SIMPLE SYNTHETIC ROUTE TO "OXA-DEAZA-FLAVINS" (2_H_-[1]-BENZOPYRANO [2,3-_d_]PYRIMIDINE-2,4(3_H_)-DIONES).

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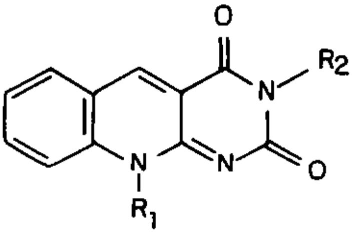
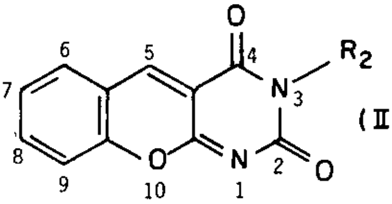
Abstract. The preparation and reduction of substituted [1]-benzopyrano [2,3-_d_]pyrimidine-2,4(3_H_)-diones, "oxa-deaza-flavins", (II), are described.

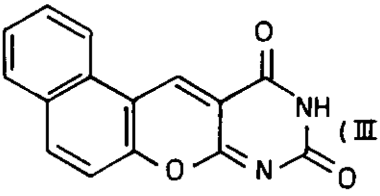
Interest has been shown recently in the oxidizing properties of 5-deazaflavins (I)[1] and several synthetic routes to this ring system have been described.[2-5] The analogous 10-oxa-5-deazaflavins (II) appear to have been little studied, either synthetically or for their chemical properties.[5a,b] The only analog in the literature prior to 1979 was a benzo- derivative (III) synthesized from 2-hydroxy-1-naphthaldehyde and barbituric acid.[6] Our attempts to prepare (II), (R_2 = H) from salicylaldehyde and barbituric acid were unsuccessful.



(I)



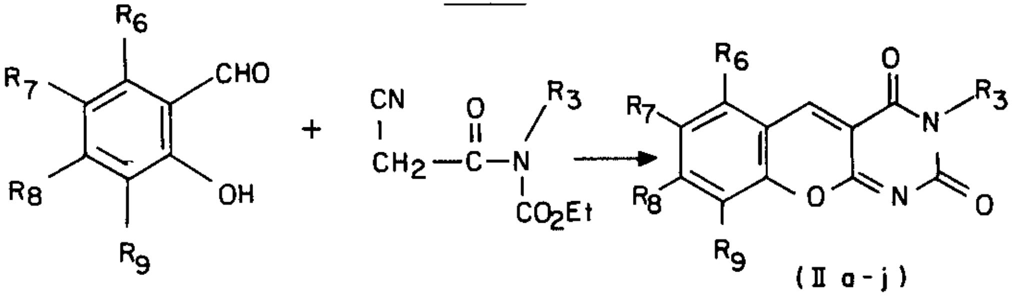
(II)



(III)

We describe here a simple, one-step synthesis of (II) from a substituted salicylaldehyde and an N-cyanoacetylurethane. In a typical procedure 5-hydroxymethyl salicylaldehyde (0.3 mole) and N-cyanoacetylurethane (0.31 mole) are dissolved in about 1.25 L of warm ethanol, morpholine (0.5 ml) is added and the mixture is refluxed for 3-4 hr. After cooling, the thick yellow-orange mixture is filtered, washed thoroughly with ethanol and dried to yield 7-hydroxymethyl-2_H_-[1]-benzopyrano[2,3-_d_]pyrimidine-2,4(3_H_)-dione, (IIh), in 75% yield. A representative selection of the derivatives synthesized is shown in Table 1.[7]

TABLE I

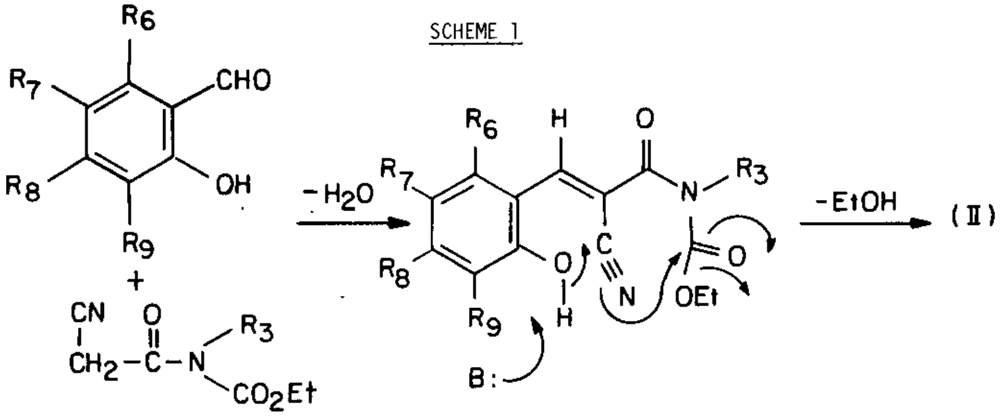


	R_3	R_6	R_7	R_8	R_9	Yield (%)	m.p.[7a]
II a	H	H	H	H	H	67	~ 320°C (dec)
b	H	H	Cl	H	H	60	> 350°C
c	H	H	OCH_3	H	H	80	~ 320°C (dec)
d	H	H	H	OCH_3	H	75	> 350°C
e	H	H	H	H	OCH_3	85	~ 350°C (dec)
f	H	OCH_3	H	OCH_3	H	80	~ 285°C (chars)
g	H	H	CH_3	CH_3	H	90	~ 295°C (dec)
h	H	H	CH_2OH	H	H	75	~ 280°C (dec)
i	CH_3	H	CH_2OH	H	H	30	287 - 290°C
j	C_2H_5	H	CH_2OH	H	H	30*	200 - 203°C

*Poor C, H, N analysis for this compound

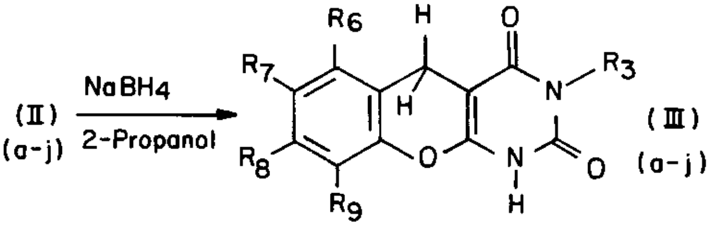
Formation of the tricyclic heterocycle from a monocyclic precursor evidently proceeds as shown in Scheme 1 in which initial aldol condensation is followed by intramolecular double-cyclization of the ideally-situated groups.[8]

SCHEME 1



The "oxa-deazaflavins" (II) are readily reduced (for instance, by $NaBH_4$ in isopropanol) to the 1,5-dihydro derivatives (III) (Table II) in yields often in excess of 90%.[9]

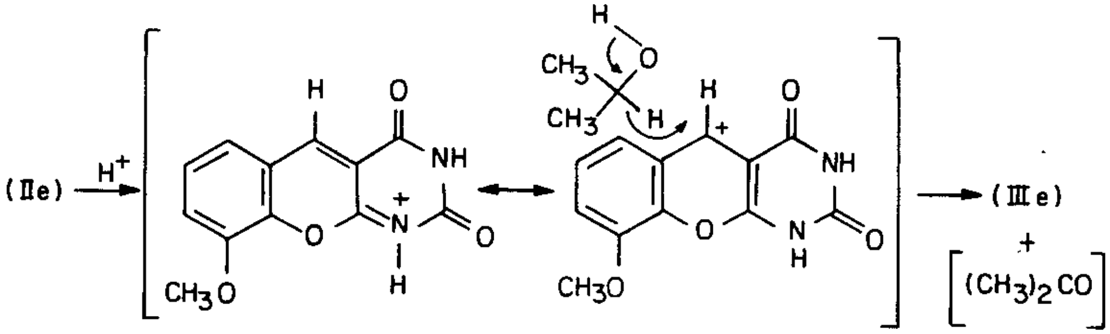
TABLE II



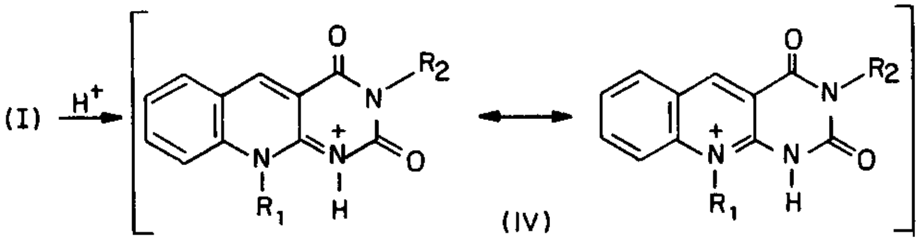
(III) a	b	c	d	e	f	g	h	i	j
95% ca. 310°C (dec)	88% ca. 320°C (dec)	81% 310°C (chars)	80% ~305°C (dec)	87% 313-315°C (dec)	94% 303-305°C (dec)	95% >330°C	82% 308-309.5°C (dec)	96% 308-312°C (dec)	75% 285°C

We have not studied the base-catalysed reduction of (II) in an analogous reaction to that of Yoneda et al.[1] but have found that under acidic conditions a similar reaction can be observed. Thus, when the compound (IIe), in isopropanol suspension, was refluxed for about 40 hr. in the presence of p-toluene sulfonic acid, an almost quantitative yield of the reduced compound (IIIe) was formed, presumably by hydride ion transfer under acidic conditions to the protonated form of (IIe), as shown in Scheme 2.[10]

SCHEME 2



These reactions demonstrate the electron-deficient nature of the 5-position of the "oxa-deazaflavins", as described by Yoneda et al.[11] for the 5-deazaflavin system. However, as far as we are aware, reduction of the 5-deazaflavins under acidic conditions has not been described. It is probable that the intermediate, a protonated quinoline derivative (IV), would be too resonance stabilized to allow hydride transfer to occur.



(IV)

The further transformations of these novel heterocycles are currently under investigation.[12]

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1. F. Yoneda, Y. Sakuma, and Y. Matsushita, J. Chem. Soc., Chem. Comm., 1978, 398.
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3. F. Yoneda, Y. Sakuma, S. Mizumoto, and R. Ito, J. Chem. Soc., Perkin Trans. I, 1976, 1805.
4. K. Mori, K. Shinozuka, Y. Sakuma, and F. Yoneda, J. Chem. Soc., Chem. Comm., 1978, 764.
5. Y. Sakuma, Y. Matsushita, F. Yoneda, and Y. Nitta, Heterocycles, 1978, 9, 1767.

5a. During preparation of this manuscript, we became aware of Professor F. Yoneda's interest in this system: F. Yoneda, Plenary Lecture, Seventh International Congress of Heterocyclic Chemistry, University of South Florida, Tampa, Florida, U.S.A.; August 12-17, 1979. Also F. Yoneda, "Lectures in Heterocyclic Chemistry," vol. V, 1980, p. S-73.

5b. F. Yoneda, R. Hirayama, and M. Yamashita, Chem. Lett., 1980, 1157.

6. M. Ridi and G. Aldo, Gazz. chim. ital., 1952, 82, 13.
7. The compounds IIa-j were characterized by microanalysis (C, H, N ± 0.4%, except IIj, as noted), and mass spectra (strong M^+ and a characteristic loss of 43 a.m.u. (HNCO) in IIa-h; 57 a.m.u. in IIi (CH_3-NCO); 71 a.m.u. in IIj (C_2H_5NCO)). Additionally, as examples of NMR properties, the compound IIi showed a 1H singlet at δ = 9.05 ppm (TMS) for the 5-H signal and δ = 3.22 ppm (s), 3-CH_3 (in d_6-DMSO). The UV spectrum of IId (MeOH) shows λmax 393 nm (log ε, 4.20) and 413 nm (log ε, 4.20).

7a. In general the melting points were of little use - much charring occurred above ca. 270-280°C. Only the N-3 alkylated products melted normally.

8. For a similar cyclization, see C.K. Ghosh, Synth. Commun., 1978, 8, 487.
9. Compounds IIIa-j were characterized by microanalysis (C, H, N ± 0.4%) and mass spectra [strong M^+, M-1, (loss of a 5-H atom) and M-44, (loss of H· and HNCO) from IIIa-h, M-58 in IIIi and M-72 in IIIj]. Additionally, as examples of NMR properties, the compound IIIh showed a 2H singlet at δ = 3.53 ppm (TMS) for the 5-H signal and compound IIIi showed a 2H singlet at δ = 3.50 ppm (5-H) and a 3H singlet at δ = 3.10 ppm (3-CH_3) in d_6-DMSO. The UV spectrum of IIIa in MeOH shows λmax 277 nm (log ε, 3.77).

10. In a trial experiment isobutyraldehyde, isolated as the semicarbazone, was identified in the volatile fractions when a suspension of IIa in isobutanol was refluxed in the presence of methanesulfonic acid. Further evidence for this type of mechanism comes from the work of Prof. Yoneda (reference 5b.).

11. F. Yoneda, Y. Sakuma, and P. Hemmerich, J. Chem. Soc., Chem. Comm., 1977, 825.

12. Including the preparation of (II) and (III) bearing strongly electron-withdrawing substituents.

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