

THE USE, FOR CONDENSATION REACTIONS, OF POTASSIUM HYDROXIDE IN SOLVENTS OF THE ACETAL TYPE

CH. WEIZMANN, E. BERGMANN, AND M. SULZBACHER

Received November 4, 1949

In a previous paper (1), it has been reported that the combination of potassium hydroxide with acetal gives a reagent which permits the condensation of aldehydes and ketones with chloroform in good yields. A further study of this system has revealed certain properties which make its application to other syntheses attractive. Even when used in its technical form (87% KOH), potassium hydroxide in these solvents does attack ester groups only slowly, so that it is possible to alkylate acetoacetic and malonic ester and similar esters containing reactive methylene and methine groups, without having to use alkali alkoxides in anhydrous alcohols (2). Upon addition of the esters to the potassium hydroxide-acetal system, the enolates are formed as thick, creamy precipitates. Obviously, hydrolysis of the esters will be more extensive when the less reactive halides are used. The best yields, are, therefore, obtained with benzyl and allyl chlorides or ethyl bromoacetate. Less reactive halides, *e.g.*, isobutyl bromide, give inferior yields, a phenomenon which has also been observed in comparative experiments with other condensing agents (3); however, these halides are not hydrolyzed or dehydrohalogenated by the potassium hydroxide-acetal system.

Potassium hydroxide and carbonate have been recommended occasionally, especially in the old literature (4, 5) as condensing agents in such alkylation reactions, but a repetition of some of the experiments described has shown that the method is limited to very few substances containing reactive methylene groups, and to low-molecular alkyl *iodides* only. On the other hand, the observation (6) is significant that ethyl acetoacetate can be alkylated by β -diethylaminoethyl chloride, using aqueous-alcoholic potassium hydroxide as condensing agent. The activity of the halide is so great¹ that the rate of alkylation is far greater than that of hydrolysis.

Table I, which summarizes our alkylation experiments, shows that the scope of the new reagent is somewhat wider than that of alkali alkoxides. Not only such hydrogen atoms as are activated by two neighboring C=O or C \equiv N groups are replaced by alkyl groups but also ethyl phenylacetate² and ethyl isobutyrate³

¹ No physical data bearing on this point appear to be available. The analogous β -acetoxyethyl chloride is half as reactive towards iodide ion as butyl chloride (7).

² Ethyl phenylacetate has been alkylated before in the form of its potassio-derivative (8). Of course, the corresponding nitrile (benzyl cyanide) has been known for a long time to have replaceable hydrogen atoms. Mostly, sodium amide has been used as a condensing agent (9), but also solid sodium hydroxide (10, 11, 12, 13) and sodium in liquid ammonia (14) have been employed.

³ Hudson and Hauser (15, compare 16, 17) have alkylated ethyl isobutyrate after converting it into its sodium enolate with triphenylmethyl sodium (yields with methyl iodide, ethyl iodide, and benzyl chloride were 58%, 42%, and 55%, respectively). Isobutyronitrile has been alkylated with sodium amide by Ziegler and Ohlinger (18), who have also observed reduced yields with isobutyl bromide (and cyclohexyl bromide).

TABLE I
 ALKYLATION REACTIONS WITH KOH^a IN ACETAL-TYPE SOLVENTS

SOL- VENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
A	300	Ethyl aceto- acetate, 0.5	Benzyl chloride, 0.5	80°	Ethyl benzyl- aceto- acetate ^b	61.4	156-160	(13)	
					Ethyl di- benzyl- aceto- acetate	6.8	204-210	(16) ^d	
A	150	Ethyl aceto- acetate, 0.25	Benzyl chloride, 0.5	80°	Ethyl- benzyl- aceto- acetate	15.0			
					Ethyl dibenzyl- aceto- acetate	75.2			
C	150	Ethyl aceto- acetate, 0.25	Benzyl chloride, 0.5	80°	Ethyl benzyl- aceto- acetate	14.5			
					Ethyl di- benzyl- aceto- acetate	74.8			
A	360	Ethyl benzyl- aceto- acetate, 0.5	Benzyl chloride, 0.5	80°	Ethyl di- benzyl- aceto- acetate	77.4			Ethyl ben- zylaceto- acetate, 14
B	300	Ethyl aceto- acetate, 0.5	Butyl bro- mide, 0.5	75 ^f	Ethyl butyl- aceto- acetate	37.6	112-115	(15)	Butyl bro- mide, 58.4
A	360	Ethyl butyl- aceto- acetate, 0.5	Benzyl chloride, 0.5	80 ^h	Ethyl benzyl- butyl- aceto- acetate	55.1 ⁱ	178-185	(16)	Ethyl butyl- aceto- acetate, 30.1 Benzyl chloride, 39.6
B	600	Ethyl aceto- acetate, 0.5	Isobutyl bro- mide, 0.5	75°	Ethyl iso- butyl- aceto- acetate ^j	43.0	104-107	(15)	Isobutyl bromide, 43.8
					Ethyl di- isobutyl- aceto- acetate ^k	4.1	135-140	(15)	

TABLE I—Continued

SOLVENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
B	400	Ethyl acetoacetate, 0.4	Methallyl chloride, 0.4	25	Ethyl methallyl-acetoacetate	100	114–116	(20)	
B	400	Ethyl acetoacetate, 0.2	Methallyl chloride, 0.4	25'	Ethyl dimethallyl-acetoacetate	90	151–152	(20)	
A	300	Diethyl malonate, 0.5	Benzyl chloride, 0.5	75'	Diethyl benzylmalonate	23.8	170–175	(15)	Diethyl malonate, 35.0 Benzyl chloride, 74.0
A	340	Ethyl ethoxyalacetate, ^{m, n} 0.5	Benzyl chloride, 0.5	75°	Diethyl benzylmalonate ^p	44.0	170–175	(15)	Benzyl chloride, 50.6
B	300	Ethyl cyclopentanone-2-carboxylate, 0.5	Benzyl chloride, 0.5	75', ^a	Ethyl 2-benzylcyclopentanone-2-carboxylate ^{a, r}	65.0 ^t	186–190	(14)	Keto-ester, 28.2 Benzyl chloride, 30.1
B	360	Ethyl cyclopentanone-2-carboxylate, 0.5	Isobutyl bromide, 0.5	75'	Ethyl 2-isobutylcyclopentanone-2-carboxylate ^{s, u}	34.0	138–142	(15)	Keto-ester, 46.2 Isobutyl bromide, 61.2
B	360	Ethyl cyclopentanone-2-carboxylate, 0.5	Ethyl bromoacetate, 0.5	70'	Diethyl cyclopentanone-2-carboxylate-2-acetate ^v	62.0	163–167	(15)	
B	300	Ethyl phenylacetate, 0.5	Benzyl chloride, 0.5	70'	Ethyl benzylphenylacetate ^w	30.3	212–214	(18)	Ethyl phenylacetate, 25.0 Phenylacetic acid, 41.2 Benzyl chloride, 63.2

TABLE I—Continued

SOL-VENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
C	300	Ethyl phenylacetate, 0.5	Benzyl chloride, 0.5	50 ^f	Ethyl benzylphenylacetate	37.8			Ethyl phenylacetate, 19.5 Phenylacetic acid, 36.7 Benzyl chloride, 50.6
A	300	Butyl isobutyrate, 0.5	Benzyl chloride, 0.5	80 ^f	Butyl benzylisobutyrate ^{z, v}	23.0	156-160	(18)	Butyl isobutyrate, 29.2 Isobutyric acid, 45.4 Benzyl chloride, 63.2
C	240	Butyl isobutyrate, 0.5	Benzyl chloride, 0.5	50 ^o	Butyl benzylisobutyrate	23.8			
B	300	Ethyl cyanoacetate, 0.5	Benzyl chloride, 0.5	45 ^f	Ethyl benzylcyanoacetate	30.5 ^o	165-170	(17)	Ethyl cyanoacetate, 39.6
					Ethyl dibenzylcyanoacetate ^z	14.3	225-227	(15) ^{bb}	Benzyl chloride, 39.6
B	300	Ethyl cyanoacetate, 0.25	Benzyl chloride, 0.5	45 ^p	Ethyl benzylcyanoacetate	14.8			Ethyl cyanoacetate, 35.4
					Ethyl dibenzylcyanoacetate	25.3			Benzyl chloride, 46.6
B	360	Ethyl cyclohexenylcyanoacetate, ^{dd} 0.5	Benzyl chloride, 0.5	35 ^{oo}	Ethyl benzylcyclohexenylcyanoacetate ^{oo}	53.7	223-225	(15)	Ethyl cyclohexenylcyanoacetate, 23.7 Benzyl chloride, 44.3

TABLE I—Continued

SOL-VENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
B	190	Ethyl phenyl-cyanoacetate, 0.6	Chloro-aceto-nitrile, 0.5	12 ^o	α -Phenyl- α carbe-thoxy-succino-ni-trile ^{f, g}	87.7	190-195	(12)	Ethyl phenyl-cyanoacetate ^h 18.2
B	190	Indene, 0.25	Benzyl chloride, 0.5	25 ⁱ	1-Benzyl-indene ⁱ	59.7	180-182	(17) ^l	
					1,3-Diben-zylin-dene ^k	14.4	205-210	(12)	
A	400	Ethyl acetoacetate, 0.5	β -Diethyl-amino-ethyl chloride, 0.5	25 ^t	Ethyl β -diethyl-amino-ethyl-acetoace-tate ^m	25.0	145-146	(24)	
A	400	Ethyl phenyl-acetate, 0.5	β -Diethyl-amino-ethyl chloride, 0.5	25 ^t	Ethyl β -diethyl-amino-ethyl-phenyl-acetate ⁿ	16.9	171-172	(15)	
A	400	Indene, 0.5	β -Diethyl-amino-ethyl chloride, 0.5	25 ^t	β -Diethyl-amino-ethyl-indene ^o	20.0	166	(21)	

^a Procedure: To 0.5 mole of KOH (equals 33 g. of technical potassium hydroxide) in acetal solvent was added a mixture of the first reactant and the halide at the temperature indicated. Solvents are: acetaldehydediethylacetal (A); acetaldehydedipropylacetal (B); 1-butoxy-2-ethoxyethane (C) [cf. Weizmann, *et al.*, *J. Soc. Chem. Ind. (London)*, **67**, 203 (1948)]. ^b The same result was obtained in butyraldehydedibutylacetal. ^c The temperature rose spontaneously to 90°; the reaction was completed at 70° (1 hour). ^d M.p. 56-57°. ^e The mixture was heated 2 hours at 80°. ^f The mixture was heated 3 hours at 90°. ^g The reaction started at 80°. ^h The mixture was heated 3 hours at 100°. ⁱ In acetaldehydedipropylacetal (3 hours at 100°), the yield was 65%. ^j Rohn, *Ann.*, **190**, 306 (1878) (alcohol-free enolate in benzene). Compare Freylon, *Ann. chim.* [8] **9**, 555 (1906); Rupe and Courvoisier, *Helv. Chim. Acta*, **6**, 1049 (1923). ^k Mixer, *Ber.*, **7**, 501 (1874). ^l 24 hours; then 2 hours at 50°. ^m Prepared according to Wislicenus, *Ann.*, **246**, 315 (1888); *Ber.*, **19**, 3225 (1886). Yield, 65%; b.p. 131-132°/24 mm. ⁿ Alkylations of esters of this type have been studied before. Wislicenus and Kiesewetter, *Ber.*, **31**, 194 (1898). Wislicenus and Silberstein, *Ber.*, **43**, 1825 (1910). Mebus, *Monatsh.* **26**, 485 (1905). Neuberger and Peterson, *Bio.Z.*, **67**, 39 (1914). ^o The mixture was heated 1 hour at 80°. ^p By thermal decomposition (evolution of carbon monoxide) of the ethyl benzylthoxalylacetate formed. Before distillation, the product showed the characteristic deep-red color reaction with ferric chloride. Wislicenus and Muenzenheimer, *Ber.*, **31**, 551 (1898). ^q The product did not show any color reaction with ferric chloride. ^r Calc'd for C₁₅H₁₅O₃: C, 73.2; H, 7.3. Found: C, 72.9; H, 7.5. ^s When the reaction

can be benzylated, or condensed with β -diethylaminoethyl chloride. The reaction applies to esters of other aryl- and dialkyl-acetic acids as well. Indene, too, can be benzylated and β -diethylaminoethylated with comparative ease.

The following additional observations result from an inspection of Table I. Diethyl malonate responds to the method less smoothly than ethyl acetoacetate or the alkyl-substitution products of the latter. In the time, *e.g.*, required for 24% benzylation, about half of the diethyl malonate and half of the benzyl chloride are destroyed. Similarly, while ethyl phenylacetate is benzylated to the extent of 30%, some 40% is hydrolyzed; in this case, no appreciable hydrolysis of the benzyl chloride takes place. Likewise, butyl isobutyrate is 45% hydrolyzed and 23% benzylated. It is interesting that ethyl cyanoacetate can be monoalkylated without difficulty, while the usual methods (19) give mainly the dialkylation products.

The question arose whether the Claisen condensation, too, would be catalyzed by the system potassium hydroxide-acetal. This is not the case. Ethyl acetate did not condense with acetone to acetylacetone, nor ethyl adipate to ethyl cyclopentanone-2-carboxylate, which is easily achieved by metallic sodium or sodium amide. In the latter case, practically all of the ethyl adipate was recovered unchanged, *i.e.*, unsaponified, even after prolonged heating.

On the other hand, it is possible to use the new reagent to effect the Michael

FOOTNOTES TO TABLE I—Continued

mixture was heated at 100° for six hours, the yield of benzylation product rose to 80.1%; 14.2% of the benzyl chloride and 12.8% of unreacted ester were recovered. ¹ The mixture was heated 6 hours at 90°. ² Calc'd for C₁₂H₂₀O₂: C, 67.9; H, 9.5. Found: C, 67.5; H, 9.6. ³ Koetz, *Ann.*, **350**, 235 (1906). ⁴ Meyer, *Ber.*, **21**, 1306 (1888). ⁵ This acid and its derivatives have been prepared so far only by somewhat devious routes. Haller and Bauer, *Compt. rend.* **149**, 8 (1909); **150**, 1474 (1910); *Ann. chim.*, [9], **1**, 29 (1914); [9], **9**, 20 (1918). Haller, *Compt. rend.*, **154**, 557 (1912). Stenzl and Fichter, *Helv. Chim. Acta*, **17**, 669 (1934). ⁶ Calc'd for C₁₁H₂₂O₂: C, 76.9; H, 9.4. Found: C, 76.57; H, 9.3. ⁷ Hessler, *Am.*, **22**, 176 (1899). ⁸ When the addition of the reagents was carried out at 30° and the mixture heated at 50° for two hours, the yield in mono- and dibenzylated product, respectively, was 46.2 and 23.1%; 15.8% of the benzyl chloride and 14.2% of the ethyl cyanoacetate were recovered. ⁹ Thick syrup, which crystallized upon standing, m.p. 33°. ¹⁰ The mixture was heated 1 hour at 70°. ¹¹ The butylation of ethyl cyclohexenylcyanoacetate was described by Weizmann, Sulzbacher, and Bergmann, *J. Chem. Soc.*, 772 (1947). ¹² The temperature rose spontaneously to 70°; the reaction was completed at 90° (3 hours). ¹³ The corresponding α -carbomethoxy compound has been described by Corson and Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928). ¹⁴ Calc'd for C₁₂H₁₂N₂O₂: N, 12.3. Found: N, 12.0. ¹⁵ Including the excess used. ¹⁶ The mixture was heated two hours at 85°. ¹⁷ Calc'd for C₁₁H₁₄: C, 93.2; H, 6.8; Mol. wt., 206. Found: C, 92.9; H, 7.0. Mol. wt., 218. Thiele and Buehner [*Ann.*, **347**, 263 (1906)] prepared this hydrocarbon from indene and benzyl chloride with powdered potassium hydroxide at 160° (6 hours), Weissgerber [*Ber.*, **44**, 1436, 2216 (1911)] from indene-sodium and benzyl chloride in toluene. In both cases, the yields appear inferior to those observed in the present investigation. ¹⁸ Thiele and Buehner (ref. 25). ¹⁹ From methyl alcohol, leaflets, m.p. 63°. ²⁰ Calc'd for C₁₂H₂₃NO₃: C, 62.9; H, 10.0; N, 6.1. Found: C, 62.8; H, 10.2; N, 5.9. ²¹ Calc'd for C₁₁H₂₃NO₂: C, 73.0; H, 9.5; N, 5.3. Found: C, 72.7; H, 9.5; N, 5.1. ²² Calc'd for C₁₁H₂₁N: C, 83.7; H, 10.0; N, 6.5. Found: C, 83.4; H, 10.0; N, 6.7.

condensation, *i.e.*, the addition of reactive methylene or methine groups to α,β -unsaturated aldehydes, ketones, and esters; the usual reagents in this case are sodium ethoxide and metallic sodium, or—occasionally—diethylamine (20). The results are listed in Table II. Again, the resistance of ester groups to hydrolysis under these experimental conditions is remarkable (21).

Equally, condensation of reactive methylene groups with aldehydes and ketones can be effected with the system potassium hydroxide-acetal. Examples studied are the preparation of triphenylacrylonitrile from benzophenone and benzyl cyanide (22, 23, 24) and of anisylidene-indene from indene and anisaldehyde (25); also, indene was condensed with acetone (26), benzophenone (26) and 2-ethylhexanal⁴ and fluorene with anisaldehyde (28). No secondary reactions were observed in contrast with those cases in which alcoholic alkali is used as condensing agent, and in which the corresponding cinnamylidene derivatives are frequently formed (29, 30, 31)⁵ together with the benzylidene compounds.

Not only acetals and ketals, both non-cyclic and cyclic, but also the dialkyl-ethers of ethylene glycol can be used as solvents in the reactions enumerated, without significant change in the results. Also the reaction between ketones and chloroform can be carried out satisfactorily in ethylbutyl glycol ether; however, in the case of acetone, it was not possible to separate the condensation product from the solvent by fractional distillation. On the other hand the reaction is limited to potassium hydroxide, since neither sodium hydroxide nor lithium hydroxide behave analogously. Apparently, we have here another of the rare instances in which potassium and sodium hydroxide are not equivalent, not merely sources of hydroxyl ion; the cation, too, plays a—so far obscure—role. Indeed, we suspect that potassium hydroxide forms a molecular compound with the above-defined solvents, although attempts to isolate such a molecular compound have failed.

The system potassium hydroxide-acetal presents a very characteristic and rather unusual picture. Upon addition of potassium hydroxide in the form of pellets or sticks to the well agitated solvents, the solid disintegrates rapidly; when heated at 150°, it melts to a heavy bottom layer, which upon cooling with continued agitation, solidifies to a mechanically stable, chemically reactive suspension of a finely divided microcrystalline powder. One can thus dispense with the cumbersome preparation of powdered potassium hydroxide, in any event as long as one uses a solvent with a boiling point not lower than 150°. Otherwise, the choice of the solvent will be determined by the boiling point of the starting materials and especially of the desired end product, so that the recovery of the solvent will not be complicated unduly by the reagents employed or the substances formed.

⁴ Practically no benzofulvene has been prepared so far by alkaline condensation of aliphatic aldehydes and indene; the customary method utilizes indenylmagnesium bromide. The only exception is the condensation of 1-methylindene with paraformaldehyde, effected with methanolic potassium hydroxide (Wuest, 27).

⁵ Also the substance of m.p. 176°, obtained by Sieglitz (32) from fluorene and *o*-chlorobenzaldehyde, is *o*-chlorocinnamylidene-, not *o*-chlorobenzylidene-fluorene.

TABLE II
 MICHAEL REACTIONS WITH KOH^a IN ACETALDEHYDEDIPROPYLACETAL

ACETAL, CC.	FIRST REACTANT	SECOND REACTANT	PRODUCT	YIELD		B.P., °C.	(MM.)	RECOVERED, ^b %	
				GRAMS	%			First Reactant	Second Reactant
180	Diethyl maleate	Diethyl malonate ^c	Ethyl pro- pane-1, 1, 2, 3-tetra- carboxy- late ^d	72.0	72.3	194-197	(16)	19.4	34.4
200	Benzal- aceto- phenone	Diethyl malonate ^c	Ethyl α -car- bethoxy- β -phenyl- γ -benzoyl- butyrate ^e	78.0	70.6	218-220	(2)	20.0	40.6
300	Benzal- acetone	Diethyl malonate ^c	Ethyl α -car- bethoxy- β -phenyl- γ -acetyl- butyrate ^f	77.0	83.9	205-210	(17)	13.7	30.5
180	Diethyl maleate	Ethyl aceto- acetate ^g	Triethyl α - acetyltri- carballyl- ate ^h	65.0	71.7	195-196 189	(16) (12)	21.3	31.7
180	Diethyl maleate ⁱ	Benzyl cyanide	Diethyl 3- phenyl-3- cyanopro- pane-1, 2- dicarboxy- late ^k	65.4	74.3	220-222	(14)	21.3	30.0
180	Benzal- acetone	Aceto- nitrile ^l	β -Phenyl- γ - acetyl- butyroni- trile ^{m, n}	35.0	82.3	235-236	(13)	13.7	Not re- covered
180	2-Butyl- idene butanal	Ethyl aceto- acetate	2-Ethyl-3- propyl-4- acetyl-4- carbeth- oxy-1-bu- tanal ^o	47.0	61.2	155-165 ^p	(12)		

^a Procedure: To 0.3 mole of KOH (1 mole equals 66 g. of technical potassium hydroxide) in the acetal was added 0.3 mole of the first reactant (unsaturated) and 0.4 mole of the second reactant at 20°; this was followed by heating for 1 hour at 90°. ^b The figure for the second component includes the 25% excess employed. ^c Exothermic reaction; the temperature rises to 40°. ^d Michael and Schulthess, *J. prakt. Chem.*, [2] 45, 56 (1892). ^e Compare

EXPERIMENTAL PART

Tables I and II are self-explanatory; the reaction products in each case were treated with ice-water (if necessary, neutralised) and the solvent layers separated, washed, dried, and subjected to fractional distillation.

Triphenylacrylonitrile. To the system potassium hydroxide (13 g.) and acetaldehydedi-butylacetal (250 cc.), a mixture of 25 g. of benzyl cyanide and 30 g. of benzophenone was added at 10°. The fairly exothermic reaction was completed at 50° (one hour) and the product isolated by removal of the acetal *in vacuo*. The nitrile crystallized upon trituration with alcohol and showed the expected melting point (165°) and the characteristic red-violet color reaction with concentrated sulfuric acid. Yield, 80%.

The condensation reactions of *indene* and *fluorene* with aldehydes and ketones are summarized in Table III.

Preparation of acetals (33). In the condensation of aldehydes with primary alcohols, a small amount of gaseous hydrochloric acid, dissolved in the appropriate alcohol was used as a catalyst; the components were mixed at 0° and the exothermic reaction was completed by keeping the mixture at room temperature for 24 hours.

Acetaldehydedibutylacetal, from 1 mole of acetaldehyde and 4 moles of butyl alcohol; conversion (calc'd on aldehyde) 77%, yield (calc'd on aldehyde) 84%; b.p. 184°.

Acetaldehydedipropylacetal, from 1 mole of acetaldehyde and 3 moles of propyl alcohol; conversion 88%, yield 100%; b.p. 143°.

Butyraldehydediethylacetal, from 1 mole of butyraldehyde and 4 moles of ethyl alcohol; conversion 87%, yield 80%; b.p. 143°.

Butyraldehydedipropylacetal, from 1 mole of butyraldehyde and 4 moles propyl alcohol; conversion 81%, yield 70%; b.p. 182°.

Butyraldehydedibutylacetal, from 1 mole of butyraldehyde and 4 moles of butyl alcohol; conversion 85%, yield 60%; b.p. 218°.

FOOTNOTES TO TABLE II—*Continued*

Beilstein, 10 (Suppl), 424. The product was a viscous oil, which solidified upon trituration with dilute methanol; from alcohol, m.p. 66–67°. Found: C, 71.5; H, 6.2. Calc'd for $C_{22}H_{24}O_5$: C, 71.7; H, 6.5. Hydrolysis with conc'd aqueous potassium hydroxide solution, acidification, and extraction with ether gave the acid which lost carbon dioxide at 150°. β -Phenyl- γ -benzoylbutyric acid formed needles (from alcohol), m.p. 152°. (Vorlaender and Knoetzsche, *Ann.*, **294**, 332 (1897)). ^r Found: C, 66.4; H, 7.2. Calc'd for $C_{17}H_{22}O_5$: C, 66.6; H, 7.2. The *dimethyl* ester has been described by Kohler and Allen, *J. Am. Chem. Soc.*, **45**, 1987 (1923), and by Qudrat-I-Khuda, *J. Indian Chem. Soc.*, **8**, 215 (1931) [*Chem. Zentral.*, I, 222 (1932)]. Treatment as in ^r gave β -phenyl- γ -acetylbutyric acid; from dilute alcohol, m.p. 84–85° [Vorlaender and Knoetzsche, *Ann.*, **294**, 321 (1897)]. ^s The temperature rises to 27°. ^t Ferric chloride gives a purple-red color reaction. [Fichter and Probst, *Ann.*, **372**, 73 (1910)]. Preparation: from diethyl fumarate and ethyl acetoacetate with sodium metal or sodium ethoxide: Ruhemann and Browning, *J. Chem. Soc.*, **73**, 727 (1898); Mitter and Roy, *J. Indian Chem. Soc.*, **5**, 3 (1928) [*Chem. Zentral.*, I, 2394 (1928)]. ^u The temperature rises to 50°. ^v Found: C, 66.8; H, 6.9; N, 4.9. Calc'd for $C_{16}H_{16}NO_4$: C, 66.4; H, 6.6; N, 4.9. Saponification, first with 60% sulfuric acid, then with concentrated aqueous potassium hydroxide gave the corresponding 1-phenylpropane-1,2,3-tricarboxylic acid, prisms, m.p. 196–199°. [Stobbe and Fischer, *Ann.*, **315**, 231, 245 (1901); Hecht, *Monatsh.*, **24**, 371 (1903); Wegscheider, *Ber.*, **44**, 908 (1911)]. For the reaction of benzyl cyanide and diethyl fumarate, see Henze, *Ber.*, **33**, 966 (1900). ^w The temperature rises to 40°; the reaction was completed at 75° (1 hour). ^x Saponification gave β -phenyl- γ -acetylbutyric acid. ^y A hard resin was also formed in this reaction. ^z The compound reduced ammoniacal silver nitrate solution and gave a purple-blue color with ferric chloride. *Anal.* Calc'd for $C_{14}H_{24}O_4$: C, 65.6; H, 9.4. Found: C, 65.9; H, 9.9. ^{aa} The two components cannot be separated by fractional distillation.

2-Ethylhexanaldimethylacetal, from 1 mole of 2-ethylhexanal and 6 moles of methanol; conversion 67%, yield 100%; b.p. 182-184°.

The preparation of *cyclic acetals* by azeotropic condensation has been described in a previous communication (34); the method is not applicable to the lowest-boiling representatives of the aliphatic ketones. It was, however, observed that the preparation of 2-methyl-2-ethylidioxolane from methyl ethyl ketone and ethylene glycol was much easier than literature data (35, 36, 37) would have led one to suspect. A mixture of 124 g. of glycol, 1152 g. of methyl ethyl ketone, 11.5 g. of gaseous hydrochloric acid, and 25 g. of anhydrous mag-

TABLE III
CONDENSATION REACTIONS OF INDENE AND FLUORENE WITH KOH^a IN
ACETALDEHYDE-DIPROPYLACETAL

ACETAL, CC.	HYDROCARBON, MOLE	CARBONYL COMPOUND, MOLE	PRODUCT	YIELD, %	M.P., °C.	RECOVERED, %
150	Indene, 0.2	Anisaldehyde, ^b 0.2	Anisylidene-indene	79.1	119 ^c	Indene, 10.8
150	Indene, 0.1	Benzophenone, ^b 0.1	Benzhydrylideneindene	62.6	111 ^d	Indene, 25.8 Benzo-phenone, 25.8
100	Indene, 0.2	Acetone, ^b 0.2	Isopropylideneindene	78.5	B.p. 142/ 16 mm.	Indene, 15.1
165	Indene, 0.17	2-Ethylhexanal, ^b 0.17	2-Ethylhexylideneindene ^e	66.4	B.p. 140- 145/ 12 mm.	
150	Fluorene, 0.2	Anisaldehyde, ^g 0.2	Anisylidene-fluorene ^{h, i}	85.4	132-133 ^f	Fluorene, 10.5

^a Procedure: To 0.25 mole of KOH (16.5 g. of technical potassium hydroxide) in the acetal was added a mixture of the hydrocarbon and the carbonyl compound at 20°. ^b The mixture was heated for one hour at 80°. ^c Recrystallization from alcohol or ethyl acetate. ^d Recrystallization from alcohol or isopropyl alcohol. ^e Golden-yellow oil. Calc'd for C₁₇H₂₂: C, 90.7; H, 9.3; Mol. wt., 226. Found: C, 90.0; H, 9.8; Mol. wt., 235. ^f Recrystallization from isopropyl alcohol. ^g The mixture was heated for two hours at 80°. ^h Calc'd for C₂₁H₁₆O: C, 88.7; H, 5.7. Found: C, 88.5; H, 5.9. ⁱ The condensation with sodium ethoxide gives, after 5 days, a yield of 64% [Thiele and Henle, *Ann.*, **347**, 301 (1906)].

nesium sulfate was kept at room temperature for one week; it was then neutralized with solid sodium carbonate, filtered, and subjected to fractionation; b.p. 115°. Conversion 95%, yield, 100%.

Alkylation with solid potassium hydroxide and alkyl iodide. Some of Michael's experiments (4) were repeated, for the sake of comparison with the method described in the present paper:

(a) *Ethylation of ethyl acetoacetate.* When 17 g. of finely powdered caustic potash (0.3 mole of KOH) was gradually added to the well agitated mixture of 39 g. (0.3 mole) of ethyl

acetoacetate and 47 g. (0.3 mole) of ethyl iodide, only a slight rise in temperature was observed. The mixture was warmed at 60° during one hour, cold water was added, and the organic layer separated, dried, and fractionated. The yield of ethyl monoethylacetoacetate, b.p. 198–200°, was 25 g. (52.7%). Michael obtained a 64.2% yield.

(b) *Methylation of diethyl malonate.* The addition of 17.0 g. of finely powdered potash (0.3 mole of KOH) to the mixture of 48 g. (0.3 mole) of diethyl malonate and 43 g. (0.3 mole) of methyl iodide caused an exothermic reaction. When it subsided, the product was worked up as above. There was isolated 32 g. (61.3%) of diethyl monoethylmalonate, b.p. 199–201° (Michael, 82.9%).

(c) Attempts to *ethylate ethyl monoethylacetoacetate* by means of powdered potassium hydroxide and ethyl iodide failed completely.

SUMMARY

The combination of potassium hydroxide with solvents of the acetal and ethylene glycol dialkylether type affords a system which can be used (a) for the alkylation of compounds containing a reactive methylene or methine group, (b) the Michael condensation, and (c) the condensation of reactive methylene groups with aldehydes and ketones, in addition to (d) the condensation of chloroform with aldehydes and ketones, reported previously. The system does not bring about the Claisen condensation. The influence of the reactivity of the components on the scope of these reactions has been studied. There are reported 26 examples of type (a), 7 of type (b), and 6 of type (c).

REHOVOTH, ISRAEL
LONDON, S.W. 1, ENGLAND

REFERENCES

- (1) WEIZMANN, BERGMANN, AND SULZBACHER, *J. Am. Chem. Soc.*, **70**, 1189 (1948).
- (2) WEIZMANN, British Patent 582191 [*Chem. Abstr.*, **41**, 2436 (1947)]; U. S. Patent 2,474,175 (1949).
- (3) RENFROW, *J. Am. Chem. Soc.*, **66**, 144 (1944).
- (4) MICHAEL, *Ber.*, **38**, 2087, footnote (1905); *J. prakt. Chem.* [2], **72**, 538 (1905).
- (5) TASSILLY, *et al.*, *Compt. rend.*, **186**, 1846 (1928).
- (6) L. HASKELBERG, private communication.
- (7) CONANT, KIRNER, AND HUSSEY, *J. Am. Chem. Soc.*, **47**, 488 (1925).
- (8) SCHEIBLER, MARHENKEL, AND BASSANOFF, *Ber.*, **58**, 1198 (1925); SCHEIBLER, EMDEN, AND KRABBE, *Ber.*, **63**, 1562 (1930).
- (9) BODROUX AND TABOURY, *Compt. rend.*, **150**, 531, 1242 (1910); *Bull. soc. chim. France* [4] **7**, 666, 732 (1910).
- (10) MEYER, *Ann.*, **250**, 123 (1889).
- (11) MEYER AND JANSSEN, *Ann.*, **250**, 128, 129 (1889).
- (12) MEYER, *Ber.*, **21**, 1306 (1888).
- (13) PFEIFFER, ENGELHARDT, AND ALFUSS, *Ann.*, **467**, 158 (1928).
- (14) NIEUWLAND AND BALDINGER, *J. Am. Chem. Soc.*, **54**, 828 (1932).
- (15) HUDSON AND HAUSER, *J. Am. Chem. Soc.*, **62**, 2457 (1940).
- (16) HAUSER AND ABRAMOVITCH, *J. Am. Chem. Soc.*, **62**, 1763 (1940).
- (17) HAUSER AND RENFROW, *J. Am. Chem. Soc.*, **59**, 1823 (1937).
- (18) ZIEGLER AND OHLINGER, *Ann.*, **495**, 84 (1932).
- (19) *Biel.* **2** Suppl. 254; **2** Second Suppl. 532.
- (20) KNOEVENAGEL AND SPEYER, *Ber.*, **35**, 395 (1902).
- (21) WEIZMANN, British Patent 594,182 [*Chem. Abstr.*, **42**, 2986 (1948)]; U. S. Patent 2,472,135.

- (22) HEYL AND MEYER, *Ber.*, **23**, 2776 (1895).
- (23) BODROUX, *Bull. Soc. Chim. France*, [4] **9**, 758 (1911).
- (24) BUU-HOI, *et al.*, *J. Chem. Soc.*, 641 (1947); *Bull. soc. chim. France*, 816 (1947).
- (25) THIELE AND BUEHNER, *Ann.*, **347**, 256 (1906).
- (26) THIELE AND MERCK, *Ann.*, **415**, 257 (1918).
- (27) WUEST, *Ann.*, **415**, 291 (1918).
- (28) THIELE AND HENLE, *Ann.*, **347**, 290 (1906).
- (29) SCHLENK AND BERGMANN, *Ann.*, **479**, 56 (1930).
- (30) BERGMANN, *Ber.*, **63**, 1617, 2598 (1930).
- (31) KLIEGL, *Ber.*, **63**, 1262, 1631 (1930).
- (32) SIEGLITZ, *Ber.*, **52**, 1513 (1919).
- (33) ADKINS, *et al.*, *J. Am. Chem. Soc.*, **55**, 299 (1933); **56**, 442 (1934).
- (34) SULZBACHER, BERGMANN, AND PARISER, *J. Am. Chem. Soc.*, **70**, 2827 (1948).
- (35) DWORZAK AND HERRMANN, *Monatsh.*, **52**, 83 (1929).
- (36) PETROV, *Chem. Abstr.* **35**, 3603 (1941).
- (37) SALMI AND RANNIKKO, *Ber.*, **72**, 600 (1939).