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CORYPALLINE AND *O*-METHYLCORYPALLINE, TWO ALKALOIDS FROM *PAPAVER BRACTEATUM**

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Key Word Index—*Papaver bracteatum*, Papaveraceae, alkaloids, tetrahydroisoquinolines, corypalline, *O*-methylcorypalline, biosynthetic pathway, 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-7-ol, synthesis

Abstract—Two new *Papaver* alkaloids, corypalline and *O*-methylcorypalline, were identified from *P bracteatum* These alkaloids are considered as the biosynthetic precursors of *N*-methylcorydaldine in this plant

INTRODUCTION

Papaver bracteatum is known to contain several minor alkaloids in addition to the major alkaloid thebaine [1] In view of the possible use of this plant species as a substitute for *P somniferum*, the pharmacological activities of its alkaloids were reviewed recently [2] In a previous paper the detection of the isoquinolone alkaloid *N*-methylcorydaldine, **1**, was reported [3] Generally, isoquinolone alkaloids are thought to originate from oxidation of accompanying 1-benzylisoquinolines [4] Yet, as pointed out by us, enzymatic oxidation of simple tetrahydroisoquinolines cannot be excluded without further preface [3] Therefore, the finding of the above-mentioned isoquinolone alkaloid as a natural constituent of *P bracteatum* prompted us to perform a closer screening of extracts of this species for the possible presence of other low MW alkaloids, which might be biogenetically related to *N*-methylcorydaldine Furthermore, in early work on the alkaloids of *P bracteatum* an alkaloid of unknown structure, bractamine, was reported, and tentatively identified as an isomer of corypalline [5] Therefore, the physical data on some synthetic tetrahydroisoquinolines were compared with those reported for bractamine

RESULTS AND DISCUSSION

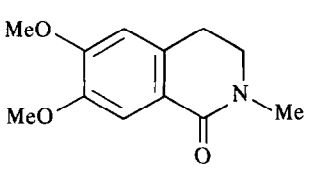
In counter-current [6] subfractions 15–24 and 25–30 traces of two low MW alkaloids, having MWs 193 and 207, respectively, were detected by GC/MS screening The mass spectrum of the MW 193 alkaloid showed a M^+ at *m/z* 193 and a prominent fragment ion at *m/z* 150, whilst in the spectrum of the other low MW alkaloid corresponding peaks were found at *m/z* 207 and 164 These data suggested retro-Diels–Alder fragmentation of the nitrogen-containing rings of tetrahydroisoquinoline alkaloids, as indicated for *O*-methylcorypalline (**2**) and corypalline (**3**) Comparison of GC R_ts and electron impact mass spectral fragmentation patterns of the natural MW 207 alkaloid and the synthetic reference compounds 7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4**) and *O*-methylcorypalline (**2**), proved the identity of the natural MW 207 alkaloid with the latter product

The structure of the MW 207 alkaloid thus having been established as *O*-methylcorypalline (**2**), the other low MW alkaloid presumably was either corypalline (**3**) or isocorypalline (**5**) Both these substances, however, proved to have virtually identical mass spectra and GC R_ts The TMSi derivatives could not be distinguished either The acetylated compounds, again exhibiting identical GC behaviour, showed, however, useful differences in their mass spectra Major differences were found in the relative intensities of the M^+ (*m/z* 235), and the fragment ions at *m/z* 234 and 176 in the mass spectra of acetylcorypalline (**6**) and acetylisocorypalline (**7**) (Table 1) In order to explain the differences observed, high resolution spectra were recorded, and the precursors of relevant fragment ions were traced using the defocusing technique of Barber and Elliot [7] The data obtained showed that the fragment ions at *m/z* 234 $[M-H]^+$ and *m/z* 176 $[M-Me\,COO]^+$ originate directly from the M^+, while the fragment ion at *m/z* 150 arises from a two-step process, involving the elimination of a ketene molecule from the M^+, yielding an ion at *m/z* 193, followed by a retro-Diels–Alder fragmentation of the nitrogen-containing ring in the latter ion These processes are similar for the isomeric compounds **6** and **7**, but result in different ion abundances The contribution to stabilization of the *p*-quinonoidal canonical form of the ion at *m/z* 234 in the mass spectrum of acetylcorypalline (**6**) is reflected in the relatively high intensity of this ion In the mass spectrum of the isomeric compound acetylisocorypalline (**7**) the lack of this type of stabilization—due to the electron-

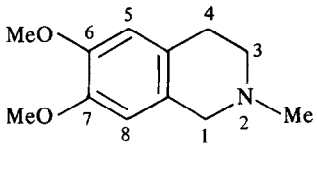
Table 1 Mass spectral data of compounds **6** and **7**

m/z	Relative intensities (%)		Intensity ratios		
	6	**7**		**6**	**7**
235	32 6	24 3	235/234	0 86	1 77
234	38 1	13 7	234/176	13 6	0 94
176	2 8	14 6			
150	100 0	100 0			

*Part 5 in the series For Part 4 see ref [3]



1



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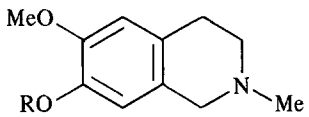
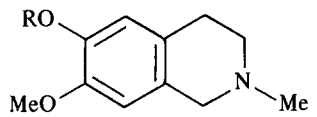
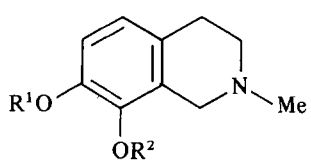


3 R = H
6 R = Ac



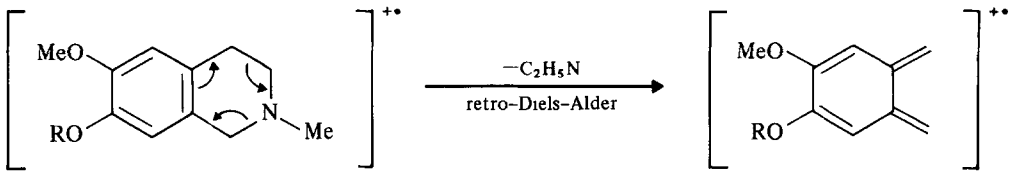
5 R = H
7 R = Ac



4 $R^1 = R^2 = Me$
8 $R^1 = Me$, $R^2 = H$
9 $R^1 = H$, $R^2 = Me$

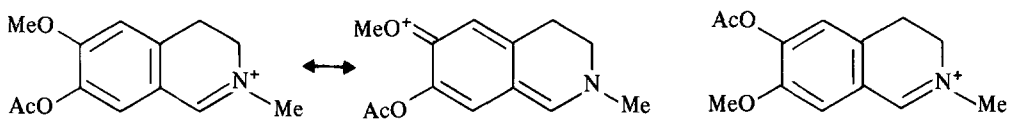
withdrawing properties of the C-6 acetyloxy function—leads to a considerably less intensive $[M - H]^+$ ion (see Scheme 1) The presence of an ion of moderate intensity at *m/z* 176 in the mass spectrum of **7** may be explained through a (multistep) proton transfer from C-4 to C-6, yielding a *p*-quinonoidal stabilized structure For **6** a corresponding C-4 → C-7 proton transfer is largely obstructed by the presence of the C-6 methoxy group It might be argued that through a C-1 → C-7 proton transfer a similar stabilization of the *m/z* 176 ion can be attained in the case of **6**, using a similar pathway, but— presumably due to the stability of the $[M - H]^+$ ion—loss of a hydrogen radical from C-1 of the latter compound is obviously favoured over the loss of an acetate radical (see Scheme 1)

A GC/MS analysis of counter-current subfraction 15–24, after complete acetylation, left no doubt as to the structure of the natural alkaloid The respective *m/z* 235/234 and *m/z* 234/176 intensity ratios were 0 87 and 8 6, in good agreement with the values observed for the synthetic reference substance **6**, indicating the presence of corypalline in the natural extract



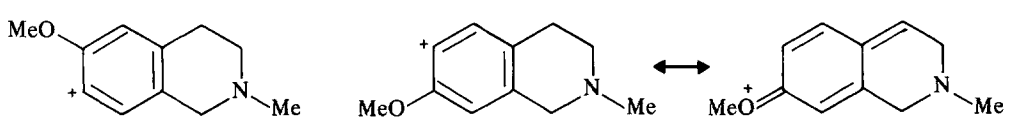
2 R = Me, M^+, *m/z* 207
3 R = H, M^+, *m/z* 193

2 R = Me, *m/z* 164
3 R = H, *m/z* 150



6 *m/z* 234

7 *m/z* 234



6 *m/z* 176

7 *m/z* 176

Scheme 1 Mass spectral fragmentation of alkaloids **2**, **3**, **6** and **7**

Previously, corypalline was identified as an alkaloid from several *Corydalis* species (Papaveraceae) [8–10], from roots of *Thalictrum dasycarpum* (Ranunculaceae) [11] and from the bark of *Doryphora sassafras* (Monimiaceae) [12] *O*-Methylcorypalline was found before as a natural alkaloid from *Nelumba nucifera* (Nymphaeaceae) seed embryo [13], from *Thalictrum polygamum* [14] and *Thalictrum dioicum* (Ranunculaceae) [15], and as a Cactaceae alkaloid [16] Therefore, this is the first report on the detection of corypalline as well as of *O*-methylcorypalline as constituents of a *Papaver* species The finding of traces of both corypalline and *O*-methylcorypalline as well as *N*-methylcorydaldine in *P bracteatum* adds strong support to our supposition that the latter alkaloid arises from enzymatic oxidation of simple tetrahydroisoquinoline alkaloids in the species, rather than from oxidation of benzylisoquinoline precursors The biosynthetic pathway therefore most likely is corypalline → *O*-methylcorypalline → *N*-methylcorydaldine

An alkaloid of unknown structure, bractamine, isolated from *P bracteatum*, has been tentatively identified as an isomer of corypalline [5] In order to add some support to the tentative identification of bractamine as an isomer of corypalline, the isomeric compounds 7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol (**8**) and 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (**9**) were prepared The latter compound was synthesized using Mannich condensation of *o*-benzyloxyphenol with formaldehyde and methylaminoacetaldehyde dimethyl acetal, followed by methylation using diazomethane, ring closure in 6 N hydrochloric acid and finally hydrogenolysis with palladium on carbon (see Experimental) Yet, judged from comparison of the mps of the corypalline isomers studied with the physical data reported for bractamine, none of these isomeric products were identical to the latter compound (see Experimental)

EXPERIMENTAL

Extraction of capsules of *P bracteatum* Lindl, var 'Arya I', cultivated by Franco-Pavot Industries, France, and counter-current separation of the extracts were performed as reported earlier [6] GC/MS and MS were recorded at 70eV ^{1}H NMR spectra were obtained at 90 MHz with TMS as int standard (δ = 0) GC was carried out on a FID instrument using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80–100 mesh), operating at 175° (system *a*), or with 3% SE-30 on Chromosorb W-HP (80–100 mesh), operating at 165° (system *b*) For GC *O*-methylcorypalline was chosen as reference (RR_t = 1 00) For silylation of samples BSTFA containing 1% TMCS (Regisil) was used in the presence of pyridine Acetylation was attained by dissolving in excess reagent (Ac_2O–pyridine–EtOAc, 1 1 1) and heating at 60° for 2 hr in a tightly closed reaction vessel Mps are corr

Detection of corypalline **3** *and O-methylcorypalline* **2** Upon GC/MS alkaloid screening traces of two alkaloids having M^+ at *m/z* 193 and 207 were detected in counter-current subfractions 15–24 and 25–30, respectively Their MS were identical to those of (iso) corypalline and *O*-methylcorypalline, respectively, by comparison with synthetic reference substances In order to distinguish between corypalline and isocorypalline as possible structures for the MW 193 alkaloid, an aliquot of counter-current subfractions 15–24 was acetylated for 2 5 hr at 60° After cooling, the reagent was removed *in vacuo*, yielding a brown syrup, which was analysed by GC and GC/MS after dilution with $CHCl_3$ The latter analysis confirmed the identity of the acetylated natural alkaloid as acetylcorypalline

Synthesis of **2** 6,7-Dimethoxyisoquinoline [17] (500 mg) was refluxed with MeI (3 ml) in MeOH (5 ml) for 6 hr Upon cooling the pptated methiodide (450 mg, 50% yield, mp 255°) was filtered off The latter product (200 mg) was stirred at room temp for 4 hr with $NaBH_4$ (60 mg) in EtOH (5 ml) and H_2O (5 ml) Extraction with $CHCl_3$ afforded *O*-methylcorypalline (**2**) (120 mg, 93%) as a colourless oil which slowly solidified ^{1}H NMR ($CDCl_3$) δ 2 43 (3H, *s*, NMe), 2 73 (4H, *m*, H-3 and H-4), 3 50 (2H, *s*, H-1), 3 84 (6H, *s*, 2 × OMe), 6 52 (1H, *s*, H-5), 6 60 (1H, *s*, H-8) GC/MS *m/z* (rel int) 208 (7), 207 (40), 206 (65), 192 (6), 190 (11), 165 (13), 164 (100), 149 (13), 121 (17)

Synthesis of 7,8-*dimethoxy-2-methyl*-1,2,3,4-*tetrahydroisoquinoline* **4** 7,8-Dimethoxyisoquinoline [17] was refluxed in C_6H_6 with excess MeI Evaporation afforded the methiodide in 100% yield The latter compound was reduced using $NaBH_4$ in H_2O and the final product **4** extracted with Et_2O ^{1}H NMR (CCl_4) δ 2 40 (3H, *s*, NMe), 2 65 (4H, *m*, H-3 and H-4), 3 49 (2H, *s*, H-1), 3 80 (6H, *s*, 2 × OMe), 6 69 (2H, *s*, H-5 and H-6) GC/MS *m/z* (rel int) 208 (11), 207 (78), 206 (91), 192 (15), 191 (8), 190 (22), 176 (11), 174 (9), 165 (13), 164 (100), 163 (14), 162 (9), 161 (6), 160 (5), 150 (11), 149 (91), 148 (13), 146 (6), 135 (9), 134 (10), 133 (5), 132 (7), 121 (20), 120 (9), 105 (9), 104 (23)

Synthesis of **3**, *isocorypalline* (**5**) *and* 7-*methoxy-2-methyl*-1,2,3,4-*tetrahydroisoquinolin*-8-*ol* (**8**) These syntheses were accomplished using the Bobbitt modification of the Pomeranz–Fritsch cyclization, as reported in ref [18] The products were identified by ^{1}H NMR and MS **3**, ^{1}H NMR (DMSO-d_6) δ 2 29 (3H, *s*, NMe), 2 60 (4H, *m*, H-3 and H-4), 3 31 (2H, *s*, H-1), 3 73 (3H, *s*, OMe), 6 44 (1H, *s*, H-5), 6 73 (1H *s*, H-8), 8 65 (1H, *brs*, OH) GC/MS *m/z* (rel int) 194 (6), 193 (48), 192 (60), 177 (19), 151 (13), 150 (100), 148 (6), 135 (21), 107 (14) Mp 171° (C_6H_6, lit 171–173° [18]), HCl salt 185° (*iso*-PrOH–EtOH), picrate 178° (H_2O, lit 178° [8]), methiodide 243° (*iso*-PrOH–EtOH) **5**, ^{1}H NMR (DMSO-d_6) δ 2 29 (3H, *s*, NMe), 2 55 (4H, *m*, H-3 and H-4), 3 33 (2H, *s*, H-1), 3 71 (3H, *s*, OMe), 6 50 (1H, *s*, H-5), 6 57 (1H, *s*, H-8), 8 64 (1H, *brs*, OH) GC/MS *m/z* (rel int) 194 (6), 193 (43), 192 (69), 177 (20), 164 (5), 151 (13), 150 (100), 148 (6), 135 (21), 107 (16) Mp 164° (C_6H_6, lit 164–165° [18]), HCl salt 285° (subl, *iso*-PrOH–EtOH, lit 285–290° [18]), picrate 168° (H_2O), methiodide 285° (*iso*-PrOH–EtOH) **8**, ^{1}H NMR (DMSO-d_6) δ 2 29 (3H, *s*, NMe), 2 58 (4H, *m*, H-3 and H-4), 3 36 (2H, *s*, H-1), 3 75 (3H, *s*, OMe), 6 52 and 6 74 (AB-pattern, 2H, J = 9 Hz, H-5 and H-6), 8 53 (1H, *brs*, OH) GC/MS *m/z* (rel int) 194 (7), 193 (53), 192 (57), 177 (18), 176 (7), 151 (11), 150 (100), 136 (5), 135 (30), 121 (7), 120 (6), 107 (14) Mp 102° (hexane, lit 99–101° [19]), HCl salt 220° (EtOH–Et_2O, lit 217–218° [19]), picrate 180° (H_2O), methiodide 223° (*iso*-PrOH–Et_2O)

Synthesis of 8-*methoxy-2-methyl*-1,2,3,4-*tetrahydroisoquinolin*-7-*ol* **9** *o*-Benzyloxyphenol (4 g), 37% HCHO soln (3 g) and methylaminoacetaldehyde dimethyl acetal (3 6 g) in EtOH (25 ml) were stirred for 72 hr at room temp, analogous to a published procedure [20] After concn of the reaction mixture *in vacuo*, the oily residue was dissolved in dilute HCl and extracted with Et_2O The pH of the aq soln was adjusted to 10 and extraction with $CHCl_3$ was performed After evaporation of the solvent, the residue in *n*-hexane was submitted to chromatography on Florisil, using *n*-hexane for elution The first fractions yielded *N*-(3-benzyloxy-2-hydroxybenzyl), *N*-methylaminoacetaldehyde dimethyl acetal **10** (1 9 g) as a slightly yellow oil The later fractions, obtained on Florisil elution of the Mannich condensation products, yielded a major side-product, that was identified by ^{1}H NMR as *o*-benzyloxyphenol, *o,p*-disubstituted with respect to the phenolic position Compound **10** was treated with excess CH_2N_2–Et_2O for 28 hr at room temp

The Et_2O was evaporated and the residue analysed by ^1H NMR δ 3 88 (3H, *s*, aromatic OMe) The residue was dissolved in 6 N HCl (75 ml), extracted with Et_2O and the aq phase left at room temp for 72 hr Traces of Et_2O were removed *in vacuo*, Pd–C (1 5 g) was added and the reaction mixture hydrogenated at 3 atm for 20 hr at room temp The catalyst was filtered off and the soln concd *in vacuo*, yielding 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol HCl (1 g) N-(3-*Benzyloxy*-2-*hydroxybenzyl*), N-*methylaminoacetaldehyde dimethyl acetal* (**10**) ^1H NMR (CCl_4) δ 2 29 (3H, *s*, NMe), 2 38 [2H, *d*, J = 5 4 Hz, $\underline{CH_2}$–CH $(OMe)_2$], 3 30 (6H, *s*, 2 × OMe), 3 54 (2H, *s*, CH_2N), 4 50 [1H, *t*, J = 5 4 Hz, $\underline{CH}$ $(OMe)_2$], 5 05 (2H, *s*, benzylic CH_2O), 6 50 (2H, *m*, aromatic H), 6 72 (1H, *m*, aromatic H), 7 33 (5H, *m*, C_6H_5–CH_2), 9 27 (1H, *brs*, OH) Upon computer simulation of the complex signals centered around δ 6 50 and 6 72 excellent agreement was obtained for the ABC system, having coupling constants $J_{A,B}$ = 6 3 Hz, $J_{A,C}$ = 3 2 Hz, $J_{B,C}$ = 9 2 Hz, while the protons A, B, and C were found at δ 6 72, 6 53 and 6 47, respectively, in agreement with structure **10** 8-*Methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinolin*-7-*ol* (**9**) ^1H NMR (DMSO-d_6) δ 2 33 (3H, *s*, NMe), 2 57 (4H, *m*, H-3 and H-4), 3 41 (2H, *s*, H-1), 3 70 (3H, *s*, OMe), 6 66 (2H, *s*, H-5 and H-6), 8 83 (1H, *brs*, OH) GC/MS *m/z* (rel int) 194 (12), 193 (79), 192 (88), 178 (13), 177 (37), 176 (12), 162 (8), 151 (12), 150 (100), 149 (52), 148 (10), 136 (12), 135 (85), 132 (17), 121 (17), 120 (15), 107 (23), 104 (8) Mp 160° (iso-PrOH, lit 163–164° [21]), HCl salt 265° (subl, iso-PrOH–EtOH), picrate 188° (H_2O), methiodide 207° (EtOH)

O-TMSi-corypalline GC/MS *m/z* (rel int) 266 (10), 265 (46), 264 (66), 250 (8), 235 (5), 234 (18), 224 (5), 223 (19), 222 (100), 193 (8), 192 (46)

O-TMSi-isocorypalline GC/MS *m/z* (rel. int) 266 (13), 265 (57), 264 (96), 250 (8), 235 (6), 234 (21), 224 (5), 223 (20), 222 (100), 193 (9), 192 (50), 177 (5), 176 (5)

O-Acetylcorypalline (**6**) GC/MS *m/z* (rel int) 236 (5), 235 (33), 234 (38), 193 (11), 192 (49), 177 (7), 151 (11), 150 (100), 135 (8), 121 (8), 107 (6)

O-Acetylisocorypalline (**7**) GC/MS *m/z* (rel int) 235 (24), 234 (14), 193 (13), 192 (54), 177 (8), 176 (15), 151 (12), 150 (100), 135 (9), 107 (6)

GC data **3**, *a* 0 86, *b* 0 91, **5**, *a* 0 86, *b* 0 91, **8**, *a* 0 79, *b* 0 85, **9**, *a* 0 66, *b* 0 71, **2**, *a* 1 00, *b* 1 00, **4**, *a* 0 67, *b* 0 74, **6**, *a* 1 88, *b* 1 56, **7**, *a* 1 88, *b* 1 56, *O*-TMSi **3**, *a* 0 91, *b* 1 18, *O*-TMSi **5**, *a* 0 91, *b* 1 18

Structure of bractamine The physical data, reported for the *P bracteatum* alkaloid bractamine, tentatively identified as an isomer of corypalline, are not compatible with any of the isomers studied **3**, **5**, **8** and **9** For bractamine were given mp 216°, HCl salt 143°, picrate 184–185°, methiodide 220–221° [5]

Acknowledgements—Thanks are due to Dr H J W Spronck and Dr W Heerma, Analytical Chemical Laboratory, State University of Utrecht, for recording MS and for helpful discussions This work forms part of a thesis by H G Theuns (in preparation), and was initiated as a consultant to the United Nations Division of Narcotic Drugs

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