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STUDIES ON HETEROCYCLIC COMPOUNDS, VI.[1] SYNTHETIC INVESTIGATION OF TAIFINE

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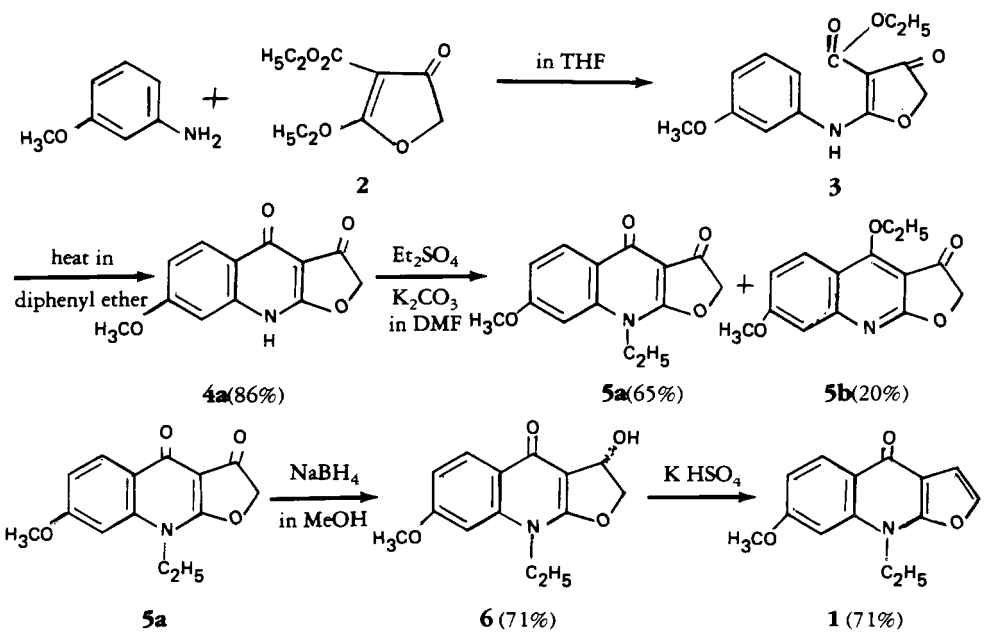
ABSTRACT.—A synthetic approach to the structure reported for the naturally isolated alkaloid named taifine has been developed. The structural assignment is established by spectral data: ir, uv, ^{1}H nmr, and ^{13}C nmr. However, both the spectral and physical properties indicate that synthetic and natural taifine are different in constitution, suggesting the original structure assigned for taifine should be revised.

Recently, a novel furo(2,3-*b*)quinolin-4-one named taifine was isolated from *Ruta chalepensis* L. (Rutaceae) by El-Tawil and co-workers, and was assigned the structure 9-ethyl-7-methoxy-4,9-dihydrofuro(2,3-*b*)quinolin-4-one (**1**) purely based upon spectral data (2). As part of our continuing interest in the synthesis and biological activities of furo(2,3-*b*)quinolin-4-one derivatives (1), we carried out a synthetic approach to the structure reported for taifine using the modified procedure of Tuppy and Böhm (3). We now report the results from this synthetic investigation which suggest that the proposed structure for taifine needs reinvestigation.

SYNTHETIC RESULTS AND DISCUSSION

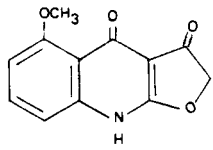
The synthetic approach to taifine is shown in summary form in Scheme 1. Ethyl



SCHEME 1

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

2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate (**2**) prepared *in situ* from chloroacetyl chloride and ethyl sodiomalonate was condensed with 3-methoxyaniline to give ethyl 2-(3′-methoxyanilino)-4-oxo-4,5-dihydrofuran-3-carboxylate (**3**). Thermal cyclization of **3** in boiling diphenylether afforded 7-methoxy-2,3,4,9-tetrahydrofuro(2,3-*b*)quinolin-3,4-dione (**4a**) in 86% yield. The ^{1}H-nmr spectrum of **4a** exhibits, besides two singlets at δ 4.10 and 5.24, a single-proton absorption at δ 8.36, which is coupled only to the proton at δ 7.31 (J=9.0 Hz), and a one-proton signal at δ 7.23, which is also a singlet. This observation is consistent with the substitution pattern of the benzene ring in structure **4a** and thus excludes the other possible cyclized product **4b**.



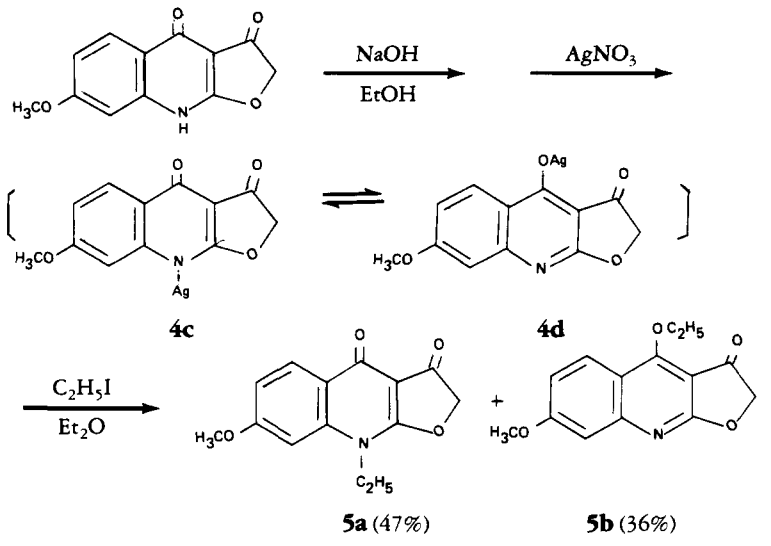
4b

When compound **4a** was treated with diethyl sulfate and K_2CO_3 in dry DMF, two products were isolated. The elemental analyses and mass spectra of both products were consistent with a molecular formula of $C_{14}H_{13}NO_4$, indicating that they are isomers of alkylation products. The major isomer (65%) exhibits a uv spectrum with λ max ($CHCl_3$) at 255, 276, and 318 nm (log ε=3.64, 3.68, and 3.30, respectively), which is very similar to that of the starting compound **4a** [λ max ($CHCl_3$) at 254, 266, and 318 nm, log ε=3.25, 3.22, and 3.22, respectively]. This product also displays two carbonyl absorption bands at 1708 and 1625 cm^{-1} but no N-H absorption band in its ir spectrum. These observations suggest that the major isomer derived from alkylation at the nitrogen atom of **4a**, and its structure is therefore assigned as 9-ethyl-7-methoxy-3-oxo-2,3-dihydrofuran(2,3-*b*)quinolin-4-one (**5a**). The structure of **5a** is further supported by its ^{1}H-nmr spectrum, which exhibits signals indicative of an ethyl group at δ 1.63 (t, J=7.0 Hz) and 4.64 (q, J=7.0 Hz), two singlets at δ 4.12 and 5.25 for respective methoxy and methylene protons, and the absorptions of protons on the benzene ring at δ 7.33 (s), 7.49 (d, J=9.0 Hz), and 8.54 (d, J=9.0 Hz).

The minor product (20%) from the alkylation reaction displays only one carbonyl absorption band at 1702 cm^{-1} and no N-H absorption in its ir spectrum, suggesting that the alkylation has occurred at the oxygen atom of the benzylic carbonyl group of compound **4a**. The ^{1}H-nmr spectrum exhibits signals for the ethyl protons at δ 1.49 (t, J=7.0 Hz) and 4.89 (q, J=7.0 Hz), and two singlets for the methoxy and methylene protons at 3.90 and 4.61 ppm, respectively. The signals for the protons on the benzene ring appear at δ 7.01 (s), 7.13 (d, J=9.0 Hz), and 8.01 (d, J=9.0 Hz), indicating that the deshielding effect of the carbonyl group on the hydrogen at C-5 in compound **4a** is removed upon alkylation. Based upon the above spectral information, the structure of the minor alkylation product was assigned as 4-ethoxy-7-methoxy-2,3-dihydrofuro(2,3-*b*)quinolin-3-one (**5b**).

Alternatively, alkylation of compound **4a** could be achieved via its silver salt (**4c, 4d**) (Scheme 2) by treatment of the salt with ethyl iodide in Et_2O (4). In this manner, the yield of *O*-alkylated product **5b** was raised to 36% as compensation for the lower yield of **5a** (47%).

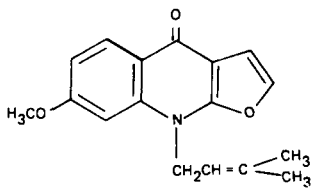
Reduction of **5a** with excess sodium borohydride in ethanolic alkali gave the corresponding alcohol **6**, which was then dehydrated with anhydrous $KHSO_4$ or concentrated HCl to yield a yellow crystalline product, mp 178°. The mass spectrum (M^+ m/z 243) and elemental analysis of this product suggest a molecular formula of $C_{14}H_{13}NO_3$. Based upon both the spectral data (see Experimental Section and Table 1)



SCHEME 2

and the course of synthetic pathway, the product is assigned the constitution 9-ethyl-7-methoxy-4,9-dihydrofuro (2,3-*b*)quinolin-4-one (**1**), the same constitution assigned to the naturally isolated taifine (2).

The structural assignment of the synthetic product **1** was supported by the similarity of its spectral data with those of acrophylline (**7**) (5). The ir spectrum of compound **7** has a carbonyl absorption band at 1620 cm^{-1}, and its ^{1}H-nmr spectrum exhibits absorptions at δ 6.83 (m, 2H) and 8.31 (d, 1H) for the protons of the benzene ring, in addition to those at δ 7.22 and 6.99 for the protons of the furan ring.



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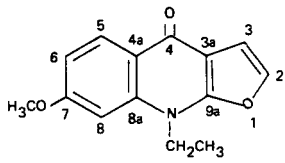
In order to gain further insight into the structure of the synthetic product, its ^{13}C-nmr spectrum was obtained, and the data is summarized in Table 1. Assignments of the ^{13}C-nmr spectrum were made possible by comparison with model compounds [furoquinoline alkaloids (6), quinolin-4-ones (7), and benzofurans (8)] and by decoupling techniques. Thus, the assignments of sp^2-hybrid methine carbons (C-2, C-3, C-5, C-6, and C-8) were made in accordance with the multiplicity (doublet) and the chemical shift of the β-carbon of anisole and furan, which appears at higher field than the carbon directly bonded to oxygen (α-carbon) (9). These assignments are further supported by the selective decoupling method on the OFR spectrum. For the quaternary carbons, the signals due to C-7, C-8a, and C-9a were confirmed by virtue of their long range coupling ($J_{C\text{-}C\text{-}H}$) in the gated spectrum, and the technique of the selective decoupling on the gated spectrum was used to confirm the signals of C-3a and C-4a.

With all of the data presented, the structure of synthetic product **1** appears to be well established. However, comparison of the physical and ^{1}H-nmr spectral properties of **1** and natural taifine (Table 2) clearly indicates that the structures are not identical.

TABLE 1. ^{13}C-Nmr Spectra of 9-Ethyl-7-methoxy-4,9-dihydrofuro (2,3-*b*) quinolin-4-one (**1**) and 4-Ethoxy-7-methoxyfuro (2,3-*b*) quinoline (**8**)



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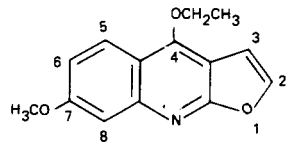

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Carbon	ppm[a]	multiplicity	ppm[a]	multiplicity
C-2	137.60	d	141.95	d
C-3	110.00	d	105.71	d
C-3a	105.91	s	113.29	s
C-4	173.00	s	160.44	s
C-4a	119.71	s	101.75	s
C-5	129.41	d	123.42	d
C-6	107.72	d	116.06	d
C-7	162.81	s	147.42	s
C-8	97.67	d	104.64	d
C-8a	138.78	s	155.88	s
C-9a	155.74	s	164.11	s
—OCH_3	55.60	q	55.10	q
—CH_2CH_3	39.65	t	66.81	t
—CH_2CH_3	13.33	q	15.01	q

[a]TMS as an internal standard; $CDCl_3$ as a solvent.

The structure of naturally isolated taifine was apparently assigned incorrectly and needs to be reinvestigated.

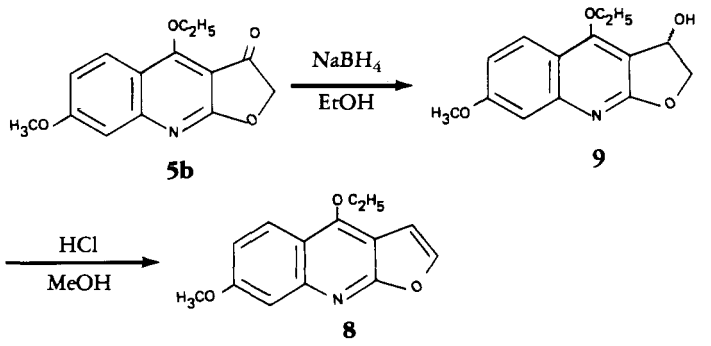
In connection with this study, we also carried out the synthesis of 4-ethoxy-7-methoxyfuro(2,3-*b*)quinoline (**8**). Compound **8** is structurally different from the synthetic taifine only in the placement of the ethyl group.

By analogy, the synthesis of compound **8** (Scheme 3) was accomplished by taking **5b** through reduction and dehydration reactions as shown in Scheme 1. Treatment of **5b** with $NaBH_4$ in EtOH gave the corresponding alcohol **9**: ir 3300 cm^{-1}. Without further purification, **9** was subjected to dehydration with concentrated HCl in MeOH to afford furo(2,3-*b*)quinoline (**8**) in an overall yield of 55% after recrystallization from $CHCl_3$/MeOH. We have also found that reduction of **4a** with $NaBH_4$ in ethanolic alkali proceeded to afford directly the furoquinolinone **10** in 54% yield (10,11).

TABLE 2. Comparison of Physical and ^{1}H-Nmr Spectral Properties of Natural Taifine and Synthetic **1** and **8**

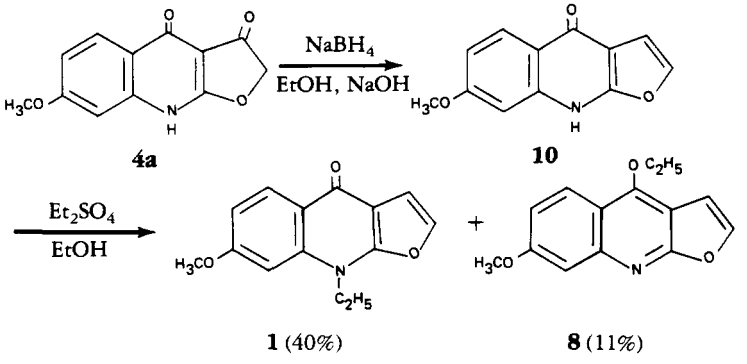
	natural[a]	Synthetic **1**[b]	**8**[b]
Appearance	white needles	yellow needles	white crystals
Mp	110° (from petroleum ether)	178° (from $CHCl_3$/EtOH)	110° (from C_6H_6)
^{1}H-nmr ppm ($CDCl_3$)	1.63 (t, 3H, J=7.0 Hz)	1.48 (t, 3H, J=7.0 Hz, CH_2CH_3)	1.52 (t, 3H, J=7.0 Hz)
	4.77 (q, 1H, J=7.0 Hz)	4.11 (q, 2H, J=7.0 Hz, CH_2CH_3)	4.57 (q, 2H, J=7.0 Hz)
	3.97 (s, 3H)	3.94 (s, 3H, OCH_3)	3.92 (s, 3H)
	7.00 (d, 1H)	7.05 (d, 1H, J=2.5 Hz, 3-H)	6.83 (d, 1H, J=2.5 Hz)
	7.65 (d, 1H)	7.27 (d, 1H, J=2.5 Hz, 2-H)	7.29 (1H, d, J=2.5 Hz)
	7.38 (dd, 1H, J=9.0 Hz; 3 Hz)	6.95 (1H, d, J=9.0 Hz, 6-H)	7.03 (1H, dd, J=9 Hz, 2.5 Hz)
	7.60 (d, 1H, J=3 Hz)	6.87 (1H, s, 8-H)	7.46 (1H, d, J=2.5 Hz)
	8.00 (d, 1H, J=9.0 Hz)	8.50 (d, 1H, J=9.0 Hz, 5-H)	8.08 (1H, d, J=9 Hz)

[a]El-Taiwil *et al.* (2).
[b]This work.



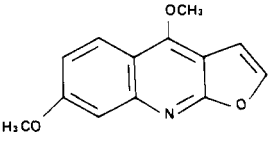
SCHEME 3

Subsequent alkylation of **10** with diethyl sulfate in ethanolic alkali gave the two isomeric alkylated products **1** and **8**, in the yield of 40% and 11%, respectively (Scheme 4).



SCHEME 4

The structure assignment to compound **8** follows reasonably from its origins. Further, its ^{1}H-nmr spectrum is completely consistent with the structure. The ethyl protons appear at δ 1.52 and 4.57 with a characteristic coupling pattern; the methoxy protons appear as a singlet at δ 3.92; and the five aromatic protons appear at δ 6.83 (d, J=2.5 Hz), 7.03 (dd, J=9 Hz, 2.5 Hz), 7.29 (d, J=2.5 Hz), 7.46 (d, J=2.5 Hz), and 8.08 (d, J=9 Hz). The ^{1}H-nmr spectrum of **8** shows great resemblance to that of evolitrine (**11**) (12).



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The ^{13}C-nmr spectrum of **8** summarized in Table 1 further substantiates the structure assignment. It has the required number of resonance lines (14-carbons) in the completely decoupled spectrum and the necessary coupling pattern in the OFR spectrum. Assignments of the ^{13}C-nmr spectrum were made by comparison with furoquinolines (13-15) such as dictamnine and skimmianine.

The physical and spectroscopic properties of **8** (Table 2), although similar to those of natural taifine, are not identical to those of the natural product. We therefore con-

clude that taifine does not have the structure 9-ethyl-7-methoxy-4,9-dihydrofuro(2,3-*b*)quinoline-4-one (**1**) or 4-ethoxy-7-methoxyfuro(2,3-*b*)quinoline (**8**).[2]

Screening tests of the pharmacological activities of the synthetic compounds **4-10** are in progresss and will be reported later.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined in open-ended capillary tubes on a Thomas Hoover apparatus and are uncorrected. Ir spectra were taken in KBr using a Shimadzu-IR-440. The ^{1}H-nmr spectra were recorded in $CDCl_3$, unless otherwise indicated, on a JEOL-PMX 60 spectrometer. The ^{13}C-nmr spectra were recorded in CD_3COOD on a JEOL-FX 100 NMR spectrometer. TMS was used as internal standard. Mass spectra were determined on Hitachi RMU 71 mass spectrometer. TLC was carried out on Wakogel B-5 FM plates.

ETHYL 2-(3'-METHOXYANILINO)-4-OXO-4,5-DIHYDROFURAN-3-CARBOXYLATE (**3**).—Sodium hydride (36 g, 1.5 mole), previously washed with dry *n*-hexane, was suspended in dry THF (250 ml) and added slowly, with shaking, over 20 min to a solution of diethyl malonate (230 ml, 1.5 mole) in dry THF (500 ml). The reaction mixture was refluxed on a water bath for 2 min, then cooled to 10-12°, and chloroacetyl chloride (63.8 ml, 0.8 mole) in dry THF (340 ml) was added dropwise over 1 h. The solution was kept at this temperature for 1 h, and at 40-50° for another h, then cooled to 10-12°. 3-Methoxyaniline (83.9 ml, 0.75 mole) in dry THF (850 ml) was then added dropwise over 1 h. The reaction mixture was left at room temperature overnight, heated under reflux for 1 h, then cooled and poured into iced H_2O. The precipitated solid was extracted with $CHCl_3$, and the extract was washed with H_2O and dried ($MgSO_4$). The solvent was partially evaporated and the concentrated residue refrigerated for 3 days. The precipitate was collected and recrystallized from EtOH to afford the tetronic ester **3** (133 g, 64%): mp 142-143°; ir ν max (KBr) 3300 (NH), 1700 ($-COOC_2H_5$), 1652 cm^{-1}; uv λ max ($CHCl_3$) 308; ^{1}H nmr δ 1.36 (3H, t, J=7.0 Hz, $-CH_2-CH_3$) 3.80 (3H, s, $-OCH_3$), 4.30 (2H, q, J=7.0 Hz, $-CH_2-CH_3$), 4.60 (2H, s, $-COCH_2O-$), 6.56-7.35 (4H, m, aromatic protons), 10.15 (1H, s, NH). Calcd for $C_{14}H_{15}NO_5$: C 66.65, H 5.42, N 5.05, Found; C 66.74, 66.60, H 5.31, 5.29, N 5.00, 5.15%.

7-METHOXY-2,3,4,9-TETRAHYDROFURO(2,3-*b*)QUINOLIN-3,4-DIONE (**4a**).—The tetronic ester **3** (7.4 g, 0.03 mole) as a fine powder was added with stirring in one lot to diphenyl ether (70 ml) 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 precipitate a dark solid that was collected and washed with hot hexane and purified by chromatography on silica gel (150 g) column. Elution with $CHCl_3$-MeOH (9:1) yielded a light-brown solid of 3-oxofuroquinolone (**4a**), 5.2 g (86%): mp 278-280°; ir ν max (KBr) 2925 (NH), 1705 ($-O-CH_2-CO-$), 1670 ($Ar-CO-C=C-$); uv λ max ($CHCl_3$) 254, 266, and 318 nm (log ϵ=3.25, 3.25, 3.22); ^{1}H-nmr δ (CF_3COOD) 4.10 (3H, s, $-OCH_3$), 5.24 (2H, s, $-OCH_2-CO-$), 7.25 (1H, s, 8-H), 7.31 (1H, d, J=9.0 Hz, 6-H), and 8.36 (1H, d, J=9.0 Hz, 5-H), calcd for $C_{12}H_9NO_4$: C 62.34, H 3.90, N 6.06. Found; C 62.48, 62.20; H 3.71, 3.62; N 6.26, 6.18%.

9-ETHYL-7-METHOXY-3-OXO-2,3-DIHYDROFURO(2,3-*b*)QUINOLIN-4-ONE (**5a**) AND 4-ETHOXY-7-METHOXY-2-DIHYDROFURO(2,3-*b*)QUINOLIN-3-ONE (**5b**).—*Method 1*.—The cyclized product **4a** (4.62 g, 0.02 mole) was suspended in DMF (140 ml) and warmed to 40°. To the suspension was added anhydrous K_2CO_3 (34.6 g, 0.25 mole). Diethyl sulfate (26.3 ml, 0.25 mole) was then added dropwise over 1 h. The reaction mixture was filtered, and the precipitate was washed with $CHCl_3$. The filtrate and washings were combined, and the solvent was evaporated in vacuo. Iced H_2O was added to the residue, and the precipitate was collected by filtration, washed with H_2O, and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (150 g). Elution with $CHCl_3$-EtOH (98:3) yielded compound **5a** (3.4 g, 65%): mp 248-250°; ir ν max (KBr) 1708 ($-CO-CH_2-O-$), 1625 ($Ar-CO-C=C-$) cm^{-1}; uv λ max ($CHCl_3$) 255, 276, and 318 nm (log ϵ=3.64, 3.68, 330); ^{1}H-nmr δ (CF_3COOD) 1.63 (3H, t, J=7.0 Hz, $-CH_2-CH_3$), 4.12 (3H, s, $-OCH_3$), 4.64 (2H; q, J=7.0 Hz, $-CH_2CH_3$), 5.25 (2H, s, $-COCH_2-O-$), 7.33 (1H, s, 8-H), 7.48 (1H, d, J=9.0 Hz, 6-H), and 8.54 (1H, d, J=9.0 Hz, 5-H). Calcd for $C_{14}H_{13}NO_4$; C 64.86; H 5.02; N 5.41. Found: C 64.71, 64.85; H 5.10, 4.93; N 5.32, 5.35%, and compound **5b** (1.0 g, 20%): mp 196-197°; ir ν max 1702 ($-CO-CH_2-O-$), 1601 cm^{-1}; uv λ max ($CHCl_3$) 264, 330 nm (log ϵ=3.76, 4.09); ^{1}H nmr δ ($CDCl_3$), 1.49 (3H, t, J=7.0 Hz, $-CH_2CH_3$), 3.90 (3H, s, $-OCH_3$), 4.61 (2H, s, $-COCH_2-O-$), 4.83 (2H, q, J=7.0 Hz, $-CH_2-CH_3$), 7.01 (1H, s, 8-H), 7.13 (1H, d, J=9.0 Hz, 6-H), 8.01 (1H, d, J=9.0 Hz, 5-H). Calcd for $C_{14}H_{13}NO_4$: C 64.86; H 5.03; N 5.41. Found: C 64.78, 65.00; H 4.95, 4.98; N 5.30, 5.50%.

[2]Regrettably, a sample of natural taifine was not available for comparison purposes.

Method 2.—Compound **4a** (1.0 g, 4.3 mmol) was dissolved in hot H_2O (20 ml) containing NaOH (2 g). To this solution was added EtOH (50 ml) to precipitate the silk-like sodium salt that was collected and dissolved in H_2O (15 ml). A $AgNO_3$ solution (1.7 g in 5 ml of H_2O) was then added to the aqueous solution. The resulting silver salt (**4c, 4d**) precipitated from the solution was collected, dried, and ground. The suspension of **4c, 4d**, in Et_2O (5 ml) containing ethyl iodide (1.5 ml) was put aside in the dark for 48 h. Excess of ethyl iodide was removed, and the residue was continuously extracted (Soxhlet apparatus) for several hours with Et_2O to give *O*-alkylated product **5b** (0.4 g, 36%) and then with $CHCl_3$ to obtain *N*-alkylated product **5a** (0.53 g, 47%).

9-ETHYL-3-HYDROXY-7-METHOXY-2,3,4,9-TETRAHYDROFURO[2,3-*b*]QUINOLIN-4-ONE (**6**).—The compound **5a** (1 g, 0.004 mole) was dissolved in MeOH (350 ml) and cooled to 20°. To the solution was added 2 N NaOH (25 ml, 0.005 mole). Sodium borohydride (3.8 g, 0.1 mole) was then added in portions over 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 ($MgSO_4$), and concentrated. Recrystallization from EtOH yielded the alcohol **6** (0.74 g, 71%); mp>300°; ir ν max (KBr) 3350 (CH-OH), 1620 cm^{-1}; ms *m/z* 260 (M^+); uv λ max ($CHCl_3$), 252, 310 nm (log ϵ=3.99, 3.68). Calcd for $C_{14}H_{15}NO_4$; C 64.37; H 5.75; N 5.36. Found: C 64.20, 64.52; H 5.56, 5.70; N 5.37, 5.29%.

9-ETHYL-7-METHOXY-4,9-DIHYDROFURO[2,3-*b*]QUINOLIN-4-ONE (**1**).—*Method 1.*—A solution of compound **6** (1.0 g, 0.004 mole) in dry dioxan was refluxed for 4 h. The hot dioxan was refluxed with freshly fused $KHSO_4$ (2 g). After 2 h, additional $KHSO_4$ (2 g) was added, and refluxing was continued for 4 h. The hot dioxan solution was filtered, and the solvent was removed in vacuo. The yellow residue was purified by chromatography over silica gel (200 g) with $CHCl_3$ as eluent. The eluate was evaporated, and the residue was crystallized from $CHCl_3$/EtOH to give yellow crystalline needles of **1** (0.69 g, 71%): mp 178°; ir ν max (KBr) 1623 cm^{-1}, 1584, 1526, 1506, 1495, 1475, 1450, 1440, 1384, 1350, 1320, 1290, 1270, 1258, 1224, 1190, 1166, 1130, 1110, 1100, 1090, 1046, 1036, 1004; ms *m/z* 243 (M+), 158 (9%), 172 (7%), 186 (14%), 200 (8%), 214 (14%), 215 (23%), 228 (48%), 243 (100%); uv λ max (MeOH) 255, 322 nm (log ϵ=4.37, 4.05); ^{1}H nmr, see Table 2. Calcd for $C_{14}H_{13}NO_3$: C 69.14, H 5.35, N 5.76, Found: C 69.00, 69.22; H 5.25, 5.37; N 5.60, 5.71%.

Method 2.—To the suspension of the 3-hydroxyfuroquinoline **6** (1.0 g, 0.004 mole) in MeOH (250 ml) was added concentrated HCl dropwise until a solution resulted. The solvent was removed in vacuo. Iced H_2O was added to the residue and neutralized with $NaHCO_3$. The mixture was then extracted with $CHCl_3$, and the solvent was removed in vacuo. The residue was crystallized from $CHCl_3$/EtOH to give compound **1** (0.73 g, 75%).

7-METHOXYFURO[2,3-*b*]QUINOLIN-4-ONE (**10**).—Compound **4a** (1.2 g, 0.05 mole) was suspended in the mixture of 2 N NaOH (20 ml) (20 ml) and EtOH (150 ml). To the suspension was added sodium borohydride (7.5 g) in portions over 1 h, and the reaction mixture was heated under reflux for 4 h. The resulting solids were removed by filtration and washed with EtOH. Removal of solvent in vacuo from the filtrate and washings gave solid residue that was dissolved in H_2O, filtered, and washed with additional H_2O. The combined filtrate and washings were neutralized with glacial HOAc and refrigerated for 2 days. The brownish precipitate thus formed was collected and taken up in $CHCl_3$, washed with H_2O, and dried ($MgSO_4$). Removal of solvent left off-white residue that was purified by column chromatography (silica gel, $CHCl_3$/4% MeOH as eluent) and recrystallization (*n*-hexane) to afford colorless crystals of **10** (0.6 g, 53.76%): mp 115°; ir ν max (KBr) 3280, 1625, 1585 cm^{-1}; ms *m/z* 215 M^+) uv λ max 252 (log ϵ=3.67), 320 (log ϵ=3.08); ^{1}H nmr δ (DMSO) 3.90 (3H, s, $-OCH_3$), 6.93 (1H, s, 8-H), 7.01 (1H, m, 6-H), 7.03 (1H, d, J=2.5 Hz, 3-H), 7.58 (1H, d, J=2.5 Hz, 2-H), 8.03 (1H, d, J=2.5 Hz, 5-H), and 8.20 (1H, NH). Calcd for $C_{12}H_9NO_3$: C 66.97; H 4.18; N 6.51. Found: C 67.02, 66.85; H 4.17, 4.21; N 6.49, 6.53%.

4-ETHOXY-7-METHOXYFURO[2,3-*b*]QUINOLINE (**8**).—*Method 1.*—To a solution of compound **10** (1.0 g, 0.0046 mole) in EtOH (50 ml) containing NaOH (1.2 g) was added dropwise diethyl sulfate (4 g, 0.025 mole) over a period of 4 h. After the addition was completed, the reaction mixture was set aside for 1 day. The solvent was removed to leave a residue that was subjected to column chromatography on silica gel (50 g). Eluted with $CHCl_3/C_6H_6$ (1:1) 200 ml and then $CHCl_3$ (400 ml) yielded, after recrystallization from C_6H_6, colorless crystals of **8** (125 mg, 11.06%): mp 110°; ir ν max (KBr) 1623, 1600, 1560, 1520 cm^{-1}; uv λ max (EtOH) 215.5, 255, and 344 nm; ^{1}H nmr δ ($CDCl_3$) 1.52 (3H, t, J=7 Hz, $-CH_2-CH_3$), 3.92 (3H, s, $-OCH_3$), 4.57 (2H, q, J=7 Hz, $-CH_2-CH_3$), 6.83 (1H, d, J=2.5 Hz, 3-H), 7.03 (1H, dd, J=9 Hz and 2.5 Hz, 6-H), 7.29 (1H, d, J=2.5 Hz, 2-H), 7.46 (1H, d, J=2.5 Hz, 8-H), and 8.08 (1H, d, J=9 Hz, 5-H); ^{13}C nmr see Table 1. Calcd for $C_{14}H_{13}NO_3$: C 69.14; H 5.35; N 5.76. Found: C 69.13; H 5.37; N 5.80%. Further elution with $CHCl_3$/2% MeOH (150 ml) affords, after recrystallization from C_6H_6, yellow crystals of **1** (450 mg, 39.82%).

Method 2.—The compound **5b** (0.4 g, 1.5 mmol) was dissolved in EtOH (50 ml) and cooled to 15°.

To the solution was added $NaBH_4$ (2.0 g) in portions over 1 h. The resultant yellow solution was allowed to reach room temperature, then stirred until it became colorless (3 h). The solvent was removed, and the residue was extracted with $CHCl_3$ to give alcohol **9** (0.3 g, 73%): ir 3300 cm^{-1}. Compound **9** thus obtained was suspended in MeOH and concentrated HCl was slowly added until solution was complete. The solution was then neutralized with aqueous $NaHCO_3$ and evaporated. The residue was extracted with $CHCl_3$ to give compound **8** (0.2 g, 75%) after recrystallization from $CHCl_3$/MeOH.

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