2. 3,6-Dimethoxy-phthalic anhydride was condensed with *o*-, *m*- and *p*-cresols.

3. The benzoyl-benzoic acids thus formed were condensed by means of sulfuric acid to the corresponding trihydroxy-methyl-anthraquinones or their ethers.

4. The exact structures of the benzoyl-benzoic acid derivatives and of the anthraquinones have been established: first, by comparison with the isomeric substances (described in the following paper) prepared by condensing 3,6-dimethoxy-phthalic anhydride with cresol ethers; and second, by comparison with the trihydroxy-methyl-anthraquinone of known structure prepared from 3,6-dimethoxy-*o*-cresolphthalein.

5. It has been established that the entering group takes the *ortho* position to the hydroxyl in the cresols.

6. The anthraquinones from the benzoyl-benzoic acids derived from *o*- and *p*-cresol form readily, and those from the *m*-cresol only with great difficulty.

7. A preliminary study of the condensation of 3,5-dimethoxy-phthalic anhydride with *m*-cresol and of the formation of the anthraquinone from the resulting benzoyl-benzoic acid derivative has been made, with the object of the synthesis and proof of the structure of the natural drug emodin.

8. The course of the condensation of the 3,5-dimethoxy-phthalic anhydride with *m*-cresol was determined by a comparison of the products obtained with this cresol and with *m*-cresol methyl ether and *o*-nitro-*m*-cresol.

9. The absorption spectra of the anthraquinones and phthaleins were obtained.

URBANA, ILLINOIS

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

TRIHYDROXY-METHYL-ANTHRAQUINONES. II

BY J. H. GARDNER[1] WITH ROGER ADAMS

RECEIVED JULY 23, 1923

In the previous paper[2] a satisfactory method was developed for the condensation of certain phthalic anhydrides containing methoxyl groups with cresols. The resulting benzoyl-benzoic acids were converted to substituted anthraquinones. A detailed study of the condensation of 3,6-dimethoxy-phthalic anhydride with cresols showed that the reactions took place very readily by means of anhydrous aluminum chloride and an excess of cresol as a solvent with the formation of products in which the ketonic carbonyl of the benzoyl-benzoic acid was *ortho* to the hydroxyl group of the cresol. Sulfuric acid in the presence of a little boric acid

---

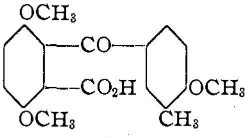
[1] This communication is an abstract of a thesis submitted by J. H. Gardner in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Graves and Adams, THIS JOURNAL, **45**, 2439 (1923).

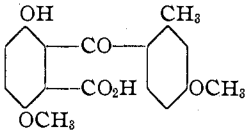
converted the benzoyl-benzoic acids thus formed into the corresponding anthraquinones and these were demethylated to the trihydroxy-methyl-anthraquinones by means of hydrobromic acid. The benzoyl-benzoic acids were accompanied by diphenyl-phthalide derivatives in the formation of which the condensation took place in the *para* position to the hydroxyl group of the *o*- and *m*-cresol residues and in the *ortho* position to the hydroxyl group of the *p*-cresol residue.

In the present work the condensation of 3,6-dimethoxy-phthalic anhydride with the methyl ethers of *o*-, *m*- and *p*-cresol has been studied. The conversion to the corresponding anthraquinone derivatives has been carried out and the structure of the intermediate and final products has been determined.

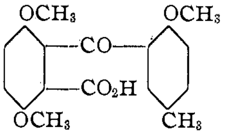
The initial condensation to the benzoyl-benzoic acids was effected by means of anhydrous aluminum chloride, using an excess of the cresol ether as a solvent. The benzoyl-benzoic acids from *o*-, *m*- and *p*-cresol methyl ethers (I, II and III) were obtained in yields of 24%, 65% and 48%, respectively, as the average of several runs.



I



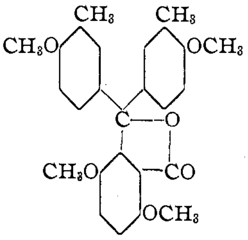
II



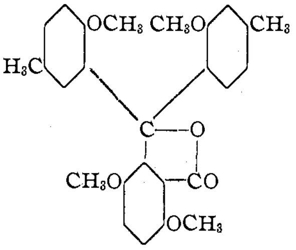
III

In the case of the *m*-cresol methyl ether, more vigorous conditions were used in the condensation than in the others, thus causing the hydrolysis of one of the ether groups (II).

The acids just mentioned from the *o*- and *p*-cresol methyl ethers were accompanied by alkali-insoluble diphenyl-phthalide derivatives (IV and V) in yields of 76% and 21%, respectively. No product of this type formed in the condensation with *m*-cresol methyl ether, possibly on account of the vigorous conditions used.



IV

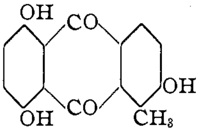


V

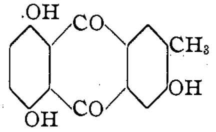
The conversion of the benzoyl-benzoic acids into anthraquinone derivatives was first accomplished with the acids from *o*- and *p*-cresol methyl ethers (I and III) by heating with concd. sulfuric acid to 150° and cooling immediately with ice. The anthraquinone derivatives thus produced were partially demethylated during their formation.

The benzoyl-benzoic acids were also converted to anthraquinones by heating with concd. sulfuric acid for 20 to 30 minutes at 145–155°. Under these conditions the products were formed and completely demethylated (VI and VIII); this method is, therefore, to be preferred to the other, as a single product is thus obtained.

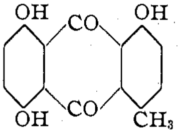
Such a very small amount of anthraquinone derivative from the acid obtained from *m*-cresol methyl ether resulted from either of the above treatments, that it could not be purified. This is in accord with the results of Weizmann[3] and of Graves and Adams[2] who had difficulty in forming anthraquinones from substituted benzoyl benzoic acids of a similar type.



VI



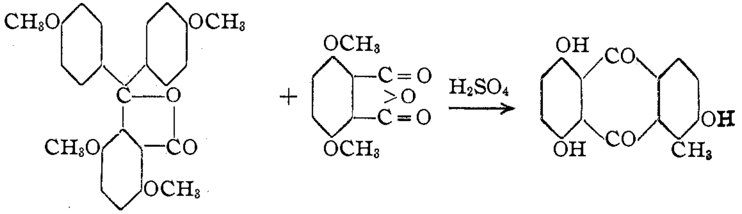
VII



VIII

The structures of the benzoyl-benzoic acids as given (I, II and III) were shown to be correct. Such structures would be expected after a consideration of the work of Nourisson[4] and Weizmann[3b] who showed that condensation of phthalic anhydride with phenol ethers took place *para* to the methoxyl group, providing that position was open. In the first place, the benzoyl-benzoic acids from *o*- and *m*-cresol methyl ethers were different from those obtained by the methylation of the benzoyl-benzoic acids from 3,6-dimethoxy-phthalic anhydride and *o*- and *m*-cresols. The benzoyl-benzoic acid from *p*-cresol methyl ether was the same as that obtained by the methylation of the condensation product from 3,6-dimethoxy-phthalic anhydride and *p*-cresol.

Second, the identity of the completely demethylated anthraquinone derivative (VI) from 3,6-dimethoxy-phthalic anhydride and *o*-cresol methyl ether with that obtained by the condensation of *o*-cresol-3,6-dimethoxy-phthalein dimethyl ether with 3,6-dimethoxy-phthalic anhydride and sulfuric acid, also shows without question the constitution of the original substance.



---

[3] Weizmann, *J. Chem. Soc.*, (a) **97**, 687 (1910); (b) **91**, 1626 (1907).

[4] Nourisson, *Ber.*, **19**, 2103 (1886).

Still further proof, and more direct, for the structure of the *o*-cresol methyl ether compound (I) was obtained. The demethylated anthraquinone (VI) from 3,6-dimethoxy-phthalic anhydride and *o*-cresol methyl ether was distilled with zinc dust in order to obtain the corresponding methyl anthracene. This, in turn, was oxidized to the methyl anthraquinone and identified as the α-methyl compound. This proves conclusively that the initial condensation must have been *para* to the methoxyl group in the cresol ether, since if it had been *ortho*, β-methyl-anthracene would have resulted.

By analogy, it is fair to assume that the *m*-cresol methyl ether also condensed in an analogous way, the ketonic carbonyl going *para* to the methoxyl group. It was mentioned above that the acid was partially demethylated during its formation and it is most probable, judging from the work of Kostanecki and Dreher,[5] that the methoxyl group *ortho* to the ketone carbonyl (II) is the one which has been split.

The constitution of the benzoyl-benzoic acid from *p*-cresol methyl ether is most certainly that given by Formula III. It is identical with the acid obtained by the methylation of the condensation product of 3,6-dimethoxy-phthalic anhydride and *p*-cresol.

With the constitution of the benzoyl-benzoic acids fixed, the structures of the anthraquinones formed from them can easily be proved. In the case of the *p*-cresol methyl ether derivative, only one anthraquinone formula is possible (VIII). The anthraquinone from the *o*-cresol methyl ether derivative might have one of two formulas (VI or VII), depending upon whether water was eliminated using the hydrogen atom *ortho* or *para* to the methyl group. It has already been mentioned, however, under the discussion of the structure of the benzoyl-benzoic acids, that α-methyl-anthracene could be obtained by reduction of this anthraquinone, thus showing that the hydrogen *ortho* to the methyl group has been eliminated and that Formula VI is correct.

It was mentioned that during the formation of the anthraquinones from the benzoyl-benzoic acids under certain conditions partial demethylation took place. From the benzoyl-benzoic acid obtained from *o*-cresol methyl ether, a monomethylated anthraquinone was formed. The exact structure was not determined, but it seems probable that the product was 2-methoxy-1-methyl-5,8-dihydroxy-anthraquinone. The benzoyl-benzoic acid from *p*-cresol methyl ether yielded an anthraquinone dimethyl ether which was identical with that obtained by Graves and Adams from 3,6-dimethoxy-phthalic anhydride and *p*-cresol, and so must be 4-hydroxy-1-methyl-5,8-dimethoxy-anthraquinone.[2] This is in accord with the observations of Oesterle who showed that one of the two methoxyl groups in the 1,8-positions in chrysazin is more reactive than the other.[6]

[5] Kostanecki and Dreher, *Ber.*, **26**, 78 (1893).

[6] Oesterle, *Arch. Pharm.*, **253**, 335 (1915).

The structures of the phthalein by-products (IV and V) are correct without doubt. The one formed from the *o*-cresol methyl ether was the same as that obtained by the methylation of the phthalein obtained by the condensation of 3,6-dimethoxy-phthalic anhydride with *o*-cresol. In the case of the condensation of the 3,6-dimethoxy-phthalic anhydride with the *p*-cresol, a fluoran was produced due to the dehydration of the phthalein first formed. When the *p*-cresol methyl ether was used, no such fluoran formation was possible and the corresponding phthalein was, therefore, produced.

Experimental Part

The 3,6-dimethoxy-phthalic anhydride was prepared as described in the previous paper. The cresol ethers were made by the usual method of treatment of the cresols with sodium hydroxide and dimethyl sulfate.

Condensation of 3,6-Dimethoxy-phthalic Anhydride with the Cresol Methyl Ethers

_p_-Cresol Methyl Ether Derivatives.[7] **3,6-Dimethoxy-2-(2-methoxy-5-methylbenzoyl) benzoic Acid** (III).—A mixture of 5 g. of 3,6-dimethoxy-phthalic anhydride and 25 cc. of *p*-cresol methyl ether was prepared in a large Pyrex test-tube provided with a mechanical stirrer. To this was added 15 g. of anhydrous aluminum chloride, and the mixture was stirred continuously for 1 hour so as to give a homogeneous reaction mixture; during this time evolution of hydrogen chloride took place. The tube was then heated for 6 hours at 70°; after 4 to 5 hours the mixture became so thick that it could no longer be stirred.

At the end of the heating the mixture was cooled and slowly treated with 50 cc. of 1:1 hydrochloric acid. The excess of cresol ether was removed by steam distillation, as well as any free cresol which might have formed during the reaction. The residual mixture in the flask was cooled and the dark brown solid was filtered. It was boiled with 10% sodium hydroxide, cooled and filtered. The residue was set aside and the alkaline solution was saturated with carbon dioxide. This caused the precipitation of aluminum hydroxide which was filtered off. From this filtrate 3.5 g. (44%) of 3,6-dimethoxy-2-(2-methoxy-5-methylbenzoyl)benzoic acid was obtained by acidification with hydrochloric acid. It was purified by recrystallization from methyl alcohol and washing with ether, forming colorless, truncated prisms melting at 203–204°.

Analyses. Subs., 0.0812: CO_2, 0.1942; H_2O, 0.0366. Calc. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.23; H, 5.01.

_p_-Cresol-3,6-dimethoxy-phthalein Dimethyl Ether, or 2,2-Bis(2-methoxy-5-methylphenyl)-3,6-dimethoxyphthalide[8] (V).—In the preparation of 3,6-dimethoxy-2-(2 methoxy-5-methylbenzoyl)benzoic acid (III) there was always obtained as a by-product a portion insoluble in sodium hydroxide solution. From the reaction mixture described, there was obtained 2.2 g. (21%) of this insoluble material. It was purified by recrystallization from glacial acetic acid, forming colorless needles melting at 187.5°. It was dried to constant weight at 100° before analysis.

Analyses. Subs., 0.0826: CO_2, 0.2164; H_2O, 0.0426. Calc. for $C_{26}H_{26}O_6$: C, 71.89; H, 5.99. Found: C, 71.45; H, 5.73.

---

[7] All melting points given in this paper are corrected.

[8] Nomenclature according to the system used in *Chemical Abstracts*.

1,5,8-Trihydroxy-4-methyl-anthraquinone.—A mixture of 5 g. of 3,6-dimethoxy-2-(2-methoxy-5-methylbenzoyl)benzoic acid (III) and 100 cc. of concd. sulfuric acid was heated rapidly to 150°. When this temperature was reached the mixture was poured over ice and the dark red precipitate which formed was filtered out. It was dissolved in 10% aqueous sodium hydroxide, the solution filtered and the mixture of anthraquinone derivatives precipitated by means of carbon dioxide; yield, 2.7 g., or 60%. By recrystallization of this crude material from acetone, two fractions were obtained in about equal amounts. The less soluble of these, which proved to be the 4,5,8-trihydroxy-1-methyl-anthraquinone, was recrystallized from glacial acetic acid for further purification. It formed fine red needles, melting at 276–278° with sublimation. It is soluble in concd. sulfuric acid with a blue-violet color, and in alkalies with a violet-red color.

Analyses. Subs., 0.0734: CO_2, 0.1784; H_2O, 0.0250. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.70. Found: C, 66.29; H, 3.78.

The more soluble compound obtained from the acetone crystallization proved to be the 1-hydroxy-4-methyl-5,8-dimethoxy-anthraquinone. It was purified further by recrystallization from glacial acetic acid from which it formed long, red needles with a yellowish, metallic gleam. It melted at 224° when pure, dissolved in concd. sulfuric acid with the development of a blue-violet color and in sodium hydroxide to give a bluish-red solution.

Analyses. Subs., 0.0620: CO_2, 0.1566; H_2O, 0.0247. Calc. for $C_{17}H_{14}O_5$: C, 68.46; H, 4.70. Found: C, 68.89; H, 4.47.

As stated in the introduction, a mixture of products consisting of partially methylated and entirely demethylated anthraquinones by the condensation of 3,6-dimethoxy-2-(2-methoxy-5-methylbenzoyl)benzoic acid (III) and sulfuric acid, could be avoided if the conditions used for the condensation were slightly modified. This latter procedure is to be preferred.

A mixture of 8.5 g. of the benzoyl-benzoic acid and 85 cc. of concd. sulfuric acid was heated at 145–155° for 20 minutes. The solution was then poured onto ice, and the precipitate filtered out and redissolved in 10% sodium hydroxide solution. The alkaline solution thus obtained was saturated with carbon dioxide, causing the precipitation of 4.5 g. (65%) of practically pure 4,5,8-trihydroxy-1-methyl-anthraquinone. This was further purified from glacial acetic acid as described above.

***o*-Cresol Methyl Ether Derivatives. 3,6-Dimethoxy-2-(4-methoxy-5-methylbenzoyl) benzoic acid (I).**—A mixture of 5 g. of 3,6-dimethoxy-phthalic anhydride and 20 cc. of *o*-cresol methyl ether was placed in a large Pyrex test-tube provided with a mechanical stirrer. To this was added 8 g. of anhydrous aluminum chloride and after the mixture had been stirred for an hour it was heated to 65° during a period of 2 hours and continuously stirred, after which it was held at that temperature for 5 hours.

The mixture was cooled and decomposed with 50 cc. of 1:1 hydrochloric acid. The resulting product was treated in exactly the same way as described under the corresponding *p*-cresol methyl ether derivative. There was thus obtained 1.9 g. (26%) of 3,6-dimethoxy-2-(4-methoxy-5-methylbenzoyl)benzoic acid. It was purified by crystallization from methyl alcohol, then from acetone, and finally dried to constant weight. It was a white powder, melting at 192°.

Analyses. Subs., 0.0934: CO_2, 0.2266; H_2O, 0.0442. Calc. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 66.17; H, 5.26.

***o*-Cresol-3,6-dimethoxy-phthalein Dimethyl Ether, 2,2-Bis(4-methoxy-5-methylphenyl)3,6-dimethoxy-phthalide (IV).**—From the condensation just described 8 g. (76%) of the material insoluble in sodium hydroxide was obtained. This was purified by recrystallization from glacial acetic acid, forming colorless needles: m. p., 202–203°.

Analyses. Subs., 0.0808: CO_2, 0.2115; H_2O, 0.0433. Calc. for $C_{26}H_{26}O_6$: C, 71.89; H, 5.99. Found: C, 71.37; H, 5.95.

2-Methoxy-1-methyl-5,8-dihydroxy-anthraquinone.—A mixture of 5 g. of 3,6-dimethoxy-2-(4-methoxy-5-methylbenzoyl)benzoic acid (I) and 100 cc. of concd. sulfuric acid was heated rapidly to 150° and then poured onto ice. The red precipitate was purified as described under the corresponding *p*-cresol methyl ether derivatives. There was thus obtained 2.5 g. (58% yield) of anthraquinone.

The crude material was recrystallized from glacial acetic acid, forming dark red needles melting at 249–249.5°. From the mother liquors small amounts of 2,5,8-trihydroxy-1-methyl-anthraquinone were obtained. The monomethyl ether is soluble in concd. sulfuric acid with the formation of a blue-violet color and dissolved in alkalies to give a blue-red solution.

Analyses. Subs., 0.0823: CO_2, 0.2025; H_2O, 0.0320. Calc. for $C_{16}H_{12}O_5$: C, 67.61; H, 4.23. Found: C, 67.11; H, 4.32.

2,5,8-Trihydroxy-1-methyl-anthraquinone (VI).—This substance was obtained in small amounts from the mother liquor from the previous condensation, but it was more readily obtained in a pure state by the following procedure.

A mixture of 4 g. of 3,6-dimethoxy-2-(4-methoxy-5-methylbenzoyl)benzoic acid (I), 3 g. of boric acid and 40 cc. of concd. sulfuric acid was heated at 150° for 30 minutes. The solution was poured onto ice, the liquid filtered and the precipitate dissolved in 10% sodium hydroxide solution. After filtration the solution was saturated with carbon dioxide, thus precipitating 1.5 g. (45%) of 2,5,8-trihydroxy-1-methyl-anthraquinone. It was purified by recrystallization from dil. acetic acid and then from chloroform. It formed dark red needles, melting at 270°.

Analyses. Subs., 0.0795: CO_2, 0.1936; H_2O, 0.0255. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.70. Found: C, 66.38; H, 3.56.

This same substance was obtained by the condensation of 2,2-bis(4-methoxy-5-methylphenyl)-3,6-dimethoxy-phthalide (IV) with 3,6-dimethoxy-phthalic anhydride and sulfuric acid. A mixture of 7 g. of the phthalide with 185 cc. of concd. sulfuric acid and 3.5 g. of 3,6-dimethoxy-phthalic anhydride was heated for 2 days at 125°. The solution was poured onto ice, the dark red precipitate filtered and dissolved in 10% sodium hydroxide solution. By saturating this solution with carbon dioxide, 7.5 g. of the anthraquinone derivative was obtained.

Since the phthalide was formed in large amounts by the condensation of 3,6-dimethoxy-phthalic anhydride with *o*-cresol methyl ether, this method of preparation of the 2,5,8-trihydroxy-1-methyl-anthraquinone was more satisfactory than that by the dehydration of 3,6-dimethoxy-2-(4-methoxy-2-methylbenozyl)benzoic acid (I).

Conversion of 2,5,8-trihydroxy-1-methyl-anthraquinone (VI) **to 1-methyl-anthraquinone.**—A sample of 2,5,8-trihydroxy-1-methyl-anthraquinone was reduced to methylanthracene by distillation with zinc dust, following the method of Gattermann.[9] The crude material thus obtained was oxidized to methyl-anthraquinone, following the method of Fischer and Reinkober.[10] The product thus obtained was purified by crystallization from dil. acetic acid, forming yellow needles melting at 167°, which is the melting point of 1-methyl-anthraquinone. When this product was mixed with a sample of pure 2-methyl-anthraquinone melting at 174°, the melting point of the mixture was lowered to 154°, indicating that the compounds were not the same.

***m*-Cresol Methyl Ether Derivatives. 3-Hydroxy-6-methoxy-2-(4-methoxy-1-**

---

[9] Gattermann, "Practical Methods of Organic Chemistry," MacMillan and Co., **1914**, p. 369.

[10] Fischer and Reinkober, *J. prakt. Chem.*, [2] 92, 49 (1915).

methylbenzoyl)benzoic acid (II).—A mixture of 5 g. of 3,6-dimethoxy-phthalic anhydride and 25 cc. of *m*-cresol methyl ether was condensed in the same manner as the *o*- and *p*-cresol methyl ethers with the exception of a few details. The mixture was heated up to 75° during the course of 1.5 hours, and maintained at that temperature for 7 hours. When worked up in the manner previously described, no alkali-insoluble product was obtained but merely 4.9 g. (65%) of a dimethyl ether, probably 3-hydroxy-6-methoxy-2-(4-methoxy-1-methylbenzoyl)benzoic acid (II). This was purified by crystallization from methyl alcohol, forming colorless prisms melting at 194–195°. It was dried to constant weight before it was analyzed.

Analyses. Subs., 0.0766: CO_2, 0.1806; H_2O, 0.0342. Calc. for $C_{17}H_{16}O_6$: C, 64.56; H, 5.06. Found: C, 64.30; H, 4.67.

Summary

1. 3,6-Dimethoxy-phthalic anhydride was condensed with *o*-, *m*- and *p*-cresol methyl ethers.
2. The benzoyl-benzoic acids formed from the *o*- and *p*-cresol methyl ethers were condensed by means of sulfuric acid to the corresponding trihydroxy-methyl-anthraquinones or their methyl ethers. By varying the conditions of condensation it was possible either to obtain partial demethylation or complete demethylation during this reaction.
3. The structures of the benzoyl-benzoic acids obtained were established: first, by comparison with the isomeric substances obtained by the condensation of 3,6-dimethoxy-phthalic anhydride with cresols; and second, by direct proof.
4. It has been established that the entering group takes the *para* position to the methoxyl groups in the *o*- and *m*-cresol ethers and the *ortho* position to the methoxyl in the *p*-cresol methyl ether.
5. The structure of the anthraquinones obtained from the benzoyl-benzoic acids was determined.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

THE YIELDS OF SOME GRIGNARD REAGENTS

BY HENRY GILMAN AND ROY McCRACKEN[1]

RECEIVED JULY 31, 1923

Introduction

In connection with a series of studies involving the Grignard reagent, it was necessary to determine the approximate yield in the preparation of a number of typical RMgX compounds. A knowledge of such yields is quite indispensable in certain studies. In particular is this true of reactions involving an excess of some compound treated with the Grignard reagent, and when the interpretation of mechanism of such a reaction

---

[1] This paper is an abstract of a thesis presented by Roy McCracken in partial fulfilment of the requirements for the degree of Master of Science in Chemistry at Iowa State College.