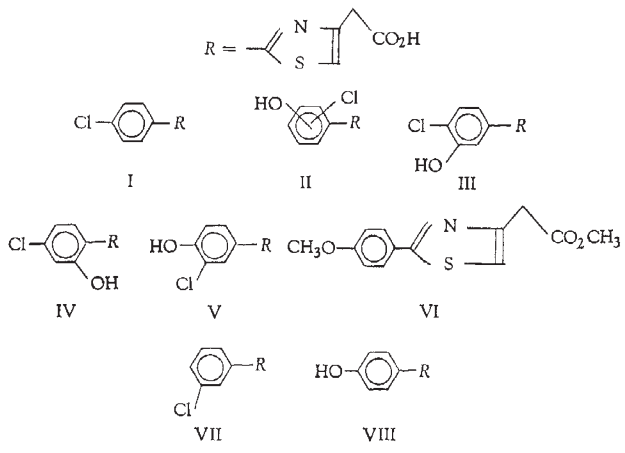
Metabolism of Thiazole Acetic Acid Derivatives and the NIH Shift

THE microsomal hydroxylation of *para*-halogen substituted anilines, acetanilides and aromatic amino-acids, with subsequent migration of the halogen function, has been termed the NIH shift[1-4].

We wish to report the observation of such a metabolic process occurring in substituted thiazole acetic acids, one of which (ICI 54,450) has been shown to possess anti-flammatory, analgesic and antipyretic activity (ref. 5 and following communication).

ICI 54,450, (I), when administered orally to rats in a concentration of 50 mg/kg, gave rise to two fluorescent metabolites in the ratio 2 : 1. The minor metabolite was shown by mass spectrometry to contain the moiety (II). For comparison with this metabolite the two phenols (III) and (IV) were synthesized. Thin-layer chromatographic behaviour, mass spectra abundance patterns and fluorescence spectra showed wide differences between these compounds and the minor metabolite. The compound (V) which would be formed by the NIH shift mechanism was then synthesized for comparison. This phenol was found to be identical in all spectroscopic and chromatographic respects to the minor metabolite. The identity of this metabolite was further established by inverse radioisotope dilution analysis with material metabolically derived from ICI 54,450 labelled with ^{14}C.



Mass spectrometry showed that the major metabolite contained a phenolic hydroxy function but no chloro substituent. The nuclear magnetic resonance spectrum of the methylation product (diazomethane) of this metabolite was consistent with the structure (VI), a symmetrical A_2B_2 aromatic proton splitting pattern being observed.

ICI 55,100 (VII) administered to rats in the manner described for ICI 54,450 gave rise to a single metabolite. This was identical to the metabolite (V) produced by ICI 54,450. The fact that the halogen had not migrated supports the findings of Daly *et al.*[4] that the NIH shift is restricted to *para* hydroxylation.

ICI 54,450 was less efficiently metabolized in dogs than in the rat. The metabolites were identical, however, with even more of the phenol (VIII) predominating. No metabolites of ICI 54,450 were detected in monkeys and man, or in the serum of any of the species examined.

When treated with pertrifluoracetic acid in methylene chloride[6], ICI 54,450 gave rise to a number of products from which it was possible to isolate the compound (V) in a yield of 10·0 per cent. This exemplifies an *in vitro* halogen migration albeit with a lower efficiency than that achieved *in vivo*. The phenols (III) and (IV) were not detected.

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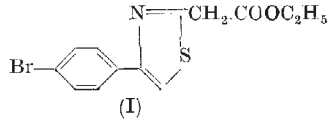
2-(4-chlorophenyl)thiazol-4-ylacetic Acid ('Myalex'): a New Compound with Anti-inflammatory, Analgesic and Antipyretic Activity

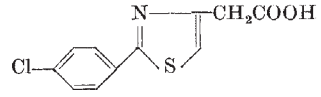
THE use of adjuvant-induced arthritis in rats for the testing of compounds which may be of value in the treatment of rheumatoid arthritis in man[1] has resulted in the discovery, in our laboratories, of two classes of compounds with different modes of action[2-5]. We wish to describe briefly the properties of a third class of compound[6] which has recently been discovered using this laboratory model.

Our initial observation was that 25 mg/kg of ethyl 4-(4-bromophenyl)thiazol-2-ylacetate, ICI 52,722 (I), given by mouth daily, reduced the inflammation associated with the development of both "primary" and "secondary" lesions in rats with adjuvant-induced arthritis.

Compound ICI 54,450, 2-(4-chlorophenyl)thiazol-4-ylacetic acid, (II), 'Myalex' (ICI), subsequently proved to be more potent and was therefore studied in more detail.



(I)



(II)

ICI 54,450 was prepared by the reaction of *p*-chlorothiobenzamide with ethyl ω-bromoacetoacetate, followed by hydrolysis of the product, ethyl 2-(4-chlorophenyl)-thiazol-4-ylacetate, to the corresponding acid. It is a colourless, crystalline solid, melting point 155°–156° C. It is soluble in most organic solvents but only sparingly soluble in water. Salts of varying solubility in water have been produced.

Tests for biological activity in rats, mice and guinea-pigs showed that ICI 54,450 is a potent anti-inflammatory agent with analgesic and antipyretic properties. Doses within the range 2·5 to 100 mg/kg by mouth produced graded responses on adjuvant-induced arthritis in rats (developing and established), carrageenin oedema in rats[7], adjuvant-induced inflammation in mice and ultraviolet light erythema in guinea-pigs[8]. The compound was also active in tests for analgesic activity, for example, the squirming syndrome in mice[9]. In tests for antipyretic activity, a single dose of 100 mg/kg given immediately before the injection of a bacterial pyrogen to rats completely prevented the increase in body temperature. Studies in adrenalectomized arthritic rats showed that the activity of ICI 54,450 was not mediated by stimulation of