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A Study on the Condensation of *o*-Phthalaldehydic Acid with Primary Hetero Aromatic Amines-Part VIII*: Synthesis of *N*-(3-Phthalidyl)amines

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In this paper the condensations of *o*-phthalaldehydic acid with twelve primary heterocyclic amines are reported. The reaction occurred selectively at carbon-3 of the lactol form of the acid, affording in all the cases studied N-(3-phthalidyl)-amines (4) exclusively. None of the Schiff bases of type (5) have been formed. The structures of the isolated products were confirmed from their spectral and analytical data.

INTRODUCTION

The chemistry of *o*-phthalaldehydic acid (1) and its derivatives has received wide attention due to their interesting ring chain tautomeric behavior. Since it was realised that (1) exist, at least in solution, mainly as a lactol form,[1] its reactions with a variety of substituted aromatic compounds in acidic medium have been studied by the author.[2–4] In all of these, the condensation occurs through electrophilic substitution reaction of the phthalidyl cation affording either 1,3-diaryl isobenzofuran (3) or 3-aryl phthalides (2). On the other hand the reactions of (1) with amines have been explained to occur through nuceophilic reactions and on the basis of both its forms. Wheeler *et al.*[5] realised that with aliphatic and simple aromatic amines the reactions occur on the lactol form affording *N*-(3-phthalidyl)amine (4; Y = Ar). Others show that some aromatic amines[6] or ethylene diamine[7] afforded Schiff bases (5), resulting from the reaction of the open form of (1) with the amine.

Although, the reaction of (1) and its derivatives with secondary amines and its mechanism has been studied by Sloan *et al.*[8] The lack of information about the mode of reaction that primary heterocyclic amines can undergo with (1), the interesting biological activity that a variety of *N*-phthalidyl amines show, as a herbicide, germicide, fungicide, as well as the importance of these compounds as a precursor for the synthesis of phthalimidine derivatives motivate us to study the reaction of (1) with aminopyridine and some of its derivatives, 2-amino-benzothiazole, 3-amino oxazole, 2-aminothiazole, 2-aminopyrazine and 2-amino-1,3,4-thiadiazole.

*For Part VII—See reference No. 2.

RESULTS AND DISCUSSION

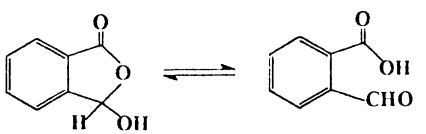
The condensation of 2-amino-, 2-amino-3-hydroxy-, 2-amino-4-methyl-, 2-amino-5-nitro-, 2-amino-5-bromo-, 2-amino-5-chloro-, 3-aminopyridine, 2-amino- benzothiazole, 2-amino-5-methylisoxazole, 2-aminothiazole, 2-amino-pyrazine and 2-amino-1,3,4-thiadiazole with (1) in refluxing methanol afforded in each a crystallisable solid product. The analytical data of isolated phthalides are given in Table-1. TLC of the crude product indicating the presence of one single component. The IR (KBr) of the isolated compounds shows the presence of two strong absorption bands at 3320–3140 cm^{-1} and 1760–1630 cm^{-1} (except in case of 2-amino-3-hydroxypyridine where it appears as 1715 cm^{-1}). The former

TABLE-1
ANALYTICAL DATA OF PHTHALIDES 4 (a–l)

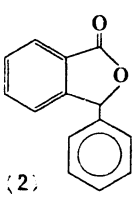
Phthalide	Mol. Formula	Melting Point (°C)	Yield (%)	Elemental analysis (found/calcd., %)		
				C	H	N
4a	$C_{13}H_{10}N_2O_2$	208–210 lit[9]: 206–207	97	69.16 (69.02)	4.58 (4.46)	12.36 (12.38)
4b	$C_{13}H_{10}N_2O_3$	185–187	82	64.60 (64.46)	4.42 (4.16)	11.68 (11.56)
4c	$C_{14}H_{12}N_2O_2$	164–166	82	69.78 (69.99)	5.20 (5.03)	11.49 (11.66)
4d	$C_{13}H_9N_3O_4$	282–284	62	57.72 (57.67)	3.43 (3.34)	15.58 (15.49)
4e	$C_{13}H_9N_2O_2Br$	151–153	90	51.22 (51.17)	2.88 (2.97)	9.24 (9.18)
4f	$C_{13}H_9N_2O_2Cl$	171–173	84	60.02 (59.90)	3.67 (3.48)	10.74 (10.75)
4g	$C_{13}H_{10}N_2O_2$	162–165	41	69.29 (69.02)	4.60 (4.46)	12.38 (12.38)
4h	$C_{15}H_{10}N_2O_2S$	204–206	71	64.34 (63.82)	4.01 (3.57)	9.88 (9.22)
4i	$C_{12}H_{10}N_2O_3$	145–146	71	62.62 (62.61)	4.50 (4.38)	12.04 (12.17)
4j	$C_{11}H_8N_2O_2S$	199–201	72	57.00 (56.89)	3.56 (3.47)	12.05 (12.06)
4k	$C_{12}H_9N_3O_2$	215–217	86	63.50 (63.43)	4.10 (3.99)	18.57 (18.49)
4l	$C_{10}H_7N_3O_2S$	194–196	69	51.60 (51.49)	3.16 (3.03)	17.88 (18.02)

can be attributed to NH stretching, while the second is due to the presence of a lactonic group. The lower frequency in case of the hydroxy derivatives can be attributed to the possible hydrogen bonding with the oxygen of the lactonic group (Table-2). On the other hand, the ^{1}H-NMR spectra (d_6-DMSO) of all products, except (4l) in ($CDCl_3$) shows the prescence of one proton either as a broad singlet or a doublet with J = 6.4–10 exchange with D_2O, in the range of 3.5–9.3 ppm due to NH proton and one proton either a doublet with J = 6.4–10.3 Hz exchanged to singlet with D_2O or a singlet in the range 7.10–7.56 ppm due to CH—N proton (Table-3). In case of (4i) this proton appears at 6.78; the difference in chemical shift is due to solvent effect (Table-2). Further more the mass spectra of most of the isolated products show fragments at m/z = 133 due to phthalidyl cation. These results rule out the possibility of Schiff base formation of type (5) and clearly indicate the formation of *N*-(3-phthalidyl)- amine of type 4 (a–l). These compounds can only arise if the starting amines react with the lactol form of the acid (1), through SN^2 nucleophilic substitution reaction on carbon No. 3.

The deshielding of H-3 in these compounds, compared with CH—N-alkyl analogs can be attributed to the anisotropic effect caused by the hetero-aromatic ring.



(1)



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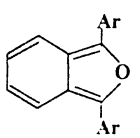

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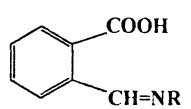

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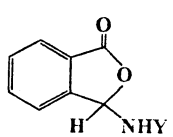

(4)

4a, Y = 2-pyridyl
4b, Y = 3-hydroxy-2-pyridyl
4c, Y = 4-methyl-2-pyridyl
4d, Y = 5-nitro-2-pyridyl
4e, Y = 5-bromo-2-pyridyl
4f, Y = 5-chloro-2-pyridyl
4g, Y = 3-pyridyl
4h, Y = 2-benzothiazoyl
4i, Y = 5-methyl-3-isoxazoyl
4j, Y = 2-thiazoyl
4k, Y = 2-pyrazoyl
4l, Y = 2-(1,3,4-thiadazoyl)

TABLE-2
SPECTRAL DATA OF PHTHALIDE 4 (a–l)

Phthalide	IR (KBr cm^{-1})	NMR (DMSO-d_6, TMS, ppm)
N-(3-phthalidyl)-2-aminopyridine (4a)	3200 ν(N—H), 1760 ν(C=O), 1590 ν(C=C)	6.6 (s, 1H), 6.7 (s, 1H), 7.4–8.14 (m, 7H + NH)
N-(3-phthalidyl)-2-amino-3-hydroxy pyridine (4b)	3320 ν(O—H), 3230 ν(N—H), 1715 ν(C=O), 1600 ν(C=C)	6.66 (dd, 1H), J_1 = 8.0 Hz, J_2 = 5.0 Hz, 6.9 (d, 1H), J = 7.0 Hz, 7.22 (s, NH), 7.5 (s, 1H), 7.5–7.86 (m, 5H), 9.89 (b, OH)
N-(3-phthalidyl)-2-amino-4-methyl pyridine (4c)	3300 ν(N—H), 1730 ν(C=O), 1590 ν(C=C)	2.22 (s, 3H), 6.51 (s, 1H), 6.65 (d, 2H), J = 6.0 Hz, 7.5 (s, 1H), 7.4–7.9 (m, 5H + NH)
N-(3-phthalidyl)-2-amino-5-nitro pyridine (4d)	3250 ν(N—H), 1740 ν(C=O), 1600 ν(C=C), 1580 and 1330 ν(NO_2)	6.84 (d, 1H), J = 9.0 Hz, 7.56 (d, 1H), J = 8.0 Hz, 7.6–8.0 (m, 4H), 8.38 (dd, 1H), J_1 = 9.0, J_2 = 2.5 Hz, 9.1 (dd, 2H), J_1 = 8.0, J_2 = 2.3 Hz
N-(3-phthalidyl)-2-amino-5-bromo pyridine (4e)	3180 ν(N—H), 1740 ν(C=O), 1570 ν(νC=C), 880 ν(C—Br)	5.7 (d, NH), J = 10.3 Hz, 6.63 (d, 1H), J = 8.7 Hz, 7.22 (d, 1H), J = 10.3 Hz, 7.57–8.1 (m, 6H)
N-(3-phthalidyl)-2-amino-5-chloro pyridine (4f)	3180 ν(N—H), 1740 ν(C=O), 1580 ν(C=C), 880 ν(C—Cl)	6.73 (d, 1H), J = 8.8 Hz, 7.38 (s, 1H), 7.5 (s, 1H), 7.61–8.27 (m, 6H)
N-(3-phthalidyl)-3-amino pyridine (4g)	3200 ν(N—H), 1730 ν(C=O), 1570 ν(C=C)	3.5 (bs, NH), 7.1 (s, 1H), 3.67–8.3 (m, 8H)
N-(3-phthalidyl)-2-amino-benzothiazole (4h)	3160 ν(N—H), 1745 ν(C=O), 1600 ν(C=C)	7.1–7.68 (m, 5H), 7.76–7.99 (m, 4H), 9.3 (d, NH), J = 6.4 Hz
N-(3-phthalidyl)-3-amino-5-methyl isoxazole* (4i)	3250 ν(N—H), 1730 ν(C=O), 1610 ν(C=C)	2.35 (s, 3H), 4.94 (d, 1H), J = 10 Hz, 5.68 (s, 1H), 6.78 (d, 1H), J = 10 Hz, 7.6–7.78 (m, 3H), 7.95 (M, 1H)
N-(3-phthalidyl)-2-amino thiazole (4j)	3140 ν(N—H), 1750 ν(C=O), 1600 ν(C=C)	6.92 (d, 1H), J = 3.5 Hz, 7.2 (d, 2H), J = 5.8 Hz, 7.6–8.9 (m, 4H), 98.9 (d, 1H), J = 8.78 Hz
N-(3-phthalidyl)-2-aminopyrazine (4k)	3220 ν(N—H), 1750 ν(C=O), 1590 ν(C=C)	7.4 (d, 1H), J = 9.5 Hz, 7.45 (s, 1 H), 7.6–8.18 (m, 6H), 847 (d, 1H), J = 9.5 Hz
N-(3-phthalidyl)-2-amino-1,3,4-thiadiazole (4l)	3200 ν(N—H), 1760 ν(C=C), 1600 ν(C=C)	7.25 (s, 1H), 7.6–7.99 (m, 4H), 8.91 (s, 1H), 9.24 (b, NH)

*In $CDCl_3$.

EXPERIMENTAL

All melting points were measured on electrotherrmal melting point and were uncorrected, infrared (IR) spectra were measured using Pye-Unicam SP-300 spectrophotometer as a potassium bromide disc. ^{1}H-NMR were measured using a Bruker WP 80 SY spectrometer. Elemental analyses were measured at M.H.W Laboratories, Pheonix, Arizona, USA.

TABLE-3
CHEMICAL SHIFT (ppm) OF NH AND CH—N PROTONS
IN COMPOUND 4 (a–l) IN d_6-DMSO

Phthalide	NH	CH—N
4a	7.4–8.14	7.4 d
4b	7.22	7.5 d
4c	7.4–7.9	7.5 s
4d	—	7.56 d
4e	5.7, d	7.22 d
4f	7.51	7.38
4g	3.5	7.1
4h	9.3,d	7.3 d
4i	4.94, d	6.78 d (in $CDCl_3$)
4j	8.9, d	7.2 d
4k	8.47, d	7.40 d
4l	9.24	7.25

Reaction of *o*-phthalaldehydic acid with heteroaromatic primary amines (General method)

A mixture of *o*-phthalaldehydic acid (1.5 g, 0.01 mole) and the primary amine (0.01 mole) in methanol (25 mL) was refluxed for about 3–5 h, then cooled; in certain cases a solid start to appear. Evaporating the solvent or filtration afforded the product, which was crystallized from the mentioned solvent.

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REFERENCES

1. R.P. Bell and B.G. Cox, *J. Chem. Soc.*, **B11**, 2247 (1971).
2. Raad Al-Hamdany and Zacharia Fataftah, *Asian J. Chem.*, **9**, 703 (1997).
3. (a) R. Al-Hamdany, J. Al-Rawi and S. Ibrahim, *J. Prakt. Chemie,* **329**, 126 (1987); (b) R. Al-Hamdany and M. Abu-Irqaiq, *Iraqi J. Chem.*, **14**, 18 (1989); (c) R. Al-Hamdani and M. Abu-Irqaiq, *Mutah, J. for Research and Studies,* **10**, 65 (1995); (d) R. Al-Hamdany and M. Raoof, *Abhath Al-Yarmouk J.* (Aceepted).
4. R. Al-Hamdany, M.T. Ayoub and R. Al-Bayati, *J. Chem. Research* (s), 82, (1989).
5. D.D. Wheeler, D.C. Young and D.S. Erley, *J. Org. Chem.*, **22**, 547 (1957).
6. Mario and Ghelordoni, *Ann. Chim. (Rome),* **64**, 421,(197)4.
7. S.A. Saleh, J.W. Borton and M.C. Goodland, *Tetrahedron*, **35**, 241 (1979).
8. K.B. Sloan and S.A. Koch, *J. Org. Chem.*, **48**, 635 (1983).
9. K. Kubota and T. Tatsuno, *Chem. Pharm. Bull.*, **19**, 1226 (1971).

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