Studies on Chemotherapeutics I. Synthesis of 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acid Derivatives

Mária Balogh, István Hermecz*, Zoltán Mészáros, Kálmán Simon, Levente Pusztay, Gábor Horváth and Péter Dvortsák

CHINOIN Pharmaceutical and Chemical Works, Budapest, Hungary

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Ethyl 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates were synthetized by reacting 1,3,5-triazine with 4-substituted ethyl acetoacetate derivatives in ethanol, in the presence of sodium ethoxide. The 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acids required for the antimicrobial studies were prepared by *N*-alkylation (with triethyl phosphate or alkyl halides) and alkaline hydrolysis of the pyridone esters.

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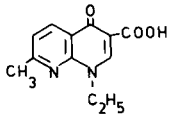
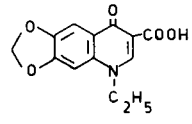
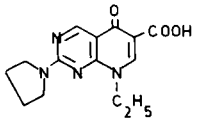
Several drugs with antibacterial activity such as nalidixic acid (1), oxolinic acid (2), pyromidic acid (3a) and pipemidic acid (3b) contain the common 1-ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid moiety.



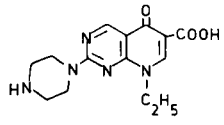
Nalidixic acid



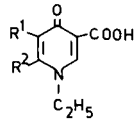
Oxolinic acid



Pyromidic acid



Pipemidic acid

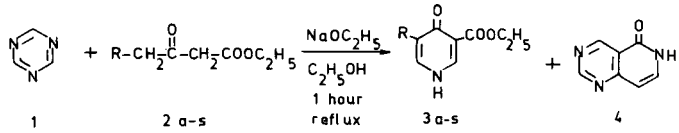


A

Studying the relationship between the chemical structure and pharmacological activity various 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid derivatives (*A*, R^2 = H) were prepared. Several methods are known from the literature for the preparation of the acids *A* (and of their esters). Japanese authors (4,5) obtained 1-ethyl-5,6-disubstituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid derivatives (*A*) in four steps, by making use of the Gould-Jacobs reaction. Taylor and Abdulla (6,7) reacted enaminoketones with *N,N*-dimethylformamide-dimethylacetal and cyclized the product with methylammoniumchloride, while Kilbourn and Seidel (8) used 4-hydroxy-5,6-cycloalkyl-2-pyrone derivatives as starting materials for the synthesis of the acids *A*.

In our work ethyl 4-oxo-1,4-dihydro-3-pyridinecarboxylate and its 5-substituted derivatives (**3a-s**) were synthetized by reacting 1,3,5-triazine (9,10) (**1**) with 4-substituted ethyl acetoacetate derivatives (**2a-s**) (11-21) in ethanol, in the presence of sodium ethoxide (see Table 1).

The above synthetic method has been described by Huffman and co-workers (22), but only two pyridine derivatives (**3a** and **3r**) have been prepared.



1 2 a-s 3 a-s 4

A thorough study of the reaction of 1,3,5-triazine (**1**) with the ethyl acetoacetate (**2a**) revealed that beyond the expected ethyl 4-oxo-1,4-dihydro-3-pyridinecarboxylate (**3a**) an additional, higher melting compound was formed, in 11.8% yield (23). Microanalytical data and mass spectrometric studies showed an empirical formula $C_7H_5N_3O$. In the nmr spectrum of the compound recorded in deuterated sodium hydroxide solution two doublets and two singlets were found in the aromatic range. The intensive absorption band at 1710 cm^{-1} in the ir spectrum (solid phase) suggested the presence of a carbonyl group, while the bands in the range 3200-2900 cm^{-1} could be assigned to an NH-group. The spectroscopic data and the X-ray diffraction analysis showed the compound to be pyrido[4,3-*d*]-pyrimidine-5(*6H*)one (**4**). Bond lengths and angles, with their estimated standard deviations in parentheses, are given in Fig. 1. The molecule is planar, the largest deviation from the best plane, formed by all non-hydrogen atoms, is 0.03 Å for the O(11) atom. Dimers are formed by the N(6)-H(6)... O(11) ($\overline{X}$, 1-y, $\overline{Z}$) hydrogen bonds, the N(6)...O(11) distance is 2.84 Å.

The reactivity of the 4-substituted ethyl acetoacetates (**2a-s**) toward 1,3,5-triazine (**1**) varies within a wide range (see Table 1). In the case of ethyl 5-ethoxy-4-oxo-1,4-dihydro-3-pyridinecarboxylate (**3m**) the yield was low due to tar formation.

In order of the reactivity is shown below (under the symbols of the substituents the yields of the ethyl 5-sub-

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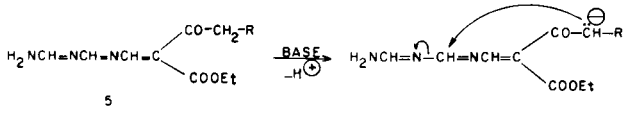
stituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates (**3a-s**) obtained after reacting the components for 1 hour are given).

$(CH_3)_2CH \approx$ cyclohexyl $\approx$ ethoxy $\ll C_{2-10}$ alkyl $< CH_3 \approx$ Ph $\approx$ *p*-Cl-benzyl $\approx COOC_2H_5 \ll$ *p*-NO_2-phenyl

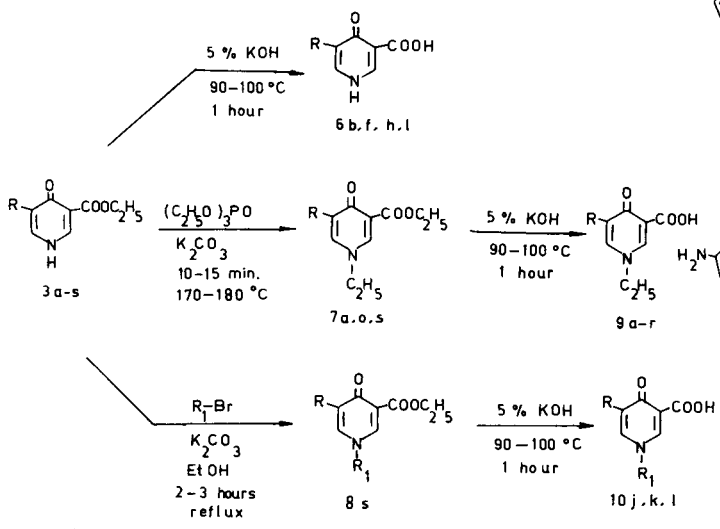
7-10% 35-45% 50-55% 98%

The above order can be explained on the basis of the mechanism of the reaction (22,24,25). Upon reaction of **1** with the compounds **2a-s** the open-chain intermediates **5** are formed the latters yielding carbanions upon removal of the "acidic hydrogen" of the methylene group by base:



Electron withdrawing substituents as R facilitate the cleavage of the proton, while electronreleasing ones make it difficult. In the case of the derivative wearing the *p*-nitrophenyl group possessing the most pronounced electron withdrawing effect the reaction proceeds rapidly and leads to only one product.

As for the intermediates **5** where R = isopropyl and cyclohexyl, respectively, presumably the steric factors also hinder the formation and further reaction of the carbanion.

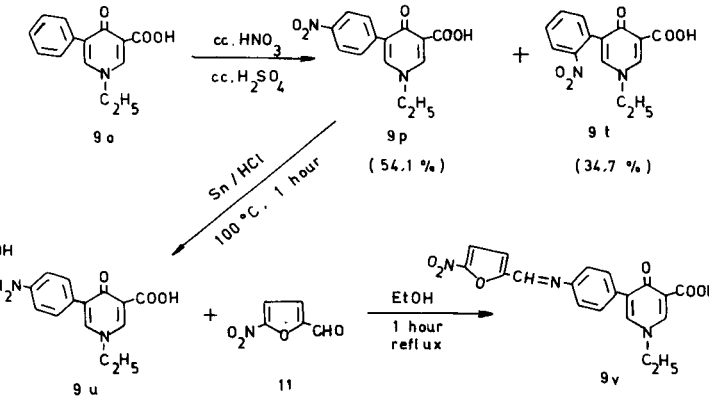


The ethyl 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates (**3b, 3f, 3h, 3l**) could be hydrolyzed to the corresponding acids (**6b, 6f, 6h, 6l**) by heating them at 90-100° for 1 hour with a 5% potassium hydroxide solution, in excellent yields (see Table 3).

The 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acids (**9a-s, 10j, k, l**) required for the antimicrobial studies were synthetized by *N*-alkylation of the pyridone esters (**3a-s**) (with triethyl phosphate or with alkyl halides), and by alkaline hydrolysis of the obtained *N*-alkyl esters (**7,8**).

Ethylation was carried out with triethyl phosphate at 170-180° for 10-15 minutes, while alkylations were performed with alkyl halides (decyl bromide and allyl bromide) in ethanol, at reflux temperature, in the presence of equimolar amount of potassium carbonate, the *N*-alkyl esters (**8**) were obtained within 2-3 hours. The *N*-alkyl esters were not isolated but in four cases (**7a, 7o, 7s, 8s**), in the rest of the cases the intermediate products were subjected to alkaline hydrolysis without isolation to yield the 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acids (**9a-r, 10j, 10k, 10l**), in high purity and good yields (see Table 3).

For the further studies of the structure-activity relationships the phenyl substituent in position 5 of the pyridine ring was transformed as follows: Upon nitration of 1-ethyl-5-phenyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**9o**) with a mixture of nitric acid and sulfuric acid at 5-10° 54.1% *para*- (**9p**) and 34.7% *ortho*-nitrophenyl derivative (**9t**) were formed. Their nmr spectra showed a significant difference in the aromatic range. The phenyl protons of **9p** formed and AB system characteristic for the *p*-disubstituted benzene derivatives, giving doublets at 8.05 ppm and 8.40 ppm, with a coupling constant J = 9 Hz. In the spectrum of the *o*-nitrophenyl derivative (**9t**) a wide multiplet could be found at 7.50-8.60 ppm.



The nitro group in compound **9p** was reduced with tin in hydrochloric acid (100°, 1 hour), and the obtained 5-(*p*-aminophenyl)-1-ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**9u**) was condensed with 5-nitro-2-furancarboxaldehyde (**11**) to yield the potentially antibacterial product **9v** in excellent yield.

The prepared new 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acids (**9a-r, 9u, 9r, 10j, 10k, 10l**) were tested for antibacterial and antifungal activities against *Shigella sonnei, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus, Proteus vulgaris, Proteus mirabilis, Salmonella typhium, Streptococcus faecus, Escherichia coli, Bacillus subtilis* and *Vibrio parahaemolyticus* strains.

5-Decyl-1-ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic

acid (**9k**) and 1-ethyl-5-(*p*-chloro-benzyl)-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**9g**) showed weak activities.

1-Ethyl-5-(4-[(5-nitro-furfurylidene)amino]phenyl)-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**9v**) was active against all of the tested strains in minimal inhibitory concentrations between 2.5 and 75μg./ml.

No significant activity was found in the case of the rest of the new compounds.

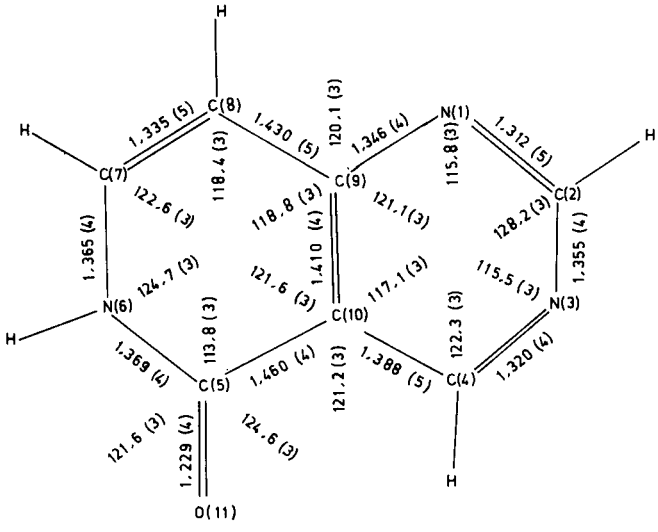


Figure 1. Bond lengths (Å) and angles (°) with their estimated standard deviations in parentheses for compound **4**.

EXPERIMENTAL

All melting points are uncorrected. The uv spectra were taken in ethanol with a Unicam SP 800 spectrophotometer, the ir spectra were recorded on a Zeiss UR 20 spectrophotometer, nmr spectra were measured with a Perkin-Elmer R-12 spectrometer using tetramethylsilane as an internal standard, and mass spectra with a MS-902 spectrometer operating at 70 eV.

Ethyl 5-(*p*-Chlorophenyl)-3-oxovalerate (**2q**).

Magnesium filings (24.3 g., 1 g-atom) were placed into a four necked, round-bottomed flask fitted with a stirrer, reflux condenser protected from moisture by a calcium chloride tube, dropping funnel and thermometer, and absolute ethanol (50 ml.) and dry tetrachloromethane (5 ml.) were added. As soon as the reaction was initiated, a mixture of ethyl acetoacetate (**2a**) (130.14 g., 1 mole), absolute ethanol (100 ml.) and absolute ether (400 ml.) was added dropwise, with vigorous stirring at a rate required for keeping the mixture boiling (during about one and a half hour).

After stirring for 4-5 hours a solution of β-(*p*-chlorophenyl)propionyl chloride (203.07 g., - 1 mole) in absolute ether (100 ml.) was added dropwise at 0-5°, within about 1 hour. The mixture was stirred at the same temperature for an additional hour, and allowed to stand overnight.

A mixture of ice (400 g.) and concentrated sulfuric acid (25 ml.) was added, the phases were separated, and the aqueous phase was extracted twice with 100 ml. of ether. The combined organic phases were washed with water (2 × 200 ml.), dried over sodium sulfate, the solvent was evaporated, and the residual α-acylacetoacetate was allowed to stand overnight with a solution of potassium hydroxide (58.8 g., 1.05 mole) in ethanol (500 ml.). The reaction mixture was poured onto ice (2 kg.) and concentrated sulfuric acid (27 ml.), and extracted with ether (4 × 200 ml.). The combined extracts were washed with water (2 × 200 ml.), dried over sodium sulfate, the solvent was distilled off, and the oily residue fractionated under vacuum, b.p. 159-162°/0.6 mm Hg, n_D^{23}: 1.5294, yield, 84.57 g. (33.2%) **2q**.

Anal. Calcd. for $C_{13}H_{15}ClO_3$ (254.72): C, 61.30; H, 5.94; Cl, 13.92. Found: C, 61.54; H, 5.79; Cl, 13.75.

Ethyl 4-Oxo-1,4-dihydro-3-pyridinecarboxylate (**3a**) and Pyrido[4,3-*d*]-pyrimidin-5(6*H*)one (**4**).

Sodium (5.75 g., 0.25 g-atom) was dissolved in absolute ethanol (75 ml.). To this solution were added ethyl acetoacetate (32.54 g. 0.25 mole) (**2a**) and 1,3,5-triazine (20.27 g., 0.25 mole) (**1**). The reaction mixture was heated under reflux for one hour, and then ethanol was distilled off. A residue was dissolved in water (200 ml.), and the solution was acidified with concentrated hydrochloric acid to *p*H = 3. On the next day the separated light brown precipitate was filtered off and washed with acetone, yield 4.35 g. (11.8%) of pyrido[4,3-*d*]pyrimidin-5(6*H*)one (**4**) were obtained (23), m.p. 298° (from water), light beige coloured crystals; uv: λ max nm (log ε), 306 (3.78), 234 (3.71); ir: ν C=O, 1710 cm^{-1}; nmr (sodium deuteroxide): δ 6.65 (d, J = 7 Hz C_8-H), 8.15 (d, J = 7 Hz C_7-H), 9.00 (s, C_2-H), 9.35 (s, C_4-H); ms: m/e (abundance) 147 (100) $C_7H_5N_3O$: 120 (75); 92 (29); 66 (7); 65 (8.4); 64 (7.8); 53 (7.6).

Anal. Calcd. for $C_7H_5N_3O$ (147.14): C, 57.14; H, 3.43; N, 28.56; O, 10.87. Found: C, 56.98; H, 3.45; N, 28.22; O, 10.88.

The crystal data is as follows: monoclinic, a = 7.275 (2), b = 3.768 (2), c = 25.089 (7) Å, β = 113.3 (1)° determined from precession photographs, V = 631.9 Å³, D_X = 1.55 g. cm^{-3}, Z = 4, μ(CuKα̅ = 1.5418 Å) 8.2 cm^{-1}, space group $P2_1/c$ from systematic absences; 968 independent reflections were collected on a Stoe semiautomatic two-circle diffractometer using Ni-filtered CuKα̅ radiation. After conventional data reduction 840 reflections with (F) - 3δ(F)>0 were taken observed. The structure was solved by direct methods and refined by the program SHELX (27). The hydrogen atom positions were determined from difference Fourier map. The final R value for the 840 observed reflections after two cycles of isotropic and three cycles of anisotropic refinement is 0.101 and 0.104 for all reflections (28). All the thermal parameters have normal value indicating that a right choice was made concerning atom type. The final coordinates are given in Table 5.

The aqueous filtrate was extracted with chloroform (5 × 100 ml.), the extracts were dried over sodium sulfate, and the solvent was evaporated. The residue was triturated with cold acetone (20 ml.), yield, 9.10 g. (21.7%) of **3a**, m.p. 226-227° (from ethanol), snow-white crystals (Lit. (22) m.p 228-229.5°). For the analytical and spectroscopical data of the product see Tables 1 and 2.

General Procedure for the Synthesis of Ethyl 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates (**3b-3s**).

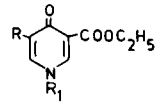
Sodium (2,3 g., 0.1 g-atom) was dissolved in 100 ml. of absolute ethanol. 4-Substituted ethyl acetoacetate (**2b-2s**) (0.1 mole) and 1,3,5-triazine (8.11 g., 0.1 mole) (**1**) were added to the sodium ethoxide solution and the mixture was stirred under reflux for one hour. The reddish-brown solution was evaporated at atmospheric pressure, the residue was dissolved in water (50 ml.), and the solution was acidified with concentrated hydrochloric acid to *p*H = 4. The mixture was allowed to stand for one day, then the separated crystals were filtered off and washed with alcohol. For the analytical, physical and spectroscopical data of the obtained esters (**3b-3s**) see Tables 1 and 2.

General Procedure for the Synthesis of the 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acids (**6b, 6f, 6h, 6l**).

A mixture of ethyl 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylate (**3b, 3f, 3h, 3l**) (0.05 mole) and 5% potassium hydroxide solution (100 ml.) was stirred at 90-100° for one hour. The solution was clarified with activated charcoal, and the filtrate was acidified with concentrated hydrochloric acid to *p*H = 2 under cooling. The separated crystals were filtered and washed with water, followed by recrystallization from a solvent given in Table 3. For m.p. yield and analytical data see Table 3, and

Table 1

Ethyl 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates and their Uv and Ir Data



Starting Material	Product	R	R_1	Yield %	M.p. °C	Appearance, Solvent of recrystallization	Formula M.W.	Analysis Calcd./Found % C	H	N	λ max nm log ε			Ir (potassium bromide) cm^{-1} ν C=O (ester)	ν C=O (ring)
2a	**3a**	H	H	21.7	226-227	white	$C_6H_5NO_3$	57.48	5.43	8.38	282	256	250	1704	1640
						96% Ethanol	167.17	57.43	5.37	8.37	3.58	4.01	3.99		
2b	**3b**	CH_3	H	54.5	226	white	$C_7H_{11}NO_3$	59.66	6.12	7.73	284	260	256i	1710	1652
						96% Ethanol	181.19	59.69	6.08	8.04	3.64	3.92	3.90		
2c	**3c**	C_2H_5	H	39.4	220	white	$C_{10}H_{13}NO_3$	61.53	6.71	7.17	285	261	256i	1710	1648
						Sublimation	195.22	61.77	6.66	7.32	3.64	3.90	3.87		
2d (11)	**3d**	C_3H_7	H	43.2	213-214	white	$C_{11}H_{15}NO_3$	63.14	7.23	6.69	286	260	255i	1710	1650
						Ethanol	209.247	63.10	7.13	7.01	3.70	3.90	3.88		
2e (12)	**3e**	$(CH_3)_2CH$	H	6.7	230	white	$C_{11}H_{15}NO_3$	63.14	7.23	6.69	285	260		1705	1645
						Ethanol	209.247	63.21	7.40	6.73	3.63	3.83			
2f (13)	**3f**	C_4H_9	H	36.4	212-213	cream-coloured	$C_{12}H_{17}NO_3$	64.56	7.67	6.27	286	260	255i	1710	1650
						Ethanol	223.274	65.00	7.83	6.32	3.68	3.91	3.88		
2g (14)	**3g**	C_6H_{13}	H	28.4	183-184	pale drab	$C_{14}H_{21}NO_3$	66.91	8.42	5.57	286	260	255i	1710	1650
						Ethanol	251.321	67.22	8.50	5.67	3.71	3.93	3.89		
2h (14)	**3h**	C_7H_{15}	H	42.1	180-182	pale drab	$C_{15}H_{23}NO_3$	67.90	8.74	5.28	285	260		1715	1650
						Ethanol	265.355	67.67	8.35	5.40	3.70	3.89			
2i (14)	**3i**	C_8H_{17}	H	33.0	167-169	pale drab	$C_{16}H_{25}NO_3$	68.79	9.02	5.01	286	260	255i	1710	1650
						Ethanol	279.38	68.92	9.05	5.18	3.74	3.94	3.91		
2j (15)	**3j**	C_9H_{19}	H	34.2	148-150	pale drab	$C_{17}H_{27}NO_3$	69.59	9.28	4.77	290	260	255i	1710	1650
						Ethanol	293.41	69.64	9.43	5.04	3.67	3.81	3.78		
2k (16)	**3k**	$C_{10}H_{21}$	H	37.7	158-160	drab powder	$C_{18}H_{29}NO_3$	70.32	9.51	4.56	287	261	256i	1710	1650
						Ethanol	307.44	70.18	9.52	4.89	3.64	3.86	3.84		
2l (16)	**3l**	$CH_2=CH-(CH_2)_7$	H	35.4	148-149	drab powder	$C_{17}H_{25}NO_3$	70.07	8.65	4.81	287	260	255i	1710	1650
						Ethanol	291.39	70.04	8.93	5.03	3.68	3.84	3.81		
2m (17)	**3m**	C_2H_3O	H	9.3	214-215	cream-coloured	$C_{10}H_{13}NO_4$	56.87	6.20	6.63	290i	272		1725	1645
						Ethanol	211.22	56.77	6.15	6.50	3.82	3.95			
2n (19)	**3n**	cyclohexyl	H	10.6	241-242	white	$C_{14}H_{19}NO_3$	67.45	7.68	5.62	287	261	257i	1710	1645
						Ethanol	249.312	67.70	7.74	5.50	3.74	3.95	3.93		
2o (20)	**3o**	C_6H_5	H	53.8	289-290	pale drab	$C_{14}H_{11}NO_3$	69.12	5.39	5.76	305	260		1714	1645
						DMF	243.264	69.38	5.11	5.81	3.76	3.64			
2p (21)	**3p**	p-NO_2-C_6H_4	H	98.0	299 dec.	pale drab	$C_{14}H_{12}N_2O_5$	58.33	4.20	9.72	330	255		1730	1650
						DMF	288.26	58.06	4.27	9.80	3.90	3.98			
2q	**3q**	p-Cl-C_6H_4-CH_2	H	49.8	253-254	white	$C_{15}H_{14}ClNO_3$	61.75	4.84	4.80	287	260	256i	1705	1650
						DMF	291.74	61.46	4.88	4.83	3.72	3.90	3.88		
								Cl: 12.15							
								12.23							
2r	**3r**	$COOCH_3$ (a)	H	30.2	256-258	white	$C_6H_5NO_5$	51.19	4.30	6.63	303	256	250	1720	1650
						Acetic Acid	211.175	51.30	4.32	6.86	3.66	3.77	3.79		
2s	**3s**	$COOC_2H_5$	H	54.5	250-251	white	$C_{11}H_{13}NO_5$	55.23	5.48	5.85	303	256	250	1715	1650
						Acetic Acid	239.23	55.10	5.50	5.84	3.69	3.75	3.79		
3a	**7a**	H	C_2H_5	75.1	112	white	$C_{10}H_{13}NO_3$	61.53	6.71	7.17	285	257		1710	1650
							195.22	61.59	6.71	7.31	3.67	4.13			
3o	**7o**	C_6H_5	C_2H_5	77.4	124-125	pale drab	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	312	270	230	1690	1650
						Ethyl acetate	271.317	70.84	6.21	5.08	3.85	3.83	4.12		
3s	**7s**	$COOC_2H_5$	C_2H_5	83.9	129-130	white	$C_{13}H_{17}NO_5$	58.42	6.41	5.24	312	263	256	1730	1650
						Ethanol	267.284	58.37	6.32	5.37	3.77	4.00	3.99		
3s	**8s**	$COOC_2H_5$	$CH_2=CH-CH_2$	69.6	92.93	pale drab	$C_{14}H_{17}NO_3$	60.21	6.14	5.01	308	262	256	1740	1650
						Ethyl acetate cyclohexane	279.295	60.98	6.66	5.23	3.77	4.03	4.04	1730 i	

(a) Dimethyl ester, i = inflexion. The ν C=O (ester) bands are very strong, the ν C=O (ring) stretching vibrations have medium intensities.

for spectroscopical data Tables 3 and 4.

Synthesis of Ethyl 1-Alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates (**7a, 7o, 7s, 8s**).

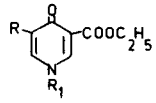
Method. A.

Ethyl 1-Ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylate (**7a**).

A mixture of ethyl 4-oxo-1,4-dihydro-3-pyridinecarboxylate (2.50 g., 0.015 mole) (**3a**), triethyl phosphate (8.20 g. 0.045 mole) and anhydrous potassium carbonate (2.07 g., 0.015 mole) was stirred at 170-180° for 15 minutes. After cooling water (25 ml.) were added, the mixture was stirred for 10 minutes at room temperature, followed by neutralization with a 5% hydrochloric acid solution. The aqueous solution was extracted with chloroform (3 × 50 ml.), the extracts were dried over sodium sulfate, and evaporated. The reddish-brown oily residue (5.3 g.) was dissolved in absolute benzene (10 ml.) and chromatographed on Kieselgel 60 (Merck, 0.2-0.5 mm) eluted with absolute benzene and with benzene containing 1-10% methanol. The appropriate fractions were combined and the solvent was evaporated, yield, 2.2 g. (75.1%) white, crystalline ester (**7a**) m.p. 112°.

Table 2

Nmr Data for Ethyl 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylates



Compound No.	Solvent	C_2-H	C_6-H	OCH_2CH_3	OCH_2CH_3		δ ppm
3a	Trifluoroacetic acid	9.20 bs	8.55 bs	4.68 q J = 7 Hz	1.50 t J = 7 Hz	C_5-H	7.55 bs
3b	Trifluoroacetic acid	9.10 bd J = 6 Hz	8.50 bd J = 6 Hz	4.67 q J = 7 Hz	1.50 t J = 7 Hz	C_5-CH_3	2.45 s
3c	Trifluoroacetic acid	9.20 bs	8.20 bs	4.68 q J = 7 Hz	1.50 t J = 7 Hz	C_5-CH_2CH_3 C_5-CH_2CH_3	1.36 t J = 7 Hz 2.91 q J = 8 Hz
3e	Trifluoroacetic acid	9.10 bd J = 6 Hz	8.50 bd J = 6 Hz	4.68 q J = 7 Hz	1.49 t J = 7 Hz	C_5-$CH(CH_3)_2$ C_5-$CH(CH_3)_2$	1.38 d J = 7 Hz 3.18-3.82 m
3h	Trifluoroacetic acid	9.09 d J = 6 Hz	8.46 d J = 6 Hz	4.65 q J = 7 Hz	1.10-1.90 m	C_5-$(CH_2)_6$-CH_3 C_5-CH_2-$(CH_2)_5$-CH_3 C_5-CH_2-$(CH_2)_5$-CH_3	0.65-1.05 m 1.10-1.90 m 2.89 t J = 8 Hz
3j	Deuteriochloroform DMSO-d_6	7.60 s	7.40 s	4.45 q J = 7 Hz	1.15-1.80 m	C_5-$(CH_2)_6$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 NH	0.70-1.05 m 1.15-1.80 m 2.40-3.00 m 9.46 s
3k	Deuteriochloroform	8.85 s	8.12 s	4.45 q J = 7 Hz	1.10-1.80 m	C_5-$(CH_2)_9$-CH_3 C_5-CH_2-$(CH_2)_6$-CH_3 C_5-CH_2-$(CH_2)_6$-CH_3 NH	0.70-1.05 m 1.10-1.80 m 2.40-2.80 m 9.46 s
3l	Trifluoroacetic acid	9.10 d J = 6 Hz	8.48 d J = 6 Hz	4.68 q J = 7 Hz	1.20-2.25 m	C_5-CH_2-$(CH_2)_6$-CH=CH_2 C_5-CH_2-$(CH_2)_6$-CH=CH_2 C_5-$(CH_2)_7$-CH=CH_2 C_5-$(CH_2)_7$-CH=CH_2	1.20-2.25 m 2.90 t J = 7 Hz 4.85-5.25 m 5.50-6.20 m
3m	Trifluoroacetic acid	8.93 bs	8.30 bs	4.68 q J = 7 Hz	1.57 t J = 7 Hz	C_5-OCH_2CH_3 C_5-OCH_2CH_3	1.50 t J = 7 Hz 4.36 q J = 7 Hz
3n	Trifluoroacetic acid	9.10 d J = 6 Hz	8.46 d J = 6 Hz	4.68 q J = 7 Hz	1.50 t J = 7 Hz	C_5-cyclohexyl	1.25-2.20 m 10H 2.80-3.40 m 1H
3r	Trifluoroacetic acid	9.40 s (b)			4.20 s		
3s	Trifluoroacetic acid	9.39 s (b)		4.70 q J = 7 Hz	1.52 t J = 7 Hz		
7a	Deuteriochloroform	8.31 d J = 2.7 Hz	7.57 dd $J_{5,6}$ = 8 Hz $J_{2,6}$ = 2.7 Hz	4.35 q J = 7 Hz	1.36 t J = 7 Hz	C_5-H NCH_2CH_3 NCH_2CH_3	6.51 d J = 8 Hz 1.50 t J = 7 Hz 4.05 q J = 7 Hz
7o	Deuteriochloroform	8.13 d J = 2.7 Hz	7.30-7.75 (a) m	4.35 q J = 7 Hz	1.36 t J = 7 Hz	NCH_2CH_3 NCH_2CH_3 C_5-phenyl	1.42 t J = 7 Hz 3.90 q J = 7 Hz 7.30-7.75 m
7s	Deuteriochloroform	8.20 s (b)		4.38 q J = 7 Hz	1.36 t J = 7 Hz	NCH_2CH_3 NCH_2CH_3	1.52 t J = 7 Hz 4.10 q J = 7 Hz
8s	Deuteriochloroform	8.10 s (b)		4.35 q	1.36 t	NCH_2CH=CH_2 NCH_2CH=CH_2 NCH_2CH=CH_2	4.61 d J = 5.5 Hz 5.20-5.65 m 5.75-6.40 m

s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. (a) C_6-H signal appears together with protons of the phenyl ring. **3d, 3f, 3g, 3i, 3o, 3p, 3q** esters were not soluble. (b) C_2-H and C_6-H signals appear together.

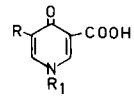
Anal. Calcd. for $C_{10}H_{13}NO_3$ (195.22): C, 61.53; H, 6.71; N, 7.17. Found: C, 61.59; H, 6.71; N, 7.31.

Ethyl 1-Ethyl-5-phenyl-4-oxo-1,4-dihydro-3-pyridinecarboxylate (**7o**).

A mixture of ethyl 5-phenyl-4-oxo-1,4-dihydro-3-pyridinecarboxylate (12.16 g., 0.05 mole) (**3o**), triethyl phosphate (27.32 g., 0.15 mole) and anhydrous potassium carbonate (6.91 g. - 0.05 mole) was allowed to react according to Method A. After evaporation of the chloroform extracts the oily, brown residue crystallized upon cooling and scratching. The crystalline material was filtered off and washed with light petrol,

Table 3

1-5-Disubstituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acids their Uv and Ir Data



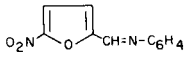
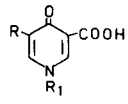
Starting Material	Product	R	R_1	Yield %	M.p. °C	Appearance, Solvent of recrystallization	Formula M.W.	Analysis Calcd./Found % C	H	N	λ max nm log ε			Ir (potassium bromide) cm^{-1} ν C=O (acid)		ν C=O (ring)
3a	**9a**	H	C_2H_5	54.2	189	white Ethanol	$C_9H_9NO_3$ 167.17	57.48 57.89	5.43 5.32	8.38 8.32	280 3.60	254 4.11		1724		1650
3b	**9b**	CH_3	C_2H_5	38.6	190	white Ethanol	$C_9H_{11}NO_3$ 181.19	59.66 59.51	6.12 6.08	7.73 7.72	285 3.52	260 3.91		1700		1645
3b	**6b**	CH_3	H	81.2	315 (a)	white Water-Acetone	$C_7H_7NO_3$ 153.14	54.90 54.87	4.59 4.70	9.15 9.27	283 3.54	255 3.83		1700i		1655
3d	**9c**	C_2H_5	C_2H_5	54.0	172	white Ethanol	$C_{10}H_{13}NO_3$ 195.22	61.53 61.02	6.71 6.76	7.17 7.00	286 3.60	260 3.97		1710		1650
3d	**9d**	C_3H_7	C_2H_5	77.2	150	white Water	$C_{11}H_{15}NO_3$ 209.25	63.14 63.10	7.23 7.31	6.69 6.56	287 3.76	260 4.10		1725		1650
3e	**9e**	$(CH_3)_2CH$	C_2H_5	77.0	132-133	white Water	$C_{11}H_{15}NO_3$ 209.25	63.14 63.56	7.23 7.32	6.69 6.75	288 3.61	261 3.93		1690		1640
3f	**9f**	C_4H_9	C_2H_5	73.1	105-106	white Ethanol	$C_{12}H_{17}NO_3$ 223.274	64.56 64.83	7.67 7.77	6.27 6.35	287 3.71	260 4.03		1715		1650
3f	**6f**	C_4H_9	H	80.2	225-226	white Water	$C_{10}H_{13}NO_3$ 195.219	61.53 61.85	6.71 6.86	7.71 7.08	283 3.55	256 3.79		1700i		1660
3g	**9g**	C_6H_{13}	C_2H_5	86.8	115-116	white Ethanol	$C_{14}H_{21}NO_3$ 251.321	66.91 67.13	8.42 8.56	5.57 5.62	287 3.70	260 4.03		1720		1650
3h	**9h**	C_7H_{15}	C_2H_5	78.2	122-123	white Ethanol	$C_{15}H_{23}NO_3$ 265.355	67.90 68.11	8.74 8.67	5.28 5.20	287 3.66	261 3.97		1700		1650
3h	**6h**	C_7H_{15}	H	71.6	215-216	cream-coloured Ethanol	$C_{13}H_{19}NO_3$ 237.30	65.80 65.76	8.07 8.12	5.90 6.04	282 3.62	254 3.85			1650	
3i	**9i**	C_8H_{17}	C_2H_5	88.0	99-100	pale drab Ethanol-water	$C_{16}H_{25}NO_3$ 279.38	68.79 69.10	9.02 9.07	5.01 4.94	287 3.68	260 4.02		1715		1650
3j	**9j**	C_9H_{19}	C_2H_5	79.0	114-115	white Ethanol	$C_{17}H_{27}NO_3$ 293.41	69.59 69.76	9.28 9.12	4.77 4.80	284 3.65	260 3.98		1700		1650
3j	**10j**	C_9H_{19}	CH_2=CH-CH_2	81.8	85-86	drab Cyclohexane	$C_{18}H_{27}NO_3$ 305.43	70.79 71.10	8.91 8.98	4.59 4.66	283 3.68	262 4.02		1680		1650
3k	**10k**	C_9H_{19}	$C_{10}H_{21}$	72.8	77-78	white Petroleum ether	$C_{25}H_{43}NO_3$ 405.63	74.03 74.31	10.69 10.80	3.45 3.51	284i 3.66	261 4.01		1715		1650
3k	**9k**	$C_{10}H_{21}$	C_2H_5	72.0	107-108	white Propanol	$C_{16}H_{29}NO_3$ 307.44	70.32 70.34	9.51 9.11	4.56 4.57	288 3.66	261 4.10		1720		1650
3l	**9l**	CH_2=CH-$(CH_2)_7$	C_2H_5	85.0	85-86	white Ethyl acetate-petroleum ether	$C_{17}H_{29}NO_3$ 291.39	70.07 70.20	8.65 8.71	4.81 4.86	287 3.62	260 3.96		1730		1650
3l	**6l**	CH_2=CH-$(CH_2)_7$	H	87.2	194-198	pale drab Ethanol-water	$C_{15}H_{21}NO_3$ 263.34	68.41 68.05	8.04 8.01	5.32 5.63	283 3.60	254 3.80		1700	1680	1655
3l	**10l**	CH_2=CH-$(CH_2)_7$	CH_2=CH-CH_2	73.8	71-73	pale drab Ethanol-water	$C_{18}H_{29}NO_3$ 303.405	71.26 71.47	8.31 8.13	4.62 4.71	285i 3.64	262 3.96		1720		1655
3m	**9m**	C_2H_5O	C_2H_5	74.0	164	white Ethanol	$C_{10}H_{13}NO_4$ 211.22	56.87 57.13	6.20 6.09	6.63 6.72	275 4.01			1720		1635
3n	**9n**	cyclohexyl	C_2H_5	88.0	152-153	white Isopropyl alcohol	$C_{14}H_{19}NO_3$ 249.312	67.45 67.72	7.68 7.81	5.62 5.53	289 3.71	262 4.03		1725		1645
3o	**9o**	C_6H_5	C_2H_5	59.0	173-174	pale yellow Ethanol	$C_{14}H_{13}NO_3$ 243.264	69.12 69.42	5.39 5.42	5.76 5.70	308 3.85	268 3.77		1730		1650
3p	**9p**	*p*-NO_2-C_6H_4	C_2H_5	84.2	247	yellow DMF	$C_{14}H_{12}N_2O_5$ 288.258	58.33 58.05	4.20 4.37	9.72 9.72	326 4.07	257 4.14		1740		1650
9o	**9t**	*o*-NO_2-C_6H_4	C_2H_5	34.7	140-145	terracotta	$C_{14}H_{12}N_2O_5$ 288.258	58.33 58.40	4.20 4.20	9.72 9.80	305	258		1725		1645
9p	**9u**	*p*-NH_2-C_6H_4	C_2H_5	28.4	218-220	pale yellow	$C_{14}H_{14}N_2O_3$ 258.278	65.11 65.19	5.46 5.17	10.85 10.83	331 3.94	249 4.27		1700		1635
9u	**9v**		C_2H_5	84.0	268-270	yellow DMF	$C_{19}H_{15}N_3O_6$ 381.347	59.84 59.61	3.97 4.09	11.02 11.07	371	318	237	1685		1635
3q	**9q**	*p*-Cl-C_6H_4-CH_2	C_2H_5	83.8	210	white Ethanol	$C_{15}H_{14}ClNO_3$ 291.74	61.75 62.04 Cl: 12.15 12.02	4.84 4.92	4.80 4.83	292 3.70	261 3.99		1720		1650
3r or **3s**	**9r**	COOH	C_2H_5	88.0	266-267	white DMF	$C_9H_9NO_5$ 211.176	51.19 51.28	4.30 4.39	6.63 6.69	307 3.73	257i 3.89	254 3.89	1740		1650

Table 4

Nmr Data for 1,5-Disubstituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acids



Compound No.	Solvent	C_2-H	C_6-H	N-CH_2-CH_3	N-CH_2-CH_3		δ ppm
9a	Sodium deuteroxide	8.19 d J = 2.7 Hz	7.84 dd $J_{5,6}$ = 8 Hz $J_{2,6}$ = 2.7 Hz	4.08 q J = 7 Hz	1.42 t J = 7 Hz	C_5-H	6.60 d J = 8 Hz
9b	Sodium deuteroxide	8.11 d J = 2.7 Hz	7.83 bs	4.06 q J = 7 Hz	1.43 t J = 7 Hz	C_5-CH_3	2.06 s
6b	Trifluoroacetic acid	9.24 bs	8.59 bs			C_5-CH_3	2.50 s
9c	Sodium deuteroxide	8.12 d J = 2.7 Hz	7.78 d J = 2.7 Hz	4.08 q J = 7 Hz	1.44 t J = 7 Hz	C_5-CH_2-CH_3 C_5-CH_2-CH_3	1.14 t J = 7 Hz 2.50 q J = 7 Hz
9d	Deuteriochloroform	8.65 d J = 2 Hz	7.76 d J = 2 Hz	4.26 q J = 7 Hz	1.60 t J = 7 Hz	C_5-$(CH_2)_2$-CH_3 C_5-CH_2-CH_2-CH_3 C_5-CH_2-CH_2-CH_3 COOH	1.00 t J = 7 Hz 1.35-1.95 m 2.59 t J = 7 Hz 17.10 bs
9e	Deuteriochloroform	8.58 d J = 2 Hz	7.55 d J = 2 Hz	4.18 q J = 7 Hz	1.55 t J = 7 Hz	C_5-CH$(CH_3)_2$ C_5-CH$(CH_3)_2$	1.24 d J = 7 Hz 3.30 qi J = 7 Hz
9f	Deuteriochloroform	8.65 s	7.75 s	4.26 q J = 7 Hz	1.58 t J = 7 Hz	C_5-$(CH_2)_3$-CH_3 C_5-CH_2-$(CH_2)_2$-CH_3 C_5-CH_2-$(CH_2)_2$-CH_3 COOH	0.75-1.10 m 1.20-1.80 m 2.60 t J = 7 Hz 16.75 bs
6f	Trifluoroacetic acid	9.18 bs	8.51 bs			C_5-$(CH_2)_3$-CH_3 C_5-CH_2-$(CH_2)_2$-CH_3 C_5-CH_2-$(CH_2)_2$-CH_3	0.80-1.15 m 1.25-2.00 m 2.90 t J = 8 Hz
9g	Deuteriochloroform	8.66 d J = 2 Hz	7.76 d J = 2 Hz	4.26 q J = 7 Hz	1.57 t J = 7 Hz	C_5-$(CH_2)_5$-CH_3 C_5-CH_2-$(CH_2)_4$-CH_3 C_5-CH_2-$(CH_2)_4$-CH_3 COOH	0.70-1.05 m 1.15-1.85 m 2.60 t J = 7 Hz 16.78 s
9h	Deuteriochloroform	8.61 d J = 2.7 Hz	7.67 d J = 2.7 Hz	4.20 q J = 7 Hz	1.57 t J = 7 Hz	C_5-$(CH_2)_6$-CH_3 C_5-CH_2-$(CH_2)_5$-CH_3 C_5-CH_2-$(CH_2)_5$-CH_3	0.70-1.05 m 1.15-1.80 m 2.60 t J = 7.5 Hz
9i	Deuteriochloroform	8.61 d J = 2 Hz	7.66 s	4.20 q J = 7 Hz	1.58 t J = 7 Hz	C_5-$(CH_2)_7$-CH_3 C_5-CH_2-$(CH_2)_6$-CH_3 C_5-CH_2-$(CH_2)_6$-CH_3 COOH	0.70-1.05 m 1.14-1.95 m 2.60 t J = 7 Hz 16.94 bs
9j	Deuteriochloroform	8.60 d J = 2.7 Hz	7.59 d J = 2.7 Hz	4.16 q J = 7 Hz	1.57 t J = 7 Hz	C_5-$(CH_2)_8$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 COOH	0.70-1.05 m 1.15-1.80 m 2.60 t J = 7 Hz 16.40 bs
10j	Deuteriochloroform	8.52 d J = 2 Hz	7.50 d J = 2 Hz			C_5-$(CH_2)_8$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 N-CH_2-CH=CH_2 N-CH_2-CH=CH_2 N-CH_2-CH=CH_2	0.70-1.05 m 1.15-1.85 m 2.58 t J = 8 Hz 4.68 d J = 5.3 Hz 5.20-5.65 m 5.80-6.45 m
10k	Deuteriochloroform	8.52 d J = 2 Hz	7.50 bs			C_5-$(CH_2)_8$-CH_3 N-$(CH_2)_9$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 N-CH_2-$(CH_2)_8$-CH_3 C_5-CH_2-$(CH_2)_7$-CH_3 N-CH_2-$(CH_2)_8$-CH_3	} 0.70-1.50 m } 1.15-2.05 m 2.60 t J = 7 Hz 4.05 t J = 7 Hz
9k	Deuteriochloroform	8.59 d J = 2.7 Hz	7.60 d J = 2.7 Hz	4.19 q J = 7 Hz	1.57 t J = 7 Hz	C_5-$(CH_2)_9$-CH_3 C_5-CH_2-$(CH_2)_8$-CH_3 C_5-CH_2-$(CH_2)_8$-CH_3 COOH	0.70-1.10 m 1.15-1.80 m 2.60 t J = 7 Hz 16.47 bs

Table 4 continued

Compound No.	Solvent	C_2-H	C_6-H	N-C*H*$_2$-CH$_3$	N-CH$_2$-C*H*$_3$		δ ppm
9l	Deuteriochloroform	8.70 d J = 2.7 Hz	7.76 d J = 2.7 Hz	4.25 q J = 7 Hz	1.58 t J = 7 Hz	C_5-CH$_2$-(CH$_2$)$_6$-CH=CH$_2$	1.20-2.30 m
						C_8-CH$_2$-(CH$_2$)$_6$-CH=CH$_2$	2.61 t J = 7 Hz
						C_5-(CH$_2$)$_7$-CH=CH$_2$	4.85-5.25 m
						C_5-(CH$_2$)$_7$-CH=CH$_2$	5.60-6.30 m
						COOH	16.55 bs
6l	Trifluoroacetic acid	9.15 bs	8.50 bs			C_5-CH$_2$(CH$_2$)$_6$-CH=CH$_2$	1.20-2.20 m
						C_8-CH$_2$-(CH$_2$)$_6$-CH=CH$_2$	2.91 t J = 7 Hz
						C_5-(CH$_2$)$_7$-CH=CH$_2$	4.80-5.20 m
10l	Deuteriochloroform	8.50 d J = 2 Hz	7.56 s			C_5-CH$_2$-(CH$_2$)$_6$-CH=CH$_2$	1.10-2.25 m
						C_8-CH$_2$-(CH$_2$)$_6$-CH=CH$_2$	2.62 t J = 7 Hz
						N-CH$_2$-CH=CH$_2$	4.70 d J = 5 Hz
						C_5-(CH$_2$)$_7$-CH=CH$_2$	4.55-5.32 m
						N-CH$_2$-CH=CH$_2$	5.40-6.40 m
9m	Deuteriochloroform	8.62 d	7.86 d	4.14 q	1.43 t	C_5-OCH$_2$-CH$_3$	1.52 t J = 7 Hz
	DMSO-d_6	J = 2 Hz	J = 2 Hz	J = 7 Hz	J = 7 Hz	C_5-OCH$_2$-CH$_3$	4.28 q J = 7 Hz
						COOH	16.30 bs
9n	Deuteriochloroform	8.63 d J = 2.7 Hz	7.57 d J = 2.7 Hz	4.20 q J = 7 Hz	1.57 t J = 7 Hz	C_5-cyclohexyl	1.00-2.15 m 10H
							2.70-3.20 m 1H
						COOH	16.55 s
9o	Sodium deuteroxide	8.20 d J = 2.7 Hz	7.70 d J = 2.7 Hz	4.07 q J = 7 Hz	1.47 t J = 7 Hz	C_5-phenyl	7.54 s
9p	DMSO-d_6	8.95 bd	8.68 bd	4.36 q J = 7 Hz	1.52 t J = 7 Hz	C_5-(*p*-NO$_2$)-phenyl	8.05 d J = 9 Hz
							8.40 d J = 9 Hz
						COOH	16.40 bs
9t	DMSO-d_6	9.02 d J = 2 Hz	8.68 d J = 2 Hz	4.40 q J = 7 Hz	1.53 t J = 7 Hz	C_5-(*o*-NO$_2$)-phenyl	7.50-8.60 m
9u	DMSO-d_6	8.80 bd	8.35 s	4.32 q J = 7 Hz	1.47 t J = 7 Hz	C_5-(*p*-NH$_2$)-phenyl	6.73 d J = 9 Hz
							7.58 d J = 9 Hz
						COOH	17.10 bs
9q	DMSO-d_6	8.86 d J = 2.7 Hz	8.34 d J = 2.7 Hz	4.27 q J = 7 Hz	1.44 t J = 7 Hz	C_5-CH$_2$-C$_6$H$_4$-Cl-*p*	3.10 s
						C_5-CH$_2$-C$_6$H$_4$-Cl-*p*	7.42 s
						COOH	16.63 bs

qi = quintet. **6h**, **9r** and **9v** acids were insoluble.

Table 5

Fractional coordinates, estimated standard deviations are given in parentheses for compound **4**

Atom			
N (1)	0.7255 (5)	0.4216 (10)	0.1999 (1)
C (2)	0.8542 (6)	0.2720 (13)	0.1822 (1)
N (3)	0.8246 (5)	0.1653 (11)	0.1279 (1)
C (4)	0.6426 (6)	0.2160 (12)	0.0881 (2)
C (5)	0.2897 (6)	0.4119 (11)	0.0566 (2)
N (6)	0.1599 (5)	0.5739 (9)	0.0763 (1)
C (7)	0.2067 (6)	0.6744 (12)	0.1324 (2)
C (8)	0.3885 (6)	0.6287 (12)	0.1742 (2)
C (9)	0.5402 (6)	0.4710 (10)	0.1591 (1)
C (10)	0.4915 (5)	0.3682 (11)	0.1010 (1)
O (11)	0.2368 (4)	0.3178 (10)	0.0059 (1)
H (2)	0.992	0.233	0.212
H (4)	0.613	0.142	0.047
H (6)	0.021	0.622	0.047
H (7)	0.099	0.784	0.142
H (8)	0.418	0.708	0.215

yield: 10.5 g. (77.4%) of the ester **7o** m.p. 124-125°, (from ethyl acetate) light beige coloured crystals.

Anal. Calcd. for $C_{16}H_{17}NO_3$ (271.317): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.84; H, 6.31; N, 5.08.

Diethyl 1-Ethyl-4-oxo-1,4-dihydro-3,5-pyridinedicarboxylate (**7s**).

The diester **7s** was prepared according to Method A, starting from diethyl 4-oxo-1,4-dihydro-3,5-pyridinedicarboxylate, yield, (83.9%), m.p. 129-130°, (from ethanol), snow-white crystals.

Anal. Calcd. for $C_{13}H_{17}NO_5$ (267.284): C, 58.42; H, 6.41; N, 5.24. Found: C, 58.37; H, 6.32; N, 5.37.

Method B.

Diethyl 1-Allyl-4-oxo-1,4-dihydro-3,5-pyridinedicarboxylate (**8s**).

A mixture of diethyl 4-oxo-1,4-dihydro-3,5-pyridinedicarboxylate (11.96 g., 0.05 mole) (**3s**), allyl bromide (9.1 g., 0.075 mole), anhydrous potassium carbonate (6.9 g., 0.05 mole) and absolute ethanol (500 ml.) was stirred under reflux for one and a half hours. The solvent was evaporated under vacuum, the residue was dissolved in water (150 ml.) and extracted with methylene chloride (3 × 80 ml.). The organic extracts were dried over sodium sulfate, evaporated, and the residue was triturated with light petrol, yield, 9.7 g. (69.6%) of a cream-coloured, crystalline **8s** m.p. 92-93° (ethyl acetate-cyclohexane).

Anal. Calcd. for $C_{14}H_{17}NO_5$ (279.295): C, 60.21; H, 6.14; N, 5.01. Found: C, 60.38; H, 6.46; N, 5.23.

For the spectroscopic data of the esters **7a**, **7o**, **7s** and **8s** see Tables 1 and 2.

Preparation of 1-Ethyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acids (**9a-r**).

A mixture of ethyl 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylate (0.08 mole) (**3a-s**), triethyl phosphate (4.36 g., 0.24 mole) and anhydrous potassium carbonate (11.0 g., 0.08 mole) was stirred at 170-180° for 15 minutes. Potassium hydroxide solution (5%) (500 ml.) was added to the reaction mixture at 80-90°, and the mixture was stirred at 90-100° for one hour. The hot solution was treated with activated charcoal, and acidified with concentrated hydrochloric acid *p*H = 2-3. On the next day the separated crystalline material was filtered off and washed with water. The obtained carboxylic acids **9a-r** were recrystallized from the solvents given in Table 3. For m.p., yield, analytical data see Table 3, and for spectroscopic data Tables 3 and 4.

Preparation of 1-Alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acids (**10j, 10k, 10l**).

A mixture of ethyl 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylate (0.02 mole) (**3j, 3l**), allyl bromide (or decyl bromide) (0.025 mole), anhydrous potassium carbonate (2.76 g., 0.02 mole) and absolute ethanol (40 ml.) was stirred under reflux for 3 hours, followed by removal of the ethanol at atmospheric pressure. The brown, oily residue was dissolved in methylene chloride (50 ml.), and the inorganic salts were removed by washing with water (3 × 50 ml.). The organic phase was dried over sodium sulfate, and evaporated under vacuum. The oily residue was hydrolysed without further purification with a 5% potassium hydroxide solution (115 ml.) at 90-100° for one hour. The hot solution was treated with activated charcoal, and acidified under cooling with concentrated hydrochloric acid to *p*H = 2. The precipitate was filtered off and washed with water. The obtained acids (**10j, 10k**, and **10l**) were recrystallized from the solvents given in Table 3. For the spectroscopical data see Tables 3 and 4.

Nitration of 1-Ethyl-5-phenyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acid (**9o**).

A mixture of 100% nitric acid (5 ml.) and concentrated sulfuric acid (7 ml.) was cooled to 10°, and added dropwise to 1-ethyl-5-phenyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (12.16 g., 0.05 mole) (**9o**) under stirring and external ice-cooling. The temperature rose upon addition of a few drops of the acid mixture from 0° to 26°. The acid mixture was added at 5-10° within 75 minutes, and the reaction mixture was stirred at 25-26° for additional two and a half hours. The red reaction mixture was then poured into ice-water (220 ml.), whereupon a brick-red precipitate was formed. The *p*H of the mixture was adjusted with a 10% sodium hydrogen sulfate solution to 1-1.5, the precipitate was filtered off and washed with water and acetone (the latter solvent partially dissolved the solids). In this manner 7.8 g. (yield, 54.1%) of 1-ethyl-5-(*p*-nitrophenyl)-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**9p**) were obtained, m.p. 216-222° (DMF). The uv, ir and nmr spectra were identical with those of the carboxylic acid **9p** obtained by ethylation and hydrolysis of the ester **3p**. From the acetone washings by evaporation and trituration with water 5.0 g. (yield, 34.7%) of the ortho-isomer (**9t**) could be isolated, m.p. 140-145°, under decomposition.

5-(*p*-Aminophenyl)-1-ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acid (**9u**).

Concentrated hydrochloric acid (50 ml.) was added dropwise within half an hour to a stirred mixture of 1-ethyl-5-(*p*-nitrophenyl)-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (8.64 g., 0.03 mole) (**9p**) and granulated tin (15 g., 0.165 g-atom) (the temperature rose during the addition to 85°), and then the reaction mixture was stirred at 100° for one hour. Upon cooling a yellow crystalline product separated, which was filtered off, washed with a little amount of water and ethanol, and dried. In this manner 10.3 g. of the **9u**·hydrochloride melting at 290-291° under decomposition was obtained. This salt was dissolved in hot water (400 ml.), the solution was filtered, and was neutralized under cooling with a 5% sodium hydroxide solution to *p*H = 6.2-6.5, yield, 2.2 g. (28.4%) of the yellow 5-(*p*-aminophenyl)derivative (**9u**) melting at 218-220° was obtained.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$ (258.278): C, 65.11; H, 5.46; N, 10.85. Found: C, 65.19; H, 5.17; N, 10.83.

Preparation of 1-Ethyl-5-[4-([5-nitrofurfurylidene]amino)phenyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic Acid (**9r**).

To a suspension of 5-(*p*-aminophenyl)-1-ethyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (2.58 g., 0.01 mole) in hot absolute ethanol (100 ml.) a solution of 5-nitro-2-furancarboxaldehyde (1.41 g., 0.01 mole) in absolute ethanol (20 ml.) was added at once, and the mixture was stirred on a steam bath for one hour. The separated orange-coloured crystals were filtered off and washed with ethanol on the next day, yield, 3.2 g. (84.0%) of the acid **9r** was obtained, m.p. 268-270°, under decomposition (from DMF). The product formed mustard-yellow crystals.

Anal. Calcd. for $C_{19}H_{15}N_3O_6$ (381.347): C, 59.84; H, 3.97; N, 11.02. Found: C, 59.61; H, 4.09; N, 11.07.

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