(2-Alkyl-1,4-benzodioxan-2-yl)carboxylic Acids as Potential Hypolipidemic Agents

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1,2-Diphenols reacted with 2-alkyl-3-chloro-1,2-epoxypropane to give a mixture of 1,4-benzodioxane, V, and 1,5-benzodioxepine, VII, alcohols. From potassium permanganate oxidation of benzodioxane compounds V the corresponding (2-alkyl-1,4-benzodioxan-2-yl)carboxylic acids II were obtained. In a preliminary pharmacological evaluation benzodioxane acids II did not show any effect on plasma cholesterol, while producing a moderate lowering of triglycerides.

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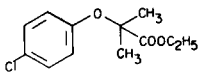
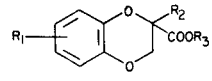
Since the discovery of the hypolipidemic activity of ethyl 2-(4-chlorophenoxy)-2-methylpropanoate (Clofibrate) (I) (1) a number of reports concerning structurally related compounds have been published (2), however very few of them were found superior to Clofibrate in all respects. Recently ethyl (1,4-benzodioxan-2-yl)carboxylate and its 6-and 7-chloro derivatives have been shown to possess some hypolipidemic properties (3). In this paper we wish to report the synthesis of a few (2-alkyl-1,4-benzodioxan-2-yl)-carboxylic acids of general formula II (Table I), which may be considered cyclic analogs of Clofibrate. The presence of a quaternary carbon atom bearing a carboxyl function was expected to favour such biological activity in the benzodioxane series.



I

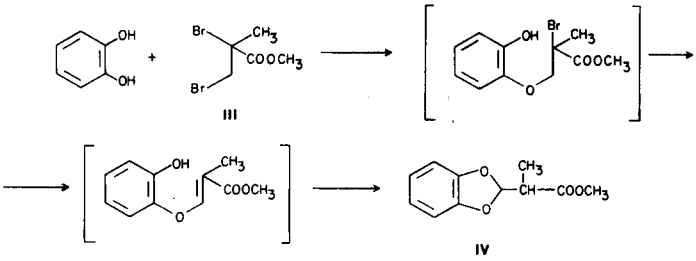


II

a, R_1=H, R_2=CH_3, R_3=H, CH_3, C_2H_5
b, R_1=6-Cl, R_2=CH_3, R_3=H
c, R_1=7-Cl, R_2=CH_3, R_3=H
d, R_1=6-CH_3, R_2=CH_3, R_3=H
e, R_1=7-CH_3, R_2=CH_3, R_3=H
f, R_1=H, R_2=C_2H_5, R_3=H
g, R_1=6-CO-C_6H_4-4-Cl, R_2=CH_3, R_3=H, C_2H_5

Condensation of catechol with methyl 2,3-dibromo-2-methylpropanoate (III) (4) did not produce the expected methyl (2-methyl-1,4-benzodioxan-2-yl)carboxylate (II a, R_3 = CH_3). In the potassium carbonate-acetone system, dehydrobromination to methyl 3-bromo-2-methyl-2-propenoate (5) was practically the only reaction, while methyl 2-(1,3-benzodioxol-2-yl)propanoate (IV) was obtained, in addition to the above product, using sodium hydride in dimethylformamide. (Scheme I). The synthesis of acids II, with the exception of IIg (R_3 = H), was achieved in moderate yields by potassium permanganate oxidation of the corresponding alcohols V (Table II), obtained from the reaction of the appropriate 1,2-diphenol with 3-chloro-2-

Scheme I

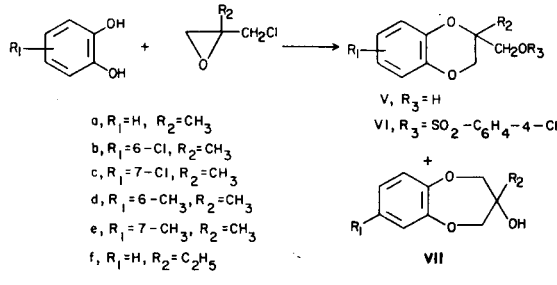


III

IV

methyl (or ethyl)-1,2-epoxypropane, using a modification of a known procedure (6). Not surprisingly, in addition to the benzodioxane derivatives V, the corresponding 1,5-benzodioxepines VII (Table III) formed in the above reaction (Scheme II). Alcohols V were isolated from the

Scheme II



a, R_1=H, R_2=CH_3
b, R_1=6-Cl, R_2=CH_3
c, R_1=7-Cl, R_2=CH_3
d, R_1=6-CH_3, R_2=CH_3
e, R_1=7-CH_3, R_2=CH_3
f, R_1=H, R_2=C_2H_5

V, R_3=H
VI, R_3=SO_2-C_6H_4-4-CH_3

VII

reaction mixture as tosylates VI (Table IV) (7), from which then they were easily obtained in pure state by alkaline hydrolysis. Carbinols VII, being more resistant than V to oxidation, were easily recovered from the potassium permanganate oxidation mixture, simply by extracting the final alkaline solution with ether. The dioxepines VIId and VIIf could also be isolated as unreacted material during the preparation of the tosylates of the corresponding benzodioxane alcohols (see Experimental).

According to the literature (8), the concurrent formation of the benzodioxane and benzodioxepine ring systems has been interpreted as occurring through the intermediate epoxide VIII, which might undergo intramolecular nucleophilic attack at either the quaternary or the primary

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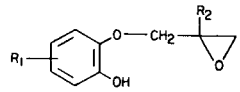

VIII

carbon atom. The approximately 3:1 ratio observed for V and VII accounts for the easier formation of the six membered ring in spite of unfavourable steric factors involved in the nucleophilic attack at the quaternary carbon atom.

In the reaction of 4-chloro- or 4-methylcatechol with 3-chloro-2-methyl-1,2-epoxypropane, mixtures of the isomeric 6- and 7-chloro (Vb,c) or 6- and 7-methylbenzodioxanes (Vd,e) were obtained. Separation of the isomeric alcohols could be achieved only in the case of Vd,e. However potassium permanganate oxidation of the crude Vb,c afforded a mixture of the acids IIb and IIc, from which the two isomers could be easily separated by fractional crystallization. The analogous reaction performed on the crude Vd,e furnished a mixture of the acids IId and IIe which however could not be separated in pure state.

Finally, benzodioxane acid (IIg, R_3 = H) was prepared from IIa ($R_3 = C_2H_5$) through Friedel-Crafts condensation with 4-chlorobenzoyl chloride, followed by hydrolysis. No effort was made to isolate the other isomers formed in the above Friedel-Crafts reaction.

Structural assignments of the substituted compounds II and V were made through the use of ^{13}C-nmr spectroscopy, unequivocably establishing the location of the substituent on the benzodioxane ring (9).

In a preliminary pharmacological evaluation, acids II did not show any effect on plasma cholesterol, while they lowered the triglycerides in a dose-unrelated manner.

EXPERIMENTAL

Melting points were obtained in open capillary tubes on a Büchi apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 257 spectrophotometer. Nmr spectra were recorded using a 60 MHz Perkin Elmer R 24 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Elementary analyses were performed by Istituto di Chimica Organica, University of Milan.

4-Chlorocatechol and 3-chloro-2-ethyl-1,2-epoxypropane have been prepared according to (10) and (11), respectively.

Reaction of Catechol with Methyl 2,3-Dibromo-2-methylpropanoate (III).

A) Condensation in Dimethylformamide in the Presence of Sodium Hydride.

To a solution of catechol (9.8 g.) in anhydrous dimethylformamide (100 ml.) a 80% sodium hydride suspension in mineral oil (5.4 g.) was added in portions. The mixture was heated at 80° for 0.5 hour and a solution of III (2.2 g.) (4) in anhydrous dimethylformamide (50 ml.) was added dropwise. After heating at 120° for 8 hours, the reaction mixture was cooled, the solvent removed under reduced pressure and the residue treated with water and extracted with ether. The extract was washed with diluted sodium hydroxide and water, dried over sodium sulphate and evaporated to dryness. The oily residue was fractionated *in vacuo*. The first fraction (2 g.) was methyl 3-bromo-2-methyl-2-propenoate, b.p. 140-145°/22 mm (lit. (5) b.p. 164°/760 mm); ir (neat): ν max 1730 (ester C=O), 1620 cm^{-1} (C=C); nmr (deuteriochloroform): δ 2.2 (3H, d, CH=C-C*H*$_3$), 3.7 (3H, s,

Table I

(2-Alkyl-1,4-benzodioxan-2-yl)carboxylic Acids

Compound	M.p.(°C)	Crystallization Solvent	Yield % (a)	Formula	Analyses % Calcd. (Found)	Ir (cm^{-1})	Nmr (δ)
IIa	126-128	Benzene	60	$C_{10}H_{10}O_4$	C, 61.85 (61.72) H, 5.19 (5.21)	2750-2300 (ν OH) 1730 (ν COOH)	1.6 (3H, s, CH_3), 3.82 (1H,d, ring CH), 4.52 (1H, d, ring CH), 6.98 (4H, m, Ar-H) (b)
IIb	183-185	Benzene	85 (c)	$C_{10}H_9ClO_4$	C, 52.53 (52.71) H, 3.97 (3.84)	2700-2500 (ν OH) 1740 (ν COOH)	1.6 (3H, s, CH_3), 3.9 (1H, d, ring CH), 4.6 (1H, d, ring CH), 6.9 (3H, s, Ar-H) (d) (e)
IIc	160-163	Benzene	85 (c)	$C_{10}H_9ClO_4$	C, 52.53 (52.40) H, 3.97 (4.01)	2700-2500 (ν OH) 1740 (ν COOH)	1.6 (3H, s, CH_3), 3.9 (1H, d, ring CH), 4.6 (1H, d, ring CH), 6.8-7 (3H, m, Ar-H) (d) (e)
IId,e (f)	120-123	Ligroin	63 (c)	$C_{11}H_{12}O_4$	C, 63.45 (63.75) H, 5.80 (5.65)	2700-2500 (ν OH) 1720 (ν COOH)	1.5 (3H, s, CH_3), 2.2 (3H, s, Ar-C*H*$_3$), 3.75 (1H, d, ring CH), 4.42 (1H, d, ring CH), 6.48-6.9 (3H, m, Ar-H) (b)
IIf	120-121	Benzene-hexane 1:5	81	$C_{11}H_{12}O_4$	C, 63.45 (63.80) H, 5.81 (5.85)	2700-2500 (ν OH) 1730 (ν COOH)	1.05 (3H, t, CH_2CH_3), 2.0 (2H q, CH_2CH_3), 4.0 (1H, d, ring CH), 4.6 (1H, d, ring CH), 7.1 (4H, m, Ar-H) (b)
IIg	179-181	Ethanol (60%)	80	$C_{17}H_{13}ClO_4$	C, 61.36 (61.11) H, 3.94 (3.97)	2700-2500 (ν OH) 1720 (ν COOH)	1.55 (3H, s, CH_3), 3.9 (1H, d, ring CH), 4.6 (1H, d, ring CH), 6.95-7.7 (7H, m, Ar-H) (d)

(a) Based on the reacted 1,4-benzodioxane alcohol, with the exception of IIg, obtained by hydrolysis of its ethyl ester (see Experimental) (b) In deuteriochloroform. (c) As a mixture of 6- and 7-isomers, in an undetermined ratio. (d) In deuterioacetone. (e) See Note 12 for nmr spectrum at 100 MHz of its methyl ester. (f) As a 3:2 mixture of 6- and 7-isomers.

Table II

(2-Alkyl-1,4-benzodioxan-2-yl)methanols

Compound	M.p. (°C) or b.p. (°C/mm)	Yield (%) (a)	Formula	Analyses % Calcd. (Found)	Nmr (δ in deuteriochloroform)
Va	64-66 (b)	54 (88)	$C_{10}H_{12}O_3$	C, 66.65 (66.76) H, 6.71 (6.48)	1.28 (3H, s, CH_3), 3.00 (1H, t, OH), 3.57 (2H, d, CH_2 OH) (singlet after deuterium oxide), 3.75 (1H, d, ring CH), 4.10 (1H, d, ring CH), 6.81 (4H, s, Ar-H)
Vb (c)	74-76 (d)	56 (67) (e)	$C_{10}H_{11}ClO_3$	C, 55.95 (56.11) H, 5.17 (5.23)	1.3 (3H, s, CH_3), 2.8 (1H, s, OH), 2.1 (2H, s, CH_2 OH), 3.85 (1H, d, ring CH), 4.15 (1H, d, ring CH), 6.75-6.9 (3H, m, Ar-H)
Vd	125-130/0.4	64 (94) (e)	$C_{11}H_{14}O_3$	C, 68.02 (67.93) H, 7.27 (7.10)	1.27 (3H, s, CH_3), 2.2 (3H, s, ArCH_3), 2.58 (1H, t, OH), 3.59 (2H, s, CH_2OH), 3.75 (1H, d, ring CH), 4.07 (1H, d, ring CH), 6.6 (3H, m, Ar-H)
Ve	170-175/1	64 (94) (e)	$C_{11}H_{14}O_3$	C, 68.02 (68.09) H, 7.27 (7.31)	1.3 (3H, s, CH_3), 2.22 (3H, s, ArCH_3), 3.0 (1H, s, OH), 3.62 (2H, s, CH_2OH), 3.8 (1H, d, ring CH), 4.12 (1H, d, ring CH), 6.5 (3H, m, Ar-H)
Vf	160-170/0.8	42 (81)	$C_{11}H_{14}O_3$	C, 68.02 (68.11) H, 7.27 (7.21)	0.98 (3H, t, CH_2CH_3), 1.7 (2H, q, CH_2CH_3), 2.6 (1H, s, OH) 3.7 (2H, s, CH_2OH), 2.97 (1H, d, ring CH), 4.3 (1H, d, ring CH), 6.97 (4H, m, Ar-H)

(a) Calculated by glc of the crude mixture of V and VII. Yields in parentheses refer to the product obtained by hydrolysis of the corresponding tosylates VI. (b) Crystallized from ligroin; lit. (6) m.p. 65-66° (from petroleum ether). (c) Isomer Vc was not isolated in the pure state. (d) Crystallized from hexane. (e) As a mixture of 6- and 7-isomers, in an undetermined ratio.

Table III

3-Alkyl-3-hydroxy-2*H*-1,5-benzodioxepines

Compound	M.p. (°C) or b.p. (°C/mm)	Yield % (a)	Formula	Analyses % Calcd. (Found)	Nmr (δ in deuteriochloroform)
VIIa	73-75 (b)	27	$C_{10}H_{12}O_3$	C, 66.65 (66.58) H, 6.71 (6.78)	1.2 (3H, s, CH_3), 3.2 (1H, s, OH), 3.75 and 4.08 (each 2H, d, CH_2O), 6.95 (4H, m, Ar-H)
VIIb	160-170/1.5	28	$C_{10}H_{11}ClO_3$	C, 55.95 (55.90) H, 5.17 (5.11)	1.2 (3H, s, CH_3), 3.5 (1H, s, OH), 3.8 and 4.05 (each 2H, d, CH_2O), 6.7-6.95 (4H, m, Ar-H)
VIId	150-160/0.6	32	$C_{11}H_{14}O_3$	C, 68.02 (68.09) H, 7.27 (7.15)	1.2 (3H, s, CH_3), 2.2 (3H, s, Ar CH_3), 3.72 and 4.05 (each 2H, d, CH_2O), 6.5-6.9 (3H, m, Ar-H)
VIIf	170-175/1.5	21	$C_{11}H_{14}O_3$	C, 68.02 (67.95) H, 7.27 (7.32)	0.95 (3H, t, CH_2CH_3), 1.6 (2H, q, CH_2CH_3), 3.3 (1H, s, OH) 3.9 and 4.12 (each 2H, d, CH_2O), 7.0 (4H, m, Ar-H)

(a) Crude product. (b) Crystallized from benzene-hexane 2:7; lit. (13) m.p. 77-79°.

$COOCH_3$), 7.45 (1H, m, C*H*=C-CH_3). The second fraction (2.7 g.) was methyl 2-(1,3-benzodioxol-2-yl)-propanoate (IV), b.p. 160-170°/0.8 mm; ir (neat): ν max 1740 cm^{-1} (ester (C=O); nmr (deuteriochloroform): δ 1.3 (3H, d, CH-C*H*$_3$), 3.0 (1H, m, C*H*-CH_3), 3.7 (3H, s, $COOCH_3$), 6.35 (1H, d, O-C*H*), 6.8 (4H, s, Ar-H).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.30; H, 5.70.

B) Condensation in Acetone in the Presence of Potassium Carbonate.

A solution of catechol (11 g.) and III (2.6 g.) (4) in anhydrous acetone (600 ml.) was refluxed under stirring (7 hours) in the presence of potassium carbonate (41.5 g.). The solid was filtered off and the solution evaporated to dryness. After the usual work-up, the organic layer gave an oily residue which was shown to be practically only methyl 3-bromo-2-methyl-2-propenoate (5).

General Procedure for the Reaction of 3-Chloro-2-methyl (or ethyl)-1,2-epoxypropane with Catechol (or its Derivatives).

A mixture of catechol (or its derivatives) (1 mole), 3-chloro-2-methyl (or ethyl)-1,2-epoxypropane (1.05 moles) and 10% sodium hydroxide (1 mole) was heated under stirring at 110° for 10 hours. The mixture was cooled and extracted with ether. The ethereal extract was washed with 5% sodium hydroxide and water, dried over sodium sulphate and evaporated. The oily residue (approximately a 3:1 mixture of V and VII by glc and nmr analyses) was dissolved in dry pyridine (600 ml.) and treated with tosyl chloride (1 mole) with stirring and kept at 5-10°. After 24 hours, the reaction mixture was poured into iced water. The separated phase was filtered (or decanted) and dissolved in ether. The ethereal solution was washed with water, dried over sodium sulphate and evaporated. By crystallization of the residue from ethanol, the tosylates VI were obtained in pure state (Table IV).

Table IV

Compound (a)	M.p. (°C)	Yield (%)
VIa	76-77 (b)	86
VIb	133-135	22
VIc	(c)	—
VId	114-116	75 (d)
VIe	54-57	75 (d)
VIf	92-94	81

(a) All compounds were crystallized from ethanol. (b) Lit. (6) 77.5-79°. (c) Not isolated in pure state. (d) As a mixture of 6- and 7-isomers, in an undetermined ratio.

In the case of VId,e and VIf, the aqueous solution, after acidification with dilute hydrochloric acid, was extracted with ether. The extract was

washed with dilute sodium hydroxide and water, dried over sodium sulphate and evaporated. The residue, by distillation *in vacuo*, afforded benzodioxepines VIId and VIIf in the pure state (Table III).

Tosylates VI (0.05 mole), dissolved in *t*-butyl alcohol (50 ml.), were treated with finely powdered potassium hydroxide (10 g.). The reaction mixture was refluxed for 5 hours under stirring. After removal of the solvent, the residue was treated with water and extracted with ether. The ethereal solution was dried over sodium sulphate and evaporated to dryness. Crystallization from ethanol or distillation afforded benzodioxane alcohols V (Table II).

General Procedure for the Potassium Permanganate Oxidations.

The crude reaction mixture of V and VII (0.2 mole) was suspended in a solution of sodium carbonate (0.005 mole) in water (45 ml.). A solution of potassium permanganate (0.4 mole) in water (2.5 l.) was added slowly under stirring, keeping the reaction temperature below 20°. After 24 hours at room temperature, the solid was filtered off through Celite and repeatedly washed with water and ether. The aqueous alkaline solution was separated from the ethereal layer (ethereal extract A), acidified with diluted hydrochloric acid and extracted with ether. The latter ethereal solution was washed with water, dried over sodium sulphate and evaporated to give the crude acids II. Crystallization from the proper solvent afforded the pure acids II (Table I).

The ethereal extract A, which contained VII and some unreacted V, after evaporation to dryness, was submitted to further oxidation with potassium permanganate. The above work-up afforded compounds VII (Table III) which were purified by distillation or crystallization.

Separation of the (6- and 7-Chloro-2-methyl-1,4-benzodioxan-2-yl)carboxylic Acids IIb and IIc.

The crude mixture (63.2 g.) of the 6-Cl and 7-Cl isomers IIb and IIc, obtained from the potassium permanganate oxidation of the crude alcohol Vb,c (225 g.), was crystallized from benzene (350 ml.). The first precipitate (18.1 g.) was the 6-chloro isomer IIb (see Table I) (12). Concentration of the mother liquors gave a second crop (11.2 g.), which, after repeated crystallizations from benzene, afforded pure crystals of the 7-chloro isomer IIc (see Table I) (12).

Ethyl (2-Methyl-1,4-benzodioxan-2-yl)carboxylate (II, a, $R_3 = C_2H_5$).

A solution of IIa ($R_3 = H$) (50 g.) in absolute ethanol (250 ml.) was refluxed for 30 hours in the presence of sulphuric acid (5 ml.). After removal of the solvent, water was added and the solution was neutralized with sodium carbonate. Extraction with ether, drying over sodium sulphate and evaporation of the solvent gave IIa ($R_3 = C_2H_5$) (49 g.) as an oil, b.p. 185-190°/0.8 mm; ir (neat): ν max 1750 cm^{-1} (ester C=O); nmr (deuteriochloroform): δ 1.2 (3H, t, CH_2CH_3), 1.6 (3H, s, CH_3), 3.9 (1H, d, ring CH), 4.2 (2H, q, CH_2CH_3), 4.6 (1H, d, ring CH), 6.9 (4H, m, Ar-H).

Ethyl [6-(4-Chlorobenzoyl)-2-methyl-1,4-benzodioxan-2-yl]carboxylate (IIg, $R_3 = C_2H_5$).

To a stirred solution of IIa, ($R_3 = C_2H_5$), (28 g.) and 4-chlorobenzoylchloride (24 g.) in dried carbon sulphide (190 ml.) aluminium chloride (17 g.) was added portionwise. After heating under reflux for 13 hours, the cooled reaction mixture was poured onto ice, acidified with 1:1 hydrochloric acid and the oil extracted with chloroform. The organic solution was washed with sodium hydroxide and water and finally dried over sodium sulphate. Removal of the solvent gave a residue (50 g.) from which the unreacted starting product was removed by distillation (b.p. 200-210°/1.5 mm). Crystallization of the residue (26 g.) from ligroin (1300 ml.) gave IIg ($R_3 = C_2H_5$) as white crystals (7.8 g.) m.p. 102-104°; ir (nujol): ν max 1750 cm^{-1} (ester C=O), 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.2 (3H, t, CH_2CH_3), 1.5 (2H, s, CH_3), 3.95 (1H, d, ring CH), 4.25 (2H, q, CH_2CH_3), 4.6 (1H, d, ring CH), 7-7.8 (7H, m, Ar-H).

Anal. Calcd. for $C_{19}H_{17}ClO_5$: C, 63.25; H, 4.75. Found: C, 63.60; H, 4.75.

[6-(4-Chlorobenzoyl)-2-methyl-1,4-benzodioxan-2-yl]carboxylic Acid (II g, $R_3 = H$).

A solution of IIg ($R_3 = C_2H_5$) (5.9 g.) in ethanol (125 ml.) was refluxed for 3 hours in the presence of sodium hydroxide (0.75 g.). After removal of the solvent, water and ether were added, the alkaline layer was separated, acidified with 50% acetic acid and extracted with ether. The extract was washed with water, dried over sodium sulphate and evaporated to dryness. The oily residue (5.7 g.) was treated with benzene and hexane to give a low melting solid. Recrystallization from 60% ethanol gave 4.5 g. of IIg ($R_3 = H$) as light yellow crystals (see Table I).

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