatile intermediates in heterocyclic synthesis. Reactions of cyclic methylidene-aminals with a number of electrophilic reagents have been successfully used to synthesize five- and six-membered and fused heterocycles in recent years. These fused heterocyclic structures are frequently found in pharmacophores and play important roles in drug discovery. They are also used as pesticides, herbicides [4], antileishmanial agents [5], antianxiety agents [6], and antibacterial drugs [7].

As part of our ongoing efforts to explore new routes for the synthesis of a variety of biologically active fused polycyclic N-heterocycles *via* one-pot synthesis and reaction of aminals [8], we decided to study the synthesis of new 'oxadeazaflavin' derivatives by nitroketene aminal intermediates.

Results and Discussion. – Due to the importance of 'oxadeazaflavins' and in continuation of our studies on the synthesis of new chromene derivatives [9], herein we report the synthesis of 'oxadeazaflavin'-bearing nitroketene aminal derivatives by reaction of salicylaldehydes **1**, barbituric acid, diamines **2**, and 1,1-bis(methylsulfanyl)-2-nitroethene in the presence of AcOH. The reactions of salicylaldehydes **1**, barbituric acid, diamines **2**, and 1,1-bis(methylsulfanyl)-2-nitroethene were performed within 6 h

Table. *Prepared Nitroketene-Aminal Moiety-Bearing Chromeno[2,3-*d*]pyrimidine-2,4-diones*



Entry	R	Diamine **2**	Product	Yield [%]
1	H		**3a**	75
2	MeO		**3b**	80
3	MeO		**3c**	70
4	MeO		**3d**	72

in EtOH/H_2O 1:1 in the presence of 1 equiv. of AcOH to produce the target derivatives, **3a**–**3d**, in excellent yields (*Table*).

The structures of **3a**–**3d** were deduced from their elemental analysis, IR, and high-field ^1H- and ^{13}C-NMR spectra, and X-ray crystal-structure analysis of **3b**. The mass spectrum of **3b** displayed a fragment-ion peak at *m/z* 321, which corresponds to the 'oxadeazaflavin' part in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to NH stretching frequencies at 3409, 3255, and 3087 cm^{-1}. Further absorption bands at 1702, 1652, 1591, and 1474 cm^{-1} were attributed to C=O, C=C, and aromatic groups. Absorption bands at 1522, 1370, 1266, 1207, 1117, and 1076 cm^{-1} were assigned to the NO_2, C–O, and C–N groups. The ^1H-NMR spectrum of **3b** showed one *multiplet* (δ(H) 3.70–3.74) for two CH_2 groups, five *singlet*s (3.83, 4.83, 8.76, 10.91, and 11.75) corresponding to MeO, CH, and four NH groups, respectively, and also two *doublet*s (6.64 ($J = 7.6$) and 6.94 ($J = 7.6$)), as well as one *triplet* (7.03 ($J = 7.6$)) for aromatic H-atoms. The ^1H-decoupled ^{13}C-NMR spectrum of **3b** showed 15 distinct resonances in agreement with the suggested structure. Final confirmation for the formation of the reaction products was derived from recrystallization of **3b** in MeOH and X-ray analysis. The ORTEP diagram of **3b** with the inclusion of MeOH and H_2O is shown in the *Figure*.

A plausible mechanism for the synthesis of products **3a**–**3d** is proposed in the *Scheme*.

Initial addition of 1,*n*-diamine to 1,1-bis(methylsulfanyl)-2-nitroethene leads to ketene aminal **4**. Then, *Knoevenagel* condensation and cyclization between salicylal-

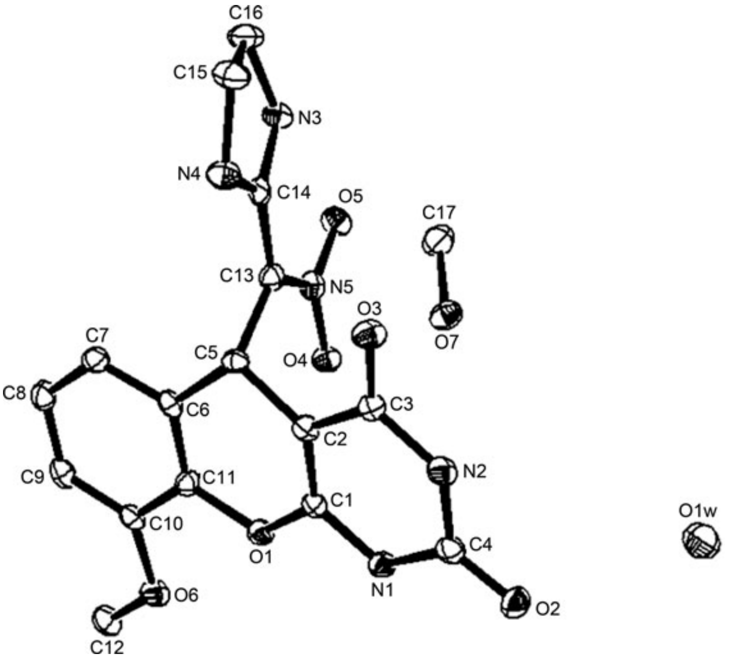
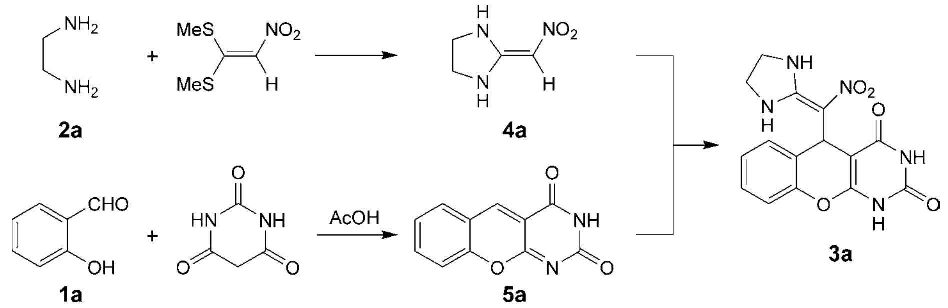


Figure. *ORTEP Diagram of* **3b**

Scheme. *A Plausible Mechanism for the Formation of* **3a**



dehyde **1** and barbituric acid, in the presence of AcOH, affords 'oxadeazaflavin' **5**. Finally, *Michael* addition of **4** and **5** gives **3**. To investigate the proposed mechanism, compound **5** was synthesized as described in [3b], and, when added to ketene aminal solution, the same product was obtained.

In summary, we have reported a concise synthesis of new 'oxadeazaflavin' derivatives by one-pot reaction of salicylaldehyde, barbituric acid, diamine, and 1,1-bis(methylsulfanyl)-2-nitroethene. Simple purification, easy performance, simple and inexpensive starting materials, and excellent yields characterize this method. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches of this type of heterocycles. Due to the importance of both oxadeazaflavin and ketene aminal moieties, synthesis of these compounds can be considered for biological applications in the near future.

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Experimental Part

General. All starting materials were obtained from *Merck* (Germany) and *Fluka* (Switzerland), and were used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer; KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *BRUKER DRX 400-AVANCE* FT-NMR instrument (400 and 100 MHz, resp.); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Finnigan-MAT 8430* mass spectrometer (EI, 70 eV); in m/z (rel. %). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure (exemplified for **3a**). A soln. of ethane-1,2-diamine (0.074 g, 1 mmol) and 1,1-bis(methylsulfanyl)-2-nitroethene (0.165 g, 1 mmol) in EtOH (3 ml) was magnetically stirred for 3 h under reflux. Then, salicyclaldehyde (0.122 g, 1 mmol) and AcOH (0.060 g, 1 mmol) were added, followed by dropwise addition of a soln. of barbituric acid (0.128 g, 1 mmol) in H_2O (3 ml) within 10 min. After 3 h, the hot mixture was filtered, and the precipitate was washed with EtOH to afford pure product **3a**.

*1,10a-Dihydro-5-[(imidazolidin-2-ylidene)(nitro)methyl]-2*H*-[1]benzopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3a**). Yield: 257 mg (75%). White powder. M.p. 252° (dec.). IR: 3321, 3160 (4 NH); 1710 (2 C=O), 1663 (C=C); 1600, 1407 (Ar), 1526, 1349 (NO_2); 1309, 1262, 1181 (C–O); 1089 (C–N). ^{1}H-NMR: 3.71 – 3.75 (*m*, 2 CH_2); 4.85 (*s*, CH); 7.00 (*d*, $J = 7.6$, 1 arom. H); 7.09 – 7.10 (*m*, 2 arom. H); 7.20 – 7.25 (*m*, 1 arom. H); 8.79 (*s*, 2 NH); 10.95 (*s*, NH); 11.78 (*s*, NH). ^{13}C-NMR: 30.4; 43.5; 95.6; 110.1; 115.1; 122.6; 124.5; 127.7; 128.3; 149.6; 150.1; 155.4; 160.6; 163.4. MS: 214 (44), 171 (83), 143 (100), 129 (72), 115 (88), 88 (51), 54 (37). Anal. calc. for $C_{15}H_{13}N_5O_5$ (343.30): C 52.48, H 3.82, N 20.40; found: C 58.39, H 3.85, N 20.23.

*1,10a-Dihydro-5-[imidazolidin-2-ylidene](nitromethyl-9-methoxy-2*H*-[1]benzopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3b**). Yield: 299 mg (80%). Beige powder. M.p. 261° (dec.). IR: 3284 (br., 4 NH), 1698 (2 C=O); 1652 (C=C); 1591, 1474 (Ar); 1522, 1370 (NO_2); 1266, 1207, 1117 (C–O); 1076 (C–N). ^{1}H-NMR: 3.70 – 3.74 (*m*, 2 CH_2); 3.83 (*s*, MeO); 4.83 (*s*, CH); 6.64 (*d*, $J = 7.6$, 1 arom. H); 6.94 (*d*, $J = 7.6$, 1 arom. H); 7.03 (*t*, $J = 7.6$, 1 arom. H); 8.76 (*s*, 2 NH); 10.91 (*s*, NH); 11.75 (*s*, NH). ^{13}C-NMR: 30.5; 43.5; 55.6; 84.7; 110.0; 110.6; 119.5; 123.3; 124.2; 139.6; 146.4; 149.5; 152.7; 160.6; 163.4. MS: 246 (52), 214 (9), 202 (57), 187 (19), 175 (57), 158 (40), 143 (60), 130 (53), 114 (37), 102 (81), 89 (44), 76 (100), 63 (70), 51 (77). Anal. calc. for $C_{16}H_{15}N_5O_6$ (373.33): C 51.48, H 4.05, N 18.76; found: C 51.52, H 4.13, N 18.81.

Crystal Data of **3b**[1]). $C_{16}H_{15}N_5O_6 \cdot MeOH \cdot H_2O$; M_r 423.38; MoK_α ($\lambda = 0.71073$ Å); $Z = 2$; $a = 8.0090(6)$, $b = 11.2369(12)$, $c = 11.6759(13)$ Å; $\alpha = 62.452(11)$, $\beta = 86.673(8)$, $\gamma = 76.093(8)°$; $V = 902.62(15)$ Å^3; D_x (calc.) = 1.558 mg m^{-3}; $F(000) = 444$; $3.3780 \leq 2\theta \leq 27.2230$; intensity data were collected at 100(2) K with an *Agilent Technologies SuperNova* dual diffractometer with *Atlas* detector, and employing $\omega/2\theta$ scanning technique, in the range of $-10 \leq h \leq 10$, $-14 \leq k \leq 14$, $-15 \leq l \leq 14$; the structure was solved by a direct method, all non-H-atoms were positioned, and anisotropic thermal parameters refined from 4166 observed reflections with $R_{\text{int}} = 0.0537$ by a full-matrix least-squares technique converged to $R^1 = 0.0676$ and $wR^2 = 0.1430$ ($I > 2\sigma(\text{I})$).

*1,10a-Dihydro-9-methoxy-5-[(nitro)(tetrahydropyrimidin-2(1*H*)-ylidene)methyl]-2*H*-[1]benzopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3c**). Yield: 271 mg (70%). Yellow powder. M.p. 258° (dec.). IR: 3406, 3255, 3087 (4 NH); 1702 (2 C=O); 1650 (C=C); 1591, 1469 (Ar); 1522, 1389 (NO_2); 1295, 1267, 1211, 1126 (C–O); 1072 (C–N). ^{1}H-NMR: 1.87 – 1.88 (*m*, CH_2); 3.42 – 3.43 (*m*, 2 CH_2N); 3.82 (*s*, MeO); 4.91 (*s*, CH); 6.60 (*d*, $J = 7.6$, 1 arom. H); 6.93 (*d*, $J = 7.6$, 1 arom. H); 7.01 (*t*, $J = 7.6$, 1 arom. H); 9.69 (*s*,

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[1]) CCDC-1015214 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk.

2NH); 10.95 (*s*, NH); 11.81 (*s*, NH). ^{13}C-NMR: 18.9; 29.3; 38.5; 55.6; 84.7; 110.6; 111.9; 119.4; 123.2; 124.0; 139.9; 146.3; 149.4; 154.7; 155.6; 163.8. MS: 260 (7), 246 (72), 214 (7), 202 (78), 187 (27), 173 (80), 158 (54), 143 (100), 130 (58), 113 (66), 97 (74), 76 (40), 56 (85). Anal. calc. for $C_{17}H_{17}N_5O_6$ (387.35): C 52.71, H 4.42, N 18.08; found: C 52.85, H 4.44, N 17.95.

*1,10a-Dihydro-9-methoxy-5-[(nitro)(tetrahydro-5,5-dimethylpyrimidin-2(1*H*)-ylidene)methyl]-2*H*-[1]benzopyrano[2,3-*d*]pyrimidine-2,4(3*H*)-dione* (**3d**). Yield: 299 mg (72%). Pale-yellow powder. M.p. 233° (dec.). IR: 3366, 3269, 3164 (4 NH); 1706 (2 C=O); 1666 (C=C); 1614, 1470 (Ar); 1528, 1393 (NO_2); 1296, 1204, 1121 (C–O); 1077 (C–N). ^{1}H-NMR: 1.04 (*s*, 2 Me); 3.11 – 3.12 (*m*, 2 CH_2); 3.83 (*s*, MeO); 4.96 (*s*, 1 arom. H); 6.58 (*d*, $J = 7.6$, 1 arom. H); 6.93 (*d*, $J = 7.6$, 1 arom. H); 7.03 (*t*, $J = 7.6$, 1 arom. H); 9.77 (*s*, 2 NH); 10.94 (*s*, NH); 11.80 (*s*, NH). ^{13}C-NMR: 23.5 (2Me); 25.6; 29.3; 49.7; 55.6; 84.7; 110.6; 111.8; 119.3; 123.2; 124.0; 139.8; 146.3; 149.4; 153.9; 155.5; 163.7. MS: 244 (59), 201 (65), 171 (81), 158 (46), 141 (36), 125 (100), 110 (23), 96 (74), 84 (83), 70 (64), 56 (82). Anal. calc. for $C_{19}H_{21}N_5O_6$ (415.41): C 54.94, H 5.10, N 16.86; found: C 55.09, H 5.21, N 16.77.

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