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SYNTHESIS OF SUBSTITUTED PYRIDINES—I

4,6-DIHYDROXY-1,3-DISUBSTITUTED PYRIDINES

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Abstract—The reaction of alkoxides i.e. sodium methoxide and sodium ethoxide with amino-pyrano-dioxins (I) is a general one and yields 1,3-disubstituted derivatives of 4,6-dihydroxy pyridine. Evidence for the structure of the products was provided by IR and UV spectroscopy. A mechanism for the reaction has been proposed.

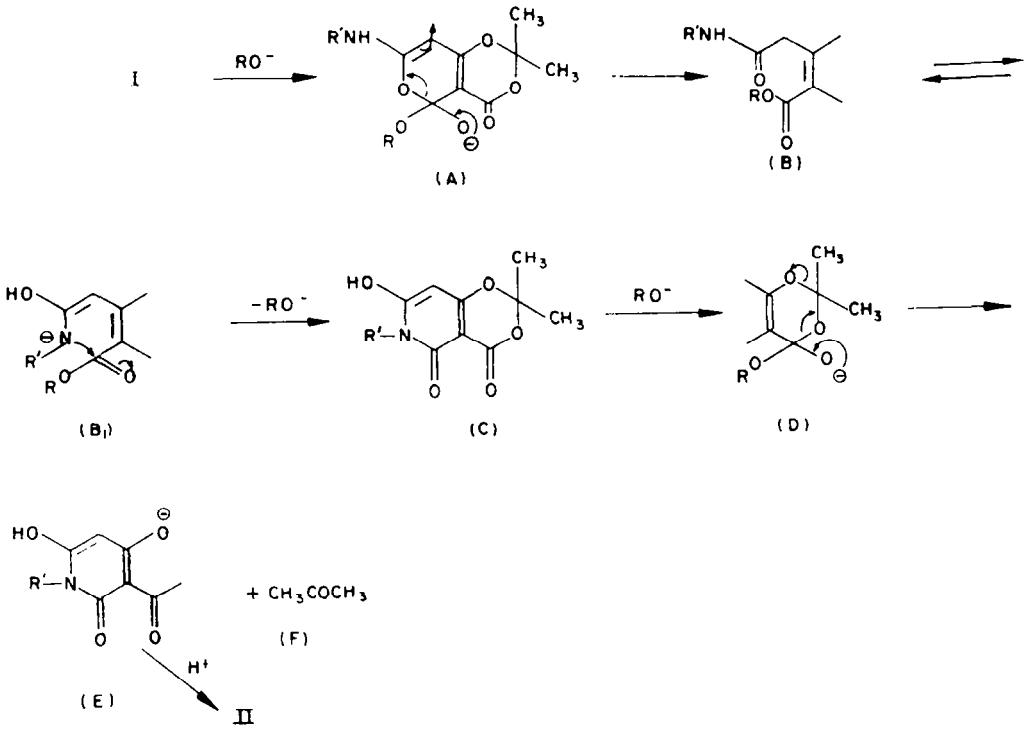
7-Anilino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxin[1] when treated with sodium ethoxide yielded ethyl 1,2-dihydro-4,6-dihydroxy-2-oxo-1-phenyl-pyridine-3-carboxylate.[2] Further examples of the preparation of dihydroxy-pyridines (II) by this route are now described. The products have different ester groupings —C(=O)—OR at position 3 depending upon the alkoxide employed, and the substituent at position 1, is that of the amino grouping of the parent pyrano-dioxin (I). For example, 7-anilino-2,2-dimethyl-4,5-dioxopyrano-(4,3-d)-(1,3)-dioxin (I; R′ = Ph), when treated with sodium methoxide, formed a methyl ester pyridone (II, R′ = Ph, R = Me) m.p. 210° (dec), λ_{max} 305 mμ, log ε, 4·50 which was identical in all respects with the compound prepared earlier by another method.[2] Similar treatment of other amino-pyrano-dioxins with sodium methoxide and sodium ethoxide in absolute methanol and ethanol respectively gave the corresponding pyridine-carboxylates, (II) as listed in Table 1. These products formed morpholinium salts (III)* which could easily be converted back into the original hydroxypyridines by dissolution in dilute acids, for example, hydrochloric acid. These pyridones were difficult to dissolve in most organic solvents and could only be crystallized from hot ethanol or chloroform. They gave reddish brown colours with aqueous ferric chloride and effervesced with aqueous sodium bicarbonate. They melted at high temperature with decomposition.

All of the pyridones (II) listed in Table 2 showed a UV absorption maximum in the 304–306 mμ region and so resembled closely the 2-pyridones reported by Specker *et al.*[3] The IR spectra of these compounds were similar to one another and all showed absorption in the region 1630–1651 cm^{-1} as expected for the 2-carbonyl. Slight variations are attributable to the various substituents at position 1 and 3.

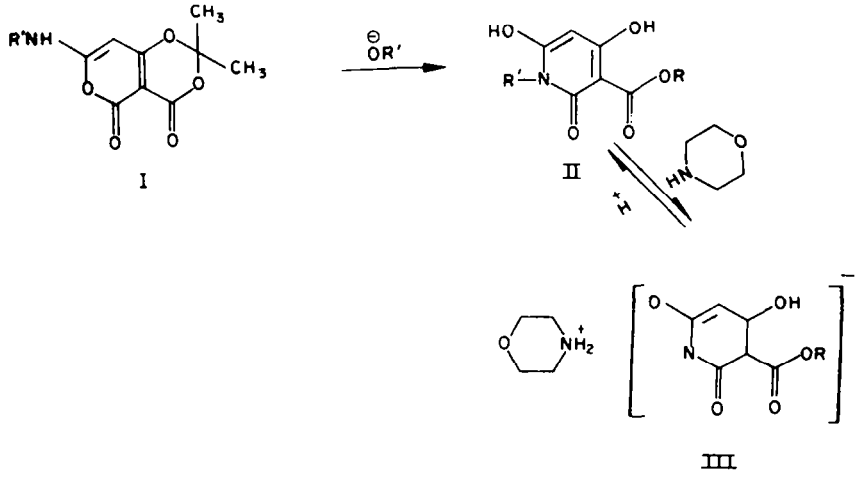
The formation of dihydroxy-pyridines (II) is believed to have occurred in two main stages as depicted below. The first stage involves an attack by a nucleophile ($R\bar{O}$) on

* cf. Ref. 2.

[1] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.* 2251 (1953).
[2] M. A. Butt, J. A. Elvidge and A. B. Foster, *J. Chem. Soc.* 3069 (1963).
[3] H. Specker and H. Gawrasch, *Ber. Dtsch. Chem. bes.* **75**, 1338 (1942).



the pyrone ring at the electron-deficient carbonyl and leads *via* A to an intermediate (B) which cyclizes to product (C). The second stage comprises a similar attack by a nucleophile ($R\bar{O}$) on the carbonyl of the oxodioxin ring and proceeds as shown at (D) with the concomitant expulsion of acetone (F) and so *via* (E) to the pyridone ester (II). Unluckily, the intermediary product (C) could not be separated in this reaction but in case of phenoxide reaction[4] (C) was the final product. The latter fact, however, does support the mechanism.



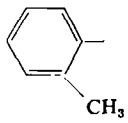
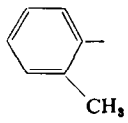
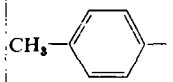
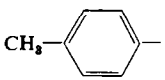
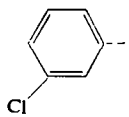
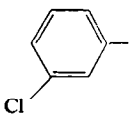
[4] A. Butt and I. A. Akhtar, *Tetrahedron* **21**, 1917 (1965).

TABLE 1. AMINOPYRANODIOXINS (I)

No.	Primary amine	Quantity (2 mols)	7-Chloro-2,2-dimethyl 4,5-dioxo-1-pyrano (4,3-d)-(1,3)-dioxin (1 mol)	Product (I)	m.p.	Yield (%)	Solvent for crystallization	Molecular formula	UV absorption (95% ethanol) λ_{max}	log ε	Analysis Found C	H	N		Required C	H	N	
1.	Ethylamine	2·65 g	6·75 g	6·4 g	165°	91·2	$CHCl_3$	$C_{11}H_{13}NO_5$	330	4·19	55·2;	5·6;	6·0		55·2;	5·5;	5·9	
2.	iso-Butylamine	1·0 g	1·0 g	0·5 g	176°	43·0	$CHCl_3$	$C_{13}H_{17}NO_5$	330	4·65	58·5;	6·5;	5·3		58·4;	6·5;	5·2	
3.	n-Butylamine	1·0 g	1·0 g	0·6 g	149°	68·9	$CHCl_3$	$C_{13}H_{17}NO_5$	330	4·15	58·3;	6·3;	4·7		58·4;	6·5;	5·2	
															Calculated			
4.*	*o*-Toluidine	1·18 g	1·0 g	1·3 g	178°	99·5	$CHCl_3$	$C_{16}H_{15}NO_5$					4·8				4·7	
5.	*p*-Toluidine	1·18 g	1·0 g	1·3 g	166°	99·5	$CHCl_3$	$C_{16}H_{15}NO_5$			64·2;	5·1;	5·0		63·8;	5·0;	4·7	
6.	*m*-Chloroaniline	2·54 g	2·3 g	2·25 g	183°	94·0	$CHCl_3$	$C_{15}H_{12}NO_5Cl$			56·0;	3·6;	4·3;	Cl 11·0	56·0;	3·7;	4·4;	Cl 11·0
7.	*p*-Chloroaniline	1·11 g	1·0 g	1·0 g	188°	78·7	$CHCl_3$	$C_{15}H_{12}NO_5Cl$			56·0;	3·9;	4·5;	Cl 11·0	56·2;	3·7;	4·4;	Cl 11·0
8.	*m*-Bromoaniline	4·5 g	3·08 g	4·08 g	184°	84·5	$CHCl_3$	$C_{15}H_{12}NO_5Br$			49·2;	3·2;	3·8;	Br 21·0	49·2;	3·3;	3·8;	Br 21·9
9.	*p*-Bromoaniline	2·9 g	2·0 g	3·0 g	185°	94·2	$CHCl_3$	$C_{15}H_{12}NO_5Br$			49·2;	3·4;	4·0;	Br 21·8	49·2;	3·3;	3·8;	Br 21·9
10.	*p*-Anisidine	2·14 g	2·0 g	1·88 g	157°	65·3	$CHCl_3$	$C_{16}H_{15}NO_6$			60·9;	4·7			60·6;	4·8		
11.	*β*-Naphthylamine	1·25 g	1·0 g	1·4 g	174°	84·6	$CHCl_3$	$C_{19}H_{15}NO_5$			67·8;	4·6;	4·3		67·7;	4·5;	4·2	

* The structure of the newly prepared aminopyranodioxins follows from their UV absorptions recorded above (cf. Ref.) (From 1–3). The UV absorption characteristic of the compounds (IV–XI) has already been reported.[3]

TABLE 2. 4,6-DIHYDROXY-1,3-DISUBSTITUTED PYRIDINE (II)

No.	4,6-Dihydroxy-1,3-disubstituted pyridones R	R′	Molecular formula	Solvent for crystallization	m.p.	Analysis Found C	H	N	Required C	H	N	UV absorption (95% ethanol) λ_{max}	log ε	IR absorption max ν(cm⁻¹) mainly for the C=O(2) Nujol Mulls
1.	CH_3—CH_2—	CH_3—	$C_9H_{11}NO_5$	MeOH	184°	50·5;	5·3;	3·6	50·71;	5·2;	6·6	304	4·3	1645 s
2.	CH_3·CH_2—	CH_3·CH_2	$C_{10}H_{13}NO_5$	EtOH	185°	52·6;	5·6;	6·1	52·9;	5·8;	6·2	306	4·5	1647 s
3.	$(CH_3)_2$>CH·CH_2—	CH_3—	$C_{11}H_{15}NO_5$	MeOH	158°	56·6;	6·1;	5·9	54·8;	6·2;	5·8	306	4·3	1645 m
4.	$(CH_3)_2$>CH CH_2—	CH_3·CH_2—	$C_{11}H_{15}NO_5$	EtOH	170°	56·6;	6·6;	5·9	56·6;	6·7;	5·5	305	4·8	1631 s
5.	$CH_3(CH_2)_3$··	CH_3—	$C_{11}H_{15}NO_5$	MeOH	182°	54·6;	6·7;	6·6	54·8;	6·2;	5·8	302	4·32	1653 s
6.	$CH_3(CH_2)_3$	CH_3·CH_2—	$C_{12}H_{17}NO_5$	EtOH	160°	56·4;	6·7;	5·6	56·5;	6·7;	5·5	—	—	1631 s
7.		CH_3—	$C_{14}H_{13}NO_5$	MeOH	182°			4·8			5·1	303	4·30	1639 m
8.		CH_3·CH_2-	$C_{15}H_{15}NO_5$	EtOH	191°	62·2;	5·4;	5·0	62·3;	5·2;	4·8	—	--	1639 m
9.		CH_3—	$C_{14}H_{13}NO_5$	MeOH	198°	61·1;	5·0;	5·2	61·1;	4·8;	5·1	304	4·32	1650 s
10.		CH_3·CH_2—	$C_{15}H_{15}NO_5$	EtOH	199°	62·2;	5·4;	5·9	62·3;	5·2;	4·8	306	4·68	1639 m
11.		CH_3—	$C_{13}H_{10}NO_5Cl$	MeOH	197°	53·2;	3·5;	4·3;	52·8;	3·4;	4·7;	304	4·30	1647 s
12.		CH_3·CH_2—	$C_{14}H_{12}NO_5Cl$	EtOH	188°			5·0; 12·0			4·5; 11·5	304	4·46	1639 s

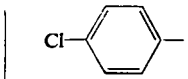
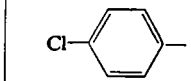
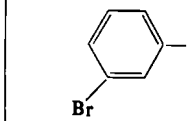
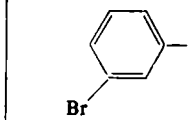
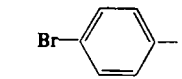
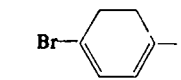
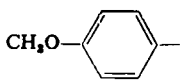
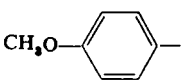
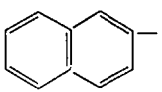
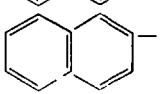
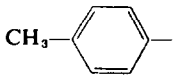
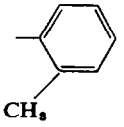
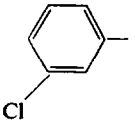
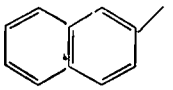
13.		CH_3 –	$C_{13}H_{10}NO_5Cl$	MeOH	170°	52·8;	3·6;	4·9;	12·0	52·8;	3·4;	4·7;	12·3	304	4·99	1639 s
14.		$CH_3{\cdot}CH_2$	$C_{14}H_{12}NO_5Cl$	EtOH	178°	53·6;	3·7;	4·3;	10·7	54·3;	3·9;	4·6;	11·5	305	4·50	1647 m
									Br				Br			
15.		CH_3—	$C_{13}H_{10}NO_5Br$	MeOH	188°	46·4;	3·2;	4·4		45·9;	2·9;	4·1;		305	4·40	1639 s
16.		$CH_3{\cdot}CH_2$	$C_{14}H_{12}NO_5Br$	EtOH	192°	47·5;	3·3;		22·5	47·5;	3·4;	4·0;	22·6	305	4·50	1647 s
17.		CH_3 –	$C_{13}H_{10}NO_5Br$	MeOH	196°	45·9;	2·7;	3·7;	22·6	45·9;	2·9;	4·1;	23·0	305	4·30	1639 s
18.		$H_3{\cdot}CH_2$—	$C_{13}H_{14}NO_5Br$	EtOH	203°	47·1;	2·3;	3·6;	21·2	47·5;	3·4;	4·0;	22·6	305	4·40	1639 s
19.		CH_3—	$C_{14}H_{13}NO_6$	MeOH	193°	57·5;	4·6;	4·4		57·7;	4·5;	4·8		305	4·33	1626 s
20.		$CH_3{\cdot}CH_2$—	$C_{15}H_{16}NO_6$	EtOH	205°	59·0;	5·0;	4·8		59·1;	5·0;	4·6		304	4·50	1639 s
21.		CH_3—	$C_{17}H_{13}NO_5$	MeOH	205°	65·3;	4·2;	4·8		65·6;	4·2;	4·5		306	4·37	1658 m
22.		$CH_3{\cdot}CH_2$—	$C_{15}H_{15}NO_6$	EtOH	184°			4·4				4·3		308	4·12	1653 m

TABLE 3. MORPHOLINIUM SALTS (III)

No.	Pyridone (II) R	R′	Quantity in chloroform	Morpholine	Yield	m.p.
1.	CH_3—		0·2 g/25 ml	0·2 ml	0·2 g	180°
2.	CH_3—	CH_3·CH_3a	0·2 g/25 ml	0·2 ml	0·2 g	142°
3.	CH_3—		0·4 g/25 ml	0·5 ml	0·42 g	176°
4.	CH_3—		0·2 g/40 ml	0·5 ml	0·15 g	183°
5.	CH_3—		0·5 g/25 ml	0·6 ml	0·5 g	178°

Analysis

No.	Molecular formula	Found C	H	N	Required C	H	N
1.	$C_{16}H_{22}N_2O_6$	59·9;	6·3;	8·0	59·7;	6·1;	7·7
2.	$C_{13}H_{20}N_2O_6$	51·9;	6·9;	9·5	52·0;	6·7;	9·3
3.	$C_{16}H_{22}N_2O_6$	59·6;	6·2;	7·9	59·7;	6·1;	7·7
4.	$C_{17}H_{19}N_2O_6Cl$	53·2;	5·0		53·3;	4·9	
5.	$C_{21}H_{22}N_2O_6$	63·8;	5·7;	6·8	63·3;	5·5;	7·0

EXPERIMENTAL

*7-Anilino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxin** (I, R = Ph) was crystallized from chloroform when it had m.p. 193° with dec. (Found: N, 4·8. Calc. for $C_{15}H_{13}NO_6$: N, 4·9%.) Other 7-Amino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxins, prepared similarly, are listed in the Table No. 1.

Formation of methyl 1,2-dihydro-4,6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxylate (II R = CH_3, R′ = Ph). The pyronodioxin (I, R = Ph; 1·0 g) was added to MeOH containing MeONa (from 1 g Na;) and the mixture was refluxed for 1 hr. The soln. on cooling, was acidified with 2N HCl. A white solid separated, and was dried. Methyl 1,2-dihydro-4,6-dihydro-2-oxo-1-phenylpyridine-3-carboxylate (0.33 g; 36·3%) was recrystallized from $CHCl_3$–MeOH, it had m.p. 210° *l* unchanged in admixture with an authentic sample of the material[3] (Found: N = 5·5; Calc. for $C_{12}H_{11}NO_6$: N, 5·3%.) Other pyridones prepared in this way are recorded in Table 2.

Morpholinum salts of the dihydroxypyridones (II)

Reaction of morpholine with methyl 1,2-dihydro-4,6-dihydroxy-2-oxo-1-phenyl pyridine-3-carboxylate. The pyridone (II, R = CH_3, R′ = Ph; 1·0 g) in $CHCl_3$ (20 ml) and morpholine (0·5 g) were refluxed

* Details. (cf. Ref. 1)

together for 15 min. The morpholinium salt (III, R = CH_3, R′ = Ph) separated and was crystallized from MeOH. It melted at 180° with dec. (Found: C, 58·6; H, 5·9; N, 8·1; Calc. for $C_{17}H_{20}N_2O_6$: C, 58·6; H, 5·7; N, 8·0%.) Other morpholinium slats prepared as above are listed in Table 3. The elementary analysis were carried out by A. Bernhardt, Microanalytisches Laboratorium, Mulheim (Ruhr), West Germany.

Acknowledgement—Thanks are due to Dr. Salimuzzaman Siddiqui, F.R.S., Chairman for his interest in this work. One of us (I. A. Akhtar) thanks P.C.S.I.R. for the award of research assistantship.