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SOME NOVEL SYNTHETIC TRANSFORMATIONS IN ADAMANTANES

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In connection with work on transition state analogues and enzyme inhibition studies,[1,2] we had cause to seek a viable synthesis of 6-hydroxyadamantane-1,3-dicarboxylic acid (6). A convenient starting material for this synthesis was diethyl 2,6-dioxoadamantane-1,3-dicarboxylate (1).[3] Our original approach to the conversion of 1 to 6 involved selective protection of the less hindered 6-keto function of 1 to form the known[3] ethylene ketal (2) followed by Wolff-Kischner reduction of the 2-keto function (with concomitant ester hydrolysis) to form (3) and subsequent simple functional group manipulation. However, Wolff-Kischner treatment (KOH, ethylene glycol; 180°) of 2 gave only the pyrazolone (4; R = C_2H_5; m.p. 287°). Such intramolecular cyclisation to form pyrazolones is common when attempting Wolff-Kischner reduction of β-keto esters.[4]

Using very vigorous conditions (NaOMe, MeOH, NH_2-NH_2; sealed autoclave 220°), Stetter[3] has reported the successful reductive removal of 2-keto functions in very similar adamantane β-keto esters. We attempted such a reaction on 2 and obtained two compounds (ratio *ca.* 1 : 1). The less polar compound was adamantane-1,3-dicarboxylic acid (5) while the more polar was unexpectedly (*vide infra*) our required compound 6 (m.p. 267°). The structure of 5 was proven by comparison (m.p., spectra) with an authentic sample.[5] The structure of 6 was established by spectral examination and microanalysis of both the diacid and its dimethyl ester but in view of the unexpected one-step conversion of 2 to 6 which involved an unusual ethylene ketal to alcohol transformation, it was essential to confirm the identity of 6 by a controlled multistep synthesis from 2.

It was envisaged that the 2-keto function could be removed from 2 *via* formation of the ethylenedithioketal (7). Raney nickel treatment to afford 8 followed by subsequent standard functional group modification *via* 10 would yield 6. However, treatment of 2 with ethane

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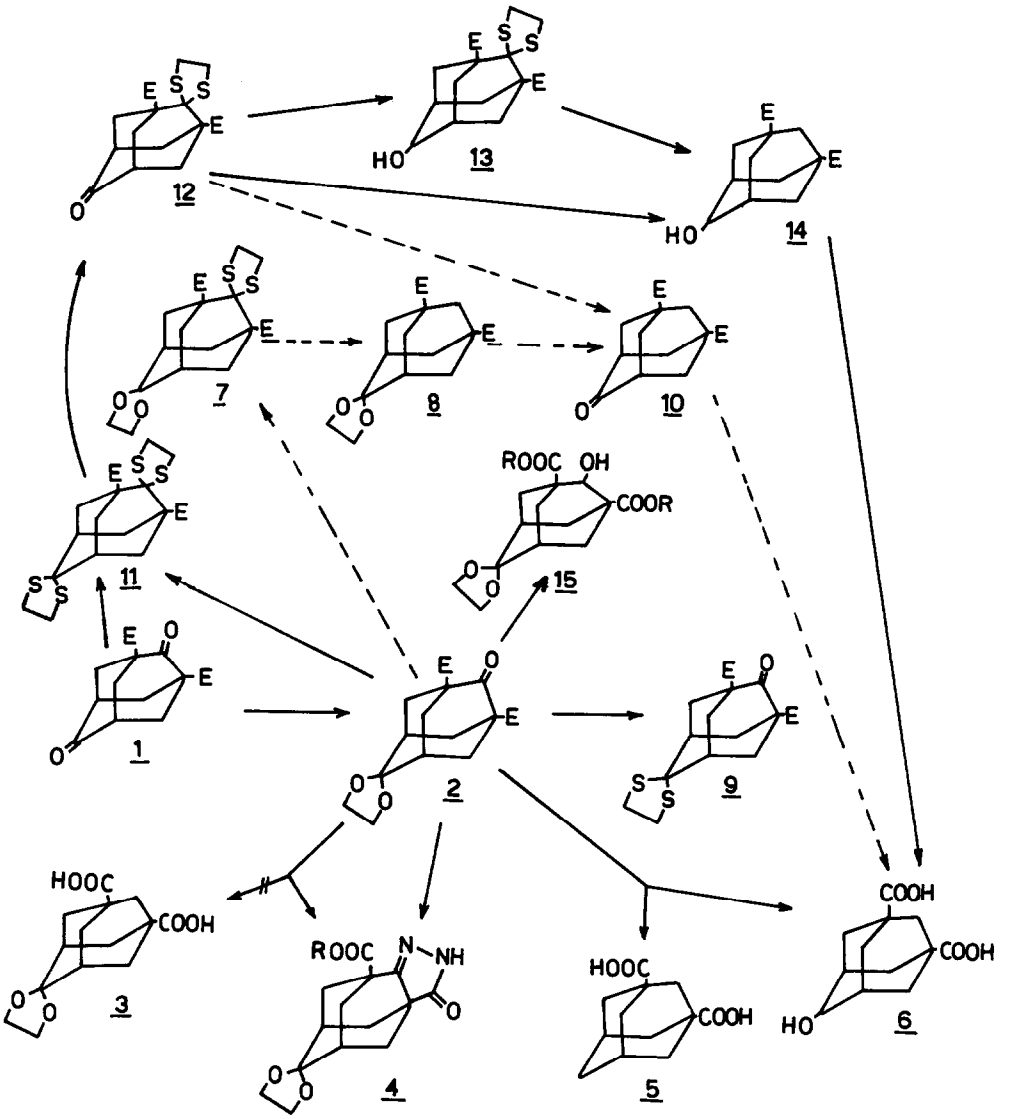
dithiol boron trifluoride gave only the known[3] ethylenedithioketal 9; it is clear that under Lewis acid catalysis, the 6-ethyleneketal function exchanges to form the ethylenedithioketal more readily than ethylenedithioketal formation at the hindered 2-keto position. More vigorous treatment of 2 (or direct treatment of 1) with excess ethane dithiol readily afforded the *bis*-ethylenedithioketal 11 (m.p. 148°). The selective removal[6] of the ethylenedithioketal protecting group at the less hindered 6-position to afford 12 then appeared to be an attractive route to the required ketone 10.

We experimented with several methods and finally achieved high yield (80%) selective conversion of 11 to 12 (m.p. 95°) using Corey's method[8] of *N*-bromosuccinimide in aqueous acetone under rigidly controlled conditions (4 equiv. NBS in 10% aqu. acetone; 0°, 20 min). Desulphurisation of 12 using Raney nickel in refluxing ethanol afforded the alcohol 14, concomitant reduction of the 6-keto function taking place. Attempts to effect this conversion stepwise *via* the ketone 10 using Raney nickel in acetone were unsuccessful, the undesulphurised alcohol 13 (m.p. 118°) being the sole product. This unusual stability of the ethylenedithioketal attests to the steric hindrance at the 2-position which has already been shown, *vide supra*, to be both useful (witness the selective transformation 11 → 12) and frustrating (the preferred formation of 9 from 2). The conversion of 12 to 14 could also be effected stepwise *via* the alcohol 13 by initial reduction of the 6-keto group with sodium borohydride. The final saponification of the diester (14) to the required diacid (6) was readily carried out using vigorous hydrolysis conditions (KOH in aqueous ethylene glycol; 185°) and the identity of 6 from the initial Wolff-Kischner reaction conclusively confirmed by m.p., mixed m.p. and complete spectral identity.

The mechanism for the conversion of 2 to 6 warrants comment. Although the conditions are very vigorous, it is certainly an unexpected transformation.[9] To gain some insight into the formation of 5 and 6 the reduction of 2 was repeated under identical conditions of solvent, temperature and pressure but (a) omitting the hydrazine and using only NaOMe in MeOH; and (b) omitting the NaOMe and using only hydrazine in MeOH. When 2 was treated with NaOMe/MeOH at 220°, a single product 15 (R = H; m.p. 238°) was obtained.[10] This confirms the stability of the ketal in the absence of hydrazine and also indicates that in the absence of hydrazine (and hence rapid hydrazone formation) reduction of the ketone functions is realizable.[4] When 2 was treated with hydrazine/MeOH at 220°, two crystalline products were obtained - the pyrazolones 4 (R = H) and 4 (R = CH_3). This is the expected reaction course and confirms the stability of


E=COOEt

the ketal under these conditions. Hence the actual mechanism for the conversion of 2 to 6 is still unclear - mechanisms can be presented but these will be discussed when more thorough experimentation has been carried out.

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2. P.R. Andrews, E.N. Cain and G.D. Smith, to be published.

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4. D. Todd in "Organic Reactions", Ed. R. Adams, Vol.4, John Wiley, N.Y., 1948, p.378.

5. H. Stetter and C. Wulff, *Chem.Ber.*, 93, 1366 (1960).

6. A search of the literature failed to reveal any such selective oxidative hydrolysis of a *bis*-ethylenedithioketal and in fact, despite several recent methods reported[7] in the literature, techniques for general high yield stoichiometric unmasking of ethylene-dithioketals are still rare.

7. H.W. Chang, *Tetrahedron Letters*, 1989 (1972), and references therein.

8. E.J. Corey and B.W. Erickson, *J.Org.Chem.*, 36, 3553 (1971).

9. Since the diacid 5 is also obtained in the reaction in good yield, it is possible that 5 and 6 both arise from a common intermediate, 1, which could conceivably result from ketal hydrolysis under the vigorous reaction conditions; 5 could then arise from standard Wolff-Kischner reduction while 6 would result from a competitive reduction of the 6-keto group. However, Stetter[3] has reported that treatment of 1 under these vigorous conditions results (as expected) in the formation of 5 only; we have repeated this reduction of 1 under precisely the same conditions as used by Stetter (and as used by us for reduction of 2) and found 5 to be the only product. So it is apparent that 6 is not formed from 2 *via* 1 although it is still possible that 5 arises from initial formation of 1 during the reaction.

10. The structure of 15 was confirmed by conversion to the known[3] diethyl ester (15; R = C_2H_5) with ethyl ortho formate and by microanalysis and spectral properties of the free diacid and its dimethyl ester (15; R = CH_3; m.p. 141°. Diazomethane).