Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.4. Found: C, 72.70; H, 5.7.

2,3-Dimethoxy-5-acetyl-6-hydroxy-8,9,10,11-tetrahydro-7H-cyclohepta[a]naphthalene (XIb).—Condensation of 9.9 g. of homoveratric anhydride and 5.8 g. of cycloheptanone in the presence of 50 ml. of boron-trifluoride-saturated glacial acetic acid, as described in the preceding experiment, and hydrolysis with 33 g. of sodium acetate and 20 g. of sodium bicarbonate in 300 ml. of water (warmed on a steam-cone for 20 minutes) gave, after cooling the mixture, semi-solid brown oil. This material was washed with 2 small portions of water (decanting) and was triturated with a small amount of methanol. There was obtained 0.6 g. of yellow crystals, m.p. 155–157°. Additional product (0.3 g.) was obtained when the original aqueous solution was allowed to stand for a week, bringing the total yield to 0.9 g. (11%). Recrystallization from methanol gave yellow needles, m.p. 157–158°. The infrared spectrum (chf.) was similar to that of XIa, and the ultraviolet spectrum had λ_{max} 235, 291 and 345 mμ (log ε 4.84, 3.56 and 4.02, respectively). The compound gave a dark green ferric chloride test.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.64; H, 7.06.

2,3-Dimethoxy-9-hydroxy-10-(α-hydroxyethyl)-4b,5,6,7,-8,8a,9,10-octahydrophenanthrene (XIIa).—Compound XIa (0.3 g.) in 200 ml. of ethyl acetate with 1.5 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for 1.2 hr. Filtration of the catalyst and evaporation of the solvent gave viscous, pale yellow oil which crystallized rapidly in the presence of methanol. Recrystallization from cyclohexane–ethyl acetate gave 0.25 g. of colorless crystals, m.p. 167–170°. Further recrystallization gave pure material, m.p. 171–173°. The infrared spectrum (chf.) had a moderately strong doublet, 2.76 and 2.98 μ. The ultraviolet spectrum (ethanol) had λ_{max} 288 mμ (log ε 3.34) and an inflection point at 225 mμ (log ε 3.99).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.23.

Similar hydrogenation of the boron complex, m.p. 239–241°, of XIa afforded a monohydroxy compound, probably **2,3-dimethoxy-9-hydroxy-10-ethyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene**, m.p. 151–152.5°. after recrystallization from cyclohexane–ether. The infrared spectrum (chf.) of this compound had a single, sharp peak at 2.73 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 280 and 285 mμ (log ε 3.17 and 3.20, respectively).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.72; H, 9.12.

2,3-Dimethoxy-5-(α-hydroxyethyl)-6-hydroxy-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalene (XIIb).—Hydrogenation of 0.4 g. of XIb as described in the preceding experiment gave 0.35 g. of colorless crystals, m.p. 138–140°. Recrystallization from cyclohexane–ethyl acetate gave pure material, m.p. 142–144°. The infrared spectrum (chf.) had a doublet 2.76 and 2.99 μ, and the ultraviolet spectrum (ethanol) had λ_{max} 291 mμ (log ε 3.43) and a point of inflection at 227 mμ (log ε 3.98).

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.44; H, 8.75.

2-Ethylcyclohexanone.—A solution of 5 g. of 2-acetylcyclohexanone[22] in 250 ml. of ethyl acetate containing 4 g. of 10% palladium–charcoal was shaken under hydrogen (40 lb.) at 80° for an hour. Two moles of hydrogen were consumed in 0.5 hr., and then the reaction became very slow. Filtration of the catalyst and evaporation of the solvent gave nearly colorless oil. The infrared spectrum (chf.) had an intense peak at 5.87–5.89 μ and a very weak band at 2.90 μ (indicating presence of some hydroxylic material). **The 2,4-dinitrophenylhydrazone** was prepared in *ca.* 80% yield from the crude product; recrystallization from ethanol gave orange needles, m.p. 160–161° (lit.[23] m.p. 159–161°).

Condensation of Homoveratric Anhydride with 2-Tetralone.—To a mixture of 7.4 g. of homoveratric anhydride and 4.2 g. of 2-tetralone was added 65 ml. of ice-cold 47% boron trifluoride etherate. The suspension was swirled in an ice-bath for 15 minutes until the anhydride dissolved and was kept in an ice-box for 2 days. Hydrolysis with a solution of 60 g. of sodium acetate in 350 ml. of water at 60–70° for 10 minutes gave oily material, which was extracted with ether–ethyl acetate. The organic solution was washed with successive portions of water, sodium bicarbonate solution (excess) and water and was dried over magnesium sulfate. The solvents were evaporated at 30°, and the residual oil (6.9 g.) was dissolved in 20 ml. of ether. Refrigeration of this solution overnight resulted in formation of 0.85 g. of gummy crystals. Trituration of the crystals with additional ether gave 0.5 g. of product, m.p. 189–192°. Recrystallization from methanol afforded colorless crystals, m.p. 194–195° dec. The infrared spectrum (chf.) showed a weak band at 2.82–2.86 μ and a moderately strong peak at 5.83 μ. The ultraviolet spectrum (ethanol) had λ_{max} 227, 275, 321 and 349 mμ (log ε 4.45, 4.61, 3.96 and 2.96, respectively).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 74.08; H, 5.90.

Efforts to dehydrate and acetylate this material as with Ia led to decomposition and formation of mixtures of products.

Acknowledgment.—I am indebted to Dr. William C. Alford and his staff for microanalytical data, and to Mr. H. Franklin Byers, Miss Catherine Monaghan and Miss Patricia Wagner for spectra.

(22) R. M. Manyik, F. C. Frostick, J. J. Sanderson and C. R. Hauser, THIS JOURNAL, **75**, 5030 (1953).

(23) H. Smith, *J. Chem. Soc.*, 803 (1953).

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MAGGIONI & CO.]

Further Research on Biphenyl, Stilbene and Diphenylethane Derivatives—Potential Anticholesterinemic, Antirheumatic Drugs. VII

BY G. CAVALLINI, E. MASSARANI, D. NARDI AND R. D'AMBROSIO

RECEIVED SEPTEMBER 21, 1956

Derivatives of biphenyl, stilbene and diphenylethane have been prepared with various substituents in the 4-position: alkylacetic acids; oxyacetic acid; and propionic, butyric, acrylic, pyruvic, crotonic, β-hydroxypropionic and γ-ethyl-β-hydroxybutyric acid.

In a previous paper[1] we prepared derivatives of biphenyl, stilbene and diphenylethane with various groups in the 4-position

$$-CH_2COOH,\ -\underset{\displaystyle C_2H_5}{\underset{|}{CH}}-COOH,\ -CH_2-CO-COOH$$

Some of these substances showed a marked anticholesterinemic activity, the most active among them being the 4-biphenylylethylacetic acid[2] which has been used therapeutically with satisfactory results.[3,4]

(1) G. Cavallini and E. Massarani, *Il Farmaco, Ed. Scient.*, **11**, 167 (1956).

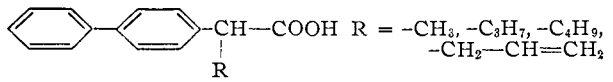
(2) S. Garattini, C. Morpurgo and N. Passerini, *Giorn. ital. Chem.*, **2**, 60 (1955).

(3) G. Annoni, *Il Farmaco*, **11**, 244 (1956).

(4) E. Sabbadini, N. Campani and M. Gazzaniga, *Minerva Med.*, XLVII, [I], 2048 (1956).

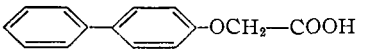
With the hope of finding substances having both anticholesterinemic and antirheumatic activity, we have prepared additional derivatives of biphenyl (and in a few cases of stilbene and diphenylethane) with the following acid groups in the 4-position:

(1) Alkyl-substituted acetic acids



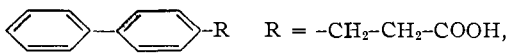
Diphenylethane, R = $-C_3H_7$

(2) Oxyacetic acid



Also stilbene and diphenylethane.

(3) 3 and 4 carbon acids



$-CH_2-CH_2-CH_2-COOH$, $-CH{=}CH-COOH$,
$-CH_2-CH{=}CH-COOH$, $-CH_2COCOOH$,
$-CH(OH)-CH_2-COOH$, $-CH(C_2H_5)-CH(OH)-CH_2-COOH$

Stilbene, R = $-CH{=}CH-COOH$

Diphenylethane, R = $-CH_2-CH_2-COOH$

4-Biphenylaldehyde, 4-biphenylylacetaldehydes and the 4-biphenylylalkylacetonitriles served as intermediates for the preparation of the acids. The 4-biphenylylalkylacetonitriles, obtained by alkylation[5] of 4-biphenylylacetonitrile, gave the corresponding acetic acids upon acid hydrolysis. Saponification of 4-biphenylylacetonitrile yielded 4-biphenylyloxyacetic acid; the oxyacetic acids of stilbene and diphenylethane were prepared in the same way. It was not possible to convert 4-biphenylyldiethylacetonitrile and 4-biphenylyl-*n*-octylacetonitrile to the corresponding acids as both the acid and alkaline hydrolyses were unsuccessful.

4-Biphenylaldehyde, which was obtained from 4-biphenylylmethyl chloride,[6] was used in the following preparations: (1) 2-phenyl-4-biphenylal-5-oxazolone which upon saponification yielded 4-biphenylylpyruvic acid; (2) 4-biphenylylacrylic acid by Knoevenagel's reaction[7]; the acrylic acid was reduced to the corresponding propionic acid; (3) 4-biphenylyl-β-hydroxypropionic acid which was obtained by the Reformatsky synthesis.[8]

4-Biphenylylacetaldehyde and the alkylacetaldehydes were prepared from the corresponding acid chlorides by Rosenmund's reaction.[9] The former was used for the synthesis of 4-biphenylylcrotonic acid which was subsequently reduced to the butyric acid.

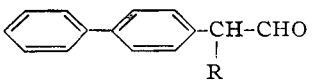
Experimental

The melting points are not corrected.

4-Biphenylaldehyde.—A mixture of 40.4 g. (0.2 mole) of 4-biphenylylmethyl chloride, 60.2 g. (0.44 mole) of hexamethylenetetramine and 90 ml. of 50% acetic acid was refluxed for 2 hours. It was then added to 200 ml. of water and extracted with ether. The organic layer was washed with saturated, aqueous sodium bicarbonate and with water, dried over sodium sulfate and concentrated. Distillation of the residue yielded 21 g. (60%) of 4-biphenylaldehyde b.p. 130° (0.5 mm.); m.p. 60°.[10]

4-Biphenylylacetaldehyde.—The following procedure was also used for the preparation of the 4-biphenylylalkylacetaldehydes. The data are reported in Table I. Thionyl chloride (59 g., 0.5 mole) was added dropwise to 10.56 g. (0.05 mole) of 4-biphenylylacetic acid. The mixture was stirred for one hour at room temperature and for one hour on a steam-bath. The thionyl chloride was then distilled at reduced pressure. The residue, dissolved in 100 ml. of dry toluene, was reduced by the procedure of Rosenmund.[9] The catalyst was filtered, and the solvent evaporated *in vacuo* at 40° under a stream of nitrogen. The residue yielded 4-biphenylylacetaldehyde which was characterized by its 2,4-dinitrophenylhydrazone.

TABLE I



R	Yield, %	M.p., °C.	Solvent for cryst.[a]	2,4-Dinitrophenylhydrazone Formula	N, % Calcd.	N, % Found
-H	81	172	A	$C_{20}H_{16}O_4N_4$	14.88	14.94
$-CH_3$	78	177	A	$C_{21}H_{18}O_4N_4$	14.35	13.94
$-C_2H_5$	84	121–123	B	$C_{22}H_{20}O_4N_4$	13.85	13.94
$-C_3H_7$	82	117	A	$C_{23}H_{22}O_4N_4$	13.39	13.27

[a] A, acetic acid; B, ethanol.

4-Biphenylyl-*n*-propylacetonitrile.—The other 4-biphenylylalkylacetonitriles, which are reported in Table II, were prepared by this method.

A mixture of 19.30 g. (0.1 mole) of 4-biphenylylacetonitrile, 6 g. (0.15 mole) of sodium amide and 60 ml. of dry ether was refluxed for 1 hour. After the addition of 25.5 g. (0.15 mole) of propyl iodide dropwise with stirring, the reaction mixture was refluxed for 6 hours. Then it was cooled, cautiously diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with aqueous sodium thiosulfate. Drying and concentration gave an oil which upon distillation yielded 4-biphenylyl-*n*-propylacetonitrile.

4-Biphenylyl-*n*-propylacetic Acid.—This procedure is typical for the hydrolysis of the 4-biphenylylalkylacetonitriles to yield the corresponding acetic acids, which are listed in Table III. A mixture of 23.5 g. (0.1 mole) of 4-biphenylyl-*n*-propylacetonitrile, 103 g. (1 mole) of concentrated sulfuric acid, 100 ml. of water and 120 g. (2 mole) of acetic acid was refluxed for 36 hours and 1 liter of water added. The mixture was made alkaline with 40% NaOH, charcoal was added and the solution was filtered. Acidification with dilute hydrochloric acid gave a white precipitate, which was filtered, dried and recrystallized from ligroin.

Oxyacetic Acids and 4-Diphenylethane-*n*-propylacetic Acid.—A mixture of 26.3 g. (0.1 mole) of 4-diphenylethane-*n*-propylacetonitrile, 120 ml. of methanol and 120 ml. of 40% sodium hydroxide was refluxed until the evolution of ammonia was complete. After cooling and evaporation of solvent, water was added to the residue, which was extracted with ether. The aqueous layer was acidified with hydrochloric acid, cooled, filtered and crystallized from 70% acetic acid, ethanol or cyclohexane; yield 13.6 g. (48%), m.p. 95°.

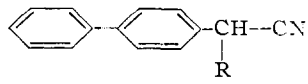
Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.21; H, 7.73.

The oxyacetic acids of biphenyl, stilbene and diphenylethane were prepared by this method; see Table IV.

4-Biphenylylethylacetic Acid Ethyl Ester.—Thionyl chloride (11.9 g., 0.1 mole) was added dropwise to 2.40 g. (0.01 mole) of 4-biphenylylethylacetic acid. The mixture was stirred for 1 hour at room temperature and for 1 hour on a steam-bath. After distillation of the thionyl chloride at reduced pressure, 16 ml. of dry ethanol was added to the residue. The mixture was stirred for 1 hour at room temperature and for 2 hours over a steam-bath. Concentration gave an oil which, upon distillation, yielded 1.6 g. (64%) of

(5) C. Bradsher and W. Jackson, THIS JOURNAL, **73**, 3235 (1951).
(6) M. Sommelet, *Compt. rend.*, **157**, 852 (1913).
(7) E. Knoevenagel, *Ber.*, **31**, 2598 (1898).
(8) S. N. Reformatsky, *ibid.*, **20**, 1210 (1887).
(9) K. W. Rosenmund and F. Zetzche, *ibid.*, **54**, 436 (1921).
(10) For other syntheses of 4-biphenylaldehyde see L. Gattermann, *Ann.*, **347**, 381 (1906); C. L. Knowles, THIS JOURNAL, **43**, 897 (1921); D. H. Hey, *J. Chem. Soc.*, 2476 (1931); D. Worländer, *Ber.*, **68**, 435 (1935).

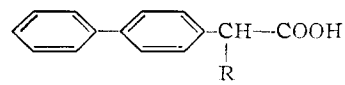
TABLE II



R	Yield, %	Boiling point °C.	Mm.	M.p., °C.	Solvent for cryst.[a]	Formula	Nitrogen, % Calcd.	Found
Methyl	63	155	1	54	A	$C_{15}H_{13}N$	6.76	6.55
n-Propyl	72	180	1	83	A	$C_{17}H_{17}N$	5.92	5.86
n-Butyl	84	158–160	0.5	58–59	A–B	$C_{18}H_{19}N$	5.61	5.60
Allyl	85	165–170	0.5	66–67	A–B	$C_{17}H_{15}N$	6.00	5.79
n-Amyl	85	160–168	1	72–73	A–B	$C_{19}H_{21}N$	5.31	5.08
n-Octyl	82	158–160	1	...	...	$C_{22}H_{27}N$	4.59	4.30
n-Propyl[b]	78	178–180	1	...	...	$C_{19}H_{21}N$	5.32	5.38
Diethyl[c]	80	167	0.5	87	A	$C_{18}H_{19}N$[d]	5.66	5.45

[a] A, Ethanol; B, water. [b] 4-Diphenylethane-*n*-propylacetonitrile. [c] Dry benzene was used instead of ether in the reaction mixture; the alkylating agent was ethyl bromide; and the extraction was made with benzene. [d] Calcd.: C, 86.70; H, 7.68. Found: C, 86.40; H, 7.71.

TABLE III[a]



R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Methyl[b]	70	145	...	...	...	...	...
n-Propyl[b]	69	117	...	...	...	...	...
n-Butyl[b]	30	107–108	...	...	...	...	...
n-Amyl	18	104	$C_{19}H_{22}O_2$	80.81	80.77	7.85	8.04
Allyl	15	117–118	$C_{17}H_{16}O_2$	80.96	80.99	6.38	6.26

[a] All products recrystallized from ligroin. Also prepared by F. F. Blicke and N. Grier, THIS JOURNAL, **65**, 1725 (1943).

TABLE IV

R = $-O-CH_2-COOH$

	Yield, %	M.p., °C.	Solvent for cryst.[a]	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Biphenyl[b]	90	189–190	A	...	...	...	...	...
Stilbene	95	208	A	$C_{16}H_{14}O_3$	75.55	75.77	5.55	5.69
Diphenylethane[c]	52	130	B	$C_{16}H_{16}O_3$	74.98	75.40	6.34	6.29

[a] A, acetic acid; B, benzene. [b] Prepared by E. Martin, M. E. Synerholm and P. W. Zimmerman, *Contr. Boyce Thomson Inst.*, 14, 91 (1945). [c] This product has been obtained also by the catalytic reduction of stilbeneoxyacetic acid in acetic acid with 0.5% of Pd on 10% C with a yield of 78%.

the ester; b.p. 161° (1 mm.). The crystals obtained from ethanol–water melted at 38°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 79.92; H, 7.50.

4-Biphenylyl-*n*-propylacetamide.—Thionyl chloride (11.9 g., 0.1 mole) was added dropwise to 2.54 g. (0.01 mole) of 4-biphenylyl-*n*-propylacetic acid. The mixture was stirred for 1 hour at room temperature and for 2 hours on a steam-bath. After distillation of the thionyl chloride at reduced pressure, 20 ml. of 15% ammonium hydroxide was added with shaking to the residue and vigorous stirring was continued for 3 hours at room temperature. The precipitate was filtered, washed with water and dried. Recrystallization from 70% acetone gave 2.4 g. (95%) of 4-biphenylyl-*n*-propylacetamide; m.p. 160°.

Anal. Calcd. for $C_{17}H_{19}ON$: N, 5.53. Found: N, 5.50.

4-Stilbenepyruvicacetamide was obtained by essentially the same procedure; m.p. 235°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: N, 5.28. Found: N, 5.41.

2-Phenyl-4-(4'-biphenylal)-5-oxazolone.—A mixture of 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 3.6 g. (0.02 mole) of hippuric acid, 3.2 g. (0.04 mole) of fused sodium acetate and 6.6 g. (0.6 mole) of acetic anhydride was stirred and heated for 4 hours on an oil-bath at 100°. After being cooled and standing overnight at room temperature, the mixture was filtered. The precipitate was washed with water and recrystallized from ethanol to give yellow crystals; yield 6 g. (92%); m.p. 182–183°.

Anal. Calcd. for $C_{22}H_{15}O_2N$: N, 4.30. Found: N, 4.29.

4-Biphenylylpyruvic Acid.—A mixture of 16.2 g. (0.05 mole) of the above oxazolone and 1750 ml. of 6% aqueous sodium hydroxide was refluxed until the evolution of ammonia was complete. It was then cooled and filtered. The precipitate was suspended in water, boiled and acidified. The precipitate, which formed upon slow cooling, was crystallized from glacial acetic acid; yield 2 g. (17%); m.p. 220°.

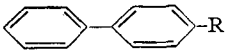
Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.00; H, 5.03. Found: C, 74.52; H, 5.15.

β-4-Biphenylylacrylic Acid (I).—A mixture of 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 2.3 g. (0.022 mole) of malonic acid, 50 ml. of 95% ethanol and 0.5 ml. of pyridine was refluxed for 6 hours. After cooling the precipitate was filtered, washed with water and recrystallized from 95% ethanol. 4-Biphenylyl-γ-crotonic acid was prepared from the acetaldehyde by the same method. The data are listed in Table V.

4-Biphenylyl-*n*-propionic Acid (II).—4-Biphenylylacrylic acid (2.24 g., 0.01 mole), dissolved in 320 ml. of glacial acetic acid, was hydrogenated at normal pressure with 0.1 g. of a 10% Pd/C catalyst. Filtration followed by vacuum distillation gave a residue which was crystallized from 70% ethanol, see Table V.

4-Biphenylyl-β-hydroxypropionic Acid (III).—A Reformatsky reaction was carried out in the usual way with 3.64 g. (0.02 mole) of 4-biphenylaldehyde, 3.32 g. (0.02 mole) of ethyl bromoacetate, 1.3 g. (0.02 mole) of zinc dust in 50 ml. of benzene. After cooling the mixture was extracted with ether. The aqueous layer was acidified with hydrochloric acid and the resulting precipitate recrystallized from 50% acetic acid. 4-Biphenylyl-γ-ethyl-β-hydroxy-*n*-butyric acid was prepared by the same method; see Table V.

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.

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

Actidione. I. The Synthesis of the Glutarimide Moiety

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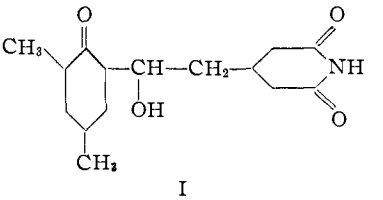
The synthesis of glutarimide-β-acetaldehyde (V) from acetone-dicarboxylic ester is described. The aldehyde is of interest as a possible intermediate in the total synthesis of actidione, an antifungal antibiotic produced by *Streptomyces griseus*.

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]

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(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.

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