Reaction of Sulfene with Heterocyclic *N,N*-Disubstituted α-Aminomethyleneketones. VIII. Synthesis of Furo[2,3-*h*]-1,2-benzoxathiin Derivatives

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Cycloaddition of sulfene to *N,N*-disubstituted (*E*)-5-aminomethylene-6,7-dihydrobenzo[*b*]furan-4(5*H*)-ones I gave, only in the case of aliphatic *N*-substitution and generally in satisfactory yields, *N,N*-disubstituted 4-amino-3,4,5,6-tetrahydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-dioxides II, which are derivatives of the new heterocyclic system furo[2,3-*h*]-1,2-benzoxathiin. The 4-dimethylamino and 4-piperidino cycloadducts IIa,e were dehydrogenated with DDQ to the corresponding 4-dialkylamino-3,4-dihydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-dioxides IIIa,e in low yield. Compounds IIIa,e were tested for photobiological activity and found to be inactive.

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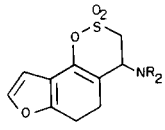
In a previous paper (1) we described a convenient synthesis of *N,N*-disubstituted 4-amino-3-chloroangelicins starting from the cycloadducts obtained by reaction of dichloroketene with a number of *N,N*-disubstituted (*E*)-5-aminomethylene-6,7-dihydrobenzo[*b*]furan-4(5*H*)-ones I. In the same paper we described also some photobiological properties of these compounds; actually, angelicin derivatives are new drugs recently proposed for the photochemotherapy of psoriasis and other hyperproliferative skin diseases (2). The therapeutic effectiveness is connected with the ability of the drug, generally a furocoumarin derivative, to photoreact with DNA forming covalent linkages with the pyrimidine bases; thus, both monoadducts and inter-strand cross-links are formed in DNA (3). In this connection angelicins represent an improvement of the therapy, because they can induce only monoadducts in

Table I

N,N-Disubstituted 4-Amino-3,4,5,6-tetrahydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-Dioxides IIa-f (a)



Formula Number	NR_2	Yield %	Mp, °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIa	$N(CH_3)_2$	47	136 (b)	$C_{12}H_{15}NO_4S$	53.51 53.20	5.61 5.58	5.20 5.40
IIb	$N(C_2H_5)_2$	45	111 (c)	$C_{14}H_{19}NO_4S$	56.54 56.52	6.44 6.40	4.71 4.61
IIc	$N[CH(CH_3)_2]_2$	3	142 (b)	$C_{16}H_{23}NO_4S$	59.05 59.19	7.12 7.28	4.30 4.21
IId	pyrrolidino	74	150 (b)	$C_{14}H_{17}NO_4S$	56.93 56.69	5.80 5.87	4.74 4.65
IIe	piperidino	64	133 (d)	$C_{15}H_{19}NO_4S$	58.23 58.20	6.19 6.30	4.52 4.63
IIf	morpholino	61	161 (b)	$C_{14}H_{17}NO_5S$	54.00 53.70	5.50 5.52	4.49 4.49

(a) All compounds were prepared according to the literature (10), using anhydrous THF as the solvent. (b) From ethyl acetate. (c) From anhydrous diethyl ether, after chromatography on Florisil. (d) From cyclohexane.

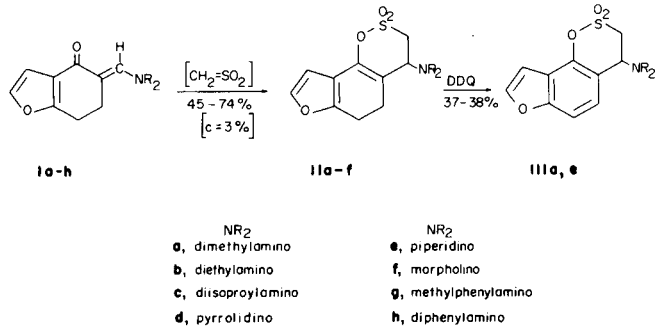
Table II

IR and NMR Spectral Data of Compounds IIa-f

	IR, cm^{-1} C=C	O=S=O		NMR, δ
IIa	1652	1370	1173	2.33 (s, $2CH_3N$), 2.79 (mc, CH_2-5 + CH_2-6), 3.25-4.20 (m, CH_2-3 + CH-4), 6.47 (d, J ~ 2, CH-9), 7.34 (d, J ~ 2, CH-8)
IIb	1655	1375	1183 1173	1.09 (t, J = 7.2, $2CH_3$), 2.47 (q, J = 7.2, $2CH_2N$), 2.78 (mc, CH_2-5 + CH_2-6), 3.15-3.60 (m, CH_2-3), 3.9-4.3 (m, CH-4), 6.43 (d, J ~ 2, CH-9), 7.29 (d, J ~ 2, CH-8).
IIc	1647	1367	1180	1.11 (d, J = 7.2, $4CH_3$), 2.78 (mc, CH_2-5 + CH_2-6), 2.95-3.60 (m, CH_2-3 + 2CHN), 4.0-4.4 (m, CH-4), 6.40 (d, J ~ 2, CH-9), 7.24 (d, J ~ 2, CH-8)
IId	1652	1372	1180	1.78 (mc, $2CH_2$ pyrr), 2.66 (mc, $2CH_2N$), 2.76 (mc, CH_2-5 + CH_2-6), 3.25-3.80 (m, CH_2-3), 4.05-4.40 (m, CH-4), 6.47 (d, J ~ 2, CH-9), 7.30 (d, J ~ 2, CH-8)
IIe	1655	1375	1183	1.54 (mc, $3CH_2$ pip), 2.53 (mc, $2CH_2N$), 2.77 (mc, CH_2-5 + CH_2-6), 3.25-4.15 (CH_2-3 + CH-4), 6.43 (d, J ~ 2, CH-9), 7.28 (d, J ~ 2, CH-8)
IIf	1655	1378	1187	2.60 (mc, $2CH_2N$), 2.78 (mc, CH_2-5 + CH_2-6), 3.2-4.2 (m, CH_2-3 + CH-4), 3.73 (mc, $2CH_2O$), 6.42 (d, J ~ 2, CH-9), 7.26 (d, J ~ 2, CH-8)

DNA, contrary to the linearly condensed furocoumarins, thus limiting some side effects such as skin phototoxicity and risk of cancer mainly connected to the formation of cross-links in DNA (4,5).

The good results obtained with the functionalized angelicins mentioned above particularly with 3-chloro-4-methylphenylaminoangelicin, prompted us to study the cycloaddition of sulfene to enaminones I in order to obtain derivatives of the heterocyclic system furo[2,3-*h*]-1,2-benzoxathiin. As a matter of fact, this new heterocycle can be considered as a sulfur analogue of angelicin, where an isosteric replacement of the 2-carbonyl group with the sulfone group has taken place. Reaction of enaminones Ia-h (1) with methanesulfonyl chloride and triethylamine (sulfene prepared *in situ*) readily occurred, generally in satisfactory yield, only in the case of aliphatic *N*-substitution to give 4-dialkylamino-3,4,5,6-tetrahydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-dioxides IIa-f (Table I), whose structure was confirmed by ir and nmr spectral data (Table II). Enaminones Ig,h (NR_2 = methylphenylamino and diphenylamino, respectively) did not react and were recovered unchanged from the reaction mixture, according to a well established general trend of this reaction [*ef.* (6)]. Enaminone Ic (NR_2 = diisopropylamino) gave the cycloadduct IIc only in 3% yield, probably owing to steric hindrance.



Dehydrogenation of adducts II was attempted only in the case of IIa,e (NR_2 = dimethylamino and piperidino, respectively). With DDQ in refluxing benzene (7) they gave in rather low yield the corresponding 4-dialkylamino-3,4-dihydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-dioxides IIIa,e (Table III), which could be considered as 2-sulfone isosteric derivatives of functionalized 3,4-dihydroangelicins.

It is noteworthy that a full aromatization (*i.e.* dehydrogenation also in 3 and 4 positions) was not reached, probably because the 1,2-oxathiin 2,2-dioxide ring was proven to be a non-aromatic 6π-electron system (8). The photobiological properties of compounds IIIa,e were evaluated by their capacity to inhibit DNA synthesis in Ehrlich ascites tumor cells as previously described (9). Both compounds, tested at the largest concentrations possible in aqueous solution (5-15 $\mu g\ ml^{-1}$) and at a radiation dose as high as 80×10^3 J m^{-2}, appeared entirely unable to produce any significant inhibition of DNA synthesis. Thus, these negative results seem to indicate that the α-pyrone ring in functionalized angelicins is a fundamental requisite for the biological activity.

EXPERIMENTAL

The uv spectra were measured in 95% ethanol with a Hitachi-Perkin-Elmer Model EPS-3T spectrophotometer. The ir spectra were taken in chloroform on a Perkin-Elmer Model 398 spectrophotometer; the nmr spectra were recorded in deuteriochloroform on a Perkin-Elmer Model R-12 instrument (60 MHz, TMS as internal standard, J in Hz). Melting points were determined with a Fisher-Johns apparatus. Enaminones I have already been described (1).

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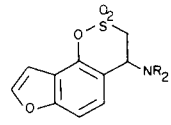
Table III

4-Dialkylamino-3,4-dihydrofuro[2,3-*h*]-1,2-benzoxathiin 2,2-Dioxides IIIa,e (a)



Formula Number	NR_2	Yield %	Mp, °C	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$N(CH_3)_2$	37	134 (b)	$C_{12}H_{13}NO_4S$	53.92 54.27	4.90 4.80	5.24 5.30
IIIe	piperidino	38	167 (b)	$C_{15}H_{17}NO_4S$	58.61 58.60	5.57 5.50	4.55 4.50

UV, IR and NMR Spectral Data

	UV λ max nm (log ε)	IR, cm^{-1} C=C	O=S=O		NMR, δ
IIIa	213 (4.28) 247 (4.04) 252 sh (3.97)	1592	1377	1166	2.36 (s, $2CH_3N$), 3.40-3.95 (m, CH_2-3), 4.50-4.85 (m, CH-4), 6.86 (d, J ~ 2, CH-9), 7.59 (d, J ~ 2, CH-8), 7.33 and 7.64 (2d, J = 9.6, CH-5 and CH-6)
IIIe	217 (4.31) 247 (4.24) 252 sh (4.21)	1595	1382	1162 1175	1.58 (mc, $3CH_2$ pip), 2.55 (mc, $2CH_2N$), 3.40-3.95 (m, CH_2-3), 4.45-4.85 (m, CH-4), 6.88 (d, J ~ 2, CH-9), 7.61 (d, J ~ 2, CH-8), 7.36 and 7.74 (2d, J = 9.6, CH-5 and CH-6)

(a) All compounds were prepared according to the literature (7); reflux time, 18 hours. (b) From anhydrous diethyl ether.

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