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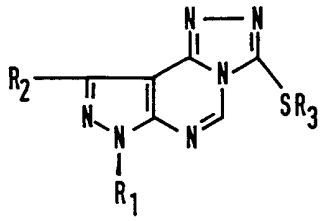
(19)

(54) PYRAZOLO [4,3-e] [1,2,4] TRIAZOLO [4,3-c] PYRIMIDINE COMPOUNDS AND THEIR PREPARATION

(71) We, E. R. SQUIBB & SONS INC., a Corporation organized and existing under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

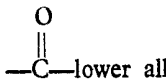
This invention relates to new pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines and salts thereof which are useful as antiinflammatory agents.

The compounds of the present invention have the general formula

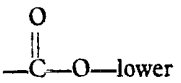


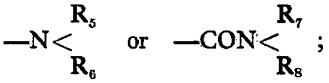
I

wherein R_1 and R_2 each is hydrogen or lower alkyl; R_3 is hydrogen, an alkali metal ion,



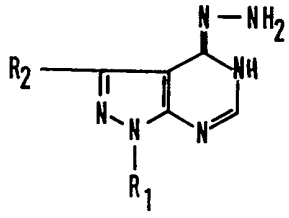
lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is hydroxy, cyano, phenyl,





R_4 is lower alkyl or phenyl; R_5 and R_6 each is hydrogen or lower alkyl or R_5 and R_6 together with the nitrogen form one of the heterocyclic radicals pyrrolidino, piperidino, morpholino or piperazino; and R_7 and R_8 each is hydrogen or lower alkyl, and lower alkyl in each case is as hereinafter defined.

The present invention also provides a process for preparing a compound of the above formula I, which comprises reacting a compound of the formula

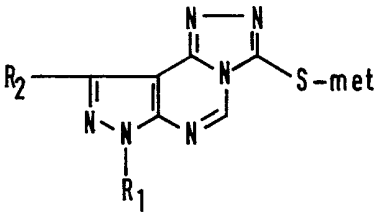


V

wherein R_1 and R_2 are defined as above, with an alkali metal alcoholate of the formula

met—O—R

wherein met is an alkali metal and R is lower alkyl, followed by reaction with carbon disulfide to form a compound of the formula

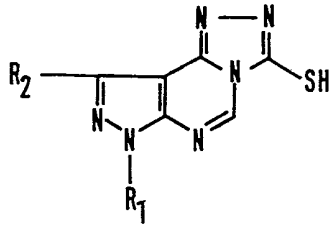


VI

wherein R_1, R_2 and met are defined as above and, if desired, acidifying the compound of Formula VI to form a compound of Formula I wherein R_3 is hydrogen or, if desired, reacting the compound of Formula VI with a compound of the formula

$$XR_3 \qquad \text{VII}$$

wherein X is a halogen and R_3 is defined as above other than hydrogen or an alkali metal ion; or reacting a compound of Formula V with 1,1-thiocarbonyldiimidazole to obtain a product of the formula



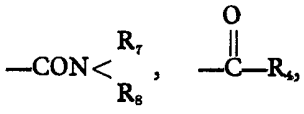
X

and, if desired, reacting the compound of Formula X with a compound of Formula VII.

The lower alkyl groups represented by the various symbols are straight or branched chain aliphatic hydrocarbon radicals having from one to seven carbon atoms, preferably the C_1—C_4 and especially C_1—C_2 members. Illustrative are methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

The alkali metal ions are, e.g., sodium or potassium.

Preferred are those compounds of Formula I wherein R_1 is lower alkyl, especially methyl, and R_2 is hydrogen. R_3 is preferably hydrogen, lower alkyl or lower alkyl substituted by hydroxy (e.g. hydroxy propyl), by phenyl or by piperidino. When the lower alkyl group is substituted by cyano,

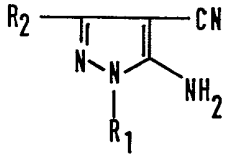


or —C(=O)—O—lower alkyl,

the bridging lower alkyl group preferably has one carbon atom. The examples illustrate particularly preferred embodiments.

The compounds of this invention can be produced by several methods of synthesis.

According to one method a 4-cyano-5-aminopyrazole of the formula

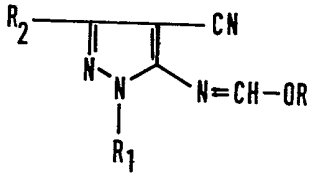


II

(which is produced, for example, from an unsubstituted or substituted ethoxymethylenemalononitrile and hydrazine or a substituted hydrazine) is made to react with an excess of a orthoformic acid ester of the formula

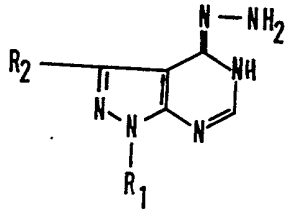
$$H—C(OR)_3 \qquad \text{III}$$

wherein R is lower alkyl, with heating, to produce an intermediate of the formula



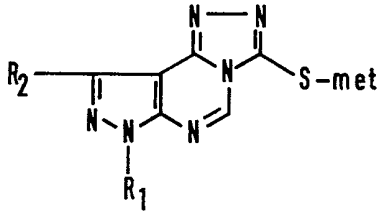
IV

Reaction of the product of Formula IV with hydrazine (or its hydrate) at elevated temperature in an organic solvent, e.g., an alcohol such as ethanol, yields a product of the formula



V

Treatment of this product (V) with an alkali metal alcoholate (met—O—R, wherein met is an alkali metal and R is lower alkyl) in a medium such as dimethylformamide, and then reaction with carbon disulfide results in cyclization and formation of the compound of the formula



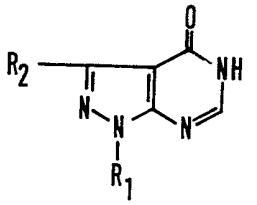
VI

Acidification of this product (VI) yields the free mercapto compound, i.e., the compound of formula I wherein R_3 is hydrogen. Treatment of the product of formula VI with a compound of the formula

XR_3 (VII)

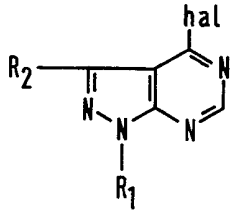
wherein X is a halogen such as iodine, bromine or chlorine and R_3 has the meaning defined above other than hydrogen or an alkali metal ion, e.g., in a medium such as dimethylformamide at about ambient temperature, provides a product of formula I wherein R_3 has any of the meanings defined above except hydrogen or an alkali metal ion.

An alternative method of synthesis comprises reacting a pyrazolo[3,4-d]pyrimidine of the formula



VIII

(or its enol form) with a phosphorus oxyhalide such as phosphorus oxychloride at elevated temperature to form the halo derivative

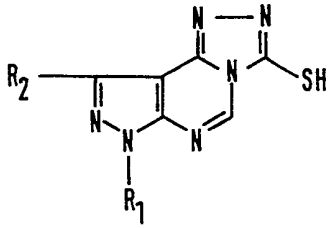


IX

wherein hal represents the halogen.

This intermediate of formula IX is then treated with hydrazine or its hydrate in an alcohol such as ethanol at about ambient temperature. The intermediate of formula V above results from this reaction.

The intermediate of formula V can now be treated as described above or it can be made to react with 1,1-thiocarbonyldiimidazole in a medium such as dimethylformamide at a reduced temperature, e.g., about 5—10°C, to obtain as a product a compound of the formula



X

This product (X) is then optionally treated as described above.

The new compounds of this invention have anti-inflammatory properties and are useful as anti-inflammatory agents, for example, to reduce local inflammatory conditions such as those of an edematous nature or resulting from proliferation of connective tissue in various mammalian species such as rats and dogs when given orally in dosages of about 5 to 100 mg/kg/day, preferably 5 to 50 mg/kg/day, in single or 2 to 4 divided doses, as indicated by the carageenan edema assay or delayed hypersensitivity reaction in rats. The active substance is utilized in a composition such as tablet, capsule, solution or suspension containing up to about 500 mg. per unit of dosage of a compound or mixture of compounds of formula I or physiologically acceptable salt(s) thereof. The material is compounded in conventional manner with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer and flavor as called for by accepted pharmaceutical practice. Topical preparations containing about 0.01 to 3 percent by weight of active substance in a conventional lotion, salve or cream can also be used.

The following examples illustrate the present invention. All temperatures are in degrees celsius.

Example 1.

a) *1 - Methyl - 4 - cyano - 5 - ethoxymethyleneaminopyrazole.*

222.0 g. of 1 - methyl - 4 - cyano - 5-aminopyrazole (produced from ethoxymethylenemalononitrile and methylhydrazine), 279 g. of orthoformic acid triethyl ester (15% excess) and 225 ml. of acetic anhydride are heated at reflux for 3 hours until a clear solution results. The alcohol thus formed, excess orthoester, ethyl acetate and acetic anhydride are distilled off. The oily residue crystallizes on rubbing. The crude product, 1-methyl-4-cyano-5-ethoxymethyleneaminopyrazole, is recrystallized from cyclohexane and obtained in 219 g. yield are colorless crystals, m.p. 48°. The crude product is sufficiently pure for further use.

b) *1,5 - Dihydro - 1 - methyl - 4H - pyrazolo-[3,4-d]pyrimidin-4-one hydrazone.*

160 g. of 1 - methyl - 4 - cyano - 5-ethoxymethyleneaminopyrazole are dissolved in 1 liter of absolute ethanol and 76.0 g. of hydrazine hydrate are added dropwise with stirring. This mixture is refluxed for 8 hours. After cooling, the product, 1,5-dihydro-1-methyl - 4H - pyrazolo[3,4 - d]pyrimidin-4-one hydrazone, is filtered under suction and crystallized from dimethylformamide, yield 135 g., m.p. 231°.

c) *7 - Methyl - 3 - mercapto - 7H - pyrazolo-[4,3 - e][1,2,4]triazolo[4,3 - c]pyrimidine, potassium salt.*

73 g. of 1,5 - dihydro - 1 - methyl - 4H-pyrazolo[3,4 - d]pyrimidin - 4 - one hydrazone are suspended in 350 ml. of dimethylformamide and 49 g. of potassium t-butylate are added. 34.8 g. of carbon disulfide are added dropwise with stirring and, after the addition, the reaction mixture is stirred at 80° for 2 hours

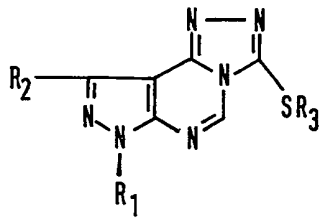
and for 12 hours at room temperature. After washing with methanol and ether, 55 g. of 7-methyl - 3 - mercapto - 7H - pyrazolo[4,3-e][1,2,4]triazolo[4,3 - c]pyrimidine, potassium salt are obtained as a light yellow powder, m.p. >300°. An additional 3.2 g. of the potassium salt are obtained by concentrating the filtrate. By acidifying the potassium salt, the free mercapto compound is obtained as yellowish crystals, m.p. 254°.

Example 2.

7 - Methyl - 3 - methylthio - 7H - pyrazolo-[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine.

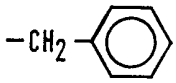
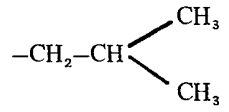
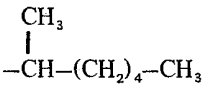
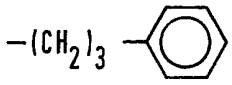
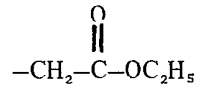
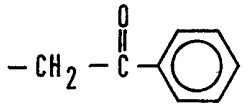
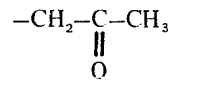
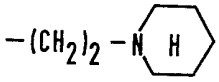
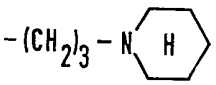
To 3 g. of 7 - methyl - 3 - mercapto-7H - pyrazolo[4,3 - e][1,2,4]triazolo[4,3-c]pyrimidine, potassium salt, in 25 ml. of dimethylformamide, 2.1 g. of methyl iodide are added and the mixture is stirred for 1 hour at room temperature. The reaction mixture is then poured into 200 ml. of water and the product, 7 - methyl - 3 - methylthio - 7H-pyrazolo[4,3 - e][1,2,4]triazolo[4,3 - c]-pyrimidine, is filtered under suction, crystallized from dimethylformamide and obtained as yellowish crystals, m.p. 204—206°.

The following additional compounds of formula I having the substituent R_3 in the table below are obtained by treating 7-methyl-3 - mercapto - 7H - pyrazolo[4,3 - e][1,2,4]-triazolo[4,3-d]pyrimidine, potassium salt, with the halide XR_3, wherein X and R_3 have the meanings indicated in the table, according to the procedure of Example 2:



I

(R_2 is hydrogen)

Example	R_1	X	R_3	m.p. °C	Crystallized from:
3	CH_3	I	$-C_2H_5$	183	Methyleneglycol
4	CH_3	Br		207–208	Methyleneglycol
5	CH_3	I	$-C_3H_7$	162	Methyleneglycol
6	CH_3	Br		196–197	Ethanol
7	CH_3	Br	$-(CH_2)_4-CH_3$	148–150	Methanol
8	CH_3	Br		133–135	Ethanol
9	CH_3	Br		144–145	Ethanol
10	CH_3	Br	$-(CH_2)_3-OH$	153–154	Isopropanol
11	CH_3	Br		142–143	Ethanol
12	CH_3	Br		198	DMF
13	CH_3	Br		196–197	Methyleneglycol
14	CH_3	Cl		169–170	Methyleneglycol
15	CH_3	Cl		135–136	Ethanol

Example	R_1	X	R_3	m.p. °C	Crystallized from:
16	CH_3	Cl	$-CH_2-CN$	168	Methyleneglycol
17	CH_3	I	$-CH_2-\overset{\overset{O}{\|}}{C}-NH_2$	283	DMSO
18	CH_3	Cl	$-\overset{\overset{O}{\|}}{C}-CH_3$	150	Methyleneglycol
19	H	Cl	H		
20	H	Cl	$-CH_3$		
21	H	Cl	$-(CH_2)_3-OH$		
22	H	Cl	$-CH_2-C_6H_5$		
23	C_2H_5	Br	$-CH_2-\overset{\overset{O}{\|}}{C}-OC_3H_7$		
24	C_3H_7	Br	$-(CH_2)_2N(CH_3)_2$		

Example 25.

a) *1 - methyl - 4 - Chloropyrazolo[3,4 - d]-pyrimidine.*

31.1 g. of 1 - methyl - 4 - hydroxy-pyrazolo[3,4-d]pyrimidine are heated at reflux with 200 ml. of phosphorus oxychloride for 12 hours. The excess phosphorus oxychloride is distilled off and the residue is boiled with benzene. After distilling off the benzene and trituration with petroleum ether, there remain 15.8 g. of 1-methyl-4-chloro-pyrazolo[3,4-d]pyrimidine as light yellow crystals, m.p. 94—96°. This product is pure enough for further use.

b) *4 - Hydrazino - 1 - methylpyrazolo[3,4-d]pyrimidine.*

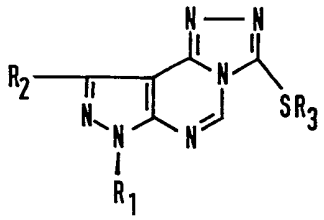
50 g. of 1 - methyl - 4 - chloropyrazolo-[3,4-d]pyrimidine are dissolved in 700 ml. of absolute ethanol and 25 g. of hydrazine hydrate in 100 ml. of ethanol are slowly added dropwise with stirring. This is stirred for 13 hours at room temperature and the product formed is then filtered under suction, water is added to the precipitate and the product, 4 - hydrazino - 1 - methylpyrazolo[3,4 - d]-pyrimidine, is crystallized from dimethylformamide as yellowish crystals, m.p. 231°.

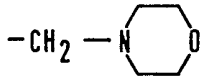
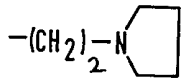
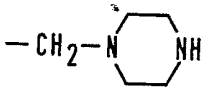
c) *7 - Methyl - 3 - methylthio - 7H - pyrazolo-[4,3 - e][1,2,4]triazolo[4,3 - c]pyrimidine.*

3.08 g. of 4 - hydrazino - 1 - methyl-pyrazolo[3,4-d]pyrimidine and 3.56 g. of 1,1-thiocarbonyldiimidazole in 100 ml. of dimethylformamide are stirred at 5° over a period of 16 hours. The 7-methyl-3-mercapto-7H - pyrazolo[4,3 - e][1,2,4]triazolo[4,3-c]pyrimidine which has been formed is filtered under suction, washed with water and recrystallized from a little dimethylformamide as yellowish crystals, m.p. 252—254°.

The crystalline free mercapto compound is suspended in dimethylformamide, and the calculated amount of potassium methoxide and then 5 g. of methyl iodide are added. After 1 hour, the 7 - methyl - 3 - methylthio-7H - pyrazolo[4,3 - e][1,2,4]triazolo[4,3-c]pyrimidine is filtered off under suction, dried and recrystallized from dimethylform-amide, yield 2.6 g., m.p. 204—206°.

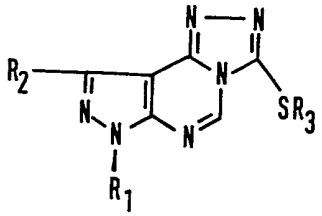
The following additional compounds are obtained by the procedures of Example 25.



Example	R_1	R_2	R_3
26	CH_3	H	
27	CH_3	CH_3	
28	H	CH_3	
29	CH_3	CH_3	$-CH_2NH_2$
30	H	H	$-(CH_2)_2CN$
31	CH_3	C_2H_5	$-CH_2OH$
32	H	H	$-(CH_2)_2CONHC_2H_5$
33	H	CH_3	$-CH_2CON(CH_3)_2$
34	CH_3	H	$-CO-C_4H_9$

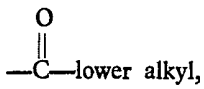
WHAT WE CLAIM IS:—

1. A compound of the formula

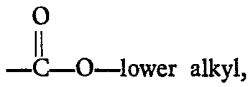


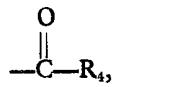
I

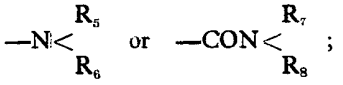
wherein R_1 and R_2 each is hydrogen or lower alkyl; R_3 is hydrogen, an alkali metal ion,



lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is hydroxy, cyano, phenyl,







R_4 is lower alkyl or phenyl; R_5 and R_6 each is hydrogen or lower alkyl, or R_5 and R_6 together with the nitrogen form one of the heterocyclic radicals pyrrolidino, piperidino, morpholino or piperazino; and R_7 and R_8 each is hydrogen or lower alkyl, wherein lower alkyl in each case is as hereinbefore defined.

2. A compound as in Claim 1 wherein R_3 is lower alkyl.

3. A compound as in Claim 1 wherein R_1 and R_3 each is lower alkyl and R_2 is hydrogen.

4. A compound as in Claim 1 wherein R_1 is methyl and R_2 is hydrogen.

5. A compound as in Claim 4 wherein R_3 is lower alkyl.

6. A compound as in Claim 4 wherein R_3 is ethyl.

7. A compound as in Claim 4 wherein R_3 is methyl.

8. A compound as in Claim 4 wherein R_3 is hydrogen.

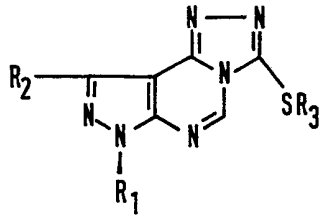
9. A compound as in Claim 4 wherein R_3 is hydroxy-lower alkyl.

10. A compound as in Claim 4 wherein R_3 is hydroxypropyl.

11. A compound as in Claim 4 wherein R_3 is phenyl-lower alkyl.

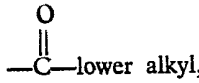
12. A compound as in Claim 4 wherein R_3 is piperidino-lower alkyl.

13. Process for preparing a compound of the formula

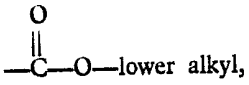


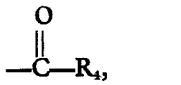
I

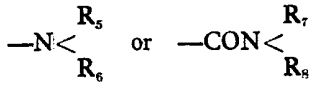
wherein R_1 and R_2 each is hydrogen or lower alkyl; R_3 is hydrogen, an alkali metal ion,



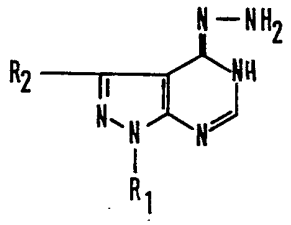
lower alkyl or substituted lower alkyl wherein the lower alkyl substituent is hydroxy, cyano, phenyl,







R_4 is lower alkyl or phenyl; R_5 and R_6 each is hydrogen or lower alkyl, or R_5 and R_6 together with the nitrogen form one of the heterocyclic radicals pyrrolidino, piperidino, morpholino or piperazino; and R_7 and R_8 each is hydrogen or lower alkyl, and wherein lower alkyl in each case is as hereinbefore defined, which comprises reacting a compound of the formula

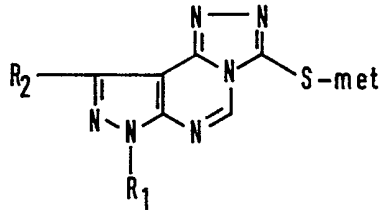


V

wherein R_1 and R_2 are defined as above with an alkali metal alcoholate of the formula

met—O—R

wherein met is an alkali metal and R is lower alkyl, followed by reaction with carbon disulfide to form a compound of the formula

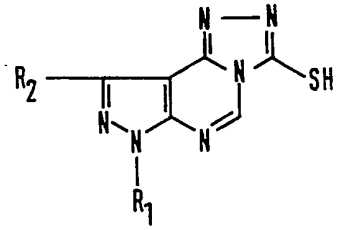


VI

wherein R_1, R_2 and met are defined as above and, if desired, acidifying the compound of Formula VI to form a compound of Formula I wherein R_3 is hydrogen or, if desired, reacting the compound of Formula VI with a compound of the formula

XR_3 VII

wherein X is a halogen and R_3 is defined as above other than hydrogen or an alkali metal ion; or reacting a compound of Formula V with 1,1-thiocarbonyldiimidazole to obtain a product of the formula



X

and, if desired, reacting the compound of Formula X with a compound of Formula VII.

14. A compound as claimed in claim 1, substantially as herein described or given in any one of the foregoing individual Examples.

15. A process for preparing a compound as defined in any of claims 1 to 12 and 14 substantially as herein described or given in any one of the foregoing individual Examples.

16. A compound as claimed in any of claims 1 to 12 and 14 when prepared using a process as claimed in claim 13 or 15.

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