An Investigation of the Abnormal Products from the Reaction of 2-Thenyl and Benzyl Grignard Reagents by Gas Chromatography. (1,2a)

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The products of the reaction of 2-thenylmagnesium chloride (I) with a variety of reagents has been studied by gas chromatography. Carbon dioxide and ethylene oxide produced significant amounts of 5-substituted ("*para*") products as well as 3-substituted ("*ortho*") and normal addition products. Several other reagents, including acetyl chloride and formaldehyde, produced mainly "*ortho*" products along with small amounts of normal products. The dependence of product distribution on temperature, added salts and solvent character was found to correlate with the reported rates of inversion about the carbon-magnesium bond in primary Grignard reagents. Blocking the "*ortho*" position, in 3-methyl-2-thenylmagnesium chloride, increased the proportion of "*para*" product from 3 to 33%. In addition, the reactions of benzylmagnesium chloride with certain reagents were re-examined.

Introduction.

The "abnormal" reaction of benzyl Grignard reagents with a variety of reactants has been known for quite some time (3,4). Usually *ortho*-tolyl products are observed, but in a few instances *para* products have been reported (5,6). The cyclic mechanism for the *ortho* abnormal reaction, first proposed by J. R. Johnson, is well-documented (7-9). It has been suggested that the *ortho* product is formed by the intracomplex reaction described by Johnson, whereas the normal product probably results from the reaction of the complex formed between the Grignard reagent and carbonyl compound (Werner complex) with a second molecule of Grignard reagent (8).

Essentially the same types of products are obtained from the heterocyclic methyl Grignard reagents with one striking exception. Carbonation of the benzyl Grignard reagents yields only the "normal" acids, whereas the heterocyclic methyl Grignard reagents yield both normal and "abnormal" acids (10-12). In these cases the product ratio observed was found to correlate with the suceptibility of the *ortho* position to electrophilic attack. For example, earlier reports have shown that carbonation of 3-thenylmagnesium bromide yields 3-methyl-2-thenoic acid and 3-thienylacetic acid in a ratio of 3:2 (10), but 2-thenylmagnesium chloride gave 2-methyl-3-thenoic acid and 2-thienylacetic acid in a ratio of 1:2 (11). Campaigne and Collins (13) have recently reported results that confirmed the "*ortho*" to normal product ratio obtained in the carbonation of 2-thenylmagnesium chloride using

[14]C-carbon dioxide. However, they also showed that a small amount of "*para*" product, 5-methyl-2-thenoic acid, was formed in the reaction. The presence of "*para*" product implied there was an alternate pathway by which the reaction could proceed, and it was suggested that the resonating carbanion derived from the 2-thenyl Grignard

Chart 1

Possible Reaction Products from 2-Thenylmagnesium Chlorides
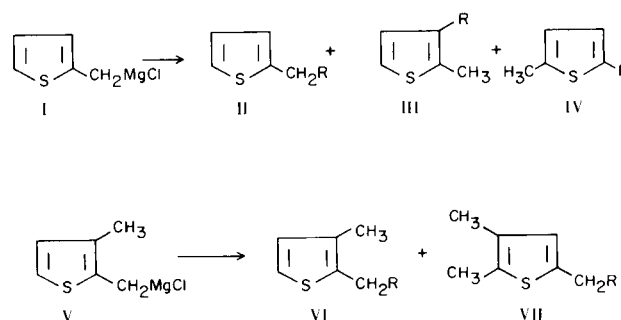
(a) R = CO₂CH₃
(b) R = CH₂CH₂OH
(c) R = COCH₃

(d) R = CH₂OH
(e) R = COOC₂H₅
(f) R = CH₂OCH₃
(g) R = COC(CH₃)₃

reagent was a reasonable explanation for the appearance of "para"-substituted product (14).

We have extended the investigation of 2-thenyl-magnesium chloride (I) reactions, using gas chromatography to analyze the products obtained. Our primary purpose was to show conclusively that "para" product formation is an important process in the reactions of I. Once that fact was established we directed our studies toward an understanding of some of the many factors which were found to influence the reactivity of I. One of the most obvious significant variables in the reaction of benzylic Grignard reagents is the nature of the electrophilic reagent. Earlier workers recognized the fact that variation in the nature of the electrophile influenced product distribution (4). However, no general classification of electrophilic reagents has yet been made, and the reason for their effect on the reactions of benzylic Grignard reagents remains obscure. Variation of solvent (15) and temperature, and the addition of certain ions have also been shown to influence product distribution. It was also interesting to check some of the early work that had been done with the benzyl Grignard reagent by modern analytical techniques (cf. Benkeser and Johnston (15)).

Results and Discussion.

Carbonation of I in ethyl ether, followed by esterification of the crude acids with diazomethane, produced three esters, as evidenced by gas chromatography. The retention times were shown to be identical to those obtained for authentic samples of methyl 2-thienylacetate (IIa), methyl 2-methyl-3-thenoate (IIIa) and methyl 5-methyl-2-thenoate (IVa). Rigorous identification was accomplished by isolation and inspection of their n.m.r. and infrared spectra. The relative percentage of each ester (Table I, Entry 10) was calculated from the gas chromatogram (see Experimental for details). These results confirm the work of Campaigne and Collins (13), showing that the "para" product, IVa, was present in 2-4% of total esters.

The reaction of I with ethylene oxide in ethyl ether (Table I) produced the three isomeric alcohols, γ-(2-thienyl)propanol (IIb), β-(2-methyl-3-thienyl)ethanol (IIIb) and β-(5-methyl-2-thienyl)ethanol (IVb) under all experimental conditions. However, the reaction of I with acetyl chloride in ether (Table I, Entry 7) produced only the "ortho" and normal ketones, 2-methyl-3-acetothienone (IIIc) and 2-thienylacetone (IIc) respectively. Rigorous identification of the products obtained from both reactions was accomplished by isolation of each component by preparative gas chromatography and comparison of their n.m.r. and infrared spectra to those obtained from authentic samples of each compound.

When magnesium perchlorate was added to the ethereal solution of ethylene oxide or acetyl chloride, the reaction with I produced an increase in "para" product, IVb or IVc

(Table I, Entries 3 and 8). A possible explanation for the effect of added perchlorate stems from the work of Winstein, Smith and Darwish (16), who have shown that the addition of 0.1 molar lithium perchlorate to ethyl ether enhanced the ionization rate of p-methoxyneophyl p-toluenesulfonate in that solvent by a factor of 10^5. The authors interpreted the results as indicating that the addition of lithium perchlorate enhanced the ionizing power of the ether. In the present case, if one assumes that magnesium perchlorate would have a similar effect on the ethyl ether, an increase in the carbanion character of I could result. An increase in carbanion character of I would increase the reactivity at the 5-position due to the resonance stabilization of the anion by the sulfur atom, and an increase in 5-substituted or "para" product would be observed. However, due to the complexity of the ions or ion pairs, and higher ion aggregates which exist in Grignard solutions, other modes of action of added perchlorate are possible, but highly speculative. That the effect is due to perchlorate rather than simple common ion is shown by the fact that the addition of magnesium bromide had no effect on the reactions of I.

The most interesting and possibly most important aspect of this investigation is the correlation between the yield of "para" product and the reported rates of inversion about the carbon-magnesium bond in primary Grignard reagents (17-19). Whitesides and Roberts (18) and Fraenkel and Dix (19) have shown by n.m.r. studies that primary Grignard reagents are not configurationally stable above -70°, and that there is an inversion process occuring at the carbon-magnesium bond. Although a simple ionization-recombination mechanism probably does not apply, an inversion process implies that there are certain carbanionic fragments existing in solution which may behave like the "free" carbanion itself. Whitesides and Roberts also found that the rate of inversion was dependent upon temperature, nature of the anion and solvent. As the last column in Table I indicates, low temperatures produced low yields of "para" product and higher temperatures produced higher yield of "para" product. If the inversion rate can be related to carbanion formation and/or stability, then at higher temperatures an increase in "para" product would be expected due to the greater carbanion character of I.

The effect of added perchlorate may also be explained in terms of this inversion process. Roberts found that the rate of inversion increased with increasing electronegativity of the anion in solution. Any exchange of chloride with perchlorate would cause an increase in carbanion character of I, hence an increase in inversion rate and an increase in "para" product would result.

The most drastic effect on product distribution in the reactions of I was that of solvent. The results obtained

from carbonation of I and reaction with ethylene oxide and acetyl chloride in dimethoxyethane are given in Table I, (Entries 6, 9, and 11). The major product of all three reactions was the "normal" product. No "para" product was observed. In fact only in the reaction with acetyl chloride was any "ortho" product obtained. Benkeser and Johnston (15) have recently reported a similar pronounced solvent effect on the reaction between benzylmagnesium chloride and acetaldehyde. They found that when the reaction was performed in tetrahydrofuran instead of ethyl ether the yield of normal product, benzylmethylcarbinol, was substantially increased. Since it is quite clear now that a change in solvent can affect the nature of the Grignard reagent itself, any explanation would be speculative (20). However, the fact that no "para" product was formed in any of the reactions with I in dimethoxyethane correlates with the effect of solvent on the inversion rate described by Whitesides and Roberts. The inversion rate was slowest in dimethoxyethane (21), hence product from the resonating carbanion should be reduced.

Several other reactants were treated with I, but no "para" products were found. Ethyl chlorocarbonate, chloromethyl methyl ether and pivaloyl chloride all yielded only the "ortho" product and no other isomers were detected. Formaldehyde gave 12% normal and 88% "ortho" product, but no "para" isomer was found. These results further illustrate the ambiguities associated with an attempt to derive some reasonable mechanistic picture of the effect of electrophilic reagent on the reactions of benzylic Grignard reagents.

Since it had been shown that substantial reaction could occur at the "para" position of I, the reactions of 3-methyl-2-thenylmagnesium chloride (V) were of interest. In this case the "ortho" position would be blocked, hence the cyclic mechanism would be inoperative. The results of two experiments are given in Table II. Carbonation of V, followed by esterification with diazomethane, produced both normal and "para" esters in a 2:1 ratio. However, the reaction with acetyl chloride produced only the normal ketone and no "para" ketone was detected. While it is significant that the carbonation of the ortho-blocked Grignard gave the "para" isomer in 33% yield, it should also be noted that acetyl chloride rarely produces "para" product, and then only with added perchlorate (see Table I).

Finally, we have examined the reactions of benzylmagnesium chloride (VIII) with acetyl chloride, ethylene oxide and ethyl sulfate. The results from these reactions in ethyl ether are given in Table III. In contradiction to earlier reports (4,7), the reaction of VIII with acetyl chloride produced both phenylacetone (IXa) and o-methylacetophenone (Xa) with IXa being the major product. There was no evidence that any p-methylacetophenone was formed in the reaction. The reaction of VIII with ethylene oxide produced a small amount of para product, p-methylphenethyl alcohol (XIb), as well as a mixture of normal and ortho alcohols, γ-phenylpropanol (IXb) and o-methylphenethyl alcohol (Xb), which could not be separated under the gas chromatography conditions employed. The presence of para product confirms the early work of Gilman and Kirby (22), who had reported

TABLE I

Relative Yields of Isomers in the Reaction Products of 2-Thenylmagnesium Chloride

	Reagent	Temp. °C	R	Normal (II)	"Ortho" (III)	"Para" (IV)
1.	$(CH_2)_2O$ (a)	-5	CH_2CH_2OH	11.0 ± 0.5	75.0 ± 1.0	14.0 ± 1.0
2.	$(CH_2)_2O$ (b)	-15	CH_2CH_2OH	14.3 ± 0.8	74.8 ± 1.5	10.9 ± 0.7
3.	$(CH_2)_2O$ (c)	-15	CH_2CH_2OH	14.0 ± 0.2	73.3 ± 0.3	12.7 ± 0.8
4.	$(CH_2)_2O$ (b)	-70	CH_2CH_2OH	25.5 ± 0.5	71.8 ± 0.5	2.7 ± 0.5
5.	$(CH_2)_2O$ (a)	-70	CH_2CH_2OH	45.2 ± 0.5	53.0 ± 0.5	1.8 ± 0.5
6.	$(CH_2)_2O$ (d)	-10	CH_2CH_2OH	>99	---	----
.7.	CH_3COCl (b)	-70	$COCH_3$	17.5 ± 0.5	82.5 ± 0.5	----
8.	CH_3COCl (c)	-70	$COCH_3$	4.5 ± 0.5	92.5 ± 1.0	3.0 ± 0.5
9.	CH_3COCl (e)	-10	$COCH_3$	54.6 ± 0.4	45.4 ± 0.4	----
10.	CO_2 (b)	f	$COOCH_3$	61.0 ± 0.5	36.0 ± 0.5	3.0 ± 0.5
11	CO_2 (e)	f	$COOCH_3$	100	-----	----

(a) Normal addition in ethyl ether. (b) Inverse addition in ethyl ether. (c) Inverse addition in ethyl ether, with magnesium perchlorate added. (d) Normal addition in dimethoxyethane. (e) Inverse addition in dimethoxyethane. (f) Ambient temperature of dry ice in solvent.

TABLE II

Relative Yields of Isomers in the Reaction Products of 3-Methyl-2-thenylmagnesium Chloride

Reactant	R	Normal (VI)	"Para" (VII)
CO_2 (a)	$COOCH_3$	66.5 ± 0.5	33.5 ± 0.5
CH_3COCl (a)	$COCH_3$	100	-----

(a) Inverse addition.

TABLE III

Relative Yields of Isomers in the Reaction Products of Benzylmagnesium Chloride

		Relative % Yield of Isomers					
		Normal (IX)		Ortho (X)		Para (XI)	
Reactant	R	Ether	DME (a)	Ether	DME	Ether	DME
CH_3COCl (b)	$COCH_3$	66.1 ± 0.7	Same	33.9 ± 0.7	Same	----	----
$(CH_2)_2O$ (c)	CH_2CH_2OH	Major	1 100	Minor	----	>5	----
Et_2SO_4 (c)	CH_2CH_3	87.5 ± 0.2	100	9.1 ± 0.1	----	3.4 ± 0.1	---

(a) Dimethoxyethane. (b) Inverse addition. (c) Normal addition.

obtaining "para" product in the same reaction. The reaction of VIII with ethyl sulfate produced the three isomeric alkylbenzenes, n-propylbenzene (IXc), o-ethyltoluene (Xc) and p-ethyltoluene (XIc). That XIc was obtained confirms the work of Burtle and Shriner (5), who found a small amount of "para" product in the reaction of VIII with ethyl sulfate. Although they reported no evidence for "ortho" product formation, our results proved that "ortho" product is formed in the reaction between ethyl sulfate and VIII.

The results obtained from the reactions of VIII in dimethoxyethane paralleled those obtained from I in dimethoxyethane with one exception. As Table III indicates, no change in product distribution was observed in the acetyl chloride experiment. In the light of the other data, this experiment remains anomalous. The two remaining experiments show the same shift to complete "normal" products in dimethoxyethane as those with I had shown.

Conclusion.

We have shown that "para" substitution is an important process in the reactions of 2-thenyl Grignard reagents, particularly when the 3-position is blocked. The differences in product distribution between the reactions of benzyl Grignard and 2-thenyl Grignard reagents may be explained

by two main factors: (1) There is only one "ortho" position in I, but two "ortho" positions in VIII. Therefore, "ortho" product formation with VIII is favored statistically; (2) there is stabilization of a negative charge at the "para" position by the sulfur atom in I, not possible in VIII, therefore, "para" product formation from I is favored.

Many factors can effect product distributions obtained from the reactions of heterocyclic methyl Grignard reagents, among which the most interesting are added perchlorate, temperature and solvent. Definite conclusions about the mechanism of action of each factor cannot be drawn, but a good correlation between the effect of these factors on "para" product formation and the rate of inversion of primary Grignard reagents is evident.

EXPERIMENTAL

The infrared spectra were obtained on a Perkin-Elmer Model 137-B Infracord Spectrometer. All spectra were taken as liquid films unless otherwise indicated. Nuclear magnetic resonance spectra were determined on a Varian Associates Model A-60 Spectrometer in carbon tetrachloride using tetramethylsilane as internal standard. Gas chromatography was performed on an F. and M. Scientific Corporation Model 500 Gas Chromatograph using helium as the carrier gas. Quantitative analyses of the gas chromatographic peaks were accomplished by the internal standard method described by Dal Nogare and Juvet (23). Analytically

pure tetralin was used as the internal standard unless otherwise stated. The peak areas were measured by the "height x width at half height" method.

Sources and Purification of Reagents.

Magnesium.

Magnesium turnings obtained from the Fisher Scientific Company, specifically labeled for the Grignard reaction, gave best results.

Nitrogen.

Pre-purified nitrogen (Matheson) was used directly from the the cylinder without further treatment in the preparation and reaction of all Grignard reagents.

Diethyl Ether.

Freshly opened cans of Matheson, Coleman and Bell anhydrous ether or Fisher reagent ether were used. It was found, however, that opened cans could be reused if the ether was stored over sodium wire.

Dimethoxyethane.

This compound (Aldrich) was refluxed for one day over lithium aluminum hydride, then distilled and stored over sodium wire.

Acetyl Chloride.

This compound (MCB) was distilled through a twenty inch Vigreaux column. The fraction distilling at 51-52° was collected for use.

Ethyl Chlorocarbonate.

This compound (MCB) was purified in the same manner as acetyl chloride. The fraction distilling at 92-93° was collected for use.

Diethyl Sulfate.

This compound (MCB) was distilled at reduced pressure through a ten inch Vigreaux column. The fraction distilling at 74-75°/4 mm. was collected for use.

Chloromethyl Methyl Ether.

This compound (MCB) was purified in the same manner as acetyl chloride. The fraction distilling at 58-60° was collected for use.

Ethyl Oxide.

This compound (Matheson) was collected from a gas cylinder by use of a dry ice-acetone condenser.

Preparation of the Benzylic Grignard Reagents.

2-Thenyl chloride (24), 3-methyl-2-thenyl chloride (25) and benzyl chloride (Baker) were converted to their corresponding Grignard reagents in ethyl ether in the cyclic Grignard reactor as described by Campaigne and Yokley (12). The concentration of the Grignard solution obtained in this manner was determined by titration. The yields of the Grignard reagents ranged from 70-95%.

The reagents in dimethoxyethane were obtained by the following procedure: A 500 ml. flask, calibrated at 250 ml., was fitted with a 250 ml. pressure-equalizing dropping funnel and a distillation head by means of a take-off adapter. The system was protected from the atmosphere by a nitrogen-inlet tube attached to the top of the dropping funnel. After the system was purged with nitrogen for five minutes, the flask was charged with a 100 ml. aliquot of the particular Grignard reagent, prepared in

ethyl ether, with a wide-bore syringe to prevent air hydrolysis. The flask was heated by an oil bath and moderate stirring was accomplished with a magnetic stirring bar. After ca. 75 ml. of ethyl ether had been distilled, dry dimethoxyethane was added slowly to the Grignard solution via the dropping funnel. A white precipitate formed initially, but as more dimethoxyethane was added the precipitate dissolved. The temperature of the oil bath was raised to 95° and heating was continued until all the ethyl ether and some dimethoxyethane had been distilled. The oil bath was removed and enough dimethoxyethane was added to bring the solution to 250 ml. Hydrolysis and titration of a 10 ml. aliquot indicated that none of the Grignard reagent had been destroyed.

Carbonation of 2-Thenylmagnesium Chloride (I).

Following the procedure of Campaigne and Yokley (12), a solution of I in ethyl ether or dimethoxyethane was added slowly and with stirring to a mixture of Dry Ice and the appropriate solvent. The crude acids obtained were converted to their methyl esters by diazomethane generated from N-methyl-N-nitrosourea (26) in the following manner: A clean, unscratched 500 ml. flask, fitted with a rubber stopper and glass tube, was charged with 60 ml. of 50% potassium hydroxide and 200 ml. of ether. The mixture was cooled to 5° and 20.6 g. of N-methyl-N-nitrosourea added. The flask was placed in a water bath at 50°, and the ethereal diazomethane was distilled through the glass tubing into a clean, unscratched 250 ml. Erlenmeyer flask containing an ethereal solution of the crude acids cooled by a Dry Ice-acetone bath. Distillation was continued until ca. two-thirds of the ether had been distilled, and the resultant solution was left at room temperature overnight. Gas chromatography of the ethereal ester solution proved that all of the acids were converted to their respective methyl esters in a quantitative fashion. There were no peaks in the gas chromatogram corresponding to those obtained upon gas chromatography of a mixture of authentic acids dissolved in ether. The ether was removed under aspirator pressure, and distillation of the crude esters at reduced pressure afforded a colorless liquid, b.p. 75-90°/2.5 mm. The yield of ester ranged from 70-80% based on I. The product was subjected to gas chromatography on an 8 ft. 20% silicon gum nitrile on Diatoport A column at 125° and programming to 200° at a rate of 2.1°/minute with a helium flow rate of 68.5 ml./minute. Three components were observed having retention times of 18.6, 21.7 and 22.8 minutes, respectively. Tentative identification of the three components was accomplished by inducing augmentation of their respective peaks upon mixing an aliquot of the product with authentic samples of the methyl esters, IIa, IIIa and IVa. In this manner peak one was established as IIIa, peak two, IIa and peak three, IVa.

Confirmation of these product assignments was accomplished in the following manner: The mixed esters were distilled through a spinning band column. Fractions were collected at every 0.5 ml., and that fraction richest in each of the three components was subjected to preparative gas chromatography under conditions as described above. The infrared and n.m.r. spectrum of each collected sample was determined and compared to those from authentic samples. A pure sample of IVa could not be obtained, but was present in high enough concentration in the mixture to be positively identified.

The relative product ratio of the esters was determined by gas chromatography under the conditions described above. Response ratios were established using authentic samples of each compound.

Reaction of the Grignard Reagents with Ethylene Oxide. General Procedure.

A. Normal Addition.

Following the procedure of Gaertner (11), the particular Grignard reagent, I or VIII in ethyl ether or dimethoxyethane, was cooled to $-10°$ by an ice-methanol bath, then treated with excess ethylene oxide. The resultant reaction mixtures were hydrolyzed with 25% sulfuric acid and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the ether removed under aspirator pressure and the crude liquids analyzed by gas chromatography on an 8 ft. 20% diethylene glycol adipate-on-Chromosorb W column at 150-175°. It was found that the normal and "ortho" alcohols, IXb and Xb, formed from VIII were not separable under the gas chromatography conditions employed. Confirmation of the product assignments was accomplished by fractional distillation through a spinning band column followed by infrared and n.m.r. spectral determinations of each compound isolated by preparative gas chromatography.

B. Inverse Addition.

The same procedure was used as in the preceding experiment except that the Grignard reagent, I of VIII, was added to the excess ethylene oxide dissolved in the appropriate solvent. In the experiment in which magnesium perchlorate was used, the perchlorate (2.1 mole per cent) was added to the ethylene oxide solution prior to the addition of the 2-thenyl Grignard reagent.

Reaction of the Grignard Reagents with Acetyl Chloride. General Procedure.

The procedure employed was that described by Gaertner (11). A ten-fold excess of acetyl chloride in either ethyl ether or dimethoxyethane was cooled to $-70°$ by a Dry Ice-acetone bath. The Grignard reagent, I, V or VIII in the appropriate solvent, was added slowly to the cold solution. After the addition was complete, the mixture was allowed to warm to room temperature, poured into ice water and hydrolyzed with ammonium chloride. The crude ketones obtained were analyzed by gas chromatography on a 8 ft. 20% carbowax 20M on Diatoport S column at 160°. Product identification was accomplished as described in the preceding experiments. In the experiment in which magnesium perchlorate was used, the perchlorate was added to the acetyl chloride solution just prior to the addition of I.

Reaction of I with Pivaloyl Chloride.

Following the procedure described in the preceding experiment, pivaloyl chloride was treated with I at $-70°$. The reaction afforded a yellow liquid, b.p. 90-100°, which proved to be only one product, IIIg, as shown by gas chromatography, infrared and n.m.r. analyses: ν max; 2955 (C-H) and 1730 cm^{-1} (C=O); δ; 7.24 d (1H) (J = 5), 6.91 d (1H) (J = 5), 2.53 (3H), 1.25 m (9H).

Reaction of I with Ethyl Chlorocarbonate.

As described in the acetyl chloride experiment, ethyl chloro-carbonate was treated with I at $-70°$. The reaction afforded a colorless liquid, b.p. 90-110°/3.5 mm., which proved to be only one product, IIIe, as indicated by gas chromatography, infrared and n.m.r. analyses: ν max; 3000 (C-H), 1720 cm^{-1} (C=O); δ; 7.3d (1H)(J = 5.5), 6.88d (1H) (J = 5.55), 4.26q (2H)(J = 7.0), 2.7 (3H), 1.32t (3H)(J = 7.0).

Reaction of I with Formaldehyde.

Following the procedure described by Campaigne and Yokley (12), a solution of I was treated with gaseous formaldehyde generated from 25 g. of paraformaldehyde and swept into the reaction mixture with a slow stream of nitrogen. The reaction afforded a colorless liquid, b.p. 70-90°/1.5 mm., and gas chromato-

graphic analysis on the diethylene glycol adipate column at 160° indicated two products, which were identified as IId and IIId by isolation and inspection of their infrared and n.m.r. spectra.

Reaction of I with Chloromethyl Methyl Ether.

Following the procedure described by Malm and Summers (6), chloromethyl methyl ether was treated with a solution of I. The reaction afforded a colorless liquid, b.p. 65-70°/1.5 mm., which proved to be only one product, IIIf, as shown by gas chromatography and n.m.r. analyses: δ; 6.89d (1H) (J = 5), 6.79d (1H) (J = 5), 4.38 (2H), 3.21 (3H), 2.38 (3H).

Reaction of VIII with Diethyl Sulfate.

Using the procedure of Gilman and Catlin (27), a solution of VIII in either ethyl ether or dimethoxyethane was treated with diethyl sulfate. The reaction afforded a pale yellow liquid, b.p. 75-85°/20 mm., which was subjected to gas chromatographic analysis on a 20% apiezon L on Chromosorb W column at 100°. The three components observed were identified as IXc, Xc and XIc by augmentation of their respective peaks with authentic samples of each compound. The relative product ratio was determined using m-xylene as the internal standard.

Methyl 2-Thienylacetate (IIa).

Esterification of 2-thienylacetic acid (28) with diazomethane, as described in the carbonation experiment, followed by preparative gas chromatography, yielded a pure sample of IIa: δ; 6.71 m (3H), 3.70 (2H), 3.60 (3H).

Methyl 5-Methyl-2-thenoate (IVa).

The Grignard reagent of 5-methyl-2-bromothiophene (29) was carbonated, and the crude acid esterified with diazomethane. A pure sample was collected by preparative gas chromatography: δ; 7.57d (1H) (J$_{AB}$ = 3.5), 6.75m (1H)(J$_{AB}$ = 3.5) (J$_{BX}$ = 1.0), 3.85 (3H), 2.51d (3H) (J$_{BX}$ = 1.0).

γ-(2-Thienyl)propanol (IIb).

Lithium aluminum hydride reduction of β-(2-thienyl)propanoic acid (30) yielded IIb: δ; 6.63-7.03m (3H), 3.57m (2H), 3.47 (1H), 2.85m (2H), 1.70-2.10m (2H).

β-(5-Methyl-2-thienyl)ethanol (IVb).

This compound was obtained from the Grignard reagent of 5-methyl-2-bromothiophene (29) by treatment with ethylene oxide: δ; 6.50d (1H) (J = 4), 6.39d (1H) (J = 4), 3.63t (2H) (J = 6.5), 3.31 (1H), 2.82t (2H) (J = 6.5), 2.37 (3H).

2-Thienylacetone (IIc).

Treating 2-thienylacetyl chloride (31) with dimethylcadmium according to the procedure of Cason and Prout (32), yielded IIc: δ: 6.70-7.07m (3H), 3.78 (2H), 2.08 (3H).

5-Methyl-2-acetothienone (IVc).

A pure sample of this compound, previously prepared in this laboratory (33), was obtained by preparative gas chromatography: δ; 7.36d (1H) (J$_{AB}$ = 3.5), 6.69m (1H) (J$_{AB}$ = 3.5) (J$_{BX}$ = 1.0) 2.49d (3H) (J$_{BX}$ = 1.0), 2.38 (3H).

β-(2-Thienyl)ethanol (IId).

Lithium aluminum hydride reduction of 2-thienylacetic acid (28) gave IId: δ; 6.70-7.10m (3H), 3.70t (2H) (J = 6.5), 3.08 (1H), 2.95t (2H) (J = 6.5).

o-Methylacetophenone (Xa).

Treating the acid chloride of o-methylbenzoic acid (Eastman) with dimethylcadmium gave a product boiling at 66-67°/3 mm.

(lit. (34) b.p. 70°/5 mm.).

Preparation of o- and p-Methylphenethyl Alcohols (Xb and XIb).

These compounds were prepared by treating o- and p-tolyl-magnesium bromide with excess ethylene oxide. In this manner Xb, b.p. 75-80°/1 mm., and XIb, b.p. 79-83°/1 mm., were obtained.

Xb, ν max: 3340 (OH), 2945 (C-H), 1004 and 745 cm^{-1} (o-disubstituted benzene).

XIb, ν max: 3340 (OH), 2945 (C-H) and 807 cm^{-1}(p-disubstituted benzene).

Preparation of the Alkylbenzenes (IXc-XIc).

Following the Huang-Minlon (35) modification of the Wolff-Kishner reduction, the appropriate ketone, phenylacetone (Eastman), o-methylacetophenone or p-methylacetophenone (Eastman), was reduced with 97% hydrazine and potassium hydroxide in diethylene glycol. Several hundred milligrams of each alkylbenzene was obtained by preparative gas chromatography on the apiezon L column. The structure of each compound was confirmed by infrared and n.m.r. analyses.

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