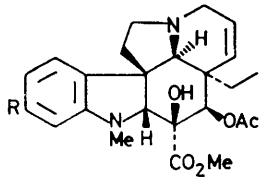
New Synthetic Routes to Synthons for the Synthesis of Functionalized Aspidosperma Alkaloids

By SEIICHI TAKANO,* KOZO SHISHIDO, MASAAKI SATO, KOHTARO YUTA, and KUNIO OGASAWARA
(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai* 980, *Japan*)

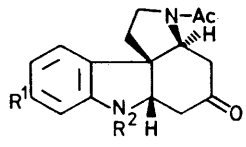
Summary The diazoketones (**3a** and **b**) and the iminomalonates (**7a** and **b**) have been converted into the tetracyclic vinylogous amides (**6a** and **b**) by an acid-catalysed single-step reaction; Birch reduction of the amides (**6a** and **b**) afforded the corresponding tetracyclic ketones (**2a** and **b**), synthons for the synthesis of functionalized aspidosperma alkaloids.

BÜCHI and his co-workers have elegantly synthesized the highly functionalized aspidosperma indole alkaloids vindorosine[1] (**1**) and vindoline[2] (**2**) using the tetracyclic ketones (**2a**) and (**2b**), respectively, as key intermediates. Although conversion of the ketones (**2a**) and (**2b**) into the required



(1)

a; R = H
b; R = MeO

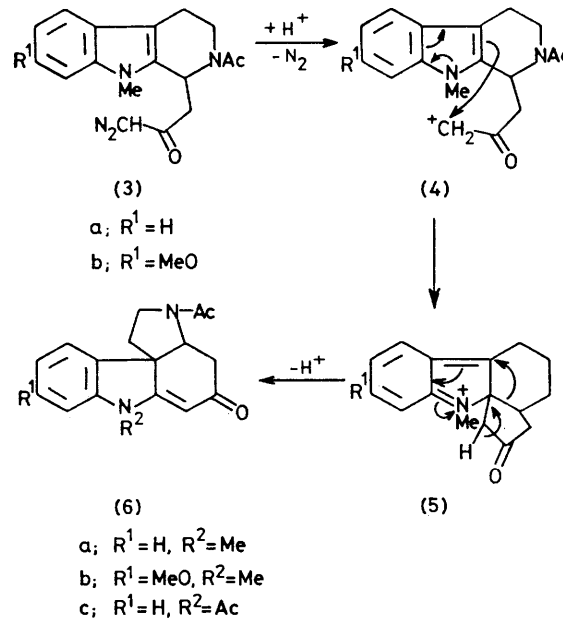


(2)

a; R^1=H, R^2=Me
b; R^1=MeO, R^2=Me
c; R^1=R^2=H

products could be carried out efficiently, the preparation of (**2a**) and (**2b**), especially the latter, required extra steps in order to eliminate undesired by-products. We report here two new approaches to the synthesis of the ketones (**2a**) and (**2b**) from the α-ketocarbonium intermediate (**4**) and from the Fischer base intermediate (**9**).

The first method involved formation of the α-ketocarbonium ion[3] (**4**) and concurrent rearrangement[4] to the tetracyclic vinylogous amide ring system (**6**) (Scheme 1).



(3) (4) (5) (6)

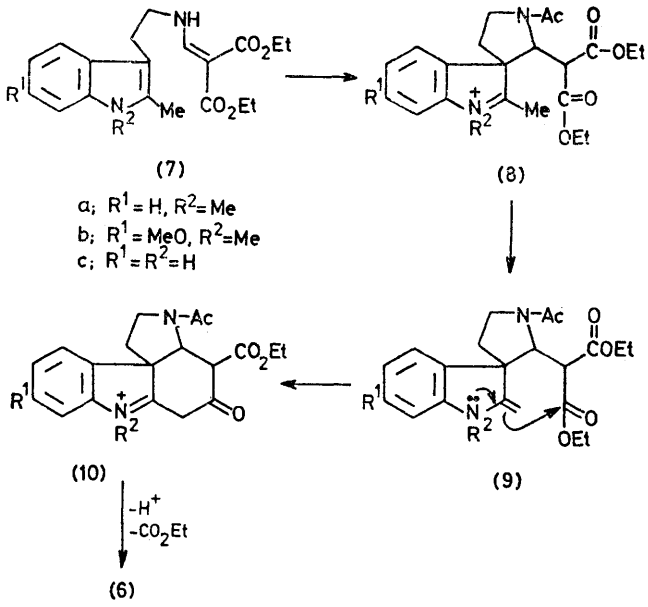
a; R^1=H, R^2=Me
b; R^1=MeO, R^2=Me
c; R^1=H, R^2=Ac

SCHEME 1

The required α-diazoketones† (**3a**) oil, and (**3b**), m.p. 76—79 °C, were obtained from the corresponding tryptamines through the four-step sequence: i, $EtOCOCH_2$-$COCO_2H$–HCl; ii, AcCl–Et_3N; iii, ethanolic KOH; iv, $ClCO_2Et$–Et_3N, then CH_2N_2.[5] Brief exposure to trifluoroacetic acid[3] in methylene chloride transformed (**3a**) into the vinylogous amide‡ (**6a**), m.p. 224—225 °C, in 12% yield. Similarly (**3b**) was transformed to (**6b**),‡ m.p.

† Satisfactory analytical and spectral data were obtained for all new compounds.

‡ This compound consisted of two conformers (3 : 2) presumably owing to the two possible configurations of the acetamide group; equilibration occurs at > 130 °C in Me_2SO solution.



SCHEME 2

126—128 °C (lit.,[6] 130—133 °C), in 35% yield. Reduction of both (**6a**) and (**6b**) with 1 mol. equiv. of lithium§ in liquid ammonia in the presence of t-butyl alcohol afforded the tetracyclic ketones (**2a**), m.p. 195—197 °C (lit.,[1] 195—197 °C) and (**2b**), m.p. 177—179 °C (lit.,[2] 176—177 °C), in 75 and 92% yield, respectively.

The second method involved formation of the Fischer base (**9**) and concurrent nucleophilic cyclization to (**6**) with loss of an ethoxycarbonyl unit (Scheme 2). Refluxing the iminomethylenemalonate (**7a**), prepared quantitatively from 1,2-dimethyltryptamine[7] and diethyl ethoxymethylenemalonate, with acetic anhydride–acetic acid (3 : 2)¶ for 70 h afforded (**6a**)‡ in 52% yield. Similarly (**7b**) gave (**6b**)‡** in 50% yield. When (**7c**) was heated under reflux under the same conditions it was converted into the diacetamide (**6c**), m.p. 232—233 °C, in 45% yield. Since (**6c**) could be selectively converted into the secondary amine (**2c**) in 65% yield by reduction using 4 mol. equiv. of lithium, it should be a useful synthon for synthesis of the strychnos type of indole alkaloids.

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§ The amount of lithium was most important, since over-reduction to the corresponding amino-alcohol was observed when an excess of the metal was used. Birch reduction has been also employed in Ban's synthesis (ref. 6).

¶ Neither acetic anhydride nor acetic acid alone initiated the cyclization.

** Trammell has studied the cyclization of the iminomethyleneacetate (**7** : R^1 = OMe, R^2 = Me, one CO_2Et replaced by H), expecting to obtain (**6b**) *via* the corresponding Fischer base intermediate (**9**) though all attempts were unsuccessful. (G. L. Trammell, Ph.D. thesis, M.I.T., August, 1973). We thank Professor G. Büchi, M. I. T., for informing us of Dr. Trammell's work and for a copy of Dr. Trammell's thesis.

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[4] *Cf.* J. Harley-Mason and M. Kaplan, *Chem. Comm.*, 1967, 915; L. J. Dolby and Z. Esfandiali, *J. Org. Chem.*, 1972, **37**, 43.
[5] *Cf.* B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1969, 1319.
[6] Y. Homma and Y. Ban, *Tetrahedron Letters*, 1978, 155; n.m.r. spectra [$CDCl_3$ and $(CD_3)_2SO$] of (**6b**) were identical with those kindly provided by Professor Ban, Hokkaido University.
[7] I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, *Doklady Akad. Nauk S.S.S.R.*, 1967, **176**, 583 (*Chem. Abs.*, 1968, **68**, 104,882j).