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STUDIES ON HETEROCYCLIC COMPOUNDS, VII. SYNTHESIS OF ISOMACULOSIDINE[1]

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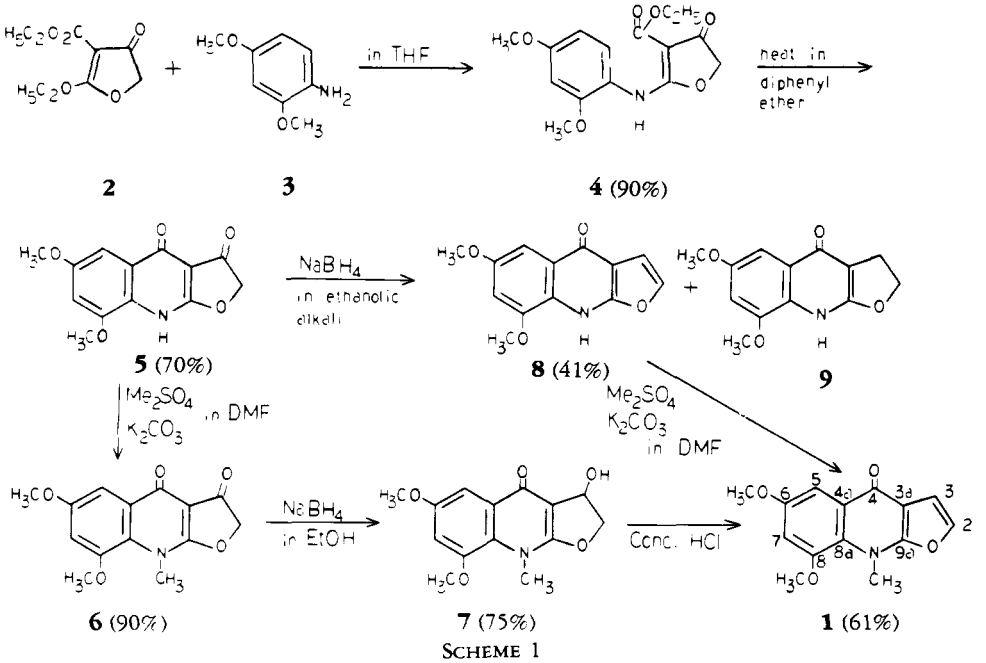
ABSTRACT.—A synthesis of the naturally occurring alkaloid, isomaculosidine, has been carried out. The synthesis starts with ethyl-2-(2,4-dimethoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate [**4**] obtained from the condensation of the readily available 2,4-dimethoxyaniline and ethyl-2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate. Thermal cyclization of **4** gives **5** which is methylated and then reduced with $NaBH_4$ 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 furo (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.



2 **3** **4** (90%)

5 (70%) **8** (41%) **9**

6 (90%) **7** (75%) **1** (61%)

SCHEME 1

[1]For Part VI, see Kuo *et al.* (1).

Ethyl 2-ethoxy-4-oxo-4,5-dihydrofuran-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-dihydrofuran-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 ^{1}H-nmr (CF_3COOD) spectrum exhibited three signals for the methyl groups at δ 4.30 (3H, s, N-CH_3), δ 4.10 (3H, s, 8-OCH_3), and δ 4.35 (3H, s, 6-OCH_3). A signal due to a methylene group was at δ 5.27 (2H, s, -OCH_2CO-) 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 $NaBH_4$ in ethanolic alkali afforded the corresponding alcohol, 3-hydroxy-6,8-dimethoxy-9-methyl-2,3,4,9-tetrahydrofuro (2,3-*b*) quinoline-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 ^{1}H-nmr spectrum ($CDCl_3$) exhibited three signals for methyl groups at δ 3.87 (3H, s, N-CH_3), δ 3.90 (3H, s, 8-OCH_3), and δ 4.08 (3H, s, 6-OCH_3, 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-dihydrofuro (2,3-*b*) quinolin-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 $NaBH_4$ 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 ^{1}H-nmr spectrum of **8** contained signals at δ 4.03 (3H, s, 8-OCH_3), δ 4.12 (3H, s, 6-OCH_3), 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,

TABLE 1. Comparison of Physical Properties and ^{1}H-nmr Chemical Shifts of 6,8-Dimethoxy-9-methyl-4,9-dihydrofuro (2,3-*b*) quinolin-4-one [**1**] and Natural Isomaculosidine

	Natural[a,b]	Synthetic[c]
Appearances	White	White
mp	170-172°	170-172°
M^+	259	259
^{1}H nmr		
N-CH_3	3.90 (s)	3.87 (s)
6-OCH_3	4.10 (s)	4.08 (s)
8-OCH_3	3.92 (s)	3.90 (s)
C_5-H	7.24 (d)	7.24 (d)
C_7-H	6.99 (d)	7.01 (d)
C_2-H	7.58 (d)	7.54 (d)
C_3-H	6.72 (d)	6.70 (d)

[a]R. Storer and D.W. Young (2).
[b]M. Gellert, *et al.* (3).
[c]This work.

J=2.5 Hz, 2-H), and δ 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 glycarpine, 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 β-carbon atom of anisole 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 quarternary 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. Ir spectra were taken in KBr using a Shimadzu-IR-400. The ^{1}H-nmr spectra were recorded in $CDCl_3$, 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 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_2O bath for 2 min, then cooled to 10-12° 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° for another hour, and then cooled to 10-12°. 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_2O. The precipitate that formed was dissolved by extraction with $CHCl_3$, and the extract was washed with H_2O and dried ($MgSO_4$). The solvent was removed in part 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°; ir ν max (KBr) 3200 (NH), 1700 (-$COOC_2H_5$), 1660, 1640, 1590, 1560 cm^{-1}; uv λ max (MeOH) 299 nm; ^{1}H nmr δ ($CDCl_3$) 1.38 (3H, t, -CH_2CH_3), 3.78 and 3.90 (6H, s, -OCH_3), 4.33 (2H, q, -CH_2CH_3), 4.62 (2H, s, -OCH_2CO-), 6.48 (H, s, 4-H), 7.46-7.64 (2H, 5-H, 6-H), and 10.3 (H, s, -NH). *Anal.* calcd for $C_{15}H_{17}NO_6$: C 58.63, H 5.33, N 4.56. Found: C 58.65, H 5.51, 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°. The temperature was then raised to 256° and kept there for 5 min. The mixture was cooled to room temperature and diluted with a large volume of hexane to provide a dark 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°; ir ν max (KBr) 3350 (-NH), 1705 (-OCH_2CO-), 1640 (ArCOC=CO-), 1580, 1540, 1460 cm^{-1}; uv λ max (MeOH) 259, 318 nm; ^{1}H nmr δ (CF_3COOD) 4.03 (3H, s, 8-OCH_3), 4.12 (3H, s, 6-OCH_3), 5.25 (2H, s, -OCH_2CO-), 7.28 (H, s, 7-H), 7.43 (H, s, 5-H). *Anal.* calcd for $C_{13}H_{11}NO_5$: C 59.77, H 4.21. Found: C 59.50, H 4.31%.

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_2O, 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_2O, dried ($MgSO_4$), and the solvent removed. The residue, after evaporation, was subjected to yield **8** (0.23 g, 41%): mp 188-189°; ir ν max (KBr) 3280 (-NH), 1660, 1630, 1610 cm^{-1}; uv λ max (MeOH) 252, 323 nm; ^1H nmr δ ($CDCl_3$) 4.03 (3H, s, 8-OCH_3), 4.12 (3H, s, 6-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 63.37, H 4.48. Found: C 64.01, 64.10, H 4.40, 4.45%.

6,8-DIMETHOXY-9-METHYL-2,3,4,9-TETRAHYDROFURO (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°. To the suspension was added anhydrous K_2CO_3 (25.0 g). Dimethyl sulfate (20.0 g) was then added to the reaction mixture dropwise over 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_2O was added to the residue, and the precipitate was collected by filtration, washed with H_2O, 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°; ir ν max (KBr) 1710, 1630, 1580, 1520 cm^{-1}; uv λ max (MeOH) 259, 318 nm; ^1H nmr δ (CF_3COOD) 4.03 (3H, s, N-CH_3), 4.10 (3H, s, 8-OCH_3), 4.35 (3H, s, 6-OCH_3), 5.27 (2H, s, -OCH_2CO-), 7.15 (H, 7-H), 7.82 (H, 5-H). *Anal.* calcd for $C_{14}H_{13}NO_5$:C 59.77, H 4.21. Found: C 60.20, 60.01, H 4.25, 4.28%.

3-HYDROXY-6,8-DIMETHOXY-9-METHYL-2,3,4,9-TETRAHYDROFURO (2,3-*b*) QUINOLIN-4-ONE [**7**].—A solution of **6** (0.4 g) in EtOH (160 ml) was cooled to 15° and treated with $NaBH_4$ (2.0 g) over a period of 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, 75%): mp 170-172°; ir ν max (KBr) 3150 (CHOH), 1640, 1615, 1585, 1530, 1510 cm^{-1}; ^1H nmr δ (CF_3COOD) 4.03 (3H, s, N-CH_3), 4.10 (3H, s, 8-OCH_3), 4.37 (3H, s, 6-OCH_3), 7.15 (H, d, 7-H), 7.45 (H, d, 3-H), 7.62 (H, d, 2-H), 7.82 (H, d, 5-H). *Anal.* calcd for $C_{14}H_{15}NO_5$: C 60.64, H 5.41. Found: C 60.10, 60.40; H 5.45, 5.48%.

6,8-DIMETHOXY-9-METHYL-4,9-DIHYDROFURO (2,3-*b*) QUINOLIN-4-ONE [**1**].—Concentrated HCl (20 ml) was added dropwise to a suspension of **7** (1.0 g) dissolved in 250 ml of MeOH until it was completely dissolved, and then the solution was brought to pH 7 with $NaHCO_3$. The mixture after neutralization was extracted with $CHCl_3$ and the solvent removed in vacuo. The residue was recrystallized from $CHCl_3$/*n*-hexane to give white crystalline needles of **1** (0.57 g, 61%): mp 170-172° (lit. 170-172°); ir ν max (KBr) 1640, 1620, 1590, 1540, 1520 cm^{-1}; ms *m/z* 259 (M^+); uv λ max (MeOH) 244, 262, 330 nm; ^1H nmr δ ($CDCl_3$) 3.87 (3H, s, N-CH_3), 3.90 (3H, s, 8-OCH_3), 4.08 (3H, s, 6-OCH_3), 6.70 (1H, d, J=2.5 Hz, 3-H), 7.01 (1H, d, J=2.5 Hz, 7-H), 7.24 (1H, d, J=2.5 Hz, 5-H), 7.54 (1H, d, J=2.5 Hz, 2-H); ^{13}C nmr ($CDCl_3$) 36.40 (NCH_3, q), 55.48 (OCH_3, q), 56.13 (OCH_3, q), 137.51 (C-2, d), 104.89 (C-3, d), 105.65 (C-3a, s), 171.96 (C-4, s), 124.72 (C-4a, s), 107.27 (C-5, d), 155.49 (C-6, s), 98.93 (C-7, d), 151.27 (C-8, s), 128.40 (C-8a, s), 157.01 (C-9a, s). *Anal.* calcd for $C_{14}H_{13}NO_4$: C 64.86, H 5.02; Found: C 64.85, 64.87; H 5.05, 5.02%.

N-METHYLATION OF **8**.—A suspension of **8** (0.3 g) in DMF (25 ml) was warmed to 40°, and anhydrous K_2CO_3 (5.0 g) was added. Dimethyl sulfate (3.0 g) was then added dropwise over a period of 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_2O was added to the residue, and the mixture was filtered. The precipitate which recollected was washed with H_2O and purified by chromatography on Si gel (50.0 g). Elution with $CHCl_3$ yielded colorless crystals of **1** (0.285 g, 90%).

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