Synthesis of a Novel Analog of Nalidixic Acid: 1-Ethyl-1,4-dihydro-4-oxo-7-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid

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Reaction of nalidixic acid (**1**) with thionyl chloride and subsequent treatment with ethanol gave a mixture of ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(trichloromethyl)-1,8-naphthyridine-3-carboxylate (**3**) and diethyl 1-ethyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3,7-dicarboxylate (**4**). Ethyl 1-ethyl-1,4-dihydro-4-oxo-7-(trichloromethyl)-1,8-naphthyridine-3-carboxylate (**3**) was reacted with antimony pentafluoride to afford 1-ethyl-1,4-dihydro-4-oxo-7-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic acid (**5**).

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Our continuing efforts on structural modifications of nalidixic acid (**1**) (1), a clinically useful antibacterial agent, have led us to the synthesis of its 7-trifluoromethyl analog **5**. To our knowledge, this represents the first example of a 1,8-naphthyridine derivative with a trifluoromethyl substituent prepared by converting a trichloromethyl to a trifluoromethyl group using antimony pentafluoride as the fluorinating agent.

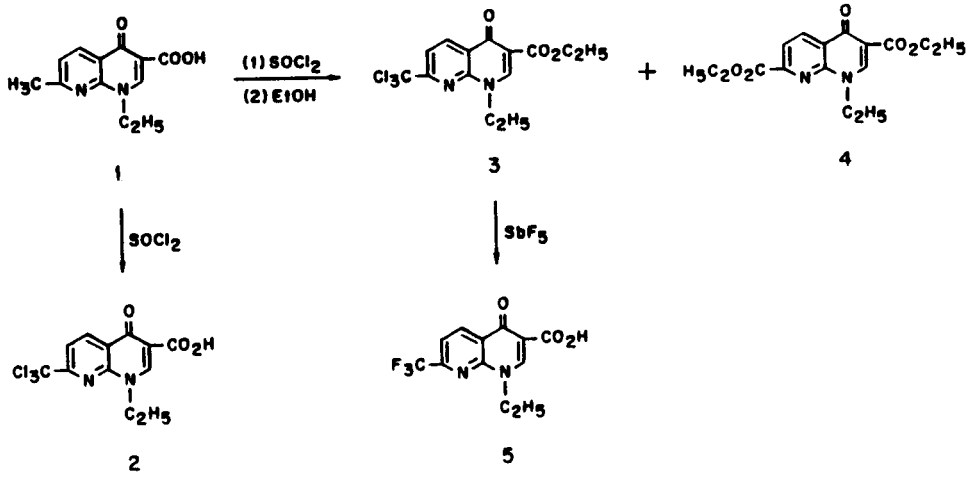
Nishigaki, *et al.* (2) reported a facile conversion of nalidixic acid (**1**) to 1-ethyl-1,4-dihydro-4-oxo-7-(trichloromethyl)-1,8-naphthyridine-3-carboxylic acid (**2**) in high yield, using thionyl chloride as the chlorinating agent. In our hands, this reaction gave a tar from which the isolation of **2** was unsuccessful. However, treatment of this tar with ethanol, followed by chromatography gave **3** and **4** in 23% and 9% yield, respectively. The formation of **4** may be due to the oxidation (3) of the methyl group by thionyl chloride.

The published procedures (4) for converting a trichloromethyl to a trifluoromethyl group using antimony trifluoride in the presence of antimony pentachloride as a catalyst were unsuccessful in our case. Starting material **3** was recovered at lower temperatures ($<110°$) whereas higher temperatures ($>150°$) resulted in decomposition giving mixtures which contained only minute quantities of **5**. This drew our attention to antimony pentafluoride which is a more powerful fluorinating agent than antimony trifluoride, although it has not been used thus far for the conversion of a trichloromethyl to a trifluoromethyl group attached to an aromatic ring. Treatment of **3** with antimony pentafluoride gave **5** in 38% yield.

EXPERIMENTAL

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-7-(trichloromethyl)-1,8-naphthyridine-3-carboxylate (**3**).

To a stirred mixture of 69.6 g (0.3 mole) of nalidixic acid and 300 ml of chloroform was added 150 ml of thionyl chloride during 20 minutes. An exothermic reaction occurred with the evolution of gases. The viscous greenish solution thus obtained was refluxed for 1 hour and then concentrated under reduced pressure to give a black tar which was treated cautiously with 500 ml of absolute ethanol. The resulting dark solution was allowed to stand at room temperature overnight and concentrated to dryness to give a black tar which was extracted with 1 ℓ of refluxing ether.



1 3 4

2 5

This process was repeated until no more material with Rf values corresponding to **3** and **4** was extracted. The combined ethereal extracts were concentrated and the residue was separated into **3** and **4** by chromatography on silica gel, eluting with ether. The less polar component was recrystallized from ether-hexane to give 24.7 g of **3**, mp 150-152°; ms: M^+ at m/e 362 ($C_{14}H_{13}Cl_3N_2O_3$); ^1H nmr (deuteriochloroform): δ 8.92 (1H, d, $J_{5,6}$ = 8 Hz), 8.70 (1H, s, H_2), 8.04 (1H, d, $J_{5,6}$ = 8 Hz), 4.58 (2H, q, $-NCH_2CH_3$), 4.44 (2H, q—OCH_2CH_3), 1.6 (3H, t, $-NCH_2CH_3$) and 1.44 (3H, t, OCH_2CH_3).

Anal. Calcd. for $C_{14}H_{13}Cl_3N_2O_3$: C, 46.24; H, 3.60; N, 7.70. Found: C, 46.13; H, 3.44; N, 7.63.

The second, more polar component was recrystallized from ethanol-ether to afford 8.7 g of **4**, mp 181-183°; ms: M^+ at m/e 318 ($C_{16}H_{18}N_2O_5$); ^1H nmr (deuteriochloroform): δ 8.88 (1H, d, $J_{5,6}$ = 8 Hz), 8.73 (1H, s, H_2), 8.09 (1H, d, $_{5,6}$ = 8 Hz), 4.50 (6H, m, $-N-CH_2CH_3$, 2x—OCH_2CH_3) and 1.50 (9H, m, $-NCH_2CH_3$, 2x—OCH_2CH_3).

Anal. Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.22; H, 5.63; N, 8.78.

1-Ethyl-1,4-dihydro-4-oxo-7-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid (**5**).

To 6 ml of antimony pentafluoride cooled in an ice bath was added 8 g (0.022 mole) of **3**. The resulting dark viscous mixture was heated gently in a water bath to 30-35° when a vigorous exothermic reaction took place. After the reaction was over 300 ml of chloroform was added and the resulting mixture was stirred at room temperature for about 1 hour. The insoluble material was concentrated to give a brown solid which was dissolved in 50 ml of 10% aqueous ammonia and was treated with charcoal. The filtrate was acidified with acetic acid whereupon a cottony, colorless solid precipitated which was filtered, washed with water and dried to yield 2.5 g of **5**, mp 194-196°; ms: M^+ at m/e 286 ($C_{12}H_9F_3N_2O_3$); ^1H nmr (deuteriotrifluoroacetic acid): δ 10.86 (1H, s, —COOH), 9.73 (1H, s, H_2), 9.36 (1H, d, $J_{5,6}$ = 8 Hz), 8.35 (1H, d, $J_{5,6}$ = 8 Hz), 5.22 (2H, q, $-N-CH_2CH_3$) and 1.84 (3H, t, $-N-CH_2CH_3$).

Anal. Calcd. for $C_{12}H_9F_3N_2O_3$: C, 50.36; H, 3.17; N, 9.79. Found: C, 50.17; H, 3.07; N, 9.98.

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