Synthesis of 7-Methoxy-2-methyl-3,5,8-isoquinolinetrione

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Synthesis of 7-methoxy-2-methyl-3,5,8-isoquinolinetrione from either 7- or 8-isoquinolinol is described. 3,5,8-Isoquinolinetrione is a novel heterocyclic quinone which constitutes the aromatic carbon skeleton of mimosamycin.

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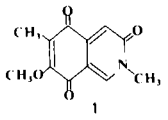
The structure of mimosamycin (1) was determined as 7-methoxy-2,6-dimethyl-3,5,8-isoquinolinetrione (**1**) by an X-ray analysis (2). The characteristic feature of mimosamycin is a new ring system composed as 3,5,8-isoquinolinetrione, on which nothing has yet been reported.

(Figure 1)



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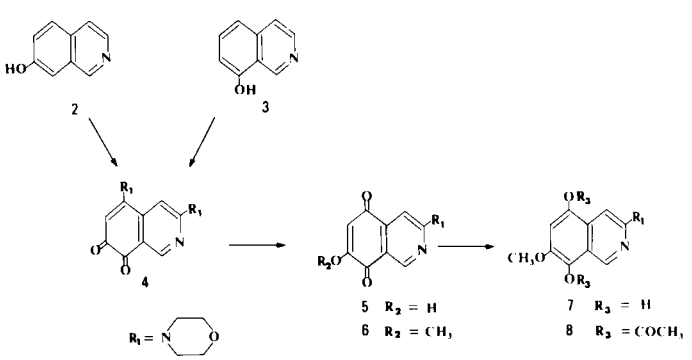
In this study, the authors report the synthesis of 7-methoxy-2-methyl-3,5,8-isoquinolinetrione (**10**), which will permit a straight-forward total synthesis of mimosamycin.

The key steps of the synthesis are, first, the introduction of the oxygen and/or potential oxygen functional groups at C-3, -5, -7 and -8 positions of the isoquinoline nucleus, and second, the transformation of the morpholinyl group at the C-3 position of substituted isoquinoline to the corresponding 2-methyl-3-isoquinolone.

According to the description of Tsizin (3), 3,5-di(4-morpholinyl)-7,8-isoquinolinedione (**4**) was prepared from 7-isoquinolinol (**2**) (4) by cupric-catalyzed oxidation with oxygen in the presence of morpholine. Cupric-catalyzed oxidation of 8-isoquinolinol (**3**) (5) proceeded equally well and gave rise to **4** in 80% yield. By the aerial oxidation, the necessities of all functional groups for the synthesis of titled compound were provided in one-step at the desired C-3, -5 and -7 or -8 positions.

Treatment of **4** with methanol in the presence of sulfuric acid gave 7-methoxy-3-(4-morpholinyl)-5,8-isoquinolinedione (**6**), which was also prepared from 7-hydroxy-3-(4-morpholinyl)-5,8-isoquinolinedione (**5**) (3) by treatment with diazomethane.

Scheme 1

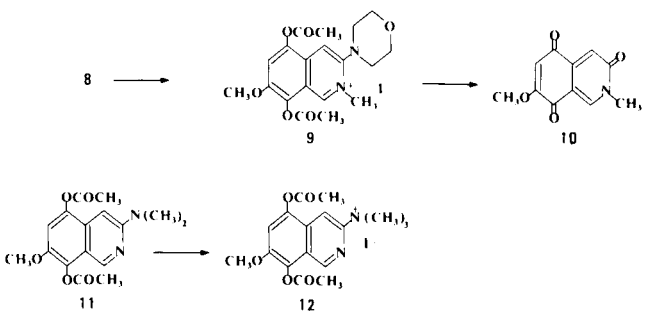


Direct quaternization of **6** with various methylating agents such as methyl iodide, methyl *p*-toluenesulfonate and methyl fluorosulfonate, was attempted but did not produce the desired quaternary salt. This failure is hardly surprising when we consider that 5,8-isoquinolinedione is distinctly less basic than 5,8-isoquinolinediol by 3.5 pK units (6). Thus, it was expected that this problem would be circumvented by reduction of the *p*-quinone moiety to hydroquinone.

The *p*-quinone (**6**) was converted to 5,8-diacetoxy-7-methoxy-3-(4-morpholinyl)isoquinoline (**8**) by treatment with sodium hyposulphite followed by acetylation with acetic anhydride in the presence of sodium acetate. The hydroquinone (**7**) could not be obtained in the pure state due to its unstable nature. Methylation of the diacetate (**8**) with methyl iodide in DMF at 100° for twelve hours afforded the alkylated product of the isoquinoline nitrogen, **9**, only and no concurrent *N*-methylation of the morpholine nitrogen was observed. The bathochromic shift (+ 9 nm) of an absorption maximum at 295 nm in the uv spectrum of the free base (**8**) to 304 nm of **9** shows that ring alkylation occurred (7). A methyl proton signal at δ 4.62 was assigned to the *N*-methyl group. The iodomethylate (**9**) exhibited an nmr spectrum very similar to that of **8**, except that the *N*-methyl proton appeared at δ 4.62 as a singlet. Furthermore, for the iodomethylate (**9**) the singlet appeared at δ 10.18 much further downfield compared to δ 9.03 for the heteroaromatic proton at C-1 position of **8**, whereas the proton signals due to two methylene groups adjacent to morpholine nitrogen remained unchanged and resonated at δ 3.2-3.6.

The difference in the reaction site of alkylation was observed in the quaternization of 5,8-diacetoxy-7-methoxy-3-dimethylaminoisoquinoline (**11**), which was prepared from 7-isoquinolinol using dimethylamine instead

Scheme 2



of morpholine in a similar manner with the procedure of **8**. The methylation of **11** with methyl iodide in acetone at room temperature gave one product (**12**), which was produced by alkylation at exocyclic nitrogen. The assignment of the structure of **12** is based on the spectral data. In the uv spectrum of **12**, a hypsochromic shift (-59 nm) of an absorption maximum at 299 nm of **11** was observed (7). The proton signal of three methyl groups in the nmr spectrum of **12** resonated at δ 3.93 as a singlet.

When the hydrolysis of **9** with potassium carbonate in methanol was carried out at ambient temperature under an atmosphere of oxygen, 7-methoxy-2-methyl-3,5,8-isoquinolinetrione (**10**) was obtained in an one-pot reaction. The formation of **10** could occur by a hydrolysis of the two acetoxyl groups followed by oxidation and by a substitution of the morpholinyl group by a hydroxide anion. The structure of **10** is based on the reaction sequence and the following data: elemental analyses and a molecular ion at m/e 219 in the mass spectrum were consistent with the empirical formula $C_{11}H_9NO_4$. The main fragmentation pattern involves an elimination of three carbonyls which originates from *p*-quinone and lactam moieties. The same type of decomposition was observed for mimosamycin (**1**). The ir and uv spectra of **10** were essentially identical with those of **1** and consistent with those expected for the assigned structure. The nmr spectrum in deuteriochloroform revealed the presence of an *N*-methyl group (δ 3.68), an *O*-methyl group (δ 3.91) and three heteroaromatic protons (δ 6.23, 7.11 and 8.39), which are assigned to the protons at C-6, -4 and -1 positions, respectively.

EXPERIMENTAL

Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian HA-60 spectrometer (using TMS as an internal standard). Ir spectra were obtained in potassium bromide, unless otherwise specified, using a JASCO IRA-2 spectrometer. UV spectra were obtained in ethanol with Hitachi 200-20 spectrophotometer. Mass spectra were recorded on a JEOL JMS-01SG at 75 ev using a direct inlet system. The relative intensity of the ions is indicated in parenthesis as a percent of the base peak.

3,5-Di(4-morpholinyl)-7,8-isoquinolinedione (**4**).

A mixture of 8-isoquinolinol (**3**) (0.4 g.) and morpholine (1.5 ml.) in methanol in the presence of cupric acetate (0.1 g.) was stirred under an atmosphere of oxygen for 1.5 hours. The reaction was exothermic. A crystalline orange-red solid, precipitated from the initially homogeneous reaction mixture, was filtered and washed with methanol to give 3,5-di(4-morpholinyl)-7,8-isoquinolinedione (**4**) (0.73 g., 80%), which was recrystallized from methanol and identified with the authentic sample (3) prepared from 7-isoquinolinol according to Tsizin's procedure; nmr (deuteriochloroform): δ 3.1-3.5 (4H, m, $2CH_2N$), δ 3.7-4.2 (4H, m, $2CH_2O$), δ 3.83 (8H, s, $2NCH_2CH_2O$), δ 6.12 (1H, s, H_6), δ 6.73 (1H, s, H_4) and δ 8.93 (1H, s, H_1); uv λ max: 323 nm (ε, 8,800) and 225 nm (ε, 66,700); ms: m/e 329 (M^+, 10), 301 (100), 270 (70), 256 (33) and 244 (53).

7-Methoxy-3(4-morpholinyl)-5,8-isoquinolinedione (**6**).

a) 3,5-Di(4-morpholinyl)-7,8-isoquinolinedione (**4**) (0.7 g.) was dissolved in methanol (10 ml.) containing concentrated sulfuric acid (0.5 ml.) and the mixture was refluxed for 20 minutes. The reaction mixture was poured into ice-water and the resulting precipitate was filtered to give **6** (0.47 g., 81%). An analytical sample was recrystallized from ethanol as reddish black needles, m.p. 206-207°; ir: 1670, 1648 and 1588 cm^{-1}; nmr (deuteriochloroform): δ 3.84 (8H, s, $2NCH_2CH_2O$), δ 3.93 (3H, s, CH_3O), δ 6.17 (1H, s, H_6), δ 7.14 (1H, s, H_4), δ 9.15 (1H, s, H_1); uv λ max: 317 nm (ε, 14,300) and 250 nm (ε, 24,500); ms: m/e 274 (M^+, 100), 243 (52), 229 (22), 218 (28) and 190 (35).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.22. Found: C, 61.19; H, 5.00; N, 10.24.

b) A solution of 7-hydroxy-3(4-morpholinyl)-5,8-isoquinolinedione (**5**) (0.20 g.) (3) in chloroform (30 ml.) was treated with excess of ethereal diazomethane at ambient temperature under stirring. Evaporation of solvents gave red crystals of **6** (0.17 g., 90%).

7-Methoxy-3(4-morpholinyl)-5,8-isoquinolinediol (**7**).

To a suspension of **6** (1.22 g.) in a mixture of methanol (60 ml.) and tetrahydrofurane (10 ml.) was added 10% aqueous sodium hyposulphite (50 ml.) at 20° under stirring. The reaction mixture came to a clear solution. After 1 hour, the precipitate was filtered and washed with water to give **7** (1.10 g., 90%) as a pale yellow powder; ir: 3530, 1642, 1617 (sh) and 1155 cm^{-1}.

5,8-Diacetoxy-7-methoxy-3(4-morpholinyl)isoquinoline (**8**).

A mixture of **7** (0.9 g.) in acetic anhydride (5 ml.) containing anhydrous sodium acetate (0.2 g.) was heated at 120° for 10 minutes. The mixture was poured into ice-water and neutralized with 5% aqueous sodium bicarbonate. The yellow precipitate was filtered to give **8** (1.0 g., 85%), which was recrystallized from a mixture of benzene and *n*-hexane and melted at 128-130°; ir: 1757 and 1592 cm^{-1}; nmr (deuteriochloroform): δ 2.46 (6H, s, $2CH_3COO$), δ 3.4 ~ 3.7 (4H, m, $2CH_2N$), δ 3.8 ~ 4.1 (4H, m, $2CH_2O$), δ 3.93 (3H, s, CH_3O), δ 6.65 (1H, d, H_4), δ 7.33 (1H, s, H_6), δ 9.03 (1H, d, H_1), JH_1H_4 = 1.0 Hz; uv λ max: 295 nm (ε, 17,400), 291 nm sh (ε, 17,200) and 248 nm (ε, 40,400); ms: m/e 360 (M^+, 67), 318 (63), 276 (100), 275 (53) and 261 (37).

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.62; H, 5.20; N, 7.58.

Iodomethylate (**9**) of **8**.

A solution of **8** (0.6 g.) and methyl iodide (8 ml.) in acetone (4 ml.) was heated at 90-100° for 12 hours in a sealed tube. After cooling, the precipitate was filtered and washed with ether to give **9** (0.74 g., 88%). An analytical sample was recrystallized from methanol to give yellowish prisms, which melted at 219-222° dec.; ir: 1777 and 1618 cm^{-1}; nmr (DMF-D_7): δ 2.53 (3H, s, CH_3COO), δ 2.56 (3H, s, CH_3COO), δ 3.1 ~ 3.4 (4H, m, $2CH_2N$), δ 3.7 ~ 4.1 (4H, m, $2CH_2O$), δ 4.10 (3H, s, CH_3O), δ 4.62 (3H, s, CH_3N^+), δ 8.19 (1H, s, H_6), δ 8.29 (1H, s, H_4) and δ 10.33 (1H, s, H_1); uv λ max: 304 nm (ε, 10,000), 262 nm (ε, 27,800) and 220 nm (ε, 33,300); ms: m/e 360 (M^+-142, 43), 318 (67), 289 (43), 276 (100), 275 (58), 261 (45) and 142 (95).

Anal. Calcd. for $C_{19}H_{23}IN_2O_6$: C, 45.42; H, 4.58; N, 5.58; I, 25.30. Found: C, 45.29; H, 4.48; N, 5.45; I, 25.64.

3,5-Bis-dimethylamino-7,8-isoquinolinedione.

A mixture of 7-isoquinolinol (**2**) (2.9 g.) in 20% methanolic dimethylamine (80 ml.) containing cupric acetate (0.2 g.) was stirred under an atmosphere of oxygen for 4 hours. Dark reddish crystals, appeared from the initially homogeneous reaction mix-

ture, were filtered and washed with methanol to give 3,5-bis-dimethylamino-7,8-isoquinolinedione (2.4 g., 49%), which was recrystallized from methanol to give orange needles and melted at 190-192° dec.; ir: 1670 and 1614 cm^{-1}; nmr (deuteriochloroform): δ 3.13 (6H, s, $2CH_3N$), δ 3.28 (6H, s, $2CH_3N$), δ 5.93 (1H, s, H_6), δ 6.68 (1H, s, H_4) and δ 8.80 (1H, s, H_1); uv λ max: 329 nm (ε, 9,100), 289 nm (ε, 8,400), 246 nm (ε, 19,100) and 212 nm (ε, 16,600); ms: m/e 245 (M^+, 23), 230 (9), 217 (100), 202 (44), 189 (56), 175 (23) and 174 (24).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.79; H, 6.06; N, 17.08.

3-Dimethylamino-7-methoxy-5,8-isoquinolinedione.

A solution of the above *o*-quinone (1.5 g.) in methanol (30 ml.) containing concentrated sulfuric acid (1.5 ml.) was refluxed for 30 minutes. The reaction mixture was poured into ice-water and the precipitated product was filtered and washed with water to give 3-dimethylamino-7-methoxy-5,8-isoquinolinedione (1.2 g., 84%). An analytical sample was recrystallized from chloroform to give reddish needles, m.p. 191-193°; ir (chloroform): 1668 and 1588 cm^{-1}; nmr (deuteriochloroform); δ 3.33 (6H, s, $2CH_3N$), δ 3.97 (3H, s, CH_3O), δ 6.19 (1H, s, H_6), δ 7.09 (1H, s, H_4), δ 9.00 (1H, s, H_1); uv λ max: 317 nm (ε, 14,700) and 248 nm (ε, 26,500); ms: m/e 232 (M^+, 100), 217 (72), 203 (63), 189 (17) and 174 (17).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.91; H, 5.27; N, 11.78.

3-Dimethylamino-7-methoxy-5,8-isoquinolinediol.

To a suspension of the above *p*-quinone (1.2 g.) in a mixture of methanol (50 ml.) and tetrahydrofurane (4 ml.) was added 10% aqueous sodium hyposulphite (40 ml.) at 30°. After 1 hour, the precipitate appeared from the clear solution was filtered and washed with water and chloroform to give the 5,8-isoquinolinediol (1.0 g., 83%); ir: 3510, 1652, 1620 (sh) and 1165 cm^{-1}.

5,8-Diacetoxy-3-dimethylamino-7-methoxyisoquinoline (**11**).

A mixture of the above hydroquinone (0.4 g.) in acetic anhydride (6 ml.) containing anhydrous sodium acetate (0.2 g.) was refluxed for 30 minutes. The mixture was poured into ice-water and neutralized with 5% aqueous sodium bicarbonate. Filtration of the precipitate afforded **11** (0.28 g., 51.5%), which was recrystallized from benzene to give yellow prisms, m.p. 130-132°; ir: 1768, 1645 (sh) and 1595 cm^{-1}; nmr (deuteriochloroform): δ 2.43 (6H, s, $2CH_3COO$), δ 3.13 (6H, s, $2CH_3N$), δ 3.88 (3H, s, CH_3O), δ 6.44 (1H, s, H_4), δ 7.25 (1H, s, H_6) and δ 8.97 (1H, s, H_1); uv λ max: 299 nm (ε, 19,500), 291 nm (ε, 18,400), 248 nm (ε, 38,400) and 214 nm (ε, 19,200), ms: m/e 318 (M^+, 83), 276 (50), 234 (100), 233 (57) and 219 (57).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.14; H, 5.81; N, 8.74.

Iodomethylate (**12**) of **11**.

A mixture of **11** (0.16 g.) and methyl iodide (1.5 ml.) in acetone (4 ml.) was stirred at room temperature for 10 hours. The precipitate was filtered and washed with acetone to give **12** (0.18 g., 78%). An analytical sample was recrystallized from methanol to afford pale yellow prisms, m.p. 176-177° dec.; ir: 1760, 1632 and 1600 cm^{-1}; nmr (DMF-D_7): δ 2.53 (3H, s, CH_3COO), δ 2.55 (3H, s, CH_3COO), δ 3.93 (9H, s, $3CH_3N^+$), δ 4.07 (3H, s, CH_3O), δ 8.13 (1H, s, H_6), δ 8.68 (1H, d, H_4) and δ 9.48 (1H, d, H_1), $J_{H_1H_4}$ = 1.0 Hz; uv λ max: 240 nm (ε, 38,900) 218 nm (ε, 31,800); ms: m/e 318 (M^+-142, 48), 276 (53), 235 (15), 234 (100), 233 (44), 219 (55) and 142 (41).

Anal. Calcd. for $C_{17}H_{21}IN_2O_5$: C, 44.32; H, 4.56; N, 6.08. Found: C, 44.42; H, 4.59; N, 6.11.

7-Methoxy-2-methyl-3,5,8-isoquinolinetrione (**10**).

A mixture of **9** (0.28 g.) and potassium carbonate (0.9 g.) in methanol (12 ml.) was stirred at room temperature for 30 minutes under an atmosphere of oxygen. The filtrate obtained by the filtration of the reaction mixture was concentrated *in vacuo*. The residue was chromatographed on silica gel. The fractions eluted with chloroform were recrystallized from chloroform to give yellow leaflets (0.062 g., 47%), which melted at 285-289°; ir: 1698, 1662 and 1604 cm^{-1}; uv λ max: 312 nm (ε, 8,800), 238 nm (ε, 10,200) and 212 nm (ε, 19,900); ms: m/e 219 (M^+, 100), 191 (37), 163 (23) and 135 (30).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.05; H, 4.16; N, 6.31.

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