ANTIBACTERIAL STRUCTURE-ACTIVITY RELATIONSHIPS IN AROMATIC RING FUSED 4-PYRIDONES: SUBSTITUTION AT C2

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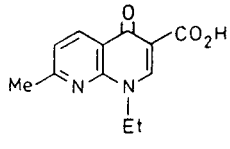
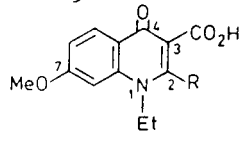
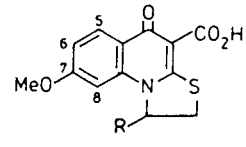
Many analogues of nalidixic acid (I; Lesher et al, 1962) comprise an N-alkyl-4-pyridone-3-carboxylic acid moiety fused to an aromatic or heteroaromatic ring substituted with an electron donating substituent at C7 (Albrecht, 1977). There is little information regarding C2 substituted derivatives and IIb ($R=CH_3$) was obtained by preparation of 1-ethyl-7-methoxy-2H-3,1-benxoxazine-2,4(1H)dione and reacting it with sodio ethyl acetoacetate in N,N-dimethyl-acetamide followed by treatment with acid. The corresponding use of sodio diethyl malonate afforded the ethyl ester of IIc (R=OH) but attempted acid or base hydrolysis caused decarboxylation. The important common intermediate IV (1,1-diethoxycarbonyl-2 (3'-methoxyanilino)-2-thioethene) was obtained by reaction of sodio diethyl malonate with 3-methoxyphenyl isothiocyanate. Methylation of this with methyl iodide followed by thermal cyclisation of the resultant 2-methylthio derivative afforded the desired ethyl 7-methoxy-2-methylthio- 4-oxo-1,4-dihydroquinoline-3-carboxylate (V) but all subsequent attempts to prepare IId ($R=SCH_3$) by ethylation of the latter resulted in attack at O4 rather than N1. Reaction of V with $NaBD_4/PdCl_2$ followed by N-ethylation and hydrolysis afforded IIe (R=D). Alkylation of IV with 1,2-dibromoethane, cyclisation of the intermediate and hydrolysis yielded IIIa (R=H:α7.2,m,2H;8.2,d,1H), but a similar sequence using 1,2-dibromopropane afforded the corresponding 5-methoxy isomer (VI:α7.1,d,1H;7.4,d,1H;7.8,t,1H) rather than the desired IIIb ($R=CH_3$).



I



II a - e



III a,b

The minimum inhibitory concentrations of several of these compounds (as their choline salts), determined against E. coli NCTC 9001 and S. aureus NCTC 6571, are reported in Table 1.

Table 1 m.i.c. (μg/ml) versus E. coli and S. aureus

Compound	I	IIa	IIb	IIe	IIIa	VI
R	-	H	CH_3	D	H	CH_3
E. coli NCTC 9001	20	20	>200	10	60	>250
S. aureus NCTC 6571	>235	>100	>200	>135	115	200

These results indicate that substituents (other than H or D) at C2 decrease the activity of such 4-quinolones against E.coli, as does the absence of an electron-donating group at C7.

Albrecht, R. (1977) Prog. Drug Res. 21: 9-104
Lesher, G.Y. et al (1962) J. Med. Chem. 5: 1063-1065