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HALO-ARENE CHROMIUMTRICARBONYL COMPLEXES

SYNTHESIS AND A MECHANISTIC STUDY
OF NUCLEOPHILIC SUBSTITUTION IN
HALO-ARENE CHROMIUMTRICARBONYL COMPLEXES

By

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ABSTRACT

Arenechromiumtricarbonyl complexes have been known for many years and numerous studies of the chemistry of these molecules have been reported. The presence of the chromiumtricarbonyl unit changes the reactivity of the complexed arene, in most cases due to its strong inductive electron withdrawing effect. The resulting lowered electron density in the aromatic ring allows reactions to be carried out which would otherwise be extremely difficult if not impossible, notably nucleophilic substitution. When methoxide ion was reacted with optically pure methyl *o*-fluorobenzoatechromiumtricarbonyl, racemization of approximately 50% was observed in the product. A brief study confirmed S_N2 kinetics, but further investigation was warranted. Having eliminated the possibility of decomplexation-recomplexation, two other mechanisms were postulated - a partial decomplexation allowing the arene to roll over, or attack by methoxide at another ring position. In an effort to determine which mechanism was operating, the synthesis of a number of appropriately substituted halo-arenechromiumtricarbonyl complexes was attempted. The successful synthesis of methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl was achieved, albeit with some difficulty and in low yield, but the corresponding 2-chloro-3-methyl complex could not be made. In the case of the corresponding 2-fluoro compounds, the arenes themselves could not be made by a variety of synthetic routes, so synthesis of the complexes could not be attempted. The results of the reaction

of methoxide ion with methyl 2-chloro-5-methylbenzoatechromiumtricarboxyl indicate that the reaction proceeds via the roll-over mechanism, although a definite conclusion cannot be drawn at this time. A potentially useful synthesis of bis-(chromiumtricarboxyl)-benzenes has also been developed.

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To
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CHAPTER ONE

INTRODUCTION, HISTORICAL BACKGROUND

1.1 Introduction

The chemistry of arenechromiumtricarbonyls began in 1957 with the synthesis of the parent compound, benzenechromiumtricarbonyl, by E.O. Fischer (1). Soon afterwards, improved methods were reported and a number of other arenes were included (2). An early study of the chemistry of these new molecules revealed some interesting effects caused by the presence of the chromiumtricarbonyl unit - the complex of benzoic acid was more acidic than its uncomplexed analogue, and chlorobenzenechromiumtricarbonyl underwent relatively facile nucleophilic substitution for chloride by methoxide (3).

These initial studies sparked a number of investigations into the chemistry of a wide variety of arenechromiumtricarbonyls. The effects of complexation can be attributed both to electron-donating and electron-withdrawing effects by the chromiumtricarbonyl moiety. The electron-donating effects are illustrated by the results of solvolysis studies of complexed benzyl (4a) and cumyl (4b) chlorides (α -cationic intermediates) and of complexed 2-arylalkylmethanesulphonates (5, β -cationic intermediates). In all cases, the rate of the solvolysis reaction was significantly increased as a result of complexation to chromium, indicating that the cationic intermediate had been stabilized as a result of complexation to the chromiumtri-

carbonyl group.

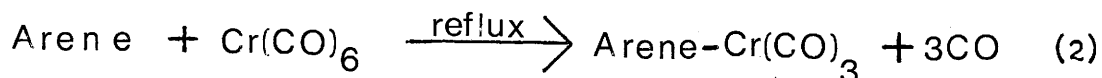
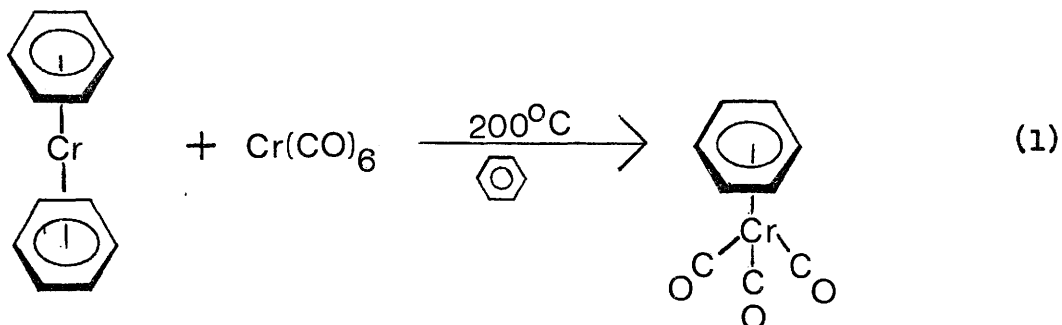
Most of the observed effects, however, can be attributed to the inductive electron-withdrawing nature of the chromium, and the ability of the chromiumtricarbonyl group as a whole to delocalize excess negative charge from the arene. This delocalizing ability is amply illustrated by a number of examples where anionic sites exist α or β to the complexed arene ring. For instance, complexed benzoic acids and phenols are more acidic than their uncomplexed analogues (6), while complexed amines are less basic than the free ones (7). The rate of the elimination reaction in 2-phenylethyl-tosylates and bromides, involving a β -carbanionic intermediate, is significantly increased when the molecules are complexed to chromiumtricarbonyl (8). In a related vein, a number of complexed aryl ketones, esters, and alkylbenzenes were reported to be cleanly alkylated by reagents such as methyl iodide under conditions where the uncomplexed analogues were inert or gave complicated product mixtures (9). These results can all be attributed to stabilization of an anionic site adjacent to the aryl ring through inductive electron-withdrawal by chromium.

The electron-withdrawing effects on the aryl ring itself are illustrated in two complementary ways. The ability of the ring to undergo electrophilic attack is severely reduced, as evidenced by the lower rates observed for Friedel-Crafts acetylation (10), partially attributable to a competing reaction between the aluminum trichloride and chromium (11), and the reduced ability of certain

complexed phenylpropanoic and phenylbutanoic acids to undergo intramolecular cyclodehydration (12), which also involves electrophilic attack. These results are consistent with reduced electron density in the ring due to electron withdrawal by the chromiumtricarbonyl moiety. Conversely, it was observed initially by Nicholls and Whiting (3), and subsequently pursued further by Semmelhack and Jaouen (see later sections), that nucleophilic substitution (difficult for unactivated arenes) was relatively facile; thus, chlorobenzenechromiumtricarbonyl underwent substitution by methoxide to produce the anisole analogue under conditions where chlorobenzene itself was inert. This observation led the way to the development of these reactions into useful synthetic tools, as will be seen in later sections (1.4 and 1.5). Before proceeding to this discussion, however, it seems useful to investigate some of the synthetic routes to these molecules.

1.2 Synthesis of Arenechromiumtricarbonyls

The first reported synthesis of benzenechromiumtricarbonyl involved the reaction of bisbenzenechromium with chromiumhexacarbonyl in benzene as solvent at 220°C in a sealed system (1, eq. 1). Nicholls and Whiting soon reported a simpler method which involved heating chromiumhexacarbonyl under reflux with an excess of arene (eq. 2), sometimes also using a molar quantity of an inert solvent (2b, 3). One of the major improvements in this method is that it allows the free release of carbon monoxide which helps to drive the



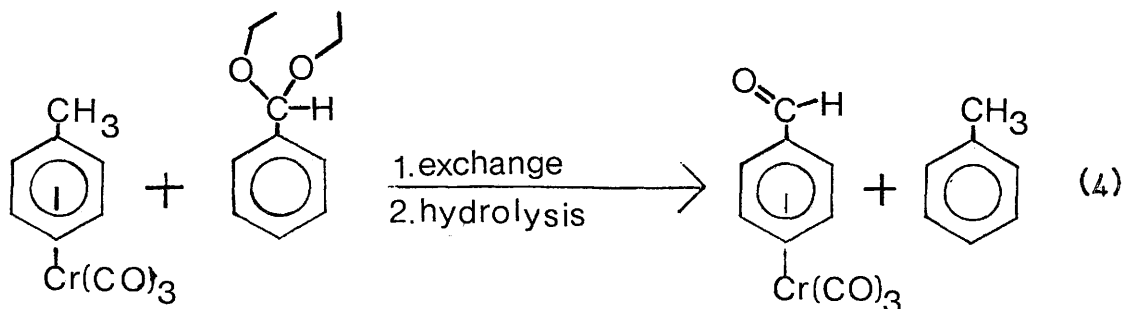
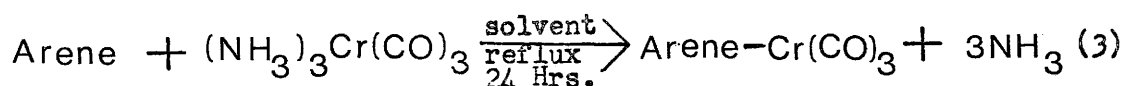
reaction to completion. The presence of the inert solvent (diglyme was preferred) was found to be essential for arenes which boil below 120°C (3).

The major inconvenience with these simple reflux methods is that chromiumhexacarbonyl which sublimes during the reaction period must be mechanically returned to the reaction vessel. This problem can be all but eliminated if a small proportion of a lower boiling solvent is used; a suitable solvent system is one part tetrahydrofuran to ten parts di-*n*-butyl ether (13), the rapidly refluxing tetrahydrofuran serving to wash the sublimed chromiumhexacarbonyl back into the reaction flask. Other solvent combinations, such as dibutyl ether/heptane have also been used successfully (14).

Ligand exchange reactions have also proven useful in the

synthesis of arenechromiumtricarboxyls, particularly for those arenes inaccessible by the above methods because of the presence of electron-withdrawing or heat-labile substituents. For example, triamminochromiumtricarboxyl has been used successfully to synthesize a variety of arenechromiumtricarboxyls in high-boiling solvents such as dioxane (15) and low-boiling solvents such as diethyl ether (16, eq. 3). Triacetonitrilechromiumtricarboxyl has been used in a similar manner (17).

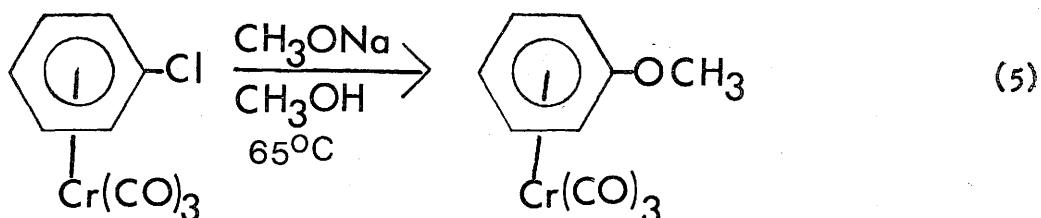
Although not as commonly used, exchange of one arene ligand for another has also been reported (18). In one reported case, the diethyl acetal of benzaldehyde displaced toluene, producing, after hydrolysis, benzaldehydechromiumtricarboxyl (eq. 4). Other workers have reported, however, that exchange of one arene for another is not generally applicable as a synthetic technique (3).



With such a variety of conditions and reagents available, it is not surprising that a large number of arenechromiumtricarbonyl complexes have been synthesized, some bearing rather labile functional groups.

1.3 Nucleophilic Substitution : Background and Mechanisms

The fact that arenes π -complexed to chromiumtricarbonyl could undergo facile nucleophilic substitution was first reported by Nicholls and Whiting in 1959 - chlorobenzenechromiumtricarbonyl reacted with sodium methoxide at 65°C to produce the anisole analogue in good yield (3, eq. 5). The development of this property as a synthetic tool was slow in coming, in fact it has only been in the past few years that Semmelhack (see section 1.4) and Jaouen (see section 1.5) have put it to extensive use.

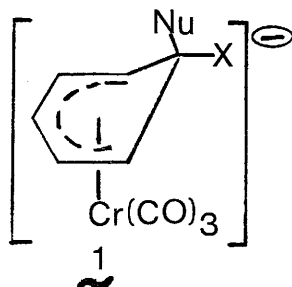


Because of its potential as an organic synthetic tool, it is of interest to know something about the mechanism of the nucleophilic substitution reaction. Based on the conclusion that the

chromiumtricarbonyl group exerts an electron-withdrawing effect similar to that of a para-nitro group (3), Brown undertook theoretical (19) and kinetic (20) studies. For his theoretical calculations, Brown assumed that the transition state was similar to the familiar Wheland structure known for S_N2 reactions of uncomplexed arenes (21) 1 - that is, that one of the arene carbon atoms is effectively removed

X = F, Cl

Nu = nucleophile



from conjugation and from complexation to chromium. Using this model, his calculations showed that for nucleophilic substitution the activation energy for the chromiumtricarbonyl complex was significantly lower than for the uncomplexed arene, while results for radical or electrophilic substitution indicated little or no change on complexation (19).

Experimental support for these conclusions came from a subsequent kinetic study by Brown and Raju (20). The reactions of methoxide ion with fluoro- and chlorobenzenechromiumtricarbonyl, their uncomplexed analogues, and the uncomplexed para-nitro derivatives were studied. The results, presented in table 1, indicated that the activation energies for the para-nitro and chromiumtricarbonyl derivatives were of similar magnitude and both substantially lower than that for the uncomplexed halobenzene. The existence of this similarity in activation energies and probability factors provided

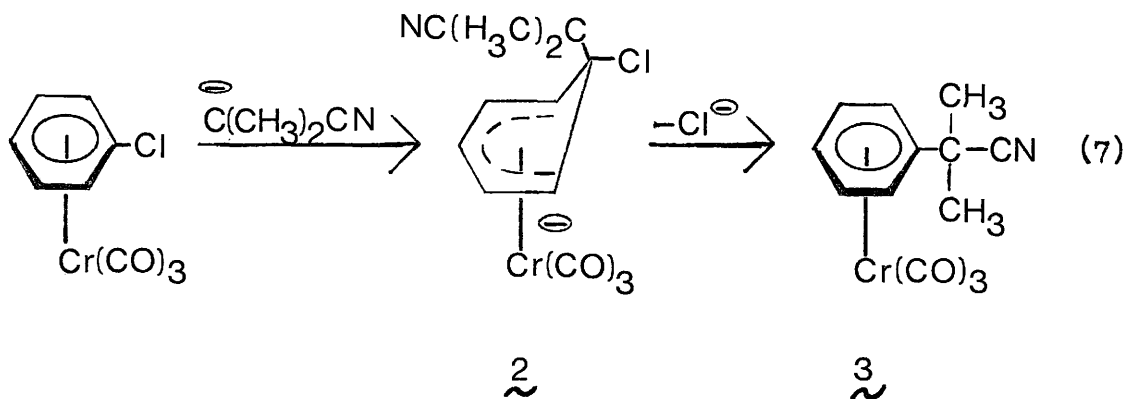
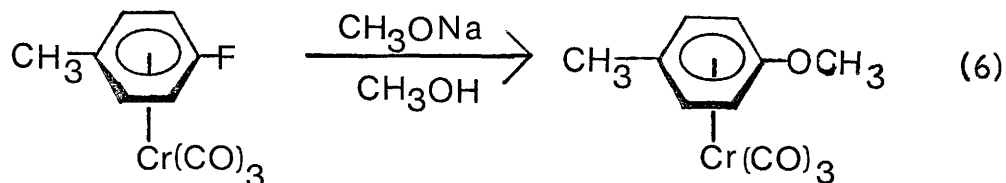
Compound	E (kcal mole ⁻¹)	log ₁₀ A
π -C ₆ H ₅ ClCr(CO) ₃	25.2	12.1
<i>p</i> -ClC ₆ H ₄ NO ₂	23.7	11.3
C ₆ H ₅ Cl	39.9	11.1
π -C ₆ H ₅ FCr(CO) ₃	17.7	10.2
<i>p</i> -FC ₆ H ₄ NO ₂	19.3	10.4
C ₆ H ₅ F	34.9	12.0

Table 1 Activation Energies in Nucleophilic Substitution Reactions (20)

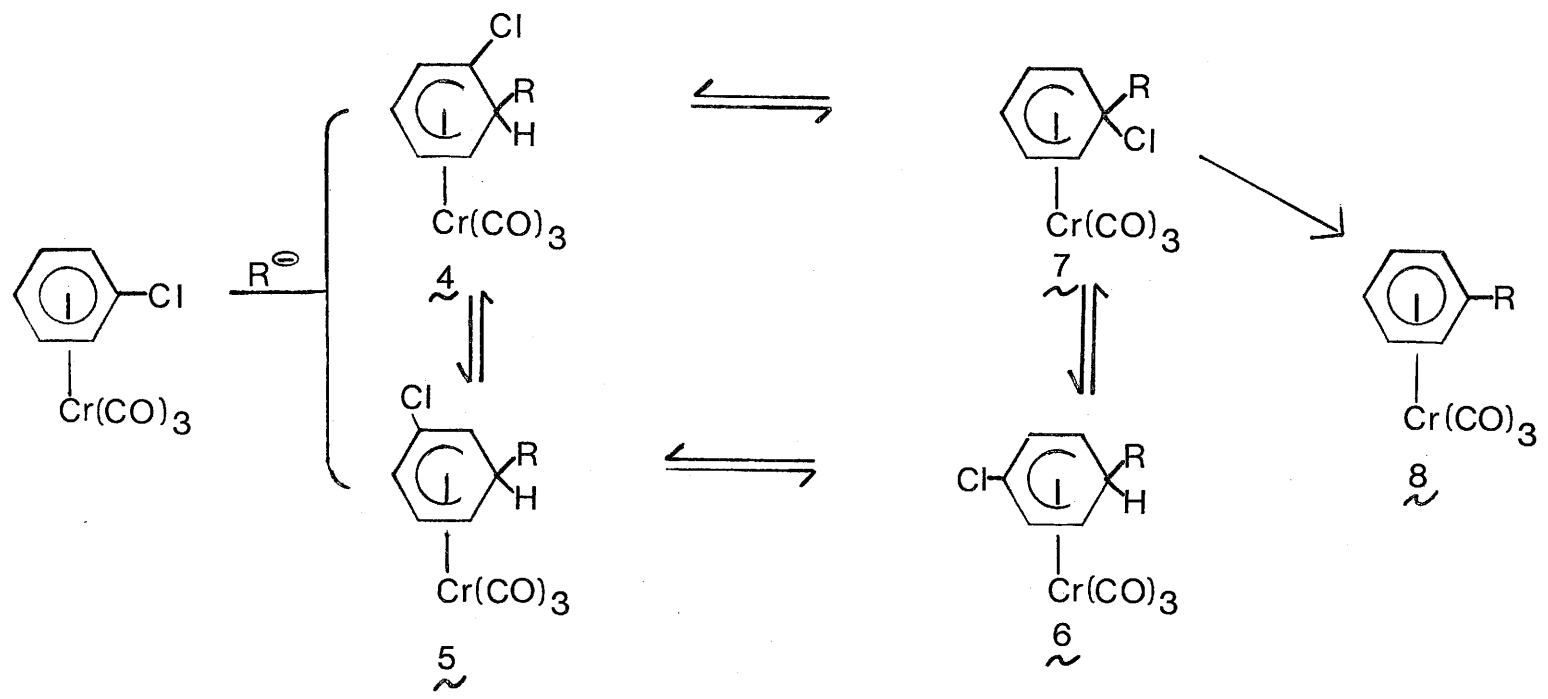
confirming evidence to support the view that the chromiumtricarbonyl derivative reacted via a Wheland-type transition state; since the uncomplexed halobenzenes and particularly their para-nitro derivatives were known to react via such a transition state, it was quite reasonable to conclude that the chromiumtricarbonyl complex did so too (20).

A benzyne-type mechanism was ruled out as a possibility based on the results of the reaction of *p*-fluorotoluenechromiumtricarbonyl with methoxide ion - only the *p*-methylanisole complex was formed (eq. 6). If the complex had reacted via a benzyne, the major product observed would have been the meta-substituted compound (20).

The more recent work by Semmelhack and co-workers gives



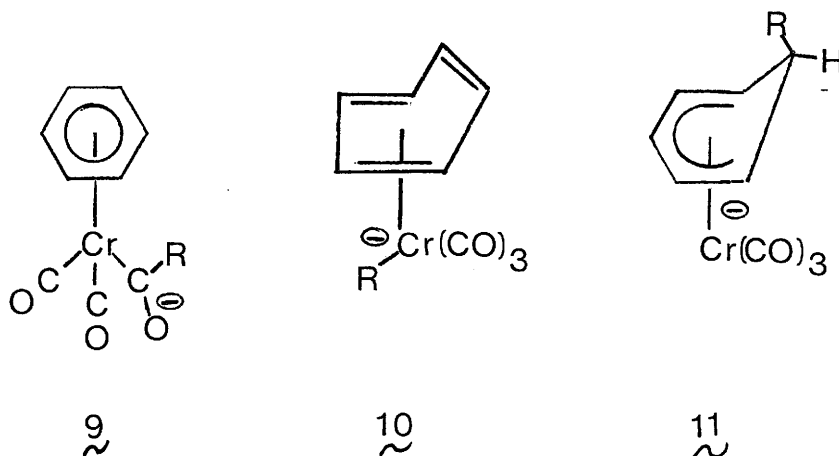
further support to an S_N2 mechanism involving the Wheland-type transition state. A typical example is the reaction of *iso*-butyronitrile anion with chlorobenzenechromiumtriacetylide (22). Although the overall reaction (eq. 7) can be postulated as attack by the carbanion to produce the π -cyclohexadienylchromiumtriacetylide anion 2 followed by loss of chloride to give the phenyl-*iso*-butyronitrile complex 3, quenching at low conversion and monitoring of the reaction by proton NMR resulted in the more complicated proposal (23) illustrated in scheme I. (24). When the reaction was allowed to proceed in the usual fashion, only product 8 derived from 7 was observed. However, when the reaction was rapidly quenched by



Scheme I

addition of iodine, the disubstituted products resulting from loss of hydride and chromiumtricarbonyl from 4, 5, and 6 were observed; no products derived from 7 were observed if the quenching was rapid enough (24). When a proton source was added rapidly, dihydro products derived from 4, 5, and 6 were observed, in addition to the disubstituted arenes and the expected product from 7 (23).

In the above examples, nucleophilic substitution for hydride was a side reaction, but its development into a synthetic tool in its own right lent further support to the Wheland-type intermediate as being involved in these reactions. Three possible intermediates can be proposed for the reaction of carbanions with benzenechromiumtricarbonyl (25), resulting from attack at a carbonyl 9, at chromium 10, or at a ring carbon 11. Proton NMR spectroscopic studies of the intermediate indicated that the carbanion was attached to the arene ring, based both on absolute peak assignments by decoupling experiments and on comparisons to other known π -cyclohexadienyl systems.



R = carbanion

Oxidation of the intermediate led to production of the arene derived from 11, resulting from formal substitution for hydride. Addition of a proton source (5-fold excess of trifluoroacetic acid) led to dihydroarenes, again only derivable from 11. Use of a weaker acid at -78°C followed by addition of iodine and subsequent warming also gave the arene derived from 11; when the solution was warmed prior to the addition of the proton source, the starting complex and the protonated carbanion were found. On the basis of these results, it was concluded that 11 was the important intermediate (25).

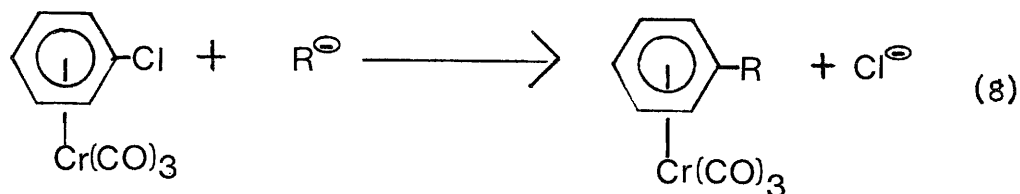
It is clear that the experimental evidence overwhelmingly supports an $\text{S}_{\text{N}}2$ mechanism involving a Wheland-type intermediate, thus it seems reasonable to use this as a starting point in mechanistic investigations of specific reactions.

1.4 Nucleophilic Substitution : Synthetic Utility

Although direct attack by a nucleophile on an aromatic ring may be, in principle, the quickest route to a desired compound, it is not usually easily accomplished by classical organic synthetic methods. In order to achieve success, the ring must be activated by the introduction of strongly electron-withdrawing groups such as nitro; these activating groups must usually be removed after the desired transformation has been achieved. This adds extra steps to a synthesis (with the accompanying lowered overall yield) and may create a number of problems, particularly when other labile functional groups are present. The strongly electron-withdrawing

nature and the relative ease with which it can be introduced and removed makes the chromiumtricarbonyl group an excellent choice as an aromatic ring activator in synthetic work; it is somewhat surprising that the development of such techniques has been reported only in the past few years.

It was in 1974 that Semmelhack reported the reaction between carbon nucleophiles (carbanions) and chlorobenzenechromiumtricarbonyl (22, eq. 8). Table 2 indicates some of the more successful carbanions



used. A typical reaction involved generating the carbanion at low temperature, adding the chlorobenzenechromiumtricarbonyl as a tetrahydrofuran solution, leaving the mixture at 25°C for 15-20 hours, partitioning between water and ether, and finally treating the ether phase with excess iodine to free the organic ligand which was then isolated and purified. (In contrast, uncomplexed chlorobenzene did not react under these conditions.) A number of other anions were also tried but did not give significant amounts of substitution product; these were usually primary or secondary carbanions for which

the expected product would possess relatively acidic protons. It was thought that the presence of these acidic protons led to rapid protonation of the carbanion, thus effectively quenching the reaction (22).

The same study also reported that the leaving-group reactivities were the same as observed in classical nucleophilic substitution reactions, that is $F > Cl \gg I$. In fact, the iodo-complex showed almost no reaction under conditions where the fluoro-complex had almost completely reacted (22).

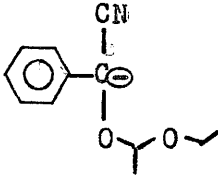
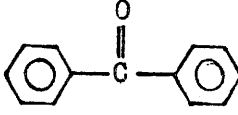
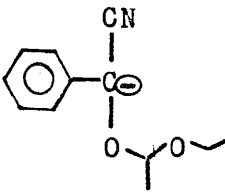
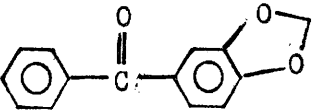
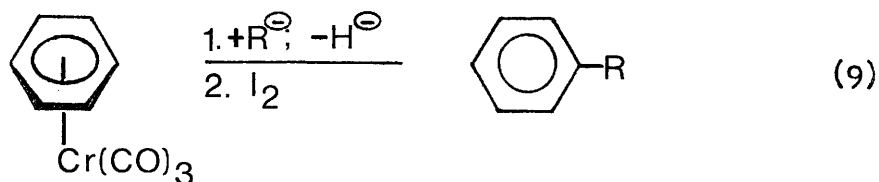
Anion	Product	% Yield
$\ominus C(CH_3)_2CN$	$PhC(CH_3)_2CN$	85-90
$\ominus C(CH_3)_2CO_2Et$	$PhC(CH_3)_2CO_2Et$	71
$\ominus C(CH_3)_2CO_2^-$	$PhC(CH_3)_2CO_2H$	63
$\ominus CH(CO_2Et)_2$	$PhCH(CO_2Et)_2$	51
		88
		90

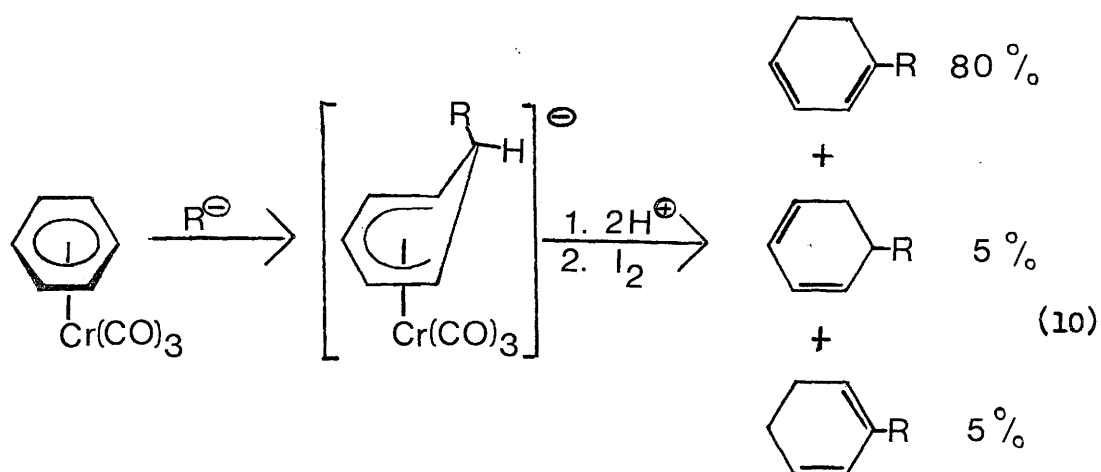
Table 2 Reactions of Chlorobenzenechromiumtricarbonyl with Carbanions (22)

As discussed in section 1.3, nucleophilic substitution for hydride was first observed as a side reaction of the chlorobenzene complex. Its development into an important reaction in its own right greatly enhanced the synthetic utility of nucleophilic substitution, since it was no longer necessary to have a specific leaving group at the position where substitution was desired. Benzenechromiumtriacarbonyl reacted with a number of carbanions, as shown in equation 9 (26). The general procedure involved adding the benzenechromiumtriacarbonyl in tetrahydrofuran to the anion at -78°C , allowing the mixture to warm somewhat to allow reaction, recooling followed by addition of excess iodine to free the organic ligand which was then isolated and purified. As was the case for the chloro-complex, some anions were much more efficient than others. Some of the better anions included reactive organo-lithiums and ester enolates in the presence of an aprotic polar solvent or with potassium as the cation. Organomagnesium halides, lithium or potassium enolates of ketones (even in aprotic polar solvents) and lithium enolates of esters were found to be very inefficient in these reactions. The first step

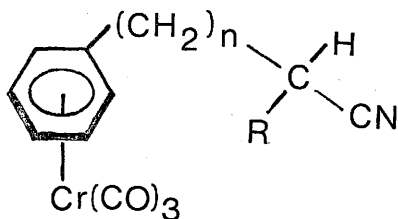
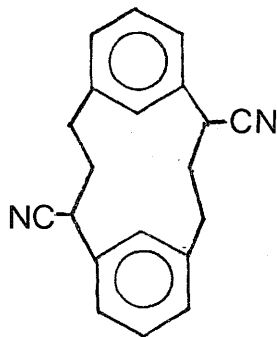
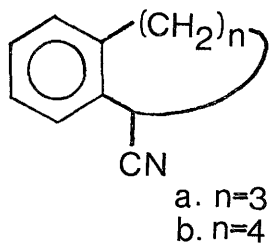
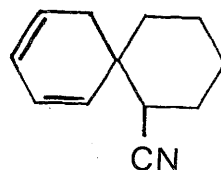


in these reactions, formation of the η^5 -cyclohexadienyl anion intermediate, is thought to be reversible; hence the efficiency of the overall reaction is dependent upon the equilibrium constant of the reversible step, which in turn depends on the relative stabilities of the carbanion and the intermediate (26). Hence factors which affect the value of the equilibrium constant will also affect the efficiency of the overall reaction.

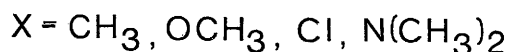
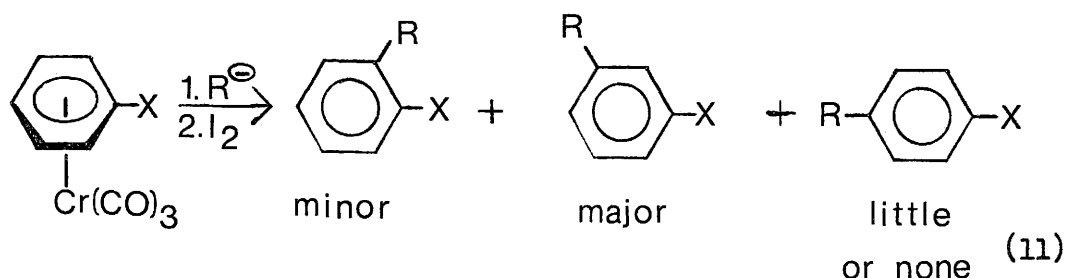
Having shown that carbanionic attack on a complexed arene is a feasible synthetic procedure, how, then, has it been used in practice? It has already been shown (section 1.3) that the η^5 -cyclohexadienyl intermediate can react in a number of ways; when an excess of strong acid is added followed by warming and removal of chromium, a mixture of 1,3-cyclohexadienes is produced - thus an arene can be reduced to a cyclohexadiene (eq. 10).



Intramolecular carbanionic attack in compounds such as 12 has also been observed, (27). The product obtained depended on the value of n . For $n=1$, unidentified high molecular weight products were obtained. In the case of $n=2$, the [3.3] metacyclophane 13 was produced. When $n=3$, a fused-ring monomer 14a was found. The most interesting result was for $n=4$, where both the fused-ring (14b) and the spirocyclic (15) compounds were obtained. The proportion of 15 increased with increasing reaction time and/or temperature, leading to the conclusion that 15 was the thermodynamic product, while 14b was the kinetic product (27).

12131415

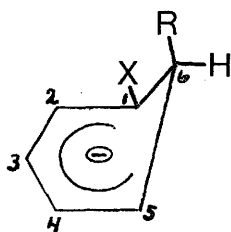
For nucleophilic substitution to be synthetically useful, it is necessary to know how the presence of non-displaceable substituents will effect the position of substitution. Studies of the reactions of complexed toluene, anisole, chlorobenzene, and N,N-dimethylaniline with a number of carbanions indicated strongly meta-directing effects for many of the anions (28, 29; eq. 11). Other



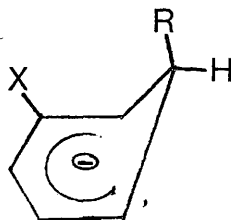
anions and other substituents produced less clear-cut results (see table 3), which are not readily explicable in terms of anion size or reactivity. Another fact which must be accounted for is the difference in behaviour between the ortho and para positions, usually considered equivalent in reactions of uncomplexed aromatic compounds. One rationalization arises by considering the structures of the η^5 -cyclohexadienyl intermediates 16. These intermediates can be thought of as being similar in character to a pentadienyl anion. Since the electron density is lowest at the 2-position, the favoured intermediate for electron-donating substituents will be 16b, where the substituent is at the 2-position of the pentadienyl fragment (24b).

Substituent	Carbanion	Product Ratio o: m: p	Combined Yield %
CH ₃	LiCH ₂ CO ₂ R	28:72: 0	89
OCH ₃	LiCH ₂ CO ₂ R	4:96: 0	93
Cl	LiCH ₂ CO ₂ R	54:46: 1	98
Cl	LiCH(CH ₃)CO ₂ R	53:46: 1	88
Cl	LiC(CH ₃)CO ₂ R	5:95: 1	84
Cl	LiCH ₂ COC(CH ₃) ₃	70:24: 0	87
Cl	LiC(CH ₃) ₂ CN	10:89: 1	84
Cl	Li-(1,3-dithianyl)	46:53: 1	56
Si(CH ₃) ₃	LiC(CH ₃) ₂ CN	0: 2:98	65
CF ₃	LiC(CN)(OR)CH ₃	0:30:70	33
N(CH ₃) ₂	LiC(CH ₃) ₂ CN	1:99: 0	92
C(CH ₃) ₃	LiC(CN)(OR)CH ₃	0:35:65	85
CH ₂ CH ₃	LiC(CN)(OR)CH ₃	0:94: 6	89

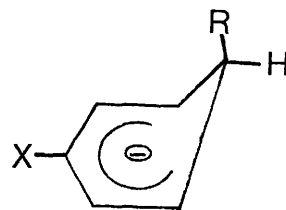
Table 3 Reactions of Carbanions with Substituted Arenechromiumtricycarbonyls (29)



16a



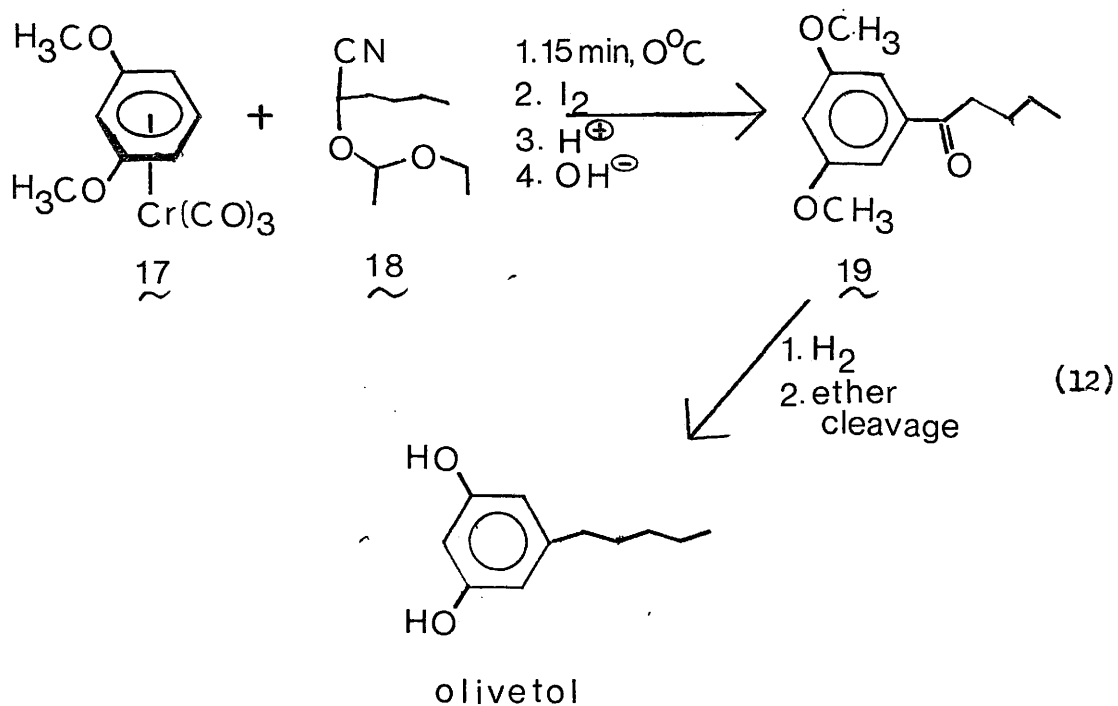
16b



16c

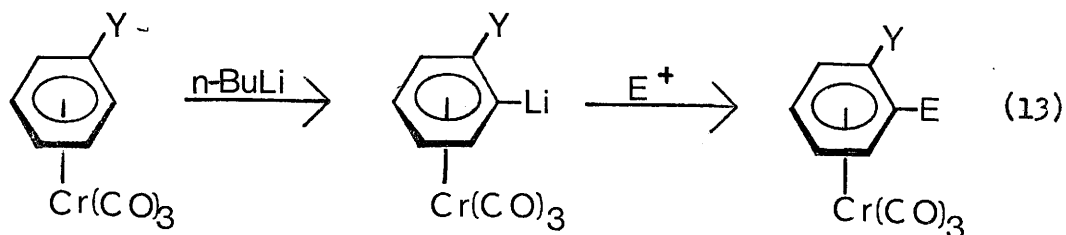
This rationalization does not, however, satisfactorily explain some of the other results, nor does it really explain the different results observed for different anions on the same substrate. Semmelhack *et. al.* have recently proposed another rationalization, involving use of the orbital coefficients at the arene atoms in the complex's LUMO (29). Since no data were available for the complexes, the values for the arene itself were used and were found to be generally useful (there were some exceptions) in correlating the position of anionic attack with the nature of the arene.

A practical application of this high degree of regioselectivity is in natural products chemistry in the synthesis of olivetol (eq. 12).

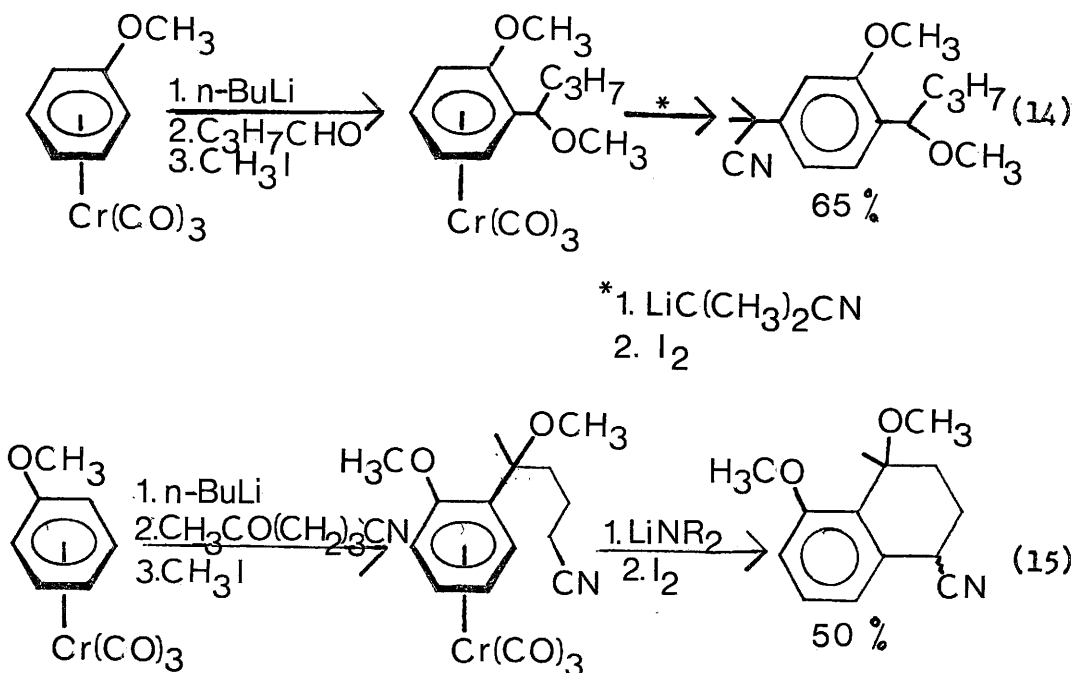


Reaction of 1,3-dimethoxybenzenechromiumtricarbonyl 17 with the anion of the cyanohydrin acetal of valeraldehyde 18 gave, after suitable work-up, the ketone 19 having the olivetol skeleton. This compound could then be hydrogenated and subjected to methyl ether cleavage to produce olivetol (28). The synthetic utility arises from the ready availability of the starting materials and the relative ease with which the transformation can be achieved.

A recent synthetic application is the metalation of arene-chromiumtricarbonyls (30). In this case the π -complex reacted with *n*-butyllithium to produce the lithio-derivative which could then react with a variety of electrophiles (eq. 13). One of the uses to which this reaction can be put is in the synthesis of certain π -complexes which are inaccessible by direct methods but which would prove useful in nucleophilic substitution. Another important result is the complete regioselectivity which can be obtained in this reaction and when it is used in conjunction with some of the previously discussed reactions with anions. Equations 14 and 15 illustrate how anisole can be converted into two much more complex molecules with complete regioselectivity (30), something rather difficult to attain by conventional organic synthetic procedures.



Y = H, OCH₃, F, Cl



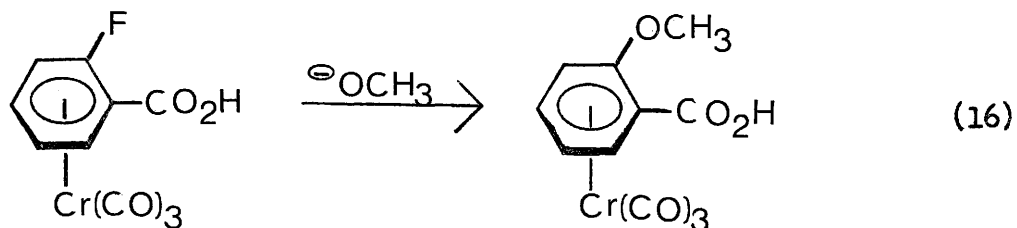
With proper choice of reagents, reaction conditions, and sequence, it is easy to envisage a large number of organic molecules whose synthesis could be greatly simplified by use of an arenechromiumtricarbonyl and the proper nucleophilic substitution reaction.

1.5 Chiral Arenechromiumtricarbonyls

Besides the variety of effects which have already been discussed, the chromiumtricarbonyl group can also introduce chirality into an arene. For instance, uncomplexed disubstituted benzenes are achiral, whereas the corresponding chromiumtricarbonyl derivatives

are chiral. The preparation and optical resolution of a number of ortho and meta disubstituted acids, esters and amines has been reported (31). The acids were resolved by formation of salts with active bases, their separation by fractional crystallization and subsequent regeneration of the active acids. The complexed esters were first hydrolysed to the corresponding acids, treated as just described, then the active acids were treated with diazomethane to obtain the active esters. The amines were separated in a similar manner by use of active acids, although with some difficulty due to their low basicities.

Having separated the enantiomers and determined their absolute configurations, it was desired to be able to inter-relate the configurations in the ortho and meta series. A previously published scheme (32) was found to be inadequate and a chemical correlation was developed (33). It was in this work that the ability of complexed arenes to undergo relatively facile nucleophilic substitution for halide was utilized. The fluoro-derivatives were found to be useful intermediates which could be subjected to substitution by various nucleophiles in order to obtain compounds whose absolute configuration was already known. One of the reactions used was that of methoxide ion with o-fluorobenzoic acid chromiumtricarbonyl (eq. 16). Although a number of such conversions were carried out in the meta series with no measurable racemization, the ortho series exhibited racemization of the order of 50% when the nucleophile was methoxide; other nucleophiles, such as $(\text{CH}_3)_2\text{NH}$ and $-\text{SCH}_3$, also exhibited some racemization (14).



These results prompted a reinvestigation of the mechanism. A kinetic study (34) showed that it was indeed an S_N2 process as had been reported by Brown (20), although it was apparent that it was not as straightforward as had been thought previously. Again the benzyne mechanism was disproved - no meta or para substituted products were obtained when starting from an ortho substituted compound (14).

Thus it is clear that further investigation into the mechanism of this reaction is necessary. Any proposed explanation should include a mechanism whereby partial racemization can occur, and it should also account for the fact that this racemization does not occur in the meta complexes.

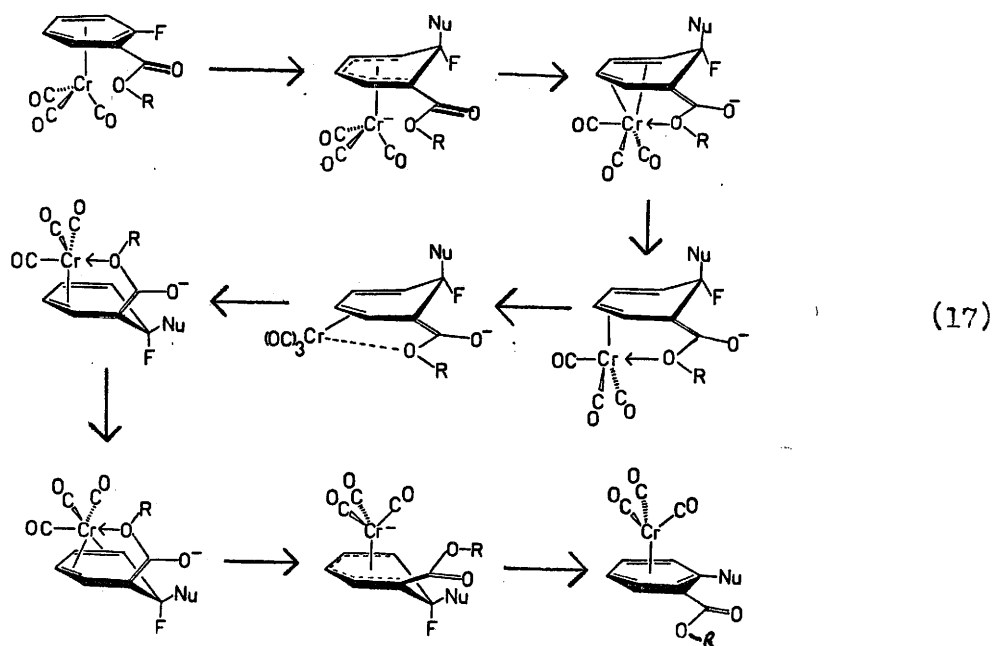
CHAPTER TWO

PROPOSED MECHANISMS, SYNTHESIS OF ARENES AND COMPLEXES, RESULTS

2.1 Possible Mechanisms of Racemization

There are several possible mechanisms which can be proposed to account for the partial racemization observed in the reactions of methyl *o*-fluorobenzoatechromiumtricarbonyl with methoxide ion. One possibility which immediately comes to mind is ligand exchange - some time after the formation of the intermediate the arene becomes detached from the chromium and then randomly reattaches to the same or a different chromium, thus leading to partial racemization. This mechanism was easily disproved by Jaouen (34); a control experiment which involved refluxing the optically active complexed ester in methanol but without methoxide ion resulted in no racemization being observed. Similarly, when the optically active complexed ester was refluxed in methanol in the presence of some uncomplexed ester, no racemization was observed. If ligand exchange had been occurring, both of these experiments would have led to some degree of racemization in the product.

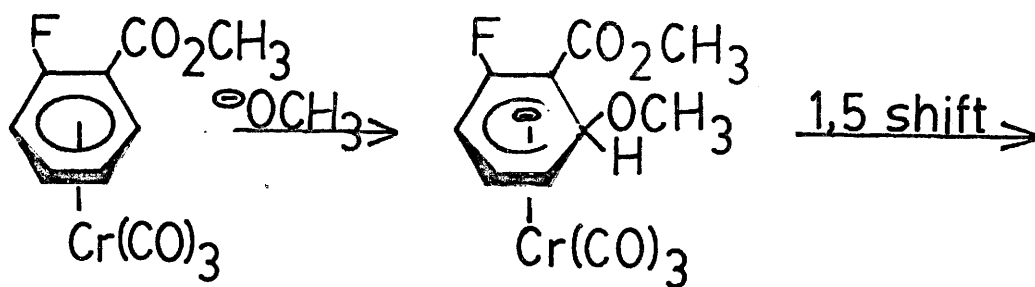
Another possible mechanism is described by the French word "basculage" or intramolecular teeter-totter (34). This mechanism describes a situation whereby the arene becomes partially decomplexed (the normally tridentate ligand becomes bidentate and then monodentate), flips over while monodentate, and then reattaches to the metal in the normal tridentate fashion (eq. 17). It is also quite possible that



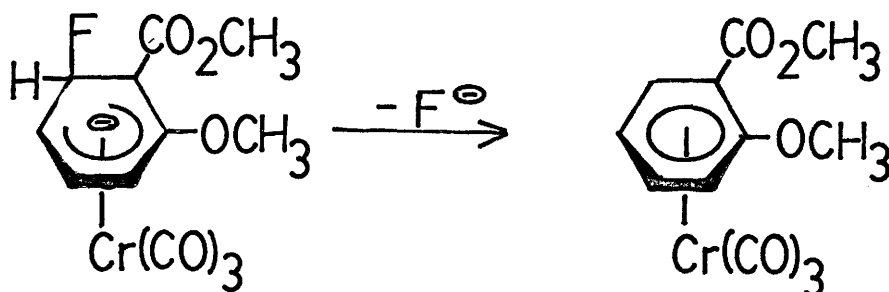
the ester carbonyl oxygen participates in some fashion, perhaps by temporarily occupying one of the co-ordination sites on the metal vacated by the arene.

A third equally viable mechanism involves attack by the nucleophile at the "other" ortho position, followed by a 1,5-hydride shift and expulsion of fluoride (eq. 18). This mode of attack is presumably less favoured, which would account for the observation of only 50% racemization. The exact role of the metal in this mechanism is unclear. It is possible that the metal merely stabilizes the Wheland intermediate so that it exists long enough for the required rearrangement to occur, or it may play a more active role in that the hydride shift occurs via some sort of bonding interaction with the chromium.

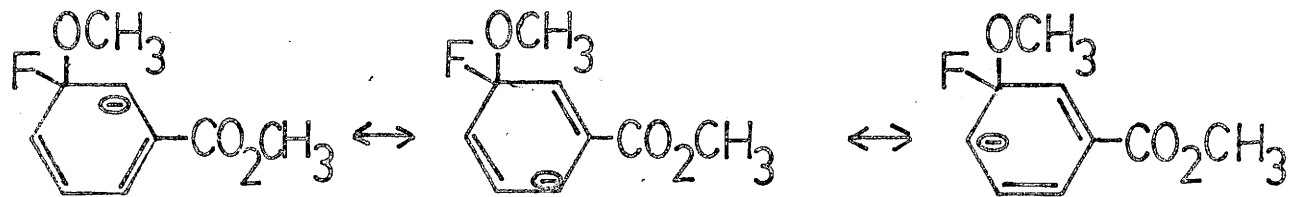
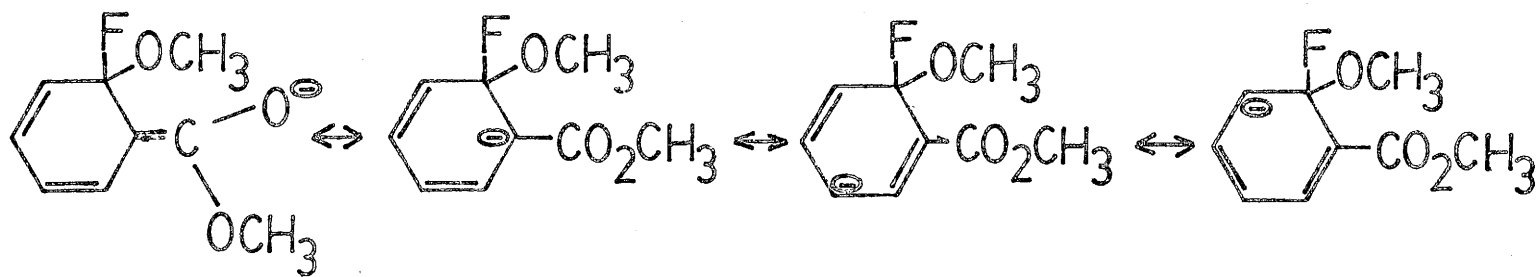
Unfortunately, none of these proposed mechanisms clearly explains why racemization is observed in the ortho series but not



(18)



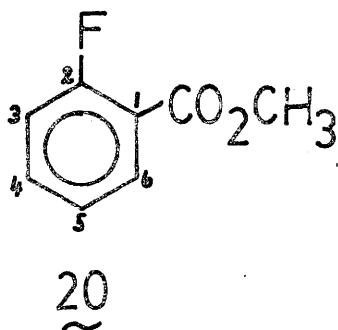
in the meta. One can rationalize this observation, however, by considering the resonance stabilization available to the arene alone, regardless of whether the metal is present or not. A consideration of the possible resonance contributors, shown in Scheme II, leads one to the conclusion that the intermediate in the ortho series would probably be somewhat more stable, since the negative charge can be delocalized into the ester group as well as around the ring. This extra stabilization is not possible in the meta series. Since it would be expected that the effects of the chromiumtricarbonyl group would be the same in both series, this extra stabilization available to the ortho series could be the deciding factor which determines whether or not the intermediate exists long enough for either the teeter-totter or the hydride shift mechanism to be operative.



Scheme II

2.2 Distinguishing Between Mechanisms

Having already eliminated a ligand exchange mechanism from consideration, it is still necessary to devise a means of deciding between the teeter-totter and hydride shift mechanisms. With only two substituents on the arene ring, it is not possible to distinguish one mechanism from the other. However, if a third, non-reactive, functional group were present on the ring, such a distinction should be possible. If a suitably placed methyl group were present, for example, attack by the nucleophile at the two positions ortho to the ester (positions 2 and 6 in 20) would produce two different compounds

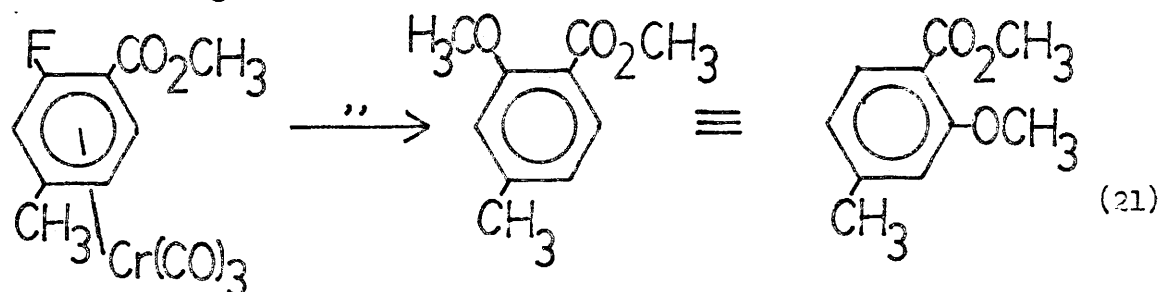
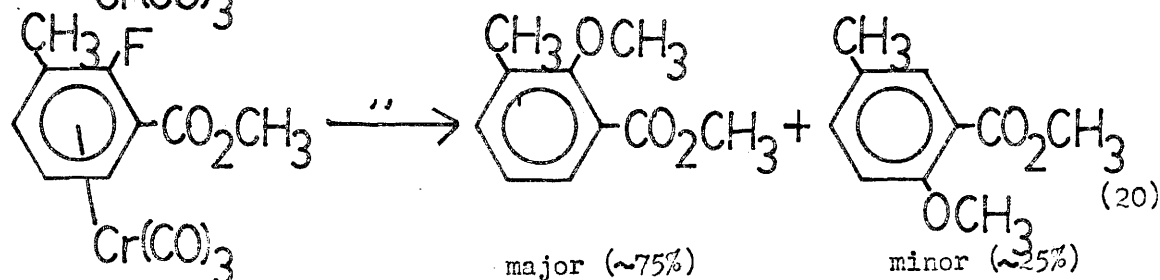
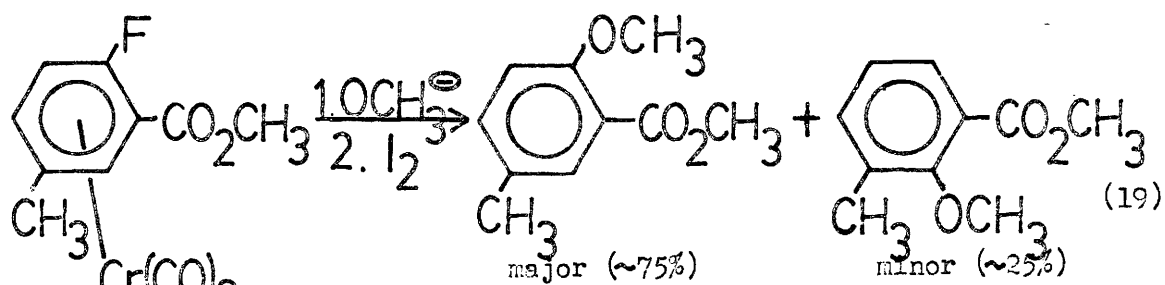


which could be identified by their spectral characteristics. If, however, the reaction proceeded via the teeter-totter mechanism, nucleophilic attack would occur only at position 2 and only one product would be observed.

The three possible positions for the methyl substituent are 3, 4, and 5; of these 4 is unsuitable since the same product would result from attack at positions 2 or 6. Therefore, either the 3-methyl or the 5-methyl compound is suitable for the desired study. Ideally, parallel studies on each compound should be carried out, to allow for any steric effects which might be caused by the presence of the

methyl group. The reactions involved are summarized in equations 19, 20 and 21 assuming the hydride shift mechanism and 50% racemization.

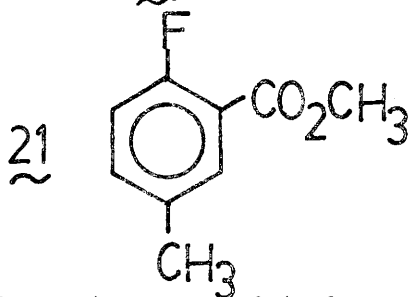
It should be noted that the products obtained in 19 and 20 are the same after decomplexation, but with the expected ratio reversed. Thus, if it were possible to prepare and characterize spectrally one or both of the expected products, and then compare these with the spectra obtained from the actual reaction products, it should be possible to draw conclusions as to whether the observed racemization is due to nucleophilic attack at an alternate position (as was observed by Semmelhack in his synthetic work (26)) followed by a hydride shift or is due to the teeter-totter mechanism.



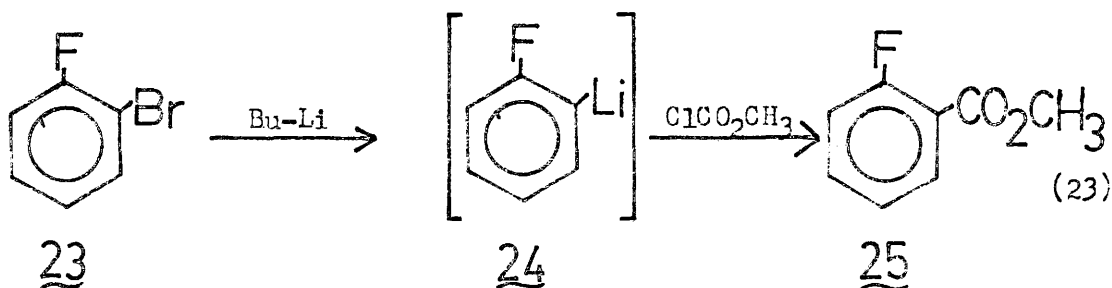
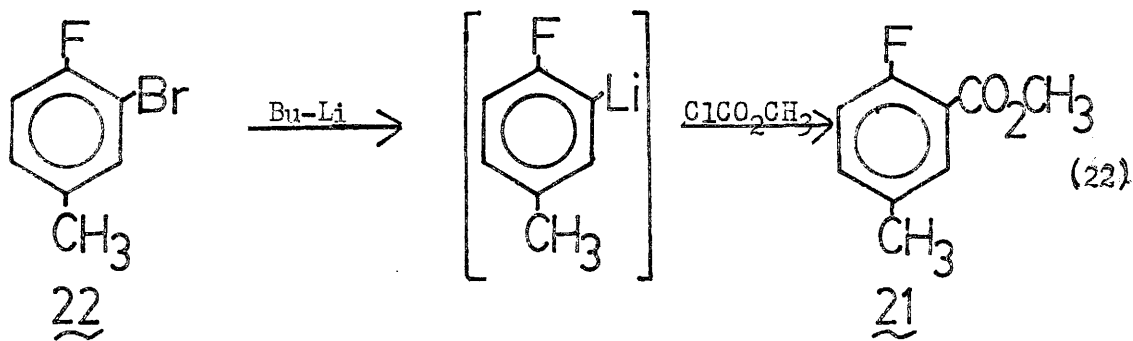
2.3 Attempted Synthesis of the Fluoro-esters

2.3.1 2-Fluoro-5-methyl Series

The required fluoro-containing compound was the methyl ester of 2-fluoro-5-methylbenzoic acid 21, for which a relatively straight-

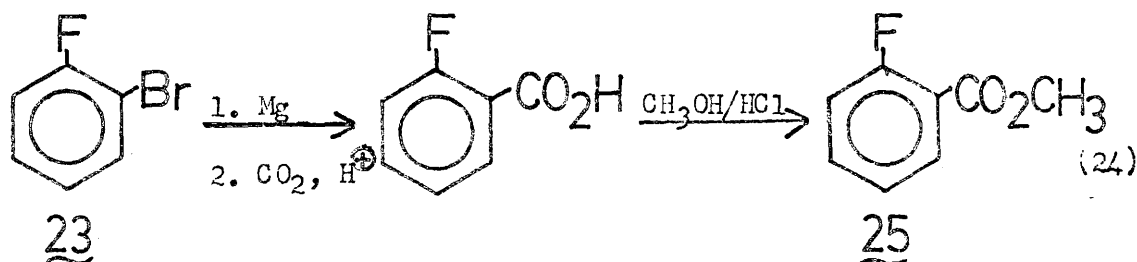


forward one-step synthetic route appeared to be available. The proposed synthesis involved reaction of 3-bromo-4-fluorotoluene 22 with butyllithium followed by reaction of the lithio intermediate with methyl chloroformate to produce the desired ester 21 (eq. 22). Because the starting compound 22 was relatively difficult to obtain, model synthetic experiments were carried out on the more readily available *o*-fluorobromobenzene 23 (eq. 23). Several attempts were made to



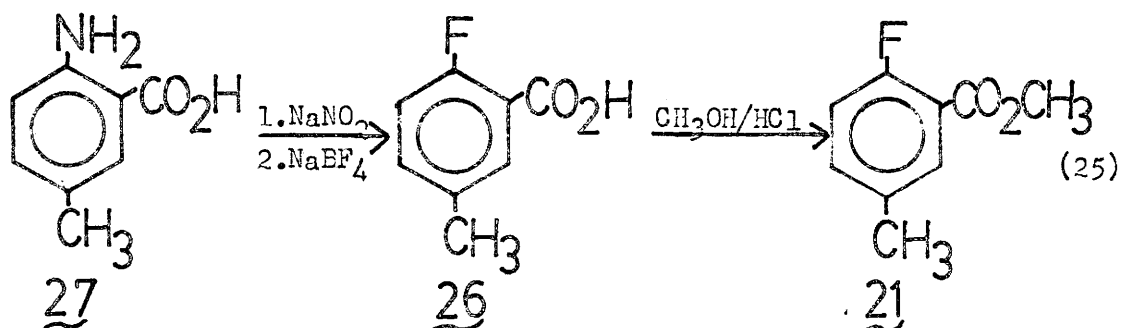
carry out this reaction sequence, none of which were successful. The initial failures could be attributed to the order of addition of the reagents - in the first instance the methyl chloroformate was added to the lithio compound 24 which presumably resulted in the formation of some of the desired compound 25, but this would be susceptible to further attack by 24. Thus, none of the desired ester could be isolated. The experimental apparatus was then redesigned so that the anion 24 could be added to the methyl chloroformate; in this way the concentration of anion could be kept low relative to that of the methyl chloroformate, thus side reactions should be minimized. However, in all instances product mixtures were obtained. Attempts at isolating the desired compound by fractional distillation under reduced pressure were not entirely successful. Although spectral evidence (NMR) indicated that 25 was probably present, it could not be isolated in a pure enough state to allow unambiguous identification; other unidentified compounds were also present.

The Grignard reaction was tried as a route to *o*-fluorobenzoic acid, which could be esterified to give methyl *o*-fluorobenzoate 25 (eq. 24); this again was a model system for the desired 2-fluoro-5-methyl system. Again, a mixture of products was obtained, none of which could be positively identified as *o*-fluorobenzoic acid.



Since the above reaction sequences were unsuccessful on the model compound, o-fluorobromobenzene 23, they were not attempted on 3-bromo-4-fluorotoluene 22.

When these one-pot reaction sequences proved unsuccessful, an alternate route to methyl 2-fluoro-5-methylbenzoate 21 via 2-fluoro-5-methylbenzoic acid 26 was investigated. The starting material for this reaction is the commercially available amino-benzoic acid 27.



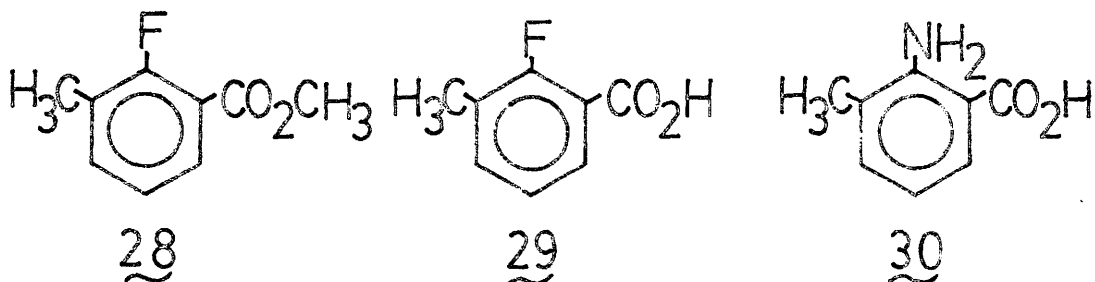
The proposed reaction sequence (eq. 25) involved carrying out a Balz-Schiemann reaction on the amino compound to obtain the fluoro compound, followed by esterification to give the desired ester 21. However, the desired 2-fluoro-5-methylbenzoic acid 26 was not obtained; the reasons for this failure are unclear. After the diazotization is complete and the sodium tetrafluoroborate has been added, the phenyldiazoniumtetrafluoroborate salt should precipitate from solution (35). When it was observed that this precipitation did not occur, a method was tried whereby a water soluble phenyldiazoniumtetrafluoroborate salt could be decomposed by the addition of cuprous chloride to the aqueous solution followed by warming (36). This led only to the chloro compound and in some instances to the hydroxy compound. A further modification in which no chloride ion from any source was present (diazotization carried out in sulphuric instead of hydro-

chloric acid) led only to the hydroxy compound. Finally, attempts to salt out the phenyldiazoniumtetrafluoroborate in order to decompose it thermally were also unsuccessful.

No obvious explanation is available to account for these results. It is clear that the diazotization stage proceeds successfully, since the chloro and hydroxy by-products were isolated (see also section 2.4). Why the tetrafluoroborate salt does not form, and the results discussed above would seem to indicate that this is the case, remains a mystery. Due to these synthetic difficulties, and because of the fact that the corresponding chloro compounds were suitable alternatives and could be synthesized with relative ease, work on the synthesis of these fluoro compounds was abandoned.

2.3.2 2-Fluoro-3-methyl Series

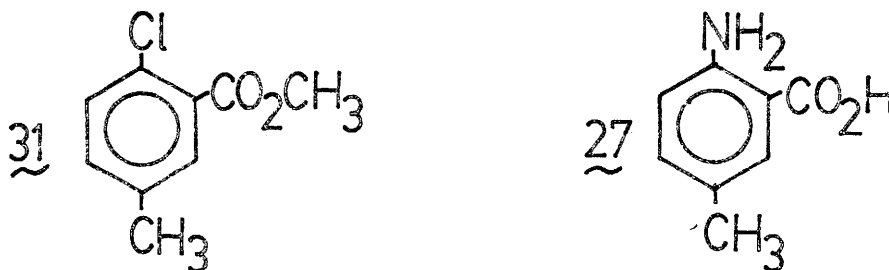
The only readily available route to the required methyl 2-fluoro-3-methylbenzoate 28 was use of the Balz-Schiemann reaction on the 2-amino-3-methylbenzoic acid 30 to give the corresponding 2-fluoro acid 29, followed by esterification in methanol. Since the Balz-Schiemann reaction proved unsuccessful in the 2,5-series, it was not attempted for the 2,3-series. Because there appeared to be no other readily obtainable precursors, the synthesis of this series of compounds was abandoned.



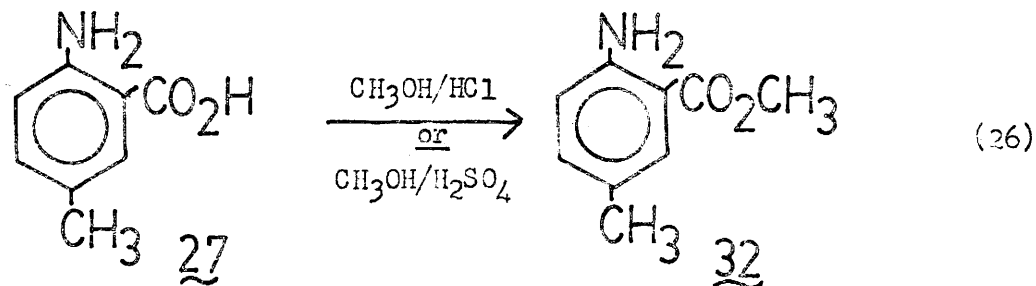
2.4 Synthesis and Characterization of the Chloro-Esters

2.4.1 2-Chloro-5-methyl Series

Although Jaouen *et. al.* based their work on the complexes of the fluoro-esters (14, 31-34), use of the corresponding chloro compounds is a suitable alternative since the first observation of nucleophilic substitution by methoxide ion in these systems was reported for chlorobenzenechromiumtricarboxyl (3). The required compound is methyl 2-chloro-5-methylbenzoate 31, which was found to be readily made from the commercially available 2-amino-5-methyl benzoic acid 27.



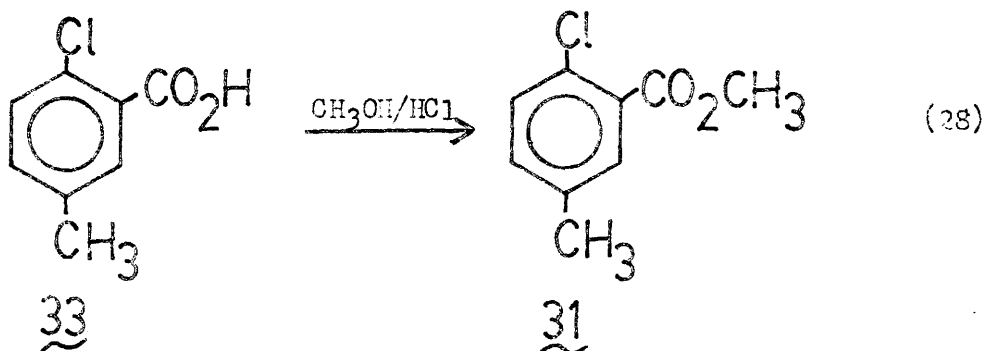
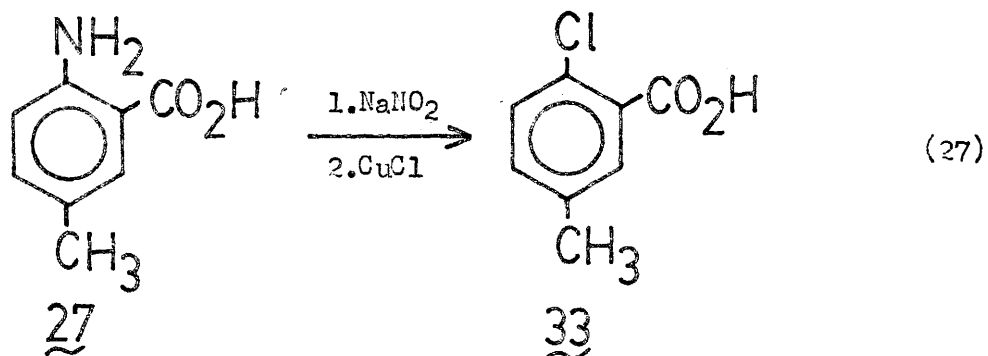
The required reactions are a Sandmeyer to convert the amino group to a chloro and an esterification of the acid group. Experience showed, however, that the proper order of these reactions was crucial to the successful synthesis of 31. Initially, it was the esterification reaction which was attempted first (eq. 26) but neither refluxing in methanol saturated with anhydrous hydrogen chloride gas nor in methanol containing a catalytic amount of concentrated sulphuric acid produced the expected ester 32.



However, when the Sandmeyer reaction was carried out first, and then the esterification was attempted (eq. 27 and 28) the required ester 31 could be obtained in good overall yield. The results seen in equation 27 are in marked contrast to what had been observed for the analogous Balz-Schiemann reaction which should have produced the corresponding fluoro compound (sec. 2.3.1). No explanation for this apparent anomaly is readily available.

The acid 33 and the ester 31 are readily identified by their physical and spectral characteristics. 2-Chloro-5-methylbenzoic acid is an off-white crystalline solid, while its methyl ester is a colorless high boiling liquid. The spectral identification of these compounds is relatively straightforward.

Considering initially acid 33 only, the mass spectrum of this



compound (the product of the Sandmeyer reaction) has a parent ion peak at $m/e=170$ accompanied by a peak of $1/3$ the intensity at 172. This is characteristic of a compound containing chlorine; 170 corresponds to the molecular weight expected for 33. Some of the major fragmentation peaks are summarized in table 4; three fragmentation patterns are easily discernible as shown in the table, although structures for the ion fragments have not been postulated. The obvious fragments lost are OH, CO, Cl, and CO_2H , as would be expected for a compound such as 33.

The presence of the chlorine in place of the amino group at position 2 of the ring has a marked effect on the 60 MHz proton NMR spectrum of the compound. As seen in table 5, three distinct signals are observed for the three aromatic protons in 2-amino-5-methylbenzoic acid; proton exchange between the amino and carboxyl groups results in a broad single peak in the same region as the aromatic protons. Replacing the amino group with a chlorine leads, of course, to loss

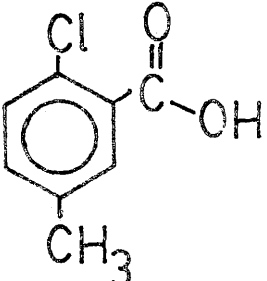
	m/e	Fragment lost		
	170			P
	153	170-17	OH	P ₁
	125	153-28	CO	P ₂
	90	125-35	Cl	P ₃
	125	170-45	CO ₂ H	P ₄
	90	125-35	Cl	P ₃
	135	170-35	Cl	P ₅
	90	135-45	CO ₂ H	P ₃

Table 4 Mass Spectral Data for 2-Chloro-5-methylbenzoic Acid

2-amino-5-methylbenzoic acid					
δ					
2.2	s	3H			CH ₃
6.75	d	1H	J _{3,4} =8.0 Hz		H-3
6.95	broad	3H			NH ₂ , CO ₂ H
7.2	d of d	1H	J _{3,4} =8.0 Hz, J _{4,6} =2.0 Hz		H-4
7.7	d	1H	J _{4,6} =2.0 Hz		H-6
2-chloro-5-methylbenzoic acid					
δ					
2.35	s	3H			CH ₃
7.45		2H			H-3, H-4
7.75		1H			H-6
11.2	broad	1H			CO ₂ H
methyl 2-chloro-5-methylbenzoate					
δ					
2.25	s	3H			CH ₃
3.85	s	3H			OCH ₃
7.25		2H			H-3, H-4
7.55		1H			H-6

Table 5 60 MHz Proton NMR Data for the 2-Chloro-5-methyl Series

of the NH_2 proton signal and the shift downfield of the carboxyl proton. The aromatic region is drastically changed, the signals becoming much more compressed and appearing almost as two singlets with intensity of 1:2. The methyl group singlet is shifted only slightly downfield. (See Appendix 1, spectra # 1 and 2)

The same compression of signals on substitution of Cl for NH_2 is observed in the ^{13}C NMR spectra of these compounds. From the tentative peak assignments given in table 6 (assignments are based on a comparison of the actual spectrum with one obtained by an empirical calculation) it can be seen that the amino group has a much greater effect on the carbon atoms near it than does chlorine. In the case of the amino-containing compound, the signals due to the ortho carbons are shifted substantially upfield relative to benzene (δ 128.6) while the signal due to the amino-bearing carbon is considerably downfield from benzene. Replacing the amino group with chlorine results in all the signals appearing over a much narrower range and shifted downfield only slightly relative to benzene. The signals due to the methyl group and the carboxyl carbon remain essentially unchanged. (See Appendix 2, spectra # 1 and 2)

The IR spectra of these molecules were not used in the identification of the reaction products but were recorded for the purpose of added confirmation for the identity of the various molecules which were synthesized in this work. The spectrum of 2-amino-5-methylbenzoic acid displays bands characteristic of the presence of NH_2 (3445, 3340, 1305 cm^{-1}), OH (broadened top of nujol band at $\sim 2900\text{ cm}^{-1}$),

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
X=NH ₂ R=H	δ 109.6	149.1	117.1	136.4	125.7	131.5	20.2	173.5	-
X=Cl R=H	δ 128.2	131.7	131.3	134.4	136.9	133.0	20.7	171.2	-
X=Cl R=CH ₃	δ 129.4	130.4 ^a	130.4	133.0	136.3	131.5	20.1	165.7	51.8

a. Peak not seen, presumed to be buried under the peak for C-3.

Table 6 ¹³C NMR Data for the 2,5 Substituted Compounds

m/e	Fragment lost		
184			P
169	184-15	CH ₃	P ₁
153	169-16	O	P ₂
125	153-28	CO	P ₃
169	184-15	CH ₃	P ₁
153	184-31	OCH ₃	P ₂
125	184-59	CO ₂ CH ₃	P ₃

Table 7 Mass Spectral Data for Methyl 2-Chloro-5-methylbenzoic Acid

CO (1680 cm^{-1}), CO_2H (1245 cm^{-1}) and a variety of bands characteristic of the aromatic ring. Again, replacement of amino by chloro leads to some changes, notably loss of the bands attributable to NH_2 , a slight shift of the CO band to $\sim 1700\text{ cm}^{-1}$, and the appearance of a band at 1050 cm^{-1} characteristic of chlorine bonded to an aromatic ring. (See appendix 3, spectra # 1 and 2)

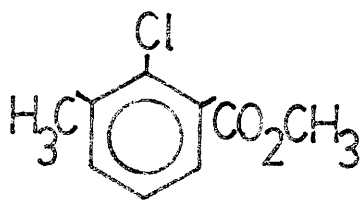
The ester 31 is also readily identified using these same spectral techniques. Its mass spectrum indicates a molecular weight of 184, and contains fragmentation peaks characteristic of the loss of CH_3 , CO, OCH_3 , CO_2CH_3 and O (see table 7). The proton NMR spectrum of 31 differs from that of 33 in the expected manner, namely loss of the broad singlet at $\delta 11.2$ and the appearance of a singlet integrating for three protons at $\delta 3.85$; the aromatic and methyl protons are shifted upfield only slightly (see table 5 and appendix 1, spectrum #3). Similarly, the ^{13}C NMR spectrum is changed only slightly by the introduction of the methoxyl group. A new signal appears at $\delta 51.8$ due to the presence of OCH_3 and with the exception of the signals due to the ring carbon bearing the carbomethoxy group and the carbonyl carbon itself, the remaining signals are shifted upfield only slightly. The effect of esterification is most pronounced for the carbonyl signal, which is shifted downfield by 4.5 ppm, and less so on C-1 which appears 1.2 ppm upfield. (See table 6 and appendix 2, spectrum #3). The IR spectrum contains bands expected for an aromatic ester ($1500, 1215\text{ cm}^{-1}$), the CO is shifted to 1745 cm^{-1} , and again the bands characteristic of the aromatic ring are present. (See appendix 3, spectrum #3).

It is thus clear that the identity of the compounds 31 and 33 is firmly established; in this work proton NMR spectroscopy was used routinely as a characterization tool since the features of the spectra for the molecules produced are quite distinct.

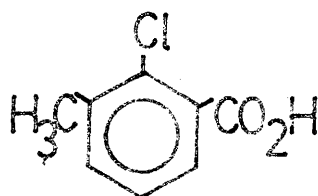
2.4.2 2-Chloro-3-methyl Series

The synthesis of methyl 2-chloro-3-methyl benzoate 34 from 2-amino-3-methylbenzoic acid 36 via 2-chloro-3-methylbenzoic acid 35 was achieved in precisely the same manner as described for the 2-chloro-5-methyl series, namely a Sandmeyer reaction to convert 36 into 35 followed by esterification to produce the ester 34. Having used the 2,5 series as a model system, no problems were encountered in making the corresponding 2,3 substituted compounds.

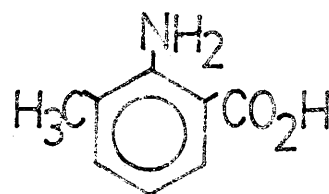
Not surprisingly, the physical characteristics of the 2,3 series are very similar to those observed in the 2,5 series; the acid 35 is a white crystalline solid while the ester 34 is a high-boiling, colourless liquid. As might have been expected, the mass spectra of 2-chloro-3-methylbenzoic acid and its methyl ester are the same as those of the corresponding 2-chloro-5-methyl compounds, at least as regards the major fragmentation peaks. (See tables 4 and 7).



34



35



36

Proton NMR data for the starting amino-benzoic acid, the chlorobenzoic acid, and its methyl ester are summarized in table 8. The spectrum of 2-amino-3-methylbenzoic acid has some features in common with its 2,5 counterpart, such as the position of the signal due to the methyl protons and the fact that the amino and carboxylic proton signals overlap with those of the aromatic protons. As expected, the coupling pattern is different since the ring substitution pattern has changed. Substitution of Cl for NH₂ again compresses the aromatic region, but the coupling pattern is still discernible even though two of the signals are partially overlapping. The position of the carboxylic proton is somewhat different from that for the 2,5 compound (δ 10.5 as compared to 11.2) but the reason for this difference is not apparent. Esterification of 35 to obtain 34 results in the expected changes in the proton NMR spectrum - the signal at δ 10.5 disappears, and a singlet at δ 3.9 integrating for three protons is observed instead. (See appendix 1, spectra # 4,5 and 6)

Table 9 contains the ¹³C NMR data for the amino and the two chloro compounds under discussion. As might have been expected, many of the features are similar to those already discussed with respect to the 2,5 isomers. The presence of the amino group results in the signals being widely spaced, only in this case it is the signals due to the para carbon and the ortho carbon bearing the carboxylic acid group which are well upfield. The presence of the methyl group seems to counteract the effects of the amino group to some extent, since the other ortho carbon, which bears the methyl group, is not seen as

2-amino-3-methylbenzoic acid					
δ					
2.19	s	3H			CH ₃
6.6	t	1H	$J_{4,5}=8.0$ Hz, $J_{5,6}=8.0$ Hz		H-5
7.25	broad d	4H	J not measurable		H-4, NH ₂ , CO ₂ H
7.85	d of d	1H	$J_{5,6}=8.0$ Hz, $J_{4,6}=2.0$ Hz		H-6
2-chloro-3-methylbenzoic acid					
δ					
2.45	s	3H			CH ₃
7.35	t	1H	$J_{4,5}=J_{5,6}=7.0$ Hz		H-5
7.50	d	1H	$J_{4,6}=2.0$ Hz		H-4
7.75	d of d	1H	$J_{5,6}=7.0$ Hz, $J_{4,6}=2.0$ Hz		H-6
10.5	broad s	1H			CO ₂ H
methyl 2-chloro-3-methylbenzoate					
δ					
2.35	s	3H			CH ₃
3.9	s	3H			OCH ₃
7.3	t	1H	$J_{4,5}=J_{5,6}=7.0$ Hz		H-5
7.4	d	1H	$J_{4,6}=3.0$ Hz		H-4
7.55	d of d	1H	$J_{5,6}=7.0$ Hz, $J_{4,6}=3.0$ Hz		H-6

Table 8 60 MHz Proton NMR Data for the 2-Chloro-3-methyl Series

far upfield. (In the case of the 2,5 isomer, it was the carbon para to the amino group which had the methyl substituent; its signal, δ 125.7, is in a similar position to the methyl-bearing ortho carbon in the 2,3 isomer, δ 123.1). The introduction of the methyl ester produces the same kind of changes as have already been discussed for the 2,5 isomer. (See appendix 2, spectra # 4, 5, and 6).

The interpretation of the IR spectra of these three compounds is also very straightforward. 2-Amino-3-methylbenzoic acid has characteristic bands (all in cm^{-1}) at 3530 and 3390 (NH_2), 1680 (CO), the top of the Nujol band at ~ 2900 is very broad (OH), and the spectrum displays a number of bands characteristic of the amino and carboxylic

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
X= NH_2 R=H	δ 109.2	149.8	123.1	135.8	115.9	130.2	17.3	173.8	-
X=Cl R=H	δ 129.8	134.1	138.5	134.9	126.2	129.8	20.8	171.9	-
X=Cl R= CH_3	δ 131.5	133.0	137.9	133.6	126.2	128.5	20.5	166.8	52.3

Table 9 ^{13}C NMR Data for the 2,3 Substituted Compounds

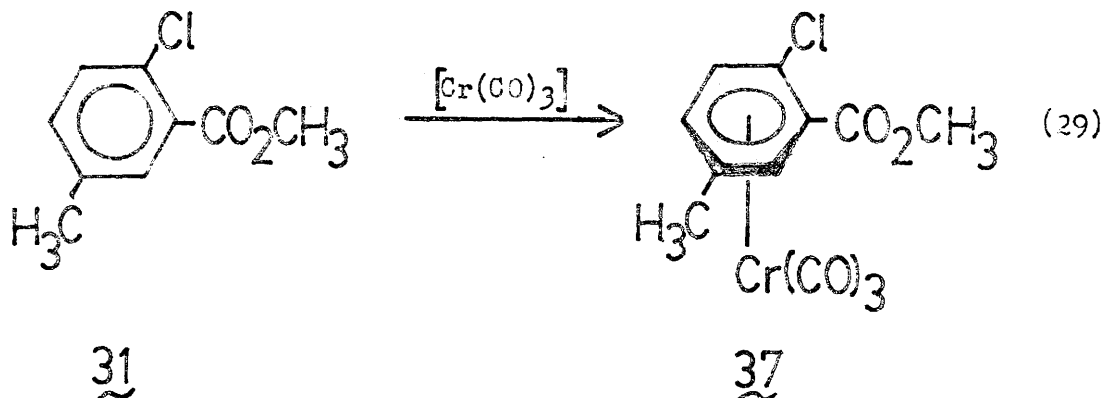
functional groups as well as the 1,2,3 substitution pattern of the aromatic ring. Substitution of Cl for NH_2 leads to the loss of the bands attributable to the amino functional group and the appearance of a band characteristic of an aromatic chloride (1055 cm^{-1}); the CO stretch is shifted to 1695 cm^{-1} , while the rest of the spectrum remains essentially unchanged. Introduction of the methyl ester function produces further changes - the CO stretch is shifted to 1740 cm^{-1} and bands characteristic of the ester group are introduced. (See appendix 3, spectra #4, 5 and 6).

As was the case for the 2-chloro-5-methyl compounds, the identity of 2-chloro-3-methylbenzoic acid and its methyl ester have been firmly established; proton NMR spectroscopy is the method of choice for routine identification.

2.5 Synthesis and Characterization of the Chromiumtricarbonyl Complexes

2.5.1 Methyl 2-Chloro-5-methylbenzoatechromiumtricarbonyl

It has been reported that a wide variety of arenechromiumtricarbonyl complexes can be readily synthesized in good yield (24b); the same cannot be said, however, of the complexes required for this work. A number of procedures had to be tried before a successful synthesis was achieved. The variables which were studied were solvent system, reaction temperature, reaction time, and source of the chromiumtricarbonyl moiety. The routine method which has been in use in this laboratory (37) involved refluxing the arene with an excess of chromiumhexacarbonyl in a solvent system of 1:3 tetrahydrofuran/*n*-butyl



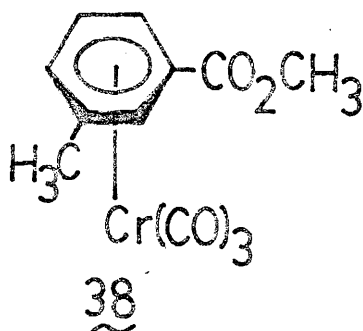
ether for two days, followed by filtration and solvent removal. This method was tried in order to achieve a successful synthesis of 37 (eq. 29); although the proton NMR spectrum of the product mixture indicated that a small amount of a complex was present, it could not be isolated. The arene 31 is not volatile enough to be removed by routine vacuum pumping, and a suitable crystallization technique for the complex 37 was not available at that time.

Several variations on the trisammoniumchromiumtricarbonyl method (15, 16) were also tried without success. Initially, two hours refluxing in dioxane was used, but no complex was isolated. Increasing the reaction time to twenty-four hours or changing the solvent to diethyl ether with reflux times from two to twenty-four hours also failed to produce the desired complex 37.

Since it had been thought that the presence of tetrahydrofuran (THF) was favourable to the formation of arenechromiumtricarbonyls via the intermediate tris(tetrahydrofuran)chromiumtricarbonyl in the THF/*n*-butyl ether solvent system, it was thought that perhaps refluxing THF alone might be a suitable reaction medium. Using a three molar

excess of chromiumhexacarbonyl, reaction periods from one to six days were tried, with three days found to produce the best results. The yield, however, was poor (less than 10 % based on arene) even under optimum conditions and the procedure could not be scaled up to produce workable quantities of material. Thus a series of reactions had to be completed in order to obtain enough of the compound for characterization. The product of these reactions was a yellow, sublimable solid, but doubts about its identity arose almost immediately. It was not consistent in colour - while some runs produced a distinctly yellow solid, others produced solids with varying degrees of an orange tinge. At times, in fact, discrete bits of orange and yellow solid could be observed; the two seemed to crystallize out together, with the yellow always the most abundant. The 60 MHz proton NMR spectra were also variable - when the compound was distinctly yellow, the chromium-complexed aromatic signal (centered around $\delta 5.8$) integrated for four rather than the expected three protons and appeared as two singlets of equal intensity. However, as the amount of orange colour increased, one of the singlets increased in intensity relative to the other and the signals integrated for less than four protons but never as low as three. (For a typical spectrum, see appendix 1, spectrum #7). The mass spectrum presented something of a puzzle - although there was a small peak at m/e 320, corresponding to the molecular weight of 37, a peak of much higher relative abundance was observed at m/e 286 which could correspond to 320-34 or, more likely, 320-35+1, i.e. loss of Cl and gain of H.

It was the ^{13}C NMR spectrum which provided the final piece of evidence leading to an explanation of these results. The spectrum showed very clearly that the compound contained four carbon atoms bearing hydrogen which were complexed to chromium and two bearing other substituents. (See appendix 2, spectrum #7). Thus it became clear that the arene had lost chlorine and it was the complex of methyl *m*-toluate 38 which had been formed. The structure of 38 is further



supported by comparisons of melting point and proton NMR data with literature reports. The reported melting point of 38 is 98°C (41), while the melting point of the compound formed in this reaction was determined to be $98.5\text{--}99^{\circ}\text{C}$. The proton NMR spectrum of 38 reported in the literature (42) and that of the yellow compound obtained from this reaction are the same - signals at δ 6.12 and 5.80 due to the ring protons, as well as singlets due to the methyl and methoxyl protons. Thus it seems quite clear that the compound formed is methyl *m*-toluatechromiumtricarbonyl 38. The presence of the orange colour was due to small amounts of the chlorine-containing complex 37, which was later made and fully characterized.

Although the mechanism of the chlorine abstraction process

was not investigated, it is postulated to occur because of the presence of trace amounts of water (13). Apparently the Cr(0) and the water react to produce a strong reducing medium which readily abstracts the chlorine.

Since the presence of water had been shown to be detrimental to the synthesis of complex 37, the THF was carefully dried and the reaction repeated. Reaction times from one to four days were tried, with two days giving the best results. Yields were very low ($\sim 3\%$ based on arene) but small amounts of an orange solid could be isolated and purified by sublimation. The proton NMR spectrum of this compound was fairly straightforward, as can be seen from an examination of table 10. The methyl and methoxyl proton signals are sharp singlets; the two singlets from the aromatic protons are somewhat broadened, but no coupling is measurable on the 60 MHz spectrum. The signals due to the aromatic protons are shifted upfield relative to those for the uncomplexed arene, reflecting the decreased π -electron density in the aromatic ring, which leads to the aromatic protons being less deshielded due to a reduced ring current. (For a more detailed discussion of these effects, see ref. 43) The ^{13}C NMR spectrum (see table 10) is also as expected. It is clear that there are three carbons which are complexed to chromium that have hydrogen bonded to them, and three complexed carbons having other substituents. Complexation to chromium has shifted the carbon resonances upfield by 30-40 ppm, again reflecting the reduced π -electron density in the aromatic ring. In contrast, the methyl and carbomethoxy carbon signals are

Methyl 2-chloro-5-methylbenzoatechromiumtricarboxyl

Proton NMR (60 MHz) δ

2.2	s	3H	CH ₃
4.0	s	3H	OCH ₃
5.55	s	2H	H-3, H-4
6.1	s	1H	H-6

¹³C NMR δ

19.9		CH ₃
53.0		OCH ₃
91.9, 94.7, 95.0		aromatic C-H, complexed
103.3, 107.3, 111.4		aromatic C-X, complexed
165.1		R-CO ₂ R
230.5		Cr(CO) ₃

Table 10 Proton and Carbon NMR Data for Methyl 2-Chloro-5-methylbenzoatechromiumtricarboxyl.

only one or two ppm. different from those found for the uncomplexed arene. (See appendix 1, spectrum #8 and appendix 2, spectrum #8.)

The mass spectrum provides further evidence to support the identity of this orange solid. The parent ion peak appears at m/e 320, which is the expected molecular weight of 37. Fragmentation

peaks characteristic of loss of successive CO, Cr, Cl, OCH₃, etc. are all present. A number of fragmentation patterns are possible, as evidenced by the presence, also, of peaks which can be attributed to loss of Cr(CO), Cr(CO)₂, Cr(CO)₃, and loss of two or three CO's at one time.

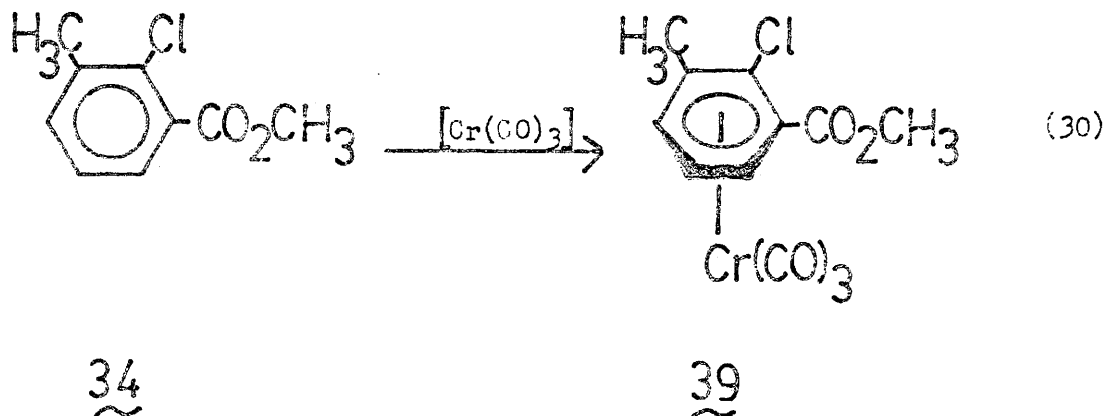
Although the IR spectrum was not used in the actual identification of the compound, its features are informative. Bands due to the chromium-bonded carbonyl stretch are found at 1995 and 1905 cm⁻¹, while the ester carbonyl stretching band is at 1745 cm⁻¹. Bands in the region 670-600 cm⁻¹ are attributable to C-O modes (38), while bands characteristic of the substitution pattern of the free arene (350-670 cm⁻¹) are no longer observed. In addition, the carbon-carbon double bond stretching frequencies found at 1610 and 1580 cm⁻¹ in the uncomplexed arene are seen to be shifted by 115 and 45 cm⁻¹ respectively. (See appendix 3, spectrum #7)

All of this spectral evidence combined leaves little doubt that the orange solid is, in fact, the desired complex 37. A final piece of confirming evidence is the elemental analysis: calculated %C 44.93, %H 2.81, found %C 45.28, %H 2.95. An alternative synthetic route can be used, but yields here are also low (13). Carefully dried THF and dibutyl ether are used as solvent (heptane has also been used in place of THF) in a ratio of 1:10; approximately equimolar amounts of arene and chromiumhexacarbonyl are added. Although reaction times of about twenty-four hours have been used routinely, monitoring of the reaction with arene 31 by TLC indicated an optimum reaction period

of eight hours; longer reaction times led to extensive decomposition. This method, therefore, seems to have no advantage over the previously described refluxing THF method since yields remain low and product isolation is somewhat more time-consuming due to the presence of the higher-boiling solvent.

2.5.2 Methyl 2-Chloro-3-methylbenzoatechromiumtricarbonyl

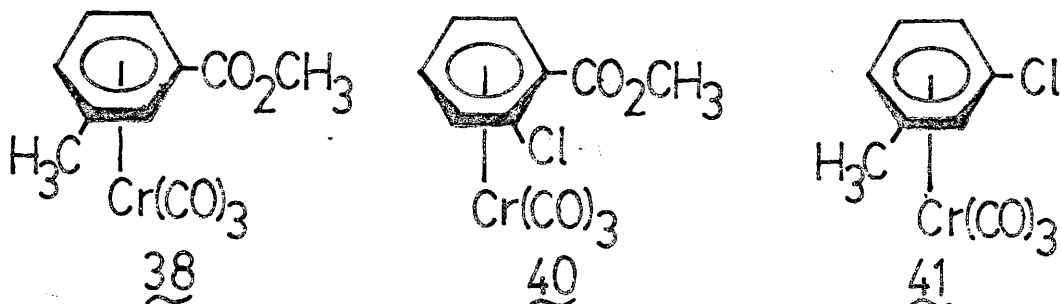
As was observed for the 2-chloro-5-methyl compound, synthesis of this complex was also extremely difficult. Since the sequence $\underline{31} \rightarrow \underline{37}$ had been used as the model system, not all of the methods tried there were tried for $\underline{34} \rightarrow \underline{39}$ (eq. 30). The first method to be tried involved refluxing the arene with chromiumhexacarbonyl in THF for three days. After suitable work-up, a yellow solid was obtained in low yield. The proton NMR spectrum was the same as that obtained using the 2-chloro-5-methyl arene, as was the mass spectrum. The two compounds also had the same melting point; a mixture of the two showed no melting point depression. Thus, it was concluded that the same product, methyl *m*-toluatechromiumtricarbonyl $\underline{38}$ had been obtained.



Once the procedure using dry THF had been established as a suitable route to 37, it was used in an attempt to obtain 39. Although optimum conditions were used, several attempts failed to produce any solid at all. It was concluded that the complex 39 could not be made by this route.

2.5.3 Possible Explanation of Synthetic Difficulties

At first glance, the synthesis of the complexes 37 and 39 would not appear to present any problems. The related disubstituted complexes 38, 40, and 41 are known (39), as are the fluoro-derivatives of 40 (34) and 41 (37). Since, of these three, 40 would probably



be the most difficult to obtain, one would not expect the presence of a methyl group (an inductively electron donating group) to increase the difficulty of the synthesis. It has already been shown, however, that the synthesis of the trisubstituted arene complexes 37 and 39 is, indeed, very difficult, so it would be informative to investigate possible reasons for these difficulties.

In a study of the hydrogenation of olefins using arene-chromiumtricarbonyls as catalysts, it was observed that symmetrically substituted arene complexes, such as 1,3,5-trimethoxybenzenechromium-

tricarbonyl, were poorer catalysts than less symmetrically substituted ones, such as 1,2,3-trimethoxybenzenechromiumtricarbonyl (44). This cannot be explained in terms of electronic factors relating to the relative stabilities of the two complexes, since these effects are essentially the same in the two complexes (this can be studied by looking at the frequencies of the carbonyl stretching bands in the IR spectra, 45). A crystal structure of the 1,2,3-trimethoxy complex revealed that the chromium-tricarbonyl moiety was not equidistant from the six ring carbons but was, in fact, displaced slightly towards the three unsubstituted carbons (13). Similar effects have been observed for certain mono-substituted arene complexes, for which crystal structures have shown that the chromium is off-center, the direction of the shift depending on the nature of the substituent. These structures also revealed that the carbon bearing the substituent was bent slightly out-of-plane, the direction again depending on the nature of the substituent. (46).

With these results in mind, it is now necessary to look briefly at the mechanism of the catalytic hydrogenation reaction using arene-chromiumtricarbonyl complexes (40). One of the proposed mechanisms when the reaction is carried out in tetrahydrofuran (THF) as solvent involves the intermediacy of $(\text{THF})_3\text{Cr}(\text{CO})_3$, the formation of which results in the decomplexation of the arene. If one assumes that the chromium is somewhat off-center, then certain of the ring-chromium bonds are "long" and thus weakened; it is easy, then, to envisage a facile attack by a THF molecule on one of these "long" bonds, leading

to the disruption of the arene complex. Using this hypothesis, it is a simple matter to propose an explanation as to why 1,2,3-trimethoxybenzenechromiumtricarbonyl is a better catalyst than the 1,3,5 derivative; the 1,2,3 complex contains "long" chromium-ring bonds, thus facilitating attack by THF. In the 1,3,5 complex, all of the chromium-ring bonds are the same, so attack by THF is somewhat more difficult, rendering the complex less effective as a catalyst.

Relating these observations to the difficulties in the synthesis of the complexes 37 and 39 should not be too difficult. In both cases the arenes are unsymmetrical; in the case of 37 it might be proposed that the forces which lead to the off-center displacement of the chromium oppose each other in such a way that a stable equilibrium position of the chromium with respect to the ring carbons is difficult to attain. The fact that the complex can be isolated (although the yield is low) attests to the fact that some sort of energetically favourable arrangement of atoms is possible. In the case of complex 39, a more direct analogy with 1,2,3-trimethoxybenzenechromiumtricarbonyl is possible. The chromium atom would be expected to be displaced in the opposite direction, however, due to the electron withdrawing characteristics of chlorine and carbomethoxy. (This latter fact might tend to destabilize both complexes, since complex formation is facilitated by increased electron density in the aromatic ring.) The net result, however, is that some "long" chromium-carbon bonds would be expected, leaving the complex susceptible to attack by THF or some other suitable solvent molecule. The fact that the complex

cannot be made in the presence of THF lends credibility to this conclusion.

Thus, it appears that the difficulties associated with the synthesis of 37 and 39 are not as surprising as was originally thought.

2.6 Synthesis of the Methoxyl Derivatives

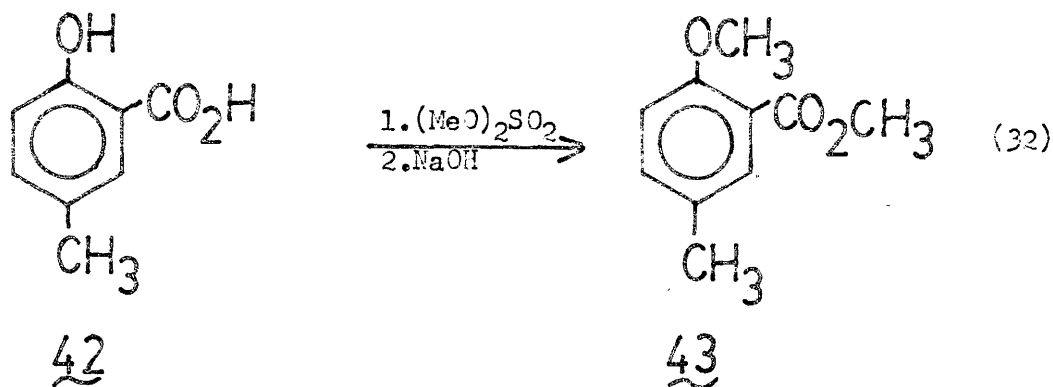
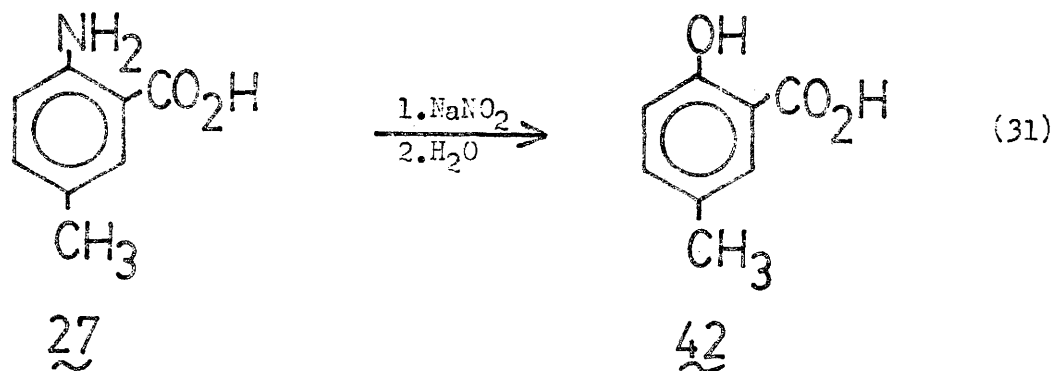
2.6.1 Reason for Synthesis

In the reaction of sodium methoxide with the complexes 37 and 39, the products, after decomplexation, are the methyl esters of 2-methoxy-5-methylbenzoate and 2-methoxy-3-methylbenzoate. Whether a mixture of the two is obtained or each complex yields only one product depends on the mechanism of the reaction. In order to identify the product(s) of the nucleophilic substitution reaction unambiguously, it is necessary to have available authentic samples of the possible product arenes obtained by an independent route. This being the case, physical and spectral characteristics of the authentic samples and the substitution reaction products could be compared and the identity of the products established. It was for this reason that attempts were made to synthesize methyl 2-methoxy-5-methylbenzoate (sec. 2.6.2) and methyl 2-methoxy-3-methylbenzoate (sec. 2.6.3).

2.6.2 Synthesis of Methyl 2-Methoxy-5-methylbenzoate

The proposed reaction sequence involves synthesis of 2-hydroxy-5-methylbenzoic acid 42 (eq. 31) followed by methylation to produce methyl 2-methoxy-5-methylbenzoate 43 (eq. 32).

The synthesis of the 2-hydroxy-5-methylbenzoic acid 42 from



the commercially available 2-amino-5-methylbenzoic acid 27 was relatively straightforward, involving diazotization of the amine followed by reaction with water. Although the isolation and purification of the product presented some difficulties (sec. 3.12) a fluffy white solid was eventually obtained which was readily characterized.

The mass spectrum showed a parent ion peak at m/e 152, as expected for 42. Fragmentation peaks representing sequential loss of H_2O , CO and OH were observed; the remaining fragmentation pattern was somewhat complex and was not interpreted further.

The 60 MHz proton NMR data are summarized in table 11. The spectrum is very similar to that of the amino compound 27 (see table 5 and appendix 1, spectra #1 & 9) but the aromatic region is much more

2-hydroxy-5-methylbenzoic acid					
δ					
2.3	s	3H			CH ₃
6.85	d	1H	$J_{3,4}=8$ Hz		H-3
7.35	d of d	1H	$J_{3,4}=8$ Hz, $J_{4,6}=2$ Hz		H-4
7.7	d	1H	$J_{4,6}=2$ Hz		H-6
11.5	s	2H			CO ₂ H, OH

methyl 2-hydroxy-5-methylbenzoate					
δ					
2.22	s	3H			CH ₃
3.9	s	3H			OCH ₃
6.85	d	1H	$J_{3,4}=8$ Hz		H-3
7.3	d of d	1H	$J_{3,4}=8$ Hz, $J_{4,6}=2$ Hz		H-4
7.6	d	1H	$J_{4,6}=2$ Hz		H-6
10.8	s	1H			OH

Table 11 60 MHz Proton NMR Data for the 2-Hydroxy-5-methyl Series

clearly defined, since the hydroxyl and carboxylic acid protons appear farther downfield than do the exchanging amino and acidic protons. Similarly, the ^{13}C NMR spectra of the amino compound 27 and the hydroxyl compound are very much alike (table 12 and appendix 2, spectra #1 and 9). The resonance signal for the carbon bearing the hydroxyl group is shifted even farther downfield than is observed when the amino group is present, but the signals for the other ring carbons change by only two or three ppm. This is not surprising, since one would expect a hydroxyl and an amino group to behave in a somewhat similar fashion when electronic effects are being considered.

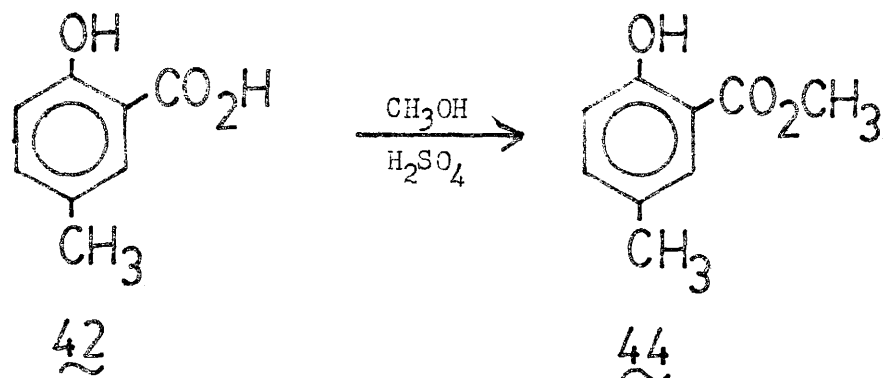
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
X=OH R=H	δ 110.9	160.3	117.7	138.1	128.9	130.6	20.3	175.1	-
X=OH R=CH ₃	δ 112.1	159.8	117.4	136.7	128.3	129.8	20.3	170.7	52.1
X=NH ₂ R=H	δ 109.6	149.1	117.1	136.4	125.7	131.5	20.2	173.5	-

Table 12 ^{13}C NMR Data for Some 2,5 Substituted Compounds

The IR spectrum of 42 contains bands characteristic of the functional groups present, namely OH (3240 cm^{-1}), COOH ($1670, 1395, 905\text{ cm}^{-1}$) and the substitution pattern of the aromatic ring ($1650-1490, 890-800\text{ cm}^{-1}$). Although not used in the actual identification of 42, its features provide further characterizing information. (See appendix 3, spectrum #8).

The second step in the synthesis of methyl 2-methoxy-5-methylbenzoate 43 (eq. 32) was not quite as straightforward. Reaction of dimethyl sulphate with the acid 42 under a variety of conditions always led to product mixtures, thought to consist of the methyl esters of 2-hydroxy- and 2-methoxy-5-methylbenzoate. The similar nature of these two compounds makes their separation somewhat difficult, unless one resorts to the more elaborate techniques of column or preparative gas-liquid chromatography. In this case, however, it is the spectral characteristics (more specifically the proton NMR spectrum) rather than a pure sample of 43 which are required, therefore use can be made of the technique of subtraction NMR spectroscopy, whereby the spectrum of a pure sample of one of the components of the mixture is electronically subtracted from that of the mixture producing, in theory, the spectrum of the other component.

To this end, it was necessary to prepare methyl 2-hydroxy-5-methylbenzoate 44, which was obtained by reacting the acid 42 with methanol containing a catalytic amount of concentrated sulphuric acid (eq. 33) The ester 44 was obtained as a high-boiling, yellow-brown liquid which was not further purified, but was characterized by its



proton and ^{13}C NMR spectra.

The 60 MHz proton NMR features of the ester 44 are summarized in table 11. As might be expected, the spectrum is very similar to that of the precursor 42, with the exceptions that the downfield resonance due to the acidic protons has shifted upfield slightly in the ester and integrates for only one proton, and the signal due to the methoxyl protons is present. The ^{13}C NMR spectrum of 44 (table 12) is also very similar to that of the acid 42; the positions of the carbon resonances are shifted by only one to two ppm., while the carboxylic carbon resonance has moved upfield by 4.4 ppm. A signal due to the methoxyl carbon is present at 52.1 ppm.

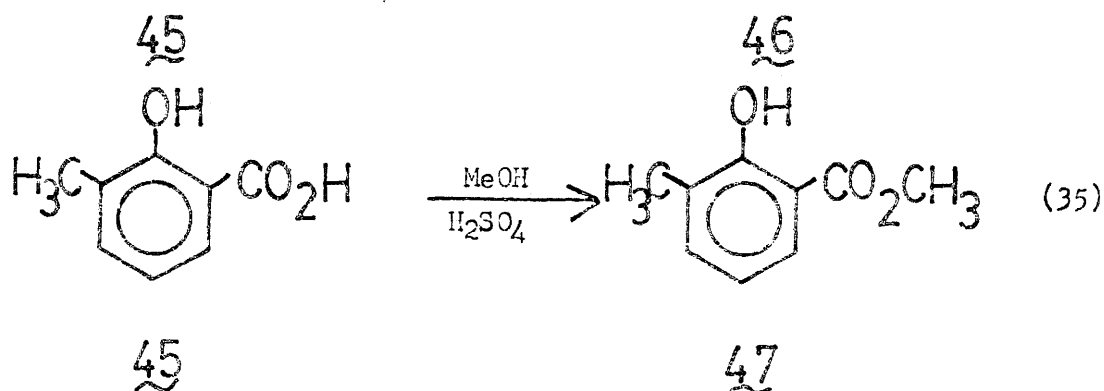
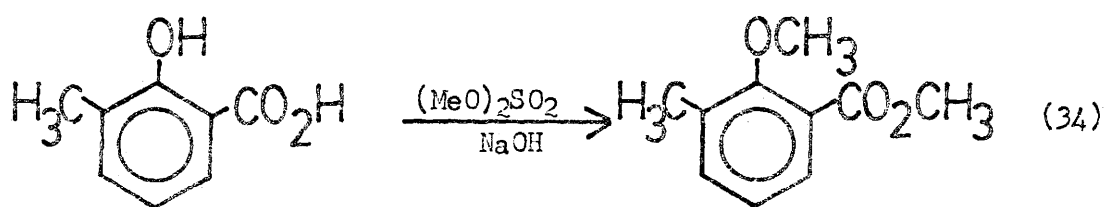
The IR spectrum of the ester 44 was also recorded. It contains bands characteristic of OH (3210 cm^{-1}), the 1,2,4 ring substitution pattern ($3020, 1625-1445, 900, 820\text{ cm}^{-1}$) and the ester group ($1630, 1295, 1090\text{ cm}^{-1}$) as well as bands due to the methyl groups in the molecule.

In order to produce the proton NMR spectrum of the ester 43, the 80 MHz proton NMR spectra of the mixture (obtained in reaction

32) and of 44 were recorded separately, then the latter was subtracted from the former. Although the electronically produced spectrum contains one or two anomalous peaks, the general features of the spectrum are clear. As expected, it is very similar to those of the acid 42 and the ester 44. An impurity appears to be present, since there is an unexpected signal in the aromatic region and more than the expected two signals for methoxyl protons. (See appendix 1, spectra # 11, 12 and 13). It should be possible, however, to use this spectrum (and those of 42 and 44) as a basis for identifying the product (or products) of the nucleophilic substitution reaction.

2.6.3 Synthesis of Methyl 2-Methoxy-3-methylbenzoate

The synthesis of methyl 2-methoxy-3-methylbenzoate 46 was somewhat simplified compared with the 5-methyl isomer, since the precursor, 2-hydroxy-3-methylbenzoic acid 45, is available commercially. Before the reaction of 45 with dimethyl sulphate was carried out,



(eq. 34) the spectral characteristics of the acid 45 and its methyl ester 47 (obtained by reacting 45 with methanol containing a catalytic amount of concentrated sulphuric acid, eq. 35) were established. The 60 MHz proton NMR spectral characteristics of 45 and 47 are summarized in table 13. The signals due to the aromatic protons in both compounds produce an easily recognizable pattern; peak assignment is relatively straightforward, based on coupling constants and chemical intuition. The differences between the two spectra are the expected ones arising from the conversion of an acid to an ester, that is loss of the signal due to the carboxylic acid proton and the appearance of the signal due to the methoxyl protons. (See appendix 1, spectra # 14 and 15).

The IR spectra of 45 and 47 were also recorded. Characteristic bands for 45 included OH (3260 cm^{-1}), aromatic C-O-H (1255 cm^{-1}), CO_2H ($1680, 1435, 1305, 900\text{ cm}^{-1}$), and the 1,2,3 ring substitution pattern ($1620, 1190, 1095, 660-620, 540\text{ cm}^{-1}$). The spectrum of the ester 47 contained many of the same bands, with the exception that those bands characteristic of the carboxylic acid group were absent, while bands characteristic of the methyl ester group ($1445, 1305\text{ cm}^{-1}$) were present. (See appendix 3, spectra # 10 and 11).

The reaction of 2-hydroxy-3-methylbenzoic acid 45 with dimethyl sulphate (eq. 34) produced a mixture, tentatively identified from its 60 MHz proton NMR spectrum as the methyl esters of the 2-hydroxy and 2-methoxy compounds. (See appendix 1, spectrum #16). No further characterization of the mixture was carried out.

It is clear, however, that the spectral characteristics of

the two isomer series have been reasonably well established, so it should be possible to determine whether one or both products are formed in the nucleophilic substitution reaction.

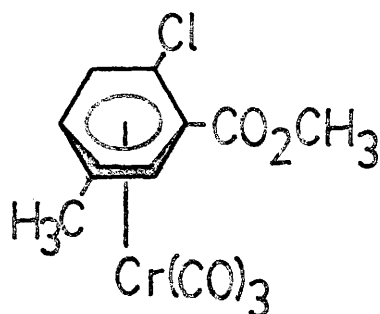
2-hydroxy-3-methylbenzoic acid					
δ					
2.2	s	3H			CH ₃
6.85	t	1H	$J_{4,5}=J_{5,6}=3$ Hz		H-5
7.45	d of d	1H	$J_{4,5}=8$ Hz, $J_{4,6}=2$ Hz		H-4
7.8	d of d	1H	$J_{5,6}=8$ Hz, $J_{4,6}=2$ Hz		H-6
11.7	broad s	2H			CO ₂ H, OH
methyl 2-hydroxy-3-methylbenzoate					
δ					
2.1	s	3H			CH ₃
3.8	s	3H			OCH ₃
6.65	t	1H	$J_{4,5}=J_{5,6}=7$ Hz		H-5
7.25	d of d	1H	$J_{4,5}=7$ Hz, $J_{4,6}=2$ Hz		H-4
7.60	d of d	1H	$J_{5,6}=7$ Hz, $J_{4,6}=2$ Hz		H-6
11.2	s	1H			OH

Table 13 60 MHz Proton NMR Data for the 2-Hydroxy-3-methyl Series

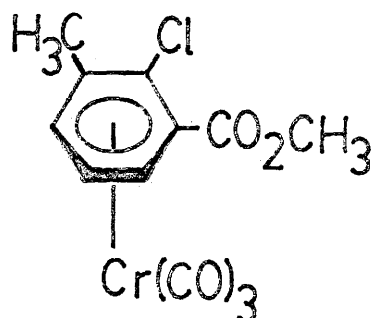
2.7 Nucleophilic Substitution by Methoxide Ion

2.7.1 Results

Although initially it was intended that the reaction of methoxide ion with halo-arenechromiumtricarbonyls would be studied using at least four such complexes (methyl 2-chloro-5-methylbenzoate-chromiumtricarbonyl 37, the 2-chloro-3-methyl analogue 39, and the



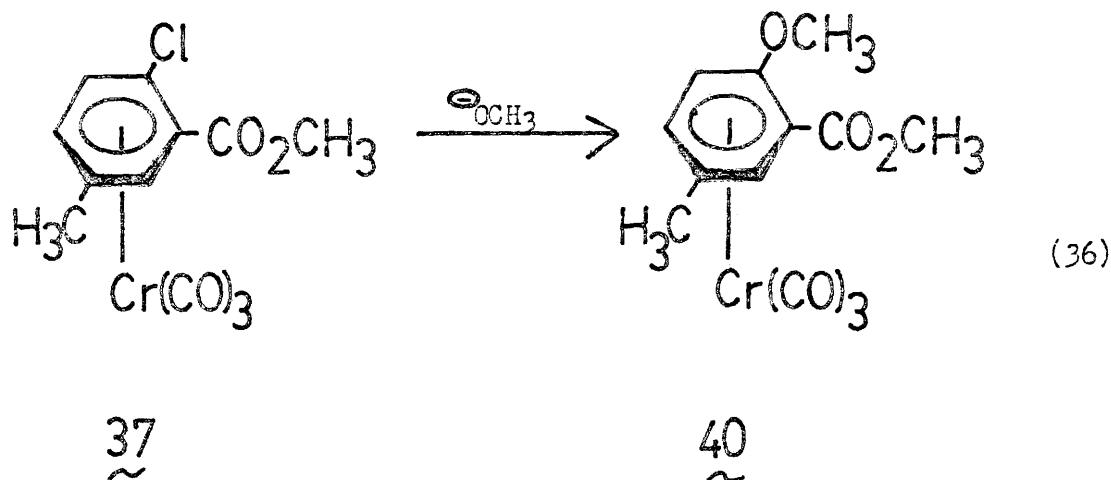
37



39

corresponding 2-fluoro compounds), synthetic difficulties resulted in only the 2-chloro-5-methyl complex 37 being available. The reaction of 37 with methoxide ion leading to the complex 40 as the expected major product (eq. 36) was carried out according to routine methods (13) - sodium was added to dry methanol and once methoxide formation was complete the complex 37 was added. The mixture was stirred overnight; after suitable work-up the organic products were isolated, treated with diazomethane (this was done in order to regenerate ester which may have been hydrolysed by the methoxide), and the solvent removed.

The 60 MHz proton NMR spectrum of the product mixture is



somewhat complex. (See appendix 1, spectrum # 17). The complex multiplet centered at δ 1.28, the doublet at δ 4.45 and the aromatic signal centered at δ 7.95 can be attributed to impurities introduced during the reaction with diazomethane; similar signals were observed in the spectrum obtained for the product of an unrelated reaction. Analysis of the remaining signals leads to the conclusion that three compounds are present, identified as the unreacted starting complex 37, methoxide-substituted product 40, and decomplexed arene 31; table 14 summarizes the peak assignments. The presence of 31 is not totally unexpected, since the reaction conditions require that 37 be in solution for twenty-four hours and it is known that many arenechromiumtricarbonyls are much less stable in solution than in the solid state.

The assignment of peaks as being due to the presence of unreacted 37 is relatively straightforward, using relative peak area measurements and comparisons with the spectrum of pure 37. Again, the presence of this compound is not surprising; it has previously

methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl					
δ					
2.25	s	3H			CH ₃
+4.15	s	3H			OCH ₃
5.75	broad s	2H			H-3, H-4
6.25	broad s	1H			H-6
methyl 2-methoxy-5-methylbenzoatechromiumtricarbonyl					
δ					
2.5	s	3H			CH ₃
3.95	s	3H			OCH ₃ (ether)
4.1	s	3H			OCH ₃ (ester)
5.3	d	1H	$J_{3,4}=7\text{Hz}$		H-3
5.9	d	1H	$J_{3,4}=7\text{Hz}$		H-4
6.4	broad s	1H			H-6
methyl 2-chloro-5-methylbenzoate					
δ					
2.15	s	3H			CH ₃
+4.15	s	3H			OCH ₃
7.6	broad s	2H			H-3, H-4
7.75	"	1H			H-6
+peak not clearly resolved					

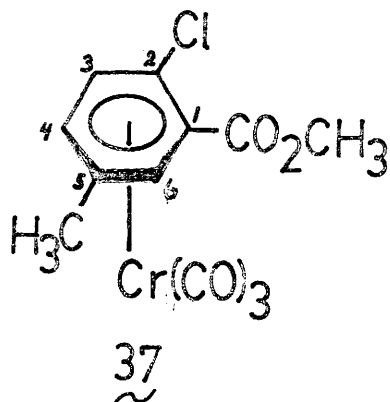
Table 14 60 MHz Proton NMR Data for Methoxide Ion Reaction Products

been reported that nucleophilic substitution by methoxide ion is much slower for chloroarene complexes than for the corresponding fluoroarene complexes (13, 20).

The remaining peaks in the spectrum are assigned to methyl 2-methoxy-5-methylbenzoatechromiumtricarbonyl 40, based on a comparison of this spectrum with that of pure methyl 2-hydroxy-5-methylbenzoate 44 and with the subtraction NMR spectrum of methyl 2-methoxy-5-methylbenzoate 43. In both cases, certain features of the aromatic region are distinctive - a cleanly resolved doublet ($J \approx 8$ Hz, resembles half of an AB quartet), a doublet of doublets ($J \approx 8$ Hz, 2 Hz), and a poorly resolved doublet ($J \approx 2$ Hz). Taking into account the upfield shift which occurs on complexation to chromium, these peaks can be seen in the spectrum of the product mixture, although the resolution is poor. The larger coupling constant is ≈ 7 Hz, while the smaller one cannot be measured. If the other isomer, methyl 2-methoxy-3-methylbenzoatechromiumtricarbonyl, were present, the spectrum would have shown a triplet in place of the doublet at $\delta 5.3$, as is seen in the spectrum of the uncomplexed arene.

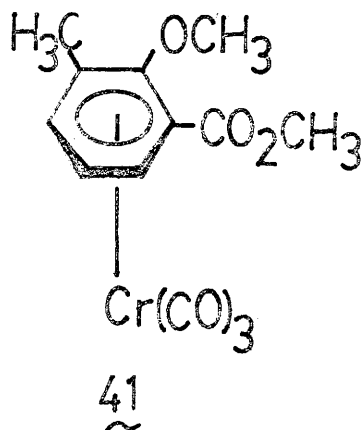
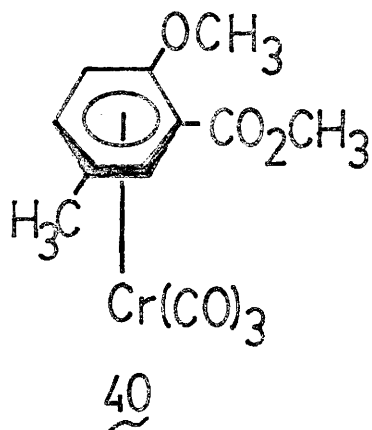
2.7.2 Conclusions

The spectral evidence would seem to indicate that only one product has been formed in the reaction of methoxide ion with methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl 37. It is useful to recall the two mechanisms which are under consideration and would lead to the partial racemization observed by Jaouen in the reaction



of methoxide ion with optically pure methyl *o*-fluorobenzoatechromium-tricarbonyl (14). One possibility is that after attack by methoxide ion at C-2, the arene becomes partially decomplexed, rolls over, reattaches itself (intramolecular teeter-totter), then loses chloride. In the case of the disubstituted complex, the other enantiomer would result; in the case of 37, only one product would be observed. The other possibility is that the methoxide ion may also attack at C-6, resulting in a 1,5-hydride shift followed by expulsion of chloride. Again, this leads to the other enantiomer in the case of the disubstituted compound, but results in the formation of two different products, 40 and 41, in the case of 37. These have different spectral characteristics, thus providing a relatively straightforward means of distinguishing between the two possible mechanisms.

Since it has been shown that only one product appears to have been formed in the reaction of 37 with methoxide ion, it might be concluded that the reaction has proceeded via the roll-over mechanism. However, it is not possible at this time to totally rule out attack

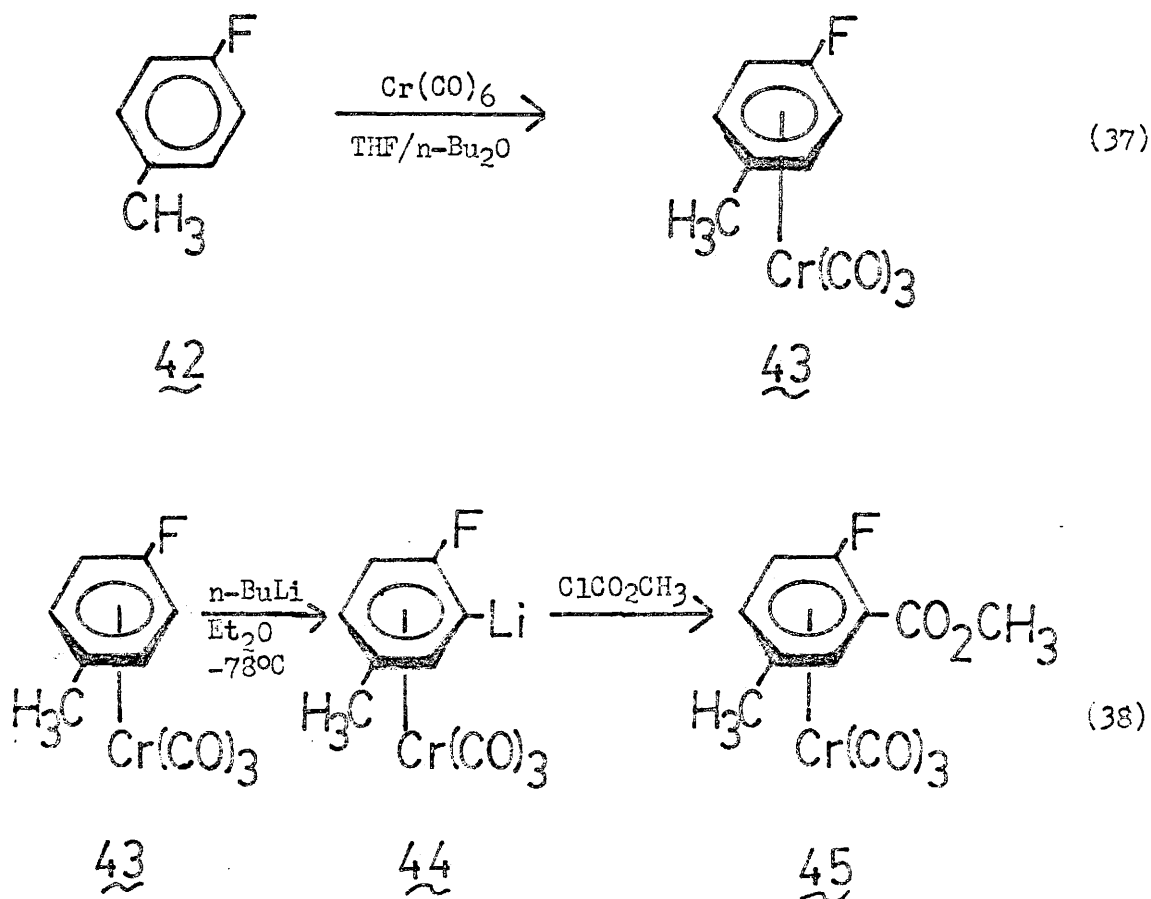


at C-6, since no information is available regarding the steric effects of the methyl group at C-5. It is not unreasonable to propose that the steric effects of the C-5 methyl group and the C-1 carbomethoxy group combine to render attack by methoxide ion at C-6 highly unfavourable. This factor cannot be studied at present, however, due to the fact that attempts to synthesize methyl 2-chloro-3-methylbenzoate-chromiumtricarbonyl 39 have so far proven unsuccessful. In the case of 39, C-6 is not excessively hindered; in fact it might be the preferred position of attack since it is C-2 which lies between the methyl and carbomethoxy groups.

Therefore, although present evidence tends to favour the roll-over mechanism, no absolute conclusion can be drawn until such time as the steric effects of the C-5 methyl group have been evaluated.

2.3 Reaction of *p*-Fluorotoluenechromiumtricarbonyl with Butyllithium and Methyl Chloroformate

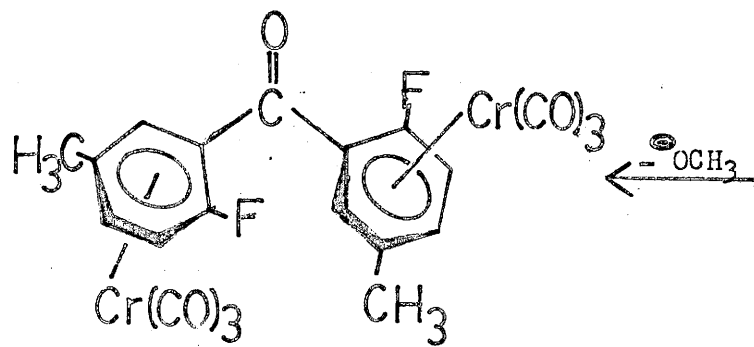
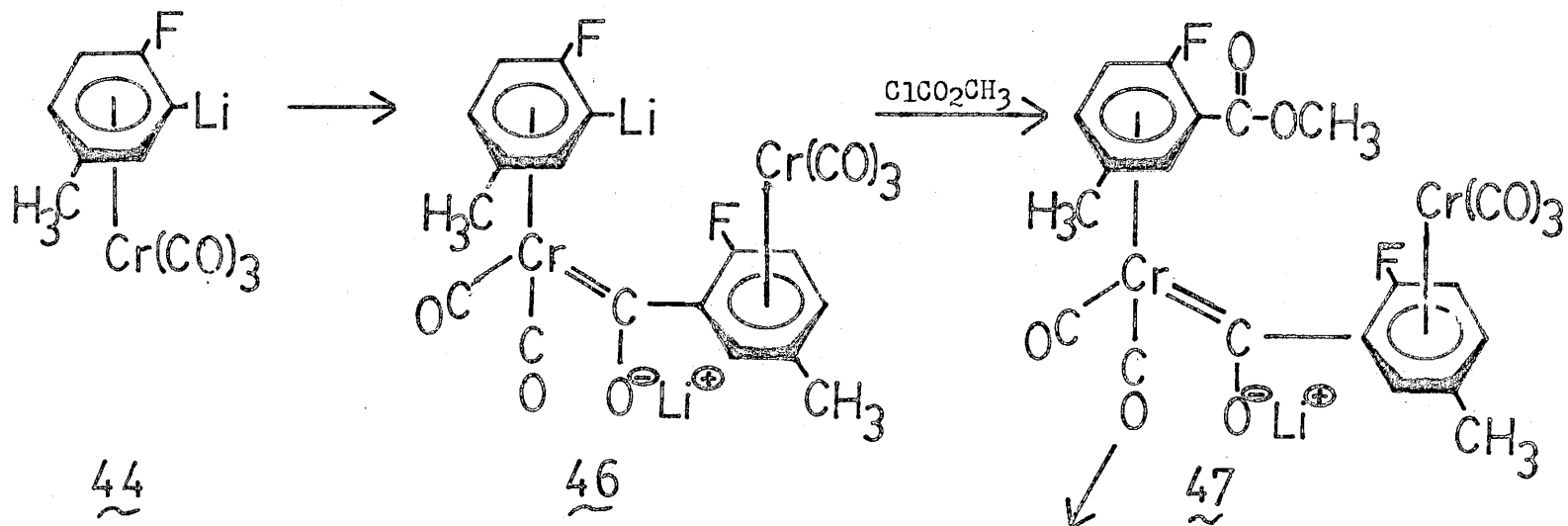
As this work was being completed, it became apparent that Semmelhack's recent report of the ortho-lithiation of various mono-substituted arenechromiumtricarbonyls (30) might provide a useful synthetic route to methyl 2-fluoro-5-methylbenzoatechromiumtricarbonyl 45, since it has already been shown that the synthesis of the arene is no simple matter (see section 2.3). In this case, the required starting material is the known *p*-fluorotoluenechromiumtricarbonyl 43, which is readily obtained by the reaction of *p*-fluorotoluene 42 with chromium hexacarbonyl in refluxing tetrahydrofuran/butyl ether (eq. 37).



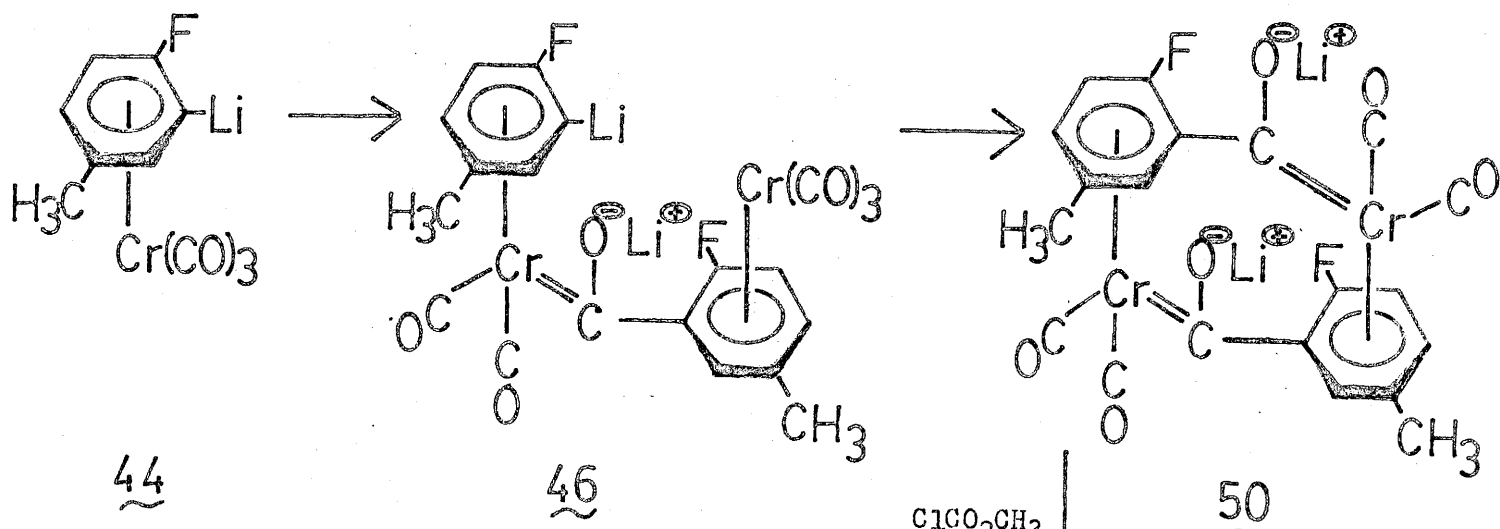
Treatment of 43 with butyllithium followed by addition of methyl chloroformate (eq. 38) was expected to produce the desired complex 45. (This procedure represents a slight modification of the method reported by Semmelhack, who treated the lithioarene complex 44 with CO_2 followed by diazomethane to obtain 45). However, when the product mixture was chromatographed, at least three air-stable products were isolated, none of which was the expected compound 45. The major product obtained was a red crystalline solid, shown by mass spectral analysis to have a molecular weight of 518. Its fragmentation pattern indicated the presence of two *p*-fluorotolyl groups, two chromium atoms and seven CO units. The proton and fluorine-19 NMR spectra of this solid were relatively simple, indicating the presence of two equivalent trisubstituted arene rings, with the third substituent ortho to the fluorine (50).

The available spectral evidence and chemical intuition lead to the proposal of two possible structures for this compound, a benzophenone and a carbonate ester, both of which result from the dimerization of the lithioarene complex 44 prior to the addition of methyl chloroformate (see eq. 39 and 40). In both cases, once the lithioarene complex 44 has formed, two molecules react to produce the dimer 46. Support for this comes from the analogous reaction of phenyllithium with arenechromiumtricarbonyls to produce carbene complexes (47). The dimer 46 then has at least two routes open to it - these shall be discussed separately.

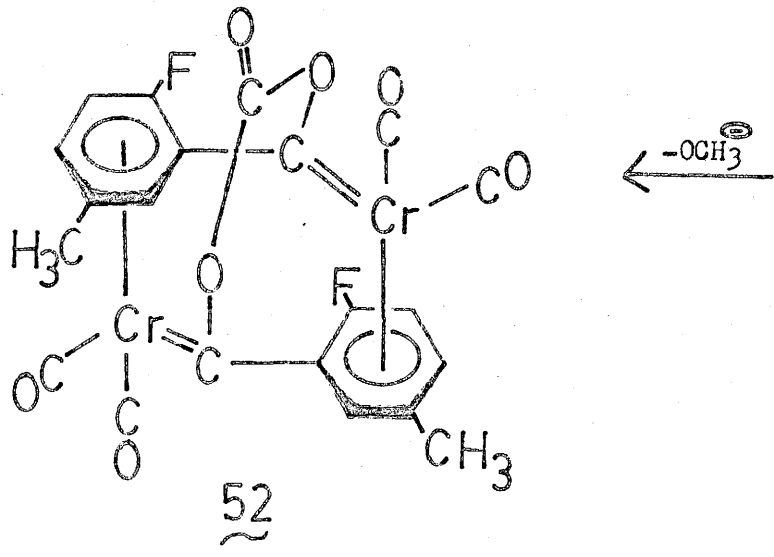
In one case (eq. 39), the dimer 46 reacts with the added methyl



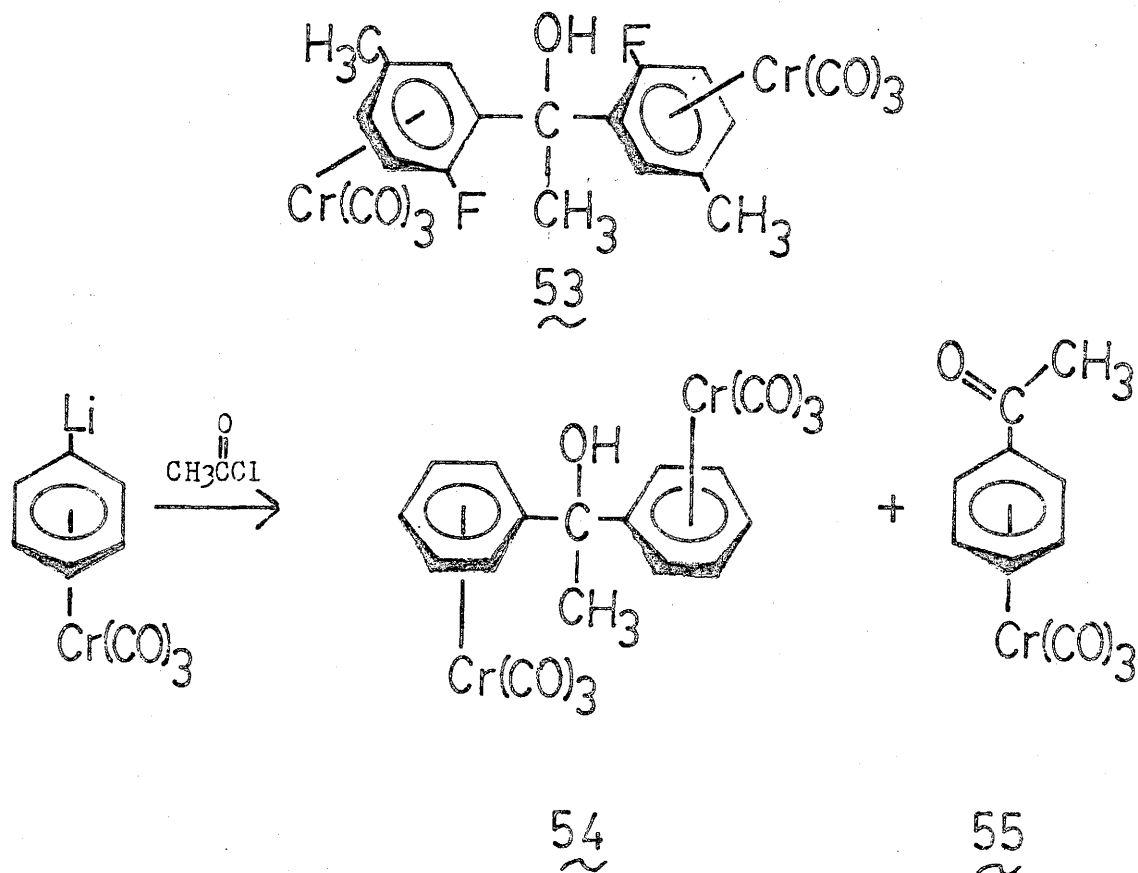
(39)



(40)



chloroformate to form the species 47. This then undergoes a rearrangement via a mechanism very similar to that observed for the well known benzilic acid rearrangement, to produce 48. A simple loss of methoxide leads to the benzophenone complex 49. It might be argued that the methyl chloroformate, which contains two reasonably good leaving groups, could have reacted in rapid succession with two molecules of 44 to give 49, but this seems very unlikely since the methyl chloroformate is present in large excess and inverse addition produces the same result. When acetyl chloride is substituted for methyl chloroformate, the tertiary alcohol 53 is formed. This result parallels the observation that the reaction of phenyllithiumchromiumtricarbonyl with acetyl



chloride (eq. 41) produces, as the major product, the alcohol 54 rather than the expected ketone 55, despite the fact that the acetyl chloride is present in large excess (48). The only way to rationalize these seemingly anomalous results, both for methyl chloroformate and acetyl chloride, is in terms of a dimerization occurring before the addition of the electrophile, as proposed for the formation of 46 (eq. 39).

Another route available to 46 involves the formation of a second carbene bridge (eq. 40), producing the double-bridged species 50. This then reacts with methyl chloroformate in two steps giving 51 and ultimately the carbonate-bridged species 52.

Since it was difficult to distinguish between 49 and 52 on the basis of their spectral characteristics, an X-ray crystallographic study of the compound was carried out (49). The results of this study (fig. 1) clearly show that the product analyzed is the benzophenone complex 49. It should be noted, however, that the mass spectrum of the product obtained initially, although almost identical to pure 49, shows a peak at P-44, indicating loss of CO₂. In addition, the ¹³C NMR spectrum had peaks at δ 265.5 and 163.9, assignable to the carbene and ester carbonate carbons, respectively. As the product was repeatedly recrystallized to obtain a sample suitable for X-ray crystallography, spectral evidence for the carbonate structure 52 disappeared. This would seem to imply that both products were formed initially, but that the carbonate was selectively eliminated during the purification steps. It is also possible that certain steps in the formation

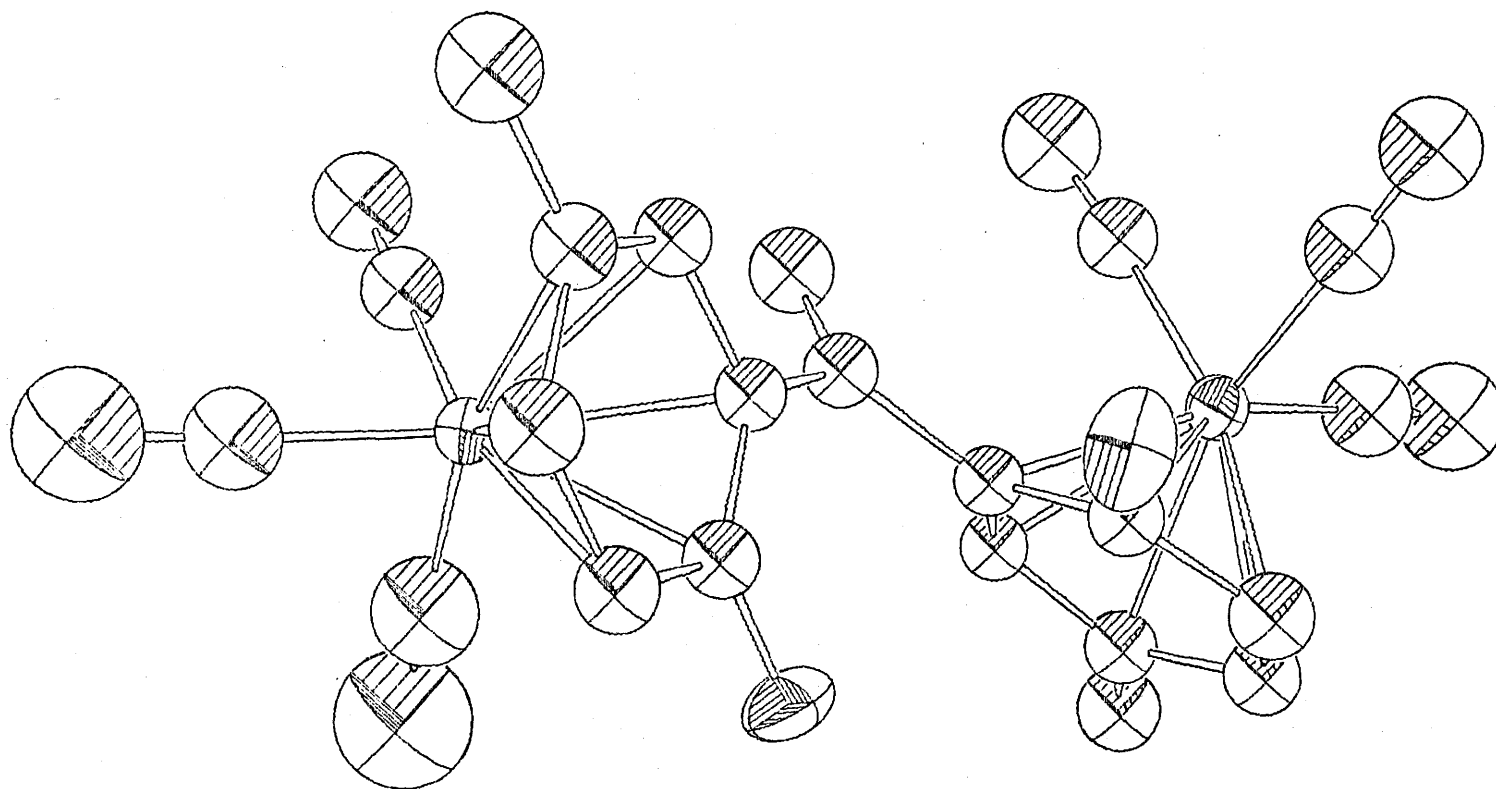


Figure 1 ORTEP Drawing of 2,2'-Fluoro-5,5'-methylbenzophenone-bis-(chromiumtricarbonyl), 12

of both products are equilibria - further investigations into the nature of this reaction are in progress.

Some details of the structure are worth noting. Although the aromatic rings are not coplanar, the chromiumtricarbonyl groups are seen to exist in an anti configuration, as might be expected on steric grounds. It is also clear that the initial attack by butyllithium occurred at the position ortho to the fluorine, as evidenced by the position of the ketone bridge.

It would seem that this reaction can provide a convenient and efficient route to bis-chromiumtricarbonyl complexes of benzophenones, and should prove useful in this regard.

CHAPTER THREE

EXPERIMENTAL

3.1 Instruments and Chemicals

Routine proton NMR spectra were recorded on a Varian T60 60 MHz NMR Spectrometer. Carbon-13 NMR spectra were recorded on a Bruker WP 80 or WH90 NMR Spectrometer. Some proton spectra (80 MHz) were also recorded on the Bruker WP80. Infrared spectra were recorded as nujol mulls or neat liquid films between NaCl plates on a Perkin-Elmer Infrared Spectrophotometer, Model 283. Mass spectra were recorded on a C.E.C. 21-110-B spectrometer operating at 70 eV. Melting points of solids were measured on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Boiling points of liquids were measured using standard micro-boiling point determination techniques and are uncorrected.

With the exceptions of tetrahydrofuran and n-butyl ether, all chemicals were used as purchased. Commercially available tetrahydrofuran was dried in the following manner - after standing for one day over CaCl_2 (with occasional shaking), the THF was refluxed over CaH_2 for about three hours and then distilled off. The distillate was then left standing over KOH pellets for two days, again with occasional shaking, after which it was again refluxed and distilled from CaH_2 . The dry solvent was stored in a stoppered flask over molecular sieve. The n-butyl ether was dried by standing over KOH for two or three days followed by the addition of small chunks of sodium. The dry solvent

was stored in a tightly capped bottle.

3.2 Attempted Synthesis of Methyl or Ethyl 2-Fluorobenzoate

(NOTE: In some preliminary work, ethyl chloroformate was used in place of methyl chloroformate; it is felt that the results are interchangeable)

3.2.1 Method A

2-Fluorobromobenzene (10.02 g, 57 mmol) was dissolved in 20 ml THF in a 100 ml 3-necked flask fitted with a magnetic stir bar, nitrogen inlet and outlet, and a serum cap. The flask and solution were flushed thoroughly with nitrogen, then the solution was cooled in a dry ice/acetone bath. *t*-Butyllithium in pentane (20 ml, 31 mmol *t*-BuLi) was added slowly via syringe; this addition was accompanied by the formation of a white vapour in the flask and a change in colour of the solution from yellow to green. After stirring at low temperature for about fifteen minutes, ethyl chloroformate (6g, 55 mmol) was added via syringe; the mixture was then allowed to warm slowly to room temperature. A white solid was filtered off, leaving a yellow liquid filtrate. Fluorine-19 NMR spectroscopy revealed that this liquid contained two major fluorine-containing components, fluorobenzene and an ortho-substituted fluorobenzene. Distillation, both at atmospheric and reduced pressure, did not produce samples which could be identified or characterized.

3.2.2 Method B

A 100 ml 3-necked flask was fitted with a magnetic stir bar, nitrogen inlet and outlet, and a serum cap. Diethyl ether (50 ml)

was added and nitrogen was bubbled through it for fifteen minutes.

2-Fluorobromobenzene (1g, 5.7 mmoles) was added and the solution was cooled in a dry ice/acetone bath. *t*-Butyllithium in pentane (10 ml, 16 mmoles *t*-BuLi) was added slowly via syringe; the mixture was kept cold and stirred for about twenty minutes.

Meanwhile, a second 100 ml 3-necked flask was fitted with a magnetic stir bar, nitrogen inlet, condenser, and a serum cap; 30 ml diethyl ether was added and cooled in a dry ice/acetone bath. Ethyl chloroformate (7 ml, 9.7 g, 90 mmoles) was added and the mixture was kept cold.

The contents of the first flask were added to the second flask slowly via syringe with constant stirring. The mixture was stirred cold for about forty-five minutes, then allowed to warm slowly to room temperature. Filtration of the reaction mixture yielded a water-soluble white solid (LiCl?) and a yellow filtrate.

The proton NMR spectrum of the filtrate (after removal of the diethyl ether) indicated that the product was a mixture. Distillation under reduced pressure produced a small degree of separation, but pure samples could not be obtained for absolute identification.

Modified versions of this method were tried, such as using longer reaction times or varying the proportions of the reagents, but in no case could positive product identification be made.

3.3 Attempted Synthesis of 2-Fluorobenzoic Acid

All glassware was cleaned and dried in an oven for at least

one hour prior to use.

Magnesium turnings (0.50 g, 20 mmoles) were placed in a dry 50 ml 3-necked flask which was then heated with a bunsen flame for a few minutes to drive out any moisture. As soon as the heating was stopped the flask was fitted with two glass stoppers and a calcium chloride drying tube. When cool, a magnetic stir bar was added and a condenser was inserted between the flask and the drying tube.

2-Fluorobromobenzene (4.4g, 25 mmoles) was dissolved in 5 ml dry diethyl ether; the solution was poured into a dropping funnel which was then fitted to the flask in place of one of the stoppers. Approximately half of the solution was added to the flask with stirring; since the reaction did not start spontaneously, the flask was warmed with a heating mantle. The reaction still did not start and neither use of a glass rod to crush the magnesium nor additional warming started the reaction. Finally, the addition of a few crystals of solid iodine succeeded in getting the reaction started. The remaining solution in the dropping funnel was added slowly, followed by about 5 ml of ether. The reaction was allowed to proceed on its own and was deemed complete when no more bubbles were observed in the solution.

The mixture was added slowly with stirring to 13 g crushed dry ice and stirred until thick and sticky. A mixture of 15g ice, 15 ml water and 2.5 ml conc. HCl was added slowly with stirring and the resulting mixture was filtered. The filtrate was transferred to a separatory funnel and extracted with ether (3x20 ml). The combined ether extracts were extracted with approximately 1M sodium hydroxide

solution (3x15 ml). The combined basic extracts were acidified using concentrated hydrochloric acid. A small amount of a sticky brown solid was filtered off. Dissolving of this solid in ether followed by solvent removal (rotovap) and vacuum pumping produced a beige-coloured foamy material. Although it was clear that the material was not 2-fluorobenzoic acid, a positive identification could not be made.

3.4 Attempted Synthesis of 2-Fluoro-5-methylbenzoic Acid

3.4.1 Method A

2-Amino-5-methylbenzoic acid (7.6 g, 50 mmol) was added to 25 ml of 1:1 concentrated hydrochloric acid in water; the mixture was cooled, with stirring, to 0°C in an ice/salt bath. A solution of 3.6g sodium nitrite in 7.5 ml water was added via a dropper, with constant stirring, at a rate such that the temperature did not rise above 5°C. Small chunks of crushed ice were added as needed to keep the temperature down. When all of the sodium nitrite solution had been added, a test for excess nitrous acid was done using potassium iodide - starch test paper - a positive result, immediate blue colouration of the paper, was obtained.

A cooled solution of 7.6g sodium tetrafluoroborate in 20 ml of water was added slowly with vigorous stirring, again maintaining the temperature below 5°C. The mixture was left to stand for about ten minutes with frequent stirring and then was filtered to give a small amount of a brown solid and a brown-coloured filtrate.

To this brown filtrate was added 2.5g cuprous chloride; the

resulting mixture was warmed to 80°C on a hot water bath and maintained there for about two hours. The solid precipitate was filtered off, dried, and recrystallized from carbon tetrachloride (decolorizing charcoal was used) giving a yellowish solid, m.p. 145-146°C. The mass spectrum indicated that the molecular weight of the compound was 170 (expected for $C_8H_7FO_2$ is 154; expected for $C_8H_7ClO_2$ is 170). The proton NMR spectrum was the same as that obtained for 2-chloro-5-methylbenzoic acid; a mixed melting point determination with the chloro compound produced no depression. It was concluded, therefore, that the compound made was 2-chloro-5-methylbenzoic acid, and not the desired 2-fluoro compound.

3.4.2 Method B

Method A was repeated as far as the completion of the addition of the sodium tetrafluoroborate solution. In this case, solid sodium nitrate was then added in an attempt to salt out the phenyldiazonium tetrafluoroborate salt. Although the solution changed colour from reddish to pale orange, no precipitate was formed and the method was abandoned.

3.4.2 Method C

Concentrated sulphuric acid, 2.7 ml, was added slowly with stirring to 20 ml water in a 100 ml round-bottomed flask. 2-Amino-5-methylbenzoic acid (3.6g, 23.8 mmoles) was added to the hot solution. After warming the mixture in a hot water bath for approximately half an hour, 20 ml of water were added and the mixture was cooled in ice with vigorous stirring. A cooled solution of 1.9g sodium nitrite in

5 ml water was added slowly with constant stirring at a rate such that the temperature did not rise above 5°C. After the addition was complete the mixture was removed from the ice bath and stirred for twenty minutes. The mixture was then returned to the ice bath and a cooled solution of 3.85g sodium tetrafluoroborate in 15 ml water was added, again maintaining the temperature below 5°C. Once this addition was completed, the mixture was allowed to warm slowly to room temperature, then it was heated slowly almost to boiling in a hot water bath; it was then stirred for about twelve hours (overnight) without heating. The brown solid which was isolated was identified as the 2-hydroxy derivative, based on a comparison of its proton NMR spectrum with that of an authentic sample (see section 3.12).

3.5 Attempted Synthesis of Ethyl 2-Amino-5-methylbenzoate

Absolute ethanol (80 ml) was saturated with anhydrous hydrogen chloride gas by means of bubbling the gas through until the weight of the ethanol had increased by about 20 g. The ethanol was transferred to a 250 ml round-bottomed flask and 2-amino-5-methylbenzoic acid (13.2g, 87 mmoles) was added. The resulting thick suspension was refluxed with stirring for two hours, during which time the suspension became somewhat thinner. After the reflux period was completed, the hot mixture was poured into 150 ml water, producing a brown solution. Solid sodium carbonate was added until the mixture was neutral (pH paper). A beige-brown precipitate was filtered off, dried, and re-crystallized from chloroform to give 2.95g of an off-white solid,

m.p. 166.5-168.5°C (dec). Comparison of its proton NMR spectrum in acetone solution with that of authentic 2-amino-5-methylbenzoic acid (m.p. 174-177°C (dec)) indicated that the starting material had been recovered unchanged.

3.6 Synthesis of 2-Chloro-5-methylbenzoic Acid

3.6.1 Preparation of Cuprous Chloride

A solution of 30.9g cupric sulphate and 8g sodium chloride in 100 ml water was made, with heating necessary for complete dissolution. A solution of 6.5g sodium bisulphite and 4.3g sodium hydroxide in 50 ml water was made and added slowly with stirring to the hot cupric sulphate/sodium chloride solution. The resulting suspension was cooled in ice, then the white solid precipitate was filtered rapidly and washed twice with water (as little air as possible was sucked through the solid). The moist solid was dissolved in 50 ml concentrated hydrochloric acid; the solution was kept in an ice bath until needed.

3.6.2 Diazotization and Sandmeyer Reaction

2-Amino-5-methylbenzoic acid (15g, 99 mmoles) was added to 30 ml concentrated hydrochloric acid in 30 ml water with vigorous stirring. The resulting suspension was cooled to below 5°C in an ice/salt bath. A solution of 7g sodium nitrite in 15 ml water was added slowly from a separatory funnel whose stem was below the liquid surface; the rate of addition was such that the temperature remained below 10°C, usually around 5°C. Small chunks of crushed ice were added as necessary to keep the temperature down. When all of the sodium

nitrite solution had been added, the solution was tested for excess nitrous acid using potassium iodide-starch test paper - a positive result was obtained. This mixture was then added slowly with stirring to the cold cuprous chloride solution; the resulting mixture was allowed to come to room temperature without external heating but with occasional swirling. Once it had reached room temperature, the mixture was warmed to about 60°C in a water bath; during this period frequent swirling was necessary to collapse the foamy purple precipitate which formed as the nitrogen was being given off. When no more nitrogen was seen to be given off, and the precipitate was grey in colour, the mixture was filtered and the grey solid was dried and recrystallized from carbon tetrachloride (decolorizing charcoal was used) to give 15.3g of a whitish solid (91% yield). Repeated recrystallizations finally produced an almost white solid, m.p. 147-147.5°C. The solid was identified as 2-chloro-5-methylbenzoic acid from its mass spectrum and proton NMR spectrum (appendix 1, spectrum #2). A later ¹³C NMR spectrum (appendix 2, spectrum #2) and an IR spectrum (appendix 3, spectrum #2) confirmed its identity.

3.7 Synthesis of Methyl 2-Chloro-5-methylbenzoate

Anhydrous methanol (80 ml) was saturated with dry hydrogen chloride gas by bubbling the gas through until the weight of the methanol had increased by about 25g. The 2-chloro-5-methylbenzoic acid (15 g, 88 mmoles) was added to the methanol giving a yellow solution which was refluxed for two hours. The hot reaction mixture was poured

into 150 ml water; solid sodium carbonate was added until the mixture was neutral (pH paper). A yellow-brown liquid had separated which was isolated by extraction with ether (3x100 ml). The combined ether fractions were dried (anhydrous magnesium sulphate), filtered, and the solvent was removed on the rotovap followed by vacuum pumping to give a yellow-brown oily liquid (14.5g, 89.5% yield). Distillation under reduced pressure produced an almost colourless liquid, b.p. 258-259°C. The liquid was identified by its mass spectrum (parent ion peak at m/e 184 which is the expected molecular weight), and 60 MHz NMR spectrum (appendix 1, spectrum #3). A ^{13}C NMR spectrum (appendix 2, spectrum #3) and an IR spectrum (appendix 3, spectrum #3) confirmed the identity of the compound as methyl 2-chloro-5-methylbenzoic acid.

The ethyl ester was also made using the same procedure, but substituting ethanol for methanol. The yellow-brown liquid was not further purified; its mass spectrum had the parent ion peak at m/e 198, as expected. The 60 MHz proton NMR spectrum differed from that of the methyl ester by the presence of a quartet (δ 4.40, 2H) and a triplet (δ 1.4, 3H) characteristic of the ethyl group in place of the methyl group singlet (δ 3.85, 3H).

3.8 Synthesis of 2-Chloro-3-methylbenzoic Acid

The procedure used was the same as the one which has already been described for 2-chloro-5-methylbenzoic acid (section 3.6) but substituting 2-amino-3-methylbenzoic acid for 2-amino-5-methylbenzoic acid. In this case the precipitate was an off-white solid which was

recrystallized twice from carbon tetrachloride (decolorizing charcoal) to give a white crystalline solid, m.p. 140.5-141°C. The identity of this compound was determined from its mass spectrum (parent ion peak at m/e 170) and its 60 MHz proton NMR spectrum (appendix 1, spectrum #5). A ^{13}C NMR spectrum (appendix 2, spectrum #5) and an IR spectrum (appendix 3, spectrum #5) provided further confirmation.

3.9 Synthesis of Methyl 2-Chloro-3-methylbenzoate

The procedure used was the same as the one which has already been described for methyl 2-chloro-5-methylbenzoate (section 3.7) but substituting 2-chloro-3-methylbenzoic acid for 2-chloro-5-methylbenzoic acid. The yellow liquid product was vacuum distilled to give a colourless liquid, b.p. 257.5-258.5°C. The compound was identified by its mass spectrum (parent ion peak at m/e 184) and its 60 MHz proton NMR spectrum (appendix 1, spectrum #6). A ^{13}C NMR spectrum (appendix 2, spectrum #6) and an IR spectrum (appendix 3, spectrum #6) provided further confirmation.

3.10 Synthesis of Methyl (or Ethyl) 2-Chloro-5-methylbenzoatechromiumtricarbonyl

(Whether the methyl or ethyl ester was used, it is believed that the results are interchangeable)

3.10.1 Method A

Ethyl 2-chloro-5-methylbenzoate (7g, 35 mmoles), chromium hexacarbonyl (10g, 42 mmoles), n-butyl ether (30 ml) and tetrahydrofuran (10 ml) were put in a 250 ml round-bottomed flask which was

flushed out with nitrogen for about five minutes. The mixture was refluxed for two days in an oil bath at 120°C. After cooling, the solvents were removed on a high vacuum line, leaving a brown gummy material. Diethyl ether was added and the mixture was filtered under nitrogen pressure to remove unreacted chromiumhexacarbonyl and other by-products. The orange filtrate was put on the rotovap to remove the solvent, producing a solid. A little more ether was added and the filtration was repeated. A proton NMR spectrum of the orange oily residue indicated that a small amount of the desired complex was present, however attempts to crystallize the complex using pentane were unsuccessful.

3.10.2 Method B

3.10.2.1 Preparation of Trisammoniachromiumtricarbonyl

Ethanol (95%, 120 ml), potassium hydroxide (7.75g, 138 mmoles), and chromiumhexacarbonyl (4.5g, 20 mmoles) were placed in a 500 ml 3-necked flask which was fitted with a condenser, a nitrogen inlet and a magnetic stir bar. After flushing with nitrogen for about ten minutes, the mixture was refluxed overnight (approximately eighteen hours). The resulting orange solution was cooled in ice, then 150 ml concentrated ammonium hydroxide was added; the mixture was stirred for two hours at room temperature under a gentle flow of nitrogen. The yellow solid which formed was filtered off under nitrogen pressure then pumped dry under vacuum. The 3.9g of trisammoniachromiumtricarbonyl were placed in a sealed vial under nitrogen and stored in the refrigerator. If not used within ten to fourteen days the material was discard-

ed and a fresh lot prepared.

3.10.2.2 Reaction of Trisammoniachromiumtricarbonyl with Methyl or Ethyl 2-Chloro-5-methylbenzoate

The ester ($\sim 0.5\text{g}$, 2.5 mmoles) was dissolved in 30 ml dioxane; the flask containing the solution was flushed with nitrogen. Trisammoniachromiumtricarbonyl (1.01g, 5mmoles) was added and the mixture was refluxed for two and one half hours. The solvent was removed from the dirty orange filtrate leaving a sticky dark green residue. The addition of ether followed by filtration and solvent removal produced an orange liquid which had a proton NMR spectrum identical with that of the starting ester.

Modified versions of this reaction were also tried, such as increasing the reaction time to as long as twenty-four hours and changing the solvent to diethyl ether, but the same results were obtained, namely that the starting arene was recovered unchanged.

3.10.3 Method C

A 100 ml 3-necked flask fitted with a magnetic stir bar and a condenser was flushed out with nitrogen, then charged with 50 ml tetrahydrofuran (used directly as purchased) and methyl 2-chloro-5-methylbenzoate (1g, 5 mmoles). After bubbling nitrogen through the solution for about five minutes, chromiumhexacarbonyl (3.6g, 17 mmoles) was added and the mixture was heated to reflux with stirring; a gentle flow of nitrogen was maintained across the top of the condenser. Reactions were done using reflux times from one to six days long; three days was found to give the best yield. At the end of the reflux period, the mixture was cooled, filtered and the sol-

vents were removed on the rotovap. A small amount of ether was added and the filtration and solvent removal steps were repeated. After about three more repetitions of the ether addition steps, pentane was added and the solution was placed in the freezer for at least several hours. Approximately 150 mg of a yellow solid was obtained, m.p. 98.5-99°C. Although it was first thought that this compound was methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl, the spectral evidence, as discussed in section 2.5.1, did not support this conclusion. Rather, the evidence pointed to a loss of chlorine and the resulting production of methyl *m*-toluatechromiumtricarbonyl.

3.10.4 Method D

The procedure was essentially the same as method C, with the exceptions that the tetrahydrofuran was dried as described in section 3.1 and the optimum reflux period was determined to be two days. In this case, 50 mg (2.9% yield) of an orange solid, m.p. 92-93.5°C was obtained and purified by sublimation. The compound was identified from its mass spectrum (parent ion peak at m/e 320), its 60 MHz proton NMR spectrum (appendix 1, spectrum #8) and its ^{13}C NMR spectrum (appendix 2, spectrum #8). An IR spectrum was also recorded (appendix 3, spectrum #7).

3.10.5 Method E

This method was very similar to method A. In this case, the solvents were dried prior to use and the ratio of *n*-butyl ether to tetrahydrofuran was ten to one (total solvent volume was 110 ml). Methyl 2-chloro-5-methylbenzoate (6g, 32mmoles) and chromiumhexa-

carbonyl (7g, 32 mmoles) were added and the mixture was refluxed for twenty-four hours. After being cooled, the mixture was filtered, then the solvents were removed under reduced pressure. Dichloromethane was added and the mixture was filtered to remove the unreacted chromiumhexacarbonyl. High boiling petroleum ether was added in an attempt to crystallize the product, but no solid was obtained. The solvents were removed and the proton NMR spectrum of the residue was recorded; the spectrum indicated the presence of the starting arene only with no peaks observed which are characteristic of the complex.

A modified version of this procedure was also tried. In this case the ratio of butyl ether to tetrahydrofuran was twelve to one, and almost equimolar proportions of chromiumhexacarbonyl (6.6g, 30 mmoles) and methyl 2-chloro-5-methylbenzoate were used. By removing samples every half hour and analyzing them by TLC it was determined that the optimum reflux time was seven to eight hours. At the end of the reflux period, nitrogen was bubbled through, then the flask was stoppered and left in the refrigerator overnight to allow precipitation of unreacted chromiumhexacarbonyl. The mixture was poured onto the top of a chromatography column packed with alumina with hexane as solvent. Elution with hexane removed the solvents (n-butyl ether and tetrahydrofuran) and unreacted arene, leaving an orange material near the top of the column. Use of a mixed solvent system (1:1 hexane/diethyl ether) allowed elution of the orange material, identified as methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl.

3.11 Synthesis of Methyl 2-Chloro-3-methylbenzoatechromiumtricarbonyl

3.11.1 Method A

This was the same procedure as method C already described for methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl (sec. 3.10.3) but substituting the 2-chloro-3-methyl arene for the 2-chloro-5-methyl arene. Again, low yields of a yellow solid were obtained. The 60 MHz proton NMR spectrum was the same as that obtained for the other isomer. It was concluded that the same product had been formed, namely methyl m-toluatechromiumtricarbonyl.

3.11.2 Method B

This was the same procedure as method D already described, section 3.10.4, but substituting the 2-chloro-3-methyl arene for the 2-chloro-5-methyl arene. In this case, however, no solid was isolated, leading to the conclusion that the synthesis had been unsuccessful.

3.12 Synthesis of 2-Hydroxy-5-methylbenzoic Acid

Concentrated sulphuric acid (27 ml) was added cautiously to water (200 ml) in a one-liter round-bottomed flask. 2-Amino-5-methylbenzoic acid (36.24g, 240 mmoles) was added to the resulting hot solution and the mixture was warmed gently on a water bath. Water (200 ml) was added to the amine suspension; the mixture was stirred vigorously while being cooled to 5°C in an ice bath. A cold solution of 18g sodium nitrite in 35 ml water was added slowly by pipette, taking care that the temperature was maintained at 5°C. When the sodium nitrite addition was completed, the mixture was stirred in ice for about one hour; it was then warmed to 50°C and kept at that temperature for one

hour. After cooling in ice for about one half hour, the mixture was filtered, giving a small amount of a black solid and a red-coloured filtrate. A make-shift continuous extractor was set up consisting of a two-liter round-bottomed flask and a condenser. The aqueous filtrate was poured into the flask, along with 200-300 ml of chloroform. The mixture was warmed in a water bath until the chloroform began to reflux. After refluxing for about sixteen hours (overnight) the two phases were separated. The chloroform phase was dried (anhydrous magnesium sulphate), filtered, and the solvent was removed on the rotovap, leaving a brown-orange solid. Repeated recrystallization from carbon tetrachloride (decolorizing charcoal) produced a white solid, m.p. 150.5-151.5°C. The chloroform extraction process was repeated until the aqueous phase was almost colourless. A total of 15g (41% yield) of solid was obtained. The compound was characterized by its 60 MHz proton NMR spectrum (appendix 1, spectrum #9) and its mass spectrum (parent ion peak at m/e 152). ¹³C NMR (appendix 2, spectrum #9) and IR (appendix 3, spectrum #8) spectra were also recorded.

3.13 Synthesis of Methyl 2-Hydroxy-5-methylbenzoate

2-Hydroxy-5-methylbenzoic acid (3g, 20 mmoles) was dissolved in 9 ml anhydrous methanol. Concentrated sulphuric acid (0.9 ml) was added dropwise with stirring. The mixture was refluxed for six hours, then the excess methanol was distilled off and the mixture was cooled. After pouring the mixture into a separatory funnel containing some

water, diethyl ether was added, the funnel was shaken, the layers were allowed to separate and the aqueous phase was drained off. The ether phase was shaken several times with saturated sodium bicarbonate solution, then twice with water. The ether phase was dried (anhydrous magnesium sulphate), filtered and the solvent was removed on the rotovap to give a yellow liquid, b.p. 243-245°C (74.5% yield). This compound was identified from its 60 MHz proton NMR spectrum (appendix 1, spectrum #10) as methyl 2-hydroxy-5-methylbenzoate. ¹³C NMR (appendix 2, spectrum #10) and IR (appendix 3, spectrum #9) spectra were also recorded.

3.14 Synthesis of Methyl 2-Methoxy-5-methylbenzoate

Sodium hydroxide (1.7g) was dissolved in water (16 ml) in a 50 ml 3-necked flask fitted with a magnetic stir bar, a condenser, and an addition funnel. 2-Hydroxy-5-methylbenzoic acid (3g, 20 mmoles) was added and the resulting yellow solution was cooled in ice. Dimethyl sulphate (7.5 ml, 10.0g, 79 mmoles) was added dropwise from the addition funnel with constant stirring. The mixture was refluxed for four hours and then cooled. After adding some water, the mixture was transferred to a separatory funnel containing some ether and shaken. The layers were allowed to separate and the aqueous layer was drained off. The ether layer was washed twice with water containing sodium chloride, twice with dilute sulphuric acid, then with the salt water until the washings were neutral (pH paper). The ether phase was dried (anhydrous magnesium sulphate), filtered, and the solvent was removed on the roto-

vap to give a yellowish liquid, identified from its 60 MHz proton NMR spectrum (appendix 1, spectrum #11) as being a mixture of methyl 2-methoxy-5-methylbenzoate and methyl 2-hydroxy-5-methylbenzoate.

3.15 Synthesis of Methyl 2-Hydroxy-3-methylbenzoate

The procedure used was the same as that described in section 3.13, but substituting 2-hydroxy-3-methylbenzoic acid for 2-hydroxy-5-methylbenzoic acid and scaling it up by a factor of five. A yellow oil, b.p. 246-248°C was obtained in 52.2% yield. It was identified from its 60 MHz proton NMR spectrum (appendix 1, spectrum #15) as methyl 2-hydroxy-3-methylbenzoate.

3.16 Synthesis of Methyl 2-Methoxy-3-methylbenzoate

This procedure was the same as that described in section 3.14, but substituting 2-hydroxy-3-methylbenzoic acid for 2-hydroxy-5-methylbenzoic acid. A yellowish oily liquid was obtained which was thought to be a mixture of methyl 2-methoxy-3-methylbenzoate and methyl 2-hydroxy-3-methylbenzoate, based on its 60 MHz proton NMR spectrum (appendix 1, spectrum #16). No further characterization of this mixture was carried out.

3.17 Reaction of Methyl 2-Chloro-5-methylbenzoate with Chromiumtriacetylacetonate and Methoxide Ion

Anhydrous methanol, (40 ml) was placed in an oven-dried 100 ml 3-necked flask fitted with a magnetic stirring bar, a nitrogen inlet, and a condenser. Nitrogen was bubbled through for a few minutes, then

sodium (200 mg, 9 mmoles) was added. After the sodium had dissolved, methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl (175mg, 0.5 mmoles) was added. The mixture was stirred for about twenty-four hours at room temperature with nitrogen bubbling gently through the solution. After the addition of 100 ml water, the mixture was acidified using 10% hydrochloric acid. The aqueous phase was extracted with ether (3x75 ml); the combined ether phases were dried (anhydrous magnesium sulphate) and filtered. The ether solution was cooled in ice, and treated with diazomethane (see 3.18). After solvent removal, a 60 MHz proton NMR spectrum showed the product to be a mixture of at least three compounds, tentatively identified as methyl 2-chloro-5-methylbenzoatechromiumtricarbonyl, methyl 2-methoxy-5-methylbenzoatechromiumtricarbonyl, and methyl 2-chloro-5-methylbenzoate (appendix 1, spectrum #17). No further characterization of the mixture was attempted.

3.18 Preparation of Diazomethane Precursor and Generation of Diazomethane

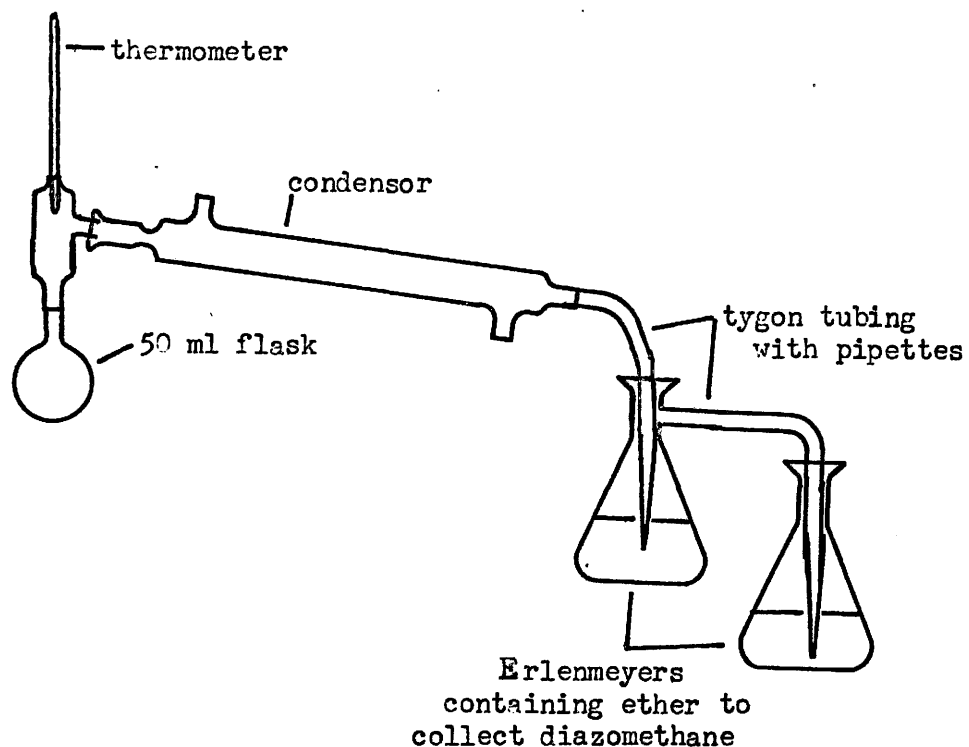
3.18.1 Preparation of p-Tolylsulfonylmethylnitrosamide

A 50% solution of sodium hydroxide in water was made and cooled to room temperature; meanwhile p-toluenesulfonylchloride (32g) was divided into portions of 19, 9 and 4 g. Methylamine (17.4 ml of 40% aqueous solution) was put in a 100 ml round bottom flask and the 19g portion of p-toluenesulfonylchloride added in portions with swirling over ten minutes; the temperature rose slowly and was maintained at 80-90°C with the aid of ice and hot water baths. After about five minutes the mixture had become acidic; 5 ml of the sodium hydroxide

solution was added with vigorous stirring, followed immediately by the 9g portion of *p*-toluenesulfonylchloride in portions with swirling. When the mixture had again become acidic, 2.5 ml of sodium hydroxide solution was added, followed by the 4g portion of *p*-toluenesulfonylchloride with swirling. Once the mixture had become acidic, sodium hydroxide solution was added until the mixture was alkaline. After rinsing the walls of the flask with some water, the mixture was heated in a boiling water bath for fifteen minutes. The hot mixture was then poured into 150 ml of glacial acetic acid in a 500 ml round-bottomed flask; the reaction flask was rinsed with a further 25 ml acetic acid. After cooling in ice to 5°C, sodium nitrite solution (12.5g in 25 ml water) was added from an addition funnel whose tip was below the surface of the liquid; the rate of addition was such that the temperature of the mixture remained below 10°C. Once the addition was complete, the mixture was stirred for fifteen minutes; *p*-tolylsulfonylmethylnitrosamide separated as a yellow crystalline solid. Water (100 ml) was added and the precipitate collected by filtration. The solid was washed with 50 ml water and sucked dry. The solid was transferred to a beaker, stirred well with 40 ml water, filtered, and washed with water until no acetic acid odour remained. The solid was dried to constant weight in a vacuum dessicator over sulfuric acid.

3.18.2 Generation of Diazomethane

The generation of diazomethane was accomplished using the



apparatus illustrated. *p*-Tolylsulfonylethylmethyl nitrosamide (1.07g) was dissolved in ether (15 ml) in the round-bottomed flask and cooled in ice. A solution of potassium hydroxide (0.2g) in ethanol (5 ml) was added. After five minutes the ethereal diazomethane was distilled off on a hot water bath and collected as shown in the diagram. The two ether portions were combined, cooled, and added dropwise to the cooled ether solution from 3.17 until excess diazomethane was present. (Excess diazomethane was detected by dipping a glass stirring rod into the mixture and then immediately into a test tube containing acetic acid. Immediate vigorous bubbling indicated the presence of excess diazomethane). The solvent was removed and the product analyzed by suitable means.

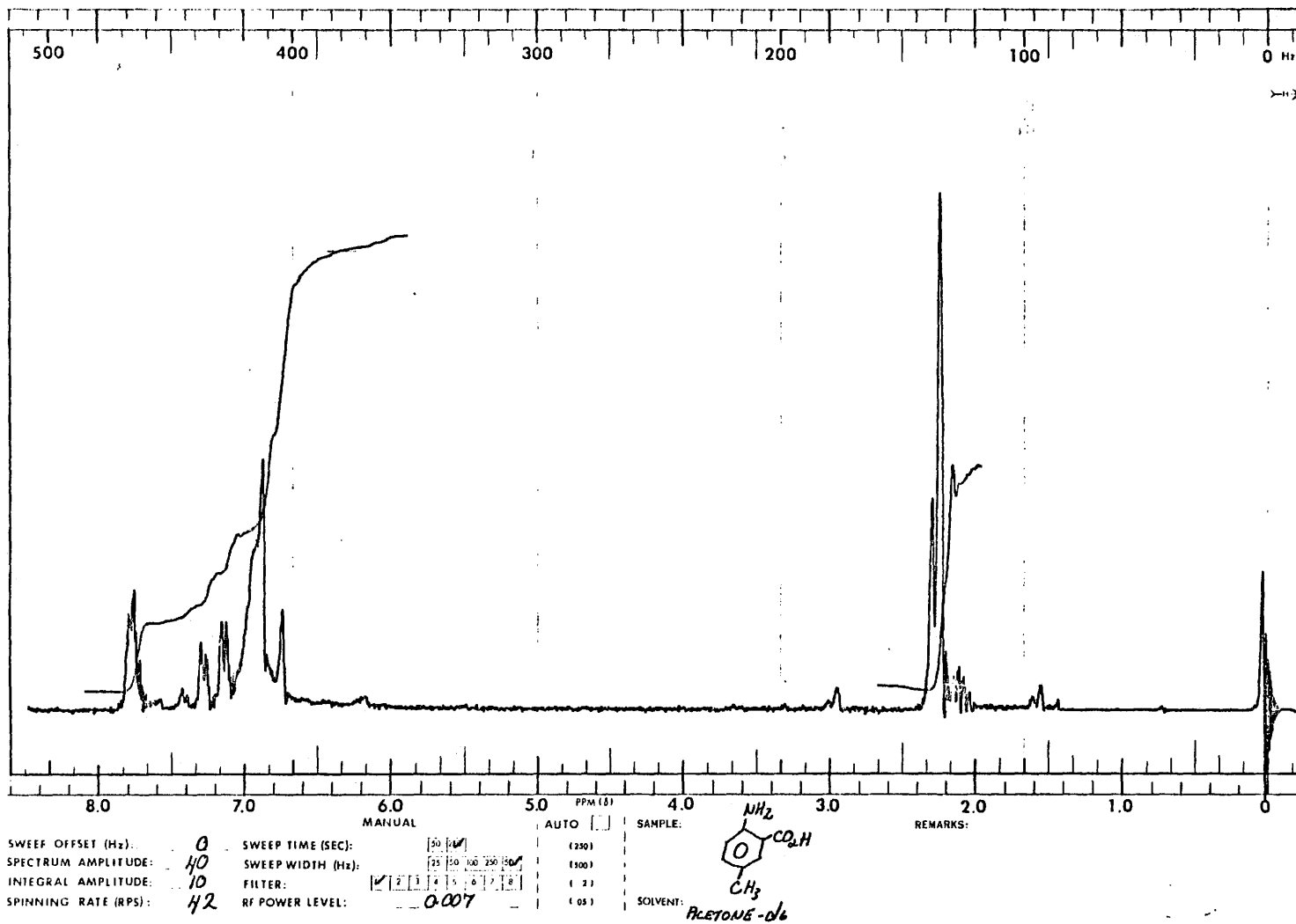
3.19 Preparation of p-Fluorotoluenechromiumtricarbonyl

p-Fluorotoluene (3g, 27 mmoles), chromium hexacarbonyl (6g, 27 mmoles), n-butyl ether (100 ml) and tetrahydrofuran (10 ml) were put in a 250 ml round-bottomed flask which was flushed out with nitrogen for about five minutes. The mixture was refluxed for two days in an oil bath at 120°C. After cooling, the solvents were removed on a high vacuum line, ether was added, the mixture was filtered to remove unreacted chromium hexacarbonyl, and the ether was pumped off, to give a yellow solid. The p-fluorotoluenechromiumtricarbonyl was purified by sublimation to give 1.02g (18% yield), m.p. 59-60°C.

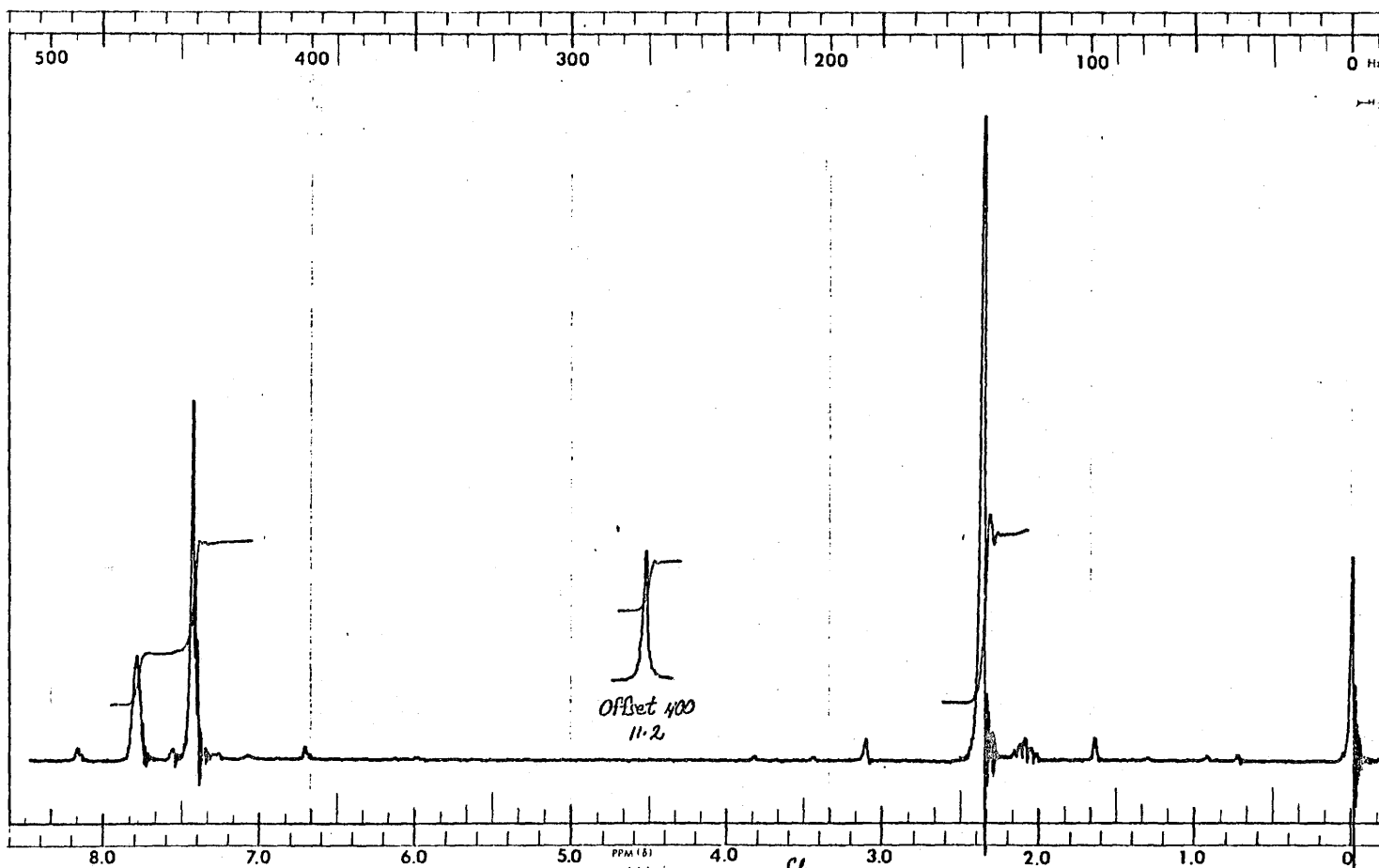
3.20 Reaction of p-Fluorotoluenechromiumtricarbonyl with Butyllithium and Methyl Chloroformate

p-Fluorotoluenechromiumtricarbonyl (1.5g) was reacted with n-butyllithium (3-fold excess) in ether at -78°C under nitrogen to give an orange-red solution which rapidly turned deep red on addition of excess methyl chloroformate at -78°C. The solvent was removed and the crude reaction product dissolved in benzene; chromatography on a short silica gel column to remove polar impurities followed by a Merck Silica Gel 60 prepacked column with elution by 10% ethyl acetate in hexane, then 25% ethyl acetate in hexane gave at least three air stable products (none was the desired methyl 2-fluoro-5-methylbenzoate-chromiumtricarbonyl). The major product (0.95g) was a red crystalline solid, m.p. 135°C, molecular weight 513. It was identified as 2,2'-fluoro-5,5'-methylbenzophenone-bis-(chromiumtricarbonyl). (See ref. 50 for spectral data).

APPENDIX ONE
PROTON NMR SPECTRA



Spectrum #1 2-Amino-5-methylbenzoic Acid



SWEEP OFFSET (Hz): 0
 SPECTRUM AMPLITUDE: 20
 INTEGRAL AMPLITUDE: 10
 SPINNING RATE (RPS): 44

SWEEP TIME (SEC): 50 ✓
 SWEEP WIDTH (Hz): 25 50 100 200 ✓
 FILTER: ✓ 2 4 5 6 7 8
 RF POWER LEVEL: 0.007

PPM (δ)

MANUAL AUTO

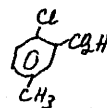
12501

15001

1.21

1.03

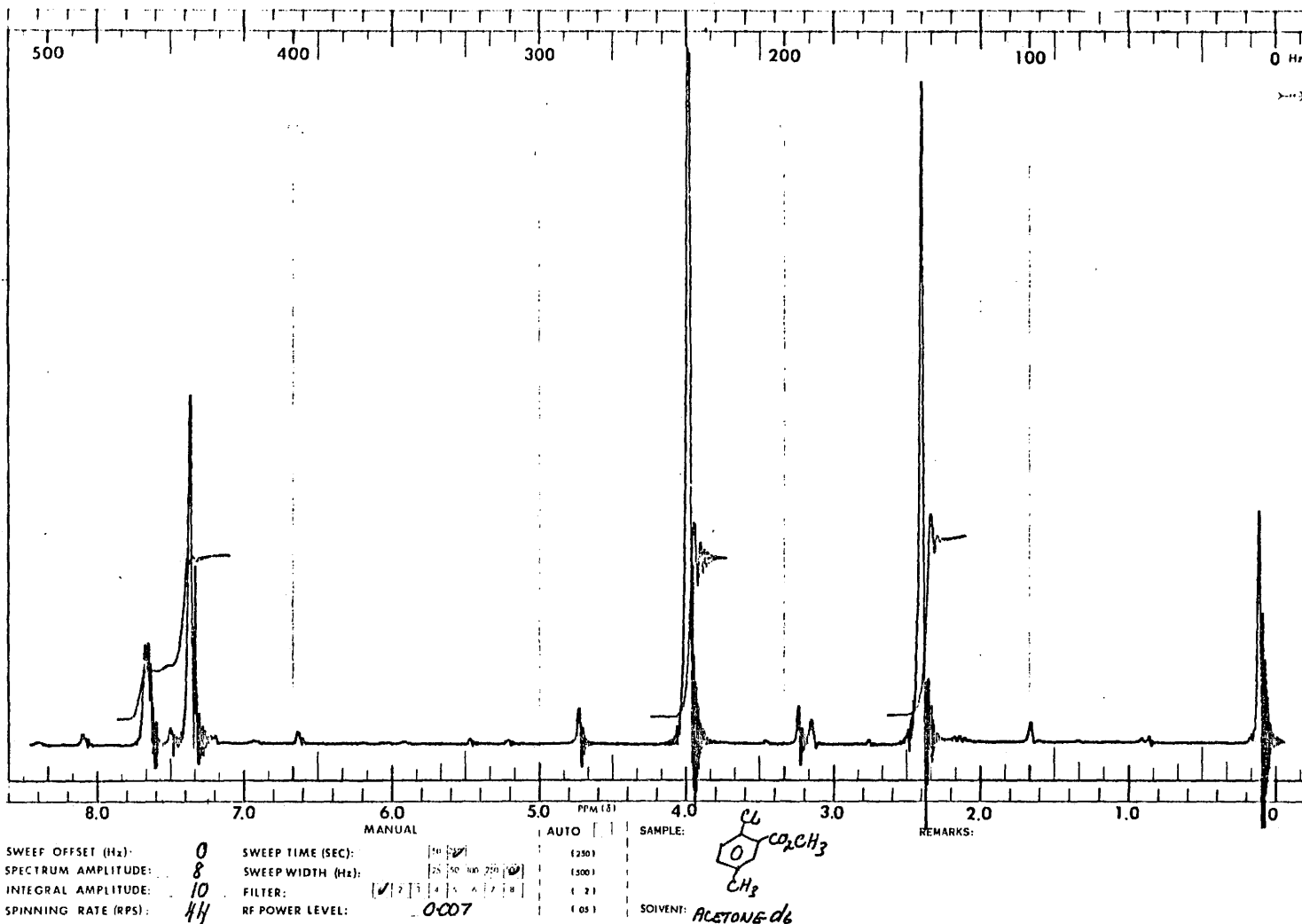
SAMPLE:



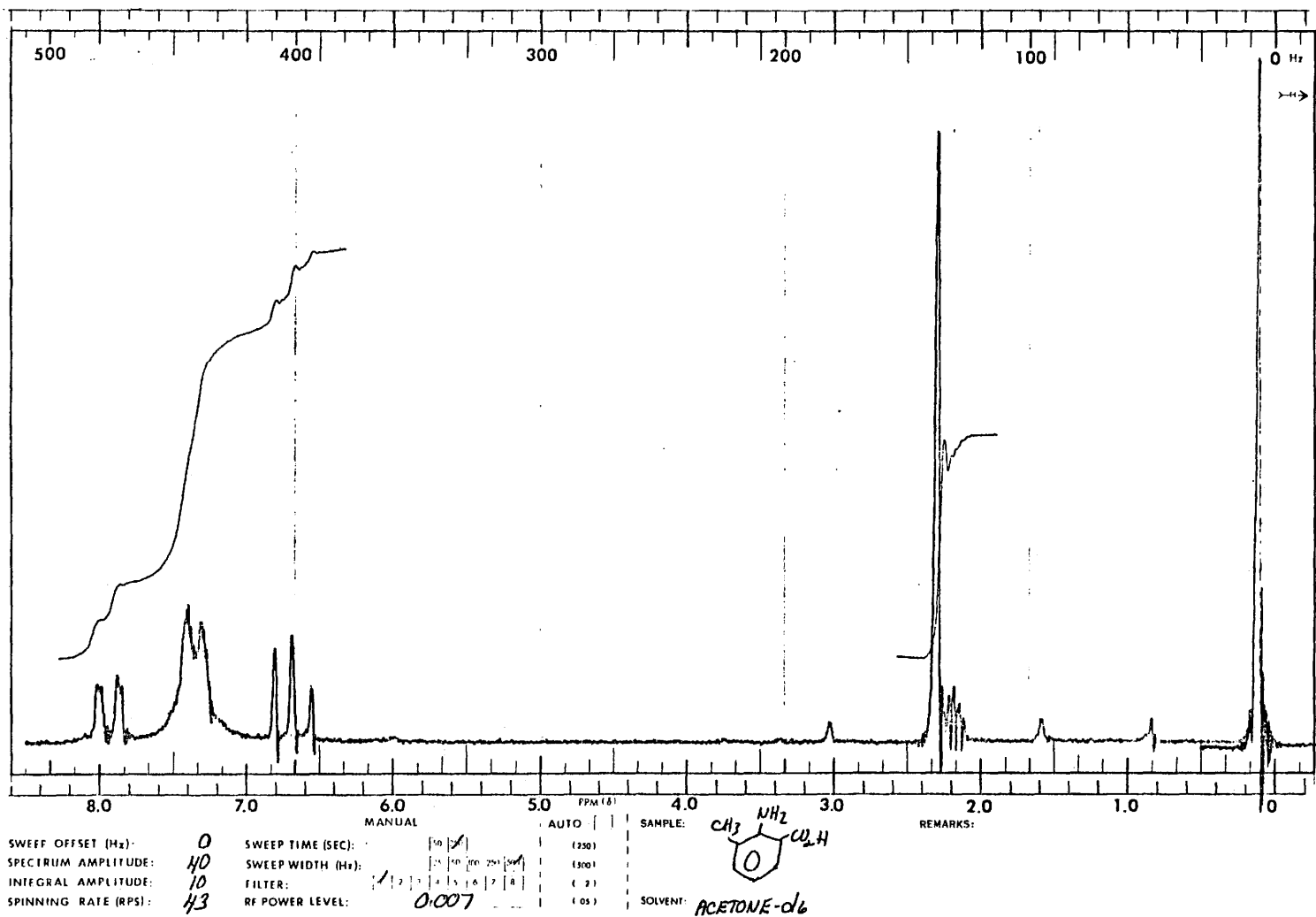
SOLVENT: ACETONE-d₆

REMARKS:

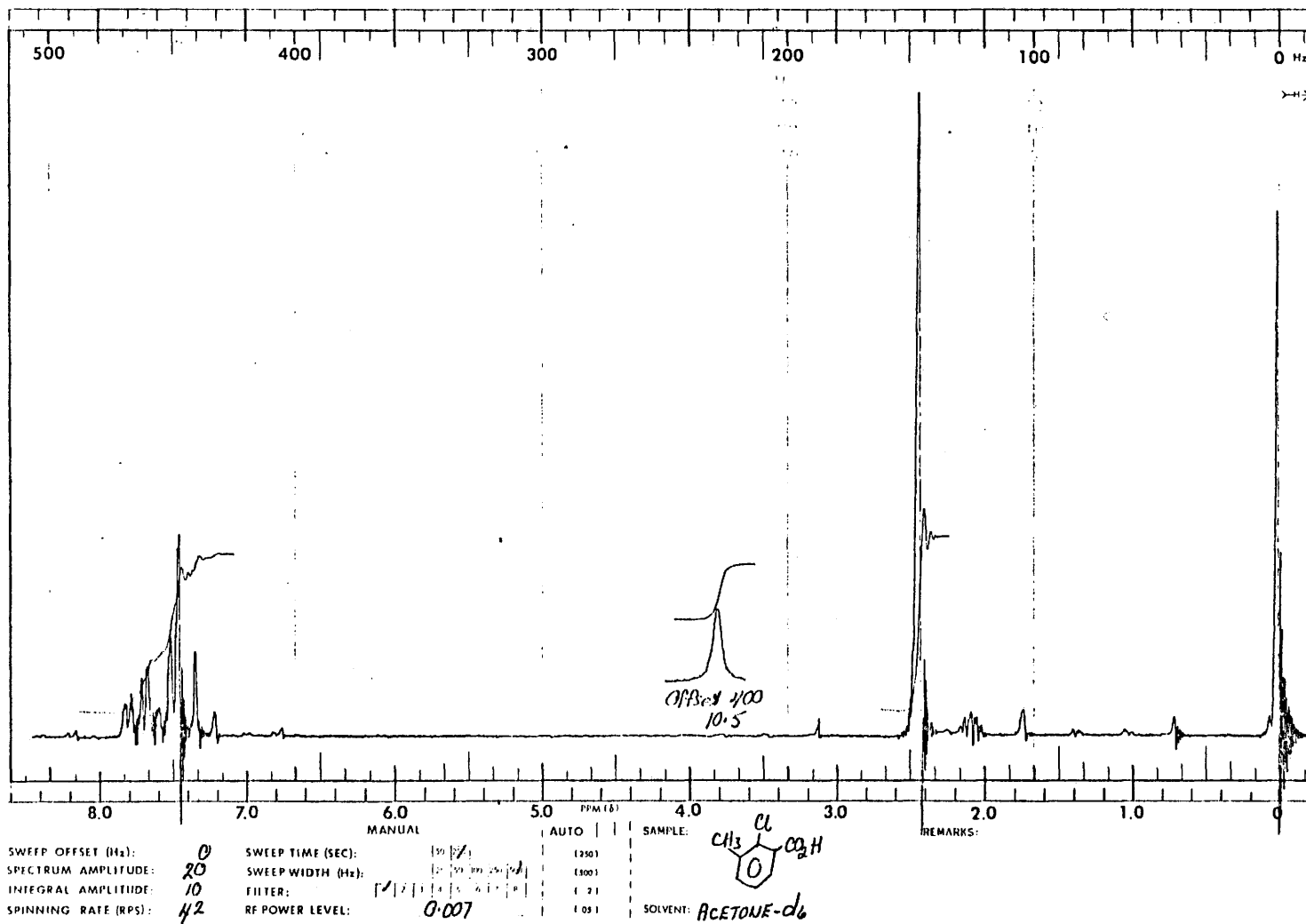
Spectrum #2 2-Chloro-5-methylbenzoic Acid



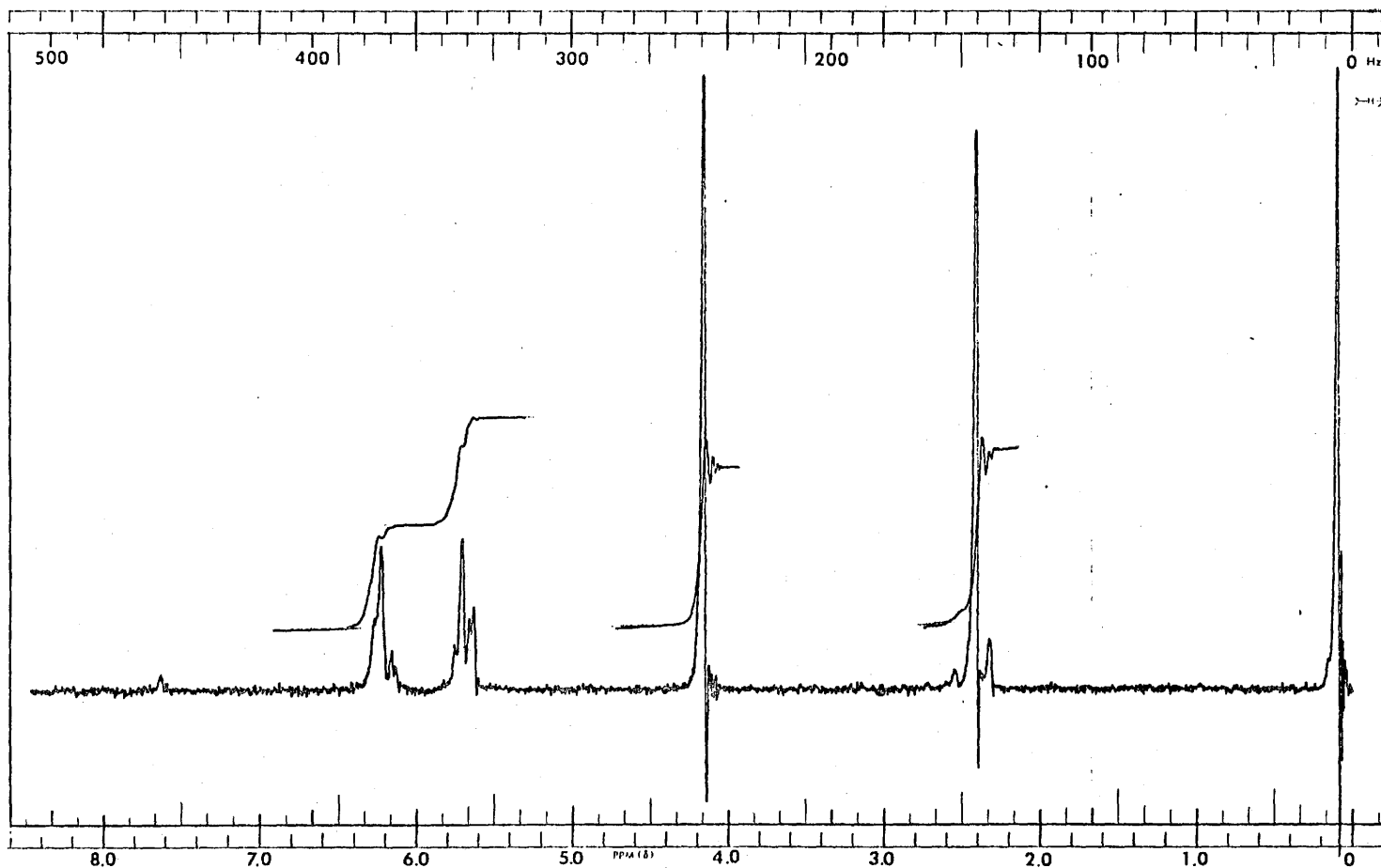
Spectrum #3 Methyl 2-Chloro-5-methylbenzoate



Spectrum #4 2-Amino-3-methylbenzoic Acid



Spectrum #5 2-Chloro-3-methylbenzoic Acid



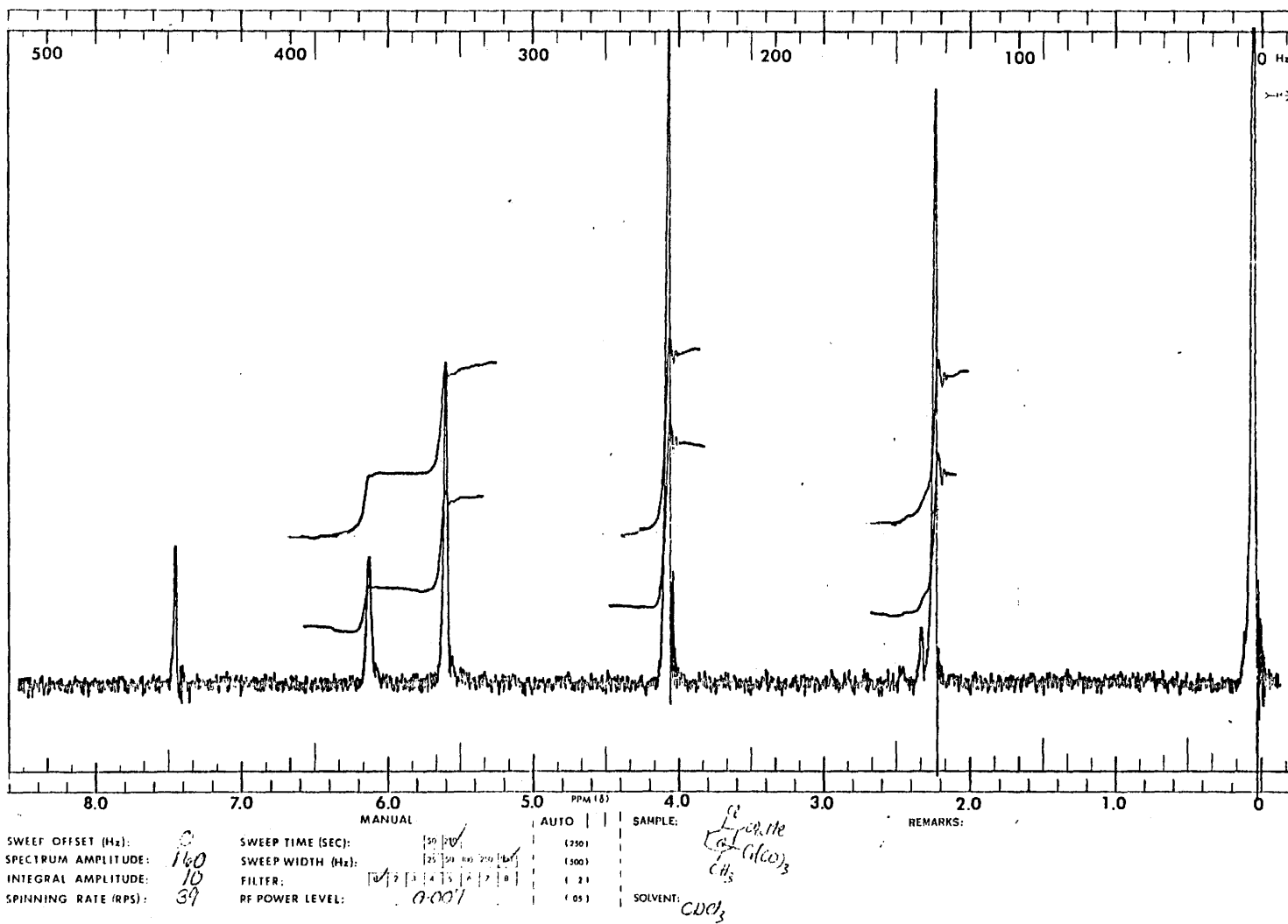
SWEEP OFFSET (Hz): 0
 SPECTRUM AMPLITUDE: 25
 INTEGRAL AMPLITUDE: 10
 SPINNING RATE (RPS): 42

MANUAL AUTO
 SWEEP TIME (SEC): 100
 SWEEP WIDTH (Hz): 1500
 FILTER: 1000
 RF POWER LEVEL: 0007

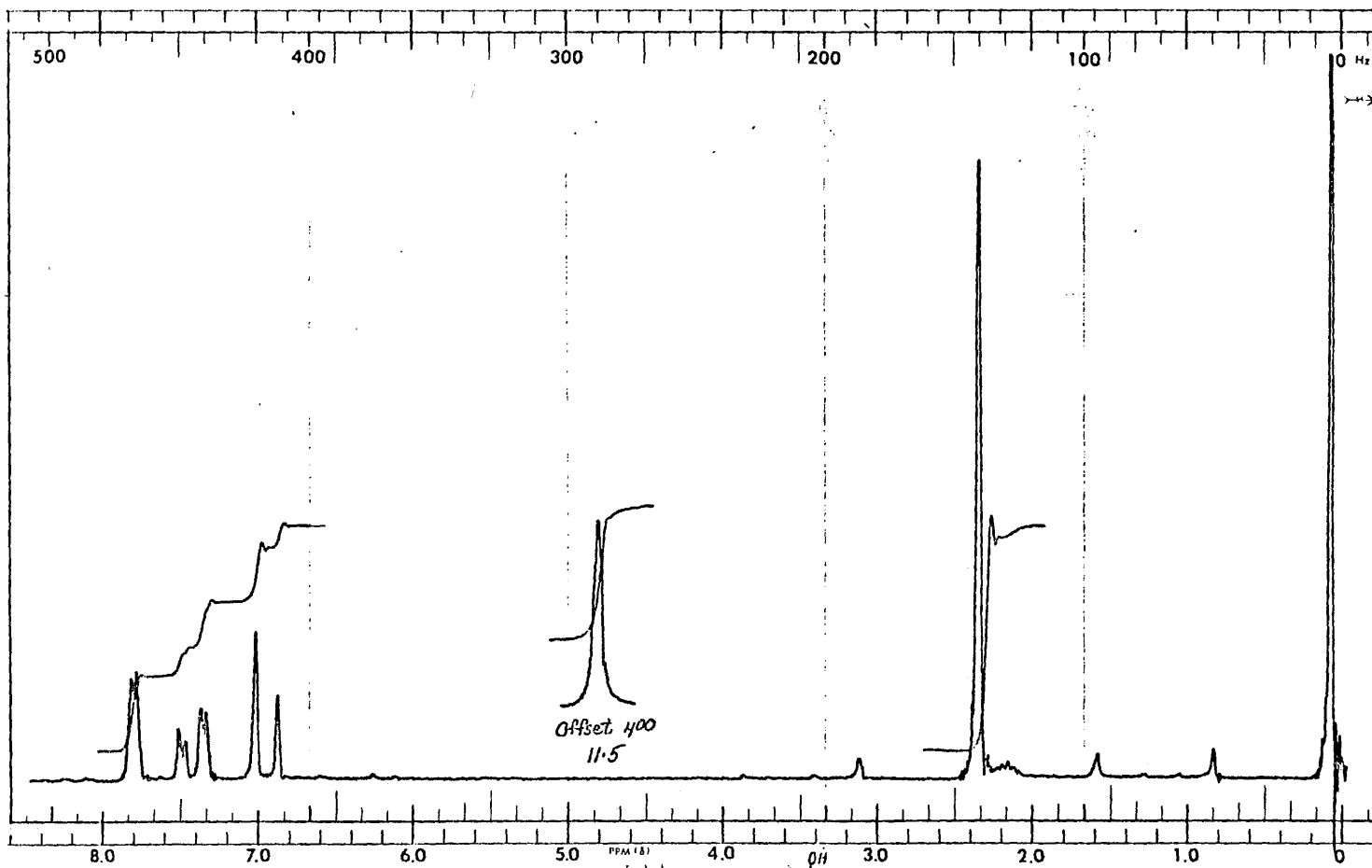
SAMPLE: *Cr(CO)₃ m-Tol*
 SOLVENT: *CDCl₃*

REMARKS:

Spectrum #7 Methyl *m*-Toluatechromiumtricarbonyl

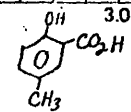


Spectrum #8 Methyl 2-Chloro-5-methylbenzoatechromiumtricarboxyl



SWEEP OFFSET (Hz):	0	SWEEP TIME (SEC):	MANUAL	10	1.250
SPECTRUM AMPLITUDE:	16	SWEEP WIDTH (Hz):	AUTO	25	1.500
INTEGRAL AMPLITUDE:	10	FILTER:		1	1.2
SPINNING RATE (RPS):	46	RF POWER LEVEL:		0.007	1.05

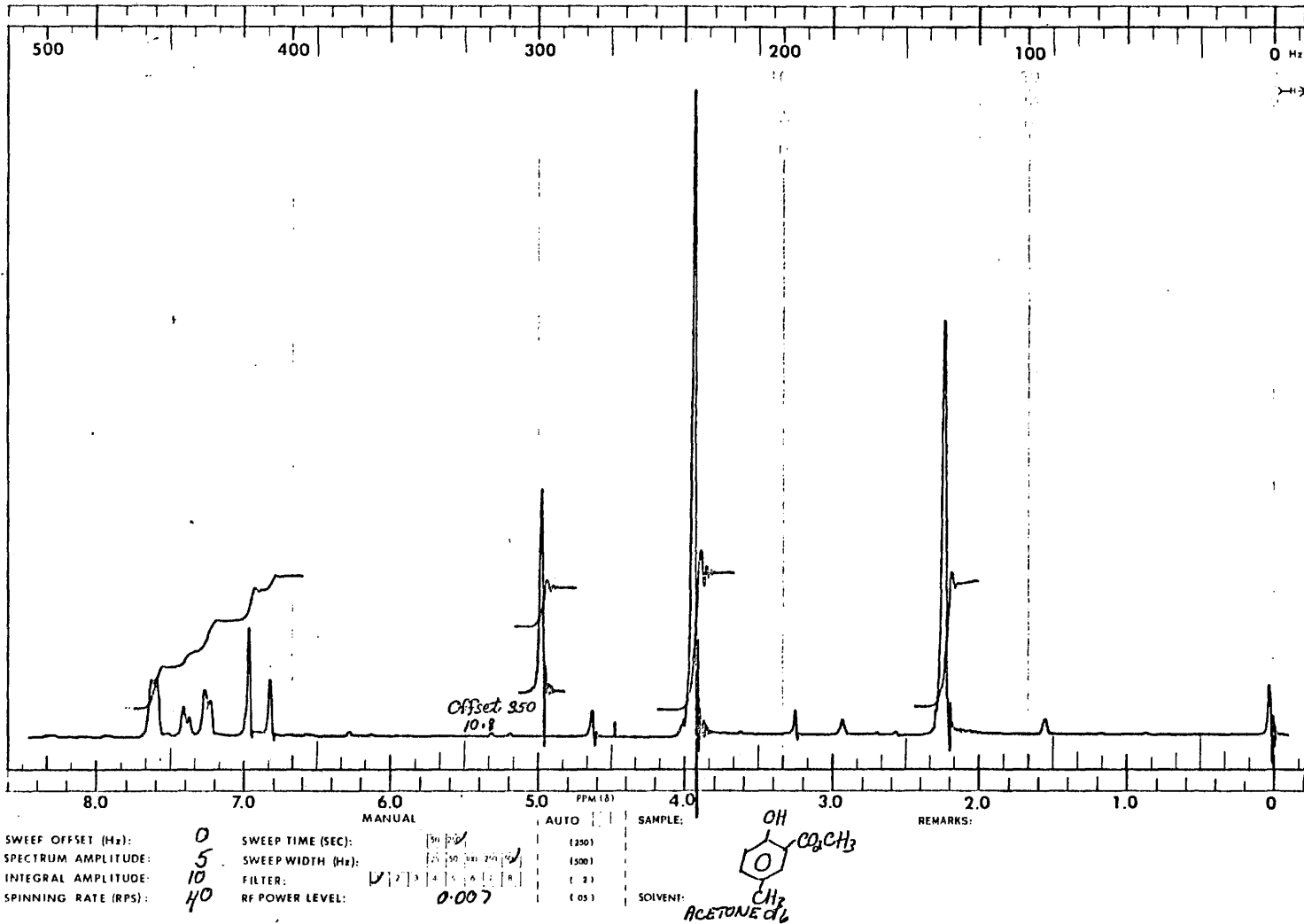
SAMPLE:



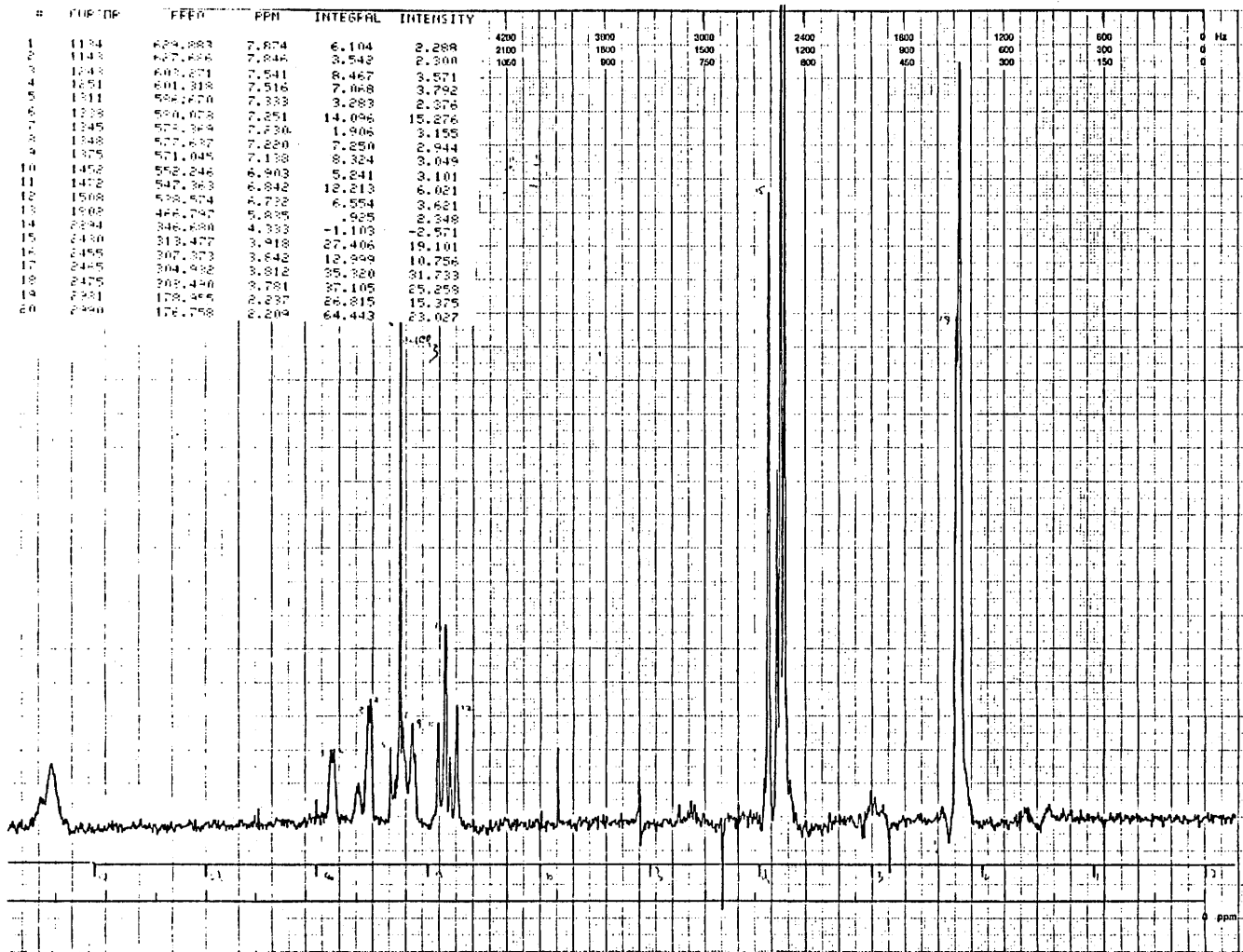
REMARKS:

SOLVENT: ACETONE-d₆

Spectrum #9 2-Hydroxy-5-methylbenzoic Acid



Spectrum #10 Methyl 2-Hydroxy-5-methylbenzoate



No. _____
BRUKER
SPECTROSPIN

80 MHz-¹H-
Spectrum

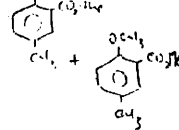
Sample _____

Conc. _____ % in CDCl₃

Int. Standard _____

Temp. amb.

°K



Signal f₁ _____

Puls width (PW) 35 μsec

Points (S) 2 / _____ k

Spectrum width (SW) 1000 Hz/cm

Offset (O) 5000 Hz

Time _____ sec

Times (NS) 1 scans

Time constant (TC) 1.2

Decoupling f₂ _____

Frequency (D₂) _____ Hz

Power _____

BB

GM

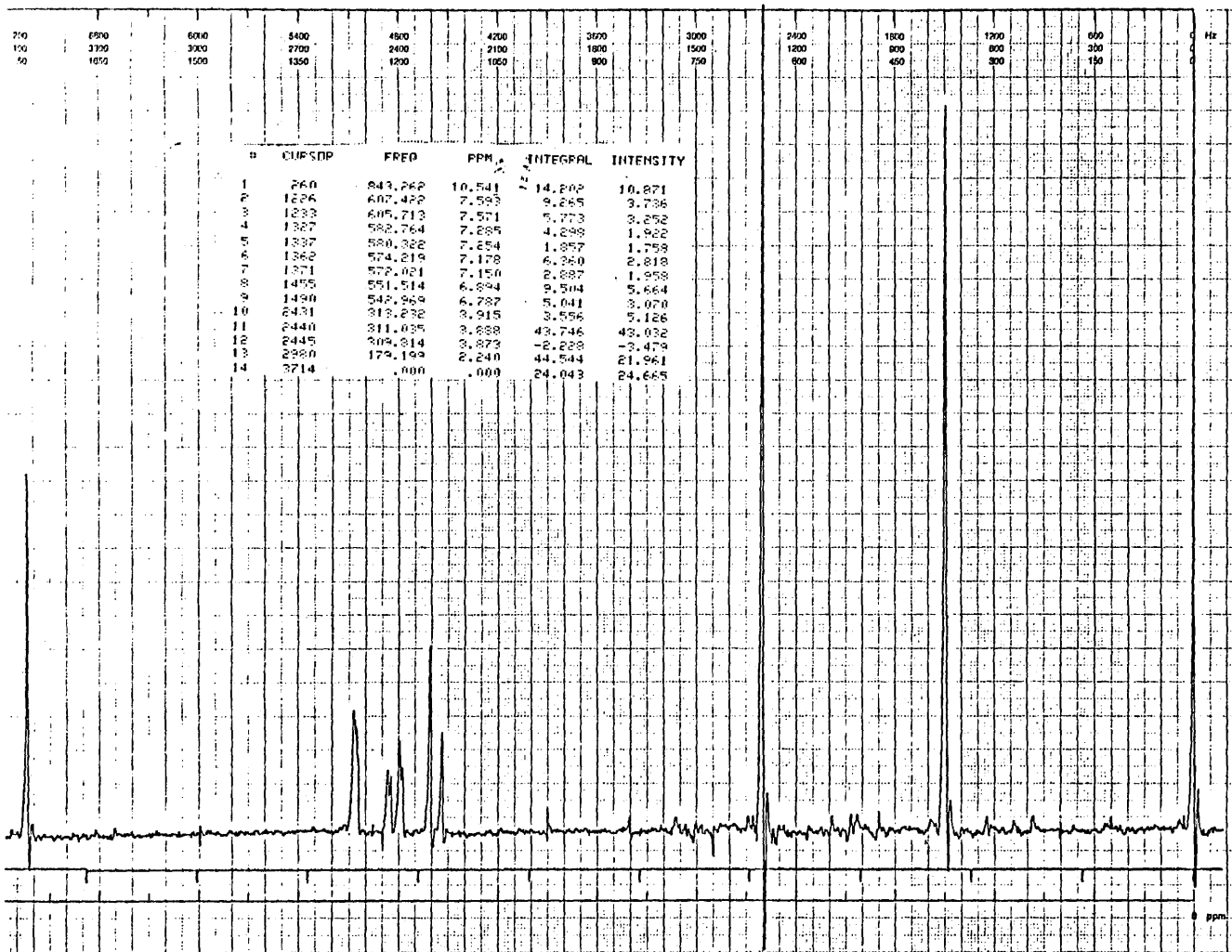
gated

Date 23.4.79

Operator _____

114

Spectrum #11 Mixture of Methyl 2-Hydroxy and 2-Methoxy-5-methylbenzoate (80 MHz)



BRUKER
SPECTROSPIN

ν C MHz = 80
Spectrum

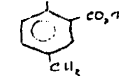
Sample _____

Conc. _____ % in $CDCl_3$

Int. Standard TMS

Temp amb.

_____ °K



Signal f_1

Pulse width (PW) 7.6 μ sec

Points (SI) 5 / _____ k

Spectrum

width (SW) f_1 1000 Hz/cm

Offset (DJ) f_1 5000 Hz

Time _____ sec

Times (NS) _____ scans

Time constant (TC) 2

Decoupling f_2

Frequency (D₂) _____ Hz

Power _____

BB

CW

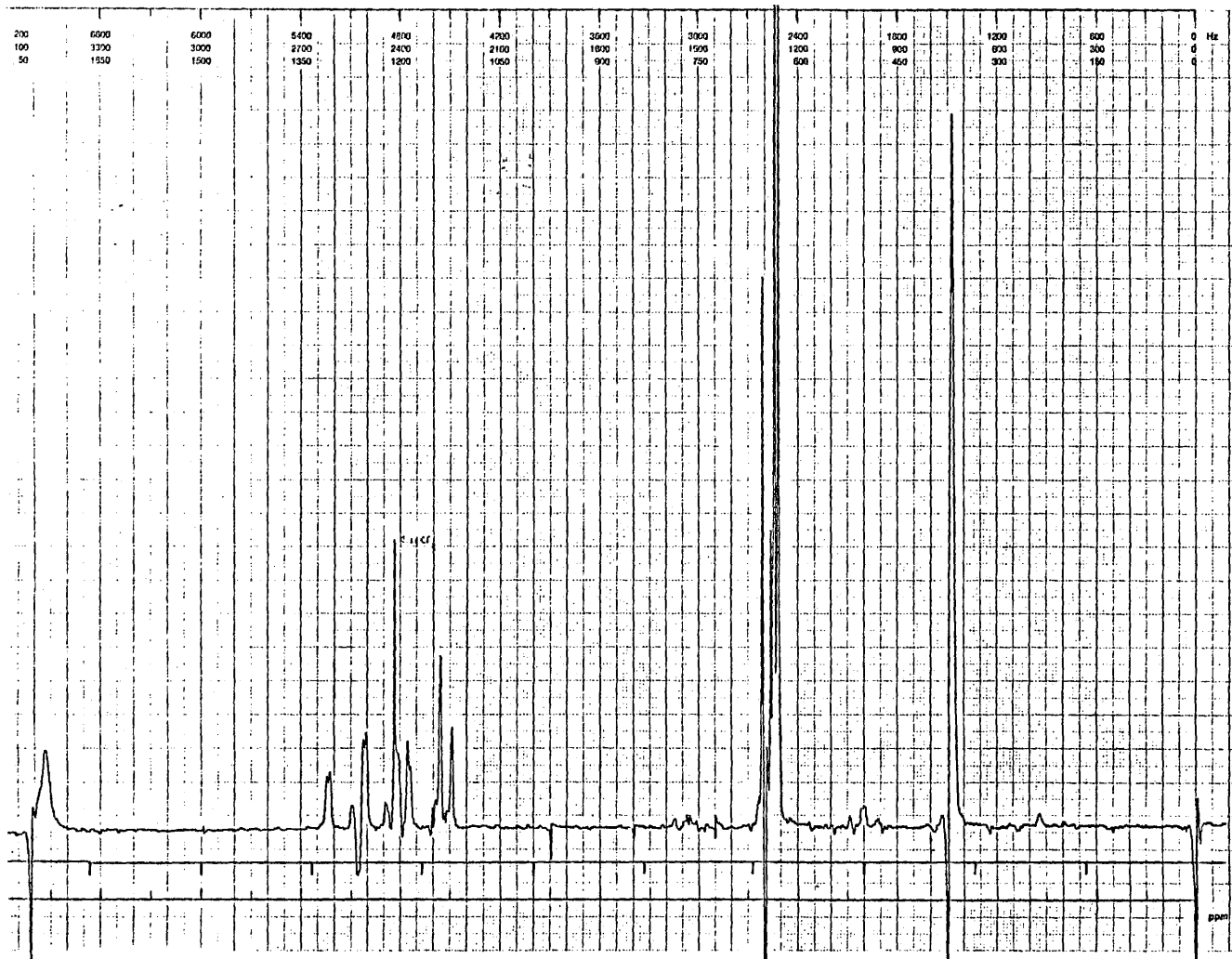
gated

Date 28 8 79

Operator _____

115

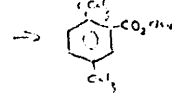
Spectrum #12 Methyl 2-Hydroxy-5-methylbenzoate (80 MHz)



No. _____
BRUKER
SPECTROSPIN

80 MHz - ¹H -
Spectrum

Sample _____
 Conc. _____ % in _____
 Int. Standard _____
 Temp. amb.
 _____ °K
 ΔS. 0.002 - ΔT. 0.001



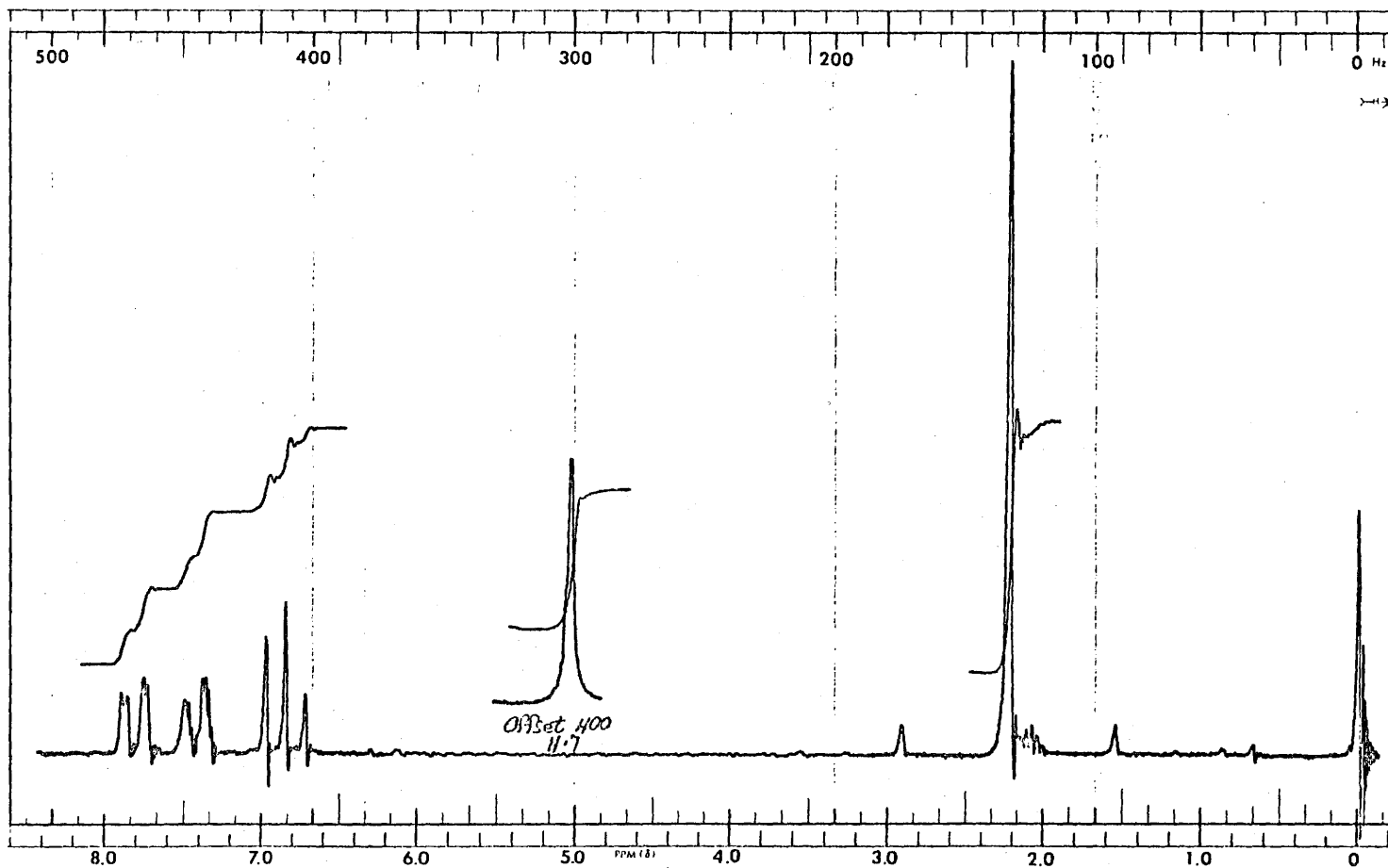
Signal f₁ _____
 Puls width (PW) _____ μsec
 Points (SI) _____ k/ _____ k
 Spectrum
 width (SW) f₁ _____ Hz/cm
 Offset (OJ) f₁ _____ Hz
 Time _____ sec
 times (NS) _____ scans
 Time constant (TC) _____

Decoupling f₁ _____
 Frequency (D₂) _____ Hz
 Power _____
 BB
 CW
 gated

Date _____
 Operator _____

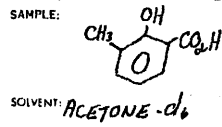
116

Spectrum #13 Methyl 2-Methoxy-5-methylbenzoate (80 MHz, difference spectrum)

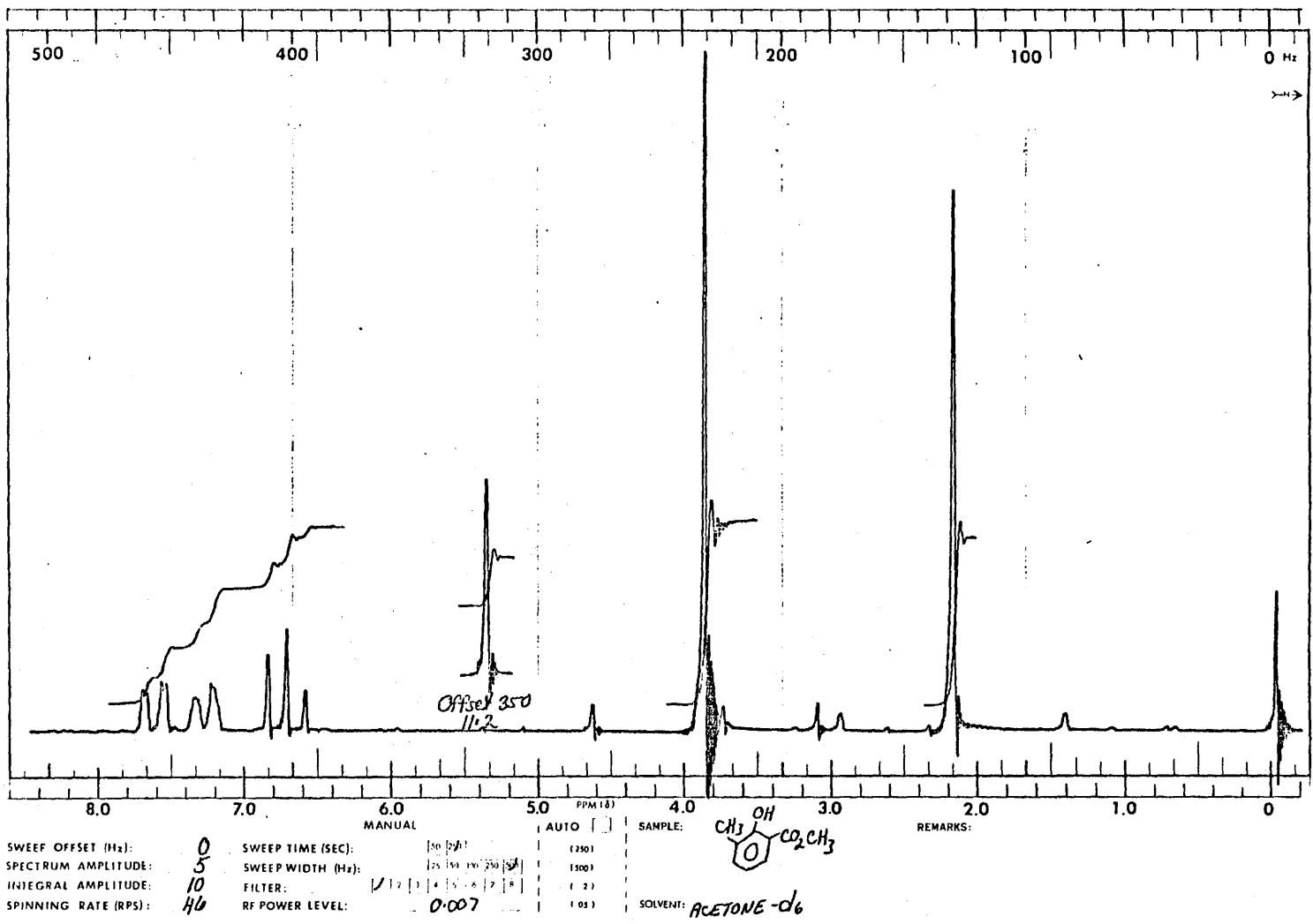


SWEEP OFFSET (Hz): 0
 SPECTRUM AMPLITUDE: 25
 INTEGRAL AMPLITUDE: 10
 SPINNING RATE (RPS): 40

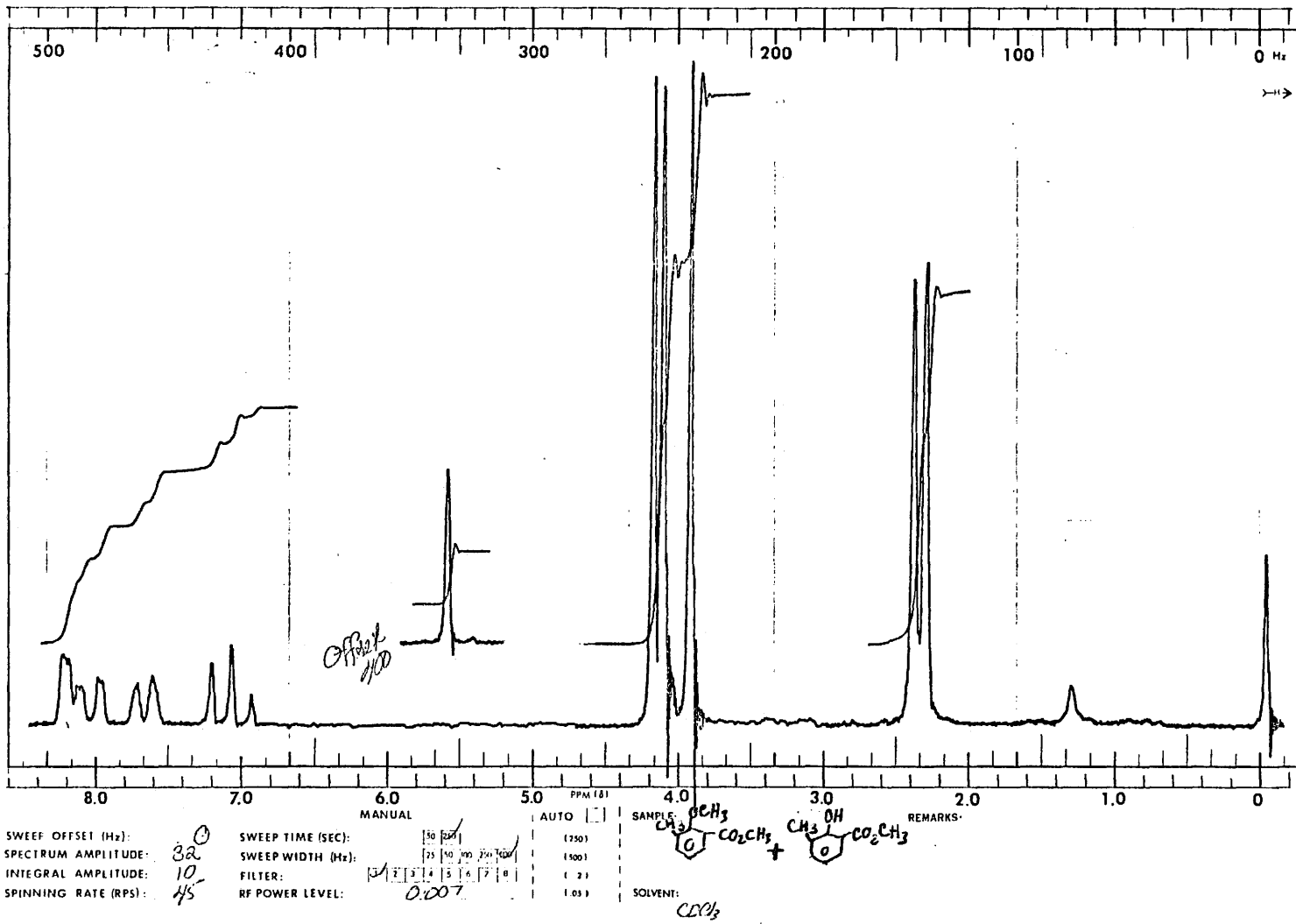
SWEEP TIME (SEC): 30
 SWEEP WIDTH (Hz): 20
 FILTER: 1/2
 RF POWER LEVEL: 0.007



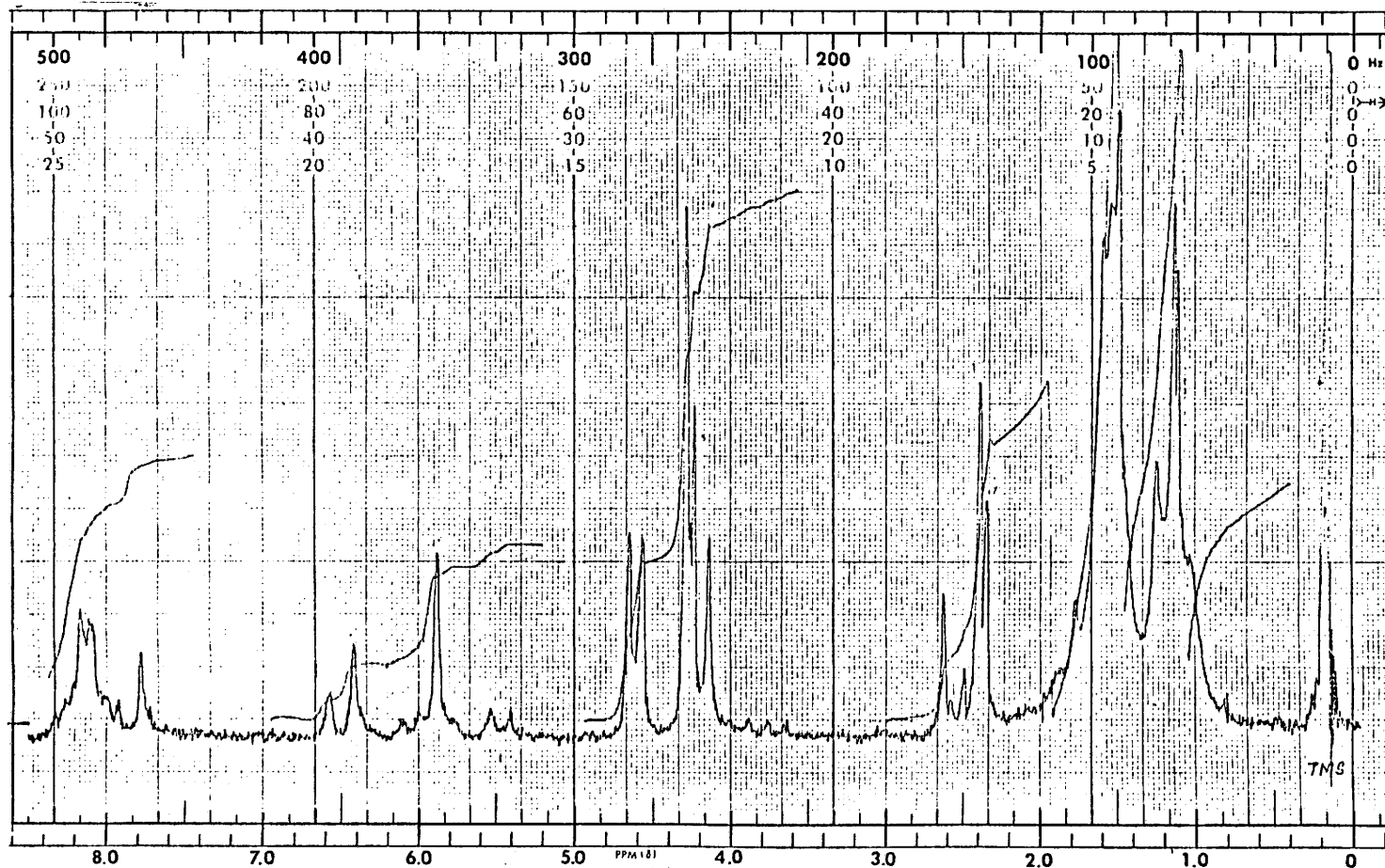
Spectrum #14 2-Hydroxy-3-methylbenzoic Acid



Spectrum #15 Methyl 2-Hydroxy-3-methylbenzoate



Spectrum #16 Mixture of Methyl 2-Hydroxy and 2-Methoxy-3-methylbenzoate



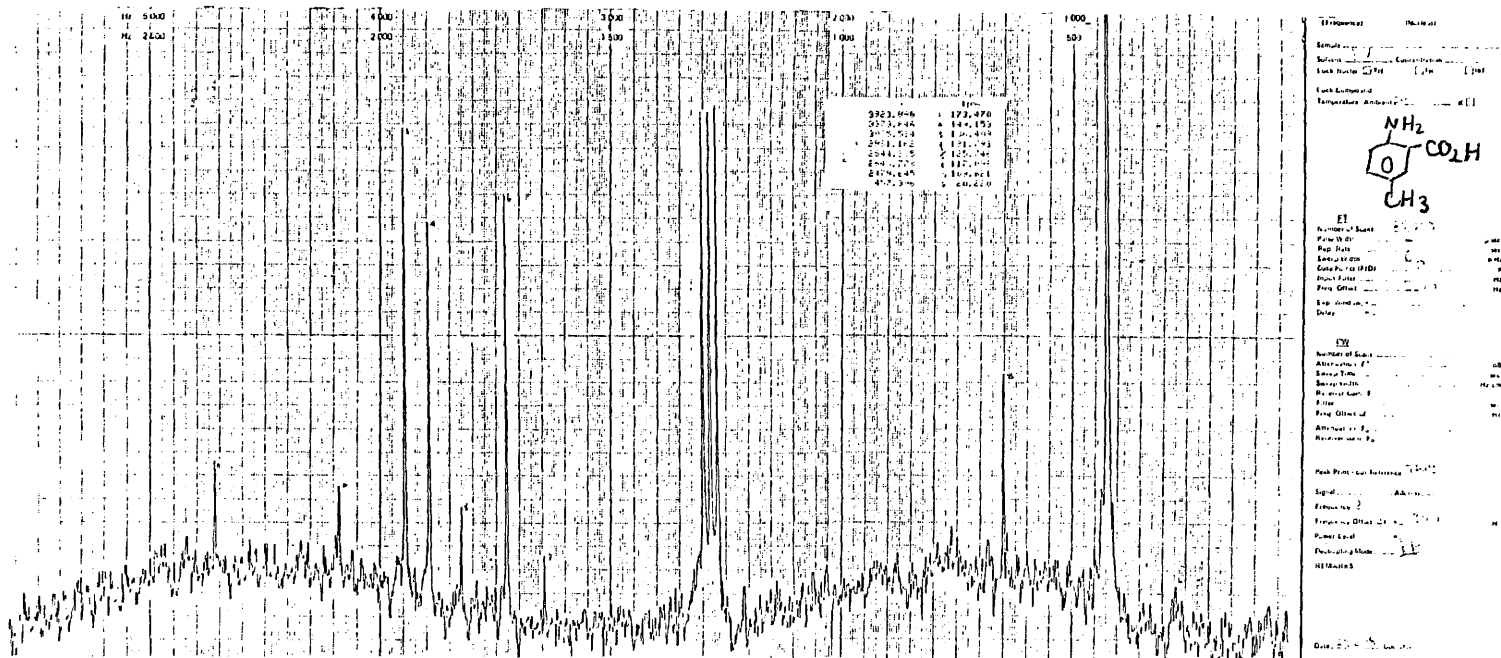
SWEEP OFFSET (Hz): 0
 SPECTRUM AMPLITUDE: 100
 INTEGRAL AMPLITUDE: 10
 SPINNING RATE (RPS): 35
 SWEEP TIME (SEC): 30
 SWEEP WIDTH (Hz): 25 30 100 250
 FILTER: 2 3 4 5 6 7 8
 RF POWER LEVEL: 0.007

MANUAL AUTO
 SAMPLE: ClC(=O)C(OC)C1=CC=CC=C1C(C)C1=CC=CC=C1
 SOLVENT: ClC(Cl)Cl
 REMARKS:

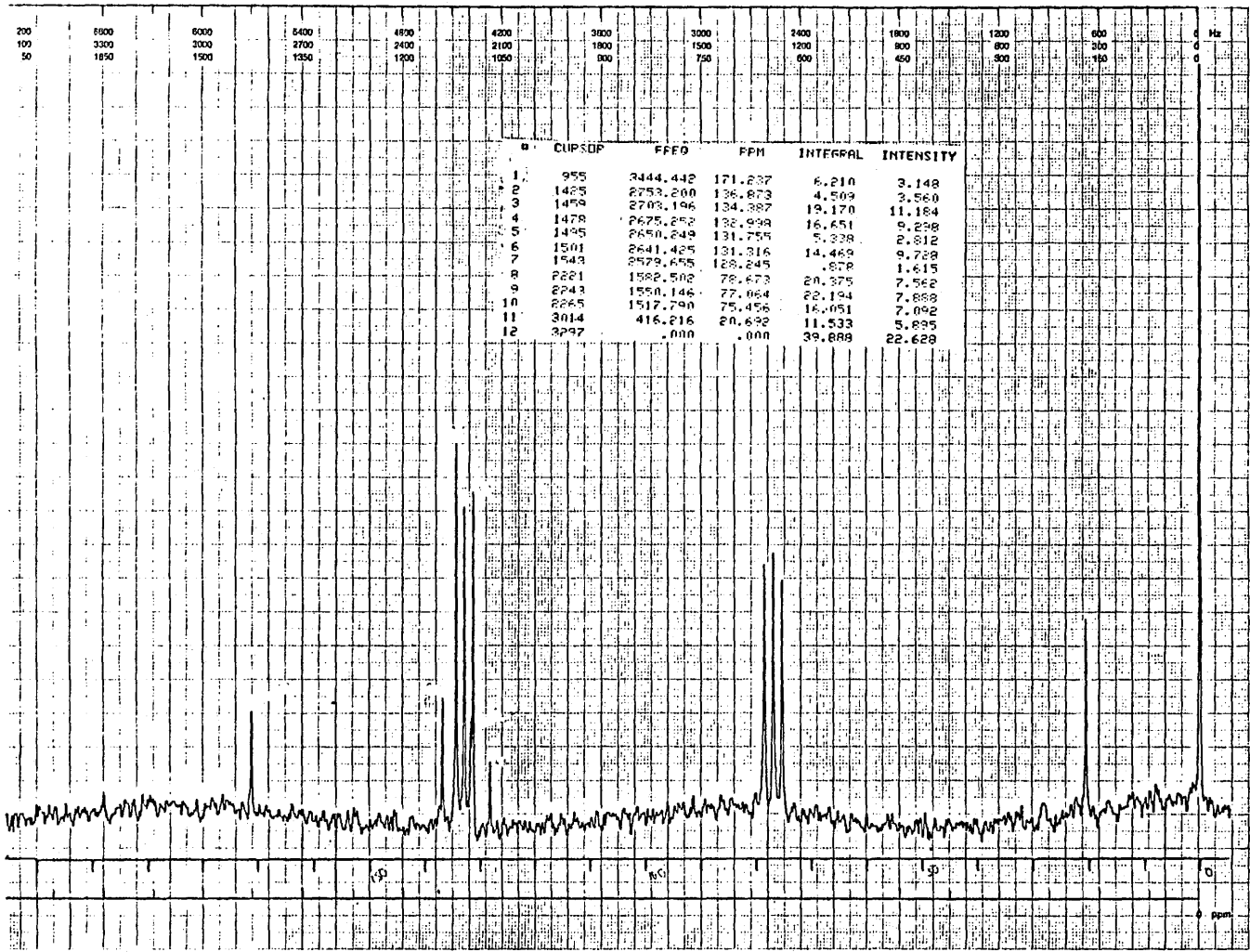
120

Spectrum #17 Product Mixture from Reaction of Methoxide Ion with Methyl 2-Chloro-5-methylbenzoatechromiumtricarbonyl

APPENDIX TWO
¹³C NMR SPECTRA



Spectrum #1 2-Amino-5-methylbenzoic Acid



BRUKER
SPECTROSPIN

20.1 MHz - ¹³C -
Spectrum

Sample _____
Conc. 0.1% CHCl₃
Int. Standard TMS

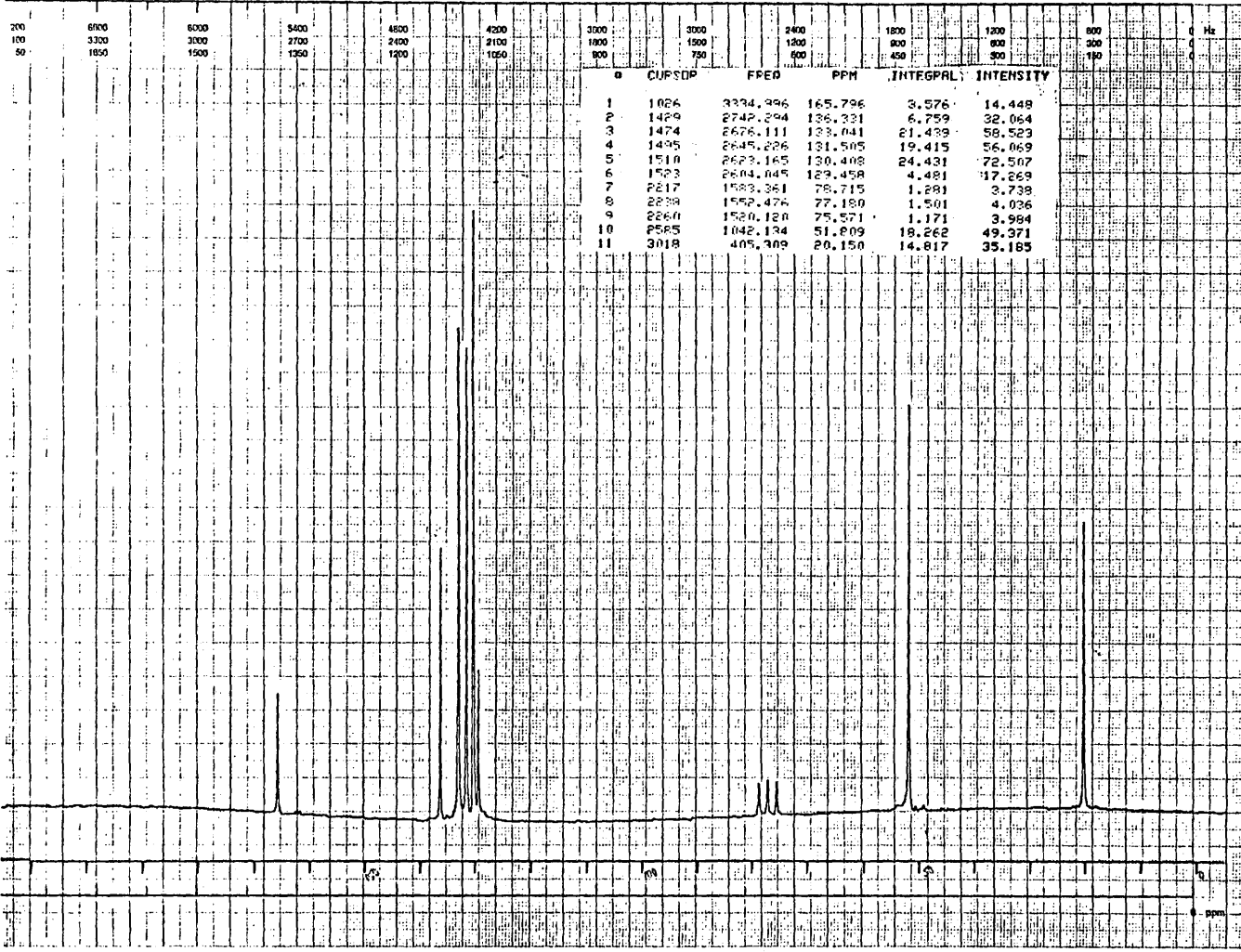
Temp. amb. RT
 °K
Cc1ccc(Cl)cc1C(=O)O

Signal f₁ _____
Pulse width (PW) 1.7 μsec
Points (SI) 8 μ _____ ft
Spectrum width (SW) 6000 Hz/cm
Offset (D) f₁ 12,490 Hz
Time _____ sec
Times (NS) 2000 scans
Time constant (TC) 3

Decoupling f₁ _____
Frequency (D) 5000 Hz
Power 2w
BB
CW
gated
Date 22.5.79
Operator _____

123

Spectrum #2 2-Chloro-5-methylbenzoic Acid



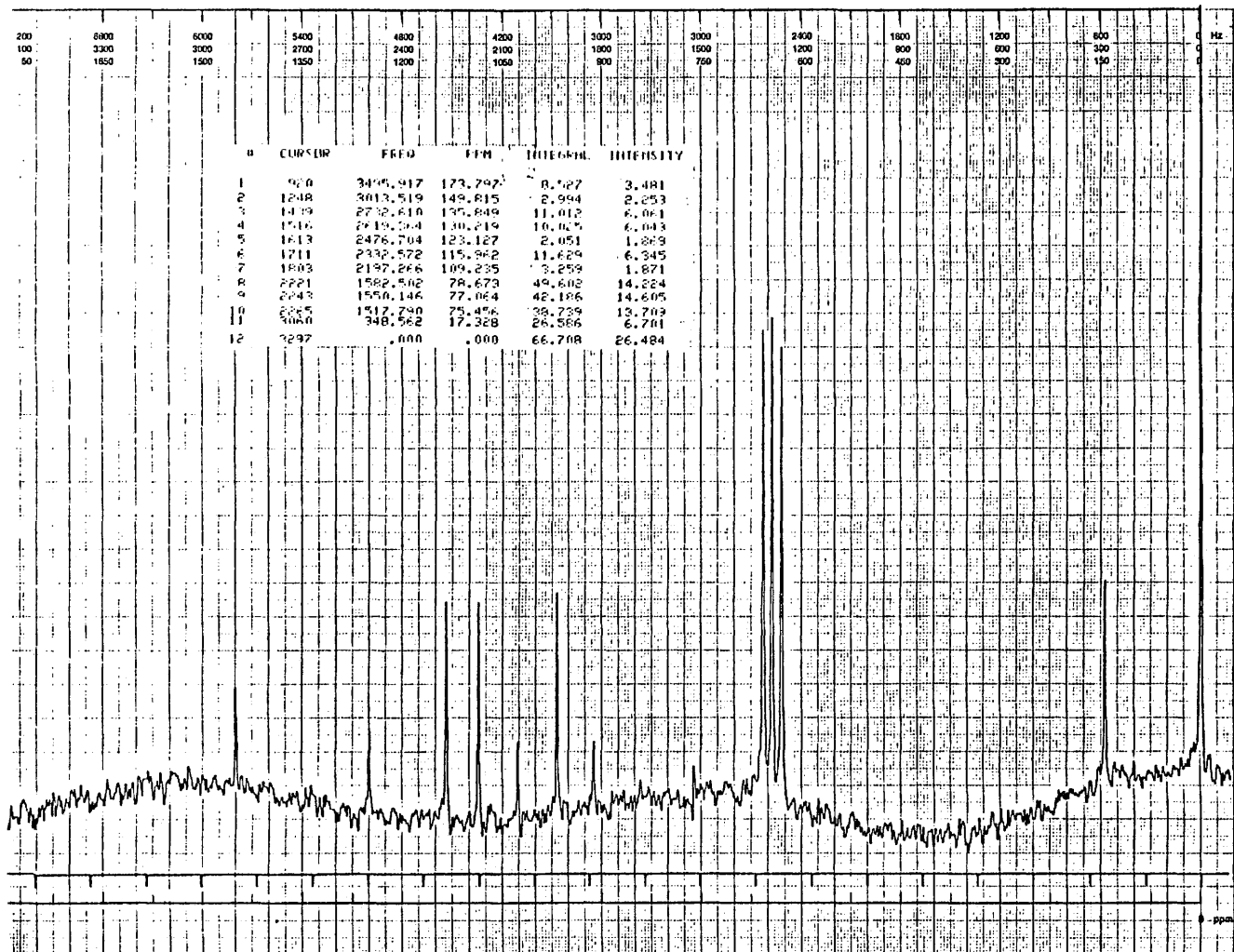
No. _____
BRUKER
SPECTROSPIN
 201.1 MHz - ¹³C -
Spectrum

Sample _____
 Conc. _____ % in CDCl₃
 Int. Standard CDCl₃
 Temp amb 17
 °K
 ¹³C
 ¹H
Cc1ccc(Cl)c(C(=O)OC)c1

Signal f. _____
 Pulse width (PW) 17 μ sec
 Points (SI) 8 W _____ k
 Spectrum
 width (SW) f. 6000 Hz/cm
 Offset (DJ) f. 12.400 Hz
 Time _____ sec
 time (NS) 6000 scans
 Time constant (TC) 15
 Decoupling f. _____
 Frequency (D₂) 5000 Hz
 Power 2w
 BB
 CW
 gated
 Date 22 5 79
 Operator _____

124

Spectrum #3 Methyl 2-Chloro-5-methylbenzoate



No. _____
BRUKER
SPECTROSPIN

201 MHz-¹³C-
Spectrum

Sample _____
 Conc. _____ % in CDCl₃
 Int. Standard TMS
 Temp. amb
 °K
Cc1cc(C(=O)O)cc(N)c1

Signal 1
 Puls width (PW) 1.5 μsec
 Points (SI) 8 / _____ k

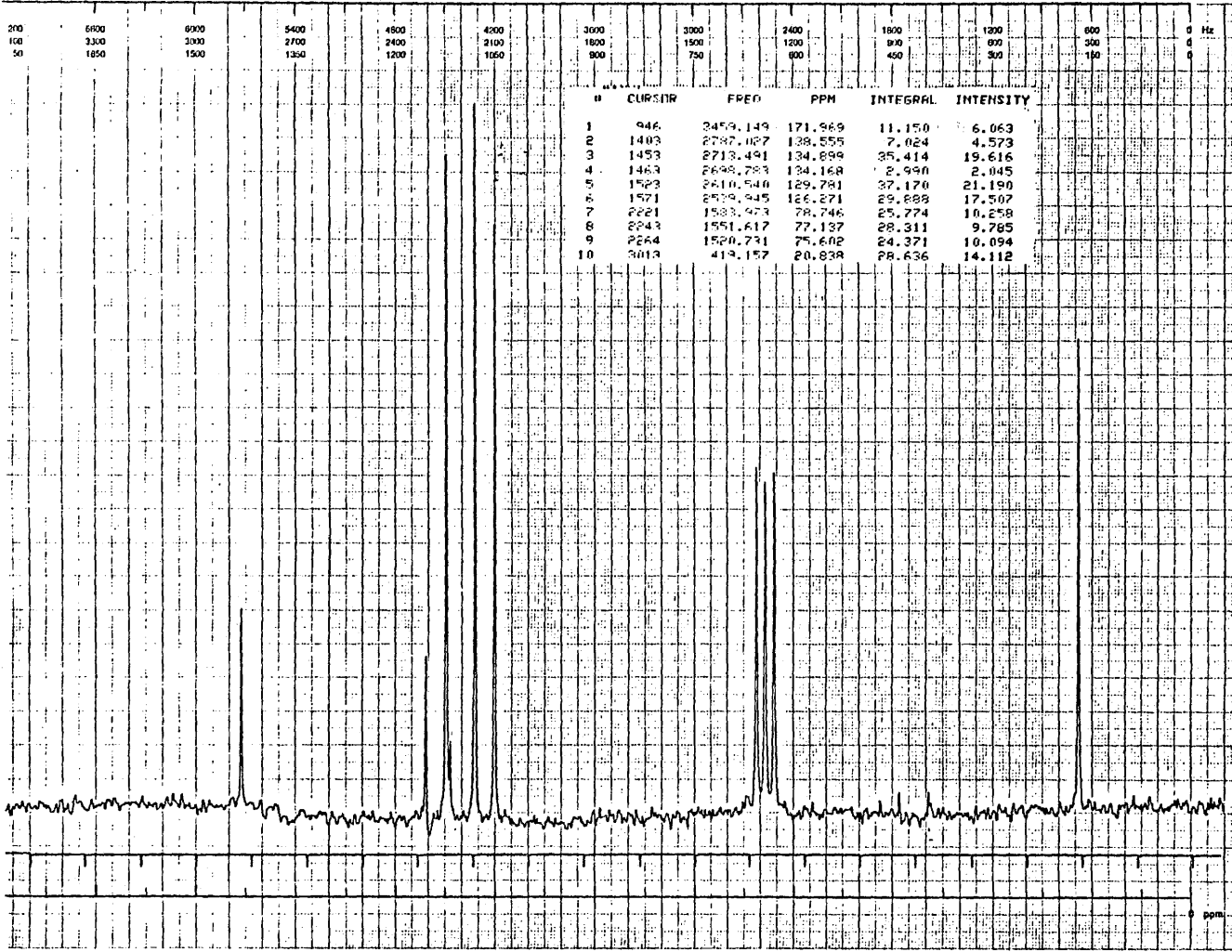
Spectrum
 width (SW) 6.000 Hz/cm
 Offset (DJ) 17.400 Hz
 Time _____ sec
 Lines (NS) 22,000 scans
 Time constant (TC) 3

Decoupling 1
 Frequency (DJ) 5000 Hz
 Power 2 W
 BB
 CW
 gated

Date 23.8.79
 Operator _____

125

Spectrum #4 2-Amino-3-methylbenzoic Acid



No. _____

BRUKER
SPECTROSPIN

20.1 MHz ¹³C -
Spectrum

Sample _____

Conc. _____ % in _____

Int. Standard CDC13

Temp. amb.

_____ °K

Cc1cc(Cl)cc(C(=O)O)c1

Signal I,
Puls width (PW) 1.7 μ sec
Points (SI) 8 M _____

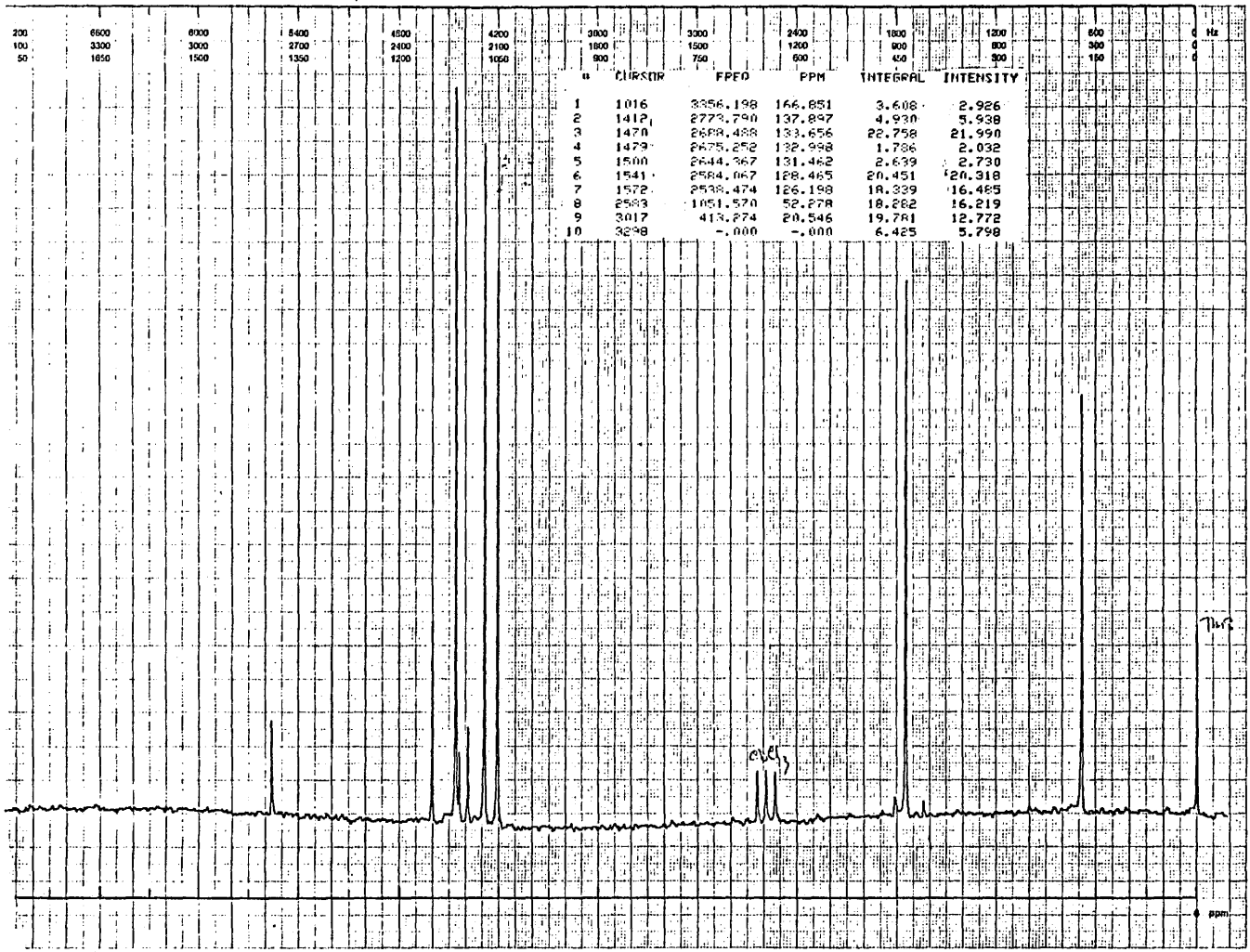
Spectrum
width (EW) 6600 Hz/cm
Offset (D) 18.450 Hz
Time _____ sec
times (NS) 15.000 scans
Time constant (TC) 3

Decoupling 1
Frequency (D) 5250 Hz
Power 200
BB
CW
gated

Date 22.3.79
Operator _____

126

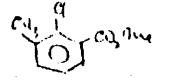
Spectrum #5 2-Chloro-3-methylbenzoic Acid



No. _____
BRUKER
SPECTROSPIN

20.1 MHz ^{13}C
Spectrum

Sample _____
 Conc. _____ % in $CDCl_3$
 Int. Standard TMS
 Temp amb
 °K 11



Signal 1
 Pulse width (PW) 1.7 μ sec
 Points (SI) 8 / k _____

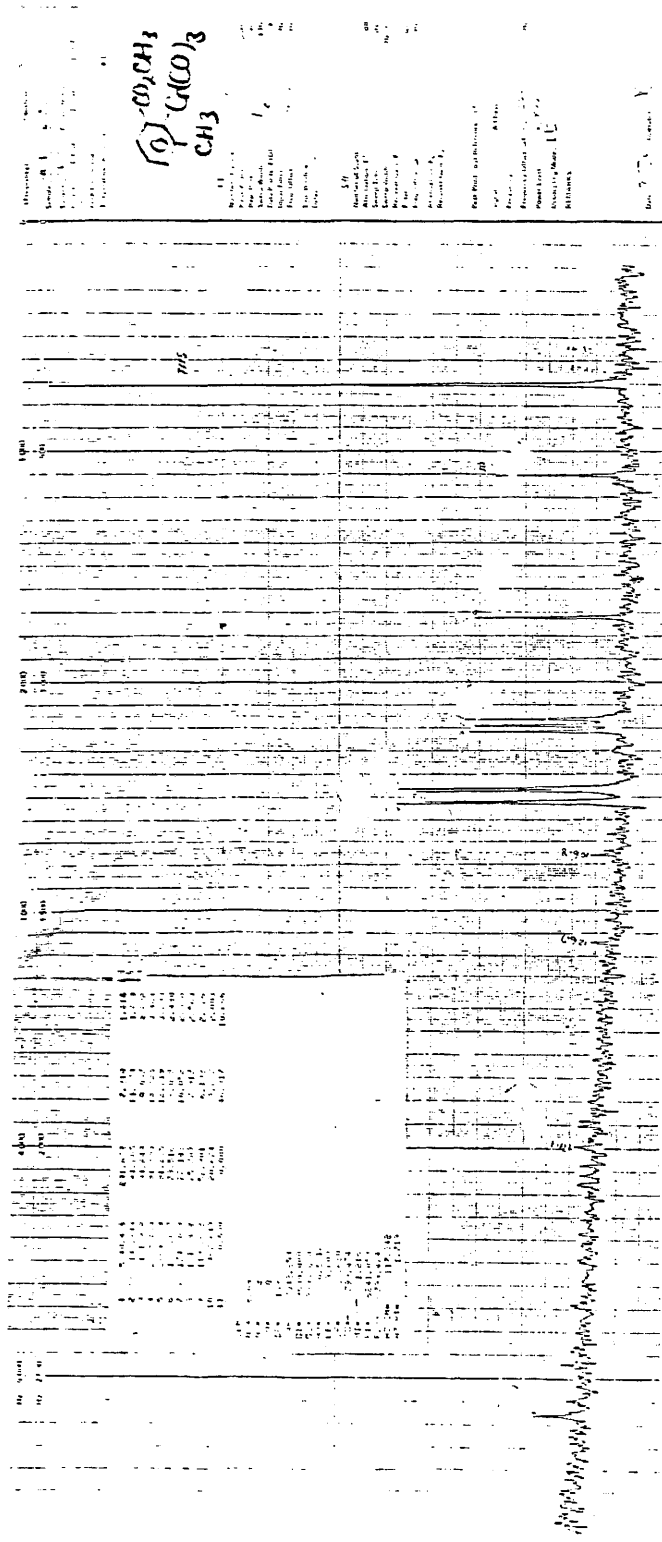
Spectrum
 width (SW) 6000 Hz/cm
 Offset (DJ) 12.100 Hz
 Time _____ sec
 Times (NS) 3000 scans
 Time constant (TC) 1

Decoupling 1
 Frequency (DJ) 5200 Hz
 Power 2w
 BB
 CW
 gated

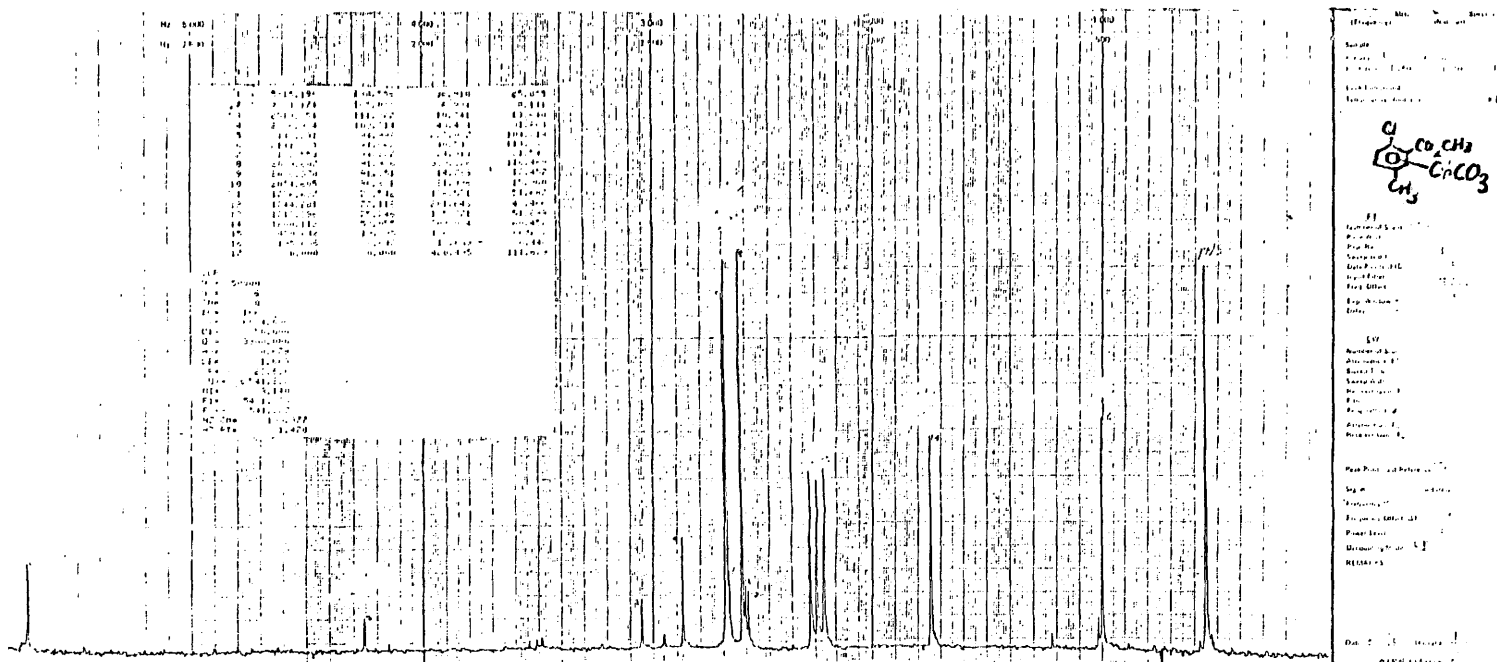
Date _____
 Operator _____

127

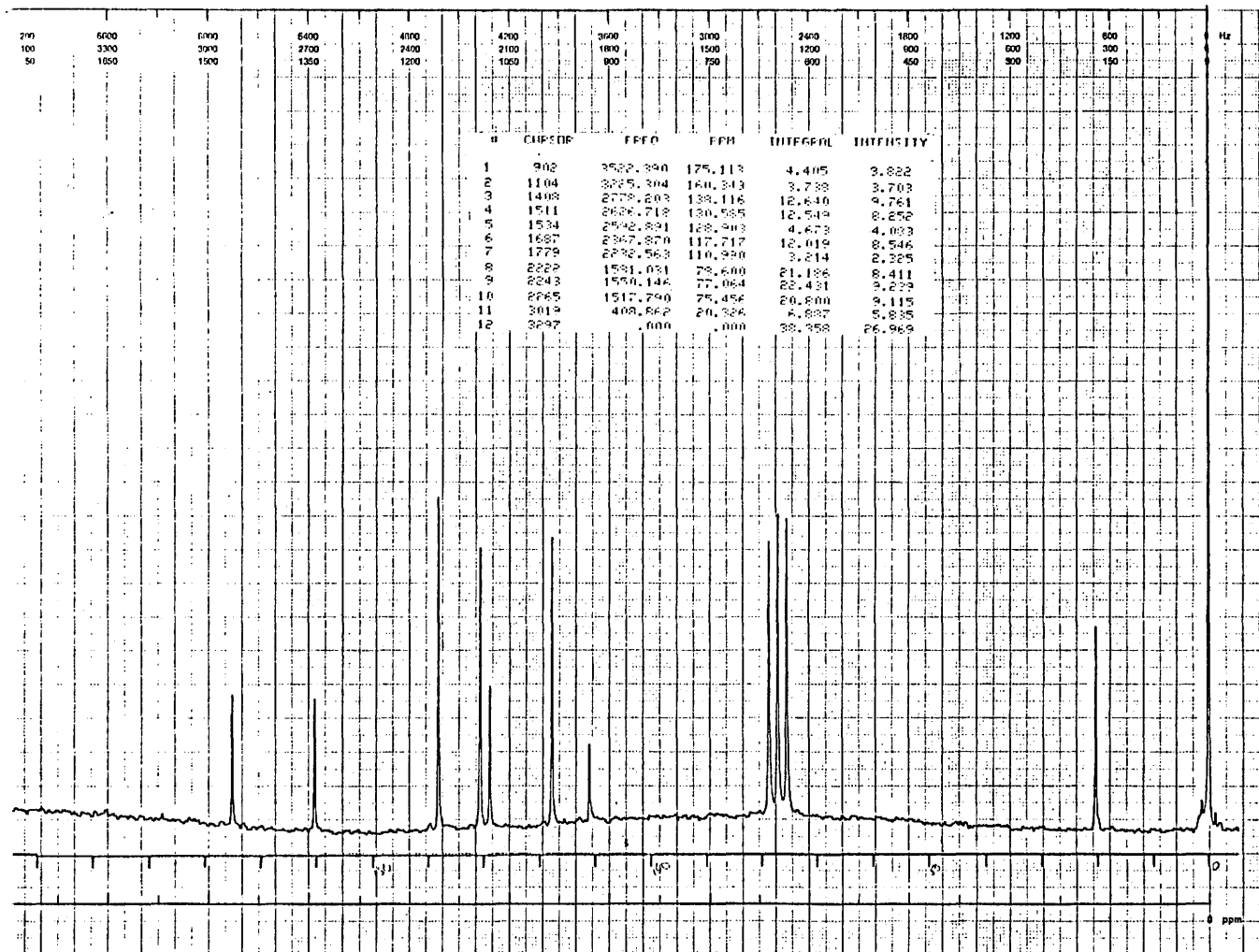
Spectrum #6 Methyl 2-Chloro-3-methylbenzoate



Spectrum #17 Methyl m-Toluatechromiumtricarboxylate



Spectrum #8 Methyl 2-Chloro-5-methylbenzoatechromiumtricarbonyl

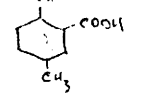


N6
BRUKER
SPECTROSPIN

201 MHz-¹³C-
Spectrum

Sample _____
 Conc 7.1% in CDCl₃
 Int. Standard TMS

Temp. amb
 °K
 CW



Signal f₁ _____
 Puls width (PW) 17 µs
 Points (SI) 5 W _____ h

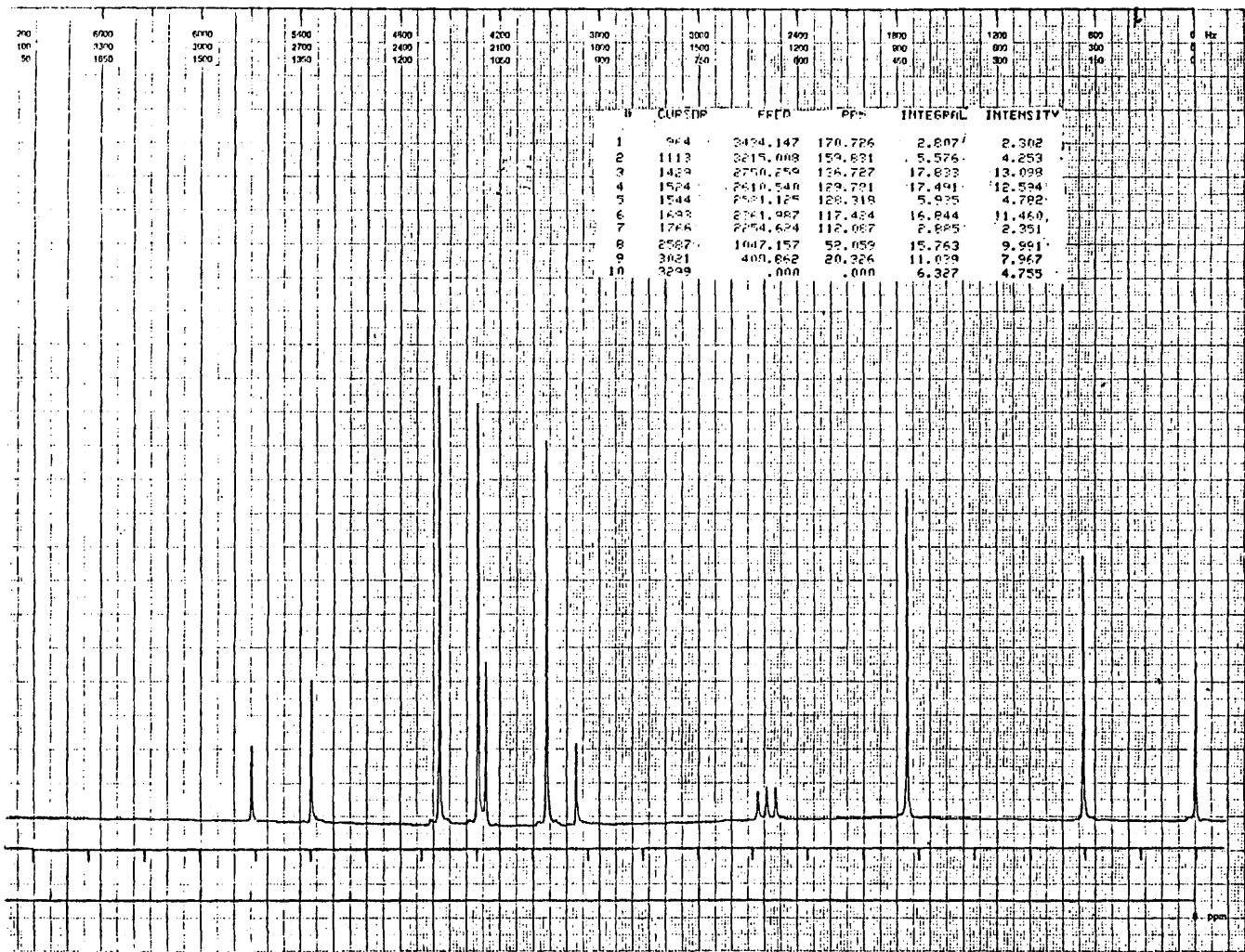
Spectrum
 width (SW) f₁ 6000 Hz/cm
 Offset (D) f₁ 12,400 Hz
 Time _____ sec
 Times (NS) 2000 scans
 Time constant (TC) 2

Decoupling f₁ _____
 Frequency (D) 2000 Hz
 Power 200
 BB
 CW
 gated

Date 2.19
 Operator _____

130

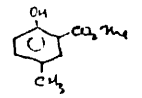
Spectrum #9 2-Hydroxy-5-methylbenzoic Acid



No. _____
BRUKER
SPECTROSPIN

201 MHz-¹³C-
Spectrum

Sample _____
 Conc. _____ % in CDCl₃
 Int. Standard THS
 Temp. amb.
 °K



Signal 1
 Pulse width (PW) 16 μsec
 Points (SI) 8 W _____ h
 Spectrum width (SW) 1100 Hz/gp
 Offset (OJ) 12.900 Hz
 Time _____ sec
 Times (NS) 10,000 scans
 Time constant (TC) 2

Decoupling 1
 Frequency (DJ) 5000 Hz
 Power 2W
 BB
 CW
 gated

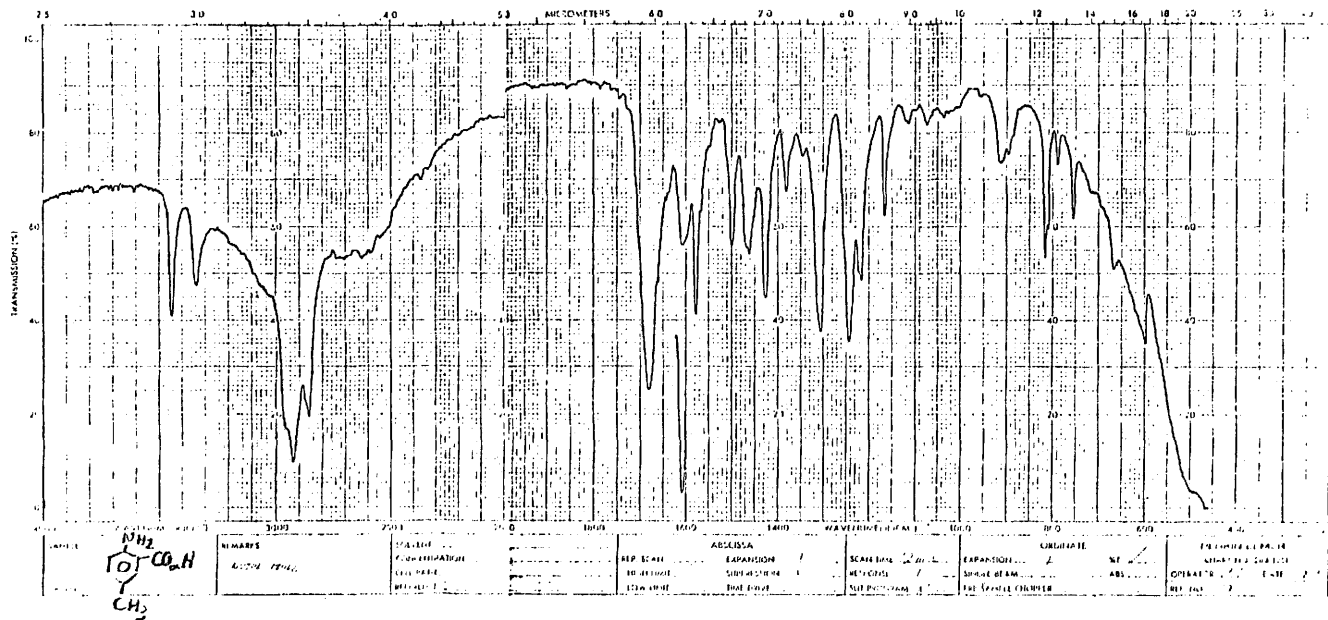
Date 27.8.79
 Operator _____

131

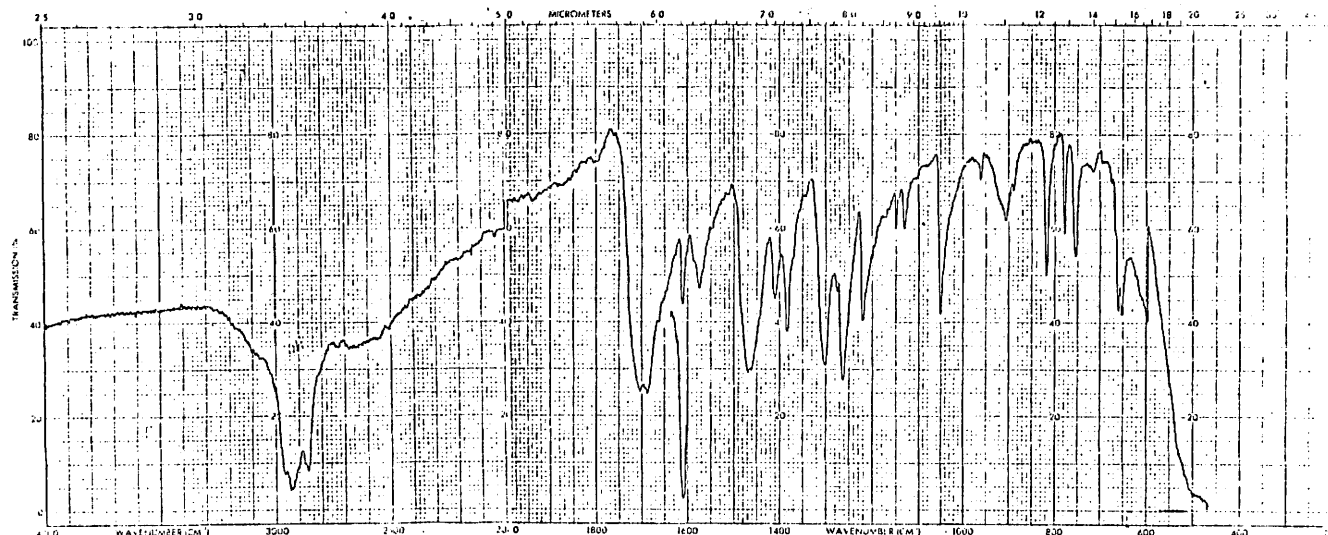
Spectrum #10 Methyl 2-Hydroxy-5-methylbenzoate

APPENDIX THREE

IR SPECTRA

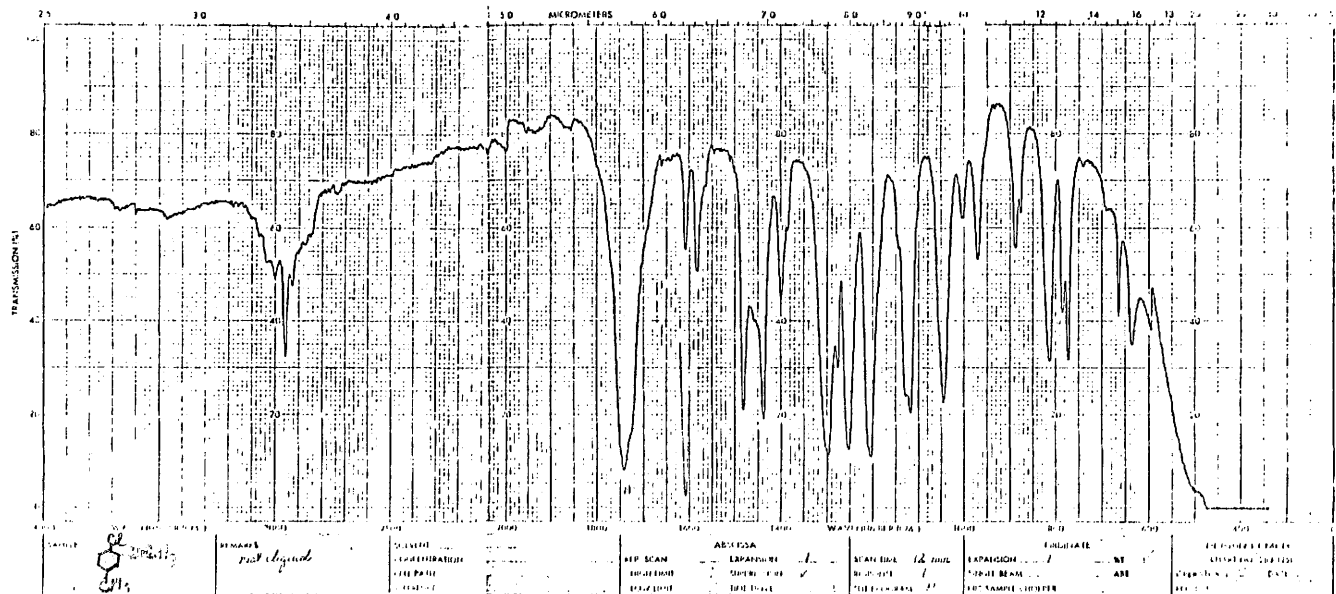


Spectrum #1 2-Amino-5-methylbenzoic Acid

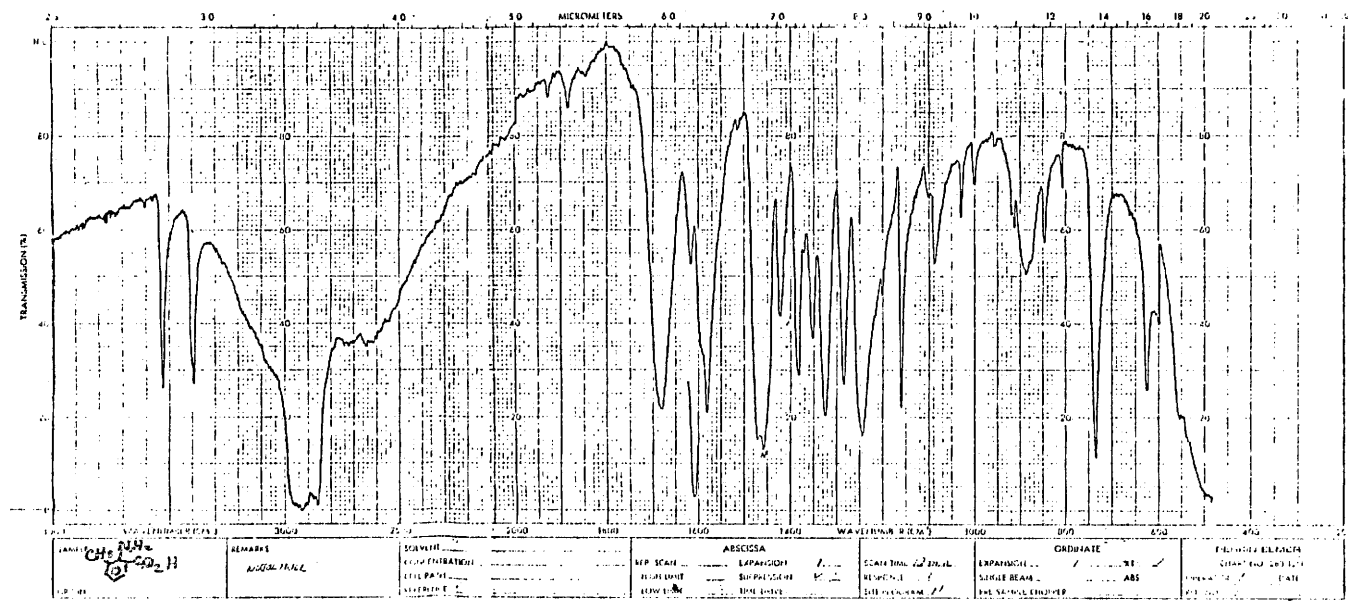


SAMPLE <i>ClO₂H</i> <i>83</i>	REMARKS <i>N-SOL NOL</i>	SOLVENT CONCENTRATION CELL PATH REFLECTOR	ABSORBA REP. SCAN HIGH LIMIT LOW LIMIT	EXPANSION SUPPRESSION TIME DRIFT	SCAN TIME <i>10 min</i> RESPONSE SFT PROGRAM	ORIGINATE EXPANSION SCALE BEAM P.E. SAMPLE CHOPPER	PRECISION BEAMER OPERATOR DATE PER
--	-----------------------------	--	---	--	--	---	---

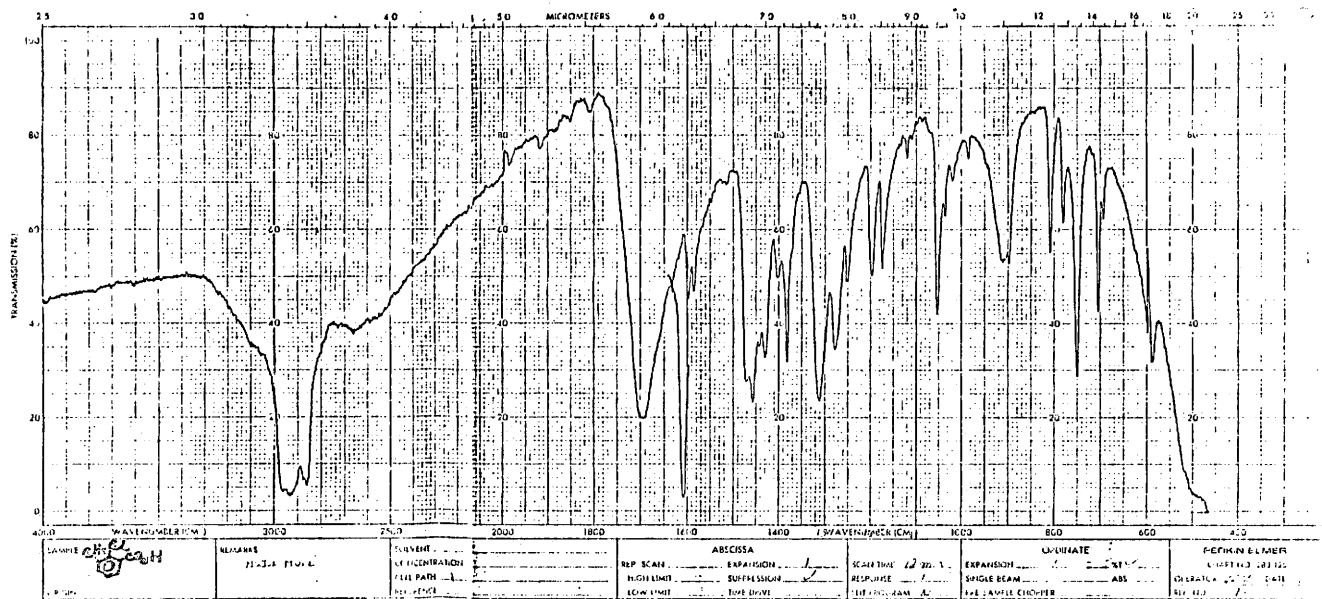
Spectrum #2 2-Chloro-5-methylbenzoic Acid



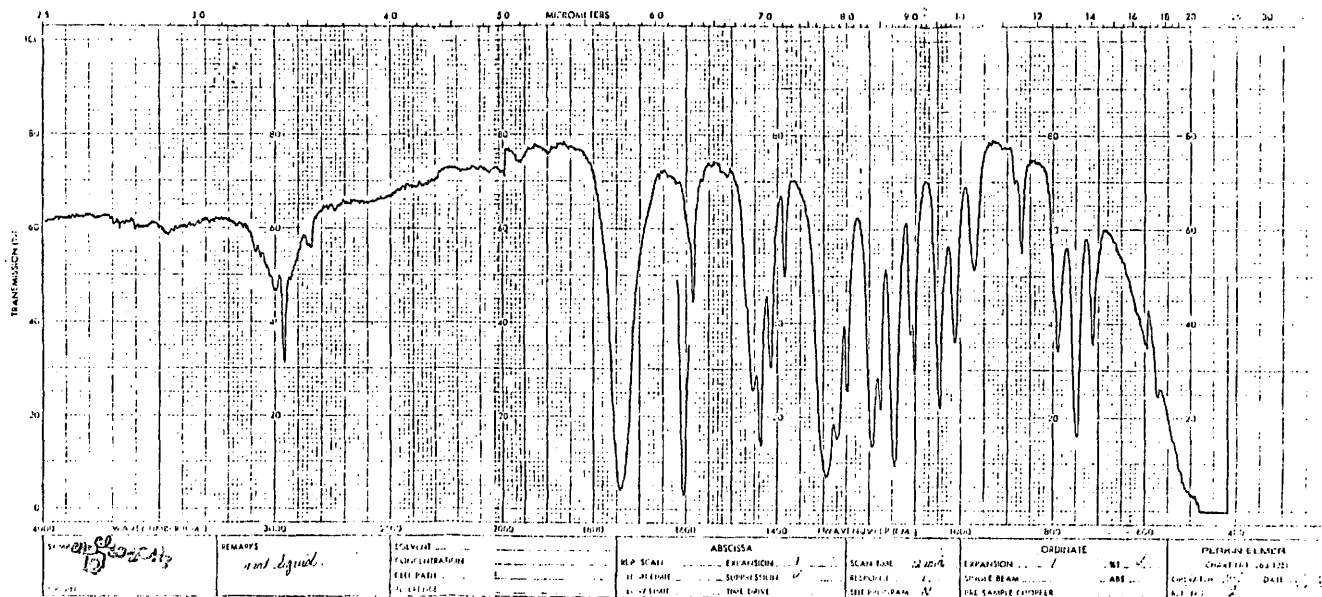
Spectrum #3 Methyl 2-Chloro-5-methylbenzoate



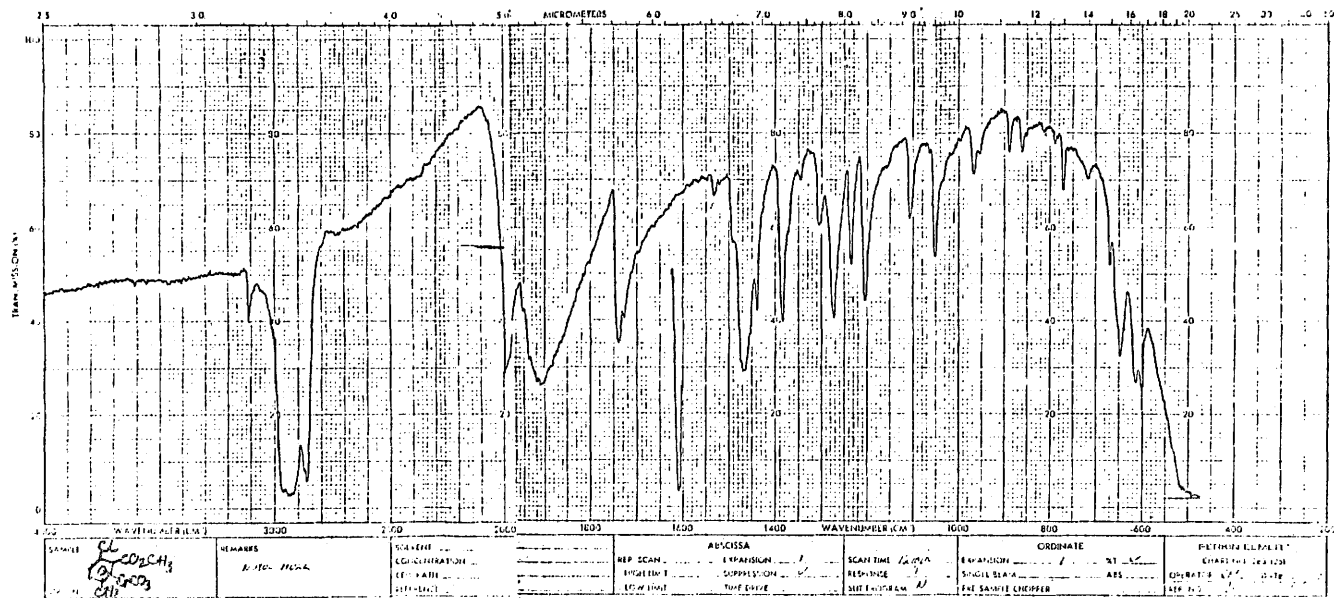
Spectrum #4 2-Amino-3-methylbenzoic Acid



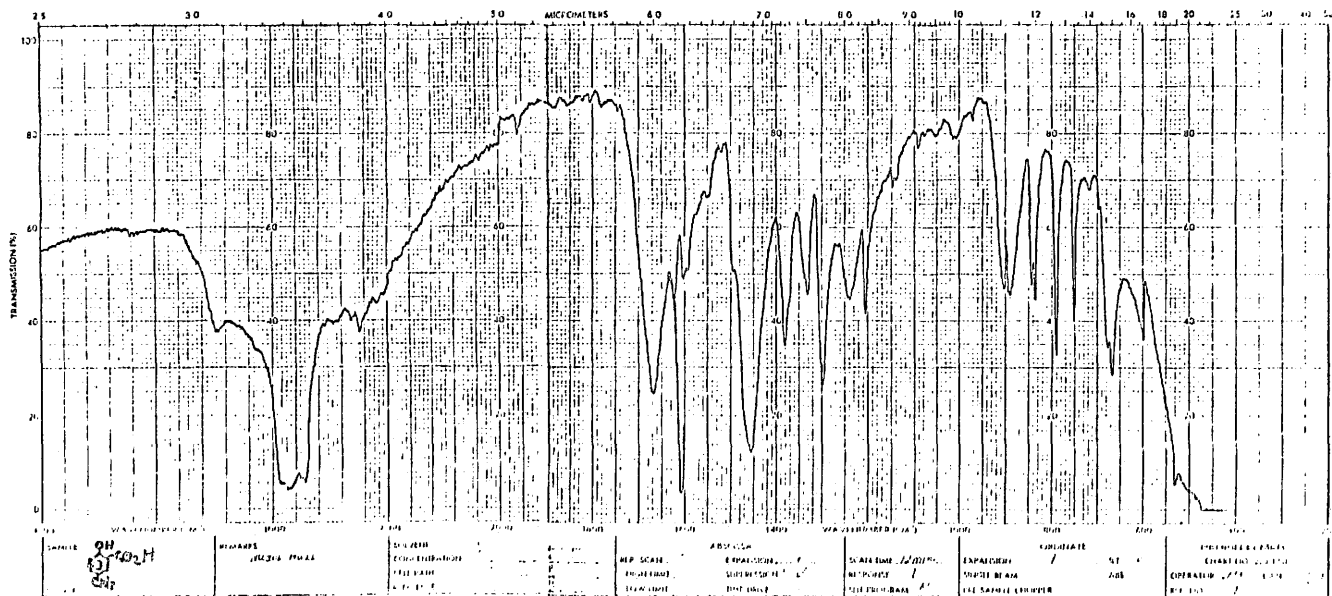
Spectrum #5 2-Chloro-3-methylbenzoic Acid



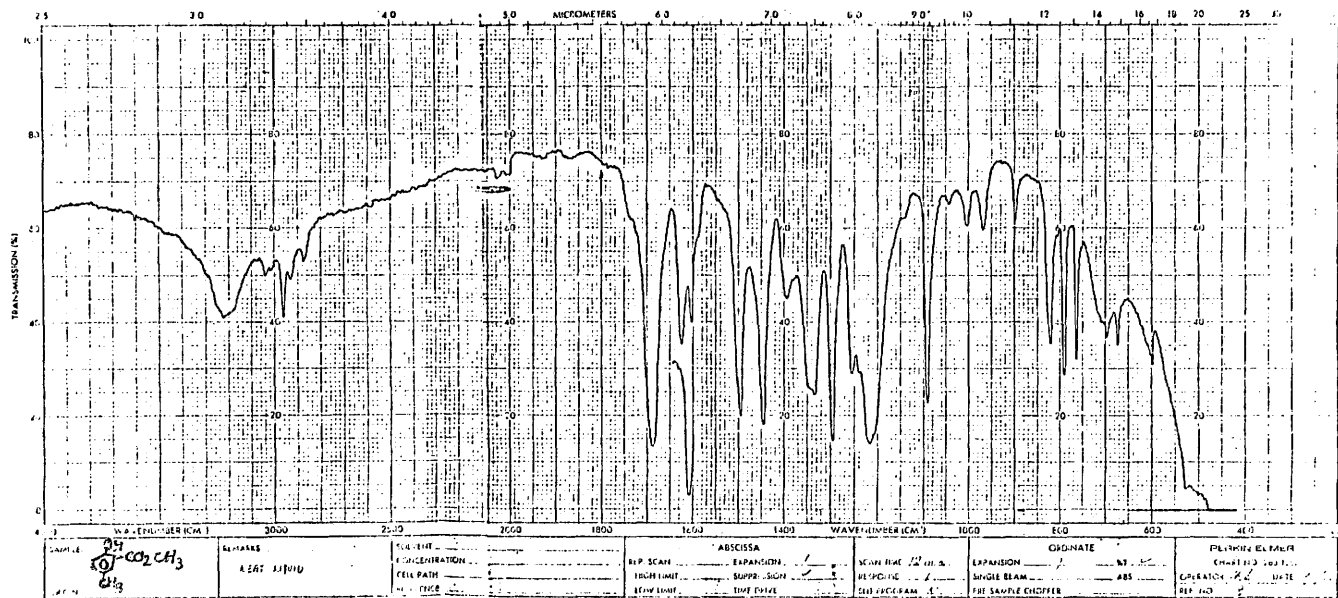
Spectrum #6 Methyl 2-Chloro-3-methylbenzoate



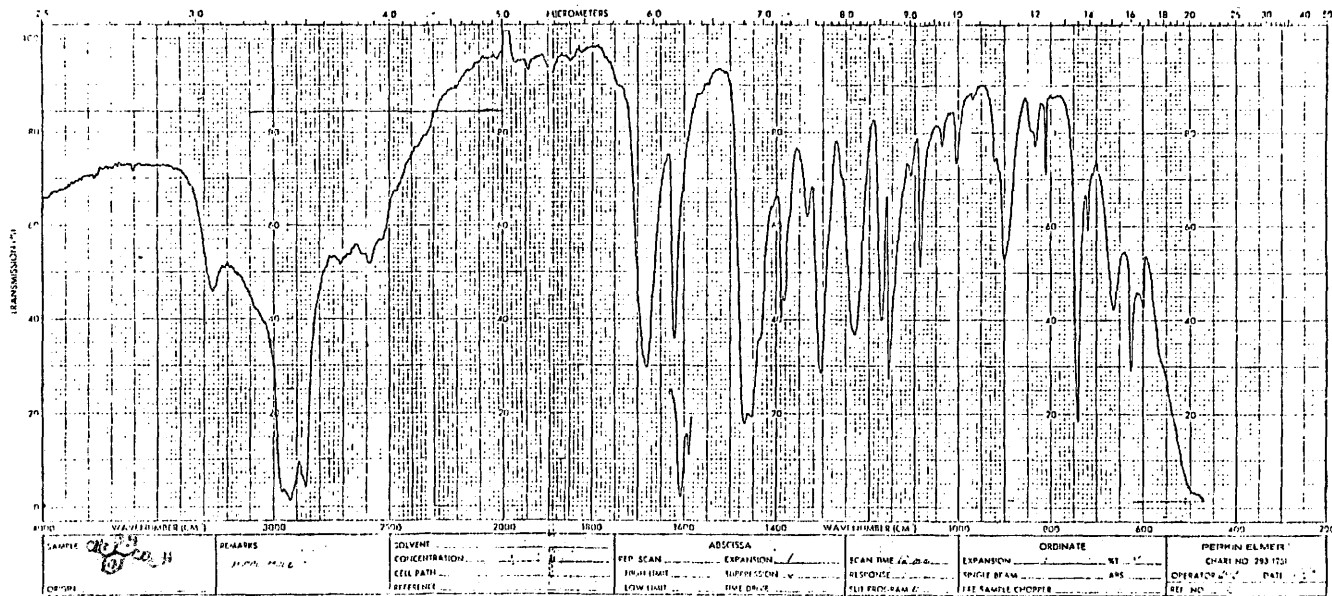
Spectrum #7 Methyl 2-Chloro-5-methylbenzoatechromiumtricarbonyl



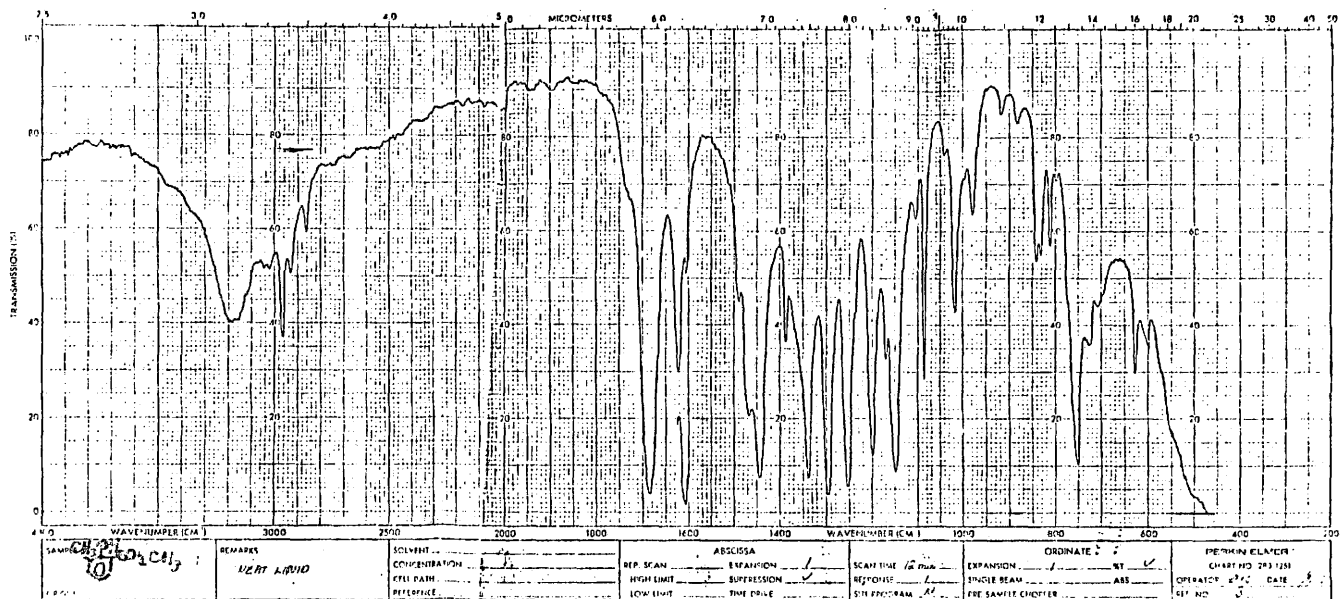
Spectrum #8 2-Hydroxy-5-methylbenzoic Acid



Spectrum #9 Methyl 2-Hydroxy-5-methylbenzoate



Spectrum #10 2-Hydroxy-3-methylbenzoic Acid



Spectrum #11 Methyl 2-Hydroxy-3-methylbenzoate

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49. The X-ray crystal structure of the product was solved by R. Faggiani and C.J.L. Lock, on crystals obtained by N. Hao. Special thanks to all three gentlemen.
50. 60 MHz proton NMR spectrum: narrow multiplet at δ 5.6 (1H), multiplet at δ 4.4 (2H), singlet at δ 1.29 (3H).
 Fluorine-19 spectrum: doublet ($J=8.85$ Hz) of triplets ($J=5.80$ Hz) at 139.3 ppm to high field of CFCl_3 .
 Carbon-13 NMR spectrum (proton decoupled): π -complexed arene resonances at δ 144.4 ($^1J_{\text{CF}}=264.5$ Hz), δ 76.9 ($^2J_{\text{CF}}=22.1$ Hz), δ 90.7 ($^2J_{\text{CF}}=11.8$ Hz), δ 94.9 ($^3J_{\text{CF}}=2.9$ Hz), δ 96.4 ($^3J_{\text{CF}}=1$ Hz), δ 101.1 ($^4J_{\text{CF}}=0$), and singlet absorptions at δ 19.0 (CH_3), 163.9, 230.4 and 265.5.