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THE SYNTHESIS OF ALDEHYDES FROM GRIGNARD REAGENTS. II. POLYMETHYLBENZALDEHYDES

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The literature records the use of eight different substances which react with Grignard reagents leading to the formation of aldehydes according to the type reaction $RX \rightarrow RMgX \rightarrow RCHO$. One of the earliest of these studies was that of Gattermann and Maffezzoli (1) who found that at very low temperatures (-50°) an excess of ethyl formate (3 moles) reacted with Grignard reagents to give products consisting largely of aldehydes rather than of the secondary alcohols formed in a subsequent reaction. In a continuation of this study, Gattermann (2) prepared a series of aldehydes in yields of from 10 to 50%, and the use of some other formates, particularly the methyl and amyl esters was meanwhile investigated by others (3).

Bodroux and Tschitschibabin (4) independently discovered a synthesis of aldehydes which involved the reaction between a Grignard reagent and ethyl orthoformate. This synthesis of aldehydes has been used by many investigators and, in favorable cases, it gives excellent yields.

Zelinsky (5) prepared aldehydes by the reaction between formic acid and Grignard reagents and although he did not state the yields, presumably they were small, for Houben (6) in a continuation of this study was able to obtain phenylacetaldehyde in a maximum yield of but 30% from benzylmagnesium chloride and formic acid. Houben also obtained butyraldehyde from propylmagnesium chloride by this method, but the yield was extremely poor and Houben was led to try the salts of formic acid, rather than the acid itself. Benzylmagnesium chloride reacted with copper formate to produce phenylacetaldehyde, but the yield was very low.

Bouveault (7) introduced the use of disubstituted formamides as reagents which were capable of converting Grignard reagents into aldehydes. This reaction, while successful in certain cases, is very complicated and frequently produces tertiary amines as the chief products. Moreover, even when the aldehyde is the chief product, the reaction does not compare in efficiency with the one using ethyl orthoformate (4).

¹ Abstracted from a thesis by Joseph Nichols, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the M.S. degree, 1941. Sachs and Loevy (8) have reported a synthesis of aldehydes which involves addition of a Grignard reagent to an isocyanide. While these authors used only phenylmagnesium bromide and methyl isocyanide, the fact that benzaldehyde was obtained led them to predict that the synthesis would be successful in other cases. Gilman and Heckert (9) attempted to extend the reaction; they added phenylmagnesium bromide to a number of isocyanides, including hydrocyanic acid (7a) but benzaldehyde was obtained only when methyl isocyanide was used.

Monier-Williams (10) discovered a synthesis for aldehydes which involved the reaction between a Grignard reagent and ethoxymethyleneaniline.

 $RMgX + C_6H_5N = CHOC_2H_5 \rightarrow RCH = NC_6H_5 + C_2H_5OMgX$ $RCH = NC_6H_5 + H_2O + HCl \rightarrow RCHO + C_6H_5NH_2 \cdot HCl$

Monier-Williams was interested chiefly in preparing aromatic aldehydes containing a thio ether group attached to the ring, but he prepared a number of other aldehydes as well, and somewhat later Gattermann (2) also used the method for preparing a series of aldehydes. The yields obtained by the two investigators checked very well and were of the order of 30-60%. It is of interest that Monier-Williams attempted to improve the yields of aldehydes by operating in boiling toluene; the results were quite unsatisfactory.

Wuyts and his collaborators discovered and developed a synthesis for aldehydes in which a Grignard reagent reacted with carbon disulfide to produce a dithio acid which was in turn, converted into an aldehyde derivative by action of semicarbazide, phenylhydrazine, or hydroxylamine. The aldehyde derivative was then hydrolyzed to the aldehyde in the usual way.

$\mathrm{RMgX} + \mathrm{CS}_2 \to \mathrm{RCSSH}$

 $RCSSH + H_2NCONHNH_2 \rightarrow RCH=NNHCONH_2 + H_2S + S$

When phenylhydrazine was used in the second step, Wuyts (11) found that in general at low temperatures a salt was first formed. As the temperature rose, this salt evolved hydrogen sulfide to give a thiohydrazide, which in turn became converted into the hydrazone with elimination of sulfur.

$$\begin{split} \mathrm{RCSSH} & \rightarrow \mathrm{RCSSNH_2NH_2C_6H_5} \rightarrow \mathrm{RCSNHNHC_6H_5} + \mathrm{H_2S} \\ \mathrm{RCSNHNHC_6H_5} \rightarrow \mathrm{RCH=\!NNHC_6H_5} + \mathrm{S} \end{split}$$

The transformation into the hydrazone was not always complete, for in many cases mixtures of the thiohydrazide and hydrazone resulted, and Wuyts (12) found that the nature of the group R in the dithio acid determined the course of the reaction. When R was aliphatic, alicyclic, or aliphatic-aromatic, thiohydrazides were formed and the presence of the hydrazone could not be established with certainty.

Hydroxylamine reacted with aromatic dithio acids to form oximes and in this way Wuyts and Koeck (13) prepared a number of aromatic aldoximes in yields of 70–90% based upon the dithio acids. However, when the dithio acid was aliphatic, alicyclic, or aliphatic-aromatic, the reaction proceeded beyond the oxime stage and nitriles were formed.

 $ArCSSH + H_2NOH \rightarrow ArCH = NOH + S + H_2S$ $RCSSH + H_2NOH \rightarrow RCN + S + H_2S + H_2O$

Hydrolysis of oximes or hydrazones to the aldehyde offers many difficulties and the yields are frequently very poor. Hydrolysis of a semicarbazone, on the other hand, usually proceeds smoothly and results in good yields of aldehydes. Consequently, as a practical method of synthesizing aldehydes, the reaction of the dithio acid with semicarbazide was the most feasible and Wuyts, Berman, and Lacourt (14) prepared a number of aldehydes in this way. The theoretical quantity of carbon disulfide was slowly added to an ethereal solution of a Grignard reagent; the reaction-mixture was allowed to stand for a few hours and was then decomposed with iced hydrochloric acid. The dithio acid was extracted from the ether solution with alkali and was immediately liberated from the alkaline solution with iced acid and taken up in ether. After drying the solution, the solvent was removed and the thio acid was dissolved in pyridine and poured into a warm solution of semicarbazide hydrochloride in pyridine. The semicarbazone was isolated, washed free of sulfur with carbon disulfide and benzene, and hydrolyzed to the aldehyde with dilute The free aldehyde was removed by steam distillation. hydrochloric acid.

The yields obtained by Wuyts and his collaborators were not clearly stated. The yields of aldehydes obtained from the semicarbazones were given, but the yields of the latter obtained from the thio acids were not always given. Moreover, the yield of dithio acid obtained from the aromatic halide was given in only one case, 46% for *p*-bromodithiobenzoic acid. Table I gives the results reported by Wuyts. The same differences in behavior were noticed between the aromatic and aliphatic dithio acids in their reaction with semicarbazide as were noticed in their reaction with phenylhydrazine. When the dithio acid was aromatic, a semicarbazone was formed, but when the dithio acid was aliphatic or alicyclic, the semicarbazide of the thio acid resulted.

Savariau (15) prepared aromatic aldehydes by action of Grignard reagents upon chloral.

$RMgX + CCl_{3}CHO \rightarrow RCHOHCCl_{3} \rightarrow RCHOHCOOH \rightarrow RCHO$

The secondary trichloro alcohols were transformed into hydroxy acids by action of alkali, and the latter, when heated with aqueous potassium carbonate, gave the aldehydes.

In addition to the reactions discussed above, in which Grignard reagents RMgX were converted into aldehydes RCHO, the literature contains a few examples in which two carbon atoms were introduced to give aldehydes RCH_2CHO . Späth (16), by a modification of the orthoformate synthesis, has used the reaction between ethoxyacetal and a Grignard reagent to prepare a number of substituted phenylacetaldehydes.

		YIELD OF ALDEHYDE, $\%$		
DITHIO ACID	ALDEHYDE	Based on semi- carbazone	Based on dithio acid	
Benzoic	Benzaldehyde	80.2	66.5	
p-Bromobenzoic	<i>p</i> -Bromobenzaldehyde	80.3	—	
<i>o</i> -Toluic	o-Tolualdehyde	83.4	81.5	
<i>p</i> -Toluic	<i>p</i> -Tolualdehyde	88.5	86 (?)	
α -Naphthoic	α -Naphthaldehyde	89.7	79.7	
β -Naphthoic	β -Naphthaldehyde	93.8		

TABLE I Yields of Aldehydes from Dithioacids

Hershberg (17) prepared phenylacetaldehyde and hexanal by the following novel series of reactions:

RMgBr (R = C₄H₉ or C₆H₅) + CH₂=CHCH₂Br
$$\rightarrow$$
 RCH₂CH=CH₂.
(82%, R = C₆H₅)
RCH₂CH=CH₂ \rightarrow RCH₂CHBrCH₂Br \rightarrow RCH₂CHOHCH₂OH
RCH₂CHOHCH₂OH + Pb(OCOCH₃)₄ \rightarrow RCH₂CHO + CH₂O

$$(\mathbf{R} = \mathbf{C}_4 \mathbf{H}_9) \cdot$$

$$C_{6}H_{5}CH_{2}CH = CH_{2} + (C_{6}H_{5}CO \cdot O)_{2}AgI \rightarrow C_{6}H_{5}CH_{2}CH(OCOC_{6}H_{5})$$
$$CH_{2}OCOC_{6}H_{5} (85\%)$$

 $\xrightarrow{\text{KOH}} C_{6}H_{5}CH_{2}CHOHCH_{2}OH (84\%) \xrightarrow{\text{Pb(OAc)}_{4}} CH_{2}O + C_{6}H_{5}CH_{2}CHO$ (72%)

Behal and Sommelet (18) prepared aldehydes of the type R_2 CHCHO from Grignard reagents RMgX by use of ethyl ethoxyacetate and Stoermer (19) also investigated this reaction, using ethyl ethoxyacetate end ethyl phenoxyacetate.

$$\begin{split} \mathrm{C_{2}H_{5}OCH_{2}COOC_{2}H_{5}} + 2 \ \mathrm{RMgX} &\rightarrow \mathrm{C_{2}H_{5}OCH_{2}C(OH)R_{2}}\\ \mathrm{C_{2}H_{5}OCH_{2}C(OH)R_{2}} \xrightarrow{\mathrm{H_{2}SO_{4}}} \mathrm{R_{2}C} \xrightarrow{} \mathrm{CHOC_{2}H_{5}} \rightarrow \mathrm{R_{2}C} \xrightarrow{} \mathrm{CHOH} \rightarrow \\ \mathrm{R_{2}CHCHO} \cdot \end{split}$$

The phenoxy compounds, which are more easily handled in the Grignard reaction, can be converted to the ethoxy compounds by heating under pressure with alcoholic potassium hydroxide; this is advantageous, because the ethoxy compounds are more readily converted into the aldehydes. Behal and Sommelet have also prepared aldehydes R¹R²CHCHO by action of Grignard reagents upon ethoxy ketones:

 $R^{1}MgX + R^{2}COCH_{2}OC_{2}H_{5} \rightarrow R^{1}R^{2}C(OH)CH_{2}OC_{2}H_{5} \rightarrow R^{1}R^{2}CHCHO$.

DISCUSSION

A consideration of the results in the literature, together with ease of manipulation and preparation of the reagents, led to the conclusion that the most promising methods for the synthesis of aldehydes from Grignard reagents, as far as yields and general applicability were concerned, were the syntheses from ethyl orthoformate, from ethoxymethyleneaniline, and from the dithio acids. Accordingly, a series of eight methylated aromatic aldehydes was prepared by each of the three methods, and the yields of aldehydes, together with the difficulties involved in each method. were compared. The halides-all bromo compounds-used were: oand p-bromotoluene, 3- and 5-bromopseudocumene, bromomesitylene, bromodurene, bromoisodurene, and bromopentamethylbenzene. All of the aldehydes, except pentamethylbenzaldehyde, were isolated and weighed either as the sodium bisulfite compounds or as semicarbazones. This was thought advisable since most of the aldehydes are liquids and the mechanical losses involved in handling small amounts of liquids might be great enough to vitiate the results of the comparisons. Pentamethylbenzaldehyde, a high-melting solid, was readily handled as such. The formation of bisulfite compounds and especially of semicarbazones is not a quantitative reaction; likewise, recovery of the aldehydes from these derivatives is not quantitative. Some data with respect to the recovery of aldehydes from their semicarbazones are shown in Table I; the yields of recovered aldehydes were between 80 and 94%. Hence yields of aldehydes figured 494

in this way represent values appreciably lower than the true ones and if one were interested in the preparation of an aldehyde for subsequent use as such, the most efficient procedure would involve a simple distillation of the aldehyde after it had been steam distilled from the reaction-mixture. Many aromatic aldehydes undergo autooxidation fairly rapidly; losses from this source can be considerable, but the bisulfite compounds and semicarbazones are quite stable and once obtained, can be handled without fear of deterioration.

HALIDE		YIELD OF GRIG- NARD REA- GENT, %	YIELD OF ALDEHYDE, %, FROM:		
	ALDEHYDE		Ethyl ortho- formate	Ethoxy- methyl- encani- line	Dithio acids
<i>p</i> -Bromotoluene	p-Tolualdehyde	94	74.4	82.2	23.3
o-Bromotoluene	o-Tolualdehyde	94	73.2	80.8	59.6
5-Bromopseudo- cumene	2,4,5-Trimethylbenzaldehyde	90	71.5	80.5	43.9
Bromomesitylene	2,4,6-Trimethylbenzaldehyde	91	57.3	63.8	2.2
Bromodurene	2,3,5,6-Tetramethylbenz- aldehyde		61.4	70.4	0
Bromopentamethyl- benzene	Pentamethylbenzaldehyde		43.1	60.1	0
3-Bromopseudo- cumene	2,3,6-Trimethylbenzaldehyde		61.2	65.4	
Bromoisodurene	2,3,4,6-Tetramethylbenzalde- hyde		60.2	64.3	—

TABLE II

YIELDS OF ALDEHYDES OBTAINED FROM GRIGNARD REAGENTS BY THREE METHODS

p-Tolualdehyde, o-tolualdehyde, 2,4,5-trimethylbenzaldehyde and 2,3,5,6-tetramethylbenzaldehyde were obtained in the form of their sodium bisulfite addition products.

2,4,6-Trimethylbenzaldehyde, 2,3,6-trimethylbenzaldehyde and 2,3,4,6-tetramethylbenzaldehyde were obtained in the form of their semicarbazones.

Pentamethylbenzaldehyde was obtained as the pure aldehyde.

SUMMARY OF RESULTS

Yields of aldehydes obtained by the three methods are given in Table II. With regard to the actual procedures used, certain observations were made which are of importance, and these will be discussed briefly.

A. The ethyl orthoformate synthesis. A complete review of this synthesis has been given in the previous paper (4) but the procedure used in the work reported there has been modified and improved. Bodroux (20)

reported that it was necessary to reflux the reaction-mixture after adding ethyl orthoformate, and it was found previously (4) that a period as long as fifteen hours was necessary. When the ester was added to the Grignard reagent, there was no immediate evidence of a reaction. In the present work, it was found that the reaction-mixtures, during the period in which they were refluxed, varied in behavior. In some instances a marked color change occurred, or a precipitate formed; in other cases there was little change in appearance throughout. Experiment showed that the best results were obtained when the reaction-mixture was refluxed for five hours; this was followed by the cautious removal of the ether on the steambath. During this process a point was reached at which a vigorous reaction set in; this point had to be watched for carefully, for it was necessary that this reaction should start, and at the same time not become uncon-The instant the vigorous reaction started, the vessel was trollable. plunged into an ice-bath; the reaction then proceeded quietly to comple-At the end of the reaction, the cooling bath was removed and the tion. product was processed. In the synthesis of p- and o- tolualdehyde, yields of 74 and 73%, respectively, were obtained when this procedure was followed; when the ether was partially removed, but not so far as to cause the vigorous reaction to set in, the yields were 51 and 47%, respectively. In view of these results, the hypothesis advanced by Wood and Comley (21) that the reaction proceeds in two stages, appears to be correct.

The reaction-product separated as a viscous, brown material which set to a hard solid mass on standing. It was decomposed by ice and 5 Nhydrochloric acid, and then the whole mixture—ether and aqueous layers —was refluxed on the steam-bath for a short time in order to decompose the acetal.

The great evolution of heat which occurs when the vigorous reaction sets in renders control of the reaction very difficult except when small amounts of material (0.1-0.2 moles) are involved, and this fact reduces somewhat the value of the ethyl orthoformate synthesis, at least for preparation of the aldehydes described in this paper. Otherwise, it is an admirable synthesis: the materials are cheap, the yields are excellent, the procedure is simple, and the synthesis is to be highly recommended for preparation of aldehydes from rare and costly aromatic halogen compounds, especially when the "entrainment" method has to be used for preparation of the Grignard reagent.

B. The ethoxymethyleneaniline synthesis. The yields of aldehydes obtained by this method were from 4 to 17% higher than those obtained by the orthoformate synthesis. When the reagents were mixed, a reaction ensued immediately. This reaction was not vigorous, but enough heat was evolved to keep the ether boiling gently while the reagents were being mixed. After addition of all of the reagent, the reaction-mixture was refluxed for a short period of time (usually 30 minutes) and was then decomposed with ice and 5 N hydrochloric acid and further processed as described above.

The fact that ethoxymethyleneaniline does not have to be "forced" to react with the Grignard reagent, and that the reaction does not involve sudden liberation of heat as is the case with ethyl orthoformate, no doubt accounts for the higher yields of aldehydes obtained. This, in turn, means that the reaction is adaptable to large quantities of material. The main difficulty with the synthesis, however, arises in the preparation and cost of the reagent, ethoxymethyleneaniline. This must be prepared from ethyl iodide and the silver salt of formanilide, and the silver salt must be carefully dried before it is used in the reaction with ethyl iodide. Monier-Williams (10) showed that if any moisture were present in the salt, the resulting ethoxymethyleneaniline undergoes more or less complete decomposition into alcohol and diphenylformamidine and is useless for the aldehyde synthesis. When operating with large quantities of material it is especially difficult to obtain the silver salt perfectly dry. In this work, the silver salt was dried in the air, then washed thoroughly with petroleum ether and finally dried over phosphorus pentoxide in a vacuum desiccator. Ethoxymethyleneaniline when properly prepared can be obtained in 74% over-all yield from formanilide and is a colorless liquid with a strong aromatic odor, boiling at 87-88° under 10 mm Monier-Williams states that his product was a light yellow oil, and he implies that it cannot be kept pure for more than a few days. The reagent used in this work was kept in a well stoppered bottle in the dark for eight days with no noticeable change; it could probably have been kept for a much longer period without deterioration, provided it was kept dry and in the dark. Comstock and Clapp (22) first prepared this substance; it was later prepared in 50% yield by Claisen (23) from ethyl orthoformate and aniline. The quality of the reagent is very important and the low yields of aldehydes obtained by previous investigators (2, 10) are doubtless due to use of an impure reagent. Monier-Williams (10) obtained o-tolualdehyde in 54% yield; Gattermann (2) obtained it in 55% yield. Gattermann did not distill his reagent and reports it as "golden yellow." In this work, using a colorless reagent, o-tolualdehyde was obtained in 81% yield.

C. The dithio acid synthesis. In this synthesis, three separate steps are involved:

(a) preparation and purification of the thio acid: $\mathrm{RMgX} + \mathrm{CS}_2 \rightarrow \mathrm{RCSSH}$

(b) reaction of the thio acid in pyridine solution with semicarbazide RCSSH + $H_2NCONHNH_2 \cdot HCl \rightarrow RCH=NNHCONH_2 + H_2S + S$

(c) hydrolysis of the semicarbazone to the aldehyde. The reaction of the Grignard reagent with carbon disulfide took place readily. The dithio acid was purified by extraction from the ether solution by 10%aqueous sodium hydroxide, followed by acidification of the alkaline solution. That purification of the thio acid was necessary was shown in the preparation of the aldehyde from 5-bromopseudocumene. When the crude thio acid was used, the yield of aldehyde was 31%; when the purified thio acid was used, the yield of aldehyde was 44%. The thio acids were all dark red oils; when the Grignard complex was decomposed some hydrogen sulfide was liberated, hence it is likely that the reaction between carbon disulfide and a Grignard reagent is accompanied by side reactions. The exact yields of this acids were not determined in this investigation, nor did Wuyts, the originator of the method, report any yields (11, 12, 13, 14) except p-bromodithiobenzoic acid, where the yield was 46%. When the pyridine solution of the dithio acid was boiled with semicarbazide hydrochloride, hydrogen sulfide and sulfur were gradually eliminated and a precipitate of the semicarbazone formed. The pyridine solution was diluted with water and the mixture of sulfur and semicarbazone was removed and washed free of sulfur with a mixture of benzene and carbon disulfide.

The yields of aldehydes obtained in this investigation by use of the thio acid method are in some respects difficult to explain. o-Tolualdehyde resulted in 59% yield, but the best yield of p-tolualdehyde was but 23%. Yet the yield of Grignard reagents in the two cases was the same—94%. The aldehyde from 5-bromopseudocumene, having one free ortho position, was obtained in 44% yield, but the one from bromomesitylene, with no free ortho position, was obtained in only 2% yield. It appears that the position of the methyl groups in the benzene ring has a great effect in this synthesis, and that not only is the ortho position of importance, but likewise the para position. Bromodurene and bromopentamethylbenzene could not be converted into aldehydes by this method.

When compared with the orthoformate synthesis and that from ethoxymethylene aniline, the dithio acid synthesis of aldehydes is distinctly inferior and in most cases is not to be recommended.

The Grignard reagents. Except for o- and p-bromotoluenes, all of the halides were converted into Grignard reagents using either the "full entrainment" method of Grignard (24) or the "partial entrainment" method (25) using ethyl bromide as the auxiliary halide. The recommendations of Gilman (26) as to the optimum conditions for formation of the reagent from the halides were followed, except that for preparation of the very insoluble Grignard reagents such as those from bromopentamethylbenzene and bromodurene, magnesium powder was used in place of turnings.

Addition of sodium bisulfite. p-Tolualdehyde (I), o-tolualdehyde (II), and 2,4,5-trimethylbenzaldehyde (duraldehyde) (III) formed bisulfite addition-compounds readily and in a few minutes when shaken with a saturated aqueous solution of sodium bisulfite. That 2,4,6-trimethylbenzaldehyde (IV) formed a bisulfite addition-compound incompletely and with difficulty was noticed by Gatterman (27); in the present work, a 46% yield of bisulfite addition-compound was obtained from this aldehyde after its concentrated ether solution was shaken (intermittently) with saturated aqueous sodium bisulfite for three weeks. On the other hand, 2,3,6-trimethylbenzaldehyde (V), which resembles IV except that it has an open para position, required only one day to form a bisulfite addi-



tion-product and after three days the yield was 82%. 2,3,5,6-Tetramethylbenzaldehyde (VI), again having an open para position but no open ortho position, formed a bisulfite compound in 93% yield after three days standing. The addition-product did not form in short periods of vigorous shaking with the reagent as do the addition-products of the unhindered aldehydes (I, II, III), but given time, it is formed in excellent yield. 2,3,4,6-Tetramethylbenzaldehyde (VII) which has its para as well as ortho positions occupied, did not begin depositing a bisulfite addition-compound until the third day and after standing with the reagent for two weeks (intermittent shaking), gave the addition-compound in but 40%yield. Pentamethylbenzaldehyde (VIII) failed to form any additioncompound even after three weeks.

It thus appears that an unsubstituted position ortho to the aldehyde group allows for ease and rapidity of formation of a sodium bisulfite addition-product, and under these circumstances the presence of a para substituent has little, if any effect. This has long been recognized, but what has not been noticed is that when both ortho positions are occupied, then the presence or absence of a group in the para position takes on considerable importance. In a *di-ortho* substituted aldehyde having a free para position, the addition-compound will not form rapidly, but given sufficient time, it will form in very good yield. If the aldehyde has both ortho positions and the para position occupied, the bisulfite compound will be formed with difficulty and in very poor yield. With the completely substituted aldehyde (VIII), no addition-product at all is obtained. The activation of the aldehyde group by the free para position, or the deactivation by a substituted para group, is also shown by the ease with which these aldehydes undergo autooxidation. 2,3,5,6-Tetramethylbenzaldehyde (VI) oxidizes in air much more rapidly than the 2,3,4,6-isomer (VII), while pentamethylbenzaldehyde (VIII) is fairly stable in the air, even after long exposure.

Pentamethylbenzaldehyde (VIII) obtained by the orthoformate synthesis and also *via* ethoxymethyleneaniline, melted at 143–148.5° and its oxime melted at 186–188°, in agreement with the values found by Smith, Webster, and Guss (25) and quite contrary to the value reported by Clément (28) who regarded the product (m.p., 130.5°) which he obtained by action of pentamethylphenylmagnesium bromide upon ethyl formate, as this aldehyde.

EXPERIMENTAL PART²

The halogen compounds. o-Bromotoluene (105 g., 61.4%) b.p., 178-180°, and p-bromotoluene (90 g., 37.5%) b.p., 176-178°, were prepared from the corresponding toluidines (107 g. and 150 g., respectively) by the procedure of Bigelow (29). 5-Bromopseudocumene (136 g., 68%), m.p., 71-72° was prepared from pseudocumene (120 g.) by the procedure of Smith and Moyle (30). Bromomesitylene (148 g., 74%), b.p., 105-107° under 16-17 mm., was prepared from mesitylene (120 g.) by the procedure of Smith (31). Bromodurene (183 g., 77%), m.p., 59-60°, was prepared from durene (150 g.) by the procedure of Smith and Moyle (32). Bromoisodurene (40 g., 76%), b.p., 105-108° under 2 mm., m.p., 7-8° was prepared from isodurene (33 g.) according to the directions of Smith and Moyle (32). Bromopentamethylbenzene (192 g., 83%), m.p., 159-160°, was prepared by slow addition of bromine (165 g.) to a solution of pentamethylbenzene (150 g.) in acetic acid (850 cc.) at room temperature. The product, which precipitated from the cooled solution, was removed, washed with water, dried, and recrystallized from chloroform-ethanol. 3-Bromopseudocumene was prepared by the Jacobsen rearrangement of the 5-bromo isomer (30, 33).

The Grignard reagents. The Grignard reagents were prepared under an atmosphere of nitrogen in a 500 cc. three-necked flask fitted with a stirrer, dropping-funnel, and condenser. All openings to the air were protected by calcium chloride guard tubes, and the nitrogen was passed through a wash bottle containing sulfuric acid before it entered the apparatus, which was carefully dried (baked) before use. The magnesium (powder) was washed well with 0.1 N hydrochloric acid, then successively

² Microanalyses by E. E. Renfrew and E. E. Hardy.

with water, acetone, and ether. It was dried in an oven and stored in a desiccator over calcium chloride. The yields of Grignard reagent were determined according to the procedure of Gilman and his collaborators (34). In calculating the yields of the reagent when the entrainment method was used, blank runs were made to determine the yield of ethylmagnesium bromide. This was found to be 95%; therefore, when ethyl bromide was used as the auxiliary halide, the yield of Grignard reagent from it was in each case assumed to be 95% and the proper amount was subtracted from the total Grignard reagent as found by titration. The yields are given in Table II. When yields are not given in Table II, it means that the Grignard reagent was insoluble and that a representative aliquot portion, free from magnesium powder, could not be obtained.

Bisulfite addition-compounds. 2,4,6-Trimethylbenzaldehyde (IV) (2.0 g.) in a small amount of ether was added to a concentrated aqueous solution of analytically pure sodium bisulfite and allowed to stand for three weeks with occasional shaking; yield 1.58 g. (46%) of the bisulfite compound. 2,3,6-Trimethylbenzaldehyde (V) (1.0 g.) similarly gave 1.40 g. (82%) of the addition-compound, but the time required was three days. 2,3,5,6-Tetramethylbenzaldehyde (VI) (2.0 g.) in three days gave 3.06 g. (93%) of addition-product. 2,3,4,6-Tetramethylbenzaldehyde (VII) (2.0 g.) gave 1.32 g. (40%) of addition-product in two weeks. Pentamethylbenzaldehyde (VIII) (2.0 g.) gave no addition-compound in three weeks. All of the aldehyde was recovered unchanged.

Procedures. One illustrative procedure will be given for each of the three methods, and any deviations or changes in connection with the other halides will be indicated by brief notes. A. The orthoformate procedure. The ethyl orthoformate was fractionated repeatedly and only the material boiling at 143-145° was used.

p-Tolualdehyde (I). The Grignard reagent was prepared in the usual way under nitrogen by adding a solution of p-bromotoluene (20.8 g., 0.122 moles) in ether (100 cc.) dropwise (45 min.) and with stirring to magnesium powder (3.3 g., 0.136 moles) suspended in ether (20 cc.). The reaction was started by addition of 0.5 cc. of ethyl bromide and a crystal of iodine, and after all the halide was added, the solution was refluxed for two hours. Ethyl orthoformate (22 g., 0.142 moles) in ether (30 cc.) was then rapidly (5 minutes) added and the reaction-mixture was refluxed for 5 hours. The ether was then distilled off on the steam-bath, and when practically all of it was removed, there was a sudden vigorous reaction. At this point the flask was quickly immersed in an ice-bath and allowed to remain there until all evidence of a reaction had disappeared. After standing overnight, ice (50 g.) and cold 5 N hydrochloric acid (125 cc.) were added, the small residual amount of ether was evaporated and the reaction-mixture was refluxed for thirty minutes on the steam-bath under an atmosphere of carbon dioxide. The aldehyde was then steam distilled in an atmosphere of carbon dioxide and the distillate was extracted three times with ether (60 cc. each time). The combined ether extracts were evaporated on the steam-bath to remove solvent and propionic aldehyde (b.p., 50°) and the residue of impure *p*-tolualdehyde was taken up in ether (20 cc.). The ethereal solution was then vigorously shaken with a freshly prepared, saturated aqueous solution of sodium bisulfite, the solid was filtered off, and the filtrate was shaken again with fresh bisulfite solution and filtered. The combined solids were washed with ether and dried. The substance weighed 20.3 g. (74.4%).

o-Tolualdehyde (II). o-Bromotoluene (18.8 g., 0.110 moles) was converted to the Grignard reagent as above, and the latter was then mixed with ethyl orthoformate (18.0 g., 0.123 moles) and processed as above. The bisulfite compound weighed 18.0 g. (73.2%).

2,4,5-Trimethylbenzaldehyde (III). 5-Bromopseudocumene (20 g., 0.10 moles) and ethyl bromide (4.35 g., 0.04 moles) were converted into Grignard reagents by the reaction with magnesium (4.0 g., 0.165 moles) as above, and then orthoformic ester (23 g., 0.155 moles) was added and the procedure was continued as above. The bisulfite compound weighed 18.1 g. (71.5%).

2,4,6-Trimethylbenzaldehyde (IV). Bromomesitylene (20.0 g., 0.10 moles), ethyl bromide (4.35 g., 0.04 moles), magnesium (4.4 g., 0.181 moles), ethyl orthoformate (25.0 g., 0.162 moles). After removing the ether and propionic aldehyde from the crude aldehyde, a solution of semicarbazide hydrochloride (15 g., 0.134 moles) and sodium acetate (20 g.) in the minimum amount of water was added and then enough ethanol was added to the mixture to bring the aldehyde into solution. After heating on the steam-bath for 20 minutes, the mixture was cooled and the semicarbazone (11.8 g., 57.3%) was removed and crystallized from ethanol. It then melted at 185–188°.

Anal. Calc'd for C11H15N8O: C, 64.35; H, 7.37.

Found: C, 64.19; H, 7.17.

2,3,6-Trimethylbenzaldehyde (V). 3-Bromopseudocumene (29 g., 0.146 moles) in ether (50 cc.), magnesium powder (7.7 g., 0.317 moles), and a crystal of iodine were mixed and to the mixture was added dropwise a solution of ethyl bromide (15.9 g., 0.146 moles) in ether (100 cc.). The green Grignard solution was refluxed for three hours and then ethyl orthoformate (44.4 g., 0.30 moles) in ether (30 cc.) was added. The mixture was processed as described above and the aldehyde was isolated as the semicarbazone, which weighed 18.3 g. (61.2%). The semicarbazone was heated for thirty minutes on the steam-bath with 5 N hydrochloric acid. Ether extraction removed the aldehyde, which was carefully fractionated under nitrogen. It was a colorless liquid which boiled at 113-114° under 10 mm., 115-116° under 12 mm., and which did not solidify at -15° .

Anal. Calc'd for C10H12O: C, 81.03; H, 8.17.

Found: C, 81.19; H, 8.51.

The oxime, prepared from 1.5 g. of the aldehyde by the procedure of Shriner and Fuson (35) apparently existed in two forms (syn and anti ?). The crude product was sublimed under reduced pressure and the sublimate was crystallized from dil. ethanol. It melted at 124-126°.

Anal. Calc'd for C10H13NO: C, 73.57; H, 8.03.

Found: C, 73.77; H, 8.05.

The semicarbazone, prepared from a small sample of the aldehyde and crystallized several times from ethanol, melted at 167-169°.

Anal. Cale'd for C₁₁H₁₅N₈O: C, 64.35; H, 7.37.

Found: C, 64.36; H, 7.21.

2, 3, 4, 6-Tetramethylbenzaldehyde (VII). Bromoisodurene (38.8 g., 0.182 moles) in ether (50 cc.), magnesium powder (9.8 g., 0.403 moles), and a crystal of iodine were converted into the Grignard reagent by adding ethyl bromide (19.8 g., 0.182 moles) in ether (130 cc.). Ethyl orthoformate (54.0 g., 0.365 moles) was added and the mixture processed as above. The aldehyde was isolated as the semicarbazone, which weighed 23.9 g. (60.2%). The aldehyde was regenerated from the semicarbazone as described above, and obtained as a colorless liquid which boiled at 136° under 10 mm., and froze at $+15^{\circ}$.

Anal. Calc'd for C₁₁H₁₄O: C, 81.43; H, 8.71.

Found: C, 81.54; H, 8.87.

The oxime was prepared as above, sublimed in vacuum, and crystallized several

times from aqueous ethanol. Apparently two forms were present in the crude oxime; the one obtained by the procedure outlined melted at 136-137°. The lower-melting form was not obtained pure; it melted, however, about 100°.

Anal. Calc'd for C11H15NO: C, 74.52; H, 8.54.

Found (form melting at 136-137°): C, 74.67; H, 8.14.

The *semicarbazone*, prepared from a small specimen of the pure aldehyde and crystallized several times from ethanol, melted at 183-185° to a liquid which quickly solidified and then remelted at 218-221° with evolution of gas.³

Anal. Calc'd for C₁₂H₁₇N₈O: C, 65.71; H, 7.86.

Found: C, 65.53; H, 7.77.

\$, \$, \$, \$, \$, 6-Tetramethylbenzaldehyde (VI). Bromodurene (16.0 g., 0.075 moles), ether (20 cc.), magnesium powder (4.0 g., 0.165 moles), a crystal of iodine, and ethyl bromide (8.12 g., 0.0745 moles) in ether (80 cc.) were processed as above and after addition of ethyl orthoformate (24.0 g., 0.162 moles) in ether (30 cc.), the procedure outlined above was followed. The aldehyde was isolated as the bisulfite compound, which weighed 12.27 g. (61.4%). The addition-product was decomposed with dilute hydrochloric acid, and the aldehyde was removed by ether extraction and distilled under nitrogen. It boiled at 135° under 11 mm. and froze at 20°. It was extremely difficult to obtain the pure aldehyde, as it autooxidized with great rapidity.

Anal. Calc'd for C₁₁H₁₄O: C, 81.43; H, 8.71.

Found: C, 80.38; H, 8.74.

Found (after redistillation and immediate analysis): C, 80.17; H, 8.73. The oxime, prepared as outlined above and crystallized repeatedly from aqueous ethanol, melted at $124.5-125.5^{\circ}$.

Anal. Calc'd for C₁₁H₁₅NO: C, 74.52; H, 8.54.

Found: C, 74.25; H, 8.65.

The semicarbazone, prepared from a specimen of redistilled aldehyde and crystallized repeatedly from ethanol, changed to a wax-like substance at $205-210^{\circ}$, and then melted at $268-270^{\circ}$ with decomposition.

Anal. Cale'd for C₁₂H₁₇N₈O: C, 65.71; H, 7.86.

Found: C, 66.11; H, 7.62.

Pentamethylbenzaldehyde (VIII). Bromopentamethylbenzene (15.0 g., 0.066 moles), ether (20 cc.), magnesium powder (3.7 g., 0.152 moles), and a crystal of iodine were converted into the Grignard reagent with ethyl bromide (7.25 g., 0.066 moles) in ether (100 cc.). Ethyl orthoformate (22 g., 0.141 moles) in ether (30 cc.) was added and the usual procedure was followed. The reaction-mixture, after decomposition with hydrochloric acid, was steam distilled and as soon as the aldehyde began to come over the process was stopped and the aldehyde was filtered from the cooled residue in the distilling flask. After sublimation in vacuum (130-140° under 2 mm.) and crystallization twice from ethanol, the substance weighed 5.0 g. (43.1%) and melted at 143-148.5°. The oxime melted at 187-188°.4

B. The ethoxymethyleneaniline procedure. Preparation of the reagent. A solution of sodium hydroxide (37.7 g., 0.942 moles) in water (50 cc.) was added dropwise and with vigorous stirring to a solution of formanilide (114 g., 0.942 moles) and silver

³ See Rapson and Shuttleworth (36) who observed a similar phenomenon in the case of the semicarbazone of methyl-*n*-amyl ketone.

⁴ These values are in agreement with those previously reported by Smith, Webster, and Guss (25), but the m.p. of the aldehyde does not agree with the value reported by Clement (28).

nitrate (160 g., 0.942 moles) in aqueous ethanol (50%, 800 cc.). It is essential to use pure alkali and to avoid an excess. The precipitate of silver salt was removed and sucked as dry as possible on the filter. The substance, somewhat sensitive to heat and light, holds water tenaciously but it must be thoroughly dried before it is used. The salt was spread out, protected from the light as much as possible, and allowed to dry in the air for three days. It was then stirred with petroleum ether (600 cc.), filtered, washed with dry ethyl ether, and allowed to dry in the air for a day. The washing process with petroleum ether and ethyl ether was then repeated, and the salt was finally dried in a vacuum desiccator over phosphorus pentoxide. The salt (200 g., 0.877 moles) was mixed with dry ether (600 cc.) and ethyl iodide (136.8 g., 0.877 moles) in a flask fitted with a calcium chloride guard tube, and allowed to stand at room temperature for forty-eight hours with occasional shaking. The precipitate of silver iodide was removed and washed with dry ether. The combined filtrate and washings were fractionated, giving 105 g. (74.2%) of ethoxymethyleneaniline, a *colorless* liquid which boiled at 87-88° under 10 mm.

The general procedure for the preparation of aldehydes was as follows: after preparation of the Grignard reagents (as described above), ethoxymethyleneaniline in ether was added dropwise to the solution at room temperature. The brownishred reaction-mixture was refluxed for thirty minutes and was then decomposed with ice and hydrochloric acid, refluxed thirty minutes to hydrolyze the anil, after which the aldehyde was isolated as described previously.

p-Tolualdehyde (I). p-Bromotoluene (15.0 g., 0.0877 moles), ether (100 cc.), magnesium powder (2.6 g., 0.107 moles), ethyl bromide (0.5 cc.), and a crystal of iodine were used to form the Grignard reagent. Ethoxymethyleneaniline (13.4 g., 0.0899 moles) in ether (30 cc.) was added and the reaction-mixture was processed as described. The aldehyde bisulfite compound weighed 16.2 g. (82.2%).

o-Tolualdehyde (II). Reagents: o-bromotoluene (15.0 g., 0.0877 moles), otherwise same as for I above. The aldehyde bisulfite compound weighed 15.88 g. (80.8%).

2,4,5-Trimethylbenzaldehyde (III). Reagents: 5-bromopseudocumene (10 g., 0.0502 moles), magnesium powder (2.5 g., 0.103 moles), ethyl bromide (3.8 g., 0.033 moles), ether (120 cc.). Ethoxymethyleneaniline (13.42 g., 0.090 moles) in ether (20 cc.). The product (bisulfite compound) weighed 10.2 g. (80.5%).

2,4,6-Trimethylbenzaldehyde (IV). Reagents: bromomesitylene (15.0 g., 0.0754 moles), magnesium powder (3.7 g., 0.152 moles), ethyl bromide (5.5 g., 0.0505 moles), ether (120 cc.). Ethoxymethyleneaniline (19.8 g., 0.133 moles) in ether (30 cc.). The product (semicarbazone) weighed 9.8 g. (63.8%).

2,3,6-Trimethylbenzaldehyde (V). Reagents: 3-bromopseudocumene (23.0 g., 0.116 moles), magnesium powder (6.3 g., 0.259 moles), ethyl bromide (12.6 g., 0.116 moles), ether (150 cc.). Ethoxymethyleneaniline (34.6 g., 0.232 moles) in ether (30 cc.). The product (semicarbazone) weighed 15.5 g. (65.4%).

2,3,5,6-Tetramethylbenzaldehyde (VI). Reagents: bromodurene (8.3 g., 0.039 moles), magnesium powder (2.3 g., 0.0946 moles), ethyl bromide (4.3 g., 0.039 moles), ether (100 cc.). Ethoxymethyleneaniline (11.7 g., 0.0785 moles) in ether (20 cc.). The product (bisulfite compound) weighed 7.3 g. (70.4%).

2,3,4,6-Tetramethylbenzaldehyde (VII). Reagents: bromoisodurene (15.0 g., 0.0704 moles), magnesium powder (3.9 g., 0.160 moles), ethyl bromide (7.63 g., 0.070 moles), ether (120 cc.). Ethoxymethyleneaniline (21.0 g., 0.141 moles) in ether (20 cc.). The product (semicarbazone) weighed 9.9 g. (64.3%).

Pentamethylbenzaldehyde (VIII). Reagents: bromopentamethylbenzene (10 g., 0.044 moles), magnesium powder (2.5 g., 0.103 moles), ethyl bromide (4.8 g., 0.044

moles), ether (100 cc.). Ethoxymethyleneaniline (13.2 g., 0.0885 moles) in ether (20 cc.). The product (aldehyde, m.p., $140-146^{\circ}$) weighed 4.66 g. (60.1%).

C. The dithio acid synthesis. The Grignard reagents were prepared as already described. Carbon disulfide (freshly distilled from phosphorus pentoxide) in ether, was added with stirring, to the Grignard reagent at room temperature. After stirring for an hour, the mixture was allowed to stand for three hours and was then decomposed with ice and 5 N hydrochloric acid. The ethereal layer was removed, and the aqueous layer was extracted thoroughly with ether. The combined ethereal solutions were then extracted three times with aqueous sodium hydroxide (10%, 75 cc. each time). The dithio acid was immediately liberated with iced dilute hydrochloric acid and taken up in ether. The ethereal solution was washed twice with water and most, but not all, of the ether was distilled off on the steam-bath. The residual ether was removed at room temperature under reduced pressure. All these operations, beginning with the decomposition of the Grignard product, were carried out as quickly as possible in order to minimize the time of contact of the thio acid with the air. The dithio acid was added to semicarbazide hydrochloride dissolved in pyridine and the solution was gradually heated to the boiling point. The original dark red solution became lighter in color, hydrogen sulfide was evolved and a mixture of sulfur and the semicarbazone separated. After refluxing for thirty minutes, the mixture was poured into cold water (600 cc.) and allowed to stand overnight. The solids were removed, dried, and then well stirred with a mixture of carbon disulfide (15 cc.) and benzene (15 cc.). The semicarbazone was then hydrolyzed as described above, and the aldehyde was removed by steam distillation and weighed as such, converted into the bisulfite compound, or reconverted into the semicarbazone. In all the experiments the crude semicarbazone initially formed was accompanied by small amounts of a material which could not be hydrolyzed by the hydrochloric acid. After crystallization from water, this substance melted at 250-252° with decomposition. While not fully identified, it is likely that the substance was hydrazodicarbonamide, frequently obtained in reactions in which semicarbazide is heated, and which Thiele and Stange (37) reported to melt at 244-245° with decomposition.

p-Tolualdehyde (I). Reagents: p-bromotoluene (20.0 g., 0.117 moles), magnesium powder (3.5 g., 0.144 moles), ethyl bromide (0.5 cc.), ether (120 cc.). Carbon disulfide (9.5 g., 0.125 moles) in ether (30 cc.). Semicarbazide hydrochloride (16.1 g.) in pyridine (80 cc.) and water (15 cc.). The product (bisulfite compound) weighed 6.12 g. (23.3%).

o-Tolualdehyde (II). Reagents: o-bromotoluene (15.4 g., 0.090 moles), magnesium powder (2.9 g., 0.119 moles), ethyl bromide (0.5 cc.), ether (120 cc.). Carbon disulfide (7.4 g., 0.0972 moles) in ether (30 cc.). Semicarbazide hydrochloride (16.1 g., 0.144 moles) in pyridine (80 cc.) and water (15 cc.). The product (bisulfite compound) weighed 12.03 g. (59.6%).

2,4,5-Trimethylbenzaldehyde (III). Reagents: 5-bromopseudocumene (20 g., 0.100 moles), magnesium powder (4.0 g., 0.165 moles), ethyl bromide (4.75 g., 0.0436 moles), ether (120 cc.). Carbon disulfide (11.0 g., 0.145 moles) in ether (30 cc.). Semicarbazide hydrochloride and pyridine as above. The product (bisulfite compound) weighed 11.13 g. (43.9%).

2,4,6-Trimethylbenzaldehyde (IV). Reagents: bromomesitylene (20.0 g., 0.100 moles), other reagents as for III above. The product (semicarbazone) weighed 0.45 g. (2.2%).

2,3,5,6-Tetramethylbenzaldehyde (VI). Reagents: bromodurene (15 g., 0.0704 moles), magnesium powder (3.9 g., 0.160 moles), ethyl bromide (7.7 g., 0.706 moles),

ether (120 cc.). Carbon disulfide in ether, and other reagents as above. No product (bisulfite compound) was obtained.

Pentamethylbenzaldehyde (VIII). Reagents: bromopentamethylbenzene (15.0 g., 0.066 moles), magnesium powder (3.7 g., 0.152 moles), ethyl bromide (7.25 g., 0.066 moles), ether (120 cc.). Other reagents as above. No product (aldehyde) was obtained.

SUMMARY

1. A series of methylated aromatic aldehydes has been prepared by each of three methods from the halides *via* the Grignard reagents.

2. Synthesis using ethoxymethyleneaniline gave the best yields (65–82%), and these yields were greater by 4–17% than those obtained using ethyl orthoformate (43–74%). Synthesis by way of dithio acids gave the poorest yields and in some cases gave no aldehyde at all.

3. The syntheses using ethoxymethyleneaniline and ethyl orthoformate are to be highly recommended as preparative methods for aromatic aldehydes from the corresponding halides. The former method is the easier to carry out, and is more adaptable to large scale preparations than the latter, but the reagent is expensive and must be carefully prepared and purified. The latter method has the advantage of cheap reagents, but the second stage of the reaction is so exothermic that it is difficult to control when quantities larger than 0.2 molar are used.

4. An important relationship has been found between para position in aromatic aldehydes and the ease and completeness with which bisulfite compounds are formed, as well as the ease with which the aldehydes undergo autooxidation.

5. Three new aldehydes, 2,3,6-trimethyl-, 2,3,4,6-tetramethyl-, and 2,3,5,6-tetramethyl- benzaldehydes, have been prepared and characterized by means of their semicarbazones and oximes.

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