Application of the Pictet–Spengler Condensation in Enantioselective Synthesis of Isoquinoline Alkaloids

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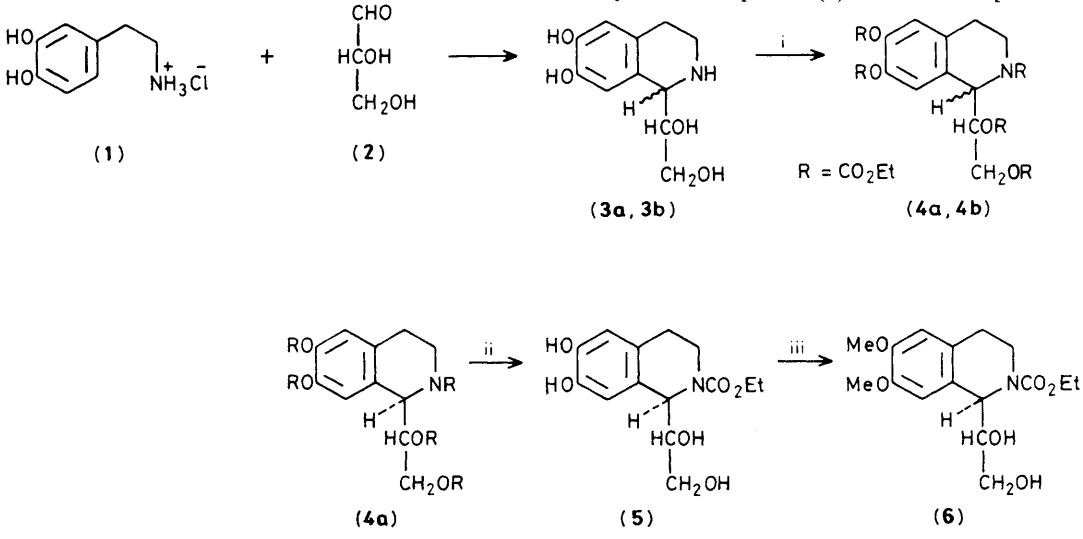
The reaction of dopamine hydrochloride and (*R*)-(+)-glyceraldehyde affords a condensation product which is a useful intermediate in the enantioselective synthesis of isoquinoline alkaloids.

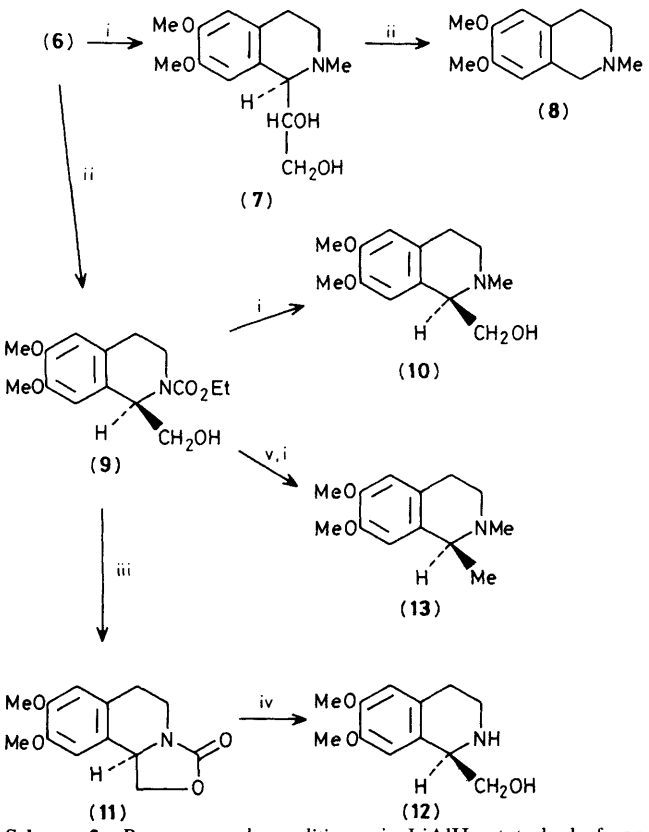
The Pictet–Spengler condensation of biogenic amines with carbonyl compounds has been widely used as a synthetic tool of importance in the preparation of a variety of isoquinoline and β-carboline systems.[1] Many isoquinoline, as well as indole, alkaloids have been synthesized using this reaction.[1—3] Recently it was found[4] that sugars and their derivatives could be used as starting materials in Pictet–Spengler condensations; a salient feature of these reactions was the asymmetric induction at C-1 of the tetrahydroisoquinoline ring system, an attribute of potential utility in total syntheses of natural products. In this communication we report a highly enantioselective synthesis of simple isoquinoline alkaloids *via* the condensation of dopamine hydrochloride (**1**) and (*R*)-(+)-glyceraldehyde (**2**); the method may be elaborated and extended to the synthesis of more complex alkaloids of the same family.

The reaction of (**1**) and (**2**) in boiling methanol gave a mixture of diastereoisomers, (**3a**) and (**3b**), in 93% yield in a 9:1 ratio. Treatment of the mixture with an excess of ethyl chloroformate afforded the corresponding carbonates from which the major component (**4a**) was isolated in 59% yield {$[\alpha]_D^{23}$ + 76.4° (*c* 1.61 in $CHCl_3$)}. Mild ammonolysis of (**4a**) afforded (**5**) in 98% yield. Methylation of (**5**) using methyl iodide and potassium carbonate gave (**6**) in 87% yield {$[\alpha]_D^{23}$ + 72.8° (*c* 1.03 in $CHCl_3$)} (Scheme 1).

Compound (**6**) was transformed into the simple alkaloid systems using a series of oxidation and reduction reactions (Scheme 2). In an attempt to prepare *N*-methylcalycotomine (**10**), compound (**6**) was converted, using lithium aluminium hydride, into (**7**) which was oxidized with sodium periodate and the product was treated, without isolation, with sodium borohydride; compound (**8**)[5] was formed [in 58% yield from



Scheme 1. *Reagents and conditions:* i, $ClCO_2Et$, H_2O, NaOH, CH_2Cl_2, room temperature, 1 h; ii, MeOH, aq. NH_3, 10 °C, overnight; iii, MeI, K_2CO_3, acetone, reflux temperature.



Scheme 2. *Reagents and conditions:* i, $LiAlH_4$, tetrahydrofuran (THF), reflux temperature, 1 h; ii, $NaIO_4$, MeOH, 3—5 °C, then $NaBH_4$; iii, 10% KOH in MeOH, reflux temperature, 2 h; iv, 10% NaOH in EtOH, reflux temperature, 6 h; v, *p*-$MeC_6H_4SO_2Cl$, pyridine, 5 °C, 12 h.

(**6**)] presumably because of overoxidation at C-1. In contrast, cleavage of the glycol system in (**6**) proceeded smoothly and, after reduction with sodium borohydride, the *N*-ethoxycarbonyl derivative (**9**) was obtained in 85% yield {$[\alpha]_D^{23}$ + 88.3° (*c* 2.83 in $CHCl_3$)}; treatment of (**9**) with lithium aluminium hydride afforded the desired (*R*)-(−)-*N*-methylcalycotomine (**10**) in 89% yield {$[\alpha]_D^{23}$ −37.1° (*c* 0.50 in $CHCl_3$)}. (−)-Calycotomine (**12**) itself was prepared by treatment of (**9**) with potassium hydroxide in methanol to give the oxazolo[4,3-*a*]isoquinoline (**11**)[6] in 98% yield {$[\alpha]_D^{23}$ −154.3° (*c* 0.94 in $CHCl_3$)} which, when subjected to the conditions of Kano *et al.*[6a] (10% NaOH in ethanol, reflux, 6 h), afforded (−)-calycotomine (**12**) in 95% yield {$[\alpha]_D^{23}$ −28.9° (*c* 1.05 in H_2O)}. The optical purity of (**12**) based upon the published data[7] is ~80% and the enantiomeric excess (e.e.) is ~90%. The *N*-ethoxycarbonyl derivative (**9**) was transformed also into (*S*)-(−)-carnegine (**13**); (±)-carnegine is the major alkaloid of the giant cactus, *Carnegiea gigantea*.[8] The *O*-tosyl derivative of (**9**) was prepared and treated with lithium aluminium hydride to afford (**13**) in 86% yield {$[\alpha]_D^{23}$ −48.3° (*c* 1.05 in C_6H_6), $[M]_D^{23}$ −106.7°}. The optical purity of the sample of carnegine based upon the published[8] value {$[M]_D^{23}$ −110°} is 97% and the e.e. is 98.5%.

All of the compounds were homogeneous on t.l.c. in several solvent systems and the mass (electron impact and chemical ionisation) and ^1H n.m.r. spectral data were consistent with the assigned structures.

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References

1 T. Kametani and K. Fukumoto, in 'The Chemistry of Heterocyclic Compounds. Isoquinolines,' ed. G. Grethe, Wiley, New York, 1981, vol. 50, part 1, p. 170.
2 M. Shamma, 'The Isoquinoline Alkaloids, Chemistry and Pharmacology,' Academic Press, New York, 1972; M. Shamma and J. L. Moniot, 'Isoquinoline Alkaloid Research 1972—1977,' Plenum Press, New York, 1978.
3 W. I. Taylor, 'Indole Alkaloids,' Plenum Press, New York, 1966.
4 D. B. MacLean, W. A. Szarek, and I. Kvarnström, *J. Chem. Soc., Chem. Commun.*, 1983, 601; I. M. Piper, D. B. MacLean, I. Kvarnström, and W. A. Szarek, *Can. J. Chem.*, 1983, **61**, 2721.
5 J. Knabe, *Arch. Pharm.*, 1959, **292**, 652.
6 (a) For details of the racemic modification, see S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, *Chem. Lett.*, 1985, 1475; (b) see also, S. Kano, Y. Yuasa, and S. Shibuya, *Heterocycles*, 1985, **23**, 395.
7 A. Brossi and F. Burkhardt, *Helv. Chim. Acta*, 1961, **44**, 1558.
8 S. D. Brown, J. E. Hodgkins, J. L. Massingill, Jr., and M. G. Reinecke, *J. Org. Chem.*, 1972, **37**, 1825.