51. New Reactions of 3-Vinyl- and 3-(2-Propenyl)indoles with *N*-Phenylmaleimide: [4 + 2] Cycloaddition, Ene Reaction, and Dimerization[1])

by **Ludwig Pfeuffer** and **Ulf Pindur***

Institut für Pharmazie, Fachbereich Chemie und Pharmazie der Universität, Saarstrasse 21, D–6500 Mainz 1

(11.I.88)

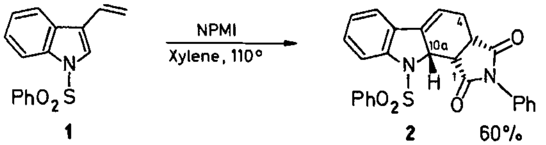
Depending on the substitution pattern of the aminobutadiene subunit in the selected 3-vinylindoles **1**, **3**, **6**, and **9**, stereospecific [4 + 2] cycloadditions (*'endo'*-preference) and dimerizations take place on reaction with *N*-phenylmaleimide. In the reaction of **9** with *N*-phenylmaleimide in the absence of a *Lewis*-acid catalyst, a competing ene reaction occurs in addition to the *Diels-Alder* reaction.

The *Diels-Alder* reaction of vinylindoles has now been established by others [1] and by us [1] [2] as a synthetically attractive concept for the preparation of [*b*]annellated indole derivatives. However, the limits to the synthetic potential of this reaction type have by no means been defined. Also, comprehensive knowledge of alternative pathways for or of reactions competing directly with the cycloadditions when using vinyl-heterocycles and dienophiles is still lacking. For this reason and in continuation of our investigations on this subject [2], we now report on new results of the reactions of 1-phenylsulfonyl-3-vinylindole (**1**) and the 3-(1-methylvinyl)indoles **3**, **6**, and **9** with *N*-phenylmaleimide (NPMI).

The stabilized, *N*-protected, parent 3-vinylindole **1**[2]), in contradiction to a recently published report [3], reacts with NPMI to give the [4 + 2] cycloadduct **2**[3]) exclusively (*Scheme 1*). The formation of an indolized adduct with the same molecular formula as postulated in [3] is unambiguously excluded on the basis of monitoring of the time course of the reaction by TLC and structural analysis by means of 400-MHz ^{1}H-NMR spectroscopy (see *Exper. Part*).

The oily and relatively unstable 3-(1-methylvinyl)indole (**3**) [6] undergoes dimerization after short periods of storage (a few hours) to give the 'linear' dimer **4** (*Scheme 2*).

Scheme 1



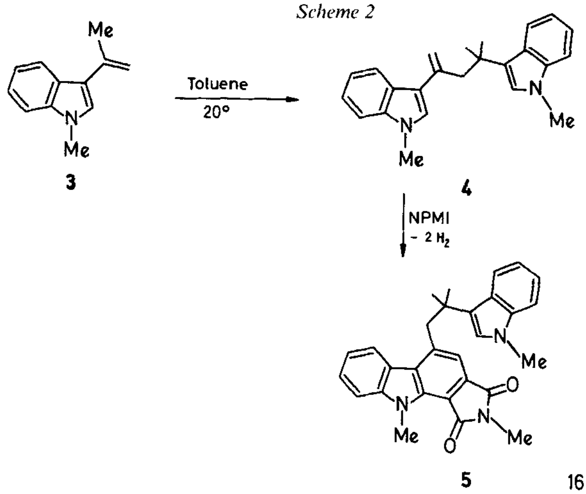
---

[1]) Part V in the series 'Cycloadditions of Vinylindoles to Annellated Indole Derivatives'; Part IV: [2].

[2]) The *N*-unprotected parent compound, 3-vinylindole, exhibits a pronounced tendency to undergo dimerization and oligomerization [4], although MNDO calculations performed by us predict a good thermodynamic stability ($\Delta H_f = 72.9$ kcal/mol) [5].

[3]) All *'endo'*-cycloadducts **2**, **7**, and **10** described here were formed in > 99.5% diastereoisomeric excess (d.e.; as determined by quantitative TLC remission measurements on silica-gel plates).

Scheme 2

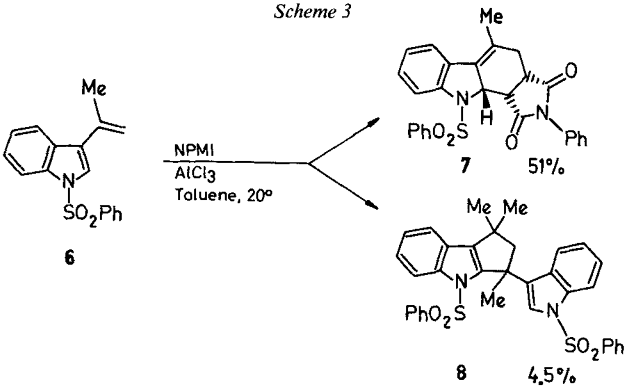


On attempts to perform a [4 + 2] cycloaddition of **3** with NPMI, it was not possible to 'trap' a 1:1 cycloadduct even under variation of the reaction conditions. The rate of dimerization of **3** is considerably higher than the rate of the *Diels-Alder* reaction of **3** with NPMI. In addition to the dimer **4**, the sole product is the novel, [*a*]annellated carbazole derivative **5**, resulting directly from **4** after a dehydrogenative *Diels-Alder* reaction.

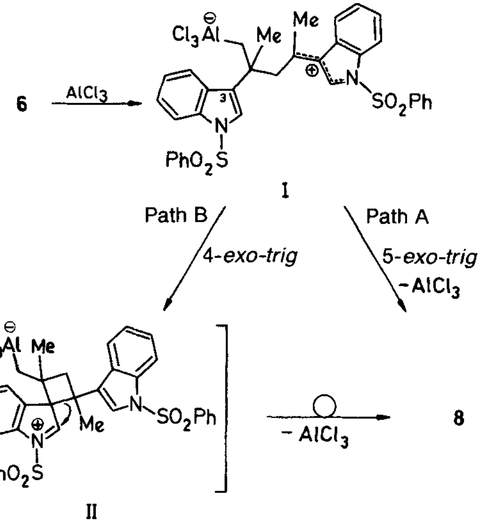
When the enophile reactivity of **3** is decreased, *e.g.* by introduction of an *N*-acceptor function, the cycloaddition proceeds in satisfactory yields only in the presence of $AlCl_3$ as a catalyst. As shown for compound **6**, this 3-vinylindole reacts stereospecifically with NPMI under *Lewis*-acid catalysis to give the '*endo*'-cycloadduct **7** and, in addition, in a polar, regiocontrolled (only one isomer) cyclodimerization to give the cyclopentano[*b*]annellated indole derivative **8** (*Scheme 3*). Analogous acid-catalyzed cyclizations have been observed previously in the reactions of other labile 2-vinylindoles [7].

Two alternative mechanisms for the formation of **8** should be considered (*Scheme 4*): *Path A*: direct cyclization of the zwitterion **I**, formed by 'linear', $AlCl_3$-induced dimerization of **6**, to furnish **8**, and *Path B*: primary intramolecular '*ipso*'-addition of the

Scheme 3



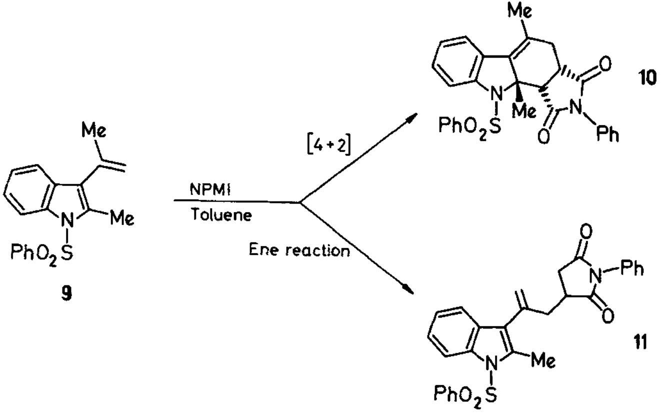
Scheme 4



zwitterion **I** at C(3) and formation of a spirocyclobutane derivative **II**. The latter undergoes a regiocontrolled *Wagner-Meerwein* rearrangement to yield **8** (*Jackson*'s hypothesis on the electrophilic substitution of 3-alkylindoles [8]). Since a relatively high ring strain is to be expected in the transition state of the '4-*exo-trig*' cyclization, we consider *Path A* to be more feasible.

The dimerization reactivity of **3** can be blocked sterically and electronically by the influence of substituents. Thus, for example, the 2-methylated 3-vinylindole **9** reacts with NPMI under *Lewis*-acid catalysis with '*endo*'-preference to give the [4 + 2] cycloadduct

Scheme 5



Catalyst	*T*	*t*	Yield [%] 10	Yield [%] 11
$AlCl_3$	20°	3d	68	–
–	110°	30h	6.4	3.2

10, and, in the absence of the *Lewis*-acid catalyst, additionally *via* an ene reaction to furnish the 'linear' adduct **11** *(Scheme 5)*. The ene reaction occurring here in competition with the *Diels-Alder* reaction is most probably the result of the steric hindrance being built up in the [4 + 2]-transition state on the way from **9** to **10**.

The constitutions and configurations of all the products mentioned have been unequivocally confirmed by ^{1}H- and ^{13}C-NMR spectroscopic measurements (selective decoupling, ^{1}H{^{1}H}-NOE experiments, J-modulated ^{13}C-spin-echo spectra). The high diagnostic value of the ^{1}H{^{1}H}-NOE measurements performed for clarification of the relative configurations of the cycloadducts has now been confirmed by us for the first time in related adducts by X-ray structural analysis [9].

We are grateful to the *Deutsche Forschungsgemeinschaft* (Bonn) for financial support of this work.

Experimental Part

General. Methods for the preparation of 3-vinylindoles are described in [6] [10]. All reactions were performed in highly pure, anh. solvents under inert gas atmospheres. Flash chromatography (FC): *Kieselgel 60* (*Merck*, 0.04–0.063-mm particle size) with petroleum ether (b.p. 40–60°)/AcOEt 8:2. M.p. *Büchi SMP 20* (not corrected). ^{1}H-NMR (400 MHz): *Bruker WM 400:* δ [ppm] scale, coupling constants (J) in Hz, TMS as internal standard: the designations 'H_α, H_β' refer to the structural formulae shown, in which only one of the enantiomers is given for clarity. EI-MS (70 eV): *Varian MAT 7;* values given in m/z (%). C, H, N Analyses: *Carlo Erba Strumentazione.*

*2-Phenyl-10-(phenylsulfonyl)-1,2,3,3aβ,4,10,10aβ,10bβ-octahydropyrrolo[3,4-*a*]carbazole-1,3-dione* (**2**). *N*-Phenylmaleimide (NPMI; 0.66 g, 3.8 mmol) in xylene (15 ml) was heated under reflux with *1-(phenylsulfonyl)-3-vinylindole* (**1**; 0.9 g, 3.1 mmol) for 6.5 h. The precipitate was then separated and recrystallized from benzene: 0.86 g (60%) of **2**. M.p. 162–164°, colorless crystals (benzene). ^{1}H-NMR (CDCl$_3$): 2.25 (*mc* (*ddddd*), $^{2}J = 15.6$, $^{3}J(3a\beta,4\beta) = 7.5$, $^{3}J(4\beta,5) = 3.6$, $^{4}J(10b\beta,4\beta) = 1.4$, $^{5}J(10a\beta,4\beta) = 1.1$, H_β–C(4)); 3.10 (*mc* (*ddd*), $^{2}J = 15.6$, $^{3}J(3a\beta,4\alpha) = 1.2$, $^{3}J(4\alpha,5) = 7.4$, H_α–C(4)); 3.35 (*mc* (*ddd*), $^{3}J(10b\beta,3a\beta) = 8.7$, $^{3}J(3a\beta,3\beta) = 7.5$, $^{3}J(3a\beta,4\alpha) = 1.2$, H_β–C(3a)); 4.21 (*mc* (*ddd*), $^{3}J(10a\beta,10b\beta) = 7.0$, $^{3}J(10b\beta,3a\beta) = 8.7$, $^{4}J(10b\beta,4\beta) = 1.4$, H_β–C(10b)); 4.63 (*mc* (*ddd*), $^{3}J(10a\beta,10b\beta) = 7.0$, $^{4}J(5,10a\beta) = 3.6$, $^{5}J(10a\beta,4\beta) = 1.1$, H_β–C(10a)); 6.14 (*mc* (*ddd*), $^{3}J(4\alpha,5) = 7.4$, $^{3}J(4\beta,5) = 3.6$, $^{4}J(5,10a\beta) = 3.6$, H–C(5)); 6.98 (*dd*, 1 arom. H); 7.02 (*dd*, H–C(2), H–C(6) of Ph-N); 7.21–7.34 (*m*, 5 arom. H); 7.44 (*dd*, H–C(3), H–C(5) of PhN or H–C(3), H–C(5) of PhSO$_2$); 7.54 (*dd*, 1 arom. H), 7.63 (*dd*, H–C(6)); 7.81 (*dd*, H–C(2), H–C(6) of PhSO$_2$). MS: 456 (51, M^{+}), 168 (100). Anal. calc. for $C_{26}H_{20}N_2O_4S$ (456.11): C 68.40, H 4.42, N 6.14; found: C 68.37, H 4.42, N 6.09.

*10-Methyl-5-[2-methyl-2-(1-methyl-3-indolyl)propyl]-2-phenyl-1,2,3,10-tetrahydropyrrolo[3,4-*a*]carbazole-1,3-dione* (**5**). *1-Methyl-3-(1-methylvinyl)indole* (**3**; 0.45 g, 2.6 mmol) and NPMI (0.41 g, 2.4 mmol) were dissolved in toluene (10 ml), and the mixture was stirred at 20° for 26 h. The soln. was concentrated on a rotary evaporator, and **4** was separated from the residue by FC: 0.11 g (16%) of **5**. M.p. 241° (petroleum ether (40–60°)/AcOEt, colorless crystals. ^{1}H-NMR (CDCl$_3$): 1.51 (*s*, (CH$_3$)$_2$C); 3.72 (*s*, CH$_3$N); 3.94 (*s*, CH$_2$); 4.44 (*s*, CH$_3$N); 6.74 (*s*, H–C(4)); 7.09–7.56 (*m*, 12 arom. H); 7.84 (*d*, $^{3}J = 8.0$, 1 arom. H); 8.36 (*d*, $^{3}J = 8.0$, 1 arom. H). ^{13}C-NMR (CDCl$_3$): 27.87 (2 CH$_3$); 32.02 (CH$_3$N); 32.95 (CH$_3$N); 36.97 ((CH$_3$)$_2$*C*); 44.64 (CH$_2$); sp^2-C: 108.99, 109.09, 109.30, 116.72, 118.07, 119.64, 120.51, 120.81, 121.96, 122.72, 123.08, 125.02, 125.64, 126.36, 126.73, 127.18, 128.36, 128.84, 128.85, 131.71, 137.98, 137.44, 142.47, 142.69, 167.05, 167.33. MS: 511 (6, $M^{+\cdot}$), 171 (100). Anal. calc. for $C_{34}H_{29}N_3O_2$ (511.62): C 79.82, H 5.71, N 8.21; found: C 79.79, H 5.69, N 8.23.

*5-Methyl-2-phenyl-10-(phenylsulfonyl)-1,2,3,3aβ,4,10,10aβ,10bβ-octahydropyrrolo[3,4-*a*]carbazole-1,3-dione* (**7**). *3-(1-Methylvinyl)-1-(phenylsulfonyl)indole* (**6**; 0.4 g, 1.3 mmol) and NPMI (0.27 g, 1.6 mmol) were dissolved in toluene (10 ml), AlCl$_3$ (0.32 g, 2.6 mmol) was added, and the mixture was stirred at 20° for 5 h. The mixture was concentrated on a rotary evaporator and the product purified by FC: 0.32 g (51%) of **7**. M.p. 229–230° (toluene), colorless crystals. ^{1}H-NMR (CDCl$_3$): 2.10 (*s*, CH$_3$–C(5)); 2.33–2.39 (*m*, H_α–C(4)); 2.90 (*dd*, $^{3}J(3a\beta,4) = 1.7$, $^{2}J(4\alpha,4\beta) = 15.1$, H_β–C(4)); 3.29–3.34 (*m*, H_β–C(3a)); 4.13 (*dd*, $^{3}J(10b\beta,3a\beta) = 8.93$, $^{3}J(10a\beta,10b\beta) = 6.7$, H_β–C(10b)); 4.58–4.61 (*m*, H_β–C(10a)); 6.83–7.01 (*m*, H–C(3), H–C(5) of PhSO$_2$, 1 arom. H); 7.18 (*pseudo-t*, 1 arom. H); 7.25–7.33 (*m*, H–C(3), H–C(5) of PhN, 1 arom. H); 7.39–7.45 (*q*, H–C(2), H–C(6) of Ph-N, H–C(9));

7.54 (*t*, H–C(7) or H–C(8)); 7.65 (*d*, ^3J = 8.2, H–C(6)); 7.89 (*d*, ^3J = 7.3, H–C(2), H–C(6) of $PhSO_2$). MS: 470 (90, $M^{+\cdot}$), 182 (100). Anal. calc. for $C_{27}H_{22}N_2O_4S$ (470.13): C 68.92, H 4.72, N 5.96; found: C 68.91, H 4.68, N 5.89.

*1,1,3-Trimethyl-4-(phenylsulfonyl)-3-[*N*-(phenylsulfonyl)-3-indolyl]-1,2,3,4-tetrahydrocyclopent[*b*]indole* (**8**). Obtained as an additional product during the isolation of **7** by FC; yield: 0.035 g (4.5%). M.p. 255° (petroleum ether (40–60°)/AcOEt), colorless crystals. ^{1}H-NMR ($CDCl_3$): 1.47 (*s*, β-CH_3–C(1)); 1.51 (*s*, α-CH_3–C(1)); 2.06 (*s*, β-CH_3–C(3)); 2.33 (*d*, ^2J = 13.5, H_β–C(2)); 2.85 (*d*, ^2J = 13.5, H_α–C(2)); 6.46–7.56 (*m*, 14 arom. H); 7.62 (*s*, H–C(2) of indole); 7.90–8.07 (*m*, 4 arom. H). MS: 594 (85, $M^{+\cdot}$), 297 (100). Anal. calc. for $C_{34}H_{30}N_2O_4S_2$ (594.16): C 68.67, H 5.09, N 4.71; found: C 68.59, H 4.96, N 4.65.

*5-10aβ-Dimethyl-10-(phenylsulfonyl)-1,2,3,3aβ,4,10,10aβ,10bβ-octahydropyrrolo[3,4-*a*]carbazole-1,3-dione* (**10**). *2-Methyl-3-(1-methylvinyl)-1-(phenylsulfonyl)indole* (**9**; 0.4 g, 1.3 mmol) and NPMI (0.27 g, 1.5 mmol) together with $AlCl_3$ (0.32 g, 2.6 mmol) were dissolved in a 1:1 mixture of toluene and CH_2Cl_2 (20 ml) and stirred for 3 days at 20°. The residue, after evaporation, was separated by FC: 0.45 g (67.5%) of **10**. M.p. 250–251° (toluene/petroleum ether (40–60°)), colorless crystals. ^{1}H-NMR ($CDCl_3$): 1.60 (*s*, CH_3–C(10a)); 2.12 (*d*, ^4J(CH_3–C(5), H–C(4)) = 0.9, CH_3–C(5)); 2.74 (*d*, ^2J(4,4) = 18.26, H_α–C(4)); 3.02 (*dd*, ^2J = 18.26, ^3J = 9.6, H_β–C(4)); 3.31 (*pseudo-t*, H_β–C(3a)); 4.46 (*d*, ^3J(10bβ,3aβ) = 8.9, H_β–C(10b)); 6.95 (*t*, ^3J = 7.5, 1 arom. H); 7.10 (*d*, ^3J = 7.32, 2 arom. H); 7.16 (*t*, ^3J = 7.7, 1 arom. H); 7.28 (*d*, ^3J = 7.2, H–C(6)); 7.34 (*pseudo-t*, ^3J = 7.1, 7.9, 2 arom. H); 7.44–7.48 (*m*, 3 arom. H); 7.53 (*pseudo-t*, 2 arom. H); 8.09 (*d*, ^3J = 7.72, 2 arom. H). MS: 484 (95, $M^{+\cdot}$), 181 (100). Anal. calc. for $C_{28}H_{24}N_2O_4S$ (484.15): C 69.40, H 5.00, N 5.78; found: C 69.17, H 5.08, N 5.72.

N*-Phenyl-2-{2-[1-(phenylsulfonyl)-2-methylindol-3-yl]-2-propenyl}succinimide* (**11**). Obtained from compound **9** (0.4 g, 1.3 mmol) and NPMI (0.28 g, 1.54 mmol) in toluene (10 ml). The mixture was heated under reflux for 30 h and the crude product was purified by FC: 0.02 g (3.2%) of **11**. M.p. 207° (petroleum ether (40–60°)/AcOEt), colorless crystals. ^{1}H-NMR ($CDCl_3$): 2.50 (*dd*, ^2J = 18.5, ^3J = 5.1, H_α–C(3')); 2.57 (*s*, CH_3-indole); 2.60–2.67 (*mc*, H_a–C(3), H_b–C(3')); 2.73–2.77 (*mc*, H–C(2)); 3.21 (*dd*, ^2J = 14.0, ^3J = 3.8, H_b–C(3)); 5.16, 5.51 (2*d*, ^2J unresolved, 1 H, =CH_2); 7.03 (*pseudo-d*, ^3J = 8.0, H–C(2), H–C(6) of PhN); 7.26–7.52 (*m*, 9 arom. H); 7.74 (*pseudo-d*, ^3J = 8.2, H–C(2), H–C(6) of $PhSO_2$); 8.19 (*pseudo-d*, ^3J = 8.3, H–C(4) of indole). ^{13}C-NMR ($CDCl_3$): 12.8 (CH_3-indole); 34.0 (CH_2); 38.8 (CH); 38.9 (CH_2); sp^2-C: 113.4, 114.9, 118.9, 120.7, 121.5, 124.0, 124.5, 126.2, 126.3, 128.5, 129.0, 129.3, 131.8, 133.5, 133.7, 136.4, 137.8, 174.9 (CO), 177.7 (CO). MS: 484 (91, $M^{+\cdot}$), 343 (100). Anal. calc. for $C_{28}H_{24}N_2O_4S$ (484.15): C 69.40, H 5.00, N 5.78; found: C 69.38, H 4.96, N 5.69.

REFERENCES

[1] Review: U. Pindur, *Heterocycles*, in press, and ref. cit. therein.

[2] L. Pfeuffer, U. Pindur, *Helv. Chim. Acta* **1987**, *70*, 1419, and ref. cit. therein.

[3] B. Saroja, P.C. Srinivasan, *Synthesis* **1986**, 748.

[4] W.E. Noland, R.J. Sundberg, *J. Am. Chem. Soc.* **1963**, *28*, 884.

[5] M.J.S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.

[6] R. Bergamasco, Q.N. Porter, C. Yap, *Aust. J. Chem.* **1977**, *30*, 1531.

[7] F.E. Ziegler, E.B. Spitzner, C.K. Wilkins, *J. Org. Chem.* **1971**, *36*, 1759.

[8] A.H. Jackson, P.P. Lynch, *J. Chem. Soc., Perkin Trans. 2* **1987**, 1215, and ref. cit. therein.

[9] W. Massa, G. Frenzen, L. Pfeuffer, U. Pindur, H.-J. Sattler, *Monatsh. Chem.*, in press.

[10] E. Akgün, U. Pindur, *J. Heterocycl. Chem.* **1985**, *22*, 585, and ref. cit. therein.