REACTIONS WITH INDOLE DERIVATIVES, XLVIII[1]

A Simple Synthesis of the Staurosporine Aglycon

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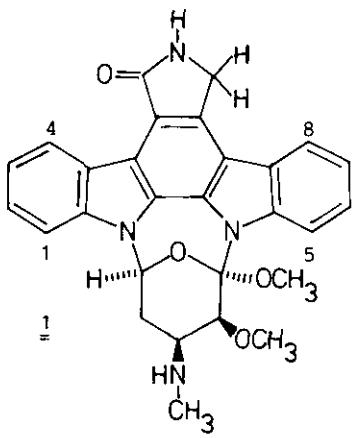
Abstract —— The staurosporine aglycon is prepared from tryptamine and ß-indole acetic acid in two consecutive cyclization reactions.

Staurosporine (1) - a metabolite of streptomyces staruosporeus was isolated by Japanese workers[2] and X-ray structure determination[3] revealed this compound to be a polycyclic indole derivative which may be regarded as a combination of a heterocyclic aglycon with a desoxy-amino sugar. Two years later Steglich and coworkers reported on compounds (2), (3), and (4) from fungi (arcyria denundata) proving the heterocyclic part to be a quite common naturally occurring compound[4]. This group after preparing symmetric compounds of this type also demonstrated the proton catalyzed cyclization converting (2) into (4).



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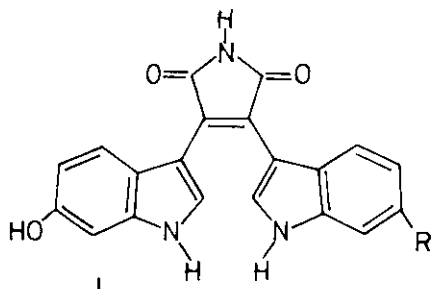
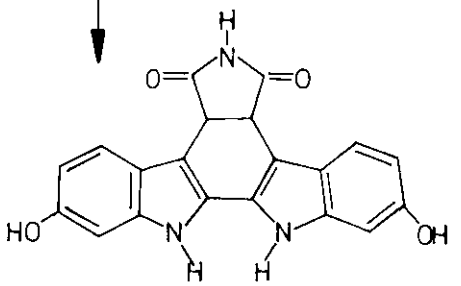


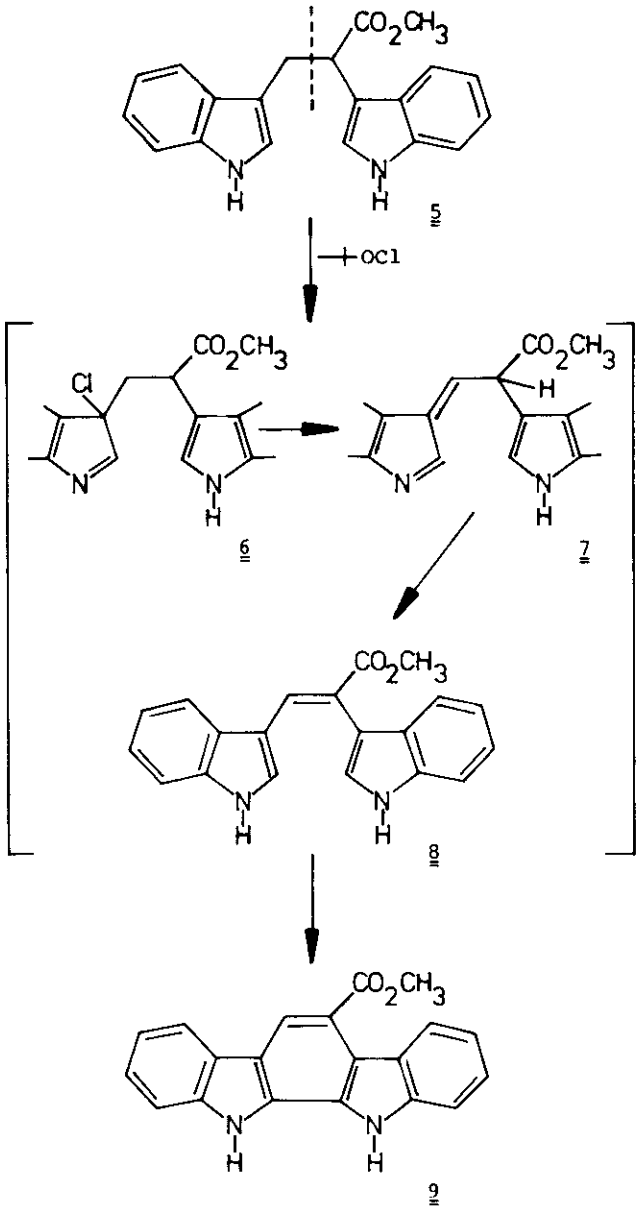
2 R = OH
3 R = H



4 Arcyriaflavin C

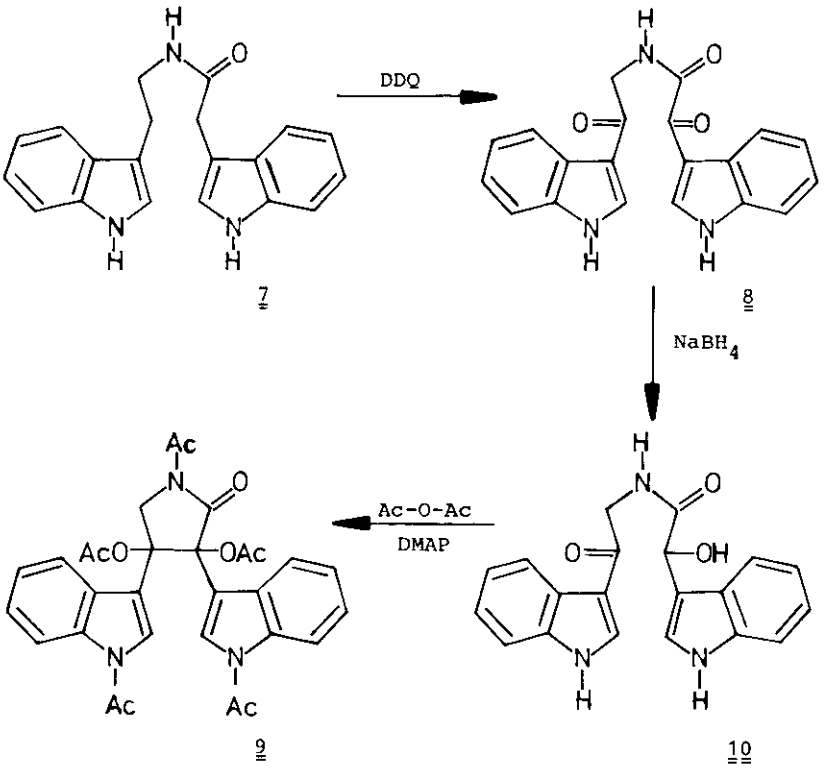
2 ⟶ Arcyriarubrin C
3 ⟶ Arcyriafubrin B

General cyclization techniques for the generation of indolocarbazols using the Fischer method have been applied by various groups[5]. As the heterocyclic part in the staurosporine case is non symmetric we got interested in the electrocyclic transformation (8) ⟶ (9) as a biosynthetic model reaction.



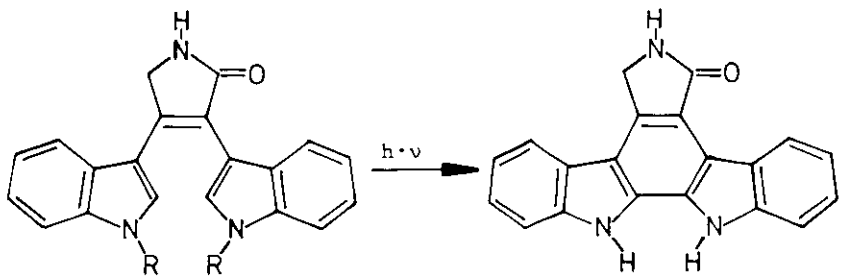
Interestingly, (5) which is easily obtained from β-indole acetate by gramine alkylation, on treatment with tert.butyl hypochlorite gave directly the pentacyclic reaction product (9). Intermediates (6), (7), and (8) are very probably involved although none of them could be isolated. Obviously the transformation into the natural product type compound is a very quick and easy process. For

the aglycon synthesis, amide (7) was prepared from the corresponding acid chloride and tryptamine and the recently reported oxydation of indole compounds with DDQ in a mixture of water and tetrahydrofuran[6] transformed it into diketone (8). On selective borohydride reduction (8) gives rise to



7 8 9 10

the hydroxyketone (10) in excellent yield. The corresponding diol is only obtained after addition of lithium chloride to the reaction mixture. Acetylation of (10) in the presence of DMAP was accompanied by cyclization and gave directly rise to pentaacetate (9). Although various procedures for the reduction of α-acetoxycarbonyl compounds are reported in the literature[7,8,9,10,11,12], acceptable yields of (11) were only obtained with $TiCl_3$[10] in aqueous acetone.



11 R = $COCH_3$
12 R = H

13

All efforts to achieve photocyclization with the diacetate (11) were completely in vain. Even after addition of oxydation reagents only starting material was reisolated. Smooth deacetylation with sodium bicarbonate in aqueous methanol gave rise to (12) which cyclized readily on irradiation in methanol to yield 65% of (13). NMR data of this compound as well as UV absorption corresponded nicely to staurosporine (see table), the absence of the α-indole proton in the NMR spectrum proving the successful cyclization beyond any doubt.

Table. δ-Value Comparison

	C_4-H	C_8-H	CH_2
(1)	9.26	7.92	4.90
(13)	9.20	8.04	4.96

As two different building blocks are involved (see 7) this method will lend itself to the preparation of non symmetric hexacyclic compounds of type (13) bearing various substituents on carbon and nitrogen atoms of both indole moieties.

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EXPERIMENTAL PART

Bis-indolyl-methylpropionate (5): 3.5 g β-Indolyl-methylacetate dissolved in 50 ml dry tetrahydrofuran are added at -78°C to 75 mmol LDA dissolved in 20 ml dry tetrahydrofuran. After 30' the temperature is allowed to rise to -20°C and 6 g of β-indolylmethylene-trimethyl ammonium iodide are added. The mixture is left at -20°C for two hours and then under constant stirring poured slowly into 60 ml 2N hydrochloric acid. After extraction with ether the organic layer is washed with saturated sodium bicarbonate solution and with brine. The solution is concentrated under vacuum, filtered through a silica column (ether - petrolether 1 : 1) and evaporated. The oily residue crystallizes from toluene yielding 3.6 g (61%) crystals melting at 121°C.

UV (CH_3OH) λ_{max} 223, 270, 279, 288 nm (ε = 21870, 8875, 9305, 8825); IR (KBr) 3410, 1720 cm^{-1}; ^{1}H-NMR (90 MHz, CD_3CN) δ 3.17 - 3.89 (2H, m), 3.54 (3H, s), 4.31 (1H, dd, J 7 Hz, J 9 Hz), 6.92 - 7.80 (10H, m), 9.1 (2H, s, broad); MS (210°C) $M^{\oplus}$ 318 ME (14%), 259 (5), 189 (10), 188 (10), 130 (100); $C_{20}H_{18}N_2O_2$ (318.4). Calcd. C, 75.45, H, 5.70, N, 8.80; Found C, 75.53, H, 5.75, N, 8.69.

Pentacyclic methyl ester (9): 490 mg of ester (5) are dissolved in 12 ml dry methylene chloride and treated with 0.21 ml triethylamine. After cooling to 0°C 0.21 ml tert.butyl hypochlorite are added. The mixture is left for 45 min at 0°C and treated with ice for work up. Extraction with methylene chloride, evaporation, and chromatography on silica (ether - petrolether 1 : 1) yielded 110 mg (23%).

UV (CH_3OH): λ_{max} 208, 218, 225, 228, 288, 325, 340, 357 nm (ε = 1780, 1810, 2015, 2030, 1330, 385, 280, 205); IR (KBr) 3395, 1710 cm^{-1}; ^{1}H-NMR (90 MHz, CD_3CN) δ 4.07 (3H, s), 6.95 - 7.89 (6H, m), 8.24 (1H, m), 8.71 (1H, m), 9.04 (1H, m), 10.74 (2H, s, broad); MS (260°C) $M^{\oplus}$ 314 ME (35%), 313 (100), 283 (14), 255 (61), 157 (15), 127 (21); $C_{20}H_{14}N_2O_2$, Calcd. 314.1055, Found 314.1054 (mass-spectroscopic).

Amide (7): 32 g Tryptamine in 900 ml dry methylene chloride are treated at room temperature with 18 g ß-indolylacetyl chloride dissolved in 750 ml dry methylene chloride. The precipitate is filtered, suspended in 1 l methylene chloride, stirred overnight and filtered again. The combined methylene chloride phases are washed with 2N HCl and with saturated sodium bicarbonate solution. After evaporation under vacuum the residue is crystallised from methanol yielding 23 g (77%) of amide (7) melting at 161°C.

UV (CH_3OH): λ_{max} 273, 280, 290 nm (ε = 10450, 11280, 9770); IR (KBr) 4308, 3300, 1644, 1529, 1340 cm^{-1}; ^{1}H-NMR (90 MHz, acetone-d_6) δ 10.11 (1H, s, broad), 9.90 (2H, s, broad), 7.63 - 6.89 (10H, m), 3.62 (2H, s), 3.67 - 3.58 (2H, m), 2.86 (2H, tr, J 7 Hz); MS (240°C) $M^{\oplus}$ 317 ME (9%), 176 (8), 143 (56), 130 (100); $C_{20}H_{19}N_3O$ (317.4). Calcd. C, 75.68, H, 6.04, N, 13.24; Found C, 75.72, H, 6.22, N, 13.19.

Diketone (8): 4.2 g DDQ are dissolved in a mixture of 15 ml tetrahydrofuran and 100 ml water. At 0°C a solution of 13.5 g amide (7) in 160 ml tetrahydrofuran and 20 ml water is added under constant stirring. Stirring is continued for 30 min at room temperature, 40 g sodium carbonate and 250 ml methylene chloride are added. The mixture is stirred for another 15 min and the organic layer is separated. The water phase is extracted with methylene chloride, the methylene chloride phases are combined, washed with saturated sodium bicarbonate solution and with brine and evaporated under vacuum. The residue crystallised from methanol (5.2 g; 35%) and melted at 265-269°C (decomposition).

UV (CH_3OH): λ_{max} 214, 243, 258, 275, 303 nm (ε = 25390, 15780, 15780, 13900, 15490); IR (KBr) 3385, 3300, 2965, 1673, 1637, 1620, 1522 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 4.72 (2H, d, J 5.5 Hz, 7.16 - 7.64 (6H, m), 8.11 - 8.37 (2H, m), 8.53 (1H, m), 8.85 (1H, m), 9.13 (1H, tr, J 5.5 Hz), 12.08 (1H, s, broad), 12.26 (1H, s, broad); $C_{20}H_{15}N_3O_3$, Calcd. 345.1113, Found 345.1112 (mass-spectroscopic).

Hydroxy-ketone (10): 3.4 g of diketone (8) and 1.1 g sodium borohydride are mixed in 220 ml dry isopropanole and stirred for 17h at room temperature. The product is filtered off and the isopropanol is diluted with water and extracted with methylene chloride. The solvent is evaporated, the residue combined with the filtered crystals and the whole material is crystallised from methanol. Yield 2.9 g (85%), m.p. 250°C.

UV (CH_3OH): λ_{max} 224, 243, 265, 284, 292, 303 nm (ε = 29210, 12750, 11520, 13300, 13990, 11660); IR (KBr) 3398, 3110, 3063, 1657, 1640, 1522 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 12.0 (1H, s, broad), 10.96 (1H, s, broad), 8.34 - 8.11 (2H, m), 7.78 - 6.91 (8H, m), 5.95 (1H, d, J 4.5 Hz), 5.25 (1H, d, J 4.5 Hz), 4.57 (1H, d, J 5 Hz); MS (280°C) $M^{\oplus}$ 347 ME (2%), 330 (6), 159 (33), 157 (35), 144 (100), 131 (38), 117 (38); $C_{20}H_{17}N_3O_3$ (347.4). Calcd. C, 69.15, H, 4.93, N, 12.10; Found C, 68.77, H, 4.96, N, 12.10.

Pentaacetate (9): 500 mg of carbinol (10) and 250 mg N,N-dimethylaminopyridine (DMAP) are dissolved in 8 ml pyridine and 4 ml acetic acid anhydride are added. After 45 min at 80°C the mixture is treated with 40 ml 1N HCl and extracted once with ether and three times with methylene chloride. The combined organic layers are washed with sodium bicarbonate and evaporated. On treatment with ether the residue crystallises yielding 700 mg (87%) crystals (m.p. 214°C).

UV (CH_3OH): λ_{max} 236, 262, 290, 298 nm (ε = 24530, 12680, 11220, 11590); IR ($CHCl_3$) 3090, 1771, 1752, 1712, 1450, 1380 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.32 - 8.10 (2H, m), 7.51 - 6.80 (8H, m), 5.19 (1H, d, J 13 Hz), 6.67 (1H, d, J 13 Hz), 2.71 (3H, s), 2.37 (3H, s), 2.33 (3H, s), 2.13 (6H, s); MS (320°C) $M^{\oplus}$ 557 ME (10%), 513 (5), 497 (30), 439 (30), 397 (15), 355 (30), 354 (30), 311 (35), 256 (95), 187 (45), 144 (100); $C_{30}H_{27}N_3O_8$. Calcd. 557.1798, Found 557.1797 (mass spectroscopic).

Diacetate (11): 1.8 g of pentaacetate (9) dissolved in 225 ml acetone are mixed with 18 ml of an aqueous $TiCl_3$ solution (15%) and refluxed for 60 min. The mixture is cooled, poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The solvent is evaporated and the residue purified by silica chromatography (reversed phase, silica 60, Merck At. 7719) with water - methanol 45/55. The pure fractions are combined and yield 350 mg of crystals melting at 151 - 153°C.

UV (CH_3OH): λ_{max} 221, 255, 291, 299, 322 nm (ε = 12620, 7440, 6270, 6850, 3340); IR (KBr) 2925, 1711, 1450, 1379 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 8.64 (1H, s, broad), 8.37 - 8.22 (2H, m), 8.09 (1H, s), 7.97 (1H, s), 7.34 - 6.95 (6H, m), 4.59 (2H, s), 2.60 (3H, s), 2.52 (3H, s); MS (200°C) $M^{\oplus}$ 397 ME (40%), 354 (45, 313 (71), 312 (70), 144 (100); $C_{24}H_{19}N_3O_3$. Calcd. 397.1426, Found 397.1424 (mass-spectroscopic).

Unsaturated Lactam (12): 350 mg of diacetate (11), dissolved in a mixture of 40 ml methanol and 10 ml water is treated with 10 ml saturated sodium bicarbonate solution and left at room temperature for 50 min. More water is added and the reaction product is extracted with methylene chloride. After evaporation of the solvent the residue is purified by TLC yielding 170 mg (62%) of pure material showing the following data:

UV (CH_3OH): λ_{max} 223, 277, 286, 338, 353 nm (ε = 9300, 4310, 4070, 3260, 2570); IR (KBr) 3400, 3055, 2950, 1665, 1540, 1262 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 11.52 (1H, s, broad), 11.39 (1H, s, broad), 8.19 (1H, s, broad), 7.50 - 6.63 (10H, m), 4.54 (2H, s); MS (210°C) $M^{\oplus}$ 313 ME (100%), 284 (68), 270 (20), 255 (11), 254 (11); $C_{20}H_{15}N_3O$. Calcd. 313.1215, Found 313.1212 (mass-spectroscopic).

Staurosporine aglykon (13): 280 mg of unsaturated lactam (12) dissolved in 50 ml methanol is irradiated with a high pressure mercury lamp till consumption of starting material is indicated by TLC. The solvent is evaporated and the residue purified by TLC (ether/methanol 9 : 1). One obtains 180 mg (65%) of 13 melting at 323-326°C (decomp.):

UV (CH_3OH): λ_{max} 237, 291, 321, 335, 346, 361 nm (ε = 5350, 13210, 3070, 3780, 2990, 2050); IR (KBr) 3440, 3310, 3060, 2960, 1650, 1588, 1490 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-d_6) δ 4.96 (2H, s), 7.10 - 7.83 (6H, m), 8.47 (1H, s, broad), 9.20 (1H, m), 12.28 (1H, s, broad), 12.50 (1H, s, broad); MS (240°C) $M^{\oplus}$ 311 ME (100%), 283 (61), 256 (30); $C_{20}H_{13}N_3O$. Calcd. 311.1059, Found 311.1056 (mass-spectroscopic).

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