CONDENSATION REACTIONS OF 2,4- AND 2,6-DIMETHYLPYRIDINES AND THEIR 1-OXIDES*

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Dedicated to Prof. Jaroslav Staněk on the occassion of his 70th birthday.

Using the reactions of 2,4- and 2,6-dimethylpyridine-1-oxides with aromatic and heteroaromatic aldehydes under catalysis with potassium tert-butoxide (*E*)-aryl- and (*E*)-heteroarylethenylpyridine-1-oxides *IIIa*—*IIIe*, *IVa*—*IVc*, *Va*, *Vb* respectively, were prepared. 1-Oxides *IIIg*, *IVd*, *IVe* and *Vc* were obtained from the appropriate pyridine bases by oxidation with peracetic acid. Condensation of 2,4- and 2,6-dimethylpyridines with 3-pyridinecarbaldehyde gives a mixture of bases *VIa* and *VIc*, and *VIb* and *VId*, respectively. On Claisen condensation of 2,6- or 2,4-dimethylpyridine-1-oxide with diethyl oxalate in the presence of sodium hydride and potassium tert-butoxide lactone *XIIa* and *XIIb* is formed in addition to α-keto ester *XIa* and *XIb*, respectively. From esters *XIa* and *XIb* amides *XId* and *XIe* were prepared.

While the preparations and the reactions of aryl- and heteroarylethenylpyridines and quaternary salts, both mono- and disubstituted, have been investigated by a number of authors, among corresponding 1-oxides only monosubstituted derivatives have been studied. 4-(2-Phenylethenyl)pyridine-1-oxide (*Ia*) displays antineoplastic activity[1], stimulates the growth of some plants[2], inhibits acetylcholinetransferase[3]. Antineoplastic effects were also observed[4,5] in arylsulfonylhydrazones of 2-pyridinecarbaldehyde-1-oxides *II*. Another paper indicates the hydrochloride of oxide *IIb* as a potential antidote of organophosphates[6] and oxide *Ic* is an intermediate in the synthesis of a tetrazole derivative with antiallergic effects[7].

2-Arylethenylpyridine-1-oxides may be obtained – in addition to the oxidation of corresponding pyridine derivatives[8–10] – from 2- or 4-methylpyridine-1-oxides by condensation with aromatic aldehydes in the presence of strongly basic reagents – methoxide[11], ethoxide[12] or also potassium tert-butoxide[13]. Condensations of 2-methylquinoline-1-oxide[14] take place in an analogous manner. Oxides are formed in low yield in addition to the deoxidized product, under catalysis with piperidinium acetate in toluene[15], and in a better yield in the presence of pyridine and potassium

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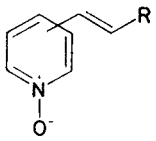
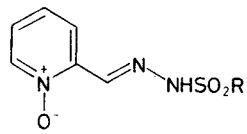
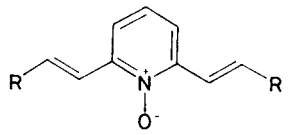
hydroxide[16]. Both 2- and 4-phenylethenylpyridine-1-oxides were prepared by the Wittig-Horner reaction via 2- or 4-pyridylmethylphosphonate-1-oxides, respectively[17].



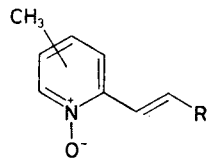
Ia, 4-(2-phenylethenyl)
Ib, 4-(2-(1-naphthyl)ethenyl)
Ic, 2-(2-phenylethenyl)



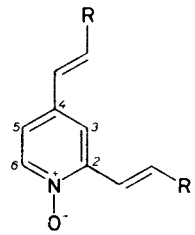
IIa, R = 4-methylphenyl
IIb, R = 2,4,6-trimethoxyphenyl

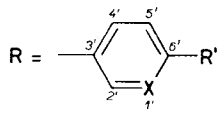


IIIa, R = 4-methoxyphenyl
IIIb, R = 4-dimethylaminophenyl
IIIc, R = 2-thienyl
IIId, R = 3-thienyl
IIIe, R = 3,4-methylendioxyphenyl
IIIf, R = phenyl
IIIg, R = 3-(1-oxido)pyridinyl



IVa, 6-methyl ; R = 3 4-methylendioxyphenyl
IVb, 4-methyl ; R = 4-dimethylaminophenyl
IVc, 4-methyl ; R = phenyl
IVd, 4-methyl ; R = 3-(1-oxido)pyridinyl
IVe, 6-methyl ; R = 3-(1-oxido)pyridinyl





Va, R' = dimethylamino ; X = CH
Vb, R' = H ; X = CH
Vc, R' = H ; X = $N^{+}-O^{-}$

We carried out the condensation of 2,6-dimethylpyridine-1-oxide by using two equivalents of potassium tert-butoxide. Through the reaction with 4-methoxybenzaldehyde, 2- or 3-thiophenecarbaldehyde or 4-dimethylaminobenzaldehyde we

TABLE I

Physical and analytical data of compounds *III*—*IX*

Compound Yield, %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
IIIa	193—196	$C_{23}H_{21}NO_3.0{\cdot}5\ H_2O$	74·98	6·02	3·80
23	(benzene)	(359·4)	75·13	5·76	3·60
IIIb	285—295	$C_{25}H_{27}N_3O$	77·89	7·06	10·90
89	(dimethylformamide)	(387·5)	77·72	7·19	10·80
IIIc	169—180	$C_{17}H_{13}NOS_2$	65·50	4·21	4·49
19	(benzene)	(311·4)	65·32	4·18	4·20
IIId	209—211	$C_{17}H_{13}NOS_2$			4·49[a]
26	(ethanol)	(311·4)			4·26
IIIe	257—265	$C_{23}H_{17}NO_5.0{\cdot}5\ H_2O$	68·14	4·27	3·45
16	(dimethylformamide)	(405·4)	67·91	4·32	3·50
IIIf	138—148[b]	$C_{21}H_{17}NO$	84·25	5·84	4·68
35		(299·5)	84·05	5·86	4·35
IIIg	265—267	$C_{19}H_{15}N_3O_3.0{\cdot}5\ H_2O$	66·66	5·00	12·27
68	(methanol–water 4 : 1)	(342·3)	66·66	4·97	12·31
IVa	160—162·5	$C_{15}H_{13}NO_3$	70·52	5·09	5·48
17	(2-propanol)	(255·3)	69·32	5·31	5·46
IVb	196—205	$C_{16}H_{18}N_2O.0{\cdot}5\ H_2O$	73·07	7·28	10·65
30	(benzene)	(263·0)	73·44	7·09	10·50
IVc	118—120	$C_{14}H_{13}NO$	79·60	6·20	6·63
41	(benzene–cyclohexane)	(211·2)	79·10	6·28	6·65
IVe	119—125	$C_{13}H_{12}N_2O_2.H_2O$	59·08	5·34	10·59
85	(2-propanol)	(263·3)	58·83	5·36	10·50
Va	258—268	$C_{25}H_{27}N_3O.0{\cdot}5\ H_2O$	76·11	7·51	10·66
15	(dimethylformamide)	(394·5)	76·41	7·28	10·66
Vb	160—166	$C_{21}H_{17}NO.0{\cdot}5\ H_2O$	81·79	5·88	4·54
25	(benzene–ethanol)	(308·3)	81·81	5·81	4·37
VIa	84·5—86	$C_{13}H_{12}N_2$	79·56	6·16	12·28
24	(cyclohexane)	(196·2)	79·85	6·01	12·28
VIb[c]	68—72	$C_{13}H_{12}N_2$	79·56	6·16	14·28
60	(b.p. 128°C/0·65 Pa)	(196·2)	79·54	6·14	14·21
VIc	120—123	$C_{19}H_{15}N_3$	79·97	5·30	14·72
19	(benzene–cyclohexane)	(285·3)	79·90	5·41	14·45
VId[d]	112	$C_{19}H_{15}N_3$	79·97	5·30	14·72
9·4	(cyclohexane–benzene, 7 : 1)	(285·3)	79·87	5·51	14·77

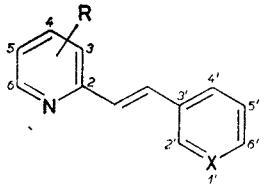
TABLE I
(*Continued*)

Compound Yield, %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
VII	218	$C_{14}H_{15}IN_2$	49·72	4·47	8·28
75	(methanol)	(388·18)	49·39	4·40	8·28
VIII	170—174	$C_{21}H_{21}I_2N_3.H_2O$	41·67	4·16	6·94[e]
96	(methanol–water)	(605·25)	41·70	4·07	6·98
IXa	226—227	$C_{20}H_{18}IN_3.0·5\ H_2O$	55·06	4·39	9·63
37	(methanol)	(436·3)	55·24	4·28	9·29
IXb	222—224	$C_{20}H_{18}IN_3.0·5\ H_2O$	55·06	4·39	9·63
31	(methanol–water)	436·3	55·42	4·26	9·74

[a] Calculated 20·91% S; found 20·90% S. [b] column chromatography; [c] *VIb* dihydrochloride, m.p. 210—213°C (ethanol–hexane); for $C_{13}H_{12}N_2.2$ HCl (269·2) calculated: 58·10% C, 5·24% H, 26·34% Cl, 10·41% N; found 57·73% C, 5·22% H, 26·28% Cl, 10·22% N; *VIb* dihydrobromide, m.p. 288—292°C (2-propanol–water, 10 : 1); for $C_{13}H_{12}N_2.2$ HBr (358·1) calculated: 43·61% C, 3·94% H, 44·63% Br, 7·82% N, found: 43·39% C, 3·94% H, 44·68% Br, 7·71% N; [d] *VId* trihydrochloride, m.p. 230—234°C (ethanol–water, 13 : 1), for $C_{19}H_{15}N_3.3$ HCl (394·7) calculated: 57·81%C, 4·59% H, 26·94% Cl, 10·65% N; found: 57·42% C, 4·66% H, 26·63% Cl, 10·50% N; [e] calculated 41·93% I, found 41·54% I.

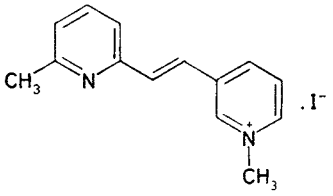
obtained oxides *IIIa*—*IIId* (Table I) in all instances as the sole products. Hence, the condensation took. place in both methyl groups. In the reaction with 3,4-methylenedioxybenzaldehyde monosubstituted derivative *IVa* was formed in addition to the disubstituted product *IIIe*. We also isolated two products, *Ve* and *IVb*, from the reaction of 2,4-dimethylpyridine-1-oxide with 4-dimethylaminobenzaldehyde. The reaction mixture also contained the second possible monosubstituted isomer, the product of the condensation in position 4, as evident from the analysis of the ^{1}H NMR spectrum of the crude oxide *IVb*. However, we were unable to isolate this oxide in a pure state. In our effort to obtain a larger amount of monosubstituted pyridine-oxides the condensation reactions were also carried out in the presence of only one equivalent of the aromatic aldehyde, but even in this case a mixture of both substances, *Va* and *IVb*, was formed and their ratio did not change much. In some reactions we were unable to obtain pure products using this method. Either complex mixtures were formed which could not be successfully separated by column chromatography (for example 2,4-dimethylpyridine-1-oxide with benzaldehyde or 2,6-dimethylpyridine-1-oxide with 3-pyridinecarbaldehyde), or, in some cases, the crude products were too hygroscopic. Therefore, further oxides were obtained from appropri-

ate arylethenylpyridines on oxidation with peracetic acid. In this manner the described (*E*)-2-(2-phenylethenyl)-4-methylpyridine and (*E,E*)-2,4-bis(2-phenylethenyl)pyridine[18] were prepared from 2,4-dimethylpyridine, and from them the oxides *IVc* and *Vb*. From the condensation of the β-picoline fraction with benzaldehyde and acetic anhydride, carried out as in ref.[18], and after separation of the bases and subsequent oxidation we obtained in addition to the known oxide[19] *Ia* (from 4-methylpyridine) also a new oxide, *IIIf* (from 2,6-dimethylpyridine). For the synthesis of arylethenyl derivatives in which R = 3-pyridinyl, we chose a modified Perkin's condensation[20]. Thus, 2,4- or 2,6-dimethylpyridine, when reacted with 3-pyridinecarbaldehyde in acetic anhydride and in the presence of anhydrous potassium acetate and under catalysis with iodine, give a mixture of mono- and disubstituted derivative *VIa* and *VIc* or *VIb* and *VId*,

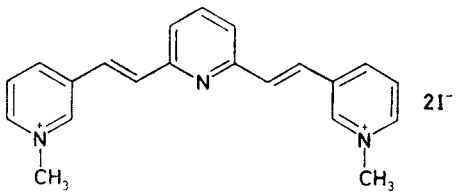


VIa, R = 4-methyl
VIb, R = 6-methyl
VIc, R = 4-(2-(3-pyridinyl)ethenyl)
VId, R = 6-(2-(3-pyridinyl)ethenyl)
In formulae *VIa*–*VId*: X = N

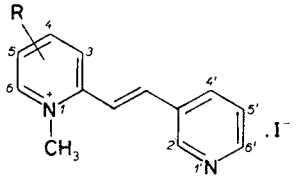
VIe, R = 6-(2-phenylethenyl)
VIf, R = 4-(2-phenylethenyl)
VIg, R = 4-methyl
In formulae *VIe*–*VIg*: X = CH



VII



VIII



IXa, 4-(2-(3-pyridinyl)ethenyl)
IXb, 6-(2-(3-pyridinyl)ethenyl)

respectively. In both cases the proportion of the disubstituted product was increased when a larger excess of aldehyde was used, but both bases were formed in all instances. After isolation by distillation or column chromatography the individual bases *VIa*–*VId* were again oxidized with peracetic acid to di- and tri-oxides *IVd*, *Vc*, or *IIIg*, *IVe*, respectively. Dioxide *IVd* is, however, contaminated with the monoxide according to its mass spectrum. From bases *VIb* and *VId* methiodides were prepared. As expected, the quaternization took place on sterically more accessible N-atoms under formation of quaternary salts *VII*, *VIII*. For the comparison of spectra we also prepared quaternary salts *IXa*, *IXb* by condensing the methiodides of 2,4- or 2,6-dimethylpyridine with 3-pyridinecarbaldehyde in the presence of piperidine, analogously as in refs[21-23].

So far the structure of arylethenylpyridine-1-oxides has been investigated by Katritzky et al.[24] by means of IR spectra and for some bases of this type the ^{1}H NMR spectra have also been published[25]. In our study high-resolution ^{1}H NMR spectroscopy was used (Table II) and for a number of derivatives the method of homocorrelated spectra (COSY), which is more advantageous than the method of selective decoupling. In the majority of cases we succeeded in assigning the signals of almost all aromatic protons. The ^{1}H NMR spectrum of(*E.E*)-2,6-bis(2-(4-dimethylaminophenyl)-ethenyl)-pyridine-1-oxide (*IIIb*) could not be measured owing to its very low solubility. This was also the obstacle for obtaining a valuable ^{1}H NMR spectrum for the analogously substituted 2,4-isomer *Va*. Its spectrum had to be measured in deuterated sulfuric acid or deuterated trifluoroacetic acid, but in these solvents this oxide is not stable. In all instances only *E,E*- or *E*-isomers were isolated; the values of the coupling constants of the double bond protons (J = 16–17 Hz) of arylethenylpyridine-1-oxides also correspond to the data published for the bases alone (e.g., (*E*)-4-(2-phenylethenyl)pyridine[25]).

In the last part of our study we investigated the condensation reactions of 2,4- and 2,6-dimethylpyridine-1-oxides with diethyl oxalate. Ethyl 3-(4-(1-oxido)pyridinyl)-2-oxopropanoate (*Xa*) is an intermediate in the synthesis of 2-(4-pyridinyl-1-oxido)--DL-, D- and L-alanine[26] and it is the starting substance in the synthesis of substituted thiazoles which are potential cardiotonics and blood pressure regulators[27]. These substances are without effect on the growth of some plants[28].

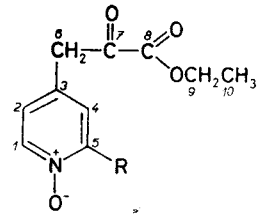
Condensation of methyl- or dimethylpyridine-1-oxides with diethyl oxalate was carried out in ethanol in the presence of potassium ethoxide[29] or sodium ethoxide[26] or sodium hydride in benzene[30]. In repeated condensations of 2,6-dimethylpyridine-1--oxide with diethyl oxalate we had to modify the conditions mentioned in literature[30] and heat the reaction mixture at 80°C, when the reaction started to proceed visibly. In addition to the already described oxopropanoate *XIa* we also obtained lactone *XIIa* which is formed probably by aldol condensation of two molecules of the sodium salt of α-keto ester *XIa* and subsequent cyclization. The structure of the compound was determined on the basis of its ^{1}H NMR and ^{13}C NMR spectra (APT techni-

TABLE II

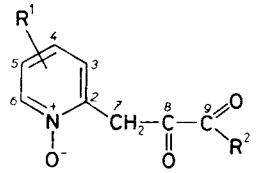
^{1}H NMR spectra of compounds *IIIa*, *IIIc*–*IIIg*, *VId*, *VIII* and *IXb*

Compound	CH=CH	H-3	H-4	Other signals
IIIc	7·36 d 7·81 d, 2 H J = 16·5	7·50 d, 2 H J = 8·0	7·20 t, 1 H J = 7·9	3·89 s, 6 H (2 × OCH_3); 6·95 dd, 4 H (2 H-1′, 2 × H-5′, J = 8·8, ^2J = 1·9); 7·60 d, 4 H (2 × H-2′, 2 × H-2′, 2 × H-4′)
IIIc	7·56 d, J = 16·0 7·70 d, J = 16·6	7·34 d, 2 H J = 7·8	7·11 t, 1 H J = 7·8	6·99–7·02 m, 2 H (2 × H-4′); 7·17 d, 2 H (2 × H-3′, J = 3·2); 7·28 d, 2 H (2 × H-5′, J = 4·7)
IIId	7·59 d, 2 H J = 16·6	7·44–7·46 m	7·17 t, 1 H J = 8·0	7·34 dd, 2 H (2 × H-5′, J = 4·9, ^2J = 3·0); 7·41 s, 2 H (2 × H-2′); 7·44–7·46 m, 6 H (2 × H-4′, H-3, H-5, CH=CH)
IIIe	7·36 d 7·70 d, 4 H J = 16·6	7·47 d, 2 H J = 7·9	7·21 t, 1 H J = 7·9	6·00 s, 4 H (2 × OCH_2O); 6·81 d, 2 H (2 × H-5′, J = 8·0); 7·04 d, 2 H (2 × H-4′, J = 8·0); 7·17 s, 2 H (2 × H-2′)
IIIf	7·44 d, 2 H 7·89 d, J = 16·6	7·52 d, 2 H J = 8·0	7·22 t, 1 H J = 8·0	7·61 d, 4 H (2 × H-2′, 2 × H-4′, J = 6·9); 7·30–7·41 m, 6 H (2 × H-1′, 2 × H-5′, 2 × H-6′)
IIIg	7·39 d, 2 H 7·83 d, 2 H	7·54–7·58 m	7·25–7·34 m	7·25–7·34 m, 3 H (H-4 and 2 H-5′); 7·54–7·58 m, 4 H (H-3, H-5 and 2 × H-4′); 8·17 d, 2 H (2 × H-6′)
VId	7·26 d, 2 H 7·72 d, 2 H J = 16·2	7·29–7·32 m	7·69 t, 1 H J = 7·7	7·29–3·32 m, 4 H (2 × H-5′); 7·92 d, 2 H (2 × H-4′, J = 8·0); 8·54 d, 2 H (2 × H-6′, J = 4·7); 8·83 s, 2 H (2 × H-2′)
VIII	7·97–7·82 m 7·82 d, 2 H J = 15·9	7·59 d, 2 H J = 7·7	7·97 t 7·82 m	4·54 s, 6 H (2 × NCH_3); 8·17 t, 4 H (2 × H-5′, 2 × H-6′); 8·91 m, 4 H (2 × H-4′, 2 × H-6′); 9·53 s, 2 H (2 × H-2′)
IXb	7·81 d, 2 H 7·86 d, 2 H J = 16·2	8·36 d, J = 8·2	8·54 t, 1 H J = 8·2	4·55 s, 3 H (NCH_3); 7·54–7·57 m, 2 H (2 × H-5′); 8·36 d, 4 H (2 × H-4′ and H-3, H-5); 8·65 d, 2 H (2 × H-6′, J = 4·6); 9·01 s, 2 H (H-2′)

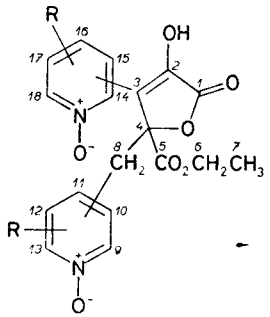
que[31]). From the two possible structures, *XIIa*, *XIII*, we give preference to *XIIa* which is an analogue of the derivative of γ-butyrolactone formed from 2-oxopropa-



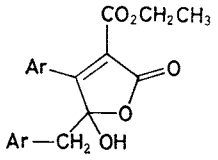
Xa, R = H
Xb, R = CH_3



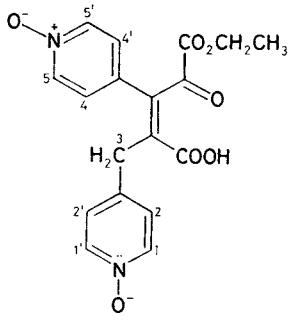
XIa, R^1 = 6-CH_3; R^2 = OC_2H_5
XIb, R^1 = 4-CH_3; R^2 = OC_2H_5
XIc, R^1 = H; R^2 = OC_2H_5
XId, R^1 = 6-CH_3; R^2 = NH_2
XIe, R^1 = 4-CH_3; R^2 = NH_2



XIIa, 2-(6-methyl-1-oxido)pyridinyl
XIIb, 2-(4-methyl-1-oxido)pyridinyl
XIIc, 4-(2-methyl-1-oxido)pyridinyl
XIId, 2-(1-oxido)pyridinyl



XIII



XIV

noic acid under the effect of hydrochloric acid or prolonged standing[32,33]. Both products, *XIa* and *XIIa*, were also obtained from a condensation carried out in the presence of potassium tert-butoxide. Condensation of 2,4-dimethylpyridine-1-oxide with diethyl oxalate by means of sodium hydride again led to a mixture of keto ester *XIb* and lactone *XIIb*. During the condensation by means of potassium tert-butoxide keto ester *Xb* is also formed in addition to compounds *XIb* and *XIIb*. During the condensation of 2-methylpyridine-1-oxide by means of potassium tert-butoxide we also isolated lactone *XIId* in addition to the described keto ester *XIIc* (ref.[29]). In the condensation of 4-methylpyridine-1-oxide keto ester *Xa* (ref.[26]) was formed, and a compound was isolated from the acidified aqueous layer as a by-product, for which we propose the structure *XIV* on the basis of its ^{1}H NMR and IR spectra. The same reaction products were described in the paper by Bixler and Niemann[26] who carried out the condensation with sodium hydride in ethanol. We consider that compound *XIV* is identical with the unidentified compound of m.p. 187–188°C, characterized as an acid with a molecular mass of about 300 (ref.[26]). From keto esters *XIIa* and *XIIb* the amides *XIId* and *XIIe* were prepared and the keto ester *XIIb* was converted to thiosemicarbazone.

EXPERIMENTAL

The NMR spectra were measured on a Bruker AM 400 instrument, ^{1}H at 400·13 MHz, ^{13}C at 100·62 MHz in deuteriochloroform, unless stated otherwise. As internal standard tetramethylsilane was used, the chemical shift values are given in δ-units (ppm), the coupling constants J in Hz. The mass spectra were measured on a Jeol DX 303/DA 5000 instrument at 70 eV, temperature of the source up to 300°C. The samples were introduced by direct inlet. The IR spectra were measured on a Perkin–Elmer 325 spectrophotometer in chloroform or in KBr pellets.

Thin-layer chromatography was carried out on Silufol UV 254; the following solvent systems were used as mobile phases: chloroform–ethanol (9 : 1), benzene–ethanol (10 : 1), benzene–2-propanol–water–25% ammonia (10 : 5 : 1 : 1) and chloroform–methanol (9 : 1). Detection was carried out using the Universal-UV Lampe Camag (Mutenz, Switzerland) at the wavelengths 254 and 366 nm, and with iodine vapours. Column chromatography was carried out on silica gel (Silpearl UV 254), gas chromatography on a Chrom 5 chromatograph with FID and 2 500 × 3 mm columns packed with 3% OV 225 on Chromaton N-AW-DMCS, using nitrogen as carrier gas.

(*E,E*)-2,6-Bis(2-(4-methoxyphenyl)ethenyl)pyridine-1-oxide (*IIIa*)

2,6-Dimethylpyridine-1-oxide (3·0 g; 25 mmol) and 4-methoxybenzaldehyde (6·8 g; 50 mmol) were added gradually and under stirring to a boiling solution of potassium tert-butoxide in tert-butyl alcohol (prepared from 2·2 g (56 mmol) of potassium in 50 ml of tert-butyl alcohol, under nitrogen) and the mixture was heated under reflux for 30 min. The tert-butyl alcohol was evaporated in a vacuum and the separated crystals were boiled with benzene. The insoluble fraction was filtered off under suction and the solid material, obtained after concentration of the benzene solution, was crystallized twice from benzene. Yield, 2·1 g of 1-oxide *IIIa*, m.p. 193–196°C. Oxides *IIIb*–*IIId* were obtained in an analogous manner (Tables I and II).

(*E,E*)-2,6-Bis(2-(3,4-methylenedioxyphenyl)ethenyl)pyridine-1-oxide (*IIIa*)
and (*E*)-6-Methyl-2-(2-(3,4-methylenedioxyphenyl)ethenyl)pyridine-1-oxide (*IVa*)

It was prepared analogously as *IIIa*. The crystals separated after the reaction were filtered off under suction and crystallized twice from dimethylformamide. Yield, 16% of oxide *IIIe*. The mother liquors were concentrated in a vacuum and water was added to precipitate a solid which was crystallized from 2-propanol. Yield, 17% of oxide *IVa* (Tables I and III).

(*E, E*)-2,4-Bis(2-(4-dimethylaminophenyl)ethenyl)pyridine-1-oxide (*Va*) and
(*E*)-2-(2-(4-Dimethylaminophenyl)ethenyl)-4-methylpyridine-1-oxide (*IVb*)

a) The reaction mixture (analogous as in the preparation of *IIIa*, the molar ratio of potassium tert-butoxide, pyridine oxide and the aldehyde was 1 : 1 : 1) was mildly refluxed for 3 h, the solid material (A) was filtered off and the filtrate concentrated in vacuo (fraction B). The working up of the fraction A: the solid material was boiled with benzene, the insoluble part was filtered off under suction while hot and then crystallized three times from dimethylformamide to give a fraction of crystalline oxide *Va*. From the benzene solution crude oxide *IVb* was obtained which was crystallized three times from benzene (Tables I, III). Fraction B was decanted using hot benzene, the insoluble part was filtered off and cyclohexane was added to the benzene solution. The separated crystals were filtered off under suction and crystallized from benzene to give a further part of oxide *IVb*. Yields, 14% of oxide *Va* and 25% of oxide *IVb*, in addition to a mixture of both compounds (about 40%), which was not further separated.

b) From the reaction mixture (potassium tert-butoxide–pyridine oxide–aldehyde 2 : 1 : 2) 15% of oxide *V* and 30% of oxide *IVb* were isolated in an analogous manner. According to ^{1}H NMR spectrum the latter compound was contaminated with the isomeric oxide with a substituent in position 4 (ratio 6 : 1). In the ^{1}H NMR spectrum the signals 2·52 s, 3 H (CH_3 in position 2 of the pyridine ring); 3·08 s, 6 H ($N(CH_3)_2$), and further analogous signals (always a little shifted to higher δ-values) were present in addition to the signals of the prevailing oxide *IVb* (Table II). The ^{1}H NMR spectrum of *Va* (CF_3COOD): 3·56 s, 12 H (CH_3); 8·39 s, 1 H (H-3 pyridine nucleus); 8·67 bs, 1 H (H-5 of the pyridine nucleus); 7·42—8·02 m, 13 H (aromatic protons, protons on double bonds and H-6 pyridine nucleus). ^{1}H NMR (D_2SO_4): 2·86 s, 12 H (CH_3); 6·8—6·85 d, 1 H, 7·10—7·23 m, 6 H, and 7·39—7·45 m, 6 H (aromatic protons, double bond protons, and the proton 1 H of the pyridine nucleus); 7·78 s, 1 H and 7·98 s, 1 H (H-pyridine nucleus). IR spectrum (KBr) cm^{-1}: 965 m (CH=CH *trans*).

(*E*)-4-(2-Phenylethenyl)pyridine-1-oxide (*Ia*)
and (*E, E*)-2,6-Bis(2-phenylethenyl)pyridine-1-oxide (*IIIf*)

Benzaldehyde (558 g) and acetic anhydride (866 g; 8·7 mol) were added to 4-methylpyridine (420 g; from Loba, Wien) containing according to GLC 38% of 2,6-dimethylpyridine and 55% of a mixture of 3-methyl- and 4-methylpyridine, and the mixture was refluxed for 25 h. After distilling off of the unreacted aldehyde and acetic anhydride 3-methylpyridine was eliminated by steam distillation. The solid compound separated from the distillation residue was filtered off under suction and washed with ethanol. Yield, 640 g of a solid product, representing a mixture of two compounds (according to TLC). After crystallization from acetone 104 g (25%) of *VIe* were obtained, m.p. 168—169°C, ref.[34] gives m.p. 165—166°C. The mother liquors were partly concentrated in a vacuum and the separated product (208 g) was suction dried and crystallized from a mixture of ethanol–water 4 : 1. The (*E*)-4-(2-phenylethenyl)pyridine obtained melted at 131°C, ref.[35] gives m.p. 132—133°C.

^{1}H NMR data of compounds *IVa*–*IVe*, *VIa*, *VIb*, *VIg* and *VII*

Compound	CH=CH	H-3	H-4	H-5	CH_3	Other signals
IVa	7·34 d, 1 H 7·70 d, 1 H J = 16·0	7·06–7·36 m	7·49 bs	7·06–7·46 m	2·54	5·98 s, 2 H (OCH_2O); 6·81 d, 1 H (H-5′, J = 8); 7·01 d, 1 H (H-4′, J = 8·0); 7·06–7·36 m, 3 H (H-3, H-5, H-2′)
IVb	7·32 d, 1 H 7·64 d, 1 H J = 16·5	7·41 s 1 H	(8·11 d) 1 H J = 7·0	6·45 d 1 H J = 7·0	2·43 s 3 H	3·00 s, 6 H ($N(CH_3)_2$); 6·70 d, 2 H (H-1′, H-5′, J = 8·7); 7·52 d, 2 H (H-2′, H-4′, J = 8·7)
IVc	7·42 d, 1 H 7·81 d, 1 H J = 16·7	7·30–7·38 m	(8·15 d) 1 H J = 6·7	6·93 dd J(5, 6) = 6·3 J(5, 3) = 2·4	2·37 s 3 H	7·30–7·38 m, 4 H (H-1′, H-5′, H-6′); 7·61 d, 2 H (H-2′, H-4′, J = 7·3)
IVd	7·39 d, 1 H 7·78 d, 1 H J = 16·8	7·40 s 1 H	8·16 d J = 6·7	7·02 d 1 H J = 6·7	2·36 s 3 H	7·27–7·31 m, 1 H (H-5′); 7·55 d, 1 H (H-4′, J = 8·1); 8·16 d, 2 H (H-6, H-6′); 8·38 s, 1 H (H-2′)
IVe	7·69 d, 1 H 7·76 d, 1 H J = 16·7	7·67–7·71 m 1 H	7·25 t 1 H J = 7·8	7·38–7·66 m	2·36 s 3 H	7·38–7·66 m, 2 H (H-3, H-5′); 8·14 d, 1 H (H-6′, J = 6·2); 8·45 s, 1 H (H-2′); 7·63 d, 1 H (H-4′, J = 7·8)
VIa	7·18 d, 1 H 8·61 d, 1 H J = 16·1	7·23 s 1 H	(8·47 d) 1 H J = 4·9	7·01 d 1 H J = 4·9	2·46 s 3 H	7·27–3·32 m, 1 H (H-5′); 7·87 m, 1 H (H-4′); 8·51 d, 1 H (H-5′, J = 4·7); 8·79 s, 1 H (H-2′)
VIb	7·21 d, 1 H 7·58 d, 1 H J = 16·4	7·05 d 1 H[a] J = 7·7	(7·56 t) 1 H J = 7·7	7·22 d 1 H[a] J = 6·9	2·59 s 3 H	7·26–7·29 m, 1 H (H-5′); 7·87 dt, 1 H (H-4′, J = 7·8, ^2J = 1·8); 8·50 dd, 1 H (H-6′, J = 4·6, ^2J = 1·5); 8·78 e, 1 H (H-2′, J = 2·0)
VIg	7·13 d, 1 H 7·62 d, 1 H J = 16·2	7·20 s 1 H	8·45 d 1 H J = 4·9	6·96 d 1 H J = 4·9	2·35 s 4 H	7·26–7·30 m, 1 H (H-6′); 7·34–7·38 m, 2 H (H-1′, H-5′); 7·57 d, 2 H (H-2′, H-4′, J = 5·3)
VII	7·72 d, 1 H 7·65 d, 1 H J = 16·2	7·41 d 1 H J = 7·7	(7·74 t) 1 H J = 7·8	7·23 d 1 H J = 7·7	2·52 s 3 H	8·10 m, 1 H (H-5′); 8·80 d, 1 H (H-6′, J = 5·9); 8·84 d, 1 H (H-4′; J = 8·1); 9·33 s, 1 H (H-2′)

[a] The assignment for H-3 and H-5 may be reserved.

Persteril (30 g; 380 mmol), i.e. a 36% aqueous solution of peracetic acid, was added to a solution of base *VIe* (10 g; 350 mmol) in ethanol (240 ml) and the mixture was refluxed for 4 h. After evaporation of the solvent in a vacuum a solid substance separated which was dissolved in water and then extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and the chloroform distilled off. The residue (6·9 g) was a yellow substance which was purified on a silica gel column. Yield, 3·7 g (35%) of oxide *IIIf* (Tables I, II).

(*E*)-2-(2-Phenylethenyl)pyridine was oxidized to oxide *Ia* in an analogous manner (ref.[12]).

(*E*)-2-(2-Phenylethenyl)-4-methylpyridine-1-oxide (*IVc*) and
(*E,E*)-2,4-Bis(2-phenylethenyl)pyridine-1-oxide (*Vb*)

(*E,E*)-2,4-Bis(2-phenylethenyl)pyridine (*VIf*) and (*E*)-2-(2-phenylethenyl)-4-methylpyridine (*VIg*) were prepared according to lit.[18]. ^{1}H NMR spectrum *VIf*: 7·02 d, 1 H, 7·18 d, 1 H, 7·32 d, 1 H, and 7·68 d, 1 H (CH=CH *trans*, J = 16·1); 7·22–7·25 m, 2 H and 7·31–7·41 m, 5 H (H-5, H-1′, H-5′, H-6′, H-1″, H-5″, H-6″); 7·44 s, 1 H, (H-3); 7·54 d, 2 H and 7·59 d, 2 H (H-2′, H-4′, H-2″, H-4″, J = 7·3); 8·56 d, 1 H (H-6, J = 5·1). The oxidation of both bases to pyridine oxides *IVc* and *Vb* was carried out analogously as in the preceding experiment. Oxide *Vb* (Table I), ^{1}H NMR spectrum: 7·01 d, 1 H and 7·20 d, 1 H (CH=CH *trans*, J = 16·2); 7·49 d, 1 H and 7·82 d, 1 H (CH=CH *trans*, J = 16·2); 7·26 dd, 1 H (H-5, ^2J = 2·5, J = 5·1); 7·31–7·42 m, 6 H (H-1′, H-5′, H-6′, H-1″, H-5″, H-6″); 7·54 d, 2 H and 7·64 d, 2 H (H-2′, H-4′, H-2″, H-4″, J = 7·2); 7·68 d, 1 H (H-3, J = 2·4) and 8·20 d, 1 H (H-6, J = 6·8).

(*E, E*)-2,6-Bis(2-(3-pyridinyl)ethenyl)pyridine-1,1′,1″-trioxide (*IIIg*)
and (*E*)-6-Methyl-2-(2-(3-pyridinyl)ethenyl)pyridine-1,1′-dioxide (*IVe*)

a) A mixture of 5·4 g (50 mmol) of 2,6-dimethylpyridine, 8·0 g (75 mmol) of 3-pyridinecarbaldehyde, 7·8 g (75 mmol) of acetic anhydride, 2·5 g of anhydrous CH_3COOK and a grain of iodine as catalyst was heated at 170–180°C (bath temperature) for 10 h, then alkalized with 40% NaOH and steam distilled. According to titration the distillate contained 12·35 mmol (24%) of unreacted 2,6-dimethylpyridine. The dark brown oily residue (a mixture of two substances according to TLC) was extracted with three 50 ml portions of chloroform, the extract was washed with water and dried over sodium sulfate. After evaporation of chloroform and vacuum distillation, 4·4 g (60%) of base *VIb* were obtained, which solidified after cooling (Tables I, III). From the distillation residue (4·2 g) the disubstituted base *VId* (Tables I, II) was obtained by column chromatography on silica gel.

b) Analogously 4·95 mmol (12%) of unreacted 2,6-dimethylpyridine, 2·76 g (45%) of *VIb* and 3·9 g (39%) of *VId* were obtained from 50 mmol of 2,6-dimethylpyridine and 150 mmol of 3-pyridinecarbaldehyde. Both new bases were oxidized with peracetic acid to the oxides *IVe* and *IIIg* (Tables I–III).

(*E, E*)-2,4-Bis-(2-(3-pyridinyl)ethenyl)pyridine-1,1′,1″-trioxide (*Vc*)
and (*E*)-4-Methyl-2-(2-(3-pyridinyl)ethenyl)pyridine-1,1′-dioxide (*IVd*)

The bases *VIa* and *VIc* were prepared analogously as *VIb* and *VId* from 2,4-dimethylpyridine, acetic anhydride and anhydrous CH_3COOK and the obtained mixture of bases was separated by column chromatography (Tables I, II). IR spectrum, *VIa* (KBr) cm^{-1}: 975 s (CH=CH *trans*); *VIc* 965 s. ^{1}H NMR spectrum, *VIc*: 7·10 d, 1 H and 1 H from the multiplet 7·27–7·35 (J = = 16·5); 7·68 d, 1 H and 7·25 d, 1 H (J = 16·1, CH=CH *trans*); 3 H from the multiplet 7·25 to

7·35 (totally 4 H) (H-5, H-5′, H-5″); 7·48 s, 1 H (H-3); 8·61 d, 1 H (H-6, J = 5·1); 7·88 d, 1 H and 7·86 d, 1 H (H-4′, H-4″, J = 8·5); 8·56 d, 1 H and 8·52 d, 1 H (H-6′, H-6″, J = 4·7).

Oxidation of *VIc* with peracetic acid gave trioxide *Vc* (Table I). ^{1}H NMR spectrum ($(CD_3)_2SO$): 7·33 d, 1 H and 7·40 d, 1 H (J = 16·4) and 7·73 d, 1 H, 7·70 d, 1 H (J = 16·7, CH=CH *trans*); 7·40–7·48 m, 2 H (H-5′, 5″); 7·53 d, 1 H (H-5, J = 6·8); 7·58 d, 1 H (J = 7·9) (H-4′, H-4″, J = 8·2); 8·03 s, 1 H (H-3); 8·14 d, 1 H, 8·26 d, 1 H (H-6′, H-6″, J = 6·5); 8·27 d, 1 H (H-6, J = 6·8); 8·48 s, 2 H (H-2′, H-2″).

Oxidation of base *VIa* gave dioxide *IVd*, which, however, was contaminated with less than 10% of mono-oxide (Table II) according to the sublimation curve taken during the MS measurement and also according to ^{1}H NMR spectrum.

(*E,E*)-1-Methyl-2,4-bis(2-(3-pyridinyl)ethenyl)pyridinium Iodide (*IXa*)

A mixture of 0·96 g (9 mmol) 3-pyridinecarbaldehyde, 0·67 g (2·7 mmol) 2,4-dimethylpyridine methiodide and 6 drops of piperidine in 12 ml of methanol was refluxed for 8 h. After evaporation of the solvent a greasy substance was obtained from which a yellow crystalline compound separated after one year's standing at room temperature. This was filtered off under suction and washed with ether. Methiodide *IXa* (Table I), ^{1}H NMR spectrum: 4·38 s, 3 H (CH_3); 8·08 dd, 1 H (H-5, $^2J(5, 3)$ = 2, $J(5, 6)$ = 7·6); 8·65 d, 1 H (H-3, J = 2); 8·74 d, 1 H (H-6, J = 6·7); 7·52–7·56 m, 2 H (H-4′, H-4″); 8·26–8·29 m, 1 H and 8·36–8·39 m, 1 H (H-5′, H-5″); 8·58 dd, 1 H and 8·61 dd, 1 H (^2J = 1·5, J = 4·6; H-6′, H-6″); 8·89 d, 1 H and 8·96 d, 1 H (H-2′, H-2″, J = 2·1); 7·61 d, 1 H (J = 16·5), 7·71 d, 1 H (J = 16·1), 8·01 d, 1 H (J = 16·1); 8·06 d, 1 H (J = 16·5), (2 × CH=CH *trans*).

Methiodide *IXb* (Tables I, II) was prepared in an analogous manner.

Ethyl 3-(2-(6-Methyl-1-oxido)pyridinyl)-2-oxopropanoate (*XIa*) and 4-Ethoxycarbonyl-2-hydroxy-3-(2-(6-methyl-1-oxido)pyridinyl)-4--(2-(6-methyl-1-oxido)pyridinylmethyl)-2-buten-4-olide (*XIIa*)

a) NaH (2·9 g) in the form of a 75% suspension in mineral oil (i.e. 90 mmol of 100% NaH) was added to a solution of 10·0 g (80 mmol) of 2,6-dimethylpyridine-1-oxide and 12·0 g (80 mmol) of diethyl oxalate in 11 ml of benzene and the mixture was stirred and heated at 85°C (bath temperature). After half an hour of heating a yellow solid started to separate. When the development of hydrogen ceased the salt was filtered off, dissolved in 100 ml of water and the mineral oil was extracted with ether. The aqueous layer was acidified with 11 ml of 3% HCl and extracted with chloroform. After drying over Na_2SO_4 and evaporation of chloroform 5 g of an oily product were obtained, representing according to TLC a mixture of substances. The mixture was chromatographed on a silica gel column with benzene and benzene–ethanol (20 : 1). Yield, 2·65 g (16%) of α-keto ester *XIa*, m.p. 40–42°C. After crystallization from benzene–light petroleum 1 : 10 the m.p. was 56–58°C (ref.[30] gives m.p. 56–58·5°C). ^{1}H NMR spectrum: 1·38 t, 3 H (CH_3CH_2O, J = 7·1); 2·59 s, 3 H (CH_3); 4·34 q, 2 H (CH_3CH_2O, J = 7·1); 4·16 s, 1 H (CH_2CO); 6·47 s, 1/2 H (CH=); 7·15–7·19 m, 2 H (H-3, H-5); 7·32 t, 1 H (H-4, J = 7·9); 10·62 s, 1/2 H (OH) (in chloroform solution the keto–enol equilibrium 1 : 1). IR spectrum ($CHCl_3$) cm^{-1}: 1 630 s, 1 720 s (CO).

Column chromatography gave a further 0·15 g (1%) of lactone *XIIa*, after crystallization from 2-propanol the m.p. was 154–156°C (Table IV). ^{1}H NMR spectrum: 1·25 t, 3 H (CH_3CH_2O, J = 7·1); 2·28 s and 2·61 s, 6 H (CH_3 on the pyridine cycles); 3·55 d, 1 H and 4·38 d, 1 H (H-8, J = 14·4); 4·30 q, 2 H (CH_3CH_2O, J = 7·1); 7·11 dd, 1 H (^2J = 2·1, J = 7·4); 7·23 dd, 1 H (^2J = 2·1, J = 7·3) and 7·29–7·32 m, 2 H (H-10, H-12, H-15, H-17); 7·04 t, 1 H (J = 7·7) and

TABLE IV

Physical and analytical data of compounds *X*—*XIV*

Compound Yield, %	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found % C	 % H	 % N	IR, cm^{-1} ($CHCl_3$)
Xb	162—166	$C_{11}H_{13}NO_4$	59·19	5·87	6·27	1 700 s (C=O)
3·4	(benzene–dioxane)	(223·2)	59·12	5·88	6·92	3 460 s (OH)
XIb	66—68·5	$C_{11}H_{13}NO_4$	59·19	5·87	6·27	1 630 s
52	(cyclohexane–benzene)	(223·2)	59·61	5·91	6·18	1 720 s (C=O)
XIb[a]	220—225	$C_{12}H_{16}N_4O_3S$	48·64	5·44	18·90	1 725 s, 1 520 s (C=O)
45	(dioxane)	(296·3)	48·61	5·40	18·37	3 150 s, 1 610 s (NH)
XId	165—170	$C_9H_{10}N_2O_3$	55·92	5·21	—	1 640 s, 1 695 s (C=O)
92	(acetone)	(193·3)	55·75	5·38	—	3 420 m, 3 540 m (NH_2)
XIe	192	$C_9H_{10}N_2O_3$	55·92	5·21	14·49	1 640 s, 1 695 s (C=O)
(68)	(acetone)	(193·3)	55·78	5·24	14·54	3 420 m, 3 540 m (NH_2)
XIIa	154—156	$C_{20}H_{20}N_2O_7$	59·99	5·03	6·99	1 740 s, 1 780 s (C=O)
1·0	(2-propanol)	(400·4)	60·79	5·15	6·90	
XIIb	142—146	$C_{20}H_{20}N_2O_7$	59·99	5·03	6·99	1 640 s, 1 740 d, 1 780 s
1·0	(benzene)	(400·4)	59·30	5·11	6·70	(C=O)
XIId	156—160	$C_{18}H_{16}N_2O_7.0{\cdot}5\ H_2O$	56·69	4·49	7·34	1 740 s, 1 757 s (C=O)
1·0	(benzene[c])	(381·3)	56·82	4·40	7·37	3 440 m, (OH)
XIV	177—179·5	$C_{18}H_{16}N_2O_7.0{\cdot}5\ H_2O$	56·69	4·49	7·34	1 740 s, 1 780 s (C=O)
11	(water)	(381·3)	57·18	5·43	7·31	3 400 s[b] (OH)

[a] Thiosemicarbazone of *XIb*; [b] KBr; [c] decantation only.

7·49 t, 1 H (J = 7·9) (H-11, H-16); 14·13 s, 1 H (OH). ^{13}C NMR spectrum (APT technique); 13·89 (C-7); 18·25 and 18·88 (CH_3 on the pyridine cycles), 33·61 (C-8), 63·30 (C-6); 83·23 (C-4): 16·39 (C-3); 121·25, 124·07, 124·57, 125·41, 126·07, 130·58 (C-10, C-11, C-12, C-15, C-16, C-17), 144·32, 144·74 and 148·87 (C-2, C-9, C-14); 150·49 and 150·59 (C-13, C-18); 165·89 and 168·95 (C-1, C-5). Mass spectrum, m/z (% rel. int.): 400 M^+ (4), 220 (39), 192 (100), 146 (72), 92 (74).

b) Potassium tert-butoxide (16·8 g; 88 mmol) was dissolved in 100 ml of ethanol and 12·0 g (80 mmol) of diethyl oxalate were added. After stirring at room temperature for 15 min a solution of 2,6-dimethylpyridine-1-oxide (10·0 g; 80 mmol) in 20 ml of absolute ethanol was added dropwise and the mixture was stirred for 4 h and then allowed to stand at room temperature for 4 days. Ethanol was evaporated in a vacuum and the separated yellow salt was triturated with benzene, filtered off under suction and washed with ether. After dissolution in water the solution was acidified with 3% HCl to pH 7, extracted with chloroform and the aqueous layer acidified to pH 5 and extracted a second time. Both chloroform extracts were dried over Na_2SO_4 and evaporated in a vacuum to dryness. From the first extract 6·4 g (36%) of α-keto ester *XIa* were obtained. After crystallization from light petroleum–benzene (10 : 1) the m.p. was 55—58°C. The second extract was triturated with benzene and filtered to give 0·3 g (2%) of lactone *XIIa*, m.p. 151—153°C (from 2-propanol).

Ethyl 3-(2-(4-Methyl-1-oxido)pyridinyl)-2-oxopropanoate (*XIb*),
4-Ethoxycarbonyl-2-hydroxy-3-(2-(4-methyl-1-oxido)pyridinyl)-4-
-(2-(4-methyl-1-oxido)pyridinylmethyl)-2-buten-4-olide (*XIIb*) and
Ethyl 3-(4-(2-Methyl-1-oxido)pyridinyl)-2-oxopropanoate (*XIVa*)

a) The reaction was carried out analogously as in the preparation of *XIa* and *XIIa* from 2·5 g (20 mmol) of 2,4-dimethylpyridine-1-oxide, 3·0 g (20 mmol) of diethyl oxalate and 0·75 g 75% NaH. After dissolution in water of the sodium salt formed and extraction with ether the aqueous layer was acidified with 3% HCl to pH 7, extracted with chloroform, acidified to pH 5 and re-extracted. From the first extract, which was dried and evaporated to dryness and triturated with light petroleum 2·3 g (52%) of α-keto ester *XIb* were obtained (Table IV). According to ^{1}HNMR the substance is present in enol form. ^{1}H NMR spectrum: 1·34 t, 3 H (CH_3CH_2O, J = 7·1); 2·39 s, 3 H (CH_3 on the pyridine cycle); 4·35 q, 2 H (CH_3CH_2O, J = 7·1); 6·42 s, 1 H (CH=); 7·03 dd, 1 H (H-5, $^2J(5, 3)$ = 2·4, $J(5, 6)$ = 6·3); 7·13 d, 1 H (H-3, J = 2·1); 8·09 d, 1 H (H-1, J = 6·7); 14·63 s, 1 H (OH). ^{13}C NMR spectrum (APT technique): 14·22 (CH_3CH_2), 20·49 (CH_3 on the pyridine nucleus); 61·93 (C-9); 98·83 (C-7); 123·96, 127·70, and 138·98 (C-9, C-5, C-6); 153·70 (C-2); 164·01 (C-9). Mass spectrum, m/z (% rel. int.); 224 M^+ (100), 150 (75), 122 (60), 92 (22).

From the mixture of substances (TLC) from the dry residue after the second extract lactone *XIIb* (40 mg; 1%) separated after trituration with benzene (Table IV). ^{1}H NMR spectrum: 1·26 t, 3 H (CH_3CH_2O, J = 7·1); 2·31 s, 3 H and 2·46 s, 3 H (CH_3 on the pyridine nuclei); 4·31 q, 2 H (CH_3CH_2O, J = 7·1); 3·55 d, 1 H and 4·35 d, 1 H (H-8, J = 14·5); 6·99 dd,1 H (^2J = 2·4, J = 6·1) and 7·15 dd, 1 H (^2J = 2·1, J = 6·4, H-12, H-17); 7·18 d, 1 H (J = 2·3) and 7·31 d, 1 H (J = 2·0), (H-10, H-15); 7·97 d, 1 H (J = 6·6) and 8·15 d, 1 H (J = 6·7) (H-13, H-18); 14·98 s, 1 H (OH).

Ethyl 3-(2-(4-*methyl*-1-*oxido*)*pyridinyl*)-2-*thiosemicarbazonopropanoate*: A mixture of 0·5 g (2·2 mmol) of α-keto ester *XIb* and 0·24 g (2·72 mmol) of thiosemicarbazide in 12 ml of ethanol was refluxed for 37 h. Yield 0·65 g (45%) of thiosemicarbazone of keto ester *XIb* (Table IV).

b) The reaction was carried out as in the preparation of *XIa* and *XIIa*. From 10·0 g (80 mmol) of 2,4-dimethylpyridine-1-oxide, 12·0 g (80 mmol) of diethyl oxalate and 16·8 g (88 mmol) of

potassium tert-butoxide in 120 ml of absolute ethanol, 35 g of potassium salt were obtained. After acidification to pH 7 and extraction with chloroform α-keto ester *XIb* (7 g; 44%) was obtained. The extract was acidified to pH 5, extracted with chloroform and the extract evaporated to dryness to yield a brown oily residue, representing according to TLC a mixture of 2—3 substances. After addition of benzene 0·6 g (3%) of α-keto ester *Xb* separated out (Table IV). ^{1}H NMR spectrum: 1·38 t, 3 H (CH_3CH_2O, J = 7·1); 2·53 s, 3 H (CH_3 on the pyridine nucleus); 4·09 s, 1 H (H-6); 4·37 q, 2 H (CH_3CH_2O, J = 7·1); 6·35 s, 1 H (CH=); 7·53 d, 1 H (H-2, J = 6·4); 7·62 s, 1 H (H-4); 8·21 d, 1 H (H-1, J = 6·8). According to ^{1}H NMR spectra the compound exists in the solution in a 1 : 1 keto–enol equilibrium. Mass spectrum, *m/z* (% rel. int.): 233 M^+ (42), 149 (100), 132 (37), 122 (87), 106 (35).

Ethyl 3-(2-(1-Oxido)pyridinyl)-2-oxopropanoate (*XIc*)
and 4-Ethoxycarbonyl-2-hydroxy-3-(2-(1-oxido)pyridinyl)-
-4-(2-(1-oxido)pyridinylmethyl)-2-buten-4-olide (*XIId*)

The reaction was carried out analogously as in the preparation of *XIa* and *XIIa* using the method *b*). From the first extract (pH 7) 51% of *XIc* was obtained, m.p. 77—80°C (benzene–cyclohexane 5 : 1), ref.[29] gives m.p. 72—73°C. ^{1}H NMR: 1·38 t, 3 H (CH_3CH_2O, J = 7·1), 4·20 s, 1 H (CH_2CO); 4·35 q, 2 H (CH_3CH_2O, J = 7·1), 6·48 s, 1 H (CH=); 7·22 dd, 1 H (H-5, ^2J = 1·9, J = 8·1); 7·33 dd, 1 H (H-3, J(3, 4) = 7·9, J(3, 5) = 1·8), 7·47 dd, 1 H (H-4, ^2J = 1·2, J = 7·0); 8·22 dd, 1 H (H-6, J(6, 5) = 6·6, J(6, 4) = 0·4); 14·19 s, 1 H (OH). From the more acid extract (pH 5) 1% of a light brown crystalline substance *XIId* separated after addition of benzene (Table IV), which was washed with benzene. ^{1}H NMR spectrum: 1·25 t, 3 H (CH_3CH_2O, J = 7·1); 3·57 d, 1 H and 4·38 d, 1 H (H-8, J = 14·5); 4·30 q, 2 H (CH_3CH_2O, J = 7·1); 7·13 to 7·20 m, 2 H (H-12, H-17); 7·36—7·38 m, 2 H (H-10, H-15); 7·51—7·53 m, 1 H and 7·60—7·64 m, 1 H (H-11, H-16); 8·06 d, 1 H (J = 5·4) and 8·30 d, 1 H (J = 6·3, H-13, H-18).

Ethyl 3-(4-(1-Oxido)pyridinyl)-2-oxopropanoate (*Xa*) and
Monoethyl Ester of 3-(4-(1-Oxido)pyridinyl)-2-(4-(1-
-oxido)pyridinylmethyl)-4-oxo-2-pentenedioic Acid (*XIV*)

The reaction with 4-methylpyridine-1-oxide was carried out analogously as in the preparation of *XIa* and *XIIa*, experiment *b*). From the chloroform extract 46% of *Xa* were obtained, which after two crystallizations from ethyl acetate had m.p. 135—136·5°C, ref.[26] m.p. 140·2—141·5°C. ^{1}H NMR spectrum: 1·39 t, 3 H (CH_3CH_2O, J = 7·1); 4·38 q, 2 H (CH_3CH_2O, J = 7·1); 6·38 s, 1 H (CH=); 7·68 d, 2 H (H-2, H-4, J = 6·9); 8·19 d, 2 H (H-1, H-5, J = 6·9); in $CDCl_3$ solution the compound is in enol form. IR spectrum ($CHCl_3$) cm^{-1}: 1 700 s (CO), 3 440 m (OH). From the acid aqueous layer a white crystalline compound separated out after one day's standing. After a partial concentration a further crop of the same crystals separated out. The two fractions were combined and crystallized from water to give 1·18 g (11%) of compound *XIV* (Table IV) which turned yellow in light. ^{1}H NMR spectrum: 1·22 t, 3 H (CH_3CH_2O, J = 7·1); 3·69 d, 1 H and 3·84 d, 1 H (H-3, J = 14·7); 4·28 q, 2 H (CH_3CH_2O, J = 7·1); 7·21 d, 2 H (J = 6·7) and 7·96 d, 2 H (J = 7·2) (H-1, H-1′, H-5, H-5′); 8·18 d, 2 H (J = 6·7) and 8·37 d, 2 H (J = 7·2) (H-2, H-2′, H-4, H-4′).

3-(2-(6-Methyl-1-oxido)pyridinyl)-2-oxopropanoic Acid Amide (*XId*)

A solution of 0·5 g (2 mmol) of α-keto ester *XIa* in 10 ml of absolute ethanol was bubbled through with dried ammonia for 4 h. The saturated solution was allowed to stand at room

temperature overnight. After evaporation of ethanol in a vacuum 0·44 g of an oil were obtained which was boiled shortly with acetone to give 0·35 g (92%) of solid amide *XId* (Table IV). ^{1}H NMR spectrum: 2·60 s, 3 H (CH_3 on the pyridine cycle); 4·23 s, 1/2 H (CH_2CO); 6·53 s, less than 1 H (CH=); 7·15–7·22 m, 2 H (H-3, H-5); 7·34 t, 1 H (H-4, J = 7·8); 5·60 s and 6·80 to 7·10 s, totally 2 H ($CONH_2$); 14·60 s, less than 1 H (OH); (keto–enol form 1 : 4).

3-(2-(4-Methyl-1-oxido)pyridinyl)-2-oxopropanoic Acid Amide (*XIe*)

It was prepared analogously as amide *XId* (Table IV). ^{1}H NMR spectrum: 2·37 s, 3 H (CH_3 on the pyridine cycle); 4·17 s, 1/7 H (CH_2CO); 6·45 s, less than 1 H (CH=); 6·99 dd, 1 H (H-5, J(5, 3) = 2·2, J(5, 6) = 6·3); 7·11 d, 1 H (H-3, J = 1·8); 8·05 d, 1 H (H-1, J = 6·8); 5·57 s, 1 H and 6·8–7·05 bs, 1 H (NH_2); 15·18 s (OH); (keto–enol form ratio approximately 14 : 1).

The elemental analyses were carried out under the direction of Dr L. Helešic, the NMR *spectra were measured under the direction of Dr P. Trška, the mass spectra were measured by Dr P. Mitera, the* IR *spectra by Dr E. Janečková and Dr A. Kohoutová in the Central Laboratories of the Prague Institute of Chemical Technology, Prague.*

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