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Synthesis of Necatorone[1,2]

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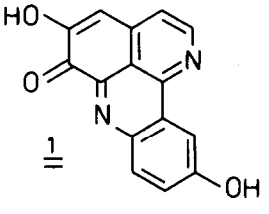
Summary: The mutagenic fungal alkaloid necatorone has been obtained by a six-step synthesis starting from 2-(3,4-dimethoxyphenyl)ethylamine and 2-nitro-5-methoxybenzoyl chloride.

Extracts of the toadstool Lactarius necator exhibit considerable mutagenic activity according to the Ames test[3]. Recently Suortti and coworkers[4] isolated a highly mutagenic compound necatorin from this fungus and proposed a coumarocinnoline formula for it[5]. Independent work on the pigments of L. necator has led us to the isolation of an alkaloid necatorone, for which structure **1** was deduced from its spectral data[6]. Necatorone has the same molecular formula as necatorin and direct comparison of both compounds has established their identity[7]. Because of the paucity of necatorone and its interesting biological activity a synthesis of this compound was desirable.



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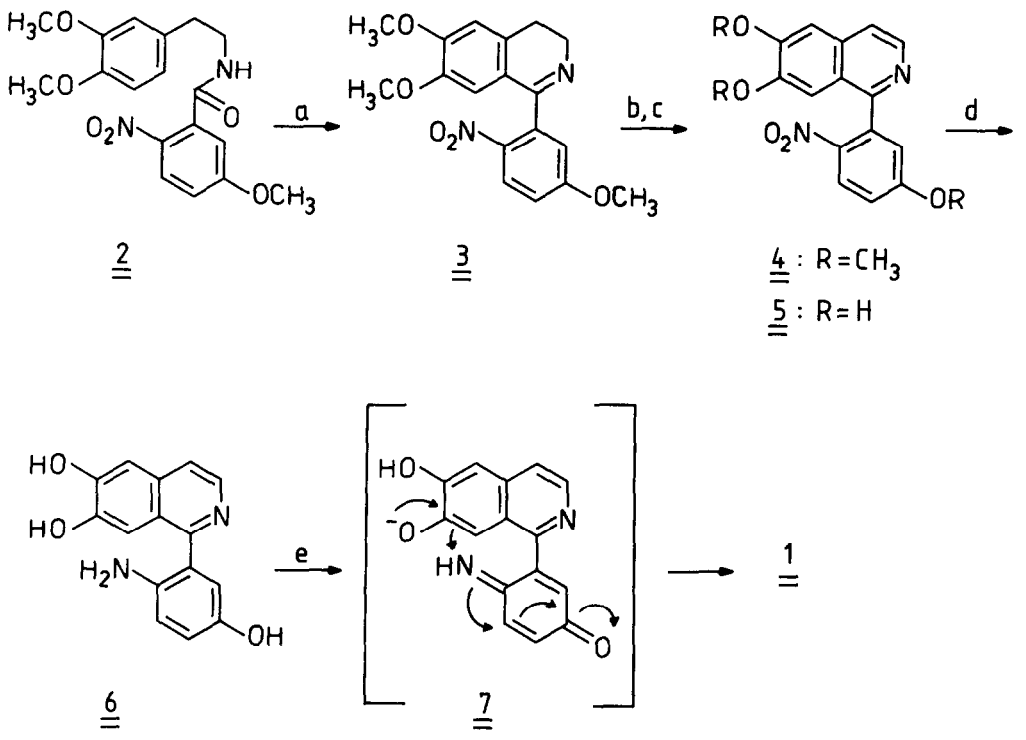
Condensation of 2-(3,4-dimethoxyphenyl)ethylamine with 5-methoxy-2-nitrobenzoyl chloride[8] yielded the amide **2**[9], which on Bischler-Napieralski cyclization ($POCl_3$, acetonitrile, reflux, 4.5 h) was converted into the dihydroisoquinoline derivative **3**. Dehydrogenation was achieved most satisfactorily

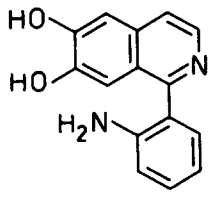


(a) $POCl_3$, CH_3CN (85-93%); (b) MnO_2, C_6H_6, 24 h, reflux (90-98%); (c) 48% HBr (64%); (d) H_2/Pd-C (80-85%); (e) 5% aqueous NaOH/O_2 (67%).

with MnO_2[10] in benzene under azeotropic water removal and the isoquinoline derivative **4** was obtained in 90-98% yield. Demethylation of **4** with 48% HBr (11 h reflux, argon atmosphere) and hydrogenation of the resulting phenol **5** with H_2/Pd-C in methanol/water/acetic acid (2:2:1) gave amine **6**, which could be oxidatively cyclized to necatorone by stirring with 5% aqueous sodium hydroxide in the presence of air (25°C, 12 h). During this reaction necatorone is partially precipitated as its purple disodium salt. The yield is strongly dependent on the amount of amine oxidized. With 10 mg batches a yield of 67% was obtained, however with increasing amounts of amine a drastic decrease in yield was observed. The product was identical with the natural compound[11]. The conversion of aminophenol **6** into **1** appears to occur via a quinone-imine intermediate **7**, formed on oxidative dehydrogenation of **6**.

Electrophilic attack of this species at the neighbouring phenol ring could lead to the formation of the C-N bond for which is ample precedent in Corbetts' work on indophenol coupling[12]. Attempts to cyclize the corresponding deoxy derivative **8** under oxidative conditions were without success. Obviously the formation of an ortho-quinone intermediate does not occur because of its high energy content.

An attempt to obtain the skeleton of necatorone by treatment of **4** with triethyl phosphite led to the formation of 2,3,11-trimethoxyindazolo[3,2-a]-isoquinoline (**9**)[13]. After heating the nitro derivative **3** in conc. sulfuric acid to 170°C small amounts of **1** could be detected in the TLC, however due to the formation of a number of byproducts this approach was not investigated further.



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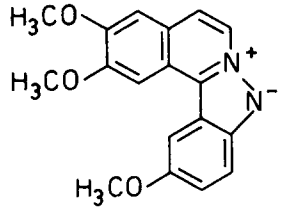

9

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References and notes

1. Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.
2. Pigments of Fungi, 48. - Part 47: W. Steglich, H.-Th. Huppertz and B. Steffan, Angew. Chem., in print.
3. O. Sterner, R. Bergmann, E. Kesler, G. Magnusson, L. Nilsson, B. Wickberg, E. Zimerson and G. Zetterberg, Mutation Research **101**, 269 (1982); O. Sterner, R. Bergman, C. Franzén, E. Kesler and L. Nilsson, ibid. **104**, 233 (1982); A. v. Wright and T. Suortti, ibid. **121**, 103 (1983).
4. T. Suortti and A. v. Wright, J. Chromatogr. **255**, 529 (1983); T. Suortti, ibid. **301**, 303 (1984).

5. T. Suortti, A. v. Wright and A. Koskinen, Phytochemistry **22**, 2873 (1983).

6. B. Fugmann, B. Steffan and W. Steglich, Tetrahedron Lett. **25**, 3575 (1984).

7. We thank Dr. Suortti for a sample of necatorin. The comparison was carried out by TLC, HPLC and ^{1}H-NMR.

8. J.W. Telley and J. Kudless, Org. Prep. Proced. Int. **13**, 189 (1981).

9. All new compounds showed satisfactory elemental analyses. The melting points and the spectroscopic data are as follows: **2**, mp 141-142°C; ^{1}H-NMR ($CDCl_3$): δ = 2.85 (t, J=6.6 Hz, 2H), 3.62 (q, J=6.6 Hz, 2H), 3.78-3.90 (m, 9H), 6.37 (t, J=6.6 Hz, 1H), 6.70-6.80 (m, 4H), 6.88 (dd, J=9+2.4 Hz, 1H), 7.99 (d, J=9 Hz, 1H). **3**, mp 138-139°C; ^{1}H-NMR ($CDCl_3$): δ = 2.83 (t, J=6.6 Hz, 2H), 3.58 (s, 3H), 3.82 (t, J=6.6 Hz, 2H), 3.87 (s, 6H), 6.32 (s, 1H), 6.77 (s, 1H), 6.91-7.11 (m, 2H), 8.08 (d, J=9.6 Hz, 1H). **4**, mp 111-112.5°C; ^{1}H-NMR ($CDCl_3$): δ = 3.70 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 6.78 (s, 1H), 6.93-7.17 (m, 3H), 7.48 (d, J=5.7 Hz, 1H), 8.17 (d, J=9.6 Hz, 1H), 8.38 (d, J=5.7 Hz, 1H). **5**, mp 310°C (decomp.); ^{1}H-NMR ([D_6]DMSO/CD_3OD): δ = 6.87 (d, J=2.7 Hz, 1H), 6.90 (s, 1H), 7.07 (dd, J=9+2.7 Hz, 1H), 7.23 (s, 1H), 7.53 (d, J=6 Hz, 1H), 8.23 (d, J=9 Hz, 1H), 8.25 (d, J=6 Hz, 1H). **6**, mp 290°C (decomp.); ^{1}H-NMR [D_2O + 1 drop CF_3CO_2D, internal standard sodium 3-(trimethylsilyl)propanesulfonate]: δ = 6.98 (s, 1H), 7.21 (d, J=2.7, 1H), 7.43 (dd, J=9+2.7 Hz, 1H), 7.46 (s, 1H), 7.73 (d, J=9 Hz, 1H), 8.19 (d, J=6.6 Hz, 1H), 8.44 (d, J=6.6 Hz, 1H). **8**, mp 248-249°C (decomp.); ^{1}H-NMR ([D_6]DMSO/CD_3OD): δ = 6.63-7.00 (m, 2H), 7.06-7.33 (m, 4H), 7.51 (d, J=5.7 Hz, 1H), 8.21 (d, J=5.7 Hz, 1H). **9**, mp 189-191°C; UV (MeOH): λ_{max}(log ε) = 208 (4.43), 221 (4.31, sh), 252 (4.50), 260 (4.47), 272 (4.30, sh), 280 (4.35), 292 (4.23), 311 (4.06), 332 (3.91), 361 (3.89), 381 (4.14), 402 nm (4.17); ^{1}H-NMR ($CDCl_3$): δ = 3.93 (s, 3H), 4.00 (s, 3H), 4.07 (s, 3H), 7.05 (s, 1H), 7.07 (d, J=7.4 Hz, 1H), 7.24 (dd, J=9.25+2.3 Hz, 1H), 7.38 (br. d, J=2.3 Hz, 1H), 7.63 (s, 1H), 7.80 (dd, J=9.25+0.75 Hz, 1H), 8.34 (d, J=7.4 Hz, 1H) ppm.

10. A.J. Fatiadi, Synthesis **1976**, 65 (procedure on page 67).

11. Synthetic necatorone showed strong activity in the Ames test (plate incorporation assay): C. Franzén, R. Bergman, L. Nilsson, O. Sterner and B. Wickberg, Mutation Research, in press, and T. Suortti, unpublished results. We thank Dr. Sterner and Dr. Suortti for informing us about their results. When the Ames test was carried out using the spot test procedure, negative results were obtained[6].

12. J.F. Corbett, J. Chem. Soc. (B) **1970**, 1502, and further publications of this author.

13. Compare J.P. Reddy, Indian J. Chem. **15B**, 1133 (1977).

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