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Studies on the Syntheses of Condensed Indole-4,7-diones. II. Synthesis of Pyrrolo[1,2-*a*]indole-5,8-dione Derivatives[1)]

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Methyl 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-5,10-dione-11-carboxylate (**9**) was synthesized starting from 2,3-dichloronaphthoquinone (**2**) through a five-step procedure including a novel cyclization reaction to methyl 1-acetyl-1,2,3,4-tetrahydro-6*H*-naphtho-[2,3-*b*]azocine-5,7,12-trione-6-carboxylate (**13**).

Keywords——mitomycin; pyrrolo[1,2-*a*]indole-5,8-dione; pyrrolo[1,2-*a*]indoloquinone; cyclization; naphthoquinone; chloroquinone; transannular reaction; aminoquinone; azocinone

Pyrrolo[1,2-*a*]indole-5,8-dione is well-known as the basic skeleton of mitomycin C (**1**) ——antitumorigenic antibiotic——and a number of synthetic studies have been reported. Generally speaking, phenolic compounds have been used as starting materials and the quinoid structure was constructed at a final stage of the synthetic courses, partly because of its instability, and therefore the synthetic routes have involved many steps. The authors planned to construct the pyrrolo[1,2-*a*]indole-5,8-dione skeleton at an early stage of the synthesis, starting from a quinoid compound. This paper deals with a synthesis of the skeleton involving only five steps, starting from commercially available 2,3-dichloronaphthoquinone (**2**).

It is known that one of the chlorine atoms of **2** is easily replaceable by various nucleophiles, such as primary and secondary amines or active methylene compounds.[1,3)] Thus, reactions of **2** with low-molecular amino acids (glycine, β-alanine, γ-aminobutylic acid and ε-aminocaproic acid) were attempted, and proceeded successfully to give the corresponding carboxyalkylaminoquinones (**3a—d**) in high yields. The reactivity of the residual chlorine atom of the chloroaminoquinones toward further nucleophiles, however, appeared to be very low, because the electrophilicity of the quinone may be decreased by the amino group introduced on the quinone nucleus. In fact, the aminoquinones (**3a—d**) did not react with active methylene compounds in the presence of potassium succinimidate (PSI).[1)]

On the other hand, the chlorine atom of chloroaminoquinones, which can be obtained from **2** or chloranil (**4**), can fortunately be activated by N-acetylation of the amino group.[4,5)] Thus, the aminoquinones (**3b** and **3c**) were converted to an acetamide (**5b**, mp 185—187° (decomp.)) in 87% yield and a lactam (**5c**, mp 156—157°) in 82% yield, respectively, by refluxing in acetic anhydride in the presence of *p*-toluenesulfonic acid (*p*-TsOH). The chlorine atom of **5c** was replaced with dimethyl malonate by reacting **5c** with dimethyl malonate in dimethyl sulfoxide (DMSO) in the presence of PSI to give a diester **6** (mp 153—158° (decomp.)) in 84% yield.[6)]

1) Part I: M. Okamoto, S. Ohta, and S. Terada, *Yakugaku Zasshi*, **99**, 1219 (1979).
2) Location: *Misasaginakauchi-cho, Yamashina-ku, Kyoto, 607 Japan.*
3) S. Patai, "The Chemistry of the Quinoid Compounds," Part 2, John Wiley and Sons, New York, 1974, p. 877.
4) F.M. Dean, K.B. Hindley, and L.E. Houghton, *J. Chem. Soc.*(*C*), **1971**, 1171.
5) J.A. Van Allan, G.A. Reynolds, and R.E. Adel, *J. Org. Chem.*, **28**, 528 (1963).
6) Color of the reaction mixture turned immediately to indigo blue and this color reaction has been known as Craven reaction (*J. Chem. Soc.*, **1931** 1605). The reaction is presumed to be due to anion which is produced from **6** and PSI. Therefore, reactivity of chloroquinones may be estimated by the reaction.

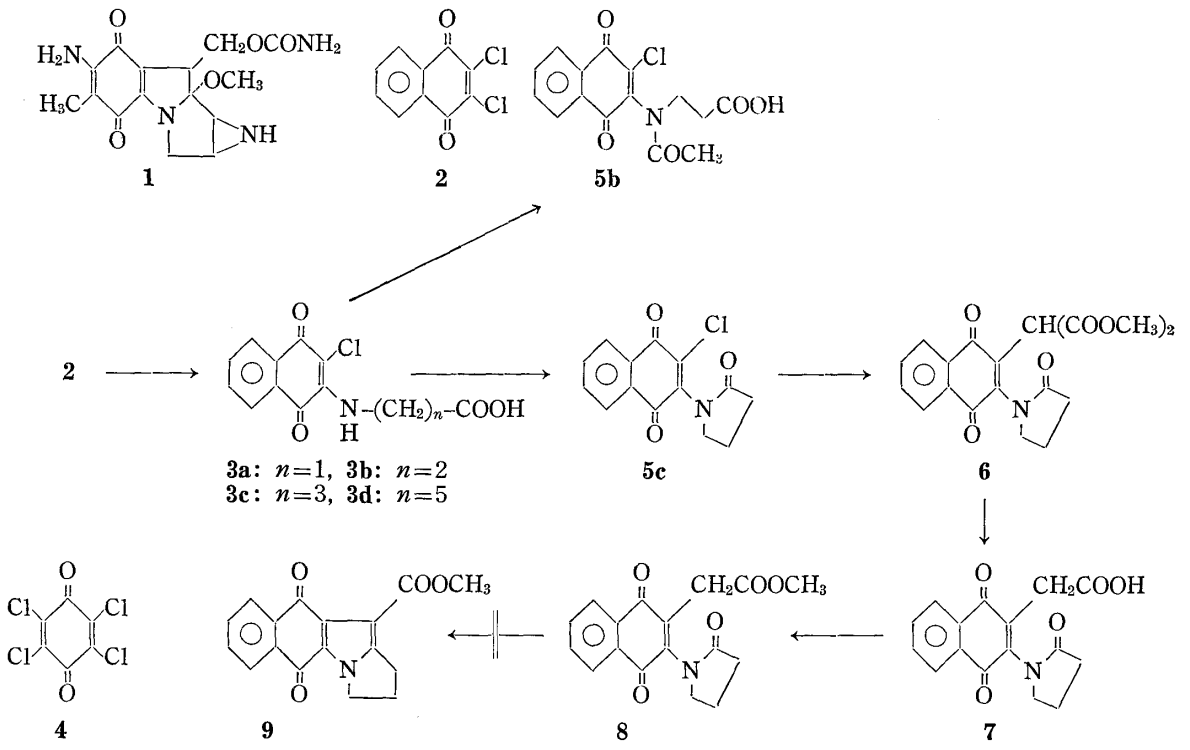


Chart 1

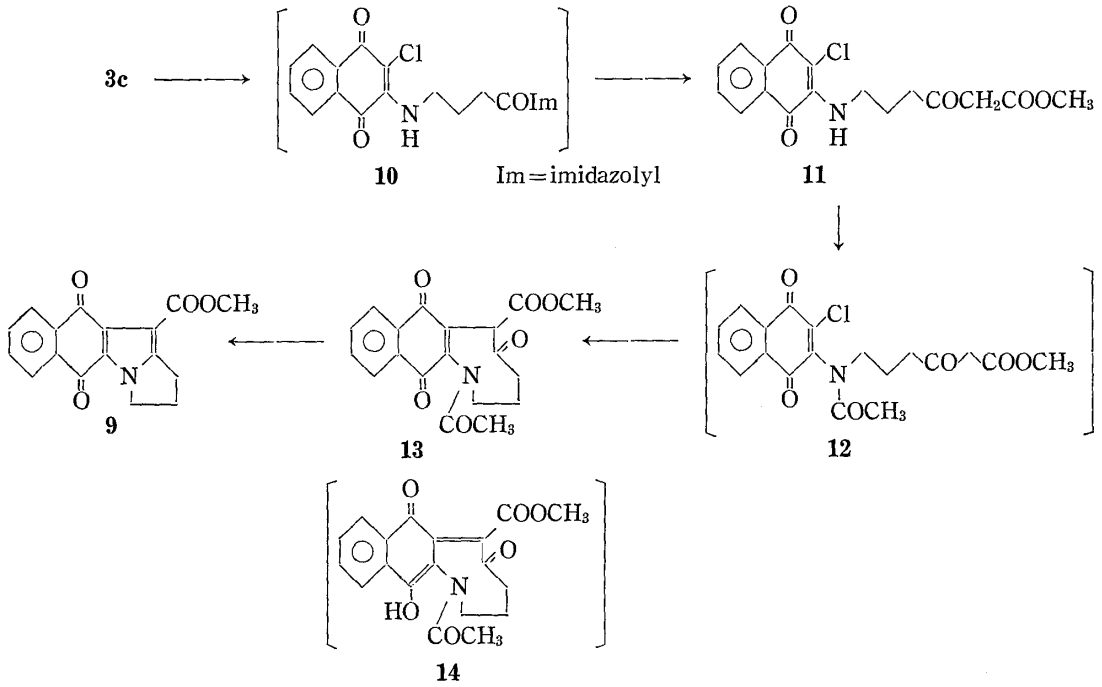
Compound **6** was hydrolyzed in hot aqueous 1N KOH, acidified with hydrochloric acid and then heated at 90—95° to yield a monocarboxylic acid **7**, mp 255—265° (decomp.), which on heating in methanol in the presence of a catalytic amount of *p*-TsOH was converted to the corresponding methyl ester (**8**, mp 150—152°) in 91% yield. The structure of **8** was confirmed by its PMR spectrum,[7] which showed an overlapping singlet signal of $-OC\underline{H}_3$ and $-C\underline{H}_2COOCH_3$ at 3.72 ppm. However, all attempts at intramolecular dehydrative condensation between the active methylene and the lactam carbonyl group to reach the target compound (**9**) were unsuccessful (Chart 1).

Masamune recently reported an elegant method for the preparation of β-ketoesters using a reaction of acid imidazolide with the neutral monomagnesium salt of malonic acid half ester.[8] The acid **3c** was converted into a β-ketoester (**11**, mp 92—94°) in 75% yield by Masamune's method. The protonmagnetic resonance (PMR) spectrum of **11** showed signals of $-OC\underline{H}_3$ at 3.73 (s) and $-COC\underline{H}_2CO-$ at 3.50 ppm (s), which supported the structure shown. N-Acetylation of **11** afforded the corresponding N-acetate (**12**) under the Thiele reaction conditions[9] using borontrifluoride etherate ($BF_3 \cdot Et_2O$) as a catalyst in acetic anhydride, but application of usual methods such as heating in acetic anhydride-pyridine or *p*-TsOH was unsuccessful. The N-acetate (**12**) was a viscous oily material, the PMR spectrum of which showed acetyl protons (3H) at 1.98 ppm (s), $OC\underline{H}_3$ at 3.72 ppm (s) and active methylene protons (2H) at 3.47 ppm (s). The acetamide (**12**) was colored in indigo blue with DMSO-PSI and azocinone derivative (**13**, mp 182° (decomp.), 83.7% yield from **12**) was obtained from the reaction mixture. Its PMR spectrum (in $CDCl_3$) showed acetyl protons (3H) at 1.74 ppm (s), $OC\underline{H}_3$ at 3.70 ppm (s) and one enolic proton, OH in the structure **14**, at 12.93 ppm (broad). Therefore, the enolic structure (**14**) appears to be preferred to the ketonic

7) Abbreviations for PMR signal patterns: s (singlet), d (doublet), t (triplet), m (multiplet). Chemical shifts are shown as δ-values using TMS as an internal standard.
8) D.W. Brooks, L.D. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **18**, 72 (1979).
9) J.F.W. McOmie and J.N. Blatchy, "Organic Reactions," Vol. 19, John Wiley and Sons, New York, 1972, p. 199.

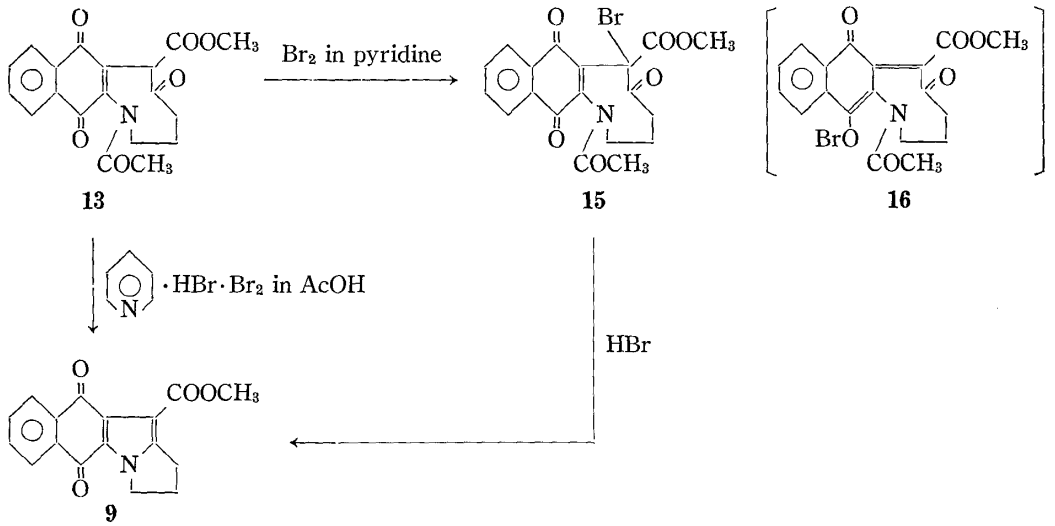
structure (**13**) in $CDCl_3$ solution, though the ketonic structure (**13**) is shown in Chart 2. Furthermore, elemental analytical and mass spectral data (M^+=355 *m/e*) were consistent with a formula $C_{19}H_{17}NO_6$ for the structure **13** or **14**. The azocinone (**13**) was easily converted to the pyrrolo [1,2-*a*]indole-5,8-dione derivative (**9**, mp 232—233°) with pyridinium bromide perbromide in acetic acid. The PMR spectrum (Fig. 1) and MS (M^+=295 *m/e* for $C_{17}H_{13}NO_4$) both supported the structure **9**. On the other hand, bromination of **13** in pyridine gave an unstable bromide (mp 105—107° (decomp.)) in 85% yield; this was easily converted to **9** by treatment with hydrogen bromide in acetic acid, and the PMR spectrum of the bromide showed an AA'BB' pattern of four aromatic protons similar to those of other naphthoquinone derivatives. Thus, the structure of the bromide can be presumed to be not **16** but **15** (Chart 3).

The authors are now applying this simple synthetic reaction to chlorobenzoquinones and the results will be reported later.



10 **11** **9** **13** **12** **14**

Chart 2



13 **15** **16** **9**

Chart 3

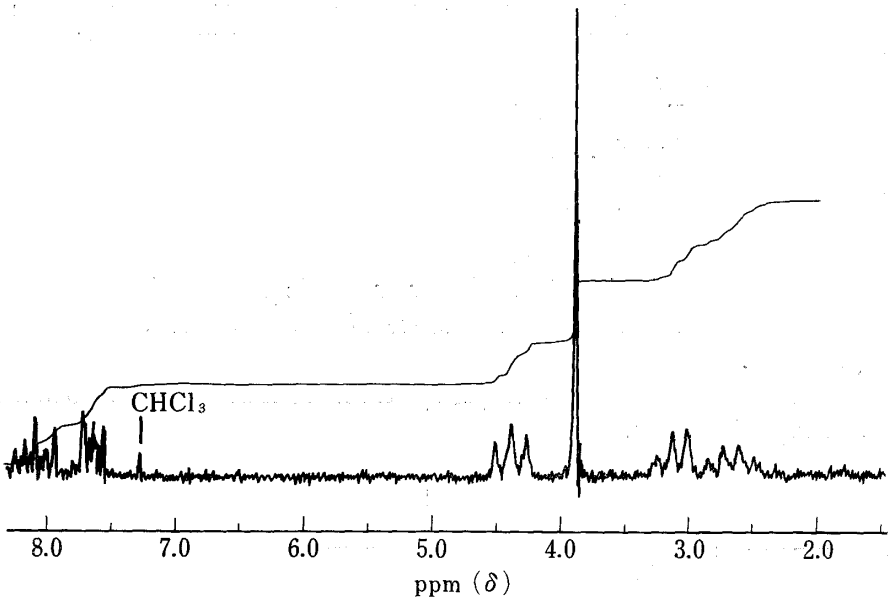


Fig. 1. PMR Spectrum of **9** in $CDCl_3$ (60 MHz)

Experimental

All melting points are uncorrected. The PMR of **15** was taken with a Varian CFT-20 spectrometer and other PMR spectra were taken with a Varian A-60A spectrometer. Infrared (IR) spectra were taken with a Shimadzu IR-420 spectrometer, the ultraviolet (UV) spectrum of **9** was taken with a Shimadzu UV-200S spectrometer and MS were taken with a Hitachi RMU-6E spectrometer.

Reaction of 2 with Amino Acids——A solution of 30 mmol of amino acid (glycine, β-alanine, γ-aminobutyric acid, ε-aminocaproic acid) in 25 ml of 1 N KOH aq. was added to a stirred suspension of **2** (10 mmol) in MeOH (50 ml). After stirring overnight, the reaction mixture was acidified with 10% HCl to precipitate red crystals, which were collected by filtration, washed with water, dried and recrystallized from MeOH.

3a: red needles, mp 170—171°; yield, 93.4%. IR ν_{max}^{KBr} cm^{-1}: 3280, 1715, 1665. *Anal.* Calcd for $C_{12}H_8ClNO_4$: C, 54.25; H, 3.04; N, 5.27. Found: C, 54.30; H, 2.94; 5.29.

3b: red needles, mp 160—161°; yield, quantitative. IR ν_{max}^{KBr} cm^{-1}: 3250, 1700, 1670. *Anal.* Calcd for $C_{13}H_{10}ClNO_4$: C, 55.83; H, 3.60; N, 5.01. Found: C, 55.99; H, 3.66; N, 4.97.

3c: red needles, mp 175°; yield, 97.8%. IR ν_{max}^{KBr} cm^{-1}: 3250, 1735, 1695. PMR (DMSO-d_6) δ ppm: 8.20—7.60 (m, 4H, arom. H), 7.45 (broad, 1H, NH), 4.00—3.60 (m, 2H, N-CH_2), 2.30 (t, 2H, -CH_2COOH, J=5.5 Hz), 2.25—1.80 (m, 2H, -$CH_2CH_2CH_2$-). *Anal.* Calcd for $C_{14}H_{12}ClNO_4$: C, 57.23; H, 4.12; N, 4.77. Found: C, 57.45; H, 4.15; N, 4.68.

The methyl ester of **3c** was prepared by refluxing **3c** in MeOH in the presence of *p*-TsOH, followed by usual work-up. Red prisms from MeOH-Et_2O, mp 90—91°. IR ν_{max}^{KBr} cm^{-1}: 3240, 1725, 1655. PMR ($CDCl_3$) δ ppm: 8.25—7.55 (m, 4H, arom.H), 6.20 (broad, 1H, NH), 3.93 (q, 2H, >NHCH_2-, J=6.5 Hz), 3.70 (s, 3H, -OCH_3), 2.48 (t, 2H, -CH_2COO-, J=6 Hz), 2.30—1.90 (m, 2H, -$CH_2CH_2CH_2$-). *Anal.* Calcd for $C_{15}H_{14}ClNO_4$: C, 58.53; H, 4.58; N, 4.55. Found: C, 58.50; H, 4.49; N, 4.39.

3d: red needles, mp 130—132°; yield, 97.0%. IR ν_{max}^{KBr} cm^{-1}: 3200, 1715, 1670. *Anal.* Calcd for $C_{16}H_{16}ClNO_4$: C, 59.72; H, 5.01; N, 4.35. Found: C, 59.73; H, 4.84; N, 4.45.

N-Acetyl-N-(2-chloro-1,4-naphthoquinonyl)-β-alanine (5b)——A mixture of **3b** (500 mg), Ac_2O (4.0 ml) and a small amount of *p*-TsOH was refluxed for 5 min. After cooling, water (10 ml) was added to the mixture and the precipitated yellow solid was collected by suction, washed with water and dried. Recrystallization from MeOH gave yellow prisms, mp 185—187° (dec.). Yield, 500 mg (87%). IR ν_{max}^{KBr} cm^{-1}: 1720, 1670, 1620. *Anal.* Calcd for $C_{15}H_{12}ClNO_5$: C, 56.00; H, 3.76; N, 4.35. Found: C, 56.00; H, 3.72; N, 4.27.

2-Chloro-3-(2-oxo-1-pyrrolidinyl)-1,4-naphthoquinone (5c)——A mixture of **3c** (8.70 g), Ac_2O (100 ml) and *p*-TsOH (1.00 g) was refluxed for 5 min to give a yellow-brown solution, the volatile portion of which was removed under reduced pressure. The residue was treated with MeOH to give a yellow needles, which were filtered and recrystallized from MeOH. mp 156—157°. Yield, 82%. IR ν_{max}^{KBr} cm^{-1}: 1705, 1670, 1660. PMR ($CDCl_3$) δ ppm: 8.27—7.95 (m, 2H, arom.H), 7.93—7.60 (m, 2H, arom.H), 3.82 (t, 2H, -NCH_2-, J= 6.5 Hz), 2.80—2.10 (m, 4H, -CH_2CH_2CO-). *Anal.* Calcd for $C_{14}H_{10}ClNO_3$: C, 60.98; H, 3.66; N, 5.08. Found: C, 61.30; H, 3.43; N, 4.98.

Dimethyl 2-(2-Oxo-1-pyrrolidinyl)-1,4-naphthoquinonyl Malonate (6)——Dimethyl malonate (1.45 g) and PSI (1.50 g) were added to a stirred suspension of **5c** (2.75 g) in DMSO (20 ml), after overnight stirring,

the resulting mixture was diluted with water and acidified with 10% HCl, then extracted with ethyl acetate. The extract was washed with water and dried over $MgSO_4$. Removal of the solvent gave a yellow crystalline mass, which was recrystallized from MeOH to give yellow prisms, mp 153—158° (dec.). Yield, 3.12 g (84%). IR ν_{max}^{KBr} cm^{-1}: 1740, 1710, 1647. PMR ($CDCl_3$) δ ppm: 8.23—7.97 (m, 2H, arom.H), 7.93—7.67 (m, 2H, arom.H), 4.82 (s, 1H, $-C\underline{H}(COOMe)_2$), 4.05 (m+s, 8H, $>NC\underline{H}_2+COOC\underline{H}_3\times2$), 2.60—2.10 (m, 4H, $>NCH_2-C\underline{H}_2C\underline{H}_2-$). *Anal.* alcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.60; H, 4.58; N, 3.75.

2-[2-(2-Oxo-1-pyrrolidinyl)-1,4-naphthoquinonyl]acetic Acid (7)——A suspension of **6** (2.50 g) in aqueous 1 N KOH was stirred for 2 hr at room temperature then the mixture was acidified to pH 1 with 10% HCl, and the acidic mixture was heated at 90—95° for 4 hr to precipitate a brown solid. After cooling, it was collected by suction, washed with water, dried and recrystallized from MeOH to give yellow prisms, mp 255—265° (dec.). Yield, 1.37 g (68%). IR ν_{max}^{KBr} cm^{-1}: 1725, 1655. PMR (DMSO-d_6) δ ppm: 8.20—7.80 (m, 4H, arom.H), 3.90—3.50 (t+s, 4H, $>NC\underline{H}_2-+-C\underline{H}_2COOH$), 2.70—2.00 (m, 4H, $-CH_2C\underline{H}_2C\underline{H}_2CO-$). *Anal.* Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.32; H, 4.22; N, 4.61.

The methyl ester (**8**) was obtained as follows; a solution of **7** (1.00 g) in 50 ml of MeOH containing a small amount of *p*-TsOH was refluxed for 3 hr while the distilled MeOH was passed through Zeolite in a Soxhlet extracting apparatus. After removal of the solvent, AcOEt and water were added to the residue. The organic layer was washed with 5% $NaHCO_3$ and water, then dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was dissolved in MeOH for crystallization. Recrystallization from MeOH gave brown prisms, mp 150—152°. Yield, 955 mg (91%). IR ν_{max}^{KBr} cm^{-1}: 1730, 1690, 1655. PMR ($CDCl_3$) δ ppm: 8.25—7.95 (m, 2H, arom.H), 7.90—7.65 (m, 2H, arom.H), 4.00—3.60 (m, 2H, $>N\,C\underline{H}_2-$), 3.72 (s, 5H, $-OC\underline{H}_3+-C\underline{H}_2COOMe$), 2.80—2.10 (m, 2H, $-CH_2C\underline{H}_2CH_2CO-$). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.16; H, 4.74; N, 4.32.

Methyl N-(2-Chloro-1,4-naphthoquinonyl)-β-oxo-ε-aminocaproate (11)——A suspension of **3c** (2.94 g) in 40 ml of DMF was treated with carbonyl diimidazole (1.70 g). After stirring for 30 min, the monomagnesium salt of malonic acid monomethyl ester[8] (1.50 g) was added to the reaction mixture and the mixture was stirred at 50° for 1.5 hr, diluted with 10% HCl (10 ml) and water (100 ml) and then extracted with AcOEt. The organic layer was washed with 5%$NaHCO_3$, water, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave orange leaflets, mp 92—94°. Yield, 2.63 g (75%). IR ν_{max}^{KBr} cm^{-1}: 3280, 1735, 1710, 1660. PMR ($CDCl_3$) δ ppm: 8.23—7.55 (m, 4H, arom.H), 6.20 (broad, 1H, N$\underline{H}$), 4.10—3.70 (m, 2H, $-NHC\underline{H}_2-$), 3.73 (s, 3H, $-OC\underline{H}_3$), 3.50 (s, 2H, $-COC\underline{H}_2CO-$), 2.37 (t, 2H, $-CH_2C\underline{H}_2CO-$, J=6 Hz), 2.02 (q, 2H, $-CH_2C\underline{H}_2CH_2-$, J=6 Hz). *Anal.* Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; N, 4.00. Found: C, 58.47; H, 4.37; N, 3.89.

Methyl 1-Acetyl-1,2,3,4-tetrahydro-6*H*-naphtho[2,3-*b*]azocine-5,7,12-trione-6-carboxylate (13)——The β-ketoester **11** (700 mg) was suspended in 5 ml of Ac_2O and 1 ml of $BF_3\cdot Et_2O$ was added with stirring. After 20 min, the mixture was warmed for a few min and the resulting solution was poured into 50 ml of ice-water. This mixture was stirred for 2 hr. The separated oily material was extracted with Et_2O. The ethereal solution was washed with water, 5% $NaHCO_3$ and brine. After drying the solution over $MgSO_4$, removal of the solvent gave a yellow oily material (**12**). Yield, 590 mg (75.4%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1720, 1680. PMR ($CDCl_3$) δ ppm: 8.33—8.00 (m, 2H, arom.H), 8.00—7.75 (m, 2H, arom.H), 3.95—3.55 (m, 2H, $-NC\underline{H}_2-$), 3.72 (s, 3H, $-OC\underline{H}_3$), 3.47 (s, 2H, $-C\underline{H}_2COOMe$), 2.68 (t, 2H, $-CH_2C\underline{H}_2CO-$, J=6.5 Hz), 2.15—1.65 (m, 2H, $-CH_2C\underline{H}_2CH_2-$), 1.98 (s, 3H, $-COC\underline{H}_3$).

A stirred solution of **12** (590 mg) in 5 ml of DMSO was treated with PSI (230 mg) to give an indigo blue solution immediately. After 3.5 hr, water and 10% HCl were added to the mixture under ice-cooling, then the separated oily material was extracted twice with AcOEt. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent gave a brown oily material, which crystallized on standing at room temperature. Yield, 445 mg (83.7%). Recrystallization from C_6H_6–Et_2O gave yellow prisms (**13**), mp 182° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1680, 1615. MS *m/e*: 355 (M^+), 105 (base peak). PMR ($CDCl_3$) δ ppm: 12.93 (s, 1H, enolic O$\underline{H}$), 8.30—8.03 (m, 2H, arom.H), 8.00—7.33 (m, 2H, arom.H), 4.77 (m, 1H, NC$\underline{H}$), 3.70 (s, 3H, $-OC\underline{H}_3$), 2.85—1.70 (m, 5H, NC$\underline{H}$ $-C\underline{H}_2C\underline{H}_2CO-$), 1.74 (s, 3H, $-COC\underline{H}_3$). *Anal.* Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.40; H, 4.65; N, 4.07.

Methyl 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-5,10-dione-11-carboxylate (9)——i) A stirred solution of **13** (178 mg) in 3.5 ml of AcOH was treated with pyridinium bromide perbromide (165 mg), and stirring was continued overnight to precipitate yellow needles. Water and $CHCl_3$ were added to the mixture. The $CHCl_3$ layer was washed water and $NaHCO_3$, then dried over $MgSO_4$. Removal of the solvent gave a crystalline mass, which was recrystallized from AcOEt to give yellow needles, mp 232—233°. Yield, 145 mg (quant.). IR ν_{max}^{KBr} cm^{-1}: 1720, 1650, 1095, 710. UV $\lambda_{max}^{JP\text{-}EtOH}$ mμ (log ε): 203 (4.15), 257 (4.36), 283 (3.93), 322 (3.64), 334 (3.61), 338 (3.55), 348 (3.40). PMR ($CDCl_3$) δ ppm: 8.28—7.90 (m, 2H, arom.H), 7.80—7.55 (m, 2H, arom.H), 4.38 (t, 2H, $>NC\underline{H}_2-$, J=7 Hz), 3.87 (s, 3H, $-OC\underline{H}_3$), 3.12 (t, 2H, $=CC\underline{H}_2-$, J=7 Hz), 2.93—2.40 (m, 2H, $-CH_2C\underline{H}_2CH_2-$), MS *m/e*: 295 ($M^+$), 263 (base peak). *Anal.* Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.87; H, 4.45; N, 4.63.

ii) A stirred solution of the bromide (**15**, 218 mg), described below, in AcOH (3.5 ml) was treated with 5 drops of 48% hydrobromic acid, and stirring continued overnight. After work-up as described in i), the desired product (**9**) was obtained quantitatively.

Methyl 1-Acetyl-6-bromo-1,2,3,4-tetrahydro-6*H*-naphtho[2,3-*b*]azocine-5,7,12-trione-6-carboxylate (15) ——A stirred solution of **13** (178 mg) in 3.5 ml of pyridine was treated with pyridinium bromide perbromide (165 mg), and after 5 min, water and $CHCl_3$ were added to the reaction mixture. The $CHCl_3$ layer was washed several times with water, then dried over $MgSO_4$. Removal of the solvent gave a crystalline mass, which was recrystallized from MeOH to give yellow needles, mp 105—107° (dec.). Yield, 185 mg (85%). IR ν_{max}^{KBr} cm^{-1}: 1730, 1680. PMR ($CDCl_3$) δ ppm: 8.25—8.00 (m, 2H, arom.H), 8.00—7.70 (m, 2H, arom.H), 4.90—4.40 (m, 1H, NC<u>H</u>), 3.10—2.00 (m, 4H, –C<u>H</u>$_2$C<u>H</u>$_2$CO–), 1.80 (s, 3H, –COC<u>H</u>$_3$). *Anal.* Calcd for $C_{19}H_{16}BrNO_6$: C, 52.55; H, 3.71; N, 3.23. Found: C, 52.15; H, 4.19; N, 2.75.

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