

## SYNTHESIS OF HETERO – BICYCLIC COMPOUNDS VI. FORMATION OF 1,2-DIHYDRO-4-HYDROXY-6-METHOXY-2-OXO-1-PHENYLPYRIDINE-3 ALKYL CARBOXYAMIDES AND ESTERS

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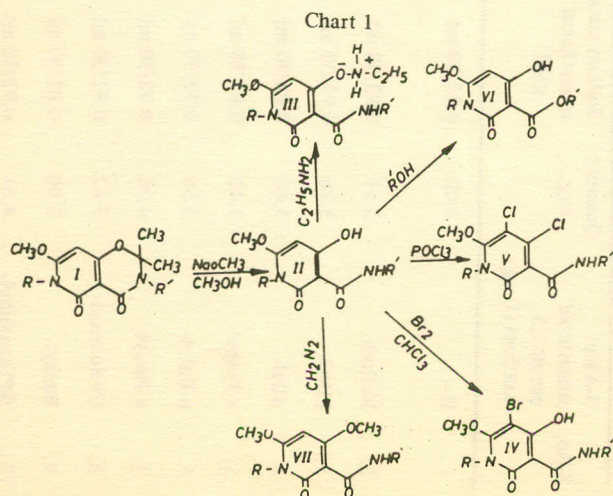
3-Substituted 2,2-dimethyl-4, 5-dioxo-2,3,5,6-tetrahydropyridine-3(3,4-e) (1-3) oxazines (I) and alkoxide (ethoxide and methoxide) react together to form 1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3 alkylcarboxyamides and esters corresponding to the alcohol used. The generality of the reaction has been demonstrated. Structural support to the new products (II, III) were gathered from UV and IR Spectroscopy along with chemical conversions.

### INTRODUCTION

3-Alkyl pyridino-oxazines (I, R=aryl, R'=alkyl) were found to disrupt stepwise first into pyridone amides (II, R=aryl, R'=alkyl) and then to pyridone esters (VI, R=aryl, R'=alkyl) when treated with alkoxide in alcohol. For instance, tetrahydropyridino-oxazine (I, R = Ph, R'=Me) on treatment with sodium methoxide in methanol produced a compound  $C_{14}H_{14}N_2O_4$  (II, R=Ph, R'=Me) m.p.  $160^\circ$  UV absorption at  $\lambda_{max}$ , 300,  $\log \epsilon$  4.2 apparently formed after the removal of one molecule of acetone. It showed a positive  $FeCl_3$  test and was dissolved in aqueous alkaline solution. The examination of its IR spectrum indicated absorption at  $\lambda$   $1660\text{ cm}^{-1}$  which appears to be due to 2-pyridone carbonyl group, and another absorption band

appeared at  $\gamma$   $3325\text{ cm}^{-1}$  due to amide grouping at position 3. These observations strictly conform to the structure assigned to the product (II, R=aryl, R'=alkyl) as shown in Chart I.

In support of the structure (II), five different derivatives have been prepared. For example, when the compound  $C_{14}H_{12}N_2O_4$  (II, R=Ph, R'=Me) was boiled with ethylamine for a short while, a compound  $C_{16}H_{20}N_3O_4$  was obtained; its m.p. was  $140^\circ$  (dec.) and had other characteristics  $\gamma$   $1620\text{ cm}^{-1}$  similar to its parent compound. Also on treatment of the compound,  $C_{15}H_{16}N_2O_4$  (II, R=Ph, R'=Et) with  $POCl_3$ , a product  $C_{15}H_{14}N_2O_3, Cl_2$ , m.p.  $160^\circ$  (dec) was formed. Its IR absorption at  $\lambda$   $1660\text{ cm}^{-1}$  was due to pyridone carbonyl at position 2 and  $\gamma$   $1720\text{ cm}^{-1}$  due to amido carbonyl at position 3. On reacting the product (II, R=Ph, R'=Et) with bromine in chloroform, it gave a compound  $C_{15}H_{15}N_2O_4Br$ , m.p.  $180^\circ$  (decomp.), UV absorption at  $\lambda_{max}$  302,  $\log \epsilon$  4.2 and IR absorption due to 2 carbonyl at  $\gamma$   $1660\text{ cm}^{-1}$ . This conforms to the structure assigned to the compound (VI, R=Ph, R'=Et). Finally, the compound (II, R=Ph, R'=Et) when treated with diazomethane in methanol, converted to a fully methylated product  $C_{15}H_{15}N_2O_5$ , m.p.  $195^\circ$  (decomp.) having the structure (VII, R=Ph, R'=Et) IR absorption at  $\gamma$   $1660\text{ s cm}^{-1}$ , UV absorption at  $\lambda_{max}$ , 302,  $\log \epsilon$  4.2. All the pyridino compounds (II, R=Ph, R'=alkyl) when subjected to prolonged treatment with alkoxide in alcohol gave pyridone esters (VI, R=Ph, R'=alkyl) which were already known [1]. This finally confirmed the structure (II, R=Ph, R'alkyl).



## EXPERIMENTAL

*1,2-Dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-carboxyl-N-ethylamide* (II, R=Ph, R'=C<sub>2</sub>H<sub>5</sub>). 2,2-Dimethyl-4,5-dioxo-7-methoxy-3-ethyl-6-phenyl-2,3,5,6-tetrahydropyrido (3,4,e)-(1,3) oxazine (I, R=Ph, R'=C<sub>2</sub>H<sub>5</sub>), 3.2 g was added to NaOCH<sub>3</sub> in methanol (0.92 g Na/10 ml CH<sub>3</sub>OH) and was refluxed for 15 min. The solvent was removed under vacuum, the residue was dissolved in water and the aqueous solution was acidified with 2N HCl. The precipitate was filtered, washed with water and dried. The yield of pyridinoamide was 55%. When recrystallised from acetone, it gave needles, m.p. 148°. Found: C,62.88; H, 5.78; N,9.47% C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>; Requires: C,62.50; H,5.55; N,9.70%.

Several other 3N-alkyl substituted carboxyamides (II, R=Ph, R'=alkyl) were prepared and are listed in Table I.

*4,5-Dichloro 1,2-dihydro-6-methoxy-2-oxo-1-phenylpyridine-3-N-ethylcarboxyamide* (II). Compound (II R=Ph, R'=C<sub>2</sub>H<sub>5</sub>), (0.2 g) and POCl<sub>3</sub>, (3 ml) were refluxed on water bath under anhydrous conditions for 15 min. The excess of POCl<sub>3</sub> was removed under vacuum; the residue was triturated with water, filtered, dried and recrystallised from acetone, m.p. 160° (dec.). Found: C,52.55; H,4.66; N,8.09; Cl,20.85% C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>Cl<sub>2</sub>; requires: C,52.94; H,4.11; N,8.20; Cl,20.58%.

*5-Bromo-1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-N-ethylcarboxyamide* IV. Compound (II, R=Ph, R'=C<sub>2</sub>H<sub>5</sub>) 0.2 g was dissolved in chloroform and a dilute solution of bromine in chloroform was added, till a yellow colour persisted. The solution was kept at room temperature for 30 min. The solvent was removed under vacuum. The residue was recrystallised from chloroform: ether (1:1) has m.p. 180° (dec.). Found: C,48.83; H,3.83;

Table 2. UV and IR spectra of 1,2-Dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-N-alkyl substituted carboxyamides

S.No.	R'	UV light absorption 95% methanol		IR spectroscopic data in the region 3 μ 6.7 μ (KBr disc)	
		λ max m μ	log <sub>ε</sub>	NH (amido)	C=O (2)
1.	H <sub>2</sub> -	295	4.2	3475 m cm <sup>-1</sup> 3328)	1660 cm <sup>-1</sup>
2.	Methyl-	300	4.2	3325s cm <sup>-1</sup>	1660s cm <sup>-1</sup>
3.	Ethyl-	302	4.2	3080 cm <sup>-1</sup>	1660s cm <sup>-1</sup>
4.	Allyl-	300	4.3	3080 cm <sup>-1</sup>	1660 cm <sup>-1</sup>
5.	n-Propyl-	302	4.3	3350s cm <sup>-1</sup>	1680s) cm <sup>-1</sup> 1660s)
6.	n-Butyl-	304	4x3	3340s cm <sup>-1</sup>	1685s) cm <sup>-1</sup> 1655s) amido)
7.	n-Nonyl-	302	4.3	2930 cm <sup>-1</sup>	1670sb) cm <sup>-1</sup> 1660s )
8.	Cyclohexyl-	304	4.2	3365 cm <sup>-1</sup>	1670s) cm <sup>-1</sup> 1660s(amido)
9.	Benzyl-	300	4.2	3380 cm <sup>-1</sup>	1720) cm <sup>-1</sup> 1680(amido)
10.	β-Phenylethyl-	300	4.2	3355 cm <sup>-1</sup>	1685sb) cm <sup>-1</sup> 1680s )

Table 1. 1,2-Dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-N-alkyl substituted carboxyamides

S.No.	3-Alkyl substituted pyrido1,3 oxazines (I) R'	Quantity in g.	Sodium metal in methanol g/ml	4-Hydroxy-6-methoxy-1-phenylpyridine-3-substituted carboxyamides (II) R'	Yield %	Solvent for crystallization	m.p. °C.	Molecular formula	Analysis required (%)			Analysis found (%)		
									C	H	N	C	H	N
1.	H-	3.00	0.92/30 ml	H <sub>2</sub> -	60	Acetone petroleum ether	218° (dec.)	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	60.00	4.61	10.76	61.21	4.63	11.28
2.	Methyl-	3.14	0.92/30 ml	CH <sub>3</sub> -	55	" "	160° "	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	61.31	5.10	10.21	61.40	5.22	10.08
3.	Ethyl-	3.28	0.92/30 ml	CH <sub>3</sub> CH <sub>2</sub> -	55	" "	148°	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	62.50	5.55	9.70	62.88	5.78	9.47
4.	Allyl-	3.40	0.92/30 ml	CH <sub>2</sub> .CH.CH <sub>2</sub> -	40	" "	192°	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	64.00	5.33	9.33	64.32	5.45	9.65
5.	n-Propyl-	3.40	0.92/30 ml	CH <sub>3</sub> .CH <sub>2</sub> CH <sub>2</sub> -	50	" "	195°	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	63.57	5.96	9.27	63.55	5.97	9.29
6.	n-Butyl-	3.56	0.92/30 ml	CH <sub>3</sub> .CH <sub>2</sub> .CH <sub>2</sub> .CH <sub>2</sub> -	40	" "	187°	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	64.55	6.32	8.86	64.43	6.48	9.18
7.	n-Nonyl	4.26	0.92/30 ml	CH <sub>3</sub> .CH <sub>2</sub> .CH <sub>2</sub> .CH <sub>2</sub> -	40	" "	190°	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	68.39	7.77	7.25	68.65	8.05	7.56
8.	Cyclohexyl-	3.82	0.92/30 ml	C <sub>6</sub> H <sub>11</sub> -	60	" "	182°	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	66.66	6.43	8.18	66.72	6.63	7.79
9.	Benzyl-	3.90	0.92/30 ml	C <sub>6</sub> H <sub>5</sub> .CH <sub>2</sub> -	50	" "	145°	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	67.45	5.32	8.28	66.91	5.31	7.95
10.	β-Phenylethyl-	4.04	0.92/30 ml	C <sub>6</sub> H <sub>5</sub> .CH <sub>2</sub> .CH <sub>2</sub> -	50	" "	135°	C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	69.23	5.49	7.69	69.40	5.55	7.53

N,7.57; Br,21.79%  $C_{15}H_{15}N_2O_4Br$ ; Requires: C,49.05; H,4.08; N,7.63; Br,21.77%.

*1,2-Dihydro, 4,6-dimethoxy-2-oxo-1-phenylpyridine-3-N-ethylcarboxamide (V).* Compound (II, R=Ph, R'=C<sub>2</sub>H<sub>5</sub>) 0.5 g was dissolved in acetone, and diazomethane solution in ether was added, till the yellow colour of diazomethane persisted, the solution was kept in the cold for 1 hr. The solvent was removed under vacuum. The residue was recrystallised from acetone: petroleum ether (1:1) had mp. 200° (dec.). Found: C,63.50; H,6.04; N,9.24; -OCH<sub>3</sub>=21.42%  $C_{16}H_{18}N_2O_4$ ; Requires: C,63.57; H,5.96; N,9.27; -OCH<sub>3</sub>=20.5%.

*Methyl 1,2-dihydro, 4,6-dimethoxy-1-phenylpyridine-3-carboxylate (VII).* Compound (VI) 2,2-dimethyl-4,5-dioxo-7-hydroxy-6-phenylpyridino (3,4-e) (1,3)-dioxin, (5 g) was taken in methanol and solution of diazomethane in ether was added, till the yellow colour of the solution persisted. The solution was kept in the cold for 2 hr. The excess of solvent was removed under vacuum and residue was recrystallised from methanol, m.p. 195° (dec.). Found: C,63.81; H,5.82; N,4.95; -OCH<sub>3</sub>; 31.00%  $C_{15}H_{15}NO_5$ ; Requires: C,62.28; H,5.19; N,4.84; -OCH<sub>3</sub>; 32.17%.

*Reaction of N-methylamide (II, R=Ph, R'=CH<sub>3</sub>) with ethylamine.* The compound (II, R=Ph, R'=CH<sub>3</sub>) was dissolved in chloroform (10 ml) and ethylamine chloroform solution (20 ml; 2.5%) was added. It was refluxed under anhydrous conditions for 15 min. The solvent was removed under vacuum and the residue was triturated with ether. A white solid (0.3 g) was obtained and was recrystallised from acetone: ether mixture (1:1). It had m.p. 140° (dec.) and gave no colour with aqueous FeCl<sub>3</sub>. Found: C,60.00; H,6.1; N,13.4%  $C_{16}H_{20}N_3O_4$ ; Requires: C,60.37; H,6.28; N,13.20%.

The salt (III, R=Ph, R'=CH<sub>3</sub>) on treatment with an acidic solution of ethanol (50%) gave back the parent compound *N*-methyl amide (II, R=Ph, R'=CH<sub>3</sub>) m.p. and mixed m.p. 174-5°. Found: C,61.4; H,5.22; N,10.1  $C_{14}H_{14}N_2O_4$ ; Requires: C,61.31; H,5.10; N,10.1.

*Methyl 1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-carboxylate (VI, R=Ph, R'=CH<sub>3</sub>) from 1,2-Dihydro-4-hydroxy-6-methoxy-1-phenylpyridine-3-N-ethylcarboxamide (II, R=Ph, R'=C<sub>2</sub>H<sub>5</sub>).* To a solution of sodium methoxide in methanol (0.28 g Na/10 ml methanol), *N*-ethylamide (II, R=Ph, R'=Et) (0.2 g) was added and the solution refluxed for 40 min. The solvent was removed. The residue on diluting with water and on acidifying with (2N HCl), gave a white solid. It was crystallised from aqueous alcohol; m.p. 218° (dec.). Mixed m.p. with authentic sample gave no depression.

It gave a reddish brown colour with aqueous ferric chloride and dissolved in aqueous sodium bicarbonate solution. Found: C,61.2; H, 4.7; N,4.9; Calculated for  $C_{14}H_{13}NO_5$  C,61.1; H,4.7; N,5.1%.

*Ethyl 1,2-dihydro-4-hydroxy-6-methoxy-2-oxo-1-phenylpyridine-3-carboxylate (VI, R=Ph, R'=Et) from 1,2-Dihydro-4-hydroxy-6-methoxy-1-phenylpyridine-3-N-ethylcarboxamide (II, R=Ph, R'=Et).* *N*-Ethylamide (0.5 g) was added to sodium ethoxide in ethanol (0.28 g Na/10 ml ethanol) and the mixture was refluxed for 40 min. The solvent was removed and the residue was diluted with water. On acidifying the mixture with 2N-HCl, a solid was obtained and filtered. It was recrystallised from aqueous ethanol, m.p. 214° (dec.). It gave no depression in admixture with an authentic sample prepared earlier [2]. Found: C,62.10; H,5.08; N,4.62; Calculated for  $C_{15}H_{15}NO_5$  C,62.28; H,5.19; N,4.84%.

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## REFERENCES

1. A. Butt, Rashid Kemal and R. Parveen, Pakistan J. Sci. Ind. Res., **21**, 101 (1978).
2. A. Butt, S.M.A. Hai and I.A. Akhtar, Pakistan J. Sci. Ind. Res., **9**, 175 (1966)..