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The synthesis of 1-benzylideneisoquinoline-3,4-diones **7** is described for the first time. This has been achieved through two new methods based on the controlled oxidation of the isoquinoline nucleus of the corresponding 1-benzylisoquinolin-3-ones.

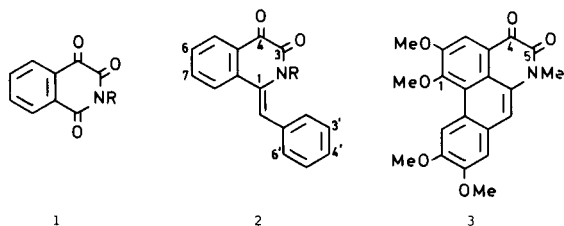
J. Heterocyclic Chem., **19**, 1469 (1982).

Although the synthesis and reactivity of isoquinoline-1,3,4-triones (Phthalonimides) **1** is well known (1), the corresponding 1-benzylidene derivatives **2** have not been described. They have the same functionalization in their isoquinoline nucleus as the 4,5-dioxoaporphine alkaloids **3**. Therefore, derivatives of **2** appear to be interesting synthetic precursors of the above alkaloids. As a preliminary stage to the total synthesis of a 4,5-dioxoaporphine, the poncevedrine **3**, (2), the synthesis of substituted 1-benzylideneisoquinoline-3,4-diones was undertaken. This has led to the synthesis of isoquinolinediones **2** through two new methods based on a controlled oxidation of compounds having a suitable carbon skeleton.

One molecule which has the above-mentioned characteristics is the 1-(3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinolin-3-one **5a** which in solution exists in a lactam-lactim tautomeric equilibrium (**5a** \rightleftharpoons **6**). It can be prepared in good yield from the self-condensation of homoveratric acid in polyphosphoric acid. Subsequent treatment of the resulting ketoacid **4a** with ammonium acetate (3) yields **5a**.

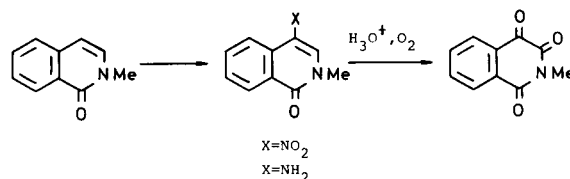
Easy specific functionalization of 6' can be achieved since it is the most reactive position for electrophilic substitution. Moreover **5a** has a carbonyl group in position 3 and its transformation into **7a** requires merely oxidation at the position 4 and generation of the benzylidene double bond.

Figure 1



In order to introduce the oxo group in position 4 of **5a**, it seemed interesting to apply the procedure of Henry *et al.* (4), used for the conversion of the 2-methylisoquinolin-1-one (5) into the corresponding phthalonimide. Based on the nitration of the former, reduction of the nitro group, hydrolysis and oxidation, it is illustrated in Scheme 1.

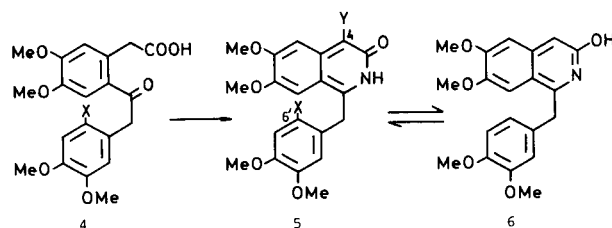
Figure II



S C H E M E I

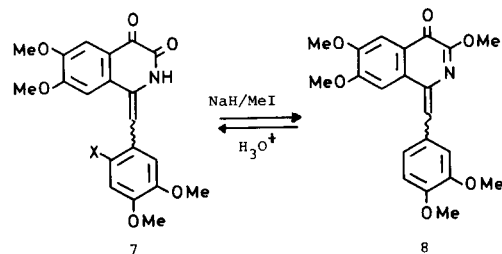
The suitability of this method for obtaining **7a** from **5a** is dependent on the regioselectivity of the nitration of **5a**. In principle, the most reactive positions of **5a** should be 4 and 6'. Thus, the nitration of 2-pyridones occurs in positions 3 and 5 (6), while in compounds like papaverine (7), analogous with **5a**, it takes place in the 6'. When **5a** was

Figure III



a) X=H
b) X=Br

a) X=Y=H
b) X=NO₂, Y=H
c) X=H, Y=NO₂
d) X=H, Y=NH₂
e) X=H, Y=Br
f) X=Br, Y=H
g) X=Br, Y=NO₂
h) X=Br, Y=NH₂



a) X=H
b) X=Br

treated with fuming nitric acid in acetic acid, a single mono-nitrated product was obtained. Its possible structure **5b** or **5c**, could not be established by nmr. However, since it is different from **5b**, prepared unambiguously by a different method (8), structure **5c** was assigned to it. This was confirmed by its subsequent chemical behaviour.

Catalytic hydrogenation (Pd/C) of **5c** gave an unstable amine **5d**. Its instability suggested that the amine must not be completely aromatic. Attempts to isolate **5d** as its hydrochloride produced a crystalline compound, which was identified as **Z-7a**. Its molecular formula $C_{20}H_{19}NO_6$ was established by analysis and mass spectrometry. The ir spectrum revealed the presence of two C=O groups at 1660 and 1690 cm^{-1} , and the nmr showed four singlets at δ 6.76, 6.85, 7.24 and 7.55 ppm whose integration indicates a total of six aromatic protons. The mother liquor from the crystallization of **Z-7a** showed two spots by tlc, one corresponding to **Z-7a**. The other, of the same colour and lower R_f , on isolation displayed similar spectroscopic properties to those of **Z-7a**. This was confirmed when equal photostationary mixtures in equilibrium (**Z-7a** \rightleftharpoons **E-7a**) were reached in few minutes, as a result of irradiating solutions of **Z-7a** and of **E-7a** with uv light. The formation of **7a** from **5d** can be explained by oxidation and hydrolysis (4).

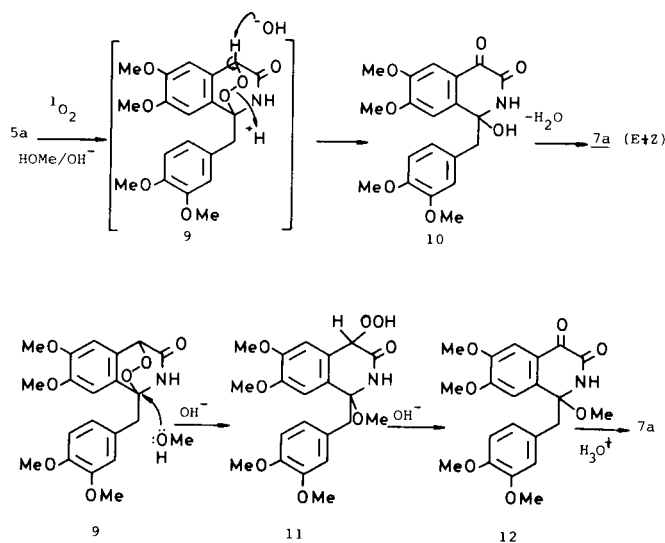
Methylation of **7a** under conditions typical of *N*-methylation of amides (9), sodium hydride/methyl iodide, gave only the *O*-methylated product **8** as deduced from its nmr spectrum which showed five methoxyl groups between δ 3.98 and 4.08 ppm. This was confirmed chemically when it was found that acid hydrolysis of **8** occurred easily giving **7a** (*E,Z* mixture) in quantitative yield.

In order to increase the ability of **7a** to photocyclize (10), the introduction of a halogen (preferably a bromine) in its 6' position was desired. Direct bromination of **7a** was attempted with bromine in acetic acid at low temperature but this gave a complex reaction mixture. Consequently, the synthesis of **7b** was projected by introducing the bromine atom at an earlier stage. It was found that the bromination of **5a** occurs in the same position as nitration, the 4-bromolactam **5e** being obtained. By bromination of **4a** with bromine in aqueous acetic acid (11), **4b** resulted. Its structure was deduced mainly from the presence in its nmr spectrum of four singlets at δ 6.72, 6.79, 7.00 and 7.34 ppm, which integrate for a total of four aromatic protons. Treatment of **4b** with ammonium acetate (3) afforded the lactam **5f**, which by nitration in the above-described conditions allowed us to obtain the 6'-bromo-4-nitroisoquinolin-3-one **5g** in good yield. Catalytic hydrogenation of **5g**, followed by hydrolysis of the amine and subsequent oxidation did not yield the desired product **7b** but **7a** instead. The loss of the bromine was attributed to the hydrogenolysis of the C-Br bond in the reduction step. In spite of at-

tempting different reaction conditions, hydrogenolysis of the bromine could not be avoided. In order to overcome this problem, a new procedure to the isoquinolinediones **7** was studied. This led to the discovery of a novel and interesting method for the synthesis of this type of compounds based on the photo-oxidation of isoquinolin-3-ones **5**.

Since it is known that the lactam **5a** is able to react as a diene with dienophiles like *N*-phenylmaleimide (3), singlet oxygen might add to **5a** giving the endoperoxide **9** (4 + 2 adduct) (12). In a basic medium, by means of a Kornblum-De la Mare reaction, (13), should be transformed into the 1-hydroxyisoquinoline-3,4-dione **10**. Through subsequent loss of water the desired product **7a** could be obtained in a "one pot" transformation (14).

Figure IV



SCHEME I

When an oxygen-saturated solution of **5a** in methanolic sodium hydroxide was irradiated until complete disappearance of the starting material, a colourless crystalline product was obtained in 80% yield. The product was not the expected **10**, but **12**. Its molecular formula $C_{21}H_{23}NO_7$ was established by mass spectrometry and elemental analysis. The presence of the methoxy group at C_1 in **12** was determined by nmr. Its 1H -nmr showed a singlet at δ 3.14 ppm, which integrated for 3H, and its ^{13}C -nmr exhibited a quaternary carbon signal at low field (δ 89.05 ppm). Structure **12** is explainable by attack of the solvent (methanol) on the endoperoxide **9**, as shown in Scheme II. The possibility that **12** may have resulted from **10** by methanolysis (13b) can not be discarded. Treatment of **12** with aqueous hydrochloric acid gave the target compound **7a**.

Finally, the use of sensitizer (eosine) in order to generate 1O_2 considerably decreased the yield of the above reaction, due to experimental difficulties in removing the sensitizer from the reaction mixture.

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were determined in potassium bromide on a Pye Unicam SP-1100 spectrophotometer. Ultraviolet spectra were recorded in ethanol solution on a Pye Unicam SP-1700 spectrophotometer. The ^1H and ^{13}C nuclear magnetic resonance spectra were determined on a Varian CFT-20 spectrophotometer in deuteriochloroform solution containing tetramethylsilane as internal standard. The tlc was carried out on silica gel GF-254 (type 60), with chloroform-ethanol (9:1) mixture as eluent. The tlc slides were visualized with uv radiation or iodine vapour. Catalytic hydrogenations were carried out in a Parr hydrogenator. Photolysis was carried out with medium-pressure mercury vapor arc lamps (Hanovia, 250 watts), using pyrex filtered light and cooling by water. The solvents were purified according to (15). 2-[(3',4'-dimethoxyphenylacetyl)-4,5-dimethoxy]phenylacetic acid **4a** and 1-(3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinolin-3-one **5a** were prepared according to (3).

1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxy-4-nitroisoquinolin-3-one (**5c**).

To a cooled suspension of the isoquinolin-3-one **5a** (1 g) in glacial acetic acid (15 ml), maintained at around 15° , 1 ml of nitrating mixture (glacial acetic acid-fuming nitric acid, 2:3 by volume) was added during five minutes with vigorous mechanical stirring. The resulting suspension was poured into 100 ml of water, and an abundant yellow precipitate was formed. The solid was filtered off, washed free of acid and crystallised from ethyl acetate to give **5c** as a yellow powder, mp 203-205 $^\circ$, yield 40%; ir: 1680 (C=O) cm^{-1} ; uv: λ max 206, 225 (sh), 243 (sh), 277, 330 (sh), 450 (sh) and 486 nm; nmr (DMSO- d_6): δ 3.67, 3.70, 3.81 and 3.87 (ss, each 3H, 4 \times MeO), 4.40 (s, 2H, -CH $_2$ -), 6.82 (s, 2H, Ar-H), 7.00, 7.07 and 7.35 (ss, each 1H, Ar-H) ppm; ms: m/e (%) 400 (18) (M $^+$), 370 (22), 369 (100), 355 (57) and 354 (28).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_7$: C, 60.00; H, 5.00; N, 7.00. Found: C, 59.76; H, 4.70; N, 6.83.

1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxy-4-aminoisoquinolin-3-one (**5d**).

A suspension of compound **5c** (1 g) in ethanol (200 ml) and 0.3 g of 10% Pd/C catalyst was hydrogenated at an initial pressure of 10 psi until uptake of hydrogen ceased. It was observed that the suspended yellow solid gradually dissolved as the hydrogenation progressed. Usual work-up produced the aminolactam **5d** (800 mg), as an unstable solid residue, which was used without further purification.

1-(E,Z)-(3',4'-Dimethoxybenzylidene)-6,7-dimethoxyisoquinoline-3,4-dione (**7a**).

A solution of the aminolactam **5d** (800 mg) in methanol (40 ml) to which 40 ml of 10% hydrochloric acid were added, was refluxed for 30 minutes and then allowed to stand for several hours. A yellow crystalline solid separated out, it was collected and washed free of acid to give Z-**7a** (250 mg).

The mother liquor from the filtration was diluted with 200 ml of water, and then extracted with chloroform. The dried extract (sodium sulfate) was concentrated and the solid residue, which showed by tlc two spots, was submitted to preparative tlc, in darkness, to give Z-**7a** (faster moving and more abundant isomer) and E-**7a**. When the above crude reaction mixture was crystallized, brown-orange crystals were obtained, mp 255-260 $^\circ$ (from chloroform-ethanol 1:1), and shown to be a mixture of Z and E-**7a** (tlc). They gave the following spectroscopic data: ir: 1660 and 1690 (C=O) cm^{-1} ; uv: λ max (log ϵ) 248 (4.25), 296 (4.15) and 420 (4.11) nm; ms: m/e (%) 369 (100) (M $^+$), 354 (14), 338 (40), 326 (40) and 298 (18).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_6$: C, 65.30; H, 4.40; N, 3.80. Found: C, 65.16; H, 4.62; N, 3.48.

Compound E-**7a**.

This compound had nmr: δ 3.40, 3.82, 3.88 and 3.95 (ss, each 3H, 4 \times MeO-), 6.79, 7.19 and 7.56 (ss, each 1H, Ar-H and C=C-H), 6.89 (s, 3H, Ar-H) and 8.75 (bs, 1H, -NH-) ppm.

Compound Z-**7a**.

This compound had nmr: δ 3.92 (s, 6H, 2 \times MeO-), 3.96 and 4.06 (ss, each 3H, 2 \times MeO), 6.76, 6.85, 7.24 and 7.55 (ss, each 1H, Ar-H and C=C-H), 6.92 (s, 2H, Ar-H) and 8.75 (bs, 1H, -NH-) ppm.

1-(3',4'-Dimethoxybenzylidene)-3,6,7-trimethoxyisoquinolin-4-one (**8**).

To a suspension of 1-benzylideneisoquinoline-3,4-dione **7a** (E,Z-mixture) (100 mg) and sodium hydride (80%) (10 mg) in 10 ml of DMF in an argon atmosphere, an excess of methyl iodide was added dropwise. The reaction mixture was stirred at room temperature for about 30 minutes until the starting material disappeared (tlc). Excess of sodium hydride was destroyed by addition of ethanol to the reaction mixture, which was then poured into 50 ml of water, neutralized with 5% hydrochloric acid and extracted with chloroform. The extract was washed with water, dried (sodium sulfate) and concentrated to give a solid residue (103 mg), which was purified by crystallization from ethanol to give red crystals, mp 199-200 $^\circ$, in 96% yield, identified as the isoquinolin-4-one **8**; ir: 1640 (C=O) cm^{-1} ; uv: λ max 215, 248, 290, 320 and 466 nm; nmr: δ 3.98 (s, 9H, 3 \times MeO-Ar), 4.08 (s, 6H, MeO-Ar and MeO-C $_3$), 6.90 (d, J = 5 Hz, 1H, Ar-H), 7.19 and 7.34 (ss, each 1H, Ar-H and C=C-H), 7.45-7.61 (m, 2H, Ar-H) and 8.19 (d, J = 1.6 Hz, 1H, Ar-H) ppm; ms: m/e (%) 383 (100) (M $^+$), 368 (53), 352 (39), 340 (31), and 309 (56).

Hydrolysis of the Isoquinolin-4-one (**8**).

To a solution of isoquinolin-4-one **8** (50 mg) in methanol (20 ml) 20 ml of 10% hydrochloric acid were added, and it was refluxed for 30 minutes. The reaction mixture was poured into 100 ml of water, neutralized with 5% sodium hydroxide and extracted with chloroform. The dried extract (sodium sulfate) was concentrated to give a solid residue (49 mg) which was identified as **7a** (E,Z-mixture).

1-(3',4'-Dimethoxybenzyl)-6,7-dimethoxy-4-bromoisoquinolin-3-one (**5e**).

One g of the lactam **5a** was dissolved, by heating, in 5 ml of glacial acetic acid, and the resulting solution was cooled externally in an ice-water bath, care being taken that the reaction mixture should not solidify. To this stirred suspension, 1.5 ml of a solution of 10% bromine in glacial acetic acid was added during 30 minutes, and the mixture was stirred for about five hours until no starting material was observed by tlc. The yellow reaction mixture was poured into 50 ml of water, basified with ammonia, and extracted with chloroform. The dried extracts (sodium sulfate) were concentrated to give a solid residue (1.1 g). This was crystallized from chloroform to afford yellow microcrystals, mp 242-244 $^\circ$, which were identified as **5e**; ir: 1690 (C=O) cm^{-1} ; uv: λ max 245, 280, 321 and 418 nm; nmr: δ 3.73, 3.74, 3.87 and 3.98 (ss, each 3H, 4 \times MeO-), 4.40 (s, 2H, -CH $_2$ -), 6.70, 7.04 and 7.08 (ss, each 1H, Ar-H), 6.75 and 6.97 (AB dd, J = 1.9 Hz, each 1H, Ar-H) ppm; ms: m/e (%) 435-433 (10) (M $^+$).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{BrNO}_5$: C, 55.29; H, 4.64; N, 3.22; Br, 18.41. Found: C, 55.66; H, 4.80; N, 3.44; Br, 18.56.

2-[(3',4'-Dimethoxy-6'-bromophenylacetyl)-4,5-dimethoxy]phenylacetic Acid (**4b**).

To a cooled solution of the ketoacid **4a** (1 g) in acetic acid-water (50 ml), kept around 10° , 1.3 ml of 10% solution of bromine in acetic acid was added dropwise and the mixture was stirred for an hour at room temperature. The reaction mixture was poured into 100 ml of water and extracted with chloroform. The dried extract (sodium sulfate) was concentrated to give the bromoketoacid **4b** as white crystals, mp 193-195 $^\circ$, yield 83%; ir: 1670 (C=O), 1720 and 2500-3300 (COOH), cm^{-1} ; uv: λ max (log ϵ) 235 (4.31), 282 (3.99), and 310 (sh, 3.77) nm; nmr: δ 3.79 (s, 5H, MeO- and -CH $_2$ -COOH), 3.83 (s, 3H, MeO-), 3.91 (s, 6H, 2 \times MeO-), 4.32 (s, 2H, -CH $_2$ -CO-), 6.72, 6.79, 7.00 and 7.34 (ss, each 1H, Ar-H) ppm; ms: m/e (%) 454-452 (2) (M $^+$), 434-432 (7), 355 (23), 223 (23), and 195 (100).

Anal. Calcd. for $\text{C}_{21}\text{H}_{20}\text{BrO}_7$: C, 52.98; H, 4.66; Br, 17.65. Found: C, 52.60; H, 4.61; Br, 17.38.

1-(3',4'-Dimethoxy-6'-bromobenzyl)-6,7-dimethoxyisoquinolin-3-one (**5f**).

A mixture of the bromoketoacid **4b** (1 g), ammonium acetate (10 g), and acetic acid (20 ml) was refluxed for 30 minutes. The resulting dark-

brown solution was poured into water (100 ml) and the resulting green-yellow precipitate removed by filtration. This was crystallized from chloroform-ethanol (1:1) to give in 89% yield the bromolactam **5f** as green-yellow crystals (0.85 g), mp 261-262°; ir: 1665 (C=O) cm^{-1} ; uv: λ max (log ϵ) 249 (4.26), 286 (sh, 3.87), 313 (sh, 3.64), 340 (3.51) and 400 (3.51) nm; nmr: δ 3.54, 3.81, 3.85 and 3.93 (ss, each 3H, 4 \times MeO-), 4.54 (s, 2H, -CH₂-), 6.65 (s, 2H, Ar-H), 6.71, 6.96 and 7.00 (s, each 1H, Ar-H) ppm; ms: m/e (%) 435-433 (6) (M⁺), 354 (100) and 323 (15).

Anal. Calcd. for C₂₀H₂₀BrNO₅: C, 55.29; H, 4.64; N, 3.22; Br, 18.41. Found: C, 55.66; H, 4.80; N, 3.44; Br, 18.56.

1-(3',4'-Dimethoxy-6'-bromobenzyl)-6,7-dimethoxy-4-nitroisoquinolin-3-one (**5g**).

To a cooled suspension of the bromolactam **5f** (1 g) in 15 ml of glacial acetic acid, kept around 15°, 1 ml of nitrating mixture (fuming nitric acid-glacial acetic acid, 3:2 by volume) was added during 5 minutes with vigorous mechanical stirring. The reaction mixture was then poured into water (100 ml) and an abundant yellow precipitate was produced, which was collected and washed free of acid. This was crystallized from chloroform to give the bromonitrolactam **5g** as yellow crystals (700 mg), mp 233-235°, yield 65%; ir: 1670 (C=O), 1510 and 1330 (NO₂) cm^{-1} ; uv: λ max 206, 225 (sh), 243 (sh), 277, 330 (sh), 450 (sh) and 486 nm; nmr: δ 3.76, 3.87, 3.97 and 4.05 (ss, each 3H, 4 \times MeO-), 4.76 (s, 2H, -CH₂-), 6.75, 7.11, 7.33 and 7.84 (ss, each 1H, Ar-H) ppm; ms: m/e (%) 399 (100), (M⁺-Br).

Anal. Calcd. for C₂₀H₁₃BrN₂O₇: C, 50.10; H, 3.99; N, 5.84; Br, 16.65. Found: C, 49.91; H, 4.07; N, 5.58; Br, 16.57.

Catalytic Hydrogenation of the Bromonitrolactam **5g** and Subsequent Oxidative Hydrolysis of the Reduction Product.

A suspension of the bromonitrolactam **5g** (500 mg) in 200 ml of ethanol and 300 mg of 10% Pd/C catalyst was hydrogenated at an initial pressure of 20 psi for 3. hours, until the disappearance of the starting material (tlc). Usual work-up gave a greyish solid residue (365 mg). This was submitted to acid hydrolysis, as indicated in the case of **5d**, to give **7a** (E,Z-mixture) as shown by tlc and nmr.

1-(3',4'-Dimethoxybenzyl)-1,6,7-trimethoxyisoquinoline-3,4-dione (**12**).

A stirred solution of lactam **5a** (1 g) in 0.1% methanolic sodium hydroxide (1 l) in a Pyrex vessel, was saturated with oxygen and then irradiated for about 3 hours, until the disappearance of the starting material (tlc). The resulting solution was neutralized by adding ammonium chloride, and most of the solvent removed at reduced pressure. The remaining suspension was diluted with 200 ml of water and extracted with chloroform. The dried extract (sodium sulfate) was concentrated to give a solid residue (1.1 g), which showed a main spot by tlc. This component was isolated by preparative tlc with chloroform-methanol (9.5:0.5) as eluent, to give a solid residue (800 mg), which was crystallized from methanol to afford compound **12** as white prismatic crystals, mp 197-198°, yield 80%; ir: 1690 (C=O) cm^{-1} ; uv: λ max (log ϵ) 247 (3.45) 278 (3.25), 304 (3.14) and 340 (3.17) nm; ¹H-nmr: δ 3.00-3.25 (m, 5H, C₁-OMe) and -CH₂-; 3.66, 3.79, 3.93 and 4.00 (ss, each 3H, 4 \times MeO-Ar), 6.25-6.50 (m, 2H, Ar-H), 6.60, 6.93 and 7.41 (ss, each 1H, Ar-H) and 6.71 (bs, 1H, -NH-); ¹³C-nmr: δ 51.07 (-CH₂- and C₁-OMe), 55.94, 56.44 and 56.73 (4 \times MeO- at sp² carbons), 89.05 (C at position 1), 107.61, 108.39, 111.13, 114.21 and 123.43 (=C-H), 125.19, 125.77 and 136.21 (=C-), 148.73, 150.47 and 155.65 (4 \times C-OMe), 158.58 (-CO-NH) and 175.87 (-CO-) ppm; ms: m/e (%) 401 (7) (M⁺), 250 (100), 222 (66) and 190 (48).

Anal. Calcd. for C₂₁H₂₃NO₇: C, 62.83; H, 5.77; N, 3.48. Found: C, 62.63; H, 5.82; N, 3.51.

1-(E,Z)(3',4'-Dimethoxybenzylidene)-6,7-dimethoxyisoquinoline-3,4-dione (**7a**).

To a solution of compound **12** (300 mg) in dioxane (15 ml) 10% hydro-

chloric acid (10 ml) was added, and this mixture was maintained at 60° for 30 minutes and then allowed to stand for several hours. Needle-shaped crystals of yellow-brown colour separated out. These were collected (150 mg) and identified as the Z isomer of **7a** (tlc, nmr). The mother liquor from the filtration was diluted with 100 ml of water, and extracted with chloroform. The dried extract (sodium sulfate) was concentrated to give a solid residue (112 mg) which, after crystallization, was identified as a mixture of the E and Z isomers of **7a** (mp, tlc, nmr).

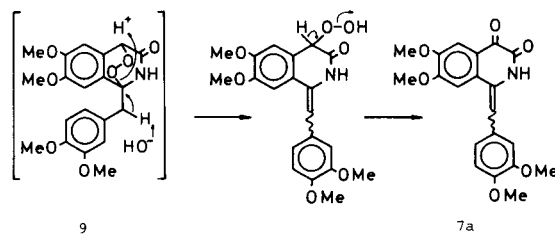
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REFERENCES AND NOTES

- (1) V. D. Gensler, "Heterocyclic Compounds", Vol 4, R. C. Elderfield, ed, John Wiley and Sons, Inc., New York, NY, 1952, Chapter II.
- (2) M. Shamma and J. L. Moniot, in "Isoquinoline Alkaloid Research, 1972-1977", Plenum Press, New York, NY, 1978, Chapter XVI.
- (3) I. W. Elliot, Jr., *J. Heterocyclic Chem.*, **9**, 853 (1952).
- (4) R. A. Henry, C. A. Heller and D. W. Moore, *J. Org. Chem.*, **40**, 1760 (1975).
- (5) The isoquinolin-3-ones (isocarbostyryles) are also oxidized to isoquinoline-1,3,4-triones with chromic oxide-acetic acid. See: N. P. Bun-Hoi, G. Saint-Raf and J. C. Bourgeade, *J. Heterocyclic Chem.*, **5**, 545 (1968); J. M. Muchowski, *Can. J. Chem.*, **47**, 857 (1969).
- (6) A. G. Burton, P. J. Halls and A. R. Katritzky, *Tetrahedron Letters*, 2211 (1971).
- (7) R. Pschorr, *Chem. Ber.*, **37**, 1926 (1904).
- (8) L. Castedo, *et al.*, to be submitted.
- (9) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).
- (10) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).
- (11) R. K. Callow, J. M. Gulland and R. D. Hawort, *J. Chem. Soc.*, 659 (1929).
- (12) The formation of the intermediate endoperoxide has been proposed in the oxidation of the N-methyl derivative of the compound **5a**. E. Kreighbaun, W. F. Kavanaugh and W. T. Comer, *J. Med. Chem.*, **15**, 1131 (1972).
- (13a) N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951); (b) A. A. Frimer, *Chem. Rev.*, **79**, 359 (1979).
- (14) An Alternative mechanism is:

Figure V



- (15) D. D. Perrin, W. L. F. Armarego and D. R. Perrin, "Purification of Laboratory Chemicals", Academic Press, London, 1966.