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## SYNTHESIS OF HETERO-BICYCLIC COMPOUNDS Part -VIII. Formation of 6-Alkyl-2,2-Dimethyl-4, 5-Dioxo-7-Hyroxy-Pyridino [4,3-d][1,3]Dioxins

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Aminopyranodioxins (II), derived from aliphatic amines, isomerise to yield the corresponding pyridino-dioxins (III). Chemical conversions and spectroscopic data are provided in support of their structure.

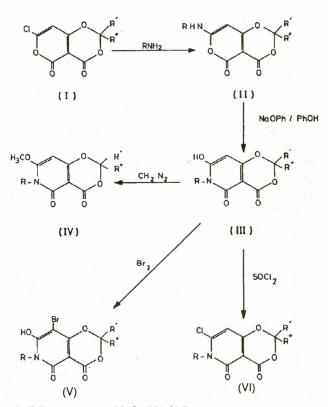
Key words. Pyrano-dioxin, Pyridino-dioxin, Aliphatic amines.

#### Introduction

Earlier it was reported [1] that the conversion of aminopyranodioxins (II, R = alkyl) into the corresponding pyridinodioxins (III, R' = R" = alkyl groups, same or different) was difficult to achieve except in case of iso-butylamine product (II, R = Isobutyl -). Re-investigation of this reaction with slightly altered conditions showed that it followed the same pattern as was reported in the case of aminopyranodioxins (II, R = aryl) derived from arylamines. For instance, the product 2,2- dimethyl-4, 5-dioxo-7-methylamino-pyrano [4,3-*d*][1,3] dioxin in the presence of sodium phenoxide in phenol formed the corresponding pyridinodioxin (III, R = R ' = R " = CH<sub>3</sub>)  $C_{10}H_{11}NO_5$ , m.p. 174°, which had phenolic properties (it gave FeCl<sub>3</sub> test and dissolved in aqueous Na<sub>2</sub>CO<sub>3</sub> solution), characteristic of such type of structures. Compounds prepared similarly are recorded in Table-1.

#### 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.



Sr. Primary	Quan- tity	7-Chloro-2,2- dimethyl-4,5	Product II(R'=		m.p. °C	Molecular formula	Analysis					UV absorbance		
No. amine							Found (%)			Requires(%)			in MeOH	
	(g)	dioxo-pyranc	$R''=CH_3$ )				С	Н	N	С	Н	N	λmax	loge
		dioxin(I)	(R)										nm	
2.6.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.		(g)				×	٠.		1.1					
1. Methyl amine	3.48	10.0	-CH3	80.4	207	C <sub>10</sub> H <sub>11</sub> NO <sub>5</sub>	53.2	4.9	6.2	53.3	4.9	6.2	330	4.62
2. Ethyl amine	2.45	5.0	-C <sub>2</sub> H <sub>5</sub>	88.0	193	C <sub>11</sub> H <sub>13</sub> NO <sub>5</sub>	55.0	5.4	5.6	55.2	5.4	5.6	327	4.05
3. <i>n</i> -Pyropyl amine	5.17	10.0	<i>n</i> -C <sub>3</sub> H <sub>7</sub> -	76.6	189	C <sub>12</sub> H <sub>15</sub> NO <sub>5</sub>	57.0	6.0	5.5	56.9	5.9	5.5	325	4.42
4. Allyl amine	5.2	10.0	CH <sub>2</sub> =CH-CH <sub>2</sub> -	74.4	176	C <sub>12</sub> H <sub>13</sub> NO <sub>5</sub>	57.2	5.5	5.5	57.4	5.2	5.6	330	4.57
5. <i>n</i> -Hexyl amine	8.8	10.0	C <sub>6</sub> H <sub>13</sub> -	78.7	160	C <sub>15</sub> H <sub>19</sub> NO <sub>5</sub>	61.0	6.9	4.5	61.0	7.1	4.7	336	4.70
6. n-Butyl amine	3.8	6.0	$n-C_4H_9-$	85.6	179	C13H17NO5	58.4	6.1	5.1	58.4	6.3	5.2	325	4.33

TABLE 1. FORMATION OF 7-AMINO-2, 2-DIMETHYL-4, 5-DIOXOPYRANO [4, 3-d][1,3] DIOXIN.

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TABLE 2. FORMATION OF 6-ALKYL-2, 2-DIMETHYL-4, 5-DIOXO-7-HYDROXY-PYRIDINO [4, 3-d] [1,3] DIOXINS (III).

Sr. 7-Amino	Quan-	Sodium/	Pyridino [4,3-d][1,3]	Yield	m.p	Molecular			Analy	sis			
No. pyrano(1,3)-	tity	phenol	dioxin(III)	(%)	°C	formula	Fo	und(%)		Rec	uired(9	6)	
dioxin (II) R=	(g)	(g/ml)					C	Н	N	C	Н	N	
1. CH <sub>3</sub> -	4.5	1.8/60	2,2-Dimethyl-4,5-dioxo 7-hydroxy-6-methyl-	80.0	174	C <sub>10</sub> II <sub>11</sub> NO <sub>5</sub>	53.2	4.9	6.2	53.3	4.9	6.2	_
2. C <sub>2</sub> H <sub>5</sub> -	3.0	1.2/35	2,2-Dimethyl-4,5-dioxo- 6-ethyl-7-hydroxy-	42.0	249	C <sub>11</sub> H <sub>13</sub> NO <sub>5</sub>	55.3	5.5	5.7	55.2	5.4	5.8	
3. <i>n</i> -C <sub>3</sub> II <sub>7</sub> -	6.0	2.2/60	2,2-Dimethyl-4,5-dioxo- 7-hydroxy-6-propyl-	72.8	168	$C_{12}H_{15}NO_{5}$	56.7	5.6	5.5	56.9	5.9	5.5	
4. CII <sub>2</sub> =CII-CH	2-4.5	1.7/50	6-Allyl-2, 2-dimethyl- 4,5-dioxo-7-hydroxy-	93.0	169	$\mathrm{C_{12}H_{13}NO_{5}}$	57.3	5.1	5.5	57.4	5.2	5.6	
5. <i>n</i> -C <sub>6</sub> H <sub>13</sub> -	6.0	2.0/60	2,2-Dimethyl-4,5-dioxo- 6-hexyl-7-hydroxy-	48.6	127	C <sub>15</sub> H <sub>19</sub> NO <sub>5</sub>	60.7	7.0	4.6	61.0	7.1	4.7	
6. $n-C_4II_9$ -	3.7	1.3/40	6-Butyl-2,2-dimethyl- 4,5-dioxo-7-hydroxy-	34.5	126	C <sub>13</sub> H <sub>17</sub> NO <sub>5</sub>	58.2	6.2	5.0	58.4	6.3	5.2	

7-*Chloro-2,2-dimethyl-4,5-dioxo-pyrano* [4,3-d][1,3] *dioxin* ( $I, R = R'R'' = CH_3$ ). The title compound was prepared according to the method of Davis and Elvidge [2].

2,2-Dimethyl-4,5-dioxo-7-methylamino-pyrano[4,3d][1,3] dioxin (I,  $R = R'R'' = CH_3$ ). A solution of 7-chloro-2,2dimethyl-4, 5-dioxopyrano-[4,3-d] [1,3] dioxin (I, R' = R'' =CH<sub>3</sub>) (10 g, 43.4 mmol) in CHCl<sub>3</sub> (15 ml), methylamine 25% solution (11.5 ml, 86.8 mmol) was added dropwise with constant stirring. The solid product was washed with water and dried. 2,2-Dimethyl-4,5-dioxo-7-methylamino-pyrano [4,3d] [1,3] dioxin (I) (7.8 g, 80.4%) was crystallized from CHCl<sub>3</sub>, m.p. 207°.

*Found*: C, 53.5; H, 4.9; N, 6.2; C<sub>10</sub>H<sub>11</sub>NO<sub>5</sub> *Requires*: C, 53.3; H, 4.9; N, 6.2%

Other 7-alkylamino-2,2-dimethyl-4, 5-dioxo-pyrano [4,3-d] [1,3] dioxins (II) were prepared as above and listed in Table 1.

2,2-Dimethyl-4, 5-dioxo-7-hydroxy-6-methylpyridino [4,3-d][1,3] dioxin (III,  $R = CH_3$ ). 2-2-Dimethyl-4, 5-dioxo-7-hydroxy-6-methylaminopyrano [4,3-d][1,3] dioxin (4.5g, 20m mol) was added to a solution of Na (1.8g, 80m mol) in phenol (60 ml) and the mixture was heated at 120° for 2 minutes. The solution was cooled, diluted with water and extracted with ether to recover excess of phenol. The ethereal layer was extracted with water and the combined aqueous extracts (150 ml) were acidified with HCl (3N). The solid product, 2,2-dimethyl-4, 5-dioxin-7-hydroxy-6-methylpyridino [4,3-d][1,3]dioxin ( $R = R' = R'' = CH_3$ ), (III, 4.0g, 88%) was crystallized from MeOH, m.p. 174°. It produced reddish brown colour with aq. FeCl<sub>3</sub> and effervescence with aq. NaHCO<sub>3</sub>.

*Found:* C, 53.2; H, 4.9; N, 6.2; C<sub>10</sub>H<sub>11</sub>NO<sub>5</sub> *Requires:* C, 53.2; H, 4.9; N, 6.2%

The products III obtained as a result of the reaction of alkyl aminopyranodioxins (II) with sodium phenoxide in

phenol are listed in Table 2.

2,2-Dimethyl-4,5-dioxo-7-methoxy-6-methylpyridino [4,3-d][1,3]dioxin (IV,  $R = CH_3$ ). An ethereal solution of diazomethane was added in portions to 2,2-dimethyl-4,5-dioxo-7-hydroxy-6-methylpyridino [4,3-d] [1,3]dioxin (0.5g) suspended in ether (20 ml) until the yellow colour persisted. The solution was kept for 2 hr. in a refrigerator and the solvent was removed. The residue showed no colouration with aq. FeCl<sub>3</sub>. 2,2-Dimethyl-4, 5-dioxo-7-methoxy-6- methylpyridino [4,3-d][1,3]dioxin (IV, 0.2g, 38%), m.p. 143°, was crystallized from MeOH.

*Found:* C, 55.4; H, 5.4; N, 5.7. C<sub>11</sub>H<sub>13</sub>NO<sub>5</sub> *Requires:* C, 55.2; H, 5.4; N, 5.8%.

8-Bromo-2, 2-dimethyl-4, 5-dioxo-7-hydroxy-6-methylpyridino [4,3-d] [1,3] dioxin (V,  $R = R' = R'' = CH_3$ ). The compound (III,  $R = R' = R'' = CH_3$ ) (0.5g) was dissolved in CHCl<sub>3</sub> (20 ml) and bromine in CHCl<sub>3</sub> was added dropwise, till an orange colour persisted. The reaction mixture was kept at room temperature for 2 hr. and the solvent was removed. The solid bromo product (V, 0.4g, 59%) was crystallized from McOH, m.p. 160°.

*Found*: C, 39.3; H, 3.2; N, 4.6. C<sub>10</sub>H<sub>10</sub>NO<sub>5</sub>Br *Requires*: C, 39.4; H, 3.2; N, 4.63%

7-Chloro-2,2-dimethyl-4,5-dioxo-6-methylpyridino [4,3d][1,3]dioxin (VI,  $R = R'' = R'' = CH_3$ ). 2,2-Dimethyl-4,5dioxo-7-hydroxy-6-methylpyridino [4,3-d][1,3] dioxin (III,  $R = R' = R'' = CH_3$ ) (0.5g) was added thionyl chloride (4.0 ml) and the mixture was refluxed under anhydrous conditions for 15 min. Thionyl chloride was removed *in vacuo* and the residue was washed with water to yield the chloro product (VI, 0.4g,68%).7-Chloro-2,2-dimethyl-4,5-dioxo-6-methylpyridino [4,3-d][1,3] dioxin (VI) was crystallized from MeOH, m.p. 300° decomp.

*Found:* C, 49.8; H, 4.1; N, 5.8. C<sub>10</sub>H<sub>10</sub>NO<sub>4</sub> *Requires:* C, 49.2; H, 4.1; N, 5.7%

### **Results and Discussion**

It has been reported earlier that pyrano-dioxins derived from aliphatic amines, except isobutylamine, produced intractable phenolic materials when subjected to phenoxide rearrangements [3]. Reinvestigation of the isomerization of pyrano-dioxins (II) with sodium phenoxide in phenol resulted in pyridino-dioxins (III, R = R' = R'' = alkyl). for instance, 7methylamino-4, 5- dioxo-2, 2-dimethyl pyrano [4,3-*d*][1,3] dioxin (II,  $R = R' = R'' = CH_3$ ) on reacting with sodium phenoxide in phenol gave an isomeric product,  $C_{10}H_{11}NO_5$ (III,  $R = R' = R'' = CH_3$ ), m.p. 174°, phenolic in nature (it gave FeCl<sub>3</sub> test and dissolved in aqueous NaHCO<sub>3</sub> solution). Other alkylamino dioxins (II) yielded the corresponding isomeric products (III).

These pyridino-dioxins (III) showed characteristic absorbance in the UV region 300 - 310 nm (Table 1). The substitution at position I, therefore, has apparently no effect on the UV absorption. An examination of IR spectra of the pyridino-dioxins showed absorbance at 1700 - 1740 cm<sup>-1</sup> due to the lactone carbonyl at position 4 and absorption peaks at 1580 - 1615 cm<sup>-1</sup> due to the amide carbonyl group at position 5.

The OH group at position 7 was methylated into the product (IV,  $R = R' = R'' = CH_2$ ),  $\lambda max 310 \text{ nm}$  (log  $\varepsilon 4.15$ ) and

renal functions etc., before giving any drag or placebo, Group 'A' was given distilled water intrapertionedly (I.P.) and was used as a control group. Group 'B' received Methotrexate 40 mg/kg body weight intraportionedly. The dores were repeated every 72 hr. up to four dores. In this way, each nibbit in group 'B' received a total of 200 mg Methoptexus, approximately.

The animals of both groups were maintained on a mixed free weight diet. The diet schedule was such that, before experimentation the manuals were feil morning and evening while during the experimentation they were given a diet in the afternoon also. Blood samples were obtained by cardine puncture technique from both groups (one animal of each group each even collected in 5ml rubber stoppered tables without using any unicoagniant. Samples were stored at 2° and maby zet within 12 hr. The alkaline phosphatase, SGOT, SGPT, by zet within 12 hr. The alkaline phosphatase, SGOT, SGPT, by zet within 12 hr. The alkaline phosphatase, SGOT, SGPT, by zet within 12 hr. The alkaline phosphatase, SGOT, SGPT, by zet determined by specific reagents kits. Merck by automation were taken after one, five and ten days of last dose respectively. The general tortelies were also dose respectively. The general tortelies were also noted at carbot score torely.

After the tenth day, the antitude were sacrificed. Autopsics were performed. All organic were examined for gross changes if any. The samples of liver and kidneys were collected for histopathological examination. Student 1' test was applied for the statistical analysis of data.  $\lambda \max 276 \operatorname{nm} (\log e, 4.10)$ . Similarly the bromo derivative (V, R = R' = R" = CH<sub>3</sub>) absorbed at  $\lambda \max$ . 317 nm (loge 4.54). These observations are in conformity with the structures assigned to the products represented by formula III.

TABLE 3. UV AND IR SPECTRA OF PYRIDINO- [4,3-d][1,3] DIOYINS(III)

Sr. No.	Pyridino [4,3-d] [1,3] dioxin	UV Light a (95% me	•	IR absorption max (cm <sup>-1</sup> ) mainly for the 3-6, 7u region, (KBr disc)					
	(III, R'=R"=CH <sub>3</sub> ) R	λmax (nm)	log ε	υ C = 0(4) (cm <sup>-1</sup> )	$v C = 0 (5) (cm^{-1})$				
1.	Methyl	308	4.28	1725	1615				
2.	Ethyl	300	3.94	1735	1610				
3.	n-Pyropyl	310	4.25	1710	1580				
4.	Allyl	308	4.23	1705	1600				
5.	n-Hexyl	310	4.36	1700	1595				
6.	n-Butyl	308	4.21	1740	1605				

#### References

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acute lymphoblastic featernia [6]. Since then the Methotrex as has become the most commonly used folic acid instagonia in the treatment of several maintanant diseases.

Methotrezate has shown dramme results both in combination and alone in anticancer therapy. It is important in the treatment of neutre lymphoblastic featernia [7,8], lymphomas [9], osteogenic saccomp [10], squamous cell carcinoma of head and neck [11] and breast caccar [12]. It is considered to produce objective responses in some patients with lung caneer, epidemoid carcihoma of the cervix and some other solid earnors [13].

The treatment schedules, based on Motholeoxate have becaue more numerous, varied and sometimes more complicated over the last twenty to thirty years, with increase in itemse by clinicians and laboratory workers. Now, it is not possible to offer a simple, clear cut guidaling that any clinician may follow and be certain of genieving a particular result in a malignancy. As the treatment schedules are not consistent with strategies and can her be used in them efficient forms in developing constructs, so it is necessary to work out a new plan in the present study, we have tread to twoive such a plan for the cancer sherrotherapy by Methorecate

biaterials and Mcfords

This study way conducted on healthy male rabbits with an average weight of 1337 gm divided in two props of seven bear of Pabolesy, 13177, Natachi

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