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Unexpected anionically driven ring opening of a norbornene system

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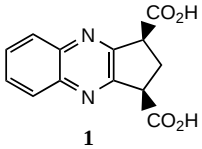
Abstract—A norbornene moiety fused to a π-deficient heterocyclic system (quinoxaline) was found to undergo ring opening in a basic medium, possibly through a mechanism of retroaldol type.

In the course of research on the synthesis of fused-heterocycle analogues of the anti-HIV agent abacavir we found we needed to prepare diacid **1**, to achieve which we considered oxidative cleavage of **2a** or **3a**.[1] In what appears to be the only published paper reporting synthesis of compound **2a**[2] it was stated that both **2a** and **2b** fail to give the corresponding diketones **3** when subjected to the conditions of Swern's reaction, which instead afford 63–75% yields of alcohols **4** as the only products. Since we found that **2a** is also unstable, undergoing spontaneous alteration at room temperature, and since we planned to use it on more than one occasion in exploring its oxidative cleavage under diverse conditions, we decided to prepare a stable derivative that could be converted to **2a** immediately before use. Accordingly, we synthesized dibenzoate **5**,[3] starting from the commercially available mixture of racemic *endo* and *exo* norbornenyl acetates **6** (Scheme 1).

Because of the likelihood of rearrangements of Wagner–Meerwein type due to its norbornene moiety, acid hydrolysis of **5** was not attempted. Initial attempts at its saponification to **2a** gave only intractable mixtures or unaltered starting material. However, when subjected to the mildest conditions compatible with effective saponification of the benzoate groups (0.9 M KOH in $MeOH/H_2O$, rt, 12 h) it afforded a crude product that upon flash chromatography on silica gel gave a 66% yield of a dark green solid. This product proved to undergo alteration when left standing in solution, but immediately after purification afforded IR, MS and ^1H and ^{13}C NMR data compatible with its being the enediol **12**.[4] This identification was confirmed by single-crystal X-ray crystallography of the stable diacetylated derivative **13** (Fig. 1),[5] which was obtained by acetylation of **12** with Ac_2O/pyridine.

Scheme 2 shows a plausible explanation of the formation of **12**. Under the basic working conditions, the diol **2a** formed from **5** will be in equilibrium with its monoalkoxide, which because of the stress in the bridged ring system must be highly susceptible to ring opening. The resulting carbanion **14** will be stabilized by its charge being formally located on the carbon α to position 3 of the π-deficient quinoxaline system, and following protonation of this carbon the resulting α-hydroxyaldehyde **15** will be susceptible to base-catalyzed isomerization to the α-hydroxyketone **17** via the enediol **16** (a well-known reaction in sugar chemistry).



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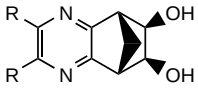
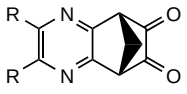
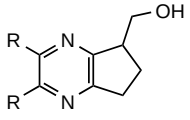


2a R,R = $(CH{=}CH)_2$
2b R = H



3a R,R = $(CH{=}CH)_2$
3b R = H



4a R,R = $(CH{=}CH)_2$
4b R = H

Keywords: quinoxaline-fused norbornene; ring opening; anionic intermediates; basic medium.
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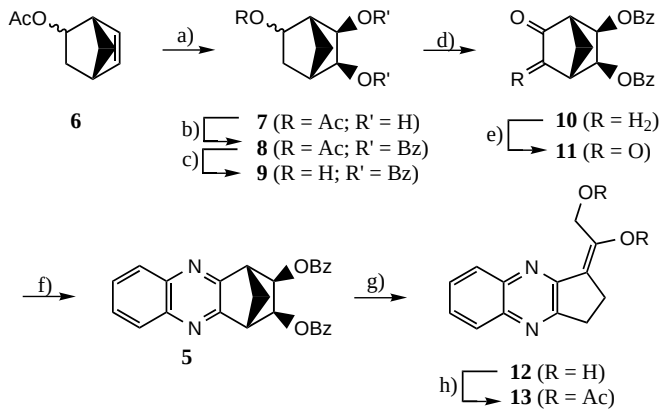

Scheme 1. *Reagents and conditions*: (a) OsO_4/NMNO/Me_2CO–H_2O, 40°C, 18 h; (b) BzCl/Py, rt, 24 h; (c) K_2CO_3/MeOH, rt, 30 min; (d) CrO_3·Py/DCM, rt, 6 h; (e) SeO_2/xylene; 140°C; 24 h; (f) *o*-$(C_6H_4)(NH_2)_2$/$ZnCl_2$/THF, 66°C, 18 h; (g) 0.9 M KOH/MeOH–H_2O, rt, 12 h; (h) Ac_2O/Py, rt; 14 h.

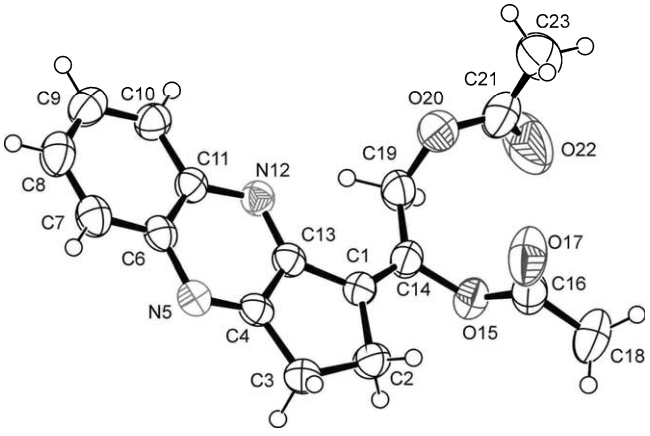

Figure 1. ORTEP plot of the molecular structure of **13** in the solid state.

Finally, isomerization of **17** to the enediol **12** will be favored by the exocyclic C=C bond of the latter being conjugated with the aromatic quinoxaline system.

There have been several reports of rearrangements of Wagner–Meerwein type and ring-opening reactions involving cationic intermediates which are undergone by systems with a bicyclo[2.2.1]heptene moiety fused to a benzene ring,[6] or to an heteroaromatic ring,[7] but as far as we know this is the first example of a base-promoted ring opening involving a carbanion intermediate. We are currently exploring the scope and utility of this novel type of reaction.

Acknowledgements

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References

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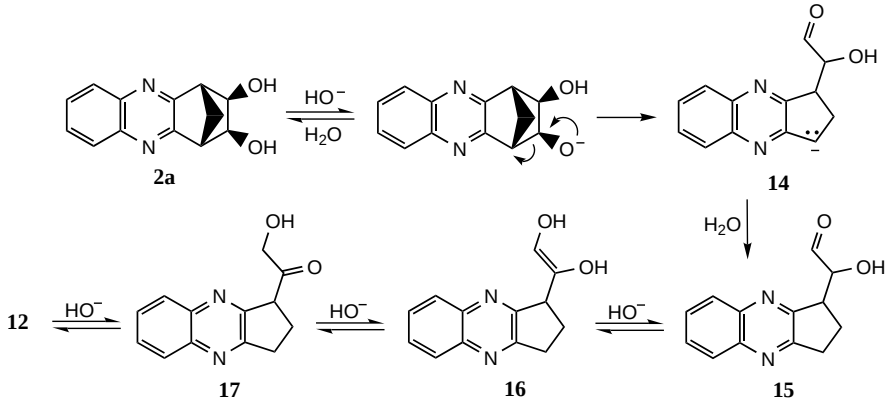
3. **(*exo*,*exo*)-1,2,3,4-Tetrahydro-1,4-methanophenazine-2,3-diyl dibenzoate (5)**: mp 194–195°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.44 (1H, d, J=10.3, 11-H_{syn}), 2.96 (1H, d, J=10.3, 11-H_{anti}), 3.87 (2H, s, 1-H+4-H), 5.48 (2H, s, 2-H+3-H), 7.28 (4H, t, J=7.7, 2×[3,5-H_2]$_{benzoyl}$), 7.50 (2H, t, J=7.3, 2×[4-H]$_{benzoyl}$), 7.73 (2H, dd, J=6.2,3.4, 7-H+8-H), 7.90 (4H, d, J=8.0, 2×[2,6-H_2]$_{benzoyl}$), 8.06 (2H, dd, J=6.2,3.4, 6-H+9-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 42.02 (CH_2, C11), 50.14 (CH, C1+C4), 73.31 (CH, C2+C3), 128.67 (CH, [C3+C5]$_{benzoyl}$), 129.62 (CH, C7+C8), 129.77 (C, [C1]$_{benzoyl}$), 129.89 (CH, C6+C9), 130.08 (CH, [C2+C6]$_{benzoyl}$), 133.59 (CH, [C4]$_{benzoyl}$), 142.37 (C, C5a+C9a), 159.87 (C, C4a+C10a), 165.56 (C, CO). IR (KBr) 1731, 1716, 1276, 1120, 971, 760, 708 cm^{-1}. EIMS (70 eV), m/z (%), 437 (14, M+1), 436 (47, M$^+$); 331 (16, M–C_6H_5CO); 209 (11), 181 (8), 169 (11), 105 (100, $C_6H_5CO^+$), 77 (24, $C_6H_5^+$).
4. **1-(2,3-Dihydro-1*H*-cyclopenta[*b*]quinoxalin-1-ylidene)-1,2-ethanediol (12)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.77–2.81



Scheme 2. Suggested mechanism for the formation of **12** from **2a**.

(2H, m, 2′-H_2), 3.02–3.06 (2H, m, 3′-H_2), 3.59 (1H, ws, D_2O exch., 2-OH), 4.34 (2H, s, 2-H_2), 7.04 (1H, d, $J=7.9$, $H_{quinoxaline}$), 7.19 (1H, t, $J=7.6$, $H_{quinoxaline}$), 7.32 (1H, t, $J=7.6$, $H_{quinoxaline}$), 7.56 (1H, d, $J=7.9$, $H_{quinoxaline}$), 10.32 (1H, ws, D_2O exch., 1-OH). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=22.71$ (CH_2, C2′), 30.17 (CH_2, C3′), 65.72 (CH_2, C2), 105.94 (C), 115.78 (CH), 124.67 (CH), 128.64 (CH), 129.27 (C), 129.64 (CH), 136.49 (C), 143.28 (C), 171.09 (C), 194.61 (C). IR (KBr) 3434, 3418, 1644, 1610, 1580, 1558, 1232, 1068, 901, 770, 600 cm^{-1}. EIMS (70 eV), m/z 228 (32, M^+), 197 (71, M–CH_2OH), 170 (41, M–$C_2H_2O_2$), 169 (61, M–$COCH_2OH$), 168 (26, M–$OCHCH_2OH$), 58 (100, $C_2H_2O_2^+$).

5. Crystallographic data for **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 185239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.
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