Diels-Alder Reactions of Methyl- and π-Acceptor-Substituted 2-Vinylindoles with Dimethyl Acetylenedicarboxylate and Tetracyanoethylene: Novel Functionalized Carbazoles

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The Diels-Alder reactions of the 2-vinylindoles **1a-1d**, which are now readily accessible, with dimethyl acetylenedicarboxylate and tetracyanoethylene give rise to the novel 1,2-dihydro- and 1,2,3,4-tetrahydrocarbazoles **2**, **4**, and **5** as well as the fully aromatized carbazoles **3**. With regard to the product spectrum, the mechanistic rationale comprises a Diels-Alder step, formal 1,3-hydrogen shift, ene reaction, and dehydrogenation. Conformational aspects of the 1,2-dihydrocarbazoles **2b** and **2c** are also discussed.

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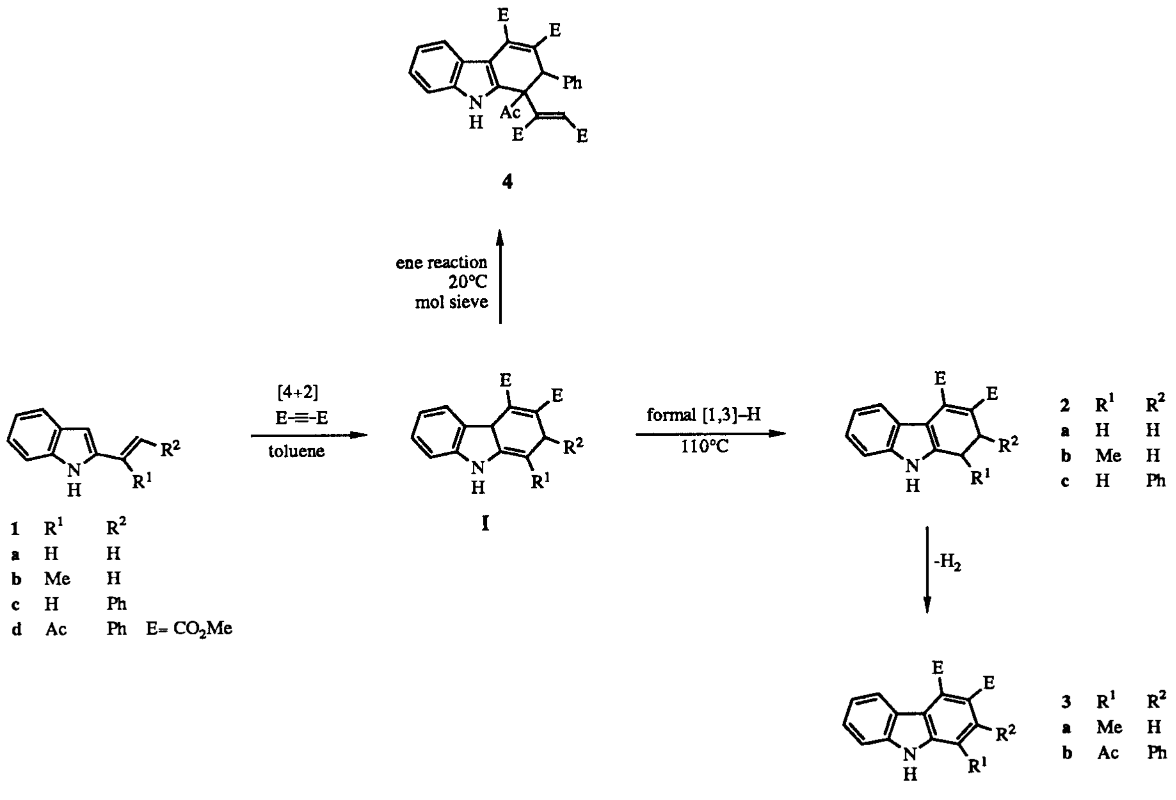
Introduction.

The Diels-Alder reactions of vinylindoles with carbo- and hetero-dienophiles have now been established as a versatile and sufficiently flexible methodology for the syntheses of pharmacologically active lead substances and alkaloids of the carbazole type [1-6]. However, the synthetic potential of this approach, in particular with regard to substrates of the 2-vinylindole series, has not yet been explored exhaustively. One reason for this was the fact that the syntheses of 2-vinylindoles with an unsubstituted 3 position were previously time-consuming and laborious; hence, we have recently developed some new and highly flexible methods for the preparation of a variety of 2-vinylindoles [7]. Thus, in continuation of our ongoing investigations in the field of pericyclic reactions with indole derivatives [8], we now report on the first Diels-Alder reactions of the σ-donor and/or π-acceptor substituted 2-vinylindoles **1a-1d** [7] with dimethyl acetylenedicarboxylate (DMAD) and tetracyanoethylene (TCNE), respectively.

Results and Discussion.

The 2-vinylindoles **1a-1c** reacted with DMAD in toluene under reflux conditions to furnish the novel 1,2-dihydro-

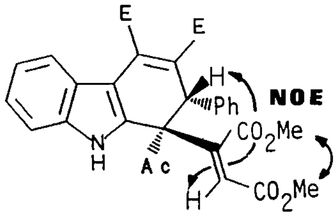
Scheme 1



carbazoles **2a**-**2c**, respectively. The reaction probably proceeded *via* the primary [4 + 2] cycloadduct **I** [4] and subsequent formal [1,3] hydrogen shift (Scheme 1). In the case of the reaction of **1b** with DMAD, the dehydrogenation product **3a** was formed as a minor product in addition to compound **2b**. The acceptor-substituted 2-vinylindole **1d** also reacted directly with DMAD to form the 14π-carbazole **3b** as the main product; this reaction probably involved the step **I** → **2** (R^1 = Ac, R^2 = Ph) where both species function as intermediates. In this case under mild conditions (room temperature) and, above all, in the presence of highly activated molecular sieves, the intermediate [4 + 2] cycloadduct of the type **I** was also trapped by an ene reaction with a further molecule of DMAD to furnish the 1,2-dihydrocarbazole **4** as a minor product together with the main product **3b**.

The reaction sequence depicted in Scheme 1 for the transformation of **1d** with DMAD to furnish **3b** and **4** was supported by the following experimental observation. The 1,2-dihydrocarbazole **4** was highly stable in refluxing toluene for 10 days even in the presence of the molecular sieves; no cleavage of **4** to give **3b** has yet been detected (tlc control).

The relative configuration of the ring system as well as the π-configuration of the vinyl group of compound **4** were unambiguously confirmed by ^{1}H, ^{1}H-nOe experiments as shown in structure **II**.



II

Conformational analyses of products **2b** and **2c** were carried out on the basis of high resolution ^{1}H-nmr spectroscopy in conjunction with MMX force field calculations [9]. Hence, the analysis of the aliphatic ring coupling constants of **2b** in hexadeuteriodimethyl sulfoxide at room temperature revealed the existence of a preferred conformer with a pseudoequatorial location of the 1-methyl group (conformation **A** in Figure 1). This was further substantiated by the fact that the related calculated [10] and experimentally determined $H1\text{-}H2_{(a,b)}$ coupling constants displayed a satisfactory agreement for the conformation **A** of **2b** (see Table 1). However, according to MMX molecular mechanics calculations the conformation **B** with a pseudoaxial location of the methyl group is energetically equally stable (Figure 1) and should, therefore, also participate in the conformational equilibrium. On the other hand, the low temperature ^{1}H-nmr spectra of **2b** in deuteriochloroform were unequivocally in favor of the conformer **A**. The general conformational stability of other 1,2-dihydrocarbazoles, or in other words the high population of one conformer in solution, was recently reported [11].

It is interesting to note that the 2-phenyl substituted 1,2-dihydrocarbazole **2c** in solution adopts a conformation with the phenyl group in a pseudoaxial location at C2, as demonstrated by an analysis of the $H1_{(a,b)}\text{-}H2$ coupling constants (Table 1). The resultant conformer belongs to the same type as the conformer **A** shown in Figure 1.

Table 1

Vicinal Aliphatic Ring Coupling Constants (400 MHz ^{1}H-NMR, Hexadeuteriodimethyl Sulfoxide) of **2b** and **2c**

Compound (Conformation)	Proton type	^3J [Hz] Calcd. [10]	Exptl.	Dihedral angle [°]
2b (A)	C1H-C2H$_a$	12.7	11.4	150
	C1H-C2H$_b$	5.0	7.7	40
(B) [a]	C1H-C2H$_a$	1.3	-	75
	C1H-C2H$_b$	7.0	-	45
2c [b]	C1H$_a$-C2H	7.0	8.0	45
	C1H$_b$-C2H	1.3	1.3	75

[a] Conformer B was not detectable within the limits of the ^{1}H-nmr detection method. [b] Corresponds to conformer of type A.

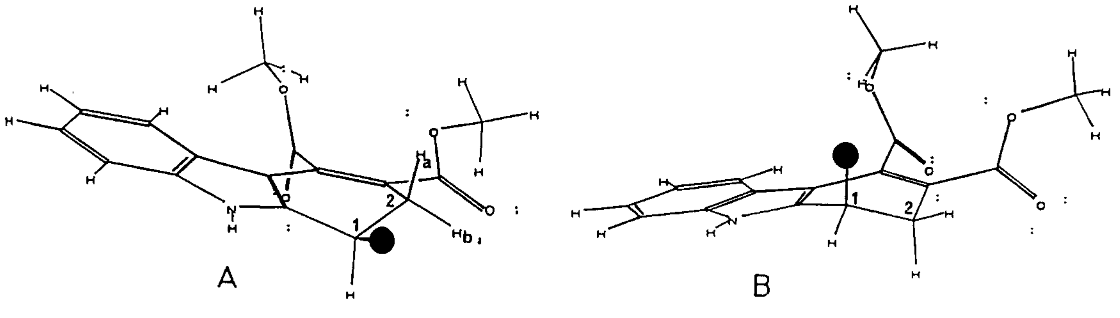
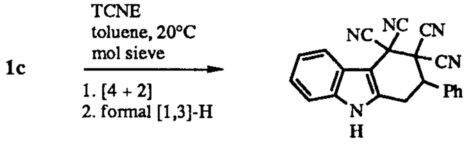


Figure 1. Calculated energy minimized conformations of **2b** according to MMX molecular mechanics calculations [9]. The energy values for both conformers **A** and **B** are equal (E_{steric} = 43.4 kcal/mol). • = CH_3 group.

In the reactions of **1a**-**1d** with the highly reactive tetracyanoethylene (TCNE) [12,13], a characterizable reaction only took place in the case of **1c**. Hence, **1c** reacted with TCNE in the presence of molecular sieves at room temperature to furnish the stable 1,2,3,4-tetrahydrocarbazole cycloadduct **5** exclusively (Scheme 2). When the reagents were mixed a blue color formed initially and dissipated within a few seconds. Thus, it has not yet been possible to record a uv/vis spectrum for the characterization of the probably formed charge transfer complex [14,15]. However, it is well known [14,15] for numerous Diels-Alder reactions with TCNE that an equilibrium between the reactants, a charge transfer complex, and the cycloadduct does exist.

Scheme 2



5

In summary, we have extended the Diels-Alder reactivity of 2-vinylindoles to encompass their reactions with carbo-dienophiles. The carbazole derivatives thus obtained possess functionalization patterns that are not so easily obtainable by the other, more classical approaches. Applications of the interesting building blocks **2**, **3**, and **4** for the syntheses of carbazole alkaloids [16] are now being studied in our laboratory.

However, our previous results [2,4] and the experimental findings presented here are in contradiction to the structures reported to result from related cycloadditions of other 2-vinylindoles [6]. In reference [6], the non-"indolized" cycloadducts (*e.g.* of the type **I** in Scheme 1) were discussed throughout as the only products formed. On the basis of our present experimental findings and numerous other examples [2,4,17], we propose that high resolution ^{1}H-nmr nOe measurements are indispensible for an unambiguous constitutional analysis of the cycloadducts of 2-vinylindoles reported in reference [6].

EXPERIMENTAL

The ^{1}H nuclear magnetic resonance (nmr) spectra were recorded on a Bruker WL 400 spectrometer operating at 400 MHz (δ scale in ppm). Mass spectra were obtained on a Varian MAT 7 spectrometer at 70 eV. The elemental analyses were determined with a Carlo Erba Strumentazione Model 1106 apparatus and melting points (uncorrected) were obtained on a Büchi SMP 200 apparatus. Column chromatography was performed on silica gel 60 (Merck, particle size 0.063-0.200 mm). Medium pressure liquid chromatography (mplc) was performed on a Büchi 681/683 apparatus with LiChroprep Si 60 (Merck, particle size 25-40 μm, pressure 3-5 bar, uv detection at 254 nm). All reactions were carried out in highly pure, anhydrous solvents under an argon atmosphere. The constitutions and stereochemistries of the products **2**, **4**, and **5** were clarified above all with the help of ^{1}H, ^{1}H-nOe measurements.

Dimethyl 1,2-Dihydro-9*H*-carbazole-3,4-dicarboxylate (**2a**).

2-Vinylindole (**1a**) (143 mg, 1.0 mmole) and dimethyl acetylenedicarboxylate (156 mg, 1.1 mmoles) in toluene (10 ml) were heated under reflux for 16 hours. The reaction mixture was then cooled and the crude product precipitated by addition of 40-60° petroleum ether (5 ml). Compound **2a** was obtained as colorless crystals, yield 131 mg (46%), mp 217° (toluene); ^{1}H-nmr (hexadeuterioacetone): 2.79-2.84 (m, 2H, H-1 or H-2), 2.97-3.01 (m, 2H, H-2 or H-1), 3.71 and 3.95 (each s, each 3H, CO_2CH_3), 7.03-7.13 (m, 2H, H-6 and H-7), 7.34 (d, J = 7.6 Hz, 1H, H-5), 7.39 (d, J = 7.8 Hz, 1H, H-8), 10.70 (br 1H, NH); ms: m/e (%) 285 ($M^{+\cdot}$, 100).

Anal. Calcd. for $C_{16}H_{15}NO_4$ (285.1): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.69; H, 5.24; N, 4.79.

Dimethyl 1-Methyl-1,2-dihydro-9*H*-carbazole-3,4-dicarboxylate (**2b**) and Dimethyl 1-Methyl-9*H*-carbazole-3,4-dicarboxylate (**3a**).

The 2-vinylindole **1b** (157 mg, 1.0 mmole) and dimethyl acetylenedicarboxylate (156 mg, 1.1 mmoles) in toluene (10 ml) were heated under reflux for 3 hours. After being allowed to cool, the reaction mixture was concentrated under vacuum. The residue was purified first by column chromatography on silica gel (40-60° petroleum ether/ethyl acetate, 3/1). The mixture of **2b** and **3a** thus obtained was further purified by mplc (chloroform/ethyl acetate, 20/1). Compound **2b** was obtained as colorless crystals, yield 60 mg (20%), mp 174° (petroleum ether/ethyl acetate); ^{1}H-nmr (hexadeuterioacetone): 1.36 (d, J = 6.9 Hz, 3H, C1-CH_3), 2.50 (dd, J = 16.5 Hz, 11.4 Hz, 1H, H_a-2), 2.93 (dd, J = 16.7 Hz, 7.7 Hz, H_b-2), 3.22 (m, 1H, H-1), 3.71 and 3.93 (each s, each 3H, CO_2CH_3), 7.04-7.13 (m, 2H, H-6 and H-7), 7.35 (d, J = 8.5 Hz, 1H, H-5 or H-8), 7.39 (d, J = 7.5 Hz, H-8 or H-5), 10.48 (br, 1H, NH); ms: m/e (%) 299 ($M^{+\cdot}$, 100).

Anal. Calcd. for $C_{17}H_{17}NO_4$ (299.1): C, 68.26; H, 5.73; N, 4.68. Found: C, 68.11; H, 5.68; N, 4.59.

Compound **3a** could not be completely separated from **2b** without decomposition occurring. The 9:1 mixture of pure **3a**/**2b** was satisfactorily characterized by spectroscopic techniques; ^{1}H-nmr (hexadeuterioacetone): 2.87 (s, 3H, C1-CH_3), 3.87 and 4.05 (each s, each 3H, CO_2CH_3), 7.22 (dd, J = 7.6 Hz, 7.6 Hz, 1H, H-6 or H-7), 7.46 (dd, J = 7.7 Hz, 7.7 Hz, 1H, H-7 or H-6), 7.58 (d, J = 8.2 Hz, 1H, H-8), 7.87 (s, 1H, H-2), 7.91 (d, J = 8.1 Hz, 1H, H-5), 10.17 (br, 1H, NH); ms: m/e (%) 297 ($M^{+\cdot}$, 80), 266 (100), 238 (27).

Dimethyl 2-Phenyl-1,2-dihydro-9*H*-carbazole-3,4-dicarboxylate (**2c**).

This compound was obtained as described for the synthesis of **2b** but with a reaction time of 12 hours. Product **2c** separated directly from the reaction mixture upon addition of 40-60° petroleum ether (10 ml) as colorless crystals, yield 85 mg (24%), mp 199° (toluene); ^{1}H-nmr (hexadeuterioacetone): 3.17 (dd, J = 17.3 Hz, 1.4 Hz, 1H, H_a-1), 3.61 (dd, J = 17.3 Hz, 9.5 Hz, 1H, H_b-1), 3.70 and 3.94 (each s, each 3H, CO_2CH_3), 4.41 (d, J = 8.1 Hz, 1H, H-2), 7.06-7.42 (m, 9H, H-phenyl and H-5 to H-8), 10.78 (br, 1H, NH); ms: m/e (%) 361 ($M^{+\cdot}$, 100).

Anal. Calcd. for $C_{22}H_{19}NO_4$ (361.1): C, 73.10; H, 5.30; N, 3.88.

Found: C, 73.01; H, 5.27; N, 3.85.

Dimethyl 1-Acetyl-2-phenyl-9*H*-carbazole-3,4-dicarboxylate (**3b**) and Dimethyl (1α-Acetyl-3,4-dimethoxycarbonyl-2α-phenyl-1,2-dihydro-9*H*-carbazole-1-yl)maleate (**4**).

The 2-vinylindole **1d** (260 mg, 1.0 mmole) and dimethyl acetylenedicarboxylate (156 mg, 1.1 mmoles) were dissolved in toluene (10 ml) and the mixture was heated under reflux for 15 hours. Alternatively, the same solution was mixed with highly activated molecular sieve (4 Å, 3 g) and allowed to stand at room temperature for 30 hours whereupon compound **4** was formed in addition to product **3b**. The two carbazole derivatives were purified by column chromatography (silica gel, 40-60° petroleum ether/ethyl acetate, 3/1). Product **3b** was obtained as colorless crystals, yield 102 mg (25%; both procedures), mp 172° (toluene); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): 1.87 (s, 3H, COCH_3), 3.47 and 3.99 (each s, each 3H, CO_2CH_3), 7.23-7.29 (m, 3H, H-aromatic), 7.46-7.68 (m, 4H, H-aromatic), 7.69 (d, J = 7.9 Hz, 1H, H-8'), 7.95 (d, J = 8.0 Hz, 1H, H-5'), 11.78 (s, 1H, NH); ms: m/e (%) 401 ($M^{+\cdot}$, 100).

Anal. Calcd. for $C_{24}H_{19}NO_5$ (401.1): C, 71.86; H, 4.77; N, 3.49. Found: C, 71.72; H, 4.69; N, 3.38.

Product **4** was obtained as colorless crystals, yield 74 mg (14%), mp 207° (40-60° petroleum ether/ethyl acetate); ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): 1.63 (s, 3H, COCH_3), 3.51, 3.79, 3.85, and 3.89 (each s, each 3H, CO_2CH_3), 4.68 (s, 1H, H-2'), 6.18 (s, 1H, H-2), 6.94-7.32 (m, 8H, H-phenyl, H-6' to H-8'), 7.65 (d, J = 8.1 Hz, 1H, H-5'), 12.02 (s, 1H, NH); ms: m/e (%) 544 ($M^{+\cdot}$, 45), 400 (100).

Anal. Calcd. for $C_{30}H_{27}NO_9$ (544.2): C, 66.21; H, 4.82; N, 2.57. Found: C, 66.15; H, 4.90; N, 2.46.

2-Phenyl-3,3,4,4-tetracyano-1,2,3,4-tetrahydro-9*H*-carbazole (**5**).

The vinylindole **1c** (219 mg, 1.0 mmole) was dissolved in toluene (10 ml) and a highly activated molecular sieve (3 g) was added. Tetracyanoethylene (150 mg, 1.1 mmoles) was added to the above mixture which was then stirred for 15 minutes at room temperature. The mixture was subsequently filtered, the filtrate was concentrated, and the residue was purified by column chromatography over silica gel (40-60° petroleum ether/ethyl acetate, 5/1) to furnish compound **5** as pale violet crystals, yield 200 mg (58%), mp 214° (petroleum ether/ethyl acetate); ^{1}H-nmr (hexadeuterioacetone): 3.68 (dd, J = 17.8 Hz, 5.2 Hz, 1H, H_a-1), 3.85 (dd, J = 17.8 Hz, 11.6 Hz, 1H, H_b-1), 4.32 (dd, J = 11.6 Hz, 5.2 Hz, 1H, H-2), 7.32-7.38 (m, 2H, H-aromatic), 7.55-7.62 (m, 4H, H-aromatic), 7.73-7.85 (m, 3H, H-aromatic); ms: m/e (%) 347 ($M^{+\cdot}$, 9%), 193 (100%).

Anal. Calcd. for $C_{22}H_{13}N_5$ (347.12): C, 76.07; H, 3.77; N, 20.16. Found: C, 76.18; H, 3.81; N, 19.98.

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