depression on mixing with a sample of acetaldehyde 2,4-dinitrophenylhydrazone.

Infrared spectra were determined on the Beckman IR-2T infrared spectrophotometer at 30° using a 0.03 mm. sodium chloride cell.

Absorption spectra are consistent with assigned structures. Spectra of the methyl and ethyl ethers of methylcyclopropylcarbinol both show absorption maxima in the region of 9 μ and at *ca.* 9.8 μ which may be associated, respectively, with the presence of ether linkages[26] and cyclopropane rings.[27] Both ethers show maxima at *ca.* 12.15 μ, in which region absorption has also been noted for cyclopropylmethyl ethyl ether.[4]

Absorption maxima (*ca.* 100%) for *trans*-3-penten-1-yl methyl ether at 8.9 and 10.3 μ were in accord with the presence of an ether linkage[26] and a *trans* double bond.[21,26a]

Acknowledgment.—It is a pleasure to acknowledge helpful discussions with Dr. L. C. King and Dr. A. S. Hussey. One of us (S. H. L.) is indebted to the United States Public Health Service for a fellowship held during the course of this work.

(26) (a) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950); (b) M. Josien, N. Fuson and A. S. Cary, THIS JOURNAL, **73**, 4445 (1951).

(27) (a) J. M. Derfer, E. E. Pickett and C. E. Boord, *ibid.*, **71**, 2482. (1949); (b) J. D. Bartleson, R. E. Burk and H. P. Lankelma, *ibid.*, **68**, 2513 (1946).

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aldol Condensation of Esters with Ketones or Aldehydes to Form β-Hydroxy Esters by Lithium Amide. Comparison with the Reformatsky Reaction[1]

BY CHARLES R. HAUSER AND W. H. PUTERBAUGH[2]

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The aldol condensation of *t*-butyl acetate and certain other esters with ketones or aldehydes to form β-hydroxy esters has been effected by means of lithium amide. This new method for preparing β-hydroxy esters is more convenient and, in certain cases (*e.g.*, with nitro ketones), more generally applicable than the Reformatsky reaction. The *t*-butyl β-hydroxy esters produced in our method were, in general, converted to α,β-unsaturated acids by treatment with mineral acids. The *t*-butyl β-hydroxy esters from aromatic nitro ketones were converted to β-hydroxy acids. Certain of the β-hydroxy esters were dehydrated to form the α,β-unsaturated esters.

A recent communication from this Laboratory[3] described the aldol condensation of *t*-butyl acetate with acetophenone to form *t*-butyl β-hydroxy-β-phenylbutyrate (I). This new process was effected in fair yield (31%) by means of sodium amide followed by zinc chloride (simulating the Reformatsky reaction), and in high yield (76%) by means of lithium amide alone. The latter, more promising method involves the metalation of the α-hydrogen of the ester by the lithium amide in liquid ammonia (equation 1), and the condensation of the resulting lithio ester with the carbonyl group of the ketone in ether (equation 2).

$$CH_3COOC(CH_3)_3 + LiNH_2 \xrightarrow{\text{liq. } NH_3} LiCH_2COOC(CH_3)_3 + NH_3 \quad (1)$$

$$LiCH_2COO(CH_3)_3 + C_6H_5COCH_3 \xrightarrow{\text{ether}} C_6H_5C(OLi)(CH_3)-CH_2COOC(CH_3)_3 \xrightarrow{HOH} C_6H_5C(OH)(CH_3)-CH_2COOC(CH_3)_3 \quad (2)$$

I (76%)

The present paper describes the further development and application of the lithium amide method (Table I). In general, *t*-butyl esters rather than the more common methyl or ethyl esters were employed both to ensure the preferential metalation of the α-hydrogen of the ester by the lithium amide (instead of partial reaction at the carbonyl carbon to form the amide),[4] and to minimize the possible self-condensation of the ester.[5]

The general procedure involves three simple operations followed by a two-hour refluxing period: (a) the ester is added to a molecular equivalent (plus 5%) of lithium amide in liquid ammonia, (b) the ammonia is replaced by ether, and (c) an equivalent of the ketone is added. Since the ester is probably converted almost immediately to its lithio derivative, these three operations should be completed as fast as feasible in order to avoid appreciable self-condensation of the ester. Operations (b) and (c) may be reversed, but, at least with *t*-butyl acetate and acetophenone, this has given a slightly lower yield (70%) than that (76%) obtained by the usual procedure. The general procedure produced only tars with aromatic nitro ketones, but satisfactory results were obtained when the lithio ester was added to the ketone at −70°. This modification is similar to the inverse addition procedure employed by Newman and Smith[6] for the condensation of Grignard reagents with nitro aldehydes.

Although the independent preparation of the lithio ester is recommended with *t*-butyl esters, this procedure has not been very satisfactory with isopropyl acetate because of the occurrence of considerable self-condensation of this ester before

(1) Paper XLVIII on Condensations; paper XLVII, THIS JOURNAL, **73**, 901 (1951).

(2) Carbide and Carbon Chemicals Company Fellow, 1950–1952.

(3) C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, **73**, 2972 (1951).

(4) *Cf.* M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950). See also C. R. Hauser, R. Levine and R. F. Kibler, *ibid.*, **68**, 26 (1946).

(5) See J. C. Shivers, M. L. Dillon and C. R. Hauser, *ibid.*, **69**, 119 (1947).

(6) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

TABLE I

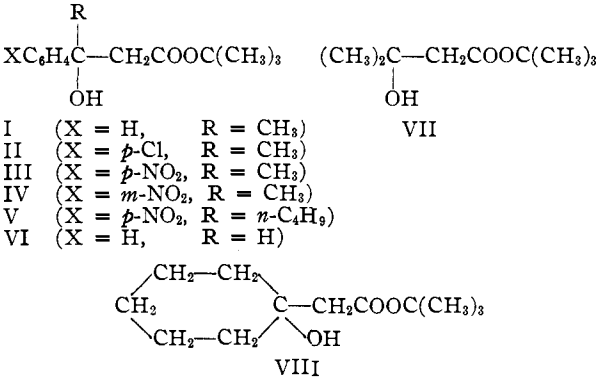
β-HYDROXY ESTERS FROM ESTERS AND KETONES OR ALDEHYDES BY LITHIUM AMIDE

Ester, *t*-butyl	Ketone or aldehyde	Product, *t*-butyl β-hydroxy	B.p. or m.p. °C.	Mm.	Yield,[a] %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Acetate	Acetophenone	β-Phenylbutyrate (I)	111–112.5	2	76 (92)	71.16	70.77	8.53	8.22
Acetate	*p*-Chloroacetophenone	β-(*p*-Chlorophenyl)-butyrate (II)[b]	116–118	1	76 (90)	62.10	62.05	7.07	7.01
Acetate	*p*-Nitroacetophenone	β-Hydroxy-β-(*p*-nitrophenyl)-butyric acid (acid of III)[c]	M. 108.5–109.5	..	59 (90)	53.33	53.73	4.92	4.93
Acetate	*m*-Nitroacetophenone	β-Hydroxy-β-(*m*-nitrophenyl)-butyric acid (acid of IV)[d]	M. 107.5–109.5	..	55 (88)	53.33	53.44	4.92	5.14
Acetate	*p*-Nitrocaprophenone	β-Hydroxy-β-(*p*-nitrophenyl)-octanoic acid (acid of V)[e]	M. 114–116	..	68 (77)	59.77	59.98	6.81	6.74
Acetate	Benzaldehyde	β-Phenylpropionate (VI)	147–149	7	53[f] (68)	70.33	69.98	8.17	7.83
Acetate	Acetone	β-Methylbutyrate (VII)	82–82.5	19	62	62.04	62.11	10.41	10.09
Acetate	Cyclohexanone	Cyclohexylacetate (VIII)[g]	132–135	17	63 (74)	67.35	67.24	10.36	10.02
Acetate	α-Tetralone	1,2,3,4-Tetrahydronaphthyl-acetate (IX)[g]	151–152	1	35 (99)	73.25	73.39	8.46	8.18
Acetate	Butyraldehyde	*n*-Caproate	105–108	12	17	63.79	63.99	10.71	10.44
Propionate	Acetophenone	α-Methyl-β-phenylbutyrate (X)	131–132.5	4	58 (93)	71.97	71.91	8.86	9.12
Propionate	Benzaldehyde	α-Methyl-β-phenylpropionate (XI)	122–125	1	48 (73)	71.16	71.11	8.53	8.53
Propionate	Acetone	α,β-Dimethylbutyrate (XII)	92.5–94.5	19	53	63.79	63.63	10.71	10.41
Isobutyrate	Acetophenone	α,α-Dimethyl-β-phenylbutyrate	.....	..	0[h]	...	...	...	...
Crotonate	Acetophenone	δ-Phenyl-2-hexenoate (XIII)[i]	137–142	0.5	18 (22)	73.25	73.03	8.45	8.24
Phenylacetate[j]	Benzaldehyde	α,β-Diphenylpropionate (XIV)[j,k]	170–175 M. 72–73	2	34 (60)	75.53	75.64	6.71	6.60

[a] The yields given in parentheses are based on the ketone or aldehyde consumed. [b] *Anal.* Calcd. for $C_{14}H_{19}O_3Cl$: Cl, 13.10. Found: Cl, 13.08. [c] *Anal.* Calcd. for $C_{10}H_{11}O_5N$: neut. equiv., 225; N, 6.22. Found: neut. equiv., 229; N, 6.02. [d] *Anal.* Calcd. for $C_{10}H_{11}O_5N$: neut. equiv., 225; N, 6.22. Found: neut. equiv., 229; N, 6.19. [e] *Anal.* Calcd. for $C_{14}H_{19}O_5N$: neut. equiv., 281; N, 4.98. Found: neut. equiv., 287; N, 5.04. [f] Reflux time was 1.5 hours. [g] These compounds are generally named 1-hydroxy rather than β-hydroxy. [h] *t*-Butyl isobutyrate (69%) and acetophenone (58%) were recovered along with some high boiling residue. [i] δ-Hydroxy ester. [j] Ethyl ester. [k] Saponification with 15% sodium hydroxide solution (refluxed 5 hours) gave a 40% yield of β-hydroxy-α,β-diphenylpropionic acid, m.p. 176.5°; reported m.p. 175°, D. Ivanoff and N. I. Nicoloff, *Bull. soc. chim.*, 51, 1325 (1932).

the addition of the ketone.[7] However, a 40% yield of the isopropyl β-hydroxy ester has been obtained by adding a mixture of isopropyl acetate and acetophenone to the lithium amide. While the maximum yield under these conditions appears to be only 50%[8] this method is fairly satisfactory with esters which, like isopropyl acetate, are preferentially metalated at the α-hydrogen but undergo self-condensation too readily for the general procedure to be suitable. Moreover, this procedure could presumably be extended to the condensations of ethyl acetate and certain higher aliphatic ethyl esters with ketones by employing, instead of lithium amide, a more complex lithium base such as lithium diisopropylamide which preferentially metalates the α-hydrogen of even these esters.[4]

It can be seen from Table I that *t*-butyl acetate gave good yields (53–76%) of the corresponding *t*-butyl β-hydroxy esters I–VIII with substituted acetophenones, *p*-nitrocaprophenone, benzaldehyde, acetone and cyclohexanone, but the yield was only fair with α-tetralone and poor with *n*-butyraldehyde. β-Hydroxy esters III, IV and V (from the aromatic nitro ketones) were isolated as their β-hydroxy acids as described below. *t*-Butyl propionate also gave satisfactory yields of the α-methyl-β-hydroxy esters with acetophenone, benzaldehyde and acetone, although the yields were lower than those of the corresponding reactions with *t*-butyl acetate. Ethyl phenylacetate gave the α-phenyl derivative in fair yield with benzaldehyde, while *t*-butyl crotonate formed the δ-hydroxy ester in low yield with acetophenone.



However, *t*-butyl isobutyrate failed to condense with acetophenone. Instead, much of the original ester and ketone was recovered along with some high boiling material which resulted presumably from self-condensation of the ketone. Evidently this lithio ester, which is relatively complex, merely enolized the ketone (equation 3). Such enolizations have been observed in connection with the Reformatsky reaction, particularly when the ketone was relatively complex or hindered such as acetomesitylene.[9] It should be pointed out that because of the possibility of enolization of the ketone, the recovery of considerable amounts of starting material in certain experiments does not necessarily

(7) Even when isopropyl acetate was added to the lithium amide in liquid ammonia within one minute, and the acetophenone added within another minute, followed by the usual two-hour refluxing period in ether, only a 27% yield of isopropyl β-hydroxy ester was obtained along with some β-keto ester resulting from self-condensation of the ester.

(8) Since the α-hydrogen of acetophenone is more reactive than that of an acetic ester, the lithio ketone as well as the lithio ester is presumably formed during the addition of the first half of the mixture of ester and ketone to the lithium amide which would be in excess during this time. Hence only half of the ketone would be left available for the aldol condensation which would occur during the addition of the second half of the mixture. In agreement with this, the yield of the *t*-butyl β-hydroxy ester also was only 42% under these conditions whereas a 76% yield was obtained when lithio *t*-butyl acetate was first prepared and the acetophenone then added (general procedure).

(9) *Cf.* M. S. Newman, THIS JOURNAL, **64**, 2131 (1942).

mean that the yields of condensation products could be improved by employing longer reaction times.

$$C_6H_5COCH_3 + LiC(CH_3)_2COOC(CH_3)_3 \longrightarrow C_6H_5C(=CH_2)OLi + CH(CH_3)_2COOC(CH_3)_3 \quad (3)$$

Although most of the β-hydroxy esters themselves were isolated, esters III, IV and V (from the nitro ketones) were isolated only as their β-hydroxy acids.[10] Ester V was converted to its β-hydroxy acid by thermal decomposition at about 220° (1 mm.), while esters III and IV were converted to the corresponding β-hydroxy acids by means of hydrochloric acid in refluxing dioxane. In all three cases the over-all yields of the β-hydroxy acids from the nitro ketones were good (see Table I). Since both the thermal decomposition and the acid treatment appear to be applicable generally, these conversions may be represented by equation (4)

$$NO_2C_6H_4C(R)(OH)-CH_2COOC(CH_3)_3 \xrightarrow[\text{heat alone}]{\text{acid or}} NO_2C_6H_4C(R)(OH)-CH_2COOH + (CH_3)_2C=CH_2 \quad (4)$$

The other *t*-butyl β-hydroxy esters (which were isolated) were converted, by treatment with acid, to the corresponding α,β- (or β,γ-) unsaturated acids (Table II). For example, β-hydroxy ester II was converted by hydrochloric acid in refluxing dioxane (method A) to *p*-chloro-β-methylcinnamic acid in 64% yield. This α,β-unsaturated acid was formed also on thermal decomposition of ester II (at about 220°).[11] These reactions may be represented by equation (5). Similar conversions of certain *t*-butyl β-hydroxy esters to α,β-unsaturated acids were effected by cold concentrated sulfuric acid (method B), or by a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene (method C).

$$p\text{-}ClC_6H_4C(CH_3)(OH)-CH_2COOC(CH_3)_3 \xrightarrow[\text{heat alone}]{\text{acid or}} p\text{-}ClC_6H_4C(CH_3)=CHCOOH + (CH_3)_2C=CH_2 + H_2O \quad (5)$$

Such conversions of *t*-butyl β-hydroxy esters to α,β-unsaturated acids, involving both hydrolysis of the *t*-butyl ester group and dehydration, were not unexpected, since strong acids or heat alone are known to effect such reactions readily. However, it should be noted that, under similar conditions, the nitro β-hydroxy esters underwent hydrolysis of the *t*-butyl group but not dehydration.[12] Evidently the nitro group, even in the meta position, has a considerable stabilizing effect on the hydroxyl group, thereby hindering the dehydration. It seems rather remarkable that δ-hydroxy ester XIII, which has no such stabilizing group, similarly underwent only hydrolysis of the *t*-butyl group (not dehydration) with hydrochloric acid in refluxing dioxane (see Table II). It should be mentioned that β-hydroxy ester XIV, which is an ethyl ester, was saponified to form the β-hydroxy acid (see note *k* in Table I).

Dehydration without affecting the *t*-butyl group was effected with certain of the *t*-butyl β-hydroxy esters. Thus, β-hydroxy esters I and VII on treatment with thionyl chloride in pyridine gave the corresponding *t*-butyl α,β-unsaturated ester. The reaction may be illustrated with β-hydroxy ester I (equation 6).

$$C_6H_5C(CH_3)(OH)-CH_2COOC(CH_3)_3 \xrightarrow[\text{pyridine}]{SOCl_2} C_6H_5C(CH_3)=CHCOOC(CH_3)_3 + H_2O \quad (6)$$

Comparison with the Reformatsky Reaction.—In general the yields of *t*-butyl β-hydroxy esters given in Table I are comparable with those of the corresponding ethyl β-hydroxy esters obtained in the related Reformatsky reaction which has usually been employed for the preparation of this type of compound. In certain cases the yields are significantly better by our method. Thus, the condensations of *t*-butyl acetate and *t*-butyl propionate with acetone were realized in yields of 62 and 53%, respectively, whereas the corresponding Reformatsky reactions using α-bromo esters have been reported to produce yields of only 40[13] and 28%,[14] respectively. Particularly striking are the good yields from the condensations of *t*-butyl acetate with the aromatic nitro ketones with which the Reformatsky reaction has apparently not been successful.[14,15] However *t*-butyl isobutyrate failed to condense with acetophenone by our methods whereas ethyl α-bromoisobutyrate has been condensed with this ketone in 25% yield under the usual Reformatsky conditions and in 50% yield under special conditions.[16]

We believe that our method is more convenient than that involving the Reformatsky reaction. Although our method has generally been entirely satisfactory only with *t*-butyl esters, whereas the

(10) β-Hydroxy ester IV distilled at 156–160° at 2 mm. (bath temperature about 220°) with only slight decomposition but esters III and V underwent considerable decomposition under these conditions. All three of these esters could probably be distilled satisfactorily at lower temperatures and pressures.

(11) Part of the α,β-unsaturated acid formed in this thermal decomposition evidently underwent decarboxylation since in addition to a 52% yield of the acid there was obtained a neutral product which had the properties characteristic of *p*-chloro-α-methylstyrene (36%).

(12) Similar resistance to dehydration has previously been observed with β-hydroxy-β-(*p*-nitrophenyl)-propionic acid; A. Basler, *Ber.*, **16**, 3007 (1883).

(13) G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, **127**, 624 (1925).

(14) R. L. Shriner, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 1.

(15) Since the zinc-halo intermediate in the Reformatsky reaction has been prepared in the presence of the ketone, the inverse addition procedure which appears to be required with nitro ketones has not been feasible. However if *t*-butyl α-halo esters were used to minimize the self-condensation of the ester, such a procedure might be satisfactory.

(16) *Cf.* A. Courtet, *Bull. soc. chim. de France*, [3] **35**, 356 (1905).

Reformatsky reaction is applicable to various esters, this may not be a disadvantage. Indeed, when the α,β-unsaturated acid is desired, a *t*-butyl β-hydroxy ester is particularly advantageous since this type of ester may usually be converted directly to the α,β-unsaturated acid by mineral acid (Table II). . On the other hand, the ethyl β-hydroxy esters obtained in the Reformatsky reaction have generally been first dehydrated and the resulting α,β-unsaturated ester then saponified. However, the *t*-butyl β-hydroxy esters (with the exceptions of those from the nitro ketones) are not generally converted readily to β-hydroxy acids, since they resist saponification while with mineral acids they usually undergo dehydration as well as hydrolysis of the *t*-butyl ester group.

TABLE II

α,β- (OR β,γ-) UNSATURATED ACIDS FROM *t*-BUTYL β-HYDROXY ESTERS BY ACID

t-Butyl β-hydroxy ester	Method[a]	Unsaturated acid	M.p., °C.	Yield, %
I	A[b]	β-Methylcinnamic	98–98.5[c]	68
II	A	*p*-Chloro-β-methylcinnamic	135–136[d]	64
VI	A[b]	Cinnamic	129–131	96
VII	B	β-Methylcrotonic	68–69[e]	51
VIII	C	α,β- and β,γ-unsatd. acid	Oil[f]	61
IX	A[b]	α,β- and β,γ-unsatd. acid	88–98[g]	73
X	A[b]	α,β-Dimethylcinnamic	Semi-solid[h]	89
XI	A[b]	Mixture	Oil[i]	67
XII	B	Trimethylacrylic	70–71[j]	64
XIII	A	δ-Hydroxy-δ-phenyl-2-hexenoic[k]	78–80	76

[a] The details are given in the Experimental section. [b] When method B was employed there was obtained, on pouring the sulfuric acid mixture onto ice, a white precipitate which soon become a sticky mass and resisted recrystallization. [c] Reported m.p. 97–98.8°, G. Schroeter, *Ber.*, **37**, 1093 (1904). [d] Reported m.p. 135.5°, J. V. Braun and K. Heider, *ibid.*, **49**, 1272 (1916). [e] Reported m.p. 69°, V. Curlescu, *C.A.*, **26**, 1897 (1932). [f] This oil on refluxing with 64% aqueous potassium hydroxide solution [R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1099 (1915)] gave cyclohexenyl-1-acetic acid, m.p. 36.5–37°; reported m.p. 37–38°, O. Wallach, *Ann.*, **343**, 51 (1905). [g] This melting point, obtained after several recrystallizations from water, corresponds to the mixture of α,β- and β,γ-unsaturated acids described by G. Schroeter, *Ber.*, **58**, 717 (1925), from hydrolysis and dehydration of the ethyl β-hydroxy ester. [h] Resisted attempts to solidify or recrystallize, corresponding to the α,β-dimethylcinnamic acid described by H. Rupe, H. Steiger and F. Fiedler, *ibid.*, **47**, 69 (1914). [i] Resisted attempts to solidify. [j] Reported m.p. 70–71°, W. H. Perkin, Jr., *J. Chem. Soc.*, **69**, 1479 (1896). [k] Recrystallized from 1:1 petroleum ether (30–60°): ether. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.17; H, 6.82.

Experimental[17]

The esters, ketones and aldehydes used in this study were obtained from commercial sources[18] except as designated below and purified in the usual manner.

t-Butyl acetate, *t*-butyl propionate and *t*-butyl isobutyrate were prepared from *t*-butyl alcohol and the appropriate acid chloride in the presence of dimethylaniline.[19] *t*-Butyl crotonate was prepared similarly from *t*-butyl alcohol and crotonyl chloride.

p-Nitroacetophenone was synthesized from *p*-nitrobenzoyl chloride and malonic ester.[20] *p*-Nitrocaprophenone was prepared from *p*-nitrobenzoyl chloride and α-*n*-butyl di-*t*-butylmalonate.[21] α-Tetralone was obtained by the oxidation of tetralin.[22]

β-Hydroxy Esters from Esters and Ketones or Aldehydes by Lithium Amide. (A) General Procedure.—In a 1-l. three-necked round bottomed flask, equipped with a rubber-sealed Hershberg stirrer, separatory funnel and reflux condenser (the system being protected with Drierite drying tubes), was placed 300 ml. of commercial anhydrous liquid ammonia. To the stirred liquid was added a small portion of lithium shot (Metalloy Corporation). After the practically immediate appearance of the blue color, a few crystals of ferric nitrate was added, followed by small portions of the lithium shot until a total of 1.5 g. (0.21 mole) had been added. After the blue color had been discharged and a gray suspension of lithium amide had formed (about 20 minutes), a solution of 0.2 mole of ester and 50 ml. of anhydrous ether was added dropwise over 15 minutes. The liquid ammonia was then driven off within 15–20 minutes by means of a hot water-bath, while 150 ml. of ether was being added. To the stirred black ether suspension of the lithio ester was added dropwise during 15–20 minutes, 0.2 mole of ketone in 50 ml. of ether. After stirring and refluxing for 2 hours, the reaction mixture was cooled in an ice-bath and decomposed with a mixture of 80 ml. of 3 *N* hydrochloric acid and 40 ml. of ice-water. The ether layer was washed with 1 *N* sulfuric acid, saturated sodium bicarbonate solution, and water, and combined with ether extracts of the aqueous and acidic layers. The ether solution was dried over Drierite and a little potassium carbonate and the solvent distilled. After adding a trace of magnesium oxide, the residue was distilled *in vacuo*, the β-hydroxy ester and recovered starting material being isolated. The results are summarized in Table I.

(B) Inverse Addition Procedure with Nitro Ketones.—The ether suspension of the lithio ester in about 150 ml. of ether, immediately after preparation in a 300-ml. flask, was rapidly transferred under nitrogen to a 250-ml. separatory funnel. The suspension was added during 1.5 hours[23] to the stirred solution of the nitro ketone in ether contained in a 500-ml. three-necked flask (equipped as described above) immersed in a Dry Ice–acetone-bath. After stirring for one hour longer at −70° (4 hours with *m*-nitroacetophenone), the mixture was allowed to warm to about 0° and worked up as described above. The solvent was removed from the dried ether solutions and the residue treated as described below.

The residue from the reaction of 0.077 mole of *p*-nitrocaprophenone, 0.077 mole of *t*-butyl acetate and 0.081 mole of lithium amide was distilled *in vacuo*. After recovering 11% of the original ketone, b.p. 157–159° at 1 mm., the bath temperature was raised to about 220° when a vigorous evolution of gas (presumably isobutylene) occurred and the pressure in the system dropped markedly. After the evolution of gas had ceased (about 5 minutes), the waxy solid remaining in the distilling flask was recrystallized from benzene, yielding the β-hydroxy acid.

The residue from the reaction of 0.146 mole of *p*-nitroacetophenone, 0.146 mole of *t*-butyl acetate and 0.153 mole of lithium amide was distilled *in vacuo* until 35% of the original ketone, b.p. 114–122° (1 mm.), was recovered and decomposition began (at a bath temperature of about 220°). The distillation was then stopped and the viscous residue remaining in the distilling flask was refluxed 1.5 hours with a solution of 15 ml. of concentrated hydrochloric acid and 75 ml. of dioxane. The solvent was distilled and the residue recrystallized from benzene to give the β-hydroxy acid.

The residue from the reaction of 0.15 mole of *m*-nitroacetophenone, 0.15 mole of *t*-butyl acetate and 0.157 mole of lithium amide was refluxed 1.5 hours with 30 ml. of concentrated hydrochloric acid in 150 ml. of dioxane. The solvent was distilled and the residue taken up in ether. The ether solution was extracted with several portions of saturated sodium bicarbonate solution and the combined extracts acidified with hydrochloric acid to yield the β-hydroxy acid, which was recrystallized from benzene. Distillation of the ether solution afforded 38% recovery of the original ketone, b.p. 124–127° (3 mm.).

(17) Analyses by Clark Microanalytical Laboratory, Urbana, Ill. Melting points and boiling points are uncorrected.

(18) We are indebted to Carbide and Carbon Chemicals Corp., South Charleston, West Va., for a generous sample of isopropyl acetate.

(19) C. R. Hauser, B. E. Hudson, B. Abramovitch and J. C. Shivers, *Org. Syntheses*, **24**, 19 (1944).

(20) G. A. Reynolds and C. R. Hauser, *ibid.*, **30**, 70 (1950).

(21) W. H. Puterbaugh, Jr., F. W. Swamer and C. R. Hauser, THIS JOURNAL, **74**, 3438 (1952).

(22) R. B. Thompson, *Org. Syntheses*, **20**, 94 (1940).

(23) Because the suspension tended to clog the separatory funnel stopcock, the addition was made in short spurts.

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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