The white solids (2.4 g., 33%) were recrystallized from aqueous ethanol to yield crystals which melted at 167–167.5°.

Anal. Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01. Found: C, 79.79; H, 7.15.

Tschugaeff-Zerewitinoff determination: 0.12 mole of active hydrogen and 0.85 carbonyl group per molecule.

Acylation of toluene with 1-n-butyl-2,5-dimethyl-3-benzoyl-4-carbonyl chloride. Because this acid chloride could not be purified without extensive decomposition, the crude product from the reaction of 1.40 g. of keto acid and thionyl chloride was dissolved in dry toluene and added dropwise to a mixture of 1.5 g. of aluminum chloride and 50 ml. of toluene in the conventional equipment. From this reaction there was isolated by the procedures previously described 0.40 g. (29%) of cyclic diketone IIIa, m.p. and mixed m.p. with IIIa from the acylation of benzene with I, 129–130°.

Preparation of 1-n-butyl-2,5-dimethylpyrrole. Acetonylacetone (57 g., 0.5 mole) and 36 g. (0.5 mole) of *n*-butylamine were placed in a flask fitted with a reflux condenser. The exothermic reaction began immediately. The mixture stood overnight and was then distilled. The product boiled at 98–100° (20 mm.), yield 64 g. (85%), n_D^{20} 1.4828.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 79.08; H, 11.27.

COLUMBIA, MO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

A Study of the Entrainment Method for Making Grignard Reagents

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Modifications of the entrainment method used in this work were: (1) introduction of all of the "inert" halide at the start of the reaction, (2) use of ethylene bromide rather than ethyl bromide as the entrainment reagent, (3) a slow rate of addition (*ca.* 12 hr.) of the entrainment reagent. In this manner, α-chloronaphthalene was converted to α-naphthoic acid in 56% yield and to naphthalene in 66% yield, *p*-bromodimethylaniline to *p*-dimethylaminobenzoic acid in 48% yield and to dimethylaniline in 71% yield, hexachlorobenzene to pentachlorobenzoic acid in 71% yield and pentachloroacetophenone in 31% yield, and *p*-bromoacetophenone azine to *p*-carboxyacetophenone in 34% yield and to phenyl-*p*-acetophenylcarbinol in 9% yield. The yields for the specific compounds are superior to any obtained heretofore by means of the entrainment method and demonstrate the utility of ethylene bromide as an entrainment agent.

A number of "inert" halogen compounds, such, for example, as α-chloronaphthalene, fail to give Grignard reagents under ordinary conditions. Four methods are available for application under these circumstances: the lithium, the reactive solvent, the activated metal, and the entrainment methods. The lithium method[1–3] has been applied occasionally for conversion of "inert" halides to organic lithium compounds, but its main use, stemming from the high reactivity of organic lithium compounds, has been to accomplish additions in a more effective way than with Grignard reagents. In one of the few papers devoted to a comparison of conversion of "inert" halides,[4] Gilman and coworkers state that chlorobenzene, *p*-chlorotoluene, α-chloronaphthalene, and *p*-bromodimethylaniline give better yields of organolithium compounds than of Grignard reagents but that the reverse is true for conversion of dihalides to organometallic compounds. An example of the former conversion is the preparation of *p*-dimethylaminobenzoic acid in 41–56% yields from the *p*-dimethylaminophenyllithium.[5] Braude and Evans have been successful recently in preparing vinyllithium compounds.[6] Examples of conversion of "inert" halides to organolithium compounds are not numerous, however. Perhaps additional factors contributing to this neglect are the possibilities of the organolithium compound being insoluble or of the lithium halide coating the surface of the lithium.

The second method of application, the reactive solvent method, is comparatively recent. Indeed, the most promising results of this method have been published after the work in this laboratory on the entrainment method had been well advanced. The reactive solvent is one which complexes with the Grignard reagent more effectively and in this manner brings about reaction or completion of reaction between magnesium and "inert" halides. Tetrahydrofuran seems to be the solvent of choice although other cyclic ethers are also effective.[7–9] The method is particularly well adapted to synthesis of vinyl Grignard reagents. We must keep in mind, however, that tetrahydro-

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(2) F. Runge, *Organometallverbindungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1944.

(3) R. G. Jones and H. Gilman, *Organic Reactions*, John Wiley & Sons, New York, N. Y. (1951), Vol. 6, 339. Halogen-Metal Interconversions.

(4) H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **55**, 1252 (1933).

(5) H. Gilman and I. Banner, *J. Am. Chem. Soc.*, **62**, 344 (1940).

(6) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3324 (1955).

(7) H. Normant, *Compt. rend.*, **240**, 1111 (1955) and preceding papers; *Bull. soc. chim. France*, 1444 (1957).

(8) H. E. Ramsden *et al.*, *J. Org. Chem.*, **22**, 1202 (1957); 1602 (1957).

(9) C. S. Marvel and R. G. Woolford, *J. Org. Chem.*, **23**, 1658 (1958).

furan is a more powerful coordinating solvent than diethyl ether. In the addition of the Grignard reagent complexed with tetrahydrofuran to slowly reacting carbonyl compounds, lower yields or even side reactions may take place.[10,11] With this single reservation of possible retardation of addition of the Grignard reagent, the reactive solvent method is an extremely attractive synthetic route.

The third method, the activated metal method, consists of activation of the magnesium by chemical reaction or by reduction of the size of the metal particles.[12a] Gilman catalyst,[13] a combination of magnesium and iodine, is a well known example of the chemical activator type. A recent example of the use of ground magnesium is the preparation of durylmagnesium bromide, from which a 70% crude yield of adduct was obtained.[14] The latter method has not been tested sufficiently to assess its general use.

In the light of the availability of the above three methods of conversion of "inert" halides to organometallic compounds, we had cause to wonder if the fourth method, the entrainment method, is passé. The yields of products have never been consistently good: of the 29 reactions listed (with yields) by Kharasch and Reinmuth,[12b] the average yield is 38%, and the yields are above 60% in only five instances. Nevertheless, we felt that the entrainment method had never been utilized under the most favorable conditions based on knowledge of the reaction and for this reason deserved further study.

The following important modifications were made for reasons to be described with each. First, all of the "inert" halide was added at the beginning of the reaction, not, as is usual, with the entrainer. In this manner, the activated magnesium surface was exposed to the highest concentration possible of the "inert" halide. Second, and more important, ethylene bromide was used as the entrainment reagent rather than ethyl bromide. With ethylene bromide and magnesium only ethylene and magnesium bromide are formed as products. Thus, only the Grignard reagent of the "inert" halide is present, mixed or complexed with magnesium bromide. With ethyl bromide and magnesium, two Grignard reagents are present, an obvious disadvantage if the carbonyl compound to be added to the Grignard reagent is valuable. We believe we were the first to use ethylene bromide as an entrainment reagent,[15] although anhydrous magnesium bromide has been prepared by reaction of ethylene bromide and magnesium covered with ether.[12c,16,17] Third, the entrainment agent was added over a long period of time (8 hr. or more). The agent acts in the main part as a cleanser and activator of the magnesium surface.[18] A fast rate of addition of entrainer will etch merely the already active surface; a slow rate will permit the "inert" halide to react with these active surfaces without wasting the entrainer by reaction on the same active surfaces. If consumption of entrainer and magnesium are not important, a fast rate of addition of entrainer can also be used with excesses (several equivalents) of each. We found the latter method to be expedient in the preparation of the Grignard reagents of bromoketazines to be described. Since the efficacy of the entrainment reagent was brought about by a mechanical action, in part at least, the amount of entrainer need not be related in any molecular way to the amount of "inert" halide. It is stated, however, that at least one equivalent of entrainer is ordinarily necessary for greatest yield.[12b]

Our first efforts were to study the efficacy of the second and third modifications using α-naphthyl chloride as the "inert" halide. Previous experiments with the Grignard reagent of this halide, made using ethyl bromide as the entrainer, gave a 16% yield of α-naphthoic acid by reaction with carbon dioxide and a 46% yield of naphthalene by reaction with water.[12b] The effect of time of addition of ethylene bromide is shown in Table I.

TABLE I

$\alpha\text{-}C_{10}H_7Cl + Mg \rightarrow \alpha\text{-}C_{10}H_7MgCl \rightarrow \alpha\text{-}C_{10}H_7COOH$

Time of addition of ethylene bromide in hours	2	7	12	26
% Yield as α-naphthoic acid (crude)	0	42	56[a]	58

[a] When isolated as naphthalene, the yield was 66%.

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(10) R. N. Lewis and J. R. Wright, *J. Am. Chem. Soc.*, **74**, 1253 (1952). Ethylmagnesium bromide did not add to benzophenone in presence of tetrahydrofuran.

(11) L. Field, J. R. Holsten, and R. D. Clark, *J. Am. Chem. Soc.*, in press. Methylsulfonylmethylmagnesium bromide and benzaldehyde in tetrahydrofuran gave half the yield of the normal adduct from the same reactants in diethyl ether and benzene.

(12) (a) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York (1954), p. 6, (b) p. 38, (c) p. 33.

(13) H. Gilman and R. H. Kirby, *Rec. trav. chim.*, **54**, 577 (1935).

(14) R. C. Fuson, W. C. Hammann, and P. R. Jones, *J. Am. Chem. Soc.*, **79**, 928 (1957).

(15) J. D. Beckler, "Grignard Reagents of *m*- and *p*-Bromoacetophenone Azines," Master's thesis, Vanderbilt University, 1955. A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Bull. Acad. Sciences, U.S.S.R.*, Div. of Chem. Science, 1389 (1957) have used "a few drops" of ethylene bromide in the preparation of the Grignard reagent of α-iodoselenophene.

(16) M. Tissier and V. Grignard, *Compt. rend.*, **132**, 835 (1901).

(17) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **76**, 4402 (1954).

(18) Part of the facilitation may also be in forming a complex of the Grignard reagent of the entrainer with that of the "inert" halide. In the case of ethylene bromide, a complex of magnesium bromide and the Grignard reagent of the "inert" halide would be formed.

From these results, a time of addition of about 12 hr. was selected for all other experiments. Comparison of ethyl bromide and ethylene bromide as entrainment reagents was next made with the results shown in Table II.

TABLE II

Entrainment Reagent	% Yield as α-Naphthoic Acid	% Yield as Naphthalene
Ethylene bromide	56	66
Ethyl bromide	56	77

From our results, the two entrainment reagents seemed comparable, and all other experiments were conducted using ethylene bromide as the entrainment agent. To demonstrate that ethylene bromide has an advantage in not forming any Grignard reagent, we synthesized α-naphthyl phenyl ketone in 49% yield using benzonitrile as the limiting reagent. With ethylmagnesium bromide, a major proportion, if not all, of the benzonitrile would have been lost as propiophenone.

Other "inert" halides besides α-naphthyl chloride were tested also. The first, hexachlorobenzene, was selected because of its alleged unreactivity. In view of a recent paper,[19] however, this compound probably is of moderate activity since it has been shown to react with amines under relatively mild conditions. Part of its alleged unreactivity is caused no doubt by its insolubility. The results of our conversion of this compound to the Grignard reagent and subsequently to the acid and to pentachloroacetophenone are shown in Table III. A large scale run also gave a 60% yield of pentachlorobenzoic acid.

TABLE III

PREPARATION OF COMPOUNDS USING ETHYLENE BROMIDE AS ENTRAINER

Mono-Grignard of	Reagent	Product	Yield, %
Hexachlorobenzene	CO_2	C_6Cl_5COOH	71
	$(CH_3CO)_2O$	$C_6Cl_5COCH_3$	31
p-Bromodimethylaniline	CO_2	$(CH_3)_2NC_6H_4COOH$	48
	H_2O	$C_6H_5N(CH_3)_2$	71

It is interesting to note that Ramsden and coworkers[8] were unable to obtain pentachlorobenzoic acid although pentachlorophenylmagnesium chloride was shown to be present in 77% yield by titration. Thus, we have one example at least in which the entrainment method is superior to the reactive solvent method. In another example, o-bromophenylmagnesium bromide in ether gave a 30% yield of acid on carbonation while the same reagent in tetrahydrofuran gave no acid.[20] Other examples should be found if we can judge from the influence of the environment. In the environment for the entrainment method, magnesium bromide, a Lewis acid, is present which should activate carbonyl compounds in their addition to Grignard reagents.[21–23] In the environment for the reactive solvent method, the strongly complexing solvent should deactivate the Grignard reagent in addition reactions as it appears to do here. However, we must admit that we were unable to see any good or bad influence of magnesium bromide in affecting the yields of acetophenone from phenylmagnesium bromide and acetonitrile[24] and for this reason are not wholly convinced of the generality of magnesium bromide activation. Another "inert" halide, p-bromodimethylaniline, was studied not because it was inert but because it tended to form an impervious coating on the magnesium surface. Compounds containing ether, hydroxyl, amino, sulfone, and other groups seem to have this tendency perhaps because of their ability to form associated polymeric Grignard reagents.[25,12b] The entrainment method in this case worked well as noted in Table III, and, as noted in the Experimental section, the time of addition of the entrainer was less critical.

In our last examples of the use of the entrainment method, we chose two halides which had never been converted to Grignard reagents. They were the m- and p-bromoacetophenone azines. The azine group was selected as a protective grouping because of its resistance to addition reactions compared to the carbonyl group through resonance stabilization: $\rangle C{=}N{-}N{=}C\langle \longleftrightarrow \rangle \overset{+}{C}{-}N{=}N{-}\overset{-}{C}\langle$ and because of considerable reduction of active methylene reactivity through loss of enolization ability.[26] If the haloketazines could be converted to Grignard reagents, derivatives of the ketones would be accessible by a new route. Slow addition of ethylene bromide as an entrainment reagent was not successful, but rapid addition of several equivalents of ethylene bromide was successful in making this Grignard reagent of unusual structure:

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(19) A. L. Rocklin, *J. Org. Chem.*, **21**, 1478 (1956).

(20) H. Heaney, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 4692 (1956).

(21) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).

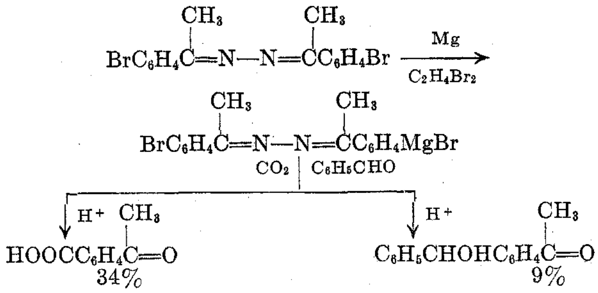
(22) V. Franzen and H. Krauch, *Chem. Ztg.*, **79**, 137 (1955).

(23) E. T. McBee, O. R. Pierce, and D. D. Meyer, *J. Am. Chem. Soc.*, **77**, 83 (1955) demonstrate that complexes between magnesium bromide and carbonyl compounds exist in the ratio 2 to 1.

(24) D. Cowan, "A Study of the Entrainment Method for Preparing Grignard Reagents," Ph.D. thesis, Vanderbilt University, 1959.

(25) L. Field, *J. Am. Chem. Soc.*, **78**, 92 (1956).

(26) E. C. Kooyman, *Rec. trav. chim.*, **74**, 117 (1955).



Although titration indicated that 83% of the two bromine atoms in the azine had been converted to Grignard groups, yields were never more than 50%, indicating that only one bromine atom was converted. For this reason the Grignard reagent of the bromoketazine did not seem attractive as an intermediate for synthesis. To avoid the synthesis of a di-Grignard reagent, as is necessary with bromoketazines, the unsymmetrical dimethylhydrazone of *m*-bromoacetophenone was converted to a Grignard reagent. This reagent however gave only traces of *m*-carboxyacetophenone and considerable amounts of a reduction product, acetophenone. Hydrazone and ketazine Grignard reagents appear to be much less useful intermediates than those for example from ethylene glycol ketals.[27]

Although the experiments with the bromoketazine were not practical (but nevertheless curious) from a preparative viewpoint, we believe that the results of the modifications introduced in this paper are promising enough to consider the entrainment method complementary and even comparable to the other three methods for conversion of "inert" halides to organometallic compounds. The presence of the magnesium bromide may confer upon the organometallic compound certain characteristic properties differing from that of the ordinary preparation in ether or tetrahydrofuran. And, above all, the use of ethylene bromide, rather than ethyl bromide, as an entrainment agent makes it possible to prepare the Grignard reagent of an "inert" halide free of a second, extraneous Grignard reagent.

EXPERIMENTAL

All melting points are corrected and boiling points uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn.

General procedure. The typical Grignard apparatus was used with condenser, stirrer and, in addition, a Hershberg dropping funnel[28] to permit the addition of the ethereal ethylene bromide over a long period of time. The assembled apparatus, together with the magnesium turnings (2.84 g., 0.116 mole), was dried by flaming the glass while dry air was drawn through. The α-chloronaphthalene (b.p. 85° at 1 mm., n_D^{25} 1.6305, 8.1 g., 0.05 mole), dissolved in 50 ml. of dry ether, was added to the flask. Gentle refluxing was maintained for the remainder of the reaction by means of a Glas-col heater. Ethylene bromide (9.3 g., 0.05 mole) in 50 ml. of dry ether was added dropwise from the Hershberg funnel over a period of 12 hr., about a drop every 15 sec. A white powdery solid formed during the initial stages but near the completion of the addition, as magnesium bromide concentration increased, the solid redissolved. At the end of the addition, two layers were noticeable, an ethereal layer on top and a sirupy brown layer on the bottom. Both layers were poured with vigorous stirring onto crushed Dry Ice.[29] A brittle, chalky mass was formed which was dissolved and dispersed by the *cautious* addition of 10% aqueous hydrochloric acid. The acidified reaction mixture was extracted with three 50-ml. portions of ether. The combined ether layers were washed with water and then extracted several times with 5% aqueous sodium bicarbonate solution. On acidification of the combined bicarbonate extracts, α-naphthoic acid precipitated as a greyish powder, m.p. 153–159°, 4.8 g., 56%; recrystallized from toluene: m.p. 160–162°, 3.0 g., 35%. The ether layer from which the acid had been removed contained 3.3 g. of a mixture of naphthalene and chloronaphthalene.

Results on variation of general procedure. Titration of the Grignard solution with acid indicated that 76% of α-chloronaphthalene was present as the Grignard reagent. No basic substance was formed from ethylene bromide and magnesium without α-chloronaphthalene present.

A 66% yield of naphthalene was obtained when the Grignard reagent was poured into cracked ice and acid rather than Dry Ice. The naphthalene was separated from all except traces of α-chloronaphthalene by sublimation at 1-mm. pressure in a short-path distillation apparatus.

The rate of addition of ethylene bromide was varied with the results shown in Table I.

The effect of excess anhydrous magnesium bromide was tested. About 0.05 mole of ethylene bromide was added to 0.164 mole of magnesium covered with ether. After magnesium bromide had formed from this addition, α-chloronaphthalene (0.05 mole) was introduced and another 0.05 mole of ethylene bromide added dropwise in the manner of the general procedure. No white precipitate formed in this experiment. The yield of crude α-naphthoic acid was 56%, m.p. 148–153° and of recrystallized acid 36%, m.p. 161–162°. The results showed no significant effect.

Two experiments using ethyl bromide rather than ethylene bromide as the entrainer were run and the results shown in Table II.

Demonstration that compound, to be added to Grignard using ethylene bromide as entrainer, may be taken as limiting reagent. α-Naphthylmagnesium chloride (0.1 mole) was prepared as in the general procedure. Benzonitrile (10.3 g., 0.1 mole) in ether was added rapidly to the Grignard solution, and the mixture allowed to stir for several hours. It was then poured on to a slurry of ice and 10% aqueous hydrochloric acid with stirring. The acid mixture was heated under reflux for several hours to insure hydrolysis of the resultant ketimine. The crude ketone was extracted with ether, and the ether extract washed with water and aqueous sodium bicarbonate and dried with anhydrous sodium sulfate. Evaporation of the ether yielded α-naphthyl phenyl ketone as a greyish solid which when recrystallized from alcohol gave slightly tan prisms, 11.4 g., 49%, m.p. 73.5–74.5°, reported m.p. 75.5–76°. A greater yield of ketone probably would have been obtained if an excess of Grignard reagent had been used.

The Grignard reagent of p-bromo-N,N-dimethylaniline. The

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[27] H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 334 (1958).

[28] L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath, Boston (1955), 3rd Ed., p. 265.

[29] In a later experiment with the Grignard reagent of hexachlorobenzene, carbon dioxide, dried by passage through calcium chloride granules, was introduced as a gas and gave better yields of acid than the method described above.

general procedure was followed, using for each run 0.05 mole of the *p*-bromodimethylaniline, m.p. 54–55°. In place of adding the aniline to magnesium and ether in the flask, however, it was added to the dropping funnel mixed with ethylene bromide and ether in the proportions previously stated. Also, in place of adding the two-layered Grignard reagent mixture to crushed Dry Ice, dry carbon dioxide was passed over the surface until the black-green color of the mixture had been discharged and the contents had solidified. Dry ether was added during this process to replace that swept out by carbon dioxide. The salt was decomposed with saturated ammonium chloride solution, and the acid finally precipitated by addition of acetic acid. The yields of *p*-dimethylaminobenzoic acid (yellowish tan needles from alcohol, m.p. 236–239°; reported[5] m.p. 240–241°), as dependent on time of addition of the entrainer, ethylene bromide, were: 2.5 hr., 48%; 2.5 hr., 42%; 5 hr., 36%. In another run, the reagent was recovered as dimethylaniline, b.p. 46–49° at 5 mm., n_D^{25} 1.5582, 71%.

Pentachlorobenzoic acid and pentachloroacetophenone from pentachlorophenylmagnesium chloride. A small scale run of pentachlorobenzoic acid was made with the results recorded in Table III. A large scale run was also made with some modification of the general procedure. Magnesium turnings (39 g., 1.6 moles) and hexachlorobenzene (142.4 g., 0.5 mole, m.p. 228–229°) in 1 l. of dry ether was brought to gentle reflux in a 3-l., three-necked flask heated by a Glas-col mantle at 20 v. Ethylene bromide (188 g., 1.0 mole) in 200 ml. of dry benzene was added through the Hershberg funnel over a period of 48 hr. (about one drop per 25 sec.). Little attention was needed provided the capillary tube of the Hershberg apparatus was properly fitted. The capillary tube was 4.5 in. long into which a B and S 24 platinum wire was inserted to fit very snugly. Efficient stirring was maintained throughout addition during which time the reaction mixture turned dark brown and formed a precipitate. The reaction mixture was allowed to cool to room temperature, and carbon dioxide, generated from Dry Ice and dried by passage through anhydrous calcium chloride, was added under the surface for at least 3 hr. and at such a rate as to minimize clogging of the entrance tube. After this addition, 10% aqueous hydrochloric acid was added slowly until the mixture was strongly acid. The ether and benzene was removed by distillation, and the crude pentachlorobenzoic acid left in the water was removed by filtration and washed free of salts with water. After solution in hot dilute ammonia water solution, filtration, and precipitation with mineral acid, 113 g., 77%, of brown-colored pentachlorobenzoic acid was obtained. Some ammonium salt was entrained with this acid if the precipitate were not digested well with hot dilute mineral acid. The color was removed by conversion of the acid to the rather insoluble sodium salt. The sodium salt was recrystallized from ethanol, m.p. 339–340°. By precipitation of the acid from a hot aqueous solution of the sodium salt, the acid was reobtained as a white powder, m.p. 202–206°, 60% over-all yield, reported[30] m.p. within the range 200 to 208°. About 8.6 g. of the acid in the form of lustrous plates, m.p. 207–211°, was obtained by recrystallization of 10 g. from 80 ml. of 50% aqueous methanol.

Pentachloroacetophenone was made also from pentachloromagnesium chloride by the method of Newman and Smith.[31] It was necessary to purify the ketone by solution in concentrated sulfuric acid and filtration through a sintered-glass funnel. The ketone in the filtrate was precipitated by dilution with water, filtered, and washed thoroughly with water. After drying, the pentachloroacetophenone was sublimed at 0.1 mm. to give colorless crystals, m.p. 89–90°, 4.5 g., 31%, reported[32] m.p. 90–92°.

Grignard reagent of p-bromoacetophenone azine. To a stirred suspension of 4.93 g., 0.0125 mole of *p*-bromoacetophenone azine (m.p. 164.5–165.5°), 1.82 g., 0.075 mole of magnesium, and 25 ml. of dry ether, a solution of 9.4 g., 0.05 mole of ethylene bromide in 25 ml. of dry ether was added dropwise over a period of 80 min. The mixture separated into a top yellow layer and a bottom reddish brown layer. Titration of aliquots indicated that 90% of the Grignard reagent was in the bottom layer. After heating the mixture an additional 3 hr. under gentle reflux, it was cooled and poured into crushed Dry Ice. The mixture was allowed to warm to room temperature and hydrolyzed after removal of the ether by stirring the residue with 150 ml. of 2*N* hydrochloric acid maintained at 75° for 30 min. The hydrolysate was cooled and extracted with 200 ml. of ether in 3 portions. The combined ether extracts were washed with 200 ml. of 5% aqueous sodium hydroxide in three portions. Acidification of the combined alkaline extracts and cooling, gave a light tan product which was removed by filtration. The tan product was recrystallized from 200 ml. of water, with a hot filtration, to yield *p*-acetobenzoic acid, 1.4 g., 34%, m.p. 206–209°. A second recrystallization from water with Norite treatment yielded white needles, m.p. 207.5–209.5°, reported[33] m.p. 208.6–209.4°; neutral equivalent 163.5, calculated 164.2.

Ethyl bromide as an entrainment reagent in place of ethylene bromide gave a 40% yield of *p*-acetobenzoic acid. In another experiment, tetrahydrofuran was used in place of ether as the solvent. Although the tetrahydrofuran was an excellent solvent for the Grignard reagent (one layer containing 83% Grignard reagent by titration), the yield of *p*-acetobenzoic acid was only 1.7%.

Phenyl-*p*-acetophenylcarbinol, m.p. 110–111.5°, needles from petroleum ether, was made in 9% yield from the addition of benzaldehyde to the Grignard reagent of *p*-bromoacetophenone azine.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.63; H, 6.24. Found: C, 79.48; H, 5.38.

The structure was confirmed by oxidation to *p*-benzoylacetophenone in 94% yield, m.p. 83–84°, reported[34] m.p. the same. The low yield in the preparation of the alcohol was attributed to the instability of a benzhydrol structure to acid hydrolysis, a step necessary to convert the azine to the ketone.

Attempts to add benzonitrile to the Grignard reagent of *p*-bromoacetophenone azine yielded only intractable, brown gums.

Grignard reagent of m-bromoacetophenone azine. The *m*-bromoketazine (m.p. 102–103°) was converted to the Grignard reagent in the same manner as the *p*-bromoketazine. The preparation differed only in that the mixture did not separate into two phases. After carbonation of the mixture in the usual manner, *m*-acetobenzoic acid, m.p. 170–173°, white needles, reported[32] m.p. 172°, was obtained in only 8% yield. The low yield was caused in part by the difficulty of purification. It was recrystallized from methylcyclohexane after recrystallization from water failed.

The Grignard reagent of *m*-chloroacetophenone azine, m.p. 86–87°, could not be made by the procedures of this paper.

Grignard reagent of the unsymmetrical dimethylhydrazone of m-bromoacetophenone. The hydrazone was made by the method of Smith and Most[35] except that azeotropic distil-

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(35) P. A. S. Smith and E. E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).

lation with toluene was used to remove the water, b.p. 105–107° at 2 mm., n_D^{25} 1.5806. The Grignard reagent was made by the general procedure and carbonated by passing dry carbon dioxide over the surface. Extraction of the ether layer with aqueous sodium hydroxide, followed by acidification of the alkaline layer gave *m*-carboxyacetophenone, m.p. 161–162°, 0.002 mole, 4%. The ether layer yielded crude acetophenone, b.p. 50° at 2 mm., 26%, n_D^{25} 1.5325, reported n_D^{25} 1.5310. A duplicate run gave 40% acetophenone of approximately the same quality.

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[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Synthesis of Some Monofluoro-1,2-benzanthracenes[1]

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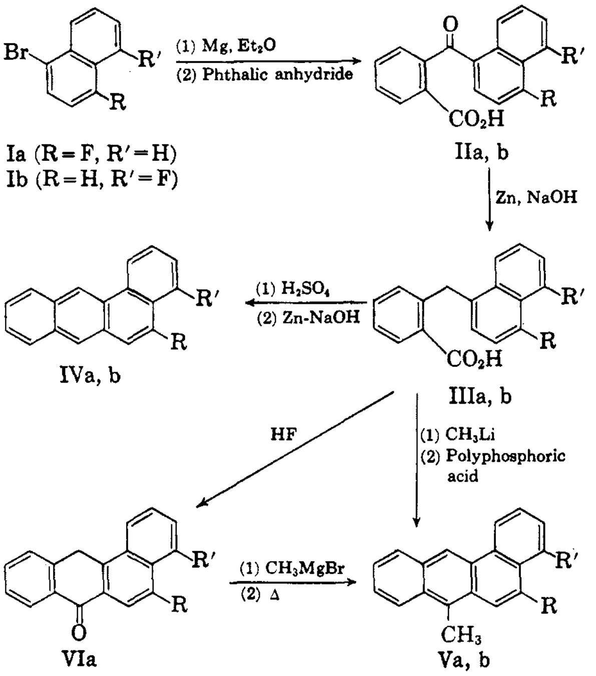
The syntheses of 3- and 4′-fluoro-1,2-benzanthracenes and of 3-fluoro- and 4′-fluoro-10-methyl-1,2-benzanthracenes are described.

Substitution of the rings in a number of aromatic carcinogens can profoundly alter their carcinogenic activity. Of the various groups available,[2] the fluoro group has several advantages, *viz*, the small size of the fluorine atom, its strong bond with carbon, and its resistance to metabolism *in situ* as contrasted with other groups. Miller, Miller, and Finger[3,4] have shown that most of the fluoro derivatives of the rat liver carcinogen 4-dimethylaminoazobenzene are as active as, or more active than, the parent dye and have further proposed that tests of the biological activity of various fluoro derivatives of biologically active molecules could be used to indicate the positions directly involved in the activity in question. If a fluoro derivative is inactive, then the position blocked may be involved in the biological activity of the nonfluorinated parent concerned. If the fluoro derivative is active, the substituted position is probably unimportant in the biological activity under study. With a view of extending this concept to a study of the carcinogenic polycyclic aromatic hydrocarbons, we have undertaken the synthesis of the various monofluoro derivatives of the carcinogens, 10-methyl-1,2-benzanthracene and 9,10-dimethyl-1,2-benzanthracene. The syntheses of the 3-fluoro- and 4′-fluoro-10-methyl-1,2-benzanthracenes as well as the corresponding parent fluoro-1,2-benzanthracenes have been carried out by the sequence of reactions outlined below:



The syntheses involved the use of 1-bromo-4-fluoronaphthalene (Ia) and 1-bromo-5-fluoronaphthalene (Ib) as starting materials. The former was obtained by standard methods involving the bromination of 1-formamidonaphthalene followed by replacement of the amino group, obtained by hydrolysis, with fluorine.[5] Ib was obtained from 1-nitronaphthalene by bromination, reduction with

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(1) This work was supported by a grant from the National Institutes of Health.

(2) J. L. Hartwell, "Survey of Compounds Which Have Been Tested for Carcinogenic Activity," 2nd ed., 1951, U. S. Public Health Service Publication No. 149, Washington, D. C.

(3) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Research*, **13**, 93 (1953).

(4) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Research*, **17**, 387 (1957).

(5) A. Roe, *Org. Reactions*, V, 193 (1949).