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Utilization of Protopine and Related Alkaloids. XIII.[1] Attempts to obtain Useful Intermediates for the Syntheses of Chelidonine and Homochelidonine

Hiroko Yamaguchi, Yoshihiro Harigaya, and Masayuki Onda*

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

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The epoxyimine (**11a**), derived from berberinium chloride, smoothly gives the naphthoquinone epoxide (**25a**) *via* several steps. The site-selective reduction of **25a** with lithium tri-*tert*-butoxyaluminohydride affords the *cis*-epoxy ketol (**27a**) (45%) and *trans* isomer (**28a**) (38%) which result from the attack of the reducing agent at the 4-position. Further reductions of **27a** and **28a** with sodium borohydride provide the *cis*-dihydroxy epoxide (**32a**) and *trans* isomer (**29a**), respectively, as a sole product in each case. The desired compounds having the 1-hydroxyl groups *trans* with respect to the oxirane rings are not formed. Treatment of **32a** with methylamine results in the formation of the amide (**33a**), which is transformed to the isoindolinone (**34**) and phthalide (**35**) during purification by preparative thin-layer chromatography using silica gel. The epoxyimine (**11b**), derived from protopine, gives similar results.

The correlation between the proton magnetic resonance data and the structures of the compounds obtained is briefly discussed.

Keywords——isoindolinone; naphthoquinone epoxide; phthalide; site-selective reduction; intramolecular hydrogen-bonding; proton magnetic resonance

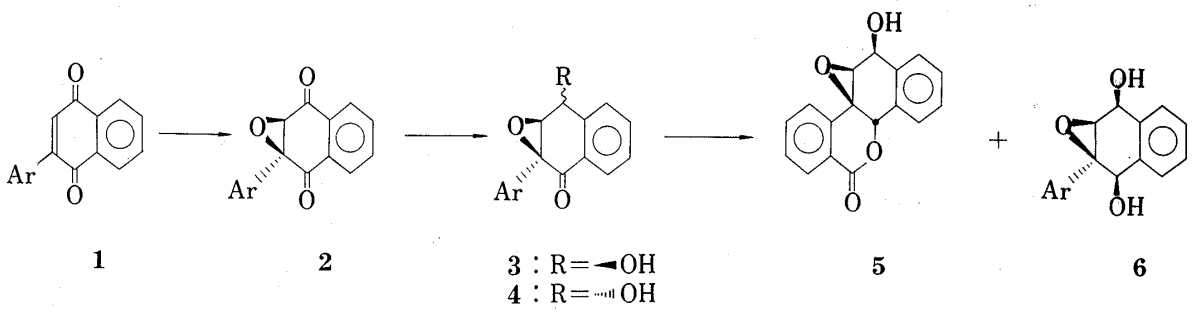
We have recently reported the stereoselective synthesis of a chelidonine analog (**8**) from the naphthoquinone (**1**).[2] On the other hand, in the courses of our investigations on the transformation of berberinium chloride (**9**) to benzo[*c*]phenanthridines, we reported that 1-oxoanhydromethylberberine (**10a**), derived from **9**, photochemically reacted with nitrosobenzene to yield the epoxyimine (**11a**).[3] Since it was found that **11a** smoothly gave the naphthoquinone corresponding to **1**, efforts to obtain homochelidonine according to the synthetic method used for **8** (shown in Chart 1) were continued. In this paper we report interesting findings obtained during the investigation although the outcome was unsuccessful.

Hydrogenation of **11a** over palladium-carbon gave the anilino tetralone (**12a**) (82%) which was reduced with sodium borohydride to yield the *cis*-anilino naphthol (**13a**) (55%) and *trans* isomer (**14a**) (44%). The proton magnetic resonance (^{1}H NMR) spectrum of **12a** showed two one-proton triplets for the 4_{eq}- and 2_{ax}-protons at δ 4.72 (J 4 Hz) and 4.32 (J 8 Hz), respectively, and the infrared (IR) spectrum exhibited two carbonyl bands of the 1-oxo and 2′-methylcarbamoyl groups at 1663 and 1650 cm^{-1}, respectively. The structures of **13a** and **14a** are deduced from the ^{1}H NMR data [**13a**: δ 4.59 (t, J 3 Hz) for 4_{eq}-H, 4.39 (d, J 10 Hz) for 1_{ax}-H and 3.18 (dt, J 5 and 10 Hz) for 2_{ax}-H; **14a**: δ 4.70 (t, J 3 Hz) for 4_{eq}-H, 4.66 (d, J 3 Hz) for 1_{eq}-H and 3.39 (dt, J 12 and 3 Hz) for 2_{ax}-H].

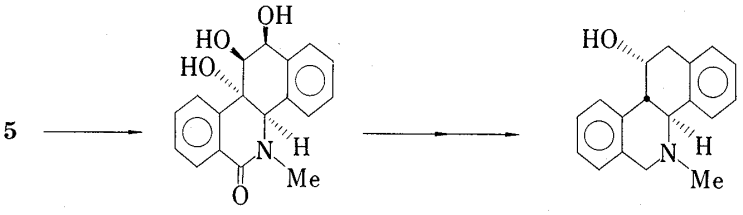
Treatments of **13a** and **14a** with hydrochloric acid afforded the naphthalene (**15a**) (38%) and anilino lactone (**16**) (84%) (IR: 1725 cm^{-1} for the δ-lactone carbonyl group), respectively, which was converted by treatment with methylamine into **14a** (76%). The B/C ring fusion in **16** is deduced to exist in the *cis* steroidal conformation with a slightly deformed C ring on the basis of coupling constants ($J_{4b,10b}$ 4 Hz and $J_{10b,11_A}=J_{10b,11_B}$ 8 Hz) observed in the ^{1}H NMR spectrum. It is clear that **13a** and **14a** did not cyclize to form the lactam group under acidic conditions.[4]

Oxidation of **12a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the naphthoquinone monoimine (**17a**) (74%). Treatment of **17a** with *tert*-butyl hydroperoxide/

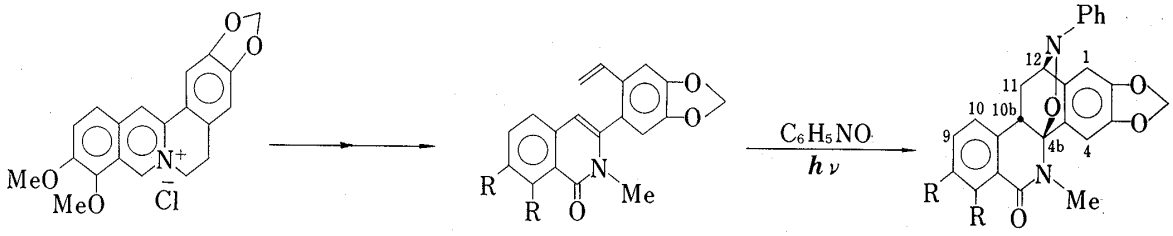
benzyltrimethylammonium hydroxide (Triton B) afforded the isoindolinone (**18**) (96%), instead of an epoxide, which showed a carbonyl band of the γ-lactam group at 1700 cm^{-1} in the IR spectrum, and an AB quartet for the 3-protons at δ 3.29 and 2.96 (each J 15 Hz) in the ^1H NMR spectrum. It was found that **17a** provided **18** (96%) by treatment with Triton B alone. Hydrolysis of **18** yielded the isoindolinone (**19**) (96%)[IR: 1700 cm^{-1} for the γ-lactam carbonyl group; ^1H NMR: δ 3.63 and 2.91 (each d, J 16 Hz) for 3-H_2].[5] Treatment of **17a**



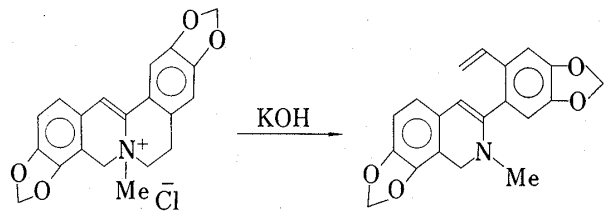
1 **2** **3** : R=⁻OH, **4** : R=···OH **5** **6**



7 **8**



9 **10a, b** **11a, b**



37 **38**

Ar=C_6H_4COOMe (o) **a** : R=OMe **b** : R+R=OCH_2O

Chart 1

with hydrochloric acid gave a mixture of **19** and the naphthoquinone (**20a**), from which **20a** (42%) was isolated by recrystallization from ethanol [^{1}H NMR: δ 6.78 (s) for 3-H]. The naphthoquinone (**20a**) was also converted by treatment with 1,5-diazabicyclo[5.4.0]undecene (DBU) into **19** (88%). Since it is apparent from these results that **17a** and **20a** did not give the desired compounds under basic epoxidation conditions, attempts to obtain the compounds with the 2′-methoxycarbonyl groups corresponding to these compounds were made.

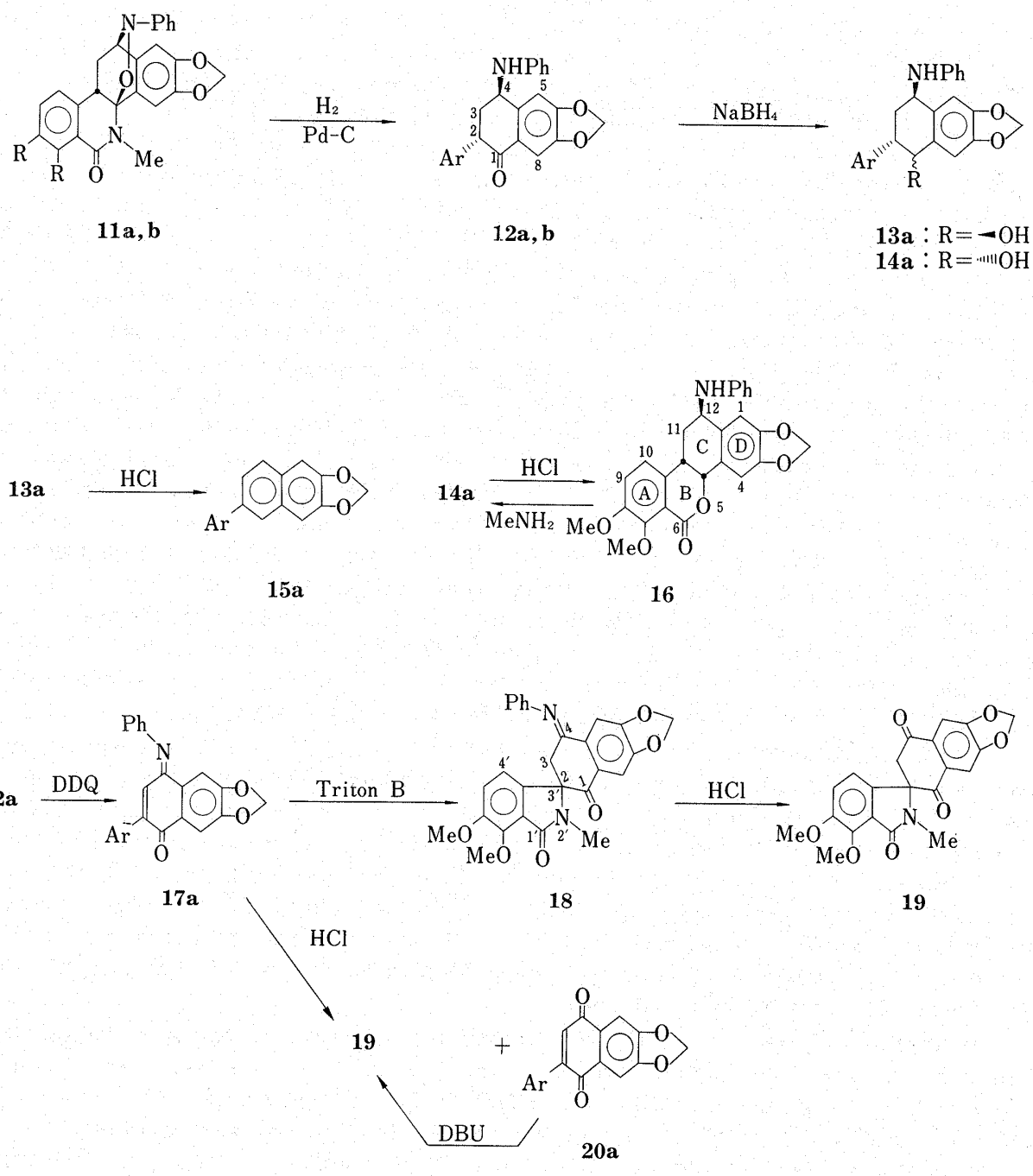


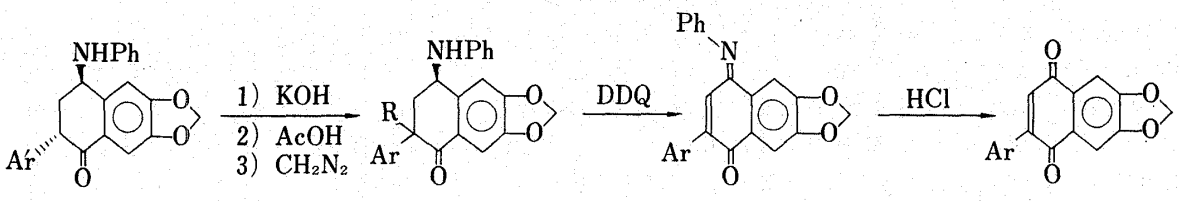
Chart 2

The anilino tetralone (**12a**) was converted by treatment with potassium hydroxide and then diazomethane into the *cis*-anilino tetralone (**21a**) (55%) and *trans* isomer (**22a**) (22%). The structures of **21a** and **22a** are deduced on the basis of the ^{1}H NMR data [**21a**: δ 4.83 (dd, J 12 and 4 Hz) for 4_{ax}-H and 3.92 (dd, J 12 and 4 Hz) for 2_{ax}-H; **22a**: δ 4.68 (t, J 4 Hz) for 4_{eq}-H and 4.21 (dd, J 12 and 4 Hz) for 2_{ax}-H]. A mixture of **21a** and **22a** was oxidized with DDQ to yield the naphthoquinone monoimine (**23a**) (72%) which was hydrolyzed with hydrochloric acid to give the naphthoquinone (**24a**) (99%) [^{1}H NMR: δ 6.83 (s) for 3-H]. Epoxidation of **24a** with *tert*-butyl hydroperoxide/DBU provided the naphthoquinone epoxide (**25a**) (90%) [^{1}H NMR: δ 3.83 (s) for 3-H]. On the other hand, **23a** was epoxidized under similar conditions to yield the epoxynaphthoquinone monoimine (**26a**) (69%) [^{1}H NMR: δ 4.03 (s) for 3-H] which quantitatively gave **25a** on hydrolysis with hydrochloric acid.

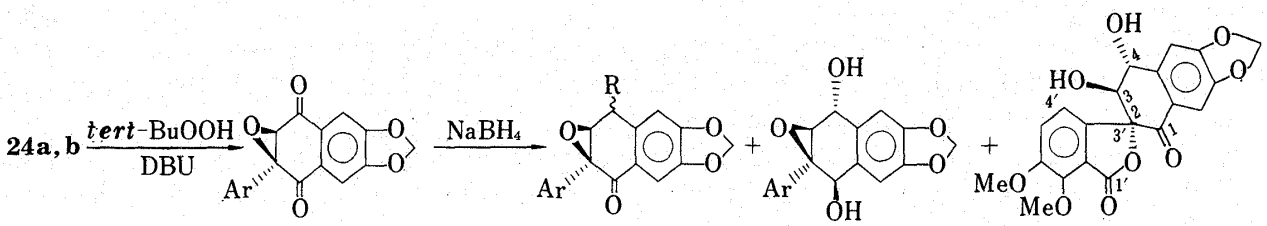
Reduction of **25a** with sodium borohydride at −80°C for 10 min gave the *cis*-epoxy ketol (**27a**) (11%), *trans* isomer (**28a**) (67%), *trans*-dihydroxy epoxide (**29a**) (8%) and phthalide (**30**) (2%). The site-selective reduction of the 4-oxo group in **25a** is confirmed by the observation of one-proton doublets for the 3-protons in the ^{1}H NMR spectra [**27a**: δ 3.73 (J 3 Hz); **28a**: δ 3.81 (J 2 Hz)]. The configurations of the 4-hydroxyl groups in **27a** and **28a** are established to be *cis* and *trans* with respect to the oxirane rings, respectively, on the basis of intramolecular hydrogen-bondings observed in the IR spectra [**27a**: 3515 cm^{-1} (OH$\cdots$O); **28a**: 3581 cm^{-1} (OH$\cdots\pi$)].[2,6] The structure of **29a** is confirmed by its identity with the compound obtained by reduction of **28a** (*vide infra*). Treatment of **28a** with silica gel gave **30** (34%), and this result suggests that **30** is formed from **28a** during work-up of the reaction mixture obtained in the reduction of **25a** (see "Experimental"). The presence of the γ-lactone and α-glycol groups in **30** is supported by the IR (1770 cm^{-1}) and ^{1}H NMR data [δ 5.11 (d, J 4 Hz) and 4.28 (d, J 4 Hz)]. A possible pathway for the formation of **30** is thought to arise *via* the carboxylic acid (**31**), which itself results from hydrolysis of the ester group in **28a** by silica gel treatment, followed by intramolecular acylolysis of the oxirane ring at the 2-position in a *trans* ring opening mode.[2] As can be seen, the reduction of **25a** predominantly gave **28a** and is in contrast to the fact that the naphthoquinone epoxide (**2**) afforded the *cis*-epoxy ketol (**3**) (75%) and *trans* isomer (**4**) (19%) under similar conditions.[2] On the other hand, reduction of **25a** with lithium tri-*tert*-butoxyaluminohydride yielded **27a** (45%) and **28a** (38%).

Further reduction of **27a** with sodium borohydride at −50°C for 1.5 h gave the *cis*-dihydroxy epoxide (**32a**) (92%). Reduction of **28a** with the same reagent at −50°C for 30 min afforded **29a** (69%) as a sole product. The configurations of the 1- and 4-hydroxyl groups in **29a** and **32a** are characterized by examining intramolecular hydrogen-bondings observed in the IR spectra [**29a**: 3581 (OH$\cdots\pi$) and 3430 cm^{-1} (OH$\cdots$O); **32a**: 3610 and 3579 (OH$\cdots\pi$), 3535 and 3425 cm^{-1} (OH$\cdots$O)]. The fact that the 1-oxo groups in **27a** and **28a** were reduced to yield the 1-hydroxyl groups *cis* with respect to the oxirane rings, with no *trans* product, is in contrast to the finding that **3** afforded the epoxyhydroxy lactone (**5**) (47%) and *cis*-dihydroxy epoxide (**6**) (38%) under similar conditions.[2]

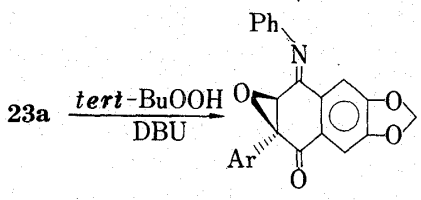
It was already reported that the reaction of **5** with methylamine exclusively afforded the benzo[*c*]phenanthridine (**7**), and **6** gave complex compounds.[2] We next examined the reaction of **32a** with methylamine in detail. Treatment of **32a** with methylamine yielded the amide (**33a**) (87%) (IR: 1645 cm^{-1} for the amide carbonyl group) which quickly equilibrated with the isoindolinone (**34**) in an approximate ratio of 1/1 on standing in solvent (see "Experimental"). Preparative thin-layer chromatography (prep. TLC) of the equilibrated mixture gave **34** (32%) and the phthalide (**35**) (46%), which were characterized on the basis of carbonyl bands observed in the IR spectra (**34**: 1698 cm^{-1}; **35**: 1765 cm^{-1}). The isoindolinone (**34**) should be formed by the attack of the amide group at the 2′-position in a *trans* ring opening mode. The formation of **35** is thought to arise *via* a carboxylic acid, produced by hydrolysis of the amide group in **33a** upon silica gel treatment, like that of **30** *via* **31**. Treatment of **32a** with methylamine and subsequent reduction with lithium aluminum hydride yielded the iso-



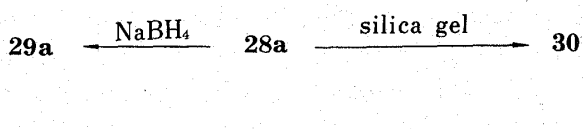
12a,b **21a,b** : R=⋯H **23a,b** **24a,b**
22a,b : R=—H

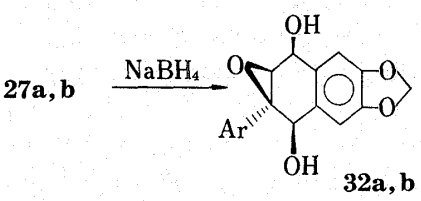


25a,b **27a,b** : R=—OH **29a** **30**
28a,b : R=⋯OH

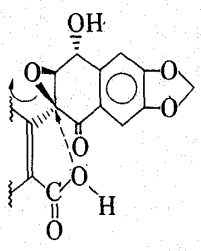


26a





32a,b



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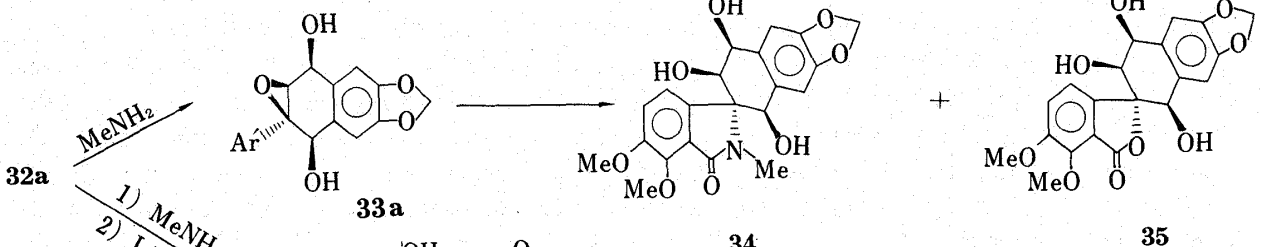
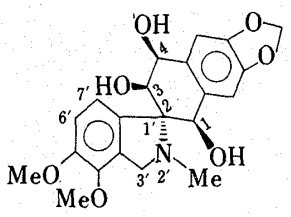


33a **34** **35**



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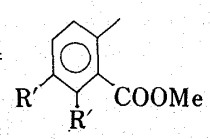
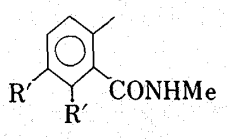
Ar=  Ar′= 

a : R′=OMe **b** : R′+ R′=OCH_2O

Chart 3

indoline (**36**) (23%) [^{1}H NMR: δ 4.03 and 3.89 (each d, J 13 Hz) for 3′-H_2].

We next examined reactions of the compounds having a methylenedioxy group instead of two methoxy groups at the 3′- and 4′-positions. Anhydroprotopine (**38**),[7] obtained from the Hofmann degradation of isoprotopine chloride (**37**), was oxidized with DDQ and then potassium ferricyanide to yield 1-oxoanhydroprotopine (**10b**) (45%). Photolysis of **10b** in the presence of nitrosobenzene afforded **11b** (77%), and its structure is established by comparison of the ^{1}H NMR data with those for **11a**. On application of the synthetic procedures described above, **25b** was smoothly obtained from **11b**. Reduction of **25b** with lithium tri-*tert*-butoxyaluminohydride gave **27b** (84%) and **28b** (15%) [IR: **27b**, 3520 cm^{-1} (OH$\cdots$O); **28b**, 3584 cm^{-1} (OH$\cdots\pi$)]. This result is similar to that obtained by reduction of **2** with the same reagent.[2] Further reduction of **27b** with sodium borohydride afforded **32b** (28%) as a sole product [IR: 3580 (OH$\cdots\pi$) and 3535 cm^{-1} (OH$\cdots$O)].[8]

In conclusion, we could not obtain the compounds corresponding to **5** from berberinium chloride (**9**) and protopine [isoprotopine chloride (**38**)], which had been expected to yield the benzo[*c*]phenanthridines corresponding to **7**.

Finally, we comment on the ^{1}H NMR data for the compounds obtained.[9] The 4-protons in **12a** and **22a**, in which the 4-anilino groups are *trans* with respect to the 2-substituents, appeared as triplets (4 Hz). If the cyclohexene rings in these compounds are assumed to exist in the 1,2-diplanar forms, the anilino groups are oriented axially. The 4-anilino groups in **13a** and **14a**, in which the cyclohexene rings exist in the half-chair forms, are deduced to be axial from the observed coupling constants of the 4-protons (each t, J 3 Hz). This may be ascribed to $A^{(1,3)}$-strain[10] between the 4_{eq}-anilino groups and 5-protons in inverted conformers. This is also the case for the 12-anilino group in **16**; a triplet (3 Hz) is seen for the 12-proton.

Since the N-phenyl groups in the naphthoquinone monoimines are thought to be *cis* with respect to the 3-protons owing to steric interactions with the 5-protons, deshieldings of the 5-protons are attributed to effects of the nitrogen lone pairs ($\Delta\delta_{17a-20a}$=0.42 or 0.39 ppm; $\Delta\delta_{23a-24b}$=0.41 ppm; $\Delta\delta_{23b-24b}$=0.42 ppm).[11] Deshieldings of the 4′-protons in **18** and **26a** are also caused by the nitrogen lone pairs ($\Delta\delta_{18-19}$=0.30 ppm; $\Delta\delta_{26a-25a}$=0.33 or 0.27 ppm).

Shieldings of the 4′-protons in **34** (δ 6.49) and **35** [δ 6.65 (dioxane)], and of the 7′-proton in **36** (δ 6.32) were observed. Three *cis*-hydroxyl groups at the 1-, 3- and 4-positions in these compounds may force the cyclohexene rings into flattened boat forms ($J_{3,4}$ 8 Hz) with the 2_{ax}-3a′ (**34** and **35**) and 2_{ax}-7a′ bonds (**36**). Thus, the protons in question are located nearly over the benzene moieties and are shielded.[12] As for **30**, owing to interaction between the 4- and 4′-protons, the cyclohexene ring may exist in a slightly flattened 1,2-diplanar form $J_{3,4}$ 4 Hz) with the 2_{ax}-3a′ bond, and the 4′-proton is slightly more remote from the benzene moiety. The 4′-proton shielding (δ 7.30) (5′-H: δ 7.13) would reflect the above steric situation[13] Owing to the presence of the 2′-methyl groups, the cyclohexene rings in **18** and **19** are also thought to exist in the 1,2-diplanar forms with the 2_{ax}-3a′ bonds. As a result, the 4′-protons in these compounds are shielded by the benzene moieties and additionally the 4-imino or 4-oxo group (**18**: δ 6.82; **19**: δ 6.53). This explains the difference between the shieldings of the 4′-protons in these compounds and **30**. The difference between the shieldings of the 4′-protons in **18** and **19** may be ascribed to the difference between the anisotropic influences of the imino and oxo groups.

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Prep. TLC's were performed on silica gel plates. Spectral data were recorded on the following spectrometers: IR—JASCO IR-G in chloroform and JASCO DS-701G (hydrogen-bondings) in tetrachloromethane; ^{1}H NMR—JEOL JNM-PS-100 (100 MHz) and Varian EM-390 (90 MHz) in deuteriochloroform unless otherwise noted; mass (MS)—JEOL JMS-01S. Synthetic procedures for the **b**-series compounds followed those for the **a**-series ones unless otherwise noted.

1-Oxoanhydroprotopine (10b)——A solution of **37** (200 mg) in 25% methanolic KOH (1 ml) was refluxed for 7 min. The reaction mixture was poured into ice-water, and the precipitate was extracted with chloro-

form. The chloroform phase was washed with water and dried over Na_2SO_4 for 30 min. Removal of the solvent *in vacuo* afforded **38** (179 mg, 99%) as an oil, which was immediately used without purification.

A solution of **38** (179 mg) in chloroform (7 ml) was added to a solution of DDQ (99 mg) in chloroform (30 ml), and the mixture was stirred at room temperature for 1 h. The chloroform phase was washed with 10% aq. NaOH and water, and dried over Na_2SO_4, then concentrated *in vacuo*. The residue was dissolved in methanol (4 ml), and added to a solution of $K_3Fe(CN)_6$ (200 mg) in 2.5% aq. KOH (1 ml). The mixture was stirred at 80°C for 2.5 h. After filtration, the reaction mixture was concentrated *in vacuo*, and the residue was extracted with chloroform. Work-up gave an oil (168 mg), which was purified by prep. TLC (benzene/ethyl acetate=2/1, v/v) to yield **10b** (84 mg, 45%), *Rf* 0.29, as light yellow prisms of mp 176—177°C (from ethanol). IR ν_{max} cm^{-1}: 1650 (NC=O). ^1H NMR (90 MHz) δ: 7.13 (1H, d, *J* 8 Hz, 5-H), 7.10 (1H, s, 6′-H), 6.92 (1H, d, *J* 8 Hz, 6-H), 6.70 (1H, s, 3′-H), 6.43 (1H, dd, *J* 18 and 11 Hz, 1″-H), 6.26 (1H, s, 4-H), 6.19 (2H, s, 7,8-OCH_2O), 6.01 (2H, s, 4′,5′-OCH_2O), 5.56 (1H, dd, *J* 18 and 1 Hz, 2″-H), 5.10 (1H, dd, *J* 11 and 1 Hz, 2″-H), 3.18 (3H, s, 2-Me). MS Calcd for $C_{20}H_{15}NO_5$: M, 349.095. Found *m/e*: M^+, 349.095.

4b,*cis*-10b,11,12-Tetrahydro-4b,12-*N*-phenylepoxyiminooxysanguinarine (11b)——A solution of **10b** (174 mg) and nitrosobenzene (59 mg) in anhyd. benzene (170 ml) was irradiated with a 100 W medium pressure mercury lamp under N_2 at room temperature for 10 min. Removal of the solvent *in vacuo* afforded an oil (230 mg) which was crystallized from ethanol to yield **11b** (175 mg, 77%) as colorless prisms of mp 196—197°C. IR ν_{max} cm^{-1}: 1649 (NC=O). ^1H NMR (90 MHz) δ: 7.17—7.08 (2H, m, aromatic H's), 6.96—6.84 (3H, m, aromatic H's), 6.72 (1H, d, *J* 8 Hz, 10-H), 6.54 (1H, s, 4-H),[14] 6.47 (1H, s, 1-H),[14] 6.36 (1H, d, *J* 8 Hz, 9-H), 6.11, 6.02 (1H each, d, *J* 1 Hz, 7,8-OCH_2O), 5.77 (2H, s, 2,3-OCH_2O), 4.78 (1H, dd, *J* 4 and 2 Hz, 12-H), 3.84 (1H, dd, *J* 10 and 6 Hz, 10b-H), 3.39 (3H, s, 5-Me), 3.06 (1H, ddd, *J* 13, 10 and 4 Hz, 11-H_A), 1.91 (1H, ddd, *J* 13, 6 and 2 Hz, 11-H_B). Decoupling: δ 4.78 (12-H)→δ 3.06 (ddd→dd, *J* 13 and 10 Hz, 11-H_A), 1.91 (ddd→dd, *J* 13 and 6 Hz, 11-H_B); δ 3.84 (10b-H)→δ 3.06 (ddd→dd, *J* 13 and 4 Hz, 11-H_A), 1.91 (ddd→dd, *J* 13 and 2 Hz, 11-H_B); δ 3.06 (11-H_A)→δ 4.78 (dd→d, *J* 2 Hz, 12-H), 3.84 (dd→d, *J* 6 Hz, 10b-H), 1.91 (ddd→dd, *J* 6 and 2 Hz, 11-H_B); δ 1.91 (11-H_B)→δ 4.78 (dd→d, *J* 4 Hz, 12-H), 3.84 (dd→d, *J* 10 Hz, 10b-H), 3.06 (ddd→dd, *J* 10 and 4 Hz, 11-H_A). MS Calcd for $C_{26}H_{20}N_2O_6$: M, 456.132. Found: *m/e*: M^+, 456.132.

***trans*-4-Anilino-2-3′,4′-dimethoxy-2′-methylcarbamoylphenyl-6,7-methylenedioxy-α-tetralone (12a)**——A solution of **11a** (101 mg) in methanol (40 ml) was shaken with H_2 over 10% Pd-C (22 mg) at room temperature for 15 min. The reaction mixture was filtered, then concentrated *in vacuo*. The residual oil (100 mg) was crystallized from ethanol to yield **12a** (84 mg, 82%) as colorless granules of mp 194—195°C. IR ν_{max} cm^{-1}: 3430 (NH), 1663 (C=O), 1650 (NC=O). ^1H NMR (100 MHz) δ: 7.42 (1H, s, 8-H), 7.17—7.09 (2H, m, aromatic H's), 6.83 (3H, s, 5-, 5′- and 6′-H's), 6.79—6.61 (3H, m, aromatic H's), 6.10 (1H, q, *J* 5 Hz, 2′-CONHMe),[15] 5.98 (2H, s, 6,7-OCH_2O), 4.72 (1H, t, *J* 4 Hz, 4-H), 4.32 (1H, t, *J* 8 Hz, 2-H), 4.04 (1H, s, 4-NHPh),[15] 3.80 (6H, s, 3′- and 4′-OMe's), 2.72 (3H, d, *J* 5 Hz, 2′-CONHMe),[16] 2.61 (2H, dd, *J* 8 and 4 Hz, 3-H_2). *Anal.* Calcd for $C_{27}H_{26}N_2O_6$: C, 68.34; H, 5.52; N, 5.90. Found: C, 68.09; H, 5.77; N, 5.69. MS *m/e*: M^+, 474.178 (M, 474.179 for $C_{27}H_{26}N_2O_6$).

***trans*-4-Anilino-2-2′-methylcarbamoyl-3′,4′-methylenedioxyphenyl-6,7-methylenedioxy-α-tetralone (12b)**——Colorless granules of mp 199—200.5°C (from ether). Yield, 89%. IR ν_{max} cm^{-1}: 3450 (NH), 1665 (NC=O). ^1H NMR (90 MHz) δ: 7.44 (1H, s, 8-H), 7.17—7.09 (2H, m, aromatic H's), 6.82 (1H, s, 5-H), 6.73—6.57 (5H, m, aromatic H's), *ca.* 5.97 (1H, 2′-CONHMe, overlapping with OCH_2O signal),[15] 5.96, 5.93 (2H each, s, 6,7- and 3′,4′-OCH_2O's), 4.89—4.69 (2H, m, 2- and 4-H's), 4.00 (1H, s, 4-NHPh),[15] 2.80 (3H, d, *J* 5 Hz, 2′-CONHMe),[16] *ca.* 2.80 (1H, 3-H, overlapping with 2′-CONHMe signal), 2.54 (1H, ddd, *J* 12, 6 and 4 Hz, 3-H). MS Calcd for $C_{26}H_{22}N_2O_6$: M, 458.148. Found: *m/e*: M^+, 458.149.

***cis*-4-Anilino-*trans*-2-3′,4′-dimethoxy-2′-methylcarbamoylphenyl-1,2,3,4-tetrahydro-1-hydroxy-6,7-methylenedioxynaphthalene (13a) and the *trans*-4-*cis*-2 Isomer (14a)**——$NaBH_4$ (24 mg) was added to a solution of **12a** (151 mg) in methanol (20 ml), and the mixture was stirred at room temperature for 20 min. After concentration *in vacuo*, the residue was extracted with chloroform. Work-up gave an oil (151 mg) which was purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to yield **13a** (83 mg, 55%), *Rf* 0.35, and **14a** (66 mg, 44%), *Rf* 0.24.

The *cis*-Anilino Naphthol (**13a**): Colorless needles of mp 226—228°C (from ethanol). IR ν_{max} cm^{-1}: 3450 (OH), 3325 (NH), 1635 (NC=O). ^1H NMR (100 MHz) δ: 7.15—7.07 (2H, m, aromatic H's), 7.10 (1H, d, *J* 8 Hz, 6′-H), 6.95 (1H, d *J* 8 Hz, 5′-H), 6.72 (2H, s, 5- and 8-H's), 6.70—6.55 (3H, m, aromatic H's), 6.12 (1H, q, *J* 5 Hz, 2′-CONHMe),[15] 5.90 (2H, s, 6,7-OCH_2O), 5.22 (1H, s, 1-OH),[15] 4.59 (1H, t, *J* 3 Hz, 4-H), 4.39 (1H, d, *J* 10 Hz, 1-H), 4.02 (1H, s, 4-NHPh),[15] 3.82 (3H, s, 3′-OMe), 3.78 (3H, s, 4′-OMe), 3.18 (1H, dt, *J* 5 and 10 Hz, 2-H), 2.89 (3H, d, *J* 5 Hz, 2′-CONHMe),[16] 2.29—2.13 (2H, m, 3-H_2). MS Calcd for $C_{27}H_{28}N_2O_6$: M, 476.195. Found *m/e*: M^+, 476.195.

The *trans* Isomer (**14a**): Colorless prisms of mp 147.5—150°C (from ethanol). IR ν_{max} cm^{-1}: 3450 (OH), 3325 (NH), 1652 (NC=O). ^1H NMR (100 MHz) δ: 7.15—7.07 (2H, m, aromatic H's), 7.06 (1H, d, *J* 8 Hz, 6′-H), 6.86 (1H, d, *J* 8 Hz, 5′-H), 6.77 (2H, s, 5- and 8-H's), 6.75—6.57 (3H, m, aromatic H's), 6.00 (1H, q, *J* 5 Hz, 2′-CONHMe),[15] 5.90 (2H, s, 6,7-OCH_2O), 4.70 (1H, t, *J* 3 Hz, 4-H), 4.66 (1H, d, *J* 3 Hz, 1-H), 3.90 (1H, s, 4-NHPh),[15] 3.80 (3H, s, 3′-OMe), 3.75 (3H, s, 4′-OMe), 3.39 (1H, dt, *J* 12 and 3 Hz, 2-H), 2.86 (3H, d, *J* 5 Hz, 2′-CONHMe),[16] 2.41 (1H, dt, *J* 3 and 12 Hz, 3-H), 2.21 (1H, s, 1-OH),[15] 2.04 (1H, dt, *J* 12

and 3 Hz, 3-H). MS Calcd for $C_{27}H_{28}N_2O_6$: M, 476.195. Found *m/e*: M^+, 476.194.

6-3′,4′-Dimethoxy-2′-methylcarbamoylphenyl-2,3-methylenedioxynaphthalene (15a)——A solution of **13a** (20.0 mg) and conc. HCl (1 drop) in methanol (10 ml) was refluxed for 30 min. After concentration *in vacuo*, the residue was extracted with chloroform. Work-up gave an oil (15.3 mg) which was purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to yield **15a** (5.8 mg, 38%), *Rf* 0.41, as colorless prisms of mp 192—193°C (from ethanol). IR ν_{max} cm^{-1}: 3450 (NH), 1660 (NC=O). ^1H NMR (100 MHz) δ: 7.68 (1H, d, *J* 2 Hz, 5-H), 7.61 (1H, d, *J* 8 Hz, 8-H), 7.38 (1H, dd, *J* 8 and 2 Hz, 7-H), 7.15 (1H, d, *J* 8 Hz, 6′-H), 7.10 (2H, s, 1- and 4-H's), 6.99 (1H, d, *J* 8 Hz, 5′-H), 6.01 (2H, s, 2,3-OCH_2O), 5.39 (1H, q, *J* 5 Hz, 2′-CONHMe),[15] 3.92 (3H, s, 3′-OMe), 3.90 (3H, s, 4′-OMe), 2.67 (3H, d, *J* 5 Hz, 2′-CONHMe).[16] MS Calcd for $C_{21}H_{19}NO_5$: M, 365.126. Found *m/e*: M^+, 365.127.

12-Anilino-*cis*-4b,*cis*-10b,11,12-tetrahydro-7,8-dimethoxy-2,3-methylenedioxynaphtho[1,2-*c*]isocoumarin (16)——A solution of **14a** (20.3 mg) and conc. HCl (1 drop) in methanol (1 ml) was stirred at room temperature for 24 h. Work-up of the reaction mixture gave an oil (19.7 mg) which was purified by prep. TLC (benzene/ethyl acetate=10/1, v/v) to yield **16** (15.9 mg, 84%), *Rf* 0.38, as colorless prisms of mp 166—168°C (from methanol). IR ν_{max} cm^{-1}: 3420 (NH), 1725 (OC=O). ^1H NMR (100 MHz) δ: 7.14—6.63 (9H, m, aromatic H's), 5.94 (2H, s, 2,3-OCH_2O), 5.26 (1H, d, *J* 4 Hz, 4b-H), 4.61 (1H, t, *J* 3 Hz, 12-H), 3.94 (3H, s, 7-OMe), 3.92 (1H, s, 12-NHPh),[15] 3.84 (3H, s, 8-OMe), 3.35 (1H, dt, *J* 4 and 8 Hz, 10b-H), 2.19 (2H, dd, *J* 8 and 3 Hz, 11-H_2). MS Calcd for $C_{26}H_{23}NO_6$: M, 445.153. Found *m/e*: M^+, 445.153.

Reaction of 16 with Methylamine to 14a——A suspension of **16** (10.0 mg) in 40% aq. methylamine (1 ml) was stirred at room temperature for 24 h. After concentration *in vacuo*, the residue was extracted with benzene. Work-up gave **14a** (8.1 mg, 76%) as colorless prisms of mp 148—150°C (from ethanol).

2-3′,4′-Dimethoxy-2′-methylcarbamoylphenyl-1,4-dihydro-6,7-methylenedioxy-1-oxo-4-phenyliminonaphthalene (17a)——A solution of **12a** (102 mg) and DDQ (100 mg) in benzene (20 ml) was refluxed for 20 min. The reaction mixture was washed with 10% aq. NaOH and water, then dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a red oil (*ca.* 100 mg) which was purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to yield **17a** (75 mg, 74%), *Rf* 0.44, as red prisms of mp 192.5—193°C (from ether). IR ν_{max} cm^{-1}: 3440 (NH), 1650 (C=O and NC=O). ^1H NMR (100 MHz) δ: 7.86 (1H, s, 5-H), 7.51 (1H, s, 8-H), 7.46—6.87 (8H, m, 3- and aromatic H's), 6.07 (2H, s, 6,7-OCH_2O), 4.02 (1H, q, *J* 5 Hz, 2′-CONHMe),[15] 3.85 (3H, s, 3′-OMe), 3.79 (3H, s, 4′-OMe), 2.84 (3H, d, *J* 5 Hz, 2′-CONHMe).[16] *Anal.* Calcd for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95. Found: C, 69.12; H, 4.76; N, 5.91. MS *m/e*: M^+, 470.148 (M, 470.148 for $C_{27}H_{22}N_2O_6$).

1,2,3,4-Tetrahydro-6,7-methylenedioxy-1-oxo-4-phenyliminonaphthalene-2-spiro-3′-6′,7′-dimethoxy-2′-methylisoindolinone (18)——40% methanolic Triton B (8.8 mg) was added to a solution of **17a** (10.0 mg) in methanol (2 ml), and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and extracted with benzene. Work-up gave an oil (10.0 mg) which was purified by prep. TLC (chloroform/ethyl acetate=3/1, v/v) to yield **18** (9.6 mg, 96%), *Rf* 0.55, as a yellow oil. IR ν_{max} cm^{-1}: 1700 (C=O and NC=O). ^1H NMR (90 MHz) δ: 7.88 (1H, s, 5-H), 7.47 (1H, s, 8-H), 7.33—7.02 (3H, m, aromatic H's), 6.89 (1H, d, *J* 8 Hz, 5′-H), 6.82 (1H, d, *J* 8 Hz, 4′-H), 6.60—6.50 (2H, m, aromatic H's), 6.15 (2H, s, 6,7-OCH_2O), 4.04 (3H, s, 7′-OMe), 3.81 (3H, s, 6′-OMe), 3.29 (1H, d, *J* 15 Hz, 3-H), 2.97 (3H, s, 2′-Me), 2.96 (1H, d, *J* 15 Hz, 3-H). MS Calcd for $C_{27}H_{22}N_2O_6$: M, 470.148. Found *m/e*: M^+, 470.147.

1,2,3,4-Tetrahydro-6,7-methylenedioxy-1,4-dioxonaphthalene-2-spiro-3′-6′,7′-dimethoxy-2′-methylisoindolinone (19)——A solution of **18** (9.4 mg) and 10% HCl (1 drop) in methanol (1 ml) was stirred at room temperature for 15 min. After concentration *in vacuo*, the residue was extracted with benzene. Work-up gave **19** (7.6 mg, 96%) as colorless prisms of mp 130.5—132°C (from benzene). IR ν_{max} cm^{-1}: 1700 (C=O and NC=O). ^1H NMR (100 MHz) δ: 7.58 (1H, s, 5-H), 7.46 (1H, s, 8-H), 6.83 (1H, d, *J* 8 Hz, 5′-H), 6.53 (1H, d, *J* 8 Hz, 4′-H), 6.20 (2H, s, 6,7-OCH_2O), 4.07 (3H, s, 7′-OMe), 3.80 (3H, s, 6′-OMe), 3.63 (1H, d, *J* 16 Hz, 3-H), 3.07 (3H, s, 2′-Me), 2.91 (1H, d, *J* 16 Hz, 3-H). MS Calcd for $C_{21}H_{17}NO_7$: M, 395.101. Found *m/e*: M^+, 395.100.

2-3′,4′-Dimethoxy-2′-methylcarbamoylphenyl-6,7-methylenedioxy-1,4-naphthoquinone (20a)——Conc. HCl (2 drops) and water (1 ml) were added to a solution of **17a** (17.5 mg) in benzene (1.5 ml), and the mixture was vigorously stirred at 90°C for 3 h. The benzene phase was washed with 5% aq. Na_2CO_3 and water, then dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded yellow crystals (15.1 mg) which were recrystallized from ethanol to yield **20a** (6.2 mg, 42%) as yellow plates of mp 205—206°C. IR ν_{max} cm^{-1}: 3450 (NH), 1650 (NC=O). ^1H NMR (100 MHz) δ: 7.47, 7.44 (1H each, s, 5- and 8-H's), 7.04 (2H, s, 5′- and 6′-H's), 6.78 (1H, s, 3-H), 6.10 (2H, s, 6,7-OCH_2O), 3.92 (3H, s, 3′-OMe), 3.88 (1H, br s, 2′-CONHMe),[15] 3.85 (3H, s, 4′-OMe), 2.85 (3H, d, *J* 5 Hz, 2′-CONHMe).[16] MS Calcd for $C_{21}H_{17}NO_7$: M, 395.101. Found *m/e*: M^+, 395.100.

Work-up of the mother liquor gave a mixture of **19** and **20a** (8.5 mg) which could not be purified by prep. TLC.

Conversion of 20a to 19——a) A solution of **20a** (20 mg) and DBU (0.8 mg) in benzene (15 ml) was stirred at room temperature for 24 h. The reaction mixture was washed with water and dried over Na_2SO_4. Work-up gave light yellow crystals (19.8 mg) which were recrystallized from benzene to yield **19** (17.6 mg, 88%) as colorless prisms of mp 130.5—132°C.

b) A solution of **20a** (1.0 mg) in 25% methanolic KOH (1 drop) was allowed to stand at room tempera-

ture for 45 min. Work-up of the reaction mixture afforded **19** (0.8 mg, 80%), which was identified by TLC.

***cis*-4-Anilino-2-3′,4′-dimethoxy-2′-methoxycarbonylphenyl-6,7-methylenedioxy-α-tetralone (21a) and the *trans* Isomer (22a)**——A solution of **12a** (100 mg) in 10% KOH/ethylene glycol (1 g) was stirred at 130°C for 3 min. After concentration *in vacuo*, the residue was acidified with 5% acetic acid, and extracted with chloroform. The chloroform phase was washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oil (104 mg). A solution of the oil (104 mg) in chloroform (1.5 ml) was added to an excess of ethereal diazomethane, and the mixture was allowed to stand at room temperature for 1 h. Work-up of the reaction mixture gave an oil (98 mg), which was purified by prep. TLC (chloroform/methanol=10/1, v/v) to yield **21a** (55.0 mg, 55%), *Rf* 0.40, and **22a** (22.0 mg, 22%), *Rf* 0.28.

The *cis* Isomer (**21a**): Colorless granules of mp 167—169°C (from ethanol). IR ν_{max} cm^{-1}: 3440 (NH), 1722 (OC=O), 1672 (C=O). ^1H NMR (100 MHz) δ: 7.50 (1H, s, 8-H), 7.20—7.10 (2H, m, aromatic H's), 6.99—6.64 (6H, m, aromatic H's), 6.00 (2H, s, 6,7-OCH_2O), 4.83 (1H, dd, *J* 12 and 4 Hz, 4-H), 3.92 (1H, dd, *J* 12 and 4 Hz, 2-H), 3.86 (4H, s, 4-NHPh[15] and 2′-COOMe), 3.82 (6H, s, 3′- and 4′-OMe's), 2.66 (1H, dt, *J* 12 and 4 Hz, 3-H), 2.29 (1H, q, *J* 12 Hz, 3-H). *Anal.* Calcd for $C_{27}H_{25}NO_7$: C, 68.20; H, 5.30; N, 2.95. Found: C, 68.31; H, 5.32; N, 2.94. MS *m/e*: M^+, 475.163 (M, 475.163 for $C_{27}H_{25}NO_7$).

The *trans* Isomer (**22a**): Light yellow prisms of mp 166—168.5°C (from ethanol/ether). IR ν_{max} cm^{-1}: 3440 (NH), 1727 (OC=O), 1675 (C=O). ^1H NMR (100 MHz) δ: 7.53 (1H, s, 8-H), 7.19—7.09 (2H, m, aromatic H's), 6.95—6.60 (6H, m, aromatic H's), 6.02 (2H, s, 6,7-OCH_2O), 4.68 (1H, t, *J* 4 Hz, 4-H), 4.21 (1H, dd, *J* 12 and 4 Hz, 2-H), 3.83 (7H, s, 4-NHPh,[15] 3′- and 4′-OMe's), 3.53 (3H, s, 2′-COOMe), 2.68 (1H, dt, *J* 12 and 4 Hz, 3-H), 2.49 (1H, dt, *J* 4 and 12 Hz, 3-H). *Anal.* Calcd for $C_{27}H_{25}NO_7$: C, 68.20; H, 5.30; N, 2.95. Found: C, 68.05; H, 5.23; N, 2.78. MS *m/e*: M^+, 475.163 (M, 475.163 for $C_{27}H_{25}NO_7$).

2-3′,4′-Dimethoxy-2′-methoxycarbonylphenyl-1,4-dihydro-6,7-methylenedioxy-1-oxo-4-phenyliminonaphthalene (23a)——A solution of **12a** (106 mg) in 10% KOH/ethylene glycol (1.1 g) was stirred at 130°C for 5 min. Work-up of the reaction mixture gave an oil (107 mg), which was dissolved in chloroform (2 ml) and treated with an excess of ethereal diazomethane to give a mixture of **21a** and **22a** (104 mg).

DDQ (100 mg) was added to a solution of the mixture of **21a** and **22a** (104 mg) in benzene (5 ml), and the mixture was refluxed for 1.5 h. Work-up of the reaction mixture gave a red oil (99 mg), which was chromatographed over neutral alumina (grade III) (10 g) using benzene/ethyl acetate (20/1, v/v) as an eluent to yield **23a** (76 mg, 72%) as red prisms of mp 158—159.5°C (from ethanol). IR ν_{max} cm^{-1}: 1730 (OC=O), 1645 (C=O). ^1H NMR (100 MHz) δ: 7.87 (1H, s, 5-H), 7.56 (1H, s, 8-H), 7.46—6.86 (8H, m, 3- and aromatic H's), 6.06 (2H, s, 6,7-OCH_2O), 3.89 (3H, s, 3′-OMe), 3.85 (3H, s, 4′-OMe), 3.68 (3H, s, 2′-COOMe). *Anal.* Calcd for $C_{27}H_{21}NO_7$: C, 68.78; H, 4.49; N, 2.97. Found: C, 68.89; H, 4.47; N, 2.76. MS *m/e*: M^+, 471.132 (M, 471.132 for $C_{27}H_{21}NO_7$).

1,4-Dihydro-2-2′-methoxycarbonyl-3′,4′-methylenedioxyphenyl-6,7-methylenedioxy-1-oxo-4-phenyliminonaphthalene (23b)——Red prisms of mp 117.5—118.5°C (from ethanol). Yield, 82%. IR ν_{max} cm^{-1}: 1722 (OC=O), 1648 (C=O). ^1H NMR (90 MHz) δ: 7.88 (1H, s, 5-H), 7.55 (1H, s, 8-H), 7.46—6.58 (8H, m, 3- and aromatic H's), 6.09, 6.07 (2H each, s, 6,7- and 3′,4′-OCH_2O's), 3.70 (3H, s, 2′-COOMe). MS Calcd for $C_{26}H_{17}NO_7$: M, 455.101. Found *m/e*: M^+, 455.100.

2-3′,4′-Dimethoxy-2′-methoxycarbonylphenyl-6,7-methylenedioxy-1,4-naphthoquinone (24a)——A solution of **23a** (50.3 mg) and 10% HCl (1 drop) in methanol (6 ml) was stirred at room temperature for 30 min. After concentration *in vacuo*, the residue was extracted with benzene. Work-up gave orange crystals (42.6 mg), which were purified by prep. TLC (benzene/ethyl acetate=5/1, v/v) to yield **24a** (42.2 mg, 99%) as orange needles of mp 194.5—195.5°C (from ethanol). IR ν_{max} cm^{-1}: 1720 (OC=O), 1652 (C=O). ^1H NMR (100 MHz) δ: 7.46 (2H, s, 5- and 8-H's), 7.04 (2H, s, 5′- and 6′-H's), 6.83 (1H, s, 3-H), 6.10 (2H, s, 6,7-OCH_2O), 3.95 (3H, s, 3′-OMe), 3.92 (3H, s, 4′-OMe), 3.73 (3H, s, 2′-COOMe). *Anal.* Calcd for $C_{21}H_{16}O_8$: C, 63.64; H, 4.07. Found: C, 63.45; H, 4.02. MS *m/e*: M^+, 396.085 (M, 396.085 for $C_{21}H_{16}O_8$).

2-2′-Methoxycarbonyl-3′,4′-methylenedioxyphenyl-6,7-methylenedioxy-1,4-naphthoquinone (24b)——Orange needles of mp 216—217°C (from methanol). Yield, 98%. IR ν_{max} cm^{-1}: 1720 (OC=O), 1655 (C=O). ^1H NMR (90 MHz) δ: 7.46 (2H, s, 5- and 8-H's), 6.95 (1H, d, *J* 8 Hz, 6′-H), 6.81 (1H, s, 3-H), 6.81 (1H, d, *J* 8 Hz, 5′-H), 6.12, 6.09 (2H each, s, 6,7- and 3′,4′-OCH_2O's), 3.70 (3H, s, 2′-COOMe). MS Calcd for $C_{20}H_{12}O_8$: M, 380.053. Found *m/e*: M^+, 380.053.

2-3′,4′-Dimethoxy-2′-methoxycarbonylphenyl-2,3-epoxy-2,3-dihydro-6,7-methylenedioxy-1,4-naphthoquinone (25a)——*tert*-Butyl hydroperoxide (75%) (142 mg) and DBU (5.9 mg) were added to a solution of **24a** (138 mg) in benzene (5 ml), and the mixture was stirred at room temperature for 24 h. The benzene phase was washed with 10% HCl, aq. $Na_2S_2O_3$ and water, then dried over Na_2SO_4. Work-up gave a yellow oil (140 mg), which was purified by prep. TLC (benzene/ethyl acetate=5/1, v/v) to yield **25a** (130 mg, 90%), *Rf* 0.49, as colorless pillars of mp 185.5—186°C (from ethanol). IR ν_{max} cm^{-1}: 1710 (OC=O), 1687 (C=O). ^1H NMR (100 MHz) δ: 7.45, 7.39 (1H each, s, 5- and 8-H's), 7.23 (1H, d, *J* 9 Hz, 6′-H), 7.06 (1H, d, *J* 9 Hz, 5′-H), 6.13 (2H, s, 6,7-OCH_2O), 3.92 (6H, s, 3′- and 4′-OMe's), 3.83 (1H, s, 3-H), 3.65 (3H, s, 2′-COOMe). *Anal.* Calcd for $C_{21}H_{16}O_9$: C, 61.17; H, 3.91 Found: C, 61.08; H, 3.92. MS *m/e*: M^+, 412.080 (M, 412.079 for $C_{21}H_{16}O_9$).

2,3-Epoxy-2,3-dihydro-2-2′-methoxycarbonyl-3′,4′-methylenedioxyphenyl-6,7-methylenedioxy-1,4-naphthoquinone (25b)——Procedure: reaction time, 48 h. Colorless granules of mp 270.5—271.5°C (from

ethanol). Yield, 67%. IR ν_{max} cm^{-1}: 1710 (OC=O), 1688 (C=O). ^{1}H NMR (90 MHz) δ: 7.46, 7.43 (1H each, s, 5- and 8-H's), 7.09 (1H, d, J 8 Hz, 6'-H), 6.98 (1H, d, J 5'-H), 6.12 (4H, s, 6,7- and 3',4'-OCH_2O's), 3.79 (1H,-s, 3-H), 3.68 (3H, s, 2'-COOMe). MS Calcd for $C_{20}H_{12}O_9$: M, 396.048. Found m/e: M$^+$, 396.048.

The naphthoquinone (**24b**) (5.6 mg, 28%) was recovered.

2-3',4'-Dimethoxy-2'-methoxycarbonylphenyl-2,3-epoxy-1,2,3,4-tetrahydro-6,7-methylenedioxy-1-oxo-4-phenyliminonaphthalene (26a)——*tert*-Butyl hydroperoxide (75%) (36 mg) and DBU (2 mg) were added to a solution of **23a** (50.0 mg) in benzene (8 ml), and the mixture was stirred at room temperature for 84 h. Work-up of the reaction mixture gave an oil (60.0 mg), which was purified by prep. TLC (benzene/ethyl acetate=10/1, v/v) to yield **26a** (35.5 mg, 69%), *Rf* 0.59, as yellow prisms of mp 181.5—183°C (from ethanol). IR ν_{max} cm^{-1}: 1712 (OC=O), 1685 (C=O). ^{1}H NMR (100 MHz) δ: 7.72 (1H, s, 5-H), 7.46 (1H, s, 8-H), 7.39 (1H, d, J 8 Hz, 6'-H), 7.25 (1H, d, J 8 Hz, 5'-H), 7.18—7.11 (2H, m, aromatic H's), 7.03—6.93 (3H, m, aromatic H's), 6.10 (2H, s, 6,7-OCH_2O), 4.03 (1H, s, 3-H), 3.89 (3H, s, 3'-OMe), 3.84 (3H, s, 4'-OMe), 3.64 (3H, s, 2'-COOMe). *Anal.* Calcd for $C_{27}H_{21}NO_8$: C, 66.52; H, 4.34; N, 2.87. Found: C, 66.34; H, 4.40; N, 2.81. MS m/e: M$^+$, 487.126 (M, 487.127 for $C_{27}H_{21}NO_8$).

From the zone with *Rf* 0.54, **23a** (15.6 mg, 31%) was recovered.

Hydrolysis of 26a to 25a——A solution of **26a** (23.3 mg) and 10% HCl (2 drops) in methanol (3 ml) was stirred at room temperature for 30 min. Work-up of the reaction mixture quantitatively afforded **25a** (19.7 mg) as colorless pillars of mp 184—186°C (from ethanol).

***trans*-2-3',4'-Dimethoxy-2'-methoxycarbonylphenyl-2,3-epoxy-*cis*-4-hydroxy-6,7-methylenedioxy-α-tetralone (27a), the *trans*-4-Hydroxy Isomer (28a), *trans*-2-3',4'-Dimethoxy-2'-methoxycarbonylphenyl-*cis*-2,3-epoxy-1,2,3,4-tetrahydro-1, *trans*-4-dihydroxy-6,7-methylenedioxynaphthalene (29a) and *r*-2-*O*-*trans*-3,*cis*-4-Dihydroxy-6,7-methylenedioxy-α-tetralone-2-spiro-3'-6',7'-dimethoxyphthalide (30)**——a) $NaBH_4$ (35 mg) was added to a solution of **25a** (148 mg) in ethanol/tetrahydrofuran (1/2, v/v) (9 ml). The mixture was stirred at −80°C for 10 min, and then acetic acid (0.4 ml) was added. After concentration *in vacuo*, the residue was extracted with ethyl acetate. Work-up gave an oil (145 mg), which was purified by prep. TLC (benzene/ethyl acetate=3/1, v/v) to yield **27a** (16.9 mg, 11%), *Rf* 0.57, **28a** (101 mg, 67%), *Rf* 0.45, **29a** (11.7 mg, 8%), *Rf* 0.42, and **30** (2.1 mg, 2%), *Rf* 0.23.

The *cis*-Epoxy Ketol (**27a**): Colorless prisms of mp 202—203.5°C (from ethanol). IR ν_{max} cm^{-1}: 3510 (OH), 1701 (OC=O), 1684 (C=O); hydrogen-bonding, 3515 (ε=93.4) (OH····O) ($c=8.2\times10^{-4}$ mol/l). ^{1}H NMR (100 MHz) δ: 7.38 (1H, s, 8-H), 7.24 (1H, d, J 9 Hz, 6'-H), 7.04 (1H, d, J 9 Hz, 5'-H), 6.92 (1H, s, 5-H), 6.03 (2H, s, 6,7-OCH_2O), 5.05 (1H, dd, J 12 and 3 Hz, 4-H),[17] 3.89 (3H, s, 3'-OMe), 3.88 (3H, s, 4'-OMe), 3.76 (3H, s, 2'-COOMe), 3.73 (1H, d, J 3 Hz, 3-H), 3.51 (1H, d, J 12 Hz, 4-OH).[15] MS Calcd for $C_{21}H_{18}O_9$: M, 414.095. Found m/e: M$^+$, 414.096.

The *trans*-Epoxy Ketol (**28a**): Colorless prisms of mp 187.5—189°C (from ethanol). IR ν_{max} cm^{-1}: 3580 (OH), 1713 (OC=O), 1685 (C=O); hydrogen-bonding, 3581 (ε=142.6) (OH····π) ($c=7.9\times10^{-4}$ mol/l). ^{1}H NMR (100 MHz) δ: 7.35 (1H, s, 8-H), 7.23 (1H, d, J 9 Hz, 6'-H), 7.15 (1H, s, 5-H), 7.02 (1H, d, J 9 Hz, 5'-H), 6.02 (2H, s, 6,7-OCH_2O), 5.13 (1H, dd, J 11 and 2 Hz, 4-H),[18] 3.91 (3H, s, 3'-OMe), 3.89 (3H, s, 4'-OMe), 3.81 (1H, d, J 2 Hz, 3-H), 3.69 (3H, s, 2'-COOMe), 2.62 (1H, d, J 11 Hz, 4-OH).[15] *Anal.* Calcd for $C_{21}H_{18}O_9$: C, 60.87; H, 4.38. Found: C, 60.89; H, 4.42. MS m/e: M$^+$, 414.095 (M, 414.095 for $C_{21}H_{18}O_9$).

The *trans*-Dihydroxy Epoxide (**29a**): A colorless oil. IR ν_{max} cm^{-1}: 3580, 3400 (OH), 1720 (OC=O); hydrogen-bondings, 3581 (ε=153.4) (OH····π), 3430 (ε=48.2) (OH····O) ($c=7.9\times10^{-4}$ mol/l). ^{1}H NMR (100 MHz) δ: 7.17 (1H, d, J 8 Hz, 6'-H), 7.03, 7.00 (1H each, s, 5- and 8-H's), 6.97 (1H, d, J 8 Hz, 5'-H), 5.89 (2H, s, 6,7-OCH_2O), 4.89 (1H, d, J 8 Hz, 1-H),[16] 4.83 (1H, dd, J 12 and 2 Hz, 4-H),[18] 3.86 (3H, s, 3'-OMe), 3.84 (3H, s, 4'-OMe), 3.81 (3H, s, 2'-COOMe), 3.55 (1H, d, J 2 Hz, 3-H), 3.21 (1H, d, J 8 Hz, 1-OH),[15] 2.43 (1H, d, J 12 Hz, 4-OH).[15] MS Calcd for $C_{21}H_{20}O_9$: M, 416.111. Found m/e: M$^+$, 416.111.

The Phthalide (**30**): Colorless granules of mp 135—136°C (from ethanol). IR ν_{max} cm^{-1}: 3570, 3420 (OH), 1770 (OC=O), 1685 (C=O). ^{1}H NMR (100 MHz) δ: 7.30 (1H, d, J 8 Hz, 4'-H), 7.26 (1H, s, 8-H), 7.13 (1H, d, J 8 Hz, 5'-H), 7.02 (1H, s, 5-H), 6.02 (2H, s, 6,7-OCH_2O), 5.11 (1H, d, J 4 Hz, 4-H), 4.28 (1H, d, J 4 Hz, 3-H), 4.01 (3H, s, 7'-OMe), 3.90 (2H, s, 3- and 4-OH's),[15] 3.85 (3H, s, 6'-OMe). MS Calcd for $C_{20}H_{16}O_9$: M, 400.079. Found m/e: M$^+$, 400.080.

b) Lithium tri-*tert*-butoxyaluminohydride (30 mg) was added to a solution of **25a** (22.7 mg) in anhyd. tetrahydrofuran (1 ml). The mixture was stirred at −70°C for 2 h, and then acetic acid (0.2 ml) was added. Work-up of the reaction mixture gave **27a** (10.2 mg, 45%) and **28a** (8.7 mg, 38%).

2,3-Epoxy-*cis*-4-hydroxy-*trans*-2-2'-methoxycarbonyl-3',4'-methylenedioxyphenyl-6,7-methylenedioxy-α-tetralone (27b) and the *trans*-4-Hydroxy Isomer (28b)——Procedure: reagent, lithium tri-*tert*-butoxyaluminohydride; reaction temperature, −35°C; time, 3 h.

The *cis*-Epoxy Ketol (**27b**): Colorless prisms of mp 229.5—230.5°C (from ethanol). Yield, 84%. IR ν_{max} cm^{-1}: 3500 (OH), 1702 (OC=O), 1687 (C=O); hydrogen-bonding, 3520 (ε=119.4) (OH····O) ($c=5.0\times10^{-4}$ mol/l). ^{1}H NMR (90 MHz) δ: 7.41 (1H, s, 8-H), 7.09 (1H, d, J 8 Hz, 6'-H), 6.96 (1H, d, J 8 Hz, 5'-H), 6.94 (1H, s, 5-H), 6.07 (2H, s, 3',4'-OCH_2O), 6.00 (2H, s, 6,7-OCH_2O), 5.02 (1H, dd, J 12 and 2 Hz, 4-H),[18] 3.77 (3H, s, 2'-COOMe), 3.72 (1H, d, J 2 Hz, 3-H), 3.45 (1H, d, J 12 Hz, 4-OH).[15] MS Calcd for $C_{20}H_{14}O_9$: M, 398.064. Found m/e: M$^+$, 398.063.

The *trans*-Epoxy Ketol (**28b**): A colorless oil. Yield, 15%. IR ν_{max} cm^{-1}: 3575 (OH), 1714 (OC=O),

1690 (C=O); hydrogen-bonding, 3584 (ε=156.8) (OH····π) ($c=5.5\times10^{-4}$ mol/l). ^{1}H NMR (90 MHz) δ: 7.34 (1H, s, 8-H), 7.13 (1H, s, 5-H), 7.08 (1H, d, J 8 Hz, 6′-H), 6.94 (1H, d, J 8 Hz, 5′-H), 6.08 (2H, s, 3′,4′-OCH$_2$O), 6.00 (2H, s, 6,7-OCH$_2$O), 5.18 (1H, dd, J 10 and 3 Hz, 4-H),[17] 3.77 (1H, d, J 3 Hz, 3-H), 3.70 (3H, s, 2′-COOMe), 2.71 (1H, d, J 10 Hz, 4-OH).[15] MS Calcd for $C_{20}H_{14}O_9$: M, 398.064. Found m/e: M$^+$, 398.064.

Conversion of 28a to 30——Column chromatography of **28a** (49.7 mg) was performed on silica gel (3 g). The first fraction (benzene/ethyl acetate=95/5, v/v) gave **28a** (26.6 mg, 54%). The second (benzene/ethyl acetate=1/1, v/v) afforded an oil (21 mg), which was purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to yield **30** (16.1 mg, 34%), *Rf* 0.23, as colorless granules of mp 135—136°C (from ethanol).

***trans*-2-3′,4′-Dimethoxy-2′-methoxycarbonylphenyl-*cis*-2,3-epoxy-1,2,3,4-tetrahydro-1,*cis*-4-dihydroxy-6,7-methylenedioxynaphthalene (32a)**——$NaBH_4$ (11.7 mg) was added to a solution of **27a** (40.6 mg) in methanol (16 ml). The mixture was stirred at −50°C for 1.5 h, and then acetic acid (0.2 ml) was added. Work-up of the reaction mixture gave an oil (38.6 mg), which was purified by prep. TLC (benzene/ethyl acetate=1/1, v/v) to yield **32a** (37.4 mg, 92%), *Rf* 0.40, as a colorless oil. IR ν_{max} cm^{-1}: 3575, 3500 (OH), 1714 (OC=O); hydrogen-bondings, 3610 (ε=40.5), 3579 (ε=88.0) (OH····π), 3535 (ε=63.5), 3425 (ε=24.3) (OH····O) ($c=7.7\times10^{-4}$ mol/l). ^{1}H NMR (90 MHz) δ: 7.29 (1H, d, J 9 Hz, 6′-H), 7.14, 6.78 (1H each, s, 5- and 8-H's), 7.03 (1H, d, J 9 Hz, 5′-H), 5.94 (2H, s, 6,7-OCH$_2$O), 5.08 (1H, d, J 10 Hz, 1-H),[16] 4.93 (1H, dd, J 9 and 3 Hz, 4-H),[17] 3.86 (9H, s, 2′-COOMe, 3′- and 4′-OMe's), 3.52 (1H, d, J 3 Hz, 3-H), 2.80 (1H, d, J 10 Hz, 1-OH),[15] 2.51 (1H, d, J 9 Hz, 4-OH).[15] Decoupling: δ 5.08 (1-H)→δ 2.80 (d→s, 1-OH); δ 4.93 (4-H)→δ 3.52 (d→s, 3-H), 2.51 (d→s, 4-OH); δ 3.52 (3-H)→δ 4.93 (dd→d, J 9 Hz, 4-H); δ 2.80 (1-OH)→δ 5.08 (d→s, 1-H). MS Calcd for $C_{21}H_{20}O_9$: M, 416.111. Found m/e: M$^+$, 416.112.

***cis*-2,3-Epoxy-1,2,3,4-tetrahydro-1,*cis*-4-dihydroxy-*trans*-2-2′-methoxycarbonyl-3′,4′-methylenedioxyphenyl-6,7-methylenedioxynaphthalene (32b)**——Procedure: reaction time, 20 h. Colorless granules of mp 214—216°C (from chloroform). Yield, 28%. IR ν_{max} cm^{-1}: 3575, 3500 (OH), 1708 (OC=O); hydrogen-bondings, 3580 (ε=128.1) (OH····π), 3535 (ε=123.7) (OH····O) ($c=4.7\times10^{-4}$ mol/l). ^{1}H NMR (90 MHz) δ: 7.15 (1H, d, J 8 Hz, 6′-H), 7.07, 6.86 (1H each, s, 5- and 8-H's), 6.99 (1H, d, J 8 Hz, 5′-H), 6.09 (2H, s, 3′,4′-OCH$_2$O), 5.94 (2H, s, 6,7-OCH$_2$O), 4.99 (1H, d, J 11 Hz, 1-H),[16] 4.90 (1H, dd, J 11 and 2 Hz, 4-H),[18] 3.85 (3H, s, 2′-COOMe), 3.54 (1H, d, J 2 Hz, 3-H), 3.27, 2.16 (1H each, d, J 11 Hz, 1- and 4-OH's).[15] MS Calcd for $C_{20}H_{16}O_9$: M, 400.079. Found m/e: M$^+$, 400.078.

The *cis*-epoxy ketol (**27b**) (6.1 mg, 22%) was recovered.

Reduction of 28a to 29a——$NaBH_4$ (10 mg) was added to a solution of **28a** (37.1 mg) in methanol (6 ml). The mixture was stirred at −50°C for 35 min, and then acetic acid (0.5 ml) was added. Work-up of the reaction mixture afforded **29a** (25.8 mg, 69%) as a colorless oil.

***trans*-2-3′,4′-Dimethoxy-2′-methylcarbamoylphenyl-*cis*-2,3-epoxy-1,2,3,4-tetrahydro-1,*cis*-4-dihydroxy-6,7-methylenedioxynaphthalene (33a), 1,2,3,4-Tetrahydro-1,*cis*-3,*cis*-4-trihydroxy-6,7-methylenedioxynaphthalene-2-spiro-3′-6′,7′-dimethoxy-2′-methyl-*trans*-3′-*N*-isoindolinone (34) and 1,2,3,4-Tetrahydro-1,*cis*-3,*cis*-4-trihydroxy-6,7-methylenedioxynaphthalene-2-spiro-3′-6′,7′-dimethoxy-*trans*-3′-*O*-phthalide (35)**——A solution of **32a** (10.0 mg) in 40% aq. methylamine (0.2 ml) was allowed to stand at room temperature for 10 min. Concentration *in vacuo* at room temperature afforded **33a** (8.7 mg, 87%) as colorless crystals of mp 164—166°C. IR ν_{max} cm^{-1}: 3570, 3400 (NH and OH), 1645 (NC=O).

On standing in solvents for several hours, an equilibrium between **33a** and **34** was established in an approximate ratio of 1/1 on the basis of relative intensities of the corresponding peaks observed in the IR and ^{1}H NMR spectra. The data for **33a** are as follows. IR ν_{max} cm^{-1}: 1645 (NC=O). ^{1}H NMR (90 MHz) δ: 7.39 (1H, d, J 8 Hz, 6′-H), 7.09, 6.82 (1H each, s, 5- and 8-H's), 7.01 (1H, d, J 8 Hz, 5′-H), 5.92 (2H, s, 6,7-OCH$_2$O), *ca.* 5.92 (1H, 2′-CONHMe, overlapping with 6,7-OCH$_2$O signal),[15] 5.15 (1H, s, 1-H), 4.88 (1H, d, J 3 Hz, 4-H), 3.88 (3H, s, 3′-OMe), 3.83 (3H, s, 4′-OMe), 3.53 (1H, d, J 3 Hz, 3-H), 2.92, 2.83 (1.5 H each, d, J 5 Hz, 2′-CONHMe),[16] 2.45 (2H, s, 1- and 4-OH's).[15] The data for **34** are as follows. IR ν_{max} cm^{-1}: 1698 (NC=O). ^{1}H NMR (90 MHz) δ: 7.11, 7.03 (1H each, s, 5- and 8-H's), 6.90 (1H, d, J 8 Hz, 5′-H), 6.49 (1H, d, J 8 Hz, 4′-H), 5.98 (2H, s, 6,7-OCH$_2$O), 5.07 (1H, s, 1-H), 4.79 (1H, dd, J 8 and 2 Hz, 4-H),[19] 4.22 (1H, dd, J 8 and 2 Hz, 3-H),[19] 3.94 (3H, s, 7′-OMe), 3.78 (3H, s, 6′-OMe), 3.17 (3H, s, 2′-Me), 2.45 (3H, br s, 1-, 3- and 4-OH's).[15]

Prep. TLC (chloroform/methanol=5/1, v/v) of the equilibrated mixture (8.7 mg) afforded **34** (3.2 mg, 32%), *Rf* 0.10, and **35** (4.4 mg, 46%), *Rf* 0.36.

The Isoindolinone (**34**): A colorless oil. MS Calcd for $C_{21}H_{21}NO_8$: M, 415.127. Found m/e: M$^+$, 415.127.

The Phthalide (**35**): Colorless granules of mp 136—138°C (from ethanol). IR ν_{max} cm^{-1}: 3580, 3530, 3400 (OH), 1765 (OC=O). ^{1}H NMR (90 MHz) (dioxane) δ: 7.42, 7.34 (1H each, s, 5- and 8-H's), 7.35 (1H, d, J 8 Hz, 5′-H), 6.65 (1H, d, J 8 Hz, 4′-H), 6.25 (2H, s, 6,7-OCH$_2$O), 5.31 (1H, d, J 5 Hz, 1-H),[16] 4.86 (1H, dd, J 8 and 3 Hz, 4-H),[19] 4.26 (1H, dd, J 8 and 3 Hz, 3-H),[19] 4.12 (3H, s, 7′-OMe), 3.95 (3H, s, 6′-OMe), 2.59 (3H, br s, 1-, 3- and 4-OH's).[15] MS Calcd for $C_{20}H_{18}O_9$: M, 402.095. Found m/e: M$^+$, 402.095.

1,2,3,4-Tetrahydro-1,*cis*-3,*cis*-4-trihydroxy-6,7-methylenedioxynaphthalene-2-spiro-1′-4′,5′-dimethoxy-2′-methyl-*trans*-1′-*N*-isoindoline (36)——A solution of **32a** (14.2 mg) in 40% aq. methylamine (0.2 ml) was stirred at room temperature for 10 min. Work-up of the reaction mixture gave colorless crystals (11.8 mg), which were dissolved in 1,2-dimethoxyethane (3 ml) and reduced with $LiAlH_4$ (10 mg) at 90°C for 15 min. Work-up of the reaction mixture afforded a yellow oil (6.0 mg), which was purified by prep. TLC (chloro-

form/methanol=5/1, v/v) to yield **36** (2.6 mg, 23%), *Rf* 0.65, as a light yellow oil. IR ν_{max} cm^{-1}: 3580, 3400 (OH). ^1H NMR (90 MHz) δ: 7.08, 7.05 (1H each, s, 5- and 8-H's), 6.62 (1H, d, *J* 8 Hz, 6′-H), 6.32 (1H, d, *J* 8 Hz, 7′-H), 5.98 (2H, s, 6,7-OCH_2O), 5.15 (1H, s, 1-H), 4.87 (1H, br s, W_H 6 Hz, 4-H), 4.28 (1H, br s, W_H 6 Hz, 3-H), 4.03, 3.89 (1H each, d, *J* 13 Hz, 3′-H_2), 3.85 (3H, s, 4′-OMe), 3.78 (3H, s, 5′-OMe), 2.73 (3H, s, 2′-Me), 2.41 (3H, s, 1-, 3- and 4-OH's).[15] MS Calcd for $C_{21}H_{23}NO_7$: M, 401.147. Found *m/e*: M^+, 401.148.

References and Notes

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8) Intramolecular hydrogen-bondings were observed at 3580 (ε=117.8) (OH$\cdots\pi$) and 3535 cm^{-1} (ε=108.1) (OH$\cdots$O) ($c=5.5\times10^{-4}$ mol/l, tetrachloromethane) in the IR spectrum of *cis*-2,3-epoxy-1,2,3,4-tetrahydro-1,*cis*-4-dihydroxy-*trans*-2-2′-methoxycarbonylphenylnaphthalene.[2]
9) Assignments were made by comparison with the data for related compounds.
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11) T.A. Crabb, "Annual Reports on NMR Spectroscopy," Vol. 6A, ed. by E.F. Mooney, Academic Press Inc., London, 1975, pp. 348—370, and references cited therein.
12) T.A. Crabb, "Annual Reports on NMR Spectroscopy," Vol. 8, ed. by G.A. Webb, Academic Press Inc., London, 1978, pp. 45—48, and references cited therein.
13) Other things being equal, the 5′-protons in related phthalideisoquinolines resonate at higher fields (δ 7.10—7.00) by *ca.* 0.3 ppm than the 4′-protons.[12]
14) Assignments may be reversed.
15) On addition of deuterium oxide, this signal disappeared.
16) On addition of deuterium oxide, this signal changed to a singlet.
17) On addition of deuterium oxide, this signal changed to a doublet with *J* 3 Hz.
18) On addition of deuterium oxide, this signal changed to a doublet with *J* 2 Hz.
19) On addition of deuterium oxide, this signal changed to a doublet with *J* 8 Hz.