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A NEW SYNTHESIS OF THE PROTOBERBERINE SYSTEM

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Abstract: The reaction of phthalide anions with 3,4-dihydroisoquinolines yields 13-hydroxy-8-oxotetrahydroprotoberberines with the hydrogen atoms at C-13 and C-14 trans to one another; reduction of the lactams yields the corresponding 13-hydroxytetrahydroprotoberberines.

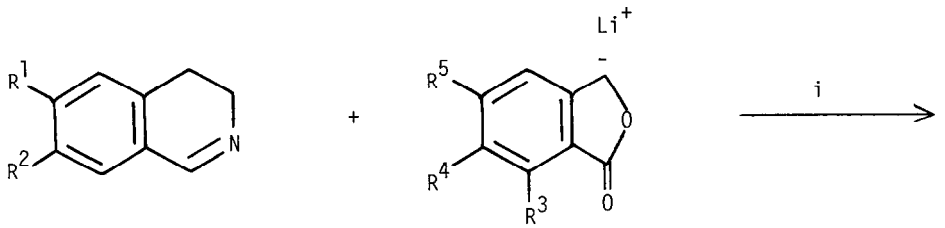
The protoberberine system has been synthesised in many different ways and there are several reviews that outline the various approaches to this class of alkaloids[1-4]. Here we report a new and convergent synthesis of the protoberberine ring system from 3,4-dihydroisoquinolines 1 and phthalide anions 2.

As part of a continuing investigation of the reactions of anions with imines and iminium salts[5,6] we have found that imines 1 react with anions 2 yielding 13-hydroxy-8-oxotetrahydroprotoberberines 3 in good yield as shown in Scheme 1. The latter may be converted by hydride reduction to 13-hydroxytetrahydroprotoberberines 4 in which the hydrogen atoms at C-13 and C-14 are trans to one another in ring C. The relative configuration of the OH group is epimeric to that found in the naturally occurring 13-hydroxytetrahydroprotoberberines, ophiocarpine[4] and 13-hydroxystylopine[7].

In a typical procedure n-BuLi was added dropwise over 5 min to a solution of diisopropylamine in THF (freshly distilled from sodium/benzophenone) at 0°C. After ca. 10 min the solution was cooled to -70°C and the phthalide 2b in THF added dropwise over 10 min yielding an orange solution of the anion. This was warmed to -40°C over 0.5 h and the imine 1b, in THF, added dropwise. (The imines and phthalides used in this study were prepared by conventional procedures[5,6]). The mixture was kept at -40°C for 1 h, allowed to warm to ca. 20°C, and kept there overnight. All operations were carried out under an argon atmosphere and additions made by syringe through serum stoppers. The neutral fraction obtained on work-up crystallized on treatment with ethyl acetate yielding 3c as a colorless solid (32%). The mother liquors, on flash chromatography[8] with ethyl acetate, gave an additional sample of 3c (33%) and other products not yet identified. Conversion of 3c to 4c ((±)-epiophiocarpine) was effected in 85% yield by reduction with $LiAlH_4$ in boiling THF for 8 h.

Compounds 3b[9], 4b[9,10a] and 4c[10a-e] are described in the literature. Noteworthy are the ^1H and ^{13}C nmr spectra reported for 4c[10e] and the ^1H nmr spectrum of 4b[10a] which are in accord with our observations. The trans relationship of the hydrogen atoms at C-13 and C-14 in 4a-4c is apparent from the coupling constants of these hydrogens: 4a, $J_{13,14}$ = 8.4 Hz; 4b, $J_{13,14}$ =

SCHEME 1[15]



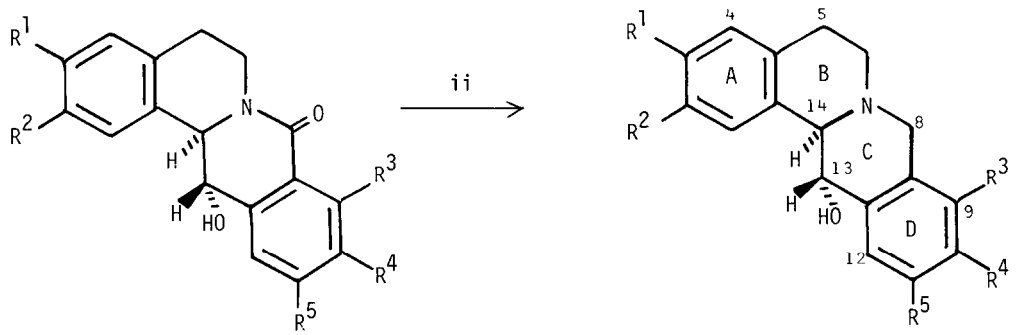
1a $R^1=R^2=OCH_3$

1b $R^1+R^2=OCH_2O$

2a $R^3=R^4=R^5=H$

2b $R^3=R^4=OCH_3$; $R^5=H$

2c $R^3=H$; $R^4=R^5=OCH_3$



3

4

3a and 4a $R^1=R^2=OCH_3$; $R^3=R^4=R^5=H$

3b and 4b $R^1=R^2=R^4=R^5=OCH_3$; $R^3=H$

3c and 4c $R^1=R^2=OCH_2O$; $R_3=R_4=OCH_3$; $R_5=H$

(i) THF, -40°C, keep at -40°C for 1 h, then warm to 20°C for 12 h

(ii) $LiAlH_4$, THF, reflux, 8 h

N.B. Phthalide anions were prepared from the corresponding phthalide and LDA in THF Compounds 3 and 4 were obtained as racemates.

8.1 Hz; 4c, $J_{13,14}$ = 8.4 Hz. By inference the same stereochemistry may be assigned to 3a-3c since hydride reduction would not be expected to affect the configuration at C-13 and C-14.

The high degree of stereoselectivity in this reaction implies that the two components must interact in an "endo" relationship with respect to each other in the formation of the bonds between C-13 and C-14 and between N and C-8. We were unable to isolate any compounds epimeric at C-13 but cannot at this time rule out their formation or their presence in small amounts in the unidentified components.

The reaction reported here has some similarities to the related condensation of imines with homophthalic anhydrides[11,12] and the unrelated condensation of α,β-unsaturated carbonyl compounds with phthalide anions[13].

The conversion to protoberberines of the 13-hydroxy derivatives has already been reported[4,10a,14]. The extension of this reaction to other systems and other aspects of this reaction are currently under investigation.

Acknowledgements

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15. Relevant physical data for compounds 3 and 4 are given below. The composition of new compounds is supported by combustion or high resolution mass spectral analysis. All ^1H nmr spectra were run on a Bruker WM 250 spectrometer, using $CDCl_3$ as solvent and TMS as internal standard.

Compound 3a exhibits m.p. 180-1°C (EtOH-pet. ether 30-60°); $\nu_{max}(CHCl_3)$ 1645 cm^{-1}; ^1H nmr δ 8.06 (1H, d, J = 7.7 Hz, C-9 H), 7.68 (1H, d, J = 7.7 Hz, C-12 H), 7.57 (1H, t, J = 7.7 Hz, C-11 or C-10 H), 7.43 (1H, t, J = 7.7 Hz, C-10 or C-11 H), 6.98 (1H, s, C-1 H), 6.72 (1H, s, C-4 H), 4.9-5.0 (1H, m, C-6 H,eq.), 4.6-4.7 (2H, distorted s, C-13 and C-14 H's), 3.88 (3H, s, -OMe), 3.86 (3H, s, -OMe), 2.7-3.0 (3H, m, C-5 H's and C-6 H, ax.); ms m/e (%) 325 (8) M^+, 192 (100), 134 (10). C-10 H and C-11 H are apparent triplets.

Compound 3c exhibits m.p. 205-6°C (EtOAc); ν_{max} $(CHCl_3)$ 1650 cm^{-1}; ^1H nmr δ 7.35 (1H, d, J = 8.4 Hz, C-12 H), 7.07 (1H, d, J = 8.4 Hz, C-11 H), 6.82 (1H, s, C-1 H), 6.70 (1H, s, C-4 H), 5.93-5.95 (2H, m, $-OCH_2O-$), 5.0-5.1 (1H, m, C-6 H,eq.), 4.4-4.5 (2H, m, C-13 and C-14 H's), 3.99 (3H, s, -OMe), 3.89 (3H, s, -OMe), 2.7-2.85 (3H, m, C-5 H's and C-6 H, ax.); ms m/e (%) 369 (1) M^+, 194 (9), 176 (100).

Compound 4a exhibits m.p. 162-4°C (CH_2Cl_2-pet. ether 30-60°); ν_{max} $(CHCl_3)$ 2850-2750 cm^{-1} (Bohlmann bands); ^1H nmr δ 7.57 (2H, broad s, C-1 and C-12 H's), 7.2-7.35 (2H, m, C-10 and C-11 H's), 7.11 (1H, d, J = 7.0 Hz, C-9 H), 6.65 (1H, s, C-4 H), 4.78 (1H, d, J = 8.4 Hz, C-13 H), 3.91 (6H, s, 2 x OMe), 3.90 (2H, s, C-8 H's), 3.55 (1H, d, J = 8.4 Hz, C-14 H), 3.0-3.2 (2H, m, C-6 H's), 2.65-2.8 (2H, m, C-5 H's); ms m/e (%) 311 (4) M^+, 192 (100), 120 (22).

Compound 3b has m.p. 208-10°C (EtOH-pet. ether 30-60°C) (lit. m.p. 210-12°C)[9]; ν_{max} $(CHCl_3)$ 1640 cm^{-1}; ^1H nmr δ 7.58 (1H, s, C-9 H), 7.17 (1H, s, C-12 H), 6.98 (1H, s, C-1 H), 6.73 (1H, s, C-4 H), 4.85-4.95 (1H, m, C-6 H, eq.), 4.5-4.7 (2H, m, C-13 and C-14 H's), 3.97 (3H, s, -OMe), 3.94 (3H, s, -OMe), 3.88 (3H, s, -OMe), 3.87 (3H, s, -OMe), 2.7-3.0 (3H, m, C-5 H's and C-6 H, ax.); ms m/e (%) 385 (3) M^+, 194 (8), 192 (100).

Compound 4b has m.p. 157-9°C (CH_2Cl_2-pet. ether 30-60°C) (lit. m.p. 158-60°C[10a], 197-9°C[9]); ν_{max} $(CHCl_3)$ 2850-2750 cm^{-1} (Bohlmann bands); ^1H nmr δ 7.58 (1H, s, C-1 H), 7.08 (1H, s, C-12 H), 6.65 (1H, s, C-4 or C-9 H), 6.59 (1H, s, C-9 H or C-4 H) 4.74 (1H, d, J = 8.1 Hz, C-13 H), 3.90 (12H, s, 4 x OMe), 3.82 (2H, s, C-8 H's), 3.51 (1H, d, J = 8.1 Hz, C-14 H), 3.0-3.2 (2H, m, C-6 H's), 2.65-2.8 (2H, m, C-5 H's); ms m/e (%) 371 (1) M^+, 192 (100), 180 (38).

Compound 4c has m.p. 177-9°C (EtOAc) (lit. m.p. 178-9°C[10b], 181-3°C[10c]), and shows ir, ^1H nmr, ^{13}C nmr, ms and tlc behaviour in agreement with literature data and with an authentic sample.

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