[Contribution from the Chemical Laboratories of Northwestern University]

Preparation of Acyclic Imides

CHARLES D. HURD and ARISTOTLE G. PRAPAS[1]

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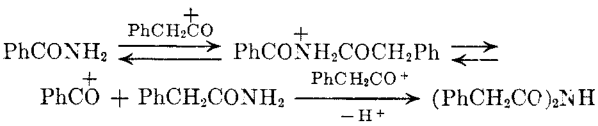
Bisphenylacetimide is produced from benzamide and phenylacetyl chloride or phenylacetic anhydride by way of *N*-benzoylphenylacetamide. The mechanism appears to involve acyl carbonium ions. The same acylating agents do not convert methyl phenaceturate to an imide. Phenyl isocyanate and ethyl isocyanatoacetate were found to react with a number of acid anhydrides, both cyclic and acyclic, to yield imides with evolution of carbon dioxide. This reaction is useful in preparing imides that contain a substituent on the nitrogen. A mechanism for this reaction is suggested.

The preparation of diacyl derivatives of ammonia or alkylamines has received considerable attention in recent years, especially the direct acylation of amides. In many instances an amide $RCONH_2$ may be acylated to the imide $(RCO)_2NH$ in good yields by reaction with an acid anhydride or acyl chloride. Such catalysts as hydrogen chloride,[2] acyl chloride,[2] or sulfuric acid[3] are helpful with acid anhydrides, and pyridine has been used with acyl halides.[4,5] As an example, dipropionimide[6] was made in good yields[3] from propionic anhydride, propionamide, and sulfuric acid. Some amides, however, take a different course, examples being benzamide which reacted with benzoic anhydride to give 33 times more benzonitrile[3] than dibenzimide, and acetanilide which reacted with benzoyl chloride and pyridine to give *N*-phenyldibenzimide[4] instead of *N*-benzoylacetanilide. The unpredictability of such reactions is witnessed again in the contrasting behavior of aceturic and phenaceturic esters: The former[7] was readily acetylated by acetic anhydride to yield diacetimidoacetic ester Ac_2NCH_2COOR, whereas the latter[8] ($PhCH_2CONHCH_2COOCH_2Ph$) was nonacylated by phenylacetic anhydride or phenylacetyl chloride alone or in the presence of bases. Thus, the objective of the present work was to study various methods of synthesis of acyclic imides, with especial reference to diacetimido esters and analogous compounds, $(RCO)_2NCH_2COOR'$.

Preliminary experiments substantiated in general the findings of other investigators. For example, when a mixture of benzamide and acetic anhydride was heated for 3 min. in the presence of concentrated sulfuric acid, a 61% yield of *N*-acetylbenzamide was obtained. Similarly, a 52% yield of *N*-acetylbenzamide was obtained. Similarly, a 52% yield of *N*-benzoylphenylacetamide resulted from heating (160–180°) a mixture of phenylacetic anhydride and benzamide for only 2 min. in the presence of sulfuric acid; but a similar mixture containing 2 equivalents of phenylacetic anhydride and heated for 10 minutes produced bisphenylacetimide, $(C_6H_5CH_2CO)_2NH$, in 60% yield. The same compound was obtained in 96% yield when benzamide was heated with an excess of phenylacetyl chloride at 80° for 24 hr. No bisphenylacetimide resulted on heating pure phenylacetamide at 180° for 6 hr. but an 11% yield was obtained together with unchanged amide if the heating was done in the presence of a trace of sulfuric acid.

The formation of the mixed imide, *N*-benzoylphenylacetamide, is a simple acylation of benzamide, but the continued reaction to form bisphenylacetimide is interesting from a standpoint of mechanism. The fact that the latter is formed from either phenylacetic anhydride or phenylacetyl chloride is evidence for the phenylacetyl carbonium ion as intermediate, since it is common to both the anhydride and chloride. This mechanism would account for the findings:



$$PhCONH_2 \overset{PhCH_2\overset{+}{C}O}{\rightleftarrows} PhCO\overset{+}{N}H_2COCH_2Ph \rightleftarrows$$
$$Ph\overset{+}{C}O + PhCH_2CONH_2 \xrightarrow[-H^+]{PhCH_2CO^+} (PhCH_2CO)_2NH$$

The benzoyl carbonium ion arising in this sequence of steps is less active than the phenylacetyl carbonium ion for it is stabilized by resonance with the aromatic nucleus. The greater reactivity of the latter, therefore, explains why the reaction progresses so nearly to completion in forming the symmetrical imide.

Methyl phenaceturate was the next amide

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(1) This work was done during 1953–1954 when one of us (A.G.P.) held a Swift and Co. Fellowship. The material is abstracted from part of a doctoral dissertation submitted to Northwestern University by A.G.P. in 1955.

(2) J. B. Polya and P. L. Tardrew, *J. Chem. Soc.*, 1081 (1948); J. B. Polya and T. M. Spotswood, *Rec. trav.chim.*, **67**, 927 (1948); P. Dunn, E. A. Parkes, and J. B. Polya, *Rec. trav. chim.*, **71**, 676 (1952).

(3) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

(4) A. W. Titherley, *J. Chem. Soc.*, **85**, 1673 (1904).

(5) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951).

(6) The compound $(C_2H_5CO)_2NH$ has been named both dipropionamide and dipropionimide. Our preference for and usage of the latter follows the practice of the London Chemical Society: A. D. Mitchell, *British Chemical Nomenclature*, E. Arnold, London, 1948, p. 66.

(7) (a) R. H. Wiley, O. H. Borum, and L. L. Bennett, Jr., *J. Am. Chem. Soc.*, **71**, 2899 (1949); (b) R. H. Wiley and O. H. Borum, *J. Am. Chem. Soc.*, **72**, 1626 (1950).

(8) J. C. Sheehan and E. Corey, *J. Am. Chem. Soc.*, **74**, 4555 (1952).

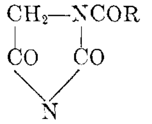
studied. Neither it nor glycine ethyl ester hydrochloride reacted in pyridine solution with phenylacetyl chloride at −60° (conditions resembling those used by Thompson[5] for acylating amides and amines). Also, no product other than unused anhydride could be isolated from the red oil that was obtained on refluxing a mixture of ethyl phenaceturate, phenylacetic anhydride, and pyridine. Heating a mixture of glycine ethyl ester hydrochloride and phenylacetic anhydride at 160° did induce monoacylation to form ethyl phenaceturate.

Another approach tested was to heat a mixture of sodium bisphenylacetimide, ethyl chloroacetate, and a trace of potassium iodide at 140°, with or without xylene as solvent. A viscous red oil was obtained from which phenylacetamide and sodium chloride were isolated but no ethyl bisphenylacetimidoacetate.

A promising approach to the synthesis of diacylated amines was reaction of isocyanates and acid anhydrides. Although this reaction has been known for over a century it has not been generally appreciated. A recent paper,[9] for example, lists a dozen reactions of isocyanates without including acid anhydrides. Wurtz[10] discovered the reaction when he heated acetic anhydride and ethyl isocyanate at 180–190° and obtained *N*-ethyldiacetimide, $(CH_3CO)_2NC_2H_5$. Brunner[11] produced diacetimide by heating acetic anhydride with potassium cyanate at 100°. A few reactions at elevated temperatures are on record between acid anhydrides and ureas, which may be regarded as precursors of isocyanates, as are a few reactions between acid anhydrides and isothiocyanates.[12] The reaction[13] of phthalic anhydride and an acid azide (precursor of isocyanate) yielding an *N*-substituted phthalimide has been reported.

To test this reaction with simple materials, phthalic anhydride was treated with phenyl isocyanate (rather than diphenylurea or benzazide). *N*-Phenylphthalimide was formed in 85% yield on heating in a bath at 180°. A lesser yield (63%) resulted by refluxing in pyridine, and a still smaller yield (27%) at 140° in the presence of a trace of perchloric acid. Dains[12] reported the formation of *N*-phenylphthalimide from phthalic anhydride and phenyl isothiocyanate without listing details or yield. We obtained 83% yield when this mixture was refluxed in pyridine.

Acyclic acid anhydrides were found to react comparably with isocyanates. Thus, from acetic anhydride and phenyl isocyanate there was produced *N*-phenyldiacetimide in 71% yield, together with a little acetanilide. About the same yields (70–74%) of ethyl diacetimidoacetate and ethyl dioctanimidoacetate, $(C_7H_{15}CO)_2NCH_2COOC_2H_5$, were obtained from ethyl isocyanatoacetate and acetic or octanoic anhydrides. As would be expected, propionic anhydride reacted similarly but the resulting ethyl dipropionimidoacetate was difficult to separate completely from ethyl 1-propionyl-3-hydantoinacetate (IB) that was formed concurrently. Some ethyl 1-octanoyl-3-hydantoinacetate (IC) was isolated also as a minor product from octanoic anhydride. At 200°, benzoic anhydride yielded ethyl dibenzimidoacetate but at 195° or lower there was no evolution of carbon dioxide and there was recovery of reagents.


I. A. R = CH_3
B. R = C_2H_5
C. R = C_7H_{15}

Two reactions of ethyl diacetimidoacetate may be mentioned at this point. One is the quantitative hydrolysis of both acetyl groups by refluxing with concentrated potassium hydroxide solution. The other is reaction with phosphorus pentachloride, an exothermic process accompanied by evolution of gas. Further heating of the reaction mixture resulted in extensive decomposition and the distillation of acetyl chloride. The amount of acetyl chloride was 50% more than the amount expected if only one of the acetyl groups had been cleaved. Hence, both acetyl groups were attacked by the phosphorus pentachloride. A very small amount of acetamide was produced also. A similar result has been observed before[14] when gaseous hydrogen chloride was passed into molten *N*-phenyldiacetimide at 150–170°. Both acetyl chloride and acetanilide were obtained.

One anhydride studied, phenylacetic anhydride, failed to yield an imide in its reaction with phenyl isocyanate. Only monoacylation was noticed. The product was phenylacetanilide in high yield.

Two by-products were observed in the reaction between acetic anhydride and ethyl isocyanatoacetate, namely, ethyl *N,N'*-carbonylbis(aminoacetate), a urea $CO(NHCH_2COOC_2H_5)_2$, and ethyl 1-acetyl-3-hydantoinacetate, IA. The first of these compounds probably results from the presence of traces of water in the original isocyanate as well as of small amounts of acetic acid in the anhydride, even though reasonable precautions were made to start with pure anhydride and to maintain anhydrous conditions. A small amount of *sym*-diphenylurea also was obtained in the experiments with phenyl isocyanate. Compound IA undoubtedly

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(9) S. Petersen, *Ann.*, **562**, 205 (1949).

(10) A. Wurtz, *Ann. Chim. Phys.*, [3], **42**, 54 (1854).

(11) K. Brunner, *Monatsh.*, **36**, 517 (1915).

(12) P. Kay, *Ber.*, **26**, 2848 (1893); F. B. Dains, *J. Am. Chem. Soc.*, **22**, 186 (1900); J. Dubsky and C. Graenacher, *Ber.*, **50**, 1689 (1917).

(13) M. Aeberli and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 470 (1948).

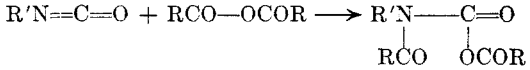
(14) A. W. Chapman, *J. Chem. Soc.*, **127**, 2819 (1925).

came from the urea by cyclization and subsequent acetylation by the acetic anhydride. Precedent for this is the formation of hydantoin on pyrolysis (140°) of ethyl ureidoacetate,[15] $H_2NCONHCH_2COOC_2H_5$; in turn, the hydantoin was converted into 1-acetylhydantoin on refluxing with acetic anhydride. Similarly, ethyl 3-hydantoinacetate was obtained[16] by heating ethyl *N*-(ureidoacetyl)-aminoacetate hydrochloride,

$$HCl{\cdot}NH_2CONHCH_2CONHCH_2COOC_2H_5$$

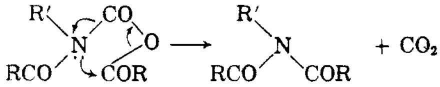
at 180–190° *in vacuo*, or by heating ethyl *N*,*N*'-carbonylbis(aminoacetate) in a saturated solution of hydrochloric acid in ethanol.[17]

To explain the formation of imides in this reaction it is assumed that there is an initial addition of anhydride to the isocyanate, resulting from partial polarization of both molecules at the temperature required by the reaction:



$$R'N{=}C{=}O + RCO{-}OCOR \longrightarrow \underset{RCO}{R'N}{-}\underset{OCOR}{C}{=}O$$

The resulting mixed acid anhydride is unstable and loses carbon dioxide by readjustment of electrons in the molecule:



In support of this mechanism it may be pointed out that mixed carboxylic-carbamic anhydrides have been actually isolated[18] and characterized.[19] Moderate heating (80–100°) of these mixed anhydrides produced a carboxylic anhydride and a symmetrically disubstituted urea. Stronger heating (160–170°) of the mixed anhydrides caused evolution of carbon dioxide and the production of an amide. Evidence that the carbon dioxide comes from the carbonyl attached to the nitrogen is supplied by the fact that in the reaction of isothiocyanates the gas evolved is carbon oxysulfide,[20] and by the liberation of ordinary carbon dioxide[21] from the reaction of phenyl isocyanate and acetic-1-C^{14} acid: $CH_3C^{14}OOH + PhNCO \rightarrow [CH_3C^{14}O{-}O{-}CONHPh] \rightarrow CH_3C^{14}ONHPh + CO_2$.

EXPERIMENTAL

Reagents. Ethyl isocyanatoacetate, b.p. 72–73° (14 mm.), was prepared[22] in 83% yield by reaction of glycine ethyl ester hydrochloride[23] with phosgene. Octanoic anhydride,[24] b.p. 136–140° (1.5 mm.); m.p. −1°, was prepared in 82% yield from octanoic acid and acetic anhydride. Benzoic anhydride, m.p. 43°, was prepared in 81% yield by the reaction of benzoic acid with benzoyl chloride[25] in pyridine.

We tested two syntheses of phenylacetic anhydride. The reaction of phenylacetic acid and acetic anhydride gave 67–70% yield of material, m.p. 71–72°, compared to the stated yield[26] of 80%. A better yield was obtained by reaction of phenylacetyl chloride and acetic anhydride, adapting a procedure recommended[27] for other acid anhydrides. A mixture of 51 g. (0.33 mole) of phenylacetyl chloride and 35 g. (0.33 mole or 100% excess) of 97% acetic anhydride was heated gently until acetyl chloride started distilling off. This distillation lasted 12 hr. All material boiling up to 140° (1 mm.) was then removed from the mixture, and the residue of phenylacetic anhydride was recrystallized from benzene-hexane; m.p. 71–72°; yield, 37 g. (88.4%).

Phenaceturic acid, m.p. 142–143°, was prepared in 64% yield by the reaction[28] of glycine with methyl phenylacetate and sodium methoxide. Its methyl ester, m.p. 87–88°, was prepared in 85% yield by reaction of the acid with diazomethane, and in 78% yield by esterification of the acid with 4 parts of methanol in ethylene dichloride together with a little concentrated sulfuric acid.

N-Acetylbenzamide. A solution of 1.21 g. (0.01 mole) of benzamide in 2.04 g. (0.02 mole) of acetic anhydride was treated with two drops (0.1 ml.) of concentrated sulfuric acid, and heated to 135–140° for 3 min. The reaction mixture was poured into 50 ml. of cold water. The precipitate was collected, washed with ethanol, and recrystallized from dilute ethanol; weight, 1.0 g. (61%); m.p. 117–118° (lit.[29] m.p. 116–117°).

N-Benzoylphenylacetamide. An equimolar (0.02 mole) mixture of phenylacetic anhydride and benzamide was fused. Two drops of concentrated sulfuric acid were added to the yellow-red melt. The mixture was heated at 160–180° for 2 min. It was left to solidify during 12 min. and the solid was remelted and poured into water. The separated solid was collected and triturated with water. In the aqueous filtrate there were a few drops of a colored oil, heavier than water, with the odor of a nitrile. The solid was recrystallized from 95% ethanol; weight 2.5 g. (52%); m.p. 129–130°, and mixed melting point with benzamide, 105–120° (lit.[30] m.p. 129–130°).

Bisphenylacetimide. (*A*) *From anhydride and benzamide.* A mixture of 5.1 g. (0.02 mole) of phenylacetic anhydride and 1.2 g. (0.01 mole) of benzamide, containing two drops of concentrated sulfuric acid, was heated at 160–180° for 10 min. After cooling it was poured into 30 ml. of water. The precipitated bisphenylacetimide was separated and recrystallized twice from 95% ethanol; weight 1.5 g.; m.p. 190–192° (lit.[31] m.p. 192°).

(*B*) *From acid chloride and benzamide.* A mixture of 9.2 g. (0.076 mole) of benzamide and 36 g. (0.233 mole) of phenylacetyl chloride was heated at 80–82° for 24 hr. A very

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(15) C. Harries and M. Weiss, *Ann.*, **327**, 369 (1903).

(16) C. Graenacher and H. Landolt, *Helv. Chim. Acta*, **10**, 799 (1927).

(17) R. Loquin and V. Cherchez, *Compt. rend.*, **188**, 177 (1929).

(18) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906).

(19) C. Naegeli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935).

(20) F. Kraft and H. Karstens, *Ber.*, **25**, 452 (1892).

(21) A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953).

(22) W. Siefken, *Ann.*, **562**, 105 (1949).

(23) C. S. Marvel, *Org. Syntheses*, Coll. Vol. II, 310 (1943).

(24) D. Holde and R. Gentner, *Ber.*, **58**, 1422 (1925).

(25) H. Adkins and Q. E. Thompson, *J. Am. Chem. Soc.*, **71**, 2242 (1949).

(26) W. Autenrieth and G. Thomae, *Ber.*, **57**, 431 (1927).

(27) F. Zetzsche, F. Enderlin, C. Fluetsch, and E. Menzi, *Helv. Chim. Acta*, **9**, 181 (1926); N. O. V. Sonntag, J. R. Trowbridge, and I. J. Krems, *J. Am. Oil Chem. Soc.*, **31**, 151 (1954).

(28) J. H. Ford, *J. Am. Chem. Soc.*, **71**, 3842 (1949).

(29) A. W. Titherley and T. H. Holden, *J. Chem. Soc.*, **101**, 1871 (1912).

(30) R. H. Wiley and W. B. Guerrant, *J. Am. Chem. Soc.*, **71**, 981 (1949).

(31) C. E. Colby and F. D. Dodge, *Am. Chem. J.*, **13**, 1 (1891).

small amount of hydrogen chloride was evolved. All the volatile material was then removed by rapid distillation at a bath temperature of up to 139° and 10 mm. The solid nonvolatile cake was triturated with pentane and collected on a filter; yield, 18.5 g.; m.p. 190–192°, after two recrystallizations from benzene and glacial acetic acid.

(*C*) *From phenylacetamide.* Two portions of phenylacetamide weighing 2.0 g. (0.016 mole) each were heated in an open tube at 180° for 6 hr. Five drops (0.2 ml.) of concentrated sulfuric acid had been added to only one of the tubes at the beginning of the reaction. The contents of the tube without the acid were readily soluble in slightly warm 95% ethanol. The solid obtained from this solution on cooling was phenylacetamide; m.p. and mixed m.p. 154–155°. Part of the contents (a few mg.) of the tube with the acid was insoluble in warm 95% ethanol. It did not melt up to 290° and possibly was cyanuric acid.[32] Fractional crystallization of the ethanolic solution yielded 0.2 g. of bisphenylacetimide (m.p. 193–194°) and 1.7 g. of unreacted phenylacetamide (m.p. 154–155°).

Ethyl phenaceturate. A mixture of 0.75 g. (0.0054 mole) of glycine ethyl ester hydrochloride and 4.1 g. (0.016 mole) of phenylacetic anhydride was heated at 165° for 3 hr. A slow stream of nitrogen was passed through the melt throughout this period. All volatile material was removed at a bath temperature up to 190° and 2 mm. Repeated extraction of the residue with boiling hexane produced 0.6 g. of ethyl phenaceturate; m.p. and mixed m.p. 81–82°.

In contrast, there was no reaction after 23 hr. when 1.4 g. of glycine ethyl ester hydrochloride was added to a cold (−60°) solution of 4 g. of phenylacetyl chloride, 100 ml. of dry chloroform, 25 ml. of dry methylene chloride, and 2.8 g. of dry pyridine. After processing, 1.35 g. of glycine ethyl ester hydrochloride was recovered, m.p. and mixed m.p. 142–143°.

Attempts to acylate phenaceturic esters. From an original 2.07 g. of powdered methyl phenaceturate 1.6 g. was recovered (m.p. and mixed m.p. 86–87°) after treatment for 21 hr. at −65° in a mixture containing 3.1 g. of phenylacetyl chloride, 100 ml. of dry, alcohol-free chloroform, 25 ml. of dry methylene chloride, and 1.8 g. of dry pyridine.

A mixture of 1.11 g. of ethyl phenaceturate and 6.35 g. of phenylacetic anhydride in 2 g. of dry pyridine was refluxed gently for 5.5 hr. Volatile materials were removed by heating the mixture up to 150° at 2-mm. pressure. Repeated extractions of the dark red oily residue with boiling hexane yielded only phenylacetic anhydride; m.p. and mixed m.p. 75–76°.

Sodium bisphenylacetimide and ethyl chloroacetate. A solution of 3.0 g. of sodium bisphenylacetimide in dry xylene was mixed with 1.35 g. of ethyl chloroacetate and a small crystal of potassium iodide. The mixture was refluxed with stirring for 1 hr., and the xylene was distilled off slowly. Ether extraction of the colored oily residue yielded 1 g. of phenylacetamide; m.p. and mixed m.p. 154.5–155.5°. Treatment of the viscous red oil with various other solvents failed to extract any solid material. Extraction with water produced sodium chloride.

The same reaction was repeated without solvent. The mixture was heated at 155° for 3 hr. The only product isolated by extraction was again 1 g. of phenylacetamide.

N-Phenylphthalimide. (*A*) *From phenyl isocyanate.* A mixture of 1.5 g. (0.01 mole) of phthalic anhydride and 1.2 g. (0.01 mole) of phenyl isocyanate was heated by a bath at 180° for 19 hr. Treatment of the solidified mixture with ethanol produced 1.9 g. of *N*-phenylphthalimide (85% yield); m.p. 204–205° (from 95% ethanol), (lit.[33] 205°); mixed melting point with phthalic acid, 185–189°.

(*B*) *From phenyl isocyanate and perchloric acid.* The same mixture as in (A) was treated with two drops of 70% perchloric acid, and it was heated at 135° for 20 min. Carbon dioxide gas was evolved and the melt turned green, then red, and finally violet. Extraction with boiling ethanol yielded 0.6 g. of *N*-phenylphthalimide; m.p. 204–205°.

(*C*) *From phenyl isocyanate and pyridine.* The same mixture as in (A) was dissolved in 40 ml. of dry pyridine and it was refluxed for 5 hr. The pyridine was then removed (35 mm.) and the residue was dissolved in boiling 95% ethanol. Pure *N*-phenylphthalimide crystallized on cooling; weight 1.4 g.; m.p. 204–205°.

(*D*) *From phenyl isothiocyanate and pyridine.* A solution of 3.0 g. (0.02 mole) of phthalic anhydride and 2.7 g. (0.02 mole) of phenyl isothiocyanate (*cf.* Dains[12]) in 50 ml. of dry pyridine was refluxed for 20 hr. The solvent was then removed at reduced pressure, and the residue was dissolved in 95% ethanol. The *N*-phenylphthalimide precipitated in fine needles on cooling; weight 3.85 g. (86%); m.p. 204–205°.

N-Phenyldiacetimide. A mixture of 5.95 g. (0.05 mole) of phenylisocyanate and 5.10 g. (0.05 mole) of acetic anhydride (98%) was heated at 175° for 11 hr. The system was provided with a reflux condenser, and it was protected from moisture. The unreacted acetic anhydride and phenyl isocyanate were removed at 12.5-mm. pressure. The *N*-phenyldiacetimide distilled over at 142–146° (12.5 mm.), and it crystallized slowly by long chilling; weight, 6.3 g. (72% yield); m.p. 36–37° (lit. 37°).

Extraction of the distillation residue with boiling ligroin yielded 1 g. of acetanilide; m.p. 113.5–114°. About 0.15 g. of *sym*-diphenylurea was obtained by chilling the forerun; m.p. 238–239°.

Phenylacetanilide. (*A*) *From phenyl isocyanate and pyridine.* A solution of 2.54 g. of phenylacetic anhydride and 1.19 g. of phenyl isocyanate in 50 ml. of dry pyridine was refluxed for 15 hr. The pyridine was removed at reduced pressure. The oily residue was very soluble in warm 95% ethanol. Removal of the ethanol and treatment of the residue with boiling hexane yielded 1.3 g. of phenylacetanilide; m.p. 115–117° (lit.[34] 117°); mixed melting point with an authentic sample, 116–117°.

(*B*) *From phenyl isothiocyanate at 180°.* A mixture of 2.54 g. of phenylacetic anhydride and 1.35 g. of phenyl isothiocyanate was heated at 180° for 4.5 hr. The product was crystallized from boiling ligroin (86–100°); yield, 2 g.; m.p. and mixed m.p. 116–117°.

(*C*) *From phenyl isothiocyanate at 215°.* The same mixture was heated, in a tube protected from moisture, at 215° for 15 hr. Again the only solid isolated was 1.8 g. of phenylacetanilide; m.p. 115–116°.

Ethyl diacetimidoacetate. An equimolar mixture of 10.7 g. of acetic anhydride (98%) and 12.9 g. of ethyl isocyanatoacetate was protected from moisture and heated at 185° for 12 hr. Fractional distillation at 2.5-mm. pressure yielded 13.75 g. (73.5%) of ethyl diacetimidoacetate; b.p. 122.5–123° (2.5 mm.); n_D^{25} 1.4490 (lit.[7b] 106–110° (2 mm.), n_D^{25} 1.4525).

When a comparable mixture was heated for only 6 hr. half of the acetic anhydride and considerable of the isocyanate were recovered. The yield of ethyl diacetimidoacetate was 6 g., but in addition two solid fractions were obtained: 0.45 g. of ethyl *N,N'*-carbonylbis(aminoacetate), m.p. and mixed m.p. 145° (lit.[35] 144–146°), and 0.52 g. of ethyl 1-acetyl-3-hydantoinacetate, m.p. 87–88°, which was analyzed. The acetic anhydride used in the last run was distilled over phosphorus pentoxide before use but the presence of these byproducts suggests that still greater precautions would be necessary to guard against the presence of water or acetic acid in the reactants.

Anal. (of the hydantoin) Calcd. for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.18; H, 4.91; N, 12.74.

Reactions of ethyl diacetimidoacetate. (*A*) *Acetyl determination.* A mixture of 3.00 g. of ethyl diacetimidoacetate and

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(32) *Cf.* O. Diels, *Ber.*, **36,** 740 (1903); C. S. Venable and F. J. Moore, *J. Am. Chem. Soc.*, **39,** 1750 (1917).

(33) O. Doebner, *Ann.*, **210,** 267 (1881).

(34) A. W. Hofmann, *Ber.*, **13,** 1225 (1880).

(35) E. Fischer, *Ber.*, **34,** 440 (1901).

6.5 ml. of a 50% potassium hydroxide solution was refluxed for 6 hr. The solution was then acidified with dilute sulfuric acid, diluted with water to 100 ml., and distilled. When two thirds of the liquid had distilled, 50 ml. of water was added and the distillation was resumed. The combined distillates were titrated with *N* sodium hydroxide solution.

Anal. Calcd. for $C_8H_{13}NO_4$: Acetyl, 45.9. Found: Acetyl, 45.3.

(*B*) *Phosphorus pentachloride.* Addition of 4.16 g. (0.02 mole) of phosphorus pentachloride to 3.74 g. (0.02 mole) caused an exothermic reaction to take place, with evolution of a gas. Further heating up to 150° produced 2.45 g. (0.031 mole) of acetyl chloride, b.p. 50–53°, which gave acetanilide, m.p. 115–116°, on reaction with aniline.

Ethyl dipropionimidoacetate. A mixture of 6.45 g. (0.05 mole) of ethyl isocyanatoacetate and 5.62 g. (0.043 mole) of propionic anhydride was heated in a bath at 200° for 6 hr. Carbon dioxide was evolved. The mixture was distilled and a fraction weighing 6.0 g., b.p. 125–150° (2 mm.), was separated and distilled again. The middle fraction was ethyl dipropionimidoacetate, b.p. 109° (0.2 mm.); n_D^{25} 1.4512; weight, 4.0 g.

Anal. Calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 54.42; H, 7.87; N, 7.08.

The discrepancy in the analysis suggests the presence of small amounts of ethyl 1-propionyl-3-hydantoinacetate, and some was actually isolated from the main fraction.

Ethyl 1-propionyl-3-hydantoinacetate. A total of 2.5 g. of this ester was extracted from the above distillation residue with boiling ligroin (86–100°). It melted at 117–118°.

Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57; neut. equiv., 242.2. Found: C, 50.03; H, 6.00; N, 11.77; neut. equiv., 242.

Ethyl dioctanimidoacetate. (A) A mixture of 10.3 g. (0.038 mole) of octanoic anhydride and 4.90 g. (0.038 mole) of ethyl isocyanatoacetate was heated in a bath at 175° for 10 hr. Distillation of the mixture yielded crude ethyl dioctanimidoacetate, which was purified by two redistillations. The final product weighed 9.5 g. (70% yield); b.p. 177–179° (0.9 mm.).

Anal. Calcd. for $C_{20}H_{37}NO_4$: C, 67.57; H, 10.49. Found: C, 67.36; H, 10.19.

Ethyl 1-octanoyl-3-hydantoinacetate. Repetition of the above experiment at 197° and with a 10% excess of the isocyanate, followed by prolonged chilling at 0° of the crude fraction of ethyl dioctanimidoacetate produced 0.3 g. of ethyl 1-octanoyl-3-hydantoinacetate, m.p. 93.5–94.5° (acetone-water).

Anal. Calcd. for $C_{15}H_{24}N_2O_5$: C, 57.67; H, 7.74; N, 8.97. Found: C, 57.84; H, 7.62; N, 9.33.

Ethyl dibenzimidoacetate. A mixture of 6.78 g. (0.03 mole) of benzoic anhydride and 3.87 g. (0.03 mole) of ethyl isocyanatoacetate was heated in a bath kept at 200° for 8.5 hr., and then distilled. The fraction distilling at 160–190° (0.15 mm.) was a very viscous liquid, which by repeated alternate chilling to 0°, and thawing, was made to crystallize in part. The crystalline material weighed 6.5 g., and melted at 96–99°. Three recrystallizations from methanol produced pure ethyl dibenzimidoacetate, m.p. 103.5–104°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.10; H, 5.50.

In another experiment with the same reagents it was observed that when the bath temperature was below 195° there was no evolution of carbon dioxide from the mixture. The evolution would start again as soon as the bath temperature was over 195°. From a reaction mixture kept at 177° for 6 hr., 98.7% of the benzoic anhydride, and 83% of the isocyanate were recovered.

Ethyl phenaceturate. A mixture of 9.7 g. (0.038 mole) of phenylacetic anhydride and 4.9 g. (0.038 mole) of ethyl isocyanatoacetate was heated in a bath at 175° for 9 hr. Carbon dioxide evolution was observed at temperatures over 160°. Distillation of the mixture at 1.5-mm. pressure yielded 10 g. of a fraction distilling at 170–195°, and 2.4 g. of a residue. The main fraction was ethyl phenaceturate, m.p. 77–78° (ether), mixed melting point with pure ethyl phenaceturate of m.p. 80–81.5° was 78–80°. Its nitrogen content by analysis was 6.35% (theory, 6.33). Extraction of the residue with various solvents failed to yield any other material.

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Evanston, Ill.

[Contribution from the Chemical Laboratories of the University of California]

The Grignard Reaction with 2-(β-Cyanoethyl)-2-ethylhexanal and Further Conversions of the Reaction Products. Limitations of Anisole as Solvent for the Grignard Reaction

JAMES CASON, KENNETH W. KRAUS, and WM. D. MacLEOD, Jr.

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Reaction of *n*-butylmagnesium bromide with an approximately equimolar amount of 2-(β-cyanoethyl)-2-ethylhexanal at 0° in diethyl ether as solvent yields about equal amounts of the reduction product, 2-(β-cyanoethyl)-2-ethyl-1-hexanol (II), and the addition product, 6-(β-cyanoethyl)-6-ethyl-5-decanol (III). There could be detected no product resulting from reaction of the nitrile grouping. Yields were similar, whether normal addition or inverse addition was used in the reaction. In anisole as solvent, considerable quantities of two unidentified by-products could be detected by gas phase chromatography, and the yield of the addition product, III, was somewhat lower. With inverse addition in anisole, the amount of reduction was much greater than observed when diethyl ether was the solvent. The addition product, the cyano alcohol III, was hydrolyzed to a lactone which was transesterified with methanol to yield a mixture of unsaturated esters. Ozonolysis of these esters indicates the mixture expected from rearrangement of the carbonium ion resulting from alkyl-oxygen fission of the lactone, and development of the double bond at less substituted positions as well as the most substituted position.

The reaction of *n*-butylmagnesium bromide with an equimolar amount of 2-(β-cyanoethyl)-2-ethylhexanal (I) has been examined, partly in order to evaluate the relative reactivities of the nitrile and the highly hindered aldehyde, and partly to supply for futher study compounds containing the highly