STUDIES IN INDOLE ALKALOID SYNTHESIS. A GENERAL SYNTHETIC ROUTE TO 2-ACYLINDOLE ALKALOIDS AND RELATED COMPOUNDS.

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A general synthetic route to 2-acylindole alkaloids has been developed. The readily available starting material, L(-)-tryptophan, is elaborated by standard methods to the β-carboline derivative 7, and the latter upon condensation with 3-methylene-pentan-2-one affords the tetracyclic ketones A-D, all of which are employed in the subsequent synthetic steps. Base-catalyzed cyclization of ketone D affords the nitriles 21 and 22 bearing the skeletal features of the sarpagine family and these compounds upon ring-opening with cyanogen bromide, convert to the desired intermediates 23, 24 and 25. Final elaboration of these intermediates to the 2-acylindole system completes the first syntheses of epi-dregamine and dregamine.

The 2-acylindole alkaloids are a large family of natural products and numerous research groups have investigated their structures and chemistry[1-3]. From a synthetic viewpoint these natural systems occupy a rather central position since the previous studies have provided various interrelationships with other indole alkaloid families. For example, the 2-acylindole alkaloid, perivine, has been converted via a trans-annular cyclization process to pericyclivine and normacusine B, members of the sarpagine series (Figure 1)[4].

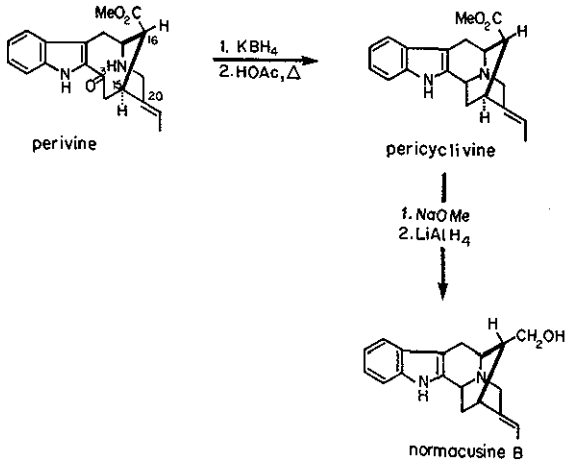

Figure 1. The conversion of perivine to pericyclivine and normacusine B.

The interconversions between the sarpagine systems and the ajmaline series are exemplified in Figures 2 and 3. Figure 2 illustrates two different reaction conditions to complete the cylization of a sarpagine skeleton to the deoxyajmaline series[5] while Figure 3 reveals the conversion of deoxyajmaline to ajmaline[6].

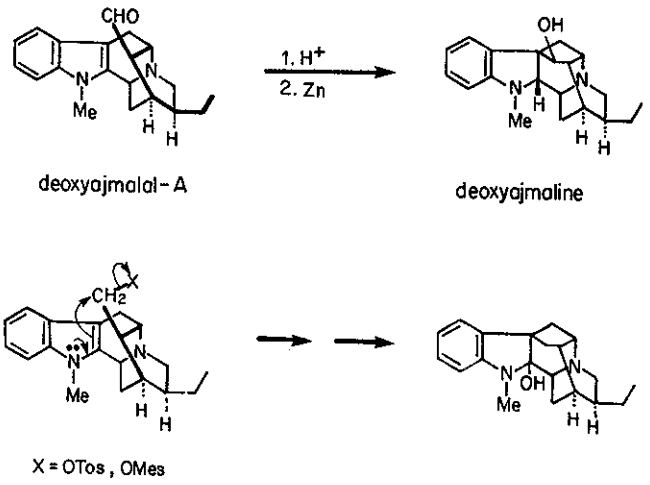

Figure 2. Two successful interrelationships between the sarpagine and ajmaline series.

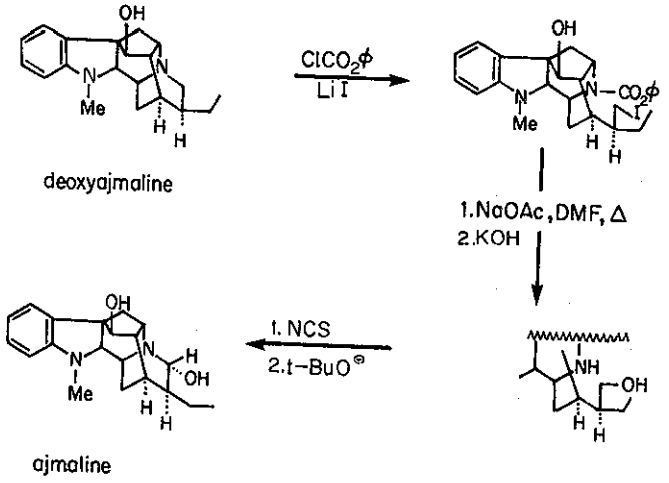

Figure 3. The conversion of deoxyajmaline to ajmaline.

The 2-acylindole alkaloids can be readily envisaged as structural units in the bisindole alkaloids of the voacamine type since the acid-catalyzed coupling of alcohol derivatives within this series, for example vobasinol, with the Iboga alkaloids provides a synthesis of the bisindole compounds, voacamine[7] (Figure 4) and tabernamine[8] (Figure 5).

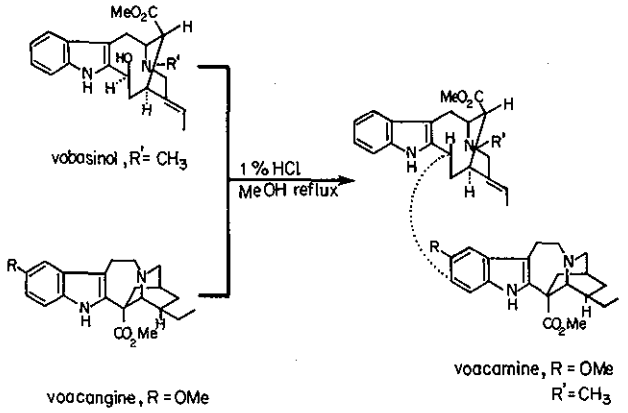

Figure 4. The synthesis of voacamine from vobasinol and voacangine.

As a result of the above-mentioned studies, it is clear that an efficient synthetic route leading to the 2-acylindole alkaloid system could be extended to the syntheses of these alkaloid families as well. This review will discuss our experiments directed toward this objective.

In developing a general and versatile synthetic route to the 2-acylindole series, the overall strategy summarized in Figure 6 was envisaged. It was considered that L(-)-tryptophan could be converted to an appropriate tetracyclic intermediate 1 (R = CO_2CH_3 or CN, R_1 = O) and the latter via anionic cyclization could be transformed to 2.

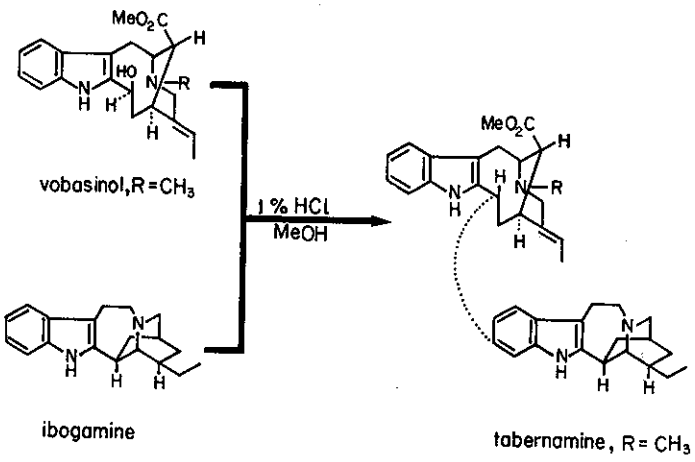

Figure 5. The synthesis of tabernamine from vobasinol and ibogamine.

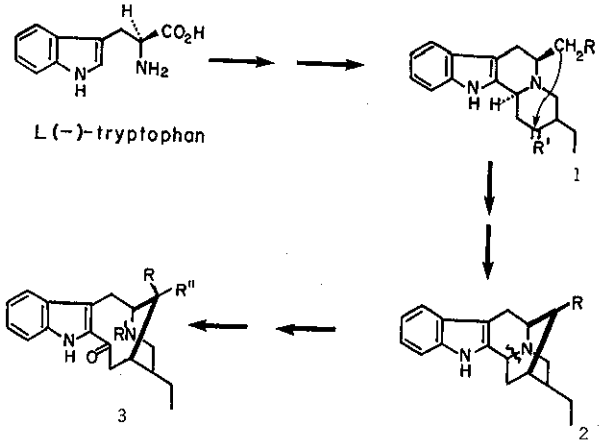

Figure 6. The overall synthetic plan utilizing L(−)-tryptophan as starting material.

This intermediate possessing the sarpagine skeleton could be converted by appropriate ring cleavage reactions to the desired 2-acylindole series (3). Indeed this approach has proved highly successful and various members within this family of alkaloids can be synthesized in an efficient manner. Figures 7 - 19 summarize some of the experiments in this area.

Figure 7 illustrates the sequence of rather standard reactions which were employed in converting L(-)-tryptophan to the important β-carboline intermediate 7. It is pertinent to note that in the cyclization of the N-formyl intermediate 6 to the β-carboline 7, polyphosphate ester (P.P.E.)[9] proved to be the reagent of choice and this situation generally prevailed in the various Bischler-Napieralski type cylizations studied.

In our earlier studies involving base-catalyzed reactions, some complications arose from the generation of indole anions via removal of the weakly acidic indole proton and for this purpose the benzyl protecting group was employed to eliminate such problems. As shown in Figure 8, the N_a-benzyl series was readily prepared and could be utilized in the synthesis of the required tetracyclic intermediates exemplified by 9. Subsequent studies with both the free indole and N_a-benzylindole series were carried out.

The conversions of the respective β-carboline derivatives to the desired tetracyclic intermediates (for example 8 → 9, Figure 8) were accomplished by acid-catalyzed condensation with 3-methylene-pentan-2-one (10), prepared according to the known sequence shown in Figure 9[10,11].

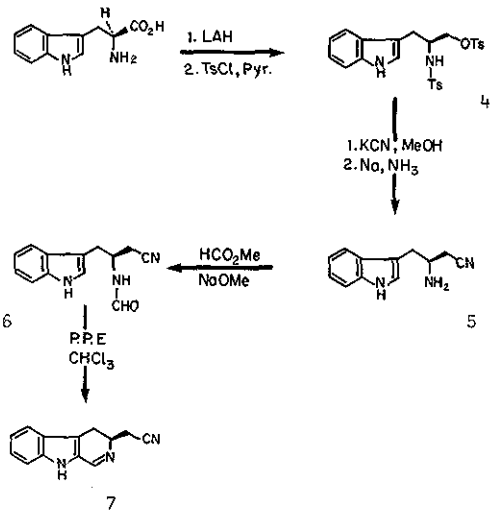

Figure 7. The conversion of L(-)-tryptophan to the β-carboline derivative 7.

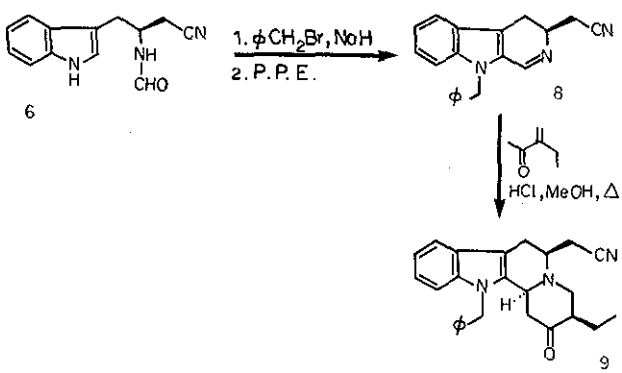

Figure 8. The conversion of the intermediate 6 to the N_a-benzyl β-carboline derivative 8 and the tetracyclic ketone 9.

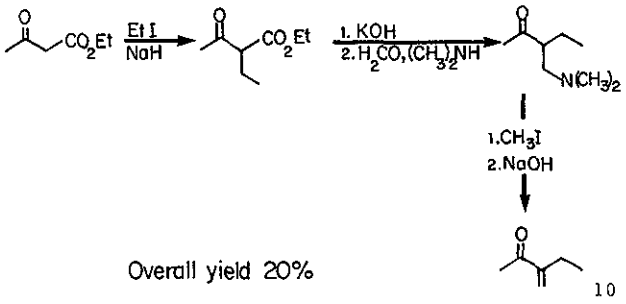

Figure 9. The synthesis of 3-methylene-pentan-2-one (10).

One of the possible approaches for the conversion of the tetracyclic series, for example 9, to the sarpagine system involved a nucleophilic displacement of a suitable leaving group generated at the carbonyl site in 9, by a carbanion center adjacent to the nitrile function. Such nucleophilic displacement is best accomplished when the leaving group occupies the axial (or α) orientation as seen in 12 (Figure 10). For this purpose a stereospecific reduction of the ketone function in 9 was required. As Figure 10 illustrates, borohydride reduction of 9 provides the equatorial alcohol 11 but reduction with isobornyloxyaluminum dichloride[12] did afford the desired alcohol 12. A detailed study of the desired nucleophilic displacement with various derivatives of the alcohol 12 was carried out but unfortunately the required cyclization reaction was not obtained. In all instances elimination rather than substitution was the exclusive reaction as shown in the conversion of the mesylate 13 to the olefin 14 (Figure 11).

Molecular models reveal that in order to achieve the desired cyclization of mesylate 13 to the sarpagine skeleton it is necessary to invert the geometry of the basic nitrogen atom from its most stable

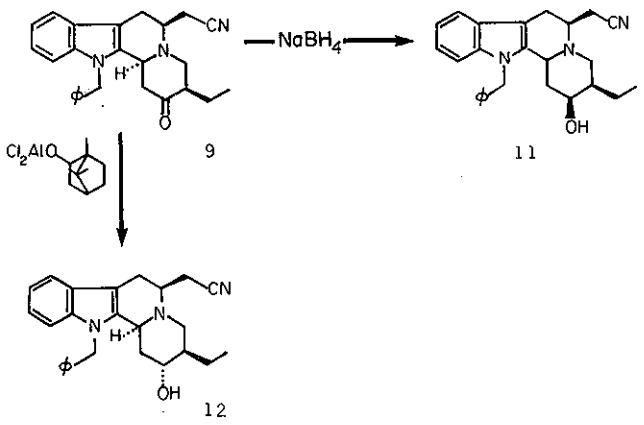

Figure 10. Reduction of the N_a-benzyl tetracyclic ketone 9.

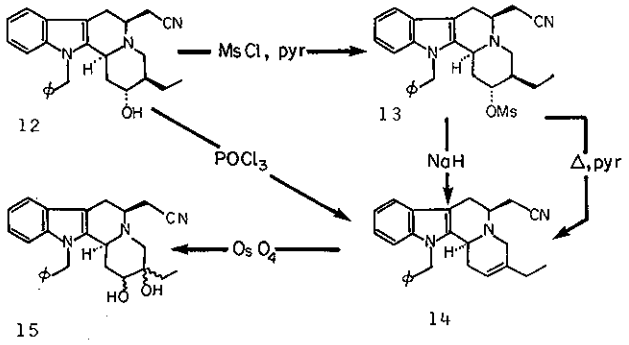

Figure 11. A summary of some reactions with the alcohol intermediate 12.

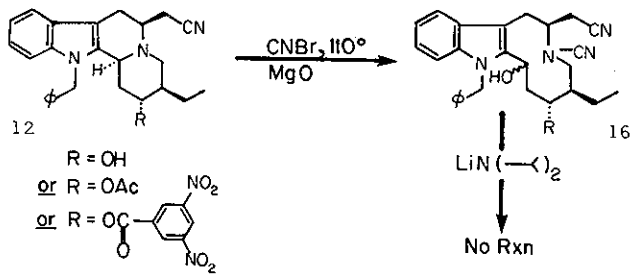

Figure 12. The reaction of alcohol 12 and several alcohol derivatives with cyanogen bromide.

(N_b electron lobe in a β-orientation) to the less stable orientation in order to allow the two reacting centers to achieve the required proximity. Perhaps the observed failure of the cyclization process is due to this energetically unfavourable inversion and the alternative elimination reaction becomes predominant. Such a restriction to the required nitrogen inversion could be eliminated in a conformationally more flexible system and it became of interest to pursue this avenue of research.

Various ring-opening reactions within the closely related tetracyclic indole alkaloids of the corynantheine series as well as in the pentacyclic yohimbine series have been developed. Of these, the cyanogen bromide reaction[13,14] appeared to possess most promise in terms of versatility and it was evaluated rather extensively in our laboratory. The reaction of alcohol 12 and several of its derivatives with cyanogen bromide (Figure 12) does indeed provide an overall efficient synthetic route to the desired conformationally flexible systems (16).

Unfortunately, as Figure 12 indicates, the subsequent cyclization of these compounds with a variety of basic reagents did not proceed in the desired fashion. In most instances starting material was recovered or extensive decomposition occurs under forcing conditions.

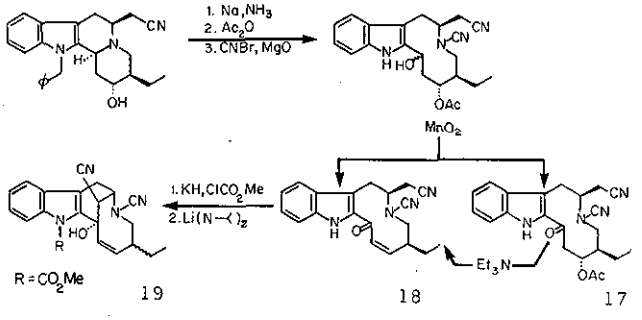

Figure 13. Base-catalyzed cyclization reactions of 2-acylindole intermediates 17 and 18.

An alternative approach to the cyclization of the ring-opened intermediates involved the utilization of 2-acylindole intermediates obtained by MnO_2 oxidation of the previously mentioned alcohol derivatives (Figure 13). Such intermediates, for example 17 and 18, were exposed to basic reagents but unfortunately the cyclization reaction involved the ketone carbonyl group of the 2-acylindole system (18 → 19, Figure 13) and the desired products were not obtained.

In addition to the various investigations involving intermediates possessing a nitrile containing side chain, a parallel series of experiments were carried out with an ester function in the side chain. These compounds (see 20), prepared according to the sequence shown in Figure 14, provided

similar difficulties to those already noted above and consequently another approach was considered.

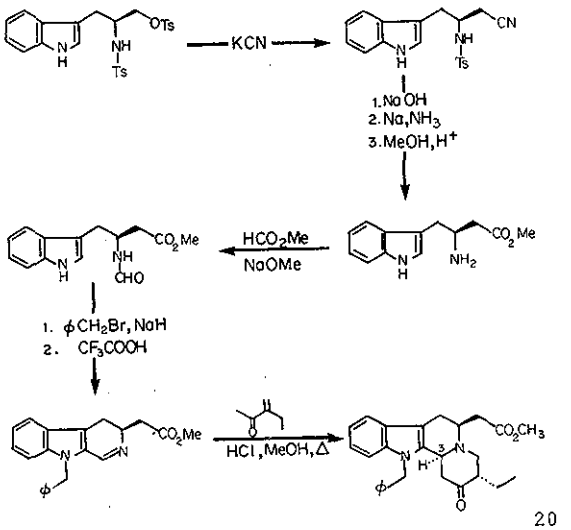

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Figure 14. The synthesis of the tetracyclic ester intermediate 20.

Condensation of the β-carboline intermediate 7 with 3-methylene-pentan-2-one in the previously described manner provided an overall 75% yield of the isomeric tetracyclic ketones A-D (Figure 15). These ketones could be interrelated by acidic, basic or thermal methods as shown in Figure 15 and consequently all of these compounds can be employed in the subsequent synthetic experiments. For the sake of brevity, only the chemistry of ketone D will be presented in the remaining portion of this discussion.

Base-catalyzed cyclization of D (Figure 16) affords the two isomeric nitriles 21 (10%) and 22 (57%), both of which can be utilized in the subsequent experiments as shown in Figures 16 and 17. Thus

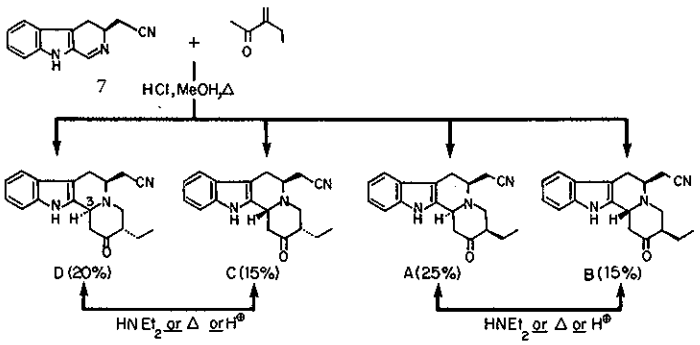

Figure 15. The synthesis of tetracyclic ketones A-D.

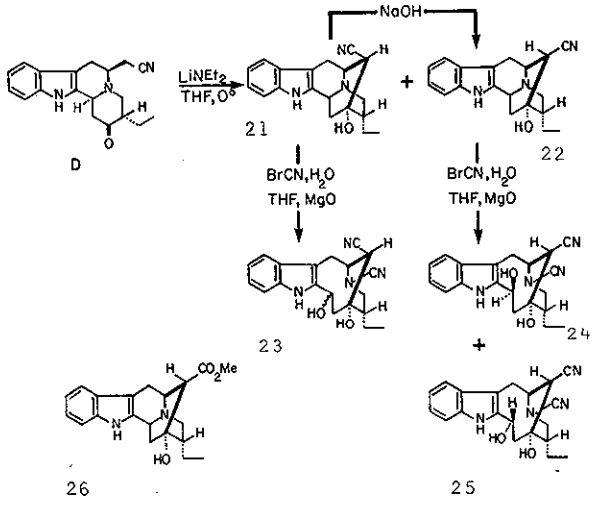

Figure 16. The base-catalyzed cyclization of ketone D and subsequent ring opening of the resultant products.

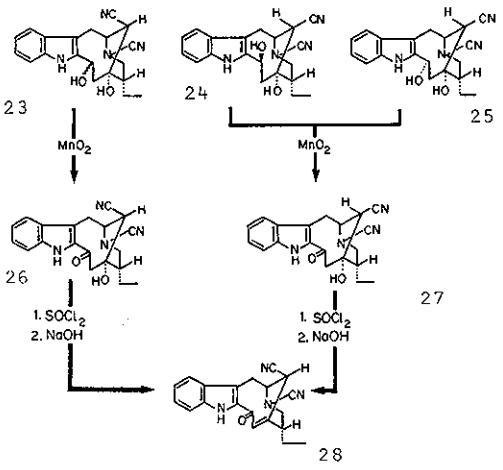

Figure 17. Conversion of ring-opened intermediates 23, 24 and 25 to the corresponding 2-acylindole intermediates 26, 27 and 28.

cyanogen bromide reaction with the nitriles 21 and 22 provides an efficient method for the desired ring-opened intermediates 23, 24 and 25. The ester series exemplified by 26 (Figure 16) is directly available from the nitriles by hydrolysis (methanol, HCl). The ester functionality can be effectively employed for the stereochemical assignments shown in the various intermediates. It is well established[4] that the chemical shift of the NMR signal for the ester methyl group in the sarpagine family is markedly dependent on the stereochemical orientation of this function since its proximity to the aromatic ring is very different in the two possible series.

As Figure 17 illustrates, generation of the required 2-acylindole intermediates is possible from the two isomeric series since manganese dioxide oxidation of 23, 24 and 25 affords 26 and 27 respectively and these two latter intermediates, upon dehydration, convert to a common

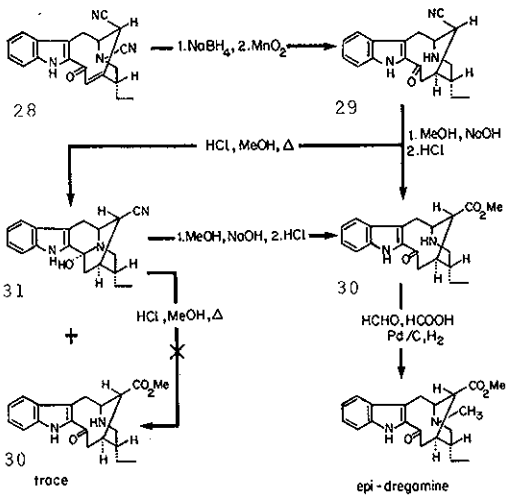

Figure 18. The synthesis of epi-dregamine from intermediate 28.

intermediate 28.

The final stages of the synthetic program leading to the first total synthesis of the dregamine series are summarized in Figure 18. The unsaturated ketone 28 is converted to the saturated ketone 29 in the manner indicated. In the sodium borohydride reaction, saturation of the double bond, reduction of the ketone and removal of the N-CN group occur simultaneously to provide the saturated alcohol (77%) and subsequent oxidation of the latter affords ketone 29 (79%). Both acidic and basic hydrolyses of the nitrile function in 29 were investigated but only the basic conditions afforded successful conversion to the desired ester 30. Under acidic media, only epimerization of the nitrile function and cyclization to the carbinol amine 31 is observed. The ester 30 is, in turn, also obtained from alkaline hydrolysis of 31 but the direct conversion, 29 → 30, is a more efficient process.

The final step in the synthesis of epi-dregamine involves N-methylation and this is accomplished by the Eschweiler-Clarke procedure as shown in Figure 18.

Epimerization of various 2-acylindole alkaloid members has been studied extensively by previous workers[15,16]. According to these procedures, epi-dregamine is converted to dregamine (Figure 19) thereby completing the synthesis of this alkaloid.

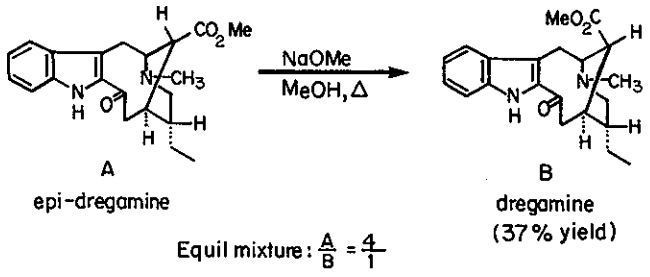

Figure 19. The conversion of epi-dregamine to dregamine.

In conclusion, the above investigations have provided a general and efficient synthetic route to the 2-acylindole alkaloids. Further experiments to complete the syntheses of other alkaloids within this or closely related families are presently underway.

Acknowledgement

The experiments presented above have been accomplished by a group of hard working, enthusiastic and persevering colleagues and it is a great pleasure for the author to acknowledge their efforts. They are: G. Eigendorf, U. Handschin, H. Matsue, A. Murai, K. Tanaka, W. Sung and K. Wada.

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