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[54] RADIOIODINATED QUINOLINE DERIVATIVES

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[52] **U.S. Cl.**.....**260/288 A,** 260/279 R, 260/288 R, 260/289 R, 424/1, 424/258

[51] **Int. Cl.**.....**C07d 33/54**

[58] **Field of Search**.....260/288, 288 A, 694; 424/1

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[57] **ABSTRACT**

Radioiodinated analogs of 4-substituted-7-iodoquinolines when administered parenterally or orally are selectively concentrated in animal tissues containing melanin and may be used for the detection and location of melanotic tumors as well as other abnormal growths. The preferred quinoline compounds are 4-(dialkylaminoalkylamino)-7-iodoquinolines, such as for example 4-(3-dimethylaminopropylamino)-7-iodoquinoline. The radioiodinated compounds are prepared by isotope exchange between the natural iodinated compounds and radioactive alkali metal iodides.

5 Claims, No Drawings

RADIOIODINATED QUINOLINE DERIVATIVES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates broadly to the field of radioactive compositions and move particularly to radioiodinated analogs of 7-iodoquinolines and to methods of preparing and using such analogs.

2. Description of the Prior Art

The use of various compounds labeled with radioactive elements for diagnosis and radiotherapy of various pathological conditions, including malignant tumors, is well known. Compounds of this kind which could be used for the early detection and treatment of melanotic tumors have not heretofore been known, and the use of certain radioiodinated compounds for this purpose was first suggested by the present applicant in the Journal of Pharmaceutical Sciences, Volume 56, No. 8, pages 1042–1044, Aug., 1967.

It has previously been noted that a number of quinoline, acridine, phenothiazine and other polycyclic drugs and dyes are rapidly absorbed by melanin whereas monocyclic compounds such as pyridine and hydroquinone as well as aliphatic compounds have no such affinity for the biopolymer.

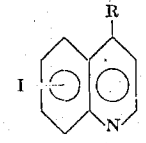
It has also been noted that certain drugs such as chloroquine and chloropromazine have a marked affinity for pigmented tissue containing melanin.

While many chloroquinolines have been prepared and tested as antimalarial drugs, few iodinated compounds of this kind have been described. A. R. Surrey and H. F. Hammer (J. Am. Chem. Soc., 68 113(1946)) reported the preparation of 4-(4-diethylamino-1-methylbutylamino)-7-iodoquinoline, but did not prepare this compound labeled with radioactive iodine or suggest any utility for such a compound.

SUMMARY OF THE INVENTION

Among the several objects of this invention may be noted the provision of radioactive iodoquinoline compounds useful for the detection of melanomas and other malignant tumors; the provision of novel derivatives of 7-iodoquinoline useful as intermediates for preparing the said radioactive compounds; and the provision of compositions and methods for detecting melanomas in animals using radioiodinated substances having an affinity for melanin.

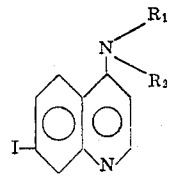
The present invention relates to iodinated quinoline derivatives corresponding to the formula:

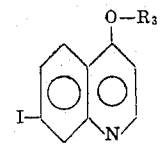


enriched in an iodine isotope

I is an iodine isotope selected from iodine-123, iodine-125, iodine-131 or iodine-132; and R is selected from alkylamino, dialkylamino, dialkylaminoalkylamino, alkoxy, hydroxyalkoxy, or dialkylaminoalkoxy groups and the acid addition salts thereof.

More particularly, the invention relates to compounds corresponding to the formulas:





in which

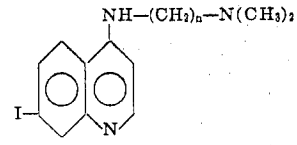
I is an iodine isotope selected from iodine-123, iodine-125, iodine-131 or iodine-132;

R_1 is H or alkyl;

R_2 is alkyl or dialkylamino-substituted alkyl;

R_3 is alkyl, hydroxyalkyl or dialkylaminoalkyl and the acid addition salts thereof.

A preferred series of compounds falling within the scope of the invention have the structure:



where *n* is a number from 0 to 5, and I is an iodine isotope selected from the group consisting of iodine-123, iodine-125, iodine-131 and iodine-132 and the acid addition salts thereof.

The invention also comprises methods of preparing iodine-containing compounds of the kind described above which methods comprise reacting 4-chloro-7-iodoquinoline, in which the iodine is preferably the stable non-radioactive isotope iodine-127, with a compound having the formula RH where R is a radical as defined above. This reaction is preferably carried out by heating the compounds at a temperature sufficient to effect replacement of the chlorine atom by the radical R-. The resulting 4-substituted-7-iodoquinoline is isolated and, if desired, it can be purified and stored for later use in preparing pharmaceutically useful radioactive compounds. To prepare such radioactive compounds, the 4-substituted-7-iodoquinoline is interacted with a radioactive alkali metal iodide to effect isotope exchange and so introduce a diagnostically useful proportion of radioactive iodine in the said quinoline compound. The isotope exchange may, for example, be carried out by dissolving the 4-substituted-7-iodoquinoline compound and the radioactive metal iodide in a suitable solvent and heating the solution at an elevated temperature for a length of time sufficient to effect substantial interchange of iodine between the iodoquinoline compound and the radioactive iodide.

The invention further relates to pharmaceutical compositions comprising a compound of the kind described above in which the iodine is a radioactive isotope, and said compound being dissolved in a pharmaceutically acceptable solvent. The iodine radioisotope is preferably one having a gamma-radiation energy of not more than 500 kev.

The invention also relates to a method for detecting and locating melanotic tumors in living animals which comprises parenterally or orally administering a detectable dose of a radioactive compound of the kind described above and then subsequently scanning the animal by means of a conventional radiation scanning device to determine the loci and intensity of radiation emitted by the radioisotopic iodine. More broadly, such methods for detecting and locating melanotic tu-

mors in living animals comprise administering to the animal a detectable dose of a compound having quinoline as its nucleus to which is attached a radioisotope of iodine, the said radioisotope preferably having a gamma-radiation energy of not more than 500 kev., allowing sufficient time for the said compound to be concentrated in any melanotic tumors present in said animal, and then scanning the animal by means of a conventional radiation scanning device for radioactive loci within the animal.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Among the preferred compounds of this invention are those in which the organic radical R in the first formula shown above is an alkylamino or substituted-alkylamino group. As examples of such compounds may be mentioned: 7-iodoquinoline compounds in which the substituent at the 4-position is an alkylamino group such as dimethylamino, diethylamino, dipropylamino, hexylamino, 4-methylpentylamino, pentylamino, 4-methylbutylamino, butylamino, propylamino, 3-methylpropylamino, etc. Likewise the substituent at the 4-position may be a substituted-alkylamino group such as a dialkylamino-substituted alkylamino group. Examples of such substituents are 2-dimethylaminoethylamino, 3-dimethylaminopropylamino, 3-diethylaminopropylamino, 3-dipropylaminopropylamino, 4-dimethylaminobutylamino, 5-dimethylaminopentylamino, and the like. Such compounds may be prepared, for example, by reacting 4-chloro-7-iodoquinoline with an appropriate amine.

The 4-substituent may also be an alkoxy or substituted alkoxy group. Examples of such groups are ethoxy, hydroxyethoxy, propoxy, 3-dimethylpropxy, pentyloxy, 4-dimethylaminopentyloxy, 4-diethylaminopentyloxy, and the like. Such 4-alkoxy-substituted compounds of the invention may be prepared, for example, by reacting 4-chloro-7-iodoquinoline with an appropriate alcohol or alkali metal alkoxide.

For diagnostic purposes radionuclides with a gamma-radiation energy of less than 500 kev. are preferred. Examples of such isotopes are iodine-125 which has a half-life of 60 days and a radiation energy of 35 kev. and iodine-131 which has a half-life of 8 days and a radiation energy of 360 kev. While the synthesis and storage of compounds containing iodine-125 is simpler, for some purposes the higher radiation energy of iodine-131 may be necessary or desirable. Other known radioisotopes of iodine, such as iodine-123 and iodine-132, are also useful and may even be advantageous for certain purposes.

The compounds of the present invention are preferably used in the form of one of their water-soluble acid addition salts. Methods for preparing such salts are well known to those skilled in the art. In practice, salts with hydrochloric acid have been found to be very satisfactory and are usually preferred, but the acid addition salts of other strong mineral acids such as hydrobromic acid, nitric acid, sulfuric acid, or strong organic acids such as glacial acetic acid are also useful.

The following examples illustrate the invention.

EXAMPLE 1

Preparation of 4-(3-Dimethylaminopropylamino)-7-iodoquinoline

A solution of 4-chloro-7-iodoquinoline (2.5 g.) in 3-dimethyaminopropylamine (10 ml.) was heated at the reflux temperature for up to 23 hrs. The excess amine was removed by distillation under reduced pressure and the residual oil dissolved in a minimum of acetone. NH_4OH was added and the resulting yellow precipitate was collected by filtration and washed with water. Several recrystallizations from acetone afforded pale yellow needles (2 g., 65 percent) of the desired product, mp 101°–103°, nmr peaks at 7.64 (NCH_3), 7.43 ($—CH_2N—$), (triplet, J = 6 cps.) and 6.67 ppm ($—CH_2NH—$, multiplet). The latter became a triplet upon deuteration (J = 6 cps.) The IR spectra was as expected. Anal. ($C_{14}H_{18}IN_3$) calcd. C 43.21, H 4.14; found C 43.34, H 4.11. Acute toxicity tests in mice gave an LD_{50} value of 58 mg./kg. with confidence limits of 49.6 to 67.9 mg./kg.

EXAMPLE 2

Preparation of 4-(4-Methylpentylamino)-7-iodoquinoline

A solution of 4-chloro-7-iodoquinoline (2 g.) in 4-methylpentylamine (4 ml.) was heated under reflux for 23 hrs. and the excess of solvent evaporated under reduced pressure. Addition of acetone to the residue gave a solid hydrochloride (1.75 g.), mp 168°–173° and V_{max} 2,700 cm^{-1} (N^+H). Recrystallization from EtOH–Me_2CO gave an analytical sample, mp 183°–4°. The motor liquors afforded a second fraction (0.35 g.), mp 130°–135°, which upon recystallization from ethyl alcohol-water gave the desired base in pure form, mp 144°–5. Treatment of an ethyl alcohol solution of the HCl salt gave the same free base. Anal. ($C_{15}H_{19}IN_2$) Calc. C 50.88, H 5.41; found C 50.74, H 5.32. The IR and nmr spectra were as expected.

EXAMPLE 3

Preparation of 4-(3-Dimethylaminopropoxy)-7-iodoquinoline

A mixture of 3-dimethylamino-1-propanol (1.45 g., 0.014M) and sodamide (0.67 g., 0.017M) in dry toluene 15 ml.) was heated under reflux until the evolution of ammonia ceased (about 3 hrs.). The grey suspension was cooled and a solution of 4-chloro-7-iodoquinoline (1 g., 0.0034M) in toluene (5 ml.) added dropwise with stirring. The reaction mixture was heated under reflux for 18 hrs. On cooling, water was added to dissolve the solid material, and the toluene phase was separated, dried over sodium sulfate, and evaporated to leave a pale brown oil which solidified upon addition of petroleum ether (bp, 30°–40°). The white solid (0.7 g., 57 percent) mp 85°–90°, was recrystallized from acetone to give an analytical sample, mp 93°–4°, V_{max}1180 cm^{-1} (C—O—C), and nmr peaks at 2.29 (NMe_2), 2.50 (triplet, J = 6 cps., —NCH_2), and 4.23 ppm (triplet, J — 6 cps., —OCH_2). Anal. ($C_{14}H_{17}IN_2O$) Calcd. C 47.22, H 4.81; found C 47.37, H 4.80.

EXAMPLE 4

Preparation of 4-(4-Methylpentyloxy)-7-iodoquinoline

A solution of 4-chloro-7-iodoquinoline (3.1 g.) in toluene (5 ml.) was added dropwise with stirring to a previously heated mixture of 4-methyl-1-pentanol (4.4 g.) and sodamide (2.1 g.) in toluene (10 ml). The reaction was carried out as in Example 3 and afforded a white solid (2.45 g.), mp 85°–88°. Recrystallization from hexane gave the desired compound in pure form, mp 97°–9°, V_{max} at 1,115 cm^{-1} (C—O—C) and nmr peaks at 9.94 [doublet, J = 6 cps, C—$(CH_3)_2$] and 4.15 ppm. (triplet, J — 6.5 cps, —OCH_2). Anal. ($C_{15}H_{18}INO$) Calcd. C 50.72, H 5.11; found C 50.80, H 4.98.

EXAMPLE 5

Preparation of 4-Dimethylamino-7-iodoquinoline

Dimethylamine gas was bubbled through an ice-cooled solution of 4-chloro-7-iodoquinoline (2 g.) in toluene (20 ml.) and methylethyl ketone (10 ml.) for 3 hours in a pressure bottle. The bottle was tightly stoppered and placed in an oven at 50°C. for 10 days. The mixture was cooled and washed with water. The organic phase was dried over sodium sulfate and the solvent removed in vacuo. Recrystallization of the solid residue gave the desired compound in pure form (1.1 g.), mp 107°–8°, and an nmr peak at 2.99 ppm. (NCH_3). Anal. ($C_{11}H_{11}IN_2$) Calcd. C 44.32, H 3.72; found C 44.42, H 3.59.

EXAMPLE 6

Preparation of 4-Hydroxyethoxy-7-iodoquinoline

A solution of the compound described in Example 5 (100 mg.) in ethylene glycol (1.5 ml.) was heated in an oil bath at 185° for 16 hours, cooled, and diluted with water. The precipitate (70 mg.), mp 153°–5°, was recrystallized from acetone-water to give the desired product in pure form, mp 154°–5°. The IR and nmr spectra were as expected. Anal. ($C_{11}H_{10}INO_2$) Calcd. C 41.94, H 3.20; found C 42.03, H 3.25.

EXAMPLE 7

Preparation of Iodine-125 Analogs by Isotope Exchange

Radioiodinated analogs of the previously described quinoline derivative are prepared as follows: A solution containing 1–3 mc. of sodium iodide-125 was placed in a 10 ml. round-bottom flask and evaporated to dryness at 100°C. under a gentle stream of nitrogen. The substituted 7-iodoquinoline (100 mg.), dissolved in the appropriate solvent (2 ml.) (see Table 1), was added. A condensor was then attached, and the bath temperature was raised. The mixture was stirred under nitrogen for the specified time and allowed to cool. In the case of the compounds described in Examples 1 and 3, water was added and the product collected by filtration and washed well with water. For the compound described in Example 2, the solution was concentrated to approximately 0.5 ml. under reduced pressure, treated with water and ammonium hydroxide, and the precipitate collected as above. For the compound described in Example 4, the solvent was removed in vacuo, the residue treated with water containing a little acetone, and the precipitate collected. In all cases, the products were purified by recrystallization and the purity established by (a) TLC and a radiochromatogram of the strip and b) admixture melting point with authentic samples. Further details of the individual preparations are given in Table 1.

TABLE I

Compound	Solvent [a]	Bath temp.	Reaction time (hr.)	Recrystallization solvent	Percent Recovery	Percent Exchange	Spec. act. μc./mg.
Example 1	A	170–5	16	$Me_2CO—H_2O$	53	56.6	5.66
Example 2	B	190–5	48	$EtOH—H_2O$	15	49	14.5
Example 3	C	205–10	24	$Me_2CO—H_2O$	55	2.5	0.51
Example 4	D	175–180	48	$EtOH—H_2O$	7	4.8	1.44

[a] A=ethylene glycol, B=pivalic acid, C=3-dimethylamino-1-propanol, D=4-methyl-1-pentanol.

EXAMPLE 8

4 to 5-week-old male, black mice of the BL6J strain were injected intraperitoneally with 10 microcuries of 4-(3-dimethylaminopropylamino)-7-iodoquinoline containing iodine-125. The animals were sacrificed at 12, 24 and 48 hrs. Control mice were injected via the same route with 10 microcuries of sodium iodide-125 and sacrificed at the same time intervals. Counting was done in a commercial well counter. This radioiodinated quinoline compound showed the same marked affinity for melanin and slow release from pigmented tissues that had earlier been observed in rats and mice using chloroquine labeled with carbon-14. Moreover, the low thyroid activity observed for the animals receiving the radioiodinated quinoline compound versus those given the sodium radioiodide, indicates that significant diodination did not occur.

EXAMPLE 9

4-(3-Dimethylaminopropylamino)-7-iodoquinoline containing iodine-125 was injected into Syrian hamsters with malignant melanomas at a dosage of 100 microcuries per animal. Excellent visualization of the melanotic tumor was obtained within 4 days. The concentration of iodine-125 in the tumor was approximately 10 times its concentration in other tissues. Its concentration in the melanoma remained constant or increased for about 5 days following the injection while concentrations in all other tissues fell rapidly during the first 3 days. There was no evidence of uptake by the thyroid. Since a portion of the injected material is excreted in the bile, the scans were also made several (3–5) days after the injection to allow time for the material to be eliminated from the bowels, spleen and liver.

EXAMPLE 10

When 1 millicurie of 4-(3-dimethylaminopropylamino)-7-iodoquinoline containing iodine-125 was injected into a melanotic dog weighing 145 lbs., concentration of the radioactive compound in the melanoma was similar to that observed in the Syrian hamsters described in Example 9.

From the preceding it is evident that the usefulness of the compounds of this invention resides in their selective concentration in melanotic tissues. It should also be noted that the utility of these compounds is not necessarily limited to the detection of melanomas, for

concentration of the compounds in other kinds of malignant tissue, such as breast tumors in mice, has also been observed.

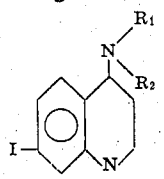
Using the sensitive scanning devices now available only minute amounts of the radioactive compound are necessary to produce diagnostically useful scans. For example, using iodine-125, a useful dose will ordinarily be about 1 millicurie. For a person of average size, this is equivalent to approximately 5 microcuries/per kilogram. The chemical dosage is therefore measured in micrograms of the chemical compound, and so it is evident that chemical dosages and toxicities in the ordinary sense are of minor significance compared with radiation dosages and toxicity.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above methods and products without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

What is claimed is:

1. A compound having the formula:

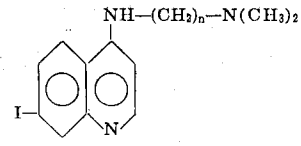


enriched in an iodine isotope selected from the group consisting of iodine-123, iodine-125, iodine-131 and iodine 132;

R_1 is selected from the group consisting of H and alkyl having 1 to 6 carbons;

R_2 is selected from the group consisting of alkyl having 1 to 6 carbons and dialkylamino-substituted alkyl having 1 to 6 carbons in each of the alkyls of the dialkyl group and 2 to 5 carbons in the other alkyl group, and the pharmaceutically acceptable acid addition salts thereof.

2. A compound having the formula:



where *n* is a number from 1 to 5, and I is an iodine isotope selected from the group consisting of iodine-123, iodine-125, iodine-131 and iodine-132, and the pharmaceutically acceptable acid addition salts thereof.

3. A compound according to claim 2 in which n is 3.

4. A compound according to claim 1 in which R_1 is hydrogen and R_2 is the radical 4-methylpentyl.

5. A compound according to claim 1 in which both R_1 and R_2 are methyl radicals.

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