SYNTHESIS OF HETERO-BICYCLIC COMPOUNDS: II. FORMATION OF PYRIDINO-DIOXINS

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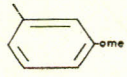
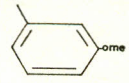
The formation of pyridino-dioxins (II) occurs from amino-pyrano-dioxins (I, R=*o,m,p*-methoxyphenyl, *p*-nitrophenyl, *o*-chlorophenyl, benzyl, and 2-methyl-5-nitrophenyl) with phenoxide. Pyrano-dioxins derived from aliphatic amines except isobutylamine, did produce phenolic but intractable materials. 7-chloro-pyrdino-dioxin (VII) with sodium alkoxides gave dialkoxy acids (VIII,IX). The structural evidence of the products was gathered from U.V. spectroscopic data.

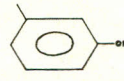
In continuation of the series,[1] the isomerisation reaction of amino-pyrano-dioxins[2] in phenol (in presence of sodium phenoxide) has been investigated further. It has been established that the reaction is quite general for aminopyrano-dioxins derived from aromatic primary amines. For instance, the product $C_{16}H_{15}NO_6$ (I,R[1]= 

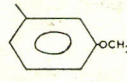
)m.p. 176° (decomp.) when subjected to phenoxide reaction in phenol, it produced a new compound $C_{16}H_{15}NO_6$ (II,R′= 

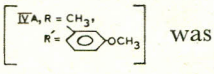
) m.p. 180°,λ max. 313, mμ log ε 4.30. It was enolic in nature and soluble in aqueous sodium bicarbonate solution, in agreement with the structure (II). Similar situation indeed existed in case of other aminopyrano-dioxins on reacting with sodium phenoxide in phenol. The details of these products are described in the experimental section.

Like the above mentioned course of reaction, the aminopyrano-dioxins derived from aliphatic amines did yield isomeric products (II). For instance, aminopyrano - dioxins (I, R′=CH_3) when heated with sodium phenoxide in phenol for two minutes and the reaction product after working up in the usual manner, gave a phenolic oil instead of a solid product, several attempts to crystallise the oil failed. Purification of the oil by distillation under reduced pressure gave an intractable tarry substance. An effort to isolate the hydroxy product by way of morpholinium salt (III) met with failure. An exactly analogous situation was faced with amino-pyrones derived from other aliphatic amines like ethylamine, butylamine and allylamine. However, the amino-pyrone obtained from isobutyl-amine underewent the "phenoxide reaction" and yielded a phenolic product $C_{13}H_{17}NO_5$ (II, R′=iso-Butyl) m.p. 183, λmax. 310 mμ, log ε 4·35.

It behaved similarly towards aqueous ferric chloride solution and aqueous sodium bicarbonate solution as the products represented by (II, R=aryl).

7-Hydroxy-pyridino-dioxin, $C_{16}H_{15}NO_6$ (II, R′= 

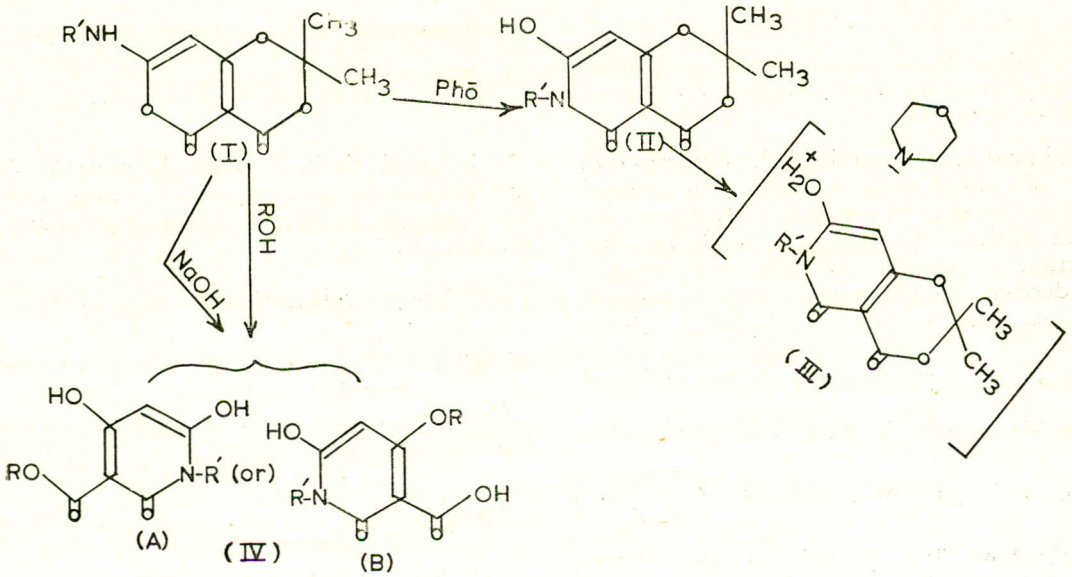
)when reacted with methanol for a long time, broke up into the 1,3-dioxin ring a compound $C_{14}H_{13}NO_6$, (IVA, R=CH_3, R′= 

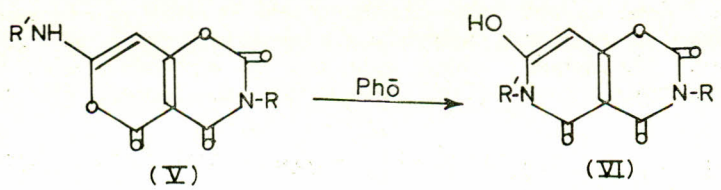
)m.p. 193. This compound absorbed U.V. light in the λmax. 305 mμ region with log ε 4.3. Study of its I.R. spectrum showed a strong peak at ν 1626 cm-[1] for 2-pyridone-carbonyl and a bonded ester group at ν 2632 cm-[1]. These data are in agreement with structure (IVA) rather than the formula (IV B). The product 

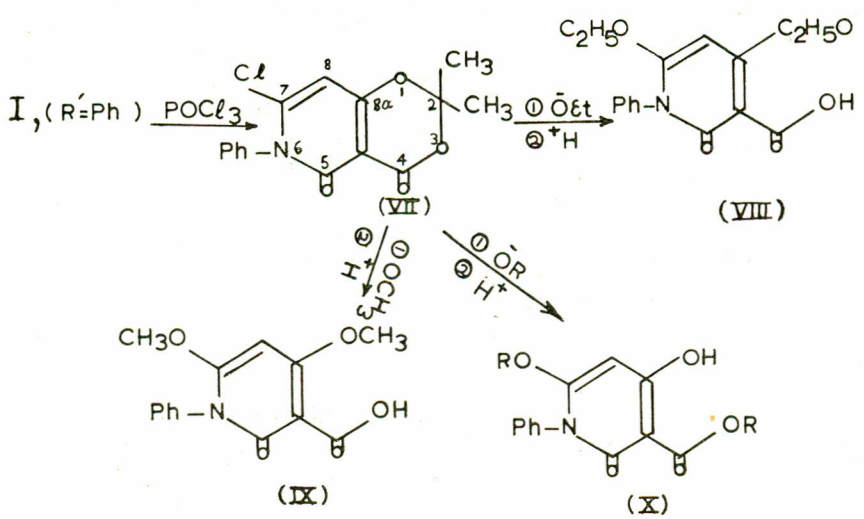
was further characterised by an authentic sample prepared previously. The 7-hydroxy - pyridino-dioxins (I, R=aryl) formed addition compounds with morpholine. For instance, the product $C_{16}H_{15}NO_6$ when reacted with morpholine, gave a substance with molecular formula $C_{20}H_{24}N_2O_7$, m.p. 188, λmax 313, mμ log ε 4.6. It was extremely soluble in water and could be converted to the parent product by the acidification of its water solution.

The chloro-product (VII) when reacted with sodium methoxide in methanol gave the dimethoxy acid $C_{14}H_{13}NO_5$ [IX] m.p. 195, λ max. 304, mμ log ε 4.20 an and examination of its I.R. spectrum showed a peak at 1681 cm-[1] due to carbonyl at position 2 and absorption due to acid carbonyl fell at 1734 cm-[1], in agreement with its structural formula. Similarly, the chloro-product (VII) on treatment with sodium ethoxide, yielded diethoxy acid $C_{16}H_{17}NO_5$ (VIII), λmax 304 mμ,

log ε 4.28. Its I.R. spectrum showed 2-carbonyl near the 1679 cm-1 region and acid carbonyl at 1732 cm-1. The formation of the acids rather than esters from the chloro-products shows that the presence of chlorine atom at position (7) increases the electrophillicity not only at the position(7) of the ring but also at the position (8a) which makes the nucleophillic attack of (Rō) easier at (8a) rather than on carbonyl at position 4 of the product (VII). This fact is however, contrary to the observation already recorded that the compounds (II, R=aryl) when subjected to the action of alkoxide in alcohol produced ester pyridones[3] (IV) rather than ethers of the type (VIII, IX). Consequently, no trace of the product (X, R=CH_3) was obtained.







An attempt to isomerize aminopyrano-oxazine (V) led to failure. For instance, anilino-pyrano-oxazine (V, R=R′=Ph) with sodium phenoxide in phenol, gave a mono-cyclic product, m.p. 205, enolic in nature, and that was evidently not isomeric with the starting material. This and the related reactions are being studied separately.

Experimental

7-(m-Methoxy-phenylamino)-2,2-dimethyl-4, 5-dioxo-pyrano (4,3-d) - (1,3) - dioxin.—To 7-chloro-2, 2-dimethyl - 4,5-dioxo - pyrano - (4,3-d) - (1,3)-dioxin (3 g.; 1 mol.) in chloroform (30 ml.) was added *m*-anisidine (3.5 g.; 2 mol.) dropwise and the mixture was stirred with cooling. A solid product separated which was, filtered and washed with water and dried. 7-(*m*-Methoxy-phenylamino(-2, 2-dimethyl-4,5-dioxopyrano - (4,3-d)-1,3) - dioxin (3.5 g.; 85%), on crystallisation from methanol melted at 164° (decomp.). Found: C, 60.8; H, 4.9; N, 4.9-$C_{16}H_{15}NO_6$; Requires: C, 60.6; H, 4.8; N 4.4%.

Several other amino-pyrano-dioxins prepared in the manner indicated above, are listed in the Tables 1(a) and 1(b).

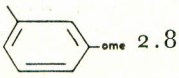
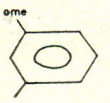
7-Hydroxy - 6 - (m-Methoxyphenyl)2, 2-dimethyl-4, 5-dioxopyridino-(4, 3-d)-(1, 3)dioxin.—7-(*m*-methoxy-phenylamino)-2, 2-dimethyl-4, 5-dioxopyrano (4, 3-d)--(1,3)-dioxin (I.R′=  2.8 g.) and sodium (1.0 g.) in phenol were refluxed for 2 min. and cooled. The solution was diluted with cold water, freed from excess of phenol by repeated extractions with ether and the remaining aqueous solution was acidified with 2NHCl. A solid

TABLE 1(a).—AMINO-PYRANO-DIOXINS (I).

No.	Primary amine	Quantity	7-Chloro-2,2-dimethyl-4,5-dioxo-pyrano (4, 3-d)-(1,3)-dioxin in $CHCl_3$	Product (I) R′	m.p.	Molecular formula	yield %	Solvent for crystallisation
1.	*p*-Anisidine	3.5 g.	3.0 g./30 ml. $CHCl_3$	p-Methoxyphenyl	176° (Decomp)	$C_{16}H_{15}NO_6$	99	$CHCl_3$
2.	*o*-Anisidine	3.5 ml.	3.0 g./40 ml. ,,	o-Methoxyphenyl	157° ,,	$C_{16}H_{15}NO_6$	75	$CHCl_3$+ CH_3OH
3.	*o*-Chloroaniline	2.8 g.	2.3 g./30 ml. ,,	o-Chlorophenyl	176° ,,	C H NO	79	$CHCl_3$
4.	*p*-Nitroaniline	2.8 g.	2.3 g./25 ml. ,,	p-Nitrophenyl-	170° ,,	$C_{15}H_{12}N_2O_7$	79	$CHCl_3$
5.	2-Amino-5-nitro-toluene.	1.4 g.	1.0 g./50 ml.	5-Nitro-tolyl-	218° ,,	$C_{16}H_{14}N_2O_7$	80	$CHCl_3$
6.	α-Napthylamine	2.9 g.	2.3 g./30 ml. ,,	α-Napthl-	184° ,,	$C_{19}H_{15}NO_5$	85	$CHCl_3$
7.	Benzylamine	2.5 g.	2.3 g./30 ml. ,,	Benzyl-	170° ,,	$C_{16}H_{15}NO_5$	96	$CHCl_3$+ CH_3OH

TABLE 1(b).

No.	λmax mμ	U.V. absorption (95 % Ethanol) log ε	Analysis Found C	H	N	Cl	Required C	H	N	Cl
1.	340	4.51	61.0	4.9	4.9	—	60.6	4.8	4.4	—
2.	340	4.47	60.9	4.7	—	—	60.6	4.8	—	—
3.	335	4.48	56.2	3.8	4.2	10.9	56.0	3.8	4.4	11.0
4.	336	4.06	—	—	8.7	—	—	—	8.4	—
5.	327	4.30	56.2	4.5		—	55.8	4.1	—	—
6.	338	4.52	67.7	4.4	3.9	—	67.7	4.5	4.2	—
7.	334	4.47	56.3	4.5	—	—	55.0	4.1	—	—

product (II, R′=  1.8 g.; 64%) was isolated. On crystallisation from methanol chloroform mixture, it melted at 209° (decomp.). It showed reddish-brown colouration with aqueous feric chloride and was dissolved by sodium bicarbonate solution. Found: C, 60.9; H, 4.8; N, 4.6. $C_{16}H_{15}NO_6$ requires. C, 60.6; H, 4.8; N, 4.4%

Various pyridino-dioxins (II) were prepared in the above fashion and are tabulated as follows: (Table 2).

7-Chloro-2, 2-dimethyl-4, 5-dioxo-6-phenylpyridino (4, 3-d)-(1, 3)-*dioxin* (VII).—The product (II, R=Ph, 2 g.) and phosphorus oxychloride (15 ml.) were heated under reflux for 15 min. The excess of $POCl_3$ was removed under reduced pressure. The residual semi-solid was dissolved in ethanol (25 ml.) and the solution decolourised with charcoal. The reddish filterate, after concentration to half of total volume, was diluted with water and on cooling, it gave crystals of the 7-chloro-compound IV (0.5 g., 24%) and on recrystallisation from methanol, it melted at 163°. Found: C, 58.3; H, 3.7; N, 4.3; Calculated for $C_{15}H_{12}ClNO_4$ C, 58.6; H, 3.9; N, 4.6.

TABLE 2(a).—PYRIDINO-DIOXINS (II)

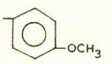
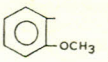
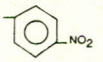
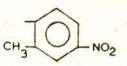
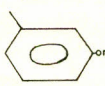
No.	7-Substituted-2, 2-dimethyl-4, 5-dioxo-pyrano-(4,3-d)-(1,3)-dioxins (I) in g. R′		Sodium in phenol ml.	6-Substituted-7-Hydro-2, 2-dimethyl-4, 5-dioxo-pyridino(4,3-d)-(1,3)-dioxin R	Yield %	Solvent for crystallisation	m.p.
1.		3.5	1.2g./20	p-Methoxyphenyl-	70	Hot benzene	180 (decomp.)
2.		2.0	0.6 g./15	o-Methoxyphenol-	50	Hot benzene	208 ,,
3.		2.7	0.9 g./15	o-Chlorophenyl-	37	Ethanol	182 ,,
4.		2.3	0.9 g./15	p-Nitrophenyl-	22	Chloroform	180 ,
5.		2.5	0.8g./15	5-Nitrotolyl-	40	Ethanol	196 ,,
6.		1.6	0.6 g./15	-Napthyl-	63	Methonol + $CHCl_3$ (1:1)	208 ,,
7.		2.0	0.7 g./15	Benzyl-	35	Methanol	156 ,,

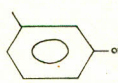
TABLE 2(b).

No.	U.V. light absorption (95% Ethanol) λmax mμ	log ε	Molecular formula	Analysis Found C	H	N	Required C	H	N
1.	313	4.3	$C_{16}H_{15}NO_6$	60.9	4.8	—	60.6	4.8	—
2.	312	4.4	$C_{16}H_{15}NO_6$	61.0	4.6	4.9	60.6	4.8	4.4
3.	313	4.3	$C_{15}H_{12}ClNO_5$	56.10	4.0	4.2	56.0	3.8	4.4
4.	312	4.3	$C_{15}H_{12}N_2O_7$			8.6			8.8
5.	311	4.3	$C_{16}H_{14}N_2O_7$	55.4	4.4	8.2	55.8	4.1	8.10
6.	312	4.4	$C_{19}H_{15}NO_5$	67.7	4.4	—	67.5	4.5	—
7.	312	4.5	$C_{16}H_{15}NO_5$	63.7	5.0	4.9	63.8	5.0	4.7

4,6-Diethoxy-2-oxo-1-phenylpyridine-3-carboxylic acid VIII).—The 7-chloroproduct (VII (0.5 g.) and sodium (0.5 g. Na/10 ml. EtOH) in ethanol were refluxed for 15 minutes. The excess of solvent removed under reduced pressure and the residue was diluted with water. On acidification with 2N/HCl, a solid product (0.4 g.; 80.8%) was obtained. On recrystallisation from methanol, it melted at 197°. It dissolved in alkalis and deepened the colour of the aqueous ferric chloride solution. Found: C, 63.8; H, 5.7; N, 4.7; OEt, 29.2%–$C_{16}H_{17}NO_5$; Requires: C, 63.4; H, 5.6; N, 4.6; OEt, 29.7%—max 304, log 4.28.

4,6- Dimethoxy - 2 - oxo-1-phenylpyridine-3-carboxylic acid (X).—The chloro-product (1.0 g.) and sodium (1 g.) in methanol (20 ml.) were refluxed for ¼ hour Treatment of the solution as indicated in the preceeding experiment gave 4,6-dimethoxy product (IX) (0.4 g.; 40%), which on crystallisation from methanol, melted at 195°-197°. Found: C, 61.0; H, 5.0; N, 5.4; ome, 21.0—$C_{14}H_{13}NO_5$; Requires: C, 61.1; H, 4.7; N, 5.1; ome, 22.5%. The compound dissolved in alkalies and deepened aqueous ferric chloride solution. λmax 304 mμ, log ε, 4.20.

Morpholium Salt of III (R′= 

).—The 7-hydroxy product III (R′= 

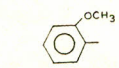
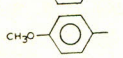
) (0.5 g.) in $CHCl_3$ (10 ml.) and morpholine (0.4 ml.) were refluxed together for 10 minutes under anhydrous conditions. The solvent was removed under reduced pressure and the residue on trituration with ether, gave a white solid (0.45 g.; 70.3%) which through several crystallisation, with ethanol, gave white needles which melted at 185° (decomp.). Found: C, 59.4; H, 5.9; N, 6.5;–$C_{20}H_{24}N_2O_7$; Requires: C, 59.4; H, 5.9; N, 6.9%.

Three more morpholium salts were prepared and the results are tabulated as follows (Table 3).

Reaction of 7-Hydroxy-6-(p-methoxyphenyl)-2-2-dimethyl-4, 5-dioxopyridino (4, 3-d)-(1,3)- *dioxin with methanol.*—The product II (R′= 

) (1 g.) methanol (50 ml.) were refluxed for 20 hours. The excess of the solvent evaporated off and the semisolid was triturated with ether. 4,6-Dihydroxy-(*p*-methoxyphenyl - 2-oxo-3 - methoxy - carbonyl-pyridine (0.6 g; 65.9%) on recrystallisation from methanol, it gave m.p. 193°, undepressed by an authentic specimen prepared another method. Found: C, 57.9; H, 3 4.6;—$C_{14}H_{13}NO_6$; Requires: C, 57.7; H, 4.5 λmax 305 mμ, log ε, 4.4.

TABLE 3.—MORPHOLINUM SALTS.

No.	Pyridino dioxin (II) R	Quantity in $CHCl_3$ ml.	Morpholine ml.	Yield g.	m.p.	Molecular formula	Analysis Found C	Found H	Found N	Required C	Required H	Required N
1.		0.3g./10	0.3	0.3	183 (decomp.)	$C_{20}H_{24}N_2O_7$	59.6	6.1	7.0	59.4	5.9	6.9
2.		0.35g./10	0.4	0.4	188 ,,	$C_{20}H_{24}N_2O_7$	59.0	5.8	7.1	59.4	5.9	6.9
3.		0.3g./15	0.3	0.38	195 ,,	$C_{23}H_{24}N_2O_6$	—	—	6.6	—	—	6.3

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References

1. Aslam Butt and I. A. Akhtar, Tetrahedron, 1917 (1965).
2. Prepared by the method of J.A. Elvidge.
3. This work is in press (Tetrahedron).