Chem. Pharm. Bull. 29(9)2557—2564(1981)

Heterocycles. XI.[1] Syntheses of Analogs of 10b-Hydroxychelidonine and 4b-Epichelidonine

Yoshihiro Harigaya, Koko Yotsumoto, Seiko Takamatsu, Hiroko Yamaguchi, and Masayuki Onda*

School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo 108, Japan

(Received March 13, 1981)

The naphthoquinone epoxide (**4**), derived from the naphthoquinone (**1**), is reduced with sodium borohydride under mild conditions to yield the *cis*-epoxy ketol (**5**) exclusively. The configuration of the 4-hydroxyl group in **5** is deduced on the basis of the intramolecular hydrogen-bonding observed in the infrared spectrum. Further reduction of **5** with sodium borohydride gives the *cis*-epoxyhydroxy lactone (**7**) as a main product, which is stereoselectively converted into the 10b-hydroxychelidonine (**17**) and 4b-epichelidonine analogs (**19**) by the following procedures: aminolysis with methylamine (**7**→**13**), reduction with lithium aluminum hydride (**13**→**14**), hydrogenolysis over a palladium catalyst (**14**→**17**), dehydration with mesyl chloride (**17**→**18**) and reduction with lithium aluminum hydride/aluminum chloride (**18**→**19**). The stereostructures for these compounds are deduced from the infrared and proton magnetic resonance data.

Keywords——Benzo[*c*]phenanthridine; naphtho[1,2-*c*]isocoumarin; naphthoquinone epoxide; stereoselective synthesis; infrared (Bohlmann band and intramolecular hydrogen-bonding); proton magnetic resonance (decoupling and nuclear Overhauser effect)

In the course of our investigations on the benzo[*c*]phenanthridine alkaloids we have attempted to utilize 2-2′-methoxycarbonylphenyl-1,4-naphthoquinone (**1**) as a starting material for syntheses of ring C-hydroxylated benzo[*c*]phenanthridines. As an example, though the desired product was not obtained, the reaction of 12-hydroxynaphtho[1,2-*c*]isocoumarin (**2**), derived from **1**, with methylamine resulted in the formation of 3-2′-methyl-3′-isoindolinonylmethyl-3-methylaminophthalide (**3**).[2] In this paper we report the stereoselective syntheses of analogs of chelidonine from **1**.

Epoxidation of **1** with *tert*-butyl hydroperoxide in the presence of 1,5-diazabicyclo[5.4.0]-undecene (DBU) afforded the naphthoquinone epoxide (**4**) (94%). Reduction of **4** with sodium borohydride at −50°C for 1 h gave the *cis*-epoxy ketol (**5**) (75%) and *trans*-epoxy ketol (**6**) (19%). The site-selective reduction of the 4-oxo group in **4** is confirmed on the basis of one-proton doublets observed for the 3-protons in **5** and **6** in the proton magnetic resonance (^{1}H NMR) spectra. The configurations of the 4-hydroxyl groups in **5** and **6** are established to be *cis* and *trans* with respect to the oxirane rings, respectively, on the basis of the presence of intramolecular hydrogen-bondings (**5**: 3520 cm^{-1}, OH···O; **6**: 3587 cm^{-1}, OH···π) in the infrared (IR) spectra. These spectral properties are in accord with those of the corresponding chiral compounds.[1] As can be seen, the 4-oxo group in **4** is reduced by the preferential attack of sodium borohydride from the opposite side with respect to the oxirane ring to give **5**.[3] Lithium tri-*tert*-butoxyaluminohydride and potassium triisopropoxyborohydride, which are expected to lead to greater stereoselectivity in the reduction of **4**, also gave **5** and **6** in ratios similar to that obtained with sodium borohydride (see "Experimental").

Further reduction of **5** with sodium borohydride yielded the *cis*-epoxyhydroxy lactone (**7**) (47%), *trans*-epoxyhydroxy lactone (**8**) (2%) and *cis*-epoxy diol (**9**) (38%). The IR spectra of **7** and **8** showed carbonyl bands of the δ-lactone groups at 1729 and 1728 cm^{-1}, respectively. The *cis* steroidal conformation of the B/C ring fusion in **7** is deduced from the ^{1}H NMR data: a W-path coupling (1 Hz) observed between the 4b- and 11-protons; a nuclear Overhauser effect (NOE) (42.5%) observed between the 4- and 4b-protons; an up-field shift of the 10-

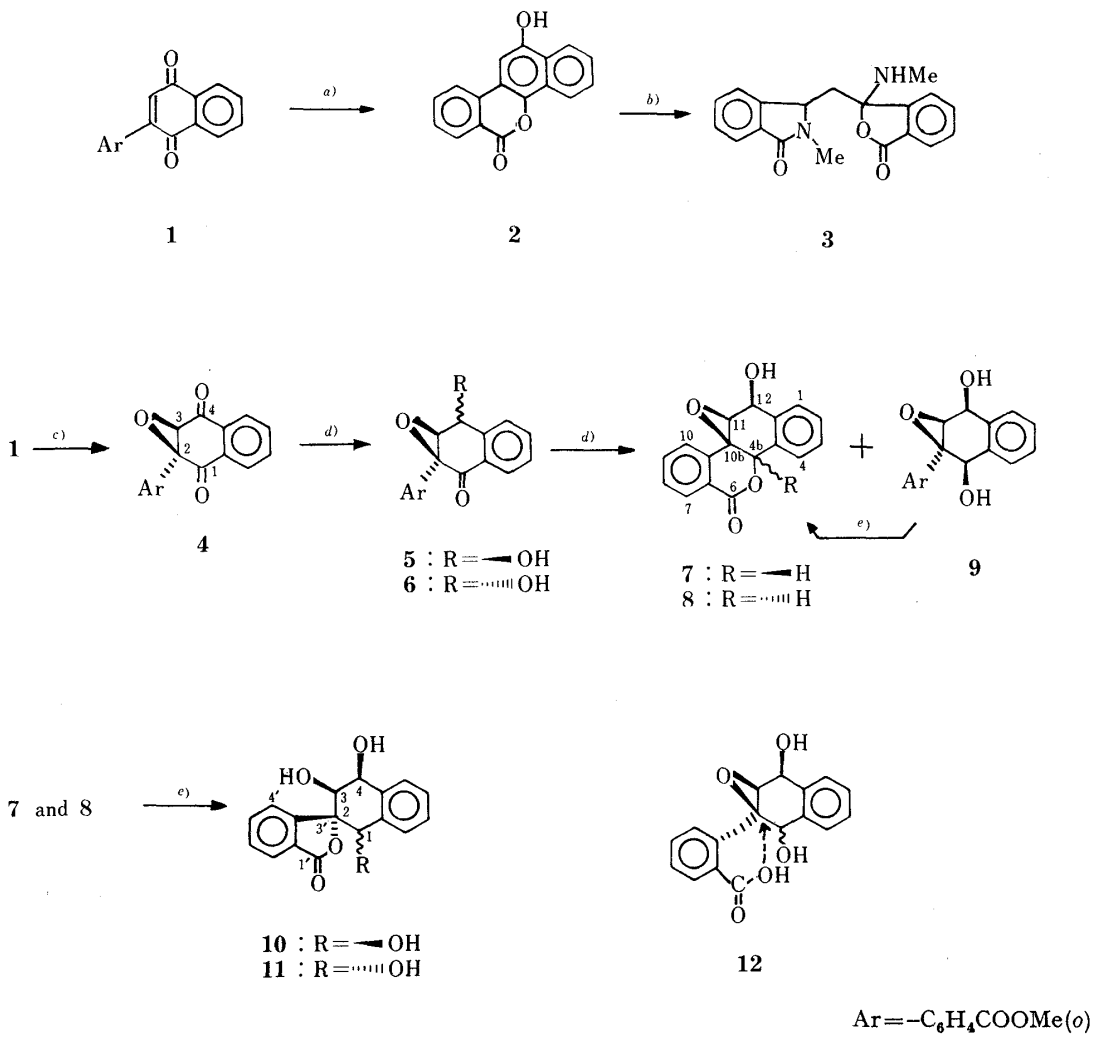


Chart 1

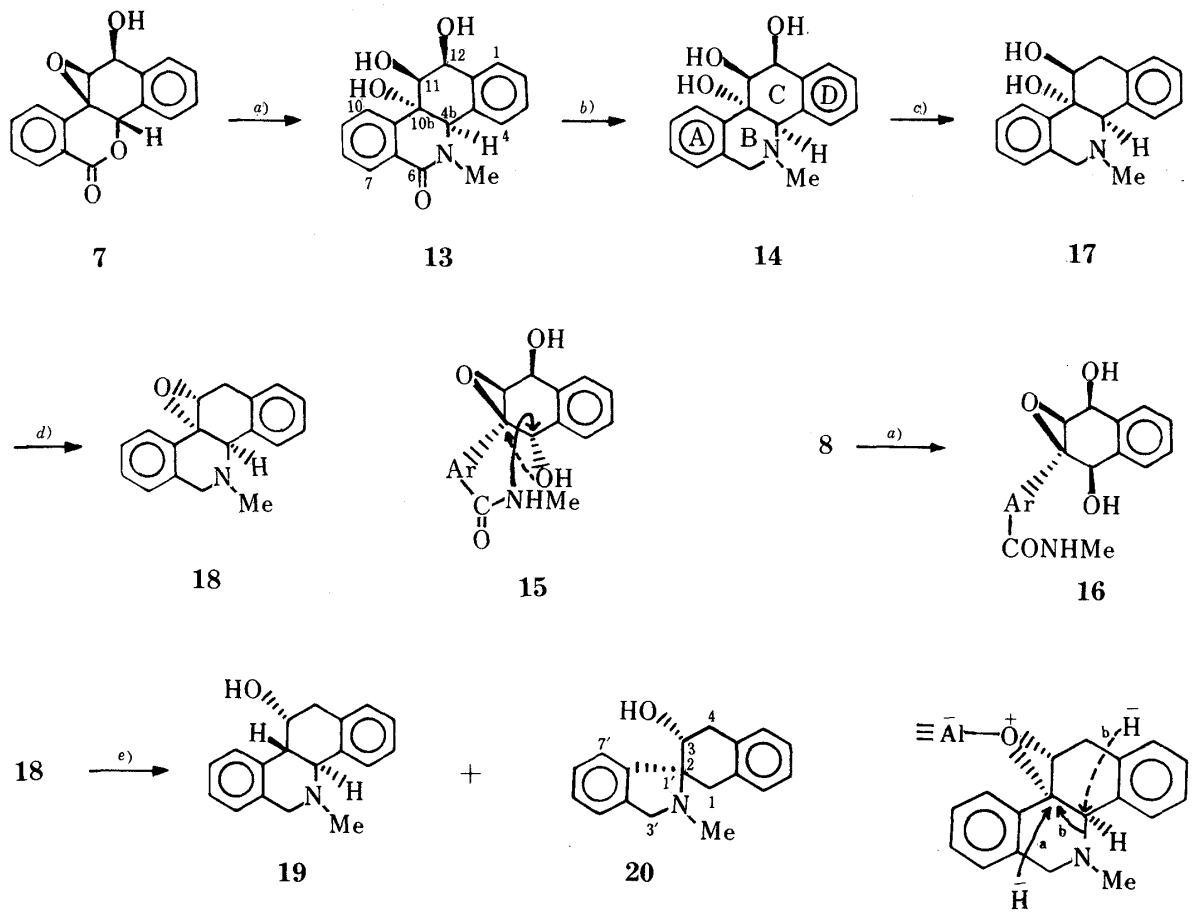
a) H_2/PtO_2; *b*) $MeNH_2$; *c*) *tert*-BuOOH/DBU; *d*) $NaBH_4$; *e*) Al_2O_3.

proton (δ 7.40) (**8**: δ 7.63) caused by the oxirane ring. The *cis*-epoxyhydroxy lactone (**7**) should be derived from the compound having the 1-hydroxyl group *trans* with respect to the oxirane ring, which is initially formed on reduction of **5**. The *trans* B/C ring fusion in **8** is also confirmed by the ^1H NMR data: a down-field shift of the 4-proton (δ 7.91) (**7**: δ 7.45) caused by an interaction with the 4b-O(5) bond; down-field shifts of the 10- (δ 7.63) (**7**: δ 7.40) and 11-protons (δ 4.47) (**7**: δ 3.67) caused by their mutual interactions. Alumina-induced lactonization of **9** afforded **8** (75%), establishing the 1-hydroxyl group in **9** to be *cis* with respect to the oxirane ring. The spectral properties of **7**, **8** and **9** are also in accord with those of the corresponding chiral compounds.[1] Reduction of **5** with sodium borohydride in the presence of cerous chloride gave **7** (57%) and **9** (34%).[4] On the other hand, lithium tri-*tert*-butoxyaluminohydride and potassium triisopropoxyborohydride did not reduce **5**. Reduction of **6** with sodium borohydride gave complex products which could not be identified.

Further treatment of **8** with alumina gave the phthalide (**10**) (92%). The *cis*-epoxyhydroxy lactone (**7**) was also rearranged by alumina treatment into the phthalide (**11**) (75%). Their IR spectra showed carbonyl bands (**10**: 1763 cm^{-1}; **11**: 1765 cm^{-1}) of the γ-lactone groups. Considering simply that the formations of **10** and **11** arise *via* the carboxylic acid (**12**), which results from hydrolysis of the lactone group, followed by intramolecular acylolysis of the oxirane ring at the 2-position in a *trans* ring opening mode, the structures for **10** and **11** can be

tentatively assigned as shown in Chart 1. The highly substituted cyclohexene rings in **10** and **11** are thought to exist in conformers that deviate from the half-chair form. Couplings (**10**: 8 Hz; **11**: 7 Hz) observed between the 3- and 4-protons *cis* to each other in the ^{1}H NMR spectra reflect the above steric situation. Owing to the "axial" 2-3a′ bonds, the 4′-protons may be located nearly over the benzene moieties and thus be shielded (**10**: δ 6.60; **11**: δ 6.78).

Treatment of **7** with aqueous methylamine gave the trihydroxy lactam (**13**) (95%), which was reduced with lithium aluminum hydride to yield the trihydroxy amine (**14**) (87%). The IR spectrum of **14** showed Bohlmann bands at 2775 and 2700 cm^{-1}, suggesting the B/C ring fusion to be *trans* or *cis* steroidal.[5] The ^{1}H NMR spectrum of **14** exhibited a W-path coupling (2 Hz) between the 4b- and 11-protons, and a coupling (3 Hz) between the 11- and 12-protons. Thus, the *cis* steroidal conformation having the $10b_{ax}$-, 11_{ax}- and 12_{eq}-hydroxyl groups in the C ring can be assigned to the B/C ring fusion in **14**. NOE's [10b-OH→4b- (7.0%) and 10-H's (9.3%); 11-H→10-H (13.6%) and 10b-OH (7.4%)] observed are compatible with this structure. The structure of **13** should be similar to that of **14**. However, its ^{1}H NMR data are quite different from those for **14**. The 4b-proton signal appeared as a singlet, and a coupling (8 Hz) was observed between the 11- and 12-protons. The trihydroxy amine (**14**) is expected to be stabilized by intramolecular hydrogen-bonding between the 11-hydroxyl group and the nitrogen atom.[6] Because of the nitrogen atom belonging to the lactam group, such a hydrogen-bonding would not be expected for **13**, so a 1,3-diaxial interaction between them contributes instead to the destabilization of the structure similar to **14**. A plausible



7 13 14 17

18 15 16

19 20 21

Chart 2

a) $MeNH_2$; *b*) $LiAlH_4$; *c*) H_2/Pd–C; *d*) $MeSO_2Cl$/pyridine; *e*) $LiAlH_4/AlCl_3$.

structure for **13** would have the *cis* nonsteroidal B/C ring fusion with a flattened boat form of the C ring, and is supported by the observation of an NOE (7.1%) of the 4b-proton on saturation of the 11-proton in the ^{1}H NMR spectrum of **13**. Treatment of **7** with anhydrous ethanolic methylamine afforded **13** (75%) as a sole product. This result demonstrates that water does not take part in the opening of the oxirane ring. Aminolysis of **7** gives the dihydroxyepoxy amide (**15**) which recyclizes to form the lactam group by an S_N reaction, accompanied by the back side attack of the 1-hydroxyl group anchimerically at the 2-position. This explains the exclusively stereoselective formation of **13** from **7**, and is in accord with the finding that aminolysis of **8** with aqueous methylamine resulted in the formation of the dihydroxyepoxy amide (**16**) (75%).

The *cis*-epoxy diol (**9**) also did not react with methylamine to give a lactam corresponding to **13**. Since **6** and **9** were oxidized with the Jones reagent to yield **4** in high yields, both compounds can be effectively introduced in the synthetic paths to analogs of chelidonine (*vide infra*).

Hydrogenolysis of **14** over palladium-carbon afforded the dihydroxy amine (**17**) (72%). Its ^{1}H NMR spectrum showed a W-path coupling (2 Hz) between the 4b- and 11-protons, and two double doublets at δ 3.26 (J=17 and 4 Hz) and 2.92 (J=17 and 2 Hz) assignable to the 12-protons by comparison with the data for **14**. As expected from the structure having the *cis* steroidal B/C ring fusion, the IR spectrum of **17** exhibited Bohlmann bands (2780 and 2700 cm^{-1}) and an intramolecular hydrogen-bonding (3225 cm^{-1}) between the 11-hydroxyl group and the nitrogen atom.[6]

Treatment of **17** with mesyl chloride gave the epoxy amine (**18**) (70%). Bohlmann bands (2780 and 2700 cm^{-1}) and a W-path coupling (1 Hz) between the 4b- and 11-protons observed in the IR and ^{1}H NMR spectra, respectively, are compatible with the *cis* steroidal B/C ring fusion. Thus, it is clear that the oxirane ring is formed by the elimination of the 11-hydroxyl group accompanied by the back side attack of the 10b-hydroxyl group.

The epoxy amine (**18**) was not reduced by treatment with lithium aluminum hydride alone. However, on repeated addition of lithium aluminum hydride and aluminum chloride, **18** was reduced to give the *trans*-hydroxy amine (**19**) (44%) and isoindoline (**20**) (9%). Bohlmann bands (2780 and 2750 cm^{-1}) and a coupling (12 Hz) between the 4b- and 10b-protons observed in the IR and ^{1}H NMR spectra of **19**, respectively, indicate the B/C ring fusion in **19** to be *trans*. Furthermore, couplings (4 and 2 Hz) observed between the 11- and 12-protons indicate the 11-hydroxyl group to be oriented axially. Thus, a structure like that of 4b-epichelidonine, which is formed by the back side attack of the hydride ion at the 10b-position (a-path) as shown in the complex (**21**), is assigned to **19**. The formation of **20** is thought to arise *via* a concerted rearrangement followed by reduction at the 4b-position (b-path) in **21**,[7] and the structure for **20** is tentatively deduced as shown in Chart 2. The ^{1}H NMR spectrum of **20** showed couplings (11 and 6 Hz) between the 3- and 4-protons. If the cyclohexene ring exists in the half-chair form, the 3-hydroxyl group would be oriented equatorially, and accordingly, the 2-7a′ bond would be oriented axially. This steric situation explains the up-field shift of the 7′-proton (δ 6.75) (*vide supra*).

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Preparative thin-layer chromatographies (prep. TLC) were performed on silica gel plates. Spectral data were recorded on the following spectrometers: IR—JASCO IR-G (chloroform) and JASCO DS-701G (intramolecular hydrogen-bondings); ^{1}H NMR—JEOL JNM-100 (100 MHz) in deuteriochloroform unless otherwise noted; mass (MS)—JEOL JMS-OIS.

2,3-Dihydro-2,3-epoxy-2-2′-methoxycarbonylphenyl-1,4-naphthoquinone (4)——*tert*-Butyl hydroperoxide (75%) (0.5 ml) and DBU (0.2 ml) were added to a solution of **1**[2] (500 mg) in benzene (30 ml), and the mixture was stirred at room temperature for 20 h. The benzene phase was separated and washed with water, 10% HCl and saturated aq. NaCl, then dried over Na_2SO_4. Work-up gave light yellow crystals (520 mg) which

were recrystallized from ethanol to afford **4** (495 mg, 94%) as colorless prisms of mp 163.5—165°C. IR ν_{max} cm^{-1}: 1705, 1700 (OC=O and C=O). ^{1}H NMR δ: 8.19—8.00 (3H, m, aromatic H's), 7.85—7.43 (5H, m, aromatic H's), 3.88 (1H, s, 3-H), 3.70 (3H, s, 2′-COOMe). *Anal.* Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92. Found: C, 70.28; H, 3.96.

2,3-Epoxy-*cis*-4-hydroxy-*trans*-2-2′-methoxycarbonylphenyl-α-tetralone (5) and 2,3-Epoxy-*trans*-4-hydroxy-*trans*-2-2′-methoxycarbonylphenyl-α-tetralone (6)——a) $NaBH_4$ (30 mg) was added to a solution of **4** (100 mg) in methanol (50 ml). The mixture was stirred at −50°C for 1 h, and then acetic acid (1 ml) was added. After concentration *in vacuo*, the residue was extracted with ethyl acetate. Work-up gave an oil (108 mg), and prep. TLC (benzene/ethyl acetate=10/1, v/v) afforded **5** (75 mg, 75%), *Rf* 0.49, and **6** (19.0 mg, 19%), *Rf* 0.32.

The *cis*-Epoxy Ketol (**5**): Colorless prisms of mp 140°C (from ether/hexane). IR ν_{max} cm^{-1}: 3520 (OH), 1702 (OC=O and C=O); hydrogen-bonding, 3520 (ε=125.6) ($c=6.5\times10^{-4}$ mol/l, tetrachloromethane). ^{1}H NMR δ: 8.15 (1H, dd, J=8 and 1 Hz, 8-H),[8] 8.04 (1H, dd, J=8 and 1 Hz, 3′-H),[8] 7.77—7.40 (6H, m, aromatic H's), 5.21 (1H, dd, J=12 and 2 Hz, 4-H),[9] 3.85 (1H, d, J=2 Hz, 3-H), 3.80 (3H, s, 2′-COOMe), 3.68 (1H, d, J=12 Hz, 4-OH).[10] *Anal.* Calcd for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.39; H, 4.49. MS *m/e*: $(M-CH_3OH)^+$, 278.063 ($M-CH_3OH$, 278.058 for $C_{18}H_{14}O_5$).

The *trans*-Epoxy Ketol (**6**): A colorless oil. IR ν_{max} cm^{-1}: 3590, 3370 (OH), 1715 (OC=O), 1695 (C=O); hydrogen-bonding, 3587 (ε=128.0) ($c=1.3\times10^{-3}$ mol/l, tetrachloromethane). ^{1}H NMR δ: 8.11 (1H, dd, J=8 and 1 Hz, 8-H),[8] 7.98 (1H, dd, J=8 and 1 Hz, 3′-H),[8] 7.83—7.34 (6H, m, aromatic H's), 5.37 (1H, br s, W_H=12 Hz, 4-H),[9] 3.87 (1H, d, J=3 Hz, 3-H), 3.73 (3H, s, 2′-COOMe), 2.69 (1H, br s, W_H=20 Hz, 4-OH).[10] MS Calcd for $C_{18}H_{14}O_5$: $M-CH_3OH$, 278.058. Found *m/e*: $(M-CH_3OH)^+$, 278.058.

b) Lithium tri-*tert*-butoxyaluminohydride (52 mg) was added to a solution of **4** (42.0 mg) in anhyd. tetrahydrofuran (16 ml). The mixture was stirred at −30°C for 16 h, and then acetic acid (5 drops) was added. Work-up of the reaction mixture gave **5** (34.3 mg, 81%) and **6** (6.8 mg, 16%).

c) 1 M Potassium triisopropoxyborohydride/anhyd. tetrahydrofuran (0.34 ml) was added to a solution of **4** (42.0 mg) in anhyd. tetrahydrofuran (16 ml). The mixture was stirred at −50°C for 4 h, and then acetic acid (5 drops) was added. Work-up of the reaction mixture gave **5** (31.0 mg, 73%) and **6** (10.3 mg, 24%).

10b,11-Epoxy-*cis*-12-hydroxy-*cis*-4b,10b,11,12-tetrahydronaphtho[1,2-*c*]isocoumarin (7), 10b,11-Epoxy-*cis*-12-hydroxy-*trans*-4b,10b,11,12-tetrahydronaphtho[1,2-*c*]isocoumarin (8) and 1,*cis*-4-Dihydroxy-*cis*-2,3-epoxy-*trans*-2-2′-methoxycarbonylphenyl-1,2,3,4-tetrahydronaphthalene (9)——a) $NaBH_4$ (80 mg) was added to a solution of **5** (130 mg) in methanol (80 ml). The mixture was stirred at −50°C for 56 h, and then acetic acid (1 ml) was added. Work-up of the reaction mixture gave an oil (143 mg) which was purified by prep. TLC (benzene/ethyl acetate=5/1, v/v) to yield **7** (55.0 mg, 47%), *Rf* 0.40, **8** (2.8 mg, 2%), *Rf* 0.33, and **9** (49.6 mg, 38%), *Rf* 0.54.

The *cis*-Epoxyhydroxy Lactone (**7**): Colorless prisms of mp 196—199°C (from ethanol). IR ν_{max} cm^{-1}: 3580, 3340 (OH), 1729 (OC=O). ^{1}H NMR δ: 8.12 (1H, dd, J=8 and 2 Hz, 7-H), 7.69 (1H, dt, J=2 and 8 Hz, 9-H),[8] 7.50 (1H, dt, J=2 and 8 Hz, 8-H),[8] 7.45 (4H, s, aromatic H's), 7.40 (1H, dd, J=8 and 2 Hz, 10-H), 5.82 (1H, d, J=1 Hz, 4b-H), 5.16 (1H, dd, J=8 and 2 Hz, 12-H),[9] 3.67 (1H, dd, J=2 and 1 Hz, 11-H), 2.38 (1H, d, J=8 Hz, 12-OH).[10] NOE: δ 7.45 (1- and 4-H's)→δ 5.82 (42.5%, 4b-H), 5.16 (18.6%, 12-H); δ 7.40 (10-H)→δ 3.67 (8.0%, 11-H). *Anal.* Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.94; H, 4.33. MS *m/e*: M^+, 280.073 (M, 280.074 for $C_{17}H_{12}O_4$).

The *trans*-Epoxyhydroxy Lactone (**8**): Colorless needles of mp 183—185°C (from ethanol). IR ν_{max} cm^{-1}: 3610, 3400 (OH), 1728 (OC=O). ^{1}H NMR δ: 8.28 (1H, dd, J=8 and 2 Hz, 7-H), 7.91 (1H, dd, J=8 and 2 Hz, 4-H), 7.72 (1H, dt, J=2 and 8 Hz, 8- or 9-H), 7.63 (1H, dd, J=8 and 2 Hz, 10-H), 7.53—7.34 (4H, m, aromatic H's), 6.10 (1H, s, 4b-H), 5.35 (1H, d, J=3 Hz, 12-H), 4.47 (1H, d, J=3 Hz, 11-H), 2.20 (1H, br s, W_H=28 Hz, 12-OH).[10] *Anal.* Calcd for $C_{17}H_{12}O_4\cdot1/10H_2O$: C, 72.39; H, 4.36. Found: C, 72.43; H, 4.36. MS *m/e*: M^+, 280.073 (M, 280.074 for $C_{17}H_{12}O_4$).

The *cis*-Epoxy Diol (**9**): Colorless prisms of mp 178—179°C (from ethanol). IR ν_{max} cm^{-1}: 3580, 3520 (OH), 1709 (OC=O). ^{1}H NMR δ: 8.10 (1H, dd, J=8 and 2 Hz, 3′-H), 7.74—7.28 (7H, m, aromatic H's), 5.20 (1H, d, J=11 Hz, 1-H),[11] 5.02 (1H, dd, J=11 and 3 Hz, 4-H),[9] 3.84 (3H, s, 2′-COOMe), 3.58 (1H, d, J=3 Hz, 3-H), 3.55, 2.45 (1H each, d, J=11 Hz, 1- and 4-OH's).[10] *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.24; H, 5.07. MS *m/e*: $(M-CH_3OH)^+$, 280.075 ($M-CH_3OH$, 280.074 for $C_{18}H_{16}O_5$).

b) $NaBH_4$ (60 mg) and 0.1 M $CeCl_3\cdot7H_2O$/methanol (0.8 ml) were added to a solution of **5** (102 mg) in methanol (12 ml), and the mixture was stirred at −50°C for 47 h. After addition of $NaBH_4$ (26 mg) and stirring at −50°C for 4 h, acetic acid (0.3 ml) was added. Work-up of the reaction mixture afforded **7** (50.6 mg, 57%) and **9** (33.7 mg, 34%).

Alumina-induced Reactions of 7, 8 and 9——a) Neutral Al_2O_3 (grade III) (1 g) was added to a solution of **7** (20.0 mg) in chloroform/methanol (1/1, v/v) (1 ml), and the mixture was allowed to stand at room temperature for 75 h. The eluent with chloroform/methanol (1/1, v/v) afforded crystals (21 mg) which were purified by prep. TLC (chloroform/ethanol=10/1, v/v) to yield 1,2,3,4-tetrahydro-1,*trans*-3,*trans*-4-trihydroxynaphthalene-2-spiro-3′-*cis*-3′-O-phthalide (**11**), (16.0 mg, 75%) as colorless prisms of mp 185°C (from ethanol), *Rf* 0.22. IR ν_{max} cm^{-1}: 3570, 3400 (OH), 1765 (OC=O). ^{1}H NMR (dimethyl sulfoxide-d_6) δ: 7.81 (1H, dd, J=7 and 3 Hz, 7′-H), 7.65—7.24 (6H, m, aromatic H's), 6.78 (1H, dd, J=7 and 3 Hz, 4′-H), 5.84 (1H, d,

J=6 Hz, 1-OH),[10] 5.65 (1H, d, J=7 Hz, 4-OH),[10] 5.64 (1H, d, J=6 Hz, 3-OH),[10] 4.67 (1H, d, J=6 Hz, 1-H),[11] 4.51 (1H, t, J=7 Hz, 4-H),[9] 4.29 (1H, dd, J=7 and 6 Hz, 3-H).[9] Decoupling: δ 5.84 (1-OH)→δ 4.67 (d→s, 1-H); δ 5.65 (3- and 4-OH's)→δ 4.51 (t→d, J=7 Hz, 4-H), 4.29 (dd→d, J=7 Hz, 3-H); δ 4.67 (1-H)→δ 5.84 (d→s, 1-OH); δ 4.29 (3-H)→δ 5.64 (d→s, 3-OH), 4.51 (t→d, J=7 Hz, 4-H). *Anal.* Calcd for $C_{17}H_{14}O_5 \cdot 1/4H_2O$: C, 67.43; H, 4.83. Found: C, 67.35; H, 4.65. MS *m/e*: $(M-H_2O)^+$, 280.072 ($M-H_2O$, 280.074 for $C_{17}H_{14}O_5$).

b) Neutral Al_2O_3 (grade III) (2 g) was added to a solution of **8** (37.0 mg) in chloroform/methanol (1/1, v/v) (1 ml), and the mixture was allowed to stand at room temperature for 1 week. Work-up of the reaction mixture gave 1,2,3,4-tetrahydro-1,*cis*-3,*cis*-4-trihydroxynaphthalene-2-spiro-3′-*trans*-3′-O-phthalide (**10**) (36.2 mg, 92%) as a colorless oil, *Rf* 0.07 (prep. TLC; benzene/ethyl acetate=2/1, v/v). IR ν_{max} cm^{-1}: 3610, 3400 (OH), 1763 (OC=O). ^1H NMR (dimethyl sulfoxide-d_6) δ: 7.83 (1H, dd, J=7 and 3 Hz, 7′-H), 7.75—7.33 (6H, m, aromatic H's), 6.60 (1H, dd, J=7 and 3 Hz, 4′-H), 6.05 (1H, d, J=6 Hz, 1-OH),[10] 5.81 (1H, d, J=7 Hz, 4-OH),[10] 5.73 (1H, d, J=5 Hz, 3-OH),[10] 5.20 (1H, d, J=6 Hz, 1-H),[11] 4.66 (1H, dd, J=8 and 7 Hz, 4-H),[9] 4.15 (1H, dd, J=8 and 5 Hz, 3-H).[9] Decoupling: δ 6.05 (1-OH)→δ 5.20 (d→s, 1-H); δ 5.81 (4-OH)→δ 4.66 (dd→d, J=8 Hz, 4-H); δ 5.73 (3-OH)→δ 4.15 (dd→d, J=8 Hz, 3-H); δ 5.20 (1-H)→δ 6.05 (d→s, 1-OH); δ 4.66 (4-H)→δ 5.81 (d→s, 4-OH), 4.15 (dd→d, J=5 Hz, 3-H); δ 4.15 (3-H)→δ 5.73 (d→s, 3-OH), 4.66 (dd→d, J=7 Hz, 4-H). MS Calcd for $C_{17}H_{14}O_5$: $M-H_2O$, 280.074. Found *m/e*: $(M-H_2O)^+$, 280.076.

c) Neutral Al_2O_3 (grade III) (1 g) was added to a solution of **9** (40.0 mg) in chloroform/methanol (1/1, v/v) (1 ml), and the mixture was allowed to stand at room temperature for 20 h. Work-up of the reaction mixture gave **8** (27.0 mg, 75%) and **10** (6.0 mg, 16%).

Oxidations of 6 and 9 to 4——a) The Jones reagent (0.8 ml)[12] was added to a solution of **6** (186 mg) in acetone (30 ml), and the mixture was stirred with cooling in an ice-bath for 2.5 h. After addition of methanol and filtration, the filtrate was concentrated *in vacuo* for extraction with ethyl acetate. Work-up gave light yellow crystals (184 mg) which were recrystallized from ethanol to yield **4** (88 mg, 48%) as colorless prisms of mp 164—165°C. The mother liquor was concentrated *in vacuo*, and the residue was purified by prep. TLC (benzene/ethyl acetate=16/1, v/v) to afford **4** (74 mg, 40%) as colorless prisms of mp 163.5—164.5°C (from ethanol), *Rf* 0.65: total yield, 88%.

b) A solution of **9** (109 mg) in acetone (20 ml) was treated with the Jones reagent (0.8 ml)[12] by the same procedure as described above, and **4** (95 mg, 88%) was obtained.

***cis*-4b,5,6,10b,11,12-Hexahydro-5-methyl-6-oxo-10b,*trans*-11,*trans*-12-trihydroxybenzo[*c*]phenanthridine** (**13**)——a) A solution of **7** (220 mg) in 40% aq. methylamine (10 ml) was stirred at room temperature for 24 h. Concentration *in vacuo* followed by dilution with water gave crystals (245 mg) which were recrystallized from methanol to yield **13** (232 mg, 95%) as colorless prisms of mp over 300°C. IR ν_{max} cm^{-1}: 3580, 3380 (OH), 1633 (NC=O). ^1H NMR (dimethyl sulfoxide-d_6) δ: 8.21 (1H, dd, J=8 and 2 Hz, 7-H), 7.69 (1H, dd, J=8 and 2 Hz, 4- or 10-H), 7.45—6.98 (6H, m, aromatic H's), 5.80 (1H, d, J=4 Hz, 11-OH),[10] 5.75 (1H, s, 10b-OH),[10] 5.67 (1H, d, J=7 Hz, 12-OH),[10] 4.60 (1H, s, 4b-H), 4.53 (1H, dd, J=8 and 7 Hz, 12-H),[9] 3.98 (1H, dd, J=8 and 4 Hz, 11-H),[9] 3.38 (3H, s, 5-Me). NOE: δ 3.98 (11-H)→δ 4.60 (7.1%, 4b-H), 4.53 (7.3%, 12-H). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.40; H, 5.51; N, 4.58. MS *m/e*: M^+, 311.116 (M, 311.116 for $C_{18}H_{17}NO_4$).

b) A solution of **7** (20.0 mg) in 20% methylamine/anhyd. ethanol (1 ml) was stirred at room temperature for 1 week. Work-up of the reaction mixture gave **13** (16.6 mg, 75%).

***cis*-4b,5,6,10b,11,12-Hexahydro-5-methyl-10b,*trans*-11,*trans*-12-trihydroxybenzo[*c*]phenanthridine** (**14**)——$LiAlH_4$ (318 mg) was added to a solution of **13** (159 mg) in 1,2-dimethoxyethane (150 ml), and the mixture was refluxed for 1 h. After addition of water (0.3 ml), 15% aq. NaOH (0.3 ml) and then water (0.9 ml), the reaction mixture was filtered, and the precipitate was washed with methanol. The combined filtrates were concentrated *in vacuo*, and the residue was dissolved in chloroform. Work-up gave **14** (132 mg, 87%) as colorless prisms of mp 226—227°C (from methanol). IR ν_{max} cm^{-1}: 3590, 3400 (OH), 2775, 2700 (Bohlmann bands). ^1H NMR (dimethyl sulfoxide-d_6) δ: 7.73 (1H, dd, J=8 and 2 Hz, 10-H), 7.60—7.06 (7H, m, aromatic H's), 6.86 (1H, br s, W_H=5 Hz, 11-OH),[10] 5.58 (1H, s, 10b-OH),[10] 5.09 (1H, d, J=8 Hz, 12-OH),[10] 4.64 (1H, dd, J=8 and 3 Hz, 12-H),[9] 3.99 (1H, d, J=16 Hz, 6-H), 3.82 (1H, br s, W_H=10 Hz, 11-H), 3.66 (1H, d, J=2 Hz, 4b-H), 3.65 (1H, d, J=16 Hz, 6-H), 2.13 (3H, s, 5-Me). Decoupling: δ 5.09 (12-OH)→δ 4.64 (dd→d, J=3 Hz, 12-H); δ 4.64 (12-H)→δ 5.09 (d→s, 12-OH), 3.82 (br s, W_H=10→6 Hz, 11-H); δ 3.82 (11-H)→δ 4.64 (dd→d, J=8 Hz, 12-H). NOE: δ 5.58 (10b-OH)→δ 7.73 (9.3%, 10-H), 3.66 (7.0%, 4b-H); δ 3.66 (4b-H)→δ 5.56 (18%, 10b-OH); δ 3.82 (11-H)→δ 7.73 (13.6%, 10-H), 5.58 (7.4%, 10b-OH). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.62; H, 6.44; N, 4.59. MS *m/e*: M^+, 297.137 (M, 297.136 for $C_{18}H_{19}NO_3$).

1,*cis*-4-Dihydroxy-*cis*-2,3-epoxy-*trans*-2-2′-methylcarbamoylphenyl-1,2,3,4-tetrahydronaphthalene (**16**)——A solution of **8** (94 mg) in 40% aq. methylamine (2.5 ml) was stirred at room temperature for 15 min. After concentration *in vacuo*, the residue was diluted with water. Crystals were collected by filtration and washed with ethanol to yield **16** (79 mg, 75%) as colorless prisms of mp 179—180°C. Because of its instability on heating in solvents, this compound was not recrystallized. IR ν_{max} cm^{-1}: 3475, 3440, 3360 (NH and OH), 1638 (NC=O). ^1H NMR (dimethyl sulfoxide-d_6) δ: 8.59 (1H, q, J=4 Hz, 2′-CONHMe),[10] 7.66—7.22 (8H, m, aromatic H's), 6.47 (1H, d, J=8 Hz, 1-OH),[10] 5.24 (2H, d, J=8 Hz, 1-H[11] and 4-OH),[10] 4.90 (1H, dd, J=8

and 4 Hz, 4-H),[9] 3.36 (1H, d, $J=4$ Hz, 3-H), 2.71 (3H, d, $J=4$ Hz, 2′-CONHMe).[11] Decoupling: δ 8.59 (2′-CONHMe)→δ 2.71 (d→s, 2′-CONHMe); δ 6.47 (1-OH)→δ 5.24 (d→s, 1-H); δ 5.24 (1-H and 4-OH)→δ 6.47 (d→s, 1-OH), 4.90 (dd→d, $J=4$ Hz, 4-H); δ 4.90 (4-H)→δ 5.24 (d→s, 4-OH), 3.36 (d→s, 3-H); δ 3.36 (3-H)→δ 4.90 (dd→d, $J=8$ Hz, 4-H); δ 2.71 (2′-CONHMe)→δ 8.59 (q→s, 2′-CONHMe). MS Calcd for $C_{18}H_{17}NO_4$: M, 311.116. Found: *m/e*: M^+, 311.115.

10b,*trans*-11-Dihydroxy-*cis*-4b,5,6,10b,11,12-hexahydro-5-methylbenzo[*c*]phenanthridine (17)——A solution of **14** (132 mg) and 70% $HClO_4$ (0.6 ml) in 10% HCl (15 ml) was shaken with H_2 over 10% Pd-C (60 mg) and PdO (66 mg) at 70°C under a pressure of 5 atm for 48 h. The reaction mixture was made alkaline with 20% aq. NaOH, and filtered, then washed with ethyl acetate. The combined filtrates were extracted with ethyl acetate. Work-up afforded light yellow crystals (113 mg) which were purified by prep. TLC (chloroform/methanol=40/1,v/v) to yield **17** (90 mg, 72%) as light yellow prisms of mp 225—227°C (from methanol), *Rf* 0.64. IR ν_{max} cm^{-1}: 3600, 3200 (OH), 2780, 2700 (Bohlmann bands); hydrogen-bonding, 3599 ($\varepsilon=56.6$) (OH···π), 3225 ($\varepsilon=35.2$) (OH···N) ($c=7.8\times10^{-4}$ mol/l, tetrachloromethane). ^1H NMR (dimethyl sulfoxide-d_6) δ: 7.64 (1H, dd, $J=8$ and 2 Hz, 10-H), 7.34—7.03 (7H, m, aromatic H's), 6.98 (1H, d, $J=8$ Hz, 11-OH),[10] 5.34 (1H, s, 10b-OH),[10] 3.99 (1H, d, $J=16$ Hz, 6-H), 3.86 (1H, br s, $W_H=12$ Hz, 11-H),[13] 3.65 (1H, d, $J=16$ Hz, 6-H), 3.55 (1H, d, $J=2$ Hz, 4b-H), 3.26 (1H, dd, $J=17$ and 4 Hz, 12-H), 2.92 (1H, dd, $J=17$ and 2 Hz, 12-H), 2.12 (3H, s, 5-Me). Decoupling: δ 3.99 (6-H)→δ 3.65 (d→s, 6-H); δ 3.86 (11-H)→δ 3.55 (d→s, 4b-H), 3.26 (dd→d, $J=17$ Hz, 12-H), 2.92 (dd→d, $J=17$ Hz, 12-H); δ 3.55 (4b- and 6-H's)→δ 3.99 (d→s, 6-H), 3.86 (br s, $W_H=12\rightarrow6$ Hz, 11-H); δ 3.26 (12-H)→δ 3.86 (br s, $W_H=12\rightarrow5$ Hz, 11-H), 2.92 (dd→d, $J=2$ Hz, 12-H). NOE: δ 5.34 (10b-OH)→δ 7.64 (8.9%, 10-H); δ 3.86 (11-H)→δ 7.64 (18.0%, 10-H). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.07; H, 6.87; N, 4.86. MS *m/e*: M^+, 281.141 (M, 281.142 for $C_{18}H_{19}NO_2$).

10b,11-Epoxy-*cis*-4b,5,6,10b,11,12-hexahydro-5-methylbenzo[*c*]phenanthridine (18)——A solution of mesyl chloride (54 mg) in anhyd. pyridine (1 ml) was added to a solution of **17** (100 mg) in anhyd. pyridine (1.8 ml), and the mixture was stirred at room temperature for 24 h. After addition of water (50 ml), the reaction mixture was extracted with ethyl acetate. Work up afforded a green oil (102 mg) which was purified by prep. TLC (chloroform/methanol=20/1, v/v) to yield **18** (65 mg, 70%) as light yellow prisms of mp 105.5—107°C (from hexane), *Rf* 0.75. IR ν_{max} cm^{-1}: 2780, 2700 (Bohlmann bands). ^1H NMR δ: 7.39—7.02 (8H, m, aromatic H's), 4.30, 4.02 (1H each, d, $J=16$ Hz, 6-H_2), 4.30 (1H, d, $J=2$ Hz, 4b-H), 3.50 (1H, m, 11-H), 3.41 (2H, br s, $W_H=4$ Hz, 12-H_2), 2.22 (3H, s, 5-Me). Decoupling: δ 4.30 (4b-H)→δ 3.50 (m→dd, $J=4$ and 2 Hz, 11-H); δ 3.50 (11-H)→δ 4.30 (d→s, 4b-H). MS Calcd for $C_{18}H_{17}NO$: M, 263.131. Found *m/e*: M^+, 263.134.

***cis*-4b,5,6,*trans*-10b,11,12-Hexahydro-11-hydroxy-5-methylbenzo[*c*]phenanthridine (19) and *r*-2-N-*trans*-3-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-spiro-1′-(2′-methyl)isoindoline (20)**——$LiAlH_4$ (9.0 mg) and $AlCl_3$ (4.6 mg) were added to a solution of **18** (23.2 mg) in anhyd. tetrahydrofuran (5 ml), and the mixture was refluxed for 25 min under N_2. After addition of further $LiAlH_4$ (3.0 mg) and $AlCl_3$ (4.0 mg), refluxing was continued for 10 min under N_2, and then 5% aq. KOH (1 drop) was added. The reaction mixture was filtered, and the precipitate was washed with ethyl acetate. Work up of the combined filtrates gave crystals (23.3 mg) which were purified by prep. TLC (benzene/ethyl acetate=2/1,v/v) to yield **19** (10.2 mg, 44%), *Rf* 0.41, and **20** (2.2 mg, 9%), *Rf* 0.09.

The *trans*-Hydroxy Amine (**19**): Colorless prisms of mp 221—222°C (from ethanol). IR ν_{max} cm^{-1}: 3610 (OH), 2780, 2750 (Bohlmann bands). ^1H NMR δ: 7.73 (1H, dd, $J=8$ and 2 Hz, 4-H),[14] 7.53—7.08 (7H, m, aromatic H's), 5.14 (1H, m, 11-H), 4.53 (1H, d, $J=17$ Hz, 6-H), 4.49 (1H, d, $J=12$ Hz, 4b-H), 3.86 (1H, d, $J=17$ Hz, 6-H), 3.32 (1H, dd, $J=18$ and 4 Hz, 12-H), 3.11 (1H, dd, $J=18$ and 2 Hz, 12-H), 3.11 (1H, dd, $J=12$ and 2 Hz, 10b-H), 2.24 (3H, s, 5-Me), 1.62 (1H, s, 11-OH).[10] Decoupling: δ 5.14 (11-H)→δ 3.32 (dd→d, $J=18$ Hz, 12-H), 3.11 (dd→d, $J=18$ Hz, 12-H), 3.11 (dd→d, $J=12$ Hz, 10b-H); δ 4.50 (4b- and 6-H's)→δ 3.86 (d→s, 6-H), 3.11 (dd→d, $J=2$ Hz, 10b-H); δ 3.86 (6-H)→δ 4.53 (d→s, 6-H); δ 3.25 (10b- and 12-H's)→δ 5.14 (m→s, 11-H), 4.49 (d→s, 4b-H). MS Calcd for $C_{18}H_{19}NO$: M, 265.147. Found *m/e*: M^+, 265.143.

The Isoindoline (**20**): Colorless pillars of mp 157—158°C (from ethanol). IR ν_{max} cm^{-1}: 3570, 3400 (OH). ^1H NMR δ: 7.30—6.92 (7H, m aromatic H's), 6.75 (1H, d, $J=7$ Hz, 7′-H), 4.33 (1H, d, $J=13$ Hz, 3′-H), 4.22 (1H, dd, $J=11$ and 6 Hz, 3-H), 4.04 (1H, d, $J=13$ Hz, 3′-H), 3.40 (1H, dd, $J=17$ and 6 Hz, 4-H), 3.25 (1H, d, $J=17$ Hz, 1-H), 3.11 (1H, dd, $J=17$ and 11 Hz, 4-H), 2.79 (1H, d, $J=17$ Hz, 1-H), 2.71 (1H, s, 3-OH),[10] 2.61 (3H, s, 2′-Me). Decoupling: δ 4.22 (3-H)→δ 3.40, 3.11 (each dd→d, $J=17$ Hz, 4-H_2). *Anal.* Calcd for $C_{18}H_{19}NO\cdot1/10H_2O$: C, 80.93; H, 7.24; N, 5.24. Found: C, 81.00; H, 7.14; N, 5.16. MS *m/e*: M^+, 265.147 (M, 265.146 for $C_{18}H_{19}NO$).

References and Notes

1) Part X: Y. Harigaya, H. Yamaguchi, and M. Onda, *Chem. Pharm. Bull.*, **29**, 1321 (1981).
2) Y. Harigaya, T. Suzuki, and M. Onda, *Chem. Pharm. Bull.*, **27**, 2636 (1979).
3) A. Defoin and J. Rigaudy, *Bull. Soc. Chem. Fr.*, **2**, **1979**, 110.
4) G. Rücker, H. Hörster, and W. Gajewski, *Synth. Commun.*, **1980**, 623.

5) M. Onda, H. Yamaguchi, and Y. Harigaya, *Chem. Pharm. Bull.*, **28**, 866 (1980); N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *ibid.*, **26**, 1880 (1978).
6) M. Onda, K. Yuasa, and J. Okada, *Chem. Pharm. Bull.*, **22**, 2365 (1974), and references cited therein.
7) J.S. Pizey, "Synthetic Reagents," Vol. I. Ellis Horwood Ltd., Chichester, 1974, pp. 115—127, and references cited therein.
8) Assignments may be reversed.
9) On addition of deuterium oxide, this signal changed to a doublet.
10) On addition of deuterium oxide, this signal disappeared.
11) On addition of deuterium oxide, this signal changed to a singlet.
12) A solution of chromic anhydride (26.7 g) in concentrated sulfuric acid (23 ml) was diluted with water to a volume of 100 ml.
13) On addition of deuterium oxide, this signal changed to a broad singlet with $W_H=6$ Hz.
14) Assignment was made by comparison with the ^1H NMR spectra of related compounds [M. Onda, Y. Harigaya, and J. Horie, *Chem. Pharm. Bull.*, **26**, 3330 (1978)].