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4-HYDROXY-2-QUINOLONES. 108*. N-R-AMIDES OF 9-FLUORO-1-HYDROXY-5-METHYL-3-OXO-6,7-DIHYDRO-3H,5H-PYRIDO[3,2,1-*ij*]QUINOLINE-2-CARBOXYLIC ACID AND THEIR ANTITUBERCULAR ACTIVITY

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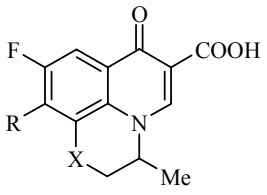
The reaction of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline with triethylmethanetricarboxylate gives di(9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-ij]quinolin-2-yl)methane and ethyl 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-ij]quinoline-2-carboxylate from which alkyl-, dialkylaminoalkyl-, and hetarylamides as well as hydrazides were prepared. The structure and antitubercular properties of the compounds synthesized are discussed.

Keywords: heterocyclic tricarbonylmethanes, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid esters and amides, antitubercular activity, X-ray structural analysis.

Fluoroquinolone preparations occupy an important place in the contemporary arsenal of antibacterial chemotherapeutic agents and amongst these $C_{(8)}/N_{(1)}$ annelated tricyclic derivatives of the general structure **1** can be mentioned. They are noted for their high activity and good pharmacokinetic properties [2, 3]. Up to recent times it was considered that the modification of the carboxyl group of fluoroquinolones leads to a marked lowering of antimicrobial activity and carboxy derivatives can be active only in examples where they are readily converted to the starting acids *in vivo*. However, this claim has gradually been disproved by many investigations. As a result there have appeared the so called "double action" antibiotics which are esters of



1a–e

1 a X = CH_2, R = H (flumequine); **b** X = CH_2, R = imidazol-1-yl (S-25932);
c X = CH_2, R = 4-methylpiperazin-1-yl (vebufloxacin); **d** X = O, R = 4-methylpiperazin-1-yl (ofloxacin);
e X = S, R = 4-methylpiperazin-1-yl (rufloxacin)

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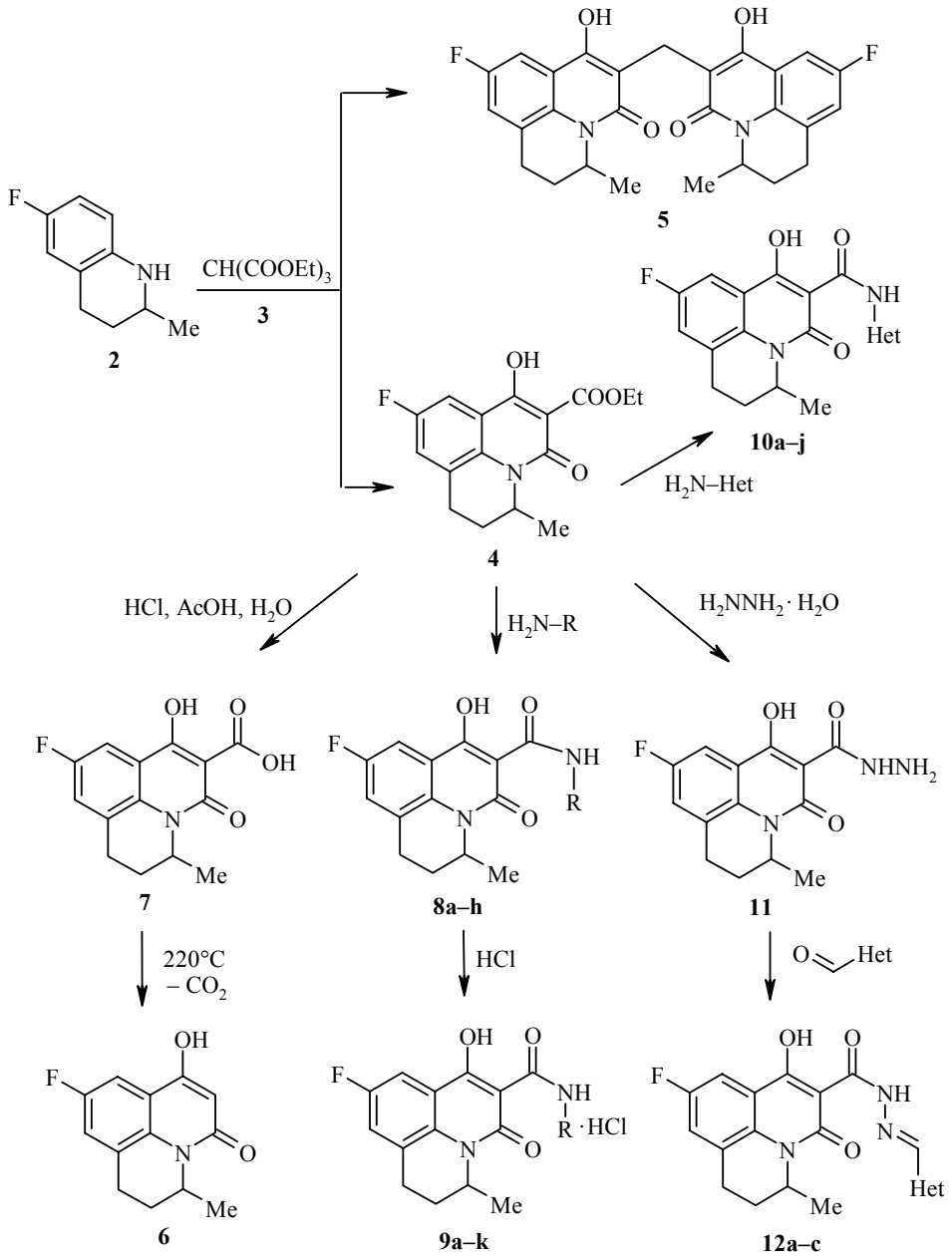
fluoroquinolone carboxylic acids and cephalosporins [4]. In a number of cases 3-quinolinecarboxamides and their cyclic analogs also show greater activity than the starting fluoroquinolones [3]. In addition, amidation has led to the appearance of novel, useful properties including antiherpes [5], antiallergy [6], antitumor [7], and other forms of biological activity.



8 a R = 2-chlorobenzyl, **b** R = 2-(3,4-dimethoxyphenyl)ethyl, **c** R = 3-phenylpropyl, **d** R = furfuryl, **e** R = tetrahydrofurfuryl, **f** R = 2-picolyl, **g** R = 3-picolyl, **h** R = 4-picolyl; **9 a** R = 2-dimethylaminoethyl, **b** R = 2-ethylaminoethyl, **c** R = 2-(2-hydroxyethylamino)ethyl, **d** R = 2-diethylaminoethyl, **e** R = 3-dimethylaminopropyl, **f** R = 3-diethylaminopropyl, **g** R = 1-ethylpyrrolidin-2-ylmethyl, **h** R = 2-piperazin-1-ylethyl, **i** R = 2-morpholin-4-ylethyl, **j** R = 3-morpholin-4-ylpropyl, **k** R = 3-piperidin-1-ylpropyl; **10 a** Het = pyridin-4-yl, **b** Het = pyridin-3-yl, **c** Het = pyridin-2-yl, **d** Het = 3-methylpyridin-2-yl, **e** Het = 4-methylpyridin-2-yl, **f** Het = 5-methylpyridin-2-yl, **g** Het = 6-methylpyridin-2-yl, **h** Het = 3-hydroxypyridin-2-yl, **i** Het = pyrimidin-2-yl, **j** Het = pyrazin-2-yl; **12 a** Het = pyridin-4-yl, **b** Het = pyridin-3-yl, **c** Het = pyridin-2-yl

With the above in mind it was of interest to extend the search for potential antitubercular agents and we have carried out this for a series of amidated derivatives of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid including the scope of structural analogs of flumequine **1a**. 6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**2**) was condensed with triethylmethanetricarboxylate (**3**) according to a previous report [8] with a slight modification. With steric hindrance at the NH group of quinoline **2** due to the neighboring methyl group in mind the reaction was carried out not with an equivalent but with a 10% excess of the triester **3**. The ethyl 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylate (**4**) formed was separated from the reaction mixture as the water soluble 4-O-sodium salt which was then acidified to give the target 4-OH form.

According to X-ray analytical data (Fig. 1) two molecules (**A** and **B**) are found in the symmetrically independent part of the crystal unit cell of this compound and they differ in the conformation of the partially hydrogenated ring and the ester group. In molecule **A** the dihydropyridone ring is planar but in molecule **B** this fragment is found to have the conformation of a strongly distorted *chair*. Atoms $N_{(1)}$ and $C_{(12)}$ deviated from the plane of the remaining ring atoms by 0.08 and 0.12 Å respectively. Some differences are also seen in the conformation of the tetrahydro ring $N_{(1)}C_{(1)}\cdots C_{(4)}C_{(9)}$. In molecule **A** this has a *chair* conformation (deviation of atom $C_{(2)}$ = -0.69Å) and in **B** the *chair* is distorted to a *half-chair* (deviations of $C_{(1)}$ and $C_{(2)}$ 0.09 and -0.60 Å respectively). In both molecules the methyl group $C_{(16)}$ is found in an axial position with torsional angles $C_{(9)}$–$N_{(1)}$–$C_{(1)}$–$C_{(16)}$ 92.7(5)° in **A** and 94.0(6)° in **B**.

The ester group has a transoid conformation (torsional angles $C_{(11)}$–$C_{(13)}$–$O_{(4)}$–$C_{(14)}$ -178.5(5)° in **A** and 179.0(4)° in **B** and $C_{(13)}$–$O_{(4)}$–$C_{(14)}$–$C_{(15)}$ 165.3(6)° in **A** and 173.9(5)° in **B)** and is somewhat rotated relative to the plane of the quinolone fragment (torsional angles $C_{(10)}$–$C_{(11)}$–$C_{(13)}$–$O_{(3)}$ -6.5(8)° in **A** and -7.3(7)° in **B**) but this does not have a marked effect of the reactivity.

The formation of a 3D lattice by intra- and intermolecular hydrogen bonds $O_{(1A)}$–H···$O_{(3A)}$ 2.05 Å, (angle $O_{(1A)}$–H···O 113°), $O_{(1A)}$–H···$O_{(3B)}$ 2.43 Å (angle O–H···O 128°), $O_{(1B)}$–H···$O_{(3A)}$ 2.46 Å (angle O–H···O 146°), $C_{(3A)}$–H···$O_{(3B')}$ (1 - *x*, -*y*, -*z*) 2.52 Å (angle C–H···O 144°), $C_{(3B)}$–H···$O_{(2A'')}$ (-*x*, 1 - *y*, -*z*) 2.44 Å (angle C–H···O 170°) leads to a lengthening of the $C_{(12A)}$=$O_{(2A)}$ 1.243(6) Å and $C_{(13A)}$=$O_{(3A)}$ 1.256(6) Å bonds when compared with the mean value of 1.210 Å [9].

It should also be noted that the separated compound **4** proved to be not the only reaction product of quinoline **2** with the triester **3** since work up of the reaction mixture with aqueous sodium carbonate solution gave a minor insoluble fraction. Bearing in mind previous similar work [1] it was logical to propose that the

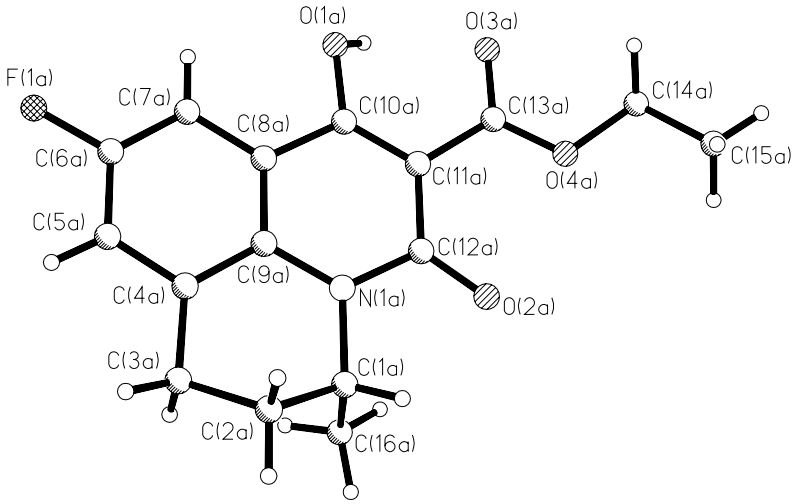


Fig. 1. Structure and atomic numbering for the molecule of ester **4**.

TABLE 1. Characteristics of the 9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid N-R-Amides **8-10**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
8a	$C_{21}H_{18}ClFN_2O_3$	62.81 / 62.93	4.44 / 4.53	6.85 / 6.99	177-179	94
8b	$C_{24}H_{25}FN_2O_5$	65.40 / 65.44	5.81 / 5.72	6.27 / 6.36	124-126	95
8c	$C_{23}H_{23}FN_2O_3$	70.10 / 70.04	5.95 / 5.88	7.02 / 7.10	103-105	88
8d	$C_{19}H_{17}FN_2O_4$	64.09 / 64.04	4.70 / 4.81	7.94 / 7.86	142-144	97
8e	$C_{19}H_{21}FN_2O_4$	63.41 / 63.32	5.76 / 5.87	7.65 / 7.77	131-133	83
8f	$C_{20}H_{18}FN_3O_3$	65.31 / 65.39	4.90 / 4.94	11.37 / 11.44	126-128	86
8g	$C_{20}H_{18}FN_3O_3$	65.46 / 65.39	4.86 / 4.94	11.51 / 11.44	162-164	90
8h	$C_{20}H_{18}FN_3O_3$	65.48 / 65.39	4.99 / 4.94	11.44 / 11.38	170-172	92
9a	$C_{18}H_{22}FN_3O_3 \cdot HCl$	56.44 / 56.32	6.15 / 6.04	10.88 / 10.95	166-168	82
9b	$C_{18}H_{22}FN_3O_3 \cdot HCl$	56.30 / 56.32	6.00 / 6.04	10.91 / 10.95	235-237	85
9c	$C_{18}H_{22}FN_3O_4 \cdot HCl$	54.14 / 54.06	5.72 / 5.80	10.43 / 10.51	197-199	77
9d	$C_{20}H_{26}FN_3O_3 \cdot HCl$	58.40 / 58.32	6.70 / 6.61	10.14 / 10.20	240-242	84
9e	$C_{19}H_{24}FN_3O_3 \cdot HCl$	57.27 / 57.36	6.39 / 6.33	10.67 / 10.56	214-216	80
9f	$C_{21}H_{28}FN_3O_3 \cdot HCl$	59.34 / 59.22	6.96 / 6.86	9.98 / 9.87	177-179	76
9g	$C_{21}H_{26}FN_3O_3 \cdot HCl$	59.41 / 59.50	6.53 / 6.42	9.82 / 9.91	205-207	88
9h	$C_{20}H_{25}FN_4O_3 \cdot 2HCl$	52.00 / 52.07	5.77 / 5.90	12.01 / 12.14	238-240	83
9i	$C_{20}H_{24}FN_3O_4 \cdot HCl$	56.50 / 56.40	5.83 / 5.92	9.97 / 9.86	181-183	89
9j	$C_{21}H_{26}FN_3O_4 \cdot HCl$	57.46 / 57.34	6.28 / 6.19	9.50 / 9.55	215-217	84
9k	$C_{22}H_{28}FN_3O_3 \cdot HCl$	60.30 / 60.34	6.57 / 6.67	9.67 / 9.59	237-239	75
10a	$C_{19}H_{16}FN_3O_3$	64.69 / 64.58	4.68 / 4.56	11.77 / 11.89	213-215	86
10b	$C_{19}H_{16}FN_3O_3$	64.71 / 64.58	4.65 / 4.56	11.95 / 11.89	206-208	85
10c	$C_{19}H_{16}FN_3O_3$	64.50 / 64.58	4.49 / 4.56	11.80 / 11.89	238-240	80
10d	$C_{20}H_{18}FN_3O_3$	65.47 / 65.39	4.99 / 4.94	11.37 / 11.44	180-182	77
10e	$C_{20}H_{18}FN_3O_3$	65.50 / 65.39	4.85 / 4.94	11.48 / 11.44	251-253	88
10f	$C_{20}H_{18}FN_3O_3$	65.52 / 65.39	5.03 / 4.94	11.37 / 11.44	256-258	83
10g	$C_{20}H_{18}FN_3O_3$	65.30 / 65.39	4.88 / 4.94	11.51 / 11.44	222-224	90
10h	$C_{19}H_{16}FN_3O_4$	61.67 / 61.79	4.48 / 4.37	11.47 / 11.38	225-227	75
10i	$C_{18}H_{15}FN_4O_3$	61.13 / 61.01	4.20 / 4.27	15.94 / 15.81	264-266	73
10j	$C_{18}H_{15}FN_4O_3$	61.11 / 61.01	4.33 / 4.27	15.90 / 15.81	246-248	86

fraction insoluble in base is the result of the amidation of compound **2** at one, two or all three ester groups of the methanetricarboxylate **3**. None the less, analysis of the ^{1}H NMR spectrum shows that the given substance contains at least one 2-substituted 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]-quinoline fragment (and not 6-fluoro-2-methyl-1,2,3,4-tetrahdroquinolylamide as proposed). The carbethoxy groups are absent in the sample and the singlet with relative integrated intensity of one proton at 3.87 ppm is unlikely to be identified as a CH group of a methanetricarboxylic acid since the mono-, di-, and triamides give a signal at a much lower field (mean value 5.5 ppm [1]).

Chromato-mass spectrometric analysis has shown that the compound analyzed is a single substance with molecular weight 478. Hence its composition must include not one but two pyridoquinoline rings combined with one methylene unit since the primary decomposition of the molecular ion is accompanied by fission of the $HetCH_2$–Het bond to form two fragments with *m/z* 246 and 232 respectively. Thus combination of the ^{1}H NMR and mass spectrometric data shows that the side product of the condensation of compound **2** with triester **3** is di(9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinolin-2-yl)methane (**5**).

The formation of analogous side products has not been noted in any of the previously reported reactions of triethylmethanetricarboxylate with N-alkylamines [10], diphenylamine [11], indoline [1, 12], 1,2,3,4-tetrahydroquinoline, or azaheterylamines [13]. Only in the pyrolytic transformation of 1R-3-carbethoxy-4-hydroxy-2-oxo-1,2-dihydroquinolines to 5,9-di-R-6,7,8-trioxodiquinolino[3,4-*b*;3',4'-*e*]-4H-pyrans have a similarly structured di(1R-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)ketones been proposed [14]. However, the question of how, in this case, the reduction of the bridging carbonyl group arises and why this only occurs in the reaction of triethylmethanetricarboxylate with 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline remains unclear. In addition, it was experimentally confirmed ester **4** under pyrolytic conditions does not cyclize to the corresponding diquinolinopyran but decomposes to 9-fluoro-1-hydroxy-5-methyl-6,7-dihydro-5H-pyrido-[3,2,1-*ij*]quinolin-3-one (**6**). It follows that the dihetarylmethane **5** is apparently formed by an alternative mechanism.

The ester **4** proved to be extremely stable towards basic hydrolysis. In addition, prolonged heating in aqueous KOH solution is accompanied by decarboxylation and ultimately gives the 2H-derivative **6**. Hence 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid (**7**) was

TABLE 2. Antitubercular Activity of the Compounds Synthesized

Compound	Inhibition of *M. Tuberculosis* growth at c = 6.25 μg/ml, %	Compound	Inhibition of *M. Tuberculosis* growth at c = 6.25 μg/ml, %
5	24	**9i**	18
7	1	**9j**	58
8a	50	**9k**	62
8b	25	**10a**	100
8c	54	**10b**	76
8d	17	**10c**	5
8e	18	**10d**	100
8f	19	**10e**	20
8g	16	**10f**	17
8h	7	**10g**	17
9a	8	**10h**	14
9b	0	**10i**	20
9c	26	**10j**	82
9d	42	**11**	21
9e	0	**12a**	1
9f	85	**12b**	5
9g	95	**12c**	12
9h	52		

TABLE 3. ^{1}H NMR Spectra of N-R-Amides **8-10**

Compound	Chemical shifts, δ, ppm (*J*, Hz)										
	9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline ring										R (Het)
	1-OH (1H, s)	CONH (1H, t)*	H-10 (1H, dd)	H-8 (1H, dd)	5-CH (1H, m)	7-CH_2		6-CH_2		CH_3 (3H, d)	
						H_a-7 (1H, td)	H_e-7 (1H, dd)	H_e-6 (1H, dt)	H_a-6 (1H, tt)		
1	2	3	4	5	6	7	8	9	10	11	12
8a	16.87	10.85 (5.8)	7.63 (8.5 and 2.6)	7.38 (6.7 and 2.5)	5.21	3.17	2.92	2.11	1.97	1.28 (6.6)	7.45 (1H, dd, *J* = 6.8 and *J* = 2.6, H-3'); 7.31-7.20 (3H, m, H arom.); 4.71 (2H, d, *J* = 8.8)
8b	17.26	10.43 (5.3)	7.58 (8.5 and 2.8)	7.37 (8.7 and 2.4)	5.14	3.14	2.93	2.11	1.92	1.24 (6.6)	6.84-6.73 (3H, m, H-2',5',6'); 3.79 (3H, s, OCH_3); 3.75 (3H, s, OCH_3); 3.61 (2H, q, *J* = 6.4, NCH_2); 2.84 (2H, t, *J* = 7.1, $C\underline{H}_2$Ar)
8c	17.23	10.44 (5.8)	7.61 (8.8 and 2.6)	7.32 (8.3 and 2.3)	5.19	3.16	2.93	2.11	Hidden by R	1.27 (6.4)	7.27-7.10 (5H, m, C_6H_5); 3.43 (2H, q, *J* = 6.5, NCH_2); 2.72 (2H, m, $CH_2C_6H_5$); 2.01-1.89 (3H, m, H_a-6 + $NCH_2C\underline{H}_2$)
8d	16.86	10.68 (5.6)	7.63 (8.8 and 2.7)	7.28 (8.7 and 2.5)	5.19	3.16	2.91	2.10	1.96	1.27 (6.1)	7.41 (1H, d, *J* = 1.9, H-5'); 6.33 (1H, t, *J* = 1.8, H-4'); 6.29 (1H, d, *J* = 3.3, H-3'); 4.61 (2H, t, *J* = 4.6, NCH_2)
8e	17.16	10.47 (5.3)	7.60 (8.8 and 2.6)	7.31 (8.5 and 2.7)	5.19	3.16	2.92	2.11	Hidden by R	1.27 (6.7)	4.03 (1H, m, OCH); 3.93-3.33 (4H, m, NCH_2 + OCH_2); 2.30-1.58 (5H, m, H_a-6 + 3'-CH_2 + 4'-CH_2)

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
8f	17.03	10.96 (5.1)	7.63 (8.4 and 2.6)	7.26 (8.6 and 2.9)	5.24	3.18	2.92	2.10	1.99	1.30 (7.2)	8.56 (1H, d, *J* = 4.4, H-6');7.68 (1H, td, *J* = 7.9 and *J* = 1.7, H-5'); 7.35 (1H, d, *J* = 8.1, H-3'); 7.20 (1H, t, *J* = 6.2, H-4'); 4.74 (2H, t, *J* = 6.2, NCH_2)
8g	16.86	10.81 (5.0)	7.64 (8.3 and 2.5)	7.30 (8.5 and 2.6)	5.19	3.17	2.92	2.11	1.96	1.27 (6.3)	8.58 (1H, s, H-2'); 8.45 (1H, d, *J* = 4.2, H-6'); 7.73 (1H, d, *J* = 7.7, H-4'); 7.25 (1H, t, *J* = 4.9, H-5'); 4.65 (2H, t, *J* = 5.3, NCH_2)
8h	16.77	10.85 (5.3)	7.64 (8.5 and 2.4)	7.31 (8.6 and 2.6)	5.21	3.18	2.93	2.12	1.98	1.29 (6.8)	8.49 (2H, d, *J* = 5.3, H-2',6'); 7.27 (2H, d, *J* = 4.6, H-3',5'); 4.66 (2H, t, *J* = 5.8, NCH_2)
9a	16.74	10.53 (5.8)	7.60 (8.6 and 2.8)	7.38 (8.8 and 2.4)	5.18	3.15	2.95	2.12	1.95	1.27 (6.6)	11.63 (1H, br. s, N^+H); 3.85 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 3.32 (2H, t, *J* = 6.2, $NCH_2C\underline{H}_2$); 2.83 (6H, s, $2CH_3$)
9b	16.80	10.49 (5.9)	7.59 (8.8 and 2.9)	7.37 (8.6 and 2.6)	5.18	3.14	2.93	2.12	1.95	1.26 (6.4)	9.49 (2H, br. s, N^+H_2); 3.79 (2H, q, *J* = 6.3, $NHC\underline{H}_2$); 2.99 (4H, m, $NH(C\underline{H}_2)_2$); 1.32 (3H, t, *J* = 7.4, $NHCH_2C\underline{H}_3$)
9c	16.81	10.48 (6.0)	7.59 (8.6 and 2.6)	7.31 (8.6 and 2.6)	5.19	3.14	Hidden by R	2.12	1.96	1.27 (6.8)	9.47 (2H, br. s, N^+H_2); 3.82 (2H, q, *J* = 6.3, $CONHC\underline{H}_2$); 3.77 (2H, t, *J* = 5.3, OCH_2); 3.20 (2H, t, *J* = 6.2, CH_2N); 3.07 (2H, t, *J* = 4.9, NCH_2); 2.92 (2H, m, H_e-7 + OH)
9d	16.73	10.52 (6.1)	7.60 (8.6 and 2.6)	7.38 (8.8 and 2.6)	5.18	Hidden by R	2.93	2.12	1.95	1.26 (6.5)	11.66 (1H, br. s, N^+H); 3.84 (2H, q, *J* = 7.2, $NHC\underline{H}_2$); 3.29-3.13 (7H, m, H_a-7 + $N(CH_2)_3$); 1.37 (6H, t, *J* = 7.0, $2CH_3$)
9e	17.05	10.45 (5.9)	7.59 (8.8 and 2.8)	7.30 (8.7 and 2.5)	5.19	Hidden by R	2.93	Hidden by R	1.96	1.27 (6.8)	12.01 (1H, br. s, N^+H); 3.54 (2H, q, *J* = 6.3, $NHC\underline{H}_2$); 3.14 (3H, m, H_a-7 + $C\underline{H}_2N(CH_3)_2$); 2.77 (6H, s, $2CH_3$); 2.12 (3H, m, H_e-6 + $NCH_2C\underline{H}_2$)

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
9f	16.99	10.46 (5.8)	7.59 (8.7 and 2.6)	7.26 (8.7 and 2.7)	5.20	Hidden by R	2.91	Hidden by R	1.98	1.27 (6.8)	12.12 (1H, br. s, N^+H); 3.56 (2H, q, J = 6.5, $NHC\underline{H}_2$); 3.14 (7H, m, H_a-7 + $N(CH_2)_3$); 2.13 (3H, m, H_e-6 + $NHCH_2C\underline{H}_2$); 1.37 (6H, t, J = 7.2, $2CH_3$)
9g	16.66	10.63 (6.5)	7.61 (8.8 and 2.7)	7.30 (8.8 and 2.7)	5.21	Hidden by R	Hidden by R	Hidden by R	Hidden by R	1.28 (6.2)	12.45 (1H, br. s, N^+H); 4.10-3.00 (9H, m, $NHC\underline{H}_2$ + 7,1',5'-CH_2 + 2'-CH); 2.30-1.93 (6H, m, 6,3',4'–CH_2); 1.44 (3H, td, J = 7.1 and J = 3.5, CH_3)
9h	16.81	10.51 (5.7)	7.60 (8.7 and 2.9)	7.42 (8.8 and 2.6)	5.17	Hidden by R	2.94	2.12	1.93	1.26 (6.2)	9.92 (3H, br. s, N^+H + N^+H_2); 3.82 (2H, q, J = 6.4, $CONHC\underline{H}_2$); 3.48-3.27 (9H, m, H_a-7 + $4CH_2$ piperazine); 3.12 (3H, t, J = 6.3, CH_2N)
9i	16.72	10.53 (5.6)	7.62 (8.4 and 2.6)	7.30 (8.4 and 2.7)	5.20	Hidden by R	2.93	2.11	1.98	1.28 (7.2)	13.02 (1H, br. s, N^+H); 3.94 (6H, m, $NHC\underline{H}_2$ + $O(CH_2)_2$); 3.34–3.10 (7H, m, H_a-7 + $N(CH_2)_3$)
9j	17.05	10.45 (5.8)	7.61 (8.7 and 2.8)	7.29 (8.7 and 2.6)	5.20	Hidden by R	2.92	2.12	1.97	1.28 (6.3)	12.81 (1H, br. s, N^+H); 3.92 (4H, m, $O(CH_2)_2$); 3.56 (2H, q, J = 6.3, $NHC\underline{H}_2$); 3.47 (2H, t, J = 7.0, CH_2N); 3.18-2.98 (5H, m, H_a-7 + $N(CH_2)_2$); 2.20 (2H, q, J = 7.7, $NHCH_2C\underline{H}_2$)
9k	17.06	10.44 (5.7)	7.59 (8.8 and 2.6)	7.33 (8.8 and 2.6)	5.18	3.16	Hidden by R	Hidden by R	1.95	1.26 (7.2)	11.74 (1H, br. s, N^+H); 3.52 (2H, q, J = 6.4, $NHC\underline{H}_2$); 3.46 (2H, t, J = 6.9, CH_2N); 3.08-2.79 (5H, m, H_e-7 + 2',6'-CH_2); 2.13 (3H, m, H_e-6 + $NHCH_2C\underline{H}_2$); 1.79 (6H, m, 3',4',5'-CH_2 piperidine)
10a	16.02	12.96	7.67 (8.8 and 2.7)	7.37 (8.5 and 2.4)	5.25	3.20	2.96	2.16	2.01	1.32 (7.2)	8.47 (2H, d, J = 5.1, H-2',6'); 7.61 (2H, d, J = 5.5, H-3',5')

TABLE 3 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
10b	16.19	12.82	7.68 (8.7 and 2.6)	7.38 (8.7 and 2.4)	5.28	3.21	2.97	2.17	2.02	1.34 (6.3)	8.77 (1H, d, *J* = 1.6, H-3'); 8.34 (1H, d, *J* = 4.5, H-6'); 8.17 (1H, d, *J* = 8.1, H-4'); 7.33 (1H, t, *J* = 6.4, H-5')
10c	16.26	12.91	7.66 (8.7 and 2.6)	7.32 (8.7 and 2.6)	5.30	3.19	2.94	2.15	2.02	1.33 (6.9)	8.35 (1H, d, *J* = 5.3, H-6'); 8.23 (1H, d, *J* = 8.9, H-3'); 7.74 (1H, td, *J* = 7.6 and *J* = 1.8, H-5'); 7.09 (1H, t, *J* = 6.3, H-4')
10d	16.53	12.44	7.65 (8.8 and 2.6)	7.38 (8.8 and 2.4)	5.27	3.20	2.95	2.15	2.00	1.33 (6.1)	8.28 (1H, d, *J* = 4.9, H-6'); 7.75 (1H, d, *J* = 6.4, H-4'); 7.18 (1H, t, *J* = 6.3, H-5'); 2.34 (3H, s, CH_3)
10e	16.32	12.85	7.68 (8.8 and 2.6)	7.32 (8.8 and 2.6)	5.30	3.19	2.94	2.15	2.02	1.33 (6.1)	8.19 (1H, d, *J* = 4.6, H-6'); 8.07 (1H, s, H-3'); 6.91 (1H, d, *J* = 5.3, H-5'); 2.42 (3H, s, CH_3)
10f	16.48	12.88	Hidden by R	7.46 (8.7 and 2.5)	5.24	3.13	2.92	2.12	2.00	1.26 (6.4)	8.20 (1H, s, H-6'); 7.97 (1H, d, *J* = 8.2, H-3'); 7.68-7.57 (2H, m, H-10 + H-4'); 2.29 (3H, s, CH_3)
10g	16.36	12.81	7.67 (8.5 and 2.6)	7.32 (8.5 and 2.4)	5.29	3.19	2.94	2.16	2.02	1.32 (6.6)	8.03 (1H, d, *J* = 7.8, H-3'); 7.61 (1H, t, *J* = 7.8, H-4'); 6.93 (1H, d, *J* = 7.7, H-5'); 2.44 (3H, s, CH_3)
10h	15.82	12.96	7.68 (8.7 and 2.1)	7.34 (8.1 and 2.4)	5.30	3.20	2.95	2.15	2.02	1.34 (6.7)	9.73 (1H, s, OH); 7.91 (1H, d, *J* = 4.4, H-6'); 7.28 (1H, d, *J* = 7.8, H-4'); 7.07 (1H, t, *J* = 6.4, H-5')
10i	16.41	13.19	7.66 (8.4 and 1.8)	7.46 (8.2 and 1.3)	5.25	3.18	2.93	2.16	1.99	1.31 (6.6)	8.71 (2H, d, *J* = 5.0, H-4',6'); 7.24 (1H, t, *J* = 4.9, H-5')
10j	15.89	13.10	7.69 (8.4 and 2.6)	7.37 (8.5 and 2.6)	5.29	3.20	2.96	2.16	2.01	1.33 (6.1)	9.49 (1H, s, H-3'); 8.36 (2H, s, H-5',6')

* Singlets in compounds **10a-j**.

prepared using a known method [10] by hydrolysis of ester **4** with an initially prepared solution of concentrated hydrochloric acid in acetic anhydride i.e. essentially an HCl solution in acetic acid with a low water content.

On the other hand the amidation of ester **4** with alkylamines in ethanol occurs readily to give the amides **8** in high yields (Table 1). The basic dialkylaminoalkylamides formed under analogous conditions are very readily soluble in the majority of organic solvents and have low melting points. For this reason they were conveniently prepared and purified as the hydrochlorides **9**. Hetarylamines do not react with ester **4** in refluxing ethanol whereas the thermolysis of equimolar amounts of the reagents gives good yields of the 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid amides **10** (Table 1). Hydrazinolysis occurs quantitatively in alcohol medium even at room temperature and the hydrazide **11** then gave rise to the isomeric pyridinemethylidenehydrazides **12** on this basis.

The ^{1}H NMR spectra of all of the synthesized compounds (Table 3) showed signals for the aliphatic protons of the 6,7-dihydropyridoquinolone ring but, at first sight, with an unexpected pattern for the spin-spin interactions. Hence the signals for both methylene groups (7-CH_2 and 6-CH_2) were seen as a combination of a doublet and triplet with a large (15-17 Hz) spin-spin coupling, each component of which underwent further splitting. The appearance of these signals becomes understandable if one takes into account that each of them is split by different couplings to the neighbouring methylene group protons. Thus one fragment of the signal for the 7-CH_2 group at lower field (a triple doublet at 3.20 ppm) is due to an axial proton and the other (a double doublet at 2.95 ppm) is due to an equatorial proton. The spin-spin coupling for the given signal is: $^3J_{7He,6He}$ = 3.5-5.5, $^3J_{7He,6Ha}$ = 3.5-5.5, $^3J_{7Ha,6Ha}$ = 12.4-13.2; $^3J_{7Ha,6He}$ = 5.2-6.2 Hz. The geminal coupling $^2J_{7He,7Ha}$ = 16.5-18.5 Hz. The 6-CH_2 signal has a component corresponding to an equatorial proton (dt at 2.15 ppm) and axial proton (tt at 2.05 ppm). There are also observed vicinal spin-spin coupling with proton H-5: $^3J_{5H,6Ha}$ = 13-14; $^3J_{5H,6He}$ = 4.5-5.5 Hz. The geminal coupling for the 6-CH_2 signal $^2J_{6He,6Ha}$ = 14.0-16.0 Hz.

TABLE 4. Bond Lengths (*l*) in the Ester **4** Structure

Bond	*l*, Å	Bond	*l*, Å
$F_{(1A)}$–$C_{(6A)}$	1.363(6)	$N_{(1A)}$–$C_{(9A)}$	1.384(6)
$N_{(1A)}$–$C_{(12A)}$	1.406(6)	$N_{(1A)}$–$C_{(1A)}$	1.502(6)
$O_{(1A)}$–$C_{(10A)}$	1.343(6)	$O_{(2A)}$–$C_{(12A)}$	1.243(6)
$O_{(3A)}$–$C_{(13A)}$	1.256(6)	$O_{(4A)}$–$C_{(13A)}$	1.282(6)
$O_{(4A)}$–$C_{(14A)}$	1.490(6)	$C_{(1A)}$–$C_{(16A)}$	1.516(6)
$C_{(1A)}$–$C_{(2A)}$	1.517(6)	$C_{(2A)}$–$C_{(3A)}$	1.547(8)
$C_{(3A)}$–$C_{(4A)}$	1.461(7)	$C_{(4A)}$–$C_{(9A)}$	1.395(6)
$C_{(4A)}$–$C_{(5A)}$	1.398(7)	$C_{(5A)}$–$C_{(6A)}$	1.383(7)
$C_{(6A)}$–$C_{(7A)}$	1.362(6)	$C_{(7A)}$–$C_{(8A)}$	1.407(7)
$C_{(8A)}$–$C_{(9A)}$	1.398(6)	$C_{(8A)}$–$C_{(10A)}$	1.445(6)
$C_{(10A)}$–$C_{(11A)}$	1.354(7)	$C_{(11A)}$–$C_{(12A)}$	1.433(7)
$C_{(11A)}$–$C_{(13A)}$	1.466(7)	$C_{(14A)}$–$C_{(15A)}$	1.453(9)
$F_{(1B)}$–$C_{(6B)}$	1.376(6)	$N_{(1B)}$–$C_{(12B)}$	1.387(5)
$N_{(1B)}$–$C_{(9B)}$	1.398(6)	$N_{(1B)}$–$C_{(1B)}$	1.485(6)
$O_{(1B)}$–$C_{(10B)}$	1.330(5)	$O_{(2B)}$–$C_{(12B)}$	1.225(6)
$O_{(3B)}$–$C_{(13B)}$	1.213(5)	$O_{(4B)}$–$C_{(13B)}$	1.300(6)
$O_{(4B)}$–$C_{(14B)}$	1.464(5)	$C_{(1B)}$–$C_{(16B)}$	1.514(7)
$C_{(1B)}$–$C_{(2B)}$	1.514(7)	$C_{(2B)}$–$C_{(3B)}$	1.517(7)
$C_{(3B)}$–$C_{(4B)}$	1.498(7)	$C_{(4B)}$–$C_{(5B)}$	1.374(7)
$C_{(4B)}$–$C_{(9B)}$	1.420(6)	$C_{(5B)}$–$C_{(6B)}$	1.356(7)
$C_{(6B)}$–$C_{(7B)}$	1.359(7)	$C_{(7B)}$–$C_{(8B)}$	1.375(7)
$C_{(8B)}$–$C_{(9B)}$	1.403(6)	$C_{(8B)}$–$C_{(10B)}$	1.452(6)
$C_{(10B)}$–$C_{(11B)}$	1.372(7)	$C_{(11B)}$–$C_{(12B)}$	1.443(6)
$C_{(11B)}$–$C_{(13B)}$	1.488(6)	$C_{(14B)}$–$C_{(15B)}$	1.512(7)

The ability of the synthesized compounds to inhibit the growth of *Mycobacterium tuberculosis H37Rv* ATCC 27294 was studied in radiometric *in vitro* experiments [15]. The results of preliminary tests (Table 2) show that compounds **7** does not have antitubercular activity. Contrary to expectations the hydrazide **11** and its pyridinemethylidene derivatives **12** also proved inactive. Only some of the alkylamides **8** show modest antimicrobial activity which generally agree with the biological structure–activity relationships seen earlier in a series of 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid derivatives [16-18]. At the same time, the 9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid 1-ethyl-pyrrolidin-2-ylmethylamide hydrochloride (**9g**) inhibited the growth of the tubercular micobacteria by 95% at a concentration of 6.25 μg/ml even though this is not typical of water soluble compounds of the class studied. In the group of hetarylamides the two substances pyridin-4-yl- and 3-methylpyridin-2-ylamides (**10a** and **10b**) were able to block the growth of *Mycobacterium tuberculosis* by 100% and show interest for further investigation.

TABLE 5. Valence Angles (ω) in the Ester **4** Structure

Valence angle	ω, deg.	Valence angle	ω, deg.
$C_{(9A)}$–$N_{(1A)}$–$C_{(12A)}$	123.5(4)	$C_{(9A)}$–$N_{(1A)}$–$C_{(1A)}$	120.5(4)
$C_{(12A)}$–$N_{(1A)}$–$C_{(1A)}$	115.9(4)	$C_{(13A)}$–$O_{(4A)}$–$C_{(14A)}$	115.8(5)
$N_{(1A)}$–$C_{(1A)}$–$C_{(16A)}$	109.4(4)	$N_{(1A)}$–$C_{(1A)}$–$C_{(2A)}$	109.2(4)
$C_{(16A)}$–$C_{(1A)}$–$C_{(2A)}$	113.7(4)	$C_{(1A)}$–$C_{(2A)}$–$C_{(3A)}$	110.1(5)
$C_{(4A)}$–$C_{(3A)}$–$C_{(2A)}$	108.1(4)	$C_{(9A)}$–$C_{(4A)}$–$C_{(5A)}$	116.4(4)
$C_{(9A)}$–$C_{(4A)}$–$C_{(3A)}$	124.1(5)	$C_{(5A)}$–$C_{(4A)}$–$C_{(3A)}$	119.5(5)
$C_{(6A)}$–$C_{(5A)}$–$C_{(4A)}$	122.2(5)	$C_{(7A)}$–$C_{(6A)}$–$F_{(1A)}$	118.9(5)
$C_{(7A)}$–$C_{(6A)}$–$C_{(5A)}$	122.1(5)	$F_{(1A)}$–$C_{(6A)}$–$C_{(5A)}$	119.0(5)
$C_{(6A)}$–$C_{(7A)}$–$C_{(8A)}$	116.9(5)	$C_{(9A)}$–$C_{(8A)}$–$C_{(7A)}$	121.6(4)
$C_{(9A)}$–$C_{(8A)}$–$C_{(10A)}$	118.0(4)	$C_{(7A)}$–$C_{(8A)}$–$C_{(10A)}$	120.4(4)
$N_{(1A)}$–$C_{(9A)}$–$C_{(4A)}$	119.6(4)	$N_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	119.5(4)
$C_{(4A)}$–$C_{(9A)}$–$C_{(8A)}$	120.9(4)	$O_{(1A)}$–$C_{(10A)}$–$C_{(11A)}$	125.5(4)
$O_{(1A)}$–$C_{(10A)}$–$C_{(8A)}$	113.1(5)	$C_{(11A)}$–$C_{(10A)}$–$C_{(8A)}$	121.4(4)
$C_{(10A)}$–$C_{(11A)}$–$C_{(12A)}$	121.1(4)	$C_{(10A)}$–$C_{(11A)}$–$C_{(13A)}$	117.1(4)
$C_{(12A)}$–$C_{(11A)}$–$C_{(13A)}$	121.8(5)	$O_{(2A)}$–$C_{(12A)}$–$N_{(1A)}$	117.9(5)
$O_{(2A)}$–$C_{(12A)}$–$C_{(11A)}$	125.7(5)	$N_{(1A)}$–$C_{(12A)}$–$C_{(11A)}$	116.3(5)
$O_{(3A)}$–$C_{(13A)}$–$O_{(4A)}$	120.1(5)	$O_{(3A)}$–$C_{(13A)}$–$C_{(11A)}$	120.7(5)
$O_{(4A)}$–$C_{(13A)}$–$C_{(11A)}$	119.1(5)	$C_{(15A)}$–$C_{(14A)}$–$O_{(4A)}$	105.7(6)
$C_{(12B)}$–$N_{(1B)}$–$C_{(9B)}$	122.7(4)	$C_{(12B)}$–$N_{(1B)}$–$C_{(1B)}$	116.6(4)
$C_{(9B)}$–$N_{(1B)}$–$C_{(1B)}$	120.7(4)	$C_{(13B)}$–$O_{(4B)}$–$C_{(14B)}$	116.5(4)
$N_{(1B)}$–$C_{(1B)}$–$C_{(16B)}$	109.6(4)	$N_{(1B)}$–$C_{(1B)}$–$C_{(2B)}$	109.4(5)
$C_{(16B)}$–$C_{(1B)}$–$C_{(2B)}$	114.0(5)	$C_{(1B)}$–$C_{(2B)}$–$C_{(3B)}$	112.0(5)
$C_{(4B)}$–$C_{(3B)}$–$C_{(2B)}$	109.2(4)	$C_{(5B)}$–$C_{(4B)}$–$C_{(9B)}$	116.9(5)
$C_{(5B)}$–$C_{(4B)}$–$C_{(3B)}$	121.4(5)	$C_{(9B)}$–$C_{(4B)}$–$C_{(3B)}$	121.7(5)
$C_{(6B)}$–$C_{(5B)}$–$C_{(4B)}$	122.1(5)	$C_{(5B)}$–$C_{(6B)}$–$C_{(7B)}$	123.0(6)
$C_{(5B)}$–$C_{(6B)}$–$F_{(1B)}$	118.7(5)	$C_{(7B)}$–$C_{(6B)}$–$F_{(1B)}$	118.2(5)
$C_{(6B)}$–$C_{(7B)}$–$C_{(8B)}$	116.8(5)	$C_{(7B)}$–$C_{(8B)}$–$C_{(9B)}$	122.4(5)
$C_{(7B)}$–$C_{(8B)}$–$C_{(10B)}$	121.3(4)	$C_{(9B)}$–$C_{(8B)}$–$C_{(10B)}$	116.2(4)
$N_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	121.0(4)	$N_{(1B)}$–$C_{(9B)}$–$C_{(4B)}$	120.2(5)
$C_{(8B)}$–$C_{(9B)}$–$C_{(4B)}$	118.8(5)	$O_{(1B)}$–$C_{(10B)}$–$C_{(11B)}$	121.8(5)
$O_{(1B)}$–$C_{(10B)}$–$C_{(8B)}$	116.0(5)	$C_{(11B)}$–$C_{(10B)}$–$C_{(8B)}$	122.2(4)
$C_{(10B)}$–$C_{(11B)}$–$C_{(12B)}$	120.0(4)	$C_{(10B)}$–$C_{(11B)}$–$C_{(13B)}$	117.5(4)
$C_{(12B)}$–$C_{(11B)}$–$C_{(13B)}$	122.5(5)	$O_{(2B)}$–$C_{(12B)}$–$N_{(1B)}$	118.4(4)
$O_{(2B)}$–$C_{(12B)}$–$C_{(11B)}$	124.4(4)	$N_{(1B)}$–$C_{(12B)}$–$C_{(11B)}$	117.2(5)
$O_{(3B)}$–$C_{(13B)}$–$O_{(4B)}$	122.5(4)	$O_{(3B)}$–$C_{(13B)}$–$C_{(11B)}$	121.6(5)
$O_{(4B)}$–$C_{(13B)}$–$C_{(11B)}$	115.9(4)	$O_{(4B)}$–$C_{(14B)}$–$C_{(15B)}$	106.1(4)

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were obtained on a Bruker WM-260 (360 MHz) instrument using DMSO-d_6 with TMS as internal standard. The chromato-mass spectrum of the dihetarylmethane **5** was recorded on a Finnigan MAT Incos 50 quadrupole spectrometer in the full scanning mode in the range *m/z* 33-700, ionization 70 eV, direct introduction of the sample, and heating rate of about 5°C/min. Commercial 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline and triethylmethanetricarboxylate from Aldrich and Fluka respectively were used in the synthesis of ester **4**.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Ethyl Ester (4). Quinoline **2** (16.52 g, 0.1 mol) was added in small portions with stirring to triethylmethanetricarboxylate (**3**) (23.2 ml, 0.11 mol) heated to 220°C at such a rate that the reaction mixture temperature did not vary by more than 5°C from the initial. The ethanol produced in the reaction process with distilled off using a suitable fractionating column. After addition of all of the quinoline **2** the reaction mixture was held for 10-15 min at the same temperature and then cooled. Aqueous sodium carbonate solution (10%, 300 ml) was added and the product was heated to 70-80°C and filtered. The residue on the filter was washed with hot water. The solution obtained of the sodium salt of ester **4** was purified using carbon, cooled, and acidified with dilute (1:1) HCl to pH 4.5-5. The precipitated ester **4** was filtered, washed with water, and dried. Yield 23.2 g (76%); mp 131-133°C (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.86 (1H, s, OH); 7.57 (1H, dd, *J* = 9.1 and 3.0, H-10); 7.46 (1H, dd, *J* = 9.0 and 3.0, H-8); 5.00 (1H, m, 5-CH); 4.30 (2H, q, *J* = 7.0, OCH_2); 3.06 (1H, td, *J* = 17.1 and 5.3, H_a-7); 2.85 (1H, dd, *J* = 17.0 and 5.1, H_e-7); 2.02 (1H, dt, *J* = 13.4 and 5.0, H_e-6); 1.82 (1H, tt, *J* = 13.6 and 5.1, H_a-6); 1.28 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.14 (3H, d, *J* = 6.6, CH_3). Found, %: C 62.84; H 5.33; N 4.54. $C_{16}H_{16}FNO_4$. Calculated, %: C 62.95; H 5.28; N 4.59.

X-Ray Analysis. Crystals of ester **4** were prepared from ethanol and are triclinic. At 20°C: *a* = 9.369(3), *b* = 11.651(3), *c* = 13.521(5) Å; α = 99.43(3)°, β = 90.29(3)°, γ = 92.67(3)°; *V* = 1454.3(8) Å^3; d_{calc} = 1.394 g/cm^3; space group *P*1; M_r = 305.3; *Z* = 4; μ(Mo*K*α) = 0.109 mm^{-1}; *F*(000) = 640. The unit cell parameters and intensities of 5146 reflections (4868 independent with R_{int} = 0.014) were measured on a Siemens P3/PC, automatic four circle diffractometer (λMo*K*α, graphite monochromator, θ/2θ scanning to $\theta/2\theta_{max}$ = 50°).

The structure was solved by a direct method using the SHELX97 program package [19]. The positions of the hydrogen atoms were revealed in electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ for non-hydrogen atoms bound to the given hydrogen (*n* = 1.5 for a methyl group and 1.2 for the remaining hydrogen atoms). The structure was refined in F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.252 for 4868 reflections (R_1 = 0.067 for 1698 reflections with $F > 4\sigma(F)$, *S* = 0.905). The full crystallographic information has been placed in the Cambridge Structural Data Base (deposit No. CCDC 283292). The interatomic distances and valence angles are given in Tables 4 and 5.

Di(9-fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinolin-2-yl)methane (5). The residue on the filter (see the example of the preparation of ester **4**) was crystallized from DMF to give 1.93 g (8%) of the dihetarylmethane **5**; mp 288-290°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.70 (2H, s, 2OH); 7.56 (2H, dd, *J* = 8.9 and 2.6, 2H-10); 7.42 (2H, dd, *J* = 9.0 and 2.6, 2H-8); 5.16 (2H, d, two 5-CH); 3.87 (2H, s, CH_2); 3.13 (2H, td, *J* = 15.7 and 5.5, $2H_a$-7); 2.92 (2H, dd, *J* = 16.8 and 3.6, $2H_e$-7); 2.07 (2H, dt, *J* = 12.1 and 4.2, $2H_e$-6); 1.91 (2H, tt, *J* = 13.7 and 4.6, $2H_a$-6); 1.22 (6H, d, *J* = 7.0, $2CH_3$). Mass spectrum, *m/z* (I_{rel}, %): 478 $[M]^+$ (66), 246 $[HetCH_2]^+$ (12), 232 $[Het]^+$ (42), 218 (68), 204 (69), 190 (57), 176 (100), 162 (29), 148 (43). Found, %: C 67.68; H 5.12; N 5.92. $C_{27}H_{24}F_2N_2O_4$. Calculated, %: C 67.77; H 5.06; N 5.85.

9-Fluoro-1-hydroxy-5-methyl-6,7-dihydro-5H-pyrido[3,2,1-*ij*]quinolin-3-one (6). A. A mixture of ester **4** (3.05 g, 0.01 mol) and 20% aqueous KOH solution (50 ml) was refluxed for 40 h, cooled, and acidified with HCl to pH 3. The precipitate was filtered, washed with water, and dried. Yield 1.93 g (83%); mp 314-316°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.52 (1H, s, OH); 7.40 (1H, dd, *J* = 8.8 and 2.7, H-10); 7.33 (1H, dd, *J* = 8.8 and 2.8, H-8); 5.86 (1H, s, H-2); 4.99 (1H, d, 5-CH); 3.06 (1H, td, *J* = 17.0 and 4.9,

H_a-7); 2.85 (1H, dd, J = 17.1 and 4.2, H_e-7); 2.00 (1H, dt, J = 13.8 and 5.1, H_e-6); 1.81 (1H, tt, J = 13.7 and 4.9, H_a-6); 1.12 (3H, d, J = 6.7, CH_3). Found, %: C 66.85; H 5.14; N 6.09. $C_{13}H_{12}FNO_2$. Calculated, %: C 66.94; H 5.19; N 6.01.

B. Acid **7** (2.77 g, 0.01 mol) was held for 10 min at 220°C. Vigorous evolution of carbon dioxide occurred at the conclusion of which the reaction product was cooled and crystallized from aqueous ethanol Yield 2.09 g (90%).

C. Ester **4** (3.05 g, 0.01 mol) was held for 20 min at 250°C, cooled, and the residue was crystallized from aqueous ethanol. Yield 1.083 g (79%).

Mixed samples of the quinolin-3-one **6** prepared by the different methods did not give a depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid (7). Ester **4** (3.05 g, 0.01 mol) was added to a solution of HCl in acetic acid (30 ml, prepared as in the method [10]) and held for 5 h at 60°C. The product was cooled and the crystals of acid **7** were filtered off, washed with alcohol and then water, and dried. Yield 2.38 g (86%); mp 183-185°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 14.10 (1H, s, OH); 7.68 (2H, d, J = 8.9 and 8, H-10); 5.07 (1H, m, 5-CH); 3.05 (1H, td, J = 17.0 and 5.1, H_a-7); 2.90 (1H, dd, J = 17.1 and 5.0, H_e-7); 2.05 (1H, dt, J = 13.6 and 5.2, H_e-6); 1.87 (1H, tt, J = 13.4 and 5.0, H_a-6); 1.20 (3H, d, J = 6.7, CH_3). Found, %: C 60.77; H 4.45; N 5.12. $C_{14}H_{12}FNO_4$. Calculated, %: C 60.65; H 4.36; N 5.05.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid 2-Chlorobenzylamide (8a). 2-Chlorobenzylamine (1.33 ml, 0.011 mol) was added to a solution of ester **4** (3.05 g, 0.01 mol) in ethanol (30 ml) and refluxed for 3 h. The product was cooled, cold water (100 ml) added, and it was then acidified with HCl to pH 4. The precipitated amide **8a** was filtered, washed with water, and dried.

Alkylamides 8b-e were prepared similarly. In the preparation of the **picolylamides 8f-h** the reaction mixture was acidified with acetic acid.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid 2-Dimethylaminoethylamide Hydrochloride (9a). 2-Dimethylaminoethylamine (1.1 ml, 0.01 mol) was added to a solution of ester **4** (3.05 g, 0.01 mol) in ethanol (15 ml) and refluxed for 3 h. The product was cooled to room temperature and saturated gaseous HCl in ethanol was added to pH 3 after which the reaction mixture was held for 7-8 h at 5°C. The separated hydrochloride **9a** was filtered, washed with ether, and dried.

Alkylamides 9b-k were prepared similarly.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Pyridin-4-ylamide (10a). A mixture of ester **4** (3.05 g, 0.01 mol), 4-aminopyridine (0.94 g, 0.01 mol), and DMF (0.5 ml) was held for 2-3 min at 170°C. The product was cooled, ethanol (15 ml) was added, and thoroughly triturated. The precipitated amide **10a** was filtered off, washed with alcohol, dried, and crystallized from DMF.

Hetarylamides 10b-j were prepared similarly.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Hydrazide (11). Hydrazine hydrate (0.011 mol, calculated on the actual content) was added to a solution of ester **4** (3.05 g, 0.01 mol) in ethanol (15 ml). After 2 h the reaction mixture was diluted with cold water. The precipitated hydrazide **11** was filtered off, washed with water, and dried. Yield 2.90 g (quantitative); mp 169-171°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 16.22 (1H, s, OH); 11.09 (1H, s, CONH); 7.59 (1H, dd, J = 8.9 and 2.8, H-10); 7.47 (1H, dd, J = 8.9 and 2.6, H-8); 5.11 (1H, m, 5-CH); 4.81 (2H, br. s, NNH_2); 3.08 (1H, td, J = 17.0 and 4.7, H_a-7); 2.84 (1H, dd, J = 12.8 and 3.5, H_e-7); 2.07 (1H, dt, J = 13.7 and 5.5, H_e-6); 1.90 (1H, tt, J = 13.4 and 4.9, H_a-6); 1.21 (3H, d, J = 6.5, CH_3). Found, %: C 57.60; H 4.71; N 14.56. $C_{14}H_{14}FN_3O_3$. Calculated, %: C 57.73; H 4.84; N 14.43.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Pyridin-4-ylmethylidenehydrazide (12a). Isonicotinic aldehyde (1.04 ml, 0.011 mol) was added to a solution of hydrazide **11** (2.91 g, 0.01 mol) in hot ethanol (20 ml) and refluxed for 1 h. The product was cooled and the precipitated crystals of pyridin-4-ylmethylidenehydrazide **12a** were filtered off, washed with alcohol, and dried. Yield 3.65 g (96%); mp 292-294°C (DMF–ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.31 (1H, s, OH); 13.52 (1H, s, CONH); 8.66 (2H, d, *J* = 5.4, H-2',6'); 8.53 (1H, s, CH=N); 7.70-7.60 (3H, m, H-10 + H-3',5'); 7.52 (1H, dd, *J* = 8.7 and 2.4, H-8); 5.16 (1H, m, 5-CH); 3.11 (1H, td, *J* = 17.1 and 5.4, H_a-7); 2.84 (1H, dd, *J* = 12.9 and 3.8, H_e-7); 2.11 (1H, dt, *J* = 13.9 and 5.4, H_e-6); 1.94 (1H, tt, *J* = 13.6 and 5.0, H_a-6), 1.27 (3H, d, *J* = 6.8, CH_3). Found, %: C 63.23; H 4.61; N 14.80. $C_{20}H_{17}FN_4O_3$. Calculated, %: C 63.15; H 4.50; N 14.73.

Compounds **12b,c** were prepared by a similar method.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Pyridin-3-ylmethylidenehydrazide (12b) Yield 95%; mp 210-212°C (DMF–ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.47 (1H, s, OH); 13.46 (1H, s, CONH); 8.89 (1H, d, *J* = 1.9, H-2'); 8.62 (1H, dd, *J* = 4.9 and 1.6, H-6'); 8.57 (1H, s, CH=N); 8.14 (1H, dt, *J* = 8.0 and 2.1, H-4'); 7.64 (1H, dd, *J* = 8.7 and 2.8, H-10); 7.56-7.43 (2H, m, H-8 + H-5'); 5.16 (1H, m, 5-CH); 3.14 (1H, td, *J* = 17.3 and 5.4, H_a-7); 2.93 (1H, dd, *J* = 17.5 and 4.2, H_e-7); 2.11 (1H, dt, *J* = 13.5 and 5.3, H_e-6); 1.95 (1H, tt, *J* = 13.7 and 4.9, H_a-6); 1.27 (3H, d, *J* = 6.5, CH_3). Found, %: C 63.26; H 4.58; N 14.85. $C_{20}H_{17}FN_4O_3$. Calculated, %: C 63.15; H 4.50; N 14.73.

9-Fluoro-1-hydroxy-5-methyl-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Pyridin-2-ylmethylidenehydrazide (12c). Yield 90%; mp 266-268°C (DMF–ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.40 (1H, s, OH); 13.44 (1H, s, CONH); 8.64 (1H, d, *J* = 4.5, H-6'); 8.42 (1H, s, CH=N); 7.98 (1H, d, *J* = 7.8, H-3'); 7.88 (1H, td, *J* = 7.4 and 1.5, H-4'); 7.63 (1H, dd, *J* = 8.8 and 2.9, H-10); 7.51 (1H, dd, *J* = 8.8 and 2.6, H-8); 7.43 (1H, td, *J* = 5.9 and 1.4, H-5'); 5.17 (1H, d, 5-CH); 3.14 (1H, td, *J* = 17.4 and 5.4, H_a-7); 2.92 (1H, dd, *J* = 17.2 and 4.0, H_e-7); 2.10 (1H, dt, *J* = 13.8 and 5.4, H_e-6); 1.94 (1H, tt, *J* = 13.5 and 4.7, H_a-6), 1.26 (3H, d, *J* = 6.5, CH_3); Found, %: C 63.11; H 4.67; N 14.64. $C_{20}H_{17}FN_4O_3$. Calculated, %: C 63.15; H 4.50; N 14.73.

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