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NAD(P)H MODELS 20[1]

CHEMOSELECTIVE METAL ION CATALYZED REDUCTION OF α-KETO-β, γ-UNSATURATED ESTERS BY 1,4-DIHYDROPYRIDINE DERIVATIVES

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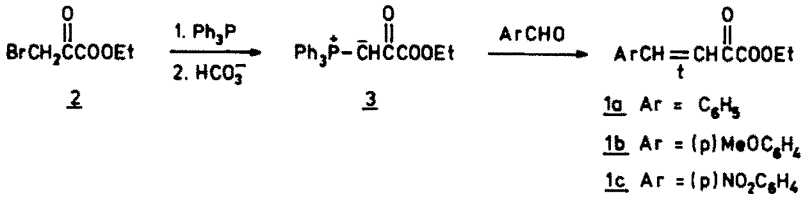
Abstract—Ethyl 2-oxo-4-aryl-3-butene-1-oates (**1a–c**) are reduced by NAD(P)H models (1-n-propyl-1,4-dihydronicotinamide (**4**) and Hantzsch ester (**5**)), in presence of magnesium perchlorate. One equivalent of the reductant reduces the substrates selectively to the corresponding 2-oxo-4-arylbutanoates (**6**, **10a**, **b**). An additional equivalent and higher temperature, converts ethyl 2-oxo-4-phenylbutanoate (**6**) to ethyl 2-hydroxy-4-phenylbutanoate (**7**). Reduction of ethyl 2-oxo-4-phenyl-3-buten-1-oate (**1a**) by Hantzsch ester in C_2H_5OD or by Hantzsch ester-4,4-d_2 in C_2H_5OH, leads to direct transfer of the hydrogen or deuterium, respectively, without isotopic scrambling. These results have been interpreted to support the hydride transfer mechanism.

Enzymatic reactions are characterized by several types of selectivity. One type of selectivity, referred to as "chemoselectivity", constitutes the specific reaction at a single functional site of a multi-functional substrate. In the case of pyridine nucleotide dependent dehydrogenases, chemoselectivity is illustrated by the reduction of either the carbon–carbon double bond[3] or the carbonyl group[4] of exemplary substrates incorporating α,β-enone functionality. Chemoselectivity has also been demonstrated in the reduction of α,β-unsaturated ketones[5] and α,β-unsaturated imines[6,7] by models of NAD(P)H coenzymes. We now present the selective reduction of the double bond of α-keto-β, γ-unsaturated esters by 1,4-dihydropyridine derivatives, in presence of Mg^{2+} ions.

α-Keto esters have been frequently employed as substrates in reductions by NAD(P)H models.[8] A study of the reduction of α-keto-β, γ-unsaturated, esters appeared to be of interest, since it is known that reduction of the analogous (protonated), α,β-unsaturated imines can lead to both C=C and C=N saturation in the primary step.[6] Furthermore, it was observed that the ratio of C=C/C=N reduction varied with the basicity of the amine component of the substrate. In case of α-keto-β, γ-unsaturated esters two questions were pertinent. Firstly, which of the two reducible groups in the substrate was reduced by NAD(P)H models and, secondly, could the site of reduction be influenced by electronic perturbation of the double bond. It was also considered of practical interest to compare the results of the NAD(P)H model reductions with those obtained by the use of other reductants. Suitable substrates for the contemplated study are represented by esters of type **1** (Scheme 1).

The nature of the aryl moiety in these compounds provides a means of altering the electron density of the β, γ-double bond, without the accompaniment of steric effects. The three esters **1a–c**, selected for investigation could be conveniently prepared by the reaction of yield **3**, itself obtained from α-bromopyruvate (**2**), with the appropriate aldehyde. The unsaturated esters were found to possess the *E*-configuration (Experimental). As NAD(P)H models, the dihydropyridines **4** (PNAH) and **5a** (Hantzsch ester) were chosen because of their difference in reactivities as reductants.



Scheme 1.

The keto ester **1a** (Scheme 2) bearing the unsubstituted phenyl ring, showed no reaction with either the Hantzsch ester (**5a**) or PNAH (**4**) at room temp. However, when one equivalent of Mg $(ClO_4)_2$ was added to a mixture of **1a** and **4** (or **5a**), in acetonitrile, a reaction commenced at room temp. The reduction reaction could be monitored by following the lowering of the vinyl proton signals in the NMR spectrum. After about an hour, these signals totally disappeared and two new signals (triplets) were observed at δ 2.95 and δ 3.16 ppm. Work up of the reaction mixture yielded saturated ester **6** (60–70%, after column chromatography, Scheme 2) as the only reduction product.[9] If, after completion of the double bond reduction, a second equivalent of **4** or **5a**, plus an additional equivalent of Mg $(ClO_4)_2$, were added, and

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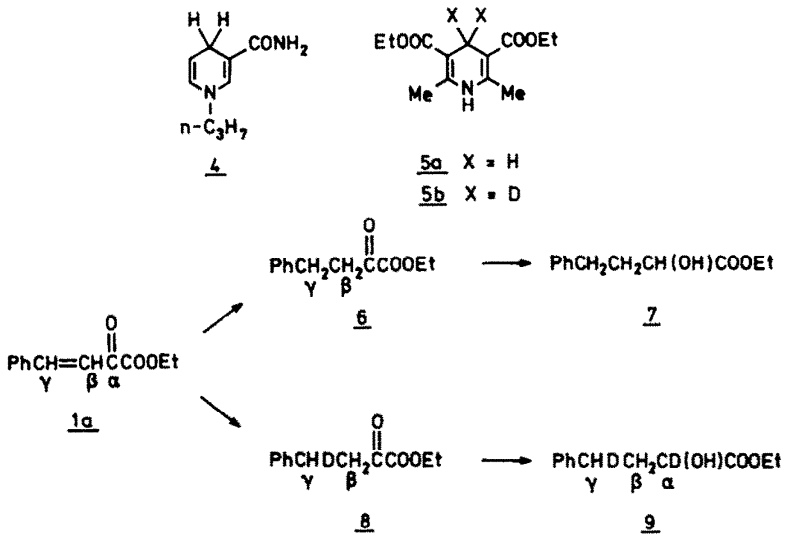


Scheme 2.

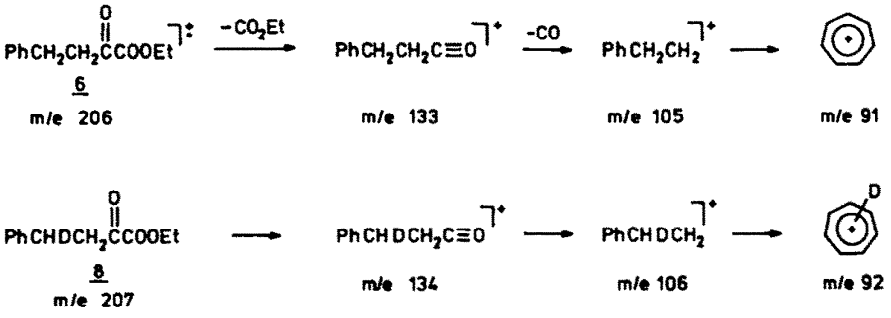
the mixture heated to reflux (overnight), the product of the second reduction step was shown to be hydroxy ester **7** (Scheme 2). The same product (**7**) was obtained, as expected, when substrate **1a** was refluxed (overnight) with two equivalents of **4** or **5a**, in presence of Mg^{2+} (2 equiv). In contrast, when keto ester **1a** was allowed to react with the dihydropyridines **4a** or **5a** (2 equiv, CH_3CN, reflux, overnight), in the absence of Mg^{2+}, the sole reduction product was found to be saturated α-keto ester **6**.

In order to ascertain the site of transfer of the hydrogen (hydride equivalent) from the dihydropyridines to the ester, **1a** was reduced with one and two equivalents of **5b**, in two separate experiments. The products of these reactions were keto ester **8** and hydroxy ester **9**, respectively. The position of the deuterium atom in **8** and **9** was established by PMR and/or mass spectrometry. Thus, in **8** the β-methylene protons appeared as a doublet at δ 3.16 (J = 7 Hz), while the C—H exhibited a triplet centered at δ 2.95. The structure of **9** was elucidated by double resonance (250 MHz). The non-deuterated alcohol **7** showed two distinct multiplets for the β-methylene protons (around 2.00 ppm) and a complex multiplet for the benzylic methylene protons (δ 2.65–2.85 ppm). The absorptions of the alcohol C—H proton and the signals of the ester methylene, formed a complex pattern (δ 4.10–4.25 ppm). The PMR spectrum of **9** showed less complex multiplets for the β-methylene protons and a double doublet for the benzylic proton. No alcohol C—H proton was detected and a simple quartet was observed for the ester methylene. Irradiation of the benzylic proton gave two doublets (δ 0.91 and 1.09 ppm, J = 13 Hz, geminal coupling) for the β-methylene protons, while irradiation, in turn, at the centre of each of these protons resulted in doublets for the benzylic proton (δ 2.72, J = 6 Hz or J = 8 Hz). The mass spectra of **8** further supported its structure. The main fragmentation pattern in the electron-impact spectrum of keto esters **6** and **8** is discussed in Scheme 3.

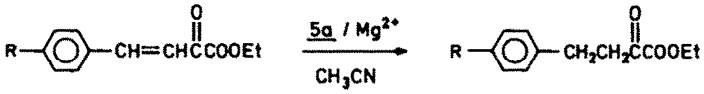
Upon incorporation of a D atom in the benzylic methylene group, masses of the fragments carrying the latter moiety will be augmented by one unit. This was indeed observed in the mass spectrum of keto ester **8**.

From the foregoing observations it is apparent that at room temperature the reduction of α-keto-β, γ-unsaturated esters by 1,4-dihydropyridine derivatives (1 equiv, in the presence of Mg^{2+}) proceeds selectively to give the corresponding dihydro-product.[10] At higher temperatures (refluxing CH_3CN), the primary reduction product is further reduced to the hydroxy ester **9**. It is significant that a product arising from an initial carbonyl reduction step could not be detected.[10]

In order to examine if electron-donating or electron-withdrawing substituents on the benzene ring could influence the selectivity of the reduction, the esters **1b** and **1c** were subjected to reactions with Hantzsch ester



Scheme 3.



1b R = OMe
1c R = NO_2

10a R = OMe
10c R = NO_2

Scheme 4.

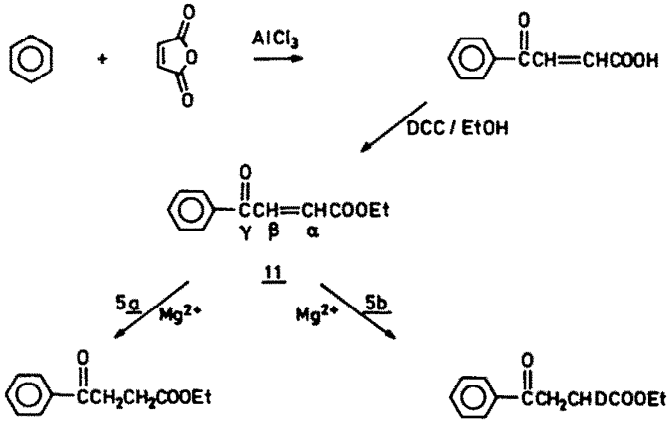
(**5a**, 1 eq., Mg^{2+}, CH_3CN), at room temp. In both cases, the products were exclusively the dihydro esters **10a** and **10b**, respectively (Scheme 4). It follows from these results that the specificity of C=C reduction in this class of substrates is not affected by variation of electronic influence emanating from the aryl group.

In view of the aforementioned results, it seemed of interest to examine the reduction of a substrate in which the C=C and C=O groups are interchanged between the aryl moiety and the ester function. The required ester **11** was prepared[11a] as described in Scheme 5 and subjected to reduction by **5a**, in the presence of Mg^{2+} ions. The formation of **12a**, as the exclusive reduction product, showed that the double bond was once again the site of the reaction. Reduction of **11** with **5b** and analysis of the labelling pattern in **12b** (PMR, Experimental) revealed that a deuterium atom had been transferred to the α-position of the substrate. It is pertinent to mention that the reduction of the corresponding acid by Hantzsch ester has been shown by Westheimer *et al.*[11b] to proceed in a similar fashion.

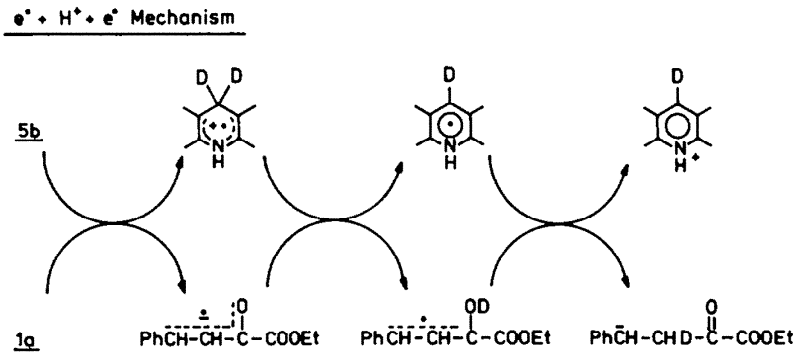
The chemoselectivity of nucleophilic attack on conjugated carbonyl compounds has been extensively studied with a wide range of nucleophiles and substrates.[12] The results have been interpreted in terms of the generalized perturbation theory; attack at C_α and C_γ of the enones being regarded as charge or frontier orbital controlled, respectively.[12e] In the reduction of α, β-unsaturated ketones by metal hydrides, selectivity of the hydride addition site has been found to be sensitive to structural characteristics of both the substrate and the reductant.[13] The essential requirement of the metal ion in the present reduction does not allow a simple rationalization of the substituent effect. It is obvious that a better understanding of the role of the metal ion, that is, of the transition state of the reaction, will have to be achieved before correlations between electronic factors and selectivity of the reduction site can be made.

The nature of the hydrogen which is transferred in dihydropyridine mediated reductions has been the subject of much debate.[14] Bruice has recently suggested[15] that the formal hydride equivalent transfer can display a duality of mechanism depending upon the nature of the substrate. In the case of oxidants (substrates) with high redox potential, which can form the putative nicotinamide radical intermediate, the mechanism follows the sequence $e^- + H^+ + e^-$, while with less powerful oxidants a direct H^- transfer constitutes the reaction pathway. To examine this aspect of the reduction reaction, let us consider the course of hydrogen transfer to substrate **1a**, according to the two possible mechanisms. A hydride transfer mechanism implies a direct movement of H^- from the C(4)-position of the dihydropyridine, to the γ-carbon of **1a**. Such a process is not expected to show hydrogen exchange in protic solvents. On the other hand, a three step ($e^- + H^+ + e^-$) mechanism would, in case of reduction by **5b** (Scheme 6), involve the radical cation (**a**) and substrate-derived intermediates of the type (**b**), (**c**) and (**d**). This should have two consequences: (i) as an acid (**a**) ought to display deuterium exchange in protic solvents[16] and (ii) assuming kinetic protonation of the oxygen of intermediate (**b**), the deuterium label should end up on the β-carbon (exchangeable position) of the reduction product. While the reduction of **1a** by **5b**, in acetonitrile, leads to **8**, which is consistent with a hydride transfer mechanism, it was felt that a direct H-transfer had to be demonstrated in protic solvents.

To this end, **1a** was reduced by **5a** and **5b** in EtOD and EtOH, respectively. The products of both reactions were examined for their deuterium content and labelling pattern. This analysis showed that reduction by **5a** (in EtOD) led to the dihydroproduct **6**, whereas, when **5b** was employed (in EtOH), the saturated ester



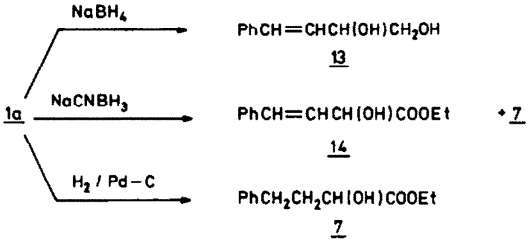
Scheme 5.



Scheme 6.

was identified as ethyl 2-oxo-4-phenyl-4-monodeuterobutyrate (**8**). These observations are consistent with a hydride transfer mechanism for the dihydropyridine mediated reduction of α-keto-β,γ-unsaturated esters. Recent studies on the pathway of hydrogen-transfer, using a cyclopropane-ring as a mechanistical probe, also provide support for a H^--transfer process.[17]

Finally, it should be mentioned that the chemoselectivity of the reduction of enones by NAD(P)H models can be of practical interest. The uniqueness of this selectivity was demonstrated by its comparison with the fate of **1a** when reduced by other reductants. The results are described in Scheme 7. Sodium borohydride



Scheme 7.

reduced **1a** to diol **13**,[18] leaving the double bond intact. Sodium cyanoborohydride, on the other hand, yielded a 1:1 mixture of hydroxy esters **7** and **14**. Yet another reduction pattern was observed when **1a** was subjected to catalytic hydrogenation (Pd/C). Initially, the reaction led to the formation of a mixture of keto ester **6** and hydroxy ester **7**. However, upon prolonged hydrogenation, both the C=C and the C=O functionalities were reduced to give **7** as the final product. Taking into account the mild conditions required for reduction of the double bond of **1a** (by **4** and **5**) and the difference in the rates of reduction of C=C and C=O groups in **1a** and **6**, respectively, it can be concluded that dihydropyridine reductions should find applications in the selective reduction of similar multi-functional substrates.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Perkin Elmer 257 Spectrometer; the absorptions are given in cm^{-1}. NMR spectra were recorded on a Varian Associates Model XL-100/12 or on a Brucker WM 250 instrument, using TMS as an internal standard. Unless stated, IR and NMR spectra were recorded in $CHCl_3$ and $CDCl_3$, respectively. Mass spectra (EI, 70 eV, unless mentioned otherwise) were obtained with a Varian Mat-711 spectrometer (all fragments are implicitly designated as cations or as radical cations). Accurate mass determinations of the molecular ions were carried out by high-resolution peak matching.

Ethyl triphenylphosphoranylidenepyruvate (**3**). The ylid was obtained by the procedure of Le Corre,[19] and recrystallized from EtOH in 85% yield (m.p. 186°). IR 1710(s), 1620(m), 1580 (s), 1560 (s). PMR δ 1.34 (3H, t, CH_3 ester), 4.25 (2H, q, CH_2 ester), 4.81 (1H, d, J = 23.5 Hz, Ph_3P=C<u>H</u>—CO—), 7.35–7.80 (15H, m, phenyl-H). MS (FDMS, 10mA–20nA) *m/e* 376 (100%).

Ethyl 2-oxo-4-phenyl-3-buten-1-oate (**1a**). The Wittig reaction between **3** and benzaldehyde was carried out on a 74 mmol scale, in 500 ml dry xylene, according to the procedure of Le Corre.[19] After removal of the solvent, the main portion of triphenylphosphine oxide was removed by recrystallization from EtOAc. This was repeated three times using EtOAc added with increasing amounts of hexane (max 1:1). After removal of the solvent, keto ester **1a** was extracted from the residue with 5 × 100 ml hexane. This soln was washed with a dil $NaHCO_3$ aq, dried over Na_2SO_4 and the solvent removed. The unreacted benzaldehyde was removed by Kugelrohr (50°/0.01 mm), followed by distillation (140°/0.01 mm) of **1a** (6.2 g, 41%, lit.[19] 40%), yellow needles after recrystallization from cold EtOAc (m.p. 25–26°). IR 1739 (s), 1692 (s), 1668 (s), 1610 (s), 1580 (s). PMR δ 1.41 (3H, t, CH_3 ester), 4.40 (2H, q, CH_2 ester), 7.33 (1H, d, J = 16 Hz, =C<u>H</u>—CO—), 7.35–7.70 (5H, m, Ph—H), 7.85 (1H, d, J = 16 Hz, Ph—C<u>H</u>=). MS *m/e*; 204 (M), 176, 165, 155, 132, 131 (100%), 103, 77, 63, 51. 39; accurate mass determination: 204.0799; Calc for $C_{12}H_{12}O_3$: 204.0786.

Ethyl 2-oxo-(4-methoxyphenyl)-3-buten-1-oate (**1b**). 4-Methoxybenzaldehyde (27.23 g, 0.2 mol) and ylid **3** (18.82 g, 0.05 mol) were refluxed (20 hr) in 300 ml dry xylene, under N_2. The work up was similar to that described for **1a**. The unreacted aldehyde was removed by Kugelrohr (80–120°/1–0.5 mm), followed by distillation (150–160°/0.5 mm) of the keto ester **1b** (3.65 g, 31%), yellow needles (m.p. 44–45°). IR 1730 (s), 1690 (s), 1660 (m), 1595 (s), 1575 (s), 1515 (s). PMR δ 1.41 (3H, t, CH_3 ester), 3.88 (3H, s, CH_3O—), 4.40 (2H, q, CH_2 ester), 6.95 (2H, d, J = 8.5 Hz, meta Ar—H), 7.23 (1H, d, J = 16 Hz, =C<u>H</u>—CO—), 7.61 (2H, d, J = 8.5 Hz, ortho Ar—H), 7.86 (1H, d, J = 16 Hz, Ar—C<u>H</u>=). MS *m/e*: 234 (M), 204, 161 (100%), 149, 133, 131, 121, 118, 103, 77, 51; accurate mass determination: 234.0878; Calc for $C_{13}H_{14}O_4$: 234.0892.

Ethyl 2-oxo-(4-nitrophenyl)-3-buten-1-oate (**1c**). The ester was prepared according to the procedure described by Le Corre;[19] yellow-ochre needles were obtained in 41% yield (m.p. 120–121°, lit.[19] 121–122°, 42%). IR 1730 (s), 1700 (s), 1670 (m), 1615 (s), 1600 (s), 1525 (s), 1350 (s). PMR δ 1.41 (3H, t, CH_3 ester), 4.41 (2H, q, CH_2 ester), 7.48 (1H, d, J = 16.5 Hz, =C<u>H</u>—CO—), 7.81 (2H, d, J = 8.5 Hz, meta Ar—H), 7.91 (1H, d,

J = 16.5 Hz, Ar—CH=), 8.30 (2H, d, J = 8.5 Hz, ortho Ar—H). MS *m/e*: 249 (M), 221, 176 (100%), 149, 146, 130, 118, 102, 94, 90, 76, 44; accurate mass determination: 249.0651; Calc for $C_{12}H_{11}NO_5$: 249.0637.

Reduction of the β, γ-unsaturated α-keto esters (**1a–c**) *by 1 equiv Hantzsch ester* (**5a, b**). To a soln of **1a–c** (1 mmol) and 253.3 mg (1 mmol) Hantzsch ester (**5a, b**) in 20 ml dry acetonitrile, was added 1 ml of a $Mg(ClO_4)_2$ soln (1 M in CH_3CN), under stirring and N_2 atm. After approx 1 hr of stirring at room temp (by which time the reaction was complete, TLC), the solvent was removed *in vacuo*, the residue taken up in $CHCl_3$ (50 ml), washed with water (3 × 5 ml), and dried over Na_2SO_4. PMR analysis (250 MHz) of this worked up reaction mixture showed keto esters **6**, **10a, b** and the oxidized Hantzsch ester in a 1 : 1 ratio. When **5a** was employed as the reductant, salient signals (triplets) of the β- and γ-methylene protons of **6**, **10a** and **10b**, were observed at 3.10 and 2.87, 3.16 and 2.98, 3.07 and 2.82 ppm respectively. No traces of doubly reduced substrate **7**, or its phenyl substituted homologs, nor the starting material, could be detected in this mixture. Isolation of these keto esters by column chromatography (Silicagel, ethyl acetate/hexanes 1 : 10) led to appreciable losses (presumably due to hydrolysis of the esters on the column). Although the reaction products were difficult to separate, in case of **1a** the product keto ester **6** could be isolated in 60–70% yield.

Ethyl 2-oxo-4-phenyl-butanoate (**6**). The material obtained upon column chromatography was distilled by Kugelrohr (120°/0.01 mm) for analytical purposes. IR 1728 (s), 1603, 1497. PMR (250 MHz) δ 1.34 (3H, t, CH_3 ester), 2.95 (2H, t, Ph—CH_2—), 3.16 (2H, t, —CH_2—CO—), 4.29 (2H, q, CH_2 ester), 7.1–7.4 (5H, m, phenyl—H). MS *m/e*: 206 (M, 93%), 188, 177, 160, 133 (98%), 105 (100%), 91 (99%), 79, 77, 65, 63, 51; accurate mass determination: 206.0917; Calc for $C_{12}H_{14}O_3$: 206.0943.

Ethyl 2-oxo-4-phenyl-butanoate 3-d_1 (**8**). The ester was isolated in the same way as **6**, from the reaction of **1a** with **5b**. PMR see: discussion. MS *m/e*: 207 (M, 30%), 189, 188, 178, 134 (72%), 106 (99%), 92 (100%), 80, 79, 78, 77, 66, 51.

Reduction of (**1a**) *by Hantzsch ester* (**5a, b**) *in ethanol*. The reduction of **1a** (1 mmol) by 1 mmol 4,4-dideuterated Hantzsch ester (**5b**) was carried out in different solvent systems (i.e. 10 ml of an actonitrile/ethanol mixture in the ratios 8 : 2, 5 : 5, 0 : 1) and in presence of 1 equiv. $Mg(ClO_4)_2$. The reaction mixtures were refluxed overnight, the solvent of a sample removed and the residue taken up in $CDCl_3$. PMR analysis (250 MHz) indicated the incorporation of the label in the benzylic methylene of the reduction product **8**.

The same procedure was followed for the reduction of **1a** by Hantzsch ester **5a** in similar solvent systems, using ethanol-d this time. PMR analysis indicated the β-methylene to be completely deuterated (proton exchange with the solvent). The benzylic methylene, thereby, appearing as a singlet. Subsequent work-up and column chromatography led to the isolation of non-deuterated **6**.

Reduction of (**1a**) *by dihydropyridine* (**4**). The reduction was carried out under exactly the same conditions as for the preceding reductions of **1**, using 166 mg (1 mmol) of **4**, instead of Hantzsch ester, as reducing agent. The working-up procedure was also identical and the residue obtained was distilled by Kugelrohr (120°/0.01 mm) to give 169 mg (82%) of α-keto ester **6**.

Reduction of the β, γ-unsaturated α-keto ester (**1a**) *by 2 equiv Hantzsch ester* (**5a, b**). To a soln of **1a** (1 mmol) and 532 mg (2.1 mmol) Hantzsch ester (**5a, b**) in 20 ml dry acetonitrile, was added 2 ml of a $Mg(ClO_4)_2$ soln (1M in CH_3CN), under stirring and N_2 atm. After refluxing overnight, the reduction was complete (TLC) and the mixture was worked up as described previously. Isolation of **7** and **9**, from the mixutre, by distillation proved to be impossible, also column chromatography (Silicagel, EtOAc/hexanes 1 : 10) led only to strongly enriched material, as the α-hydroxy ester was eluted very closely after the oxidized Hantzsch ester. PMR analysis and comparison of **7** with an authentic sample obtained by catalytic hydrogenation of **1a**, allow the conclusion that **7**/**9** and the oxidized Hantzsch ester were the only reaction products.

Reduction of (**1a**) *with 2 equiv dihydropyridine* (**4**). Reduction of 1 mmol of **1a** by 2.2 mmol of **4** led, under the same experimental conditions and after similar work-up as for the preceding experiments, to 141 mg of **7** (Kugelrohr distillation, 130°/0.01 mm).

Ethyl 2-hydroxy-4-phenyl-butanoate (**7**). Catalytic hydrogenation (Pd/C, 2.5 atm) of 408 mg (2 mmol) of **1a** in 70 ml EtOH, led after 4 hr to a 1 : 1 mixture of **6** and **7** (PMR). A similar experiment under 5 atm gave after 6 hr, **6** and **7** in a 1 : 8 ratio. Continuation of this experiment yielded, after 20 hr, exclusively **7** in quantitative yield. This material was distilled by Kugelrohr (120–140°/0.01 mm) for analytical purposes.

IR: 3515 (ν_{O-H}, br), 1725 (s), 1603, 1500. PMR (250 MHz) δ 1.26 (3H, t, CH_3 ester), 1.55 (1H, s, CHOH), 1.80–2.00 and 2.04–2.20 (2H, m, two separate multiplets for each H of —CH_2—CHOH), 2.70–2.85 (2H, m, Ph—CH_2), approx. 4.13 (1H, covered by ester signals, CHOH), 4.20 (2H, q, CH_2 ester), 7.1–7.4 (5H, m, phenyl-H). MS *m/e*: 208 (M), 190, 177, 149, 134, 121, 117, 104 (100%), 91 (100%), 85, 76, 69, 57, 51, 41, 39; accurate mass determination: 208.1108; Calc for $C_{12}H_{16}O_3$: 208.1099.

Reduction of β, γ-unsaturated α-keto ester (**1a**) *by sodium borohydride*. To a soln of 50 mg $NaBH_4$ in 20 ml MeOH was added, in one batch, a soln of 204 mg (1 mmol) of **1a** in 5 ml MeOH. Decoloration of the mixture was instantaneous and stirring was continued for 15 min at ambient temp. The solvent was removed *in vacuo*, water (5 ml) and $CHCl_3$ (10 ml) added, followed by decomposing through addition of a 3% HCl aq. After neutralization by a dil Na_2CO_3 aq, the chloroform layer was removed, and the solution extracted with chloroform (2 × 10 ml). The combined $CHCl_3$ layers were dried over Na_2SO_4 and after removal of the solvent 125 mg (76%) of 2-hydroxy-4-phenyl-3-buten-1-ol, was obtained. Attempts at distillation led to decomposition of this compound. PMR δ 2.98 (2H, br, s, OH), 3.65 (2H, m, CH_2OH), 4,35 (1H, m, CHOH), 6.17 (1H, dd, J = 16 Hz, J = 6 Hz, CH=CH—CHOH), 6.67 (1H, d, J = 16 Hz, Ph—CH=), 7.15–7.55 (5H, m, Ph—H).

Reduction of (**1a**) *with sodium cyanoborohydride*. To a soln of 70 mg sodium cyanoborohydride in 20 ml EtOH was added, in one batch, a soln of 204 mg (1 mmol) of **1a** in 5 ml EtOH. The mixture was stirred overnight at ambiant temp and worked up as in the preceding experiment ($NaBH_4$). PMR of the mixture indicated that the presence of a 1 : 1 mixture of **7** and a β, γ-unsaturated α-hydroxy ester. The latter resulting from the selective reduction of the keto function. This allylic alcohol exhibited PMR signals at 1.30 (3H, t, CH_3 ester), 4.28 (2H, q, CH_2 ester), 4.82 (1H, dd, J = 6 Hz, J = 1.5 Hz, CH=CHOH), 6.23 (1H, dd, J = 16 Hz, J = 6 Hz, CH=CH—CHOH), 6.81 (1H, dd, J = 6 Hz, J = 1.5 Hz, Ph—CH=CH), 7.10–7.45 (5H, m, Ph—H).

Ethyl β-benzoylacrylate (**11**). A soln of 4.12 g (20 mmol) N,N'-dicyclohexylcarbodiimide and 5.0 ml (85 mmol) dry EtOH in 50 ml dry benzene was heated at 60° for 1 hr. The β-benzoylacrylic acid[11] (1.76 g, 20 mmol) was added in one batch, and the soln refluxed for 4 hr. After standing overnight a substantial amount of N,N'-dicyclohexylurea was filtered off and the solvent evaporated *in vacuo*. The viscous residue was purified by column chromatography (Silicagel, EtOAc/hexanes 1 : 10); the first fraction collected contained **11**. Distillation by Kugelrohr (120°, 0.01 mm) yielded 832 mg (4.08 mmol, 20%) of **11**.

IR: 1720 (s, $\nu_{C=O}$, ester), 1670 (s, $\nu_{C=O}$, keto), 1633 (m, $\nu_{C=C}$), 1600 (m, $\nu_{C=C}$, phenyl), 1580. PMR δ 1.36 (3H, t, CH_3 ester), 4.33 (2H, q, CH_2 ester), 6.93 (1H, d, J = 16 Hz, =CH—COOEt), 7.45–7.75 (3H, m, Ph—H), 7.97 (1H, d, J = 16 Hz, CO—CH=), 8.00–8.15 (2H, m, Ph—H). MS *m/e*: 204 (M), 176, 175, 159, 131 (M—CO_2Et, 50%), 105 (Ph—CO, 100%), 77, 51; accurate mass determination: 204.0741; Calc for $C_{12}H_{12}O_3$: 204.0786.

Ethyl 4-oxo-4-phenyl-1-butanoate (**12a**). The ester was the only product in the reduction of **11** (204.2 mg, 1 mmol) by **4** (166 mg, 1 mmol), in the presence of 1 ml Mg $(ClO_4)_2$ (1M soln in CH_3CN), in 20 ml acetonitrile (reflux, 24 hr, under N_2 atm). The solvent was removed *in vacuo*, the residue taken up in 75 ml $CHCl_3$, washed with 3×10 ml H_2O and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled by Kugelrohr (150°/0.05 mm) to yield 175 mg (85%) of γ **12a**. Reduction of **11** by 214.2 mg (1 mmol) 1-benzyl-1,4-dihydronictotinamide yielded in the same way 171 mg (83%) of **12a**. IR: 1732 (s, $\nu_{C=O}$, ester), 1690 (s, $\nu_{C=O}$, keto), 1600 (m, $\nu_{C=C}$, phenyl), 1585. PMR δ 1.27 (3H, t, CH_3 ester), 2.77 (2H, t, $C\underline{H}_2$—COOEt), 3.33 (2H, t, Ph—CO—$C\underline{H}_2$), 4.29 (2H, q, CH_2 ester), 7.30–7.65 (3H, m, Ph—H), 7.95–8.05 (2H, m, Ph—H). MS *m/e*: 206 (M, 52%), 178, 161 (M—OEt, 87%), 133 (M—COOEt, 11%), 131 (15%), 106 (31%), 105 (Ph—CO, 100%), 77 (100%), 50 (42%); accurate mass determination: 206.0958; Calc for $C_{12}H_{14}O_3$: 206.0943.

The reduction of β-benzoylacrylate (**11**) *by Hantzsch ester* (**5a, b**). The reduction was carried out under exactly the same conditions as for the preceding reduction, using 253.3 mg (1 mmol) Hantzsch ester (**5a/5b**), instead of **4**, as reducing agent. The working-up procedure was also identical and a mixture (421 mg) of **12a/12b** and oxidized Hantzsch ester were obtained (PMR ratio 15:17), representing a 96% yield of **12a/12b**. Compound **12b** was identified by the salient PMR signals at δ 2.77 (1H, t (br), —C$\underline{H}$D—COOEt) and 3.33 (2H, d, Ph—CO—C$\underline{H}_2$).

REFERENCES AND NOTES

[1] NAD(P)H MODELS 19. See L. H. P. Meijer, J. C. G. van Niel and U. K. Pandit, *Tetrahedron* **40**, (1984).

[2] Taken in part from the forthcoming doctorate thesis of L. H. P. Meijer, University of Amsterdam.

[3] [a]Cholestenone 5α- and 5β-reductases (1.3.1.22 and 1.3.1.23); [b]Dihydrouracil dehydrogenases (1.3.1.1 and 1.3.1.2).

[4] [a]Allyl alcohol dehydrogenase (1.1.1.54); [b]Shikimate dehydrogenase (1.1.1.25).

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[9] The isolated yield of **6** is lowered due to losses during work-up.

[10] At room temp the reduction of the double bond is quantitative and not complicated by further reduction of the carbonyl group. This is attested by UV spectral data (isobestic points at 220 and 270 nm), which will be discussed in connection with kinetic studies, to be described in a forthcoming paper.

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