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SYNTHESIS OF SUBSTITUTED PYRIDINES

Part IX. Formation of 1,2-Dihydro-6-(O-Carboethoxy)-4-Hydroxy-2-Oxo-1-Substituted Pyridines-3-Carboxyanilides

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Ethyl chloroformate reacts with 2,4-dihydroxy-1-substituted pyridinecarboxyanilides (I) to yield derivatives of 6-(O-carboethoxy)-1, 2-dihydro-4-hydroxy pyridine-3-carboxyanilide (II). IR and UV data of the new products have been recorded in support of their assigned structure.

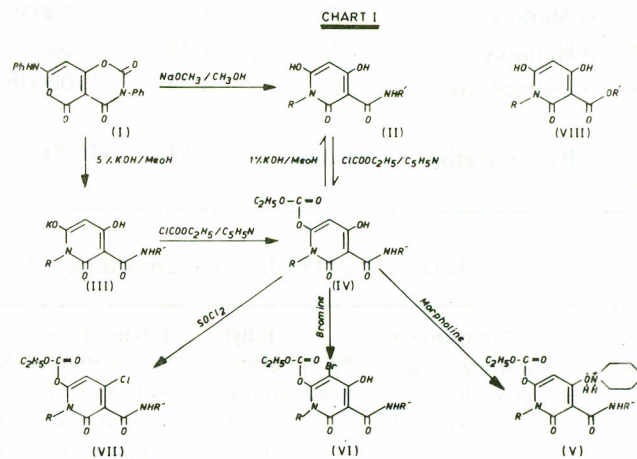
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INTRODUCTION

In the preceding paper [1], the formation of carbamates and thiocarbamates at position 6 of the products (VIII) was reported. Now the formation of various (O-carboethoxy) esters at the same position 6 of the compounds (II), is described. It was noticed that when 1,2-dihydro-4, 6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (II, R=R' = Ph) was reacted with ethyl chloroformate in the presence of a base (pyridine) under ice-cold condition, it gave a product $C_{21}H_{18}N_2O_6$, (III, R=R' = Ph) m.p. 160° , $\lambda_{max} = 320 \text{ m}\mu$, $\log \epsilon = 4.63$. It was also obtained in better yield when the mono potassium salt of the compound (II, R=R' = Ph) and ethyl chloroformate were reacted together under the same condition. The latter was apparently formed by the replacement of hydrogen at position 6 by a carboethoxy group. As usual, the O-H at position 4 remained intact, and its presence was evident from the enolic properties of this product. In conformity with the assigned structural formula (IV), the carbonyl of the carboethoxy group showed a strong peak at 1740 cm^{-1} , which is clearly analogous to the absorption frequency of a similar product reported by J.D. Crum [2], 2-pyridone and anilido carbonyl invariably appeared between $1690\text{--}1700 \text{ cm}^{-1}$. The OH at position 4 was not bonded and appeared between $3130\text{--}3160 \text{ cm}^{-1}$. Thus the IR and UV spectral data (Table 1) tally well with the assigned structure (IV).

The hydroxyl at position 4, as usual, formed a morpholinium product $C_{25}H_{26}N_3O_7$, m.p. 170° . In the IR spectra, the absorption frequency due to CO at position 6, appeared at 1730 cm^{-1} , while pyridone CO (2) and CO due to anilide at 1690 cm^{-1} . Similarly other derivatives of the product

(IV, R=R' = Ph), i.e. its bromo and chloro (VI) and (VII) respectively have been prepared. The IR and UV data for these products have been recorded in the experimental while the reactions described above are depicted in the Chart 1 below.



EXPERIMENTAL

1. *Reaction of 7-anilino-3, 4-dihydro-2, 4,5-trioxo-phenyl-2H, 5H-pyrano-(4,3-e)-(1,3)-oxazine with sodium methoxide.* The product (I) (I, R=Ph) (1g, 0.0028 mole) and sodium methoxide in methanol (Na, 0.4 gm; methanol 30 ml) were refluxed (30 mins) under anhydrous condition. The solvent was removed under vacuum, the residue was diluted with water, was filtered and dried to weigh 0.8g (86.5%). 1,2-Dihydro-4, 6-dihydroxy-2-oxo-1-phenyl pyridine-3-carboxyanilide (II, R=R' = Ph), was further recrystallised from MeOH: CHCl₃ (1:1) mixture, had m.p. 234° (dec.) undepressed on admixture with an authentic

sample. Found: C, 67.01; H, 4.21; N, 8.63. Calculated for $C_{18}H_{14}N_2O_4$ C, 67.08; H, 4.34; N, 8.69%. All the other anilides (II) were prepared as described earlier [3].

2. Reaction of 1,2-dihydro-4, 6-dihydroxy-2-oxo-1-phenyl pyridine-3-carboxyanilide (II) with ethyl chloroformate. To the compound (II, R=Ph, R' = Ph) (1.61g; 0.005 mole) in ice-cooled pyridine (5 ml), ethyl chloroformate

(1.08g, 0.01 mole) was added dropwise and after addition the solution was allowed to attain room temperature and was heated on water bath (30 Min) under anhydrous condition. During the process, the solution became red that was diluted with ice cold water (100 ml). The precipitate was filtered, washed with water, dried and weighed (1.3g; 66.3%). 1,2-Dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-

Table 1. UV and IR spectra of 1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenyl pyridine-3-carboxyanilide IV.

S. No.	R	UV light absorption in MeOH		IR-spectroscopic data in the region 3–6.7 μ (KBr-disc)				
		λ_{max} , m μ	log ϵ	C=O (2) and anilido	C=O(6) ester	C=C	H–N	H–O
1.	Phenyl-	320	4.63	1705s	1740s	1610(s)b	3240(w)b	3140m
2.	<i>o</i> -Tolyl-	320	4.59	1695s	1745s	1600) _s 1610) _s	3580(w)b	3140(w)b
3.	<i>m</i> -Tolyl-	320	4.56	1700s	1745s	1610(s)	3240m	3150(m)b
4.	<i>p</i> -Tolyl	320	4.59	1685s	1745s	1600) _m 1625) _m	3180m	3130s
5.	<i>o</i> -Methoxy-	320	4.58	1690(s)b	1750(s)b	1600(m)b	3200(w)b	3150m
6.	<i>m</i> -Methoxy-	320	4.51	1700(s)b	1745(s)b	1600m	3250m	3150m
7.	<i>p</i> -Methoxy-	320	4.58	1700s	1740(s)	1610s	3240(w)b	3150m
8.	<i>m</i> -Nitrophenyl-	320	4.54	1700(s)b	1750s	1600(s)b	3260) 3280) _m	3160m
9.	<i>p</i> -Bromophenyl-	320	4.61	1690(s)b	1740) 1750) _{(s)b}	1620m	3240(w)b	3130m

Table 2. 1,2-Dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenyl pyridine-3-carboxyanilides IV.

S. No.	1,2-dihydro 4,6-hydroxy-2-oxo-1-aryl substituted-3-carboxyanilides	Pyridine (0.01 mole)	Ethyl chloroformate (0.01 mole)	1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-aryl substituted-3-carboxyanilide		Solvent for crystallization	m.p. °C	Molecular formula	Analysis required (%)			Analysis found %			
				Yield (g)	Yield (%)				C	H	N	C	H	N	
1.	Phenyl	1.61	5	1.08	1.30	66.3	MeOH	160°	$C_{21}H_{18}N_2O_6$	63.95	4.56	7.10	63.83	4.57	7.41
2.	<i>o</i> -Tolyl	1.68	"	"	1.32	65.0	"	140°	$C_{22}H_{20}N_2O_6$	64.70	4.90	6.86	65.04	4.99	6.73
3.	<i>m</i> -Tolyl	1.68	"	"	1.33	65.5	"	128°	$C_{22}H_{20}N_2O_6$	64.70	4.90	6.86	65.10	4.92	6.81
4.	<i>p</i> -Tolyl	1.68	"	"	1.34	66.0	"	163°	$C_{22}H_{20}N_2O_6$	64.70	4.90	6.86	64.73	4.98	6.66
5.	<i>o</i> -Methoxy	1.76	"	"	1.38	65.5	"	182°	$C_{22}H_{20}N_2O_7$	62.26	4.75	6.60	61.87	4.37	6.48
6.	<i>m</i> -Methoxy	1.76	"	"	1.36	64.5	"	165°	$C_{22}H_{20}N_2O_7$	62.26	4.75	6.60	62.07	4.43	6.45
7.	<i>p</i> -Methoxy	1.76	"	"	1.39	66.0	"	135°	$C_{22}H_{20}N_2O_7$	62.26	4.75	6.60	62.00	4.47	6.29
8.	<i>m</i> -Nitrophenyl	1.83	"	"	1.40	64.0	"	177°	$C_{21}H_{17}N_3O_8$	57.40	3.90	9.56	57.68	3.92	9.64
9.	<i>p</i> -Bromophenyl	2.004	"	"	1.55	66.0	"	167°	$C_{21}H_{17}N_2O_6Br$	53.28	3.59	5.92	53.35	3.56	6.04

phenyl pyridine-3-carboxyanilide (IV) was recrystallised from CH_3OH m.p. 160° . Found : C, 63.83; H, 4.57; N, 7.41 requires for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_6$ C, 63.95; H, 4.56; N, 7.10% $\lambda_{\text{max}} = 320 \text{ m}\mu$, $\log \epsilon = 4.63$.

3. *Potassium salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (III)*. The compound (I, $\text{R}=\text{R}' = \text{Ph}$) (1 g, 0.0028 mole) and methanolic KOH (5%; 20 ml) were refluxed together (30 min). Excess of the solvent was removed under vacuum and the residue was triturated with a little water (50 ml). The salt precipitated out, was filtered and washed with cold water (20 ml). It was dried and weighed (0.7g, 61.5%). On recrystallisation from methanol: chloroform mixture (1:1), it melted at 245° (decomp).

Found : C, 59.45, H, 3.25, N, 7.53, K, 10.24, requires for $\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_4\text{K}$ C, 60.00, H, 3.61, N, 7.77, K, 10.83%.

4. *Reaction of K-salt of 1,2-dihydro-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (III) with ethyl chloroformate*. To the K-salt (III, $\text{R}=\text{R}' = \text{Ph}$) (2.16g; 0.005 mole) in ice cooled pyridine (5 ml), was added ethyl chloroformate (1.08g, 0.01 mole) dropwise. The solution was heated under anhydrous condition on water bath (30 min). The contents were diluted with ice cold water (100 ml). The resulting red precipitate was filtered, washed with water, dried and weighed (1.48g; 68.5%). 1,2-Dihydro-6-(0-carbo-ethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) on recrystallising from methanol, at m.p. 160° , remained undepressed on admixture with the sample prepared as above.

Found : C, 63.61; H, 5.23; N, 7.34 requires for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_6$; C, 4.56; H, 4.56; N, 7.10%.

Several other 0-carboethoxy derivatives prepared likewise are recorded in Table 2

5. *Reaction of 1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) with morpholine*. The compound (IV, $\text{R}=\text{Ph}$, $\text{R}' = \text{Ph}$) (0.2g; 0.0005 mole) in chloroform (10 ml), and morpholine (0.1 ml; 0.001 mole) in chloroform (5 ml) were heated under an anhydrous condition (30 min). The solvent was removed under vacuum and the residue on trituration with ether gave white solid. It was filtered, dried and weighed (0.21g, 86.4%). Morpholinium salt of 1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (V, $\text{R} = \text{Ph}$, $\text{R}' = \text{Ph}$) on recrystallisation from CH_3OH , showed m.p. 170° .

Found : C, 63.00; H, 5.55; N, 8.97 requires for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_7$; C, 62.50; H, 5.41; N, 8.75% $\lambda_{\text{max}} = 320 \text{ m}\mu$, $\log \epsilon = 4.62$.

6. *Reaction of 1,2-dihydroxy-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) with bromine*. To the compound (IV, $\text{R} = \text{R}' = \text{Ph}$) 0.5g; 0.0012 mole) in CHCl_3 (20 ml) was added bromine solution in chloroform (2 ml; 5%) dropwise till the bromine colour persisted. The solution was kept at room temperature (1 hr). The solvent was evaporated under vacuum, and the residue was triturated with ether. The solid was filtered, dried and weighed (0.5g; 83.3%). 5-bromo-1, 2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (VI) was recrystallised from CH_3OH which melted at 150° .

Found : C, 53.38; H, 3.60; N, 5.93 requires for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_6\text{Br}$; C, 53.28; H, 3.59; N, 5.92%, $\lambda_{\text{max}} = 320 \text{ m}\mu$, $\log \epsilon = 4.67$.

7. *Reaction of 1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) with thionyl chloride*. The compound (IV, $\text{R} = \text{R}' = \text{Ph}$) (0.5g; 0.0012 mole) and thionyl chloride (3 mole) were gradually heated on water bath under anhydrous condition (10 min). Excess of thionyl chloride was removed under vacuum. The residue was triturated with ice cold water. The yellow compound thus obtained was filtered, washed, dried and weighed (0.45g; 86.5%) 4-Chloro-1, 2-dihydro-6-(0-carboethoxy)-2-oxo-1-phenyl-pyridine-3-carboxyanilide (VII) was recrystallised from CH_3OH , it had m.p. 145° .

Found: C, 61.61; H, 4.15; N, 6.84 requires for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_5\text{Cl}$ C, 61.09; H, 4.12; N, 6.78%, $\lambda_{\text{max}} = 320 \text{ m}\mu$ $\log \epsilon = 4.54$.

8. *Reaction of 1,2-dihydro-6-(0-carboethoxy)-4-hydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) with KOH*. The compound (IV: $\text{R} = \text{Ph}$, $\text{R}' = \text{Ph}$) (0.2 g; 0.005 mole) and potassium hydroxide solution in methanol (10 ml; 1.0%) were refluxed together under anhydrous condition (30 min). The solvent was removed under vacuum. The residue was diluted with water, and on acidifying with 2N-HCl, gave white precipitate which was filtered, washed with water, dried and weighed (0.15g; 92%) 1,2-dihydro-4, 6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (II) was formed and on recrystallising from CH_3OH : CHCl_3 (1:1), had m.p. 234° (dec) undepressed on admixture with an authentic sample prepared earlier.

Found: C, 67.00; H, 4.31; N, 8.64 calculated for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_4$; C, 67.08; H, 4.34; N, 8.69%.

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