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Synthesis of 2-carbamoyloxy benzoates as analgesic and anti-inflammatory agents*

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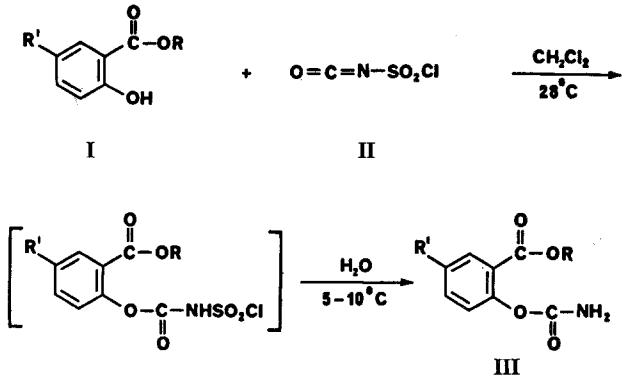
Introduction

Some years back, a wide ranging program was initiated in this laboratory with the objective of developing non-narcotic analgesic and non-steroidal anti-inflammatory agents that elicited minimal side effects as compared to those in use (*e.g.*, aspirin, phenylbutazone). Rainsford and Whitehouse [1] made the important observation that methyl and some other esters of acetylsalicylic acid possess much lower gastric ulcerogenic activities compared to the corresponding acid, while there was no loss in anti-inflammatory and anti-pyretic activities in rats. Thus, these results have provided further evidence for the hypothesis that the carboxylic acid moiety of salicylates is a major factor in the gastric ulcerogenic activity of these compounds. There are some reports [2] which suggest that the acetyl group of acetyl salicylic acid is also responsible for ulcerogenic and anti-inflammatory properties.

Therefore, it occurred to us that it might be possible to combine both these features and evolve a suitable strategy by protecting the acid function with an ester and replacing the acetyl group by a carbamoyl group in the acetylsalicylic acid. This led to preparation of 2-carbamoyloxy benzoates as a chemical modification approach. This paper describes the synthesis, pharmacological evaluation and structure—activity relationships of various representative 2-carbamoyloxy benzoates **III**. Many compounds in this series show good analgesic and anti-inflammatory activities with excellent tolerance. One of them, **III.3 (4003/2)** is undergoing clinical evaluation as an analgesic agent, and two of them, **III.4** and **III.9**, are being subjected to advanced pharmacological study in various animal models. During the course of these studies, 2-carbamoyloxy methylbenzoate/benzylbenzoate have also been reported [3] as agents for the modification of hemoglobins.

Chemistry

The synthesis of 2-carbamoyloxy benzoates [4] was carried out by the reaction of 2-hydroxy benzoates **I** with chlorosulfonyl isocyanate, **II** [5] in dry aprotic solvents such as ether, dichloromethane, benzene, *etc.*, followed by the hydrolysis of the intermediate adduct to give **III** in almost quantitative yields. The structure of these compounds was confirmed by elemental analysis, IR, ^{1}H NMR and mass spectra. Some representative compounds synthesized in this series are described in Table I (**1**—**30**).



Scheme 1. R = alkyl, aryl; R^1 = H, halogen, alkyl.

Results and Discussion

Most of the compounds showed an interesting profile of analgesic and anti-inflammatory activities. Some exhibited superior analgesic and anti-inflammatory actions in comparison to aspirin, while their gastric irritancy (ulcerogenicity),

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Table I. 2-Carbamoyloxy benzoates **III. 1—30.**

Compd.	R	R′	mp (°C)	Yield (%)	Formula[a]
1	CH_3	H	149—150	83	$C_9H_9NO_4$
2	CH_3	Cl	151—152	75	$C_9H_8ClNO_4$
3	C_2H_5	H	150—152	88	$C_{10}H_{11}NO_4$
4	C_2H_5	Cl	148	78	$C_{10}H_{10}ClNO_4$
5	C_2H_5	Br	146—147	68	$C_{10}H_{10}BrNO_4$
6	*i*-C_3H_7	H	145—147	71	$C_{11}H_{13}NO_4$
7	*i*-C_3H_7	Cl	148—149	74	$C_{11}H_{12}ClNO_4$
8	C_4H_9	H	152—154	67	$C_{12}H_{15}NO_4$
9	C_6H_5	H	141—142	85	$C_{14}H_{11}NO_4$
10	C_6H_5	Cl	128—130	83	$C_{14}H_{10}ClNO_4$
11	C_6H_5	Br	132—134	76	$C_{14}H_{10}BrNO_4$
12	C_6H_5	CH_3	124—125	71	$C_{15}H_{13}NO_4$
13	2-ClC_6H_4	H	155—157	73	$C_{14}H_{10}ClNO_4$
14	4-ClC_6H_4	H	164—165	66	$C_{14}H_{10}ClNO_4$
15	2,4-diClC_6H_3	H	158—159	82	$C_{14}H_9Cl_2NO_4$
16	2,5-diClC_6H_3	H	160—161	76	$C_{14}H_9Cl_2NO_4$
17	2,5-diClC_6H_3	Cl	163—164	73	$C_{14}H_8Cl_3NO_4$
18	2-$CH_3C_6H_4$	H	90—92	71	$C_{15}H_{13}NO_4$
19	2-$CH_3C_6H_4$	Cl	94—96	68	$C_{15}H_{12}ClNO_4$
20	3-$CH_3C_6H_4$	H	95—97	75	$C_{15}H_{13}NO_4$
21	3-$CH_3C_6H_4$	Cl	93—95	81	$C_{15}H_{12}ClNO_4$
22	4-$CH_3C_6H_4$	H	98—99	78	$C_{15}H_{13}NO_4$
23	3-CH_3, 4-ClC_6H_3	H	150—151	86	$C_{15}H_{12}ClNO_4$
24	3-CH_3, 4-ClC_6H_3	Cl	153	88	$C_{15}H_{11}Cl_2NO_4$
25	3-$C_{15}H_{31}C_6H_4$	H	108—110	65	$C_{29}H_{41}NO_4$
26	3-$C_{15}H_{31}C_6H_4$	Cl	114—115	63	$C_{29}H_{40}ClNO_4$
27	4-$OCH_3C_6H_4$	H	120	68	$C_{16}H_{15}NO_5$
28	4-$OC_2H_5C_6H_4$	H	124—126	66	$C_{16}H_{15}NO_5$
29	2-$NO_2C_6H_4$	H	168	72	$C_{14}H_{10}N_2O_6$
30	2-$NO_2C_6H_4$	H	165	75	$C_{14}H_{10}N_2O_6$

[a]All compounds were analyzed for C, H and N. The results had a maximum deviation of ±0.4% from the theoretical values.

behavioral test and acute toxicity studies revealed them to be many times safer than aspirin. The LD_{50} values for most of these compounds were more than 2000—2500 mg/kg in rats (oral) and more than 800 mg/kg in mice by intraperitoneal route. No obvious gross effects pertaining to the central nervous system were observed with these compounds. The pharmacological data which are summarized in Table II, allow some considerations to be made in terms of structure—activity relationships concerning mainly: 1) the nature of the ester and that of the substituent in the aryl esters and 2) the nature of the substituent in the benzene ring.

Variation of the ester group showed that the analgesic and anti-inflammatory activities are maximal in the phenyl esters (**9** and **10**), whereas in the case of alkyl esters these activities are maximal in ethyl esters (**3** and **4**). Incorporation of a substituent into the aryl esters (**13—30**) did not show any potentiation of activity and, in fact, values were lower than the unsubstituted aryl, *i.e.*, phenyl esters (**9—12**).

A chloro substituent at 5-position in the benzene ring resulted in slightly superior activities (*e.g.*, **2**, **4**, **7** and **10**).

Compounds **1—8**, which have alkyl esters, are less ulcerogenic than those having an aryl ester (**9—30**), except for compound **25**. Furthermore, a chloro substituent in the benzene ring enhanced the ulcerogenic activity.

As can be seen from the data presented in Table II, compound **3** possesses the least ulcerogenic potency while showing significant analgesic and anti-inflammatory activities, which led to a detailed investigation of this compound in experimental animals and, finally, to clinical evaluation in humans. The detailed metabolic studies of these compounds are in progress.

Experimental protocols

Chemical methods

Melting points were taken on a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Jeol FX90Q 90 MHz FT NMR instrument using tetramethylsilane (TMS) as the internal standard. IR spectra were obtained with a Perkin—Elmer 283B spectrophotometer in a potassium bromide pellet. Chemical ionization mass spectra were recorded on a VG 7070H mass spectrometer. All evaporations were carried out on a rotary evaporator at reduced pressure. The purity of all the compounds was verified by thin—layer chromatography (TLC) and high pressure liquid chromatography (HPLC).

General procedure

2-Carbamoyloxy methyl benzoate ***III.1***
To a stirred solution of 2-hydroxy methyl benzoate (6.98 g, 0.046 mol) in dichloromethane (50 ml) at 4—6°C was added chlorosulfonyl isocyanate (4 ml, 0.046 mol) in dichloromethane (6 ml) dropwise over a period of 20 min. After completion of the addition, the reaction mixture was brought to ambient temperature and stirred for an additional 3 h. The dichloromethane was then removed under vacuum and the residue was added to cold water with stirring and left for 36 h. The colorless crystalline solid that separated out was filtered and dried. Recrystallization from chloroform—hexane gave pure 2-carbamoyloxy methyl benzoate in 83% yield, mp: 149—150°C. IR (KBr): 3420, 3305, 1730, 1690, 1600 cm^{-1}, ^1H NMR ($CDCl_3$): 8.2—7.1 (4H, m, Ar-H); 5.8 (2H, br, s, $—NH_2$); 3.9 (3H, s, $—OCH_3$).

Biological methods

These compounds were screened for analgesic, anti-inflammatory, ulcerogenic activities and for anti-cancer potential employing the following procedures. All test compounds were administered orally by gavage in 5% gum acacia suspension at a dose of 100 mg/kg in analgesic and anti-inflammatory assays. Aspirin was included in all analgesic, anti-inflammatory and ulcerogenic tests for comparison.

Analgesic activity
Acetic acid writhing test, modified method of Koster *et al.* [6]: groups of 8 male albino mice, weighing 20—25 g were used.

Tail clip test method of Bianchi and David described by Turner [7]: groups of 8 male albino mice, weighing 18—25 g, were used.

Anti-inflammatory activity
Carrageenin rat paw edema [8]: groups of 10 Wistar rats of both sexes weighing between 180 and 200 g were used.

Cotton pellet granuloma, modified method reported by Turner [9]: groups of 10 male Wistar rats weighing between 150 and 250 g were used.

Ulcerogenic activity
The compounds were assessed for their ulcerogenicity by the method of Okabe *et al.* [10]: groups of 10 rats weighing 180—200 g were used.

These results are given in Table II.

Behavioral test and acute toxicity
Representative compounds were investigated for their acute toxicity (approximate LD_{50}) in mice (20—25 g) of either sex. Approximate

Table II. Analgesic, anti-inflammatory and ulcerogenic activities of compounds **III**.

Compds.	Analgesic and anti-inflammatory actions (100 mg/kg)				Ulcer index (200 mg/kg)
	% protection from pain		% inhibition of inflammation		
	writhing	tail clip	paw edema	cotton pellet granuloma	
1	49.8	65.0[a]	36.2	32.3[a]	5.6
2	61.5[a]	68.2[a]	38.3[a]	26.4	6.2
3	68.1[a]	72.3[a]	44.6[a]	28.6	3.3
4	70.0[a]	ne[b]	45.1[a]	23.3	5.2
5	46.2	ne	33.5	22.0	5.7
6	53.5[a]	38.5	32.0	28.8	5.0
7	56.0[a]	ne	26.6	23.6	6.1
8	47.3	ne	28.4	18.6	6.4
9	73.3[a]	66.0[a]	48.4[a]	34.6[a]	8.6
10	75.8[a]	ne	40.3[a]	31.2	10.2
11	56.2[a]	36.4	28.6	22.4	9.5
12	43.2	56.3	31.2	ne	7.8
13	63.5[a]	ne	26.8	28.0	8.3
14	65.0[a]	43.5	27.8	31.3	10.5
15	56.0[a]	ne	23.7	21.4	8.4
16	48.2	ne	29.2	20.6	10.0
17	49.1	38.0	28.1	23.4	12.4
18	45.3	41.2	25.3	20.2	7.3
19	51.0	46.4	27.2	23.4	7.8
20	38.2	41.5	31.4	ne	6.8
21	43.4	46.3	32.6	27.2	6.5
22	39.2	ne	23.3	22.4	7.1
23	41.5	ne	24.5	21.2	6.8
24	47.3	38.2	27.3	24.5	7.6
25	48.2	31.2	23.2	21.4	5.2
26	53.5[a]	ne	26.5	ne	8.8
27	42.3	ne	21.3	ne	7.1
28	37.6	ne	25.6	19.5	6.3
29	36.4	ne	23.3	31.2	7.6
30	48.2	ne	27.7	34.4[a]	6.5
Aspirin	62.3[a]	58.2[a]	32.8	ne	18.6

[a] $p<0.01$; Student's t test *versus* controls.
[b] ne = no effect.

LD_{50} values were calculated, according to the method of Smith [11], from the data generated.

The anti-cancer screening (3PS31) of some representative compounds was performed under the auspices of the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. The results revealed that the test compounds were inactive, since the $T/C\%$ was less than 125.

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