COMMUNICATION TO THE EDITOR

1,8-Naphthyridine Derivatives. A New Class of Chemotherapeutic Agents

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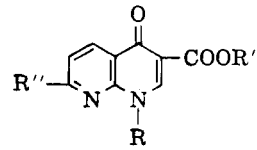
As part of a general investigation of new antibacterial agents,[1] we have prepared a series of 1-alkyl-1,8-naphthyridin-4-one-3-carboxylic acid derivatives. Several members of the series, listed in Table I, were found to be highly effective antibacterial agents both *in vitro* and *in vivo*.

These 1-alkyl-1,8-naphthyridines are prepared as outlined. The appropriate 6-substituted-2-aminopyridine (I) is condensed with diethyl ethoxymethylenemalonate and the resulting diethyl N-(6-substituted-2-pyridyl)-aminomethylenemalonate (II) is cyclized in refluxing Dowtherm A or diethyl phthalate to give the ethyl 4-hydroxy-1,8-naphthyridine-3-carboxylate derivative (III).[2] Hydrolysis of the ester (III) to the corresponding acid and alkylation in alcohol–water with potassium hydroxide gives the desired 1-alkyl-1,8-naphthyridin-4-one-3-carboxylic acid (IV). Alternatively, the same

TABLE I

1-ALKYL-1,8-NAPHTHYRIDIN-4-ONE-3-CARBOXYLIC ACID DERIVATIVES

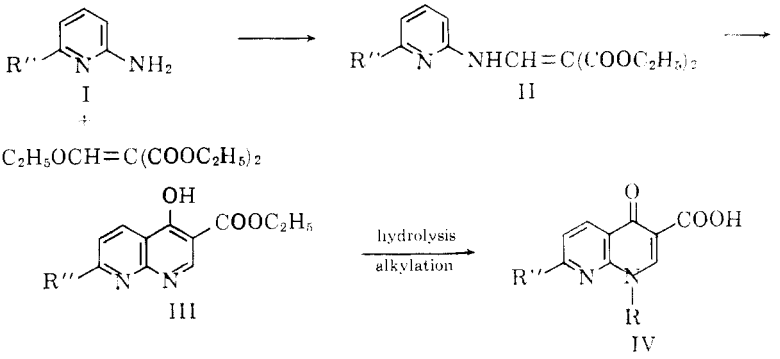


R	R′	R″	M.p., °C. (corr.)
C_2H_5	C_2H_5	CH_3	120.8–121.6
C_2H_5	H	CH_3	226.8–230.2
C_3H_7	H	CH_3	209.4–210.2
$CH_2CH{=}CH_2$	H	CH_3	207.6–208.2
C_2H_5	H	CH_2OH	253.2–256.2
C_2H_5	H	C_2H_5	174.2–176.0

(1) *In vitro* and *in vivo* antibacterial activity was found in a series of 1-alkyl-4-quinolone-3-carboxylic acid derivatives: A. R. Surrey and G. Y. Lesher, *et al.*, to be published.

(2) G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

product is obtained by alkylation of the ester (III) in dimethylformamide with potassium carbonate and then hydrolysis. Analyses for all intermediates and products were satisfactory.



The outstanding compound of this series is 1-ethyl-7-methyl-1,8-naphthyridin-4-one-3-carboxylic acid (IV, R = C_2H_5, R″ = CH_3).[3]

The antibacterial activity of nalidixic acid has been demonstrated against a variety of microörganisms causing disease in man and animals (Table II).

The *in vivo* activity of the compound is most pronounced against Gram-negative bacteria, while Gram-positive organisms are generally more resistant. Chemotherapeutic studies of nalidixic acid in acute experimental infections of mice have shown a similar pattern of activity. Maximal activity was observed against systemic infections caused by *E. coli*, *A. aerobacter*, *Proteus mirabilis*, *Shigella flexneri*.

TABLE II

ANTIBACTERIAL ACTIVITY OF NALIDIXIC ACID

Microörganism	Minimal bacteriostatic concentration, mcg./ml.	ED_{50} (mg./kg.) in mice, p.o.
Escherichia coli	5.0 – 12.5	<25
Pasteurella spp.	0.5 – 2.5	<25
Klebsiella pneumoniae	0.8 – 25.0	60
Aerobacter aerogenes	1.6 – 25.0	35
Proteus spp.	1.25– 30.0	50
Salmonella spp.	3.2 – 50.0	62
Shigella spp.	0.8 – 3.2	<25
Brucella spp.	7.5 – 10.0	>400
Staphylococcus aureus	50.0 –100.0	>400
Diplococcus pneumoniae I	250	>400

(3) This compound was initially investigated clinically under the code number Win 18,320; Generic name, nalidixic acid.

Past. multocida and *Salm. typhimurium*. Under similar experimental conditions, the compound exhibited no therapeutic effect in mice against lethal infections with *Staph. aureus*, *Strep. pyogenes*, *D. pneumoniae* and two strains of *Brucella*. In all instances, therapeutic response was related to the dose, and no toxic side-effects were observed upon single or multiple dose medications at dose levels ranging from 25 to 400 mg./kg. The activity was evident upon both oral and parenteral administration, indicating absorption by both routes of medication. Other compounds in the series had a similar spectrum of activity, but required larger doses to obtain the same therapeutic effect.

The acute toxicity ($LD_{50} \pm$ s.e.) of nalidixic acid in mice following oral and parenteral administration is: oral, 3300 ± 975 mg./kg.; intravenous, 176 ± 11 mg./kg., and subcutaneous, 500 ± 52 mg./kg.

Nalidixic acid is excreted mainly by the kidneys. Urine from treated dogs, monkeys and human subjects was found to possess antibacterial activity against most species of Gram-negative organisms causing urinary tract infections in man. Single oral doses of 0.5 and 1.0 g. in human volunteers produced peak urinary levels of biologically active drug ranging from 25 to 250 mcg./ml. In general, more than 50% of the compound is excreted in the urine within the first 6 hours. Consistently high urinary concentrations ranging from 50 to 200 mcg./ml. have been maintained during medication with 0.5 g. doses of the drug administered orally at 4-hr. intervals. Levels of biologically active drug also were found in the blood. Nalidixic acid is presently under extensive clinical investigation.

Further laboratory investigations of nalidixic acid and other members of the series are in progress. Papers describing chemical and biological aspects in more detail will be forthcoming.