Synthesis and Structural Investigation of N-Pyridyl-1, 3-Dihydroxyisoindoines

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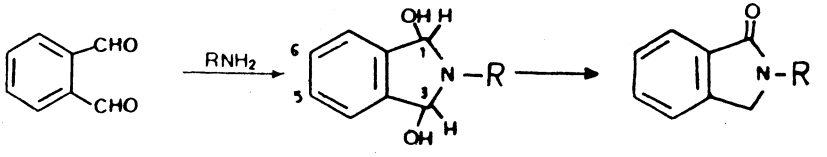
Condensation of *o*-phthalaldehyde (OPTA) with appropriate hetero aromatic amines has led to the formation of N-pyridyl-1, 3-dihydroxy-isoindolines (1) in high yield. Some of (1) were converted into isoindol-1-one (2). Structures of these products were investigated by chemical and spectroscopic methods.

INTRODUCTION

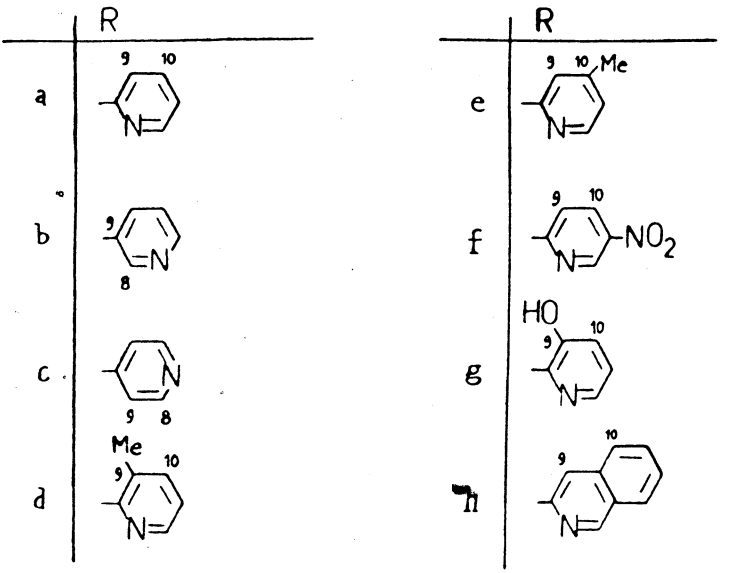
Although *o*-phthalaldehyde (OPTA) undergo a vast number of different types of reactions with a variety of reagent,[1-3] their reactions with amino compounds appear to be of great interest from mechanistic and synthetic point of view,[4,5] as well as in connection with the fluorescence reaction described earlier.[6]

Reactions of *o*-phthalaldehyde with various primary amines gave different products[7] and its condensation with urea and thiourea gave products based on substituted isoindoline.[8] Reactions of OPTA with different hetero-aromatic amines have now been investigated.

At room temperature, OPTA reacts with amino-pyridines and some substituted amino-pyridines to afford a series of new N-pyridyl-1,3-dihydroxyisoindoline (1 a-h) in high yields, some of which were converted into their oxidized form, isoindol 1-one (2). To the best of our knowledge, such products have not been synthesised before.



(1) (2)



RESULTS AND DISCUSSION

Reaction of O-phthalaldehyde with aminopyridines in benzene afforded crystalline solid products which gave satisfactory analyses (Table 1). The spectral data of each product agreed with the substituted-N-pyridyl-2, 3-dihydroxyisoindolines (1 a-h). The i.r. spectra showed a strong band at *ca.* 3400 cm^{-1} characteristic for the hydroxyl group which supports

TABLE 1

MELTING POINTS, YIELDS AND ELEMENTAL ANALYSES OF COMPOUND (1 a-h)

Product	m.pt. (°C)	Yield (%)	Elemental analysis (%)
(1a)	117–119(d)	85	Found: C, 68.15; H, 5.42: N, 12.73 $C_{13}H_{12}N_2O_2$ req. C, 68.42; H, 5.26; N, 12.28.
(1b)	118–120(d)	75	Found: C, 68.23; H, 5.21; N, 12.52 $C_{13}H_{12}N_2O_2$ req. C, 68.42; H. 5.26; N, 12.28.
(1c)	170–172	82	Found: C, 67.95; H, 5.44; N, 12.58 $C_{13}H_{12}N_2O_2$ req. C, 68.42; H, 5.26; N, 12.28.
(1d)	108–110	90	Found: C, 70.66; H, 5.25; N, 12.49 $C_{14}H_{14}N_2O_2$ req. C, 69.42; H, 5.78; N, 11.57.
(1e)	100–110(d)	80	Found: C, 70.10; H, 5.12; N, 11.92 $C_{14}H_{14}N_2O_2$ req. C, 69.42; H, 5.78; N, 11.57.
(1f)	258–260(d)	79	Found: C, 57.61; H, 3.96; N, 15.72 $C_{13}H_{11}N_3O_4$ req. C, 57.14; H, 4.02; N, 15.38.
(1g)	140–142	72	Found: C, 64.31; H, 4.62; N, 11.72 $C_{13}H_{12}N_2O_3$ req. C, 63.93; H, 4.91; N, 11.47.
(1h)	192–194	76	Found: C, 73.66; H, 5.30; N, 10.26 $C_{17}H_{14}N_2O_2$ req. C, 73.38; H, 5.03; N, 10.07.

the structure (1). The ^1H n.m.r. spectrum of compound (1a) (Table 2) in dimethyl sulphoxide-d_6 showed four aromatic protons centered at δ 7.5 ppm and four pyridine protons resonated at δ 6.8, 7.0, and 8.2 ppm. The chemical shift of the tertiary hydrogen attached to sp^3 carbon (C*H*OH) which is adjacent to nitrogen atom would be expected to fall to δ 6.25 ppm

TABLE 2

I.r. AND ^1H-n.m.r. DATA OF COMPOUNDS (1 a-h).

Product	I.r. (cm^{-1})† (O—H)	^1H-n.m.r. (δ)*
(1a)	3400	5.9 (2H, d, J = 10 Hz, exchange with D_2O, CHO*H*) 6.3 (2H, d, J = 10 Hz, collapsed to singlet when added D_2O, C*H*OH); 6.8 (1H, m, H-py); 7.0 (1H, d, J = 6 Hz. H-py); 7.5 (4H, m, H-Ar); 7.7 (1H, m, H-py); 8.2 (1H, d, J = 6 Hz, H-py)
(1b)	3500	5.8 (2H, d, J = 10 Hz, exchange with D_2O, CHO*H*); 5.9 (2H, d, J = 9 Hz, C*H*OH); 7.2 (1H, m, H-py); 7.3 (1H, m, H-py); 7.4 (4H, m, H-Ar); 7.85 (1H, m, H-py); 8.3 (1H, m, H-py).
(1c)	3490	6.0 (4H, broad singlet collapsed to sharp singlet when added D_2O, 2CHO*H*); 7.1 (2H, m, H-py); 7.4 (4H, s, H-Ar)) 8.2 (2H, m, H-py).
(1d)	3300	2.1 (3H, s, Me); 6.1 (2H, d, J = 10 Hz, collapsed to singlet when added D_2O, C*H*OH); 6.2 (2H, m, exchange with D_2O), 6.8 (1H, m, H-py): 7.1 (1H, m, H-py); 7.4 (4H, m, H-Ar); 8.0 (1H, m, H-py).
(1e)	3420–3300	2.2 (3H, g, Me); 5.8 (2H, p, J = 10 Hz, exchange with D_2O, CHO*H*); 6.2 (2H, d, J = 8 Hz, collapsed to singlet when added D_2O, C*H*OH); 6.5 (1H, d, J = 6 Hz, H-py); 6.9 (1H, s, H-py); 7.4 (4H, m, H-Ar); 8.1 (1H, d, J = 6 Hz, H-py).
(1f)	3420–3200	6.3 (2H, d, J = 10 Hz, exchange with D_2O, CHO*H*); 6.4 (2H, d, J = 10 Hz, C*H*OH); 7.4 (4H, m, H-Ar); 7.8 (1H, d, J = 6 Hz, H-py); 8.1 (1H, d, J = 6 Hz, H-py); 8.8 (1H, s, H-py).
(1g)	3300	5.9 (2H, d, J = 10 Hz, exchange with D_2O, CHO*H*): 6.2 (2H. d, J = 10 Hz, collapsed to singlet when added D_2O, C*H*OH); 6.6 (1H, m, H-py); 6.9 (1H, m, H-py); 7.4 (4H, m, H-Ar); 8.1 (1H, m, H-py); 8.3 (1H, s, exchanged with D_2O, OH).
(1h)	3320	6.0 (2H, d, J = 10 Hz, exchange with D_2O, CHO*H*); 6.2 (2H, d, *J* = 10 Hz, collapsed to singlet when D_2O added); 7.6 (9H, m, H-Ar); 9.0 (1H, s, H-py).

*Dimethyl sulphoxide—d_6 is used for the measurements.
†In KBr disc.

which resembles the chemical shift of tertiary protons found in the cis-phthalaldehyde hydrate[4] i.e. δ 6.0–6.2 ppm. A D_2O exchangable signal integrated for two protons at around δ 6.0 is due to the hydroxyl groups.

It is noteworthy that, when the dihydroxy products (1 a-e) allowed to stand overnight in vacuo at 50°C, H_2O-elimination took place and pale yellow compounds were obtained, these were proved to be the isoindol-1-one (2 a-e). On the other hand, treatment of the ethanolic solution of the dihydroxy product (1 a-e) with dilute hydrochloric acid furnished product similar to that obtained from thermal H_2O-elimination of (1 a-e). The identity of compound (2 a-e) was established from its spectroscopic data (Table 4).

TABLE 3

MELTING POINTS AND YIELDS OF COMPOUND (2 a-e)

Product	M.Pt. (°C)	Yield (%)
(2a)	126–128	55
(2b)	140–142	60
(2c)	176–178	64
(2d)	82–84	70
(2e)	158–163	43

TABLE 4

I.r. AND ^{1}H-n.m.r. DATA OF COMPOUND (2 a-e)

Product	I.R. (cm^{-1})† C=O	^{1}H-n.m.r, (δ)*
(2a)	1680	5.1 (2H, s, CH_2); 7.1 (1H, m, H-py); 7.4–7.9 (4H, m, H-Ar); 8.2 (1H, m, H-py); 8.4 (1H, m, H-py); 8.7 (1H, m, H-py).
(2b)	1685	5.1 (2H, s, CH_2); 7.2 (1H, m, H-py); 7.4 (4H. m, H-Ar); 7.8 (1H, m, H-py); 8.3 (1H, m, H-py); 9.0 (1H, m, H-py).
(2c)	1680	5.1 (2H, s, CH_2); 7.0 (1H, m, H-py); 7.4 (4H, m, H-Ar); 7.9 (2H, m, H-py); 8.5 (1H, m, H-py).
(2d)	1685	2.0 (3H, s, Me); 5.1 (2H, s, CH_2); 6.8 (1H, m, H-py); 7.1 (1H, m, H-py); 7.4 (4H, m, H-Ar); 7.8 (1H, m, H-py).
(2e)	1680	2.3 (3H, s, Me); 5.1 (2H, s, CH_2); 7.0 (1H, m, H-py); 7.7 (4H, m, H-Ar); 8.4 (1H, m, H-py); 8.5 (1H, s, H-py).

*Dimethyl sulphoxide-d_6 is used for the measurements.
†In KBr disc.

TABLE 5

CARBON-13 CHEMICAL SHIFTS ASSIGNMENTS OF COMPOUNDS 1 AND 2 RELATIVE TO TMS AND IN D_6-DMSO

Compound	C-1	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-9	C-10	C-11	C-12	C-13
(1a)	82.6	82.6	140.4	123.4	128.6	128.6	123.4	140.4	156.6	108.7	137.3	114.0	147.7	—
(1c)	82.7	82.7	132.9	123.4	121.9	128.9	123.4	139.9	149.4	109.1	149.7	109.1	149.4	—
(1d)	83.5	83.5	141.8	122.7	128.7	128.7	122.7	141.8	155.6	117.5	137.6	114.0	144.7	16.7
(1e)	82.5	82.5	140.4	123.4	128.6	128.6	123.4	140.4	156.1	108.9	147.4	115.4	147.7	20.9
(1f)	82.7	82.7	139.4	123.6	129.1	129.1	123.6	139.4	158.7	108.0	132.7	136.3	145.5	—
(1g)	82.5	82.5	139.0	123.5	128.7	128.7	123.2	134.0	145.0	135.9	123.5	107.7	158.2	—
(2a)	166.6	49.4	147.5	123.0	127.8	132.2	123.3	141.0	157.0	112.9	137.6	113.2	147.5	—
(2b)	166.6	49.7	144.4	123.0	127.0	132.1	123.3	140.2	135.9	144.4	123.0	125.7	140.1	—
(2c)	167.6	49.6	145.8	123.5	128.4	131.7	123.5	141,1	150.4	112.8	150.4	112.8	150.4	—
(2e)	166.8	49.6	147.6	123.4	128.2	132.0	123.6	141.4	151.5	113.8	121.8	120.7	148.8	20.4

^{13}C n.m.r. Chemical Shifts Assignments of compounds 1 and 2

Proton decoupled as well as coupled spectra were used in the assignment. Further evidence was obtained from structural related compounds[9,10] (see Table 5). In compound 1a (R=2-aminopyridine moiety) the assignment of the R group carbons was based on the reported ^{13}C-chemiscal shifts of the corresponding 2-aminopyridine itself[9] (^{13}C, 156.0, 108.7, 137.3, 114.0 and 147.7 ppm), which showed very close analogy. The remaining four carbon signals in the spectrum of 1a were easily assigned for the 1,3-dihydroxyisoindoline moiety. δ 82.6 ppm was assigned for the sp^3 carbon bearing the hydroxyl group (C-1 and C-3). The signal for the quaternary carbon (C-3a and C-7a) were easily assigned to δ 140.4 ppm. The two remaining carbon-13 signals at 123.4 and 128.6 ppm were assigned to C-4, 7 and C-5, 6 respectively using the corresponding part of the reported chemical shifts of N-arylisoindoline-1, 3-dione[10]. Similarly, carbon-13 chemical shifts of compounds 1 c, d, e and f were analysed (Table 5).

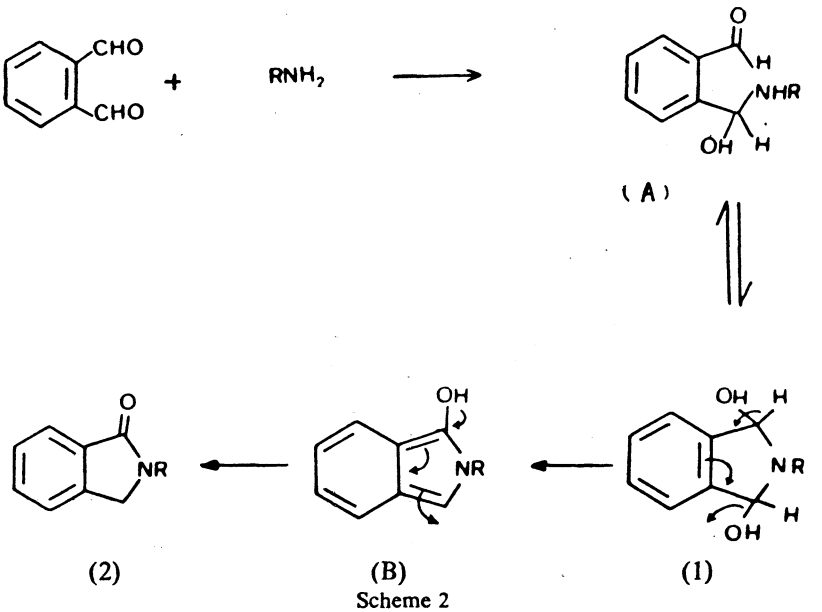
It is worth noticing that there is no, or very small, effect (within experimental error) on the carbon-13 chemical shifts of the 1,3-dihydroxyisoindoline moiety on changing R group. This indicated that no steric influence or mesomeric effects and no extended resonance is observed as a result of introducing different R groups. These results are unlikely to be observed in the oxidized product (N-arylisoindoline-1,3-diones[10]).

The carbon-13 n.m.r. spectral assignment of N-pyridyl-2,3-dihydro-1H-isoindol-1-one (2 a-e) (a thermal or acid rearrangement products of the corresponding compound 1) were assigned using the reported chemical shifts of the related amino-pyridine moiety[10]. The assignments of the isoindole part in 2 were achieved using the partial assigned N-arylisoindol-1-one and N-aryl-isoindoline-1,3-diones[10]. Therefore the carbon-13 spectra of 1 and 2 confirm their structures.

However, compound (A) is a possible product for the reaction of amine with phthalaldehyde (Scheme 2). Structure (1) was proved by spectroscopic data (i.r. showed the absence of carbonyl group; ^1H-n.m.r. showed structure of symmetry; in ^{13}C-n.m.r. of compound (1) no aldehydic carbonyl signal is observed). Therefore, the structure of the isolated product is (1) and not (A). Transannular dehydration of (1), then, gives the intermediate 1-hydroxyisoindole (*B*) which can rearrange to the compound (2).

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting points apparatus and are uncorrected. Infrared spectra were recorded in KBr disc using Pye-Unicam SP 3-300 Infrared Spectrophotometer. ^1H and



(2) (B) (1)

Scheme 2

^{13}C n.m.r. spectra were determined with a Bruker WH 90 DS spectrometer operating at 90 and 22.63 MHz for proton and carbon-13, respectively, with deuterium internal lock and TMS as internal reference. Microanalysis was performed in the analytical laboratory, Chemistry Department at Mosul University.

Synthesis of Substituted N-pyridyl-1,3-dihydroxyisoindoline (1 a-h)
(General procedure)

Phthalaldehyde (0.01 mole) and substituted amino pyridine (0.01 mole) were dissolved in (50 ml) benzene. The reaction mixture was stirred for 2 hrs at room temperature. The white precipitate was filtered off and crystallised from ethyl acetate-petroleum ether (40–60°C) to give the pure product. Melting points, yields and elemental analysis of the isolated products are listed in Table 1. The structures of the compounds 1 a-h were confirmed by i.r., ^{1}H n.m.r. data (Table 2) and ^{13}C n.m.r. (Table 5). Further structural proof was achieved chemically by converting some of the dihydroxy products into isoindolin-1-one.

Synthesis of Substituted N-pyridyl-2,3-dihydro-1H-isoindol-1-one (2 a-e)
(General procedure)

Method A

N-Pyridyl-1, 3-dihydroxyisoindolines were allowed to stand overnight in vacuo at 50°C to give pale yellow products which were crystallized from petroleum ether (40–60°C) to afford the pure products. Melting

points and yields are listed in Table 3. The structures of the prepared compounds were confirmed by spectral data (Table 4).

Method B

To a solution of N-pyridyl-1,3-dihydroxyisoindolines in ethanol was added 6N hydrochloric acid dropwise with stirring. The reaction mixture was stirred for 4 hrs at room temperature, then neutralised with aqueous sodium carbonate and extracted with ethyl acetate. Crystallisation of the products, after evaporation of the solvent, gave the desired products whose spectral data were identical to the samples prepared by method A.

REFERENCES

1. J. Thiele and E. Winter, *Annalen*, **311**, 353 (1900).
2. H. Wachsmuth, R. Denissen and L. Koeckhoven, *J. Pharm. Belg.*, **14**, 386 (1959).
3. D. R. Norton and C. K. Mann, *Analyt. Chem.*, **26**, 1180 (1954).
4. T. Domnish, A. L. Johnson, J. E. Jones and P. P. Senise, *J. Org. Chem.*, **42**, 4217, (1977).
5. T. Amano and S. Mizukami, *Yakugaku Zasshi*, 1035 (1965).
6. M. Roth, *Analyt. Chem.*, **43**, 880 (1971).
7. L. Chunchatprasert, *Ph.D. Thesis*, University College, Cardiff, 1979.
8. R. D. Reynolds, D. F. Guanci, C. B. Neynaber and R. J. Conboy, *J. Org. Chem.*, **43**, 3838 (1978).
9. E. Brestmaier and W. Voelter, Carbon-13-NMR Spectroscopy, Verlag Chemie, New York, p. 216, (1978).
10. M. A. Khadim and L. D. Colebrook, *Man. Reson. Chem.*, 23, 259 (1985).

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