

SYNTHESIS OF SUBSTITUTED PYRIDINES

Part V.—Formation of 6-Hydroxy-4-(*o,m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-Carboxyanilides

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The formation of *N*-substituted pyridine-3-carboxyanilides (the substituent at position 1, being phenyl, *o*, *m*, *p*-tolyl, *o*, *m*, *p*-methoxyphenyl, benzyl, and α -naphthyl, β -naphthyl; while the substituent at position 4, being *o*-methylphenoxy and *m*-methylphenoxy respectively) was achieved in yields 50–90%. In support of structure II, various chemical transformations were carried out.

The transformation of aminopyranooxazines I, into 4-phenoxy pyridine-3-carboxyanilides (II, R=R'=aryl, R''=Ph) has been reported.¹ Details of the reaction discussed in Part IV made it appear likely that other substituted or unsubstituted aryloxy compounds would react similarly. This was found so. For instance when *o*-methylphenoxy, obtained by reacting *o*-cresol with sodium and aminopyranooxazine (I, R=R'=Ph), were heated in *o*-cresol as solvent, a new product C₂₅H₂₀N₂O₄ (II, R=R'=Ph, R''=*o*-tolyl) m.p. 180°, enolic in nature, easily soluble in basic solutions, was formed. An analogous situation was observed when the product (I, R=R'=Ph) was reacted with *m*-methylphenoxy in *m*-cresol to yield a product, C₂₅H₂₀N₂O₄ (II, R=R'=Ph, R''=*m*-tolyl) m.p. 195°, isomeric with the above compound. The latter has similar physical properties as the previous compound. Several products resembling these compounds were prepared and are recorded in Table I, along with their UV and IR spectroscopic measurements.

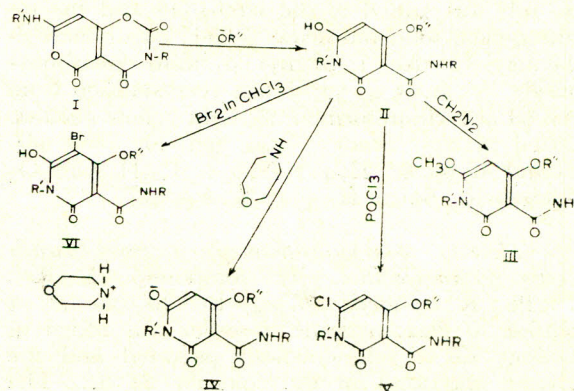
TABLE I.—UV AND IR SPECTRA OF 4-ARYLOXY-6-HYDROXY-2-OXO-1-PHENYLPYRIDINE-3-CARBOXYANILIDES (II).

R	R'	R''	λ_{\max} m μ (95% ethanol)	log ϵ	ν_{\max} (cm ⁻¹) (Nujol mulls)
(C=O at 2)					
Ph	Phenyl	<i>o</i> -Tolyl	318	4.76	1681s
Ph	<i>o</i> -Tolyl	<i>o</i> -Tolyl	321	4.66	1667s
Ph	<i>m</i> -Tolyl	<i>o</i> -Tolyl	319	4.51	1681s
Ph	<i>p</i> -Tolyl	<i>o</i> -Tolyl	319	4.54	1681s
Ph	<i>o</i> -Methoxyphenyl	<i>o</i> -Tolyl	320	4.45	1667s
Ph	<i>m</i> -Methoxyphenyl	<i>o</i> -Tolyl	319	4.56	1667s
Ph	<i>p</i> -Methoxyphenyl	<i>o</i> -Tolyl	321	4.78	1672s
Ph	Benzyl	<i>o</i> -Tolyl	318	4.51	1681s
Ph	α -Naphthyl	<i>o</i> -Tolyl	319	4.52	1681s
Ph	β -Naphthyl	<i>o</i> -Tolyl	320	4.41	1672s
Ph	Phenyl	<i>m</i> -Tolyl	321	4.54	1678s
Ph	<i>o</i> -Tolyl	<i>m</i> -Tolyl	322	4.53	1667s
Ph	<i>m</i> -Tolyl	<i>m</i> -Tolyl	322	4.51	1681s
Ph	<i>o</i> -Methoxyphenyl	<i>m</i> -Tolyl	322	4.53	1667s
Ph	<i>m</i> -Methoxyphenyl	<i>m</i> -Tolyl	322	4.51	1667s
Ph	<i>p</i> -Methoxyphenyl	<i>m</i> -Tolyl	323	4.53	1667s
Ph	Benzyl	<i>m</i> -Tolyl	322	4.45	1661s
Ph	α -Naphthyl	<i>m</i> -Tolyl	322	4.47	1661s
Ph	β -Naphthyl	<i>m</i> -Tolyl	322	4.56	1669s

It was further noted that the product C₂₅H₂₀N₂O₄ (II, R=R'=Ph, R''=*o*-tolyl) on reacting with phosphorus oxychloride, formed a monochloro product with a formula C₂₅H₁₉ClN₂O₃ (V, R=R'=Ph, R''=*o*-tolyl) m.p. 245°, λ_{\max} 322, log ϵ 3.98. The compound was evidently produced by the removal of one hydroxyl group at position 6. Similarly it (II, R=R'=Ph, R''=*o*-tolyl) was methylated with diazomethane to give a compound C₂₈H₂₂N₂O₄ (III, R=R'=Ph, R''=*o*-tolyl) m.p. 238°, neutral in character, λ_{\max} 319, log ϵ 4.39. On treatment with bromine in chloroform, the compound (II, R=R'=Ph, R''=*o*-tolyl) gave a monobromo product, C₂₅H₁₉BrN₂O₄ (VI) m.p. 166°, formed by the removal of a proton present at position 5, λ_{\max} 299, log ϵ 3.91. The compound was enolic in nature, easily soluble in basic solution and thus resembled the parent product in its physical properties.

With morpholine in chloroform the compound (II, R=R'=Ph, R''=*o*-tolyl) formed easily a water-soluble morpholinium salt, C₂₉H₂₉H₃O₅ (IV, R=R'=Ph, R''=*o*-tolyl) m.p. 165° λ_{\max} 322, log ϵ 4.69.

Similarly, the product (II, R=R'=Ph, R''=*m*-tolyl) gave a morpholinium salt, C₂₉H₂₉H₃O₅.



(IV, R=R'=Ph, R''=m-tolyl) m.p. 163°, λ_{\max} 325, $\log \epsilon=4.5$. A 6-methoxy product C₂₆H₂₂N₂O₄ (III, R=R'=Ph, R''=m-tolyl) m.p. 219°, λ_{\max} 322, $\log \epsilon=4.4$ and a 5-bromo-product C₂₅H₁₉BrN₂O₄ (VI, R=R'=Ph, R''=m-tolyl) m.p. 190° that was enolic in nature. The chemical transformations described support structure II and are depicted diagrammatically.

Experimental

6-Hydroxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—7-Anilino-2,4,5-trioxo-3-phenyl-(3,4-e)-pyrano-(1,3) oxazine I (1.85 g; 1 mole) was added to a solution of sodium (0.6 g; 4 mole) in 25 ml *o*-cresol at a temperature of 110-120° and kept as such for 5 min. The dark brown solution was cooled, diluted with water (200 ml) and extracted with ether to remove excess of *o*-cresol. On acidifying the aq. solution with 2N HCl, 6-hydroxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide II (1.6 g, 86%) was obtained which crystallized from MeOH-Chf (2:1), melted at 180° (dec). (Found: C, 72.3; H, 4.8; N, 6.8 C₂₅H₂₀N₂O₄ requires: C, 72.8; H, 4.8; N, 6.8%).

6-Hydroxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—It was prepared from 7-anilino-2,4,5-trioxo-3-phenyl-(3,4-e)-pyrano (1,3)-oxazine (1.8 g; 1 mole) and a solution of sodium (0.6 g; 4 mole) in *m*-cresol (25 ml) in the above fashion. 6-Hydroxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide (II, R=R'=Ph, R''=m-tolyl) crystallised from Chf-MeOH (1:2), had m.p. 195°. It was enolic in character. (Found: C, 72; H, 5.1; N, 6.7. C₂₅H₂₀N₂O requires: C, 72.8; H, 4.9; N, 6.8%).

6-Chloro-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—Compound II (R=R'=Ph; R''=o-tolyl) (0.1 g) and POCl₃ (3 ml) were refluxed for 15 min. The excess of POCl₃ was removed under reduced pressure. On cooling, water (20 ml) was added to the semi-solid and the resulting clear solid was dried. 6-Chloro-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide (V; 0.05 g, 50%) was recrystallised from MeOH and chloroform (1:1), light yellow needles, melted at 245° (dec) λ_{\max} 322, $\log \epsilon=3.98$. (Found: C, 69.4; H, 4.7; N, 6.1. C₂₅H₁₉ClN₂O₃ requires: C, 69.7; H, 4.4; N, 6.5%).

6-Methoxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—To compound II (R=R'=Ph, R''=o-tolyl) (0.5 g) in Chf (20 ml) a solution of diazomethane in ether was added in portions till a yellow colour persisted and the mixture was kept in the cold for 24 hr. The

TABLE 2.—4-ARYLOXY-6-HYDROXY-1-SUBSTITUTED PYRIDINE-3-CARBOXYANILIDES (II).

Aminopyrano oxazine (I) R	Amount of Na/ <i>o</i> -Cresol ml	Product II			Yield	Solvent for crystallisation	m.p.	Formula of product II	N%	
		R	R'	R''					Found	Required
Ph	2.8 g	Ph	<i>o</i> -Tolyl	<i>o</i> -Tolyl	91	MeOH:CHCl ₃	175	C ₂₆ H ₂₂ N ₂ O ₄	6.9	6.5
Ph	3.2 g	Ph	<i>m</i> -Tolyl	<i>o</i> -Tolyl	81	MeOH	170	C ₂₆ H ₂₂ N ₂ O ₄	6.8	6.6
Ph	3.0 g	Ph	<i>p</i> -Tolyl	<i>o</i> -Tolyl	93	MeOH	178	C ₂₆ H ₂₂ N ₂ O ₄	6.8	6.6
Ph	2.5 g	Ph	<i>o</i> -Methoxyphenyl	<i>o</i> -Tolyl	50	MeOH:CHCl ₃	200	C ₂₆ H ₂₂ N ₂ O ₅	6.6	6.3
Ph	3.0 g	Ph	<i>m</i> -Methoxyphenyl	<i>o</i> -Tolyl	85	MeOH:CHCl ₃	182	C ₂₆ H ₂₂ N ₂ O ₅	6.5	6.3
Ph	3.0 g	Ph	<i>p</i> -Methoxyphenyl	<i>o</i> -Tolyl	36	MeOH:CHCl ₃	205	C ₂₆ H ₂₂ N ₂ O ₅	6.6	6.3
Ph	3.0 g	Ph	Benzyl	<i>o</i> -Tolyl	50	MeOH:CHCl ₃	157	C ₂₆ H ₂₁ N ₂ O ₄	6.9	6.6
Ph	3.0 g	Ph	α -Naphthyl	<i>o</i> -Tolyl	40	MeOH:CHCl ₃	210	C ₂₉ H ₂₂ N ₂ O ₄	6.4	6.1
Ph	3.0 g	Ph	β -Naphthyl	<i>o</i> -Tolyl	75	MeOH:CHCl ₃	207	C ₂₉ H ₂₂ N ₂ O ₄	6.3	6.1
Ph	3.6 g	Ph	<i>o</i> -Tolyl	<i>m</i> -Tolyl	73	MeOH:CHCl ₃	211	C ₂₆ H ₂₂ N ₂ O ₄	6.7	6.6
Ph	3.6 g	Ph	<i>m</i> -Tolyl	<i>m</i> -Tolyl	80	MeOH:CHCl ₃	177	C ₂₆ H ₂₂ N ₂ O ₄	6.7	6.6
Ph	3.6 g	Ph	<i>p</i> -Tolyl	<i>m</i> -Tolyl	88	MeOH:CHCl ₃	204	C ₂₆ H ₂₂ N ₂ O ₄	6.6	6.6
Ph	3.5 g	Ph	<i>o</i> -Methoxyphenyl	<i>m</i> -Tolyl	92	MeOH:CHCl ₃	208	C ₂₆ H ₂₂ N ₂ O ₅	6.5	6.3
Ph	3.5 g	Ph	<i>m</i> -Methoxyphenyl	<i>m</i> -Tolyl	80	MeOH:CHCl ₃	210	C ₂₆ H ₂₂ N ₂ O ₅	6.6	6.3
Ph	3.5 g	Ph	<i>p</i> -Methoxyphenyl	<i>m</i> -Tolyl	60	MeOH:CHCl ₃	223	C ₂₆ H ₂₂ N ₂ O ₅	6.4	6.3
Ph	3.0 g	Ph	Benzyl	<i>m</i> -Tolyl	57	MeOH:CHCl ₃	201	C ₂₆ H ₂₁ N ₂ O ₄	6.8	6.6
Ph	3.9 g	Ph	α -Naphthyl	<i>m</i> -Tolyl	74	MeOH:CHCl ₃	230	C ₂₉ H ₂₂ N ₂ O ₄	6.1	6.1
Ph	3.9 g	Ph	β -Naphthyl	<i>m</i> -Tolyl	61	MeOH:CHCl ₃	232	C ₂₉ H ₂₂ N ₂ O ₄	6.0	6.1

excess of solvent was evaporated off and the residue on trituration with ether gave 6-methoxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide (IV) (0.2 g; 40%) after recrystallisation with MeOH-Chf, it yielded colourless crystals, m.p. 238° (dec), λ_{\max} 319, $\log \epsilon=4.39$. (Found: C, 73.7; H, 5.2. $C_{26}H_{22}N_2O_4$ requires: C, 73.2; H, 5.2; N, 6.6%.)

6-Methoxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—Treatment of compound II ($R=R'=Ph$, $R''=m$ -tolyl) (0.5 g) in Chf (25 ml) and diazomethane in ether in the above manner of preparing compound IV, gave 6-methoxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide (III, $R=R'=Ph$, $R''=m$ -tolyl) (0.25 g; 45%), which was crystallised from MeOH-Chf, m.p. 219°. (Found: C, 73.1; H, 5.3; N, 6.7. $C_{26}H_{22}N_2O_4$. C, 73.2; H, 5.2; N, 6.6%.)

5-Bromo-6-hydroxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—To compound II ($R=R'=Ph$, $R''=o$ -tolyl) (0.2 g) in Chf (10 ml), Br_2 in CCl_4 (5 ml) was added. The reaction mixture was shaken and kept at room temperature for 30 min. The excess of solvent was evaporated off and the solid 5-bromo-6-hydroxy product VI, ($R=R'=Ph$, $R''=o$ -tolyl) (0.1 g; 50%) was recrystallised from Chf-ether in colourless crystals, m.p. 165-166° (dec). (Found: C, 60.9; H, 3.9; N, 5.7. $C_{25}H_{19}BrN_2O_4$ requires: C, 61.2; H, 3.9; N, 5.7%.)

5-Bromo-6-hydroxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide.—Compound II ($R=R'=Ph$, $R''=m$ -tolyl) (0.5 g) in Chf (25 ml) was treated with Br_2 in CCl_4 in the manner described above for compound VI. The resulting 5-bromo-6-hydroxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide VI ($R=R'=Ph$,

$R''=m$ -tolyl) (0.3 g, 50%) was recrystallised from Chf-ether in colourless needles, m.p. 190°. (Found: C, 61.6; H, 3.8; N, 5.4. $C_{25}H_{19}N_2O_5Br$ requires: C, 61.2; H, 3.9; N, 5.7%.)

Reaction of 6-Hydroxy-4-(*o*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide with Morpholine.—To compound II ($R=R'=Ph$, $R''=o$ -tolyl) (0.5 g) was added Chf (15 ml) and morpholine (0.5 ml) and the mixture refluxed for 30 min. The excess of solvent was removed under reduced pressure and the semi-solid triturated with ether. The morpholinium salt IV ($R=R'=Ph$, $R''=o$ -tolyl) (0.43 g, 85%) was recrystallised from methanol-ether mixture as colourless crystals, m.p. 165-166° (dec) λ_{\max} 322, $\log \epsilon=4.69$. (Found: C, 69.5; H, 5.9; N, 8.9; $C_{29}H_{29}N_3O_5$ requires: C, 69.7; H, 5.8; N, 8.4%.)

Reaction of 6-Hydroxy-4-(*m*-methylphenoxy)-2-oxo-1-phenylpyridine-3-carboxyanilide with Morpholine.—In an analogous manner as above, compound II ($R=R'=Ph$, $R''=m$ -tolyl) (0.5 g) in Chf (15 ml) with morpholine (0.5 ml) gave the morpholinium salt IV, ($R=R'=Ph$, $R''=m$ -tolyl) (0.43 g, 85%), which was crystallised from MeOH, m.p. 163° (dec). (Found: N, 8.7. $C_{29}H_{29}N_3O_5$ requires: N, 8.4%.)

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Reference

1. M.A. Butt and I.A. Akhtar, *Tetrahedron*, **23**, 1551 (1967).