

AN IMPROVED PROCESS FOR THE SYNTHESIS OF
5-[(SUBSTITUTED)AMINO]-8-[PHENYL OR
SUBSTITUTED-PHENYL]-3H,6H-1,4,5a,8a-
TETRAAZAACENAPHTHYLEN-3-ONES

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The invention relates to a process for the synthesis of 5-[(substituted)amino]-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphth-
ylen-3-ones and to the novel 5-(lower alkyl-thio)-8-
[phenyl or substituted-phenyl]-3H,6H,1,4,5a,8a-tetra-
azaacenaphthylene-3-ones useful as intermediates in the
process.

2. DESCRIPTION OF THE RELATED ART

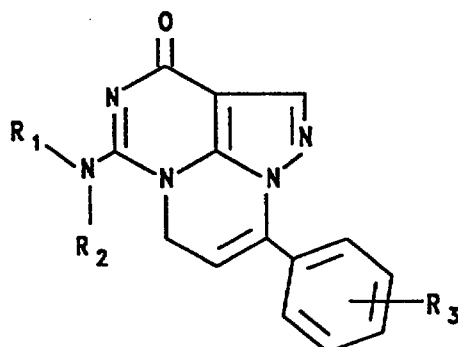
The 5-(substituted-amino)-8-(phenyl or substituted-phenyl)-3H,6H-1,4,5a,8a-tetraazaace-
naphthylene-3-ones as disclosed in U.S. Patent No.
4,916,137 possess the ability to enhance neural
function in warm-blooded animals affected by behavioral
neurological problems, including the cognitive de-
terioration associated with decreased neural function
which occurs with cerebral insufficiency, aging,
dementia, and similar conditions. In addition syn-
thetic procedures to prepare the 5-(substituted-
amino)-8-(phenyl or substituted-phenyl)-3H,6H-1,4,5a-
8a-tetraazaacenaphthylene-3-ones are also disclosed. A
series of reactions in which a 4,5-dihydro-7-[phenyl or

substituted phenyl]-pyrazolo-[1,5-a]pyrimidine-3-carboxamide is reacted with 1,1'-thiocarbonyl-diimidazole in the presence of sodium hydride to prepare 4,5-dihydro-5-thioxo-8-[phenyl or substituted phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-ones which are subsequently reacted with an amine in the presence of aqueous sodium hydroxide and hydrogen peroxide to give the 5-(substituted-amino)-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaace-naphthylen-3-ones is disclosed.

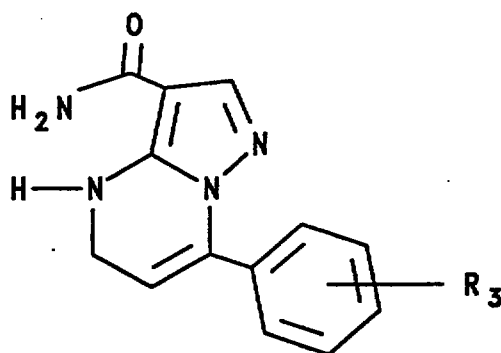
It has been found that the 5-(substituted-amino)-8-(phenyl or substituted-phenyl)-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-ones can be advantageously synthesized by reaction of 4,5-dihydro-7-[phenyl or substituted-phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxamide with carbon disulfide in the presence of a lower alkyl iodide and suitable base to give the 5-(lower alkylthio)-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-ones which are subsequently reacted with an amine to afford the 5-[(substituted)amino]-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-ones.

SUMMARY OF THE INVENTION

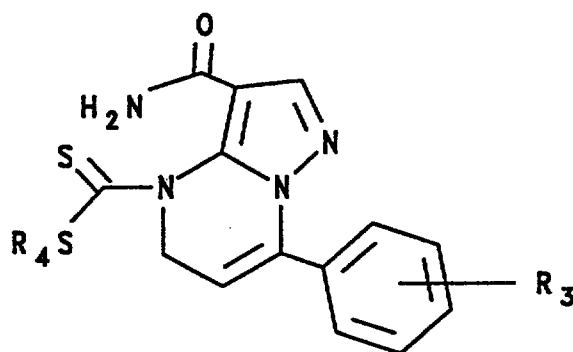
The invention provides an improved process for the preparation of 5-[(substituted)amino]-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-ones which can be represented by the following structural formula:



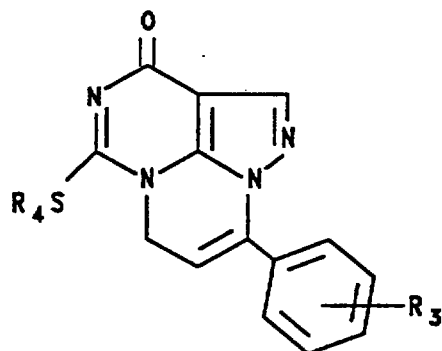
wherein R_1 and R_2 are each individually selected from the group consisting of hydrogen, branched or unbranched alkyl(C_1-C_4) or benzyl; R_3 is hydrogen, halogen, alkyl(C_1-C_3), alkoxy(C_1-C_3) or trifluoromethyl. For the purposes of this invention, halogen may be fluorine, chlorine, bromine or iodine. The improved process comprises reacting a 4,5-dihydro-7-[phenyl or substituted phenyl]-pyrazolo[1,5-a]pyrimidine-3-carboxamide having the formula: -



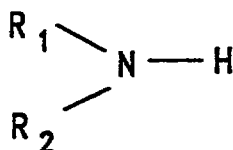
wherein R_3 is as defined above with carbon disulfide and a compound of the formula R_4I , wherein R_4 is defined as lower alkyl(C_1-C_3), to give a xanthate of the formula:



which can be isolated or further reacted in situ to afford a 5-(lower alkylthio)-8-[phenyl or substituted phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one having the formula:



10 wherein R_3 is as defined above, which is subsequently reacted with an amine having the formula:



wherein R_1 and R_2 are defined above and recovering the 5-[(substituted)amino]-8-[phenyl or substituted-phenyl]-3H,6H,1,4,5a,8a-tetraazaacenaphthylen-3-one so produced.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

The process and compounds of the present invention are described in the following reaction scheme:

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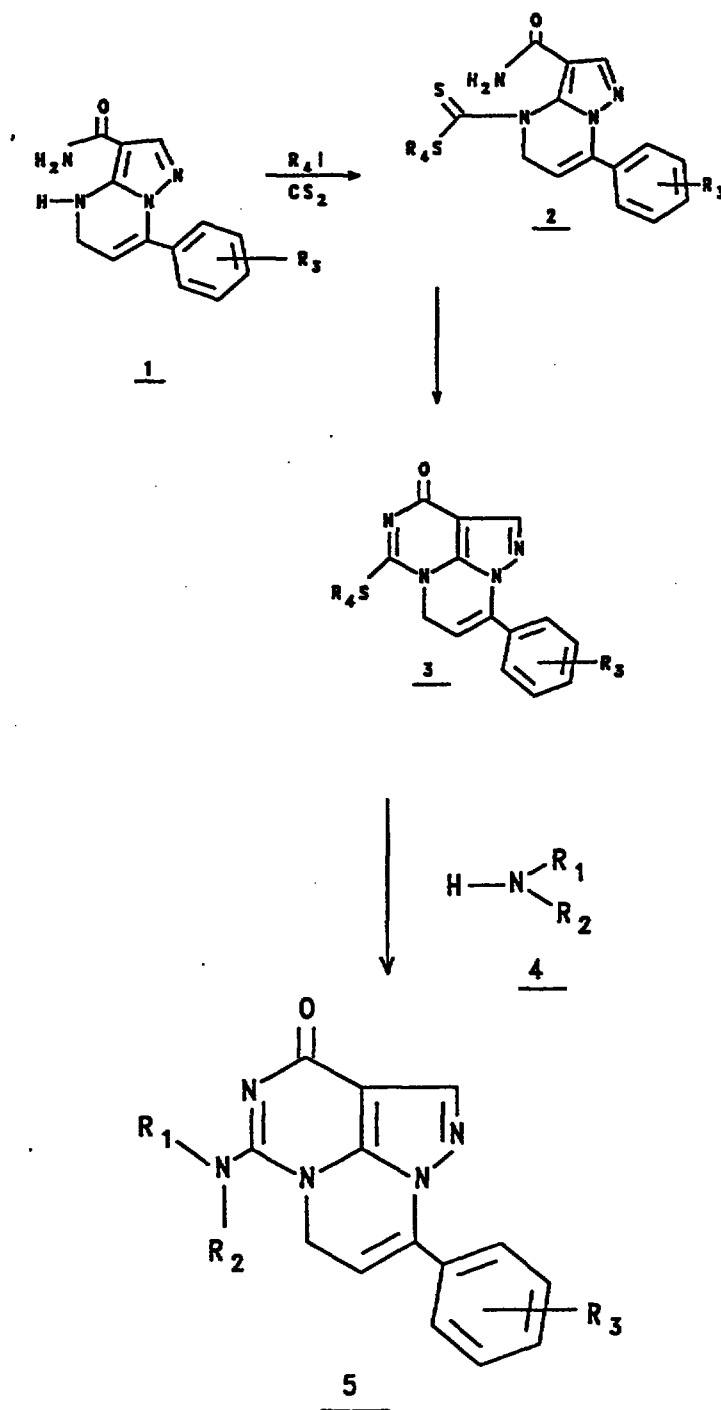
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In accordance with the above reaction scheme, 4,5-dihydro-7-[phenyl or substituted-phenyl]pyrazolo-1,5-a]pyrimidine-3-carboxamide 1 where R_3 is as described above, is reacted with carbon disulfide in the presence of a suitable base and R_4I , where R_4 is as described above to afford the xanthate 2. This reaction is preferably conducted at temperatures from about $-7^{\circ}C$ to about $6^{\circ}C$ for up to one hour. Longer reaction times of up to 18 hours, with the addition of excess base, dilution with ice and water and collection of the solid on a funnel gives the fully closed 5-(lower alkylthio)-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one 3. Suitable bases include sodium hydride, sodium methoxide and potassium t-butoxide but other bases as known in the art may be substituted.

The 5-(lower alkylthio)-8-[phenyl or substituted-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one 3 is reacted with amine 4, where R_1 and R_2 are as described above, to yield the final compound, 5. The reaction of 3 with 4 is preferably conducted in a weak acid such as acetic acid at about $80^{\circ}C$ to about $100^{\circ}C$ for about 18 hours. The solution is cooled to room temperature, diluted with ethanol, cooled to $0^{\circ}C$ and the 5-[(substituted)amino]-8-[phenyl or substituted-phenyl]-3H,6H,1,4,5a,8a-tetraaza-acenaphthylen-3-one 5 collected by filtration and dried.

The above process is an improvement over the procedures described in U.S. Patent No. 4,916,137. As described herein above, the yields of each of the steps are higher and the workup of the reactions are less labor and time intensive.

The following non-limiting examples illustrate the process of the present invention as well as the preparation of the novel compounds.

Example 1

5-(Methylthio)-8-[3-(trifluoromethyl)phenyl]-
3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one

A solution of 162 g of 4,5-dihydro-7-[3-(trifluoromethyl)phenyl]pyrazolo[1,5a]-pyrimidine-3-carboxamide in 1.62 L of warm tetrahydrofuran is dried with 40.3 g of anhydrous sodium sulfate, stirred for 3 hours and allowed to stand at room temperature for 18 hours. The mixture is filtered and the cake washed with 200 ml of tetrahydrofuran. The tetrahydrofuran solution is cooled to -3°C under inert gas. While stirring, 28.4 g of sodium methoxide is added in small portions over a 10 minute period. The temperature is kept from -3°C to -4.5°C . A solution of 45 ml of carbon disulfide in 45 ml of tetrahydrofuran is added dropwise while keeping the temperature from -7°C to -4.5°C . The temperature is brought to -1°C and stirring continued for 35 minutes. A solution of 96 ml of methyl iodide in 96 ml of tetrahydrofuran is added dropwise over 20 minutes while maintaining the temperature from -1°C to $+4^{\circ}\text{C}$. Following an additional 1 hour of stirring, 56.7 g of sodium methoxide is added portionwise over 20 minutes under inert gas while keeping the temperature from -8°C to 6°C . Following each portionwise addition the temperature rose to 6°C . The reaction mixture is stirred at room temperature for 18 hours. The reaction mixture is diluted with 3.0 L of water and 600 g of ice. The solid is collected on a filter and the cake washed with 3 x 500 ml of water then dried to give 160.5 g of the desired product. The collected solid is stirred with a solution of 700 ml of n-heptane and 1400 ml of ethyl acetate for 1 hour then collected by filtration. The cake is washed with 3 x 160 ml of (2:1) ethyl acetate:n-heptane and dried to afford 105 g (54.8%) of the desired product.

Example 2

5-(Methylthio)-8-[3-(trifluoromethyl)phenyl]-
3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one

A solution of 1055 g of 4,5-dihydro-7-[3-(trifluoromethyl)-phenyl]pyrazolo[1,5a]pyrimidine-3-carboxamide in 9L of tetrahydrofuran is stirred with 263.4 g of sodium sulfate of 0.5 hours and allowed to stand at room temperature overnight. The reaction mixture is filtered and the cake washed with tetrahydrofuran (3 x 250 ml). The filtrate is cooled to -3.5°C and 136.5 g of a 60% dispersion of sodium hydride in mineral oil added over a 30 minute period while maintaining the temperature from -3.5°C to 4°C. The solution is stirred about 20 minutes at 0°C to +4°C and a solution of 272.2 g of carbon disulfide in 215 ml of tetrahydrofuran added dropwise over a 22 minute period while an orange solid precipitates. The reaction mixture is stirred for 20 minutes at 2°C to -3.5°C followed by the addition of a solution of 1453 g of methyl iodide in 637 ml of tetrahydrofuran dropwise over 40 minutes while maintaining the temperature from -3.5°C to 1°C. The reaction mixture is stirred 1.5 hours at -5°C to -8°C, while maintaining the temperature below 2°C, 237 g of sodium hydride is added portionwise over 2.75 hours. The reaction mixture is stirred overnight while warming to room temperature. The reaction mixture is diluted with 250 ml of ethanol, 16L of water, 3.82 kg of ice and stirred for 1 hour. The resulting solid is collected by filtration and then slurried with 9L of ethyl acetate and 4.5L of heptane for 1 hour. The solid is collected by filtration and washed with a 2:1 ethyl acetate-heptane (3 x 1L) solution, dried at 23mmHg at 40°C to afford 648 g (75%) of the desired product.

Example 3

5-(Methylthio)-8-[3-(trifluoromethyl)phenyl]-
3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one

A solution of 3.18 kg of 4,5-dihydro-7-
5 [3-(trifluoromethyl)-phenyl]pyrazolo[1,5-a]pyrimidine-
-3-carboxamide in 30L of tetrahydrofuran is cooled to
2.8°C under nitrogen and stirred while 1370 g of
potassium tert-butoxide is added portionwise over 25
minutes while maintaining a temperature less than 4°C.
10 The reaction mixture is stirred at -6.2°C for 45
minutes. To the reaction mixture is added 850 g of
carbon disulfide through a dropping funnel over a 10
minute period while maintaining the temperature below
2°C. The funnel is rinsed with 500 ml of tetra-
15 hydrofuran and the reaction mixture allowed to stir for
45 minutes. While maintaining the temperature from
-0.8°C to 3.2°C, 1870 g of methyl iodide is added
dropwise through a dropping funnel. The funnel is
rinsed with 500 ml of tetrahydrofuran and the reaction
20 mixture allowed to stir for 1 hour. An additional 3804
g of methyl iodide is added. The reaction mixture is
stirred for 50 minutes while cooling to -23.1°C. An
additional 2530 g of potassium tert-butoxide is added
over 2 hours while maintaining a temperature of -23.1°C
25 to -10.0°C. After half of the potassium tert-butoxide
is added another 300 ml of methyl iodide is added. The
remaining potassium tert-butoxide is added and the
reaction mixture stirred while warming to room
temperature overnight. The reaction mixture is diluted
30 with 3 kg of ice and 10L of water then added to 80L of
water with stirring. The reaction flask is rinsed
with 26L of water which is added to the ice and water
containing the original reaction mixture. Stirring is
continued for 40 minutes and the solids collected by
35 filtration. The filter cake is washed with 20L of
water and dried at 30 mm Hg, 35°C to afford 3.4 kg
(90%) of the desired product.

5 A solution of 3.0 g of 4,5-dihydro-7-[3-(trifluoromethyl)phenyl]pyrazolo-[1,5a]pyrimidine-3-carboxamide in 30 ml of tetrahydrofuran is cooled to 0°C. While stirring, 0.40 g of a 60% dispersion of sodium hydride is added and stirring continued at 0°C for 30 minutes. While maintaining the temperature at 0°C, 1.11 g of carbon disulfide is added dropwise at a rate to maintain the temperature. Following 30 minutes of stirring the temperature is lowered to -7°C and 2.07 g of methyl iodide is added at a rate to maintain the temperature at -7°C to -4°C. The reaction mixture is allowed to warm to room temperature and stir overnight. While stirring, 66 g of ice water is added with continued stirring over 20 minutes. The solid is collected, washed with water (3 x 25 ml), hexane (3 x 25 ml) and air dried to provide 3.5 g (90%) of the desired product.

Example 5

To a suspension of 5.0 g of 5-(methylthio)-8-[3-(trifluoromethyl)phenyl]-3H,6H-1,4,5a,8a-tetrazaacenaphthylen-3-one in 35 ml of acetic acid is added 4.78 g of benzylamine. The reaction mixture is heated on a steambath for 18 hours. The solution is cooled to room temperature and 17 ml of ethanol is added followed by cooling to 10°C. An additional 35 ml of ethanol and 20 g of ice are added and the resulting slurry stirred for 30 minutes at 0°C. The product is collected by filtration, washed with ethanol (2 x 20 ml) and dried at 40°C/30mm Hg to give 3.6 g (62.1%) of the desired product.

Example 6

5-[(1-Methylethyl)amino]-8-[3-(trifluoromethyl)-phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one

To a suspension of 5.0 g of 5-(methylthio)-
5 8-[3-(trifluoromethyl)phenyl]-3H,6H-1,4,5a,8a-tetraaza-
acenaphthylen-3-one in 35 ml of acetic acid is added
2.64 g of isopropylamine. The reaction mixture is
heated on a steambath for 18 hours. The resulting
solution is cooled to room temperature and 17 ml of
10 ethanol added. The mixture is cooled to 10°C and 35 ml
of ethanol and 20 g of ice added. The mixture is
stirred for an additional 30 minutes at -10°C. The
product is collected by filtration, washed with ethanol
(2 x 20 ml) and air-dried to give 3.2 g (62.3%) of the
15 desired product.

Example 7

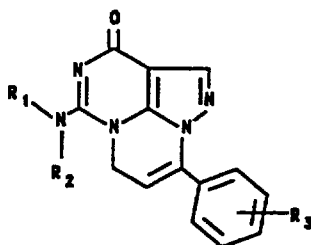
5-[(2-Methylpropyl)amino]-8-[3-(trifluoromethyl)phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one

To 11.1 L of acetic acid is added 2.23 kg of
20 isobutylamine dropwise, under nitrogen over 0.75 hour
at a rate such that the temperature does not go above
45°C. The temperature is controlled with external
cooling. Following complete addition, 2.78 kg of 5-
25 (methylthio)-8-[3-(trifluoromethyl)phenyl]-3H,6H-1,4-
5a,8a-tetraazaacenaphthylen-3-one is added. The re-
action mixture is heated at 95°C for 18 hours. The
reaction mixture is cooled to 45°C and transferred to a
larger vessel with an additional glacial acetic acid
30 wash (2 x 500 ml). While stirring, 22.2 L of ethanol
and 11.1 kg of crushed ice is added. Stirring is con-
tinued for 1 hour, the solid collected and washed with
(3 x 2L) of 2:1 ethanol water to afford 2.82 kg (90.7%)
of the desired product as a dried solid.



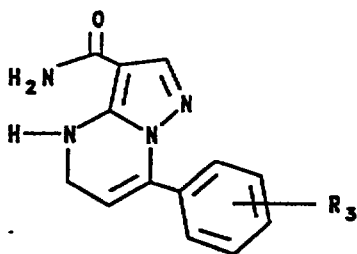
We claim:

1. A process for producing a tetraazaacena-
phthylen-3-one compound of the Formula I:



(I)

wherein R_1 and R_2 are each individually selected from
the group consisting of hydrogen, branched and
unbranched alkyl(C_1-C_4) and benzyl and R_3 is selected
from the group consisting of hydrogen, halogen,
alkyl(C_1-C_3), alkoxy(C_1-C_3) and trifluoromethyl; which
comprises (a) reacting a 4,5-dihydro-7-[phenyl or
substituted-phenyl]pyrazolo[1,5a]pyrimidine-3-carboxa-
mide having the Formula II:



(II)

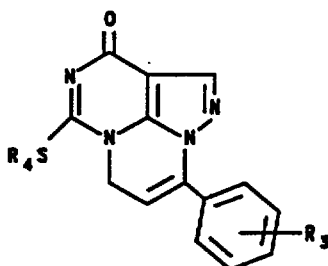
with carbon disulfide and a lower alkyl (C_1-C_3) iodide
and recovering the 5-(lower alkyl thio)-8-[phenyl or
substituted-phenyl]-3H,6H-1,4,5a, 8a-tetraazaacenaphth-
ylen-3-one having the Formula III:

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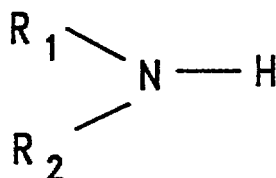
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(III)

10 wherein R_4 is lower alkyl (C_1-C_3), and (b) reacting the compound of Formula III with an amine having the formula:

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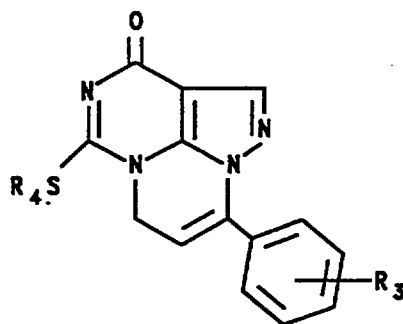


and recovering the tetraazaacenaphthylen-3-one compound of Formula (I).

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2. A compound of the formula:

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wherein R_3 is selected from the group consisting of hydrogen, halogen, alkyl (C_1-C_3), alkoxy (C_1-C_3) or trifluoromethyl and R_4 is lower alkyl (C_1-C_3).

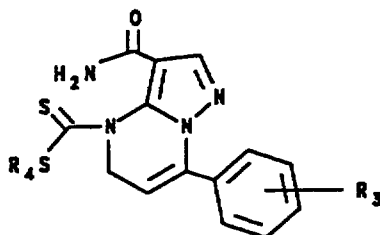
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3. A compound of the formula:



wherein R_3 is selected from the group consisting of hydrogen, halogen, alkyl(C_1-C_3), alkoxy(C_1-C_3) or trifluoromethyl and R_4 is lower alkyl(C_1-C_3).

4. A process according to claim 1 in which the reaction of step (a) is carried out in a suitable base selected from the group consisting of sodium hydride, sodium methoxide and potassium t-butoxide.

5. The compound according to claim 2, 5-(methylthio)-8-[3-(trifluoromethyl)phenyl]-3H,6H-1,4,5a,8a-tetraazaacenaphthylen-3-one.

6. The compound according to claim 3, 3-(aminocarbonyl)-7-[3-(trifluoromethyl)phenyl]pyrazolo-[1,5-a]pyrimidine-4(5H)-carbodithionic acid methyl ester.

