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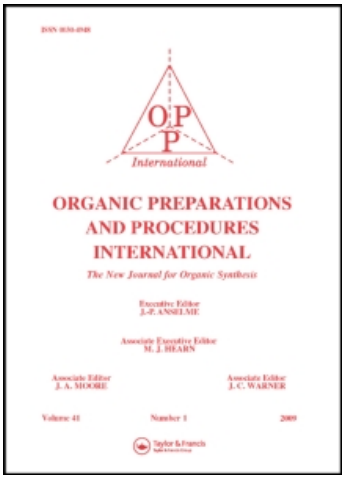

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A SHORT SYNTHESIS OF THE CARBAZOLE ALKALOID CLAUSINE E

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A SHORT SYNTHESIS OF THE CARBAZOLE ALKALOID CLAUSINE E

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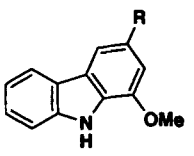
The first carbazole alkaloid to be isolated was murrayanine (**1**), extracted from the stem bark of the small tree *Murraya koenigii* in India.[1] Since then, the field has expanded enormously, largely due to the promising biological activities of many of these alkaloids. This class of alkaloids has primarily been isolated from plants of the genus *Murraya*, *Glycosmis* and *Clausena* from the Rutaceae family and characteristic members include 1-oxygenated carbazole alkaloids such as aldehyde **1**, mukoeic acid (**2**),[2] and mukonine (**3**).[3,4] The shrub *Clausena excavata* has traditionally been used in China for the treatment of snakebites, abdominal pain and as a detoxification agent. Extensive studies of the *Clausena* genus have resulted in isolation of several compounds with interesting biological activities. Clausine E (**4**), for instance, isolated from *C. excavata*[5-7] and *Clausena anisata*,[8] has displayed antiplatelet aggregating[5] and antitumor properties (*Fig. 1*).[8]



1 R = CHO
2 R = COOH
3 R = COOMe

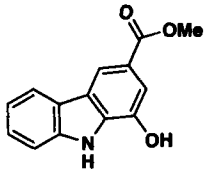


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Fig. 1

Widely used methods for the synthesis of 1-oxygenated carbazoles include the classical Fischer indolization with appropriate phenylhydrazones,[9] intramolecular cyclizations of indoles,[10,11] and oxidative cyclization of diarylamines.[12] Increasingly important are transition metal-mediated and -catalyzed processes for preparation of derivatives of carbazoles.[4] Herein we would like to disclose a rapid and uncomplicated two-step synthesis of the carbazole alkaloid clausine E (**4**).

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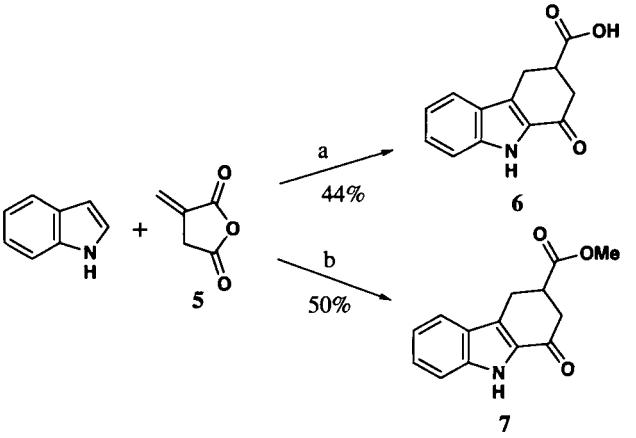
The synthesis of clausine E (**4**) has been reported previously by Brenna *et al.*[11] (34%, 3 steps) and by Bringmann *et al.*[13] (44%, 7 steps). Both methods involve the activation and intramolecular cyclization of monoester acids obtained *via* a Stobbe condensation or a Horner-Wadsworth-Emmons reaction, respectively. Regioselective acylation of indoles under Friedel-Crafts conditions has been reported in the presence of Lewis acids.[14] We were interested in the outcome of an attempted Lewis acid-assisted acylation reaction of indole with itaconyl chloride, judging that the reaction could occur at either one of the carbonyls or, perhaps more likely, proceed in a Michael type addition fashion. Following the acylation protocol devised by Okauchi[14] and co-workers, indole was reacted with itaconyl chloride in the presence of diethylaluminium chloride (Et_2AlCl) and the known carbazole **6**[15] could be isolated from the reaction mixture. Hence, it seems as if the addition reaction was preferred over the acylation reaction under the given conditions. The reaction worked better with itaconic anhydride (**5**), but still gave the carbazole **6** only in a modest yield of 44% (*Scheme 1*). Compound **6** has a mp of 240-242°C, which is significantly higher than previously reported (203-204°C) for that compound[15], a deviation which is rather puzzling, since all other data do match. Changing the Lewis acid to boron trifluoride etherate (BF_3•OEt_2) instead of Et_2AlCl resulted in the precipitation of **6** directly from the reaction mixture in sufficiently pure state for further transformation to the methyl ester in refluxing MeOH/H_2SO_4. The ester **7** was thus obtained in 50% yield from indole in a simple procedure involving inexpensive and readily available starting materials.

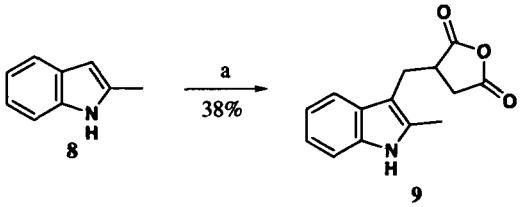


a) i) Et_2AlCl, CH_2Cl_2, 0°C 30 min. ii) **5**, 0°C 2 h, room temperature 2.5 h; b) i) **5**, BF_3•OEt_2, CH_3CN, room temperature 5 min. ii) Indole, reflux 2.5 h. iii) H_2SO_4, MeOH, reflux 1 h.

Scheme 1

It was considered that the reaction proceeds *via* initial addition to the double bond of itaconic anhydride in the acidic environment, attack at the carbonyl to form a spiro-indole intermediate followed by subsequent 1,2-migration affording the six-membered ring **6**, thus also implying the possibility of formation of a 4-oxygenated isomer. In an attempt to support this

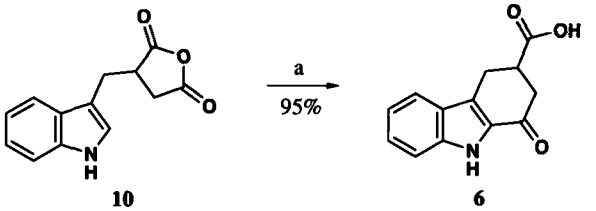
mechanism, indole was replaced by 2-methylindole (**8**) in the reaction with itaconic anhydride in presence of BF_3•OEt_2. Since the 2-methyl substituent of 2-methylindole would conceivably block the assumed 1,2-migration, it was speculated that the presumed spiro-indole derivative would be obtained. However, only the anhydride **9** was isolated (*Scheme 2*), which is in line with the previously reported experiments in this area by Noland[16] and Kuryla,[17] who described a simple procedure for heating 2-methylindole with itaconic anhydride, leading to the succinic anhydride **9** in good yields. Significantly, the parent anhydride **10** reportedly could not be prepared using this method.[17] These findings indeed support a reaction mechanism wherein an initial Michael addition of indole to the double bond of itaconic anhydride takes place. It is also tempting to speculate that the substituent in 2-methylindole blocks the presumed reaction with the second carbonyl, thus stopping at compound **9**.



a) i) **5**, BF_3•OEt_2, CH_3CN, room temperature 5 min. ii) **8**, reflux 1 h.

Scheme 2

Anhydride **10** had been synthesised previously by Lewis *et al.* from gramine and triethyl 1,1,2-ethanetricarboxylate, followed by saponification, decarboxylation and cyclization.[18] It was expected that treatment of **10** with BF_3•OEt_2 in refluxing acetonitrile, would result in the formation of **6**, which indeed proved to be the case (*Scheme 3*). This further substantiates the mechanism suggested, wherein **10** is a presumed intermediate.



a) BF_3•OEt_2, CH_3CN, reflux 1 h.

Scheme 3

Dehydrogenation of the carbazole **7** was performed in diphenyl ether using Pd/C as the catalyst. Clausine E (**4**) was isolated in a good yield from the reaction mixture, together with small amounts of the carbazole **11**, which has been isolated previously from another *Clausena* species, namely *C. lansium*.[19] Addition of a diluent to diphenyl ether, in this case mesitylene, seems to be necessary for minimizing dehydration (*Scheme 4*).[20-22]

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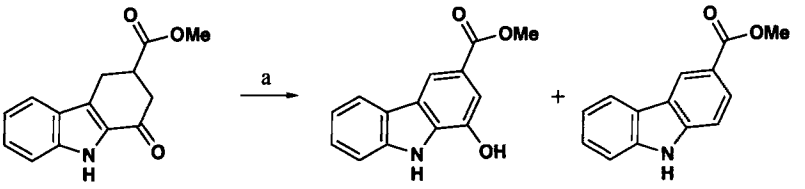

7 4 (76%) 11 (6%)

a) Pd/C 10%, Ph_2O, mesitylene, ~210°C 20 h.

Scheme 4

The presence of a 1-oxygenated carbazole was supported using difference-NOE experiments, as irradiation of the OH resonance of **4** produced enhancement of the signals corresponding to the NH of the indole and the proton at position 2 of the carbazole, as well as the methyl group, enhancements that are not likely to be present in a 4-oxygenated isomer.

In conclusion, an efficient and uncomplicated synthesis of the carbazole alkaloid clausine E (38% yield, 2 steps) has been developed, utilizing a Michael addition type reaction between itaconic anhydride and indole in the presence of a Lewis acid catalyst. Although described here for indole and itaconic anhydride, the method should have additional applications for preparation of other 1-oxygenated carbazole alkaloids.

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EXPERIMENTAL SECTION

NMR spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, using the solvent signal as reference. δ values are given in ppm, coupling constants are given in Hz. The IR spectra were acquired using an FT-IR instrument. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined on a capillary melting point or a hot stage apparatus. All reagents used were purchased from Aldrich, Lancaster or Merck and were used as received. All solvents were purified by distillation or were of analytical grade. Chromatographic separations were performed on silica gel 60 (230-400 mesh).

1-Oxo-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic Acid (6), Method 1.- Indole (585 mg, 5 mmol) was dissolved in CH_2Cl_2 (15 mL) at 0°C and Et_2AlCl (15 mL, 1M sol. in hexane) was added in small portions. After 30 min itaconic anhydride (**5**) (520 mg, 5 mmol) was added as a solid in one portion. The resulting yellow/brown reaction mixture solution was kept at 0°C for 2 h, then at room temperature for 2.5 h. The mixture was carefully quenched with 2 M KOH (20 mL) and additional CH_2Cl_2 (30 mL) was added. The organic phase was extracted with another portion of 2 M KOH (20 mL). The combined water phases were washed with CH_2Cl_2 (20 mL) and thereafter acidified with 2 M HCl until pH ~2-3. The pinkish precipitate was extracted with EtOAc (2 x 20 mL), washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$ and evaporated to give **6** as a yellow solid (503 mg, 44%). An analytical sample was obtained by crystallization by MeOH/H_2O, mp. 240-242°C (*lit.*[15] 203-204°C).
IR (neat): 3263, 3054, 1701, 1641, 1618, 1477, 1330, 1233, 745 cm^{-1}.

^{1}H-NMR (DMSO-d_6): d 11.72 (br, 1H) 11.64 (s, 1H), 7.71 (d, J = 8.0, 1H), 7.41-7.28 (m, 2H), 7.11-7.06 (m, 1H), 3.38-3.13 (m, 3H), 2.82-2.71 (2H).

^{13}C-NMR (DMSO-d_6): d 188.3 (s), 174.8 (s), 138.2 (s), 130.8 (s), 126.3 (d), 125.5 (s), 125.1(s), 121.2 (d), 119.8 (d), 112.9 (d), 41.2 (d), 40.0 (t), 23.8 (t).

The spectral data agreed with those previously published.[15]

1-Oxo-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic Acid (6), Method 2.- 3-(1*H*-Indol-3-yl-methyl)succinic anhydride (**10**)[18] (229 mg, 1 mmol) was dissolved in CH_3CN (15 mL) and BF_3•OEt_2 (0.13 mL, 1 mmol) was added. The reaction mixture was heated at reflux for 1 h and was thereafter allowed to cool. The solvent was evaporated and the residue was dissolved in EtOAc (25 mL), washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and thereafter evaporated, affording **6** as a brownish solid (217 mg, 95%). The spectral data were identical with those of the product prepared from indole and itaconic anhydride as described above (Method 1).

1-Oxo-2,3,4,9-tetrahydro-1*H*-carbazolecarboxylic Acid Methyl Ester (7).- BF_3•OEt_2 (6.30 mL, 50 mmol) was added to a suspension of itaconic anhydride (**5**) (5.60g, 50 mmol) in CH_3CN (20 mL) and the resulting mixture was stirred at room temperature for 5 min. Indole (5.85 g, 50 mmol) was then added to the clear yellow solution and the reaction mixture was heated at reflux for 1 h, whereupon a red precipitate was formed. The reaction mixture was allowed to cool and the precipitate was collected by to give **6** as a red solid (8.63 g), sufficiently pure for the next step.

Compound **6** was heated at reflux for 1 h in MeOH (40 mL) containing 3% conc. H_2SO_4. The reaction mixture was then poured onto ice (100 mL) and the resulting precipitate was collected and washed with MeOH to afford compound **7** as a pale pinkish solid (6.07 g, 50% yield from indole), which was recrystallised from toluene, mp. 217-219°C.

IR (neat): 3261, 1725, 1638, 1619, 1241, 1170, 1002, 731 cm^{-1}.

^{1}H-NMR (DMSO-d_6): d 11.67 (s, 1H), 7.72 (d, J = 8.0, 1H), 7.41-7.29 (m, 2H), 7.12-7.06 (m, 1H), 3.63 (s, 3H), 3.44-3.18 (m, 3H), 2.83-2.80 (m, 2H).

^{13}C-NMR (DMSO-d_6): d 187.9 (s), 173.6 (s), 138.2 (s), 130.7 (s), 126.4 (d), 125.3 (s), 125.1 (s), 121.2 (d), 119.8 (d), 112.8 (d), 51.9 (d), 41.1 (q), 39.7 (t), 23.6 (t).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.30; H, 5.42; N, 5.76.

3-(2-Methyl-1*H*-indol-3-yl-methyl)succinic Anhydride (9)[23].- Itaconic anhydride (**5**) (560 mg, 5 mmol) was dissolved in CH_3CN (15 mL) and BF_3•OEt_2 (0.63 mL, 5 mmol) was added. After 5 min at room temperature, 2-methylindole (**8**) (656 mg, 5 mmol) was added as a solid in one portion and the resulting mixture was heated at reflux for 1 h. The dark red solution was allowed to cool and evaporated to dryness. The residue was dissolved in EtOAc (20 mL) and washed with aq. sat. $NaHCO_3$ (2 x 10 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residual red oil was purified by silica gel column chromatography using hexane/EtOAc (60:40) as the eluent to afford 461 mg (38%) of compound **9** as a pale yellow

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solid, mp. 135-136°C (*lit.*[16] 134-135°C), which darkened upon storage.

IR (KBr): 3399, 1844, 1773, 1462, 1219, 1068, 1039, 912, 744 cm^{-1}.

^{1}H-NMR (DMSO-d_6): d 10.82 (s, 1H), 7.44 (d, J = 7.4, 1H), 7.25 (d, J = 7.4, 1H), 7.03-6.92 (m, 2H), 3.57-3.51 (m, 1H), 3.14-3.11 (m, 2H), 2.89-2.80 (m, 1H), 2.73-2.65 (m, 1H), 2.34 (s, 3H).

^{13}C-NMR (DMSO-d_6): d 175.1 (s), 171.1 (s), 135.2 (s), 133.1 (s), 127.9 (s), 120.2 (d), 118.4 (d), 117.2 (d), 110.5 (d), 105.9 (s), 41.7 (d), 33.8 (t), 24.1 (t), 11.3 (q).

Clausine E (4) and 9H-carbazole-3-carboxylic Acid Methyl Ester (11).- Compound **7** (729 mg, 3 mmol) was suspended in diphenyl ether (3 mL) and mesitylene (3 mL) with Pd/C (10%, 109 mg), and the mixture was heated at ~210°C for 20 h. After removal of the catalyst by filtration the residue was purified by column chromatography, starting with hexane as eluent with increasing amounts of EtOAc (up to 60:40 hexane/EtOAc). This afforded compound **11** (40 mg, 6%) followed by clausine E (**4**) (547 mg, 76%) as white solids. Both compounds could be recrystallised from toluene.

9H-Carbazole-3-carboxylic Acid Methyl Ester (11).- mp. 183-185°C (*lit.*[19a, 19b] 168-170°C; 175-180°C).

IR (neat): 3324, 3287, 1684, 1626, 1603, 1244, 1098, 724 cm^{-1}.

^{1}H-NMR (DMSO-d_6): d 11.71 (s, 1H), 8.80 (d, J = 1.5, 1H); 8.28 (d, J = 7.8, 1H), 8.05 (dd, J = 1.7, 8.6, 1H), 7.59-7.54 (m, 2H), 7.48-7.46 (m, 1H), 7.26-7.21 (m, 1H), 3.90 (s, 3H).

^{13}C-NMR (DMSO-d_6): d 167.0 (s), 142.6 (s), 140.3 (s), 126.7 (d), 126.4 (d), 122.4 (s), 122.3 (d), 122.2 (s), 120.7 (d), 119.8 (s), 119.5 (d), 111.4 (d), 110.8 (d), 51.7 (q).

The spectral data agreed with those previously published, see reference 19b.

Clausine E (4).- mp 215-216.5°C (*lit.*[5] 218-220°C).

IR (neat): 3345, 1653, 1630, 1597, 1435, 1354, 1315, 1257, 1002, 727 cm^{-1}.

^{1}H-NMR (DMSO-d_6): d 11.55 (s, 1H), 10.22 (s, 1H), 8.32 (d, J = 1.2, 1H), 8.18 (d, J = 7.8, 1H), 7.54-7.39 (m, 3H), 7.21-7.16 (m, 1H), 3.87 (s, 3H).

^{13}C-NMR (DMSO-d_6): d 167.1 (s), 142.9 (s), 140.2 (s), 132.7 (s), 126.0 (d), 123.4 (s), 123.0 (s), 120.6 (s), 120.5 (d), 119.3 (d), 114.1 (d), 111.7 (d), 110.1 (d), 51.7 (q).

The spectral data agreed with those previously published, see reference 5.

REFERENCES

1. D. P. Chakraborty, B. K. Barman and P. K. Bose, *Tetrahedron,* **21**, 681 (1965).

2. B. K. Choudhury and D. P. Chakraborty, *Phytochemistry,* **10**, 1967 (1971).

3. D. P. Chakraborty, P. Bhattacharyya, S. Roy, S. P. Bhattacharyya and A. K. Biswas, *Phytochemistry,* **17**, 834 (1978).

4. For an in-depth review of biologically active carbazole alkaloids, which covers occurrence, biological acitivities and total synthesis of carbazole alkaloids, see (a) H. J. Knölker and K. R Reddy, *Chem. Rev.,* **102**, 4303 (2002) (b) H. J. Knölker, *Top. Curr. Chem.,* **244**, 115 (2005).

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5. T.-S. Wu, S.-C. Huang, P.-L. Wu and C.-M. Teng, *Phytochemistry,* **43**, 133 (1996).

6. C. Ito, S. Katsuno, H. Ohta, M. Omura, I. Kajura and H. Furukawa, *Chem. Pharm. Bull.,* **45**, 48 (1997).

7. T.-S. Wu, S.-C. Huang, P.-L. Wu and C.-S. Kuoh, *Phytochemistry,* **52**, 523 (1999).

8. C. Ito, S. Katsuno, M. Itoigawa, N. Ruangrungsi, T. Mukainaka, M. Okuda, Y. Kitagawa, H. Tokuda, H. Nishino and H. Furukawa, *J. Nat. Prod.,* **63**, 125 (2000).

9. D. P. Chakraborty and B. K Choudhury, *J. Org. Chem.*, **33**, 1265 (1968).

10. C. J. Moody, *Synlett,* 681 (**1994**).

11. E. Brenna, C. Fuganti and S. Serra, *Tetrahedron,* **54**, 1585 (1998).

12. H. Furukawa, C. Ito, M. Yogo and T.-S., Wu *Chem. Pharm. Bull.,* **34**, 2672 (1986).

13. G. Bringmann, S. Tasler, H. Endress, K. Peters and E.-M. Peters, *Synthesis,* 1501 (**1998**).

14. (a) T. Okauchi, M. Itonaga, T. Minami, T. Owa, K. Kitoh and H. Yoshino, *Org. Lett.,* **2**, 1485 (2000). (b) O. Ottoni, A. de V. F. Neder, A. K. B. Dias, R. P. A. Cruz and L. B. Aquino, *Org. Lett.,* **3**, 1005 (2001).

15. Y. Ergüen, S. Patir and G. Okay, *Synth. Commun.,* **34**, 435 (2004).

16. W. Noland and C. F. Hammer, *J. Org. Chem.,* **25**, 1536 (1960).

17. W. Kuryla Ph. D. Thesis, University of Minnesota, Minneapolis 1960.

18. R. T. Lewis, A. M. Macleod, K. J. Merchant, F. Kelleher, I. Sanderson, R. H. Herbert, M. A. Cascieri, S. Sadowski, R. G. Ball and K. Hoogsteen, *J. Med. Chem.*, **38**, 923 (1995).

19. (a) Isolation: W.-S. Li, J. D. McChesney and S. E.-F. Farouk, *Phytochemistry,* **30**, 343 (1991). (b) Synthesis: T. G. Back, A. Pandyra and J. E. Wulff, *J. Org. Chem.,* **68**, 3299 (2003).

20. R. P. Linstead and K. O. A. Michaelis, *J. Chem., Soc.,* 1134 (**1940**).

21. G. Bringmann, A. Ledermann and F. François, *Heterocycles,* **40**, 293 (1995).

22. T. L. Scott and B. C. G. Söderberg, *Tetrahedron,* **59**, 6323 (2003).

23. The literature procedure for compound **9**, described by Noland and Hammer (see reference 16), was also repeated and found to work well.

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