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SYNTHESIS OF SUBSTITUTED PYRIDINES

Part X. Derivatives of 7-[2 (4)-Acetylaminophenyl) amino] -2, 2-Dimethyl-4, 5-Dioxopyrano [4, 3-d] [1, 3] Dioxin and Methyl 1-(2 (4) -Acetylaminophenyl) - 1, 2-Dihydro-4, 6-Dihydroxy-2-Oxopyridine-3-Carboxylate

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The reaction of a 1,2-or 1,4-monoacetylated aromatic diamines (IVa or IVb) with a chloropyranodioxin (I) yields a corresponding acetylaminopyranodioxin (Va or Vb) which is difficult to deacetylate to form products (IIIa or IIIb). The former (Va or Vb) reacts with methoxide and phenoxide in methanol and phenol respectively to generate usual monocyclic and bicyclic products, (VIIa or VIIb) and (IX). Reaction of the product VIIb with morpholine, bromine and ethyl isothiocyanate yields a morpholinium salt, a bromo compound and a thiocarbamato derivative respectively.

Key words: Chloropyranodioxin, Morpholinium salt, Thiocarbomato derivative.

Introduction

Several methods for the synthesis of substituted pyridines have been reported in literature [1-9]. The authors have demonstrated synthetic utility of a chloropyranodioxin (I) in the synthesis of substituted pyridines in their preceding papers of the series [10].

They have now tried to explore further synthetic utility of the product (I). The product (I) was converted into an acetylaminopyranodioxin (Va) or (Vb). The product (Va) or (Vb) could not be converted into the product (IIIa) or (IIIb). However, the product (Va or Vb) was converted into a variety of products (VIIa) or (VII b), (VIII) and (IX). Derivatives of (VIIb) were also prepared. The reactions are depicted in Chart 'A'.

Experimental

Melting points were determined with a Thomas-Hoover Capillary apparatus and are uncorrected. U.V. and I.R. spectra were recorded on Beckman 36 and Perkin-Elmer 283 B spectrophotometers respectively. Mass spectra were obtained on AE1 MS30 instrument.

(1). *7-[(4-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d][1,3] dioxin (Vb, R=4-CH_3 $CONHC_6H_4$–).* To 7-chloro-2, 2-dimethyl-4, 5-dioxopyrano

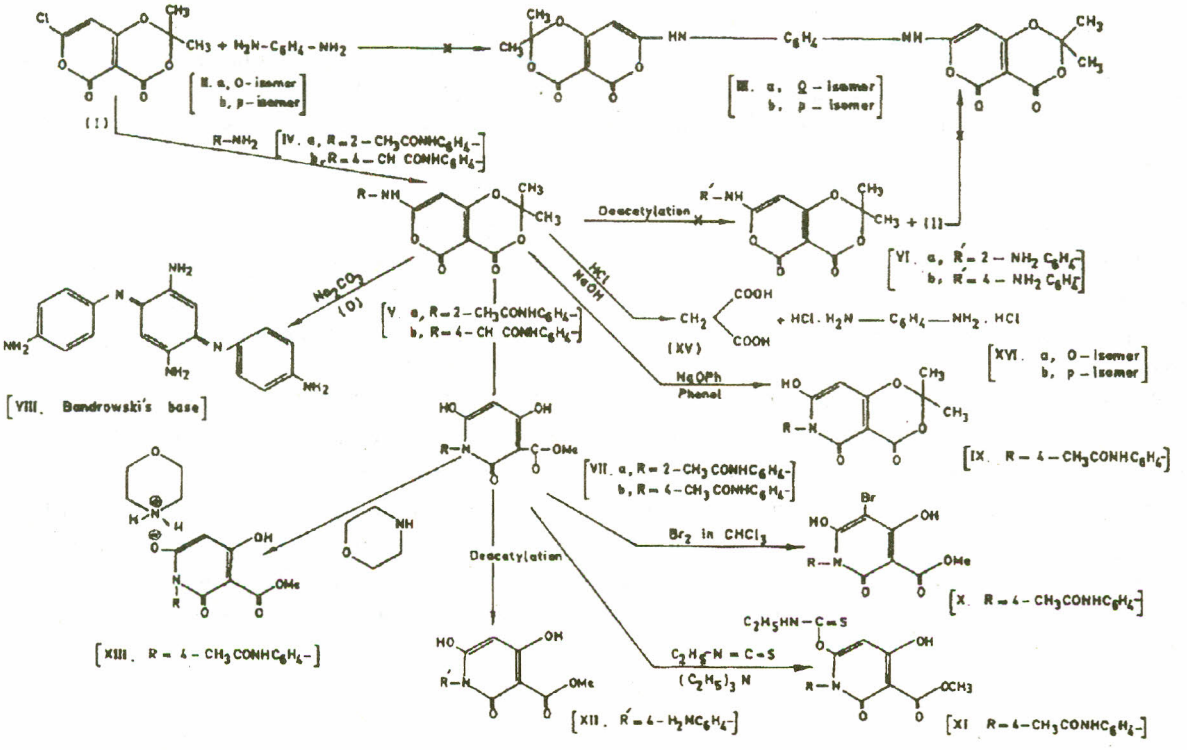


Chart A

[4, 3-d] [1,3] dioxin [11] (I) (2, 3g, 0.01 mole) in acetone (20 ml) was added dropwise into solution of 4-aminoacetanilide (IVb) (2.3gm; 0.01 mole) in acetone (30 ml) with constant stirring. After 30 mins, the product was filtered, washed with hot water and dried. 7-[4-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d][1,3] dioxin (Vb, R=4-$CH_3CONHC_6H_4$)(1.5gm; 65.2%) on crystallisation from MeOH-$CHCl_3$ mixture (1:3), melted at 260° (decomp.), UV (MeOH) λ_{max} 330nm; log ε 4.44.

Found (%): C, 59.20; H, 4.60; N, 8.00. $C_{17}H_{16}N_2O_6$ requires (%) C, 59.30, H, 4.70, N, 8.10.

(2). *Reaction of 7-[(4-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d][1,3] dioxin (Vb, R=4-$CH_3CONHC_6H_4$-) with HCl (5N).* The compound (Vb, R=4-$CH_3CONHC_6H_4$), (1gm) was taken in a beaker containing 50ml HCl (5N) and the solution was heated at 80°, while agitating with a magnetic stirrer. Effervescence started after 30 mins. The solid dissolved gradually and clear solution resulted that was evaporated at low temperature. The resulting shining crystals (0.5gm), or recrystallising from MeOH, had m.p. 255° (decomp.). The compound was identified as *p*-phenylenediamine dihydrochloride (XVIb=HCl-$NH_2C_6H_4NH_2$-HCl). It gives no depression on taking mixed m.p. with an authentic sample of the compound, λ_{max} 240nm, log ε, 4.03.

Found %. C, 39.90, H, 5.60, N, 15.30. Calc. for $C_6H_4Cl_2N_2$ (%), C, 39.80, H, 5.50; N, 15.4.

(3). *Formation of Bandrowski's base (VIII).* 1, 4-Phenylenediamine dihydrochloride (XVI) (1 gm) was taken in water (50ml) in a beaker and was neutralized with Na_2CO_3. The resulting dark brown solution was kept for 24 hrs. Brownish black shining crystals separated (VII) (0.5gm, 28%) which on recrystallisation from MeOH-$CHCl_3$ (1:1) had m.p. 238° (decomp.), identified as Bandrowski's base (VIII). It gave no depression in m.p. when admixed with an authentic sample. Its identity was also confirmed by mass spectral data. It showed M^+ peak at 318 and other peaks at 211 and 108 as expected, λ_{max} 335nm; log ε, 4.2.

Found %. C, 67.80; H, 6.60; N, 25.50. Calc. for $C_{18}H_{18}N_6$(%). C, 67.90; H, 6.60; N, 26.10.

(4). *Reaction of 7-[(4-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1, 3] dioxin (Vb, R=4-$CH_3CONH_6H_4$-) with sodium methoxide in methanol.* The compound (Vb, R=4, $CH_3CONHC_6H_4$) (1 gm, 0.003 mole) was added to sodium methoxide in methanol [Na, 0.46 gm (0.2 mole/methanol), 30 ml] under anhydrous conditions. The solution was refluxed for 30 mins, and the solvent was reduced to half of its volume. On cooling it was diluted with water (100ml) and neutralized with HCl (2N). A white solid separated. It was filtered, washed with water, dried and weighed (0.55gm; 55%). It was identified as methyl 1-(4-acetylaminophenyl)-1, 2-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$), which on recrystallisation from MeOH-$CHCl_3$ (1:1) had m.p. 280° (decomp.), λ_{max} 30.5nm; log ε, 4.31.

Found (%): C, 56.60; H, 4.10; N, 8.80. $C_{15}H_{14}N_2O_6$ requires (%). C, 56.60; H, 4.40; N, 8.80.

(5). *Reaction of methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) with HCl (5N).* A mixture of compound (IX, R=4-$CH_3CONHC_6H_4$-) (1.0 gm) and hydrochloric acid (5N, 50 ml) was heated at 80° with stirring for 30 mins. Evolution of CO_2 from the solution was noted while it became clear. It was evaporated to dryness and shining light brown crystals separated and weighed (0.5 gm). 1, 4-Phenylenediamine dihydrochloride (XVIb) was formed and was recrystallised from MeOH. The compound (XVIb) had m.p. 255° (decomp.). It gave no depression on taking mixed m.p. with an authentic sample, $\lambda_{max.}$ 240nm; log ε, 4.06.

Found (%). 39.40, H, 5.70, N, 15.30. calc. for $C_6H_{10}Cl_2N_2$(%) C, 39.80, H, 5.50, N, 15.40.

(6). *Formation of 7-[(2-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1,3] dioxin (Va, R=2-$CH_3CONHC_6H_4$-).* 7-Chloro-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1,3] dioxin (I, 2.3gm; 0.01 mole) was taken in acetone (30 ml) and 2-aminoacetanilide (Ia) (3gm; 0.02 mole) in acetone (20ml) was added gradually while stirring. The resulting solution was stirred for a further period of 1 hr. A white solid separated, filtered and washed with water. It was dried and weighed. The product identified as 7-[(2-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1,3] dioxin (Va, R=2-$CH_3CONHC_5H_4$-) (1.5 gm; 65%), on recrystallisation from MeOH:$CHCl_3$ (1:1), melted at 230° (decomp.), λ_{max} 336nm, log ε, 4.47.

Found (%): C, 59.60, H, 4.50, N, 8.00. $C_{17}H_{16}N_2O_6$ requires (%). C, 59.30; H, 4.70; N, 8.10.

(7). *Reaction of 7-[(2-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1, 3] dioxin (Va, R=2-$CH_3CONHC_6H_4$–) with sodium methoxide in methanol.* The compound (VIb, R=2-$CH_3CONHC_6H_4$-) (1gm, 0.003 mole) was added to sodium methoxide in methanol [Na, 0.46 gm (0.2 mole) methanol, 30ml] under anhydrous conditions. The mixture was refluxed for 30 mins. Solvent was reduced to half of its volume. The solution was diluted with water 100ml, neutralized with HCl (2N). The precipitate was filtered, washed with water, dried and weighed, (0.50 gm; 55%). The product, identified as methyl 1-(2-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIa, R=2-$CH_3CONHC_6H_4$-) on recrystallisation from MeOH, had m.p. 220° (decomp.), $\lambda_{max.}$ 304nm, log ε, 4.34.

(8). *Reaction of 7-[(4-acetylaminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano [4, 3-d] [1,3] dioxin (Vb, R=4-*

$CH_3CONHC_6H_4$-) with sodium phenoxide. The compound (Vb, R=4-$CH_3CONHC_6H_4$-) (2gm, 0.006 mole) was added to the sodium phenoxide solution [Na, 0.92 gm (0.23 mole); phenol (25 ml) under anhydrous conditions, heated for 5 mins at 100°. The brown solution was cooled diluted with water (30 ml) and extracted with ether to remove excess of phenol. The aqueous solution was neutralised with HCl (2N). A white solid was filtered, washed with water, dried and weighed, (1gm; 50%). The residue, 6-(4-acetylaminophenyl)-2, 2-dimethyl-7-hydroxy-4, 5-dioxopyridino [4, 3-d] [1,3] dioxin (IX, R=4-$CH_3CONHC_6H_4$-) on recrystallisation from MeOH: $CHCl_3$ (1:2), melted at 275° (decomp.), λmax 310, log ε, 4.47.

Found (%). C, 59.10, H, 4.60, N, 8.10. $C_{17}N_{16}N_2O_6$ requires (%). C, 59.30; H, 4.70; N, 8.10.

(9). *Reaction of 6-(4-acetylaminophenyl)-2, 2-dimethyl-7-hydroxy-4,5-dioxo-pyridino [4, 3-d] [1,3] dioxin (IX, R=4-$CH_3CONHC_6H_4$-) with HCl (5N).* The compound (IX, R=4-$CH_3CONHC_6H_4$-) (1gm) was taken in HCl (5N, 50ml) and solution was heated at 80° with stirring. Effervesence was noted and the solution became clear. The solution was concentrated at low temperature under reduced pressure. It afforded light brown shing plates, (0.5 gm), which were recrystallised from methanol. The product had the same m.p. and mixed m.p. i.e. 255° (decomp.) with an authentic sample of *p*-phenylene-diamine dihydrochloride (XVIb).

Found (%). C, 40.00, H, 5.50, N, 25.20. calc. for $C_6H_{10}Cl_2N_2$(%). C, 39.80, H, 5.50, N, 15.40.

(10). *Reaction of methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) with morpholine.* The compound (VIIb, R=4-$CH_3CONHC_3H_4$-) (0.5gm, 0.002 mole) was dissolved in $CHCl_3$ (20ml) and morpholine (0.01m 1; 0.002 mole) in chloroform (5 ml) was added dropwise. The mixture was refluxed for 30 mins under anhydrous conditions. Solvent was removed under vacuum and the residue was triturated with ether. A solid separated, filtered, dried and weighed (0.5, 64%). This was identified as methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4-hydroxy-2-oxo-pyridine-3-carboxylate-6-morpholinium salt (XIII, R=4-$CH_3CONHC_6H_4$-). This after recrystallisation from MeOH had m.p. 190° (decomp.), λ_{max} 300mn, log ε, 4.41.

Found (%): N, 9.60. $C_{19}H_{21}N_3O_6$ requires (%) N, 10.00.

(11). *Reaction of methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) with bromine.* The compound (VIIb, R=4-$CH_3CONHC_6H_4$-) (0.6 gm; 0.002 mole) was taken in MeOH : $CHCl_3$ (1:1) (20ml). To this, bromine solution 5ml (2% bromine in chloroform, was added. The reaction mixture was kept at room temperature for 2 hrs. Solvent was removed under reduced pressure and the residue was triturated with ether. It vave a solid, (0.5g; 62%) which was identified as methyl 1-(4-acetyl-aminophenyl)-5-bromo-1,2-dihydro-4,6-dihydroxy-2-oxo-pyridine-3-carboxylate (X, R=4-$CH_3CONHC_6H_4$-). This was recrystallised from MeOH:$CHCl_3$ (1:1) m.p. 209° (decomp.), λmax, 310nm, log ε, 4.43.

Found (%). C, 45.40, H, 3.10, N, 7.00. $C_{15}H_{13}BrN_2O_6$ requires (%). C, 45.30, H, 3.30, N, 7.00

(12). *Reaction of methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) with ethyl isothiocyanate and triethyl-amine as catalyst.* The compound (VIIb, R=4-$CH_3CONHC_6H_4$) (0.6gm; 0.002 mole) ethyl isothiocyanate (0.1m), 0.002 mole) and triethylamine (0.5ml) was taken in a R.B. flask and the reaction mixture was heated under anhydrous conditios on a water bath for 30 mins. The residue was shaken with ether to remove excess of triethylamine, and was dissolved in MeOH. It was then acidified with HCl (2N), a white solid separated. This was filtered and washed with water, dried and weighed (0.5gm; 65%). The product, methyl 1-(4-acetylaminophenyl)-6-ethylthiocarbamato)-1, 2-dihydro-4-hydroxy-2-oxo-pyridine-3-carboxylate (XI, R=4-$CH_3CONHC_6H_4$-) on recrystallisation from acetone, had m.p. 220° (decomp.), λ_{max} 300nm, log ε, 4.26.

Found(%). C, 53,32, H, 4.59, N, 10.18. $C_{18}H_{19}O_6N_3$ S requires (%). C, 53.33, H, 4.69; N, 10.37.

Results and Discussion

It was considered possible to prepare a product (IIIa) or (IIIb) from (I). This could be achieved in two ways. The first is to react an aromatic diamine (IIa) or (IIb) with a chloro-pyranodioxin (I) directly while the second is to react a mono-acetylated diamine (IVa) or (IVb) with (I) and react the amino group thus generated with the parent product (I) again to achieve the desired product (IIIa) or (IIIb). Both the routes were tried but a partial success was achieved in the latter case. When the chloropyranodioxin (I) was reacted with p-phenylenediamine (IIb, R=4-$NH_2C_6H_4$-) in chloroform, a product was obtained which was extremely difficult to dissolve in any solvent and decomposed above 260°, presumably product (IIIb) and its UV absorption showed a peak at max 324nm. Several attemps to isolate it in the pure form did not succeed and an attempt to isolate it as an addition compound also failed. The product thus obtained is still under study and will be reported later.

However, when 1-acetylamino-4-aminobenzene (IVb) reacted with the product (I), it quickly formed a compound $C_{17}H_{16}N_2O_6$ of the structural formula (Vb, R=4-$CH_3CONHC_6H_4$-) m.p. 260°, (decomp.), λ_{max} 330nm, log ε, 4.49, apparently similar to the products reported earlier [12].

TABLE 1. UV AND IR SPECTRA OF 7-1-[2(4)-ACETYLAMINOPHENYL) AMINO]-2, 2-DIMETHYL-4, 5-DIOXOPYRANO [4, 3-d] [1, 3] DIOXIN AND METHYL 1-(2-OR 4-ACETYLAMINOPHENYL)-1, 2-DIHYDRO-4, 6-DIHYDROXY-PYRIDINE-3-CARBOXYLATE AND THEIR DERIVATIVES.

S. No.	Name of the product	UV light absorption in 95% MeOH		IR-spectroscopic data in the region 3–6.7μ (KBr disc) υ_{max} (cm^{-1})			
		λ_{max}, nm	Log ε	$C_{ester} = O_{lactone}$	$C_{acetyl} = O$	H–N	H–O
1.	7-[(4-Acetylaminophenyl)amino]-2, 2-dimethyl-4, 5-dioxo-pyrano[4, 3-d][1-3]dioxin (Vb, R=4-$CH_3CONHC_6H_4$-)	330	4.44	1770s	1660m	3350m	–
2.	7-[(2-Acetylaminophenyl)amino]-2, 2-dimethyl-4, 5-dioxo-pyrano[4, 3-d][1-3]dioxin (Va, R=2-$CH_3CONHC_6H_4$-)	336	4.47	1780s	1665s	3340s	–
3.	6-(4-Acetylaminophenyl)-2, 2-dimethyl-7-hydroxy-4, 5-dioxo-pyridino [4, 3-d] [1, 3] dioxin (IX, R=4-$CH_3CONHC_6H_4$-)	310	4.47	1650s	1530s	3100w	3300s
4.	Methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-1-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-)	305	4.31	1650s	1610s	3300s	2950s
5.	Methyl 1-(2-acetylaminophenyl)-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIa, R=2-$CH_3CONHC_6H_4$-)	304	4.34	1660m	1540w	3240m	3060m
6.	Methyl 1-(4-acetylaminophenyl)-1, 2-dihydro-4-hydroxy-2-oxo-pyridino-3-carboxylate-6-morpholinium salt (XIII, R=4-$CH_3CONHC_6H_4$-)	300	4.41	1650s	1540	3240m	3065m
7.	Methyl 1-(4-acetylaminophenyl)-5-bromo-1, 2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (X, R=4-$CH_3CONHC_6H_4$-)	310	4.43	1650s	1535	3200w	3090s
8.	Methyl 1-(4-acetylaminophenyl)-6-(ethylthio-carbomato)-1, 2-dihydro-4-hydroxy-2-oxo-pyridine-3-carboxylate (XI, R=4-$CH_3CONHC_6H_4$-)	300	4.26	–	–	–	–

TABLE 2. 7-[(2(4)-ACETYLAMINOPHENYL) AMINO]-2, 2-DIMETHYL-4, 5-DIOXOPYRANO[4, 3-d] [1, 3]DIOXIN (V) AND METHYL 1-(2(4)-ACETYLAMINOPHENYL)-1, 2-DIHYDRO-4, 6-DIHYDROXY-2-OXO-1-(2(4)-ACETYLAMINOPHENYL)-PYRIDINE-3-CARBOXYLATE (VII).

S. No.	Compound	Reactants/g	Product	Yield		Solvent of crystallisation	m.p. °C (decomp.)	Molecular Formula	Analysis					
				gm	%				Requires (%)			Found(%)		
									C	H	N	C	H	N
1.	7-Chloro-2, 2-dimethyl-4, 5-dioxopyrano-[4, 3-d] [1,3] dioxin-(I) (2.3gm; 0.01 mole)	4-Aminoacetanilide (IVb, R=4-$CH_3CONHC_6H_4$-) (3gm; 0.02 mole)	7-[(4-acetylamino-phenyl)amino]-2, 2-dimethyl-4, 5-dioxopyrano-[4, 3-d] [1, 3] dioxin (Vb, R=4-$CH_3CONHC_6H_4$-)	1.5	65	MeOH:$CHCl_3$ (1:1)	260	$C_{17}H_{16}N_2O_6$	59.30	4.70	8.10	59.20	6.40	8.00
2.	-do-	2-Aminoacetanilide (IVa, R=2-$CH_3CONHC_6H_4$-) (3gm; 0.02 mole)	7-[(2-Acetylamino-phenyl) amino]-2, 2-dimethyl-4, 5-dioxo-pyrano-[4, 3-d][1,3] dioxin (Va, R=2-$CH_3CONHC_6H_4$-)	1.5	65	MeOH:$CHCl_3$ (1:1)	230	$C_{17}H_{16}N_2O_6$	59.30	4.70	8.10	59.60	4.50	8.00
3.	7-[(4-acetyl-aminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano-[4, 3-d][1,3]	Na/PhOH(0.92gm/ 25 ml)	6-(4-Acetylamino-phenyl)-2, 2-dimethyl-7-hydroxy-4, 5-dioxopyridino [4, 3-d] [1, 3] dioxin (IX, R=4-$CH_3CONHC_6H_4$-)	1.00	50	MeOH:$CHCl_3$ (1:2)	275	$C_{17}H_{16}N_2O_6$	59.30	4.70	8.10	59.10	4.60	8.10

(Contd.....)

(Table 2, contd.)

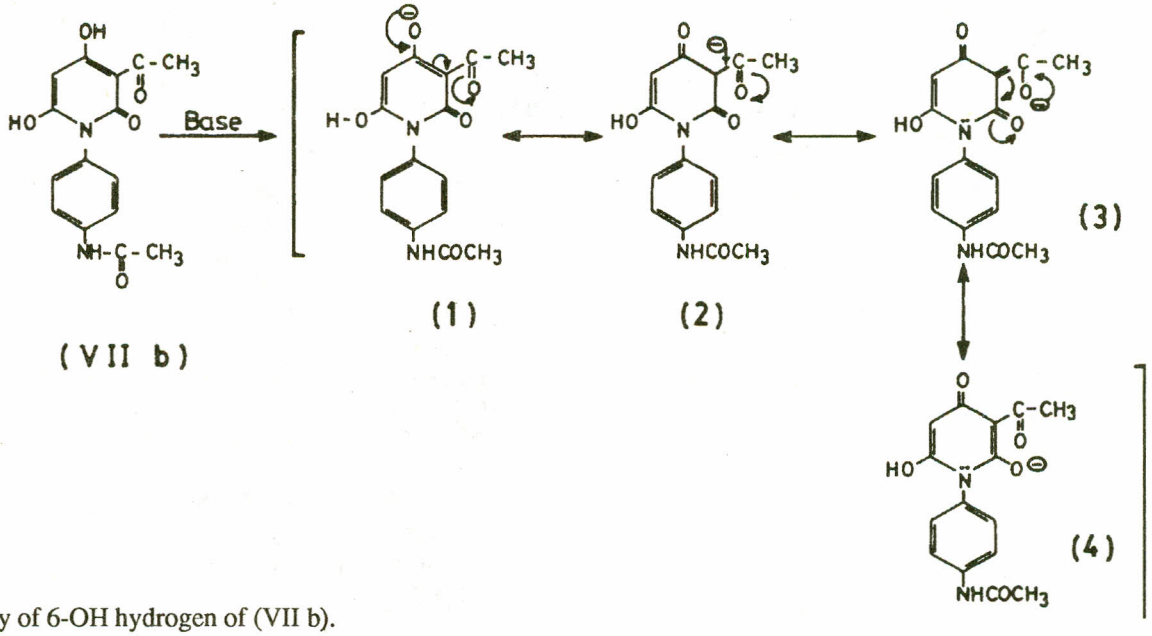
	dioxin(Vb,R=4-$CH_3CONHC_6H_4$-) (2g;0.006 mole)													
4.	7-[(4-Acetyl-aminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano-[4, 3-d] [1,3] dioxin(Vb,R=4-$CH_3CONHC_6H_4$-) (1gm; 0.003 mole)	Na/MeOH (0.46g/30ml)	Methyl 1-(4-acetyl-aminophenyl)-1, 2-di-hydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, (R=4-$CH_3CONHC_6H_4$-)	0.55	55	MeOH:$CHCl_3$ (1:1)	280	$C_{15}H_{14}N_2O_6$	56.60	4.40	8.80	56.60	4.10	8.80
5.	7-[(2-Acetyl-aminophenyl) amino]-2, 2-dimethyl-4, 5-dioxopyrano-[4, 3-d][1,3] dioxin(Va,R=2-$CH_3CONHC_6H_4$-) (1gm; 0.003 mole)	Na/MeOH (0.46gm/30ml)	Methyl 1-(2-acetyl-aminophenyl)-1, 2-dihydro-4, 6-dihy-droxy-2-oxo-pyridine-3-carboxylate (VIIa, (R=2-$CH_3CONHC_6H_4$-)	0.5	55	MeOH	220	$C_{15}H_{14}N_2O_6$	56.60	4.40	8.80	56.60	4.40	8.70
6.	Methyl 1-(4-acetylamino-phenyl)-1, 2-dihydro-4, 6-dihydroxy-2 oxo-pyridine-3-carboxylate-(VIIb, R=4-$CH_3CONHC_6H_4$-) (0.5gm; 20 ml $CHCl_3$	Morpholine/$CHCl_3$ (0.5g/20ml)	Methyl 1-(4-acetyl-aminophenyl)-1, 2-dihydro-4-dihydroxy-2-oxo-pyridine-3-carboxylate-6-morpholinium salt (XIII, R = 4-$CH_3CONHC_6H_4$-)	0.5	64	MeOH	190	$C_{19}H_{21}N_3O_6$	–	–	10.00	–	–	9.70
7.	Methyl 1-(4-acetylamino phenyl)-1,2-dihydro-4, 6-dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) (0.6gm/$CHCH_3$ MeOH	Bromine/$CHCl_3$ (0.6gm/20 ml)	Methyl 1-(4-aceyl-aminophenyl)-5-bromo-1,2-di-hydro-4-, 6-dihydro-xy-2-oxo-pyridine-3-carboxylate (X, R=4-$CH_3CONHC_6H_4$-)	0.5	62	MeOH:$CHCl_3$ (1:1)	209	$C_{13}H_{13}BrN_2O_6$	45.30	3.30	7.10	45.45	3.10	7.00
8.	Methyl 1-(4-acetylamino phenyl)-1,2-dihydro-4,6 dihydroxy-2-oxo-pyridine-3-carboxylate (VIIb, R=4-$CH_3CONHC_6H_4$-) (0.6 gm)	Ethylisothio-cynate/tri ethylamine (0.1 ml/ 0.5 ml)	Methyl 1-(4-acetyl-aminophenyl)-6-(ethyl thiocarbo-mato)-1, 2-dihydro 4-hydroxy-2-oxo pyridine-3-carb-oxylate (XI, R=4-$CH_3CONHC_6H_4$	0.5	65	Acetone	220	$C_{18}H_{19}N_3O_6S$	53.30	4.70	10.40	53.30	4.60	10.20

The same situation was observed when 1-acetylamino-2-aminobenzene (IVb) was reacted with the chloropyranodioxin (I) and an analogous product, $C_{17}H_{16}N_2O_6$ (Va, R=4-$CH_3CONHC_6H_4$-) m.p. 230° (decomp.), UV, λ_{max} 336nm, log ε, 4.47 was obtained. Several attempts were made to deacetylate the product (Va and Vb) to achieve the product (IIIa) and (IIIb) via (VIa) and (VIb) but the molecule disrupted easily into the starting materials like malonic acid (XV) and *o*-or *p*- phenylenediamine dihydrochloride (XVIa) or (XVIb). Evidently, the product (Vb) is susceptible to alkaline and acid treatment. It was found further that treatment of the product (Vb, R=4-$CH_3CONHC_6H_4$-) with a base like sodium carbonate in presence of aerial oxygen resulted in a product $C_{18}H_{18}N_6$ m.p. 230°, which was identified as Bandrowski's base (VIII). It gave no depression in m.p. when admixed with an authentic sample[13]. Its identity was also confirmed by its mass spectral data. It showed M^+ peak at 318 and other peaks at 211 and 108 as expected.

The product (Vb, R=4-$CH_3CONHC_6H_4$-) underwent smoothly isomerisation with phenoxide in phenol and formed a new product (IX, R=4-$CH_3CONHC_6H_4$-) heterobicyclic in nature analogous to products reported earlier [14], and similarly when the product (Vb, R=4-$CH_3CONHC_6H_4$-) was reacted with methoxide in methanol, a monocyclic pyridone methylester (VIIb, R=4-$CH_3CONHC_6H_4$-) [15] was formed. It melted at 280° (decomp.) λmax 305nm, log ε, 4.31. Structures of (V, VII and IX) have been confirmed by their elemental analysis (Table-2) and spectral data (Table 1).

Several derivatives of the product (VIIb, R=4-$CH_3CONHC_6H_4$-) were also prepared for instance, the latter when reacted with morpholine in chloroform, gave a morpholinium compound (XIII, R=4-$CH_3CONHC_6H_4$-) $C_{19}H_{21}N_3O_6$, m.p. 190° (decomp.) λmax 300nm, log ε, 4.41. Similarly on treatment with bromine in chloroform solution, it gave a bromo compound (X), $C_{15}H_{13}BrN_2O_6$ m.p. 209° (decomp.) and with ethyl isothiocyanate in presence of a base, triethylamine, it gave a thiocarbamato derivative (XI, R=4-$CH_3CONHC_6H_4$-), $C_{18}H_{19}N_3O_6S$, m.p. 220° (decomp.). There

1. Acidity of 4-OH hydrogen of (VII b).



2. Acidity of 6-OH hydrogen of (VII b).

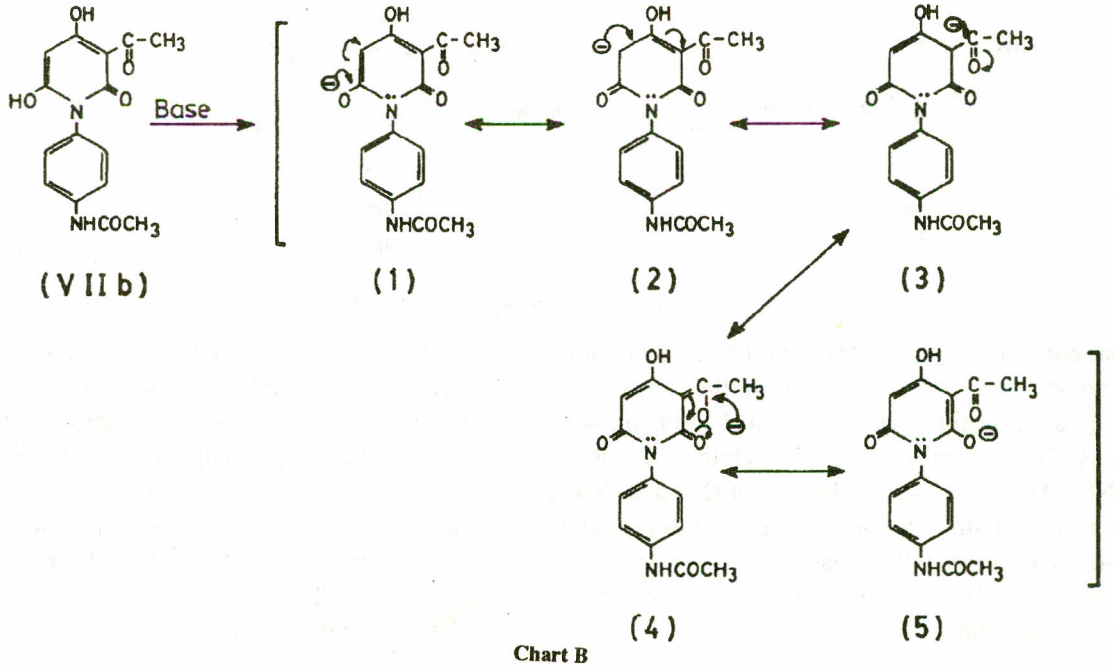
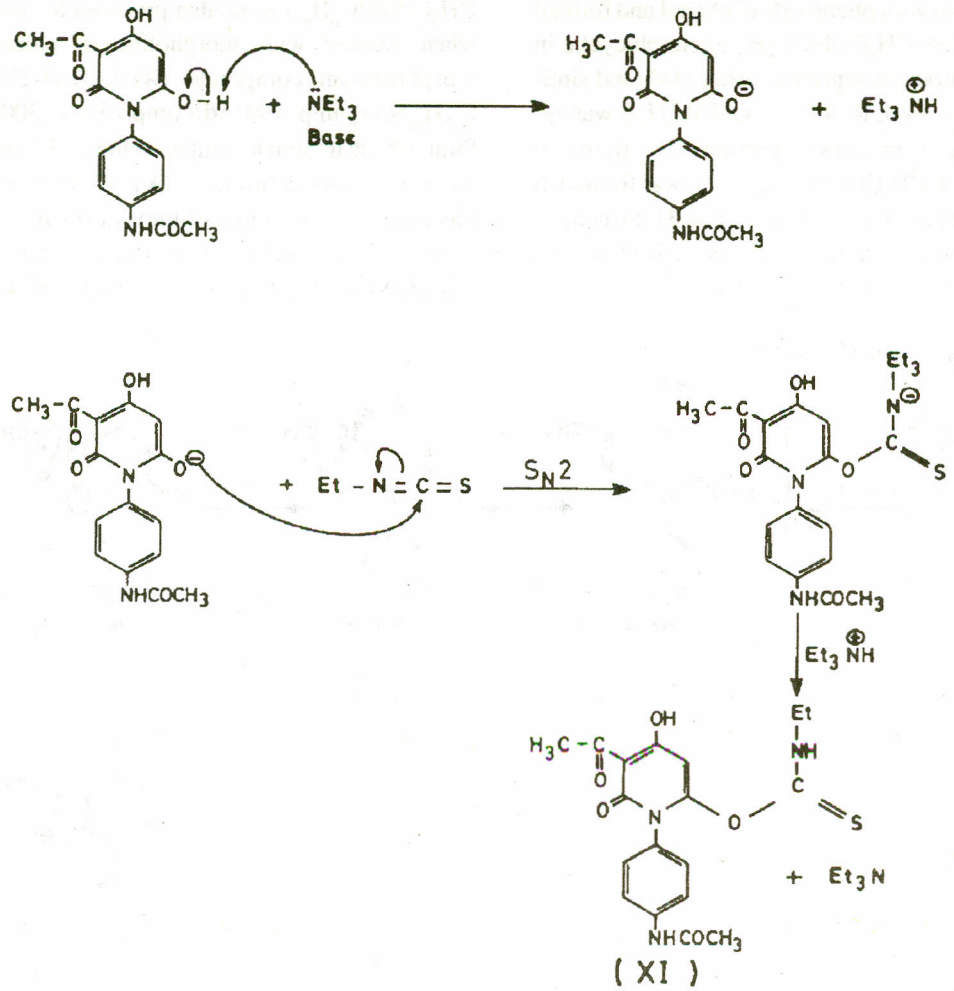


Chart B

1. Mechanism of reaction of (VII b) with ethyl isothiocyanate in the presence of Et_3N.



(XI)

2. Mechanism of reaction of (VII b) with morpholine.

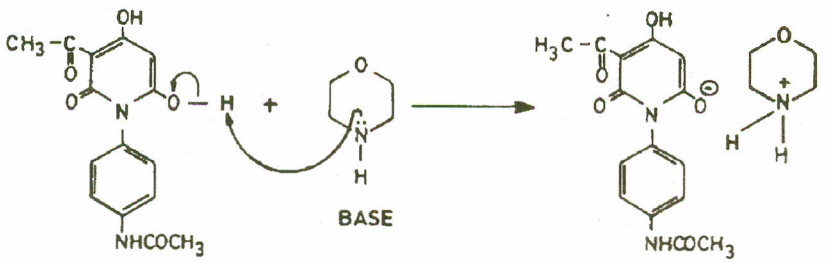


Chart C (XIII)

is only one possibility of attack of bromine i.e. at the 5-position of the pyridine ring. This would result in the formation of methyl 2-(4-acetyl-aminophenyl)-5-bromo-1,2-dihydro-4,6-dihydroxy-2-oxo-pyridine-3-carboxylate (X, R=4-$CH_3CONHC_6H_4$-). However, in the case of (XI) and (XIII), there are two possibilities in each case: the product could be either 4-0-derivative or 6-0-derivative. These structural assignments are based on the reactions of 1-phenylpyridine [16] and 1-methoxypyridine [17] analogues.

The reaction of methyl 1, 2-dihydro-4, 6-dihydroxy-1-phenyl-pyridine-3-carboxylate with diazomethane in chloroform-ethanol mixture afforded methyl 1, 2-dihydro-4-hydroxy-6-methoxy-1-phenylpyridine-3-carboxylate [16] whose m.p. 218° was different from that of the already known 4-methoxy isomer, m.p. 252° whose structure was established by its unambiguous synthesis [18]. Theoretically also, in the compound (VIIb), the 6-OH group adjacent the electron-withdrawing nitrogen is more acidic in character than 4-OH

group adjacent to the comparatively weaker electrn-withdrawing carbomethoxy group. This is also evident from the greater number of canonical forms of the conjugated base of the former (Chart B). Consequently the 6-0-derivatives are preferably obtained. The mechanism of reaction of (VIIb) with each of the reagents, morpholine and ethyl isothiocyanate, is given in the Chart C. The structure of each of the products, (X), (XI) and (XII), is further confirmed by its spectral data (Table 1) and elemental analysis (Table 2).

Further work to explore the synthetic utility of the product (1) is in progress.

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References

1. Chichibabin, Bull. Soc. Chim. France, **4**(5), 1326 (1937).
2. R.L. Frank, J.R. Blengen, R.J. Dearborn, R.L. Myers and F.E. Woodward, J. Am. Chem. Soc., **68**, 1368 (1946).
3. Durikopf and Gollsch, Ber., **23**, 1110 (1890).
4. *An Introduction to the Chemistry of Heterocyclic Compounds*, ed. R.M. Acheson (John Wiley & Sons, New York, 1976), 3rd ed., pp. 271-272.
5. French Patent, 1, 339, 175, Aug. 26, 1963, Assigned to J.R. Giegy, S.A.
6. J.D. Crum and C.H. Fuchsman, J. Heterocycl. Chem., **3**, 252 (1966).
7. R. Albrecht and G. Kresze, Chem. Ber., **98**, 1431 (1965).
8. T.B. Windholz, L.H. Peterson and G.J. Kent, J. Org. Chem., **28**, 1443 (1963).
9. G. Stork, M. Ohashi, H. Kamashi and H. Kakisawa, J. Org. Chem., **36**, 2784 (1971).
10. M.A. Butt, Rashida Perveen, Rashid Kamal and M. Aleem Ahmad, Pak. j. sci. ind. res., **30**, 721 (1987).
11. S.J. Davis and J.A. Elvidge, J. Chem. Soc., 4111 (1952).
12. S.J. Davis and J.A. Elvidge, J. Chem. Soc., 2251 (1953).
13. J.F. Corbett, J. Chem. Soc. (B), 818 (1969).
14. M.A. Butt and I.A. Akhtar, Tetrahedron, **21**, 1917 (1965).
15. A. Butt, S.M.A. Hai and I.A. Akhtar, Tetrahedron, **22**(2), 461 (1966).
16. A. Butt, R. Kamal and R. Parveen, Pak. j. sci. ind. res., **21**, 101 (1978).
17. A. Butt, I.A. Akhtar, S.A. Qureshi and (Mrs.) M. Akhtar, Pak. j. sci. ind. res., **10** , 240 (1967).
18. M.A. Butt, J.A. Elvidge and A.B. Foster, J. Chem. Soc., 3060 (1963).