2-*n*-pentanoyl-α-naphthol, 2-isopentanoyl-α-naphthol and 2-*n*-caproyl-α-naphthol, respectively.

2. 2-*n*-Pentyl-α-naphthol, 2-isopentyl-α-naphthol and 2-*n*-hexyl-α-naphthol are obtained in each case by reduction of 2-*n*-pentanoyl-α-naphthol, 2-isopentanoyl-α-naphthol and 2-*n*-caproyl-α-naphthol according to Clemmensen's method.

3. The bacteriological properties of these new naphthols are now under investigation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations. XVI. Various Acylations and Alkylations of the Sodium Enolates of Aliphatic Esters. Methods for the Syntheses of α,α-Disubstituted β-Keto Esters and of Certain Other Compounds[1]

BY BOYD E. HUDSON, JR., AND CHARLES R. HAUSER

The classical acetoacetic ester condensation of esters probably involves the acylation of the sodium enolate[2] of the ester; in the presence of sodium ethoxide a small portion of the ester is first converted into its sodium enolate which is then acylated by molecules of unchanged ester.[3] The scope of reactions of the sodium enolates of esters, however, was considerably limited until a base was found which would convert esters largely into their sodium enolates. In 1931 Schlenk, Hillemann and Rodloff[4] showed that sodium triphenylmethyl converts methyl diphenylacetate largely into its sodium enolate which could be acylated with acid chlorides or alkylated with alkyl halides. Since that time sodium triphenylmethyl has been used (mainly in this Laboratory) to effect certain acylations and alkylations of purely aliphatic esters. The present paper is a report of a more complete study of these types of reaction in which their preparative value is further demonstrated. Because of the increasing importance of sodium triphenylmethyl as a condensing agent a procedure is described for its preparation in approximately molar quantities. Also, the synthesis of a high grade of triphenylchloromethane (from which sodium triphenylmethyl is prepared) in kilogram quantities is described.

Preparation of Triphenylchloromethane.—The following procedure is a modification of the basic method of Gomberg[5] and employs a controlled hydrolysis of the reaction mixture making the use of large quantities of acetyl chloride unnecessary.[6]

A mixture of 2000 g. (2280 cc.) of dry thiophene-free benzene and 800 g. (500 cc.) of dry sulfur-free carbon tetrachloride was placed in a 5-liter three-necked flask equipped with a mercury-sealed mechanical stirrer and a reflux condenser, the latter being connected to a trap for the absorption of hydrogen chloride. The third neck of the flask was connected, by means of short pieces of 15-mm. glass and rubber tubing, to a 1-liter Erlenmeyer flask containing 600 g. (4.51 moles) of fresh resublimed aluminum chloride. The reaction flask (containing the benzene and carbon tetrachloride) was immersed in an ice-bath. The aluminum chloride was added to the reaction flask during a period of one and one-half to two hours, the reaction mixture not being allowed to reflux during the addition. Fifteen minutes after the addition of the aluminum chloride was complete, the reaction mixture was removed from the ice-bath. When spontaneous reaction ceased, the mixture was boiled until the evolution of hydrogen chloride subsided. The cooled product was then added to a vigorously stirred mixture of 1 liter of thiophene-free benzene and 2 liters of 6 *M* hydrochloric acid contained in a copper can (22.5 cm. diameter by 30 cm. deep) immersed two-thirds its depth in an ice-bath to maintain a reaction temperature not exceeding 25°. Stirring was continued for ten minutes longer. The benzene solution was decanted, 1 liter of ice-water was added to the aqueous layer and the diluted product extracted with one-half liter of benzene. The combined benzene solutions were washed with 250 cc. of concentrated hydrochloric acid and dried with calcium chloride. Solvent was distilled from the dried solution until the temperature of the residual solution reached 120°. The residue was then transferred to a 2-liter Erlenmeyer flask, cooled to about 40°, 25 cc. of acetyl chloride added and the mixture heated nearly to boiling. The solution was then cooled rapidly to room temperature, the crystallized triphenylchloromethane was crushed thoroughly and collected on a suction filter. The crystals were washed with two 300-cc. portions of ligroin (b. p. 70–90°) and dried *in vacuo* over mineral oil or paraffin; yield, 938 g.; m. p. 112–113° cor.; color, very light greenish-yellow. Concentration of the filtrate (solution temperature up to 110°) and

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[1] This paper has been constructed from portions of a Thesis presented by Boyd E. Hudson, Jr., in partial fulfillment of the requirements for the Ph.D. degree at Duke University.

[2] The sodium enolate of an ester is a salt, the anion of which is a resonance hybrid of keto and enol forms.

[3] (a) See Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); (b) Hauser, *ibid.*, **60**, 1957 (1938).

[4] Schlenk, Hillemann and Rodloff, *Ann.*, **487**, 135 (1931).

[5] Gomberg, *Ber.*, **33**, 3144 (1900).

[6] See Reynolds and Evans, THIS JOURNAL, **60**, 2559 (1938).

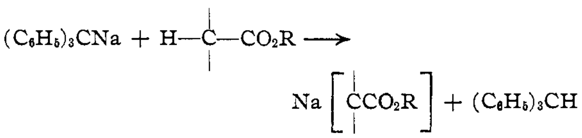
the ligroin extracts (temp. up to 100°) yielded, respectively, 73 g. (m. p. 111–112°, sintering at 108°) and 51 g. (m. p. 111–112°, sintering at 107°) of triphenylchloromethane, somewhat more colored than the main product.

Preparation of Sodium Triphenylmethyl.—In most experiments, sodium triphenylmethyl was prepared essentially as described in Organic Syntheses,[7] but using 950 g. (22% excess) of 1.5% semi-solid amalgam, 70 g. (0.25 mole) of triphenylchloromethane and 1.5 l. of ether. The amalgam was prepared by melting 14 g. (0.61 atom) of sodium under mineral oil, rapidly adding 935 g. of mercury from a separatory funnel (the stem passed through a cardboard shield for protection of the operator) and shaking the mixture until the amalgam was liquid. When the amalgam began to crystallize (about 80°) the flask was cooled with cold water, the mineral oil was decanted and the amalgam washed with benzene or ligroin.

For convenience, the delivery tube of the pressure siphon (maximum pressure of nitrogen, 100 mm.) used in transferring the ether solution of sodium triphenylmethyl (after the solids have settled) was fitted with a stopcock and the receiver (a 2-liter Erlenmeyer flask) was graduated in divisions of 100 cc. The solutions were analyzed as described previously[7] and the quantity of base transferred (approx. 1.4 l. of solution) was usually 0.20–0.21 mole.

In two experiments, much more concentrated solutions of sodium triphenylmethyl were prepared with 3% amalgam, which was prepared as described above from 51 g. of sodium and 1649 g. of mercury. The amalgam (cut into pieces about 1 cm. on each edge and washed with benzene or ligroin), 278 g. (1 mole) of triphenylchloromethane (m. p. 112–113°) and 1.5 l. of dry ether contained in a 2-liter Pyrex bottle (with a ground-glass stopper) were shaken mechanically. Agitation (stopped if the reaction temperature exceeded 40–50°) was continued until no solid amalgam remained and then for two hours longer (volume of final solution, 1712 cc.). After deposition of the suspended solids, the solution was analyzed,[7] a 10-cc. aliquot being withdrawn and diluted with 25 cc. of ether before extraction and titration. These preparations contained 0.85–0.93 mole of the sodium triphenylmethyl. Without separation of the solids, these concentrated solutions of sodium triphenylmethyl were used in acylations of ethyl isobutyrate with acid chlorides.

The General Method of Preparation and Reaction of the Sodium Enolates of Esters.—The sodium enolates were prepared simply by mixing equivalent amounts of the ester and sodium triphenylmethyl in ether solution, the formation of the enolate being indicated by the fading or disappearance of the characteristic deep red color of the sodium triphenylmethyl.[8]

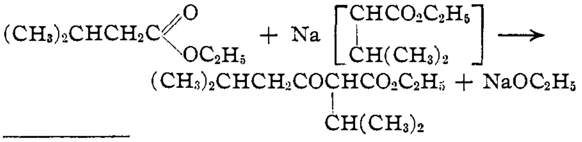


$$(C_6H_5)_3CNa + H{-}\overset{|}{\underset{|}{C}}{-}CO_2R \longrightarrow Na\left[\overset{|}{\underset{|}{C}}CO_2R\right] + (C_6H_5)_3CH$$

The rate of this acid-base reaction varies greatly with different esters. For example, with ethyl acetate the color disappears completely almost immediately even when the reaction is carried out at 0°, but with ethyl isobutyrate the color changes to light red only after a few minutes at room temperatures, while with ethyl diethylacetate there is no noticeable decrease in depth of color until after a few hours.

The acylation of the sodium enolate (which usually is not isolated) with the original ester, that is, self-condensation, is effected generally at room temperature, an excess of the ester sometimes being used to increase the rapidity of the condensation. To minimize self-condensation in other acylations, and in alkylations, an excess of the ester is avoided and reaction of the sodium enolate with the selected reagent is effected as soon as the deep red color of the sodium triphenylmethyl has disappeared or has become a much lighter red.

The Self-condensation of Ethyl Isovalerate.—Although most esters having two hydrogens on the α-carbon atom undergo self-condensation in the presence of sodium ethoxide, Roberts and McElvain[9] found that two such esters, ethyl isovalerate and ethyl *t*-butylacetate fail to condense. Recently, it was shown that ethyl isobutyrate, which has only one α-hydrogen and fails to undergo self-condensation in the presence of sodium ethoxide, is converted to ethyl isobutyrylisobutyrate by sodium triphenylmethyl[3a] and in this investigation it is shown that ethyl isovalerate similarly undergoes self-condensation when treated with this stronger base, giving a good yield (63%) of ethyl isovalerylisovalerate. The acylation of the sodium enolate of ethyl isovalerate by molecules of unchanged ester may be represented as follows



$$(CH_3)_2CHCH_2C\left\langle\begin{matrix}O\\OC_2H_5\end{matrix}\right. + Na\begin{bmatrix}CHCO_2C_2H_5\\|\\CH(CH_3)_2\end{bmatrix} \longrightarrow (CH_3)_2CHCH_2CO\underset{\underset{\displaystyle CH(CH_3)_2}{|}}{C}HCO_2C_2H_5 + NaOC_2H_5$$

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(7) Renfrow and Hauser, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83.

(8) Thus far sodium triphenylmethyl is the only base that has been found to be generally satisfactory for the preparation of the sodium enolates of purely aliphatic esters. Scheibler and co-workers [*Ber.*, **53**, 388 (1920); **58**, 1189, 1198 (1925)] reported that the sodium or potassium enolates of esters may be prepared by means of metallic sodium or potassium but there is little doubt that the metals are unsatisfactory for this purpose.[4] In the present investigation an attempt was made to prepare and benzoylate the magnesium enolate of ethyl isobutyrate by means of mesitylmagnesium bromide and benzoyl chloride; the ester was added to an ether solution of the Grignard reagent and, after several minutes, the benzoyl chloride was added but none of the benzoylated ester, ethyl benzoyldimethylacetate, could be isolated from the reaction mixture.

(9) Roberts and McElvain, THIS JOURNAL, **59**, 2007 (1937).

Ethyl isovalerate (27.5 g., 0.21 mole, b. p. 134–135°) was added to a solution of 0.21 mole of sodium triphenylmethyl in 1.4 liters of ether contained in a 2-liter Erlenmeyer flask and, after sixty hours at room temperature, 15 cc. of glacial acetic acid was added. The mixture was extracted with 100 cc. of water, the ether solution was washed with 10% sodium carbonate solution until free from acid and solvent was distilled from the dried solution. The residue was distilled *in vacuo* (b. p. up to 170° at 15 mm.). The distillate upon fractionation with a 6-inch Widmer column, gave 13.3 g. (63%) of ethyl α-isovalerylisovalerate, b. p. 118–119° at 15 mm. (133–134° at 32 mm.); Spielman and Schmidt[10] report 128–133° at 32 mm.).

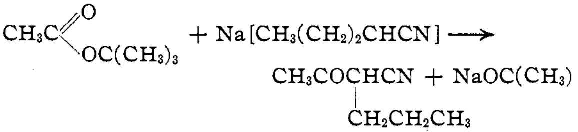
Spielman and Schmidt[10] have shown that ethyl isovalerate undergoes self-condensation in the presence of mesitylmagnesium bromide, but sodium triphenylmethyl gives a better yield and apparently a purer product than this Grignard reagent. It seems likely that ethyl *t*-butylacetate, which has been self-condensed by means of mesitylmagnesium bromide,[10] could also be self-condensed by means of sodium triphenylmethyl.

The Acylation of the Sodium Enolates of Esters with Other Esters.—The acylation of the sodium enolate of an ester by a different ester appears to be satisfactory only when the latter has no active hydrogen. Presumably the sodium enolate attacks an available active hydrogen of the second ester more readily than the carbonyl group to give a mixture of two enolates and two free esters from which four β-keto esters might be formed. Thus, although *t*-butyl acetate undergoes self-condensation relatively slowly,[11] when the sodium enolate of this ester was treated with either ethyl *n*-butyrate or ethyl isobutyrate, a mixture of β-keto esters was obtained.

t-Butyl acetate (23.2 g., 0.20 mole, b. p. 97.0–97.5°) was added with shaking to a solution of 0.20 mole of sodium triphenylmethyl; the color of the base was discharged almost immediately. After twenty seconds, 11.6 g. (0.10 mole) of ethyl *n*-butyrate was added with shaking. After five minutes, the mixture was acidified and fractionation of the product gave 10 g. of material, b. p. 79–101° at 15 mm. (apparently a mixture of β-keto esters), which was not identified. Acidification of the mixture after a reaction period of one-half hour gave similar results and with ethyl isobutyrate no better results were obtained.

Similarly the sodium enolate of *t*-butyl acetate and *n*-valeronitrile gave, as the main product, α-acetyl-*n*-valeronitrile, resulting presumably, from a hydrogen exchange followed by the condensation of the sodium enolate of the nitrile with *t*-butyl acetate, thus

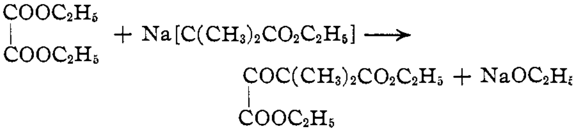
$$CH_3(CH_2)_2CH_2CN + Na[CH_2CO_2C(CH_3)_3] \longrightarrow Na[CH_3(CH_2)_2CHCN] + CH_3CO_2C(CH_3)_3$$



$$CH_3C\begin{array}{l}\diagup O\\ \diagdown OC(CH_3)_3\end{array} + Na[CH_3(CH_2)_2CHCN] \longrightarrow \begin{array}{l}CH_3COCHCN\\ \quad\quad\;|\\ \quad\quad CH_2CH_2CH_3\end{array} + NaOC(CH_3)$$

t-Butyl acetate (23.2 g., 0.20 mole, b. p. 97.0–97.5°) was added to a solution of 0.20 mole of sodium triphenylmethyl and, after thirty seconds, 16.6 g. (0.20 mole) of *n*-valeronitrile was added. After one hour, the mixture was acidified. Fractionation of the product gave 6 g. of recovered *t*-butyl acetate, 8 g. of recovered *n*-valeronitrile and 6.3 g. (25%) of α-acetyl-*n*-valeronitrile, b. p. 96–97° at 15 mm.[12]; phenylhydrazone, m. p. 63–64°[12]; semicarbazone, m. p. 170°.[12]

With ethyl oxalate, the sodium enolate of ethyl isobutyrate gave ethyl α-ethoxalylisobutyrate in a yield of 61%, but with ethyl formate only a 16% yield of ethyl α-formylisobutyrate was obtained.



$$\begin{array}{l}COOC_2H_5\\ |\\ COOC_2H_5\end{array} + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow \begin{array}{l}COC(CH_3)_2CO_2C_2H_5\\ |\\ COOC_2H_5\end{array} + NaOC_2H_5$$

$$HCOOC_2H_5 + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow HCOC(CH_3)_2CO_2C_2H_5 + NaOC_2H_5$$

Ethyl isobutyrate (23.8 g., 0.205 mole) was added with shaking to a solution of 0.205 mole of sodium triphenylmethyl in 1.4 liters of ether. After five minutes at room temperature, 30 g. (0.205 mole) of ethyl oxalate was added with shaking. The reaction was vigorous and the mixture became warm. After ten minutes, 15 cc. of glacial acetic acid was added and the mixture extracted with 100 cc. of water. The ether solution was washed with saturated sodium bicarbonate solution, dried with sodium sulfate followed by "Drierite" and the solvent distilled. The residue was distilled *in vacuo* (b. p. up to 200° at 50 mm.) The distillate upon fractionation with a Widmer column gave 27.2 g. (61%) of ethyl α-ethoxalylisobutyrate, b. p. 122–123° at 15 mm.[13,14]; the semicarbazone melted at 97°.[13]

The sodium enolate of ethyl isobutyrate, prepared from 24.0 g. (0.207 mole) of the ester and 0.207 mole of sodium triphenylmethyl, was treated with 15.4 g. (0.207 mole) of ethyl formate (b. p. 54–55°). After one-half hour the mixture was acidified and the solvent distilled from the dried ether solution. The residue was distilled up to 180° at 50 mm. The distillate on fractionation at atmospheric pressure gave 9 g. of recovered ethyl isobutyrate and 4.7 g

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[10] Spielman and Schmidt, This Journal, 59, 2009 (1937).

[11] In the presence of sodium triphenylmethyl, *t*-butyl acetate undergoes self-condensation much more slowly than ethyl acetate or ethyl propionate and even somewhat more slowly than ethyl isobutyrate.

[12] Mohr, *J. prakt. Chem.*, **90**, 208, 210, 247 (1914).

[13] Rassow and Bauer, *Ber.*, **41**, 964 (1908); *J. prakt. Chem.*, **80** 95 (1909). Boiling point reported for ethyl α-ethoxalylisobutyrate 115–120° at 11 mm.

[14] Wislicenus and Keisewetter, *Ber.*, **31**, 197 (1898). Boilin point reported for ethyl α-ethoxalylisobutyrate, 130–136° at 20–2 mm.

TABLE I

SUMMARY OF RESULTS OF EXPERIMENTS WITH $Na[CR_2CO_2C_2H_5]$ AND RCOCl

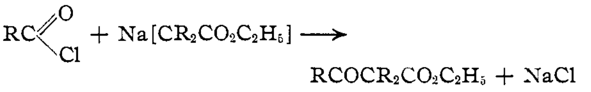
Ester used, ethyl			$(C_6H_5)_3CNa$,	Acid chloride used			Yield of keto ester		B. p.	
	G.	Mole	Mole		G.	Mole	G.	%	°C.	Mm.
Isobutyrate	23	0.198	0.195	Acetyl	32	0.408	15.7	51[a]	75– 76 183–184	15 760[b]
Isobutyrate	22	.190	.185	*n*-Butyryl	21.5	.20	20.2	58	109–111	29[c]
Isobutyrate	110	.95	.93[d]	Isobutyryl	102	.95	128	74[d]	92– 94	15
Isobutyrate	102	.875	.85[d]	Benzoyl	123	.875	122	65[d]	146–148	15
Methylethyl-acetate	26	.20	.20	Propionyl	18.5	.20	19.3	52	97–102 Mainly at	15 98–100[f]
Me-Et-acetate	26	.20	.20	Isovaleryl	24.6	.20	21.7	51[g]	116–119	15
Me-Et-acetate[e]	25.6	.197	.197	Benzoyl	27.7	.197	24.0	52	164	18[h]
Diethylacetate[i]	28	.20	.195	Benzoyl	28	.20	28.8	59	175–177	20[h]

[a] The keto ester gave a semicarbazone melting at 119° after crystallization from ligroin (b. p. 90–120°); the m. p. was the same after crystallization from water. *Anal.* Calcd. for $C_9H_{17}O_3N_3$: N, 19.6. Found: N, 19.8. A semicarbazone prepared apparently from a mixture of mono- and dimethylacetoacetic ester has been reported to melt at 183–187° [Michael, THIS JOURNAL, **41**, 423 (1919)]. [b] Perkin, *J. Chem. Soc.*, **65**, 827 (1894). [c] Blaise, *Compt. rend.*, **132**, 479 (1901). [d] Carried out previously on approximately 0.2 mole scale, the yields being 10–20% lower ("Org. Syn.," Vol. XIX, 1939, p. 43). [e] Methylethylacetyl chloride was prepared in 82% yield from methylethylacetic acid and benzoyl chloride [see Brown, THIS JOURNAL, **60**, 1325 (1938)]. The acid chloride was esterified in the usual manner with ethanol and yielded (80%) the ethyl ester, b. p. 132°. [f] Dieckmann and Kron, *Ber.*, **41**, 1269 (1908). [g] *Anal.* Calcd. for $C_{12}H_{22}O_3$: C, 67.2; H, 10.4. Found: C, 67.5; H, 10.4. [h] Hope and Perkin, *J. Chem. Soc.*, **95**, 2042 (1909). [i] Diethylacetic acid was converted to the acid chloride which was esterified in the usual manner with ethanol and yielded the ethyl ester, b. p. 151–153° (over-all yield 60%).

(16%) of ethyl α-formylisobutyrate, b. p. 165–168°[15]; the semicarbazone melted at 163–164°.[15]

This direct method of preparation of ethyl α-ethoxalylisobutyrate is considered superior to those described previously involving the methylation of ethyl α-ethoxalylpropionate[14] and the reaction of ethyl α-bromoisobutyrate with ethyl oxalate in the presence of magnesium.[13] Although the yield of the formyl ester was low, the direct method of preparation is more convenient than the previously described method involving the oxidation of ethyl β-hydroxypivalate.[15]

The Acylation of the Sodium Enolates of Esters with Acid Chlorides.[16]—The acylation of the sodium enolates of ethyl isobutyrate, ethyl methylethylacetate and ethyl diethylacetate with acid chlorides gave the corresponding α,α-disubstituted β-keto esters; the general reaction may be represented as follows



$$RC\overset{O}{\underset{Cl}{\lessgtr}} + Na[CR_2CO_2C_2H_5] \longrightarrow RCOCR_2CO_2C_2H_5 + NaCl$$

In reactions using approximately 0.2 mole of reactants, the ester was added with shaking to the ether solution of sodium triphenylmethyl at room temperature. After the color of the solution had become a much lighter red (three to ten minutes with ethyl isobutyrate or ethyl methylethylacetate and four and one-half hours with ethyl diethylacetate), the acid chloride was added with shaking. The reaction was vigorous and the mixture boiled gently. After the mixture had cooled to room temperature, it was extracted with 100 cc. of water. The ether solution was washed with 10% sodium carbonate solution until carbon dioxide ceased to be evolved, dried with sodium sulfate followed by "Drierite" and the solvent distilled from a water-bath. On cooling, the residue precipitated triphenylmethane (in certain cases the triphenylmethane was precipitated by shaking the warm residue with absolute alcohol). The liquid was decanted or the precipitate was filtered off (the crystals being washed with ether) and the liquid distilled *in vacuo* (b. p. generally up to 175–185° at 15 mm.). The distillate upon fractionation with a 6-inch Widmer column gave the β-keto ester.

In reactions using approximately 0.9 mole of reactants, the sodium triphenylmethyl solution (contained in the bottle in which it was prepared) was chilled in an ice-bath. The stopper was removed in an atmosphere of nitrogen and the bottle quickly fitted with a mechanical stirrer, dropping funnel and a tube delivering dry nitrogen into the mouth of the bottle. The ester was added rapidly to the vigorously stirred contents of the bottle and, after five to ten minutes, the acid chloride was added during five minutes. Stirring was continued five minutes longer and, after standing thirty minutes, the reaction mixture was transferred to a 2.5 liter separatory funnel and the mercury drained off. The mixture was extracted with water and the ether solution washed with sodium carbonate solution, dried and distilled as described above.

The results of the experiments are summarized in Table I. In view of the satisfactory yields (51–74%) obtained in these acylations, this direct synthesis of the α,α-disubstituted β-keto esters is undoubtedly the best method of preparation of many of the compounds. It is not only more conveniently carried out than the method of

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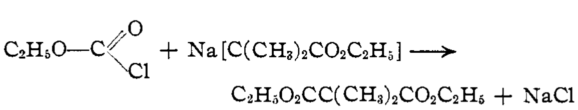
(15) Blaise and Marcilly, *Bull. soc. chim.*, [3] **31**, 160 (1904).

(16) Microanalyses by Saul Gottlieb, Columbia University, New York, N. Y.

di-alkylation of unsubstituted β-keto esters of the type $RCOCH_2CO_2C_2H_5$, but with the exceptions of ethyl acetoacetate and ethyl benzoylacetate, these unsubstituted β-keto esters are not generally available. Moreover, in certain cases, complete alkylation is difficult to effect[17] and it is difficult to obtain the di-alkylated product entirely free from the mono-alkylated derivative. Our method, on the other hand, gives products free from mono-alkylated derivatives.

The acylation of the sodium enolate of ethyl isobutyrate with ethyl chlorocarbonate gave diethyl dimethylmalonate in a yield of 75%.



$$C_2H_5O{-}C\langle{}^{O}_{Cl} + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow C_2H_5O_2CC(CH_3)_2CO_2C_2H_5 + NaCl$$

The sodium enolate of ethyl isobutyrate (prepared from 23 g. of the ester and 0.198 mole of sodium triphenylmethyl) treated with 23 g. of ethyl chlorocarbonate gave 27.8 g. (75%) of diethyl dimethylmalonate, b. p. 88° at 15 mm. (b. p. 195–196° at 760 mm.);[18] the amide prepared from the di-ester and concentrated ammonia, melted at 267–268°.[19]

Unfortunately, the acylation of the sodium enolate of ethyl acetate with acid chlorides does not stop with mono-acylation, but gives mainly the di-acylated acetate. Thus, when the sodium enolate of ethyl acetate was treated with an equivalent of *n*-butyryl chloride, no appreciable amount of the mono-acylated ester, ethyl *n*-butyrylacetate, could be isolated but, instead, the di-acylated ester, ethyl dibutyrylacetate, was obtained in 49% yield. Presumably, ethyl *n*-butyrylacetate was first formed, but in the presence of the sodium enolate of ethyl acetate (or of sodium triphenylmethyl) this β-keto ester was converted into its sodium enolate which was then acylated by the acid chloride. Addition of the sodium enolate of ethyl acetate to a large excess of propionyl chloride at 0° gave a 15% yield of the mono-acylated compound, ethyl propionylacetate, but in this experiment[20] also the main product (39% yield) was the di-acylated compound, ethyl di-propionylacetate. Treatment of the sodium enolate of ethyl isovalerate with an equivalent of ethyl chlorocarbonate gave a 13% yield of the mono-acylated ester, diethyl isopropylmalonate, but again the yield (29%) of the di-acylated product, triethyl 2-methyl-propanetricarboxylate-1,1,1, exceeded that of the mono-derivative.

A solution of 0.216 mole of sodium triphenylmethyl was cooled to approximately 0°, the stopper removed and a stream of dry nitrogen led into the mouth of the flask. The solution was stirred vigorously with a mechanical stirrer and 19 g. (0.216 mole) of ethyl acetate (boiling range, 0.1°) was added, the color of the sodium triphenylmethyl disappearing almost immediately. After 30 seconds, 26.7 g. (0.216 mole) of *n*-butyryl chloride was added rapidly and the stirring continued for three minutes. After standing for one hour at room temperature the mixture was extracted with water, the ether solution dried and the solvent distilled. The residue was distilled *in vacuo* (b. p. up to 165° at 4 mm.) and upon fractionation the distillate gave 12.1 g. (49%) of ethyl dibutyrylacetate, b. p. 117–122° (mostly at 120–121°) at 4 mm. (after five months, b. p. 141–145° at 24 mm.).[21] The copper enolate changed from lavender to gray-green at 88–90° and melted to a dark green liquid at 98–99°.[21]

A solution of 0.16 mole of sodium triphenylmethyl was cooled to 0° and, in an atmosphere of dry nitrogen, 14.1 g. (0.16 mole) of ethyl acetate was added. The solution was immediately shaken and poured into a cold solution of 150 g. (1.6 mole) of propionyl chloride in 200 cc. of dry ether. After shaking vigorously for several minutes, the mixture was poured with stirring into excess of a cold saturated solution of sodium carbonate. After the evolution of carbon dioxide ceased, the ether solution was dried and the solvent distilled. The cooled residue precipitated triphenylmethane which was filtered off. The filtrate upon fractionation with a 15-cm. Vigreux column gave 1.7 g. of ethyl acetoacetate (b. p. 65–73° at 9 mm.; m. p. of phenylpyrazolone, 127°), 3.6 g. (15%) of ethyl propionylacetate (b. p. 73–76° at 9 mm.; m. p. and mixed m. p. of phenylpyrazolone, 100°[22]), and 6.2 g. (39%) of ethyl dipropionylacetate (b. p. 98–102° at 9 mm.).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.05. Found: C, 59.3; H, 7.90.

Treatment of the dipropionylacetate with dry ammonia gave a 50% yield of ethyl propionylacetate (b. p. 90–92° at 17 mm.[23]; m. p. of phenylpyrazolone, 100°).[22]

Ethyl isovalerate (25.7 g., 0.198 mole) was added to a solution of 0.198 mole of sodium triphenylmethyl and, after five minutes, 21.5 g. (0.198 mole) of ethyl chlorocarbonate was added. The mixture was extracted with water, the ether solution was washed with sodium carbonate, dried and the solvent distilled. The residue was distilled *in vacuo* (up to 165° at 15 mm.). The distillate upon fractionation gave 10 g. of ethyl isovalerate (b. p. 130–134° at 760 mm.), 5.15 g. (13%) of diethyl isopropylmalonate (b. p. 98–108° at 15 mm.; 212–215° at 760 mm.)[24] and 8.70 g. (29%) of triethyl 2-methyl-propanetricarboxylate-1,1,1 (b. p. 150–152° at 15 mm.).

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.1. Found: C, 56.9; H, 8.3. The tricarboxylate was hydrolyzed to isovaleric acid which was identified by its boiling point and the preparation of its *p*-bromophenacyl ester.

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[17] See Hope and Perkin, *J. Chem. Soc.*, **95**, 2042 (1909).

[18] Michael, *J. prakt. Chem.*, [2] **72**, 551 (1905).

[19] Perkin, *J. Chem. Soc.*, **83**, 1242 (1903).

[20] Experiment by B. Abramovitch.

[21] Luniak, *Ber.*, **42**, 4808 (1909).

[22] Blaise, *Compt. rend.*, **132**, 979 (1901).

[23] Ref. 22, p. 970.

[24] Conrad and Bischoff, *Ann.*, **204**, 144 (1880).

The Acylation of the Sodium Enolate of Ethyl Isobutyrate with Phenyl Isocyanate.[20]—With phenyl isocyanate the sodium enolate of ethyl isobutyrate gave α,α-dimethylmalonanilide ethyl ester in good yield (33% of pure product).

$$C_6H_5N{=}C{=}O + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow$$

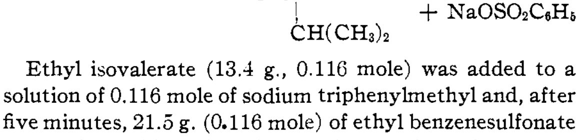
$$Na[C_6H_5NCOC(CH_3)_2CO_2C_2H_5] \xrightarrow{\text{acid}} C_6H_5NHCOC(CH_3)_2CO_2C_2H_5$$

Ethyl isobutyrate (23.2 g., 0.20 mole) was added to a solution of 0.20 mole of sodium triphenylmethyl and, after ten minutes, the resulting enolate was treated with 23.8 g. (0.20 mole) of phenyl isocyanate, the mixture being stirred mechanically in an atmosphere of nitrogen. After forty minutes, 20 cc. of glacial acetic acid was added and the mixture extracted with water. The ether solution was washed with 10% sodium carbonate solution, dried and concentrated to a volume of 90 cc. After chilling, the crystalline triphenylmethane (37 g.) was filtered off and washed with ether. Solvent was distilled *in vacuo* (water pump) from the combined filtrate and washings and the residue dissolved in 80 cc. of hot ethanol. The cold solution deposited 8 g. of triphenylmethane which was filtered off. Solvent was distilled *in vacuo* from the filtrate, the residue was stirred with 100 cc. of petroleum ether (b. p. 40–50°) in a bath of dry-ice and acetone, and the oily product solidified. After five hours in the refrigerator, the crude crystals (23 g.) were collected on a filter, washed with petroleum ether and, after recrystallization from petroleum ether, gave 15.5 g. (33%) of dimethylmalonanilide ethyl ester, m. p. 47–48°.[25] Hydrolysis of the esteranilide (5 g.) with 100 cc. of 10% potassium hydroxide gave 2.5 g. of dimethylmalonic acid, m.p. 192–193°;[26] neutral equivalent, calcd., 66; found, 66.

This direct synthesis is considered superior to that described previously[25] involving the partial hydrolysis of diethyl dimethylmalonate to the mono-acid ester, conversion of the latter to the mono-acid chloride and the condensation of this with aniline.

Treatment of the sodium enolate of ethyl acetate with phenyl isocyanate gave a mixture of high melting products which were not identified.

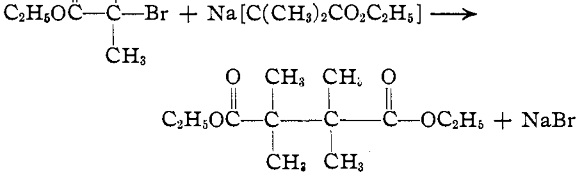
Certain Alkylations of the Sodium Enolates of Esters.—Recently,[27] the sodium enolates of ethyl isobutyrate and of ethyl methylethylacetate were condensed successfully with certain alkyl halides, the method serving as a satisfactory preparation of certain tri-substituted acetic acid esters. Although the alkylation of the sodium enolate of ethyl acetate was unsuccessful (apparently because this ester undergoes self-condensation too readily) the sodium enolate of ethyl isovalerate gave a fair yield (22%) of the alkylated ester when the sodium enolate was treated with ethyl iodide. In the present investigation a better yield (33%) of the ethylated product has been obtained by treating the sodium enolate of ethyl isovalerate with ethyl benzenesulfonate instead of ethyl iodide.



$$C_2H_5OSO_2C_6H_5 + Na\begin{bmatrix} CHCO_2C_2H_5 \\ | \\ CH(CH_3)_2 \end{bmatrix} \longrightarrow \begin{matrix} C_2H_5CHCO_2C_2H_5 \\ | \\ CH(CH_3)_2 \end{matrix} + NaOSO_2C_6H_5$$

Ethyl isovalerate (13.4 g., 0.116 mole) was added to a solution of 0.116 mole of sodium triphenylmethyl and, after five minutes, 21.5 g. (0.116 mole) of ethyl benzenesulfonate was added. After three hours, the reaction mixture was extracted with water, the ether solution dried and the solvent distilled. The residue was distilled *in vacuo* (b. p. up to 115° at 100 mm.). The distillate on fractionation at ordinary pressure gave 4.3 g. of recovered ethyl isovalerate (b. p. 120–163°) and 6.1 g. (33%) of ethyl α-ethylisovalerate (b. p. 163–166°).[27]

With ethyl α-bromoisobutyrate, the sodium enolate of ethyl isobutyrate gave diethyl tetramethylsuccinate in a 30% yield.



$$C_2H_5O\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-Br + Na[C(CH_3)_2CO_2C_2H_5] \longrightarrow C_2H_5O\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5 + NaBr$$

The same product has been obtained in 26% yield by the "coupling" of the sodium enolate of ethyl isobutyrate by means of iodine. It seems likely that a portion of the enolate was first converted by the iodine into ethyl α-iodoisobutyrate which then condensed with the enolate.

Ethyl isobutyrate (24.2 g., 0.208 mole) was added to a solution of 0.208 mole of sodium triphenylmethyl and, after two minutes, 40.6 g. (0.208 mole) of ethyl α-bromoisobutyrate was added slowly. After ten minutes, the mixture was acidified with 5 cc. of glacial acetic acid and extracted with 100 cc. of water. The ether solution was washed twice with saturated sodium bicarbonate solution, dried and the solvent distilled. The residue was distilled up to 175° at 15 mm. The distillate on fractionation gave 9.1 g. of recovered ethyl isobutyrate (b. p. 105–110°), 4.2 g. of recovered ethyl α-bromoisobutyrate (b. p. 58–65° at 15 mm.) and 14.2 g. (30%) of diethyl tetramethylsuccinate, b. p. 115–121° (mostly, 119–121°) at 15 mm. (b. p. 238–240° at atmospheric pressure).[28] Two cc. of the diethyl tetramethylsuccinate was heated with 5 cc. of concentrated sulfuric acid on the water-bath for several hours. The solution was added to ice and gave tetramethylsuccinic anhydride, m. p. 145–146° after recrystallization from li-

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[25] Robertson and Sandrock, *J. Chem. Soc.*, 1617 (1933).

[26] Koenigs and Horling, *Ber.*, **26**, 2049 (1893).

[27] Hudson and Hauser, THIS JOURNAL, **62**, 2457 (1940).

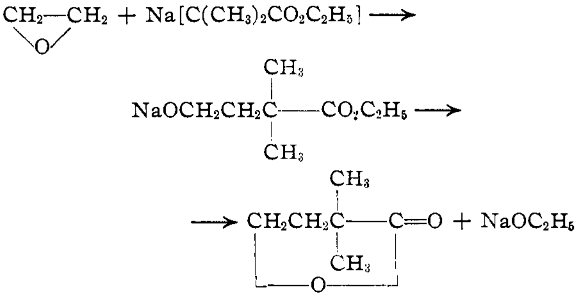
[28] Auwers and Meyer, *Ber.*, **23**, 293 (1890).

groin (b. p. 90–120°) and at 147°[28] after sublimation. The aqueous filtrate was made alkaline, concentrated, acidified and gave tetramethylsuccinic acid, m. p. 194–196° when immersed in the bath at 190° and then heated.[28]

The sodium enolate, prepared from 24 g. (0.207 mole) of ethyl isobutyrate and 0.207 mole of sodium triphenylmethyl, was treated with an ether solution (200 cc.) of 26.3 g. (0.207 atom) of iodine and yielded 6.2 g. (26%) of diethyl tetramethylsuccinate; b. p. 122° at 15 mm. The product was slightly pink in color.

Although the yields of the tetramethylsuccinate were rather low the method is doubtless superior to those described previously involving the reaction of α-bromoisobutyrate with silver powder[28] and the pyrolysis of ethyl azoisobutyrate,[29] both of which gave impure products.

The Reaction of Ethylene Oxide with the Sodium Enolate of Ethyl Isobutyrate.—With ethylene oxide the sodium enolate of ethyl isobutyrate gave α,α-dimethylbutyrolactone in a 55% yield. The reaction presumably takes place as follows



Ethyl isobutyrate (21.0 g., 0.180 mole) was added to 0.178 mole of sodium triphenylmethyl in ether solution. After three minutes, 30 g. (0.68 mole) of ethylene oxide was distilled into the solution (the glass tube carrying the gas reaching to the bottom of the flask) during ten minutes. After twelve to fifteen hours, the mixture was acidified with 12 cc. of glacial acetic acid and extracted with 50 cc. of water. The ether solution was washed twice with saturated sodium bicarbonate solution, dried and the solvent distilled. The residue was distilled *in vacuo* (b. p. up to 175° at 25 mm.). The distillate on fractionation at ordinary pressure gave 11.2 g. (55%) of α,α-dimethylbutyrolactone, b. p. 195.5–197.5°.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.1; H, 8.9. Found: C, 63.2; H, 9.0.

This method is to be preferred to that described previously[30] involving the reduction of α,α-dimethylsuccinic anhydride, in which the isomeric β,β-dimethyllactone is also formed.

Summary

1. Several esters have been converted to the sodium enolates with sodium triphenylmethyl and the acylation and alkylation reactions have been investigated.

2. With ethyl isovalerate, the enolate of the ester gave ethyl α-isovalerylisovalerate.

3. With ethyl oxalate and ethyl formate, the enolate of ethyl isobutyrate gave, respectively, ethyl α-ethoxalylisobutyrate and ethyl α-formylisobutyrate. With ethyl *n*-butyrate or ethyl isobutyrate, the enolate of *t*-butyl acetate gave a mixture of β-keto esters. With *n*-valeronitrile and the enolate of *t*-butyl acetate, α-acetyl-*n*-valeronitrile was obtained.

4. With acid chlorides, the enolates of ethyl isobutyrate, ethyl methylethylacetate and ethyl diethylacetate gave the corresponding β-keto esters. With ethyl chlorocarbonate, the enolate of ethyl isobutyrate gave diethyl dimethylmalonate. With acid chlorides, the enolates of ethyl acetate and ethyl isovalerate gave mainly the diacylated ester.

5. With phenyl isocyanate, the enolate of ethyl isobutyrate gave α,α-dimethylmalonanilide ethyl ester.

6. With ethyl benzenesulfonate, the enolate of ethyl isovalerate gave ethyl α-ethylisovalerate. With ethyl α-bromoisobutyrate, the enolate of ethyl isobutyrate gave diethyl tetramethylsuccinate; the same product was obtained by treating the enolate with iodine.

7. With ethylene oxide, the enolate of ethyl isobutyrate gave α,α-dimethylbutyrolactone.

8. Large scale laboratory preparations of triphenylchloromethane and of sodium triphenylmethyl have been developed.

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[29] Thiele and Heuser, *Ann.*, **290**, 41 (1896).

[30] Blanc, *Bull. soc. chim.*, [3] **33**, 883 (1905).