

## The Reformatsky Reaction. II. The Nature of the Reagent

WYMAN R. VAUGHAN<sup>1,2</sup> AND H. PETER KNOESS<sup>3</sup>

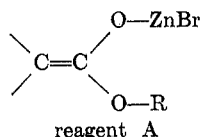
*Departments of Chemistry of The University of Connecticut, Storrs, Connecticut 06268,  
and The University of Michigan, Ann Arbor, Michigan 48104*

Received December 16, 1969

The chemical behavior of the immediate 1,4-addition product of phenylmagnesium bromide and methyl cinnamate has been compared with that of the reaction product of zinc with methyl 2-bromo-3,3-diphenylpropanoate. In each instance completely analogous behavior was observed: direct work-up afforded methyl 3,3-diphenylpropanoate; reaction with benzoyl chloride afforded the enol-benzoate of methyl 3,3-diphenylpropanoate; fluorenone afforded methyl 3,3-diphenyl-2-(9-hydroxy-9-fluorenyl)propanoate; and prolonged standing or heating afforded a "dimeric" reagent which upon work-up yielded methyl 5,5-diphenyl-2-diphenylmethyl-3-oxopentanoate, or a readily explained derivative thereof. The experimental data are interpreted as compelling evidence in support of describing the Reformatsky reagent as the bromozinc enolate of an ester and as providing support for describing the "dimerized" Reformatsky reagent as the bromozinc derivative of a hemiketal of an unsymmetrical ( $\beta$ -lactone) ketene dimer.

In a previous paper<sup>4</sup> a preliminary study of the preparation of the discrete Reformatsky reagent from zinc and ethyl  $\alpha$ -bromoisobutyrate in solution was reported. Two types of organic compounds associated with zinc were shown to be present in solution: reagent A, which is formed first and which behaves as expected for the so-called Reformatsky reagent; and reagent B, which is inactive toward a reference ketone (fluorenone) and which can, most simply, be viewed as a "dimeric" compound derived from 2 mol of reagent A with the elimination of the elements of 1 mol of ethoxyzinc bromide. The present research was designed to provide experimental evidence for a choice between the two simplest alternatives for the structure of reagent A, the discrete Reformatsky reagent in solution: an  $\alpha$ -bromozinc ester (*i.e.*, the classical Grignard formulation); or a bromozinc enolate of an ester (as suggested by comparison of its behavior with that of the Ivanov reagent,<sup>5</sup> *e.g.*,  $RR'C=C(OMgX)_2$  from  $RR'CHCO_2H + 2 i\text{-PrMgX}$ . The former structure is supported by the obvious parallels in its reactions with carbonyl compounds<sup>6</sup> with those of Grignard reagents, and the latter for its resemblance to the Ivanov reagent as well as by the slowness with which it appears to "dimerize"<sup>4</sup> and the apparent reluctance with which it adds to the ester carbonyl of unreacted  $\alpha$ -bromo ester in the course of its formation. The possibility that the suggested "dimeric" product is formed principally by addition of reagent A to unreacted  $\alpha$ -bromo ester is excluded by the fact that reagent A can be prepared in high yield virtually without concurrent production of presumed dimer, which can then be formed directly from reagent A by standing or heating.<sup>4</sup>

If reagent A is to be formulated as the second alternative, one must ask whether or not the zinc-oxygen bond



is not equally well pictured as  $-O^- + ZnBr$ , which after all is a necessary contributor to the resonance hybrid. Such a formulation suggests that the organic moiety might better be considered a discrete ester enolate anion. In the case of ethyl isobutyrate, this question may be answered by pointing to the nature of the tritylsodium-induced self-condensation of the ester which has been shown to proceed to completion only if the desired product, ethyl isobutyrylisobutyrate is removed from the solution by tritylsodium-induced  $\gamma$  enolization.<sup>7</sup> One must conclude that a highly unfavorable equilibrium exists for the reaction between ethyl isobutyrate anion and ethyl isobutyrate to give ethyl isobutyrylisobutyrate and ethoxide ion. Thus there is little tendency for the discrete ethyl isobutyrate anion to react with its parent ester carbonyl group. In contrast, the Reformatsky reagent adds to ester carbonyls,<sup>6</sup> albeit slowly. Consequently, it is reasonable to infer that there is a fundamental difference between reagent A and a sodium enolate. The latter, most simply pictured, involves a truly ambident ion<sup>8</sup> with sodium as the counterion, and the former, most simply, is better considered as an essentially covalent system. That one may expect a difference between anions with sodium as counterion and halozinc, halomagnesium, and lithium as counterions has been demonstrated by Hauser<sup>9</sup> and specifically for the "reverse Reformatsky"<sup>6</sup> by one of us.<sup>4</sup>

It has been pointed out by Fuson<sup>10</sup> that acid chlorides react with sodium enolates to give C-acylation, except under special conditions. However, the benzoyl chloride acylation of the bromomagnesium enolate of methyl 3,3-diphenylpropanoate leads to the O-benzoyl derivative *without* the aid of pyridine,<sup>11</sup> an observation which supports the argument favoring covalent character for the O-metal bond in a bromomagnesium enolate, which, if anything, should be less covalent than a corresponding bromozinc enolate. Whatever the exact situation may be, the discrete Reformatsky metal reagent and a corresponding sodio enolate *behave* respectively like "covalent enolate" and discrete enolate anions.

It is clear from the earliest reported synthesis of ethyl

(1) To whom inquiries should be addressed: The University of Connecticut.

(2) Work supported in part by a grant from The University of Connecticut Research Foundation.

(3) Abstracted from the Ph.D. Dissertation of H. P. Knoess, The University of Michigan, 1968.

(4) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).

(5) H. E. Zimmerman and M. D. Traxler, *J. Amer. Chem. Soc.*, **79**, 1920 (1957).

(6) R. L. Shriner, *Org. React.*, **1**, 1 (1942).

(7) C. R. Hauser and W. B. Renfrow, Jr., *J. Amer. Chem. Soc.*, **59**, 1823 (1933).

(8) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6275 (1955).

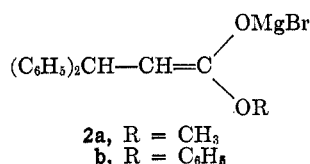
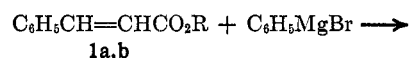
(9) C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 4756 (1953).

(10) R. C. Fuson, "Reactions of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1962, p 481.

(11) E. P. Kohler and G. Heritage, *Amer. Chem. J.*, **33**, 21 (1905).

isobutyrylisobutyrate from ethyl  $\alpha$ -bromoisobutyrate and magnesium<sup>12</sup> that there may be parallels between the behavior of the Reformatsky reagent and the analogous bromomagnesium reagent which are closer than the suggested analogy<sup>5</sup> between the Reformatsky and Ivanov reagents. Consequently, it was decided to compare the chemical behavior of a bromomagnesium enolate formed by 1,4-Grignard addition to an  $\alpha,\beta$ -unsaturated ester with that of the analogous Reformatsky reagent (*i.e.*, reagent A) formed from the corresponding  $\alpha$ -bromo ester. If identical or strikingly similar behavior is encountered, the case for formulating reagent A as shown above (*i.e.*, as a bromozinc enolate of an ester) is greatly strengthened, if not completely settled.

Grignard reagents react with  $\alpha,\beta$ -unsaturated esters by both 1,2 and 1,4 addition.<sup>13</sup> In 1905 Kohler and Heritage studied the reactions of phenylmagnesium bromide with methyl cinnamate<sup>11</sup> (**1a**) and phenyl cinnamate<sup>14</sup> (**1b**). With both esters 1,4 addition was observed. In both cases, treatment with water

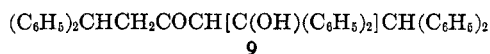
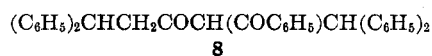
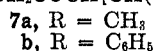


afforded 3,3-diphenylpropanoate ester (**3a,b**) and with benzoyl chloride, the enol benzoate of the ester (**4a,b**).

In addition to confirming the observations of Kohler and Heritage with the methyl ester, the Reformatsky reagent (**5**) was prepared from methyl 2-bromo-3,3-diphenylpropanoate and zinc and allowed to react with water and with benzoyl chloride, whereupon the same products were obtained, **3a** and **4a**, respectively.

Next, **5** was allowed to react with fluorenone to give the typical Reformatsky product, methyl 3,3-diphenyl-2-(9-hydroxy-9-fluorenyl)propanoate (**6**). It was then shown that the same product (**6**) could be obtained from **2a**, prepared according to Kohler and Heritage's instructions, albeit in lower yield. Thus **5** and **2a** have three reactions in common: hydrolysis to **3a**, O-benzoylation to **4a**, and reaction with fluorenone to give **6**.

Besides the formation of **2a** and **2b**, Kohler and Heritage observed formation of "complex products derived from two molecules of the unsaturated compound" on reaction with phenylmagnesium bromide. Among these were the following: **7b**, phenyl 5,5-diphenyl-2-(diphenylmethyl)-3-oxopentanoate; **8**, 1,1,5,5-tetraphenyl-2-benzoyl-3-pentanone; and **9**, 1,1,5,5-tetraphenyl-2-diphenylhydroxymethyl-3-pentanone.



(12) Y. Salkind, *J. Russ. Phys. Chem. Soc.*, **38**, 97 (1906); J. Zeltmer, *Ber.*, **41**, 589 (1908).

(13) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, New York, N. Y., 1954, pp 564 ff.

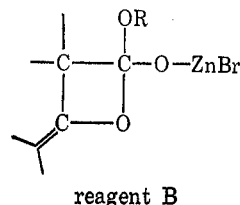
(14) E. P. Kohler and G. Heritage, *Amer. Chem. J.*, **34**, 568 (1905).

The foregoing compounds were characterized by molecular weights, elemental analyses, and degradative experiments. In addition, the formation of **7a** was reported along with **8** and **9** from methyl cinnamate and phenylmagnesium bromide; but for **7a** only the elemental analysis was reported, no molecular weight being determined.

The dimerization of reagent A (**5**), as in the case of isobutyrate, was readily realizable for the reaction between zinc and methyl 2-bromo-3,3-diphenylpropanoate, the product isolated being **7a** which was independently synthesized *via* the Claisen condensation of methyl 3,3-diphenylpropanoate. However, our **7a** corresponded in no way with that reported by Kohler and Heritage which we, too, were able to obtain under their conditions. Mass spectrometric analyses on the Kohler and Heritage compound strongly suggest that it is a "trimeric"  $\beta,\delta$ -diketo ester probably containing tightly bound solvent molecules sufficient to account for the observed elemental analyses which varied somewhat on prolonged vacuum drying. Conventional molecular weight determination for this supposed **7a** came within 4.5% of the calculated value for the "trimeric" compound, and nmr analysis provided support for the trimeric structure through integration for aromatic, methylene + methine, and methyl protons. A very similar product was detected as a minor product in the "dimerization" of **5**. However, the effective "dimerization" of bromomagnesium enolates is clearly evident in the formation of **7b** and in the synthesis of ethyl isobutyrylisobutrate.<sup>12</sup>

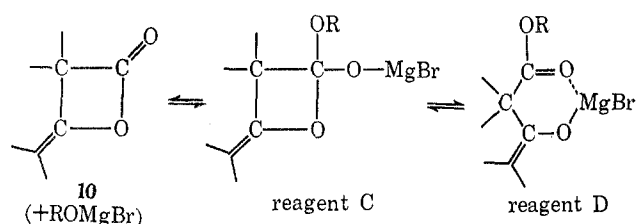
That no **8** or **9** is formed in the Reformatsky case follows from the absence of phenylmagnesium bromide under the usual conditions. However, it is surprising that, when the Grignard reagent is added to fully "dimerized" **5** (reagent B), compounds **8** and **9** still fail to appear. This would appear to be evidence that reagent B has no readily accessible carbonyl group. Infrared spectroscopy provides support for this inference (see below).

It has been suggested by one of us, with supporting arguments,<sup>4</sup> that "dimerization" of reagent A to reagent B proceeds by elimination of the elements of an alkoxyzinc bromide, leaving a ketene to which residual reagent A then adds, leading to



This clearly can yield **7a** on acidification,<sup>4</sup> and, provided only that the oxygen-zinc bond is sufficiently covalent, it need not react with Grignard reagent. The related ketene dimer (*e.g.*, **10**) would have a distinctive, high-frequency carbonyl absorption, which is totally lacking in the infrared spectra of samples of reagent B in solution (see below). If **2a**, the bromomagnesium analog of **5**, affords a reagent C (the bromomagnesium analog of reagent B) as a precursor to **8** and **9**, the only substantive difference between reagents B and C must reside in the oxygen-metal bond, which for magnesium

is less covalent than for zinc.<sup>15</sup> This difference can facilitate either or both of the following reactions.



Reagent D has the ester carbonyl required for the production of **8** and **9** by reaction with 1 or 2 mol of phenylmagnesium bromide, and **10** is a  $\beta$ -lactone of the unsymmetrical ketene dimer type which has been shown to afford analogs of **8** and **9**.<sup>16</sup> Failure to obtain similar products from phenylmagnesium bromide and reagent B may be attributed to the greater covalent stability of the oxygen-zinc bond.<sup>15</sup>

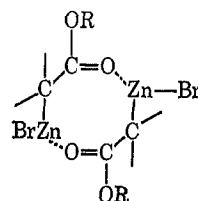
To be sure, Kohler and Heritage proposed an alternative route to **7**, **8**, and **9** which involved first a Claisen-type reaction between **2** and unreacted cinnamate ester, but this postulate is seriously to be questioned, since the essential intermediate is a 2-cinnamoyl-3,3-diphenylpropanoate ester (**11**) which could not be isolated. Further, the only derivative of **11** whose intermediacy could reasonably be inferred was the 1,4-phenylmagnesium bromide adduct across the  $\alpha,\beta$ -unsaturated ketone system of **11**, which is in fact D, whose genesis we have formulated *via* an entirely different route.

In summary, the chief difference between **2a** and **5** appears to be a greater propensity for **2a** to "dimerize" (and "trimerize") which seems to be more characteristic of magnesium enolates than of zinc enolates.<sup>12</sup> This, too, is reasonably attributed to lesser covalency in the oxygen-magnesium bond; however, one may wish to formulate the "dimerization" reaction.

In the preceding paragraphs we have presented evidence for three types of chemical reactions: O-benzoylation, addition to the fluorenone carbonyl group, and "dimerization," each of which is realizable with both the 1,4-phenylmagnesium bromide adduct of methyl cinnamate (**2a**) and the reaction product of zinc with methyl 2-bromo-3,3-diphenylpropanoate (**5**). These taken in concert with earlier evidence<sup>4,5</sup> establish a formal identity for the two reagents (**2a** and **5**) in solution, and the mode of formation of **2a** leaves little or no room for doubt as to the simplest compatible formulation for it and, therefore, for **5** (reagent A), the discrete Reformatsky reagent in solution. The case for formulating the Reformatsky "dimer" (reagent B) as a covalent bromozinc derivative of a hemiketal of the unsymmetrical ( $\beta$ -lactone) ketene dimer is strengthened by the failure of reagent B to afford **8** and **9** with added phenylmagnesium bromide. This failure would appear to rule out *any* appreciable equilibria involving a free ketene dimer (*e.g.*, **10**) and/or a chelated ester carbonyl (*e.g.*, the bromozinc analog of reagent D).

Finally a few words concerning infrared spectra are appropriate. At best it is extremely difficult to obtain good spectra of the Reformatsky reagent (A and/or B) in solution,<sup>4</sup> and the complexity of products from the

1,4-Grignard additions effectively rules out meaningful spectra in that system. However, we did examine a few cases of the Reformatsky reagent from methyl 2-bromo-3,3-diphenylpropanoate with results completely analogous to those obtained from the Reformatsky reagent derived from ethyl  $\alpha$ -bromoisobutyrate. The only identifiable carbonyl absorption is clearly attributable to residual unreacted  $\alpha$ -bromo ester; there is no high-frequency carbonyl stretching or still higher frequency-ketene absorption; and there is (in reagent A) a relatively strong absorption at 1555  $\text{cm}^{-1}$  analogous to that at 1525  $\text{cm}^{-1}$  in the simpler Reformatsky reagent.<sup>4</sup> That this is *not* to be attributed to a chelated carbonyl group (*e.g.*, the bromozinc analog of reagent D) or to



follows from the failure to obtain appropriate reaction products from the reagent solution and phenylmagnesium bromide.

#### Experimental Section<sup>17-21</sup>

**Reformatsky-Zinc.**—A 110-g portion of 20 mesh (Baker, granular, 99.8%) zinc was covered with concentrated sulfuric acid containing a few drops of nitric acid and was heated to 100° for 20 min with occasional stirring. Then the mixture was cooled to room temperature, suction filtered through a sintered-glass funnel, and washed with three 50-ml portions of water, three 50-ml portions of acetone, and three 50-ml portions of ether. The treated zinc was then stored in a vacuum desiccator over phosphorus pentoxide.

**Methyl 2-Bromo-3,5-diphenylpropanoate.**—A mixture of 24.3 g (107 mmol) of 3,3-diphenylpropionic acid, 1.3 g (43 mmol) of red phosphorus, and 25 ml of benzene was treated dropwise and with mechanical stirring with 35.2 g (217 mmol) of bromine. Stirring was continued with heating on the steam bath overnight, after which excess bromine and hydrogen bromide were removed by a water aspirator. The red upper layer was decanted from the phosphoric acid into cooled (0°) 80 ml of absolute methanol, and the resultant red solution was stirred for 45 min with intermittent warming on the steam bath. Next it was concentrated, dissolved in 100 ml of benzene, and washed with three 100-ml portions of water, two of 5% sodium carbonate solution, three of sodium thiosulfate solution, and one of saturated sodium chloride solution. Then the organic layer was dried over anhydrous magnesium sulfate, concentrated, and allowed to stand overnight, whereupon it partially solidified. The crystals were collected by filtration and washed with petroleum ether (bp 30–60°) leaving 13.11 g of crude product which was dissolved in 200 ml of cyclohexane, refluxed with Norit, filtered, and concentrated to give two crops of white crystals (7.23 and 1.48 g, 21.9% yield). An analytical sample was recrystallized from cyclohexane, mp 106.5–107.0°.

*Anal.* Calcd for  $\text{C}_{16}\text{H}_{15}\text{BrO}_2$ : C, 60.20; H, 4.74; Br, 25.04. Found: C, 60.28; H, 4.74; Br, 25.16.

The infrared and nmr spectra are consistent with the assigned structure.

(17) The molecular weight determination and all microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(18) The mass spectra were recorded on a AEI-MS 12 mass spectrometer at The University of Connecticut by O. W. Norton.

(19) All melting points and boiling points are uncorrected.

(20) The vapor phase chromatography (vpc) was done on an Autoprep 705 instrument using a 5 ft  $\times$  1/8 in. column of 4% SE-30 on Chromosorb 6, a nitrogen flow rate of 5 ml/min, and a column temperature program of 50–200° with a 15°/min temperature rise.

(21) The silica gel used for all thin layer chromatography (tlc) was Brinkmann S. G. PF<sub>24</sub> with 5% calcium sulfate.

(15) H. Gilman [in H. Gilman, "Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1943, p 489 ff.

(16) D. V. Nightingale and R. H. Turley, Jr., *J. Org. Chem.*, **26**, 2656 (1961).

**Preparation of Reagent 2a.**—Preparation of phenylmagnesium bromide was carried out in the usual manner and in a nitrogen atmosphere. Upon completion of the reaction, the solution of the Grignard reagent from 2.0 g (82 mg-atoms) of magnesium and 13.5 g (86 mmol) of bromobenzene in 40 ml of ether in one run was cooled in ice water and treated with 1.77 g (~15 mol %) of dry cuprous bromide; however, no readily observable difference in results was obtained if this step was omitted. Addition dropwise of 10.0 g (63 mmol) of methyl cinnamate in 40 ml of absolute ether over a 1.5-hr period with stirring for an additional hour provided the solution of reagent 2a.

**Preparation of Reagent 5.**—This reaction was also conducted in a nitrogen atmosphere. Zinc, 295 mg (4.5 mg-atoms), and a small crystal of iodine were covered with 5 ml of 1:1 (v/v) absolute ethyl ether-dry benzene (called "solvent" in the sequel). The zinc-solvent mixture was stirred and warmed to effect reflux, and a few drops of a solution of methyl 2-bromo-3,3-diphenylpropanoate ("ester") (1.60 g, 5.00 mmol) in 12.5 ml of solvent was added. If needed, a few drops of methylmagnesium iodide solution was also added to initiate the reaction. The whole amount of the ester solution was added dropwise over a 3-hr period, but at 1.25 hr there was added an additional 197 mg (3.00 mg-atoms) of zinc, and at the end of ester addition there was added 154 mg (2.0 mg-atoms) of zinc, after which the mixture was refluxed for 2.25 hr. The resulting solution was used for experiments requiring reagent 5.

**1-Methoxy-2-benzhydrylvinyl Benzoate (4a).** (a) *Via 1,4-Grignard Addition.*—To the full amount (above) of reagent 2a solution was added a solution of 11.55 g (82 mmol) of benzoyl chloride in 20 ml of absolute ether over a 10-min period. The resulting solution was refluxed for a few minutes and then was transferred with the aid of a little acetone into a beaker containing 200 ml of ether. Upon addition of 100 ml of 1% hydrochloric acid, the black tar dissolved leaving a precipitate of crude benzoate which was collected by filtration, washed with ether, dissolved in acetone, hot-filtered, and allowed to crystallize. The light green crystals were washed white with acetone, and two additional crops were obtained from the concentrated mother liquor: total yield, 3.38 g, 15.4%. An analytical sample was twice recrystallized from benzene-petroleum ether (bp 30–60°), mp 155–156° (lit.<sup>11</sup> 130–133°).

*Anal.* Calcd for C<sub>23</sub>H<sub>20</sub>O<sub>3</sub>: C, 80.21; H, 5.85. Found: C, 80.27; H, 5.92.

The infrared and nmr spectra are consistent with the assigned structure.

(b) *Via the Reformatsky Reaction.*—To the full amount (above) of reagent 5 was added 703 mg (5.00 mmol) of benzoyl chloride in 10 ml of 1:1 ether-benzene over a 15-min period. Reflux was continued for 5 hr. The reaction mixture was hydrolyzed with 50 ml of half-saturated ammonium chloride solution, and the aqueous phase was extracted with 25 ml of benzene. The combined organic layers were washed with 25 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated to a yellow oil which partially crystallized on standing. The crystals were collected by filtration, washed with petroleum ether (bp 30–60°), and dried: 171.5 mg of crude 4a, mp 144.0–144.5°. Purification as before afforded white crystals, mp 154.5–155.5° with no depression in mixture melting point. The infrared spectrum was identical with that of the previous sample.

**Methyl 2-(9-Hydroxy-9-fluorenyl)-3,3-diphenylpropanoate (6).** (a) *Via 1,4-Grignard Addition.*—Using half of the solution of reagent 2a prepared from 1.22 g (50.0 mg-atoms) of magnesium, there was added a solution of 3.6 g (20 mmol) of fluorenone in 30 ml of absolute ether, and the reaction mixture was refluxed for 2 hr. It was then poured into 50 ml of ice water and was treated with saturated ammonium chloride solution until the magnesium salts dissolved. The separated aqueous layer was extracted with two 25-ml portions of ether, and the combined ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to give 6.69 g of a six-component oil (thin layer chromatography): biphenyl, 3,3-diphenylpropionophenone, fluorenone, 9-phenylfluorenone, methyl cinnamate (trace), and the product, 6. Two successive chromatographs on Florisil (100–200 mesh) afforded from 6.07 g of the oil, respectively, 1.11 g (29.2%)<sup>22</sup>

(22) Using 319 g of Florisil in a 4.5-cm-o.d. column, 200-ml fractions; no. 1–25, benzene; no. 26, 1:3 ether-benzene; no. 27, 1:1 ether-benzene; no. 28–39, ether. Crude 6 was found in fraction no. 25–35 (1.4 g).

and 340 mg of relatively pure 6<sup>23</sup> which was recrystallized twice from carbon disulfide: mp 143–145°; ir (CS<sub>2</sub> solution) 3560 and 1735 cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>29</sub>H<sub>24</sub>O<sub>3</sub>: C, 82.83; H, 5.75. Found: C, 82.87; H, 5.71.

The nmr spectrum is consistent with the assigned structure. Treatment of a colorless ethanol solution of 6 with a little dilute sodium hydroxide immediately produced a yellow color, fluorenone from a "reverse Reformatsky," as observed elsewhere.<sup>4</sup>

(b) *Via the Reformatsky Reaction.*—A solution prepared from 3.19 g (10 mmol) of the bromo ester was treated with 1.80 g (10 mmol) of fluorenone in 15 ml of the "solvent" and refluxing was continued for 2 hr. The reaction mixture was then hydrolyzed with 20 ml of saturated ammonium chloride solution; the aqueous layer was separated and extracted with 10 ml of benzene, and the organic layers were combined and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 4.43 g of a yellow oil. As in the previous procedure chromatography on Florisil yielded 6,<sup>24</sup> which was recrystallized from carbon disulfide-petroleum ether (bp 30–60°), in two crops: 0.91 g, mp 147.5–149.0°, and 0.38 g, mp 146.5–148.5°. The total yield was 34%. The melting point was not depressed by the previous sample, and the infrared spectra of the samples from both procedures were identical. The present product behaved identically with sodium hydroxide.

**Methyl 5,5-Diphenyl-2-diphenylmethyl-3-oxopentanoate (7a).**

(a) *Via the Claisen Condensation.*—A solution of 48.1 g (200 mmol) of methyl 3,3-diphenylpropanoate in 50 ml of *o*-xylene (freshly distilled from calcium hydride) was treated under nitrogen with 9.6 g (200 mmol in 50% oil dispersion) of sodium hydride. Stirring was started and the gray mixture was slowly warmed to reflux in an oil bath. After 3.25 hr of refluxing, the dark brown mixture was cooled and hydrolyzed with 100 ml of 50% acetic acid. The solvents were removed in a rotary evaporator leaving a yellow solid which was titrated with hot chloroform and filtered. The filtrate was concentrated, diluted with absolute ethanol, and allowed to crystallize. Two crops of white crystals were obtained, 29.1 g (61.8%). An analytical sample was recrystallized from 2:1 (v/v) ethanol-acetone: mp 152.5–153.2°; ir (KBr) 1735 and 1710 cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>31</sub>H<sub>28</sub>O<sub>3</sub>: C, 83.01; H, 6.29. Found: C, 83.12; H, 6.19.

The nmr spectrum is consistent with the assigned structure.

(b) *Via the Reformatsky Reaction.*—A solution of reagent 5 was prepared from 3.19 g (10 mmol) of bromo ester and then was refluxed for 24 hr. The reaction mixture was hydrolyzed with 50 ml of half-saturated ammonium chloride solution, the aqueous layer was separated and extracted with 25 ml of ether, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to give 2.24 g of yellow oil. Trituration of the oil with ether left a white solid which was washed with ether and recrystallized from ethanol and then from 2:1 (v/v) ethanol-acetone to give 321 mg of satin-white needles of 7a, mp 154.0–154.5° with no depression on mixture with product from Claisen condensation whose infrared spectrum was identical with that of the present product. A number of complex products were isolated from the mother liquors from recrystallization and trituration of which only dimethyl 2,3-dibenzhydrylsuccinate was identified: 210 mg; mp 188.5–190.0°; ir (KBr) 1755 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>) 7.20 (s, 11.4) 7.12 (s, 8.6), 4.05 (m, 3.9), 2.99 (s, 6.1); mass spectrum (70 eV) *m/e* 478 (parent ion).

*Anal.* Calcd for C<sub>32</sub>H<sub>30</sub>O<sub>4</sub>: C, 80.31; H, 6.32. Found: C, 80.22; H, 6.28.

An additional 25.8% yield of 7a was isolated from the mother liquors by column and thin layer chromatography.

The infrared spectrum of reagent 5 during the above dimerization was taken at the end of ester addition and at the end of 3 hr of refluxing. The first spectrum shows residual bromo ester (1750 cm<sup>-1</sup>, strong) and a weak band at 1555 cm<sup>-1</sup>; the second spectrum shows residual ester (1750 cm<sup>-1</sup>, moderate) and a mod-

(23) Using 32.9 g of Florisil in 20-mm-o.d. column, 75-ml fractions: no. 1–6, benzene; no. 7–19, 1:19 ether-benzene; no. 20–24, 1:1 ether-benzene. Compound 6 was found in fraction no. 7–12 (340 mg).

(24) Using 90 g of Florisil in 30-mm-o.d. column, 250-ml fractions: no. 1–8, benzene; no. 9–10, 5% ether-benzene; no. 11–14, 25% ether-benzene. Product 6 was obtained from fraction in no. 4–6. Preparative tlc (20 × 20 cm<sup>2</sup> × 1.25 mm silica gel, five benzene elutions) afforded 44.7 mg of 6 from an aliquot. This corresponds to 132 mg in the total eluate from no. 4–6. More product was obtained from later fractions, and 6 was isolated by recrystallization.

erately intense band at  $1555\text{ cm}^{-1}$ . No other carbonyl bands were observed nor was there any absorption between the carbon-hydrogen stretching region and  $1750\text{ cm}^{-1}$ .

**2-Diphenylhydroxymethyl-1,1,5,5-tetraphenyl-3-pentanone (9).**—A 15.4% yield of this compound was isolated, following the procedure of Kohler and Heritage,<sup>11,14</sup> mp (fast)  $154\text{--}155^\circ$ , lit.<sup>11</sup>  $153^\circ$ . The infrared spectrum is compatible with the assigned structure. Refluxing with 10% sodium hydroxide solution for 2 hr followed by ether extraction afforded 1,1,5,5-tetraphenylpentanone-3, mp  $125.5\text{--}127.0^\circ$  (lit.<sup>14</sup>  $130^\circ$ ). On heating in a *kugelrohr* at  $30^\circ$  (11 mm) two pure products condensed on the cooler parts of the tube: the white solid was the above pentanone, and the liquid proved to be benzophenone by tlc (silica gel-benzene) comparison with authentic samples.

Attempts to prepare 9 from reagent 5 by addition of phenylmagnesium bromide solution were fruitless, only 7a being isolated in 41.5% yield (crude). A considerable variety of unidentified products was obtained by chromatographic procedures and each, which could be isolated relatively pure (tlc), was

checked by tlc for identity with 9 and its two decomposition products, none of which was detected.

**Kohler's 7a.**—The crude product had mp  $200.5\text{--}206.5^\circ$  and was recrystallized from ethanol-chloroform to give satin-white needles [dried over phosphorus pentoxide at  $80^\circ$  (5 mm)], mp  $209.2\text{--}210.7^\circ$ . A second recrystallization with 3 days of drying as before gave mp  $216.0\text{--}217.5^\circ$  (lit.<sup>14</sup>  $211\text{--}213^\circ$ ); ir (KBr)  $1760$ ,  $1720$ , and  $1665\text{ cm}^{-1}$ ; nmr chemical shifts nearly identical with those for authentic 7a. The integrated nmr peaks fit methyl 2,4-dibenzhydryl-3,5-dioxo-7,7-diphenylheptanoate: mass spectrum (70 eV) *m/e* 656 (parent ion); isotopic abundance ratios at *m/e* 656 (Calcd: 100, 51.65, 14.10. Found: 100, 51.5, 14.3.); conventional mol wt (vapor pressure<sup>1</sup> in chloroform) 680.

**Registry No.**—Methyl 2-bromo-3,3-diphenylpropanoate, 24689-50-7; dimethyl 2,3-dibenzhydrylsuccinate, 24728-01-6; 6, 24689-51-8; 7a, 24647-01-6.

## Enthalpy, Entropy, and Free-Energy Changes in the Equilibration of *cis*- and *trans*-Ethyl 3-*t*-Butylcyclobutanecarboxylate and 3-*t*-Butylcyclobutanol

GARY M. LAMPMAN, GORDON D. HAGER, AND GERALD L. COUCHMAN

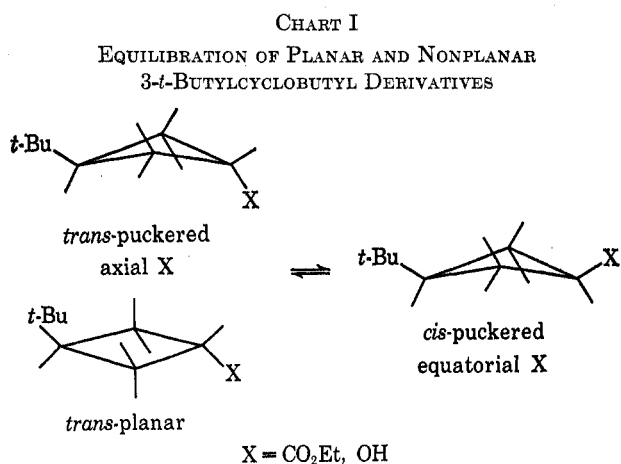
Department of Chemistry, Western Washington State College, Bellingham, Washington 98225

Received November 6, 1969

The *cis*- and *trans*-3-*t*-butylcyclobutanols have been prepared and equilibrated with aluminum isopropoxide in isopropyl alcohol at different temperatures. The thermodynamic parameters (*trans* to *cis*) are  $\Delta H = -1.6$  kcal/mol,  $\Delta S = -1.1$  cal/(deg mol), and  $\Delta G_{100} = -1.15$  kcal/mol. The equilibration of ethyl 3-*t*-butylcyclobutanecarboxylate with sodium ethoxide in ethanol at different temperatures gives  $\Delta H = -0.8$  kcal/mol,  $\Delta S = -0.7$  cal/(deg mol), and  $\Delta G_{100} = -0.58$  kcal/mol. The *cis* isomers are enthalpically favored while the *trans* isomers are entropically favored. The results have been explained on the basis of a relatively rigid puckered *cis* isomer and a somewhat flexible *trans* isomer.

The free-energy change in the equilibration of ethyl *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylate has been previously reported.<sup>1</sup> The *cis* isomer predominates at equilibrium in support of the idea that the ring is puckered leading to the groups being placed in equatorial positions similar to those in cyclohexane (Chart I, X = CO<sub>2</sub>Et). The *trans* isomer, on the other hand, would have an equatorial *t*-butyl and an axial carbethoxyl group provided that the ring is puckered to the same extent as in the *cis* isomer (Chart I, X = CO<sub>2</sub>Et). The argument commonly used in conformational studies in cyclohexane would indicate that the enthalpy of the *trans* isomer would be higher than that of the *cis* one due to a 1,3 interaction. However, it is possible that this interaction may be great enough to result in a planar ring (Chart I, X = CO<sub>2</sub>Et). Either way, the *trans* isomer should have the higher enthalpy since the puckered form would have a greater 1,3 interaction, increased angle strain, and better torsional angles, while the planar form would have a reduced 1,3 interaction, decreased angle strain, and poorer torsional angles. The actual structure for the *trans* isomer may be somewhere between the extremes.<sup>1</sup>

Experimental evidence supports conformations of rings varying between significantly puckered to planar ones for substituted cyclobutanes. For example, the *cis* isomers of methyl 3-methylcyclobutanecarboxylate,<sup>2</sup>



3-isopropylcyclobutyl alcohols and amines,<sup>3</sup> methyl 3-isopropylcyclobutanecarboxylate,<sup>4</sup> 2,2,4,4-tetramethylcyclobutane-1,3-dinitrile,<sup>5</sup> 1,3-dibromocyclobutane,<sup>6</sup> and 1,3-cyclobutanedicarboxylic acid<sup>7</sup> all have been shown to be puckered, and calculations on 1,3-dimethylcyclobutane indicate that this should be expected.<sup>8</sup> On the other hand, conformations of the

(3) I. Lillien and R. A. Doughty, *J. Amer. Chem. Soc.*, **89**, 155 (1967).

(4) I. Lillien and R. A. Doughty, *Tetrahedron*, **23**, 3321 (1967).

(5) F. Lautenschlaeger and G. F. Wright, *Can. J. Chem.*, **41**, 863 (1963).

(6) K. B. Wiberg and G. M. Lampman, *J. Amer. Chem. Soc.*, **88**, 4429 (1966).

(7) E. Adam and T. N. Margulis, *J. Phys. Chem.*, **73**, 1480 (1969).

(8) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, **90**, 1199 (1968).

(1) G. M. Lampman, K. E. Apt, E. J. Martin, and L. E. Wangen, *J. Org. Chem.*, **32**, 3950 (1967).

(2) N. L. Allinger and L. A. Tushaus, *ibid.*, **30**, 1945 (1965).