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Short Communications

Reduction of Barbituric Acids with Sodium Borohydride. Reduction of 5,5-Diallyl-1-methylbarbituric Acid

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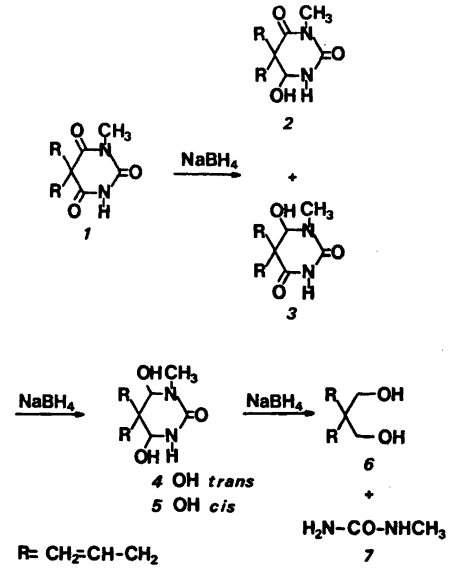
Sodium borohydride has been shown to reduce cyclic imides to hydroxylactams.[1–5] It has also been shown to reduce the amide carbonyl groups of substituted 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione derivatives (barbituric acids) in positions 4 and 6 to secondary hydroxyl groups.[6–7] In aqueous solvents the barbiturate ring may undergo reductive cleavage to yield primary alcohols. The rate of reduction and the structure of the reduction products depend on the ring substituents.

The aim of the present investigation was to determine whether the differences found in the previous reductions[6] were caused by different substituents at position 5 or merely by the effect of the methyl group at one of the nitrogen atoms.

Results. When the reduction behaviour of 5,5-diallyl-1-methylbarbituric acid *1* is compared with that of 5,5-diallylbarbituric acid,[6] there are two obvious differences. Firstly, the *N*-methylated derivative is reduced more easily. The starting material is, however, one of the main constituents (20 %) of the reaction mixture in both solvent systems. The reduction was followed for 8 h by TLC and it was found that after 1 h there were no major changes in the amounts of the reduction products. Secondly, different reduction products were formed.

In absolute methanol the reduction products were the closed-ring compounds except for a very small amount of a substance whose IR spectrum was indicative of an open-chain amide with an alcoholic hydroxyl group. The structure of this substance could not be determined with the spectroscopic methods used throughout this work and it will, therefore, be subjected to further study. In the dioxane-water solution the main product was the 1,3-propanediol, which was formed *via* reductive ring cleavage from *4* and *5*. The reduction was found to follow Scheme 1. Reduction of *2* and *3* led to the formation of *4* and *5*. Further reduction of the latter in dioxane-water was found to lead to the 1,3-propanediol and the open-chain amide. The latter, however, was not found to be reduced to 1,3-propanediol. It was not formed even on further reduction of *2* and *3*.



Scheme 1.

The identification of *2* and *3* was made on the basis of their IR, ^{1}H NMR and mass spectra. The IR spectra of the 4- and 6-hydroxy forms can almost be superimposed on the corresponding spectra of the 4- and 6-hydroxy forms of 5-ethyl-1-methyl-5-phenylbarbituric acid apart from the substituents at position 5. Their ^{1}H NMR resonances also show good correlations. The greatest difference between the two forms is in the resonance position of the amide proton, which appears as a doublet of 5.5 Hz at δ 8.40 in the spectrum of form *2* and as a sharp singlet at δ 10.20 in the spectrum of form *3* where the amide proton experiences a less marked change in its chemical surroundings. The triplet structure of the methine proton at 4.37 in the spectrum of derivative *2* is caused by its three bond couplings of 5.5 Hz to both the hydroxyl proton and the vicinal amide

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proton. This feature, too, provides a good means of differentiating between *2* and *3*.

The mass spectra of *2* and *3* show $M^{\cdot+}$ at *m/e* 224. In both spectra the base peak is at *m/e* 41 due to one allyl group. The difference between the two spectra is mainly the peak at *m/e* 149 present in the spectrum of *2* and absent in that of *3*. This peak is formed *via* thermal 1,2 elimination of water with a successive *retro*-Diels-Alder process.[8] The fragmentation of these compounds is, however, so strongly influenced by the ready loss of the allyl group that the relative intensity of this peak is quite small.

When *2* and *3* were separated using column chromatography, pure *3* was eluted first, the middle fractions contained both compounds and the last fractions pure *2*. After concentration of the middle fractions, fine needles were separated which melted sharply at 110–111 °C. The IR and ^{1}H NMR spectral data of the needles indicated a 1:1 mixture of *2* and *3* (determined by ^{1}H NMR integration of the *N*-methyl resonances at δ 3.00 and 2.93, respectively). TLC showed two spots of equal intensity. When equal amounts of the pure derivatives were mechanically mixed and ground, the m.p. of the mixture was 99 °C. When equal amounts of the pure derivatives were mixed and crystallized from absolute ethanol, crystals melting at 110–111 °C were obtained. Microscopic investigation revealed highly homogeneous needles. Because of the very small cross-section of the crystals, X-ray diffraction data could not be obtained to yield exact information on the stereochemistry and packing of the molecules.

The *trans* and *cis* 4,6-diol identifications of *4* and *5* were based on the ^{1}H NMR spectral data. In the spectrum of *4* the resonances of both the hydroxyl and methine protons are two one-proton doublets even if the former are superimposed on the =CH resonance pattern. The methylene protons of the allyl groups show chemical equivalence, appearing as a doublet integrating as 4 protons. In the spectrum of *5*, the methine protons are shielded almost equally. After the addition of D_2O this slight nonequivalence is seen as a shoulder in the singlet. The hydroxyl protons show a 0.13 ppm difference in their chemical shifts obviously due to the NCH_3 group. The methylene protons of the allyl groups, too, are shielded differently and resonate as doublets with a 0.14 ppm difference in their chemical shifts.

The formation of *6* was expected in the light of a previous investigation.[6] In this case, the methyl group at one of the nitrogen atoms does not change the position of the reductive ring cleavage. This seems to be affected by the substituents at position 5. The highly symmetric structure of the 1,3-propanediol is clearly visible in its ^{1}H NMR spectrum, thus confirming the existence of the two primary alcohol groups. In the mass spectrum one of the $-CH_2OH$ groups is very easily lost and therefore $M^{\cdot+}$ is not visible.

Experimental General. Reagents and solvents were of analytical grade. Melting points are uncorrected. Elemental analyses were performed by Ilse Beetz, Microanalytical Laboratory, West Germany. IR spectra were recorded on a Unicam SP 1000 Infrared Spectrometer, ^{1}H NMR spectra on a Jeol JNM-PMX 60 spectrometer and mass spectra on a Jeol JMS-D 100 spectrometer using direct inlet. TLC experiments were performed using silica gel plates and chloroform–ethyl acetate–2-propanol (5:5:1) as eluent. The plates were sprayed with alkaline potassium permanganate (equal volumes of 4 % sodium bicarbonate and 2 % potassium permanganate solutions were mixed before use).

Reduction methods. To a magnetically stirred solution of 2.2 g (10 mmol) of 5,5-diallyl-1-methylbarbituric acid in 100 ml of absolute methanol (or dioxane: water 4:1) 1.5 g (40 mmol) sodium borohydride was added during 10 min at such a rate as to avoid excess foaming. The solution was stirred for an additional 40 min. Then the solvent was evaporated under reduced pressure and 100 ml of water was added to the residue. The mixture was shaken vigorously for 1 min and then immediately extracted with 4 × 100 ml of ethyl acetate. After drying ($MgSO_4$) the solvent was evaporated.

Separation of the products. The products were separated using a silica gel column and 200 ml of the following eluents: chloroform–ethyl acetate (9:1), chloroform–ethyl acetate (1:1), chloroform–ethyl acetate–2-propanol (5:5:1), chloroform–ethyl acetate–2-propanol (1:1:1) and 2-propanol.

*5,5-Diallyl-4-hydroxy-1-methyl-2,6-(1*H,*3*H,*5*H*)-pyrimidinedione (2).* Compound *2* was formed in both solvent systems. It was eluted in fractions (5 ml) 112–130, m.p. 103–104 °C (from acetone–light petroleum, 40–60 °C), Found: C 58.06; H 7.17; N 12.70. Calc. for $C_{11}H_{16}N_2O_3$: C 58.93; H 7.14; N 12.50. TLC. R_F 0.31. IR (KBr): 3450 (OH), 3260 (NH), 1730 and 1688 (CO), 1490, 1100–1090 (OH) cm^{-1}. MS [IP 75 eV: *m/e* (% rel.int.)]: 224 (15, M), 207 (95), 183 (69), 182 (93), 165 (63), 149 (17), 122 (97), 109 (68), 79 (74), 41 (100). ^{1}H NMR [$(CD_3)_2SO$]: δ 2.05–2.4 (m, 4, CH_2), 3.00 (s, 3, NCH_3), 4.37 (t, 1, C*H*OH, *J* 5.5 Hz), 4.7–6.0 (m, 6, CH_2=CH), 6.27 (d, 1, CHO*H*, *J* 5.5 Hz), 8.40 (d, 1, NH, *J* 5.5 Hz).

*5,5-Diallyl-6-hydroxy-1-methyl-2,4-(1*H,*3*H,*5*H*)-pyrimidinedione (3).* Compound *3* was eluted in fractions (5 ml) 82–122, and was formed in both solvent systems, m.p. 140–141 °C (from acetone–light petroleum, 40–60 °C). Anal. $C_{11}H_{16}N_2O_3$: C, H, N. TLC. R_F 0.36. IR (KBr): 3440–3380 (OH), 3250, 3100 (NH), 1730–1680 (CO), 1490, 1085, 1035 (OH) cm^{-1}. MS [IP 75 eV; *m/e* (% rel.int.)]: 225 (6, M+1), 224 (6, M), 207 (39), 183 (24),

182 (70), 165 (40), 122 (51), 109 (55), 79 (89), 41 (100). ^{1}H NMR [$(CD_3)_2SO$]: δ 2.1–2.4 (m, 4, CH_2), 2.93 (s, 3, NCH_3), 4.54 (d, 1, C*H*OH, *J* 5.5 Hz), 4.7–6.0 (m, 6, CH_2=CH), 6.68 (d, 1, CHO*H*, *J* 5.5 Hz), 10.20 (s, 1, NH).

*5,5-Diallyl-4,6-trans-dihydroxy-1-methyl-2-(1*H,*3*H,*5*H*)-pyrimidone (4)*. Compound *4* was eluted in fractions (5 ml) 160–196 and was formed in both solvent systems, m.p. 110–111 °C (from abs. ethanol). Found: C 56.45; H 7.87; N 12.30. Calc. for $C_{11}H_{18}N_2O_3$: C 58.41; H 7.96; N 12.38. TLC. R_F 0.07. IR (KBr): 3400–3260 (OH, NH), 1650–1670 (CO), 1540 and 1010 (OH) cm^{-1}. MS [IP 75 eV; *m/e* (% rel.int.)]: 226 (7, M), 167 (68), 124 (36), 95 (44), 83 (100), 81 (40), 67 (50), 60 (61), 55 (60), 41 (96). ^{1}H NMR [$(CD_3)_2SO$)]: δ 2.16 (d, 4, CH_2), 2.76 (s, 3, NCH_3), 4.39 (d, 1, C*H*OH), 4.70 (d, 1, C*H*OH), 4.8–6.4 (m, 6, CH_2=CH), 5.66 (d, 1, CHO*H*), 6.00 (d, 1, CHO*H*), 6.44 (s, 1, NH). Deuterium exchange caused the disappearance of the δ 5.66 and 6.00 doublets revealing the structure of the CH_2=CH groups and collapse of the δ 4.39 and 4.70 doublets to sharp one-proton singlets. The broad singlet of the N–H group was also quenched.

*5,5-Diallyl-4,6-*cis*-dihydroxy-1-methyl-2-(1*H,*3*H,*5H)-pyrimidone (5)*. Compound *5* was eluted in fractions (5 ml) 154–170 and was formed in both solvent systems, m.p. 125–127°C (from abs. ethanol). Anal. $C_{11}H_{18}N_2O_3$ C, H, N. TLC. R_F 0.13. IR (KBr): 3400 (OH), 3320–3220 (NH), 1665 (CO), 1085 and 1030 (OH) cm^{-1}. MS [IP 75 eV *m/e* (% rel.int.)]: 226 (16, M), 167 (42), 124 (50), 103 (44), 95 (35), 83 (97), 80 (42), 60 (100), 55 (39), 41 (64). ^{1}H NMR [$(CD_3)_2SO$)]: δ 1.9–2.4 (m, 4, CH_2), 2.93 (s, 3, NCH_3), 4.30 (d, b, 2, C*H*OH), 4.8–6.5 (m, 6, CH_2=CH), 5.67 (t, 2, CHO*H*), 7.15 (b, 1, NH). Deuterium exchange caused the disappearance of the two partially overlapping doublets appearing as a triplet at δ 5.67 and collapse of the 4.30 two-proton doublet to a broad two-proton singlet.

2,2-Diallyl-1,3-propanediol (6). Compound *6* is a colourless oil, which was formed in dioxane–water and eluted together with *2* and *3* in fractions (5 ml) 84–130. It was obtained as pure on further reduction of *4*. TLC. R_F 0.36. IR (CCl_4), 20 %): 3380–3440 (OH), 1070–1035 (OH) cm^{-1}. MS [IP 75 eV; *m/e* (% rel.int.)]:, 125 (27), 93 (15), 79 (40), 67 (50), 55 (44), 41 (100), 39 (50). ^{1}H NMR (CCl_4): δ 2.10 (d, 4, CH_2 *J* 7 Hz), 3.45 (s, 4 CH_2OH), 4.05 (s, 2 CH_2O*H*), 4.8–6.0 (m, 6, CH_2=CH).

Methylurea (7). Methylurea was formed simultaneously with *6*. It was obtained as pure by using Dowex 1 × 2 anion exchange resin. It was identified from its m.p. and IR-spectrum.

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