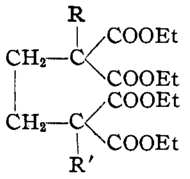
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

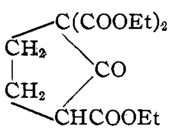
The Cyclization of Certain Ethylene Dimalonic Esters by Sodium Ethoxide

BY E. RUSSELL MEINCKE, RICHARD F. B. COX AND S. M. MCELVAIN

If the recently suggested[1] mechanism for the acetoacetic ester condensation is valid, it seemed that such an ester as ethylene dimalonic ester, (I, R = R′ = H), should undergo the condensation, with the elimination of alcohol, to produce the tricarbethoxycyclopentanone (II). When, however, this dimalonic ester was heated with sodium ethoxide it was found that the material which distilled from the reaction mixture was ethyl carbonate with only an insignificant amount of alcohol. From the reaction mixture none of the expected tricarbethoxycyclopentanone (II) was obtained, but instead 2,5-dicarbethoxycyclopentanone (III) and 2-carbethoxycyclopentanone (VI) were isolated in 31 and 15% yields, respectively.



I



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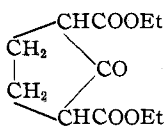
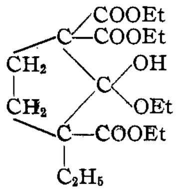


III



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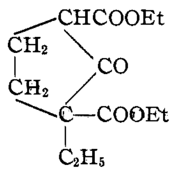
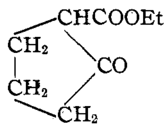


V



VI

The monocarbethoxycyclopentanone (VI) was probably the result of alcoholysis of the dicarbethoxycyclopentanone (III), but the manner in which the latter was formed[2] was less obvious. It may have been formed as the result of alcoholysis of the expected product II or it may have resulted from the direct elimination of ethyl carbonate from two adjacent α- and α′-carbethoxy groups of the open chain ester (I), a reaction analogous to the formation of a ketone by the elimination of a metallic carbonate from the salt of a dicarboxylic acid. Meerwein and Schürmann[3] used the latter scheme to explain the formation of 2,4,4,6-tetracarbethoxycyclohexanone from diethyl α,α′,γ,γ′-tetracarbethoxypimelate.

It seemed that some light might be shed on this question by a study of the action of sodium ethoxide on those ethylene dimalonic esters (I), in which R and/or R′ were alkyl substituents. In the case of ethyl α-ethyl-α,α′-dicarbethoxyadipate (I, R is H and R′ is C_2H_5) it was found that sodium ethoxide produced a 74% yield of the 2-ethyl-2,5-dicarbethoxycyclopentanone (V) together with equivalent amounts of alcohol and ethyl carbonate. This condensation took place much more readily and completely than the one in which III was formed. Ethyl α,α′-diethyl-α,-α′-dicarbethoxyadipate (I, R = R′ = C_2H_5), however, showed no reaction with sodium ethoxide and after heating for considerable periods at temperatures as high as 250° this ester was recovered unchanged.

It is apparent from the behavior of the dialkyl substituted ester that the reaction does not involve simply the elimination of ethyl carbonate from two α- and α′-carbethoxy groups of the open chain ester (I). At least one α-hydrogen atom is necessary for the cyclization and this fact leads to the conclusion that the hemiacetal type of intermediate (IV), similar to that which has been suggested[1] for the acetoacetic ester condensation, also functions in this condensation. The absence of an α-hydrogen in this intermediate does not allow it to follow the acetoacetic ester type by the elimination of a molecule of alcohol. Consequently, ethyl carbonate is eliminated and it is reasonable to presume that the ethoxy of the hemiacetal grouping goes out with one of the carbethoxy groups of the malonic ester structure rather than with the other single carbethoxy group. The resultant product is the enolic form of V which then produces alcohol by reacting with sodium ethoxide. The analogous precursor of III would be IV with a hydrogen atom in the place of the α-ethyl group. With such a structure it is possible for alcohol to be split out, but since the distillate from this reaction was relatively pure ethyl carbonate it appears that this latter compound is eliminated preferentially. It would

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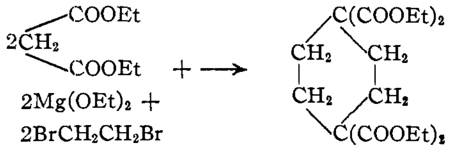
[1] Cox, Kroeker and McElvain, THIS JOURNAL, 56, 1173 (1934).

[2] Since the completion of this work Guha and Seshadriengar, *Current Sci.*, 3, 20 (1934), have reported the formation of 2,6-dicarbethoxycyclohexanone from the action of sodium ethoxide on trimethylenedimalonic ester. However, they made no mention of any other products of reaction.

[3] Meerwein and Schürmann, *Ann.*, 398, 196 (1913).

seem, therefore, that these cyclizations represent a special type of acetoacetic ester condensation in which an equivalent of ethyl carbonate is eliminated in the place of one of the two molecules of alcohol generally produced in this condensation.

Ethyl α,α′-dicarbethoxyadipate (I, R = R′ = H) was prepared by the reaction of ethylene bromide and magnesio-malonic ester.[4] In the purification of this ester a small amount of a solid ester, m. p. 76–77°, was obtained. This solid ester proved to be 1,1,4,4-tetracarbethoxycyclohexane which had formed by a further reaction of the ethylene bromide with malonic ester (or ethyl α,α′-dicarbethoxyadipate), thus



Ethyl α-ethyl-α,α′-dicarbethoxyadipate (I, R is H and R′ is C_2H_5) was prepared by the condensation of ethyl (β-bromoethyl)-ethylmalonate with sodiomalonic ester

$$C_2H_5C(COOEt)_2CH_2CH_2Br + NaCH(COOEt)_2 \longrightarrow C_2H_5C(COOEt)_2CH_2CH_2CH(COOEt)_2$$

Ethyl α,α′-diethyl-α,α′-dicarbethoxyadipate was obtained by the alkylation of disodio-ethyl α,α′-dicarbethoxyadipate with ethyl bromide.

Experimental

Ethyl α,α′-Dicarbethoxyadipate and 1,1,4,4-Tetracarbethoxycyclohexane.—The procedure of Noyes and Kyriakides[4] was used for the preparation of the former ester except that magnesium ethoxide was prepared according to the method of Lund and Bjerrum.[5] A fraction boiling at 185–210° (15 mm.) was collected as the crude ester and this material refractionated through a Widmer column surrounded by a heated jacket. The fraction boiling at 193–195° (15 mm.); d^{25}_4 1.1305; n^{25}_D 1.4470, was collected as ethyl α,α′-dicarbethoxyadipate. The material, which boiled at 195–207° (15 mm.), on cooling yielded crystals which on recrystallization from alcohol melted at 76–77°. This substance was shown to be 1,1,4,4-tetracarbethoxycyclohexane by the following data.

Anal. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.54; sap. eq., 93. Found: C, 57.87; H, 7.55; sap. eq., 91.4.

The saponification of this ester yielded an acid, m. p. 249–250° with decomposition, which had a neutral equivalent of 65.7; calcd. for 1,1,4,4-tetracarboxycyclohexane, 65.

When this acid was heated to 250° and resulting material recrystallized from alcohol hexahydroterephthalic acid, m. p. 172–173°, neutral equivalent 85.7 (calcd., 86), was obtained.

Ethyl α-Ethyl-α,α′-dicarbethoxyadipate.—To 40.8 g. (0.6 mole) of sodium ethoxide suspended in 500 cc. of benzene contained in a flask fitted with a dropping funnel, stirrer and a fractionating column was added 114.8 g. (0.7 mole) of malonic ester. The benzene-alcohol mixture was distilled off until the temperature at the top of the column reached 80°. The fractionating column then was replaced by a reflux condenser, 177 g. (0.6 mole) of ethyl (β-bromoethyl)-ethylmalonate[6] added and the resulting mixture refluxed, with stirring, on a steam-bath for fifteen hours. After this time the reaction mixture was poured into 600 cc. of water and 30 cc. of acetic acid added. The aqueous layer was separated and extracted twice with 75-cc. portions of benzene. The benzene was removed from the combined benzene extracts and the residue distilled. The yield of ester boiling at 192–195° (8 mm.), n^{25}_D 1.4512, d^{25}_4 1.1210, amounted to 106 g. (47%).

Anal. Calcd. for $C_{18}H_{30}O_8$: C, 57.75; H, 8.02%. Found: C, 58.20; H, 8.05.

Ethyl α,α′-Diethyl-α,α′-dicarbethoxyadipate.—This ester was prepared by the method of Lean[7] except that ethyl bromide instead of ethyl iodide was used to alkylate the ethyl α,α′-dicarbethoxyadipate. The product obtained had the same melting point, 94–95°, as that reported by Lean.

Reaction of the Ethylenedimalonic Esters with Sodium Ethoxide, (a) Ethyl α,α′-Dicarbethoxyadipate.—A mixture of 87 g. (0.25 mole) of this ester and 17 g. (0.25 mole) of sodium ethoxide was placed in a flask provided with a coil condenser for distillation and a stirrer fitted with machined conical bearings to allow for operation under diminished pressure. The condenser was kept surrounded by an ice-salt mixture. The flask was heated in an oil-bath at 85° for five hours and at 120° for another five-hour period under a pressure of 200 mm. The distillate receiver was emptied at intervals during the reaction. Most of the distillate came over during the first hours of heating, but small amounts continued to come over up to the end of the reaction period. The collected distillate on redistillation boiled at 124–126°, and consisted of 1.04 g. (0.023 mole) of alcohol and 19.42 g. (0.167 mole) of ethyl carbonate, as determined from the refractive index. The material in the reaction flask, which toward the end of the reaction had become too viscous to stir, was treated with 150 cc. of water and acetic acid equivalent to the amount of sodium ethoxide used. The aqueous layer was separated, extracted with ether and the mixed non-aqueous layer and ether extract, after drying over anhydrous sodium sulfate, distilled. After removal of the lower boiling materials the following fractions were collected under 8 mm. of pressure: (1) 109–112°, 6 g.; (2) 112–154°, 0.75 g.; (3) 154–162°, 17.6 g.; (4) 162–185°, 3 g.; (5) 185–195°, 13.6 g.; undistillable residue, 17 g.

Fraction (1) by its boiling point, the melting point (142–143°), its semicarbazone[8] and the fact that it gave cyclopentanone, b. p. 130–131°, oxime, m. p. 56–57°,[9] on hydrolysis with 10% sulfuric acid, was shown to be 2-carbethoxycyclopentanone. The yield of this product amounted to 15% of the theoretical.

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[4] Noyes and Kyriakides, THIS JOURNAL, **32**, 1057 (1910).

[5] Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

[6] Cope and McElvain, THIS JOURNAL, **54**, 4314 (1932).

[7] Lean, *J. Chem. Soc.*, **65**, 1007 (1894).

[8] Bouveault, *Bull. soc. chim.*, [3] **21**, 1021 (1899).

[9] *Cf.* Mitchell and Thorpe, *J. Chem. Soc.*, **97**, 1004 (1910).

Fraction (3) was shown to be 2,5-dicarbethoxycyclopentanone by its boiling point, the melting point (194–195°) of its dianilide[9] and the fact that it also yielded cyclopentanone on hydrolysis. The yield of this product was 31% of the theoretical.

Fraction (5) was unchanged starting material.

(b) Ethyl α-Ethyl-α,α′-Dicarbethoxyadipate.—A mixture of 46.3 g. (0.125 mole) of this ester and 8.5 g. (0.125 mole) of sodium ethoxide was treated in the same manner as described under (a) above, except that the reaction was run and completed in two and one-half hours at 115°. The distillate was found by refractive index to consist of 4.5 g. (0.093 mole) of alcohol and 11.1 g. (0.096 mole) of ethyl carbonate. Fractionation of the other reaction products gave the following fractions under 8 mm. of pressure: (1) 125–147°, 2.6 g.; (2) 147–154°, 23.9 g.; (3) 154–185°, 1.1 g.; (4) 185–195°, 3.8 g.; (5) undistillable residue, 5 g.

Fraction (2) was shown to be 2-ethyl-2,5-dicarbethoxycyclopentanone by analyses and the fact that it yielded 2-ethylcyclopentanone, b. p. 160–161°; semicarbazone, m. p. 189–190°.[10] The yield of this material amounted to 74.3% of the theoretical.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.93; H, 7.81%. Found: C, 60.75; H, 7.91.

Fraction (4) represented 8.1% of the starting material.

(c) Ethyl α,α′-Diethyl-α,α′-dicarbethoxyadipate.—A mixture of 100 g. (0.25 mole) of this ester, m. p. 94–95°, and 17 g. (0.25 mole) of sodium ethoxide was heated under diminished pressure, as described under (a) above, for two and one-half hours at 115° and for half-hour periods at 125, 150, 200 and 250°. Only 2.75 g. of distillate came over. This distillate consisted of 1.13 g. of alcohol and 1.62 g. of ethyl carbonate as estimated from its refractive index. The reaction mixture was acidified with dilute acetic acid and the insoluble solid material recrystallized from petroleum ether. In this way 52.3 g. of starting material, m. p. 92–93°, and 34.2 g., m. p. 85–86°, were recovered.

Summary

A study of the reaction of certain ethylenedimalonic esters with sodium ethoxide is reported. It has been found that those esters which have α- and α′-hydrogens or even a single α-hydrogen are cyclicized to cyclopentanone derivatives with the elimination of ethyl carbonate. When no α-hydrogen is present the ester shows no appreciable reaction with sodium ethoxide. These facts suggest that the same intermediate, as previously proposed for the acetoacetic ester condensation, is also involved in this condensation.

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[10] Case and Reid, THIS JOURNAL, **50**, 3062 (1928).

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Relative Reactivities of Certain 2- and 2,6-Substituted Piperidines

BY ALVIN W. SINGER AND S. M. MCELVAIN

In the preparation of various substituted piperidino-alkyl benzoates by the condensation of a chloro-alkyl benzoate with the substituted piperidine, it was noticed[1] that those piperidines containing a substituent in the 2-position were very much less reactive than both the unsubstituted piperidine and those piperidines substituted in the 3-position. This observation suggested a study of the effect of various groups in the 2-position on the reactivity of the piperidine with an organic halide.

This paper presents the results obtained with a representative halide, *n*-butyl bromide, and nine different 2- and 2,6-substituted piperidines. The general procedure which has been previously reported,[2] consisted of heating 2 moles of the amine with one mole of the bromide in petroleum naphtha (b. p. 95–150°) solution and determining, after a given time, the amount of precipitated secondary amine hydrobromide.

Exploratory experiments showed that the reaction temperature (90°) which was used[2] for the rate determinations with piperidine was too low to give a sufficient amount of reaction in a reasonable time with these substituted piperidines. For example, while piperidine was found to react with *n*-butyl bromide to the extent of 88.4% in forty-eight hours at 90°, 2-methylpiperidine, 2-phenylethylpiperidine and 2,6-dimethylpiperidine showed 52.7, 57.2, and 4.9% reaction, respectively, in the same time. It was decided, therefore, in order to get more complete reaction with the substituted piperidines, to carry out the reactions at 150–155°.

Table I shows the rates at which the various substituted piperidines react with *n*-butyl bromide. Each value in this table represents the average of at least two determinations, the variations of which were less than 3%.

The most significant feature of the data shown in Table I is the depressing effect of the

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[1] McElvain, THIS JOURNAL, **49**, 2837 (1927).

[2] Semb and McElvain, *ibid.*, **53**, 692 (1931).