



US00RE33907E

United States Patent [19]

[11] E

Patent Number: Re. 33,907**Davis**[45] **Reissued Date of Patent: Apr. 28, 1992**[54] **ANTI-SPASMODIC AGENTS HAVING A HETEROCYCLIC RING**[75] **Inventor: William M. Davis, Tucson, Ariz.**[73] **Assignee: United Pharmaceuticals, Inc., Tucson, Ariz.**[21] **Appl. No.: 394,274**[22] **Filed: Aug. 15, 1989****Related U.S. Patent Documents**

Reissue of:

[64] **Patent No.: 4,721,783**
Issued: Jan. 26, 1988
Appl. No.: 817,443
Filed: Jan. 9, 1986

U.S. Applications:

[63] **Continuation of Ser. No. 189,957, May 3, 1988, abandoned.**[51] **Int. Cl.⁵ C07D 207/09; C07D 249/08; C07D 265/30; C07D 279/12**[52] **U.S. Cl. 544/58.1; 544/158; 544/335; 544/398; 546/112; 546/124; 546/133; 546/239; 548/268.2; 548/341; 548/342; 548/378; 548/379; 548/572; 548/573; 548/268.6; 548/264.4**[58] **Field of Search 544/58.1, 158, 335, 544/398; 546/117, 124, 133, 239; 548/262, 341, 342, 378, 379, 572, 573**[56] **References Cited****U.S. PATENT DOCUMENTS**

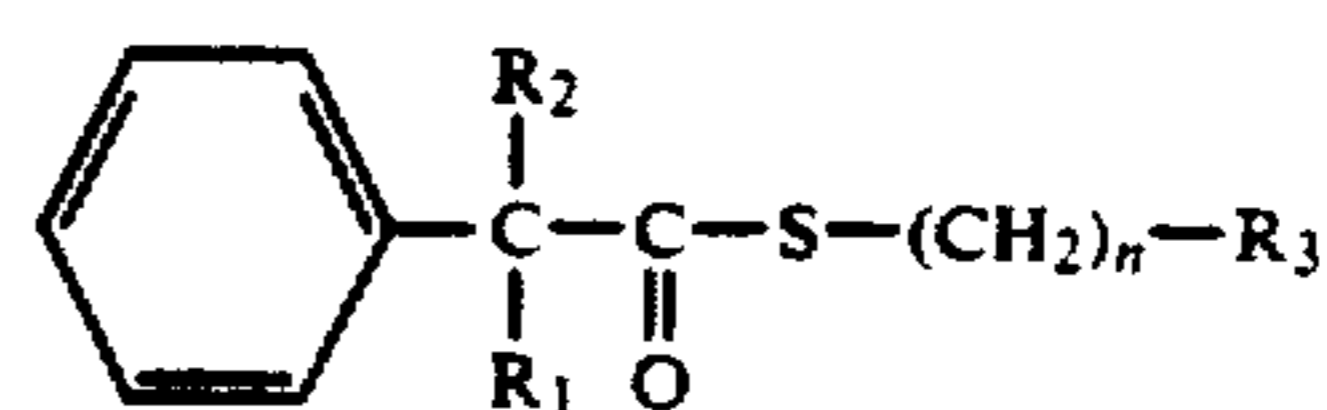
2,390,555 12/1945 Richardson 544/158
 4,432,977 2/1984 Davis 424/248.5

OTHER PUBLICATIONSBuehler et al., *Chemical Abstracts*, vol. 58 (1963) 12458b.Buehler et al., *Chemical Abstracts*, vol. 63 (1965) 10496g.Dupre et al., *Compte Rendu de la Societe de Biologie*, vol. 140 (1946) pp. 477-479.Clinton et al., *Journal of the American Chemical Society*, vol. 65 (1946) pp. 2076-2077.Tchouban et al., *Bulletin de la Societe Chimique* (1947) pp. 792-794.Liberman, *Farmakol. i Toksikol*, vol. 19, No. 6 (1956) pp. 10-17.Buehler et al., *Journal of Medicinal Chemistry*, vol. 6 (1963) pp. 230-233.Goodman et al., *The Pharmacological Basis of Therapeutics*, 6th Ed, MacMillan Publishing, New York, p. 132.Buehler et al., *Journal of Medicinal Chemistry*, vol. 8 (1965) pp. 643-647.

Primary Examiner—Richard L. Raymond
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[57] **ABSTRACT**

A new class of anti-spasmodic thioester compounds having a heterocyclic ring containing the nitrogen atom of a secondary or tertiary amine or a bicycloheterocyclic ring system containing the nitrogen atom of a secondary or tertiary amine. These compounds have the general formula I



wherein:

n is an integer from 0 to 2;

R₁ is aryl or cycloalkyl;R₂ is hydrogen or hydroxyl; and

R₃ is selected from the group consisting of heterocyclic containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and no other hetero atoms are present in the ring structure; heterocyclic containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and one or more hetero atoms selected from the group consisting of N, O and S are present in the ring structure; bicycloheterocyclic ring system containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and no other hetero atoms are present in the ring system; and bicycloheterocyclic ring system containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and one or more hetero atoms selected from the group consisting of N, O and S are present in the ring system.

4 Claims, No Drawings

ANTI-SPASMODIC AGENTS HAVING A HETEROCYCLIC RING

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 a continuation, of application Ser. No. 189,957, filed May 3, 1988, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to new pharmaceutical compounds having useful anti-spasmodic properties.

2. Description of the Prior Art

The purpose of an anti-spasmodic drug is to relieve spasms of the smooth muscles. Smooth muscles line most of the visceral organs. The peristalsis and muscular activity of the stomach, intestines, gall bladder, urinary bladder, lung, the uterus, and to a degree the heart are all largely controlled by smooth muscles. Smooth muscles are innervated by the autonomic nervous system. The autonomic nervous system consists of two antagonistic branches—the sympathetic branch and the parasympathetic branch. On all visceral organs except the heart the parasympathetic nerve impulses increase the irritability and tension of the smooth muscles; contrariwise, the sympathetic nerve impulses increase the tension and irritability of the muscles of the heart muscle and relax the smooth muscles of the other visceral organs.

A spasm in a smooth muscle may be due to one of two causes. Either the smooth muscle may be receiving exaggerated impulses from the autonomic nervous system which create violent contractions in the muscle, or the muscle may be intrinsically stimulated into a spasm (most likely from chemical changes in the surrounding tissue). A spasm due to exaggerated impulses from the parasympathetic branch of the autonomic nervous system may often be corrected by administering atropine (an active alkaloid of belladonna, which serves to break a connection between the parasympathetic nerve and the smooth muscle. This ability and effect of atropine is called a "neurotropic effect". A spasm intrinsic in the smooth muscle itself may often be corrected by papaverine (a derivative of opium which is classed as a narcotic). Papaverine has an ability to decrease intrinsically the contractility of smooth muscle; it has the ability to relax smooth muscles directly. This ability and effect of papaverine is called a "musculotropic effect."

In relieving spasms of smooth muscles generally, a musculotropic effect is acknowledged to be superior to a neurotropic effect. A neurotropic effect cannot relieve spasms intrinsic in the smooth muscle itself, while a musculotropic effect, by relaxing and decreasing the irritability and responsiveness of smooth muscle to stimulation from the autonomic nervous system, can help to relieve a smooth muscle spasm even when it is due to exaggerated impulses from the autonomic nervous system.

Atropine produces undesirable side-reactions which presents a clinical difficulty. Atropine when given in effective doses, serves to break or partly break all the parasympathetic nerve-smooth muscle connections throughout the body. Thus when atropine is given in sufficient dosage to relieve a spasm in a specific visceral

organ, such as a gastric or intestinal spasm (the spasm caused by exaggerated nerve impulses from the parasympathetic nervous system) undesirable side-actions due to the breaking of the parasympathetic nerve-muscle connections elsewhere in the body may occur. The most easily recognized of these undesirable side reactions are dilation of the pupil and dryness of the mouth, caused by the breaking of the parasympathetic connections to the iris and the saliva producing mechanism respectively.

Atropine is acknowledged to have also a musculotropic effect, but its neurotropic effect is so strong that atropine must be given in minute doses not exceeding (1/60 to 1/40 grain). A dosage of 1/6 to 1/40 of a grain is too small to permit a significant musculotropic effect and when larger doses are administered undesirable side reactions are encountered.

U.S. Pat. No. 2,390,555 discloses a class of compounds comprising di-N-substituted aminoethyl esters of diphenylthioacetic acid of the general formula $(C_6H_5)_2-CH-COS-CH_2CH_2-R$ in which R represents a disubstituted amino radical of either the diethyl-amino group, the morpholino group or the piperidino group with N as the point of attachment. This patent discloses that the thio analogs of certain disubstituted acetic acid esters of aminoalcohols have desirable anti-spasmodic properties. These compounds have proven to be very effective and are widely used as anti-spasmodics without encountering the undesirable side reactions due to excessive neurotropic effect.

U.S. Pat. No. 4,432,977 disclosed new uses, especially for the dilation of the smooth muscles of the upper urinary tract, of the compounds disclosed in U.S. Pat. No. 2,390,555.

In *Compte Rendu de la Societe de Biologie*, 140, pp 477-9, (1946) Dupre, Levy and Tchoubar disclose a series of compounds having the formula $C_6H_5(R)CH-C(O)-S-CH_2CH_2N(CH_2CH_3)_2$ where R is either a phenyl group, a propyl group, an isopropyl group, a butyl group or an isoamyl group. These compounds are all disclosed as being spasmolytic agents.

Compounds of the same general formula given above are disclosed by Tchoubar and Letellier-Dupre in *Bulletin de la Societe Chimique*, pp 792-4 (1947) wherein R was a phenyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isoamyl group or hydrogen.

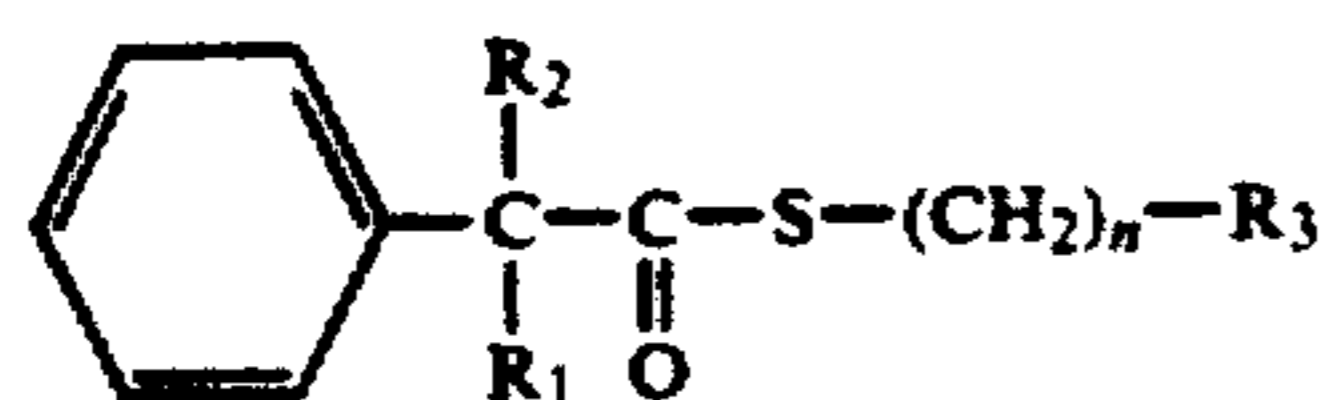
In *Farmakol. i. Toksikol.* pp 10-17 (1956), Liberman discloses a class of compounds having the general formula $(C_6H_5)_2CHCOSCH_2CH_2N-R_2$, wherein both R's are the same and are selected from methyl, ethyl, propyl and butyl groups; and a class of compounds having the general formula $(C_6H_5)-CH(C_6H_{11})-COSCH_2CH_2N-R_2$, wherein both R's are the same and are selected from methyl, ethyl, propyl and butyl groups.

C. A. Buehler et al. in the *Journal of Medicinal Chemistry*, 6, pp 230-3 (1963) disclose physiologically active compounds of the general formula $RR'C(OH)-COS(CH_2)_xNR_2 \cdot HCl$ wherein R and R' are aryl groups, x is 2 or 3, and R₂' is a methyl or ethyl group.

R. O. Clinton et al. in the *Journal of the American Chemical Society*, 68, pp 2076-7 (1946) disclose synthesis of a number of dialkyl aminoalkyl diarylthiolacetates including fluorene-9-carbothioic acid, S-[2-diethylaminoethyl]ester.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A new class of anti-spasmodic compounds is provided wherein a heterocyclic nitrogen ring is connected via carbon linkage to the main chain. The new compounds are those having the general formula I



wherein:

n is an integer from 0 to 2;

R₁ is aryl or cycloalkyl;

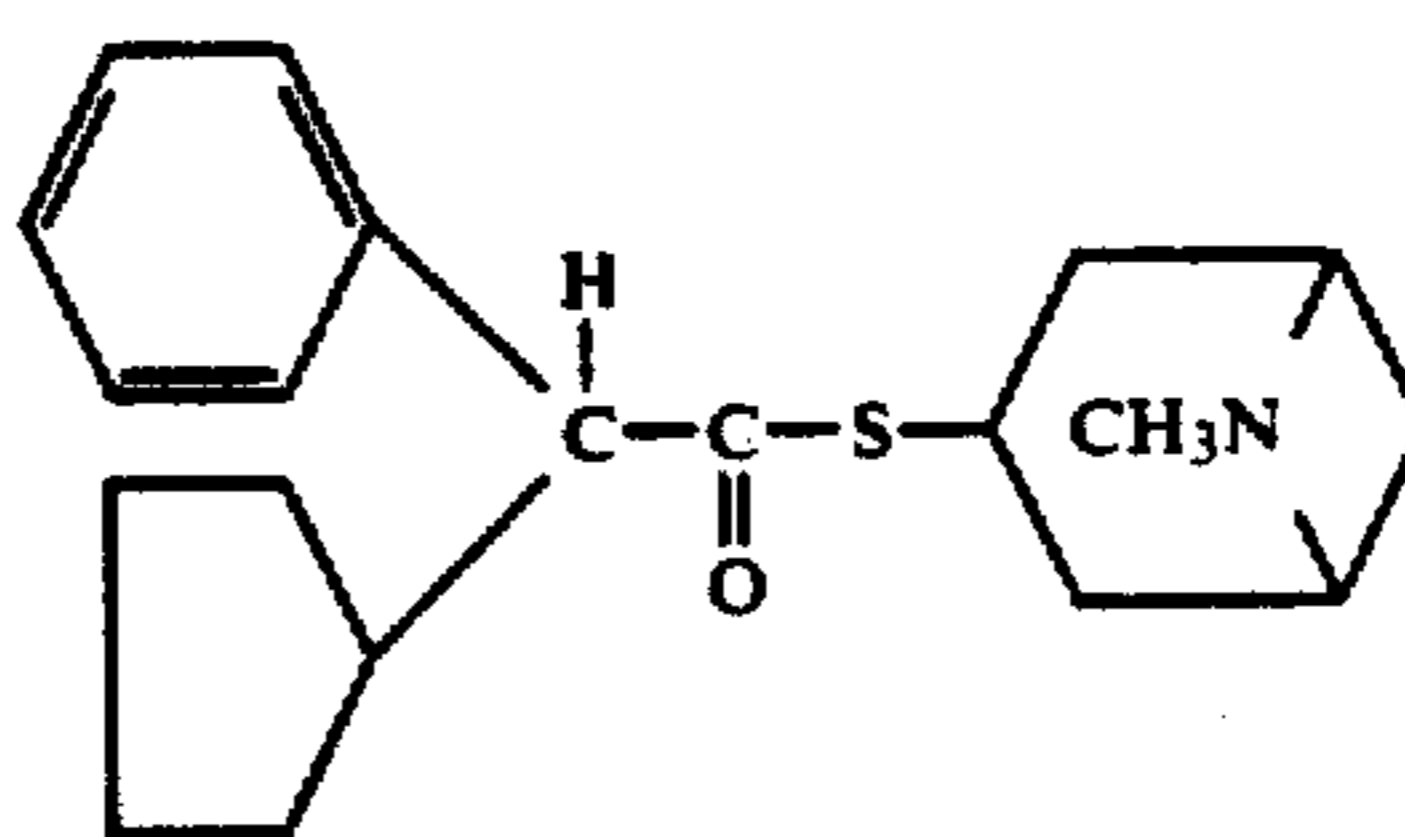
R₂ is hydrogen or hydroxyl; and

R₃ is selected from the group consisting of heterocyclic containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and no other hetero atoms are present in the ring structure; heterocyclic containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and one or more hetero atoms selected from the group consisting of N, O and S are present in the ring structure; bicycloheterocyclic ring system containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and no other hetero atoms are present in the ring system; and bicycloheterocyclic ring system containing the nitrogen atom of a secondary or tertiary amine to which an alkyl group having from 0 to 3 carbon atoms is bonded and one or more hetero atoms selected from the group consisting of N, O and S are present in the ring system.

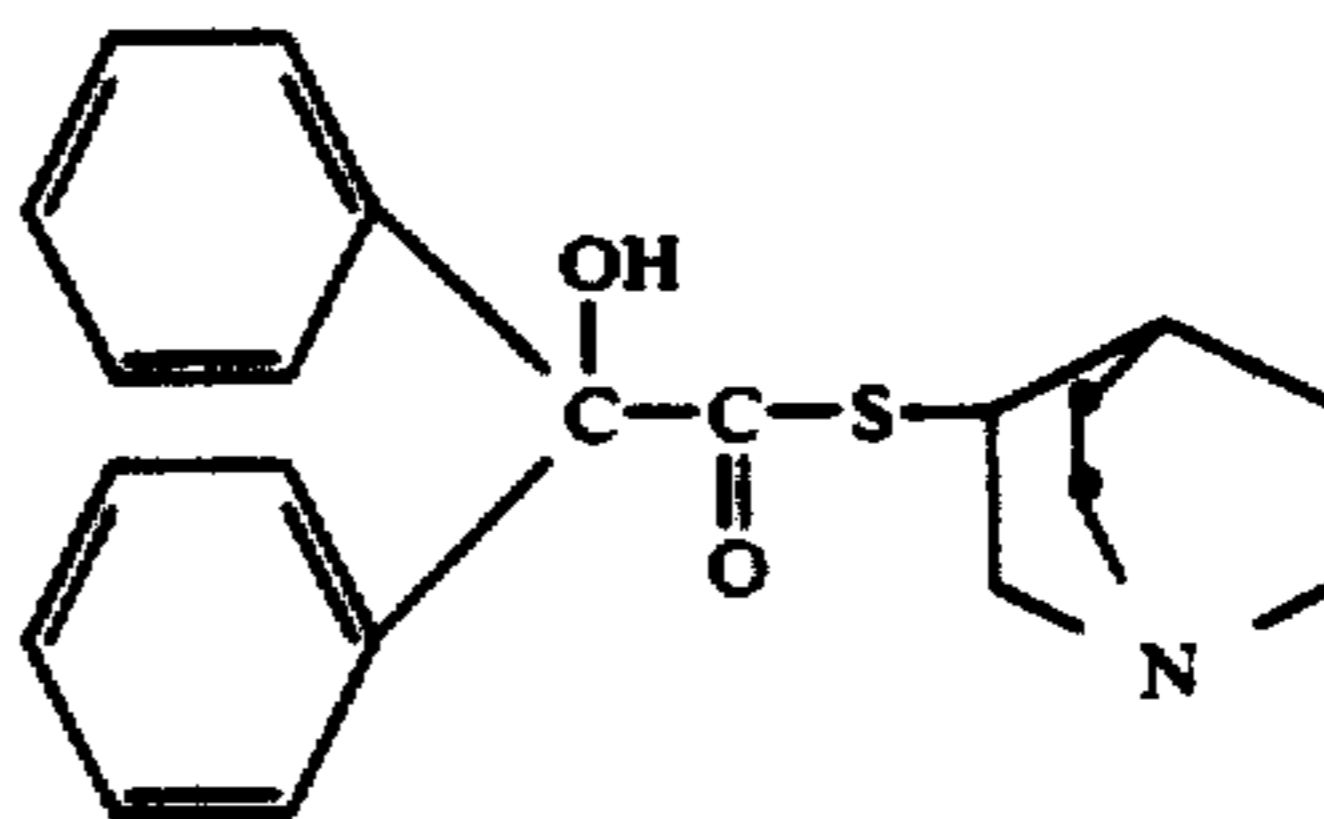
The present invention also comprises methods of administering the above-described compounds for, but not limited to, the treatment of patients suffering from spasms in the upper and lower gastrointestinal tract, spasm associated with the gall bladder and common bile duct, as well as diarrhea, the irritable bowel syndrome, ureterspasm, bladder irritation, asthma, emphysema, and ophthalmologic injuries.

Representative heterocyclic rings include, but are not limited to, the following: 1-methyl-imidazoliny, 1-ethyl-imidazoliny, 1-n-propylimidazoliny, 1-iso-propyl-imidazoliny, 1-methyl-imidazolyl, 1-ethyl-imidazolyl, 1-n-propyl-imidazolyl, 1-iso-propylimidazolyl, 1-methyl-morpholiny, 1-ethyl-morpholiny, 1-n-propyl-morpholiny, 1-iso-propyl-morpholiny, 1-methyl-piperaziny, 1-ethyl-piperaziny, 1-n-propyl-piperaziny, 1-iso-propyl-piperaziny, 1-methyl-piperidiny, 1-ethyl-piperidiny, 1-n-propyl-piperidiny, 1-iso-propyl-piperidiny, 1-methyl-pyrazolyl, 1-ethyl-pyrazolyl, 1-n-propyl-pyrazolyl, 1-iso-propyl-pyrazolyl, 1-methyl-pyrrolidiny, 1-ethylpyrrolidiny, 1-n-propyl-pyrrolidiny, 1-iso-propyl-pyrrolidiny, 1-methyl-3-pyrroliny, 1-ethyl-3-pyrroliny, 1-n-propyl-3-pyrroliny, 1-iso-propyl-3-pyrroliny, 1-methyl-thiomorpholiny, 1-ethyl-thiomorpholiny, 1-n-propyl-thiomorpholiny, 1-isopropyl-thiomorpholiny, 4-methyl-1,2,4-triazolyl, 4-ethyl-1,2,4-triazolyl, 4-n-propyl-1,2,4-triazolyl, 4-iso-propyl-1,2,4-triazolyl.

Representative compounds of this invention which contain bicycloheterocyclic ring systems include, but are not limited to, the following:

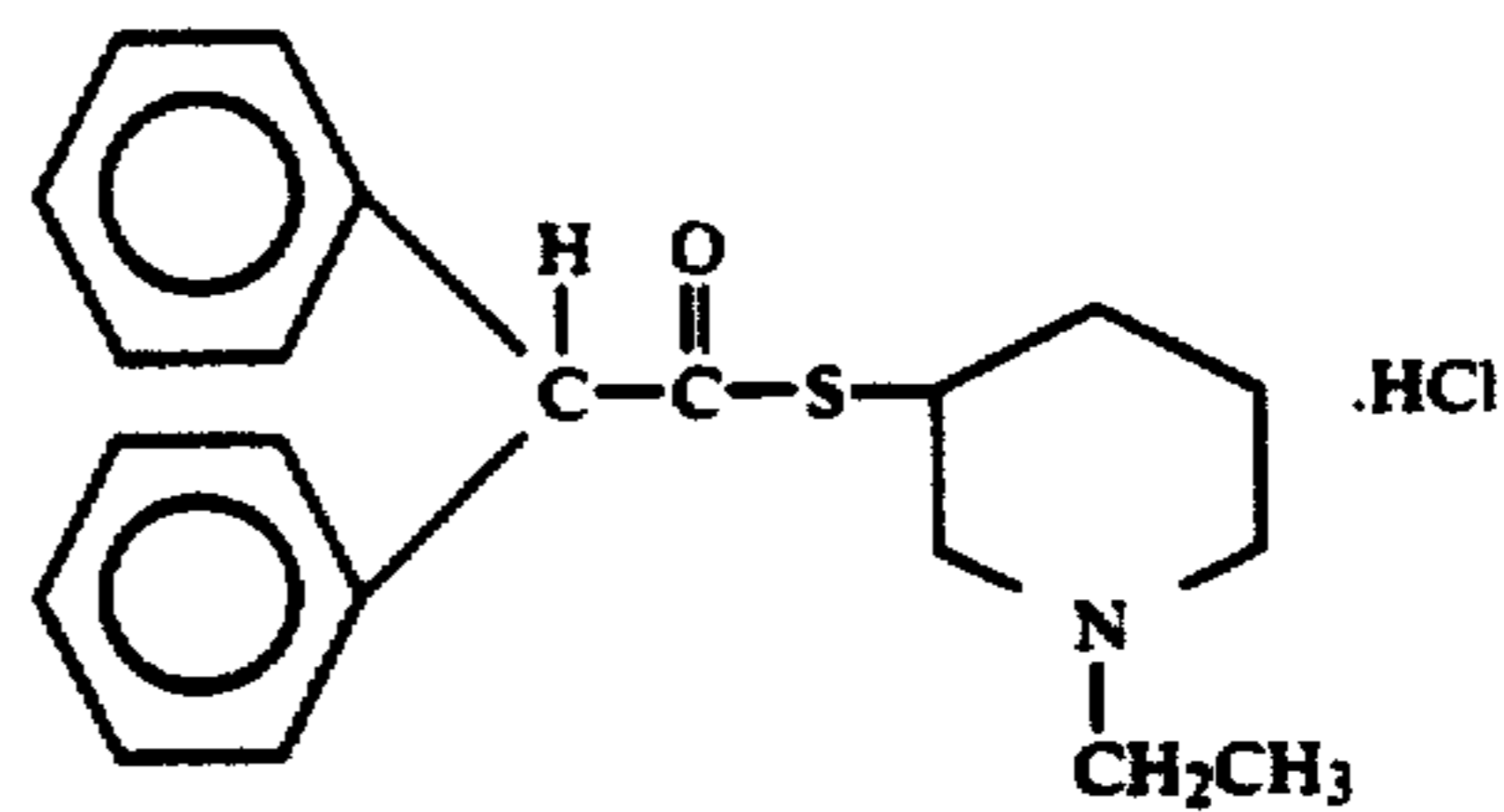
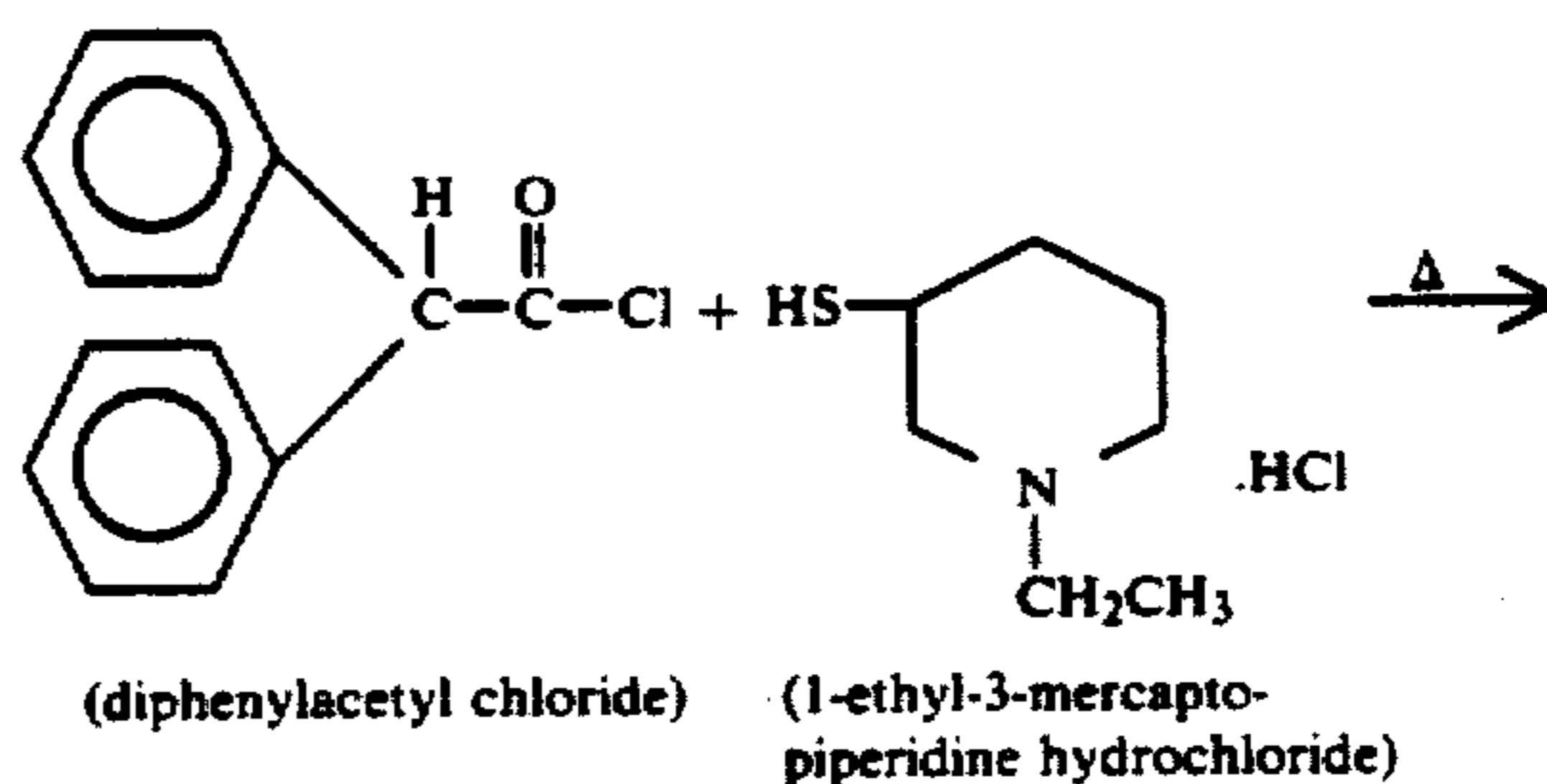


Cyclopentaneacetic acid, alpha-phenylthio, S-(3-alpha-tropanyl)ester



Benzilic acid, thio, S-(3-quinuclidinyl)ester

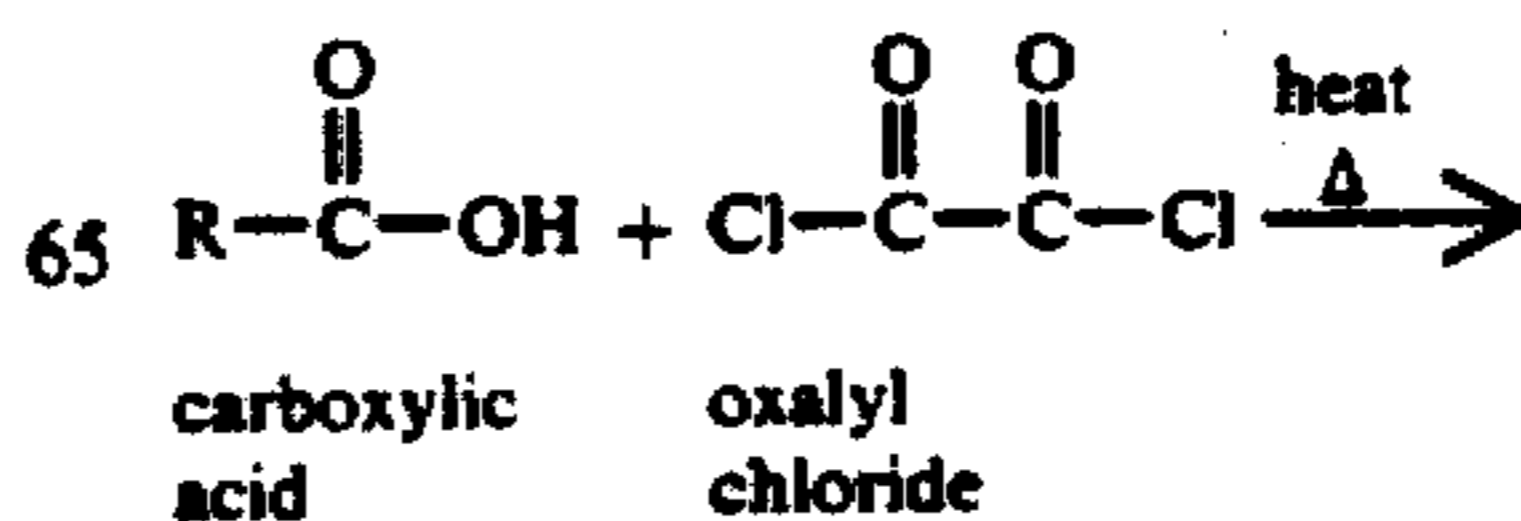
The general reaction in the synthesis of the antispasmodic compounds described in the following examples of the present invention involves the nucleophilic substitution of, for instance, diphenylacetyl chloride with certain heterocyclic thiol compounds. This reaction may be illustrated in the following scheme:



(3-diphenylthioacetyl-1-ethyl-piperidine hydrochloride)

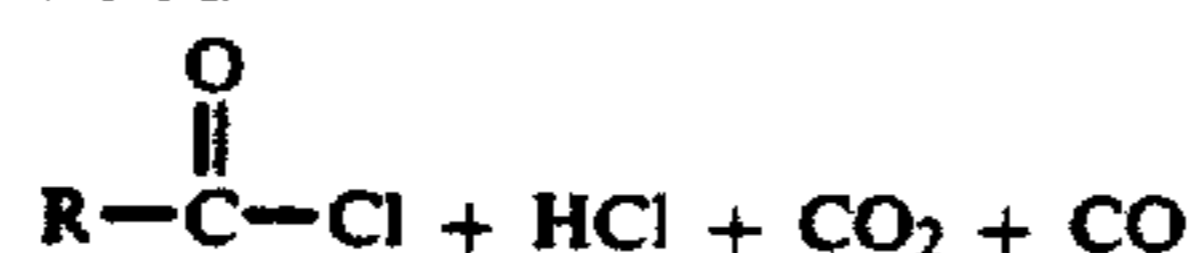
The thiol containing a heterocyclic ring may be reacted with diphenylacetyl chloride in dichloromethane by combining the reactants in a 1:1 molar ratio and gently heating under reflux condensation for approximately 1-2 hours.

The desired acyl chlorides may be prepared from the carboxylic acid analogues by reaction with oxalyl chloride as follows:



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acid
chloride

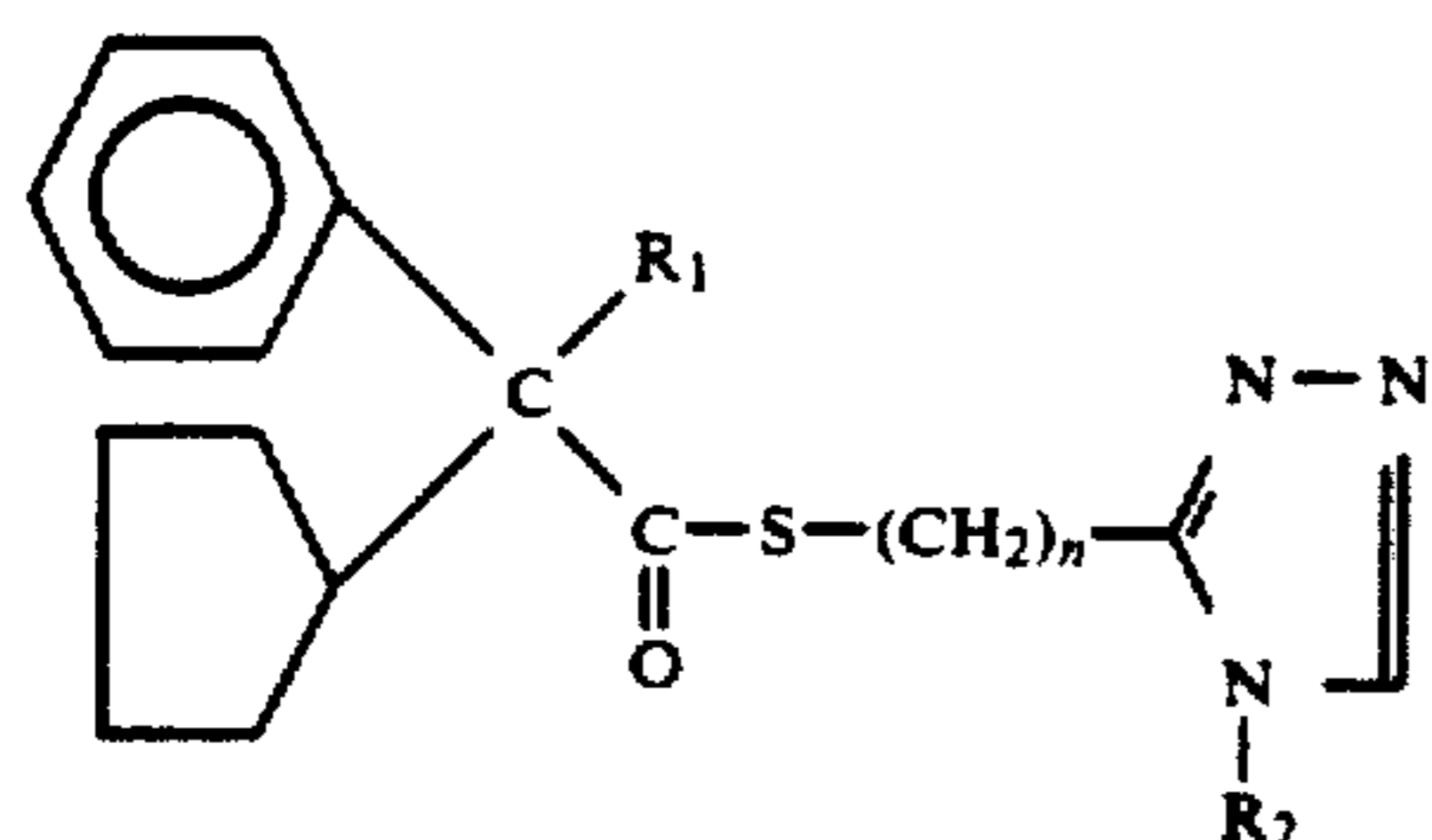
The reaction may be performed under reflux condensation. Following the reaction, which may be complete within a few hours, the acid chlorides may be vacuum-distilled and reacted with a thiol compound as described above.

The anti-spasmodic compounds of the present invention may be effective in a dosage range of from about 1 to about 15 mg/kilogram of body weight per day. A preferred dosage is in the range of from about 1.5 to about 11.5 mg/kilogram of body weight per day. A still more preferred dosage range is from about 3 to about 6 mg/kilogram of body weight per day.

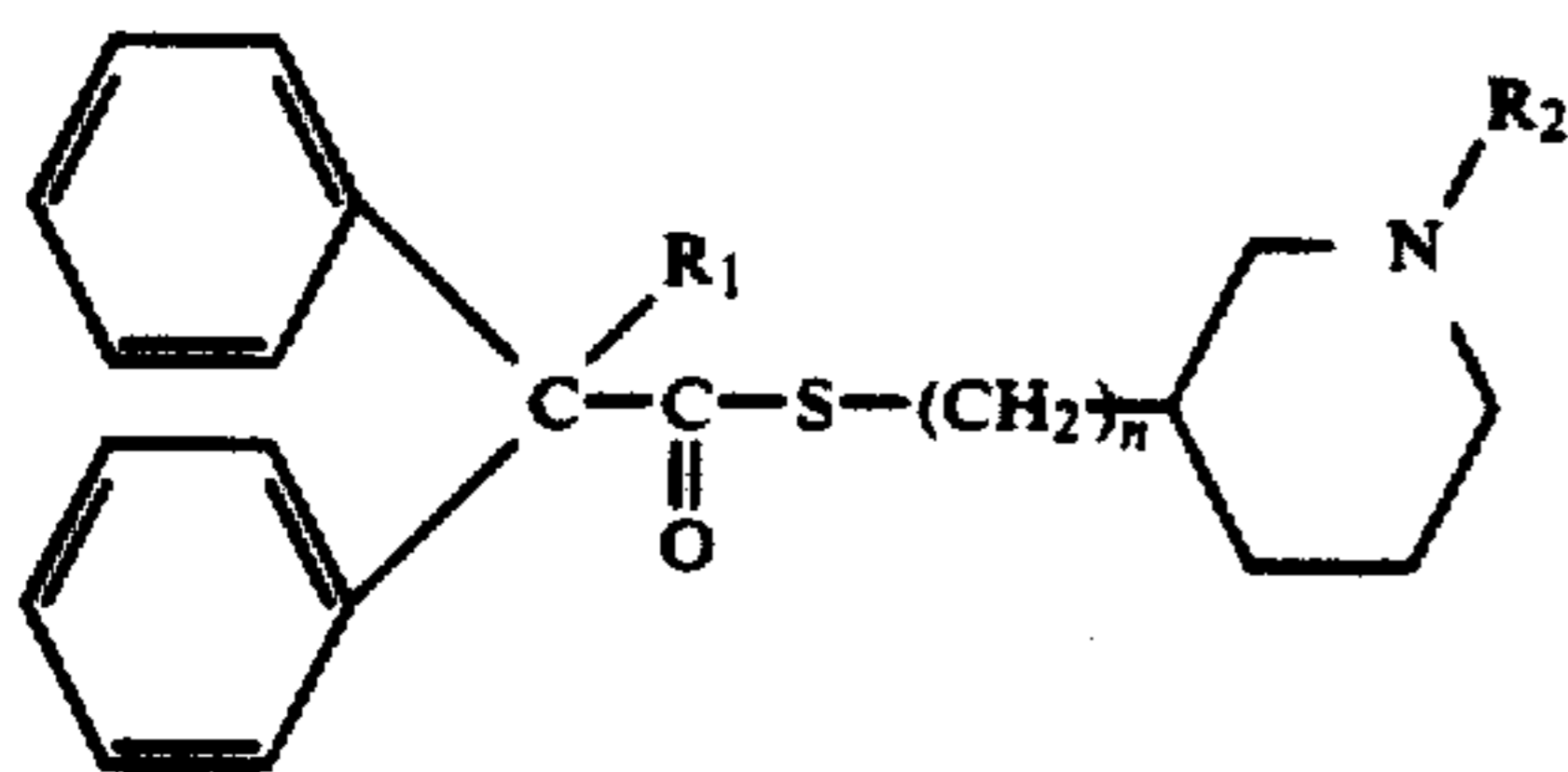
The anti-spasmodic compounds of the present invention may be combined with a pharmaceutically acceptable carrier and may be administered orally, typically in tablets of 400 mg active ingredient, total 1155 mg, or by intravenous injection, or by topical application.

Because the anti-spasmodic compounds of the present invention may hydrolyze slowly in water, they are preferably not used as a solution or aqueous suspension unless freshly prepared compounds. It may be possible, however, to suspend the microspheres of these compounds in non-aqueous liquids for administration to patients.

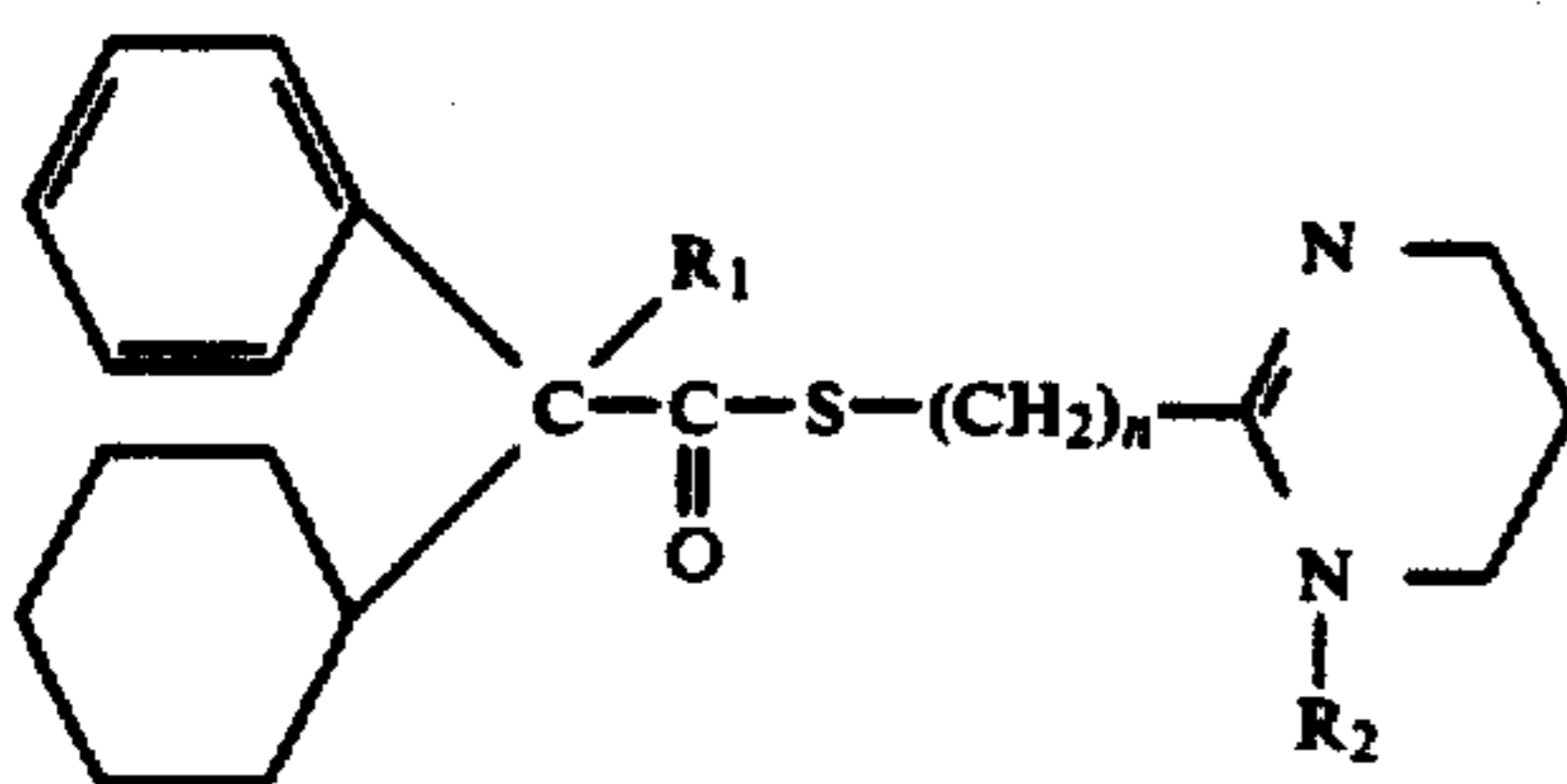
As examples which are illustrative of, but are not limited to, the compounds of the present invention, there may be mentioned the following compounds designated as 1(a-x) through 9(a-x). R₁, R₂ and n for these compounds are located in Table I [on page 12]:



1(a-x)



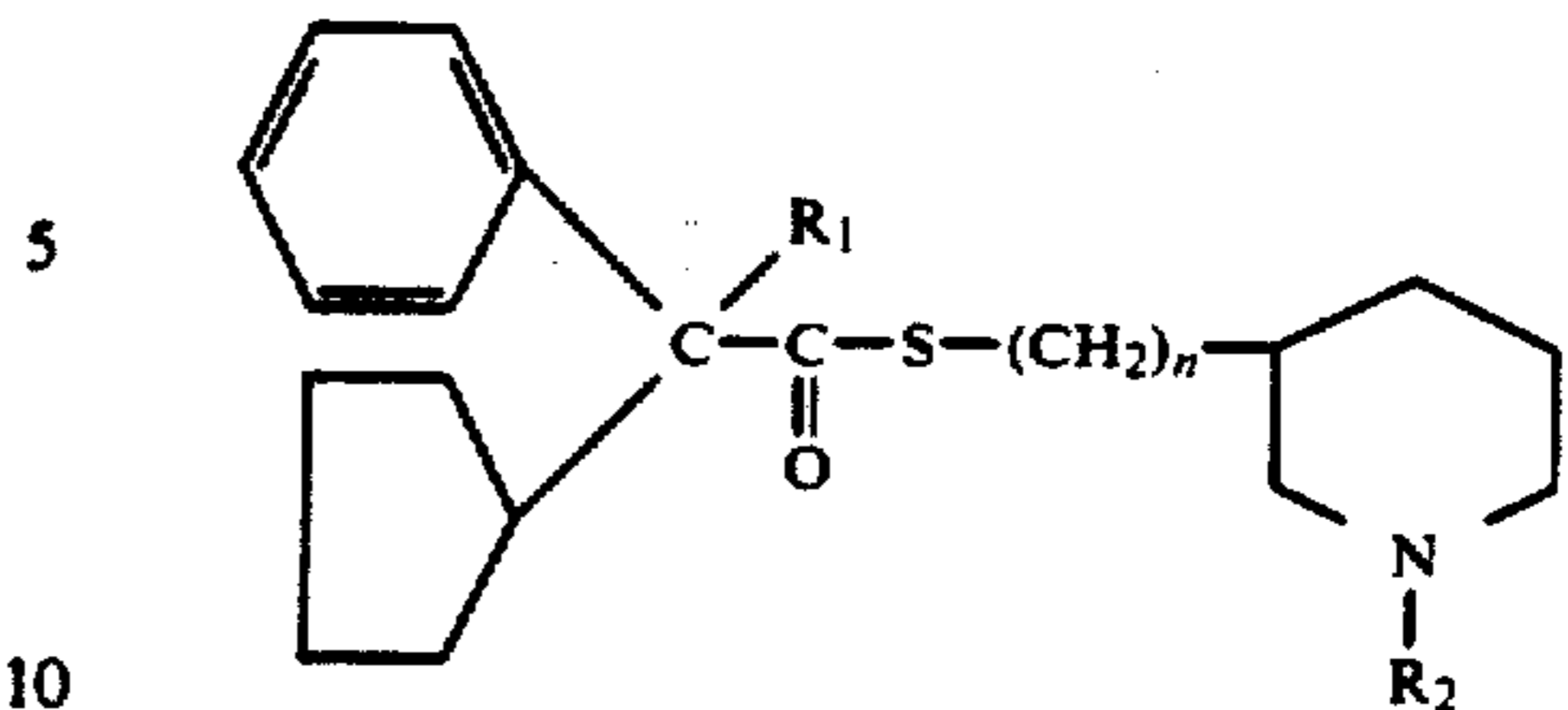
[2(a-x)]
2(a-m)
2(o-x)



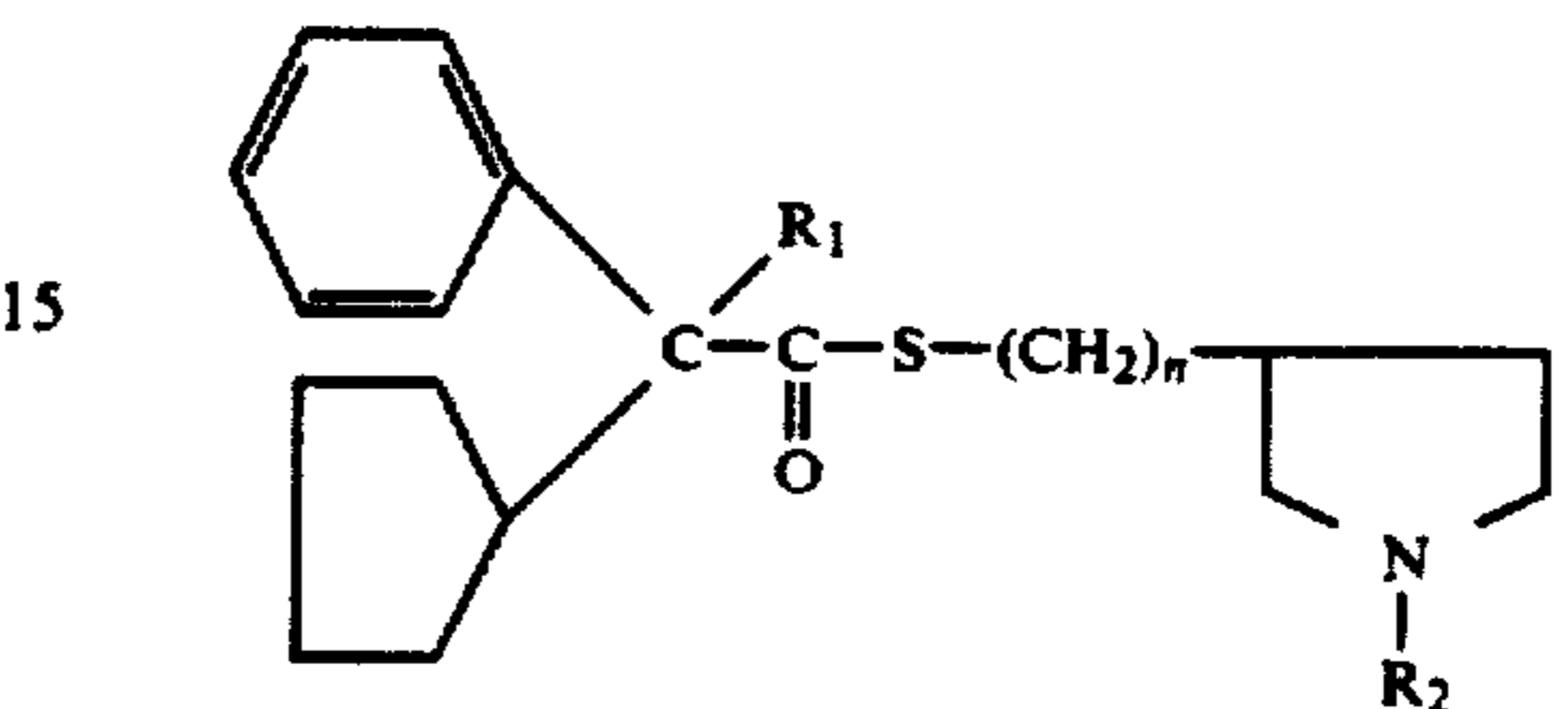
3(a-x)

6

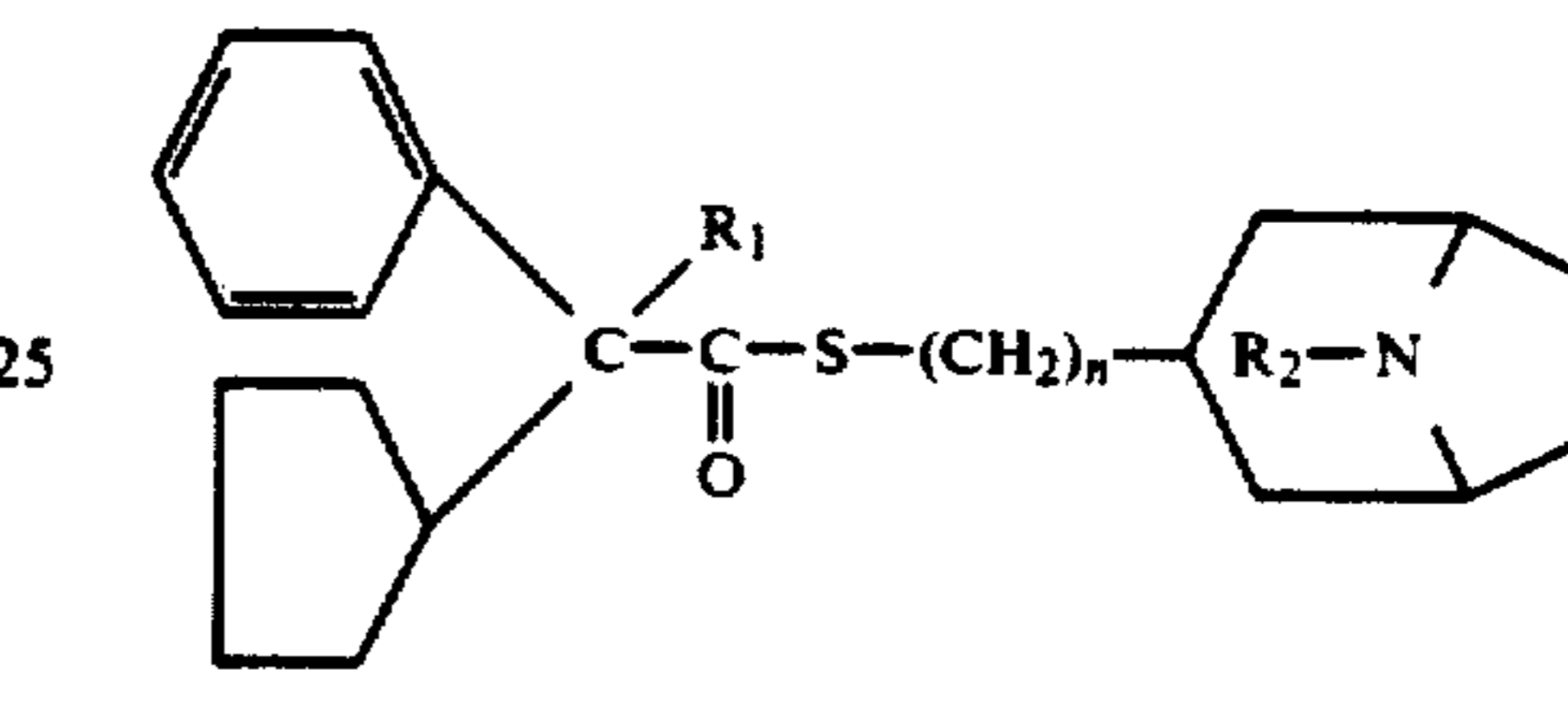
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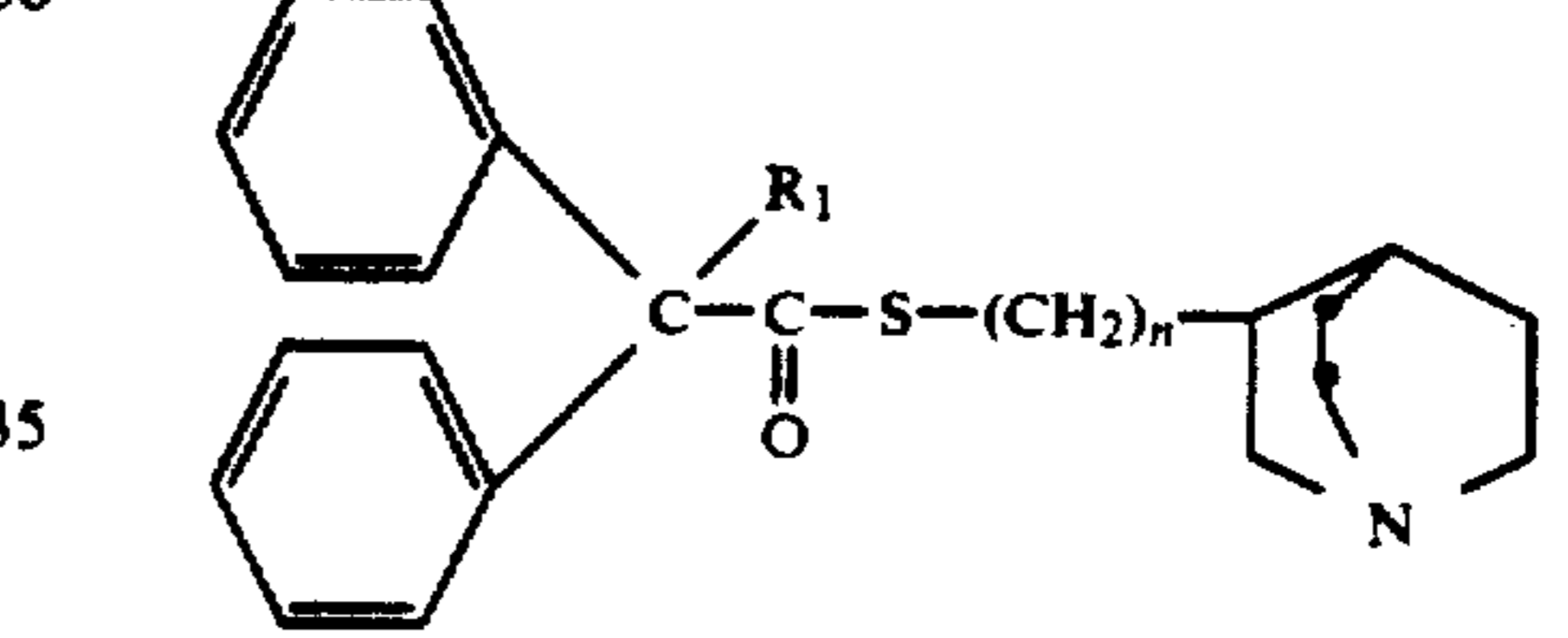
[4(a-x)]
4(a-m)
4(o-x)



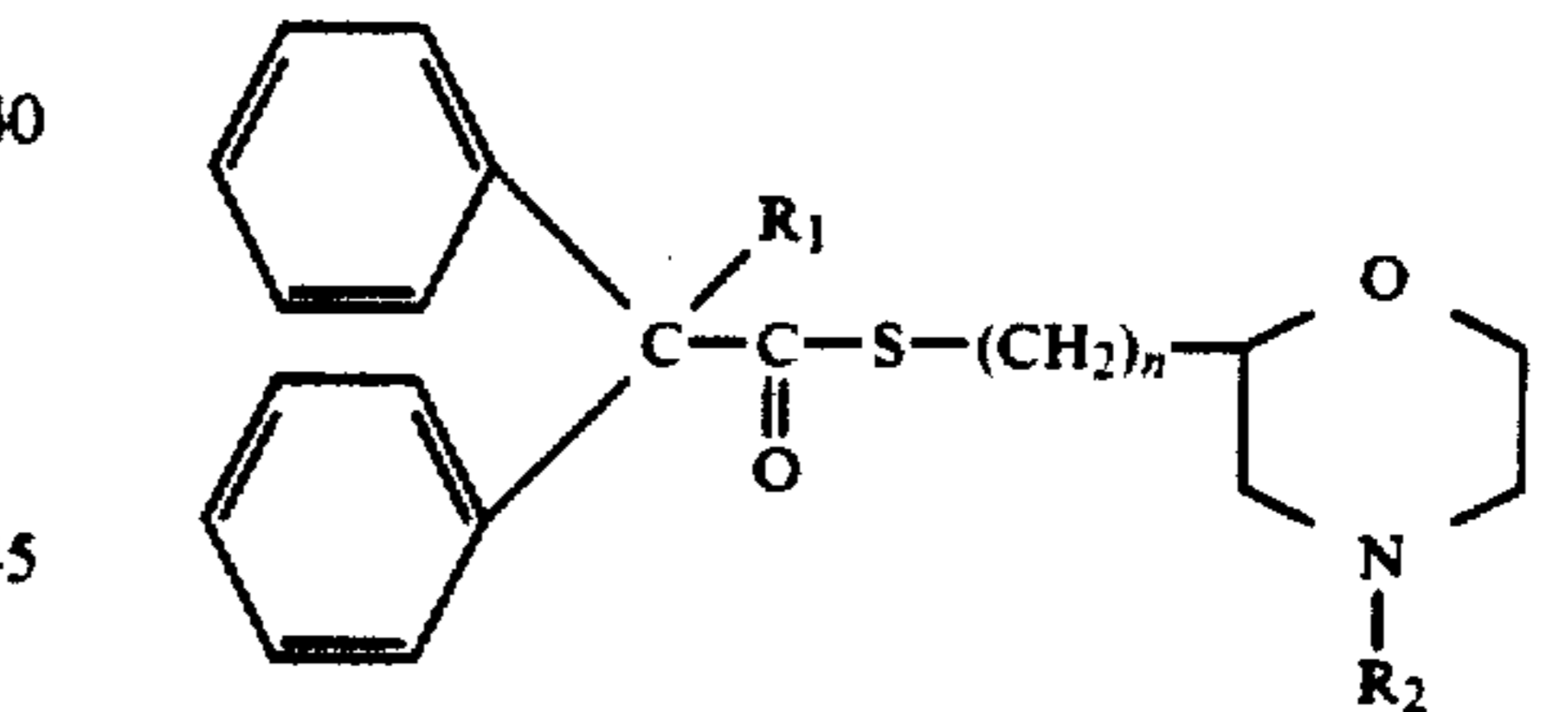
5(a-x)



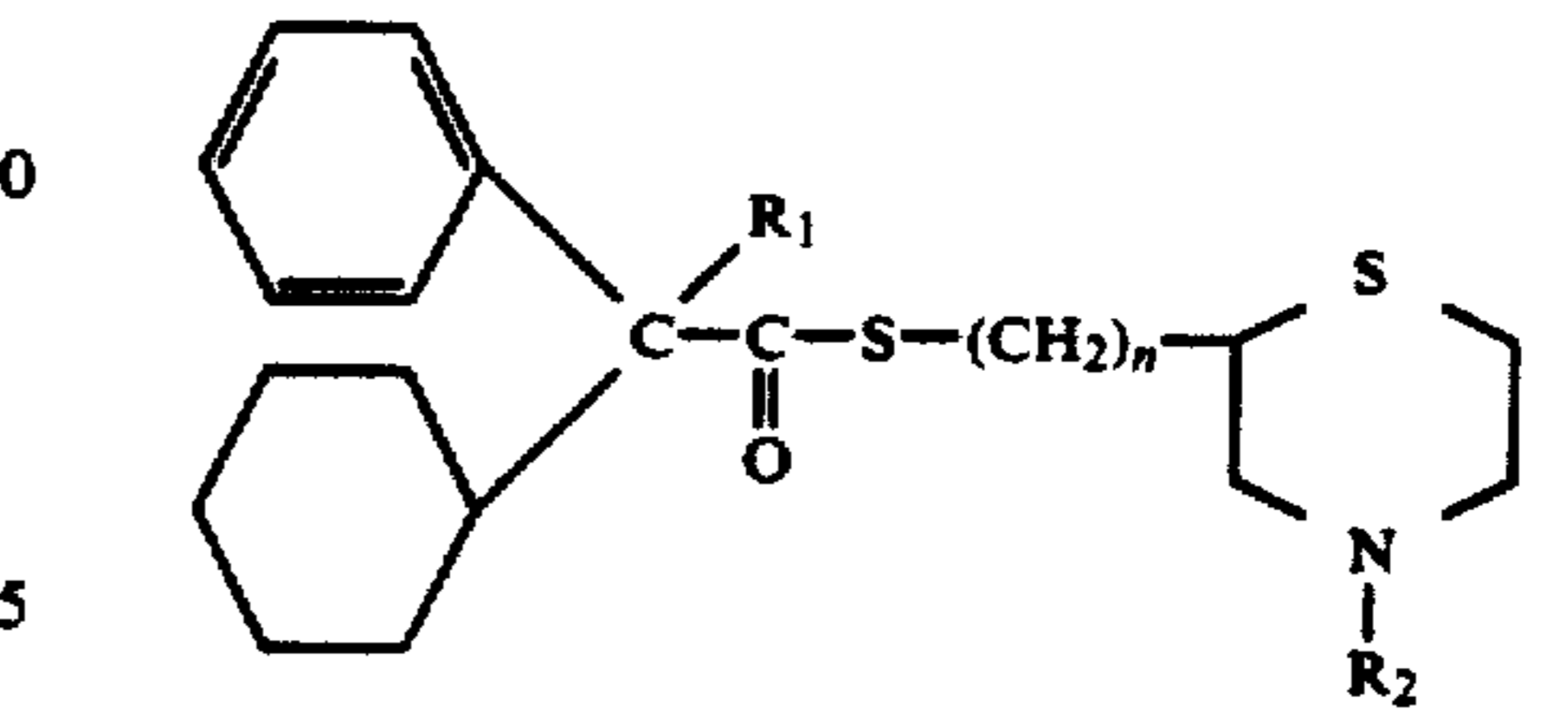
6(a-x)



7(a-x)



8(a-x)



9(a-x)

TABLE I

	n	R ₁	R ₂
1a-9a:	0	H	methyl
1b-9b:	0	H	ethyl
1c-9c:	0	H	n-propyl
1d-9d:	0	H	iso-propyl
1e-9e:	1	H	methyl
1f-9f:	1	H	ethyl
1g-9g:	1	H	n-propyl
1h-9h:	1	H	iso-propyl
1i-9i:	2	H	methyl
1j-9j:	2	H	ethyl

TABLE I-continued

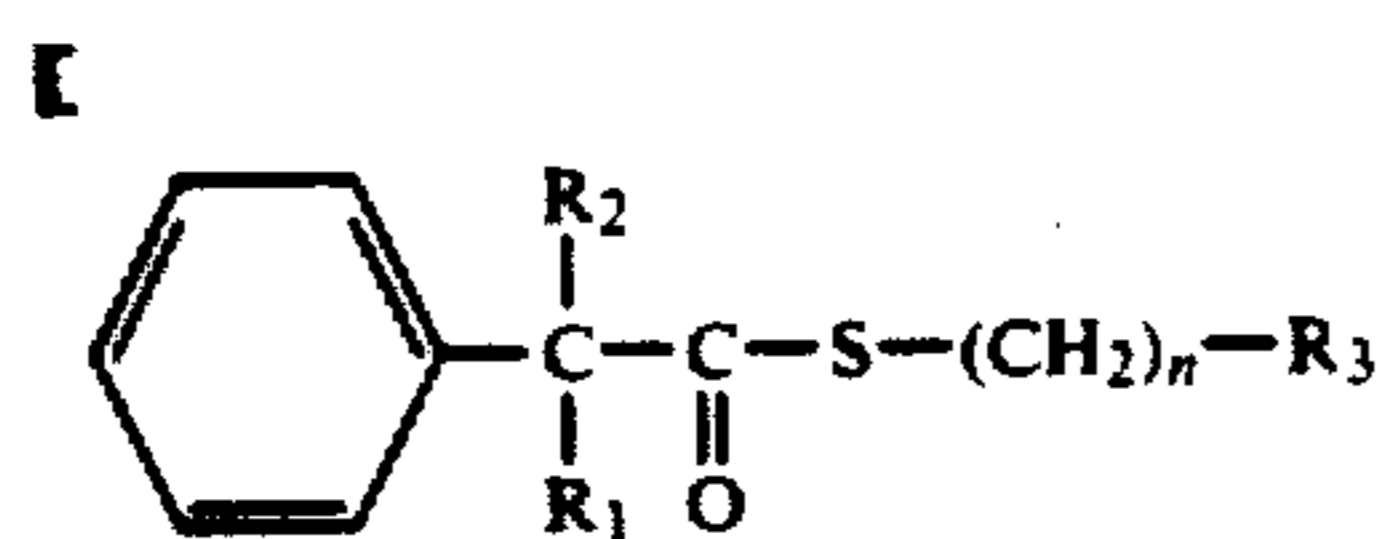
	n	R ₁	R ₂
1k-9k:	2	H	n-propyl
1l-9l:	2	H	iso-propyl
1m-9m:	0	OH	methyl
1n-9n:	0	OH	ethyl
1o-9o:	0	OH	n-propyl
1p-9p:	0	OH	iso-propyl
1q-9q:	1	OH	methyl
1r-9r:	1	OH	ethyl
1s-9s:	1	OH	n-propyl
1t-9t:	1	OH	iso-propyl
1u-9u:	2	OH	methyl
1v-9v:	2	OH	ethyl
1w-9w:	2	OH	n-propyl
1x-9x:	2	OH	iso-propyl

The compounds of this invention are anti-muscarinic agents (cholinergic-muscarinic receptor antagonists) which inhibit the actions of acetylcholine on autonomic effectors innervated by postganglionic cholinergic nerves as well as on smooth muscle that lacks cholinergic innervation. Since a major component of parasympathetic control of smooth muscle occurs via muscarinic receptors, these compounds may be effective as modifiers of smooth muscle activity.

Thiphenamil hydrochloride has been shown to decrease spasms of the gastrointestinal tract, biliary tract, ureter and uterus without producing characteristic atropinic side effects, on salivary and sweat glands, GI glands, or the cardiovascular system. This invention results in compounds which may be as efficacious as thiphenamil hydrochloride, or more so, in relaxing various smooth muscle systems while at the same time demonstrating thiphenamil hydrochloride's lack of associated side-effects.

I claim:

[1. An antispasmodic agent having the formula]



[wherein:

n is an integer from 0 to 2;

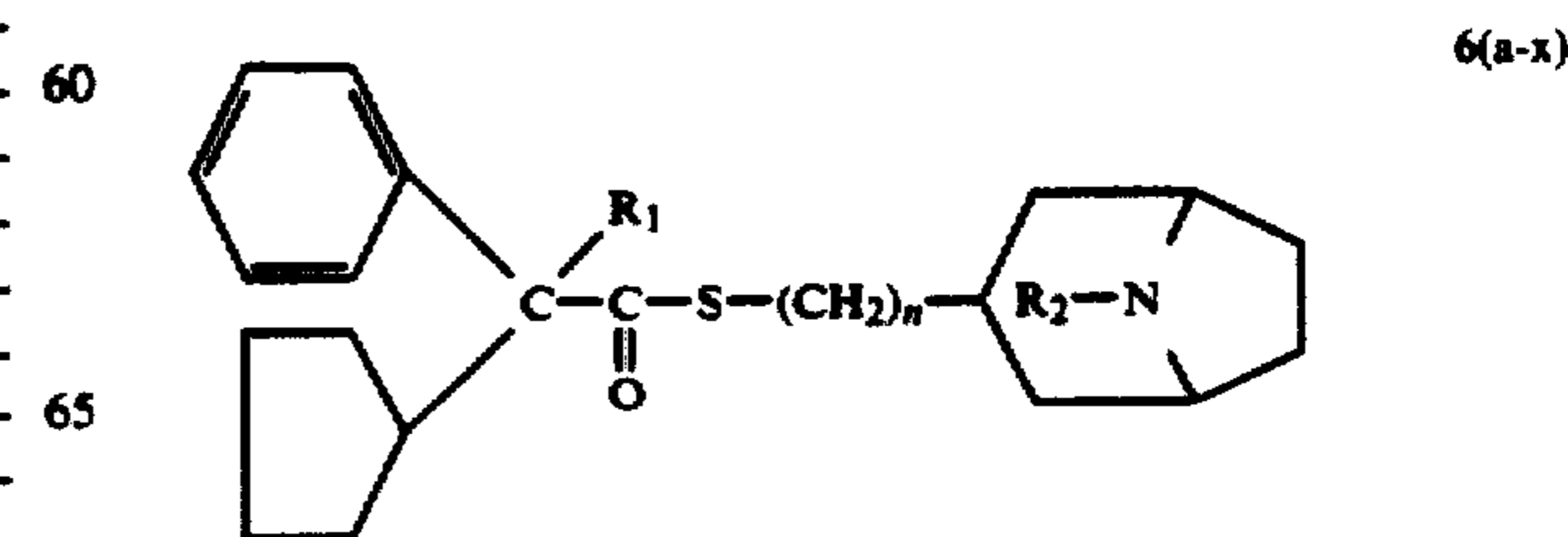
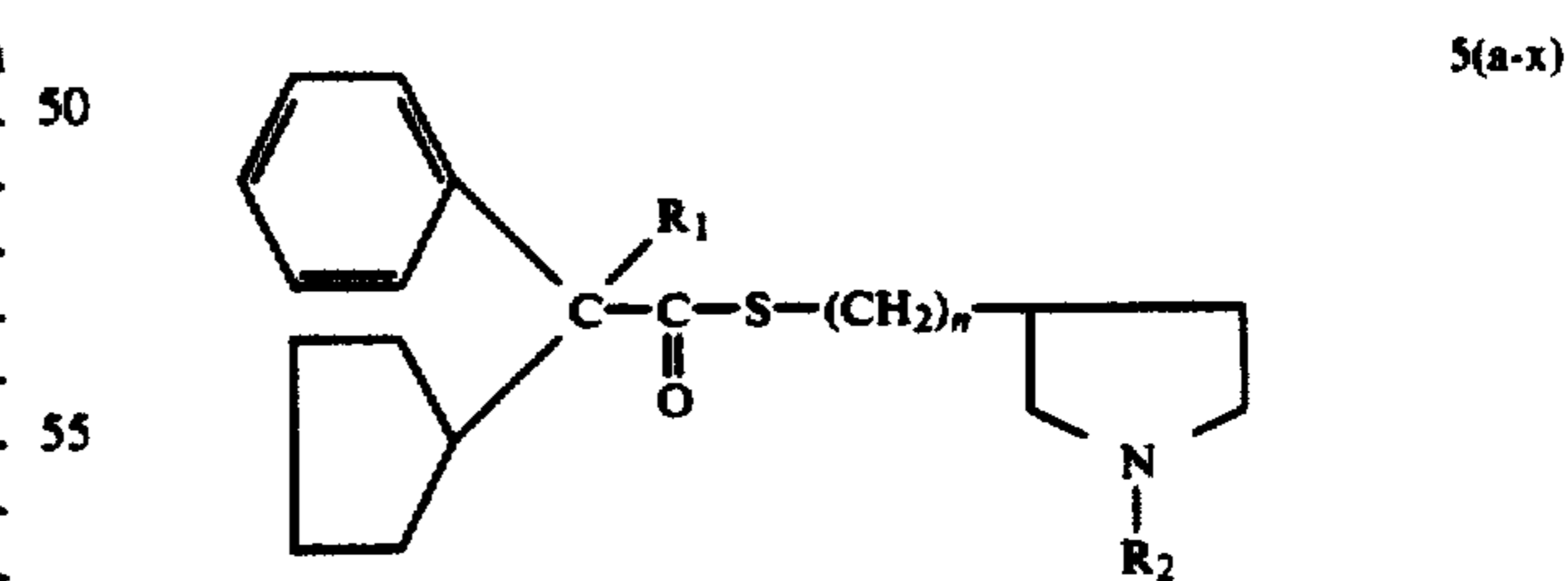
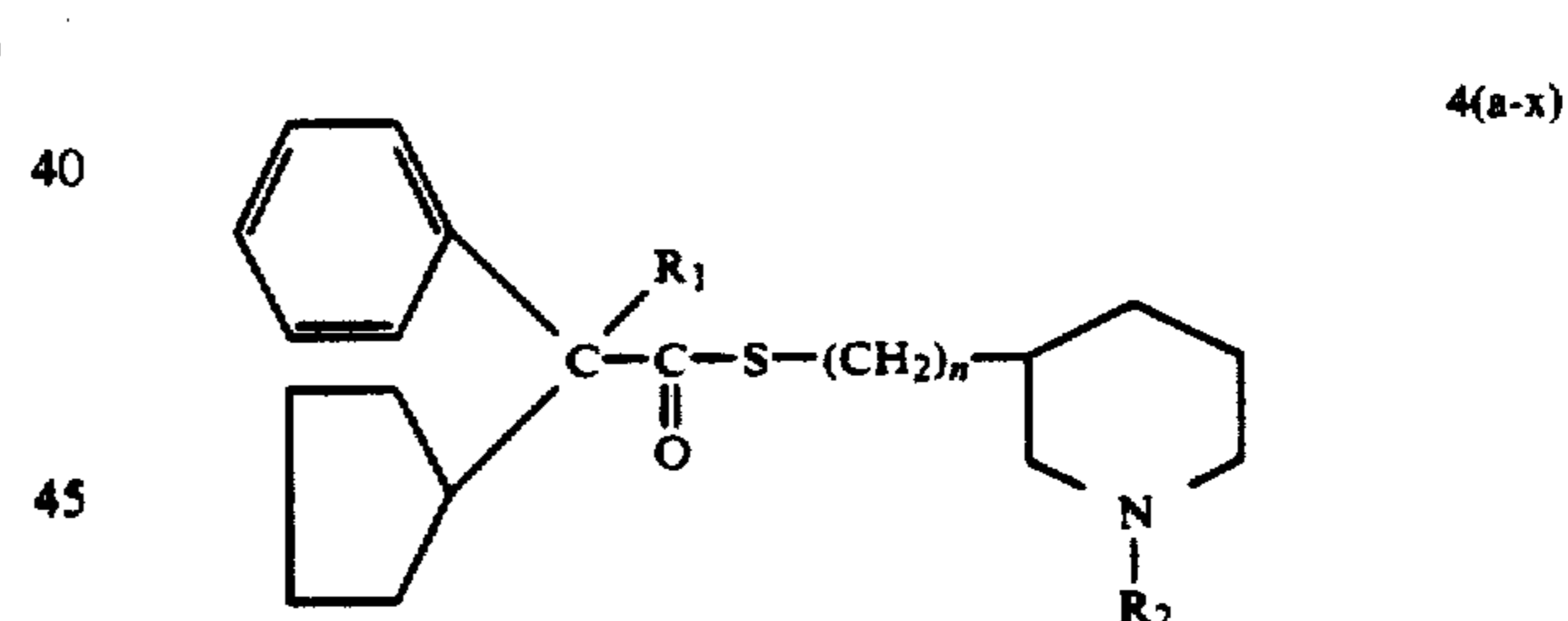
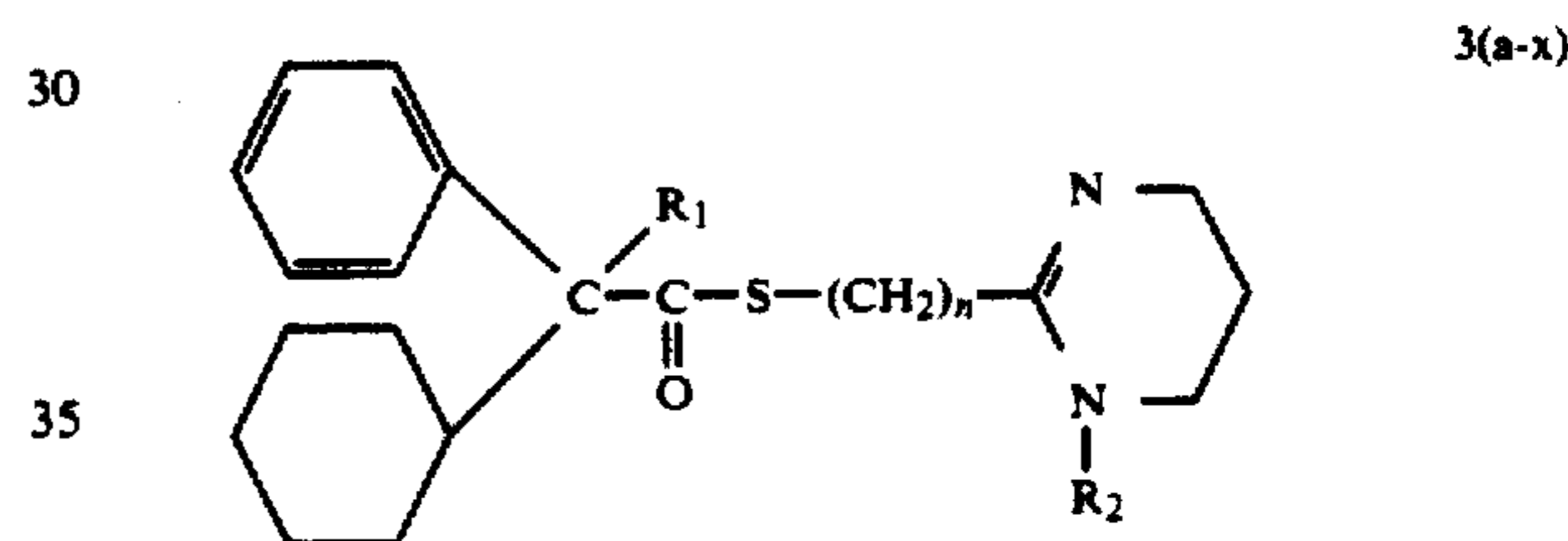
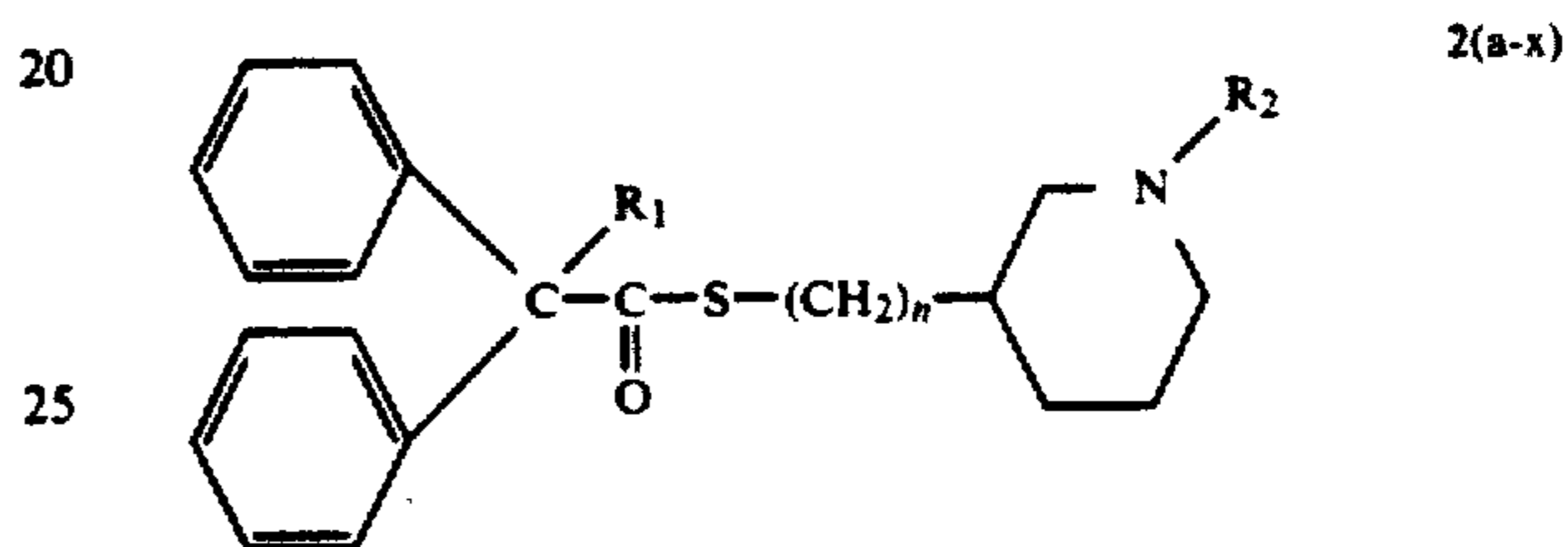
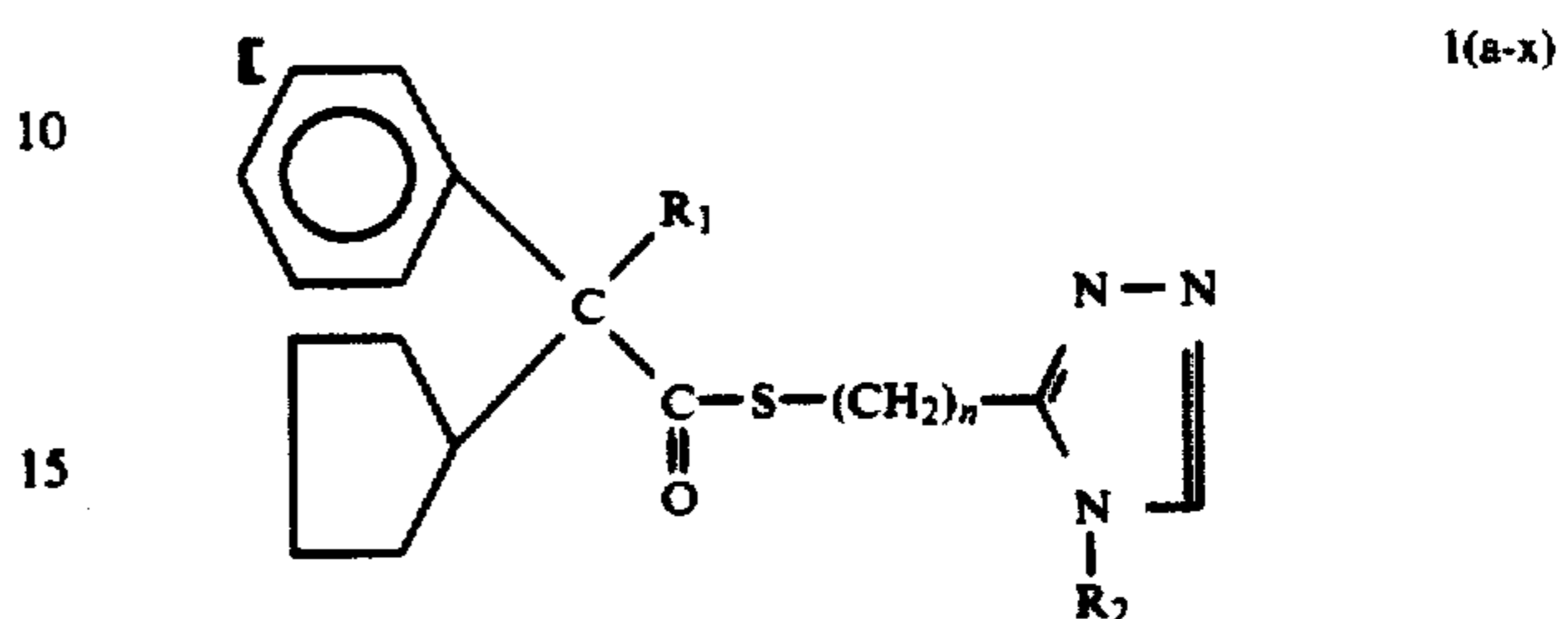
R₁ is aryl or cycloalkyl;

R₂ is hydrogen or hydroxyl; and

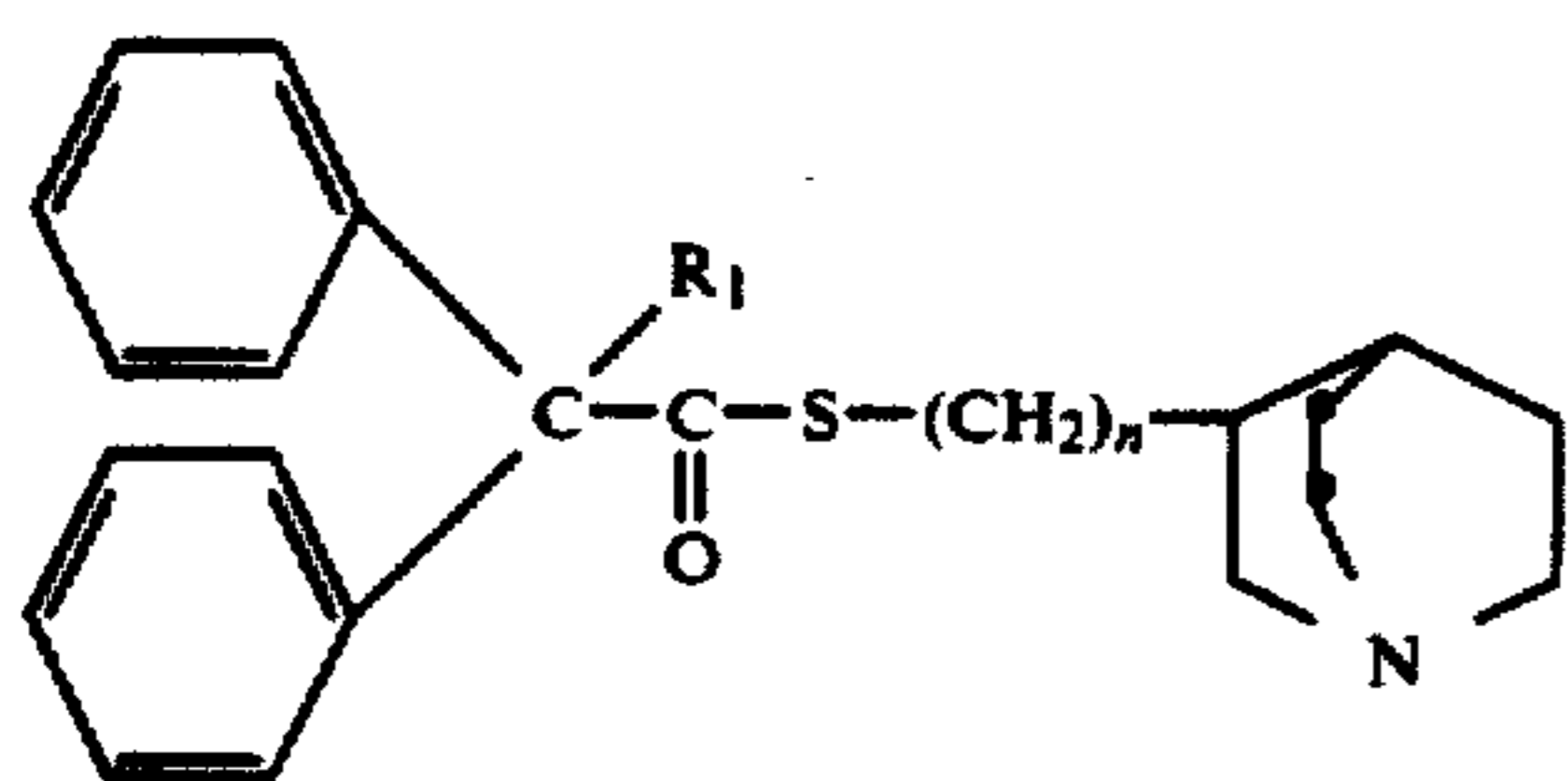
R₃ is a heterocyclic nitrogen ring connected via carbon linkage to the main chain and is selected from the group consisting of 1-methyl-imidazoliny, 1-ethyl-imidazoliny, 1-n-propyl-imidazoliny, 1-iso-propyl-imidazoliny, 1-methyl-imidazolyl, 1-ethyl-imidazolyl, 1-n-propyl-imidazolyl, 1-iso-propylimidazolyl, 1-methyl-morpholiny, 1-ethyl-morpholiny, 1-n-propyl-morpholiny, 1-iso-propyl-morpholiny, 1-methylpiperaziny, 1-ethyl-piperaziny, 1-n-propyl-piperaziny, 1-isopropyl-piperaziny, 1-methyl-piperidiny, 1-ethyl-piperidiny, 1-n-propyl-piperidiny, 1-iso-propyl-piperidiny, 1-methylpyrazoly, 1-ethyl-pyrazoly, 1-n-propyl-pyrazoly, 1-iso-propylpyrazoly, 1-methyl-pyrrolidiny, 1-ethyl-pyrrolidiny, 1-n-propyl-pyrrolidiny, 1-iso-propyl-pyrrolidiny, 1-methyl-3-pyrroliny, 1-ethyl-3-pyrroliny, 1-n-propyl-3-pyrroliny, 1-isopropyl-3-pyrroliny, 1-methyl-thiomorpholiny, 1-ethylthiomorpholiny, 1-n-propyl-thiomorpholiny, 1-iso-propylthiomorpholiny, 4-methyl-1,2,4-triazoly, 4-ethyl-1,2,4-triazoly, 4-n-

propyl-1,2,4-triazoly, 4-iso-propyl-1,2,4-triazoly.]

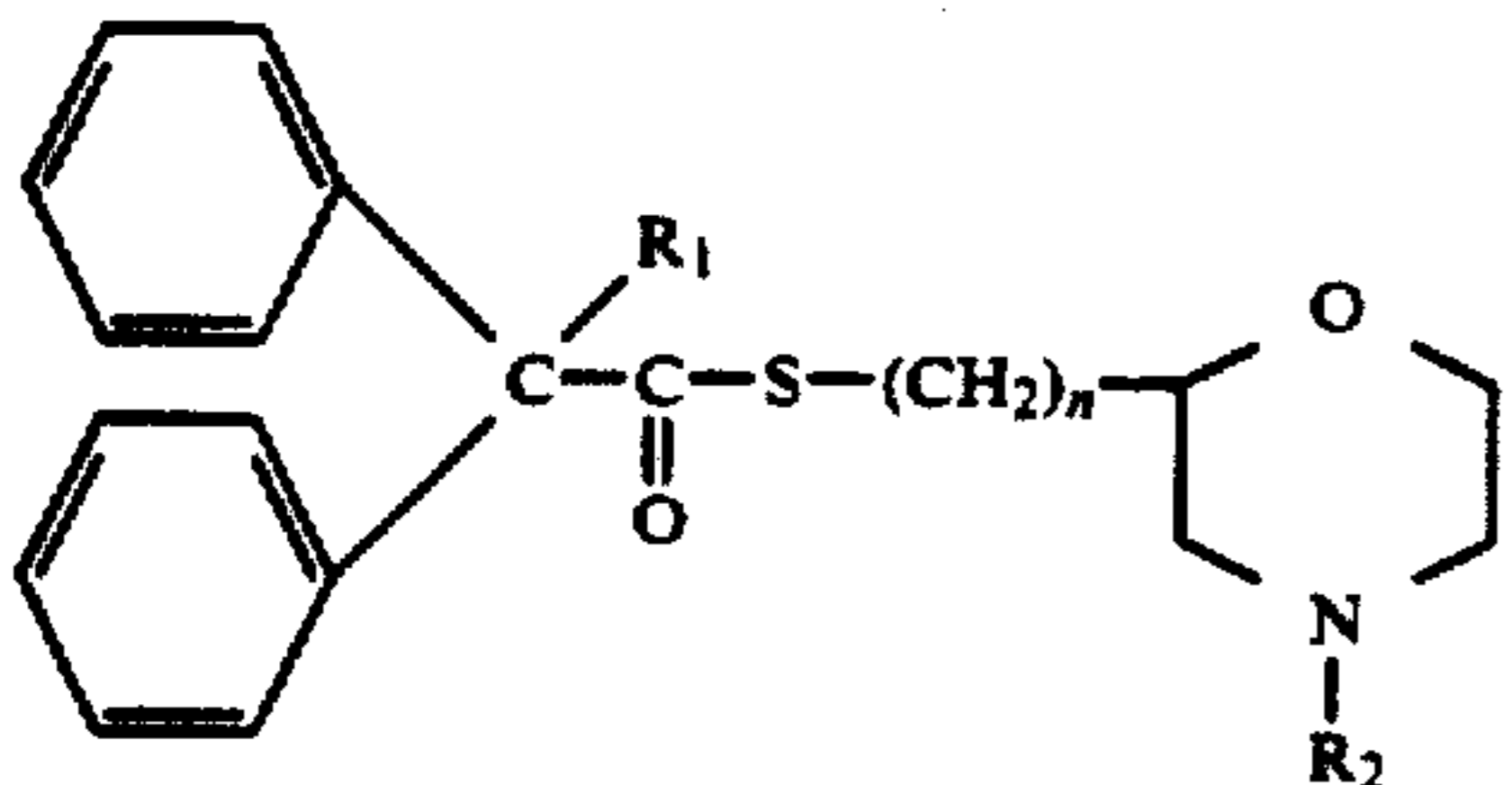
[2. An antispasmodic agent having a formula selected from the group consisting of]



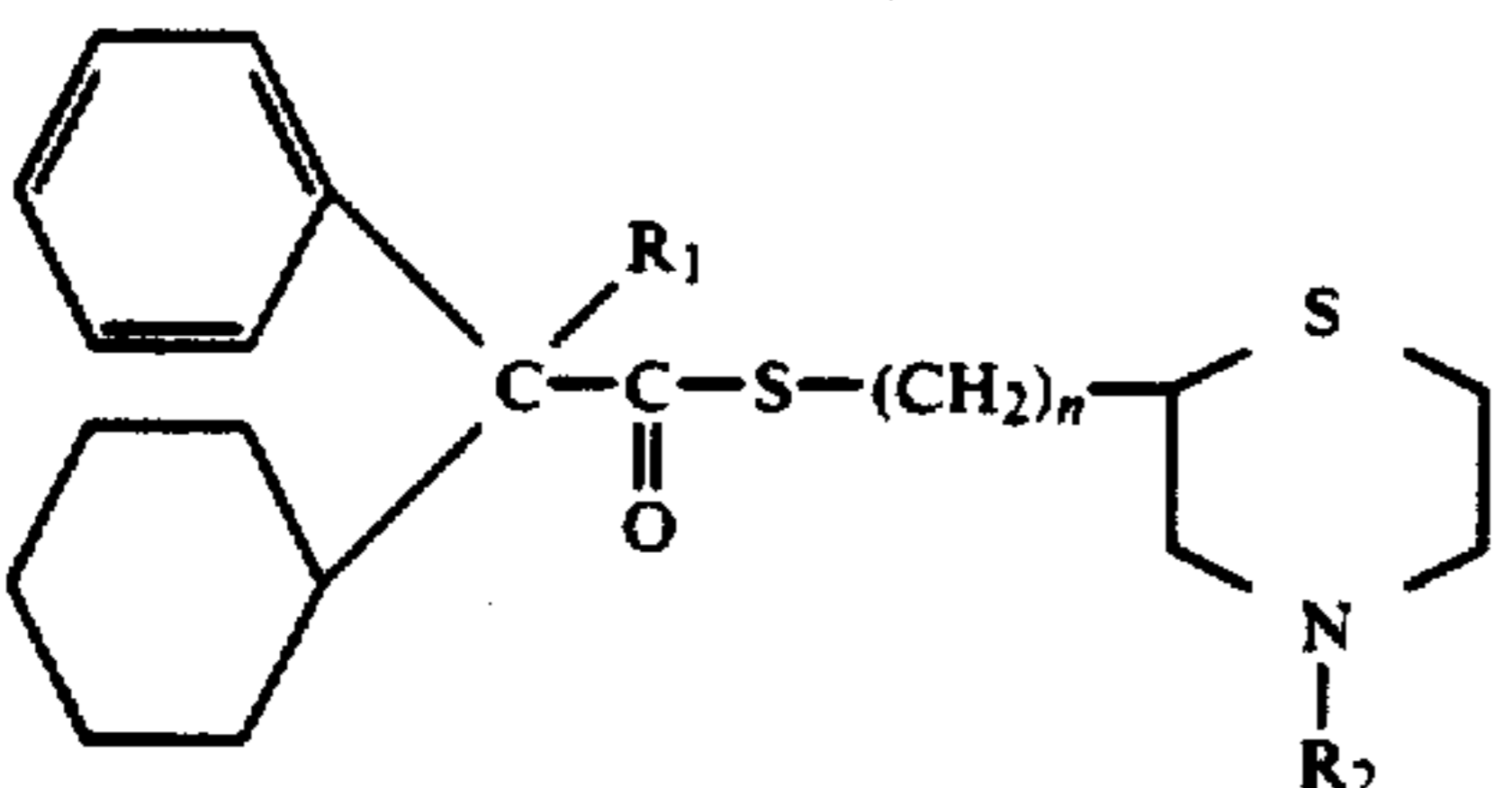
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8(a-x)

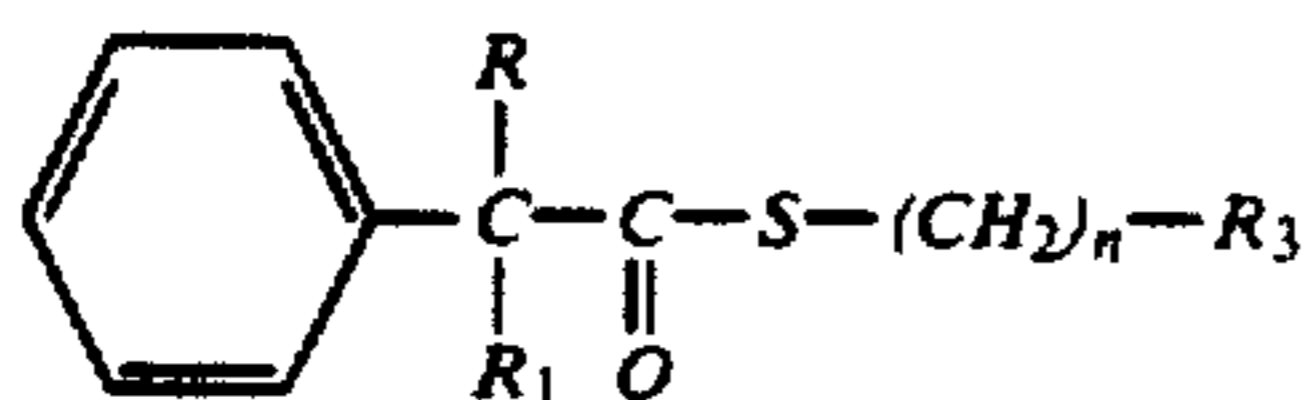


9(a-x)



【where n is an integer from 0-2, R₁ is H or OH and R₂ is methyl, ethyl, n-propyl or isopropyl.】

3. An antispasmodic agent having the formula



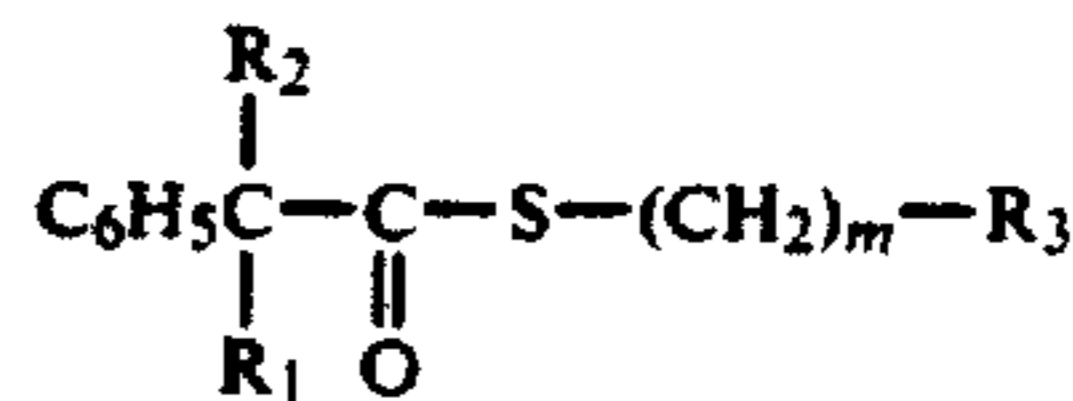
wherein:

n is an integer from 0 to 2;

R₁ is aryl or cycloalkyl;

R₃ is a heterocyclic nitrogen ring and is selected from the group consisting of 1-methyl-imidazoliny, 1-ethyl-imidazoliny, 1-n-propyl-imidazoliny, 1-iso-propyl-imidazoliny, 1-methyl-imidazolyl, 1-ethyl-imidazolyl, 1-n-propyl-imidazolyl, 1-iso-propylimidazolyl, 1-methyl-morpholiny, 1-ethyl-morpholiny, 1-n-propyl-morpholiny, 1-iso-propylmorpholiny, 1-methyl-piperaziny, 1-ethyl-piperaziny, 1-n-propyl-piperaziny, 1-iso-propyl-piperaziny, 1-methyl-piperidiny, 1-ethyl-piperidiny, 1-n-propyl-piperidiny, 1-iso-propyl-piperidiny, 1-methylpyrazolyl, 1-ethyl-pyrazolyl, 1-n-propyl-pyrazolyl, 1-iso-propylpyrazolyl, 1-methyl-pyrrolidiny, 1-ethyl-pyrrolidiny, 1-n-propyl-pyrrolidiny, 1-iso-propylpyrrolidiny, 1-methyl-3-pyrroliny, 1-ethyl-3-pyrroliny, 1-n-propyl-3-pyrroliny, 1-iso-propyl-3-pyrroliny, 1-methylthiomorpholiny, 1-ethylthiomorpholiny, 1-n-propylthiomorpholiny, 1-iso-propylthiomorpholiny, 4-methyl-1,2,4-triazolyl, 4-ethyl-1,2,4-triazolyl, 4-n-propyl-1,2,4-triazolyl, 4-iso-propyl-1,2,4-triazolyl.

4. An antispasmodic agent having the formula



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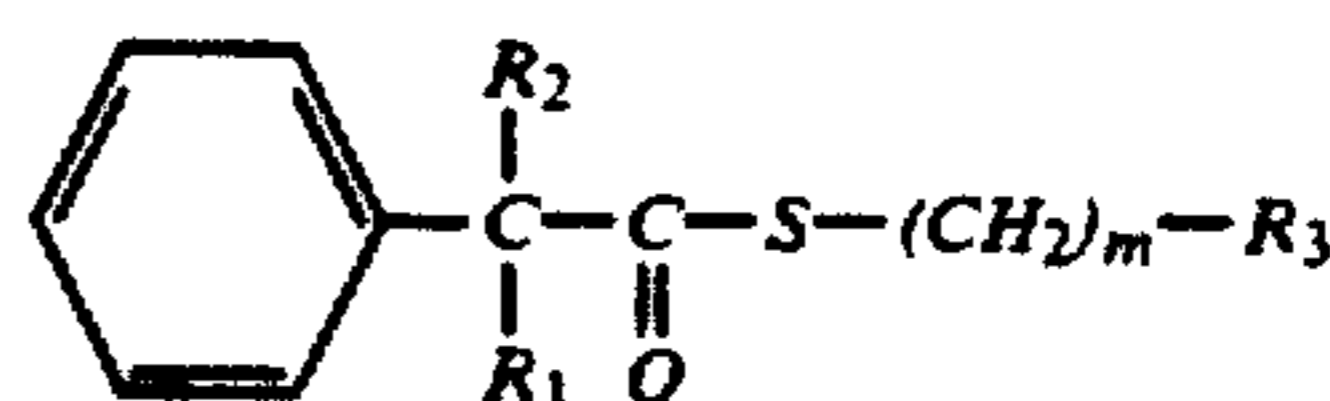
wherein m is an integer from 0 to 2,

R₁ is aryl or cycloalkyl,

R₂ is hydrogen or hydroxyl, and

R₃ is a heterocyclic or bicycloheterocyclic ring connected via carbon linkage to the main chain and is selected from the group consisting of imidazoliny, imidazolyl, morpholiny, thiomorpholiny, pyrazolyl, 1,2,4-triazolyl, tropanyl and quinuclidyl.

5. An antispasmodic agent having the formula



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wherein:

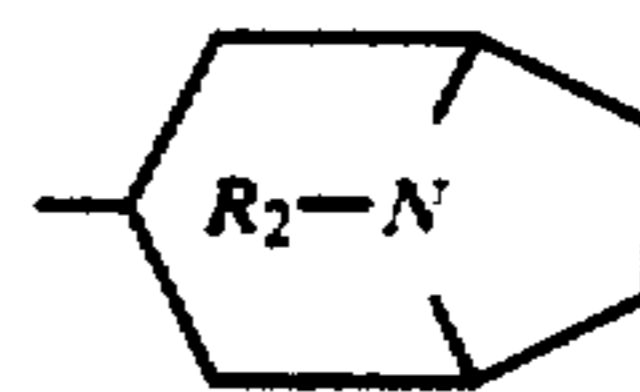
m is an integer from 0 to 2;

R₁ is aryl or cycloalkyl;

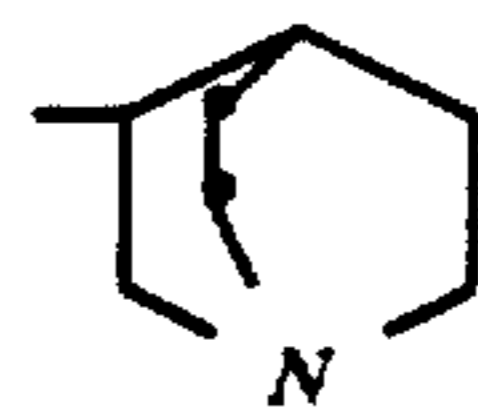
R₂ is hydrogen or hydroxyl; and

R₃ is a heterocyclic or bicycloheterocyclic ring selected from the group consisting of 1-methyl-imidazoliny, 1-ethyl-imidazoliny, 1-n-propyl-imidazoliny, 1-iso-propyl-imidazoliny, 1-methyl-imidazolyl, 1-ethyl-imidazolyl, 1-n-propyl-imidazolyl, 1-iso-propylimidazolyl, 1-methyl-morpholiny, 1-ethyl-morpholiny, 1-n-propyl-morpholiny, 1-iso-propylmorpholiny, 1-methylpyrazolyl, 1-ethyl-pyrazolyl, 1-n-propyl-pyrazolyl, 1-iso-propylpyrazolyl, 1-methyl-3-pyrroliny, 1-ethyl-3-pyrroliny, 1-n-propyl-3-pyrroliny, 1-iso-propyl-3-pyrroliny, 1-methyl-thiomorpholiny, 1-ethyl-thiomorpholiny, 1-n-propylthiomorpholiny, 1-iso-propylthiomorpholiny, 4-methyl-1,2,4-triazolyl, 4-ethyl-1,2,4-triazolyl, 4-n-propyl-1,2,4-triazolyl, 4-iso-propyl-1,2,4-triazolyl,

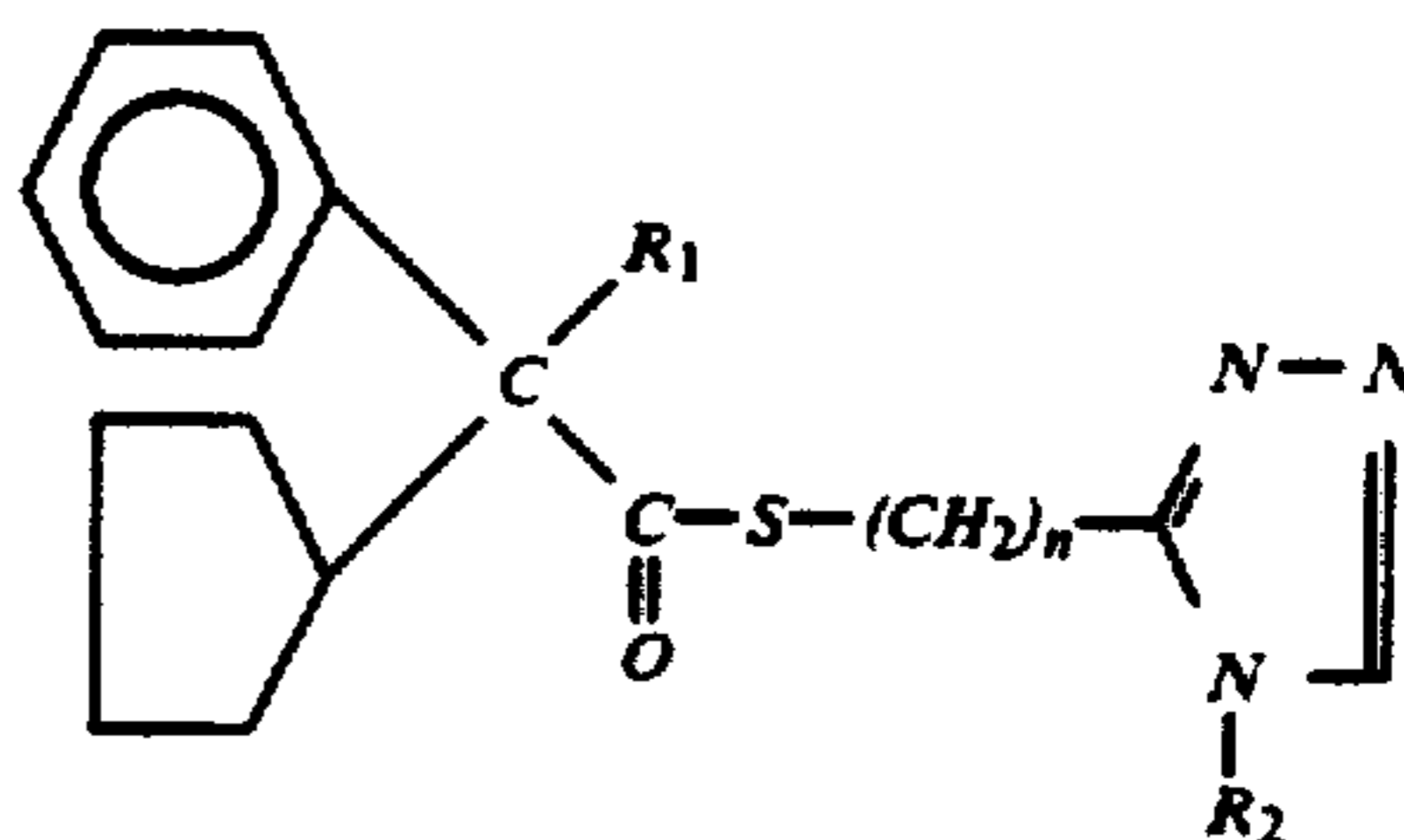
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and



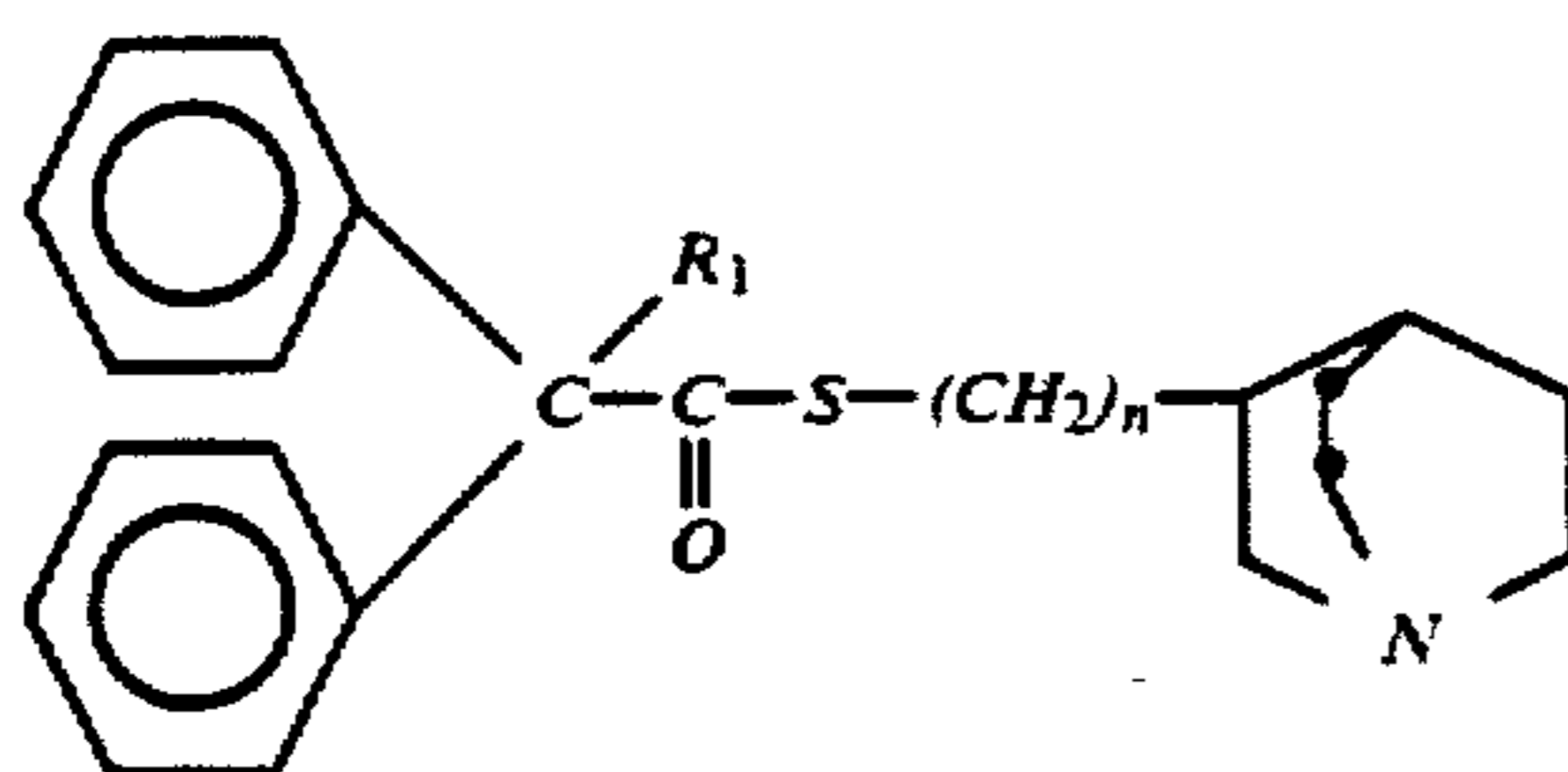
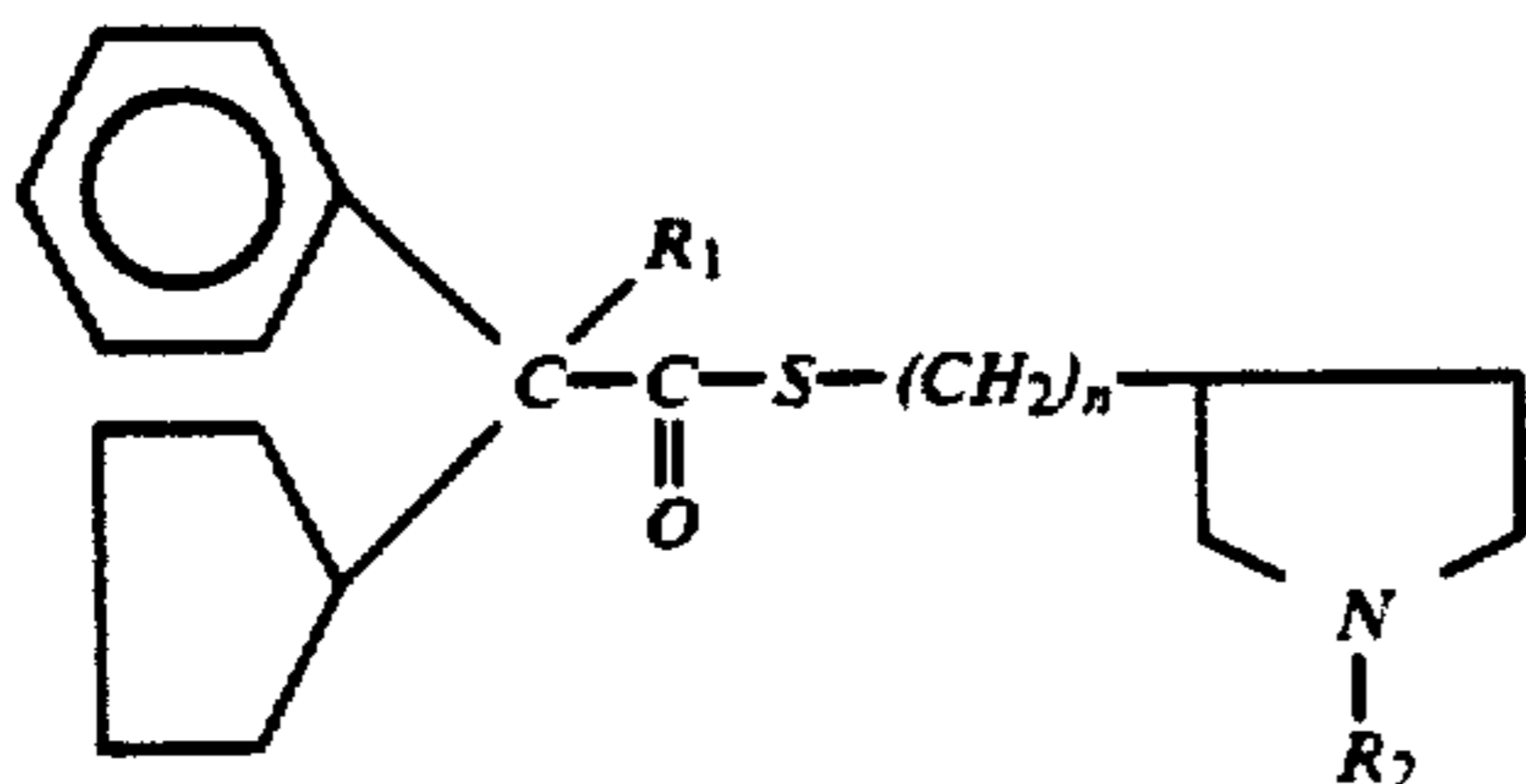
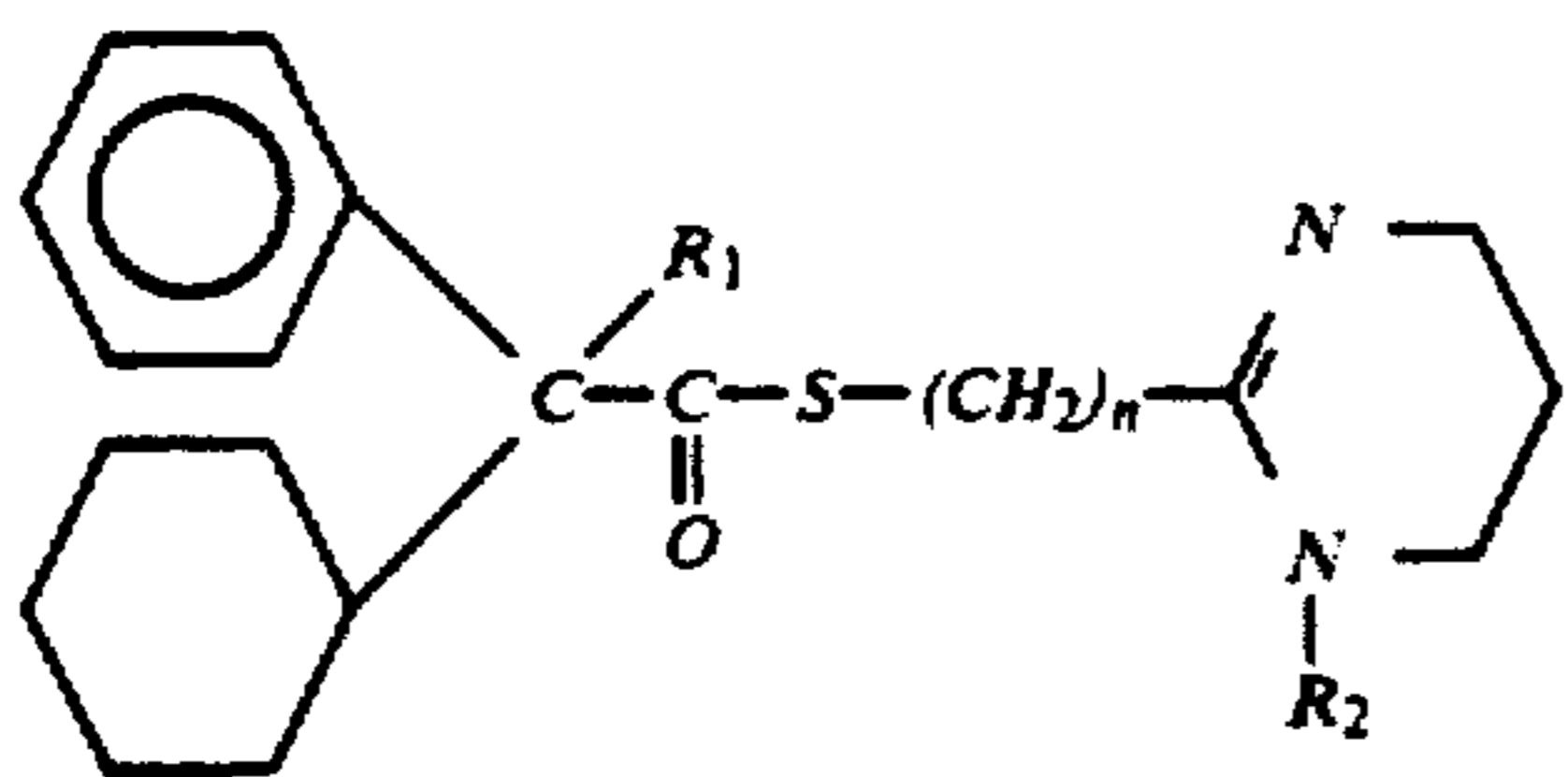
6. An antispasmodic agent having a formula selected from the group consisting of



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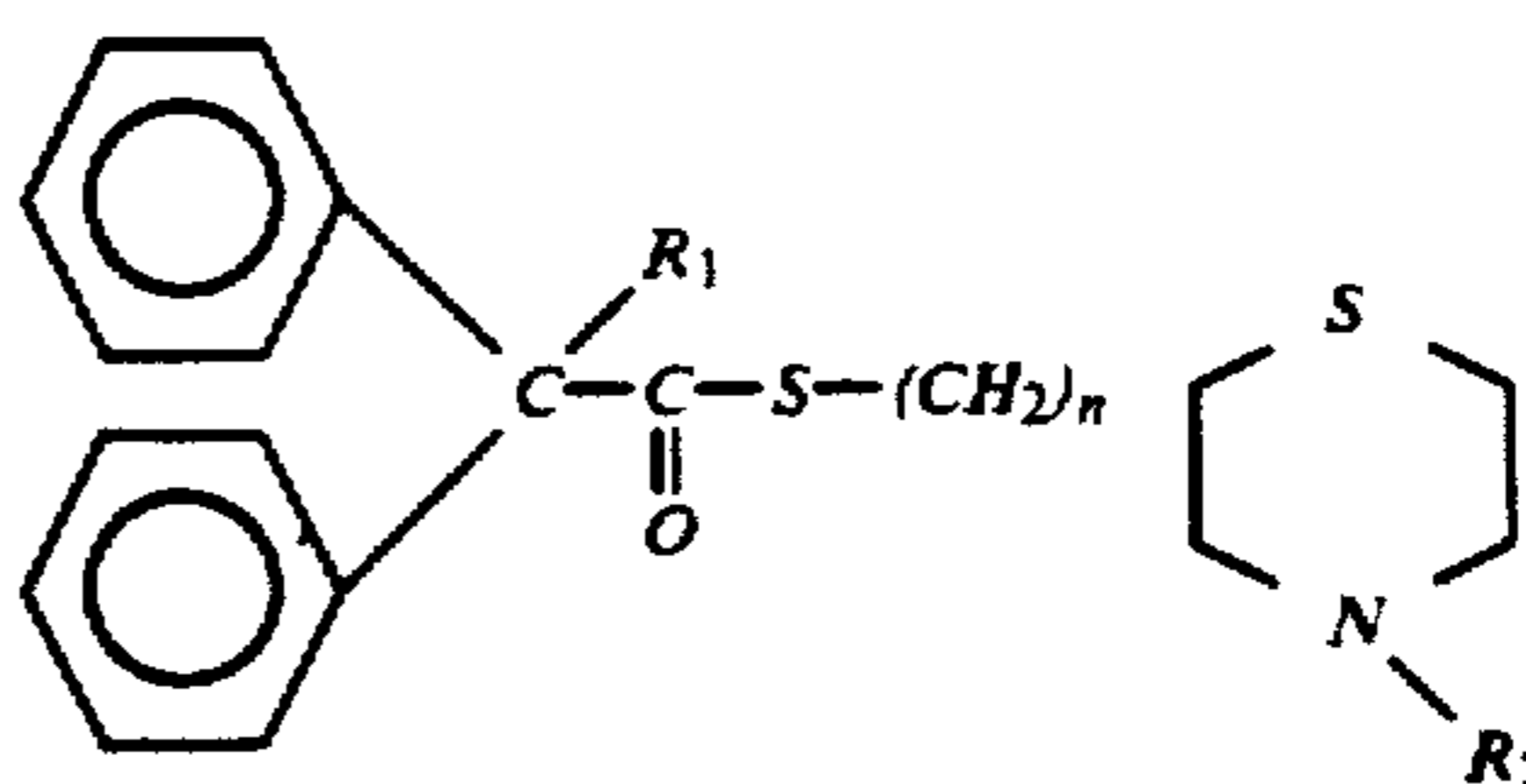
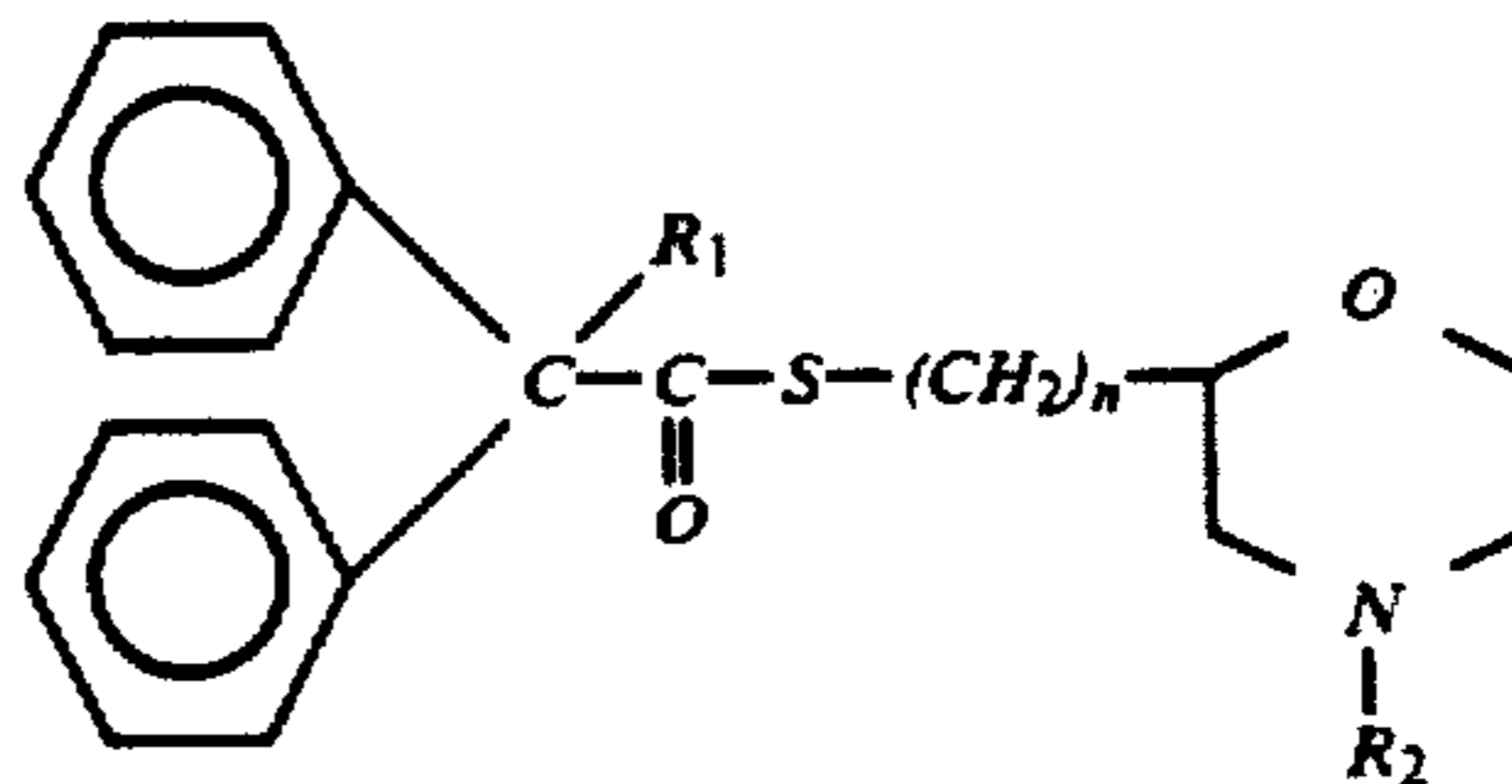
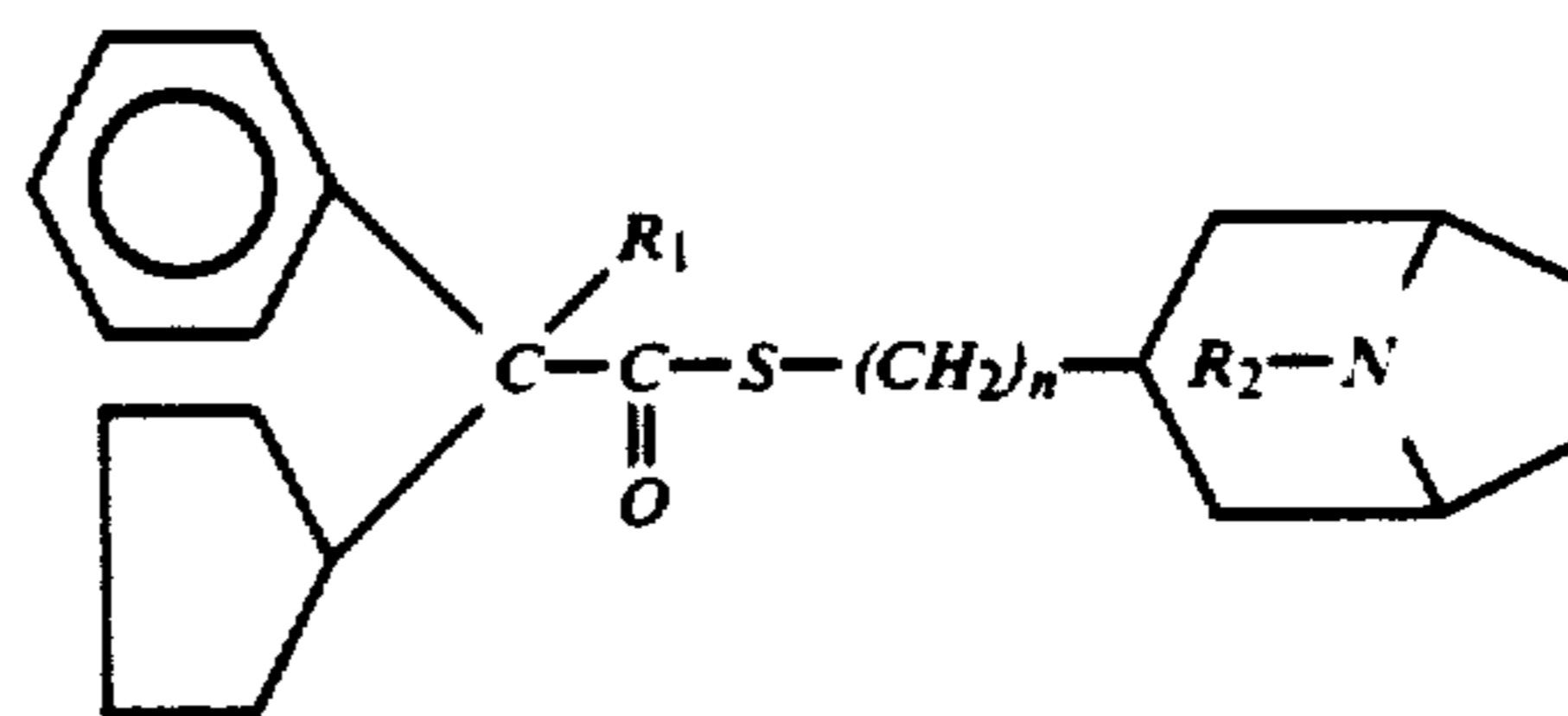
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-continued



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30 where n is an integer from 0-2, R_1 is H or OH and R_2 is methyl, ethyl, n -propyl or isopropyl.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : Re. 33,907
DATED : April 28, 1992
INVENTOR(S) : William M. Davis

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

In Column 9, Line 35, in the formula, please change "R" to
--H--.

Signed and Sealed this
Sixth Day of July, 1993

Attest:



MICHAEL K. KIRK

Attesting Officer

Acting Commissioner of Patents and Trademarks