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New products

2-[10,11-Dihydro-11-oxodibenz[b,f][1,4]oxazepin-7 or 8-yl] propanoic acids as potential anti-inflammatory agents

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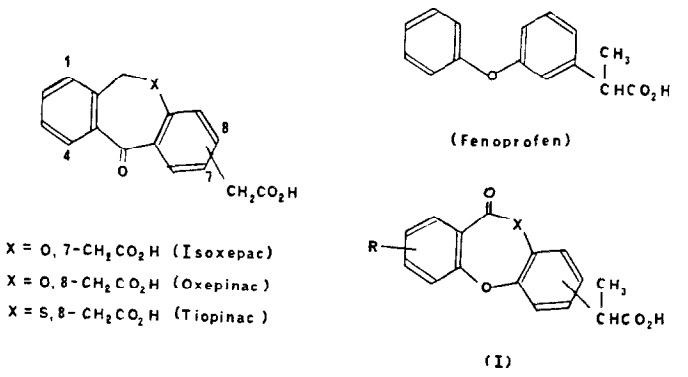
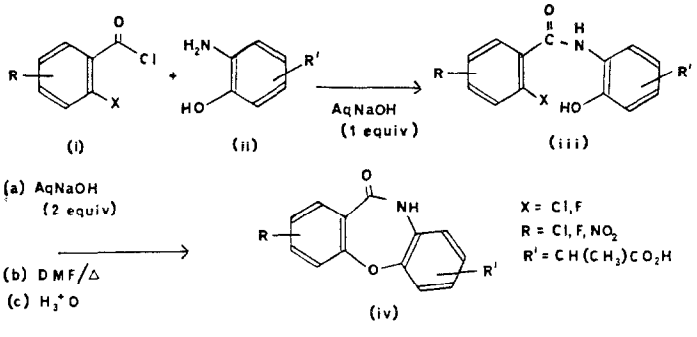
Introduction

During recent years, a number of compounds, isoxepac, oxepinac, tiopinac, possessing a tricyclic nucleus with an acidic side chain have been developed as anti-inflammatory agents. These compounds are more potent than indomethacin in their anti-inflammatory and analgesic tests, but much less ulcerogenic in animal models [1—5]. The latter effect has been attributed to their low efficacy in the inhibition of prostaglandin synthetase (cyclooxygenase). Prostaglandins (PGs) are derived from arachidonic acid (AA) by the enzyme cyclooxygenase (CO). A detailed conformational analysis led Salvetti *et al.* [6] to propose a low energy conformer of AA as a model of the hydrophobic CO site. Using molecular shape recognition methods, they also showed a considerable degree of complementarity between this conformation and the structures of indoprofen and indomethacin. Their results seem to confirm a hydrophobic interaction between this type of anti-inflammatory agent and the CO site. This is further delineated by the evidence of two hydrophobic sites, catalytic and supplementary, on the enzyme. It is believed that the degree of interaction of non-steroidal anti-inflammatory drugs with the catalytic site contributes to their potency, whereas their efficacy as CO inhibitors is determined by their interaction with the supplementary site [7].

The potent CO inhibitors, such as the indomethacin type of compound, contain planar aromatic groups, while tricyclic anti-inflammatory agents, such as isoxepac have notably a non-planar (6—7—6) fused ring system. Since a complementarity between a drug and a receptor site is essential for any interaction, a variation in the conformation of the lipophilic part of a molecule, as noted above, may contribute to the different level of CO activity. The development of these tricyclic compounds can be considered as a progression from the ketoprofen type of drug by cyclisation of the two aromatic rings with a fragment —CH_2—X— (X = O, S), while retaining the carbonyl (C=O) bridge. A similar extension to the fenoprofen type of drug, where the two aryl rings are joined through an ether linkage, would lead to a dibenzo-epine class of compound with an alkanoic acid chain. These tricyclic ring systems are non-planar, and they exist in a boat or butterfly conformation [8, 9]. Our interest in various tricyclic ring systems related to the CNS programme [10, 11] prompted us to examine a number of dibenzoxazepine derivatives incorporating an acidic chain for their potential as anti-inflammatory agents. We report here the synthesis of a number of dibenzoxazepines with an attached propionic acid chain (**I**). The anti-inflammatory activity of these derivatives has been evaluated in terms of their effects in improving the adjuvant-induced arthritis in rats.



Scheme 1.



Besides the CO pathway, AA is metabolised by lipoxygenase (LPO) to generate hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs). These are highly potent, biologically active substances believed to be involved in anaphylactic and inflammatory responses. It has thus been suggested [12, 13] that dual enzyme inhibitors should have properties similar to those of the anti-inflammatory corticosteroids, which reduce PG and LT production by preventing the release of AA from phospholipids [14]. We have examined two compounds (**1**) and (**2**) for their *in vitro* effects on the production of both CO and LPO metabolites of AA in guinea pig peritoneal polymorphonuclear leukocytes (PMNs).

Results and Discussion

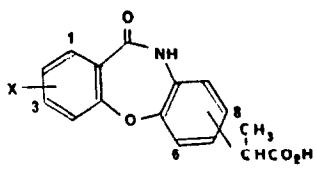
The compounds were not potent inhibitors of adjuvant-induced arthritis in rats and effects, where seen, were only moderate. It would appear that improvement against primary and secondary paw lesions was associated with the compounds (**1**) and (**2**) possessing a propionic acid chain. The location of the acid group either at the 7 or 8 position did not make much difference. A fluorine atom at the 3 position seemed to have been effective. An electron withdrawing nitro group or a chlorine atom at the 2 position in the 8 series of acids was of no advantage. Compounds (**1**) and (**2**) showed moderately weak *in vitro* reduction of CO products of AA in guinea pig PMNs. They are about 300× less potent than indomethacin. This level of activity, as expected, is consistent with the postulated interaction of the non-planar tricyclic part of the molecule with the hydrophobic (supplementary) site of CO. However, they also tend to show a slight increase, not dose related, in LPO products. This is similar to the effect shown by indomethacin in rabbit neutrophils [17] and guinea pig PMNs [18]. The modest cyclooxygenase activity of these compounds may well predict a low ulcerogenic potential, but their anti-inflammatory activity compares poorly with that of indomethacin.

Experimental protocols

Chemistry

The compounds were prepared using conventional methods. The reaction of an appropriately substituted *o*-aminophenol (*e.g.*, 3(4)-amino-4(5)-hydroxy-phenyl-2-methylacetic acids [15, 16]) with an *o*-halobenzene carbonyl chloride in the presence of 1 equivalent of aqueous NaOH produced the intermediate carboxamides II. The

Table I. Dibenz[b,f][1,4]oxazepine acids and intermediates.



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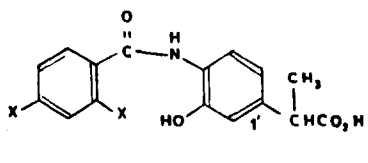

II

No.	X	Acid	Yield[a] %	mp,°C	Crystn.Solv.	Formulae	LD_{50} p.o. mg/kg	Adj. A	Arth., B	% reduction[f] C	J
I (1)	3-F	7	46.1	231-33	Aq. EtOH	$C_{16}H_{12}FNO_4$	1200	28[c]	26	35	12
(2)	3-F	8	42.1	260-61	Aq. MeOH	$C_{16}H_{12}FNO_4$	>1600	25[c]	22	38[c]	11
(3)	2-Cl	8	37.9	234-36	Aq. MeOH	$C_{16}H_{12}ClNO_4$	1200	0	2	21	15
(4)	2-NO_2	8	11.9	194-96	EtOAc	$C_{16}H_{12}N_2O_6$	1600	16	0	20	2
(5)	2-NH_2	8	55.0[b]	229-30	Aq. EtOH	$C_{16}H_{14}N_2O_4$	>1600	23	17	20	14
(6)	3-F	H	62.8	257-58	Aq.DMF/MeOH	$C_{13}H_8FNO_2$	>1600	9	29[c]	25	13
II (7)	F	H	78.6	201-03		$C_{13}H_9F_2NO_2$	>1600	5	-5	-4	-3
(8)	Cl	1'	89.0	110-11	EtOAc/Pet ether (40-60°)	$C_{16}H_{13}Cl_2NO_4$	>1600	17	-5	-42	-7
Indomethacin								46[e]	63[d]	82[d]	53

Adjuvant A = right primary lesion, volume change in the injected paw measured from day 0—8.
B = right secondary lesion, volume change in the injected paw measured from day 9—18.
C = left secondary lesion, volume change in the uninjected paw measured from day 9—18.
J = joint mobility of the paw.

[a]Obtained in the cyclisation step, not optimised for (**1**)—(**4**) and (**6**). [b]Obtained by reduction (10% Pd-C/DMF) of (**4**). [c]$P < 0.05$. [d]$P < 0.001$. [e]$P < 0.01$. [f]Daily dose 33 mg/kg p.o. except for indomethacin (3 mg/kg); (—) increase in paw lesions (not significant).

Table II. % Change in metabolites of arachidonic acid.

Compound No.	Concn.	Cyclooxygenase products			Lipoxygenase products	
	(μmol)	$PGF_{2\alpha}$	PGE_2	TXB_2	5-HETE	5,12-diHETEs
(1)	100	— 56.9[a]	— 67.4[b]	— 80.3[a]	10.0	25.4[c]
	30	— 47.2[a]	— 68.9[b]	— 53.6[b]	15.1	28.8[b]
	10	— 16.4[d]	— 8.3	— 21.6	0.9	26.7[b]
(2)	100	— 60.4[a]	— 67.4[b]	— 75.8[a]	29.3[d]	20.7[d]
Indomethacin	IC_{50}		0.17×10^{-6}	0.133×10^{-6}		[e]

[a]$P < 0.001$. [b]$P < 0.01$. [c]$P < 0.02$. [d]$P < 0.1$. [e]Variable potentiation.

disodium salt of the above, prepared with 2 equivalents of NaOH in aqueous methanol, and dried *in situ*, was cyclised in refluxing DMF to give the products as sodium salts, from which the desired acids (1—4,6) were generated by neutralisation. All the compounds were characterised by IR, UV and NMR. Elemental microanalyses were within ± 0.4% of the calculated values.

Biological methods

Acute toxicity. The compounds were administered to mice in doses up to 1600 mg/kg p.o. The mice were observed over 48 h for mortalities and other gross behavioural changes. LD_{50} values were approximated from the results.

Adjuvant arthritis. Female Sprague—Dawley rats (150—170 g) were used in groups of 6. Arthritis was induced and assessed by the method described previously [19]. The results are recorded in Table I.

Assay of CO and LPO metabolites of AA. The method used for detecting inhibitors of AA metabolism in guinea pig PMNs was described in a previous paper [18]. The results in terms of $PGF_{2\alpha}$, PGE_2 and TXB_2 as CO products and 5-HETE and 5,12-diHETE as LPO metabolites are shown in Table II.

Acknowledgements

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