Studies on Quinoline Derivatives and Related Compounds. III. A Novel Pyridine Synthesis to give Substituted 1,4-Dihydro-4-oxonicotinic Acids (1).

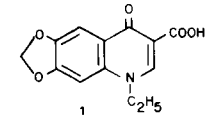
Hideo Agui, Hisao Tobiki and Takenari Nakagome (2)

Research Department, Pharmaceuticals Division, Sumitomo Chemical Co.,
2-1, 4-Chome, Takatsukasa, Takarazuka-shi, Hyogo-ken, 665 Japan

Received June 16, 1975

A variety of 5-mono- and 5,6-disubstituted 1,4-dihydro-4-oxonicotinates were prepared by a novel pyridine synthesis which involves thermal cyclisation of enaminomethylenemalonates **9**. The intermediates **9** were readily prepared through a few steps from commercially available starting materials.

The three urinary tract antiseptics (**1-3**) (3-5), which have been marketed, contain a common 1-ethyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety in their structures. In connection with our previous studies (1,6) on 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids, it seemed to be of interest to prepare the compounds of type **4** and examine their antibacterial activities.



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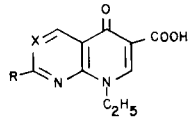
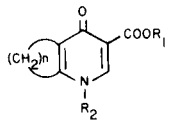


2 (X = CH, R = CH_3)
3 (X = N, R = -N⟨ ⟩)



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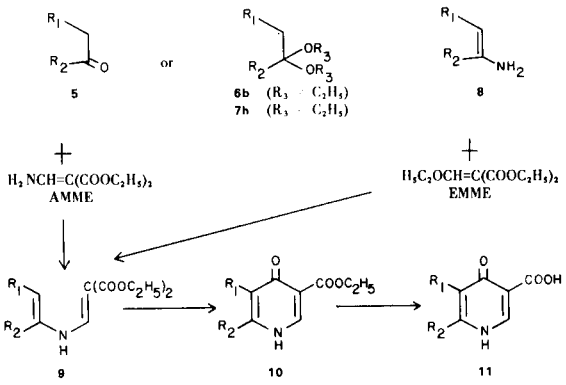
a	R_1 = C_2H_5	R_2 = C_2H_5	n =	3
b	R_1 = CH_3	R_2 = CH_3	n =	4
c	R_1 = C_2H_5	R_2 = CH_3	n =	4
d	R_1 = C_2H_5	R_2 = C_2H_5	n =	4
e	R_1 = C_2H_5	R_2 = C_2H_5	n =	5
f	R_1 = CH_3	R_2 = CH_3	n =	5
g	R_1 = C_2H_5	R_2 = CH_3	n =	5
h	R_1 = H	R_2 = C_2H_5	n =	3
i	R_1 = H	R_2 = CH_3	n =	4
j	R_1 = H	R_2 = C_2H_5	n =	4
k	R_1 = H	R_2 = C_2H_5	n =	5
l	R_1 = H	R_2 = CH_3	n =	5

The Gould-Jacobs reaction (7) is well known as the most useful method for the preparation of 4-hydroxy-3-quinolinecarboxylic acid derivatives. It involves condensation of aromatic amines with ethoxymethylenemalonate (EMME) and thermal cyclization of the resulting anilinomethylenemalonates. So far as we know no attempt to apply the reaction to aliphatic amines has been accomplished. The present authors planned to synthesize the novel cycloalkano-1,4-dihydro-4-oxonicotinates **10a-c**, the intermediates for the objective *N*-alkylated carboxylic acids **4h-l**, by a novel synthesis based on the Gould-Jacobs reaction.

Cyclopenta-, cyclohexa- and cycloheptanones (**5a-c**) condensed successfully with diethyl aminomethylenemalonate (AMME) (8) in refluxing xylene in the presence of a catalytic amount of *p*-toluenesulfonic acid, yielding the desired enaminomethylenemalonates **9a-c** (Table I). The enamine structure represented in the formula **9** was adopted rather than the imine structure for the products in view of their nmr spectra which show a NH signal as a doublet, coupled with an adjacent olefinic proton.

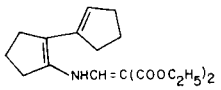
When cyclohexanone diethylketal (**6b**) (9) derived from cyclohexanone (**5b**) was heated with AMME, the same enaminomethylenemalonate, *i.d.* diethyl *N*-(1-cyclohexen-1-yl)aminomethylenemalonate (**9b**) was obtained. The yield, however, was not improved.

Scheme I



a	R_1 = $-(CH_2)_3-$ = R_2		
b	R_1 = $-(CH_2)_4-$ = R_2		
c	R_1 = $-(CH_2)_5-$ = R_2		
d	R_1 = $COCH_3$	R_2 = CH_3	
e	R_1 = $COOC_2H_5$	R_2 = CH_3	
	(11e R_1 = COOH	R_2 = CH_3)	
f	R_1 = SO_2CH_3	R_2 = CH_3	
g	R_1 = $SO_2C_6H_4CH_3$ (*p*)	R_2 = CH_3	
h	R_1 = $COCH_3$	R_2 = H	
i	R_1 = $-COCH_2CH_2-$ = R_2		
j	R_1 = $-COCH_2C(CH_3)_2CH_2-$ = R_2		

In the reaction of cyclopentanone (**5a**), AMME and phosphorus pentoxide in tetrahydrofuran, on the other hand, the compound isolated was not identical with **9a** described above. This was assumed to be diethy *N*-[2-(1-cyclopenten-1-yl)-1-cyclopenten-1-yl]aminomethylenemalonate (**12**). The assignment was based on the elemental analysis, the nmr, uv and mass spectra. Two olefinic protons appeared at 5.53 δ and 7.95 δ, as a multiplet and a doublet, respectively, in addition to signals assigned to one NH, two ethyl and twelve methylene protons.



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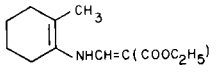

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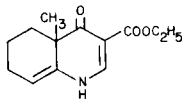

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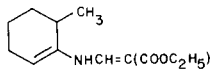

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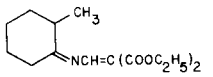

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The fragmentation pathways consisting of components m/e 319 (M^+), 273, 253, 207 (base peak), 161 and 160 indicated the further evidence for the structure **12** in the mass spectrum. The uv spectrum showed absorption maxima at 206, 239 and 346 mμ. These bands exhibit a bathochromic shift relative to the compound **9a**.

Other variations of condensation agents were attempted in the reaction of cyclopentanone (**5a**) and AMME; ethanolic hydrochloric acid quantitatively decomposed AMME to diethyl malonate, acetic anhydride gave acetylaminomethylenemalonate, and unchanged AMME was recovered with zinc chloride in tetrahydrofuran or Triton B in dioxane. The use of aluminium chloride, titanium tetrachloride and molecular sieves all failed.

The cyclization of the enaminomethylenemalonates **9a-c** was effected by heating them in Dowtherm at 250-255°, and moderate yields of ethyl 4-hydroxynicotinates (**10a-c**) were obtained. However, the attempt to cyclize the malonates **9b** and **9e** by means of polyphosphate ester, polyphosphoric acid or phosphorus oxychloride gave only intractable materials. These esters **10a-c** were readily converted to the corresponding free acids **11a-c** by basic hydrolysis. Then the esters **10a-c** were alkylated by the method originally employed by Kaminsky and Meltzer (3) for the synthesis of oxolinic acid (**1**) using sodium hydride and an alkyl iodide in dimethylformamide. The hydrolysis or ester exchange reaction accompanied the alkylation reaction. The esters and acids in the product may be separated by fractional recrystallization or the mixture of the products may be subjected to hydrolysis *in situ*. 1-Alkyl-1,4-dihydro-4-oxonicotinic acids (**4h-l**) and two of their ethyl esters (**4a** and **4d**) were thus isolated.

The pyridine structure of the cyclization products **10a-c** was established by the fact that two of the alkylated nicotinic acids melted at the same temperatures and exhibited the same ir absorptions as those reported for 1,4,5,6,7,8-hexahydro-1-methyl-4-oxo-3-quinolinecarboxylic acid (**4i**) and 1,4,6,7,8,9-hexahydro-1-methyl-4-oxo-5*H*-cyclohepta[*b*]pyridine-3-carboxylic acid (**4l**) (10). Moreover, the nmr spectra of the nicotinic acids **4h-l** and

Table I

Condensation of Ketones (**5a-g**) or Ketal (**7h**) with AMME

Method A (Phosphorus Pentoxide)

Starting Material	Amount, g. (mole)	AMME, g. (mole)	Phosphorus Pentoxide, g. (mole)	Tetrahydrofuran, ml.	Reaction Time, hours	Yield, %	Product
5a	5.9 (0.074)	12 (0.064)	20 (0.141)	120	24	8	**12**
5d	2.7 (0.027)	5 (0.027)	8 (0.0563)	50	20	56	**9d**
5e	26 (0.2)	37.4 (0.2)	50 (0.352)	300	2 days	42	**9e**
5f	21.8 (0.16)	30 (0.16)	50 (0.352)	300	5 days	5	**9f**
5g **5g**	68 (0.227)	60 (0.321)	100 (0.704)	600	24	12	**9g**
7h	2.72 (0.017)	3.64 (0.019)	8 (0.0563)	40	25	32	**9h**

Method B (*p*-Toluenesulfonic Acid)

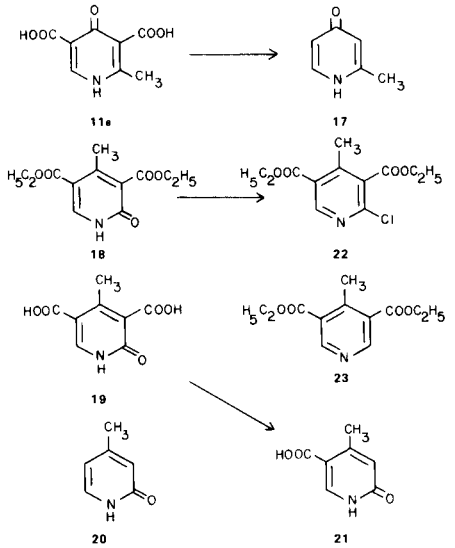
Starting Material	Amount g. (mole)	AMME, g. (mole)	*p*-TsOH, g.	*o*-Xylene, ml.	Reaction Time, hours	Yield, %	Product
5a	37 (0.43)	60 (0.321)	0.6	300	15.5	15	**9a**
5b	41.5 (0.423)	60 (0.321)	0.6	300	15	36	**9b**
5c	30 (0.268)	40 (0.214)	0.25	100	16	23	**9c**
5d	26.8 (0.268)	40 (0.214)	0.25	100	16	15	**9d**
2-Methylcyclohexanone	50 (0.446)	36.8 (0.197)	0.4	300	22	36	**13**

11a-c as well as their intermediate esters **4a-g** and **10a-c** were consistent with the expected structures.

Then attempts were undertaken to extend the present new synthesis to other substituted cyclic and acyclic ketones.

2-Methylcyclohexanone likewise condensed with AMME in the presence of *p*-toluenesulfonic acid to afford *N*-(2-methylcyclohexen-1-yl)aminomethylenemalonate (**13**). The two other possible isomeric structures **14** and **15** were ruled out by the nmr spectrum which showed the

Scheme II



the methyl group as a broad singlet at 1.80 δ. Cyclization of **13** gave the oxoquinolinecarboxylate **16**. Again, the methyl proton as a singlet, an olefinic proton and an NH signal as doublets and another olefinic proton as a multiplet were observed in the nmr spectrum of **16**.

On the contrary to the fact (11) that the condensation of ethyl β-aminocrotonate with EMME normally gives diethyl 2-hydroxy-6-methyldinicotinate, the cyclic β-aminovinylketones **8i** and **8j** readily condense with EMME to give the enaminomethylenemalonates **9i** and **9j**. The reaction proceeds by heating both the starting materials, and a small amount of *p*-toluenesulfonic acid catalyzes the reaction. The malonates **9i** and **9j** were cyclized thermally in a similar fashion to that described above, giving the corresponding 4-oxonicotinates **10i** and **10j**. The malonate **9j** was viscous oil and could not be distilled, hence it was directly used in its crude state for cyclization.

Although simple acyclic ketones, for example methyl ethyl ketone and acetophenone did not react with AMME under the reaction conditions such as *p*-toluenesulfonic acid in xylene and phosphorus pentoxide in tetrahydrofuran, acetylacetone (**5d**), ethyl acetoacetate (**5e**), methylsulphonylacetone (**5f**) (12) and *p*-toluenesulfonylacetone (**5g**) (13) condensed successfully with AMME in the presence of phosphorus pentoxide in tetrahydrofuran, the desired enaminomethylenemalonates **10d-g** being obtained. An inferior yield was obtained by using *p*-toluenesulfonic acid in xylene for the condensation of acetylacetone (**5d**) and AMME.

The scope of the synthesis was extended further to a ketoaldehyde. β-Ketobutyraldehyde (**5h**), being unstable under the reaction conditions as above and giving only intractable products, was converted to the dimethyl acetal (**7h**) (14) which condensed with AMME under the same reaction conditions as those for β-diketones. The masked aldehyde group reacted preferentially and the malonate isolated was diethyl *N*-(3-keto-1-buten-1-yl)aminomethylenemalonate (**9h**).

Cyclization of all these enaminomethylenemalonates **9d-h** gave the corresponding nicotinates **10d-h** which led to the nicotinic acids **11d-h** by subsequent basic hydrolysis. The nmr studies supported the proposed structures of

Table II

Diethyl *N*-Substituted Aminomethylenemalonates (**9a-i**, **12** and **13**)

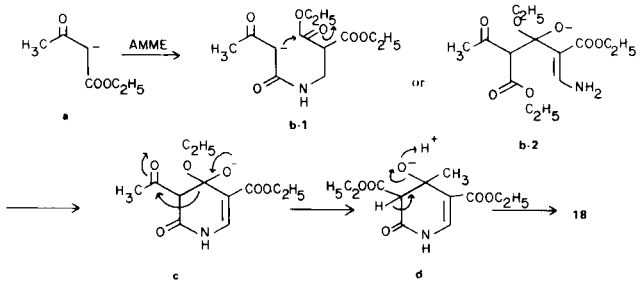
Compound No.	Recrystallization Solvent	M.p., °C	B.p./mm	Empirical Formula	Calcd., % C	H	N	Found, % C	H	N
9a		47-49	148-150/1	$C_{13}H_{19}NO_4$	61.64	7.56	5.53	61.59	7.60	5.52
9b			166-167/0.5	$C_{14}H_{21}NO_4$	62.90	7.58	5.24	62.95	7.41	5.00
9c			177-178/1	$C_{15}H_{23}NO_4$	64.04	8.24	4.98	63.97	8.15	4.71
9d	Ethyl acetate-petroleum ether	87-88		$C_{13}H_{19}NO_5$	57.98	7.11	5.21	58.10	7.13	5.26
9e	*n*-hexane	74-75		$C_{14}H_{21}NO_6$	56.19	7.02	4.68	55.92	6.99	4.55
9f	Ethyl acetate-petroleum ether	97-100		$C_{12}H_{19}NO_6S$	47.20	6.27	4.59	46.98	6.41	4.69
9g	Ethyl acetate-petroleum ether	124-126		$C_{18}H_{23}NO_6S$	56.66	6.08	3.68	56.89	6.30	3.59
9h	*n*-hexane	90-93		$C_{12}H_{17}NO_5$	56.47	6.67	5.49	56.51	6.71	5.45
9i	Ethyl acetate-isopropyl ether	118-120		$C_{12}H_{17}NO_5$	58.43	6.37	5.24	58.25	6.27	5.31
12	petroleum benzin	97-98		$C_{18}H_{25}NO_4$	67.69	7.89	4.39	67.44	7.85	4.43
13			160-162/1	$C_{15}H_{23}NO_4$	64.04	8.24	4.98	64.19	8.16	5.00

these malonates **9d-h** and nicotinates **10d-h** (Tables V and VI).

Thus, the development of the novel synthesis described in the present paper made a wide variety of new 4-oxonicotinates accessible. An important feature of this preparative route is that these 4-oxonicotinates could be synthesized only in a few steps from easily available materials.

One of the nicotinates synthesized in the present study, diethyl 1,4-dihydro-2-methyl-4-oxodinicotinate (**10e**), had been reported by Ochiai and Ito (11) who prepared it by reaction of ethyl acetoacetate with AMME in the presence of sodium in benzene. However, the products prepared by the two methods were not identical with each other. The dicarboxylic acid **11e** obtained by our procedure was decarboxylated by heating at 300-310° (bath) to yield 2-methyl-4(1*H*)pyridone (**17**), identical with the sample prepared from 4-chloro-2-picoline according to the procedure of Kato (15). This transformation proves the structure of **11e**.

Scheme III



Compound **18** obtained in 11% yield from ethyl acetoacetate and AMME according to the method of the foregoing literature (11) was analyzed for $C_{12}H_{15}NO_3$, and shown to possess a methyl group, two ethyl ester groups and one ring proton by its nmr studies. The methylpyridone **20**, derived from **18** by basic hydrolysis followed by decarboxylation of the resulting diacid **19**, was identical with 4-methyl-2(1*H*)pyridone (**20**) prepared by diazotizaion of 2-amino-4-picoline (16). This proves the position of the methyl and hydroxy groups in **18**. Treatment of the diacid **19** with boiling hydrobromic acid gave the monocarboxylic acid **21**. The nmr spectrum of **21** showed two singlet ring protons at 7.20 δ and 8.92 δ, indicating the position of one of the two ethoxycarbonyl groups in **18**. Therefore, the second ethoxycarbonyl group must occupy the 3 or 6 position. Finally, compound **18** was chlorinated with phosphorous oxychloride, giving the 2-chloroderivative **22** in 62% yield. Catalytic hydrogenation of **22** over palladium on charcoal afforded diethyl 4-methyl-3,5-dinicotinate (**23**) (17). The positions of the ethoxycarbonyl groups of **23** were evidenced by the presence of one singlet signal at 9.0 δ integrating for two protons in the nmr spectrum. Therefore, the compound **18** incorrectly designated as diethyl 1,4-dihydro-2-methyl-4-oxodinicotinate unambiguously proved to be diethyl 1,2-dihydro-4-methyl-2-oxodinicotinate.

The formation of **18** from the reaction of sodium salt of ethyl acetoacetate (**5e**) with AMME is explained by a probable mechanistic pathway as given in Scheme III. In the key intermediate **c**, a mesomeric migration of the lone pair electrons on the oxygen atom at the 4-position would facilitate the intramolecular nucleophilic rearrangement of the C_5 atom to the carbonyl group of the acetyl moiety, giving the anion **d**. Elimination of water from **d** would then afford diethyl 1,2-dihydro-4-methyl-2-oxodinicotinate (**18**).

The 1-alkyl-1,4-dihydro-4-oxonicotinic acids **4h-l** prepared in the present study were tested for antimicrobial activities against *Staphylococcus aureus* 209 p, *Escherichia coli* NIHJ, *Klebsiella pneumonia* PCI 602, *Proteus mirabilis*

Table III

Thermal Cyclization of Malonates (**9a-j**, **13**)

Starting Material	Product	Yield, %	Recrystallization Solvent	M.p., °C	Empirical Formula	Calcd., % C	H	N	Found, % C	H	N
9a	**10a**	40	Ethanol	245 dec.	$C_{11}H_{13}NO_3$	63.76	6.32	6.76	63.45	6.52	6.72
9b	**10b**	38	Ethanol	229-300	$C_{12}H_{15}NO_3$	65.14	6.82	6.33	65.01	6.95	6.20
9c	**10c**	59	Ethanol	204-205 dec.	$C_{13}H_{17}NO_3$	66.36	7.28	5.95	66.05	7.11	5.71
9d	**10d**	56	Ethanol	216-217	$C_{11}H_{13}NO_4$	59.19	5.87	6.28	59.32	5.92	6.20
9e	**10e**	74	Benzene-*n*-Hexane	156-158	$C_{12}H_{15}NO_5$	56.91	5.97	5.53	56.82	5.85	5.58
9f	**10f**	44	Ethanol	230-231	$C_{10}H_{13}NO_5S$	46.37	5.06	5.41	46.35	4.98	5.34
9g	**10g**	88	Acetic Acid	242 dec.	$C_{16}H_{17}NO_5S$	57.30	5.12	4.18	57.48	4.92	3.91
9h	**10h**	65	DMF	270-271 dec.	$C_{10}H_{11}NO_4$	57.42	5.26	6.70	56.99	5.44	6.81
9i	**10i**	51		>300	$C_{11}H_{11}NO_4$	59.72	5.01	6.33	59.61	4.98	6.13
9j	**10j**	30	Ethyl Acetate	215-216	$C_{14}H_{17}NO_4$	63.88	6.46	5.32	63.79	6.52	5.32
13	**16**	59	Ethanol	216-217	$C_{13}H_{17}NO_3$	66.36	7.28	5.95	66.33	7.06	5.78

GN 2425, *Proteus vulgaris* HX 19 and *Pseudomonas aeruginosa* 104 using two-fold tube dilution method. No significant activity, however, was observed.

EXPERIMENTAL (18)

Condensation of Ketones (**5**) or a Ketal with AMME.

Method A (Phosphorus Pentoxide).

A mixture containing a ketone or ketal, AMME (9), phosphorus pentoxide and dry tetrahydrofuran was stirred at room temperature. The reaction was followed by tlc using a mixture of chloroform and methanol (10:1). After the reaction was over, the pasty mass was separated by means of decantation and several times washed with tetrahydrofuran. The combined tetrahydrofuran solution was evaporated *in vacuo* and the residue was three times extracted with ethyl acetate. The extracts were washed with aqueous potassium carbonate, and then with water, dried over magnesium sulfate and evaporated under reduced pressure. The resulting material was purified by silica gel column chromatography using chloroform as eluent. The substituted aminomethylenemalonate obtained in this manner was again purified by recrystallization.

Method B (*p*-Toluenesulfonic Acid).

A solution containing a ketone, AMME, *o*-xylene and a small amount of *p*-toluenesulfonic acid was refluxed until evolution of water ceased. The volatile materials were evaporated *in vacuo*. The residue was dissolved in benzene and the solution passed through a silica gel column for chromatography. Evaporation of the solvent from the eluate afforded a viscous oil, which was distilled under reduced pressure to give the pure aminomethylenemalonate.

The reaction conditions and the yields of the products are listed in Table I.

Condensation of Cyclohexanone Diethylketal (**6b**) with AMME.

A mixture containing 17.2 g. of cyclohexanone diethylketal (**6b**) (9) and 18.7 g. of AMME was stirred at 140° for 34 hours, during which period the liberated ethanol was removed. After the reaction had been completed, the resulting syrup was passed through a silica gel column for chromatography using benzene as solvent. Evaporation of the solvent from the eluate gave a yellow oil, which was distilled to give 11 g. (35%) of **9b** (Table II), b.p. 166-167° at 0.5 mmHg.

Condensation of β-Aminovinylketones (**8i,j**) with AMME.

Diethyl *N*-(3-Keto-1-cyclopenten-1-yl)aminomethylenemalonate (**9i**).

A mixture containing 4 g. of 1-amino-1-cyclopenten-3-one (**8i**) (19), 10.8 g. of AMME and 0.05 g. of *p*-toluenesulfonic acid was stirred at 120-130° for 39 hours. During this period the liberated ethanol was removed. After cooling, the resultant syrupy material was dissolved in *ca.* 100 ml. of ethyl acetate. The insoluble material was removed by filtration and washed with a small amount of ethyl acetate. The combined ethyl acetate solution was washed with water, dried over magnesium sulfate and evaporated under reduced pressure. Recrystallization of the residual yellow solid from a mixture of ethyl acetate and isopropyl ether gave 1.7 g. (14%) of **9i** as colorless needles, m.p. 118-120°.

Diethyl *N*-(3-Keto-5,5-dimethyl-1-cyclohexen-1-yl)aminomethylenemalonate (**9j**).

A mixture containing 1.4 g. of 1-amino-5,5-dimethyl-1-cyclohexen-1-one (**8j**) (20), 2.16 g. of EMME and 0.01 g. of *p*-toluenesulfonic acid was stirred at 130° for 18 hours in the same manner as described above. The resultant brown oil was dissolved in chloroform, treated with charcoal and filtered. Evaporation of the

Table IV

1,4-Dihydro-4-oxonicotinic Acids (**11a-j**)

Compound No.	Yield, %	Crystalline Form	M.p., °C	Empirical Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
11a	83	Colorless scales (ethanol)	263-264 dec.	$C_9H_9NO_3$	60.33	5.06	7.82	60.15	5.06	7.82
11b	83	Colorless prisms (ethanol	285 dec.	$C_{10}H_{11}NO_3{\cdot}\frac{1}{2}H_2O$	59.40	5.98	6.93	59.33	5.95	6.89
11c	82	Colorless prisms (ethanol)	248-249 dec.	$C_{11}H_{13}NO_4{\cdot}\frac{1}{2}H_2O$	61.02	6.52	6.48	61.42	6.20	6.21
11d	84	Pale yellow needles (water)	260-263 dec.	$C_9H_9NO_4$	55.38	4.64	7.18	55.41	4.52	7.21
11e	90	White powder	285 dec.	$C_8H_7NO_5$	48.74	3.58	7.11	48.45	3.30	7.04
11f	86	Colorless prisms (water)	235-236 dec.	$C_8H_9NO_5S$	41.59	3.93	6.06	41.47	3.81	6.08
11g	66	Colorless needles (acetic acid)	279-281 dec.	$C_{14}H_{13}NO_5S$	54.77	4.27	4.56	54.77	3.97	4.61
11h	92	Pale yellow needles (water)	272-274 dec.	$C_8H_7NO_4$	53.04	3.90	7.73	53.16	3.87	7.56
11i	71	White powder	> 300	$C_9H_7NO_4$	55.96	3.65	7.25	55.91	3.64	7.18
11j	58	Yellow needles (aqueous dimethylformamide)	> 300	$C_{12}H_{13}NO_4$	61.28	5.53	5.96	61.34	5.59	6.06

Table V

Nmr Data for Diethyl *N*-Substituted Aminomethylenemalonates

Compound No.	CH_2CH_3	CH_2CH_3	Methylene or Phenyl Protons	CH_3	Olefinic Protons	NH
9a	1.12 (t) J = 7, 1.33 (t) J = 7	4.22 (q) J = 7, 4.27 (q) J = 7	1.57-3.07 (m)	----	5.27 (bs), 8.27 (d) J = 15	9.17 (bd) J = 15
9b	1.28 (t) J = 7, 1.33 (t) J = 7	4.20 (q) J = 7, 4.27 (q) J = 7	1.52-2.43 (m)	----	5.43 (bt) J = 3, 8.16 (d) J = 16	9.02 (bd) J = 16
9c	1.30 (t) J = 7, 1.33 (t) J = 7	4.20 (q) J = 7, 4.23 (q) J = 7	1.50-1.93 (m) 1.93-2.60 (m)	----	5.57 (t) J = 7, 8.18 (d) J = 13	10.37 (bd) J = 13
9d	1.30 (t) J = 7, 1.37 (t) J = 7	4.27 (q) J = 7, 4.42 (q) J = 7	----	2.15 (s), 2.18 (s)	5.55 (s), 8.15 (d) J = 14	13.50 (bd) J = 14
9e	1.27 (t) J = 7, 1.30 (t) J = 7, 1.33 (t) J = 7	4.23 (q) J = 7, 4.37 (q) J = 7	----	2.17 (s)	5.12 (s), 8.12 (d) J = 14	13.50 (bd) J = 14
9f	1.30 (t) J = 7, 1.33 (t) J = 7	4.23 (q) J = 7, 4.35 (q) J = 7	----	2.18 (s) 4.70 (s)	5.43 (s), 8.05 (d) J = 14	10.23 (bd) J = 14
9g	1.30 (t) J = 7, 1.37 (t) J = 7	4.23 (q) J = 7, 4.42 (q) J = 7	7.30 (d) J = 10, 7.87 (d) J = 10	2.10 (s) 2.42 (s)	5.43 (s), 8.03 (d) J = 14	12.17 (bd) J = 14
9h	1.30 (t) J = 7, 1.38 (t) J = 7	4.25 (q) J = 7, 4.38 (q) J = 7	----	2.20 (s)	5.57 (d) J = 8, 6.70 (bd) J = 14, J = 8, 7.87 (d) J = 14	12.65 (bs)
9i	1.33 (t) J = 7, 1.38 (t) J = 7	4.25 J = 7, 4.32 (q) J = 7	2.40-3.00 (m)	----	5.7 (bs), 8.1 (d) J = 13	11.00 (bd)
9j	1.33 (t) J = 7, 1.37 (t) J = 7	4.25 (q) J = 7, 4.33 (q) J = 7	2.08-2.72 (m)	1.10 (s)	5.80 (bs), 8.31 (d) J = 13	10.50 (bd)
12	1.26 (t) J = 7, 1.33 (t) J = 7	4.18 (q) J = 7, 4.25 (q) J = 7	1.60-3.00 (m)	----	5.53 (bs), 7.95 (d) J = 14	11.33 (bd) J = 14
13	1.32 (t) J = 7, 1.37 (5 J = 7	4.20 (q) J = 7, 4.27 (q) J = 7	1.53-2.67 (m)	1.80 (bs)	8.13 (d) J = 14	11.25 (bd) J = 14

Chemical shift in δ units (ppm) in deuteriochloroform with TMS as internal Standard. Coupling constants J in cps. Signals are designated as follows: s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, doublet of doublets; t, triplet; bt, broad triplet; q, quartet;

chloroform filtrate gave 2.95 g. (93%) of a viscous yellow oil (**9j**), which showed one spot on tlc using a mixture of chloroform and methanol (10:1) as solvent and used for the next step without further purification.

The physical properties and the analytical data of the malonates (**9a-j, 13**) obtained above are listed in Tables II and V.

Thermal Cyclization of Malonates (**9a-j, 13**).

A malonate was added to a 20-fold volume of boiling Dowtherm A (255-260°) and the mixture maintained at this temperature with stirring for 5-20 minutes. The liberated ethanol was collected in a Dean-Stark trap during the reaction. After cooling, about the same volume of *n*-hexane as Dowtherm A was added. A fawn solid that deposited was collected by filtration and washed with *n*-hexane. Recrystallization from the solvent shown in Table III yielded the ethyl 4-oxonicotinate. Melting points, yields and analytical data of the nicotinates are summarized in Table III.

General Preparation of 4-Oxonicotinic Acid (**11a-j**).

The ethyl 4-oxonicotinate obtained above was stirred in 10% aqueous sodium hydroxide solution at 90-95° for 2 hours. The resulting solution was acidified by the addition of 6 *N* hydrochloric acid. The precipitated solid was collected by filtration, washed with water and dried. Recrystallization from the solvent shown in Table IV yielded the 4-oxonicotinic acid. Melting points, yields and analytical data are also listed in Table IV.

Alkylation of Ethyl 4-Oxonicotinates (**10a-c**).

Ethyl 1-Ethyl-1,4,6,7-tetrahydro-4-oxo-5*H*-cyclopenta[*b*]pyridine-3-carboxylate (**4a**) and 1-Ethyl-1,4,6,7-tetrahydro-4-oxo-5*H*-cyclopenta[*b*]pyridine-3-carboxylic Acid (**4h**).

Table VI

Nmr Data for Ethyl 1,4-Dihydro-4-oxonicotinates

Compound No.	CH_2CH_3	CH_2CH_3	Methylene or Phenyl Protons	CH_3	C_2-H or C_6-H	NH or OH
10a	1.50 (t) J = 7	4.63 (q) J = 7	2.50 (bq) (a) J = 7, 3.00-3.60 (m)	----	8.97 (d) J = 6	----
10b	1.50 (t) J = 7	4.65 (q) J = 7	1.77-2.40 (m) 2.67-3.33 (m)	----	8.93 (d) J = 7	----
10c	1.43 (t) J = 7	4.53 (q) J = 7	1.60-2.33 (m) 2.80-3.33 (m)	----	8.65 (d) J = 7	----
10d (a)	1.35 (t) J = 7	4.34 (q) J = 7	----	2.42 (s), 2.54 (s)	8.71 (s)	>13.33 (b)
10e (a)	1.36 (t) J = 7	4.38 (q) J = 7	----	2.50 (s)	8.8 (s)	9.73 (bs)
10f	1.53 (t) J = 7	4.72 (q) J = 7	----	3.20 (s), 3.60 (s)	9.15 (s)	----
10g	1.30 (t) J = 7	4.47 (q) J = 7	7.50 (d) J = 8, 8.02 (d) J = 8	2.33 (s), 3.15 (s)	8.93 (s)	----
10h	1.54 (t) J = 7	4.72 (q) J = 7	----	2.95 (s)	9.30 (d) J = 1, 9.35 (d) J = 1	----
10i	1.53 (t) J = 7	4.68 (q) J = 7	2.97-3.30 (m), 3.47-3.83 (m)	----	9.32 (s)	----
10j	1.51 (t) J = 7	4.64 (q) J = 7	2.89 (bs), 3.35 (bs)	1.28 (bs)	9.20 (s)	----
16 (a)	1.30 (t) J = 7	4.20 (q) J = 7	1.50-2.43 (m)	1.30 (s)	8.26 (d) J = 8, 5.73 (m) (c)	10.03 (bd) J = 8

Chemical shift in δ units (ppm) in trifluoroacetic acid with TMS as internal standard. The symbol of (bq) signifies a broad singlet. (a) Taken in deuteriochloroform. (b) No signal of the hydroxy group appeared within δ 13.33. (c) The signal of an olefinic proton.

Table VII

Nmr Data for 1,4-Dihydro-4-oxonicotinic Acids

Compound No.	Methylene or Phenyl Protons	CH_3	C_2-H or C_6-H
11a	2.55 (bq), 3.02-3.65 (m) J = 7	----	9.05 (bs)
11b	1.73-2.37 (m), 2.63-3.33 (m)	----	8.97 (d) J = 7
11c	1.50-2.43 (m), 2.97-3.50 (m)	----	8.85 (d) J = 6
11d	----	2.83 (s)	9.13 (s)
11e	----	3.07 (s)	9.07 (bs)
11f	----	3.13 (s), 3.57 (s)	9.13 (s)
11g	7.45 (d), 8.00 (d) J = 9 J = 9	2.53 (s), 3.33 (s)	9.17 (s)
11h	----	3.00 (s)	9.38 (bs), 9.47 (bs)
11i	2.90-3.35 (m), 3.40-3.83 (m)	----	9.23 (s)
11j	2.90 (bs), 3.30 (bs)	----	9.18 (bs)

Chemical shift in δ units (ppm) in trifluoroacetic acid with TMS as internal standard.

A mixture containing 2.07 g. of ethyl 1,4,6,7-tetrahydro-4-oxo-5*H*-cyclopenta[*b*]pyridine-3-carboxylate (**10a**), 0.86 g. of 56% sodium hydride and 40 ml. of dimethylformamide was stirred at 70-75° for 30 minutes. To the resulting mixture was added dropwise 2.65 g. of ethyl iodide for 10 minutes. The same temperature was maintained for an additional 2 hours. This was followed by an additional ethyl iodide (1.33 g.) and 2 hours of stirring at 70-75°. Being kept at room temperature overnight, the reaction mixture was concentrated under reduced pressure. Water was added to the residue and the mixture extracted with chloroform. The chloroform extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent to dryness yielded 1.85 g. of a solid consisting of **4a** and **4h** as indicated by the nmr spectrum. Recrystallization from ethyl acetate afforded 1.1 g. (47%) of **4a**, colorless scales, m.p. 127-128°; nmr spectrum (deuteriochloroform): 1.37 δ (CH_3, t), 1.43 δ (CH_3, t), 1.77-3.33 δ ($CH_2CH_2CH_2$, m), 3.92 δ (CH_2, q), 4.32 δ (CH_2, q), 8.08 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.30; H, 7.31; N, 5.56. Found: C, 66.36; H, 7.28; N, 5.95.

The mother liquor from recrystallization was evaporated under reduced pressure. The residue was heated in 20 ml. of 5% aqueous potassium hydroxide solution at 90-95° for 15 minutes. The resulting solution was adjusted to *p*H 6 by the addition of 6 *N* hydrochloric acid and evaporated to dryness. The residue was extracted several times with anhydrous ethanol. Evaporation of the solvent gave 0.42 g. of a yellow solid. Recrystallization from ethanol yielded 0.12 g. (5.8%) of **4h** as colorless needles, m.p. 243° dec.; nmr spectrum: 1.67 δ (CH_3, t), 2.2-3.63 δ ($CH_2CH_2CH_2$, m), 6.13 δ (CH_2, q), 8.97 δ.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.91; H, 6.32; N, 6.68.

Ethyl 1-Ethyl-1,4,5,6,7,8-hexahydro-4-oxo-3-quinolinecarboxylate (**4d**) and 1-Ethyl-1,4,5,6,7,8-hexahydro-4-oxo-3-quinolinecarboxylic Acid (**4j**).

Ethyl 1,4,5,6,7,8-hexahydro-4-oxo-3-quinolinecarboxylate (**10b**) (2.21 g.) was ethylated in the same procedure as described above. The chloroform extract was evaporated to dryness and the residue (1.5 g.) was recrystallized from ethanol giving 0.1 g. (4.5%) of the acid (**4j**) as colorless needles, m.p. 265-265.5°; nmr spectrum: 1.37 δ (CH_3, t), 1.7-4.8 δ [$(CH_2)_4$, m], 4.38 δ (CH_2, q), 8.53 δ (C-2 proton, s).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.84; H, 7.08; N, 6.30.

Evaporation of the ethanolic filtrate and recrystallization of the residue from a mixture of ethyl acetate and petroleum benzin gave the ester (**4d**) as colorless prisms, m.p. 121-122°; nmr spectrum (deuteriochloroform): 1.37 δ (CH_3, t), 1.4 δ (CH_3, t), 1.6-2.13 δ (CH_2CH_2, m), 2.3-2.77 δ (CH_2, m), 3.93 δ (CH_2, q), 4.3 δ (CH_2, q), 8.13 δ (C-2 proton, s).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62.

1,4,5,6,7,8-Hexahydro-1-methyl-4-oxo-3-quinolinecarboxylic Acid (**4i**).

Ethyl 1,4,5,6,7,8-hexahydro-4-oxo-3-quinolinecarboxylate (**10b**) (2.21 g.) was methylated by the same procedure as described above by using methyl iodide as an alkylating agent. After evaporation of the chloroform extract there was obtained 1.8 g. of a yellow solid containing **4b** and **4c** in the ratio of 3:2 as determined by nmr examination. The solid was hydrolyzed in 10 ml. of 5% potassium hydroxide solution under reflux for 1 hour. The resulting solution was adjusted to *p*H 4 by the addition of 6 *N* hydrochloric acid. The deposited solid was filtered and dried. Recrystallization from methanol gave 1.3 g. (57%) of the acid (**4i**) as colorless needles, m.p. 281° dec., [lit. (10) m.p. 281-283° dec.]. The absorption bands (1700, 1630 cm^{-1}) in the infrared spectrum (Nujol) of **4i** were identical with those reported (10); nmr spectrum, 1.77-2.4 δ (CH_2, m), 2.73-3.27 δ (CH_2CH_2, m), 4.18 δ (CH_3, s), 8.85 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.63; H, 5.91; N, 6.68.

1-Ethyl-1,4,6,7,8,9-hexahydro-4-oxo-5*H*-cyclohepta[*b*]pyridine-3-carboxylic Acid (**4k**).

Ethyl 1,4,6,7,8,9-hexahydro-4-oxo-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (**10c**) (0.3 g.) was ethylated in the same procedure as described above. The chloroform extract gave 0.15 g. of the crude ester (**4e**) as a yellow oil on evaporation. Hydrolysis of **4e** in 5 ml. of 10% aqueous sodium hydroxide under reflux for 1 hour, gave 0.15 g. of **4k** as a white solid. Recrystallization from ethanol gave 0.13 g. (43%) of **4k** as colorless needles, m.p. 265-265.5° dec.; nmr spectrum (deuteriochloroform): 1.43 δ (CH_3, t), 1.57-3.2 δ [$(CH_2)_5$, m], 4.2 δ (CH_2, q), 8.42 δ (C-2 proton, s).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.89; H, 7.42; N, 5.88.

1,4,6,7,8,9-Hexahydro-1-methyl-4-oxo-5*H*-cyclohepta[*b*]pyridine-3-carboxylic Acid (**4l**).

Ethyl 1,4,6,7,8,9-hexahydro-4-oxo-5*H*-cyclohepta[*b*]pyridine-3-carboxylate (**10c**) (0.3 g.) was methylated in the same procedure as described above. The chloroform extracts were evaporated under reduced pressure to give a brown oil, which was triturated with *n*-hexane, affording 0.22 g. of a mixture of **4f** and **4g** as a fawn solid. The mixture was hydrolyzed in 10% aqueous sodium hydroxide under reflux for 1 hour. After the reaction was over, the solution was adjusted to *p*H 4 by the addition of 6 *N* hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water, dried over sodium sulfate and evaporated *in vacuo* to give 0.1 g. of a white solid. Recrystallization from methanol gave 0.08 g. (29%) of **4l** as colorless needles, m.p. 225-226°, [lit. (10) m.p. 225-230°]. The absorption bands (1710, 1630 cm^{-1}) in the infrared spectrum (Nujol) were identical with those reported (10); nmr spectrum: 1.53-2.33 δ (CH_2, m), 3.6-3.0 δ (CH_2, m), 4.27 δ (CH_3, s), 8.92 δ (C-2 proton, s).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.33; N, 6.80. Found: C, 64.90; H, 6.80; N, 6.40.

2-Methyl-4(1*H*)pyridone (**17**).

4-Oxodinicotinic acid (**11e**) (0.9 g.) was heated in a current of nitrogen at 300-310° (bath) for half an hour. After cooling, the fawn solid which had formed was extracted wtih chloroform. The chloroform extracts were treated with charcoal and filtered. Removal of the solvent from the filtrate gave a pale yellow solid. Recrystallization from a mixture of chloroform and petroleum ether gave 0.31 g. (62%) of **17** as colorless prisms, m.p. 174-176°, undepressed on admixture with a sample prepared according to the procedure of Kato (15). The infrared spectra of the two samples were identical; nmr spectrum (deuteriochloroform): 2.75 δ (CH_3, s), 7.06-7.37 δ (C-3, C-2 protons, m) 8.23 δ (C-2 proton, t).

Anal. Calcd. for C_6H_7NO: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.83; H, 6.28; N, 12.64.

1,2-Dihydro-4-methyl-2-oxodinicotinic Acid (**19**).

A mixture containing 1.3 g. of diethyl 1,2-dihydro-4-methyl-2-oxodinicotinate (**18**) and 20 ml. of 10% aqueous sodium hydroxide was heated under reflux for 3 hours. After cooling, the solution was acidified to *p*H 1-2 by the addition of 6 *N* hydrochloric acid, the deposited solid was collected by filtration, washed with water and dried. Recrystallization from water gave 0.8 g. (78%) of **19** as colorless needles, m.p. 278-280° dec.; nmr spectrum: 3.16 δ (CH_3, s), 8.9 δ (C-6 proton, s).

Anal. Calcd. for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.11. Found: C, 48.70; H, 3.55; N, 7.34.

4-Methyl-2(1*H*)pyridone (**20**).

1,2-Dihydro-4-methyl-2-oxodinicotinic acid (**19**) (0.8 g.) was heated in a current of nitrogen at 300° for 15 minutes. After cooling, the solid which had formed was three times recrystallized from benzene to afford 0.1 g. (23%) of **20** as colorless needles, m.p. 127-128°, undepressed on admixture with a sample prepared according to the procedure of Adams and Schrecker (15). The infrared spectra of the two samples were identical.

1,2-Dihydro-4-methyl-2-oxonicotinic Acid (**21**).

A solution containing 0.5 g. of 1,2-dihydro-4-methyl-2-oxodinicotinic acid (**19**) and 10 ml. of 48% hydrobromic acid solution was heated under reflux for 4 hours. After the reaction was completed, the excess reagent was evaporated under reduced pressure. The resulting fawn solid was washed with water and recrystallized from dimethylformamide to yield 0.3 g. (77%) of **21** as colorless prisms, m.p. over 300°; nmr spectrum: 2.9 δ (CH_3, s), 7.2 δ (H-2, s), 8.92 δ (6-H, s).

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.75; H, 4.65; N, 9.06.

Diethyl 2-Chloro-4-methyldinicotinate (**22**).

A solution containing 1.2 g. of diethyl 1,2-dihydro-4-methyl-2-oxodinicotinate (**18**) and 30 ml. of phosphorus oxychloride was heated under reflux for 4 hours. After the reaction had been completed, the excess phosphorus oxychloride was removed *in vacuo*. The residue was poured into ice water, made alkaline by the addition of aqueous sodium carbonate and extracted with ether. The ethereal solution was washed with water and dried over magnesium sulfate. Evaporation of the ether gave a dark brown oil (1.0 g.), which was dissolved in chloroform and the solution passed through a silica gel column for chromatography. Evaporation of the solvent from the eluate afforded 0.8 g. (62%) of **22** as a pale yellow oil; nmr spectrum (deuteriochloroform): 1.4 δ (CH_3, t), 2.58 δ (CH_3, s), 4.13-4.7 δ (CH_2, m), 8.9 δ (C-6 proton, s).

Anal. Calcd. for $C_{12}H_{14}ClNO_4$: Cl, 13.05. Found: Cl, 13.04.

Diethyl 4-Methyldinicotinate (**23**).

A mixture containing 0.6 g. of diethyl 2-chloro-4-methyldinicotinate (**22**), 0.33 g. of triethylamine, 0.05 g. of 5% palladium-charcoal and 40 ml. of ethanol was hydrogenated at atmospheric pressure. The reduction stopped when the calculated amount of hydrogen had been absorbed. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The residue was chromatographed using a silica gel column and chloroform as solvent. Evaporation of the solvent from the eluate gave 0.2 g. (39%) of **23** as a yellow oil; nmr spectrum (deuteriochloroform): 1.43 δ (CH_3, s), 4.43 δ (CH_2, q), 9.0 δ (C-2, C-6 protons, s).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 46.31; H, 3.86; N, 12.01. Found: C, 46.21; H, 3.89; N, 11.92.

The picrate gave yellow needles, m.p. 69-70° (from ethanol) [lit. (17) m.p. 75.5-76.5°].

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