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SYNTHETIC STUDIES ON OXINDOLE SPIRO-LACTONES WITH THALLIUM(III) TRINITRATE: A FORMAL TOTAL SYNTHESIS OF (±)-TRYPTOQUIVALINE G

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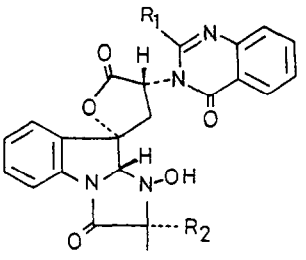
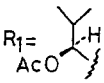
(±) – Tryptoquivaline G was formally synthesized through shortened steps from tryptophan, in which oxidation with thallium(III) trinitrate(TTN) was effected at the crucial stage. The present work also constitutes the first synthesis of oxindole lactones carrying 2-alkyl quinazolinones.

Tryptoquivalines(1-3), the potent tremorgenic toxins isolated from *Aspergillus clavatus* and *Aspergillus fumigatus* of mold damaged rice, have a unique hexacyclic skeleton including a spiro-γ-lactone, which structure was elucidated by two groups of Büchi[1] and Yamazaki[2], independently. Later, Büchi and co-workers[3] reported the first total synthesis of tryptoquivaline G(3).[4] Another synthetic approach had been attempted by us, which was realized by the effective synthesis of the Büchi's intermediate through TTN oxidation at the crucial step. Thus, we report here not only a formal synthesis of (±)-tryptoquivaline G(3), but also the synthesis of oxindole spiro-γ-lactones carrying 2-alkyl quinazolinones(20 and 21).

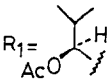


1, tryptoquivaline



R_1= , R_2= Me

2, nortryptoquivaline



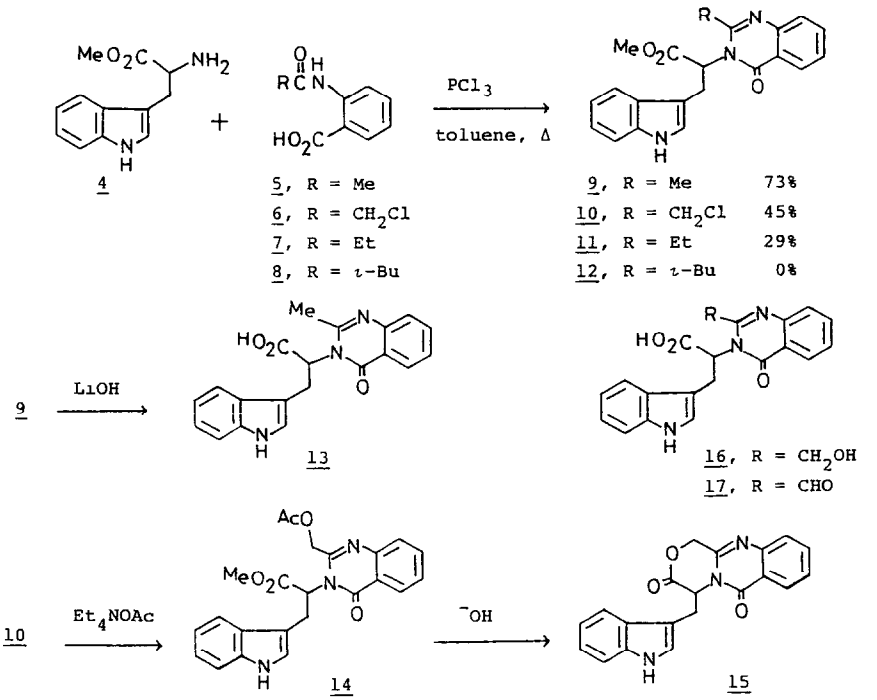
R_1= , R_2= H

3, tryptoquivaline G

R_1 = H , R_2 = Me

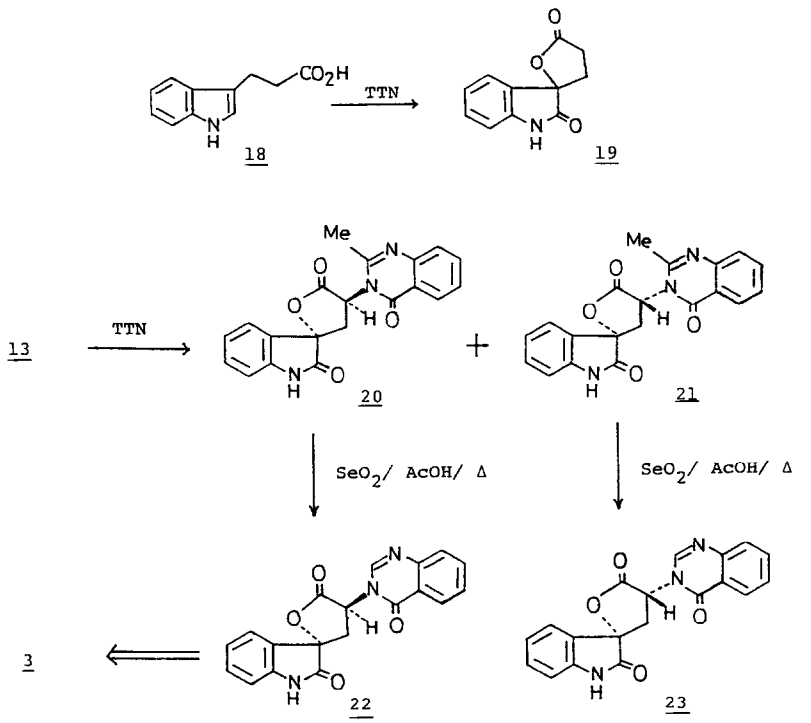
The synthesis of the congested quinazolinones 9-12 by condensation of L-tryptophan methyl ester(4) with N-acyl-anthranilic acids(5-8) was not easy, and effected by use of phosphorus trichloride[5] in toluene-HMPA(50:1) at reflux for 3 h to give the products 9-10[6] in moderate yields except the most desired one 12 because of the extraordinary steric hindrance. Hydrolysis of 9 with lithium hydroxide (10 equiv) in aq MeOH at reflux afforded unfortunately the racemized

acid 13[IR(Nujol) 1700 and 1670 cm^{-1}; ^1H NMR(acetone-d_6) δ1.96(s, 3), 4.82(d, 2, J=10Hz), 5.25(t, 1, J=10Hz), 6.9-8.3(m, 8) and 10.87(broad, 1)ppm; MS m/e 347 (M^+) and 187(base peak); a quantitative yield]. However, hydrolysis(K_2CO_3, aq MeOH, rt) of racemic acetoxy derivative 14[7] which was derived from 10 with tetraethylammonium acetate in acetone, afforded the δ-lactone 15 (80%)[mp 225-227°, IR(Nujol) 3400, 1760 and 1680 cm^{-1}; ^1H NMR(DMSO-d_6) δ4.54(d, 1, J=15Hz), 4.71(d, 2, J=5Hz), 6.59(d, 1, J=15Hz), 5.77(t, 1, J=5Hz), 6.7-7.9(m, 7), 8.34(d, 1, J=8Hz) and 10.29(broad, 1); MS m/e 345(M^+) and 130(base peak)], on which the desired alcohol 16 was not obtained, although it was expected to furnish the aldehyde 17 at the subsequent step.



Prior to oxidative lactonization of 13 with TTN,[8] the oxidation of some indole compounds with this reagent was investigated and proved to give the spiro-γ-lactones and the isatin derivatives in moderate yields.[9] As a typical example, indole-3-propionic acid(18) was oxidized [TTN(2.0 equiv), 5% aq CH_3CN, -10°, 15 min] to give spiro-lactone 19 (54%)[mp 121-2°(lit[10] 120-3°)]. Based upon these experimental data, oxidative cyclization of the acid 13 was effected [TTN(2.5 equiv), CH_3CN-DMF-H_2O(12:4:1), -60°→20°, 3 h] to give 20[11] (24%)(mp 236-237°) and 21[12] (47%)(mp 276-277°) after careful separation by silica gel

chromatography(2% MeOH-CH_2Cl_2). Contrary to expectation, treatment of 20 with selenium oxide(2 equiv) in glacial acetic acid at 90° for 2 h afforded the demethylated product 22[13] in 34% yield. In a similar manner, the isomer 21 gave 23[14] in 59% yield. The spectral data (IR and NMR) of 22 and 23 were identical with those of the known respective isomers.[3] The yield of the isomer 22 was raised up to 62% overall yield (from 13) on carrying out the oxidative demethylation reaction without separation of 20 after TTN oxidation of 13. It was observed that the isomer 20 was easily epimerized to the isomer 21 during silica gel chromatography, but the isomer 22 was more predominant over 23, although the reason has not yet been clarified. As the synthesis of (±)-tryptoquivaline G(3) from 22 was achieved by Büchi,[3] the present work constitutes a formal synthesis of 3, suggesting a possible route to the synthesis of other tryptoquivalines. In line with this principle, further studies are in progress.



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6. The compound 9[mp 212°, $[\alpha]_D^{20}$ -555°(c 0.2, acetone) IR(Nujol)3250, 1735 and 1715 cm^{-1}; ^1H NMR($CDCl_3$) δ1.85(s, 3), 3.74(s, 3), 3.6-3.8(m, 2), 4.91(m, 1), 6.62(d, 1, J=3Hz), 6.9-7.7 (m, 7), 8.25(d, 1, J=7Hz), and 8.56(broad s, 1) ; MS m/e 361(M^+) and 201(base peak)]: the compound 10[mp 192-5°, IR(Nujol) 3350, 1750 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.32(d, 1, J=13Hz), 3.79(s, 3), 3.86(d, 1, J=13Hz), 3.7-4.0(m, 2), 5.06(q, 1, J=5Hz), 6.68(d, 1, J=3Hz), 7.8-8.8(m, 7), 8.31(d, 1, J=8Hz) and 8.36(broad s, 1); MS m/e 397, 395(M^+) and 201(base peak)].

7. The compound 14[IR(Nujol) 3375, 1760, 1759 and 1655 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.93(s, 3), 3.77(s, 3), 3.6-3.9(m, 3), 4.36(s, 2), 4.92(q, 1, J=6Hz), 6.64 (d, 1, J=3Hz), 6.8-7.8(m, 7) and 8.39(m, 2); MS m/e 419(M^+) and 201(base peak)].

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11. The compound 20[IR(Nujol) 1780, 1740 and 1670 cm^{-1}; ^1H NMR($CDCl_3$-DMSO-d_6) δ 2.88(s, 3), 5.60(t, 1, J=8Hz), 6.98(d, 1, J=8Hz), 7.07(t, 1, J=8Hz), 7.2-7.5 (m, 3), 7.7-7.8(m, 1), 8.30(d, 1, J=8Hz), and 10.41(s, 1); MS m/e 361(M^+)].

12. The compound 21[IR(Nujol) 1790, 1750 and 1675 cm^{-1}; ^1H NMR($CDCl_3$-DMSO-d_6) δ 2.78(s, 3), 5.58(t, 1, J=8Hz), 6.96(d, 1, J=8Hz), 7.12(t, 1, J=8Hz), 7.3-7.5 (m, 3), 7.6-7.8(m, 1), 8.25(d, 1, J=8Hz) and 10.34(s, 1); MS m/e 361(M^+)].

13. The compound 22[IR(Nujol) 1790, 1745 and 1670 cm^{-1}; ^1H NMR(DMSO-d_6) δ3.07(d, 2, J=10Hz), 3.62(t, 1, J=10Hz), 7.9-8.0(m, 7), 8.41(d, 1, J=8Hz), 8.70(s, 1) and 10.94(s, 1); MS m/e 347(M^+), 303 and 157(base peak)].

14. The compound 23[IR(Nujol) 1790, 1745 and 1670 cm^{-1}; ^1H NMR($CDCl_3$-DMSO-d_6) δ 2.95(dd, 1, J=8, 10Hz), 3.51(dd, 1, J=8, 10Hz), 5.80(t, 1, J=8Hz), 6.94(d, 1, J=8Hz), 7.12(d, 1, J=8Hz), 8.35(t, 1, J=8Hz), 8.57(t, 1, J=8Hz), 8.7-8.8(m, 2), 8.50(s, 1) and 10.64(s, 1); MS m/e 347, 303 and 130(base peak)].

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