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11-(Tetrahydro-3 and 4-pyridinyl)dibenzo[*b*,*e*][1,4]diazepines undergo novel rearrangements on treatment with concentrated HBr

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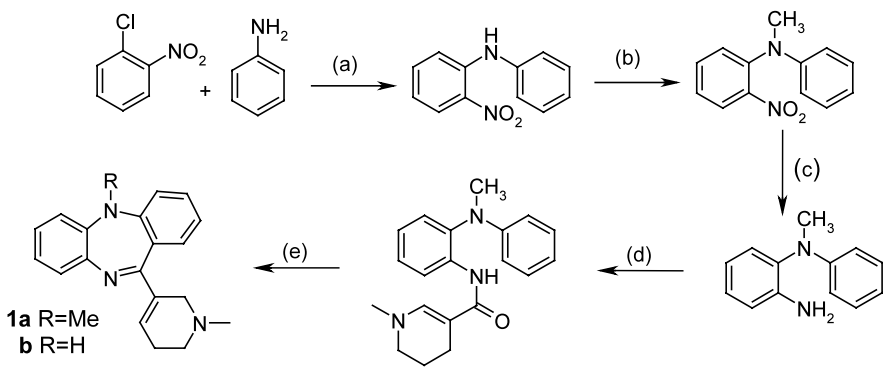
Abstract—11-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine on heating in conc. HBr afforded *trans*-5-(2-aminophenyl)-1,3,4,4a,5,10a-hexahydro-2-methylbenzo[*b*][1,6]naphthyridin-10(2*H*)-one in one step. The isomer 11-(1,2,5,6-tetrahydro-1-methyl-4-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine underwent a novel rearrangement resulting in the pentacycle, 4-amino-5,13-diaza-13-methyl-bicyclo[3.3.1]nonan[6,7,8-*k*,*l*]acridine. © 2002 Published by Elsevier Science Ltd.

mAs part of a project to find novel anti-psychotics[1] a series of 11-(1,2,5,6-tetrahydro-1-methyl-3-pyridinyl)-5-alkyl-5*H*-dibenzo[*b*,*e*][1,4]diazepines **1** were prepared (Scheme 1). The des-alkyl compound, 11-(1,2,5,6-tetrahydro-1-methyl-3-pyridinyl)-5*H*-dibenzo[*b*,*e*][1,4]-diazepine **1b**, was required for biological testing. Protection of the diphenylamine as an amide was not an option as reduction of *N*-(2-nitrophenyl)-*N*-phenyl acetamide to the aniline results in immediate cyclisation to 2-methyl-1-phenyl-1*H*-benzimidazole.[3]

Dimethyl-[2-(5-methyl-5*H*-dibenzo[*b*,*f*]azepin-10-yl]-amine **2** has been *N*-demethylated with 48% hydrobromic acid.[4] Heating 5-methyl-11-(pyridin-3-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine in conc. HBr under reflux indeed affords the *N*-demethylated product **3** (Fig. 1).[5]

We attempted *N*-demethylation of 11-(1,2,5,6-tetrahydro-1-methyl-3-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*]-[1,4]diazepine **1a**[6] in conc. HBr under reflux for 4 h. The reaction afforded a product which infrared spec-



Scheme 1. *Conditions*: (a) Na_2CO_3, neat 200°C, 18 h, 24%. (b) KOH, Me_2SO_4, acetone, reflux, 1.5 h. (c) Sn, aq. HCl, EtOH, reflux, 0.5 h, 95% (over two steps). (d) *N*-Methyl-1,2,5,6-tetrahydropyridine-3-carbonyl chloride,[2] Et_3N, rt, 1 h, 77%. (e) PPA, $POCl_3$, 120°C, 45 min, 84%.

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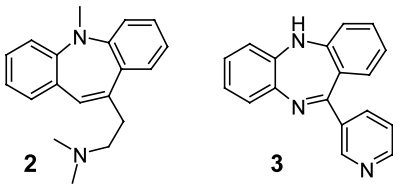


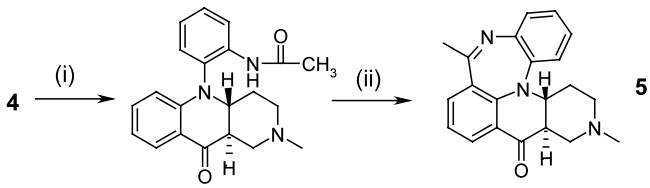
Figure 1.

troscopy indicated contained a carbonyl (1670 cm^{-1}), this and absence of an olefinic signal in its NMR spectrum indicated the product was not **1b**. NMR (360 MHz in $CDCl_3$) analysis of the product showed the proton on the 4 position, δ 3.48 (q, 4ax, $J=7.2$ Hz), of the piperidinyl ring was now adjacent to a nitrogen and a large coupling with the proton at 3, indicating *trans* stereochemistry at the ring fusion. The product was identified as *trans*-5-(2-aminophenyl)-1,3,4,4a,5,10a-hexahydro-2-methylbenzo[*b*][1,6]naphthyridin-10(2*H*)-one **4**. A mechanism for the rearrangement is shown in Scheme 2: the imine function is rapidly hydrolysed under acidic conditions opening the dibenzodiazepine ring and an intramolecular Michael addition (6-*endo*-trig) affording **4** follows. *N*-Acetylation of **4** followed by cyclisation under Bischler–Napieralski conditions afforded the novel pentacyclic compound 3,9-dimethyl-1,2,3,4,4a,14c-hexahydro-3,10,14b-triaza-benzo[4,5]-cyclohepta[1,2,3-*de*]anthracene-5-one **5**[7] (Scheme 3).

The same demethylation conditions were applied to 11-(1,2,5,6-tetrahydro-1-methyl-4-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine **6**. No infrared absorption was observed in the carbonyl stretch region, indicating the expected hydrolysis-Michael product had not been formed. ^1H NMR analysis of the product showed the presence of only six protons attached to aromatic rings and the piperidine ring still intact but fully saturated, while ^{13}C contained a total of 13 aromatic carbons. The product was identified as 4-amino-5,13-diaza-13-methyl-bicyclo[3.3.1]nonan[6,7,8-*k*,*l*]acridine **7**, and a mechanism has been tentatively proposed (Scheme 4).

Experimental

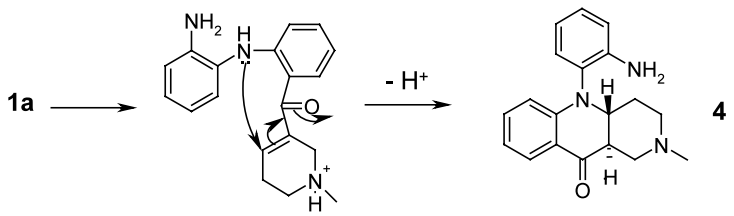
trans-5-(2-Aminophenyl)-1,3,4,4a,5,10a-hexahydro-2-methylbenzo[b][1,6]naphthyridin-10(2H)-one **4**. 11-(1,2,5,6-Tetrahydro-1-methyl-3-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine **1** (19.7 g 0.065 mol) was dissolved in 48% hydrobromic acid (100 cm^3) and heated under



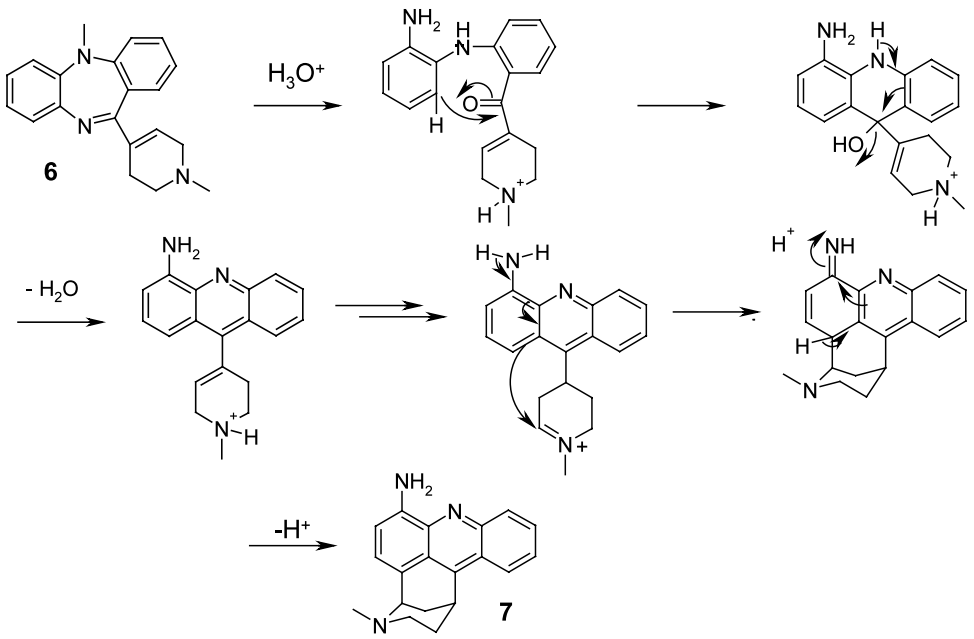
Scheme 3. Conversion of **4** to the pentacyclic dibenzodiazepine. *Conditions*: (i) Ac_2O, $ZnCl_2$, 65°C, 1 h, 68%. (ii) PPA, $POCl_3$, 120°C, 45 min, 73%.

reflux for 4 h. The warm solution was poured onto ice and allowed to stand overnight at room temperature. Ammonium hydroxide was added to neutralise the solution and 17 g of a green solid collected. Purification by chromatography on silica (eluent dichloromethane/methanol, 9/1), followed by conversion to the fumarate salt and crystallisation from methanol–ether afforded 3.38 g (12.3% yield) of **4** fumarate salt. ^1H NMR (200 MHz, DMSO-d_6): δ 7.75 (d, 1H, $J=7$ Hz), 7.25 (t, 1H, $J=8$ Hz), 7.02 (t, 1H, $J=8$ Hz), 6.90 (d, 1H, $J=9$ Hz), 6.87–6.60 (m, 3H), 6.60 (s, 2H, fumaric acid), 6.10 (d, 1H, $J=8$ Hz), 4.50–5.70 (broad peak, 4H), 3.70–3.50 (m, 1H), 3.45–3.20 (m, 2H), 2.85 (d, 1H, $J=11$ Hz), 2.32 (s, 3H), 2.15–1.90 (m, 2H), 1.70–1.50 (m, 2H). Anal. calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found C, 65.22; H, 6.08; N, 9.83. IR 0.5% KBr disc 3300–3500 cm^{-1} (two peaks, NH stretch), 1670 cm^{-1} (carbonyl), 1615 cm^{-1} and 1492 cm^{-1} (Ar-H). Melting point = 197°C.

4-Amino-5,13-diaza-13-methyl-bicyclo[3.3.1]nonan-[6,7,8-k,l]acridine **7**. 11-(1,2,5,6-Tetrahydro-1-methyl-4-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine **6** (0.5 g, 1.65 mmol) was treated with conc. HBr as described above. After chromatography 150 mg of a red gum was isolated (21% yield). ^1H NMR (360 MHz, $CDCl_3$): δ 8.22 (d, 1H, $J=9$ Hz), 8.14 (d, 1H, $J=9$ Hz), 7.71 (dd, 1H, $J=8.6$, 1.5 Hz), 7.53 (dd, 1H, $J=7.9$, 1.5 Hz), 7.02 (d, 1H, $J=9$ Hz), 6.89 (d, 1H, $J=9$ Hz), 5.10–5.40 (br, 2H), 4.13 (m, 1H), 4.02 (t, 1H, $J=2.7$ Hz), 2.62–2.57 (m, 1H), 2.52–2.40 (m, 2H), 2.27 (s, 3H), 2.24–2.17 (m, 1H), 1.89–1.82 (m, 1H), 1.65–1.56 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.6 (q), 145.1 (q), 143.4 (q), 138.9 (q), 130.6 (CH), 128.9 (CH), 126.5 (CH), 125.7 (CH), 125.3 (q), 123.5 (q), 123.0 (CH), 117.6 (q), 106.8 (CH), 58.4 (NCH), 46.3 (NCH_2), 42.5 (NCH_3), 33.1 (CH_2), 31.4 (CH_2), 28.2 (CH). $C_{19}H_{19}N_3$, EI GC-MS 289 (M^+).



Scheme 2. Mechanism of rearrangement of **1**. *Conditions*: conc. HBr, reflux, 4 h, 20%.



Scheme 4. Proposed mechanism for the rearrangement of **6**.

Acknowledgements

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5. Data for 11-pyridin-3-yl-5*H*-dibenzo[*b*,*e*][1,4]diazepine **3**: ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.85 (d, 1H, $J=3$ Hz), 8.65 (s, 1H), 8.23 (d, 1H, $J=8$ Hz), 7.95 (d, 1H, $J=7$ Hz), 7.85 (m, 1H), 7.72 (m, 1H), 7.57 (s, 2H), 7.33 (t, 1H, $J=8$ Hz), 6.90 (d, 1H, $J=7$ Hz), 6.65 (d, 1H, $J=7$ Hz), 6.33 (s, 2H).
6. Data for 11-(1,2,5,6-tetrahydro-1-methyl-3-pyridinyl)-5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine maleate salt **1a**: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (t, 1H, $J=7$ Hz), 7.02–7.24 (m, 7H), 6.32 (m, 1H), 6.25 (s, 2H), 4.47 (d, 1H, $J=12$ Hz), 4.16 (d, 1H, $J=16$ Hz), 3.51–3.37 (m, 2H), 3.20 (s, 3H), 3.08 (s, 3H), 2.74–2.64 (m, 2H).
7. Data for 3,9-dimethyl-1,2,3,4,4a,14c-hexahydro-3,10,14b-triaza-benzo[4,5]cyclohepta[1,2,3-*de*]anthracene-5-one (2:3) oxalate salt **5**: ^{1}H NMR (400 MHz, DMSO-d_6): 7.95 (d, 1H, ArH, $J=7$ Hz), 7.79 (d, 1H, ArH, $J=7$ Hz), 7.35 (d, 1H, ArH, $J=8$ Hz) 7.23 (t, 1H, ArH, $J=8$ Hz) 7.08–7.18 (m, 3H, ArH), 4.45 (m, 1H, CHN), 3.95 (m, 2H, CHCO and 1H of adjacent CH_2NMe), 3.16 (d, 1H, CH_2NMe, $J=10$ Hz), 3.09 (m, 1H, CH_2N adjacent to CHCO), 2.85 (m, 1H, CH_2N), 2.64 (s, 3H, N=CCH_3), 2.50 (s, 3H, NCH_3), 2.00 (m, 2H, CH_2). Melting point = 170°C.