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CHLOROACETAMIDE PHOTOCYCLIZATION OF INDOLE DERIVATIVES. SYNTHESIS OF DESETHYLCATHARANTHINE DERIVATIVES

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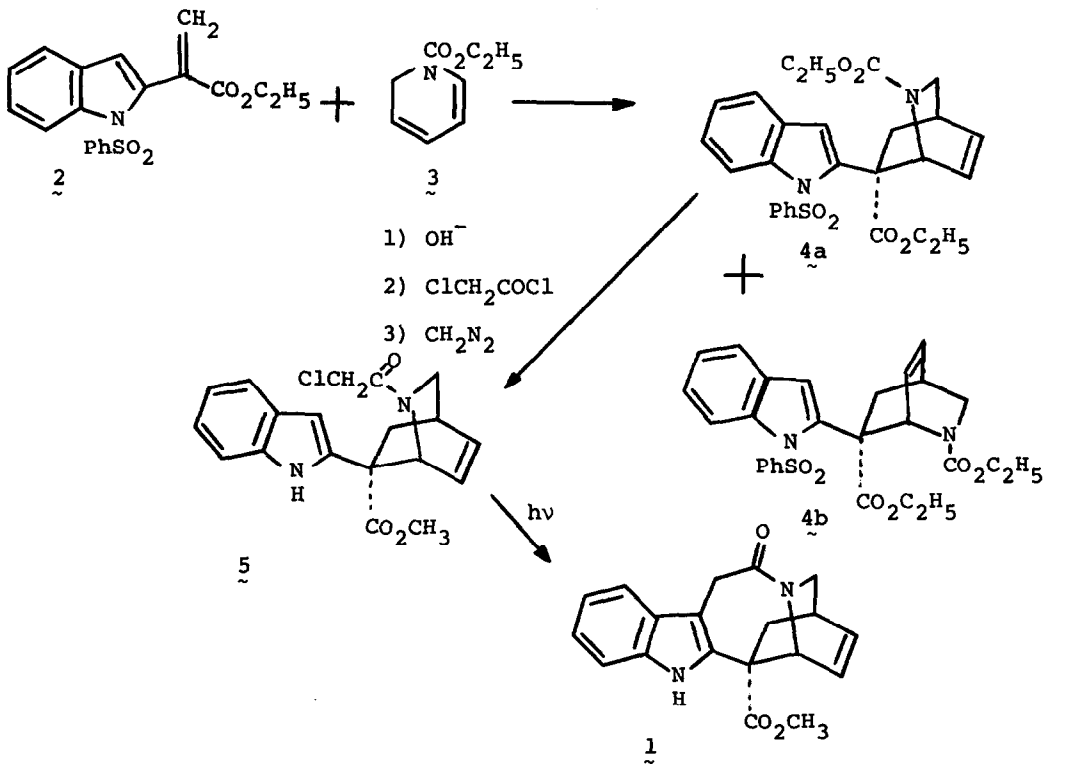
The development of a fragmentative method, based on the Polonovski reaction for synthesis of dimeric Vinca alkaloids by coupling catharanthine derivatives with vindoline derivatives[1] has spurred great interest in chemical transformations of catharanthine.[2] Cathananthine has been totally synthesized in the course of pioneering synthetic work on the Iboga[3] and Vinca[4] alkaloids. The existing syntheses, however, depend on introduction of the carbomethoxy group at a late stage of the synthesis via nucleophilic displacement by cyanide ion on a chloroindolenine intermediate and the reported yields are not high. Availability of a synthetically versatile analog of catharanthine could permit investigation of the structure-activity relationships within a series of analogs of the dimeric Vinca alkaloids. The lactam 1 (7-oxodesethylcatharanthine) seemed to us to be a suitable intermediate and the combination of chloroacetamide photocyclization[5] with Diels-Alder chemistry offered promise of a short synthesis. This communication reports the realization of this plan as summarized in the Scheme.

Condensation of 1-benzenesulfonyl-2-lithioindole[6] with ethyl pyruvate gives the expected carbinol (mp 111-113°, 64%) which is dehydrated to 2 (mp 107-108°, 69%) on heating to 145° in vacuum with p-toluenesulfonic acid. Diels-Alder addition occurred on heating 2 with excess 1-carboethoxy-1,2-dihydropyridine[7] for 36-48 hr at 85°. Treatment with maleic anhydride and base extraction removed much of the remaining dihydropyridine and its decomposition products. Separation of the remaining neutral material by chromatography[8] gave the adducts 4a (mp 145-146°, 38%) and 4b (mp 191-196° d, 5%). Some ethyl 2-(1-benzenesulfonylindol-3-yl)propionate was also isolated. The structure of 4a and 4b, excluding stereochemistry, is deduced from nmr data,

in particular the appearance in both adducts of the C-1 bridgehead proton of the isoquinuclidine ring as a doublet coupled only to a vinyl proton.[9] The regiochemistry of the addition is consistent with that noted for acyclic dienamides[10] and for a closely related dihydropyridine[11] with simpler dienophiles. Besides permitting the addition of the acrylate substituent via the 2-lithio derivative, the benzenesulfonyl group is considered to perform the dual role of stabilizing the sensitive vinylindole moiety[12] and attenuating the undesirable electron-donor character of the indole ring toward the acrylate moiety.[13]

SCHEME



Selective alkaline hydrolysis removes the ester and benzenesulfonyl groups and under more vigorous conditions (2 days, 8% KOH in EtOH-H_2O) the urethane group is also hydrolyzed. Chloroacetylation of the buffered (tris buffer, pH>8.5) hydrolyzed solution with chloroacetyl chloride, followed by careful[14]

acidification and methylation yields 5 (mp 210-211°, 35-50%). Photolysis[5] of 5 in methanol gives 1 (mp 275-277°, 55%).

The structure of 1 was indicated by the nmr spectrum which showed the absence of an indole 3-H signal and the appearance of the C-8 methylene protons as a prominent AB pattern. The structure was confirmed by interrelation with synthetic desethylibogamine[15] via the thioamide, Raney nickel desulfurization to 3,4-dihydrodesethylcatharanthine (mp 176-177°), followed by hydrolysis and decarboxylation under the conditions described for catharanthine.[16] Desethylibogamine obtained by this route was identical by spectral (ir, nmr) and chromatographic comparison with authentic material.[17] The successful photocyclization establishes the stereochemistry of 4a.

This synthesis is sufficiently short that successful scale-up should make 1 accessible for preparation of new desethyl analogs of the dimeric Vinca alkaloids.

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8) The adducts were separated using Silica Gel 60 (Merck, neutral, Activity II-III) and 1:1:1 ether-chloroform-hexane.

9) At room temperature there is additional complexity due to slow rotation of the urethane group. At 80° the spectra show the expected multiplicity in all peaks.

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14) Acidification to pH 3 was carried out by adding 2% HCl at 0° with vigorous stirring. The ease of decarboxylation of 18-carboxyl derivatives in the iboga series requires that more strongly acidic conditions be avoided.

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