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THE MELOSATINS—A NOVEL CLASS OF ALKALOIDS FROM *MELOCHIA TOMENTOSA*[a]

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Abstract—Details of the isolation of malosatin A, B, and C and the synthesis of melosatin A are presented. Melosatin C has been characterized as 7-methoxy-4-(5-phenylpentyl)isatin. Several Me and OMe substituted isatins are synthesized as models and UV and mass spectra of the series are discussed.

RECENTLY we reported the isolation and structures of several of the constituents of the tumorigenic plant, *Melochia tomentosa L.* (Sterculiaceae), including an unusual quinolinone alkaloid, melochinone (**1**)[1], its open chain anlog, melovinone (**2**)[2], 6-methoxy-7,8-methylenedioxycoumarin (**3**)[3], the cyclopeptide alkaloids, melonovines A (**4**) and B (**5**), and scutianine B (**6**).[4] We have also communicated on two novel isatin alkaloids melosatin A and B[5] (**7** and **8** respectively) from the same source. This paper details further the structure of these compounds and reports the isolation and characterization of another alkaloid in this series, melosatin C.

As reported earlier, melosatins A and B (**7** and **8** respectively) are yellow alkaloids giving the bluish green color reaction with sulfuric acid typical of isatins.[6] Melosatin A[7] also reduces to an alcohol with sodium borohydride, undergoes ring expansion[6] to quinolines **10** and **11**, forms a methoxime, and condenses with *o*-phenylenediamine to adducts **12** and **13**: details are reported below. While the structure of the unsubstituted melosatin B (**8**) was unequivocally determined from its ^{1}H NMR spectrum,[5] the NMR of melosatin A was in accord both with **7** and an isomer having the two methoxyls located in the 5 and 6 positions of the isatin ring. Because 5-nitrovanillin was more readily available than intermediates leading to 2,3-dimethoxy-5-nitrobenzaldehyde, isomer **7** was synthesized. Thus 5-nitrovanillin was methylated with diazomethane producing methyl ether (**14**) rather than the reported acetophenone.[8] This was condensed with benzalacetone (**15**) and the resulting substituted dibenzalacetone (**16**) reduced to an amorphous mixture of saturated and unsaturated alcohols with sodium borohydride. Without further purification, the remaining olefinic bonds as well as the nitro group were reduced with Pd-C yielding a crystalline, saturated amino alcohol (**17**).[9] This was dehydrated with P_2O_5, forming a mixture of olefins which were reduced directly to the desired aniline (**18**) which was cyclized with oxalyl chloride affording a product, isolated by tlc, identical in all respects (m.p., m.m.p., IR, UV, NMR, MS) with melosatin A, establishing its structure as **7**.

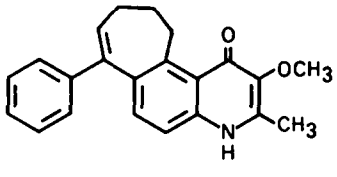
Melosatin C is a red alkaloid isolated from the same crude product as melosatins A and B. Its IR, mass, and ^{1}H NMR spectra are very similar to those of melosatins A and B, but its formula ($C_{20}H_{21}NO_3$) and ^{1}H NMR permit a single OMe group. This group is located on the isatin nucleus as proved both by the presence of five phenyl protons in the ^{1}H NMR (δ 7.26) and by the masses of the benzyl ion (*m/z* 91) and isatin fragment (*m/z* 232) in its mass spectrum (see below).

The five carbon side chain was easily located at C-4 as proved by a pronounced downfield shift of the benzylic methylene group at C_4 (δ 2.90) caused by the *peri* carbonyl at C_3. This effect has been observed earlier with melosatins A and B[5] and melochinone (**1**).[1] In the phenylenediamine adduct of melosatin A (**12**) the effect was especially pronounced (δ 3.50), undoubtedly due to the influence of the newly formed phenazine ring.

Location of the aromatic OMe on the isatin ring was less straightforward. Two vicinal aromatic protons are present at δ 6.84 and δ 7.06. Using melosatins A, B and N-methylisatin as models,[5] the latter is approximately the value expected for a C-6 proton shifted upfield 0.36 ppm by an adjacent OMe group. The remaining proton can be located either at C-5 or C-7. The former was favored (structure **9**) because of its relatively broad signal which we ascribe to coupling with the adjacent benzylic methylene group of the side chain. To confirm this feature, 4-methyl-7-methoxyisatin was synthesized from the readily available 2-methoxy-5-methylaniline via the Sandmeyer reaction.[10] The chemical shifts of the aromatic protons of the product agree closely with those of melosatin C [δ 6.79(d, J = 8.5 Hz), δ 7.04 (d, J = 8.5 Hz) and δ 6.84 (d, J = 8 Hz), δ 7.06 (d, J = 8 Hz), respectively]. Furthermore, the upfield doublet (H-5) of the model was indeed broadened by coupling to the adjacent 4-Me group. The UV spectra of both also agree (Fig. 2) and melosatin C is assigned structure **9**.

The colors of the melosatins and isatins range from light yellow to dark red as indicated by variation of the long wavelength absorption tail (Figs 1 and 2) arising from the $n \rightarrow \pi^*$ transition of the dicarbonyl system. The structural features responsible for this variation are not

[a]Part 13 in the series, Potential Carcinogens. For Part 12 see Ref. 2.



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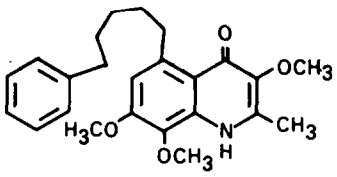

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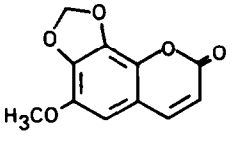

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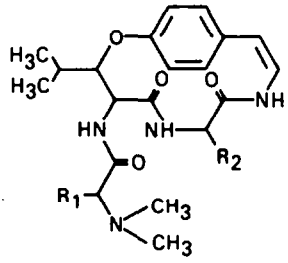
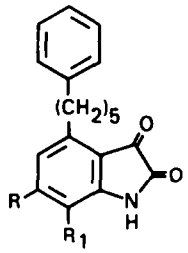
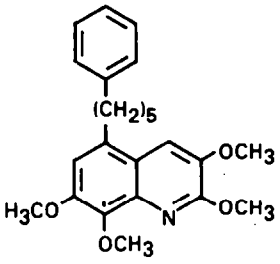


4. $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$
5. $R_1 = CH(CH_3)_2$, $R_2 = CH_2C_6H_4OH$
6. $R_1 = R_2 = CH_2C_6H_5$



7. $R = R_1 = OCH_3$
8. $R = R_1 = H$
9. $R = H$; $R_1 = OCH_3$



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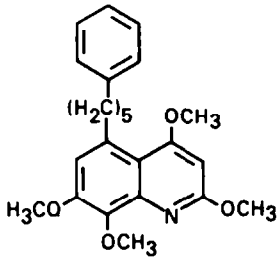

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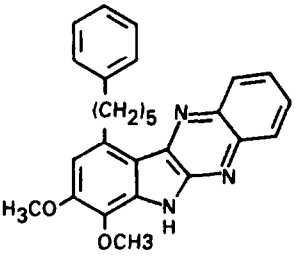

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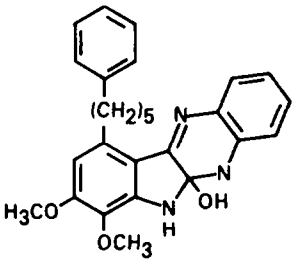


13

entirely clear from this series, but it appears that a single substituent (alkyl or OMe) in the 4-position of the isatin nucleus causes a shift to yellow. Attachment of a second OMe in the 7-position offsets this hypsochromic effect *unless* the OMe is forced out of the plane of the ring by yet a third substituent in the 6-position.

The mass spectra of melosatins A–C exhibit ions for loss of 1 and 2 moles of CO as expected for isatins, ions at *m/z* 91 and $M^{+\cdot}$-91 from cleavage of the benzyl groups. Important ions, supported by metastables, are observed at $[M-131]^+$ which apparently arise via transfer of hydrogens from the pentyl side chain to locations on the isatin ring via a process such as a→b:

$[M-131]^+$ ions then lose the isatin carbonyls in rapid sequence (one metastable ion for C_2HO_2) in an unusual reversion to an odd-electron ion represented above as c or d.

The ions at $(M-131)^+$ are always accompanied by ions at $(M-132)^{+\cdot}$ involving transfer of only one hydrogen that may arise from the process e→f.

The mass spectra of the isatins synthesized in this study are unexceptional (Experimental); all show good molecular ions with loss of CO taking precedence over all other fragmentations. This is followed by loss of HCN in the case of isatin, 4-methylisatin, and 4,7-dimethoxyisatin. In all other cases, loss of the combination of methyl and CO, in either sequence, is an important process.

Indole and oxindole alkaloids are widely distributed in nature but to our knowledge this is the first recorded

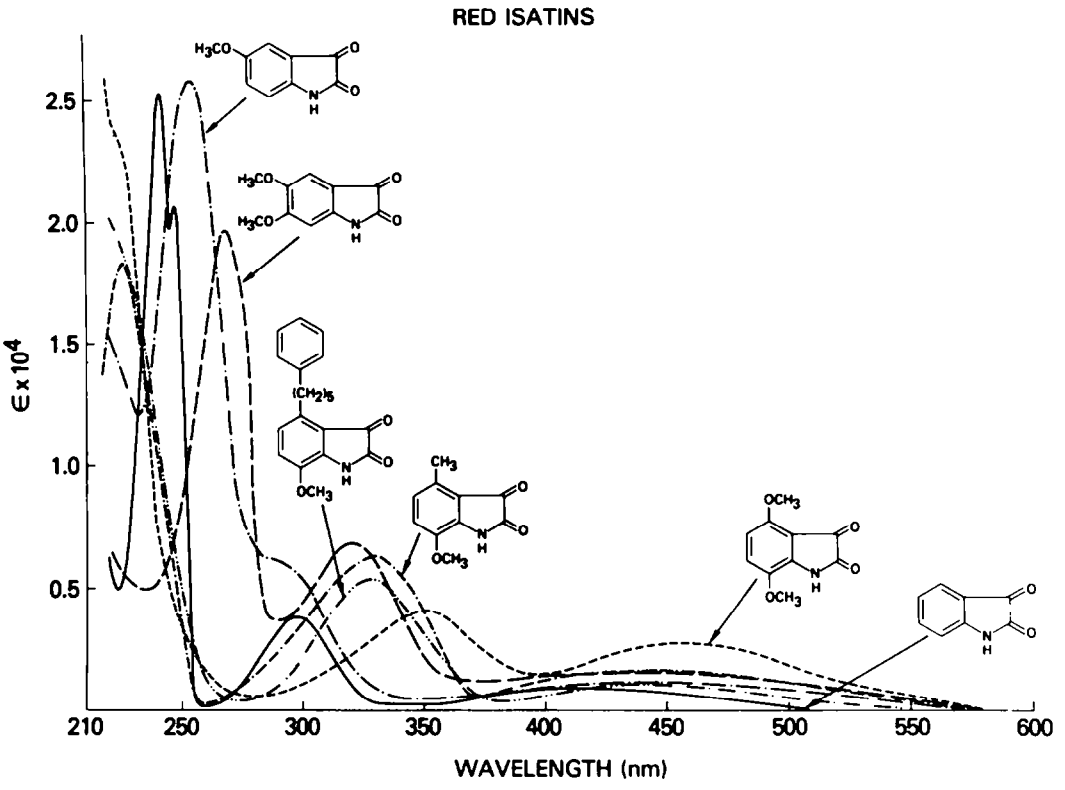

RED ISATINS
2.5
2.0
1.5
1.0
0.5
ε x 10⁴
210
250
300
350
400
450
500
550
600
WAVELENGTH (nm)

Fig. 1.

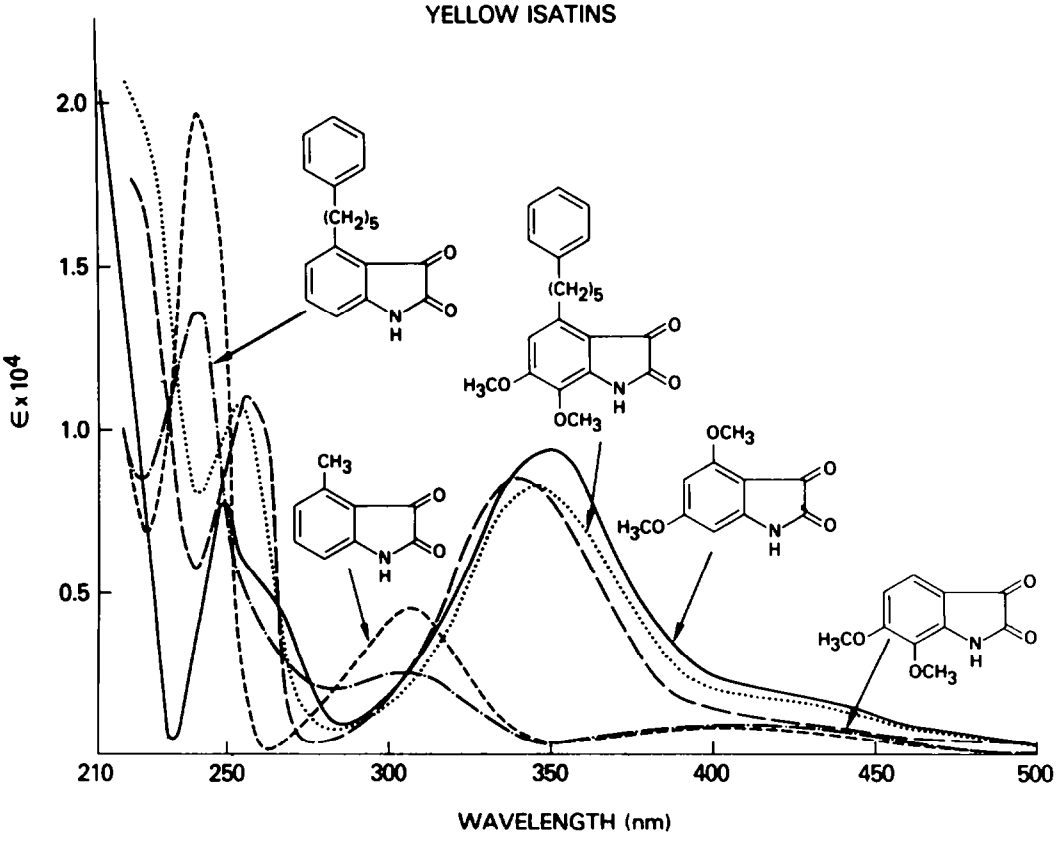
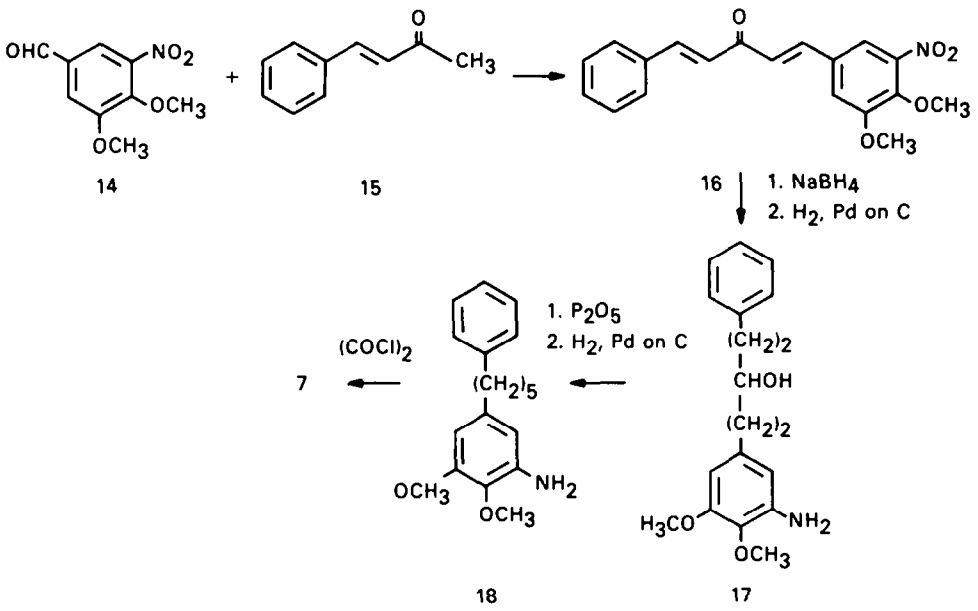
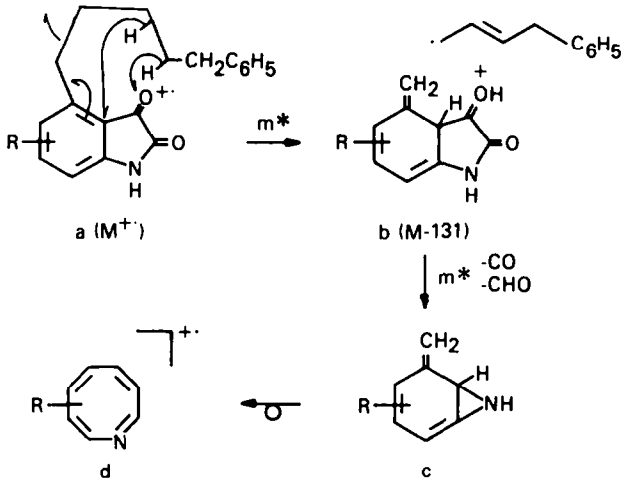
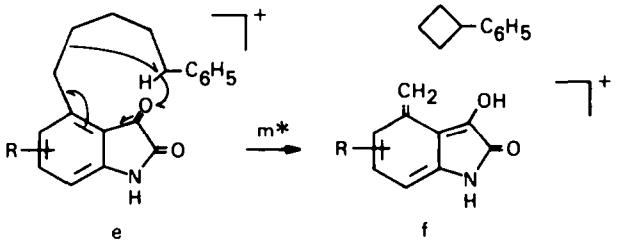
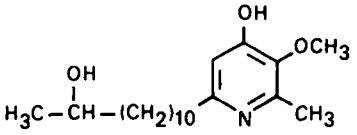

YELLOW ISATINS
2.0
1.5
1.0
0.5
ε x 10⁴
210
250
300
350
400
450
500
WAVELENGTH (nm)

Fig. 2.


OHC
NO2
OCH3
OCH3
14
15
16
1. NaBH4
2. H2, Pd on C
1. P2O5
2. H2, Pd on C
(COCl)2
7
(CH2)5
(CH2)2
CHOH
(CH2)2
OCH3
NH2
OCH3
H3CO
NH2
OCH3
18
17


CH2C6H5
C6H5
m*
a (M+·)
b (M-131)
m* -CO -CHO
d
c


C6H5
C6H5
m*
e
f


OH
OCH3
OH
H3C–CH–(CH2)10
N
CH3
19

instance where they have reached the oxidation state of isatin. The isatins are unlikely to be artifacts, however, since their presence is easily observed by tlc prior to extensive work-up.

Melosatin A appears to be closely related to melovinone (**2**), except that the hypothetical anthranilate-pyruvate construction of the quinolinone ring[11] has been replaced by anthranilate-formate. Alternatively, *o*-aminophenylpyruvate from degradation of kynurenine could be the source of this ring. Melosatin B is similarly related to melochinone (**1**) except that cyclization of the 5-carbon chain to a 7-membered ring has not occurred.

Recently, Medina and Spiteller[12] have reported the isolation of a pyridone alkaloid, melochinin (**19**) from the closely related *Melochia pyramidata L.* (Sterculiaceae). Although it bears some resemblance to the quinolinone alkaloids melochinone (**1**) and melovinone (**2**) insofar as the substitution of the pyridone ring is concerned, its biogenesis appears to be quite different.

EXPERIMENTAL

M. ps were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined in nujol and UV spectra in EtOH. 100 MHz ^{1}H NMR spectra were determined on a Varian XL-100 spectrometer equipped with a Digilab Fourier Transform data system in $CDCl_3$ with TMS as internal reference. All tlc was carried out on Silica gel-60 precoated plates, F-254 (E. Merck). Visualization of tlc was effected by short and long-wave UV and 2,4-dinitrophenylhydrazine and Dragendorff sprays. 5-Methoxyisatin, isatin, and 5,6-dimethoxyisatin were purchased from K&K Chemical Co.

A voucher specimen, identified by Dr. Julia Morton, has been deposited in the Morton Collecteana, Univ. of Miami, Coral Gables, Florida.

Extraction and isolation. Dried and ground roots (1.6 kg) of *M. tomentosa* (collected at Curacao by Mr. W. P. Maal) were extracted in turn with boiling petroleum ether, benzene, and methylene chloride (2 days, 5 l each solvent). The residual material was combined with $Ba(OH)_2$ (50 g) and 50% aqueous EtOH (1.2 l), air dried and then continuously extracted with CH_2Cl_2 (2 days, 5 l). The benzene extract and the first CH_2Cl_2 extract were identical on tlc and combined (extract A) while the later CH_2Cl_2 extract was labelled B.

Melosatin A (**7**). The residue (7 g) obtained by the removal of solvent from extract A was chromatographed on silica gel (100 g). The column was eluted with increasingly polar mixtures of petroleum ether, benzene, and chloroform. The fractions obtained in benzene–chloroform (3:1) were combined and further purified by preparative tlc in benzene EtOH (3:1). The yellow residue isolated from the adsorbent at R_f 0.5 was crystallized from benzene–petroleum ether to give 16 mg (0.001%) of yellow melosatin A (**7**): m.p. 119-21°; IR (nujol) ν_{max} 3200 (NH), 1750, 1725 (CO), 1645, (CONH), 1250 and 1135 cm^{-1} (OMe); MS *m/e* 353.162 (100, M^+. $C_{21}H_{23}NO_4$ requires 353.1626), 262 (13), 222 (35), 221 (40), 91 (98); for ^{1}H NMR see Ref. 5.

Melosatin B (**8**). The residue (4 g) obtained by the removal of solvent from extract B was chromatographed over silica gel (300 g). The column was eluted with solvents of increasing polarity. A viscous material was obtained with benzene–chloroform (1:3) which was purified by preparative tlc using $CHCl_3$–MeOH (95:5) to give 4 mg (0.00025%) of yellow amorphous melosatin B: MS *m/z* 293 (95, $M^{+\cdot}$ $C_{19}H_{19}NO_2$), 202 (57), 162 (80), 161 (84), 133 (47), 91 (100); for ^{1}H NMR see Ref. 5.

Melosatin C (**9**). During the chromatography of extract B, a red material was obtained from the chloroform–benzene (1:1) eluate. It was purified by preparative tlc using $CHCl_3$–MeOH (95:5) (R_f 0.67) and crystallized from benzene-petroleum ether providing 5 mg (0.0003%) of red needles of melosatin C: m.p. 124–5°; IR (nujol) ν_{max} 3200 (NH), 1745, 1730 (CO), 1635 (CONH), 1595, 1515, 1242 and 1155 cm^{-1}; MS *m/z* 323 (100, $M^{+\cdot}$ $C_{20}H_{21}NO_3$), 232 (33), 192 (60), 191 (47), 176 (25), 162 (21), 135 (72), 91 (88); ^{1}H NMR δ 1.56 (broad m, CCH_2C, 6 H), 2.62 (t, $C_6H_5CH_2$, 2 H), 2.90 (t, isatin CH_2, 2 H), 3.90 (s, OMe, 3 H), 6.84 (d, J = 8 Hz, 5 H of isatin, 1 H), 7.06 (d, J = 8 Hz, 6 H of isatin, 1 H), 7.24 (m, C_6H_5, 5 H), 7.68 (broad s, NH, 1 H).

o-Phenylenediamine adduct (**12**) *of melosatin A.* Melosatin A (2 mg) and *o*-phenylenediamine (4 mg) in AcOH (1 ml) were refluxed on the water bath for 2 hr. At the end of the reaction, the solvent was removed under N_2. The residue obtained was subjected to preparative tlc in $CHCl_3$–EtOAc (3:1) and two yellow products were obtained. The most mobile, R_f 0.35, is the adduct **12**: MS 425 (40, M^+ $C_{27}H_{27}N_3O_2$), 334 (25), 320 (25), 306 (53), 293 (100), 278 (46), 91 (34), ^{1}H NMR δ 1.55 (broad m, $C(CH_2)_3C$, 6 H), 2.70 (t, $C_6H_5CH_2$, 2 H), 3.50 (t, isatin CH_2, 2 H), 4.05 (s, OMe, 6 H), 6.77 (s, isatin 5 H, 1 H). 7.25 (m, C_6H_5, 5 H), NH too broad to observe. The less mobile spot is assumed to be the incompletely dehydrated adduct **13** on the basis of its mass spectrum: *m/z* 443 (20, $M^{+\cdot}$ $C_{27}H_{29}N_3O_3$), 425 (45, $M^{+\cdot} - H_2O$), 334 (24), 320 (25), 310 (100), 306 (45), 293 (80), 278 (40), 91 (32).

Treatment of melosatin A (**7**) *with diazomethane.* Melosatin A (2 mg) was dissolved in an excess of ethereal diazomethane (10 ml) and the mixture was allowed to stand overnight at room temp. The solvent was removed and the residue subjected to GC-MS. Two isomeric methoxyquinolines eluted, one at 270° and one at 291° when programmed at 10°/min on a 1% OV-17 column. The two are assumed to be structures **10** and **11** on the basis of their molecular ions and the known reactions of isatins with diazomethane.[6] The early-eluting isomer shows far more loss of Me than the second, but differentiation between their structures on this basis is not obvious: MS (isomer eluting at 270°) 395 (100), $M^{+\cdot}$ $C_{24}H_{29}NO_4$), 380 (59), 366 (34), 262 (49), 91 (10); MS (isomer eluting at 291°) 395 (100, $M^{+\cdot}$ $C_{24}H_{29}NO_4$), 380 (13), 366 (7), 262 (15), 91 (7).

Melosatin A methoxime. A submilligram quantity of melosatin A was allowed to stand in pyridine overnight with an excess of methoxyamine hydrochloride. The solvents were evaporated under a stream of N_2 and the residue extracted into $CHCl_3$ from added water. Upon evaporation, the residue was applied directly to the direct insertion probe of the mass spectrometer: MS N_2 382 (45, $M^{+\cdot}$ $C_{22}H_{26}m/zO_4$), 351 (100), 335 (35), 91 (45).

Sodium borohydride reduction of melosatin A. Melosatin A (2 mg) was dissolved in MeOH (5 ml) and $NABH_4$ (2 mg) added slowly at room temp. After complete addition, the mixture was stirred at room temp for 3 hr. It was then diluted with water, extracted with $CHCl_3$, and the $CHCl_3$ layer washed twice with water. Removal of solvent left a colorless alcohol: m.p. 110–12°; MS *m/z* 355 (100, M^+ $C_{21}H_{25}NO_4$), 321 (16, $M^+ - CH_3 - H_2O$), 223 (24), 208 (48).

Methylation of 5-nitrovanillin. 5-Nitrovanillin (20 g) (Aldrich Chem. Co.) was dissolved in 50 ml MeOH and 100 ml ether, treated with 4 equivs diazomethane in 200 ml ether and left for 4 days.[8] The solvent was then removed and the residue extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 4% NaOH aq. to remove unreacted 5-nitrovanillin, then washed with water and dried over Na_2SO_4. Removal of solvent left a residue of **14** that crystallized from EtOH as needles: m.p. 89–90° (lit. m.p. 90–1°[13]); ^{1}H NMR 4.05, 4.12 (2s, 2 OCH_3, 6 H), 7.66, 7.86 (2d, J = 2 Hz, 2 ArH), 9.96 (s, CHO, 1 H); MS *m/z* 211 (100, $M^{+\cdot}$ $C_9H_9NO_5$), 135 (31), 150 (20), 164 (26), 119 (23), 105 (29).

1-Phenyl-5-(3,4-dimethoxy-5-nitrophenyl)-1,4-pentadiene-3-one (**16**). Compound **14** (5.3 g) was dissolved in 150 ml EtOH and 3.65 g benzalacetone added. The mixture was cooled in an ice bath and 50 ml of 2% NaOH aq. added slowly with vigorous stirring. The stirring was continued for 3 hr whereupon **16** separated and was removed by filtration, (yield

4.69 g, 35%): m.p. 125–30°; MS *m/z* 339 (100, $M^{+\cdot}$ $C_{19}H_{17}NO_5$), 322 (37), 131 (40), 103 (45).

1-*Phenyl-5-(3,4-dimethoxy-5-aminophenyl)pentan-3-ol hydrochloride* (**17**). Compound **16** (2.39 g) was dissolved in 200 ml MeOH and 1 g $NaBH_4$ added slowly with stirring at room temp. The stirring was continued for 4 hr. The crude product was combined with 1 g of 10% Pd-C and hydrogenated for 5 hr. The catalyst was removed by filtration and the filtrate concentrated to dryness, diluted with 200 ml water, extracted twice with 200 ml $CHCl_3$ and the extract washed with water. The $CHCl_3$ extract was dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in 500 ml ether and treated with ethereal HCl. The hydrochloride of **17** was separated by filtration (0.684 g, 28% from **16**): m.p. 180-5°; MS *m/z* 315 (39, M^+ $C_{19}H_{25}NO_3$), 180 (9) 167 (100), 154 (10), 152 (25), 91 (19).

2,3-*Dimethoxy-5-(5-phenylpent-x-enyl)aniline hydrochloride.* The derivative **17** recovered from its hydrochloride (600 mg) was dissolved in 500 ml dry benzene, 600 mg P_2O_5 added, and the mixture refluxed for 24 hr. The benzene was removed, and the residue diluted with water and neutralized with 5% Na_2CO_3. The free base was then extracted with $CHCl_3$ and the extracts washed with water, dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in 10 ml ether and precipitated with ethereal HCl. The crude hydrochloride (210 mg, 37%) melted at 170–5°: MS *m/z* 297 (54, $M^{+\cdot}$ $C_{19}H_{23}NO_2$), 206 (60), 167 (70), 166 (100), 152 (23), 91 (41).

Melosatin A (7). The above mixture of olefins (200 mg) was dissolved in 50 ml MeOH, 200 mg 10% Pd-C added, and hydrogenated for 4 hr. The catalyst was removed by filtration and the solvent evaporated leaving 100 mg (50%) of amorphous **18**. This was treated with 1 ml oxalyl chloride and stirred at 165–70° for 2 hr. The reaction was monitored by tlc and a portion of the crude product purified by preparative tlc (R_f 0.61), $CHCl_3$–MeOH (95:5). The product was crystallized from benzene–petroleum ether and found identical in all respects (m.p., m.m.p., IR, UV, MS, ^{1}H NMR) with natural melosatin A.

4-*Methylisatin.* A soln of 9 g chloral hydrate in 120 ml water was combined with 130 g $NaSO_4$, 4.5 g *m*-toluidine in 30 ml water, 5.1 ml conc HCl and 11 g hydroxylamine hydrochloride in 50 ml water. This mixture was refluxed vigorously for two min and cooled, whereupon crystalline 3-methyl isonitrosoacetanilide separated (3.92 g, 53%): m.p. 142° (lit. m.p. 145°[10]). This product (3.5 g) was added slowly to 2 ml conc H_2SO_4 preheated to 60°. After complete addition, the temp was raised to 80° for 10 min. It was then cooled, poured onto ice, filtered, and the ppt washed with water. The crude 4-methylisatin was purified by dissolving it in 100 ml 8% NaOH aq. and carefully neutralizing the soln with dil HCl, and filtering precipitated impurities. The filtrate was then strongly acidified to pH 3 with dil HCl, precipitating the yellow 4-methylisatin which was filtered and recrystallized from EtOH (0.5 g, 16%): m.p. 185–8° (lit. m.p. 189°[14]); MS *m/z* 161 (63, M^+ $C_9H_7NO_2$), 133 (100), 106 (41), 105 (23), 104 (22), 103 (24); ^{1}H NMR δ 2.58 (s, $ArCH_3$, 3 H), 6.76 (d, J = 7 Hz, Ar5 H, 1 H), 6.88 (d, J = 7 Hz, Ar7 H, 1 H), 7.42 (t, J = 7 Hz, Ar6 H, 1 H), 8.60 (broad s, NH, 1 H).

4-*Methyl-7-methoxyisatin.* This compound was prepared by the method used above for 4-methylisatin, starting with 4.5 g 2-methoxy-5-methyl-aniline (Aldrich Chem. Co.). It gave a nearly quantitative yield of the isonitrosoacetanilide: m.p. 100–5°. Cyclization of 6 g of the isonitrosoacetanilide as above gave 3 g (54%) of red crystals of 4-methyl-7-methoxyisatin which were recrystallized from EtOH: m.p. 237–8° (lit. m.p. 235–6°[15]); MS *m/z* 191 (100, M^+ $C_{10}H_9NO_3$), 163 (48), 162 (39), 135 (77), 120 (30), 106 (30), 105 (28); ^{1}H NMR δ 2.52 (s, $ArCH_3$), 3.88 (s, OCH_3, 3 H), 6.79 (d, J = 8.5 Hz, Ar5 H, 1 H), 7.04 (d, J = 8.5 Hz, Ar6 H, 1 H), 7.75 (broad s, NH, 1 H).

4,7-*Dimethoxyisatin.* This compound was synthesized by the above method starting with 4.5 g of 2,5-dimethoxyaniline (Aldrich Chem. Co.). The isonitrosoacetanilide formed in nearly quantitative yield: m.p. 120-5°; MS *m/z* 224 (100, $M^{+\cdot}$ $C_{10}H_{12}N_2O_4$), 209 (43), 193 (19), 179 (34), 164 (59), 138 (96). Cyclization of 1 g of this product and purification via tlc afforded 100 mg (11%) pure 4,7-dimethoxyisatin which was recrystallized from EtOH as red needles: m.p. 250–2°; MS *m/z* 207 (100, $M^{+\cdot}$ $C_{10}N_9NO_4$), 179 (79), 178 (43), 164 (28), 150 (43), 149 (31), 136 (31), 135 (31), 122 (50), 121 (32); ^{1}NMR δ 3.89 (s, OCH_3, 3 H), 3.91 (s, OCH_3, 3 H), 6.70 (d, J = 8.8 Hz, Ar5 H, 1 H), 7.36 (d, J = 8.8 Hz, Ar6 H, 1 H), 7.78 (broad s, NH, 1 H).

2,3-*Dimethoxybenzamide.* 2,3-Dimethoxybenzoic acid (5.5 g) was converted to the acid chloride by refluxing it in dry benzene with 3.6 g $SOCl_2$ and treating the crude product with conc NH_4OH. The crude amide was extracted into benzene, washed with bicarbonate, and the solvent evaporated. The residue recrystallized from benzene–petroleum ether giving the amide (2.39 g, 44%): m.p. 90° (lit. m.p. 93–4°C[16]).

2,3-*Dimethoxyaniline hydrochloride.* NaOH (2.4 g) in 20 ml water was combined with 0.6 ml Br_2 at 0°. Finely powdered 2,3-dimethoxybenzamide (1.81 g) was added and stirred until soln was complete whereupon it was heated at 70–80° for 30 min. Water (30 ml) was added and the aniline extracted with $CHCl_3$, the extracts washed with water, and the solvent evaporated. The residue was dissolved in ether and treated with HCl. The precipitated hydrochloride was then recrystallized from EtOH (1.15 g 61%): m.p. 193-4°. The picrate recrystallized from EtOH: m.p. 174–6°; lit. mp 173–5°[17].

6,7-*Dimethoxyisatin.* 2,3-Dimethoxyaniline hydrochloride (0.5 g) was stirred with 1.26 g oxalyl chloride and the mixture then heated to 170° in an oil bath for 1.5 hr. The crude product was extracted with $CHCl_3$ and purified using preparative tlc with 5% MeOH in $CHCl_3$ (R_f 0.49). The yellow product crystallized from chloroform–petroleum ether as yellow needles (25 mg, 5%); m.p. 209–10° (lit. m.p. 212–3°[18]); MS *m/z* 207 (78, M^+ $C_{10}H_9NO_4$), 179 (30), 178 (33), 151 (76), 149 (100), 136 (20), 119 (20); ^{1}H NMR δ 3.91 (s, 7 OCH_3, 3 H), 3.98 (s, 6 OCH_3, 3 H), 6.59 (d, J = 8.36 Hz, Ar5 H, 1 H), 7.42 (d, J = 8.4 Hz, Ar4 H, 1 H), NH too broad to observe.

5-*Methoxyisatin.* Reddish-brown crystals (K&K Chemical Co.): ^{1}H NMR δ 3.84 (s, OCH_3, 3 H), 6.80 (d, J = 9.5 Hz, Ar 7 H, 1 H), 7.14 (m, Ar4 H and 6 H, 2 H), 7.60 (broad s, NH, 1 H).

5,6-*Dimethoxyisatin.* Reddish-brown crystals (K&K Chemical Co.): ^{1}H NMR δ 3.88 (s, Ar 5 OCH_3, 3 H), 4.02 (s, Ar 6 OCH_3, 3 H), 6.52 (s, Ar 7 H, 1 H), 7.12 (s, Ar 4 H, 1 H), 8.20 (broad s, NH, 1 H).

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[7] Due to the small quantities available, these reactions were run on melosatin A only.
[8] We did not obtain any of the 5-nitro-3,4-dimethoxyacetophenone reported by O. L. Brady and L. B. Manjunath, *J. Chem. Soc.* **125**, 1060 (1924), even with 4 moles excess diazomethane.

[9]An attempt to catalytically hydrogenate **16** directly to **17** led to high molecular weight products in acid or neutral solvents, due, perhaps, to easy reduction of the nitro group to an amine followed by Michael addition to the unsaturated CO of another molecule.
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