

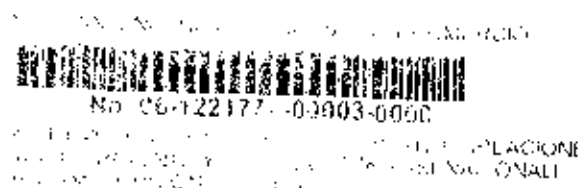
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145

SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____



Expediente No. 06-122.177

Solicitud de Patente de Invención titulada: "DERIVADOS DE QUINAZOLINONA
UTILES COMO ANTAGONISTAS VANILLOIDES".

Solicitante: NOVARTIS AG

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado de la sociedad de la referencia, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 de 26 de diciembre 2007.

Atentamente,


CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$420.000 pesos

IMPRESIONADA 02/01/04 541 Bcm

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 15,375
FECHA : FEBRERO 21 DE 2008

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
PARTE RAISEBECK	CONSIGNACION	BANCO DE BOGOTA	962754387	1483221	21/02/2008	22,239,000.00

***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
	TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-122177

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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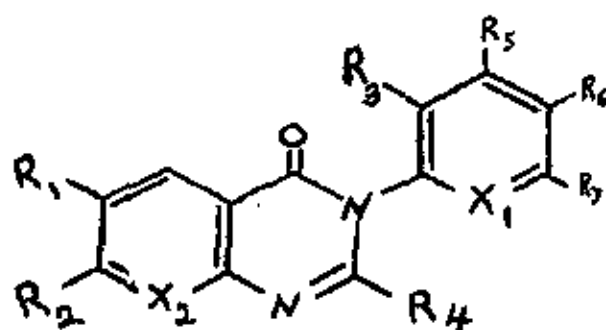
PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US91/00788 (22) International Filing Date: 6 February 1991 (06.02.91) (71)(72) Applicants and Inventors: DWIVEDI, Chandradhar [US/US]; 1825 Skyview Lane, Brookings, SD 57006 (US); OMODT, Gary, W. [US/US]; 112 Lincoln Lane So., Brookings, SD 57006 (US). (74) Agent: KARNY, Geoffrey, M.; Dickstein, Shapiro & Morin, 2101 L Street, N.W., Washington, DC 20037 (US). (81) Designated States: CA, JP.		Published With international search report.

(54) Title: ANTICONVULSANT SUBSTITUTED QUINAZOLONES



(II)

(57) Abstract

Disclosed herein are substituted quinazolinones and their N1-oxide derivatives, methods of synthesizing such compounds, and methods of using them to treat or prevent convulsions in mammals. The substituted quinazolinones are represented by formula (II): wherein X₁ is N, S, O, or CH, X₂ is N or CH, R₁ and R₂ are H, NO₂, or NH₂ except that when one of R₁ and R₂ is NO₂ or NH₂ the other is H, R₃ and R₄ are alkyl with 1-5 C atoms, and R₅, R₆, and R₇ are H or halogen, provided that when X₁ is N, S, or O, X₂ is CH.

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In a particularly preferred embodiment, X_1 is N, X_2 is CH, and one of R_1 and R_2 is NO_2 or NH_2 . Preferably, one of R_1 and R_2 is NH_2 , and the other is H. In this case, it is also preferred that R_3 and R_4 are methyl and further that R_5 , R_6 , and R_7 are H.

In another particularly preferred embodiment of the invention, X_1 is N, X_2 is CH, and R_1 and R_2 are H. Most preferably, R_3 and R_4 are methyl and R_5 - R_7 are H, which provides the especially preferred compound 2-methyl-3-(3-methyl-2-pyridyl)-4-quinazolone.

In another particularly preferred embodiment of the invention, X_1 in Formula II is CH, X_2 is CH, and one of R_1 and R_2 is NO_2 or NH_2 . Most preferably, one of R_1 or R_2 is NH_2 and the other is H. In this case, R_3 and R_4 are preferably methyl, and R_5 , R_6 , and R_7 are H. Thus, another especially preferred compound of the invention is 2-methyl-3-o-tolyl-7-amino-4-quinazolone.

The compounds of the invention are prepared according to the following scheme:

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EXAMPLE 4

2-Methyl-3-o-tolyl-7-amino-4-quinazolone (compound no. 14)

This compound was prepared from 2-methyl-3-o-tolyl-7-nitro-4-quinazolone, which was prepared as follows. 7-nitro-acetantranil (2.1 g, 0.011 mole) was mixed with o-toluidine (1.1 g, 0.010 mole) and heated in an erlenmeyer flask, first over a low flame and then over a high flame to complete the reaction. On cooling overnight, the reaction mixture solidified. The solid mass was stirred and broken up after the addition of ether. Suction filtration yielded 2.7 g (98%), mp 183-186°C. After recrystallization from ethanol, the yield was 2.5 g (91%), mp 181-183°C.

To a mixture of 2.0 g of iron powder (reduced) and 1.0 g 2-methyl-3-o-tolyl-7-nitro-4-quinazolone (0.0036 mole) in a test tube (8" x 1") was added 2 ml of 1 N ammonium chloride and 8 ml ethanol. The mixture was warmed gently in a water bath until the initial vigorous reaction had subsided. The test tube was then heated in the water bath until the solvents had evaporated (about 1 hr). The residue was extracted with four 10 ml portions of benzene, and the extracts were suction-filtered. The filtrate was heated with stirring, and n-hexane was added to cloudiness. The suspension was placed in the refrigerator overnight, and the white crystals were removed by suction-filtration. The yield was 0.9 g (100%), mp 211-212°C.

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form of a pharmaceutical composition. The invention includes a pharmaceutical composition comprising from about 1% to about 95% by weight of the compounds, or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable carrier.

In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compounds, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, flavoring agents, or other active ingredients. The compositions of the invention may be

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TABLE 2

Substituted Quinazolones*

Compound No.	R ₁	R ₂	R ₃	X ₁	X ₂	m.p. °C	Recrystallization solvent
2	H	H	CH ₃	N	CH	135-137	Ethanol-water
3	H	H	CH ₃	CH	N	148-150	Ethanol
4	H	H	CH ₃	N	N	252-253	Ethanol
5**	H	H	CH ₃	CH ₂	CH	160-162	Ethanol
6	H	H	COOH	CH	CH	244-246	Ethanol-water
7	H	H	NO ₂	CH	CH	155-165	Ethanol-water
8	H	H	NO ₂	N	CH	152-160	Ethanol
9	NO ₂	H	CH ₃	CH	CH	181-183	Ethanol
10	NH ₂	H	CH ₃	CH	CH	221-223	Benzene-n-hexane
11	NO ₂	H	CH ₃	N	CH	220-221	Ethanol
12	NH ₂	H	CH ₃	N	CH	250-253	Benzene-n-hexane
13	H	NO ₂	CH ₃	CH	CH	181-183	Ethanol
14	H	NH ₂	CH ₃	CH	CH	211-212	Benzene-n-hexane
15	H	NO ₂	CH ₃	N	CH	156-158	Ethanol
16	H	NH ₂	CH ₃	N	CH	201-203	Benzene-n-hexane

* All the compounds were characterized by sharp melting points and elemental analyses (C, H, & N within ±0.5%).

** In this compound, the ring at position 3 is saturated (cyclohexyl).

1076.747



PATENT SPECIFICATION

NO DRAWINGS

1076.747

Date of Application and filing Complete Specification: Sept. 9, 1964.

No. 36951/64.

Application made in Germany (No. B73447 IVd/12p) on Sept. 9, 1963.

Complete Specification Published: July 19, 1967.

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Index at acceptance:—C3 C(1D, 1F2A2, 1F2C4, 1F2C8, 1F2D3, 1Q2, 1Q6C, 1Q7A, 1Q8A, 1Q8B, 1Q9C, 1Q11G, 1Q11J, 2B4A4, 2B4D, 2B4F, 2B4G1, 2B4G2, 2B4G3, 2B4G8, 2B4G11, 2B7, 2B9, 2B31, 2B50D1, 2B50G1, 2B50G7)

Int. Cl.:—C 07 d 51/46

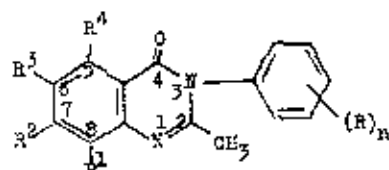
COMPLETE SPECIFICATION

Substituted Quinazolones

We, BOEHRINGER INGELHEIM, G.M.B.H., a German Body Corporation, of Ingelheim am Rhein, Germany, 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 concerns new 2-methyl-3-phenyl-3H-4-quinazolones having valuable pharmacological properties.

According to the invention, we provide new 2-methyl-3-phenyl-3H-4-quinazolones of the general formula



I

in which one of the substituents R^1 , R^2 , R^3 and R^4 is an unsubstituted amino group, and the remainder of the substituents R^1 , R^2 , R^3 and R^4 , which may be the same or different, are hydrogen or halogen atoms, or alkyl groups; n is a whole number from 1 to 5, and the substituents R , which may be the same or different when n is a whole number from 2 to 5, are halogen atoms or alkyl, alkoxy, acylamino, dialkylamino, carbalkoxy or haloalkyl groups, except that, when $R^1=R^2=R^4=H$, $R^3=NH_2$, and $n=1$, R cannot represent an *o*-methyl group; and non-toxic salts thereof.

By "non-toxic salts" we mean those salts the anionic portions of which are physiologically compatible in the dosages at which the salts are administered.

As mentioned above, the new compounds of formula I have valuable pharmacological

properties. In particular, they have a powerful sedative action together with very low toxicity. Many of the compounds according to the invention also possess anticonvulsive activity and muscle-relaxing and tranquillising properties, without inducing cramp or exciting the central nervous system.

Preferred compounds according to the invention are those having at least one R group which is an alkyl or alkoxy group having from 1 to 5 carbon atoms, e.g., a methyl, ethyl, isopropyl, methoxy or ethoxy group. At least one R group may also conveniently be a trifluoromethyl group, e.g., a trifluoromethyl group. When R is halogen, it is preferably chlorine or bromine; when R is dialkylamino or carbalkoxy, the alkyl or alkoxy groups preferably contain from 1 to 4 carbon atoms, and thus R may for example be dimethylamino or carbethoxy; when R is an acylamino group, it preferably contains from 2 to 4 carbon atoms and is conveniently acetylamino.

The three of the symbols R^1 , R^2 , R^3 and R^4 which are other than amino groups preferably represent hydrogen atoms. At least one of R^1 , R^2 , R^3 and R^4 may however represent an alkyl group containing 1 to 5 carbon atoms, e.g., a methyl group, or a chlorine atom.

Compounds which possess especially valuable therapeutic activity are those of general formula I in which n is 1, R is a dimethylamino group and one of the symbols R^1 , R^2 , R^3 and R^4 represents a free amino group and the remainder represent hydrogen atoms.

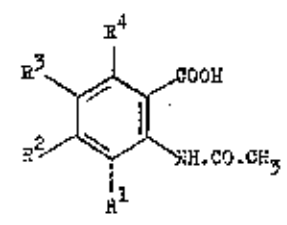
Particularly preferred compounds according to the invention by virtue of their especially valuable pharmacological properties are as follows:—

- 2-methyl-3-(2'-methylphenyl)-7-amino-3H-4-quinazolone
- 2-methyl-3-(2,4'-dimethylphenyl)-7-amino-3H-4-quinazolone

[Price 4s. 6d.]

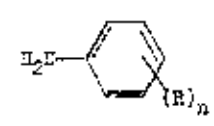
156A

- ~~2 - methyl - 3 - (2' - methyl - 4' - chlorophenyl) - 6-amino-3H-4-quinazolinone,~~
- ~~2 - methyl - 3 - (2' - methyl - 3' - chlorophenyl) - 6-amino-3H-4-quinazolinone,~~
- 5 ~~2 - methyl - 3 - (2' - chlorophenyl) - 6-amino-3H-4-quinazolinone,~~
- 2 - methyl - 3 - (4' - bromophenyl) - 6-amino-3H-4-quinazolinone,
- 2 - methyl - 3 - (2',5' - dimethoxyphenyl) - 6-amino-3H-4-quinazolinone,
- 10 2 - methyl - 3 - (2',6' - dimethylphenyl) - 6-amino-3H-4-quinazolinone,
- 2 - methyl - 3 - (2' - bromophenyl) - 6-amino-3H-4-quinazolinone,
- 15 2 - methyl - 3 - (4' - bromo - 2' - methylphenyl) - 6-amino-3H-4-quinazolinone,
- 2 - methyl - 3 - (2' - dimethylaminophenyl) - 5-amino-3H-4-quinazolinone,
- 2 - methyl - 3 - (2' - dimethylaminophenyl) - 6-amino-3H-4-quinazolinone,
- 20 2 - methyl - 3 - (4' - dimethylaminophenyl) - 6-amino-3H-4-quinazolinone,
- ~~2 - methyl - 3 - (2' - dimethylaminophenyl) - 7-amino-3H-4-quinazolinone,~~
- 25 ~~2 - methyl - 3 - (3' - dimethylaminophenyl) - 7-amino-3H-4-quinazolinone,~~
- ~~2 - methyl - 3 - (4' - dimethylaminophenyl) - 7-amino-3H-4-quinazolinone,~~
- 30 ~~2 - methyl - 3 - (2' - dimethylaminophenyl) - 8-amino-3H-4-quinazolinone~~



II

(in which one of the substituents R¹, R², R³ and R⁴ is a nitro group or a nitroso group and the remainder of the substituents are as hereinbefore defined with reference to formula I), with an aromatic amine of the formula

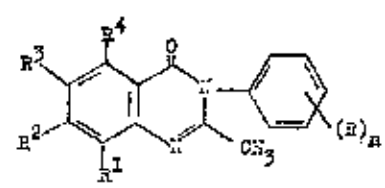


III

(in which R and n are as hereinbefore defined) in the presence of a dehydrating agent.

The compounds of formula I may also be prepared as follows:—

a) Removal of the protecting group of the reversibly protected amino group of a 2-methyl-3-phenyl-3H-4-quinazolinone of the formula



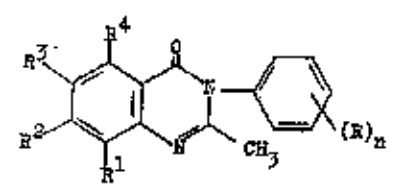
I'

(in which one of the substituents R¹, R², R³ and R⁴ is a reversibly protected amino group, and R and n and the remainder of the substituents R¹, R², R³ and R⁴ are as hereinbefore defined with regard to formula I). The removal of the protecting group(s) is/are effected in known manner. Suitable protecting groups are, for example, acyl groups, the carbobenzoxy group, or the benzyl radical. The acyl group can be derived from any convenient aliphatic, alicyclic or aromatic acid. Preferably, however, the acyl radical is one which can readily be eliminated. The elimination of the carbobenzoxy group or of the benzyl radical is conveniently effected by hydrogenolysis.

The 2 - methyl - 3 - phenyl - 3H - 4-quinazolones of the formula I'' may be pre-

and non-toxic acid addition salts thereof.

The compounds of formula I hereinbefore defined may be prepared by any convenient method. According to a further feature of the invention, we provide a process for the preparation of a compound of formula I which comprises reducing a 2-methyl-3-phenyl-3H-4-quinazolinone of the general formula

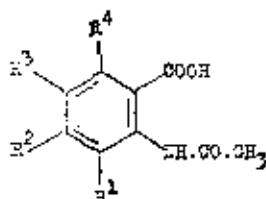


I

(in which one of the substituents R¹, R², R³ and R⁴ is a nitro group or a nitroso group, R, n, the remainder of the substituents R¹, R², R³ and R⁴ being as hereinbefore defined). The reduction may be effected, for example, by means of hydrogen in the presence of a catalyst or nascent hydrogen.

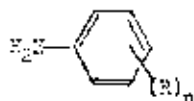
The 2 - methyl - 3 - phenyl - 3H - 4-quinazolinone of the formula I' may be prepared, for example, by condensation of an acetyl-anthranilic acid of the formula

pared, for example, by condensation of an acetylthranilic acid of the formula



II'

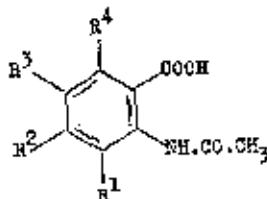
(in which one of the substituents R^1 , R^2 , R^3 and R^4 is a reversibly protected amino group and R and n and the remainder of the substituents R^1 , R^2 , R^3 and R^4 are as hereinbefore defined with reference to formula I) with an aromatic amine of the formula



III

(where R and n are as hereinbefore defined) in the presence of a dehydrating agent.

b) Condensation of an acetylthranilic acid of the formula



II''

wherein R^1 , R^2 , R^3 and R^4 are as hereinbefore defined with regard to formula I, with an aromatic amine of formula III (as hereinbefore defined) in presence of a dehydrating agent.

The compounds of formula I may be converted into their non-toxic acid addition salts in any convenient manner with suitable inorganic and organic acids; for example: hydrochloric acid, hydrobromic acid, phos-

phoric acid, sulphuric acid, acetic acid, lactic acid, salicylic acid, tartaric acid, methane sulphonc acid, and benzoic acid.

As stated above, the new 2-methyl-3-phenyl-3H-4-quinazolones of the general formula I have valuable pharmacological properties, and in particular possess strong sedative action with very low toxicity. It is especially surprising that the compounds according to the invention do not in addition excite the central nervous system, as the structurally similar 2-methyl-3-*o*-tolyl-3H-4-quinazolone (known by the trade name Methaqualone) does not have the latter effect.

Another similar compound, 2-methyl-3-*o*-tolyl-6-amino-3H-4-quinazolone, with muscle-relaxing and spasmolytic properties, is described in British Patent Specification No. 916,139, although there is no mention therein of its having a sedative action. Our own experiments have shown that this substance which possesses a moderate sedative action also excites the central nervous system.

Pharmacological tests have been carried out designed to compare the sedative actions and toxicities of the compounds according to the invention with those of closely related known compounds. The sedative activity was determined from the "atactic dose" (AD_{50}), at which the movements of the animals under experiment are no longer co-ordinated, and the "position reflex dose" (PD_{50}) at which the animals are no longer capable of getting on to their feet from the side position by their own efforts. The lethal doses (LD_{50}) are also determined, and the therapeutic index (T) was calculated as quotient.

$$T = \frac{LD_{50}}{\frac{1}{2} (AD_{50} + PD_{50})}$$

The dose for the "cancellation of the back-tension reflex" (BD_{50}), and the dose for the "inhibition of electric-shock induced cramp," (CD_{50}), were also determined for some of the compounds.

In the tests the compounds were administered orally to mice in the form of an oil-water emulsion.

The results of the pharmacological experiments are summarised in the following table:—

Test Compound	AD ₅₀ mg./kg.	PD ₅₀ mg./kg.	BD ₅₀ mg./kg.	LD ₅₀ mg./kg.	CD ₅₀ mg./kg.	T
Methaqualone (known compound)	145	580	590	2100	70	5.7
2-Methyl-3-o-tolyl-6-amino-3H-4-quinazoline (described in B.P. Specification No. 916,139)	115	400		2050		7.9
2-Methyl-3-(3'-methylphenyl)-7-amino-3H-4-quinazoline	69	375		>2385		>10.8
2-Methyl-3-(2',4'-dimethylphenyl)-7-amino-3H-4-quinazoline	130	150		1400		10
2-Methyl-3-(2'-methyl-4'-chlorophenyl)-7-amino-3H-4-quinazoline	30	430	500	>2700	100	>10
2-Methyl-3-(2'-methyl-3'-chlorophenyl)-6-amino-3H-4-quinazoline	74	110		1550		16.8
2-Methyl-3-(2'-chlorophenyl)-6-amino-3H-4-quinazoline	38	105	136	640	16	9
2-Methyl-3-(4'-bromophenyl)-6-amino-3H-4-quinazoline	28	92	90	420	36	7
2-Methyl-3-(2',5'-dimethoxyphenyl)-6-amino-3H-4-quinazoline	115	175	185	720	>100	5
2-Methyl-3-(2',6'-dimethylphenyl)-6-amino-3H-4-quinazoline	52	86		900		13
2-Methyl-3-(2'-bromophenyl)-6-amino-3H-4-quinazoline	50	110		600		7.5
2-Methyl-3-(4'-bromo-2'-methylphenyl)-6-amino-3H-4-quinazoline	50	115		590		7.1

It could not have been foreseen that the compounds according to the invention would show such marked sedative properties without exciting the central nervous system. Indeed, experience gained from the synthesis of substituted barbituric acids (see B. Duran, Barbituric acid hypnotics, p. 34 in Medicinal Chemistry, Vol. IV, Wiley & Sons, New York, 1959) did lead one to expect that the sedative effect would in fact be reduced by the introduction of a basic group. This is not the case, however, as is apparent from the above Table. It is evident that the introduction of an amino group into the 5-, 6-, 7- or 8-position of a 2-methyl-3-phenyl-3H-4-quinazoline increases the sedative and anti-convulsive activity of these compounds; the compounds also exhibit tranquillising and muscle-relaxing action. Furthermore, the cramp-inducing side-effects (F. Hauschild, H. Harmann, H. Wellkörn and C. Morgenstern, *Acta Biol. Med. Germ.*, 9, 2: 161 (1962), and Steinmann, 4,

Frühjahrstagung der Deutschen Pharmacologischen Gesellschaft in Mainz, 28.4-1.5. 1963), characteristic of the non-amined compounds is reduced or completely removed by the introduction of the amino-group. The new compounds according to the invention therefore possess special advantages as compared with the previously known non-amined substances.

In further pharmacological tests, the sedative activity was demonstrated on mice, rats, rabbits, cats and dogs. The anti-convulsive activity was also demonstrated in electric shock experiments on the mouse. The sleeping time achieved in mice after administration of 100 mg./kg. of hexobarbital was extended several times by an additional administration of 50-100 mg./kg. of a compound according to the invention. Electroencephalographic experiments on cats and rabbits resulted in a brain current diagram similar to that observed in natural sleep.

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The invention further provides pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient. The compounds may be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of capsules, tablets, coated tablets, suspensions, etc., such compositions comprising carriers or excipients conveniently used in the pharmaceutical art. Thus suitable tableting excipients include lactose, potato and maize starches, talc, gelatine, and stearic and silicic acids, magnesium stearate and polyvinyl pyrrolidone.

For parenteral administration, the carrier or excipient may be a sterile, parenterally acceptable liquid, e.g., pyrogen-free water or an aqueous solution of polyvinyl pyrrolidone, or a parenterally acceptable oil, e.g., arachis oil, contained in ampoules.

In compositions for rectal administration, the carrier may comprise a suppository base, e.g., cocoa butter or a glyceride.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, ampoules and suppositories are examples of preferred dosage unit forms according to the invention. Each dosage unit may advantageously contain 20 to 500 mg., preferably 100 to 150 mg., of active ingredient.

For the better understanding of the invention, the following Examples are given by way of illustration only:

EXAMPLE 1.

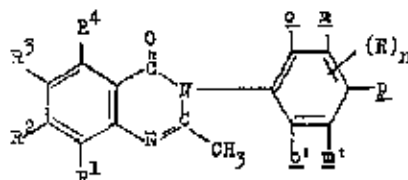
2-Methyl-3-o-tolyl-7-amino-3H-4-quinazoline

8.85 g. of 2-methyl-3-o-tolyl-7-nitro-3H-4-quinazoline (0.03 mol) are dissolved in 100 cc. of ethanol and hydrogenated with Raney nickel at atmospheric pressure until hydrogen uptake is complete, i.e., about 1 hour. The solution is separated from the catalyst and is then evaporated to dryness *in vacuo*, the hydrogenation product remaining behind crystalline. The yield is almost quantitative. The compound crystallises from ethanol/water in colourless blocks of m.p. = 213–215°C. The corresponding hydrochloride is obtained by reacting the free base with conc. hydrochloric acid.

The same compound is obtained if the nitro compound is reduced with stannous chloride and hydrochloric acid and the tin then precipitated out by passing in hydrogen sulphide.

The starting compound, 2-methyl-3-o-tolyl-7-nitro-3H-4-quinazoline, of m.p. 182–184°C., is obtained in the usual manner from o-toluidine and 4-nitro-acetylanthranil or from toluidine and 4-nitro-acetylanthranilic acid in the presence of dehydrating agents, for example, phosphorus oxychloride or phosphorus trichloride.

The following compounds of the general formula have also been prepared:—



Serial No.	R ¹	R ²	R ³	R ⁴	R	M.p.t.(°C.)
1	—NH ₂	—H	—H	—H	—o-CH ₃	255–57
2	„	„	„	„	—o-CH ₃ , —p-CH ₃	223–25
3	„	„	„	„	—o-CH ₃ , —p-CH ₃ , —o'-CH ₃	181–82
4	„	„	„	„	—o-C ₂ H ₅	196–98

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Serial No.	R ¹	R ²	R ³	R ⁴	R	M.pt. (°C.)
5	-NH ₂	-H	-H	-H	-o-OCH ₃	270-71
6	"	"	"	"	-o-OCH ₃ , -p-OCH ₃	233-34
7	"	"	"	"	-o-CH ₃ , -p-OCH ₃	196-98
8	"	"	"	"	-o-OCH ₃ , -p-CH ₃	257-59
9	"	"	"	"	-p-Cl	205-207
10	"	"	"	"	-p-Br	217-19
11	"	"	"	"	-o-CH ₃ , -m-Cl	252-54
12	"	"	"	"	-o-CH ₃ , -p-Cl	222-24
13	"	"	"	"	-o-Cl, -p-Cl	217-19
14	"	"	"	"	-m-CH ₃ , -p-Br	207-209
15	"	"	"	"	-p-CF ₃	224-26
16	"	"	"	"	-o-OCH ₃ , -p-Cl	244-46
17	"	"	"	"	-o-CH ₃ , -m'-OCH ₃	258-60
18	"	"	"	"	-o-N(CH ₃) ₂	189-90
19	H	-NH ₂	"	"	-o-CH ₃	250-51
20	"	"	"	"	-p-CH ₃	221-23
21	"	"	"	"	-o-CH ₃ , -m-CH ₃	254-56
22	"	"	"	"	-o-CH ₃ , -p-CH ₃	180-82
23	"	"	"	"	-o-CH ₃ , -m'-CH ₃	229-31
24	"	"	"	"	-o-CH ₃ , -o'-CH ₃	224-26
25	"	"	"	"	-m-CH ₃ , -p-CH ₃	217-19
26	"	"	"	"	-o-CH ₃ , -m-CH ₃ , o'-CH ₃	158-60
27	"	"	"	"	-o-C ₂ H ₅	187-88
28	"	"	"	"	-o-CH(CH ₃) ₂	208-10
(½ molecule of water of crystallisation)						
29	"	"	"	"	-o-OCH ₃	186-87
30	"	"	"	"	-m-OCH ₃	106-108
31	"	"	"	"	-p-OCH ₃	234-35

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Serial No.	R ¹	R ²	R ³	R ⁴	R	M.pt.(°C.)
57	H	-NH ₂	-H	-H	<i>o</i> -OCH ₃ , <i>p</i> -Cl, <i>m'</i> -OCH ₃	132-133
58	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl, <i>m'</i> -CH ₃	248-49
59	"	"	"	"	<i>o</i> -COOC ₂ H ₅	218-19
60	"	"	"	"	<i>p</i> -COOC ₂ H ₅	205-206
61	"	"	"	"	<i>o</i> -N(CH ₃) ₂	198-200
62	"	"	"	"	<i>m</i> -N(CH ₃) ₂	187-89
					(monohydrate)	
63	"	"	"	"	<i>p</i> -N(CH ₃) ₂	228-29
64	"	"	"	"	<i>o</i> -NHCOCH ₃	260-63
					($\frac{1}{2}$ molecule of dimethylformamide of crystallisation)	
65	"	"	"	"	<i>o</i> -CH ₃ , <i>m'</i> -Cl	268-88
66	"	"	"	"	<i>o</i> -CF ₃	182-84
67	"	"	"	"	<i>o</i> -F	173-75
68	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -F	207-209
69	"	"	"	"	<i>o</i> -CH ₃ , <i>m'</i> -F	199-201
70	"	H	-NH ₂	"	<i>o</i> -CH ₃ , <i>m</i> -CH ₃	207-209
71	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -CH ₃	153-56
72	"	"	"	"	<i>o</i> -CH ₃ , <i>m'</i> -CH ₃	206-208
73	"	"	"	"	<i>o</i> -CH ₃ , <i>o'</i> -CH ₃ , <i>p</i> -CH ₃	247-49
74	"	"	"	"	<i>o</i> -C ₂ H ₅	152-54
75	"	"	"	H	<i>o</i> -OCH ₃	236-37
76	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -OCH ₃	228-30
77	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -OCH ₃	234-35
78	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -OCH ₃	175-76
79	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -CH ₃	121-22
80	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -CH ₃	237-38
81	"	"	"	"	<i>o</i> -CH ₃ , <i>o'</i> -CH ₃	274-76

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Serial No.	R ¹	R ²	R ³	R ⁴	R	M.Pt.(°C.)
32	—H	—NH ₂	—H	—H	<i>o</i> -OCH ₃ , <i>p</i> -OCH ₃	245—46
33	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -OCH ₃	256—57
34	"	"	"	"	<i>o</i> -OC ₂ H ₅ , <i>m'</i> -OC ₂ H ₅	267—68 (hydrochloride)
35	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -OCH ₃	162—65
36	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -CH ₃	180—82
37	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -CH ₃	257—59
38	"	"	"	"	<i>m</i> -OCH ₃ , <i>p</i> -CH ₃	230—31
39	"	"	"	"	<i>p</i> -CF ₃	223—25
40	"	"	"	"	<i>o</i> -Cl	218—20
41	"	"	"	"	<i>m</i> -Cl	185—87
42	"	"	"	"	<i>p</i> -Cl	220—22
43	"	"	"	"	<i>o</i> -Br	233—35
44	"	"	"	"	<i>m</i> -Br	135—37
45	"	"	"	"	<i>p</i> -Br	218—21
46	"	"	"	"	<i>o</i> -Cl, <i>p</i> -Cl	155; 231—32 (1 molecule of dimethylformamide of crystallisation)
47	"	"	"	"	<i>o</i> -CH ₃ , <i>m</i> -Cl	233—35
48	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -Cl	222—23
49	"	"	"	"	<i>o</i> -CH ₃ , <i>m'</i> -Cl	315—17 (hydrochloride)
50	"	"	"	"	<i>o</i> -CH ₃ , <i>o'</i> -Cl	196—98
51	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -Br	225—27
52	"	"	"	"	<i>o</i> -Br, <i>p</i> -CH ₃	215—17
53	"	"	"	"	<i>m</i> -CH ₃ , <i>p</i> -Br	107—109 (1 molecule of methanol of crystallisation)
54	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl	218—20
55	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -Cl	286—88
56	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -OCH ₃ , <i>m'</i> -Cl	241—42

Serial No.	R ¹	R ²	R ³	R ⁴	R	M.pt.(°C.)
82	H	H	-NH ₂	H	<i>m</i> -OCH ₃	148—150 (hemihydrate)
83	"	"	"	"	<i>o</i> -OC ₂ H ₅ , <i>m'</i> -OC ₂ H ₅	133—36 (½ molecule of water of crystallisation)
84	"	"	"	"	<i>o</i> -Cl	233—35
85	"	"	"	"	<i>m</i> -Cl	210—12
86	"	"	"	"	<i>p</i> -Cl	201—03
87	"	"	"	"	<i>o</i> -Br	239—41
88	"	"	"	"	<i>m</i> -Br	223—25
89	"	"	"	"	<i>p</i> -Br	209—11
90	"	"	"	"	<i>o</i> -CH ₃ , <i>m</i> -Cl	219—21
91	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -Cl	192—94
92	"	"	"	"	<i>o</i> -CH ₃ , <i>m'</i> -Cl	249—50
93	"	"	"	"	<i>o</i> -CH ₃ , <i>o'</i> -Cl	272—74
94	"	"	"	"	<i>o</i> -Cl, <i>p</i> -Cl	213—14
95	"	"	"	"	<i>o</i> -Br, <i>p</i> -CH ₃	199—201
96	"	"	"	"	<i>o</i> -OCH ₃ , <i>m'</i> -Cl	256—57
97	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl	200—202
98	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl, <i>m'</i> -OCH ₃	221—23
99	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -OCH ₃ , <i>m'</i> -Cl	223—25 (½ molecule of ethyl acetate of crystallisation)
100	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl, <i>m'</i> -CH ₃	228—30
101	"	"	"	"	<i>p</i> -CF ₃	226—28
102	"	"	"	"	<i>p</i> -F	195—97
103	"	"	"	"	<i>m</i> -CH ₃ , <i>p</i> -Br	181—82
104	"	"	"	"	<i>o</i> -COOC ₂ H ₅	157—59 (monohydrate)
105	"	"	"	"	<i>p</i> -COOC ₂ H ₅	167—69 (hemihydrate)

Serial No.	R ¹	R ²	R ³	R ⁴	R	M.p.t.(°C.)
106	H	H	-NH ₂	H	<i>o</i> -N(CH ₃) ₂	153; 191
107	"	"	"	"	<i>p</i> -N(CH ₃) ₂	266-67
108	"	"	"	"	<i>p</i> -OCH ₃	224-26
109	"	"	"	"	<i>m</i> -CH ₃ , <i>p</i> -CH ₃	172-73
110	"	"	"	"	<i>m</i> -OCH ₃ , <i>p</i> -CH ₃	215-16
111	"	"	"	"	<i>p</i> -I	210-12
112	"	Cl	"	"	<i>o</i> -CH ₃	189-91
113	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -CH ₃	166-168
114	"	"	"	"	<i>o</i> -C ₂ H ₅	170-72
					(monohydrate)	
115	"	"	"	"	<i>m</i> -OCH ₃ , <i>p</i> -CH ₃	196-98
116	"	CH ₃	"	"	<i>o</i> -CH ₃	195-97
117	"	H	NH ₂	"	<i>o</i> -CH ₃ , <i>m</i> '-Cl	256-257
118	"	"	"	"	<i>o</i> -CF ₃	244-246
119	"	"	"	"	<i>o</i> -F	207-209
120	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -F	164-166
121	"	"	"	"	<i>o</i> -CH ₃ , <i>m</i> '-F	198-200
122	"	"	H	NH ₂	<i>o</i> -CH ₃	168-70
123	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -CH ₃	143-45
124	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -CH ₃ , <i>o</i> '-CH ₃	125-27
					(3 molecule of dimethylformamide of crystallization)	
125	"	"	"	"	<i>o</i> -C ₂ H ₅	148-150
126	"	"	"	"	<i>o</i> -OCH ₃	155-57
127	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -OCH ₃	182-84
128	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -OCH ₃	161-62
129	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -CH ₃	198-200
130	"	"	"	"	<i>o</i> -OCH ₃ , <i>m</i> '-OCH ₃	166-68
131	"	"	"	"	<i>p</i> -Cl	252-54
132	"	"	"	"	<i>p</i> -Br	261-62

Serial No.	R ¹	R ²	R ³	R ⁴	R	M.pt.(°C.)
133	H	H	H	NH ₂	<i>o</i> -Cl, <i>p</i> -Cl	212-14
134	"	"	"	"	<i>o</i> -CH ₃ , <i>m</i> -Cl	176-78
135	"	"	"	"	<i>o</i> -CH ₃ , <i>p</i> -Cl	174-76
					(hemihydrate)	
136	"	"	"	"	<i>p</i> -CF ₃	214-216
137	"	"	"	"	<i>m</i> -CH ₃ , <i>p</i> -Br	216-18
138	"	"	"	"	<i>o</i> -N(CH ₃) ₂	187-89
139	"	"	"	"	<i>o</i> -OCH ₃ , <i>p</i> -Cl	201-203
140	"	"	NH ₂	H	<i>o</i> -CH ₃ , <i>p</i> -Br	190-192

EXAMPLE 2.

This Example illustrates pharmaceutical compositions according to the invention. Another active substance according to the invention, or a salt thereof, may be substituted for that named.

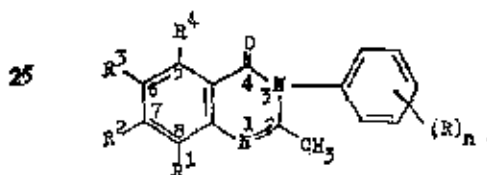
Preparation of Tablets:

Each tablet contains:	
2-Methyl-3-(2'-methyl-4'-chlorophenyl)-7-amino-3H-4-quinazoline	100.0 mg.
Lactose (powdered)	130.0 mg.
Maize starch	156.0 mg.
Silica (highly dispersed)	8.0 mg.
Soluble starch	4.0 mg.
Magnesium stearate	2.0 mg.
	400.0 mg.

The tablets are prepared by standard procedures. On administration *per os*, they disintegrate in about 20 seconds.

WHAT WE CLAIM IS:—

1. 2-Methyl-3-phenyl-3H-4-quinazolones of the general formula



I

in which one of the substituents R¹, R², R³

and R⁴ is an unsubstituted amino group, and the remainder of the substituents R¹, R², R³ and R⁴, which may be the same or different, are hydrogen or halogen atoms, or alkyl groups;

n is a whole number from 1 to 5, and the substituents R, which may be the same or different when *n* is a whole number from 2 to 5, are halogen atoms or alkyl, alkoxy, acylamino, dialkylamino, carbalkoxy or haloalkyl groups, except that, when R¹=R²=R⁴=H, R³=NH₂, and *n*=1, R cannot represent an *o*-methyl group; and non-toxic salts thereof.

2. Compounds as claimed in claim 1 in which R, or, where *n* is 2 to 5, at least one of the substituents R, is an alkyl or alkoxy group containing from 1 to 5 carbon atoms.

3. Compounds as claimed in claim 2 in which the said alkyl or alkoxy group is a methyl, ethyl, isopropyl, methoxy or ethoxy group.

4. Compounds as claimed in claim 1 in which R, or where *n* is 2 to 5, at least one of the substituents R, is a halomethyl group.

5. Compounds as claimed in claim 4 in which the said halomethyl group is a trifluoromethyl group.

6. Compounds as claimed in claim 1 in which R, or where *n* is 2 to 5, at least one of the substituents R, is a chlorine or bromine atom.

7. Compounds as claimed in claim 1 in which R, or where *n* is 2 to 5, at least one of the substituents R, is a dialkylamino group in which the alkyl groups contain 1 to 4 carbon atoms.

8. Compounds as claimed in claim 7 in which the said dialkylamino group is a dimethylamino group.

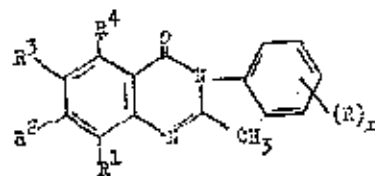
9. Compounds as claimed in claim 1 in which R , or where n is 2 to 5, at least one of the substituents R , is an acylamino group containing from 2 to 4 carbon atoms.
10. Compounds as claimed in claim 9 in which the said acylamino group is an acetyl-amino group.
11. Compounds as claimed in claim 1 in which R , or where n is 2 to 5, at least one of the substituents R , is a carbalkoxy group the alkoxy group of which contains from 1 to 4 carbon atoms.
12. Compounds as claimed in claim 11 in which the said carbalkoxy group is a carbethoxy group.
13. Compounds as claimed in any of claims 1 to 12 in which one of R^1 , R^2 , R^3 and R^4 is an amino group, the remainder being hydrogen atoms.
14. Compounds as claimed in any of claims 1 to 12 in which at least one of the groups R^1 , R^2 , R^3 and R^4 is an alkyl group containing from 1 to 5 carbon atoms.
15. Compounds as claimed in claim 14 in which at least one of the groups R^1 , R^2 , R^3 and R^4 is a methyl group.
16. Compounds as claimed in any of claims 1 to 13, in which at least one of the symbols R^1 , R^2 , R^3 and R^4 represents a free amino group and the remainder represents hydrogen atoms, n is 1, and R is a dimethylamino group.
17. 2 - Methyl - 3 - (2' - methylphenyl)-7-amino-3H-4-quinazoline and the non-toxic acid addition salts thereof.
18. 2 - Methyl - 3 - (2',4' - dimethylphenyl)-7-amino-3H-4-quinazoline.
19. 2 - Methyl - 3 - (2' - methyl - 4'-chlorophenyl)-7-amino-3H-4-quinazoline.
20. 2 - Methyl - 3 - (2' - methyl - 3'-chlorophenyl)-6-amino-3H-4-quinazoline.
21. 2 - Methyl - 3 - (2' - chlorophenyl) - 6-amino-3H-4-quinazoline and the non-toxic acid addition salts thereof.
22. 2 - Methyl - 3 - (4' - bromophenyl)-6-amino-3H-4-quinazoline.
23. 2 - Methyl - 3 - (2',5' - dimethoxyphenyl)-6-amino-3H-4-quinazoline.
24. 2 - Methyl - 3 - (2',6' - dimethylphenyl)-6-amino-3H-4-quinazoline.
25. 2 - Methyl - 3 - (2' - bromophenyl) - 6-amino-3H-4-quinazoline.
26. 2 - Methyl - 3 - (4' - bromo - 2'-methylphenyl)-6-amino-3H-4-quinazoline.
27. 2 - Methyl - 3 - (2' - dimethylamino-phenyl)-5-amino-3H-4-quinazoline.
28. 2 - Methyl - 3 - (2' - dimethylamino-phenyl)-6-amino-3H-4-quinazoline.
29. 2 - Methyl - 3 - (4' - dimethylamino-phenyl)-6-amino-3H-4-quinazoline.
30. 2 - Methyl - 3 - (2' - dimethylamino-phenyl)-7-amino-3H-4-quinazoline.
31. 2 - Methyl - 3 - (3' - dimethylamino-phenyl)-7-amino-3H-4-quinazoline.
32. 2 - Methyl - 3 - (4' - dimethylamino-phenyl)-7-amino-3H-4-quinazoline.

33. 2 - Methyl - 3 - (2' - dimethylamino-phenyl)-8-amino-3H-4-quinazoline.

34. Compounds as claimed in any of claims 18 to 33 in the form of non-toxic acid addition salts thereof.

35. Compounds as claimed in any of claims 1 to 17, 21 and 34 in the form of their non-toxic salts with hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, acetic acid, lactic acid, salicylic acid, tartaric acid, methane sulphonic acid, and benzoic acid.

36. A process for the preparation of a compound of formula I (as defined in claim 1) which comprises reducing a 2-methyl-3-phenyl-3H-4-quinazoline of the formula



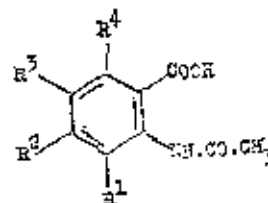
I'

wherein one of the substituents R^1 , R^2 , R^3 and R^4 is a nitro group or a nitroso group, R , n , and the remainder of the substituents R^1 , R^2 , R^3 and R^4 being as defined in claim 1.

37. A process as claimed in claim 36 in which the reduction is effected with hydrogen in the presence of a catalyst.

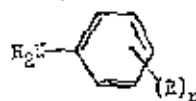
38. A process as claimed in claim 36 in which the reduction is effected with nascent hydrogen.

39. A process as claimed in any of claims 36 to 38 in which the compound of formula I' (as defined in claim 36) is prepared by condensation of an acetylanthranilic acid of the formula



II

(wherein one of the substituents R^1 , R^2 , R^3 and R^4 is a nitro or nitroso group and the remainder of the substituents R^1 , R^2 , R^3 and R^4 are as defined in claim 1) with an aromatic amine of the formula



III

- (wherein R and n are as defined in claim 1) in the presence of dehydrating agent.
40. A process as claimed in any of claims 36 to 39 in which the compound of formula I (as defined in claim 1) is thereafter converted to a non-toxic acid addition salt thereof with an appropriate acid.
- 5 41. A process as claimed in claim 40 in which the acid is hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, acetic acid, lactic acid, salicylic acid, tartaric acid, methane sulphonic acid and benzoic acid.
- 10 42. A process as claimed in any of claims 36 to 41 substantially as herein described.
- 15 43. A process as claimed in any of claims 36 to 41 substantially as herein described in Example 1.
44. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 36 to 43.
- 20 45. A pharmaceutical composition comprising, as active ingredient, a compound as claimed in any of claims 1 to 35 and 44 together with a pharmaceutical carrier or excipient.
46. A composition as claimed in claim 45 in the form of dosage units.
47. A composition as claimed in claim 46 containing from 20 to 500 mg. of active ingredient per dosage unit.
- 30 48. A composition as claimed in claim 47 containing from 100 to 150 mg. of active ingredient per dosage unit.
49. A composition as claimed in any of claims 46 to 48 in the form of tablets, coated tablets, capsules, ampoules or suppositories.
- 35 50. A composition as claimed in any of claims 45-49 in which the active ingredient is a compound as claimed in claim 17 or claim 21.
- 40 51. A composition as claimed in claim 45 substantially as herein described.
52. A composition as claimed in claim 45 substantially as herein described in Example 2.

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AUSLEGESCHRIFT

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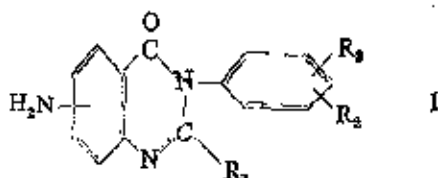
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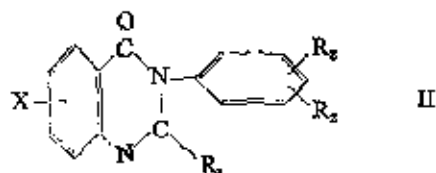
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Die Erfindung betrifft ein Verfahren zur Herstellung von 3-Phenylchinazolinon-(4)-derivaten der allgemeinen Formel I



In dieser Formel bedeutet R₁ ein Wasserstoffatom oder einen niedermolekularen Alkylrest, R₂ und R₃ Wasserstoff-, Halogenatome oder niedermolekulare Alkylreste.

Die Herstellung dieser Verbindungen erfolgt nach an sich bekannter Arbeitsweise, indem man in Verbindungen der allgemeinen Formel II



in der X eine Nitro- oder Acylaminogruppe bedeutet, die Nitrogruppe durch Hydrierung, besonders mit katalytisch erregtem Wasserstoff, und die Acylaminogruppe durch Hydrolyse in die Aminogruppe überführt.

Die erfindungsgemäß hergestellten Produkte sind wertvolle Arzneimittel mit sedativen, hypnotischen, anticonvulsiven und muskelrelaxierenden Eigenschaften. Gegenüber bekannten Chinazolinonen, die in 2-Stellung Wasserstoff oder Alkylreste und in 3-Stellung substituierte Phenylreste tragen, wie dem 2-Methyl-3-o-tolyl-chinazolinon-(4), zeigen die Verfahrensprodukte, die durch eine zusätzliche freie Aminogruppe in 5-, 6-, 7- oder 8-Stellung des Chinazolinokerns gekennzeichnet sind, eine zum Teil erhebliche Wirkungssteigerung.

Um die Überlegenheit der Verfahrensprodukte gegenüber bekannten Verbindungen mit ähnlicher Struktur und solchen mit ähnlicher Wirkungsweise nachzuweisen, wurden Vergleichsversuche angestellt:

Zum Beispiel weisen die erfindungsgemäß erhältlichen Verbindungen 2-Methyl-3-o-tolyl-6-aminochinazolinon-(4) (I), 2-Methyl-3-p-tolyl-6-aminochinazolinon-(4) (II), 2-Methyl-3-p-chlorphenyl-6-aminochinazolinon-(4) (III), 2-Methyl-3-(2-methyl-4-chlorphenyl)-6-aminochinazolinon-(4) (IV), 2-Äthyl-3-o-tolyl-6-aminochinazolinon-(4) (V), 2-Äthyl-3-p-tolyl-6-aminochinazolinon-(4) (VI), 2-Äthyl-3-o-chlorphenyl-6-aminochinazolinon-(4) (VII), 2-Methyl-3-(2-methyl-3-chlorphenyl)-6-aminochinazolinon-(4) (VIII), 2-Methyl-3-(2',4'-dimethylphenyl)-7-aminochinazolinon-(4) (IX) und 2-Methyl-3-o-tolyl-7-aminochinazolinon-(4) (X) hervorragende, durch Hemmung polysynaptischer Spinalreflexe hervorgerufene muskelrelaxierende Eigenschaften auf. Sie werden mit zwei bekannten zentral wirkenden Muskelrelaxantien, dem Carisoprodol (Y) und dem Chlormezanone (Z) sowie mit dem Hypnoticum Methaqualon (A) verglichen.

Verfahren zur Herstellung von
3-Phenylchinazolinon-(4)-derivaten

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nyl)-6-aminochinazolinon-(4) (IV), 2-Äthyl-3-o-tolyl-6-aminochinazolinon-(4) (V), 2-Äthyl-3-p-tolyl-6-aminochinazolinon-(4) (VI), 2-Äthyl-3-o-chlorphenyl-6-aminochinazolinon-(4) (VII), 2-Methyl-3-(2-methyl-3-chlorphenyl)-6-aminochinazolinon-(4) (VIII), 2-Methyl-3-(2',4'-dimethylphenyl)-7-aminochinazolinon-(4) (IX) und 2-Methyl-3-o-tolyl-7-aminochinazolinon-(4) (X) hervorragende, durch Hemmung polysynaptischer Spinalreflexe hervorgerufene muskelrelaxierende Eigenschaften auf. Sie werden mit zwei bekannten zentral wirkenden Muskelrelaxantien, dem Carisoprodol (Y) und dem Chlormezanone (Z) sowie mit dem Hypnoticum Methaqualon (A) verglichen.

Die muskelrelaxierende Wirksamkeit der Versuchspräparate wurde bei Mäusen und Ratten mittels einer speziell entwickelten Modifikation des Dynamometers nach Sommer bestimmt; als ED (50 g) wurde diejenige durch graphische Interpolation ermittelte Dosis bezeichnet, die bei Mäusen die Greifkraft von dem normalen Ausgangswert (etwa 100 g) auf 50 g reduziert. In entsprechender Weise stellt die ED (250 g) bei Ratten die durch graphische Interpolation gewonnene Dosis dar, die die normalerweise bei 500 bis 700 g liegende Greifkraft von Ratten auf 250 g verringerte. Der Cornealreflex wurde bei Mäusen bestimmt, indem die Hornhaut des Auges vorsichtig mit einer Reizborste berührt wurde; erfolgte kein Lidschluß auf diese Berührung hin, so wurde der Cornealreflex als negativ bezeichnet. Mit ED₅₀ ist beim Cornealreflex die Dosis gemeint, die bei 50% der Tiere den Cornealreflex ver-

hinderte. — Da keines der Präparate eine ausreichende Wasserlöslichkeit besitzt, wurden alle Präparate als Suspension verabreicht, und zwar in 0,25%iger Agarlösung bei Mäusen intraperitoneal und in 5%iger Gummiarabikumlösung bei Ratten durch die Schlundsonde. Die Toxizität an Ratten wurde nach 14tägiger Beobachtungszeit ermittelt.

In der folgenden Tabelle sind die mit diesen Versuchen gewonnenen Ergebnisse zusammengestellt sowie die daraus errechneten Quotienten Cornealreflex/Greifkraft ($\frac{C}{G}$) und Toxizität/Greifkraft ($\frac{T}{G}$), die Aufschluß über die therapeutische Breite der Verfahrensprodukte geben.

Präparat	Maus intraperitoneal			Ratte per os		
	Greifkraft ED (50 g) in mg/kg	Cornealreflex ED ₅₀ in mg/kg	Quotient $\frac{C}{G}$	Greifkraft ED (250 g) in mg/kg	Toxizität LD ₅₀ in mg/kg	Quotient $\frac{T}{G}$
I	41	> 70	> 1,7	23	60	2,6
II	30	87	2,9	24	123	5,1
III	50	168	3,4	47	110	2,3
IV	18	73	4,1	18	60	3,3
V	24	105	4,4	16	68	4,3
VI	29	84	2,9	52	220	4,2
VII	27	> 80	> 3,0	15	72	4,8
VIII	44	130	3,0	42	355	8,5
IX	50	120	2,4	47	220	4,7
X	120	> 300	> 2,5	180	335	1,9
Y	150	310	2,1	600	1420	2,4
Z	190	310	1,6	330	960	2,9
A	59	100	1,7	80	145	1,8

Aus der Zusammenstellung der Ergebnisse ist ersichtlich, daß die Verfahrenserzeugnisse im allgemeinen wesentlich stärkere Muskelrelaxantien sind als die Vergleichssubstanzen Carisoprodol und Chlormezanone. Für die therapeutische Verwendung als Muskelrelaxans ist erwünscht, daß eine muskelrelaxierende wirksame Dosis des Präparates möglichst keine oder nur eine sehr geringe sedative Aktivität aufweist. Wie die relativ schwach hemmende Wirkung auf den Cornealreflex bei Mäusen beweist, die in dem Quotienten $\frac{C}{G}$ zum Ausdruck kommt, sind die meisten Verfahrenserzeugnisse auch in dieser Hinsicht den bekannten Verbindungen Carisoprodol und Chlormezanone deutlich überlegen. Die Toxizität der Verfahrenserzeugnisse bei Ratten entspricht, wenn man sie in Relation zur muskelrelaxierenden Wirksamkeit setzt,

etwa der der Vergleichspräparate; dies wird durch den Quotienten $\frac{T}{G}$ ausgedrückt.

Die Verbindungen I und X unterscheiden sich vorteilhaft von den muskelrelaxierenden Vergleichspräparaten Carisoprodol und Chlormezanone nicht nur durch ihre bezüglich der erforderlichen Dosen stärkere Wirksamkeit sondern auch durch ihre spezifischere reflexhemmende Aktivität bzw. durch ihre bessere Resorption vom Magen-Darm-Kanal aus.

In der untenstehenden Tabelle sind die bei Mäusen nach intraperitonealer Injektion der Versuchspräparate zu beobachtenden Hemmungen des Corneal- und des Pinnareflexes sowie die die Greifkraft bei Mäusen auf 50 g verringernden Dosen nach oraler und nach intraperitonealer Verabfolgung gegenüber-

Präparat	ED ₅₀ in mg/kg		Quotient $\frac{C}{P}$	ED ₅₀₍₅₀₎ in mg/kg Greifkraft (= G)		Quotient $\frac{G \text{ peroral}}{G \text{ intraperitoneal}}$
	Cornealreflex (= C)	Pinnareflex (= P)		peroral	intraperitoneal	
X	> 300	200	> 1,5	242	120	2,0
I	> 70	61	> 1,0	42	41	1,0
Y	310	390	0,8	700	150	4,7
Z	310	475	0,7	300	190	1,6

Die Hemmung des Pinnareflexes ist nach Goodsell und Mitarbeitern (The Journal of Pharmacology and experimental Therapeutics, Bd. 110, 1954, S. 251) charakteristisch für Präparate mit zentralmuskelrelaxierender Wirkung. Sowohl die Verbindung I als auch die Verbindung X hemmen den Pinnareflex mit Dosen, die den Cornealreflex noch nicht aufheben; bei den beiden Vergleichspräparaten liegen die Verhältnisse dagegen genau umgekehrt. Die Tatsache, daß der Quotient $\frac{C}{P}$ bei den von uns beanspruchten Verbindungen über 1,0 liegt, ist aber von größerer praktischer

Bedeutung als die Höhe des Quotienten $\frac{T}{G}$. Die Werte für den Quotienten

$$\frac{G \text{ peroral}}{G \text{ intraperitoneal}}$$

lassen erkennen, daß vom Magen-Darm-Kanal die Verbindung X besser als Carisoprodol und die Verbindung I besser als Chlormezanone und Carisoprodol resorbiert werden.

Eine Überlegenheit gegenüber beiden Vergleichspräparaten läßt sich somit besonders augenfällig für Verbindung X an Hand des Quotienten $\frac{C}{P}$ und für die Verbindung I an Hand des Quotienten

$$\frac{G_{\text{peroral}}}{G_{\text{intrapertoneal}}}$$

zeigen.

Beispiel 1

14 g 2-Methyl-3-o-tolyl-6-nitrochinazolinon-(4) [Schmelzpunkt 184 bis 185°C] wurden in 400 cm³ Essigsäureäthylester suspendiert und die Suspension in Gegenwart von Raney-Nickel hydriert. Gegen Ende der Hydrierung begann das Hydrierungsprodukt auszukristallisieren. Nach leichtem Anwärmen wurde vom Katalysator abfiltriert und die Lösung auf ein geringes Volumen eingeeengt. Von den ausgeschiedenen Kristallen wurde abgesaugt. Es wurden 11,9 g 2-Methyl-3-o-tolyl-6-aminochinazolinon-(4) vom Schmelzpunkt 221°C erhalten, die aus Äthanol umkristallisiert werden können und dann bei 223 bis 224°C schmelzen.

Das 2-Methyl-3-o-tolyl-6-nitrochinazolinon-(4) kann in nicht beanspruchter Weise wie folgt dargestellt werden: Zu einer auf 100 bis 110°C erwärmten Lösung von 22,4 g 5-Nitro-N-acetylthranilsäure und 11,8 g o-Toluidin in 200 cm³ Eisessig wird tropfenweise unter Rühren 13,7 g Phosphorochlorid hinzugegeben. Danach wird 2 Stunden bei 110°C gerührt. Dann wird die Essigsäure im Vakuum abdestilliert, bis Kristallisation einsetzt. Nach dem Abkühlen wird das Hydrochlorid des 2-Methyl-3-o-tolyl-6-nitrochinazolinon-(4) abgesaugt. Aus dem Hydrochlorid wird durch Behandlung mit verdünnter Natronlauge die freie Base hergestellt. Es werden 21,8 g (etwa 75% der Theorie) erhalten. Das Produkt hat einen Schmelzpunkt von 182 bis 183°C. Nach dem Umkristallisieren aus Äthanol schmilzt die Verbindung bei 184 bis 185°C.

Beispiel 2

13 g 2-Methyl-3-o-chlorphenyl-6-nitrochinazolinon-(4) [Schmelzpunkt 218 bis 220°C, hergestellt aus 5-Nitro-N-acetylthranilsäure und o-Chloranilin] wurden in 400 cm³ Essigsäureäthylester in Gegenwart von einem Palladium-Bariumsulfat-Katalysator hydriert. Nach Beendigung der Wasserstoffaufnahme wurde vom Katalysator abfiltriert, die Lösung eingeeengt und der Rückstand in verdünnter Salzsäure gelöst. Die Lösung wurde mit Aktivkohle behandelt, filtriert und das 2-Methyl-3-o-chlorphenyl-6-aminochinazolinon-(4) durch langsame Zugabe von Natronlauge ausgefällt. Der erhaltene Niederschlag wurde nach dem Trocknen aus Äthanol umkristallisiert. Schmelzpunkt 234 bis 236°C.

Beispiel 3

6,1 g 3-o-Tolyl-6-nitrochinazolinon-(4) [Schmelzpunkt 160 bis 161°C, darstellbar z. B. durch Umsetzung von 6-Nitrochinazolinon-(4) mit o-Toluidin unter Erwärmen] wurden in 300 cm³ Essigsäureäthylester gelöst und in Gegenwart von Raney-Nickel bei Normaldruck und Raumtemperatur hydriert. Die Wasserstoffaufnahme war nach 70 Minuten beendet.

Es wurden 4,6 g 3-o-Tolyl-6-aminochinazolinon-(4), welches nach dem Umkristallisieren aus Äthanol einen Schmelzpunkt von 207 bis 208°C zeigte, erhalten.

Beispiel 4

1 g 2-Methyl-3-(2-methyl-4-chlorphenyl)-6-acetylaminochinazolinon-(4) [Schmelzpunkt 255 bis 256°C, darstellbar aus 2,5-Diacetylaminobenzoessäure, Schmelzpunkt 248 bis 250°C, und 2-Methyl-4-chloranilin] wurde 15 Minuten mit 5 ml 70%iger Schwefelsäure auf 150°C erwärmt. Nach dem Abkühlen wurde mit Wasser verdünnt und mit Natronlauge neutralisiert. Es kristallisierten 0,7 g 2-Methyl-3-(2-methyl-4-chlorphenyl)-6-aminochinazolinon-(4) aus. Der Schmelzpunkt lag nach dem Umkristallisieren aus Äthanol bei 195 bis 196°C.

Beispiel 5

60 g 2-Äthyl-3-o-tolyl-6-nitrochinazolinon-(4) [Schmelzpunkt 130 bis 131°C] und 200 g Eisenpulver werden in 120 cm³ Benzol kräftig gerührt und unter Rückfluß gekocht. Es werden langsam 1,5 cm³ konzentrierte Salzsäure und anschließend 15 cm³ Wasser zugegeben. Danach wird noch 2½ Stunden gekocht. Zu der etwas abgekühlten Lösung werden unter Rühren auf einmal 30 cm³ Wasser zugegeben. Die Benzollösung läßt sich dann bequem vom Eisenhydroxydschlamm abgießen. Sie wird mit etwas Aktivkohle gerührt und filtriert. Nach dem Einengen auf etwa ein Drittel des ursprünglichen Volumens wird die Lösung mehrmals mit 15%iger Salzsäure ausgeschüttelt und die salzsaure Lösung unter Rühren mit 30%iger Natronlauge versetzt, bis das 2-Äthyl-3-o-tolyl-6-aminochinazolinon-(4) ausgefallen ist. Es werden 47 g 2-Äthyl-3-o-tolyl-6-aminochinazolinon-(4) erhalten, Schmelzpunkt 163 bis 164°C. Das Produkt kann aus Isopropanol umkristallisiert werden.

Das als Ausgangsprodukt verwendete 2-Äthyl-3-o-tolyl-6-nitrochinazolinon-(4) kann in nicht beanspruchter Weise folgendermaßen dargestellt werden:

44 g 5-Nitropropionylthranilsäure (dargestellt durch Kochen von 5-Nitrothranilsäure mit Propionsäureanhydrid), 23,6 g o-Toluidin und 500 cm³ Toluol werden unter Rühren auf 100 bis 110°C erwärmt. Dann werden 30,6 g Phosphorochlorid zugegeben und noch 2 Stunden bei 100 bis 110°C gerührt. Zu dem noch warmen Reaktionsgemisch werden unter gutem Rühren tropfenweise zunächst 100 cm³ 2n-Natronlauge, dann 30%ige Natronlauge bis zur gerade alkalischen Reaktion zugegeben. Die Schichten werden getrennt, die toluolische Lösung zweimal mit etwas warmem Wasser gewaschen und dann auf ein kleines Volumen eingeeengt. Das auskristallisierende Produkt wird aus Isopropanol umkristallisiert. Es werden 52,8 g Substanz erhalten.

Beispiel 6

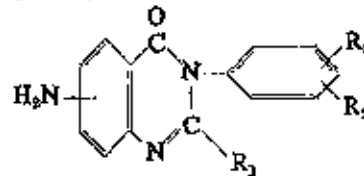
19,5 g 2-n-Butyl-3-o-tolyl-6-nitrochinazolinon-(4) wurden in 420 cm³ Essigsäureäthylester gelöst und nach Zugabe von Raney-Nickel mit Wasserstoff hydriert. Nach dem Filtrieren wurde das Lösungsmittel abdestilliert. Der Rückstand, 2-n-Butyl-3-o-tolyl-6-aminochinazolinon-(4), kristallisierte und wurde aus Isopropanol umkristallisiert. Ausbeute 10,8 g, Schmelzpunkt 132 bis 133°C.

Das 2-n-Butyl-3-o-tolyl-6-nitrochinazolinon-(4) kann in nicht beanspruchter Weise wie folgt dargestellt werden:

27,1 g 5-Nitroanthranilsäure-o-toluidid werden in 100 ml trockenem Dimethylformamid gelöst, unter Rühren 22 g n-Valeroylchlorid zugegeben und noch 3 Stunden weitergerührt. Dann wird unter Kühlung und Rühren Wasser hinzugegeben, bis das 5-Nitro-N-valeroylanthranilsäure-o-toluidid vollständig ausgefallen ist. Es wird abgesaugt und getrocknet. Das trockene Rohprodukt wird in 150 cm³ Tetrahydrofuran aufgeschlämmt und mit 15,3 g Phosphoroxchlorid

versetzt. Es entsteht bald eine klare Lösung, aus der nach und nach das Hydrochlorid des 2-n-Butyl-3-o-tolyl-6-nitrochinazolinons-(4) ausfällt. Nach Stehen über Nacht wird abgesaugt, das feuchte Produkt durch Verreiben mit Natriumbicarbonatlösung neutralisiert, erneut abgesaugt, mit Wasser gewaschen und getrocknet. Das Rohprodukt wird aus Äthanol umkristallisiert. Ausbeute 19,3 g, Schmelzpunkt 94 bis 95° C.

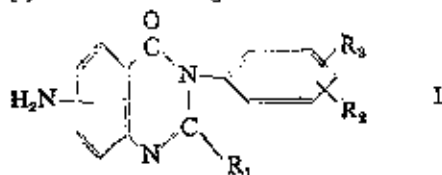
Die in der folgenden Übersicht zusammengestellten Verbindungen sind gemäß den Beispielen 1 bis 6 erhältlich.



R ₁	R ₂	R ₃	Stellung der Aminogruppe	Schmelzpunkt in °C	Schmelzpunkt der Vorstufe in °C X = NO ₂
H	H	H	6	189/190	224/225
H	o-CH ₃	H	6	207/208	160/161
H	m-CH ₃	H	6	236/237	206/207
H	o-CH ₃	p-CH ₃	6	159/160	168/169
H	o-CH ₃	p-Cl	6	151/152	219/220
H	p-CH ₃	H	6	183/184	229/230
CH ₃	o-CH ₃	H	5	173/174	201/202
CH ₃	H	H	6	244/245	223/224
CH ₃	o-CH ₃	H	6	223/224	182/183
CH ₃	m-CH ₃	H	6	235/236	154/155
CH ₃	p-CH ₃	H	6	179/180	222/223
CH ₃	o-Cl	H	6	234/236	218/220
CH ₃	m-Cl	H	6	214/215	201/202
CH ₃	p-Cl	H	6	202/203	264/265
CH ₃	o-CH ₃	p-CH ₃	6	161/162	169/170
CH ₃	o-CH ₃	m-Cl	6	225/226	193/194
CH ₃	o-CH ₃	p-Cl	6	195/196	210/211
CH ₃	o-CH ₃	p-Br	6	182/183	233/234
CH ₃	H	H	7	246/247	204/210
CH ₃	o-CH ₃	H	7	206/208	183/186
CH ₃	m-CH ₃	H	7	231/232	175/176
CH ₃	p-CH ₃	H	7	219/220	228/229
CH ₃	m-Cl	H	7	185/186	201/202
CH ₃	p-Cl	H	7	222/223	282/283
CH ₃	o-CH ₃	p-CH ₃	7	182/183	183/184
CH ₃	o-CH ₃	m-Cl	7	231/232	176/177
CH ₃	o-CH ₃	p-Cl	7	219/220	223/224
CH ₃	o-CH ₃	H	8	255	207/209

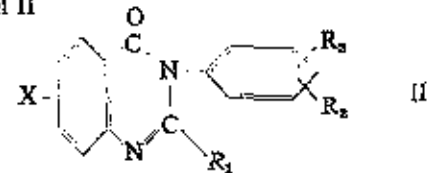
Patentanspruch:

Verfahren zur Herstellung von 3-Phenylchinazolinon-(4)-derivaten der allgemeinen Formel I



in der R₁ ein Wasserstoffatom oder einen niedermolekularen Alkylrest, R₂ und R₃ Wasserstoffatome, Halogenatome oder niedermolekulare Alkyl-

reste bedeutet, dadurch gekennzeichnet, daß man in einer Verbindung der allgemeinen Formel II



in der X eine Nitro- oder Acylaminogruppe bedeutet, den Rest X in an sich bekannter Weise durch Reduktion bzw. Hydrolyse in die Aminogruppe überführt.

DS 165 160

REPUBLIQUE FRANÇAISE

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BREVET D'INVENTION

P.V. n° 938.570

N° 1.367.738

Classification internationale

A 61 k — C 07 d

Procédé de préparation des 3-phénylquinazolones substituées par des groupes amino et de leurs dérivés.

Société dite : OLIN MATHIESON CHEMICAL CORPORATION résidant aux États-Unis d'Amérique.

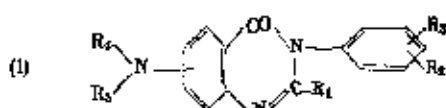
Demandé le 19 juin 1963, à 12^h 48^m, à Paris.

Délivré par arrêté du 15 juin 1964.

(Bulletin officiel de la Propriété industrielle, n° 30 de 1964.)

(Demande de brevet déposée en République Fédérale d'Allemagne le 27 juin 1962, sous le n° C 27.325, au nom de Société dite : CHEMISCHE FABRIK VON HEYDEN AKTIENGESELLSCHAFT.)

La présente invention a pour objet un procédé de préparation de dérivés de la quinazolone. Plus particulièrement, elle concerne la préparation de nouvelles quinazolones de formule :



et leurs sels d'addition d'acides.

Dans la formule (I), R₁ représente un atome d'hydrogène ou un radical alkyle inférieur, R₂ et R₃ représentent chacun un atome d'hydrogène, un radical alkyle inférieur, un radical alkoxy inférieur, un atome d'halogène ou un radical trihalométhyle, R₄ et R₅ représentent chacun un atome d'hydrogène, un radical alkyle inférieur ou un radical aryle.

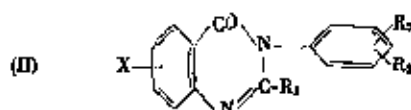
Dans la formule (I), les radicaux alkyle inférieurs représentés par les symboles R sont des radicaux hydrocarbonés saturés à chaîne droite ou ramifiée tels que les radicaux méthyle, éthyle, propyle, isopropyle, butyle, isobutyle t-butyle, amyle et les analogues. Les radicaux alkoxy inférieurs représentés par R₂ et R₃ sont les substituants éther dans lesquels un radical alkyle inférieur tel que défini ci-dessus est lié à un atome d'oxygène, par exemple, les radicaux méthoxy, éthoxy, propoxy et les analogues. Les symboles R₄ et R₅ représentent tous les quatre halogènes, les halogènes préférés étant le chlore et le brome. D'une manière semblable, les radicaux trihalométhyle comportent tous les quatre halogènes, mais le radical trifluorométhyle est le radical préféré.

Dans la formule (I), les radicaux aryle représentés par R₁ et R₅ comprennent le radical aryle des acides alcanoïques, spécialement des radicaux

alcanoyle inférieurs tels que les radicaux acétyle, propionyle et analogues, le radical alcanoyle des acides alcanoïques spécialement les radicaux alcanoyle inférieurs tels que les radicaux acétoxy, propionoxy et analogues, de même que le radical acide des acides sulfoniques, par exemple des acides alcane sulfoniques tels que le radical méthane sulfonyle, éthanesulfonyle et des acides aryle sulfoniques tels que les radicaux benzènesulfonyle et toluènesulfonyle.

Les composés de formule (I) sont des bases faibles qui forment des sels par addition d'acides, en particulier avec les acides minéraux. Lesdits sels comprennent par exemple les halogénures tels que le chlorhydrate, le bromhydrate, etc., les sulfates, les nitrates et les analogues. Ces sels sont utiles pour isoler le produit.

Conformément à la présente invention on prépare les composés de formule (I) à partir de composés de formule :



dans laquelle X représente un substituant que l'on peut convertir en un radical amino libre.

Par les substituants que l'on peut convertir en radical amino, on désigne les radicaux qui, par exemple par réduction ou par hydrolyse, donnent le radical amino, par exemple les radicaux nitro, nitroso, acylamino, ou benzylamino.

On obtient des composés représentés par une modification préférée de la formule I, c'est-à-dire des composés dans lesquels à la fois R₁ et R₂ représentent un atome d'hydrogène, en réduisant le

- 2 -

nitro-4-quinazoline. On obtient la base libre en traitant le chlorhydrate par une solution de soude diluée. On fait recristalliser le produit au sein d'éthanol p.f. 184-185 °C.

Exemple 2. — On hydrogène, en présence comme catalyseur de palladium-sulfate de baryum, 18 g de 2-méthyl-3-o-chlorophényl-6-nitro-4-quinazoline (P.F. 218-220°C, préparée à partir d'acide 5-nitro-N-acétylarthranique et de o-chloroaniline par la méthode décrite dans l'exemple 1) dans 400 cm³ d'acétate d'éthyle. Quand l'hydrogène cesse de se dégager, on sépare le catalyseur par filtration. On concentre la solution et on dissout le résidu dans de l'eau chlorhydrique diluée. On traite avec du charbon actif cette solution de chlorhydrate de 2-méthyl-3-o-chlorophényl-6-amino-4-quinazoline, on la filtre et on la précipite la base libre par addition lente d'une solution de soude. On sèche le produit qui a précipité et on le fait recristalliser au sein d'éthanol, p.f. 234-236°C.

Exemple 3. — On ajoute 2,5 g de 2-méthyl-3-tolyl-6-amino-4-quinazoline à 5 cm³ d'anhydride acétique. La substance se dissout quand on la chauffe. Après un court moment, la 2-méthyl-3-tolyl-6-acétylamino-4-quinazoline cristallise. On ajoute une petite quantité d'éther que l'on enlève ensuite sous aspiration. Le produit fond à 222-230 °C.

Exemple 4. — On dissout dans 300 cm³ d'acétate d'éthyle 6,1 g de 3-*o*-tolyl-6-nitro-4-quinazoline (p.f. 163-161 °C, préparée en chauffant la 6-nitro-4-quinazoline avec de l'*o*-toluidine) et on l'hydrogène à l'aide d'hydrogène en présence de nickel Raney à la température ambiante et sous une pression normale. Après 70 minutes, l'hydrogène cesse de se dégager. On fait recristalliser au sein d'éthanol le produit qui est la 3-*o*-tolyl-6-amino-4-quinazoline, p.f. 207-208 °C.

Exemple 8. — On met en suspension 13,3 g de 2-méthyl-3-o-tolyl-6-amino-4-quinazoline dans 50 cm³ de pyridine à l'état sec et on ajoute 1,1 g de chlorure de *p*-toluène sulfonique. Après chauffage, il se forme une solution claire colorée en brun-rouge que l'on chauffe sur un bain de vapeur pendant plusieurs minutes. On ajoute de l'eau pour précipiter le 2-méthyl-3-o-tolyl-6-p-tosyl-amino-4-quinazoline que l'on purifie en la dissolvant dans une solution de soude diluée et que l'on précipite avec de l'acide chlorhydrique dilué. Un échantillon, après recristallisation au sein d'éthanol, fond à 208-210 °C.

On dissout le produit brut dans une solution de soude diluée et on le traite avec un excès de sulfate de diméthyle sous agitation vigoureuse. On filtre sous aspiration le précipité qui se forme et on le fait recristalliser au sein d'éthanol. Le 2-méthyl-3-*o*-tolyl-6-(N-tolueyl-N-tolyl)amino-4-quinazoline ainsi obtenue fond à 163-165 °C.

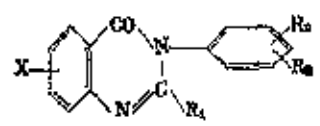
On prépare le 2-méthyl-3-o-tolyl-6-nitro-4-quinazoline de la manière suivante. On chauffe à une température de 100-110 °C une solution de 22,4 g d'acide 5-nitro-N-acétylanthraniquique et 11,6 g de *o*-toluidine dans 200 cm³ d'acide acétique glacial et on y ajoute goutte à goutte en agitant 13,7 g de trichlorure de phosphore. On agit ensuite le mélange pendant 2 heures supplémentaires à 110 °C. On élimine l'acide acétique par distillation sous vide jusqu'à ce que la cristallisation commence. On refroidit le mélange et on filtre sous aspiration le chlorhydrate de 2-méthyl-3-*o*-tolyl-6-

166
161

On chauffe à 150 °C pendant 20 minutes 10 g de ce produit dans 50 cm³ d'acide sulfurique à 70 %. On dilue ensuite la solution avec de l'eau et on la neutralise avec une solution de soude diluée. La 2-méthyl-3-o-tolyl-6-méthylamino-4-quinazoline cristallise, p.f. 173-175 °C.

15 minutes 1 g de 2-méthyl-3-(2-méthyl-4-chlorophényl)-6-acétylamino-4-quinazoline (p.f. 255-256 °C, préparée à partir de l'acide 2,5-di-*o*-tylamino benzoïque et de 2-méthyl-4-chloroaniline) dans 5 cm³ d'acide sulfurique à 70 %. Après refroidissement on dilue le mélange réactionnel avec de l'eau et on le neutralise avec une solution de soude.

Exemple 6. — On chauffe à 150 °C pendant



29
36

R ₁	n ₁	R ₂	X	P. F.	p. F. du composé intermédiaire (X = NO ₂)
				°C	°C
H	H	H	NH ₂ (6) *	189-90	224-25
H	<i>o</i> -CH ₃	H	NH ₂ (6)	207-08	160-61
H	<i>m</i> -CH ₃	H	NH ₂ (6)	236-37	205-07
H	<i>p</i> -CH ₃	H	NH ₂ (6)	183-84	229-30
H	<i>o</i> -CH ₃	<i>p</i> -CH ₃	NH ₂ (6)	159-60	168-69
H	<i>o</i> -CH ₃	<i>p</i> -Cl	NH ₂ (6)	151-52	219-20
CH ₃	<i>o</i> -CH ₃	H	NH ₂ (6)	173-74	201-02
CH ₃	H	H	NH ₂ (6)	244-45	223-24
			NH ₂ (6)	229-24	
			NH-CH ₃ (6)	173-75	
CH ₃	<i>o</i> -CH ₃	H	N-(CH ₃) ₂ (6)	168-64	182-83
			NH-CO (6)	237-38	
			NH-CO-CH ₃ (6)	228-30	
			NH-CO-C ₆ H ₅ (6)	245-46	
CH ₃	<i>m</i> -CH ₃	H	NH ₂ (6)	295-36	154-55
CH ₃	<i>p</i> -CH ₃	H	NH ₂ (6)	179-80	222-23
			NH-CO-CH ₃ (6)	249-50	
CH ₃	<i>o</i> -Cl	H	NH ₂ (6)	284-36	218-20
CH ₃	<i>m</i> -Cl	H	NH ₂ (6)	214-15	201-02
CH ₃	<i>p</i> -Cl	H	NH ₂ (6)	202-09	264-65
CH ₃	<i>o</i> -CH ₃	H	NH ₂ (6)	252-53	279-80
CH ₃	<i>o</i> -CH ₃	<i>p</i> -CH ₃	NH ₂ (6)	161-62	169-70
CH ₃	<i>o</i> -CH ₃	<i>p</i> -CH ₃	NH ₂ (6)	161-62	169-70
CH ₃	<i>o</i> -CH ₃	<i>m</i> -Cl	NH ₂ (6)	225-26	193-94
CH ₃	<i>o</i> -CH ₃	<i>p</i> -Cl	NH ₂ (6)	196-96	210-11
CH ₃	<i>o</i> -CH ₃	<i>p</i> -Br	NH-CO-CH ₃ (6)	255-56	
CH ₃	<i>o</i> -CH ₃	<i>p</i> -Br	NH ₂ (6)	182-83	239-34
CH ₃	H	H	NH ₂ (7)	246-47	204-10
CH ₃	<i>o</i> -CH ₃	H	NH ₂ (7)	206-08	188-86
CH ₃	<i>m</i> -CH ₃	H	NH ₂ (7)	231-32	175-76
CH ₃	<i>p</i> -CH ₃	H	NH ₂ (7)	219-20	228-29
CH ₃	<i>m</i> -Cl	H	NH ₂ (7)	185-86	201-02
CH ₃	<i>p</i> -Cl	H	NH ₂ (7)	223-23	222-83
CH ₃	<i>o</i> -CH ₃	<i>p</i> -CH ₃	NH ₂ (7)	182-83	181-84
CH ₃	<i>o</i> -CH ₃	<i>m</i> -Cl	NH ₂ (7)	231-32	176-77
CH ₃	<i>o</i> -CH ₃	<i>p</i> -Cl	NH ₂ (7)	219-20	223-24
CH ₃	<i>o</i> -CH ₃	H	NH ₂ (8)	255	207-09

* Le nombre entre parenthèses indique la position du substituant dans le noyau de la quinazoline.

[1.367.738]

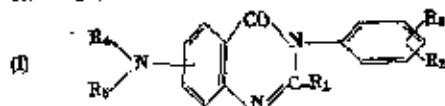
On recristallise au sein d'éthanol la 2-méthyl-3-(2-méthyl-4-chlorophényl)-6-amino-4-quinazolone qui cristallise, p.f. 195-196 °C.

Exemple 7. — On met en suspension 2,7 g de 2-méthyl-3-o-tolyl-6-amino-4-quinazolone dans 100 cm³ de pyridine à l'état sec et l'on y ajoute goutte à goutte 1,1 cm³ de chloroformate d'éthyle. Le mélange réactionnel s'échauffe et il en résulte une solution claire. On chauffe la solution pendant peu de temps au bain de vapeur ensuite on la laisse refroidir. On ajoute de l'eau jusqu'à ce que la solution commence à devenir trouble. Par agitation et froissement le long des parois, le produit commence à cristalliser. L'addition d'eau achève la cristallisation et on fait recristalliser au sein de méthanol le produit brut qui est la 2-méthyl-3-o-tolyl-6-éthoxycarbonylamino-4-quinazolone, p. f. 245-246 °C. Le tableau suivant énonce des composés supplémentaires que l'on obtient par des modes opératoires décrits dans les exemples précédents.

(Voir tableau, page précédente)

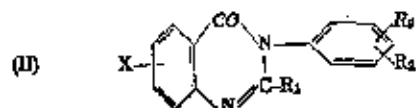
RÉSUMÉ

La présente invention a pour objet un procédé pour préparer des dérivés de la quinazolone de formule :



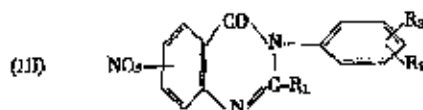
dans laquelle (I), R₁ représente un atome d'hydrogène ou un radical alkyle, R₂ et R₃ représentent chacun un atome d'hydrogène, un radical alkyle, un radical alkoxy, un atome d'halogène ou un radical trihalométhyle, R₄ et R₅ représentent chacun un atome d'hydrogène, un radical alkyle ou un radical acyle et les sels d'addition d'acides des composés de formule (I), ledit procédé étant caractérisé par les points suivants considérés isolément ou en combinaisons diverses :

1° Il consiste à traiter un composé de formule :



dans laquelle X est un radical capable d'être converti en un radical amino libre, R₁, R₂ et R₃ sont tels qu'ils ont été définis ci-dessus, d'une manière connue afin de former un radical amino libre et si on le désire on effectue une N-acylation ou une N-alkylation d'une manière connue.

2° On réduit catalytiquement le composé de formule :



dans laquelle R₁ représente un atome d'hydrogène ou un radical alkyle, R₂ et R₃ représentent chacun un atome d'hydrogène, un radical alkyle, un radical alkoxy, un atome d'halogène ou un radical trihalométhyle.

3° On N-acyle en N-alkyle le radical amino libre.

4° On réduit catalytiquement la 2-méthyl-3-tolyl-6-nitro-4-quinazolone.

5° On réduit catalytiquement la 2-méthyl-3-o-chlorophényl-6-nitro-4-quinazolone.

6° On réduit catalytiquement la 2-méthyl-3-o-tolyl-6-nitro-4-quinazolone et on l'acétyle à l'aide d'anhydride acétique.

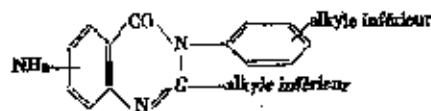
7° On réduit catalytiquement la 3-o-tolyl-6-nitro-4-quinazolone.

8° On réduit la 2-méthyl-3-o-tolyl-6-nitro-4-quinazolone et on traite le composé formé avec du chlorure de p-toluènesulfonyle et ensuite avec du sulfate de diméthyle.

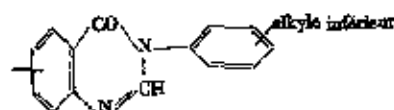
9° On hydrolyse la 2-méthyl-3-(2-méthyl-4-chloro-phényl)-6-acétyl-amino-4-quinazolone avec de l'acide sulfurique.

10° On obtient notamment les composés de formule (I) suivants :

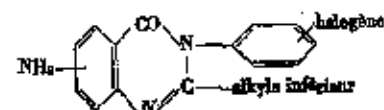
Un composé de formule :



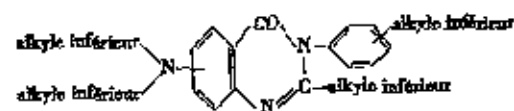
Un composé de formule :



Un composé de formule :



Un composé de formule :



La 3-o-tolyl-6-amino-4-quinazolone :

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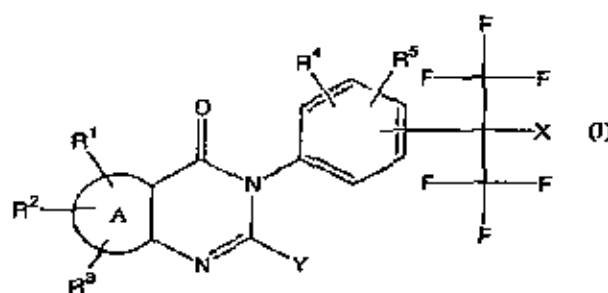
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(54) Title: FUSED-RING PYRIMIDIN-4(3H)-ONE DERIVATIVES, PROCESSES FOR THE PREPARATION AND USES THEREOF



N-(haloalkylsulfonyl)-N-(alkyl)amino, alkylcarbonyl, alkoxy carbonyl, alkylaminocarbonyl or dialkylaminocarbonyl group, or R₁ and R₂ together are alkylenedioxy; R₄ and R₅ are the same or different and each represents hydrogen, hydroxyl, amino, halogen, mercapto, alkyl, haloalkyl, alkoxy, alkoxy carbonyl or alkylthio; X represents hydrogen, hydroxyl, halogen, alkoxy or haloalkoxy; and Y represents an optionally substituted alkyl, cycloalkyl, heterocyclyl, aryl, cycloalkylalkyl, heterocyclylalkyl or aralkyl group.

WO 03/106435 A1

Specification

Fused-Ring Pyrimidin-4(3H)-one Derivatives, Processes for the Preparation and Uses Thereof

[Technical field of the invention]

The present invention relates to novel fused-ring pyrimidin-4(3H)-one derivatives or pharmacologically acceptable salts or esters thereof that exhibit excellent anti-arteriosclerotic and anti-inflammatory activity. This is due to the ability of said derivatives to improve lipid metabolism disorders and/or through their regulation of the production of inflammatory mediators, both being based on the ability of these derivatives to regulate liver X receptors (LXR).

The present invention further relates to pharmaceutical compositions comprising fused-ring pyrimidin-4(3H)-one derivatives or pharmacologically acceptable salts or esters thereof as an active ingredient, preferably pharmaceutical compositions for the treatment and/or prevention of arteriosclerosis including that derived from the diseases described below, atherosclerosis, arteriosclerosis derived from diabetes mellitus, hyperlipidemia, lipid-related diseases, inflammatory diseases mediated by inflammatory cytokines such as chronic rheumatoid arthritis, osteoarthritis, allergic diseases, asthma, septicemia, psoriasis and osteoporosis, autoimmune diseases such as systemic lupus erythematosus, ulcerative colitis, and Crohn's disease, cardiovascular diseases such as ischemic heart diseases and cardiac failure, cerebrovascular diseases, renal diseases, diabetes mellitus, diabetic complications such as retinopathy, nephropathy, neuropathy and coronary diseases, obesity, nephritis, hepatitis, cancer and Alzheimer's disease; more preferably pharmaceutical compositions for the treatment and/or prevention of arteriosclerosis, atherosclerosis, arteriosclerosis derived from diabetes mellitus, hyperlipidemia, lipid-related diseases, inflammatory diseases mediated by inflammatory cytokines, and diabetes mellitus; and most preferably pharmaceutical compositions for the treatment and/or prevention of arteriosclerosis.

The present invention further relates to the use of fused-ring pyrimidin-4(3H)-one derivatives or pharmacologically acceptable salts or esters thereof in the preparation of pharmaceutical compositions, preferably pharmaceutical compositions for the treatment and/or prevention of the diseases described above.

The present invention further relates to a method for the treatment and/or prevention of diseases, preferably the diseases described above, which method comprises administering a pharmaceutically effective amount of a fused-ring pyrimidin-4(3H)-one derivative or a pharmacologically acceptable salt or ester thereof to a warm-blooded animal, preferably a human.

2,2,3,3-tetraMe-cPr represents a 2,2,3,3-tetramethylcyclopropyl group,

Tfm represents a trifluoromethyl group,

Thi represents a 2-thienyl group,

Thiz-2 represents a 1,3-thiazol-2-yl group,

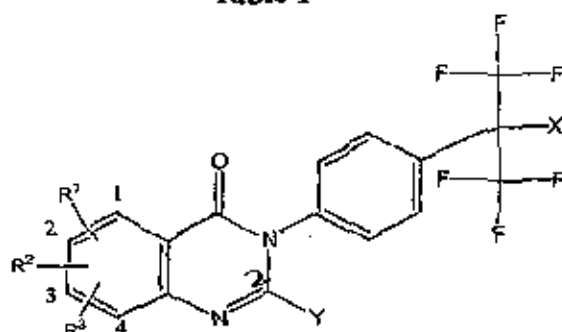
Thiz-4 represents a 1,3-thiazol-4-yl group,

Thiz-5 represents a 1,3-thiazol-5-yl group,

Exemp. Comp. No. represents exemplification compound number, and

Sub. Pos. represents substitution position.

Table 1



Exemp. Comp. No.	R ¹	R ²	R ³	X	Y → position ²
1-1	H	H	H	OH	Me
1-2	H	H	H	OH	Et
1-3	H	H	H	OH	Pr
1-4	H	H	H	OH	iPr
1-5	H	H	H	OH	Bu ⁱ
1-6	H	H	H	OH	tBu
1-7	H	H	H	OH	pentyl
1-8	H	H	H	OH	-(CH ₂)-tBu
1-9	H	H	H	OH	Hx
1-10	H	H	H	OH	Tfm
1-11	H	H	H	OH	fluoromethyl
1-12	H	H	H	OH	difluoromethyl
1-13	H	H	H	OH	chloromethyl
1-14	H	H	H	OH	dichloromethyl
1-15	H	H	H	OH	bromomethyl
1-16	H	H	H	OH	dibromomethyl

1-91	2-F	H	H	OH	Pr
1-92	2-F	H	H	OH	iPr
1-93	2-F	H	H	OH	Bu
1-94	2-F	H	H	OH	tBu
1-95	2-F	H	H	OH	pentyl
1-96	2-F	H	H	OH	-(CH ₂)-tBu
1-97	2-F	H	H	OH	Hx
1-98	2-F	H	H	OH	Tfm
1-99	2-F	H	H	OH	fluoromethyl
1-100	2-F	H	H	OH	difluoromethyl
1-101	2-F	H	H	OH	chloromethyl
1-102	2-F	H	H	OH	dichloromethyl
1-103	2-F	H	H	OH	bromomethyl
1-104	2-F	H	H	OH	dibromomethyl
1-105	2-F	H	H	OH	1-bromoethyl
1-106	2-F	H	H	OH	1-chloroethyl
1-107	2-F	H	H	OH	pentafluoroethyl
1-108	2-F	H	H	OH	aminomethyl
1-109	2-F	H	H	OH	N,N-dimethylaminomethyl
1-110	2-F	H	H	OH	N,N-diethylaminomethyl
1-111	2-OH	H	H	OH	Me
1-112	2-OH	H	H	OH	Et
1-113	2-OH	H	H	OH	Pr
1-114	2-OH	H	H	OH	iPr
1-115	2-OH	H	H	OH	Bu
1-116	2-OH	H	H	OH	tBu
1-117	2-OH	H	H	OH	pentyl
1-118	2-OH	H	H	OH	-(CH ₂)-tBu
1-119	2-OH	H	H	OH	Hx
1-120	2-OH	H	H	OH	Tfm
1-121	2-OH	H	H	OH	fluoromethyl
1-122	2-OH	H	H	OH	difluoromethyl
1-123	2-OH	H	H	OH	chloromethyl
1-124	2-OH	H	H	OH	dichloromethyl
1-125	2-OH	H	H	OH	bromomethyl
1-126	2-OH	H	H	OH	dibromomethyl
1-127	2-OH	H	H	OH	1-bromoethyl

120
165

1-128	2-OH	H	H	OH	1-chloroethyl
1-129	2-OH	H	H	OH	pentafluoroethyl
1-130	2-OH	H	H	OH	aminomethyl
1-131	2-OH	H	H	OH	N,N-dimethylaminomethyl
1-132	2-OH	H	H	OH	N,N-diethylaminomethyl
1-133	2-OMe	H	H	OH	Me
1-134	2-OMe	H	H	OH	Et
1-135	2-OMe	H	H	OH	Pr
1-136	2-OMe	H	H	OH	iPr
1-137	2-OMe	H	H	OH	Bu
1-138	2-OMe	H	H	OH	tBu
1-139	2-OMe	H	H	OH	pentyl
1-140	2-OMe	H	H	OH	-(CH ₂)-tBu
1-141	2-OMe	H	H	OH	Hx
1-142	2-OMe	H	H	OH	Tfm
1-143	2-OMe	H	H	OH	fluoromethyl
1-144	2-OMe	H	H	OH	difluoromethyl
1-145	2-OMe	H	H	OH	chloromethyl
1-146	2-OMe	H	H	OH	dichloromethyl
1-147	2-OMe	H	H	OH	bromomethyl
1-148	2-OMe	H	H	OH	dibromomethyl
1-149	2-OMe	H	H	OH	1-bromoethyl
1-150	2-OMe	H	H	OH	1-chloroethyl
1-151	2-OMe	H	H	OH	pentafluoroethyl
1-152	2-OMe	H	H	OH	aminomethyl
1-153	2-OMe	H	H	OH	N,N-dimethylaminomethyl
1-154	2-OMe	H	H	OH	N,N-diethylaminomethyl
1-155	2-AcNH	H	H	OH	Me
1-156	2-AcNH	H	H	OH	Et
1-157	2-AcNH	H	H	OH	Pr
1-158	2-AcNH	H	H	OH	iPr
1-159	2-AcNH	H	H	OH	Bu
1-160	2-AcNH	H	H	OH	tBu
1-161	2-AcNH	H	H	OH	pentyl
1-162	2-AcNH	H	H	OH	-(CH ₂)-tBu
1-163	2-AcNH	H	H	OH	Hx
1-164	2-AcNH	H	H	OH	Tfm

of ethyl acetate and methanol as the eluant to yield the title compound as a colorless solid (41.4 mg, yield: 66 %). This product was recrystallized from a mixed solvent of hexane and ethyl acetate to yield colorless crystalline powder.

mp 215-217°C.

IR (KBr): $\nu_{\max}$ 3298, 1672, 1592, 1485, 1270, 1227, 1215, 1192, 968, 934 cm^{-1} .

$^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ 9.79 (1H, s), 8.91 (1H, s), 7.65 (2H, d, $J = 8.1$ Hz), 7.53 (1H, d, $J = 7.3$ Hz), 7.38 (1H, t, $J = 7.1$ Hz), 7.28 (1H, d), 7.24 (2H, d, $J = 8.8$ Hz), 7.14 (1H, d, $J = 7.2$ Hz), 7.08 (2H, t, $J = 7.3$ Hz), 6.70 (2H, d, $J = 7.3$ Hz), 3.90 (2H, s).

FABMS (m/z): 533 ($[\text{M}+\text{K}]^+$), 495 ($[\text{M}+\text{H}]^+$).

FABHRMS (m/z): calcd. for $\text{C}_{24}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_3$ ($[\text{M}+\text{H}]^+$): 494.3859; found: 495.1148.

Anal. calcd. for $\text{C}_{24}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_3$: C, 58.31; H, 3.26; N, 5.67; found: C, 57.66; H, 3.03; N, 5.51.

(Example 60)

2-Benzyl-5-hydroxy-3-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4(3H)-quinazolinone (Exemplification compound number 3-225)

The title compound was obtained as a colorless solid (170 mg, yield: 89 %) from 2-benzyl-5-methoxy-3-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4(3H)-quinazolinone (206 mg, 0.405 mmol) prepared as described in Example 49 above in a similar manner to that described in Example 59 above. This product was recrystallized from a mixed solvent of hexane and ethyl acetate to yield a colorless crystalline powder.

mp 175-178°C.

IR (KBr): $\nu_{\max}$ 3283, 1658, 1590, 1474, 1270, 1214, 1192, 935 cm^{-1} .

$^1\text{H-NMR}$ (400MHz, CDCl_3): δ 11.31 (1H, s), 7.69 (1H, t, $J = 7.8$ Hz), 7.43 (2H, d, $J = 7.8$ Hz), 7.27 (1H, d, $J = 7.8$ Hz), 7.11-7.17 (3H, m), 7.05 (2H, d, $J = 8.8$ Hz), 6.74 (2H, d, $J = 7.8$ Hz), 3.90 (2H, s).

FABMS (m/z): 533 ($[\text{M}+\text{K}]^+$), 495 ($[\text{M}+\text{H}]^+$).

Anal. calcd. for $\text{C}_{24}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_3$: C, 58.31; H, 3.26; N, 5.67; found: C, 58.20; H, 2.98; N, 5.81.

(Example 61)

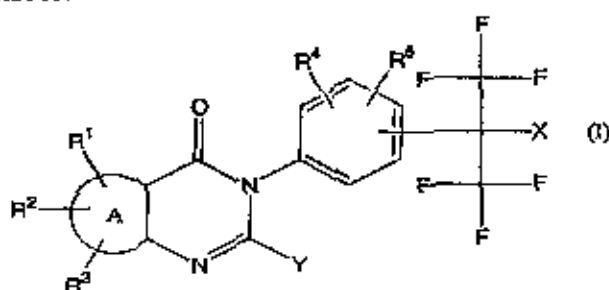
2-Benzyl-7-hydroxy-3-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4(3H)-quinazolinone (Exemplification compound number 3-659)

The title compound was obtained as a colorless solid (114 mg, yield: 52 %) from 2-benzyl-7-methoxy-3-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4(3H)-quinazolinone (228 mg, 0.448 mmol) prepared as described in Example 51 above in a similar manner to that described in Example 59. This product was recrystallized from a mixed solvent of hexane and ethyl acetate to yield a colorless crystalline powder.

mp 242-244°C.

[Claims]

1. A compound of the following formula (I) or a pharmacologically acceptable salt or ester thereof:



wherein:

A represents a C₆-C₁₄ aryl group or a 5- to 7-membered heteroaryl group;

R¹, R² and R³ are the same or different and each represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, an amino group, a halogen atom, a carboxy group, a carbamoyl group, a mercapto group, a C₁-C₆ alkyl group, a C₁-C₆ alkyl group substituted with from 1 to 7 halogen atoms, a C₂-C₇ alkylcarbonyloxy group, a C₁-C₆ alkoxy group, a C₁-C₆ alkylthio group, a C₁-C₆ alkylsulfinyl group, a C₁-C₆ alkylsulfonyl group, a C₁-C₆ alkylamino group, a di(C₁-C₆ alkyl)amino group (wherein the alkyl groups are the same or different), a C₂-C₇ alkylcarbonylamino group, an N-(C₂-C₇ alkylcarbonyl)-N-(C₁-C₆ alkyl)amino group, a C₂-C₇ alkoxycarbonylamino group, an N-(C₂-C₇ alkoxycarbonyl)-N-(C₁-C₆ alkyl)amino group, a C₁-C₆ alkylsulfonylamino group, an N-(C₁-C₆ alkylsulfonyl)-N-(C₁-C₆ alkyl)amino group, a C₁-C₆ haloalkylsulfonylamino group (wherein said C₁-C₆ haloalkylsulfonylamino group is a C₁-C₆ alkylsulfonylamino group which is substituted with from 1 to 7 halogen atoms), an N-(C₁-C₆ haloalkylsulfonyl)-N-(C₁-C₆ alkyl)amino group (wherein said C₁-C₆ haloalkylsulfonyl group is a C₁-C₆ alkylsulfonyl group which is substituted with from 1 to 7 halogen atoms), a C₂-C₇ alkylcarbonyl group, a C₂-C₇ alkoxycarbonyl group, a C₂-C₇ alkylaminocarbonyl group or a di(C₁-C₆ alkyl)aminocarbonyl group (wherein the alkyl groups are the same or different), or R¹ and R² may be taken together to form a C₁-C₄ alkylenedioxy group;

R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a hydroxyl group, an amino group, a halogen atom, a mercapto group, a C₁-C₆ alkyl group, a C₁-C₆ alkyl group substituted with from 1 to 7 halogen atoms, a C₁-C₆ alkoxy group, a C₂-C₇ alkoxycarbonyl group or a C₁-C₆ alkylthio group;

X represents a hydrogen atom, a hydroxyl group, a halogen atom, a C₁-C₆ alkoxy group or a C₁-C₆ alkoxy group substituted with from 1 to 7 halogen atoms;

Y represents a C₁-C₆ alkyl group, a C₁-C₆ alkyl group substituted with from 1 to 7 substituents (said substituents are the same or different and are selected from substituent

group α defined below), a C_3 - C_{10} cycloalkyl group, a C_3 - C_{10} cycloalkyl group substituted with from 1 to 7 substituents (said substituents are the same or different and are selected from substituent group α defined below), a 5- to 9-membered heterocyclyl group, a 5- to 9-membered heterocyclyl group substituted with from 1 to 7 substituents (said substituents are the same or different and are selected from substituent group α defined below), a C_6 - C_{10} aryl group, a C_6 - C_{10} aryl group substituted with from 1 to 4 substituents (said substituents are the same or different and are selected from substituent group β defined below), a C_4 - C_{14} cycloalkylalkyl group, a C_4 - C_{14} cycloalkylalkyl group substituted with from 1 to 7 substituents (said substituents are the same or different and are selected from substituent group α defined below), a (5- to 9-membered heterocyclyl)-(C₁-C₄ alkyl) group, a (5- to 9-membered heterocyclyl)-(C₁-C₄ alkyl) group substituted with from 1 to 7 substituents (said substituents are the same or different and are selected from substituent group α defined below), a C_7 - C_{14} aralkyl group or a C_7 - C_{14} aralkyl group substituted with from 1 to 5 substituents (said substituents are the same or different and are selected from substituent group β defined below);

substituent group α represents a group consisting of a halogen atom, a hydroxyl group, a cyano group, an amino group, a C_2 - C_7 alkylcarbonyloxy group, a C_1 - C_6 alkyl group, a C_1 - C_6 alkoxy group, a C_1 - C_6 alkylthio group, a C_1 - C_6 alkylsulfinyl group, a C_1 - C_6 alkylsulfonyl group, a phenyl group, a C_1 - C_6 alkylamino group, a di(C₁-C₆ alkyl)amino group (wherein the alkyl groups are the same or different), a C_2 - C_7 alkylcarbonylamino group, a C_1 - C_6 alkylsulfonylamino group, and a C_1 - C_6 haloalkylsulfonylamino group (wherein said C_1 - C_6 haloalkylsulfonylamino group is a C_1 - C_6 alkylsulfonylamino group which is substituted with from 1 to 7 halogen atoms); and

substituent group β represents a group consisting of a halogen atom, a hydroxyl group, a nitro group, a cyano group, an amino group, a C_1 - C_6 alkyl group, a C_1 - C_6 alkyl group substituted with from 1 to 7 halogen atoms, a C_2 - C_7 alkylcarbonyloxy group, a C_1 - C_6 alkoxy group, a C_1 - C_6 alkylthio group, a C_1 - C_6 alkylsulfinyl group, a C_1 - C_6 alkylsulfonyl group, a C_1 - C_6 alkylamino group, a di(C₁-C₆ alkyl)amino group (wherein the alkyl groups are the same or different), a C_2 - C_7 alkylcarbonylamino group, an N-(C₂-C₇ alkylcarbonyl)-N-(C₁-C₆ alkyl)amino group, a C_2 - C_7 alkoxy carbonylamino group, an N-(C₂-C₇ alkoxy carbonyl)-N-(C₁-C₆ alkyl)amino group, a C_1 - C_6 alkylsulfonylamino group, an N-(C₁-C₆ alkylsulfonyl)-N-(C₁-C₆ alkyl)amino group, a C_1 - C_6 haloalkylsulfonylamino group (wherein said haloalkylsulfonylamino group is a C_1 - C_6 alkylsulfonylamino group which is substituted with from 1 to 7 halogen atoms), an N-(C₁-C₆ haloalkylsulfonyl)-N-(C₁-C₆ alkyl)amino group (wherein said haloalkylsulfonyl group is a C_1 - C_6 alkylsulfonyl group which is substituted with from 1 to 7 halogen atoms), a C_6 - C_{10} aryl group, a C_7 - C_{14} aralkyloxy group, C_4 - C_4 alkylenedioxy group, a C_7 - C_7 alkylcarbonyl group, a C_2 - C_7 alkoxy carbonyl group, a C_2 - C_7

Studies on the Reduction Rate of Aromatic Nitrocompounds by Bechamp's Method

By Sakae YAGI, Terukatsu MIYAUCHI and Chia You YEH

(Received August 2, 1955)

I. Introduction

Since 1854, the year in which Béchamp reduced aromatic nitrocompounds to corresponding primary amino-compounds using iron particles and acetic acid, many investigations into Béchamp's reduction have been carried out by various authors¹⁾ from the scientific and technical standpoints. The curious catalytic action of hydrochloric acid which came into use later was investigated by Witt²⁾, Wohl³⁾, Raikow⁴⁾ and others.

Effective catalysts for the reaction were greatly extended in their scope by Lyons and Smith⁵⁾, and recently the reaction mechanism has been discussed by Luder and Zuffanti⁶⁾ from the electronic point of view.

Technical preparations of primary amines by this method are now generally performed by batchwise operation.

Some investigations⁷⁾ into a continuous process have been reported in the literature, but their industrial success is yet uncertain. With the same purpose as mentioned above, we have studied the technical reaction rate of this reduction as a fundamental approach to an industrially feasible continuous operation. No systematic data on the reaction rate seem to have been published yet.

First, we investigated a batchwise process using an agitated vessel and later a continuous process by means of a fluidized bed reactor proposed by one of the authors⁸⁾. Studies reported here only cover the former.

II. Experimental Procedures

Fig. 1 illustrates the assembly of the reactor. The reaction vessel is composed of double cylindrical tanks, both made of mild steel. The dimensions of the inner part are 100 mm. dia. $\times$ 114 mm. height (about one liter in volume). The annular space between the tanks is filled with a boiling

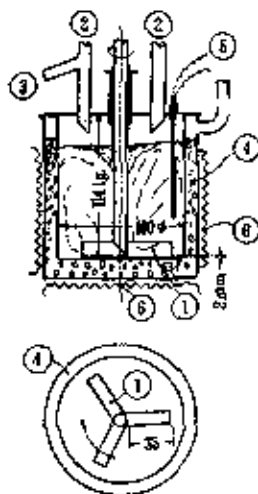


Fig. 1. Experimental apparatus.

1. Three-blades impeller.
2. Reflux condenser.
3. Sampling tube for condensate.
4. Constant-temperature bath.
5. Thermocouple.
6. Electric heater.

liquid as a heat-transfer medium, choice being made among water, methanol, ethanol and a mixture of water and ethanol, each for its own reaction temperature.

Two reflux condensers at the upper part of the reactor and a sampling tube, to obtain samples of refluxing condensate for analysis, are arranged as shown in the figure.

An impeller composed of three brass blades and a mild steel shaft (blade length 35 mm., blade width 13 mm., blade inclination to the horizontal plane 30° and diameter of the shaft 10 mm.) is rotated in the inner vessel at the axial position, with variable speed.

After the temperature is raised to the desired point, weighed aqueous hydrochloric acid solution of known concentration and weighed iron particles are introduced into the reaction vessel and agitated. When evolution of hydrogen gas ceases about three or four minutes later, the weighed nitrocompound preheated to the reaction temperature is introduced as fast as possible within about 20 sec. The lapse of time from the completion of the introduction to the sampling is regarded as the reaction time. Prior to the runs, the iron particles are pretreated as follows. To remove oily matter, the particles are kept in a loosely closed glass flask and exposed to the

1) P.M. Groggins, "Unit process in Organic Synthesis", McGraw-Hill Publ. Co., 4th ed., (1952).

2) O.N. Witt, *Chemische Ind.*, 10, 218 (1887).

3) A. Wohl, *Ber.*, 27, 1432, 1815 (1894).

4) F.N. Raikow, *Zeit. für Angew. Chem.*, 36, 126, 239 (1916).

5) R.E. Lyons and L.T. Smith, *Ber.*, 80, 173 (1927).

6) W.F. Luder and S. Zuffanti, refer to 1), p. 89.

7) A.G. Kalle, (I.G.), *Ind. Eng. Chem.*, 40, 2574 (1948); Vikman and Mukhanova, *Russian P.*, 52006 (1937).

8) Sakae Yagi, *Japanese Pat.* 204, 536 (1954).

temperature of 450°C for ninety minutes. They are cooled and then etched with dilute hydrochloric acid. Nitrobenzene and hydrochloric acid are respectively of "extra-pure grade" and the other nitrocompounds are of "chemically-pure grade".

III. Analytical Methods

Liquid mixtures such as $\text{PhNO}_2\text{-PhNH}_2\text{-H}_2\text{O}$ or *o*-nitrotoluene-*o*-toluidine-water are analysed under ordinary temperature as follows:

Provided the value of ϕ , the molar ratio of the residual nitrocompound to its initial quantity, is higher than about 0.1, a fairly good linearity holds between amine mole fraction, in an equilibrium mixture of three components, and its refractive index, as shown in Fig. 2. Then with

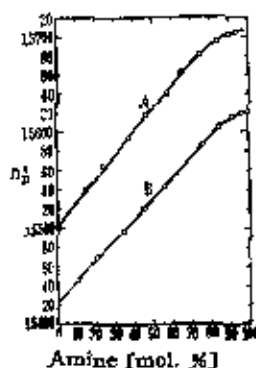


Fig. 2. Refractive index vs. ϕ .

(a) $\text{Ph.NO}_2\text{-Ph.NH}_2\text{-H}_2\text{O}$ System at 42.5°C.

(b) *ortho*- $\text{CH}_3\text{C}_6\text{H}_4\text{NO}_2$ -*ortho*- $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2\text{-H}_2\text{O}$ at 23.0°C.

a small quantity of refluxing condensate taken at intervals, its refractive index is measured with an Abbe Refractometer after separating the sample into two liquid layers by a centrifuge. The true value of ϕ can then be determined from the equilibrium relationship between composition of the refluxing condensate and that of the bulk.

A polarographic determination⁹⁾ is made when ϕ is smaller than 0.05 because the linearity does not hold in this range. Samples are taken from liquid bulk in this case.

p-nitrotoluene and α -nitronaphthalene are determined by volumetric analysis since their reaction mixtures remain in solid state under ordinary temperatures.

During reduction, a few ml. of the oil layer is taken from the liquid bulk, neutralized with a saturated aqueous solution of sodium carbonate and diluted with a known quantity of ethanol.

Analysing this filtrate, total amine and nitrocompound are determined respectively. The former is back-titrated¹⁰⁾ with 0.1N sulfanilic acid solution after an excess of 0.1N sodium

nitrite solution is added. The reduction method¹¹⁾ with TiCl_3 is employed to determine the content of nitro-compound.

IV. Expression of the Reaction Rate

As will be later described, it is experimentally found out that the reaction rate is proportional to the surface area of iron, provided the iron particles are fully fluidized into the reaction mixture.

The overall reaction rate, R is expressed as the rate of nitrocompound consumption per unit surface area of active iron, as

$$R = -\frac{1}{A_T} \frac{dN_N}{d\theta} = -\frac{1}{a_T} \frac{d\phi}{d\theta} \quad (1)$$

$$= -\frac{1}{a_p + a_w} \frac{d\phi}{d\theta}$$

where R =Overall reaction rate (mol./ $\text{cm}^2\text{min.}$)

θ =Reaction time (min.).

$A_T=(A_p+A_w)$, the total surface area of reacting iron after the lapse of time θ (cm^2).

A_p =Surface area of iron particles after θ (cm^2).

A_w =Inside wall area of the reaction vessel plus the surface area of mild steel shaft both of which keep contact with the reaction mixture (cm^2).

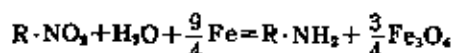
N_{N_0} =Initial molar quantity of nitrocompound (mol.).

N_N =Residual molar quantity of ϕ nitrocompound after θ (mol.).

$$\phi = N_N/N_{N_0}, \quad a_T = A_T/N_{N_0} = a_p + a_w,$$

$$a_p = A_p/N_{N_0}, \quad a_w = A_w/N_{N_0}$$

From the material balance between reactants, N_F , the residual atomic quantity of iron particles after θ , is given by Eq. (2), with an assumption that the overall stoichiometric chemical equation is as follows since hydrochloric acid behaves ultimately as a catalyst



$$N_F = N_{F_0} - \frac{9}{4} \{ (N_{N_0} - N_N) - \int_0^\theta A_w R d\theta \} \quad (2)$$

where N_{F_0} is the initial atomic quantity of iron particles (atms).

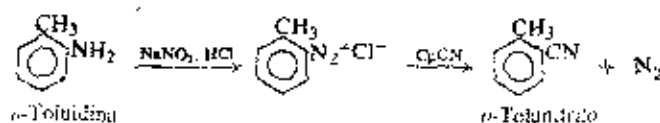
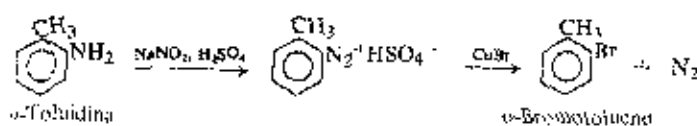
On the other hand, F_p , the weight of iron particles after θ , and A_p are assumed to be expressed by Eqs. (3) and (4) respectively

$$F_p = \psi \rho_F d_p^2 n = N_F M_F \quad (3)$$

9) T. Takeuchi and M. Kanaoki, *J. Soc. Chem. Ind. Japan*, 52, 69 (1949).

10) J. Phillips and A. Lowy, *Ind. Eng. Chem., Anal. Ed.*, 2, 281 (1937).

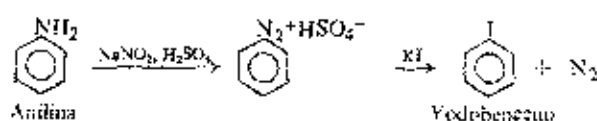
11) F. L. English, *Ind. Eng. Chem.*, 12, 994 (1920).



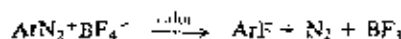
(b) Reemplazo por -I. Estudiado en 23.12.



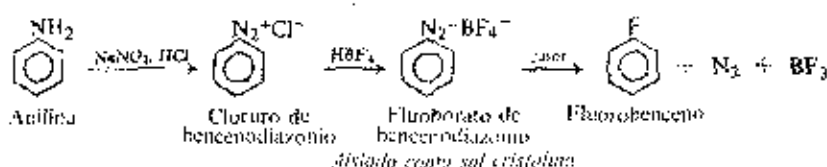
Ejemplo:



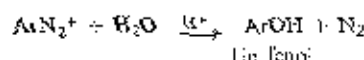
(c) Reemplazo por -F. Estudiado en 23.12.



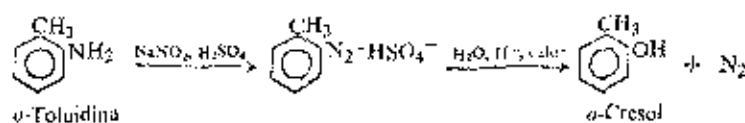
Ejemplo:



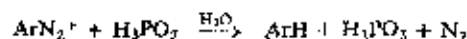
(d) Reemplazo por -OH. Estudiado en 23.14.



Ejemplo:



(e) Reemplazo por -H. Estudiado en 23.15.



174-169

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C.,

Abogado

CARLOS R. OLARTE

ASUNTO

Radicación: 06122177

Trámite: 002

Evento: 001

Actuación: 430

Oficio: 030

Folios: 030

Patente de Invención



Patente de Modelo de Utilidad



Vía Nacional



Vía PCT (fase nacional)



Cap. I



Cap. II



No. Sol. Internacional

PCT/EP2005/006253

Fecha de Presentación Interna

08-06-2005.

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados

Descripción:

Folios: 55 a 101 (como se radicó inicialmente)

Reivindicaciones:

Folios: 102 a 110 (como se radicó inicialmente)

Prioridad:

Folio 1 (08-06-2004, GB 0412769.2).

Objeto de la invención

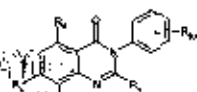
Título : Derivados de Quinazolinona útiles como antagonistas vanilloides.

El objeto de la presente solicitud de patente de invención consiste en:
Derivados de 7 hidroxí o amino - 3-fenil-Quinazolinona.

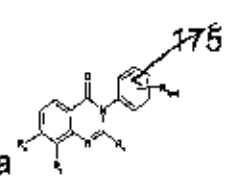
Reivindicación 1 : Un compuesto de fórmula I

Reivindicación 2 : De uso.

Reivindicaciones 3 : Un método de tratamiento.



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Reivindicación 4: Un compuesto de Quinazolinona de Fórmula Ia

Reivindicación 5: Una composición farmacéutica que comprende un compuesto de la reivindicación 4.

Reivindicación 6: Un proceso para la preparación de un compuesto de fórmula Ia de la reivindicación 4.

El problema planteado en esta solicitud es la necesidad proporcionar compuestos caracterizados exhibir una actividad antagonista vanilloide humana, más particularmente que sean activos en el receptor TRPV1, útiles como agentes antiinflamatorios como en enfermedades la osteoartritis, , respuestas alérgicas, enfermedad de crohn, colitis ulcerativa, psoriasis entre otras

Para solucionar este problema técnico la solicitud en estudio proporciona derivados de Quinazolinona, composiciones farmacéuticas que los contiene y un proceso para elaborarlos.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): C07D239/88, A61K31/505, A61P11/06.

De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Concisión

- Las reivindicaciones 1 y 4 no son concisas cuando se refiere a un grupo hidroxilo esterificado o hidroxilo eterificado, ya que no se definen inequívocamente ninguna estructura.

Para este punto se sugiere introducir dentro de la reivindicación la definición de hidroxilo esterificado o hidroxilo eterificado dada en la descripción (folio 60, líneas 21-25) .

Claridad.

- Para la reivindicación 1 se sugiere eliminar la frase " para utilizarse como un producto farmacéutico para el tratamiento o la prevención de una enfermedad o condición en donde tenga un papel o esté implicada la activación del receptor vanilloide" , ya que no aporta ninguna característica técnica adicional.

Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Se aclara que, de acuerdo al Art 20 literal d), el método de tratamiento de la reivindicación 3, no es patentable.

Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, el uso de la reivindicación 2, no es patentable.

Determinación del Estado de la Técnica

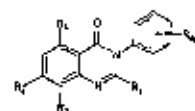
Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 08-06-2004, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO92/13535	ANTICONVULSIVANT SUBSTITUTED QUINAZOLONES	20-08-92
D2	Ericsson et al Acta Pharmaceutica Suecica, 10(4), 254- 262	METHAQUALONE METABOLITES. SYNTHESIS OF EIGHT PHENOLIC MONOHYDROXY DERIVATIVES OF METHAQUALONE.	1973
D3	GB1076747	SUBSTITUTED QUINAZOLONES	19-07-1967
D4	DE1232152	Verfahren zur Herstellung von 3- Phenylchinazolinon-(4)-derivaten	12-01-1967
D5	FR1367738	Procédé de préparation des 3- phénylquinazolones substituées par des groupes amino et de leurs dérivés.	24-07-1967
D6	WO03106435	FUSED-RING PYRIMIDIN-4(3H)-ONE DERIVATIVES, PROCESSES FOR THE PREPARATION AND USES THEREOF.	24-12-2003
D7	Sakae Yagi, Terukatsu Miyauchi and Chia You Yeh Bulletin of the Chemical Society of Japan Vol.29, No.1pp.194- 200	Studies on the Reduction Rate of Aromatic Nitrocompounds by Bechamp's Method	1956
D8	Morrison/ Boyd Química Orgánica Capítulo 23 página 787	Aminas II Reacciones	1976

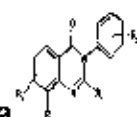
Análisis de patentabilidad (artículo 14 D486)

Novedad (artículo 16 D486)

La reivindicación 1 dice "Compuesto de la fórmula (I)

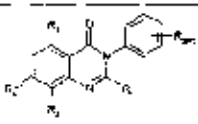
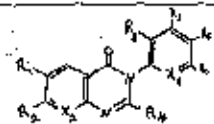
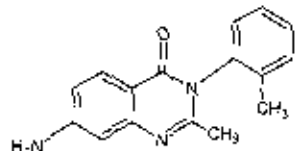
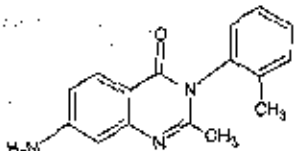


La reivindicación 4 dice "Un compuesto de Quinazolinona de Fórmula Ia

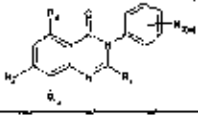
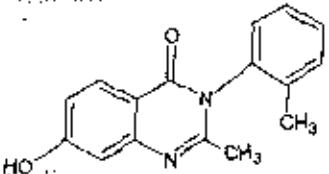
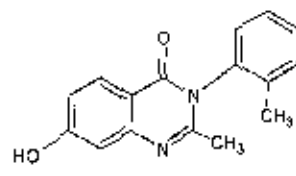


- Al comparar elemento por elemento el objeto de la presente solicitud con el estado de la técnica, esta oficina encuentra:

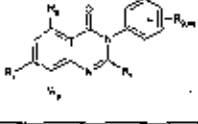
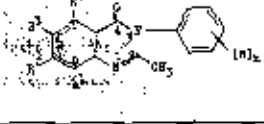
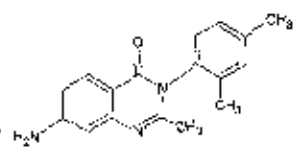
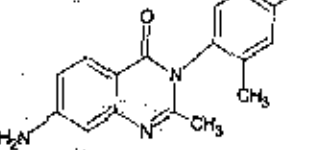
D1 (Folios 152 a 154) enseña compuestos derivados quinazolinona y composiciones farmacéuticas que los contienen, caracterizados por ser anticonvulsivantes.

Solicitud	Documento D1
	
	
m es 1, R2 es alquilo C1-6 átomos de carbono.	X1 es CH. R5, R6 y R7 son hidrógeno.
R1 es es alquilo C1-6 átomos de carbono.	R3 es CH3
R3 es hidrógeno	R4 es- CH3
R4 es NH2	R1 es hidrógeno
R5 es hidrógeno.	R2 es amino
	X2 es CH.

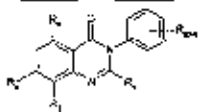
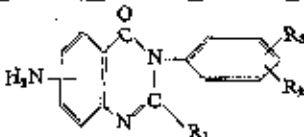
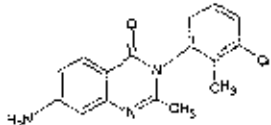
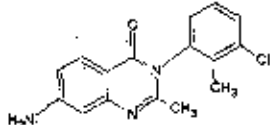
D2 (Folio 155) enseña compuestos derivados quinazolinona caracterizados por ser metabolitos de la metacualona.

Solicitud	Documento D2
	
	Compuesto Página 260, Tabla 2, No 31
m es 1, R2 es alquilo C1-6 átomos de carbono.	
R1 es es alquilo C1-6 átomos de carbono.	
R3 es hidrógeno	
R4 es -OH.	
R5 es hidrógeno.	

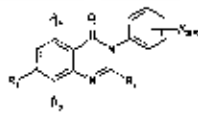
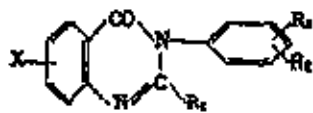
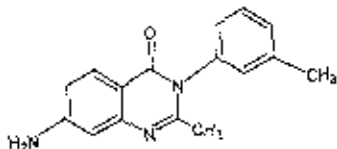
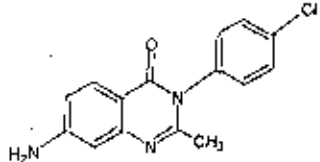
D3 (Folios 156 a 162) enseña compuestos derivados quinazolinona caracterizados por poseer actividad anticonvulsiva, tranquilizante, sedativa y de relajación muscular y composiciones farmacéuticas que los contienen.

Solicitud	Documento D3
	
	
R es alquilo C1-6, halógeno, alquilo C1-6 sustituido por halógeno.	R es CH3, C2H5, CH(CH3)2, Cl, Br, F, CF3
n es 1 o 2.	n es 1 o 2.
R3 y R5 son hidrógeno	R1, R3 y R4 son hidrógeno
R1 es alquilo C1-6	Ultimo compuesto folio 156, líneas 76-77
R4 es amino	R2 es amino.

D4 (Folios 163 a 164) enseña compuestos derivados quinazolinona caracterizados por poseer actividad anticonvulsiva, tranquilizante, sedativa y de relajación muscular

Solicitud		Documento D4	
			
			
R es alquilo C1-6, halógeno, n es 1 o 2. R3 y R5 son hidrógeno R1 es alquilo C1-6 R4 es amino		R2 es o-CH3, m-CH3, p-CH3, m-Cl, p-Cl. R3 es hidrógeno, p-CH3, m-Cl, p-Cl. Compuesto 2B, folio 164A R2 es amino.	

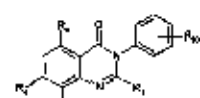
D5 (Folios 165 a 167) enseña un proceso para preparar compuestos derivados quinazolinona

Solicitud		Documento D5	
			
			
R es alquilo C1-6, halógeno, n es 1 o 2. R3 y R5 son hidrógeno R1 es alquilo C1-6 R4 es amino		R2 es o-CH3, m-CH3, p-CH3, m-Cl, p-Cl. R3 es hidrógeno, p-CH3, m-Cl, p-Cl. R1 es CH3 Compuesto 33 folio 166 X es amino	

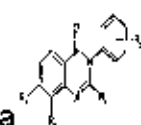
Que D1 (folio 153A ,página 16, ejemplo 4 y Folio 154, tabla 2 , compuesto 14) , D2 (folio 155, compuesto 31), D3 (Folio 156, página 1, columna de la derecha , líneas 74 a 77 , Folio 156A , líneas 1 y 2 ; Folio 157A, tres primeros compuestos, Folio 158A, compuestos 19-25 y 27-28, Folio 159 , compuestos 65-69, Folio 159A, compuestos 39-53) , D4 (Folios 164A, compuestos 20-27) y D5 (folio 166, compuestos 29-36) ya divulgan compuestos reclamados bajo la fórmula I de la solicitud, tal como se expone en el cuadro comparativo. En consecuencia, los compuestos reclamados y ya divulgados, así como las composiciones farmacéuticas que los contienen no son nuevos.

Nivel inventivo.

La reivindicación 1 dice "Compuesto de la fórmula (I)

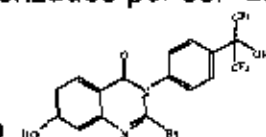


La reivindicación 4 dice "Un compuesto de Quinazolinona de Fórmula Ia



El documento del estado de la técnica más cercano es D6 (Folios 168 a 171) , el cual divulga compuestos derivados de quinazolinona caracterizados por ser útiles

como agentes antiinflamatorios entre ellos el compuesto



Ver

folio 170A, página 302, ejemplo 61).

La solicitud se diferencia de D6 en que la posición 6 se encuentra sustituida por un grupo bencilo y en la posición 3 el fenilo se encuentra sustituido por un grupo $C(OH)(CF_3)_2$.

Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja a los compuestos reclamados en esta solicitud ya que siguen siendo útiles como agentes antiinflamatorios como los compuestos del estado de la técnica más cercano.

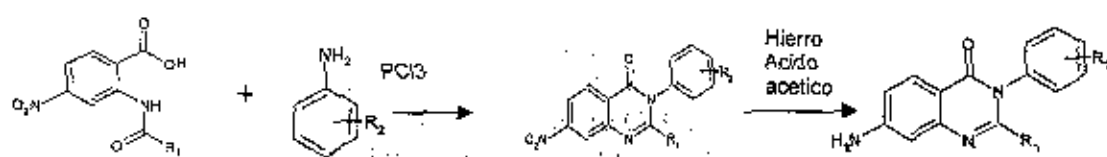
El Problema Técnico Objetivo de esta solicitud es la necesidad de compuestos derivados de quinazolina útiles como agentes antiinflamatorios, alternativos a los ya conocidos en el estado del arte.

D6 también sugiere en la reivindicación 1 (Ver folios 171 y 171 A) que la posición 2 de la estructura quinazolinona puede estar sustituida por radical Y (el cual puede ser alquilo C1-6, un cicloalquilo C3-10) y que equivale a R1 en la actual solicitud, que el fenilo de la posición 3 puede estar sustituido por un grupo alquilo sustituido por halogeno (en el cual X puede ser hidrogeno $CH(CF_3)_2$) el cual equivale a R2 en la actual solicitud y que el anillo benceno de la estructura de la quinazolinona puede estar sustituida por un grupo amino en la posición 7.

El Experto en la Materia, enfrentado al Problema Técnico Objetivo y conociendo el Estado de la Técnica (D6) hubiera sugerido sin mucho esfuerzo de su parte variar la naturaleza de los sustituyentes sobre la posición 2, sobre el anillo fenilo de la posición 3 y sustituir el grupo hidroxilo por el grupo amino en la posición 7 en el anillo de la quinazolinona para obtener más compuestos útiles como agentes antiinflamatorios.

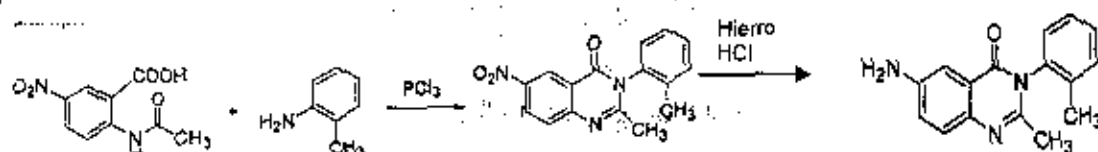
De manera que la solución propuesta por esta solicitud en las reivindicaciones 1 y 4-5 es obvia y no tiene Nivel Inventivo.

La reivindicación 6 dice: "Un procedimiento para preparar un compuesto de fórmula la que consiste en:



Donde en el compuesto de fórmula la R1 es alquilo C1-6, R2 es alquilo C1-6, R3 es hidrógeno y R4 es amino

El documento del estado de la técnica más cercano es D4 (folio 164, ejemplo 5, líneas 21-57) que divulga un procedimiento para preparar un compuesto derivado de quinazolina:



La solicitud se diferencia de D4 en que se utiliza Acido acético en el paso de hidrogenación.

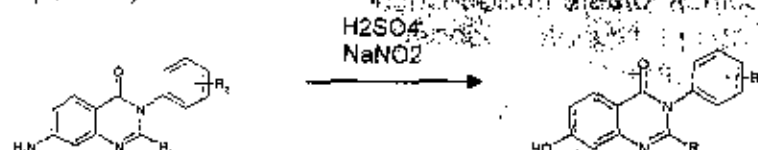
Esta diferencia no parece conceder un efecto técnico inesperado o una ventaja al proceso reclamado ya que permite obtener también compuestos derivados de 3-fenil-7-amino-quinazolinonas a partir de la reducción del derivado nitro por el paso de hidrogenación con polvo de hierro.

El Problema Técnico Objetivo de esta solicitud es el uso de un ácido alternativo en el paso de hidrogenación con polvo de hierro durante el proceso de reducción del derivado nitro.

D7 (folio 172, 4 primeras líneas de la introducción) enseña que los compuestos nitro aromáticos pueden ser reducidos a aminas en presencia de hierro y ácido acético.

El Experto en la Materia, enfrentado al Problema Técnico Objetivo y conociendo el Estado de la Técnica (D4 y D7) hubiera sugerido sin mucho esfuerzo cambiar el ácido clorhídrico divulgado en D4 por el ácido acético divulgado en D7 en el paso de hidrogenación con polvo de hierro durante la reducción del derivado nitro para obtener los compuestos 3-fenil-7-amino-quinazolinonas reclamados en la actual solicitud.

El paso b) de la reacción que consiste en reducir el compuesto



Carece de nivel inventivo a la luz de D8 (Folio 173, numeral (d)), ya que la reacción de obtención de alcoholes a partir de aminas bajo estas condiciones son del conocimiento general para el experto en la materia .

De manera que la solución propuesta por esta solicitud en la reivindicación 6 es obvia y no tiene Nivel Inventivo.

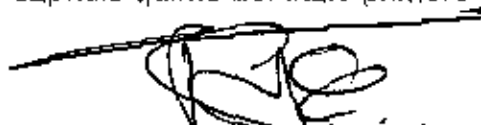
Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO92/13535	1, 4 y 5	Novedad
D2	Ericsson et al Acta Pharmaceutica Suecica 10(4), 254-262	1, 4 y 5	Novedad
D3	GB1076747	1, 4 y 5	Novedad
D4	DE1232152	1, 4 y 5 6	Novedad Nivel inventivo
D5	FR1367738	1, 4 y 5	Novedad
D6	WO03106435	1, 4 y 5	Nivel inventivo.
D7	Sakae Yagi, Terukatsu Miyauchi and Chia You Yeh Bulletin of the Chemical Society of Japan Vol. 29, No. 1 pp. 194-200	6	Nivel inventivo
D8	Morrison/ Boyd Química Orgánica Capítulo 23 página 787	6	Nivel inventivo.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



JOSE LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (E).

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO No. 70	EXAMINADOR TÉCNICO Código No. 202075
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