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O-Alkylation of 3-Pyridinols

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A general recipe for the preparation of 3-alkoxypyridines by alkylation of 3-pyridinols in dimethyl sulfoxide is given. The recipe has been used to prepare 35 new 3-alkoxypyridines. Alkylation of disodium salts of 3-hydroxy-2-pyridones under the same conditions gave 1-alkyl-3-alkoxy-2-pyridones. Of this new group of compounds three have been prepared.

Most alkylations of 3-pyridinols reported in the literature give low yields of 3-alkoxypyridines. Alkylation preferably takes place at the pyridine nitrogen atom, whereby quaternary pyridinium compounds are formed (*cf.* Refs. 1, 2).

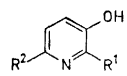
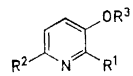
We have found (*cf.* also Ref. 3) that sodium salts of 3-pyridinols are preferentially *O*-alkylated in dimethyl sulfoxide (DMSO), and have worked out a general recipe for such reactions. The recipe is simple and usually gives good yields of 3-alkoxypyridines. A solution of the sodium salt is first prepared by dissolving the 3-pyridinol in a methanolic solution of an equimolar amount of sodium methoxide. Then DMSO is added and all methanol removed by distillation. Finally the alkyl halide is added to the resulting solution or suspension of the sodium salt, whereby alkylation takes place.

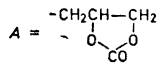
The recipe has been used to prepare 35 new 3-alkoxypyridines (Table 1). Their structures follow from the syntheses, from analyses, and from the fact that the compounds gave no color reaction with a ferric chloride solution.

Alkylation of the disodium salts of 3-hydroxy-2-pyridones after the recipe was also attempted. It was found that *N*,*O*-dialkylation takes place. The reactions carried out are shown in Table 2. The three reaction products are new. They give no color reaction with a ferric chloride solution. The IR spectra showed absorption at 1645—1660 cm^{-1} (amide-carbonyl). These facts, together with the syntheses and the analyses, prove the structures shown in Table 2. No 1-alkyl-3-alkoxy-2-pyridones are known from the literature.

Preliminary experiments showed that dimethylformamide is as good a solvent for the preparation of 3-alkoxypyridines as is DMSO. When we have used DMSO throughout, it is because only this solvent enables one to prepare sodium salts of 3-pyridinols *in situ* in the easy way described here.

Table 1. 3-Alkoxypyridines.

3-Pyridinol 		Alkylating agent XR^3	3-Alkoxypyridine 		
R^1	R^2	X	R^3	No.	Yield %
H	H	Cl	$-(CH_2)_4CH_3$	I	50
H	H	Cl	$-CH_2CON(C_2H_5)_2$	II	62
Br	H	I	$-CH_3$	III	60
Br	H	Cl	$-CH_2COOCH_3$	IV	82
Br	H	Cl	$-CH_2COC_6H_5$	V	45
Br	H	Cl	*A*	VI	44
Cl	H	Cl	*A*	VII	35
Cl	H	Cl	*B*	VIII	74
NO_2	H	Cl	*A*	IX	39
H	CH_3	Cl	$-CH_2COOCH_3$	X	58
H	CH_3	Cl	$-CH_2COOC_2H_5$	XI	86
H	CH_3	Cl	$-CH_2CONH_2$	XII	52
NO_2	CH_3	I	$-CH_3$	XIII	77
NH_2	H	Br	$-CH_2CH=CH_2$	XIV	34
NH_2	H	Br	$-CH_2C\equiv CH$	XV	45
NH_2	H	Br	$-CH_2CH(OCH_3)_2$	XVI	59
NH_2	H	Cl	$-(CH_2)_3N(CH_3)_2$	XVII	58
NH_2	H	Cl	$-CH_2C_6H_5$	XVIII	61
CH_2OH	H	Cl	$-CH_2CONH_2$	XIX	47
$COOCH_3$	H	I	$-CH_3$	XX	59
$COOCH_3$	H	Cl	$-CH_2COOCH_3$	XXI	81
$COOCH_3$	H	Cl	$-CH_2CONH_2$	XXII	40
$CONH_2$	H	I	$-CH_3$	XXIII	40

A = 

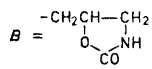
B = 

Table 1. Continued.

$CONH_2$	H	Br	$-(CH_2)_3CH_3$	XXIV	52
—	—	Br	$-CH_2CH=CH_2$	XXV	64
—	—	Br	$-CH_2CH(CH_3)_2$	XXVI	52
—	—	Cl	$-CH_2C_6H_5$	XXVII	66
—	—	Cl	$-CH_2COOCH_3$	XXVIII	63
—	—	Cl	$-CH_2CON(C_2H_5)_2$	XXIX	37
—	—	Br	$-CHCOOC_2H_5$ C_2H_5	XXX	45
CN	H	I	$-CH_3$	XXXI	29
—	—	Br	$-CH_2C_6H_5$	XXXII	45
C	H	Cl	$-CH_2COOCH_3$	XXXIII	35
D	H	Br	$-CH_2CH=CH_2$	XXXIV	41
E	H	Br	$-CH_2CH=CH_2$	XXXV	60

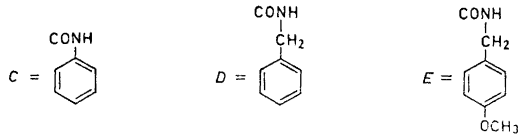
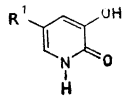
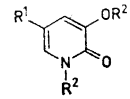


Table 2. 1-Alkyl-3-alkoxy-2(1*H*)-pyridones.

3-Hydroxy-2-(1*H*)-pyridone	Alkylating agent	Reaction product	
	Hal R^2		
		No.	Yield %
$R^1 = H$	$ClCH_2C_6H_5$	XXXVI	80
$R^1 = H$	$ClCH_2COOCH_3$	XXXVII	42
$R^1 = Cl$	$Br(CH_2)_3CH_3$	XXXVIII	41

EXPERIMENTAL

O-Alkylation of 3-pyridinols, general recipe. The 3-pyridinol (0.100 mole) is added to a solution of sodium methoxide in methanol [from sodium (2.30 g, 0.100 mole) and methanol (25 ml)] in a 250 ml reaction flask. So much DMSO, as is necessary to get a clear solution, is added (usually 100—150 ml). The mixture may be heated to 80—90° to accelerate dissolution. The solution is evaporated on the water bath under reduced pressure, until pure DMSO distils (b.p.$_{10}$ 69°). The remaining methanol-free solution or suspension of sodium salt is cooled to room temperature. The alkylating agent (0.100 mole) is added in one portion with vigorous stirring. The reaction temperature is kept below 30° and strong cooling may be necessary the first few minutes. Fast reactions are complete after 15 min or less and the reaction mixture may be worked up immediately. Slow reactions are left standing with slow stirring at room temperature overnight. In 5 cases, mentioned particularly in the following list of preparations, it was necessary to keep the reaction mixture at 80° for a number of hours. The resulting reaction mixture, which is usually turbid or contains varying amounts of crystals, is evaporated to dryness on the water bath (100°) under 10 mm. Water is added to the residue and the alkoxypyridine isolated by filtration, or, if no precipitate is formed, by extraction with chloroform. Unreacted 3-pyridinol may be removed from the chloroform extract by shaking with N sodium hydroxide solution. The crude product is usually easy to purify, by distillation, or by crystallization. The 35 alkoxypyridines prepared are listed below. They gave no color reaction with a ferric chloride solution.

3-Pentyloxypyridine (I). From 3-pyridinol and 1-chloropentane; b.p.$_9$ 116°, n_D^{25} 1.4946. [Found: C 72.9; H 9.2; N 8.6. Calc. for $C_{10}H_{15}NO$ (165.2): C 72.7; H 9.2; N 8.5].

N,N-*Diethyl-2-(3-pyridyloxy)acetamide (II).* From 3-pyridinol and 2-chloro-*N*,*N*-diethylacetamide; b.p.$_{0.4}$ 137°, n_D^{25} 1.5267. [Found: C 63.7; H 7.9; N 13.5. Calc. for $C_{11}H_{16}N_2O_2$ (208.3): C 63.4; H 7.7; N 13.5]. A monohydrochloride was prepared in the usual way and crystallized from 2-propanol, yield 69 %, m.p. 140—142°. [Found: C 53.7; H 7.2; Cl^- 14.7; N 11.5. Calc. for $C_{11}H_{17}ClN_2O_2$ (244.7): C 54.0; H 7.0; Cl^- 14.7; N 11.4].

2-Bromo-3-methoxypyridine (III). From 2-bromo-3-pyridinol and iodomethane; b.p.$_9$ 123°, m.p. 45° [from benzine (40—65°)]. [Found: C 38.3; H 3.1; Br 42.9; N 7.3. Calc. for C_6H_6BrNO (188.0): C 38.5; H 3.2; Br 42.5; N 7.5].

[*(2-Bromo-3-pyridyl)oxy*]*acetic acid methyl ester (IV).* From 2-bromo-3-pyridinol and chloroacetic acid methyl ester; m.p. 65—69° (from ether). [Found: C 39.1; H 3.4; Br 32.2; N 5.6; OCH_3 12.7. Calc. for C_8H_8BrNO (214.1): C 39.0; H 3.3; Br 32.4; N 5.7; one OCH_3 12.6].

2-[*(2-Bromo-3-pyridyl)oxy*]*acetophenone (V).* From 2-bromo-3-pyridinol and 2-chloroacetophenone; m.p. 105—107° (from benzene-cyclohexane 1:1). [Found: C 53.9; H 3.6; Br 27.3; N 4.7. Calc. for $C_{13}H_{10}BrNO_2$ (292.1): C 53.5; H 3.5; Br 27.4; N 4.8].

3-[*(2-Bromo-3-pyridyl)oxy*]-*1,2-propanediol cyclic carbonate (VI).* From 2-bromo-3-pyridinol and 3-chloro-1,2-propanediol cyclic carbonate. The reaction mixture in DMSO was kept at 80° for 40 h, otherwise the directions of the general recipe were followed; m.p. 143—144° (from ethanol). [Found: C 39.4; H 2.9; Br 29.3; N 5.3. Calc. for $C_9H_8BrNO_4$ (274.1): C 39.4; H 2.9; Br 29.2; N 5.1].

3[*(2-Chloro-3-pyridyl)oxy*]-*1,2-propanediol cyclic carbonate (VII).* From 2-chloro-3-pyridinol and 3-chloro-1,2-propanediol cyclic carbonate as described for the preparation of compound VI; m.p. 124—126° (from dioxane-2-propanol 1:1). [Found: C 46.8; H 3.6; Cl 15.4; N 6.0. Calc. for $C_9H_8ClNO_4$ (229.6): C 47.1; H 3.5; Cl 15.5; N 6.1].

5-[*(2-Chloro-3-pyridyl)oxymethyl*]-*2-oxazolidinone (VIII).* From 2-chloro-3-pyridinol and 5-chloromethyl-2-oxazolidinone as described for the preparation of compound VI; m.p. 186—188° (from dioxane). [Found: C 47.5; H 4.2; Cl 15.3; N 12.4. Calc. for $C_9H_9ClN_2O_3$ (228.6): C 47.3; H 4.0; Cl 15.5; N 12.3].

3-[*(2-Nitro-3-pyridyl)oxy*]-*1,2-propanediol cyclic carbonate (IX).* From 2-nitro-3-pyridinol and 3-chloro-1,2-propanediol cyclic carbonate as described for the preparation of compound VI; m.p. 162—164° (from dioxane). [Found: C 45.3; H 3.5; N 11.7. Calc. for $C_9H_8N_2O_6$ (240.2): C 45.0; H 3.4; N 11.7].

[*(6-Methyl-3-pyridyl)oxy*]*acetic acid methyl ester (X).* From 6-methyl-3-pyridinol and chloroacetic acid methyl ester; m.p. 50—51° [(from ether-benzine (b.p. 40—60°) 1:1].

[Found: C 59.7; H 6.0; N 7.8; OCH_3 17.2. Calc. for $C_9H_{11}NO_3$ (181.2): C 59.7; H 6.1; N 7.7; one OCH_3 17.1].

[(6-Methyl-3-pyridyl)oxy]acetic acid ethyl ester (XI). From 6-methyl-3-pyridinol and chloroacetic acid ethyl ester; b.p.$_{0.1}$ 111°, n_D^{25} 1.5029, m.p. 10°. [Found: C 61.8; H 6.8; N 7.3; OC_2H_5 22.5. Calc. for $C_{10}H_{13}NO_3$ (195.2): C 61.5; H 6.7; N 7.2; one OC_2H_5 23.0].

2-[(6-Methyl-3-pyridyl)oxy]acetamide (XII). From 6-methyl-3-pyridinol and 2-chloroacetamide; m.p. 154—156° (from water, dried at 100° under 1 mm). [Found: C 58.0; H 6.2; N 17.0. Calc. for $C_8H_{10}N_2O_2$ (166.2): C 57.8; H 6.1; N 16.9].

3-Methoxy-6-methyl-2-nitropyridine (XIII). From 6-methyl-2-nitro-3-pyridinol and iodomethane; m.p. 88—89° (from cyclohexane). [Found: C 50.2; H 5.0; N 16.8. Calc. for $C_7H_8N_2O_3$ (168.2): C 50.0; H 4.8; N 16.7].

3-Allyloxy-2-aminopyridine (XIV). From 2-amino-3-pyridinol and 3-bromopropene; b.p.$_{0.1}$ 82—83°, m.p. 42—44° [from ether-benzine (40—65°) 1:2]. [Found: C 63.8; H 6.7; N 18.5. Calc. for $C_8H_{10}N_2O$ (150.2): C 64.0; H 6.7; N 18.7].

2-Amino-3-(2-propynyloxy)pyridine (XV). From 2-amino-3-pyridinol and 3-bromopropyne; b.p.$_{0.2}$ 91—92°, m.p. 58—59° [from ether-benzine (40—65°) 1:1]. [Found: C 65.1; H 5.8; N 18.9. Calc. for $C_8H_8N_2O$ (148.2): C 64.9; H 5.4; N 18.9].

[(2-Amino-3-pyridyl)oxy]acetaldehyde dimethyl acetal (XVI). From 2-amino-3-pyridinol and bromoacetaldehyde dimethyl acetal. The reaction mixture in DMSO was kept at 80° for 4 h, otherwise the directions of the general recipe were followed; b.p.$_{0.3}$ 111°, n_D^{25} 1.5360. [Found: C 54.8; H 7.3; N 14.2; OCH_3 30.8. Calc. for $C_9H_{14}N_2O_3$ (198.2): C 54.5; H 7.1; N 14.1; two OCH_3 31.3].

2-Amino-3-[3-(dimethylamino)propyloxy]pyridine (XVII). From 2-amino-3-pyridinol and 3-chloro-*N*,*N*-dimethylpropylamine; b.p.$_{0.2}$ 112°, m.p. 67—69° (from cyclohexane). [Found: C 61.3; H 8.9; N 21.5. Calc. for $C_{10}H_{17}N_3O$ (195.3): C 61.5; H 8.8; N 21.5].

2-Amino-3-benzyloxypyridine (XVIII). From 2-amino-3-pyridinol and α-chlorotoluene; b.p.$_{0.05}$ 150°, m.p. 96—97° (from methanol). [Found: C 72.2; H 6.2; N 14.0. Calc. for $C_{12}H_{12}N_2O$ (200.2): C 72.0; H 6.0; N 14.0].

2-[(2-Hydroxymethyl-3-pyridyl)oxy]acetamide (XIX). From 3-hydroxy-2-pyridinemethanol and 2-chloroacetamide; m.p. 157—158° (from 2-propanol). [Found: C 52.6; H 5.7; N 15.6. Calc. for $C_8H_{10}N_2O_3$ (182.2): C 52.7; H 5.5; N 15.4].

3-Methoxypicolinic acid methyl ester (XX). From 3-hydroxypicolinic acid methyl ester and iodomethane; b.p.$_{0.1}$ 85°, n_D^{25} 1.5240. [Found: C 57.5; H 5.7; N 8.3; OCH_3 37.3. Calc. for $C_8H_9NO_2$ (167.2): C 57.5; H 5.4; N 8.4; two OCH_3 37.1].

3-(Methoxycarbonylmethoxy)picolinic acid methyl ester (XXI). From 3-hydroxypicolinic acid methyl ester and chloroacetic acid methyl ester; m.p. 78—79° (from benzene). [Found: C 53.6; H 4.6; N 6.3. Calc. for $C_{10}H_{11}NO_5$ (225.2): C 53.3; H 4.9; N 6.2].

3-(Carbamoylmethoxy)picolinic acid methyl ester (XXII). From 3-hydroxypicolinic acid methyl ester and 2-chloroacetamide; m.p. 185—186° (from 2-propanol). [Found: C 51.0; H 4.6; N 13.5; OCH_3 14.5. Calc. for $C_9H_{10}N_2O_4$ (210.2): C 51.4; H 4.8; N 13.3; one OCH_3 14.7].

3-Methoxypicolinamide (XXIII). From 3-hydroxypicolinamide and iodomethane; m.p. 198—200° (from propanol). [Found: C 55.3; H 5.8; N 18.5; OCH_3 19.6. Calc. for $C_7H_8N_2O_2$ (152.2): C 55.3; H 5.3; N 18.4; one OCH_3 20.4].

3-Butoxypicolinamide (XXIV). From 3-hydroxypicolinamide and 1-bromobutane; m.p. 109—110° (from toluene). [Found: C 61.9; H 7.3; N 14.7. Calc. for $C_{10}H_{14}N_2O_2$ (194.2): C 61.8; H 7.3; N 14.4].

3-Allyloxypicolinamide (XXV). From 3-hydroxypicolinamide and 3-bromopropene; m.p. 125—126° (from toluene). [Found: C 60.5; H 6.0; N 15.4. Calc. for $C_9H_{10}N_2O_2$ (178.2): C 60.7; H 5.7; N 15.7].

3-Isobutoxypicolinamide (XXVI). From 3-hydroxypicolinamide and 1-bromo-2-methylpropane; m.p. 109—110° (from toluene). [Found: C 62.0; H 7.4; N 14.6. Calc. for $C_{10}H_{14}N_2O_2$ (194.1): C 61.8; H 7.3; N 14.4].

3-Benzyloxypicolinamide (XXVII). From 3-hydroxypicolinamide and α-chlorotoluene; m.p. 106—107° (from toluene). A polymorfic form, m.p. 116—117°, is obtained by sublimation (130°, 0.1 mm). [Found, low melting form: C 68.4; H 5.4; N 12.4. Found, high melting form: C 68.7; H 5.2; N 12.5. Calc. for $C_{13}H_{12}N_2O_2$ (228.2): C 68.4; H 5.3; N 12.3].

[*(2-Carbamoyl-3-pyridyl)oxy]acetic acid methyl ester (XXVIII)*. From 3-hydroxypicolinamide and chloroacetic acid methyl ester; m.p. 141—143° (from methanol-2-propanol 1:4). [Found: C 51.7; H 4.9; N 13.5; OMe 14.9. Calc. for $C_9H_{10}N_2O_4$ (210.2): C 51.4; H 4.8; N 13.3; one OCH_3 14.7].

3-[(N,N-Diethylcarbamoyl)methoxy]picolinamide (XXIX). From 3-hydroxypicolinamide and 2-chloro-*N*,*N*-diethylacetamide; m.p. 134—135°. [Found: C 57.4; H 6.8; N 16.7. Calc. for $C_{12}H_{17}N_3O_3$ (251.3): C 57.4; H 6.8; N 16.7].

2-[(2-Carbamoyl-3-pyridyl)oxy]butyric acid ethyl ester (XXX). From 3-hydroxypicolinamide and 2-bromobutyric acid ethyl ester; m.p. 101—108° (from toluene). [Found: C 57.3; H 6.4; N 11.0; OC_2H_5 17.8. Calc. for $C_{12}H_{16}N_2O_4$ (252.3): C 57.1; H 6.4; N 11.1; one OC_2H/ 17.9]. Sublimation as well as repeated crystallizations do not change the analytical values nor the unusually large melting range.

3-Methoxypicolinonitrile (XXXI). From 3-hydroxypicolinonitrile and iodomethane; m.p. 111—113° (from 2-propanol). [Found: C 62.6; H 4.7; N 21.0. Calc. for $C_7H_6N_2O$ (134.1): C 62.7; H 4.5; N 20.9].

3-(Benzyloxy)picolinonitrile (XXXII). From 3-hydroxypicolinonitrile and α-chlorotoluene; m.p. 99—101° (from 2-propanol). [Found: C 74.5; H 5.0; N 13.2. Calc. for $C_{13}H_{10}N_2O$ (210.2): C 74.3; H 4.8; N 13.3].

{[2-(N-Phenylcarbamoyl)-3-pyridyl]oxy}acetic acid methyl ester (XXXIII). From 3-hydroxy-*N*-phenylpicolinamide and chloroacetic acid methyl ester; m.p. 109—110° (from toluene). [Found: C 63.1; H 5.1; N 10.1. Calc. for $C_{15}H_{14}N_2O_4$ (286.3): C 62.9; H 4.9; N 9.8].

3-Allyloxy-N-benzylpicolinamide (XXXIV). From 3-hydroxy-*N*-benzylpicolinamide and 3-bromopropene; m.p. 72—73° (from 2-propanol). [Found: C 71.8; H 6.1; N 10.3. Calc. for $C_{16}H_{16}N_2O_2$ (268.3): C 71.6; H 6.0; N 10.4].

3-Allyloxy-N-(p-methoxybenzyl)picolinamide (XXXV). From 3-hydroxy-*N*-(*p*-methoxybenzyl)picolinamide and 3-bromopropene; m.p. 74—75° (from 2-propanol). [Found: C 68.2; H 6.1; N 9.6. Calc. for $C_{17}H_{18}N_2O_3$ (298.3): C 68.4; H 6.1; N 9.4].

O,N-*Alkylations of 3-hydroxy-2(1H)-pyridones*. These reactions were carried out after the general recipe by substitution of 0.100 mole of the 3-pyridinol by 0.050 mole of the 3-hydroxy-2(1*H*)-pyridone. The three products prepared gave no color reaction with a ferric chloride solution.

1-Benzyl-3-benzyloxy-2(1H)-pyridone (XXXVI). From 3-hydroxy-2(1*H*)-pyridone and α-chlorotoluene; m.p. 115—116° (from ethanol-water 2:1), IR absorption (in KBr) 1645 cm^{-1}. [Found: C 78.4; H 6.0; N 5.0. Calc. for $C_{19}H_{17}NO_2$ (291.3): C 78.3; H 5.9; N 4.8].

3-(Methoxycarbonylmethoxy)-2-oxo-1(2H)-pyridineacetic acid methyl ester (XXVII). From 3-hydroxy-2(1*H*)-pyridone and chloroacetic acid methyl ester; m.p. 102—103° (from 2-propanol-ether 1:1), IR absorption (in KBr) 1660 cm^{-1}. [Found: C 51.4; H 5.3; N 5.6; OCH_3 23.7. Calc. for $C_{11}H_{13}NO_6$ (255.2): C 51.8; H 5.1; N 5.5; two OCH_3 24.3].

3-Butoxy-1-butyl-5-chloro-2(1H)-pyridone (XXXVIII). From 5-chloro-3-hydroxy-2(1*H*)-pyridone and 1-bromobutane; $b.p._{0.3}$. 139—140°, n_D^{25} 1.5289, m.p. 46—47° [from ether-benzine (40—65°) 1:1], IR absorption (in KBr) 1660 cm^{-1}. [Found: C 60.6; H 7.7; Cl 13.7; N 5.2. Calc. for $C_{13}H_{20}ClNO_2$ (257.8): C 60.6; H 7.8; Cl 13.8; N 5.4].

Starting materials. All starting materials used are known compounds, which were obtained in an analytically pure grade from Wolff & Kaaber, Farum, Denmark.

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