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SYNTHESIS OF SUBSTITUTED PYRIDINES

Part VII. Formation of 1,2-Dihydro-6-hydroxy-2-oxo-4-(thiophenyl)-1-substituted-pyridine-3-carboxyanilides

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Abstract. Sodium thiophenoxide in thiophenol reacts with aminopyranooxazines (I) to yield 1-substituted derivatives of 1,2-dihydro-6-hydroxy-2-oxo-4-thiophenylpyridine-3-carboxyanilide (III). Chemical conversions alongwith IR and UV data are provided to support the structural formulation (III) of the new products.

Aminopyranooxazines (I) and nucleophiles (phenoxide, cresoxide) interacted to form monocyclic products[1] of the structure (II). Now their reaction with thiophenoxide has been investigated and the end products were found definitively to be thioethers of the type (III).

For instance, the 7-anilino compound (I, R=R' =Ph) when treated with sodium thiophenoxide in thiphenol at 180° gave a thio product $C_{24}H_{18}N_2O_3S$, m.p. 154°. This decomposed with loss of thiophenol characterisable by its distinct odour, and by analysis of the residual product. It was enolic in nature ($FeCl_3$ test) and readily dissolved in sodium bicarbonate solution. The new product (III, R= R'=R″=Ph) absorbed UV light at λ_{max} 339, log ε, 4.5; i.e. at 18 μ longer wavelength than that of an oxygen analogue (III, R=R'=Ph) caused by the sulphur atom and its substituents as noted earlier.[2] In the IR absorption spectrum, the compound (III,R=R'=Ph) absorbed at a frequency *v* 1654 cm-1 attributable to the presence of C=O at 2 (pyridonecarbonyl) and 3 (anilido).

On reacting the product (II, R=*m*-tolyl, R'=R″=Ph) with diazomethane and ethyl chlorocarbonate, a methoxy derivative $C_{26}H_{22}N_2O_3S$ (V,R=*o*-tolyl, R'=R″=Ph), m.p. 234° (decomp), λ_{max} 330 log ε, 4.5, and 6-carboethoxy derivative $C_{27}H_{24}N_2O_3S$ (XI, R=*m*-tolyl, R'=R″=Ph), m.p. 147° (decomp), λ_{max}, 333; log ε 4.5, were formed respectively. Both were neutral in character and did not dissolve in bicarbonate solution in agreement with the structure. Reaction of $POCl_3$ with the compound (III, R=*m*-tolyl; R'=R″=Ph), produced a monochloro product $C_{25}H_{19}ClN_2O_2S$ (VI, R=tolyl, R'=R″=Ph), m.p. 259° (decomp), λ_{max} 335; log ε 4.4. It gave no colouration with $FeCl_3$ but with thionyl chloride it (III, R=*m*—tolyl; R'=R″=Ph) gave a dichloro product $C_{25}H_{18}Cl_2N_2O_2S$, which showed no $FeCl_3$ colour, was insoluble in bicarbonate solution, and was presumably formed by substitution at the 5- and 6- positions and was, therefore, assigned the formula (VII, R=*m*-tolyl; R'=R″=Ph).

Furthermore, the product (III, R=*m*-tolyl, R'=R″=Ph) with ammonia and morpholine gave ammonium (X, R=*m*-tolyl, R'=R″=Ph) and morpholinium salts. On bromination, only a monobromo product $C_{25}H_{24}BrN_2O_3S$ was recovered that was enolic in nature and was assigned the structure (IX, R=*m*-tolyl, R'=R″=Ph) accordingly. Final proof of the structure (III) was obtained when treatment of the product (III, R=*m*-tolyl, R'=R″=Ph) with acidic methanol gave a compound $C_{20}H_{18}N_2O_4$, known[3] already and now formed by the hydrolysis of the thiophenyl group at the 4-position with simultaneous methylation of the 6-hydroxyl group.

It may further be mentioned here that preparation of alkyl ethers of the type (II, R=R'=R″=Ph, R″=CH_3) was not achieved through this procedure because the reaction of methoxide with the anilinopyranooxazine (I, R=R'=Ph) in absolute methanol invariably gave the dihydroxy compound (II, R=R'= Ph, R″=H) (Table 1).

Experimental

All the aminopyranooxazines (I) were synthesised as described earlier.[4]

1,2-Dihydro-6-hydroxy-2-oxo-1-phenyl-4-thiophenylpyridine Carboxyanilide. (III,R=R'=R″=Ph). Aminopyranooxazine (I, R=R'=Ph) (2 g; 1 mol.) and sodium (0.7 g; 5 ml) in thiophenol (40 ml) were refluxed under anhydrous conditions at 168-170°C for 3 hr. The mixture was cooled, diluted with water (500 ml) and the thiophenol compound (III, R=R'=R″=Ph) (1.45 g; 61.5%) was obtained on acidification with 2N HCl. From chloroform-methanol mixture, the product crystallised with a molecule of CH_3OH and it melted at 153.5° (decomp). It was enolic in nature and dissolved in bicarbonate solution. (Found: C, 66.9; H, 4.4; N, 6.8; S, 7.1.%. $C_{24}H_{18}N_2O_3S$. CH_3OH requires: C, 67.3; H, 4.9; N, 6.3; S, 7.2%.) Other products (III) were prepared in an analogous manner and the results are recorded in Table 2.

1,2-Dihydro-6-chloro-2-oxo-4-thiophenyl-1-(m-tolyl) pyridine-3-carboxyanilide. The compound (III, R=*m*-tolyl, R'=R″=Ph) 100 mg and $POCl_3$ (3 ml) were heated under reflux for 1/2 hr. Excess of $POCl_3$ was removed under reduced pressure and the residue was titurated with water. The solid was titurated with ether. The product (100 mg) was recrystallised

* Part VI. Pakistan J. Sci. Ind. Res., 13, 212 (1970).

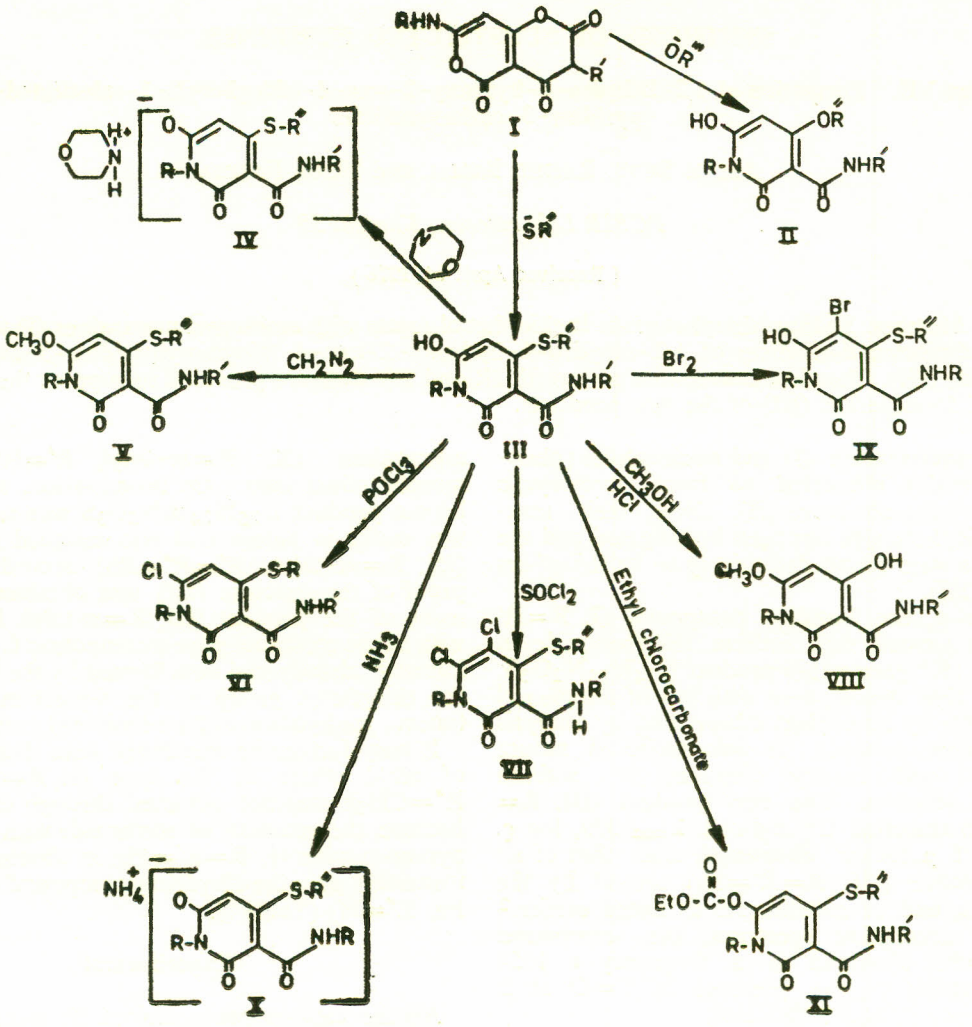

TABLE 1. UV AND IR SPECTRA OF AMIDO PYRIDONES (III.)

1,2-Dihydro-6-hydroxy-2-oxo-4-thiophenyl-1-substituted-pyridine-carboxyanilides (III) R	UV light absorption (95% methanol) λ_{max}	log ε	IR absorption (region 3-6.7) ν_{max} cm^{-1} (C=O at 2 and anilide).	(Hydroxyl, bonded)
Phenyl	339	4.51	1654, 1667	2500, 2680 wb
o-Tolyl	339	4.51	1657	2500, 2600
m-Tolyl	339	4.50	1658	2540, 2622
p-Methoxyphenyl	338	4.50	1660	2500, 2600
m-Methoxyphenyl	339.5	4.43	1626	2560, 2620 wb
p-Chlorphenyl	339.5	4.50	1660	2500, 2600 wb
p-Bromophenyl	336	4.55	1660	2540, 2618 wb
p-Tolyl	337	4.44	1670	2540, 2640 wb
α-Naphthyl	337	4.45	1660	2540, 2640 eb

TABLE 2

Aminopyranooxazine (I) (R)	Amount (g)	Sodium thiophenol (g/ml)	1-Substituted-1,2-dihydro-6-hydroxy-2-oxo-4-thiophenylpyridine-3-carboxyanilide (R)	Yield (g)	Solvents for crystallisation	M.p. (decomp)	Formula		Analysis (%) C	H	N	S	X
o-Tolyl	1.8	6/40	*o*-Tolyl	0.85	$CHCl_3$+CH_3OH	150°	$C_{25}H_{20}N_2O_3S.CH_3OH$	Found	67.05	4.90	6.0	7.6	
								Reqs	67.80	5.2	6.1	6.9	
m-Tolyl	2.0	7/40	*m*-Tolyl	1.7	"	145°	$C_{25}H_{20}H_2O_3S.CH_3OH$	Found	68.30	4.8	6.40	7.5	
								Reqs	67.80	5.20	6.00	7.1	
p-Anisyl	2.0	7/40	*p*-Anisyl	1.5	"	160°	$C_{25}H_{20}N_2O_4S.$	Found	67.80	4.4	5.20	6.20	
								Reqs	67.60	4.50	6.30	7.2	
m-Anisyl	2.0	7/40	*m*-Anisyl	1.4	"	158°	$C_{25}H_{20}H_2O_4S.CH_3OH$	Found	65.1	4.7	6.0	619	
								Reqs	65.6	5.0	5.9	6.70	
p-Chlorophenyl	2.0	7/40	*p*-Chlorophenyl	1.0	"	150°	$C_{25}H_{20}N_2O_4S.Cl_2CH_3OH$	Found	65.1	4.7	5.9	6.70	7.6 Cl
								Reqs	62.4	4.3	5.8	6.70	7.4 Cl
p-Bromophenyl	2.0	7/40	*p*-Bromophenyl	0.8	"	150°	$C_{24}H_{17}BrN_2O_3.CH_3OH$	Found	57.1	4.0	5.40	5.5	15.0 Br
								Reqs	57.1	4.0	5.0	6.1	15.2 Br
p-Tolyl	2.0	7/40	*p*-Tolyl	1.4	"	148°	$C_{25}H_{20}N_2O_3S.CH_3OH$	Found	67.3	5.2	6.1	6.9	
								Reqs	67.8	5.20	6.1	7.0	
α-Naphthyl	2.0	7/40	α-Naphthyl	1.0	"	167°	$C_{28}H_{20}N_2O_3S$	Found	70.3	4.5	5.8	6.5	
								Reqs	70.2	4.8	5.6	5.6	

from chlorform-methanol to yield light yellow needles of the 6-chloro compound (VI, R=*m*-tolyl, R′=R″=Ph), m.p. 259 (decomp); no colouration with $FeCl_3$. Found: C, 66.80; H, 4.15; N, 5.99; S, 7.62; Cl, 7.95% $C_{25}H_{19}N_2O_2SCl$ requires: C, 67.19; H, 4.26; N, 6.29; S, 7.17; and Cl, 8.87%.

6,5-*Dichloro*-1,2-*dihydro*-2-*oxo*-1-*phenyl*-4-*thiophenylpyridine*-3-*carboxyanilide*. (VII, *R=m-tolyl, R′=R″=Ph*): The *m*-tolylpyridone (III, R=*m*-tolyl R′=R″=Ph) (1.0 g.) and thionyl chloride (4 ml) were refluxed under anhydrous conditions for 1 hr. The mixture was freed from thionyl chloride and on tituration with ether it gave a crystalline solid (0.2 g). On recrystallisation from methanol-chloroform (1:1) mixture, it crystallised with a molecule of water and melted at 166-167° (decomp). (Found: C,60.50; H, 3.70; N, 5.5: S, 6.60; Cl, 14.25%. $C_{25}H_{18}Cl_2N_2O_2SH_2O$ requires: C, 60.10; H, 4.0; N, 5.6; S, 6.50; Cl, 14.20%.)

Ammonium Salt of 1,2-*Dihydro*-6-*hydroxy*-2-*oxo*-4-*thiophenyl*-1-(m-*tolyl*) *pyridine*-3-*carboxyanilide* (X). The compound (III, R=*m*-tolyl, R′=R″=Ph) (0.4 g) was suspended in MeOH (15 ml; dry) and dry NH_3 was passed for 3 hr while heating under reflux. The solution was evaporated to dryness and from the residue, the ammonium salt was crystallised from a mixture of chloroform and ether (m.p. 193.4°C). (Found: C,67.3; H,5.2; N,9.4; S,7.2%. $C_{25}H_{23}O_3N_3S$ requires: C,67.4; H,5.2; N,9.4; S,7.2%.)

5-*Bromo*-1, 2-*dihydro*-6-*hydroxy*-2-*oxo*-4-*thiophenyl*-1-(m-*tolyl*)-3-*carboxyanilide* (IX). The compound (III, R=*m*-tolyl, R′=R″=Ph) (100 mg) was dissolved in chloroform (5 ml) and a solution of Br_2 in chloroform (1%, 5 ml) was added to it and kept at room temperature for 2 hr. The solvent was removed under reduced pressure and the residue was crystallized from chloroform-ether mixture to yield (60 mg) of 5-bromo compound, (m.p. 148.9 dec.). (Found: C,58.O; H,3.5; N,5.5; S, 6.5; Br, 16.5%. $C_{25}H_{19}BrO_3N_2S$ requires: C,58.4; H, 3.5; N, 5 .79; S, 6.5 and Br, 16.20%.)

1,2-*Dihydro*-6-*methoxy*-2-*oxo*-4-*thiophenyl*-1-(m-*tolyl*) *pyridine*-3-*carboxynanilide* (V). The compound (III, R=*m*-tolyl, R′=R″=Ph) (0.1 g) dissolved in chloroform was mixed with diazomethane in ether till a yellow colour persisted. The solution was kept in the cold for 25 hr and then unreacted diazomethane was destroyed with water. The solution was dried (Na_2SO_4) and the solvent was removed. The residue, 6-methoxy product (70 mg) was crystallised from chlorform-methanol, m.p. 234-35°C (decomp). It was neutral to aq $NaHCO_3$ and gave no colouration with aq $FeCl_3$. (Found: C, 70.6; H, 5.00; N, 6.40; S, 7.30%. $C_{26}H_{22}O_3N_2S$, requires: C, 70.6; H, 5.00; N 6. 40;S, 7.2%.)

Morpholinium Salt of 1,2-*Dihydro*-6-*hydroxy*-2-*oxo*-4-*thiophenyl*-1-(m-*tolyl*) *pyridine*-3-*carboxyanilide* (IV). The compound (III, R=R′=R″=Ph) (0.1 g) morpholine (0.5 ml) and chloroform (5 ml) were refluxed for 1/2 hr. The solvent was removed from the reaction mixture and the residue was titurated with ether. The white amorphous residue thus obtained was filtered, washed with ether and was dissolved in a minimum quantity of chloroform. The solution was diluted with enough ether and kept in the cold to yield

(80 mg) crystals of the salt, m.p. 195.9°C. Found: C,67.60; H, 5.80; N,8.2; S,6.10%. $C_{29}H_{28}N_3O_4S$ requires: C,67.60; H, 5.8; N,8.8; S, 6.10%).

1,2-*Dihydro*-4-*hydroxy*-6-*methoxy*-2-*oxo* - m - *tolyl*-*pyridine*-3-*carboxyanilide* (VII). The compound (III, R=*m*-tolyl; R′=R″=Ph) (0.1 g) was dissolved in an excess of pure methanol (200 ml). Dry HCl gas was passed through the solution for 30 min. The solution was evaporated and the solid product (0.50 g) crystallised from MeOH-$CHCl_3$ and it melted at 234°C (decomp). The compound showed no depression on admixture with a pure sample. The product was enolic and free from sulphur. Found: N, 7.8% Calc. for $C_{20}H_{18}N_2O_4$: N, 8.0%.

Reaction of 7-*Anilino*-2,4,5-*trioxo*-3-*phenyl*-2H,-5H-*pyrano* (3,4-e)-(1,3)-*oxazine with Sodium Methoxide in Methanol.* 7-Anilino compound (I,R=R′=R″ =Ph) (O.87 g) was refluxed with sodium methoxide from sodium (0.348 g) in absolute methanol (30 ml) for 30 min. The solution was cooled and acidified with dilute acid (2N). The white ppt was filtered, washed and dried. 1,2-Dihydro-4,6-dihydroxy-2-oxo-1-phenylpyridine-3-carboxyanilide (0.54 g) was crystallised from benzene; it melted at 234° (decomp) and showed no depression when admixed with an authentic sample.[2] (Found: N, 8.8%. Calculated for $C_{18}H_{14}N_2O_4$: N, 8.7%.)

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References

1. M. A. Butt and I. A. Akhtar, Tetrahedron, **23,** 1551 (1967).
2. M. A. Butt, J.A. Elvidge and A. B. Foster, J. Chem. Soc., 3069 (1963).
3. M. A. Butt, Z. Munnawar and M. Hassan, Tetrahedron, **23**, 2461 (1967).