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SYNTHESIS OF HETERO-BICYCLIC COMPOUNDS—I

SYNTHESIS OF PYRIDINO-(1,3)-DIOXINS

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Abstract—The reaction between amino-pyrano-1,3-dioxins (I) and phenoxide in phenol has been investigated. The reaction is a general one and yields 6-substituted derivatives of 7-hydroxy-2,2-dimethyl-4,5-dioxopyridino(4,3-d)-(1,3)-dioxin—a new unsaturated heterobicyclic system formed by internal rearrangement. The constitution of the products (II) was established by transformation into ester pyridones (VI, VIII) of known structure and by UV and IR spectroscopy.

THE conversion of 7-anilino-2,2-dimethyl-4,5-dioxo-pyrano(4,3-d)-(1,3)-dioxin into ethyl 1,2-dihydro-4,6-dihydroxy-1-phenyl-2-oxo-pyridine-3-carboxylate (VI) under the influence of sodium ethoxide has already been reported[1] and generality of this reaction has been confirmed and is to be published later. It was anticipated that by the use of phenoxide ($Ph\bar{O}$) in place of ethoxide, phenyl ester pyridones (III) would be produced but it was found that instead a new hetero-bicyclic system was formed.

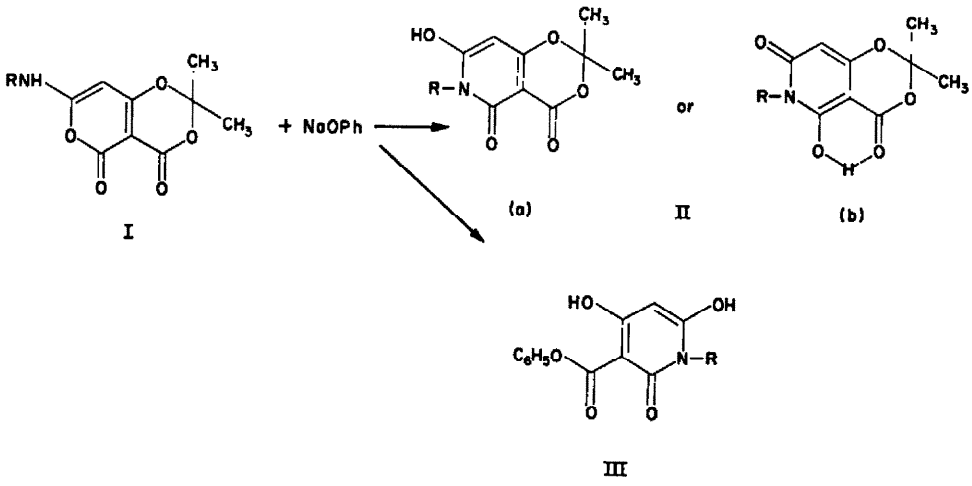
For instance, the compound $C_{15}H_{13}NO_5$ (I, R = Ph) on reacting with phenoxide in phenol, affords a colourless product (IIa, R = Ph), m.p. 214° (dec), isomeric with the starting material. It is phenolic in nature, effervesces with aqueous sodium bicarbonate and gives a reddish brown colour with aq. ferric chloride. It was fairly stable towards alcohols but decomposed when boiled with these for a long time. Various other amino pyrano-dioxins[2] (I) on treatment with phenoxide in phenol yield analogous products (IIa).

TABLE 1. UV AND IR SPECTRA OF PYRIDINO-(4,3-d)-(1,3)-DIOXINS (IIa)

No.	Pyridino(4,3-d)-(1,3)-dioxins(IIa) R	UV light absorption (95% ethanol) λ_{max} mμ	log ε	IR absorption max (cm^{-1}) mainly for the 3–6·7 μ region. (Nujol Mulls). C—O(4) cm^{-1}	C—O(5) cm^{-1}
1.	Phenyl	316	4·69	1698s	1664s
2.	*o*-Tolyl	316	4·57	1745s	1631s
3.	*m*-Tolyl	313	4·51	1686s	1653s
4.	*p*-Tolyl	312	4·39	1692s	1664s
5.	*m*-Chlorophenyl	312	4·68	1712s	1664s
6.	*p*-Chlorophenyl	312	4·67	1727s	1664m
7.	*m*-Bromophenyl	313	4·43	1712m	1664s
8.	*p*-Bromophenyl	313	4·39	1704s	1664s
9.	β-Naphthyl	313	4·49	1718m	1661s

[1] M. A. Butt, J. A. Elvidge and A. B. Foster, *J. Chem. Soc.* 3069 (1963).
[2] Prepared by the method of S. J. Davis and J. A. Elvidge, *J. Chem. Soc.* 4109 (1962).

It is evident from the above Table that these new products have a characteristic absorption in the region λ_{max} 316–312 mμ and, therefore, they closely resemble chloro-pyrano-(1,3)-dioxins.[3] The formation of these products may be represented as follows:



Of the two probable structures II (a, b) the formula IIa was assigned to these new products, because the compound $C_{15}H_{13}NO_5$, (IIa, R = Ph) shows in the IR a peak at ν 1698s cm^{-1} due to the ester carbonyl at position 4 which is apparently unbonded and the frequency ν 1664 cm^{-1} arises from the pyridone carbonyl at position 5. An hydroxyl group at position 7 of the same product shows a broad band near ν 2632 cm^{-1} and is bonded. It (IIa, R = Ph) reacts with phosphorous oxychloride to form a chloro-product $C_{15}H_{12}ClNO_4$ (IV), m.p. 163°, which absorbs in the UV at λ_{max} 328 mμ, 12 mμ higher in wavelength than the parent compound.

A similar shift of 21 mμ has been observed during conversion of hydroxypyridone (VI), λ_{max} 305 mμ, into ethyl 4,6-dichloro-1,2-dihydro-2-oxopyridine-3-carboxylate which absorbs at λ_{max} 326 mμ. The IR spectrum of the chloro-product (IV), has a peak near ν 1751s cm^{-1} attributable to an ester carbonyl at position 4 and a peak at ν 1664 cm^{-1} due to a pyridone carbonyl at position 5. (Table 1).

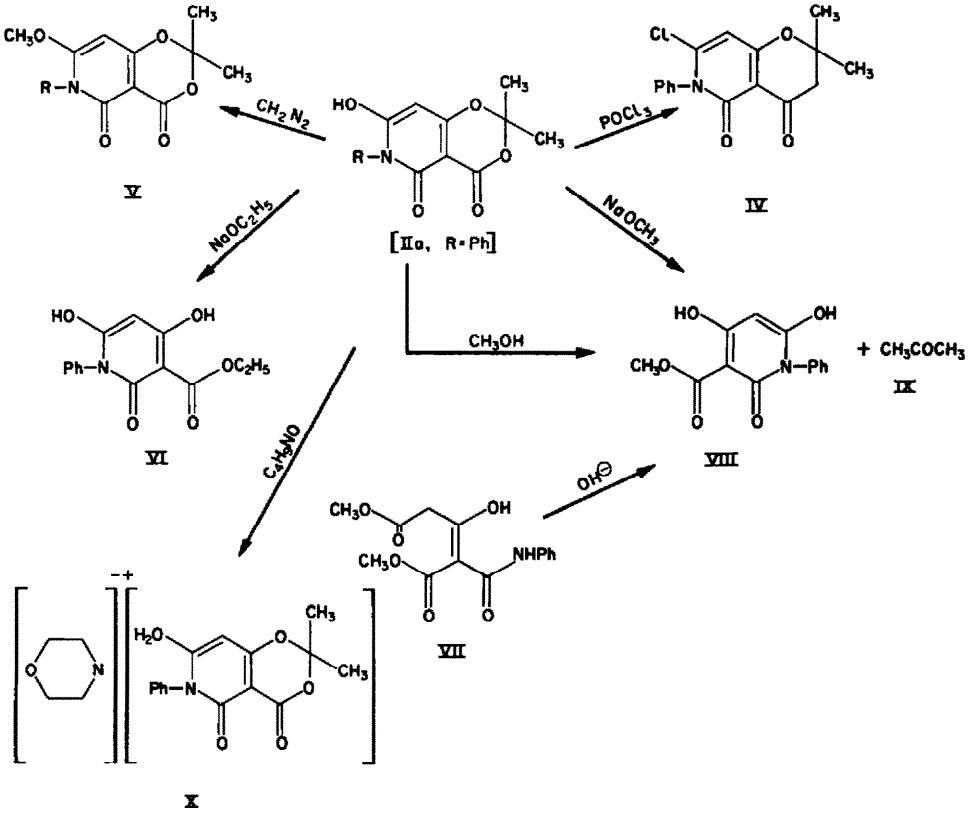
Treatment of the product (IIa, R = Ph) with diazomethane in chloroform—ether solution yields a new methylated product $C_{16}H_{15}NO_5$ (V), m.p. 183° which is neutral in character. It absorbs UV light in the region λ_{max} 300 mμ (log ε, 4·03), λ_{max} 276 mμ (log ε, 4·3). The IR spectrum is in agreement with the assigned formula, showing peaks at ν 1724 cm^{-1} and ν 1672 cm^{-1} due to an ester carbonyl at position 4 and pyridone carbonyl at position 5, respectively. With sodium methoxide and with sodium ethoxide the compound (IIa, R = Ph) yields methyl 1,2-dihydro-4,6-dihydroxy-1-phenyl-2-oxopyridine-3-carboxylate (VIII) and its ethyl ester analogue (VI), which were identified by comparison with authentic samples prepared by the standard method.

Finally the structure (IIa) for the new products was confirmed (IIa, R = Ph) by boiling in and formation of a methyl ester pyridone (VIII) and acetone (IX). The

[3] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.* 2, 2251 (1953).

latter was characterized as the 2,4-dinitrophenylhydrozone. The compound (IIa, R = Ph) also reacts with morpholine to give a morpholinium salt (X), $C_{19}H_{22}N_2O_6$, m.p. 183°, from which on acidification with dilute acid, the parent compound (IIa, R = Ph) is regenerated. This property of forming morpholinium salts is common to the dihydroxy-pyridones previously prepared.[1]

The foregoing degradative reactions may be represented as follows:



It is evident that the formation of these new products involves an attack by a nucleophile ($Ph\bar{o}$) at the electron-deficient carbonyl at position 5 to give an acyclic anion (d) which recyclizes in the manner indicated, the 1,3-dioxin ring being kept intact.

EXPERIMENTAL

7-Anilino-2-2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxin (I, R = Ph)

To a solution of 7-chloro-2,2-dimethyl-4,5-dioxopyrano-(4,3-d)-(1,3)-dioxin (2·3 g; 1 mole) in $CHCl_3$ (20 ml), aniline (1·9 g; 2 moles) in $CHCl_3$ (10 ml) was added dropwise with constant stirring. A solid product was washed with water and dried over P_2O_5. 7-Anilino-2,2-dimethyl-4,5-dioxopyrano-(4,3-d)-(1,3)-dioxin (2·8 g; 97·5%) was crystallized from $CHCl_3$, m.p. 193° (dec). (Found: N, 4·8 Calc. for $C_{15}H_{13}NO_5$: N, 4·9%.)

Other 7-Amino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxins prepared as above, are listed in Table 2.*

TABLE 2

No.	Primary amine (2 moles)	Chloro-compound (1 mole)	Product (I) (R)	Yield (%)	Solvent for crystal-lization	UV light absorption (95% ethanol) λ_{max} mμ	log ε
1.	*o*-Toluidine (2·2 g)	2·3 g	*o*-Tolyl	96	C_2H_5OH	340	4·52
2.	*m*-Toluidine (2·2 g)	2·3 g	*m*-Tolyl	98	C_2H_5OH	340	4·92
3.	*p*-Toluidine (2·2 g)	2·3 g	*p*-Tolyl	98	C_2H_5OH	336	4·48
4.	*m*-Chloroaniline (2·6 g)	2·3 g	*m*-Chlorophenyl	97	$CHCl_3$	338	4·56
5.	*p*-Chloroaniline (2·6 g)	2·3 g	*p*-Chlorophenyl	95	$CHCl_3$	347	4·73
6.	*m*-Bromoaniline (3·5 g)	2·3 g	*m*-Bromophenyl	96	$CHCl_3$	347	4·72
7.	*p*-Bromoaniline (3·5 g)	2·3 g	*p*-Bromophenyl	96	C_2H_5OH	338	4·20
8.	β-Naphthylamine (3·9 g)	2·3 g	β-Naphthyl	95	$CHCl_3$	347	4·53
9.	Aniline (1·9 g)	2·3 g	Phenyl	97·5	$CHCl_3$	350	4·69

No.	m.p.	Formula	Found (%)			Required (%)		
			C	H	N	C	H	N
1.	178°	$C_{16}H_{15}NO_5$	63·3;	5·0;	4·8	63·8;	5·0;	4·7
2.	180	$C_{16}H_{15}NO_5$	63·6;	4·9;	4·7	63·8;	5·0;	4·7
3.	166	$C_{16}H_{15}NO_5$	64·3;	5·1;	4·9	63·8;	5·0;	4·7
4.	170	$C_{15}H_{12}ClNO_5$	56·0;	3·9;	4·5	56·0;	3·7;	4·4
5.	186	$C_{15}H_{12}ClNO_5$	56·0;	3·6;	4·4	56·0;	3·7;	4·4
6.	190	$C_{15}H_{12}BrNO_5$	48·9;	3·2;	3·8	49·2;	3·3;	3·8
7.	183	$C_{15}H_{12}BrNO_5$	49·2;	3·4;	3·9	49·2;	3·3;	3·8
8.	176	$C_{19}H_{15}NO_5$	67·8;	4·6;	4·3	67·5;	4·5;	4·2

Reaction of 7-Anilino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxin with sodium phenoxide in phenol

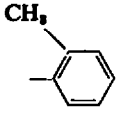
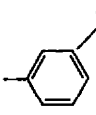
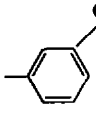
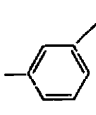
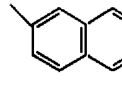
7-Anilino-2,2-dimethyl-4,5-dioxopyrano(4,3-d)-(1,3)-dioxin (3 g; 1 mole) was added to a cold solution of Na (1·0 g, 4 moles) in phenol (20 ml) and the mixture heated under reflux for 2 min, and protected by a $CaCl_2$ tube. The brown solution was cooled, diluted with water (200 ml) and extracted with ether to remove excess phenol. The aqueous solution was then acidified with 2 N HCl, and the solid product, *2,2-dimethyl-7-hydroxy-4,5-dioxo-6-phenylpyridino* (4,3-d)-(1,3)-*dioxin* (IIa, R = Ph; 1·2 g, 40%) crystallized from EtOH. It reddened at 160° and melted at 214° (dec). It produced reddish brown colour with $FeCl_3$ aq and effervesce with $NaHCO_3$ aq. (Found: C, 62·8; H, 4·4; N, 4·7; O, 27·2 tit. Eq., 287. $C_{15}H_{13}NO_5$ requires: C, 62·7; H, 4·5; N, 4·9; O, 27·7%.)

Reaction of other aminopyrano-dioxins (I) *with sodium phenoxide in phenol*

The products (II) listed in the Table 3 were prepared as above:

* The structural evidence of these products (I) follows from their UV light absorptions recorded above.

TABLE 3

No.	Aminopyrano-[2] (1,3)-dioxins (I) R		Sodium in phenol	Pyridino(4,3-d)-(1,3)-dioxins (IIa)	Yield	Solvent of crystallization.
1.		(3 g)	0·8 g/10 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*ortho*tolyl-	55%	CH_3OH
2.		(3 g)	1 g/10 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*meta*tolyl-	50%	Hot C_6H_6
3.		(3 g)	1 g/20 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*para*tolyl-	40%	CH_3OH
4.		(3·2 g)	1·25 g/20 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*meta*-chlorophenyl-	33%	CH_3OH
5.		(3·2 g)	1·25 g/20 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*para*-chlorophenyl-	40%	CH_3OH
6.		(3·6 g)	1·2 g/20 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*meta*-bromophenyl-	56%	CH_3OH
7.		(3·6 g)	1·2 g/20 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6-*para*-bromophenyl-	53%	CH_3OH
8.		(3·4 g)	1·8 g/30 ml	7-Hydroxy-2,2-dimethyl-4,5-dioxo-6β-naphthyl-	58%	CH_3OH

No.	m.p.	Formula	Found (%)				Required (%)			
			C	H	N		C	H	N	
1.	188°	$C_{16}H_{15}NO_6$	63·8;	4·8;	5·0		63·8;	5·0;	4·7	
2.	184	$C_{16}H_{15}NO_6$	63·8;	4·9;	4·7		63·8;	5·0;	4·7	
3.	178	$C_{16}H_{15}NO_6$	64·0;	5·0;	4·7		63·8;	5·0;	4·7	
						Cl				Cl
4.	184	$C_{15}H_{12}ClNO_6$	55·7;	3·7;	4·7;	12·3	56·0;	3·7;	4·4;	11·1
5.	190	$C_{15}H_{12}ClNO_6$	55·8;	3·7;	4·4;	11·1	56·0;	3·7;	4·4;	11·1
						Br				Br
6.	174	$C_{15}H_{12}BrNO_6$	48·8;	3·2;	3·7;	20·9	49·2;	3·3;	3·8;	21·8
7.	207	$C_{15}H_{12}BrNO_6$	49·3;	3·3;	3·9;	21·8	49·2;	3·3;	3·8;	21·8
8.	194	$C_{19}H_{15}NO_6$	67·2;	4·4;	4·2		67·5;	4·5;	4·2	

Degradation of 7-hydroxy-2,2-dimethyl-4,5-dioxo-6-phenyl pyridino(4,3-d)-(1,3)-dioxin (R = Ph, IIa)

With sodium ethoxide in ethanol. The compound IIa (R = Ph; 1 g) was added to abs. EtOH (20 ml) to which Na (1 g) had been added and the mixture heated under reflux for 15 min. The solution was cooled and evaporated to dryness and the residue diluted with water (200 ml). Acidification of the clear solution with 2 N HCl, yielded VI (0·6 g; 60%) m.p. 204° (dec). It crystallized from hot EtOH. (Found: C, 61·1; H, 4·7; N, 5·1; Calc. for $C_{14}H_{13}NO_6$: C, 61·5; H, 4·7; N, 5·1%.) The product showed no depression in mixed m.p. with an authentic sample prepared by the method of 'Butt and Elvidge'.[1] The IR spectra were also identical.

With sodium methoxide. The compound IIa (R = Ph; 0·5 g) was added to a solution of Na (0·5 g) in MeOH (15 ml) and the mixture heated under reflux for 15 min. On cooling and acidification with 2 N HCl the product separated and VIII (0·36 g; 79%), after crystallization from MeOH, melted at 208–210° (dec). A mixed m.p. with an authentic sample showed no depression. (Found: C, 60·1; H, 4·5; N, 5·5; Calc. for $C_{13}H_{11}NO_6$: C, 59·8; H, 4·2; N, 5·3%.)

With methanol alone. The compound IIa (R = Ph; 1 g) was added to MeOH (50 ml) and the mixture heated under reflux for 24 hr. At the end of the reaction time, the solution showed a strong green fluorescence. The excess of solvent was distilled off and from the distillate acetone was separated by Bradys reagent as its 2,4-dinitrophenyl-hydrazone, having m.p. 119·5°, undepressed by authentic material. The residue in the distillation flask, on trituration with ether yielded VIII (0·6 g, 69%) which crystallized from MeOH, m.p. 210° (dec). It was identical in all respects with the sample prepared by the previous method. (Found: N, 5·5; Calc. for $C_{13}H_{11}NO_6$: N, 5·3%.)

7-Methoxy-2,2-dimethyl-4,5-dioxo-6-phenylpyridino(4,3-d)-(1,3)-dioxin (V)

To 7-hydroxy-2,2-dimethyl-4,5-dioxo-6-phenylpyridino(4,3-d)-(1,3)-dioxin (1 g) in $CHCl_3$ (500 ml), a solution of diazomethane in ether (about 0·5 g in 50 ml) was added in portions and the mixture kept in the cold for 24 hr. Evaporation of the solvent and trituration of the residue with ether, gave a neutral product which showed no colour with $FeCl_3$ aq. The *7-methoxy-2,2-dimethyl-4,5-dioxo-6-phenylpyridino*(4,3-d)-(1,3)-*dioxin* (V; 0·9 g, 81·1%), m.p. 183° decomposed, after recrystallization from EtOH. (Found: C, 63·8; H, 4·9; N, 4·8; OCH_3, 10·2; Calc. for $C_{16}H_{15}NO_5$: C, 63·8; H, 5·0; N, 4·6; OCH_3, 10·3%.)

7-chloro-2,2-dimethyl-4,5-dioxo-6-phenylpyridino(4,3-d)-(1,3)-*dioxin* (IV)

The compound IIa (R = Ph; 2 g) and $POCl_3$ (15 ml) were heated under reflux for 15 min. The excess $POCl_3$ was removed under red. press. The residual semi-solid was dissolved in EtOH (25 ml) and decolourized with charcoal. The reddish filtrate after concentration to half volume, was diluted with water (3 ml). On keeping in the cold for several hr a crystalline product was obtained. *7-chloro-2,2-dimethyl-4,5-dioxo-6-phenylpyridino*-(4,3-d)-(1,3)-dioxin (IV; 0·5 g, 24%), was recrystallized from MeOH, m.p. 163°. (Found: C, 58·3; H, 3·7; N, 4·3; Cl, 11·1; Calc. for $C_{15}H_{12}ClNO_4$: C, 58·6; H, 3·9; N, 4·6; Cl, 11·3%.)

Reaction of 7-hydroxy-2,2-dimethyl-4,5-dioxo-6-phenylpyridino-(4,3-d)-(1,3)-*dioxin with morpholine*

To the compound IIa (R = Ph; 0·5 g) was added $CHCl_3$ (10 ml) and morpholine (0·5 ml) and the mixture heated under reflux for 15 min. Excess solvent was removed under red. press. and the solid triturated with ether. The morpholinium salt (X, 0·6 g; 83%) had m.p. 183° (dec) after recrystallization from EtOH. (Found: C, 60·9; H, 6·0; N, 7·5; Calc. for $C_{19}H_{22}N_2O_6$: C, 61·0; H, 5·9; N, 7·5%.)

The elementary analyses were carried out by A. Bernhardt, micro analytisches laboratorium 22a, Mulheim (Ruhr) West Germany.

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