SHORT PAPER

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Antitumour polycyclic acridines. Part 13.[1] Synthesis of 2-substituted 7*H*-pyrido[4,3,2-*kl*]acridines by thermolysis of 9-(5-alkyltriazol-1-yl)acridines †

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Interaction of phosphoranylidene ketones with 9-azidoacridine in refluxing benzene affords 9-(5-substituted triazol-1-yl)acridines, which, on thermolysis in boiling diphenyl ether at 259 °C, yield 2-substituted 7*H*-pyrido[4,3,2-kl] acridines in high yields. These tetracyclic acridines are less potent inhibitors of human tumour cells in vitro than their pentacyclic analogues.

Keywords: lithiation, triazoles, thermolysis, pyridoacridines

In previous parts of this series we have explored synthetic routes to, and biological properties of, DNA-affinic aromatic pentacyclic systems, inspired by the bioactive properties of polycyclic acridines elaborated by marine organisms.[2] During this work we have identified potent inhibitors of topoisomerase II such as the indolizino[7,6,5-*kl*]acridinium salt **1**[3] and, more recently, the trimethylquino[4,3,2-*kl*]acridinium methosulphate **2** which is a potent telomerase inhibitor.[4,5] We have confirmed by high-field NMR studies that **1** intercalates into 5′-CpG sequences in duplex DNA[6] and **2** forms two stabilising end-stacking interactions (**I**) at d(TTA**I**GGG**I**T)$_4$ sites in G-quadruplex structures of telomeric DNA.[7] Apart from the selectivity of their DNA associations, both compounds have the desirable attributes of being prepared by short synthetic routes, are water soluble and have robust pharmaceutical properties.

Tetracyclic 7*H*-pyrido[4,3,2-*kl*]acridines **3** have been prepared previously by thermolysis of 9-(triazol-1-yl)acridines available from the reactions of 9-azidoacridine with alkynes,[8] reactive methylenic substrates[9] and phosphorus ylides.[10] We have now exploited lithiation reactions of phosphorus ylides and triazoles to expand the availability of triazolylacridines suitable for conversion to 2-substituted pyrido[4,3,2-*kl*] acridines.

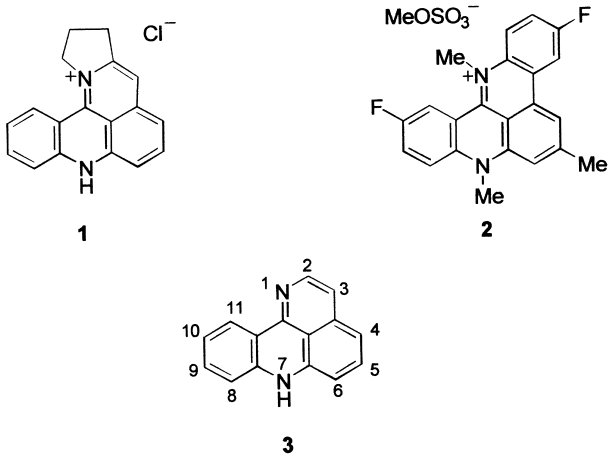

Fig. 1 Structures of polycyclic acridines.

Chloromethylketones **4a–c** were reacted with triphenylphosphine in refluxing THF to afford triphenylphosphoranylidene ketones **5a–c**. Lithiation of **5a** with *n*-BuLi in THF at –78 °C, followed by quenching with methyl, ethyl or chloropropyl iodides, and benzyl bromide, respectively, afforded the phosphoranylidene ketones **5d–g**.[11] Cycloaddition of ylides **5a–e** with 9-azidoacridine in refluxing benzene afforded the triazolylacridines **6a–e** in yields > 75% (Scheme 1). No reaction was observed between **5f** and 9-azidoacridine.

Raap has shown that lithiation/methylation of 1-phenyl-1,2,3-triazole leads exclusively to 5-methyl-1-phenyl-1,2,3-triazole.[12] It was anticipated that lithiation of 9-(triazol-1-yl)acridine **7** at the triazole 5-position would be favoured with the orthogonal conformation between the two aromatic heterocyclic rings helping to stabilise the lithio species **8**. When the conditions used by Raap (*n*-BuLi in THF at –78 °C, followed by MeI) were applied the only product of the reaction was 9-butylacridine (**9**). Clearly, the π-deficient acridine ring activates the triazole substituent to nucleophilic displacement and this feature is more influential than the acidity of the proton on the triazole 5-position. In anticipation that use of a less nucleophilic (more sterically hindered) base might tip the scales towards proton abstraction, other bases such as *s*-BuLi, *t*-BuLi and LDA were employed, but without success; only starting triazole was recovered. Finally, conditions used to thwart competitive nucleophilic substitution of the chloro group in the lithiation of 6-chloro-(3-pivaloylamino)pyridine using an *n*-BuLi-TMEDA combination in THF at –78 °C, followed by MeI,[13] were employed with partial success: the ^{1}H NMR spectrum of the crude product showed the presence of the required 5-methyltriazole **6a** (~13%), together with starting material (**7**, 16%), 9-butylacridine (**9**, 8%) and a product tentatively identified as 9,9-dibutyl-10-methylacridan (**10**, 14%; EIMS *m/z* 307.2308; calc. for $C_{22}H_{29}N$, 307.2300) (Scheme 2).

Differential scanning calorimetry (DSC) has been employed to identify precisely the temperatures at which 9-triazolylacridines undergo thermolytic fragmentation to polycyclic acridines.[14] Triazole **6a** showed a melting endotherm at 185.7°C, followed by a decomposition exotherm with an onset at 235.9°C: corresponding temperatures for **6d** were 176.1 and 235.7°C, and for **6e** were 146.9 and 233.9°C, respectively. Thus boiling diphenyl ether (b.p. 259°C) was chosen as a suitable medium for Graebe-Ullmann[15] cyclisation of these triazoles. High yields of tetracycles **11a,c,d** (> 80%) were formed from thermolysis of the triazoles **6a,c,d** (Scheme 3). Conversion of **11a** to its anion (*t*-BuLi/THF/–78°C) followed by methylation with MeI gave the 2,7-dimethylpyridoacridine

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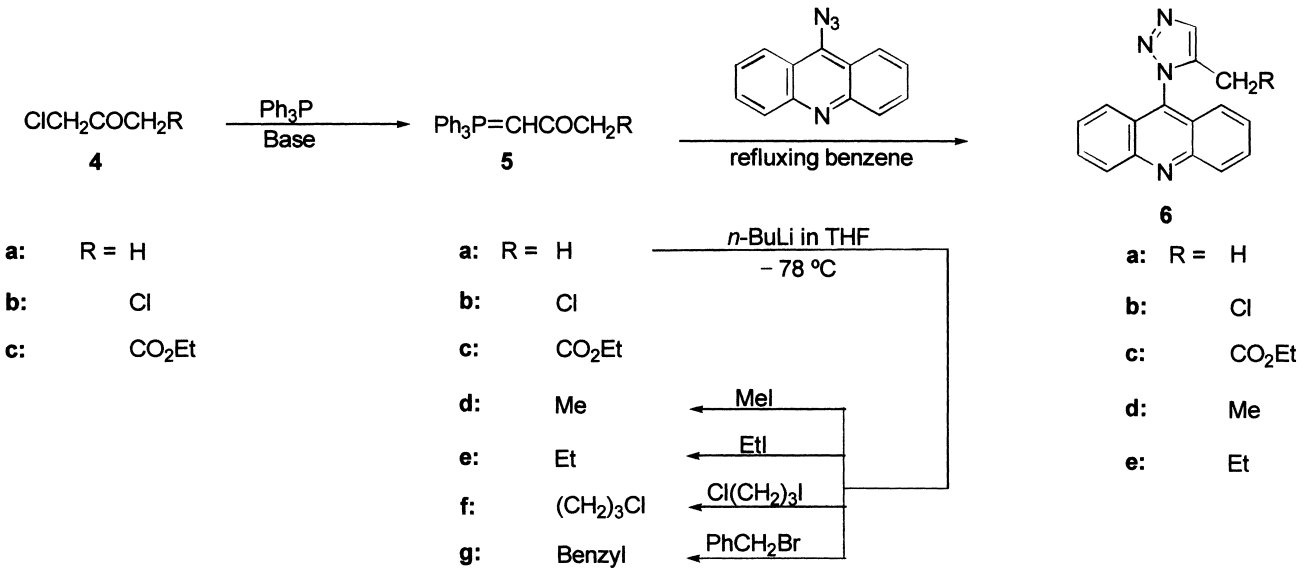
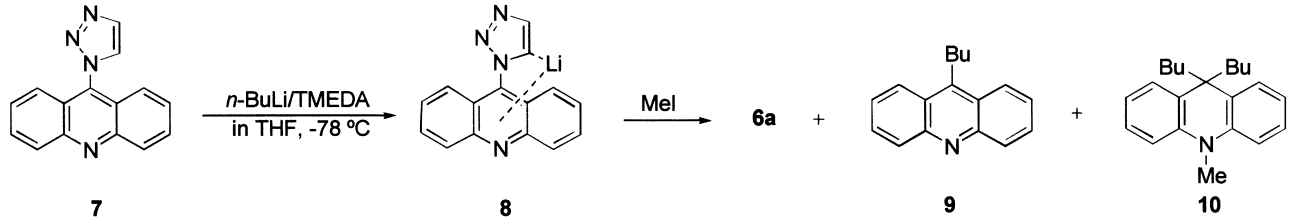
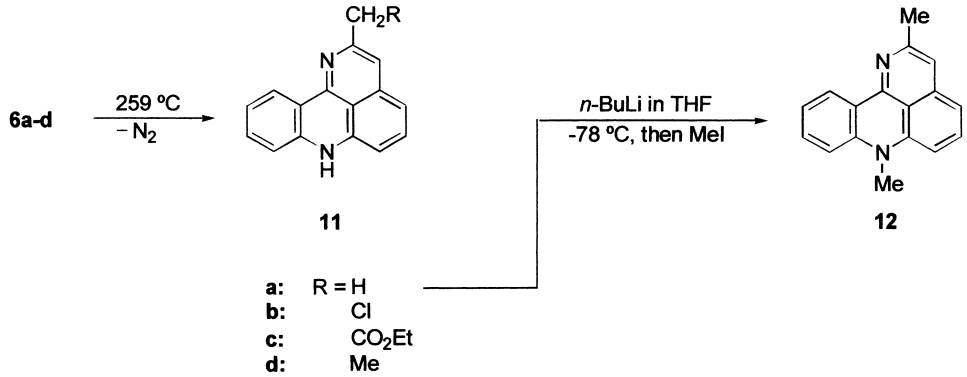
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1 The synthesis of 9-(triazol-1-yl)acridines.



Scheme 2 Attempted lithiation/substitution of 9-(triazol-1-yl)acridine.



Scheme 3 Synthesis of 2-substituted 7*H*-pyrido[4,3,2-*kl*]acridines.

12 (92%). Disappointingly, we were unable to isolate any 2-chloromethylpyridoacridine **11b** from **6b** despite varying the timespan of thermolysis and the nature of the solvent, presumably because intra- and/or inter-molecular alkylations complicate this otherwise efficient transformation. Compound **11b** would have been a valuable synthon to construct more elaborate and desirable 2-substituted pyridoacridines bearing basic side chains.

Two of the tetracyclic compounds were tested in the NCI 60 human tumour cell panel.[16] The mean GI_{50} values for **11a** and **11c** were 2.45 and 22.9 μM, respectively: this compares with a value of 0.09 μM for the indolizino[7,6,5-*kl*]acridinium salt **1** and confirms earlier work which concluded that the tetracyclic systems have less antitumour potency than their pentacyclic counterparts.[3]

Experimental

All NMR spectra were acquired on a Bruker ARX 250 instrument. Chemical shifts are reported in δ units and referenced to the solvent as internal standard. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Micromass Platform spectrometer.

General procedure for the synthesis of triphenylphosphoranylideneketones **5d–g**: A solution of triphenylphosphine (5.16 g, 20 mmol) and a chloroketone (20 mmol) in THF was refluxed for 6 h. The cooled solution deposited colourless crystals of the triphenylphosphoranylideneketones. Yields and melting points of products were: **5d** 83%, m.p. 208–210 °C; **5e** 37%, m.p. 103–104 °C; **5f** 58%, m.p. 193–195 °C; **5g** 60%, m.p. 142–143 °C. Compounds **5d-f** have been prepared by alternative routes.[11]

General procedure for the synthesis of 9-(5'-substituted-1,2,3-triazol-1'-yl)acridines **6a-e**: A solution of 9-azidoacridine (2.11 g, 9.6 mmol) and the appropriate triphenylphosphoranylidene-ketone (9.6

mmol) was refluxed in benzene (2 h). Solvent was removed by vacuum evaporation and products purified by column chromatography. Yields, melting points and physical properties of the triazolylacridines are as follows:

5′-Methyl compound (**6a**): 96%, m.p. 178–180 °C (from EtOAc), δ_H ($CDCl_3$) 8.38 (2H, d, *J* 9 Hz, H-4, 5), 7.88 (3H, m, H-3, 6, 4′), 7.60 (2H, m, H-2,7), 7.32 (2H, d, *J* 8 Hz, H-1, 8), 2.08 (3H, s, CH_3) (Found: C, 73.70; H, 4.54; N, 21.38. $C_{16}H_{12}N_4$ requires C, 73.83; H, 4.65: N, 21.52%); *5′-Chloromethyl* (**6b**): 67%, m.p. 181–182 °C (for physical properties see ref. 10); *5′-Acetic acid ethyl ester* (**6c**): 83%, m.p. 116–118 °C, δ_H ($CDCl_3$) 8.37 (2H, d, *J* 9 Hz, H-4,5), 8.11 (1H, s, H-4′), 7.88 (2H, m, H-3,6), 7.60 (2H, m, H-2,7), 7.31 (2H, d, *J* 9 Hz, H-1,8), 3.85 (2H, q, *J* 7 Hz, $CH_2CO_2CH_2CH_3$), 3.45 (2H, s, CH_2CO_2Et), 0.96 (3H, t, *J* 7 Hz, CH_3) (Found: C, 68.39; H, 4.84; N, 16.63. $C_{19}H_{16}N_4O_2$ requires C, 68.66; H, 4.85: N, 16.86%); 5′-Ethyl (**6d**): 73%, m.p. 170–172 °C (from EtOAc), δ_H ($CDCl_3$) 8.38 (2H, dd, *J* 1, 9 Hz, H-4,5), 7.88 (3H, m, H-3,6,4′), 7.60 (2H, ddd, *J* 1, 7, 9, H-2,7), 7.30 (2H, m, H-1,8), 2.36 (2H, q, *J* 8, CH_2), 1.12 (3H, t, *J* 8, CH_3) [Found: *m/z* (HRMS-FAB) 275.1282. $C_{17}H_{15}N_4$ requires 275.1297 ($M^+ + 1$)]; *5′-n-Propyl* (**6e**): 83%, m.p. 147 °C, δ_H ($CDCl_3$) 8.41 (2H, dd, *J* 9 Hz, H-4,5), 7.90 (3H, m, H-3,6,4′), 7.60 (2H, ddd, *J* 1, 7, 9 Hz, H-2,7), 7.31 (2H, d, *J* 9 Hz, H-1,8), 2.32 (2H, t, *J* 8 Hz, $CH_2CH_2CH_3$), 1.49 (2H, sex, J 8 Hz, $CH_2CH_2CH_3$), 0.79 (3H, t, *J* 7 Hz, CH_3) [Found: *m/z* (ES) 289.2].

General procedure for the synthesis of pyridoacridines by thermolysis of triazolylacridines: The appropriate triazolylacridine (1.0 g) was suspended in diphenyl ether (15 ml) and heated to 250 °C for 5–20 min, or until effervescence had ceased. The cooled mixture was placed on a silica column and eluted with hexane (to remove diphenyl ether), followed by methanol to isolate the product. Yields, melting points and physical properties of 7H-pyrido[4,3,2-*kl*]acridines are: *2-Methyl derivative* (**11a**): 85%, m.p. 193-194 °C (from EtOAc), δ_H (DMSO-d_6) 10.67 (1H, NH), 8.32 (1H, dd, *J* 2, 8 Hz, H-11), 7.40 (1H, t, *J* 8 Hz, H-5), 7.39 (1H, m, H-9), 7.11 (1H, d, *J* 8 Hz, H-8), 7.02 (1H, t, *J* 9 Hz, H-10), 6.98 (1H, s, H-3), 6.85 (1H, d, *J* 8 Hz, H-4), 6.69 (1H, d, *J* 8 Hz, H-6), 2.45 (3H, s, CH_3) (Found: C, 82.37; H, 5.14; N, 11.79. $C_{16}H_{12}N_2$ requires C, 82.73; H, 5.21; N, 12.06%); *2-Acetic acid ethyl ester* (**11c**): 96%, m.p. 166-168 °C (from EtOAc), δ_H ($CDCl_3$) 8.42 (1H, dd, *J* 1, 8 Hz, H-11), 7.69 (1H, br s, NH), 7.32 (2H, m, H-5,9), 7.05 (1H, s, H-3), 7.00 (1H, m, H-10), 6.85 (2H, m, H-4,5), 6.59 (1H, d, *J* 8 Hz, H-6), 4.27 (2H, q, *J* 7 Hz, $CH_2CO_2CH_2CH_3$), 3.89 (2H, s, CH_2CO_2Et), 1.33 (3H, t, *J* 7 Hz, CH_3) (Found: C, 74.93; H, 5.27; N, 9.41. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20%); *2-Ethyl* (**11d**): 80%, m.p. 144-145 °C, δ_H ($CDCl_3$) 8.56 (1H, dd, *J* 2, 8 Hz, H-11), 7.47 (1H, br s, NH), 7.36 (1H, m, H-5), 7.32 (1H, ddd, *J* 2, 7, 8 Hz, H-9), 7.06 (1H, ddd, *J* 1, 7, 8 Hz, H-10), 7.01 (1H, s, H-3), 6.94 (1H, dd, *J* 1,8, H-4), 6.84 (1H, dd, *J* 1, 8 Hz, H-8), 6.54 (1H, dd, *J* 1, 8 Hz, H-6), 2.89 (2H, q, *J* 8 Hz, CH_2), 1.41 (3H, t, *J* 8 Hz, CH_3) [Found; *m/z* (HRMS-FAB) 247.1247. $C_{17}H_{15}N_2$ requires 247.1235 ($M^+ + 1$)].

2,7-Dimethyl-7H-pyrido[4,3,2-kl]acridine (**12**). 2-Methylpyridoacridine **11a** (73 mg, 0.31 mmol) in dry THF (5 ml) was treated with *t*-BuLi (0.22 ml of a 1.7 M solution, 0.38 mmol) at 0 – 78 °C for 2 h. Excess methyl iodide (0.28 g, 1.6 mmol) was added and the solution was allowed to warm to 25 °C. The mixture was quenched with water, extracted into EtOAc and combined extracts dried ($MgSO_4$). After vacuum evaporation of solvent the residue was purified by column chromatography (eluting solvent EtOAc-hexane, 1:4). The pyridoacridine **12** (92%), had m.p. 149-150 °C; δ_H ($CDCl_3$) 8.73 (1H, d, *J* 7 Hz, H-11), 7.48 (1H, t, *J* 8 Hz, H-5), 7.47 (1H, m, H-9), 7.20 (1H, d, *J* 9 Hz, H-8), 7.15 (1H, t, *J* 7 Hz, H-10), 7.08 (1H, s, H-3), 6.99 (1H, d, *J* 8 Hz, H-4), 6.65 (1H, d, *J* 8 Hz, H-6), 3.54 (3H, s, 7-CH_3), 2.63 (3H, s, 2-CH_3) (Found: C, 82.69; H, 5.70; N, 11.28. $C_{17}H_{14}N_2$ requires C, 82.90; H, 5.73; N, 11.37%).

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