ANTIBACTERIAL STRUCTURE-ACTIVITY RELATIONSHIPS IN AROMATIC RING FUSED 4-PYRIDONES: NOVEL NITROGEN SUBSTITUENTS AT N_1

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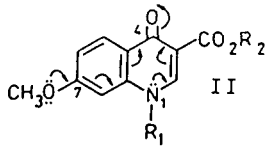
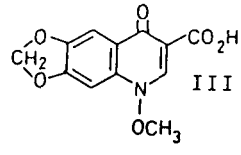
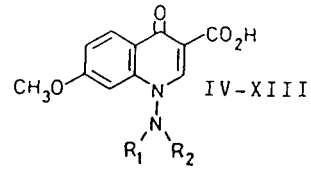
Certain analogues of nalidixic acid (I, Lesher et al, 1962) are quinolones which must possess a tertiary nitrogen and an electron releasing substituent at C_7 (e.g. II, R_2=H, R_1=C_2H_5) for activity. The resultant increased electron density on the oxygen atom at C_4 of the vinylogous amide (as in II) is consistent with the view that the chelation of divalent metal ions by this pharmacophore and binding to the DNA of prokaryotic organisms are important for the antimicrobial activity of such compounds (Vincent et al, 1981).
Variation in the nature of substituents at position 1 (Albrecht, 1977) has been essentially restricted to those with a carbon atom linked to N_1. A rare exception is miloxacin (III, Agui et al, 1977) and the high activity of this compound prompted us to investigate the synthesis and antimicrobial activity of the series of analogues, (IV-XIII). The initial route for synthesis of the parent molecule (IV) was condensation of diethyl ethoxymethylenemalonate with N-3-methoxyanilinophthalimide followed by cyclisation, hydrazinolysis and hydrolysis. The resultant poor yield led us to employ direct N-amination of II (R_2=C_2H_5, R_1=H) with O-2,4-dinitrophenylhydroxylamine followed by base hydrolysis. Since the low basicity of the N-amino group obviated its direct alkylation it was activated to substitution with a variety of alkyl and alkenyl halides by monoformylation with acetic/formic anhydrides and subsequent hydrolysis of the intermediate substituted formamide esters to give compounds VI-X. Reaction of the ethyl ester of IV with refluxing acetic anhydride, 2,5-dimethoxytetrahydrofuran and 2,5-hexanedione followed by hydrolysis afforded respectively XI, XII and XIII.
The results of antibacterial evaluation of these analogues (as their sodium salts) are shown in Table 1. It may be seen that VI, the bioisostere of II(R_2=H, R_1=-C_2H_5 and -OCH_3), is the most active and that increase in size of the alkyl substituent progressively decreases activity. Electron-withdrawing substituents cause reduction in activity although ^{1}H n.m.r. data indicate that the pyrrole ring is not co-planar with the quinolone nucleus in XII and XIII. There is no obvious correlation between the pKa values of the members of this series and their antibacterial activity.



II



III



IV-XIII

Table 1 pKa and m.i.c. (μg/ml) for I-XIII

Number	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
R_1	-	C_2H_5	-	H	CHO	CH_3	C_2H_5	n-C_3H_7	$CH_2CH{=}CH_2$	$CH_2CH_2CO_2H$	$COCH_3$		
R_2	-	H	-	H	H	H	H	H	H	H	H		
pKa	6.11	6.53	-	6.77	-	6.72	6.61	6.61	-	-	5.85	6.62	6.70
E.coli NCTC 9001	9	9	1	>200	>100	1	9	18	>100	>100	>300	54	>300
S.aureus NCTC 6571	85	185	3	>200	>1000	96	375	375	>1000	>1000	>140	225	>300

Agui, H. et al (1977) J, Med. Chem. 20: 791-796
Albrecht, R. (1977) Prog. Drug Res. 21: 9-104
Lesher, G.Y. et al (1962) J. Med. Chem. 5: 1063-1065
Vincent, W.R. et al (1981) Int. J. Pharm. 9: 191-198