New Synthetic Approaches to Isoquinoline Alkaloids. (±)Laudanosine (1)

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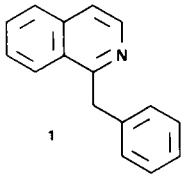
Sir:

The hypothesis that the 1-benzylisoquinolines (**1**) occupy a central place in the biogenetic sequence of structurally diverse isoquinoline alkaloids has been substantiated by recent biosynthetic studies. We sought a convenient synthesis of an intermediate with the essential carbon skeleton of the 1-benzylisoquinolines and, with the addition of a carbon, is common also to the protoberberine (**2**) and the benzo[*c*]phenanthridine alkaloids (**3**) among others. The requisite structure is provided by compound **5**, and the preparation of **5** and its conversion to some isoquinoline derivatives is the subject of this communication.



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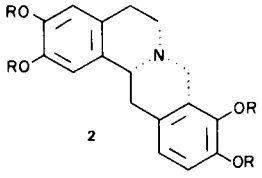

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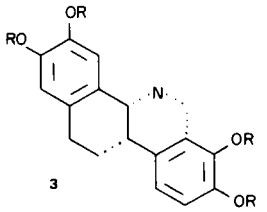
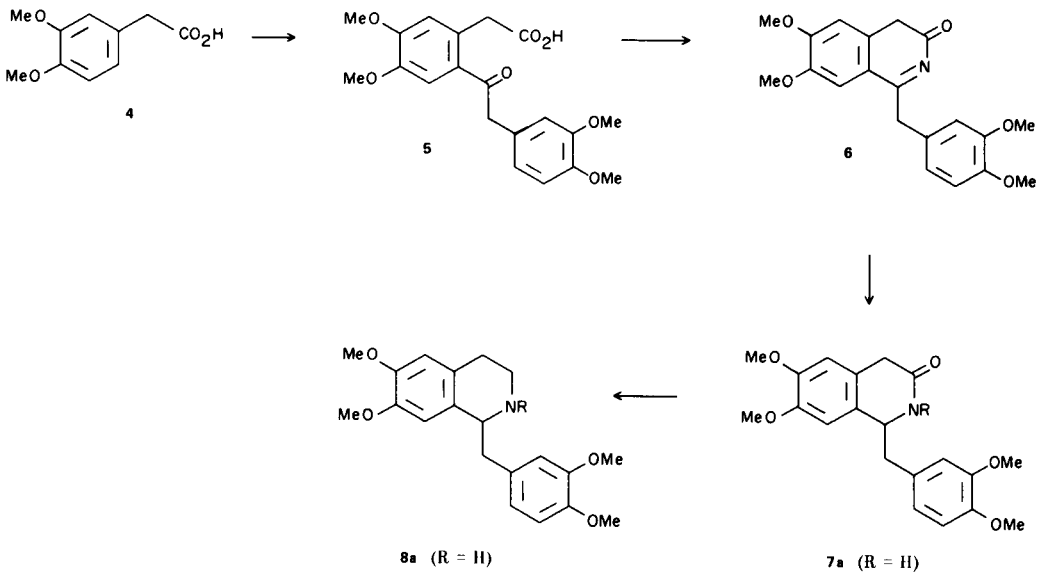


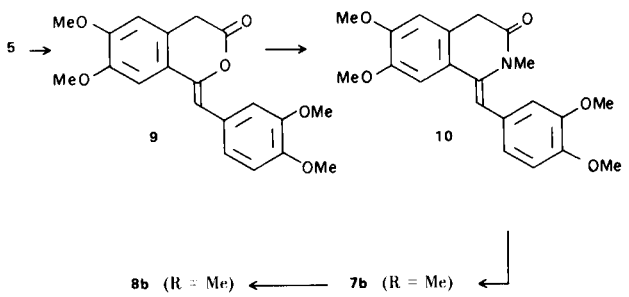
3

Intermolecular acylation between two molecules of 3,4-dimethoxyphenylacetic acid (**4**) in polyphosphoric acid at room temperature for 24 hours afforded 2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxyphenylacetic acid (**5**), m.p. 153-154°, in 60% yield. Structure proof of the keto acid (**5**) was obtained from the infrared and nmr spectra and by new syntheses of 1,2,3,4-tetrahydropapaverine (**8a**) and (±)laudanosine (**8b**) as outlined in Schemes I and II.

SCHEME I



SCHEME II



The keto acid (**5**) was heated with ammonium acetate in acetic acid, and the reaction mixture was diluted with water to precipitate the 3-isoquinolone derivative (**6**), m.p. 228-230°. Hydrogenation of **6** over platinic oxide afforded the amide (**7a**), m.p. 156-157°, and borane-THF solution readily reduced **7a** to 1,2,3,4-tetrahydropapaverine (**8a**) identified as the hydrochloride by direct comparison with a sample prepared by the usual Bischler-Napieralski route (2).

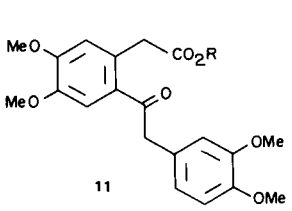
Although tetrahydropapaverine can be converted to (±)laudanosine (**8b**) (2) a new total synthesis of laudanosine was achieved (Scheme II) by a parallel route from the keto acid (**5**). The *N*-methyl-3-isoquinolone derivative (**10**) could be prepared directly from **5** by heating with methylamine in diethylene glycol, but **10** was better prepared in a purer state by a room temperature reaction of methylamine with 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-3-isochromanone (**9**), m.p. 166-167°, which in turn was produced in 80% yield by heating **5** in decalin at 190° for 0.5 hours. The remainder of the synthesis was similar to that for tetrahydropapaverine. The intermediate amide (**7b**), m.p. 148-149°, was reduced by borane-THF, and the product was identical with authentic (±)laudanosine (3).

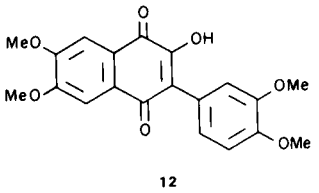
A similar approach to the papaverine alkaloids was attempted earlier using the keto ester (**11**, R = Me) prepared in a conventional Friedel-Crafts reaction (4). In the projected isoquinoline synthesis, **11** was allowed to react with ammoniacal alcohol, but the actual product was 2-hydroxy-3-(3,4-dimethoxyphenyl-6,7-dimethoxy-1,4-naphthaquinone (**12**). We converted **5** to the ethyl ester (**11**, R = Et) and confirmed this behavior of the ester under basic conditions; however, **11** with the ammonium acetate-acetic acid combination yielded **6**.

The problem of the proper tautomeric forms for the isoquinolone derivatives (**6** and **10**) and the 3-isochromanone compound (**9**) has been the subject of numerous papers (5), and a discussion of and evidence for the proposed constitutions of these particular examples of these ring systems will be given in the more detailed paper.

A recent publication reports the syntheses of **5** and **6** (6).

Satisfactory analytical and spectral data have been obtained for all compounds reported.





REFERENCES

(1) Presented in part at the 1st International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, June, 1967 and at the 2nd International Congress of Heterocyclic Chemistry, Montpellier, France, July, 1969.

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(5) See *inter alia:* (a) J. M. Holland and D. W. Jones, *J. Chem. Soc.* (C), 536 (1970); (b) D. A. Evans, G. F. Smith and M. A. Wahid, *J. Chem. Soc.* (B), 590 (1967); (c) T. Kametani, H. Iida and C. Kibayashi, *J. Heterocyclic Chem.*, 6, 61 (1969); (d) N. J. Murk and H. Tieckelmann, *Tetrahedron Letters*, 1209 (1970); (e) N. Bodor, M. J. S. Dewar and A. J. Harget, *J. Am. Chem. Soc.*, 92, 2921 (1970).

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