[CONTRIBUTION FROM THE MEDICAL CHEMISTRY RESEARCH LABORATORIES]

Biphenyl, Stilbene, Diphenylmethane and Diphenylethane Derivatives. New Anticholesterinemic and Antilipemic Drugs. XII

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Some derivatives of biphenyl, stilbene, diphenylmethane and diphenylethane were synthesized in an attempt to find anticholesterinemic and antilipemic agents. 2-(4-Biphenylyl)-Δ-4-hexenic acid was found to possess marked activity.

In previous work[1,2] we prepared some 4 substitutes derivatives of biphenyl, stilbene and diphenylethane. 4-Biphenylyl-α-butyric acid, which was found to have the highest anticholesterinemic activity,[3] was marketed as a therapeutic agent.[4,5] Tavormina[6] compared the anticholesterinemic activity of the most promising substances by an *in vitrc* test. He measured the inhibition which the compound exerted on the biosynthesis of cholesterol both from acetate and from mevalonic acid. On the basis of this test biphenylyl-α-butyric acid also appeared to be the most active compound, especially in regard to mevalonate incorporation.

In an attempt to find substances of greater and more specific activity, we have synthesized a series of *p*-biphenylyl-2-substituted aliphatic acids and the corresponding derivatives of stilbene, diphenylmethane and diphenylethane. Because of the frequency with which these aliphatic chains occur in natural substances, the following acids were taken into consideration: (a) unsaturated chain: Δ-4-pentenoic, 2-oxy-Δ-4-pentenoic, Δ-4-hexenoic; (b) branched chain: 2-oxybutyric, 3-methylbutyric, 5-methylcaproic, 2-oxymethylcaproic, 2-oxy-3-methylbutyric; (c) long chain acids(*n*-decanoic and *n*-2-oxydecanoic).

In addition we prepared the aminoalkyl esters of some of these acids in order to compare their absorption from the gut with that of the acids. The alcohols of the most active acids were made, *viz.*, *n*-butyl, 5-methylhexyl and Δ-4-hexenyl. In order to study the influence of substitution, we have also prepared some 2-*p*-biphenylyl-2-alkyl-1,3-propanediols and *p*-biphenylyl-2-oxybutyric acid.

The alkyl acetic acid derivatives of biphenyl, diphenylmethane and diphenylethane were obtained by alkylation of the corresponding acetonitrile, followed by alkaline hydrolysis (method I). This method is exemplified in the Experimental section by the preparation of 4-methoxy-3-biphenylyl-α-*n*-butyric acid. The intermediate, 4-methoxy-3-biphenylylacetonitrile, obtained by the reaction of the chloromethyl compound with cyanide, upon hydrolysis yielded 4-methoxy-3-biphenylylacetic acid.[7] The crude chloromethyl compound was oxidized to the 4-methoxy-3-carboxylic acid of biphenyl which is identical with the acid described by Fieser and Bradsher.[8]

Another method (II) used for the preparation of some 4-biphenylylacetic acids was reduction of the corresponding α-hydroxy-α-alkylacetic acids. The latter compounds, $C_6H_5CH_2CH_2C_6H_4C(R)(OH)COOH$ and $C_6H_5C_6H_4C(R)(OH)COOH$, were prepared by the Grignard synthesis with the corresponding ethyl glyoxylates. Ethyl 4-diphenylethaneglyoxalate was prepared by a Friedel–Crafts reaction of diphenylethane with oxalyl ethyl chloride. That condensation occurred at the 4-position is shown by the fact that saponification of the glyoxylate gave an acid which is identical with the acid obtained by the catalytic reduction of stilbenecarboxylic acid.[9]

The aminoalkyl esters were prepared by condensation of the corresponding acids with the aminoalkyl chlorides (method III). Reaction of the acid chlorides with alcohols yielded the alkyl esters (method IV). Reduction of the esters with lithium aluminium hydride gave the β-4-biphenylyl-β-alkylethanols (method VIII). The 2-*p*-biphenylyl-2-alkyl-1,3-propanediols were synthesized from the corresponding *p*-biphenylyl-alkylacetaldehydes and formaldehyde in an aqueous ethanolic solution containing sodium hydroxide (method IX).

The oxyacetic and oxy-α-butyric acid derivatives of 4-diphenylethane, 4-stilbene were prepared by condensation of the corresponding phenol with ethyl bromoacetate or α-bromobutyrate followed by alkaline hydrolysis (method VI).

These products were fed to rats in which hypercholesterolemia and hyperlipemia had been induced by the administration of Triton.[10] The results of the pharmacological testing are given in Table I from which the following conclusions can be drawn: for the biphenyl derivatives, conversion of the acid to alcohol led to a decrease of activity. Of the diphenylethane compounds, only the acetic and α-propionic acid derivatives inhibit both hypercholesteremia and serum hyperlipemia; the other compounds inhibit the hyperlipemia only. The most active products were subjected to other tests. In every experiment 2-(4-biphenylyl)-Δ-4-hexenic acid proved to be the most promising derivative. The pharmacological data will be published in detail elsewhere.

Experimental

The melting and boiling points are not corrected.

Ethyl 4-Diphenylethaneglyoxylate.—Aluminum chloride (33.4 g., 0.25 mole) dissolved in 85 ml. of nitrobenzene was

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

(2) G. Cavallini, E. Massarani, D. Nardi and E. D'Ambrosio, THIS JOURNAL, **79**, 3514 (1957).

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

(4) G. Annoni, *Il Farmaco, Ed. Scient.*, **11**, 244 (1956).

(5) E. Sabbadini, N. Campani and M. Cazzaniga, *Minerva Medica, XLVII*, Vol. I, 2048 (1956).

(6) P. A. Tavormina and M. Gibbs, THIS JOURNAL, **79**, 758 (1957).

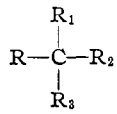
(7) N. H. Sunnel and H. J. Smith, *J. Chem. Soc.*, 908 (1958).

(8) L. F. Fieser and C. K. Bradsher, THIS JOURNAL, **58**, 1738 (1936).

(9) G. Kon, *J. Chem. Soc.*, 224 (1948).

(10) M. Friedman and S. O. Byers, *J. Exp. Med.*, **97**, 117 (1953).

TABLE I[a]

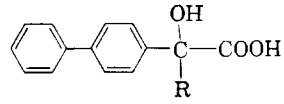


R = X = $C_6H_5C_6H_4$–
XO = $C_6H_5C_6H_4O$–
Y = $C_6H_5CH_2C_6H_4$–
Z = $C_6H_5CH_2CH_2C_6H_4$–
ZO = $C_6H_5CH_2CH_2C_6H_4O$–
SO = $C_6H_5CH{=}CHC_6H_4O$–

No.	R	R_1	R_2	R_3	Activity[b] Lipid[c]	Activity[b] Cholesterol[d]
1[e]	X	–H	–COOH	$-CH_2CH_2CH_3$	0.63	0.45
2	X	–H	–COOH	$-CH(CH_3)CH_3$	0	1.20
3	X	–H	–COOH	$-CH_2CH_2CH(CH_3)CH_3$	2.26	1.25
4	X	–H	–COOH	$-(CH_2)_7CH_3$	0	1.25
5[e]	X	–H	–COOH	$-C_6H_5$	0.51	0.68
6[e]	X	–H	–COOH	$-CH_2CH{=}CH_2$	1.40	1.20
7	X	–H	–COOH	$-CH_2CH{=}CHCH_3$	2.92	1.59
8[e]	X	–OH	–COOH	$-C_2H_5$	0.31	0.48
9	X	–OH	–COOH	$-CH(CH_3)CH_3$	.65	0
10[e]	X	–OH	–COOH	$-C_6H_5$	.28	0.61
11	X	–H	$-CH_2OH$	$-CH_2CH_3$	1.10	0.36
12	X	–H	$-CH_2OH$	$-CH_2CH_2CH(CH_3)CH_3$	0.10	1.50
13	X	–H	$-CH_2OH$	$-CH_2CH{=}CHCH_3$	0.50	0.54
14	X	$-C_3H_7$	$-CH_2OH$	$-CH_2OH$	0	0
15	XO	–H	–COOH	$-CH_2CH_3$	0.69	0
16	Y	–H	–COOH	$-CH_2CH_3$	.24	0
17	Y	–H	–COOH	$-CH_2CH{=}CH_2$	.23	0
18	Z	–H	–COOH	–H	1.55	1.07
19[f]	Z	–H	$-CH_2COOH$	–H	0.52	0
20	Z	–H	–COOH	$-CH_3$	1.76	1.21
21[1]	Z	–H	–COOH	$-CH_2CH_3$	1.12	0
22	Z	–H	–COOH	$-CH_2CH{=}CH_2$	0.38	0
23	Z	–OH	–COOH	$-CH_2CH_3$	.99	0
24	ZO	–H	–COOH	$-CH_2CH_3$	.81	0
25	SO	–H	–COOH	$-CH_2CH_3$	.69	0.67

[a] Wistar strain, male rats averaging 250 g. were fasted for 24 hours. Triton dissolved in 8% saline was injected intravenously in doses of 200 mg./kg. (2.5 ml./kg.; see ref. 10). At the same time a suspension of the substance under examination in a 5% gum arabic solution was given by mouth in a dose of 0.003 mole. After 18 hours the animals were killed, and the cholesterol and serum lipids estimated. [b] The activity of 4-biphenylyl-α-butyric acid was taken as 1; the activity given is the ratio of the lipid (or cholesterol) lowering effect of the substance to that of 4-biphenylyl-α-butyric acid. [c] The serum lipids were determined according to B. J. Bragdon, *J. Biol. Chem.*, **190**, 513 (1951). [d] Serum cholesterol was determined according to M. D. Colman and A. P. McPhee, *J. Am. Clin. Pathol.*, **26**, 185 (1956). [e] F. F. Blicke and U. Grier, THIS JOURNAL, **65**, 1725 (1945). [f] Contrary to a previous communication,[1] the melting point is 112°.

TABLE II



R	Yield, %	M.p., °C.	Solvent of crystn.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl[b]	30	133	A	$C_{18}H_{20}O_3$	76.03	76.18	7.09	6.84
Isopropyl	49	165–166	A	$C_{17}H_{18}O_3$	75.53	75.35	6.71	6.24
Allyl	35	156	A	$C_{17}H_{16}O_3$	76.10	75.88	6.01	5.86
Isoamyl	36	164	B–C	$C_{19}H_{22}O_3$	76.48	76.18	7.43	7.23
o-Octyl	28	137	D	$C_{22}H_{28}O_3$	77.61	77.02	8.29	8.27
Phenyl[b]	61	133–135	A	$C_{22}H_{20}O_3$	79.49	79.66	6.06	6.29

[a] A, benzene; B, ethyl acetate; C, benzine; D, hexane with a few drops of ethyl acetate. [b] 4-Diphenylethane derivative.

added dropwise (about 2 hours) to a mixture of 45.5 g. (0.25 mole) of diphenylethane and 38 g. (0.28 mole) of ethyloxalyl chloride at 30–40°. The mixture was stirred for 8 hours at room temperature and then kept overnight at room temperature. Dilute hydrochloric was added, the mixture was extracted with ether, and the extract dried and concentrated. The resulting oil, upon distillation, yielded 16 g. (35%) of diphenylethane, b.p. 90–100° (3 mm.), and 29 g. (43%) of crude ethyl 4-diphenylethaneglyoxylate, b.p. 200–203° (3 mm.). The latter, after hydrolysis and recrystallization from dilute ethanol or acetic acid, yielded 4-diphenylethanecarboxylic acid, m.p. 170–171°. Catalytic reduction of 4-stilbenecarboxylic acid in tetrahydrofuran with 0.5% Pd on 10% C gave the same acid.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.23. Found: C, 79.14; H, 6.51.

(4-Diphenylethane)-α-hydroxy-α-ethylacetic Acid.—This procedure was used for the preparation of the acids listed in Table II. The solution of the Grignard reagent (obtained from 4.25 g. (0.027 mole) of ethyl iodide, 0.81 g. (0.03 mole) of magnesium and 15 ml. of ether) was added slowly to a solution containing 5.64 g. (0.02 mole) of crude ethyl 4-diphenylethaneglyoxylate in 30 ml. of ether with stirring and cooling. Then the mixture was stirred for 1 hour at room temperature, refluxed for 3 hours, and allowed to stand overnight. Dilute sulfuric acid was added, the ether layer which separated was washed with water and the solvent removed. The residue was refluxed with a 10%

TABLE III R—CH(R₁)—CN

R	R_1	Yield, %	Boiling point—°C.	Mm.	Formula	Nitrogen, %—Caled.	Found
4-Biphenylyl	Crotyl	75	165	0.5	$C_{18}H_{17}N$	5.66	5.80
4-Biphenylyl	Isoamyl	85	160–165	.2	$C_{19}H_{21}N$	5.32	5.10
4-Biphenylyl[a]	Dipropargyl	50	164	.5	$C_{20}H_{15}N$	5.20	5.29
4-Diphenylmethane	Methyl	84	145	.2	$C_{16}H_{15}N$	6.33	6.20
4-Diphenylmethane	Ethyl	91	190	2	$C_{17}H_{17}N$	5.95	5.90
4-Diphenylmethane	Allyl	75	155	0.6	$C_{18}H_{17}N$	5.66	5.30
4-Diphenylethane	Methyl	90	160	.5	$C_{17}H_{17}N$	5.95	5.90
4-Diphenylethane	Allyl	89	164	.4	$C_{19}H_{19}N$	5.36	5.33
4-Diphenylethane	*n*-Butyl	78	180–185	2	$C_{20}H_{23}N$	5.05	5.00

[a] Recrystallized from ethanol; m.p. 127–129°; in this product the H– of general formula is substituted by a propargyl group.

TABLE IV R—CH(R₁)—COOH

R	R_1	Method	Yield, %	M.p., °C.	Solvent of crystn.[a]	Formula	Carbon, % Caled.	Found	Hydrogen, % Caled.	Found
4-Biphenylyl	Isopropyl	II	80	161	A–B	$C_{17}H_{18}O_2$	80.28	80.78	7.13	7.16
4-Biphenylyl[b]	Crotyl	I	81	118–119	C–B	$C_{18}H_{18}O_2$	81.17	81.16	6.81	6.80
4-Biphenylyl	Isoamyl	I–II	90	97–98	A–B	$C_{19}H_{22}O_2$	80.81	80.32	7.85	8.21
4-Biphenylyl	*n*-Octyl	II	89	81–83	A–B	$C_{22}H_{28}O_2$	81.44	81.33	8.70	8.81
4-Diphenylmethane	Methyl	I	80	120	A–B	$C_{16}H_{16}O_2$	79.97	79.85	6.71	6.57
4-Diphenylmethane	Ethyl	I	60	72	D	$C_{17}H_{18}O_2$	80.28	80.04	7.13	6.98
4-Diphenylmethane	Allyl	I	58	80–81	E	$C_{18}H_{18}O_2$	81.17	80.85	6.81	6.81
4-Diphenylethane	Methyl	I	70	84–85	F	$C_{17}H_{18}O_2$	80.28	80.75	7.13	7.26
4-Diphenylethane	Allyl	I	50	75	D	$C_{19}H_{20}O_2$	81.39	81.74	7.19	7.28
3-(4-Methoxybiphenylyl)	Ethyl	I	71	118	G–F	$C_{17}H_{18}O_3$	75.53	75.15	6.71	6.54

[a] A, ethanol; B, water; C, acetic acid; D, hexane; E, cyclohexane; F, benzine; G, ethyl acetate; [b] B.p. 182–183° (0.1 mm.).

ethanolic potassium hydroxide solution for 2 hours. After distillation of ethanol at reduced pressure, 100 ml. of water was added to the residue. The solution was acidified with hydrochloric acid and extracted with ether. Drying and concentration gave a residue which crystallized from benzene.

4-Methoxy-3-biphenylylacetonitrile.—Sulfuric acid (29 ml.) was added slowly to a mixture of 18.4 g. (0.1 mole) of 4-methoxybiphenyl, 50 ml. of acetic acid, 40 ml. of hydrochloric acid (d. 1.18) and 75 ml. of 38% aqueous formaldehyde. The addition was carried out under stirring at 60° over a period of 7 hours. The mixture was poured into water and extracted with methylene chloride. The extract was washed with water, dried and evaporated. The crude 4-methoxy-3-biphenylylmethyl chloride thus obtained was refluxed with 60 ml. of 80% ethanol and 5.5 g. (0.11 mole) of sodium cyanide for 6 hours. After the evaporation of ethanol the residue was extracted with ether and the extract washed with water. Drying and concentration gave an oil which, upon distillation, yielded 14.7 g. (67%) of the nitrile, b.p. 165–170° (0.4 mm.). The crystals obtained from ethanol melted at 61–62°.

Anal. Caled. for $C_{15}H_{13}ON$: $-OCH_3$, 13.90. Found: OCH_3, 13.50.

The 4-methoxy-3-biphenylylmethyl chloride was oxidized by potassium permanganate to give the corresponding acid, m.p. 167°.[8]

4-Methoxy-3-biphenylyl-α-*n*-butyronitrile.—A mixture of 22.32 g. (0.1 mole) of 4-methoxy-3-biphenylylacetonitrile, 6 g. (0.15 mole) of sodium amide and 60 ml. of dry ether was refluxed for 1 hour. After the addition of 16.9 g. (0.15 mole) of ethyl bromide 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. Drying and concentration of the extract gave an oil which, upon distillation, yielded 20 g. (80%) of 4-methoxy-3-biphenylyl-α-*n*-butyronitrile, b.p. 160 (0.5 mm.). The crude product was used for the preparation of the corresponding acid. The other nitriles, which are reported in Table III, were prepared according to this method.

4-Methoxy-3-biphenylyl-α-*n*-butyric Acid (Method I).—A mixture of crude 4-methoxy-3-biphenylyl-α-*n*-butyronitrile (25.1 g., 0.1 mole), 120 ml. of ethanol and 120 ml. of 40% potassium hydroxide was refluxed until the ammonia disappeared. After cooling and evaporation of the solvent, water was added to the residue which was acidified with hydrochloric acid, cooled and extracted with ether. Drying and concentration of the extract gave a residue which crystallized from ethyl acetate–benzine. This procedure was also used for the hydrolysis of 4-biphenylylalkylacetonitrile to obtain the corresponding acetic acids which are listed in Table IV.

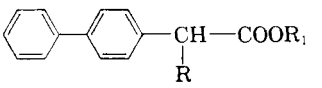
4-Biphenylyl-α-isovaleric Acid (Method II).—A mixture of 5.4 g. (0.02 mole) of isopropyl-4-biphenylyl-hydroxyacetic acid, 0.5 g. of iodine, 1.2 g. (0.04 mole) of red phosphorus and 60 ml. of acetic was refluxed for 14 hours. After cooling, the mixture was filtered and diluted with water. The precipitate was filtered and crystallized from dilute ethanol. Some acids among those listed in Table IV were prepared by this method.

β-Dimethylaminoethyl 4-Biphenylylacetate (Method III).—A mixture of 2.12 g. (0.01 mole) of 4-biphenylylacetic acid, 0.4 g. (0.01 mole) of sodium hydroxide and 60 ml. of acetone was refluxed for 1 hour; 2 g. (0.015 mole) of β-dimethylaminoethyl chloride was added dropwise, and the mixture was refluxed for 5 hours. The reaction mixture was filtered, the solvent removed and the residue distilled. The amino-alkyl esters prepared by this procedure are listed in Tables V and VI.

4-Biphenylyl-α-butyric Acid Methyl Ester (Method IV).—Thionyl chloride (11.9 g., 0.1 mole) was added dropwise to 2.40 g. (0.01 mole) of 4-biphenylyl-α-butyric 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 methanol 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 was distilled. The alkyl esters prepared by this procedure are listed in Table V.

β-N-Piperidinoisopropyl 4-Diphenylethaneoxyacetate (Method V).—A mixture of 2.56 g. (0.01 mole) of 4-diphen-

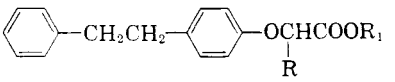
TABLE V



R	R_1	Method	Yield, %	Boiling point °C.	Mm.	M.p., °C.	Solvent of crystn.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	β-Dimethylaminoethyl	III	60	180[b]	2	166–168[c]	A	$C_{18}H_{22}O_2NCl$	4.37[e]	4.45[e]	11.08[f]	11.00[f]
Hydrogen[d]	β-Diethylaminoethyl	III	75	192–195[b]	0.5	121–122[c]	B	$C_{22}H_{30}O_2NCl$	3.72[e]	3.71[e]	9.43[f]	9.04[f]
Ethyl	Methyl	IV	45			53	A	$C_{17}H_{18}O_2$	80.28	80.70	7.13	7.15
Ethyl	Isopropyl	IV	70	174–176	.6			$C_{21}H_{26}O_2$	81.25	81.19	8.44	8.19
Ethyl	Octyl	IV	65	188	.5			$C_{24}H_{32}O_2$	81.77	81.57	9.15	9.06
Ethyl[d]	β-Diethylaminoethyl	III	53	195[b]	1	122[c]	C–D	$C_{24}H_{34}O_2NCl$	3.47[e]	3.59[e]	8.77[f]	8.59[f]
Crotyl	Methyl	IV	50	140–141	0.2			$C_{19}H_{20}O_2$	81.39	81.23	7.19	7.14
Crotyl	Crotyl	IV	30	161–163	.4			$C_{22}H_{24}O_2$	82.46	81.51	7.55	7.52
Crotyl	Isoamyl	IV	65	163	.1			$C_{23}H_{28}O_2$	82.10	82.70	8.39	8.29
Crotyl	Citronellyl	IV	45	165–168	.2			$C_{28}H_{36}O_2$	83.12	82.36	8.97	8.91
Isoamyl	Methyl	IV	50	154–156	.4			$C_{20}H_{24}O_2$	81.04	81.31	8.16	8.08
Isoamyl	Crotyl	IV	80	193	.4			$C_{23}H_{28}O_2$	82.10	81.72	8.39	8.45
Isoamyl	Isoamyl	IV	62	148–151	.5			$C_{24}H_{32}O_2$	81.77	81.89	9.15	9.03
Isoamyl	Citronellyl	IV	70	202	.4			$C_{29}H_{40}O_2$	82.81	83.17	9.59	9.49

[a] A, ethanol; B, isopropyl alcohol; C, acetone; D, ethyl ether. [b] Base. [c] Hydrochloride. [d] 4-Diphenylethane. [e] Nitrogen, %. [f] Chlorine, %.

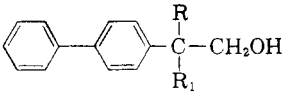
TABLE VI



R	R_1	Method	Yield, %	Boiling point °C.	Mm.	M.p., °C.	Solvent of crystn.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Hydrogen	α-Me-β-N-piperidinethyl	V	79			155[c]	A	$C_{24}H_{32}O_3NCl$	3.35[f]	3.35[f]	8.48[g]	8.13[g]
Ethyl	Hydrogen	VI	75			115	B–C	$C_{18}H_{20}O_3$	76.03	75.97	7.09	7.22
Ethyl[d]	Hydrogen	VI	60			145	D	$C_{16}H_{16}O_3$	74.98	74.70	6.29	6.29
Ethyl[d]	β-Diethylaminoethyl	III	75	180[b]	1	141[c]	E	$C_{22}H_{30}O_3NCl$	3.57[f]	3.59[f]	9.04[g]	8.96[g]
Ethyl[e]	Hydrogen	VI	92			168–169	B–C	$C_{18}H_{18}O_3$	76.57	76.14	6.43	6.46

[a] A, isopropyl alcohol; B, acetic acid; C, water; D, ligroin; E, acetone. [b] Base. [c] Hydrochloride. [d] 4-Biphenylyl. [e] 4-Stilbene. [f] Nitrogen, %. [g] Chlorine, %.

TABLE VII



R	R_1	Method	Yield, %	Boiling point °C.	Mm.	M.p., °C.	Solvent of crystn.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
–H	$-C_2H_5$	VII	70			70	A	$C_{16}H_{18}O$	84.91	84.88	8.02	7.98
–H	$-CH_2CH{=}CHCH_3$	VII	90	160	0.5	47		$C_{18}H_{20}O$	85.67	85.15	7.99	8.12
–H	$-CH_2CH_2CH(CH_3)CH_3$	VII	70	170–172	0.4	52		$C_{19}H_{24}O$	85.02	84.93	9.01	9.05
$-CH_2OH$	$-CH_3$	VIII	20			140	B–A	$C_{16}H_{18}O_2$	79.31	78.67	7.49	7.44
$-CH_2OH$	$-C_2H_5$	VIII	23			115	C	$C_{17}H_{20}O_2$	79.65	79.77	7.86	7.96
$-CH_2OH$	n-C_3H_7	VIII	46			97–98	C	$C_{18}H_{22}O_2$	79.96	80.53	8.20	8.32

[a] A, benzene; B, ethyl ether; C, cyclohexane.

ylethaneoxyacetic acid, 2.24 g. (0.015 mole) of β-N-piperidinoisopropyl chloride and 75 ml. of isopropyl alcohol was refluxed for 5 hours. Upon cooling, the hydrochloride crystallized. The melting point and the analytical data are reported in Table VI.

4-Diphenylethane-oxy-α-butyric Acid (Method VI).—A mixture of 9.9 g. (0.05 mole) of 4-oxydiphenylethane, 2 g. (0.05 mole) of sodium hydroxide and 350 ml. of isopropyl alcohol was refluxed for 1 hour. Then 9.75 g. (0.05 mole) of ethyl α-bromobutyrate was added dropwise and the mixture was refluxed for 5 hours then 100 ml. of 20% aqueous sodium hydroxide was added and the mixture refluxed for 2 hours. After evaporation of the isopropyl alcohol, the solution was acidified with hydrochloric acid. The precipitate was filtered and crystallized from acetic acid. The products obtained by this procedure are listed in Table VI.

4-Biphenylyl-β-1-butanol (Method VII).—Methyl 4-biphenylyl-α-*n*-butyrate (5.08 g., 0.02 mole), dissolved in 25 ml. of ether, was added dropwise to a mixture of 3.49 g. (0.1 mole) of lithium aluminum hydride and 100 ml. of ether. After the addition, the mixture was stirred for 1 hour at room temperature and then refluxed for 1 hour. After cooling, dilute hydrochloric acid was added and the mixture was extracted with ether. Drying and concentration of the extract gave a residue which crystallized. The alcohols prepared by this procedure are listed in Table VII.

2-*p*-Biphenylyl-2-methyl-1,3-propanediol (Method VIII).—A mixture of 4.2 g. (0.02 mole) of 4-biphenylyl-α-propionaldehyde, 100 ml. of 95% ethanol and 4.2 ml. (0.054 mole) of 38% aqueous formaldehyde was added dropwise (about 2 hours) to 1 g. of sodium hydroxide and 5 ml. of 95% ethanol. The reaction mixture was refluxed for 18 hours and concentrated. The residue was extracted with ether and washed with water. Drying and evaporation gave a residue which was crystallized. The alcohols prepared by this procedure are listed in Table VII.

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