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SYNTHESIS OF 1-METHOXY CANTHINE-6-ONE

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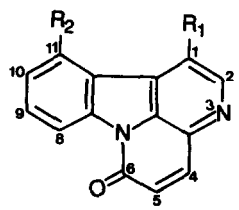
SUMMARY: The six step synthesis of the cytotoxic antileukemic alkaloid 1-methoxy canthine-6-one **2** is described. The pivotal steps are represented by the oxidation (DDQ) of **9** to afford the 3-acylindole **14** and the conversion of **11** into the 4-methoxy-1-alkyl β-carboline **15**.

A number of canthine-6-one alkaloids have been isolated recently from various plants. Among these are canthine-6-one **1**, 1-methoxy canthine-6-one **2** and 1-hydroxy canthine-6-one **3** from Ailanthus altissima;[1-4] canthine-6-one **1**, 11-hydroxy canthine-6-one **4** and 1,11-dimethoxy canthine-6-one **5** from Brucea antidysenterica;[5] canthine-6-one **1**, 1-methoxy canthine-6-one **2** and 1,11-dimethoxy canthine-6-one **5** from Soulamea pancheri.[6] Several of these alkaloids possess significant cytotoxic and antileukemic activity.[5,7] Oxidation of the canthine-6-one skeleton at positions C-1 and C-11 greatly enhances the cytotoxic, antileukemic activity of these alkaloids. We wish to report a general approach to the synthesis of these 1-oxysubstituted alkaloids which has resulted in the synthesis of **2** and should provide facile entry into more potent antitumor agents.

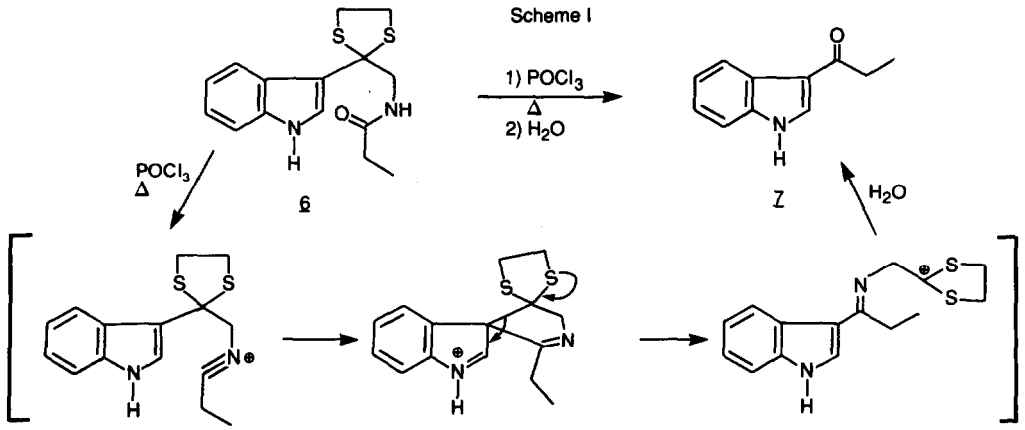


1, R_1=R_2=H
2, R_1=OMe, R_2=H
3, R_1=OH, R_2=H
4, R_1=H, R_2=OH
5, R_1=R_2=OMe

Realitively few methods for the incorporation of oxygen functionality into position-4 of β-carbolines are available. Three (3) acyl indoles are known to form oxazole derivatives under Bischler-Napieralski conditions.[8] Moreover, the Pictet-Spengler reaction of 3-acyl indole derivatives[9] or Bischler-Napieralski reaction of the corresponding thioketals[10] do not furnish a 4-oxygenated, 1,2,3,4-tetrahydro β-carboline derivative. For example, the transformation of **6** -> **7** was earlier reported by Murakami *et al.*[10]; however, no mechanism or explanation was proposed for this process. Difficulties arise because of the intermediacy of the spiroindolenine intermediate.[11] In both the 3-acyl[9] and 3-thioketal derivative[10] the spiroindolenine intermediate rearranges with the migration of the acyl or thioketal moiety, respectively, which interferes with the formation of the desired

4-oxygenated-1,2,3,4-tetrahydro β-carboline. Outlined below (Scheme I) is our proposed mechanism for the conversion of the thioketal **6** into the 3-propionyl indole **7**. This amply illustrates the problems encountered by

Scheme I

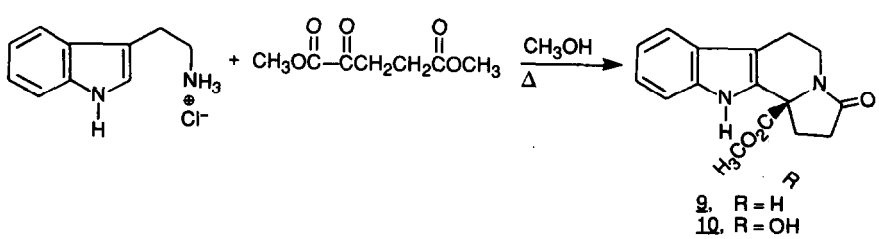


incorporation of heteroatoms at the 3-acyl indole position of tryptamine derivatives prior to the Pictet-Spengler cyclization.

The cytotoxic alkaloid 1-methoxy canthine-6-one has not been synthesized previously and there are only two reported synthesis of the related 1-ethyl, 4-methoxy β-carboline (crenatine).[10,12] Both selenium dioxide (SeO_2)[13,14] and dichlorodicyanoquinone (DDQ)[12,15] have been employed for the preparation of 3-acylindoles in our laboratory, the later of which was employed for the synthesis of crenatine.[12] The use of DDQ or SeO_2 for the preparation of 4-oxo β-carbolines, from previous work,[12,13] required protection of position-1 of a 1,2,3,4-tetrahydro β-carboline from oxidation,[12] moreover the N_b-nitrogen atom must also be rendered inactive. These goals were readily achieved via a Pictet-Spengler reaction between tryptamine hydrochloride **8** and dimethyl α-ketoglutarate **9** in refluxing methanol, as outlined in Scheme II. This sequence furnished the desired 3-oxo-9-methoxycarbonyl indolizino[8,7-b]indole **9** in 92% yield.

The reagent chosen to accomplish the desired oxidation was DDQ. Previously we had shown that the

Scheme II

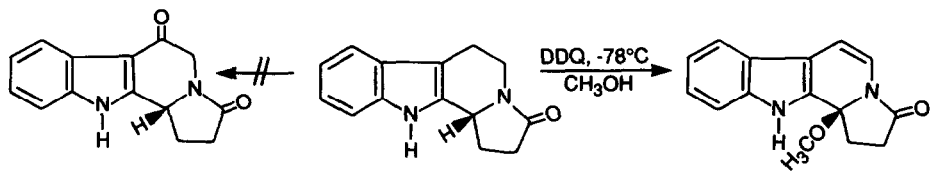


9, R = H
10, R = OH

tetracyclic γ-lactam **11**, when reacted with DDQ in aqueous media, was not converted into the 3-acyl indole **12**. When the analogous oxidation was carried out in methanol at -78°C the methyl ether **13** was formed in 44% yield.

The formation of **13** illustrates the importance of protecting position-1 from oxidation. Treatment of the indolizinoindole **9** with DDQ (7 equivalents over 3 days at room temperature) gave the desired 3-acylindole **14**

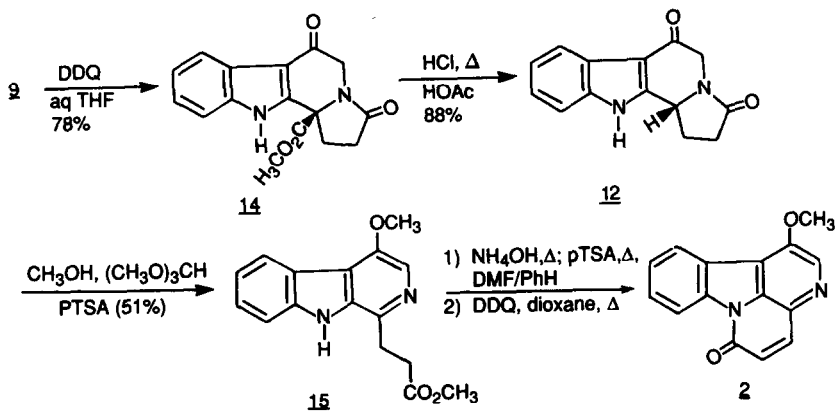
Scheme III



12, not observed 11 13

in good yield. As illustrated in Scheme IV, the 3-acyl indole **14** could be readily hydrolyzed, followed by decarboxylation, to provide the ketoamide **12**. When **12** was heated with aqueous sodium hydroxide (1N) no reaction took place, moreover, treatment of **12** with peroxide (Na_2O_2) led to extensive decomposition. However, heating **12** with para toluenesulfonic acid in methanol in the presence of trimethylorthoformate yielded 4-methoxy, 1-(methyl-3-

Scheme IV



propionate) β-carboline **15** (51%). In this reaction the enol ether is formed, the γ-lactam is cleaved, and the intermediate 1,2-dihydro β-carboline is oxidized to the fully aromatic β-carboline in one pot.[16] The ester **15** was hydrolyzed with NH_4OH (6%) in methanol, followed by removal of solvent. The residue was directly converted into 4,5-dihydro 1-methoxy canthine-6-one (86% yield) on heating in refluxing DMF/benzene in the presence of pTSA. Oxidation of the dihydro canthine-6-one to provide the natural product 1-methoxy canthine-6-one **2** was carried out in 70% yield with DDQ in refluxing dioxane. The alkaloid was purified via flash chromatography (SiO_2; $CHCl_3$ -- EtOH, 9:1). The NMR and IR spectra of **2** were identical to that reported in the literature for 1-methoxy canthine-6-one.[2,7]

This approach provides the first synthesis of **2** and represents a much improved route[10,12] to 4-methoxy

β-carbolines. The key step in the reaction sequence is the conversion of **12** into **15** in which three steps occur in one pot; application of this process to other systems should permit facile synthesis of 4-alkoxy β-carbolines. The reaction sequence illustrated here for tryptamine, should provide synthetic entry into a wide variety of cytotoxic antileukemic 1-oxygenated canthine-6-one alkaloids.

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16. Initial attempts to increase the yield of this oxidation-disproportionation reaction *via* addition of Pd/C or $Cu(OAc)_2$ to the reaction medium have not been successful; further work is in progress.

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