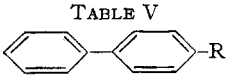
TABLE V



R	Starting product	Method	Yield, %	M.p., °C.	Solvent for cryst.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
-CH=CH—COOH[b]	4-Biphenylaldehyde	I	54	225	A	...	...	...	...	...
-CH_2—CH=CH—COOH	4-Biphenylylacetaldehyde	I	21	188	B	$C_{16}H_{14}O_2$	80.65	79.61	5.92	6.32
-CH_2—CH_2—COOH[c]	β-4-Biphenylacrylic acid	II	70	150	A–C	...	...	...	...	...
-CH_2—CH_2—CH_2—COOH[d]	γ-4-Biphenylyl crotonic acid	II	98	113–115	...	...	...	...	...	...
-CH(OH)—CH_2—COOH	4-Biphenylaldehyde	III	62	171	B–C	$C_{15}H_{14}O_3$	74.36	73.95	5.82	5.48
-CH(C_2H_5)—CH(OH)—CH_2—COOH	4-Biphenylylethylacetaldehyde	III	68	175–176	B	$C_{18}H_{20}O_3$	76.03	76.04	7.09	6.98

[a] A, ethanol; B, acetic acid; C, water. [b] Prepared also by D. H. Hey, *J. Chem. Soc.*, 2438 (1931); J. V. Brawn and J. Nelles, *Ber.*, **66**, 1464 (1933). [c] R. W. Dodson and P. Sollman, THIS JOURNAL, **73**, 4197 (1951). [d] C. Willgerodt and Th. Scholtz, *J. prakt. Chem.*, **81**, 397 (1910); M. Weizmann, E. Bergmann and E. Bograchov, *Chemistry and Industry*, 402 (1940).

4-Stilbeneacrylic Acid.—This acid was prepared from 4-stilbenealdehyde in the following three ways: 1, procedure I, yield 65%, m.p. 256–258°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.78. Found: C, 81.20; H, 5.89; O, 13.03.

2. Procedure II, yield 83%, m.p. 256–258°. This compound gave no depression of the melting point when mixed with the sample obtained above.

Anal. Found: C, 81.34; H, 5.90; O, 12.97.

3. A Perkin reaction[11] was carried out in the usual way with 4.16 g. (0.02 mole) of 4-stilbenealdehyde, 6.12 g. (0.06 mole) of acetic anhydride and 1.15 g. (0.014 mole) of fused sodium acetate. The mixture was added to water and filtered, and the residue recrystallized from glacial acetic acid; yield 1.1 g. (22%). The product gave no depression of melting point (256–258°) with the sample obtained above.

4-Diphenylethane-*n*-propionic Acid.—4-Stilbeneacrylic acid (2.50 g., 0.01 mole), dissolved in 2 liters of ethanol, was hydrogenated as described in (II). Filtration followed by vacuum distillation gave a residue which was crystallized from 80% acetic acid; yield 2.3 g. (92%), m.p. 170–172°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.57; H, 6.67.

MILANO, ITALY

(11) W. H. Perkin, *J. Chem. Soc.*, **21**, 53 (1868).

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY, CORNELL UNIVERSITY]

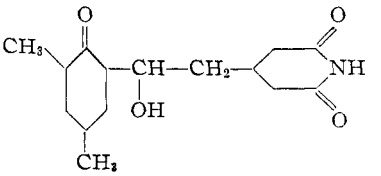
Actidione. I. The Synthesis of the Glutarimide Moiety

BY DONALD D. PHILLIPS,[1] MARIO A. ACITELLI[2] AND JERROLD MEINWALD

RECEIVED FEBRUARY 1, 1957

The synthesis of glutarimide-β-acetaldehyde (V) from acetone-dicarboxylic ester is described. The aldehyde is of interest as a possible intermediate in the total synthesis of actidione, an antifungal antibiotic produced by *Streptomyces griseus*.

The presence of an antifungal antibiotic in culture filtrates from streptomycin-producing strains of *Streptomyces griseus* was first reported in 1946.[3] The empirical formula $C_{27}H_{42}N_2O_7$ was originally assigned to the crystalline antibiotic[4] and the name "actidine" was proposed on the erroneous assumption that the compound was a diketone. The molecular formula was later corrected[5] to $C_{15}H_{23}NO_4$ and further investigations on the antibiotic indicated that it contained only one ketone group.[6] The total structure (I) for the antibiotic was established[7] in 1949, principally on the basis of the hydrolysis products obtained from I and the corresponding β-



I

diketone. To date, however, this assignment has not been verified by total synthesis.

Although the structure assigned to actidione (I) can hardly be in doubt, a total synthesis is of more than academic interest in view of the increasing importance of the antibiotic in plant disease control.[8]

(1) To whom inquiries regarding this article should be sent.

(2) From the dissertation presented by M.A.A. in partial fulfillment of the requirements for the degree of Doctor of Philosophy. This paper was delivered at the 131st Meeting of the A.C.S., Miami, Florida, April 7–12, 1957.

(3) A. J. Whiffen, N. Bohonos and R. L. Emerson, *J. Bacteriol.*, **52**, 610 (1946).

(4) B. E. Leach, J. H. Ford and A. J. Whiffen, THIS JOURNAL, **69**, 474 (1947).

(5) J. H. Ford and B. E. Leach, *ibid.*, **70**, 1223 (1948).

(6) E. C. Kornfeld and R. G. Jones, *Science*, **108**, 437 (1948).

(7) E. C. Kornfeld, R. G. Jones and T. V. Parke, THIS JOURNAL, **71**, 150 (1949).

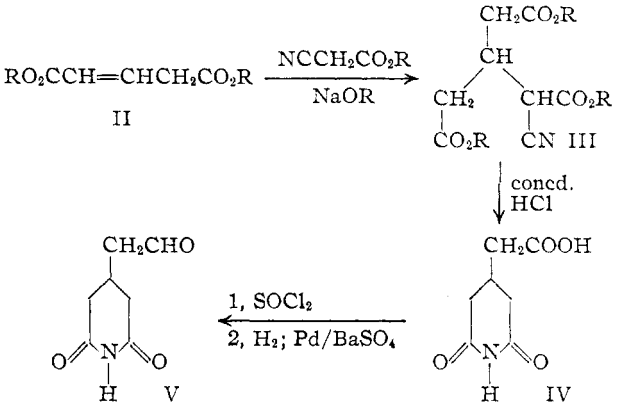
(8) I. M. Felber and C. L. Hamner, *Botan. Gaz.*, **110**, 324 (1948); J. R. Vaughn and C. L. Hamner, *Proc. Am. Soc. Hort. Sci.*, **54**, 435 (1949); H. W. Anderson and D. Gottlieb, *Econ. Botany*, **6**, 294 (1952); C. Leben and G. W. Keitt, *J. Agr. Food Chem.*, **2**, 234 (1954); P. W. Brian, *Chem. Products*, **17**, 139 (1954); J. C. Dunegan, *J. Agr. Food Chem.*, **2**, 1020 (1954); and W. J. Zaumeyer, *ibid.*, **3**, 112 (1955).

It has seen commercial application in the control of cherry leaf spot[9] and various turf diseases[10] and shows promise as a rodent repellent.[11] Moreover, its ability to prolong the life of leukemic mice[12] and its limited control of sarcoma 180[13] are of more than passing interest in cancer research.

We have approached the problem of total synthesis with the view that actidione (I) might be obtained from an aldol condensation between (+)-2,4-dimethylcyclohexanone and glutarimide-β-acetaldehyde (V). For this reason, we have synthesized the glutarimide moiety (V) and experiments designed to test our hypothesis are in progress.

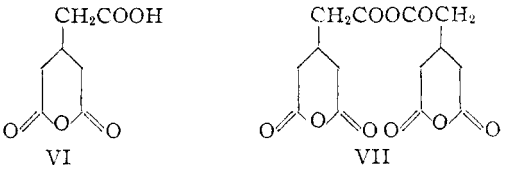
The pertinent equations for the most satisfactory synthesis of the aldehyde are listed in Chart 1.

CHART 1



In the early stages of the problem, glutaconic ester (II) was prepared from chloroform and malonic ester,[14] but the yields were erratic and the reaction was difficult to control. A far superior method involved the catalytic reduction of acetone-dicarboxylic ester to dimethyl β-hydroxyglutarate which then could be dehydrated to II. This approach was particularly attractive in view of the recently announced commercial availability of dimethyl acetonedicarboxylate.[15] Although the corresponding hydroxy ester was surprisingly inert to a variety of dehydrating agents, good yields of glutaconic ester were obtained in the presence of phosphorus pentoxide. Under scrupulously anhydrous conditions, methyl cyanoacetate could be condensed with dimethyl glutaconate to afford the cyanotriester III in yields as high as 70%.

The controlled hydrolysis of III to glutarimide-β-acetic acid (IV) was the most difficult step in the reaction scheme and many variants were investigated before satisfactory yields were obtained (see Experimental). An indirect approach entailed the complete hydrolysis of III to methanetriacetic acid. It was anticipated that the corresponding anhydride VI would yield IV (or its amide) on ammonolysis,



but the only anhydride that could be isolated from methanetriacetic acid was VII and ammonolysis experiments on VII were inconclusive. The Guareschi imide synthesis was equally unsuccessful as no crystalline product could be obtained from the reaction between chloroacetaldehyde and methyl cyanoacetate. Moreover, the recently reported[16] hydrolysis of cyano esters to glutarimides in basic media resulted in the formation of intractable oils when applied to III (R = CH_3 and C_2H_5).

The preparation of the acid chloride from glutarimide-β-acetic acid (IV) presented no difficulties and a beautifully crystalline product (m.p. 129–130°) was obtained readily. When subjected to the conditions of the Rosenmund reduction, this acid chloride afforded good yields of the desired aldehyde, m.p. 122–123°, although it was found necessary to omit completely the catalyst poison often suggested.

Acknowledgment.—The antifungal and antibiotic properties of glutarimide β-acetaldehyde (V) and acid (IV) are being tested by the Upjohn Laboratories, Kalamazoo, Mich., through the courtesy of Dr. Alan J. Lemin. We are also indebted to the Upjohn Laboratories for generous samples of actidione.

Experimental[17]

Trimethyl α-Cyanomethanetriacetate (III, R = CH_3).[14]—To a flame-dried flask was added 50 ml. of methanol and 79.2 g. (0.8 mole) of methyl cyanoacetate (both of which had been dried by distillation from magnesium methoxide) followed by 63.2 g. (0.4 mole) of freshly distilled dimethyl glutaconate.[18] To this mixture was added 18 drops of freshly prepared sodium methoxide solution (from 0.9 g. of sodium and 30 ml. of absolute methanol). The reaction mixture, adequately protected from moisture by phosphorus pentoxide tubes, was heated under reflux for 12 hours with the addition of 18 drops of sodium methoxide solution every two hours to ensure alkalinity.

The reaction was allowed to stand overnight at room temperature after which time it was quenched by the addition of a few drops of acetic acid. Solvent methanol was removed at the water-pump and the residue was fractionally distilled to give 62 g. (60%) of the cyano ester as a colorless, viscous oil, b.p. 162–165° (2.5 mm.), $n^{25}D$ 1.4521.

Anal. Calcd. for $C_{11}H_{15}O_6N$: N, 5.44. Found: N, 5.50.

Complete Hydrolysis of III.—A stirred mixture of 5.5 g. (0.02 mole) of trimethyl α-cyanomethanetriacetate (III) and 50 ml. of concentrated hydrochloric acid was heated for three hours on the steam-bath. The volatile components were removed by distillation *in vacuo* and the residue was

(9) D. Cation, *Am. Fruit Grower*, **74**, 29 (1954); T. T. McClure, *Phytopathology*, **42**, 14 (1952); J. M. Hamilton and M. Szkolnik, *Proc. N. Y. State Hort. Soc.*, 58 (1955).

(10) J. R. Vaughn, *Phytopathology*, **41**, 36 (1951); H. D. Wells and B. P. Robinson, *ibid.*, **44**, 509 (1954).

(11) J. F. Welch, *J. Agr. Food Chem.*, **2**, 142 (1954).

(12) J. C. Bateman and C. T. Klopp, *Proc. Am. Assoc. Cancer Research*, **1**, 3 (1953).

(13) H. C. Reilly, C. C. Stock, S. M. Buckley and D. A. Clark, *Cancer Research*, **13**, 684 (1953).

(14) E. P. Kohler and G. H. Reid, THIS JOURNAL, **47**, 2803 (1925).

(15) We are grateful to the Chas. Pfizer Co. of Brooklyn, N. Y., for generous samples of this ester.

(16) E. Tagmann, E. Sury and K. Hoffmann, *Helv. Chim. Acta*, **35**, 1235 (1952).

(17) Boiling points and melting points are both uncorrected. Analyses are by Schwarzkopf Microanalytical Labs., Woodside 77, N. Y.

(18) Prepared from dimethyl acetonedicarboxylate by catalytic hydrogenation followed by dehydration (phosphorus pentoxide) of the resultant dimethyl β-hydroxyglutarate (A. L. Lochte and P. L. Pickard, THIS JOURNAL, **68**, 721 (1946)). We are grateful to the Chas. Pfizer Co., Brooklyn, N. Y., for generous samples of dimethyl acetonedicarboxylate.

taken up in 50 ml. of dry acetone. The ammonium chloride was removed by filtration and the acetone was evaporated to an oil. This oil was dissolved in ether and, on slow evaporation of the solvent, 1.9 g. (47%) of **methanetriacetic acid** precipitated, m.p. 115–118°. This material could not be recrystallized without large losses and was used directly in the next step.

(Glutaric Anhydride β-Acetic)-anhyride (VII).—Two grams of (0.02 mole) of acetic anhydride was added to 1.9 g. (0.01 mole) of methanetriacetic acid and the mixture was heated on the steam-bath for 15 minutes. Excess anhydride and acetic acid were removed by distillation *in vacuo* and the dark, residual oil was triturated with acetone. This induced the crystallization of needles that were recrystallized from acetone to give 0.6 g. of VII as colorless needles, m.p. 150–151°; λ_{max}^{KBr} 5.55, 5.60 and 5.70 μ.

Anal. Calcd. for $C_{14}H_{14}O_9$: C, 51.53; H, 4.32; neut. equiv., 54.4. Found: C, 51.45; H, 4.33; neut. equiv., 55.9.

Glutarimide-β-acetic Acid (IV).—A mixture of 30 g. (0.117 mole) of cyano ester III in 100 ml. of concentrated hydrochloric acid was stirred for one hour at room temperature. The reaction mixture was poured into 100 ml. of water and the resulting solution was evaporated on the steam-bath at a reduced pressure of approximately 50 mm. The yellow residual oil was taken up in 200 ml. of dry acetone leaving behind a small amount (*ca.* 10%) of ammonium chloride.

On concentration of the acetone to about 20 ml., colorless crystals were deposited. These were removed by filtration to yield 10 g. (50%) of the glutarimide, m.p. 168–170°. The analytical sample crystallized from acetone–hexane as colorless crystals, m.p. 172–173°, λ_{max}^{KBr} 5.82 and 6.00 μ.

Anal. Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.15; H, 5.59; N, 7.89.

Yields in this reaction were subject to considerable variation because the hydrolysis conditions were difficult to duplicate, but usually they were in the range of 26–55%.

Glutarimide-β-acetyl Chloride. a. From the Sodium Salt of IV.—A solution containing 1.1 g. (0.008 mole) of glutarimide-β-acetic acid (IV) in 25 ml. of 95% alcohol was titrated to phenolphthalein with 1.0 *N* sodium hydroxide. The solvent was removed *in vacuo* and to the colorless solid was added 4.8 g. of thionyl chloride. The resulting slurry was heated on the steam-bath for 15 minutes and the excess thionyl chloride was removed by distillation under reduced pressure. The last traces were taken off by codistillation with dry benzene.

The dark red residue was taken up in warm benzene, filtered and the filtrate was concentrated to about 15 ml. On cooling there was deposited 0.5 g. (33%) of the acid chloride as colorless needles, m.p. 129–132°. A purified sample crystallized from acetone–hexane as colorless needles, m.p. 129–130°, λ_{max}^{KBr} 5.50 and 5.95 μ.

Anal. Calcd. for $C_7H_8O_3NCl$: C, 44.34; H, 4.25; Cl, 18.70. Found: C, 44.56; H, 4.39; Cl, 18.64.

The residue that did not dissolve in benzene was shown by infrared analysis to be a mixture of the acid and acid chloride. This mixture could be recycled so that the actual yield of acid chloride was probably higher than 33%.

b. From the Free Acid IV.—A slurry of 8.6 g. (0.05 mole) of the acid and 30 g. of thionyl chloride was heated under reflux for 30 minutes. The deep orange solution was cooled and the crystalline solid that precipitated was filtered rapidly, washed with dry acetone and stored immediately in a desiccator. The yield of impure acid chloride by this procedure was 6.3 g. (66%), m.p. 125–130°.

On some occasions the excess thionyl chloride was distilled under reduced pressure and the last traces were removed by codistillation with benzene. The orange residue then was triturated with cold acetone and dried. Yields of acid chloride, m.p. 126–131°, by this method were generally in the range of 50–55%. Repeated crystallizations of this impure material were seldom profitable and once-recrystallized acid chloride usually was employed in the Rosenmund reduction.

Glutarimide-β-acetaldehyde (V).—To a flask equipped with a gas inlet tube, stirrer and condenser were added 150 ml. of dry toluene, 3.4 g. (0.018 mole) of once-recrystallized glutarimide-β-acetyl chloride and 0.3 g. of 10% palladium-on-barium sulfate catalyst. The mixture was heated to reflux and hydrogen was passed through the system. The hydrochloric acid formed was titrated with standard alkali.

After three hours, 82% of the theoretical amount of acid had been titrated. The reaction was stopped and the hot toluene solution was filtered free of catalyst. On cooling, there was deposited long colorless needles of the aldehyde. These were removed and a second crop was obtained by concentrating the filtrate. In total, there was obtained 1.8 g. (64%) of the aldehyde, m.p. 121–123°. The analytical sample crystallized as colorless needles from acetone–hexane, m.p. 122–123°; λ_{max}^{KBr} 3.19, 3.73, 5.82 and 5.95 μ.

Anal. Calcd. for $C_7H_9O_3N$: C, 54.19; H, 5.84; N, 9.03. Found: C, 54.23; H, 5.47; N, 8.93.

The semicarbazone crystallized from dilute alcohol as colorless needles, m.p. 230–231°.

Anal. Calcd. for $C_8H_{12}O_3N_4$: N, 26.40. Found: N, 26.53.

When the catalyst was poisoned with quinoline and sulfur as suggested[19] in the literature, no aldehyde could be obtained in this reduction.

(19) E. B. Hershberg and J. Cason, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 627.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Terpenes. VII.[1] The Structures of the Dieucarvelones

BY G. BÜCHI AND W. S. SAARI

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The structures of the isomeric dieucarvelones obtained earlier by Wallach have been reinvestigated. β-Dieucarvelone was shown to be a mixture of the α- and ε-isomers. The γ- and ϑ-isomers described by this author never could be isolated but two new isomers, ε and ζ, were found. Two substances reported by Rupe from the reaction of eucarvone with magnesium and methyl iodide were shown to be identical with α- and β-dieucarvelone. Chemical and spectroscopic findings are in agreement with structure III for these isomers. The conjugate bimolecular reduction of eucarvone is discussed.

In 1899, and again in 1914, Wallach[2] reported that the reduction of eucarvone (I), with zinc in basic solution gave a series of compounds, $C_{20}H_{30}O_2$, which he named the dieucarvelones. Wallach found that these isomers could be separated by recrystallization from an acetic acid–water mixture into an α-isomer, m.p. 177°; β-isomer, m.p. 143°; γ-isomer, m.p. 128°; and a ϑ-isomer, m.p. 111°.

Because the α- and β-isomers only slowly decolorized a solution of bromine in acetic acid *with* liberation of hydrobromic acid and because they were not

(1) Paper VI, G. Büchi and David Rosenthal, THIS JOURNAL, **78**, 3860 (1956).

(2) O. Wallach, *Ann.*, **305**, 223 (1899); **403**, 96 (1914).