Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.82; H, 4.92; N, 12.84.

Attempted Condensation of N-Hydroxymethylphthalimide and Malonic Acid.—Ten and four-tenths grams of malonic acid (0.1 mole) and 17.7 g. of N-hydroxymethyl phthalimide were dissolved in 50 ml. of concentrated sulfuric acid. No appreciable heat was evolved. After standing overnight the solution was poured on ice, filtered, washed and dried, yield 7.4 g. The product was totally insoluble in sodium bicarbonate and was therefore not investigated further.

Attempted Condensation of N-Hydroxymethylphthalimide and Ethyl Malonate.—Seventeen ml. of ethyl malonate and 17.7 g. of N-hydroxymethylphthalimide were dissolved in sulfuric acid and allowed to stand three days. Pouring on ice yielded 11.0 g. of a product melting at 150–195°. Crystallization once from ethanol, once from acetic acid, twice from ethanol and once from toluene brought the m. p. to 224–226°. The material was insoluble in sodium hydroxide in the cold.

Anal. Calcd. for the hypothetical condensation product $C_{16}H_{17}NO_6$: N, 5.37. Found: N, 9.51. The compound was not investigated further.

Summary

1. N-Hydroxymethylphthalimide reacts with certain nitriles in concentrated sulfuric acid to yield the N-(phthalimido methyl) derivatives of the amides corresponding to the nitriles.

2. It seems probable that the similar condensation of English and Clapp yielded a product analogous to those reported here.

3. N-Hydroxymethylphthalimide does not react with the active methylene group of malonic acid or ester in sulfuric acid solution.

EASTON, PENNSYLVANIA RECEIVED SEPTEMBER 27, 1946

[CONTRIBUTION FROM NATIONAL OIL PRODUCTS COMPANY, NOPCO CHEMICAL DIVISION]

The Reaction of Certain Secondary Amines with Phthalic Anhydride. A New Synthesis of β-Alanine

BY SAUL CHODROFF, ROLAND KAPP AND CHARLES O. BECKMANN[1]

The synthesis of β-alanine, a subject of many recent investigations,[2] has generally involved the hydrolysis of either β-amino, or β-phthalimidopropionitrile,[3] as obtained, respectively, by the action of ammonia and phthalimide upon acrylonitrile.

An excess of ammonia, dependent upon experimental conditions, converted acrylonitrile to β-aminopropionitrile in yields of 20–30%, with almost the entire balance appearing as the secondary amine, β,β-iminodipropionitrile. Whereas the secondary amine has been hydrolyzed at high temperatures and pressures to β-alanine in yields of 35%,[4] a simpler conversion was desirable and this paper describes a method of preparing β-alanine from three secondary amines derived from acrylonitrile, (I) β,β'-iminodipropionitrile, (II) β,β'-iminodipropionic acid and (III) the diethyl ester of (II) through preliminary conversion with phthalic anhydride at 200° to the corresponding pthalimide, with the simultaneous formation of water, together with acrylonitrile acrylic acid and its ester in the respective reactions.

The phthalimido derivatives, identified through analysis and comparison with authentic samples as was the acrylonitrile through its refractive index as well as boiling point and the acrylic acid through conversion to the hitherto undescribed S-benzylthiouronium salt, were hydrolyzed with 30% sulfuric acid, phthalic acid was removed from the products by filtration and the filtrates, neutralized with barium hydroxide and refiltered for the removal of barium sulfate prior to concentration to a sirup and subsequent dilution with alcohol, gave β-alanine in yields of 65–90%.

In practice, it is desirable to use the β,β'-iminodipropionitrile in the reaction with phthalic anhydride since the acrylonitrile is recoverable and can be recycled.

Primary amines and phthalic anhydride generally yield acid amides, convertible to imides on fusion, while secondary amines usually form stable acid amides[5] and the anomalous formation of imides from the secondary amines under discussion led to a study of the course of the reactions involved. Condensation of equimolecular quantities of phthalic anhydride and β,β'-iminodipropionitrile in methyl isobutyl ketone yielded the acid phthalamide of β,β'-iminodipropionitrile which, at 200°, was converted quantitatively to the β-phthalimidopropionitrile, characterized by hydrolysis with concentrated sulfuric acid to β-phthalimidopropionamide. Contrasting with this condensation was that of β-aminopropionitrile which, in non-aqueous as well as non-hydroxylated and even in so low boiling solvents as carbon tetrachloride, gave, instead of the anticipated acid amide, β'-phthalimidopropionitrile, characterized as hereinbefore mentioned by hydrolysis to β-phthalimidopropionamide.

The following mechanism has been postulated to explain the behavior of the secondary amines when fused with phthalic anhydride

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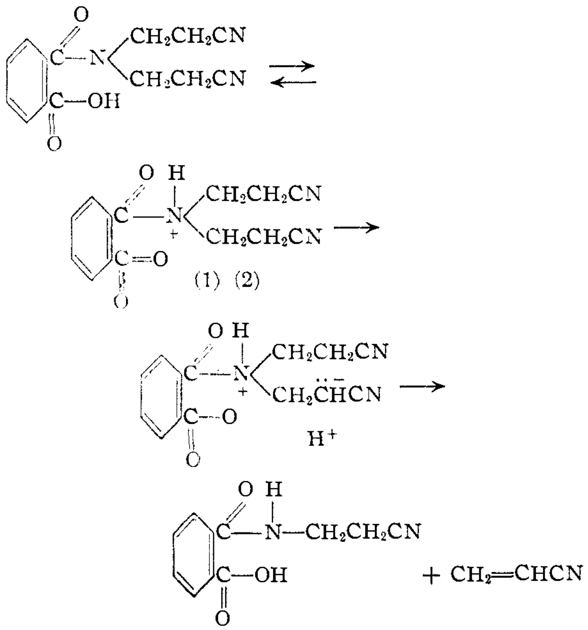
[1] Present address: Department of Chemistry, Columbia University, New York 27, N. Y.

[2] J. H. Paden and P. M. Kirk, U. S. Patent 2,335,605; R. T. Dean, U. S. Patent 2,335,653; G. H. Carlson and C. N. Hotchkiss, U. S. Patent 2,335,997; G. H. Carlson, U. S. Patent 2,336,067; S. R. Buc, J. H. Ford and E. C. Wise, THIS JOURNAL, **67**, 92 (1945).

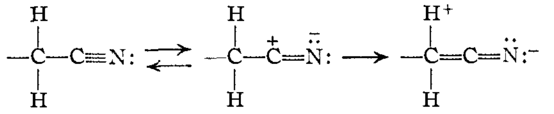
[3] A. Galat, THIS JOURNAL, **67**, 1414 (1945).

[4] P. M. Kirk, U. S. Patent 2,334,163.

[5] O. Kamm, "Qualitative Organic Analysis," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1932, pp. 69–70.



Because of the positive charge on the N, electrons will be displaced toward it, making carbon atoms 1 and 2 successively positive, an effect which, augmented by the presence of a CN, $COOC_2H_5$, or COOH group, will result in the loss of a proton from carbon 2. The mechanism is a function of the combined effect of the charge on the NH, augmented by the carbonyl of the phthalic acid as well as the usual effect of CN which is given by



and the cleavage, accordingly, is similar to that of α,β-keto sulfones[6] and the thermal scission of *p*-toluenesulfonate of ethylene cyanohydrin.[7]

Experimental

Phthalic Anhydride Fusions. (a) **β,β'-Iminodipropionitrile.**—(24.6 g.; b. p. 168–170° (3 mm.))[8] was heated three-quarters of an hour (oil-bath temperature 200°) with 29.6 g. of phthalic anhydride in a 100-cc. round-bottom flask equipped for distillation. The mass became molten at 175–180° and at 200° water (3 cc.) and acrylonitrile (10 cc.; 80% of theory; separated from water, dried with calcium chloride and distilled, b. p. 76–77°; n^{20}_D 1.3928)[9] distilled rapidly; the final traces of volatile material being collected *in vacuo* (100 mm.). The hot fused mass, poured into 300 cc. of agitated water, deposited β-phthalimidopropionitrile quantitatively as a pale yellow solid (m. p. 140–143°) which, upon crystallization from aqueous methanol, gave a 75% yield of the pure product, melting at 151–152° and, after recrystallization, at 153°,[10] as did an admixture with the crystallized product obtained by fusion of β-aminopropionitrile with phthalic anhydride.

Anal. Calcd. for $C_{11}H_8O_2N_2$: C, 65.99; H, 4.03; N, 14.00. Found: C, 66.00; H, 4.00; N, 14.00.

(b) **β,β'-Iminodipropionic acid**[11] (32.2 g.) and 29.6 g. of phthalic anhydride were fused as previously indicated, and the acrylic acid in the distillate, after neutralization with sodium hydroxide, was converted to the S-benzylthiouronium salt,[12] m. p. 157–158°, after crystallization from methanol.

Anal. Calcd. for $C_{11}H_{14}N_2SO_2$: C, 55.42; H, 5.92; N, 11.76; S, 13.42. Found: C, 55.41; H, 5.91; N, 11.90; S, 13.35.

The fusion product, treated as previously noted, gave a quantitative yield of β-phthalimidopropionic acid which crystallized in an 85% yield from aqueous methanol and melted at 151°,[13] as did a mixture with the recrystallized fusion product of β-aminopropionic acid and phthalic anhydride.

Anal. Calcd. for $C_{11}H_9O_4N$: N, 6.74; neut. equiv., 208. Found: N, 6.53; neut. equiv., 207.

(c) **Diethyl-β,β'-iminodipropionate**[14] (4.34 g.) and 2.96 g. of phthalic anhydride, fused as previously indicated, gave a product which congealed slowly in water and melted at 65–66° after crystallization from ethanol; yield 3.55 g. (75%).

An authentic sample of ethyl β-phthalimidopropionate prepared by treating the sodium salt of β-phthalimidopropionic acid with thionyl chloride and the resulting acid chloride with ethanol, melted at 66–67° as did a mixture with the above-described purified fusion product.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 4.66. Found: C, 62.94; H, 5.30; N, 5.53.

The Acid Phthalamide from β,β'-Iminodipropionitrile.—A mixture of 7.4 g. of phthalic anhydride and 6.15 g. of β,β'-iminodipropionitrile was boiled four hours in 50 cc. of methyl isobutyl ketone, the solution was cooled and deposited 11.93 g. (89% yield) of the acid amide, melting at 111.5–113°, as it did after crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{13}O_3N_3$: C, 61.98; H, 4.83; N, 15.49; neut. equiv., 271. Found: C, 61.56; H, 4.69; N, 16.14; neut. equiv., 274.

During one-half hour at 200° the amide was converted quantitatively to β-phthalimidopropionitrile, melting at 150–151°, as did the admixture with an authentic sample.

Reaction of β-Aminopropionitrile with Phthalic Anhydride in Solvents.—A mixture of 14 g. of β-aminopropionitrile and 29.6 g. of phthalic anhydride was boiled two hours in methyl isobutyl ketone, the solution was cooled and deposited 32 g. (75% yield) of β-phthalimidopropionitrile (m. p. 140–142°) which crystallized from methanol in 85% yield, melted at 152–153° and proved identical with the product similarly formed in carbon tetrachloride.

On warming 5 g. of the nitrile in 10 cc. of concentrated sulfuric acid for ten minutes on the steam-bath, pouring

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(6) E. P. Kohler and R. G. Larsen, THIS JOURNAL, **57**, 1448 (1935).

(7) G. R. Clemo and E. Walton, *J. Chem. Soc.*, 723 (1928).

(8) U. Hoffmann and B. Jacobi, U. S. Patent 1,992,615.

(9) E. C. Hurdis and C. P. Smyth, THIS JOURNAL, **65**, 89 (1943); reported n^{22}_D 1.3907.

(10) J. F. Olin and T. B. Johnson, THIS JOURNAL, **53**, 1475 (1931), reported 153° and Galat[3] reported 154–155.5° as the melting point for this compound.

(11) This compound was prepared in 60% yield by an eight-hour hydrolysis under reflux of β,β'-iminodipropionitrile with 20% barium hydroxide (1.1 mole $Ba(OH)_2 \cdot 8H_2O$ per mole of nitrile). Removal of barium with an equivalent of sulfuric acid, filtration of the barium sulfate and concentration of the filtrate yielded the acid as a thick sirup which crystallized when triturated with methanol; m. p. 149–150.5°. J. H. Ford, THIS JOURNAL, **67**, 876 (1945), reported 151–151.5°.

(12) J. J. Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(13) W. J. Hale and E. C. Britton, THIS JOURNAL, **41**, 841 (1919), reported 151° as the melting point.

(14) The ester, b. p. 137–139 (12 mm.), was prepared in 40% yield by reacting β,β'-iminodipropionic acid with absolute ethanol containing 4% dry hydrogen chloride and isolated in the manner described by G. M. Kuettel and S. M. McElvain, THIS JOURNAL, **53**, 2692 (1931).

the brown solution into 100 cc. of water and crystallizing the precipitated product from aqueous methanol, 4.15 g. (76% yield) of β-phthalimidopropionamide was obtained, melting at 204–206°, as did an admixture with the amide obtained on hydrolyzing the β-phthalimidopropionitrile previously described.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.50; H, 4.58; N, 12.84. Found: C, 60.40; H, 4.80; N, 13.00.

β-Alanine.—Hydrolysis of β-phthalimidopropionitrile and β-phthalimidopropionic acid with 20% hydrochloric acid requires four and one-half hours,[3,15] whereas conversion of the nitrile with 30% sulfuric acid is complete in three hours. The crude β-phthalimidopropionitrile (20 g.) was heated for ten minutes with 20 cc. of 96% sulfuric acid on the steam-bath for conversion to the amide and, following dilution of the cooled solution with 40 cc. of water, the mixture was boiled for one hour to redissolve precipitated solids and for an additional two hours following the crystallization of phthalic acid. The precipitated acid (slightly yellow, m. p. 200°, 16.1 g. or 97%) was filtered from the cooled solution and washed with two 20-cc. portions of cold water, the filtrate was diluted to 400 cc. and treated with barium hydroxide equivalent to the sulfuric acid initially used and after removal and lixiviation of the precipitated sulfate, the combined filtrates were concentrated to a sirup prior to trituration with methanol, which deposited crystalline β-alanine, melting at 197° (with decomposition) after being washed with methanol and dried at 60°; yield 8.2 g.; 92%.

The authors are indebted to Mr. J. F. Alicino of the Squibb Institute, New Brunswick, N. J., for the analyses.

Summary

A convenient method has been described for preparing β-alanine from β,β′-iminodipropionic acid and its derivatives, involving conversion with phthalic anhydride to the corresponding β-phthalimido compounds and a subsequent hydrolysis.

HARRISON, N. J.

RECEIVED JULY 11, 1946

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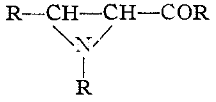
[15] Gabriel, *Ber.*, **38**, 633 (1905).

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

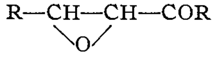
Ethylene Imine Ketones.[1] Reaction with Grignard Reagents[2]

BY NORMAN H. CROMWELL

The unique combination of functional groups present in the ethylene imine ketones (A) suggests that an extensive investigation of reactions likely to lead to combination with the carbonyl group and/or opening of the ethylene imine ring should prove to be quite interesting.



(A)



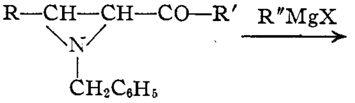
(B)

The structural relationship between the ethylene imine ketones (A) and the epoxy ketones (B) suggests a comparison of the properties of the two series. Several investigations of the latter series are to be found in the literature. The present communication is concerned with the reaction of ethylene imine ketones with Grignard reagents, a reaction which was extensively investigated with epoxy ketones several years ago by E. P. Kohler and his students.[3]

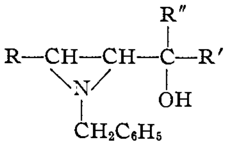
Three new ethylene imine ketones, 1-benzyl-2-(*m*-nitrophenyl)-3-benzoylethylenimine (I), 1-benzyl-2-phenyl-3-(*p*-methylbenzoyl)-ethylenimine (II) and 1-benzyl-2-(*p*-tolyl)-3-benzoylethylenimine (III) have been prepared from benzylamine and the corresponding α,β-dibromobenzylacetophenones by the method described in the previous papers dealing with ethylene imine ketones.[1,4]

1-Benzyl-2-phenyl-3-benzoylethylenimine[4] was treated with an excess of methylmagnesium iodide, phenylmagnesium bromide and *p*-tolylmagnesium bromide, respectively, while the ethylene imine ketones (II) and (III) were each allowed to react with an excess of phenylmagnesium bromide.

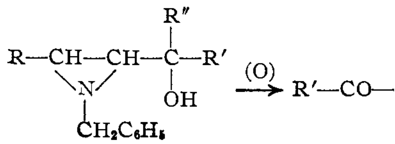
The crystalline product in each case corresponded to the reaction of the ethylene imine ketone with one equivalent of Grignard reagent. Oxidative cleavage experiments indicated these compounds to be the enimine carbinols (IV), (V), (VI), (VII) and (VIII), respectively.



(I) R, m-$NO_2C_6H_4$; R′, C_6H_5
(II) R, C_6H_5; R′, p-$CH_3C_6H_4$
(III) R, p-$CH_3C_6H_4$; R′, C_6H_5



(IV) R and R′, C_6H_5; R″, CH_3
(V) R, R′ and R″, C_6H_5
(VI) R and R′, C_6H_5; R″, p-$CH_3C_6H_4$
(VII) R and R″, C_6H_5; R′, p-$CH_3C_6H_4$
(VIII) R′ and R″, C_6H_5; R, p-$CH_3C_6H_4$



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[1] For the previous paper in this series see Cromwell and Caughlan, THIS JOURNAL, **67**, 2235 (1945).

[2] Presented before a session of the Division of Organic Chemistry, 110th Meeting of the American Chemical Society, Chicago, Illinois, September 12, 1946.

[3] Kohler, Richtmyer and Hester, THIS JOURNAL, **53**, 205 (1931).

[4] Cromwell, Babson and Harris, THIS JOURNAL, **65**, 312 (1943).