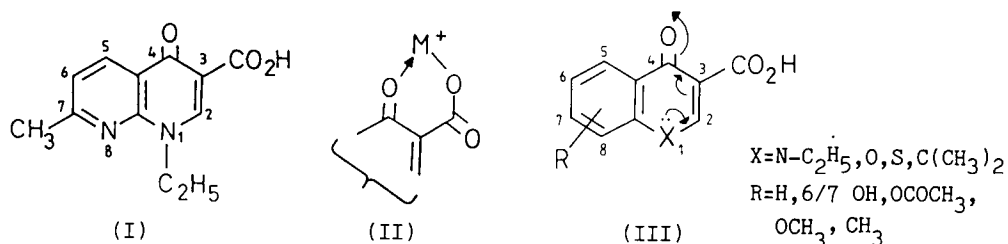


STRUCTURE-ACTIVITY RELATIONSHIPS IN AROMATIC RING-FUSED
4-PYRIDONES: REPLACEMENT OF N₁

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Nalidixic acid (I, Lesher et al, 1962) is a synthetic agent used mainly for the treatment of urinary tract infections caused by Gram-negative organisms. Many analogues have been synthesised (Albrecht, 1977) and it appears that chelation of certain divalent metal ions (II) and binding to the DNA of prokaryote organisms are important for activity (Vincent et al, 1981). Such quinolones bearing H at N₁ are inactive and the nature of the substituent at N₁ may be altered only within narrow limits if activity is to be maintained (Albrecht, 1977). Furthermore we report here that pyrazoles, uracils and thiouracils containing the pharmacophore (C₃, C₄) of I are also inactive. Since the structural moiety N₁-C₄ is a vinylogous amide the tertiary nitrogen may have a profound effect upon biological activity (e.g. the chelation of metal ions) by increasing the electron density of the pharmacophore (III). In order to investigate the role of this substituent we have synthesised suitable isosteres (III, X=O,S,C(CH₃)₂).



Chromenone analogues were produced by formylation of suitably substituted *o*-hydroxyacetophenones and photo-oxidation of the resultant 3-aldehyde with *N*-bromosuccinimide (Nohara et al, 1974). Thiochromenone analogues were synthesised by thermal condensation of appropriately substituted thiophenols with diethyl ethoxymethylenemalonate and cyclisation in polyphosphoric acid. Subsequent hydrolysis of the ester was acid catalysed since alkaline hydrolysis caused rearrangement to give the corresponding 3-formyl-4-hydroxythiocoumarin. The failure of diverse attempts to oxidise the sulphide analogues (III, X=S) to the corresponding sulphones was presumably due to the electron withdrawing effect of the 3-substituent. Carbocyclic analogues were prepared by adaptation of a method of Arnold et al (1947).

These compounds (as their sodium salts) were not antibacterially active against *E. coli* NCTC 9001 and *S. aureus* NCTC 6571 in concentrations as high as 250 µg/ml of nalidixic acid (I, m.i.c., 7 and 45 µg/ml respectively); III (X=N-C₂H₅, R=7-OCH₃; m.i.c., 3 and 25 µg/ml respectively). These results clearly illustrate that a tertiary nitrogen atom at position 1 is essential for activity and that insertion at C₇ of an electron releasing substituent (e.g. -OCH₃) which may increase the electron density of the carbonyl group does not confer activity upon compounds such as III (X=O,S,C(CH₃)₂; C₇=H,OCH₃). However it is possible that the inherent instability to nucleophiles (e.g. HCO₃⁻) of chromenones lacking a substituent at C₂ may contribute to this loss of activity.

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