Reduction of Isopropylidene Acylmalonates, 5-Acylbarbituric Acids, and 3-Acyl-4-hydroxycoumarins to the Corresponding Alkyl Derivatives by Sodium Cyanoborohydride–Acetic Acid

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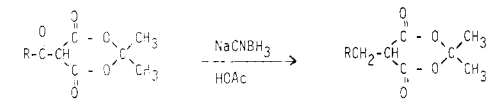
Isopropylidene acylmalonates, 5-acylbarbituric acids, and 3-acyl-4-hydroxycoumarins are readily reduced to the corresponding alkyl derivatives by sodium cyanoborohydride–acetic acid. The cyclic substrates are readily prepared by the acylation of isopropylidene malonate, barbituric acid (or its *N,N'*-dimethyl derivative), and 4-hydroxycoumarin, according to procedures developed by other workers. The reductions take place upon addition of a 2 mol equiv of sodium cyanoborohydride to a mixture of the acyl compound and acetic acid. This reductive transformation completes a synthetic method for the preparation of the alkyl derivatives starting from the parent compound.

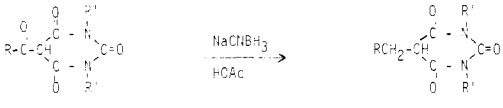
The applicability of various borohydride reagents for reductive transformations has been extensively studied and well documented.[1] We report an unusual and potentially useful application: the reduction of isopropylidene acylmalonates (**1**), 5-acylbarbituric acids (**2**), and 3-acyl-4-hydroxycoumarins (**3**) to the corresponding alkyl derivatives by treatment with sodium cyanoborohydride–acetic acid.



1a R = CH_3CH_2- 4a

1b R = $(CH_3)_2CH$- 4b

1c R = $PhCH_2$- 4c

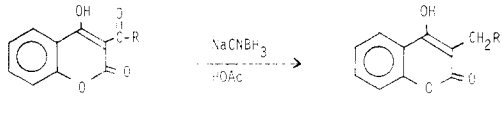


2a R = $CH_3CH_2CH_2$- , R' = H 5a

2b R = $(CH_3)_2CH_2CH_2$- , R' = H 5b

2c R = $CH_3(CH_2)_3CH_2$- , R' = H 5c

2d R = $CH_3(CH_2)_{13}CH_2$- , R' = CH_3- 5d



3a R = CH_3CH_2- 6a

3b R = $CH_3CH_2CH_2$- 6b

3c R = $CH_3(CH_2)_2CH_2$- 6c

3d R = $CH_3(CH_2)_{13}CH_2$- 6d

We have uncovered a few literature procedures that bear some resemblance to our reported reductions. The catalytic hydrogenation (Pt/CH_3OH) of dehydroacetic acid (**9**) to 3-ethyl-4-hydroxy-6-methyl-2-pyrone[2] (**10**) and similar catalytic reductions of 3-[β-(3,4-dimethoxyphenyl)-propionyl]-4-hydroxy-6-methyl-2-pyrone[3] and 3-benzoyl-4-hydroxycoumarin[4] have been reported. In the carbocyclic series, some similar reductions of 2-acyl-1,3,4-cyclopentatriones by sodium borohydride in methanol[5] and catalytic hydrogenation[5] (Pt/CH_3OH) and also similar reductions of 2-acetyl-1,3-cyclohexanediones by catalytic hydrogenation[6] (Pd/EtOH) and zinc–acetic acid[7] have been reported. More recently, the catalytic deuteration (Pt/ethyl acetate) of isopropylidene (methoxymethylene)malonate[8] (which can be considered to be the *O*-methyl derivative of the enol form of isopropylidene

Table I. Reductions by Sodium Cyanoborohydride–Acetic Acid

product	yield, %	mp, °C	recryst solvent	lit. mp, °C
4a	80	80-81[a,b]	EtOH-H_2O	
4b	50	120-122[a,c]	hexane	
4c	85	112-114[d]	hexane	114[20]
5a	75	207-208	EtOH-H_2O	208-209[21]
5b	75	240-241[e]	EtOH-H_2O	242[21]
5c	88	214-215	*i*-PrOH	216[22]
5d	96	78-79[a,e]	hexane	
6a	86	139-140	EtOH-H_2O	139[23]
6b	78	156-157[f]	EtOH	157[23]
6c	86	132-133	EtOH-H_2O	135[23]
6d	85	95-97[e]	EtOH	96-97[24]
8	77	89-90[a,e]	Et_2O-EtOH	
10	70	185-187	EtOH-H_2O	188-188.1[25]

[a] Compound gave satisfactory analysis (±0.4%) for C, H, and N where present. [b] Converted to *n*-pentanoic acid in 82% yield by refluxing in concentrated HCl for 1 day. IR of product identical with that of authentic sample. [c] Converted to 4-methylpentanoic acid in 86% yield by refluxing in concentrated HCl for 1 day. IR of product identical with that of authentic sample. [d] Converted to 4-phenylbutanoic acid in 76% yield by refluxing in concentrated HCl for 1 day; mp 48-51 °C (lit.[26] mp 52 °C). [e] Reduction performed at 65 °C. [f] IR identical with that of a sample prepared from methyl *O*-hexanoylsalicylate by treatment with sodium.[27]

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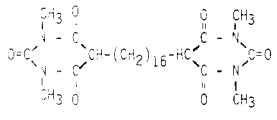
formylmalonate) to a deuterated form of isopropylidene methylmalonate, 2,2,5-trimethyl-1,3-dioxane-4,6-dione (5-D,5-CHD_2), has been recorded.

Our initial experiments were performed with isopropylidene (phenylacetyl)malonate.[9] Treatment with sodium borohydride in methanol gave only a small amount of the reduced product after several hours. Varying yields of the phenethyl derivative were obtained by treatment with H_2/Pt in acetic acid and by sodium borohydride in acetic acid. However, the most consistently high yields were obtained by treatment with sodium cyanoborohydride in acetic acid (see Table I). The acylated derivatives, **1**, **2**, **3**, **7**, and **9** were dissolved in acetic acid and reduction proceeded rapidly upon the addition of 2 mol equiv of sodium cyanoborohydride. The monoalkyl derivatives of isopropylidene malonate (**4**) and barbituric acid (**5**) obtained have potentially useful synthetic applications.[10] The isopropylidene alkylmalonates can be easily hydrolyzed and monodecarboxylated to the carboxylic acids;[11] this would complete a synthetic method for the two carbon atom homologation of carboxylic acids. More vigorous conditions were required for the conversion of 1,16-bis-[5-(*N*,*N*′-dimethylbarbituryl)]hexadecane (**8**), which was



8

prepared from 1,16-bis[5-(*N*,*N*′-dimethylbarbituryl)]hexadecane-1,16-dione (**7**), to eicosanedioic acid. The reduction of compounds **3** to the products **6** constitutes a useful method for preparing 3-alkyl-4-hydroxycoumarins. Also, dehydroacetic acid (**9**) readily reduced to the ethyl analogue (**10**) under the general conditions.

Borohydride reagents in carboxylic acid media have been previously utilized for such transformations as the reductive alkylation of nitrogen-containing compounds,[12] the reduction of amides to amines,[13] and the reduction of alcohols and ketones to the methylene derivatives.[14] However, in these latter cases, the reductions were limited to those compounds capable of forming a stabilized carbonium ion under the reaction conditions. We believe the reductions reported in this paper proceed on the basis of the following suggested mechanism: reduction first occurs with the acyl derivative in either the keto or enol form to produce an α-hydroxyalkyl group; subsequent loss of water occurs to form an alkylidene derivative, and finally conjugate reduction gives the alkyl derivative. We have previously shown that alkylidene and arylidene derivatives if isopropylidene malonates are readily reduced by borohydride.[15] It is interesting to note that for diethyl benzoylmalonate, borohydride reduction in methanol reportedly[16] proceeded to the α-hydroxyalkyl stage, followed by a reverse Knoevenagel-type reaction. Another literature report[17] on the borohydride reduction of an acyclic acylmalonate indicates that an (α-hydroxylalkyl)malonate was obtained with no subsequent dehydration or further reduction under the reaction conditions employed. Also, we subjected diethyl acetylmalonate to the treatment employed in this paper for the reduction of the cyclic compounds, and observed the formation of only a small amount of diethyl ethylmalonate by TLC. We feel that the success of our reductions depends on the ability of the cyclic α-hydroxyalkyl intermediates to rapidly dehydrate. Indeed, it is well-known that alkylidene or arylidene derivatives of isopropylidene malonate[18] and barbituric acid[19] are readily titratable as nonprotic Lewis acids with hydroxide ion due to rapid conjugate addition and that this reaction is reversible with acid.

Experimental Section

Melting points were determined on an oil bath apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Compounds **1a–c**,[9] **2a–c**,[28] and **3a–d**[29] were prepared according to the literature methods. The yields cited are based on the products obtained directly from the reaction mixture and demonstrated to be virtually free of starting material by IR or TLC examination.

General Procedure for Reduction. Caution: The entire procedure should be conducted in a well-ventilated hood, with suitable precautions, since HCN is formed during the reaction and during the aqueous workup. The acyl derivative (10 mmol) was stirred in 15 mL of acetic acid. Sodium cyanoborohydride, 1.25 g (20 mmol), was added over a period of 2 min. After being stirred for 1 h, the reaction mixture was diluted with 50 mL of water and acidified with 2 mL of concentrated hydrochloric acid. After the solution was chilled for a few hours, the crystalline product was removed by filtration and washed with water. For the reduction of **2b**, **2d**, **3d**, and **7**, the reaction mixture was warmed to 65 °C in order to dissolve the starting material.

1,16-Bis[5-(*N*,*N*′-dimethylbarbituryl)]hexadecane-1,16-dione (7). Hexadecanedioic acid, 2.86 g (10 mmol), was converted to the acid chloride by refluxing with 15 mL of thionyl chloride for 1 h. The excess thionyl chloride was removed under reduced pressure and the residue added to a solution of *N*,*N*′-dimethylbarbituric acid, 3.12 g (20 mmol), in 25 mL of pyridine. The reaction mixture was stirred overnight, diluted with 150 mL of water, acidified with hydrochloric acid, and allowed to stand. The crystalline product was collected by filtration and washed with water. The colorless crystals, mp 135–137 °C, weighed 5.07 g (90% yield). Recrystallization from acetic acid gave colorless crystals,

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mp 141–142 °C. Anal. Calcd for $C_{28}H_{42}N_4O_8$: C, 59.77; H, 7.52; N, 9.96. Found: C, 59.98; H, 7.21; N, 9.96.

5-Hexadecanoyl-*N,N'*-dimethylbarbituric Acid (2d). This compound was prepared in a manner similar to that described above for 7. Colorless crystals were obtained in 96% yield, mp 68–69 °C after recrystallization from hexane. Anal. Calcd for $C_{22}H_{38}N_2O_4$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.92; H, 9.71; N, 7.07.

Conversion of 8 to Eicosanedioic Acid. Compound 8, 0.50 g (0.88 mmol), was refluxed with 2.0 g of KOH in 10 mL of ethylene glycol under a nitrogen atmosphere for 1 day. The ethylene glycol was distilled off under reduced pressure and 15 mL of a 30% solution of HBr in acetic acid added to the residue. The mixture was refluxed for 1 day, filtered while hot, rinsed with 5 mL of hot acetic acid, and diluted with 65 mL of water. The dark colored crude product was removed by filtration and washed with water to give 0.22 g, mp 108–115 °C. Recrystallization from acetic acid afforded 90 mg (30% yield) of pure product as colorless crystals, mp 121–123 °C (lit.[26] mp 122–123 °C), which was converted to the diethyl ester, mp 53–54 °C (lit.[26] mp 54.5–55 °C).

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Registry No. 1a, 64074-05-1; **1b**, 74965-86-9; **1c**, 74965-87-0; **2a**, 58713-10-3; **2b**, 74965-88-1; **2c**, 58713-08-9; **2d**, 74965-89-2; **3a**, 4139-73-5; **3b**, 4139-74-6; **3c**, 36953-87-4; **3d**, 74965-90-5; **4a**, 74965-91-6; **4b**, 74965-92-7; **4c**, 3709-38-4; **5a**, 1953-33-9; **5b**, 14077-80-6; **5c**, 1953-34-0; **5d**, 74965-93-8; **6a**, 6617-70-5; **6b**, 21315-30-0; **6c**, 74965-94-9; **6d**, 74965-95-0; **7**, 74965-96-1; **8**, 74965-97-2; **9**, 771-03-9; **10**, 50607-35-7; pentanoic acid, 109-52-4; 4-methylpentanoic acid, 646-07-1; 4-phenylbutanoic acid, 1821-12-1; sodium cyanoborohydride, 25895-60-7; acetic acid, 64-19-7; hexadecanedioic acid, 505-54-4; hexadecanedioic acid chloride, 34959-19-8; *N,N'*-dimethylbarbituric acid, 769-42-6; eicosanedioic acid, 2424-92-2; diethyl eicosanedioate, 42235-39-2.

Reaction of 3-Amino-2-benzoylcrotonate Esters with Phosgene

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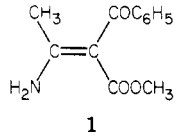
Phosgene, in the presence of 2,6-lutidine, reacts with alkyl esters of 3-amino-2-benzoylcrotonic acid to give as major products 1,3-oxazin-2-ones, formally derived from the reaction of 2 equiv of amino ester with 2 and 3 equiv of phosgene. Ethyl 3-amino-2-benzoyl-2-pentenoate reacts with phosgene–2,6-lutidine to give a 1,3-oxazin-2-one derived from the reaction of 1 equiv of phosgene and 1 equiv of amino ester. Diethyl 3-amino-2-benzoylglutaconate reacts with phosgene–2,6-lutidine to give both a "1:1" 1,3-oxazin-2-one and a 4-aminopyrone.

Some time ago, we reported that benzoyl chloride reacts with methyl 3-aminocrotonate to produce the C-benzoylated isomer 1.[1] Recently we examined the reaction



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of 1 with phosgene to see if cyclic products could be obtained. In fact, phosgene reacts readily with an ether solution of 1 and 2,6-lutidine at room temperature to produce a complex mixture which was separated into an ether-soluble and an ether-insoluble fraction.

The ether-insoluble material (50% of the mass balance) was fractionally crystallized from glacial acetic acid to give two compounds in a 4:1 ratio. The major component was a yellow solid, mp 192 °C [UV ($CHCl_3$) λ_{max} 353 nm (ϵ_{max} 36 445)], which exhibited a carbonyl stretching absorption at 1775 cm^{-1} characteristic of 1,3-oxazin-2-one.[2] Its empirical formula of $C_{26}H_{22}N_2O_8$ (high-resolution mass spectrum and elemental analysis) corresponded to a product of the reaction of 2 equiv of 1 and 2 equiv of phosgene. In addition to the 1775-cm^{-1} absorption and an ester carbonyl band at 1740 cm^{-1}, an infrared absorption band was present at 1667 cm^{-1}, typical of the benzoyl group of starting material 1. The ^1H NMR spectrum indicated one allylic methyl group, two dissimilar methoxy groups, one vinyl hydrogen, and two dissimilar amide protons. Two kinds of aromatic resonances were present. One was the typical 3:2 multiplet pattern centered at δ 7.5 and 8.3

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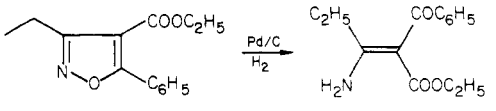
(3) The oxazine 12 exhibited only bonded NH in the IR spectrum and the position of its vinyl proton in the ^1H NMR spectrum (δ 5.22) was exactly the same as that in 4. On this basis we assign *Z* stereochemistry to the side chains of both 4 and 12.

(4) Prepared by first heating 24 g (0.1 mol) of ethyl 3-pyrrolidin-1-ylcinnamate, 10.7 g (0.12 mol) of 1-nitropropane, and 26.2 g (0.22 mol) of phenyl isocyanate in benzene/triethylamine [G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 89, 5461 (1967)] to give 4-carbethoxy-3-ethyl-5-phenylisoxazole (ii): b.p. 108–118 °C (0.1 mmHg); IR (CCl_4) 1720 cm^{-1} (CO); ^1H NMR (CCl_4) δ 1.3 (t, J = 8 Hz, 3 H, CH_2CH_3), 1.35 (t, J = 6 Hz, 3 H, OCH_2CH_3), 2.95 (q, J = 8 Hz, 2 H, CH_2CH_3), 4.3 (q, J = 6 Hz, 2 H, OCH_2CH_3), 7.3–8.0 (m, 5 H, C_6H_5); exact mass calcd for $C_{14}H_{15}NO_3$ *m/e* 245.105 10, found 245.106 22. Hydrogenation of 10.4 g of ii (Pd/C, 50 psig, EtOH) gave a quantitative yield of ethyl 3-amino-2-benzoylpent-2-enoate (iii) as a clear oil: IR ($CHCl_3$) 3470 (NH), 1700–1600 (CO's); ^1H NMR ($CDCl_3$) δ 0.7 (t, J = 8 Hz, 3 H, OCH_2CH_3), 1.3 (t, J = 8 Hz, 3 H, CH_2CH_3), 2.62 (q, J = 8 Hz, 2 H, CH_2CH_3), 3.9 (q, J = 8 Hz, 2 H, OCH_2CH_3), 7.2–8.0 (m, 5 H, C_6H_5); exact mass calcd for $C_{14}H_{17}NO_3$ *m/e* 247.120 74, found 247.124 17.



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