A. D. Dunn

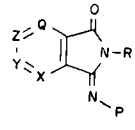
Dundee College of Technology, Bell Street,
Dundee DD1 1HG, Scotland UK

Received February 29, 1984

The synthesis of the aza analogues **3a-d** of 1-iminoisoindolin-3-one **1** and their use in the preparation of pyrrolopyridines and pyridopyridazines is described. The synthesis of derivatives of these imines is also reported.

J. Heterocyclic Chem., **21**, 965 (1984).

In an earlier paper [1] we have referred to the use of 1-iminoisoindolin-3-one (**1**) [2] as an intermediate in the synthesis of 1-aminoiminoisoindolin-3-ones [3]. Recently the synthesis of an aza analogue of this useful compound was reported [4] but no examples of its use in the preparation of other heterocycles have as yet been recorded.

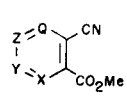


	X	Y	Z	Q	P	R
1	CH	CH	CH	CH	H	H
3a	N	CH	CH	CH	H	H
3b	CH	CH	CH	N	H	H
3c	CH	N	CH	CH	H	H
3d	CH	CH	N	CH	H	H
3e	N	CH	CH	CH	Et	H
3f	N	CH	CH	CH	$PhCH_2$	H
4a	N	CH	CH	CH	Me_2N	H
4b	CH	CH	CH	N	Me_2N	H
4c	CH	N	CH	CH	Me_2N	H
4d	CH	CH	N	CH	Me_2N	H
9a	CH	CH	CH	CH	H	CH_2CO_2Et
9b	CH	CH	CH	N	H	CH_2CO_2Et
9c	CH	CH	CH	CH	CONHPh	H
9d	N	CH	CH	CH	CONHPh	H

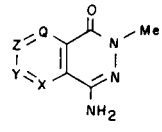
This paper describes the synthesis of all four aza analogues of **1** *ie* **3a-d** and their reactions with substituted hydrazines, active methylene compounds, phenyl isocyanate and ethyl bromoacetate.

When the cyanoesters **2a-d** were treated with methanolic ammonia [4] the bicyclic imines **3a-d** were obtained in high yield. Although recrystallisation was possible, these compounds could be obtained analytically pure by merely washing the crude reaction product with methanol. It was also possible to prepare 1-substituted imines by using a primary amine in place of ammonia. Thus ethylamine gave **3e** and benzylamine produced **3f**. In both these reactions thin layer chromatography indicates that one major and one minor product of very similar Rf value are produced. However in either case only the major product could be isolated.

The major product from these two reactions was assigned the *Z* configuration for steric reasons. The collected



2a-d



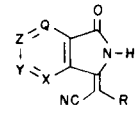
5a-d

	X	Y	Z	Q
2a, 5a	N	CH	CH	CH
2b, 5b	CH	CH	CH	N
2c, 5c	CH	N	CH	CH
2d, 5d	CH	CH	N	CH

data for all these imines are presented in Table 1.

Reaction between imines **3a-d** and 1,1-dimethylhydrazine gave the pyrrolopyridines **4a-d** whilst treatment with methylhydrazine led to the formation of the pyridopyridazines **5a-d**. Again it is assumed that for steric reasons **4a-d** will possess the *Z* configuration. All these new compounds gave satisfactory analytical data and their spectroscopic properties are in accord with the proposed structures (Tables 2 and 3).

Condensation between the imines and active methylene compounds containing a cyano group occurred by heating the reactants together at 150° until no more ammonia was evolved. Under these conditions **1, 3a, 3b** and **3d** gave the cyanoesters **6a-d**. The dinitrile **7** resulted from the reaction between **1** and malononitrile in refluxing 2-propanol.



	X	Y	Z	Q	R
6a	CH	CH	CH	CH	CO_2Et
6b	N	CH	CH	CH	CO_2Et
6c	CH	CH	CH	N	CO_2Et
6d	CH	CH	N	CH	CO_2Et
7	CH	CH	CH	CH	CN
8	CH	CH	CH	CH	$CONH_2$

(An uncontrollable exothermic reaction proceeds if these reactants are heated together in the absence of solvent). Treatment of the ester **6a** with concentrated aqueous ammonia gave the amide **8**. No condensation was observed when the active methylene compound used was ethyl acet-

Table 1

Compound	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
3a	97	316-317 dec	1710	C 57.15 H 3.1 N 28.9	C 57.1 H. 3.4 N 28.6
3b	96	>260 dec [b]	1720	C 57.0 H 3.1 N 28.8	C 57.1 H 3.4 N 28.6
3c	83	240-241 dec (methanol)	1710	C 57.1 H 3.4 N 29.0	C 57.1 H 3.4 N 28.6
3d	86	264-266 dec (methanol)	1700	C 57.05 H 3.1 N 28.9	C 57.1 H 3.4 N 28.6
3e	27	118-119 (propan-2-ol/ether)	1730	C 56.0 H 5.7 N 21.8	C 56.0 [c] H 5.7 N 21.8
3f	49	171 (methanol)	1730	C 70.6 H 4.8 N 17.7	C 70.9 H 4.6 N 17.8

[a] Yield % of pure isolated compound. [b] Lit mp 162° [2]. [c] Monohydrate. Because of the insolubility of **3a-d** pmr data is largely meaningless, in the mass spectrum all show m/e 147 (100%) M^+; compound **3e** (90 MHz, D_6-DMSO): 9.60 (1H, s, exchangeable), 8.89 (1H, dd), 8.20 (1H, dd), 7.70 (1H, dd), 3.82 (2H, q), 1.23 (3H, t); compound **3f** (90 MHz, d_6-DMSO): 9.76 (1H, s, exchangeable), 8.92 (1H, dd), 8.28 (1H, dd), 7.73 (1H, dd), 7.30 (5H, s), 4.97 (2H, s).

Table 2

Compound	Reaction Time (hours)	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
4a	24	77	147.5-148.5 (dichloromethane/petrol)	1700	C 56.5 H. 5.2 N 29.7	C 56.8 H 5.3 N 29.5
4b	20	56	159-162 (dichloromethand/petrol	1740	C 56.5 H 5.2 N 29.9	C 56.8 H 5.3 N 29.5
4c	4	47	214.5-215.5 (methanol)	1735	C 56.5 H 5.1 N 29.8	C 56.8 H 5.3 N 29.5
4d	1¼	48	225-226 (methanol)	1730	C 56.8 H 5.4 N 29.2	C 56.8 H 5.3 N 29.5
5a	2½	41	264-266 (methanol)	1620	C 54.6 H 4.7 N 32.1	C 54.5 H 4.5 N 31.8
5b	20	37	255-257 (ethanol)	1620	C 51.3 H 5.6 N 29.8	C 51.1 [b] H 5.0 N 29.8
5c	2	26	255-258 (ethanol)	1635	C 54.0 H 4.4 N 31.3	C 54.5 H 4.5 31.8
5d	1½	22	310-314 (methanol)	1630	C 54.4 H 4.3 N 31.8	C 54.5 H 4.5 N 31.8

[a] Yield % of pure isolated compound. [b] $C_8H_8N_4O.0.66H_2O$.

Table 3

PMR

Compound	δ (90 MHz, D_6-DMSO)
4a	11.6-10.6 (1H, broad, exchangeable), 8.84 (1H, dd), 8.18 (1H, dd), 7.61 (1H, dd), 2.68 (6H, s)
4b	10.6-10.2 (1H, broad, exchangeable), 8.86 (1H, dd), 8.19 (1H, dd), 7.63 (1H, dd), 2.67 (6H, s)
4c	12.0-10.1 (1H, broad, exchangeable), 8.96 (1H, d), 8.82 (1H, d), 7.70 (1H, dd), 2.74 (6H, s)
4d	11.6-10.1 (1H, broad, exchangeable), 9.01 (1H, d), 8.85 (1H, d), 7.72 (1H, dd), 2.68 (6H, s)
5a	9.04 (1H, dd), 8.56 (1H, dd), 7.77 (1H, dd), 5.00 (2H, broad, exchangeable), 3.55 (3H, s)
5b	9.01 (1H, dd), 8.48 (1H, dd), 7.82 (1H, dd), 4.07 (2H, broad, exchangeable), 3.56 (3H, s)
5c	9.42 (1H, d), 8.95 (1H, d), 8.05 (1H, dd), 6.20 (2H, broad, exchangeable), 3.55 (3H, s)
5d	9.41 (1H, d), 8.98 (1H, d), 7.95 (1H, dd), 6.18 (2H, broad, exchangeable), 3.54 (3H, s)

oacetate, or diethyl malonate. The data for all these compounds are collected in Tables 4 and 5.

Treatment of **1** with ethyl bromoacetate led to alkylation of the pyrrolo ring nitrogen and **9a** was obtained in good yield. Acidic hydrolysis of **9a** gave ethyl phthalimidoacetate which confirmed the site of alkylation. Similar treatment of **3b** gave **9b** but it was not possible to confirm the structure of this compound by degradation and consequently its structure is assumed by analogy with **9a**.

In toluene solution **1** reacted with phenyl isocyanate to yield **9c**. Acidic hydrolysis of **9c** gave phthalimide indicating that this time reaction had occurred on the imine nitrogen atom. Similarly **3a** gave **9d** and again its structure was assumed by analogy with **9c**.

EXPERIMENTAL

For general methods see reference [1].

Preparation of Imines **3a-d**.

A suspension of the appropriate cyanoester **2a-d** in methanol (100 ml) was treated with a stream of dry ammonia gas for a few minutes. After standing overnight the product was filtered and washed with cold methanol or if no product was evident the solvents were removed under reduced pressure and the residue washed with ice cold methanol.

Preparation of Substituted Imines **3e-f**.

The above procedure was followed using the appropriate primary amine (5 molar equivalents) in place of gaseous ammonia and allowing the reaction mixture to stand at room temperature for three days.

Reaction of Imines **3a-d** with Hydrazines.

A suspension of the imine (1 molar equivalent) and the appropriate hydrazine (5 molar equivalents) in methanol (20 ml/g imine used) was heated under reflux (see Table 2). The solvents were removed *in vacuo* only if no solid appeared on cooling and the crude products recrystallised from the reported solvent (see Table 2).

Condensation of Imines **1**, **3a**, **3b** and **3d** With Ethyl Cyanoacetate.

A mixture of the imine (1 g) and ethyl cyanoacetate (10 ml) was heated at 150° ±5° for about ten minutes until no more ammonia was evolved. On cooling, the solid was filtered, washed with ether and where necessary recrystallised from ethanol.

Reaction of **1** with Malononitrile.

A mixture of **1** (0.94 g), malononitrile (1.94 g) and 2-propanol (50 ml) was heated under reflux for about one hour until no more ammonia was evolved. The solution was cooled to yield a tan/orange solid (780 mg) which was recrystallised from ethanol to yield **7** as a white solid (480 mg).

Table 4

Compound	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
6a	49	177-178 (ethanol)	1755 1690	C 64.1 H 4.2 N 11.5	C 64.5 H. 4.1 N 11.6
6b	80	241-243 (ethanol)	1740 1690	C 58.9 H 3.7 N 17.1	C 59.3 H 3.7 N 17.3
6c	57	213-216 (ethanol)	1755 1690	C 59.4 H 3.8 N 17.3	C 59.3 H 3.7 N 17.3
6d	95	250-252 [b]	1755 1705	C 58.9 H 3.6 N 17.2	C 59.3 H 3.7 N 17.3
7	38	254-255 (ethanol)	1750	C 67.4 H 2.5 N 21.6	C 67.7 H 2.6 N 21.5
8	60	>300 (dimethylformamide)	1735 1670	C 61.8 H 3.2 N 19.7	C 62.0 H 3.3 N 19.7

[a] Yield % of pure isolated compound. [b] Highly insoluble in all organic solvents.

Table 5

PMR

Compound	δ (90 MHz, D_6-DMSO)
6a	11.8 (1H, broad, exchangeable), 8.47 (1H, complex), 8.0-7.8 (3H, complex), 4.20 (2H, q), 1.32 (3H, t)
6b	11.4 (1H, broad, exchangeable), 9.01 (1H, dd), 8.32 (1H, dd), 7.78 (1H, dd), 4.36 (2H, q), 1.33 (3H, t)
6c	10.80 (1H, broad, exchangeable), 8.97 (1H, dd), 8.75 (1H, dd), 7.84 (1H, dd), 4.37 (2H, q), 1.33 (3H, t)
6d	11.20 (1H, broad, exchangeable), 9.62 (1H, d), 9.06 (1H, d), 7.91 (1H, dd), 4.37 (2H, q), 1.33 (3H, t)
7	12.62 (1H, broad, exchangeable), 8.28 (1H, complex), 7.92 (3H, complex)
8	11.12 (1H, broad, exchangeable), 8.40 (1H, complex), 8.1-7.2 (5H, complex, becoming 3H complex on exchange)

Table 6

Compound	Yield [a]	mp (°C)	IR (potassium bromide) cm^{-1}	Found	Calcd.
9a	72	108-110 (ethyl acetate/ether)	1750 1725	C 61.7 H 5.1 N 12.0	C 62.1 H 5.2 N 12.1
9b	90	155-156 (ethanol)	1750 1730	C 55.5 H 4.6 N 17.6	C 55.2 [b] H 4.9 N 17.6
9c	80	174-176 (toluene)	1740 1660	C 67.9 H 4.1 N 15.8	C 68.1 H 4.2 N 15.9
9d	51	175-177 (toluene)	1755 1665	C 63.4 H 3.8 N 20.9	C 63.2 H 3.8 N 21.1

[a] Yield % of pure isolated compound. [b] For $C_{11}H_{11}N_3O_3.0.33H_2O$.

Table 7

PMR

Compound	δ (90 MHz, D_6-DMSO)
9a	10.20 (1H, s, exchangeable), 8.21 (1H, complex), 7.81 (3H, complex), 4.50 (2H, s), 4.15 (2H, q), 1.20 (3H, t)
9b	9.94 (1H, s, exchangeable), 8.97 (1H, dd), 8.32 (1H, dd), 7.77 (1H, dd), 4.57 (2H, s), 4.16 (2H, q), 1.20 (3H, t)
9c	11.12 (1H, s, exchangeable), 10.00 (1H, s, exchangeable), 8.0-7.5 (6H, complex), 7.5-6.9 (3H, complex)
9d	11.72 (1H, s, exchangeable), 10.20 (1H, s, exchangeable), 9.00 (1H, dd), 8.28 (1H, broad, s), 8.0-6.9 (6H, complex)

Reaction Between **6a** and Aqueous Ammonia.

A suspension of **6a** and aqueous ammonia (25 ml, sp. g. 0.88) was stirred at room temperature for 24 hours. The product **8** (370 mg) was filtered off. A further quantity of the same material (160 mg) was obtained by concentration of the aqueous filtrate. Recrystallisation from DMF gave fine white needles (350 mg) of pure **8**.

Reaction Between Ethyl Bromoacetate and Imines **1** and **3b**.

The imine (1 molar equivalent), ethyl bromoacetate (1.1 molar equivalents), potassium iodide (100 mg), anhydrous potassium carbonate (2 molar equivalents) and acetone (30 ml/g imine) were stirred at room temperature for 72 hours. The mixture was filtered, to remove inorganic solids which were washed with acetone. The combined filtrate and washings were concentrated *in vacuo* to give a solid which was recrystallised from the appropriate solvent to yield the pure esters **9a** and **9b** (see Tables 6 and 7).

Hydrolysis of **9a**.

A mixture of **9a** (500 mg) and 5% hydrochloric acid (20 ml) were heated under reflux for a few minutes until a clear solution was obtained. On cooling fine needles (200 mg) separated. Recrystallisation from water gave ethyl phthalimidoacetate (120 mg) mp 111-112° (reported [5] mp 112-113°).

The ir spectrum (potassium bromide) of this solid was completely superimposable with an ir spectrum of the authentic compound.

Reaction Between Phenyl Isocyanate and Imines **1** and **3a**.

The imine (1 molar equivalent), phenyl isocyanate (1 molar equivalent) and dry toluene (50 ml/g imine) was heated under reflux for 5 hours. The crude urea crystallised on cooling and was filtered, washed with cold toluene and then recrystallised from toluene to yield pure ureas **9c** and **9d** (see Tables 6 and 7).

Hydrolysis of **9c**.

A mixture of **9c** (280 mg) and 5% hydrochloric acid (20 ml) was treated as above. On cooling a white solid was produced. Recrystallisation from hot water gave pure phthalimide (70 mg) identical in all respects to an authentic sample (mp, mmp and ir).

Acknowledgements.

I am indebted to the late Dr. J. S. Nicholson for his advice and suggestions during the course of this work and to the Boots P. L. C. for generous financial support.

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