CHEMISTRY LETTERS, pp. 1127-1130, 1982.

AUTORECYCLING OXIDATION OF ALCOHOL CATALYZED BY PYRIMIDOPTERIDINES AS A FLAVIN MODEL

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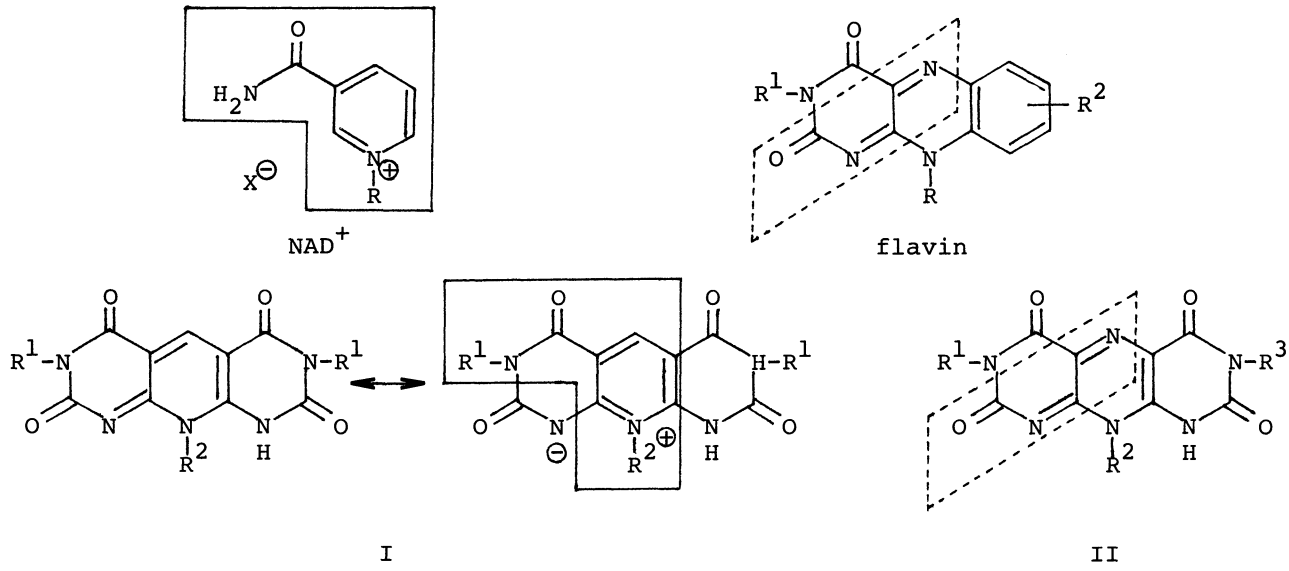
10-Substituted pyrimido[5,4-g]pteridines (II) were prepared by the condensation of 6-alkylamino-5-nitrosouracils (IV) with appropriate 6-chlorouracils. The compounds II oxidized cyclopentanol under neutral conditions to yield cyclopentanone and a remarkable autorecycling in the oxidation was observed.

Since the discovery in our labolatory that 5-deazaflavins[1] and their analogues such as 4-deazatoxoflavins[2] oxidized alcohols under weakly basic conditions and thereupon exhibited some recycling in the oxidation, the autorecycling alcohol oxidation which is catalyzed by the new type $NAD(P)^+$ model compounds working under neutral conditions has aroused considerable recent interest. Indeed, it has been found that some pyridodipyrimidines (I)[3] showed strong ability and remarkable autorecycling toward oxidation of alcohols to give the corresponding carbonyl compounds in several thousand or more percent yield. It is noted that the pyridodipyrimidines are the structurally cyclized compounds of the amino analogues of the Hantzsch esters and have a conjugated system similar to that of 5-deazaflavins.

It is known that flavin (isoalloxazine) derivatives have no abilities to oxidize all but the most electron-rich substrate in nonenzymatic systems. In fact, they have been shown not to oxidize usual alcohols in any appreciable degree.[4] However, from a recycling standpoint, the flavin derivatives have the notable merit that the free 1,5-dihydroflavins initially formed are reoxidized very rapidly to the original flavins in air.

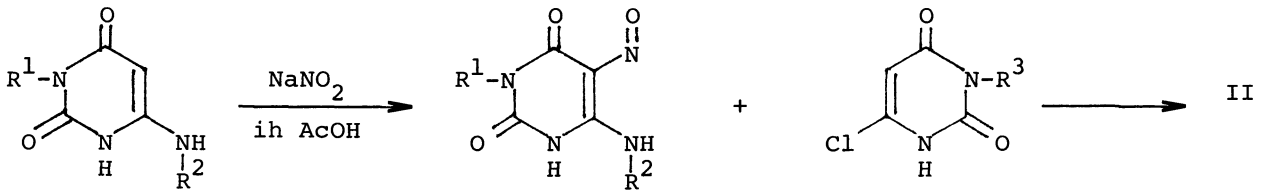
On the basis of the above observations, we have designed to prepare the pyrimidopteridines which are the 5-aza analogues of the pyridodipyrimidines (I) and have the same conjugated system as that of flavins (Scheme 1). The pyrimidopteridines are expected to act as efficient turnover catalysts in the oxidation of alcohol, because the reduced pyrimidopteridines initially formed in the reaction would be rapidly reoxidized to the original pyrimidopteridines by air just like flavin derivatives. We here report the new convenient synthesis of flavin-type pyrimido[5,4-g]pteridines (II) and the autorecycling oxidation of cyclopentanol[5] which is catalyzed by them under neutral conditions.

The 6-alkylamino-5-nitrosouracils (IV) which are precursors of pyrimido[5,4-g]pteridines (II) were prepared by the conventional nitrosation of 6-alkylaminouracils (III).[6] That is, the 6-alkylaminouracils (III) (0.011 mol) were dissolved in glacial acetic acid (60 ml) and saturated aqueous sodium nitrite



Scheme 1

(0.018 mol) was added dropwise to the solution under stirring and cooling at 10 °C. The cryatals were collected, washed with water and recrystallized from ethanol to give the corresponding nitroso-derivatives (IV) (Scheme 2) (Table 1).



Scheme 2

The pyrimido[5,4-g]pteridines (II) were synthesized by the condensation of the corresponding 6-alkylamino-5-nitrosouracils (IV) with appropriate 6-chlorouracils. A typical reaction procedure is as follows. A mixture of 5-nitroso-6-octylaminouracil (IVa) (0.5 g, 1.86 mmol) and 6-chlorouracil (0.33 g, 2.24 mmol) in N,N-dimethylformamide (10 ml) was heated with stirring at 140 °C for 4 h. Concentration of the solution under reduced pressure and treatment of the residue with ethanol gave 10-octylpyrimido[5,4-g]pteridine-2,4,6,8(3H,7H,9H,10H)-tetrone (IIa). The crude pyrimidopteridine (IIa) was treated with 2N HCl under stirring for 2 h and recrystallized from N,N-dimethylformamide to give the pure compound. Similarly, the heating of compounds IVb-f with appropriate 6-chlorouracils in N,N-dimethylformamide or n-butanol at 140-160 °C for 2-6 h, followed by treatment as described above, led to the formation of the corresponding pyrimido[5,4-g]pteridine derivatives (IIb-i) in the yields indicated in Table 2.

10-Substituted pyrimido[5,4-g]pteridines have up to this time been synthesized by the condensation of alloxane with 6-alkylamino-5-aminouracils.[7] The procedure as described above is a new and convenient synthetic method for the preparation of 10-substituted pyrimido[5,4-g]pteridines.

Table 1. 6-Alkylamino-5-nitrosouracils (IV)

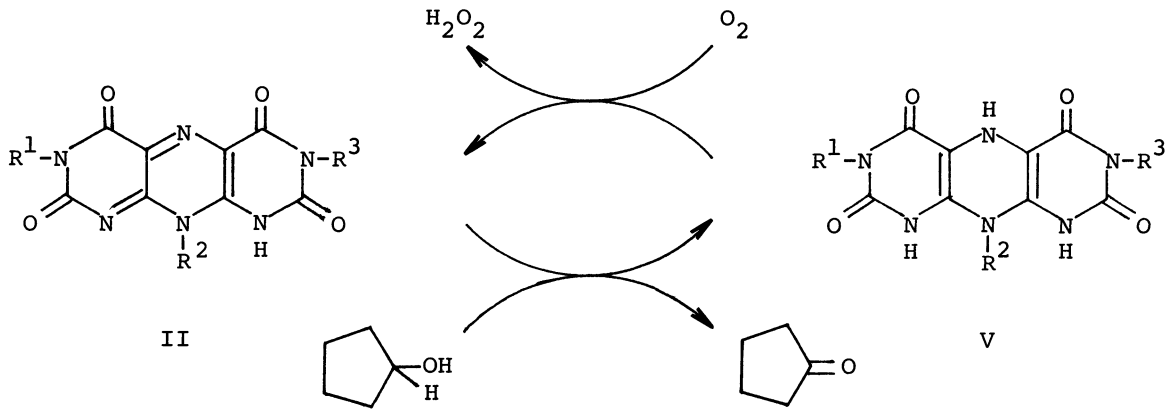
Compd. No.	R^1	R^2	Appearance	Mp (°C)	Yield (%)
IVa	H	n-C_8H_{17}	purple powder	155	95
IVb	CH_3	CH_3	cherry red powder	294[6]	98
IVc	CH_3	n-C_3H_7	pale orange powder	242[8]	86
IVd	CH_3	n-C_4H_9	pale orange powder	240[9]	70
IVe	CH_3	n-C_8H_{17}	pale orange powder	218	98
IVf	CH_3	n-$C_{12}H_{25}$	pale orange powder	214	87

Table 2. Pyrimido[5,4-g]pteridine-2,4,6,8(3H,7H,9H,10H)-tetrones (II)

Compd. No.	R^1	R^2	R^3	Mp (°C)[a]	Yield (%)
IIa	H	n-C_8H_{17}	H	> 340	56
IIb	CH_3	CH_3	H	> 330	61
IIc	CH_3	n-C_8H_{17}	H	> 320	72
IId	CH_3	n-$C_{12}H_{25}$	H	260	57
IIe	CH_3	CH_3	CH_3	> 320	63
IIf	CH_3	n-C_3H_7	CH_3	> 340	62
IIg	CH_3	n-C_4H_9	CH_3	> 320	58
IIh	CH_3	n-C_8H_{17}	CH_3	> 320	67
IIi	CH_3	n-$C_{12}H_{25}$	CH_3	215	58

a) All products were obtained as yellow needles.

We have now found that the pyrimido[5,4-g]pteridine (II) thus obtained oxidized cyclopentanol[5] under neutral conditions (in the absence of base) to yield cyclopentanone and, furthermore, a remarkable autorecycling in the oxidation was observed. Namely, a mixture of II (15 mg) with cyclopentanol (3 ml) was constantly stirred in a flask joined with a refluxing condenser at 120 °C for 25 h. The reaction mixture was diluted with ether, and the catalyst thus separated was filtered off. The filtrate was treated with a 2N HCl solution of 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of cyclopentanone. Under



Scheme 3

these conditions, 1,5-dihydropyrimido[5,4-g]pteridine (V) initially formed is re-oxidized rapidly to the original II by the air which comes in naturally from the top of the condenser, and thus II acts as a turnover catalyst (Scheme 3). In order to confirm the autorecycling of the catalyst, we have tried to isolate the corresponding 1,5-dihydropyrimido[5,4-g]pteridines (V) by the sodium dithionite reduction of II, but it was unsuccessful because of the rapid air oxidation of V into the original II.

The Table 3 shows the oxidation yield of cyclopentanol by II. As shown in the Table, II demonstrated in general strong autorecycling oxidation toward cyclopentanol. However the significant difference of the yield with changing of the substituent was not observed. The preparation of other types of pyrimidopteridines in order to get more efficient catalysts is currently under investigation.

Table 3. Autorecycling Oxidation of Cyclopentanol (3 ml) by II (15 mg) at 120 °C for 25 h

Compd. No.	R^1	R^2	R^3	Yield (%)[a-c] of Cyclopentanone
IIa	H	n-C_8H_{17}	H	4430 (5.6)
IIc	CH_3	n-C_8H_{17}	H	3674 (4.5)
IId	CH_3	n-$C_{12}H_{25}$	H	5650 (6.0)
IIe	CH_3	CH_3	CH_3	4432 (7.0)
IIf	CH_3	n-C_3H_7	CH_3	7602 (10.5)
IIg	CH_3	n-C_4H_9	CH_3	4498 (6.2)
IIh	CH_3	n-C_8H_{17}	CH_3	4403 (5.2)
IIi	CH_3	n-$C_{12}H_{25}$	CH_3	6848 (7.1)

a) Yields have not been optimized. Based on the pyrimido[5,4-g]pteridines.
b) Isolated as the 2,4-dinitrophenylhydrazone.
c) Yields based on the starting cyclopentanol are given in parentheses.

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(Received May 6, 1982)