The regioselectivity of the formation of dihydro- and tetrahydrocarbazoles by the Fischer indole synthesis

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The cyclohexanone **3** and the cyclohexenone **13** have been prepared, converted to their phenylhydrazones, and subjected to the Fischer indole synthesis under conditions ranging from 7% to 60% sulfuric acid in methanol. The tetrahydrocarbazoles **4** and **5** were isolated in a 2:1 ratio in the sequence starting from **3** and no significant variation in the ratio was observed through the range of conditions used. In the sequence starting with **13**, the dihydrocarbazoles **14** and **15** were isolated in a 1:1 ratio when 7% or 15% sulfuric acid was used; when more concentrated acid was used, normal Fischer products were not obtained but some transformation products were isolated from the complex mixture of products obtained. The observed regioselectivity of these reactions is not predicted from mechanistic considerations, and no mechanistic explanation for the results is apparent. As part of the proof of structure of **4** and **14**, their *N*-benzyl derivatives were prepared from 1-benzyl-2-vinylindole by Diels–Alder reactions.

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On a préparé la cyclohexanone **3** et la cyclohexènone **13**, ainsi que leurs phénylhydrazones qui subissent la synthèse de l'indole de Fisher lorsque mises en solution dans de l'acide sulfurique à des concentrations de 7 à 60% dans le méthanol. On a recueilli les tétrahydrocarbazoles **4** et **5** dans un rapport 2:1 en partant du composé **3** et ce rapport reste invariable dans les conditions utilisées. Dans le cas du composé **13**, on pu isoler les tétrahydrocarbazoles **14** et **15** dans un rapport de 1:1 lorsqu'on utilise des solutions d'acide sulfurique à 7 ou 15%. En solutions plus concentrées, on n'obtient pas les produits normaux de Fisher, mais on a isolé quelques produits de transformation à partir d'un mélange complexe de produits obtenus. la régiosélectivité observée pour ces réactions n'est pas prévue à partir des mécanismes connus, et on n'a aucun mécanisme apparent qui permette d'expliquer ces résultats. On établit la structure des composés **4** et **14** en préparant leurs dérivés *N*-benzyle à partir du benzyl-1 vinyl-2 indole par des réactions de Diels–Alder.

[Traduit par le journal]

Tetrahydrocarbazoles carrying reactive substituents at assigned locations could serve as intermediates in syntheses of more complex structures, including a range of indole alkaloids. The classical Fischer indole synthesis (1) offers a convenient route to such tetrahydrocarbazoles, provided that the appropriate cyclohexanone is available as a precursor and that a reasonable degree of regioselectivity can be established when an unsymmetrically substituted cyclohexanone is taken through the Fischer sequence. The regioselectivity observed experimentally and the question of whether it can be controlled by varying the reaction conditions are matters of practical importance in such cases, and are the subject of the present study. It is also of interest to see whether mechanistic considerations can be used to predict and explain the results obtained.

We studied first the simple case using the cyclohexanone **3**, which was conveniently prepared (70% yield) by the Diels–Alder reaction of the trimethylsiloxybutadiene **1** (2) with *N*-methylmaleimide followed by methanolysis of the adduct **2** (see Scheme 1). The phenylhydrazone of **3** was isolated (90% yield) and subjected to the Fischer indole reaction under a range of acidic conditions (see Table 1). The crystalline adducts **4** and **5** were isolated in the yields shown in the table; the overall yields diminished as the concentration of acid used increased, but the **4**/**5** ratio remained close to 2:1 until yields were significantly lowered.

Although the structures assigned to **4** and **5** on the basis of their spectroscopic properties appeared secure, confirmation of the structure of **4** was obtained by the synthesis of a derivative by the unambiguous route outlined in Scheme 2. Indole-2-carboxylic acid (**6**) was converted by diazomethane to its methyl ester, which was *N*-benzylated to provide **7**. The ester was converted by the action of hydrazine in ethanol to the hydrazide, which was tosylated with tosyl chloride, and then subjected to a McFadyen–Stevens reduction. Yields at each step were excellent and the aldehyde **8** was obtained from **6** in 83% overall yield. The vinyl compound **9** was obtained in 85% yield from **8** by a Wittig reaction. A Diels–Alder reaction of **9** with *N*-methylmaleimide then led to the isolation of **10**, the *N*-benzyl derivative of **4**, in 52% yield. Unfortunately, the benzyl group of **10** resisted hydrogenolysis and attempts to *N*-benzylate **4** led to a complex mixture of products none of which was **10**. Nevertheless, comparison of the critical spectroscopic properties of **4** and **10** served to demonstrate that they possessed the same tetracyclic skeleton. Fur-

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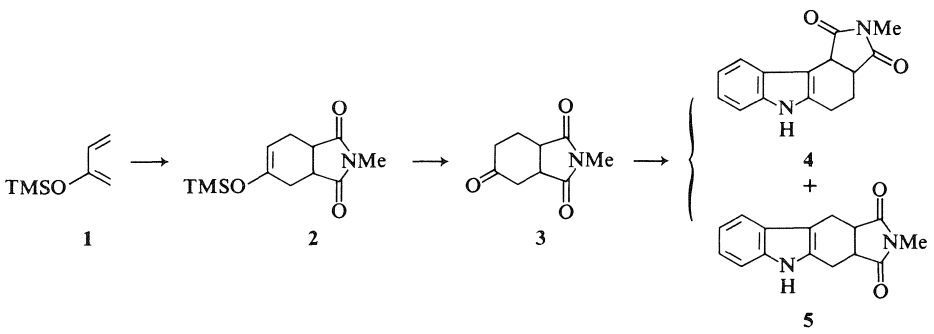


SCHEME 1

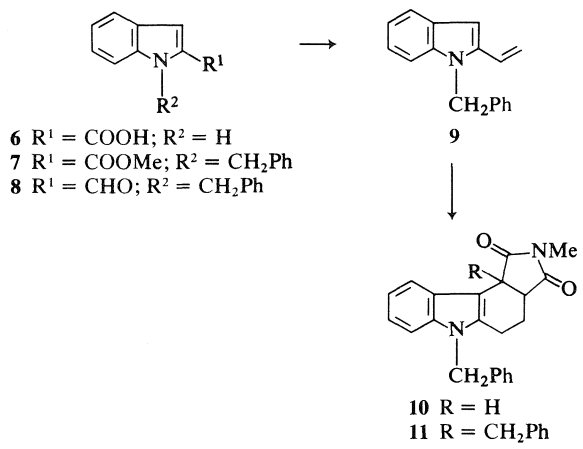
thermore, the major product isolated (albeit in only 35% yield) from the treatment of **4** with sodium hydride (1 equiv.) and benzyl chloride in HMPT was a dibenzyl compound. The probable structure of this compound is shown as **11**. Its uv spectrum strongly resembles that of **10** and both compounds show the same carbonyl ir absorptions, but there are key differences in their proton nmr spectra: a one-proton doublet at τ 5.69 in the spectrum of **10**, assigned to the C-4 proton, is absent in **11**, and a two-proton AB quartet centred at τ 6.35 appears instead and is assigned to the *C*-benzyl methylene protons; the *N*-benzyl methylene protons have the same chemical shift in both spectra, but those of **10** appear as a singlet, while in the spectrum of **11**, the signal is split. For present purposes, the main importance of this compound obtained from **4** is that it could also be obtained from **10** (in 25% yield) by benzylation, and so demonstrates that **4** and **10** have the same tetracyclic skeleton.

The Diels–Alder reaction of diene **1** with dimethyl acetylenedicarboxylate led to an oily product in 86% yield, the spectroscopic properties of which were consistent with the structure **12** expected for the adduct. Conversion of **12** to a ketone (Scheme 3) even under the mildest conditions (stirring with methanol at room temperature), led to the formation of the conjugated cyclohexenone **13** in excellent yield; this compound showed λ_{max} 223 nm (ε 10 500) in its uv spectrum, a one-proton doublet with $J = 1.5$ Hz at τ 3.20 in its proton nmr spectrum, and other features in its ir and nmr (^{1}H and ^{13}C) spectra in accord with the assigned structure. Compound **13** was converted to its crystalline phenylhydrazone which was then subjected to the Fischer indole reaction under the range of acidic conditions used previously. In this series the yields of the Fischer products were lower even from reactions carried out in 7% or 15% sulfuric acid in methanol (see Table 1), and the use of more strongly acidic conditions led to the formation of very complex mixtures of products which afforded none of the normal Fischer products, the dihydrocarbazoles **14** and **15**. The carbazole **16**, presumably an oxidation product of **15**, was isolated from the mixture obtained from reactions in concentrated acids. (It was also detected in some runs even when the reaction was carried out in 15% sulfuric acid.) The corresponding oxidized derivative of **14**, the carbazole **17**, was not identified in the mixture, but a compound that appeared to be **18**, its reduction product, was isolated. (Reference samples of **16** and **17** were prepared by treatment of the corresponding dihydrocarbazole with dichlorodicyanoquinone.) A considerable amount of polymeric material was also evident, and consequently it was deemed unwise to attempt to quantify the regioselectivity of the Fischer reaction under these

TABLE 1. Product distributions in Fischer reactions

Conditions	Products* from Phenylhydrazone of **3**		Products* from Phenylhydrazone of **13**	
	4	**5**	**14**	**15**
7% H_2SO_4/MeOH	45	21	24	23
15% H_2SO_4/MeOH	45	22	23	22
30% H_2SO_4/MeOH	45	24	Complex mixture of products	
45% H_2SO_4/MeOH	36	18		
60% H_2SO_4/MeOH	15	6		

*Yields (%) of isolated products are shown.



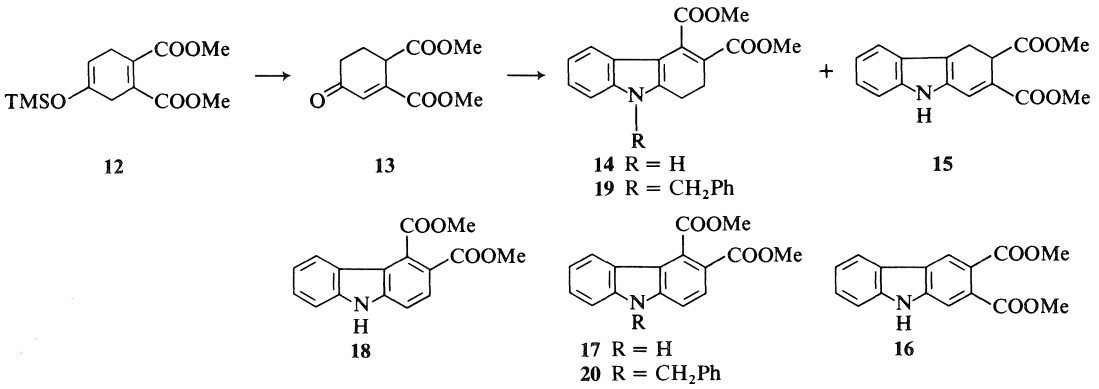
SCHEME 2

circumstances; undoubtedly the reaction of interest is accompanied by undesired competitive and consecutive reactions and even if all of the products from the complex mixture formed could be isolated in the hope of throwing light on any regioselectivity in the Fischer reaction, the procedure under these conditions is of no preparative value. We may note, however, that in the more restricted range of 7% to 15% sulfuric acid, there was no apparent regioselectivity and the **14**/**15** ratio remained 1:1.

As with the previous series, the *N*-benzyl derivative **19** of the diester **14** was prepared by the Diels–Alder reaction of the vinylindole **9** with dimethyl acetylenedicarboxylate. In this case, however, the yield of adduct was only 25%; a complex mixture of by-products was also obtained, some of which appeared to result from oxidation–reduction reactions involving **19** that took place under the Diels–Alder conditions (in the presence of hydroquinone) since the carbazole **20** was isolated from the mixture. Confirmation of the structure assigned to Fischer product **14** was obtained by its *N*-benzylation; in this case monobenzylation could be effected and **19** was isolated in 30% yield. Once again, there was evidence that some of the product had undergone aromatization during the reaction, providing at least a partial explanation for the poor yield.

The mechanism of the Fischer indole synthesis has been the subject of several investigations (1). It is generally agreed that a complex series of events occurs, in which the phenylhydrazone is converted to its enehydrazine tautomer which undergoes a reaction corresponding to a [3,3] sigmatropic rearrangement to form the new C—C bond and cleave the N—N bond; subsequently the indole ring is formed with the elimination of one nitrogen. Normally the reaction is acid-catalyzed, but neither its kinetic dependence on the acid catalyst nor the identity of the rate-determining step has been established unequivocally. In most proposed mechanisms it is a protonated enehydrazine that undergoes rearrangement, and it is the rearrangement step that is probably rate-determining.

The phenylhydrazone of an unsymmetrically substituted cyclohexanone can clearly form two enehydrazine tautomers (e.g. **21** and **22**) and the regioselectivity of the overall Fischer reaction will depend on which of these preferentially undergoes the rearrangement process (Scheme 4). It appeared, *a priori*, that any electronic effects of the substituents (R^1, R^2) in this case should have a negligible influence on the **21**/**22** ratio; steric effects, if of any significance, would appear to disfavor bond development in the rearrangement of **21**, and consequently favor reaction through **22**. In the case of a cyclohexenone derivative, however, the electronic effects of substituents may be expected to be significant in determining the ratio of enehydrazines (e.g. **23** and **24**) formed; it can also

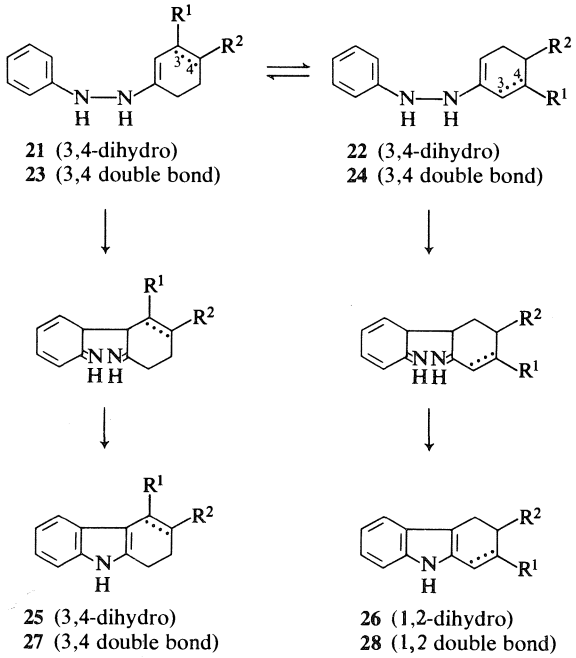


SCHEME 3

be seen, however, that the ratio under kinetic control may differ from that under thermodynamic control, and that each isomer may undergo the rearrangement at a different rate. In any event, these factors seem likely to lead to some degree of regioselectivity, and this would probably be sensitive to reaction conditions.

In practice, the distribution of isomers isolated from the Fischer reaction of our cyclohexanone **3** was not approximately 1:1 as predicted, but 2:1 in favor of the route through **21**, and the ratio was not sensitive to the conditions of the reaction. There is a report (3) that only products corresponding to **25** were isolated from the Fischer reaction of a series of compounds corresponding to our **3** but with other substituents on the nitrogen atom; the reaction through **21** again seemed to be favored. However, in another case that appears to be similar, two groups of workers (4) have obtained the opposite regioselectivity; in this case the starting material was cyclohexanone-3-carboxylic acid and only **26** (R^1 = COOH; R^2 = H) was isolated, indicating that the route through **22** was strongly preferred. It seems clear from these results that the reaction is influenced by effects more subtle than those we have already considered.

In the sequence starting from the cyclohexenone **13**, no regioselectivity was observed when the Fischer reaction was carried out in solutions containing 7% or 15% sulfuric acid, and a 1:1 ratio of isomers was obtained. When more concentrated sulfuric acid was used, no regioselectivity was observable because normal Fischer products were not isolated. Undoubtedly the dihydrocarbazoles are subject to further transformations in the strongly acidic media and they probably undergo some degradation even when the conditions are less acidic. If the two products underwent degradation at different rates, the 1:1 ratio observed for the isolated products could reflect the selective destruction of the major isomer. However, the absence of any significant change in yield or product ratio when the conditions were varied from 7% to 15% sulfuric acid provides some evidence against this possibility, although it does not exclude it. The results in this series must consequently be treated with circumspection but, with the reservations stated, they indicate that reactions through **23** and **24** are equally favored.



SCHEME 4

In summary then, some regioselectivity (2:1) was observed in the Fischer reaction starting with cyclohexanone **3**, but none was observed in the case of cyclohexenone **13**. These results are not those expected from mechanistic considerations, and we can present no mechanistic explanation for them.

Experimental

Melting points were determined on a calibrated Thomas–Kofler micro hot stage. A Perkin–Elmer 237B infrared spectrometer was used; the wavelengths (μ) of selected ir absorptions of solutions in chloroform are reported. A Unicam SP 1800 ultraviolet spectrometer was used. The λ_{max} values (nm) followed by the extinction coefficients (ε) in parentheses of principal uv absorptions of solutions in methanol are reported. Varian T-60, HA 100, XL 100, and HR 220 nmr spectrometers were used. Unless otherwise indicated, the ^{1}Hmr spectra reported were obtained at 100 MHz with solutions in $CDCl_3$; chemical shifts are reported on the τ scale, followed in parentheses by an indication of the multiplicity (initial letter) of the signal, the coupling constant (in Hz units) when available, and the number of protons associated with the signal. Unless otherwise indicated, ^{13}Cmr spectra were obtained with solutions in $CDCl_3$ and chemical shifts are reported on the δ_C scale (ppm relative to TMS = 0) followed in parentheses by an indication of the multiplicity of the signal. An AEI MS-902 mass spectrometer was used to make accurate mass measurements.

The cyclohexanone 3

A solution of 2-trimethylsiloxy-1,3-butadiene (2) (2.00 g; 0.014 mol) and *N*-methylmaleimide (1.56 g; 14.0 mmol) in 10 mL of dry benzene was heated at 65°C for 24 h. Benzene was removed on a rotary evaporator and adduct **2** (2.99 g) was obtained as an oily residue. The residue was dissolved in 20 mL of methanol and stirred at room temperature for 48 h. Evaporation on a rotary evaporator provided the oily ketone **3** (1.92 g; 11.0 mmol) which was purified by vacuum distillation; ir: 5.66, 5.75, 5.85; ^{1}Hmr (220 MHz): 6.62–6.87 (m, 2), 6.98 (s, 3), 7.26 (d, J = 6; 2), 7.56–7.94 (m, 4); ^{13}Cmr: 207.63 (s), 178.34(s), 177.98(s), 37.96(d), 37.11(d), 36.89(t), 36.14(t), 24.66(q), 21.49(t);

Exact Mass calcd. for $C_9H_{11}NO_3$: 181.0734; found: 181.0740. Phenylhydrazone, mp 190–195°C. 2,4-Dinitrophenylhydrazone, mp 225–227°C. *Anal.* calcd. for $C_{15}H_{15}N_5O_6$: C 49.86, H 4.18, N 19.39; found: C 49.81, H 4.26, N 19.40.

The cyclohexenone ***13***

2-Trimethylsiloxy-1,3-butadiene (10.0 g; 0.70 mol) and dimethyl acetylenedicarboxylate (10.0 g; 0.70 mol) were converted by the sequence described above into the cyclohexenone **13** (12.5 g; 0.60 mol), which was purified by vacuum distillation; ir: 5.79, 5.92, 6.13; uv: 223 (10 500); ^{1}Hmr: 3.20 (d, J = 1.5; 1), 6.16 (s, 3), 6.2 (m, 1; irradiation collapses τ3.20 doublet), 6.26 (s, 3), 7.6 (m, 4); ^{13}Cmr: 198.56(s), 171.71(s), 166.29(s), 144.90(s), 133.88(d), 52.86(q), 52.70(q), 40.53(d), 34.91(t), 25.80(t). *Anal.* calcd. for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.72, H 5.82. Phenylhydrazone, mp 140–141.5°C. *Anal.* calcd. for $C_{16}H_{18}N_2O_4$: C 63.56, H 6.00, N 9.27; found: C 63.51, H 5.83, N 9.36.

Fischer indole syntheses

Standard procedure

The phenylhydrazone (1.0 g) was dissolved in 5 g of methanolic sulfuric acid of the required composition (w./w.), and the solution was heated in an oil bath at 80°C for 6 h. The solution was cooled and poured into about 100 mL of water, neutralized with sodium carbonate, and extracted thoroughly with dichloromethane. The combined extracts were washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel with elution by 1:1 ethyl acetate – hexane, and the separated products were isolated.

Cyclohexanone ***3*** *series*

The results obtained by the standard procedure are reported in Table 1. For preparative purposes, the procedure using 15% methanolic sulfuric acid was scaled up. Compound **4** was eluted first, followed by compound **5**, and no other identifiable material was obtained.

Tetrahydrocarbazole **4** was recrystallized from benzene–cyclohexane and obtained as crystals, mp 180–183°C; ir: 2.88, 5.61, 5.88; uv: 223 (30 000), 273 (6040), 278 (6100), 282 (6040), 289 (5150); ^{1}Hmr: 2.05 (complex, 2, D_2O reduces to 1), 2.66–2.94 (m, 3), 5.73 (d, J = 8; 1), 6.66 (m, 1), 7.10 (s, 3), 7.26–7.58 (m, 3), 8.05 (m, 1); ^{13}Cmr: 179.07(s), 177.35(s), 135.56(s), 134.30(s), 126.76(s), 122.03(d), 120.18(d), 119.69(d), 110.59(d), 103.61(s), 40.18(d), 39.58(d), 24.74(q), 21.32(t), 19.79(t). *Anal.* calcd. for $C_{15}H_{14}N_2O_2$: C 70.85, H 5.55, N 11.02; found: C 70.98, H 5.66, N 11.06.

Tetrahydrocarbazole **5** was recrystallized from benzene–methanol and obtained as crystals, mp 219–223°C; ir: 2.89, 5.63, 5.89; uv: 224 (28 000), 274 (6450), 282 (6740), 290 (5500); ^{1}Hmr: 1.78 (broad s, 1, D_2O removes), 2.45–3.05 (m, 4), 6.50–6.65 (m, 4), 6.85–7.05 (m, 2), 7.15 (s, 3); ^{13}Cmr: ($CDCl_3$/DMSO-d_6): 181.04(s), 180.80(s), 136.55(s), 133.54(s), 127.51(s), 121.46(d), 119.61(d), 118.16(d), 112.07(d), 107.15(s), 25.81(q), 22.91(t), 21.33(t). *Anal.* calcd. for $C_{15}H_{14}N_2O_2$: C 70.85, H 5.55, N 11.02; found: C 70.75, H 5.71, N 11.13.

Cyclohexenone ***13*** *series*

The results obtained by the standard procedure with 7% and 15% methanolic sulfuric acid are reported in Table 1. The reactions in 30%, 45%, and 60% methanolic sulfuric acid produced complex mixtures which were not successfully separated by the standard chromatographic procedure. The material obtained from the 60% sulfuric acid was subsequently subjected to preparative tlc on alumina with elution by 95:5 benzene–methanol; the carbazole **16** (20%) and a trace of material considered to be the tetrahydrocarbazole **18** were isolated in this way. For preparative purposes the procedure using 15% methanolic sulfuric acid was scaled up. Compound **15** was eluted first followed by compound **14**; very small amounts of **16** and **18** were also obtained by a combination of chromatographic and fractional crystallization procedures.

Dihydrocarbazole **14** was recrystallized from benzene and obtained as crystals, mp 223–225°C; ir: 2.88, 5.78, 5.89; uv: 233 (20 750), 272 (8950), 278 (8700), 305 (3550), 369 (12 050); ^{1}Hmr (220 MHz): 1.38 (br s, 1), 2.50–2.94 (m, 4), 5.97 (s, 3), 6.21 (s, 3), 7.17 (narrow m, 4; in C_6D_6 soln. becomes 7.41 (t, 2), 7.95 (t, 2), J = 8). *Anal.* calcd. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found: C 67.49, H 5.31, N 4.81.

Dicarbazole **15** was recrystallized from benzene–cyclohexane and obtained as crystals, mp 192–193°C; ir: 2.79, 5.79, 5.90; uv: 214 (end absorption; 15 350), 258 (10 200), 374 (13 600); ^{1}Hmr (220 MHz): 2.33 (br s, 1), 2.44 (s, 1), 2.48–2.95 (complex, 4), 5.97 (dd, J = 9, 2.5; 1), 6.29 (s, 3), 6.36 (s, 3), 6.38 (dd, J = 17, 2.5; 1), 6.88 (dd, J = 17, 9; 1). *Anal.* calcd. for $C_{16}H_{15}NO_4$: C 67.36, H 5.30, N 4.91; found: C 67.03, H 5.51, N 5.17.

Carbazole **16** was recrystallized from benzene and obtained as crystals, mp 136–137°C; ir: 2.89, 5.83; uv: 220 (end absorption; 20 000), 236 (23 600), 245 (25 000), 270 (45 500), 297 (12 800), 305 (11 500), 341 (3750); ^{1}Hmr (60 MHz): 0.99 (br s, 1), 1.52–2.96 (complex, 6), 6.06 (s, 3), 6.10 (s, 3). *Anal.* calcd. for $C_{16}H_{13}NO_4$: C 67.84, H 4.63, N 4.95; found: C 67.88, H 4.69, N 5.04. Compound **16** was also prepared by stirring a solution of the dihydrocarbazole **15** (150 mg; 0.53 mmol) and dichlorodicyanoquinone (125 mg; 0.55 mmol) in 10 mL of dioxane at 80°C for 1 h. Filtration and evaporation afforded a residue which was chromatographed on alumina with elution by benzene to provide **16** (110 mg; 0.39 mmol). The same method was used to convert dihydrocarbazole **14** to carbazole **17**, mp 224–225°C; ir: 2.89, 5.80, 5.85; uv: 226 (end absorption; 27 200), 243 (19 200), 264 (25 400), 279 (44 000), 314 (5250), 323 (4800); ^{1}Hmr (60 MHz): 2.40–2.80 (complex, 6), 5.83 (s, 3), 6.05 (s, 3). *Anal.* calcd. for $C_{16}H_{13}NO_4$: C 67.84, H 4.63, N 4.95; found: C 67.89, H 4.57, N 4.96.

Compound **18** was recrystallized from benzene in cyclohexane and obtained as crystals, mp 139–142°C; ir: 2.89, 5.79; uv: 225 (13 000), 274 (3050), 278 (3050), 282 (3050), 290 (2400); ^{1}Hmr (60 MHz): 2.05 (broad s, 1), 2.44 (m, 1), 2.74–3.06 (complex, 3), 5.70 (d, J = 6; 1), 6.26 (s, 3), 6.33 (s, 3), 6.68 (m, 1), 7.13–8.10 (complex, 4); *Exact Mass* calcd. for $C_{16}H_{17}NO_4$: 287.1157; found: 287.1157.

*Methyl 1-benzylindole-2-carboxylate (****7****)*

A solution of methyl indole-2-carboxylate (12.0 g; 68.6 mmol) in 60 mL of dry hexamethylphosphoric triamide (HMPT) was added over 2 h to a stirred slurry of sodium hydride (83 mmol) in 40 mL of HMPT maintained at 0°C. The reaction mixture was stirred at 0°C for a further hour and then allowed to warm to room temperature. Benzyl chloride (9.1 g; 72 mmol) was added over 0.5 h and the reaction mixture was stirred for a further 2 h. The mixture was poured into 700 mL of water containing 20 mL of concentrated hydrochloric acid and extracted with ether. The ether extract afforded **7** (16.4 g; 61.7 mmol), which was recrystallized from cyclohexane–acetone and obtained as crystals, mp 84–86°C; ir: 5.86; uv: 230 (end absorption, 20 000), 248 (4500), 293 (20 500); ^{1}Hmr: 2.31 (dd, J = 6.5, 1.5; 1), 2.61–3.05 (complex, 9), 4.18 (s, 2), 6.17 (s, 3). *Anal.* calcd. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28; found: C 76.94, H 5.79, N 5.22.

*1-Benzylindole-2-carboxaldehyde (****8****)*

A solution of ester **7** (8.2 g; 30.9 mmol) and hydrazine hydrate (15 mL; 0.309 mol) in 25 mL of absolute ethanol was refluxed for 3 h and then allowed to stand. Crystals separated and were collected; the mother liquor afforded a further crop of crystals on evaporation (total yield 95%). Recrystallization from metha-

nol provided a sample, mp 186–189°C; ir: 2.90, 3.00, 6.00, 6.15; uv: 214 (end absorption; 28 800), 292 (16 100); ^{1}Hmr: 2.33 (dd, J = 7, 2; 1), 2.47 (broad m, 1), 2.64–3.10 (complex, 9), 4.22 (s, 2), 6.43 (broad m, 2). *Anal.* calcd. for $C_{16}H_{15}N_3O$: C 72.43, H 5.70, N 15.84; found: C 72.62, H 5.72, N 15.88.

Tosyl chloride (5.7 g; 30.0 mmol) was added to a stirred solution of the hydrazide (7.8 g; 29.4 mmol) in 90 mL of pyridine at 0°C; after 0.5 h at 0°C, the cooling bath was removed, and the stirring was continued for 2 h. The reaction mixture was poured into a mixture of ice and concentrated hydrochloric acid and the product was obtained as a solid which was collected by filtration and washed with dilute hydrochloric acid and water. The partially dry material was dissolved in methylene chloride and dried (magnesium sulfate). The methylene chloride afforded the crystalline tosylhydrazide (97% yield); recrystallization from ethanol provided a sample, mp 231–230°C; ir: 2.99, 5.98, 6.04; uv: 218 (end absorption; 30 200), 294 (17 700); ^{1}Hmr: 0.55 (d, J = 4; 1), 1.24 (m, 1), 2.13–3.22 (complex, 14), 4.46 (s, 2), 7.69 (s, 3); *Exact Mass* calcd. for $C_{23}H_{21}N_3SO_3$: 419.1304; found: 419.1304.

The tosylhydrazide (3.0 g; 7.1 mmol) was dissolved in a minimum (about 300 mL) of ethylene glycol at 150°C in a wide-mouthed vessel, and potassium carbonate (2.1 g; 15 mmol) was added in one lot. As soon as the vigorous effervescence ceased (about 1 min), the solution was poured into a large volume of ice. Ether extraction afforded the aldehyde **8** (1.6 g; 6.8 mmol); recrystallization from methanol provided a sample, mp 68–70°C; ir: 3.54, 5.99, 6.04, 6.19; uv: 210 (end absorption; 18 900), 231 (12 100), 307 (18 400); ^{1}Hmr: 0.19 (s, 1), 2.33 (dd, J = 8, 1; 1), 2.65–3.00 (complex, 9), 4.27 (s, 2). *Anal.* calcd. for $C_{16}H_{13}NO$: C 81.68, H 5.57, N 5.95; found: C 81.77, H 5.69, N 6.01.

1-Benzyl-2-vinylindole (9)

Methyltriphenylphosphonium bromide (3.4 g; 9.5 mmol) and butyllithium (9.5 mmol) in 50 mL of dry ether were stirred at reflux under a nitrogen atmosphere for 1.5 h, and then cooled to 0°C. An ether solution of aldehyde **8** (2.12 g; 9.0 mmol) was added and the mixture was refluxed for 1.5 h. The mixture was cooled and then treated with a solution of sodium sulfate (6.8 g) in 100 mL of water. The organic layer was washed with water, dried, and evaporated. The residue obtained was repeatedly triturated with petroleum ether (30–60°C); the petroleum ether solution was filtered and evaporated to provide the product as a yellow oil (1.78 g; 7.7 mmol): ir: 6.22; uv: 225 (16 000), 242 (10 900), 306 (12 900), 345 (1350); ^{1}Hmr: 2.24–3.29 (complex, 10), 3.39 (dd, J = 17.5, 11; 1), 4.31 (dd, J = 17.5, 1.5; 1), 4.80 (s, 2), 4.85 (dd, J = 11, 1.5; 1); *Exact Mass* calcd. for $C_{17}H_{15}N$: 233.1204; found: 233.1204.

*Diels–Alder adduct **10***

A solution of the vinylindole **9** (1.60 g; 6.9 mmol) and *N*-methylmaleimide (0.76 g; 6.9 mmol) in 35 mL of benzene was heated at 70°C for 21 h. Concentration of the solution and addition of cyclohexane caused the product **10** to separate as crystals; several crops were collected (total yield 52%). Recrystallization from benzene–cyclohexane provided a sample, mp 186–188°C; ir: 5.64, 5.86; uv: 224 (21 600), 276 (4100), 283 (4400), 292 (4000); ^{1}Hmr: 1.97 (dd, J = 6, 2; 1), 2.60–3.10 (complex, 8), 4.80 (s, 2), 5.69 (d, J = 8; 1), 6.72 (m, 1), 7.10 (s, 3), 7.3–8.0 (complex, 4). *Anal.* calcd. for $C_{22}H_{20}N_2O_2$: C 76.72, H 5.85, N 8.13; found: C 76.77, H 6.04, N 8.06.

*Diels–Alder adduct **19***

A solution of the vinylindole **9** (2.0 g; 8.6 mmol), dimethyl acetylenedicarboxylate (1.2 g; 8.5 mmol), and hydroquinone (50 mg) in 50 mL of benzene was heated at 60°C for 1 h and at 40°C for 20 h. Evaporation of the solvent left a red oily residue; chromatography on an alumina column gave a fraction (1.0 g) that contained adduct **19** and some oxidized material **20**. This mixture of products (about 9:1) was separated by preparative tlc on alumina. Recrystallization of **19** from benzene–cyclohexane gave a sample, mp 151–153°C; ir: 5.75, 5.88; uv: 219 (end absorption; 19 000), 234 (24 900), 274 (11 600), 306 (5600), 369 (16 100); ^{1}Hmr: 2.44–3.14 (complex, 9), 4.74 (s, 2), 5.95 (s, 3), 6.22 (s, 3), 7.16 (s, 4; in benzene forms symmetrical complex multiplet centred ~τ 7.5). *Anal.* calcd. for $C_{23}H_{21}NO_4$: C 73.58, H 5.64, N 3.73; found: C 73.74, H 5.76, N 3.76.

The carbazole **20** was also prepared by heating a solution of adduct **19** (250 mg; 0.67 mmol) and dichlorodicyanoquinone (160 mg; 0.70 mmol) in 5 mL of dioxane to 90°C for 25 min. Evaporation, chromatography on alumina, and recrystallization from benzene–cyclohexane provided **20**, mp 164–165°C; ir: 5.80, 5.85; uv: 216 (end absorption; 17 200), 231 (21 600), 247 (17 200), 266 (19 000), 281 (34 000), 316 (3750), 330 (3000), 342 (1500); ^{1}Hmr: 1.94–2.10 (complex, 2), 2.57–3.16 (complex, 9), 4.64 (s, 2), 5.85 (s, 3), 6.10 (s, 3). *Anal.* calcd. for $C_{23}H_{19}NO_4$: C 73.98, H 5.13, N 3.75; found: C 74.11, H 4.96, N 3.85.

*Benzylation of **4***

A solution of compound **4** (100 mg; 0.39 mmol) in 5 mL of dry HMPT was added to a stirred slurry of sodium hydride (0.56 mmol) in 3 mL of HMPT maintained at 0°C. After 10 min the mixture was allowed to warm to room temperature, benzyl chloride (55 mg; 0.44 mmol) was added, and stirring was continued for 3 h. The reaction mixture was poured into water and extracted with methylene chloride. The extract afforded the product (**11**) as a white solid (42 mg; 0.10 mmol); recrystallization from benzene provided a sample, mp 264–265°C; ir: 5.63, 5.88; uv: 225 (end absorption; 25 800), 286 (5700), 293 (5750); ^{1}Hmr: 1.33 (m, 1), 2.60–3.20 (m, 13), 4.81 (two peaks, 3 Hz separation; 2), 6.19 (d, J = 14; 1), 6.50 (d, J = 14; 1), 6.92 (m, 1), 7.15 (s, 3), 7.48–7.82 (complex, 4).

Compound **11** (31 mg; 0.07 mmol) was also prepared by treating compound **10** (101 mg; 0.29 mmol) with sodium hydride (0.31 mmol) in 5 mL of HMPT and benzyl chloride (45 mg; 0.35 mmol) in the manner just described.

*Benzylation of **14***

Compound **14** (60 mg; 0.20 mmol) was treated with sodium hydride (0.25 mmol) and benzyl chloride (30 mg; 0.26 mmol) in the manner described above, and converted to the compound **19** (20 mg; 0.70 mmol) described previously.

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