United States Patent [19]

Fauran et al.

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[54] **DERIVATIVES OF 5-HYDROXYMETHYL-3-SUBSTITUTED-2-OXAZOLIDINONES, PROCESS OF PREPARATION THEREOF AND THERAPEUTIC APPLICATION**

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[21] Appl. No.: **692,744**

[22] Filed: **Jun. 4, 1976**

Related U.S. Patent Documents

Reissue of:

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[2] **C07D 263/24**
[52] **U.S. Cl.** ..... **260/307 C;** 424/272
[58] **Field of Search** ..... 260/307 C

[56] **References Cited**

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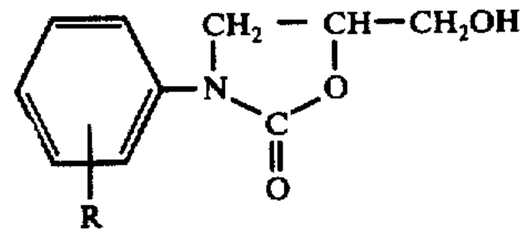
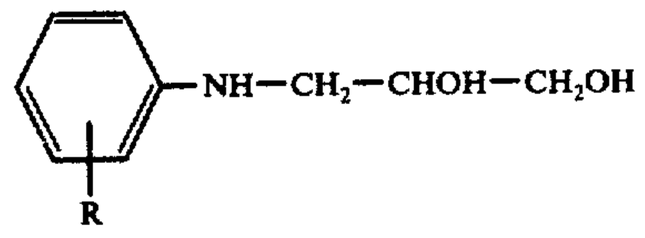
Primary Examiner—Raymond V. Rush
Attorney, Agent, or Firm—Blanchard, Flynn, Thiel, Boutell & Tanis

[57] **ABSTRACT**

Compounds of the formula



in which R is H, [Cl, F, CH_3 or CF_3] *m-F, p-F, o-F, p-Cl, p-CH_3, m-CH_3 or m-CF_3*. The compounds are prepared by cyclizing with ethyl carbonate, a compound of the formula



The compounds have anti-depressive, myorelaxing, tranquilizing, sedative, analgesic, anti-convulsive, anti-pyretic, anti-inflammatory and uricosuric activities.

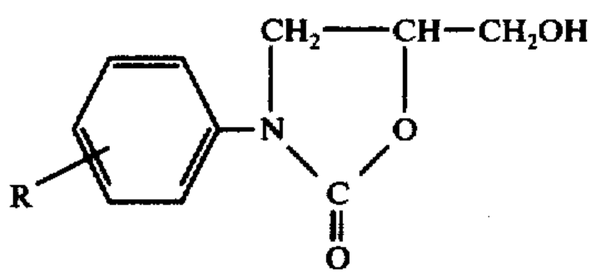
5 Claims, No Drawings

DERIVATIVES OF 5-HYDROXYMETHYL-3-SUBSTITUTED-2-OXAZOLIDINONES, PROCESS OF PREPARATION THEREOF AND THERAPEUTIC APPLICATION

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present invention concerns novel derivatives of 5-hydroxymethyl-3-substituted-2-oxazolidinones, their process of preparation and their therapeutic application.

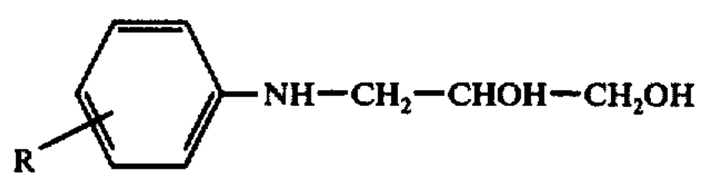
The compounds according to the present invention correspond to the general formula:



(I)

in which R represents [a hydrogen atom, a halogen atom, an alkyl radical having 1 to 4 carbon atoms or a trifluoromethyl radical] *m-F, p-F, o-F, p-Cl, p-CH_3, m-CH_3 or m-CF_3*.

The process for the preparation of the compounds according to the present invention comprises cyclising, by the action of ethyl carbonate, a 1-phenylamino-2,3-propanediol of the general formula:



(II)

in which R has the same significance as in Formula I.

The following preparation is given, by way of non-limitative example, to illustrate the present invention.

EXAMPLE

5-hydroxymethyl-3-(m-trifluoromethyl phenyl)-2-oxazolidinone. (Code No. 68121)

59 g. of 1-(m-trifluoromethyl phenylamino)-2,3-propanediol and 118 g. of ethyl carbonate are introduced into a distillation apparatus. The mixture is progressively heated to about 110° C. when dissolution is obtained. Then, 12 ml. of a 5% solution of sodium methylate in methanol is added thereto. The distillation of the ethanol formed during the course of the reaction is then observed. Upon completion thereof any excess ethyl carbonate is removed under reduced pressure and the residue obtained is crystallized in isopropyl ether.

Melting point = 80° C.

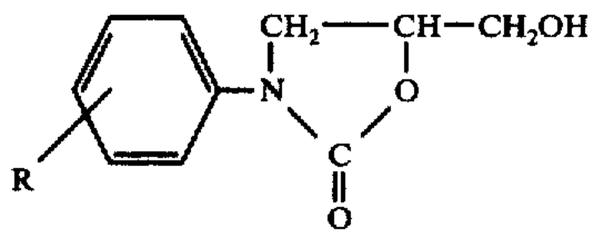
Yield = 80%

Empirical formula = $C_{11}H_{10}F_3NO_3$

Elementary analysis.—Calculated percent: C, 50.58; H, 3.86; N, 5.36. Found percent: C, 50,74; H, 3.76; N, 5.56.

The compounds listed in the following table have been prepared according to the process of the above example:

TABLE I



Code No.	R	Empirical formula	Mol wt.	M.P. ° C.	Yield, percent	Elementary analysis, percent Calculated C	H	N	Found C	H	N
67360	H	$C_{10}H_{11}NO_3$	192.20	129	75	62.16	5.74	7.25	62.20	5.87	7.40
68292	m-F	$C_{10}H_{10}FNO_3$	211.19	96	87	56.87	4.77	6.63	56.88	4.92	6.79
69155	p-F	$C_{10}H_{10}FNO_3$	211.19	116	68	56.87	4.77	6.63	56.97	4.77	6.83
69275	o-F	$C_{10}H_{10}FNO_3$	211.19	94	60	56.87	4.77	6.63	56.75	4.73	6.67
6922	p-Cl	$C_{10}H_{10}ClNO_3$	227.64	104	55	52.75	4.43	6.15	53.01	4.53	6.05
69204	p-CH_3	$C_{11}H_{13}NO_3$	207.22	145	66	63.75	6.32	6.76	63.93	6.10	6.88
69276	m-CH_3	$C_{11}H_{13}NO_3$	207.22	76	70	63.75	6.32	6.76	63.70	6.43	6.78
[9217	o-CH_3	$C_{11}H_{13}NO_3$	207.22	64	69	63.75	6.32	6.76	63.71	6.37	6.88]

The compounds of Formula I experimentally exert anti-depressive. myorelaxing, tranquillising, sedative, analgesic, anti-convulsive, anti-pyretic, anti-inflammatory and uricosuric activities. Moreover, their toxic effects on animals in the laboratory are little marked.

(1) Anti-depressive properties.—The compounds of Formula I are capable of opposing hypothermia and the ptosis provoked by reserpine in the rat and the mouse, as well as the ulcers provoked by reserpine in the rat. Moreover, they oppose the catalepsy provoked by prochlorperazine in the rat.

By way of example, several results obtained are listed in the following table:

TABLE II

Code No.	Hypothermia Dose[1]	Hypothermia Effect, ° C.	Ptosis Rat Dose[1]	Ptosis Rat Effect, percent	Ptosis Mouse Dose[1]	Ptosis Mouse Effect, percent	Ulcers Dose[1]	Ulcers Effect, percent
67360	200	−3.3	200	70	200	55	—	—
68121	100	−3.3	—	—	100	45	100	77
68292	100	−2.6	100	75	100	50	100	85
6922	—	—	100	45	100	55	—	—
69201	100	−2.9	—	—	—	—	—	—

TABLE II-continued

Code No.	Hypothermia Dose[1]	Hypothermia Effect, ° C.	Ptosis Rat Dose[1]	Ptosis Rat Effect, percent	Ptosis Mouse Dose[1]	Ptosis Mouse Effect, percent	Ulcers Dose[1]	Ulcers Effect, percent
69276	—	—	—	—	—	—	100	50

[1]Expressed in mg./kg./p.o.

(II) Myorelaxing properties.—The compounds of Formula I provoke in the mouse the loss of the righting reflex and inhibit the traction reflexes and the maintenance on a rotating rod.

By way of example, the results obtained with two compounds of Formula I are listed in the following table:

TABLE III

Code No.	Traction test, ED_{50}	Rotating rod test, ED_{50}
67360	300 mg./kg./p.o.	160 mg./kg./p.o.
68121		110 mg./kg./p.o.

(III) Tranquillising and sedative action.—These effects are shown by a diminution of exploration curiosity in the enclose of an actimetric cage and of escape in an open field. The compound of Formula I reduce the aggressiveness provoked in the passage of an electric current and lower the body temperature of animals. The narcotic effects of penthiobarbital are equally reinforced.

The results obtained with two compounds of Formula I are listed in the following table:

TABLE IV

Code No.	Actimetric cage Dose[1]	Actimetric cage Effect, percent	Evasion test Dose[1]	Evasion test Effect, percent	Potentialisation penthiobarbital Dose[1]	Potentialisation penthiobarbital Effect, percent
67360	90	50	200	70	200	80
68121	100	70	—	—	80	50

[1]Expressed in mg./kg./p.o.

(IV) Analgesic activity.—This activity is particularly pronounced against the painful stretching provoked in the mouse by the intraperitoneal administration of phenyl benzoquinone or acetic acid.

The results obtained with two compounds of Formula I are shown in the following table:

TABLE V

Code No.	Protection against phenylbenzoquinone Dose in mg./kg./p.o.	Protection against phenylbenzoquinone Effect, percent
67360	90	50
68121	45	50

(V) Anti-convulsive properties.—The compounds of Formula I exert in the mouse an antagonism against the lethal effects of cardiazol, strychnine and nicotine. They equally show activity against the tonic hyperextension of an excessive electric shock.

By way of example, the results obtained with several compounds of Formula I are listed in the following table:

TABLE VI

Code No.	Antagonism against Cardizol Dose[1]	Cardizol Effect, percent	Strychnine Dose[1]	Strychnine Effect, percent	Nicotine Dose[1]	Nicotine Effect, percent
67360	—	—	140	50	—	—
68121	120	50	100	50	100	80
68292	—	—	100	70	100	60
6922	—	—	100	100	—	—
69155	—	—	100	65	—	—

[1]Expressed in mg./kg./p.o.

(VI) Anti-pyretic action.—This action is manifested by a diminution of the experimental fever provoked by the administration of barm in the cat.

(VII) Anti-inflammatory effect.—The under-plantar oedema provoked in the rat by the administration of carraghenine is diminished by the compounds of the present invention.

(VIII) Uricosuric action.—After repeated oral administration in the rat, the compounds of Formula I provoke an augmentation of the urinary eliminations of uric acid.

In consequence of the results shown above, and the values appearing in the following table, the difference between the pharmacologically-active dose and the lethal dose is sufficiently great to enable the compounds of Formula I to be utilised in therapeutics.

TABLE VII

Code No.	LD50 P.O. (mouse,) mg./kg.
67360	>1600
68121	1400
68292	1500
6922	1050
69155	1200
69204	>4000
69276	1850

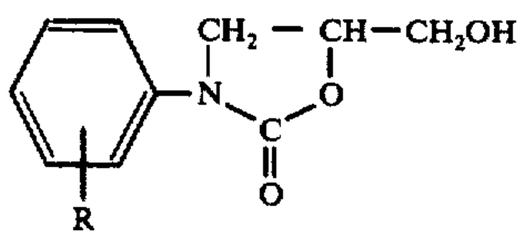
The compounds of Formula I are indicated in the case of depression and neurosis by depressive and anxious components. They equally possess a favourable effect against contractural and inflammatory pains, with or without hyperthermia.

They may be administered in the form of tablets and gelules containing 50 to 250 mg. of active ingredient.

Hence, according to the present invention there is also provided a therapeutic composition comprising a compound of Formula I together with a therapeutically-acceptable carrier.

What we claim is:

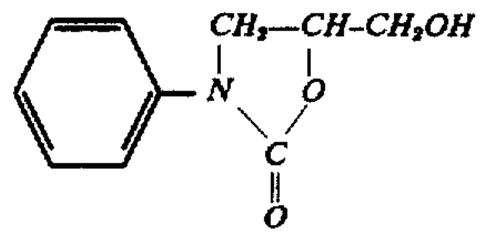
[1. A compound of the formula



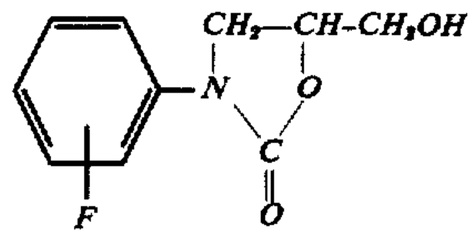
in which R is selected from the group consisting of hydrogen, chlorine, fluorine, methyl and trifluoromethyl.]

[2. A compound as claimed in claim 1, in which R is chlorine or fluorine.]

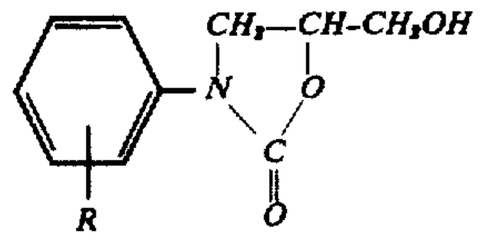
3. A compound of the formula



4. A compound of the formula

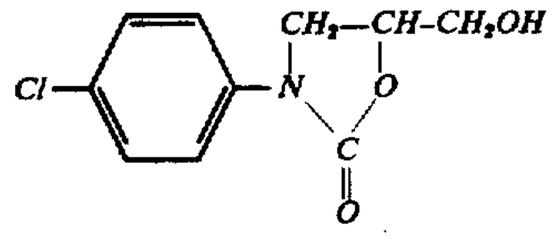


5. A compound of the formula

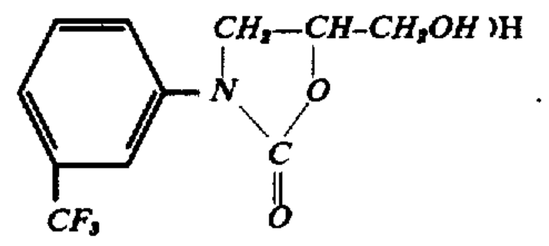


in which R is selected from the group consisting of p-methyl and m-methyl.

6. A compound of the formula



7. A compound of the formula



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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 29607

DATED : April 11, 1978

INVENTOR(S) : Claude P. Fauran et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 6, line 22; (line 1 of the formula) change

"CH-CH_2OH)H" to ---CH-CH_2OH---.

Signed and Sealed this

Fifteenth Day of *August 1978*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

DONALD W. BANNER
Commissioner of Patents and Trademarks