XXXII.—*A Synthesis of Aldehydes by Grignard's Reaction.*

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WHEN two molecules of an organo-magnesium compound are allowed to react with one molecule of ethyl formate, the chief product of the reaction is a secondary alcohol, but if the formic ester is in excess, an aldehyde is formed according to the following equation (Gattermann and Maffezzoli, *Ber.*, 1903, **36**, 4152):

In addition to this, the first synthesis of aldehydes by Grignard's reaction, numerous other methods have been proposed by various investigators, which all depend on the action of organo-magnesium compounds on derivatives of ethyl formate. Bromoform, iodoform, ethyl orthoformate, disubstituted formamides, and isonitriles have all yielded aldehydes when allowed to react with organo-magnesium compounds. It might appear superfluous to look for a further synthesis of aldehydes along these lines, were it not for the fact that most of the above methods, although giving very good results with certain substances, are found to fail completely in other cases, or to give at most an exceedingly small yield. On this account it seemed desirable to find some other method by which better yields might be obtained.

The following synthesis depends on the action of organo-magnesium compounds on ethoxymethylaniline, $\text{C}_6\text{H}_5\text{N} \cdot \text{CH} \cdot \text{O} \cdot \text{C}_2\text{H}_5$, which leads in the first place not to the aldehydes themselves, but to the anhydro-compounds of these with aniline:

By the action of mineral acids, the anhydro-compounds are hydrolysed with formation of free aldehyde and aniline:

To determine the most favourable conditions of reaction, experi-

ments were first carried out with bromobenzene and *o*-bromotoluene, from which the yields of the respective aldehydes were more than 50 per cent. The method was then applied to the synthesis of α - and β -naphthaldehydes from α - and β -bromonaphthalenes, and the yields in both cases indicated a considerable improvement on the older methods. The latter of these naphthaldehydes has been comparatively little investigated, and several derivatives of it were therefore prepared.

My chief object was the preparation of a new class of aldehydes of the aromatic series, namely, those containing a thio-ether group attached to the benzene ring. The starting point for this synthesis was *p*-chloronitrobenzene, the chlorine atom of which is easily exchanged for the SH group. From the resulting *p*-nitrothiophenol, the ethyl ether was obtained, and this on reduction yielded the hitherto unknown *p*-thiophenetidine, the amino-group of which was diazotised and replaced by iodine. The resulting *p*-iodothiophenetole was used for the synthesis of *p*-thiophenetylaldehyde, $C_6H_5 \cdot S \cdot C_6H_4 \cdot CHO$.

For the preparation of ethoxymethyleneaniline, I made use at first of Claisen's method (*Annalen*, 1895, 287, 362), that is, the condensation of aniline with ethyl orthoformate, but this was afterwards abandoned in favour of the method given by Comstock and Kleeberg (*Amer. Chem. J.*, 1890, 12, 497), which consists in treating with ethyl iodide the silver derivative, $C_6H_5N:CH \cdot OAg$, of formanilide. The dry silver derivative is mixed with the calculated quantity of the iodide in absolute ether, the mixture left for twenty-four hours, after which the silver iodide formed is filtered off, and the ether evaporated. It is somewhat difficult to obtain the silver formanilide perfectly pure and dry when operating with large quantities. If any moisture is present, the resulting ethoxymethyleneaniline undergoes more or less complete decomposition into diphenylformamidine and alcohol, and cannot be used for the aldehyde synthesis. The silver salt, precipitated according to Comstock and Kleeberg's method, forms a finely-divided white powder, which decomposes on heating and gives up its moisture with difficulty under reduced pressure over calcium chloride. It was, however, found that the moist substance could be quickly and completely dried by treating it in a porcelain dish with light petroleum, which has the effect of expelling the water and causing it to collect in drops on the surface, whence it can be easily removed by pouring off the main portion and taking up the rest with pieces of filter paper. This action of the petroleum is evidently due to surface tension; the substance is found to have completely exchanged its water for petroleum, and if spread out on a porous plate may be obtained perfectly dry in a few minutes. It is very sensitive to the

action of light. An analysis of the salt dried in this way gave the following result :

0.5122 gave 0.2426 Ag. $\text{Ag} = 47.36$.

$\text{C}_7\text{H}_6\text{ONAg}$ requires $\text{Ag} = 47.34$ per cent.

The ethoxymethyleneaniline, obtained from the dried silver form-anilide, is a light yellow oil. When perfectly dry it can be kept for several days in a well-closed vessel, and need not be distilled before use.

Preparation of Benzaldehyde, o-Tolualdehyde, and α - and β -Naphthaldehydes.

Numerous experiments were made to ascertain the conditions under which the best results could be obtained. The method will therefore be given in the form in which it was eventually applied to the preparation of β -naphthaldehyde.

Five grams of β -bromonaphthalene dissolved in a small quantity of anhydrous ether are heated with 0.6 gram of magnesium filings in a reflux apparatus until almost all the magnesium is dissolved. The addition of traces of iodine and ethyl iodide helps the reaction considerably. Anhydrous ether is added until the volume is about 90 c.c., and the mixture heated again to boiling for a few minutes. A solution of 3.6 grams of ethoxymethyleneaniline in a small quantity of anhydrous ether is then added gradually from a dropping funnel to the warm ethereal solution of the magnesium naphthyl bromide, the liquid being well stirred during the addition. The product separates on the bottom and sides of the flask as a viscid, reddish-brown mass, soluble with difficulty in ether. The mixture is then carefully treated with well-cooled, moderately dilute hydrochloric acid in a large flask, the ether evaporated, and the β -naphthaldehyde together with naphthalene distilled over with steam. The aldehyde is separated from the naphthalene by means of a fairly-concentrated solution of sodium hydrogen sulphite, and is obtained pure by a second steam distillation. Thus obtained, it is a white, crystalline substance melting at 61° , and is only very slowly oxidised by the air. The yield amounted to 36 per cent., and in the case of benzaldehyde, o-tolualdehyde, and α -naphthaldehyde the yields were 46, 54, and 48 per cent. respectively.

It will be seen from the accompanying tables how large is the influence on the yield of (1) the concentration of the ethereal solution and (2) the temperature at which the reaction is effected.

(i) *Influence of Concentration.*

Temperature = 35°. Volume of ether = 50—60 c.c.

Amount of bromonaphthalene.	Yield of aldehyde.
2.5 grams	23 per cent.
5 "	27 "
10 "	18 "
14 "	14 "
30 "	5 "

(ii) *Influence of Temperature.*

Amount of bromonaphthalene = 5 grams. Volume of ether = 90 c.c.

Temperature.	Yield.
+ 35°	36 per cent.
- 15°	3 "

It is therefore evident that the reaction proceeds best at considerable dilution and at a fairly high temperature. An attempt was made to improve the yield still further by using boiling toluene as a solvent, as recommended by Bodroux in his synthesis with ethyl orthoformate (*Compt. rend.*, 1904, 133, 700), but in this case unsatisfactory results were obtained, the temperature being evidently too high.

The *bisulphite* compound of β -naphthaldehyde,

was obtained by dissolving the aldehyde in an excess of sodium hydrogen sulphite solution, and crystallises on cooling in lustrous, white plates. It is only sparingly soluble, 100 c.c. of moderately dilute sodium hydrogen sulphite solution dissolving 0.5 gram at the ordinary temperature.

0.1009 gave 0.0936 BaSO_4 . $S = 12.77$.

$\text{C}_{11}\text{H}_9\text{O}_4\text{NaS}$ requires $S = 12.31$ per cent.

The *phenylhydrazone*, $\text{C}_{10}\text{H}_7\cdot\text{CH:N}\cdot\text{NH}\cdot\text{C}_6\text{H}_5$, crystallises in colourless leaflets which melt at 205—206° with partial decomposition and become reddish-brown when exposed to light.

0.1126 gave 11.35 c.c. nitrogen at 16.2° and 750 mm. $N = 11.58$.

$\text{C}_{17}\text{H}_{14}\text{N}_2$ requires $N = 11.40$ per cent.

The *semicarbazone*, $\text{C}_{10}\text{H}_7\cdot\text{CH:N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$, forms long, white needles, soluble with difficulty in water and alcohol (m. p. 245°).

0.1389 gave 24.75 c.c. nitrogen at 18.4° and 744 mm. $N = 19.89$.

$\text{C}_{12}\text{H}_{11}\text{ON}_3$ requires $N = 19.74$ per cent.

The *azine*, $\text{C}_{10}\text{H}_7\cdot\text{CH:N}\cdot\text{N}\cdot\text{CH}\cdot\text{C}_{10}\text{H}_7$, crystallises in microscopic, yellow needles, melting at 232°.

0.0808 gave 6.50 c.c. nitrogen at 12° and 747 mm. $N = 9.38$.

$\text{C}_{22}\text{H}_{16}\text{N}_2$ requires $N = 9.11$ per cent.

β -Naphthylideneaniline, $\text{C}_{10}\text{H}_7\cdot\text{CH:N}\cdot\text{C}_6\text{H}_5$, is easily obtained by

warming together β -naphthaldehyde and aniline; it forms microscopic needles of a light yellowish-green colour and melts at 113° .

0.1997 gave 10.4 c.c. nitrogen at 16° and 750 mm. $N = 5.99$.

$C_{17}H_{13}N$ requires $N = 6.06$ per cent.

β -Naphthylacrylic acid, $C_{10}H_7 \cdot CH:CH \cdot CO_2H$, is best prepared by the condensation of β -naphthaldehyde with aniline or ammonia and malonic acid (Knoevenagel, *Ber.*, 1898, 31, 2585); when thus obtained, it forms small, white needles melting at 203° , which are fairly soluble in hot water.

0.1075 gave 0.3113 CO_2 and 0.0535 H_2O . $C = 78.96$; $H = 5.57$.

$C_{13}H_{10}O_2$ requires $C = 78.75$; $H = 5.10$ per cent.

β -Naphthylpropionic acid, $C_{10}H_7 \cdot CH_2 \cdot CH_2 \cdot CO_2H$, is obtained by reducing β -naphthylacrylic acid with sodium amalgam. It forms brilliant, white leaflets melting at 129 — 130° , and is much more easily soluble in hot water than the corresponding acrylic acid.

0.1961 gave 0.5619 CO_2 and 0.1104 H_2O . $C = 78.14$; $H = 6.31$.

$C_{13}H_{12}O_2$ requires $C = 78.00$; $H = 6.00$ per cent.

The nitration of the aldehyde was effected by adding the finely-powdered substance gradually to a well-cooled solution of potassium nitrate (1 mol.) in concentrated sulphuric acid. After standing for three hours at 0° , the liquid was poured into ice and the precipitate collected. By repeated extraction with xylene, treatment with animal charcoal, and precipitation with ligroin, a small quantity of a crystalline substance was obtained which, on recrystallisation from xylene, formed silky, white needles melting at 206.5° . On analysis, it proved to be a dinitro- β -naphthaldehyde, $C_{10}H_5(NO_2)_2 \cdot CHO$.

0.1372 gave 14.2 c.c. nitrogen at 23° and 744 mm. $N = 11.36$.

$C_{11}H_6O_5N_2$ requires $N = 11.41$ per cent.

From the xylene and ligroin filtrates, a very small quantity of a substance crystallising in long, yellow needles melting at 139 — 140° was obtained, together with much unchanged aldehyde. The amount was too small for analysis, but there can be little doubt that the compound is a mononitro-aldehyde. Both substances give azines of high melting point, that of the dinitro-aldehyde being slightly soluble in hot water. They are both decomposed on warming with caustic soda, giving a yellow coloration, and with acetone and caustic soda they give a dark red coloration, but no indigo. This seems to show that neither of them is an *o*-nitro-aldehyde.

Preparation of p-Thiophenetylaldehyde.

Willgerodt showed in 1885 (*Ber.*, 1885, 18, 331) that *p*-nitrothiophenol, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SH}$, may be obtained by the action of alcoholic potassium hydrosulphide on *p*-chloronitrobenzene, and by the action of sodium and methyl or ethyl iodide on *p*-nitrothiophenol, Blanksma (*Rec. Trav. chim.*, 1901, 20, 403) has obtained *p*-nitrothioanisole, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{S} \cdot \text{CH}_3$, and *p*-nitrothiophenetole, $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{S} \cdot \text{C}_2\text{H}_5$. *p*-Nitrothiophenol, prepared by Willgerodt's method, was heated with the calculated quantity of sodium ethoxide and ethyl iodide in a reflux apparatus until the dark red colour of the liquid changed to light yellow. On filtering from the sodium iodide and allowing to cool, long, yellow needles of the thio-ether separated out, and on adding water to the mother liquor the remainder was obtained as an amorphous or semi-crystalline mass. The pure substance melts at 44° .

The *p*-nitrothiophenetole was reduced by warming gently with tin and hydrochloric acid on the water-bath. A violet, crystalline substance was formed which is probably a compound of the amine hydrochloride with stannous chloride. The liquid was made alkaline with sodium hydroxide and the *p*-thiophenetidine, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{S} \cdot \text{C}_2\text{H}_5$, distilled over with steam. On distillation it was obtained as a faintly yellow oil boiling at $280\text{--}281^\circ$ with a somewhat unpleasant odour. The crude oil, however, before it has been distilled, has hardly any odour. The yield is 93 per cent.

0.2058 gave 0.3139 BaSO_4 . $\text{S} = 20.96$.

$\text{C}_8\text{H}_{11}\text{NS}$ requires $\text{S} = 20.91$ per cent.

The acetyl compound of the amine, thiophenacetin,

prepared by warming the amine with acetic anhydride and precipitating with water, crystallises from dilute alcohol in flat, colourless needles several centimetres in length. On account of its insolubility in cold water, this substance does not exert the physiological action of phenacetin.

0.1323 gave 0.1587 BaSO_4 . $\text{S} = 16.50$.

$\text{C}_{10}\text{H}_{13}\text{ONS}$ requires $\text{S} = 16.41$ per cent.

The amine was dissolved in dilute hydrochloric acid and diazotised with a solution of sodium nitrite. The clear diazo-solution was treated with the calculated quantity of potassium iodide in water, and the *p*-iodothiophenetole, $\text{I} \cdot \text{C}_6\text{H}_4 \cdot \text{S} \cdot \text{C}_2\text{H}_5$, which separated out was obtained on distilling with steam as a reddish-yellow oil. When distilled under atmospheric pressure, the substance was almost completely decomposed, but by distilling in a partial vacuum it was obtained as a faintly

yellow oil of pleasant odour boiling at 146—147° under 11 mm. pressure. The yield was 85 per cent.

0.2234 gave 0.1938 BaSO₄ and 0.1994 AgI. S = 11.93; I = 48.23.

C₈H₉IS requires S = 12.12; I = 48.10 per cent.

p-Thiophenetylaldehyde, C₂H₅·S·C₆H₄·CHO, was prepared from the iodo-compound by the method given above for β-naphthaldehyde, the best results being obtained with 5 grams of the iodo-compound and 70 c.c. of ether. It is a yellow liquid of very characteristic and not unpleasant odour boiling at 244—245°; the yield is 32 per cent. It is remarkable that the boiling point is not very different from that of the corresponding *p*-phenetylaldehyde; from the analogy of other nearly related oxy- and thio-compounds, a higher boiling point would be expected.

The *azine* of *p*-thiophenetylaldehyde,

is very characteristic, crystallising from glacial acetic acid in well-defined, golden-yellow leaflets which melt at 152°; it gives with concentrated sulphuric acid an intense red coloration, a reaction which is also shown by other compounds of this series.

0.1154 gave 0.1653 BaSO₄. S = 19.71.

0.1779 „ 14.3 c.c. nitrogen at 26° and 740.3 mm. N = 8.63.

C₁₈H₂₀N₂S₂ requires S = 19.51; N = 8.54 per cent.

The *phenylhydrazone*, C₂H₅·S·C₆H₄·CH:N·NH·C₆H₅, crystallises from dilute alcohol in colourless plates which melt at 115° and are coloured reddish-brown by exposure to light.

0.1120 gave 0.1033 BaSO₄. S = 12.68.

C₁₅H₁₆N₂S requires S = 12.50 per cent.

The *semicarbazone*, C₂H₅·S·C₆H₄·CH:N·NH·CO·NH₂, forms long, white needles melting at 193°; it is only sparingly soluble in dilute alcohol.

0.1717 gave 0.1819 BaSO₄. S = 14.55.

C₁₀H₁₃ON₃S requires S = 14.36 per cent.

The aldehyde combines even in the cold with *p*-aminothiophenetole to form a solid condensation product, C₂H₅·S·C₆H₄·CH:N·C₆H₄·S·C₂H₅; it crystallises from alcohol in large leaflets of a faint golden-yellow colour (m. p. 114—115°).

0.2263 gave 0.3522 BaSO₄. S = 21.37.

C₁₇H₁₉NS requires S = 21.26 per cent.

The oxidation of the aldehyde was carried out with alkaline permanganate, the mixture being gently warmed on the water-bath.

Contrary to expectation, the acid $C_2H_5 \cdot S \cdot C_6H_4 \cdot CO_2H$ was not obtained, but a further oxidation took place giving phenylethylsulphone-carboxylic acid, $C_2H_5 \cdot SO_2 \cdot C_6H_4 \cdot CO_2H$. This acid forms white leaflets soluble in water and melting at 211° ; an analysis of the silver salt gave the following result :

0.1975 gave 0.0664 Ag. $Ag = 33.62$.

$C_9H_9O_4S$ Ag requires $Ag = 33.64$ per cent.

In conclusion, I wish to express my sincere thanks for the assistance received during the progress of the work from Professor Ludwig Gattermann, Director of the Chemical Laboratory at Freiburg University. Further investigations on the thioanisyl and thio-phenetyl compounds are being carried out in the above laboratory.