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Anti-inflammatory activity of ethyl esters of straight chain fatty acids

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While testing a series of straight chain esters of phenylglycine and phenylalamine, Thomas and West [1] found that anti-inflammatory activity was demonstrable only when the amino acids were esterified with alcohols of high molecular weight. Optimal activity in both dextran and carrageenan models of inflammation in rats resided with the heptyl esters and activity remained high in esters with even higher molecular weight alcohols. In contrast, the heptyl ester of alanine has since been shown to be much less active, suggesting that a phenyl ring structure attached to the ester linkage may be important for anti-inflammatory activity.

Recently, Khedouri *et al.* [2] tested a series of straight chain esters of acetic acid and found optimal anti-inflammatory activity on intraperitoneal injection into rats again with the heptyl compound, although heptyl acetate was less active than the heptyl esters of phenylalanine and phenylglycine. The importance of the ester bond was established by showing that each alcohol used for esterification, as well as acetic acid, was inactive in these tests. The receptor site for inhibition of the inflammatory responses may therefore be optimally filled by the heptyl compounds.

We have tested the activity of four ethyl esters of straight chain fatty acids to study the significance of the position of the ester bond in the molecule. The test compounds were chosen for synthesis so that the hydrophobic chain contained 4 (butyric), 6 (caproate), 8 (caprylate) and 10 (caprate) carbon atoms. Inflammation was induced in the rat's paw by carrageenan (1 mg), as previously described, [2], and compounds suspended in 1% Tween 80 in 0–15 M phosphate buffer were injected peritoneally 30 min before the carrageenan. The activity of a compound was expressed as the percentage inhibition of the inflammation relative to that found in untreated control rats.

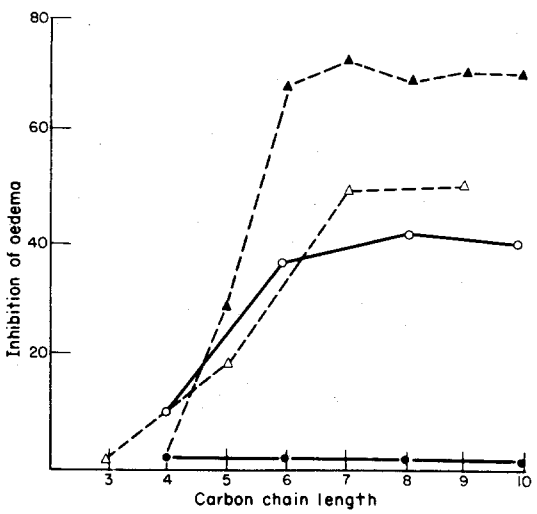
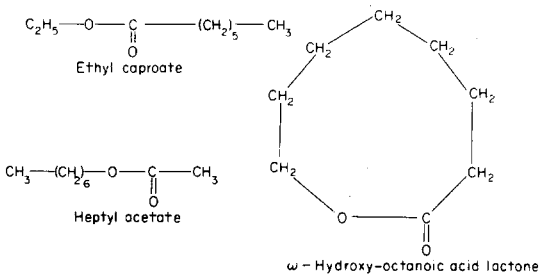


Fig. 1. Two of the more active esters and the inactive lactone. Relationship of carbon chain length in ethyl esters of fatty acids (○) and activity against carrageenan oedema in rat paws measured as mean percentage inhibition at 3 hr (Ordinate). Doses used were 100 mg kg^{-1} intraperitoneally. Activity of the free fatty acids (●) is also recorded. Also shown for reference are the activities of esters of phenylglycine (▲) and of esters of acetic acid (△). Note in all cases of esters that optimal activity lies with a carbon chain length of at least six.



The results obtained at 3 hr using molar dose levels equivalent to 100 mg kg^{-1} ethyl caproate are shown in Fig. 1. Optimal activity was found with the caproate when the fatty acid chain length was six and the degree of inhibition was comparable with that previously reported for the corresponding esters of acetic acid at this dose level. Increasing the dose of the fatty acid esters increased activity in most cases but the four fatty acids were inactive, again suggesting that the ester linkage is important for anti-inflammatory activity. The active esters were also tested for their ability to reduce extravasation of Azovan Blue dye induced by putative mediators of inflammation such as histamine, 5-hydroxytryptamine, bradykinin, PGE_1 and PGE_2 but none showed activity, a result in sharp contrast with that found for the corresponding acetic acid esters.

Having found that the orientation of the ester bond with respect to the hydrophobic component of the molecule appeared to be relatively unimportant for anti-inflammatory activity, it seemed possible that the active compounds may be able to assume cyclic conformations which would make them almost indistinguishable and each would bind specifically to the same site. Alternatively, there may be a non-specificity between the ester and the inflammatory site. To test these ideas, the lactone of ω-hydroxy-octanoic acid was synthesised [3] and tested fully. It was inactive in the carrageenan model of inflammation and evidence points to non-specificity in binding of the ester bond. Nevertheless, work is in hand to examine heptyl caproate, a compound containing an ester group and two straight carbon chains of optimal length, and heptyl benzoate where the phenyl ring is attached to an ester linkage and a straight carbon chain of optimal length.

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REFERENCES

1. G. Thomas and G. B. West *J. Pharm. Pharmac.* **26**, 151 (1974).
2. E. Khedouri, P. J. Warne and G. B. West, *J. Pharm. Pharmac.* **28**, 839 (1976).
3. R. Huisgen and H. Ott, *Anglo. Chem.* **70**, 312 (1958).