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SYNTHESIS OF SUBSTITUTED PYRIDINES—III

FORMATION OF 6-HYDROXY-4-PHENOXY-2-OXO-1-SUBSTITUTED (ALKYL OR ARYL) PYRIDINE-3-CARBOXYANILIDES

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Abstract—6-Hydroxy-4-phenoxy-2-oxo-1-substituted (alkyl or aryl) pyridine-3-carboxyanilides have been synthesized from 7-amino-2,4,5-trioxo-3-phenylpyrano(3,4-e)-(1,3)-oxazines with sodium phenoxide in phenol. Chemical transformations, IR and UV spectroscopic data supported the structure of the product.

Isomerization of amino-pyrano-1,3-dioxines(I) into pyridino-dioxines(II) with sodium phenoxide has been reported.[1] Isomerization of amino-pyrano-oxazines(III) into pyridino-oxazines of the type IV with sodium phenoxide under comparable conditions has now been examined and the products identified as monocyclic derivatives of the pyridine(VI).

7-Anilino-2,4,5-trioxo-3-phenylpyrano(3,4-e)-(1,3)-oxazine (III, R = R′ = Ph), for example, when heated with sodium phenoxide in phenol, formed a product $C_{24}H_{18}N_2O_4$ (VI, R = Ph) m.p. 212 (dec) which was not isomeric with the parent substance. It contained at least one enolic group (brown colouration with aq. ferric chloride) and dissolved in aqueous sodium bicarbonate solution. It was stable towards organic solvents, dilute alkalies and acids.

Other products VI formed similarly are listed in Table 1.

Table 1. UV and IR spectra of pyridino-carboxyanilides(VI)

S. No.	Pyridino-carboxyanilides(VI) R′	R	UV (95% EtOH) λ_{max} mμ	Log ϵ	IR ν_{max} (cm^{-1}) (Nujol mulls) C=O (2) and anilido
1.	Phenyl-	Ph	321	4·51	1681s
2.	*o*-Tolyl-	Ph	322	4·50	1669s
3.	*m*-Tolyl-	Ph	322	4·55	1667s
4.	*p*-Tolyl-	Ph	320	4·54	1672s
5.	*o*-Methoxyphenyl-	Ph	322	4·55	1667s
6.	*m*-Methoxyphenyl-	Ph	321	4.60	1667s
7.	*p*-Methoxyphenyl-	Ph	322	4·60	1672s
8.	*m*-Hydroxyphenyl-	Ph	322	4·61	1667s
9.	Isobutyl-	Ph	322	4·50	1667s
10.	Allyl-	Ph	322	4·45	1669s

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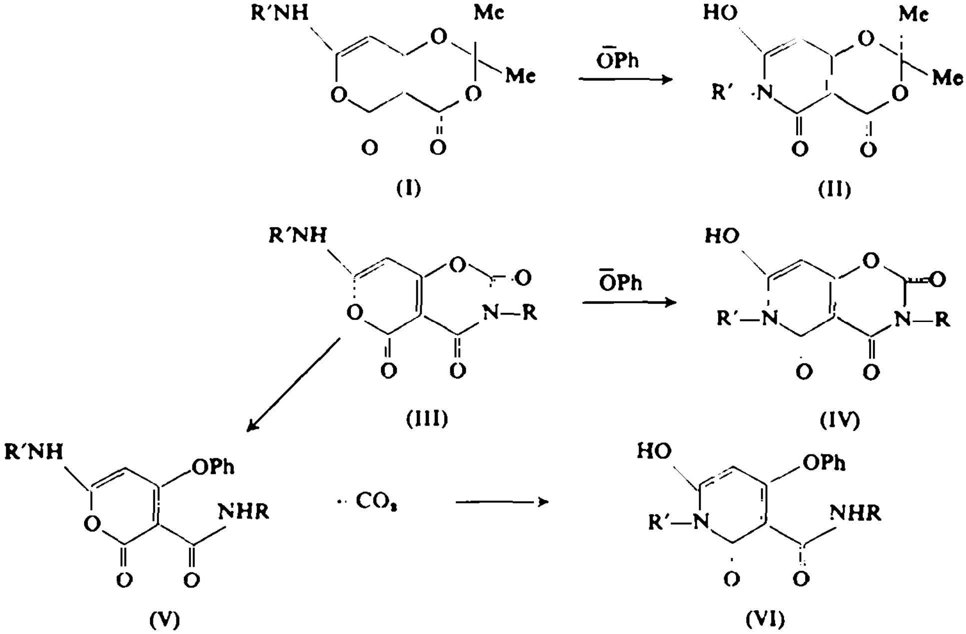
[1] M. A. Butt and I. A. Akhtar, *Tetrahedron* 21, 1917–1922 (1965).

These new products have characteristic UV absorption in the region λ_{max} 322–323 mμ; log ε, 4·4–4·6 and therefore, they resemble 2-pyridones.[2] The formation of these products could be represented as follows:

Chart "A"



Although structures V and VI could be considered, formula V was discounted for the following reasons:

(1) The UV absorption max of aminopyrones[3] of type V is in the range λ_{max} 335–345 mμ but in the case of these products it is λ_{max} 322 mμ, characteristic of 2-pyridones.[2]

(2) The absorption frequency in the IR spectra for the 2-carbonyl of the products V in general[3] lies near ν 1770 cm^{-1} but the new products invariably absorb near ν 1669 cm^{-1}, which is in keeping with the C=O of 2-pyridones.[2]

(3) In the IR spectra there is a bonded OH absorption in the region ν 2500 cm^{-1} which the formula V does not explain. Moreover, the ferric chloride colour test indicates structure VI which is further supported by the following chemical transformation.

The product $C_{24}H_{18}N_2O_4$ (VI, R = R' = Ph) when treated with diazomethane, yielded a methyl ether $C_{25}H_{20}N_2O_4$ (VII, R = R' = Ph) m.p. 233°, neutral in character and absorbed UV in the region λ_{max} 314–315 mμ, log ε, 4·47. In the IR, it absorbed at the ν 1689 cm^{-1} due to the anilido substituent at position 3 and due to the 2-carbonyl. It (VI, R = R' = Ph) reacted with morpholine and produced an addition product $C_{28}H_{27}N_3O_5$ (VIII, R = R' = Ph), m.p. 163°, UV λ_{max} 322 mμ, log ε, 4·52.

On treatment with phosphorous oxychloride, it gave a chloro-product $C_{24}H_{17}N_2O_3Cl$

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[2] M. A. Butt, I. A. Akhtar and Malika Akhtar, *Tetrahedron* **23**, 199 (1967).

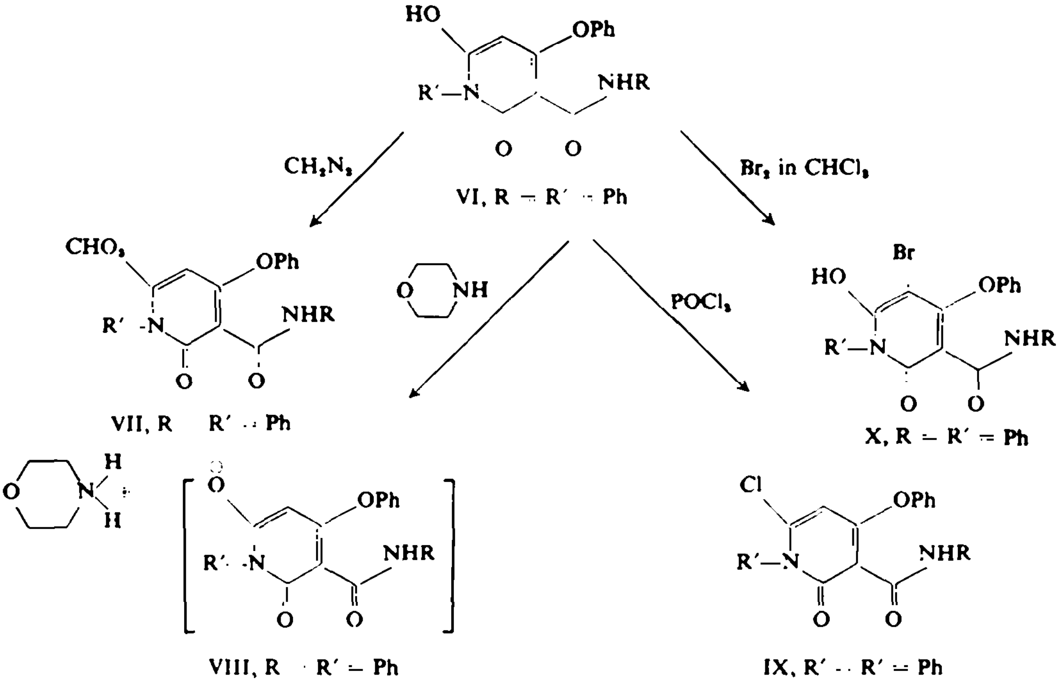
[3] S. J. Davis, J. A. Elvidge, *J. Chem. Soc.* 3554 (1962).

(IX, R = R′ = Ph), m.p. 190 with UV characteristic absorption at λ_{max} 326 mμ, log ε, 4·4, formed by the replacement of an OH group.

On bromination it gave a monobromo product $C_{24}H_{17}N_2BrO_4$ m.p. 194° UV λ_{max} 345 mμ, log ε, 4·53. IR spectra at ν 1678 cm^{-1} attributable to 2-carbonyl position and due to anilido group at position 3.

The foregoing reactions can be represented as follows:

Chart "B"



The formation of the product could be explained by the following mechanism:

Chart "C"

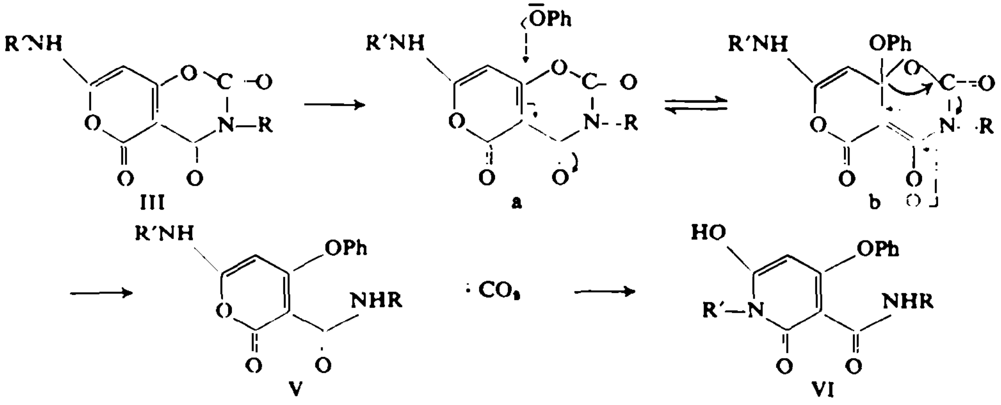
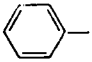
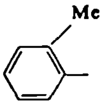
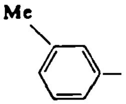
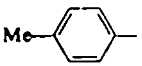
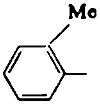
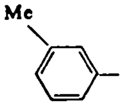
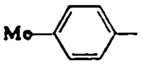
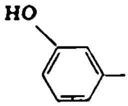
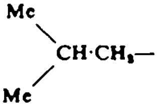


TABLE 2.

	Amino-pyrano (1,3)-oxazine (III)			Sodium in phenol	4-Phenoxy-6-hydroxy-1-substituted-3-carboxyanilide (VI)			Solvent for
No.	R′	R	quantity in g	g/ml	R′	R	Yield %	crystallization
1.		Ph	3·5	1·2/12	Phenyl-	Ph	75	MeOH
2.		Ph	3·4	1·0/10	*o*-Tolyl-	Ph	66	MeOH
3.		Ph	3·4	1·0/10	*m*-Tolyl-	Ph	66	MeOH
4.		Ph	3·4	1·0/10	*p*-Tolyl-	Ph	68	MeOH
5.		Ph	3·5	1·2/12	*o*-Methoxyphenyl-	Ph	72	MeOH
6.		Ph	3·5	1·2/12	*m*-Methoxyphenyl-	Ph	72	MeOH
7.		Ph	3·5	1·2/12	*p*-Methoxyphenyl-	Ph	67	MeOH
8.		Ph	3·0	1·0/10	*m*-Hydroxyphenyl-	Ph	51	MeOH
9.	$CH_2{=}CH{\cdot}CH_2{-}$	Ph	3·1	1·0/10	Allyl-	Ph	50	MeOH
10.		Ph	3·3	1·1/12	Isobutyl-	Ph	53	MeOH

			Analysis					
				Found			Required	
No.	M.p.	Formula	C	H	N	C	H	N
1.	212	$C_{24}H_{18}N_2O_4$	72·2	4·6	7·1	72·3	4·7	7·1
2.	220	$C_{25}H_{20}N_2O_4$	—	—	6·9	—	—	6·8
3.	218	$C_{25}H_{20}N_2O_4$	—	—	7·0	—	—	6·8
4.	198	$C_{25}H_{20}N_2O_4$		—	6·9	—	—	6·8
5.	211	$C_{25}H_{20}N_2O_5$	—	—	6·8	—	—	6·6
6.	199	$C_{25}H_{20}N_2O_5$			6·7	—	—	6·6
7.	202	$C_{25}H_{20}N_2O_5$		—	6·6	—	—	6·6
8.	225	$C_{24}H_{18}N_2O_5$	—	—	6·8	—	—	6·8
9.	143	$C_{21}H_{18}N_2O_4$	—		7·7	—	—	7·9
10.	132	$C_{22}H_{22}N_2O_4$	—		7·4	—	—	7·5

It appears that the strong nucleophile (Phŏ) attacks at the electron deficient position (8a) with the concomitant expulsion of CO_2 leading to the formation of an intermediate V, which then isomerizes into the product VI in the manner previously described.[1] The product V could not be isolated in spite of several attempts, and thus it has to be assumed that under the reaction conditions, the step V to VI is extremely rapid.

EXPERIMENTAL

All the amino-pyrano-oxazines(III) were prepared as described previously.[8]

6-Hydroxy-4-phenoxy-2-oxo-1-phenylpyridine-3-carboxyanilide (VI, R = R′ = Ph). Compound III (R = R′ = Ph; 3·5 g; 1 mole) and Na (1·2 g; 4 moles) in phenol (12 ml) was refluxed for 3–5 min at 120°. The soln was diluted with water (250 ml) and excess phenol separated with ether. The aqueous soln on acidification with 2N HCl gave *6-hydroxy-4-phenoxy-2-oxo-1-phenyl pyridine-3-carboxyanilide* (3·0 g; 75%) which crystallized form MeOH. m.p. 212, enolic in nature. (Found C, 72·2; H, 4·6; N, 7·1. $C_{24}H_{18}N_2O_4$, requires: C, 72·3; H, 4·7; N, 7·1%.) Other *6-hydroxy-4-phenoxy-2-oxo-1-substituted-pyridine-3-carboxyanilides* (VI) are described in Table 2.

6-Methoxy-4-phenoxy-2-oxo-1-phenylpyridine-3-carboxyanilide. Compound VI (R = R′ = Ph; 0·7 g) dissolved in Chf (50 ml) was mixed with diazomethane in ether till a yellow colour persisted. The soln was allowed to remain at room temp for 48 hr and then the unreacted diazomethane was destroyed by conc. HCl. The organic layer was separated, dried over Na_2SO_4 and solvent recovered. The *6-methoxy* product VII (0·4, 50%) was recovered from the residue. It was crystallized from MeOH, m.p. 233° (dec). It was neutral to $NaHCO_3$aq and gave no colouration with $FeCl_3$aq. (Found: C, 72·8; H, 4·9; N, 6·9. $C_{25}H_{20}N_2O_4$ requires: C, 72·7; H, 4·8; N, 6·8%.)

Morpholium salt of 6-hydroxy-4-phenoxy-2-oxo-1-phenyl pyridine-3-carboxyanilide [VIII]. Compound VI (R = R′ = ph; 0·8 g), morpholine (2 ml) and Chf (20 ml) were refluxed for ½ hr. The soln was freed from excess solvent. The residual liquid was mixed with MeOH (2 ml) and diluted with excess ether (50 ml). On keeping overnight it deposited crystals of VIII (0·6 g, 60%), m.p. 163° (methanol–ether), (Found: N, 8·8. $C_{28}H_{27}N_3O_5$ requires: N 8·7%.)

6-Chloro-4-phenoxy-2-oxo-1-phenylpyridine-3-carboxyanilide (IX). Compound VI (R = R′ = Ph; 0·5 g) and $POCl_3$ (20 ml) were refluxed for 30 min. Excess chloride was removed under reduced press and the residue triturated with water. The solid product (0·51 g, 90%) was recrystallized from MeOH as coloured crystals, m.p. 190°, no colour with $FeCl_3$aq. (Found: N, 6·8. $C_{24}H_{17}N_2O_3$ requires: N, 6·7.)

5-Bromo-6-hydroxy-4-phenoxy-2-oxo-1-phenylpyridine-3-carboxyanilide (X). Compound VI (R = R′ = Ph; 0·5 g) was dissolved in Chf (15 ml). To this soln was added Br (dissolved in Chf), till a brown colour persisted. The soln was freed from solvent and the residue triturated with water, and filtered. The product V (0·4 g, 67%) crystallised from Chf–MeOH (1:2) in needles, m.p. 194° (dec). (Found: C, 59·9; H, 3·7; N, 5·8. $C_{24}H_{17}N_2O_4Br$ requires: C, 60·4; H, 3·6; N, 5·9%.)

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