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

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(Received September 16, 1966)

The reaction of aminopyranodioxins (I) with alkoxides, i.e. sodium methoxide and sodium ethoxide, has been investigated further. The UV and IR spectra of the new products has been recorded.

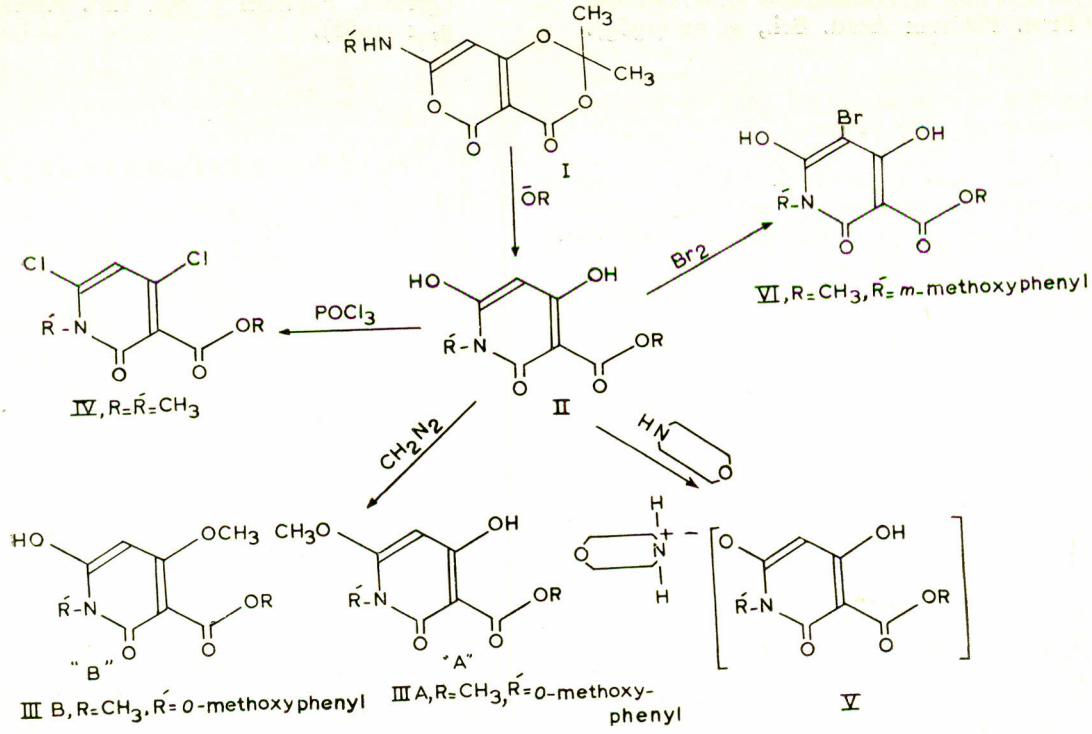
One step formation of the dihydroxypyridines (II) from aminopyranodioxins (I) was reported earlier.[1] The reaction appeared to be capable of further extension, by reacting the easily available aminopyranodioxins [2] with sodium methoxide and ethoxide to yield pyridines in the range 50-80%.

For example, the compound $C_{16}H_{15}NO_5$, (I, R′ = *m*-tolyl) when reacted with sodium methoxide in methanol formed a product with formula $C_{14}H_{13}NO_5$ (II, R=CH_3, R′=*m*-tolyl), m.p. 190° (dec). It had all the characteristics of dihydroxypyridines. It absorbed UV light at λ_{max} 306, log ε, 4.4. A similar situation has been observed in case of several aminopyranodioxins and alkoxides. The analyses and physical data of the new products are recorded in Table 1.

Apart from UV and IR spectra recorded in support of the structural formula (II) various chemical transformations of the new products were also carried out. For instance, the product $C_8H_9NO_5$ (II, R=R′=CH_3) with phosphorus oxychloride, gave a dichloropyridine $C_8H_7NO_3Cl_2$ (IV), m.p. 126, λ_{max} 326 and log ε 4.6. IR absorption occurred at ν 1639s cm-1, due to 2-pyridone carbonyl. With diazomethane, the product (II, R=CH_3, R′=*o* methoxyphenyl) gave a monomethoxy compound with a formula $C_{15}H_{15}NO_6$. m.p. 205, λ_{max} 206, log ε 4.5. It could have two structures, i.e. IIIA or IIIB. The latter formula was discounted because it is the hydroxyl group adjacent to the electrophilic nitrogen which is most likely to be attacked rather than the one further removed from it.

On treatment with morpholine in chloroform, it (II, R=CH_3, R′=benzyl) gave a morpholinium adduct $C_{22}H_{26}N_2O_6$ (V), m.p. 167, λ_{max} 308, log ε, 4.6. When reacted with bromine in CCl_4 solution, the compound (II, R=CH_3,

CHART I.



R′=*m*-methoxyphenyl readily formed a bromo product, $C_{14}H_{16}BrNO_6$, m.p. 118. It retained its enolic nature. The bromo derivative can possibly have only one structure, i.e. (VI). Moreover, several examples[3,4] are known where bromine atom preferably enters the already vacant position in the substituted pyridine ring rather than to replace the hydroxyl group under such mild conditions. The foregoing reactions are depicted in Chart 1.

Experimental

Formation of methyl-1,2-dihydro-4,6-dihydroxy-2-oxo-1-(m-tolyl)-pyridine-3-carboxylate (II, R=CH_3, R′=*m*-tolyl).—The pyranodioxin (I, R′=*m*-tolyl), (1.0 g) was added to methanol (20 ml) containing dissolved sodium (1.0 g), and the mixture refluxed for 1 hr. The solution was cooled and acidified with 2N HCl. The resulting white solid, methyl-1,2-dihydro-4,6-dihydroxy-2-oxo-1-(*m*-tolyl)-pyridine-3-carboxylate (0.6 g, 60%), was crystallised from $CHCl_3$-methanol, m.p. 190°, undepressed on admixture with an authentic sample.[2] (Found: C, 61.4; H, 4.8; N, 5.2. Calc. for $C_{14}H_{13}NO_5$: C, 61.1; H, 4.8; N, 5.1%.)

Other dihydroxypyridine esters prepared as above are recorded in Table 1.

Methyl-4,6-dichloro-1,2-dihydro-2-oxo-1-methyl-pyridine-3-carboxylate (IV).—Compound II (R=R′ CH_3) (1.0 g) was heated with phosphorus oxychloride (10 ml) for 15 min on water bath. The excess of phosphorus oxychloride was removed under reduced pressure. The residual semi-solid was dissolved in ethanol (25 ml) and the solution was decolourised with charcoal.

The filtrate was reduced to half its volume and then diluted with water (3 ml). On keeping it for several hours, a crystalline product, methyl-4,6-dichloro-1,2-dihydro-2-oxo-1-methylpyridine-3-carboxylate (III, 0.6 g, 55%) was obtained. It crystallised from ethanol (80%), m.p. 126°. (Found: C, 40.8; H, 3.1; N, 6.1. $C_8H_7Cl_2NO_3$ requires: C, 40.6; H, 3.0; N, 5.9%.)

Methyl-1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-(o-methoxyphenyl)-pyridine-3-carboxylate (III).— To compound II (R′=*o*-methoxyphenyl, R=CH_3) (0.5 g) in chloroform (20 ml) was added diazomethane in ether till a yellow colour persisted. The mixture was kept in cold for 12 hr. Evaporation of the solution to dryness gave methyl-1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-(*o*-methoxyphenyl)-pyridine-3-carboxylate (IV, 0.25 g, 50%), which was crystallised from methanol, m.p. 205°C. (Found: C, 59.2; H, 5.3; N, 4.8 $C_{15}H_{15}NO_6$ requires: C, 59.0; H, 4.9; N, 4.6%.)

TABLE 1.—4,6-DIHYDROXY PYRIDINES (II).

7-Amino-pyrano-1,3-dioxines (I)		Na in EtOH	Product 4,6-dihydroxy-pyridines (II)		Molecular Formula (II)	Yield %	Solvent crystallisation	M.p.	Analysis						UV absorption in 95% EtOH		IR absorption max (cm^{-1}) mainly for C=O(2)
									Found			Required					
R′	Qty/g	g/ml	R	R′					C	H	N	C	H	N	λ_{max}	log ε	Nujolmull
Methyl	1.0	1.0/25	Methyl	Me	$C_8H_9NO_5$	51	MeOH	202	48.0	4.6	7.2	48.0	4.5	7.0	303	4.8	1647m
m-Tolyl	1.0	1.0/25	*m*-Tolyl	Me	$C_{14}H_{13}NO_5$	63	MeOH	204	61.5	4.8	5.2	61.1	4.5	7.5	306	4.4	1647m
o-Tolyl	1.0	1.0/25	*m*-Tolyl	Et	$C_{15}H_{15}NO_5$	60	EtOH	196	62.4	5.3	4.8	62.3	5.2	4.8	306	4.5	1639s
o-Methoxyphenyl	1.0	1.0/25	*o*-Methoxyphenyl	Me	$C_{14}H_{13}NO_6$	47	MeOH	198	58.0	4.9	4.6	57.7	4.5	4.8	306	4.4	1629s
o-Methoxyphenyl	1.0	1.0/25	*o*-Methoxyphenyl	Et	$C_{15}H_{15}NO_6$	50	EtOH	190	59.5	5.3	4.7	52.1	5.0	4.6	306	4.3	1639s
m-Methoxyphenyl	1.0	1.0/25	*m*-Methoxyphenyl	Me	$C_{14}H_{13}NO_6$	50	MeOH	190	57.9	4.6	4.6	57.7	4.5	4.8	306	4.4	1636s
m-Methoxyphenyl	1.0	1.0/25	*m*-Methoxyphenyl	Et	$C_{15}H_{15}NO_6$	55	EtOH	180	59.0	4.8	4.8	59.1	5.0	4.8	306	4.5	1642m
o-Chlorophenyl	1.0	1.0/25	*o*-Chlorophenyl	Me	$C_{13}H_{10}CLNO_5$	40	MeOH	184	52.5	3.6	4.6	52.7	3.4	4.7	305	4.5	1639s
o-Chlorophenyl	1.0	1.0/25	*o*-Chlorophenyl	Et	$C_{14}H_{12}CLNO_5$	52	EtOH	192	54.3	4.0	4.7	54.3	3.9	4.5	305	4.4	1647m
Benzyl	1.0	1.0/25	Benzyl	Me	$C_{14}H_{13}NO_3$	47	MeOH	178	60.8	4.8	5.3	61.1	4.8	5.1	306	4.4	1639s
Benzyl	1.0	1.0/25	Benzyl	Et	$C_{15}H_{15}NO_5$	54	EtOH	168	62.8	5.4	5.1	62.3	5.2	4.9	306	4.4	1665n
m-Hydroxyphenyl	1.0	1.0/25	*m*-Hydroxyphenyl	Me	$C_{13}H_{12}NO_6$	30	MeOH	193	57.8	4.1	5.0	57.7	4.5	4.8	306	4.3	1647m
m-Hydroxyphenyl	1.0	1.0/25	*m*-Hydroxyphenyl	Me	$C_{13}H_{12}NO_6$	30	MeOH	193	57.8	4.1	5.0	57.7	4.5	4.8	306	4.3	1647m
Nitrophenyl	1.0	1.0/25	Nitrophenyl	Et	$C_{14}H_{13}NO_6$	45	EtOH	190	59.2	4.4	4.7	57.0	5.0	4.6	306	4.3	1647m
Phenyl	1.0	1.0/25	Phenyl	Me	$C_{13}H_{17}NO_5$	62	MeOH	176	58.6	6.5	5.4	58.4	6.3	5.3	305	4.4	1649m
Phenyl	1.0	1.0/25	Phenyl	Et	$C_{14}H_{19}NO_5$	67	EtOH	163	59.5	6.8	5.3	59.8	6.7	5.0	306	4.4	1658m
α-Naphthyl	1.0	1.0/25	Naphthyl	Me	$C_{17}H_{13}NO_5$	72	MeOH	203	65.4	4.2	4.4	65.5	4.2	4.5	305	4.5	1653m
α-Naphthyl	1.0	1.0/25	Naphthyl	Et	$C_{18}H_{15}NO_5$	78	EtOH	210	65.4	4.7	4.5	65.6	4.7	4.3	305	4.3	1658m

Morpholinium Salt of Dihydroxypyridine (V).—Compound II (R′=benzyl R=CH_3) (0.5 g) in chloroform (15 ml) and morpholine (0.5 ml) were refluxed for ½ hr. The morpholinium salt (V, R′=benzyl, R=CH_3) was obtained after evaporating the solvent under reduced pressure (0.4 g) and recrystallising from methanol, m.p. 167°C. (Found: C, 59.3; H, 6.0; N, 7.6. $C_{22}H_{26}N_2O_6$: requires C, 59.7; H, 6.1; N, 7.7%).

Methyl, 5-bromo-1,2-dihydro-4,6-dihydroxy-2-oxo-1-(m-methoxyphenyl)-pyridine-3-carboxylate (VI).—To compound II (R=CH_3, R′=*m*-methoxyphenyl (1.0 g) in chloroform (20 ml) bromine (in chloroform) was added drop-wise till a brown colour persisted. It was kept as such for 3 hr at room temperature and the solvent recovered by distillation. The residue, on trituration with water gave the 5-bromo product (VI, 0.9 g, 80%), which was crystallised from chloroform, m.p. 118°C. (Found: C, 45.0; H, 3.2; N, 3.8 $C_{14}H_{16}NO_6$ Br requires C, 45.4; H, 3.0; N, 3.8%).

Acknowledgement.—Thanks are due to Dr. Salimuzzaman Siddiqui, F.R.S., former Chairman, P.C.S.I.R., for his keen interest in this work. All the analyses were carried out by A. Bernhardt, Microanalytisches Laboratorium, 22a, Mulheim Ruhr, West Germany.

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