

DIVIDED ON

No. 8510449

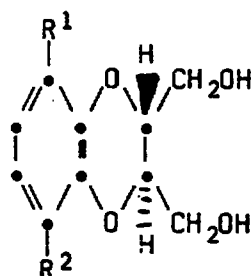
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AROMATIC DIOLS

This invention relates to aromatic diols. More specifically this invention relates to benzodioxindiols useful as intermediates in the preparation of therapeutically useful benzodioxinopyrrole derivatives.

The present invention accordingly provides compounds of general formula (III)



(III)

wherein

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom or a substituent as defined above for R^1 .

In general formula (III), the alkyl groups represented by R^1 and R^2 may be straight or branched chain groups.

The halogen atoms represented by R^1 and R^2 may be fluorine, chlorine, bromine or iodine atoms. Examples of alkyl and alkoxy groups represented by R^1 and R^2 are methyl, ethyl, methoxy and ethoxy groups. The group $-NR^3R^4$ may be, for example, an amino, methylamino, ethylamino, dimethylamino or diethylamino group.

It will be appreciated that each compound of general formula (III) is a trans isomer and exists as two enantiomers. The structural formulae herein are to be understood to depict either enantiomer of each compound as well as mixtures of the enantiomers, including racemates, even though the precise structure as set out only relates to one enantiomer.

A preferred group of compounds of formula (III) is that in which R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group, in particular a chlorine or fluorine atom or a methyl or methoxy group.

A further preferred group of compounds of formula (III) is that in which R^2 is a hydrogen or fluorine atom, particularly a hydrogen atom.

Particularly important compounds of formula (III) are those in which R^1 is a chlorine or fluorine atom or a methyl or methoxy group, particularly a chlorine or fluorine atom and especially a fluorine atom; and R^2 is a hydrogen or fluorine atom, especially a hydrogen atom.

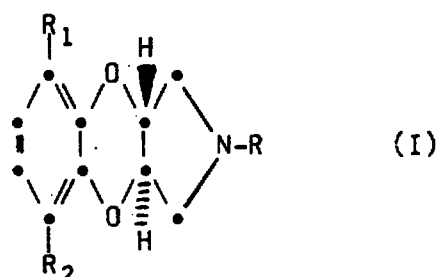
Important compounds are:-

- (±)-(trans)-5-methyl-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol;
- (±)-(trans)-5-chloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol; and
- (±)-(trans)-5,8-difluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol.

Particularly preferred compounds include:-

- (±)-(trans)-5-fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol.

The compounds of formula (III) are useful as intermediates in the preparation of benzodioxinopyrrole derivatives for example as described in UK Patent Application No. 8510449 (2157691A) which describes and claims compounds of the general formula (I)



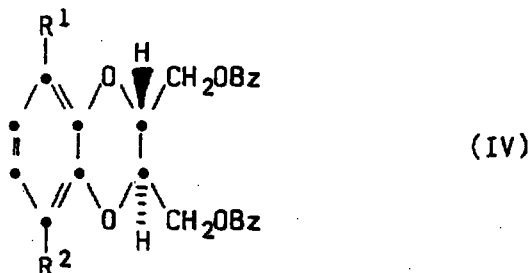
wherein

R is a hydrogen atom or a group selected from C_{1-6} alkyl (optionally substituted by C_{3-7} cycloalkyl), C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl, aralkyl (in which the alkyl moiety contains 1-5 carbon atoms) and -CHO;

R^1 and R^2 are as defined for compounds of formula (III) above and the physiologically acceptable salts and hydrates thereof.

The compounds of formula (I) may be prepared from compounds of formula (III) by the methods disclosed in UK Patent Application No. 8510449 (2157691A).

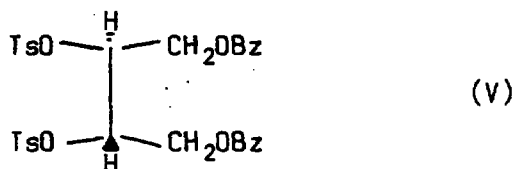
The compounds of formula (III) may be prepared by reduction of a corresponding dibenzyl ether of formula (IV):



(where Bz represents benzyl) using hydrogen and palladium on charcoal with a solvent e.g. ethanol.

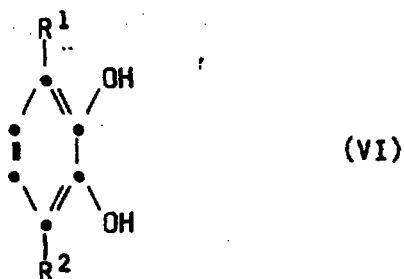
Alternatively, an ether of formula (IV) may be treated with a Lewis acid, such as aluminium chloride, in a solvent such as toluene to yield a diol of formula (III).

A compound of formula (IV) may be prepared by heating the bis-tosylate (V):



(where Ts represents $\text{CH}_3\text{-C}_6\text{H}_4\text{-SO}_2\text{-}$) with a catechol of formula

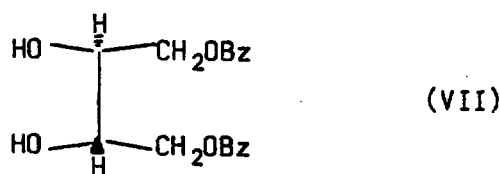
(VI)



in acetonitrile or dimethylformamide containing cesium fluoride or cesium carbonate.

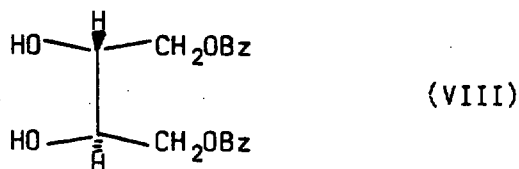
The intermediates of formula (VI) are known compounds and may be prepared by standard methods of benzene ring substitution (cf. for example Barton, Linnell & Senior, *Quat.J.Pharmacy & Pharmac.*, 1945, 18, 41-47 and Ladd & Weinstock, *J.Org.Chem.* 1981, 46, 203-206).

The bis-tosylate of formula (V) may be prepared by reaction of the known dibenzyl threitol of formula (VII)



with 4-toluenesulphonyl chloride in pyridine.

To obtain a specific enantiomer of the compounds formula (I), a diol of formula (III) having the required chirality is desirable. The required enantiomeric diol of formula (III) starting material can be prepared from the appropriate dibenzyl threitol of formula (VII) or (VIII)



as described above.

A specific enantiomer of general formula (III) may also be prepared by resolution of a mixture of enantiomers of formula (III) by conventional methods. Alternatively, resolution may be effected at any suitable intermediate stage.

It may be desirable to protect various reactive substituents in the starting materials for a particular reaction or sequence of reactions and subsequently to remove the protecting group after completion of the reaction or sequence. Such protection and subsequent deprotection may be particularly pertinent when R_1 and/or when R_2 is a

hydroxy or amino substituent. Conventional protection and deprotection procedures can be employed cf. "Protective Groups in Organic Chemistry" Ed. by J. F. W. McOmie (Plenum Press, 1973). Thus, for example, a primary amine may be protected by formation of a phthalimide group which may subsequently be cleaved by treatment with a hydrazine, e.g. hydrazine hydrate or a primary amine, for example methylamine, and a phenolic hydroxyl group may be protected as an ether e.g. a 2-tetrahydropyranyl or methyl ether, which may subsequently be cleaved by a Lewis acid such as boron tribromide or aqueous hydrogen bromide.

It will be appreciated that certain of the reactions described above are capable of affecting other groups in the starting material (e.g. nitro, cyano) which are desired in the end product; care must therefore be taken in accordance with conventional practice, either to use reaction conditions under which such groups remain substantially inert, or to perform the reaction as part of a sequence which avoids its use when such groups are present in the starting material.

The following examples illustrate the invention. All temperatures are in °C. In the following, ER represents ether, IMS represents industrial methylated spirits, MeOH represents methanol, EtOH represents ethanol and "light petroleum" refers to the fraction boiling at 60-80°. "Dried" refers to drying over magnesium sulphate unless otherwise stated.

Intermediate 1

(±)-(trans)-5-Fluoro-2,3-dihydro-2,3-bis[(phenylmethoxy)methyl]-1,4-benzodioxin

A mixture of 3-fluorobenzene-1,2-diol (5.12g) and (R*,R*)-(±)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate) (24.4g) was stirred with dimethylformamide (D.M.F.) (160ml) under a nitrogen stream for 45 min. Anhydrous cesium carbonate (13.0g) was added and the mixture was heated to 150° under reflux for 18 hours. The dark brown mixture was cooled to 30° and diluted with di-isopropyl ether (370ml) and water (320ml). The layers were separated and the aqueous layer was re-extracted with di-isopropyl ether (150ml then 100ml).

The extracts were sequentially washed with M hydrochloric acid (300ml), 30% aqueous sodium chloride (100ml) and were combined and evaporated in vacuo to a dark brown oil (12.6g) which was dissolved in light petroleum-dichloromethane (3:1) (40ml) and chromatographed over Sorbsil (126g) using light petroleum-dichloromethane mixtures of gradually increasing polarity. Combination of appropriate fractions and evaporation of the solvents gave the title compound as a yellow oil (7.0g), NMR τ (CDCl_3) 2.6-2.8 (10H, m, Ph), 3.18-3.38 (3H, m, 6-H, 7-H, 8-H), 5.32-5.58 (4H, m, CH_2 Ph), 5.64 (2H, m, 2-H, 3-H), 6.06-6.32 (4H, m, CH_2O).

Intermediates 2-8 (shown in Table 1) were prepared in a similar manner from the appropriate catechol and (R*,R*)-($\pm$)-1,4-bis(phenylmethoxy)-2,3-butanediol, bis(4-methylbenzenesulphonate).

TABLE 1

R ¹	R ²	Reaction Solvent	NMR τ (CDCl_3)						
			Ph	Ph CH_2	OCH_2	2-H,3-H	Aromatic	Me	OMe
CH_3 (2)	H	CH_3CN	2.68	5.41	6.21	5.6-5.8	3.29	7.78	-
CH_3O (3)	H	CH_3CN	2.7	5.2-5.8	5.8-6.5	5.2-5.8	3.0-3.6	-	6.13
Cl (4)	H	CH_3CN	2.66	5.3-5.55	6.0-6.3	5.55-5.7	3.0-3.3	-	-
NO_2 (5)	H	D.M.F.	2.6-2.8	5.3-5.54	6.05-6.27	5.6	2.51, 2.85 3.12	-	-
CH_3 (6)	CH_3	CH_3CN	2.6-2.8	5.38-5.44	6.1-6.3	5.67	3.39	7.82	-
Cl (7)	Cl	CH_3CN	2.73	5.43	6.18	5.6	3.17	-	-
F (8)	F	D.M.F.	2.5-2.8	5.37, 5.48	6.1, 6.2	5.58	3.39	-	-

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Example 1

(±)-(trans)-5-Chloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

A solution of (trans)-(±)-5-chloro-2,3-bis[(phenylmethoxy)methyl]-2,3-dihydro-1,4-benzodioxin (2.2g) (Intermediate 24) in trifluoroacetic acid (T.F.A.) (50mls) was hydrogenated over 10% palladium on carbon (0.22g). The solid was filtered off, washed with chloroform and the solution was evaporated to dryness to give the diol as a colourless liquid 1.2g, NMR τ (CDCl₃) 2.9-3.3 (3H, m, aromatic), 7.72 (2H, s, OH), 5.7-6.2 (6H, m, 2-H, 3-H, CH₂O).

Examples 2-6 (shown in Table 2) were prepared in a similar manner.

Example 2 (±)-(trans)-5-Methyl-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (from Intermediate 2)

Example 3 (±)-(trans)-5-Methoxy-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (from Intermediate 3)

Example 4 (±)-(trans)-5,8-Dimethyl-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (from Intermediate 6)

Example 5 (±)-(trans)-5,8-Dichloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (from Intermediate 7)

Example 6 (±)-(trans)-5,8-Difluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (from Intermediate 8).

Example 7

(±)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol

Intermediate 1 (7.0g) was dissolved in a mixture of toluene (70ml) and anisole (7.8ml) and the solution was stirred and cooled to -5° under a gentle stream of nitrogen. Anhydrous aluminium chloride (2.4g) was added and the temperature was maintained at 0-5° for 20 min. More anhydrous aluminium chloride (2.4g) was added and after 20 min. at 0-5° the mixture was allowed to warm to 20° with continued stirring. After 20 min. at 20°, it was cooled back to 0°, water (25ml) was added and after 5 min. stirring at 20°, the mixture was diluted with ethyl acetate (75ml) and the layers were separated. The aqueous (lower) layer was re-extracted with ethyl acetate (2x50ml) and

the organic solutions were washed with 30% aqueous sodium chloride (25ml) and were combined and concentrated in vacuo to 36g, giving a thick slurry of slightly purple crystals. After 30 min. at 20°, the crystals were harvested, washed with toluene (10ml), light petroleum (20ml) and di-isopropyl ether (20ml) and dried to give the title compound (2.93g) m.p. 122-124°. Concentration of the mother liquor gave a crude second crop of title compound (0.32g) which after chromatographic purification afforded a further quantity of pure title compound (0.24g) m.p. 121-123°. NMR τ (DMSO-d₆) 3.1-3.3 (3H, m, aromatic), 4.85-5.0 (2H, m, OH) 5.8-5.9 (2H, m, 2-H,3H) 6.1-6.4 (4H, m, CH₂O).

Example 8 ($\pm$)-(trans)-5-Nitro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol (shown in table 2) was prepared in a similar manner from intermediate 5.

TABLE 2

R ¹	R ²	Reaction Solvent	NMR (τ)						M.pt
			Solvent	Aromatic	CH ₂ OH	2-H,3-H	OH	Me	
CH ₃ (2)	H	EtOH	CDCl ₃	3.3	5.8-6.1	5.8-6.1	7.59	7.8	-
CH ₃ O (3)	H	EtOH	compound unstable, used without characterisation						
CH ₃ (4)	CH ₃	MeOH	DMSO-d ₆	3.42	6.3	5.9	5.04	7.89	77-9°
Cl (5)	Cl	TFA	DMSO-d ₆	3.02	6.0-6.4	5.75	4.8-5.5	-	172-5°
F (6)	F	EtOH	DMSO-d ₆	3.2	6.08-6.32	5.8	4.89	-	128-130°
NO ₂ (8)	H	Toluene	used without characterisation						

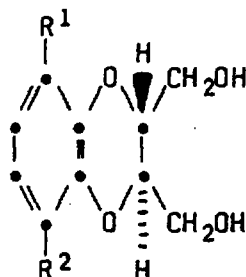
TABLE 2

R ¹	R ²	Reaction Solvent	NMR (τ)						M.pt
			Solvent	Aromatic	CH ₂ OH	2-H,3-H	OH	Me	
CH ₃ (2)	H	EtOH	CDCl ₃	3.3	5.8-6.1	5.8-6.1	7.59	7.8	-
CH ₃ O (3)	H	EtOH	compound unstable, used without characterisation						
CH ₃ (4)	CH ₃	MeOH	DMSO-d ₆	3.42	6.3	5.9	5.04	7.89	77-9 ⁰
Cl (5)	Cl	TFA	DMSO-d ₆	3.02	6.0-6.4	5.75	4.8-5.5	-	172-5 ⁰
F (6)	F	EtOH	DMSO-d ₆	3.2	6.08-6.32	5.8	4.89	-	128-130 ⁰
NO ₂ (8)	H	Toluene	used without characterisation						



Claims.

1. A compound of formula (III)



(III)

wherein

R^1 is a halogen atom or a group selected from C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, cyano, nitro and $-NR^3R^4$ where R^3 and R^4 is each a hydrogen atom or a C_{1-4} alkyl group; and

R^2 is a hydrogen atom or a substituent as defined above for R^1 .

2. A compound according to Claim 1 wherein R^1 is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group.

3. A compound according to Claim 1 or Claim 2 wherein R^2 is a hydrogen or fluorine atom.

4. A compound according to any one of Claims 1 to 3 wherein R^1 is a chlorine or fluorine atom or a methyl or methoxy group and R^2 is a hydrogen or fluorine atom.

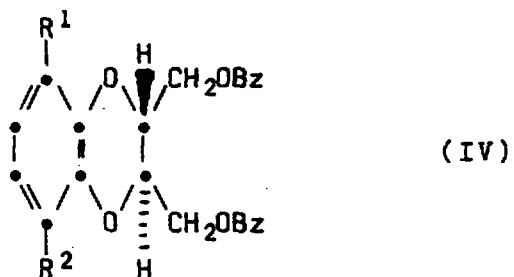
5. A compound according to any one of Claims 1 to 4 wherein R^1 represents a fluorine atom and R^2 represents a hydrogen atom.

6. A compound selected from (+)-(trans)-5-methyl-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol; (+)-(trans)-5-chloro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol; and (+)-(trans)-5,8-difluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol.

7. (+)-(trans)-5-Fluoro-2,3-dihydro-1,4-benzodioxin-2,3-dimethanol.



8. A process for the preparation of a compound of formula (III) as defined in Claim 1 which comprises debenzylation of a compound of formula (IV):-



wherein R^1 and R^2 are as defined in Claim 1 and Bz represents a benzyl group.