

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH, AND THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Some Derivatives of *cis*-3,6-Endomethylene- Δ^4 -tetrahydrophthalic AcidBY MARCUS S. MORGAN,¹ R. STUART TIPSON, ALEXANDER LOWY² AND W. E. BALDWIN

The compound *cis*-3,6-endomethylene- Δ^4 -tetrahydrophthalic anhydride (I), formed by the addition of cyclopentadiene to maleic anhydride, was first described³ in 1928. Although it has since been investigated extensively as regards reactions of its double bond,⁴ very little has been reported on reactions involving its dicarboxylic anhydride grouping.

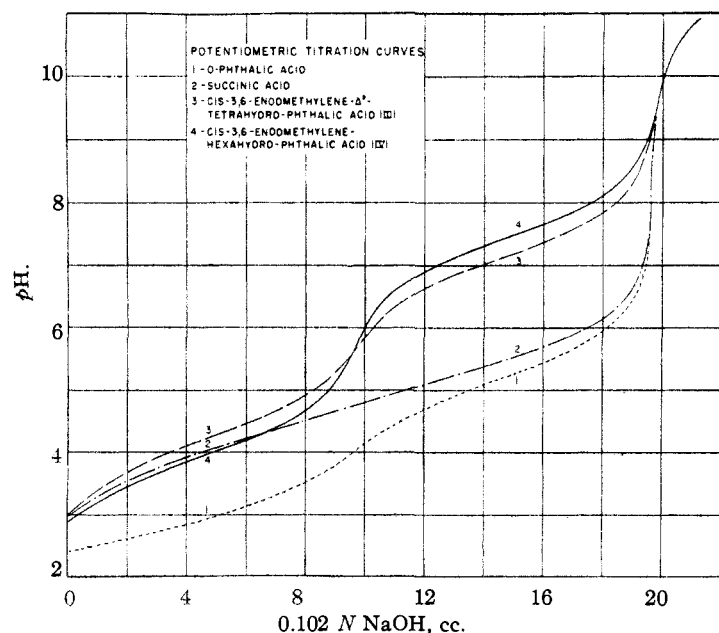


Fig. 1.—Potentiometric titration curves.

The present study was therefore initiated to obtain information on this aspect of the chemistry of compound I and its dihydro derivative II. Known reactions of phthalic anhydride served as a guide for the experimental procedures employed but modifications in mode of preparation and isolation of the products were usually necessary since compounds I and II were found to behave differently, in many respects, from phthalic anhydride.

Diels and Alder³ had prepared compound II by converting I to the free acid III, thence to the sodium salt which was hydrogenated (palladium catalyst) under low pressure; the free saturated

(1) Based on a thesis submitted by M. S. Morgan to the Graduate School of the University of Pittsburgh in partial fulfillment of the requirements for the degree of Doctor of Philosophy, January, 1943. Contribution No. 507 of the Department of Chemistry, University of Pittsburgh.

(2) Deceased December 25, 1941.

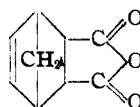
(3) Diels and Alder, *Ann.*, **460**, 98 (1928).

(4) Alder and Stein, *ibid.*, **504**, 216 (1933); **514**, 1 (1934); Alder and Schneider, *ibid.*, **524**, 189 (1936).

acid IV was then liberated and transformed to the saturated anhydride II. This method is tedious for the preparation of II in large quantities and we have now found that hydrogenation of I to give II can be accomplished directly, in one step and in quantitative yield, by catalytic hydrogenation (Raney nickel catalyst) under high pressure.

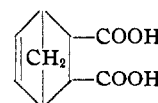
The potentiometric titration curves for the two dibasic acids, III and IV, determined by means of a glass-electrode titration assembly, are given in Fig. 1. For comparison, the potentiometric titration curves for succinic and *o*-phthalic acids were determined under identical experimental conditions and the four curves have been superimposed on the same set of coordinates. The magnitude of the inflection at the midpoint of each curve is proportional to the value of K_1/K_2 , calculated for acids III and IV from the figures for K_1 and K_2 determined by Bode.⁵

Certain di-esters of the unsaturated acid III were prepared using *p*-toluenesulfonic acid as catalyst (since it was found to have no effect on the sensitive double bond at position 4). The monomethyl ester, monoamide, monoamide monoammonium salt, ammonium salts, and certain imides (V) of acids III and IV have been prepared. It is seen that, with the exception of the unsubstituted imide, the melting point of each saturated compound is higher than that of its unsaturated analog. Attempts to isolate an anilic acid derivative of III or IV invariably resulted in the anil (V, R = C₆H₅).



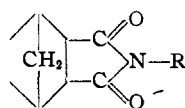
I

(II = dihydro deriv.)

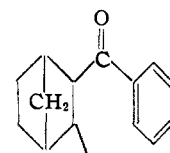


III

(IV = dihydro deriv.)



V



VI

The unsubstituted imide was not changed by prolonged boiling with concentrated ammonium

(5) Bode, *Z. physik. Chem.*, **170A**, 231 (1934).

hydroxide. Similarly, the dimethyl ester of III was unaffected by treatment with a saturated solution of ammonia in methanol, during several days at room temperature. This resistance to ammonolysis may be contrasted with the reactivity of the corresponding phthalic acid derivatives.

Anhydride II reacts readily with benzene in the presence of anhydrous aluminum chloride (Friedel-Crafts) to form the expected 3-benzoylnorcamphane-2-carboxylic acid (VI). However, formation of the corresponding derivative of anhydride I by this reaction could not be detected. On heating VI with concentrated sulfuric acid at 100°, ring closure to a quinone structure did not appear to take place.

Experimental

Dicyclopentadiene was obtained by purification of the commercial material⁶ by distillation at atmospheric pressure to give the monomer and repolymerization to the dimer which was fractionally distilled at diminished pressure (about 10 mm.). Cyclopentadiene was prepared, as needed, by distillation of the purified dimer at atmospheric pressure in an atmosphere of nitrogen. The fraction boiling at 40.5 to 41° at 760 mm. was retained, and stored in a receptacle cooled in solid carbon dioxide-acetone.

***cis*-3,6-Endomethylene- Δ^4 -tetrahydrophthalic anhydride (I)** was prepared as described by Diels and Alder³ and recrystallized from dry benzene. It had m. p. 165°.

***cis*-3,6-Endomethylene-hexahydrophthalic Anhydride (II).**—The unsaturated anhydride (250 g.) was dissolved in 500 cc. of dry dioxane, 30 g. of Raney nickel catalyst was added and the suspension shaken, in an atmosphere of hydrogen at 45° and an initial pressure of 2,050 pounds per square inch, during ninety minutes. The suspension was then cooled, filtered and the filtrate evaporated to small volume; yield of crude product, 245 g. (97% of theoretical). It was recrystallized from dry benzene and then had m. p. 167.5–168°.

Potentiometric Titration.—Acids III and IV were prepared and purified as described by Diels and Alder.³ A dry sample of the dibasic acid (0.001 mole) was dissolved in 75 ml. of carbon dioxide-free water. The pH of the original solution was measured and sodium hydroxide solution (0.102 *N*) then added in small increments of such size as to yield pH readings which were about 0.3 pH unit apart. All measurements were made under equilibrium conditions. The pH values corresponding to the volume of alkali added are summarized in the titration curves shown in Fig. 1.

Alkyl Esters; Monomethyl.—A solution of 6 g. of the appropriate anhydride (I or II) in 30 cc. of absolute methanol was boiled under a reflux condenser (closed by a calcium chloride tube) during ninety minutes. It was then cooled and evaporated to dryness under diminished pressure at 25°, giving a quantitative yield of crystalline product.

The Δ^4 -compound was purified by washing with three successive 5-cc. portions of pentane. It had m. p. 76–78.5°.

*Anal.*⁷ Calcd. for C₁₀H₁₂O₄: C, 61.21; H, 6.17; neut. equiv., 196.1. Found: C, 61.23; H, 6.14; neut. equiv., 200.7.

The saturated compound was recrystallized from hexane. It had m. p. 77–79°. The melting point of an intimate 50:50 mixture of the two esters was 60–62°.

Anal. Calcd. for C₁₀H₁₄O₄: C, 60.59; H, 7.12; neut.

(6) Kindly presented by the Carnegie-Illinois Steel Corporation Fellowship at Mellon Institute.

(7) All carbon and hydrogen determinations were performed microanalytically by Dr. Carl Tiedcke, New York, N. Y.

equiv., 198.2. Found: C, 60.96; H, 6.58; neut. equiv., 201.5.

Dimethyl.—A mixture of 32.8 g. of the unsaturated anhydride with 0.5 g. of *p*-toluenesulfonic acid was dissolved in 60 cc. of absolute methanol and the solution boiled under a reflux condenser during ten hours. It was then cooled, evaporated to small volume and dissolved in 96% ether. The solution was washed successively with water, dilute sodium bicarbonate solution and water, dried with anhydrous calcium sulfate, filtered and the filtrate evaporated to dryness. The sirupy product was purified by distillation under diminished pressure: yield, 29 g. (69%) boiling at 136–137° at 12.5 mm. It was redistilled at 9 mm. (b. p. 129–130°) and then had n_D^{20} 1.4852, d_4^{21} 1.164 and neutral equiv., zero.

Anal. Calcd. for C₁₁H₁₄O₄: sapon. equiv., 105.1. Found: sapon. equiv., 106.5.

A solution of 5.4 g. of the dimethyl ester in absolute methanol saturated with dry ammonia at 0° was kept in the refrigerator during three days. The dimethyl ester was recovered unchanged on evaporation of the alcohol and ammonia in a vacuum desiccator over concentrated sulfuric acid. The refractive index was practically identical with that of the dimethyl ester and the nitrogen content was zero.

Diethyl.—The unsaturated anhydride (32.8 g.) was treated with 60 cc. of absolute ethanol, as for the dimethyl ester, giving 28 g. (59%) of product boiling at 136–140° at 7 mm. It was redistilled at 8 mm. (b. p. 138–140°) and then had n_D^{20} 1.4761, d_4^{21} 1.100 and neutral equiv., zero.

Anal. Calcd. for C₁₃H₁₈O₄: sapon. equiv., 119.1. Found: sapon. equiv., 118.5.

Di-*n*-butyl.—A mixture of the unsaturated anhydride (20 g.) with 0.5 g. of *p*-toluenesulfonic acid was dissolved in 50 g. of *n*-butanol and the solution boiled under reflux during ten hours, in an apparatus having a water-trap between the condenser and the flask. Most of the water formed during the reaction collected in this trap. The product was then isolated as for the dimethyl ester, giving 30.6 g. (85%) of material boiling at 187–188° at 12.5 mm. It was redistilled at 8 mm. (b. p. 174–176.6°) and then had n_D^{20} 1.4721, d_4^{21} 1.044, and neutral equiv., zero.

Anal. Calcd. for C₁₇H₂₆O₄: sapon. equiv., 147.1. Found: sapon. equiv., 148.6.

Imides—Unsubstituted Imides: (a) Using Ammonium Carbonate.—An intimately ground mixture of anhydride I (16.4 g.) and dry ammonium carbonate (18.0 g.) was heated slowly in an oil-bath until no more vapors were evolved (maximum reaction temperature, 200°). The product was extracted with hot 95% ethyl alcohol. On cooling, the extract yielded 7.3 g. of imide, m. p. 183–185°. With a maximum reaction temperature of 250° a dark red product, from which no imide could be readily isolated, was obtained.

(b) **Using Dry Ammonia.**—Dry ammonia was passed over the molten anhydride (I or II) in an oil-bath at 170° until the gas was no longer absorbed.

(Δ^4) **Imide.**—As the ammonia was absorbed, the product solidified to an almost colorless substance (except for a yellowish color on the surface, due to oxidation). Recrystallization from hot water resulted in a yield of 13.7 g. (84% of theoretical) of crystalline imide, m. p. 186.5–187°. On admixture with a sample of the product from (a) the m. p. was 185–186.5°.

Anal. Calcd. for C₉H₉O₂N: C, 66.23; H, 5.56; N, 8.59. Found: C, 66.30; H, 5.53; N, 8.58.

(Sat.) **Imide.**—On cooling, the product solidified to a colorless mass, m. p. 143–149°. A portion of the crude imide (9 g.) was extracted with pure, dry ethyl acetate in a Soxhlet extractor. On evaporation at room temperature, the extract yielded a colorless, crystalline product weighing 7.5 g. and having m. p. 168–174°.

The following method of recrystallization gives an analytically pure, crystalline product. The imide (5 g.) was dissolved in dilute ammonium hydroxide (30 cc. of 2:1)

and refluxed during thirty minutes. On slowly cooling the solution to 5°, colorless, hexagonal-shaped crystals, m. p. 174–175.5°, separated in quantitative yield.

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.48. Found: N, 8.47.

Substituted Imides. (Δ^4) **N-Phenyl-imide.**—A solution of 5 ml. (slight excess) of aniline in 20 ml. of dry benzene was added to a warm solution of 8.2 g. of anhydride I in 40 ml. of benzene. The resulting precipitate was filtered off and washed successively with benzene, hydrochloric acid (1:1) and cold water. It was recrystallized by dissolving in hot glacial acetic acid and adding water to the warm solution almost to turbidity, resulting in the crystalline anil, m. p. 144°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.59.

(Sat.) **N-Phenyl-imide.**—Aniline (4.4 ml.) was slowly added to a solution of 8.3 g. (slight excess) of anhydride II in 25 ml. of chloroform. An exothermic reaction took place with the formation of a heavy, colorless precipitate. This was filtered off, washed with chloroform and air-dried. The yield was 12 g. of product having m. p. 175–176° (dec.). If the anhydride (II) exhibits all the properties typical of a dicarboxylic anhydride,⁸ this material is the anilic acid derivative. However, all attempts to purify the "anilic acid" resulted in the anil. (a) Recrystallization from either hot glacial acetic acid or hot ethyl alcohol (95%) (to each of which water was added almost to turbidity) resulted solely in the crystalline anil, m. p. 152–153°. A mixed m. p. with the analytically pure anil described in (b) showed no depression.

(b) An attempt to isolate the sodium salt of the anilic acid resulted in the anil. The substance (3 g.) with m. p. 175–176° (dec.) was suspended in 100 ml. of 50% ethyl alcohol (at 25°) and the suspension rendered slightly alkaline with 10% sodium carbonate solution (15 ml.). Evaporation of the solution at room temperature (vacuum desiccator) to half its original volume gave 2.3 g. of beautiful, needle-like crystals, m. p. 151.5–152.5°. On recrystallization from ethyl alcohol-water (5:3), the crystalline anil had m. p. 152–153°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: C, 74.65; H, 6.27; N, 5.81. Found: C, 74.58; H, 6.50; N, 5.81 (Dumas); N, 5.55 (Kjeldahl).

(Δ^4) **N-p-Tolyl-imide.**—A solution of 5.4 g. of *p*-toluidine in 20 ml. of dry benzene was added to a solution of 8.2 g. of anhydride I in 30 ml. of dry benzene. On standing, a heavy colorless precipitate (11.2 g.) was formed. This was filtered off and washed successively with benzene, dilute hydrochloric acid and water. Crystallization from either hot glacial acetic acid or ethanol, each diluted with water almost to turbidity, resulted in the *N-p*-tolyl-imide, m. p. 156.5–157°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: N, 5.53. Found: N, 5.52 (Dumas); N, 5.20 (Kjeldahl).

N-Benzyl Imides.—A solution of sodium ethoxide was prepared by dissolving 0.15 g. of oxide-free sodium in absolute ethanol (25 ml.) under a reflux condenser (anhydrous calcium sulfate tube). The imide (1.12 g.) was then added and the mixture refluxed during twenty minutes. A solution of benzyl chloride in 10 ml. of absolute ethanol was now added to the suspension and refluxing was continued during one hour. The ethanol suspension was filtered while still hot and water added to the hot filtrate, almost to turbidity. This solution gave the crystalline *N*-benzyl-imide on rapid cooling and agitation with a glass rod or, preferably, on evaporating under diminished pressure at 40°.

Unsaturated: m. p. 82.5–83.5°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.31; H, 5.87; N, 5.46.

Saturated: m. p. 101–103°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: N, 5.49. Found: N, 5.47.

Amides—A. Monoamide Monoammonium Salts.—The finely powdered anhydride (0.05 mole) was added in small portions to 20 ml. of concentrated ammonium hydroxide in a mortar and the mixture intimately ground after each addition. Finally, 10 ml. of ethyl alcohol was added, the insoluble salt filtered off and dried to constant weight in a vacuum desiccator over sulfuric acid.

Unsaturated: m. p. 172° (dec.).

Anal. Calcd. for $C_9H_{11}O_2N_2$: N, 14.14. Found: N, 14.00.

Saturated: m. p. 177° (dec.).

Anal. Calcd. for $C_9H_{11}O_2N_2$: N, 13.99. Found: N, 13.20.

B. Amidic Acids.—Concentrated hydrochloric acid (5.8 ml.) was added dropwise, with continuous stirring, to a suspension of the monoamide monoammonium salt in water (55 ml.) until just acid to congo red, while maintaining the temperature between 0 and 5°. The resulting colorless precipitate was filtered off and washed with successive small portions of cold water until the last washing was not acid to congo red. The product was lixiviated with two 20-ml. portions of acetone, giving a dry, colorless product. Owing to its instability, recrystallization was not attempted. (When a solution of the monoamide monoammonium salt was treated in the cold with an excess of concentrated hydrochloric acid and allowed to stand at 5° for twenty-four hours before filtering, the resulting product proved to be the dibasic acid.)

Unsaturated: m. p. 136° (dec.).

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.73. Found: N, 7.93.

Saturated: m. p. 165–166° (dec.).

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.65. Found: N, 7.74.

Ammonium Acid Salts.—The amidic acid (0.8 g.) was suspended in carbon dioxide-free water (10 ml.) and the acid was dissolved by boiling the suspension under a reflux condenser on a steam-bath during forty minutes. The colorless solution was then evaporated to dryness in a vacuum desiccator. After washing the crystalline residue with 20 ml. of purified acetone (dried with anhydrous potassium carbonate and distilled), it was dried in a vacuum desiccator over phosphorus pentoxide.

Unsaturated: m. p. 148° (dec.).

Anal. Calcd. for $C_9H_{13}O_4N$: N, 7.03. Found: N, 6.91.

Saturated: m. p. 149–150° (dec.).

Anal. Calcd. for $C_9H_{13}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.82; H, 7.58; N, 6.96.

Diammonium Salt.—An excess of concentrated ammonium hydroxide (6 ml.) was added to a suspension of 5 g. of the dibasic acid (III) in 80 ml. of water, with constant stirring. The resulting solution was evaporated in a vacuum desiccator over concentrated sulfuric acid. On removal of most of the solvent the product set to a solid mass of colorless crystals. It was filtered off and dried thoroughly at room temperature.

Unsaturated: m. p., indefinite.

Anal. Calcd. for $C_9H_{15}O_4N_2$: C, 49.99; H, 7.46; N, 12.97. Found: C, 49.83; H, 7.06; N, 12.51.

Attempted Preparation of the Diamide.—A solution of the saturated unsubstituted imide (1.5 g.) in concentrated ammonium hydroxide (6 ml.) was refluxed during twenty minutes. On cooling, a crystalline product was obtained which, after drying, weighed 1.3 g. and had m. p. 175–176°. After sublimation at 160° under reduced pressure it had m. p. 174.5–175°.

Anal. Calcd. for $C_9H_{14}O_2N_2$ (diamide): N, 15.38. Calcd. for $C_9H_{11}O_2N$ (imide): N, 8.48. Found: N, 8.47.

3-Benzoyl-norcamphane-2-carboxylic Acid (VI).—One-tenth mole (16.6 g.) of II was dissolved in 100 ml. of dry,

(8) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1936, p. 198.

thiophene-free benzene, and anhydrous aluminum chloride (30.5 g.; 0.23 mole) added in one portion with continuous stirring and cooling. The temperature of the reaction mixture was now raised slowly to 45° during thirty minutes and maintained at 45° for thirty minutes.

After cooling the reaction mixture in an ice-bath, 100 g. of chopped ice was added slowly, followed by 20 cc. of concentrated hydrochloric acid and enough water to bring the final volume to about 250 ml. The excess benzene was then removed by steam distillation. The colorless reaction product was filtered, washed with cold water, dissolved in 75 ml. of aqueous sodium carbonate solution (10%) and the solution boiled during three hours. After filtering, the solution was rendered acid to congo red by addition of concentrated hydrochloric acid (10 ml.) and the resulting colorless precipitate was filtered off, and washed with cold water. The yield of dry, crude 3-benzoyl-norcamphane-2-carboxylic acid was 20.3 g. (87% of theoretical), m. p. 150–158°.

The compound is soluble in benzene, ether, glacial acetic acid, hot ethyl acetate, acetone or chloroform. It is insoluble in water or petroleum ether.

A portion (12 g.) of the acid was recrystallized by dissolving in 300 ml. of hot, dry benzene and adding 50 ml. of petroleum ether to the warm solution. On cooling, a crystalline precipitate was obtained which, after filtering and drying, weighed 6.7 g. and had m. p. 170–173°. The filtrate was evaporated until the volume was about 50 ml., whereupon an equal volume of petroleum ether was added, resulting in a second crop of crystalline product (5.2 g.) having m. p. 170–171°.

Anal. Calcd. for C₁₈H₁₆O₃: C, 73.75; H, 6.60; neut. equiv., 244.2. Found: C, 74.12; H, 6.84; neut. equiv., 247.0.

Attempted Cyclization of VI to the Substituted Anthraquinone.—A small portion of the acid (VI) was dissolved in 1 ml. of concentrated sulfuric acid and heated on the steam-bath during forty-five minutes. On pouring the resulting yellow-colored solution into 10 ml. of water, a colorless precipitate was formed. It was filtered off and washed free of acid. On examining the product for the presence of the quinone structure, the tests were negative, indicating that cyclization to the substituted anthraquinone had not occurred.

Summary

1. *cis*-3,6-Endomethylene-hexahydrophthalic anhydride (II) has been prepared by direct catalytic hydrogenation (under high pressure) of *cis*-3,6-endomethylene-Δ⁴-tetrahydrophthalic anhydride (I).

2. A number of new alkyl esters, imides, amides and ammonium salts of the two acids corresponding are described.

3. The synthesis of 3-benzoyl-norcamphane-2-carboxylic acid (VI) by a Friedel-Crafts reaction is given.

PITTSBURGH, PA.

RECEIVED OCTOBER 6, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

N⁴-Substituted Sulfonamides

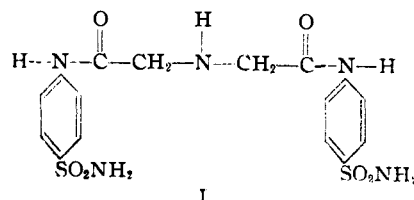
BY JACOB FINKELSTEIN*

In 1938, Fourneau and co-workers¹ showed the formyl and acetyl sulfanilamides were considerably less active than sulfanilamide against streptococcal infections. However, in a rather thorough study of the effect of various acyl groups on the activity of sulfanilamide, Miller, Rock and Moore² found that the caproyl derivative was as effective as the parent drug and yet, less toxic. During that time, we have prepared several N⁴-substituted derivatives of the several widely used sulfa drugs. Among these compounds are several already recorded in the literature. However, they are included in this report because the work has been extended to include their action against other pathogenic organisms and to present a more complete basis for comparison with related substances.

The chloroacetyl compounds were prepared by two methods. In one, the required chloroacetyl chloride was added dropwise to an ice-cooled suspension of the drug in an inert solvent, and in the other, the chloroacetyl chloride was added to an aqueous solution of the sulfa drug in dilute sodium hydroxide. The aminoacetyl compounds were obtained by dissolving the chloroacetyl derivatives in aqueous ammonia, warming at 40° for

twenty-four to forty-eight hours, followed by evaporation of the solvent. These compounds were difficult to purify because of their unfavorable solubility properties.

The preparation of N⁴-aminoacetylsulfanilamide was reported by Pollak, *et al.*,³ who recorded a melting point of 259°, whereas our product melted at 216–218°. Therefore, we repeated their work using liquid ammonia in place of aqueous ammonia, and obtained a product which melted at 256–258°. The analysis of this compound indicated the empirical formula C₁₆H₁₉N₃S₂O₆ and it most likely is (I) α,α'-iminobis-(N⁴-



acetylsulfanilamide), which the above authors erroneously reported as glycyl sulfanilamide, in spite of the fact that their recorded analytical values agree with those of the desired compound.

The substances here discussed were tested at the Merck Institute for Therapeutic Research by

* Present address: Hoffmann-LaRoche, Inc., Nutley, N. J.

(1) Fourneau, *Compt. rend. soc. biol.*, **122**, 258 (1938).

(2) Miller, Rock and Moore, *THIS JOURNAL*, **61**, 1198 (1939).

(3) Pollak, *et al.*, *Monatsh.*, **66**, 118 (1931).