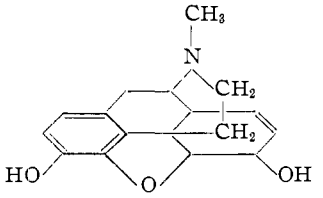
[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

# Morphine Studies. The Phenanthrene Unit

BY E. C. HORNING, M. G. HORNING AND E. JANE PLATT[1]

The relation between structure and physiological activity in the morphine series has been investigated extensively through the preparation of many derivatives of the parent alkaloid. In those cases where the furan and piperidine rings of morphine (I) are preserved, the derived compounds generally show the characteristic activity of morphine; cleavage of either of these rings usually results in loss or change in type of activity. In recent years interest in this field has been stimulated by the discovery that certain synthetic compounds (Amidone series) possess very nearly the same kind of activity as morphine itself, although lacking in either a benzofuran or piperidine ring. There are certain structural features common to all of these molecules, of which apparently the most important are a quaternary carbon (in morphine at C-13) and a $\beta$-relationship of the amino nitrogen to this carbon.

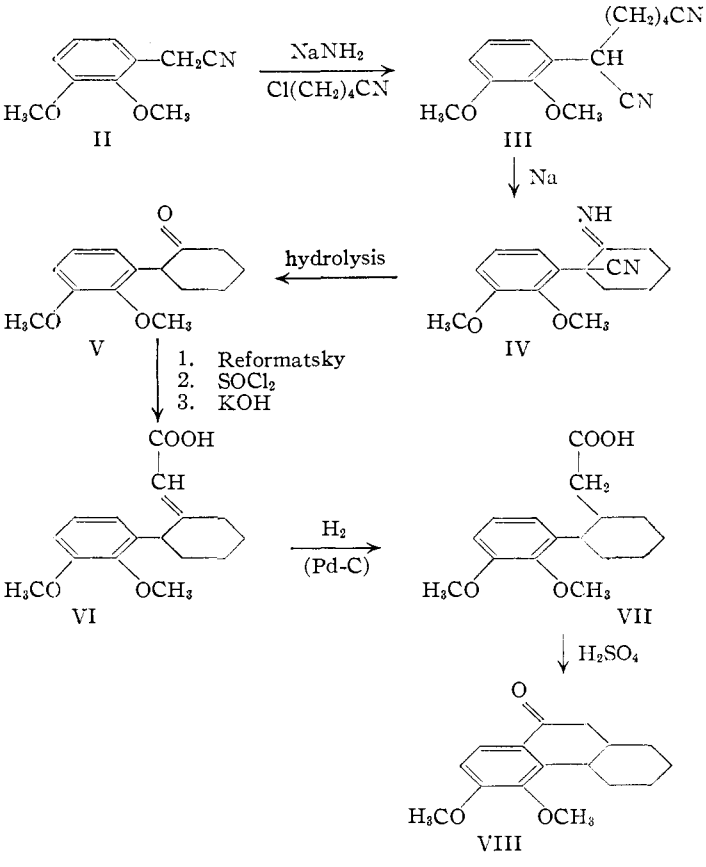


I

In order to explore further the structural requirements for morphine-like activity, we have taken up a study directed toward the synthesis of compounds related to the morphine molecule. This paper reports work on the synthesis of the methoxyphenanthrene skeleton found in many morphine derivatives, and particularly the development of a method for preparing a key intermediate, 2-(2′,3′-dimethoxyphenyl)-cyclohexanone.

It has been recognized for some time that 2-arylcyclohexanones might provide a useful starting point for the synthesis of many partially hydrogenated phenanthrene derivatives. The preparation and reactions of 2-phenylcyclohexanone were investigated by Cook[2] in 1936, and the reaction sequence needed here to build a phenanthrene system was demonstrated. The Reformatsky reaction, followed by the usual steps of dehydration and reduction of the unsaturated acid, led to 2-phenylcyclohexaneacetic acid. Cyclization with sulfuric acid or aluminum chloride gave 9-keto-1,2,3,4,9,10,-11,12-octahydrophenanthrene. Evidence was obtained for two stereoisomeric forms of this ketone, and the nature of the carbon skeleton was confirmed by reduction of the keto group to the alcohol, followed by dehydration–dehydrogenation to phenanthrene.

For studies in the morphine series, the arylcyclohexanone needed is 2,3-dimethoxyphenylcyclohexanone. A preparative method for this compound has been developed, starting with 2,3-dimethoxyphenylacetonitrile, by way of the reactions shown in the accompanying diagram. This nitrile was obtained by conventional methods from 2,3-dimethoxybenzaldehyde. Of the various methods available, those employed were reduction of the aldehyde by the crossed Cannizzaro reaction, followed by conversion of the alcohol to the chloride with anhydrous hydrogen chloride, and reaction of the chloride in the usual way with sodium cyanide. The alkylation of 2,3-dimethoxyphenylacetonitrile with $\delta$-chlorovaleronitrile was accomplished by the sodamide method. Under the proper experimental conditions, the product




(1) Rohm and Haas Research Assistant.

(2) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

was α-(2,3-dimethoxyphenyl)-pimelonitrile. Apparently minor variations in conditions resulted in some cases in partial formation of the cyclized product, and in others in partial or complete loss of product. Cyclization to 2-cyano-(2′,3′-dimethoxyphenyl)-cyclohexanone imine was carried out with metallic sodium, to which a small amount of potassium was added. A sodium–potassium alloy, containing about 10% potassium, has a melting point considerably below that of sodium itself, and is much more reactive than sodium when used in the form of the usual sodium sand. Hydrolysis of the imino-nitrile gave the desired product, obtained as a colorless, low-melting solid.

The preparation of 3,4-dimethoxy-10-keto-5,6,-7,8,9,10,13,14-octahydrophenanthrene followed the general method of Cook, and is shown in the diagram. The intermediates were viscous oils which could not be obtained in crystalline form, and which may have been mixtures of isomers. The final ketone was obtained as an oil, but fractional crystallization at low temperatures permitted the isolation of a crystalline form of one of the two possible racemic forms. In this compound, the methoxyl groups occupy the 3,4-positions characteristic of morphine derivatives.

The possibility of obtaining dihydrodesoxytetrahydromethylmorphimethine and tetrahydrodesoxycodeine, by way of the intermediates reported here, is being investigated.

## Experimental

All melting points are corrected. Analyses are by Miss Sarah H. Miles.

**δ-Chlorovaleronitrile.**—In a flask equipped with a reflux condenser and stirrer were placed 260 g. (5.0 mole) of sodium cyanide (95%) and 300 ml. water. Most of the sodium cyanide was dissolved by warming; a solution of 630 g. (4.96 mole) of 1,4-dichlorobutane[3] in 1.0 liter of 95% ethanol was then added. A little (about 3.0 g.) Dupanol was added and the mixture was maintained under reflux with stirring for six hours. After standing overnight, 1.0 liter of water was added, and the alcohol was removed by distillation. The solution was cooled and the organic layer separated. The aqueous layer was washed once with 300 ml. of ether, and the ether wash was added to the organic fraction. The combined organic material was washed once with 300 ml. of water and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was distilled under reduced pressure through a 60-cm. Vigreux column. There was obtained 90 g. of recovered 1,4-dichlorobutane fraction, b. p. 65–95° (19 mm.), and 201 g. (40%, based on unrecovered dichlorobutane) of δ-chlorovaleronitrile, b. p. 100–106° (19 mm.).

**2,3-Dimethoxybenzyl Alcohol.**—2,3-Dimethoxybenzaldehyde was reduced to the corresponding alcohol by a crossed Cannizzaro reaction.[4] In runs of 2.0 mole of commercial material, yields of 220–240 g. (66–71%) were obtained. The product was a colorless solid, b. p. 172–174° (33 mm.), m. p. 45–48°.

**2,3-Dimethoxybenzyl Chloride.**—A solution of 314 g. of 2,3-dimethoxybenzyl alcohol in 500 ml. of dry ether was saturated with hydrogen chloride at ice-bath temperature. The solution was allowed to stand for fifteen hours at 0°. The ether was then removed by distillation, and the product distilled rapidly under reduced pressure. There was obtained 300 g. (86%) of 2,3-dimethoxybenzyl chloride, as a light yellow liquid, b. p. 154–156° (33 mm.).

This compound could be preserved by freezing in Dry Ice, but it was generally converted at once to the desired nitrile. It has been prepared previously by the action of thionyl chloride on the alcohol.[5]

**2,3-Dimethoxyphenylacetonitrile.**—The "Organic Syntheses" procedure[6] for the preparation of phenylacetonitrile from benzyl chloride was followed. From 300 g. of 2,3-dimethoxybenzyl chloride there was obtained 242 g. (85%) of 2,3-dimethoxyphenylacetonitrile, b. p. 181–185° (33 mm.).

In later experiments, crude 2,3-dimethoxybenzyl chloride was converted into the nitrile without purification. The yield obtained by this direct procedure was about the same, and it provided a more satisfactory method of dealing with the chloride, which was a potent lachrymator. After removal of ether from the solution of 2,3-dimethoxybenzyl chloride, the residue was treated with several 100-ml. portions of cold water. The water was separated by decantation, and the residue washed with cold saturated sodium bicarbonate solution until neutral. The crude product was used immediately. From 314 g. of 2,3-dimethoxybenzyl alcohol there was obtained 243 g. (74% over-all) of 2,3-dimethoxyphenylacetonitrile.

**α-(2,3-Dimethoxyphenyl)-pimelonitrile.**—Sodamide was prepared from 12.5 g. (0.54 mole) of sodium in a 1-liter, three-necked flask, by the "Organic Syntheses" procedure,[7] using approximately 400 ml. of liquid ammonia. To the stirred sodamide–liquid ammonia mixture was added 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile, over about fifteen minutes. The mixture was stirred for one hour; the flask was then fitted with a water-cooled condenser, and a mixture of 250 ml. of dry toluene and 25 ml. of dry ether was added dropwise while the ammonia was evaporated by warming. The mixture was then heated to about 50° and 67.0 g. (0.57 mole) of δ-chlorovaleronitrile was added over about twenty minutes, with stirring. Stirring under reflux was continued for two hours; the mixture was then cooled and treated with 25 ml. of methanol and 100 ml. of water. The toluene layer was separated, and washed with 100 ml. of 5% sodium hydroxide solution, with 100 ml. of water, with 100 ml. of 5% hydrochloric acid, and with saturated sodium bicarbonate solution until neutral. After drying over anhydrous magnesium sulfate, the toluene was removed by distillation at atmospheric pressure and the residue distilled under reduced pressure. The forerun contained small amounts of δ-chlorovaleronitrile and 2,3-dimethoxyphenylacetonitrile; the product was collected at 197–220° (1 mm.) as a light yellow viscous oil; yield 55–57 g. (43–45%). On redistillation the boiling point was found to be 199–201° (0.8 mm.).

*Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02. Found: C, 69.84; H, 7.15.

In some runs the product obtained was a mixture of α-(2,3-dimethoxyphenyl)-pimelonitrile and 2-cyano-2-(2′,3′-dimethoxyphenyl)-cyclohexanone imine. When the latter compound was present, the initial boiling point was slightly lower, and the product crystallized in part on standing. Treatment with dry ether containing a little petroleum ether (35–60°) served to separate the crystalline material, which was identified as the imine-nitrile.

It was not possible to determine completely the conditions which brought about these variations in the product, but unreacted sodamide was apparently responsible for the cyclization.

**2-Cyano-2-(2′,3′-dimethoxyphenyl)-cyclohexanone Imine.**—A suspension of sodium sand was prepared from 2.30 g. of sodium and 0.25 g. of potassium in 200 ml. of dry toluene under a nitrogen atmosphere. A solution of 25.8 g. of α-(2,3-dimethoxyphenyl)-pimelonitrile in 20 ml. of benzene was added at 80°, and the mixture was maintained at 80–85° with good stirring for four hours. After addition of 20 ml. of ethanol and 100 ml. of water,

(3) We are indebted to E. I. du Pont de Nemours and Company, Inc., for a gift of this material.

(4) "Organic Syntheses," Coll. Vol. **2**, 590 (1943).

(5) Kaufmann and Müller, *Ber.*, **51**, 123 (1918).

(6) "Organic Syntheses," Coll. Vol. I, 107 (1941).

(7) "Organic Syntheses," **25**, 25 (1945).

the mixture was cooled and washed with 5% sodium hydroxide solution. The toluene solution was treated with 200 ml. of 10% hydrochloric acid, and steam distilled to remove the solvent. The organic material was separated with ether (about 500 ml.); the ether solution was washed with 5% sodium hydroxide solution, with 5% aqueous acetic acid, and dried over anhydrous magnesium sulfate. The product was obtained by distillation under reduced pressure, b. p. 185–205° (0.5–1.0 mm.); yield, 12.9 g. The colorless distillate solidified immediately; trituration with 2:1 ether–petroleum ether (35–60°), followed by crystallization from cyclohexane or ether, gave a colorless crystalline sample melting at 115–116°.

*Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.8. Found: C, 69.81; H, 6.84; N, 10.7.

The **2,4-dinitrophenylhydrazone** was recrystallized from aqueous alcohol; bright yellow, m. p. 187–188°.

*Anal.* Calcd. for $C_{21}H_{21}O_6N_5$: C, 57.40; H, 4.82. Found: C, 57.51; H, 4.48.

**2-(2′,3′-Dimethoxyphenyl)-cyclohexanone.**—A solution of 23.0 g. of 2-cyano-2-(2′,3′-dimethoxyphenyl)-cyclohexanone imine in 100 ml. of methanol was saturated with hydrogen chloride. The solution was heated under reflux for twenty minutes, and most of the methanol was then removed on a steam-bath, with the aid of an air jet. To the residue was added 100 ml. of acetic acid, 50 ml. of concentrated hydrochloric acid and 50 ml. of water. This mixture was heated under reflux for three hours, cooled, and poured into 600 ml. of water. The product was extracted with ether and ethyl acetate (two 100-ml. portions of each). The combined organic solutions were washed with 5% sodium hydroxide solution, with water, and with saturated sodium bicarbonate solution. After drying, the solvents were removed and the residue distilled under reduced pressure. There was obtained 11.9 g. of colorless distillate, collecting to 210° (1.7 mm.). A considerable residue remained. The distillate solidified immediately; m. p. 65–70°.

Recrystallization from ether–petroleum ether (35–60°) (in Dry Ice) yielded a colorless sample, m. p. 67–68.5°.

*Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.82; H, 7.82.

The **oxime** was prepared in ethanol–pyridine solution and was recrystallized from cyclohexane; almost colorless needles, m. p. 137–138°.

*Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.51; H, 7.64.

The **azine** was prepared in ethanol and recrystallized from cyclohexane–ethyl acetate; colorless, m. p. 147–147.5°.

*Anal.* Calcd. for $C_{28}H_{36}O_4N_2$: C, 72.38; H, 7.81. Found: C, 72.49; H, 7.68.

The **2,4-dinitrophenylhydrazone** was prepared as usual and recrystallized from aqueous ethanol; yellow, m. p. 123–124°.

*Anal.* Calcd. $C_{20}H_{22}O_6N_4$: C, 57.96; H, 5.35. Found: C, 57.82; H, 5.14.

**3,4-Dimethoxy-10-keto-5,6,7,8,9,10,13,14-octahydrophenanthrene. A. 2-(2′,3′-Dimethoxyphenyl)-cyclohexylideneacetic Acid.**—To a mixture of 3.00 g. of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone, 2.3 ml. of ethyl bromoacetate, and 35 g. of zinc (30-mesh, previously washed with 5% hydrochloric acid, water, acetone, and dry ether) in 50 ml. of dry toluene was added a crystal of iodine. The mixture was heated under reflux with stirring for thirty minutes. An additional 15 g. of zinc, and 2.3 ml. of ethyl bromoacetate in 5 ml. of toluene, was added, and heating under reflux was continued for thirty minutes longer. The mixture was cooled and treated with 1:1 acetic acid–methanol to decompose the gummy addition product. The solutions were added to 150 ml. of water containing 10 ml. of acetic acid, and the toluene layer was separated. The aqueous solution was extracted with three 30-ml. portions of ether. The combined organic solutions were washed with water and repeatedly with dilute ammonium hydroxide solution. After preliminary drying over anhydrous magnesium sulfate, the solution was reduced in volume by distillation to about 10–12 ml.

The toluene solution of the Reformatsky ester was added to a chilled mixture of 2.3 ml. of pyridine, 3.8 ml. of thionyl chloride and 15 ml. of dry toluene. After standing at room temperature for one hour, the mixture was poured into 100 ml. of 5% hydrochloric acid. The toluene layer was separated and the aqueous layer extracted with two 15-ml. portions of benzene. The combined organic solutions were washed with water and reduced in volume by distillation to about 5–7 ml. This solution was added to a solution of potassium hydroxide prepared by dissolving 5 g. of potassium hydroxide in 5 ml. of water, and diluting with 45 ml. of methanol. The resulting mixture was heated under reflux for one hour to effect dehydrohalogenation and saponification. After dilution with 50 ml. of water, the solution was distilled until 40 ml. of distillate was obtained. The remaining solution was added to 100 ml. of 10% hydrochloric acid, and the product extracted with three 50-ml. portions of ether.

Preliminary purification of the unsaturated acid was effected by extraction from the ether solution with two 50-ml. portions of 5% sodium hydroxide solution. The alkaline solution was made acid with 10% hydrochloric acid, and the product extracted with three 50-ml. portions of ether. After drying over anhydrous magnesium sulfate, the ether was evaporated, leaving a dark residue of 2.80 g. of crude unsaturated acid.

Purification of the unsaturated acid was effected by way of the methyl ester. The crude acid was dissolved in anhydrous ether and treated with slightly more than the calculated equivalent of diazomethane in ether. The ether was removed with the aid of an air jet, and the residue evaporatively distilled at 110–155° (1.5 mm.). There was obtained 2.31 g. of methyl ester, as a light yellow, very viscous oil.

The ester was treated with a solution prepared from 2.0 g. of sodium hydroxide, 5 ml. of water, and 30 ml. of methanol. This mixture was heated under reflux for five hours; a small amount of undissolved material remained in suspension. The solution was then evaporated on a steam-bath to a volume of about 10 ml., and diluted with 100 ml. of water. After filtration, the solution was acidified with 5 ml. of concentrated hydrochloric acid, and the organic material extracted with three 100-ml. portions of ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. Removal of the ether yielded 2.13 g. of the unsaturated acid, as a viscous, slightly discolored oil.

This viscous oil could not be induced to crystallize; it may have been a mixture of isomers. It was reduced directly to the saturated acid.

**B. 2-(2′,3′-Dimethoxyphenyl)-cyclohexaneacetic Acid.**—The unsaturated acid (2.13 g.) was dissolved in 25 ml. of acetic acid and hydrogenated at atmospheric pressure at 60° with a palladium–carbon catalyst. Three portions of 600 mg. each of 5% palladium catalyst[8] were needed to bring about complete reduction of the double bond. The first two portions evidently removed a catalyst poison; reduction proceeded rapidly with the third portion. The catalyst was removed by filtration, and the colorless filtrate was evaporated on a steam-bath. About 15 ml. of dry ether was added to the residue, and the solution was again evaporated. After drying for several days *in vacuo* over potassium hydroxide pellets there was obtained 2.02 g. of 2-(2′,3′-dimethoxyphenyl)-cyclohexaneacetic acid, as a viscous, slightly discolored oil.

**C. Cyclization.**—To a solution of 1.50 g. of crude 2-(2′,3′-dimethoxyphenyl)-cyclohexaneacetic acid in 5.0 ml. of acetic acid was added 15 ml. of concentrated sulfuric acid. The resulting solution, which became quite warm, was allowed to stand for one and one-half hours. After pouring on ice-water, the product was extracted with ether. The ether solution was washed well with saturated sodium bicarbonate solution and with water, and dried over an-

(8) "Organic Syntheses," **26**, 77 (1946).

hydrous magnesium sulfate. After removal of the ether, the residue was evaporatively distilled at 0.5 mm. There was obtained 0.99 g. of nearly colorless, viscous oil.

Fractional crystallization of this material from ether–petroleum ether (35–60°) (Dry Ice) yielded 350 mg. of material melting at 79–82°. Further recrystallization gave a total of 205 mg. of product, melting at 84–86° to an opaque liquid, clearing at 86–88°. Additional purification was effected by sublimation at 115–125° (0.8 mm.); m. p. 86–89° with slow clearing.

*Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.69; H, 7.75.

The maroon **2,4-dinitrophenylhydrazone**, prepared from a sample of crystalline ketone (m. p. 84–86°), was recrystallized from ethanol–benzene; m. p. 237–238°.

*Anal.* Calcd. for $C_{22}H_{24}O_6N_4$: C, 59.99; H, 5.49. Found: C, 60.09; H, 5.40.

The cyclization product may have consisted chiefly of a single isomer, although separation of crystalline material in good yield was difficult. A 2,4-dinitrophenylhydrazone sample prepared from a small portion of oil, as obtained directly from the cyclization reaction, melted only a few degrees below the derivative obtained from crystalline material.

## Summary

Syntheses of 2-(2′,3′-dimethoxyphenyl)-cyclohexanone and 3,4-dimethoxy-10-keto-5,6,7,8,9,10,-13,14-octahydrophenanthrene are described.

PHILADELPHIA, PENNSYLVANIA RECEIVED MAY 10, 1947

---

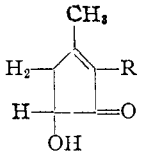
[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH ADMINISTRATION, BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE]

# Constituents of Pyrethrum Flowers. XXI. Revision of the Structure of Dihydrocinerolone

BY F. B. LAFORGE AND S. B. SOLOWAY

The insecticidal constituents of pyrethrum flowers consist mainly of a mixture of the pyrethrins and cinerins, the pyrethrolone and cinerolone esters of chrysanthemum monocarboxylic acid, and chrysanthemum dicarboxylic acid monomethyl ester. The cinerins have been prepared by partial synthesis by esterification of cinerolone with the chrysanthemum acids. They have been shown to approach the pyrethrins closely in their insecticidal action[1] and to possess the important advantage of decidedly greater stability.

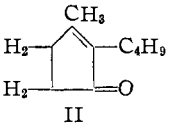
The structure heretofore assigned to pyrethrolone is represented by formula Ia and that of cinerolone by Ib.[2]



Ia, R = $-CH_2-CH=CH-CH=CH_2$
Ib, R = $-CH_2-CH=CH-CH_3$
Ic, R = $-CH_2-CH_2-CH_2-CH_3$

I

These compounds are converted to their respective tetrahydro and dihydro derivatives by hydrogenation of their side chains. Dihydrocinerolone, to which formula Ic had been assigned, is converted to the corresponding desoxy compound, dihydrocinerone, by replacement of the hydroxyl group with hydrogen. The structure of dihydrocinerone, as represented by formula II, has been established by degradation and by synthesis.[3,4]



II

(1) LaForge and Barthel, *J. Org. Chem.*, **12**, 199 (1947); Gersdorff, *J. Econ. Ent.*, in press.
(2) LaForge and Barthel, *J. Org. Chem.*, **10**, 114 (1945).
(3) LaForge and Barthel, *ibid.*, **10**, 222 (1945).
(4) Hunsdiecker, *Ber.*, **75B**, 447, 455, 460 (1942).

It was with a view to the synthesis of cinerolone, and hence, of cinerin itself, that our efforts were first directed to the synthesis of the compound of structure Ic. After attempts to substitute chlorine or bromine directly into position 5 of dihydrocinerone (II), to be followed by replacement with hydroxyl, were unsuccessful, the synthesis of 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic) was accomplished by two routes, each involving four steps.

## Synthesis No. 1

In the preparation of dihydrocinerone by the procedure of Hunsdiecker,[4] we had worked out the conditions for preparing ethyl β-oxocaprylate in good yields by carbethoxylation of methyl *n*-amyl ketone with ethyl carbonate, employing sodium hydride as the condensing agent.[5] By the same condensation procedure, or one employing sodium ethoxide, 5-carbethoxydihydrocinerone (III) was obtained from dihydrocinerone (II). This derivative furnished 5-acetoxy-5-carbethoxydihydrocinerone (IV) on treatment with lead tetraacetate. On treatment with concentrated ammonium hydroxide, compound IV was converted to the crystalline 5-carbamyl-5-hydroxydihydrocinerone (V), which by acid hydrolysis furnished the end-product, 2-butyl-5-hydroxy-3-methyl-2-cyclopenten-1-one (Ic).

This synthesis does not constitute a rigorous proof that the acetoxy group entered at the 5-position. The presence of the carbethoxy group at this position was indicated by the purple color obtained with alcoholic ferric chloride, whereas the compound with the carbethoxy group at the 4-position,[6] which is a vinylog of the 5-carbethoxy compound, gives only an orange coloration with this reagent. That the nuclear methyl group is

(5) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947).
(6) Unpublished result.