dium isopropoxide but is only slightly more reactive than is the complex with sodium 2-pentoxide. No differentiation in reactivity with diisopropyl ether was noted.

These results are nicely explained by the assumption of the doubly coördinated cyclic ring formula for the Alfin catalyst.

CAMBRIDGE, MASS. RECEIVED JANUARY 3, 1947

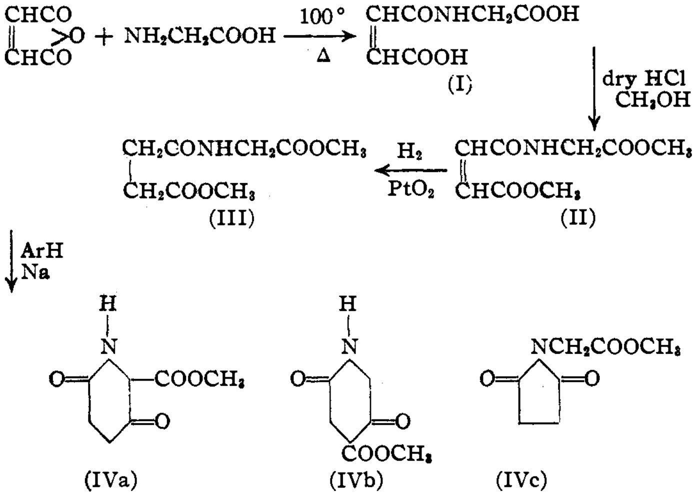
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

# Cyclization of N-Succinylglycine Dimethyl Ester

BY HAROLD WERBIN AND PAUL E. SPOERRI

This paper describes the synthesis of N-succinylglycine dimethyl ester (III), which appears to be unreported in the literature, and its cyclization to 2,5-diketo-1-pyrrolidineacetic acid methyl ester (IVc). Although a Dieckmann cyclization of (III) might have resulted in the formation of 6-carbomethoxy-2,5-diketopiperidine (IVa) or 4-carbomethoxy-2,5-diketopiperidine (IVb), neither of these products was isolated.

The synthesis and cyclization of N-succinylglycine dimethyl ester (III) was brought about through the sequence of reactions



Although the condensations of phthalic anhydride[1] and of succinic anhydride[2] on glycine have been reported in the literature, there seems to be no report of the action of maleic anhydride on glycine. It has been found that under mild reaction conditions amines, such as aniline[3] and benzalhydrazine,[4] add on to rather than condense with maleic anhydride. This has been found to hold true for the reaction of glycine and maleic anhydride. When heated together at 100°, the addition product, N-maleylglycine (I), resulted. The structure of (I) was shown to be $HOOCCH{=}CHCONHCH_2COOH$ as follows: a nitrogen analysis proved that addition rather than condensation had taken place. If the addition had taken place across the double bond, the resulting compound on heating with water should give rise to a tribasic acid. If, on the other hand, the addition resulted in N-maleylglycine (I), this compound on heating with water might either remain unaffected structurally, or if it is sufficiently soluble in hot water to raise the latter's acidity, the amide linkage might be hydrolyzed, giving rise to glycine and maleic acid. Titration of a sample of the addition product which had been dissolved in boiling water required two equivalents of alkali, thus eliminating the structure resulting from addition across the double bond. The addition across the oxygen bridge was confirmed when maleic acid and glycine were isolated from a solution of the addition product in boiling water.

The fact that (I) was converted to N-maleylglycine dimethyl ester (II) by passing dry hydrogen chloride gas through a refluxing suspension of (I) in absolute methanol was further proof for the structure of (I) cited above. The unsaturated diester (II) was obtained in 35% yields. The use of cold rather than refluxing methanol decreased the yields to 15%. The low yields of (II) appeared to be due to hydrolysis as evidenced by the isolation of the hydrochloride of glycine methyl ester from the reaction mixture. N-Maleylglycine dimethyl ester (II) melting at 137° was converted to a diamide, m. p. 272°.

The reduction of (II) to N-succinylglycine dimethyl ester (III) with Raney nickel or platinum oxide as catalysts at 50 pounds pressure was quantitative.

The saturated dimethyl ester (III) was cyclized using the conditions usually employed in a Dieckmann condensation, *i.e.*, sodium or sodium methoxide and an aromatic hydrocarbon such as toluene or benzene. Table I shows the various conditions that were employed and the yields of 2,5-diketo-1-pyrrolidineacetic acid methyl ester (IVc) that were obtained. The latter was the only product that was isolated from every condensation reaction.

At first it was thought that the product result-

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(1) Drechsel, *J. prakt. Chem.*, [2] **27**, 418 (1883).

(2) Scheiber and Reckleben, *Ber.*, **46**, 2412 (1913).

(3) Anschütz and Wirtz, *Ann.*, **239**, 137 (1887).

(4) Snyder, Levin and Wiley, THIS JOURNAL, **60**, 2025 (1938).

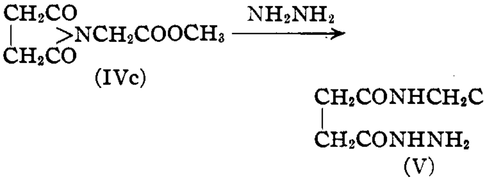
TABLE I

CONDENSATION OF N-SUCCINYLGLYCINE DIMETHYL ESTER

| Solvent, 10 ml. | SGD[a] | Condensing agent, mole Na | Condensing agent, mole NaOCH$_3$ | Reaction time, hr. | Yield, % |
|---|---|---|---|---|---|
| Benzene | 0.005 | 0.01 | .. | 2 | 67 |
| | .005 | .. | 0.01 | 2 | 15 |
| Toluene | .005 | .01 | .. | 2 | 60 |
| | .01 | .. | .02 | 1 | 0 |
| Xylene | .005 | .01 | .. | 2 | 78 |
| | .005 | .007 | .. | 1 | 24 |

[a] SGD is used for N-succinylglycine dimethyl ester.

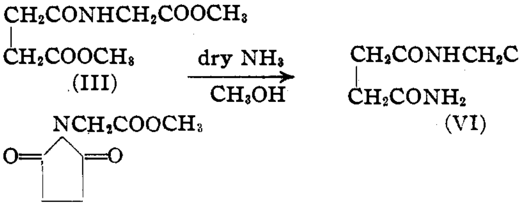
ing from the cyclization of (III) was either (IVa) or (IVb). However, the cyclized product gave no color with aqueous ferric chloride, did not form an oxime, a semicarbazide or a benzaldehyde condensation product. It appeared likely then that the cyclized compound might be (IVc). The latter seems to be unreported in the literature although the free acid[2] and the ethyl ester[5] are known. Curtius and Hechtenberg[5] on attempting to prepare a hydrazide from 2,5-diketo-1-pyrrolidineacetic acid ethyl ester found that the ring was cleaved and a dihydrazide, succinylhydrazide-N-acethydrazide (V) was actually formed. It seemed reasonable to expect that the same dihydrazide could be obtained from the methyl ester (IVc). On treating the latter with 100% hydrazine hydrate, succinylhydrazide-N-acethydrazide, (V) melting at 170°, was formed. This is three degrees higher than the 167° reported by Curtius and Hechtenberg[5] for the same compound.



$$\begin{matrix}CH_2CO\\ |\quad >NCH_2COOCH_3\\ CH_2CO\end{matrix} \xrightarrow{NH_2NH_2} \begin{matrix}CH_2CONHCH_2CONHNH_2\\ |\\ CH_2CONHNH_2\end{matrix}$$

(IVc) (V)

To demonstrate conclusively that the cyclized product was (IVc), the latter was synthesized following the procedure of Curtius and Hechtenberg[5] for the preparation of the ethyl ester homolog, by heating a mixture of succinyl chloride and the hydrochloride of glycine methyl ester in refluxing benzene for twenty hours. The compound obtained by this synthesis proved to be identical with the cyclized product (IVc). Both compounds when dissolved in absolute methanol and treated with dry ammonia in the cold gave N-succinylglycine diamide (VI) which was also prepared from (III).



$$\begin{matrix}CH_2CONHCH_2COOCH_3\\ |\\ CH_2COOCH_3\end{matrix} \xrightarrow[CH_3OH]{dry\ NH_3} \begin{matrix}CH_2CONHCH_2CONH_2\\ |\\ CH_2CONH_2\end{matrix}$$

(III) (VI)

(IVc)

## Experimental[6]

**N-Maleylglycine** (I).—In a 1-liter round-bottom flask was placed 75 g. (1 mole) of glycine and 115 g. (1.17 moles) of finely powdered maleic anhydride. The glycine and maleic anhydride were mixed by rotating the flask which was then placed on a 100° oil-bath for one hour. Whenever any portion of the powder in the flask became caked, it was broken up with a stirring rod. During the course of the reaction the material in the flask usually became tan colored. At the end of one hour of heating, the solid in the flask was extracted first with hot ethanol and then with cold water several times to remove any excess maleic anhydride, the unreacted glycine, and the tan color. The white solid was dried in the air and crushed to a powder. The yield was 141 g. (81%) of N-maleylglycine, m. p. 196°. It was insoluble in ethanol, chloroform, glacial acetic acid, acetone and dioxane. Small amounts of the acid were recrystallized from isobutyl alcohol. The recrystallized acid melted at 189–190°.

*Anal.* Calcd. for $C_6H_7NO_5$: N, 8.09. Found: N, 8.23.

N-Maleylglycine (I) was insoluble in cold but soluble in boiling water. One gram of the acid was dissolved in boiling water and the latter was then removed under reduced pressure leaving behind a white solid which was extracted with hot ethanol and filtered. The residue was identified as glycine by conversion to acetylglycine,[7] m. p. 207°. The alcoholic extract was evaporated to dryness leaving white crystals which melted at 129° and did not depress the melting point of an authentic sample of maleic acid.

Titration of 0.110 g. of (I) dissolved in boiling water gave a neutral equivalent of 59. The calculated neutral equivalent for the liberated maleic acid was 58.

**N-Maleylglycine Dimethyl Ester** (II).—Fifty grams (0.29 mole) of (I) and 50 ml. (0.8 mole) of absolute methanol were placed in a two-necked, round-bottom flask fitted with a reflux condenser (protected by a calcium chloride tube) and an inlet tube for the introduction of dry hydrogen chloride gas. The suspension was heated on an oil-bath, and when the methanol began to reflux, dry hydrogen chloride gas was passed through it until all of (I) had gone into solution. The latter was then cooled, the flask stoppered and placed in the refrigerator overnight. On the following day the white precipitate which had crystallized from the methanol was filtered and washed with small amounts of acetone. The precipitate was dried in a vacuum desiccator over calcium chloride. The yield was 20 g. (34%), m. p. 134°. On recrystallization from absolute methanol the melting point was raised to 137°.

*Anal.* Calcd. for $C_8H_{11}NO_5$: C, 47.75; H, 5.51; N, 6.96; sapn. equiv., 100.1. Found: C, 48.00, 48.13; H, 5.77, 5.63; N, 7.00, 7.00; sapn. equiv., 99.7, 100.2.

Ether was added to the filtrate from which (II) had been filtered off. White crystals appeared which were filtered and washed with ether. There was obtained 5 g. of a compound which melted at 177°. A mixed melting point with an authentic sample of the hydrochloride of glycine methyl ester, m. p. 175–176°, showed no depression.

The use of cold rather than refluxing methanol in the esterification of (I) decreased the yield of (II) to 15%.

**N-Maleylglycine Diamide**.—One gram of (II) was dissolved in 10 ml. of hot absolute methanol and the solution was cooled to 5° causing some precipitation of (II). Dry ammonia was passed through the cold suspension for fifteen minutes during which time the ester went into solution. The latter was placed in the refrigerator over-

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[5] Curtius and Hechtenberg, *J. prakt. Chem.*, **105**, 289 (1923).

[6] All melting points are corrected.

[7] Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 11.

night and on the following day the white crystals which had deposited were filtered off, washed with cold methanol, and dried in a vacuum desiccator. There was obtained 0.5 g. of diamide, m. p. 270° with decomposition. On recrystallization from water, the decomposition point was raised to 272°.

*Anal.* Calcd. for $C_6H_9N_3O_3$: N, 24.5. Found: N, 24.3.

**N-Succinylglycine Dimethyl Ester (III).**—Ten grams (0.058 mole) of (II) was dissolved in 100 ml. of refluxing absolute ethanol and placed in the bottle in which the hydrogenation was to be carried out. Although some of (II) precipitated, it all dissolved during the hydrogenation which was carried out using 0.1 g. of platinum oxide catalyst at 50 lb. pressure in a Parr reduction apparatus. After fifty minutes, the hydrogenation was stopped, the catalyst filtered off and the alcohol removed under reduced pressure leaving 10 g. (quantitative yield) of a crystalline white solid cake which was broken up with a stirring rod and dried in a vacuum desiccator over calcium chloride. The product melted at 83°. On recrystallization from acetone, the melting point was raised to 84–85°. The diester was soluble in chloroform and methanol. It could be recrystallized from water. Very small amounts could be recrystallized from ether.

*Anal.* Calcd. for $C_8H_{13}NO_5$: C, 47.28; H, 6.45; N, 6.89; sapn. equiv., 101.6. Found: C, 47.08, 47.25; H, 6.50, 6.31; N, 6.91; sapn. equiv., 100.0.

In another run 30 g. (0.149 mole) of (II) was hydrogenated in 150 ml. of absolute ethanol at 50 lb. pressure using about 0.3 g. of Raney nickel catalyst.[8] The hydrogenation was run for one and one-half hours at the end of which time the theoretical amount of hydrogen had been taken up. After the catalyst was filtered, the alcoholic solution was placed in the refrigerator overnight. On the following day, 15 g. of a white crystalline precipitate was filtered off, which when dried, melted at 84.5°. An additional 15 g. of (III) was obtained as a crystalline residue after the alcohol was distilled off under reduced pressure.

**N-Succinylglycine Diamide (VI).**—This was prepared in the same manner described above for the preparation of N-maleylglycine diamide. From 1 g. of (III) there was obtained 0.425 g. of (VI), m. p. 203°. On recrystallization from alcohol–water solution, the melting point was raised to 203–204°.

*Anal.* Calcd. for $C_6H_{11}N_3O_3$: N, 24.3. Found: N, 24.0.

**Cyclization of N-Succinylglycine Dimethyl Ester (III).**—All the Dieckmann condensations were carried out with reagents that had been distilled over sodium.

The apparatus used for the condensations consisted of a 2-necked, 150-ml., pear-shaped flask (with standard taper joints) fitted with a mercury-seal stirrer and a reflux condenser protected with a calcium chloride tube.

See Table I for the various conditions employed. Two typical condensations which were carried out, one using metallic sodium and the other using sodium methoxide as condensing agents, are described below.

(1) To 0.230 g. (0.01 mole) of sodium sand was added 10 ml. of toluene and 1.0 g. (0.005 mole) of N-succinylglycine dimethyl ester. The mixture was refluxed and stirred for two hours at the end of which time the toluene was filtered while hot. The filtrate was cooled on an ice-bath and petroleum ether (b. p. 65–110°) was added until no more precipitation took place. The flask was stoppered and placed in the refrigerator overnight.

On the following day the solution was filtered and the fine white needles were washed with cold petroleum ether and dried in the air. The yield was 0.520 g. (60%) of a product melting between 92–93°. On recrystallization from ether the melting point was raised to 94.5–95.5°.

(2) Four ml. of absolute methanol was added to 0.230 g. (0.01 mole) of sodium in the two-necked flask fitted with a downward condenser for distillation. The unreacted methanol was distilled off using an oil-bath. The white solid sodium methoxide which remained was broken up with a stirring rod and to it 1.0 g. (0.005 mole) of N-succinylglycine dimethyl ester and 10 ml. of benzene were added, after which the mixture was refluxed and stirred for two hours. The benzene was then filtered while hot and to the filtrate petroleum ether was added as in procedure (1) above. The yield was 0.125 g. (15%) of fine white needles melting at 91°. On recrystallization from ether the melting point was raised to 94.5–95.5°.

The only product resulting from all the Dieckmann cyclizations was one which melted at 94.5–95.5° after recrystallization from ether. This product was soluble in acetone and chloroform. It was less soluble in methanol and could be recrystallized from water.

*Anal.* Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.15, 49.02; H, 5.52, 5.60; N, 8.20.

**Identification of Cyclized Product (IVc).**—The fact that the cyclized product gave no color with aqueous ferric chloride solution and that it was isolated without the neutralization of the excess sodium and sodium methoxide indicated that the cyclized compound did not exist in the enol form.

Attempts to prepare an oxime, a semicarbazide, and a benzaldehyde condensation product were unsuccessful.

**Succinylhydrazide N-Acethydrazide (V).**—To 0.700 g. of 100% hydrazine hydrate in a 50-ml. beaker cooled to −10° was added slowly and with constant stirring 0.700 g. of the cyclized product (IVc). After about one-half of the latter had been added, the mixture in the beaker became a thick white paste. After all the cyclized product had been added, 2 ml. of absolute alcohol was added to the paste and the beaker was placed on a steam-bath. Water was now added drop by drop until all the white paste had dissolved. On cooling the entire yellow solution crystallized. The white precipitate was filtered, washed with alcohol–water solution, and dried in a vacuum desiccator over calcium chloride. The yield was 0.314 g., m. p. 158–164°. On recrystallization from alcohol–water solution twice, its melting point was raised to 170°. The dihydrazide prepared by Curtius and Hechtenberg[5] from 2,5-diketo-1-pyrrolidineacetic acid ethyl ester melted at 167°.

*Anal.* Calcd. for $C_6H_{13}N_5O_3$: N, 34.5. Found: N, 34.0.

**Synthesis of 2,5-Diketo-1-pyrrolidineacetic Acid Methyl Ester (IVc).**—The following procedure was that employed by Curtius and Hechtenberg[5] for the preparation of the ethyl ester homolog. In a 150-ml., round-bottom flask fitted with a reflux condenser (protected with a calcium chloride tube) was placed 2.0 g. (0.016 mole) of the hydrochloride of glycine methyl ester, 2.4 g. (0.016 mole) of succinyl chloride, and 50 ml. of dry benzene. The mixture was refluxed for twenty hours during which time hydrogen chloride gas was evolved, the benzene turned dark brown, and the glycine ester went almost completely into solution. The latter was now filtered and the benzene was distilled off under reduced pressure. The remaining red oil was vacuum distilled at 135–138° (2 mm.). The distillate crystallized as a white solid in the receiver. Yield was 1.52 g. (56%), m. p. 68–80°. After three recrystallizations from ether, the compound melted between 94–95°. A mixed melting point with the cyclized product (IVc) from the Dieckmann condensation showed no depression.

**Attempted Synthesis of 2,5-Diketo-1-pyrrolidineacetamide.**—An amide was prepared from the cyclized compound (IVc) in the same manner as described above for the preparation of N-maleylglycine diamide. It melted at 204–205° and had 24.1% nitrogen. The melting point and the nitrogen analysis were the same as that found for N-succinylglycine diamide (VI). A mixed melting point of the latter diamide with the one prepared from (IVc) showed no depression. The same diamide was prepared from (IVc) (synthesized by the procedure of Curtius and Hechtenberg).

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[8] Covert and Adkins, This Journal, **54**, 4116 (1932).

## Summary

The synthesis of N-succinylglycine dimethyl ester has been described.

A Dieckmann cyclization of this compound gave rise to 2,5-diketo-1-pyrrolidineacetic acid methyl ester. The structure of the latter was confirmed by an independent synthesis using a method known to give rise to the 2,5-diketopyrrolidine ring.

Brooklyn, N. Y. Received March 21, 1947

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[Contribution from the Chemical Laboratory of Smith College]

# High Molecular Weight Hydrocarbons. II. Five New Hydrocarbons Derived from Sebacic Acid

By Milton D. Soffer, Natalie S. Strauss,[1a] Marjorie D. Trail[1b] and Kenneth W. Sherk

The highly purified hydrocarbons prepared in the present undertaking[2] are 1,14-diphenyltetradecane, 1-phenyl-12-*n*-propylpentadecane, 4-phenyl-13-*n*-propylhexadecane, and the cyclohexyl analogs of the latter two.

Dimethyl sebacate was a convenient starting material serving all of these syntheses. Partial saponification under proper conditions gave the diacid and the acid-ester in the ratio required for the subsequent work. These acids, through their acid chlorides, were converted by treatment with di-β-phenylethylcadmium to 1,14-diphenyl-3,12-tetradecadione and to methyl 10-keto-12-phenyldodecanoate; the acid ester through its acid chloride, by treatment with diphenylcadmium, was converted to methyl 10-keto-10-phenyldecanoate.

The symmetrical hydrocarbon was obtained by Wolff–Kishner reduction of the diketone and the same method, applied to the 18-carbon keto-acid derived from the corresponding ester, above, gave rise to 12-phenyldodecanoic acid. These reductions were carried out at atmospheric pressure[3] in single operations which in the case of the keto-acid involved as much as 700 g. of starting material.

The branched phenyl alkanes were obtained from the methyl ester of the latter acid, and from the 9-keto-dodecanoic ester, by treatment with excess *n*-propylmagnesium bromide, dehydration of the tertiary mono- and di-alcohols, and hydrogenation of the resulting olefins (1-phenyl-12-*n*-propylpentadecene and 4-phenyl-13-*n*-propylhexadecadiene).

The selective hydrogenation of the ethylenic linkages in the presence of the aromatic nucleus required special study. The difficulties involved in effecting this type of preferential attack on a quantitative basis have been remarked by Whitmore, *et al.*,[4] who in a similar case used a nickel catalyst. Inasmuch as nickel is generally recognized as "the most satisfactory catalyst for the hydrogenation of the benzenoid nucleus"[5] it appeared to us that the selectivity of the reaction might be enhanced by the use of a catalyst more indifferent to this part of the molecule.[6] The results of a large number of trial hydrogenations with copper–chromium oxide and several with Adams catalyst indicated that the desired conversion could be carried out most effectively by high pressure hydrogenation over copper–chromium oxide at *ca.* 225°.

The cyclohexyl derivatives were obtained by high pressure hydrogenation with Raney nickel.

In planning these syntheses emphasis was placed upon the selection of reactions involving a minimum of difficultly separable by-products, and throughout the work special pains were taken to insure the purity of the products. None of the substances in these synthetic series except the simple derivatives of sebacic acid have appeared previously in the literature.

## Experimental

**Monomethyl Sebacate and Sebacic Acid.**—In a typical batch preparation a cold solution of 841.5 g. of C.P. potassium hydroxide (87.6% potassium hydroxide, 13.1 moles) in 3 liters of absolute methanol was stirred into a solution of 3965 g. (17.22 moles) of pure[7] dimethyl sebacate (m. p. 26.5–27.5°) in 11 liters of the same solvent. While a voluminous precipitate of the potassium salts separated,

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[1] Present addresses (a) Shawinigan Resin Corp., Springfield, Mass.; (b) Chemical Abstracts, Ohio State University, Columbus, Ohio.

[2] Preceding paper in this series: Sherk, Augur and Soffer, This Journal, 67, 2239 (1945). This work is being carried out at Smith College in coöperation with the Technical and Research Division of the Texas Company.

[3] Soffer, Soffer and Sherk, This Journal, 67, 1435 (1945); Huang-Minlon, *ibid.*, 68, 2487 (1946).

[4] Whitmore, Crosby, Sloatman and Clarke, *ibid.*, 64, 1801 (1942).

[5] Gilman, "Organic Chemistry," 2 ed., Vol. 1, 1943, p. 817. See also Adkins, "Reactions of Hydrogen, etc.," The University of Wisconsin Press, Madison, Wis., 1937, p. 57.

[6] Adkins, ref. 5, p. 48, has advised that "the use of Cu–Cr oxides is desirable if there is any possibility that nickel will induce the hydrogenation of a benzenoid ring in the compound," and that "quantitative preferential hydrogenation of the alkene linkages may be easily accomplished" in the presence of benzenoid nuclei (*ibid.*, pp. 121–122). While some later evidence (Folkers, This Journal, 58, 1559 (1936); see also Durland and Adkins, *ibid.*, 59, 135 (1937)) made it plain that the original claims for complete inactivity of this catalyst toward the benzenoid nucleus were not valid in cases of extreme treatment, there never has been any question of its marked relative inertness toward simple aromatic rings.

[7] Except where otherwise indicated all primary starting materials were the best samples obtained by fractionation of the Eastman "White Label" product through a Fenske column with an efficiency of approximately twenty plates. Only those fractions of the distillate which had a constant boiling point and a constant index of refraction ±0.0001), and in the case of solids a constant melting point, were accepted. In the case of dimethyl sebacate, 6.20 kg. of the commercial product gave 5.46 kg. of material satisfying these criteria.