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TWO-STEP SYNTHESIS OF dl-ELAEOCARPINE: UTILITY OF DIHYDROPYRIDINES AS A VERSATILE SYNTHETIC INTERMEDIATE*1

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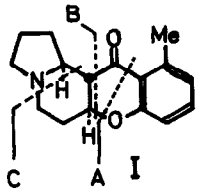
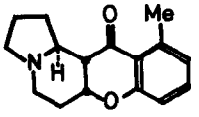
Elaeocarpine (I) and isoelaeocarpine (II), major alkaloids of Elaeocarpus polydactylus Schl., have been proved to have a unique chromanoindolizidine skeleton by the chemical and X-ray crystallographic investigations.[1a] We now wish to report an effective method for constructing chromano[3,2-c]piperidine ring system and a two-step synthesis of these alkaloids by taking advantage of this method, in that we want to exemplify the utility of dihydropyridines as a versatile synthetic intermediate.

To design the synthesis of these alkaloids;*2 we have conceived various



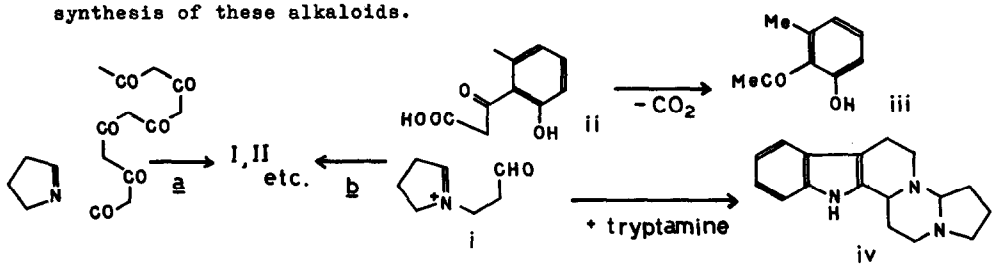
I



II

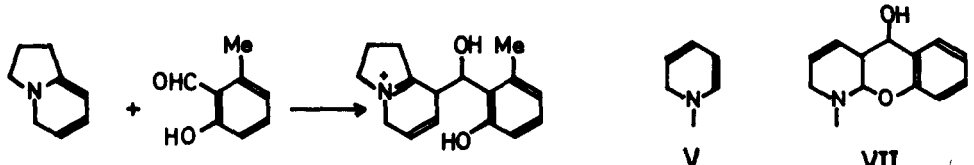
*1 Presented at the 14th Symposium on the Chemistry of Natural Products (Japan), Fukuoka, Oct. 28 1970. Symposium Papers, p. 127. Another synthesis of the same alkaloids was reported simultaneously by T. Tanaka, I. Iijima and M. Miyazaki: ibid., p. 143. See also ref. 3.

*2 Concerning the biogenesis of these alkaloids Johns et al. (ref. 1b) have proposed the route indicated by a in the following scheme. The possibility that these alkaloids are formed from the precursor i and ii (or its partially reduced equivalent (ref. 1b)) cannot be excluded, since iii (ref. 1a) and elaeocarpidine (iv) (ref. 1c), the accompanying products of the same plant, conceivably originate also from i and ii, but neither of the mechanisms provides a direct route for the laboratory synthesis of these alkaloids.

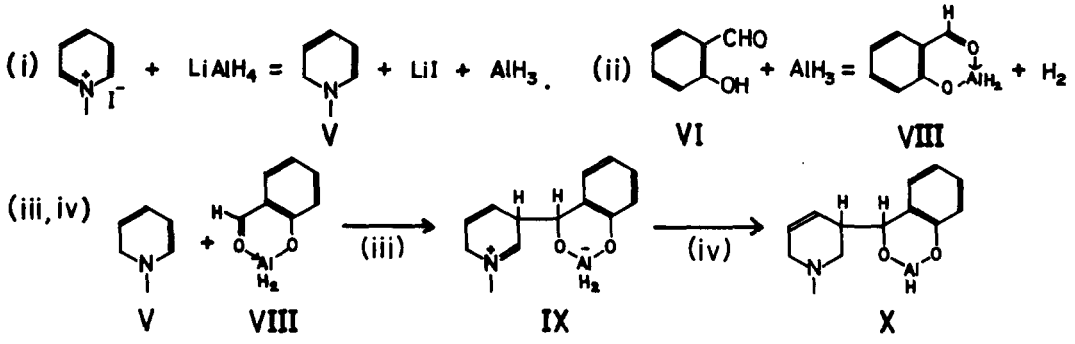


combinations of bond disconnection of the target molecule, and examined the "availability" of the fragments ("synthon"[2]) thus obtained. These contemplative analysis have deduced three rational manners for constructing the target molecule which are indicated by the "severance"*3 A, B, and C in the structure I.

Among them,*4 an imaginative bond disconnection by B seems to provide the simplest route for I when one envisages the reaction of III with IV as an actual synthetic method. While an analogous reaction elaborated by Paquette and Stucki[6] has ensured the correctness of the above consideration, there still remains an ambiguity of whether dihydropyridines will react with salicylaldehyde at all as normal enamines do. To date little is known about the enamine or dienamine character of dihydropyridines, although they are evidently promising precursors in the synthesis of naturally occurring bases. Taking these into account, we first examined the condensation of the simplest dihydropyridine (V) with salicylaldehyde (VI) as a fundamental model reaction.



Although the experiments under various condition according to a reported procedure[6] failed to afford the desired condensation product (VII), we finally found a new reductive condensation reaction of 1-methyl-1,2-dihydropyridine (V) with salicylaldehyde (VI) in the presence of $LiAlH_4$ after many unsuccessful attempts. The reaction is speculated to consist of four different stages of sequential reactions; (i) reduction of pyridinium halide with equivalent mole of $LiAlH_4$ may form dihydropyridine,[7] LiX, and AlH_3; (ii) addition of salicylaldehyde to the above mixture produces an instantaneous formation of quasi-

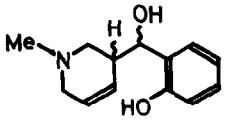


*3 The concept of "severance" and "severability" that would facilitate a logical approach to synthesis design will be discussed elsewhere. A relevant example of such logical method was illustrated by the synthetic analysis of the route to iboga alkaloid (see ref. 4).

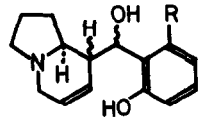
aromatic chelate[8] (VIII), in which aluminium behaves as a Lewis acid and activates the aldehydic carbon; (iii) attack on the electrophilic carbon of the chelate (VIII) by the nucleophilic enamine carbon of dihydropyridine (V) gives the intermediary condensation product (IX); (iv) internal or external reduction of immonium intermediate (IX) yields the condensation product (X).

Troublesome as it seems from the mechanistic explanation, the actual procedure of the reaction is very simple and can be conducted with ease. Thus, after 1-methylpyridinium iodide in anhydrous ether was reduced with equimolar $LiAlH_4$, an equivalent mole of salicylaldehyde in ether was added and the reaction mixture was stirred overnight. Isolation and purification in the conventional manner afforded a condensation product (XI) in 12% yield. The analogous reaction of 2,3-dihydro-1H-indolizinium bromide[9] with salicylaldehyde and 6-methyl-salicylaldehyde[10] furnished the condensation products, (XII and XIII), in the respective yield of 6% and 18%. Physical and spectroscopic characters of these products*5 are given in the following table.

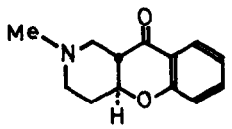
		NMR spectra (δ from TMS)	
	mp(°C)	$\geq C\underline{H}OH$	$-C\underline{H}_A=C\underline{H}_B-$
XI	137-138	5.14(d,J=2.0)	5.91(dd,J=11, 4), 5.56(br.d,J=11)
XII	178-179	4.81(d,J=4.5)	5.84(br.s, W(½h)=2.6)
XIII	270-272	4.78(d,J=8.0)	5.78(dd,J=10, 5), 5.25(br.d,J=10)



XI



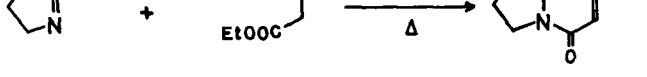
XII(R=H), XIII(R=Me)



XIV

The second stage of this synthesis is a selective oxidation of benzylic hydroxyl group and the chromanone cyclization. These were achieved simply by oxidation with Jones' reagent. When the model compound XI was subjected to the Jones oxidation, it provided the desired chromanopiperidine derivative (XIV), mp 127-128.5°, whose structure was confirmed by the spectral data (IR: ν_{CO}^{KBr} 1688; NMR: δ 4.28-3.70(v.br.m, 1H, $\geq C\underline{H}O-$)). Similar oxidation of XIII afforded two stereoisomers which were separated by chromatography on alumina. The spectral properties (NMR, IR, and MS) of the less polar product (colorless plates from

*4 The synthetic process corresponding to the "severance" C had already been realized (ref. 5) by the following reaction, but several obvious difficulties precluded further studies along this line.



benzene-hexane, mp 79-80°) and of the polar ones (gum[*6]) were in good agreement with the reported ones for natural elaeocarpine (I) and isoelaeocarpine (II), respectively. By the direct comparison of IR spectra and chromatographic behavior (TLC and GC), the synthesized materials were proved to be identical with the natural bases which were kindly supplied by Dr. Johns of Melbourne. The melting point of synthesized elaeocarpine was not depressed by admixture with the natural specimens, thus providing the final evidence of the identity.

Acknowledgment

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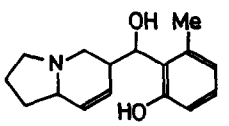
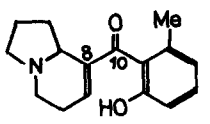
*5 Though the spectral data cannot eliminate the alternative structure XIII', the conversion of XIII to elaeocarpine unequivocally confirms its structure. The stereochemical structure of these products has not been elucidated, since the subsequent oxidation process must destroy the configuration at C-8 and C-10 to form the intermediate v.



XIII'



v

*6 In spite of its virtual identity with natural isoelaeocarpine in NMR, IR, MS, TLC (Al_2O_3 and SiO_2) and GC, the synthetic product did not crystallize. During their studies on these alkaloids, Johns et al. (ref. 1b) observed a similar phenomenon and stated that isoelaeocarpine derived from isoelaeocarpicine and isoelaeocarpiline was a gum while their IR and NMR spectra were perfectly superimposible with the naturally occurring crystalline isoelaeocarpine.