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ALKALOIDS OF *PAPAVER BRACTEATUM*: 14-β-HYDROXYCODEINONE, 14-β-HYDROXYCODEINE AND *N*-METHYLCORYDALDINE*

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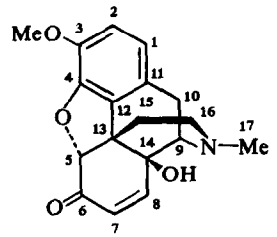
Key Word Index—*Papaver bracteatum*; Papaveraceae; alkaloids; 14-β-hydroxycodeinone; 14-β-hydroxycodeine; *N*-methylcorydaldine.

Abstract—Three new alkaloids have been identified from *Papaver bracteatum*, 14-β-hydroxycodeinone, 14-β-hydroxycodeine and *N*-methylcorydaldine. The presence of alpinigenine was also confirmed.

INTRODUCTION

The species *Papaver bracteatum* Lindl. var. 'Arya I', a native of Iran [1], is considered as a new plant source of opiates [2]. Previous studies have demonstrated the presence of the morphinane alkaloids thebaine [3], codeine [4], neopine [4], oripavine [5], salutaridine [6] and, recently, the isomeric *N*-oxides of thebaine [7]. We now wish to report on the isolation and structural elucidation of two new morphinane alkaloids, not previously found as naturally occurring substances: 14-β-hydroxycodeinone (1) and 14-β-hydroxycodeine (2). The previously reported detection of oripavine and salutaridine could not be reproduced (see Experimental). The presence of the Papaver alkaloid *N*-methylcorydaldine [8] (3) was unequivocally demonstrated by comparison with a reference sample. Furthermore, alpinigenine (4), already reported [9] to be present in *P. bracteatum* was isolated.



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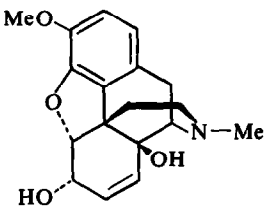

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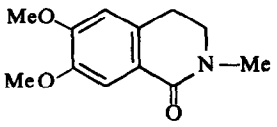

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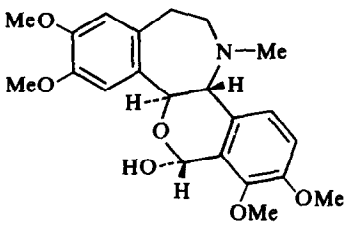

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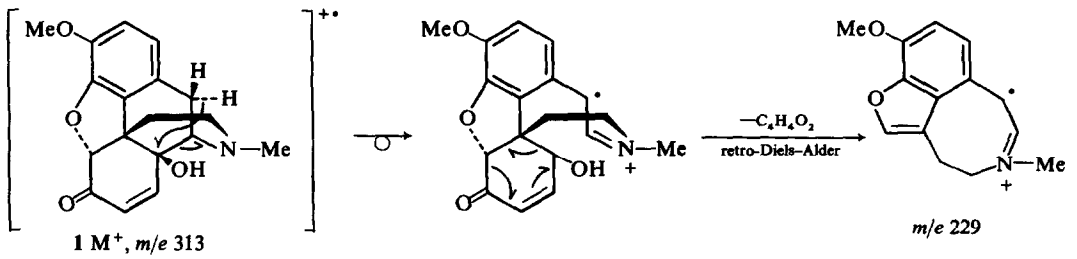
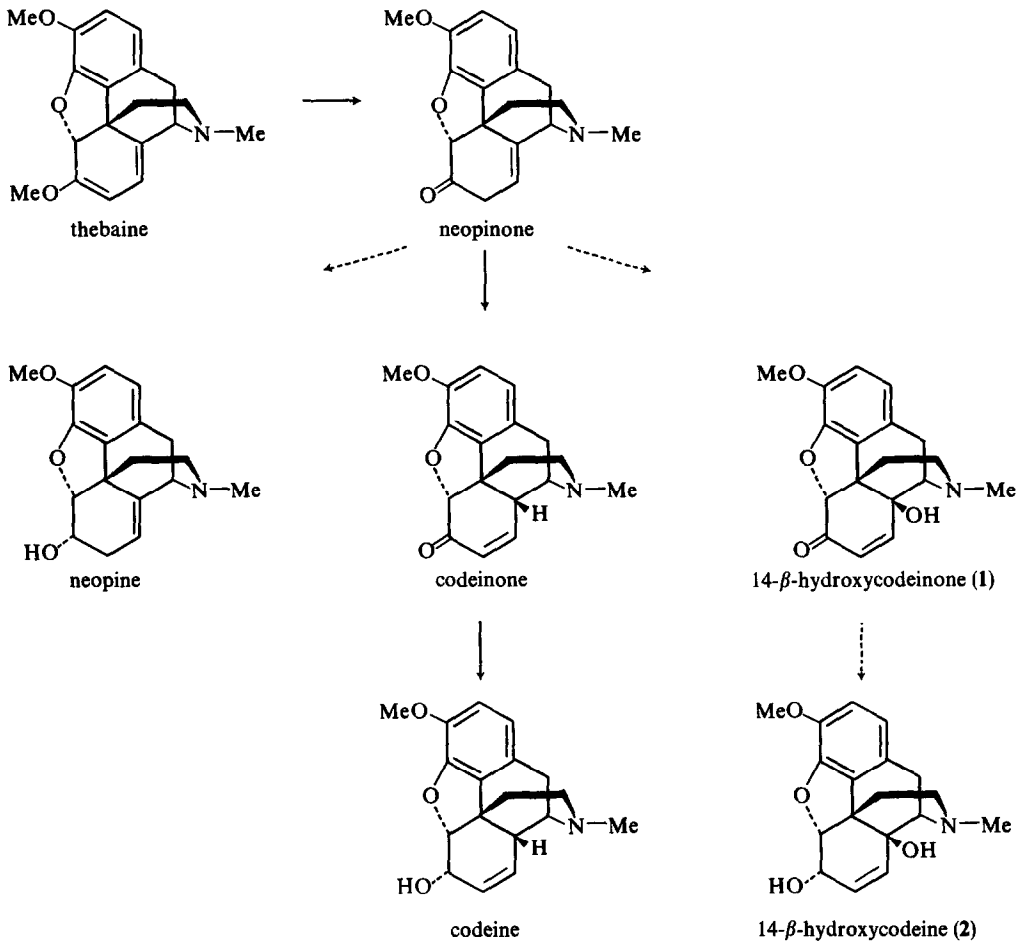


1 M^+, *m/e* 313

m/e 229

*Part 4 in a series; for Part 3 see ref. [4].



RESULTS AND DISCUSSION

After initial countercurrent fractionation of the crude acetic acid extract, 14-β-hydroxycodeinone (1) and 14-β-hydroxycodeine (2) were obtained from countercurrent fractions 15–30 [4] by chromatography on silica gel columns. The presence of *N*-methylcorydaldine (3) in fractions 99–127 was demonstrated by comparison with a reference sample, using a GC–MS computer combination for analysis. Alpinigenine (4) was obtained from the same countercurrent fraction by elution from silica gel columns.

14-β-Hydroxycodeinone (1) was obtained in very small amounts as a pale yellow oil. The MS of 1 showed a M^+ at *m/e* 313.131 ($C_{18}H_{19}NO_4$) and a prominent fragment ion at *m/e* 229.110 ($C_{14}H_{15}NO_2$).

This fragmentation, in full agreement with earlier observations [10], strongly suggested that formula 1 represented the correct structure for the isolated compound. Therefore, thebaine was oxidized by hydrogen peroxide in glacial acetic acid [11] and the product, identified by PMR [(90 MHz, $CDCl_3$): δ 4.70 (1H, *s*, H-5β), 6.15 (1H, *d*) and 6.62 (1H, *d*) ($J_{7,8}$ = 10 Hz, H-7 and H-8)] was identical (GLC and GC–MS) with the natural alkaloid. This is the first report of 14-β-hydroxycodeinone as a naturally occurring alkaloid.

The second new morphinane alkaloid to be reported here, 14-β-hydroxycodeine (2), was obtained as slightly yellow crystals. The important features to note in the PMR spectrum (see Experimental) are the presence of the strong broad signal for the two OH protons, and the pattern, obtained for the ring C protons, in full accordance to literature data [12]. The MS of 2 had a M^+ at *m/e* 315.147 ($C_{18}H_{21}NO_4$) and a prominent peak at *m/e* 229.110 ($C_{14}H_{15}NO_2$), in full agreement with retro-Diels–Alder fragmentation of ring C, as for 14-β-hydroxycodeinone. Synthetic 14-β-hydroxycodeine, prepared from 14-β-hydroxycodeinone, was identical in all aspects (PMR, GLC, GC–MS) with the natural product.

This first report of 14-β-hydroxycodeine as a naturally occurring alkaloid, accompanied by small amounts of 14-β-hydroxycodeinone, reveals a new biosynthetic pathway. A possible route for biosynthetic formation of these new Papaver alkaloids could be from thebaine through neopinone as well as the known compounds codeine and neopine.

A low MW alkaloid, *N*-methylcorydaldine (3), was identified by comparison with a reference sample, prepared by oxidation of laudanosine. The GLC and GC–MS characteristics of synthetic *N*-methylcorydaldine were in agreement with those of the natural product, and

with the literature data [13] for *Thalictrum fendleri* Engelm. ex Gray (Ranunculaceae) species. This alkaloid has already been reported as a constituent of *Papaver urbanianum* Fedde species [8].

Isoquinolones are supposed to originate in the plant by oxidation of benzylisoquinolines [14]. However, since tetrahydroisoquinolines, like corypalline, also occur in the *Papaveraceae* it also seems probable that isoquinolones are formed in the plant by enzymatic oxidation of tetrahydroisoquinolines.

EXPERIMENTAL

General procedures. GC–MS was effected using a modified instrument with a double stage jet separator and a 200 × 0.2 cm glass column with He carrier gas. The stationary phase was 3% OV-17 on Chromosorb G and the column temp. was 260°. For screening procedures GC–MS was carried out using a capillary GLC (45 m glass column, i.d. 0.5 mm, coated with SE-30, column temp. 225°, carrier gas He 5 ml/min) directly coupled to a single focussing mass spectrometer connected to a spectrosystem. The scan speed was 2.3 sec/decade; mass range 20–620. Between scans 0.3 sec was allowed for correction of the hysteresis of the magnet.

PMR spectra were obtained using a 90 MHz spectrometer; the solvent was $CDCl_3$ and TMS the internal standard. GLC was carried out on 3% OV-17 on Chrompack SA, column temperature 270°.

TLC was on Si gel GF 254 plates using EtOAc–Et_2NH (19:1). Alkaloid detection was accomplished using iodoplatinate reagent and UV light (254 nm).

Plant extraction. Capsules of *P. bracteatum* cv "Arya I", cultivated by Franco-Pavot Industries, France, were extracted by aq. HOAc, and the crude extract was submitted to countercurrent fractionation, as earlier reported [4].

Isolation and purification of 14-β-hydroxycodeinone (1) *and 14-β-hydroxycodeine* (2). Counter-current fractions 15–30 [4] were separated by column chromatography on Si gel G (type 60) for TLC. Elution was carried out using toluene–EtOAc mixtures, with increasing EtOAc content. Using pure EtOAc first 15.3 mg pure 2 was eluted, and then a mixture of 1 and 2. This mixture was separated on a column of the same type, eluted with EtOAc–Et_2NH (39:1), yielding 3 mg of 1.

14β-Hydroxycodeine (2). PMR (90 MHz, $CDCl_3$): δ 2.40 (3H, *s*, N—Me), 3.61 (2H, broad, C-6 and C-14 O—H), 3.83 (3H, *s*, C-3 O—Me), 4.67 (1H, *m*, C-6), 4.88 (1H, *d*, J = 6 Hz, C-5), 5.48 (1H, *dd*, J = 3 Hz, J = 10 Hz, C-8), 5.92 (1H, *d*, J = 10 Hz, C-7), 6.54, 6.67 (2H, AB pattern, J = 9 Hz, C-1 and C-2).

Isolation and identification of alpinigenine (4). Counter-current fractions 99–127 [4] were eluted from a Si gel column, using increasing portions of EtOAc in toluene, in order to remove thebaine from alpinigenine. The fractions, containing alpinigenine, were combined, and eluted from a column of the same type, using n-hexane–Et_2NH (19:1). The obtained pure alpinigenine was identified by comparison of PMR and MS (probe) to the spectra recorded in the lit. [9, 15].

Chromatographic and MS data. N-*methylcorydaldine*: R_f 0.65, RR_t (thebaine) = 0.27, *m/e* (%): 222 (14), 221 (71), 220 (10), 179 (13), 178 (88), 163 (8), 151 (12), 150 (100), 135 (12), 110.5 (9), 107 (8), 92 (11), m at *m/e* 126.5 (178 → 150) and 143.5 (221 → 178) [13]. *14-β-hydroxycodeinone*: R_f 0.64, RR_t 1.1, *m/e* (%): 314 (23), 313 (100), 270 (9), 257 (9), 256 (12), 230 (20), 229 (65), 214 (30), 188 (28), 156.5 (1.3). *14-β-hydroxycodeine*: R_f 0.58, RR_t 0.9, *m/e* (%): 316 (21), 315 (100), 298 (9), 286 (6), 258 (9), 243 (8), 231 (7), 230 (21), 229 (33), 216 (9), 215 (8), 214 (13), 201 (8), 189 (10), 188 (20), 187 (6), 179 (9), 175 (17), 157.5 (1). *Alpinigenine*: R_f 0.77, *m/e* (%): 402 (5), 401 (19), 383 (3), 223 (14), 222 (100), 208 (18), 207 (6), 206 (10), 200.5 (0.5), 193 (8), 180 (8), 179 (57), 178 (9).

Screening of the countercurrent fractions for oripavine and salutaridine. All countercurrent fractions were screened for the presence of the morphinane alkaloid masses of oripavine and salutaridine. Prominent peaks in the MS of oripavine and salutaridine are found, according to lit. [10, 16] at *m/e* 297, 282, 266, 254, 241, 211, 176 and at *m/e* 327, 312, 299, 284 respectively. Using mass-fragmentography the countercurrent fractions were screened for these fragments. However, these alkaloids could not be detected. The same procedure, applied for morphine (*m/e* 285, 215) and its 14-β-hydroxyanalogue (*m/e* 301) also yielded negative results.

Synthesis of 1 *from thebaine.* This synthesis was accomplished using H_2O_2 in HOAc, as recorded in ref. [11], yielding quantitatively pure *14-β-hydroxycodeinone* (identified MS and PMR).

Synthesis of 2 *from* 1. 14-β-Hydroxycodeinone (90 mg) was suspended in MeOH (5 ml) and a soln of $NaBH_4$ (50 mg) in H_2O (2 ml) was added dropwise, and the remaining soln was stirred for 2 hr at room temp. 2 N NaOH (5 ml) was added, and the soln was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried and the solvent evaporated under red. pres., yielding 79 mg 14-β-hydroxycodeine 2 (88%). The product was identified by PMR and MS.

Oxidation of laudanosine to 3. A soln of laudanosine (100 mg) in 20 ml Me_2CO was treated with 1% $KMnO_4$ in Me_2CO (5 ml) and stirred at room temp. for 4 hr. MeOH was added dropwise to decompose the excess permanganate; the mixture filtered and evaporated to dryness. The residue was extracted with Et_2O (30 ml), washed with 5% K_2CO_3 (10 ml), 2% H_2SO_4 (10 ml) and H_2O, and then dried. Evaporation of the solvent gave a quantitative yield of *N*-methylcorydaldine, identified by comparison of its PMR and MS to ref. [13].

Concentration of alkaloids. The *ca* concn of alkaloids [4] as % dry wt of capsule material are 14-β-hydroxycodeinone 0.005, 14-β-hydroxycodeine 0.025, *N*-methylcorydaldine 0.044 and alpinigenine 0.12.

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