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SYNTHESIS OF SUBSTITUTED PYRIDINES—II*

4,6-DIHYDROXY-1-SUBSTITUTED PYRIDINE-3-CARBOXYANILIDES

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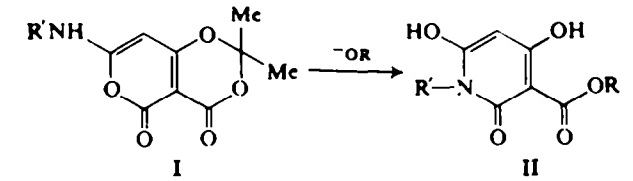
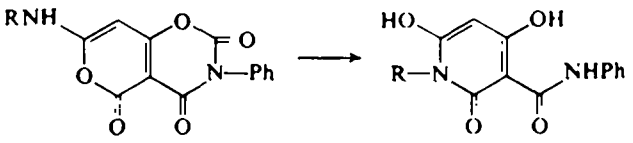
Abstract—The reaction between amino-pyrano-oxazines (III) and sodium and potassium hydroxides yields 1-substituted derives of 4,6-dihydroxy-2-oxo-pyridine-3-carboxyanilide.

AMINOPYRANODIOXIN derivatives (I) react with alkoxides to form ester pyridones.[1] The reaction of aminopyranooxazines (III) with strong bases under comparable conditions of time and temperature, yield dihydroxypyridines of the type (IV) in amounts varying from 65–87%. 7-Anilinopyranooxazine (III, R=Ph) reacts with

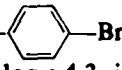
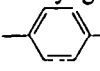


I II



III IV

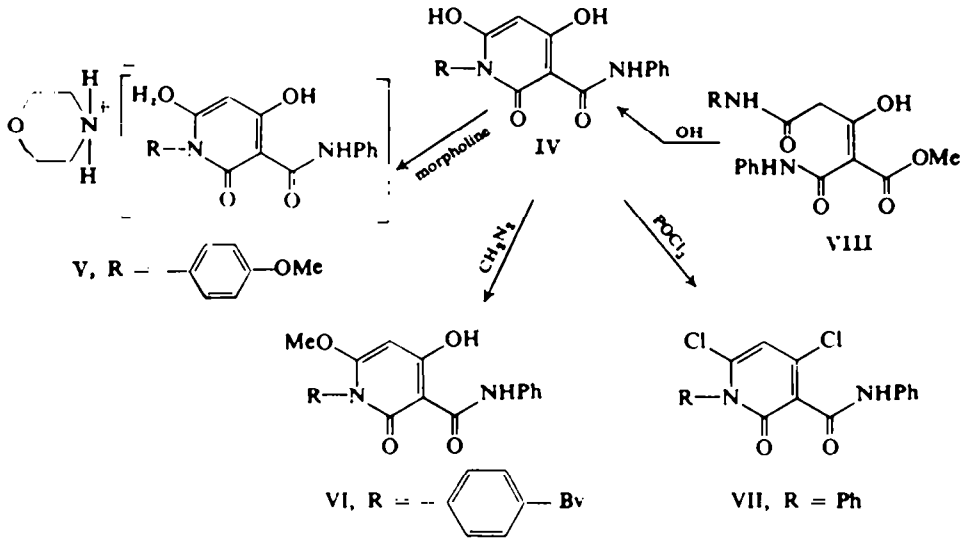
sodium or potassium hydroxide, yielding a product $C_{18}H_{14}N_2O_4$, m.p. 234 (dec), 315 mμ, log ε 4·5. It is enolic in character and reacts with phosphorus oxychloride, to give a dichloro compound ($C_{18}H_{12}N_2Cl_2O_2$, m.p. 218, 319 mμ log ε 4·3) formed by the removal of two hydroxyl groups.

On reacting with diazomethane, the compound IV (R = ) gives a mono-methoxy product, $C_{19}H_{15}N_2O_4Br$, m.p. 243 (dec) 311 mμ, log ε 4·3, indicating that only one hydroxyl group is methylated under the prevalent conditions. Similarly, when IV (R = ) is treated with morpholine, a product $C_{23}H_{25}N_3O_6$

* Part I, *Tetrahedron* **22**, 455 (1966).

m.p. 171 (dec), 317 mμ, log ε 4·52 is formed in accordance with other dihydroxypyridines.[1]

The reactions are described diagrammatically as follows:



Final proof of the structure IV was obtained by comparison with an authentic sample.[2] A mixed m.p. and IR spectra were found identical.

Several other products prepared are listed in Table 1 together with their UV and IR data.

TABLE 1. UV AND IR SPECTRA OF AMINOPYRIDINES (IV)

S.No.	1,2-Dihydro-4,6-dihyrdoxy-2-oxo-1-substituted pyridine-3-carboxyanilides (IV) R	UV (95% EtOH) mμ	log ε	IR mainly for the 3–6·7 μ region (KBr) C = O[a]
1.	n-Butyl-	322	4·50	1667 s
2.	Isobutyl-	322	4·48	1664 s
3.	Allyl-	321	4·50	1669 s
4.	Cyclohexyl-	322	4·54	1669 s
5.	Benzyl-	323	4·46	1667 s
6.	*p*-Tolyl-	316	4·46	1667 s
7.	*p*-Chlorophenyl-	316	4·30	1653 s
8.	*p*-Bromophenyl-	315	4·32	1667 s
9.	*p*-Methoxyphenyl-	315	4·50	1667 s
10.	Phenyl-	315	4·50	1664 s

The parent aminopyranooxazines (III) were prepared by a method analogous to that described by Elvidge.[3,5]

[1] A. Butt and I. A. Akhtar, *Tetrahedron* **22**, 455 (1966).
[2] Elvidge, *J. Chem. Soc.* 3080 (1963).
[3] Elvidge, *J. Chem. Soc.* 2251 (1953).
[4] M. A. Butt and I. A. Akhtar, *Tetrahedron* **21**, 1917 (1965).
[5] M. A. Butt, Ph.D. Thesis (1963), Imp. College (London).

The formation of the product (IV) can be explained as follows:

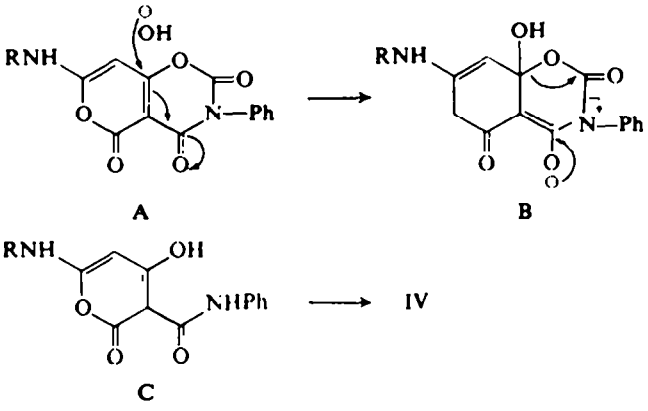


TABLE 2. AMINO-PYRANO-OXIZINES (III)

S.No.	Primary amine (2 moles)	7-Chloro-3,4-dihydro-2,4,5-trioxo-phenyl 2H,5H-pyrano-(4, 3-c)-(1,3)-oxazine (1 mole)	Amino-pyrano oxazine (III) R	Yield	Solvent for crystallization
1.	n-Butylamine (1·5 g)	2·0 g	n-Butyl-	1·3 g	$CHCl_3$—CH_3OH
2.	Isobutylamine (1·5 g)	2·0 g	Isobutyl-	1·4 g	$CHCl_3$—CH_3OH
3.	Allylamine (0·8 g)	2·0 g	Allyl-	1·7 g	$CHCl_3$—CH_3OH
4.	Cyclohexylamine (1·4 g)	2·0 g	Cyclohexyl-	1·9 g	$CHCl_3$—CH_3OH
5.	Benzylamine (1·5 g)	2·0 g	Benzyl-	1·8 g	$CHCl_3$—CH_3OH
6.	*p*-Toluidine (1·5 g)	2·0 g	*p*-Tolyl-	2·4 g	$CHCl_3$—CH_3OH
7.	*p*-Chlorophniline (2·6 g)	2·0 g	*p*-Chlorophenyl-	2·4 g	$CHCl_3$—CH_3OH
8.	*p*-Bromoquiline (2·4 g)	2·0 g	*p*-Bromophenyl-	2·9 g	$CHCl_3$—CH_3OH
9.	*p*-Ansidine (1·7 g)	2·0 g	*p*-methoxyphenyl-	2·5 g	$CHCl_3$—CH_3OH

	UV (95% EtOH)				Found (%)			Required (%)		
	mμ	log ε	m.p.	Formula	C	H	N	C	H	N
1.	334	4·45	185	$C_{17}H_{16}N_2O_6$	61·8	5·1	8·7	62·2	4·9	8·5
2.	336	4·52	210	$C_{17}H_{16}N_2O_6$	62·1	5·0	8·5	62·2	4·9	8·5
3.	335	4·44	195	$C_{16}H_{12}N_2O_6$	61·1	4·0	10·5	61·5	3·9	9·0
4.	335	4·52	203	$C_{16}H_{16}N_2O_6$	64·3	5·3	8·4	64·4	5·1	7·9
5.	337	4·50	258	$C_{20}H_{14}N_2O_6$	66·3	4·0	7·7	66·3	3·9	7·8
6.	350	4·51	225	$C_{20}H_{14}N_2O_6$	66·2	4·3	7·6	66·3	3·9	7·7
7.	351	4·40	197	$C_{19}H_{11}N_2O_6Cl$	60·1	3·0	7·2	59·7	2·9	7·3
8.	351	4·40	214	$C_{19}H_{11}N_2O_6Br$	53·5	2·7	6·6	53·4	2·6	6·6
9.	350	4·40	195	$C_{20}H_{14}N_2O_6$	63·0	3·9	7·8	63·5	3·7	7·5

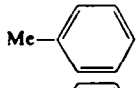
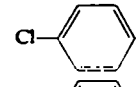
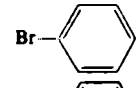
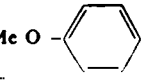
Several attempts to isolate C were unsuccessful as the conversion of A → C is probably as rapid as C → IV and the mechanism of the formation of IV from C is as already explained.[4]

EXPERIMENTAL

Reaction of 7-anilino-2,4-5-trioxo-3-phenyl-2H,5H-pyrano(3,4-e)-1,3-oxazine (III, R = Ph) *with potassium hydroxide*

(a) Compound III (R = Ph; 1 g) in EtOH (40 ml; 75%) and KOH (1 g) were refluxed for 30 min. The soln was cooled and acidified with 2N HCl. The white curdy precipitate was washed with water and dried. The compd IV (R = Ph; 0·7 g; 79%) crystallized from MeOH, m.p. 234° and was undepressed on admixture with the sample prepared according to method b. (Found: C, 67·3; H, 3·9; N, 8·8; calc. for $C_{18}H_{14}N_2O_4$: C, 67·1; H, 4·4; N, 8·7%.)

TABLE 3

S. No.	Aminopyrano-oxazines (III) R	Amount	Potassium-hydroxide in Enthanol (50%)	1-substituted 1,2-dihydro-4,6-di-hydroxy-2-oxopy-ridine-3-carboxy-anilides (IV) R	Yield	Solvents for crys-tallization
1.	$Me.(CH_2)_3-CH_2-$	0·6 g	1 g KOH/30 ml	n-Butyl	0·4 g 73%	MeOH
2.	$(Me)_2CH.CH_2-$	1g	1g KOH/30 ml	Iso-butyl-	0·8 g 87%	MeOH
3.	$CH_2=CH-CH_2-$	0·9 g	0·9 g KOH/30 ml	Allyl-	0·6 g 73%	MeOH
4.		0·5 g	0·4 g KOH/25 ml	Cyclohexyl-	0·3 g 65·2%	MeOH
5.		1 g	1 g KOH/25 ml	Benzyl-	0·6 g 66·0%	MeOH
6.		1 g	1 g KOH/25 ml	*p*-Tolyl-	0·7 g 81%	Benzene
7.		1·8 g	1·8 g KOH/25 ml	P-Chlorophenyl	1·0 g 58%	Benzene
8.		2·0 g	2·0 g KOH/30 ml	*p*-Bromophenyl	1·0 g 73%	Benzene
9.		2·0 g	2·0 g KOH/30 ml	P-Methoxy-phenyl	1·5 g 83·3%	Benzene

S. No.	M.p.	Formula	Analysis					
			Found (%)			Required (%)		
			C	H	N	C	H	N
1.	173	$C_{18}H_{18}N_2O_4$	63·6	6·1	9·3	63·6	6·0	9·3
2.	163	$C_{18}H_{18}N_2O_4$	63·6	6·1	9·3	63·6	6·0	9·3
3.	158	$C_{18}H_{16}N_2O_4$	62·8	5·1	9·1	62·9	4·9	9·8
4.	199	$C_{18}H_{20}N_2O_4$	65·8	6·2	8·6	65·7	6·1	8·5
5.	180	$C_{19}H_{16}N_2O_4$	67·4	4·5	8·7	67·9	4·8	8·3
6.	195	$C_{19}H_{16}N_2O_4$	67·4	4·5	8·7	67·9	4·8	8·3
7.	220	$C_{18}H_{15}N_2O_4Cl$	60·3	3·7	—	60·7	3·7	—
8.	238	$C_{18}H_{15}N_2O_4Br$	54·3	3·5	6·5	53·9	3·2	7·0
9.	214	$C_{19}H_{18}N_2O_5$	65·5	4·7	7·7	64·8	4·5	7·9

(b) *Cyclization of the ester di-anilide* (VIII). Compound VIII (0·4 g) and KOH (0·3 g) and MeOH (10 ml) were refluxed for 5 min. The soln was cooled, then acidified with 2N HCl and IV (R = Ph) (0·2 g; 55%) crystallized from MeOH, m.p. 234° undepressed on admixture with the specimen prepared as above.

Several other compds (VI) were prepared according to method (a) and are recorded in Table 3.

(c) *Action of* $POCl_3$ *on* 1,2-*dihydro*-4,6-*dihydroxy*-2-*oxo*-1-*phenyl-pyridine*-3-*carboxyanilide*. Compound IV (R = Ph; 1·0 g) and $POCl_3$ (20 ml) were heated under reflux for ½ hr. Excess $POCl_3$ was recovered and the residue triturated with water. The 4,6-*dichloro*-1,2-*dihydro*-2-*oxo*-1-*phenyl pyridine*-3-*carboxyanilide* (1·0 g; 91%) crystallized from EtOH (75%), m.p. 218°. (Found, N, 8·0 $C_{18}H_{12}N_2Cl_2O_2$ requires: N = 7·8°.)

(d) *Reaction of morpholine with* 1,2-*dihydro*-4,6-*dihydro-oxy*-2-*oxo*-1-(p-*methoxyphenyl*) *pyridine*-3-*carboxyanilide*. Compound IV (R = MeO—C$_6$H$_4$—; (0·2 g), morpholine (0·2 ml) and chf (10 ml) were heated under reflux for 20 min under dry conditions. The solvent and unreacted morpholine were removed under red press. The residue on trituration with ether gave V (0·21 g; 84·0%) which crystallized from dil EtOH, m.p. 171°, dec. (Found: C, 62·9; H, 5·9; N, 9·5. $C_{23}H_{24}N_2O_6$ requires: C, 62·9; H, 5·7; N, 9·1%.)

(e) *Reaction of diazomethane with* 1,2-*dihydro*-4,6-*dihydroxy*-2-*oxo*-1-(p-*bromophenyl*)*pyridine*-3-*carboxyanilide*. Compound IV (R = —C$_6$H$_4$—Br; 0·3 g) dissolved in chf was treated with excess diazomethane soln in ether. The mixture was kept for 2 days. The excess diazomethane was decomposed with HCl and the organic layer separated, dried over Na_2SO_4 and the solvent removed. The residue, on trituration with ether, gave VI (R = —C$_6$H$_4$—Br; 0·1 g; 32·2%) which recrystallized from chf, m.p. 259°, dec. (Found: N = 6·9, $C_{19}H_{15}N_2O_4Br$ requires: N = 6·9%.)

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