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ALPININE, EPIALPININE AND OTHER ALKALOIDS FROM *PAPAVER BRACTEATUM**

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Key Word Index—*Papaver bracteatum*; Papaveraceae; alkaloids; alpinine; epialpinine; alpinigenine; muramine; protopine; codeine; neopine; *O*-methylflavinantine.

Abstract—Alpinine, epialpinine, muramine and protopine were identified as alkaloids of *Papaver bracteatum*. The earlier reported presence of alpinine is revised. The structures of codeine and neopine, earlier reported for this species, are assessed. Screening for the presence of *O*-methylflavinantine was negative.

INTRODUCTION

Papaver bracteatum is regarded as a most promising substitute for *Papaver somniferum*, in being a source of medically needed codeine equivalents. Many minor alkaloids have already been identified in this plant: the morphinans codeine [1, 2], neopine [1, 2], 14β-hydroxycodeine [2, 3], 14β-hydroxycodeinone [3], oripavine [4], thebaine methochloride [5], and both isomeric thebaine *N*-oxides [6, 7]; the promorphinan alkaloid *O*-methylflavinantine [2]; the thebinan alkaloid 6,7,8,9,10,14-hexadehydro-4,5-epoxy-3,6-dimethoxy-17-methylthebinan [7], most likely derived from the major isomer of the thebaine *N*-oxides; two dibenz[*d*,*f*]azonine alkaloids, neodihydrothebaine and bractazonine [8], probably biogenetically related to the major alkaloid thebaine [9]; the rhoeadines alpinigenine [3, 10] and alpinine [1]; the protopines protopine [2, 11] and (only detected by tracer dilution techniques) muramine [12]; the tetrahydroisoquinolines corypalline and *O*-methylcorypalline [13]; the isoquinolone alkaloid *N*-methylcorydaldine [3]; and the aporphine alkaloid isothebaine [14]. By tracer dilution techniques the tetrahydroprotoberberines tetrahydropalmatine and its metho salt were also demonstrated [12]. Among the non-alkaloidal constituents, α-thebaol [1] and *O*-methyl-α-thebaol [14] deserve mention, because of their surmized origin as degradation products of thebaine.

In this paper, we report the isolation of codeine, neopine, alpinine, epialpinine and muramine from this species. Furthermore, protopine was detected in GC/MS, but no trace of *O*-methylflavinantine was found.

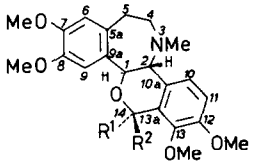
RESULTS AND DISCUSSION

Besides the major alkaloid thebaine, another alkaloid, alpinigenine (**1**), may be present in *Papaver bracteatum*, though literature evidence indicates that the amount present may be highly variable [15]. Apart from alpinigenine, two more rhoeadine bases have been reported from *P. bracteatum*. Alpinine (**2**) was reported to be present by Küppers *et al.* [1] and later by Denisenko *et al.* [16] for plants having an aberrant alkaloid profile. The latter plants cannot be identified as *P. bracteatum* [17].

Epialpinine (**3**) has been mentioned as a constituent of *P. bracteatum* in a review article [18]; the paper cited therein, however, does not give any evidence that this alkaloid actually was identified in this species. The identification of alpinine by Küppers was based on comparison of its mass spectral data, obtained by GC/MS, with literature data. The latter data [19], however, describe the characteristics of the acid catalysed methanolysis product of alpinigenine, which later was recognized as epialpinine (**3**) [20]. Denisenko *et al.* [16] isolated a product and the ^{1}H NMR data presented in their paper clearly prove that their alpinine in fact was identical to epialpinine (**3**). The structural assignment of the *P. bracteatum* constituent not being certified, isolation of the compound, reported in Ref. [1], was deemed necessary for structural proof. The need to do so was stressed even more, because another MW 415 alkaloid, present in much lower amounts, was detected by GC/MS alkaloid screening. Both MW 415 alkaloids were isolated from the alpinigenine-rich *P. bracteatum* variety 'Arya I'. The separation of alpinine and epialpinine is known to be very difficult. Therefore, it was regarded satisfactory to obtain two fractions, the one containing a single compound, which on account of its ^{1}H NMR analysis was identified as epialpinine (**3**), and the other (minor) fraction containing a mixture of alpinine (**2**) and epialpinine (**3**), in which alpinine preponderated (**2**–**3**, 8:1). The structural assignments of both these alkaloids were based on the ^{1}H NMR characteristics of the C-14 epimeric pair glaudine and epiglaudine [21].

The GC/MS data of the fractions mentioned above indicated that epialpinine gives a higher *m/z* 311 fragment ion abundance upon electron impact than alpinine (**2**). Careful comparison of these data with the GC/MS data given in ref. [1], as well as the original GC trace, showed that the alkaloid, earlier identified as alpinine [1], actually was its C-14 epimer epialpinine. Therefore, this is the first report on the natural occurrence of alpinine (**2**) in *P. bracteatum*, as well as the first certified account on the

*Part 13 in the series. For Parts 10–12 see refs. [9, 30, 31].



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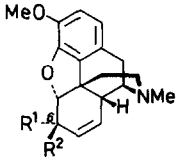
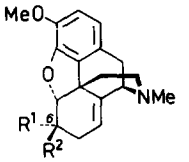
2 R^1=H, R^2=OMe
3 R^1=OMe, R^2=H



4 R^1=OH; R^2=H
8 R^1=H; R^2=OH



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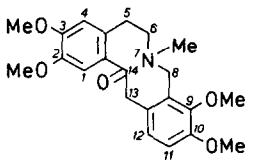

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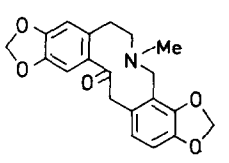

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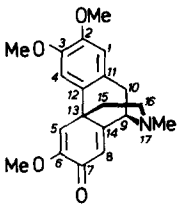

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presence of epialpinine (**3**). These data were further substantiated by a partial synthesis of both alpinine and epialpinine. Treatment of alpinigenine (**1**) with thionyl chloride in tetrahydrofuran, followed by *in situ* treatment with sodium methoxide, yielded a mixture of **2** and **3** (2:1–3:1). When the first step was performed in the presence of a small amount of pyridine, the products consisted mainly of **2** and **3** in an approximate proportion of 2:3. These results being in agreement with expectations (mainly retention of configuration at C-14 for treatment with thionyl chloride in the absence of pyridine, and in any instant inversion of configuration upon treatment of the initial products with sodium methoxide), the structures of both *P. bracteatum* alkaloids have now been established beyond any doubt. This work, thus, describes also the first synthetic conversion of alpinigenine (**1**) to alpinine (**2**).

The ^{13}C NMR spectra of alpinine and epialpinine (See Table 1) support their structural assignments. The data on alpinigenine, which are in agreement with earlier assignments [22], are also included. Comparison of the spectrum of epialpinine (**3**) with that of alpinigenine (**1**) shows that these compounds have the same anomeric configuration. In alpinine (**2**), however, C-1 and C-14 are deshielded with respect to those corresponding in **1** and **3**. These results are in agreement with the absence of the 1,3-diaxial interaction between the axial C-14 substituent and the C-1 hydrogen atom, which causes a shielding of the carbons mentioned in compounds **1** and **3**. These data are in line with the ^1H NMR chemical shifts for H-1. In alpinine (**2**), H-1 is more effectively shielded (δ5.11) than in alpinigenine and epialpinine (δ5.78 and 5.58, respectively). These ^1H and ^{13}C NMR results are in conformity with earlier observations in carbohydrate research [23].

Codeine (**4**) and neopine (**5**) have been detected earlier [1] in this plant material by means of GC/MS analysis. Isolation of these compounds was considered necessary, because GC/MS analysis alone is insufficient for discrimination between 6α- and 6β-hydroxy substitution of these alkaloids. The orientation of the hydroxy group in the compound, identified as neopine (**5**) is of particular interest, in view of the possibility that the latter compound could be an artifact resulting from the acidic conditions prevailing throughout the extraction procedure. Non-enzymatic reduction of neopinone (**7**), a product of acidic enol ether hydrolysis of thebaine, is known to yield both neopine (**5**) and isoneopine (**6**). Neopine and codeine, isolated from *Papaver bracteatum*, have been proved through ^1H NMR analysis [24] to have the same configuration around C-6 as the natural products present in *P. somniferum*. No indication whatsoever was obtained for

Table 1. ^{13}C NMR chemical shifts of rhoeadine alkaloids from *Papaver bracteatum*

Identification of carbon	1	2	3
1	62.8	70.1	62.6
2	61.5	61 7	61.7
4	55.8	54.0	55.7
5	31.0	31.5	30.9
5a	131.3	130.6	131.0
6	113.0	113.0	113.1
7	146.9*	147 0*	147.1*
8	146.7*	146.9*	146.8*
9	108.2	108.8	108.3
9a	135.2	134.5	134.9
10	124.3	123.5	124.4
10a	128.2	130.0	129.7
11	113.4	113.0	113.4
12	150.6	151.3	150.9
13	144.8	145.7	145.0
13a	130.2	130.6	129.7
14	87.6	98.3	94.5
NMe	33.5	34 5	33.5
OMe-7	55.8	55 8	55.8†
OMe-8	55.8	55.8	55.9†
OMe-12	55.8	55.8	55.9†
OMe-13	61.0	61.0	61.0
OMe-14	—	55.8	55.6†

*,†Assignments may be interchanged.

the presence of the 6β-hydroxy isomers **6** and **8**. So, strong support is obtained for the natural origin of these alkaloids in *P. bracteatum*.

The protopine alkaloid muramine (**9**), earlier detected by means of tracer dilution techniques, was present in isolatable quantities in some of our counter-current fractions. The ^{1}H NMR and GC/MS spectra of this compound were in agreement with literature data on muramine [25]. The IR spectrum showed a strong carbonyl absorption at 1638 ± 2 cm^{-1} (lit. [26]: 6.05 μm), typical for a carbonyl group in proximity of a nitrogen function. These data indicated muramine (**9**) as the structure of the *P. bracteatum* alkaloid. Herewith, further support is added to the intricate biosynthetic scheme developed by Rönsch [27] for alpinigenine and, hence, for alpinine and epialpinine.

Protopine (**10**) was detected in GC/MS alkaloid screening and identified by comparison of its GC/MS characteristics with those of an authentic sample (see also Ref. [28]). Screening, however, for the possible presence of *O*-methylflavinantine (**11**) reported for *P. bracteatum* by Meshulam and Lavie [2], was negative. The ^{13}C NMR spectrum of **11** (see Experimental) was assigned by comparison with literature data on related compounds [29].

EXPERIMENTAL

Extraction of capsules of *P. bracteatum*, cv 'Arya I', cultivated by Franco-Pavot Industries, France, and counter-current separation of the extracts were performed as reported earlier [1].

GC/MS was carried out using a Carlo-Erba GLC/Kratos MS 80 apparatus connected to a Kratos DS 55 data system. Electron impact spectra were recorded at 70 eV. Capillary GC/MS screening of counter-current fractions was performed as reported earlier [3]. ^{1}H NMR spectra were recorded in $CDCl_3$ at 90 MHz with TMS as int. standard (δ0). The ^{1}H NMR spectra of **2** and **3** were recorded in $CDCl_3$ at 200 MHz. ^{13}C NMR spectra (in $CDCl_3$) were recorded at 20 or 50 MHz with $CDCl_3$ as int. reference (δ77.0). For **2** and **3** APT (Attached Proton Test) and DEPT (Distortionless Enhanced Polarization Transfer) spectra were recorded. GC was carried out on a Pye Series 104 GC, equipped with a FID, using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80–100 mesh), operating at 270° (system a), or with 3% SE-30 on Chromosorb W-HP (80–100 mesh), operating at 270° (system b). For GC R_ts thebaine was chosen as a reference ($RR_t \equiv 1.00$). TLC was performed on silica gel GF 254 plates with EtOAc–Et_2NH (19·1) (system a), or on Al_2O_3 F 254 (type E) plates using *n*-heptane–$CHCl_3$–Et_2O (4:5:1) (system b). Alkaloid detection was accomplished with iodoplatinate spray reagent.

Isolation of alpinine and epialpinine. Counter-current fractions 126 and 127 (1.929 g) were shown by GC/MS to contain two MW 415 alkaloids, in addition to alpinigenine and a trace of thebaine. The hemiketal alkaloid alpinigenine decomposes in GC and GC/MS, giving several GC peaks. The response to thebaine is highly dependent upon memory effects of the GC column. All these GC peaks in the decomposition pattern of **1** have a MS indicating a virtual MW 355 instead of 401. Crystallization of this fraction from MeOH afforded 1.46 g alpinigenine. The mother liquors were submitted to CC (Al_2O_3 W200 neutral, activity III; $CHCl_3$–*n*-heptane, 5:2, satd with H_2O), giving first epialpinine (**3**, 74 mg), then a mixture of alpinine (**2**) and epialpinine (**3**) (8:1, 13 mg) and, finally, more alpinigenine (**1**; 0.42 g). Crystallization and chromatographic separation were monitored by GC. No change in the alpinine–epialpinine ratio was observed.

Alpinigenine (**1**). GC/MS *m/z* (rel. int.): 356 (27), 355 (60), 354 (25), 341 (22), 340 (100).

Alpinine (**2**). ^{1}H NMR: δ2.24 (3H, *s*, NMe), 3.75 (3H, *s*, OMe-14), 3.91, 3.92, 3.93 and 3.95 (12H, 4 × *s*, 4 × OMe), 4.16 (1H, *d*, J = 9.2 Hz, H-2), 5.11 (1H, *d*, J = 9.2 Hz, H-1), 5.92 (1H, *s*, H-14), 6.71 (1H, *s*, H-6), 6.97 and 7.32 (2H, AB-pattern, J = 8.6 Hz, H-11, H-10, respectively), 7.47 (1H, *s*, H-9). GC/MS *m/z* (rel. int.): 416 (14), 415 (53), 401 (11), 400 (43), 222 (31), 206 (15), 194 (15), 193 (100).

Epialpinine (**3**). ^{1}H NMR: δ2.36 (3H, *s*, NMe), 3.59 (3H, *s*, OMe-14), 3.88, 3.90, 3.92 and 3.93 (12H, 4 × *s*, 4 × OMe), 4.12 (1H, *d*, J = 9.2 Hz, H-2), 5.58 (1H, *d*, J = 9.2 Hz, H-1), 5.87 (1H, *s*, H-14), 6.71 (1H, *s*, H-6), 6.96 and 7.33 (2H, AB-pattern, J = 8.6 Hz, H-11, H-10, respectively), 7.34 (1H, *s*, H-9). GC/MS *m/z* (rel. int.): 416 (19), 415 (71), 401 (13), 400 (53), 384 (8), 311 (9), 222 (37), 206 (31), 194 (15), 193 (100). The ratio of the *m/z* 311 ion abundances of **3** and **2** is 4:1.

Synthesis of **2** *and* **3** *from alpinigenine* (**1**). Alpinigenine (100 mg) was dissolved in THF (5 ml). The yellow soln was treated with $SOCl_2$ (40 μl) and stirred at 0°. A ppt was observed after 45 min. Stirring was continued for another 15 min. Excess NaOMe was added and the mixture was stirred for 1 hr at 0°. Water (7 ml) was added and the solvents were removed *in vacuo*. $CHCl_3$ extraction was performed. The extract was dried (Na_2SO_4), and concd. Yield 100%. ^{1}H NMR analysis showed that the products consisted of a mixture of **2** and **3** in the ratio 2:1–3:1. When this reaction was performed in THF–pyridine (25:2) the products were shown by ^{1}H NMR and GC/MS analysis to consist mainly of a mixture of **2** and **3** in an approximate proportion 2:3.

Isolation of codeine (**4**) *and neopine* (**5**). Prep. TLC of counter-current fractions 9–14 (51 mg) and 31–36 (27.1 mg), using system a, yielded neopine (5.1 mg) and codeine (6.4 mg), respectively. Alkaloids **4** and **5** were both identified by ^{1}H NMR [24] and GC/MS, by comparison with authentic samples.

Codeine (**4**). GC/MS *m/z* (rel. int.): 300 (19), 299 (100), 298 (11), 282 (7), 242 (8), 230 (6), 229 (21), 214 (9), 188 (10), 162 (36), 146 (6), 124 (22).

Neopine (**5**). GC/MS *m/z* (rel. int.): 300 (19), 299 (100), 298 (9), 284 (14), 255 (14), 254 (49), 243 (9), 242 (7), 225 (7).

Isoneopine (**6**). GC/MS *m/z* (rel. int.): 300 (19), 299 (100), 298 (15), 284 (14), 282 (7), 255 (11), 254 (38), 243 (11), 242 (7), 240 (7), 225 (8).

Isolation of muramine (**9**). Preparative TLC (system a) of counter-current fractions 31–50 yielded 23.1 mg crude **9**. The isolation procedure was repeated, giving 7.2 mg pure **9**. M.p. 176–177° (lit. [25] m.p. 176–177°). ^{1}H NMR: δ1.88 (3H, *s*, NMe), 2.63 and 2.95 (4H, *br*, ArC<u>H</u>$_2$C<u>H</u>$_2$N), 3.80 (3H, *s*, OMe), 3.86 (3H, *s*, OMe), 3.90 (6H, *s*, OMe), 6.66 (1H, *s*, H-4), 6.81 and 6.90 (2H, AB-pattern, J = 8.4 Hz, H-11, H-12), 7.04 (1H, *s*, H-1) GC/MS *m/z* (rel. int.): 385 (3), 299 (3), 283 (5), 206 (9), 193 (3), 180 (3), 179 (17), 178 (3), 165 (13), 164 (100), 163 (3), 151 (3), 150 (9), 149 (14), 135 (3), 121 (5), 104 (3), 91 (3), 77 (3).

Detection of protopine (**10**). In GC/MS screening of counter-current fraction 124–125 a small amount of protopine was detected. This alkaloid was identified by GC/MS comparison with an authentic sample.

Protopine (**10**). GC/MS *m/z* (rel. int.): 353 (3), 281 (5), 267 (4), 252 (3), 209 (4), 207 (6), 190 (9), 165 (4), 164 (6), 163 (17), 149 (12), 148 (100), 135 (4), 134 (8), 91 (7), 89 (5).

Screening for the presence of O-methylflavinantine (**11**). GC/MS screening of all counter-current fractions for the presence of *O*-methylflavinantine, earlier reported as a *P. bracteatum* constituent [2], was negative.

O-Methylflavinantine (**11**). ^{1}H NMR: δ2.46 (3H, *s*, NMe), 3.83, 3.88 and 3.91 (9H, 3 × *s*, 3 × OMe), 6.34, 6.39, 6.65 and 6.84 (4H,

4 × s, H-1, H-4, H-5, H-8). ^{13}C NMR: δ31.7 (C-10), 40.4 and 40.9 (C-13, C-15), 41.6 (NMe), 44.9 (C-16), 54.3 (OMe-6), 55.1 (OMe-4), 55.6 (OMe-3), 60.1 (C-9), 108.1 (C-1), 109.8 (C-4), 118.5 (C-5), 121.2 (C-8), 128.0 (C-11), 129.3 (C-12), 147.3 and 147.6 (C-2, C-3), 150.5 (C-14), 161.4 (C-6), 180.1 (C-7) (see also Ref. [29]). GC/MS *m/z* (rel. int.): 342 (22), 341 (100), 326 (28), 285 (16), 284 (10), 171 (11).

GC data. (*RR*,s): **2**, a 5.0, b 4.0; **3**, a 4.5, b 3.4; **4**, a 0.60; **5**, a 0.66; **6**, a 0.66; **9**, a 3.7, b 2.7; **10**, a 3.2, b 2.6. GC analysis of **2** and **3** is best performed on SE-30, because of a better peak shape.

TLC data. (R_f values): **1**, b 0.15; **2**, b 0.55; **3**, b 0.61; **4**, a 0.23; **5**, a 0.24; **9**, a 0.67; thebaine, a 0.45, b 0.40.

Concentration of alkaloids. The amounts [1] of the alkaloids per dry wt of capsule material were: alpinine (**2**) 0.003%; epialpinine (**3**) 0.022%; muramine (**9**) 0.005%; protopine (**10**) 0.002%.

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REFERENCES

1. Küppers, F. J. E. M., Salemink, C. A., Bastart, M. and Paris, M. (1976) *Phytochemistry* **15**, 444.
2. Meshulam, H. and Lavie, D. (1980) *Phytochemistry* **19**, 2633.
3. Theuns, H. G., van Dam, J. E. G., Luteyn, J. M. and Salemink, C. A. (1977) *Phytochemistry* **16**, 753.
4. Hodges, C. C., Horn, J. S. and Rapoport, H. (1977) *Phytochemistry* **16**, 1939.
5. Rönsch, H. and Schade, W. (1979) *Phytochemistry* **18**, 1089.
6. Phillipson, J. D., Handa, S. S. and El-Dabbas, S. W. (1976) *Phytochemistry* **15**, 1297.
7. Theuns, H. G., Janssen, R. H. A. M., Biessels, H. W. A., Menichini, F. and Salemink, C. A. (1984) *J. Chem. Soc., Perkin Trans* 1, 1701.
8. Theuns, H. G., Lenting, H. B. M., Salemink, C. A., Tanaka, H., Shibata, M., Ito, K. and Lousberg, R. J J. Ch. (1984) *Phytochemistry* **23**, 1157.
9. Theuns, H. G., La Vos, G. F., ten Noever de Brauw, M. C. and Salemink, C. A. (1984) *Tetrahedron Letters* **25**, 4161.
10. Guggisberg, A., Hesse, M., Schmid, H., Böhm, H., Rönsch, H. and Mothes, K. (1967) *Helv. Chim. Acta* **50**, 621.
11. Böhm, H. (1965) *Planta Med.* **13**, 234.
12. Rönsch, H. (1977) *Phytochemistry* **16**, 691.
13. Theuns, H. G., Vlietstra, E. J. and Salemink, C. A. (1983) *Phytochemistry* **22**, 247.
14. Theuns, H. G., Janssen, R. H. A. M., Biessels, H. W. A. and Salemink, C. A. (1985) *Phytochemistry* (in press).
15. Böhm, H. (1973) Dissertation. Akademie der Wissenschaften der D. D. R., Berlin.
16. Denisenko, O. N., Israilov, I. A., Moerajeva, D. A. and Yunusov, M. S. (1977) *Khim. Prir. Soedin.* 547.
17. Böhm, H. (1981) *Pharmazie* **36**, 666.
18. Nyman, U. and Bruhn, J. G. (1979) *Planta Med.* **35**, 97.
19. Maturová, M., Potěšilová, H., Šantavý, F., Cross, A. D., Hanuš, V. and Dolejš, L. (1967) *Collect. Czech. Chem. Commun.* **32**, 419.
20. Shamma, M., Weiss, J. A., Pfeifer, S. and Döhnert, H. (1968) *J. Chem. Soc., Chem. Commun.*, 212.
21. Shamma, M. (1972) *The Isoquinoline Alkaloids, Chemistry and Pharmacology* p. 405. Academic Press, New York.
22. Lavie, D., Berger-Josephs, H., Yehezkel, T., Gottlieb, H. E. and Levy, E. C. (1981) *J. Chem. Soc., Perkin Trans.* 1, 1019.
23. Haverkamp, J., de Bie, M. J. A. and Vliegenthart, J. F. G. (1975) *Carbohydr. Res.* **39**, 201.
24. Batterham, T. J., Bell, K. H. and Weiss, U. (1965) *Aust. J. Chem.* **18**, 1799.
25. Cross, A. D., Dolejš, L., Hanuš, V., Maturová, M. and Šantavý, F. (1965). *Collect. Czech. Chem. Commun.* **30**, 1335.
26. Boit, H.-G. and Flentje, H. (1960) *Naturwissenschaften* **47**, 180.
27. Rönsch, H. (1972) *Eur. J. Biochem.* **28**, 123.
28. Dolejš, L., Hanuš, V. and Slavík, J. (1964) *Collect. Czech. Chem. Commun.* **29**, 2479.
29. Olieman, C., Maat, L. and Beyerman, H. C. (1980) *Recl. Trav. Chim. Pays-Bas* **99**, 169.
30. Theuns, H. G., Lenting, H. B. M., Salemink, C. A., Tanaka, H., Shibata, M., Ito, K. and Lousberg, R. J. J. Ch (1984) *Heterocycles* **22**, 1995.
31. Theuns, H. G., Lenting, H. B. M., Salemink, C. A., Tanaka, H., Shibata, M., Ito, K. and Lousberg, R. J. J. Ch. (1984) *Heterocycles* **22**, 2007