UNITED STATES PATENT OFFICE.

HEINRICH BAUM, OF MANCHESTER, ENGLAND, ASSIGNOR TO VEREINIGTE CHININFABRIKEN, ZIMMER & CO., GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, OF FRANKFORT-ON-THE-MAIN, GERMANY.

PARAPHENETIDIN COMPOUND.

SPECIFICATION forming part of Letters Patent No. 574,874, dated January 12, 1897.

Application filed May 5, 1896. Serial No. 590,328. (No specimens.)

To all whom it may concern:

Be it known that I, HEINRICH BAUM, a subject of the Emperor of Germany, and a resident of Manchester, England, (assignor to the firm of VEREINIGTE CHININFABRIKEN, ZIMMER & CO., GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, of Frankfort-on-the-Main, Germany,) have invented certain new and useful Improvements in Medical Compounds, of which the following is a specification.

It is well known that salicylate of soda, salypyrin, malakin, and other preparations have been employed as remedies for rheumatism. These agents, when used in greater or smaller doses, exercise a certain antirheumatic action, but they are at the same time in part apt to affect, more or less injuriously, the function of the heart, while some of them do not act upon the heart at all.

Sufferers from rheumatism are frequently very sensitive as regards their cardiac functions and in some cases suffer from a weak heart. Therefore the employment of such agents as remedies for rheumatism gives rise in many instances to injurious secondary effects. Where it is desirable also to favorably influence the action of the heart, they fail to do so.

This invention has for its object to prepare medicinal matters which while exercising a powerful antirheumatic action at the same time very beneficially influence the action of the heart. This result is attained, according to the present invention, by preparing derivatives of paraphenetidin or paraänisidin, not, as has been usual in the case of malakin, by means of the phenol series, but by the aid of the hydroquinone series, and thus the alkyloxy group of phenetidin or anisidin and the alkyloxy group of an aldehyde of the hydroquinone series are present in the same compound. The derivatives of gentisinaldehyde have proved to be satisfactory agents for the accomplishment of this object. The preparations thus obtained act upon the heart in such a manner as to regulate, invigorate its action, tending to moderate the pulsations and to increase the pressure of the blood, an action which digitalis alone has hitherto been known to produce. The preparations or compounds forming the subject of this invention have, however, this advantage over digitalis, that, in addition to being free from any poison, they can, owing to the individuality of their chemical nature, in all cases be exactly and reliably dosed, which is not the case with the poisonous digitalis preparations, owing to the irregularity of their composition. The effect of this latter is therefore frequently unreliable and may in many cases be converted into the contrary, in addition to which, owing to their cumulative action, digitalis preparations are apt to prove positively poisonous, which is never the case with the products obtained in accordance with this invention. Furthermore, the products according to this invention are not liable to produce the unpleasant secondary effects upon the digestive organs and nerves which in many cases characterize digitalis preparations.

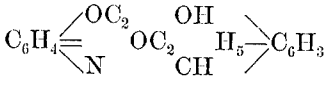
According to the experiments which have had the result hereinbefore indicated, the product of the present invention constitutes condensation product from paraphenetidin or paraänisidin on the one hand and metamethoxysalicylaldehyde or metaethoxysalicylaldehyde on the other, and these products are excellent cardio tonic and antirheumatic agents, besides being free from the objectionable secondary effects which attend many of the antirheumatic and cardiac medicines hitherto known.

The method of manufacture of the paraphenetidin compounds, for example, consists in condensing gentisinaldehyde with paraphenetidin and in alkylating the product. Paraphenetidin can also be condensed with the alkylated gentisinaldehyde—*i. e.*, with metaälkyloxysalicylaldehyde. The desired product is also obtainable by condensing methalkyloxysalicylaldehyde with paraamidophenol and alkylating the product of condensation by means of halogenalkyl. The manufacturing of the product according to this invention may be modified by condensing gentisinaldehyde with paraämidophenol and by introducing first one alkyl group and then another into the condensation product or by introducing both groups together.

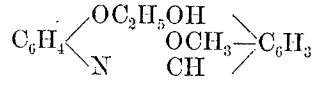
The following examples may better illustrate the several modifications of the process:

Example 1: Fourteen kilograms of gen-

tisinaldehyde are mixed with fourteen kilograms of paraphenetidin and ten kilograms of spirits of wine in a distilling vessel. The alcohol is slowly distilled off and the mixture heated for some time at a temperature of from 120° to 140° centigrade. The dark-red mass thus obtained is crystallized from benzene or dilute alcohol. It is obtained from benzene in the form of small, stout, salmon-colored needles, (paradioxybenzylideneparaphenetidin,) which weather on exposure to air. From alcohol the substance crystallizes in reddish-yellow leaflets, melting at 119° to 120° centigrade. 25.7 kilograms of this compound are then dissolved in one hundred and twenty-five kilograms of alcohol, 5.6 kilograms of caustic potash, dissolved in the minimum quantity of water, being then added. When cold, the mass is mixed with eleven kilograms of hydrobromic ether and heated for several hours in a reflux apparatus, the operation very carefully conducted at first. Excess of hydrobromic ether may be used and hydrochloric or hydroiodic ether may be substituted for it. The required product (metaethoxysalicylidenparaphenetidin) having the constitution



separates, on cooling, in large brownish yellow plates. It dissolves with great difficulty in water, but is readily soluble in hot alcohol, benzene, ether, and chloroform, and it dissolves in alkalies, forming a yellow solution. Mineral acids resolve it into paraphenetidin and metaethoxysalicylaldehyde. The melting-point is about 99° centigrade. By employing bromid of methyl instead of bromid of ethyl the corresponding methoxy compound, having the constitution



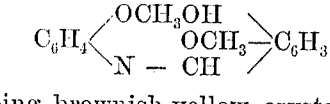
is obtained. This separates in brownish-yellow crystals, which melt at 94° centigrade, and behaves similarly to the ethoxy compound in every respect.

Example 2: Instead of alkylating at a subsequent stage of the operation, alkylated gentisinaldehyde (metaälkyloxysalicylaldehyde) may be condensed with the paraphenetidin. Thus 13.7 kilograms of paraphenetidin may be dissolved in thirty kilograms of spirits of wine and be treated with 15.2 kilograms of metamethoxysalicylaldehyde, the mixture being heated for a considerable period and then allowed to cool, when the required metamethoxy compound crystallizes out. The metaethoxy compound is obtained in a corresponding manner by the application of the metaethoxyaldehyde.

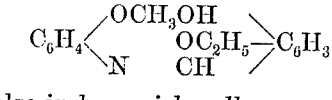
Example 3: The mode of treatment may also be modified by condensing metaälkyloxysalicylaldehyde with paraämidophenol and then alkylating the product. Thus 15.2 kilograms of methamethoxysalicylaldehyde may be dissolved in fifteen kilograms of alcohol and be treated with 10.9 kilograms of paraamidophenol, the alcohol slowly distilled off, and the residue heated for some time at from 120° to 140° centigrade. The product of the reaction is crystallized from alcohol. This product, consisting of metamethoxysalicylidenparaämidophenol, forms reddish-brown prisms, which melt at 161° centigrade. By ethylating in accordance with well-known methods the corresponding phenetidin derivative is obtained. If instead of the metamethoxysalicylaldehyde molecular proportions of the metaethoxysalicylaldehyde be employed, metaethoxysalicylidenparaämidophenol will be obtained, which crystallizes in red needles and melts at 185° centigrade, and this may be converted into the corresponding phenetidin compound by ethylation.

Example 4: In employing paraämidophenol, gentisinaldehyde may also be used to start with, in which case a double alcylation of the resulting condensation product will have to be effected. 13.8 kilograms of gentisinaldehyde should in this case be dissolved in twelve kilograms of alcohol and treated with 10.9 kilograms of paraämidophenol, the process being continued in accordance with the directions given in Example 3. The dioxybenzylidenparaphenetidin thus obtained crystallizes in reddish-yellow needles which melt at 192° centigrade, and is soluble to a limited extent in water and readily soluble in alcohol and ether. This product may be converted into paradioxybenzylidenparaphenetidin by means of one molecule of halogen ether in the usual manner, and then by further treatment with methylhaloid or ethylhaloid there can be obtained therefrom metamethoxysalicylidenparaphenetidin or the corresponding metaethoxy derivative. The last-mentioned derivative may also be obtained directly by ethylating the paradioxybenzylidenparaphenetidin with two molecular proportions or an excess of halogen ether.

The paraänisidin derivatives may be prepared in an analogous manner, the metamethoxysalicylidenparaänisidin having the constitution



and being brownish-yellow crystals with a melting-point of 82° centigrade, while the metaethoxysalicylidenparaänisidin has the constitution



and is also in brownish-yellow crystals with a melting-point of 88° centigrade.

This product is used preferably in the form of powder in wafers or gelatin capsules or

the like, but it can also be stirred into water or other suitable fluid, or made into the form of pills. While the dose depends on the decision of the physician in every special case, it may in general be taken in doses of 0.5 to 1.0 grams several times a day, with corresponding doses to children, and variations in accordance with the views of the practitioner.

Having now particularly described and ascertained the nature of the said invention and in what manner the same is to be performed, I declare that what I claim is—

1. The method substantially as hereinbefore set forth of manufacturing medicinal paraphenetidin compounds, which consists in condensing gentisinaldehyde with paraphenetidin, and in alkylating the product of condensation.

2. The new medicinal crystalline product meta - alkyloxy salicylidenparaphenetidin having the constitution herein set forth, which dissolves with difficulty in water, is readily soluble in alcohol, benzene, ether, chloroform, and alkalies, substantially as described.

In testimony whereof I have signed my name to this specification in the presence of two subscribing witnesses.

HEINRICH BAUM.

Witnesses:
ROBERT H. CLAYTON,
JOHN CRAVEN, Jr.