

TABLE I
HYDROGENATION OF ALDEHYDES WITH AMMONIA

Aldehyde	Moles	Yield of amine product, ^a %					
		¹ / ₂ Eq. NH ₃		² / ₃ Eq. NH ₃		1 Eq. NH ₃	
		Primary	Secondary	Primary	Secondary	Primary	Secondary
Benz-	3	11.8	80.8	30.5(91.6)	62.6(94.0)	89.4	7.1
<i>o</i> -Me-benz-	1.67	11.2	81.7	30.8(92.1)	63.1(94.5)	82.6	15.5
<i>o</i> -Chlorobenz-	0.5	3.6	84.6	87.5	7.6
Furfur-	1.5	12.2	65.5	30.3(91)	66.5(94.1)	79	6.0

^a The figures in parenthesis are yields computed on the assumption of hydro-amide as starting material. All other figures are based on the aldehyde used.

TABLE II
HYDROGENATION OF MIXTURES

Mixture	Moles	Product	Yield ^a
Hydrobenzamide	0.33	Benzylamine	30.7 (92.5)
		Dibenzylamine	60.9 (92.4)
Hydrobenzamide	0.33	Benzylamine	81
Ammonia	Excess	Dibenzylamine	8
Hydrobenzamide	0.37	Benzylamine	11.7
Benzaldehyde	0.37	Dibenzylamine	67
Hydrofuralamide	0.75	Furfurylamine	29.4 (88.7)
		Difurfurylamine	62.8 (94.0)
Hydrofuralamide	0.75	Furfurylamine	62.5
Ammonia	Excess	Difurfurylamine	12.4
Hydrofuralamide	0.75	Furfurylamine	16.4
Furfural	0.75	Difurfurylamine	60.5

^a Yield data are based on the aldehyde equivalent of hydro-amide used. Figures in parentheses are based on hydro-amide directly.

cess, the gas was led from a storage cylinder through high pressure connections directly into the autoclave.

A typical hydrogenation is described in detail. Three gram moles of benzaldehyde was added to a solution of 51 g. (3 moles) of ammonia in 300 ml. of cooled alcohol in the hydrogenation autoclave with 10 g. of Raney catalyst. Under an initial pressure of 90 atmospheres hydrogen

absorption started at 40° and in half an hour was complete at a final temperature of 70°. Distillation of the filtered reaction product gave 287 g. (89.4%) of benzylamine, b. p. 70–80° (8 mm.), and 21.7 g. (7.1%) of dibenzylamine, b. p. 140–150° (7 mm.).

Ethyl alcohol was used as reaction medium throughout because it is miscible with both starting materials and products. A solvent of this type is necessary to maintain homogeneity where water is one of the products.

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Summary

The hydrogenation of aldehydes, such as benzaldehyde, containing no reactive hydrogen on the alpha carbon atom, in alcoholic ammonia solution may be accomplished at temperatures below 75°. By suitable control of the ratio of aldehyde to ammonia, the product may be predominantly primary amine or secondary amine.

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Condensations Brought about by Bases. VII. The Acylation of Ethyl Isobutyryl-isobutyrate and the Cyclization of a 3,5-Diketo-ester by Means of Sodium Triphenylmethyl¹

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

Ethyl isobutyryl-isobutyrate is readily synthesized in good yield either from the enolate of ethyl isobutyrate (prepared from the ester and sodium triphenylmethyl) and isobutyryl chloride,² or from ethyl α -bromoisobutyrate and magnesium³;

(1) This work was supported in part by a grant from the Duke University Research Council.

(2) (a) See Hauser and Renfrow, *THIS JOURNAL*, **59**, 1826 (1937); (b) See also Hauser and Renfrow, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 44.

(3) Salkind, *Chem. Zentr.*, **77**, II, 315 (1906); Zeltner, *Ber.*, **41**, 592 (1908).

the former method gives a purer product.⁴

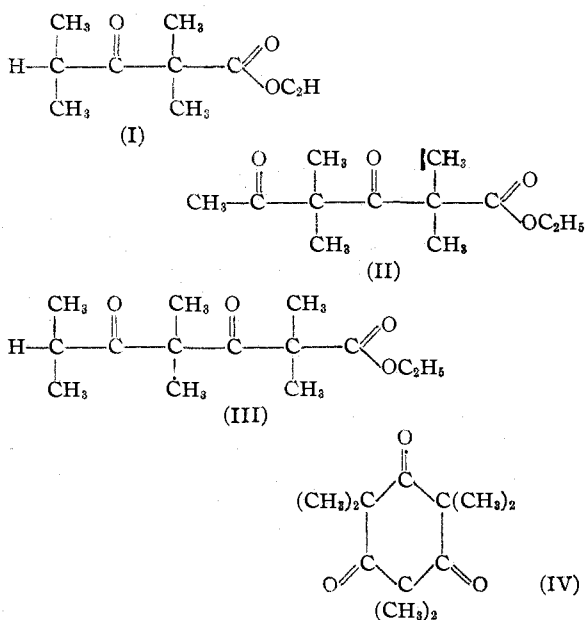
Ethyl isobutyryl-isobutyrate (I) on treatment with sodium triphenylmethyl is converted into its sodium enolate, which is readily acylated. The enolate of (I) with acetyl chloride gives presumably compound (II), and with isobutyryl chloride gives compound (III).

In connection with the preparation of com-

(4) Ethyl isobutyryl-isobutyrate also has been prepared by the self-condensation of ethyl isobutyrate in the presence of sodium triphenylmethyl, see Ref. 2a, p. 1823.

pound (III), it has been shown that this diketo ester is obtained when the reaction mixture, resulting from the self-condensation of ethyl isobutyrate⁴ in the presence of sodium triphenylmethyl, is treated with isobutyryl chloride. The yield (42%) of compound (III) isolated in this case was only slightly less than that (46%) obtained when ethyl isobutyryl-isobutyrate was converted into its enolate, and the latter treated with isobutyryl chloride as discussed above. Since the free β -keto-ester does not condense with the acid chloride, this result shows that the ethyl isobutyryl-isobutyrate produced by the self-condensation of ethyl isobutyrate by means of sodium triphenylmethyl (even in the presence of excess ethyl isobutyrate) is in the form of its sodium enolate as postulated previously.⁴

Compound (III) on treatment with sodium triphenylmethyl undergoes cyclization to give compound (IV). Compound (III) on treatment with sodium ethoxide undergoes cleavage, forming ethyl isobutyrate. Attempts to cyclize compound (II) with sodium ethoxide and with sodium triphenylmethyl apparently were unsuccessful; in both cases an alkali-soluble oil that could not be crystallized was obtained. Reisch⁵ reported that the tetramethylphloroglucinol, which should result from cyclization of compound (II), is a solid melting at 187–188°.



The cyclization of compound (III) to give hexamethylphloroglucinol (IV) by means of sodium

(5) Reisch, *Monatsh.*, **20**, 488 (1899).

triphenylmethyl is of interest in connection with the acetoacetic ester condensation. In most ester-condensations of this type the β -keto-ester formed is converted into its enolate. However, similar to the case recently reported in which ethyl isobutyrate was condensed with ethyl benzoate,⁶ the cyclization of compound (III) is an instance in which the Claisen⁷ or acetoacetic ester type of condensation occurs even though the product formed cannot be converted into an enolate. It should be pointed out that neither of these condensations takes place in the presence of sodium ethoxide as condensing agent, and that they have been effected only by means of a stronger base, sodium triphenylmethyl.

Experimental⁸

Preparation of Ethyl Isobutyryl-isobutyrate. (a) **From the Enolate of Ethyl Isobutyrate and Isobutyryl Chloride.**²—To an ether solution of sodium triphenylmethyl⁹ prepared from 63 g. of triphenylchloromethane (m. p. 112–113°), 1500 cc. of dry ether (dried with sodium), and 2000 g. of 1% sodium amalgam was added 21 g. (0.18 mole) of purified ethyl isobutyrate (b. p. 111–112°). After the solution had stood for ten minutes at room temperature with occasional shaking, 19.5 g. (0.18 mole) of isobutyryl chloride (Eastman Kodak Co.) was added rapidly with shaking. After standing in a closed flask for several hours, the reaction mixture was worked up by extracting with water, washing with 10% sodium carbonate solution, and drying first with anhydrous sodium sulfate and then with "Drierite." The solution was filtered and the ether distilled off until the volume of the residue was approximately 75 cc. The residue was chilled overnight in the refrigerator. The triphenylmethane which crystallized out was filtered off and washed with a small quantity of ether, the washings being added to the filtrate. After all the ether was removed by distillation at atmospheric pressure, the filtrate was vacuum-distilled, collecting up to 160° at 15 mm. The distillate was refractionated and the fraction boiling at 93.5–94.5° at 15 mm. collected; yield, 19 g., 55% of the theoretical amount.

(b) **From Ethyl α -Bromoisobutyrate and Magnesium.**⁸—A solution of 100 g. (0.52 mole) of ethyl α -bromoisobutyrate (Eastman) in an equal volume of dry ether was added to 16.6 g. (0.68 mole) of fresh magnesium turnings contained in a round-bottomed flask equipped with a reflux condenser. The reaction was started by adding a small crystal of iodine and warming the flask gently. After the reaction started, vigorous refluxing took place spontaneously. The reflux rate was moderated by the occasional application of an ice-bath. When spontaneous refluxing ceased, heat was applied and the mixture re-

(6) Renfrow and Hauser, *THIS JOURNAL*, **60**, 463 (1938).

(7) For a general discussion of the Claisen type of condensation, see Hauser, *ibid.*, **60**, 1957 (1938).

(8) All melting points and boiling points given are corrected.

(9) Renfrow and Hauser, "Organic Syntheses," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83; See also Ref. (2a), p. 1825.

fluxed for three hours longer. At the end of that time the reaction mixture was worked up by the cautious addition of ice, followed by dilute sulfuric acid. The ether layer was separated, washed with 10% sodium carbonate solution, and dried with anhydrous sodium sulfate. The ether was distilled off and the residue was vacuum-distilled on a metal-bath from a round-bottomed flask equipped with a six-inch (15 cm.) Widmer column. The fraction boiling at 90–94° at 15 mm. was collected; yield, 34 g., 72% of the theoretical amount.

Reaction of the Enolate of Ethyl Isobutyryl-isobutyrate with Isobutyryl Chloride.—To an ether solution of sodium triphenylmethyl⁹ (containing 0.085 mole of base), prepared from 28 g. of triphenylchloromethane, 1000 g. of 1% sodium amalgam, and 750 cc. of dry ether, was added with shaking 16 g. (0.086 mole) of ethyl isobutyryl-isobutyrate. The flask was stoppered and the mixture allowed to stand at room temperature for four hours with frequent shaking. At the end of this time, the mixture was poured rapidly into a solution of 15 g. (0.14 mole) of isobutyryl chloride (Eastman) in 500 cc. of dry ether, the latter being agitated vigorously with a mechanical stirrer. The vessel was closed and the reaction mixture allowed to stand for four hours longer. Then the mixture was extracted twice with water, washed several times with 10% sodium carbonate solution, and dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and most of the ether distilled off. The residue (approximately 40 cc.) was chilled overnight in the refrigerator. The triphenylmethane which had crystallized out was filtered off and washed with a small quantity of ether, the washings being added to the filtrate. After all of the ether was removed by distillation at atmospheric pressure, the filtrate was vacuum-distilled, collecting up to 160° at 15 mm. The distillate was refractionated and the fraction of ethyl 2,2,4,4,6-pentamethyl-3,5-diketoheptanoate (III) boiling at 136–138° at 15 mm. was collected; yield, 10 g., 46% of the theoretical amount based on the quantity of either ethyl isobutyryl-isobutyrate or of sodium triphenylmethyl used. A portion of the diketo-ester boiling at 137–138° was analyzed.

*Anal.*¹⁰ Calcd. for $C_{14}H_{24}O_4$: C, 65.6; H, 9.45. Found: C, 65.2, 65.0; H, 9.57, 9.77.

Cyclization of Ethyl 2,2,4,4,6-Pentamethyl-3,5-diketoheptanoate to Hexamethylphloroglucinol.—Seven and one-half grams (0.029 mole) of the pentamethyl-diketoheptanoate was added to 250 cc. of an ether solution of sodium triphenylmethyl (containing about 0.03 mole of base) prepared as described in the preceding experiment. The red color of the base disappeared immediately with the formation of a precipitate. The reaction flask was stoppered and allowed to stand for three days with occasional shaking. At the end of this time, the mixture was acidified with excess glacial acetic acid, extracted with water, washed with 10% sodium carbonate solution, and dried with anhydrous sodium sulfate. The ether was distilled off and the residue vacuum-distilled. A fraction which solidified in the condenser came over at about 130–140° at 15 mm. The crystalline material was washed from the condenser with ether. The ether was evaporated and

the residue recrystallized by dissolving in a minimum of ligroin (90–120°) at about 40° and chilling in a mixture of ice and acetone. A yield of 1.85 g. (30% of the theoretical amount) of hexamethylphloroglucinol melting at 79–80° was obtained. This melting point is in agreement with that reported in the literature for hexamethylphloroglucinol,¹¹ and was not lowered by the addition of an authentic specimen of that compound prepared¹¹ by the methylation of phloroglucinol.

Evidence that the Ethyl Isobutyryl-isobutyrate Obtained from Ethyl Isobutyrate and Sodium Triphenylmethyl is in the Form of its Enolate.—To an ether solution of sodium triphenylmethyl⁹ (containing approximately 0.18 mole of base) prepared from 63 g. of triphenylchloromethane (m. p. 112–113°), 1500 cc. of dry ether (dried with sodium), and 2000 g. of 1% sodium amalgam was added 45 g. (0.39 mole) of purified ethyl isobutyrate (b. p. 111–112°). The flask was stoppered and allowed to stand for twenty-four hours with occasional shaking. At the end of that time the mixture was poured into a solution of 24 g. (0.22 mole) of isobutyryl chloride (Eastman) in 500 cc. of dry ether with vigorous mechanical stirring. The reaction mixture was allowed to stand in a closed vessel for an hour. It was then extracted with water, washed with several portions of 10% sodium carbonate solution, and dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered and the ether distilled off until the volume of the residue was approximately 75 cc. The liquid remaining was chilled overnight in the refrigerator. The crystallized triphenylmethane was filtered off and washed with a small quantity of ether, the washings being added to the filtrate. After the ether was removed by distillation (up to 50°), the remaining liquid was distilled, collecting up to 150° at atmospheric pressure. The residue was then vacuum-distilled, collecting up to 180° at 15 mm. Refractionation of the two distillates yielded the following fractions: (a) 106–121° at atm. press., 22 g. (ethyl isobutyrate); (b) 120° at atm. press. to 131° at 15 mm., 3 g.; (c) 136–138° at 15 mm., 6.3 g. (ethyl 2,2,4,4,6-pentamethyl-3,5-diketoheptanoate); (d) 131–139° at 15 mm., 2.2 g. (impure heptanoate).

Fraction (a) consisted practically entirely of ethyl isobutyrate; on redistillation most of the fraction boiled within the range commonly reported for this ester. Fraction (b) may have contained a little ethyl isobutyryl-isobutyrate but because of the wide boiling range and small quantity obtained no attempt was made to isolate this compound. It should be pointed out that ethyl isobutyryl-isobutyrate would be expected if the isobutyryl chloride used contained any isobutyric acid, since the latter would immediately convert the enolate into the free β -keto-ester.

Fraction (c) was regarded as pure ethyl 2,2,4,4,6-pentamethyl-3,5-diketoheptanoate, while fraction (d) probably consisted largely of this compound. The yield of heptanoate in fractions (c) and (d) was 42% of the theoretical amount, based on the quantity of sodium triphenylmethyl used. In the calculation of this yield it was taken into account that one-half the sodium triphenylmethyl was consumed in condensing ethyl isobutyrate with itself, and

(10) Micro-analysis by R. L. Peck.

(11) Spitzer, *Monatsh.*, **11**, 104 (1890).

that only the remaining half of the base served to enolize the condensation product, ethyl isobutyryl-isobutyrate. The heptanoate was cyclized to hexamethylphloroglucinol as described above; the latter was identified by the mixed melting point method.

Cleavage of Ethyl 2,2,4,4,6-Pentamethyl-3,5-diketohexanoate by Sodium Ethoxide.—Sodium ethoxide was prepared by dissolving 1.80 g. (0.078 mole) of sodium in 150 cc. of absolute alcohol¹² contained in a flask equipped with a ground-glass joint. The excess alcohol was distilled off on an oil-bath and the residue heated for thirty minutes at 200° under a pressure of 10 mm. Dry nitrogen was admitted into the flask which was then allowed to cool to room temperature. To the sodium ethoxide was added a solution of 5.75 g. (0.022 mole) of ethyl 2,2,4,4,6-pentamethyl-3,5-diketohexanoate in 500 cc. of dry ether. Several pieces of glass tubing about 2 cm. long were dropped into the flask and a well lubricated glass stopper was inserted and clamped in place. The flask was shaken vigorously until most of the cake of sodium ethoxide had been changed to a fine suspension. The mixture was allowed to stand for seven days with occasional shaking. At the end of that time the reaction mixture was acidified with 7 cc. of glacial acetic acid, extracted with water, washed with 10% sodium carbonate solution, and dried with anhydrous magnesium sulfate. Ether was distilled off through a six-inch (15-cm.) Widmer column. Practically all of the residue distilled over at 100–112°; yield, 5.5 g. This material was presumably ethyl isobutyrate; on redistillation most of it boiled at 109–112°, which is the boiling point commonly reported for this ester. The yield of 5.5 g. of ethyl isobutyrate obtained corresponds to 74% of the theoretical amount.

Reaction of Enolate of Ethyl Isobutyryl-isobutyrate with Acetyl Chloride.—To an ether solution of sodium triphenylmethyl,⁹ prepared from 28 g. of triphenylchloromethane, 1000 g. of 1% sodium amalgam, and 750 cc. of dry ether, was added 15.6 g. (0.084 mole) of ethyl isobutyryl-isobutyrate. After standing for thirty minutes, the mixture was poured, with vigorous stirring, into a solution of 10 g. (0.126 mole) of acetyl chloride (Baker and Adamson, reagent grade) in 500 cc. of dry ether. After standing for thirty minutes longer, the mixture was extracted with water, washed several times with 10% sodium carbonate solution, and dried with anhydrous sodium sulfate followed by "Drierite." The solution was filtered, the ether distilled off, and the residue vacuum-distilled, collecting up to 160° at 15 mm. The distillate was vacuum-fractionated on a metal-bath, using a flask equipped with a five-inch (13-cm.) Vigreux column, and

without the use of an ebullition tube. The fraction boiling at 122–124° at 15 mm., presumably ethyl 2,2,4,4-tetramethyl-3,5-diketohexanoate (II), was collected; yield, 10 g., 52% of the theoretical amount.

*Anal.*¹⁰ Calcd. for C₁₂H₂₀O₄: C, 63.1; H, 8.83. Found: C, 62.9, 63.6; H, 8.92, 8.78.

Attempts to cyclize the compound synthesized above were unsuccessful. Five grams (0.022 mole) of the compound was added to an ether solution of sodium triphenylmethyl containing approximately 0.044 mole of base. The red color of the base disappeared immediately with the formation of a precipitate. The reaction mixture was allowed to stand overnight; it was then acidified with excess dilute hydrochloric acid and extracted with water. The resulting ether solution was extracted three times with 20% sodium hydroxide solution. The combined alkaline extracts were acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the ether left an oily residue (2–3 g.) which could not be made to crystallize. A similar alkali-soluble oil was obtained when the reaction mixture was acidified ten minutes after the addition of the sodium triphenylmethyl. An alkali-soluble oil also was obtained when an ether solution of the compound was allowed to stand for four days with sodium ethoxide. The oil isolated in these experiments has not yet been identified. The reaction will be studied further.

Summary

1. The sodium enolate of ethyl isobutyryl-isobutyrate has been acylated with acetyl chloride and with isobutyryl chloride. The 3,5-diketo-ester, obtained with the latter acid chloride, on treatment with sodium triphenylmethyl undergoes cyclization to form hexamethylphloroglucinol. This cyclization does not take place in the presence of sodium ethoxide.

2. The significance of the cyclization reaction in relation to the acetoacetic ester type of condensation is discussed.

3. Evidence is presented that the ethyl isobutyryl-isobutyrate obtained from the self-condensation of ethyl isobutyrate by means of sodium triphenylmethyl is in the form of its sodium enolate.

4. Two syntheses of ethyl isobutyryl-isobutyrate are described.

(12) Prepared by the method of Lund and Bjerrum, *Ber.*, **64**, 210 (1931).