[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

An Abnormal Reaction of an Organocadmium Reagent: *para*-Acylation of *m*-Methoxythenylcadmium Reagent

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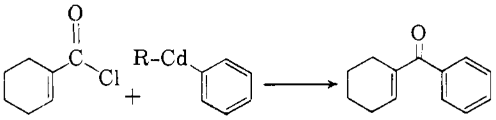
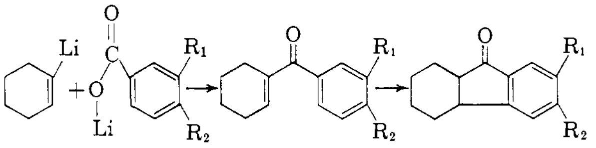
RECEIVED AUGUST 21, 1958

When the cadmium reagent prepared from *m*-methoxybromobenzene was allowed to react with an acid chloride, acylation occurred on the carbon atom adjacent to that originally holding the halogen atom. The amount of this abnormal reaction varied with the acyl halide used but was always the major pathway, the normal reaction being less favored. The abnormal acylation reaction was found to occur with no other aryl halides. The mechanism of the reaction was investigated and it was found that no rearrangement of the cadmium reagent itself had occurred, since upon reaction with diacetyl the expected *m*-substituted product resulted. The mechanism was shown to be that of an electrophilic aromatic substitution where the organocadmium reagent acts as an internal Lewis acid. A similar abnormal substitution was found to occur with acid anhydrides and from these studies it was shown that the process was intramolecular.

Previously, the synthesis of tetrahydrobenzophenones has been achieved by one of two methods, the reaction of an aroyl chloride with cyclohexene in the presence of aluminum chloride (Darzens' reaction) and the reaction of cyclohexenyllithium with an aromatic acid.[2,3] In both of these methods the potential carbonyl group finds its source in the carbonyl of the aromatic acid. An alternate procedure which would allow for a more ready preparation of tetrahydrobenzophenones containing substituents in the tetrahydro ring is the reaction of a cyclohexenyl-1-carbonyl chloride with an aromatic organocadmium reagent. Such a reaction system utilizing the unsaturated acid derivative, cinnamoyl chloride, and diphenylcadmium has been reported by Nightingale[4] to yield the expected benzalacetophenone in 44% yield.



When cyclohexenyl-1-carbonyl chloride was allowed to react with the cadmium reagent derived from *m*-bromoanisole, an 18% yield of analytically pure material was obtained, but the product showed unexpected spectral properties. The ultraviolet spectrum showed a maximum at 268 mμ (ε 11,100) with a shoulder at 285 mμ (ε 9000) and the infrared spectrum possessed carbonyl bands at 5.92 and 6.09 μ. Looking first at the doublet in the infrared, Zimmerman[3] has reported that the unsubstituted 3,4,5,6-tetrahydrobenzophenone (IIIa), prepared by the reaction of cyclohexenyllithium and lithium benzoate, possesses only a single carbonyl absorption at 6.09 μ. Although the band at lower wave length in the previous material might be due to abnormal transannular effects on the chromophore, it seemed more likely that the first formed unsaturated ketone, due to the presence of the methoxyl group, had undergone cyclization to a fluorenone. Such was found to be the case since 3-methoxy-3′,4′,5′,6′-tetrahydrobenzophenone (IIIb), prepared from cyclohexenyllithium and lithium *m*-methoxybenzoate, possessed the expected band at 6.09 μ and this material upon ring closure with formic acid yielded 2-methoxy-4b,5,6,7,8,8a-hexahydrofluorenone (IVb) which showed only the band at 5.92 μ.



I II III IV

a, $R_1 = R_2 = H$; b, $R_1 = OCH_3$, $R_2 = H$; c, $R_1 = H$, $R_2 = OCH_3$

When the ultraviolet spectra of IIIb and IVb were examined, it was found that the former had a λ_{max} 248 mμ (ε 11,500) and the latter had a λ_{max} 250 mμ (ε 9400). The comparison of these values with those obtained with the product from the cadmium reaction (λ_{max} 268 mμ, ε 11,100) clearly showed that this material was more complex than simply having ring closed material present. The spectral data indicated that an isomerization had occurred since by examination of the ultraviolet spectral values of the methoxyl-substituted acetophenones,[5] a similar bathochromic shift is obtained in going from the *m*- to the *p*-isomer. That isomerization had occurred was established in two ways. First, the authentic 4-methoxy-3′,4′,5′,6′-tetrahydrobenzophenone (IIIc) and its ring closed derivative IVc were prepared *via* the cyclohexenyllithium procedure followed by ring closure. It was found that IIIc possessed λ_{max} 281 mμ (ε 11,600) and 6.09 μ while IVc possessed λ_{max} 268 mμ (ε 14,600) and 5.92 μ with a shoulder at 287 mμ (ε 10,000). Second, by fractional crystallization of the 2,4-dinitrophenylhydrazones prepared from the cadmium reaction product, the derivative of IIIc and IVc was isolated. Upon chromatography of the reaction mixture directly, the fluorenone IVc was obtained. By examination of the infrared spectrum of the cadmium reaction product it was found that approximately 40% of the fluorenone and 60% of the uncyclized tetrahydrobenzophenone were present. Furthermore, the spectrum also indicated that in the uncyclized fraction some of the *m*-isomer was present to the extent of about 10% of that fraction.

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[1] Abraham Rosenberg Fellow, 1956–1957; General Electric Co. Fellow, 1957–1958.

[2] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950); 1430 (1952); 2209 (1953).

[3] H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

[4] D. Nightingale and F. Wadsworth, THIS JOURNAL, **67**, 417 (1945).

[5] The spectral data for the methoxyacetophenones were found to be: *ortho*, λ_{max} 247 mμ (ε 8750); *meta*, λ_{max} 249 mμ (ε 8800); *para*, λ_{max} 271 mμ (ε 6600).

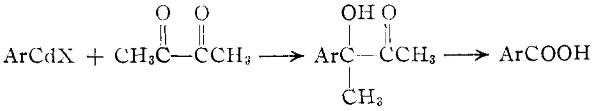
These results clearly demonstrated that in the reaction of the acid chloride with the cadmium reagent derived from *m*-bromoanisole, the carbonyl group is placed on the carbon atom adjacent to the position of the starting bromide. It next was of interest to investigate the generality of the abnormal cadmium reaction and the reaction of acetyl chloride with the cadmium reagents derived from the three isomeric bromoanisoles was examined. It was found that with *o*-bromoanisole, a mixture containing 96% of *o*-methoxyacetophenone and 4% of the *p*-isomer was obtained. With *m*-bromoanisole, a mixture containing 35% *m*- and 65% *p*-methoxyacetophenone was isolated. The *p*-bromoanisole yielded only *p*-methoxyacetophenone. Thus, the abnormal reaction occurs to an appreciable extent only with the *m*-methoxy derivative. The small amount of *p*-isomer derived from the *o*-methoxy derivative was formed in the reaction since the starting *o*-bromoanisole was shown to contain less than 0.5% of the *p*-isomer. The pathway for the formation of this small amount of *p*-isomer will be discussed later.

Turning attention to other substituted bromobenzenes, the products obtained in an earlier study[6] were examined. Previously, the three isomeric bromotoluenes, *o*- and *p*-bromochlorobenzene, and 1- and 2-bromonaphthalene in the form of their cadmium reagents were allowed to react with β-carbomethoxypropionyl chloride. The resulting methyl β-aroylpropionates from all of these materials were shown to be of the expected normal structure. When the same acid chloride was allowed to react with the three isomeric methoxyphenylcadmium derivatives, again only the *m*-methoxy isomer showed the abnormal reaction, *i.e.*, from *m*-bromoanisole *only* methyl β-(*p*-methoxybenzoyl)-propionate was obtained.[7] This finding of the abnormal reaction only with the *m*-methoxyphenylcadmium reagent[8] establishes the requirement of a highly activated position adjacent to the carbon atom originally holding the bromine atom if the abnormal course is to be followed. Furthermore, the finding of different isomer composition with different acid chlorides shows the dependence of the reaction upon the nature of this reactant.

Consideration of the over-all reaction shows there are three steps where the abnormal reaction could occur: the formation of the Grignard reagent, its conversion to a cadmium reagent and the reaction of this reagent with the acid chloride. Abnormalities in the first step can be discounted since previous work[9] has clearly demonstrated that the magnesium derivative possesses the expected *m*-structure. In order to evaluate the second step (the conversion of the Grignard to the cadmium reagent), a reaction was sought in which the diarylcadmium could be allowed to react with a compound other than an acyl halide. It has been shown that a cadmium reagent will react with certain ketonic compounds[10] and anhydrides.[11] The latter substances did not seem favorable due to the close similarity of their reactions to those of acyl halides and so the reaction with diacetyl to form an α-hydroxy-ketone was investigated.

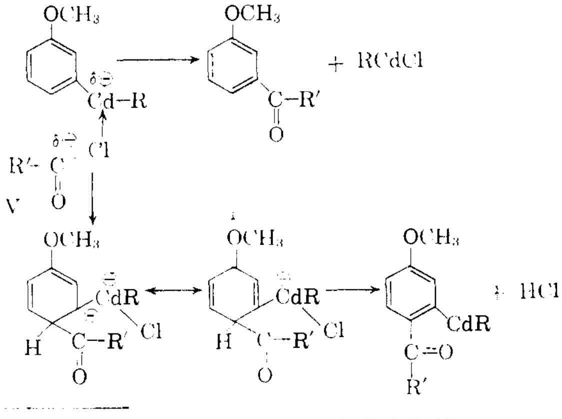
$$\mathrm{ArX} \longrightarrow \mathrm{ArMgX} \longrightarrow \mathrm{ArCdX} \longrightarrow \mathrm{ArCOR}$$

When the diarylcadmium reagent derived from *p*-bromoanisole was allowed to react in ether with biacetyl, there was obtained 3-hydroxy-3-(*p*-methoxyphenyl)-2-butanone which upon oxidation with alkaline permanganate yielded only *p*-methoxybenzoic acid. Using the reagent derived from *m*-bromoanisole, 3-hydroxy-3-(*m*-methoxyphenyl)-2-butanone was formed and this material upon oxidation yielded only *m*-methoxybenzoic acid. It is apparent that the cadmium reagent is of the expected orientation and that the abnormal reaction must occur during the reaction with the acyl halide.



$$\mathrm{ArCdX} + \mathrm{CH_3}\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle O}{\|}}{C}\mathrm{CH_3} \longrightarrow \mathrm{Ar}\underset{\underset{\displaystyle \mathrm{CH_3}}{|}}{\overset{\overset{\displaystyle \mathrm{OH}}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}\mathrm{CH_3} \longrightarrow \mathrm{ArCOOH}$$

There is much evidence to suggest that the reaction of an organocadmium reagent[12] with an acyl halide proceeds through initial coördination of the cadmium to the halide atom with the resulting polarization of the carbon–halogen bond. Utilizing this concept, a mechanism to explain the formation of *p*-substituted product from *m*-methoxyphenylcadmium reagent can be formulated. In the initial cadmium–acid chloride complex (V) there is a competition for the attack of the de-



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[6] W. G. Dauben and H. Tilles, *J. Org. Chem.*, **15**, 785 (1950).

[7] In the earlier work,[6] the product from the *m*-methoxyphenylcadmium reagent had been assigned the expected *meta* structure even though the m.p. of the acid (obtained after saponification) was about 40° higher than that reported in the literature. Such an assignment was made since the semicarbazone derivative possessed the m.p. reported for the *m*-isomer and since aroylpropionic acids often are polymorphic. Subsequently, the semicarbazones of the *m*- and *p*-isomers have been prepared in this Laboratory and shown to possess the same m.p. and a m.p. of a mixture of the two isomers melted only 1° lower than the pure components. Thus, this correction of the erroneous structure assignment in the earlier work should be noted.

[8] Klemm, Mann and Lind kindly informed us previous to publication of their results (*J. Org. Chem.*, **23**, 349 (1958)), that they had found the product formed in the reaction of the *m*-methoxyphenylcadmium derivative with *m*-methoxybenzoyl chloride was a mixture of two parts of the 3,4,- and one part of the 3,3′-dimethoxybenzophenones.

[9] E. Votocek and J. Matejka, *Ber.*, **46**, 1755 (1913).

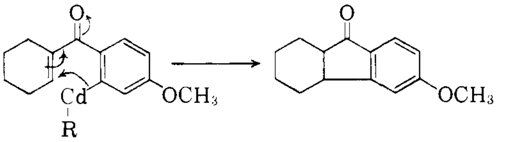
[10] R. Pinson, Jr., and S. L. Friess, THIS JOURNAL, **72**, 5333 (1950); G. W. Stacy and R. M. McCurdy, *ibid.*, **76**, 3816 (1954); G. W. Stacy, R. A. Mikulec, S. L. Razinak and L. D. Starr, *ibid.*, **79**, 3587 (1957).

[11] P. L. deBenneville, *J. Org. Chem.*, **6**, 462 (1940).

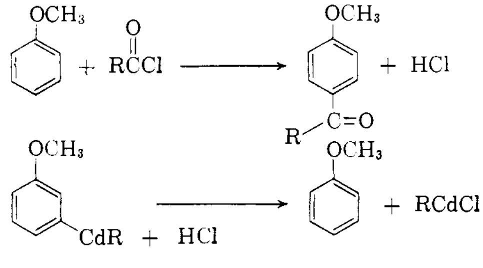
[12] J. Cason, *ibid.*, **13**, 277 (1948); J. Cason and R. D. Smith, *ibid.*, **18**, 1201 (1953).

veloping acylonium ion at the *m*- and *p*-position of the anisole ring. Substitution at the *p*-position is favored due to the ability of the methoxyl group to lower the transition state energy for substitution at this position. The over-all formulation of the mechanism is that of an electrophilic substitution in which the organocadmium reagent acts as an internal Lewis acid. According to this postulate the primary acylated material still retains the organocadmium bond and demonstration of its presence would be evidence pointing to the correctness of the mechanistic postulate.

Along this line, it should be recalled in the reaction of cyclohexenyl-1-carbonyl chloride that, in addition to the tetrahydrobenzophenone, there was isolated the 3-methoxyhexahydrofluorenone (IVc). A logical pathway for the formation of this latter material is that the initially formed reaction product still retains the organocadmium bond and this material undergoes a Michael addition to the α,β-unsaturated ketone system. In line with this suggestion, Wittig[13] has shown that diphenylcadmium adds quantitatively to benzalacetophenone. The possibility existed, however, that the ring closure was induced by one of the Lewis acids present. This was shown not to be so by attempting to ring close IIIc using cadmium chloride in refluxing benzene in the absence and in the presence of hydrogen chloride. Under the former conditions no reaction occurred and under the latter conditions, ring closure occurred to less than 7%. Thus, the formation of a fluorenone directly in the reaction indicates the presence of the organocadmium linkage in the initial product.

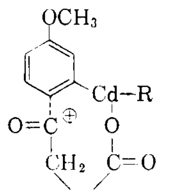


There is implicit in the mechanism the assumption that the reaction is intramolecular. The finding of *para* acylated material in the reaction of *o*-methoxyphenylcadmium, however, suggested that at least part of the reaction could occur by an intermolecular process. This process would be the usual Friedel-Crafts reaction between an acyl halide and anisole and it could be brought into function by the following steps. In all of the reactions studied there certainly is present some anisole formed by hydrolysis of the organometallic bond. Due to the extreme reactivity of anisole in electrophilic substitution, this material might be acylated under the catalytic influence of cadmium chloride. The hydrogen chloride generated would, in turn, hydrolyze more of the diarylcadmium reagent to generate anisole which then would enter the cycle. That such a reaction could occur seemed to be supported by the studies of Burton and Praill[14] in which it was found that anisole was so reactive that zinc chloride would readily catalyze the acylation by acetic anhydride or acetyl chloride. It is stated, however, that cadmium chloride was ineffective but that this non-reactivity could have been due to insolubility of the catalyst in the medium. In our hands it was found that when anisole was refluxed in benzene with one equivalent of acetyl chloride and 0.5 equivalent of cadmium chloride, a 6% yield of *p*-methoxyacetophenone was isolated in the form of the 2,4-dinitrophenylhydrazone. Thus, the external process is possible but is too inefficient a pathway to account for the results with *m*-methoxyphenylcadmium reaction. Such a process, however, most likely is the source of the 4% of *p*-isomer obtained from the *o*-methoxyphenylcadmium reagent.



Having postulated that the abnormal substitution in the reaction between an organocadmium reagent and an acyl halide occurs *via* the formation of an acylonium type of intermediate, it was of interest to test this hypothesis. Cason in his studies of the reaction of these reagents with acid anhydrides has shown that here too an acylonium type of intermediate is involved.[12] Such being the case, the reaction of *m*-methoxyphenylcadmium reagent with an anhydride should yield abnormal substitution. It was found that when acetic anhydride was used, 35% of *p*-methoxyacetophenone and 65% of *m*-methoxyacetophenone was formed. These results would suggest that in the reaction of the anhydride, there is less charge separation in the transition state, a feature which is in line with the known lesser reactivity of anhydrides.

When *m*-methoxyphenylcadmium reagent was allowed to react with succinic anhydride, the mixture of β-(methoxybenzoyl)-propionic acids was found to be 95% of the *m* isomer and only 5% of the *para* substance. The fact that almost no *p*-substitution occurred in the case of succinic anhydride could be due to the fact that if the abnormal substitution reaction must occur by an intramolecular process, then substitution at the *p*-position would involve the formation of an 8-membered ring in the transition state. The relationship between ring size and intramolecular interchanges has been studied by Cason[12] who found that in the reaction of ester acid chlorides with a Lewis acid, when a 6- or 7-membered ring was involved interchange of the alkoxyl and chloride occurred but not when an 8-membered ring was needed. It must be concluded from the



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(13) G. Wittig, F. J. Meyer and C. Lange, *Ann.*, **571**, 178 (1950).

(14) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 726 (1951).

comparison of the results obtained with acetic and succinic anhydrides that these materials react with a cadmium reagent by an intramolecular process. By inference, the same conclusion can be extended to the reaction of acyl halides.

Finally, the mechanism of the reaction of *m*-methoxyphenylcadmium reagent with acid chlorides and anhydrides can be summarized: the reaction proceeds by initial coördination of cadmium reagent with either the chloride of the acyl chloride or the ethereal oxygen of the anhydride; this coördination results in polarization of the carbonyl group to develop an acylonium type of intermediate which then attacks, intramolecularly, either the *m*- or *p*-position of the ring.

Experimental[15]

3′-Methoxy-3,4,5,6-tetrahydrobenzophenone (IIIb).—To 1.58 g. (0.228 mole) of finely divided lithium wire in 200 ml. of dry ether was added 12.9 g. (0.111 mole) of 1-cyclohexenyl chloride[2] in 50 ml. of dry ether. After stirring for 20 hours, nearly all of the lithium had been utilized. Then, 15.1 g. (0.096 mole) of lithium 3-methoxybenzoate was added and the solution refluxed overnight. The reaction was decomposed by the addition of water, the layers separated and the aqueous phase extracted once with ether.

Acidification of the aqueous layer with concentrated hydrochloric acid yielded 7.5 g. (51%) of unreacted 3-methoxybenzoic acid. The ethereal layer was dried, the solvent evaporated and the residue (10.2 g.) distilled, b.p. 164–167° (4 mm.), yield 5.68 g. The infrared spectrum of the product indicated the presence of hydroxylated material so that it was dissolved in benzene–ether (1:1), filtered through alumina (Act. I), the solvent removed and the liquid evaporatively distilled, block temperature 110–120° (4 mm.), yield 3.05 g. (30%); $\lambda_{\max}^{\text{chl}}$ 6.09, 6.24 μ; $\lambda_{\max}^{\text{alc}}$ 220 mμ (ϵ 16,200), 248 mμ (ϵ 11,500), 304 mμ (ϵ 2,300); n^{5}D 1.5622.

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.39): C, 77.75; H, 7.46; OMe, 14.34. Found: C, 77.82; H, 7.62; OMe, 14.20.

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–ethyl acetate, m.p. 120–122°, $\lambda_{\max}^{\text{chl}}$ 388 mμ (ϵ 32,700).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.39): C, 60.60; H, 5.09; N, 14.14. Found: C, 60.69; H, 5.02; N, 13.88.

2-Methoxy-4b,5,6,7,8,8a-hexahydrofluorenone (IVb).—A mixture of 1.019 g. (0.047 mole) of IIIb, 2 g. of formic acid and 1.5 g. of phosphoric acid (85%) was heated at 85–95° for 24 hours under a nitrogen atmosphere. The reaction mixture was cooled, decomposed by the addition of 50 ml. of water and the aqueous solution extracted twice with ether. The ethereal solution was washed with sodium bicarbonate and sodium chloride solutions, dried over sodium sulfate and the solvent evaporated. The remaining yellow oil (0.916 g.) was crystallized twice from petroleum ether–acetone, yield 0.323 g. (32%), m.p. 99–100°; $\lambda_{\max}^{\text{chl}}$ 5.89, 6.20 μ; $\lambda_{\max}^{\text{alc}}$ 220 mμ (ϵ 28,000), 250 mμ (ϵ 9,400), 323 mμ (ϵ 3,900).

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.39): C, 77.75; H, 7.46; OMe, 14.34. Found: C, 77.90; H, 7.43; OMe, 14.55.

The 2,4-dinitrophenylhydrazone crystallized as scarlet needles from ethanol–ethyl acetate, m.p. 221.0–222.5°, $\lambda_{\max}^{\text{chl}}$ 394 mμ (ϵ 32,700).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.39): C, 60.60; H, 5.09; N, 14.14. Found: C, 60.87; H, 5.22; N, 14.39.

4′-Methoxy-3,4,5,6-tetrahydrobenzophenone (IIIc).—A mixture of 10.5 g. (0.09 mole) of 1-cyclohexenyl chloride, 1.24 g. (0.179 mole) of finely divided lithium wire and a few drops of methyl iodide in 250 ml. of dry ether was allowed to stir at room temperature for 20 hours at which time most of the lithium had reacted. Then, 15.8 g. (0.10 mole) of lithium 4-methoxybenzoate was added in one portion, the ixture stirred overnight at room temperature and refluxed for 12 hours. The mixture still gave a positive Gilman test[16] so 150 ml. of ether was distilled, 100 ml. of dry tetrahydrofuran was added and the mixture refluxed for 30 minutes. At this point the Gilman test was negative and the reaction mixture was decomposed with 170 ml. of water. The ether layer was washed once with water and dried. Acidification of the combined aqueous layers yielded 7.9 g. (54%) of starting 4-methoxybenzoic acid, m.p. 184°. Evaporation of the ether solution yielded 11.5 g. of oil which was distilled from a Claisen flask to give 0.57 g. of forerun, b.p. 90–160° (3 mm.), followed by 6.86 g. (66.5% allowing for recovered acid) of product, b.p. 168–172° (3 mm.), n^{25}D 1.5732: $\lambda_{\max}^{\text{chl}}$ 6.09, 6.24, 6.32 μ; $\lambda_{\max}^{\text{alc}}$ 223 mμ (ϵ 11,200), 281 mμ (ϵ 11,600), with a shoulder at 250 mμ (ϵ 8,100). After standing in ethanol for three weeks, the above solution showed a maximum at 270 mμ (ϵ 13,400) and the shoulder at 250 mμ had disappeared.

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.27): C, 77.75; H, 7.46; OMe, 14.34. Found: C, 76.99; H, 7.26; OMe, 14.45.

The 2,4-dinitrophenylhydrazone after filtration through alumina and two crystallizations from ethanol–ethyl acetate was obtained as fine reddish-orange plates, m.p. 173–175°, $\lambda_{\max}^{\text{chl}}$ 384 mμ (ϵ 30,800).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.39): C, 60.60; H, 5.09. Found: C, 60.91; H, 5.23.

The oxime after two recrystallizations from diluted ethanol showed preliminary softening at 120° and melts from 133–135°.

Anal. Calcd. for $C_{14}H_{17}NO_2$ (231.29): C. 72 70; H, 7.41; N, 6.06. Found: C, 72.80; H. 7.29; N, 5.89.

3-Methoxy-4b,5,6,7,8,8a-hexahydrofluorenone (IVc).—A mixture of 1.04 g. (0.05 mole) of IIIc and 20 g. of polyphosphoric acid[17] was heated on a steam-bath for 30 minutes. The reaction mixture was poured, cautiously, into 100 ml. of water, the product extracted with ether, the ethereal solution washed with sodium bicarbonate and sodium hydroxide until neutral and dried. After evaporation of the ether, the residue (0.911 g.) which showed carbonyl bands both at 5.90 and 6.00 μ was chromatographed on 45 g. of alumina (Act. III). Elution with 400 ml. of petroleum ether–benzene (4:1) followed by 425 ml. of benzene yielded 0.537 g. (51%) of yellowish solid which was recrystallized from petroleum ether–acetone, yield 0.325 g. (30%), m.p. 67–68°; $\lambda_{\max}^{\text{chl}}$ 5.92, 6.25 μ; $\lambda_{\max}^{\text{alc}}$ 224 mμ (ϵ 17,500), 268 mμ (ϵ 14,600), 287 mμ (ϵ 10,900).

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.27): C, 77.75; H, 7.46; OMe, 14.34. Found: C, 77.58; H, 7.52; OMe, 14.15.

The 2,4-dinitrophenylhydrazone dissolved in benzene was filtered through alumina and recrystallized from ethanol–ethyl acetate to give deep maroon needles, m.p. 192–193° dec., $\lambda_{\max}^{\text{chl}}$ 402 mμ (ϵ 31,000).

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.39): C, 60.60; H, 5.09; N, 14.14. Found: C, 60.89; H, 5.19; N, 14.05.

Further elution with ether of the alumina column containing the reaction product yielded 0.213 g. of solid which was recrystallized from petroleum ether–benzene to give 4′-methoxy-2(?)-hydroxy-1,2,3,4,5,6-hexahydrobenzophenone, m.p. 80.0–81.5°; $\lambda_{\max}^{\text{chl}}$ 2.90, 6.02 μ.

Anal. Calcd. for $C_{14}H_{18}O_3$ (234.28): C, 71.77; H, 7.74; OMe, 13.24. Found: C, 72.01; H, 7.71; OMe, 12.72.

Cyclohexene-1-carbonyl Chloride.—To 14.5 g. (0.115 mole) of cyclohexene-1-carboxylic acid[18] was added 33 ml. of thionyl chloride (0.46 mole). After the initial reaction had subsided, the solution was refluxed for one hour, cooled and the product distilled, b.p. 98–104° (20 mm.), yield 14.3 g. (88%), $\lambda_{\max}^{\text{CS}_2}$ 5.74 μ.

The Reaction of Cyclohexene-1-carbonyl Chloride with Di-(*m*-methoxyphenyl)-cadmium.—Di-(*m*-methoxyphenyl)-cadmium, from 22.4 g. (0.12 mole) of *m*-bromoanisole, 2.9 g. (0.12 mole) of magnesium and 12 g. (0.065 mole) of anhydrous cadmium chloride, in 50 ml. of benzene was allowed to react with 5.5 g. (0.038 mole) of cyclohexene-1-carbonyl chloride in 10 ml. of benzene. After refluxing for 6 hours, the reaction was decomposed with dilute hydrochloric acid, the layers separated and the aqueous phase extracted twice with ether. The combined ether and benzene layers were

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[15] All melting points are uncorrected. Ultraviolet spectra were measured in redistilled 95% ethanol or spectral grade chloroform. Analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California.

[16] H. Gilman and F. Schulze. THIS JOURNAL, **47**, 2002 (1925).

[17] S. Sev, *J. Indian Chem. Soc.*, **34**, 169 (1957).

[18] O. Wheeler, THIS JOURNAL, **78**, 61, 3217 (1956).

washed with water, saturated sodium bicarbonate and saturated sodium chloride solutions and then evaporated. The residual oil was steam distilled for 30 minutes, the residue from the distillation extracted into ether, the extract dried and the solvent evaporated. The material (7.7 g.) was chromatographed on 150 g. of alumina (Act. I) and after removing the coupling product with petroleum ether, the desired ketonic material was eluted with benzene–ether (1:1). This latter fraction was evaporatively distilled at 4 mm., yield 1.56 g. (18%); $\lambda_{\max}^{\text{alc}}$ 220 mμ (ε 15,000), 268 mμ (ε 11,100) with a shoulder at 285 mμ (ε 9,000); $\lambda_{\max}^{\text{chl}}$ 5.92, 6.09 μ.

Anal. Calcd. for $C_{14}H_{16}O_2$ (216.27): C, 77.75; H, 7.46; OMe, 14.34. Found: C, 77.69; H, 7.29; OMe, 14.24.

The 2,4-dinitrophenylhydrazone from 0.198 g. of ketone formed as a low melting solid. One recrystallization from ethanol–ethyl acetate yielded 0.205 g. (57%) of derivative melting around 160°.

Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.39): C, 60.60; H, 5.09; N, 14.14. Found: C, 60.76; H, 4.96; N, 13.93.

Under the microscope, the dinitrophenylhydrazone was found to contain both orange and red crystals. The derivative was dissolved in benzene and filtered through alumina. The material obtained by evaporation of the solvent was dissolved in ethyl acetate in such an amount so as to give a dilute solution and allowed to stand at room temperature for two days during which time dark red crystals precipitated. The solid showed a m.p. of 190–191°, mixed melting point with same derivative of IVc (m.p. 192–193°) was undepressed, $\lambda_{\max}^{\text{chl}}$ 402 mμ (ε 29,800). Concentration of the mother liquor yielded two additional fractions having melting ranges of 130–150° and 110–124°. The former was recrystallized once from ethanol–water and then from ethanol–ethyl acetate to yield orange-red leaflets, m.p. 172–175°, m.m.p. with derivative from IIIc (m.p. 173–175°) showed no depression, $\lambda_{\max}^{\text{chl}}$ 393 mμ (ε 30,300).

In another preparative run, the crude reaction product obtained by direct hydrolysis of the reaction mixture was distilled through a short column. The higher boiling fraction (b.p. 155–170°, 5 mm.) was examined directly. A portion (1.356 g.) was chromatographed on 65 g. of alumina (Act. III) and after removing non-carbonyl containing components with petroleum ether, elution with 300 ml. of petroleum ether–benzene (1:1) gave 0.446 g. of oil possessing carbonyl bands at 5.90 (weak) and 6.09 μ (strong). Further elution with 200 ml. of benzene yielded 0.118 g. of solid, m.p. 45–60°. After two recrystallizations from petroleum ether–acetone, there was obtained 0.033 g. of product, m.p. 65–66.5°, m.m.p. with IVc showed no depression; $\lambda_{\max}^{\text{alc}}$ 224 mμ (ε 16,100), 268 mμ (ε 15,000), 287 mμ (ε 11,300).

A second portion of the distilled ketone was chromatographed in a similar manner and by use of infrared bands at 5.92 (characteristic of IVc), 6.09 (characteristic of IIIb and IIIc) and 8.55 μ (characteristic of IIIc) it was estimated that the material contained 40% IVc and 60% IIIc and IIIb. From the intensity of the 8.55 μ band, a total amount of 50% of IIIc was present. A similar analysis of the crude distilled mixture gave the same answer showing that no enrichment had occurred on chromatography.

3-Hydroxy-3-(*p*-methoxyphenyl)-2-butanone.—The cadmium reagent from *p*-bromoanisale was prepared from 18.4 g. (0.098 mole) of *p*-bromoanisole, 2.4 g. magnesium (0.099 mole) and 9.8 g. (0.054 mole) of cadmium chloride in 100 ml. of ether and 5.615 g. (0.065 mole) of biacetyl in 50 ml. of ether was added dropwise so as to maintain the exothermic reaction.[10] The mixture was refluxed for 19 hours and then decomposed by the addition of 150 ml. of ice-cold acetic acid (1 *N*). The layers were separated, the aqueous layer was extracted twice with ether and the combined organic layers were washed twice with saturated sodium chloride and dried over magnesium sulfate. After evaporation of the solvent, the material was distilled, yield 6.269 g. (49%), b.p. 155–159° (11 mm.); $\lambda_{\max}^{\text{chl}}$ 2.88, 5.88, 6.20, 6.29 μ; $n^{25}\mathrm{D}$ 1.5309.

Anal. Calcd. for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.27; MeO, 15.96. Found: C, 67.98; H, 7.19; MeO, 15.79.

The semicarbazone was recrystallized from dilute ethanol, m.p. 195–196.5°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$ (251.28): C, 57.35; H, 6.82; N, 16.72. Found: C, 57.28; H, 6.51; N, 16.65.

Oxidation of 3-Hydroxy-3-(*p*-methoxyphenyl)-2-butanone.—A mixture of 0.534 g. of ketolone with 3 g. of potassium permanganate and 5 ml. of 10% sodium hydroxide in 50 ml. of water was refluxed for 1.5 hours, the mixture was cooled, an additional 1 g. of potassium permanganate and 2 ml. of 10% sodium hydroxide was added and the mixture was refluxed for an additional 0.5 hour. After cooling to room temperature, 10 ml. of sulfuric acid (6 *N*) was added very cautiously in portions. After the evolution of gas had abated, the solution was refluxed for 5–10 minutes and then cooled. The excess permanganate was decomposed with sodium bisulfite, the solution made strongly acidic with sulfuric acid (6 *N*) and extracted three times with ether. The ether solution was washed once with water and then extracted four times with 5% sodium hydroxide. The basic solution was filtered through glass wool, acidified with concentrated hydrochloric acid and the precipitate filtered and dried. There was obtained 0.200 g. (48%) of *p*-methoxybenzoic acid, m.p. and m.m.p. with an authentic sample, 183–184°.

3-Hydroxy-3-(*m*-methoxyphenyl)-2-butanone.—The cadmium reagent from *m*-bromoanisole was prepared from 12.1 g. (0.064 mole) of *m*-bromoanisole, 1.57 g. (0.064 mole) of magnesium and 6.43 g. (0.35 mole) of cadmium chloride in 75 ml. of ether and 3.741 g. (0.0435 mole) of biacetyl was added.[10] The reaction was treated as before, yield 2.79 g. (33%), b.p. 148–151° (10 mm.), $n^{25}\mathrm{D}$ 1.5259; $\lambda_{\max}^{\text{chl}}$ 2.87, 6.24, 6.29 μ.

Anal. Calcd. for $C_{11}H_{14}O_3$ (194.22): C, 68.02; H, 7.27; MeO, 15.96. Found: C, 67.80; H, 7.14; MeO, 15.80.

The semicarbazone formed in 90% yield, m. p. 164–165°. One recrystallization from ethanol raised this to 165–166°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$ (251:28): C, 57.35; H, 6.82; N, 16.72. Found: C. 57.44; H, 6.93; N, 16.78.

Oxidation of 3-Hydroxy-3-(*m*-methoxyphenyl)-2-butanone.—Oxidation of 0.538 g. of 3-hydroxy-3-(*m*-methoxyphenyl)-2-butanone was carried out as before. The precipitated crystals were filtered, washed twice with ice-water, and dried to yield 0.209 g. (49.6%) of *m*-methoxybenzoic acid, m.p. and m.m.p. with authentic sample, 107–108°.

Attempted Ring Closure of IIIc with Cadmium Chloride (a).—A solution of 0.530 g. of IIIc in 15 ml. of benzene was refluxed over 9.60 g. of cadmium chloride for 64 hours. The solution then was cooled, the cadmium chloride filtered and washed well with benzene. The benzene was removed *in vacuo* to give 0.447 g. of liquid whose infrared spectrum was identical with that of starting material.

(b).—A solution of 0.390 g. of IIIc in 20 ml. of benzene was refluxed over 6.6 g. of cadmium chloride for 2 hours. During the first half-hour, dry hydrogen chloride was bubbled in at a slow rate. After filtration of the cadmium chloride, the solvent was removed *in vacuo* to give 0.359 g. of oil, the infrared of which showed a weak broad shoulder from 5.9–6.0 μ. Comparison with an authentic mixture showed that less than 7% fluorenone could be present.

The Reaction of Acetyl Chloride with Di-(*p*-methoxyphenyl)-cadmium.—Di-(*p*-methoxyphenyl)-cadmium, prepared from 18.7 g. (0.1 mole) of *p*-bromoanisole, in 100 ml. of dry benzene was allowed to react with 6.608 g. (0.084 mole) of freshly distilled acetyl chloride, added in 25 ml. of dry benzene. After refluxing for one hour, the reaction mixture was processed in the usual manner. The product (5.60 g., 45%, b.p. 120–130° (16 mm.); Br, 0.39%) possessed an infrared spectrum identical with *p*-methoxyacetophenone. The ultraviolet spectrum showed the values: ϵ_{217} 11,600; ϵ_{249} 5,000, $\epsilon_{271.5}$ 15,800; ϵ_{306} 800.

The Reaction of Acetyl Chloride with Di-(*m*-methoxyphenyl)-cadmium.—Di-(*m*-methoxyphenyl)-cadmium, prepared from 18.7 g. (0.1 mole) of *m*-bromoanisole, in 100 ml. of freshly distilled acetyl chloride, added in 25 ml. of dry benzene. The deep purple reaction mixture was processed in the usual manner. The product (6.63 g., 54%, b.p. 115–135° (16 mm); Br, 0.36%) showed no band at 13.15 μ which is characteristic of *o*-methoxyacetophenone. The ultraviolet spectrum showed the values: ϵ_{217} 15,600, ϵ_{249} 6,350, ϵ_{271} 10,800. These values correspond to a mixture of 65% *p* and 35% *m* methoxyacetophenones.

The Reaction of Acetyl Chloride with Di-(*o*-methoxyphenyl)-cadmium.—In the usual manner starting with 18.6 g. of *o*-bromoanisole and using 6.756 g. (0.092 mole) of acetyl chloride, there was obtained 8.081 g. of product, b.p. 94–126° (16 mm.), 5.71% Br; corrected yield of ketone was 7.0 g. (54.3%). The material showed no absorption at 14.35 and 14.60 μ which is characteristic of *m*-methoxyacetophenone and the ultraviolet spectrum had the values:

ϵ_{247} 8,100, $\epsilon_{271.5}$ 1,230; ϵ_{306} 3,560. These values correspond to a mixture of 96% of *o*-methoxyacetophenone and 4% of the *p*-isomer. The presence of the *p*-isomer was confirmed by vapor phase chromatography.

The Reaction of Acetic Anhydride with Di-(*m*-methoxyphenyl)-cadmium.—The cadmium reagent prepared from 28.0 g. (0.15 mole) of *m*-bromoanisole was allowed to react n benzene solution with 7.54 g. (0.074 mole) of acetic anhydride (freshly distilled) for two hours and the reaction mixture processed in the usual manner. Upon distillation there was obtained 3.95 g. of material containing 0.87% Br and thus the yield of ketone is 3.87 g. (35%), b.p. 118–125° (16 mm.). The ultraviolet spectrum showed the values: ϵ_{217} 19,000, ϵ_{249} 7,420, $\epsilon_{271.5}$ 5,540, ϵ_{306} 2,080. These values correspond to a mixture of 68% of *m*-methoxyacetophenone and 32% of the *p*-isomer.

The Reaction of Succinic Anhydride with Di-(*m*-methoxyphenyl)-cadmium.—The cadmium reagent from 13.2 g. (0.07 mole) of *m*-bromoanisole in 100 ml. of dry benzene was allowed to react for one hour with 3.02 g. (0.03 mole) of succinic anhydride. The reaction mixture was decomposed with 50 ml. of 5% hydrochloric acid, the organic material extracted with ether, the ether solution washed with water and then extracted with 10% sodium bicarbonate solution. Acidification of the alkaline extract followed by ether extraction and evaporation of the solvent yielded 2.55 g. of a semi-solid. The material was dissolved again in sodium bicarbonate, extracted with ether and reprecipitated, yield 2.02 g. of yellow solid. The acid (1.82 g.) was chromatographed on 90 g. of Florex XXS and after elution with benzene and benzene–ether (4:1) to remove oily material, benzene–ether (1:1) and ether yielded a total of 0.992 g. of solid. These latter fractions were dissolved in ether, extracted into sodium bicarbonate and precipitated with concentrated hydrochloric acid, yield 0.697 g.; ultraviolet spectrum: ϵ_{217} 22,400, ϵ_{249} 8,000, $\epsilon_{271.5}$ 1,000, ϵ_{306} 2,560. These values correspond to 94–98% of β-(*m*-methoxybenzoyl)-propionic acid and 2–6% of the *p*-isomer.

Anal. Calcd. for $C_{11}H_{12}O_4$ (208.21): C, 63.45; H, 5.81; neut. equiv., 208. Found: C, 63.68; H, 6.09; neut. equiv., 206.

β-(*m*-Methoxybenzoyl)-propionic Acid.—The keto-acid was prepared following the procedures of Thompson and of Martin,[19] m.p. 107–108° (lit.[19] m.p. 107–108°); λ^{alc}_{mxx} 217 mμ (ε 23,400), 249 mμ (ε 8,200), 306 mμ (ε 2,600). The methyl ester was prepared with diazomethane, λ^{alc}_{max} 217 mμ (ε 25,800), 249 mμ (ε 8,560), 307 mμ (ε 2,600). The semicarbazone was prepared, m.p. 173–174° (lit.[19] 177–178°), λ^{alc}_{max} 275 mμ (ε 11,100).

Anal. Calcd. for $C_{12}H_{14}O_4$ (222.23): C, 64.85; H, 6.35; OMe, 27.94. Found: C, 64.44; H, 6.43; OMe, 28.20.

β-(*p*-Methoxybenzoyl)-propionic Acid.—The keto-acid was prepared following the procedure of Fieser and Hershberg,[20] m.p. 146.0–147.5° (lit.[20] 146–147°), λ^{alc}_{max} 217 mμ (ε 11,900), 271 mμ (ε 17,000). The methyl ester was prepared with dizomethane, m.p. 48.6–49.5° (lit.[21] 7.5–49.5°); λ^{alc}_{max} 217 mμ (ε 11,500), 271.5 mμ (ε 16,900). The semicarbazone was prepared, m.p. 175–176° dec. (lit.[22] 185–186°), λ^{alc}_{max} 281 mμ (ε 17,000). The semicarbazones of the *m*- and *p*-isomers when mixed showed a melting point depression of only 1–2°.

The Product from the Reaction of Di-(*m*-methoxyphenyl)-cadmium with β-Carbomethoxypropionyl Chloride.[6]—The infrared spectrum of the resulting keto-ester was essentially identical with that of methyl β-(*p*-methoxybenzoyl)-propionate. The ultraviolet spectrum had maxima at 217 mμ (ε 13,600) and 271 mμ (ε 17,200). The keto-acid, derived by saponification of the ester, had a m.p. of 147.5–148.5° and was not depressed upon admixture with authentic *p*-isomer. The semicarbazone was prepared from the acid and had a m.p. of 174–175° and a maximum at 281 mμ (ε 16,900).

***o*-Methoxyacetophenone** was prepared by allowing dimethylcadmium to react with *o*-methoxybenzoyl chloride. The material had the properties: b.p. 127° (15 mm.), $n^{20}D$ 1.5395 (lit.[23] b.p. 126.5° (15 mm.), $n^{20}D$ 1.5395); λ^{alc}_{max} 211 mμ (ε 20,800), 247 mμ (ε 8,350), 306 mμ (ε 3,780); $\epsilon_{271.5}$ 650; λ^{liq}_{max} 6.00, 12.40, 13.15 μ.

***m*-Methoxyacetophenone** was prepared by allowing dimethylcadmium to react with *m*-methoxybenzoyl chloride; b.p. 129–132° (19 mm.), $n^{20}D$ 1.5408 (lit.[23] b.p. 125–126° (12 mm.), $n^{20}D$ 1.5410); λ^{alc}_{max} 217 mμ (ε 22,600), 249 mμ (ε 8,800), 306 mμ (ε 2,450); $\epsilon_{271.5}$ 700; λ^{liq}_{max} 5.98, 12.70, 14.35, 14.60 μ.

***p*-Methoxyacetophenone.**—The commercial material (Eastman Organic Chemicals) was recrystallized twice from ether, m.p. 37–38° (lit.[24] m.p. 37.5–38.5°); spectral properties: λ^{alc}_{max} 217 mμ (ε 11,700), 271.5 mμ (ε 16,600); ϵ_{247} 4,270, ϵ_{249} 5,200, ϵ_{306} 780; λ^{Nujol}_{max} 6.00, 11.95, 12.05, 12.25 μ.

Pertinent Spectral Properties of Isomeric Bromoanisoles: (a) *ortho:* λ_{max} 13.35 μ, ϵ_{306} 0, $\epsilon_{271.5}$ 2,480, ϵ_{247} 100; (b) *meta:* λ_{max} 13.00 μ, 14.72 μ, $\epsilon_{271.5}$ 1,640, ϵ_{249} 400; (c) *para:* λ_{max} 12.15 μ.

Method of Analysis.—Infrared analyses were carried out by comparison of the spectrum of the mixture to that of a mixture of known composition. Ultraviolet analyses were carried out by measurement of the spectrum from 210 μ to 400 mμ using a model 14 Cary spectrophotometer. If any starting bromoanisole was present, as indicated by bromine analysis, the concentration of the solution and the observed optical density were corrected. The extinction coefficients due to the ketones then were calculated at several wave lengths and the proportion of *p*-isomer determined by simultaneous equations. When the amount of *p*-isomer present was appreciable, this value was checked by merely dividing the extinction at 271.5 mμ by 16,000.

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[CONTRIBUTION FROM THE RAHWAY RESEARCH LABORATORY OF THE METAL AND THERMIT CORPORATION]

The Preparation of Some Unsymmetrical Organotin Bromides and Acetates

BY SANDERS D. ROSENBERG,[1] EUGENE DEBRECZENI AND ELLIOTT L. WEINBERG

RECEIVED JULY 28, 1958

A series of unsymmetrical organotin bromides has been prepared by the stepwise cleavage of appropriate organotin compounds with bromine in carbon tetrachloride or chloroform at −50, 0 or 40°. The bromides have been converted to acetates by treatment with aqueous potassium hydroxide to form bisorganotin oxides, followed by reaction of these intermediate compounds with glacial acetic acid at 100°.

As part of a systematic investigation on the biological properties of triorganotin halides, hydroxides, oxides and esters, a series of new unsymmetrical triorganotin compounds of the type $R_2R'SnX$ has been prepared for microbiological testing. Evaluation of compounds of the type R_3SnX has shown that there is little or no difference in activity, on a tin-contained basis, where X is chloride, bromide, hydroxide, oxide or acetate.

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