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A New Class of Hypocholesteremic Agents: Arylalkyl Hydrogen Succinates and Glutarates

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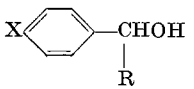
During the last few years many investigations have been carried out on substances endowed with hypocholesteremic activity, which belong to a wide variety of chemical series and whose mechanism of action is most divergent. The group comprising the inhibitors of the biosynthesis of cholesterol offered the most obvious possibilities and hence most of the synthetic and experimental products may be found in this class. Chemically these substances are generally, with the exception of triparanol and its congeners, carboxylic acids and their amides.[1] Moreover, nearly all of them derive from α-phenylbutyric acid, the pharmacological activity of which was described for the first time by Cottet.[2]

On the basis of observations made in our laboratories, we were led to suspect the existence of hypocholesteremic activity in substances in no way analogous to α-phenylbutyric acid. This pharmacological action seems to be much more widespread than is generally believed. This paper describes a class of compounds, the arylalkyl hydrogen succinates and glutarates, endowed with a striking activity *in vitro* on cholesterol biosynthesis and *in vivo* on Triton-induced hypercholesteremia in rats.

The alkylarylcarbinols were prepared according to conventional methods, i.e. by reaction of an aromatic aldehyde with an alkylmagnesium halide or by the action of an arylmagnesium halide on an aliphatic aldehyde. In some cases reduction of the corresponding ketone, with catalysts or by the Meerwein–Ponndorf–Verley method, was employed. New compounds of this group

are listed in Table I. The carbinols were then transformed into acid succinates, glutarates, and maleates by subsequent treatment with the corresponding anhydrides.

Table I. Alkylarylcarbinols

General formula 

X	R	m.p., °C	b.p., °C/mm	Formula	Analysis, % Calcd.		Found
F	C_2H_5		65/0·1	$C_9H_{11}FO$	12·32	F	12·33
F	C_4H_9		130/16	$C_{11}H_{15}FO$	10·43	F	10·60
F	$CH(CH_3)_2$		121/28	$C_{10}H_{13}FO$	11·30	F	11·42
Cl	$CH(CH_3)_2$		147/25	$C_{10}H_{13}ClO$	65·04	C	64·82
					7·10	H	7·11
Cl	C_4H_9		164/27	$C_{11}H_{15}ClO$	66·49	C	66·59
					7·60	H	7·50
Cl	C_5H_9		142/2·5	$C_{12}H_{15}ClO$	16·83	Cl	16·92
Cl	C_5H_{11}		130/0·5	$C_{12}H_{17}ClO$	16·67	Cl	16·41
Cl	$C_2H_4CH(CH_3)_2$		107/0·2	$C_{12}H_{17}ClO$	16·67	Cl	16·54
I	C_2H_5	56–7		$C_9H_{11}IO$	48·41	I	48·65
I	C_4H_9	51		$C_{11}H_{15}IO$	45·53	C	45·42
					4·97	H	5·21
CH_3	C_4H_9		118/3	$C_{12}H_{18}O$	80·85	C	80·80
					10·18	H	10·18
C_6H_5	C_2H_5	58		$C_{15}H_{16}O$	84·87	C	84·73
					7·60	H	7·61

All the substances listed in Table II were studied pharmacologically for toxicity in mice and for the minimum dose significantly active on Triton-induced hypercholesteremia in rats.[3] Many of these compounds were also considered in terms of other factors: e.g. inhibition of Coenzyme A, inhibition of cholesterol biosynthesis *in vitro*, starting with labelled acetic and mevalonic acids, and

inhibition of cortisone-induced hypercholesteremia. The results of these investigations, together with data concerning toxicity and activity, will be published elsewhere. Here we have limited ourselves to the activity manifested in the Triton test.

The following conclusions may be drawn concerning relationships between activity and structure in this particular series.

(1) As far as the dicarboxylate ester groups are concerned, activity is slight in the only two acid maleates considered, but higher in the corresponding succinates and glutarates. In general, there is an increase of activity (sometimes considerable) when passing from a succinate to the corresponding glutarate ester.

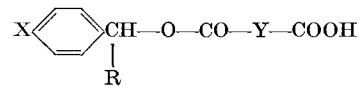
(2) In regard to the R radical, activity increases from ethyl to propyl. It remains approximately the same in the butyl derivatives and begins to decrease in the pentyl and hexyl derivatives. Alicyclic substituents confer a greater activity than the corresponding normal or branched ones. Products in which R = H or R = C_6H_5 are inactive.

(3) As far as the substitutions in the benzene nucleus are concerned, activity does not vary a great deal unless there is in the *para*-position an atom of H, F, Cl or Br or an OCH_3 group. Activity is reduced by iodine and CH_3 in the *para*-position; it is increased by C_6H_5.

However, one can never be too cautious in limiting the practical application of such relationships between activity and structure, in view of the fact that a proportionality between the administered dose and the effect observed in animals does not exist for all substances. For example, the hypocholesteremic effect of 1-phenylpentyl hydrogen succinate, observed even at 10 mg/kg, remains unchanged (25 per cent) at 100 mg/kg. On the other hand, for the three most active members of the series, the pharmacological effect increases with an increase in the administered dose, until the cholesterol level is at a more or less normal value.

An examination of the three products in Table III, including the hydrogen 3-pyridylalkyl succinates, reveals the fallacy of postulating similar relationships in chemically closely related series. Hydrogen 1-(2-pyridyl)propyl succinate is effective at 25 mg/kg, while the corresponding hydrogen 1-(2-pyridyl)pentyl succinate does not exhibit a hypocholesteremic action even at

Table II. Acid succinates, glutarates and maleates of alkylarylcarbinols

General formula 

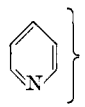
	X	R	Y	m.p., °C or n_D^{20}	Formula	Analysis, % Calcd.		Found	Activity[d]
1.	H	C_3H_5[a]	CH_2CH_2	1·5340	$C_{14}H_{16}O_4$	67·73 6·50	C H	67·53 6·50	+ +
2.	H	C_4H_9	CH=CH	1·5142	$C_{15}H_{18}O_4$	68·68 6·92	C H	68·35 7·07	—
3.	H	C_4H_9	CH_2CH_2	54	$C_{15}H_{20}O_4$	68·16 7·63	C H	68·27 7·67	+ + +
4.	H	C_4H_9	$CH_2CH_2CH_2$	1·4961	$C_{16}H_{22}O_4$	69·04 7·97	C H	69·12 7·94	+ + +
5.	F	C_2H_5	CH_2CH_2	54	$C_{13}H_{15}FO_4$	61·41 6·21	C H	61·44 5·95	+
6.	Cl	H	CH_2CH_2	79	$C_{11}H_{11}ClO_4$	14·61	Cl	14·37	—
7.	Cl	C_2H_5	CH_2CH_2	71	$C_{13}H_{15}ClO_4$	57·89 5·60	C H	58·03 5·75	—
8.	Cl	C_2H_5	$CH_2CH_2CH_2$	1·5113	$C_{14}H_{17}ClO_4$	12·45	Cl	12·20	+ + +
9.	Cl	C_3H_5	$CH_2CH_2CH_2$	1·5212	$C_{15}H_{17}ClO_4$	11·95	Cl	11·87	+ +
10.	Cl	$CH(CH_3)_2$	CH=CH	75	$C_{14}H_{15}ClO_4$	59·47 5·34	C H	59·49 5·20	+

11.	Cl	$CH(CH_3)_2$	CH_2CH_2	97	$C_{14}H_{17}ClO_4$	59·05 6·01	C H	58·84 5·88	+
12.	Cl	$CH(CH_3)_2$	$CH_2CH_2CH_2$	1·5101	$C_{15}H_{19}ClO_4$	60·30 6·56	C H	60·38 6·36	+ + + +
13.	Cl	C_4H_9	CH_2CH_2	38	$C_{15}H_{19}ClO_4$	11·86	Cl	11·72	+ + +
14.	Cl	C_5H_9 [b]	CH_2CH_2	95	$C_{16}H_{19}ClO_4$	11·41	Cl	11·65	+ + + +
15.	Cl	C_6H_{11} [c]	CH_2CH_2	136	$C_{17}H_{21}ClO_4$	10·92	Cl	10·97	+
16.	Cl	C_5H_{11}	CH_2CH_2	1·5071	$C_{16}H_{21}ClO_4$	11·33	Cl	11·21	+ + +
17.	Cl	$C_2H_4CH(CH_3)_2$	CH_2CH_2	36	$C_{16}H_{21}ClO_4$	11·33	Cl	11·03	+ + +
18.	Cl	C_6H_5	CH_2CH_2	85	$C_{17}H_{15}ClO_4$	11·13	Cl	10·82	—
19.	Br	C_4H_9	CH_2CH_2	53	$C_{15}H_{19}BrO_4$	23·28	Br	23·50	+ + +
20.	I	C_2H_5	CH_2CH_2	76	$C_{13}H_{15}IO_4$	35·04	I	35·04	+
21.	I	C_4H_9	CH_2CH_2	88	$C_{15}H_{19}IO_4$	32·52	I	32·30	+ +
22.	CH_3	C_4H_9	CH_2CH_2	1·4989	$C_{16}H_{22}O_4$	68·16 7·63	C H	68·45 7·82	—
23.	OCH_3	C_4H_9	CH_2CH_2	1·5070	$C_{16}H_{22}O_5$	65·29 7·53	C H	64·81 7·24	+ +
24.	C_6H_5	C_2H_5	CH_2CH_2	66	$C_{19}H_{20}O_4$	73·06 6·45	C H	73·32 6·75	+ +
25.	C_6H_5	C_2H_5	$CH_2CH_2CH_3$	62	$C_{20}H_{22}O_4$	73·60 6·79	C H	73·44 6·90	+ + +
26.	C_6H_5	C_4H_9	CH_2CH_2	80	$C_{21}H_{24}O_4$	74·09 7·11	C H	74·06 7·13	+ + + +

[a] Cyclopropyl. [b] Cyclopentyl. [c] Cyclohexyl. [d] + = 100–200 mg/kg, + + = 25–100 mg/kg, + + + = 10 mg/kg, + + + + = 5 mg/kg or less.

100 mg/kg, although an increase in activity would be reasonably anticipated.

Table III

General formula  $CH(R)—O—COCH_2CH_2COOH$

Chain position in pyridine ring	R	m.p., °C	Formula	Analysis, % Calcd.		Found	Activity[a]
2	C_2H_5	83	$C_{12}H_{15}NO_4$	5·95	N	5·71	++
2	C_4H_9	95	$C_{14}H_{19}NO_4$	63·38	C	63·35	—
				7·22	H	6·99	
3	C_2H_5	103	$C_{12}H_{15}NO_4$	5·95	N	5·83	—

[a] Scale of activity as in Table II.

Experimental

Alkylarylcarbinols. The carbinols listed in Table I were prepared according to three different methods:

A. By the action of an alkylmagnesium halide on an aromatic aldehyde. The preparation of 1-*p*-chlorophenylpentanol may serve as an example.

1-p-Chlorophenylpentanol. A Grignard reagent is prepared from magnesium (3 g), butyl bromide (18·5 g) and anhydrous ether (70 ml). To the cooled solution, a solution of *p*-chlorobenzaldehyde (14 g) in ether (50 ml) is added dropwise. After the addition the mixture is heated for 30 min to complete the reaction. It is then cooled and decomposed with 10 per cent sulphuric acid. The ether layer is separated and washed with water, 5 per cent sodium carbonate solution, and again with water. After drying over sodium sulphate and evaporation of the solvent, the residue is distilled at reduced pressure. A yield of 16 g (81 per cent) of 1-*p*-chlorophenylpentanol was obtained, b.p. 164°/27 mm.

B. By the action of an arylmagnesium halide on an aliphatic aldehyde, as described below for 1-*p*-fluorophenyl-2-methylpropanol.

1-p-*Fluorophenyl-2-methylpropanol.* To a cooled solution of *p*-fluorophenylmagnesium bromide from magnesium (2·6 g), *p*-fluorobromobenzene (17·5 g) and ether (100 ml), a solution of isobutyraldehyde (7·2 g) in 50 ml of ether is added dropwise with stirring. The resulting mixture is left for a few hours at room temperature, decomposed with 8 per cent sulphuric acid, and worked up as above. 1-*p*-Fluorophenyl-2-methylpropanol (9·8 g, 58 per cent) was obtained, b.p. 121°/28 mm.

C. By the reduction of a ketone. Two examples are listed below.

1-p-*Iodophenylpropanol.* A solution of ethyl *p*-iodophenyl ketone (5·2 g) and aluminium isopropoxide (4 g) in isopropyl alcohol (35 ml) was heated in a flask equipped with a Hahn condenser.[4] Heating was regulated so that approximately eight drops distilled per minute. After about 2 h the distillate no longer gave the acetone reaction and at that point the isopropyl alcohol was distilled at reduced pressure. The residue was cooled and hydrolyzed with 2N HCl (40 ml). An oil separated which solidified after a short time. Filtration and crystallization from petroleum ether gave 5 g (95 per cent) of 1-*p*-iodophenylpropanol; m.p. 56–57°.

1-(4-Biphenyl)propanol. A solution of ethyl 4-biphenyl ketone (42 g) in absolute ethanol (300 ml) was placed in an autoclave with 4·2 g of Raney nickel. Hydrogen was introduced at 60 atm, and the mixture heated at 100° and agitated for 15 min, when absorption reached the required value. Agitation was stopped and the mixture cooled to room temperature. The catalyst was filtered off and the solvent removed under reduced pressure. The residue crystallized and consisted of practically pure 1-(4-biphenyl)propanol. The yield was quantitative. For analysis crystallization from hexane was carried out, m.p. 58–59°.

Alkylpyridylcarbinols. As already described in the literature, both 1-(2-pyridyl)propanol and 1-(3-pyridyl)propanol were synthesized in a manner analogous to 1-(2-pyridyl)pentanol, whose preparation is reported herewith.

1-(2-Pyridyl)pentanol. A Grignard reagent was prepared from magnesium (5·1 g), butyl bromide (22·8 g) and anhydrous ether (80 ml). Over a period of approximately 30 min, with cooling and stirring, pyridine-2-aldehyde (21·4 g) dissolved in

40 ml of anhydrous ether was added. The mixture was left overnight at room temperature and subsequently refluxed for 30 min. With caution it was decomposed with cracked ice (50 g) and 18 per cent hydrochloric acid (50 ml); in this way one avoids bringing the product into solution as the hydrochloride. The ether layer was extracted with 2N hydrochloric acid and the aqueous solution was made basic with 2N sodium hydroxide. Extraction with ether, drying over Na_2SO_4, removal of the solvent and distillation at reduced pressure yielded 15 g (46 per cent) of 1-(2-pyridyl)-pentanol; b.p. 95°/0·5 mm.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72·69; H, 9·15; N, 8·48. Found: C, 72·58; H, 9·18; N, 8·55.

Hydrogen succinates and glutarates. Not all of the substances listed in Table II were isolated in the solid state. Many appear as highly viscous oils which are subject to decomposition upon distillation, even at highly reduced pressure. For this reason, they were analyzed without further purification beyond repeated solution in 5 per cent sodium carbonate and reprecipitation with acid. Even though analytical results corresponded rather well to theoretical values, it may be assumed that several substances, when absolutely pure, may be solids. In several cases, an oil kept for many months at room temperature began to solidify.

The reaction between carbinol and acid anhydride was carried out with equimolar amounts at 110–140° in pyridine or xylene, or without solvent. In one case (without solvent) studied in detail, it was noted that yields are considerably influenced by the duration of the treatment, and while at first the equilibrium is favourable to formation of the ester, during prolonged heating it reverses direction toward the starting materials. In order to obtain better yields, it is advisable therefore to study case by case the optimum duration of reaction. The three examples below are typical of slightly different techniques.

1. *Hydrogen 1-phenylpentyl succinate* (in pyridine). A mixture of 1-phenylpentanol (16·4 g) and succinic anhydride (10 g) was heated at 115° for 8 h with anhydrous pyridine (20 ml). After cooling, the mixture was treated with 2N hydrochloric acid, extracted with chloroform and washed with water, and then the solvent was removed. The residue was treated with a slight excess of 10 per cent sodium carbonate and the few undissolved impurities

were extracted with ether. The basic solution was acidified with hydrochloric acid, and the oil which separated was extracted with ether. After drying over Na_2SO_4 the ether was removed. The remaining oil soon solidified, m.p. 50–53°; yield 21·3 g (81 per cent). Recrystallized from petroleum ether, hydrogen 1-phenylpentyl succinate melted at 54°.

2. *1-p-Chlorophenyl-2-methylpropyl hydrogen succinate* (in xylene). A mixture of 1-*p*-chlorophenyl-2-methylpropanol (4·6 g), succinic anhydride (2·5 g) and xylene (30 ml) was heated at 120° for 8 h. After cooling it was treated with water and the layers were separated. The xylene layer was evaporated under reduced pressure and the residue treated with a solution of 7 per cent sodium carbonate and ether. The basic layer was acidified with 2N hydrochloric acid. An oil (4 g, 56 per cent) which almost immediately solidified was thus separated. After crystallization from hexane, its m.p. was 97–98°.

3. *1-p-Chlorophenylpentyl hydrogen succinate* (without solvent). One mole of 1-*p*-chlorophenylpentanol and 1·25 moles of succinic anhydride were heated at 140° with constant stirring. To follow the course of the reaction, checks were performed on the solubility of samples of the mixture in 10 per cent sodium carbonate. After 1·5 h the material was completely soluble. After cooling, sufficient 5 per cent sodium carbonate solution was added to pH 8, and the basic solution was washed immediately (in order to avoid the separation of the only slightly soluble sodium salt) several times with ether, until the ether layer was colourless. On acidification with 18 per cent hydrochloric acid, an oil separated and was extracted with ether. After washing with water to neutrality and drying with Na_2SO_4, the ether was distilled off, the last traces being removed at reduced pressure. The residual oil solidified, m.p. 38°. Yield, 80 per cent.

The *hydrogen pyridylalkyl succinates* were prepared by the following general method. Equimolar quantities of alkylpyridylcarbinol and succinic anhydride in five volumes of anhydrous xylene were heated at 120° for 7 h. Upon cooling hydrogen 1-(2-pyridyl)pentyl succinate (yield 67 per cent) and hydrogen 1-(2-pyridyl)propyl succinate (yield 60 per cent) solidified. They were washed with water and crystallized from petroleum ether–benzene. Hydrogen 1-(3-pyridyl)propyl succinate remained oily.

Extraction with ether, washing with water, drying over Na_2SO_4 and removal of the solvent left a residue which solidified (yield 50 per cent) and was crystallized from petroleum ether–benzene.

Hydrogen maleates. The two hydrogen maleates described were obtained by heating equimolar quantities of carbinol and maleic anhydride in xylene at 120° for 7 h.

1-p-Chlorophenyl-2-methylpropyl hydrogen maleate. A mixture of maleic anhydride (3·3 g), 1-*p*-chlorophenyl-2-methylpropanol (6·1 g) and xylene (40 ml) was heated at 120° for 7 h, and the reaction mixture was cooled and treated with water. The organic layer was dried over Na_2SO_4 and then evaporated at reduced pressure. The residue was treated with a solution of 5 per cent sodium carbonate and ether, the basic solution was acidified, and the oil which separated extracted with ether. After drying with Na_2SO_4 and removing the solvent, 4 g (53 per cent) of 1-*p*-chlorophenyl-2-methylpropyl hydrogen maleate was obtained in the form of an oil which solidified after a number of days. After crystallization from hexane, its m.p. was 75°.

Summary. The synthesis of a series of arylalkyl and pyridylalkyl hydrogen succinates and glutarates, endowed with hypocholesteremic activity in the Triton test on rats, is described.

1-*p*-Chlorophenyl-2-methylpropyl hydrogen glutarate, α-cyclopentyl-*p*-chlorobenzyl hydrogen succinate and 1-*p*-biphenylpentyl hydrogen succinate all give positive reactions in this test at doses as low as 5 mg/kg.

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