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SELECTIVE MONO-ALKYLATION OF CARBON NUCLEOPHILES WITH GRAMINE[1]

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Abstract: Mono-alkylation method of carbon nucleophiles, especially for nitroalkanes, with gramine derivatives is reported.

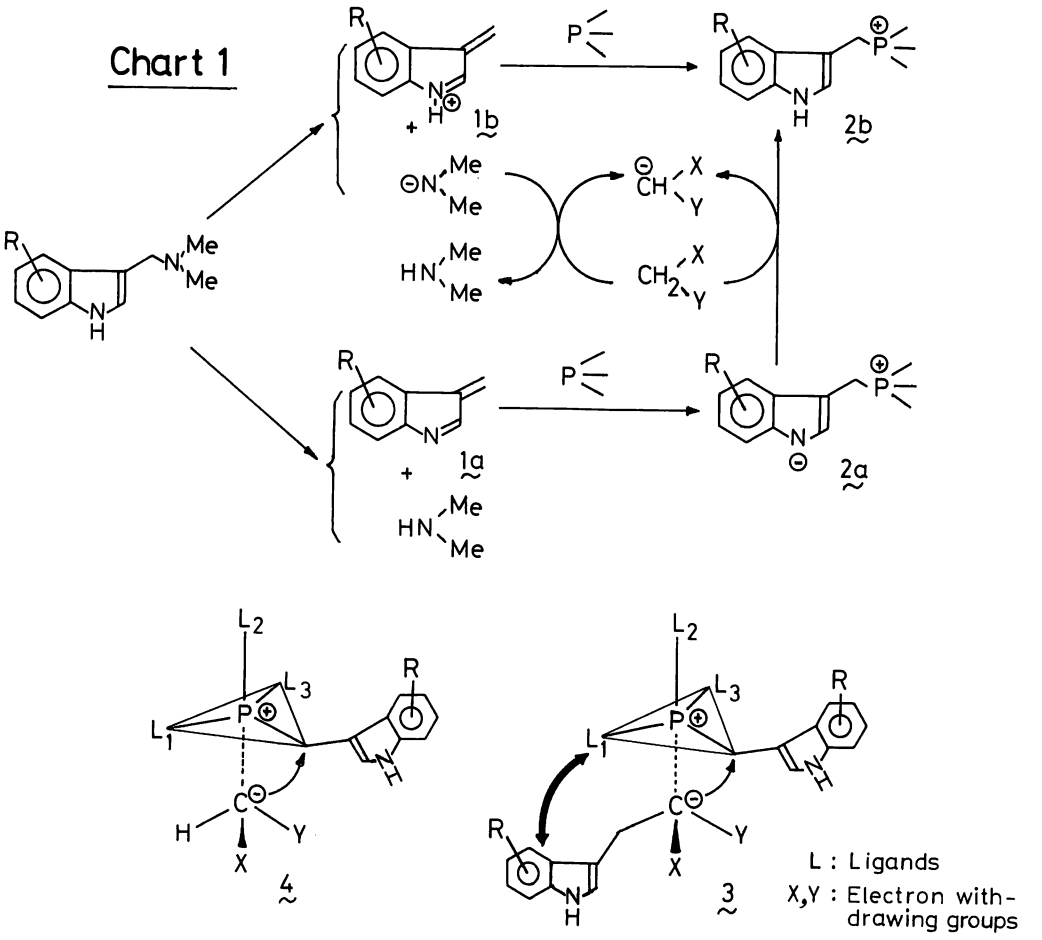
Various carbon nucleophiles have been successfully alkylated by gramine and its derivatives and the reaction has general significance as a synthetic tool for elaboration of indole derivatives.[2] However, when nucleophiles carry more than two activated hydrogens, the reaction often undergoes dialkylation, predominantly. Fspecially, in the case of nitroalkanes,[3] mono-alkylated products are quite difficult to obtain.

Recently, Plieninger et al.[4] reported a new procedure for mono-alkylation of nitroalkanes with dimethyl acetylenedicarboxylate as a catalyst but the yield was still not satisfactory. Alternative nitroethylation of indoles with nitroolefins may be used but the yields are somewhat low.[5]

Our interest in the synthesis of ergot alkaloids[6] led us to develop a selective and high yield method for mono-alkylation of carbon nucleophiles by gramine derivatives in the presence of tri-n-butylphosphine as a catalyst. In this paper, we describe the method in detail.

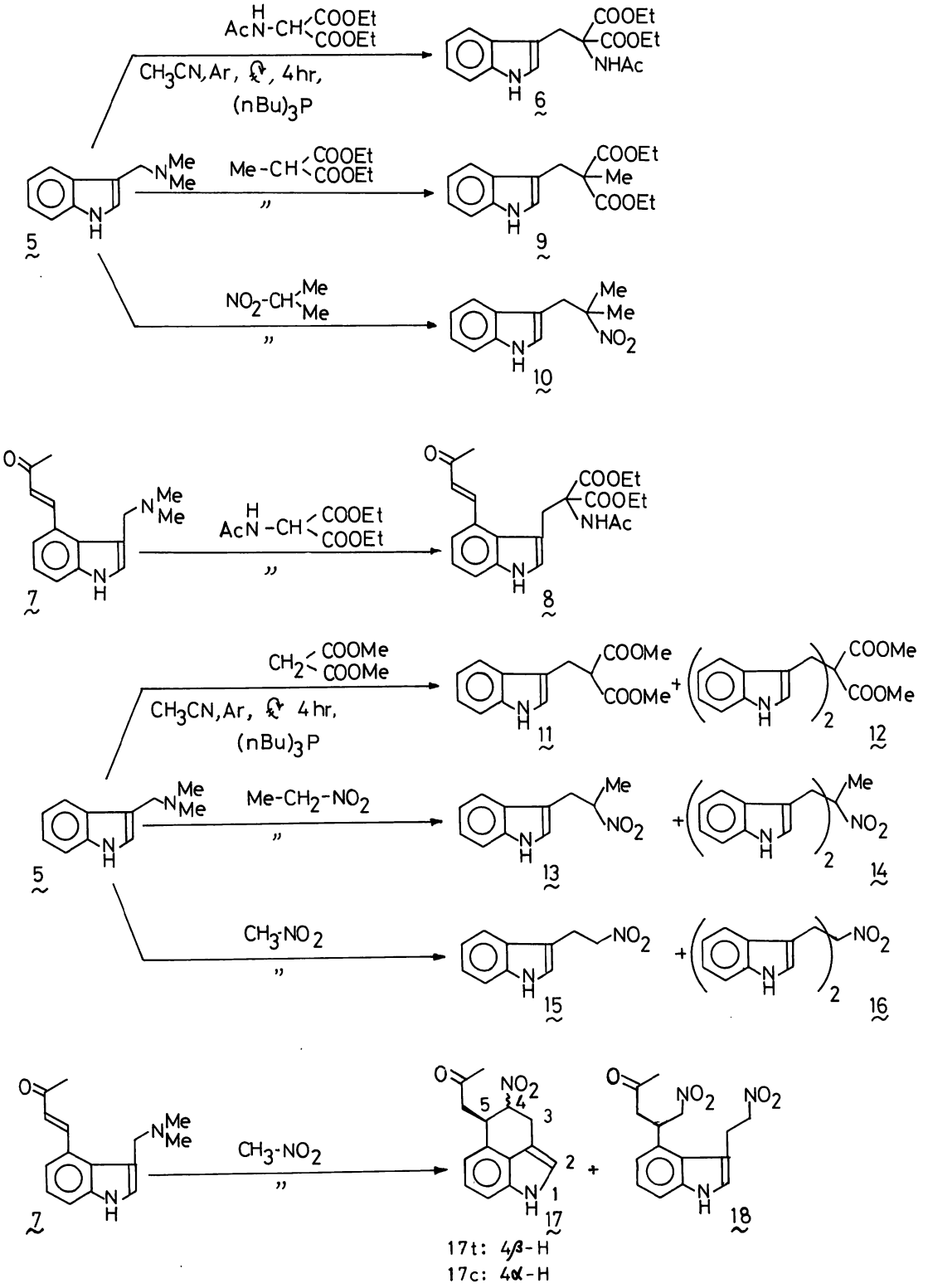
Alkylation of gramine derivatives is believed to be a sort of Michael type addition reaction. Though the reaction is generally carried out in the presence of strong bases such as metal carbonate, metal hydroxide, or metal alkoxides,[7] amines,[8] potassium fluoride,[9] and tertiary phosphines[10] are also found to be mild and effective catalysts.

In order to achieve our attempt, we chose tri-n-butylphosphine among them as a suitable catalyst from the following reason: i) a mild basicity (pK 6.00 in ethanol-water, 2:1, v/v)[11] and the least susceptibility to oxidation reactions among the related tertiary phosphines,[12] ii) strong nucleophilicity to trap 3-methylene-indolenine type intermediate (1a or 1b, Chart 1) as a phosphonium



betaine (2a) or its protonated form (2b), and iii) in the transition state, nitronates (or carbanion), probably generated by the action of dimethylamide anion liberated from the gramine or by the betaine (2a), are attracted to the central phosphorus atom in its ligand field and consequently placed in close vicinity to the electrophilic carbon which is connected directly to the centered phosphorus atom. Taking these concepts into consideration, we believe that there would be a chance to form a carbon-carbon bond between the nitronates and the electrophilic carbon in the phosphorus ligand field. Furthermore, if the ligand of phosphorus is large enough, dialkylation would be suppressed owing to the sterical repulsion between the ligands in the transition state (3) compared with that (4) of mono-alkylation.

Based upon these working hypotheses, gramine (5) was reacted with diethyl acetamidomalonate in acetonitrile in the presence of tri-n-butylphosphine to


AcN-CH(COOEt)(COOEt)
CH3CN,Ar, Δ, 4hr,
(nBu)3P
6
Me-CH(COOEt)(COOEt)
"
9
NO2-CH(Me)(Me)
"
10
5
7
8
CH2(COOMe)(COOMe)
11
12
Me-CH2-NO2
13
14
CH3-NO2
15
16
17
17t: 4β-H
17c: 4α-H
18

afford diethyl acetamido(3-indolylmethyl)malonate (6) in 99.5% yield. Under the same reaction conditions except for the absence of tri-n-butylphosphine, only starting material was recovered in 68.9% yield and none of the compound (6) was isolated. Diethyl acetamidomalonate reacted with 4-[3-(dimethylaminomethyl)-indol-4-yl]-3-buten-2-one (7) to give ethyl α-acetamido-α-ethoxycarbonyl-4-[(3-oxo-1-buten)-1-yl]indol-3-propionate (8) in 71.5% yield under the same reaction conditions. The reaction of diethyl methylmalonate also proceeded smoothly with gramine by the catalysis of tri-n-butylphosphine, producing ethyl α-ethoxycarbonyl-α-methylindole-3-propionate (9) in 90.4% yield. Trial with 2-nitropropane gave 1-(indol-3-yl)-2-nitro-2-methylpropane (10) in yield as high as 99.1%. On the other hand, dimethyl malonate, having two activated hydrogens, was found to afford ethyl α-ethoxycarbonylindole-3-propionate (11) in 81.3% yield in addition to dimethyl di(indol-3-ylmethyl)malonate (12) in 16.0% yield.

Since these results were obviously superior to those so far reported in the literature,[2,3,13] the above method was then applied to primary nitroalkanes. Thus, nitroethane reacted smoothly with gramine affording 3-(indol-3-yl)-2-nitropropane (13) and 1,3-di(indol-3-yl)-2-nitropropane (14) in 69.7% and 0.03% yields, respectively. Similarly, nitromethane gave mono-alkylated product, predominently. Namely, 3-(2-nitroethyl)indole (15) was obtained in 83.0% yield together with 13.7% yield of di(indol-3-ylmethyl)nitromethane (16). These facts are remarkable as compared with the reported ones,[2,3] which afforded only the dialkylated products in poor yields.

The versatility of the present method was clearly exhibited in the reaction of nitromethane with 4-[3-(dimethylaminomethyl)indol-4-yl]-3-buten-2-one (7) producing 5-acetonyl-1,3,4,5-tetrahydro-4-nitrobenz[cd]indole (17) in 77.0% yield. On the other hand, the reaction with sodium carbonate, sodium hydroxide, potassium fluoride, potassium fluoride and 18-crown-6, or triphenyl phosphine as a catalyst gave poorer results owing to concomitant formation of dimeric compound (18) and unknown products.

Although optimum reaction conditions have not been determined as yet, the present procedure provides a valuable mono-alkylation method of nitroalkanes with gramine derivatives. The mechanism mentioned above is still speculative, however, it seems to be more attractive than a simple S_N2 mechanism, because the latter mechanism can not explain a preferencial mono-alkylation reaction.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Preparative thin layer chromatography (p-TLC) was performed on Merck Kieselgel GF_{254} (type 60). NMR spectra were determined with a JEOL JNM-C60H spectrometer (with tetramethylsilane as an internal standard), mass spectra with a JEOL-JNM-01SG spectrometer, and IR spectra with a Shimadzu IR-420 spectrophotometer.

General Procedure

To a stirred solution of gramine (0.5 mmol) and nitroalkane (or carbon nucleophile) in CH_3CN (7.0 ml) was added a solution of $(n\text{-}Bu)_3P$ (0.3-0.4 mol equiv. to gramine) in CH_3CN (3.0 ml) as a single portion. The mixture was refluxed for 4 hr with stirring under argon atmosphere. After removal of the solvent under a reduced pressure, the whole was made acidic by adding 0.5N-HCl and extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed with sat. aq. NaCl, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to p-TLC on kieselgel (SiO_2) with an appropriate solvent. Under a UV lamp, dark bands were detected on the whole luminescent plate. Extraction from each bands with CH_2Cl_2-MeOH (95:5, v/v) gave products.

Diethyl Acetamido(3-indolylmethyl)malonate (6)——In the above procedure, gramine (91.0 mg, 0.52 mmol), diethyl acetamidomalonate (123.5 mg, 0.57 mmol), and $(n\text{-}Bu)_3P$ (42.0 mg, 0.20 mmol) were used. After the work-up and subsequent p-TLC with CH_2Cl_2-MeOH (96:4, v/v), 6 (180.0 mg, y. 99.5%) was obtained. 6: mp 158-159° (colorless prisms from benzene, lit.[13] mp 158-159°).

Ethyl α-Ethoxycarbonyl-α-methylindole-3-propionate (9)——In the general procedure, gramine (87.4 mg, 0.50 mmol), ethyl α-methylmalonate (79.2 mg, 0.54 mmol), and $(n\text{-}Bu)_3P$ (31.0 mg, 0.15 mmol) were used. After the work-up and subsequent p-TLC with hexane-ether (1:1, v/v), 9 (125.5 mg, y. 90.4%) was obtained. 9: colorless oil, IR ν_{max}^{film} cm^{-1}: 3400, 1728, 1459. NMR ($CDCl_3$) δ: 1.18 (6H, t, J=7.0 Hz), 1.58 (3H, s), 3.37 (2H, s), 4.08 (4H, q, J=7.0 Hz), 6.80 (1H, d, J=2.0 Hz), 6.87-7.30 (3H, m), 7.30-7.63 (1H, m), 8.20 (1H, br.s). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.00; H, 6.98; N, 4.88.

1-(Indol-3-yl)-2-nitro-2-methylpropane (10)——In the general procedure, gramine (87.3 mg, 0.50 mmol), 2-nitropropane (33.7 mg, 0.38 mmol), and $(n\text{-}Bu)_3P$ (28.6 mg, 0.14 mmol) were used. After the work-up and subsequent p-TLC with hexane-

ether (1:1, v/v), 10 (138.5 mg, y. 99.1%, calculated based on 2-nitropropane) was obtained. 10: mp 75.5-76.5° (colorless prisms from MeOH-H_2O, lit.[3d] mp 66.5-68°). IR ν_{max}^{KBr} cm^{-1}: 3450, 1522, 1350, 1340. NMR ($CDCl_3$) δ: 1.55 (6H, s), 3.28 (2H, s), 6.80 (1H, br.s), 6.88-7.53 (4H, m), 8.60 (1H, br.s). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.28; H, 6.55; N, 12.59.

Ethyl α-Acetamido-α-ethoxycarbonyl-4-[(3-oxo-1-buten)-1-yl]indol-3-propionate (8)——In the general procedure, 7 (36.0 mg, 0.15 mmol), diethyl-acetamidomalonate (34.0 mg, 0.16 mmol), (n-Bu)$_3$P (33.0 mg, 0.16 mmol) were used. After the usual work-up and subsequent p-TLC with CH_2Cl_2-MeOH (95:5, v/v), 8 (44.0 mg, y. 71.5%) was obtained. 8: mp 173-175° (pale yellow prisms from MeOH). MS m/e: 414 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1760, 1742, 1664, 1648. NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.0 Hz), 1.94 (3H, s), 2.51 (3H, s), 4.02 (2H, s), 4.11 (2H, q, J=7.0 Hz), 4.13 (2H, q, J=7.0 Hz), 6.53 (1H, d, J=16.0 Hz), 6.68-7.41 (4H, m), 8.36 (1H, d, J=16.0 Hz), 8.58 (1H, br.s). Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75;H, 6.32; N, 6.76. Found: C, 63.68; H, 6.37; N, 6.50.

Ethyl α-Ethoxycarbonylindole-3-propionate (11) and Dimethyl Di(indol-3-ylmethyl)malonate (12)——In the general procedure, gramine (88.5 mg, 0.50 mmol), dimethyl malonate (79.3 mg, 0.60 mmol), and (n-Bu)$_3$P (29.6 mg, 0.14 mmol) were used. After the usual work-up and subsequent p-TLC with hexane-ether, 11 (98.1 mg, y. 81.3%) and 12 (15.8 mg, y. 16.0%) were obtained. 11: colorless oil. MS m/e: 237 (M^+). IR ν_{max}^{film} cm^{-1}: 3400, 1740 (br.). NMR ($CDCl_3$) δ: 3.35 (2H, B_2 part of AB_2), 3.60 (6H, s), 3.75 (1H, A part of AB_2), 6.78-7.30 (4H, m), 7.30-7.60 (1H, m), 8.12 (1H, br. s). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.28; H, 5.85; N, 5.20. 12: mp 166-167° (colorless prisms from MeOH). MS m/e: 390 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 1708, 1619, 1428. NMR ($CDCl_3$) δ: 3.47 (10H, s, COOMe x 2, $ArCH_2$ x 2), 6.87 (2H, d, J=2.0 Hz), 6.90-7.24 (6H, m), 7.24-7.55 (2H, m), 7.93 (2H, br.s). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.88; H, 5.65; N, 7.14.

3-(Indol-3-yl)-2-nitropropane (13) and 1,3-Di(indol-3-yl)-2-nitropropane (14)——In the general procedure, gramine (75.4 mg, 0.43 mmol), nitroethane (1.5 ml), and (n-Bu)$_3$P (29.2 mg, 0.14 mmol) were used. After the work-up and subsequent p-TLC with CH_2Cl_2-hexane (2:1, v/v), 13 (61.6 mg, y. 69.7%) and 14 (1.8 mg, y. 0.03%) were obtained. 13: mp 171-172° (colorless prisms from MeOH, lit.[3d] mp 171-172°). IR ν_{max}^{KBr} cm^{-1}: 3400, 1530, 1351, 1341. NMR ($CDCl_3$) δ: 1.50 (3H, d, J=7.5 Hz),

3.05 (1H, dd, J=15.0 and 7.5 Hz), 3.42 (1H, dd, J=15.0 and 7.5 Hz), 4.76 (1H, sextet, J=7.5 Hz), 6.76 (1H, d, J=2 Hz), 6.88-7.23 (3H, m), 7.23-7.56 (1H, m), 7.88 (1H, br.s). 14: mp 147-148° (colorless prisms from MeOH). MS m/e: 333 (M^+). IR $\nu_{max}^{KBr}cm^{-1}$: 3390, 1618, 1526, 1345, 1338. NMR ($CDCl_3$) δ: 1.43 (3H, s), 3.20 (2H, d, J=16.0 Hz), 4.67 (2H, d, J=16.0 Hz), 6.75 (2H, d, J=2.0 Hz), 6.87-7.21 (6H, m), 7.21-7.63 (2H, m), 7.87 (2H, br.s). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.61. Found: C, 72.13; H, 5.74; N, 12.46.

3-(2-Nitroethyl)indole (15) and Di(indol-3-ylmethyl)nitromethane (16)——In the general procedure, gramine (99.0 mg, 0.57 mmol), nitromethane (1.5 ml), and (n-Bu)$_3$P (41.0 mg, 0.20 mmol) were used. After the work-up and subsequent p-TLC with CH_2Cl_2-hexane (7:3, v/v), 15 (89.7 mg, y. 83.0%) and 16 (12.4 mg, y. 13.7%) were obtained. 15: mp 54.0-55.0° (colorless prisms from MeOH, lit.[3c] mp 53.5-54°). MS m/e: 190 (M^+). IR $\nu_{max}^{KBr}cm^{-1}$: 3390, 1552, 1382. NMR ($CDCl_3$) δ: 3.35 (2H, t, J=7.0 Hz), 4.50 (2H, t, J=7.0 Hz), 6.80 (1H, d, J=2.0 Hz), 6.90-7.30 (3H, m), 7.30-7.57 (1H, m), 7.88 (1H, br.s). 16: mp 212-213° (colorless prisms from MeOH, lit.[3d] mp 206°). MS m/e: 319 (M^+). IR $\nu_{max}^{KBr}cm^{-1}$: 3400, 1543, 1530, 1452, 1337. NMR (10% CD_3OD in $CDCl_3$) δ: 3.25 (2H, d.d, J=16.0 and 6.0 Hz), 3.54 (2H, d.d, J=16.0 and 7.0 Hz), 5.13 (1H, q, J=6.0 and 7.0 Hz), 6.93-7.66 (10H, m).

5-Acetonyl-1,3,4,5-tetrahydro-4-nitrobenz[cd]indole (17t and 17c) and 4-[3-(2-Nitroethyl)indol-4-yl]-3-nitromethylbutan-2-one (18)——In the general procedure, 7 (1.151g, 4.75 mmol), nitromethane (45.0 ml), (n-Bu)$_3$P (160.8 mg, 0.79 mmol), and CH_3CN (total, 30.0 ml) were used. The mixture was refluxed for 9 hr under argon atmosphere. The residue, obtained after the work-up as described in the general procedure, was subjected to column chromatography on SiO_2 gel with CH_2Cl_2-hexane (4:1, v/v) as an eluent. From the early part of the fraction, 17 (950.0 mg, y. 77.3%) was obtained. From the later part of the fraction, 18 (74.3 mg, y. 4.9%) was obtained. Since 17 was a mixture of diastereoisomers (ca. 3:1 ratio judged by NMR), separation of them was performed by p-TLC on SiO_2 gel with hexane-ether (1:1, v/v) as a developing solvent. From the upper band, 17c was obtained. From the lower band, 17t was obtained. The ratio of 17t to 17c was 2.6:1.0. 17t: mp 136-138° (colorless prisms from MeOH). MS m/e: 258 (M^+). IR $\nu_{max}^{KBr}cm^{-1}$: 3368, 1708, 1548, 1366. NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.81 (2H, d, J=6.0 Hz, CH_2CO), 3.28 (1H, d.d, J=16.0 and 4.8 Hz, C_3-H), 3.70 (1H, d.d, J=16.0 and 6.0 Hz, C_3-H), 4.31 (1H, d.d.d, J=6.0, 6.0, and 6.0 Hz, C_5-H), 5.00 (1H, d.d.d, J=6.0, 6.0, and 4.8 Hz, C_4-H), 6.61-7.18 (4H, m), 7.93 (1H, br.s, NH). Anal. Calcd for

$C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.19; H, 5.35; N, 10.72. 17c: mp 136-138° (colorless prisms from MeOH). MS m/e: 258 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3410, 1713, 1536, 1365. NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.78 (2H, d, J=7.0 Hz, CH_2-CO), 3.45 (2H, d, J=7.0 Hz, C_3-H_2), 4.36 (1H, d.t, J=4.0 and 7.0 Hz, C_5-H), 5.03 (1H, d.t, J=4.0 and 7.0 Hz, C_4-H), 6.73-7.27 (4H, m), 7.98 (1H, br.s, NH). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.21; H, 5.39; N, 10.58. 18: mp 130.5-131.5° (colorless prisms from MeOH). MS m/e: 319 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1708, 1698, 1555, 1543. IR $\nu_{max}^{MeOH-CHCl_3(1:1, v/v)}$ cm^{-1}: 1703. NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.95 (2H, m), 3.62 (2H, t, J=6.5 Hz), 4.47-4.67 (3H, m), 4.70 (2H, t, J=6.5 Hz), 6.67-7.22 (4H, m), 8.32 (1H, br.s). Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.40; H, 5.27; N, 12.96.

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