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TERTIARY AMINE DERIVATIVES OF N- AND O-SACCHARIN

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7 Claims. (Cl. 260—301)

This invention relates to compositions of matter, particularly to chemotherapeutic organic compounds and methods of their preparation and more particularly to compounds useful as analgesic and antihistaminic agents in mammals.

Specifically, the invention involves the discovery and contemplates the disclosure of novel types of compounds hereinafter referred to as the N- and O- saccharin derivatives, the parent bases, simple salts, and quaternary salts thereof.

These novel compounds possess unique solubility characteristics, which is unusual in the whole class of saccharin compounds except for the sodium salt. The simple salts and quaternary salts formed from the parent bases hereinafter disclosed are water soluble. This desirable property makes them suitable for administration by injection routes as well as orally in the form of liquids, syrups, tablets, etc. Thus rapid absorption of these compounds when used medicinally is obtained.

These novel types of compounds have been found suitable for the symptomatic relief of certain types of neuralgia, rheumatoid and arthritic disorders and in addition, have been found to possess varying degrees of antihistaminic activity.

Accordingly, it is a basic object of the present invention to provide novel organic compounds and methods for the preparation thereof.

Another object is to provide novel compounds characterized by chemotherapeutic or medicinal properties and particularly by analgesic and antihistaminic physiological activity in the mammalian species.

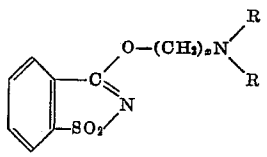
Another specific object is to provide novel compounds, namely, N- and O- saccharin derivatives, the parent bases, simple salts and quaternary salts thereof.

An equally important object of the invention is to provide methods of synthesizing the novel compounds referred to in the foregoing objects.

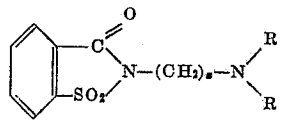
These and other subordinate objects and the manner in which they are accomplished will become apparent to those conversant with the art from the following description of the general types of novel compounds discovered and certain specific examples of particular members thereof as well as general and specific methods of their synthesis.

Generally stated, the novel compounds embraced by this discovery are made by placing suitable groupings on the imide nitrogen of the saccharin nucleus or on the carbon adjacent to the imide nitrogen, coupled through an oxygen ether linkage or an amino nitrogen linkage, and forming suitable simple or quaternary salts of the bases thus obtained.

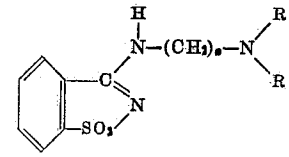
The types of compounds discovered are specifically illustrated by Formulae 1(*a*), 1(*b*) and 1(*c*) which follow:



1(*a*)

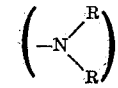


1(*b*)



1(*c*)

In these formulae, x represents a number from 2 to 6 and R represents an alkyl group having from 1 to 6 carbon atoms, or the grouping



may represent a heterocyclic ring system such as pyrrolidine, morpholine and piperidine.

Formula 1(*a*) shows the type of compound derivable from linkage of the side chain to the saccharin nucleus through an ether link; Formula 1(*b*) the type obtainable by substituting on the imide nitrogen; and Formula 1(*c*) the type obtainable by linkage through an amino group to the carbon adjacent to the imide nitrogen.

The first class of saccharin derivatives, i. e., those represented by Formula 1(*a*), are obtained by reacting equimolecular amounts of pseudo-saccharin chloride with the desired amino alcohol in suitable media. Conveniently the derivative is isolated from the reaction mixture as the hydrochloride, from which the various bases and other salts may be obtained by suitable means such as ion exchange or ion interaction. This class of compounds readily forms quaternary salts by treatment of the bases with desired alkyl halides.

The second class of saccharin derivatives (Formula 1(*b*)) are obtained by reacting equimolecular quantities of sodium saccharide with the desired dialkylaminoalkyl (or heterocyclic alkyl) halide in a polar solvent such as dimethylformamide. The free bases are obtained directly by this reaction and may then be converted to the desired simple salts or quaternary salts by neutralization or treatment with appropriate alkyl halides.

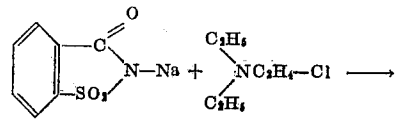
The third class of saccharin derivatives (Formula 1(*c*)) are obtained by reaction of equimolecular quantities of pseudo-saccharin chloride with the desired dialkylaminoalkyl (or heterocyclic alkyl) amine in a suitable medium such as acetone or benzene. These compounds are obtained from the reaction mixture as the hydrochloride salts which may be converted into the base, other simple salts, or may be quaternized as desired.

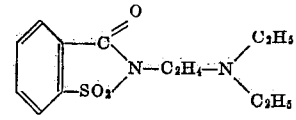
Following are particularized examples of the general synthesizing processes described above and specific resulting members of the novel general classes of compounds discovered.

EXAMPLE I

N-diethylaminoethyl saccharin

The synthesizing reaction for the preparation of this compound is illustrated by the following equation:





In carrying out the synthesis indicated by this equation, 51 grams (0.25 mole) of sodium saccharide was dissolved in 100 ml. of dimethylformamide and the solution refluxed for 3 hours with 33 grams of diethylaminoethyl

chloride. Separation of sodium chloride was evident after a few minutes and the reaction was essentially complete in 3 hours. The reaction mixture was then filtered to remove the salt formed and the dimethylformamide removed from the filtrate under reduced pressure. Finally, the resulting oil was filtered through glass wool and distilled in vacuo and a yield of 55 grams of the free base was obtained. The substance solidified in the receiver and had a melting point of 61–63° C. and boiled at 144–150° C. at a pressure of 0.06 mm.

The hydrochloride

On treatment of the free base dissolved in methanol or ethanol with a saturated solution of HCl in ethanol and precipitation with ether, the hydrochloride was obtained. It was characterized by a melting point 217–218° C. and a chloride ion content of 11.25%. The theoretically predicted chloride ion content was 11.12%.

The methiodide

The free base, dissolved in anhydrous acetone and treated with an excess of methyl iodide, upon standing for several hours yielded the methiodide, which had a melting point of 199–200° C. The iodide content found was 30.04% which compares very closely to the theoretical iodide content, which is 29.91%.

EXAMPLE II

N-morpholinoethyl saccharin

In the manner described under Example I, the N-morpholinoethyl derivative was obtained in 80% yield of the free base when the reaction was run in 0.25 molar quantity. This substance had a boiling point of 180–184° C. at 0.1 mm. pressure and a melting point of 103–104° C.

The hydrochloride

Conversion to the hydrochloride was effected in the same manner as outlined in Example I and yielded the salt with a melting point of 236° C. The analysis for chloride ion content gave a value of 10.76% which checks closely with the theoretical value of 10.65%.

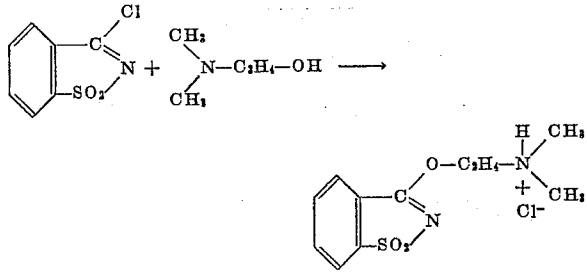
The methiodide

Conversion to the methiodide was effected in anhydrous methanol by means of an excess quantity of methyl iodide. This quaternary salt had a melting point of 259–260° C. and iodide ion was found to be present in the amount of 29.36% as compared to 28.96% calculated theoretically for this salt.

EXAMPLE III

Dimethylaminoethyl pseudo-saccharin ether

The synthesizing reaction for the preparation of this compound is illustrated by the following equation:



In carrying out the synthesis indicated by this equation, 40 grams (0.2 mole) of pseudo-saccharin chloride was dissolved in 250 ml. of anhydrous acetone with gentle heating. After solution had been effected, 18 grams (0.2 mole) of dimethylaminoethyl alcohol dissolved in 50 ml. of acetone was slowly added. The reaction was instantaneous and exothermic. The mixture, after refluxing gently for ½ hour, was cooled and filtered and

a yield of 55 grams of the hydrochloride was thus obtained. This salt had a melting point of 175–176° C. and a chloride ion content of 12.03% or very close to the theoretical chloride ion content of 12.19%.

Examples IV, V and VI of the compounds discovered are tabulated below.

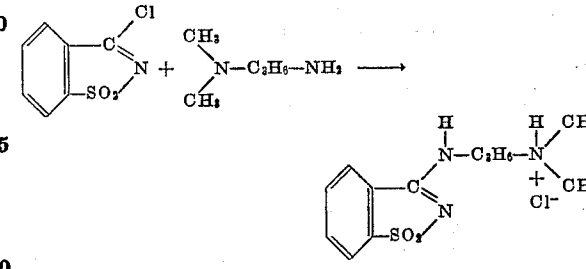
These compounds are prepared by the reaction explained in Example III above, using the appropriate alcohol, and are yielded in the form of the hydrochloride salt.

Example	Compound	Melting Point, ° C.	Percent chloride ion	
			Actual	Theoretical
IV	Piperidinoethyl pseudo-saccharin ether (hydrochloride).	150–151	10.33	10.72
V	Pyrrolidinoethyl pseudo-saccharin ether (hydrochloride).	151–152	11.46	11.19
VI	Beta-di-n-butylaminopropyl pseudo-saccharin ether (hydrochloride).	135–137	9.30	9.16

EXAMPLE VII

C-dimethylaminopropyl amino pseudo-saccharin

The synthesizing reaction for the preparation of this compound is illustrated by the following equation:



In carrying out this synthesis, 40 grams (0.2 mole) of pseudo-saccharin chloride was dissolved with gentle heating in 250 ml. of anhydrous acetone. After solution was complete, 20.4 grams (0.2 mole) of 3-dimethylaminopropyl amine dissolved in 50 ml. of acetone was added rapidly but cautiously. An exothermic reaction ensued and the product precipitated out in the form of colorless crystals. The mixture was refluxed gently for an additional ½ hour, cooled, filtered and washed with anhydrous acetone and then ether and dried. The resulting compound had a melting point of 206–207° C. and analysis thereof showed a chloride ion content of 11.67% which is exactly the value arrived at by theoretical calculations.

EXAMPLE VIII

C-diethylaminoethylamino pseudo-saccharin

This compound, prepared by means of a reaction analogous to that described in Example II using the appropriate amine, on standing 4 days yielded a crystalline product which on filtering, washing with acetone and ether, and drying, had a melting point of 165–166° C. and a chloride ion content (11.18%) extremely close to the theoretical value (11.16%).

EXAMPLE IX

C-morpholinoethylamino pseudo-saccharin

This compound was also prepared by the reaction explained in Example VII, using the appropriate amine. The compound precipitated immediately and on filtering, washing and drying had a melting point of 269–271° C. Chloride ion was found to be present in the amount of 10.77% as compared with a theoretically calculated content of 10.69%.

The efficacy of certain of the compounds embraced by

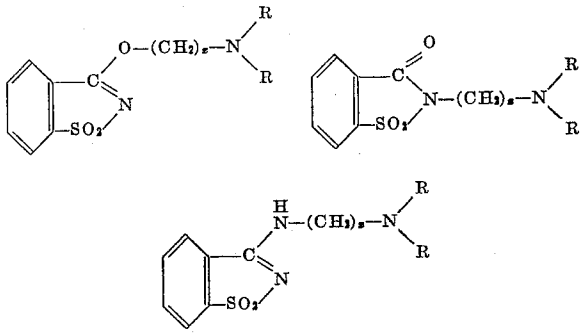
this discovery in the symptomatic treatment of certain diseases has already been mentioned hereinabove. The O-saccharins have been found to be of particular value as analgesics in the treatment of neuralgia, arthritic and various related rheumatoid disorders. To this end a recommended effective dosage is 250 to 330 milligrams given orally or 50 milligrams by injection, in either case once a day.

The N-saccharins are similarly effective administered orally, twice daiiy in 60 milligram dosages.

From the foregoing description of novel classes of compounds, particular exemplary members of the classes and general and specific methods of synthesizing same, it will be understood that on the basis of the discovery and knowledge disclosed herein other specific compounds have been and can be made and variations in the methods of synthesis resorted to. Therefore specific compounds and methods disclosed herein are to be considered in all respects as illustrative and not restrictive, the scope of the discovery being indicated by the appended claims rather than by the foregoing description, and all specific compounds and variations in method which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

What is claimed and desired to be secured by the United States Letters Patent is:

1. As novel compositions of matter, the N- and O-saccharin derivatives taken from the group consisting of

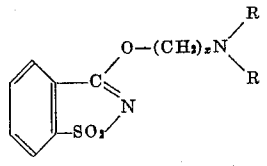


where x represents a number from 2 to 6, and

$N\begin{matrix}R\\R\end{matrix}$

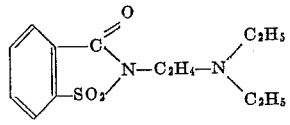
is taken from the group consisting of the dialkylamino having 1 to 6 carbon atoms in each alkyl chain and the heterocyclic ring systems of pyrrolidine, morpholine and piperidine.

2. As novel compositions of matter the saccharin derivatives having the formula



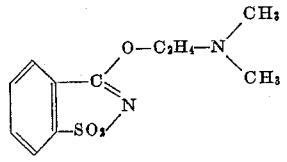
where, in said formula, x is 2 and R is methyl.

3. As novel compositions of matter, the saccharin derivative having the formula



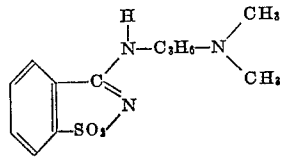
namely, N-diethylaminoethyl saccharin.

4. As novel compositions of matter, the hydrochloride salt of the saccharin derivative having the formula



namely, dimethylaminoethyl pseudo-saccharin ether.

5. As novel compositions of matter, the saccharin derivative having the formula



namely, C-dimethylaminopropylamino pseudo-saccharin.

6. The method of preparing saccharin derivatives comprised in reacting sodium saccharide with an alkyl halide selected from the group consisting of dialkylaminoalkyl and heterocyclic alkyl halides in a polar solvent.

7. The method of preparing saccharin derivatives comprised in reacting pseudo-saccharin chloride with an amine selected from the group consisting of dialkylaminoalkyl and heterocyclic alkyl amines.

References Cited in the file of this patent

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