The Synthesis of Isoindolin-3-ones, Phthalazin-4(3*H*)-ones and Related Systems

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The reaction between methyl 2-cyanobenzoate and its pyridine analogues gave isoindolin-3-ones, phthalazin-4(3*H*)-ones and their corresponding aza analogues. Some reactions of 1-benzylaminoiminoisoindolin-3-one **5b** were investigated.

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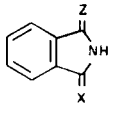
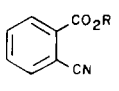
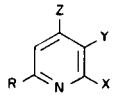
1-Substituted aminoisoindolin-3-ones are usually prepared [1] by the reaction of substituted hydrazines with phthalic acid derivatives such as **1a-d**. Surprisingly, esters of 2-cyanobenzoic acid have been largely ignored as useful precursors to the isoindole ring system [2] and this despite the facile synthesis of the required cyanobenzoates [3]. We now report the synthesis of 1-substituted aminoiminoisoindolin-3-ones and 1-aminophthalazin-4(3*H*)-ones and their aza analogues from the reaction of cyanoesters **2a** and **3a-c** with substituted hydrazines **4a-e**.



1a X = O, Z = NH
b X = S, Z = NH
c X = Z = NH
d X = O, Z = S



2a R = Me
2b R = Et

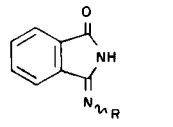


3a R = Z = H, Y = CN, X = CO_2Me
b R = Z = H, Y = CO_2Me, X = CN
c R = X = H, Z = CO_2Me, Y = CN
d R = Me, Z = CO_2Et, Y = CN, X = H

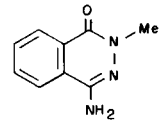
$R-NH_2$

4a R = Me_2N-
b R = $PhCH_2NH$
c R = PhNH-
d R = PhCH(Me)NH-
e R = MeNH-

When **2a** was treated with the hydrazines **4a-d** in the presence of methanolic sodium methoxide the expected isoindolin-3-ones **5a-d** were obtained only in low yield. In all cases the reaction mixtures were complex (tlc) and 2-cyanobenzoic acid could be isolated from the aqueous extracts. When either **4b** or **4d** was used the crude product was a two component solid (tlc) and it was only possible in the case of crude **5d** to separate both components (by fractional recrystallisation). Repeated fractional recrystallisation of **5b** gave only one pure product which was the major component of the original mixture. Elemental analyses indicated that the two products obtained from **4d** were isomeric. Their spectra were similar and both substances produced phthalimide on acidic hydrolysis. We conclude that these compounds are the *E* & *Z* isomers of **5d** and the major product is assumed to be the latter on steric grounds. When **2a** was treated with methyl hydraz-



5a R = Me_2N-
b R = $PhCH_2NH$
c R = PhNH-
d R = PhCH(Me)NH
e R = PhCH=N-



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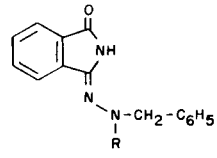
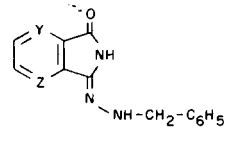
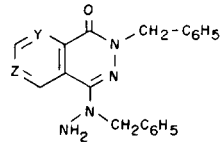


7 R = CO_2Et
8 R = CO_2H
9 R = -CONHPh



10a Y = N, Z = CH
b Z = N, Y = CH



11a Y = N, Z = CH
b Z = N, Y = CH

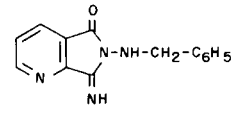


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Table 1

Compound	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
5a	15	133-134.5 [b] (ethyl acetate)	1720	C 63.3 H 5.8 N 21.9	C 63.5 H. 5.8 N 22.2
5b	24	149-150 (ethanol)	1700	C 71.5 H 5.2 N 16.5	C 71.7 H 5.2 N 16.7
5c	27	221-223 [c] (ethyl acetate)	1690	C 70.6 H 4.6 N 17.7	C 70.9 H 4.6 N 17.7
5d *Z*	51	156-156.5 (ethanol)	1710	C 72.75 H 5.7 N 15.9	C 72.4 H 5.7 N 15.8
E	6	131-132 (ethanol)	1695	C 72.4 H 5.9 N 15.9	C 72.4 H 5.7 N 15.8
6	24	164-165 [d] (ethanol)	1620	C 61.5 H 5.0 N 23.8	C 61.7 H 5.1 N 24.0

[a] Yield % pure isolated compound. [b] Lit mp 132-134° [1f]. [c] Lit mp 222° [1j] and 234° [1a]. [d] Lit mp 158-160° [6].

ine **4e**, 1-aminophthalazin-4(3*H*)-one **6** was the only heterocyclic product detected. This result is not too surprising in view of the reported behaviour of **2b** [4] and **3d** [5] with hydrazine hydrate. The collected data for all these compounds are shown in Tables 1 and 2.

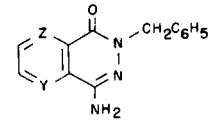
Table 2

P M R

Compound	δ (90 MHz, D_6-DMSO)
5a	11.30 (1H, broad, exchangeable), 7.9-7.5 (4H, complex), 3.62 (6H, s)
5b	10.5 (1H, broad, exchangeable), 7.7-7.10 (9H, complex), 6.75 (1H, t, J = 5 Hz, exchangeable), 4.35 (2H, d, J = 5 Hz becoming 2H, s on exchange)
5c	11.05 (1H, broad, exchangeable), 9.36 (1H, s, exchangeable), 8.0-6.8 (9H, complex)
5d (Z)	10.73 (1H, s, exchangeable), 7.8-7.1 (9H, complex), 6.74 (1H, d, J = 6 Hz, exchangeable), 4.55 (1H, complex becoming 1H, q on exchange), 1.50 (3H, d, J = 7 Hz)
(E)	10.54 (1H, s, exchangeable), 8.30 (1H, complex), 7.9-7.1 (8H, complex), 6.94 (1H, d, J = 5 Hz, exchangeable), 4.41 (1H, complex becoming 1H, q on exchange), 1.48 (3H, d, J = 7 Hz)
6	8.4-7.6 (4H, complex), 5.6-4.9 (2H, broad, exchangeable), 3.58 (3H, s)

In an attempt to prepare tricyclic compounds, **5b** was initially converted into **7** with ethyl chloroformate; however **7** failed to cyclise under the influence of sodium hydride and the major reaction product was **8**. Treatment of **5b** was sulphuryl chloride in dry tetrahydrofuran in the presence of dry triethylamine gave the benzylidene derivative **5e**. This latter compound is not the compound reported by Kohler [1j] and is probably a stereoisomer. When **5b** was treated with phenyl isocyanate the semicarbazone **9** resulted. This compound has not, as yet, shown any promise as a precursor to tricyclic systems.

In the presence of methanolic sodium methoxide **3a-c** reacted with **4b** to yield complex reaction mixtures. In the case of **3a** both the pyrrolopyridine **10a** and pyridopyridazine **11a** were produced. However when **3c** was reacted in a similar manner only **11b** could be isolated whilst **3b** afforded a two component solid. The two components were separated by column chromatography and shown to be isomeric. The minor product was assigned structure **10b** from its spectroscopic data and hydrolysis product. Tentatively we assign structure **12** to the major isomer as its ir spectrum contains two strong absorptions at 1725 and 1690 cm^{-1}.



13a Z = CH, Y = N
b Z = N, Y = CH

From the acidic hydrolysis of **10a** and **10b** the isomeric pyridopyridazine **13a** and **13b** were recovered in low yield produced presumably *via* an acid catalysed intramolecular rearrangement process. It seems probable that **13b** could only have arisen from hydrolysis of a compound with structure **10b** rather than **12**. The collected data for all these compounds are shown in Tables 3 and 4.

All new compounds gave satisfactory analytical figures (CHN) and molecular ions consistent with the proposed molecular formulae.

Table 3

Compound	Reaction Time (hours)	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
10a	3.5	23	223-225 (ethanol)	1720	C 66.3 H 5.0 N 22.4	C 66.7 H. 4.8 N 22.2
10b (E isomer)	8	4	176-177 (ethyl acetate)	1690	C 67.1 H 5.0 N 22.3	C 66.6 H 4.8 N 22.2
11a	–	5	169-170 (methanol)	1655	C 70.3 H 5.3 N 19.6	C 70.6 H 5.3 N 19.6
11b	–	11	156-157 (ethanol)	1655	C 70.6 H 5.4 N 19.5	C 70.6 H 5.3 N 19.6
12	8	14	155-156 (dichloromethane/ ethyl acetate)	1720	C 66.8 H 4.9 N 22.4	C 66.7 H 4.8 N 22.2
13a	–	14	178-180 (methanol)	1620	C 67.1 H 5.1 N 21.8	C 66.7 H 4.8 N 22.2
13b	–	20	185-187 (methanol)	1650	C 67.0 H 5.0 N 22.5	C 67.0 H 4.8 N 22.2

[a] Percent of pure isolated compound.

Table 4

PMR

Compound	δ (90 MHz, D_6-DMSO)
10a	11.0 (1H, s, exchangeable), 8.74 (1H, dd), 8.14 (1H, dd), 7.9-7.1 (6H, complex), 7.08 (1H, t, J = 5 Hz, exchangeable), 4.46 (2H, d, J = 5 Hz becoming 2H, s on exchange)
10b	10.92 (1H, s, exchangeable), 9.20 (1H, t, J = 5 Hz, exchangeable), 8.95 (1H, dd), 8.28 (1H, dd), 7.65 (1H, dd), 7.38 (5H, s), 4.53 (2H, d, J = 5.5 Hz becoming 2H, s on exchange)
11a	8.99 (1H, dd), 8.54 (1H, dd), 7.29 (1H, dd), 7.45-7.14 (10H, complex), 5.20 (2H, s), 4.51 (2H, s), 4.40 (2H, s, exchangeable)
11b	9.45 (1H, d), 8.97 (1H, d), 8.05 (1H, dd), 7.4-7.2 (10H, complex), 5.17 (2H, s), 4.62 (2H, s, exchangeable), 4.52 (2H, s)
12	10.84 (1H, s, exchangeable), 8.68 (1H, dd), 8.14 (1H, dd), 7.5-7.0 (7H, complex becoming 6H complex on exchange) 4.49 (2H, d, J = 5 Hz becoming 2H, s on exchange)
13a	9.06 (1H, dd), 8.51 (1H, dd), 7.86 (1H, dd), 7.38 (5H, s), 6.12 (2H, broad, exchangeable), 5.19 (2H, s)
13b	9.07 (1H, dd), 8.62 (1H, dd), 7.86 (1H, dd), 7.29 (5H, s), 6.15 (2H, s, exchangeable), 5.16 (2H, s)

EXPERIMENTAL

General.

Microanalyses were performed by the Analytical Department of Boots P.L.C. Infrared spectra were recorded for potassium bromide disc on a Perkin-Elmer 397, pmr spectra were recorded at 90 MHz in D_6-DMSO with tetramethylsilane as internal standard on a Jeol FX 90Q, mass spectra were measured at 70 eV using a AEI MS 920S. Thin layer chromatography was performed on silica-gel plates 7 × 5 cm cut from sheets (Merck DC - Alufolien, Kieselgel 60 F_{254}).

Methyl 3-cyanopyridine-2-carboxylate and methyl 3-cyanopyridine-4-carboxylate were prepared by the literature method [7]. Methyl 2-cyanopyridine-3-carboxylate was obtained from 2-carbamoylnicotinic acid by the method of Carpino [3].

Reaction Between **2a** and Substituted Hydrazines **4a-e**.

Methyl 2-cyanobenzoate **2a** (5 g) and the appropriate hydrazine (1 molar equivalent) were added to a solution of sodium (1.43 g, 2 molar equivalents) in methanol (100 ml). The mixture was stirred at room temperature overnight during which time a yellow colour developed. The solvents were removed at reduced pressure and the residue partitioned between water and ethyl acetate. The dried organic phase was concentrated *in vacuo* and the crystalline residue filtered and washed thoroughly with ether. The compounds were recrystallised from the solvents shown in Table 1.

Acidification of the aqueous phase gave 2-cyanobenzoic acid which was obtained as long colourless needles mp 188° from ethyl acetate (reported [8] mp 187°).

Reaction Between **3a-c** and Benzylhydrazine.

The cyanoester (1 molar equivalent) and benzylhydrazine (1 molar equivalent) were added to a solution of sodium methoxide (2 molar equivalents) in methanol (30 ml/g of the ester) and the mixture stirred at room temperature and monitored by tlc. The solvents were removed *in vacuo* when no starting material remained and the residue extracted with ether. The residue was acidified (dilute sulfuric acid) and the product either extracted with ethyl acetate or filtered. The crude products were recrystallised from the solvents shown in Table 3 or in the case of the reaction product from **3b** chromatographed and the pure components recrystallised from the stated solvents. The ethyl acetate extracts were

dried and on concentration the compounds **12a-b** separated. After washing with a little ether the pure products were obtained by recrystallisation from ethanol.

Acidic Hydrolysis of **11a** and **11b**.

The method of Elvidge [1a] was used. The products were obtained by concentration of the solution and neutralisation with sodium bicarbonate. The crude products were washed with water, cold methanol and recrystallised from methanol.

Reaction Between **5b** and Ethyl Chloroformate.

A solution of **5b** (2.0 g) dry triethylamine (6 ml) in dry tetrahydrofuran (50 ml) was stirred at 0° and ethyl chloroformate (2 ml) was added dropwise. The mixture was allowed to warm to room temperature then heated under reflux for 8 hours. The cooled mixture was filtered and the solvent removed under reduced pressure to yield a yellow oil (1.4 g). The oil crystallised on the addition of light petroleum-ether to yield a white solid (1.15 g). Recrystallisation from ether gave fine white needles of pure **7** (0.75 g, 29%) mp 135-136°; ir (potassium bromide): 3210, 1740, 1670, 1640 cm^{-1}; pmr (90 MHz, D_6-DMSO): 11.25 (1H, s, exchangeable), 7.85 (4H, ~d), 7.31 (5H, ~d), 4.79 (2H, s), 4.15 (2H, q), 1.16 (3H, t); ms: m/e 323 M^+.

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.9; H, 5.3; N, 13.0. Found: C, 67.2; H, 5.7; N, 13.2.

Attempted Cyclisation of **7**.

A solution of **7** (3.1 g) in dry tetrahydrofuran (20 ml) was added to a suspension of sodium hydride (400 mg, 50% mineral oil dispersion) and the mixture stirred at room temperature for 24 hours. Thin layer chromatography indicated little or no reaction. A further quantity of sodium hydride (400 mg) was added and the mixture heated under reflux for 4 hours. The excess hydride was destroyed by the addition of ethanol, the solvents removed under reduced pressure and the mixture poured onto dilute sulphuric acid/ice. The mixture was extracted (×3) with ethyl acetate to yield on concentration crude **8** (1.25 g). After repeated recrystallisation from methanol the pure acid **8** (400 mg, 14%) mp 241-243° was obtained; ir (potassium bromide): 3280, 3100-2100 (broad), 1700 (broad) cm^{-1}; pmr (90 MHz, D_6-DMSO): 12.63 (1H, broad, exchangeable), 11.97 (1H, broad, exchangeable), 7.91-7.23 (9H, complex), 4.92 (2H, s); ms: m/e 295 M^+.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.1; H, 4.4; N, 14.2. Found: C, 65.2; H, 4.5; N, 14.3.

By concentration of the mother liquors another product (480 mg) was obained. However, it was not possible to purify this compound and its structure remains unknown.

Reaction of **5b** With Sulphuryl Chloride.

A solution of **5b** (2.0 g) in dry tetrahydrofuran (100 ml) containing dry triethylamine (2 ml) was cooled to 0°C and with vigorous stirring sulphuryl chloride (1.08 g) was added dropwise. The mixture was stirred overnight, filtered and the solvents removed *in vacuo* to yield a yellow solid (1.84 g). Recrystallisation from ethyl acetate gave the pure benzylidene derivative **5e** (1.75 g, 88%) mp 201-203° as small yellow needles; ir (potassium bromide): 3020 (broad), 1730 cm^{-1}; pmr (90 MHz, D_6-DMSO): 11.05 (1H, s, exchangeable), 8.7-8.6 (2H, complex), 8.0-7.5 (8H, complex); ms: m/e 249 M^+.

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.3; H, 4.4; N, 16.9. Found: C, 72.4; H, 4.5; N, 17.0.

Reaction of **5b** With Phenyl Isocyanate.

A solution of **5b** (2.29 g) and phenyl isocyanate (1.5 g) in dry tetrahydrofuran (80 ml) was heated under reflux for two hours. The solvents were removed *in vacuo* to yield a pale yellow solid (2.70 g). Recrystallisation from ethanol gave pure **9** (2.13 g, 63%) mp 175-177° as fine white needles; ir (potassium bromide): 3370, 3255, 1720, 1690, 1660 cm^{-1}; pmr (90 MHz, D_6-DMSO): 11.47 (1H, s, exchangeable), 8.75 (1H, s, exchangeable), 8.05-6.92 (14H, complex), 5.00 (2H, s); ms: m/e 370 M^+.

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.4; H, 4.9; N, 15.1. Found: C, 71.1; H, 5.1; N, 14.9.

Acknowledgement.

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