[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Branched-Chain Fatty Acids. IV. A Further Study of the Preparation of Ketones and Keto Esters by Means of Organocadmium Reagents

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In previous papers[1] of this series it has been shown that keto esters may be conveniently prepared by the reaction between a dialkylcadmium compound and the ester acid chloride of a dibasic acid. Although conditions have been defined[2] under which there may usually be obtained yields of keto esters in the range 70–84%, several of the variables in this reaction have not been properly evaluated. Since the reaction continues to be useful in the synthesis of branched-chain acids and since several other investigators have utilized the method during the past two years, a more critical study of the reaction has been undertaken.

When it was reported[2] that the yield of keto ester is greatly improved by running the reaction in benzene, rather than ether, it was emphasized that this change of solvent nearly eliminates the formation of di-ester arising from reaction of the ester acid chloride with ether. It was implied that the increased yield of keto ester is due to reduction of di-ester formation; however, a critical examination of the data shows this to be only partly true, for the increase in yield of keto ester is much larger than the decrease in the amount of di-ester formed. Actually, the increased yield in benzene has now been found to depend largely on two other factors.

The first of these factors is a mechanical one. The reaction complex obtained when the keto ester is formed is a heavy precipitate insoluble in both benzene and ether. In ether as solvent, the agglutination of this precipitate often stops the stirrer before reaction is complete, and further heating of the unstirrable mass is of no value in promoting the desired reaction. In benzene as solvent, the precipitate rarely forms a stirrer-stopping mass, and in the only case (ethyl 10-ketohendecanoate) where the stirrer was stopped the reaction was so much more rapid at the temperature of refluxing benzene that the reaction was complete before the stirrer was stopped. Data illustrating this effect are assembled in Table I on the preparation of methyl 4-keto-7-methyloctoate. It should be emphasized that this difficulty varies with the ketone being prepared and is, in general, much more troublesome with keto esters than with simple ketones.

The second factor effecting an improvement in yield in benzene as solvent was encountered in connection with the preparation of α-chloroketones, a type of synthesis recently reported by Bunnett and Tarbell.[3] These investigators, using ether as solvent, prepared α-chloroketones in 15.5–26% yield (based on alkyl bromide), by the reaction of dialkylcadmium reagents with chloroacetyl chloride. Using benzene as solvent, we have obtained 1-chloro-2-hexanone in 51% yield and 1-chloro-2-hexadecanone in 33% yield. In the latter preparation, there was obtained an amount of tetradecane corresponding to 37% of the tetradecyl bromide used. The reaction was carried out in a nitrogen atmosphere in a rigorously dry apparatus, the reaction between the ditetradecylcadmium and chloroacetyl chloride was shown to be complete, and the chloroacetyl chloride was shown to contain practically no acid. Thus, it was indicated that the only possible source of the large amount of tetradecane is reaction between the ditetradecylcadmium and the enol form of the ketone being prepared. If this is correct, the hydrocarbon should be isolable before the organometallic complex is decomposed. In order to further investigate this matter, a reaction was carried out between dibutylcadmium and α-chloropropionyl chloride, using benzene as solvent. During the addition of the acid chloride and its subsequent reaction the gas evolved was collected in a trap cooled by solid carbon dioxide. On redistillation of the material collected in the trap, there was isolated a quantity of nearly pure butane corresponding to 17% of the butyl bromide used for the preparation. The yield of 2-chloro-3-heptanone was 43%, in contrast with the 13% yield obtained by Bunnett and Tarbell[3] in the preparation of 2-chloro-3-pentadecanone. When this experiment was repeated, using ether as solvent, the yield of 2-chloro-3-heptanone was only 29%, and the butane isolated corresponded to 23% of the bromide used. Separation of the butane from ether presumably entailed some loss. Thus, the loss of dialkylcadmium reagent through enolization of the ketone is greater in ether than in benzene. This side reaction is much more serious in the preparation of α-chloroketones than in the preparation of simple ketones due to the effect of the chlorine atom in promoting enolization. The yields obtained in the preparation of simple ketones are such as to indicate very little loss through enolization.

For further investigation of the enolization reaction, a hot benzene solution of dibutylcadmium was treated with an equivalent amount of 1-chloro-2-hexanone. During the highly exothermic reaction which ensued, there was evolved an amount of butane corresponding (after redistillation) to 70% of the butyl bromide used for preparing the dibutylcadmium. On working up the reaction, there was isolated only 9.5% of the chloroketone

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[1] Preceding paper in this series, Cason, Adams, Bennett and Register, THIS JOURNAL, **66**, 1764 (1944).

[2] Cason and Prout, *ibid.*, **66**, 46 (1944).

[3] Bunnett and Tarbell, *ibid.*, **67**, 1944 (1945).

used, the remainder of the product being high boiling or non-volatile at 4 mm. pressure. Since most of the dibutylcadmium was converted to butane the chloroketone must have been lost by some type of self-condensation, possibly alkylation of the enolate ion.

Since the Grignard reagents from which the cadmium derivatives are prepared are formed conveniently only in ether, but the yields of ketone are much better in benzene, partly on account of its higher boiling point, it was thought that dibutyl ether might be a useful solvent for the preparation of keto esters. This should be especially true of methyl or ethyl ketones, which are not separable by distillation from the corresponding ethyl esters formed from diethyl ether but are separable from the corresponding butyl esters. This solvent was used for the preparation of ethyl 10-ketohendecanoate, but proved unsatisfactory. The Grignard reagent reacts very slowly with cadmium chloride in butyl ether and, in some manner, this solvent promotes further reaction of the dialkylcadmium reagent with the keto ester. Much high-boiling material was obtained and the best yield of keto ester was only 57%, in contrast with the 84% yield obtained in benzene as solvent.

In the paper by Gilman and Nelson[4] in which the use of dialkylcadmium reagents was first recommended for the preparation of ketones, it is reported that iodides give much poorer yields in this type of preparation than do bromides. We have verified this finding and also found that chlorides are somewhat inferior to bromides. In the preparation of methyl 4-ketooctoate from dibutylcadmium and β-carbomethoxypropionyl chloride, the yields from butyl bromide, chloride and iodide were, respectively, 79.5, 63 and 45%.

Gilman and Nelson[4] reported the preparation of a variety of ketones and the yields are quite variable in comparison with the rather consistent yields obtained in the present work. This erratic behavior of the reaction is also evident from the report by Suter and Weston[5] of yields of 26 and 34% in the preparation of propiophenone from benzoyl chloride and diethylcadmium, a preparation in which Gilman and Nelson reported a 50% yield. This compound was obtained by the latter workers in 76% yield when the reagents were propionyl chloride and diphenylcadmium. On the basis of these results, they concluded that in such preparations it is preferable for the aromatic radical to be in the cadmium reagent rather than in the acid chloride. Since this seems improbable these preparations have been repeated, using benzene as solvent and following the optimum procedure as now developed. The yields of propiophenone were 81% when diphenylcadmium was used and 76% when diethylcadmium was used. The slightly lower yield in the latter case was due to loss of some diethylcadmium during distillation of ether, for when an excess of diethylcadmium was employed (as in the experiments of Gilman and Nelson) the yield was 84.5%.

It is indicated that the erratic results previously reported may be due in part to the use of ether as solvent, but are largely due to two recommendations included in the procedure of Gilman and Nelson. It was recommended that the cadmium chloride be added to an ice-cold solution of the Grignard reagent and the mixture stirred one half hour after removal of the ice-bath before proceeding with addition of the acid chloride. Only the more reactive Grignard reagents, such as those from methyl and aromatic radicals, are completely converted to the cadmium derivatives under these conditions, even with finely-ground cadmium chloride. The mixture should be heated under reflux until a negative Gilman test[4,6] for Grignard reagent is obtained, usually twenty to fifty minutes in boiling ether. It was also recommended by Gilman and Nelson that the mixture of cadmium reagent and acid chloride be heated under reflux in ether for one hour. The reaction is complete under these conditions only if the cadmium reagent or the acid chloride or both are relatively reactive. These factors are illustrated by the data on preparation of methyl 4-keto-7-methyloctoate as well as that of several other ketones described herein.

Further efforts to obtain a good yield from a di-*s*-alkylcadmium reagent have failed. It also has been found that glutaric anhydride gives no better yield in the reaction with a dialkylcadmium reagent than does succinic anhydride[2], so the poor yield with succinic anhydride cannot be ascribed to its low solubility in benzene or ether.

In summary, it may be stated that in the preparation of any type of simple or substituted ketone not containing a highly reactive keto group,[4] if the cadmium reagent does not contain a secondary or tertiary alkyl radical a yield of at least 50% based on acid chloride may be expected, and in most cases yields of 70–84% are obtainable. The yields on the basis of halide are about 20% lower since the maximum useful ratio of acid chloride to bromide is 0.8.

Experimental

All starting materials and reaction products were distilled, unless otherwise specified, through a one-half meter column containing a tantalum wire spiral of the Podbielniak type. The column was equipped with a heated jacket and partial reflux head. All cadmium reactions were carried out in an atmosphere of nitrogen. The cadmium chloride was a C. P. grade which had been dried to constant weight at 110°, thoroughly ground and stored in a desiccator over calcium chloride. The alkyl halides were purified commercial products, except for 2-bromopentane[1] and tetradecyl bromide.[2] The acid chlorides were purified commercial products except for α-chloropropionyl chloride which was obtained in 25% yield from α-chloropropionic acid and phosphorus trichloride. The ester acid chlorides of succinic and sebacic acids were prepared as

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[4] Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[5] Suter and Weston, THIS JOURNAL, **61**, 234 (1939).

[6] Gilman and Schulze, *ibid.*, **47**, 2002 (1925); Gilman and Heck, *ibid.*, **52**, 4949 (1930).

previously described.[2] It has been found that ester acid chlorides may be stored for years without deterioration if moisture is excluded; however, the half esters of dibasic acids undergo appreciable disproportionation to di-ester and di-acid, on long storage.

Methyl 4-Keto-7-methyloctoate.—The general method of preparation previously described[2] was followed, using in all runs 0.2 mole of isoamyl bromide, 0.2 mole of magnesium turnings, 0.107 mole of anhydrous cadmium chloride, and 0.16 mole of β-carbomethoxypropionyl chloride. Variations from the previously-used conditions are specified under Table I.

TABLE I

PREPARATION OF METHYL 4-KETO-7-METHYLOCTOATE

Run no.	Yield, g.	%	Di-ester, g.	Distn. residue, g.	Solvent
1	12.0	40.5	1.1	5.5	Benzene
2	23.3	78.7	0.7	1.4	Benzene
3	17.1	57.8	2.5	1.3	Ether
4	11.7	39.4	3.5	4.7	Ether
5	17.6	59.4	1.5	2.7	Benzene

Run 1: Ether distilled rapidly five minutes after addition of cadmium chloride, thus allowing insufficient time for cadmium chloride to react. In all other runs, solvent was not removed until after a negative Gilman test was obtained. This was obtained after 30–35 minutes stirring under reflux. Run 2: Reaction with the acid chloride continued for one hour in refluxing benzene, with stirring. Run 3: Reaction continued for two hours in refluxing ether, with stirring. Run 4: Reaction continued for forty five minutes in refluxing ether with stirring, the stirrer being stopped at the end of this time. Heating without stirring continued an additional twenty-four hours. Run 5: Reaction continued for two hours at 30–40°, with stirring, the stirrer being stopped at the end of this time. At time stirrer was stopped, reaction was still exothermic. Reaction continued one hour after stirrer stopped.

Ethyl 10-Ketohendecanoate.[2]—The yield was improved about 10% by some modification of the previously-described procedure. Procedure A is recommended as the best developed for preparation of methyl keto esters.

A. Benzene as Solvent.—A Grignard reagent was prepared from excess methyl bromide and 4.9 g. (0.2 mole) of magnesium in 100 cc. of ether. To the ice-cold solution was added, during five minutes, 19.6 g. of cadmium chloride, then the mixture was stirred under reflux until a negative Gilman test was obtained (fifteen to twenty minutes). Ether was distilled rapidly from the stirred mixture by heating on a steam-bath until distillation became slow and a nearly dry residue remained. After addition of 65 cc. of benzene, distillation was continued until an additional 25 cc. of distillate had been collected. There was then added 120 cc. of benzene, the stirred solution was heated to boiling and there was added without external heating 24.9 g. (0.1 mole) of ω-carbethoxynonoyl chloride in 30 cc. of benzene as rapidly (two minutes) as consistent with control of the exothermic reaction. Heating under reflux with stirring was continued for ten minutes, at which time the stirrer was stopped by the mass of precipitate. Ten minutes later the reaction was worked up as previously described; yield of ethyl 10-ketohendecanoate, b. p. 147.5–149.5° (4 mm.), 19.1 g. (83.7%). The distillation residue weighed 2.7 g.

Saponification of this sample of keto ester gave 15.7 g. (94%) of 10-ketohendecanoic acid, m. p. 54–57°. From the distillation residue could be isolated only 0.1 g. of sebacic acid, m. p. 123–128°. This corresponds to about 0.5% di-ester in the keto ester.

B. Butyl Ether as Solvent.—A Grignard reagent was prepared from excess methyl bromide and 0.25 mole of magnesium in 125 cc. of anhydrous butyl ether, at a temperature of 40–50°. After addition of 0.134 mole of cadmium chloride the mixture was stirred at 55–65° for one hour and at 75–85° for an additional fifteen minutes, but the Gilman test was still positive. After an additional 0.11 mole of cadmium chloride had been added and stirring at 75–85° continued for an additional fifteen minutes a negative Gilman test was obtained. A solution of 49.7 g. (0.20 mole) of ω-carbethoxynonoyl chloride in 50 cc. of butyl ether was added during one minute at an initial temperature of 55°. After seven minutes the temperature had risen to 106° and the stirrer was stopped. The reaction was worked up ten minutes later and the yield of keto ester was 25.1 g. (55%), b. p. 148–149° (4 mm.). A fraction boiling at 142–170° (2.5 mm.) was also collected. After saponification of this fraction, which should contain any butyl ethyl sebacate formed in the reaction, there was isolated 0.3 g. of sebacic acid which, after recrystallization from water and from acetone–benzene, melted at 131–132° (no depression with an authentic specimen of sebacic acid).

When this preparation was repeated except that the acid chloride was added in benzene and the reaction temperature was maintained at 35–50°, the yield was 57%. In both runs, there was a large distillation residue, 10–12 g.

Methyl 4-keto-5-methyloctoate was prepared as previously described[2] except that the reaction between di-2-amylcadmium and β-carbomethoxypropionyl chloride was continued for twenty-four hours at −5 to −10°. The yield of keto ester boiling at 129.5–130.5° (22 mm.) was only 10.4%.

5-Ketononoic acid was prepared from dibutylcadmium and glutaric anhydride by the procedure described for the preparation of 4-keto-7-methyloctoic acid,[2] except that the anhydride was added in benzene solution; yield, 30.5%; b. p. 152–154° (4.5 mm.); m. p. 40–44° (literature,[7] m. p. 43.5°).

Methyl 4-ketoöctoate[8] was prepared from dibutylcadmium and β-carbomethoxypropionyl chloride by the procedure described for methyl 4-keto-7-methyloctoate, Run 2. When the cadmium derivative was prepared from butylmagnesium bromide, the reaction proceeded normally and the yield was 79.6%, b. p. 115–117° (14 mm.). When butylmagnesium chloride was used, the reaction mixture became semi-solid thirty minutes after addition of the acid chloride and stirring was largely ineffective; yield, 62.8%. When butylmagnesium iodide was used, a heavy precipitate stopped the stirrer six minutes after addition of the acid chloride, and the yield was only 44.7%.

Propiophenone.—A. A solution of diphenylcadmium in benzene (110 cc.) was prepared in the usual manner from 4.9 g. of magnesium, 32.4 g. of bromobenzene and 19.5 g. of cadmium chloride. To this solution, cooled to 10°, there was added during three minutes a benzene (30 cc.) solution of 14.8 g. of propionyl chloride, external cooling with an ice-bath being used to prevent the temperature from rising above 40°. The mixture was stirred at 25–35° for two hours, the reaction not being exothermic after fifteen minutes. There was no difficulty with a precipitate stopping the stirrer. The reaction was worked up in the manner described for keto esters,[2] and there was obtained 17.3 g. (80.8% based on acid chloride) of propiophenone, b. p. 100–103° (16 mm.). When the acid chloride solution was added to the dialkylcadmium solution at the boiling temperature and heating under reflux continued for one hour the yield was 70.5%. Thus, a lower reaction temperature seems desirable in cases where there is no difficulty with a stirrer-stopping precipitate.

B. To a cold solution of diethylcadmium in benzene (170 cc.), prepared from 0.3 mole of ethyl bromide, there was added during two minutes a benzene (50 cc.) solution of 0.24 mole of benzoyl chloride, the temperature being kept at 5–14° by cooling in an ice-bath. The mixture was stirred for one and one-half hours at 40–45°, the reaction remaining exothermic for forty minutes. The yield of propiophenone was 75.7%, based on acid chloride. When the reaction was carried out in the same manner except that 0.21 mole of benzoyl chloride was used, the yield based on acid chloride was 84.4%.

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[7] Franke, *et al.*, *Monatsh.*, **69**, 167 (1936).

[8] Blaise and Koehler, *Bull. soc. chim.*, [4] **7**, 226 (1910).

1-Chloro-2-hexanone.—A solution of dibutylcadmium in benzene (175 cc.), prepared from 0.35 mole of butyl bromide, 0.35 mole of magnesium, and 0.188 mole of cadmium chloride, was cooled to 5°, and with continued cooling in an ice-bath there was added during forty seconds a benzene (70 cc.) solution of 0.35 mole of chloroacetyl chloride. The temperature rose to 12°, then began to drop; so cooling was moderated and the mixture was stirred at 15–20° for three hours, at which time the reaction was still exothermic. After stirring an additional one and one-half hours at 20–25°, the reaction mixture was worked up as usual except that a sodium bicarbonate wash was substituted for the usual sodium carbonate wash. The yield of chloroketone boiling at 71.0–72.5° (15 mm.) was 23.9 g. (50.8% based on bromide). When only 0.28 mole of chloroacetyl chloride was used the yield on the basis of butyl bromide remained essentially the same. The same yield was also obtained by conducting the reaction at 30–40° for two hours, but when the reaction temperature was that of refluxing benzene the yield was 36.8% when the reaction time was fifteen minutes and was 30% when the reaction time was one hour and forty minutes. In all of these runs, the magnesium remaining after formation of the Grignard reagent was also present at the end of the reaction; so its removal is unnecessary.

1-Chloro-2-hexadecanone.—A cold benzene (70 cc.) solution of ditetradecylcadmium, prepared from 0.063 mole of tetradecyl bromide, was treated with a solution of 0.05 mole of chloroacetyl chloride in 25 cc. of benzene, then the mixture was heated under reflux for one hour and twenty minutes. After the reaction had been worked up as described for 1-chloro-2-hexanone, the product was distilled from a Claisen flask at reduced pressure. After a low-boiling fraction, weighing 5.9 g. and distilling principally at 116–120° (9 mm.), had been separated, the chloroketone was collected at 160–175° (3 mm.); yield, 5.7 g. (33%, based on tetradecyl bromide); m. p. 45–49.5° (softens at 28°). The distillation residue weighed 3.7 g.

In another run of the same size, the reaction was continued for one hour at 26–28° and for an additional two hours at 38–42°, the reaction being exothermic only during the first half hour. The product was distilled through the half meter column, and there was obtained 5.3 g. of low-boiling material, 4.3 g. (26.5%) of chloroketone and 4.5 g. of distillation residue. Thus, the relatively low yield of this chloroketone and the large distillation residue are apparently due in part to pyrolytic decomposition at the high temperature necessary for its distillation.

A sample of the same lot of chloroacetyl chloride used for this preparation was redistilled through the half meter column, and 98% of it boiled in the range 104.8–105.5°.

The low-boiling fractions from these preparations were combined and refractionated to yield 8.8 g. of nearly pure tetradecane, b. p. 118.2–118.6° (10 mm.), freezing point, 0°, insoluble in concentrated sulfuric acid. For decolorization of one drop of 2% potassium permanganate in 2 cc. of acetone there was required 0.4 cc. of hydrocarbon. For tetradecane, Bachmann and Clarke[9] report b. p. 115–117° (10 mm.), m. p. 4–4.5°.

2-Chloro-3-heptanone.—To an ice-cold benzene (110 cc.) solution of dibutylcadmium, prepared from 0.216 mole of butyl bromide, there was added during seventy seconds a solution of 22.0 g. (0.173 mole) of α-chloropropionyl chloride (b. p. 109–110°) in 35 cc. of benzene. Before this addition was begun the nitrogen supply was cut off and the mercury valve closing the system was connected to a trap cooled in a Dry Ice–acetone-bath. After removal of the cooling bath from the reaction flask the temperature of the reaction mixture rose to 40° during twenty minutes. A temperature of 30–40° was maintained for an additional seventy minutes, the reaction not being exothermic during the last thirty minutes. For removal of butane, the mixture was finally stirred under reflux for ten minutes, at the end of which time gas had ceased to pass the mercury valve. On working up the reaction as described for 1-chloro-2-hexanone there was obtained 13.7 g. (42.7% based on bromide) of 2-chloro-3-heptanone, b. p. 65–68° (15 mm.), 79–82° (30 mm.). A cut boiling at 67.5–67.7° (15 mm.) was used for analysis.

Anal.[10] Calcd. for $C_7H_{13}OCl$: C, 56.54; H, 8.81; Cl, 23.87. Found: C, 56.77; H, 9.37; Cl, 23.86.

The material collected in the cold trap weighed 3.0 g. After redistillation from a water-bath at 20–23°, there was obtained 2.1 g. of nearly pure butane, b. p. (capillary tube method) 0.8°. It was insoluble in concentrated sulfuric acid, and 0.4 cc. had not decolorized one drop of 2% permanganate solution after thirty minutes.

In another run of the same size carried out in ether as solvent, the reaction mixture began to reflux spontaneously fifteen minutes after addition of the acid chloride to the ice-cold solution of dibutylcadmium, and spontaneous refluxing continued for thirty minutes. After heating under reflux for an additional hour the reaction was worked up to yield 9.3 g. (29%) of 2-chloro-3-heptanone, b. p. 67–68° (15 mm.). The material collected in the cold trap weighed 3.8 g., and on redistillation gave 2.9 g. of butane, b. p. (capillary tube method) 2.0°.

Reaction of Dibutylcadmium with 1-Chloro-2-hexanone.—To a hot benzene (110 cc.) solution of dibutylcadmium, prepared from 0.2 mole of butyl bromide, there was added during ten minutes a solution of 24.2 g. (0.18 mole) of 1-chloro-2-hexanone in 30 cc. of benzene. Spontaneous refluxing was vigorous during the entire addition and for two minutes afterwards. Heating under reflux was continued for an additional ten minutes, at the end of which time passage of gas through the mercury valve had ceased. When the reaction mixture was worked up as described for the preparation of 1-chloro-2-hexanone there was obtained only 2.3 g. of material boiling in the 1-chloro-2-hexanone range. The remaining material consisted of 3.5 g. of material boiling at 70–91° (4 mm.) and 12.8 g. of dark viscous material which did not reflux at a bath temperature of 160° at 4 mm. pressure.

The material collected in the cold trap during the above reaction weighed 10.2 g., and after redistillation from a water-bath at 20–23° there was obtained 8.1 g. of butane, b. p. (capillary tube method) 1.8°. It did not decolorize permanganate or dissolve in concentrated sulfuric acid.

Summary

A critical examination of the preparation of ketones by the reaction between a cadmium reagent and an acid chloride has been made, with the following results.

1. Procedures are reported for obtaining consistently good yields in the preparation of a variety of ketones, and the effect of several variables has been established.
2. Dibutyl ether is an unsatisfactory solvent for this type of preparation.
3. Optimum yields are obtained when benzene is used as solvent.
4. Di-*s*-alkylcadmium reagents give poor yields of ketones.
5. Reaction of cadmium reagent with the enol form of the ketone being prepared has been established as a side reaction, especially in the preparation of α-chloroketones.

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[9] Bachmann and Clarke, THIS JOURNAL, **49**, 2097 (1927).

[10] Microanalysis by Mr. C. W. Koch.