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# REACTIVITY OF 4a,5-EPOXY-5-DEAZAFLAVINS

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Abstract: Reactions of 4a,5-epoxy-5-deazaflavins with aqueous potassium carbonate, Vilsmeier reagent (dimethylformamide-phosphorus oxychloride), acetic anhydride-acetic acid, pyridine and triethanolamine gave the corresponding oxazolonoquinolines, 5-chloro-5-deazaflavins, 4a,5-diacetoxy-5-deazaflavins, 1,5-dihydro-5-deazaflavin-5-ones, and deoxygenated 5-deazaflavins, respectively.

The 4a,5-epoxy-5-deazaflavins (I)[1] are isoelectronic with $N^5$-oxides[2] of the isoalloxazine (flavin) as well as the 4a,5-oxaziridinoflavins[3] as a possible intermediate[3,4] during flavin monooxygenation. Compounds I are known to be formed by reactions of the corresponding 5-deazaflavins with hydrogen peroxide, tert-butyl hydroperoxide, or m-chloroperbenzoic acid.[1]

Recently, we found that 5-deazaflavin-dependent oxidation of alcohols or amines to carbonyl compounds is automatically recycled under weakly basic conditions.[5] Hereupon, the 1,5-dihydro-5-deazaflavins initially formed are reoxidized to the original 5-deazaflavins by adventitious oxygen (air), while oxygen may be hydrogenated to hydrogen peroxide.[6] It may be possible that the hydrogen peroxide thus formed will partially catch the 5-deazaflavins to give birth to the corresponding 4a,5-epoxy-5-deazaflavins (I). Therefore, to know the reactivity of I might be of concern in connection with the fate of 5-deazaflavins in the oxidation procedures. In this communication, we report the reactions of I with several reagents which may serve as a basis for understanding reactivity of the 5-deazaflavin cofactor (e.g. coenzyme $F_{420}$)[7] in biological system and also providing new relevant preparative procedure in synthetic heterocyclic chemistry.

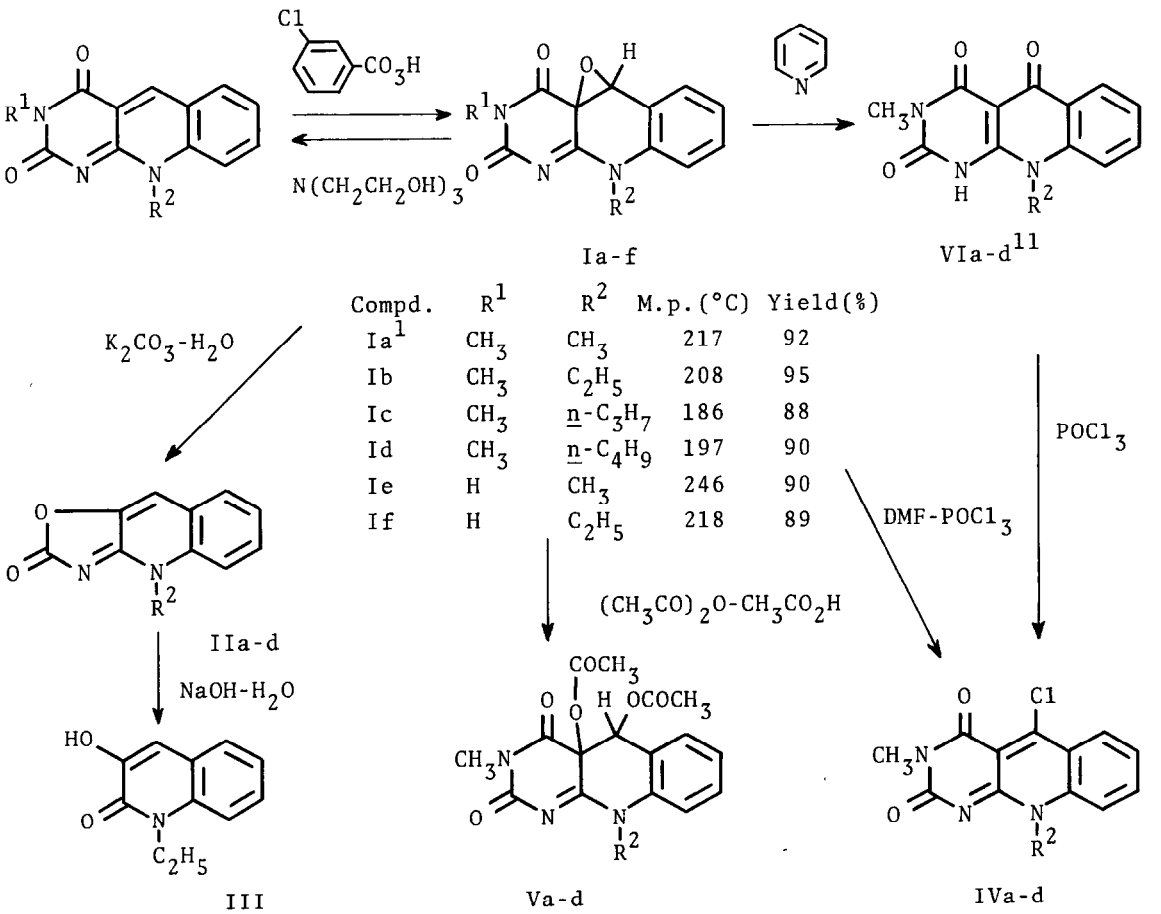
The starting 4a,5-epoxy-5-deazaflavins (Ia-f)[8] were synthesized by the oxidation of the corresponding 5-deazaflavins[9,10] with m-chloroperbenzoic acid in chloroform according to the known procedure,[1] in the yields as indicated in Scheme 1. First, we studied the reaction of I with hydroxide ion as a representative nucleophile. Stirring of 4a,5-epoxy-3-methyl-5-deazaflavins (Ia-d) (2 mmol) in 10% aqueous potassium carbonate (5 ml) at room temperature for 5 h caused the separation of oxazolonoquinoline derivatives (IIa-d) (Table 1) in high yields. The structures of these compounds were determined by $^1$H-NMR (the $C_4$-proton resonance at 8.5 ppm region in trifluoroacetic acid) and IR

Table 1. Formation of oxazolonoquinoline derivatives by the hydrolysis of I with aqueous potassium carbonate

| Compound No. | $R^2$ | M.p. (°C)[a] | Yield (%) |
|---|---|---|---|
| IIa | $CH_3$ | 247 | 82 |
| IIb | $C_2H_5$ | 181 | 85 |
| IIc | n-$C_3H_7$ | 171 | 93 |
| IId | n-$C_4H_9$ | 162 | 91 |

[a] Recrystallized from ethanol.

(C=O at 1770 $cm^{-1}$ region) as well as by consideration of their probable mode of formation (see Scheme 2). Moreover, IIb was converted into 1-ethyl-3-hydroxy-2-oxoquinoline (III) (87%), m.p. 262°, $M^+$ 189, by further hydrolysis with 10% aqueous sodium hydroxide at room temperature for 4 h.




| Compd. | $R^1$ | $R^2$ | M.p.(°C) | Yield(%) |
|---|---|---|---|---|
| Ia[1] | $CH_3$ | $CH_3$ | 217 | 92 |
| Ib | $CH_3$ | $C_2H_5$ | 208 | 95 |
| Ic | $CH_3$ | n-$C_3H_7$ | 186 | 88 |
| Id | $CH_3$ | n-$C_4H_9$ | 197 | 90 |
| Ie | H | $CH_3$ | 246 | 90 |
| If | H | $C_2H_5$ | 218 | 89 |

Scheme 1

Treatment of compounds Ia-d (2 mmol) with Vilsmeier reagent [dimethylformamide-phosphorus oxychloride (5:1)] (3 ml) at 90° for 2 h, followed by cooling precipitated the corresponding 5-chloro-5-deazaflavins (IVa-d) (Table 2). The latter compounds were identical with the authentic samples which were unequivocally prepared by chlorination of the corresponding 1,5-dihydro-5-deazaflavin-5-ones (VIa-d)[11] with phosphorus oxychloride.

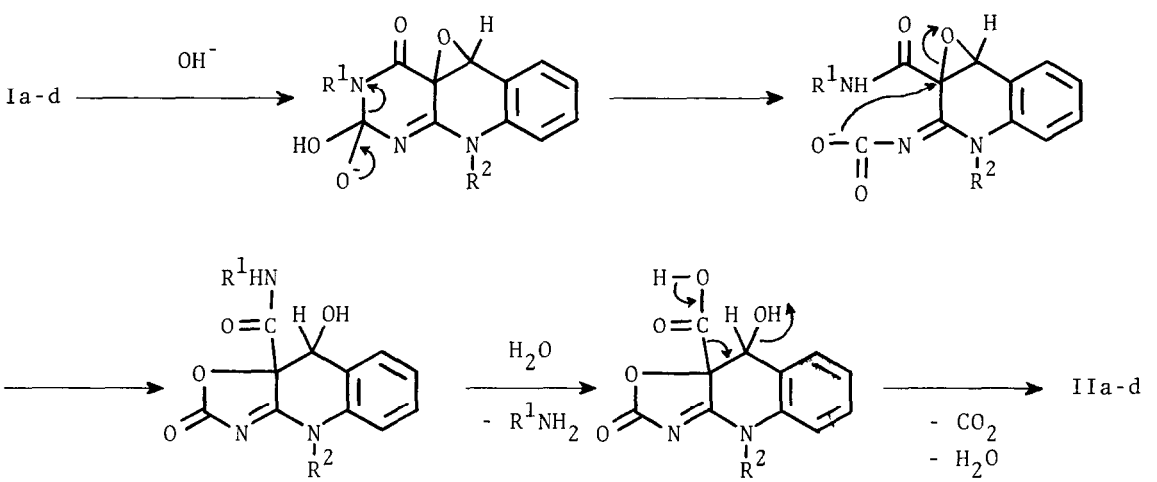
Treatment of compounds Ia-d (2 mmol) with a mixture of acetic anhydride and acetic acid (1:1) under reflux for 3 h, followed by concentration of the reaction mixture and dilution with water yielded 4a,5-diacetoxy-5-deazaflavins (Va-d) (Table 3) in high yields.

Table 2. Formation of 5-chloro-5-deazaflavins by treatment of I with Vilsmeier reagent (dimethylformamide-phosphorus oxychloride)

| Compound No. | $R^2$ | M.p. (°C)[a] | Yield (%) |
|---|---|---|---|
| IVa | $CH_3$ | 247 | 74 |
| IVb | $C_2H_5$ | 254 | 51 |
| IVc | n-$C_3H_7$ | 265 | 57 |
| IVd | n-$C_4H_9$ | 212 | 49 |

[a] These compounds were unstable and could not be recrystallized.

When compounds Ia-d (2 mmol) were refluxed in pyridine (3 ml) for 1 h, the reaction mixture was evaporated in vacuo, and the residue was diluted with ether, compounds VIa-d were obtained in 80-90% yields.




Scheme 2

Stirring of compound Ib (0.5 g, 1.8 mmol) in triethanolamine (3 ml) at 90° for 5 h, followed by dilution with water caused the separation of the deoxygenated 10-ethyl-3-methyl-5-deazaflavin (0.37 g, 79%). To our knowledge, this is

the first example in which triethanolamine was used in the deoxygenation of an epoxide to an olefine.

Table 3. Formation of 4a,5-diacetoxy-5-deazaflavins by treatment of I with a mixture of acetic anhydride and acetic acid

| Compound No. | $R^2$ | M.p. (°C)[a] | Yield (%) |
|---|---|---|---|
| Va | $CH_3$ | 185 | 97 |
| Vb | $C_2H_5$ | 183 | 95 |
| Vc | n-$C_3H_7$ | 148 | 90 |
| Vd | n-$C_4H_9$ | 145 | 97 |

[a] Recrystallized from acetic acid.

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