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Partial synthesis of camptothecin analogs. Part 1: Pyrroloquinolone and pyrroloquinoline derivatives

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Abstract

Pyrroloquinolone 7 and pyrroloquinoline derivatives 11a-c have been synthesized from the alkaloid tetrahydroalstonine 1 according to sequential oxidation reactions. © 1999 Published by Elsevier Science Ltd. All rights reserved.

A considerable amount of effort has been expended to synthesize camptothecin and derivatives because of their original anticancer activity resulting from the inhibition of topoisomerase-I. However, a number of syntheses of camptothecin itself are only academic exercises. Recent molecular modeling studies¹ provide the structure-activity relationship based upon various camptothecin derivatives. As far as topoisomerase-I is concerned the critical features are the lactone ring and the 20(S)-hydroxyl group. The interaction of camptothecin, DNA and topoisomerase-I creates a ternary complex which is stabilized by stacking of the planar part of the pentacylic system.

Our interest in biomimetic rearrangements of indole alkaloids led us to evaluate this methodology for the partial synthesis of camptothecin and analogs in connection with these requirements.

The plausible sequence of biochemical pathways from the early stage of the biosynthesis of monoterpene alkaloids to the quinoline alkaloid camptothecin 3 (Fig. 1) is known.² The key step of this biogenesis is the oxidation of the tetrahydro- β -carboline moiety into pyrrolo[3,4-*b*]quinoline. The biomimetic equivalent for this transformation is Winterfeldt's oxidation of the indole ring.³

We have devised a program based on this attractive method for the preparation of camptothecin analogs from the easily available heteroyohimbine alkaloids tetrahydroalstonine 1 and ajmalicine 2 extracted from *Catharanthus* sp.

Our aim was not to synthesize the natural product itself since a biomimetic rearrangement of rings D and E of 1 or 2 into the lactam-lactone bicyclic system of 3 would be troublesome. At first we were interested to synthesize analogs wherein ABC rings are planar, however, without lactam function. Such

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Figure 1.

unknown derivatives would be of interest among the large variety of camptothecin derivatives synthesized for the structure–activity relationship.⁴

For this purpose we decided to take advantage of previous results from our laboratory⁵ on the synthesis of pyrrolo[3,4-*b*]quinolone. Both the C-20 epimeric alkaloids 1 and 2 are possible starting materials since this stereogenic center is abolished in the target molecules.

We wish to report in this paper our first results on the study of the reactivity of these two alkaloids. Success in this project would set the stage for the chemical manipulations of the indole alkaloids, i.e. oxidation of the indole ring into quinolone or quinoline followed by rearrangement of ring E. The alternative possibility consisting of performing first the rearrangement of ring E and then oxidation of the indole ring appeared easier to use. In a first experiment lactol **4** (Scheme 1) was prepared from **1** which was in turn hydrolyzed and decarboxylated in a one-pot procedure. The resulting hydroxy-aldehyde cyclized into epimeric lactols. The reaction could be performed at a 10 g scale with excellent yield. This transformation was only reported for ajmalicine **2** in either a two-step procedure (52% yield)⁶ or in a one-pot reaction (80% yield),⁷ performed in a sealed tube which is obviously not convenient for large quantities. However, using the same conditions as for **1**, **2** led to the corresponding lactol in 80% overall yield.



The Winterfeldt oxidation of the indole ring of 4 into quinolone 5 was quantitative when using standard conditions.⁸ We were singularly unsuccessful in many attempts to oxidize lactol 5 into lactone 6. A variety of possible methods was investigated which, however, did not convert the lactol function probably due to solubility problems. The best procedure turned out to be CrO_3 in DMF. However, lactone 6^9 was obtained in low yield due to degradation.

We have recently shown that the pyrroloquinolone system could be synthesized via metachloroperbenzoic acid (*m*-CPBA) oxidation of the parent pyrroline.⁵ Thus, we were interested to insert this new ring system in the pentacyclic quinolone-lactone **6** in order to evaluate if an isosteric system of acridone in this series was compatible with antitumor activity. Treatment of a dry CH_2Cl_2 solution of 6 with *m*-CPBA at room temperature did afford pyrroloquinolone 7,¹⁰ however in moderate yield.

We also explored the possibility of preparing a pyrroloquinoline equivalent of 7. Such an aromatic tricyclic ring system has never been described. The alkylation of quinolone-lactol 5 into ethoxyquinoline 8 was easily achieved and we were pleased to observe that oxidation of the lactol function into lactone 9 was efficient in this series using Oppenauer conditions.

It is worthy of note that in the ajmalicine series the lactol equivalent of 5 has different reactivity. Indeed, alkylation of its quinolone moiety led to a mixture of products due to rearrangement and alkylation of the lactol moiety.¹¹





Thus, we concentrated on the easy acquisition of 9 from tetrahydroalstonine 1 that was highly encouraging since it represents a key intermediate containing crucial features for the next steps of our project.

Repeating the oxidation of 9 with *m*-CPBA, only the formation of the corresponding N(b)-oxide was observed and no formation of the novel fused pyrrolo[3,4-*b*]quinoline **11a** could be detected. Thus, it was interesting to check if the modification of the Polonovski reaction studied in this laboratory¹² could be efficient to prepare the target compound.

Formation of the N-oxide and its treatment with $(CF_3CO)_2O$ in a one-pot reaction gave a mixture of three derivatives $11a-c^{13}$ in non-reproducible ratios and yields.

Derivative 11a is the result of the preliminary formation of the expected conjugated iminium 10 (Fig. 2) followed by isomerization. Compound 11b and 11c are the consequence of, respectively, electrophilic oxidation and acylation of the pyrrole ring of 11a.





The interesting formation of the novel pyrroloquinoline system of 11a-c has to be improved since it opens the way to further potential oxidation reactions leading to a pyridone ring D. At this stage the crucial alkylation and oxidation of C-20 of the lactone ring are well documented.¹⁴

The partial synthesis of analog 12 (Scheme 2) of camptothecin should thus be possible and is currently under investigation.

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- 9. Compound 6: Amorphous; ¹H NMR (250 MHz, CDCl₃+CD₃OD, 9:1), δ (ppm), J (Hz): 8.37 (d, 1H, J=8.0), 7.60–7.50 (m, 2H), 7.45 (m, 1H), 4.79 (qd, 1H, J=6.2, 12.2), 4.05 (masked, 1H), 3.78 (m, 2H), 3.05 (dd, 1H, J=12.0, 4.0), 2.86 (dd, 1H, J=12.0, 3.3), 2.75 (dd, 1H, J=17.4, 6.1), 2.45 (dd, 1H, J=17.4, 3.6), 2.30–2.20 (m, 2H), 1.96 (m, 1H), 1.71 (dd, 1H, J=13.2, 11.2), 1.42 (d, 3H, J=6.2); ¹³C NMR (62.5 MHz, CDCl₃+CD₃OD, 9:1), δ (ppm): 172.0, 163.0, 153.2, 134.0, 131.3, 125.6, 125.0, 123.7, 118.0, 116.6, 76.6, 65.1, 53.8, 50.3, 39.0, 35.2, 31.1, 29.6, 20.1; MS (E.I.): [M]⁺=324.
- 10. Compound 7: Amorphous; ¹H NMR (200 MHz, DMSO) δ (ppm), J (Hz): 10.80 (s, 1H), 8.20 (d, 1H, J=7.4), 8.10 (t+s overlapped, 2H, J=7.0), 7.42 (d, 1H, J=8.3), 7.08 (dd, 1H, J=J'=7.4), 4.41 (m, 2H), 4.20 (dd, 1H, J=13.3, 6.4), 3.30 (dd, 1H, J=14.0, 4.4), 2.70–2.50 (masked by DMSO, 3H), 2.43 (broad s, 1H), 1.49 (d, 3H, J=6.1); ¹³C NMR (50 MHz, DMSO), δ (ppm): 174.2, 171.4, 142.4, 131.9, 126.1, 125.3, 119.4, 117.9, 116.4, 113.6, 113.2, 108.3, 74.3, 44.7, 34.3, 28.2, 24.2, 19.1; MS (E.I.): [M]⁺⁼=322.
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- Compound **11b**: Amorphous; ¹H NMR (250 MHz, CD₃OD), δ (ppm), J (Hz): 8.22 (d, 1H, J=9.1), 7.84 (dd, 1H, J=J'=8.3),
 7.50 (dd, 1H, J=J'=8.3), 7.35 (d, 1H, J=8.2), 5.08 (q, 2H, J=6.9), 4.71 (dd, 1H, J=5.2, 14.0), 4.35 (m, 2H), 3.45 (dd, 1H, J=15.8, 5.2), 3.05 (dd, 1H, J=7.4, 15.7), 2.55–2.80 (4H, m), 1.76 (t, 3H, J=6.9), 1.54 (d, 3H, J=5.9); ¹³C NMR (62.5 MHz, CD₃OD) δ (ppm): 136.5, 125.9, 123.5, 118.6, 76.2, 72.4, 48.0, 39.9, 35.0, 29.6, 25.0, 19.8, 15.2; MS (C.I.): [MH]⁺=367.
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