Tetrahedron Vol. 40, No. 14, pp. 2795 to 2797, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd.

INDOLE-2,3-QUINODIMETHANES

SYNTHESIS OF SELECTIVELY PROTECTED DERIVATIVES OF THE FUSED DIMERIC INDOLE ALKALOID STAUROSPORINONE

PHILIP D. MAGNUS* and NANCY L. SEAR
Department of Chemistry, Indiana University, Bloomington, IN 47405, U.S.A.

(*Received in USA* 5 *August* 1983)

Abstract—The imine **1** was converted via an indole-2,3-quinodimethane cyclization to the hexahydroindolocarbazole **7**, which was further converted to the N-carbomethoxy derivative of staurosporinone **2**.

In the preceding paper[1] we described the use of indole-2,3-quinodimethane intermediates for the synthesis of indolocarbazoles. We indicated that a protected tryptamine derivative such as **1** could provide the appropriate functionality for making the lactam ring to complete the synthesis of staurosporinone **2**, the aglycone of staurosporine **3**.[2] Here is reported the implementation of that plan. Raphael[3a] has recently described a synthesis of N-benzylstaurosporinone, and Winterfeldt[3b] a synthesis of staurosporinone itself.

Tryptamine was converted into the phthalimido derivative **4** by standard methods,[4] and the indole N atom protected by treatment of **4** with *p*-$MeOC_6H_4SO_2Cl$/NaH/DMF to give **5** (83%). The 2-formyl group was introduced into **5** by treatment with α,α-dichloromethylmethylether–$TiCl_4$–35° to give **6** (82%). Condensation of **6** with 2-aminostyrene, readily gave the required imine **1**. It was subjected to the standard conditions for generating an indole-2,3-quinodimethane intermediate (methylchloroformate–chlorobenzene–140°) to give the pentacyclic carbamate **7** as a 4:1 mixture of epimers at the methylenephthalimido group (C-6). Dehydrogenation of **7** (DDQ–toluene–reflux) gave the indolocarbazole **8** (63% from **1**). The phthalimido protecting group was selectively removed by treatment of **8** with hydrazine hydrate in THF at 20° to give **9** (60%). Treatment of the amine **9** with phosgene in dichloromethane, followed by titanium tetrachloride (0°) gave the hexacyclic indolocarbazole **10** (54%).

Because of the different protecting groups on the carbazole N atoms, we were able to selectively remove the *p*-$MeOC_6H_4SO_2$-group using Li–NH_3–THF to give **11** (76%). Also treatment of **10** with KOH/glyme gave **12** (57%), thereby offering the potential to regiospecifically attach carbohydrate substances to the free carbazole N atoms in a controlled manner.

EXPERIMENTAL

1 - [(p - *Methoxyphenyl*)*sulfonyl*] - 3-(2'-*phthalimidoethyl*) *indole* **5** (R = p-$MeOC_6H_4SO_2$–; R^1 = H) N-Phthaloyl tryptamine **4** ($R = R^1$ = H)[4] (3.48 g 12 mmol) in dimethylformamide (30 ml) was added dropwise to a slurry of NaH [(607 mg, 15 mmol) 59.3% dispersion in mineral oil, which was washed with dry hexane (3 × 10 ml) in DMF (20 ml) at 0°. The red soln was stirred at 20° for 1 hr and p-methoxybenzene sulfonyl chloride (3.09 g 15 mmol) in DMF (20 ml) added. After 0.5 hr at 20° the mixture was poured into ice water (50 ml), stirred vigorously for 0.5 hr and the tan ppt filtered off. The ppt was purified by flash chromatography over silica gel, eluting with $CHCl_3$–hexane (1:1) to give **5** (4.62 g 83%), m.p. 170–171° (from EtOAc–hexane). IR ($CHCl_3$) 1770, 1709, and 1599 cm^{-1}. NMR ($CDCl_3$) δ 3.04 (3H, t, J = 8 Hz), 3.74 (3H, s), 3.96 (2H, t, J = 8 Hz), 6.82 (2H, d, J = 9 Hz), 7.35–7.19 (2H, m), 7.45 (1H, s), 7.63 (1H, d, J = 8 Hz), 7.84–7.68 (5H, m), 7.96 (1H, d, J = 8 Hz). (Found; C, 64.92; H, 4.42; N, 5.96. Calc for $C_{25}H_{20}N_2O_5S$. C, 65.21; H, 4.38; N, 6.08%.)

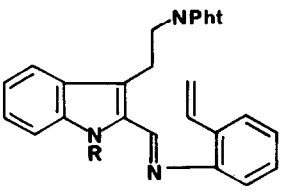
1-[(p-*Methoxyphenyl*)*sulfonyl*]-3-(2'-*phthalimidoethyl*)-2-*formylindole* **6** (R = p-$MeOC_6H_4SO_2$–; R^1 = CHO). To a soln of **5** (920 mg 2 mmol) in CH_2Cl_2 (20 ml) was added α,α-dichloromethylmethylether (2.30 g 20 mmol) and the mixture cooled to −35°. $TiCl_4$ (3.79 g 20 mmol) in CH_2Cl_2 (5 ml) was added and the mixture stirred at −35° for 0.5 hr.

The mixture was poured into ice water (50 ml), stirred for 0.5 hr and the CH_2Cl_2 layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml), and the combined extracts washed with NaCl aq (30 ml), dried (Na_2SO_4) and evaporated to give a foam. Flash chromatography of this foam over silica gel, eluting with EtOAc–hexane (10–50%) gave **6** (805 mg 82%), m.p. 183–184° (from EtOAc–hexane). IR ($CHCl_3$) 1770, 1710, 1663, and 1592 cm^{-1}. NMR ($CDCl_3$) δ 3.39 (2H, t, J = 8 Hz), 3.78 (3H, s), 3.98 (2H, t, J = 8 Hz), 6.83 (2H, d, J = 9 Hz), 7.21 (1H, t, J = 8 Hz), 7.44 (1H, t, J = 8 Hz), 7.76–7.58 (7H, m), 9.04 (2H, d, J = 8 Hz), 10.62 (1H, s). (Found; C, 63.72; H, 4.17; N, 5.54. Calc for $C_{26}H_{20}N_2O_6S$. C, 63.93; H, 4.13; N, 5.73%.)

Methyl 12 [(p-*methoxyphenyl*)*sulfonyl*]-6-*methylenephthalimido*-11H-*indolo*[2,3-a]*carbazole*-11-*carboxylate* **8**. To a soln of **6** (488 mg 1 mmol) in CH_2Cl_2 (50 ml) was added 2-aminostyrene (131 mg 1.1 mmol). Freshly activated 4 Å molecular sieves (*ca* 6.0 g) were added, and the mixture stirred at 20° for 48 hr. The mixture was filtered, and the solvent evaporated *in vacuo* to give a yellow foam. Crystallization from CH_2Cl_2–hexane gave **1** (542 mg 92%), m.p. 186–187°. IR ($CHCl_3$) 1770, 1711, 1595 cm^{-1}. NMR ($CDCl_3$) δ 3.48 (2H, t, J = 8 Hz), 3.77 (3H, s), 4.02 (2H, t, J = 8 Hz), 5.31 (1H, d, J = 12 hz), 5.76 (1H, d, J = 17 hz), 6.83 (2H, d, J = 9 Hz), 7.02 (1H, d, J = 8 hz), 7.39–7.14 (6H, m), 7.65–7.51 (8 H, m), 8.1 (1H, d, J = 9 hz), 9.01 (1H, s). (Found: C, 69.04; H, 4.62; N, 6.94. Calc for $C_{34}H_{27}N_3O_5S$. C, 69.26; H, 4.62; N, 7.13%.)

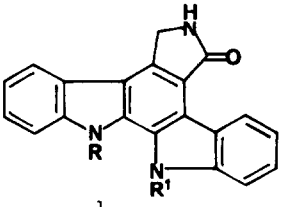
The above imine **1** (150 mg 0.25 mmol) in chlorobenzene (3 ml) was treated with methyl chloroformate (1.2 g 13 mmol) and heated at 110° for 12 hr. The mixture was evaporated *in vacuo*, and the residue flash chromatographed eluting with EtOAc–hexane to give **7** (140 mg) as a foam which was used directly in the next step.

A soln of **7** (582 mg 0.9 mmol) in toluene (10 ml) was



1

(R = p-MeOC$_6$H$_4$SO$_2$-)

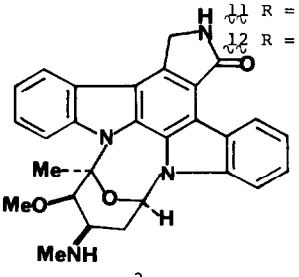


2 R = R^1 = H

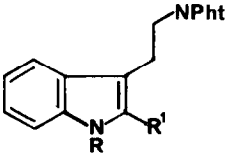
10 R = p-MeOC$_6$H$_4$SO$_2$-, R^1 = CO$_2$Me

11 R = H, R^1 = CO$_2$Me

12 R = p-MeOC$_6$H$_4$SO$_2$-, R^1 = H



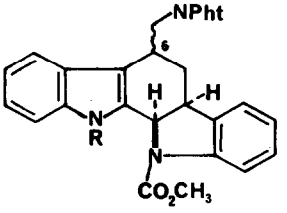
3



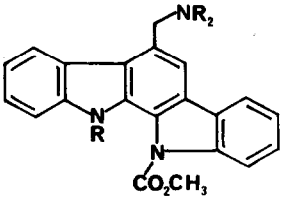
4 R = H, R^1 = H

5 R = p-MeOC$_6$H$_4$SO$_2$-, R^1 = H

6 R = p-MeOC$_6$H$_4$SO$_2$-, R^1 = CHO



7



8 R = p-MeOC$_6$H$_4$SO$_2$, R$_2$ = Pht

9 R = p-MeOC$_6$H$_4$SO$_2$, R$_2$ = H,H

treated with DDQ (817 mg 3.60 mmol), and heated at reflux for 4 hr. The mixture was evaporated *in vacuo* and the residue flash chromatographed eluting with EtOAc–hexane (1:1) to give **8** (365 mg 63%) m.p. 200–201° (from EtOAc–$CHCl_3$–hexane). IR ($CHCl_3$) 2960, 1715, 1595 cm^{-1}. NMR ($CDCl_3$) δ 3.60 (3H, s), 4.22 (3H, s), 5.43 (2H, s), 6.44 (2H, d, J = 10 Hz), 6.88 (2H, d, J = 10 Hz), 7.33 (1H, t, J = 7 Hz), 7.38 (1H, t, J = 7 Hz), 7.55–7.46 (2H, m), 7.71 (1H, s), 7.81 (1H, d, J = 4 Hz), 7.87 (1H, d, J = 4 Hz), 7.90 (1H, d, J = 7 Hz), 8.01–7.93 (3H, m), 8.31 (1H, d, J = 7 Hz), 8.43 (1H, d, J = 7 Hz). λ_{max} (EtOH) 222, 242, 277, 289, 313, 344 (ϵ = 43690, 42530, 22850, 21500, 20730, 4630 respectively). (Found: C, 67.07; H, 3.75; N, 6.29. Calc for $C_{36}H_{25}N_3O_7S$. C, 67.18; H, 3.91; N, 6.53%.)

Methyl 12 [(p-*methoxyphenyl*)*sulfonyl*]-6-*methylene*-*amino*-11H-*indolo* [2,3-a] *carbazole*-11-*carboxylate* **9**. A mixture of **8** (800 mg, 1.2 mmol) in THF (4 ml) and hydrazine–hydrate (0.5 ml) was stirred at 20° for 3 hr. EtOAc (5 ml) and water (5 ml) were poured into the mixture and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 10 ml), and the combined organic extracts were washed with water (10 ml), brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give **9** (510 mg) as a golden ppt, (83% crude) which was used directly in the next stage. IR ($CHCl_3$) 3600–3000, 2950, 2920, 1713, 1660 cm^{-1}.

Methyl 4c,5,7,7a-*tetrahydro*-12[(p-*methoxyphenyl*)*sulf*-*onyl*]-5-*oxo*-6H-*indolo*[2,3-a]*pyrrolo*(3,4-c]*carbazole*-13-*carboxylate* **10**. An ice-cold stirred slurry of **9** (175 mg, 0.32 mmol) in CH_2Cl_2 (10 ml) was treated with phosgene (10 ml) and the resultant soln stirred at 0° for 1 hr, 20° for 1 hr; heated at 40° for 0.5 hr. The mixture was then cooled to −78° and $TiCl_4$ (0.1 ml, 0.96 mmol) in CH_2Cl_2 (0.2 ml) was added in one portion. The mixture was allowed to warm to 20° over 2 hr; ice water was added and this stirred vigorously for 15 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined extracts were washed with $NaHCO_3$ aq and dried (Na_2SO_4). Concentration and flash chromatography eluting with EtOAc–hexanes gave **10** (89 mg, 54%). Recrystallization of **10** from EtOAc–hexanes gave colorless crystals: m.p. 310–312°. IR ($CHCl_3$) 3400, 1700 cm^{-1}. NMR (d_6 DMSO) 3.68 (3H, s), 4.20 (3H, s), 4.98 (2H, d, J = 4 Hz), 6.71 (2H, d, J = 9 Hz), 6.95 (2H, d, J = 9 Hz), 7.38–7.72 (4H, m), 7.99–7.46 (4H, m), 9.82 (1H, s, broad). (Found C, 64.42; H. 3.83; N, 7.60. Calc for $C_{29}H_{21}N_3O_6S$. C, 64.55; H, 3.92; N, 7.79%). λ_{max} (MeOH) 236, 272, 284, 310, 316, 342 nm (ϵ = 11620, 5680, 5070, 6890, 6820, 2430 respectively).

Methyl 4c,5,7,7a-*tetrahydro*-5-*oxo*-6H-13H-*indolo*[2,3-a] *pyrrolo*[3,4-c]*carbazole*-12-*carboxylate* **11**. Liquid ammonia (10 ml) was stirred at −78° and treated with Li (25 mg) and then with a soln of **10** (21 mg, 0.039 mmol) in THF. After 15 min TLC showed loss of starting material. NH_4Cl aq (5 ml) was added and stirring continued until the mixture reached 20°. EtOAc (5 ml) was added and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 5 ml). The combined extracts were washed with H_2O (5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated. Flash chromatography eluting with EtOAc–hexanes gave **11** (11 mg, 76%) m.p. 267–270°. IR ($CHCl_3$) 3395, 2950, 1710.

NMR ($CDCl_3$) 4.25 (3H, s), 5.22 (2H, s), 7.0 (1H, s, broad), 7.21–7.52 (5H, m), 8.03 (2H, t, J = 8 Hz), 8.15 (1H, d, J = 8 Hz). λ_{max} (MeOH) 237, 283, 321, 341, 355 (ϵ = 10720, 8560, 5260, 2600, 1550 respectively).

4c,5,7,7a-*Tetrahydro*-13[p-*methoxyphenyl*)*sulfonyl*]-5-*oxo*-6H,12H-*indolo*[2,3-a]*pyrrolo*[3,4-c]*carbazole* **12**. A solution of **10** (40 mg, 0.07 mmol) in glyme (2 ml) and 20% KOHaq was heated at reflux for 24 hr. The cooled mixture was diluted with H_2O (5 ml) and extracted with EtOAc (3 × 5 ml), dried ($MgSO_4$), evaporated *in vacuo* and flash chromatographed to give **12** (20 mg, 57%). IR ($CHCl_3$) 3400, 1710 cm^{-1}. NMR (d_6 DMSO) 4.16 (3H, s), 5.11 (s, 2H), 7.31 (2H, m), 7.42–7.64 (5H, m), 7.78–8.02 (5H, m), 8.15–8.25 (2H, m), 9.20 (1H, s), 11.18 (1H, s).

Acknowledgements—The National Institute of Health (GM 29801) are gratefully thanked for their financial support. The National Science Foundation (CHE 81-05004) are thanked for funds to purchase a Nicolet 360 NMR spectrometer.

REFERENCES

[1]P. Magnus, C. Exon, N. L. Sear, *Tetrahedron* **39**, 3725 (1983).

[2]A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai and S. Omura, *J. Chem. Soc.* Chem. Commun. 800 (1978); S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi and R. Masuma, *J. Antibiotics* **30**, 275 (1977). For a similar class of heterocycles see: W. Steglich, B. Steffan, L. Kopsanski and G. E. Eckhardt, *Agnew. Chem.* **92**, 463 (1980).

[3a]I. Hughes and R. A. Raphael, *Tetrahedron Letters*, 1441 (1983); [b] B. Sarstedt and E. Winterfeldt, *Heterocycles* 469 (1983).

[4]S. O. De Silva and V. Snieckus, *Can. J. Chem.*, **56**, 1612 (1978).