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# Aerobic epoxidation and hydroxylation of a pyrrolo[2,1-*b*]quinazoline under ambient conditions

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ABSTRACT

A pyrrolo[2,1-*b*]quinazoline has been found to undergo both epoxidation and hydroxylation on the pyrrole nucleus upon simple exposure of an acetone solution to air or oxygen. The oxygenation reaction occurs most readily when the starting compound contains a *t*-butyl ester at the 3-position, compared to a cyano or phenylsulfonyl. The structure of the product has been confirmed by X-ray crystal analysis.


## 1. Introduction

The photooxygenation of nitrogen containing heterocycles has attracted considerable interest over the years.[1–4] With pyrroles, which are highly reactive substrates, ring oxygenation typically leads to a mixture of products including hydroxylated derivatives, lactams and acyclic carbonyl compounds.[1–4] The lack of chemoselectivity appears to arise from non-selective addition of singlet oxygen to the pyrrole nucleus, and from non-selective decomposition of intermediate hydro- or endoperoxides. In some cases, however, pyrrole ring oxygenations are selective enough to be synthetically useful and such reactions have mostly led to hydroxylated pyrrolones,[4–8] and 1,4-dicarbonyl compounds.[9,10] In one unique case, pyrroles have been substituted in the 5-position in good yield via selective oxygenation to a hydroperoxy intermediate.[11] Several of these types of reactions have been used to prepare pyrrole-containing natural products.[5,12,13] In contrast, preparation and isolation of epoxidated pyrroles by oxygenation appears to be rather uncommon. Rare examples include the oxygenation of 2,3,4,5-tetraphenylpyrrole in methanol to yield the 3,4-epoxy-5-methoxypyrrole derivative (55% yield)[10] and the oxygenation of a 2-alkoxycarbonyl-3-methoxypyrrole to form the 2,3-epoxy derivative (10% yield).[14]

Recently, we have described the synthesis of some 4,9-dihydropyrrolo[2,1-*b*]quinazolines containing different functional groups at the 3-position.[15] This ring system has attracted synthetic interest of late as it is contained in several bioactive natural products.[16] In working with these compounds, we have observed that they slowly undergo a rather selective oxidation reaction upon being dissolved in common solvents and when exposed to air. We anticipated that the product of this reaction was the fully unsaturated ring system, as dehydrogenations of partially saturated aromatics by air are quite common. However, upon isolation and characterization of the product arising from *t*-butyl ester analogue **1a** (Scheme 1), we determined that an oxygenation reaction had occurred to give hydroxy-containing epoxide **3** in good yield. Herein, we describe this interesting reaction and our characterization of the product.

## 2. Results

To prepare the oxygenation product on a significant scale, 1.0 mmol of tricyclic **1a** was dissolved in acetone (10–12 mL) in a 50 mL beaker and left to stand on the bench-top exposed to atmosphere under ambient conditions.[17] After about 12 days, TLC analysis showed that the starting material had been consumed and that one major product had formed. The acetone was thus allowed to evaporate and the light brown solid was triturated with EtOAc/hexanes (1:1) and collected by suction to yield an off white solid in 70% yield. Recrystallization from EtOAc/hexanes gave **3** as a fine white solid, while recrystallization from MeOH gave colorless crystals.

Product **3** was characterized by MP, IR, $^{1}$H and $^{13}$C NMR, HRMS, combustion analysis and X-ray crystallography.[18] The $^{1}$H NMR shows that the two benzylic hydrogens are still present, and that they are non-equivalent based on the presence of two doublets ($J$ = 13.6 Hz) at 4–5 ppm. This eliminates the possibility that

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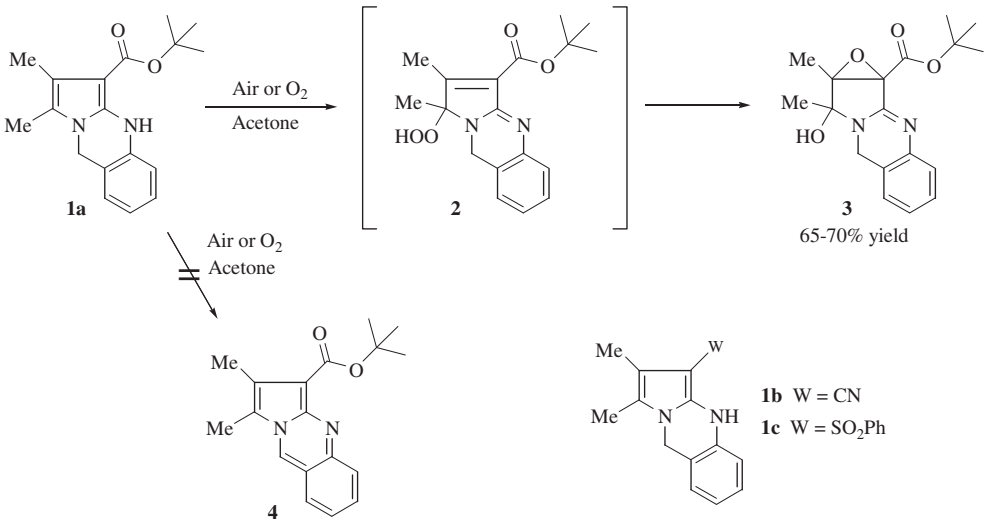


**Scheme 1.**

compound **1** has been dehydrogenated to the fully conjugated compound **4**, and also indicates the presence of a chiral center in the product. In the IR spectrum, the carbonyl stretch is shifted to a much higher value (1743 $cm^{-1}$) compared to that of the starting material (1640 $cm^{-1}$), which is consistent with the carbonyl no longer being conjugated with nitrogen. The IR also shows a broad OH absorbance centered at about 2800 $cm^{-1}$. In addition, the HRMS and combustion analysis results indicate that an oxygenation reaction has occurred rather than dehydrogenation. Based on these data, we initially hypothesized that compound **2** had been obtained, as hydroperoxides are commonly proposed as intermediates in pyrrole oxygenations,[3] although we only know of one that has been isolated.[19] Also, 2-aminopyrroles are known to be nucleophilic at the 5-position via enamine type reactions.[20] However, X-ray structure analysis (Fig. 1)[21] shows that hydroxy-containing epoxide **3** was formed, perhaps via hydroperoxide **2** as an intermediate. The crystal structure also indicates that the hydroxyl group and the epoxide oxygen are trans to each other. In retrospect, all other analytical data also support our assignment of the product as compound **3**.

In an effort to increase the rate of formation of **3**, the reaction was conducted in a sealed vial after being evacuated with pure oxygen. In this case, the starting material **1a** was consumed in 6 days and product **3** was obtained in 65% yield. At this point, we have made no other attempts at increasing the reaction rate, such as by irradiating with a light source, adding a photosensitizer, or using high pressures of oxygen. However, we have performed the oxygenation reaction with substrates containing a cyano (**1b**) or phenylsulfonyl (**1c**) group in place of the *t*-butyl ester. In these cases, the oxygenation proceeds much more slowly, and appears to be less selective. This suggests that the *t*-butyl ester has a beneficial effect on the reaction. To further explore this effect, we are currently in the process of preparing the methyl and ethyl ester analogues of compound **1**. We are also currently exploring the reactivity of product **3**, particularly that of the epoxide towards various nucleophiles.

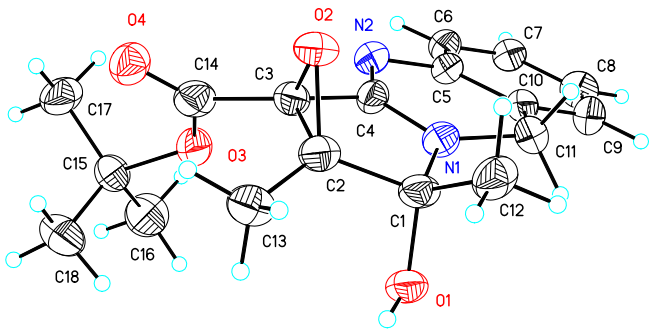


**Figure 1.** X-ray crystal structure of compound **3**. Atoms are drawn with 40% probability ellipsoids.

## 3. Conclusion

In conclusion, we have found that pyrrolo[2,1-*b*]quinazoline **1a** undergoes a slow, but rather selective, oxygenation reaction upon simple exposure of an acetone solution to air or oxygen. The product has been isolated in 65–70% yield and identified as hydroxy-containing epoxide **3**. The selective preparation of epoxidated pyrroles by oxygenation is uncommon. It is also uncommon for such oxygenations to take place without the aid of strong photo-irradiation or chemical additives. Considering the highly functionalized nature of product **3**, this chemistry may be useful for preparing substituted derivatives of the pyrrolo[2,1-*b*]quinazoline ring system.

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17. The only light sources were the standard fluorescent laboratory lighting, which was on during the day and off during the night and the daylight from two windows about 15 feet away from the bench. The beaker was covered by a watchglass. To compensate for evaporation, additional acetone was occasionally added to maintain the volume above 2–3 mL.
18. Mp: >190 °C dec (MeOH). IR (ATR): 3100–2500 (broad), 2983, 1743 (strong), 1629, 1598, 1141 (strong), 1107, 1083, 807, 768 (strong), 738 $cm^{-1}$. $^{1}H$ NMR (300 MHz, DMSO-$d_6$): 1.33 (s, 3H), 1.47 (s, 9H), 1.48 (s, 3H), 4.36 (d, $J$ = 13.6 Hz, 1H), 4.57 (d, $J$ = 13.6 Hz, 1H), 6.56 (s, OH, $D_2O$ exchangeable), 6.92 (d, $J$ = 7.6 Hz, 1H), 7.00–7.02 (m, 2H), 7.09–7.14 (m, 1H). $^{13}C$ NMR (75 MHz, DMSO-$d_6$): 162.1, 154.2, 142.0, 128.0, 126.5, 125.0, 124.6, 120.7, 88.4, 82.8, 70.3, 64.1, 40.0, 27.7 (3C), 17.8, 9.3 ppm. HRMS ($ESI^+$) calcd for $C_{18}H_{23}N_2O_4$: 331.1658. Found: 331.1645. Anal. calcd for: $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found C, 65.52; H, 6.70; N, 8.43.
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21. Good quality crystals of **3** were obtained by recrystallization from MeOH. Crystal data: monoclinic, $a$ = 13.053(4), $b$ = 6.453(2), $c$ = 21.007(8) Å, $\alpha = 90^{o}$, $\beta$ = 101.05(3)°, $\gamma = 90°$. $V$ = 1736.7(10) $Å^3$, space group $P2(1)/n$, $Z$ = 4, $D_{calcd}$ = 1.264 $Mg/m^3$, abs coeff = 0.736 $mm^{-1}$, $F(0\,0\,0)$ = 704. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 780834. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).