The results are summarized in Table I.

(C) **Procedure with Isopropyl Acetate.**—To a stirred suspension of 0.2 mole of lithium amide in 250 ml. of liquid ammonia was added during 2 minutes a solution of 20.4 g. (0.2 mole) of isopropyl acetate, 24 g. (0.2 mole) of acetophenone and 50 ml. of ether. After stirring 10 minutes longer, a hot water-bath was applied and 100 ml. of ether added as the ammonia was driven off. The ether suspension was stirred and refluxed for 2 hours, then worked up as described above in the general procedure. Distillation *in vacuo*, yielded 17.6 g. (40%) of isopropyl β-hydroxy-β-phenylbutyrate, b.p. 145–147° (15 mm.), and at 136–137° (10 mm.) on redistillation.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.13; H, 8.16.

α,β(or β,γ-)-Unsaturated Acids from *t*-Butyl β-Hydroxy Esters by Acids (Table II). Method A.—The ester (5 g.) was refluxed for 1.5 hours with a solution of 10 ml. of concentrated hydrochloric acid and 40 ml. of dioxane. The solvents were removed under reduced pressure (water-pump), and the residual solid acid recrystallized from an appropriate solvent.

Method B.—The ester (1.5 g.) was added dropwise to 5 ml. of ice-cold concentrated sulfuric acid. After standing at 0° for 10 minutes, the mixture was poured onto cracked ice and the resulting solid acid filtered with suction, washed with water, dried and recrystallized.

Method C.—The ester (5 g.) was refluxed 1.5 hours with 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of toluene. The mixture was washed with water and extracted with several portions of saturated sodium bicarbonate solution. Acidification of the basic extracts yielded the acid.

Dehydration of *t*-Butyl β-Hydroxy Esters.—In a 300-ml. flask equipped with a reflux condenser were placed 22 g. (0.28 mole) of pyridine, 32 g. (0.27 mole) of thionyl chloride and 75 ml. of anhydrous benzene. To the agitated mixture was added in small portions through the top of the condenser 30 g. (0.127 mole) of *t*-butyl β-hydroxy-β-phenylbutyrate in 35 ml. of benzene. After standing for 3 hours the mixture was poured onto a mixture of cracked ice and 20 ml. of 5 *N* sodium hydroxide solution. The benzene layer was washed with 3 *N* hydrochloric acid, several portions of saturated sodium bicarbonate solution and finally with water. After drying over Drierite and potassium carbonate, the solvent was removed, a trace of magnesium oxide added and the residue distilled *in vacuo* to give 14.4 g. (52%) of *t*-butyl β-methylcinnamate, b.p. 104.5–108° (1 mm.).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.09; H, 8.11.

Similarly from 25 g. (0.143 mole) of *t*-butyl β-hydroxy-β-methylbutyrate, 25 g. (0.316 mole) of pyridine, 36 g. (0.3 mole) of thionyl chloride and 70 ml. of benzene there was obtained 11.5 g. (52%) of *t*-butyl β-methylcrotonate, b.p. 68–74° (23 mm.).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 68.62; H, 10.11.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, SHARP AND DOHME, INC.]

The Alkylation of Phenylacetones[1]

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The synthesis of alkylated derivatives of phenylacetone and diphenylacetone was investigated. In the presence of powdered sodium hydroxide, phenylacetone reacts with normal and selected branched-chain lower-alkyl halides to produce 1-alkyl-1-phenylacetones in good yields. 1-Alkyl-1,1-diphenylacetones have been prepared by treating 1-bromo-1-alkyl-1-phenylacetones with benzene and anhydrous aluminum chloride or, in some cases, by direct alkylation of diphenylacetone with an alkyl halide in the presence of potassium *t*-butoxide or sodium hydroxide.

The alkylation of ketones that possess active methyl or methylene groups is usually accomplished by reaction with an alkyl halide in an anhydrous solvent in the presence of a base such as sodium amide,[2,3] sodium ethoxide,[4] sodium isopropoxide[5] or sodium amoxide.[6] However, desoxybenzoin[7] and *p,p'*-dimethoxydesoxybenzoin[8] have been ethylated by means of ethyl iodide, essentially without solvent, in the presence of powdered sodium hydroxide. The application of such a simple procedure to the alkylation of aralkyl methyl ketones apparently has not been exploited.

In this Laboratory, we have found that sodium hydroxide is an excellent condensing agent for the preparation of 1-alkyl-1-phenylacetones from phenylacetone and alkyl halides. The procedure is simple since a solvent is not required and no special precautions to exclude moisture must be taken. The ketones prepared by this method are listed in Table I where it will be apparent that the reaction is quite general and that the yields are acceptable. The alkylation failed when easily dehydrohalogenated alkyl halides, such as *t*-butyl or cyclohexyl halides, were submitted to the reaction and only olefins corresponding to the halides resulted. In the case of known ketones the products were identified by their physical properties and by derivatives. The only new ketone prepared was 1-allyl-1-phenylacetone, and this was converted for identification to the known 1-propyl-1-phenylacetone by catalytic hydrogenation. Though the introduction of one alkyl group into the phenylacetone molecule occurred readily, dialkylphenylacetones could not be prepared by this method.

Since methyl ketones and ketones having active methylene groups are known to polymerize in the presence of alkalies, the successful alkylation of phenylacetone under the present conditions appears to be due to the rapidity of the condensation and to the enhanced stability toward polymerization of the resulting monoalkyl derivative. It was found that prolonged heating of phenylacetone with powdered sodium hydroxide in the absence of an alkylating agent caused almost complete polymerization, whereas under the same treatment the 1-

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[1] Presented before the Third Meeting-in-miniature of the Philadelphia Section of the American Chemical Society, January 20, 1949.

[2] A. Haller and E. Bauer, *Compt. rend.*, **150**, 582 (1910); *Ann. chim.*, [8] **29**, 313 (1913).

[3] I. N. Nasarow, *Ber.*, **70**, 594 (1937).

[4] M. Tiffeneau and J. Levy, *Bull. soc. chim.*, [4] **33**, 767 (1923).

[5] C. M. Suter and A. W. Weston, THIS JOURNAL, **64**, 535 (1942).

[6] G. Vavon and J. Conia, *Compt. rend.*, **223**, 157 (1946).

[7] H. Janssen, *Ann.*, **250**, 132 (1889).

[8] W. Braker, *et al.*, U. S. Patent 2,252,696 (1941).

alkyl-1-phenylacetones are much more stable and can be recovered to an extent of about 50%.

The preparation of 1-alkyl-1,1-diphenylacetones by the alkylation of diphenylacetone[9] was not as simple or as general as was the case with phenylacetone. With sodium hydroxide as the condensing agent, methyl iodide and benzyl chloride reacted to form alkylated products in 55 and 30% yields, respectively. *n*-Propyl iodide failed to condense and unchanged diphenylacetone was recovered. The yields were somewhat improved when potassium *t*-butoxide in *t*-butyl alcohol was used as a condensing agent with the methyl and benzyl halides and allyl bromide, but halides such as ethyl iodide and *n*-propyl iodides still failed to condense. That the alkylated products are 1-alkyl-1,1-diphenylacetones is concluded from the following considerations. The reaction between diphenylacetone and methyl iodide produced 1-methyl-1,1-diphenylacetone, a known compound.[10] The product from diphenylacetone and allyl bromide could be hydrogenated to produce 1-*n*-propyl-1,1-diphenylacetone[5] and was, therefore, 1-allyl-1,1-diphenylacetone. By analogy, it was assumed that the product from benzyl chloride and diphenylacetone was 1-benzyl-1,1-diphenylacetone.

Since direct alkylation of 1,1-diphenylacetone appeared to be possible only with very active halides, a more general way of preparing 1-alkyl-1,1-diphenylacetones was sought. In this connection, a Friedel–Crafts reaction similar to that used for the preparation of phenylacetone itself[9] was investigated. As an example, 1-methyl-1-phenylacetone was first brominated and the crude product then was treated with aluminum chloride and benzene. In this case and when the procedure was applied to 1-ethyl- and 1-*n*-propylphenylacetone the corresponding 1-alkyl-1,1-diphenylacetones were obtained in 43–73% yields, but only tars resulted when the procedure was applied to 1-benzyl- and 1-isopropylphenylacetone. The products of the Friedel–Crafts reaction are rather difficult to purify. They exhibit a blue fluorescence and darken slowly on storage. The structures of these ketones were proved by comparing the physical properties of the ketones and their derivatives with authentic samples and, in the case of 1-ethyl-1,1-diphenylacetone, by hypobromite oxidation to α-ethyl-α,α-diphenylacetic acid.[11]

Experimental[12]

General Alkylation Procedure: 1-Phenyl-1-*n*-propylacetone.—Powdered sodium hydroxide (44 g., 1.1 moles) was placed in a round-bottomed flask equipped with a Hershberg stirrer, a reflux condenser and a dropping funnel. Phenylacetone[13] (134 g., 1 mole) was added in one portion. The mixture was stirred vigorously for 15 minutes without cooling during which time the sodium hydroxide partially dissolved and the contents of the flask became deep red. *n*-Propyl iodide (204 g., 1.2 moles) was added dropwise over a period of one hour while the temperature was maintained at 30–35° by means of a water-bath. The bath was removed and the mixture was stirred for about two hours. When the evolution of heat diminished, the flask was heated on a steam-bath for three hours, cautiously at first. During the heating period sodium iodide separated and the solution became light yellow. Then 250 ml. of cold water was added with stirring. After cooling, the oily product was taken up in ether and the ether solution was washed with water and dried over sodium sulfate. Evaporation of the ether left an oil that was distilled from a modified claisen flask.[14]

Hydrogenation of 1-Allyl-1-phenylacetone.—The ketone (17.4 g., 0.1 mole) was dissolved in dry benzene (100 ml.) and Adams platinum oxide catalyst (0.3 g.) was added. The mixture was hydrogenated in a Parr apparatus under an initial pressure of 35.5 p.s.i. Hydrogenation was completed in about 10 minutes during which time 0.1 mole of hydrogen was absorbed and considerable heat was produced. After removal of the catalyst, the solvent was evaporated and the residue was distilled to yield 14.7 g. (83%) of 1-*n*-propyl-1-phenylacetone identified by its semicarbazone, m.p. 135–136°.[5]

Action of Solid Sodium Hydroxide on Phenylacetone.—A mixture of phenylacetone (60 g., 0.448 mole) and sodium hydroxide (19.7 g., 0.49 mole) was stirred and heated at 90–100° for 16 hours. A dark brown, viscous paste resulted. Upon working up the mixture in the usual manner, only 4.2 g. (7%) of the original phenylacetone, b.p. 95–98° (14 mm.), was recovered. The remainder of the product was an amber, viscous, non-distillable polymer. The recovered ketone was characterized through its 2,4-dinitrophenylhydrazone, m.p. 150° alone or mixed with an authentic sample.

Action of Sodium Hydroxide on 1-Ethyl-1-phenylacetone.—In the same manner as described above, the ketone (16 g., 0.1 mole) was heated for 16 hours with sodium hydroxide (4.0 g., 0.1 mole). Upon working up and distilling there was obtained 7.4 g. (46%) of unchanged 1-ethyl-1-phenylacetone, b.p. 105–107° (14 mm.). The 2,4-dinitrophenylhydrazone melted at 125–126° alone or mixed with an authentic sample.

1-Methyl-1,1-diphenylacetone. (A) **By Alkylation of Diphenylacetone.**—Potassium (7.5 g., 0.19 mole) was dissolved under an atmosphere of nitrogen in *t*-butyl alcohol (150 ml.) in a four-necked flask equipped with an efficient stirrer, a dropping funnel, a reflux condenser and a nitrogen inlet tube. Diphenylacetone (39.9 g., 0.19 mole) was added in one portion and the mixture was stirred and heated to boiling and then cooled to 30°. Methyl iodide (35.5 g., 0.25 mole) then was added dropwise at a temperature of 30–35° over a period of 15 minutes. The mixture was stirred at 40–45° for an additional hour, after which the alcohol was distilled. Water was added to dissolve the potassium iodide and the oily product was taken up in ether. After the ether solution had been dried over sodium sulfate, the solvent was evaporated. The product (67.3 g., 79%) had the following physical constants: b.p. 137–139° (1–2 mm.), $n^{20}\mathrm{D}$ 1.5775, m.p. 38–40°. The literature gives m.p. 41°.[10]

(B) **By Friedel–Crafts Reaction.**—Bromine (42 g., 0.26 mole) in carbon tetrachloride (50 ml.) was added dropwise with stirring at 25–30° to 1-methyl-1-phenylacetone (37 g., 0.25 mole) dissolved in carbon tetrachloride (500 ml.). The rate of addition was regulated so that each drop of bromine was decolorized before the next drop was added (one to two hours). Then dry nitrogen was passed through the flask until no more hydrogen bromide could be swept out (1.25 hr.). The carbon tetrachloride was removed by vacuum distillation at 40–45°, after which the temperature was raised to 90° and several portions of dry benzene were added and evaporated under diminished pressure to remove the residual carbon tetrachloride. The residue was dissolved in an equal volume of benzene, filtered and added with stirring over a period of 20 minutes to a mixture of anhydrous aluminum chloride (65 g., 0.5 mole) in boiling benzene (200 ml.) contained in a one-liter flask equipped with a stirrer, dropping funnel and reflux condenser. The red mixture was boiled for one hour longer, cooled and poured onto a mixture of ice (500–700 g.) and concentrated hydrochloric acid (150 ml.). When the ice had melted the pale yellow benzene layer was separated and the aqueous layer was extracted with ether. The combined organic solution was washed with water and saturated sodium bi-

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(9) E. M. Schultz and S. Mickey, *Org. Syntheses*, **29**, 38 (1949).

(10) H. Meerwein, *Ann.*, **396**, 259 (1913).

(11) H. Meerwein, *ibid.*, **419**, 156 (1919).

(12) All melting and boiling points are uncorrected.

(13) Eastman Kodak Co., Rochester, N. Y.

(14) W. A. Noyes and G. S. Skinner, THIS JOURNAL, **39**, 278 (1917).

Table I

$C_6H_5CHRCOCH_3$

R	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	Derivative	M.p., °C.	Ref.
Methyl	65	106–110	22	1.5100	2,4-Dinitrophenylhydrazone	125–126	5
Ethyl	79	116–123	23	1.5048	Semicarbazone	190–191	5
n-Propyl	71	120–124	18	1.5022	Semicarbazone	135–136	4
i-Propyl	59	109–114		1.5000	Semicarbazone	153–154	15
Allyl	80	119–121	14–15	1.5158	2,4-Dinitrophenylhydrazone	133–134	[a]
n-Butyl	44	131–135	16	1.4995	Semicarbazone	154–155.5[b]	16
i-Butyl	32	119–124	14	1.4966	Semicarbazone	116–118	17
Benzyl	62	119–122	1	1.5622	Oxime	133–134	18

[a] Structure demonstrated by hydrogenation to 1-*n*-propyl-1-phenylacetone. [b] The literature value is 156–158°. *Anal.* Calcd. for $C_{14}H_{21}N_3O$: C, 68.02; H, 8.50. Found: C, 67.95; H, 8.57.

carbonate solution and dried over sodium sulfate. On distillation, 40.75 g. (73%) of pale yellow 1-methyl-1,1-diphenylacetone was obtained, b.p. 127–128° (2 mm.), m.p. 38–40°.[10]

1-Ethyl-1,1-diphenylacetone.—This compound was prepared from 1-ethyl-1-phenylacetone by a Friedel–Crafts reaction exactly as described above. There was obtained a 53% yield of a clear yellow oil, b.p. 120–125° (0.5 mm.), $n^{20}D$ 1.5758. An authentic sample, b.p. 126–127° (0.75 mm.), $n^{20}D$ 1.5737, was prepared from 1,1-diphenyl-2-ethyl-2-methylethylene glycol.[11]

Semicarbazone: m.p. 199–200° from alcohol–water; gave no depression of m.p. with an authentic sample.[11]

2,4-Dinitrophenylhydrazone: m.p. 131–132° from alcohol; gave no depression of m.p. with an authentic sample.

Anal. Calcd. for $C_{23}H_{22}N_4O_4$: C, 66.00; H, 5.31. Found: C, 66.09; H, 5.35.

Oxidation to Ethyldiphenylacetic Acid.—Ten grams of the ketone was oxidized by means of sodium hypobromite solution by the procedure of Meerwein[11] to obtain ethyldiphenylacetic acid (1.8 g.), m.p. 169–170°.[11]

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.96; H, 6.71. Found: C, 79.99; H, 6.88.

1-Allyl-1,1-diphenylacetone.—This compound was prepared in 50–60% yield by alkylation of 1,1-diphenylacetone with allyl bromide in the same manner as described for 1-methyl-1,1-diphenylacetone except that the reaction mixture was boiled during the addition of the allyl bromide and for 15 minutes additionally. The product was distilled; b.p. 121–124° (1 mm.). The distillate solidified and the purified compound melted at 61–62° after crystallization from petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.40; H, 7.21. Found: C, 86.58; H, 7.47.

The 2,4-dinitrophenylhydrazone melted at 162–164° after crystallization from alcohol.

Anal. Calcd. for $C_{24}H_{22}O_4N_4$: C, 66.96; H, 5.15. Found: C, 67.00; H, 5.13.

1-Benzyl-1,1-diphenylacetone.—The reaction of benzyl chloride and diphenylacetone in the presence of potassium *t*-butoxide in boiling *t*-butyl alcohol provided a 51% yield of 1-benzyl-1,1-diphenylacetone, b.p. 183–186° (2 mm.) and m.p. 63–64° from petroleum ether (b.p. 30–60°). The literature records m.p. 66°.[19]

Anal. Calcd. for $C_{22}H_{20}O$: C, 88.00; H, 6.67. Found: C, 87.88; H, 6.72.

1-*n*-Propyl-1,1-diphenylacetone. (a) By Hydrogenation of 1-Allyl-1,1-diphenylacetone.—The allyl ketone (10 g., 0.04 mole) was dissolved in absolute alcohol (100 ml.) and Adams catalyst (0.3 g.) was added. The mixture was shaken under an atmosphere of hydrogen at atmospheric pressure. In 25 minutes, 1036 ml. of hydrogen had been absorbed (theory, 1108 ml.) and the absorption of hydrogen ceased. If shaking was interrupted before hydrogenation was complete, the reaction did not begin again upon resumption of shaking. After removal of the catalyst and solvent, the residue was distilled; b.p. 117–120° (0.5 mm.), $n^{20}D$ 1.5664. The yield was 7.7 g. (76.5%).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.71; H, 7.94. Found: C, 85.94; H, 8.21.

2,4-Dinitrophenylhydrazone: m.p. 174–175° from alcohol.

Anal. Calcd. for $C_{24}H_{24}N_4O_4$: C, 66.65; H, 5.59. Found: C, 66.81; H, 5.65.

Semicarbazone: m.p. 189–191° from alcohol.

Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.77; H, 7.50. Found: C, 73.79; H, 7.43.

(b) By Friedel–Crafts Reaction.—By this procedure, carried out as described above, there was obtained a 43% yield of a yellow oil, b.p. 125–127° (0.7 mm.), $n^{20}D$ 1.5674.

The 2,4-dinitrophenylhydrazone was crystallized from 95% alcohol and melted at 174–175° alone or mixed with an authentic sample.

West Point, Pa.

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(15) J. Levey, *et al.*, *Bull. soc. chim.*, **45**, 941 (1929).

(16) M. Tiffeneau, *et al.*, *ibid.*, **49**, 1788 (1931).

(17) P. L. Jullien, *ibid.*, [5] **3**, 1347 (1936).

(18) C. Goldschmidt and H. Krzmar, *Monatsh.*, **22**, 661 (1901).

(19) M. Tiffeneau and J. Levy, *Bull. soc. chim.*, **33**, 759 (1923); *C. A.*, **17**, 3029 (1923).