THE MICHAEL CONDENSATION.¹ VII. ACTIVATION OF THE METHYLENE GROUP BY CARBON—CARBON UNSATURATION²

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In discussing (1) the structure of addenda in the Michael condensation, the statement was made that L_2 — CH_2 — L_3 is known to react in cases where the labilizing groups (L_2 and L_3) are —COOR, —COR, —CONH₂, —CN, —NO₂, —SO₂R, and —CHO and that one of the groups may be an aryl group. It has been reported (2) that fluorene adds to mesityl oxide in the presence of potassium hydroxide, but the reaction has apparently not been extended. This paper describes the results of an investigation to determine if both L_2 and L_3 may be aromatic and if they may be olefinic.

Fluorene, cyclopentadiene, and pentadiene-1,4 were the compounds selected for study. Fluorene is known to undergo several reactions which are considered typical of active methylene compounds: condensation with aldehydes (3), the Claisen condensation with esters (4), formation of metallic derivatives by reaction with sodamide (5) or the Grignard reagent (6), and condensation with aromatic nitroso compounds (7). Exchange reactions with ethoxydeuterium (8) and a study of the acid strength (9) of fluorene also suggested that this might be a fairly active substance to study as an example of a compound containing a methylene group attached to two aromatic rings. Cyclopentadiene also condenses with aldehydes (3) and reacts with sodamide (5) and the Grignard reagent (6). It was therefore chosen as a representative compound containing a methylene group attached to two olefinic groups. Cyclopentadiene, however, is a conjugated system, and some of its reactions [e.g., the reaction with diazonium salts (10)] may be attributed to this structure or a resonance hybrid (11) rather than to the activity of the methylene group. For this reason it seemed advisable to test the behavior of pentadiene-1,4. While

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Grignard and Lapayre (6) have found that allylacetylenes react with sodamide and the Grignard reagent, it appears that no previous study has been made of the reactions of a methylene group attached to two nonconjugated olefinic bonds.

In the presence of one equivalent of sodium ethoxide, fluorene (I) reacted (2-27%) with benzalacetophenone, benzal-*p*-bromoacetophenone, and benzalacetone. Since no condensation occurred with piperidine or one-sixth of an equivalent of sodium ethoxide (1), fluorene must be considered as a relatively weak addendum. 2,7-Dibromofluorene (II) gave similar results but was somewhat more reactive (11-48%) of the adducts).



Even in the presence of an equivalent of sodium ethoxide, fluorene and 2,7-dibromofluorene did not react with α , β -unsaturated esters or with m- or p-nitrobenzalacetophenone. It has previously been noted (1) that nitro groups decreased the activity of acceptors in the Michael condensation.

Cyclopentadiene (III) reacted with α , β -unsaturated ketones when piperidine was used as a catalyst. This fact is worthy of special emphasis, since it appears to place cyclopentadiene in a class of highly active compounds; several substances (e.g., ethyl phenylacetate) which are commonly regarded as typical active methylene compounds do not add (1) to benzalacetophenone under these conditions. While some addition product was obtained by refluxing a benzene solution of cyclopentadiene, unsaturated ketone, and piperidine, better yields (25–30%) were obtained by carrying out the reaction under pressure to prevent the loss of cyclopentadiene. The adduct from benzalacetophenone did not crystallize and was isolated as the oxime; the adduct from benzal-*p*-bromoacetophenone was isolated.

Since cyclopentadiene undergoes the Diels-Alder reaction with vinyl phenyl ketone (12), the product obtained from the reaction of the diene with benzal-p-bromoacetophenone might be expected to have the structure IV or V, depending upon whether the Michael condensation or Diels-Alder reaction occurred.



The adduct isolated absorbed two moles of hydrogen and gave a product (VI) identical with that obtained by the reaction of cyclopentylmagnesium bromide with benzal-*p*-bromoacetophenone. This establishes the structure of the adduct as that (IV) obtained from a Michael condensation.



Attempts to carry out the condensation of cyclopentadiene with unsaturated ketones in the presence of sodium ethoxide gave deep red tars, possibly because of fulvene formation. When the sodium derivative of cyclopentadiene, prepared by the use of sodamide in liquid ammonia, was allowed to react with benzalacetophenone, tars were also produced, but it was possible to isolate a "trimolecular" product (VI), from the reaction of two moles of the ketone with one of the diene.

Pentadiene-1,4 (VIII) reacted with benzal-p-bromoacetophenone in the presence of an equivalent of sodium ethoxide. The same product (IX) was obtained using the sodium derivative of the hydrocarbon, prepared by the action of sodamide in liquid ammonia; in this case a small amount of "trimolecular" product (X) was also obtained.



In order to establish that the action of sodamide did not cause a shift in the double bonds of pentadiene-1,4, the sodium derivative of the latter was treated with carbon dioxide, hydrogenated, and the acid converted to the amide. This was identified as diethylacetamide by comparison with an authentic sample.

 $\begin{array}{c} (CH_2=CH)_2 CHNa \xrightarrow{CO_2} (CH_2=CH)_2 CHCOONa \xrightarrow{H_2} \\ (CH_3 CH_2)_2 CHCOOH \\ \downarrow \\ (CH_3 CH_2)_2 CHCONH_2 \end{array}$

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EXPERIMENTAL PART

Michael Condensation with Fluorene (I) and 2,7-Dibromofluorene (II)

Table I summarizes the results of the experiments using fluorene and 2,7-dibromofluorene with an equivalent of sodium ethoxide at room temperature in dry benzene [conditions previously (1) designated as D]. The reaction mixture was neutralized

ADDENDUM	ACCEPTOR	TIME (HRS.)	YIELD ^b (%)
I۰	Benzalacetophenone	20	10
I	Benzalacetophenone	168	27
I	Benzalacetophenone	336	17ª
I	m-Nitrobenzalacetophenone ^e	168	0
I	p-Nitrobenzalacetophenone/	168	0
I	Benzal-p-bromoacetophenone	168	15
I	Benzalacetone	168	29
I	Ethyl cinnamate	168	0
I	Ethyl benzalmalonate	168	0
IIh	Benzalacetophenone	20	22
II	Benzal-p-bromoacetophenone	168	48 ⁱ
II	Benzalacetone	168	11
II	Ethyl cinnamate	216	0
II	Ethyl crotonate	168	0
II	Ethyl benzalmalonate	168	0

TABLE I

Michael Condensations⁴ with Fluorene and 2,7-Dibromofluorene

^a These reactions were carried out in the presence of an equivalent of sodium ethoxide as described elsewhere in the experimental part.

^b The yields reported are those of purified products. The crude condensation products weighed one and one-half to three times as much as the quantities indicated in the table. In the experiments for which the yields are listed at 0%, 80% to 95% of unchanged addendum was recovered.

 $^{\rm c}$ Eastman's technical grade of fluorene was recrystallized from glacial acetic acid and from alcohol.

^d This reaction was carried out with half as much of the reagents as in the other experiments. The mechanical losses are therefore relatively higher.

^e Prepared by the method of Sorge (13).

' Prepared by the method of Wieland (14).

⁹ A "trimolecular" product.

^h Prepared by the method of Sieglitz (4).

'The "trimolecular" product (12% based on II) was also formed.

with dilute acetic acid, washed three times with water, and the benzene layer dried over sodium sulfate. After distillation of the benzene, alcohol was added to the residue and the product crystallized. This crude material was recrystallized from an appropriate solvent. β -(9-Fluorenyl)- β -phenylpropiophenone, m.p. 127-128° (corr.), was obtained from the reaction of benzalacetophenone and I. It was purified by repeated recrystallization from alcohol.

Anal. Calc'd for C₂₈H₂₂O: C, 89.9; H, 5.93; Mol. wt., 374.

Found: C, 89.3, 89.4; H, 6.03, 6.02; Mol. wt., 368, 369.

 β -(9-Fluorenyl)- β -phenyl-p-bromopropiophenone, m.p. 159-160° (corr.), was obtained from the reaction of fluorene with benzal-p-bromoacetophenone, and recryssallized from a mixture of benzene and ligroin (1:1).

Anal. Calc'd for C₂₈ H₂₁BrO: C, 74.2; H, 4.63; Br, 17.6.

Found: C, 73.9, 74.0; H, 4.73, 4.78; Br, 17.4, 17.4.

A "trimolecular product", m.p. 250° with decomposition, was obtained from the reaction of fluorene with benzalacetone, and recrystallized from a mixture of ether and ligroin (1:1). The exact structure was not established, but from previous work (15) it would be expected that in the initial condensation product the methylene adjacent to the carbonyl would be the reactive group in further addition; the product is therefore considered to be 4, 6-diphenyl-5-acetyl-6-(9-fluorenyl)hexanone-2.

Anal. Calc'd for C₃₈H₃₀O₂: C, 86.4; H, 6.59; Mol. wt., 458.

Found: C, 86.4, 86.5; H, 6.38, 6.58; Mol. wt., 435, 430.

 β -[9-(2,7-Dibromo)fluorenyl]- β -phenylpropiophenone, m.p. 184–185° (corr.), was obtained from the reaction of 2,7-dibromofluorene with benzalacetophenone, and was recrystallized from glacial acetic acid.

Anal. Calc'd for $C_{28}H_{20}Br_2O: C, 63.1; H, 3.79; Br, 30.1.$

Found: C, 62.9, 63.1; H, 4.01, 4.03; Br, 29.7, 29.8.

 β -[9-(2,7-Dibromo)fluorenyl]- β -phenyl-p-bromopropiophenone, m.p. 170-171° (corr.), was obtained from the reaction of II with benzal-p-bromoacetophenone, and was recrystallized from a mixture of alcohol and benzene (3:1) and then from benzene-ligroin (1:1).

Anal. Calc'd for C28H19Br3O: C, 55.0; H, 3.11; Br, 39.3.

Found: C, 54.8, 55.1; H, 3.43, 3.48; Br, 38.9, 38.9.

From the same reaction there was obtained a small amount of a trimolecular compound (m.p. 255° with decomposition) which, for the reason noted above, is probably α -(α -phenyl- β -p-bromobenzoylethyl)- β -phenyl- β -[9-(2,7-dibromo)fluorenyl]-p-bromopropiophenone.

Anal. Calc'd for C43H23Br4O2: C, 57.2; H, 3.3; Br, 35.4.

Found: C, 57.1, 57.3; H, 3.51, 3.52; Br, 35.1, 35.0.

4-Phenyl-4-[9-(2,7-dibromo) fluorenyl] butanone-2, m.p. 159-160° (corr.), was obtained from the reaction of II with benzalacetone and recrystallized from a mixture of alcohol and benzene (3:1).

Anal. Calc'd for C23H18Br2O: C, 58.8; H, 3.62; Br, 34.1.

Found: C, 58.8, 58.9; H, 3.80, 3.81; Br, 33.9, 33.8.

Using one-sixth of an equivalent of sodium ethoxide, I did not react with benzalacetophenone or ethyl cinnamate after twenty hours at room temperature. Refluxing for seventy-two hours with piperidine as a catalyst caused no condensation with I or II and benzalacetophenone. These conditions are described in more detail in an earlier paper (1) and are there referred to as B and A, respectively.

Michael Condensation with Cyclopentadiene (III) using Piperidine as a Catalyst

1. A solution of 6.6 g. (0.1 mole) of III, 20.8 g. (0.1 mole) of benzalacetophenone and 2 ml. of piperidine in 50 ml. of alcohol was refluxed for seventy-two hours. No product could be crystallized from the alcohol. Twelve grams of hydroxylamine hydrochloride and 20 g. of potassium hydroxide were dissolved in water, added to the alcoholic reaction mixture, and refluxed for one hour. Most of the alcohol was removed by distillation, the residue dissolved in benzene and washed three times with water. The benzene was removed by distillation, and the residue crystallized from alcohol. The first fraction that crystallized (4.0 g., 14%, m.p. 149-156° uncorr.) was recrystallized twice from alcohol. The product was β -phenyl- β -cyclopentadienyl-propiophenone oxime, m.p. 165.5-166.5° (corr.).

Anal. Calc'd for C₂₀H₁₉NO: C, 83.0; H, 6.63; N, 4.84.

Found: C, 83.2, 83.1; H, 6.72, 6.74; N, 4.91, 4.93.

Concentration of the mother liquor gave 1.0 g. of the dioxime of dibenzoylmethane, m.p. 208-209°, formed by the reaction of hydroxylamine with unreacted benzalacetophenone (16). The identity of this was confirmed by analysis and by a mixed melting point with an authentic sample.

The reaction of III with benzal-p-bromoacetophenone under conditions similar to those described above gave, from 0.025 mole of the reactants, 0.4 g. (5%) of β -phenyl- β -cyclopentadienyl-p-bromopropiophenone (IV), m.p. 107-108°. The product was recrystallized from alcohol.

Anal. Calc'd for C20H17BrO: C, 68.1; H, 4.83; Br, 22.6.

Found: C, 68.1, 68.2; H, 5.01, 4.96; Br, 22.4, 22.4.

2. A mixture of 20.8 g. (0.1 mole of benzalacetophenone, 6.6 g. (0.1 mole of III and 2 ml. of piperidine were placed in the glass liner of a high pressure bomb and heated at 180° for fifteen hours under a hydrogen pressure of 100 atmospheres. The product did not crystallize, and was isolated by conversion to the oxime as described above. The yield of β -phenyl- β -cyclopentadienylpropiophenone oxime was 9.0 g. (31%). Two grams of dibenzoylmethane dioxime was also isolated.

A solution of 9.9 g. (0.15 mole) of III, 43.1 g. (0.15 mole) of benzal-*p*-bromoacetophenone, and 6 ml. of piperidine in 150 ml. of dry benzene was heated at 80° for fifty hours under a hydrogen pressure of 100 atmospheres. From the reaction mixture was obtained 14.5 g. (27%) of β -phenyl- β -cyclopentadienyl-*p*-bromopropiophenone (IV).

Michael Condensation with Sodium Derivative of Cyclopentadiene

The sodium derivative of cyclopentadiene was prepared by adding 6.6 g. (0.1 mole) of the hydrocarbon to a solution of sodamide prepared by dissolving 2.3 g. (0.1 gram atom) of sodium in 100 ml. of liquid ammonia. The ammonia was allowed to evaporate, 100 ml. of dry ether added, and a solution of 20.8 g. (0.1 mole) of benzal-acetophenone in 100 ml. of dry ether added. The reaction mixture stood for 168 hours at room temperature and was then neutralized with dilute acetic acid, washed three times with water, and the ether layer dried over anhydrous magnesium sulfate. The ether was removed by distillation and the black, tarry residue taken up in benzene. From the benzene solution was obtained 0.6 g. of α -(α -phenyl- β -benzoylethyl)- β -phenyl- β -cyclopentadienylpropiophenone (VII), m.p. 260° with decomposition.

Anal. Calc'd for C₃₅H₃₀O₂: C, 87.1; H, 6.22.

Found: C, 87.0, 87.1; H, 6.34, 6.40.

Several attempts to carry out Michael condensations with III, using one-sixth or one equivalent of sodium ethoxide or potassium hydroxide as catalysts gave deep red tars.

β -Phenyl- β -cyclopentyl-p-bromopropiophenone (VI)

1. A solution of 14.4 g. (0.05 mole) of benzal-*p*-bromopropiophenone in 200 ml. of dry ether was slowly added to a solution of cyclopentylmagnesium bromide pre-

pared from 8 g. (0.05 mole) of cyclopentyl bromide. After standing overnight the reaction mixture was poured over cracked ice, neutralized with dilute hydrochloric acid and the ethereal layer washed three times with water. After drying and distilling the ether, the residue was recrystallized from alcohol. The yield of pure β -phenyl- β -cyclopentyl-p-bromopropiophenone (VI) was 8.5 g. (48%), m.p. 109-110° (corr.).

Anal. Calc'd for C20H21BrO: C, 67.2; H, 5.89.

Found: C, 67.0, 67.3; H, 5.94, 5.97.

There was also obtained from this reaction 1 g. of 3-phenyl-1-(p-bromophenyl)-1,3-dicyclopentylpropanol-1, m.p. 165-166°.

Anal. Cale'd for C₂₅H₃₁BrO: C, 70.3; H, 7.26.

Found: C, 69.9, 70.2; H, 7.34, 7.24.

2. A solution of 7.5 g. (0.021 mole) of IV in 50 ml. of dry ether was shaken in an Adams machine in the presence of 2.0 g. of palladium-palladium oxide catalyst (17) under an initial hydrogen pressure of 2 atmospheres. After two minutes the shaker was stopped and the mixture allowed to come to room temperature. The hydrogen absorption was about 0.05 mole. The catalyst was removed by filtration, the ether evaporated and the residue recrystallized from alcohol. The yield of pure VI was 7.0 g. (93%), m.p. 109-110°. This did not depress the melting point of the material prepared from the Grignard reagent as described above.

Michael Condensation with Pentadiene-1,4 (VII)

1. One-hundredth molar quantities of pentadiene-1,4 (18) and benzal-p-bromoacetophenone were treated with an equivalent amount of sodium ethoxide in the usual way (1) and allowed to stand for two weeks in a refrigerator at 0°. The product was recrystallized from alcohol and gave 0.14 g. (4%) of γ, γ -divinyl- β -phenyl-p-bromo-nbutyrophenone (IX), m.p. 107-108° (corr.).

Anal. Calc'd for C20H19BrO: C, 67.6; H, 5.35; Br, 22.5.

Found: C, 67.4, 67.4; H, 5.44, 5.47; Br, 22.3, 22.3.

2. The sodium derivative of pentadiene-1,4 was prepared by adding 0.68 g. (0.01 mole) of the hydrocarbon to a solution of sodamide prepared by dissolving 0.23 g. (0.01 gram atom) of sodium in 10 ml. of liquid ammonia. The ammonia was allowed to evaporate and a solution of 2.87 g. (0.01 mole) of benzal-p-bromoacetophenone in 100 ml. of dry ether added. The reaction mixture stood for two weeks in a refrigerator at 0° and was then neutralized with dilute hydrochloric acid. The ethereal layer was washed three times with water, dried over anhydrous sodium sulfate, and the ether removed by distillation. The residue, upon crystallization from alcohol, gave 0.39 g. (11%) of IX and 0.15 g. of a "trimolecular" product which, for the reasons mentioned above, is considered to be α -(α -phenyl- β -p-bromobenzoylethyl)- β -phenyl- γ , γ -divinyl-n-butyrophenone (X), m.p. 225° with decomposition.

Anal. Calc'd for $C_{35}H_{30}Br_2O_2$: C, 65.4; H, 4.71; Br, 24.9.

Found: C, 65.4, 65.4; H, 4.81, 4.74; Br, 24.7, 24.8.

Structure of the sodium derivative of pentadiene-1,4. The sodium derivative of VII was prepared by adding 3.4 g. (0.05 mole) of the hydrocarbon to 0.05 mole of sodamide in liquid ammonia. The ammonia was allowed to evaporate, 100 ml. of ether added, the flask immersed in a carbon dioxide-acetone bath, and 20 g. of pulverized solid carbon dioxide added. The flask was removed from the heating bath, allowed to come to room temperature and transferred to an Adams shaker. Two grams of palladium-palladium oxide catalyst (17) was added and the mixture shaken for seven hours under two atmospheres of hydrogen pressure. The reaction mixture was evaporated to dryness, dissolved in water, acidified with dilute sulfuric acid, and the solution

extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and, after removal of the drying agent, treated with 15 ml. of thionyl chloride and refluxed for thirty minutes. The resulting mixture was poured into 15 ml. of concentrated ammonium hydroxide, cooled, extracted three times with ether, and the ethereal solution dried. The solid obtained after removal of the ether was recrystallized from a mixture of ligroin and benzene (3:1). The pure product weighed 1.5 g. (13%), m.p. 106-107° (corr.) and was shown to be diethylacetamide by a mixed melting point with an authentic sample.

SUMMARY

The methylene group is reactive in the Michael condensation when it is activated by two carbon-carbon double bonds. These double bonds may be parts of aromatic systems (fluorene and 2,7-dibromofluorene) or conjugated olefinic linkages (cyclopentadiene) or non-aromatic and nonconjugated (pentadiene-1,4).

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