TABLE II

Carbon-14 Assays

Compound	Activity in C./M. Mole
t-Butyl *p*-nitrobenzoate (from *t*-butyl alcohol)	0.283; 0.280
Pivalanilide (from *t*-butyl-magnesium chloride)	0.266; 0.263
2,4-Dinitrophenylsulfenyl chloride adduct of isobutylene	0.277[a]; 0.277[a]; 0.271[b]
Phenyl-*t*-butylcarbinol[c]	0.000; 0.000

[a] Isobutylene collected during addition of *t*-butylmagnesium chloride to pivalophenone. [b] Isobutylene collected in Dry Ice trap after Grignard complex was destroyed with water. [c] This compound is a solid, m.p. 44–45°.

pivalophenone and *t*-butylmagnesium chloride was repeated many times without significant variation on the amount of isobutylene evolved. Even when the reaction was run in butyl ether, only 10% of the isobutylene was evolved during the addition and reflux period.

In reviewing the reactions of these ketones with various Grignard reagents[4b] certain generalizations are evident: (1) isopropylmagnesium bromide has the greatest tendency to promote enolization; (2) ethylmagnesium bromide gives the greatest amount of addition; (3) *t*-butylmagnesium chloride gives the largest amount of reduction. These results are consistent with previous reports on the reaction of ketones with Grignard reagents.[9]

EXPERIMENTAL[10]

Reaction of t-butylmagnesium chloride and ketones. The same molar quantities and same procedure as previously reported[4b] were used in studying the reaction of each ketone with *t*-butylmagnesium chloride. Each reaction product was fractionally distilled and the fractions corresponding to secondary and tertiary alcohols were isolated and analyzed as shown in Table I. When *t*-butylmagnesium chloride was added to pivalophenone and to *p*-methylpivalophenone, only a small amount of gas was evolved. However, when after heating, refluxing, and carefully decomposing the magnesium complexes with water,[4b] the ether was removed prior to fractional distillation, almost the entire theoretical amount of isobutylene was collected.

Experiments using C^{14}. 1-C^{14} acetone (activity 0.285μ c./m. mole) was converted in 83% yield into C^{14}-*t*-butyl alcohol. The *p*-nitrobenzoate ester, m.p. 114–114.5°, reported,[11] showed an activity of 0.282μ c./m. mole. C^{14}-*t*-Butyl alcohol was converted in 85% yield into C^{14}-*t*-butyl chloride.[12] A small sample of the Grignard reagent made from this chloride was treated with phenylisocyanate[13] to produce C^{14} pivalanilide, m.p. 129–129.5°,[14] with an activity of 0.2666μ c./m. mole. Pivalophenone was added to the bulk of the C^{14}-*t*-butylmagnesium chloride as previously described.[4b] The isobutylene gas evolved during the addition of the ketone was collected in a Dry Ice trap and a portion converted to the solid 2,4-dinitrosulfenyl chloride adduct m.p. 86–87°.[15] This showed an activity of 0.277μ c./m. mole. A 2,4 dinitrosulfenyl chloride adduct of the isobutylene gas collected after decomposition of the magnesium complex showed an activity of 0.271μ c./m. mole. The secondary alcohol, phenyl-*t*-butylcarbinol was subsequently isolated by distillation of the reaction products. There was no forerun or residue in the distillation. The first and each subsequent fraction collected crystallized on standing. The m.p. of each fraction was 44–45°. The secondary alcohol showed no C^{14} activity.

Emory University
Atlanta 22, Ga.

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[9] M. S. Kharasch and Otto Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, N. Y., 1954, pp. 138–76.

[10] All boiling points and melting points are uncorrected. The C^{14} used in this work was obtained as 1-C^{14}-acetone from the Oak Ridge National Laboratory as part of Subcontract 647 under W-7405 eng-26.

[11] S. M. McElvain, *The Characterization of Organic Compounds*, The Macmillan Co., New York, N. Y., 1953, p. 201.

[12] Robertson, G. R., *Laboratory Practice of Organic Chemistry*, 3rd ed. The Macmillan Co., New York, N. Y., 1954, p. 194.

[13] Ref. 10, p. 243.

[14] I. M. Heilbron, *Dictionary of Organic Compounds*, Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 224.

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Methyl Hydrogen Fumarate

Sydney M. Spatz and Herman Stone

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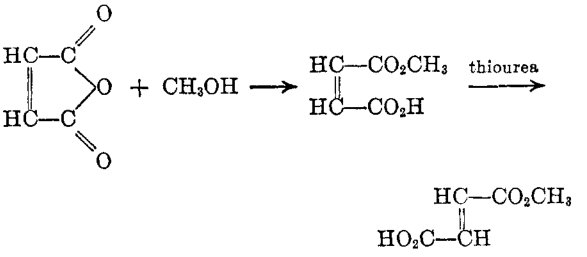
The preparation of a half-ester from a dibasic anhydride, such as maleic or phthalic is, as a rule, effected very simply by the controlled, mild heating of a stoichiometric mixture of the anhydride and the alcohol. On the other hand, the half-esterification of a dibasic acid (as fumaric, adipic, terephthalic) is, in theory and practice, complicated by the formation of an equilibrium consisting of the free acid, the half-ester, and the diester.

In connection with other studies requiring a convenient source of alkyl hydrogen fumarates, it was found that the *cis-trans* inversion effect of thiourea[1] and substituted thioureas,[1] converting maleic to fumaric acid, could be applied to methyl hydrogen maleate. Thus, an aqueous solution of the latter was isomerized by thiourea at room temperature to yield the relatively insoluble methyl hydrogen fumarate in quantity.



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[1] S. M. Spatz (to Allied Chemical & Dye Corp.), U. S. Patent 2,548,687, (April 10, 1951).

Application of the thiourea isomerization to ethyl hydrogen maleate failed to yield the corresponding fumarate, suggesting limitation of the isomerization to methyl hydrogen maleate.

Although mineral acids[2] are also known to invert maleic acid, the choice of the relatively neutral thiourea for methyl hydrogen maleate is advantageous in avoiding or minimizing the possibilities of hydrolysis and of disproportionation to fumaric acid and dimethyl fumarate.

Hitherto, methyl hydrogen fumarate has been prepared by the partial saponification of dimethyl fumarate,[3] from fumaryl chloride, methanol, and water,[4] and by the oxidation of methyl sorbate.[5] Our inversion of methyl hydrogen maleate, as a preparative method for the fumarate, is characterized by simplicity and ease of isolation of the product. The over-all yield of the two-step synthesis is 74% of theory.

EXPERIMENTAL

Methyl hydrogen maleate. A 2-liter, three-necked flask, fitted with an agitator, thermometer, dropping funnel, and a reflux condenser topped by a sodium sulfate drying tube, was charged with 980 g. (10.0 moles) of maleic anhydride (hood!). The dropping funnel was charged with 320 g. (10.0 moles) of anhydrous methanol and 10–15% of the alcohol was added to the reaction flask. The mixture was heated on a water bath to 50–55°, and stirred by hand until the maleic anhydride was in solution. The remainder of the alcohol was added under mechanical agitation over a period of 1–2 hr., keeping the temperature at 50–55°. After the addition was completed the agitated solution was held at 50–55° for one more hour, cooled to room temperature, and bottled without further treatment. The yield of methyl hydrogen maleate (n_D^{20} 1.4634, d_4^{20} 1.2520) was quantitative.

Anal. Calcd. for $C_5H_6O_4$: neut. equiv., 130.0; MR_D, 28.0.[6] Found: neut. equiv., 129.5; MR_D, 28.6.

Methyl hydrogen fumarate. Six grams of thiourea was added to a stirred solution of 125 g. (0.96 mole) of methyl hydrogen maleate in 125 g. of water. After 3.5 hr. of agitation at room temperature, the mixture was cooled to 5° and centrifuged at 2500 r.p.m. in a porcelain basket. The white, voluminous precipitate of methyl hydrogen fumarate was washed three times with 100-ml. portions of ice water, and centrifuged once more for 20 min.

To the combined first filtrate and first two washes was added 5 g. of thiourea, and the solution stirred for an additional 12 hr. at room temperature. After cooling, the isolation procedure was repeated. The combined precipitates were dried in a vacuum oven at 50°. The yield was 93 g. (74.6%) and the m.p. of 142–144° compared favorably with the previously reported values[4,7–9] of 143° and 144.5°. Our product is 95.4% pure; it is contaminated with 4.6% fumaric acid, as determined by the alkali titration (calcd. neut. equiv., 130.0; found neut. equiv., 123.5).

Ethyl hydrogen maleate.[10] Four hundred and sixty grams (10.0 moles) of anhydrous ethanol, previously dried further by refluxing over calcium oxide, was reacted with 980 g. (10.0 moles) of maleic anhydride in the manner described for the preparation of the methyl half-ester. The yield of product (n_D^{20}, 1.4560; d_4^{20} 1.1760) was quantitative.

Anal. Calcd. for $C_6H_8O_4$: neut. equiv., 144.0; MR_D, 32.6.[6] Found: neut. equiv., 141.7; MR_D, 33.3.

Attempted isomerization of ethyl hydrogen maleate. The action of 5 g. of thiourea on a stirred solution of 100 g. (0.695 mole) of ethyl hydrogen maleate in 100 g. of water for 72 hr. failed to yield detectable quantities of the water-insoluble ethyl hydrogen fumarate.

NATIONAL ANILINE DIVISION
ALLIED CHEMICAL CORP.
BUFFALO 5, N. Y.

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Deamination of 2,2,3,3-Tetrafluorocyclobutanemethylamine

DONALD R. BAER

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The Demjanow rearrangement of cycloalkanemethylamines to produce the corresponding ring-enlarged alcohol on treatment with nitrous acid has been successfully applied to rings containing three to eight carbon atoms.[1,2,3] The presence of a halogen atom on the ring appears to prevent ring expansion. In the one case reported,[4] 2-chlorocyclohexanemethylamine was found to give only the corresponding unrearranged alcohol under conditions normally leading to ring expansion of the unhalogenated ring. Elphimoff-Felkin and Tchoubar[5] have shown that in certain cases cyclopentane rings will show ring expansion where the corresponding cyclohexane compounds will not. This is presumed due to the relative ease of formation of the six- versus seven-membered ring.

In the course of another investigation, 2,2,3,3-tetrafluorocyclobutanemethylamine, I, was prepared by the cyclodimerization of acrylonitrile and tetrafluoroethylene followed by catalytic hydrogenation of the carbonitrile. It was expected that on deamination relief of ring strain would provide sufficient

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