Studies of Heterocyclic Compounds. VIII. Synthesis, Anti-inflammatory and Antiallergic Activities of *N*-Alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones and Related Compounds†

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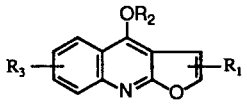
A series of new *N*-alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-dione and *N*-alkyl-4,9-dihydrofuro[2,3-*b*]-quinolin-4-one derivatives were prepared and evaluated for their anti-inflammatory activity by the carrageenin hind paw edema method and antiallergic activity by the rat passive cutaneous anaphylaxis method. Among those tested compounds, *N*-ethyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-dione was the most promising agent which could provide a novel structural prototype for antiallergic agents.

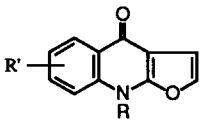
J. Heterocyclic Chem., **28**, 955 (1991).

Introduction.

The furoquinoline alkaloids are well known in nature, some of these compounds of type **1** have been found to possess many interesting pharmacological activities [2]. However, the biological activity of furo[2,3-*b*]quinolin-4-ones of type **2** have not been reported.

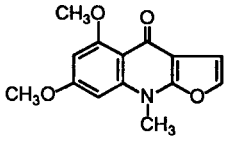


1



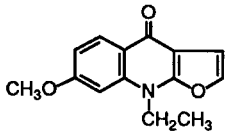
2

In the course of our project directed toward the investigation of synthesis and biological activities of furo-[2,3-*b*]quinolin-4-ones **2**, we have already published the work on the total synthesis of glycarpine (**3**) [3], taifine (**4**) [4] and isomaculosidine (**5**) [5].



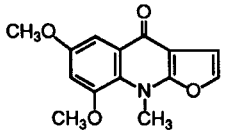
Glycarpine

3



Taifine

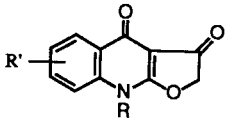
4



Isomaculosidine

5

In continuation of our research program, some more substituted 4,9-dihydrofuro[2,3-*b*]quinolin-4-ones **2** were synthesized and their anti-inflammatory and antiallergic activities were investigated. Additionally, some of the intermediates, *N*-alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-4,9-diones **6** were found to possess significant anti-inflammatory and/or antiallergic activities. Therefore, using 2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-dione **6a** as the basic nucleus, a variety of derivatives were synthesized and their anti-inflammatory and antiallergic activities are reported in this paper.

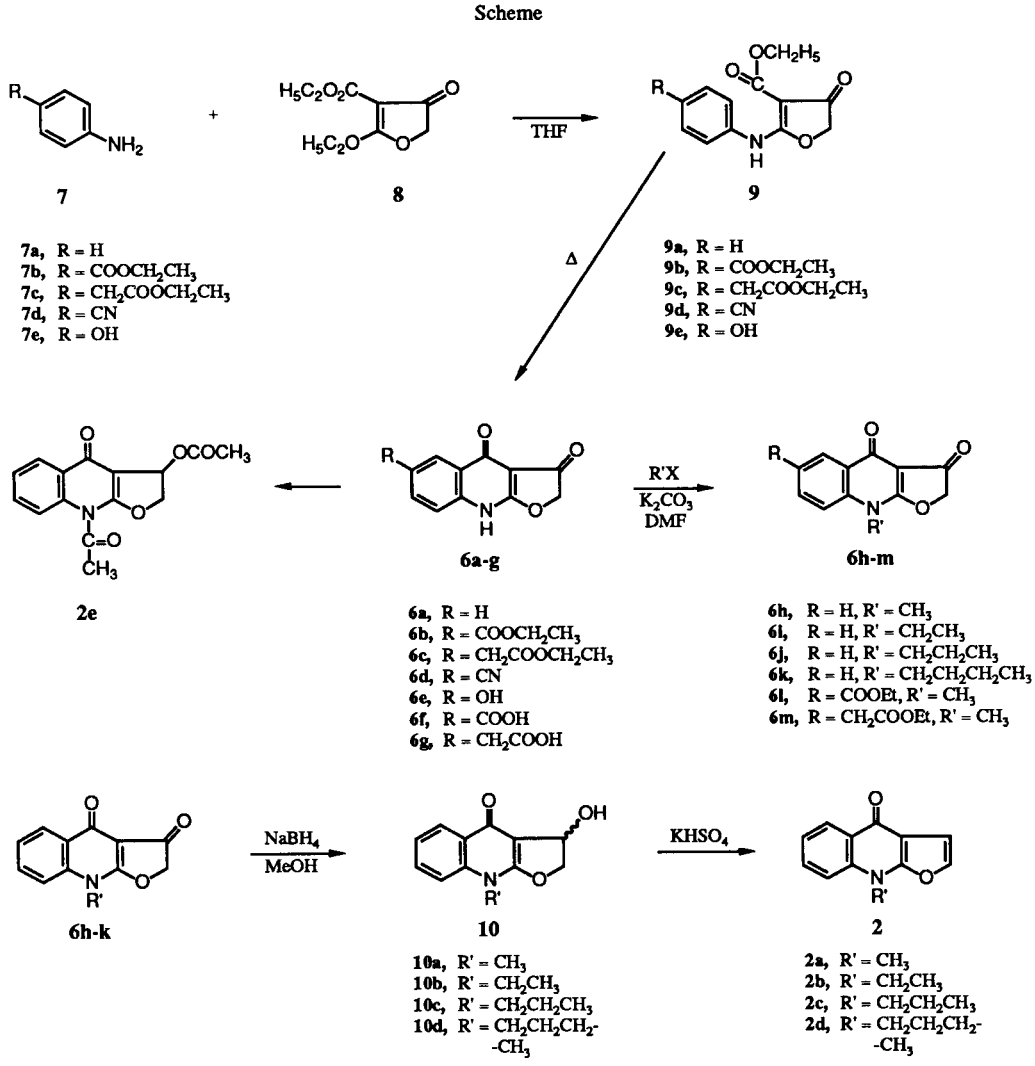


6

Chemistry.

The synthetic route to the majority of the tested compounds is outlined in the Scheme. Ethyl 2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate (**8**) prepared *in situ* from chloroacetyl chloride and ethyl sodiomalonate was condensed with 4-substituted anilines **7a-e** to give the corresponding ethyl 2-(4-substitutedanilino)-4-oxo-4,5-dihydrofuran-3-carboxylates **9a-e** (Table I). Thermal cyclization of compounds **9a-e** in boiling diphenyl ether afforded the corresponding 6-substituted-2,3,4,9-tetrahydrofuro-[2,3-*b*]quinoline-3,4-diones **6a-e** (Table II). When 2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6a** was treated with a variety of alkyl halides and potassium carbonate in dry DMF, the corresponding *N*-alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-4,9-diones **6h-k** (Table III)

Scheme



were obtained. Reduction of **6h-k** with excess sodium borohydride in ethanolic alkali gave the corresponding alcohols **10a-d** (Table IV) which were then dehydrated with anhydrous potassium bisulfate to yield the corresponding *N*-alkyl-4,9-dihydrofuro[2,3-*b*]quinolin-4-ones **2a-d** (Table V).

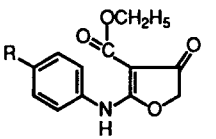
Nevertheless, when compound **6a** was treated with sodium hydroxide in dry DMF followed by reaction with acetyl chloride at room temperature, instead of forming *N*-acetyl derivative of **6a**, a novel product was obtained. Based on the mass spectrum (M^+ 285) and elemental analysis, the molecular formula of this product was determined as $C_{15}H_{11}NO_5$. The ir spectrum showed three carbonyl absorption at 1775, 1760 and 1658 cm^{-1}. The uv absorption at λ max (methanol) 251 and 325 nm (log ε = 3.63 and 3.12 respectively) which is similar to that of taifine (**4**) [3] [λ max (methanol) = 255 and 322 nm (log ε = 4.37 and 4.05 respectively]. The ^{1}H-nmr spectrum exhibited two acetyl groups at δ 2.33 and 2.53 and the signals for protons on the benzene and furan rings appear at δ 7.60-7.93 (5H, m). From the data cited above, the novel product was elucidated to be 3-acetoxy-*N*-acetylfuro[2,3-*b*]quinolin-4-one (**2e**).

Pharmacological Results and Discussion.

The anti-inflammatory and antiallergic activities of the compounds studied are summarized in Tables VI-VIII. Among the compounds tested, compounds **6h** and **6i** showed significant anti-inflammatory activity, whereas somewhat weaker than that of aspirin and compounds **6i** and **6j** had significant antiallergic activity about half as potent as that of theophylline (Table VI). The order of antiallergic activity was $C_3H_7 > C_2H_5 > H$ for R_4, where R_1, R_2 and R_3 = H. Thus, substitution with lower alkyl groups at R_4 resulted in an increase in both activities as compared with compound **6a** (H at R_1, R_2, R_3 and R_4). On

Table I

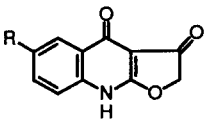
Physical Characteristics of Ethyl 2-(4'-Substituted-anil ino)-4-oxo-4,5-dihydrofuran-3-carboxylates **9**



Compound	R	Crystallization solvent	Yield (%)	Mp °C	Formula [a]	Analysis (%) Calcd.(Found) C	H	N	IR (KBr) ν C=O cm^{-1}	NMR Chemical Shifts δ ppm	MS (m/z) M^+
9a	-H	EtOH	66	115-117	$C_{13}H_{13}NO_4$	60.15 (60.40)	5.30 (5.02)	5.67 (5.76)	1700 1645	in $CDCl_3$ δ 1.38 (t, J = 7.0 Hz, 3H, $-CH_2CH_3$), 4.35 (q, J = 7.0 Hz, 2H, $-CH_2-CH_3$), 4.65 (s, 2H-CH_2-CO) 7.35 (m, 5H, aromatic protons), 10.25 (s, 1H, NH)	247
9b	$-COOCH_2CH_3$	EtOH	33	195-197	$C_{16}H_{17}NO_6$	60.18 (60.00)	5.37 (5.31)	4.39 (4.30)	1710 1700 1635	in $CDCl_3$ δ 1.38 (t, J = 7.0 Hz, 6H, $-CH_2CH_3$ x 2), 4.34 (q, J = 7.0 Hz, CH_2CH_3 x 2), 5.04 (s, 2H, -O-CH_2-CO-), 7.05 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 2-H, 6-H), 8.02 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 3-H, 5-H), 10.34 (s, 1H, NH)	319
9c	$-CH_2COOCH_3CH_3$	EtOH	36	187-189	$C_{17}H_{19}NO_6$	61.25 (61.50)	5.75 (5.54)	4.20 (4.52)	1710 1700 1630	in $CDCl_3$ δ 1.24 (t, J = 7.0 Hz, 3H, $-CH_2COOHCH_2CH_3$), 1.40 (t, J = 7.0 Hz, 3H, $-COOCH_2CH_3$), 3.53 (s, 2H, CH_2-COOEt), 4.14 (q, J = 7.0 Hz, 2H, $-CH_2$ $-COOCH_2CH_3$), 4.32 (q, J = 7.0 Hz, 2H $-COOCH_2CH_3$), 4.63 (s, 2H, $-OCH_2CO-$), 7.28 (m, 4H, aromatic protons), 10.16 (br, 1H, NH)	333
9d	-CN	EtOH	35	240 (dec.)	$C_{14}H_{12}N_2O_4$	61.76 (61.53)	4.44 (4.60)	10.29 (10.51)	1710 1700 1645	in $CDCl_3$ δ 1.40 (t, J = 7.0 Hz, 3H, $-CH_2CH_3$), 4.36 (q, J = 7.0 Hz, 2H, $-CH_2-CH_3$), 5.10 (s, 1H, $-OCH_2-CO-$), 7.23 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 2-H, 6-H), 7.70 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 3-H, 5-H), 10.15 (s, 1H, NH)	272
9e	-CH	EtOH	52	196-198	$C_{13}H_{13}NO_5$	59.31 (59.03)	4.98 (4.69)	5.32 (5.63)	1660 1620	in DMSO-d_6 δ 1.25 (t, J = 7.0 Hz, 3H, CH_3), 4.22 (q, J = 7.0 2H, CH_2CH_3), 4.60 (s, 2H, -O-CH_2-CO-), 6.80 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 3-H, 5-H), 7.20 (dd, J = 1.0 Hz, 9.0 Hz, 2H, 2-H, 6-H), 9.51 (br, 1H, OH or NH), 9.97 (s, 1H, OH or NH)	263

Table II

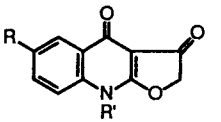
Physical Characteristics of 6-Substituted-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6a-g**



Compound	R	Crystallization solvent	Yield (%)	Mp °C	Formula	Analysis (%) Calcd.(Found) C	H	N	IR (KBr) ν C=O cm^{-1}	NMR Chemical Shifts δ ppm	MS (m/z) M^+
6a	-H	$CHCl_3$-EtOH	85	271-272	$C_{11}H_7NO_3$	65.67 (65.36)	3.51 (3.21)	6.96 (6.68)	1720 1635	in CF_3COOD δ 5.20 (s, 2H, -O-CH_2-CO-), 7.66-8.20 (m, 3H, 6-H, 7-H, 8-H), 8.57 (dd, J = 1.0 Hz, 8.5 Hz, 5-H)	201
6b	-$COOCH_2CH_3$	$CHCl_3$EtOH	70	297-299	$C_{14}H_{11}NO_5$	61.54 (61.80)	4.06 (4.27)	5.13 (4.95)	1720 1700 1640	in DMSO-d_6 δ 1.56 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 4.58 (q, J = 7.0 Hz, 2H, -CH_2-CH_3), 4.80 (s, 2H, -O-CH_2-CO), 7.45 (d, J = 8.5 Hz, 1H, 8-H), 8.00 (dd, J = 1.0 Hz, 8.5 Hz, 1H, 7-H), 8.51 (d, J = 1.0 Hz, 1H, 5-H), 9.79 (br, 1H, NH)	273
6c	-$CH_2COOCH_3CH_3$	$CHCl_3$-EtOH	82	260-262	$C_{15}H_{13}NO_5$	62.71 (62.53)	4.56 (4.38)	4.58 (4.58)	1720 1700 1640	in DMSO-d_6 δ 1.26 (t, = 7.0 Hz, 3H, -CH_2CH_3), 3.53 (s, 2H, -OCH_2-CO-), 4.16 (q, = 7.0 Hz, 2H, -CH_2CH_3), 7.40-8.30 (m, 3H, aromatic protons), 10.03 (br, 1H, NH)	287
6d	-CN	$CHCl_3$-EtOH	71	310-311 dec	$C_{12}H_6N_2O_3$	63.72 (63.90)	2.67 (2.54)	12.39 (13.30)	1720 1630	in DMSO-d_6 δ 4.85 (s, 2H, -O-CH_2-CO-), 7.45 (d, J = 8.5 Hz, 1H, 8-H), 7.97 (dd, J = 1.0 Hz, 8.5 Hz, 1H, 7-H), 8.30 (d, J = 1.0 Hz. Hz, 1H, 5-H), 9.53 (s, 1H, NH)	226
6e	-OH	$CHCl_3$-EtOH	84	284-286	$C_{11}H_7NO_4$	60.83 (59.98)	3.25 (3.54)	6.45 (6.07)	1700 1640	in DMSO-d_6 δ 4.32 (s, 2H, -O-CH_2-CO-), 7.23-7.86 (m, 3H, aromatic protons), 9.78 (br, 1H, NH or OH), 10.21) (br, 1H, NH or OH)	217
6f	COOH	$CHCl_3$-EtOH	83	330-331 dec	$C_{12}H_7NO_5$	58.78 (58.39)	2.88 (2.48)	5.71 (5.35)	1720 1700 1640	in DMSO-d_6 δ 4.82 (s, 2H, O-CH_2-CO-), 7.45 (d, J = 8.5 Hz, 1H, 8-H), 8.00 (dd, J = 1.0 Hz, 8.5 Hz, 7-H), 8.50 (d, J = 1.0 Hz, 1H 5-H), 10.00 (br, 2H, -OH, NH)	245
6g	-CH_2COOH	$CHCl_3$-EtOH	85	340-341 dec	$CH_{13}H_9NO_5$	60.23 (59.98)	3.50 (3.12)	5.40 (5.78)	1720 1700 1640	in DMSO-d_6 δ 3.58 (s, 2H, O-CH_2-CO-), 7.45-8.33 (m, 3H, aromatic protons), 10.21 (br, 2H, -OH, NH)	259

Table III

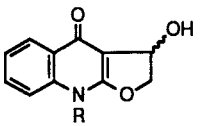
Physical Characteristics of 6-Substituted-9-alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6h-m**



Compound	R	R'	Crystallization solvent	Yield (%)	Mp °C	Formula	Analysis (%) Calcd.(Found) C	H	N	IR (KBr) ν C=O cm^{-1}	NMR Chemical Shifts δ ppm	MS (m/z) M^+
6h	-H	$-CH_3$	$CHCl_3$-EtOH	66	265-267	$C_{12}H_9NO_3$	66.97 (67.13)	4.22 (4.12)	6.51 (6.30)	1709 1640	in CF_3COOD δ 4.20 (s, 3H, N-CH_3), 5.36 (s, 2H, -OCH_2CO-), 7.64-8.34 (m, 3H, 6-H, 7-H, 8-H), 8.66 (dd, 1H, J = 1.0 Hz, 8.0 Hz, 5-H)	215
6i	-H	$-CH_2CH_3$	$CHCl_3$-EtOH	65	237-238	$C_{13}H_{11}NO_3$	68.11 (68.27)	4.84 (4.53)	6.11 (6.40)	1710 1630	in $CDCl_3$ δ 1.45 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 4.29 (q, J = 7.0 Hz, 2H, -CH_2CH_3), 4.66 (s, 2H, -OCH_2CO-), 7.21-7.57 (m, 3H, 6-H, 7-H, 8-H), 8.35 (dd, J = 1.0 Hz, 8.0 Hz, 1H, 5-H)	229
6j	-H	$-CH_2CH_2CH_3$	$CHCl_3$-EtOH	64	234-236	$C_{14}H_{13}NO_3$	69.12 (69.33)	5.39 (5.60)	5.76 (5.62)	1710 1634	in $CDCl_3$ δ 1.04 (t, J = 7.0 Hz, 3H, -$CH_2CH_2CH_3$) 1.60-2.08 (m, 2H, -$CH_2CH_2CH_3$), 4.19 (t, J = 7.0 Hz, 2H, -$CH_2CH_2CH_3$), 4.66 (s, 2H, -OCH_2CO-), 7.21-761 (m, 3H, 6-H, 7-H, 8-H), 8.34 (d, J = 7.0 Hz, 1H, 5-H)	243
6k	-H	$-(CH_2)_3-CH_3$	$CHCl_3$-EtOH	62	273-275	$C_{15}H_{15}NO_3$	70.02 (69.86)	5.88 (5.90)	5.44 (5.47)	1708 1635	in $CDCl_3$ δ 0.99 (t, J = 7.0 Hz, 3H, -$CH_2CH_2CH_2CH_3$), 1.20-2.00 (m, 4H, -$CH_2CH_2CH_2CH_3$), 4.22 (d, J = 7.0 Hz, 2H, -NCH_2), 4.66 (s, 2H, -OCH_2-CO-), 7.22-7.61 (m, 3H, 6-H, 7-H, 8-H), 8.30 (d, J = 7.0 Hz, 1H, 5-H)	257
6l	-COOEt	$-CH_3$	$CHCl_3$-EtOH	34	278-280	$C_{15}H_{13}NO_3$	62.71 (62.51)	4.56 (4.44)	4.88 (4.64)	1745 1702 1642	in $CDCl_3$ δ 1.56 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 4.16 (s, 3H, N-CH_3), 4.58 (q, J = 7.0 Hz, 2H, -CH_2 CH_3), 5.04 (s, 2H, -OCH_2 -CO-), 8.16 (d, J = 8.5 Hz, 1H, 8-H), 8.53 (dd, J = 1.0 Hz, 8.5 Hz, 1H, 7-H), 8.83 (d, J = 0.5 Hz, 1H, 5-H)	287
6m	$-CH_2COOEt$	$-CH_3$	$CHCl_3$-EtOH	38	188-190	$C_{16}H_{15}NO_5$	63.78 (63.93)	5.02 (5.24)	4.65 (4.46)	1715 1638	in $CDCl_3$ δ 1.27 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 3.71 (s, 2H, -CH_2-COOEt), 3.94 (s, 3H, N-CH_3), 4.14 (q, J = 7.0 Hz, 2H, -CH_2CH_3), 4.70 (s, 2H, -OCH_2-CO-), 7.40 (d, J = 8.5 Hz, 8-H), 7.60 (dd, J = 1.0 Hz, 8.5 Hz, 7-H), 8.25 (d, J = 0.5 Hz, 1H, 5-H)	301

Table IV

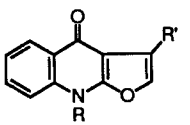
Physical Characteristics of 3-Hydroxy-6-substituted-9-alkyl-,2,3,4,9-tetrahydrofuro[2,3-*b*]quinolin-4-ones **10a-d**



Compound	R	Crystallization solvent	Yield (%)	Mp °C	Formula	Analysis (%) Calcd.(Found) C	H	N	IR (KBr) ν C=O cm^{-1}	MS (m/z) M+
10a	$-CH_3$	EtOH	72	196-197	$C_{12}H_{11}NO_3$	66.35 (66.08)	5.10 (5.00)	67.45 (6.32)	1625	217
10b	$-CH_2CH_3$	EtOH	70	189-191	$C_{13}H_{13}NO_3$	67.52 (67.71)	5.67 (5.59)	6.06 (6.10)	1625	231
10c	$-CH_2CH_2CH_3$	EtOH	73	189-191	$C_{14}H_{15}NO_3$	68.55 (68.37)	6.16 (6.10)	5.71 (5.70)	1620	245
10d	$-(CH_2)_3-CH_3$	EtOH	68	185-186	$C_{15}H_{17}NO_3$	69.48 (69.30)	6.61 (6.82)	5.40 (5.43)	1620	259

Table V

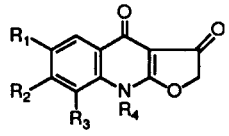
Physical Characteristics of 6-Substituted-9-alkyl-4,9-dihydrofuro[2,3-*b*]quinolin-4-ones **2a-e**



Compound	R	R'	Crystallization solvent	Yield (%)	Mp °C	Formula	Analysis (%) Calcd.(Found) C	H	N	IR (KBr) ν C=O cm^{-1}	NMR Chemical Shifts (in $CDCl_3$) δ ppm	MS (m/z) M+
2a	$-CH_3$	H	$CHCl_3$-EtOH	74	182-184	$C_{12}H_9NO_2$	72.35 (72.21)	4.55 (4.39)	7.03 (7.02)	1630	δ 3.84 (s, 3H, N-CH_3), 7.00-7.70 (m, 5H, 2-H, 3-H, 6-H, 7-H, 8-H), 8.50 (dd, J = 1.0 Hz, 8.0 Hz, 5-H)	199
2b	$-CH_2CH_3$	H	$CHCl_3$-EtOH	76	152-154	$C_{13}H_{11}NO_2$	73.22 (73.40)	5.20 (5.02)	6.57 (6.35)	1630	δ 1.45 (t, J = 7.0 Hz, 3H, -CH_2CH_3), 4.20 (q, J = 7.0 Hz, 2H, -CH_2CH_3), 7.00-770 (m, 5H, 2-H, 3-H, 6-H, 7-H, 8-H), 8.53 (dd, J = 1.0 Hz, 8.0 Hz, 5-H)	213
2c	$-CH_2CH_2CH_3$	H	$CHCl_3$-EtOH	78	149-151	$C_{14}H_{13}NO_2$	73.99 (73.68)	5.77 (5.55)	6.16 (6.04)	1630	δ 1.04 (t, J = 7.0 Hz, 3H, -$CH_2CH_2CH_3$), 1.54-2.00 (m, 2H, -$CH_2CH_2CH_3$), 4.22 (t, J = 7.0 Hz, 2H, -N-CH_2 -), 7.00-7.70 m, 5H, 2-H, 3-H, 6-H, 7-H, 8-H), 8.52 (dd, J = 1.0 Hz, 8.0 Hz, 5-H)	227
2d	$-CH_2CH_2CH_2CH_3$	H	$CHCl_3$-EtOH	73	150-152	$C_{15}H_{15}NO_2$	74.66 (74.79)	6.27 (6.21)	5.81 (5.63)	1630	δ 1.00 (t, J = 7.0 Hz, 3H, -$CH_2CH_2CH_2CH_3$), 1.25-2.00 (m, 4H, -$CH_2CH_2CH_2CH_3$), 4.20) (t, J = 7.0 Hz, 2H, -N-CH_2-), 7.00-7.70 (m, 5H, 2-H, 3-H, 6-H, 7-H, 8-H), 8.50 (dd, J = 1.0 Hz, 8.0 Hz, 5-H)	214
2e	$-COCH_3$	$-COCH_3$	$CHCl_3$-EtOH	31	152-154	$C_{15}H_{11}NO_4$	66.91 (66.67)	4.12 (4.37)	5.20 (5.04)	1770 1750 1650	δ 2.33 (s, 3H, CH_3), 2.53 (s, 3H, CH_3 7.15-8.50 (m, 5H, aromatic protons)	269

Table VI

AntiInflammatory and Antiallergic Activities of Substituted-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6**

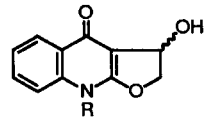


Compound	R1	R2	R3	R4	Dose mg/kg P.O.	Antiinflammatory inhibition % [a] 2	3	Rat PCA inhibition %
6a	H	H	H	H	80	0.6	0.6	2.4
6b	-COOEt	H	H	H	80			9.6
6c	$-CH_2COOEt$	H	H	H	80			2.9
6d	CN	H	H	H	80			0.0
6f	-COOH	H	H	H	80			16.5
6g	$-CH_2COOH$	H	H	H	80			18.9
6h [b]	H	H	H	$-CH_3$	80	15.8	20.3**	16.5
6i	H	H	H	$-CH_2CH_3$	80	15.9	22.2*	27.8*
6j	H	H	H	$-CH_2CH_2CH_3$	80	11.1	12.0	46.8**
6n	H	$-OCH_3$	H	$-CH_3$	80	11.8	8.7	11.3
6o	H	$-OCH_3$	H	H	80	9.2	4.4	-10.1
6p	H	H	$-OCH_3$	H	80			8.2
6q	$-OCH_3$	H	$-OCH_3$	H	80			-9.5
Asprin					80	30.8**	25.8**	
Indomethacin					32			12.6
					4	26.4**	26.9**	
Theophylline					80			67.2**

* $0.01 < p < 0.05$ ** $p < 0.01$ Significantly different from each control group. [a] At 2 hours, 3 hours after carrageenin ingection in the hind-paw edema test in rats. [b] The synthesis of compounds **6h, 10h, 10i** and **10j** have been reported previously.

Table VII

AntiInflammatory and Antiallergic Activities of *N*-Alkyl-3-hydroxy-2,3,4,9-tetrahydrofuro[2,3-*b*]quinolin-4-ones **10**



Compound	R	Dose mg/kg P.O.	Antiinflammatory inhibition % [a] 2	3	Rat PCA inhibition %
10a	CH_3	80	4.2	2.3	9.5
10b	$-CH_2CH_3$	80	-5.8	-3.6	16.3
Asprin		80	30.8**	25.8**	
Indomethacin		32			12.6
		4	26.4**	26.9**	
Theophylline		80			67.2*

* $0.01 < p < 0.05$ ** $p < 0.01$ Significantly different from each control group. [a] At 2 hours, 3 hours after carrageenin ingection in the hind-paw edema test in rats.

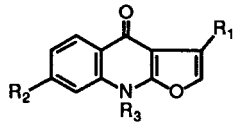
the other hand, no significant increase in these activities was seen by substitution with methoxy, carboxy, acetic acid and carboxymethyl groups at R_1, R_2 and/or R_3 (Table VI).

In a series of *N*-alkyl-3-hydroxy-2,3,4,9-tetrahydrofuro-[2,3-*b*]quinolin-4-ones **10a-b**, compounds **10a** and **10b** exhibited neither anti-inflammatory nor antiallergic activity (Table VII), and all 7-substituted 4,9-dihydrofuro[2,3-*b*]-quinolin-4-ones **2a-g** were inactive in the PCA test, though compound **2b** exhibited slight anti-inflammatory activity (Table VIII). These results suggest that carbonyl group on the furan ring may be important for the pharmacological activities.

There was no correlation between anti-inflammatory

Table VIII

AntiInflammatory and Antiallergic Activities of Substituted-4,9-dihydrofuro[2,3-*b*]quinolin- 4-ones 2



Compound	R1	R2	R3	Dose mg/kg P.O.	Antiinflammatory inhibition % [a] 2	3	Rat PCA inhibition %
2a	H	H	$-CH_3$	80	-0.5	-3.2	11.5
2b	H	H	$-CH_2CH_3$	80	19.8**	7.6	10.7
2c	H	H	$-CH_2CH_2CH_3$	80	9.2	6.8	8.1
2d	H	H	$-CH_2CH_2CH_2CH_3$	80	8.5	4.7	9.1
2e	$-OCOCH_3$	H	$-COCH_3$	20			11.7
2f [b]	H	$-OCH_3$	$-CH_3$	80	14.8*	11.3	
2g [b]	H	$-OCH_3$	$-CH_2CH_3$	80			-2.3
Asprin				80	30.8**	25.8**	
Indomethacin				32			12.6
				4	26.4**	26.9**	
Theophylline				80			67.2**

* $0.01 < p < 0.05$ ** $p < 0.01$ Significantly different from each control group. [a] At 2 hours, 3 hours after carrageenin ingection in the hind-paw edema test in rats. [b] The synthesis of compounds **2f** and **2g** have been reported previously [4].

and antiallergic activities of *N*-alkyl-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones and their related compounds.

Compound **6i** did not inhibit the increased vascular permeability induced by histamine in the rat skin at an oral dose of 80 mg/kg (data not shown), suggesting that compound **6i** had no antagonistic activity for the histamine H_1-receptor. Compound **6i**, structurally different from the known anti-asthmatic agents, is a promising compound which could provide a novel structural prototype for antiallergic agents.

EXPERIMENTAL

Chemistry.

Melting points were determined in open-ended capillary tubes on a Thomas Hoover apparatus and are uncorrected. Infrared spectra were determined with Shimadzu IR-440, and the nmr spectra were determined with a JEOL-FX-90Q NMR spectrometer. Elemental analyses were performed by the analytical section of Dainipon Pharmaceutical Co. Ltd (Japan) and Chung Shan Institute of Science Technology (Republic of China). The structures of all new compounds were determined by their mass spectra which were taken on HP 5995 GC-MS spectrometer.

Ethyl 2-(4'-Substituted-anilino)-4-oxo-4,5-dihydrofuran-3-carboxylates **9a-e**. Sodium hydride (56 g, 1.5 moles), previously washed with dry *n*-hexane, was suspened in dry THF (250 ml) and added slowly, with shaking, over 20 minutes to a solution of diethyl malonate (250 ml, 1.5 moles) in dry THF (500 ml). The reaction mixture was refluxed on a water bath for 2 minutes then cooled to 10-12°, and chloroacetyl chloride (63.8 ml, 0.8 mole) in dry THF (340 ml) was added dropwise over 1 hour. The solution was kept at this temperature for 1 hour and at 40-50° for another hour, then cooled to $10 \pm 2°$, *p*-substituted anilines (0.75 mole) in dry THF (850 ml) was then added dropwise over 1 hour. The reaction mixture was left at room temperature overnight, heated under reflux for 2 hours, then cooled and poured into ice water. The precipitated solid was extracted with chloroform, and the extract was washed with water and dried (magnesium sulfate). The solvent was partially evaporated and the concentrated residue refrigerated for 6 days. The precipitate was collected and recrystallized from appropriate solvent to afford the corresponding ethyl 2-(4-substituted-anilino)-4-oxo-4,5-dihydrofuran-3-carboxylates **9a-e** (Table I).

6-Substituted-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6a-e**.

Compounds **9a-e** (0.06 mole) as fine powders were added with stirring in one lot to diphenyl ether (100 ml) maintained at 240°. The temperature was then raised to $250 \pm 5°$ and kept there for 10 minutes. The mixture was cooled to room temperature and diluted with a large volume of *n*-hexane to precipitate a dark solid that was collected and washed with hot *n*-hexane and purified by chromatography on silica gel (200 g) column. Elution with chloroform-ethanol (9:1) yielded the corresponding 3-oxofuroquinolones **6a-e** (Table II).

3,4-Dioxo-2,3,4,9-tetrahydrofuro[2,3-*b*]quinolin-6-carboxylic Acid (**6f**).

Compound **6b** (2.73 g, 0.01 mole) was dissolved in ethanol (150 ml). The solution was stirred at 50° and 2*N* sodium hydroxide (100 ml) was added dropwise until the reaction mixture became clear. The stirring was continued for a further 30 minutes then the mixture was poured into ice-water and acidified with 10% hydrochloric acid. The crystals formed were filtered off and recrystallized from chloroform-ethanol to give pale-yellow **6f** (Table II).

3,4-Dioxo-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-6-acetic Acid (**6g**).

Compound **6c** (2.86 g, 0.01 mole) was treated as in the preparing of **10f** to afford **6g** (2.43 g, 85%) Table II).

N-Alkyl-6-substituted-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-diones **6h-m**.

Compound **6a-c** (0.02 mole) was suspended on DMF (140 ml) and warmed to 40°. To the suspension was added anhydrous potassium carbonate (34.6 g, 0.25 mole) and alkyl halide (0.25 mole) was then added in portions at 30° ± 2°, stirring was continued for an additional 1 hour. The reaction mixture was filtered and the precipitate was washed with chloroform. The filtrate and washings were combined, and the solvent was evaporated *in vacuo*, iced water was added to the residue, and the precipitate was collected by filtration washed with water and dissolved in chloroform. The chloroform solution was dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (200 g). Elution with chloroform-ethanol (95:3) yield compound **6h-m** (Table II).

N-Alkyl-3-hydroxy-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-4-ones **10a-d**.

Compounds **6h-k** (0.004 mole) was dissolved in methanol (400 ml) and cooled to 20°. To the solution was added 2*N* sodium hydroxide (25 ml, 0.005 mole), sodium borohydride (3.8 g, 0.1 mole) was then added in portions over 1 hour. The resulting yellow solution was left at room temperature until it became colorless (3 hours). The solvent was removed *in vacuo*, the residue was extracted with chloroform, dried over magnesium sulfate and concentrated. Recrystallization from a suitable solvent yielded the corresponding alcohols **10a-d** (Table IV).

N-Alkyl-4,9-dihydrofuro[2,3-*b*]quinolin-4-ones (**2a-d**).

A solution of compounds **10a-d** (0.004 mole) in dry dioxane (15 ml) was refluxed with freshly fused potassium sulfate (0.3 g). After 2 hours additional potassium sulfate (0.4 g) was added, and refluxing was continued for 4 hours. The hot dioxane solution was filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel (100 g) eluting with chloroform. The eluate was evaporated and the residue crystallized from a suitable solvent to give the compounds **2a-d** (Table V).

3-Acetoxy-*N*-acetylfuro[2,3-*b*]quinolin-4-one (**2e**).

2,3,4,9-Tetrahydrofuro[2,3-*b*]quinoline-3,4-dione (**6a**) (2 g, 0.01 mole) was suspended in dry DMF (20 ml) and sodium hydride (0.012 mole) was added portionwise with stirring for 30 minutes at 5-10°. Acetyl chloride (1.6 g, 0.02 mole) was then added dropwise at 5-10°. Stirring was continued for an additional 2 hours and then the reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (silica gel-chloroform) and recrystallized from chloroform-ethanol yield colorless crystalline **2e** (Table V).

Pharmacology.

Anti-inflammatory Assay [6].

Male Wistar rats (110-130 g) were used. Hind paw edema was induced by a subcutaneous injection of 0.1 ml of a 1% carrageenan solution into the right food pad of rats. Hind paw volume was measured 1 hour before and 2 and 3 hours after carrageenin injection. Test compounds were administered orally to the rats 1 hour before carrageenin injection. The anti-inflammatory activity of the compounds was expressed as precent inhibition of the swelling rate of hind paw compared with the vehicle control. Five rats were used for each dose (8 rats for the control).

Anti-allergic Assay (PCA) [7,8].

Male Std:Wistar rats (140-200 g) were injected intradermally with 0.1 ml of a dilute solution of mouse antiserum to egg albumin in two sites of the shaved ventral skin. Fourty-eight hours later each rat was challenged by an intravenous injection of 2 mg of the antigen together with 1 ml of 10.5% Evan's blue saline solution. The blueing area was measured 30 minutes after the challenge. Test compounds were administered orally to the rats 1 hour before antigen challenge. The antiallergic activity of the compounds was expressed as percent inhibition of the blueing area compared with the vehicle control. Three to eight rats were used for each dose.

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REFERENCES AND NOTES

[†] For part **VII**, see [1].

[*] Author to whom correspondence should be addressed.

[1] Part **VII**, S. C. Kuo, L. J. Huang, J. S. Wu, C. H. Wu and T. C. Chou, *J. Heterocyclic Chem.*, **26**, 605 (1989).

[2] T. R. Govindachan, S. Ptabhaker, V. N. Ramachan and B. R. Pai, *Indian J. Chem.*, **9**, 1031 (1971).

[3] S. C. Kuo, T. P. Lin, H. Y. Hsu, and C. H. Wu, *J. Nat. Prod.*, **47**, 47 (1984).

[4] S. C. Kuo, T. P. Lin, S. S. Chang, C. H. Wu, B. Shieh and T. C. Chou, *J. Nat. Prod.*, **49**, 48 (1986).

[5] T. P. Lin, B. Shieh and S. C. Kuo, *J. Nat. Prod.*, **50**, 631 (1987).

[6] H. Nakamura, Y. Yokoyama, S. Motoyoshi, Y. Seto, T. Kadokawa, M. Shimizu, *Folia Pharmacol. Japan*, **79**, 509 (1982).

[7] R. J. Perper, A. L. Oronsky, and V. Blancuzzi, *J. Pharmacol. Exp. Ther.*, **193**, 594 (1975).

[8] B. B. Levine and N. M. Vaz, *Int. Arch. Allergy Appl. Immunol.*, **39**, 156 (1970).