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Indole-β-Nucleophilic Substitution. Part 9[1] Nitrogen Nucleophiles. Syntheses of Hydroxycryptolepine, Cryptolepine, and Quindoline

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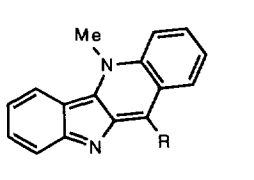
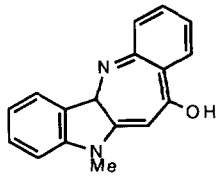
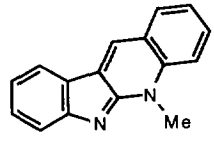
Abstract: The alkaloids hydroxycryptolepine, cryptolepine and quindoline have been synthesised utilising the intramolecular β-nucleophilic substitution of a 1-phenylsulfonyl-2-acylindole.



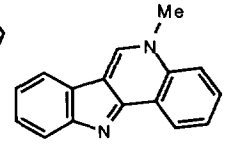
cryptolepine (R=H)
hydroxycryptolepine (R=OH)



cryptoheptine

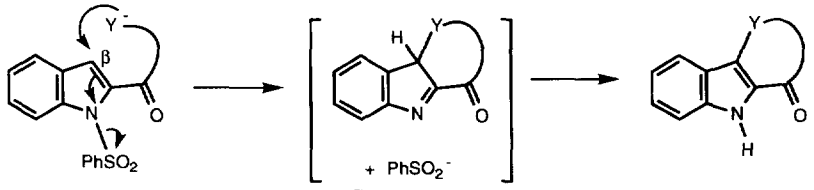


neocryptolepine



isocryptolepine

Various *Cryptolepis* species, extracts of which are used in traditional medicine in Central and West Africa, have yielded nine alkaloids. Four tetracyclic skeleta have been recognised, representatives being cryptolepine and hydroxycryptolepine,[3] cryptoheptine,[3] neocryptolepine,[4] and isocryptolepine.[5] Cryptospirolepine[6] is a spirocyclic dimer of cryptoheptine and cryptolepine types. Pharmacological investigations[7,8] on cryptolepine have shown it to have hypotensive, antipyretic, anti-inflammatory, anti-bacterial, and anti-malarial activities. Quindoline (= des-*N*-methylcryptolepine) was obtained from cryptolepine by selenium dehydrogenation; conversely, *N*-methylation of quindoline gave the hydriodide of cryoptolepine.[9] Quindoline had been known as a synthetic material,[10] from reaction of indoxyl with isatin in alkali, long before its isolation[11] as an alkaloid.

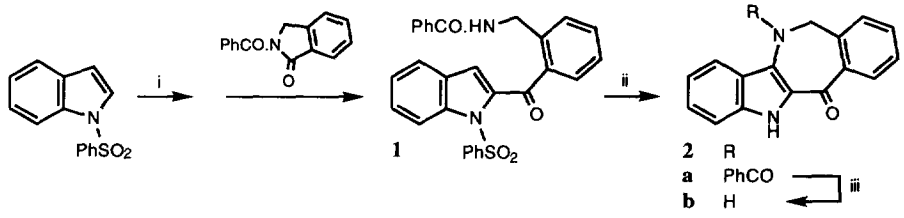


Scheme 1

In previous work we have demonstrated the operation of a process (Scheme 1) of overall intramolecular nucleophilic substitution at an indole β-position, where the indole carries a phenylsulfonyl group on nitrogen and

a ketonic substituent at C-2; the *N*-substituent is expelled as phenylsulfinate; the process may be synchronous (Scheme 1), or may involve an intermediate in which the nucleophile has added to the formal enone unit. In the examples we have so far described[1] the nucleophilic centre (Y) was an alcoholic oxygen. We report here the use of amide nitrogen as nucleophile and thence the synthesis of hydroxycryptolepine, cryptolepine and quindoline.

Our earliest work utilised the condensation product from 2-lithiated 1-phenylsulfonylindole[12] and phthalide to illustrate the operation of the indole-β-nucleophilic substitution process producing thereby a [2]benzoxepino[4,3-*b*]indole.[13] Extrapolating this to a nitrogen equivalent required[14] *N*-benzoylphthalimidine which was prepared from phthalimidine[15] by reaction with benzoyl chloride in *N,N*-dimethylaniline.[16] Reaction with 2-lithio-1-phenylsulfonylindole took place at both carbonyl groups generating a mixture of desired ketone **1**,[17,18] together with 2-benzoyl-1-phenylsulfonylindole, in a ratio of 4:3, separated by chromatography. If the reaction was allowed to proceed for longer than *ca.* 15 min a different, yellow product **2a**[19] was also formed which proved to be the result of the desired intramolecular nucleophilic substitution by the anion of the amide, and could be obtained from ketone **1** in good yield on exposure to NaH in refluxing THF. The corresponding amino-ketone **2b**[20] was readily obtained by alkaline hydrolysis of **2a** (Scheme 2).

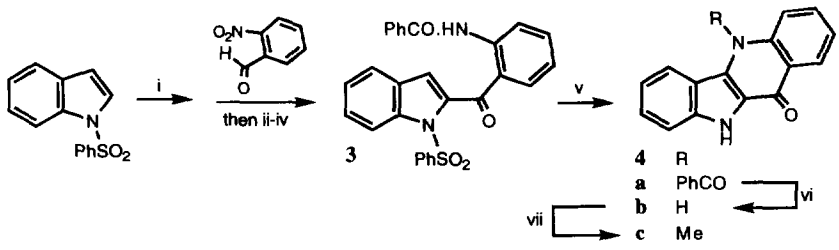


Scheme 2

Reagents: i, BuLi, THF, -78 °C (38%) plus 2-benzoyl-1-phenylsulfonylindole (29%); ii, NaH, THF, reflux (89%); iii, NaOH, MeOH, reflux (80%).

Addition of lithiated 1-phenylsulfonylindole to 2-nitrobenzaldehyde followed by MnO_2 oxidation of the alcohol, catalytic reduction of the nitro group and *N*-benzoylation gave amido-ketone **3**.[21] *N*-Deprotonation using NaH allowed ring closure in hot THF to tetracycle **4a**,[22] hydrolysis of which produced **4b** (Scheme 3).[23]

N-Methylation of the quinolone **4b** with NaH as base and at room temperature produced crystalline material to which we ascribe the structure **4c**[24] and which had electronic absorption and tlc behaviour[25] identical with those of hydroxycryptolepine.[3] The carbonyl tautomeric forms of **4b** and **4c**, shown, are established by spectroscopic comparisons. Thus the UV/VIS absorptions of **4b** and **4c** and of the alkaloid,[3] in neutral and acidic solution, were identical; only **4b** showed a significant change in alkaline solution, no doubt due to deprotonation at the quinolone *N*-hydrogen. The carbonyl stretching frequency of 1-methylquinolin-4-one is 1625 cm^{-1}, that of **4b** is 1640 cm^{-1}, and that of **4c** is 1621 cm^{-1}, where hydroxycryptolepine was reported[3] as

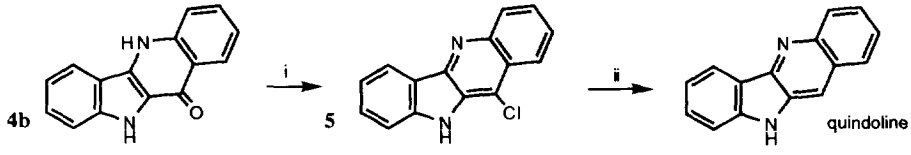


Scheme 3

Reagents: i, BuLi, THF, -78 °C (40%); ii, MnO_2, CH_2Cl_2, RT(88%); iii, H_2, Pd-C (72%); iv, PhCO.Cl, $PhNMe_2$, RT (87%); v, NaH, THF, reflux (80%); vi, NaOH, MeOH, heat (85%); vii, NaH, MeI, DMF, RT (30%).

having an IR peak at 1623 cm^{-1}. The ^{13}C shift of the carbonyl carbon of 1-methylquinolin-4-one is 178.08 ppm where ketones **4b** and **4c** have signals at 165.93 and 166.98; the alkaloid was reported[3] as having a signal at 167.01. We conclude that 'hydroxycryptolepine' is properly represented by structure **4c**.

Treatment of **4a** with $NaBH_4$ in refluxing ethanol did not effect hoped for reduction of the carbonyl group however heating **4b** in $POCl_3$ produced **5**, catalytic hydrogenolysis of which gave quindoline (Scheme 4); quindoline has previously been converted into cryptolepine (*loc. cit.*).



Scheme 4

Reagents: i, $POCl_3$, reflux (95%); ii, H_2, Pd-C, EtOH, (95%).

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REFERENCES AND NOTES

1 Part 8 to be ref 12(b); Part 7 and references therein: Dalton, L.; Humphrey, G. L.; Cooper, M. M.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2417.

2 Present address: Department of Chemistry, 223, Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-1905, U.S.A.

3 Paulo, A.; Gomes, E. T.; Houghton, P. J., *J. Nat. Prod.*, **1995**, *58*, 1485.

4 Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A.; *Tetrahedron Lett.*, **1996**, *37*, 1703

5 Pousset, J.-L.; Martin, M.-T.; Jossang, A.; Bodo, B., *Phytochemistry*, **1995**, *39*, 735.

6 Tackie, A. N.; Boye, G. L.; Sharaf, M. H. M.; Schiff, P. L.; Crouch, R. C.; Spitzer, T. D.; Johnson, R. L.; Dunn, J.; Minick, D.; Martin, G. E., *J. Nat. Prod.*, **1993**, *56*, 653.

7 Cimanga, K.; De Bruyne, T.; Lasure, A.; Van Poel, B.; Pieters, L.; Claeys, M.; Vanden Berghe, D.; Vlietinck, A., *Planta Med.*, **1995**, in press.

8 As cited in reference 3.

9 Gellért, E.; Raymond-Hamet; Schlittler, E., *Helv. Chim. Acta*, **1951**, *34*, 642.

10 Holt, S. J.; Petrow, V., *J. Chem. Soc.*, **1947**, 607 and references therein.

11 Dwuma-Badu, D.; Ayim, J. S. K.; Fiagbe, F. N. I. Y.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J., *J. Pharm. Sci.*, **1978**, *67*, 433.

12 Sundberg, R. J.; Russell, H. F., *J. Org. Chem.*, **1973**, *38*, 3324.

13 (a) Cooper, M. M.; Hignett, G. J.; Newton, R. F.; Joule, J. A.; Harris M.; Hinchley, J. D., *J. Chem. Soc., Chem. Commun.*, **1977**, 432; Cooper, M. M.; Hignett, G. J.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1*, **1981**, 3008; (b) Glendinning, A.; Hunter, W. N.; Joule, J. A.; Leonard, G. A., *Acta Crystallogr., Sect. C*, **1993**, *49*, 2126.

14 *N*-Methylphthalimidine did not react with 2-lithio-1-phenylsulfonylindole.

15 Graebe, C., *Justus Liebigs Ann. Chem.*, **1888**, *247*, 288.

16 Tull, R.; O'Neill, R. C.; McCarthy, E. P.; Pappas, J. J.; Chernarda, J. M., *J. Org. Chem.*, **1964**, *29*, 2425.

17 All new compounds gave satisfactory microanalytical data; for selected spectroscopic data conditions are: IR (nujol), UV (EtOH) and NMR ($CDCl_3$) except where otherwise specified.

18 m.p. 157-159 °C; ν_{max} 3300, 1660, 1640 cm^{-1}; λ_{max} 250sh, 302 nm; δ_H 6.9 (1H, s, indole-3-H), 5.25 (2H, s, CH_2).

19 m.p. 202-204 °C (MeOH); ν_{max} 3380, 1650 cm^{-1}; λ_{max} 266, 347, 395sh nm; δ_H 9.6 (1H, bs, NH), 4.7 (2H, s, CH_2).

20 m.p. 207-209 °C (EtOAc); ν_{max} 3350, 3290, 1620 cm^{-1}; λ_{max} 232, 262, 337, 445 nm; δ_H 9.8 (1H, bs, NH), 6.2 (1H, bs, NH), 5.6 (2H, s, CH_2).

21 m.p. 166-167 °C ($CHCl_3$/MeOH); ν_{max} 3400, 1635 cm^{-1}; λ_{max} 255, 345 nm; δ_H 9.5 (1H, bs, NH), 6.9 (1H, s, indole-3-H).

22 m.p. 241-246 °C (MeOH); ν_{max} 1725, 1620 cm^{-1}; λ_{max} 232, 267, 315sh, 326, 380sh, 395 nm; δ_H (d_6-DMSO) 12.2 (1H, bs, NH).

23 m.p. >300 °C (dec) (MeOH); ν_{max} 1640 cm^{-1}; λ_{max} 234, 274, 309, 323, 360sh, 376, 390 nm; λ_{max} (EtOH/HCl) 230, 257, 281, 295sh, 310, 328, 343, 400 nm; λ_{max} (EtOH/NaOH) 227, 278, 302, 320, 333, 360, 380, 410 nm; δ_H (d_6-DMSO) 12.95 (1H, bs, NH), 11.67 (1H, bs, NH).

24 m.p. >300 °C (dec.) (MeOH); λ_{max} 220sh, 234, 272, 312, 326, 368sh, 388, 404 nm; λ_{max} (MeOH/HCl) 224, 234, 260sh, 282, 314, 332sh, 346, 406 nm; δ_H (d_6-DMSO) (300 MHz) 12.0 (1H, bs), 8.56 (1H, d, J 7.9), 8.50 (1H, d, J 8.5), 8.03 (1H, d, J 8.8), 7.89 (1H, bt), 7.68 (1H, d, J 8.2), 7.59 (1H, bt), 7.47 (1H, bt), 7.31(1H, bt).

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