thin, irregular platelets melting 74–76°. The oxime of VIb crystallized from ethanol as thin, irregular plates melting 184–186°.

Anal. Calcd. for $C_{16}H_{27}O_2N$: C, 72.4; H, 10.3. Found: C, 72.8; H, 10.3.

Recrystallization of VIc from ligroin produced well-formed rods melting 88–89°. The oxime of VIc crystallized from ethanol as small needles melting 204–206°.

Anal. Calcd. for $C_{16}H_{27}O_2N$: as above. Found: C, 72.0; H, 10.2.

2-Acetoxy-4a-methylperhydro-8-phenanthrones (VIIa, VIIb, VIIc).—Cleavage of the methoxy group in the methoxy ketones (VIa, VIb, VIc) with hydrogen bromide in acetic acid was carried out as described above for diethers.

dl-2α-Acetoxy-4a-methyl-1,2,3,4,4a,4bα,5,6,7,8,8aβ,9,-10,10aα-tetradecahydro-8-phenanthrone (VIIa) crystallized from ethanol as small, irregular plates melting 125–127°.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.4; H, 9.4. Found: C, 73.1; H, 9.0.

dl-2β-Acetoxy-4a-methyl-1,2,3,4,4a,4bβ,5,6,7,8,8aα,9,-10,10aβ-tetradecahydro-8-phenanthrone (VIIb) crystallized from benzene–ligroin as large rods and melted 133–134°. The melting point was not depressed by admixture with a sample of the "A" acetoxy ketone prepared by Cornforth and Robinson.[3] A solvated form of this acetate was previously reported[3] to melt at 129–130°. Recrystallization of the original specimen from benzene–ligroin gave material m.p. 133–134°.

dl-2α-Acetoxy-4a-methyl-1,2,3,4,4a,4bβ,5,6,7,8,8aα,9,-10,10aβ-tetradecahydro-8-phenanthrone (VIIc) crystallized as irregular fragments from ligroin, and melted gradually over the range 90–115°.

Anal. Calcd. for $C_{17}H_{26}O_3$: Found: C, 73.5; H, 9.4.

4a-Methylperhydro-2,8-phenanthrenediones (VIIIa, VIIIbc).—The acetoxy ketones were saponified to hydroxy ketones with potassium hydroxide in aqueous methanol. The procedure for oxidation of the hydroxy ketones to diketones was the same as described above for oxidation of 2-methoxy-4a-methylperhydro-8-phenanthrol. Yields of diketones from acetoxy ketones were 30–60%.

dl-4a-Methyl-1,2,3,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydro-2,8-phenanthrenedione (VIIIa) crystallized from cyclohexane or ligroin as thin, fragile plates melting 79–81°. The bis-dinitrophenylhydrazone of VIIIa was prepared by gently boiling for 30 min. a solution of the diketone (13 mg.), dinitrophenylhydrazine (30 mg.) and one drop of sulfuric acid in 10 ml. of *n*-butanol. The bis-dinitrophenylhydrazone crystallized from the reaction mixture as small needles melting with decomposition at 245°. The bis-ethyleneketal of VIIIa crystallized from ligroin as thin needles melting 149–150°.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.9; H, 9.5. Found: C, 76.5; H, 9.7. Calcd. for $C_{27}H_{30}O_8N_4$: C, 54.5; H, 5.1. Found: C, 54.3; H, 5.3. Calcd. for $C_{19}H_{30}O_4$: C, 70.8; H, 9.4. Found: C, 70.5; H, 9.5.

Another diketone (VIIIbc) was obtained from both VIIb and VIIc. This diketone crystallized from cyclohexane as well-formed prisms melting 146–148°, and was identical with the "A" diketone prepared by Cornforth and Robinson.[2,3]

***dl*-4a,7-Dimethyl-1,2,3,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydro-2,8-phenanthrenedione (X).**—The methoxy ketone (VIa, 2.00 g.) was formylated, methylated with methyl iodide in the presence of potassium carbonate and, after separation of O-methylated material, the formyl group was removed by alkaline hydrolysis in the manner described previously.[3] The 2-methoxy-4a,7-dimethylperhydro-8-phenanthrone (0.9 g., 41%) so obtained melted 78–79° after crystallization from ligroin.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.2; H, 10.7. Found: C, 77.3; H, 10.6.

Cleavage of the methoxy group with hydrogen bromide in acetic acid afforded an acetoxy ketone (IX, 0.6 g., 60%) which melted 129–132° after crystallization from ligroin. A small part of the acetoxy ketone was recrystallized from ethanol and the melting point raised to 134–135°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 73.9; H, 9.7. Found: C, 73.7; H, 9.7.

The acetoxy ketone (IX, 0.6 g.) was saponified and oxidized as described above for VII. The dimethylperhydro-2,8-phenanthrenedione (0.4 g., 78%) thus obtained crystallized from ligroin as flat, rectangular plates and melted 87–88°.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.4; H, 9.8.

2β-Acetoxy-4a,7-dimethyl-1,2,3,4,4a,4bα,5,6,7,8,8aβ,-9,10,10aα-tetradecahydro-8-phenanthrone and 4a,7-dimethyl-1,2,3,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydro-2,8-phenanthrenedione were prepared from the Koester-Logemann acetate by the procedure of Billeter and Miescher.[8]

OBERLIN, OHIO

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

The Structure of Ketene Dimer

BY JOHN R. JOHNSON AND V. J. SHINER, JR.

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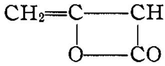
The isotope exchange reactions of ketene dimer, the liquid methylketene dimer, and related acetoacetic esters with methanol-*d* have been studied. Exchanges with the α-hydrogens of the acetoacetic esters are extremely rapid, while with ketene dimer the exchange is quite slow (even at reflux temperature) and with methylketene dimer the rate is exceedingly slow. Methanolysis of these dimers leads to acetoacetic esters in which a substantial proportion of deuterium enters into the γ-position. This evidence is used to support the conclusion that ketene dimer is a single molecular species to be represented as 3-butenoic β-lactone (II). Methylketene dimer, and presumably the liquid dimers of other alkylketenes, can be represented as 2,4-dialkyl-3-butenoic β-lactone structures.

The structure of ketene dimer has been the subject of considerable investigation and controversy since the first appearance of its description in the chemical literature in 1908.[1] The following five formulas have at one time or another received serious consideration.[2]

$CH_3—CO—CH═C═O$

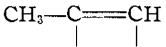
I

acetylketene



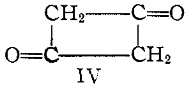
II

3-butenoic β-lactone



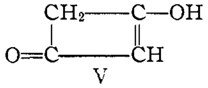
III

2-butenoic β-lactone



IV

1,3-cyclobutanedione



V

mono-enol of IV

[1] F. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908).

[2] For a review of the earlier work see: W. E. Hanford and J. G. Sauer, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 127.

Recent work[3,4] on some of the chemical reactions of ketene dimer, while possibly not conclusive, has indicated the presence of material of formula II. Infrared spectral measurements have been in best agreement with this formula but have been interpreted also as indicating the presence of an equilibrium mixture of compounds, presumably II and III.[5] The suggestion[5c] that diketene is a mixture of II and IV in rapid equilibrium is untenable.

Analysis of the crystal structure of solid ketene dimer[6] gives relative positions of the atoms which could correspond to either II or III, but bond length calculations show that the molecule, at least at low temperatures in the solid state, is 3-butenoic β-lactone (II).

The established acid–base mechanism of prototropic change leads to the view that interconversion of structures II and III in a medium containing active deuterium would result in an isotope exchange between the dimer and the medium. In a mobile transition this would give rapid equilibration of all of the hydrogen atoms involved in the prototropic system, as is known to be the case with acetoacetic ester, nitromethane, and other tautomeric structures. Further, if the dimer could be caused to react with methanol-*d* under conditions which eliminated any confusing isotope exchanges of the starting material or product with the methanol-*d*, the establishment of the site of attachment of the deuterium in the product would give valuable structural evidence. Studies of this type were undertaken with ketene dimer and with the liquid methylketene dimer (obtained by dehydrohalogenation of propionyl chloride).

Preliminary experiments were carried out to establish the behavior of the α- and γ-hydrogens of methyl acetoacetate in a medium such as deuterium oxide or methanol-*d*. In a series of experiments, the ester and deuterium oxide were mixed and allowed to react for a specified time at 25°. The ester was separated by continuous ether extraction and the recovered deuterium oxide purified and analyzed by density determination. From the decrease in mole fraction of deuterium oxide in the recovered deuterium oxide–water mixture and the stoichiometry of the exchange reaction, the number of active (exchangeable) hydrogen atoms per molecule was calculated, with the assumption that the equilibrium constant for the exchange reaction is unity.

The values obtained from five runs, out of a total of six, extending from 15 minutes to 65 hours, were 1.90 ± 0.02 exchangeable atoms per molecule. Consequently, it was concluded that the two α-hydrogen atoms of methyl acetoacetate exchanged completely within 15 minutes and that the three γ-hydrogens did not exchange at all under these conditions. Combustion analyses confirmed the presence of the expected amount of deuterium in the ester and exchanges of the recovered deuterated ester with water showed that all of the deuterium was exchangeable. This demonstrates that methyl acetoacetate can be recovered from an exchange reaction and distilled without causing any deuterium migration between the α- and γ-positions.

A second series of experiments was designed to show the exchange characteristics of methyl acetoacetate under the conditions chosen for the reaction between methanol *d* and ketene dimer, and to give a method of analyzing for α- and γ-deuterium in the methyl acetoacetate. The exchanges were carried out in refluxing methanol-*d* solution. The compounds were separated by fractional distillation after the allotted reaction time and then analyzed for deuterium content by combustion and the use of the gradient density tube. The results of six exchange reactions are shown in Table I.

TABLE I

ISOTOPE EXCHANGE BETWEEN METHANOL-*d* AND METHYL ACETOACETATE AT REFLUX TEMPERATURE

Run	Time, hr.	Atoms D per molecule in recovered compounds Methanol	Ester	Atoms H exchanged per molecule of ester	Atoms D per molecule in ester after washing-out Found	Estimated
1	0.13	0.656	0.968	1.48	0.018[a]	0.022
2	0.20	.565	.705	1.25		
3	1.00	.499	.932	1.86	.085	.103
4	46.5	.512	.904	1.76	.072[a]	.040
5	87.3	.592	1.105	1.86		
6	89.0	.312	0.537	1.73	.052[b]	.016

[a] Ester from runs 1 and 2, and also runs 4 and 5, were combined before the washing-out treatment. [b] In run 6 the exchange reaction was carried out deliberately in the presence of non-volatile side products of the reaction between ketene dimer and methanol-*d* (dehydracetic acid, etc.) to determine whether these products would catalyze the γ-exchange. The result showed that they did not; the slightly higher than expected amount of deuterium present in the ester recovered from this run is attributable to unremoved traces of ester left from the ketene dimer reaction.

The number of hydrogen atoms exchanged was determined by dividing the number of deuterium atoms per molecule found in the recovered ester by the number found in the recovered methanol-*d*. This value was 1.86 in the one hour experiment and never more than this even though the time of reaction was extended to 89 hours. A value of 1.6 exchangeable hydrogens has been reported for the exchange between ethanol-*d* and ethyl acetoacetate after three days at room temperature.[7]

Evidently the exchange of the two α-hydrogen atoms of the ester required only 15 minutes to one hour for completion but the γ-hydrogens did not exchange at all under the conditions used. The variation from 1.75 to 1.86 in the number of exchangeable hydrogen atoms per molecule appeared to be due to analytical difficulties encountered with small samples of methanol, resulting from the volatility of methanol and its tendency to pick up moisture from the atmosphere and from glass surfaces. In general the deuterium determinations on the methanol are believed to be accurate to ±5% while the analyses on the other compounds should be within 2% of the correct value.

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(3) C. D. Hurd and C. A. Blanchard, THIS JOURNAL, **72**, 1461 (1950).

(4) A. T. Blomquist and F. J. Baldwin, *ibid.*, **70**, 29 (1948).

(5) (a) D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946); (b) F. A. Miller and S. D. Koch, THIS JOURNAL, **70**, 1890 (1948); (c) R. S. Rasmussen, *Fortschr. Chem. Org. Naturstoffe*, **5**, 375 (1948).

(6) L. Katz and W. N. Lipscomb, *J. Org. Chem.*, **17**, 515 (1952).

(7) M. S. Kharasch, W. G. Brown and J. McNab, *ibid.*, **2**, 36 (1937).

The detection of deuterium which might have entered the γ-position of the ester during the initial exchange was accomplished by subjecting the deuterated ester to a washing-out process to remove the readily exchangeable deuterium from the α-position and then analyzing for residual deuterium. Thus, the deuterated ester was refluxed for two hours with two successive portions of about ten molar equivalents of ordinary methanol, the ester was recovered, redistilled and analyzed for deuterium. This procedure would reduce the amount of deuterium in the α-position of the ester by a factor (usually about 1/25th) that could be calculated from the known amounts of ester and methanol present. The results of the washing-out procedure on the exchanged ester are shown in the last two columns of Table I. The amount of residual deuterium found by combustion of the recovered washed-out ester agrees fairly well with the amount calculated. The higher observed figures for runs 4, 5 and 6 are just within the limits of our experimental error but may indicate a minute amount of γ-exchange of the ester. Even if the indicated amount of deuterium in the γ-position were real, it is clear that the extent of exchange in this position is negligibly small.

Since the conditions used in these exchanges were sufficiently vigorous to cause ketene dimer to react with methanol-*d*, it was now established that methanolysis of the dimer could be carried out experimentally under conditions that would ensure the absence of any γ-hydrogen exchange between the methyl acetoacetate product and the methanol-*d* solvent. Also, from these preliminary experiments were developed two methods for breaking down the total amount of deuterium present in the recovered acetoacetic ester into the fractions present in the α- and γ-positions. The amount in the α-position could be obtained by multiplying the number of atoms of deuterium per molecule in the recovered methanol-*d* by 1.80, and the number of atoms per molecule in the γ-position could be determined by subtracting the number in the α-position from the total amount in the ester, as determined by combustion. The amount in the γ-position of the ester could also be determined by direct analysis after the washing-out process had been applied.

Deuterium exchange between ketene dimer and methanol-*d* and the concurrent methanolysis of the dimer to methyl acetoacetate were studied in the following way. Ketene dimer was dissolved in methanol-*d* and allowed to stand at 25°, or refluxed, for a definite time; after this, the methanol, unreacted dimer, and the reaction product (methyl acetoacetate) were separated by distillation and analyzed for deuterium. The ratio of the number of deuterium atoms per molecule of the recovered dimer to that of the recovered methanol expresses the extent to which the dimer had entered into the isotope exchange reaction. In Table II are given the exchange data for six runs varying from about six hours at 25° to 86 hours at reflux temperature (bath at 78–80°). It is clear from these data that the exchange reaction with ketene dimer is very much slower than that with methyl acetoacetate. Methanolysis of the recovered deuterated dimer showed that the exchange reaction with methanol-*d* involved only the α-position of the dimer (see below).

TABLE II

ISOTOPE EXCHANGE BETWEEN METHANOL-*d* AND KETENE DIMER

Run	Time, hr.	Temp., °C.	Atoms D per molecule in recovered compounds Methanol	Dimer	Atoms H exchanged per molecule of dimer
1	5.8	25	0.896	0.035	0.04
2	209	25	.856	.149	.18
3	5.0	Reflux	.849	.103	.12
5	20	Reflux	.724	.384	.53
6	59.5	Reflux	.398	.345	.87
8	85.5	Reflux	.552	.484	.88

In Table III are shown the deuterium analyses of the methyl acetoacetate isolated from four test reactions between methanol-*d* and ketene dimer. The two independent methods for determining the amount of deuterium in the γ-position gave results in reasonable agreement. The value obtained by the washing-out process is the more accurate because of the much smaller figure for α-deuterium that has to be subtracted from the total amount.

TABLE III

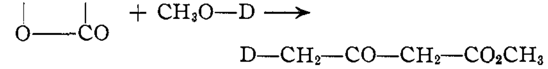
ANALYSIS OF METHYL ACETOACETATE FROM THE REACTION OF METHANOL-*d* AND KETENE DIMER

Run	Atoms D per molecule in CH_3OD	Atoms D per molecule in ester Total[a]	α[b]	γ[c]	Atoms D per molecule in ester after washing-out Total[d]	α[e]	γ[f]
6	0.398	0.920	0.716	0.204	0.286	0.024	0.262
9[h]	.456	1.07	.820	.25	.300	.026	.274
8	.552	1.40	.994	.41	.403	.016	.387
10	.820	2.08	1.47	.61	.78[g]	.04	.74
					.73	.00	.73

[a] By analysis of recovered ester. [b] By multiplying the number of atoms of D per molecule in the CH_3OD by 1.80. [c] Obtained by subtracting the value in column 4 from that in column 3. [d] Obtained by analysis of recovered ester after most of the α-deuterium was washed out. [e] Residual amount calculated from value in column 3 and stoichiometry of the washing-out reaction. [f] Obtained by subtracting the value in column 7 from that in column 6. [g] Sample 10 washed-out and analyzed two times. [h] Exchanged ketene dimer recovered from run 6 was used in this reaction.

An experiment was performed to demonstrate that the deuterium which appeared in the γ-position of the methyl acetoacetate resulting from methanolysis of the dimer was not introduced through the slow isotope exchange shown to take place between ketene dimer and methanol-*d*. A sample of the exchanged ketene dimer recovered from run 6 (Table II), containing 0.345 atom of deuterium per molecule, was caused to react with methanol-*d* in the usual procedure. The methyl acetoacetate recovered from this run (Table III, run 9)contained essentially the same amount of deuterium in the γ-position as the original methanolysis product from run 6. Consequently the methanolysis reaction is responsible for introducing deuterium in the γ-position and the exchange reaction must actually involve only the α-position of the ketene dimer.

In the methanolysis reactions the dimer was reacting with a mixture of methanol and methanol-*d*. Since hydrogen usually reacts faster than deuterium in proton transfer reactions, it was not surprising to find that the acetoacetic ester contained less deuterium in the γ-position than the methanol contained in its active position. From the relative concentrations of deuterium in the methanol and in the γ-position of the ester, the relative reactivity of methanol and methanol-*d* toward the dimer can be calculated roughly.[8] The rate ratios obtained in this way range from 2.8 to 3.6, which does not appear to be too high when compared with values reported by other investigators for the relative reactivity of hydrogen and deuterium in proton transfer reactions.[9] In view of this difference in reactivity it is significant that a methanolysis experiment in which methanol-*d* having a high deuterium concentration was used (82 mole %), gave ester with 0.73 atom of deuterium in the γ-position. This furnishes strong support for the view that the entering hydrogen or deuterium goes only to the γ-position.



The liquid methylketene dimer was selected as a typical example of the homologs of ketene dimer and was subjected to methanolysis and deuterium exchange with methanol-*d*. This liquid dimer, which is obtained readily by the action of triethylamine on propionyl chlorides,[10] resembles ketene dimer in its reactions and is quite different from the crystalline methylketene dimer prepared by Staudinger[2] and by Schroeter. The crystalline dimer has been shown to be the mono-enol of 2,4-dimethylcyclobutane-1,3-dione (homolog of structure V).[11] The ring system of the crystalline dimer is quite stable and does not undergo scission with methanol. Structures analogous to I, II and III are in question for the liquid dimer.

A preliminary isotope exchange reaction with the product of methanolysis, methyl α,γ-dimethylacetoacetate, established that this ester exchanged 0.91 atom hydrogen per mole and that the exchange occurred exclusively at the α-position. The results of three experiments on the isotope exchange between methylketene dimer and methanol-*d* are summarized in Table IV.

TABLE IV

ISOTOPE EXCHANGE BETWEEN METHANOL-*d* AND METHYLKETENE DIMER AT THE REFLUX TEMPERATURE

Run	Time, hr.	Atoms D per molecule in recovered compounds Methanol	Dimer	Number of H atoms exchanged per molecule
1	7	0.904	0.000	0.000
2	7	.916	.000	.000
3	86	.716	.027	.038

The rate of exchange with methylketene dimer is very much slower than that with ketene dimer (Table II), so slow that the opportunity for any deuterium to enter the product by prior exchange with the dimer is eliminated. The methyl α,γ-dimethylacetoacetate isolated from one experiment (Table IV, run 3) was analyzed for deuterium in the α- and γ-positions, with the results

Atoms D per molecule in	
Recovered methanol-*d*	0.715
Methyl dimethylacetoacetate	1.25
α-Position of ester	0.665
γ-Position of ester	0.585
After washing-out exchangeable D	
Atoms D, total, in ester	0.613
In α-position	.024
In γ-position	.589

The observed behavior of methylketene dimer in the exchange and the methanolysis reactions is in excellent agreement with that expected on the basis of the results with ketene dimer, and confirms the view that these dimers have similar structures.

Discussion of Results

The fact that ketene dimer reacts with methanol-*d* to give γ-deuterated methyl acetoacetate is strong evidence that the dimer consists essentially of 3-butenoic β-lactone (structure II). This evidence in itself does not mean that the material must necessarily be a single species made up entirely of structure II, but the significance of the observed γ-deuteration is enhanced by the circumstance that the known difference in reactivity of hydrogen and deuterium in the reactions involved is relatively unfavorable to the deuteration.

The cyclobutanone structures (IV and V) would be expected to react with methanol-*d* to give the γ-deuterated ester but these formulas have been eliminated by evidence of various kinds.[4] Apart from the previously published evidence, our observation that the dimer undergoes isotope exchange in methanol-*d* at a very slow rate is incompatible with a β-diketone or enol structure such as IV or V. Such structures would undergo rapid equilibration that would involve all four of the hydrogen atoms in the molecule.

The acetylketene structure (I) furnishes a satisfactory basis for accounting for most of the chemical reactions of the dimer, particularly the conversion to dehydracetic acid, but is incompatible with the observed deuteration in the γ-position of the methanolysis product. The 2-butenoic β-lactone structure (II) also gives a fairly good account of the chemical reactions but it, too, is incompatible with the introduction of deuterium into the γ-position upon reaction with methanol-*d*.

The possibility that ketene dimer is a mobile prototropic system involving an equilibrium between structure II and either acetylketene or 2-butenoic β-lactone, or both of these, is excluded by the very slow rate of exchange observed between the dimer and methanol-*d* and by the fact that this exchange introduces deuterium exclusively in the α-position. Consequently we conclude that ketene dimer is a homogeneous chemical individual consisting of one molecular species represented by the 3-butenoic β-lactone structure (II). This system

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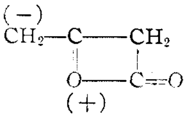
[8] Such calculations are made on the assumption that the active hydrogen or deuterium of the methanol enters only the γ-position of the ester. An inherent error is introduced by the circumstance that the deuterium concentration of the methanol-*d* is reduced through exchange with hydrogen of the α-position of the methyl acetoacetate produced in the methanolysis.

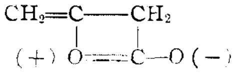
[9] F. H. Westheimer and N. Nicolaides, THIS JOURNAL, **71**, 25 (1949).

[10] J. G. Sauer, *ibid.*, **69**, 2444 (1947).

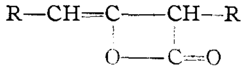
[11] R. B. Woodward and G. Small, *ibid.*, **72**, 1297 (1950).

may be stabilized by resonance hybridization involving the polarized forms IIa and b.


IIa


IIb

In view of the similarity of the lactone dimers of alkylketenes, such as the liquid methylketene dimer, in chemical behavior to ketene dimer and of the observed parallel behavior of methylketene dimer in the isotope exchange and methanolysis reactions, it is evident that the structures are strictly analogous to that of ketene dimer. Consequently, the alkylketene dimers can be represented as 2,4-dialkyl-3-butenoic β-lactones (VI).


VI

These compounds should exist in *cis* and *trans*-forms, capable of being separated by fractional distillation or crystallization. Some preliminary experiments with methylketene dimer did not give indication of any definite separation.

Experimental

Deuterium Oxide.—The deuterium oxide, 99.66 mole % pure, used in these experiments was obtained from the Norsk Hydro-Elektrisk Kvaelstofaktieselskab in Oslo, Norway, and was used without further purification. This material with the analysis given by the supplier was also used as a standard of reference for the determination of deuterium oxide concentration in the gradient density tube.

Combustion of the Samples and Analysis in the Gradient Density Tube.—The procedure used for combustion of the organic samples and the purification of the resulting water was that of Keston, Rittenberg and Schoenheimer.[12] The gradient density tube was set up and used in essentially the fashion described by Anfinsen.[13] One modification of the procedure which was found to be important with the concentrations of deuterium oxide used in this work was the necessity to keep the standard samples from exchanging with atmospheric moisture. This was done by storing the samples under hypodermic stopples and withdrawing portions of them for use with a hypodermic needle attached by means of a Leur joint to the dropping pipet. The gradient used covered the zero to ten mole % deuterium oxide range. Organic compounds containing more than ten atom % deuterium were diluted before combustion with a compound containing only ordinary hydrogen and a dilution factor was used in the calculations. The gradient density tube gave the concentration of deuterium in the compounds in atom %, which when divided by one-hundred and multiplied by the total number of hydrogen and deuterium atoms per molecule gave the number of deuterium atoms per molecule. The figures in the tables are given in this unit.

Methanol-*d*.—The methanol-*d* used was prepared by the method of du Vigneaud[14] from sodium methoxide, dimethyl phthalate and deuterium oxide.

Ketene Dimer.—The ketene dimer used was obtained from Carbide and Carbon Chemicals Company as a 30% solution in acetone. About 75 to 90% of the acetone was distilled from a sample and the 50 ml. of residue was subjected to careful fractional distillation in a 60 × 1.1 cm. glass-helix packed column with a partial take-off head, at a constant pressure of 99 mm. Of the nine approximately equal fractions collected, numbers 5, 6 and 7 had a constant boiling point, 69.4–69.5° (99 mm.), and refractive index, n^{20}_D 1.4378. These fractions were combined and used to obtain a cooling curve, which showed an initial freezing point of −7.56° and a temperature of −7.69° at the half-frozen point. Another sample of 35 g. of the dimer was fractionally distilled as described above and five fractions of constant boiling point and refractive index were obtained. The infrared absorption spectra of the first, second, fourth and fifth of these were all recorded on the same paper using a Perkin-Elmer Model 21, double-beam recording infrared spectrophotometer. There was no discernible difference between spectra of the different fractions. Fractions 4 and 5 had the following density, d^{20}_4 1.0943.

Special significance is attached to the question of the purity of the dimers in view of the suggestion that they might actually be mixtures of closely related compounds. In this regard it has been previously reported that aseptic distillation[15] and fractional melting[16] afforded no separation of ketene dimer into different fractions, using refractive index as the criterion. Our own observations on the constancy of the boiling point, refractive index and infrared absorption spectrum lend weight to the view that the dimer actually consists of a single molecular species. The cooling-curve data were supplemented by a determination of the molal freezing point depression constant. With acetic anhydride as the solute, the constant was found to be 3.4°. Using this value and the observed difference between the initial temperature and the half-frozen point (0.13°), the concentration of the impurities present was calculated to be less than 0.4 mole %.

The same treatment was given the methylketene dimer and the conclusions concerning purity were essentially the same.

Methylketene Dimer.—This material was prepared by the method of Sauer[10] but the yields were substantially less than those reported and slightly different physical constants were observed. A sample of 40 g. of methylketene dimer was carefully distilled in a vacuum in a 60 × 1.1 cm. glass-helix packed column with a partial take-off head. Seven fractions were obtained of which numbers 3 to 6 had a constant boiling point, 48.0–48.5° (13 mm.), and refractive index, n^{20}_D 1.4365. The density was found to be d^{20}_4 0.9926. Cooling curve data gave: initial freezing point −49.36°, half-frozen point −49.47°.

Methyl α,γ-Dimethylacetoacetate.—A sample of 15 g. of methylketene dimer was treated with 75 ml. of anhydrous methanol and 0.5 ml. of concentrated hydrochloric acid. The mixture was heated under reflux overnight, the excess alcohol distilled off and 10 g. of crude material was then collected at 76–81° (12 mm.). Fractionation in a small glass-helix packed column gave a fraction of constant boiling point, 74.5° (11 mm.) and refractive index, n^{20}_D 1.4230, d^{20}_4 1.0140. Reaction with phenylhydrazine gave a product which on recrystallization melted at 110–111°; Schroeter[17] reported for 1-phenyl-3-ethyl-4-methyl-5-pyrazolone, m.p. 111.5°.

Exchanges in Methanol-*d*.—All of the exchanges were carried out in a 25-ml. three-neck flask. The materials were added through one neck by the use of a small dropping funnel which could be weighed before and after addition. A stream of nitrogen was bubbled into the reaction mixture through a capillary inlet in the second neck. In the third neck was placed a 20-cm. jacketed glass-helix packed tube which could be used as a reflux condenser or as a distilling column. The following is a characteristic sample procedure for the exchange reactions.

A mixture of 8.70 g. (0.104 mole) of ketene dimer and 8.02 g. (0.252 mole) of methanol-*d*, 23.2 atom % deuterium, was refluxed in the exchange apparatus described above for 85.5 hours. During this period the oil-bath surrounding the flask was kept at 78–82°. The methanol-*d* was distilled from 64–65° (740 mm.), n^{20}_D 1.3288. The pressure was reduced to 68 mm. and the ketene dimer started to distil. A small fore-run was discarded and then two fractions (2.5 ml.) of diketene were collected; b.p. 55–58° (60 mm.), n^{20}_D 1.4280. The pressure was then lowered and two fractions (3.5 ml.) of the ester product of the reaction were collected at 77–78° (38 mm.), n^{20}_D 1.4188. The three compounds

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(12) A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1937).

(13) C. Anfinsen in O. W. Wilson, A. O. C. Nier and S. R. Reimann's "Preparation and Measurement of Isotopic Tracers," J. W. Edwards, Ann Arbor, Mich., 1946, pp. 61–65.

(14) H. T. Clarke, J. R. Johnson and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 583.

(15) P. F. Gross, Doctoral Thesis, Cornell University, 1936.

(16) F. O. Rice and R. Roberts, THIS JOURNAL, **65**, 1677 (1943).

(17) G. Schroeter, *Ber.*, **49**, 2719 (1916).

were analyzed by the gradient density tube method for deuterium. The methanol contained 13.8 atom %, the ketene dimer 12.05 atom % and the methyl acetoacetate 17.48 atom %. These figures correspond to 0.552, 0.482 and 1.398 atoms of deuterium per molecule. The ester recovered was boiled for two hours with 15.5 molar equivalents of methanol. The methanol was distilled away and then the process was repeated with another 14.4 molar equivalents of methanol. The ester was distilled from the flask and analyzed for deuterium: found, 5.04 atom % or 0.403 atom of deuterium per molecule.

ITHACA, N. Y.

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

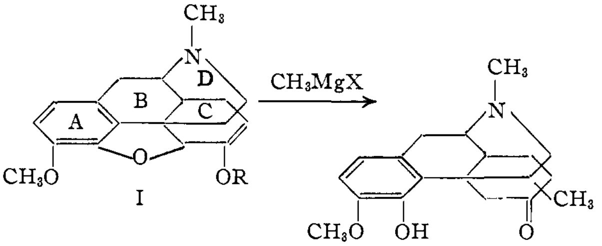
The Mode of Addition of a Grignard Reagent to an Aryl Allyl Ether[1]

BY ROBERT I. MELTZER AND JOHN A. KING

RECEIVED JUNE 23, 1952

By the reaction of phenylmagnesium bromide with *o*-methoxyphenyl crotyl ether it has been shown that a Grignard reagent can cleave an aryl allyl ether by both 1,2- and 1,4-addition.

It was discovered by Small and his co-workers[2] that when a molecule of the codeine type having a double bond in the 6,7-position (I, R = H, $COCH_3$, CH_3) is treated with a methyl Grignard reagent there is produced methyldihydrothebainone (II) in which the 4,5-oxide linkage has been broken and the carbanion from the Grignard reagent has added to the molecule, presumably in the C-ring. Further transformations of II lead to the clinically useful analgesic Metopon. In the hope that the results might give an indication of the structure of methyldihydrothebainone and thus indirectly of Metopon, we undertook an investigation of the direction of addition of a Grignard reagent to an aryl allyl ether.



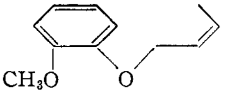
I

II

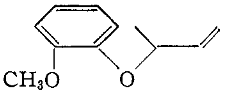
It was shown, a number of years ago, by Luttringhaus and his co-workers[3,4] that phenyl and substituted phenyl allyl ethers (as well as *n*-octyl allyl ether, phenyl allyl thioether and butyl allyl thioether) were readily cleaved by phenyl- and alkylmagnesium bromides at 50–70°, with the carbanion from the Grignard reagent adding to the allyl portion of the ether and formation of a phenol or alcohol from the other portion; in only one case was an ether with a substituted allyl radical used and in this case the hydrocarbon product was not reported, so that no information was available on the direction of the addition. The direction of addition of the Grignard carbanion to the crotyl radical of crotyl mesitoate has been reported,[5] but the mechanism suggested for the Grignard cleavage of allyl esters permits of only one product and is not applicable to allyl ethers. Likewise, results obtained from the Grignard addition to the modified allylic ether butadiene monoxide (3,4-epoxy-1-butene)[6,7] are not translatable to a nonoxidic allyl ether because of two obvious structural differences.[8]

If rings B and D are removed from structure I, and the OR group is replaced by hydrogen, there remains *o*-methoxyphenyl crotyl ether (III), our model substance. That the OR group is not essential to the reaction was evidenced by its occurrence with desoxycodeine-C (I, OR = H).[2]

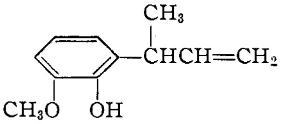
This model compound was obtained as the product of a sequence of reactions designed to give the isomeric substance, *o*-methoxyphenyl methylvinylcarbinyl ether (IV), whose relationship to I is likewise obvious from a comparison of the structures. 1,3-Butyleneglycol was treated with acetyl chloride to yield a product reported[9] to be 3-chlorobutyl acetate. This acetate was saponified to a chloroalcohol which was permitted to react with an ethanolic solution of sodium *o*-methoxy-



III



IV



V

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[1] Presented before the Medicinal Chemistry Section of the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September 12, 1951.

[2] L. Small and K. C. Yuen, THIS JOURNAL, **58**, 192 (1936); L. Small, H. M. Fitch and W. E. Smith, *ibid.*, **58**, 1457 (1936); L. Small, S. G. Turnbull and H. M. Fitch, *J. Org. Chem.*, **3**, 204 (1938); L. F. Small and H. M. Fitch (to the Government of the United States), U. S. Patent 2,178,010 (October 31, 1939). See also F. C. Whitmore and A. H. Homeyer (to Mallinckrodt Chemical Works), U. S. Patent 2,510,731 (June 6, 1950); A. H. Homeyer and J. A. Caughlan (to Mallinckrodt Chemical Works), U. S. Patent 2,510,732 (June 6, 1950).

[3] A. Luttringhaus, G. v. Saaf and K. Hanschild, *Ber.*, **71**, 1673 (1938).

[4] A. Luttrioghaus, G. v. Saaf, E. Sucker and G. Borth, *Ann.*, **557**, 46 (1947).

[5] R. T. Arnold and R. W. Liggett, THIS JOURNAL, **67**, 337 (1945).

[6] N. G. Gaylord and E. I. Becker, *J. Org. Chem.*, **15**, 305 (1950).

[7] R. W. Freedman and E. I. Becker, *ibid.*, **16**, 1701 (1951).

[8] A possibly more analogous case is the reaction between a Grignard reagent and an α,β-unsaturated acetal or ketal (*e.g.*, F. Straus and M. Ehrenstein, *Ann.*, **442**, 93 (1925)). Since the course of this type of reaction is being investigated by Dr. T. A. Geissman (personal communication) we are not discussing it here.

[9] I. G. Farbenind A.-G., German Patent 524,435 (May 7, 1931).