STUDIES ON HETEROCYCLIC COMPOUNDS, VII.
SYNTHESIS OF ISOMACULOSIDINE

TSUNG-PING LIN, BORJINN SHIEH,
Graduate Institute of Chemistry, Chung-Yuan Christian University, Chung Li 320, Taiwan, Republic of China

and SHENG-CHU KUO
Department of Pharmacy, China Medical College, Taichung 400, Taiwan, Republic of China

ABSTRACT.—A synthesis of the naturally occurring alkaloid, isomaculosidine, has been carried out. The synthesis starts with ethyl-2-(2,4-dimethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate [4] obtained from the condensation of the readily available 2,4-dimethoxyaniline and ethyl-2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate. Thermal cyclization of 4 gives 5 which is methylated and then reduced with NaBH₄ to afford the corresponding alcohol 7. Dehydration of 7 with concentrated HCl gives 1 in an overall yield of 28% from 4. Alternatively, reduction of 5 followed by methylation affords 1 in an overall yield of 26%.

Isomaculosidine, a fur0 (2,3-b) quinolin-4-one alkaloid, was isolated from Dictamnus albus by Storer and Young in 1973 (2). The structure of isomaculosidine was assigned as 9-methyl-6,8-dimethoxy-4,9-dihydrofuro (2,3-b) quinolin-4-one [1], based on spectral data (2,3) and on partial synthesis from maculosidine (2). In connection with our continuing interest in the synthesis and biological activity of systems related to furo (2,3-b) quinolin-4-one such as glycarpine (4) and taifine (1), we have carried out a synthesis of the structure reported for isomaculosidine, which confirms that the proposed structure is correct.

RESULTS AND DISCUSSION

Our synthetic route to isomaculosidine is shown in Scheme 1.

\[ \text{Scheme 1} \]

\[ \text{2} \rightarrow \text{3} \rightarrow \text{4 (90%) \text{ in THF}} \]

\[ \text{5 (70% \text{ in dimethyl sulfoxide}} \]

\[ \text{6 (90\% \text{ in EtOH}} \]

\[ \text{7 (75\% \text{ in conc. HCl}}} \]

\[ \text{1 (61\%}} \]
Ethyl 2-ethoxy-4-oxo-4,5-dihydropyran-3-carboxylate [2] prepared in situ from chloroacetyl chloride and ethyl sodiomalonate was condensed with 2,4-dimethoxyaniline [3] to afford ethyl-2-(2,4-dimethoxyanilino)-4-oxo-4,5-dihydropyran-3-carboxylate [4]. Thermal cyclization of 4 in boiling diphenyl ether gave 6,8-dimethoxy-2,3,4,9-tetrahydrofuro [2,3-b] quinolin-3,4-dione [5]. Compound 5 was methylated with dimethyl sulfate in DMF to afford the N-methyl derivative 6. The IR spectrum of 6 contained two carbonyl absorption bands located at 1710 and 1630 cm⁻¹. Its 1H-nmr (CDCl₃) spectrum exhibited three signals for the methyl groups at δ 4.30 (3H, s, N-CH₃), δ 4.10 (3H, s, 8-OCH₃), and δ 4.35 (3H, s, 6-OCH₃). A signal due to a methylene group was at δ 5.27 (2H, s, -OCH₂CO-) and signals at δ 7.15 and δ 7.82, respectively, were assigned to the aromatic protons. Based on the spectral data, the structure of 6 was assigned as 6,8-dimethoxy-9-methyl-2,3,4,9-tetrahydrofuro [2,3-b] quinolin-3,4-dione.

Reduction of 6 with excess NaBH₄ in ethanolic alkali afforded the corresponding alcohol, 3-hydroxy-6,8-dimethoxy-9-methyl-2,3,4,9-tetrahydrofuro [2,3-b] quinolin-4-one [7]. Compound 7 was then dehydrated with concentrated HCl to afford 1, mp 170-172°. The uv spectrum of 1 showed λ max (EtOH) at 249, 262, 330 nm. Its ir spectrum had a carbonyl absorption band at 1640 cm⁻¹ and the 1H-nmr spectrum (CDCl₃) exhibited three signals for methyl groups at δ 3.87 (3H, s, N-CH₃), δ 3.90 (3H, s, 8-OCH₃), and δ 4.08 (3H, s, 6-OCH₃), respectively. The signals for the two protons on the aromatic ring were located at δ 7.01 and 7.24 (2H, s). An AB quartet was observed at δ 6.70 (H, d, J=2.5 Hz) and δ 7.54 (H, d, J=2.5 Hz), which represented the protons at positions -2- and -3- of the furan ring. Based on the above data, the structure of 1 was determined to be 6,8-dimethoxy-9-methyl-4,9-dihydropyran-4-one.

The spectral data of the synthetic product 1 were almost superimposable on those reported for natural isomaculosidine (Table 1). In order to further confirm the structure of 1, the method of Govindachari (5) which involves the treatment of 5 with excess NaBH₄ and ethanolic alkali was employed to prepare 1. After usual work-up procedure (1,4), a mixture of two products was isolated. After chromatography over Si gel and repeated recrystallization, pure 8 was isolated. The 1H-nmr spectrum of 8 contained signals at δ 4.03 (3H, s, 8-OCH₃), δ 4.12 (3H, s, 6-OCH₃), δ 7.47 (H, d, J=2.5 Hz, 5-H), δ 7.20 (H, d, J=2.5 Hz, 2-H), δ 6.91 (H, d, J=2.5 Hz, 3-H), δ 7.27 (H, d, J=2.5 Hz, 4-H), δ 6.72 (H, d, J=2.5 Hz, 3-H), δ 7.27 (H, d, J=2.5 Hz, 4-H).

**Table 1.** Comparison of Physical Properties and 1H-nmr Chemical Shifts of 6,8-Dimethoxy-9-methyl-4,9-dihydropyran-4-one [1] and Natural Isomaculosidine

<table>
<thead>
<tr>
<th></th>
<th>Naturala,b</th>
<th>Syntheticc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearances</strong></td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td><strong>mp</strong></td>
<td>170-172°</td>
<td>170-172°</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>259</td>
<td>259</td>
</tr>
<tr>
<td><strong>1H nmr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-CH₃</td>
<td>3.90 (s)</td>
<td>3.87 (s)</td>
</tr>
<tr>
<td>6-OCH₃</td>
<td>4.10 (s)</td>
<td>4.08 (s)</td>
</tr>
<tr>
<td>8-OCH₃</td>
<td>3.92 (s)</td>
<td>3.90 (s)</td>
</tr>
<tr>
<td>C₂-H</td>
<td>7.24 (d)</td>
<td>7.24 (d)</td>
</tr>
<tr>
<td>C₃-H</td>
<td>6.99 (d)</td>
<td>7.01 (d)</td>
</tr>
<tr>
<td>C₄-H</td>
<td>7.58 (d)</td>
<td>7.54 (d)</td>
</tr>
<tr>
<td>C₅-H</td>
<td>6.72 (d)</td>
<td>6.70 (d)</td>
</tr>
</tbody>
</table>

*a R. Storer and D.W. Young (2).
bM. Gellert, et al. (3).
cThis work.
J=2.5 Hz, 2-H), and $\delta$ 8.24 (H, b, -NH) consistent with the structure of 6,8-dimethoxy-4,9-dihydrofuro (2,3-b) quinolin-4-one. Methylation of 8 with dimethyl sulfate in DMF yielded the N-methyl derivative 1 that was the same as the dehydration product from 7.

The tentative assignments for the $^{13}$C-nmr spectrum of 1 were made possible by comparison of these signals with those of model compounds [furoquinoline alkaloids (7), furoquinolone compounds (such as galcarpine, taifine) (1,4), quinolin-4-one compounds (8), and benzofuran compounds (9)] and by decoupling techniques. The assignments of the sp$^2$-hybridized methine carbons (C-2, C-3, C-5, C-7) were made in accordance with their multiplicity (doublet) and the chemical shifts of the $\beta$-carbon atom of aniso and furan, which appear at higher field than the carbon directly bonded to oxygen. The assignments are further supported by selective decoupling of the off-resonance spectrum. Of the two quinolin-4-one tertiary carbon signals, carbon 7 was assigned to that located at 98.93 ppm because of its promixity to the two -OCH$_3$ groups, and, thus, the lower field signal at 104.89 ppm was assigned to carbon atom 5. The quarterary carbons at C-6, C-8, C-9a were assigned by virtue of their long-range coupling in the gated spectrum. The technique of selective decoupling on the gated spectrum was used to confirm the signals of C-3a and C-4a.

The pharmacological activity of 1 is still under investigation, and further results will be reported later.

**EXPERIMENTAL**

**GENERAL PROCEDURES.**—Melting points were determined on a Thomas Hoover apparatus and are uncorrected. I.r. spectra were taken in KBr using a Shimadzu-IR-400. The $^1$H-nmr spectra were recorded in CDC$_3$ unless otherwise indicated, on a JEOL-PMX 60 spectrometer; TMS was used as the internal standard. Mass spectra were determined on a Hitachi RMU 7L mass spectrometer. Tlc was carried out on a Wakogel B-5FM plates.

**ETHYL 2-(2,4-DIMETHOXYANILINO)-4-OXO-4,5-DIHYDROFURAN-3-CARBOXYLATE (4).—**Sodium hydride (2.0 g), previously washed with dry n-hexane, was suspended in dry n-hexane, was suspended in dry THF (100 ml) and added slowly, with shaking, over 10 min to a solution of diethyl malonate (13.7 ml) in dry THF (20 ml). The reaction mixture was heated to reflux on a H$_2$O bath for 2 min, then cooled to 10-12$^\circ$ and chloroacetyl chloride (3.7 ml) in dry THF (20 ml) was added dropwise over 10 min. The solution was kept at this temperature for 1 h at 40-45$^\circ$ for another hour, and then cooled to 10-12$^\circ$. 2,4-Dimethoxyaniline (5.0 g) in dry THF (50 ml) was added dropwise over 20 min. The reaction mixture was left at room temperature overnight. It was then heated under reflux for 1 h, cooled, and poured into ice H$_2$O. The precipitate that formed was dissolved by extraction with CHCl$_3$, and the extract was washed with H$_2$O and dried (MgSO$_4$). The solvent was removed in pan and the concentrated residue refrigerated for 2 days. The precipitate which formed was collected and recrystallized from EtOH to afford the tetronic ester 4 (8.6 g, 90%): mp 135-136$^\circ$; i.r. $\nu$ max (KBr) 3200 (NH), 1700 (-COOC$_2$H$_5$), 1660, 1640, 1590, 1560 cm$^{-1}$; u.v. A$_{max}$ (MeOH) 299 nm; $^1$H nmr $\delta$ (CDCl$_3$) 1.38 (3H, t, -CH$_2$CH$_3$), 3.78 and 3.90 (6H, s, -OCH$_3$), 4.33 (2H, q, -CH$_2$CH$_3$), 4.62 (2H, s, -OCH$_2$CO-), 6.48 (H, s, 4-H), 7.46-7.64 (2H, 5-H, 6-H), and 10.3 (H, s, -NH). Anal. calcd for C$_{15}$H$_{14}$N$_2$O$_6$: C 58.63, H 5.33, N 4.56. Found: C 58.65, H 5.51, N 4.65%.

**ESTER 4 (4.0 g) was added with stirring in one portion to diphenyl ether (35 ml) and the solution maintained at 240$^\circ$. The temperature was then raised to 256$^\circ$ and kept there for 5 min. The mixture was cooled to room temperature and diluted with a large volume of hexane to provide a solid that was collected and washed with hot hexane and purified by chromatography on a Si gel column (100 g). Elution with CHCl$_3$-MeOH (9: 1) yielded a light brown solid which was found to be 3-oxofuroquinolone (5), (2.54 g, 70%): mp 231-233$^\circ$; i.r. $\nu$ max (KBr) 3350 (NH), 1705 (-OCH$_2$CO-), 1640 (ArCOC=CO-), 1580, 1540, 1460 cm$^{-1}$; u.v. A$_{max}$ (MeOH) 259, 318 nm; $^1$H nmr 3 (CDCl$_3$) 1.38 (3H, t, -CH$_2$CH$_3$), 3.78 and 3.90 (6H, s, -OCH$_3$), 4.33 (2H, q, -CH$_2$CH$_3$), 4.62 (2H, s, -OCH$_2$CO-), 6.48 (H, s, 4-H), 7.46-7.64 (2H, 5-H, 6-H), and 10.3 (H, s, -NH). Anal. calcd for C$_{13}$H$_{11}$N$_2$O$_4$: C 59.77, H 5.33, N 4.56. Found: C 59.80, H 5.21, N 4.65%.

**6,8-DIMETHOXY-2,3,4,9-TETRAHYDROFURO (2,3-b) QUINOLIN-3,4-DIONE (5).—**The tetronic ester 4 (4.0 g) as a fine powder was added with stirring in one portion to diphenyl ether (35 ml) and the solution maintained at 240$^\circ$. The temperature was then raised to 256$^\circ$ and kept there for 5 min. The mixture was cooled to room temperature and diluted with a large volume of hexane to provide a solid that was collected and washed with hot hexane and purified by chromatography on a Si gel column (100 g). Elution with CHCl$_3$-MeOH (9: 1) yielded a light brown solid which was found to be 3-oxofuroquinolone (5), (2.54 g, 70%): mp 231-233$^\circ$; i.r. $\nu$ max (KBr) 3350 (NH), 1705 (-OCH$_2$CO-), 1640 (ArCOC=CO-), 1580, 1540, 1460 cm$^{-1}$; u.v. A$_{max}$ (MeOH) 259, 318 nm; $^1$H nmr 3 (CDCl$_3$) 1.38 (3H, t, -CH$_2$CH$_3$), 3.78 and 3.90 (6H, s, -OCH$_3$), 4.33 (2H, q, -CH$_2$CH$_3$), 4.62 (2H, s, -OCH$_2$CO-), 6.48 (H, s, 4-H), 7.46-7.64 (2H, 5-H, 6-H), and 10.3 (H, s, -NH). Anal. calcd for C$_{13}$H$_{11}$N$_2$O$_4$: C 59.77, H 5.33, N 4.56. Found: C 59.80, H 5.21, N 4.65%.

**6,8-DIMETHOXY-4,9-DIHYDROFURO (2,3-b) QUINOLIN-4-ONE (8).—**3-Oxofuroquinolone (5) (0.6 g) was suspended in a mixture of EtOH (150 ml) and 2 N NaOH solution (20 ml) and treated portionwise with an excess of NaBH$_4$ (7.5 g) over a period of 1 h. The mixture was heated at reflux for 6 h until a solid
separated. It was then filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in 
H$_2$O, and the combined aqueous solution was filtered. The filtrate was neutralized with glacial HOAc and 
refrigerated for 2 days. The brown solid which formed was collected and dissolved in CHCl$_3$, washed with 
H$_2$O, dried (MgSO$_4$), and the solvent removed. The residue, after evaporation, was subjected to yield 8 
(0.23 g, 41%): mp 188-189$^\circ$; ir v max (KBr) 3280 (-NH), 1660, 1630, 1610 cm$^{-1}$; uv $\lambda$ max (MeOH) 
252, 323 nm; $^1$H nmr (CDCl$_3$) 4.03 (3H, s, -OCH$_3$), 4.12 (3H, s, -OCH$_3$), 6.91 (H, d, $J=2.5$ Hz, 
3-H), 7.20 (H, d, $J=2.5$ Hz, 7-H), 7.27 (H, d, $J=2.5$ Hz, 2-H), 7.47 (H, s, 5-H), 8.24 (H, b, NH). 
Anal. calcd for C$_{13}$H$_{11}$NO$_4$: C 63.67, H 4.48. Found: C 63.64, H 4.40, 4.45%.

6,8-DIMETHOXY-9-METHYL-2,3,4,9-TETRAHYDROFURAN (2,3-b) QUINOLIN-3,4-DIONE [6].—The cyclized product 5 (3.0 g) was suspended in DMF (20 ml) and warmed to 40$^\circ$. To the suspension was added anhydrous K$_2$CO$_3$ (25.0 g). Dimethyl sulfate (20.0 g) was then added to the reaction mixture dropwise over 
h 1 h. The slurry was filtered, and the precipitate was washed with CHCl$_3$. The filtrate and washings were 
combined, and the solvent was evaporated in vacuo. Ice H$_2$O was added to the residue, and the mixture was 
filtered. The precipitate which recollected was washed with H$_2$O and purified by chromatography on Si gel 
(100 g).

Elution with CHCl$_3$ yielded colorless crystals of 6 (2.84 g, 90%): mp 255-257$^\circ$; ir v max (KBr) 1710, 
1630, 1580, 1520 cm$^{-1}$; ms m/z 341 (M$^+$); $^1$H nmr 6 (CDCl$_3$) 3.87 (3H, s, -NCH$_3$), 3.90 (3H, 
-s, -OCH$_3$), 7.15 (H, d, 7-H), 7.78 (H, d, 5-H). Anal. calcd for C$_{14}$H$_{13}$N$_2$O$_5$: C 60.20, 60.20; H 4.25, 
4.28%.

3-HYDROXY-6,8-DIMETHOXY-9-METHYL-2,3,4,9-TETRAHYDROFURAN (2,3-b) QUINOLIN-4-ONE [7].—A solution of 6 (0.4 g) in EtOH (160 ml) was cooled to 15$^\circ$ and treated with NaBH$_4$ (2.0 g) over a period of 
h 1 h. The resulting yellow solution was left at room temperature until it became colorless (3 h).

The solvent was removed in vacuo, and the residue was extracted with CHCl$_3$, dried, and concentrated.
Recrystallization from CHCl$_3$/MeOH yielded the alcohol 7 (0.3 g) which recrystallized from DMF (25 ml) was 
warmed to 40$^\circ$, and anhydrous K$_2$CO$_3$ (3.0 g) was then added to the reaction mixture dropwise over a period of 
h 1 h, and the precipitate that formed was filtered off and washed with CHCl$_3$. The filtrate and washings were 
combined, and the solvent was evaporated in vacuo. Ice H$_2$O was added to the residue, and the mixture was 
filtered. The precipitate which recollected was washed with H$_2$O and purified by chromatography on Si gel (50.0 g). Elution with CHCl$_3$ yielded colorless crystals of 1 (0.285 g, 90%).

ACKNOWLEDGMENTS

The authors wish to thank the National Science Council of China for its financial support. We also wish to thank Drs. D. W. Young and R. Storer, School of Molecular Science, University of Sussex, for providing us with ir, uv, and $^1$H-nmr spectral data for comparison purpose.

LITERATURE CITED

(1971).
American Society of Pharmacognosy
Awards and Grants

To stimulate interest in all phases of natural product research, the American Society of Pharmacognosy is offering the following awards and grants:

1. **Research Starter Grants:**
   Members of the Society who are within the first five years of assuming their first professional position are eligible for a grant of $2000 to $5000 to aid in their research. These grants will not provide overhead monies to the grantee institution. Applications are due February 1, 1988.

2. **Travel Grants for Active Members:**
   Members of the Society who are within the first five years of assuming their first professional position are eligible for a grant of $300 to $500 to enable them to present a paper at the annual meeting of the Society. Applications are due May 1, 1988.

3. **Travel Grants for Graduate Students:**
   Graduate students under supervision of a Society member are eligible for a grant of $300 to $500 to enable them to present a paper at the annual meeting of the Society. Applications are due May 1, 1988.

4. **Undergraduate Research Awards:**
   Undergraduate students interested in investigating a career in natural product research are eligible for a research award to study under the direction of a Society Member on the faculty of an American college or university. These awards ($2000 to the student and $500 to the advisor) do not provide overhead monies to the grantee institution. The research project is to be accomplished in a summer during the student's academic program leading to the B.S. or Pharm.D. degrees. Applications are due February 1, 1988.

Address inquiries and requests for application information to:

Chris M. Ireland, Ph.D.
Chairman, Awards Committee
American Society of Pharmacognosy
College of Pharmacy
University of Utah
Salt Lake City, UT 84112