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QUINAZOLINONE DERIVATIVE AND PROCESS FOR THE PRODUCTION THEREOF

Karl-Heinz Boltze, Bensberg-Kippekausen, and Dietrich Lorenz, Kleinhurden Post, Immekeppel, near Bensberg, Germany, assignors to Troponwerke Dinklage & Co., Cologne-Mulheim, Germany

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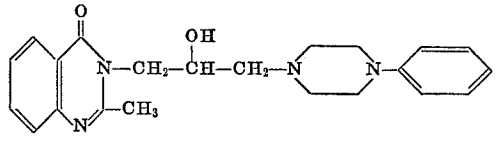
ABSTRACT OF THE DISCLOSURE

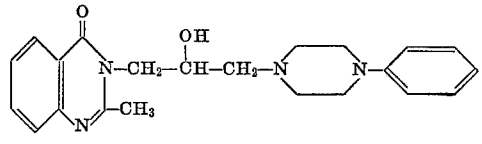
A quinazolinone compound of the formula:



2-methyl-3-{3-[4-phenylpiperazinyl-(1)] - 2 - hydroxypropyl}-quinazoline-4-one. This compound has antitussive and analgesic activity.

This invention relates to a new quinazolinone derivative and to a process for the production thereof.

The invention provides as a new chemical compound 2-methyl-3-{3-[4-phenylpiperazinyl-(1)] - 2 - hydroxypropyl}-quinazoline-4-one (hereinafter referred to as I) having the following formula:



(I)

This compound is effective as an analgesic and antitussive, as more fully described below.

Quinazolinone derivatives are already known and common as drugs for use in human medicine.

As examples of such derivatives there may be mentioned 2-methyl-3-o-tolylquinazoline - 4 - one, which has anti-convulsive, sedative and hypnotic activity and 2-methyl-3-o-ethylphenylquinazoline - 4 - one, which has a hypnotic action. In addition certain other quinazolinone derivatives are reputed to be active against malaria.

It has now been found that the aforementioned pharmacological effects are completely overshadowed in favour of an antitussive and analgesic quality, if the substituted phenyl ring on the quinazolinone skeleton in the 3-position is replaced by a 3-[4-phenylpiperazinyl-(1)]-2-hydroxypropyl group. For example, in the hotplate test on the mouse, the ED_{50} (i.e. the dose with which 50% of the animals are protected from pain), amounts to 25 mg./kg. with oral administration, which corresponds in this test approximately to the analgesic effect which results from codeine. In the benzoquinone test (chemical irritation on the peritoneum of the mouse), an ED_{50} of 97 mg./kg. on oral administration was found, corresponding approximately to the effective strength of the known 1-ethyl-4-methylamino-2,2-diphenylpentyl acetate (dextropropoxyphene). After doses of 25–250 mg./kg. per os, and using electrical irritation of the tooth pulp of the rabbit as the test method, the irritation threshold of the pain was increased by 60–500% with long-lasting effect. In this test, I is even more strongly active than morphine or codeine.

The antitussive efficacy of the compound was tested on the guinea pig and the cat. With the former, using a sulphuric acid spray as cough irritant, and ED_{50} of 10 mg./kg. was produced with subcutaneous administration, this once again corresponding approximately to the effectiveness of codeine. With the cat (electric stimulation of the laryngicus cranialis nerve) the effectiveness of codeine was reached, with an ED_{50} of 1.7 mg./kg. (intravenous) and 10–20 mg./kg. (enteral). By contrast with the opium alkaloids, when I is used in doses of 5 mg./kg. intravenously on the unnarcotised rabbit, the respiration (breath intake/breathing phase) is not impaired but it is even improved.

Since sedative, anticonvulsive and hypnotic active components extending into the sub-toxic dose range were not to be found in the appropriate tests, the analgesic and antitussive action cannot be caused by a general central sedation.

The LD_{50} values with the mouse are very high, being 120 mg./kg. intravenously and 710 mg./kg. per os; 500 mg./kg. per os are tolerated without reaction by the rabbit. This shows a very low toxicity of the compound I.

The compound according to the invention may be prepared by the condensation of 1-phenylpiperazine with 2-methyl-3-[3-bromo-2-hydroxypropyl] - quinazoline-4-one or by the addition to it of 2-methyl-3-[2,3-epoxypropyl]-quinazoline-4-one or by condensing 2-methylquinazoline-4-one with epichlorhydrin and then adding to it 1-phenylpiperazine preferably without isolation of the intermediate.

The invention therefore also provides a process for the preparation of the 2-methyl-3-{3 - [4 - phenylpiperazinyl-(1)]-2-hydroxypropyl}-quinazoline-4-one in which

(a) 1-phenylpiperazine is condensed with 2-methyl-3-[3-bromo-2-hydroxypropyl]-quinazoline-4-one or
(b) 2 - methyl-3-[2,3-epoxypropyl]-quinazoline-4-one is reacted with 1-phenylpiperazine; or
(c) 2-methylquinazoline-4-one is first condensed with epichlorhydrin and the product reacted with 1-phenylpiperazine if desired without intermediate isolation.

The reactions can be carried out in the absence of solvents at temperatures above 150° C. and also in the presence of organic solvents, such as ethyl alcohol, at room temperature or higher temperature.

For administration, the compound according to the invention may be formulated with a pharmaceutical carrier to provide formulations adapted for the particular route of administration in particular the oral route, for example in the form of a syrup, elixir or the like or as a tablet or capsule.

The following examples illustrate the invention:

EXAMPLE 1

2.5 g. of 2-methyl-3-(3-bromo-2-hydroxypropyl)-quinazoline-4-one and 2.7 g. of 1-phenylpiperazine are maintained for 5 minutes in an oil bath at 160°. The melt which is obtained is cooled and chloroform is added to it. The precipitate which is formed (1-phenylpiperazine dihydrobromide) is filtered off, the filtrate is evaporated and the residue crystallised from 96% ethanol. The 2-methyl-3-{3-[4-phenylpiperazinyl-(1)]-2-hydroxypropyl}-quinazoline-4-one which is formed melts at 145–144° C.; the yield is 2.6 g., corresponding to 82% of the theoretical.

For $C_{22}H_{26}N_4O_2$.—Calculated (percent): C, 69.81; H, 6.93; N, 14.80. Found (percent): C, 70.25; H, 6.66; N, 14.60.

EXAMPLE 2

10.8 g. of 2-methyl-3-(2,3-epoxypropyl)-quinazoline-4-one and 8.1 g. of 1-phenylpiperazine are boiled for 4

hours in 70 ml. of absolute ethanol and the solution is kept for several hours at room temperature and then in the cold. The substance which precipitates is filtered off, the contents of the filter are washed with ether and then crystallised from ethanol. 14.2 g. of 2-methyl-3-{3-[4-phenylpiperazinyl - (1)]-2-hydroxypropyl}-quinazoline-4-one are formed, corresponding to 75% of the theoretical.

EXAMPLE 3

29.2 g. of 2-methylquinazoline-4-one and 70 ml. (= 82.5 g.) of epichlorhydrin are dissolved in methanol and then an equimolar quantity of sodium methylate in methanol is added. After standing for 12 hours at room temperature, the viscous mass which forms (39.6 g.) is filtered off, removed from the filter and maintained with 44.5 g. of 1-phenylpiperazine for 30 minutes in an oil bath at 110° C. The mass (84 g. crude yield) is then worked up as previously described.

What is claimed is:

1. 2-methyl-3-{3-[4-phenylpiperazinyl-(1)]-2-hydroxypropyl}quinazolin-4-one.

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ALEX MAZEL, Primary Examiner

R. V. RUSH, Assistant Examiner

U.S. Cl. X.R.

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