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GENERAL METHODS OF ALKALOID SYNTHESIS. XII. THE TOTAL SYNTHESIS OF (±)-ISORETRONECANOL AND (±)-δ-CONICEINE

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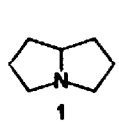
The pyrrolizidine nucleus (1) is incorporated into a relatively large number of alkaloids,[1] of which isoretronecanol (2), trachelanthamidine (3) and platynecine (4) may be regarded as typical.



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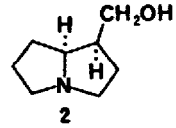

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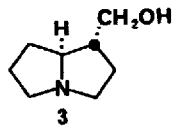

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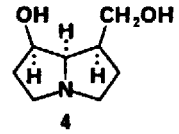

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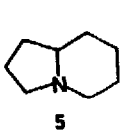
Similarly, the indolizidine[2] skeleton (5=δ-coniceine) is found in such structurally diverse bases as ipalbidine (6), septicine (7) and elaeocarpine (8), to mention a few. As part of a research program[3] aimed at developing new general methodology for the synthesis of a variety of different families of alkaloids, we turned our attention to these two groups. The simple bases δ-coniceine (5) and isoretronecanol (2) were selected as our initial targets to test the feasibility of this methodology in anticipation of subsequent application to more complex alkaloids such as ipalbidine (6) and septicine (7).



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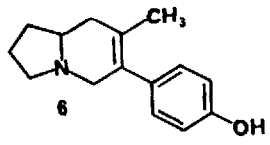

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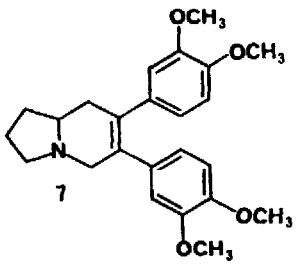

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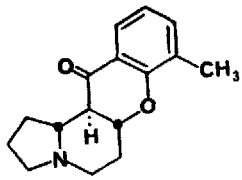

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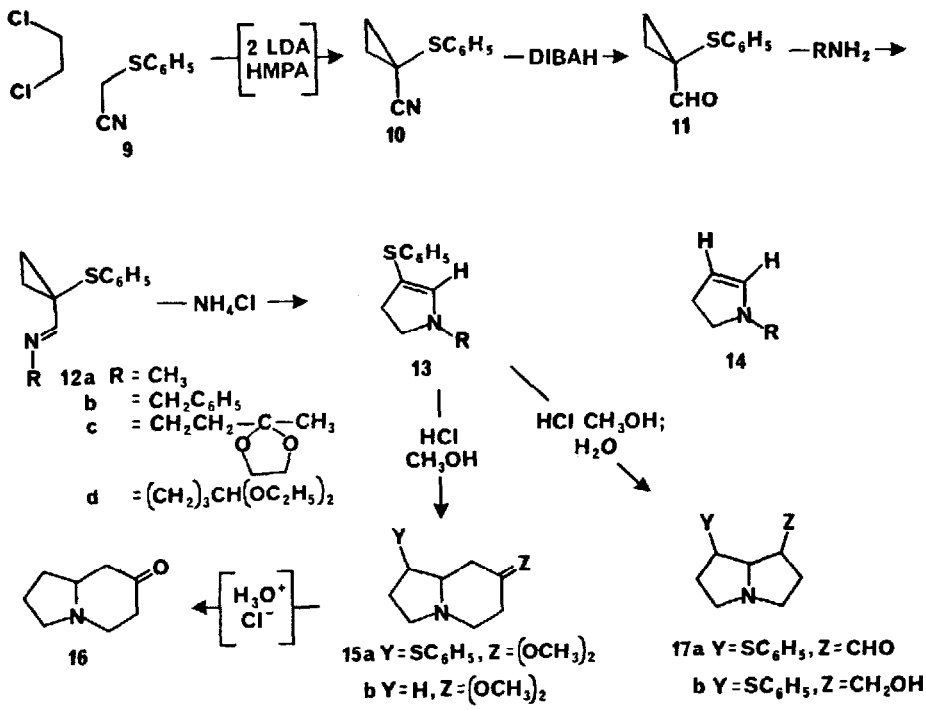
Cyclopropanation of phenylthioacetonitrile (9) with ethylene dichloride was achieved in 72% yield by employing lithium diisopropylamide/hexamethylphosphoramide in THF. Selective reduction of 10[4] to the key aldehyde 11 was accomplished with diisobutylaluminum hydride (98%). In order to test the efficacy of the rearrangement step, two simple aldimines (12a, b) were prepared. After some experimentation, it was discovered that heating each of these substances in refluxing xylene in the presence of suspended NH_4Cl afforded greater than 90% yields of pyrrolines 13a and 13b. It should be noted that 13 serves as a relatively stable equivalent synthon for the corresponding unstable unsubstituted endocyclic enamine 14 which is notoriously unstable[5] and rapidly undergoes oligomerization reactions. Armed with these encouraging results, we focused our attention on utilizing this methodology to generate functionalized indolizidine and pyrrolizidine nuclei. Thus, imine 12c was secured from aldehyde 11 and the corresponding known[6] ketal amine (95%). Rearrangement of this substance as described above afforded pyrroline 13c (88%) which was treated with methanolic HCl to induce cyclization to indolizidine 15a (90%). Having served its ordained mission to stabilize endocyclic enamine 13, the sulfur moiety was now removed with Raney-nickel to provide ketal 15b (85%). Hydrolysis of 15b afforded the known ketone 16 (picrate: mp 197-198°, lit[7] mp 198-200°). Finally, Wolff-Kishner reduction of 16 yielded (±)-δ-coniceine (5, bp 161°, lit[8] bp 161°, picrate: mp 230-231°, lit[9] mp 233-234°; mass spectrum calcd for 125.1204, found 125.1205).



The total synthesis of (±)-isoretronecanol (3) was executed in almost precisely the same manner. Imine 12d was prepared from aldehyde 11 and the corresponding acetal amine which is available commercially. Rearrangement to 13d proceeded as before, as did cyclization to pyrrolizidine 17a. Although the relative stereochemistry of 17a remains uncertain, its reduction to 17b with lithium aluminum hydride and subsequent Raney-nickel desulfurization afforded (±)-isoretronecanol (3) contaminated with less than 4% of the isomeric trachelanthamidine (3) as determined by gas chromatography.[10] Thus, the synthesis is highly stereoselective. The structure of 3 was confirmed further by preparation of picrate and picrolonate salts and comparing them with authentic[11] samples. In each case no mp depression was observed. Once again, the overall yield of this seven-stage synthesis was a respectable 35%. These results clearly strengthen further the utility of the cyclopropylimine rearrangement and pave the way for further exploitation.

Acknowledgments. We are indebted to the National Science Foundation and The Robert A. Welch Foundation for financial support.

References and Notes

(1) For a recent review see F. L. Warren, "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, p. 246. Cf. also J. E. Saxton in "The Alkaloids" (Specialist Periodical Reports), The Chemical Society, London, Vol. 1-5.

(2) For recent reviews see V. A. Snieckus in "The Alkaloids," Ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, Vol. 1-5.

(3) For Part XI in this series see R. V. Stevens, P. M. Lesko, and R. Lapalme, J. Org. Chem., 40, 3495 (1975) and references cited therein.

(4) The structures of all new compounds in this paper are supported by IR, ^{1}H NMR, and low resolution mass spectral data and, of course, by the success of the syntheses.

(5) Cf. O. Červinka in "Enamines," Ed. A. G. Cook, Marcel Dekker, New York, N. Y., 1969, Chapter 7.

(6) A. M. Islam and R. A. Raphael, J. Chem. Soc., 3152 (1955).

(7) F. Lions and A. M. Willison, J. Proc. Roy. Soc. N. S. Wales, 73, 240 (1940); Chem. Abstr., 34, 5841 (1940).

(8) E. Lellman, Ann., 259, 193 (1890).

(9) R. Lukeš and Z. Veselý, Coll. Czech. Chem. Comm., 24, 944 (1959).

(10) O. Červinka, K. Pelz, and I. Jirkovsky, ibid., 26, 3116 (1961).

(11) N. J. Leonard and T. Sato, J. Org. Chem., 34, 1066 (1969) and references cited therein. We are most grateful to Professor Leonard for providing us with authentic examples of these substances.