An additional recrystallization from a mixture of acetonitrile, methanol, and ether gave yellow crystals, mp 115–116.5 °C. Anal. ($C_{16}H_{18}O_5$) C, H.

Acknowledgment. The author wishes to express his gratitude to Mrs. Irene Tsina for determination of NMR spectra, to Ms. Adrienne Minet and Mr. Jeff Wilker for performing pharmacological assays, and to Ms. Linda Cuiskelly for assistance in preparation of the manuscript.

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Hypolipidemic Activity of 5-Aryl-3-methylvaleric Acid Derivatives

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Several 5-aryl-3-methylvaleric acid derivatives have been shown to be more potent hypolipidemic agents than the previously reported 5-(4-biphenylyl)-3-methylvaleric acid (**1**). The most active compound in this series was 5-(4-phenylsulfonylphenyl)-3-methylvaleric acid (**10**) which lowered serum cholesterol levels 45% and serum triglyceride levels 60% in normal rats. Significant lowering of the serum triglyceride levels was the predominant effect noted with most of the compounds tested.

Several *p*-biphenylyl-substituted acids have been reported[1] to exhibit hypocholesterolemic activity in both animal and human studies. Eades and Solberg[2-4] have reported the synthesis of a number of *p*-biphenylyl derivatives, the most potent of which was 5-(4-biphenylyl)-3-methylvaleric acid (**1**).[5] Although this compound exhibited excellent in vitro and in vivo activity in rat studies, it was inactive as a hypolipidemic agent when tested in the dog. More recently, Boots and co-workers[6-9] have reported the synthesis of a large number of *p*-biphenylyl derivatives which have shown potent in vitro inhibition of yeast and rat liver β-hydroxy-β-methylglutaryl coenzyme A reductase (HMG Co A reductase).

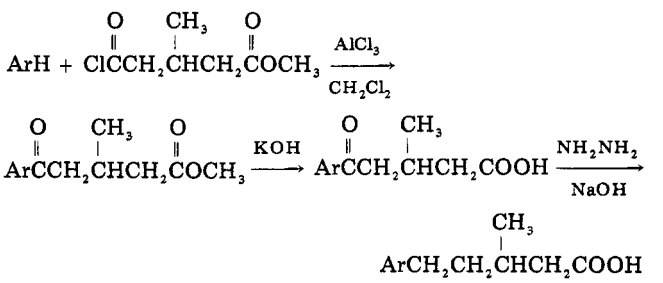
As part of a structure–activity study designed to find competitive inhibitors of HMG Co A reductase, we have prepared a series of 5-aryl-3-methylvaleric acids. Inhibition of cholesterol biosynthesis at the HMG Co A reductase stage appears to be an ideal approach for the treatment of hyperlipemia, and the reasons for this have been enumerated by Boots and co-workers.[6] We have found that the biphenyl group in **1** can be replaced by a variety of ring systems without loss of the hypolipidemic activity observed when this compound is administered to rats. Several of the arylvaleric acid derivatives have shown in vitro inhibition of [^{14}C]acetate incorporation into lipids and have also exhibited good in vivo hypolipidemic activity in normal rats.

Chemistry. The compounds reported in this study were prepared by the general sequence outlined in Scheme I where Ar represents the various aryl groups described in Tables I and II.

Acylation of the appropriate aromatic derivatives with 4-chlorocarbonyl-3-methylbutanoic acid methyl ester under Friedel–Crafts conditions gave the corresponding keto esters in moderate yields. Hydrolysis of the esters with aqueous methanolic potassium hydroxide gave the keto acids **2–7** which were reduced via a modified Wolff–Kishner[10] procedure to give the title compounds. The sulfones **10** and **13** were prepared by oxidation of the corresponding sulfides **9** and **12** using either *m*-chloroperbenzoic acid or peracetic acid.

Friedel–Crafts acylation[11] of 9,10-dihydrophenanthrene, dibenzofuran, and dibenzothiophene is known to give

Scheme I



substitution predominantly in the 2 position. In order to ensure the absence of undesired isomers, the keto esters derived from these ring systems were purified by column chromatography on silica gel prior to hydrolysis. The crude keto esters derived from biphenyl, diphenyl ether, and diphenyl sulfide, however, could be hydrolyzed without prior purification since acylation[11] of these ring systems is known to give substitution exclusively in the 4 position.

Results and Discussion

All of the aryl-substituted acids listed in Tables I and II were tested in vitro for their capacity to inhibit total lipid, nonsaponifiable lipid and fatty acid biosynthesis when the microsomal–cytosol fraction of rat liver was used as the source of the enzyme systems. It was anticipated that a competitive inhibitor of HMG Co A reductase would exhibit a specificity for the nonsaponifiable fraction while having little or no effect on the fatty acid fraction. While all the compounds demonstrated some capacity to inhibit lipogenesis when tested in the millimolar concentration range, a comparison of the IC_{50} values (see Table III) indicated that none of the compounds appeared to be as potent as **1** in their ability to inhibit nonsaponifiable lipid biosynthesis. However, compounds **7–10** and **13** proved to be at least as potent as **1** in their inhibition of fatty acid biosynthesis.

Although the desired separation of activities was not observed in vitro, the compounds were tested in vivo in male rats to determine their hypolipidemic activity in the intact animal. The results are listed in Table III. With the exception of compounds **5**, **7**, and **12**, all of the

Table I. 4-Aroyl-3-methylbutyric Acids

$$ArC(=O)CH_2CH(CH_3)CH_2COOH$$

Compd	Ar	Formula	% yield[a]	Crystn solvent	Mp, °C	Analyses
2	4-Biphenylyl	$C_{18}H_{18}O_3$	44	EtOAc-Skelly B[b]	122-123.5	C, H
3	4-Phenoxyphenyl	$C_{18}H_{18}O_4$	66	Et_2O-Skelly B[b]	86-87.5	C, H
4	4-Phenylthiophenyl	$C_{18}H_{18}O_3S$	67	EtOAc-Skelly B[b]	119-120	C, H, S
5	2-Dibenzofuranyl	$C_{18}H_{16}O_4$	39	EtOAc-Skelly B[b]	139-141	C, H
6	2-Dibenzothienyl	$C_{18}H_{16}O_3S$	45	EtOAc	139-142	C, H, S
7	2-(9,10-Dihydrophenanthryl)	$C_{20}H_{20}O_3$	53	Et_2O	94-95	C, H

[a] Overall yield of chromatographically homogeneous material obtained for the acylation and hydrolysis reactions. [b] Skelly B is the commercial name for a mixture of hexanes, bp 60-71 °C.

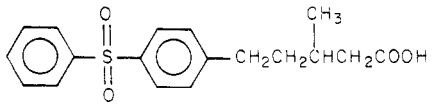
Table II. 5-Aryl-3-methylvaleric Acids

$$ArCH_2CH_2CH(CH_3)CH_2COOH$$

Compd	Ar	Formula	% yield[a]	Crystn solvent	Mp, °C	Analyses
1	4-Biphenylyl	$C_{18}H_{20}O_2$	84	EtOAc-Skelly B	94-95	C, H
8	4-Phenoxyphenyl	$C_{18}H_{20}O_3$	86	Et_2O-Skelly F[b]	35-37	C, H
9	4-Phenylthiophenyl	$C_{18}H_{20}O_2S$	87	Et_2O-Skelly F[b]	30-32	C, H, S
10	4-Phenylsulfonylphenyl	$C_{18}H_{20}O_4S$	68	Et_2O-CH_2Cl_2	154-155	C, H, S
11	2-Dibenzofuranyl	$C_{18}H_{18}O_3$	88	Et_2O-Skelly F[b]	55-57	C, H
12	2-Dibenzothienyl	$C_{18}H_{18}O_2S$	79	Et_2O-Skelly B	85-86	C, H, S
13	2-(5,5-Dioxodibenzothienyl)	$C_{18}H_{18}O_4S$	74	Et_2O	174-176	C, H, S
14	2-(9,10-Dihydrophenanthryl)	$C_{20}H_{22}O_2$	76	Et_2O-Skelly B	92-94	C, H

[a] Yield based on amount of chromatographically homogeneous material obtained. [b] Skelly F is the commercial name for a mixture of pentanes, bp 35-60 °C.

compounds in this study were as active or more active than 1 in their ability to reduce serum cholesterol levels. The predominant effect of these agents, however, was their ability to reduce the serum triglyceride levels. Compound 2 was the only compound in this series which was less active than 1 as a triglyceride lowering agent. The most potent compound in the series was 5-(4-phenylsulfonylphenyl)-3-methylvaleric acid (10) which lowered serum cholesterol levels 45% and serum triglyceride levels 60% when administered at 0.2% in the diet.



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We have not attempted to correlate the in vitro activity with the in vivo activity since such a correlation would necessitate a detailed study of the absorption, metabolism, and excretion of each compound tested.

In summary, we have demonstrated that the biphenyl group in 1 can be replaced by the various ring systems listed in Table II without loss of the hypolipidemic activity previously observed with 1. Further structural modifications have led to agents which appear to be more specific in their inhibition of cholesterol biosynthesis than those reported in this study. These compounds will be the subject of a future report.

Experimental Section

Chemistry. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses, indicated by symbols of the elements, were within ±0.4% of the theoretical values. IR, UV, and NMR spectra of all new compounds were consistent with the proposed structures.

4-Chlorocarbonyl-3-methylbutanoic acid methyl ester was prepared from 3-methylglutaric anhydride according to the procedure of Cason and co-workers.[12]

General Synthesis of Keto Acids 2-7. A solution of 4-chlorocarbonyl-3-methylbutanoic acid methyl ester (0.10 mol) was added dropwise to a stirred slurry of $AlCl_3$ (0.22 mol) in 75 mL of CH_2Cl_2. After stirring at room temperature for 15 min the complex was added to a solution of the appropriate aromatic compound (0.10 mol) in 300 mL of CH_2Cl_2 and the resulting mixture was stirred under N_2 for 1-3 days until TLC indicated no further reaction. The mixture was poured onto ice water and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and filtered and the solvent was removed in vacuo. The keto esters derived from 9,10-dihydrophenanthrene, dibenzofuran, and dibenzothiophene were chromatographed on silica gel using benzene and EtOAc as eluents while the keto esters derived from biphenyl, diphenyl ether, and diphenyl sulfide were used without purification. The keto ester was taken up in a mixture of 200 mL of CH_3OH and 100 mL of water and treated with 14.0 g (0.25 mol) of KOH. The mixture was heated on a steam bath for 1 h, poured onto ice water, and extracted with CH_2Cl_2 to remove any neutral material. The aqueous phase was acidified with HCl and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and filtered and the solvent was removed in vacuo to give a crude product which was chromatographed on SilicAR CC-4 using benzene and increasing amounts of EtOAc as eluents. Recrystallization from the solvents listed in Table I gave the pure keto acids.

General Synthesis of Valeric Acids 1, 8, 9, 11, 12, and 14. A solution of the keto acid (0.025 mol), 8.4 g (0.15 mol) of KOH, 10 mL of hydrazine hydrate, and 50 mL of triethylene glycol was heated at 110 °C for 15 min and the volatile materials were allowed to distill out of the reaction mixture. The solution was then heated at 170-180 °C under N_2 for 2 h, cooled, and poured onto 1 L of dilute HCl. The aqueous phase was extracted with ether and the extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was chromatographed on SilicAR CC-4 using benzene and EtOAc as eluents. Recrystallization from the solvents listed in Table II gave the pure valeric acids.

5-(4-Phenylsulfonylphenyl)-3-methylvaleric Acid (10). *m*-Chloroperbenzoic acid (2.27 g, 13.1 mmol) was added portionwise to a stirred solution of 9 (1.62 g, 5.40 mmol) in 100 mL of CH_2Cl_2. After stirring at room temperature for 1.5 h the mixture was diluted with CH_2Cl_2 and washed several times with water. The organic phase was dried over $MgSO_4$ and filtered and the solvent was removed in vacuo. Recrystallization of the residue from CH_2Cl_2-Et_2O afforded 1.22 g (68%) of 10, mp 154-155 °C.

5-[2-(5,5-Dioxodibenzothienyl)]-3-methylvaleric Acid (13). Twenty-five milliliters of 40% peracetic acid was added dropwise to a solution of 12 (13.6 g, 43.7 mmol) in 300 mL of CH_2Cl_2. After

Table III. Inhibitory Effect of Compounds on Lipogenesis in Rat Liver Fractions and Their Hypolipidemic Activity in Rats

	Lipogenesis[b]			Serum lipid[c]		
Compd[a]	Total lipid	N.S. ($IC_{50} \times 10^4$)	F.A.	Dosage, mmol/kg/day	Cholesterol	Triglyceride
1	0.2	0.02	0.8	0.45	+	++
2	1.8	0.7	12	0.43	++	+
3	8.5	2.9	21	0.40	+	+++
4	5.7	2.4	7.8	0.38	+	+++
5	2.6	1.1	4.3	0.41	0	++
6	3.1	1.6	9.3	0.38	+	++
7	0.6	0.3	0.9	0.39	0	+++
8	0.3	0.2	0.8	0.42	++	+++
9	0.4	0.2	1.0	0.40	++	+++
10	0.7	0.4	0.8	0.36	+++	+++
11	8.1	3.6	16	0.43	++	+++
12	1.9	0.7	8.6	0.43	0	+++
13	0.5	0.8	0.3	0.36	+	+++
14	0.3	0.1	2.7	0.41	++	+++
15[d]	6.3	8.6	4.4	0.51	++	++

[a] Compounds were added to the lipogenesis assay systems in Me_2SO and to the diet at a level of 0.2% for evaluation of serum lipid effects. [b] Lipogenesis was measured using [^{14}C]acetate incorporation into various lipid fractions; total lipid = lipid extractable into the organic phase; N.S. = nonsaponifiable lipid including cholesterol; F.A. = fatty acid. Assays were done in duplicate with at least four concentrations of compound. Results are expressed as IC_{50} values which represent the molar concentration of compound required to inhibit [^{14}C]acetate incorporation into the fraction by 50%. The coefficient of variation for the respective lipid fractions was total lipid = 11%, nonsaponifiable lipid = 13%, fatty acid = 20%. [c] Results for serum lipids are expressed for ranges of reduction from control values as follows: 0 indicates results were not statistically significant at $p \leq 0.05$ for the Student's t test or percent reduction of 0–15%; + indicates a reduction of 16–25%; ++ indicates a reduction of 26–35%; +++ indicates a reduction of 36% or greater. [d] Sodium salt of Atromid-S was used as a reference compound.

stirring at room temperature for 1 h the mixture was washed with water and dried over $MgSO_4$. The mixture was filtered and the solvent was removed in vacuo. The residue was recrystallized from Et_2O to give 10.6 g (74%) of **13**, mp 174–176 °C.

Biological Methods. Hypolipidemic Effect in Rats. Male rats of the CD strain from Charles River Breeding Laboratories weighing 300–380 g at the start of the experiment were used. The rats were housed in pairs in mesh-bottomed cages. Animals were housed in air-conditioned rooms with alternate 12-h periods of light and dark. Rats had free access to food (Purina Rat Chow) and water. The compounds to be tested were mixed with ground Purina Rat Chow at the 0.2% level. Control and experimental groups consisted of eight rats per group. The control group received ground chow without addition of test compound. Body weights were measured at the start and end of the experiment and the total food consumption for each group was recorded to ensure that the test compounds were not affecting food intake. After feeding the test compound to rats for 5 days, the rats were anesthetized on day 6 and blood was collected. Total cholesterol[13] and triglyceride[14] in serum were determined.

Values for serum cholesterol and triglyceride concentrations in the treated rats were compared with the values obtained for the untreated control rats run simultaneously. The statistical significance of the difference between treated and control values was evaluated by Student's t test at $p \leq 0.05$. Data are expressed as the percentage reduction compared to controls.

Inhibition of Lipogenesis. Male rats of the CD strain from Charles River were used in these studies. Rats were housed in pairs until the start of the pretreatment period. Rats weighing 150–200 g were generally selected and housed individually for 5 days while they received the standard rat diet (Purina Rat Chow) supplemented with 2% DEAE-cellulose.

Body weight change and food consumption were recorded as supplemental data to reject animals which were not eating and/or growing properly. These factors will influence lipogenic activity. Rats were killed by cervical dislocation.

The enzyme assays were based on techniques previously described in the literature.[15-20] The liver microsomal–cytosol fraction was used as the source of the enzymes. Lipid synthesis was measured using [2-^{14}C]acetate as the substrate. Incubation was for 90 min at 37 °C. After the reaction had been stopped, an aliquot of the lipid extract was counted using Spectrafluor (Amersham/Searle) in a Mark II scintillation counter with correction to disintegrations per minute (dpm) made by use of the external standard method.

Correction for nonenzymatic acetate incorporation into the lipid fraction was determined by incubation of the heat-inactivated liver supernatant fraction. All assays were done in duplicate.

Compounds to be tested were dissolved in a solvent compatible with the enzyme systems and which was miscible with water. The test compound was compared with a solvent control system which was related to the complete system without solvent addition. Activity of a test compound was rated based on its inhibition of radioactive acetate incorporation into the lipid fraction.

Acknowledgment. We wish to thank Mr. Bipin Desai and Mrs. Mary Ellen Baum for technical assistance. We also wish to thank Mrs. Esther Muir for the pharmacological screening data, Miss Judith Schmal for the cholesterol and triglyceride determinations, Mr. Robert Nicholson for the chromatographic separations, and Mr. Emanuel Zielinski for the microanalytical determinations.

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Additions and Corrections

1977, Volume 20

C. Robin Ganellin: Relative Concentrations of Zwitterionic and Uncharged Species in Catecholamines and the Effect of N-Substituents.

Page 580. Corrected values for Table I are given (only those columns where errors occurred are shown).

pH 7.4		pH 8.4			
Z^+	Z^-	Z^+	$Z^\pm$	Z^0	Z^-
95.5	0.02	67.3	20.3	11.2	1.2
96.1	0.008	70.6	23.4	5.4	0.6
96.6	0.005	73.9	21.1	4.5	0.4
96.4	0.006	72.6	22.2	4.7	0.4
96.3	0.004	72.2	24.1	3.4	0.3

Walter J. Gensler,* C. D. Murthy, and Marion H. Trammell: Nonenolizable Podophyllotoxin Derivatives.

Page 635. For contributing authors, C. D. Murthy should be C. A. Murthy.

James L. Kelley,* Carl A. Miller, and Helen L. White: Inhibition of Histidine Decarboxylase. Derivatives of Histidine.

Page 509. In column 1 the equation should read

$$\%\, I = \left[1 - \frac{\text{CPM (+ inhibitor)}}{\text{CPM (- inhibitor)}}\right] \times 100$$

George E. Wright* and Neal C. Brown: Inhibitors of *Bacillus subtilis* DNA Polymerase III. Structure–Activity Relationships of 6-(Phenylhydrazino)uracils.

Page 1182. In Table I the following footnote should be added to compounds **1**, **10**, **25–28**, and **32**: these azo compounds are completely reduced to hydrazinouracils under assay conditions (see Experimental Section). Also, compound **27** should have substituents 3′-Br-4′-OH.

Book Reviews

Antihypertensive Drugs with a Central Action. Progress in Pharmacology. Volume 1. No. 1. By P. A. vanZwieten. Gustav Fischer Verlag, Stuttgart. 1975. 17 × 24 cm. 63 pp. $16.40.

This small volume presents a concise overview of the pharmacology of centrally acting antihypertensive agents.

After a brief outline of the physiology of regulation of arterial blood pressure and the etiology of hypertension, the mode of action of each of the commonly recognized classes of antihypertensive agents is discussed.

The experimental procedures used to study the central actions of antihypertensive agents are reviewed and their physiological and pharmacological basis is explained in the second chapter.

The chapter headed "Antihypertensive agents with a central action; structure–activity relationship" does not undertake an in-depth review of the medicinal chemical literature; only six structures related to clonidine are mentioned. Other centrally acting agents discussed are methyl-Dopa, a heterogeneous group including reserpine, cocaine, amphetamine, tricyclic antidepressants, and MAO inhibitors that act indirectly through their various effects on central norepinephrine levels, and the more recently discovered benzodioxanyl-2-hydroxyethylpiperidine derivatives related to pimozide.

The chapter on mechanism of action is very well written and provides an extensively documented "guided tour" through the pharmacological literature describing the multiple factors that have been implicated in explaining the actions, both central and peripheral, of clonidine and methyl-Dopa.

Subsequent chapters discuss drugs that influence brain norepinephrine, the comparison between central and peripheral α-adrenergic receptors, evidence pro and con for the central antihypertensive action(s) of β-adrenergic blocking agents, and the clinical utilization of centrally acting antihypertensive drugs.

This book should be helpful to all medicinal chemists interested in antihypertensive research. It presents a concise overview that will be useful to the nonexpert. Chemists more familiar with the field will find this volume valuable for the perspective it gives to the complex interactions of this heterogeneous group of antihypertensive agents with the various physiological mechanisms that regulate blood pressure.

The bibliography is extensive. It is to be hoped that this valuable work will be kept up to date with timely revisions or supplements.

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Prolactin 1976. By D. F. Horrobin. Eden Press, Montreal. 1976. 208 pp. 15.5 × 21.5 cm. $20.00.

The present volume is the fourth book on human and mammalian prolactin that the author has written in the past 4 years. The author's first book, "Prolactin Physiology and Clinical Significance", published in 1973, is a review of the research on prolactin up until the end of 1972. Each succeeding year the author has written a review of the new material which has appeared each year since the first book. "Prolactin 1976" is intended to review all of the new material published in 1975. The "Index Medicus" was used as a primary source of the papers reviewed in this book.

The review covers new developments in several aspects of prolactin physiology including isolation, assays, control of secretion, effects of drugs, receptors, effects on reproduction and