[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

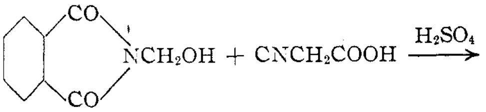
The Reaction of N-Hydroxymethyl Phthalimide with Nitriles

BY SAUL R. BUC[1]

Monti[2] has shown that N-hydroxymethylbenzamide reacts with certain β-diketones with elimination of water to yield benzoylaminomethyl derivatives

$$C_6H_5CONHCH_2OH + CH_2(COR)_2 \longrightarrow C_6H_5CONHCH_2CH(COR)_2 + H_2O$$

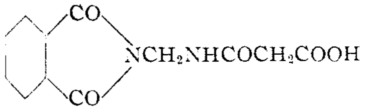
English and Clapp[3] have carried out a similar reaction with the same benzamide derivative and diethyl α-cyanopimelate. We have studied the closely related reaction of N-hydroxymethyl phthalimide with cyanacetic acid, expecting to obtain a product from which β-alanine could be obtained by decarboxylation and hydrolysis.



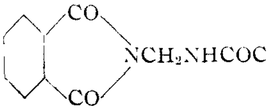
$$\underset{\text{I}}{C_{12}H_{10}N_2O_5} \longrightarrow \underset{\text{II}}{C_{11}H_{10}N_2O_3} + CO_2$$

An acid having the expected analysis for compound I was obtained in the condensation. This yielded on decarboxylation a compound II also having the expected composition. Compound II, however, did not yield β-alanine on hydrolysis. It yielded instead phthalic acid, acetic acid, ammonia and formaldehyde. Furthermore, it was not identical with β-phthalimidopropionamide prepared from β-phthalimidopropionitrile.[4] The latter was prepared (1) by a slight variation of the method of Galat,[5] (2) by the reaction of β-aminopropionitrile[6] with phthalic anhydride and (3) in very poor yield by the reaction of β-phthalimido ethyl chloride[7] with potassium cyanide.

It follows from these observations that compound I does not have the expected structure but is N-(phthalimidomethyl)-malonamic acid, while compound II is N-(phthalimidomethyl)-acetamide

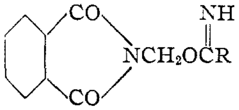


I



II

The only alternative structures which can be written are the isomeric phthalimidomethyl imino ethers. We consider this possibility excluded by



the following considerations: (1) the compounds are non-basic since they do not form sulfates in the presence of dilute sulfuric acid; (2) they are stable in the presence of boiling water, ethanol or acetic acid, a property which is not characteristic of imino ethers.

Compound II was synthesized under similar conditions from N-hydroxymethylphthalimide and acetonitrile. It was not obtained when acetamide was used. Benzonitrile yielded the analogous compound, N-(phthalimidomethyl)-benzamide, whose structure was similarly proved by hydrolysis.

From these results it seems likely that compound IV of English and Clapp[3] was not 7-benzoylamino-6-carbamylheptylic acid, but N-(benzoylaminomethyl)-pimelamic acid, C_6H_5CONH-$CH_2NHCO(CH_2)_5COOH$, and that their intermediates had the corresponding structures. This interpretation accounts for the failure of their compound IV to cyclize to a homolog of nordesthiobiotin.

The failure of N-hydroxymethylphthalimide to react with the active methylene group of cyanoacetic acid does not, of course, exclude the possibility that it might react with malonic derivatives in the absence of the nitrile group. This possibility was explored under similar conditions using malonic acid and ester. The results were negative.

Experimental[8,9]

N-Hydroxymethyl Phthalimide.—This compound was prepared essentially according to Sachs[10] except that use of a pressure vessel was found to be unnecessary. Five hundred and eleven g. of phthalimide, 260 ml. of 40% formalin and 1750 ml. of water were boiled under reflux until a clear solution resulted. This required five minutes after the boiling point was reached. After cooling overnight in the refrigerator the product was filtered with suction, washed with ice water and air-dried; yield 594 g., 96%, m. p. 137–141°. The product must not be oven-dried since it loses formaldehyde. Recrystallization from alcohol yields 94% of the original material, but the melting point is not improved.

N-(Phthalimidomethyl)-malonamic Acid.—Seventeen and seven-tenths grams (0.10 mole) of N-hydroxymethylphthalimide and 10.0 g. of cyanoacetic acid (Dow)

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[1] Present address: General Aniline and Film Corporation, Easton, Pa.

[2] Monti, *Gazz. chim. ital.*, **60**, 39 (1930); *C. A.*, **24**, 4013 (1930).

[3] English and Clapp, THIS JOURNAL, **67**, 2262 (1945).

[4] Olin and Johnson, *ibid.*, **53**, 1477 (1931).

[5] Galat, *ibid.*, **67**, 1414 (1945).

[6] Buc, Ford and Wise, *ibid.*, **67**, 92 (1945).

[7] Wenker, *ibid.*, **59**, 422 (1937).

[8] All melting points are uncorrected.

[9] Microanalyses by Messrs. Harold Emerson and William Struck, Misses Celia Triemstra and Barbara Faunsnaugh of these Laboratories.

[10] Sachs, *Ber.*, **31**, 3230 (1898).

were placed in a flask and 50 ml. of concentrated sulfuric acid previously chilled to 0° were added. The temperature rose rapidly to 45° and the reactants dissolved. The temperature was maintained at 45° by use of an ice-bath, since some decarboxylation occurs at higher temperatures. After standing overnight the mixture was poured over cracked ice. The product was filtered, washed with cold water until free of mineral acid and air-dried; yield 25.2 g., 96%. One recrystallization from 450 ml. of boiling water yielded 23.8 g., 91%, m. p. 157–158° with gas evolution, immediate resolidification and remelting at 206–208°. The analytical sample was crystallized once more from water.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.86; N, 10.68. Found: C, 55.75, 55.55; H, 3.60, 3.61; N, 10.29.

N-(Phthalimidomethyl)-acetamide. (1) By Decarboxylation of the Above Compound.—Fifty-two and four-tenths grams of N-(phthalimidomethyl)-malonamic acid were heated on an oil-bath at 170° for three hours. The crude residue weighed 43.2 g. = 99%. The product was recrystallized from 1500 ml. of alcohol yielding 36.3 g. = 84% of a product melting at 212.5–214.5°. The analytical sample was crystallized once more from alcohol.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.75; H, 4.85; N, 12.86.

(2) **From N-Hydroxymethylphthalimide and Acetonitrile.**—Seven ml. of acetonitrile, 17.7 g. of N-hydroxymethylphthalimide and 50 ml. of concentrated sulfuric acid were mixed without cooling; the temperature reached 75–80° spontaneously. After standing overnight, the mixture was poured over cracked ice, filtered, washed and dried; yield 20.3 g., 93%. One recrystallization from 650 ml. of ethanol yielded 18.0 g., 83% of product; m. p. 213–214.5°; mixed melting point with product above 212.5–214°.

Attempted Reaction of N-Hydroxymethylphthalimide with Acetamide.—Six grams of acetamide, 17.7 g. of N-hydroxymethyl phthalimide and 50 ml. of concentrated sulfuric acid were mixed. There was very little heat of reaction. After standing overnight the solution was poured over cracked ice. The precipitated solid was filtered, washed and dried; yield 8.0 g. After three crystallizations from ethanol and one from toluene the product melted at 206–208° and was shown by mixed melting point (207–208°) to be identical with a sample of diphthalimidomethyl ether[11] prepared by treatment of N-hydroxymethylphthalimide with sulfuric acid.

Hydrolysis of N-(Phthalimidomethyl)-acetamide.—Twenty-one and eight-tenths grams (0.1 mole) of this compound were refluxed eighteen hours with 24 ml. of concentrated hydrochloric acid and 50 ml. of water. The nearly colorless solution contained a mass of large crystals. After chilling these were filtered and washed, yield 15.3 g., 93%, identified as phthalic acid by conversion to β-phthalimidopropionitrile (see below), m. p. 151.3–152.5°, mixed melting point with authentic sample 151.5–152.5°. The aqueous filtrate was distilled to dryness *in vacuo* leaving a residue of 11.7 g., theory for ammonium chloride, 10.7 g. The excess weight is presumably phthalic acid which remained in solution. The ammonium chloride was identified by conversion to benzamide with benzoyl chloride and sodium hydroxide in the usual manner, m. p. 126.5–128°, m. m. p. with authentic sample 127–128°.

To the distillate was added 2 ml. of concentrated hydrochloric acid and the entire solution added to 2.0 g. of 2,4-dinitrophenylhydrazine in 100 ml. of boiling ethanol. The yellow dinitrophenylhydrazone of formaldehyde crystallized at once, m. p. 163.5–164.5°, m. m. p. with authentic sample 163.5–164.5.

A second 0.1-mole batch was hydrolyzed identically and the distillate obtained as above. This was made just basic to phenolphthalein and distilled to dryness *in vacuo* to remove formaldehyde. A sample of the residual mixture of sodium chloride and sodium acetate was converted to *p*-phenylphenacyl acetate in the usual manner, m. p. 109.5–110.5°, m. m. p. with authentic sample 110–111°.

N-(Phthalimidomethyl)-benzamide.—This compound was prepared in the identical manner as the corresponding acetamide derivative except that 11.0 ml. of benzonitrile were used instead of the acetonitrile, yield of crude product 27.0 g., 96.5%. After one crystallization from 150 ml. of glacial acetic acid the yield was 21.7 g., 77.5%, m. p. 182–184°. The analytical sample was crystallized from ethanol, m. p. 184–185°.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. N, 10.00. Found: C, 68.39, 68.67; H, 4.57, 4.65; N, 10.17, 10.36.

Hydrolysis of N-(Phthalimidomethyl)-benzamide.—Fourteen grams of the compound was refluxed for forty-eight hours with 12 ml. of concentrated hydrochloric acid and 25 ml. of water. After chilling and filtering of the precipitated acids, formaldehyde was identified in the filtrate as described above; m. p. of dinitrophenylhydrazone 163–164°, m. m. p. 163.2–164.2°. Benzoic acid was separated from phthalic acid by steam distillation; m. p. 121–122°, m. m. p. with authentic sample 122–123°. The other hydrolysis products were not identified since identification of benzoic acid and formaldehyde provides adequate proof of structure.

β-Phthalimidopropionitrile.—(1) A sample was prepared according to Galat[5] except that 3.0 g. of potassium phthalimide was used as the catalyst for a 0.2-mole run instead of trimethylbenzylammonium hydroxide. Three hours of refluxing were required for completion. The crude yield, 42.9 g., 105%, contained potassium phthalimide; yield after crystallization from 700 ml. of methanol, 32.1 g., 76%; m. p. 151–152°.

(2) **From Phthalic Anhydride and β-Aminopropionitrile.**[6]—Seventy-four ml. (one mole) of β-aminopropionitrile and 148 g. (one mole) of phthalic anhydride were mixed. The mixture rose spontaneously to 110°, liquefied and began to crystallize. It was heated to 190° and poured into 250 ml. of glacial acetic acid. After cooling the product was filtered and washed; yield 187 g., 93.5%, m. p. 149–150°. A small sample, crystallized from methanol, melted at 151–152°; m. m. p. with sample above 151–152°.

(3) **From β-Phthalimido Ethyl Chloride[7] and Potassium Cyanide.**—Forty ml. of dry ethylene glycol, 20.9 g. (0.1 mole) of phthalimido ethyl chloride, 6.5 g. of potassium cyanide and 1.7 g. of potassium iodide were heated at 125–130° for eighteen hours. The black mixture was poured into 500 ml. of water, yielding a tar. The water was decanted and the tar extracted with 200 ml. of boiling benzene, which dissolved the product and left most of the tar. The benzene solution was treated with charcoal, filtered and evaporated to dryness. The residual oil was treated with 20 ml. of petroleum ether. On standing overnight in the ice box, crystals were obtained. These were recrystallized once from methanol and once from benzene yielding 670 mg., 3% of a product melting at 145–149°. Two crystallizations from water with charcoal and one from methanol brought the melting point to 151–152°; triple m. m. p. with samples (1) and (2) above, 151–152°. Exhaustive attempts to improve the yield by variations of solvent, time, temperature and use of cuprous cyanide instead of potassium yielded no product whatever.

β-Phthalimidopropionamide.—Twenty grams (0.1 mole) of β-phthalimidopropionitrile was dissolved in 80 ml. of concentrated sulfuric acid and allowed to stand overnight. The solution was poured over cracked ice, filtered, washed with water and dried; yield 20.9 g., 96%; m. p. 202–203°. Crystallization from 600 ml. of ethanol yielded 19.9 g., 91.4% of a product melting at 203–204°; mixed melting point with the isomeric N-(phthalimidomethyl)-acetamide, 181–190°. The analytical sample was crystallized once more from ethanol. It held solvent tenaciously and was dried at 100° at the oil pump to obtain satisfactory analyses.

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(11) Sachs, *Ber.*, **31**, 1232 (1898); Tscherniac, German Patent 134,979; *Beilstein*, **21**, 476.

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.

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[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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(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.