Reduction of Barbituric Acids with Sodium Borohydride. Reduction of 5-Allyl-5-(2-hydroxypropyl)barbituric Acid

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Our continuing interest in the sodium borohydride reduction of 2,4,6-(1H,3H,5H)-pyrimidinetrione derivatives (barbituric acids) led us to examine the reduction behaviour of 5-allyl-5-(2-hydroxypropyl)-barbituric acid. This acid is known to produce lactone-type products when hydrolyzed in alkaline solutions.[1,2] The same products have been found among the metabolites of this drug.[3] Earlier we have shown the structure of the reduction products of barbituric acids and the rate of reduction to depend on the ring substituents.[4]

The aim of the present investigation was to examine whether the 2-hydroxypropyl side chain responsible for the anomalous hydrolysis products of 5-allyl-5-(2-hydroxypropyl)barbituric acid also affects the structure of the products from sodium borohydride reduction.

Results. 5-Allyl-5-(2-hydroxypropyl)barbituric acid *1* was found to be reduced completely within only 5 min. The relative amounts of final products were dependent on solvent system and temperature, but compound *2* was the initial reduction product in every solvent system. In an earlier study with similar conditions, cyclic reduction products with one hydroxyl group were found to be the first as well as the main products.[5] In the present case, the barbiturate ring was cleaved even in the nonhydroxylic solvent at room temperature (Scheme 1).

In absolute ethanol, compound *2*, where the ring hydroxyl groups are *trans* to each other, is the sole product for 90 min; only thereafter do the first signs of compound *3* and compound *5* appear. In dioxane and 2-propanol they appear after 15 min. The best yield of compound *3* was obtained from aqueous dioxane. In this same solvent system 5,5-diallyl-1-methylbarbituric acid produced the greatest amount of *cis*-diol.[5] When we attempted to isomerize compound *2* with hydrochloric acid to the *cis*-diol, compound *3* was formed. Cyclization was found to occur even when compound *2* was left standing as a concentrated solution in deuterated dimethylsulfoxide for an extended period of time.

Simultaneous formation of the analogous alcohols *4* and *5* has previously been found in the
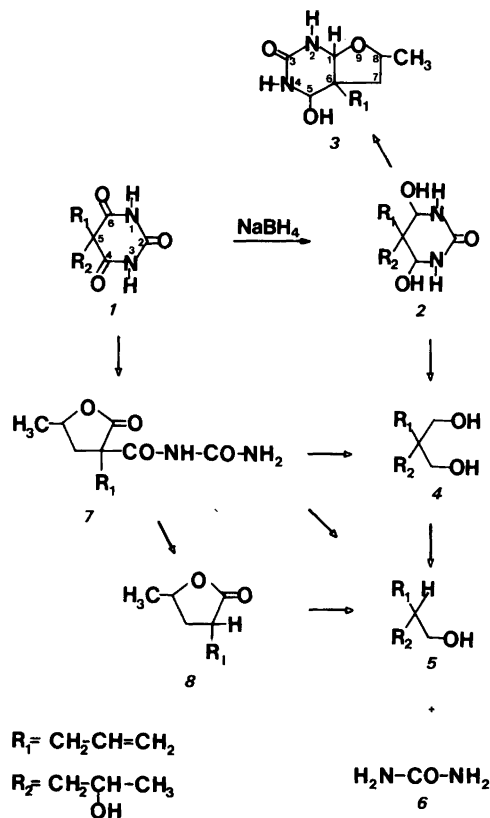
Scheme 1.

reduction of 5-methyl-5-phenylbarbituric acid, which occurred within 15 min.[4] The position of ring cleavage depends on substituents at position 5. Compounds that are easily reduced produce both primary alcohols even in nonaqueous solvents. In aqueous ethanol, compound *4* was the main product from *1*, but in other solvents compound *5* was formed in greater yield.

The lactones *7* and *8* were formed in dioxane and 2-propanol at room temperature after 15 min. They were not formed in absolute ethanol or in aqueous solvents. Further reduction of *7* afforded *4* and *5* and compound *8* was reduced to *5*. This explains the disappearance of the lactones after 5 h from the reaction mixtures.

Structure determinations: The *trans*-diol assignment of *2*, where one hydroxyl group is oriented axially and the other equatorially to the pyrimidine ring, was made on the basis of its ^{1}H NMR spectrum. In this spectrum the methine protons H-4 and H-6 are differently shielded ($\Delta\delta$ 0.37). They are also differently coupled to the vicinal amide protons:

According to the Karplus-type equation the stronger coupling of 4.3 Hz can be assigned to the equatorial methine proton and the 0.9 Hz coupling to the axial methine proton.[6] The amide protons, too, show a shielding difference of 0.27 ppm. A complete ^{1}H and ^{13}C NMR spectral analysis of 2 and 3 will be published elsewhere.[7]

In the mass spectrum of 2, M$^{\cdot+}$ is not visible because of the ready loss of water from the molecule. Otherwise, the relative abundances of the fragment ions are critically dependent on temperature. At about 100 °C the ions at m/e 124 and 153 give strongest peaks, of almost equal intensity, whereas at higher temperatures the ions at m/e 55 and 81 are more abundant. The difference may be due to the loss of water from different sites of the molecule: It may take place thermally *via* 1,2-elimination from the pyrimidine ring or *via* the formation of 3. The similarity in the spectra of 2 and 3 suggests that the latter route is the favoured one.

Compound 3 showed the same TLC characteristics and the *cis*-diols from other barbituric acid derivatives. Its mass spectrum showed the same molecular weight as 2, and the most abundant fragment ions were at identical mass numbers. The ^{1}H NMR spectrum showed two less hydroxyl proton resonances when compared with the spectrum of 2. The simultaneous presence of both amide protons and pronounced nonequivalence of the protons from the methylene groups suggested structure 3 for this product. In addition, the spectrum showed it to be a mixture of two isomers of almost equal abundance. This was confirmed by GLC, which showed two readily separable peaks for the silylated 3.

The structures of the alcohols 4 and 5 were determined from their ^{1}H NMR and mass spectra. The ^{1}H NMR spectrum of 4 showed the presence of a single isomer, which was confirmed by GLC. The spectrum of 5 showed the presence of two diastereoisomers. The methyl protons appeared as two doublets with a slight difference in their chemical shifts. Otherwise, owing to the superposition and multiplicity of the isomeric resonance patterns, assignment of the spectral parameters to a particular isomer was not possible. According to GLC analysis the isomeric ratio is 1:1.3.

The lactones were prepared for reference purposes, compound 7 by heating 1 above its melting point and compound 8 by alkaline hydrolysis of 1. The compounds were identified from their IR [2] and mass spectra.[3] The ^{1}H NMR spectrum of 7 was recorded in deuteriated dimethylsulfoxide. The chemical nonequivalence of the primary amide protons found in deuteriated acetonitrile was not observed in this solvent. This may be due to the formation of stronger hydrogen bonds with dimethylsulfoxide and disturbance of the proposed cyclic

structure of the allophanyl chain.[3] The isochronous primary amide protons resonate at 7.40 ppm.

Experimental. 5-Allyl-5-(2-hydroxypropyl)barbituric acid 1 was kindly donated by Hommel S. A. and was used without further purification. The 100 MHz ^{1}H NMR spectra were recorded on a Jeol PS/PFT-100 spectrometer. Otherwise the equipment was as described earlier.[5] The reductions were performed in absolute ethanol, 2-propanol, dioxane water 4:1 and 50 % ethanol. Reduction and separation of the products were performed as before.[5]

Gas chromatography. The purities of the reduction products were checked with a glass capillary gas chromatograph. A Carlo Erba Fractovap 4200 was equipped with a 30 m SE-30 capillary column and helium was used as the carrier gas. The reduction products were silylated by adding N,O-bis(trimethylsilyl)trifluoroacetamide, BSTFA, (200 μl) to each sample (400 μl). For compounds 2 and 3 ethyl acetate was used as the solvent.

5-Allyl-5-(2-hydroxypropyl)-4,6-trans-dihydroxy-2-(1H,3H,5H)-pyrimidone (2). Compound 2 melted at 146−147 °C (from acetone-light petroleum, 40−60 °C). Anal. $C_{10}H_{18}N_2O_4$: C, H, N. TLC. R_F 0.05. IR (KBr): 3340−3180 (OH, NH), 1710 (CO), 1530, 1130, 1100 and 1040 (OH) cm^{-1}. MS [IP 75 eV: m/e (% rel. int.)]: 212 (M−H$_2$O, 35), 153 (99), 124 (100), 109 (77), 95 (33), 81 (40), 67 (31), 55 (43), 41 (60). ^{1}H NMR [(CD$_3$)$_2$SO, +58 °C]: δ1.08 (d, 3, CH$_3$), 1.17 and 1.53 (ABX,2,CH$_2$), 2.29 (d, 2, CH$_2$), 3.90 (m, 1, CH), 4.20 (dd, 1, CH, J 5.0 and 4.3 Hz), 4.57 (dd, 1, CH, J 8.9 and 0.9 Hz), 5.1 (m, 2, CH$_2$=), 5.63 (d, 1, CHOH, J 4.3 Hz), 5.68 (d, 1, CHOH, J 5.0 Hz), 5.8 (m, 1, CH=), 6.55 (d, 1, CHOH, J 8.9 Hz), 6.43 (b, 1, NH, J 0.9 Hz), 6.70 (b, 1, NH, J 4.3 Hz).

6-Allyl-5-hydroxy-8-methyl-2,4-diaza-9-oxabicyclo-[4,3,0]nonan-3-one (3). Compound 3 is a mixture of two isomers. It was formed in every solvent system. An analytical sample was prepared by treating 2 with 2 M HCl in dioxane, m.p. 165−167 °C (from abs. ethanol). Anal. $C_{10}H_{16}N_2O_3$:C,H,N. TLC. R_F 0.11. IR (KBr):3300 (OH, NH), 1690 (CO), 1520, 1160 (C−O−C), 1060 (OH) cm^{-1}. MS [IP 75 eV:m/e(% rel. int.)]:212 (M, 0.5), 153 (26), 124 (100), 109 (41), 95 (37), 81 (34), 67 (26), 55 (21), 41 (46). ^{1}H NMR [(CD$_3$)$_2$SO,+58 °C)] Isomer I:δ 1.17 (d, 3, CH$_3$), 1.52 and 1.98 (ABX,2, CH$_2$), 2.12 and 2.42 (ABX, 2, CH$_2$), 4.09 (m, 1, CH), 4.47 (dd, 1, CH, J 5.1 and 4.1 Hz), 4.62 (d, 1, CH, J 2.2 Hz), 5.08 and 5.10 (m, 2, CH$_2$=), 5.74 (d, 1, CHOH, J 5.1 Hz), 5.80 (m, 1, CH=), 6.73 (b, 1, NH, J 2.2 Hz), 6.80 (b, 1, NH, J 4.1 Hz). Isomer II:δ1.17 (d, 3, CH$_3$), 1.42 and 1.95 (ABX, 2, CH$_2$), 2.20 and 2.42 (ABX, 2, CH$_2$), 4.06 (m, 1, CH), 4.49 (dd, 1, CH, J 5.1 and 4.1 Hz), 4.73 (d, 1, CH, J 1.9 Hz), 5.08 and 5.10 (m, 2, CH$_2$=), 5.73 (d, 1, CHOH, J 5.1 Hz), 6.72 (b, 1, NH, J 1.9 Hz), 6.73 (b, 1, NH, J 4.1 Hz).

2-Allyl-2-(2-hydroxypropyl)-1,3-propanediol   (4).
Compound 4 is a colourless oil which was obtained
in pure form on further reduction of 2. TLC. R_F 0.20.
IR (CHCl$_3$, 20 %): 3420−3360, 1135 and 1060−
1050 (OH) cm^{-1}. MS [IP 75 eV: m/e (% rel. int.)]:
143 (M−CH$_2$OH, 5), 114 (20), 97 (44), 82 (63),
79 (80), 67 (100), 55 (75), 41 (93). ^{1}H NMR (CDCl$_3$):
δ1.18 (d, 3, CH$_3$, J 6.1 Hz), 1.46 (d, 2, CH$_2$, J 5.3 Hz),
2.06 (d, 2, CH$_2$, J 7.1 Hz), 3.49 (m, 4, CH$_2$), 4.02
(m, 1, CH), 4.68 (b, 3, OH), 5.05 (m, 2, CH$_2$=),
5.8 (m, 1, CH=).

2-Allyl-4-hydroxy-1-pentanol (5). Compound 5 is a
colourless oil which was obtained in pure form on
further reduction of 2. TLC. R_F 0.32 IR (CCl$_4$, 20 %):
3370−3290, 1130 and 1050 (OH) cm^{-1}. MS [IP 75
eV: m/e (% rel. int.)]: 126 (M−H$_2$O, 3), 113 (M
−CH$_2$OH, 20), 93 (34), 84 (69), 67 (100), 55 (77), 43
(92), 41 (79). ^{1}H NMR (CDCl$_3$): δ 1.17 and 1.18 (d, 3,
CH$_3$), 1.48 (m, 2, CH$_2$), 1.76 (m, 1, CH), 2.03 (m, 2,
CH$_2$), 3.56 (m, 2, CH$_2$), 3.90 (m, 1, CH), 4.69 (b, 2,
OH), 5.05 (m, 2, CH=), 5.6 (m, 1, CH=).

Urea (6). Urea was eluted together with
compound 4. It was crystallized from a solution of 4
in chloroform in the refrigerator and identified from
its m.p. and IR-spectrum.

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