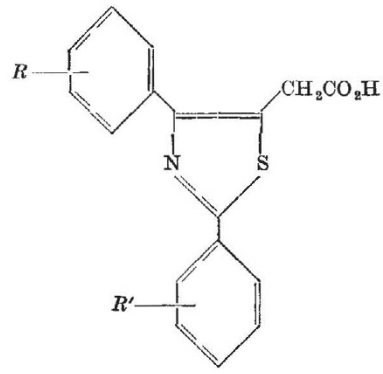
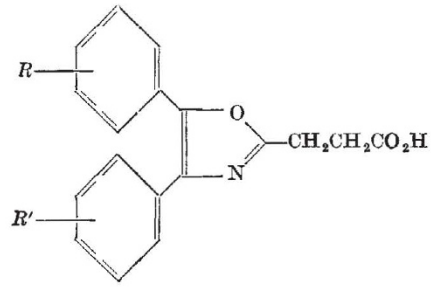
Diaryloxazole and Diarylthiazolealkanoic Acids: Two Novel Series of Non-steroidal Anti-inflammatory Agents

SINCE the reports of the anti-inflammatory activity of indomethacin (1-*p*-chlorobenzoyl-5-methoxy-2-methylindol-3-ylacetic acid)[1] and ibufenac (*p*-isobutylphenylacetic acid)[2], there has been much interest in the pharmacological properties of aryl and heteroarylalkanoic acids. This paper describes the anti-inflammatory activity found in two series of new alkanoic acids, namely the 2,4-diphenylthiazol-5-ylacetic acids (I) and the β-(4,5-diphenyloxazol-2-yl) propionic acids (II). The thiazoles (I) were prepared by the Hantzsch method from thioamides and β-bromo-β-ketoacids, and the oxazoles (II) were prepared by the procedure of Davidson[3].



I



II

Compounds from both series showed anti-inflammatory activity in a variety of animal tests. In the rat, they inhibited the oedema response of the hind-paw to injected carrageenin, the duration of action of maximally effective doses being of the order of 4–8 h. This anti-oedema action was not caused by the release of endogenous adrenocortical steroids, for it occurred in bilaterally adrenalectomized animals. Both the immediate and the delayed inflammatory responses of the rat to injected Freund's adjuvant were inhibited and the granuloma response to implanted cotton wool pellets was also suppressed. In the anaesthetized guinea-pig, many compounds in the two series resembled aspirin and phenylbutazone in blocking the bronchoconstrictor response to intravenous bradykinin. *In vitro* studies showed that compounds from both series inhibited the heat denaturation of serum albumin and reduced the binding of trinitrobenzaldehyde to albumin, the concentrations used being similar to those required for comparable activity with phenylbutazone.

Although the spatial arrangement of the two phenyl rings with respect to the alkanoic side chain is different in the two series, the structure–activity patterns in the carrageenin oedema experiments were very similar. Increasing the length and/or branching of the alkanoic side chain and the preparation of ester, amide and hydroxamic acid derivatives reduced the activity. Substitution in the *para*-position of either or both of the phenyl rings generally increased activity and, in some cases, the increase was pronounced (Table 1).

Table 1. RELATIVE ANTI-OEDEMA POTENCY OF SELECTED THIAZOLES AND OXAZOLES ADMINISTERED ORALLY TO RATS

Series	*R*	*R'*	Relative potency (phenylbutazone = 1)
I	H	H	0·6
	H	*p*-N(CH$_3$)$_2$	2·0
	p-Cl	H	5·0
II	H	H	0·3
	p-Cl	*p*-OCH$_3$	1·0

Carrageenin (0·05 ml. of 1 per cent solution) was injected subcutaneously into the hind-paw 1 h after dosing with compound and the effect measured 3 h later.

Treatment of disorders of connective tissue in man with anti-inflammatory drugs is often complicated by evidence of gastrointestinal bleeding. Lange[4] reported occult blood in the faeces in a majority of patients treated with 2·5–3 g aspirin/day. Kuzell[5] reported gastrointestinal symptoms in 16 per cent of patients treated with phenylbutazone, and in an early trial of indomethacin Wanka[6] recorded occult blood loss in twelve of thirteen patients. Similarly, rats treated with doses of aspirin, phenylbutazone or indomethacin which were sufficient to cause significant inhibition of the oedema-response to carrageenin showed severe gastric mucosal erosion and haemorrhage at post-mortem examination. The thiazoles and oxazoles reported here have not been evaluated in man, but the evidence obtained in the rat indicates that gastric mucosal erosions and haemorrhage are absent or less severe with these compounds than with equi-effective doses of aspirin, phenylbutazone or indomethacin.

K. BROWN
J. F. CAVALLA
DAVID GREEN
A. B. WILSON

John Wyeth and Brother, Ltd,
Huntercombe Lane South,
Taplow,
Maidenhead, Berkshire.

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Disappearance of γ BHC from Avian Liver after Death

FROM 1956, the dressing of cereal seeds with organochlorine insecticides was responsible for the deaths of many grain feeding birds[1–3] and analyses suggested that the mortality was chiefly caused by dieldrin, aldrin and heptochlor[1]. Following these events the Nature Conservancy undertook a nationwide survey of organochlorine residues in wild birds. Nearly all the specimens examined contained detectable amounts of organochlorine insecticides, the more common of which were dieldrin and DDT and its metabolites[4]. Although γ BHC (gamma 1,2,3,4,5,6-