sible to obtain an additional crop of crystals from the mother liquor by evaporation to a smaller volume, yield 0.38 g. (80.2%), decomposes at about 230°.

The free base was prepared and recrystallized from methanol with almost quantitative yield; m. p. 131–132°. This agrees with the melting point reported in the literature.[3]

1-Methyl-2-(*p*-aminophenyl)-3-ethyl-6-aminoindane Dihydrochloride (VIIIA).—One-half gram of the indene was reduced in the same manner as was the above ketone. After chilling overnight, the aqueous portion was decanted and the residue washed a number of times with water. The residue was taken up in a small quantity of absolute ethanol to which was added 1 ml. of concentrated hydrochloric acid. The alcohol was evaporated and the acid solution chilled overnight. The crystals were filtered and washed with a 20% solution of absolute ethanol in ethyl acetate; yield 0.42 g. (84.5%); m. p. 280–283° (dec.).

Anal. Calcd. for $C_{18}H_{24}N_2Cl_2$: C, 63.71; H, 7.13; N, 8.25. Found: C, 63.82; H, 7.23; N, 8.22.

Acknowledgment.—We wish to thank the Microanalytical Laboratory of the National Institutes of Health and Mr. Ervin Pritchett of this department for the microanalyses.

Summary

A method has been developed for the preparation of α,β-dimethyl- and α,β-diethyl-4,4′-stilbenediamine by a pinacol–pinacolone type rearrangement of the respective pinacol. Reduction of the ketone formed with subsequent retro-pinacol rearrangement and dehydration gave the desired stilbene.

The 3,4-bis-(*p*-aminophenyl)-3,4-hexanediol was prepared by bimolecular electrolytic reduction.

In the rearrangement of the pinacols it was found that varying concentrations of acid would yield either the ketone exclusively or a mixture of ketone and substituted 6-aminoindene.

It has also been shown that apparently the presence of the $-\overset{+}{N}H_3$ under conditions of the experiment will activate the molecule so it will undergo ring closure more readily than when a phenyl group alone is present.

BALTIMORE 18, MARYLAND RECEIVED OCTOBER 18, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

The Mechanism of the Willgerodt Reaction[1]

BY W. G. DAUBEN,* J. C. REID,[2] P. E. YANKWICH[3] AND M. CALVIN

The question as to whether the Willgerodt reaction[4] involves a rearrangement of the molecule when a ketone is converted to a carboxylic acid of the same number of carbon atoms has been the subject of wide investigation.[5] Willgerodt[5] originally postulated that the reaction did not involve a rearrangement of the carbon skeleton of the molecule while later the work of Fieser and Kilmer[5] tended to cast doubt on the validity of his proof. Kinkler and Li,[5] on the other hand, proposed an elaborate mechanism for this reaction which involved a molecular rearrangement. Recently, Carmack and DeTar[5] and King and McMillan[5] have re-examined the original evidence of Willgerodt and have concluded that no migration of groups occurs in the reaction. The most conclusive proof, however, was offered by Shantz and Rittenberg[6] who showed that when acetophenone labeled in the carbonyl group with C^{13} was converted to phenylacetic acid, the carboxyl group of the acid contained no excess over normal of C^{13}. At the same time, the authors of the present paper reported similar results.[1] In addition, it was stated that the acidic product of the reaction appeared to be formed, in part, by an actual migration of the phenyl group. The complete results of our work are summarized in Chart I.[7]

Phenylmagnesium bromide was carbonated with radioactive carbon dioxide following the procedure described in a previous publication[8] and benzoic acid (I) was obtained in a yield of 85%. The acid was converted to benzoyl chloride with thionyl chloride. Two procedures were investigated for the preparation of acetophenone (II). In one case, the acid chloride was allowed to react with the sodium derivative of diethylmalonate and the resulting diethyl benzoylmalonate hydrolyzed and decarboxylated to the ketone[9] in an over-all yield of 78%. In the other case, benzoyl chloride was allowed to react with an excess of dimethylcadmium[10] and acetophenone was obtained in 85% yield. The Willgerodt reaction was conducted following the procedure described by Carmack and DeTar,[5] using sulfur, ammonium hydroxide and pyridine. The main product (62%) was phenylacetamide (IIIa)

* Harvard University Ph.D. 1944.

(1) A preliminary announcement of this work was reported in a Communication to the Editor, THIS JOURNAL, **68**, 2117 (1946).

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(4) An excellent review of this reaction is to be found in "Organic Reactions," Volume III, John Wiley and Sons, Inc., New York, N. Y., 1946.

(5) Willgerodt and Merk, *J. prakt. Chem.*, [2] **80**, 192 (1909); Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940); Kindler and Li, *Ber.*, **74**, 321 (1941); Carmack and DeTar, THIS JOURNAL, **68**, 2029 (1946); King and McMillan, *ibid.*, **68**, 632 (1946).

(6) Shantz and Rittenberg, THIS JOURNAL, **68**, 2109 (1946).

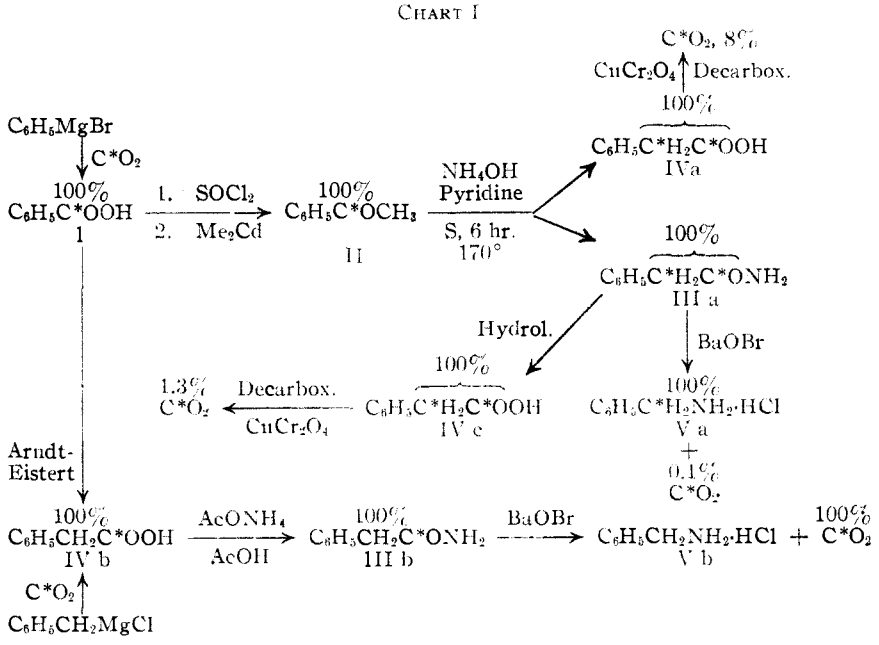
(7) The asterisk denotes the labeled carbon atom and the percentage is that of the *initial specific activity* found in that carbon.

(8) Dauben, Reid and Yankwich, *Anal. Chem.*, **19**, 828 (1947).

(9) Wilds and Beck, THIS JOURNAL, **66**, 1688 (1944).

(10) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936); Cason, THIS JOURNAL, **68**, 2078 (1946).

CHART I



and a small amount (1.5%) of phenylacetic acid (IVa) was also isolated. The amide was degraded in two ways, firstly, by hydrolysis to phenylacetic acid (IVc) which in turn was decarboxylated and, secondly, by a Hofmann reaction[11] with barium hypobromite. The decarboxylation of the acid IVc with copper chromite catalyst in quinoline at 230° showed that 1.3%[12] of the activity originally present in the carbonyl carbon of acetophenone was apparently in the carboxyl group. The carbon dioxide from the Hofmann reaction, however, contained only a trace of radioactivity (~0.1%) and the benzylamine hydrochloride, on the other hand, contained 100% of the original radioactivity (within experimental error of ±2%).

In view of this discrepancy of results, phenylacetic acid labeled in the carboxyl group was prepared by the carbonation of benzylmagnesium chloride[8] with radioactive carbon dioxide and by the Arndt–Eistert reaction[13] on labeled benzoyl chloride. The amide (IIIb) from this acid was degraded by the Hofmann reaction and the generated carbon dioxide contained 100% of the radioactivity. The benzylamine hydrochloride was non-radioactive. When the acid (IVb) was decarboxylated, the carbon dioxide formed possessed a specific activity slightly less (3%) than that of the carboxyl carbon of the original acid. Recently,[14] this decarboxylation reaction was investigated using methylene-labeled phenylacetic acid and it was shown that approximately 1% of the radioactivity originally present in the methylene group was found in the generated carbon dioxide.[15] It can thus be concluded that the Hofmann reaction is a reliable method of degradation of a labeled amide. The decarboxylation reaction, however, is unreliable when one is searching for trace amounts of radioactivity. Hence, the phenylacetamide (IIIa) is formed by a route which does not require rearrangement of the carbon skeleton. It may be added that phenylacetic acid (IVd) obtained from radioactive acetophenone (II) by the morpholine modification used by Shantz and Rittenberg[6] was found to give decarboxylation results analogous to those reported above.

The phenylacetic acid (IVa) which was isolated directly from the Willgerodt reaction was decarboxylated and the carbon dioxide evolved was found to contain 8.3%[16] of the original activity of the acetophenone. Since this value was higher than could be reconciled with the decarboxylation results obtained above, it seemed likely that this activity was an inherent part of the carboxyl group or that the product was contaminated with benzoic acid (I) which could have been formed by cleavage of acetophenone.[17] The purity of the phenylacetic acid was established by the melting point (76–77°) and by the neutralization equivalent (calcd., 136; found, 135). Furthermore, the presence of an amount of benzoic acid necessary to give the observed activity would lower the melting point approximately twenty degrees. It was also found that when the isolated acid was diluted with an approximately equal amount of non-radioactive phenylacetic acid and this product highly purified and decarboxylated, the specific activity of the carbon dioxide was approximately 4% of the original specific activity of the carbonyl carbon of the acetophenone.

(11) Hoogewerf and van Dorp, *Rec. trav. chim.*, **5**, 251 (1886).

(12) The counting error is ±2% of the value measured.

(13) Huggett, Arnold and Taylor, THIS JOURNAL, **64**, 3043 (1942).

(14) Dauben and Coad, *ibid.*, **71**, 2928 (1949).

(15) The difference between the amount of radioactivity found in the carbon dioxide from carboxyl-labelled and methylene-labelled acids is within the total error of the assay procedure.

(16) This value is much lower than that reported previously in ref. 1. It has been found that as the size of the reaction increases and consequently the time required for processing increases, the amount of acid produced by hydrolysis of the amide increases. The data reported here are from runs which were approximately thirty times larger than those experiments reported earlier and thus this lower value is to be expected. It should also be pointed out that the exchange reaction between the acid and the amide, referred to later, is highly dependent upon temperature and that unless special precautions are taken, this variable can also cause a large change in the carbon fourteen content of the carboxyl group of the acid.

(17) Arnold, Schultz and Klug, THIS JOURNAL, **66**, 1606 (1944).

The finding of a lower specific activity in the carboxyl carbon of the phenylacetic acid IVa than in the carbonyl carbon of the acetophenone clearly indicates that an exchange reaction between phenylacetic acid and phenylacetamide occurs under the conditions of the Willgerodt reaction.

$$RC^*OOH + RCONH_2 \rightleftharpoons RCOOH + RC^*ONH_2$$

This type of a reaction was shown to occur as outlined in Chart II.

CHART II

$$\text{equimolar} \left\{ \begin{matrix} C_6H_5CH_2C^*OOH \\ \\ C_6H_5CH_2CONH_2 \end{matrix} \right\} \xrightarrow[\text{S, } \sim 6 \text{ hrs.}]{\begin{matrix} NH_4OH \\ \text{Pyridine} \\ 170^\circ \end{matrix}} \underset{90\%}{C_6H_5CH_2C^*OOH} + \underset{10\%}{C_6H_5CH_2C^*ONH_2}$$

This exchange readily accounts for the slight activity found in the carboxyl carbon of the phenylacetamide isolated from the Willgerodt reaction.

The appearance of a significant amount of radioactivity in the carboxyl group of the phenylacetic acid isolated directly from the Willgerodt reaction mixture shows that part of the acid is formed by a rearrangement of the acetophenone. It is not possible to establish to what extent this rearrangement occurs as compared to the non-rearrangement path since the isolation of the acid is not quantitative and part of the acid may be formed by hydrolysis of the amide in the processing of the reaction and since exchange occurs between acid and amide. It is believed, however, that the rearrangement is a very insignificant route (<1%). This path would not be found in the normal non-isotopic reaction since in cases where the rearrangement of the ketone could be ascertained by the means of the formation of isomeric acids,[5] the reaction proceeds in a yield of only a few per cent. and the small amount of a rearranged product would go undetected. The use of ketones other than methyl ketones has not been explored.

Experimental[18]

Carboxyl-labeled Benzoic Acid (I).—Phenylmagnesium bromide was carbonated with radioactive carbon dioxide following the procedure described in a previous publication.[9] The yield based on carbon dioxide was 85%; m. p. 122–123°; specific activity × 7[19]: 830 cts./min./mg. barium carbonate.

Carboxyl-labeled Phenylacetic Acid (IVb). (a) By Carbonation Procedure.—Benzylmagnesium chloride[8] was carbonated with radioactive carbon dioxide in the above manner. The yield based on carbon dioxide was 88.3%, m. p. 75.5–76.5°, specific activity × 8: 360 cts./min./mg. barium carbonate.

(b) **By Arndt-Eistert Reaction.**—A solution of 1.26 g. (0.008 mole) of carboxyl-labeled benzoyl chloride in 5 cc. of dry ether was added at zero degrees to a solution of 1.15 g. (0.026 mole) of diazomethane in 78 cc. of dry ether and the resulting solution kept at this temperature for three hours and then allowed to come to room temperature. The reaction mixture was evaporated under reduced pressure and the residual diazoacetophenone dissolved in 20 cc. of methanol. This solution was treated at 70° with 50 mg. of silver oxide, added in portions over a period of six hours, and then refluxed for twelve hours. After removal of the catalyst by centrifugation, 10 cc. of 20% potassium hydroxide was added and the ester saponified. The alcohol was boiled from the alkaline mixture, the solution extracted with ether and then acidified. The yield of purified acid was 47%, m.p. 74–76°.

The phenylacetic acid was converted to phenylacetamide by heating with ammonium acetate.[20] A mixture of 0.52 g. of phenylacetic acid, 0.47 g. of ammonium acetate and 0.78 cc. of glacial acetic acid was distilled very slowly through a 5-cc. modified Claisen flask. The distillation was interrupted when the head temperature reached 245°. The residue was dissolved in 1 cc. of boiling water and poured into 2 cc. of 2 *N* sodium hydroxide. The precipitated amide was washed with cold ether and recrystallized from hot water. The yield of purified amide was 40%, m.p. 157.0–157.5°.

Carboxyl-labeled Benzoyl Chloride.—A mixture of carboxyl-labeled benzoic acid (47.5 g., 0.39 mole) and thionyl chloride (75 cc.) was heated at 70° for three hours, the excess thionyl chloride removed under vacuum, and the benzoyl chloride distilled; b.p. 79° (16 mm.), yield 52.5 g. (96%).

Carbonyl-labeled Acetophenone (II). (a) From Dimethylcadmium.—The ketone was prepared following the dimethylcadmium procedure of Gilman and Nelson[10] as modified by Cason.[10] From 52.5 g. (0.374 mole) of carboxyl-labeled benzoyl chloride, 38.0 g. (85%) of acetophenone was obtained, b.p. 84–85° (20 mm.).

(b) **From Diethyl Malonate.**—The general procedure of Wilds and Beck[9] for the preparation of methyl ketones by the acylation of the sodium derivative of diethyl malonate was followed. From 2.81 g. (0.02 mole) of carboxyl-labeled benzoyl chloride and 16 g. (0.1 mole) of diethyl malonate, 1.89 g. (78.5%) of acetophenone was obtained.

Willgerodt Reaction. (a) With Ammonia.—The reaction was conducted and processed in the manner described by Carmack and DeTar.[5] From 32 g. of carbonyl-labeled acetophenone, 22.3 g. (62%) of phenylacetamide and 0.55 g. (1.5%) of phenylacetic acid was obtained. The acid melts 75–76° and the amide 159–160°, specific activity × 8: 830 cts./min./mg. barium carbonate.

Phenylacetamide was saponified by heating with 3 *N* sodium hydroxide and the crude phenylacetic acid recrystallized twice from petroleum ether, m.p. 75–76°, specific activity × 8: 820 cts./min./mg. barium carbonate.

(b) **With Morpholine.**—The reaction was run as described by Shantz and Rittenberg.[6] From 1.9 g. (0.016 mole) of carbonyl-labeled acetophenone, 0.5 g. (23%) of phenylacetic acid was obtained, m.p. 76–77°, specific activity × 8: 830 cts./min./mg. barium carbonate.

Decarboxylation of Phenylacetic Acid.—A mixture of 50 mg. of phenylacetic acid, 50 mg. of copper chromite catalyst[21] and 3 cc. of quinoline was heated for forty minutes at 230° in a stream of nitrogen. After the heating, the nitrogen flushing was continued for forty minutes at room temperature. The carbon dioxide evolved was collected in aqueous barium hydroxide solution. The barium carbonate was processed in the usual manner. The yields varied from 60–80%.

(18) All melting points are corrected. Microcombustions by Mr. C. W. Koch and Mr. V. H. Tashinian.

(19) All measurements were carried out with a thin mica-window Geiger-Muller tube on a scale of 64 circuit with a geometry of 17.6 ± 2.5 disintegrations per count. The activity was determined with thin uniform layers of barium carbonate according to the procedure described in an earlier publication.[9] To correct for the dilution of the activity of a specific carbon in the compound, the observed activity obtained when the compound was combusted is always multiplied by the total number of carbon atoms in the molecule.

(20) Rao and Shao-Yuan, *J. Chem. Soc.*, 443 (1931).

(21) Copper Chromite Catalyst, No. Cu-186-powder, Harshaw Chemical Company, Cleveland, Ohio.

TABLE I

DECARBOXYLATION OF PHENYLACETIC ACID

	Acid specific activity	Carbon dioxide specific activity
IVa	830	66
IVb	360	350
IVc	820	11
IVd	830	6

Hofmann Degradation of Phenylacetamide.—The reaction was carried out with barium hypobromite rather than sodium hypobromite in order to eliminate the blank due to the carbonate that is always present in sodium hydroxide. A mixture of 135 mg. (0.001 mole) of phenylacetamide and 13.5 cc. of a solution containing 513 mg. (0.003 mole) of barium hydroxide and 324 mg. (0.002 mole) of bromine was placed in a heavy-walled Pyrex tube, the tube chilled in liquid nitrogen, evacuated and sealed. The contents were allowed to warm up to zero degrees and then shaken to dissolve the amide in the barium hypobromite solution. After complete solution the tube was placed in a steam-bath for two hours. After cooling, the tube was opened and the barium carbonate collected; yield 199 mg. (101%). The benzylamine was isolated from the filtrate by the addition of solid potassium hydroxide and ether extraction. Benzylamine hydrochloride was obtained by adding the dried ethereal solution of the amine to a small volume of dry ether saturated with hydrogen chloride; yield 64 mg. (45%).

TABLE II

HOFMANN DEGRADATION OF PHENYLACETAMIDE

	Phenylacetamide specific activity	Benzylamine·HCl specific activity	Carbon dioxide specific activity
Va	830	825	1
Vb	360	0	360

Summary

The Willgerodt reaction has been studied using acetophenone labeled in the carbonyl group with C^{14}. It has been shown that the major pathway of the reaction is to an amide by a non-rearrangement mechanism. The acidic portion, however, arises in part by a molecular rearrangement.

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[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Isolation and Structure of a Dihydroxyoctadecadienoic Acid from Tung Oil

BY SELBY B. DAVIS,* EDWARD A. CONROY[1] AND NANCY E. SHAKESPEARE

In the course of a search for the reported hypotensive principle of tung oil,[2] an acidic fraction was separated by treatment of the oil with an anion-active ion exchange resin (Ionac A300) followed by elution of the resin with alkali, and extraction of the acidified eluate with carbon tetrachloride. Storage of the extract at 5° resulted in the separation of a partially crystalline precipitate which was further separated into crystalline Fraction I, m. p. 93–98°, and carbon tetrachloride-insoluble oil, Fraction II. Evaporation of the carbon tetrachloride filtrate left a soluble oil, Fraction III.[3]

Recrystallization of Fraction I yielded a microscopically homogeneous isolate consisting of colorless tabular crystals, m. p. 104–104.5°, devoid of optical activity. The results of qualitative and quantitative analysis, molecular weight determination and titration showed the substance to be an unsaturated, hydroxylated, monocarboxylic acid, $C_{18}H_{32}O_4$. The formation of an S-benzylthiuronium salt, $C_{26}H_{42}N_2O_4S$, m. p. 133–134°, and methyl ester, $C_{19}H_{34}O_4$, m. p. 63–64°, in high yield attested the chemical homogeneity of the isolate, m. p. 104–104.5°, and confirmed the presence of one carboxyl group in the molecule.

Quantitative acetylation showed the presence of two hydroxyl groups, and quantitative oximation demonstrated the absence of aldehydic or ketonic carbonyl groups. On hydrogenation the substance absorbed two moles of hydrogen, indicating the presence of two double bonds, and yielded a saturated tetrahydro derivative, $C_{18}H_{36}O_4$, m. p. 102–104°.

Attempted oxidation of the tetrahydro derivative, m. p. 102–104°, with periodic acid resulted in complete recovery of the starting material, indicating that the hydroxyl groups were not situated on adjacent carbon atoms.[4]

Oxidation of the tetrahydro derivative with potassium permanganate yielded a diketoacid, $C_{18}H_{32}O_4$, m. p. 95–96°, from which a dioxime, $C_{18}H_{34}N_2O_4$, m. p. 111–113°, was prepared. The diketoacid, m. p. 95–96°, was found to be not identical with the 9,12-diketostearic acid, m. p.

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(2) Grollman, *J. Pharm. Exp. Ther.*, **84**, 128 (1945).

(3) We are indebted to Professor Arthur Grollman, Department of Experimental Medicine, The Southwestern Medical College, Dallas, Texas, for assays of the original tung oil, the whole carbon tetrachloride extract and the three fractions. These assays were carried out by oral administration to rats made hypertensive by ligature of the kidneys [Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944)]. The blood pressure of the warmed, unanesthetized rats was measured with a tail plethysmograph and pressure cuff [Williams, Harrison and Grollman, *J. Clin. Invest.*, **18**, 373 (1939)]. The original oil, whole extract and Fractions II and III were reported active. Later assays, using the above technique, were carried out in these laboratories by Dr. R. H. Hall. The presence of hypotensive activity in the oil, or in any fraction thereof, was not confirmed.

(4) Malaprade, *Bull. soc. chim.*, [5] **1**, 833 (1934).