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THE CHEMISTRY OF VICINAL TRICARBONYL COMPOUNDS. APPLICATIONS IN THE SYNTHESIS OF ISOQUINOLINE ALKALOIDS

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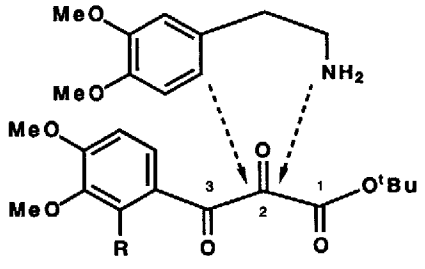
Abstract: The central carbonyl of a vicinal tricarbonyl system is used as a dielectrophile with substituted phenethylamines in short, efficient syntheses of the isoquinoline alkaloids, papaveraldine, hydrastine and cordrastine.

The central carbonyl group in a vicinal tricarbonyl system embodies a highly reactive electrophilic site with strong potential for bond formation in organic synthesis. We have reported the use of this system in the formation of fused-ring β-lactams,[1a-c] and more recently, in the synthesis of vincamine-related derivatives.[1d] This letter describes a new application of this functional group aggregate in the synthesis of isoquinoline alkaloids.[2]

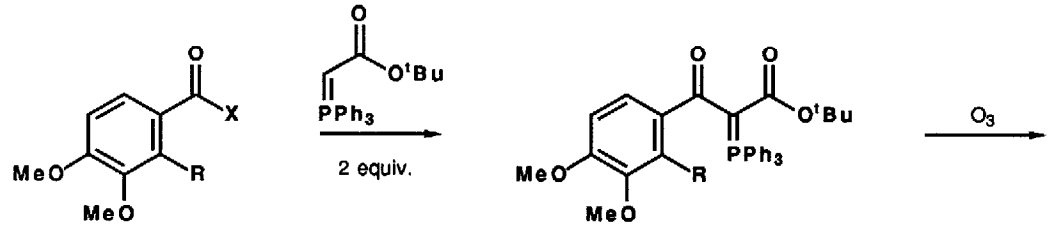
Our method involves a flexible, efficient and mild route to members of this alkaloid family through reaction of a suitably substituted vicinal tricarbonyl with an appropriate phenethylamine. In our plan, the central (C–2) carbonyl of **1** acts as the acceptor site for bond formation with both the primary amino group and the aromatic ring. The C–1 carboxyl function, which acts as an activating group in the first step, is removed by decarboxylation, and the C–3 carbon becomes the ketone group of papaveraldine (**2**) or the lactone oxygen atom in hydrastine and cordrastine (**3** and **4**).[3,4]



1 a. R = H
1 b. R = CO_2Et

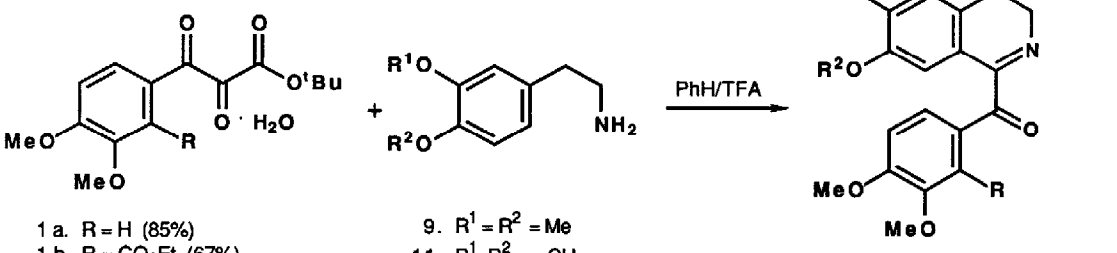
The commercially available acid chloride **5a** reacts with 2 equivalents of *t*–butyl (triphenylphosphoranylidine)acetate[5] to generate the corresponding keto-ylide **8a** (93%, mp 204-205°C).[6] Ozonolysis of **8a** proceeds smoothly to the tricarbonyl monohydrate (**1a**) (85%, mp 97-99°C).[7] When a benzene solution of **1a** is combined with 2-(3,4-dimethoxyphenyl)ethylamine (**9**)

and treated with trifluoroacetic acid, the only product isolated is 3,4-dihydropapaveraldine (**10a**) (71%, mp 189.5-190°C; lit. mp 190-191°C).[8] The reaction appears to take place by initial formation of a Schiff base at the central carbonyl, followed by a Pictet-Spengler type of cyclization and rapid decarboxylation of the resulting β-keto ester. Air oxidation occurs under the reaction conditions to form the conjugated keto-imine **10a**.[9] Aromatization of **10a** is then easily accomplished by dehydrogenation with methanolic potassium hydroxide[10] to afford papaveraldine (2) (80%, mp 206-207°C; lit. mp 208-209°C).[11,12]



5 a. R = H, X = Cl
6 b. R = CO_2Et, X = H
7 b. R = CO_2Et, X = OH (84%)
5 b. R = CO_2Et, X = Cl

8 a. R = H (93%)
8 b. R = CO_2Et (99%)



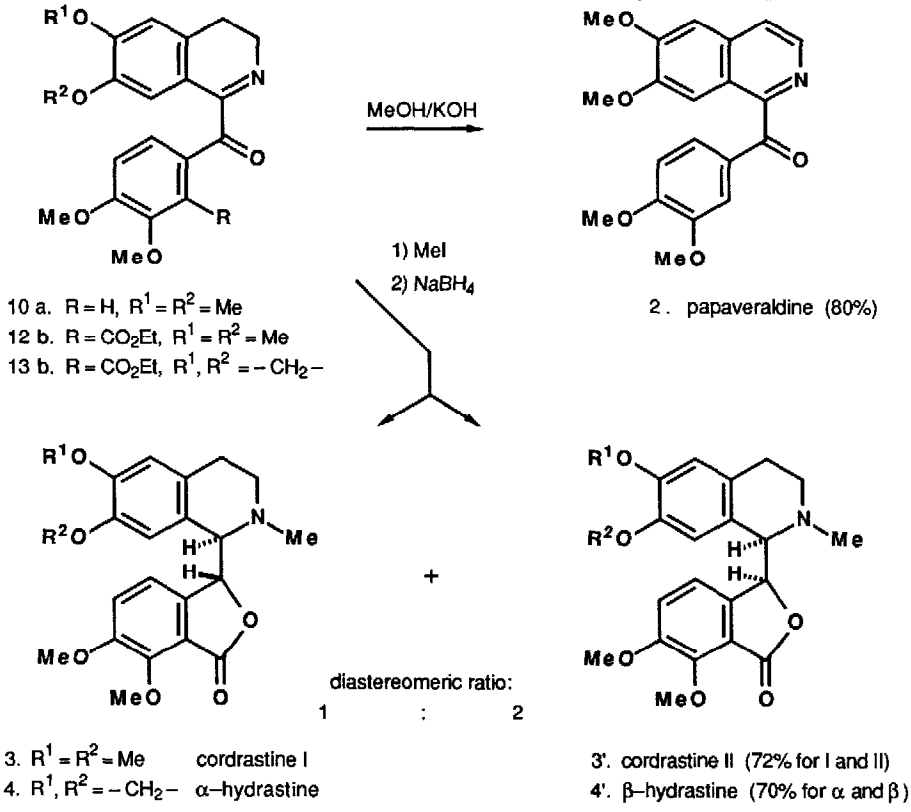
1 a. R = H (85%)
1 b. R = CO_2Et (67%)

9. $R^1 = R^2 = Me$
11. $R^1, R^2 = -CH_2-$

10 a. R = H, $R_1 = R_2 = Me$ (71%)
12 b. R = CO_2Et, $R_1 = R_2 = Me$ (61%)
13 b. R = CO_2Et, $R_1, R_2 = -CH_2-$ (67%)

A related approach was pursued for the synthesis of the hydrastines and cordrastines by utilizing an alternative mode of reactivity for the initially formed keto-imine. The crude acid chloride **5b**, prepared by oxidation and chlorination of the readily available aldehyde[13] **6b**, was used without purification in the reaction with *t*-butyl (triphenylphosphoranylidine)acetate to afford **8b** (99% from the corresponding acid **7b**). Ozonolysis of **8b** provided the tricarbonyl hydrate **1b** (67%, mp 94-95°C). Reaction of **1b**, in turn, with the phenethylamine derivatives **9** and **11**, afforded the keto-imines **12b** (61%) and **13b** (67%), respectively. Methylation (80% and 75%), and subsequent hydride reduction[14] led directly to the cordrastines (**3**,**3'**) and hydrastines (**4**,**4'**) as separable mixtures of diastereomers (cordrastine I and II, 72%; α- and β-hydrastine, 70%).[15] In both cases the diastereomeric ratio was approximately 1:2 in favor of the erythro compounds.

The structurally diverse isoquinoline alkaloids and their derivatives are of special interest in connection with their unique pharmacological properties.[2,16] Our method provides a useful addition to the methodology for synthesizing fully aromatic and partially saturated isoquinoline derivatives utilizing readily obtainable starting materials and a convenient experimental procedure.



10 a. R = H, $R^1 = R^2 = Me$
12 b. R = CO_2Et, $R^1 = R^2 = Me$
13 b. R = CO_2Et, $R^1, R^2 = -CH_2-$

2. papaveraldine (80%)

3. $R^1 = R^2 = Me$ cordrastine I
4. $R^1, R^2 = -CH_2-$ α–hydrastine

3'. cordrastine II (72% for I and II)
4'. β–hydrastine (70% for α and β)

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1 (a) Wasserman, H.H.; Han, W.T. *J. Am. Chem. Soc.* **1985**, *105*, 1444.(b) Wasserman, H.H.; Han, W.T. *Tetrahedron Lett.* **1984**, *25*, 3743. (c) Wasserman, H.H.; Han, W.T. *Tetrahedron Lett.* **1984**, *25*, 3747. (d) Wasserman, H.H.; Kuo, G.-H. *Tetrahedron Lett.* following paper.

2 For recent references concerning the isolation and properties of these compounds see: (a) Bentley, K.W. *Natural Products Reports* **1987**, 667. (b) MacLean, D.B. in *The Akaloids* Manske, R.H.F., ed.; Academic Press, New York, **1985**. (c) Shamma, M. *The Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic Press, New York, **1972**.

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[4] For recent work, and leading references, on phthalideisoquinoline syntheses, see: (a) Seebach, D.; Huber, I.M.P.; Syfrig, M.A. *Helv. Chim. Acta* **1987**, *70*, 1357. (b) MacLean, R.D.; Marsden, R. *Can. J. Chem.* **1984**, *62*, 306.

[5] (a) Cooke, M.P.; Burman, D.L. *J. Org. Chem.* **1982**, *47*, 4955. (b) Cooke, M.P. *J. Org. Chem.* **1982**, *47*, 4963.

[6] All new substances were characterized by the appropriate spectroscopic data and, in most cases, exact mass measurements. Yields given are unoptimized.

[7] Bestmann, H.J.; Kloeters, W. *Tetrahedron Lett.* **1978**, 3343.

[8] The structure of **10a** was established by comparison of physical properties with the product prepared by an independent synthesis: (a) Kametani, T.; Fukumoto, K. *J. Pharm. Soc. Japan* **1963**, *83*, 1031. (b) Wert, K.L.; Chackalamannil, S; Miller, E.; Dalton, D.R.; Zacharias, D.E.; Glusher, J.P. *J. Org. Chem* **1982**, *47*, 5141. (3) Buck, J.S.; Perkin, W.H., Jr.; Stevens, T.S. *J. Chem. Soc.* **1925**, *127*, 1462.

[9] The oxidation which generates this conjugated imine is not unexpected considering previous work on air oxidations of related systems: Aubagnac, J-L.; Elguero, J.; Jacquier, R.; Robert, R. *Bull. Soc. Chim. Fr.* **1972**, 2859.

[10] (a) Makuzier, G.; Hamon, M. *Bull. Soc. Chim. Fr.* **1969**, 687. (b) McMahon, R.M.; Thornber, C.W.; Ruchirawat, S. *J. Chem. Soc. Perkin I* **1982**, 2163.

[11] (a) Merck Index, 9th Ed. (b) Lespagnol, A.; Debaert, M.; Deverginies, M.; Gargot, N. *Bull. Soc. Chim. Fr.* **1972**, 699.

[12] In practice, this reaction sequence may be conveniently carried out in one pot (55% overall yield from **1a**) by evaporating the acidic solvent at the stage of the keto-imine (**10a**) and immediate treatment of the crude mixture with methanolic potasium hydroxide.

[13] Napolitano, E.; Giannone, E.; Fiaschi, R.; Marsili, A. *J. Org. Chem.* **1983**, *48*, 3653.

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[15] The physical and spectroscopic properties of these products are in complete agreement with published values (see reference 4).

[16] References 2-4 provide a summary of previous achievements in the synthesis of isoquinoline derivatives.

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