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ALKYLATION OF 3-CYANO-2-OXOPYRIDINE DERIVATIVES

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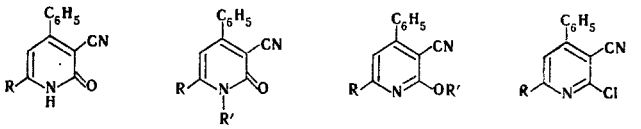
A number of N- and O-alkylpyridines were obtained by alkylation of 3-cyano-2-oxopyridines with alkyl halides and diazomethane.

This paper is devoted to the study of the alkylation of 3-cyano-2-oxopyridines I with alkyl or phenyl substituents in the 6 position [1]. Since 2-oxopyridines in alkaline media are capable of giving ambident anions [2], alkylation may occur both at the nitrogen atom and at the oxygen atom. It is known that the alkylation of 2-oxopyridines in the presence of alkali metal hydroxides proceeds primarily via an S_N2 mechanism at the nitrogen atom, whereas in the presence of silver salts alkylation takes place at the oxygen atom via an S_N1 mechanism [3].

In the present research we accomplished the alkylation of 2-oxopyridine salts with alkyl halides in the presence of potassium hydroxide. It was found that the structure of the final product is determined by the structure of the starting 2-oxopyridine (I) and the stability of the cation of the alkyl halide.

Thus oxopyridine Ia, with an electron-donor methyl group in the 6 position that increases the nucleophilicity of the nitrogen atom, is alkylated by methyl and ethyl iodides exclusively at nitrogen to give 1-alkyl-2-oxopyridines IIa, b (Table 1). As the length of the alkyl chain increases, the stability of the cation of the alkyl halide increases. and competitive reaction via an S_N1 mechanism becomes possible; this explains the formation of a mixture of N- and O-alkylpyridines (IIc, d and IIIc, d) in the butylation and benzylation of 2-oxopyridines Ia. Only N-hexyl product IIe was isolated in 43% yield in the case of hexylation.



I a, b II a-f III a-h IV a, b

I a R=CH_3; b R=C_6H_5; II a R=CH_3, R′=CH_3; b R=CH_3, R′=C_2H_5; c R=CH_3, R′=C_4H_9; d R=CH_3, R′=$CH_2C_6H_5$; d R=CH_3, R′=C_6H_{13}; f R=C_6H_5, R′=C_6H_{13}; III a R=CH_3, R′=CH_3; b R=CH_3, R′=C_2H_5; c R=CH_3, R′=C_4H_9; d R=CH_3, R′=$CH_2C_6H_5$; e R=C_6H_5, R′=C_2H_5; e R=C_6H_5, R′=C_4H_9; g R=C_6H_5, R′=C_6H_{13}; f R=C_6H_5, R′=CH_3

In contrast to the methyl group, the phenyl group in the 6 position of oxopyridine Ib decreases the nucleophilicity at the adjacent nitrogen atom and sterically hinders the approach of the reagent to it. The methylation and butylation of Ib therefore give O-alkyl derivatives IIIf, h. Hexyaltion proceeds even less selectively, and the N-hexyl product can therefore be isolated in ~30% yield along with the O-hexyl product.

The solvent has a great effect on the alkylation of 2-oxopyridines I. Thus 2-oxopyridine Ia undergoes methylation, ethylation, butylation, and benzylation in ethanol, but hexylation occurs only in dimethyl sulfoxide (DMSO) or acetonitrile. 2-Oxopyridine Ib undergoes only methylation in ethanol. The remaining alkyl halides react with 2-oxopyridine Ib only in DMSO or acetonitrile.

In addition to the alkyl halides, diazomethane was also used as an alkylating agent. In this case, according to [4], the rather acidic hydrogen of 2-oxopyridine adds to the diazoalkane to give the methyldiazonium salt

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TABLE 1. Characteristics of Pyridines II and III

Compound	R	R'	mp, °C	Crystallization solvent	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
IIa	CH_3	CH_3	143—144[6]	Ethanol	$C_{14}H_{12}N_2O$	74,7	5,4	12,5	75,0	5,4	12,5	84
IIb	CH_3	C_2H_5	148—149	Ethanol	$C_{15}H_{14}N_2O$	75,7	5,7	11,6	75,6	5,9	11,8	71
IIc	CH_3	C_4H_9	128,5—129,5	Ether	$C_{17}H_{18}N_2O$	76,8	7,0	10,7	76,6	6,8	10,5	32
IId	CH_3	$CH_2C_6H_5$	121—122	Ether	$C_{20}H_{16}N_2O$	80,1	5,8	9,9	80,0	5,4	9,3	24
IIe	CH_3	C_6H_{13}	77— 78	Ether	$C_{19}H_{22}N_2O$	78,0	7,8	9,7	77,5	7,5	9,5	43
IIf	C_6H_5	C_6H_{13}	114—115	Ether	$C_{24}H_{24}N_2O$	80,0	6,9	7,5	80,6	6,8	7,9	28
IIIa	CH_3	CH_3	102—104	Ethanol	$C_{14}H_{12}N_2O$	75,1	5,4	12,4	75,0	5,4	12,5	72
IIIb	CH_3	C_2H_5	84— 85	Petroleum ether	$C_{15}H_{14}N_2O$	75,6	5,9	11,6	75,6	5,9	11,8	72
IIIc	CH_3	C_4H_9	38,5—39,5	Ethanol	$C_{17}H_{18}N_2O$	76,7	6,9	10,5	76,7	6,8	10,5	24
IIId	CH_3	$CH_2C_6H_5$	106—107	Ethanol	$C_{20}C_{16}N_2O$	80,3	5,6	9,0	80,0	5,4	9,3	42
IIIe	C_6H_5	C_2H_5	109—110[7]	Petroleum ether	$C_{20}C_{16}N_2O$	79,8	5,4	9,2	80,0	5,4	9,3	81
IIIf	C_6H_5	C_4H_9	108—109	Ether	$C_{22}H_{20}N_2O$	80,7	6,1	8,3	80,5	6,1	8,5	54
IIIg	C_6H_5	C_6H_{13}	80—81	Hexane	$C_{24}H_{24}N_2O$	80,7	6,9	7,9	80,7	6,8	7,9	42
IIIh	C_6H_5	CH_3	96—97[7]	Ethanol	$C_{19}H_{14}N_2O$	79,4	5,1	9,7	79,7	4,9	9,8	93

TABLE 2. IR and PMR Spectra of Pyridines II and III

Compound	IR spectra cm^{-1}	PMR spectra	
		solvent	δ, ppm
IIa	1653, 2223	$CDCl_3$	2,43(CH_3), 3,52(N—CH_3), 6,20(CH), 7,45(C_6H_5)
IIb	1652, 2223	CF_3COOH	1,48(CH_3), 2,68(CH_3), 4,34(N—CH_2), 6,90(CH), 7,61(C_6H_5)
IIc	1658, 2222	$CDCl_3$	1,02(CH_3), 1,60(2-CH_2), 2,50(CH_3), 4,08(N—CH_2), 6,19(CH), 7,51(C_6H_5)
IId	1645, 2224	CF_3COOH	2,60(CH_3), 5,38(N—CH_2), 6,83(CH), 7,32(C_6H_5), 7,54(C_6H_5)
IIe	1648, 2221	CCl_4	0,89(CH_3), 1,35(4-CH_2), 2,45(CH_3), 3,91(N—CH_2), 6,05(CH), 7,42(C_6H_5)
IIf	1650, 2220	CCl_4	0,90—1,40(CH_3+4-CH_2), 4,33(N—CH_2), 7,26(2-C_6H_5), 7,80(CH)
IIIa	1140, 2218	d_6-DMSO	2,52(CH_3), 4,00(O—CH_3), 7,06(CH), 7,53(C_6H_5)
IIIb	1142, 2223	CF_3COOH	1,69(CH_3), 2,89(CH_3), 4.90(O—CH_2), 7,52(CH), 7,72(C_6H_5)
IIIc	1143, 2222	CCl_4	1,01(CH_3), 1,72(2-CH_2), 2,46(CH_3), 4,43(O—CH_2), 6,82(CH), 7,53(C_6H_5)
IIId	1142, 2222	CF_3COOH	2,61(CH_3), 5,59(O—CH_2), 6,81(CH), 7,26(C_6H_5), 7,58(C_6H_5)
IIIe	1148, 2220	CF_3COOH	1,75(CH_3), 5,06(O—CH_2), 7,74(2-C_6H_5),8,10(CH)
IIIf	1150, 2229	CCl_4	0,98(CH_3), 1,70(2-CH_2), 4,50(O—CH_2), 7,30(2-C_6H_5), 7,85(CH)
IIIg	1145, 2221	CCl_4	0,93(CH_3), 1,47(4-CH_2), 4,57(O—CH_2), 7,62(2-C_6H_5), 8,07(CH)
IIIh	1146, 2220	DMSO	4,21(O—CH_3), 7,72(2-C_6H_5), 8,34(CH)

($CH_3-\overset{+}{N}\equiv N$), which reacts with the oxopyridine anion. Exclusively the O-methyl derivative IIIh was isolated in the case of 2-oxopyridine Ib, whereas a mixture of N- and O-methyl products in a ratio of 2 : 1 was isolated in the case of oxopyridine Ia.

O-Alkylpyridines IIIa,h were obtained by alternative synthesis from 2-chloropyridines IV [5] and sodium alkoxide. However, O-alkyl derivatives IIIb, e were obtained only from 2-chloropyridines IV.

The IR spectra (Table 2) of N-alkyl derivatives II contain the absorption frequencies of a carbonyl group at 1645-1658 cm^{-1} and of a nitrile group (2220-2224 cm^{-1}).

The absorption band of a carbonyl group is absent in the spectra of all O-alkyl products III, but there are bands of stretching vibrations of an ether group at 1140-1150 cm^{-1} and of a nitrile group at 2218-2229 cm^{-1}.

The PMR spectra contain signals from the protons of all of the fragments of the molecules in the necessary regions (Table 2); the signal from the methylene group attached to the nitrogen atom in II appears at 3.91-5.38 ppm, and the signal of the methylene group attached to oxygen in pyridines III shows up at 4.43-5.59 ppm.

EXPERIMENTAL

The IR spectra of mineral oil and hexachlorobutadiene suspensions of the substances were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Perkin—Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. The course of the reactions and the individuality of all of the

synthesized compounds were monitored by means of thin-layer chromatography (TLC) on Silufol in an acetone–hexane system.

1,6-Dimethyl-2-oxo-3-cyano-4-phenylpyridine (IIa). A mixture of 0.5 g (2.38 mmole) of 2-oxopyridine Ia in 20 ml of ethanol, 0.2 g (3.6 mmole) of KOH in 2 ml of water, and 2 ml (32 mmole) of methyl iodide was refluxed for 2 h, after which the solvent was vacuum evaporated, and the residue was washed with water and crystallized from ethanol to give 0.45 g (84%) of methylpyridine IIa.

1-Ethyl-2-oxo-3-cyano-4-phenyl-6-methylpyridine (IIb). This compound was similarly obtained from 2-oxopyridine Ia and ethyl iodide.

1-Butyl-2-oxo-3-cyano-4-phenyl-6-methylpyridine (IIc) and 2-Butoxy-3-cyano-4-phenyl-6-methylpyridine (IIIc). A mixture of 0.5 g (2.38 mmole) of 2-oxopyridine Ia in 10 ml of ethanol, 0.2 g (3.6 mmole) of KOH in 5 ml of water, and 1 ml (8.8 mmole) of butyl iodide was refluxed for 20 h, after which the solvent was vacuum evaporated, and the residue was treated with water. The aqueous mixture was extracted with hexane, and the extract was worked up to give 0.15 g (24%) of 2-butoxypyridine IIIc. The residue was crystallized from ether to give 0.2 g (32%) of 2-oxopyridine IIc.

1-Benzyl-2-oxo-3-cyano-4-phenyl-6-methylpyridine (IId) and 2-Benzyloxy-3-cyano-4-phenyl-6-methylpyridine (IIId). A mixture of 0.5 g (2.38 mmole) of 2-oxopyridine Ia in 10 ml of ethanol, 0.2 g (3.6 mmole) of potassium hydroxide in 5 ml of water, and 0.6 ml (5.04 mmole) of benzyl bromide was refluxed for 7 h, after which the solvent was removed by vacuum evaporation, and the residual oil was washed with water and triturated with ether. The ether extract was worked up to give N-benzylpyridine IId. The residue was crystallized from ethanol to give 0.3 g (42%) of pyridine IIId.

1-Hexyl-2-oxo-3-cyano-4-phenyl-6-methylpyridine (IIe). A mixture of 0.5 g (2.38 mmole) of 2-oxopyridine Ia in 15 ml of acetonitrile, 0.2 g (3.6 mmole) of KOH in 5 ml of water, and 3 ml (20.4 mmole) of hexyl iodide was refluxed for 3 h, after which the solvent was removed by vacuum evaporation, and the residue was washed with water and crystallized from ether to give 0.3 g (43%) of pyridine IIe.

1-Hexyl-2-oxo-3-cyano-4,6-diphenylpyridine (IIf) and 2-Hexyloxy-3-cyano-4,6-diphenylpyridine (IIIg). A solution of 0.2 g (3.6 mmole) of KOH in 5 ml of water and 3 ml (20.4 mmole) of hexyl iodide were added dropwise to a refluxing solution of 0.5 g (1.95 mmole) of 2-hydroxypyridine Ib in 10 ml of acetonitrile in the course of 2 h, after which the mixture was vacuum evaporated, and the residue was treated with water. Fractional crystallization from hexane yielded 0.3 g (42%) of pyridine IIIg; 0.2 g (28%) of 2-hydroxypyridine IIf precipitated from ether.

2-Methoxy-3-cyano-4-phenyl-6-methylpyridine (IIIa). A) A solution of 0.1 g (4.38 mmole) of sodium in 10 ml of methanol was added to 1 g (4.38 mmole) of 2-chloropyridine IVa, and the mixture was refluxed for 1 h. The NaCl was removed by filtration, and the solvent was removed from the filtrate by evaporation. The residue was crystallized from ether to give 0.7 g (72%) of pyridine IIIa.

B) An ether solution (40 ml) of diazomethane (~1 g) was added to 0.5 g (2.38 mmole) of 2-hydroxypyridine Ia in 100 ml of acetone, and the mixture was allowed to stand at room temperature for 24 h. It was then vacuum evaporated, and the residual oil was treated with water and subjected to fractional crystallization from ether to give 0.15 g (29%) of methoxypyridine IIIa; ethanol yielded 0.3 g (57.5%) of N-methylpyridine IIa.

2-Ethoxy-3-cyano-4-phenyl-6-methylpyridine (IIIb). This compound was similarly obtained from chloropyridine IVa and sodium ethoxide by method A.

2-Ethoxy-3-cyano-4,6-diphenylpyridine (IIIe). This compound was similarly obtained from chloropyridine IVa and sodium ethoxide by method A.

2-Butoxy-3-cyano-4,6-diphenylpyridine (IIIf). A mixture of 0.3 g (1.16 mmole) of 2-oxopyridine Ib in 10 ml of acetonitrile, 0.2 g (3.6 mmole) of KOH in 5 ml of water, and 2 ml (17.7 mmole) of butyl iodide was refluxed for 3 h, after which the solvent was removed by vacuum evaporation, and the residue was treated with water and crystallized from ether.

2-Methoxy-3-cyano-4,6--diphenylpyridine(IIIh). A) A mixture of 0.7 g (2.5 mmole) of 2-oxopyridine Ib in 40 ml of acetone, 0.2 g (3.6 mmole) of KOH in 3 ml water, and 4 ml (64 mmole) of methyl iodide was refluxed for 8 h, after which the solvent was vacuum evaporated, and the residue was treated with water and crystallized from ethanol to give 0.5 g (70%) of pyridine IIIh.

B) An ether solution (40 ml) of ~1 g of diazomethane was added to a solution of 0.4 g (1.47 mmole) of 2-oxopyridine Ib in 100 ml of acetone, and the mixture was allowed to stand at room temperature for 24 h. It was then vacuum evaporated, and the residue was treated with water and crystallized from ether to give 0.35 g (83%) of pyridine IIIh.

C) This compound was obtained in 93% yield from chloropyridine IVb by method A in the synthesis of IIIa.

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CONFORMATIONAL STUDY OF trans-(+)-(9S,10S)-DECAHYDRO-4-QUINOLONE AND ITS N-SUBSTITUTED DERIVATIVES*

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The spectropolarometric study of trans-(+)-(9S,10S)-decahydro-4-quinolone indicates the existence of invertomers with respect to the nitrogen atom, conformers formed during rotation of the substituent attached to the nitrogen atom about the C–N bond for trans-(9S,10S)-N-(α-phenylethyl)decahydro-4-quinolone, and conformers formed through conversion of the two-ring system for cis-(9R,10S)-N-(α-phenylethyl)decahydro-4-quinolone.

The hydrogenolysis of the two isomeric N-(α-phenylethyl)decahydro-4-quinolones (I) with cis- and trans-fused rings leads to removal of the chiral phenylethyl substituent and the formation of the same trans-(+)-(9S,-10S)-decahydro-4-quinolone in both cases [4]. This subsequently made it possible, during the preparation of optically active trans-decahydro-4-quinolone (II), to subject a mixture of the cis and trans isomers of I to hydrogenolysis without their separation. trans-(+)-Decahydro-4-quinolone was recrystallizef from hexane until its melting point was constant. The presence of a second substance, which we assumed to be the cis isomer of II, was detected during a chromatographic study of the mother liquor; however, it was found to be impossible to isolate it because of the small quantity present. The formation of the same substance can be detected chromatographically after UV irradiation or thermal isomerization of a solution of pure trans isomer II.

Both rings in trans-decahydro-4-quinolone are linked rigidly, and ring conversion is impossible. However, different positions of the substituents on nitrogen – equatorial (IIA) and axial (IIB) – are possible as a result of inversion of the nitrogen atom:

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