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THE CHEMISTRY OF VICINAL TRICARBONYL COMPOUNDS. APPLICATIONS IN THE SYNTHESIS OF VINCAMINE-RELATED ALKALOIDS

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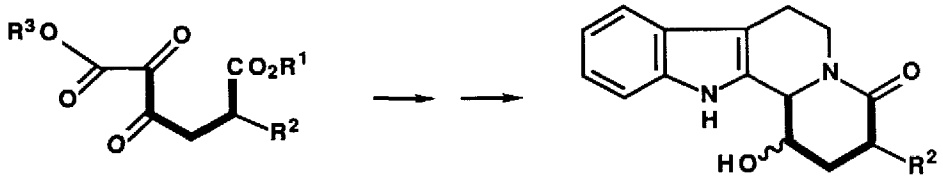
Abstract: A vicinal tricarbonyl system attached to a suitable ester residue has been used as a key unit in the synthesis of the indole alkaloids, eburnamonine and tacamonine.

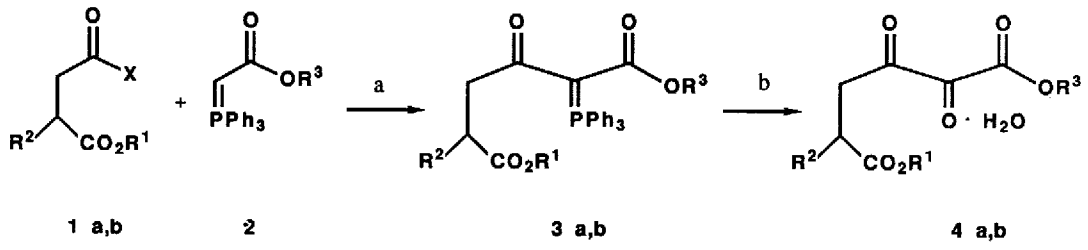
The vicinal tricarbonyl system is a functional group aggregate incorporating a powerful electrophilic site at the central carbon-oxygen double bond. We have recently shown the use of this synthon in the formation of fused ring β-lactams and in the synthesis of isoquinoline alkaloids.[1,a-d] We now report the use of compound **4** in the facile formation of alkaloids in the vincamine family.[2,9]



4 a, R^1=Et; R^2=H; R^3=t-Bu
4 b, R^1=t-Bu; R^2=Et; R^3=t-Bu

7 a,b

In our synthetic procedure, incorporating the tricarbonyl unit as shown above, addition of the primary amino group of tryptamine to **4** generates an iminium salt which undergoes cyclization at the α-position of the indole ring, forming **5** (Scheme 1). Following decarboxylation and reduction to **6**, lactam formation takes place with the ester at $COOR^1$ yielding **7**. After reduction of the amide group in **7**, the resulting alcohol **8** may be dehydrated to the enamine. In the case of **8a**, the product is the enamine **9a**, convertible to eburnamonine **10a**.[8] The enamine **9b**, derived from the ethyl analog **8b**, may be readily transformed to tacamonine **10b**.[3]



1 a,b 2 3 a,b 4 a,b

For construction of the enamine **9a** according to the above plan, the requisite vicinal tricarbonyl system **4a** was prepared in two steps. Treatment of the commercially available ethyl succinyl chloride with two equivalents of *t*-butyl (triphenylphosphoranylidine)acetate **2** gave **3a**.[4] Reaction of the ylide **3a** with ozone at -78° C generated the ester tricarbonyl **4a** in the form of a hydrate, mp 48-49° C.[5]

When tryptamine was heated to reflux in chloroform with **4a**, the tricyclic, β-carboline derivative **5a** was formed directly. The intermediate imine could be isolated if the reactants were combined in methylene chloride and kept at room temperature. Refluxing **5a** in ethanol in order to form the lactam resulted only in a retro-Claisen reaction.[6] To avoid this cleavage, the *t*-butyl ester group was removed before attempts were made to close the fourth ring. Treatment of **5a** with 98% formic acid at 38°C for 1h, followed by reduction with sodium cyanoborohydride *in situ*,[7] gave **6a** as a mixture of diasteromers. Refluxing **6a** in ethanol then yielded the desired tetracyclic lactam **7a**. Reduction of **7a** with $LiAlH_4$ gave the amino alcohol **8a** which could be dehydrated with 48% HBr to form the enamine **9a**. This intermediate has previously been transformed into eburnamonine **10a** by Martel.[8]

In the next phase of our work, we extended this synthetic scheme to the formation of the ethyl derivative **10b**. In this procedure, we found it necessary to use the mixed anhydride of **1b**[9,10] rather than the acid chloride. Ozonolysis converted **3b** to the ester tricarbonyl **4b**. Reaction of tryptamine with **4b** then furnished the tricyclic compound **5b** which, after decarboxylation, reduction and ring closure,[11] yielded **7b**. Reduction of **7b** with lithium aluminum hydride formed the amino alcohol **8b**, which underwent dehydration with HBr to form **9b**. The enamine **9b** has been converted to tacamonine **10b** by Massiot.[3]

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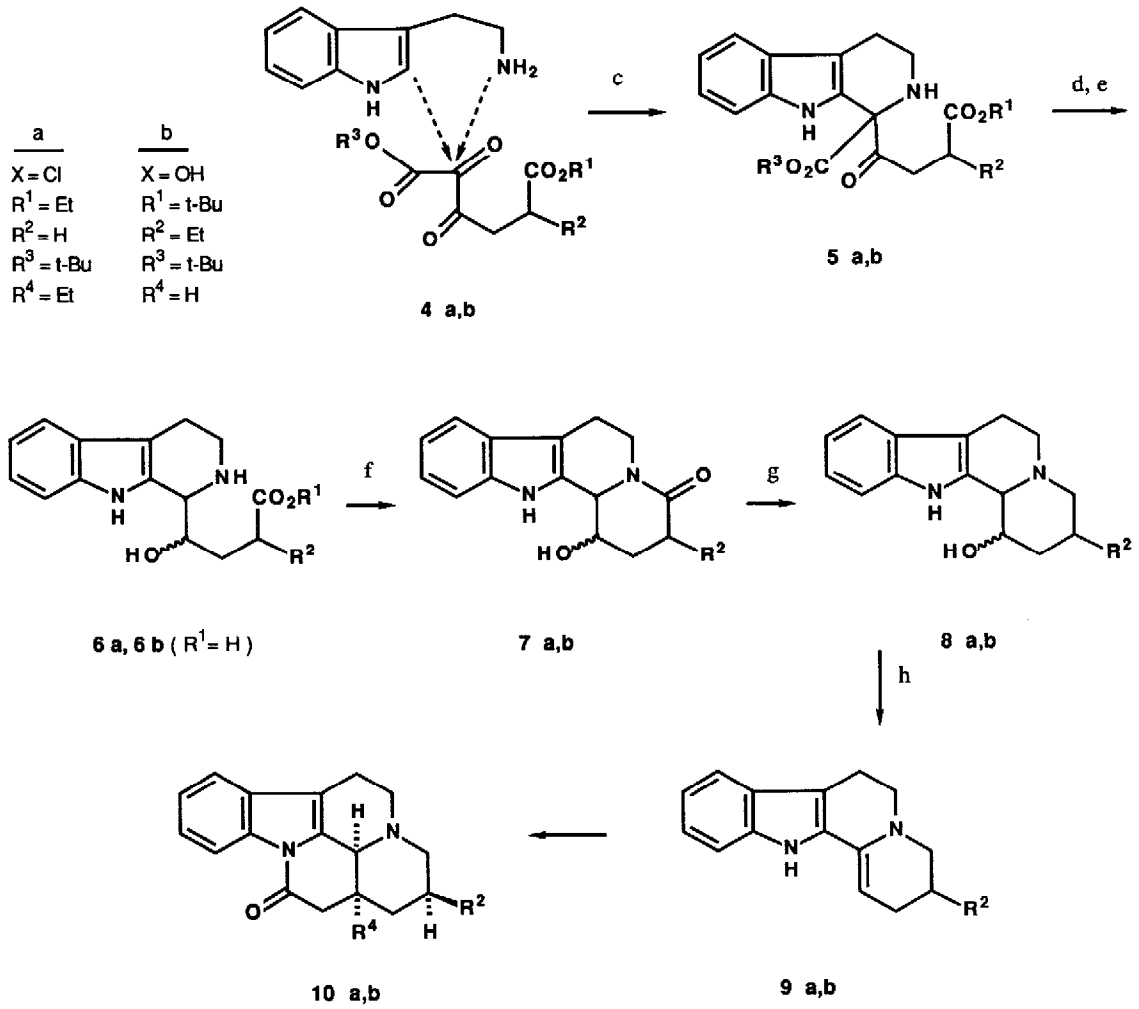
Scheme 1



a) for **3a**, 8→ 20°C, PhH, 1.5h, (87%); for **3b**, i, ethyl chloroformate, diisopropyl ethyl amine, methylene chloride, 0°C, 0.5h; ii, **2** (2 equiv), 20°C, 20h, (83%); *b)* O_3, CH_2Cl_2/CH_3OH, -78°C, (70% for **4a**), (87% for **4b**); *c)* tryptamine, $CHCl_3$, 65°C, 17-26h, (65% for **5a**), (66% for **5b**); *d)* 98% HCOOH, 38°C, 1h; *e)* $NaBH_3(CN)$, 20°C, 3h, 45% (**6a**, two steps); *f)* for **7a**, C_2H_5OH, 78°C, 16h, 83%; for **7b**, silica gel, C_2H_5OH, 78°C, 48h, 37% (three steps); *g)* $LiAlH_4$, THF, 67°C, 3h, (75% for **8a**), (70% for **8b**); *h)* 48% HBr, sealed tube, 120°C, 18h, (83% for **9a**), (68% for **9b**).

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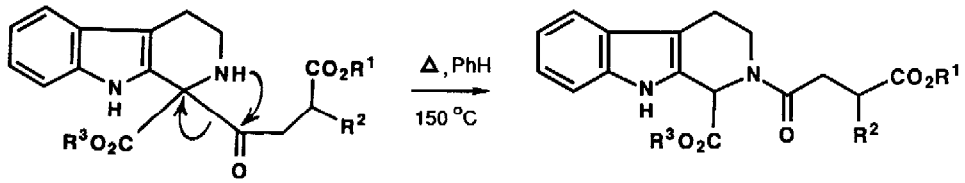
5. All new compounds have been fully characterized by combustion analyses and/or high resolution mass spectroscopy. Spectroscopic data are in full accord with the structural assignments.

6. In the absence of nucleophiles such as ethanol, one might expect lactam formation on heating **5a**. Instead, the rearrangement product **11** was isolated (74%). Cleavage of the β-keto ester grouping takes place most probably by intramolecular attack of the secondary amine.



5 a **11**

7. The corresponding ketone was too unstable to be isolated.

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