and a stirrer, were added 24.1 g. (0.122 mole) of diethyl α,α-dimethylglutarate (VIII), 10 ml. of water, and 200 ml. of methyl alcohol. A solution of 4.5 g. (0.08 mole) of potassium hydroxide in 15 ml. of water was then added at a rate sufficient to keep the reaction mixture below 26° over a period of 6 hr. The mixture was then stirred at room temperature for an additional 10 hr. After the major portion of the methyl alcohol was removed by distillation under reduced pressure, 300 ml. of water was added and the residue was acidified to pH 4 by the dropwise addition of concentrated hydrochloric acid. The aqueous solution was then extracted with four 100-ml. portions of ether. After the ether extracts had been dried over anhydrous magnesium sulfate, the mixture was fractionated through a 2-ft. spiral-wire column to yield 13.7 g. (65%) of 4-methyl-4-carbethoxypentanoic acid (VIII), b.p. 100° (0.4 mm.), $n^{25}D$ 1.4355.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.36; H, 8.72.

Vapor phase chromatography under the exact conditions described above for diethyl α,α-dimethylglutarate (VII) gave only one peak with a retention time of 4.6 min.

Reduction of the Double Bond in Ethylidenemalonic Ester by Lithium Aluminum Hydride

WILLIAM J. BAILEY AND MATTHEW E. HERMES[1]

Department of Chemistry, University of Maryland, College Park, Maryland

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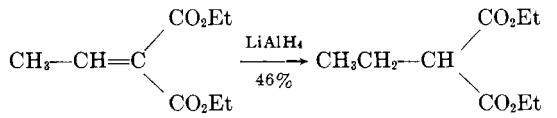
In an attempt to prepare a sample of 2-hydroxymethyl-2-buten-1-ol, ethylidenemalonic ester was treated with a large excess of lithium aluminum hydride. Surprisingly, the product was not the unsaturated diol but the saturated ester, ethyl ethylmalonate.



The reduction of the double bond in several unsaturated esters with lithium aluminum hydride has been previously reported in the literature. Ethyl *o*-hydroxycinnamate was reduced to *o*-(3-hydroxypropyl)-phenol[2] and methyl α-cyanocinnamate was reduced to 2-benzyl-3-amino-1-propanol[3] in a 30% yield. Cinnamaldehyde is also reduced to 3-phenylpropanol, but in this case it has been shown that the mechanism of the reduction involves the reduction of the carbonyl group to give a salt of cinnamyl alcohol which is subsequently reduced to the saturated alcohol.[4] In fact cinnamyl alcohols can be prepared in good yields by the reverse addition of the lithium aluminum hydride to various ethyl cinnamates.[5] A few other cases are reported in which a carbon–carbon double bond is reduced in preference to a highly reducible group in the same molecule. Gilsdorf and Nord[6] found that the reverse addition of the hydride to 1-phenyl-2-nitropropene at −40 to −50° gave a 56% yield of 1-phenyl-2-nitropropane. At higher temperature they isolated some benzylacetoxime. Since this work was completed LeMoal, Carrie, and Bargain[7] reported the reduction of α-cyano-β-phenylcinnamonitrile and the related cyanoacetic ester to the corresponding dihydro derivatives with several complex hydrides. Surprisingly they also reported that it was not possible to reduce the α-carbethoxy-β-phenylcinnamic ester to its dihydro derivatives with any of the hydrides used.

Since prolonged reflux during the reduction of unsaturated esters with lithium aluminum hydride resulted in lower yields[8] than with the saturated esters, ethylidenemalonic ester was reduced with a large excess (eight equivalents) of hydride for 1 hr. at 15° to give a 31% yield of ethyl ethylmalonate. Vapor phase chromatography showed that the material gave only one symmetrical peak and its infrared spectrum was identical with that for an authentic sample of ethyl ethylmalonate. When the reduction was carried out with a 10% excess of hydride, a 43% yield of ethylmalonic ester was obtained, together with a large amount of polymeric residue. With two equivalents of hydride a 46% yield of the ethylmalonate was obtained plus a somewhat smaller amount of polymeric residue.

Brown, Mead, and Subba Rao[9] showed that sodium borohydride plus lithium bromide in diglyme gave excellent yields of alcohols from esters. Its increased selectivity was illustrated by the reduction of ethyl cinnamate to cinnamyl alcohol in high yields. However, the reduction of ethyl ethylidenemalonate with an excess of this reagent gave a 30% yield of ethylmalonate plus a large amount of a high boiling residue. With an equivalent amount of this hydride, a 20% yield of the ethylmalonate resulted.

One can rationalize the results described by the assumption that the hydride ion preferentially adds in a 1,4 manner to the ethylidenemalonate to produce the stable enolate of ethylmalonic ester. The charge on the enolate retards further reduction to the saturated diol. With only a slight excess of hydride the low concentration of enolate favors the Michael addition to the starting unsaturated ester to produce the polymeric residue.

Experimental[10]

Reduction of Ethyl Ethylidenemalonate with Lithium Aluminum Hydride.—To a slurry of 2.36 g. (0.0625 mole) of lithium aluminum hydride in 100 ml. of dry ether was added a solution of 23.2 g. (0.125 mole) of ethyl ethylidenemalonate in 50 ml. of ether at a rate such as to keep the temperature of the reaction mixture below 15° while the flask was immersed in an ice bath. After the mixture had been stirred for an additional hour, it was poured into a mixture of ice and dilute hydrochloric acid. The aqueous layer was extracted with two 50-ml. portions of ether. After the combined ether layer and ether extracts were dried over anhydrous magnesium sulfate and the ether had been removed by distillation at atmospheric pressure, the residue was fractionated through a 10-in. Vigreux column to give 11.1 g. (46%) of ethyl ethylmalonate, b.p. 70° (4 mm.), $n^{25}D$ 1.4172 [lit.[11] b.p. 94–96° (13 mm.), $n^{20}D$ 1.4170].

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.81; H, 8.55.

V.p.c. of this ester at 205° on a silicone grease–Chromosorb column gave only one symmetrical peak; under the same condi-

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tion a synthetic mixture of authentic ethyl ethylmalonate and ethyl ethylidenemalonate were completely resolved.

Reduction of Ethyl Ethylidenemalonate with Sodium Borohydride and Lithium Bromide.—To a solution of 3.78 g. (0.10 mole) of sodium borohydride in 100 ml. of diglyme was added 8.7 g. (0.10 mole) of anhydrous lithium bromide (prepared by the addition of bromine to a slurry of lithium in ether, followed by the evaporation of the ether). After the mixture had been stirred for 30 min., 14.8 g. (0.08 mole) of ethyl ethylidenemalonate was added dropwise. Spontaneous heating was noted during the addition. After the mixture had been stirred for 1 hr. without external heating and 1.5 hr. on a steam bath, 24 g. (0.40 mole) of acetic acid was added to decompose the excess hydride and alkoxide complexes. The reaction mixture was then heated at 120° for 18 hr. with 24 g. (0.24 mole) of acetic anhydride. After the salts were removed by filtration, the filtrate was poured into 300 ml. of a 5% sodium carbonate solution. The oily layer was dried over anhydrous magnesium sulfate and fractionally distilled through a 6-in. Vigreux column to yield 4.5 g. (30%) of ethyl ethylmalonate, b.p. 62° (1.0 mm.), $n^{25}D$ 1.4165; and 9.0 g. of a higher boiling residue.

Intramolecular Participation of the Amide Group in Ester Hydrolysis[1]

MARGARET T. BEHME AND E. H. CORDES

Department of Chemistry, Indiana University, Bloomington, Indiana

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Numerous hydrolytic reactions are known to occur with intramolecular nucleophilic participation of an amide function.[2] Considerable evidence exists which suggests that, in suitable instances, the intramolecular participation of the amide group in ester hydrolysis results in very large rate increases over the uncatalyzed reaction.[2a,b] Particularly striking is the observation of Bernhard, *et al.*, that properly constituted β-benzyl esters of aspartyl peptides are cleaved, with amide participation, more than one-millionfold more rapidly than similar substrates not possessing a neighboring amide function.[2a] Results of this type have led several authors to suggest that amide groups present in protein or substrate molecules may be directly involved in the catalytic process of some enzymatic reactions. This suggestion is particularly appealing in light of the usual exchange reactions observed by Katchalski, *et al.*,[3] and by Fruton, *et al.*,[4] in the course of pepsin-catalyzed cleavage of peptide substrates. These reactions may be rationalized in terms of the intermediate formation of imides resulting from the attack of an amide group of a substrate molecule on the carboxyl group of a second substrate molecule.

We have examined the kinetics of amide group participation in ester hydrolysis employing substrates derived from salicylamide and phthalamic acid. These substrates were chosen to provide a basis for quantitative comparison of the catalytic efficiency of the amide group with other nucleophilic catalysts, previously studied in similar systems, for ester hydrolysis. While these studies were in progress, Shafer and Morawetz reported similar results on amide group participation in ester and amide hydrolysis in substrates derived from phthalamic acid.[2b]

The first-order rate constants for imide formation from O-acetylsalicylamide and methyl phthalamate increase linearly with hydroxide ion concentration in the pH range 6.2 to 8.8. The calculated second-order rate constants for these reactions are 1.2×10^6 and 1.8×10^5 M^{-1} min.$^{-1}$, respectively, at 25° and ionic strength 0.50. The latter value is in excellent agreement with the figure of 1.86×10^5 M^{-1} min.$^{-1}$ obtained by Shafer and Morawetz for this reaction at 25.9° and ionic strength 0.12.[2b] That imide formation was, in fact, the reaction being followed was established from the identity of the ultraviolet spectra and rate of hydrolysis of the initial reaction products with the corresponding properties of authentic samples of the imides. These results, together with those of Shafer and Morawetz,[2b] demonstrate that, for systems of these types in neutral or basic aqueous solutions, the amide group is several orders of magnitude more effective as an intramolecular nucleophilic reagent toward ester or amide linkages than either the imidazolyl[5] or the carboxylate[6] functions. The neighboring formyl group is similar to the neighboring amide group in terms of nucleophilic reactivity toward methyl esters.[7] On the other hand, the intermediate product (imide) obtained from amide group participation is somewhat more resistant to hydrolysis, completing the catalytic process, than corresponding intermediates for reactions involving the nucleophilic reagents indicated above.[2b]

Imide formation from O-acetylsalicylamide was found not to be detectably subject to general acid–base catalysis by 1.0 M N-methylmorpholine at pH 7.5.

Imide formation from O-acetylsalicylamide was not subject to detectable acid catalysis in hydrochloric acid solutions ranging in concentration from 1 to 5 M.

The reaction of acetamide with *p*-nitrophenyl acetate, an intermolecular analog for imide formation from O-acetylsalicylamide, was studied at 25° and pH 10.2. Under these conditions, the rate of *p*-nitrophenolate release was not detectably increased over the background hydrolysis rate, $k_{obsd} = 0.047$ min.$^{-1}$, by the presence of 2 M acetamide. Assuming that a 10% increase in this first-order rate constant might have been overlooked, this data indicates that the intramolecular reaction is at least 60,000 times more rapid than the intermolecular reaction in the presence of 1 M acetamide.[8] This is a minimum value since *p*-nitrophenyl acetate is almost certainly more reactive toward nucleophilic reagents than O-acetylsalicylamide. The observation of Shafer and Morawetz[2b] that the reactivity of amides in systems of this type is largely independent

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