

UNITED STATES PATENT OFFICE.

WILHELM MAJERT, OF BERLIN, GERMANY, ASSIGNOR TO THE CHEMISCHE
FABRIK AUF ACTIEN, (VORMALS E. SCHERING,) OF SAME PLACE.

PROCESS OF MAKING PIPERAZIN.

SPECIFICATION forming part of Letters Patent No. 471,520, dated March 22, 1892.

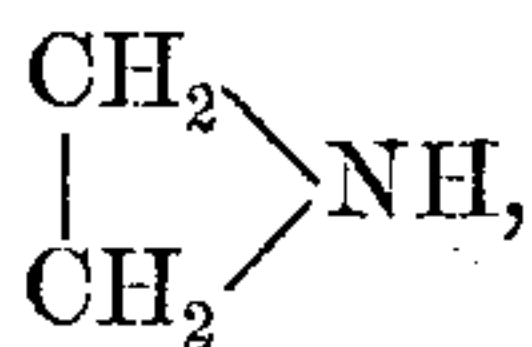
Application filed November 13, 1890. Serial No. 371,356. (No specimens.) Patented in Germany September 14, 1890, No. 60,545; in Belgium September 29, 1890, No. 92,145; in France September 29, 1890, No. 208,521; in England September 29, 1890, No. 15,404; in Norway September 29, 1890, No. 1,910; in Sweden September 29, 1890, No. 2,969; in Italy September 30, 1890, XXIV, 28,393, and LV, 482; in Luxemburg September 30, 1890, No. 1,355; in Spain November 14, 1890, No. 11,280, and in Denmark March 25, 1891.

To all whom it may concern:

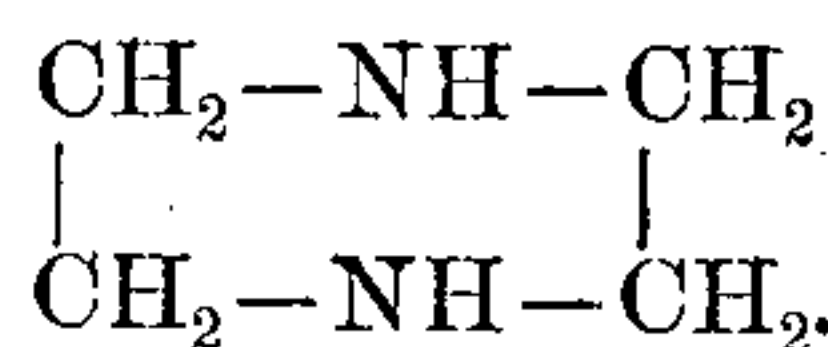
Be it known that I, WILHELM MAJERT, doctor of philosophy and chemist, a subject of the King of Prussia, residing at 10 Madaistr., in Berlin, Prussia, German Empire, have invented certain new and useful Improvements in the Manufacture of Spermine, (Spermin,) (for which Letters Patent have been granted in Belgium, No. 92,145, dated September 29, 1890; in Denmark, dated March 25, 1891; in France, No. 208,521, dated September 29, 1890; in Germany, No. 60,545, dated September 14, 1890; in Great Britain, No. 15,404, dated September 29, 1890; in Italy, Vol. XXIV, No. 28,393, and Vol. LV, No. 482, dated September 30, 1890; in Luxemburg, No. 1,355, dated September 30, 1890; in Norway, No. 1,910, dated September 29, 1890; in Spain, No. 11,280, dated November 14, 1890, and in Sweden No. 2,969, dated September 29, 1890;) and I do hereby declare the following to be a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

The invention consists in a novel process or mode of obtaining pure piperazin having all the properties of pure spermin, and therefore better adapted for therapeutic uses than spermin, which has not heretofore been obtained in a chemically-pure state.

Spermin, as defined by Schneider, is a base he discovered in human and animal sperm, and corresponds to the empirical formula C_2H_5N . Ladenburg (see *Berichte der Deutsche Chemischen Gesellschaft*, Vol. 21, p. 758) obtained by heating to a rather high degree hydrochloride of ethylenediamine obtained a base that not only has the same composition as spermin, but also its chemical properties, and he concluded that spermin and its base were simply ethylenediamine



which in an aqueous solution should be readily condensable to the piperazin,



According to my invention, I find the above formula to correspond with that of piperazin, and a substantially similar chemical can be obtained in a chemically-pure state or substantially so by means of a hydrocarbon compound of piperazin containing at least two aromatic hydrocarbon groups.

Any of the following piperazin hydrocarbon compounds may be used, as diphenyl, dimethyl, ditolyl, dixylyl, dimesityl, dipseudocumyl, or dinaphthylpiperazin, which yields the pure piperazin by treatment with an alkali or an alkaline earth, or both, the said piperazin hydrocarbon compounds containing in each aromatic nucleus at least one, in general therefore at least two, nitro or nitroso groups or two atoms of a haloid thereof—such as chlorine, bromine, or iodine—in the ortho or para position relatively to the nitrogen contained in said compounds.

Morley (see *Berichte der Deutsche Chemischen Gesellschaft*, Vol. 12, p. 1795) states that dinitrosodiethylenediphenyldiamine (dinitrosodiphenylpiperazin) does not undergo any changes when treated with boiling soda-lye. According to my invention and discovery, this is not the case, as dinitrosodiphenylpiperazin, when treated with an alkali or an alkaline earth, or both, is split up into one molecule of piperazin and two molecules of nitrosophenol. My novel process may therefore be carried out as follows: by combining one part, by weight, of any of the piperazin hydrocarbon compounds hereinafter named with from two to four parts, by weight, of a soda or potash lye containing about twenty-five per cent. of the alkali. The mixture is then distilled, the piperazin passing over with the aqueous vapors, hydrochloric or other suitable acid—such as phosphoric or sulphuric acid—being added to the products of distillation to form salts, which are then crystallized out by evaporation. Instead of the solution of an alkali referred to above a

solution of an alkaline earth may be used in the treatment of the hydrocarbon compounds of piperazin, or a solution of an alkali and an alkaline earth may be used with equally good results. When an alkaline earth is used, it is advisable to effect the separation of the piperazin in a closed vessel under pressure and at a rather high temperature. As a solvent for the alkalies or alkaline earths I employ water, and in the use of the less soluble alkaline earths I form a milky lye thereof by holding them in suspension in water to complete the reaction. In this manner I obtain a hydrochloride of a base that has all the properties of spermin or ethylenimine, is substantially chemically pure, and consequently well adapted for therapeutic purposes. The free base has the characteristic smell of sperm, is readily soluble in water but not so readily in soda-lye, and crystallizes out of an aqueous solution in the form of square tablets, that glitter like glass, while the hydrochloride crystallizes out of an alcoholic solution in the form of branched spear-like crystals that contain water of crystallization. When an acid solution of the base, even a very weak solution, is treated with potassium iodide and bismuth, a precipitate or deposit of a pomegranate color is obtained, which under the microscope shows a foliated form. The gold-salt crystallizes into yellow glittering foliated crystals, while the base, when treated with picric acid, forms a yellow precipitate or deposit.

The following are the piperazin hydrocarbon compounds which may be used in my process: Dinitro, dinitroso, trinitro, tetranitro, pentanitro, hexanitro, dichlorine, trichlorine, tetrachlorine, pentachlorine, hexachlorine, dibromine, tribromine, tetrabromine, pentabromine, hexabromine, di-iodine, tri-iodine, tetra-iodine, penta-iodine, hexa-iodine, diphenyl, ditolyl, dixylyl, dimesityl, dipseudocumyl, dinaphtyl, piperazin.

According to Schreiner the spermine obtained by him has the following chemical formula: C_2H_5N ; while piperazin has the formula $C_4H_{10}N_2$, a duplication of the Schreiner formula, the percentages of the compound being the same. The difference between spermine as obtained by Schreiner and piperazin as obtained by the process described are fully set forth in the report of the German Chemi-

cal Society (*Deutsche Chemische Gesellschaft*) of 1891, first half year, page 241, &c., of which the following are the most salient: Spermine has more of the odor of trimethylamine than piperazin. With potassium-iodide and bismuth-iodide in a weak solution of hydrochloric acid an orange-floccular crystalline precipitate is obtained, which under the microscope shows long points in soft feather-like groups. Piperazin, on the contrary, yields a heavy precipitate of a pomegranate red, and shows under the microscope rectangular elongated tablets that can be obtained from a solution not too attenuated, while from an attenuated solution parallel bars grouped in the form of stars are obtained. The phosphate of spermine crystallizes out of water in a pyramidal form with rounded point that collect into ornamental rosettes. The piperazin phosphate, on the contrary, crystallizes out of water in flat rectangular tablets, the corners of which are often blunted diagonally.

Having thus described my invention, the following is what I claim as new therein and desire to secure by Letters Patent:

1. The process of obtaining piperazin from its compounds, which consists in isolating the piperazin in the compound by means of an alkaline solution and separating the piperazin, as set forth.

2. The process of obtaining piperazin from its compounds, which consists in isolating the piperazin in a hydrocarbon compound thereof containing relatively to the nitrogen therein two or more aromatic hydrocarbon groups holding in each nucleus one or more nitro or nitroso groups or an atom or atoms of a haloid thereof in the ortho or para position by means of an alkaline solution, and separating the piperazin, as set forth.

3. The process of obtaining piperazin, which consists in isolating the piperazin in a compound thereof by means of an alkaline solution, distilling off the piperazin into a suitable acid to form salts, and crystallizing out the salts, as set forth.

In testimony whereof I affix my signature in presence of two witnesses.

WILHELM MAJERT.

Witnesses:

CARL FEHLERT,
ADOLF DEMELIUS.