Synthetic Studies on Chemotherapeutics. II. (1) Synthesis of Phenyl-substituted 1,4-Dihydro-4-oxonicotinic Acid Derivatives. [Studies on the Syntheses of Heterocyclic Compounds. Part 704 (2)]

Tetsuji Kametani (3), Kazuo Kigasawa, Mineharu Hiiragi, Kikuo Wakisaka, Osamu Kusama, Hideo Sugi, and Kumeo Kawasaki

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan and
Research Laboratories, Grelan Pharmaceutical Co. Ltd., Sakurashinmachi, Setagayaku, Tokyo, Japan

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The thermal cyclization of the aminomethylenemalonates (**8**) gave the 4-hydroxynicotinates (**9**), ethylation of which yielded *N*-ethylated (**11**) and *O*-ethylated products (**12**). Hydrolysis of **9**, **11**, and **12** led to the desired nicotinic acids (**10**, **4**, and **13**), respectively.

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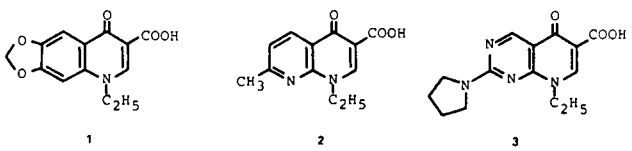
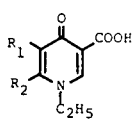
It is well known that oxolinic acid (**1**) (4), nalidixic acid (**2**) (5) and pyromidic acid (**3**) (6) have an antibacterial activity for Gram negative bacteria. In order to get effective antibacterially active compounds which have the similar structure with **1-3**, we investigated a synthesis of the phenyl-substituted nicotinic acid derivatives and here we wish to report the synthesis of phenyl-substituted 1-ethyl-1,4-dihydro-4-oxonicotinic acids (**4**) which have the common partial structure of the above three compounds.

Recently the synthesis of alkylated 1,4-dihydro-4-oxonicotinic acid (**5**) was reported (7), but we expected the nicotinic acid substituted by phenyl function at 5 and/or 6 position to be effective as an antibacterial substance because the active compounds (**1-3**) have the structure of nicotinic acid fused with aromatic ring at 5 and 6 positions.

Chart 1

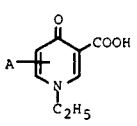


1 **2** **3**



4

R_1, R_2 = phenyl or methyl

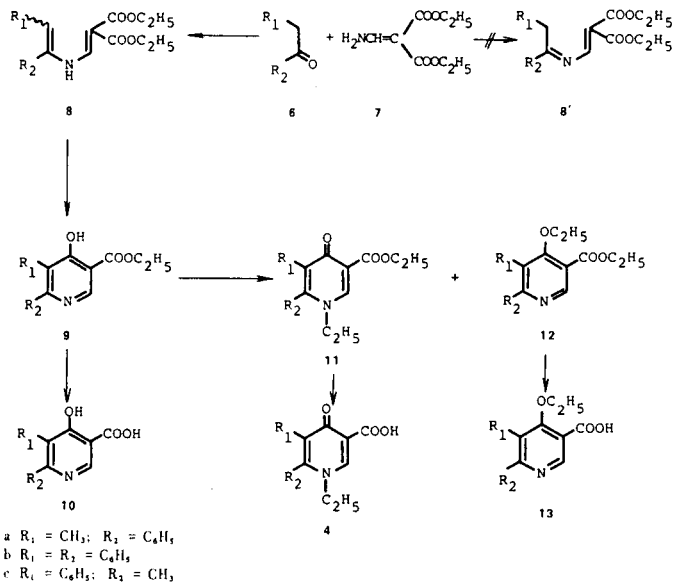


5

A = aliphatic or alicyclic group

Condensation of the phenyl ketone derivatives (**6**) and diethyl aminomethylenemalonate (**7**) (8) in the presence of *p*-toluenesulfonic acid afforded the enaminomalonates (**8**) as a mixture of two geometrical isomers, determined by their nmr spectra (9), whose data also ruled out the imine structures (**8'**) as a possible one.

Chart 2



8 **6** **7** **8'**

9 **11** **12**

10 **4** **13**

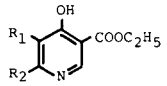
a $R_1 = CH_3$; $R_2 = C_6H_5$
b $R_1 = R_2 = C_6H_5$
c $R_1 = C_6H_5$; $R_2 = CH_3$

Gould-Jacobs reaction of these isomers at 250-280° in diphenyl ether gave 4-hydroxynicotinates (**9**) (10), which were converted into nicotinic acids (**10**) by hydrolysis.

Alkylation of 4-hydroxynicotinates (**9**) with ethyl iodide in the presence of potassium carbonate in dimethylformamide and water gave the expected *N*-ethylated

Table I

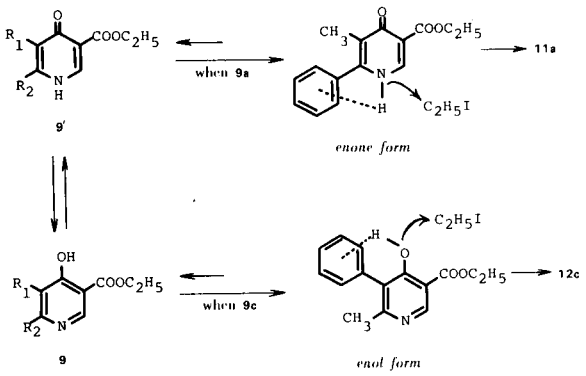
Ethyl 4-Hydroxynicotinates (**9**)



Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield (%)	Formula	Analysis Calcd. (Found)	Ir (Potassium bromide) ν max cm^{-1}	Nmr (δ in deuteriochloroform)
9a	176-177	colorless crystals (ethanol)	58	$C_{15}H_{15}NO_3$	C; 70.02 (69.75) H; 5.88 (6.27) N; 5.44 (5.47)	1700 1620	1.34 (3H, t, J = 7 Hz, -CH_2CH_3) 2.24 (3H, s, C_5-CH_3), 4.30 (2H, q, J = 7 Hz, -CH_2CH_3) 7.45 (5H, s, -C_6H_5) 8.84 (1H, s, C_2-H)
9b	224-225	colorless crystals (ethanol)	64	$C_{20}H_{17}NO_3$	C; 75.22 (75.12) H; 5.37 (5.33) N; 4.39 (4.40)	1700 1615	1.43 (3H, t, J = 7 Hz, -CH_2CH_3) 4.45 (2H, q, J = 7 Hz, -CH_2CH_3) 7.20 (10H, s, -C_6H_5 x 2) 8.97 (1H, s, C_2-H)
9c	178-180	colorless crystals (ethanol)	59	$C_{15}H_{15}NO_3$	C; 70.02 (69.86) H; 5.88 (5.49) N; 5.44 (5.43)	1700 1625	1.38 (3H, t, J = 7 Hz, -CH_2CH_3) 2.12 (3H, s, C_6-CH_3) 4.39 (2H, q, J = 7 Hz, -CH_2CH_3) 7.1-7.6 (5H, m, -C_6H_5) 8.46 (1H, s, C_2-H)

products (**11**) together with the undesired *O*-ethylated compounds (**12**). The formation ratio of **11** and **12** depended upon the structure of the starting materials (**9**). These results were shown in Table IV.

Chart 3

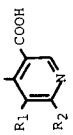


If a 4-hydroxynicotinate (**9**) exists as tautomeric isomers of enol form (**9**) and enone form (**9'**), an electronic interaction would occur between π-electron on phenyl group and hydrogen of amino or hydroxyl group on ethylation of **9a** and **9c** which is shown in Chart 3. Therefore ethylation of **9a** gave mainly the *N*-ethylated product (**11a**) *via* the enone type intermediate and, in case of the reaction of **9c**, the yield of the *O*-ethylated product (**12c**) would increase *via* an enol intermediate. The objective 1-ethyl-1,4-dihydro-4-oxonicotinic acids (**4**) and 4-ethoxynicotinic acid (**13**) were obtained from **11** and **12** by hydrolysis.

The test of antibacterial activity of these nicotinic acid (**4**; **9**, **10**, **11**, **12**, and **13**) by Agar dilution method is under investigation.

Table II

4-Hydroxynicotinic Acids (**10**)



Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield (%)	Formula	Analysis Calcd. (Found)			Ir (Potassium bromide) ν max cm^{-1}	Nmr (δ in d_6-DMSO)
10a	274-276 dec.	colorless prisms (ethanol)	79	$C_{13}H_{11}NO_3$	C; 68.11 (67.59)	H; 4.84 (5.06)	N; 6.11 (5.84)	3100, 3000-2400, 1635	1.98 (3H, s, C_5-CH_3) 7.52 (5H, s, -C_6H_5) 8.40 (1H, s, C_2-*H*)
10b	292-292.5 dec.	colorless prisms (ethanol)	84	$C_{18}H_{13}NO_3$	C; 74.21 (74.04)	H; 4.50 (4.61)	N; 4.81 (4.55)	3180, 3050-2800, 1620	7.13 and 7.25 (each 5H, s, C_6H_5 x 2) 8.45 (1H, s, C_2-*H*)
10c	265-267 dec.	colorless prisms (ethanol)	76	$C_{13}H_{11}NO_3$	C; 68.11 (68.01)	H; 4.84 (4.72)	N; 6.11 (6.05)	3600-2500 1630	2.20 (3H, s, C_6-CH_3) 7.0-7.5 (5H, m, -C_6H_5) 8.47 (1H, s, C_2-*H*)

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were measured with a Hitachi-215 recording spectrophotometer, nmr spectra with a JNM-MH-60 spectrometer using tetramethylsilane as an internal standard.

General Procedure for Condensation of Phenyl Ketones (**6**) with Diethyl Aminomethylenemalonate (**7**).

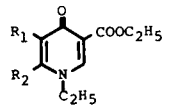
A solution of 1 mole of phenyl ketone (**6**) and 1.2-1.5 moles of diethyl aminomethylenemalonate (**7**) in xylene or decalin was heated under stirring in the presence of a catalytic amount of *p*-toluenesulfonic acid at 180±5° for 24 hours, during which genarated water was removed. The reaction mixture was extracted with benzene. The extract was washed with water, dried over sodium sulfate and evaporated to give an oil. This was chromatographed on silica gel using benzene as eluent to afford **8** as a pale yellow oil, whose yields and physical data are shown as follows.

Compound **8a**.

This compound was obtained in 14% yield; ir ν max (neat): 1720, 1700, 1655 and 1595 cm^{-1}; nmr δ (deuteriochloroform)

Table III

Ethyl 1-Ethyl-1,4-dihydro-4-oxonicotinates (**11**)



Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Formula	Analysis Calcd. (Found)	Ir (Potassium bromide) ν max cm^{-1}	Nmr (δ in deuteriochloroform)
11a		pale yellow oil	$C_{17}H_{19}NO_3$ (a)		1720 (b)	1.20 (3H, t, J = 7 Hz, N-CH_2CH_3), 1.41 (3H, t, J = 7 Hz, O-CH_2CH_3), 1.75 (3H, s, C_5-CH_3), 3.67 (2H, q, J = 7 Hz, N-CH_2CH_3), 4.39 (2H, q, J = 7 Hz, O-CH_2CH_3), 7.1-7.7 (5H, m, C_6H_5), 8.23 (1H, s, (C_2-H)
11b	190-191	colorless crystals (C_6H_6-*n*-hexane)	$C_{22}H_{21}NO_3$	C; 76.07 (76.42) H; 6.09 (5.97) N; 4.03 (4.32)	1675 1615	1.07 (3H, t, J = 7 Hz, N-CH_2CH_3), 1.21 (3H, t, J = 7 Hz. O-CH_2CH_3), 3.73 (2H, q, J = 7 Hz, N-CH_2CH_3), 4.37 (2H, q, J = 7 Hz, O-CH_2CH_3), 7.00 (5H, s, -C_6H_5), 7.00-7.30 (5H, m, C_6H_5), 8.28 (1H, s, C_2-H)
11c	120-122	colorless crystals (C_6H_6-*n*-hexane)	$C_{17}H_{19}NO_3$	C; 71.56 (71.72) H; 6.71 (6.58) N; 4.91 (4.68)	1700 1620	1.35 (3H, t, J = 7 Hz, N-CH_2CH_3) 1.47 (3H, t, J = 7 Hz, O-CH_2CH_3) 2.15 (3H, s, C_6-CH_3), 3.97 (2H, q, J = 7 Hz, N-CH_2CH_3), 4.33 (2H, q, J = 7 Hz, O-CH_2CH_3) 7.0-7.5 (5H, m, C_6H_5), 8.18 (1H, s, C_2-H)

(a) The mass spectrum showed a molecular ion peak (M^+) at m/e 285 with other major peaks at m/e 284, 256, 238, 214, 213 (base peak, M^+-CO_2-CH_2=CH_2) and 212. (b) The ir spectrum was taken on a liquid film.

Table IV

The Yield of Ethylation of **9**

Starting material	*N*-Ethylated product (%)	*O*-Ethylated product (%)
9a	**11a** (85)	**12a** (not isolated)
9b	**11b** (69)	**12b** (16)
9c	**11c** (56)	**12c** (25)

(11): 1.33 and 1.25 (6H, t, J = 7 Hz, 2 x CH_2CH_3), 1.90 and 1.70 (3H, d, J = 7 Hz, =CH-CH_3), 4.32 and 4.13 (4H, q, J = 7 Hz, 2 x CH_2CH_3), 5.28 and 5.42 (1H, q, J = 7 Hz, =CH-CH_3), 7.33 (5H, s, -C_6H_5), 8.0 (1H, d, J = 13 Hz, > N-CH=), and 10.8 (1H, br d, J = 13 Hz, >NH). A ratio of two geometrical isomers was 1 to 4.4 (12).

Compound **8b**.

This compound was obtained in 32% yield; ir ν max (neat): 1710, 1680, 1650, 1635 and 1595 cm^{-1}; nmr δ (deuteriochloroform) (11): 1.29 and 1.12 (6H, t, J = 7 Hz, 2 x CH_2CH_3), 4.18 and 3.99 (4H, q, J = 7 Hz, 2 x CH_2CH_3), 6.32 and 5.39 (1H, s, =CH-C_6H_5), 7.2-7.5 (10H, m, 2 x C_6H_5), 7.86 and 7.95 (1H, d, J = 13.5 Hz, >N-CH=), and 11.25 and 10.95 (1H, d, J = 13.5 Hz, >NH). A ratio of two geometrical isomers was 1:2.3 (12).

Compound **8c**.

This compound was obtained in 52% yield; ir ν max (neat): 1720, 1690, 1650 and 1600 cm^{-1}; nmr δ (deuteriochloroform) (11): 1.26 and 1.35 (6H, t, J = 7 Hz, 2 x CH_2CH_3), 2.25 and 2.15 (3H, s, >C-CH_3), 5.65 and 6.18 (1H, s, =CH-C_6H_5), 7.27 (5H, s, -C_6H_5), 7.86 and 7.95 (1H, d, J = 13 Hz, > N-CH=) and 11.25 and 10.95 (1H, d, J = 13 Hz, >NH). A ratio of two geometrical isomers was 1 to 1.3 (12).

General Procedure for Thermal Cyclization of Aminomethylenemalonates (**8**).

A stirred solution of diethyl aminomethylenemalonates (**8**) in 5-20 fold weight of diphenyl ether was heated at 250-280° for 0.5-1.5 hours checking by thin layer chromatography. The reaction mixture was chromatographed on silica gel. After the elution with a mixture of *n*-hexane-benzene (1:1) to remove diphenyl ether, the elution with benzene and/or chloroform gave **9** as a solid, whose physical data were shown in Table I.

General Procedure for Ethylation of Ethyl 4-Hydroxynicotinates (**9**).

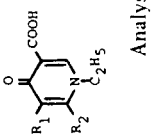
A stirred mixture of 1 g. of ethyl 4-hydroxynicotinate (**9**), 1.5 ml. of ethyl iodide, 6 ml. of dimethylformamide, 3 ml. of water and 1.5 g. of potassium carbonate was heated at 70-75° for 3 hours. The solvent was evaporated off to leave an oil, which was extracted with benzene. The extract was washed with water, dried over sodium sulfate and evaporated to give a reddish brown oil, which was chromatographed on 50 g. of silica gel. The elution with benzene and/or benzene-chloroform (2:1) mixture gave *O*-ethylated compounds (**12**) and the elution with chloroform and/or chloroform-methanol (100:1-2) mixture afforded *N*-ethylated products (**11**), whose physical data were shown in Table III and IV.

Compound **12b**.

This compound was a pale yellow oil; ir ν max (neat): 1710 and 1570 cm^{-1}; nmr δ(deuteriochloroform): 1.00 (3H, t, J = 7 Hz, C_4-OCH_2CH_3), 1.43 (3H, t, J = 7 Hz, -$COOCH_2CH_3$), 3.72

Table V

1-Ethyl-1,4-dihydro-4-oxonicotinic Acids (**4**)



Compound No.	M.p. (°C)	Appearance (Solvent of recrystallization)	Yield (%)	Formula	Analysis Calcd. (Found)	Ir (Potassium bromide) ν max cm^{-1}	Nmr (δ in d_6-DMSO)
4a	207.5-209	colorless prisms (ethanol)	81	$C_{15}H_{15}NO_3$	C; 70.02 (69.60) H; 5.88 (6.00) N; 5.44 (5.33)	1700-1625	1.33 (3H, t, J = 7 Hz, N-CH_2CH_3) 1.72 (3H, s, C_5-CH_3) 3.90 (2H, q, J = 7 Hz, N-CH_2CH_3) 8.77 (1H, s, C_2-H)
4b	281-282	colorless prisms (ethanol)	91	$C_{20}H_{17}NO_3$	C; 75.22 (74.68) H; 5.37 (5.43) N; 4.39 (4.46)	1710-1625	1.22 (3H, t, J = 7 Hz, N-CH_2CH_3) 7.07 and 7.28 (each 5H, s, -C_6H_5 x 2) 8.88 (1H, s, C_2-H)
4c	177-178	colorless prisms (ethanol)	65	$C_{15}H_{15}NO_3$	C; 70.02 (69.83) H; 5.88 (5.76) N; 5.44 (5.32)	1705 1625	1.40 (3H, t, J = 7 Hz, N-CH_2CH_3) 2.28 (3H, s, C_6-CH_3) 4.30 (2H, q, J = 7 Hz, N-CH_2CH_3) 7.15-7.55 (5H, m, -C_6H_5) 8.81 (1H, s, C_2-H)

(2H, q, J = 7 Hz, C_4-OC*H*$_2$CH$_3$), 4.42 (2H, q, J = 7 Hz, -COOC*H*$_2$CH$_3$), 7.22 (10H, s, 2 x C_6H_5), and 9.00 (1H, s, C_2-H).

Compound **12c**.

This compound was a pale yellow oil; ir ν max (neat): 1715 and 1590: nmr δ (deuteriochloroform): 1.00 (3H, t, J = 7 Hz, C_4-OCH$_2$C*H*$_3$), 1.43 (3H, t, J = 7 Hz, COOCH$_2$C*H*$_3$), 2.38 (3H, s, C_6-CH$_3$), 3.72 (2H, q, J = 7 Hz, C_4-OC*H*$_2$CH$_3$), 4.46 (2H, q, J = 7 Hz, COOC*H*$_2$CH$_3$), 7.2-7.6 (5H, m, C_6H_5) and 8.90 (1H, s, C_2-H).

General Procedure for Hydrolysis of Ethyl Nicotinates (**9**, **11**, and **12**).

A solution of 0.5 g. of ethyl nicotinates (**9**, **11** or **12**), 0.5 g. of sodium hydroxide, 5 ml. of ethanol and 5 ml. of water was heated under reflux for 1.5-2 hours. Evaporation of the solvent gave an oil, which was dissolved in a small amount of water. The aqueous layer was filtered to remove undissolved substance and adjusted at *p*H 5-6 using hydrochloric acid to afford a precipitate, which was purified by recrystallization. The physical data are Table II and V.

Compound **13b**.

This compound was obtained as colorless crystals, m.p. 176-178° (from ether-*n*-hexane), 87% yield; ir ν max (potassium bromide): 3600-3300 and 1700 cm^{-1}; nmr δ (deuteriochloroform): 1.00 (3H, t, J = 7 Hz, OCH$_2$C*H*$_3$), 3.73 (2H, q, J = 7 Hz, OC*H*$_2$CH$_3$), 7.21 (10H, s, 2 x C_6H_5), and 9.08 (1H, s, C_2-H).

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.02; H, 5.51; N, 4.25.

Compound **13c**.

This compound was obtained as colorless crystals, m.p. 274-276° dec. (from benzene), 74% yield; ir ν max (potassium bromide): 3600-3300 and 1695 cm^{-1}; nmr δ (deuteriochloroform): 1.02 (3H, t, J = 7 Hz, OCH$_2$C*H*$_3$), 2.47 (3H, s, C_6-CH$_3$), 4.07 (2H, q, J = 7 Hz, OC*H*$_2$CH$_3$), 7.1-7.5 (5H, m, C_6H_5), and 8.95 (1H, s, C_2-H).

Acknowledgement.

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(3) To whom correspondence should be addressed.

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(9) The nmr spectra showed two doublets with the same J-value due to NH and olefinic proton of **8** and no peaks due to **8'**.

(10) The thin layer chromatography of this reaction mixture showed no spot of the starting material (**8**) on the final stage. Presumably, the Z-form of **8** would be converted into the E-form *via* an imino form (**8'**) during thermal cyclization, and then be cyclized to **9**.

(11) Since this compound is a mixture of Z- and E-form, the chemical shifts are described firstly regarding major signal and then minor signal.

(12) This ratio was calculated by its nmr integration.