United States Patent [19]

Klingler

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[54] **XANTHINES SUBSTITUTED IN THE 8-POSITION**

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[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.**.....**260/247.2 A;** 260/239 BF; 260/243 B; 260/256; 424/246; 424/248; 424/250

[51] **Int. Cl.**..... **C07d 87/34**

[58] **Field of Search**..... 260/247.2, 256, 243 B, 260/239 BC

[56] **References Cited**

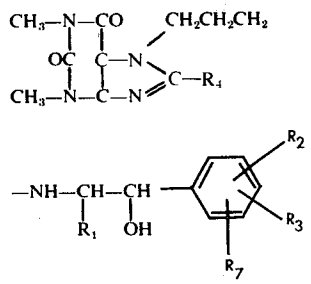
OTHER PUBLICATIONS

Kubotz et al., Pharmaceutical Society of Japan, Vol. 89, pp. 441–444, 1969.

Primary Examiner—Robert Gerstl
Assistant Examiner—Paul J. Killos
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

Compound are prepared having the formula:

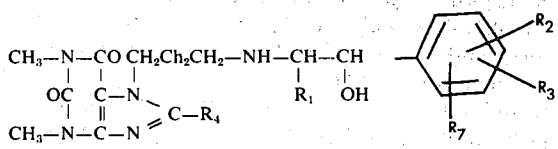


where R_1 is hydrogen or methyl, R_2 and R_3 are hydrogen, methyl, hydroxy, or hydroxymethyl, R_7 is hydrogen or methyl and R_4 is alkyl of 1 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or $-NR_5R_6$ where R_5 and R_6 individually are hydrogen or alkyl of 1 to 6 carbon atoms or R_5 and R_6 together with the nitrogen atom form a 5 to 7 membered ring which can have an additional oxygen, nitrogen or sulfur atom and also can contain 0 to 2 alkyl substituents with 1 to 4 carbon atoms or salts thereof. The compounds have outstanding broncholytic activity.

23 Claims, No Drawings

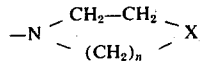
XANTHINES SUBSTITUTED IN THE 8-POSITION

The present invention relates to compounds of the formula:



where R_1 is hydrogen or methyl, R_2 and R_3 are hydrogen, methyl, hydroxy, or hydroxymethyl, R_7 is hydrogen or methyl and R_4 is alkyl of 1 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or

where R_5 and R_6 individually are hydrogen or alkyl 1 to 6 carbon atoms or R_5 and R_6 together with the nitrogen atom form a 5 to 7 membered ring which can have an additional oxygen, nitrogen or sulfur atom and also can contain up to 2 alkyl substituents with 1 to 4 carbon atoms or acid addition salts thereof. The substituents R_2 and R_3 are preferably located in the 3, 4 and 5 positions of the phenyl nucleus. Especially favorable properties are possessed by those compounds in which at least one of the R_2 and R_3 groups is a hydroxy group and the other is either hydrogen, hydroxy, methyl or hydroxymethyl, R_4 is preferably a morpholino group or an alkyl substituted morpholino group. Also especially suitable are those compounds in which R_1 is hydrogen, R_2 and R_3 are hydroxy groups in the 3, 4 or 3, 5 positions and R_4 is a ring of the formula:



where *n* is a member from 1 to 3 and X is a CH_2 group or in the case *n* is 2 or 3 X can also be either oxygen or nitrogen or R_4 can be a methyl substituted morpholino group.

The compounds of the invention are pharmacologically active and especially have a strong broncholytic activity. There are also present valuable circulatory activity.

As salts of the amines of formula I, there can be prepared and employed salts of any non-toxic pharmacologically acceptable acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, propionic acid, succinic acid, maleic acid, malonic acid, fumaric acid, lactic acid, tartaric acid and citric acid.

The compounds can be converted from the salts to the free bases again in customary manner, for example, by treating a solution in an organic medium such as alcohols, e.g., methanol with sodium carbonate or soda lye.

Examples of compounds within the invention in addition to those mentioned in the specific examples include 7 -{3-[2-(3-hydroxymethyl-4-hydroxy-5-methylphenyl)-2-hydroxyethylamino]-propyl} -8-dimethylamino-theophylline; 7- {3-[2-(3,4-di(hydroxymethyl)-phenyl)-2-hydroxyethylamino]-propyl} -8-morpholinotheophylline; 7- {3-[2-(4-hydroxymethyl phenyl)-1-methyl-2-hydroxyethylamino]-propyl} -8-methyl aminotheophylline;

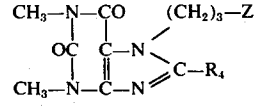
7-{3-[

2-(phenyl)-2-hydroxyethylamino]-propyl -8-(2,6-dimethyl) morpholino-theophylline; 7- {3-[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl-amino]-propyl}-8-amino-theophylline; 7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl-amino]-propyl}-8-hexylaminotheophylline; 7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-hexylamino-theophylline; 7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl-amino]-propyl- } -8-di sec. butylamino-theophylline; 7-{3-[2-(3,5-dihodroxyphenyl)-2-hydroxyethyl-amino]-propyl}-8-phenethyl-theophylline; 7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-thiomorpholino-theophylline; 7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-piperidino-theophylline; 7-{3-[2-(2-hydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-piperazino-theophylline; 7-{3-[2-(3,5-dihydroxyphenyl)-2-hydroxyethyl-amino]-propyl}-8-(2-butyl) morpholino-theophylline; 7-{3-[2(3,4-dihydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-pyrrolidino-theophylline; 7-{3-[2-(3,4-dihydroxylphenyl)-2-hydroxyethylamino]-propyl}-8-azacycloheptyl-theophylline; 7-{3-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-propyl-8-(1-oxa-4-azacycloheptyl)-theophylline.

The compounds of the invention can be prepared by methods which are known in themselves. Thus, there can be used the procedures employed in Klingler U.S. Pat. application Ser. No. 163,468 filed July 16, 1971, now U.S. Pat. No. 3,728,346 and in Klingler U.S. Pat. application Ser. No. 284,911 filed Aug. 30, 1972, now U.S. Pat. 3,855,221 entitled "Hydroxyphenyl Hydroxyethylaminoalkyl Theophyllines" (corresponding to Austrian application 7745/71 filed Sept. 6, 1971) by replacing the hydrogen nucleus in the 8-position of the theophylline nucleus of the starting material of those applications with the grouping R_4 as defined above. The entire disclosures of the two above-mentioned Klinger U.S. applications is hereby incorporated by reference.

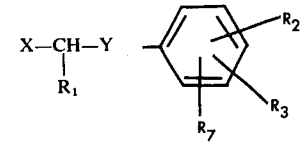
Thus, the compounds of the present invention can be prepared by reacting:

a. a compound of the formula:



II.

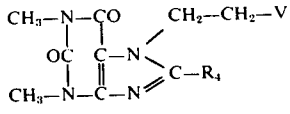
with a compound of the formula:



III.

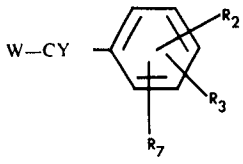
where Y is oxygen or hydroxyl plus a hydrogen and X and Y are different one being a halogen and the other an amino group except that if Z is an amino group and Y is a hydroxyl group plus hydrogen X can also form an ethylene oxide ring; if a keto group is present in the compound obtained, it is reduced to a hydroxyl group;

b. by condensing a compound of the formula:



IV.

with a compound of the formula:



V.

where V and W are always different and V is the aldehyde group —CHO or the group $—CH_2NH_2$ and W is the group $—C(R_1)=O$ or $—CH(R_1)=O$ or $—CH(R_1)—NH_2$ and Y is an oxygen atom or a hydroxyl group plus a hydrogen atom, with simultaneous or subsequent hydrogenation.

In the above recited processes, it is frequently expedient to protect the phenolic hydroxyl groups as well as the amino groups by a known protective group. Frequently such protective groups are already required for the starting compounds. These protective groups are easily splittable from the end products. It is either a matter of easily solvolytic splittable acyl groups or hydrogenating splittable groups as for example the benzyl group. the solvolytic splittable protective groups are split off for example by saponification with dilute acids at room temperature or by a short boiling. According to the type of protective group, however, the splitting also takes place during the reaction process. For example, the latter is the case if the amino group as well as, in a given case, the phenolic hydroxyl group also are protected by a benzyl group or a carbobenzoxy group and for example a keto group is hydrogenated. If the protective group is not split off during the reaction, a simple after treatment of the reaction product is necessary wherein then the splitting off of the protective groups takes place, for example under the conditions given above.

As protective groups for the amino groups there can be used, for example: the benzyl group, α-phenylethyl group, benzyl groups substituted in the benzene nucleus such as, for example, the p-bromo or p-nitrobenzyl group, the carbobenzoxy group, the carbobenzthio group, the trifluoroacetyl group, the phthalyl group, the trityl group, the p-toluenesulfonyl group and similar groups. These same protective groups can be used for the phenolic hydroxyl groups; additionally there can be used simple acyl groups as, for example, the acetyl group.

Process (a) is suitably carried out in a solvent such as alcohols, e.g., methanol, ethanol, propanol, isopropanol, or butanol, alcohol-water mixtures, dimethyl formamide, aromatic hydrocarbons such as benzene, toluene, xylene and other aromatic solvents at elevated temperatures such as for example 50° to 200°C. In a given case an acid acceptor is employed such as alkali carbonates, for example, potassium carbonate and sodium carbonate, tertiary amines, e.g., tributylamine or excess amine reactant. On occasion the process also can be carried out without a solvent.

In the case where Y is oxygen, the keto groups in the compound obtained must be reduced to the hydroxyl group. As catalysts, there can be used, for example, the customary finely divided metal catalysts such as noble metal catalysts, for example, platinum and especially palladium. The reduction can be carried out at normal temperature or elevated temperature. Suitably there is used a temperature range of about 40° to 100°C in a solvent such as lower aliphatic alcohols, e.g., methanol, ethanol, isopropanol, propanol and butanol, alcohol-water-mixtures dimethyl formamide, etc. There can be employed the free bases of formula II or the salts. If the phenolic hydroxyl groups as well as the secondary amino groups contain benzyl protective groups then these are split off simultaneously in the catalytic hydrogenation if, for example, a palladium catalyst is used. The reduction of the keto group can also take place with the aid of other known reducing agents which reduce a keto group to the hydroxyl group. These types of reducing agents are, for example, nascent hydrogen, (for example zinc-acid such as zinc-glacial acetic acid or zinchydrochloric acid, aluminum amalgam, metal hydride or complex metal hydrides (such as LiH, $LiAlH_4$, alkali borohydrides such as sodium borohydride or lithium borohydride, sodium-triexthoxyaluminum hydride), aluminum alcoholates such as aluminum isopropylate-isopropanol (Meerwein-Ponndorf process), etc.

If R is the hydroxymethyl group under mild conditions, there is obtained the end product of formula I when R is $—CH_2OH$ and by stronger conditions the end product where R is CH_3. If it is desired to maintain the CH_2OH group it is suitable to work at low or only slightly elevated temperatures as well as at normal pressure and to add the starting compound as the base. Another possibility is to reduce the ketone with a reducing agent which only attacks keto groups, especially complex metal hydrides such as sodium borohydride or lithium aluminum hydride and in a given case to subsequently split off the protective group by catalytic hydrogenation under mild conditions. This type of process is illustrated by example 2 of Klingler application Ser. No. 284,911, filed Aug. 30, 1972, now U.S. Pat. No. 3,855,221 entitled "Hydroxyphenyl Hydroxyethylaminoalkyl Theophyllines".

To recover the end product of formula I in which R is CH_3 in the case that R is CH_2OH in the starting material of formula II hydrogenation is carried out until the amount of hydrogen calculated for the reduction of the

keto group and the hydroxymethyl as well as in a given case for the splitting off of the protective group is taken up (pH in the acid region and elevated pressure are favorable for this).

In process (b) there can be used room temperature or elevated temperature. There can be used normal pressure or elevated pressure. The raction according to this process is carried out in a solvent such as alcohols, e.g., methanol, ethanol, isopropanol, propanol and butanol, water-alcoholmixtures, dimethyl formamide or dimethyl formamide containing mixture. There can be used the customary hydrogenation catalysts such as platinum, palladium or nickel with or without carriers. If hydrogenolytically splittable protective groups are present on the nitrogen of the side chain or on the hydroxyl groups of the phenyl radical these are simultaneously split off by using palladium as the hydrogenation catalyst.

The reduction step can take place simultaneously with the condensation or the Schiff's base can be first isolated and this reduced subsequently.

In processes (a) and (b) there can also be employed starting materials of formulas II and IV in which R_4 is replaced by an unsaturated radical such as for example an aliphatic alkenyl group having 1 to 6 carbon atoms or a phenyl alkenyl group having at least 8 to 12 carbon atoms. In this case, catalytic hydrogenation must always be employed whereby the unsaturated residue is converted to the corresponding saturated radical.

Those compounds which contain asymmetric carbon atoms and which as a rule are obtained as recemates can be split in known manner, for example, by means of optically active isomers, into optically active acid. However, it is also possible from the outset to employ optically active or disastereometric starting materials whereby there is obtained as the final product a corresponding pure optically active form or a disastereomer configuration. There can also occur stereoisomer racemates since they are present in the compounds produced two or more asymmetrical carbon atoms. Separation is possible in the customary manner, for example, by recrystallization.

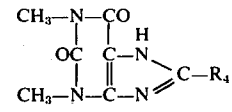
As stated previously the compounds of the invention are useful in the production of pharmaceutical compositions. The pharmaceutical compositions or medicaments can contain one or more of the compounds of the invention or mixtures of these with other pharmaceutically active materials. For the production of pharmaceutical preparations there can be used the customary pharmaceutical carriers and assistants. The medicines can be used enterally, parenterally, orally or perlingually. Dispensing can take place in the form of tablets, capsules, pills, dragees, plugs, ointments, powders, liquids or aerosols. As liquids there can be used oily or aqueous solutions or suspensions, emulsions, injectable aqueous and oily solutions or suspensions.

Unless otherwise indicated all parts and percentages are by weight.

Many of the starting theophylline derivatives are known. Those which are not (as well as those which are) can be obtained by the following processes:

PROCESS (a)

Compounds of Formula II in which Z is a halogen can be produced by reacting a compound of the following formula:



with a 1,3-dihalopropane, e.g., 1,3-dichloropropane or 1,3-dibromopropane with addition of an alkaline agent such as soda lye for example. The reaction is carried out at 50° to 200°C with solvents such as water, alcohols, e.g., methanol, ethanol, isopropanol, propanol or butanol, dimethyl formamide, dioxane or mixtures of these solvents.

The compounds of Formula II where Z is NH_2 or, for example a benzylamino group are prepared from the corresponding halo compounds by reaction with excess ammonia in an autoclave at a temperature between 80° and 150°C or by reaction with benzylamine without pressure in the same temperature range. As solvents there can be used water, alcohols, e.g., methanol, ethanol, isopropanol, propanol or butanol, water-alcohol-mixtures, dimethyl formamide, hydrocarbons such as toluene and xylene.

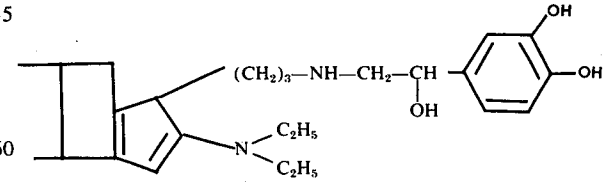
Those starting compounds of Formula II in which X with Y form an ethylene oxide ring can be produced from the corresponding halohydrins by reaction with alcoholic KOH at low temperatures. Phenolic hydroxyl groups are likewise preferably protected. This general procedure is disclosed in Houben/Weyl Vol. 6/3/ pages 374 et seq.

PROCESS (b)

To produce the aldehydes of Formula IV for example potassium theophylline substituted in the 8-position by R_4 can be reacted with β-chloropropionaldehyde diethyl acetal in a manner analogous to that disclosed in Kohlstaedt German patent is hereby incorporated by reference.

EXAMPLE 1

7-{3-[2-(3,4-dihydroxyphenyl)-2-hydroxyethylamino]-propyl}-8-diethylamino-theophylline



40.5 grams of 7-(3-benzylamino-propyl)-8-diethylamino-theophylline were dissolved in 95 ml of 25% ethyl alcohol and there was added by dropping inside two hours with stirring and introduction of nitrogen to

the mixture of a solution of 9.5 grams of o-chloroacetyl-pyrocatechol in 48 ml of ethyl alcohol. The mixture was heated for an additional 2 hours, made up to 800 ml with ethyl alcohol, acidified with alcoholic hydrochloric acid and filtered with suction after two days. To purify the product, it was boiled with ethyl alcohol and after cooling filtered with suction. The yield of the dried hydrochloride was 24 grams, M.P. 237°–239°C.

Unreacted starting material was easily recovered from the filtrate.

22.6 grams of the 7-{3-[2-(3,4-dihydroxyphenyl)-2-oxoethyl-benzylamino]-propyl}-8-diethylamino-theophylline hydrochloride thus obtained were dissolved in a mixture of 226 ml of distilled water, 300 ml of ethyl alcohol and 200 ml of methanol and hydrogenated at 550°C after addition of 2.3 grams of 10% palladium-activated carbon catalyst. The mixture was filtered after the end of the hydrogen take-up and the solvents distilled off. The residue was boiled under reflux with ethyl alcohol with stirring in a nitrogen atmosphere, the crystalline reduction product HCl-salt) filtered off with suction and dried at 50°C. Yield: 5.7 grams, M.P. 216°–217°C (with decomposition).

Production of the starting material (1) 7-chloropropyl-8-diethylamino-theophylline

57.3 grams of 8-diethylamino-theophylline were boiled with 226 grams of 1-chloro-3-bromopropane in 183 ml of isopropanol and 27 ml of water at reflux. Inside of 7 hours there were added dropwise with stirring a solution of 23.3 grams of potassium hydroxide in 87 ml of water. The excess chlorobromopropane was distilled off in a vacuum, the residue dissolved by addition of chloroform and dilute caustic potash solution, the two layers separated and the chloroform phase shaken twice with 5% caustic potash and finally with water.

In a given case the process can be carried out as follows:

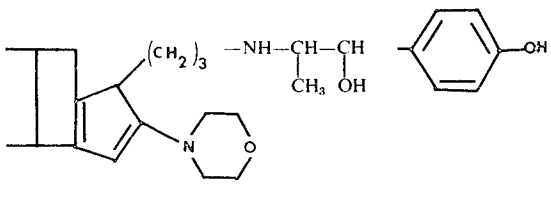
The mixture was strongly concentrated in a vacuum. After addition of 100 ml of chloroform, it was stirred a short time, filtered, the chloroform phase separated and this phase shaken with 5% caustic potash. The chloroform solution was dried with potassium carbonate, the chloroform distilled off and the residue recrystallized from methanol. There were obtained 47.4 grams of 7-chloropropyl-8-diethylamino-theophylline having a melting point of 129°–131°C.

2. 7-(3-benzylaminopropyl)-8-diethylamino-theophylline

24 grams of 7-chloropropyl-8-diethylamino-theophylline were dissolved in 57 ml of toluene and this solution boiled at reflux together with 14.7 grams of benzylamine and 15 grams of potassium carbonate with stirring for two days. Then the product was treated with water and stirred until the inorganic salts were dissolved. The separate toluene phase was evaporated in a vacuum, the residue washed well with water and the reaction product brought to crystallization by stirring with petroleum ether. The melting point was 73°–77°C.

EXAMPLE 2

7-{3-[1-methyl-2-hydroxy-2-(4-hydroxyphenyl)-ethylamino]-propyl}-8-morpholino-theophylline

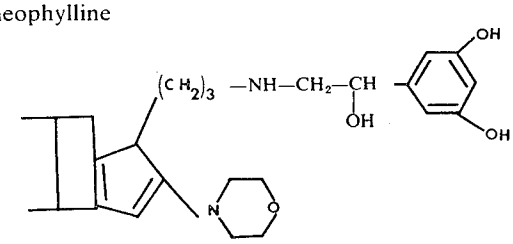


33.3 grams of 7-(3-benzylaminopropyl)-8-morpholinotheophylline together with 12.8 grams of p-benzyloxy-α-bromopropiophenone in 120 ml of xylene were boiled at reflux with stirring for 8 hours. Suction filtering was then employed and the filtrate evaporated in a vacuum. The residue was dissolved in hot ethanol, filtered and acidified with alcoholic hydrochloric acid. After the reaction mixture had stood for two days in the refrigerator, it was filtered with suction and dried at 80°C. There were obtained 23 grams of{7- 3-[1-methyl-2-oxo-2-(4-benzyloxyphenyl)-ethyl-benzylamino]-propyl } -8-morpholino-theophylline hydrochloride having a melting point of 204° to 205°C.

10 grams of the thus recovered material were dissolved in 200 ml of ethanol and after the addition of 1.0 gram of 5% palladium-activated carbon catalyst hydrogenated at 60°C. The product was filtered, evaporated and the residue recrystallized from ethanol. There were obtained 5.8 grams of the hydrochloride having a melting point of 220°–221°C.

EXAMPLE 3

7- 3-[2-(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-propyl -8-morpholiono-theophylline



12.8 grams of 7-(3-aminopropyl)-8-morpholino-theophylline were caused to react with 7.5 grams of 2-(3,5-dibenzyloxyphenyl)-2-hydroxyethyl bromide in the molten condition for 5 hours at 135°C with stirring. The reaction product was heated with toluene, filtered with suction and stirred with a little water, again filtered with suction and dried at 80°C. By solution in alcohol and acidification with alcoholic hydrochloric acid there were obtained 3.6 grams of 7-{3-[2-(3,5-dibenzyloxyphenyl)-2-hydroxyethyl-amino]-propyl-} 8-morpholino-theophylline hydrochloride, that was purified by recrystallization from aqueous ethanol, M.P. 199°–203°C.

15 grams of the intermediate product recovered in this manner were dissolved in 300 ml of ethanol and 60 ml of distilled water and after addition of 1.5 grams of 5% palladiumactivated carbon catalyst hydrogenated at 60°C. The product was filtered, evaporated and the residue heated with ethanol whereupon the hydrochloride crystallized out. Yield: 10.4 grams; M.P. 253°–256°C.

Production of the starting material 8-morpholino-theophylline was reacted with 1-chloro-3-bromopropane in the process described in example 1 and the compound obtained (M.P. 151°–153°C, likewise as described in example converted with benzylamine into the 7-(3-benzylaminopropyl)-8-morpholino-theophylline (melting point of the hydrochloride 243°–245°C). From this there were obtained the 7-(3-aminopropyl)-8-morpholinotheophylline (M.P. 90°–93°C) by catalytic hydrogenation in alcoholic solution at 60°C with use of palladium-activated carbon.

Further examples are given in Table 1 below. The production of compounds 4 to 10 was carried out in a manner analogous to example 1 and the compounds of examples 11–13 were produced in a manner analogous

to example 3. In table 2 there are given the melting points of the starting materials for examples 4–8. It may be noted that the melting points of the two starting materials which were not given in example 2 are the same as those in example 7. In Table 3 are given the melting points of those intermediate compounds for making compounds 9 to 13 which are new.

TABLE 1

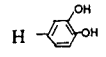
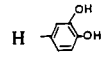
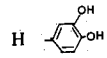
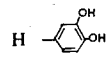
EXAMPLE NO.	COMPOUND OF FORMULA I R_1	R_4	M.P.°C. Hydrochloride
4		$-CH_2-C_6H_5$	115
5		$-(CH_2)_3-CH_3$	193–194
6			210–211
7			195–196 (decomposition)

TABLE 1-Continued

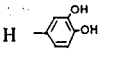
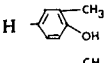
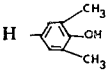
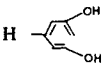
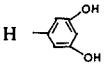
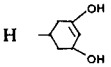
EXAMPLE NO.	COMPOUND OF FORMULA I R_1	R_4	M.P.°C. Hydrochloride
8	H 		188–189 (decomposition)
9	H 		197–198°
10	H 		201–204°
11	H 	$-N(C_2H_5)_2$	277–278°
12	H 		261–262°
13	H 		208–210°

TABLE 2

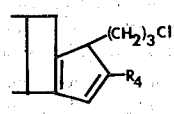
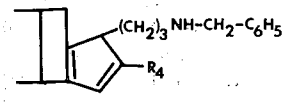
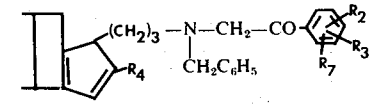
INTERMEDIATES FOR COMPOUND OF	MELTING POINT °C of Intermediates 		
EXAMPLE 4 $R_4 = CH_2-C_6H_5$ R_2R_3=3,4—OH	130 – 132°C	179 – 185°C (Hydrochloride)	180 – 184°C (Hydrochloride)
EXAMPLE 5 $R_4 = C_4H_9$ R_2R_3=3,4—OH	124 – 125°C (from Methanol)	232 – 234°C (Hydrochloride)	150 – 155°C (Hydrochloride)
EXAMPLE 6 R_4 =  R_2R_3=3,4—OH	126 – 130°C	90 – 98°C	166 – 172°C (Hydrochloride)
EXAMPLE 7 R_4 =  R_2R_3=3,4—OH	151 – 153°C	243 – 245°C Methanol (Hydrochloride)	246 – 247°C (Hydrochloride)
EXAMPLE 8 R_4 =  R_2R_3=3,4—OH	121 – 123°C	113 – 115°C from Methanol (free base)	218 – 220°C (Hydrochloride)

TABLE 3

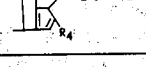
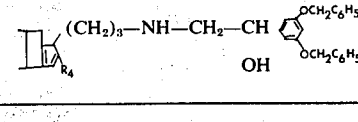
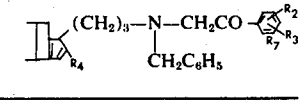
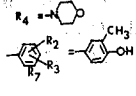
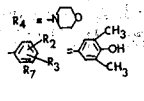
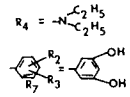
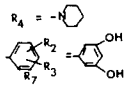
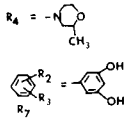
INTERMEDIATES FOR COMPOUND OF	MELTING POINT °C. of Intermediates 		
EXAMPLE 9 	known 90–93°C (free base)	no intermediate of this type	172–176°C (Hydrochloride)
EXAMPLE 10 	known 90–93°C (free base)	no intermediate of this type	199–202°C (Hydrochloride)

TABLE 3 —Continued

INTERMEDIATES FOR COMPOUND OF	MELTING POINT °C. of Intermediates		
		$(CH_2)_3-NH-CH_2-CH$ OH	$(CH_2)_3-N(CH_2C_6H_5)-CH_2CO$
EXAMPLE 11			
	87–89°C (free base)	166–168°C (Hydrochloride)	no intermediate of this type
EXAMPLE 12			
	235–237°C (Hydrochloride)	193–197°C (Hydrochloride)	no intermediate of this type
EXAMPLE 13			
	100–102°C (free base)	208–209°C (Hydrochloride)	no intermediate of this type

The compounds of the invention are suited for the production of pharmaceutical compositions and preparations. The pharmaceutical compositions or drugs contain as the active material one or several of the compounds of the invention, in a given case in admixture with other pharmacologically or pharmaceutically effective materials. The production of the medicine can take place with the use of known and customary pharmaceutical carriers and diluents, as well as other customary assistants.

Such carriers and assistants are set forth for example in Ullmann's Encyklopadie der technischen Chemie, Vol. 4 (1953), pages 1 to 39; Journal of Pharmaceutical Sciences, Vol. 52 (1963), pages 918 et seq; Hiv. Czetsch-Lindenwald, Hilfstoffe fur Pharmazie und angrenzende Gebiete; as well as in Pharm. I Vol. 2 (1961) pages 72 et seq.

Examples of such materials include gelatin, sucrose, pectin, starch, tylose, talc, lycopodium, silica, lactose, cellulose derivatives, micropulverized cellulose, stearates, e.g., methylstearate and glyceryl stearate, emulsifiers, vegetable oils, water, pharmaceutically compatible mono- or polyvalent alcohols and polyglycols such as glycerine, mannitol, sorbitol, pentaerythritol, ethyl alcohol, diethylene glycol, triethylene glycol, ethylene glycol, propylene glycol, dipropylene glycol, polyethylene glycol 400, as well as derivatives of such alcohols and polyglycols, dimethyl sulfoxide, esters of saturated and unsaturated fatty acids with mono- or polyvalent alcohols such as glycols, glycerine, diethylene glycol, perthaerythritol, sorbitol, mannitol, etc., e.g., glyceryl stearate, glyceryl palmitate, glyceryl oleate, ethylene glycol stearate; such esters of polyvalent alcohols can in a given case also be etherified, benzyl benzoate, dioxolane, glycerine formal, glcyol furfural, dimethyl acetamide, lactamide, lactates, e.g., ethyl lactate, ethyl carbonate, etc.

Furthermore, there can be added preservatives, stabilizers, buffers, taste correctives, antioxidants and complex formers (for example ethylenediaminotetraacetic acid) and the like.

As antioxidants there can be used for example sodium metal bisulfite and ascorbic acid, as preservatives there can be used for example sorbic acid, p-hydroxybenzoic acid esters, e.g., methyl p-hydroxybenzoate and ethyl p-hydroxybenzoate and similar materials.

The pharmacological and galenical treatment of the compounds of the invention takes place according to the usual standard methods.

The drugs can be used enterally, parenterally, orally, perlingually or in the form of sprays.

The addition of other medicinally active materials is also possible.

The compounds of the invention have a good bronchospasmolytic activity as exhibited, for example, on the isolated tracheal spiral of the guinea pig.

The bronchospasmolytic activity is comparable to that of the known drug orciprenaline.

The middle of the bronchospasm at 50–100% expectorant dosage in the above animal experiments expressed as ED50, for example, at 10^{-7} to 10^{-9} gram/ml.

The compounds of the invention have utility in treating bronchial asthma, chronic asthmatic bronchitis, emphysema bronchitis with spasmic components and additional respiratory illnesses.

The compounds can be delivered in the form of tablets, capsules, pills, dragees, liquids or aerosols. As liquids there can be used oily or aqueous solutions or suspensions, emulsions, injectable aqueous or oily solutions or suspensions. The preferred forms of use are tablets which contain between 1 and 50 mg. of active material or solutions which contain between 0.1 and 5% of active material.

In individual doses the amount of active component of the invention can be used for example in an amount of 2 mg dispensed orally or 10 strokes of a 0.2% solu-

tion dispensed as an aerosol. These doses can be dispensed once or several times a day.

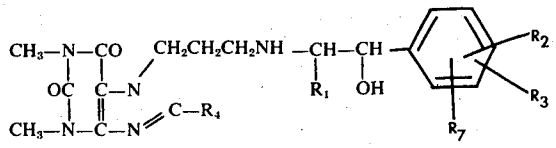
For example there is recommended the use of 1 tablet containing 2 mg of active ingredients 3 times daily or dispensed as an aerosol 1 to 4 times a day up to 10 strokes of the 0.2% solution.

The acute toxicity of the compounds of the invention in the mouse (expressed by the LD 50 mg/kg method of Miller and Tainer, Proc. Soc. Exph. Biol. and Med., Vol. 57 (1944) pages 261 et seq.) in i.v. application is between 80 mg/kg and 150 mg/kg.

The drugs can be used in human medicine or in veterinary medicine, e.g., to treat cats, dogs, horses, sheep, cattle, goats and pigs.

What is claimed is:

1. A compound having the formula:



wherein R_1 is hydrogen or methyl, R_2 and R_3 are hydrogen, methyl, hydroxy or hydroxymethyl, R_7 is hydrogen or methyl and R_4 is

where R_5 and R_6 individually are hydrogen or alkyl of 1 to 6 carbon atoms or R_5 and R_6 collectively together with the nitrogen atom form a 5 to 7 membered heterocyclic ring with 0 to 1 additional hetero atom and 0 to 2 alkyl substituents, said additional hetero atom being nitrogen, sulfur or oxygen, or a pharmacologically acceptable salt thereof.

2. A compound according to claim **1** wherein R_5 and R_6 are hydrogen or alkyl of 1 to 6 carbon atoms.

3. A compound according to claim **2** wherein R_3 is hydroxyl.

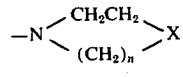
4. A compound according to claim **2** wherein both R_5 and R_6 are alkyl of 1 to 6 carbon atoms.

5. A compound according to claim **4** wherein R_3 is hydroxyl.

6. A compound according to claim **4** wherein both R_5 and R_6 are ethyl.

7. A compound according to claim **6** wherein R_3 is hydroxyyl.

8. A compound according to claim **1** wherein when R_5 and R_6 are taken collectively with the nitrogen atom the heteroCyclic ring has the formula



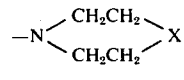
or is methyl morpholino, where n is 1 to 3 and X is CH_2, nitrogen or oxygen.

9. A compound according to claim **8** wherein R_2 is hydrogen, methyl or hydroxyl, R_3 is hydroxyl, and R_4 is dialkylamino wherein the alkyl group has 1 to 6 carbon atoms, morpholino, methylmorpholino or piperidino.

10. A compound according to claim **9** wherein R_2, R_3, and R_7 are in the 3, 4 and 5 positions.

11. A compound according to claim **8** wherein R_2 is hydrogen, methyl, hydroxy or hydroxymethyl, R_3 is hydroxy and R_2, R_3 and R_7 are in the 3,4 and 5 positions, and R_4 is morpholino or methylmorpholino.

12. A compound according to claim **8** wherein R_1 is hydrogen, R_2 and R_3 are hydroxyl groups in the 3,4 or 3,5 position and R_4 is a ring of the formula:



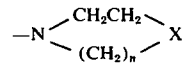
where X is CH_2, N or O or $R_4$is methyl morpholino.

13. A compound according to claim **8** wherein R_7 is methyl.

14. A compound according to claim **8** wherein R_7 is hydrogen.

15. A compound according to claim **14** wherein R_2 is hydrogen, methyl or hydroxyl, R_3 is hydroxyl, R_4 is diethylamino, morpholino, or methyl morpholino.

16. A compound according to claim **1** wherein R_4



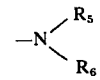
where X is CH_2, nitrogen or oxygen, n is 1 to 3 or heterocyclic ring compounds of said formula wherein up to 2 of the hydrogen atoms are replaced by alkyl.

17. A compound according to claim **16,** wherein X is oxygen and n is 2.

18. A compound according to claim **17** wherein

is morpholino or alkyl morpholino having 1 to 4 carbon atoms in the alkyl group.

19. A compound according to claim **18** wherein



is morpholino or methyl morpholino.

20. A compound according to claim **19** wherein R_2 is hydrogen, methyl or hydroxyl and R_3 is hydroxyl.

21. A compound according to claim **20** wherein R_2, R_3 and R_7 are in the 3, 4 and 5 positions.

22. A compound according to claim **18,** wherein R_7 is methyl.

23. A compound according to claim **18,** wherein R_7 is hydrogen.

* * * * *