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Synthesis of a Novel Fused Tricyclic Quinolone system *via* Oxidation of 1,2,3,4-Tetrahydro-β-Carbolines.

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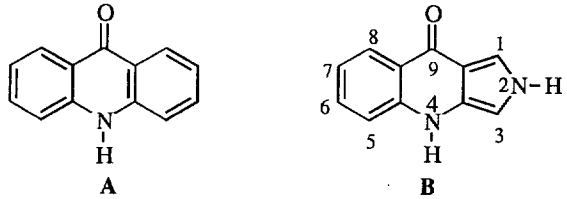
Abstract : The new pyrrolo[3,4-b]quinolin-9-one system has been synthesized *via* metachloroperbenzoic acid oxidation of quinolones **5** and **10**. These latter compounds were obtained by O_2 oxidation of 1,2,3,4-tetrahydro-β-carbolines. The unexpected *m*-CPBA oxidation has been studied in connection with the Polonovski reaction. © 1997 Published by Elsevier Science Ltd.

Our interest in the search of alternative drug structures based on the isosteric replacement of one ring of acridone **A** led us to consider the isoelectronic pyrrole ring of pyrrolo[3,4-b]quinolin-9-one **B** (Figure).



Figure

Although there is a number of synthetic and natural pyrroloquinolines,[1] the ring system of **B** has never been synthesized or found in Nature. Our strategy was based upon aromatization of pyrrolinoquinolones to pyrroloquinolones.

Oxidation of 2,3-disubstituted indole derivatives and particularly 1,2,3,4-tetrahydro-β-carbolines with O_2/potassium *tert*-butoxide (*t*-BuOK),[2] metachloroperbenzoic acid (*m*-CPBA),[3] $NaIO_4$,[4] or singlet oxygen[5] is well documented. Among these, Winterfeldt's biomimetic auto-oxidation[2,6] appeared to be the most attractive method for the preparation of quinolones **5** and **10**, which were key intermediates for the synthesis of the title compounds.

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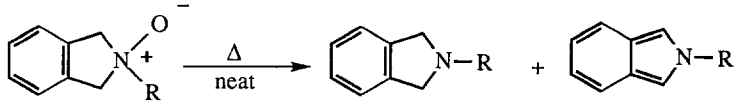
Tetrahydro-β-carbolines **4** were prepared by a standard Pictet-Spengler condensation of tryptamine or its *N*(b)-alkyl derivatives with formaldehyde or trimethoxybenzaldehyde in acidic conditions. Treatment of a dimethylformamide (DMF) solution of compounds **4** with O_2 bubbling in the presence of *t*-BuOK afforded quinolones **5**[7] (Scheme 2) in fair to excellent yields. The *N*(a)-alkylated derivatives are not oxidized in these conditions, demonstrating that prior formation of a nitrogen anion is necessary.

It has been previously shown that *N*-alkylisoindoline *N*-oxides **1** could be transformed into isoindoles **3** on treatment with acetic anhydride (Polonovski reaction). It has also been observed that heating the *N*-oxide **1** neat can give an inseparable mixture of *N*-alkylisoindoline **2** and *N*-alkylisoindole **3**[8] (Scheme 1).

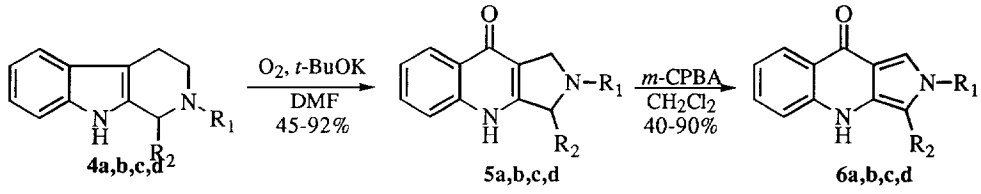


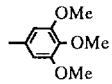
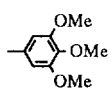
1 **2** **3**

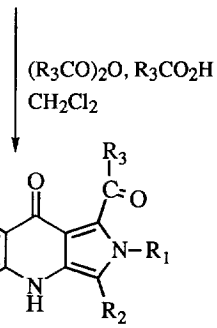
Scheme 1

We were interested to see if the modification of the Polonovski reaction studied in this Laboratory[9,10] could be efficient for the preparation of an iminium salt of **5**, which is a tautomeric form of **6** (Scheme 2).

Thus quinolones **5** were added to a dry CH_2Cl_2 solution of *m*-CPBA (1.6 equiv.) which was allowed to stand at room temperature for 1 h. The crude product was then reacted directly with $(CF_3CO)_2O$ (Polonovski-Potier reaction) in a CH_2Cl_2 solution. The expected pyrrolo[3,4-b]quinolin-9-ones **6** were isolated in poor yield. Interestingly, trifluoroacetyl derivative **7b** was identified as a by-product in this series. A mixture of isomeric trifluoroacetyl derivatives was formed in the case of **5a** as a consequence of the two nucleophilic positions.



	R_1	R_2	yields for **5**	yields for **6**
a	CH_3	H	92%	40%
b	CH_3		45%	90%
c	CH_2-Ph	H	79%	59%
d	CH_2-Ph		59%	72%



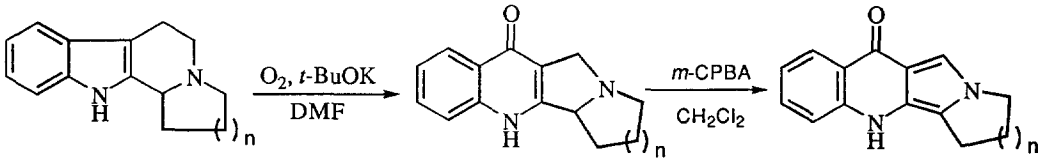
7b $R_3 = CF_3$ (40%)
8b $R_3 = CH_3$ (18%)

Scheme 2

During attempts to purify the supposed *N*-oxides we noticed that they were unstable and spontaneously gave small amounts of pyrroles **6** (shown by thin layer chromatography). Thus we decided to leave the reaction for *N*-oxide formation for a further 3 h.[11] In these conditions, pyrroles **6**[12] were formed in acceptable yields without the intermediacy of Polonoski reaction. Such a reaction is reminiscent of what happened in the isoindoline series (*vide supra*) but proceeds smoothly under mild conditions without isolation of pyrroline **5**.

In the case of isoindoline, one could imagine an oxido-reduction process in which the *N*-oxide plays the role of oxidizing agent. As far as we are concerned the same process might be invoked, and the use of an excess of *m*-CPBA explained the complete transformation of pyrrolinoquinolones **5** to pyrroloquinolones **6**. The question as to whether a Polonovski reaction might be in part implicated is excluded since there is no example of such a reaction without an acylation agent.

The formation of by product **7b** does not constitue evidence for its implication in the Polonovski reaction since it has been shown that, after purification, pyrrole rings of **6b** could be acylated with $(CF_3CO)_2O$ and $(CH_3CO)_2O$ to give **7b**[13] and **8b** respectivly.



9a n=1
9b n=2

10a n=1 (63%)
10b n=2 (58%)

11a n=1 (10%)
11b n=2 (13%)

Scheme 3

We then studied the oxidation of indolopyrrolizidine **9a**[14] and indoloquinolizidine **9b** (Scheme3). The same kind of reaction occurred, affording compounds **11**.[15] The low yields are explained by the ring strain of **11a** and by the low solubility of product **10b**. However the same reaction applied to a series of indoloquinolizidine alkaloids which are completely soluble in CH_2Cl_2 afforded fair to excellent yields.[16]

It is noteworthy that the treatement of **5** and **10** with other oxidizing agents gave either unreacted starting material (MnO_2; Pd/C) or decomposition products (DDQ).

In summary, two successive oxidation reactions of 2,3-disubstituted indole derivatives allow facile preparation of the new pyrrolo[3,4-b]quinolin-9-one system.

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11. Typical procedure : To a solution of quinolone **5** (1.4 mmol) in CH_2Cl_2 (70ml) was added a solution of 1.1 equivalent *m*-CPBA in CH_2Cl_2 (30ml) dried over Na_2SO_4 . After 1h at r.t., 0.5 equivalent m-CPBA was added and the reaction left for a further 3h. The solvent was removed under reduced pressure and after purification by flash chromatography, the pyrroloquinolone **6** was obtained as a fluorescent yellow amorphous solid.
12. Compound **6a:** ^{1}H NMR (300MHz, CD_3OD) δ (ppm), J (Hz): 3.9 (s, 3H); 6.71 (d,1H, J=2); 6.98 (ddd, 1H, J=8.2 6.8 0.85); 7.22 (d, 1H, J=8.5); 7.41 (d, 1H, J=1.3); 7.46 (ddd, 1H, J=8.5 6.8 1.3); 8.18 (dd, 1H, J=8.2).

    ^{13}C NMR (62.5 MHz, CD_3OD) δ (ppm): 38.0; 104.0; 115.3; 117.6; 118.7; 119.9; 120.0; 127.3; 132.1; 133.8; 144.0; 1787.2

    I.R. ν (cm^{-1}): 1634 ; 1579.

    Compound **6b:** ^{1}H NMR (200MHz, $CDCl_3$) δ (ppm), J (Hz): 3.7 (s, 3H); 3.8 (s, 9H) 6.5 (s, 2H); 7.0 (dd,1H, J=7.6 7.3); 7.1 (s, 1H); 7.4 (dd, 1H, J=7.5 7.3); 8.05 (s_{bd}, 1H); 8.3 (d, 1H, J=7.6).

    ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 36.1; 56.0; 60.6; 107.3; 113.6; 114.2; 116.6; 117.9; 119.0; 120.3; 125.4; 126.8; 127.7; 132.3; 132.7.; 142.7; 153.4; 176.1.

    I.R. ν (cm^{-1}): 1630 ; 1583 ; 1127.
13. Compound **7b:** ^{1}H NMR (200MHz, $CDCl_3$ + CD_3OD) δ (ppm), J (Hz): 3.7 (s, 3H); 3.8 (s, 9H); 6.5 (s, 2H); 7.0 (dd, 1H, J=8.1 7.1); 7.25 (d, 1H, J=8.2); 7.4 (ddd, 1H, J=8.2 7.1 1.2); 8.2 (d, 1H, J=8.1); 9.4 (s, 1H).

    ^{13}C NMR (50 MHz, $CDCl_3$ +CD_3OD) δ (ppm): 34.3; 56.2; 60.8; 108.5; 116.3; 117.8; 118.4; 120.0; 120.4; 124.5; 126.2; 127.0; 133.7; 138.4; 141.8; 153.6; 176.3.

    I.R. ν (cm^{-1}) : 1632 ; 1581 ; 1500 ; 1129.
14. Unpublished synthesis from this Laboratory.
15. Compound **11b:** ^{1}H NMR (250MHz, CDl3+CD3OD) δ (ppm), J (Hz): 1.83-1.65 (m, 5H); 2.7 (t, 1H, J=7.0); 3.88 (t, 2H, J=7.0); 3.88 (t, 2H, J=7.0); 6.89 (t, 1H, J=7.5); 7.15 (m,2H); 7.3 (t,1H, J=7.5); 8.25 (d,1H,J=8); 9.0 (s,1H).

    ^{13}C NMR (62.5 MHz, $CDCl_3$ +CD_3OD) δ (ppm): 20.5; 20.7; 23.4; 46.8; 108.9; 113.7; 116.3; 118.7; 119.9; 125.3; 126.9; 132.2; 142.3; 176.9.

    I.R. ν (cm^{-1}) : 1635 ; 1583 ; 1555.
16. To be published at a later date.

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