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[54] **PROCESS FOR THE PREPARATION OF 1-SUBSTITUTED-PHENYL-2(1H)-QUINAZOLINONES**

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[52] **U.S. Cl.** ..... **260/251 QB,** 260/471 C, 424/251

[51] **Int. Cl.** **C07d 51/48**

[58] **Field of Search** ..... 260/251 QB

[56] **References Cited**

OTHER PUBLICATIONS

Brown – "Fused Pyrimidines – Pt. I – Quinazolines" Interscience Publishers – 1967 – pp. 39–40, 70.

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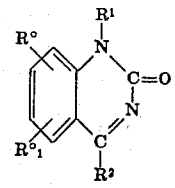
[57] **ABSTRACT**

1-alkyl-4-phenyl-2(1H)-quinazolinones, e.g., 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone, are prepared by the reaction of an alkyl-N-alkyl-N-(substituted or unsubstituted-2-benzoyl-phenyl)-carbamates with ammonium salts of aliphatic carboxylic acids. The compounds are useful as anti-inflammatory and analgesic agents.

10 Claims, No Drawings

PROCESS FOR THE PREPARATION OF 1-SUBSTITUTED-PHENYL-2(1H)-QUINAZOLINONES

This invention relates to 1-substituted-4-phenyl-2(1H)-quinazolinones. More particularly, the invention concerns a process for preparing 1-substituted-4-phenyl-2(1H)-quinazolinones which may be represented structurally as follows:



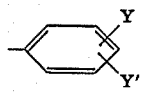
(I)

wherein

R° and R°$_1$ independently, represent hydrogen; halo having an atomic weight no greater than 80, i.e., fluoro, bromo and chloro; lower alkyl containing one to five carbon atoms; lower alkoxy containing one to five carbon atoms; or nitro, provided that only one of R° and R°$_1$ is nitro; or one of R° and R°$_1$ is trifluoromethyl and the other hydrogen; or R° and R°$_1$ together form 6,7-methylenedioxy;

R^1 represents lower alkyl containing from one to five carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tertiary butyl; allyl; methallyl; or propargyl; or cyclolower alkyl of three to six carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclohexyl or cyclolower alkyl alkyl of four to seven carbon atoms, cyclopropylmethyl, cyclohexylbutyl;

R^2 represents phenyl or substituted phenyl of the formula:

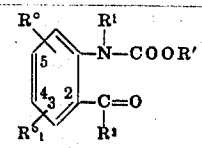


wherein

Y represents halo having an atomic weight no greater than 80; lower containing from one to four carbon atoms, e.g., methyl and ethyl; lower alkoxy containing from one to four carbon atoms, e.g., methoxy and ethoxy; or trifluoromethyl; and

Y′ represents hydrogen; halo having an atomic weight no greater than 80; lower alkyl containing from one to four carbon atoms, e.g., methyl and ethyl; or lower alkoxy containing from one to four carbon atoms, e.g., methoxy and ethoxy.

The process of the present invention involves the reaction of an ammonium salt of an aliphatic carboyxlic acid with an intermediate carbamate of the formula (III):



(III)

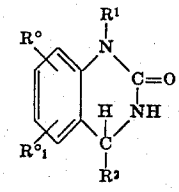
wherein

R°, R°$_1$, R^1 and R^2 are as defined above; and

R′ is lower alkyl of one to four carbon atoms, preferably ethyl.

More particularly, compounds of formula I may be produced in accordance with the invention by reactively combining a compound II with an ammonium salt of a lower alkyl (C_1–C_4) mono- or dicarboxylic acid e.g., ammonium formate, ammonium acetate, ammonium oxalate and ammonium succinate. The production of compound I may be carried out at elevated temperatures, typically in the range of to 180°C., preferably 110° to 140°C. However, the temperature is not critical and the reaction may be carried out at lower temperatures, although there may be a reduction in the yield. The reaction may be carried out in the absence or presence of solvents. Solvents of conventional type may be used including the polar and non-polar solvents such as ethanol, glyme, di-glyme, chloroform, tetrahydrofuran, benzene, toluene and the lower carboxylic acids, e.g., acetic acid. The mole ratio of the ammonium salt to compound III is not particularly critical and desirably such to provide one molar equivalent of ammonium ion per mole of compound III. In the preferred forms of practice a substantial excess of the ammonium salt up to a molar equivalent ratio of 15:1 is employed to obtain the more efficient reaction rates. The reaction time may vary widely and is usually in the range of 5 to 120 hours. Recovery of the product of the formula I is effected in a conventional manner.

The process of the present invention in addition to producing the compounds of the formula I also results in the production of a corresponding compound of the formula II:



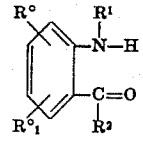
(II)

wherein

R°, R°$_1$, R^1 and R^2 are as defined above.

It has been found that, in general, the amount of the compounds of the formula II produced will vary depending upon the manner in which the process is carried out. For example, when the process is carried out under preferred conditions employing ammonium acetate in the absence of an added solvent, it has been found that little of the compound of the formula II is obtained. On the other hand, increased amounts of the formula II may be obtained when the reaction is carried out employing ammonium formate in the absence of an added solvent. In general, the compounds of the formula II may be separated and recovered, if desired, from the process by employing conventional techniques. In addition, if desirable, the compound of the formula II may readily be converted to the compound of formula I with or without separation from the compounds of the formula II from the compound of the formula I by oxidizing the compound of the formula II in a known manner, e.g., by treatment with potassium permanganate in an inert solvent at a temperature of from 10°C to 80°C.

The compounds of formula III may be prepared from a 2-aminobenzophenone of the formula IV



(IV)

wherein

R°, R°_1, R^1 and R^2 are as defined above, by reacting said 2-amino- benzophenone with a lower alkyl chloroformate or bromoformate, preferably a chloroformate. Such reaction with alkyl haloformate may be carried out in the range of 30° to 180° C., preferably 50° to 100°C. In the preferred forms of practice, there is employed a substantial excess of the haloformate which also serves as the preferred solvent for the reaction. Other suitable well-known inert organic solvents may also be employed, if desired. Reaction time is usually in the range of ½ to ten hours. Recovery may be effected in a conventional manner. The 2-aminobenzophenone which are compounds IV and reacted with the alkylhaloformate to obtain compounds III are either known or can be prepared from available materials by procedures known in the art.

The compounds of structural formula I are useful because they possess pharmacological activity in animals. In particular, the compounds are useful as anti-inflammatory agents as indicated by the Carrageenan-induced edema test on rats (oral administration). For such use, the compounds may be combined with a pharmaceutically acceptable carrier, and such other conventional adjuvants as may be necessary, and administered orally in such forms as tablets, capsules, elixirs, suspensions and the like or parenterally in the form of an injectable solution or suspension. The dosage administered will, of course, vary depending upon the compounds used and mode of administration. However, in general, satisfactory results are obtained when administered at a daily dosage of from about 0.15 milligram to about 100 milligrams per kilogram of body weight, preferably given in divided doses 2 to 4 times a day, or in a sustained release form. For larger mammals, the administration of from about 10 milligrams to about 1,000 milligrams of the compound per day provides satisfactory results and dosage forms suitable for internal administration comprises from about three milligrams to about 500 milligrams of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

The compounds I of the invention are also administration). as analgesics uses, indicated by application of pressure to yeast-inflamed foot of the rat (oral administration). They are also useful as anti-pyretics as indicated by inhibition of bacterial lipoplysaccharide-induced fever (oral adminstration). For such uses; the compound may be administered to obtain satisfactory results at dosages and in modes similar to those employed in the treatment of inflammation.

The compounds of the structural formula II are also useful as anti-inflammatory agents as indicated by the Carragneenan-induced edema test on rats. The dosage administered will, of course, vary depending upon known factors such as the compounds used and mode of administration. However, in general, satisfactory results are obtained when administered at a daily dosage of from about 2 milligrams to about 180 milligrams per kilogram of body weight, preferably given in divided does two to four times a day, or in sustained release form. For most mammals the administration of from about 140 milligrams to about 2,000 milligrams of the compound per day provides satisfactory results and dosage forms suitable for internal administration comprise from about 70 milligrams to about 1,000 milligrams of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

EXAMPLE 1

Preparation of ethyl-N-isopropyl-N-(2-benzoyl-5-methyl phenyl)-carbamate

50 Grams of 2-N-isopropylamino-4-methyl benzophenone and 170 grams of ethyl chloroformate are heated at a temperature from 90° to 100°C. for 3 hours. The excess ethyl chloroformate is concentrated under vacuum and the residue crystallized from cyclohexane to obtain ethyl-N-isopropyl-N-(2-benzoyl-5-methyl phenyl)-carbamate; m.p. 91°–92°C.

EXAMPLE 2

Preparation of methyl-N-isopropyl-N-(2-benzoyl-5-methyl phenyl)-carbamate

50 grams of 2-N-isopropylamino-4-methyl benzophenone and **125** grams of methyl chloroformate are heated at a temperature from 55° to 75°C. for 3 hours. The excess methyl chloroformate is concentrated under vacuum and the residue dissolved in 200 ml. of petroleum ether and then cooled to 5°C. to obtain -methyl-N-isopropyl-N-(2-benyoyl-5-methyl phenyl)-carbamate; m.p. 65°–66°methyl-N-isopropyl-N-(2-benzoyl-5

Following the procedure of Example 1 but using an equivalent amount of:

a. 2-N-methylamino-4'-chlorobenzophenone;
b. 2-N-isopropylamino-4,6-dimethylbenzophenone;
c. 2-N-isopropylamino-4'-methylbenzophenone;
d. 2-N-propargylamino-4,5-dimethylbenzophenone;
e. 2-N-ethylamino-5-trifluoromethylbenzophenone;
f. 2-N-ethylamino-5-nitrobenzophenone;
g. 2-N-isopropylamino-5-bromobenzophenone;
h. 2-N-allylamino-4-chlorobenzophenone;
i. 2-N-isopropylamino-5-methoxybenzophenone;
j. 2-N-isopropylamino-4-methyl-4'-methoxybenzophenone;
k. 2-N-methylamino-3'-trifluoromethylbenzophenone;
l. 2-N-methallylamino-benzophenone;
m. 2-N-isopropylamino-4,5-dichlorobenzophenone
n. 2-N-isopropylamino-4-fluorophenyl-4,5-methylenedioxybenxophenone;
o. 2-N-isopropylamino-4,5-methylenedioxyphenone
p. 2-N-isopropylamino-4-methyl-4'-fluorobenzophenone

in place of the 2-N-isopropylamino-4-methyl-2-benzophenone used therein, there is obtained:

a. ethyl-N-methyl-N-(2[4-chlorobenzoyl]-phenyl)-carbamate;
b. ethyl-N-isopropyl-N-(2-benzoyl-3,5-dimethyl-phenyl)-carbamate; c. ethyl-N-isopropyl-N-(2-[4-methylbenzoyl]-phenyl)-carbamate;
d. ethyl-N-propergyl-N-2-benzoyl-4,5-dimethyl-phenyl)-carbamate;
e. ethyl-N-ethyl-N-(2-benzoyl-4-trifluoromethyl-phenyl)-carbamate;
f. ethyl-N-ethyl-N-(2-benzoyl-4-nitrophenyl)-carbamate;

g. ethyl-N-isopropyl-N-(2-benzoyl-4-bromophenyl)-carbamate;

h. ethyl-N-allyl-N-(2-benzoyl-5-chlorophenyl)-carbamate;

i. ethyl-N-isopropyl-N-(2-benzoyl-4-methoxy-phenyl)-carbamate;

j. ethyl-N-isopropyl-N-(2-[4-methoxybenzoyl]-5-methylphenyl)-carbamate; k. ethyl-N-methyl-N-(2[3-trifluoromethylbenzoyl]-phenyl)-carbamate;

l. ethyl-N-methallyl-N-(2benzoylphenyl)-carbamate;

m. ethyl-N-isopropyl-N-(2-benzoyl-4,5-dichloro-phenyl)-carbamate;

n. ethyl-N-isopropyl-N-(2-[fluorobenzoyl]-4,5-methylenedioxyphenyl)-carbamate;

o. ethyl-N-isopropyl-N-(2 benzoyl-4,5-methylenedioxyphenyl)-carbamate;

p. ethyl-N-isopropyl-N-(2-[4-fluorobenzoyl]-5-methylphenyl)-carbamate.

EXAMPLE 3

1-Isopropyl-7-methyl-4-phenyl-2 (1H)-quinazolinone

10 grams of ethyl-N-isopropyl-N-(2-benzoyl-5-methyl phenyl)-carbamate is added to 30 grams of ammonium acetate and heated to a temperature from 120° to 130°C. for 66 hours. At the end of this period the resulting product is cooled to room temperature and dissolved in chloroform and extracted four times with 20 ml. of water for each extraction. The chloroform is then concentrated under vacuum and the residue crystallized from ethylacetate to obtain 1-isopropyl-7-methyl-4-phenyl-2(lH)-quinazoline; m.p. 139°–141°C.

EXAMPLE 4

1isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone

10 Grams of ethyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate and 90 grams of ammonium acetate are added to 132 ml. of blacial acetic acid and heated to reflux for 90 hours. The reaction mixture is cooled to 40°C. and concentrated under vacuum. The resulting solution is then dissolved in 100 ml. of toluene and extracted four times with 20 ml. of water for each extraction. The toluene layer is concentrated under vacuum and the residue is crystallized from 20 ml. of ethylacetate to obtain 1-isopropyl-7-methyl-4-phenyl-(1H)-quinazolinone; m.p. 139° to 141°C.

EXAMPLE 5

1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone

10 Grams of methyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate and 62 grams of ammonium acetate are added to 95 cc. of glacial acetic acid and heated to reflux for 20 hours. The reaction mixture is concentrated under vacuum and dissolved in 100 cc. of toluene. The resulting solution is then extracted four times with 20 ml. of water for each extraction. The toluene layer is concentrated under vacuum and the residue is crystallized from 20 ml. of ethylacetate to obtain 1-isopropyl-7-methyl- 4-phenyl-2(1H)-quinazolinone; m.p. 139° to 141°C.

Following the above procedure but using an equivalent amount of: a. ethyl-N-methyl-N-(2-[4-chlorobenzoyl]-phenyl)-carbamate;

b. ethyl-N-isopropyl-N-(2-benzoyl-3,5-dimethyl-phenyl)-carbamate; c. ethyl-N-isopropyl-N-(2[4-methylbenxoyl]-phenyl-carbamate;

d. ethyl-N-propargyl-N-(2-benzoyl-4,5-dimethyl-phenyl)-carbamate:

e. ethyl-N-ethyl-N-(2-benzoyl-4-trifluoromethyl-phenyl)-carbamate;

f. ethyl-N-ethyl-N-(2-benzoyl-4-nitrophenyl)-carbamate;

g. ethyl-N-isopropyl-N-(2-benzoyl-4-bromophenyl)-carbamate;

h. ethyl-N-allyl-N-(2-benzoyl-5-chlorophenyl)-carbamate;

i. ethyl-N-isopropyl-N-(2-benzoyl-4-methoxy-phenyl)-carbamate;

j. ethyl-N-isopropyl-N-(2-[4-methoxybenzoyl]-5-methylphenyl)-carbamate;

k. ethyl-N-methyl-N-(2-[3-trifluoromethylbenzoyl]-phenyl)-carbamate;

l. ethyl-N-methallyl-N-(2-benzoylphenyl)-carbamate;

m. ethyl-N-isopropyl-N-(2-benzoyl-4,5-dichloro-phenyl)-carbamate;

n. ethyl-N-isopropyl-N-(2-[fluorobenzoyl]-4,5-methylenedioxyphenyl)-carbamate;

o. ethyl-N-isopropyl-N-(2-benzoyl-4,5-methylenedioxyphenyl)-carbamate;

p. ethyl-N-isopropyl-N-(2-[4-fluorobenzoyl]-5-methylphenyl)-carbamate in place of the ethyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate therein, there is obtained:

a. 1-methyl-4-(4-chorophenyl)-2(1H)-quinazolinone; m.p. 122°–123°C.

b. 5,7-dimethyl-1-isopropyl-4-phenyl-2(1H)-quinazolinone; m.p. 145°–147°C.

c. 1-isopropyl-4-(4-methylphenyl)-2(1H)-quinazolinone; m.p. 138° to 140°C.

d. 6,7-dimethyl-4-phenyl-1-propargyl-2(1H)-quinazolinone; m.p. 170°–180°C.

e. 1-ethyl-6-trifluoromethyl-4-phenyl-2(1H)-quinazolinone; m.p. 214°–215°C.

f. 1-ethyl-6-nitro-4-phenyl-2(1H)-quinazolinone; m.p. 214°–°C.

g. 6-bromo-1-isopropyl-4-phenyl-2(1H)-quinazolinone; m.p. 142°–143°C.

h. 1-allyl-7-chloro-4-phenyl-2(1H)-quinazolinone; m.p. 173°–174°C.

i. 1-isopropyl-6-methoxy-4-phenyl-2(1H)-quinazolinane; m.p. 148°–150°C.

j. 1-isopropyl-7-methyl-4-(4-methoxyphenyl)-2(1H)-quinazolinone; m.p. 163°–165°C.

k. 1-methyl-4-3-trifluoromethylphenyl)-2(1H)-quinazolinone

l. 1-methallyl-4-phenyl-2(1H)-quinazolinone; m.p. 142°–143°C.

m. 6,7-dichloro-1-isopropyl-4-phenyl-2(1H)-quinazolinone; m.p. 191°–194°C.

n. 1-isopropyl-4-(4-fluorophenyl)-6,7-methylene-dioxy-2(1H)-quinazolene; m.p. 169°–170°C.

o i-isopropyl-4-phenyl-6,7-methylenedioxy-2(1H)-quinazolinone; m.p. 215°–218°C.

p. 1-isopropyl-7-methyl-4-(4-fluorophenyl)-2(1H)-uinazolinone; m.p. 176°–178°C.

EXAMPLE 6

o. 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone and 3,4-dihydro-1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone

20 Grams of ethyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate and 48.5 grams of ammonium formate is heated at a temperature of 130° to 145°C. for 116 hours. The reaction mixture is dissolved

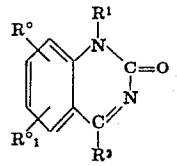
in 200 ml. chloroform and washed twice with 50 ml. of water for each washing. The chloroform layer is then washed twice with 25 ml. of 10 percent sodium bicarbonate and concentrated under vacuum to obtain a yellow oil. The yellow oil is then dissolved in 60 ml. of cyclohexane and cooled to obtain 3,4-dihydro-1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone contaminated with ethyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)- carbamate.

The mother liquor is concentrated under vacuum and dissolved in 25 ml. of cyclohexane and cooled to obtain ethyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate.

The mother liquor was once again concentrated under vacuum to obtain a yellow oil which is chromatographed with benzene in a silica-gel column to obtain 3,4-dihydro-1-isopropyl-7-methyl-4-phenyl-2(1H)quinazolinone; m.p. 157°–159°C. and 1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazolinone; m.p. 138°C. to 140°C.

What is claimed is:

1. A process for the preparation of a compound of the formula:

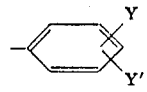


wherein

R° and R°1 represent, independently, hydrogen; halo having an atomic weight no greater than 80, alkyl of one to five carbon atoms, alkoxy of one to five carbon atoms; nitro, provided that only one of R° and $R°_1$, is nitro, or one of R° and $R°_1$ is trifluoromethyl and the other hydrogen, or R° and $R°_1$ together form 6,7-methylenedioxy;

R^1 represents alkyl of one to five carbon atoms, allyl, methallyl, or propargyl, or cycloalkyl of three to six carbon atoms and cycloalkylalkyl of four to seven carbon atoms;

R^2 represents phenyl, or substituted phenyl of the formula

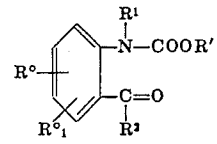


wherein

Y represents halo of atom weight not greater than 80, alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, or trifluoromethyl and

Y′ represents hydrogen, halo of atom weight not greater than 80alkyl of one to four carbon atoms, or alkoxy of one to four carbon atoms,

said process comprising reacting a carbamate of the formula:



wherein R°, $R°_1$, and R^1 and R^2 are as above defined and R′ is alkyl of one to four carbon atoms with an ammonium salt of an alkyl mono or dicarboxylic acid of one to four carbon atoms at a temperature in the range of from 70° to 180°C.

2. The process of claim **1** where R° and $R°_1$ is 6,7-methylenedioxy and R^1 is cycloalkyl or cycloalkylalkyl.

3. The process of claim **1** in which the ammonium salt is ammonium formate.

4. The process of claim **1** in which the ammonium salt is ammonium acetate.

5. The process of claim **1** in which the ammonium salt is ammonium oxalate.

6. The process of claim **4** in which the reaction temperature is in the range of 110° to 140°C.

7. The process of claim **6** which is carried out substantially in the absence of added solvent.

8. The process of claim **6** which is carried out in the presence of acetic acid.

9. The process of claim **6** in which the carbamate is an alkyl-N-isopropyl-N-(2-benzoyl-5-methylphenyl)-carbamate.

10. The process of claim **7** in which the carbamate is the ethyl carbamate.

* * * * *