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Schwender

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[54] **ARALKYL-SUBSTITUTED PURINES AND PYRIMIDINES AS ANTIANGINAL BRONCHODILATOR AGENTS**

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[52] **U.S. Cl.** ..... **260/252,** 260/253, 260/254, 260/256.4 N, 424/253

[51] **Int. Cl.** **C07d 57/38**

[58] **Field of Search** 260/252, 253, 254

[56] **References Cited**

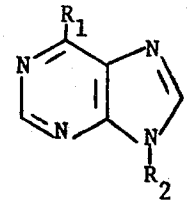
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[57] **ABSTRACT**

The present invention relates to compounds of formula I:



I

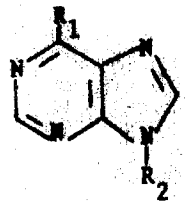
wherein R_1 is hydroxy, methoxy, mercapto, hydrazino, substituted hydrazino, chloro, amino, alkylamino, dialkylamino, hydroxyalkylamino, aralkylamino or substituted aralkylamino and R_2 is phenylalkyl having 1 to 3 carbon atoms in the alkyl moiety and at least two alkoxy, alkyl, halogen, hydroxy, nitro, amino, substituted amino, aminomethyl, acylamino, carboxy, carboxyalkyl or hydroxymethyl groups in the benzene ring or naphthylalkyl, tetrahydronaphthylalkyl, quinolylalkyl, tetrahydroquinolylalkyl or isoquinolylalkyl, each having 1 to 3 carbon atoms in the alkyl moiety and pharmaceutically acceptable acid addition salts thereof.

These compounds are useful as antianginal or bronchial dilator agents.

20 Claims, No Drawings

ARALKYL-SUBSTITUTED PURINES AND PYRIMIDINES AS ANTIANGINAL BRONCHODILATOR AGENTS

The present invention is concerned with novel compounds and, more particularly, the present invention is concerned with aralkyl-substituted purines and pyrimidines having structural formula I:



I

wherein R_1 is hydroxy, methoxy, mercapto, hydrazino, substituted hydrazino, chloro, amino, alkylamino, dialkylamino, hydroxyalkylamino, aralkylamino or substituted aralkylamino and R_2 is phenylalkyl having 1 to 3 carbon atoms in the alkyl moiety and at least two alkoxy, alkyl, halogen, hydroxy, nitro, amino, substituted amino, aminomethyl, acylamino, carboxy, carboxyalkyl or hydroxymethyl groups in the benzene ring or naphthylalkyl, tetrahydronaphthylalkyl, quinolylalkyl, tetrahydroquinolylalkyl or isoquinolylalkyl, each having 1 to 3 carbon atoms in the alkyl moiety and pharmaceutically acceptable acid addition salts thereof.

In addition, esters or amides of the above compounds utilizing alkanoyl or aralkanoyl, such as acetyl, propionyl, benzoyl, succinoyl and the like, and the pharmaceutically acceptable acid addition salts are also within the scope of this invention.

In the above definitions for R_1, the term "alkyl" means an aliphatic hydrocarbon having 1 to 6 carbon atoms, for example, methyl, propyl, isopropyl, isobutyl and the like. The term "aryl" denotes an aromatic hydrocarbon having 6 to 14 carbon atoms, for example, phenyl, naphthyl, anthryl and the like. The term "aralkyl" designates a combination of the hereinbefore defined alkyl and aryl groups. Substituted hydrazino denotes hydrazino substituted on either nitrogen atom or both nitrogen atoms by one or more alkyl or aryl groups.

In the above definitions for R_2, the term "alkyl" stands for an aliphatic hydrocarbon of 1 to 6 carbon atoms, unless otherwise specified, and applies to the alkyl residues of the alkoxy and acyl moieties. Substituted amino includes within its scope amino groups substituted by alkyl and aryl groups defined in the preceding paragraph. Halogen encompasses all of the halo groups, chloro, bromo, iodo and fluoro.

Among the preferred compounds of this invention are those purine derivatives wherein R_1 is chloro, amino, hydroxy, hydrazino, n-propylamino or 2-hydroxyethylamino and R_2 is dimethoxybenzyl and R_1 is amino and R_2 is dichlorobenzyl, 3,4-dimethylbenzyl.

The compounds of this invention exhibit a unique mode of biological action in that they produce selective dilation of certain coronary arteries causing a redistribution of blood flow towards ischemic areas of the heart enhancing perfusion and reducing anoxia which cause anginal pains. This biological activity is demonstrated in accordance with the procedure described in J. Pharmacol. Exp. Ther., 176,184 (1971). Only nitroglycerin and some β-adrenergic blockers have been demonstrated to similarly redistribute blood flow to ischemic areas by large coronary artery dilation. See Eur. J. Pharmacol., 16, 271 (1971). The compounds of this invention offer an advantageous treatment of angina without interference with adrenergic control of the heart or without resorting to the use of nitrates.

Existing coronary vasodilators such as dipyridamole and chromonar dilate smaller vessels increasing coronary blood flow without redistributing flow to needed ischemic areas. In severe ischemia, dipyridamole actually induced anginal attacks in man since it diverted blood flow away from ischemic areas through its dilator action on smaller coronary vessels. See Ann. Rep. Med. Chem., 7, 69 (1972).

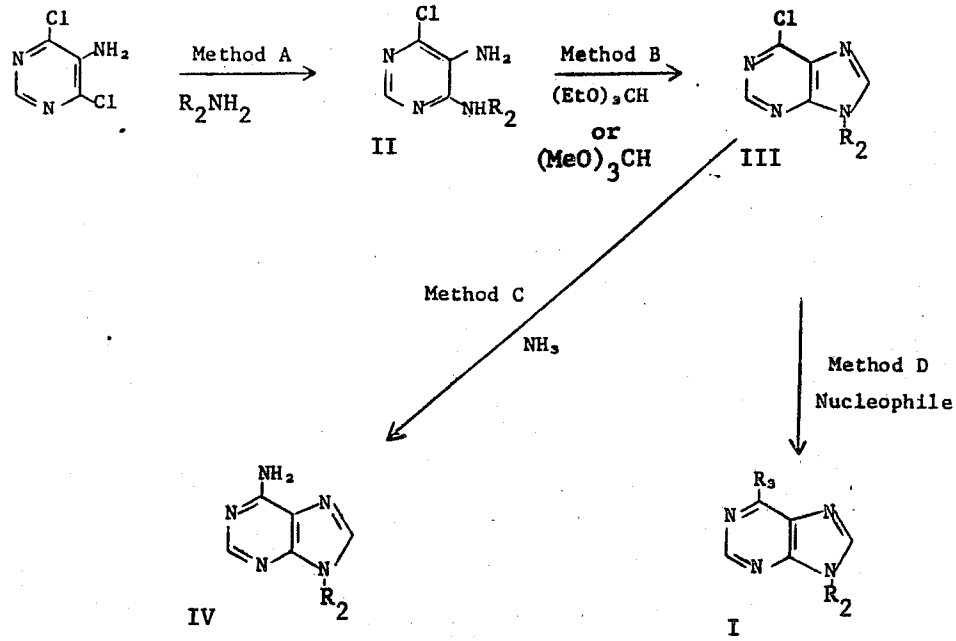
Experimentally, this blood flow redistribution is demonstrable in a dog by measuring changes in resistance to blood flow of larger coronary arteries (RL) relative to small vessel physical resistance to flow (RT), using the protocol described in J. Pharmacol. Exp. Ther., 176, 184 (1971).

Generally, the compounds of this invention at a dose of about 1–10 mg/kg were observed to effect a drop in the RL:RT ratio. Known coronary vasodilators such as dipyridamole and chromonar caused an increased RL:RT ratio reflecting a redistribution of blood flow away from ischemic tissues.

The compounds of this invention, particularly the preferred species, are indicated in the management of angina pectoris. A usual dose of 1–10 mg/kg by injection or orally two or three times daily is suggested to prevent anginal attack. These compounds can be administered by combining with excipients such as lactose or water for injection.

In addition to the antianginal effects described above, the compounds of this invention were also observed to protect guinea pigs from histamine-induced bronchial spasm. Thus tested in accordance with the procedure described in J. Pharmacol. Exp. Ther., 90, 254 (1947) at a dose of 1–50 mg/kg intraperitoneally, they were effective to protect the guinea pigs against bronchial spasms which had been induced by the administration of one mg of histamine. At this dosage level, a mild cardiotonic effect was also observed. Hence, the compounds of this invention are also useful in the treatment of bronchial spasms such as in bronchial asthma. Generally speaking, a dose of 1–50 mg/kg administered orally or by intramuscular injection is suggested.

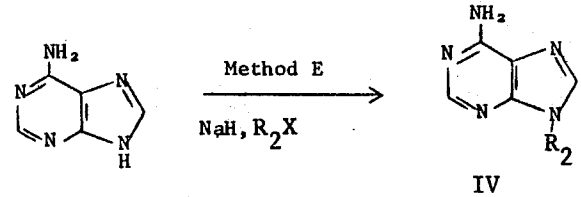
According to the present invention, the above compounds are prepared by processes as illustrated in the following reaction scheme:



Referring now to the reaction scheme, in Method A 5-amino-4,6-dichloropyrimidine is condensed with a substituted amine in butanol and triethylamine. The resultant substituted amino pyrimidine II is cyclized with triethyl or trimethyl orthoformate to the 6-chloropurine derivative III as in Method B. Treating said 6-chloropurine derivative with ammonia as brought out in Method C, or an appropriate nucleophile as in Method D, gives the 6-substituted purine derivative I.

The starting material for the first process, 5-amino-4,6-dichloropyrimidine, is available from commercial chemical suppliers such as Krishell Laboratories, Inc. The amino compounds utilized in Method A, triethyl- and trimethyl orthoformate of Method B and the nucleophiles of Method D are available from the Aldrich Chemical Company or readily prepared by methods well known to those skilled in the art.

In addition, treatment of adenine with a substituted benzyl or aralkyl halide in the presence of a base such as sodium hydride gives the desired 9-substituted adenine directly. This reaction is illustrated by the following reaction scheme:



Adenine, the starting material for the second process is commercially available from the Aldrich Chemical Company as are the requisite aralkyl halides, R_2X.

The following experiments are general procedures for the preparation of the compounds of this invention: all temperatures are in degrees centigrade.

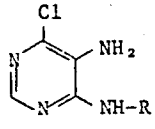
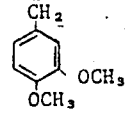
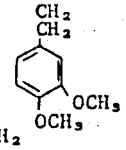
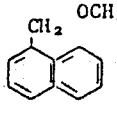
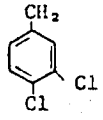


TABLE I

R	Formula	Analysis*	mp°C	Recrystallization Solvent	Method Preparation
	$C_{13}H_{13}ClN_4O_2$	CHNCl	188-191	MeOH/H_2O	A
	$C_{14}H_{17}ClN_4O_2$	CHNCl	133-135	MeOH/H_2O	A
	$C_{15}H_{13}ClN_4$	CHNCl	219-223	MeOH/H_2O	A
	$C_{11}H_9Cl_3N_4$	CHNCl	197-198.5	EtOH/H_2O	A

*Compounds reported analyzed within ±0.4% of theory.

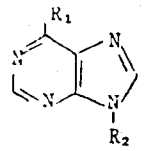
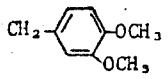
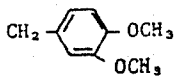
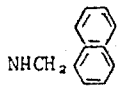
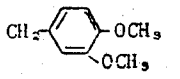
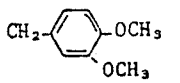
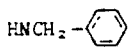
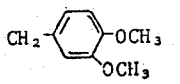
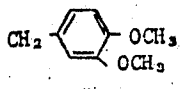
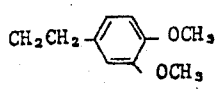
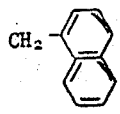
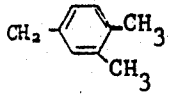
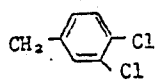


TABLE II (Con't)

R_1	R_2	Formula	Analysis*	mp°C	Solvent Recrystallization	Method Preparation
Cl		$C_{14}H_{13}ClN_4O_2$	CHNCl	160-164	EtOH/H_2O	B
SH		$C_{14}H_{14}N_4O_2S$	CHNS	200-205	DMF/ether	D and thiourea
	"	$C_{25}H_{23}N_5O_2$	CHN	150-153	acetone/hexane	D
NH_2		$C_{14}H_{13}N_5O_2$	CHN	192-194	EtOH/H_2O	C
OH		$C_{14}H_{14}N_4O_3$	CHN	200-202	MeOH	D and HCl, dilute
		$C_{21}H_{21}N_5O_2$	CHN	165-167	EtOH	D
$NHCH_2CH_2OH$	"	$C_{16}H_{19}N_5O_3$	CHN	144-146	2-PrOH	D

*Satisfactory analysis within ±0.4% of theoretical was obtained for all compounds reported.

R_1	R_2	Formula	Analysis*	mp°C	Solvent Recrystallization	Method Preparation
OCH_3		$C_{15}H_{14}N_4O_3$	CHN	129-132	2-PrOH	D
$NHNH_2$	"	$C_{14}H_{16}N_6O_2$	CHN	181-184	EtOH	D
$NHCH_2CH_2CH_3$	"	$C_{17}H_{21}N_5O_2$	CHN	123-125	acetone	D
Cl		$C_{15}H_{15}ClN_4O_2$	CHNCl	116-119	CCl_4/heptane	B
NH_2	"	$C_{15}H_{17}N_5O_2$	CHN	194-197	benzene/heptane	C
Cl		$C_{16}H_{11}ClN_4$	CHNCl	156-158	MeOH	B
NH_2	"	$C_{16}H_{13}N_5$	CHN	269-272 dec	EtOH	C
$NHCH_2CH_2CH_3$	"	$C_{19}H_{19}N_5$	CHN	161.5-163.5	MeOH/H_2O	D
$NHCH_2CH_2OH$	"	$C_{18}H_{17}N_5O$	CHN	199.5-200	EtOH/H_2O	D
NH_2		$C_{14}H_{15}N_5$	CHN	211-213	CH_3OH	E
Cl		$C_{12}H_7Cl_2N_4$	CHNCl	141-143	EtOH/H_2O	B
NH_2	"	$C_{12}H_9Cl_2N_5$	CHNCl	255-258	EtOH/H_2O	C

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6. O. H. Siegmund, H. R. Granger and A. M. Lands, J. Pharmacol. Exp. Ther., 90, 254 (1947).

METHOD A

5-Amino-4-chloro-6-(3,4-dimethoxybenzylamino)-pyrimidine. A reaction mixture containing 1.00 g (6.09 mmols) of 4,6-dichloro-5-aminopyrimidine, 1.22 g (7.30 mmols) of 3,4-dimethoxybenzylamine, 1.02 ml (7.30 mmols) of triethylamine and 35 ml of 1-butanol was refluxed overnight for 17 hours. Evaporation of the reaction mixture in vacuo gave a residual oil which was crystallized by trituration with water. The crude yellow solid was recrystallized from methanol-water to give 1.61 g (90.1 percent), mp 185°–188°, of crystalline product. The analytical sample was obtained by recrystallization from methanol-water; yield, 1.36 g (76.9 percent); mp 188°–191°.

METHOD B

6-Chloro-9-(3,4-dimethoxybenzyl)purine. To a suspension of 15.6 g (52.8 mmols) of 5-amino-4-chloro-6-(3,4-dimethoxybenzylamino)-pyrimidine in 100 ml of triethyl orthoformate was added 149 mg (1.36 mmols) of ethanesulfonic acid and the resulting mixture was heated at 80° for 15 min. Upon cooling and addition of hexane to the reaction mixture, a yellow precipitate formed which was collected by filtration; yield, 15.4 g (95.6 percent) mp 159°–163°. Recrystallization from EtOH—H_2O gave the analytical sample; yield 13.2 g (82.2 percent) mp 160°–164°.

METHOD C

9-Veratryl-9H-adenine. In a steel bomb was heated a mixture of 4.00 g (13.1 mmols) of 6-chloro-9-veratrylpurine and 20 ml of liquid NH_3 for 17 hours at 54°. The excess NH_3 was allowed to evaporate and the white solid residue was recrystallized from EtOH—H_2O to give the crude product; yeild 3.42 g (91.3 percent) mp 191°–193°. The analytical sample was obtained by a second recrystallization from EtOH—H_2O giving 2.33 g (62.3 percent) mp 192°–194°.

METHOD D

6-Propylamino-9-veratrylpurine. A reaction mixture containing 5.14 g (16.8 mmol) of 6-chloro-9-veratrylpurine, 7.0 ml (84.9 mmol) of propylamine and 60 ml of EtOH was refluxed for 2.5 hrs. Evaporation of the reaction mixture gave a residual solid which was recrystallized from acetone to give the crude product; yield 4.78 g (87.0 percent) mp 117°–120°. Further recrystallizations of the crude white material from acetone gave the analytical material; mp 122°–125°.

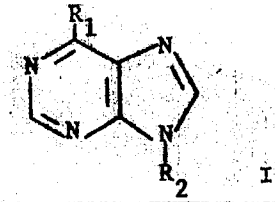
METHOD E

9-(3,4-Dimethylbenzyl)adenine (W10,813). An ice cold suspension containing adenine (10.0 g, 74 mmol), 3.74 g (89.0 mmol) of NaH (57 percent suspension in oil) and 120 ml of DMF was allowed to reach RT and stirred for one additional hour. 3,4-Dimethylbenzyl chloride 13.7 g (89 mmol) was added to the reaction mixture. The resultant mixture was allowed to react at RT for 17 hrs with stirring. The reaction mixture was cooled and the resultant precipitate was collected by filtration giving the crude reaction product. Recrystallization of the crude white solid from methanol gave 3.90 g (21 percent) of white crystalline material; mp 206°–209°. The analytical sample was obtained by recrystallization from methanol; mp 211°–213°.

Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65. Found: C, 66.38; H, 6.10; N, 27.80.

I claim:

1. A compound of the formula I:



I

wherein R_1 is, chloro, hydroxy, mercapto, alkoxy of 1 to 6 carbon atoms, hydrazino, amino, amino substituted by one or two alkyl groups each of 1 to 6 carbon atoms, amino substituted by 1-naphthylmethyl or benzyl, or hydroxy-alkylamino of 1 to 6 carbon atoms and R_2 is 1-naphthylmethyl, phenylmethyl, and phenylethyl substituted on the phenyl group by two or three alkoxy groups of 1 to 6 carbon atoms, 2 or 3 alkyl groups of 1 to 6 carbon atoms, or two chloros and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in which R_1 is methoxy and R_2 is 3,4-dimethoxybenzyl.

3. A compound according to claim 1 in which R_1 is mercapto and R_2 is 3,4-dimethoxybenzyl.

4. A compound according to claim 1 in which R_1 is 1-naphthylmethylamino and R_2 is 3,4-dimethoxybenzyl.

5. A compound according to claim 1 in which R_1 is amino and R_2 is 3,4-dimethoxybenzyl.

6. A compound according to claim 1 in which R_1 is hydroxy and R_2 is 3,4-dimethoxybenzyl.

7. A compound according to claim 1 in which R_1 is benzylamino and R_2 is 3,4-dimethoxybenzyl.

8. A compound according to claim 1 in which R_1 is 2-hydroxyethylamino and R_2 is 3,4-dimethoxybenzyl.

9. A compound according to claim 1 in which R_1 is chloro and R_2 is 3,4-dimethoxybenzyl.

10. A compound according to claim 1 in which R_1 is hydrazino and R_2 is 3,4-dimethoxybenzyl.

11. A compound according to claim 1 in which R_1 is 1-propylamino and R_2 is 3,4-dimethoxybenzyl.

12. A compound according to claim 1 in which R_1 is chloro and R_2 is 2-(3,4-dimethoxyphenyl)ethyl.

13. A compound according to claim 1 in which R_1 is amino and R_2 is 2-(3,4-dimethoxyphenyl)ethyl.

14. A compound according to claim 1 in which R_1 is chloro and R_2 is 1-naphthylmethyl.

15. A compound according to claim 1 in which R_1 is amino and R_2 is 1-naphthylmethyl.

16. A compound according to claim 1 in which R_1 is propylamino and R_2 is 1-naphthylmethyl.

17. A compound according to claim 1 in which R_1 is 1-hydroxyethylamino and R_2 is 1-naphthylmethyl.

18. A compound according to claim 1 in which R_1 is amino and R_2 is 3,4-dimethylbenzyl.

19. A compound according to claim 1 in which R_1 is chloro and R_2 is 3,4-dichlorobenzyl.

20. A compound according to claim 1 in which R_1 is amino and R_2 is 3,4-dichlorobenzyl.

* * * * *