HOMOLYTIC ALKOXYCARBONYLATION REACTIONS IN TWO-PHASE SYSTEMS 3[1]. INTRODUCTION OF A SINGLE CARBOXYLIC ACID ESTER FUNCTION INTO CYANO- OR ALKOXYCARBONYL SUBSTITUTED N-HETEROAROMATICS[2]

Gottfried Heinisch* and Gerhard Lötsch
Institut fur Pharmazeutische Chemie der Universität Wien
Währingerstraße 10, A-1090 Vienna, Austria

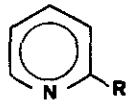
Abstract - Homolytic alkoxycarbonylation reactions with cyanopyridines 1a, 2a, 3a, alkyl pyridinecarboxylates 1b, 2b, 3b, 3c and ethyl 4-pyridazinecarboxylate 4 in presence of dichloromethane were studied. It is demonstrated that under these conditions multiple substitution in general is suppressed markedly. Thus, this experimentally simple procedure represents an efficient and versatile method for single-step preparations of alkyl cyanopyridinecarboxylates 7a, 8a, 9a, 10a. Furthermore, it provides convenient access to so far not available mixed esters 5b, 7b, 8b, 10b, 13, derived from 2,3-pyridine-, 2,4-pyridine-, 3,4-pyridine- and 4,5-pyridazinedicarboxylic acid.

Whereas the substitution of protonated π-deficient N-heteroaromatic bases by nucleophilic carbon centered radicals[3] is now a well established method for the introduction of a wide variety of carbon side chains into positions of heteroaromatic systems which are not susceptible for electrophilic attack, homolytic alkoxycarbonylation until recently was considered a relatively unimportant branch of Minisci-type reactions.[4] This lack of interest mainly was due to the fact that the activation of the heteroarene caused by the first alkoxycarbonyl group introduced in general favours the formation of polysubstitution products if the heteroaromatic substrate has more than one ring-carbon atom attackable by a nucleophilic radical. Since it was thought that multiple substitution can be suppressed only with acceptance of low conversion rates,[5] the preparative value of Minisci-type reactions with regard to the introduction of a single carboxylic acid ester function appeared

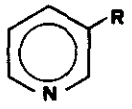
to be rather limited. Our recent success in high-yield single-step preparations of alkyl 5-alkyl-4-pyridazinecarboxylates,[6] of ethyl 2-pyrazinecarboxylate,[1] and of ethyl 4-methyl-2-pyridinecarboxylate[1] achieved by performing radicalic alkoxycarbonylation in a two-phase system, now stimulated investigations aimed at the development of facile syntheses of π-deficient N-heteroaromatics bearing two different carboxylic functional groups (e.g. COOR and CN or COOR and COOR').[7] Only a few compounds of this type, which are anticipated to be versatile synthetic building blocks so far were accessible (see below).

RESULTS AND DISCUSSION

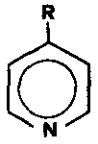
A representative series of functional derivatives of N-heteroaromatic monocarboxylic acids [i.e. cyanopyridines 1a, 2a, 3a, alkyl pyridinecarboxylates 1b, 2b, 3b, 3c and ethyl 4-pyridazinecarboxylate (4)] was selected for the present study. These compounds were reacted with ethoxycarbonyl or methoxycarbonyl radicals. Generation of radicals was accomplished by redox decomposition of oxyhydroperoxides of alkyl pyruvates, according to a reported procedure.[5]



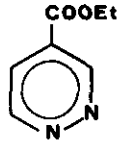
1a, R=CN
b, R=COOEt



2a, R=CN
b, R=COOEt

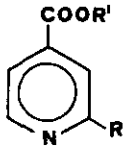


3a, R=CN
b, R=COOEt
c, R=COOMe

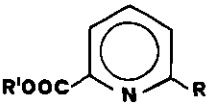


4

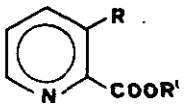
The results obtained under different reaction conditions [varying (a) base:peroxide ratios and (b) amounts of dichloromethane added to the reaction mixture] are collected in Tables I - III. Preliminary experiments, carried out in the presence of diethyl ether, toluene or dichloromethane, indicated the latter to be most suitable to protect the initially formed monosubstitution products from further radicalic attack. Unless otherwise noted, the yields given in Tables I - III were determined by glc-analyses; for yields of isolated target compounds, obtained in analytically pure form by medium-pressure liquid chromatography, see experimental section. Structure proof of the novel functional derivatives of pyridine and pyridazinedicarboxylic acids rests on ir and ^{1}H-nmr data as well as on elemental analyses and ms molecular weight determinations.



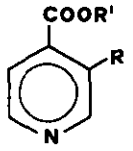
5a, R=CN, R'=Et
b, R=COOEt, R'=Me



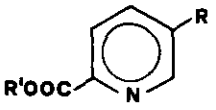
6, R=CN, R'=Et



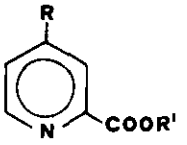
7a, R=CN, R'=Et
b, R=COOEt, R'=Me



8a, R=CN, R'=Et
b, R=COOEt, R'=Me



9a, R=CN, R'=Et
b, R=COOEt, R'=Me



10a, R=CN, R'=Et
b, R=COOEt, R'=Me

Syntheses of Alkyl Cyanopyridinemonocarboxylates. Among the procedures so far proposed for the synthesis of ethyl cyanopyridinecarboxylates,[8] there is no method of general applicability permitting single-step preparations starting with commercially available materials. Most of these syntheses additionally suffer from low yields. On the other hand, the results obtained in attempts to introduce a single carboxylic acid ester function into cyanopyridines 2a, 3a under conditions usually applied in Minisci-type reactions (i.e. in the absence of an organic layer) expectedly turned out to be rather disappointing (compare Table 1). However, by performing the reactions of 3-cyanopyridine (2a) and 4-cyanopyridine (3a) in the presence of dichloromethane we succeeded in a significant suppression of multiple substitution, even if an excess of radicals, sufficient for high conversions, was applied. Thus, by choosing appropriate base:peroxide ratios and amounts of dichloromethane added, this simple method permits convenient access to ethyl cyanopyridinecarboxylates 7a, 8a, 9a, 10a.

Ethyl 4-cyano-2-pyridinecarboxylate (10a) can be prepared in >80% yield by reacting 3a with a tenfold amount of ethoxycarbonyl radicals in the presence of 150ml of dichloromethane.[7] Due to three different carbon atoms of low electron density being present in compound 2a, in this case a mixture of three cyanopyridinemonocarboxylic acid esters is obtained, the γ-ethoxycarbonyl substituted compound (8a) being pre-

dominant. Nevertheless, the homolytic alkoxycarbonylation of 2a in the presence of 30ml of dichloromethane, employing a base:peroxide ratio of 1:3, appears to be superior to methods previously used for preparing compounds 8a[8b] and 9a[8c,d] and to be useful for the synthesis of the new compound 7a, since these isomers can be separated easily by means of medium-pressure liquid chromatography.

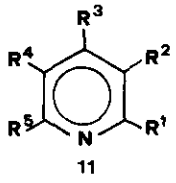
In contrast to the findings with 2a and 3a, multiple substitution of 2-cyanopyridine 1a takes place only to a minor degree, even under standard conditions of Minisci-type alkoxycarbonylations (compare Table 1). The moderate yields of cyanopyridinecarboxylic acid esters 5a and 6 in this case are caused by a low conversion rate (64%). Although it turned out that the conversion rate can not be increased either by raising the amount of radicals or by performing the reaction in the presence of an organic layer, homolytic ethoxycarbonylation of 1a seems to be advantageous to the procedure formerly used for the preparation of ethyl 2-cyano-4-pyridinecarboxylate (5a).[8a]

TABLE I: Product Distribution in Ethoxycarbonylation Reactions of Cyanopyridines

Educt (10 mmol)	mole ratio base:peroxide (ml CH_2Cl_2 added)	% conversion rate	Products (% yield)[a] monosubstitution products	polysubstitution products	unidentified products
1a	1:3 (-)	64	5a[b](36), 6 (15)	-	(13)
	1:3 (10)	52	5a[b](34), 6 (13)	-	(4)
	1:3 (30)	33	5a[b](14), 6 (10)	-	(-)
	1:10 (150)	0	-	-	(-)
2a	1:3 (-)	98	7a[c](19),8a[c,d](6),9a[e](22)	11a(16),11b(6),11c(30)	(-)
	1:3 (30)	99	7a[c](27),8a[c,d](41),9a[e](27)	11a(2),11c(3)	(-)
	1:3 (150)	90	7a[c](28),8a[c,d](35),9a[e](25)	11a(1),11c(1)	(-)
	1:10 (150)	98	7a[c](26),8a[c,d](20),9a[e](23)	11a(8),11b(3),11c(18)	(-)
3a	3:1[f](-)	19	10a (14)	11d+11e+11f (3)[g]	(3)
	1:3 (-)	76	10a (36)	11d(5),11e(25),11f(10)[h]	(2)
	1:3 (30)	94	10a (80)	11d+11e+11f (6)[g]	(9)
	1:3 (150)	51	10a (42)	11d+11e+11f (3)[g]	(6)
	1:10 (150)	100	10a (85)	11d+11e+11f (4)[g]	(11)

a) Based on starting heteroaromatic substrate, determined by glc analysis; b) compare ref. 8a; c) compare ref. 7; d) compare ref. 8b; e) compare refs. 8c,d; f) also compare ref. 5; g) since we did not succeed in complete separation of the compounds by means of glc, individual yields could not be determined; h) yields determined by means of ^{1}H-nmr spectroscopy.

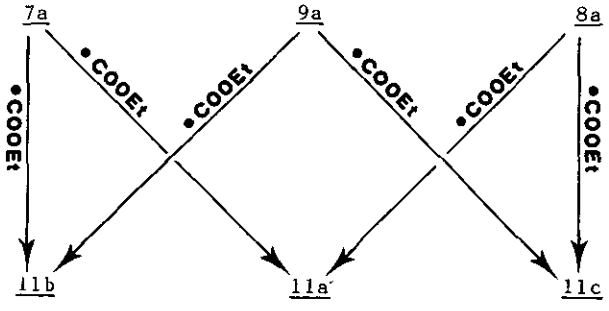
To our knowledge, the cyanopyridinedicarboxylates 11a-f also obtained in these reactions have not been described yet. Like with the new ethyl cyanopyridinemonocarboxylates 6, 7a, 10a, also in the case of compounds 11a, 11b, 11d, 11e, 11f ^{1}H-nmr spectroscopic data permit one to determine unequivocally the ring positions which are occupied by the ethoxycarbonyl substituents.



11

11	R^1	R^2	R^3	R^4	R^5
a	COOEt	CN	COOEt	H	H
b	COOEt	CN	H	H	COOEt
c	H	CN	COOEt	H	COOEt
d	COOEt	COOEt	CN	H	H
e	COOEt	H	CN	COOEt	H
f	COOEt	H	CN	H	COOEt

In case of the diethyl cyanopyridinedicarboxylate, mp 107 - 108°C, obtained in up to 30% yield from 2a, it is not possible to distinguish between the isomeric structures to be taken into consideration by means of ^{1}H-nmr spectroscopy. However, structure proof of compound 11c easily could be accomplished by ethoxycarbonylation experiments starting with the monoethoxycarbonylated cyanopyridines 7a, 8a and 9a followed by comparison of the glc retention behaviour of the products formed with the retention behaviour of the isolated compounds mentioned above (compare Scheme 1). These experiments provide further evidence for the structures assigned to compounds 11a and 11b.



SCHEME I

Syntheses of Mixed Esters Derived from Pyridine- and Pyridazinedicarboxylic Acids. These encouraging results obtained in two-phase system ethoxycarbonylations of cyanopyridines prompted us to apply this method also in reactions with alkyl pyridinemonocarboxylates 2b, 3b, 3c (compare Table II), in the hope of finding convenient access to so far not known mixed esters derived from pyridinedicarboxylic acids. Indeed, this experimentally simple procedure affords methoxycarbonyl-ethoxycarbonylpyridines 5b, 7b, 8b, 9b, 10b as the main products, chromatographically easi-

ly separable from polysubstitution products formed only to a minor degree.

Mixed esters derived from pyridine-2,4-dicarboxylic acids are best prepared by reacting an alkyl 4-pyridinecarboxylate with an excess of alkoxycarbonyl radicals in the presence of a large amount of dichloromethane. Again, the yields in this case are particularly high (86% 5b, starting with 3c; 81% 10b, starting with 3b). Homolytic alkoxycarbonylation of an alkyl 2-pyridinecarboxylate is much less suitable for preparing compounds of type 5b or 10b, since, due to one α and one γ position being free, more complex product mixtures are formed. Additionally, as shown from experiments employing 1b (compare table II), the conversion rates of alkyl 2-pyridinecarboxylates in general are disappointing.[9]

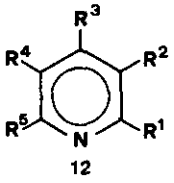
TABLE II: Product Distributions in Alkoxycarbonylation Reactions of Alkyl Pyridinecarboxylates

Educt (10 mmol)	mole ratio base:peroxide (ml CH_2Cl_2 added)	% conversion rate	Products (% yield)[a] monosubstitution products	polysubstitution products	unidentified products
1b	1:3 (-)	34	5b (12)	-	(22)
	1:3 (30)	47	5b (34)	-	(13)
	1:3 (150)	43	5b (29)	-	(14)
	1:10 (-)	100	5b (15)	-	(86)
	1:10 (150)	36	5b (22)	-	(13)
2b	1:3 (-)	81	7b (15),8b (14),9b (4)	12a (14), 12b (30)	(4)
	1:3 (30)	86	7b (21),8b (38),9b (20)	12a (3), 12b (3)	(-)
	1:3 (150)	95	7b (29),8b (36),9b (20)	12a (3), 12b (6)	(-)
	1:10 (150)	99	7b (27),8b (37),9b (21)	12a (4), 12b (10)	(-)
3b	1:3 (30)	74	10b (61)	-	(13)
	1:10(150)	98	10b (81)	-	(17)
3c	1:3 (-)	80	5b (29),8b (2)	12c (6),12d (27),12e (11)	(3)
	1:3 (30)	95	5b (80),8b (4)	12c (4),12d (5),12e (2)	(1)
	1:3 (150)	96	5b (86),8b (8)	12c (1),12d (2)	(-)
	1:10 (150)	97	5b (82),8b (8)	12c (2),12d (3)	(-)

a) Based on starting heteroaromatic substrate, determined by glc analysis.

The β carbon atoms in a 4-pyridinecarboxylic acid ester expectedly are attacked by alkoxycarbonyl radicals only to a minor degree (compare reactions of 3c with COOEt radicals, Table II). However, mixed esters derived from 3,4-pyridinedicarboxylic

acids easily can be obtained from a 3-pyridinecarboxylic acid ester. Thus, experiments starting with 2b resulted in up to 38% yield of 8b. By means of medium-pressure liquid chromatography also the mixed ester 7b derived from 2,3-pyridinedicarboxylic acid could be isolated from the reaction mixture in analytically pure form. Attempts to obtain the third isomer 9b uncontaminated by 7b, failed.

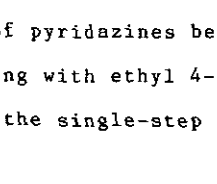


12

12	R^1	R^2	R^3	R^4	R^5
a	COOMe	COOEt	COOMe	H	H
b	COOMe	H	COOMe	COOEt	H
c	COOEt	COOEt	COOMe	H	H
d	COOEt	H	COOMe	COOEt	H
e	COOEt	H	COOMe	H	COOEt

The substitution patterns in the novel pyridinedicarboxylic acid esters 5b, 7b, 8b, 9b, 10b as well as in the pyridinetricarboxylic acid esters 12a-e unambigously could be determined on basis of ^{1}H-nmr chemical shifts, signal multiplicities and coupling constants, despite the fact that only two of the trisubstituted compounds, namely 12b and 12e, were isolated in pure form. Since there is no overlapping of the pyridine proton signals in the spectrum of a mixture of 12e and 12d, the structure of compound 12d unequivocally can be deduced. The chemical shifts of the protons at C-3 and C-6 in compound 12d completely correspond with the δ-values observed with the two singlets of aromatic protons appearing in the spectrum of compound 12b, thus permitting structure assignment also of the latter compound.

From the results, displayed in Table III it becomes evident, homolytic alkoxycarbonylation reactions performed in a two-phase system to be of high utility also in the synthesis of pyridazines bearing two different alkoxycarbonyl groups at C-4 and C-5. Starting with ethyl 4-pyridazinecarboxylate (4), homolytic methoxycarbonylation permits the single-step preparation of the mixed ester 13 in high yield. It should be mentioned that the orientation of radicalic attack at pyridazine and derivatives thereof in Minisci-type reactions significantly differs from that observed with other π-deficient N-heteroaromatic systems.[10]



13

TABLE III: Product Distributions in Methoxycarbonylation Reactions of Ethyl 4-Pyridazinecarboxylate

Educt (10mmol)	mole ratio base:peroxide (ml CH_2Cl_2 added)	% conversion rate	Products (% yield)[a] 13	unidentified products
4	1:3 (-)	100	(63)	(37)
	1:3 (30)	95	(79)	(16)
	1:3 (150)	74	(53)	(21)
	1:10 (150)	50	(37)	(13)

a) Based on starting 4, determined by glc analysis.

CONCLUSIONS

We have demonstrated that multiple substitution being the main reason for restricted synthetic utility of Minisci-type alkoxycarbonylations simply can be avoided even in those cases, where a large excess of radicals is required in order to obtain high conversion rates, by performing these reactions in the presence of dichloromethane. The regioselective introduction of a single alkoxycarbonyl group into pyridine- and pyridazinemonocarboxylic acid esters, thus achieved, represents an experimentally simple procedure for the synthesis of mixed esters derived from 2,3-pyridine-, 2,4-pyridine-, 3,4-pyridine- and 4,5-pyridazinedicarboxylic acid. Since the alkyl group in the starting heteroaromatic carboxylic acid ester as well as in the pyruvic acid ester (which is source for alkoxycarbonyl radicals) is variable within a wide range, this convenient method can be anticipated to provide access to bisalkoxycarbonyl substituted N-heteroaromatics characterized by ester functions of markedly different reactivity. One might expect compounds of this type to be useful synthetic tools. Furthermore, again starting with commercially available materials, this method permits facile syntheses of alkyl 2-cyano-4-pyridine-, alkyl 3-cyano-2-pyridine-, alkyl 3-cyano-4-pyridine-, alkyl 5-cyano-2-pyridine- and alkyl 4-cyano-2-pyridinecarboxylates, thus being highly advantageous to so far existing cumbersome multi-step procedures.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Infrared spectra were recorded with a Jasco IRA-1 spectrometer (KBr disks, $\tilde{\nu}$ in cm^{-1}). ^{1}H-nmr spectra were recorded with a Varian EM 390 (90MHz), using $CDCl_3$ as solvent; chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra, obtained on a Varian MAT CH-7, were carried out by Dr. Nikiforov at the "Institut fur Organische Chemie", University of Vienna. Microanalyses were performed by Dr. Zak, "Institut für Physikalische Chemie". Glc analyses were carried out with an Erba Fractovap 2351 AC, using a 25m x 0.22mm OV 17 WCOT-FS (for reaction mixtures obtained from 1a, 2a, 3a) and a 25m x 0.22mm SE 30 WCOT-FS (for reaction mixtures obtained from 1b, 2b, 3b, 3c, 4), respectively; N_2, FID. Medium-pressure liquid chromatography (mplc) was carried out in Lobar® glass columns, filled with silica gel LiChroprep® Si 60, 40-63µm (Merck), flow rate 4-6ml/min. Preparative thin-layer chromatography (prep. tlc) was carried out on silica gel 60 F_{254} (Merck). 4 was prepared according to a reported procedure.[11] All other materials were commercial products and were reacted without further purification.

All reactions were carried out following the general procedure. Base:peroxide ratios and amounts of CH_2Cl_2 to be added for optimal syntheses of the target compounds can be taken from tables I - III.

General Procedure for the Reactions of Cyanopyridines, Alkyl Pyridinecarboxylates and Ethyl 4-Pyridazinecarboxylate with Alkoxycarbonyl Radicals

[Base:peroxide ratio = 1:3 (or 1:10)]

3.4g of (30mmol) 30% H_2O_2 [or 11.3g (100mmol)] was added with stirring to 45mmol (or 150mmol) of alkylpyruvate at -10 - 0°C. This solution was then added with stirring and cooling (-5 - 0°C) to a mixture of the heteroarene (10mmol), 3g of conc. H_2SO_4, 8g of H_2O, 8.3g (30mmol) [or 28.0g (100mmol)] of $FeSO_4.7H_2O$ and CH_2Cl_2. After further stirring for 15min, the resulting mixture was poured into ice water and the aqueous phase was exhaustively extracted with CH_2Cl_2. After drying the combined organic layers over anhydrous Na_2SO_4, the solvent and excess alkyl pyruvate were removed in vacuo.

Ethyl Cyanopyridinemonocarboxylates and Dialkyl Pyridine- and Pyridazinedicarboxylates:

Ethyl 2-Cyano-4-pyridinecarboxylate (5a).[8a] Separation by mplc (dichloromethane/ethyl acetate 18/1), analytic sample by recrystallisation from diethyl ether, yield:528mg (30%) of colourless crystals, mp 44 - 45°C (ref.[8a]: 44 - 45°C).

Ir 2250 ($\nu_{C\equiv N}$), 1730 ($\nu_{C=O}$); nmr 9.03 (d, J=5, 1H, H-6), 8.38 (d, J=2, 1H, H-3), 8.23 (dd, J=5, J=2, 1H, H-5), 4.54 (q, J=7, 2H, CH_2), 1.47 (t, J=7, 3H, CH_3).

Ethyl 6-Cyano-2-pyridinecarboxylate (6). Separation by mplc (dichloromethane/ethyl acetate 18/1), analytic sample by recrystallisation from diethyl ether, yield: 193mg (11%) of colourless crystals, mp<30°C. Ms M^+ at m/z 176, major peaks at 131, 104 (100%), 103, 76, 51, 50; ir 2255 ($\nu_{C\equiv N}$), 1732 ($\nu_{C=O}$); nmr 8.59-7.70 (m, 3H, H-3, H-4, H-5), 4.45 (q, J=7, 2H, CH_2), 1.41 (t, J=7, 3H, CH_3); Anal. calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.33; H, 4.65; N, 16.01.

Ethyl 3-Cyano-2-pyridinecarboxylate (7a). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 366mg (21%) of pale yellow crystals, mp 85 - 89°C. Ms M^+ at m/z 176, major peaks at 131, 104 (100%), 103, 77, 76; ir 2240 ($\nu_{C\equiv N}$), 1733 ($\nu_{C=O}$). For nmr data cf. ref.[7].

Ethyl 3-Cyano-4-pyridinecarboxylate (8a).[8b] Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 580mg (33%) of colourless crystals, mp 64°C (ref.[8a] mp 64°C). Nmr 9.12 (s, 1H, H-2), 9.03 (d, J=6, 1H, H-6), 8.03 (d, J=6, 1H, H-5), 4.51 (q, J=7, 2H, CH_2), 1.48 (t, J=7, 3H, CH_3).

Ethyl 5-Cyano-2-pyridinecarboxylate (9a).[8c] Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 394mg (22%) of colourless crystals, mp 70 - 73°C (ref.[8c] mp 73 - 74°C).

Ethyl 4-Cyano-2-pyridinecarboxylate (10a).[7] Spontaneously crystallizing colourless needles, yield: 1400mg (81%).

2-Ethoxycarbonyl-4-methoxycarbonylpyridine (5b). [From reactions starting with 1b: Separation by prep. tlc (dichloromethane/acetone 10/1)]. From reaction starting with 3c: Spontaneously crystallizing colourless crystals, yield: 1730mg (83%), mp 48 - 54°C. Ms M^+ at m/z 209, major peak at 137 (100%); ir 1738 ($\nu_{C=O}$); nmr 9.00 (d, J=6, 1H, H-6), 8.72 (d, J=2, 1H, H-3), 8.09 (dd, J=6, J=2, 1H, H-5), 4.55 (q, J=7, 2H, $\underline{CH_2}$-CH_3), 4.03 (s, 3H, CH_3), 1.47 (t, J=7, 3H, CH_2-$\underline{CH_3}$); Exact mass calcd. for $C_{10}H_{11}NO_4$: 209.068(81). Found: 209.067(5) ±0.001.

3-Ethoxycarbonyl-2-methoxycarbonylpyridine (7b). Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by subsequent mplc [diethyl ether/light petroleum (bp 50-70°C)10/1], yield: 522mg (25%) of a pale yellow oil. Ms M^+ at m/z 209, major peaks at 150, 107, 106, 79 (100%), 78; ir 1725, 1743 ($\nu_{C=O}$); nmr 8.90-8.77 (m, 1H, H-6), 8.36-8.19 (m, 1H, H-4), 7.68-7.43 (m, 1H, H-5), 4.42 (q, J=7,

2H, $\underline{CH_2}$-CH_3), 4.04 (s, 3H, CH_3), 1.40 (t, J=7, 3H, CH_2-$\underline{CH_3}$); Exact mass calcd. for $C_{10}H_{11}NO_4$: 209.068(81). Found: 209.067(3) ±0.001.

3-Ethoxycarbonyl-4-methoxycarbonylpyridine (8b). [From reactions starting with 3c: Separation by prep. tlc (dichloromethane/ethyl acetate 10/1)]. From reaction starting with 2b: Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 627mg (30%) of a pale yellow oil. Ms M^+ at m/z 209, major peaks at 165, 164 (100%), 150, 137, 78; ir 1738 ($\nu_{C=O}$); nmr 9.13 (s, 1H, H-2), 8.88 (d, J=6, 1H, H-6), 7.52 (d, J=6, 1H, H-5), 4.41 (q, J=7, 2H, $\underline{CH_2}$-CH_3), 3.88 (s, 3H, CH_3), 1.41 (t, J=7, 3H, CH_2-$\underline{CH_3}$); Exact mass calcd. for $C_{10}H_{11}NO_4$: 209.068(81). Found: 209.067(7) ±0.001.

5-Ethoxycarbonyl-2-methoxycarbonylpyridine (9b). Separation by mplc (dichloromethane/ethyl acetate 5/1), yield: 208mg of a 3:2 mixture of 7b and 9b. Nmr (besides signals of 7b) 9.31 (d, J=3, 1H, H-6), 8.53-8.38 (m, 1H, H-4), 8.34-8.10 (m, 1H, H-3, overlapping with H-4 of 7b), 4.60-4.23 (m, 2H, $\underline{CH_2}$-CH_3, overlapping with $\underline{CH_2}$-CH_3 of 7b), 4.02 (s, 3H, CH_3), 1.53-1.24 (m, 3H, CH_2-$\underline{CH_3}$, overlapping with CH_2-$\underline{CH_3}$ of 7b).

4-Ethoxycarbonyl-2-methoxycarbonylpyridine (10b). Separation by mplc (dichloromethane/ethyl acetate 1/1), analytic sample by recrystallisation from diethyl ether, yield: 1580mg (76%) of colourless crystals, mp 39 - 43°C. Ms M^+ at m/z 209, major peaks at 151 (100%), 123; ir 1725, 1735 ($\nu_{C=O}$); nmr 9.00 (d, J=6, 1H, H-6), 8.71 (d, J=2, 1H, H-3), 8.11 (dd, J=6, J=2, 1H, H-5), 4.48 (q, 2H, J=7, $\underline{CH_2}$-CH_3), 4.08 (s, 3H, CH_3), 1.44 (t, J=7, 3H, CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.29; N, 6.69. Found: C, 57.33; H, 5.32; N, 6.51.

4-Ethoxycarbonyl-5-methoxycarbonylpyridazine (13). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 1550mg (74%) of a pale yellow oil. Ms M^+ at m/z 210 (100%), major peaks at 165, 151, 138, 59, 51, 50; ir 1725, 1740 ($\nu_{C=O}$); nmr 9.57 (s, 2H, H-3, H-6), 4.47 (q, J=7, 2H, $\underline{CH_2}$-CH_3), 4.00 (s, 3H, CH_3), 1.41 (t, J=7, 3H, CH_2-$\underline{CH_3}$); Exact mass calcd. for $C_9H_{10}N_2O_4$: 210.064(06); Found: 210.064(3) ±0.001.

Diethyl Cyanopyridinedicarboxylates and Trialkyl Pyridinetricarboxylates:

Diethyl 3-Cyano-2,4-pyridinedicarboxylate (11a). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 322mg (13%) of colourless crystals, mp 46 - 47°C. Ms M^+ at m/z 248, major peaks at 203, 176 (100%), 148, 105, 103, 76;

ir 1743 ($\nu_{C=O}$); nmr 9.02 (d, J=5, 1H, H-6), 8.07 (d, J=5, 1H, H-5), 4.73-4.39 (m, 4H, 2x $\underline{CH_2}$-CH_3), 1.61-1.33 (m, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28; Found: C, 58.12; H, 4.88; N, 11.15.

Diethyl 3-Cyano-2,6-pyridinedicarboxylate (11b). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 5/1), yield: 99mg (4%) of colourless crystals, mp 113 - 115°C. Ms M^+ at m/z 248, major peaks at 204, 176 (100%), 148, 130, 104, 102, 76; ir 2250 ($\nu_{C\equiv N}$), 1743, 1723 ($\nu_{C=O}$); nmr 8.41-8.27 (m, 2H, H-4, H-5), 4.74-4.39 (m, 4H, 2x $\underline{CH_2}$-CH_3), 1.64-1.31 (m, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.00; H, 4.92; N, 11.16.

Diethyl 5-Cyano-2,4-pyridinedicarboxylate (11c). Separation by mplc (dichloromethane/ethyl acetate 5/1), analytic sample by recrystallisation from diisopropyl ether, yield: 669mg (27%) of colourless crystals, mp 107 - 108°C. Ms M^+ at m/z 248, major peaks at 176 (100%), 148, 103; ir 2245 ($\nu_{C\equiv N}$), 1737 ($\nu_{C=O}$); nmr 9.21 (s, 1H, H-6), 8.76 (s, 1H, H-3), 4.73-4.40 (m, 4H, 2x $\underline{CH_2}$-CH_3), 1.63-1.32 (m, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.13; H, 4.90; N, 11.37.

Diethyl 4-Cyano-2,3-pyridinedicarboxylate (11d). Separation and analytic sample by mplc (dichloromethane/ethyl acetate 8/1), yield: 95mg (4%) of a yellow oil. Ms M^+ at m/z 248, major peaks at 175, 131, 104 (100%), 103; ir 2245 ($\nu_{C\equiv N}$), 1735, 1728 ($\nu_{C=O}$); nmr 8.99 (d, J=5, 1H, H-6), 7.80 (d, J=5, 1H, H-5), 4.70-4.36 (m, 4H, 2x $\underline{CH_2}$-CH_3), 1.59-1.30 (m, 6H, 2x CH_2-$\underline{CH_3}$); Exact mass calcd. for $C_{12}H_{12}N_2O_4$: 248.079(7). Found: 248.078(9) $\pm$0.0012.

Diethyl 4-Cyano-2,5-pyridinedicarboxylate (11e). Separation by mplc (dichloromethane/ethyl acetate 8/1), recrystallisation from diisopropyl ether yields 513mg of a 9:1 mixture of 11e and 11f as colourless needles. Ir 1718, 1708 ($\nu_{C=O}$); nmr (besides signals of 11f) 9.50 (s, 1H, H-6), 8.49 (s, 1H, H-3), 4.73-4.40 (m, 4H, 2x $\underline{CH_2}$-CH_3), 1.64-1.33 (m, 6H, 2x CH_2-$\underline{CH_3}$). Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.01; H, 4.87; N, 11.37.

Diethyl 4-Cyano-2,6-pyridinedicarboxylate (11f). Separation by mplc (dichloromethane/ethyl acetate 8/1), analytic sample by recrystallisation from diethyl ether, yield: 124mg (5%) of colourless needles, mp 64°C (sinters). Ms M^+ at m/z 248, major peaks at 176 (100%), 148, 130; ir 1705 ($\nu_{C=O}$); nmr 8.50 (s, 2H, H-3, H-5), 4.52 (q, J=7, 4H, 2x $\underline{CH_2}$-CH_3), 1.47 (t, J=7, 6H, 2x CH_2-$\underline{CH_3}$); Anal. calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87 ; N, 11.28. Found: C, 57.99; H, 4.77; N, 11.42.

3-Ethyl 2,4-Dimethyl 2,3,4-Pyridinetricarboxylate (12a). Separation by mplc (dichloromethane/ethyl acetate 5/1), yield: 103mg of a 3:7 mixture of 12a and 8b as a yellow oil. Nmr (besides signals of 8b) 8.90 (d, J=6, 1H, H-6, overlapping with H-6 of 8b), 8.00 (d, J=6, 1H, H-5), 4.41 (q, J=7, 2H, $\underline{CH_2}$-CH_3, overlapping with $\underline{CH_2}$-CH_3 of 8b), 4.01 (s, 3H, CH_3), 3.90 (s, 3H, CH_3, overlapping with CH_3 of 8b), 1.41 (t, J=7, 3H, CH_2-$\underline{CH_3}$, overlapping with CH_2-$\underline{CH_3}$ of 8b).

5-Ethoxycarbonyl-2,4-dimethoxycarbonylpyridine (12b). Separation by mplc (dichloromethane/ethyl acetate 5/1), yield: 480mg (18%) of a pale yellow oil. Ms M^+ at m/z 267, major peaks at 222, 209 (100%), 151; ir 1740, 1730 ($\nu_{C=O}$); nmr 9.16 (s, 1H, H-6), 8.37 (s, 1H, H-3), 4.44 (q, J=7, 2H, $\underline{CH_2}$-CH_3), 4.06 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 1.40 (t, J=7, 3H, CH_2-$\underline{CH_3}$).

2,3-Diethoxycarbonyl-4-methoxycarbonylpyridine (12c). Separation by prep. tlc (dichloromethane/acetone 10/1), yield: 126mg of a 1:3 mixture of 12c and 5b as a pale yellow oil. Nmr (besides signals of 5b) 8.90 (d, J=6, 1H, H-6, overlapping with H-6 of 5b), 8.00 (d, J=6, 1H, H-5, overlapping with H-5 of 5b), 4.70-4.38 (m, 4H, 2x $\underline{CH_2}$-CH_3, overlapping with $\underline{CH_2}$-CH_3 of 5b), 3.98 (s, 3H, CH_3), 1.56-1.31 (m, 6H, 2x CH_2-$\underline{CH_3}$, overlapping with CH_2-$\underline{CH_3}$ of 5b).

2,5-Diethoxycarbonyl-4-methoxycarbonylpyridine (12d). Separation by prep. tlc (dichloromethane/acetone 10/1), yield: 98mg of a 2:1 mixture of 12d and 12e as a pale yellow oil. Nmr (besides signals of 12e) 9.19 (s, 1H, H-6), 8.34 (s, 1H, H-3), 4.52 (q, J=7, 4H, 2x $\underline{CH_2}$-CH_3, overlapping with $\underline{CH_2}$-CH_3 of 12e), 3.96 (s, 3H, CH_3), 1.45 (t, J=7, 6H, 2x CH_2-$\underline{CH_3}$, overlapping with CH_2-$\underline{CH_3}$ of 12e).

2,6-Diethoxycarbonyl-4-methoxycarbonylpyridine (12e). Separation by prep. tlc (dichloromethane/acetone 10/1), yield: 140mg (5%) of colourless crystals, mp 48°C (sinters). Ms M^+ at m/z 281, major peaks at 237, 209 (100%), 163; ir 1738 ($\nu_{C=O}$); nmr 8.79 (s, 2H, H-3, H-5), 4.52 (q, J=7, 4H, 2x $\underline{CH_2}$-CH_3), 4.03 (s, 3H, CH_3), 1.48 (t, J=7, 6H, 2x CH_2-$\underline{CH_3}$).

REFERENCES AND NOTES

1. Part 2: G. Heinisch and G. Lötsch, Tetrahedron, in the press.
2. Presented in part at the 12th European Colloquium on Heterocyclic Chemistry, Reims, France, 1986.
3. a. F. Minisci, Synthesis, 1973, 1;
   b. F. Minisci and O. Porta, Advan. Heterocycl. Chem., 1974, 123;

c. F. Minisci, Topics Curr. Chem., 1976, 62, 1.

4. E. Anders, H. Boldt, T. Clark, R. Fuchs and T. Gaßner, Chem. Ber., 1986, 119, 279.
5. R. Bernardi, T. Caronna, R. Galli, F. Minisci and M. Perchinunno, Tetrahedron Lett., 1973, 645.
6. G. Heinisch and G. Lotsch, Tetrahedron, 1985, 41, 1199.
7. Some of these results recently were presented in a preliminary communication: G. Heinisch and G. Lötsch, Angew. Chem., 1985, 97, 695; Angew. Chem. Int. Ed. Engl., 1985, 24, 692.
8. a. J. Seydel, K. Schaper, E. Wempe and H. Cordes, J. Med. Chem., 1976, 19, 483;
   b. L. Novacek, K. Palat, M. Celadnik and E. Matuskova, Ceskoslov. Farm., 1962, 11, 76; Chem. Abstr., 1962, 57, 15067i;
   c. H. Watanabe, Y. Kikugawa and S. Yamada, Chem. Pharm. Bull., 1973, 21, 465;
   d. B. Suvorov and O. Lebedeva, Izv. Akad. Nauk Kaz. SSR Ser. Khim., 1977, 27, 89; Chem. Abstr., 1978, 88, 50610m.
9. We were not able to separate completely the products obtained in this reaction. Compound 5b was identified by comparison of the ^{1}H-nmr spectrum of a crude product with the spectrum of an analytically pure sample isolated from the reaction of 3c. No attempts were made to identify further reaction products, they all are collected in table II as "unidentified products".
10. For a recent review see: G. Heinisch, Heterocycles, in the press.
11. W. Leanza, H. Becker and E. Rogers, J. Am. Chem. Soc., 1953, 75; 4086.

Received, 4th November, 1986