PATENT SPECIFICATION (11) 1 563 832

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(21) Application No. 16230/78 (22) Filed 15 Oct. 1976
(62) Divided out of No. 1 563 831
(31) Convention Application No. 7 531 566
(32) Filed 15 Oct. 1975 in
(33) France (FR)
(44) Complete Specification published 2 April 1980
(51) INT CL³ C07D 273/04
(52) Index at acceptance
C2C 1640 215 21X 220 226 227 22Y 255 25Y 281 305 30Y 311 313 314 31Y 321 32Y 332 338 339 342 345 349 34Y 351 352 360 361 36Y 373 37Y 386 388 43X 464 509 50Y 553 583 613 620 621 623 625 62X 652 660 661 681 694 699 758 761 802 80Y AA KT KV MM QT RC RN RV TX

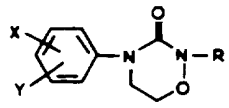
(19)

(54) NOVEL 1,2,4-OXADIAZINES

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7eme, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel 1,2,4-oxadiazines.

Our Co-pending Application No. 42880/76 (Serial No. 1,563,831) from which this Application has been divided, describes the following 1,2,4-oxadiazines of the general formula:

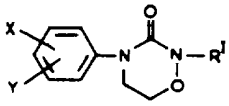


(I)

(in which X and Y, which may be the same or different, each represent a hydrogen atom, a halogen atom, a trifluoromethyl radical, a nitro radical or an alkylthio radical having from 1 to 4 carbon atoms, and R represents a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, a phenyl radical, a benzyl radical, or a hydroxymethyl radical), which have local action, anti-androgenic activity.

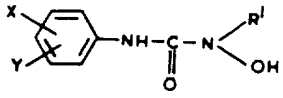
The 1,2,4-oxadiazines of general formula I may conveniently be prepared by the methods described below.

The compounds of general formula I*b*:



(Ib)

(in which X and Y are as defined hereinbefore and R′ represents an alkyl radical having from 1 to 6 carbon atoms, a phenyl radical or a benzyl radical, *with the proviso* that *either* at least one of X or Y represent an alkylthio radical having from 1 to 4 carbon atoms, *or* R′ represents a benzyl radical), may be prepared by a process in which an appropriate compound of general formula II*b*:



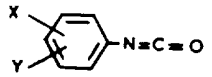
(II*b*)

(in which X, Y and R′ are as defined hereinbefore) is treated with a 1,2-dihaloethane, to obtain the corresponding product of formula I*b*. The preferred 1,2-dihaloethane for use in this process is 1,2-dichloroethane, but 1,2-dibromoethane can also be used.

The reaction is preferably performed in a polar solvent such as dimethylsulphoxide, but other polar solvents, such as dimethylformamide or hexamethylphosphorotriamide, may be employed.

The presence of a base in the reaction mixture is advantageous, and potassium carbonate is preferred, but other inorganic bases such as sodium carbonate or organic tertiary amines, such as triethylamine, may also be employed.

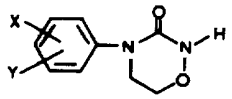
The products of formula II*b* may themselves be prepared by the action of a suitable alkyl hydroxylamine R'NHOH (in which R' is as defined hereinbefore) on an appropriate isocyanate of the general formula:



(III)

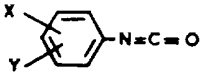
in which X and Y are as defined hereinbefore. The isocyanate III can be prepared, if necessary, by the action of phosgene on the corresponding aniline. This aniline may itself be prepared by any convenient method — for example an aniline having an alkylthio substituent on the phenyl nucleus may be prepared by reacting an appropriate mercaptan with a suitable chloro-substituted nitrobenzene, and then reducing the nitro function to form the desired aniline.

The products of the general formula:



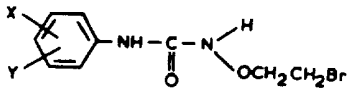
(I*c*)

(in which X and Y are as defined hereinbefore) — that is to say, the compounds of general formula I in which R represents a hydrogen atom — may be prepared by a process in which an appropriate compound of general formula:



(III)

is treated with O-(2-bromoethyl)-hydroxylamine, to obtain the corresponding addition product of general formula:



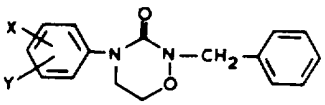
(IV)

which is then treated with a base to obtain, by cyclisation, the desired product of general formula I*c*.

The addition reaction is conveniently carried out in the presence of a base. The base is preferably an organic tertiary amine such as triethylamine, although other bases, such as sodium or potassium carbonate may be employed. The reaction medium is preferably a polar solvent, such as dimethyl formamide, but other polar solvents, such as dimethylsulphoxide or hexamethylphosphorotriamide, can also be used.

The cyclisation reaction is conveniently also performed in the presence of a base. The base is in this case preferably potassium carbonate, but sodium carbonate or a tertiary amine, such as triethylamine, may be used. The reaction medium is preferable a polar solvent such as acetone, but other solvents, such as methyl ethyl ketone or ethyl acetate may be used.

The products of general formula I*c* may also be prepared by a process characterised in that an appropriate compound of the general formula:

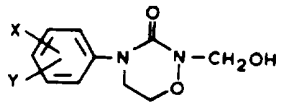


(I*d*)

(in which X and Y are as defined hereinbefore) — that is to say, a compound of general formula I in which R is a benzyl radical — is hydrogenolised, in the presence of a hydrogenolysis catalyst, to obtain the desired compound of general formula I*c*.

The hydrogenolysis catalyst is preferably palladium chloride on charcoal in acetic acid, but other catalysts, such as platinum, on other supports, such as barium sulphate, and in other solvents, such as methanol or ethanol may also be used.

The compounds of the general formula:

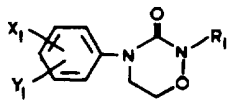


(Ie)

(in which X and Y are as defined hereinbefore) — that is to say, the compounds of general formula I in which R represents a hydroxymethyl radical — may be prepared by a process in which an appropriate compound of general formula Ic is treated with formaldehyde to obtain the desired compound of general formula Ie.

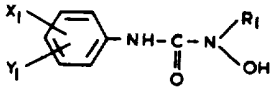
The above reaction is conveniently carried out in a solvent, dioxane being preferred but other solvents such as tetrahydrofuran may be used. It is desirable that a salt be present in the reaction mixture, and sodium acetate is the preferred salt, although other salts, such as sodium or potassium carbonate or bicarbonate may be used.

Finally, the compounds of the general formula:



(If)

(in which X_1 and Y_1, which may be the same or different, each represent a hydrogen atom, a halogen atom, a trifluoromethyl radical or a nitro radical, and R_1 represents an alkyl radical having from 1 to 6 carbon atoms or a phenyl radical) may be prepared by a process in which a 1,2-dihaloethane is reacted with an appropriate compound of general formula II:



(II)

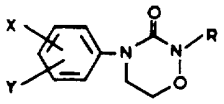
(in which X_1, Y_1 and R_1 are as just defined) to obtain the corresponding compound of general formula If. The preferred 1,2-dihaloethane is 1,2-dichloroethane, but 1,2-dibromoethane may be used.

The reaction is preferably carried out in a polar solvent and dimethylsulphoxide is preferred, although other polar solvents such as dimethylformamide or hexamethylphosphorotriamide may be used.

The presence of a base, preferably potassium carbonate, in the reaction mixture is advantageous although again sodium carbonate or a teritary amine such as triethylamine, may also be used.

Certain of the compounds of the general formula I are new, and this invention provides such compounds *per se*.

Thus, in one respect this invention provides the 1,2,4-oxadiazines of general formula:



(V)

wherein X and Y, which may be the same or different, each represent a hydrogen atom, a halogen atom, a trifluoromethyl radical, a nitro radical or an alkylthio radical having from 1 to 4 carbon atoms; and R represents a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, a phenyl radical, a benzyl radical, or a hydroxymethyl radical; *with the proviso* that *either* at least one of X and Y represents an alkylthio radical having from 1 to 4 carbon atoms *or* R represents a benzyl or hydroxymethyl radical.

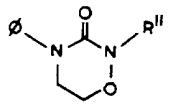
Preferred compounds of general formula V are:

2 - methyl - 3 - oxo - 4 - (4' - methylthio - 3' - trifluoromethyl - phenyl) - 5,6-dihydro - 1,2,4 - oxadiazine;

2 - benzyl - 3 - oxo - 4 - (3',4' - dichlorophenyl) - 5,6 - dihydro - 1,2,4 - oxadiazine; and

2 - hydroxymethyl - 3 - oxo - 4 - (3',4' - dichlorophenyl) - 5,6 - dihydro - 1,2,4-oxadiazine.

In another aspect, this invention also provides the 1,2,4-oxadiazines of general formula:



(VI)

where *either* R'' represents a methyl radical and Ø represents a phenyl group substituted:—

a) by a chlorine atom at the 2' and 4' positions or the 3' and 5' positions;

b) by a trifluoromethyl radical at the 3' position and a nitro radical or a chlorine atom at the 4' position; or

c) by a nitro radical at the 3' position

or R'' represents a phenyl radical, a hydrogen atom or an *n*-pentyl radical, and Ø represents a phenyl group substituted by a chlorine atom at the 3' and 4' positions.

The preferred compound of general formula VI is 2-methyl-3-oxo-4'-(3'-trifluoromethyl-4'-nitrophenyl)-5,6-dihydro-1,2,4-oxadiazine.

Of course, the compounds of general formula V and VI may be prepared by the methods described hereinbefore in relation to the compounds of general formula I.

As might be expected from the foregoing, the 1,2,4-oxadiazines of general formulae V and VI possess anti-androgenic activity.

Thus in a further aspect, this invention provides local-action, anti-androgenic compositions comprising, as active principle, one or more of the 1,2,4-oxadiazines of general formula V or general formula VI, together with a pharmaceutical vehicle.

The preferred composition of this invention contains 2-methyl-3-oxo-4-(3'-trifluoromethyl-4'-nitrophenyl)-5,6-dihydro-1,2,4-oxadiazine as active principle.

The term "pharmaceutical" is used herein in relation to the vehicle of the compositions of the invention to exclude any possibility that the nature of the vehicle, considered of course, in relation to the route by which the composition is intended to be administered, could be harmful. The choice of a suitable mode of presentation for the compositions, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations.

The compositions of this invention may be administered by the usual routes, but they are preferably administered by topical application, and in respect of this route of administration the pharmaceutical vehicle is conveniently the solid or liquid medium of a paste, lotion, salve, ointment, solution, emulsion, cream or unguent.

The pharmaceutical compositions are prepared according to the usual methods and the vehicle may incorporate excipients conventionally employed in these compositions, such as aqueous or non-aqueous vehicles, lactose, starch, fatty substances of animal or vegetable origin, paraffin derivatives and glycols. One or more of various wetting, dispersing or emulsifying agents, and/or preservatives may also be incorporated in the compositions.

Whilst the dosages of the pharmacologically active principle will depend on the subject treated and the complaint concerned, by way of general indication the dosage for an adult human may be from 1 to 3 applications per day of an ointment containing from 5 to 10% by weight of active principle.

The anti-androgenic activity of the 1,2,4-oxadiazines of general formulae V and VI may serve to inhibit the effects of the androgens on peripheral receptors without effecting the normal functioning of the hypophysis. Thus, the compounds can be used, preferably in the form of compositions of the invention, as medicaments in adolescents without causing a check in growth, and in adults without producing any effects of chemical castration. They may be particularly suitable for use as medicaments for the treatment of local complaints connected with hyper-androgenicity, such as hirsutism, acne, seborrhoea or hyperpilosity.

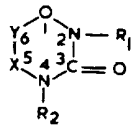
The 1,2,4-oxadiazines of general formula V and VI may also be useful in veterinary medicine.

Therefore in yet another aspect this invention provides a method for inhibiting the effects of androgens in non-human animals, in which there is administered to the animal to be treated, preferably by topical application, an effective amount of one or more of the compounds of general formula V or of general formula VI to achieve the desired anti-androgenic effect.

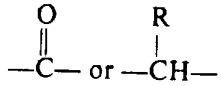
Preferably the compounds of general formulae V and VI are administered in the form of a composition as described herein.

It should be noted that some of the compounds of general formula VI fall within the scope of claim 1 of British Patent No. 1,272,558, which reads as follows:

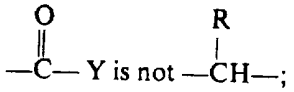
"An oxidiazine of the general formula:



in which each of X and Y, which may be the same or different, represents a



group, in which R represents hydrogen or a methyl group with the proviso that when X is



and each of R_1 and R_2, which may be the same or different represents a lower alkyl radical or a phenyl radical which is unsubstituted or substituted by one or more halogen atoms or nitro, alkyl, alkoxy or trifluoromethyl groups".

The aforesaid Patent No. 1,272,558 discloses that the compounds so claimed can be used as biocidal agents.

The following Examples and Formulations are given, though only by way of illustration, to show some preferred aspects of the invention.

Example 1.

2 - methyl - 4 - (2',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

A mixture of 11 g of N-methyl-N-hydroxy-N'-(2,4-dichlorophenyl) urea and 55 g of potassium carbonate in 66 cm^3 of dimethyl sulphoxide was agitated for 15 minutes at 20°C. 11 g of dichloroethane were introduced and the mixture was agitated for 16 hours at 20—25°C.

The mixture was poured into water, and the precipitate thus obtained was vacuum-filtered and taken up with ethyl acetate. The solution was dried and the solvent was distilled off under vacuum. The product was recrystallised from isopropyl ether and 8 g of the desired product were obtained. M.Pt. = 94—95°C.

Analysis: $C_{10}H_{10}Cl_2N_2O_2$

	C%	H%	Cl%	N%
Calculated:	46.0	3.86	27.16	10.73
Found:	46.0	3.9	27.1	10.6

Example 2.

2 - methyl - 4 - (3',5' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro- 1,2,4 - oxadiazine

Following the method of Example 1, starting with 16 g of N-methyl-N-hydroxy-N'-(3,5-dichlorophenyl)-urea, 80 g of potassium carbonate, 100 cm^3 of dimethylsulphoxide and 16 g of dichloroethane, 20 g of product were obtained. The product was chromatographed on silica gel with an 8:2 benzene:acetone mixture and 12 g of the desired product were obtained. M.Pt.=105—106°C.

Analysis: $C_{10}H_{10}Cl_2N_2O_2$

	C%	H%	Cl%	N%
Calculated:	46.0	3.86	27.16	10.73
Found:	45.8	3.9	27.0	10.5

The N-methyl-N-hydroxy-N'-(3,5-dichlorophenyl)-urea, used as a starting material for Example 2, was prepared as follows:

A mixture of 10 g of N-methylhydroxylamine hydrochloride in 100 cm³ of chloroform was agitated, cooled to 0°C, and 18 cm³ of triethylamine were introduced. 20 g of 3,5-dichlorophenylisocyanate in 30 cm³ of chloroform were introduced at 10—15°C, and the reaction mixture was then agitated for 5 hours at 20°C and distilled under vacuum. The residue was taken up with water and dried to give 22 g of the desired product. M.Pt=131—132°C.

Example 3.

2 - methyl - 4 - (4' - nitro - 3' - trifluoromethylphenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4-oxadiazine

A mixture of 15 g of N-methyl-N-hydroxy-N'-(3-trifluoromethyl-4-nitrophenyl)-urea, 75 g of potassium carbonate and 90 cm³ of dimethylsulphoxide were agitated at 20°C. 15 g of dichloroethane were then introduced and the mixture was agitated for 16 hours at 20°C. It was then poured into iced water, decanted, and the oil left was taken up with methylene chloride. The formed solution was washed with water, dried and the solvent was distilled off under reduced pressure. The product was purified by chromatography with an 8:2 benzene:acetone mixture and 8 g of the desired product were obtained: M.Pt.=104—105°C.

Analysis: $C_{11}H_{10}F_3N_3O_4$

Calculated:	C% 43.28	H% 3.30	N% 13.77	F% 18.67
Found:	43.5	3.4	13.8	18.5

The N-hydroxy-N-methyl-N'-(4-nitro-3-trifluoromethylphenyl)-urea used as a starting material in Example 3 was prepared as follows:

A mixture of 15 g of N-methylhydroxylamine hydrochloride in 100 cm³ of chloroform was agitated and cooled to 0°C, and 24 cm³ of triethylamine were gradually introduced over a period of 5 minutes, then 37.5 g of 3-trifluoromethyl-4-nitro-phenyl-isocyanate were introduced at 20—25°C. The mixture was agitated for 16 hours at 20°C before being poured into water to form crystals which were separated by vacuum-filtration and dried under vacuum.

The crude product obtained was dissolved in isopropyl ether. The solution was treated with active charcoal and the solvent was distilled under reduced pressure to give 20 g of the desired product. M.Pt.=129—130°C.

Example 4.

2 - phenyl - 4 - (3',4' - dichlorophenyl) - 3 - oxo - 5.6 - dihydro - 1,2,4 - oxadiazine

Using a method analogous to that described in Example 1, 28 g of the desired product were obtained starting from 40 g of N-(3',4'-dichlorophenyl)-N'-hydroxy-N'-phenyl-urea.

The product obtained had a melting point of 112—113°C,

Analysis: $C_{15}H_{12}Cl_2N_2O_2$

Calculated:	C% 55.74	H% 3.74	Cl% 21.94	N% 8.67
Found:	55.7	3.7	21.7	8.6

Example 5.

4 - (3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

Stage A: N - 2 - bromoethoxy - N' - (3,4 - dichloro phenyl) - urea

25 g of O-(2-bromoethyl)-hydroxylamine hydrobromide and 250 cm³ of dimethylformamide were mixed, 11 g of triethylamine were added dropwise, the whole mixture was agitated at 20—25°C, and the triethylamine hydrobromide thus formed was separated by vacuum-filtration. 18.8 g of 3,4-dichloro-phenyl-isocyanate were added to the filtrate in small portions. The mixture was agitated for 3 hours, poured into water, and the product extracted with methylene chloride and dried under vacuum. 11 g of the desired product were obtained. M.Pt.=126°C.

Stage B: 4 - (3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

A mixture of 40 g of product prepared in stage A and 27 g of potassium carbonate in 400 cm³ of acetone was agitated for 16 hours at 20—25°C, filtered and dried under vacuum. After crystallisation from ethyl acetate, 5 g of the desired product were obtained. M.Pt.=152°C.

Analysis: $C_9H_8Cl_2N_2O_2$

Calculated:	C% 43.75	H% 3.26	N% 11.34	Cl% 28.70
Found:	43.8	3.3	11.3	28.7

Example 6.

2 - methyl - 4 - (3' - nitrophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

Following the method previously described in Example 1, but starting with 30 g of N-methyl-N-hydroxy-N'-(3'-nitrophenyl)-urea, 10 g of the desired product were obtained after chromatography with a 7:3 benzene:acetone mixture. M.Pt.=107—108°C.

Analysis: $C_{10}H_{11}N_3O_4$

Calculated:	C% 50.63	H% 4.67	N% 17.71
Found:	50.6	4.6	17.8

Example 7.

2 - methyl - 4 - (4' - chloro - 3' - trifluoromethylphenyl) - 3 - oxo - 5,6 - dihydro-1,2,4 - oxadiazine

Following the method analogous to that of Example 1, 23 g of the desired product were obtained (M.Pt.=72—73°C) starting with 30 g of N-methyl-N-hydroxy-N'-(4'-chloro-3'-trifluoromethylphenyl)-urea.

Analysis: $C_{11}H_{10}ClF_3N_2O_2$

Calculated:	C% 44.83	H% 3.42	F% 19.34	N% 9.51
Found:	45.1	3.5	19.0	9.3

The N-methyl-N-hydroxy-N'-(4-chloro-3-trifluoromethylphenyl)-urea used as starting material in Example 7 was prepared as follows:

A mixture of 21 g of N-methyl-hydroxylamine hydrochloride in 200 cm³ of chloroform was agitated and cooled to 0°C. 33 cm³ of triethylamine, followed by 44.3 g of 4-chloro-3-trifluoromethylphenyl-isocyanate in 200 cm³ of chloroform were then introduced. The mixture was agitated for 16 hours at 20°C, washed with water and distilled under vacuum until the volume of the mixture reached 100 cm³. It was then ice-cooled, vacuum-filtered, washed with water and dried to give 37 g of the desired product. M.Pt.=114—115°C.

Example 8.

2 - methyl - 4 - (4' - methylthio - 3' - trifluoromethylphenyl) - 3 - oxo - 5,6 - dihydro-1,2,4 - oxadiazine

Following the method analogous to Example 1, 0.9 g of the desired product were obtained, starting from 2.5 g of N-(3-trifluoromethyl-4-methylthiophenyl)-N'-methyl-N'-hydroxy-urea and after purification by chromatography on silica with a 9:1 methylene chloride:ethyl acetate mixture. M.Pt.=60°C.

Analysis: $C_{12}H_{13}F_3N_2O_2S$

Calculated:	C% 47.05	H% 4.27	N% 9.14	F% 18.60	S% 10.46
Found:	46.9	4.4	9.2	18.4	10.6

The N - (3 - trifluoromethyl - 4 methylthiophenyl) - N' - methyl - N' - hydroxy-urea, used at the start of Example 8, was prepared as follows:

Stage A: 4-methylthio-3-trifluoromethyl-nitrobenzene

12.5 g of sodium were introduced into 500 cm³ of ethanol, then the solution was cooled to 10°C and 30 g of methyl mercaptan in 50 cm³ of ethanol were introduced. Then 63 g of 3-trifluoromethyl-4-chloro-nitrobenzene were introduced. The mixture was left for 17 hours at ambient temperature and the precipitate obtained was separated by vacuum-filtration, washed with water and dried to give 22 g of the required product. M.Pt.=158°C.

Stage B: 4-methylthio-3-trifluoromethylaniline

16.5 g of product prepared in stage A were introduced into a mixture containing 110 cm³ of ethanol, 100 cm³ of water and 1 cm³ of 22°Be hydrochloric acid. 47 g of pulverulent cast iron was then introduced. The mixture was refluxed for 6 hours and filtered whilst hot, washing with methylene chloride, and then concentrated under vacuum to give 6 g of the desired product $n_D^{22} = 1.553$.

Stage C: 4-methylthio-3-trifluoromethyl-phenylisocyanate

6 g of the product prepared in stage B were introduced into 60 cm³ of toluene and the mixture was poured onto 150 cm³ of toluene saturated with phosgene. This mixture was refluxed for 4 hours in an atmosphere of phosgene and left for 17 hours at ambient temperature. It was then evaporated to dryness under reduced pressure and the dry extract was taken up in isopropyl ether, being dissolved with heating and the formed solution was ice-cooled, vacuum-filtered and dried to give 3.4 g of the desired product. M.Pt.=40°C.

Stage D: N-(4-methylthio-3-trifluoromethyl-phenyl)-N'-methyl-N'-hydroxy-urea

A mixture of 1.6 g of N-methyl-hydroxylamine hydrochloride in 16 cm³ of chloroform and 2.4 cm³ of triethylamine was agitated 3.4 g of 4-methylthio 3-trifluoro-methyl phenyl isocyanate prepared in stage C in 34 cm³ of chloroform, were then added at 0°C. The mixture was left for 48 hours at ambient temperature and then evaporated to dryness under vacuum. The residue was taken up with ether and filtered to give 2.5 g of the desired product. M.Pt.=125°C.

Example 9.

2 - benzyl - 4 - (3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

15.5 g of N-hydroxy-N-benzyl-N'-(3',4'-dichlorophenyl)-urea and 77.5 g of potassium carbonate in 93 cm³ of dimethylsulphoxide were mixed. The mixture was agitated for half-an-hour, and the 15.5 g of dichloroethane were then added. This mixture was agitated for a further 16 hours at ambient temperature, then poured into water, and the product precipitated was separated by vacuum-filtration and washed with water. The product was dissolved in ethyl acetate and the solution was dried, filtered and concentrated to dryness to give 18 g of crystalline product. This was recrystallised from isopropyl ether to give 14.5 g of the desired product. M.Pt.=76°C.

Analysis: $C_{16}H_{14}Cl_2N_2O_2$

Calculated:	C% 56.99	H%	4.18	N%	8.30	Cl%	21.02
Found:	56.7		4.3		8.36		21.0

The N-hydroxy-N-benzyl-N'-(3',4'-dichlorophenyl)-urea, used as a starting material in Example 9, was prepared as follows:

Into a solution of 20.3 g of 3,4-dichlorophenylisocyanate in 400 cm³ of anhydrous benzene, 13.3 g of N-benzyl hydroxylamine in 260 cm³ of anhydrous benzene were introduced. The mixture was heated under reflux for half-an-hour and then agitated as it cooled. The crystalline product is separated by vacuum-filtration and then formed into a paste with benzene. 28.2 g of the desired product were thus obtained. M. Pt. = 157°C.

Example 10

2 - pentyl - 4 - (3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

Following the method analogous to Example 1, 13 g of the desired product were obtained from 20 g of N-pentyl-N-hydroxy-N'-(3',4'-dichlorophenyl)-urea. The final product was obtained by chromatography on alumina eluting with an 8:2 cyclohexane: ethyl-acetate mixture: M. Pt. = 40°C.

Analysis: $C_{14}H_{18}Cl_2N_2O_2$

Calculated:	C% 53.01	H% 5.72	Cl% 22.35	N% 8.83
Found:	52.7	5.7	22.6	8.7

The N-pentyl-N-hydroxy-N'-(3,4-dichlorophenyl)-urea used in Example 10 was prepared as follows:

29.2 g of 3,4-dichlorophenylisocyanate were placed in 500 cm³ of isopropyl ether, then 16 g of N-pentyl-hydroxylamine in 80 cm³ of isopropyl ether were introduced. The mixture was agitated for 16 hours, evaporated to dryness and the residue was taken up with petroleum ether. 45 g of the desired product were obtained. M.Pt.=88°C.

Example 11.

2 - hydroxymethyl - 4(3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4-oxadiazine

To a mixture of 30 g of 4-(3',4'-dichlorophenyl)-3-oxo-5,6-dihydro-1,2,4-

oxadiazine, prepared as in Example 5, and 30 g of anhydrous sodium acetate in 300 cm³ of dioxane, 300 cm³ of 30% aqueous solution of formaldehyde were added. The mixture was agitated for 2 hours at 20—25°C and then acidified. The product was extracted with ethyl acetate, the extract dried, and evaporated to dryness under vacuum. The residue was taken up with isopropyl ether, vacuum-filtered and dried. 30 g of the desired product were obtained. M.Pt.=134°C.

Analysis: $C_{10}H_{10}N_2Cl_2O_3$

Calculated:	C% 43.34	H% 3.64	N% 10.11	Cl% 25.59
Found:	43.4	3.8	10.0	25.3

Example 12.

4 - (3',4' - dichlorophenyl) - 3 - oxo - 5,6 - dihydro - 1,2,4 - oxadiazine

3.37 g of 2-benzyl-4-(3',4'-dichlorophenyl)-3-oxo-5,6-dihydro-1,2,4-oxadiazine, prepared as in Example 9, 70 cm³ of acetic acid, 680 mg of animal charcoal and 0.6 cm³ of palladium chloride in a 20% solution were mixed. The mixture was hydrogenated until absorption was complete, filtered, rinsing with acetic acid, and the filtrate obtained was poured into iced water. The formed product was extracted with methylene chloride and the extract was dried and then evaporated to dryness. The crystalline product was taken up with isopropyl ether. 2.37 g of the desired product were obtained. M.Pt.=152°C.

Formulation 1: Ointment

An ointment for topical application was prepared from the following:

2 - methyl - 4 - (3' - trifluoromethyl - 4' - nitrophenyl) - 3 - oxo-5,6 - dihydro - 1,2,4 - oxadiazine	100 mg
Excipient q.s.v.	1 g

Formulation 2: Dermatological composition

A composition for dermatological application was prepared from the following: (the percentages being by weight)

2 - methyl - 4 - (4' - nitro - 3' - trifluoromethylphenyl) - 3 - oxo-5,6 - dihydro - 1,2,4 - oxadiazine	10%
Propylene carbonate	30%
Eutanol	8%
Ethanol	52%

The following Pharmacological Studies are given to illustrate the anti-androgenic activity of some of the 1,2,4-oxadiazines of this invention.

A) Test for the inhibition of prostatic uptake of radioactivity following injection of a trace ^{3}H-testosterone dose in the castrated rat

Groups of 3 male Sprague-Dawley SPF rats, weighing 70 ±10 g, and castrated twenty-four hours previously, received 5 mg of the product to be tested by intraperitoneal injection. Sixteen hours later, the animals received 10 μCi/100 g of 1α^3-H-testosterone (26 ci/mmol) in alcoholic solution by intramuscular injection. The animals were sacrified one hour after this injection of tritiated hormone, and the ventral prostate gland was removed, rinsed in an isotonic solution of sodium chloride, weighed and then rendered soluble in 1 ml of Soluene R (Packard): a strong organic base in toluene. The radioactivity of the samples was measured after the addition of 15 ml of scintillating liquid.

The results obtained are expressed in terms of percentage inhibition of the uptake of testosterone, as follows:

Product of Example 1:	41% inhibition;
Product of Example 2:	61% inhibition;
Product of Example 3:	68% inhibition;
Product of Example 4:	50% inhibition;
Product of Example 5:	35% inhibition;
Product of Example 6:	37% inhibition;
Product of Example 7:	44% inhibition.

B) Local anti-androgenic activity: test on prostate organotypical culture

Rats were anaesthetised with ether 24 hours after castration. Their prostate glands were then removed asceptically and rinsed in a Tyrose solution at 0—4°C. The prostate tissue was divided into pieces measuring about 2 x 3 x 3 mm, by cutting the stroma separating the alveolar formations.

The pieces were then placed under cultivation, according to a slightly modified Lasnitzki method (J. Endocr. 1964, *30*, 325), in 2 ml of a modified synthetic medium 199 (Institut Pasteur) containing 100 IU/ml of penicillin G and 0.1 mg/ml of streptomycin. The explants obtained were cultivated a) in a medium without hormone (control); b) in a medium containing androgenic hormone (androstanolone); or c) in a medium containing a combination of androstanolone and the product to be tested.

1 μCi of ^{3}H-Thymidine (26 Ci/mmole) as 0.1 ml of aqueous solution was added to the medium at the start of each cultivation described above.

After 72 hours cultivation, the explants were rinsed and homogenised, using a Potter homogeniser, with a 0.25 M saccharose solution containing 1.5 mM of $CaCl_2$. The activity of the alkaline phosphatase in the supernatant liquid obtained by centrifuging the homogenate, was determined at pH 10.5, according to the method of Bessey and associates (J. Biol. Chem. *164*, 321).

In order to measure the uptake of the ^{3}H-Thymidine by desoxyribonucleic acid (DNA), the centrifugal deposit was taken up in 1 ml of N sodium hydroxide solution by contact therewith for one hour at 37°C, then washed 3 times with 4 ml of 5% trichloracetic acid. The radioactivity of the centrifuged deposit was measured in 0.5 ml of Soluene R.

The results obtained, expressed in terms of uptake (dpm) of ^{3}H-Thymidine in DNA per mg of tissue, are set out in Table I below.

The antagonism of the effects caused by the androstanolone (increase in the alkaline phosphatase activity and in the uptake of ^{3}H-Thymidine by DNA) demonstrate the local anti-androgenic activity of the product tested.

TABLE I

Cultivation	Concentration (M)	Alkaline phosphatase (m U/mg)	Uptake of ^{3}H-Thymidine (dpm/mg)
Control	—	52	208
Androstanolone	5×10^{-8}	108	724
Androstanolone + product of Example 3	5×10^{-8} / 10^{-6}	86	343

The product of Example 3 causes a 74% inhibition of the uptake of the tritiated hormone.

C) Anti-androgenic activity by topical administration on the costrovertebral sebaceous organ of a hamster

Principle — The syrian hamster (Mesocricetus auratus) has at the level of the dorsal skin two sebaceous formations, on both sides of the spinal column, the development of which is androgenodependent.

Local treatment of this organ by daily applications of a lotion containing an anti-androgen inhibits the increase in weight of the costovertebral organ of the female, which should result from the simultaneous administration of testosterone propionate by a sub-cutaneous route.

Observation of the untreated contralateral organ enables the "secondary" or non-local anti-androgenic effect of the product to be evaluated.

Method

Batches of 5 female hamsters weighing 110—130 g were subjected to daily treatment for 14 days.

The first batch received testosterone propionate dissolved in Sesame oil +5% benzyl alcohol, at a dosage of 0.2 ml per hamster per day (corresponding to 125 μg of testosterone propionate per day), by a sub-cutaneous route.

The second batch received, concurrently with the treatment described above, a local treatment of the right costovertebral organ with 0.02 ml of a solution containing (by weight): 25% of the product of Example 3; 30% of propylene carbonate; 37% of ethanol; and 8% of Eutanol. Each animal thus received 5 mg of the product of Example 3 per day.

Measurement:

The animals were sacrificed 24 hours after the last treatment, and the costovertebral organs were removed and weighed.

Results:

TABLE II

Treatment	Weight of costovertebral organs (in mg)	
	Left	Right (treated)
Control	9.6 ± 1.1	9.2 ± 1.2
Testosterone propionate	48.8 ± 2.7	43.3 ± 4.4
Testosterone propionate + Product of Example 3	41.8 ± 3.3	25.4 ± 2.4

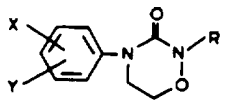
Local applications of the product of Example 3 to the right costovertrebral organ causes a non-significant variation in the increase in weight of the left costovertebral organ. However, the application to the right costovertebral organ causes an inhibition of the increase in weight of this organ of 52%.

Conclusion:

The product of Example 3 antagonises testosterone propionate locally without showing any "secondary" antiandrogenic effect.

WHAT WE CLAIM IS:—

1. The 1,2,4-oxadiazines of general formula:



(V)

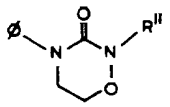
wherein X and Y, which may be the same or different, each represent a hydrogen atom, a halogen atom, a trifluoromethyl radical, a nitro radical or an alkylthio radical having from 1 to 4 carbon atoms; and R represents a hydrogen atom, an alkyl radical having from 1 to 6 carbon atoms, a phenyl radical, a benzyl radical, or a hydroxymethyl radical; *with the proviso* that *either* at least one of X and Y represents an alkylthio radical having from 1 to 4 carbon atoms *or* R represents a benzyl or hydroxymethyl radical.

2. 2 - methyl - 3 - oxo - 4 - (4' - methylthio - 3' - trifluoromethylphenyl) - 5,6-dihydro - 1,2,4 - oxadiazine.

3. 2 - benzyl - 3 - oxo - 4 - (3',4' - dichlorophenyl) - 5,6 - dihydro - 1,2,4-oxadiazine.

4. 2 - hydroxymethyl - 3 - oxo - 4 - (3',4' - dichlorophenyl) - 5,6 - dihydro-1,2,4 - oxadiazine.

5. The 1,2,4-oxadiazines of general formula:



(VI)

where *either* R'' represents a methyl radical and Ø represents a phenyl group substituted:—

a) by a chlorine atom at the 2' and 4' positions or the 3' and 5' positions;

b) by the trifluoromethyl radical at the 3' position and a nitro radical or a chlorine atom at the 4' position; or

c) by a nitro radical at the 3' position

or R'' represents a phenyl radical, a hydrogen atom or an *n*-pentyl radical and Ø represents a phenyl group substituted by a chlorine atom at the 3' and 4' positions.

6. 2 - methyl - 3 - oxo - 4 - (3' - trifluoromethyl - 4' - nitrophenyl) - 5,6-dihydro - 1,2,4 - oxadiazine.

7. A local-action anti-androgenic pharmaceutical composition containing, as active principle, one or more of the 1,2,4-oxadiazines of general formula V (as defined in claim 1) and/or of general formula VI (as defined in claim 5), together with a pharmaceutical vehicle.

8. A composition as claimed in claim 7, which contains 2-methyl-3-oxo-4-(3'-trifluoromethyl-4'-nitrophenyl)-5,6-dihydro-1,2,4-oxadiazine as active principle.

9. A composition as claimed in claim 7 or claim 8, in which the vehicle is the solid or liquid medium of a paste, lotion, salve, ointment, solution, emulsion, cream or unguent.

10. A composition as claimed in claim 9, being an ointment containing from 5 to 10% by weight of active principle.

11. A local-action anti-androgenic pharmaceutical composition substantially as described herein with reference to the Formulations.

12. A method for inhibiting the effects of androgens in non-human animals, in which there is administered to the animal to be treated an effective amount of one or more compounds of general formula V (as defined in claim 1) and/or general formula VI (as defined in claim 5) to achieve the desired anti-androgenic effect.

13. A method as claimed in claim 12, in which the compound(s) of general formula V and VI are administered by topical application to the animal to be treated.

14. A method as claimed in claim 12 or claim 13 in which the compound claimed in claim 6 is administered.

15. A method as claimed in any of claims 12 to 14, in which the compound(s) of general formula V or VI are administered in the form of a composition as claimed in any of claims 7 to 11.

16. A method as claimed in claim 15, in which the compound claimed in claim 6 is administered in the form of a composition as claimed in claim 8 or as claimed in claim 9 or 10 when claim 9 is dependent on claim 8.

SANDERSON & CO.,
97 High Street,
Colchester,
Essex CO1 1TH.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.