Fused quinoline heterocycles V. Synthesis of novel 1,2,3,5,6-pentaazaaceanthrylene derivatives

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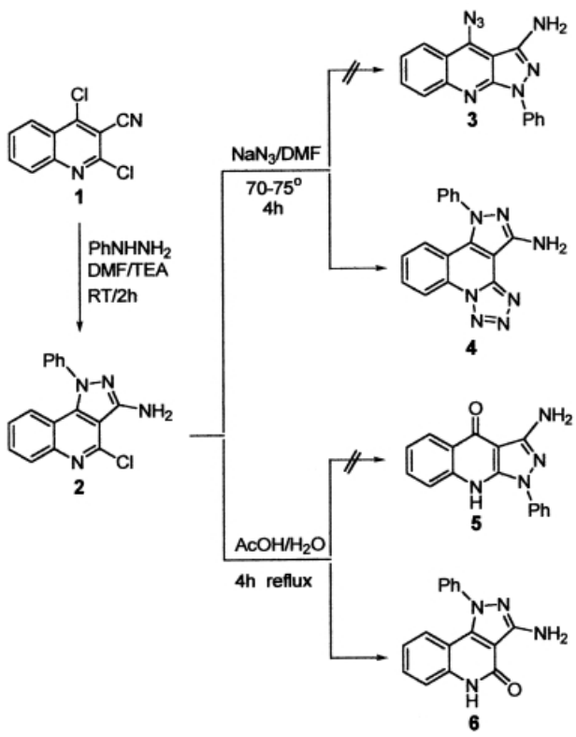
2,4-Dichloroquinoline-3-carbonitrile (**1**) with phenylhydrazine in DMF at room temperature gave the 3-amino-4-chloro-1-phenylpyrazolo[4,3-*c*]quinoline (**2**). Reaction of **2** with phenyl isothiocyanate afforded the novel fused tetracyclic ring system 1,5-diphenyl-1,5-dihydro-1,2,3,5,6-pentaazaaceanthrylene-4(3*H*)-thione (**7**). Refluxing **2** with excess of a primary amines **8a**-**d** in boiling DMF yielded the corresponding aminopyrazolo[4,3-*c*]quinolines **9a**-**d** which react with an excess of triethyl orthoformate to furnish 5-substituted 1-phenyl-1,2,3,5,6-pentaaza-aceanthrylenes **11a**-**d**. Reacting **9a** with acetic anhydride does not give the expected tetracyclic compound **12**, but instead the acetamide **13** is obtained. With triethyl orthoacetate the corresponding iminoester **14** is formed. When compound **14** was refluxed in DMF containing NaH it cyclised to the 4-methyl analogue **12**.

Keywords: fused quinoline heterocycles

In previous research work we have investigated new syntheses of heterocyclic compounds containing a quinoline unit, and their transformation products, starting from 2,4-dichloroquinoline-3-carbonitrile. Derivatives of the pyrazolo[3,4-*d*]pyrimidine ring system have aroused considerable interest on account of their therapeutic potential.[1-4] Pyrazolo[3,4-*c*]quinolines also represent an important class of compound that has been shown to have interesting biological properties as antiinflammatory reagents.[5,6] As a part of our continued effort to synthesise new systems containing the quinoline moiety with pharmaceutical activity, we have previously described different successful approaches for the synthesis of a series of tetracyclic systems containing the quinoline moiety.[7-10] In this paper, we present the first synthetic entry to the novel tetracyclic 1,2,3,5,6-pentaazaaceanthrylenes ring system, through 3-amino-4-chloro-1-phenylpyrazolo[4,3-*c*]quinoline (**2**) as intermediate. To the best of our knowledge, no similar strategy for the synthesis of a pyrazolopyrimidoquinoline skeleton has previously been reported.

We find that the key intermediate (**2**) can be prepared easily and in high yield by reacting 2,4-dichloroquinoline-3-carbonitrile (**1**)[7] with phenylhydrazine in DMF at room temperature. Alternative uncyclised structures could be eliminated on the basis of the disappearance of the CN signal in the IR spectrum, while NMR spectral and chemical evidence eliminated the linearly fused system. Thus, reaction of the pyrazoloquinoline **2** with sodium azide in DMF at 75–80°C for 4 hours did not afford an azidoquinoline (**3**), but instead gave the isomeric ring-closed pyrazolotetrazoloquinoline (**4**)**.** The IR spectrum of **4** had no azido band. We may therefore deduce that the first chlorine atom in **1** that was replaced by the phenylhydrazine was that at position 4. Furthermore, refluxing compound **2** with a mixture of acetic acid and water for 4 hours resulted in the formation of a pyrazoloquinolone (**6**). The isomeric quinolin-4-one structure (**5**) could be excluded because the IR spectrum showed significantly an amide carbonyl function at 1665 cm^{-1};[11,12] 4-quinolinones generally have carbonyl absorptions below 1600 cm^{-1}.[13-15]

The pyrazolo[4,3-*c*]quinolines **2** served as a starting point for the construction of novel tetracyclic systems incorporating both a pyrimidine nucleus and a pyrazoloquinoline moiety. Thus, the reaction of compound **2** with phenyl isothiocyanate in dry pyridine at reflux for 15 min led to the novel 1,5-diphenyl-1,5-dihydro-1,2,3,5,6-pentaazaaceanthrylene-4(3*H*)-thione (**7**). The compound **7**, to the best of our knowledge, is the first example of the 1,2,3,5,6-pentaazaaceanthrylene ring system. The IR spectrum displayed bands at 3400 cm^{-1} (NH) and 1255 cm^{-1} (C=S).[16] The ^{1}H NMR spectrum showed no signal for the pyrazole C(3)-NH_2 group at δ = 7.65 ppm (present in the spectrum of **2**) but the presence of a singlet at δ = 10.93 ppm assignable to the pyrimidine NH. In addition, signals due to aromatic protons were observed in their expected positions. Furthermore, the ^{13}C NMR spectrum of **7** confirmed the presence of the C=S group at δ = 179.9 ppm.[17] Structure **7** is also supported by its mass spectrum which showed peak at m/z 393, consistent with M^+ for $C_{23}H_{15}N_5S$.



Scheme 1 Pyrazolo[4,3-c]quinoline formation from nitrile 1.

Reaction of compound **2** with aliphatic amines **8a–d** in DMF gave the corresponding aminopyrazolo[4,3-*c*]quinolines **9a–d**, in good yields. Heating the amines **9a–d** with excess of TEO for 4 hours under reflux gave the new 1-phenyl-5-substituted-1,5-dihydro-1,2,3,5,6-pentaazaaceanthrylenes **11a–d** (Scheme 2). Compounds **11a–d** could also be obtained by an alternative route: compound **11c** was prepared by

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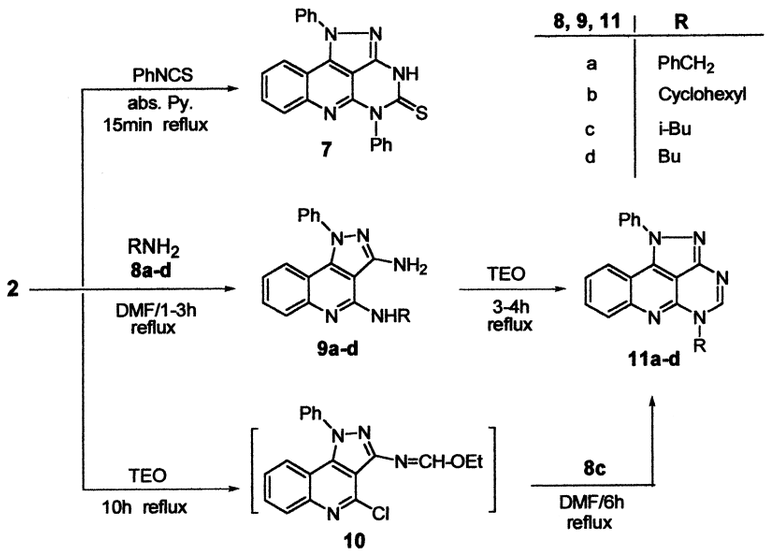
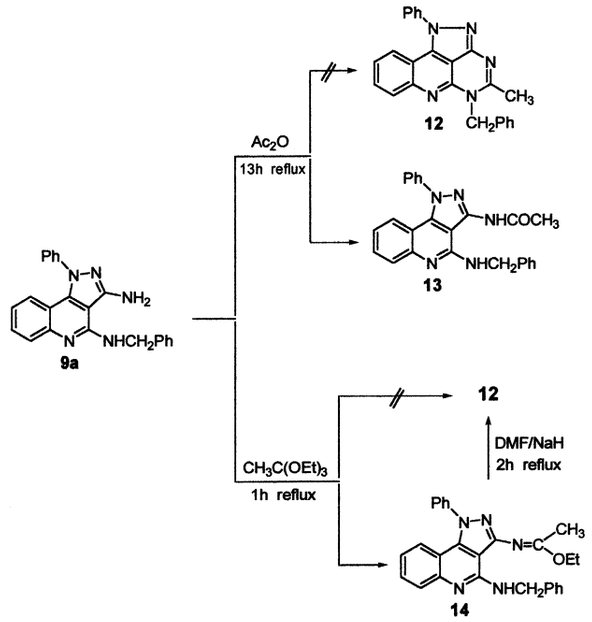


Scheme 2 Formation of 1,5-dihydro-1,2,3,5,6-pentaazaaceanthrylene derivatives **(7, 11a–d)**.



Scheme 3 The 4-methyl compound **12**, and derivatives of the amine **9a**.

reacting compound **2** with TEO at reflux temperature to yield the intermediate 4-chloro-3-(ethoxymethyleneamino)-1-phenyl-pyrazolo-[4,3-*c*]quinoline (**10**). When this compound was treated *in situ* with isobutylamine (**8c**) in DMF at reflux temperature for 7 hours it underwent cyclisation to give **11c** (Scheme 2). The elemental analysis, mass spectra and ^{1}H NMR spectra supported the structures of **11a-d**.

We investigated compound **9a** further, with a view to obtaining 4-methyl derivatives of the pentaaza-tetracyclic system. Reflux of **9a** with acetic anhydride gave a solid product identified as the acetamide derivative **13** (Scheme 3). With triethyl orthoacetate at reflux temperature for 1hour, compound **9a** afforded the imino-ester **14**. In an attempt to obtain the desired pyrimidine-fused compound **12**, we first tried the cyclisation of **14** under various conditions for extended periods. However, when only starting material was recovered, we attempted the reaction under more basic conditions and higher reaction temperatures. Refluxing compound **14** in DMF containing NaH for 2 hours gave 5-benzyl-4-methyl-1-phenyl-1,2,3,5,6-pentaazaaceanthrylene (**12**) (Scheme 3). The structure of **12** was substantiated for the reaction product on the basis of its elemental and spectral data.

In summary, we have established a simple, convenient and efficient method for the synthesis of the interesting 1,2,3,5,6-pentaazaaceanthrylene derivatives, a novel tetracyclic system containing the quinoline ring, to submit to biological evaluation. This is the first time that such novel perianellated tetracyclic systems has been described. Work is currently under way to prepare a sixth generation of novel tetracyclic compounds utilising 2,4-dichloroquinoline-3-carbonitrile as starting material.

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