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SYNTHESIS OF NOVEL ANALOGUES OF THE 4-QUINOLONES

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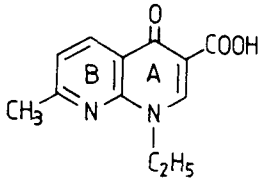
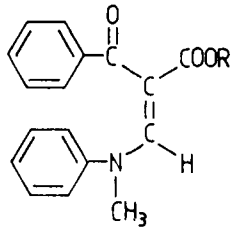
The 4-quinolones are a new class of antibacterial agent effective against a wide variety of bacterial infections (Smith, 1984). The first clinically important agent of this class was nalidixic acid (I,Lesher et al, 1962), which was used principally for the treatment of urinary tract infections. The work described involves the synthesis of an acyclic analogue (II), an analogue containing an expanded A-ring (III) and a tricyclic analogue (IV).



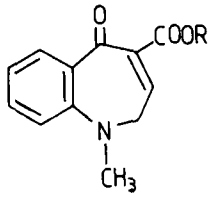
(I)



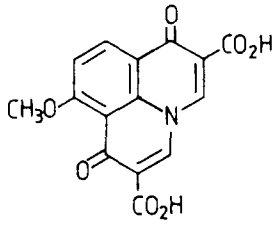
(II)

The acyclic analogue (II, R=CH_2CH_3) was prepared by reaction of N-methylaniline, ethyl benzoylacetate and triethyl orthoformate under conditions described by Snyder and Jones (1946). The failure of diverse attempts to hydrolyse the ester (II, R=CH_2CH_3) was due to the facile degradation of the molecule under the hydrolytic conditions.

The benzazepine derivative (III, R=CH_3) was prepared via a Dieckmann cyclisation of ethyl γ-N-(2-methoxycarbonylphenyl)-N-methylbutyrate, obtained by reaction of N-methylaniline and 4-bromobutyrate. Dehydrogenation was achieved with phenyl selenylchloride to give the carboxylate (III, R=CH_3). Subsequent hydrolysis attempts resulted in complete decomposition of the benzazepine system without isolation of the desired carboxylic acid (III,R=H).



(III)



(IV)

The synthesis of the tricylic analogue (IV) was attempted via a 1,6 - diketo-julolidone system, described by Braunholtz and Mann (1952). m-Anisidine was reacted with acrylonitrile and the bis-cyanoethyl derivative obtained was cyclised using a Friedel-Crafts reaction. Carboxymethylation of the resultant julolidine derivative was completed with methyl cyanoformate (Mander, 1983). However, dehydrogenation was only partially achieved and hydrolysis resulted in partial decarboxylation.

All compounds gave the requisite elemental analysis, infrared and ^1H nuclear magnetic resonance spectra.

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Braunholtz,J.T.,Mann,F.G.(1952) J.Chem.Soc. 3046
Lesher,G.Y.(1962) J.Med.Chem. 5: 1063
Mander,L.N.,Sethi,P.(1983) Tet.Lett. 24: 5425
Smith,J.T.(1984) Pharmaceutical Journal. 233: 299
Snyder,H.R.,Jones,R.E.(1946) J.Amer.Chem.Soc. 68:1253