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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XVII[1]. SYNTHESIS OF DEETHYLCATHARANTHINE

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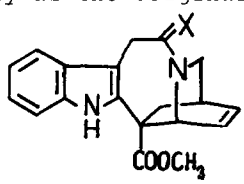
Summary: *Starting from indolylacetic acid the synthesis of (±)deethylcatharanthine was achieved using fewer steps than the previous pathways.*

The *Vinca rosea* (*Catharanthus roseus*) alkaloids vincristine and vinblastine are widely used in the chemotherapy of cancer. 20'-Deethylanhydrovinblastine was synthetized by *Langlois* and others *via* coupling of /±/-deethylcatharanthine (1a) N-oxide with vindoline and was found to have essentially the same *in vitro* activity as the original alkaloids[2].

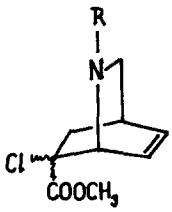


1a X=H_2
b X=O

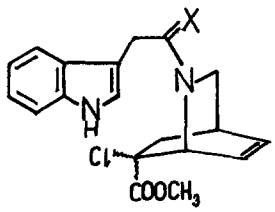
Two syntheses of 1a have been published so far[3,4]. Now we report a new approach using fewer steps than the previous pathways.

On reacting N-benzyloxycarbonyl-1,2-dihydropyridine[5] with 2-chloroacrylic acid chloride (in acetonitrile, rt., 24 hr.), followed by treatment of the product with methanol, the isoquinuclidine derivative 2a was obtained (mp. 89-93° from ethylacetate-hexane, overall yield 20 % based on the starting material pyridine). After removal of the N-acyl group by acetic acid/HBr (rt., 10 min) the resulting 2b was allowed to react with tryptophyl bromide (in methanol, Et_3N, rt., 24 hr.) to yield compound 3a (mp. 129-131° from ethylacetate-hexane).

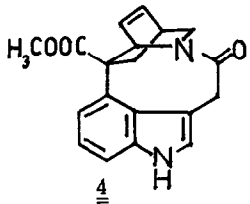
Attempted ring closure of 3a by boiling in butanol or by using Lewis acids in different solvents furnished unexpected rearranged products, the structures of which were elucidated; the results are to be published in a subsequent paper.



2a R=COOCH$_2$Ph
b R=H



3a X=H$_2$
b X=O



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The amine 2b was then acylated by the mixed anhydride of indolylacetic acid and pivalic acid giving rise to compound 3b (mp. 199-201° from chloroform-methanol, yield 68 %). Irradiation of 3b in methanol-water with a low-pressure mercury lamp (4-6 hr.) furnished two products in a ratio of about 1:1. After chromatographic separation (Silicagel 60 (0.063-0.200,) chloroform: ethyl acetate: Et_3N = 20:8:1) one of them proved to be identical with the already described[3,6] 1b (yield: 16 %), which was transformed in two known[3] steps to the target compound 1a (overall yield 6,5 % based on indolylacetic acid).

The structure of the second product 4 (mp. 298-302 ° from chloroform) was substantiated also by X-ray analysis.

All the spectral data (IR, MS, NMR) of the new products were in accord with the given structures.

Using the above described procedure, the syntheses of catharanthine and allo-catharanthine are in progress.

R e f e r e n c e s

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6. The authors are grateful to Prof. R.J.Sundberg for sample and spectra of compound 1b.

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