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# SYNTHESIS OF SUBSTITUTED PYRIDINES

## Part VI.—Formation of 6-Hydroxy-4-(p-methylphenoxy)-2-oxo-1-phenyl Pyridine-3-carboxyanilides*

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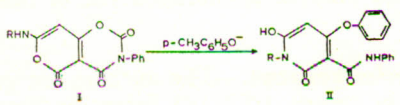
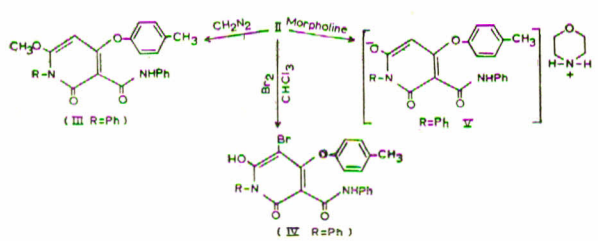
6-Hydroxy pyridine-3-carboxyanilides (II), with varying substituent at N, (II, R=Ph, *o*, *m*, *p*-tolyl, benzyl, etc.) have been synthesised. The IR and UV spectra of the new products have also been recorded.

In continuation of our studies on the substituted pyridines, the reaction of the sodium salt of *p*-cresol and 7-aminopyranooxazines (I) has been investigated.† Several products of structure II were prepared and their physical and chemical characteristics were examined



For instance, when the aminopyranooxazine (I, R=Ph) and sodium in *p*-cresol, were heated together, a new product $C_{25}H_{20}N_2O_4$, m.p. 226°, is formed, isomeric with the products obtained by reacting I with sodium, and *o*- or *m*-cresol.[1] It had all the physical properties of a hydroxypyridine. The product (II, R=Ph) formed easily a monomethoxy derivative, $C_{26}H_{22}N_2O_4$, m.p. 232°, $\lambda_{max}$ 316, log $\varepsilon$=4.5 and a morpholinium salt $C_{29}H_{29}N_3O_5$, m.p. 176°, $\lambda_{max}$ 320, log $\varepsilon$=4.7. The compound was susceptible to electrophillic substitution as bromination of II (R=Ph) gave a bromo product $C_{25}H_{19}BrN$ $C_{25}H_{19}BrN_2O_4$, m.p. 187°, $\lambda_{max}$ 320, log $\varepsilon$=4.4.

The foregoing reactions are detailed below:



The isomeric product having *o*-methylphenoxy and *m*-methylphenoxy group at position 4, that were prepared earlier,[1] showed UV light absorption $\lambda_{max}$ 321, log $\varepsilon$=4.6 and $\lambda_{max}$ 319, log$\varepsilon$ =4.5, whereas the *p*-methylphenoxy compound showed absorption at $\lambda_{max}$ 318, log $\varepsilon$=4.9. Thus a simple comparison of the three isomeric products indicates uniformity in UV light absorption. Due to the blocking effect of the ring nitrogen, the substituents at position 1 did not affect the absorption frequencies of IR and UV spectra.

## Experimental

*Preparation of* 6-*Hydroxy*-4-(p-*methylphenoxy*)-2-*oxo*-1-*phenyl Pyridine*-3-*carboxyanilide*.—7-Anilino-2,4,5-trioxo-3-phenylpyrano (3,4-e)-(1,3)-oxazine‡ (I, R=Ph) (1.165 g, 1 mole) was added to a solution of sodium metal (0.47 g, 4 moles) in *p*-cresol 15 ml at 110–120° and kept for 5 min. The dark-brown solution was cooled, diluted with water (200 ml) and extracted with ether to remove excess of cresol. The aqueous solution was acidified with hydrochloric acid (2N) and the solid product 6-hydroxy-4-*p*-methylphenoxy)-2-oxo-1-phenylpyridine-3-caroboxyanilide (II) (0.91 g, 66.2%) crystallised from methanol–chloroform solution (1:2) and melted at 225–226° (dec). (Found: C, 72.8; H, 5.3; N, 6.9. $C_{25}H_{29}N_2O_4$ requires: C, 72.8, H, 4.9, N, 6.8%.) $\lambda_{max}$ 319, log $\varepsilon$=4.8.

All other pyridine carboxyanilides (II) were prepared as above and are listed in Table 1 and 2.

6-*Methoxy*-4-(p-*methylphenoxy*)-2-*oxo*-1-*phenylpyridine*-3-*carboxyanilide*.—To the compound II (R=Ph) (0.68 g) in chloroform (20 ml), a solution of diazomethane in ether was added in portions till the yellow colour persisted and the mixture was kept in the refrigerator overnight. Excess of the solvent was evaporated and the residue on trituration with ether gave the 6-methoxy derivative (III) (0.4 g, 57.1%). After recrystallization from methanol–chloroform (1:1) it melted at 232°C (dec). (Found: C, 72.9; H, 5.0; N, 6.5.

*Part V. Ref. 1.

†For mechanism of the reaction, see Part III in Tetrahedron, **23**, 1551-1555 (1967).

‡Preparation of all the pyranooxazines(I) employed in the work has been described in Part II, Tetrahedron, **23**, 199 (1967).

TABLE 1.—PREPARATION OF PYRIDINE DERIVATIVES OF TYPE II.

| Compound No. | Aminopyrano-oxazines (I) | Quantity in g | Sodium in *p*-cresol | % yield | Solvent for crystallization |
|---|---|---|---|---|---|
| 1 | *o*-Tolyl | 1.228 | 0.43g/15 ml | 67.3 | MeOH:$CHCl_3$ 1:2 |
| 2 | *m*-Tolyl | 1.24 | 0.43g/15 ml | 75.3 | MeOH:$CHCl_3$ 1:2 |
| 3 | *p*-Tolyl | 1.39 | 0.49g/15 ml | 75.3 | MeOH:$CHCl_3$ 1:2 |
| 4 | *o*-Methoxyphenyl | 1.524 | 0.53g/25 ml | 61.6 | MeOH:$CHCl_3$ 1:2 |
| 5 | *m*-Methoxyphenyl | 1.46 | 0.51g/25 ml | 69.9 | MeOH:$CHCl_3$ 1:2 |
| 6 | *p*-Methoxyphenyl | 1.636 | 0.57g/25 ml | 66.9 | MeOH |
| 7 | Benzyl | 1.334 | 0.47g/20 ml | 50.8 | MeOH:$CHCl_3$ 1:2 |
| 8 | α-Naphthyl | 1.367 | 0.48g/20 ml | 65.5 | MeOH:$CHCl_3$ 1:1 |
| 9 | β-Naphthyl | 1.774 | 0.62g/25 ml | 56.8 | MeOH:$CHCl_3$ |
| 10 | *o*-Bromophenyl | 1.99 | 0.697g/25 ml | 59.2 | MeOH:$CHCl_3$ 2:1 |
| 11 | *p*-Bromophenyl | 1.83 | 0.64g/25 ml | 64.5 | MeOH:$CHCl_3$ 1:1 |
| 12 | *o*-Chlorophenyl | 1.282 | 0.45g/20 ml | 54.7 | MeOH:$CHCl_3$ 1:2 |
| 13 | *m*-Chlorophenyl | 1.835 | 0.64g/25 ml | 54.2 | MeOH:$CHCl_3$ 1:2 |

TABLE 2.—ANALYTICAL DATA OF PYRIDINE DERIVATIVES OF TYPE II.

| Compound No. | M.p. °C | Formula | Found % | | | Required (%) | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N |
| 1 | 221° (d) | $C_{26}H_{22}N_2O_4$ | 72.9 | 5.0 | 6.59 | 73.20 | 5.2 | 6.58 |
| 2 | 206° (d) | $C_{26}H_{22}N_2O_4$ | 73.1 | 5.1 | 6.68 | 73.20 | 5.2 | 6.58 |
| 3 | 221° (d) | $C_{26}H_{22}N_2O_4$ | 72.9 | 5.0 | 7.31 | 37.20 | 5.2 | 6.58 |
| 4 | 214° (d) | $C_{26}H_{22}O_2O_5$ | 70.7 | 4.9 | 6.48 | 70.58 | 5.0 | 6.33 |
| 5 | 205° (d) | $C_{26}H_{22}N_2O_5$ | 70.8 | 4.8 | 6.26 | 70.58 | 5.0 | 6.33 |
| 6 | 226° (d) | $C_{26}H_{22}N_2O_5$ | 70.7 | 4.9 | 6.82 | 70.60 | 5.0 | 6.33 |
| 7 | 231° (d) | $C_{26}H_{21}N_2O_5$ | 73.6 | 4.9 | 6.79 | 73.40 | 4.9 | 6.58 |
| 8 | 240° (d) | $C_{29}H_{22}N_2O_4$ | 73.3 | 4.9 | 5.97 | 73.16 | 4.8 | 6.06 |
| 9 | 213° (d) | $C_{29}H_{22}N_2O_4$ | 73.1 | 4.8 | 5.92 | 37.16 | 4.8 | 6.06 |
| 10 | 230° (d) | $C_{25}H_{19}BrN_2O_4$ | 61.0 | 4.0 | 5.34 | 61.1 | 3.9 | 5.70 |
| 11 | 223° (d) | $C_{25}H_{19}BrN_2O_4$ | 61.1 | 4.1 | 5.24 | 61.10 | 3.9 | 5.70 |
| 12 | 225° (d) | $C_{25}H_{19}ClN_2O_4$ | 67.2 | 4.0 | 6.87 | 67.10 | 4.3 | 6.38 |
| 13 | 215° (d) | $C_{25}H_{19}ClN_2O_4$ | 67.3 | 4.4 | 6.18 | 67.10 | 4.3 | 6.38 |

$C_{26}H_{22}N_2O_4$. requires: C, 73.2; H, 5.2; N, 6.6%.) $\lambda_{max}$ 316, log $\varepsilon$=4.5.

5 - *Bromo* -6-*Hydroxy*-4-(p-*methylphenoxy*) 2-*oxo*-1-*phenylpyridine*-3-*carboxyanilide*.—To the compound II (R=Ph) (0.5 g) in chloroform (15 ml) bromine solution in chloroform (10 ml) was added dropwise till the bromine colour persisted. The solution was kept at room temperature for 2 hr. On evaporation of the solution the 5-bromo derivative (IV) (0.5 g, 84.03%) was recrystallised from chloroform–ether solution which gave colourless needles, m.p. 187°C (dec), $\lambda_{max}$ 320, log $\varepsilon$=4.4. (Found: C, 61.0; H, 3.8; Br, 16.8; N, 6.00. $C_{25}H_{19}BrN_2O_4$ requires: C, 61.1; H, 3.9; N, 5.7; Br, 16.3%.)

*Reaction of* 6-*Hydroxy*-4-(p-*methylphenoxy*) 2-*oxo*-1-*phenyl pyridine*-3-*carboxyanilide with Morpholine*.—To the compound II (R=Ph) (0.5 g) in chloroform (15 ml), morpholine (0.5 ml) was added, and the mixture refluxed for 0.5 hr. The reaction was carried out under anhydrous conditions. Excess of solvent was evaporated and the product triturated with ether to give the morpholinium salt V (0.46 g, 76%) which on recrystallization from methanol–ether solution, melted at 176°C (dec), $\lambda_{max}$ 320, log $\varepsilon$=4.7. (Found: C, 69.61; H, 5.81; N, 8.21. $C_{29}H_{29}N_3O_5$ requires: C, 69.7; H, 5.8; N, 8.4%.)

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## Reference

1. A. Butt, M. Akhtar and R. Parveen, Pakistan J. Sci. Ind. Res., **10**, 243 (1967).