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Fischer Indolization and Its Related Compounds. XIX.[1] Syntheses of Ethyl 4-Methoxy- and Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylates

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Ethyl 4-methoxy- (**7**) and ethyl 5-methoxy- (**3**) -1-phenyl-3*H*-benz[*e*]indole-2-carboxylates were prepared by Fischer indolization of ethyl phenylpyruvate 2-naphthylhydrazone derivatives bearing a methoxy group at the C_3- (**26**) and the C_4- (**8**) positions, respectively.

Keywords——synthesis; methoxy-3*H*-benz[*e*]indole; methoxy-2-naphthylhydrazone; ethanolic hydrogen chloride; Fischer indolization

In the preceding paper,[1] we reported that Fischer indolization of ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**1**) gave four angular benz[*e*]indole products, ethyl 5-methoxy- (**3**), ethyl 4-chloro-5-methoxy- (**4**), ethyl 5-ethoxy- (**5**), and ethyl 4-chloro-5-ethoxy- (**6**)-1-phenyl-3*H*-benz[*e*]indole-2-carboxylates. In connection with that work, we required authentic specimens of the first compound (**3**) and of the isomeric ethyl 4-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**7**), in order to establish the position of the ethoxy group of the 5-ethoxybenz[*e*]indole products (**5** and **6**). In this report we describe the syntheses of the two compounds *via* more definitive pathways.

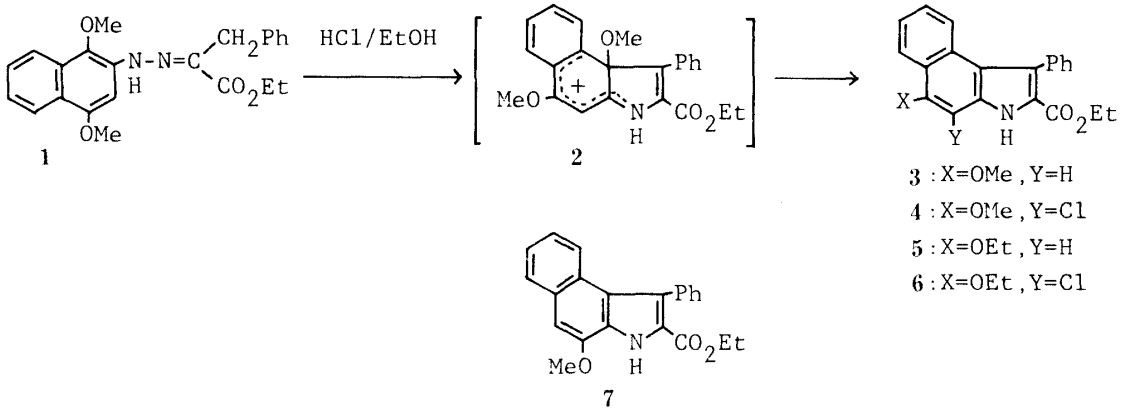


Chart 1

First, we aimed at synthesizing the 5-methoxybenz[*e*]indole (**3**) by Fischer indolization of ethyl phenylpyruvate 2-[(4-methoxy-2-naphthyl)hydrazone] (**8**), which was expected to be prepared by Japp–Klingemann reaction[2] of 4-methoxy-2-naphthylamine[3] (**9**) with ethyl α-benzylacetoacetate.[4] The starting naphthylamine (**9**) was obtained *via* Curtius rearrangement of 4-methoxy-2-naphthoic acid[5] (**10**), which was prepared from ethyl acetosuccinate[6] (**11**) according to the reported method. However, treatment of the naphthylamine (**9**) with sodium

nitrite in acidic medium gave no corresponding diazonium salt, but only a C-nitrosation product which was supposed to be 4-methoxy-1-nitroso-2-naphthylamine[7] (**14**) on the basis of elemental analysis and other physical data.

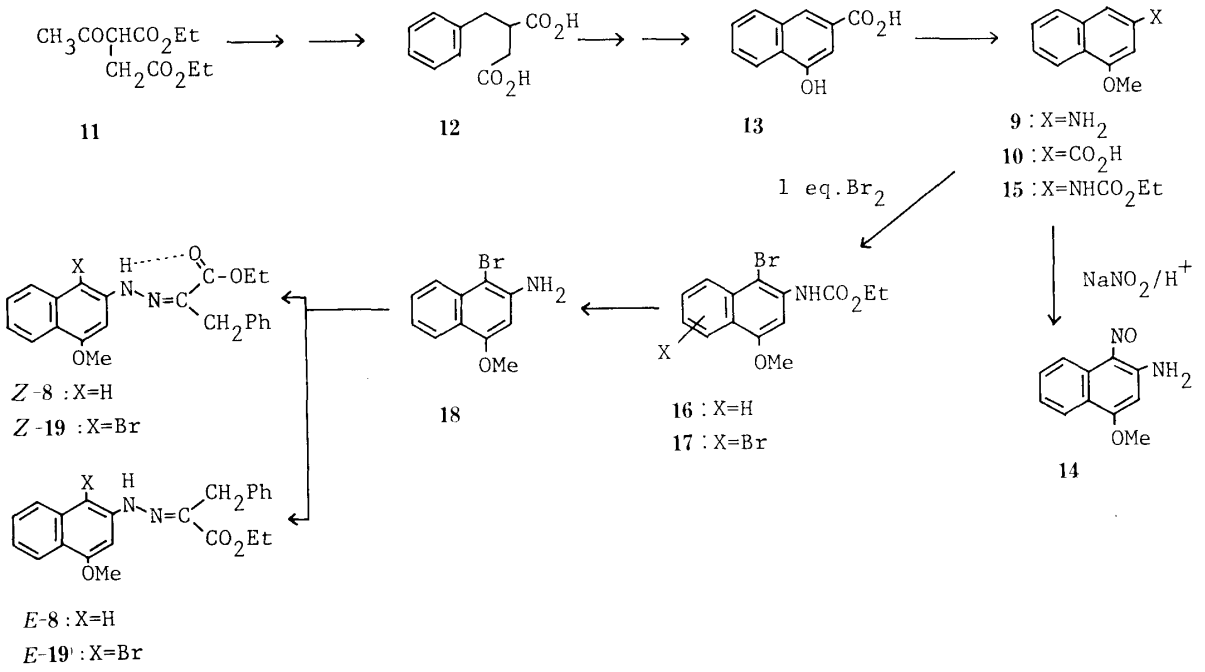


Chart 2

Subsequently, in order to protect the C_1-position of the 4-methoxy-2-naphthylamine (**9**) against nitrosation, ethyl 4-methoxy-2-naphthalenecarbamate (**15**) was brominated with equimolar bromine in chloroform to give a monobromide (**16**). It should be added here that when an excess amount of bromine was used, the dibromide (**17**) was easily formed, although the exact position of the second bromine atom was not determined. The resulting monobromide (**16**) was hydrolyzed with potassium hydroxide in ethanol under argon to give the 1-bromo-4-methoxy-2-naphthylamine (**18**). Japp–Klingemann reaction[2] of the bromonaphthylamine (**18**) with ethyl α-benzylacetoacetate[4] gave a mixture of geometrical isomers of the (*Z*)- and (*E*)-1-bromo-4-methoxy-2-naphthylhydrazones [(*Z*)- and (*E*)-**19**], for which assignment of the geometrical structures was done by comparison[8] of their spectral data, especially, the chemical shifts of the imino protons. The catalytic hydrogenation of the (*E*)-isomer [(*E*)-**19**] over palladium-carbon in the presence of calcium oxide gave the desired dehalogenated (*E*)-4-methoxy-2-naphthylhydrazone [(*E*)-**8**].

Treatment of the 4-methoxy-2-naphthylhydrazone (**8**) with ethanolic hydrogen chloride gave a methoxybenzindole product (**3**) in 73.2% yield along with a minute amount of a benzindole derivative (**5**) bearing an ethoxy group instead of a methoxy group. The former (**3**) was identical with the methoxybenz[*e*]indole[1] which was obtained on Fischer indolization of the 1,4-dimethoxy-2-naphthylhydrazone derivative (**1**). The mother skeleton of the methoxybenzindole (**3**) had been confirmed to be benz[*e*]indole by converting it to the *o*-quinone (**20**) by oxidation with chromic acid in acetic acid according to the method reported in the preceding paper.[1] The finding that the same methoxybenz[*e*]indole was obtained from both the 4-methoxy-2-naphthylhydrazone (**8**) and the 1,4-dimethoxy-2-naphthylhydrazone (**1**) definitively established the structure of the methoxybenz[*e*]indole as ethyl 5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**3**).

Although the starting 2-naphthylhydrazone (**8**) could in principle cyclize at the C_1- and C_3-positions in the above experiment, we could not find any evidence of the formation of a

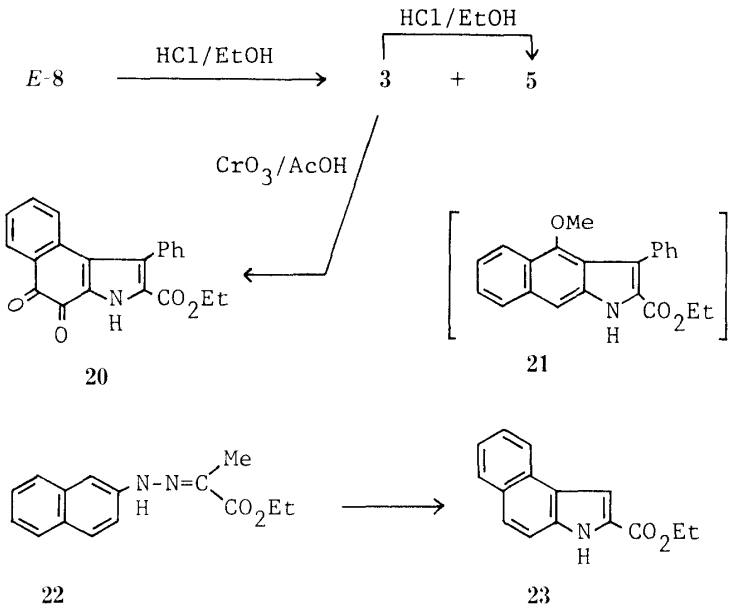


Chart 3

benz[*f*]indole derivative (**21**), a linear benzindole, indicating that cyclization took place only at the C_1-position, but not at C_3. Since our observation agreed with Schlieper's observation[9] that Fischer indolization of ethyl pyruvate 2-napthylhydrazone (**22**) gave the benz[*e*]indole (**23**) as a sole product, we may say that cyclization takes place exclusively at the C_1-position in the Fischer indolization of 2-naphthylhydrazone derivatives bearing no substituent at both *ortho*-positions, the C_1- and C_3-positions.

The ethoxybenz[*e*]indole produced on Fischer indolization of the 4-methoxy-2-naphthylhydrazone (**8**) was also identical with the 5-ethoxybenz[*e*]indole (**5**) which was prepared from the above 5-methoxybenz[*e*]indole (**3**) by treatment with ethanolic hydrogen chloride as reported in the preceding paper,[1] indicating that it should be ethyl 5-ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**5**).

Next, we undertook to synthesize ethyl 4-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**7**). The starting 3-methoxy-2-naphthylamine[10] (**24**) was prepared from commer-

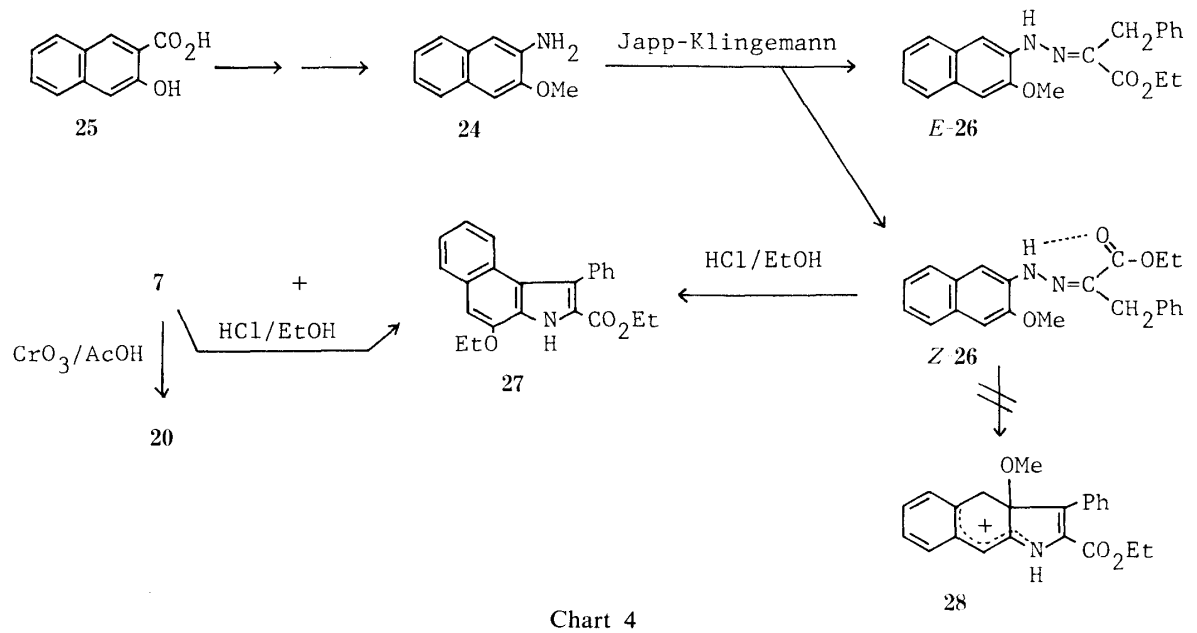
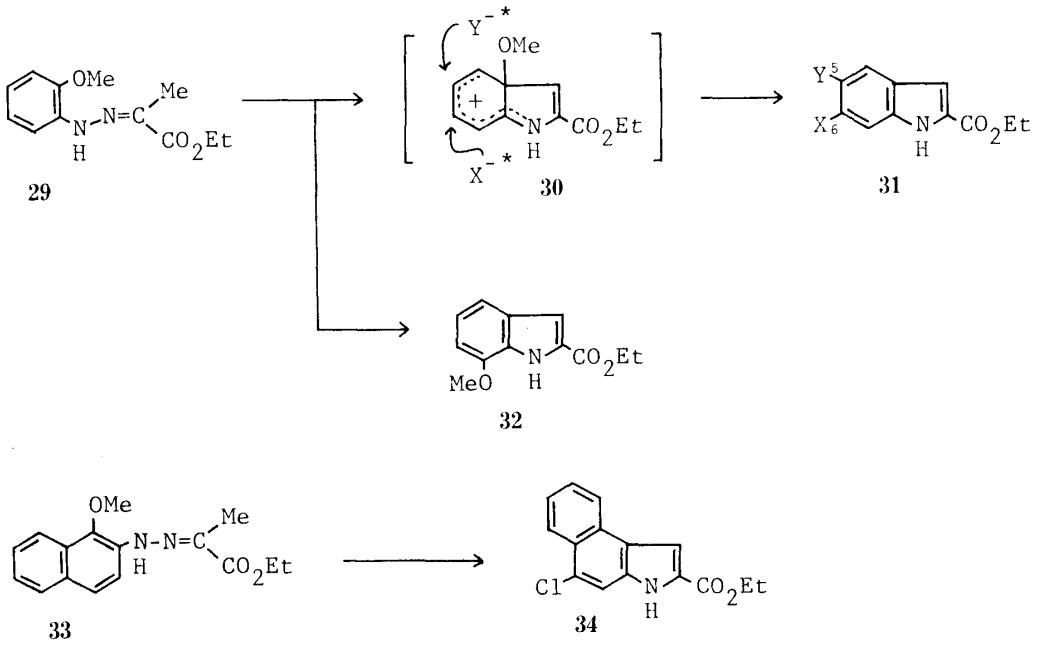


Chart 4

cial 3-hydroxy-2-naphthoic acid (**25**) according to the reported method. Japp–Klingemann reaction[2] of the methoxynaphthylamine (**24**) with ethyl α-benzylacetoacetate[4] gave a mixture of geometrical isomers of the (*Z*)- and (*E*)-3-methoxy-2-naphthylhydrazones [(*Z*)- and (*E*)-**26**]. The assignment of the geometrical structures of these isomers was based on comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of these products, as in the case of the bromonaphthylhydrazone (**19**) described above.

Fischer indolization of the (*E*)-3-methoxy-2-naphthylhydrazone [(*E*)-**26**] with ethanolic hydrogen chloride gave two benzindole products (**7** and **27**) in 73.2 and 3.0% yields, respectively. In the ^{1}H-NMR spectrum, the major product (**7**) shows a 3H singlet due to a methoxy group at δ 4.01. Oxidation of the product (**7**) with chromic acid in acetic acid afforded the *o*-quinone derivative[1] (**20**), indicating that the methoxybenz[*e*]indole product was the desired ethyl 4-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**7**).

The minor product (**27**) has an ethoxy group instead of the methoxy group of the above 4-methoxybenz[*e*]indole (**7**). This material was confirmed to be 4-ethoxybenz[*e*]indole[1] (**27**), which could be obtained on treatment of the 4-methoxybenz[*e*]indole (**7**) with ethanolic hydrogen chloride as reported in the preceding paper.[1]



* Either X or Y is a nucleophile involved in the Fischer indolization.

Chart 5

It should be emphasized here that we obtained no evidence for formation of the product derived by cyclization at the *ortho*-position (the C_3-position) occupied by the methoxy group in the Fischer indolization of the 3-methoxy-2-naphthylhydrazone (**26**). As we reported, Fischer indolization of the 2-methoxyphenylhydrazone (**29**) tends to give various 6-substituted or 5-substituted indole derivatives (**31**) (Chart 5) together with the anticipated 7-methoxyindole derivative (**32**) as a minor product, indicating that cyclization at the *ortho*-position occupied by a methoxy group took place as a main pathway in the case of the phenylhydrazone itself. Moreover, in the case of 1-methoxy-2-naphthylhydrazone derivatives (**1** and **33**), this phenomenon could be more definitely demonstrated by the absence[1,12] of the product derived by cyclization at the vacant position (the C_3-position) in the reaction mixture. Thus, there is a striking contrast in mode of cylization between Fischer indolization of these two 2-naphthylhydrazone derivatives bearing a methoxy group at the C_1-position and at C_3.

This consideration allows us to deduce that 2-naphthylhydrazone derivatives react at the C_1-position regardless of the presence of a methoxy group at the C_3-position. In other words, in the case of the 3-methoxy-2-naphthylhydrazone (**26**), the preference for substitution at the C_1-position rather than the C_2-position, a characteristic of naphthalene derivatives, overcomes the preference for cyclization at the *ortho*-position occupied by a methoxy group, which is characteristic of the Fischer indolization of the *o*-methoxyphenylhydrazones. In conclusion, we may say that cyclization of 2-naphthylhydrazone derivatives bearing no substituent at the C_1-position should take place exclusively at the C_1-position regardless of the species of substituent at the C_3-position in Fischer indolization.

Experimental

Instruments, *etc.*, were as described in the preceding paper.[1]

4-Methoxy-2-naphthoic Acid[5] (10)——Prepared from ethyl acetosuccinate[6] (**11**) *via* 2-benzylsuccinic acid[13] (**12**) according to the reported procedure. Colorless needles (recrystallized from benzene–hexane), mp 207—208 °C (lit.[5] mp 202—202.5 °C). IR ν_{max} cm^{-1}: 3200—2400 (COOH), 1675 (CO). ^{1}H-NMR (DMSO-d_6) δ: 2.80—4.00 (1H, br s, COOH), 4.05 (3H, s, OCH_3), 7.30—8.45 (6H, m, arom. H).

Ethyl 4-Methoxy-2-naphthalenecarbamate (15)——Diphenyl phosphorazidate[14] (DPPA, 4.78 ml) and then Et_3N (4.13 ml) was added to a solution of 4-methoxy-2-naphthoic acid[5] (**10**) (2.99 g) in dioxane (27 ml). The mixture was stirred at room temperature for 5 min, then refluxed for 10 min. After addition of EtOH (8 ml), the solution was refluxed for a further 2 h and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and the solution was washed with 5% citric acid followed by 5% Na_2CO_3 aq. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with benzene to give colorless prisms (3.27 g), mp 131—131.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55: H, 6.16; N, 5.71. Found: C, 68.57; H, 6.21; N, 5.64. IR ν_{max} cm^{-1}: 3320 (NH), 1715 (CO). ^{1}H-NMR δ: 1.35 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.97 (3H, s, OCH_3), 4.26 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.75 (1H, br s, NH), 6.98—8.30 (5H, m, arom. H), 7.01 (1H, d, J=2.5 Hz, C_1- or C_3-H). MS m/z: 245 (M^+, 100%).

4-Methoxy-2-naphthylamine (9)——The carbamate (**15**) (3.58 g) and KOH (5.47 g) were dissolved in ethylene glycol (35 ml) under Ar gas. The mixture was heated at 160 °C for 1.5 h and poured into a large amount of H_2O. After extraction with Et_2O, the ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with benzene–AcOEt (10 : 1, v/v) to give pale brown prisms (2.21 g), mp 58—59 °C (lit.[3] mp 57.5—58.5 °C), which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.31; H, 6.25; N, 8.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 br, 3365 (NH). ^{1}H-NMR δ: 3.77 (2H, br, NH_2), 3.91 (3H, s, OCH_3), 6.24 (1H, d, J=2.0 Hz, C_3-H), 6.54 (1H, d, J=2.0 Hz, C_1-H), 7.00—7.70 (3H, m, arom. H), 8.04 (1H, dd, J=8.0 and 2.0 Hz, C_5- or C_8-H). MS m/z: 173 (M^+, 100%).

4-Methoxy-1-nitroso-2-naphthylamine (14)——The naphthylamine (**9**) (0.436 g) was dissolved in EtOH (5 ml) containing conc. HCl (1.0 ml) and H_2O (4.0 ml) and diazotized with $NaNO_2$ (0.180 g) under ice-cooling. The resulting solution of the diazonium salt was added dropwise to a solution of ethyl α-benzylacetoacetate[1,4] (0.550 g) in EtOH (2.0 ml) containing 50% KOH (0.9 ml) and ice (5.0 g) under ice-cooling. Then the mixture was stirred at room temperature for 2 h, poured into a large amount of H_2O, and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (0.79 g) was chromatographed on silica gel with benzene–AcOEt (2 : 1, v/v), followed by AcOEt. The first eluate (0.489 g) gave the recovered ethyl α-benzylacetoacetate.

The second eluate gave dark violet needles (0.20 g), mp 202—204 °C, which were recrystallized from EtOH. *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.63; H, 5.10; N, 13.85. IR ν_{max} cm^{-1}: 3200—2600 (NH). ^{1}H-NMR (DMSO-d_6) δ: 4.03 (3H, s, OCH_3), 6.37 (1H, s, C_3-H), 7.25—7.80 (2H, m, C_6- and C_7-H), 7.97 (1H, dd, J=8.0 and 2.0 Hz, C_5-H), 8.48 (1H, br s, NH), 8.93 (1H, dd, J=8.0 and 2.0 Hz, C_8-H), 12.15 (1H, br s, NH). MS m/z: 202 (M^+, 100%), 172 ($M^+ - NO$, 76%).

Ethyl 1-Bromo-4-methoxy-2-naphthalenecarbamate (16)——A solution of Br_2 (0.392 ml) in $CHCl_3$ (32 ml) was added dropwise to a solution of ethyl 4-methoxy-2-naphthalenecarbamate (**15**) (1.968 g) in $CHCl_3$ (16 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and diluted with $CHCl_3$. The solution was washed with 5% $Na_2S_2O_3$ aq. and sat. NaCl aq., dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue (2.63 g) was chromatographed on silica gel with benzene to give colorless needles (2.32 g), mp 85.5—86.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.92; H, 4.33; N, 4.01. IR ν_{max} cm^{-1}: 3320 (NH), 1702 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.01 (3H, s, OCH_3), 4.26 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.20—8.30 (6H, m, arom. H and NH). MS m/z: 325 (M^++2, 74% intensity of M^+), 323 (M^+, 21%), 216 (100%).

Ethyl Dibromo-4-methoxy-2-napthalenecarbamate (17)——A solution of Br_2 (0.065 ml) in $CHCl_3$ (4.0 ml) was

added dropwise to a solution of the naphthalenecarbamate (**15**) (0.123 g) in $CHCl_3$ (1.0 ml) under ice-cooling. After being stirred at room temperature for 2 h, the reaction mixture was worked-up as described above. The crude product was purified by column chromatography on silica gel with benzene followed by recrystallization from benzene–hexane to give colorless prisms (0.176 g), mp 156—158.5 °C. *Anal.* Calcd for $C_{14}H_{13}Br_2NO_3$: C, 41.72; H, 3.25; N, 3.48. Found: C, 41.94; H, 3.17; N, 3.27. IR ν_{max} cm^{-1}: 3390 (NH), 1730 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.99 (3H, s, OCH_3), 4.27 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.40 (1H, br s, NH), 7.54 (1H, dd, J=9.0 and 2.0 Hz, C_6 or C_7–H), 7.88 (1H, d, J=9.0 Hz, C_5 or C_8–H), 7.90 (1H, s, C_3–H), 8.28 (1H, d, J=2.0 Hz, C_8– or C_5–H). MS m/z: 405 (M^++4, 96.6% intensity of M^+), 403 (M^++2, 189% intensity of M^+), 401 (M^+, 47%), 294 (100%).

1-Bromo-4-methoxy-2-naphthylamine (18)——A solution of the bromocarbamate (**16**) (5.00 g) in EtOH (130 ml) containing KOH (10.18 g) was refluxed for 6 h under Ar gas. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 10% HCl aq. (100 ml). The solution was stirred at room temperature for 15 min, basified with 20% NaOH aq., and extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and evaporated to dryness *in vacuo* to give pale brown prisms (3.66 g), mp 90.0—92.5 °C (dec.). IR ν_{max} cm^{-1}: 3445, 3355, 3185 (NH). ^{1}H-NMR δ: 3.78 (2H, br s, NH_2), 3.92 (3H, s, OCH_3), 6.31 (1H, s, C_3–H), 7.04—7.65 (2H, m, C_6– and C_7–H), 7.82—8.18 (2H, m, C_5– and C_8–H). This material was characterized as the picrate, dark brown prisms, which were recrystallized from EtOH, mp 145—150 °C. *Anal.* Calcd for $C_{11}H_{10}BrNO \cdot C_6H_3N_3O_7$: C, 42.43; H, 2.72; N, 11.64. Found: C, 41.93; H, 2.58; N, 11.52.

(*Z*)-Ethyl Phenylpyruvate 2-[(1-Bromo-4-methoxy-2-naphthyl)hydrazone] [(*Z*)-19]——A suspension of 1-bromo-4-methoxy-2-naphthylamine (**18**) (3.50 g) in dil. HCl aq. [conc. HCl (4.90 ml) and H_2O (28 ml)] was diazotized with $NaNO_2$ (0.987 g) under ice-cooling. The resulting diazonium salt solution was added dropwise to a solution of ethyl α-benzylacetoacetate[1,4] (3.06 g) in EtOH (14 ml) containing 10 N KOH aq. (6.0 ml) under ice-cooling. After being stirred under ice-cooling for 2 h, the reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal layer was washed with saturated NaCl aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (6.11 g) was chromatographed on silica gel with benzene–hexane (1 : 1, v/v) to give dark red prisms (0.160 g), mp 128—129.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{22}H_{21}BrN_2O_3$: C, 59.87; H, 4.80; N, 6.35. Found: C, 60.09; H, 4.75; N, 6.06. IR ν_{max} cm^{-1}: 3170 (NH), 1665 (CO). ^{1}H-NMR δ: 1.30 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.88 (2H, s, $C\underline{H}_2Ph$), 3.92 (3H, s, OCH_3), 4.28 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.05—7.70 (2H, m, C_6– and C_7–H), 7.15 (1H, s, C_3–H), 7.25 (5H, s, arom. H), 7.90—8.25 (2H, m, C_5– and C_8–H), 12.59 (1H, br s, NH). MS m/z: 442 (M^++2, 102% intensity of M^+), 440 (M^+, 94%), 170 (100%).

(*E*)-Ethyl Phenylpyruvate 2-[(1-Bromo-4-methoxy-2-naphthyl)hydrazone] [(*E*)-19]——Further elution with benzene in the above column chromatography gave pale red needles (4.68 g), mp 130.5—131.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{22}H_{21}BrN_2O_3$: C, 59.87; H, 4.80; N, 6.35. Found C, 60.15; H, 4.65; N, 6.19. IR ν_{max} cm^{-1}: 3320 (NH), 1698 (CO). ^{1}H-NMR δ: 1.43 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.03 (3H, s, OCH_3), 4.09 (2H, s, $C\underline{H}_2Ph$), 4.38 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.29 (5H, s, arom. H), 7.10—7.70 (3H, m, C_3–, C_6–, and C_7–H), 7.70—8.33 (2H, m, C_5– and C_8–H), 8.69 (1H, br s, NH). MS m/z: 442 (M^++2, 98% intensity of M^+), 440 (M^+, 100%).

(*E*)-Ethyl Phenylpyruvate 2-[(4-Methoxy-2-naphthyl)hydrazone] [(*E*)-8]——A solution of the (*E*)-bromonaphthylhydrazone [(*E*)-**19**] (0.516 g) in EtOH (200 ml) was hydrogenated over 10% Pd-C (0.372 g) in the presence of CaO (0.459 g) at room temperature for 2 h under atmospheric pressure. After the catalyst had been removed by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with benzene to give yellow prisms (0.376 g), mp 111.5—113.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.79; H, 6.12; N, 7.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3325 (NH), 1693 (CO). ^{1}H-NMR δ: 1.41 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.98 (3H, s, OCH_3), 4.06 (2H, s, $C\underline{H}_2Ph$), 4.36 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.75—6.90 (2H, m, C_1– and C_3–H), 7.10—7.68 (3H, m, arom. H), 7.26 (5H, s, arom. H), 7.92—8.19 (2H, m, C_5–H and NH). MS m/z: 362 (M^+, 100%).

Fischer Indolization of (*E*)-Ethyl Phenylpyruvate 2-[(4-Methoxy-2-naphthyl)hydrazone] [(*E*)-8]——i) Ethyl 5-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**5**): A solution of the naphthylhydrazone [(*E*)-**8**] (0.331 g) in saturated ethanolic hydrogen chloride (50 ml) was stirred at room temperature until the starting hydrazone disappeared (monitored by thin layer chromatography (TLC)). The reaction mixture was concentrated *in vacuo*, diluted with H_2O, and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–hexane (1 : 2, v/v). The first eluate gave colorless needles (10 mg), mp 247.5—249 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.70; H, 5.84; N, 3.97. IR ν_{max} cm^{-1}: 3290 (NH) 1655 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.04 and 1.54 (each 3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.06 and 4.26 (each 2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.01 (1H, s, C_4–H), 7.08—7.60 (3H, m, arom. H), 7.41 (5H, s, arom. H), 8.02—8.21 (1H, m, C_6–H), 11.95 (1H, br s, NH). MS m/z: 359 (M^+, 100%).

ii) Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**3**): The second eluate on the above column chromatography gave colorless needles (0.231 g), mp 233.5—235.5 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.35; H, 5.50; N, 4.20. IR ν_{max} cm^{-1}: 3310 (NH), 1655 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.02 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.01 (3H, s, OCH_3), 4.06 (2H, q, J=7.0 Hz,

OCH_2CH_3), 7.02 (1H, s, C_4–H), 6.95—7.60 (3H, m, arom. H), 7.40 (5H, s, arom. H), 8.00—8.30 (1H, m, C_6–H), 11.99 (1H, br s, NH). MS *m/z*: 345 (M^+, 100%).

(*Z*)-Ethyl Phenylpyruvate 2-[(3-Methoxy-2-naphthyl)hydrazone] [(*Z*)-26]——A solution of isoamyl nitrite (0.485 ml) in EtOH (10 ml) was added dropwise to a solution of 3-methoxy-2-naphthylamine[10] (**24**) (0.520 g), mp 107—109 °C (lit.[10] mp 109—110 °C), in EtOH (20 ml) containing conc. HCl (1.32 ml) under ice-cooling. The mixture was stirred for 30 min under ice-cooling. The resulting diazonium salt solution was then added to a solution of ethyl α-benzylacetoacetate[1,4] (0.793 g) in 0.3 N KOH aq. (60 ml) containing EtOH (10 ml) under ice-cooling. After being stirred for 2 h, the reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in EtOH (12 ml) containing commercial 85% H_3PO_4 (0.5 ml) and the solution was refluxed for 20 min. The mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with benzene–hexane (1 : 2, v/v) followed by benzene. The eluate with benzene–hexane gave yellow prisms (0.063 g), mp 141—142 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73; Found: C, 72.78; H, 6.06; N, 7.65. IR ν_{max} cm^{-1}: 3255 (NH), 1680 (CO). ^{1}H-NMR δ: 1.24 (3H, t, J=7.0 Hz, CH_2CH_3), 3.89 (2H, s, CH_2Ph), 3.98 (3H, s, OCH_3), 4.19 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.05 (1H, s, C_1- or C_4–H), 7.21 (5H, s, arom. H), 7.10—7.80 (4H, m, arom. H), 7.79 (1H, s, C_1- or C_4–H), 12.21 (1H, br s, NH). MS *m/z*: 362 (M^+, 95%), 115 (100%).

(*E*)-Ethyl Phenylpyruvate 2-[(3-Methoxy-2-naphthyl)hydrazone] [(*E*)-26]——Recrystallization of the second fraction of the above column chromatography from benzene–hexane gave pale yellow needles (0.769 g), mp 117—119 °C. *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.77; H, 6.07; N, 7.68. IR ν_{max} cm^{-1}: 3325 (NH), 1690 (CO). ^{1}H-NMR δ: 1.43 (3H, t, J=7.0 Hz, CH_2CH_3), 3.82 (3H, s, OCH_3), 4.03 (2H, s, CH_2Ph), 4.38 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.96 (1H, s, C_4- or C_1–H), 7.25 (5H, s, arom. H), 7.00—7.85 (4H, m, arom. H), 7.77 (1H, s, C_1- or C_4–H), 8.59 (1H, br s, NH). MS *m/z*: 362 (M^+, 100%).

Fischer Indolization of (*E*)-Ethyl Phenylpyruvate 2-[(3-Methoxy-2-naphthyl)hydrazone] [(*E*)-26]——i) Ethyl 4-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**27**): A solution of the naphthylhydrazone [(*E*)-**26**] (1.00 g) in saturated ethanolic hydrogen chloride (40 ml) was stirred at room temperature for 3 h until the hydrazone [(*E*)-**26**] could not be detected on TLC. After being concentrated under reduced pressure, the mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–hexane (1 : 4, v/v). The first eluate gave colorless prisms (0.066 g), mp 167—168.5 °C (lit.[1] mp 167—168.5 °C), which were recrystallized from $CHCl_3$–EtOH. This material was identical with a sample of ethyl 4-ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**27**) which was prepared by treatment of ethyl 4-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**7**) in the preceding paper.[1]

ii) Ethyl 4-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**7**): Recrystallization of the second eluate from $CHCl_3$–EtOH gave colorless needles (0.763 g), mp 211.5—214 °C. *Anal.* Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.64; H, 5.58; N, 4.05. IR ν_{max} cm^{-1}: 3305 (NH), 1690 (CO). ^{1}H-NMR δ: 1.10 (3H, t, J=7.0 Hz, CH_2CH_3), 4.06 (3H, s, OCH_3), 4.16 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.91 (1H, s, C_5–H), 7.41 (5H, s, arom. H), 6.95—7.80 (4H, m, arom. H), 9.38 (1H, br s, NH). MS *m/z*: 345 (M^+, 100%).

Oxidation of Ethyl 4-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (the 4-Methoxybenz[*e*]indole) (7) with Chromic Acid [the *o*-Quinone (20)]——A solution of CrO_3 (0.073 g) in 80% AcOH (0.5 ml) was added to a solution of the 4-methoxybenz[*e*]indole (**7**) (0.100 g) in AcOH (1.0 ml). The mixture was stirred at room temperature for 30 min and then heated at 100 °C for 30 min. The reaction mixture was poured into H_2O and then extracted with AcOEt. The organic layer was washed with dil. $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ to give orange prisms, mp 263.5—265 °C, which were recrystallized from $CHCl_3$–hexane. This compound was identical with an authentic sample of the *o*-quinone (**20**) which was prepared in the preceding paper.[1]

References and Notes

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7) In the ^{1}H-NMR spectrum, a signal due to an aromatic proton was observed at δ 6.54, at rather high field, as a 1H doublet which was easily exchangeable with D_2O in **9** but not in the C-nitrosation product (**14**). It should be noted here that this observation is consistent with the chemical behavior of **9** (easy C-nitrosation on treatment

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