[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS, FORDHAM UNIVERSITY, AND BROOKHAVEN NATIONAL LABORATORY]

Studies on the Mechanism of the Willgerodt Reaction. I. The Over-all Mechanism[1]

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Whether there is a single mechanism of the Willgerodt reaction without rearrangement of the carbon skeleton or whether there are several paths, one of which involves rearrangement, are questions which have been studied recently by tracer methods. The over-all course of the Willgerodt reaction on acetophenone has been reinvestigated using C^{14}. By employing the Hofmann degradation in the study of the reaction products of acetophenone, phenylacetic acid and phenylacetamide, it is shown that no skeletal rearrangements occur. Data are also presented indicating that thermal decarboxylation reactions may be the source of unreliable information concerning mechanism studies.

The mechanism of the Willgerodt reaction has been of interest to many investigators since Willgerodt published[3,4] the result of his original experiment with acetophenone. In the case of aryl alkyl ketones the question was decided by discovering that isovalerophenone yields α-methyl-γ-phenylbutyramide (A) not β-methyl-γ-phenylbutyramide (B).

$$C_6H_5COCH_2CH(CH_3)CH_3 \xrightarrow[H_2O]{(NH_4)_2SS_x} C_6H_5CH_2CH_2CH(CH_3)CONH_2 \quad (A)$$

$$\text{Not} \quad C_6H_5CH_2CH(CH_3)CH_2CONH_2 \quad (B)$$

This experiment was originally performed by Willgerodt and was later checked by Carmack and DeTar[5] and also by McMillan and King.[6]

Carbon isotopes have been employed by two groups of workers who have investigated the Willgerodt reaction mechanism. The Kindler modification of the original Willgerodt reaction was studied by Shantz and Rittenberg,[7] who employed acetophenone-(carbonyl)-C^{13}. They reported that the phenylacetic acid, obtained by hydrolysis of the thiomorpholide, was not rearranged.

Dauben, Reid, Yankwich and Calvin[8] studied another modification of the original Willgerodt reaction in which the ketone is treated with sulfur, ammonia and pyridine in a sealed tube. They first reported that acetophenone-(carbonyl)-C^{14} yields phenylacetamide-α-C^{14} and phenylacetic acid-(carboxyl)-C^{14}. The amide was said, therefore, to be formed by migration of a functional group along the carbon chain, while the acid was pictured as resulting from a different mechanism involving rearrangement of the carbon chain.

In a second publication Dauben and co-workers[9] have modified their original contention and believe that the rearrangement takes place only to a minor extent.

Our interest in the problem was aroused by the first publication[8] of this group, since it appeared unlikely to us that two mechanisms would operate—one yielding amide, the other acid. We noted that in both pieces of work by the Dauben group the determination of the position of activity of carbon fourteen in the phenylacetic acid was made by the method of thermal decarboxylation. If this method were reliable, then conversion of the acid to amide followed by subsequent degradation of the amide should confirm the results of the Dauben group. As we shall see later, this was not the case. In our independent study of the matter, both acetophenone-ω-C^{14} and acetophenone-(carbonyl)-C^{14} were employed. Willgerodt reactions were carried out on each and the product studied. The ketones were prepared by the following sequences of reactions, the yield for each step being indicated in parentheses to the right of the equation.

$$C^{14}H_3I + NaCN \longrightarrow C^{14}H_3CN + NaI \quad (70\%)$$

$$C^{14}H_3CN + C_6H_5MgBr \xrightarrow{H^+} C_6H_5COC^{14}H_3 \quad (70\%)$$

and

$$(CH_3)_2SO_4 + NaC^{14}N \longrightarrow CH_3C^{14}N + NaCH_3SO_4 \quad (90\%)$$

$$CH_3C^{14}N + C_6H_5MgBr \xrightarrow{H^+} C_6H_5C^{14}OCH_3 \quad (70\%)$$

The synthesis of acetonitrile-2-C^{14} followed the method of Auger,[10] modified[11] by conducting the reaction in a sealed tube at room temperature. A fraction, b.p. 76–100°, was distilled from the mixture and the desired nitrile was extracted from the water by means of benzene in a closed liquid–liquid extractor of the type described by Collins.[12] In adding the dry benzene solution of the nitrile to the Grignard reagent, we employed a ratio of one mole of nitrile to four of arylmagnesium salt. This is in accordance with the suggestion of Shriner and Turner,[13] whose procedure was followed in its entirety. Walden's[14] original instructions were followed for the preparation of acetonitrile-1-C^{14}. Although Kilmer and du Vigneaud[11] declared this method to be unsatisfactory (using C^{13}) we found no difficulty here. Pure dimethyl sulfate was added in small portions to an aqueous solution of the radioactive sodium cyanide. The product was distilled and the rest of the procedure was that followed with acetonitrile-2-C^{14}.

The Willgerodt reactions were accomplished by treating each of the labeled acetophenones with sulfur, ammonia and pyridine in a sealed tube for five

(1) Work carried out under the auspices of the Atomic Energy Commission.

(2) AEC Predoctoral Fellow.

(3) C. Willgerodt and F. H. Merk, *J. prakt. Chem.*, [2] **80**, 192 (1909); *Ber.*, **21**, 534 (1888).

(4) For a review of the Willgerodt reaction, see M. Carmack and M. A. Spielman, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, Chap. 2.

(5) M. Carmack and D. F. DeTar, THIS JOURNAL, **68**, 2029 (1946).

(6) J. A. King and F. H. McMillan, *ibid.*, **68**, 632 (1946).

(7) E. M. Shantz and D. Rittenberg, *ibid.*, **68**, 2109 (1946).

(8) W. G. Dauben, J. C. Reid, P. E. Yankwich and M. Calvin, *ibid.*, **68**, 2117 (1946).

(9) W. G. Dauben, J. C. Reid, P. E. Yankwich and M. Calvin, *ibid.*, **72**, 121 (1950).

(10) V. Auger, *Compt. rend.*, **145**, 1287 (1907).

(11) G. W. Kilmer and V. du Vigneaud, *J. Biol. Chem.*, **154**, 247 (1944).

(12) C. J. Collins, THIS JOURNAL, **70**, 2418 (1948).

(13) R. L. Shriner and T. A. Turner, *ibid.*, **52**, 1267 (1930).

(14) P. Walden, *Ber.*, **40**, 3214 (1907).

hours at 165°. The products, phenylacetamide and phenylacetic acid, were separated and purified.

To determine the specific activity of each compound, the ketones, amides and acids were oxidized by a modified Van Slyke–Folch reagent. The evolved carbon dioxide was trapped first in sodium hydroxide–hydrazine sulfate solution, then in a barium hydroxide–barium chloride reagent. The dried barium carbonate precipitate from each combustion was counted in a Nucleometer and the specific activity in each case (as listed in Tables I and II) represents counts per minute, above background, per square centimeter of a barium carbonate layer of infinite thickness.[15]

Each purified amide was subjected to a Hofmann degradation with barium hypobromite.[16] The evolved carbon dioxide was obtained directly as barium carbonate and the amine was distilled from the alkaline filtrate. It was subsequently combusted as the crystalline hydrochloride. The free acid obtained in each Willgerodt reaction was converted to amide by way of the acid chloride. The amide so obtained was also degraded with barium hypobromite.

Diagrams I and II summarize the reactions with acetophenone-ω-C^{14} and acetophenone-(carbonyl)-C^{14}, respectively. The "percentage specific activity" figures were computed from the data of Tables I and II, to which the "standard error" (±1.5%) was applied.[17]

TABLE I

	Compound	Specific activity
(A)	$C_6H_5COC^{14}H_3$	600 (8 × 75)
(B)	$C_6H_5CH_2C^{14}ONH_2$	600 (8 × 75)
(C)	$C^{14}O_2$	600
(D)	$C_6H_5CH_2NH_2$	0
(E)	$C_6H_5CH_2C^{14}OOH$	592 (8 × 74)
(F)	$C_6H_5CH_2C^{14}ONH_2$	608 (8 × 76)
(G)	$C^{14}O_2$	612
(H)	$C_6H_5CH_2NH_2$	0

TABLE II

	Compound	Specific activity
(A)	$C_6H_5C^{14}OCH_3$	640 (8 × 80)
(B)	$C_6H_5C^{14}H_2CONH_2$	632 (8 × 79)
(C)	CO_2	0
(D)	$C_6H_5C^{14}H_2NH_2$	630 (7 × 90)
(E)	$C_6H_5C^{14}H_2COOH$	640 (8 × 80)
(F)	$C_6H_5C^{14}H_2CONH_2$	624 (8 × 78)
(G)	CO_2	0
(H)	$C_6H_5C^{14}H_2NH_2$	637 (7 × 91)

On the basis of the above results we find that no rearrangement of the carbon skeleton is indicated in the formation of either the phenylacetamide or the phenylacetic acid obtained in the Willgerodt reaction using acetophenone.

DIAGRAM I

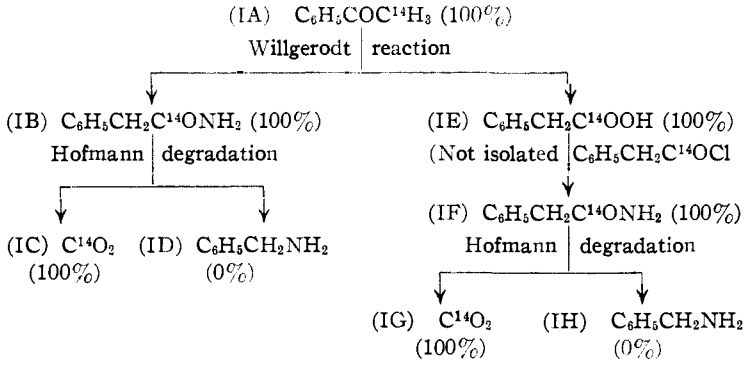
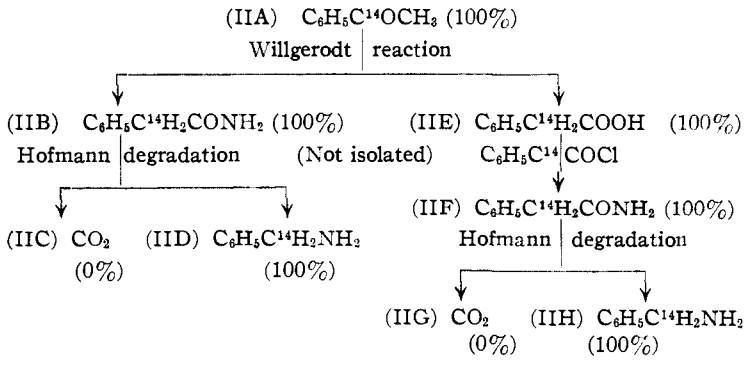


DIAGRAM II



Decarboxylation of Phenylacetic Acid

We have also carried out a number of experiments in which labeled phenylacetic acid was decarboxylated in the presence of a metallic catalyst. The results obtained were not nearly so unequivocal as those found by means of the Hofmann degradation. This observation has also been made by Dauben.[9]

Thus far there has been no study reported in the literature of the products resulting from the decarboxylation of phenylacetic acid with copper bronze or copper powder. Shantz and Rittenberg[7] assumed the product to be "mostly dibenzyl ketone" in their decarboxylation of phenylacetic acid-α-C^{13} with iron filings. However, they did not isolate this product but oxidized the residue to benzoic acid. Decarboxylation of this benzoic acid accounted for only 80% of the expected C^{13}. Although this discrepancy does not necessarily invalidate the result of their experiment, it points up the fact that the true reaction equation is unknown.

Dauben and Coad,[18] on the other hand, assumed the reaction product to be toluene. Partial oxidation of this product is presented as the explanation for the appearance of traces of C^{14} in the carbon dioxide obtained

(15) The method of assay and carbon analysis will be published shortly. It follows in a general way the method described by R. Steele and T. Sfortunato in "Techniques in the Use of C^{14}" (BNL-T-6).

(16) S. Hoogewerf and W. A. van Dorp, *Rec. trav. chim.*, **5**, 251 (1886).

(17) When the carbon dioxide is evolved from the isotopic carbon atom exclusively, as for example in the Hofmann degradation of $C_6H_5CH_2C^{14}ONH_2$, the specific activity is equal to the number of counts above background directly indicated. When, however, the carbon dioxide is evolved from the other carbon atoms as well (as in the combustion of the same amide) the number of counts indicated is multiplied by eight in order to correct for dilution by the seven nonradioactive carbon atoms in the molecule.

(18) W. G. Dauben and P. Coad, THIS JOURNAL, **71**, 2928 (1949).

by decarboxylation of phenylacetic acid-α-C^{14}.

In accordance with a suggestion given by Dauben and Coad,[18] we attempted at first to decarboxylate phenylacetic acid with copper powder and quinoline. Pure copper metal (Mallinckrodt) was heated with the acid and quinoline in the presence of "prepurified" nitrogen. No decarboxylation was observed up to a temperature of 260°. Copper chromite catalyst was then successfully employed under the same conditions. This catalyst had been made by the method of Harman[19] for our synthesis of methyl iodide-C^{14}.[20] The catalyst was used in its unreduced form. Decarboxylation was observed to start at about 170° (sand-bath) and to proceed smoothly at an optimum temperature of 230°. Yields of CO_2 varied in different experiments from 40 to 80%.

Four labeled phenylacetic acids were then decarboxylated by this method in an attempt to compare the specific activities thus obtained with those resulting by Hofmann degradation of the corresponding amides. They were (1) phenylacetic acid-α-C^{14} obtained directly from the Willgerodt reaction, (2) phenylacetic acid-(carboxyl)-C^{14} obtained in the same manner, (3) phenylacetic acid-α-C^{14} prepared by saponification of phenylacetamide-α-C^{14}, (4) phenylacetic acid-(carboxyl)-C^{14} prepared by saponification of phenylacetamide-(carbonyl)-C^{14}. Table III summarizes the results.

TABLE III

Compound	Percentage of specific activity	Yield CO_2, %	Final temperature of decarboxylation, °C.
(1) $C_6H_5C^{14}H_2COOH$ (IIE)	9	70	265
(2) $C_6H_5CH_2C^{14}OOH$ (IE)	83	80	265
(3) $C_6H_5C^{14}H_2COOH$	5, 0, 3, 0 (four runs)	40–50	230
(4) $C_6H_5CH_2C^{14}OOH$	95, 99 (two runs)	40–50	230

As yet we are unable to explain the discrepancies in these results. It is noteworthy, however, that if the reaction proceeds according to the equation

$$(A)\quad 2C_6H_5CH_2COOH \longrightarrow C_6H_5CH_2COCH_2C_6H_5 + CO_2 + H_2O$$

the expected "yield" of carbon dioxide based on phenylacetic acid is 50% as compared with a "yield" of 100% from

$$(B)\quad C_6H_5CH_2COOH \longrightarrow C_6H_5CH_3 + CO_2$$

Moreover, with the production of toluene there exists the possibility of its oxidation, in part, by an unknown mechanism. The production of toluene as well as its oxidation products would result in a higher yield of carbon dioxide according to (B), as was the case with compounds (1) and (2), where the final decarboxylation temperature was higher. The consequence of such oxidation might be to introduce in the case of (1) some radioactive carbon dioxide and in the case of (2) non-radioactive carbon dioxide. Carbon dioxide arising from some part of the molecule other than the carboxyl group thus explains the greater "yields" in cases (1) and (2). The ambiguous nature of the decarboxylation data that we obtained suggests the desirability of knowing the reaction mechanism involved, so that attempts could be made to isolate and assay both fragments of the degraded molecule.

(19) D. Harman, T. D. Stewart and S. Ruben, THIS JOURNAL, **64**, 2293 (1942).

(20) D. B. Melville, J. R. Rachele and E. B. Keller, *J. Biol. Chem.*, **169** 419 (1947).

Experimental

Preparation of Acetophenone-ω-C^{14}.—Methyl iodide-C^{14} [18] (7.75 g., 0.055 mole) was shaken for 24 hours in a sealed tube with sodium cyanide solution containing 3 g. (0.061 mole) of the salt in 6 ml. of water. The solution was slowly distilled in a microdistillation apparatus fitted with an indented fractionating column. A fraction, b.p. 76–100°, amounting to 4.0 ml. was collected as crude acetonitrile-2-C^{14}. The fraction was then extracted ten times with benzene in a liquid–liquid extractor[12] that had been especially constructed for work with radioactive liquids. The acetonitrile–benzene was dried with a little anhydrous sodium sulfate before being added to a 0.16 molar solution of phenylmagnesium bromide. The method of addition as well as the separation and hydrolysis of the resulting ketimine were performed according to the procedure of Shriner and Turner.[13] The acetophenone resulting from hydrolysis of the ketimine hydrochloride was distilled in a short path still under reduced pressure. There was obtained 3.5 g. of liquid, b.p. 83–85° (12 mm.), representing 53% of the theoretical yield based on methyl iodide-C^{14}.

Preparation of Acetophenone-(carbonyl)-C^{14}.—To a solution of 4.9 g. (0.1 mole) of radioactive sodium cyanide in 10 ml. of water there was added in small portions 12.6 g. (0.1 mole) of freshly distilled methyl sulfate. Each addition was followed by shaking, which initiated the exothermic reaction, whereupon the solution was cooled in an ice-bath. The preparation should be carried out in the hood and, if properly performed, there should be no loss of acetonitrile by volatilization as a result of the exothermic character of the reaction. After addition of all the methyl sulfate, the solution was distilled in the same manner as noted in the preparation of acetonitrile-2-C^{14}, yielding 8.6 ml. of a fraction which boiled at 76–100°.

Acetonitrile-1-C^{14} was extracted from aqueous solution by the use of benzene, the benzene solution of nitrile was added to the Grignard reagent and the resulting complex was hydrolyzed in the same manner as described in the preparation of acetophenone-α-C^{14}. The product, acetophenone-(carbonyl)-C^{14}, was collected and distilled under reduced pressure in a short path still. There was obtained 7.5 g. of liquid, boiling at 83–85° (12 mm.). This represented a yield of 63% based on the weight of sodium cyanide-C^{14}.

The Willgerodt Reaction.—In a Carius tube were sealed 3.75 g. of sulfur, 2.5 g. of acetophenone, 3.0 ml. of pyridine and 5.0 ml. of 15 molar aqueous ammonia. Five such tubes were charged with acetophenone-ω-C^{14} and the tubes were heated for four hours in a calibrated electric furnace at 165°. After cooling, the tubes were opened and the reaction products from the run were washed into a single beaker with concentrated ammonia solution. The reaction products and washings were evaporated to dryness on the water-bath. The dry residue was ground in a mortar, then extracted with 200 ml. of boiling water in several portions. Upon cooling, the first crop of crude phenylacetamide, amounting to 10 g., crystallized and was removed by filtration. A second crop of about 1.2 g. was obtained by evaporation of the filtrate to half its volume, followed by cooling. At this time the filtrate was acid (pH 5), which was no doubt due to decomposition, at least in part, of ammonium phenylacetate to phenylacetic acid during the process of evaporating the reaction mixture to dryness.

In order to remove the residual amide before extracting the free acid, it was therefore necessary to make the filtrate alkaline with sodium carbonate. By extracting five times with ether the remaining amide (0.5 to 1.0 g.) was completely removed, since no residue remained after allowing a drop of the final extract to evaporate on a watch glass. The filtrate was now made acid with hydrochloric acid and the phenylacetic acid product of the Willgerodt reaction was removed by extraction with ether. Five such extractions were performed. Evaporation of this ether yielded 0.5 g. of crude phenylacetic acid in the form of an oil. This oil was dissolved in a little aqueous sodium carbonate solution, from which crystalline phenylacetic acid was obtained by

slow addition of hydrochloric acid. The phenylacetamide was recrystallized from hot water and melted at 156.5–157.5°. There was obtained 80% of the theoretical amount. The phenylacetic acid was recrystallized from petrol ether and melted at 76.5–77.5°, the yield amounting to 2% of theoretical. The identical procedure was followed using acetophenone-(carbonyl)-C^{14}.

Conversion of Phenylacetic Acid from Willgerodt Reaction to Phenylacetamide.—Phenylacetic acid (100 mg.) was refluxed with 1 ml. of thionyl chloride in a microdistillation flask fitted with a reflux condenser. After ten minutes the mixture was cooled and the excess thionyl chloride, with some hydrogen chloride, was taken off under vacuum. The crude acid chloride was dissolved in 1 ml. of absolute ether and added dropwise to 5 ml. of cold concentrated ammonia. Evaporation of the ether gave crystalline phenylacetamide. To obtain the best possible yield the ammoniacal solution was evaporated to dryness and the crude amide recrystallized from hot water. Phenylacetamide obtained in this way melted at 156.7–157.5°. (The yield was 75% based on phenylacetic acid.)

Hofmann Degradation of Phenylacetamide.—Pure phenylacetamide (45 mg., 0.33 millimole) was suspended in 6.0 ml. of 0.18 molar barium hydroxide and bromide (0.67 millimole) was added to the flask by means of a lambda pipet. The receiver flask was then attached to an apparatus which contained a three-way stopcock permitting evacuation and sealing of the receiving flask. Before evacuation, however, the contents were frozen with liquid nitrogen to prevent loss of bromine. After the evacuation and sealing the flask was allowed to warm to room temperature and was shaken until all the amide dissolved in the barium hypobromite. The degradation reaction started at 70° (hot water-bath) as shown by precipitation of barium carbonate and was complete in three or four minutes. Coagulation of the precipitate was effected by immersing the flask in boiling water for an additional minute. After cooling the flask the vacuum was released by means of the stopcock. The precipitate was separated on a suction funnel and washed with two or three portions of water to remove as much benzylamine as possible.

The barium carbonate still contained traces of amine and cyanide and was reprecipitated before counting. The precipitate was therefore dissolved with concentrated sulfuric acid in an assay apparatus and the evolved carbon dioxide was collected in barium hydroxide solution.

The alkaline barium carbonate-free filtrate with washings was then slowly distilled in a microdistillation apparatus with an indented column. The oily benzylamine distilled with the first few milliliters of water. Addition of two drops of concentrated hydrochloric acid to the distillate converted the amine to its hydrochloride. To obtain the dry salt the solution was evaporated to dryness *in vacuo*. Before the benzylamine hydrochloride was oxidized it was recrystallized from butanol and melted at 256°. The yield of barium carbonate was quantitative based on phenylacetamide, while the yield of amine was 70–80% of the theoretical amount.

Decarboxylation of Phenylacetic Acid.—Phenylacetic acid (50 mg.) and 50 mg. of copper chromite catalyst were placed in a small flask fitted with a reflux condenser and a gas inlet tube. Purified quinoline (5 ml.) was added and the mixture was flushed for 20 minutes with "prepurified" nitrogen. The mixture was then heated in a sand-bath at 230° for 30 minutes with nitrogen being passed in continuously and the evolved carbon dioxide was passed with the nitrogen stream through the top of the condenser into a barium hydroxide bubbler. The reaction mixture was allowed to cool while the apparatus was flushed with nitrogen for an additional ten minutes. In order to remove traces of quinoline, the barium carbonate was dissolved in concentrated sulfuric acid and the evolved carbon dioxide reprecipitated from barium hydroxide solution, as in the treatment of the barium carbonate resulting from the Hofmann degradation of phenylacetamide. Yields of barium carbonate were 40–80% based on phenylacetic acid.

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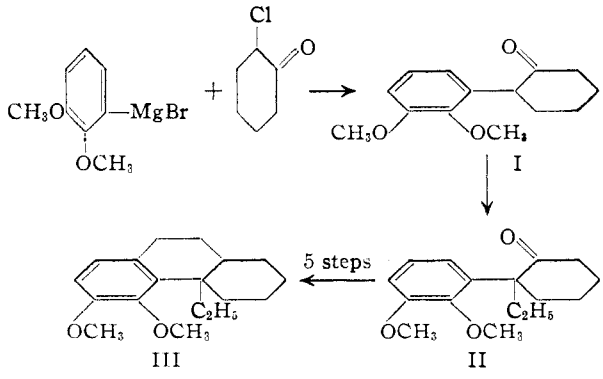
Attempted Synthesis of a Morphine Degradation Product

BY MELVIN S. NEWMAN AND WILLIAM L. MOSBY[1]

The synthesis of 2-ethyl-2-(2,3-dimethoxyphenyl)-cyclohexanone is described. This ketone is extremely unreactive as it fails to react with any of the usual carbonyl group reagents including Grignard reagents. It is reduced by lithium aluminum hydride.

In this paper are described our efforts to prepare 5,6 - dimethoxy - 4a - ethyl - 1,2,3,4,5a,9,10,10a-octahydrophenanthrene (III) a compound which, it was hoped, would provide a meeting place for synthetic and degradative operations designed to remove the last doubt concerning the structure of morphine.[2] Recent synthetic work has removed the uncertainty regarding the location of the ethaneamine side chain.[2a] The proposed synthesis is obtained briefly in the chart.



Although we have not succeeded in synthesizing III, we have made a number of observations of interest. The preparation of I as indicated[3] failed when we were unable to prepare a Grignard or organolithium reagent from 3-bromo- or 3-iodo-

(1) Taken from the Ph.D. thesis of W. L. M., 1949. General Aniline and Film Corp., Easton, Pennsylvania.

(2) A compound, supposedly III, has been synthesized by R. Ghosh and R. Robinson, *J. Chem. Soc.*, 506 (1944). It was an oil and of unproven composition inasmuch as it might have been a mixture of stereoisomers of III and also might have had another structure.

(2a) R. Grewe, A. Mondon and E. Nolte, *Ann.*, **564**, 161 (1949); M. Gates and G. Tschudi, THIS JOURNAL, **72**, 4839 (1950); O. Schnider and J. Hellerbach, *Helv. Chim. Acta*, **33**, 1438 (1950).

(3) Compare M. S. Newman and M. Farbman, THIS JOURNAL, **66**, 1550 (1944).