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N-BENZENE-SULFONYL-INDOLE AS TERMINATOR IN A BIOMIMETIC POLYENE CYCLIZATION : SYNTHESIS OF A PENTACYCLIC INDOLOSESQUITERPENE

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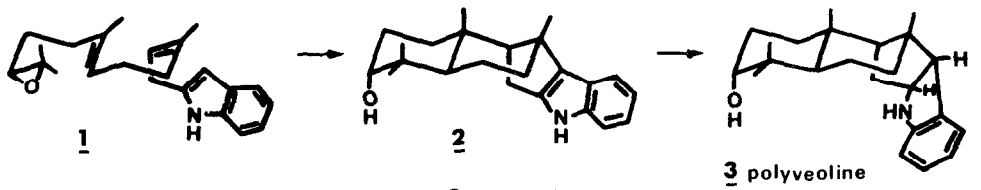
Summary. Epoxide 14 was cyclized with BF_3 to the pentacyclic derivative 17, which was further elaborated to 19, a stereoisomer of the natural indolosesquiterpene polyveoline.

Polyveoline 3[1] (scheme 1), a representative of a series of indolosesquiterpenes[2], might result in the plant from the linkage of a preformed drimane sesquiterpene with an indole[2], or from the polyenic cyclization of an ω-epoxido-farnesyl-indole. The second hypothesis brings up the question of indole acting as terminator in a polyene cyclization.

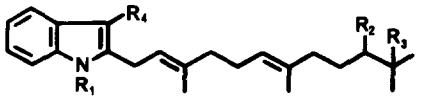


Scheme 1

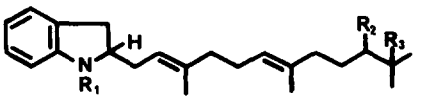
A preceding paper[3] described the synthesis and attempted cyclization of 3'-ω-epoxido-farnesyl-indoles. This study refers to the 2'-farnesyl-indole series, with regard to the possibly biogenetic sequence 1 → 2 → 3. However the *in vitro* feasability of the sequence was evaluated starting with the more easily available E,E-farnesol instead of the Z-E-isomer required by the actual ring junctions of polyveoline.

The farnesyl chain was branched using Sundberg's 2-alkylation of 1-benzenesulfonyl indole[4]. E,E-farnesyl bromide thus gave 4[5] (70%) (scheme 2). The Van Tamelen regiospecific epoxidation[6] next needed protecting the labile indole nucleus with an otherwise lipophilic group; in a first route, the N-trifluoroacetyl indoline 7 was prepared from 4 through successive hydrolysis (1N ethanolic KOH, refl., 14 h.→ 5, 90%), reduction ($NaBH_3CN/HClO_4$/MeOH, rt, 20 min. → 6, 75%) and acylation (TFAA, rt, 15 min. → 7, 100%). It was then elaborated *via* bromohydrin 8 to epoxide 9 (60% : i) NBS, 1.2 eq/DME/H_2O 9:1, rt, 2 h. ; ii) K_2CO_3/MeOH, rt, 1 h.), which was N-deprotected ($NaBH_4$, 1 eq/MeOH, rt, 20 min. → indoline 10, 80%). The final step involved reoxidation of the indole nucleus through a Rushig procedure[3] : i) NCS, 1.1 eq/Et_3N, 1.1 eq/CH_2Cl_2, -10°C, 5 min. ; ii) DBU. However C-3' suffered a very easy oxida-

tion in this series and the 3'-chloroindole 11 was the only isolated product (30%)[7].



	R_1	R_2,R_3	R_4
4	SO_2Ph	Δ	H
5	H	Δ	H
11	H	-O-	Cl
12	SO_2Ph	Br,OH	H
13	H	-O-	H
14	SO_2Ph	-O-	H

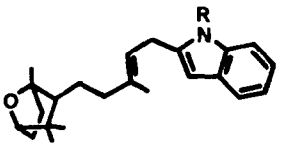


	R_1	R_2,R_3
6	H	Δ
7	$COCF_3$	Δ
8	$COCF_3$	Br,OH
9	$COCF_3$	-O-
10	H	-O-

Scheme 2

This failure prompted to test sulphonamide 4 as a protected indole in the epoxidation process. Actually it reacted with NBS to yield the N-protected bromohydrin 12, which then gave the required epoxide 13 upon reaction with 1N ethanolic KOH (75°C, 7 h. : 11 → 13, 25%). Alternatively, treatment of the bromohydrin with K_2CO_3/MeOH (rt, 1 h.) yielded the N-protected epoxide 14 (95%).

Attempts of cyclization of epoxide 13 with BF_3 etherate in CH_2Cl_2 led to a complex mixture from which only the tricyclic oxide 15 (10%) could be isolated and characterized with confidence[8] (scheme 3).



15 R = H
16 R = SO_2Ph

17 R = SO_2Ph
18 R = H

19

Scheme 3

An adverse unfolding of 13 was then suspected to originate from fixation of BF_3 on both oxygen and nitrogen atom, which designated the sulphonamide 14 as a more appropriate substrate. Gratifying enough, the sulphonamide group proved to lower the basicity of indole to such an extent that it did not prevent it from terminating the polyene cyclization : this time again BF_3 etherate gave a number of derivatives. Repeated tlc allowed isolation of the tricyclic oxide 16 (13%) and of a crystalline compound (13%, mp 265°C), which was ascribed the pentacyclic structure 17.

This compound, $M^{+\cdot}$ 477, had no olefinic proton or carbon and no indolic H-3'. Its four methyl groups were borne by quaternary carbons (^{1}H and ^{13}C NMR). The eight other aliphatic carbons were three tertiary and five secondary ones. An equatorial OH group had resulted from the cyclization as indicated by a sharp singlet at 1.5 ppm, by a dd at 3.3 ppm (J=10.4 and 5.8Hz, H-3), and by the signal of C-3 at 79.0 ppm. Completion of the cyclization by the closure of a cyclopentene ring was supported by the base peak M-15 in the MS of 17 (cleavage of the benzylic 8,12-bond) and by homonuclear and heteronuclear NMR correlations : signals at 67.0 and 26.4 ppm were unequivocally attributed to C-9 and C-11, respectively, and the three protons on these carbons were seen as a 3-spin system at 2.10 (H-9), 2.83 and 2.99 (H-11) ppm (J=6, 12 and 15Hz). These three protons did not exhibit any other short range coupling.

These results leave little doubt as to the structure of 17. Its configuration rests on its synthesis from E,E-farnesyl indole, on the chemical shifts of the methyl groups[9,2], and on the coupling constants of H-3 and H-9[10].

Finally, the sulphonamide 17 was N-deprotected to 18 (1N KOH/EtOH, 50%) and further reduced to indoline 19, mp 210°C, $M^{+\cdot}$ 339 ($NaBH_3CN$/TFA, 65%), a stereoisomer of polyveoline. Reduction of the indole nucleus from the α-face results in a clear anisotropic effect of the benzene ring on the C-12 methyl (δ=0.65 ppm).

The N-benzylsulfonyl group thus behaved as a highly efficient assistant in this synthesis, as it successively contributed to the 2'-alkylation of indole, to the regioselective epoxidation of the resulting 2'-farnesyl-indole, and to the termination of the biomimetic cyclization.

References and Notes

1) a) C.Riche, A.Chiaroni, G.Dubois, R.Hocquemiller, M.Leboeuf and A.Cavé, Planta Medica, 39, 206 (1980) ; b) R.Hocquemiller, G.Dubois, M.Leboeuf, A.Cavé, N.Kunesch, C.Riche and A.Chiaroni, Tetrahedron Lett., 22, 5057 (1981).

2) P.G.Waterman in "Alkaloids", S.W.Pelletier, J.Wiley Ed., New-York, Vol.3, 91 (1985).

3) C.Mirand, M.Dŏé de Maindreville and J.Lévy, Tetrahedron Lett., 26, 3985 (1985).

4) R.J.Sundberg and H.F.Russel, J.Org.Chem., 38, 3324 (1973).

5) The NMR and mass spectra of all intermediates were fully consistent with the structures. Selected data : UV(MeOH,λmax nm); ^{1}H NMR(300MHz ; $CDCl_3$) ; ^{13}C NMR(75MHz, $CDCl_3$ unless otherwise specified).
13 : $M^{+\cdot}$ 337 ; UV 230,280,292 ; ^{1}H NMR 1.27(s,3H), 1.29(s,3H), 1.64(s,3H), 1.68(s,3H), 2.7(t,1H,J=6), 3.47(d,2H,J=7.5), 5.17(t,1H,J=7), 5.38(t,1H,J=7), 6.22(s,1H), 6.8-7.6(m,4H), 8.05(brs,1H)

14 : $M^{+\cdot}$ 477 ; UV 215,250 ; ^{1}H NMR 1.26(s,3H), 1.30(s,3H), 1.60(s,3H), 1.63(s,3H), 2.72(t,1H,J=6), 3.66(d,2H,J=7.5), 5.18(t,1H,J=7), 5.40(t,1H,J=7), 6.35(s,1H), 7.17-7.83(m,8H), 8.18(d,1H,J=8)

15 : $M^{+\cdot}$ 337 ; ^{1}H NMR 1.02(s,3H), 1.06(s,3H), 1.32(s,3H), 1.72(s,3H), 3.50(d,2H,J=7.5), 3.72(d,1H,J=6), 5.40(t,1H,J=7), 6.22(s,1H), 7.0-7.6(m,4H), 7.87(s,1H) ; ^{13}C NMR 16.2, 18.9, 23.4, 26.1(CI), 25.7, 26.1, 27.0, 39.0, 39.8(CII), 55.3, 86.0, 99.5, 110.3, 119.6, 119.7, 120.1, 120.9(CIII), 45.2, 86.7, 128.8, 135.8, 138.4, 138.5(CIV)

16 : $M^{+\cdot}$ 477 ; ^{1}H NMR 1.04(s,3H), 1.08(s,3H), 1.35(s,3H), 1.60(s,3H), 3.68(d,2H,J=7.5), 3.74(d,1H,J=6), 5.40(t,1H,J=7), 6.35(s,1H), 7.15-7.85(m,8H), 8.18(d,1H,J=8)

17 : $M^{+\cdot}$ 477 ; UV 210, 255 ; IR(KBr) 3350 ; ^{1}H NMR 0.87(s,3H), 1.01(s,3H), 1.08(s,3H), 1.10(s,3H), 1.50(s,1H), 2.10(dd,1H,J=12, 6), 2.27(dd,1H,J=8, 3), 2.83(dd,1H,J=15, 12), 2.99(dd,1H,J=15.0, 6), 3.30(dd,1H,J=10.4,5.8), 7.10-7.60(m,8H), 8.0(m,1H) ; ^{13}C NMR 15.1, 16.6, 21.3, 28.0(CI), 19.0, 26.4, 27.1, 37.0, 38.5(CII), 56.1, 67.0, 79.0, 114.6, 118.7, 123.2, 123.3, 126.4, 129.2, 135.6(CIII), 36.9, 39.0, 43.3, 125.9, 136.0, 138.7, 139.2, 141.8(CIV)

18 : $M^{+\cdot}$ 337 ; UV 225,277,289 ; ^{1}H NMR 0.87(s,3H), 1.00(s,3H), 1.10(s,3H), 1.13(s,3H), 2.21(dd,1H,J≈12, 6), 2.38(dd,1H,J=8, 3), 2.56(dd,1H,J=15, 6), 2.65(dd,1H,J=15, 12), 3.27(dd,1H,J≈10, 6), 6.90-7.50(m,4H), 7.85(brs,1H) ; ^{13}C NMR (CD_3OD) 15.8, 17.1, 22.4, 28.6(CI), 20.4, 24.6, 27.8, 39.6, 39.9(CII), 57.9, 69.7, 79.9, 112.5, 118.5, 119.6, 120.5(CIII), 38.1, 40.1, 44.4, 124.3, 129.4, 141.1, 142.8(CIV)

19 : $M^{+\cdot}$ 339 ; UV 208,245,295 ; ^{1}H NMR 0.65(s,3H), 0.80(s,3H), 0.90(s,3H), 1.00(s,3H), 3.15(d,1H,J=10), 3.23(dd,1H,J=10, 6), 4.36(ddd,1H,J=10, 7.5, 6), 6.5-7.0(m,4H) ; ^{13}C NMR (CD_3OD) 15.2, 16.2, 16.6, 28.1(CI), 18.9, 27.1, 31.6, 38.8, 40.8(CII), 56.0, 61.4, 62.5, 63.0, 79.2, 109.3, 118.4, 125.0, 127.6(CIII), 36.7, 44.5, 61.4, 129.9, 152.2(CIV).

6) E.E. van Tamelen and T.J.Curphey, Tetrahedron Lett., 121 (1962).

7) Chlorination of 13 (NCS,Et_3N) was shown to give 11 (75%).

8) No significative improvement was gained by using less lipophilic solvents in the cyclization step or by acetylation of the reaction mixture.

9) E.Wenkert, G.V.Baddeley, I.R.Burfitt, L.N.Moreno, Org.Magnetic Resonance, 11, 337 (1978).

10) H-5 resonated in the 1 ppm area with the methyl groups so that its coupling constants could not be measured.

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