Summary

1. 2-Nitrophenyl benzenesulfonate and a number of its substitution products have been reduced to the corresponding 2-aminophenyl derivatives. Under the conditions of our experiments these products showed no tendency to rearrange.

2. Latimer's theory does not seem to us to account for the remarkable differences in behavior of the acyl derivatives of *o*-aminophenol obtained from carboxylic and sulfonic acids, respectively.

IOWA CITY, IOWA RECEIVED MAY 5, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations. XX. Certain Acetoacetic Ester Condensations Effected by Means of Sodium or Potassium Amide and Isopropylmagnesium Bromide

BY J. C. SHIVERS, B. E. HUDSON, JR., AND CHARLES R. HAUSER

Although ethyl acetate gives only low yields (8–15%) of ethyl acetoacetate with sodium amide,[1] and apparently little if any of the β-keto ester with isopropylmagnesium bromide,[2] certain esters having a relatively reactive α-hydrogen or a relatively unreactive carbonyl carbon undergo the acetoacetic ester condensation very satisfactorily in the presence of these reagents.

Conant and Blatt[3] have shown that, in the presence of isopropylmagnesium bromide, ethyl phenylacetate, in which the α-hydrogen is relatively reactive, gives an excellent yield (93%) of its self-condensation product, ethyl α,γ-diphenylacetoacetate. Ivanov and Spassov[4] found that in the presence of this Grignard reagent, ethyl *p*-chlorophenylacetate similarly undergoes the acetoacetic ester condensation in excellent yield. We have found that the self-condensation of ethyl phenylacetate may be effected very satisfactorily in the presence of potassium amide in ether, and that, in the presence of either isopropylmagnesium bromide or sodium amide in ether, *t*-butyl acetate, in which the carbonyl carbon is relatively unreactive, gives fair to good yields (40–50%) of its self-condensation product, *t*-butyl acetoacetate.

$$2C_6H_5CH_2CO_2C_2H_5 \xrightarrow[(CH_3)_2CHMgBr]{KNH_2\text{ or}} C_6H_5CH_2COCH(C_6H_5)CO_2C_2H_5 + C_2H_5OH$$

$$2CH_3CO_2C(CH_3)_3 \xrightarrow[(CH_3)_2CHMgBr]{NaNH_2\text{ or}} CH_3COCH_2CO_2C(CH_3)_3 + (CH_3)_3COH$$

Similarly, in the presence of these reagents, *t*-butyl isovalerate undergoes self-condensation to form *t*-butyl isovalerylisovalerate, but the yields are lower; with isopropylmagnesium bromide the yield was 29%, while with potassium amide in benzene the yield was only 11%, some of the ester being recovered in each case. Spielman and Schmidt[5] found that ethyl isovalerate is self-condensed by isopropylmagnesium bromide to only a very small extent (1%).

It should be pointed out that, while the activation of the α-hydrogen by the phenyl group or the deactivation of the carbonyl carbon by the *t*-butyl group favors the attack of the amide ion or isopropylmagnesium bromide at the α-hydrogen of the ester, this does not necessarily mean that the acetoacetic ester reaction can be effected. The reaction depends not only upon the primary ionization of the α-hydrogen to form the ester anion (or magnesium enolate) but also upon the condensation of the ester anion with molecules of unchanged ester,[6] and this second step may occur too slowly for the reaction to be realized.

Experimental

Condensation of Ethyl Phenylacetate by Potassium Amide.—Essentially dry commercial ammonia (300 cc.) was placed in a 500-cc. three-necked, round-bottomed flask, equipped with a mercury sealed stirrer, dropping funnel and a drying tube of drierite. Pieces of clean potassium (7.8 g., 0.20 g. atom) and a small strip of rusty iron gauze were placed in the ammonia and the mixture stirred about thirty minutes until the blue solution became

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(1) Titherly, *J. Chem. Soc.*, **81**, 1520 (1902); Freund and Speyer, *Ber.*, **35**, 2321 (1902). These workers used a benzene suspension of sodium amide or carried out the reaction without a solvent. We have found that in the presence of potassium amide in liquid ammonia, either with excess ester or excess base, ethyl acetate similarly gives only low yields (5–10%) of ethyl acetoacetate.

(2) With isopropylmagnesium chloride, ethyl acetate gives a 65% yield of the ketol of methyl isopropyl ketone; Ivanov and Spassov, *Bull. soc. chim.*, [5] **2**, 816 (1935).

(3) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

(4) Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

(5) Spielman and Schmidt, THIS JOURNAL, **59**, 2009 (1937).

(6) See Hauser and Hudson in Adams' "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter IX.

colorless. The ammonia was allowed to evaporate until the volume of the solution was approximately 75 cc. Ether (100 cc.) was added and the mixture stirred. After the rest of the ammonia had evaporated more ether (100 cc.) was added. A 12-inch condenser was inserted between the drying tube and flask.

To the stirred suspension of potassium amide was added slowly from the dropping funnel 41.0 g. (0.25 mole, 41.0 cc.) of ethyl phenylacetate (b. p. 107–110° at 15 mm.). Ammonia was evolved slowly and the mixture became warm. After standing one-half hour at room temperature, the mixture was refluxed over an electric bulb heater for two hours. Ammonia ceased to be evolved and a clear solution was obtained. After standing overnight 13 cc. of glacial acetic acid in 150 cc. of ether was added. The ether solution was washed twice with water, once with sodium bicarbonate solution, and dried over sodium sulfate followed by drierite. After distilling the solvent, the residue was distilled at 15 mm. A small amount (0.88 g., 2%) of the unchanged ester was recovered boiling at 107–110°. No other fractions were obtained up to 125°. On cooling, the residue in the flask crystallized. The yield of crude slightly colored ethyl α,γ-diphenylacetoacetate (m. p. 77–78°) was 27.6 g. (97% based on potassium amide, 77% based on the ester). Recrystallization from alcohol (using Norite) yielded white crystals melting at 78.0–78.5°.[3] The β-ketoester was further identified by reaction with phenylhydrazine, yielding benzyldiphenylpyrazolone melting at 230.0–231.5°.[7]

Condensation of *t*-Butyl Acetate. Method (A).—Sodium amide was prepared from 200 cc. of liquid ammonia and 4.6 g. (0.2 atom) of metallic sodium in an insulated 500-cc. Erlenmeyer flask, powdered ferric nitrate being used as the catalyst.[8] When the reaction was complete, the insulation was removed from the flask and the ammonia allowed to evaporate, through a capillary tube of 1 to 2 mm. bore. When little or no ammonia remained, 200 cc. of dry ether was added and the sodium amide stirred into suspension. To the suspension was added 23.2 g. (0.2 mole) of *t*-butyl acetate.[9] The flask was equipped with a drying tube and shaken at frequent intervals. Ammonia was evolved slowly. After three hours, when the evolution of ammonia had ceased, the mixture was refluxed overnight. The reaction mixture was cooled and acidified with 13 cc. of glacial acetic acid in 200 cc. of ether. The ether solution was washed with water, followed by saturated sodium bicarbonate solution, and dried with sodium sulfate followed by drierite. The solvent was distilled and the residue was distilled through a six-inch Widmer column yielding 9 g. (57%) of *t*-butyl acetoacetate boiling at 75–80° (mostly at 77°) at 15 mm.

Method (B).—To an ether solution of 0.185 mole[10] (390 cc.) of isopropylmagnesium bromide,[11] contained in a 1-liter, 3-necked flask equipped with a mechanical stirrer, reflux condenser and a dropping funnel, was added with stirring 21.5 g. (0.185 mole) of *t*-butyl acetate.[9] Gas was evolved steadily and at a moderate rate for approximately fifteen minutes. The reaction mixture was then warmed gently on a water-bath for forty-five minutes. During the latter part of the heating, the solution refluxed and little or no gas was given off. The solution was cooled to room temperature and acidified with 12 cc. of glacial acetic acid. The ether solution was washed with water, followed by saturated sodium bicarbonate solution, and dried with sodium sulfate and drierite. The solvent was distilled up to 50°, and the residue distilled *in vacuo* through a six-inch Widmer column, yielding 6.1 g. (41%) of *t*-butyl acetoacetate, boiling at 75–78° at 15 mm. A slightly higher yield (42%) was obtained by allowing the reaction mixture to stand overnight before acidifying. When the reaction was carried out on two and one-half times the scale, the yield was only 34%. When carried out on a larger scale, still lower yields were obtained.

The boiling points of *t*-butyl acetoacetate, prepared by methods (A) and (B), were in approximate agreement with that of 71° at 11 mm. reported by Fisher and McElvain.[12] The β-keto ester was further identified by the preparation of its semicarbazone. The common procedure[13] for water-insoluble compounds gave very low yields of the derivative but the following procedure was satisfactory. A mixture composed of 2 cc. of alcohol, 1.5 cc. of the ketoester, 2 g. each of sodium acetate and semicarbazide hydrochloride, and 10 cc. of water was shaken for three to four hours in a mechanical shaker. The mixture was diluted with 10 cc. of cold water, shaken, filtered and sucked dry. The crystals were covered with 20 cc. of absolute alcohol and the mixture heated quickly to boiling, filtered immediately through a warm funnel and allowed to crystallize. The crystals were filtered, pressed free from mother liquor, and washed with 2 cc. of absolute alcohol; yield, 0.9 g., m. p. 151–152°. After recrystallization from 10 cc. of absolute alcohol, the derivative melted sharply at 153°.

Anal.[14] Calcd. for $C_9H_{17}O_3N_3$: N, 19.6. Found: N, 19.7.

Condensation of *t*-Butyl Isovalerate. Method (A).—Potassium amide was prepared from 5.08 g. (0.13 g. atom) of potassium and 200 cc. of liquid ammonia as described in the experiment with ethyl phenylacetate. When the liquid ammonia had evaporated to a volume of about 75 cc., a mixture of 50 cc. of benzene and 50 cc. of ether was added, and when all of the ammonia had evaporated 100 cc. of benzene was added. To the stirred suspension of potassium amide was added slowly 25.6 g. (0.16 mole) of *t*-butyl isovalerate[9] in 30 cc. of benzene. The flask became warm and ammonia was evolved. After refluxing for nine hours, 8 cc. of glacial acetic acid was added, and the benzene solution washed with water and bicarbonate solution. The solvent was distilled from the dried solution and the residue was fractionated using a 6-inch Vigreux column. *t*-Butyl isovalerate (7.0 g., 27%), b. p. 152.0–156.0°, was recovered, and 1.5 g. (11%) of *t*-butyl α-isovalerylisovalerate, b. p. 125–126° at 15 mm., was obtained. From the bicarbonate wash solution there was isolated 2 g. of isovaleric acid, b. p. 170–176°; m. p. of the *p*-bromophenacyl ester, 66.5–67.5°.

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(7) Volhard, *Ann.*, **296**, 1 (1897).

(8) Vaughn, Vogt and Nieuland, THIS JOURNAL, **56**, 2121 (1934).

(9) Abramovitch, Shivers, Hudson and Hauser, *ibid.*, **65**, 986 (1943).

(10) Gilman, Wilkinson, Fishel and Myers, *ibid.*, **45**, 156 (1923).

(11) Drake and Cooke, "Organic Syntheses," Vol. XII, 48 (1935).

(12) Fisher and McElvain, THIS JOURNAL, **56**, 1766 (1934).

(13) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 142.

(14) Microanalysis by Saul Gottlieb, New York, N. Y.

Method (B).—To an ether solution of 0.0925 mole[10] (300 cc.) of isopropylmagnesium bromide[11] contained in a 500-cc. 3-necked flask equipped with a mechanical stirrer, reflux condenser and a dropping funnel, was added with stirring 35.5 cc. (29.2 g., 0.185 mole) of *t*-butyl isovalerate.[9] Gas was evolved and the mixture became warm. The mixture was refluxed for forty-five minutes (some gas being evolved). Another 0.0925 mole of isopropylmagnesium bromide was then added and the mixture allowed to stand overnight. After refluxing for four additional hours, 17 cc. of glacial acetic acid was added. The ether solution was washed with water, followed by bicarbonate solution, and dried. The solvent was distilled and the residue fractionated in a Claisen flask. *t*-Butyl isovalerate (4.5 g., 15%) boiling at 154.0–157.0° was recovered and 5.9 g. (29%) of *t*-butyl isovalerylisovalerate boiling at 125–128° at 15 mm. was obtained.

Anal.[15] Calcd. for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.39; H, 10.48.

When *t*-butyl isobutyrate[9] was treated with isopropylmagnesium bromide in a similar manner, no gas was evolved, and on working up the mixture, 45% of the ester was recovered boiling at 127–129°.

Summary

The acetoacetic ester condensation has been effected with certain esters having relatively reactive α-hydrogens or relatively unreactive carbonyl carbons by means of sodium or potassium amide and isopropylmagnesium bromide. Ethyl phenylacetate gives excellent yields, *t*-butyl acetate gives fair to good yields, and *t*-butyl isovalerate gives poor to fair yields of their respective condensation products.

DURHAM, NORTH CAROLINA RECEIVED JULY 6, 1943

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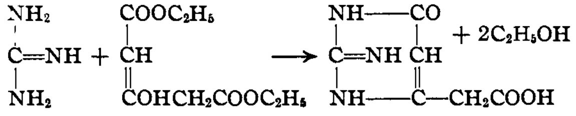
[15] Microanalysis by T. S. Ma, University of Chicago, Chicago, Ill.

[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY, TUFTS COLLEGE]

Derivatives of Pyrimidine-4-acetic Acid

BY DAVID E. WORRALL

It was found some years ago[1] that ethyl acetonedicarboxylate condensed smoothly with guanidine carbonate, producing a substance that was regarded as a pyrimidine derivative. Because of increasing interest in diazine derivatives, the reaction has been investigated more completely. Additional evidence has been obtained of the pyrimidine nature of the product, while certain derivatives have been prepared.



$$\begin{array}{llcll} \mathrm{NH_2} & \mathrm{COOC_2H_5} & & \mathrm{NH{-}{-}CO} & \\ | & | & & |\qquad\ | & +\ 2\mathrm{C_2H_5OH} \\ \mathrm{C{=}NH}\ + & \mathrm{CH} & \longrightarrow & \mathrm{C{=}NH\ CH} & \\ | & \| & & |\qquad\ \| & \\ \mathrm{NH_2} & \mathrm{COHCH_2COOC_2H_5} & & \mathrm{NH{-}{-}C{-}CH_2COOH} & \end{array}$$

(I) (II)

Experimental

1,2,3,6-Tetrahydro-2-imino-6-ketopyrimidine-4-acetic Acid (II).—Fifty grams of I and 44.5 g. of guanidine carbonate, mixed with 250 cc. of alcohol, was heated under a reflux condenser for a day, after which the insoluble product was removed and dissolved in the minimum volume of hot water containing charcoal. The filtrate was then made slightly acid with acetic acid, causing the separation of II as colorless plates. It forms soluble salts with both mineral acids and alkali, including ammonium hydroxide, but not with acetic acid. It partially melts with foaming at 189–190°, a fact which was overlooked in the previous communication.

The methyl ester was prepared by suspending 10 g. of II in methyl alcohol, followed by saturation with hydrogen chloride gas. On standing overnight, the clear solution deposited about 10 g. of the ester hydrochloride. This salt was dissolved in a small volume of water, neutralized with ammonia, and the insoluble product crystallized from alcohol as lustrous plates, m. p. 192–193° with slight foaming.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.9; H, 4.9. Found: C, 46.2; H, 5.2. HCl salt. Calcd. for $C_7H_{10}ClN_3O_3$: Cl, 16.2. Found: Cl, 16.1.

1,2,3,6-Tetrahydro-2-imino-6-ketopyrimidine-4-acetamide.—One gram of II dissolved in concd. ammonia solution formed, in a few minutes, a crystalline product that was recrystallized from a large volume of water as slender needles, m. p. indefinite with decomposition above 285°.

Anal. Calcd. for $C_6H_9N_4O_2$: C, 42.8; H, 4.8. Found: C, 43.2; H, 4.7.

[β-Chloroethyl]-1,2,3,6-tetrahydro-2-imino-6-ketopyrimidine-4-acetate.—Prepared from 5 g. of II suspended in ethylene chlorohydrin using hydrogen chloride. The product separated after a few hours on stirring and crystallized from alcohol after neutralization with ammonia in the form of lustrous plates, m. p. 164°.

Anal. Calcd. for $C_8H_{10}ClN_3O_3$: Cl, 15.3. Found: Cl, 15.0.

1,2,3,6-Tetrahydro-2-imino-1-methyl-6-ketopyrimidine-4-acetic Acid.—Two grams of II dissolved in water containing two equivalents of sodium hydroxide after mixing with a slight excess of methyl iodide and sufficient alcohol

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[1] Worrall, THIS JOURNAL, 40, 1133 (1918).