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Fauran et al.

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

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[73] Assignee: **Delalande S. A.,** Courbevoie, France

[21] Appl. No.: **663,563**

[22] Filed: **Mar. 3, 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;** C07D 295/20

[52] **U.S. Cl.** ..... **544/369;** 260/307 C; 424/250; 424/272

[58] **Field of Search** ..... 260/268 C, 307 C, 268

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,641,036 2/1972 Fauran et al. ..... 260/268 C

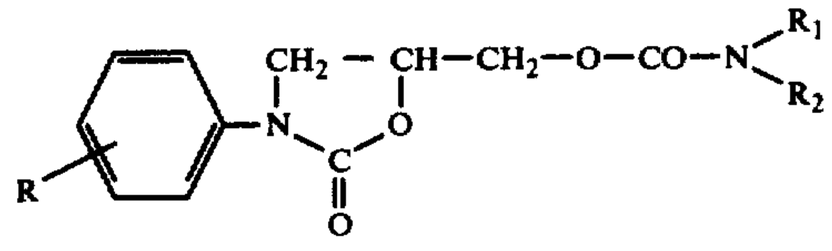
OTHER PUBLICATIONS

Morrison et al., "Organic Chemistry," Allyn and Bacon, 1959, p. 692.

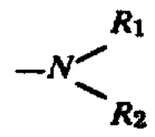
Primary Examiner—Raymond V. Rush
Attorney, Agent, or Firm—Blanchard, Flynn, Thiel, Boutell & Tanis

[57] **ABSTRACT**

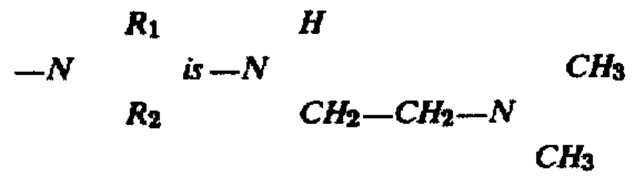
A compound of the formula



[in which R is H, halogen, alkyl having 1 to 4 carbon atoms or trifluoromethyl, and R_1 and R_2 each is H or dialkylaminoalkyl or together with N comprise methylpiperazino.] *in which (1)*

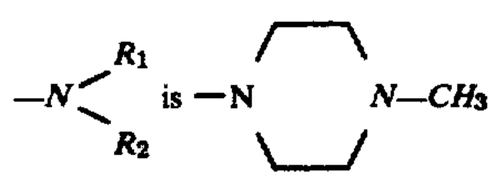


is —NH_2 and R is H, m-CH_3, o-CF_3, m-Cl, p-Cl, m-Br, m-F, p-F, o-F, p-CH_3, or m-CH_3, or



(2)

and R is H, m-CF_3 or m-F, or



(3)

and R is H, m-CF_3 or m-F.

The compound is prepared by treating the corresponding 5-hydroxymethyl compound with ammonia or an amine in the presence of phosgene.

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

1 Claim, No Drawings

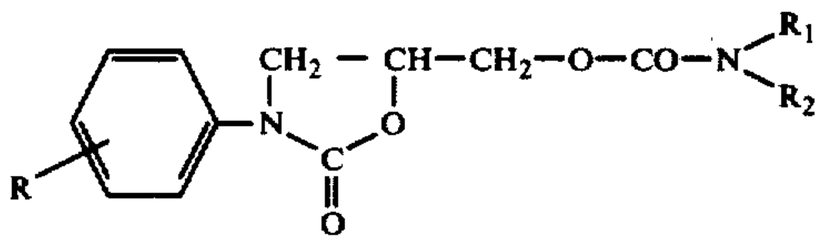
DERIVATIVES OF 5-CARBAMOYLOXYMETHYL-3-SUBSTITUTED-2-OXAZOLIDINONES, PROCESS OF PREPARATION THEREOF AND THERAPEUTIC APPLICATION

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.

This application is related to our application Ser. No. 20,020, filed Mar. 16, 1970 *now abandoned.*

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

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

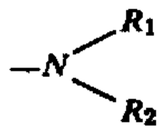


[in which:]

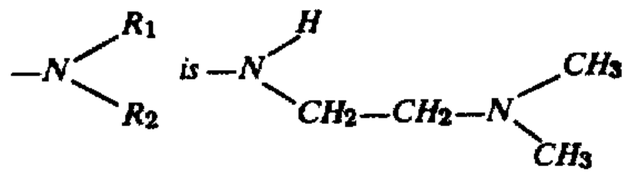
[R is a hydrogen atom, a halogen atom, an alkyl radical having 1 to 4 carbon atoms or a trifluoromethyl radical; and]

[R_1 and R_2 each represent a hydrogen atom or a dialkylaminoalkyl radical, or together with the nitrogen atom to which they are attached form a methylpiperazino radical.]

in which (1)

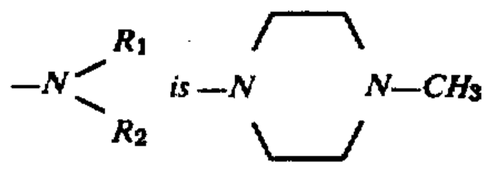


is —NH_2 and R is H, m-CF_3, o-CF_3, m-Cl, p-Cl, m-Br, m-F, p-F, o-F, p-CH_3 or m-CH_3, or



(2)

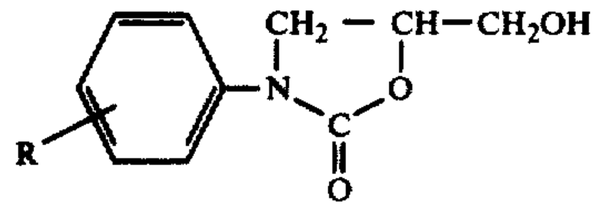
and R is H, m-CF_3 or m-F, or



(3)

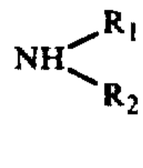
and R is H, m-CF_3 or m-F.

The process for the preparation of the compounds according to the present invention comprises treating an oxazolidinone of the general formula:



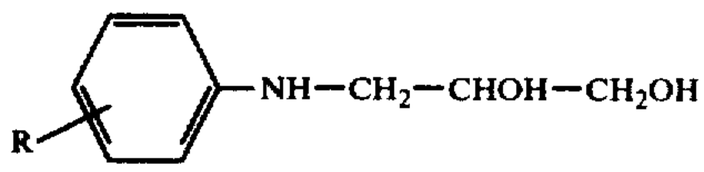
(II)

in which R has the same significance as in Formula I, with phosgene in the presence of ammonia or an amine of formula:



in which R_1 and R_2 have the same significance as in Formula I.

The oxazolidinone of Formula II is prepared by cyclising, by the action of ethyl carbonate, a 1-phenylamino-2,3-propanediol of the general formula:



(III)

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-carbamoyloxymethyl-3-m-trifluoromethylphenyl-2-oxazolidinone (Code No. 68175).

(1) Preparation of 5-hydroxymethyl-3-(m-trifluoromethylphenyl)-2-oxazolidinone (Code No. 68121).

59 g. of 1-(m-trifluoromethylphenylamino)-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 5% solution of sodium methylate in methanol is added thereto. The distillation of the ethanol formed in the course of the reaction is then observed. Upon completion thereof, any excess ethyl carbonate is removed under reduced pressure; the solid residue obtained is crystallised 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.

(2) Preparation of 5-carbamoyloxymethyl-3-m-trifluoromethyl phenyl)-2-oxazolidinone.

300 ml. of a 20% solution of phosgene in toluene is rapidly added to a solution of 100 g. of 5-hydroxymethyl-3-(m-trifluoromethylphenyl)-2-oxazolidinone in 250 ml. of benzene. 63 g. of N,N-diethylaniline is then slowly added thereto with agitation. The hydrochloride which precipitates is dried and the clear organic solution also obtained is treated with a rapid current of gaseous ammonia. The solution is then treated with water, decanted and the organic phase is concentrated. The solid residue obtained is crystallised in absolute ethanol.

Melting point = 123° C.

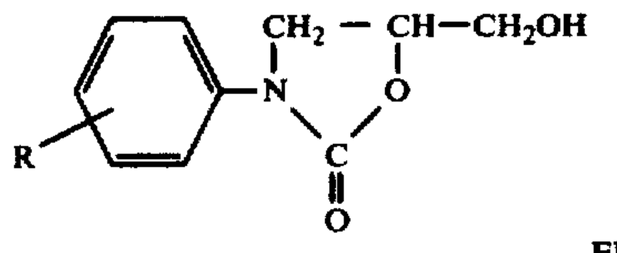
Yield = 50%.

Empirical formula = $C_{12}H_{11}F_3N_2O_4$.
Elementary analysis.—Calculated (percent): C, 47.37; H, 3.64; N, 9.21. Found (percent): C, 47.50; H, 3.86; N, 9.39.

The following Table I lists a certain number of intermediate compounds of Formula II prepared according to the first part of the above example, and Table II enumerates a certain number of compounds of Formula

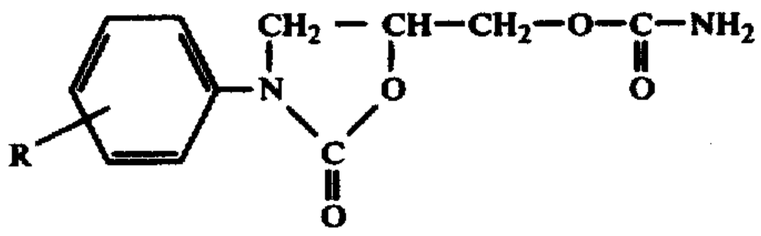
I prepared according to the second part of the above example.

TABLE I

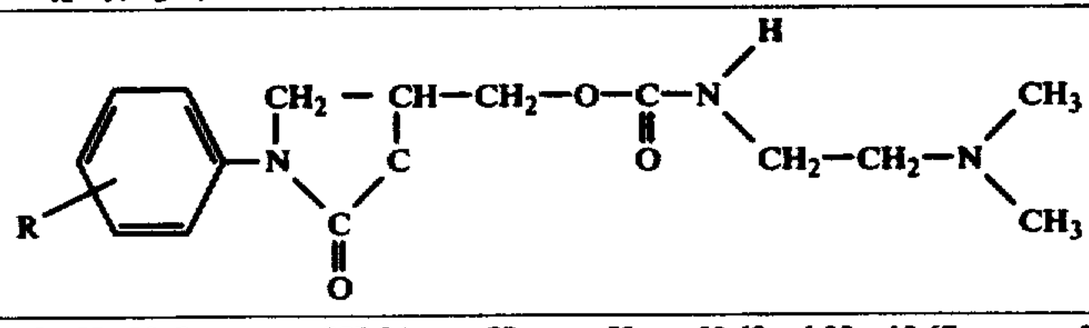


Code No.	R	Empirical formula	Mol. Wt.	M.P., °C.	Yield, percent	Elementary analysis Calculated C	H	N	Found C	H	N
67360	H	$C_{10}H_{11}NO_3$	193.20	129	75	62.16	5.74	7.25	63.20	5.87	7.40
68292	m.F.	$C_{10}H_{10}FNO_3$	211.19	96	87	56.87	4.77	6.63	56.88	4.92	6.79
69155	p.F.	$C_{10}H_{10}FNO_3$	211.19	116	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
[69217	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]

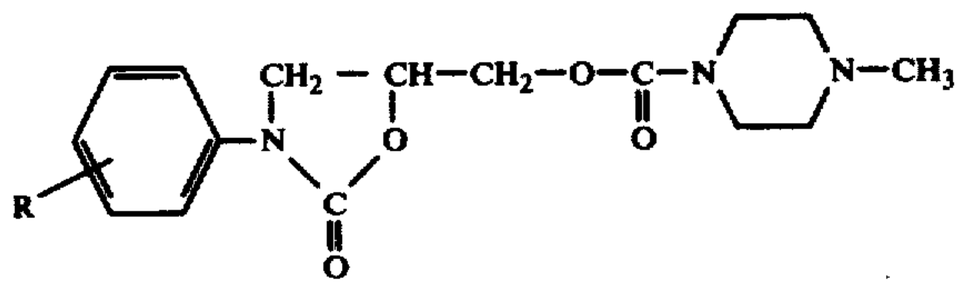
TABLE II



Code No.	R	Salt	Empirical formula	Mol. wt.	M.P., °C.	Yield, percent	Elementary analysis Calculated C	H	N	Cl	Found C	H	N	C_1
6878	H	—	$C_{11}H_{12}N_2O_4$	236.22	130	50	55.93	5.12	11.86	—	55.73	5.27	11.72	—
6978	o.CF_3	—	$C_{12}H_{11}F_3N_2O_4$	304.22	135	—	47.37	3.64	9.21	—	47.40	3.82	9.41	—
68291	m.Cl	—	$C_{11}H_{11}Cl\ N_2O_4$	270.67	102	40	48.81	4.10	10.35	—	48.80	3.88	10.22	—
6902	p.Cl	—	$C_{11}H_{11}Cl\ N_2O_4$	270.67	120	74	48.81	4.10	10.35	—	49.01	4.25	10.35	—
6945	m.Br	—	$C_{11}H_{11}Br\ N_2O_4$	315.12	132	50	41.92	3.52	8.89	—	42.01	3.72	9.06	—
6901	m.F.	—	$C_{11}H_{11}FN_2O_4$	254.21	110	70	51.97	4.36	11.02	—	51.93	4.44	11.13	—
69254	p.F.	—	$C_{11}H_{11}FN_2O_4$	254.21	140	60	51.97	4.36	11.02	—	52.07	4.34	10.82	—
69263	o.F.	—	$C_{11}H_{11}FN_2O_4$	251.21	80	40	51.97	4.36	11.02	—	52.16	4.34	10.94	—
69252	p.CH_3	—	$C_{12}H_{14}N_2O_4$	250.25	148	60	57.59	5.64	11,20	—	57.40	5.56	11.40	—
59237	m.CH_3	—	$C_{12}H_{14}N_2O_4$	250.25	105	70	57.59	5.64	11.20	—	57.40	5.44	11.13	—
[69239	O.CH_3	—	$C_{12}H_{14}N_2O_4$	250.25	126	35	57.59	5.64	11.20	—	57.79	5.72	11.26	—]



68327	H	—	$C_{15}H_{21}N_3O_4$	307.34	77	50	58.62	6.89	19.67	—	59.18	7.14	—	—
	—	HCl	$C_{15}H_{22}Cl\ N_3O_4$	313.80	168	90	52.40	6.45	12.22	—	52.32	6.68	12.43	—
6985	m.CF_1	—	$C_{16}H_{20}F_3N_2O_4$	375.34	78	40	51.20	5.37	11.20	—	51.18	5.52	11.40	—
69253	m.F	—	$C_{15}H_{20}FN_3O_4$	325.33	78	35	55.37	6.20	12.92	—	55.27	6.13	12.96	—
	—	HCl	$C_{15}H_{21}Cl\ FN_3O_4$	361.80	140	—	49.79	5.85	11.62	—	49.59	5.97	11.50	—



68306	H	—	$C_{16}H_{21}N_3O_4$	319.35	70	50	60.17	6.63	13.16	—	59.98	6.42	13.36	—
	—	HCl	$C_{16}H_{22}ClN_3O_4$	355.82	220	98	54.01	6.23	11.81	9.96	53.81	6.39	11.78	10.13
6089	m.CF_3	—	$C_{17}H_{20}F_3N_3O_4$	359.34	66	—	52.71	5.20	10.85	—	52.71	5.33	10.76	—
	—	Maleate	$C_{21}H_{24}F_3N_3O_4$	503.43	120	80	50.10	4.81	8.35	—	49.96	5.12	8.54	—
69235	m.F	—	$C_{16}H_{20}FN_3O_4$	337.34	75	31	56.96	5.98	12.46	—	56.77	5.79	12.58	—
	—	HCl	$C_{16}H_{21}FN_3O_4$	373.81	210	40	51.41	5.66	11.24	—	51.33	5.46	11.26	—

The following Table I lists a certain number of intermediate compounds of Formula II prepared according to the first part of the above example, and Table II enumerates a certain number of compounds of Formula

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.

(I)—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 art.

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

TABLE III

Code Number	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	Catalepsy Dose[1]	Catalepsy Effect, percent
6878	200	−3.4	200	53	200	55	200	60	—	—
68175	100	−4	—	—	100	85	—	—	—	—
6901	100	−2.4	100	50	100	60	100	55	200	2.9
68921	100	−3	100	60	100	50	—	—	—	—
6902	100	−2.7	100	45	100	50	—	—	—	—
6945	100	−2.5	100	55	100	45	—	—	—	—
69237	—	—	100	45	100	45	—	—	—	—
69252	—	—	100	50	100	50	—	—	—	—
6985	100	−2	—	—	—	—	—	—	—	—
69254	—	—	—	—	100	54	—	—	—	—
69263	—	—	—	—	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, for the compound No. 68175, the Ed_{50} in the traction test and also on the rotating rod is 130 mg./kg./P.O.

(III)—Tranquilising and sedative action

These effects are shown by a diminution of the exploration curosity in the enclosure of an actimetric cage and of escape in an open field. The compounds of Formula I reduce the aggresiveness provoked by 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 Number	Actimetric Dose[1]	Actimetric Effect, percent	Evasion test Dose[1]	Evasion test Effect, percent	Potentialisation of penthiobarbital Dose[1]	Potentialisation of penthiobarbital Effect, percent
6878	—	—	—	—	180	50

TABLE IV-continued

Code Number	Actimetric Dose[1]	Actimetric Effect, percent	Evasion test Dose[1]	Evasion test Effect, percent	Potentialisation of penthiobarbital Dose[1]	Potentialisation of penthiobarbital Effect, percent
68175	95	50	200	50	100	60

[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 Number	Protection against phenyl benzoquinone Dose in mg./kg./P.O.	Protection against phenyl benzoquinone Effect, percent
68175	62	60
6902	100	40

(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 Number	Antagonism against- Cardiazol Dose[1]	Cardiazol Effect, percent	Strychnine Dose[1]	Strychnine Effect, percent	Nicotine Dose[1]	Nicotine Effect, percent	Electric shock Dose[1]	Electric shock Effect, percent
6878	—	—	43	60	—	—	—	—
68175	90	50	20	50	100	90	100	80
6901	—	—	50	90	—	—	—	—
68291	—	—	100	100	100	90	—	—
6902	100	60	100	100	100	80	—	—
6945	—	—	100	100	100	75	—	—
[69239	—	—	—	—	100	40	—	—]
69237	—	—	100	80	—	—	—	—
69252	—	—	100	80	—	—	—	—
6985	—	—	—	—	100	70	—	—
69254	—	—	100	100	100	55	—	—
69263	—	—	100	90	—	—	—	—

[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-planatar oedema provoked in the rat by the administration of carraghenine is diminished by the compounds of the present invention.

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

TABLE VII

Code Number	Dose in mg./kg./P.O.	Reduction of the oedema, percent
68175	200	65
68291	100	40

(VIII)—Uricosuric action

After repeated oral administration in the rat, the compounds of Formula I provoke an augmentation of the urinary elimination 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 VIII

Code No.:	$L.D._{60}$ P.O. (mouse) Mg./kg.
6878	2,700
68175	2,100
6901	2,800
68291	>3,200
6902	1,500
6945	>3,200
[69239	>4,000]
69237	4,000
69252	>4,000
6985	1,350
69254	2,500
69263	3,400

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.

Several clinical tests to show the activity of the compounds of the present invention are given below:

EXAMPLE 1.—Compound No. 6901

1st observation: Mr. M. aged 46.

An intellectual, working in a scientific field of high precision, this man was affected by a spasmodic stiff neck due to anxious and hypochondriac grounds. He complained of cervical pains which prevented him from keeping his head upright and concentrating on his work. As a result, he became apathetic, depressed and profoundly restless about his future.

Compound No. 6901, in tablet form containing 100 mg. of active ingredient, was administered three times daily for 15 days. The cervical pains disappeared and he

was able to hold his head in an upright position. Besides this myorelaxant action, there is equally ascertained a complete sedation of his depressive anxieties.

2nd observation: Mr. Z. aged 55.

Professional and financial worries were provoked by a reactive neurosis, manifesting itself by an important irritability making family life very difficult. He complained as well as obstinate insomnia and particularly of diverse symptoms characterised by extra-systoles and occasionally of paroxysmic tachycardia, of globus epigastrus and of transient intestinal troubles. His hands trembled uncontrollably. He sometimes had autolysis notions.

Compound No. 6901 in tablet form containing 100 mg. of active ingredient, was administered daily for three weeks, brought the subject back to a normal state, his hands no longer trembled, his sleep returned to normal and he no longer suffered from cardiac or digestive troubles. His troubles disappeared and he was able to attack his commercial problems with courage.

EXAMPLE 2.—Compound No. 68175

Observation: Mrs. A. aged 48.

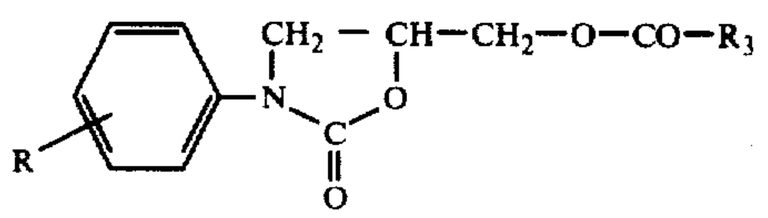
This woman was in a pre-menopause phase. For two years, she complained apart from menstrual troubles, exacerbated nervousness, interior tension sensations and trouble with precordial striction. She also complained of insomnia and a certain pain in the legs in the sleeping position.

Compound No. 68175, in tablet form containing 100 mg. of active ingredient, was administered 3 times a day for 12 days.

The sedative and tranquillising action is rapidly manifested, causing the irritability to disappear as well as the pain and insomnia. Simultaneously, the myorelaxant action was equally evidenced, as shown by the complete disappearance of the interior tension and the pain in the legs. Moreover, her sleep returned to normal.

What we claim is:

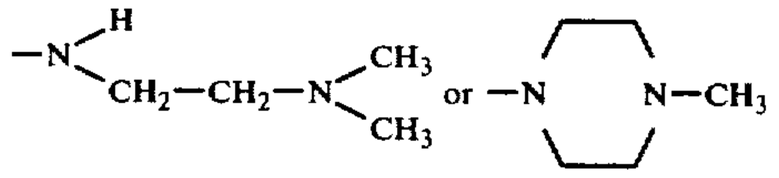
[1. A compound of the formula



in which

R is hydrogen, halogen, alkyl having 1 to 4 carbon atoms and trifluoromethyl, and

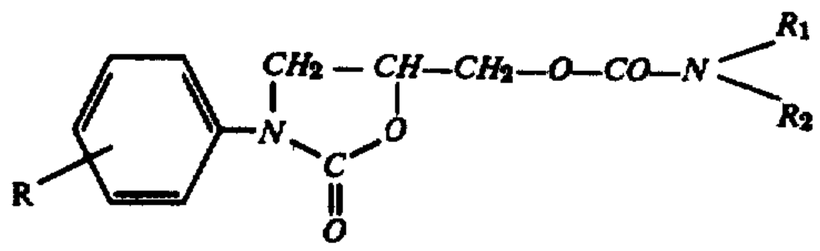
R_3 is $-H_2$,



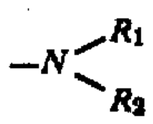
and the pharmaceutically acceptable acid addition salts thereof.]

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

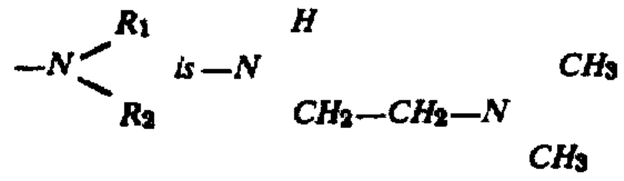
3. A compound of the formula



in which (1)

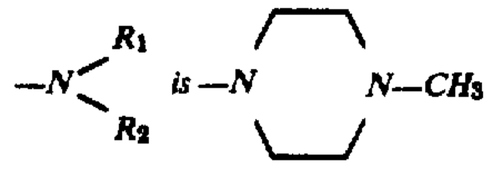


is —NH_2 and R is H, m-CF_3, o-CF_3, m-Cl, p-Cl, m-Br, m-F, p-F, o-F, p-CH_3 or m-CH_3, or



(2)

and R is H, m-CF_3 or m-F, or



(3)

and R is H, m-CF_3 or m-F, and the pharmaceutically acceptable acid addition salts thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

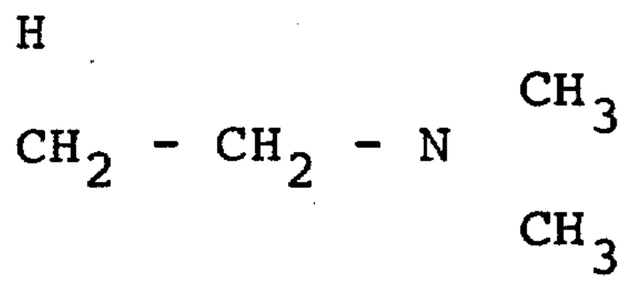
CERTIFICATE OF CORRECTION

PATENT NO. : RE 29 934

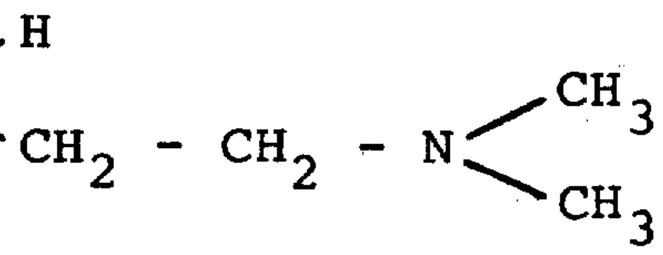
DATED : March 13, 1979

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 10, line 3; change " -N  (2) "

to

--- -N  (2)---.

Signed and Sealed this

Tenth **Day of** *July* **1979**

[SEAL]

Attest:

Attesting Officer

LUTRELLE F. PARKER

Acting Commissioner of Patents and Trademarks