Synthesis of *N*-Phenylpyrrole and Pyrazole Amidines and Related Diamines

Richard L. Jarvest* and Joanne E. Marshall

SmithKline Beecham Pharmaceuticals, Great Burgh,
Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, U.K.

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N-Phenylpyrrole and pyrazole nitriles **3,4,10** were prepared in one step from the corresponding aldehydes. The nitriles were converted into novel amidines **5,6,14** and related diamines **7,8,12** were also prepared from the aldehydes. The orientation of the phenyl ring to the basic function was controlled by modifying the torsional angle between the rings by methyl group substitution on the heterocycle.

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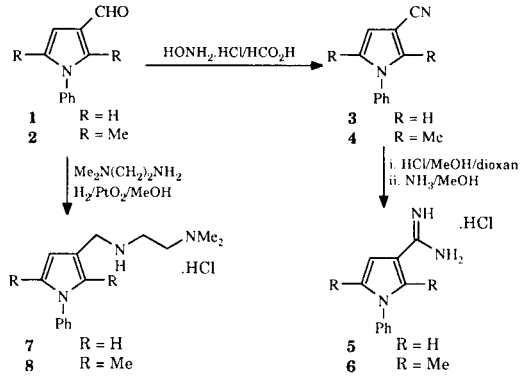
As part of a programme of designing potential antagonists of the interaction of Human Immunodeficiency Virus (HIV) surface protein gp120 with the cellular receptor CD4, we became interested in phenyl heterocyclic amidines and related compounds. For the binding interaction with gp120, two particularly significant residues on the surface of CD4 are the phenyl ring of phenylalanine 43 and the guanidine moiety of arginine 59 [1], and in the X-ray structure of a soluble form of CD4 these are closely located [2,3]. It seemed possible that phenyl heterocyclic amidines could act as possible topological mimics of these functions with the following useful features: *i*) the heteroaromatic ring acts as an appropriate spacer unit between the amidine and phenyl moieties; *ii*) the substitution *ortho* to the phenyl ring controls the torsional angle between the phenyl ring and the rest of the molecule, allowing the amidine to be oriented out of plane from the phenyl ring as desired; and *iii*) the amidine moiety is a planar highly basic functionality like the guanidine moiety. Diamine substituents were also investigated in place of the amidine as a more flexible group that should also be monoprotonated at neutral *p*H.

We chose to prepare amidines of *N*-phenylpyrroles and *N*-phenylpyrazoles from the corresponding heterocyclic nitriles which in turn should be available from the corresponding aldehydes. One-step conversion of *N*-unsubstituted pyrrole aldehydes to cyanopyrroles has been reported with aqueous hydroxylamine *O*-sulphonic acid [6]. We found that the one-step conversion using hydroxylamine hydrochloride in formic acid [7] was a convenient route to the desired *N*-phenylheterocyclic nitriles.

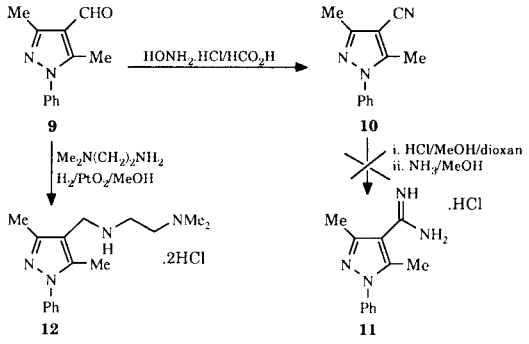
The cyanopyrrole **3** has previously been obtained by rearrangement of a thiophene [4] and the dimethyl homologue **4** has been obtained in 5% yield by electrochemical means [5]. We prepared the cyanopyrroles from the aldehydes **1** and **2** by the one-step method using hydroxylamine hydrochloride in formic acid [7] to obtain **3** and **4** in yields of 61% and 40% respectively (Scheme 1). The cyanopyrroles were converted to the methyl imidate esters with methanolic hydrogen chloride in dioxan and these were treated with methanolic ammonia to afford the amidines **5** and **6** (isolated in yields of 76% and 31% respectively). The aldehydes **1** and **2** were also converted to the diamines **7** and **8** by reductive amination with *N,N*-dimethylethylenediamine in the presence of Adam's catalyst under hydrogen, affording **7** and **8** in yields of 34% and 39% respectively after conversion to their hydrochloride salts.

Scheme 1

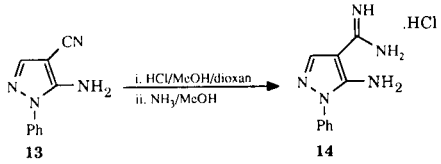


The pyrazole aldehyde **9** was converted by the same one-step procedure to the cyanopyrazole **10** [8] in 57% yield (Scheme 2). Whilst **10** could be converted to the intermediate imidate, attempts to take this through to the amidine **11** were unsuccessful, resulting in very slow conversion to the amide. The failure of this reaction is not due to the change to the pyrazole system as the cyanopyrazole **13** was converted to the amidine **14** in 63% yield by this method (Scheme 3). The difficulty in forming **11** is presumably a result of steric hindrance from the two *ortho* methyl groups: attack on the cyano group can occur from above the ring and is not sterically demanding whereas the imidate is probably twisted out of conjugation with the ring and nucleophile approach is then hindered by the methyl groups, resulting in the slower attack at the imidate methyl group to afford the amide. Reductive amination of **9** was successful and the diamine **12** was obtained in 37% yield after conversion to the dihydrochloride salt.

Scheme 2



Scheme 3



Calculations of the torsional angle of the phenyl ring to the heterocycle in the minimum energy forms of the pyrroles **5** and **7**, the dimethylpyrroles **6** and **8**, and the pyrazoles **12** and **14** were performed by molecular mechanics methods [9]. They were found to be 40° for **5**, **7** and **14**, 65° for **12**, and 90° for **6** and **8**, thus spanning the desired range. The increase in torsional angle in going from **5** to **6**, and from **7** to **8** was manifested in major differences in their uv spectra. The effect was particularly pronounced in going from **7** which had a λ max of 251 nm to **8** which had only an inflexion at 215 nm, reflecting complete loss of conjugation as the phenyl group is twisted perpendicular to the heterocyclic ring.

The second pK_a of the diamine **8** was experimentally determined to be 6.24, confirming that the diamines **7**, **8** and **12** exist predominantly as the monoprotonated species at neutral *p*H.

EXPERIMENTAL

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. The nmr spectra were recorded with a Jeol GX-270 270 MHz spectrometer using dimethyl sulphoxide-d_6 as a solvent unless otherwise indicated. Ir spectra were recorded with a Bio-Rad FTS-7 spectrometer with the sample prepared as a potassium bromide disc unless otherwise indicated. The uv spectra were recorded on a Uvikon 810 or a Cary 219 spectrometer using methanol as solvent. Mass spectra were recorded on a Jeol JMS-SX102 spectrometer and microanalyses were performed on a Carlo Erba model 1106 analyser. The pK_a determination was carried out by titration of a solution of **8** in 0.1*M* potassium chloride with 0.1*M* hydrochloric acid at 25°. Column chromatography was carried out on Merck 7736 silica gel. All compounds were homogeneous by tlc on silica gel $60F_{254}$ coated aluminium sheets.

1-Phenylpyrrole-3-carbonitrile (**3**).

A solution of 0.97 g (5.08 mmoles) of the aldehyde **1** and 0.46 g (6.6 mmoles) of hydroxylamine hydrochloride in 4.2 ml of 96% formic acid was heated under reflux for 1 hour. The mixture was allowed to cool, diluted with water, neutralised by addition of 5% aqueous sodium hydroxide, and extracted with ethyl acetate. The organic layer was dried (magnesium sulphate), the solvent evaporated, and the residue purified by column chromatography on silica gel eluting with 15% ethyl acetate in hexane to afford 0.52 g (61%) of 1-phenylpyrrole-3-carbonitrile (**3**) [4]; ir (film): 3136, 2227, 1600, 1535, 1511 cm^{-1}; ^1H nmr (deuteriochloroform): 6.59 (dd, J = 1.7 and 3.3 Hz, 1H, 4-H), 7.03 (dd, J = 2.2 and 3.3 Hz, 1H, 5-H), 7.35-7.52 (m, 6H, 2-H and C_6H_5); ms: (CI, ammonia) m/z 186 (MNH_4^+), 168 (M^+).

2,5-Dimethyl-1-phenylpyrrole-3-carbonitrile (**4**).

Compound **4** was prepared in a similar way to **3** but using 1.00 g (5.0 mmoles) of the aldehyde **2** and a 30 minute reflux to afford 0.39 g (40%) 2,5-dimethyl-1-phenylpyrrole-3-carbonitrile (**4**) [5]; ir: 2218, 1596, 1532, 1495, 1414 cm^{-1}; ^1H nmr (deuteriochloroform): 1.93 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 6.27 (d, J = 1.1 Hz, 1H, 4-H), 7.35 (m, 2H, C_6H_5), 7.55 (m, 3H, C_6H_5); ms: (CI, ammonia) m/z 214 (MNH_4^+), 197 (MH^+).

3,5-Dimethyl-1-phenylpyrazole-4-carbonitrile (**10**).

Compound **10** was prepared in a similar way to **3** but using 0.24 g (1.2 mmoles) of the aldehyde **9** and eluting with 20% ethyl acetate in hexane to afford 0.14 g (57%) 3,5-dimethyl-1-phenylpyrazole-4-carbonitrile (**5**) [8]; ir: 2221, 1596, 1554, 1508, 1483, 1428 cm^{-1}; ^1H nmr (deuteriochloroform): 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.44 (m, 5H, C_6H_5); ms: m/z (CI, ammonia) 198 (MH^+).

1-Phenylpyrrole-3-carboxamidine Hydrochloride (**5**).

Hydrogen chloride was passed through an ice-cooled solution of 0.11 g (0.65 mmole) of the cyanopyrrole (**3**) in 5 ml of dioxan and 0.5 ml of methanol for 4 minutes and the solution was allowed to stand at room temperature for 16 hours. The solvent was evaporated to afford 0.12 g of the intermediate imidate ester which was dissolved in 1 ml of methanolic ammonia. The solution was allowed to stand at room temperature for 24 hours, the solvent evaporated, and the residue purified by column chromatography on C_{18}-reverse phase silica gel eluting with water followed by 10% methanol in water. Product containing fractions were pooled, acidified with dilute hydrochloric acid, and the solvent evaporated to afford 0.11 g (76%) of 1-phenylpyrrole-3-carboxamidine hydrochloride (**5**) as a white crystalline solid, mp 265-267°; uv: λ max 267 nm (ε 16,800); ir: 3291, 3127, 1660, 1577, 1515 cm^{-1}; ^1H nmr: 7.02 (dd, J = 1.8 and 3.2 Hz, 1H, 4-H), 7.40 (m, 1H, 5-H), 7.59 (m, 5H, C_6H_5), 8.53 (t, J = 1.9 Hz, 1H, 2-H), 8.64 (s, 2H, deuterium oxide-exchangeable, NH_2), 8.99 (s, 2H, deuterium oxide-exchangeable, NH_2); ms: (CI, ammonia) m/z 186 (MH^+ of free base).

Anal. Calcd. for $C_{11}H_{11}N_3 \cdot HCl \cdot 0.5H_2O$: C, 57.26; H, 5.68; N, 18.21. Found: C, 57.36; H, 5.47; N, 18.07.

2,5-Dimethyl-1-phenylpyrrole-3-carboxamidine Hydrochloride (**6**).

Compound **6** was prepared in a similar way to **5** but using 0.20 g (1 mmole) of cyanopyrrole **4**. The imidate formation was left for 48 hours and the final product was eluted from the reverse phase column with water to afford 78 mg (31%) of 2,5-dimethyl-1-phenylpyrrole-3-carboxamidine hydrochloride (**6**), mp >300°; uv: λ

max 241 (ε 11,500) and 277 nm (ε 5,800); ir (potassium chloride): 3412, 3313, 3158, 1657, 1584, 1561, 1496, 1405 cm^{-1}; ^1H nmr: 1.96 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 6.35 (d, J = 0.8 Hz, 1H, 4-H), 7.31 (m, 2H, C_6H_5), 7.58 (m, 3H, C_6H_5), 8.48 (s, 2H, deuterium oxide-exchangeable, NH_2), 8.52 (s, 2H, deuterium oxide-exchangeable, NH_2); ms: (CI, ammonia) m/z 214 (MH^+ of free base).

Anal. Calcd. for $C_{13}H_{15}N_3 \cdot HCl \cdot 1.5H_2O$: C, 56.42; H, 6.92; N, 15.18. Found: C, 56.10; H, 6.55; N, 15.05.

5-Amino-1-phenylpyrazole-4-carboxamidine Hydrochloride (**14**).

Compound **14** was prepared in a similar way to **5** but using 0.18 g (1 mmole) of the cyanopyrazole **13**. The final product was eluted from the reverse phase column with water to afford 0.15 g (63%) of 5-amino-1-phenylpyrazole-4-carboxamidine hydrochloride (**14**), mp 219-221°; uv: λ max 240 nm (ε 16,800); ir: 3414, 3337, 3306, 3179, 3062, 1657, 1576, 1502 cm^{-1}; ^1H nmr: 6.55 (br, 2H, deuterium oxide-exchangeable, 5-NH_2), 7.50 (m, 5H, C_6H_5), 8.00 (s, 1H, 3-H), 8.42 (br, 4H, deuterium oxide-exchangeable, $C(NH_2)_2$); ms: (CI, ammonia) m/z 202 (MH^+ of free base).

Anal. Calcd. for $C_{10}H_{11}N_5 \cdot HCl \cdot 0.2H_2O$: C, 49.78; H, 5.18; N, 29.02. Found: C, 49.90; H, 5.34; N, 29.13.

3-{[2-(Dimethylamino)ethylamino]methyl}-1-phenylpyrrole Hydrochloride (**7**).

To a solution of 0.95 g (5.0 mmoles) of the aldehyde **1** and 0.43 g (5.0 mmoles) of *N,N*-dimethylethylenediamine in 16 ml of methanol under nitrogen, was added 60 mg of platinum dioxide and the mixture was stirred under an atmosphere of hydrogen for 14 hours. The solution was filtered, the solvent evaporated and the residue purified by column chromatography on silica gel eluting with 5% methanol in chloroform containing ammonia to afford 0.73 g (60%) of the free amine of **7**. To a solution of 0.29 g (1.2 mmoles) of this amine in 2 ml of ethyl acetate was added a few drops of a solution of hydrogen chloride in ethyl acetate and the solution cooled in an ice-bath for 30 minutes. The precipitated white solid was filtered off to afford 0.19 g (57% from free amine, 34% from **1**) of 3-{[2-(dimethylamino)ethylamino]methyl}-1-phenylpyrrole hydrochloride (**7**), mp 162-164°; uv: λ max 251 nm (ε 13,300); ir (potassium chloride): 3397, 2941, 2782, 2673, 2424, 1601, 1516, 1453 cm^{-1}; ^1H nmr: 2.24 (s, 6H, $N(CH_3)_2$), 2.60 (t, J = 6.1 Hz, 2H, CH_2N), 2.97 (t, J = 6.3 Hz, 2H, CH_2N), 3.99 (s, 2H, 3-CH_2), 6.45 (dd, J = 1.8 and 2.9 Hz, 1H, 4-H), 7.28 (m, 1H, 5-H), 7.40 (t, J = 2.8 Hz, 1H, 2-H), 7.54 (m, 5H, C_6H_5); ms: (CI, ammonia) m/z 244 (MH^+ of free base).

Anal. Calcd. for $C_{15}H_{21}N_3 \cdot HCl \cdot 0.4H_2O$: C, 62.77; H, 7.86; N, 14.64. Found: C, 62.91; H, 7.91; N, 14.58.

2,5-Dimethyl-3-{[2-(dimethylamino)ethylamino]methyl}-1-phenylpyrrole Hydrochloride (**8**).

Compound **8** was prepared in a similar way to **7** but using 1.05 g (5.27 mmoles) of the aldehyde **2** to afford 0.65 g (39%) of 2,5-dimethyl-3-{[2-(dimethylamino)ethylamino]methyl}-1-phenylpyrrole hydrochloride (**8**), mp 161-165°; uv: λ max 215 nm (inflexion, ε 13,200); ir (potassium chloride): 3406, 2977, 2922, 2776, 2710, 2647, 2477, 1597, 1585, 1533, 1498, 1468, 1414 cm^{-1}; ^1H nmr: 1.95 (s, 3H, 2/5-CH_3), 1.98 (s, 3H, 5/2-CH_3), 2.32 (s, 6H, $N(CH_3)_2$), 2.72 (br, 2H, CH_2N), 2.97 (br t, J = 5.6 Hz, 2H, CH_2N), 3.93 (s, 2H, 3-CH_2), 6.09 (s, 1H, 4-H), 7.25 (m, 2H, C_6H_5), 7.52 (m, 3H, C_6H_5); ms: (FAB, glycerol) m/z 272 (MH^+ of free base).

Anal. Calcd. for $C_{17}H_{25}N_3 \cdot HCl \cdot 0.75H_2O$: C, 63.53; H, 8.63; N, 13.08. Found: C, 63.53; H, 8.46; N, 12.98.

3,5-Dimethyl-4-{[2-(dimethylamino)ethylamino]methyl}-1-phenylpyrazole Dihydrochloride (**12**).

Compound **12** was prepared in a similar way to **7** but using 0.60 g (3.0 mmoles) of the aldehyde **9** to afford 0.35 g (37%) of 3,5-dimethyl-4-{[2-(dimethylamino)ethylamino]methyl}-1-phenylpyrazole dihydrochloride (**12**), mp 218-222°; uv: λ max 244 nm (ε 11,200); ir (potassium chloride): 3406, 2919, 2737, 2671, 2710, 2567, 2461, 1599, 1590, 1570, 1505, 1456, 1430 cm^{-1}; ^1H nmr: 2.33 (s, 3H, 3/5-CH_3), 2.39 (s, 3H, 5/3-CH_3), 2.80 (s, 6H, $N(CH_3)_2$), 3.44 (br, 4H, CH_2CH_2), 4.07 (s, 2H, 4-CH_2), 7.47 (m, 5H, C_6H_5); ms: (FAB, nitrobenzyl alcohol) m/z 273 (MH^+ of free base).

Anal. Calcd. for $C_{16}H_{24}N_4 \cdot 2HCl \cdot 1.3H_2O$: C, 52.12; H, 7.82; N, 15.19. Found: C, 52.06; H, 8.02; N, 15.01.

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