Section on Microanalytical Services and Instrumentation of this laboratory.

3-Ethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine (2d). To 20 ml of 2-butanone was added 1.6 g (6.6 mmol) of 2a·HCl, 1.1 g (7.0 mmol) of EtI, and 1.5 g of K_2CO_3 (DMF as solvent and the appropriate alkyl bromide were used for the remainder of the series). The mixture was stirred overnight at 90–95°, filtered, and evaporated to dryness in vacuo. The residue was dissolved in 50 ml of $CHCl_3$ and washed with H_2O. Drying and evaporation of the $CHCl_3$ gave a residue which was refluxed (for O-demethylation) with 48% HBr (10 ml, 30 min) and evaporated to dryness in vacuo. The residue, in 50 ml of $CHCl_3$, was washed with saturated $NaHCO_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give, after purification by preparative TLC (silica gel), white crystals, mp 171–172°. Anal. ($C_{14}H_{21}NO$) C, H, N.

1,2,3,4,5,6-Hexahydro-8-hydroxy-6-methyl-3-propyl-3-benzazocine (2e). As described for **2d** above, **2e**, mp 147–148° (from *n*-hexane), was obtained. Anal. ($C_{15}H_{23}NO$) C, H, N.

3-Butyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine (2f). This base, prepared as described for **2d**, crystallized from Me_2CO-H_2O: mp 147–149°. Anal. ($C_{16}H_{25}NO$) C, H, N.

3-Amyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine (2g). This compound, prepared as described for **2d**, melted at 127–129° after recrystallization from *n*-hexane. Anal. ($C_{17}H_{27}NO$) C, H, N.

3-Hexyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine (2h) crystallized from *n*-hexane: mp 89–90°. Anal. ($C_{18}H_{29}NO$) C, H, N.

3-Heptyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine (2i) was recrystallized from *n*-hexane: mp 90–92°. Anal. ($C_{19}H_{31}NO$) C, H, N.

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Synthesis and Antibacterial Evaluation of 1,2,3,4-Tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Esters, Carbonitriles, and Carboxamides

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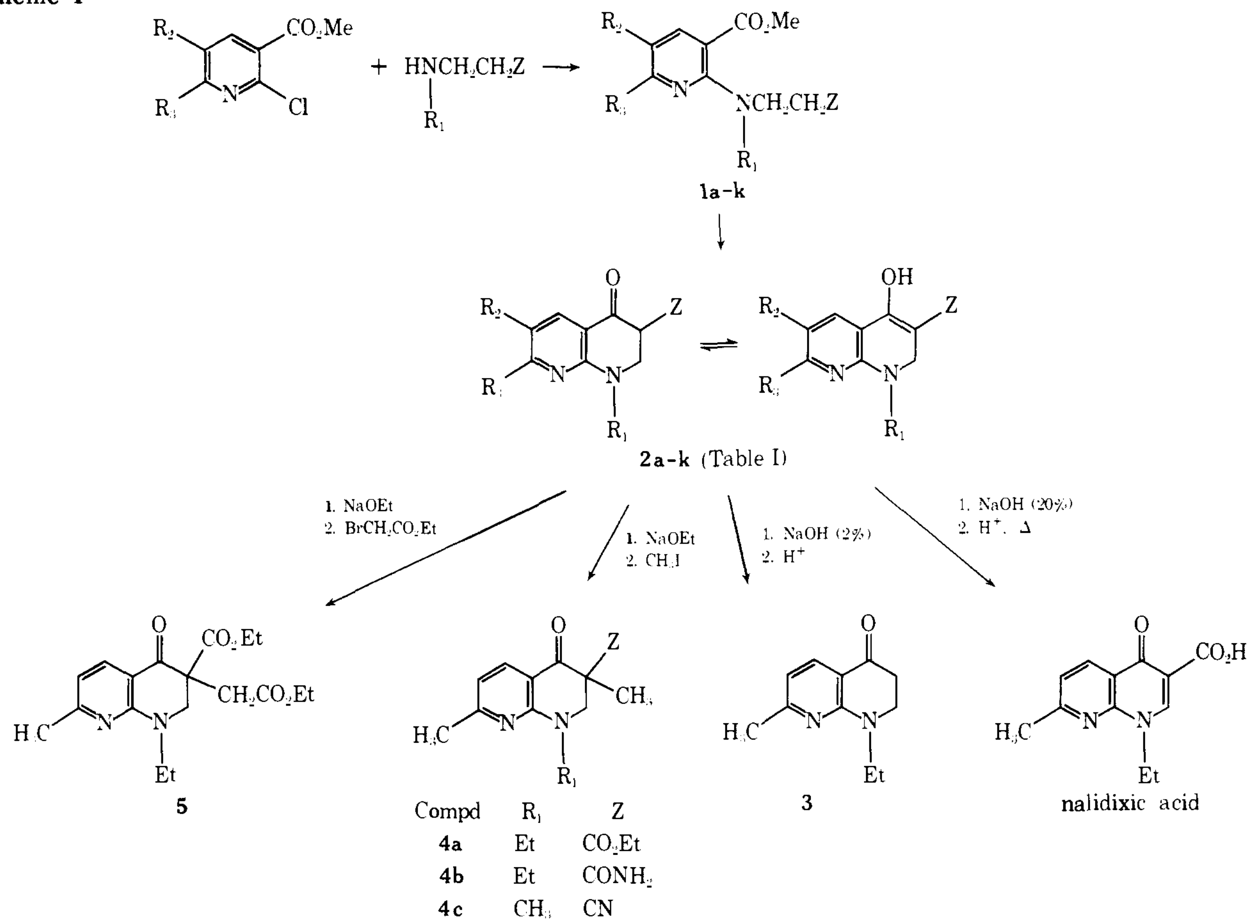
A series of 1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic acid esters, carbonitriles, and carboxamides (**2a–k**) was synthesized and initially evaluated (dose range 50–400 mg/kg) in mice infected with *Escherichia coli*. Only two derivatives, the ethyl and butyl esters of 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid, protected the animals against *E. coli* and several other gram-negative bacterial pathogenic infections. A pro-drug type of mechanism appears to be operable since neither agent showed in vitro activity.

Several reports have appeared in the literature describing the preparation of 1,8-naphthyridine derivatives[1] that are structural variants of the antibacterial agent 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (nalidixic acid), first described by Lesher and coworkers.[2] The 1,8-naphthyridines produced by various modifications of the Lesher synthesis invariably possess a double bond at the 2,3 position. Comparably substituted 1,8-naphthyridines having the 2,3 position fully saturated have not been accessible through syntheses thus far reported in the literature. Furthermore, it has been shown that catalytic hydrogenation of nalidixic acid type naphthyridines results in saturation of the 5,6,7,8 positions leaving the 2,3 double bond intact.[1c] We now report the synthesis and antibacterial screening results of several 1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic acid esters, carbonitriles, and carboxamides (**2a–k**, Scheme I and Table I) in which the 2,3 bond is fully saturated. The preparation of ethyl 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**2a**) illustrates the synthetic procedure used.

Chemistry. Treatment of methyl 2-chloro-6-methylnicotinate with ethyl 3-ethylaminopropionate in refluxing dichlorobenzene resulted in dechloroamination, giving compound **1a** (Scheme I, R_1 = Et; R_2 = H; R_3 = Me; Z = CO_2Et). Cyclization of this diester under Dieckmann conditions afforded ethyl 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (**2a**). A number of other 1,2-dihydro-4-hydroxy-1,8-naphthyridine-3-carboxylic acid esters (**2b–g**) were prepared in this way, starting with the appropriately substituted esters of 3-aminopropionic acid and 2-chloronicotinic acid.[3] In these examples, however, the open-chain diesters **1b–g** were prepared using just 1 equiv of aminopropionate ester and sodium carbonate in dimethylformamide. The diesters were then converted directly to the corresponding 1,8-naphthyridines **2b–g** without purification.

The infrared spectrum of **2a** in KBr indicates the compound exists almost entirely in the enolic ester form, as indicated by the presence of a conjugated chelated ester C=O band at 6.0 μ with broad chelated OH absorption in the 3.5–4.3-μ region. In solution, the presence of both enol

Scheme I



and keto forms was made apparent by ^{1}H NMR spectroscopy. In deuteriochloroform solution the enol form predominates over the keto form in a 3:1 ratio. In $CDCl_3$ the hydrochloride of **2a** shows only the presence of the enol tautomer.

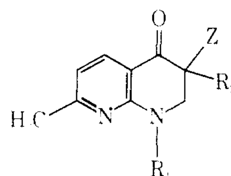
Hydrolysis of **2a** with 2% sodium hydroxide solution at ambient temperature gave the decarboxylated derivative 1-ethyl-2,3-dihydro-7-methyl-1,8-naphthyridin-4-(1*H*)-one (**3**). The ease with which decarboxylation occurs in unconjugated β-keto acids has been well documented in the liter-

Table I. 1,2,3,4-Tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Esters, Carbonitriles, and Carboxamides

Compd	R_1	R_2	R_3	Z	Mp, °C	Recrystn solvent	Formula	Analyses	*E. coli* CD_{50}, mg/kg po
2a	Et	H	CH_3	CO_2Et	162–164	Acetonitrile	$C_{14}H_{18}N_2O_3 \cdot HCl$	C, H, N, Cl	159
2b	Et	H	H	CO_2Et	87–91	Ethanol	$C_{13}H_{16}N_2O_3$	C, H, N	>400
2c	*n*-Bu	H	CH_3	CO_2Et	116–119	Petr ether[a]	$C_{16}H_{22}N_2O_3 \cdot HCl$	C, H, N	>400
2d	Et	H	CH_3	CO_2-*n*-Bu	124–127	Ethyl acetate	$C_{16}H_{22}N_2O_3 \cdot HCl$	C, H, N, Cl	113
2e	Et	H	*i*-Bu	CO_2Et	121–124	Ethyl acetate–petr ether	$C_{17}H_{24}N_2O_3 \cdot HCl$	C, H, N	>400
2f	CH_3	H	CH_3	CO_3Et	195–197	Ethyl acetate–ethanol	$C_{13}H_{16}N_2O_3 \cdot HCl$	C, H, N	>400
2g	Et	NO_2	CH_3	CO_2Et	139–142	Heptane	$C_{14}H_{17}N_3O_5$	C, H, N	>400
2h	Et	H	CH_3	$CONH_2$	127–128.5	Benzene	$C_{12}H_{15}N_3O_2$	C, H, N	>400
2i	Et	H	H	$CONH_2$	160–161	Ethyl acetate–petr ether	$C_{11}H_{13}N_3O_2$	C, H, N	>400
2j	Et	H	CH_3	CN	125–130	Heptane	$C_{12}H_{13}N_3O$	C, H, N	>400
2k	CH_3	H	CH_3	CN	147–150	Heptane	$C_{11}H_{11}N_3O$	C, H, N	

[a]Prepared directly in petroleum ether from pure free base without subsequent recrystallization.

Table II. 1,2,3,4-Tetrahydro-4-oxo-1,8-naphthyridine-3-substituted-3-carboxylic Acid Esters, Carbonitriles, and Carboxamides



Compd	R_1	R_2	Z	Mp, °C	Recrystn solvent	Formula	Analyses	*E. coli* CD_{50}, mg/kg po
4a	Et	CH_3	CO_2Et	117–120	Ethyl acetate	$C_{15}H_{20}N_2O_3 \cdot HCl$	C, H, N	>400
4b	Et	CH_3	$CONH_2$	203–207	Ethanol	$C_{13}H_{17}N_3O_2$	C, H, N	
4c	CH_3	CH_3	CN	192–196	Ethyl acetate	$C_{12}H_{13}N_3O \cdot HCl$	C, H, N	>400
5	Et	CH_2CO_2Et	CO_2Et	150–153	Ethyl acetate	$C_{18}H_{24}N_2O_5 \cdot HCl$	C, H, N	>400

Table III. Antibacterial Profile of 2a, 2d, and Nalidixic Acid

Organism	CD_{50}, mg/kg po		
	Compd 2a	Compd 2d	Nalidixic acid
Escherichia coli (920)	159	113	126
Salmonella typhosa (SaD-12)	116	106	67
Salmonella typhimurium (SaB-1)	341		172
Proteus vulgaris (Pr. 347)	194	212	102
Proteus mirabilis (Pr. 3)	122	237	79

ature. In another experiment, when the hydrolysis was carried out using 20% sodium hydroxide solution at elevated temperature, oxidation of the 2,3 bond also took place, affording the more stable nalidixic acid after acidification. Apparently under the milder hydrolysis conditions this oxidation did not occur, and a more labile acid was formed.[4]

Reactions of the sodium salt of **2a** with methyl iodide or with ethyl bromoacetate in dimethylformamide resulted in the expected C_3-alkylation, affording **4a** and **5**, respectively.

The synthesis was further extended to include the preparation of 1,8-naphthyridines containing a carboxamide (**2h,i**) or carbonitrile functional group (**2j,k**) in the 3 position. The method of preparation was identical with that used for preparing the esters except that suitably substituted 3-alkylaminopropionamides or 3-alkylaminopropionitriles were used in the first step. It is of interest to note that the 1,8-naphthyridinecarboxamides and -carbonitriles, unlike their carboxylic ester counterparts, exist predominantly in their keto forms, as discerned by infrared and ^1H NMR evidence.

Biological Results and Discussion. The 1,8-naphthyridines were tested in vivo (dose range 50–400 mg/kg) for antibacterial activity in CD-1 mice infected with *Escherichia coli*. The curative dose (CD_{50}) for each compound is given in Tables I and II. The highest oral dose used was 400 mg/kg which was considered as the upper practical limit for therapeutic action. Compounds whose CD_{50} values against *E. coli* were less than 400 mg/kg were further tested against other gram-negative organisms (Table III). Nalidixic acid was used as a standard for comparison.

The carboxylic acid esters **2a** and **2d** were the only two compounds showing activities (CD_{50} values) comparable to that of nalidixic acid. All other molecular modifications failed to produce compounds that protected the animals against *E. coli* infection in the dose range tested.

When the 1,8-naphthyridines given in Tables I and II were tested in vitro for antibacterial activity, using an agar serial dilution technique and within a dose range of 1.95–250 μg/ml, all were found to be inactive against *E. coli*.

As noted in Table III, compounds **2a** and **2d** showed a spectrum of in vivo activity similar to that of nalidixic acid against several gram-negative bacterial pathogens. However, with the exception of *E. coli*, the remaining organisms were more sensitive to nalidixic acid by factors of 2–3. Since neither **2a** nor **2d** shows in vitro antibacterial activity but gives good protection in vivo against several gram-negative pathogens, some type of biotransformation of these substances must take place. Whether or not this apparent pro-drug type of action produces a nalidixic acid type derivative or some other active species is not clear at present. One may assume that an in vivo conversion of **2a** or **2d** to nalidixic acid accounts for the comparable CD_{50} values against *E. coli* given in Table III. However, it then becomes difficult to reconcile why the CD_{50} values against other gram-negative organisms differ by factors of 2–3 relative to nalidixic acid. Furthermore, Lesher[5] has shown that significant in vivo gram-negative activity in nalidixic acid derivatives can be retained with wide variation in substituents at the 1, 3, 5, 6, and 7 positions of the naphthyridine ring. The 1,8-naphthyridines of the present study appear to differ markedly from these nalidixic acid derivatives in this respect. Additional studies are in progress to establish the metabolic fate of compounds such as **2a** and **2d**.

Experimental Section

All structural assignments were based on compatible ir, ^1H NMR, and satisfactory analyses. Ir spectra were measured in KBr disks in a Perkin-Elmer Model 21 spectrophotometer; ^1H NMR spectra were obtained with a Varian A-60 or a JEOL C60-HL spectrometer using dimethyl sulfoxide (Me_2SO-d_6) or deuteriochloroform. The chemical shifts were measured in parts per million (δ) downfield from tetramethylsilane. Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. All compounds were analyzed for C, H, and N and were within ±0.4% of the theoretical values unless otherwise indicated.

The in vivo studies were done with inbred albino male mice (CD-1 strain) weighing 18 ± 1 g. The animals were infected intraperitoneally with a standardized LD_{95} ± 5% dose of the respective organisms suspended in 0.5% gastric mucin; mice were distributed at random into groups of ten each. The test agents were prepared in sterile distilled water immediately before use; the concentrations ranged from 50 to 400 mg/kg. In these studies the curative dose (CD_{50}) of the compounds tested was determined from the ac-

tivity of a single dose administered orally 6 hr after infection. All animals were observed for 14 days, deaths were recorded daily, and the CD_{50} values were calculated by the method of Reed and Muench.[6]

Methyl 2-[(2-Ethoxycarbonylethyl)ethylamino]-6-methylnicotinate (1a). A solution containing 337.6 g (1.82 mol) of methyl 2-chloro-6-methylnicotinate[7] and 571.3 g (3.94 mol) of ethyl 3-ethylaminopropionate[8] in 1 l. of o-dichlorobenzene was heated under reflux for 6 hr. The solvent was removed by vacuum distillation. The fraction distilling at 163–165° (0.5 mm) amounted to 129.4 g (44%) of **1a**: ir (film) 5.74 (aliphatic ester C=O), 5.80 μ (aromatic ester C=O). Anal. ($C_{15}H_{22}N_2O_4$) C, H, N.

Ethyl 1-Ethyl-1,2-dihydro-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (2a). To a solution of sodium ethoxide prepared from 10.1 g (0.44 g-atom) of sodium in 1 l. of ethanol was added 129.4 g (0.44 mol) of **1a**. The reaction mixture was heated under reflux for 10 min and then cooled in ice. The insoluble material was collected on a filter and triturated with 20% aqueous acetic acid solution. There was obtained 81.5 g of product (yield 71%), mp 75–80°. Recrystallization from petroleum ether gave an analytical sample: mp 69–71°; ir (KBr) 5.95 (ester C=O), 3.5–4.3 μ (chelated OH); ^1H NMR ($CDCl_3$) δ 7.98 (d, 1, arom), 6.48 (d, 1, arom). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

The hydrochloride salt of **2a** was prepared in 95% yield by adding an ethereal solution of hydrogen chloride to the free base in ethyl acetate. The analytical sample (mp 162–164°) was obtained by recrystallization from acetonitrile: ^1H NMR ($CDCl_3$) δ 4.60 (s, 2, CH_2), 12.12 (s, 1, OH). Anal. ($C_{14}H_{19}N_2ClO_3$) C, H, N, Cl.

1-Ethyl-2,3-dihydro-7-methyl-1,8-naphthyridin-4(1*H*)-one Hydrochloride (3). To 200 ml of 2% sodium hydroxide solution were added 0.2 g of **2a** and a few milliliters of ethanol to aid solubility. The solution was stirred at room temperature for 4 hr and extracted with ether (2 × 50 ml). The ether extracts were combined, dried over magnesium sulfate, and filtered. The filtrate was evaporated to dryness. The oily residue was dissolved in a few milliliters of dry ether and acidified with ethereal hydrogen chloride. Recrystallization of the salt from ethyl acetate gave a product with mp 179–184°: ir (KBr) 5.88 μ (aromatic ketone). Anal. ($C_{11}H_{15}ClN_2O$) C, H, N.

1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid (Nalidixic Acid). To 40 ml of a 20% sodium hydroxide solution was added 0.2 g of **2a** and a few milliliters of ethanol to aid solubility. The solution was heated for 5 min at 40–50°, acidified with glacial acetic acid, and cooled to room temperature. Recrystallization of the resulting precipitate from ethanol gave nalidixic acid, mp 225–230°. No depression of melting point was observed on admixture with an authentic sample. Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

Ethyl 1-Ethyl-1,2,3,4-tetrahydro-3,7-dimethyl-4-oxo-1,8-naphthyridine-3-carboxylate Hydrochloride (4a). To a solution of sodium ethoxide prepared from 0.35 g (0.015 g-atom) of sodium in 75 ml of ethanol was added 3.9 g (0.015 mol) of **2a** in 40 ml of ethanol. The precipitate which formed was collected and dissolved in 75 ml of *N,N*-dimethylformamide. To this solution was added 2.1 g (0.015 mol) of iodomethane. The mixture was stirred for 5 min, diluted with 150 ml of water, and extracted with ether (2 × 50 ml). The ether layer was dried over magnesium sulfate, filtered, and acidified with an ethereal hydrogen chloride solution. Ethyl acetate was added to initiate crystallization. The solid was recrystallized from ethyl acetate to give 0.7 g of product: mp 117–120°; ir (KBr) 5.73 (ester C=O), 5.84 μ (aromatic ketone). Anal. ($C_{15}H_{21}ClN_2O_3$) C, H, N.

Ethyl 3-Carbethoxy-1-ethyl-1,2,3,4-tetrahydro-7-methyl-4-oxo-1,8-naphthyridine-3-acetate Hydrochloride (5). To a solution of sodium ethoxide prepared from 0.09 g (0.004 g-atom) of sodium in 50 ml of ethanol was added 1.0 g (0.004 mol) of **2a** in 50 ml of ethanol. The sodium salt thus formed was collected, dried, and dissolved in 50 ml of *N,N*-dimethylformamide. To this solution was added 0.6 g (0.004 mol) of ethyl bromoacetate. The reaction mixture was stirred for 10 min, 150 ml of water was added, and the mixture was extracted with ether (2 × 100 ml). The ether layer was dried over magnesium sulfate, filtered, and diluted with 20 ml of ethyl acetate. The oil which initially separated crystallized on cooling. Recrystallization from ethyl acetate gave 0.6 g of product, mp 150–153°. Anal. ($C_{18}H_{25}ClN_2O_5$) C, H, N.

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Synthesis of Tritium- and Deuterium-Labeled 9-β-D-Arabinofuranosyladenine and the Tritium-Labeled 5′-Monophosphate Ester with Increased Metabolic Stability

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Preparation of both a 5′-deuterium and a 5′-tritium-labeled 9-β-D-arabinofuranosyladenine (**6a** and **6b**) by reduction of the protected 5′-aldehyde **4** is described. Conversion of **6b** to the 5′-tritium-labeled 5′-monophosphate **7b** was effected directly with a phosphoryl chloride–formic acid reagent. The product **7b** exhibited consistently higher blood levels of nonvolatile tritium than the 2-labeled compound when tested in dogs.

Pharmacological studies on the nucleoside antiviral agent, 9-β-D-arabinofuranosyladenine (1),[1-4] and the 5′-phosphate (**7a**)[1] require a stable tritium-labeled derivative that is metabolically resistant to tritium removal in vivo by the various enzymic processes of exchange and oxidation. While an exchange reaction with tritium oxide[5] or more elegant catalytic exchange procedures[6] are available for labeling respectively the C-8[5] and C-2[6] positions of adenine nucleosides, neither process provides a derivative of 1 or **7a** that will retain high levels of its label in a wide range of test