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Short Communication

Synthesis of new *N*,*N*-disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones

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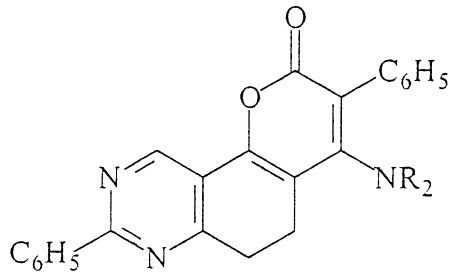
Abstract

The synthesis of some *N*,*N*-disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones (**4a**–**f**), by reaction of phenylchloroketene with a series of *N*,*N*-disubstituted (*E*)-5-aminomethylene-6,7-dihydrobenzo[b]thiophen-4(5)-ones, followed by dehydrochlorination in situ of the primary adducts with DBN, is described. A moderate local anaesthetic activity was observed in the title compounds, particularly in **4e**. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: *N*,*N*-Disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones; Anaesthetic activity.

1. Introduction

In a previous paper [1], we reported the synthesis and the pharmacological screening of derivatives of the fused pyran heterocyclic system 2*H*-pyrano[2,3-*f*]quinazoline (**1**) endowed with platelet anti-aggregating and local anaesthetic activities, prepared from the primary adducts obtained by 1,4 cycloaddition of phenylchloroketene to *N*,*N*-disubstituted heterocyclic α-aminomethyleneketones.



1

Some years ago P. Schenone et al. [2] described the facile reaction of dichloroketene with *N*,*N*-disubstituted (*E*)-5-aminomethylene-6,7-dihydrobenzo[b]thiophen-4(5*H*)-ones (**2**) to give, after dehydrochlorination with triethylamine of the primary adducts, a number of *N*,*N*-disubstituted 4-amino-3-chloro-5,6-dihydro-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones derivatives of 2*H*-thieno[2,3-*h*]-1-benzopyrano heterocyclic system.

Such a fused pyran heterocyclic system, where the thiophene five-membered ring substitutes the pyrimidine six-membered ring of the above mentioned structure, seemed to us worth of attention in order to compare the changes induced in the pharmacological activities of **1** by this substitution. Therefore we have now synthesized and tested some *N*,*N*-disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones (**4**) prepared by a similar pathway.

2. Chemistry

The synthesis of *N*,*N*-disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones (**4a**–**f**), started by the polar 1,4 cycloaddition of

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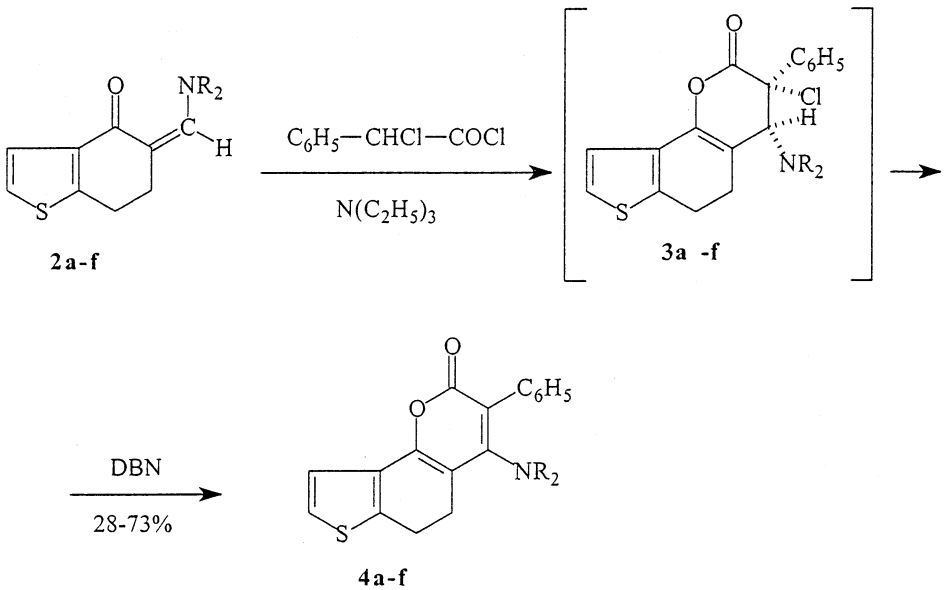
phenylchloroketene (prepared in situ from 2-chloro-2-phenylacetyl chloride and triethylamine) to a series of (*E*)-5-aminomethylene-6,7-dihydrobenzo[b]thiophen-4(5*H*)-ones (**2a–f**) [3] in toluene solution. As in similar cases [4], the resulting adducts **3a–f** were unstable and were dehydrochlorinated in situ with DBN in an one-pot sequence to give the required final compounds **4a–f**.

The products obtained have been characterized on the basis of analytical and spectroscopic data.



	NR_2		NR_2
4a	$N(CH_3)_2$	**4d**	4-Morpholinyl
4b	1-Pyrrolidinyl	**4e**	$N(CH_3)C_6H_5$
4c	1-Piperidinyl	**4f**	$N(C_6H_5)_2$

3. Pharmacology

Compounds **4a–f** were submitted to a preliminary screening for analgesic, anti-inflammatory, local anaesthetic, antiarrhythmic and platelet anti-aggregating activities.

4. Experimental

4.1. Chemistry

Melting points were determined with a Fisher–Johns apparatus. IR spectra were measured in $CHCl_3$ solution with a Perkin–Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Hitachi Perkin–Elmer R-600 (60 MHz) instrument, chemical shifts are reported as δ (ppm) relative to TMS as internal standard; *J* in Hz. Analyses for C, H, N were within $\pm 0.2\%$ of the theoretical values.

4.1.1. General procedure for N,N-disubstituted 4-amino-5,6-dihydro-3-phenyl-2H-thieno[2,3-h]-1-benzopyran-2-ones (4a–f)

A solution of 2-chloro-2-phenylacetyl chloride (2.84 g, 15 mM) in anhydrous toluene (30 ml) was slowly added (1 h) at room temperature under nitrogen to a stirred solution of enaminones (**2a–f**) (10 mM) and triethylamine (1.52 g, 15 mM) in the same solvent (130 ml). The mixture was filtered and the solution was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1.86 g, 15 mM), refluxed for 4 h and evaporated under reduced pressure. The solid residue was dissolved in benzene and chromatographed on Florisil®, using benzene as eluent.

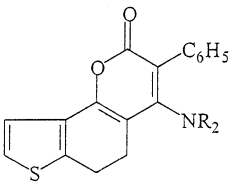
Yields were in general low in the case of aliphatic *N*,*N*-disubstitution (**4a–d**) and high in the case of partial or complete aromatic *N*,*N*-disubstitution (**4e**,**f**).

Yields, mps and recrystallization solvents of compounds **4a–f** are reported in Table 1; IR and ^{1}H NMR spectral data are reported in Table 2.

4.2. Pharmacology

Analgesic activity was evaluated by hot plate test in mice [5]; anti-inflammatory activity was evaluated by carrageenan-induced paw edema in rats [6]; local anaesthetic activity was evaluated as infiltration anaesthesia by pinch-tail test in mice [7]; antiarrhythmic activity was evaluated as protection index against ecgraphic effects from aconitine in rats [8]; and platelet anti-aggregating activity was evaluated by the inhibitory test of platelet aggregation induced by collagen in vitro [9].

Table 1
N,*N*-Disubstituted 4-amino-5,6-dihydro-3-phenyl-2*H*-thieno[2,3-*h*]-1-benzopyran-2-ones **4a–f**



Comp.	NR_2	Yield (%)	M.p. (°C)	Molecular formula	Analyses
4a	$N(CH_3)_2$	38	217–218 [a]	$C_{19}H_{17}NO_2S$	C, H, N
4b	1-Pyrrolidinyl	52	231–232 [a]	$C_{21}H_{19}NO_2S$	C, H, N
4c	1-Piperidinyl	28	218–219 [a]	$C_{22}H_{21}NO_2S$	C, H, N
4d	4-Morpholinyl	31	265–266 [a]	$C_{21}H_{19}NO_3S$	C, H, N
4e	$N(CH_3)C_6H_5$	70	236–237 [a]	$C_{24}H_{19}NO_2S$	C, H, N
4f	$N(C_6H_5)_2$	73	260–261 [a]	$C_{29}H_{21}NO_2S$	C, H, N

[a] From ethyl acetate.

Table 2
IR and ^{1}H NMR spectral data of compounds **4a–f**

Comp.	IR ($CHCl_3$, cm^{-1})		^{1}H NMR ($CDCl_3$, δ ppm)
	C=O	C=C	
4a	1678	1610, 1522	2.52 (s, 6 H, 2 CH_3N), 2.98 (s, 4 H, CH_2-5+CH_2-6), 7.10–7.60 (m, 7 H, CH-8+CH-9+5 H ar.)
4b	1670	1610, 1512	1.54–1.90 (m, 4 H, 2 CH_2 pyr.), 2.78–3.10 (m, 8 H, 2 CH_2N+CH_2-5+CH_2-6), 7.10–7.62 (m, 7 H, CH-8+CH-9+5 H ar.)
4c	1675	1610, 1518	1.36–1.66 (m, 6 H, 3 CH_2 pip.), 2.50–2.80 (m, 4 H, 2 CH_2N), 2.82–3.13 (m, 4 H, CH_2-5+CH_2-6), 7.08–7.69 (m, 7 H, CH-8+CH-9+5 H ar.)
4d	1682	1610, 1518	2.65–2.81 (m, 4 H, 2 CH_2N), 2.99 (s, 4 H, 2 CH_2O), 3.58–3.78 (m, 4 H, CH_2-5+CH_2-6), 7.12–7.67 (m, 7 H, CH-8+CH-9+5 H ar.)
4e	1690	1598, 1518	2.28–2.58 (m, 2 H, CH_2-5), 2.75 (s, 3 H, CH_3N), 2.75–2.93 (m, 2 H, CH_2-6), 7.10–7.60 (m, 12 H, CH-8+CH-9+10 H ar.)
4f	1692	1598, 1520	2.25–2.55 (m, 2 H, CH_2-5), 2.76–2.94 (m, 2 H, CH_2-6), 6.90–7.66 (m, 17 H, CH-8+CH-9+15 H ar.)

5. Results and conclusions

All tested compounds showed weak or negligible analgesic, anti-inflammatory and antiarrhythmic activities. In comparison with derivatives **1**, a decrease of platelet anti-aggregating activity has been evidenced and only a fair local anaesthetic activity was confirmed, particularly for compound **4e**.

In the light of these results we can state that the thiophene/pyrimidine substitution in compounds **1** was not fruitful. Moreover the maintenance in **4a–f** of local anaesthetic activity could enforce the assumption that this property was related only to the dihydrobenzopyranone moiety.

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