[Contribution from the Department of Chemistry, University of New Hampshire]

Organocadmium Reagents. II. Evidence for a Displacement Reaction Effected by the Methylcadmium Reagent[1,2]

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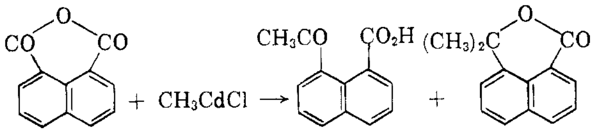
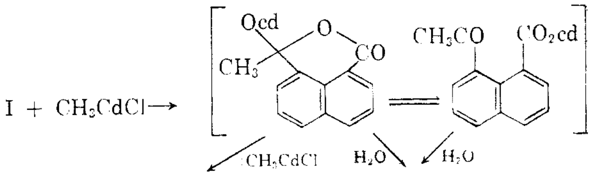
Naphthalic anhydride reacts with methylcadmium chloride to form 3,3-dimethylnaphthalide, as well as the normal product, 8-acetyl-1-naphthoic acid. Formation of the lactone can be formulated as the result of a direct displacement by the cadmium reagent, and this idea is supported by the observation that a series of 3-substituted phthalides are converted to 3-methylphthalides when subjected to the same conditions.

In connection with our previous observations[2] on the formation of both *o*-acetylbenzoic acid and 3,3-dimethylphthalide from phthalic anhydride and the methylcadmium reagent, it was of great interest to determine the behavior of the six-membered ring in naphthalic anhydride (I) under the same conditions. If it were similarly reactive, then the expected products with methylcadmium reagent would be 8-acetyl-1-naphthoic acid (II) and 3,3-dimethylnaphthalide (III). We have found that both II and III are formed from I, although the extent of reaction is considerably lower than that in the case of phthalic anhydride. Even the reaction of I with the methyl Grignard reagent led to II and III in low yields. In both instances, the anhydride was recovered in substantial amount. While this difference in the reactivities of phthalic and naphthalic anhydrides toward the methylcadmium reagent might be ascribed to the difference in size of the anhydride rings, it is most likely a result of the lower solubility of I in diethyl ether. It has been shown previously[3] that I will react extensively with both cadmium and Grignard reagents when toluene is used as solvent. We have found that the yield of II with methylmagnesium iodide can be increased three-fold by using benzene-ether as solvent.



I II III

In order to explain the unexpected formation of lactone with the cadmium reagent, we suggested it might arise by a direct displacement reaction on the initial adduct (a cyclic tautomer) by additional reagent. The alternative explanation—that the lactone was formed by reaction of methylcadmium reagent at the ketone function of *o*-acetylbenzoic acid—was rejected because it was found that the latter acid was extremely unreactive under comparable conditions. Similar reasoning to rationalize the formation from I of III, an "abnormal product," as well as the normal product II, may be represented as follows.

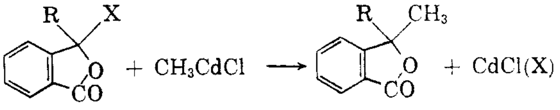


III II

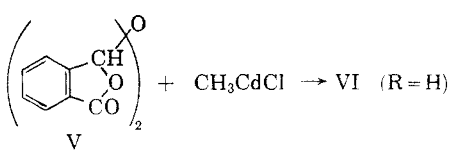
("cd" = $^1/_2$Cd or its equivalent)

Chemical evidence for this series of transformations comes from the observation that II, like *o*-acetylbenzoic acid, is not converted to lactone under the usual reaction conditions. Only a trace of III could be isolated, and II was recovered to the extent of 88%.

The validity of this explanation was, of course, highly questionable because it necessitated postulation of an unusual displacement of some oxycadmium species by the alkylcadmium reagent. We have tested the feasibility of such a displacement by subjecting a series of 3-substituted phthalides (IV. R = H, CH_3; X = Br, OH, OCH_3, OC_2H_5, $OCOCH_3$) and di-3-phthalidyl ether (V) to the action of excess methylcadmium chloride. If reaction were to proceed by the proposed displacement pathway, the expected products would be 3-methylphthalides (VI).



IV VI



V

Indeed, under the relatively mild conditions of the cadmium reaction previously employed with phthalic and naphthalic anhydrides, all but one of

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[1] This work was generously supported by a Frederick Gardner Cottrell grant from the Research Corporation of New York.

[2] Part I: P. R. Jones and S. L. Congdon, *J. Am. Chem. Soc.*, **81**, 4291 (1959).

[3] D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Am. Chem. Soc.*, **75**, 4701 (1953).

the substrates were converted to the corresponding lactones. The yields of VI under standard conditions, which are a rough measure of the relative reactivities, vary considerably with the structure of IV. With 3-bromophthalide, for example, the displacement product, 3-methylphthalide, was isolated in 90% yield, while the same product was formed in only 9% yield from either 3-methoxy- or 3-ethoxyphthalide. When the substituent was hydroxyl (3-hydroxyphthalide, the cyclic tautomer of *o*-phthalaldehydic acid),[4] the conversion to lactone was found to be only 31%, the starting material being recovered to the extent of 46%. Perhaps most surprising was the extremely low reactivity of 3-acetoxyphthalide, which failed to yield any isolable lactonic product. By contrast, di-3-phthalidyl ether (V), in which the group being displaced is the phthalaldehydic acid radical, was converted to VI in quantitative yield (based on formation of two moles of lactone per mole of ether). This remarkable reactivity implies that a facile displacement on the ether occurs, and this is followed by a second reaction of methylcadmium chloride with the phthalaldehydic acid radical that has been displaced.

If this unusual displacement were considered to be nucleophilic in nature, one would expect the relative reactivities of IV to vary in accord with Swain's scale of nucleophilicity.[5] Thus, acetoxyl, one of the poorest nucleophiles, should undergo displacement most readily, and a bromo substituent should be somewhat less reactive. Since the predicted order is not observed, there is no justification for classifying this reaction as another example of nucleophilic displacement. It is interesting to note, however, that the 3-methoxy- and 3-ethoxy- derivatives react only slightly, according to expectation. The extent of displacement is apparently sensitive to structural features other than the leaving group, as evidenced by the observation that 3-methyl-3-acetoxyphthalide reacts to the extent of 44%, although 3-acetoxyphthalide failed to react at all.

It is presumed that 3-substituted naphthalides would undergo a similar displacement, but this series was not investigated because of the difficulty in preparing derivatives. The reaction may be of broad scope and, indeed, can be utilized to rationalize some previously reported abnormal products formed from cadmium reagents. For example, the formation of 3,3-diphenylphthalide from phthaloyl chloride[6] and of 3-phenyl-3-ethylnaphthalide from the acid chloride of 8-benzoyl-1-naphthoic acid[3] might be the result of direct displacement of a chloro substituent in the corresponding pseudo acid chlorides.

EXPERIMENTAL[7]

1,8-Naphthalic anhydride. Crude anhydride, obtained from Koppers Co., Inc., was purified in one of two ways: solution in 10% sodium hydroxide, decolorization with charcoal, and precipitation with mineral acid; or adsorption chromatography on a Florisil column eluted successively with benzene, ether, and 95% ethanol. The recovery of pure anhydride by these two methods was, respectively, 44% (m.p. 259–262°) and 9% (m.p. 260–263°).

Action of methylcadmium reagent on 1,8-naphthalic anhydride. The cadmium reagent was prepared as previously described[2] from 3.1 g. (0.13 mole) of magnesium, 20.4 g. (0.14 mole) of methyl iodide, 27.5 g. (0.15 mole) of cadmium chloride, and 180 ml. of ether. To this mixture, cooled in an ice-bath, was added 8.5 g. (0.043 mole) of solid 1,8-naphthalic anhydride, with stirring, in 10 min. Stirring and heating under reflux were maintained for 75 min.; then the flask was surrounded by an ice-bath and the mixture decomposed with dilute sulfuric acid. The solid was removed by filtration, taken up in base, and the alkaline mixture filtered. By acidification of the filtrate with dilute hydrochloric acid, 2.1 g. (25%) of 1,8-naphthalic anhydride was recovered, m.p. 257–261°. The ether layer from the original filtrate was separated and combined with ether washings of the water layer. The organic phase was washed with 0.06 mole of potassium carbonate, and the alkaline solution added to dilute sulfuric acid. The precipitated 8-acetyl-1-naphthoic acid, recrystallized from aqueous ethanol, separated as tiny clusters of needles, m.p. 171–173°, yield 2.1 g. (23%). After two more recrystallizations the melting point was 173–174°.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 73.14; H, 4.71.

The infrared spectrum (Nujol) contains strong, broad bands at 3410 and 1690 cm.$^{-1}$

All attempts to prepare the oxime, phenylhydrazone, and semicarbazone of 8-acetyl-1-naphthoic acid by standard methods[8] were unsuccessful, as were attempts to prepare the cyclic acetyl derivative by the method previously described.[2]

By concentration of the remaining ether solution, crystalline 3,3-dimethylnaphthalide was collected and washed with ice-cold ether, m.p. 103–105°, yield 1.4 g. (17%). It was recrystallized several times from ether, m.p. 110.5–111.0°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.70. Found: C, 79.49; H, 5.82.

The infrared spectrum (Nujol) contains a carbonyl band at 1706 cm.$^{-1}$

Reaction of naphthalic anhydride with methylmagnesium iodide. An ethereal solution of methylmagnesium iodide was prepared (about 0.1 mole) and to this was added, with stirring, solid naphthalic anhydride during 30 min. The Grignard reagent was always used in excess. Reaction conditions

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[4] Our previous suggestion that phthalaldehydic acid be assigned the open chain tautomeric structure in the solid state was based on infrared data (See Refs. 2 and 10). Because it reacts considerably more readily with cadmium reagent than either *o*-acetylbenzoic acid or 8-acetyl-1-naphthoic acid, however, there is justification for assuming the existence of some ring tautomeric form in ether solution. It is clearly indicated that neither infrared absorption nor reactivity with the methylcadmium reagent is an unequivocal criterion for assigning ring or chain tautomeric structures to compounds of this type.

(5) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

(6) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, **10**, 55 (1945).

(7) The infrared spectra were determined with a Perkin-Elmer Model 21 recording double-beam spectrophotometer with sodium chloride optics. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds,* John Wiley and Sons, Inc., New York, 1957.

varied in several runs from 0.5 hr. at room temperature to 1.5 hr. at reflux, and products were isolated as described above. The yield of 8-acetyl-1-naphthoic acid ranged from 0–13%, that of 3,3-dimethylnaphthalide from 2–14%. Anhydride was recovered to the extent of 50–68%. When benzene was added to the reaction mixture before the reflux period of 1.5 hr., the yield of keto acid was 36%; and only a trace of lactone could be isolated.

Action of methylcadmium reagent on 8-acetyl-1-naphthoic acid. To the cadmium reagent, prepared from 0.47 g. (0.02 mole) of magnesium, 3.0 g. (0.021 mole) of methyl iodide, 4.1 g. (0.023 mole) of cadmium chloride, and 80 ml. of ether, was added, with stirring, 1.2 g. (0.006 mole) of 8-acetyl-1-naphthoic acid during 30 min. When the mixture had been heated under reflux for 1.5 hr. and was worked up as described above, 1.05 g. (88%) of the keto acid was recovered. Only a trace of 3,3-dimethylnaphthalide, m.p. 108–110°, was obtained by concentration of the ether layer.

3-Acetoxyphthalide. Phthalaldehydic acid was converted to the acetyl derivative in 63% yield by the method previously described[2] for *o*-acetylbenzoic acid. The lactol acetate was recrystallized from *n*-hexane, m.p. 64–67°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.69; H, 4.36.

The infrared spectrum (Nujol) contains strong carbonyl bands at 1777 and 1760 cm.$^{-1}$ but none attributable to a hydroxyl group.

The displacement by methylcadmium reagent of 3-substituted phthalides. The following description for phthalaldehydic acid is typical of the reaction conditions for the displacement of various 3-substituted phthalides, including 3-methoxy-,[9] 3-ethoxy-,[10] 3-bromo-,[11] 3-acetoxy-,[10] 3-methyl-3-acetoxyphthalide,[2] and di-3-phthalidyl ether.[12] The reaction time was held constant throughout; and the cadmium reagent, always in excess, was that prepared from approximately equimolar amounts of magnesium and cadmium chloride. All samples of 3-methylphthalide exhibited identical infrared spectra (film, strong carbonyl band at 1760 cm.$^{-1}$); and the 3,3-dimethylphthalide was compared by mixture melting point and infrared spectrum with an authentic sample.[2] The results are tabulated below.

The methylcadmium reagent, prepared from 2.2 g. (0.09 mole) of magnesium, 15.0 g. (0.12 mole) of methyl iodide, 19.6 g. (0.12 mole) of cadmium chloride, and 150 ml. of ether, was cooled in an ice bath; 7.5 g. (0.05 mole) of phthalaldehydic acid was added with stirring, in 30 min. The mixture was heated under reflux for 1.5 hr., cooled, and decomposed with dilute sulfuric acid. The ether layer was separated and combined with ether washings of the water layer. This organic phase was washed with four 60-ml. portions of 10% potassium carbonate. From the ether layer, which was dried and distilled, was obtained 2.4 g. (32%) of 3-methylphthalide, b.p. (aspirator) 170–175°. When the product was heated at atmospheric pressure to its reported boiling point,[13] it decomposed.

Anal. Calcd. for $C_9H_8O_2$: C,72.96; H,5.44. Found: C, 72.73; H, 5.57.

SUMMARY OF RESULTS

Phthalide	Product	Yield, %
3-Hydroxy-(IV; R = H, X = OH)	VI (R = H)	31[a]
3-Methoxy-(IV; R = H, X = OCH_3)	VI (R = H)	9
3-Ethoxy-(IV; R = H, X = OC_2H_5)	VI (R = H)	9
3-Bromo-(IV; R = H, X = Br)	VI (R = H)	90
3-Acetoxy-(IV; R = H, X = $OCOCH_3$)	—	—[b]
3-Acetoxy-3-methyl-(IV; R = CH_3, H = $OCOCH_3$)	VI (R = CH_3)	44
Di-3-phthalidyl ether-(V)	VI (R = H)	100[c]

[a] Starting material recovered, 46%. [b] Starting material recovered, 59%. [c] Based on formation of two moles of lactone from one mole of ether.

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(13) G. Giebe, *Ber.*, **29**, 2533 (1896).