[Chem. Pharm. Bull.
29(3) 739—743 (1981)]

N-Alkylation of Ethyl 1,4-Dihydro-4-oxopyridine-3-carboxylates *via* Their Thallium(I) Salts

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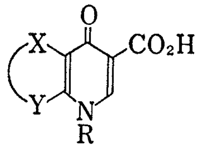
(Received October 2, 1980)

Reaction of the thallium(I) salt of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates with alkyl halides was shown to be a useful method for the regioselective N-alkylation of these compounds.

Keywords——thallium ethoxide; thallium(I) salt of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates; regiospecific-N-alkylation; 1-ethyl-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety; antibacterial drug

Antibacterial drugs such as nalidixic acid (**1a**), oxolinic acid (**1b**), piromidic acid (**1c**), and pipemidic acid (**1d**), whose structures have the common 1-alkyl-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety, are usually prepared by N-alkylation of the corresponding ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates (2) followed by alkaline hydrolysis. Generally, N-alkylation of 2 is carried out with i) NaH/DMF/RX,[1-4] ii) K_2CO_3 or NaOH/DMF or EtOH/RX,[5-7] or iii) $(RO)_3P{=}O/K_2CO_3$,[8,9] but these methods are not always satisfactory in yields or procedures for the isolation of the N-alkylated esters or acids (3) (the reaction mixtures usually contain decomposed materials). For instance, ethyl 2-phenyl-7-oxothiazolo[5,4-*b*]pyridine-6-carboxylate (**2a**) could not be successfully alkylated at the N-position with either methyl or ethyl iodide by utilizing various basic catalysts and solvents,[10] probably because of complication caused by the ambident nature of the starting 4-pyridone-3-carboxylate (**2a**). Taylor and McKillop reported the regiospecific alkylation of thallium(I) salts of enolizable carbonyl compounds such as β-dicarbonyl compounds, α-pyridones, quinolones, and phenanthridones.[11,12] A search of the literature, however, failed to reveal any reports concerning the application of the procedure to the alkylation of 4-pyridone-3-carboxylates. We have now found that the alkylation of **2a** utilizing its thallium(I) salt is quite useful for selective N-alkylation, and we applied this reaction to the regiospecific alkylation of various types of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylates (**2b**—**f**), obtaining essentially quantitative yields of the desired N-alkylated esters or acids (3) without formation of any decomposed materials.



1a—d

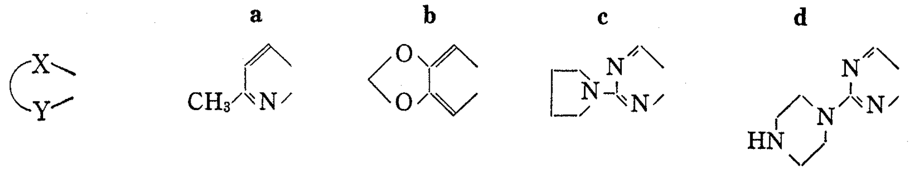


Fig. 1

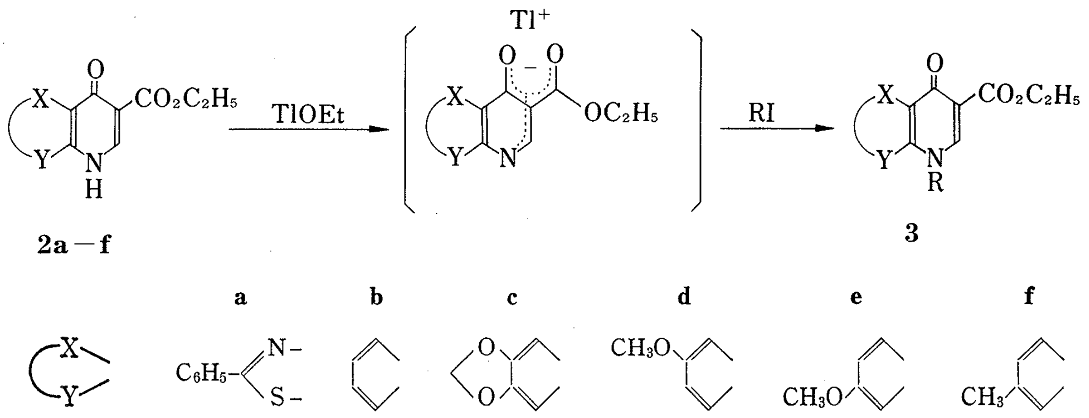
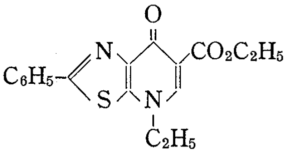
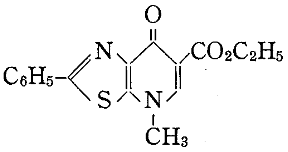
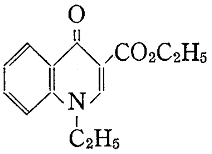
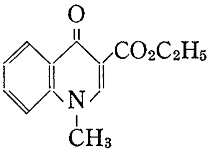
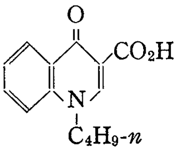
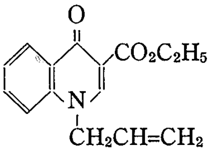
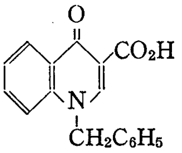
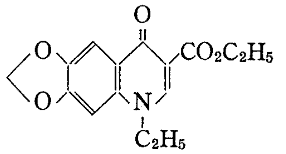
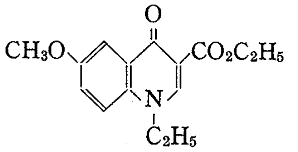
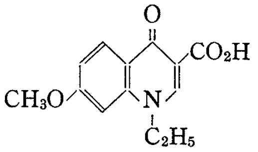
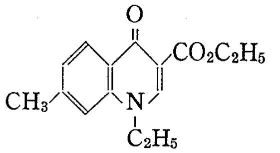


Chart 1

TABLE I. N-Alkylation of Ethyl 1,4-Dihydro-4-oxopyridine-3-carboxylates (**2a**—**e**)

Entry	Substrate (**2**)	Product (**3**)	Yield (%) of **3**[a]		mp (from)	Lit. mp
			TlOEt/ RX	Reported method		
1	**2a**		80	4[b]	237—238° (ethanol)	237—238°[10]
2	**2a**		66	12[b]	247—249° (ethanol)	248—249°[10]
3	**2b**		92	—[c]	108—109° (ethyl acetate–pet-ether)	110—111°[14]
4	**2b**		84	—[c]	125—126° (ethyl acetate)	117—118°[15]
5	**2b**		80[d]	12[b,d]	168—169° (isopropanol–water)	164—166°[4]
6	**2b**		99	—	98—100° (ethyl acetate–*n*-hexane)	
7	**2b**		62[d]	27[b,d]	228—229° (chloroform–ethanol)	232—234°[4]

Entry	Substrate (2)	Product (3)	Yield (%) of **3**[a] TlOEt/ RX	Yield (%) of **3**[a] Reported method	mp (from)	Lit. mp
8	**2c**		95	78[b]	177—178° (chloroform–*n*-hexane)	177—178°[1]
9	**2d**		92	—[c]	152—153° (benzene)	146—148°[14]
10	**2e**		84[d]	—	265—267° (chloroform)	
11	**2f**		96	84[e]	153—154° (ethyl acetate–*n*-hexane)	—[6]

a) Yield of isolated product.
b) Yield by method i) using NaH/DMF/RX.
c) The yield was not given since the compound was prepared by a different route.
d) Overall yield of the hydrolyzed acid from **2**.
e) Yield by method ii) using KOH or K_2CO_3/DMF or EtOH/RX.

The requisite thallium(I) salts are readily obtained by adding a slight excess of thallium(I) ethoxide[13] to an ethanolic solution of **2** at room temperature. These salts can be reacted with electrophilic reagents under neutral and mild conditions. Thus, heating of a mixture of the thallium(I) salt and a large excess of alkyl iodide at 70—80° for several hours followed by removal of the precipitated thallium(I) iodide gave quantitative yields of the desired N-alkylated pyridones (**3**). The structural assignments of **3** are based on microanalyses, and mass, infrared (IR) and nuclear magnetic resonance (NMR) spectral data. Representative examples are given in the table, in which the yields are compared with the reported values.

Exclusive N-alkylation of the thalliun(I) salt of ethyl 1,4-dihydro-4-oxopyridine-3-carboxylate itself did not occur, and the reaction gave a mixture of N- and O-alkylated products.[16] The reactivity of the bicyclic ethyl 1,4-dihydro-4-oxopyridine-3-carboxylate system, though formally analogous to that of a monocyclic system, is significantly different, probably due to the effects, both steric and electronic, of the fused benzene or thiazole ring.[17]

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a Hitachi-G2 spectrometer, and NMR spectra on a Hitachi R-20A spectrometer (with tetramethylsilane as an internal standard). Mass spectra were obtained with a Hitachi RMU-6M instrument with a direct inlet system operating at 70 eV. Column chromatography was carried out on Merck Silica-gel 60.

N-Alkylation of Ethyl 1,4-Dihydro-4-oxopyridine-3-carboxylates (2)——General Procedure: Ethyl 1,4-dihydro-4-oxopyridine-3-carboxylate (**2**) (1.0 mmol) was added to a solution of thallium(I) ethoxide (1.2 mmol) in ethanol (5 ml). The thallium(I) salt precipitated immediately, and stirring was continued for 2 hr at room temperature. The solid was collected and dried under reduced pressure. A stirred suspension of alkyl iodide (*ca.* 40 mmol) and the salt was heated at 70—80° for 3—4 hr. The precipitated thallium(I) iodide was filtered off and washed well with chloroform, and the combined filtrates were evaporated to dryness under reduced pressure to yield crude 3 as crystals. Pure samples were obtained by recrystallization from the solvents listed in the table.

Ethyl 4-Ethyl-2-phenyl-7-oxothiazolo[5,4-*b*]pyridine-6-carboxylate (3a)——This was prepared from **2a** (100 mg, 0.33 mmol), TlOEt (102 mg, 0.40 mmol) and C_2H_5I (4 ml, 50 mmol). *Anal.* Calcd for C, 62.19; H, 4.91; N, 8.83. Found: C, 62.34; H, 4.82; N, 8.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680 and 1610; NMR ($CDCl_3$) δ: 8.28 (1H, s, NCH=), 8.2—7.3 (5H, m, ArH), 4.41 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.16 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 1.64 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$) and 1.41 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Ethyl 4-Methyl-2-phenyl-7-oxothiazolo[5,4-*b*]pyridine-6-carboxylate (3b)——This was prepared from **2a** (300 mg, 1.00 mmol), TlOEt (350 mg, 1.40 mmol) and CH_3I (5 ml, 80 mmol). *Anal.* Calcd for C, 61.14; H, 4.49; N, 8.91. Found: C, 61.14; H, 4.44; N, 8.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680 and 1615; NMR ($CDCl_3$) δ: 8.10 (1H, s, NCH=), 8.05—7.30 (5H, m, ArH), 4.31 (2H, d, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.88 (3H, s, NCH_3) and 1.35 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Ethyl 1-Ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (3c)——This was prepared from **2b** (103 mg, 0.47 mmol), TlOEt (137 mg, 0.55 mmol) and C_2H_5I (4 ml, 50 mmol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1630 and 1610; NMR ($CDCl_3$) δ: 8.53 (1H, s, NCH=), 8.50 (1H, d, $J=9$ Hz, 5-H), 7.65—7.30 (3H, m, 6-, 7- and 8-H), 4.44 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.28 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$). 1.57 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$) and 1.43 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Ethyl 1-Methyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (3d)——This was prepared from **2b** (217 mg, 1.00 mmol), TlOEt (350 mg, 1.40 mmol) and CH_3I (4 ml, 64.2 mmol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1630 and 1610; NMR ($CDCl_3$) δ: 8.40 (1H, s, NCH=), 8.50 (1H, dd, $J=9$ and 2 Hz, 5-H), 7.77—7.20 (3H, m, ArH), 4.36 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.86 (3H, s, NCH_3) and 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

1-*n*-Butyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3e)——Ethyl 1-*n*-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate was prepared from **2b** (217 mg, 1.00 mmol), TlOEt (350 mg, 1.40 mmol) and *n*-C_4H_9I (4 ml, 35.1 mmol). The crude oily ester was hydrolyzed with 10% aqueous NaOH at 90° for 2 hr. The reaction mixture was acidified with 10% aqueous HCl, and the resulting crystals were collected, washed with water and dried. Recrystallization from the solvent given in the table gave **3e**. IR ν_{max}^{tablet} cm^{-1}: 1710, 1615 and 1475; NMR (DMSO-d_6) δ: 12.80 (1H, s, CO_2H), 9.04 (1H, s, NCH=), 8.40 (1H, d, $J=9$ Hz, 5-H), 8.05—7.45 (3H, m, 6-, 7- and 8-H), 4.57 (2H, t, NCH_2) and 2.18—0.54 (7H, m, $CH_2\times 2$ and CH_3).

Ethyl 1-Allyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (3f)——This was prepared from **2b** (217 mg, 1.00 mmol), TlOEt (350 mg, 1.40 mmol) and CH_2=$CHCH_2Br$ (4 ml, 46.2 mmol). *Anal.* Calcd for C, 70.01; H, 5.89; N, 5.44. Found: C, 70.03; H, 5.85; N, 5.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680, 1630, 1610 and 1490; NMR ($CDCl_3$) δ: 8.53 (1H, dd, $J=9$ and 2 Hz, 5-H), 8.47 (1H, s, NCH=), 7.85—6.75 (3H, m, 6-, 7- and 8-H), 6.45—4.60 (5H, m, NCH_2CH=CH_2), 4.38 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$) and 1.41 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

1-Benzyl-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3g)——This was directly prepared by treatment of the thallium(I) salt obtained from **2b** (217 mg, 1.00 mmol) and TlOEt (300 mg, 1.20 mmol) with $C_6H_5CH_2Br$ (4 ml, 33.6 mmol) at 140—150° for 4 hr. The precipitated TlBr was removed by filtration, and the filtrate was concentrated *in vacuo* to give a solid, which was recrystallized from the solvent given in the table to give **3g**. IR ν_{max}^{tablet} cm^{-1}: 1725, 1615 and 1480; NMR (DMSO-d_6) δ: 9.26 (1H, s, NCH=), 8.40 (1H, d, $J=9$ Hz, 5-H), 8.02—7.02 (8H, m, $NCH_2C_6\underline{H}_5$ and 6-, 7- and 8-H) and 5.84 (2H, s, NCH_2).

Ethyl 5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylate (3h)——This was prepared from **2c** (130 mg, 0.50 mmol), TlOEt (140 mg, 0.56 mmol) and C_2H_5I (4 ml, 50 mmol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1675, 1620 and 1590; NMR ($CDCl_3$) δ: 8.37 (1H, s, NCH=), 7.80 (1H, s, 5-H), 6.88 (1H, s, 8-H), 6.13 (2H, s, OCH_2), 4.37 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.31 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 1.52 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$) and 1.41 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Ethyl 1-Ethyl-6-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate (3i)——This was prepared from **2d** (247 mg, 1.00 mmol), TlOEt (300 mg, 1.20 mmol) and C_2H_5I (5 ml, 62.5 mmol). *Anal.* Calcd for C, 65.43; H, 6.24; N, 5.08. Found: C, 65.60; H, 6.23; N, 5.04. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1675 and 1610; NMR ($CDCl_3$) δ: 8.44 (1H, s, NCH=), 7.96 (1H, d, $J=2$ Hz, 5-H), 7.55—7.23 (2H, m, 7- and 8-H), 4.40 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.27 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.94 (3H, s, OCH_3), 1.56 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$) and 1.44 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

1-Ethyl-7-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (3j)——Ethyl 1-ethyl-7-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was prepared from **2e** (247 mg, 1.00 mmol), TlOEt (350 mg, 1.40 mmol) and C_2H_5I (4 ml, 50 mmol). The crude ester was hydrolyzed with 10% aqueous NaOH at 90° for 2 hr. The reaction mixture was acidified with 10% aqueous HCl, and the resulting crystals were extracted with $CHCl_3$ (10 ml × 2). The combined extract was washed with sat. aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to give **3j**, which was recrystallized from the solvent given in the table. *Anal.* Calcd for C, 63.09; H, 5.31; N, 5.66. Found: C, 62.97; H, 5.19; N, 5.55. IR ν_{max}^{tablet} cm^{-1}: 1705, 1615, 1520, 1460 and 1440; NMR (DMSO-d_6) δ: 13.00 (1H, s, CO_2H), 8.96 (1H, s, NCH=), 8.27 (1H, d, $J=9$ Hz, 5-H), 7.39—6.94 (2H, m, 6- and 8-H), 4.55 (2H, q, $J=7$ Hz, NCH_2), 3.97 (3H, s, OCH_3) and 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Ethyl 1-Ethyl-7-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylate (3k)——This was prepared from **2f** (231 mg, 1.00 mmol), TlOEt (300 mg, 1.20 mmol) and C_2H_5I (5 ml, 62.5 mmol). *Anal.* Calcd for C, 69.48; H, 6.61; N, 5.40. Found: C, 69.23; H, 6.53; N, 5.38. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1680, 1615 and 1470; NMR ($CDCl_3$) δ: 8.60 (1H, s, NCH=), 8.44 (1H, d, $J=9$ Hz, 5-H), 7.47—7.22 (2H, m, 6- and 8-H), 4.44 (2H, q, $J=$

7 Hz, $C\underline{H}_2CH_3$), 4.32 (2H, q, $J=7$ Hz, CH_2CH_3), 2.58 (3H, s, $ArCH_3$), 1.59 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$) and 1.47 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$).

Acknowledgement The authors acknowledge financial assistance of this work in the form of a Grant-in-Aid for Special Project Research (Grant No. 311704), "Chemical Research in Development and Utilization of Nitrogen-Organic Resources," from the Ministry of Education, Science and Culture, Japan. The authors thank Miss Minako Inoue and Miss Yuko Ueda for technical assistance.

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