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METHOD OF MANUFACTURING AZO COMPOUND OF CINCHONA ALKALOID

Takeo Takayanagi, Tomokomai-Machi, Yufutsu-Gun, Hokkaido, Japan; vested in the Alien Property Custodian

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The present invention relates to a method of manufacturing anti-bacterial azo compound, which comprises diazotising monocyclic or polycyclic aromatic amine or heterocyclic amine and causing the same to act upon a substance retaining the hydroxyl group of phenol in the quinoline residue of cinchona alkaloid. The object thereof is to obtain new anti-bacterial azo compound of cinchona alkaloid. There has been already proposed a method of manufacturing azo compound which shows anti-bacterial action. Now, according to this invention it has been found that if monocyclic or polycyclic aromatic amine or heterocyclic amine is diazotized in the usual manner and is caused to act upon a substance having the hydroxyl group of phenol in the quinoline nucleus of cinchona alkaloid, it is possible to obtain new antibacterial azo compound. This invention is based on such insight and is characterised by the fact that in the manufacture of anti-bacterial azo compound monocyclic or polycyclic aromatic amine or heterocyclic amine is diazotized and is made to act upon a substance retaining the hydroxyl group of phenol in quinoline residue of cinchona alkaloid. In this case, the cyclic amine to be diazotized for the object of this invention may be to the compounds described in the following two categories:

I. Carbocyclic compounds.
  (a) Monocyclic aromatic compounds.
    (1) Aromatic amines.
      Toluidine, xylidine, phenylene-diamine, amino N.-alkylated aniline, amino N.-acylated aniline and aniline substitution product.
    (2) Amino azo compounds.
      Amino azo benzol, amino azo toluene, diamino azo benzol, diamino azoxy benzol, amino azo benzol sulphonic acid, benzol disazo benzol aniline, amino azo benzol-4′-sulphone amide, amino azo benzol-4′-arsenic acid and amino azo benzol-4′-stibinic acid.
    (3) Amino phenols.
      Amino phenol, amino phenol alkyl ether and amino resorsine.
    (4) Amino benzol sulphonic acid, its sulphon amide and a compound with the hydrogen of the amino group of this sulphon amide substituted by the following atomic groups or a compound with the amino group substituted by cyclic aromatic amine:—
      Amino benzol sulphonic acid, amino benzol sulphon amide, amino benzol sulphon acylamide, amino benzol sulphon alkyl amide, amino benzol sulphon amide benzol sulphon amide, amino benzol sulphon pyridine amide, amino benzol sulphon azo benzol amide and amino benzol sulphon anilide.
    (5) Aromatic carboxylic acid having amino group, its carboxylic acid amide, a compound with the hydrogen of the amide group of this carboxylic acid amide substituted by the following atomic groups or a compound with the amino group substituted by cyclic amine, namely:—
      Amino benzoic acid, amino benzoic acid alkyl, anthra-nilinic acid, amino salicylic acid, amino salicylic acid alkyl ester, amino cinnamic acid, amino benzoic acid amide, amino benzoic acid acyl amide, amino benzoic acid alkyl amide, amino benzoic acid diethyl amide and amino benzoic acid pyridine amide.
    (6) Aromatic amines having a metal-containing atomic group as a substituted group.
      Amino phenyl arsinic acid, amino phenyl oxyarsinic acid, amino phenyl stibinic acid, amino oxyphenyl stibinic acid, amino oxyphenyl arsenic oxide, amino phenyl arsenic oxide, amino thiophenyl, amino oxyphenyl stibine oxide, amino phenyl arsen chlor stibinine, amino phenyl arsen chlor bismuth and amino arsen phenyl stibinic acid.
  b. Polycyclic aromatic amines.
    (1) Amino diphenyls.
      Benzidine, dianisidine, benzidine sulphone, diamino azo diphenyl, diamino diphenyl methane, diamino stilbene, diamino diphenyl amine and diamino carbazol.
    (2) Amino naphthalenes.
      Naphthyl amine, naphthylene diamine, amino naphthol and amino naphthol sulphonic acid.
    (3) Amino anthracenes.
    (4) Amino phenanthrenes.
II. Heterocyclic compounds.
    (1) Amino pyridines.
    (2) Amino quinolines.
    (3) Amino pirazolones.
      Amino antipyrine.
    (4) Amino iso quinolines.
    (5) Amino acridines.
      3-6-diamino. 10-methyl acridinium chloride and 2-ethoxy 6-9-diamino acridine.

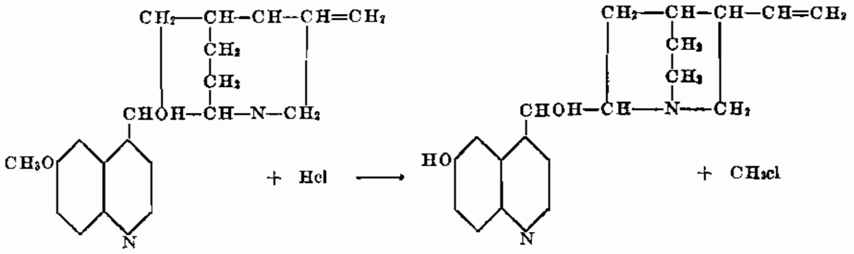
The other nucleus bound to azo bridge, viz. cinchona alkaloid must retain free hydroxyl group in its quinoline nucleus like the natural cupreine. But in the general cinchona alkaloid said hydroxyl group being present as alkyl ether, it is saponified with mineral acid, alkali, or a halogen-supplying substance by heating and after thus liberating the hydroxyl group, is acted upon by the above-mentioned cyclic diazo compound.

For instance, cupreine is bound directly to diazonium and forms azo dyes. Quinine has no such property. But if it is demethylated, apoquinine is produced, while if hydroquinin is demethylated, hydrocupreine is produced. If this is bound to the above cyclic diazonium compound, azo dye is formed quantitatively. The natural cupreine is applicable to the object of this invention as such, but the under-mentioned cinchona alkaloid and its derivatives may be used for the object of this invention after they are saponified and de-alkylated to retain free hydroxyl group:

Quinine, quinidine, quinotoxin, quininone, isoquinine or a compound obtained by dihydratng, hydrohalogenatng, dihalogenating or hydroxylating the vinyl group of the above cinchona alkaloid, a compound with the alcoholic hydroxyl of the above cinchona alkaloid substituted by halogen or a compound obtained by halogenating the quinoline nucleus of the above cinchona alkaloid.

To saponify and de-alkylate cinchona alkaloid and its derivatives, they are saponified by heating directly or in a suitable solvent with mineral acids such as fuming hydrochloric acid, nitric acid, sulphuric acid, hydrobromic acid, etc. or halogen supplying substances such as aluminium chloride, sublimated chloride of iron, tin tetrachloride, antimony pentachloride, phosphorous oxychloride or caustic alkali.

The reaction in this case takes place according to the following formula:



Quinine

Apoquinine

If, when the quinoline residue of cinchona alkaloid has the hydroxyl group of phenol as stated before, the before-mentioned cyclic compound having amino group is bound to it systematically by diazo band in the usual manner as enumerated below, there is obtained the new azo compounds of cinchona alkaloid which show various anti-bacterial actions.

To bind cyclic diazo compound to cinchona alkaloid having hydroxyl group, alkaline reaction is necessary, and the reaction is most satisfactory where the solution becomes weak alkaline or reutral after the completion of the reaction. Further, the temperature of the solution at the time of combination is properly 0° C. or below 5° C. The yield is good in all the cases and is quite quantitative.

The product of the present invention is specially effective against warm blooded animals' (man or animal) pneumonia, suppurative diseases, diseases relating to cold, the diseases caused by spiroworm, gonococcus diseases and other diseases for which quinine is good.

It is known that quinine has a special virtue for protozoally and bacterially caused diseases. This pharmacological action is said to be done by the quinoline nucleus of quinine as the root and the three accessory side chains, namely, methoxyl, vinyl and hydroxyl groups. What is interesting is that it is publicly known to prepare a remedy for pneumonia by merely substituting ethoxyl for the methoxyl of quinine. Also, the change of these three side chains and chemical treatment have been studied deeply.

According to the present invention, a new departure has been made in chemical treatment by introducing various kinds of cyclic amines into the quinoline nucleus of cinchona alkaloid with a new side chain (fourth side chain), diazo bridge N.N, in addition to be known three ones.

The products of this invention are azo dyes of orange deep red, reddish purple and dark green colors and have a bitter taste. They generally have the property of cinchona alkaloid and are hard to dissolve in water, but easily dissoluble in alcohol and other organic solvents. By combining with acids, they form a salt soluble in water fairly well. They generally produce insoluble precipitates by alkaloid reagent.

The following are examples of the manner of manufacturing the new azo compound of cinchona alkaloid by binding cyclic amine systematically to cinchona alkaloid having hydroxyl group according to the classification already described:

Example I

Obtaining anti-bacterial azo compound by causing the diazo compound of aromatic amines to act upon the before-mentioned cinchona alkaloid group.

(1) 10 grams of para-toluidine is dissolved in 30 cubic litres of hydrochloric acid and 100 cubic centimeters of water and the solution is diazotized by 7 grams of sodium nitrite. If it is added to 32 grams of hydro cupreine, 20 grams of caustic soda and 400 litres of water with the addition of ammonia, red crystals of the melting point of 148° C. are obtained, while if para nitro aniline is diazotized and bound to apoquinine, crystals of vermilion color of the melting point of 118° C. are produced.

(2) 14 grams of para amino dimethyl aniline is dissolved in 50 cubic centimeters of concentrated hydrochloric acid and the solution is diazotised by 7 grams of sodium nitrite. Then, it is added to a mixed solution of 32 grams of apoquinine, 35 grams of caustic soda and 500 cubic centimeters of water. From the thus-obtained solution of purple grey color, crystals of the melting point of 156° C. are obtained by ammonia.

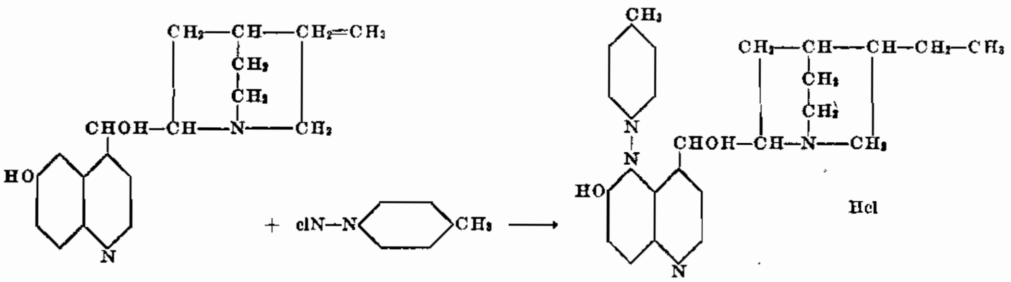
(3) By similarly diazotising 13 grams of ortho chlor aniline and causing it to act upon 32 grams of apoquinine, crystals of orange color of the melting point of 85° C. are obtained.

(4) By diazotising 15 grams of para amino acethanilide in the similar manner and making it act upon 32 grams of apoquinine, red azo compound is obtained.

(5) After adding 15 grams of sodium nitrite to 80 cubic centimeters of concentrated hydrochloric acid and 400 grams of pieces of ice while cooling the latter with a cooling agent, a solution obtained by dissolving 11 grams of paraphenylene diamine in 15 cubic centimeters of concentrated hydrochloric acid and 10 cubic centimeters of water is added. Next, this solution is added to a

mixed solution of 64 grams of hydrocupreine, 60 grams of caustic soda and 400 cubic centimeters of water, and from the thus-obtained dark purple color solution crystals are produced by ammonia.

The following is the formula of the typical reaction in this example:



Example II

If amino azo compound is diazotised and is made to act upon the abovementioned cinchona alkaloid group, an anti-bacterial dye of the property capable of dyeing fat is obtained.

(1) 20 grams of paraamino benzol is dissolved in 50 cubic centimeters of concentrated hydrochloric acid and 400 cubic centimeters of water, and after diazotising the solution by 7 grams of sodium nitrite, it is added to 32 grams of apoquinine, 35 grams of caustic soda and 400 cubic centimeters of water and bound to them after the completion of the reaction, it is acidified by hydrochloric acid and crystals of bloody red color of the melting point of 145° C. are obtained from it by ammonia. In the similar way, crystals of deep red color are obtained from hydrocupreine. If paraamino azo toluol is diazotised in the usual manner and bround to apoquinine, red crystals of the melting point of 128° C. are obtained.

(2) By diazotising orth amino azo toluol and binding it to apoquinine, crystals of carmine red color of the melting point of 160° C. are produced.

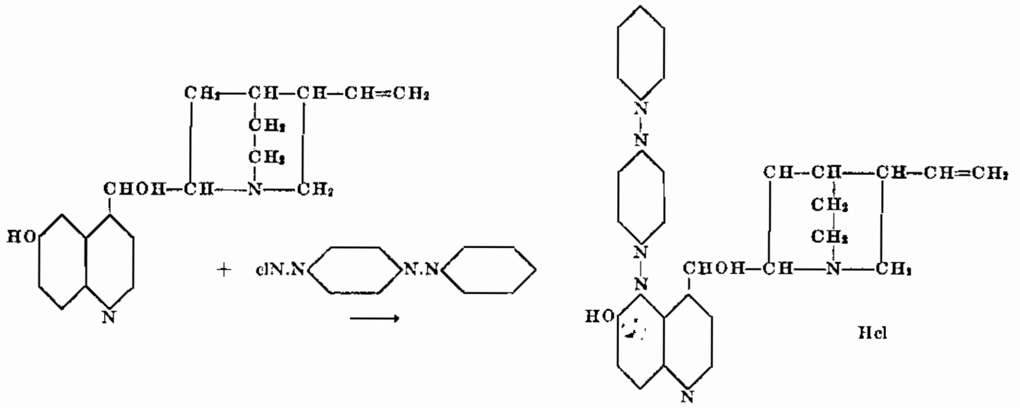
(3) Similarly, if amino azo benzol sulphon amide is diazotized and bound to apoquinine, crystals of dark red color of the melting point of 165° C. are obtained.

(4) In the similar way, if it is bound to hydro cupreine, crystals of deep red color are produced.

(5) If amino azo benzol disulphonic acid is diazotised and bound to hydro cupreine, red crystals are obtained.

Further, if amino azo benzol is diazotised and bound to chlor hydrocupreine, apoquinine chloride, hydrocupreine chloride and hydrocuprine iodide, a dye of deep red color of the property capable of dyeing fat is obtained. Moreover, by binding amino azo benzol to the before-mentioned cinchona alkaloid, azo compound is produced.

The formula of the typical reaction in this example is as follows:



Example III

If a compound obtained by substituting an atomic group for amino benzol sulphonic acid and its sulphon amide and the hydrogen of its amide group or a compound obtained by substituting cyclic aromatic amine for amino group is diazotised and caused to act upon the before-mentioned cinchona alkaloid group, an anti-bacterial azo compound is obtained.

(1) If the above compounds are diazotised by 18 grams of sulphonic acid, 50 cubic centimeters of hydrochloric acid and 7 grams of sodium nitrite in the usual manner and bound to apoquinine, the red crystals of azo compound are produced.

(2) If 20 grams of para amino benzol sulphon amide is dissolved in 50 cubic centimeters of hydrochloric acid and 100 cubic centimeters of water and the solution is diazotised by 7 grams of sodium nitrite and then is caused to act upon 32 grams of hydro cupreine and 35 grams of caustic soda and bound to them, crystals of orange color of the melting point of 192° C. are obtained. Similarly, by binding para amino benzol sulphon amide to apoquinine, crystals of orange color of the melting point of 175° C. can be had.

(3) In the similar manner, if 23 grams of para amino benzol sulphon diethyl amide and dimethyl amide are diazotised and bound to apoquinine, crystals of orange color are obtained.

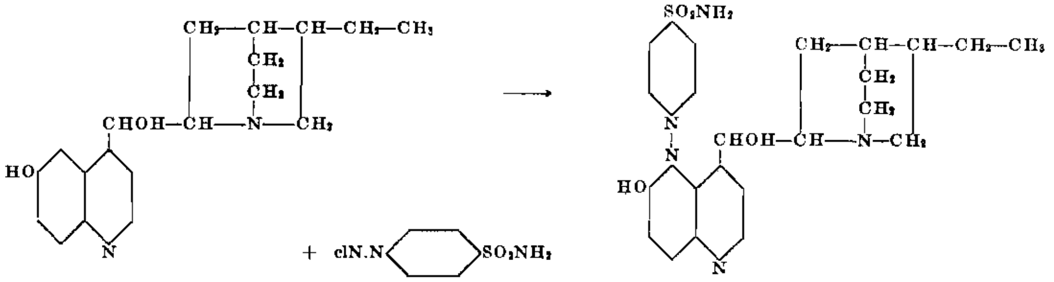
(4) By diazotising 35 grams of para amino benzol sulphon amide benzol sulphon amide in the usual manner and combining it with 30 grams of apoquinine, crystals of orange color of the melting point of 178° C. are got.

(5) Similarly, azo dye of orange color is obtained from hydrocupreine.

Further, if para amino benzol sulphon amide is diazotised by the usual process and bound to chlor hydro-cupreine, apoquinine chloride, hydrocupreine chloride and hydrocupreine iodide, the crystals of azo compound of orange color are obtained.

The product of this invention is not only anti-bacterial as already stated, but also is effective especially against streptococcus.

The following is the formula of the typical reaction in this example:



Hydrocupreine

Hydrocupreine azo benzol Sulphon amide

Example IV

If amino phenols are diazotised and made to act upon the before-mentioned cinchona alkaloid group, it is possible to obtain anti-bacterial azo compound.

(1) If 10 grams of para amino phenol, 30 cubic centimeters of hydrochloric acid and 100 cubic centimeters of water are diazotised by 7 grams of sodium nitrite and are added and bound to 32 grams of hydro cupreine, 21 grams of caustic soda and 100 cubic centimeters of water, purple grey crystals of the melting point of 178° C. are obtained.

(2) Similarly, by binding 12 grams of 5-amino resorcine with hydrocupreine, purple grey crystals are obtained.

Example V

If aromatic carboxylic acid having amino group, its carboxylic acid amide and a compound with the hydrogen of its amide group substituted by an atomic group or a compound with the amino group substituted by cyclic amine are diazotised and caused to act upon the above-stated cinchona alkaloid group, anti-bacterial azo compound is produced.

(1) If 17 grams of para amino benzoic acid ethyl is diazotised by 7 grams of sodium nitrite and bound to 32 grams of apoquinine, crystals of dark brown color of the melting point of 210° C. are obtained.

(2) In the similar manner, if 15 grams of para amino benzoic acid is bound to hydro cupreine, reddish brown crystals are obtained.

(3) By diazotising 15 grams of 5-amino salicylic acid and making it act upon apoquinine, crystals of dark pink color of the melting point of 188° C. are obtained.

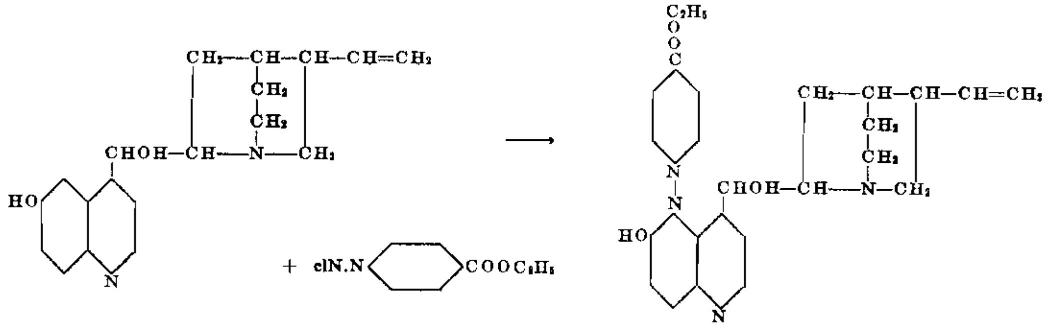
(4) Similarly, if 17 grams of para amino cinnamic acid is diazotised and bound to hydro cupreine, brown crystals are obtained.

(5) If 17 grams of para amino benzoic acid amide is diazotised and bound to apoquinine, crystals of reddish brown color arc produced.

(6) If para amino benzoic acid diethyl amide is diazotised and caused to act upon hydrocupreine, crystals of reddish brown color are obtained.

(7) If 17 grams of anthranilic acid is diazotised and bound to apoquinine, crystals of deep orange color of the melting point of 187° C. are obtained.

The following is the formula of the typical reaction in this example:



Apoquinine

Apoquinine azo benzol carboxylic acid ethyl

Example VI

If aromatic amines having a metal-containing atomic group as the group to be substituted are diazotised and bound to the before-mentioned cinchona alkaloid group, anti-bacterial azo compound is obtained.

The product of this invention has a special virtue for the diseases caused by spiro-worm.

(1) If 21 grams of para amino phenyl arsinic acid and 30 cubic centimeters of hydrochloric acid are diazotised by 7 grams of sodium nitrite and added and bound to a solution consisting of 32 grams of apoquinine and 21 grams of caustic soda, crystals of orange color of the melting point of 187° C. are produced.

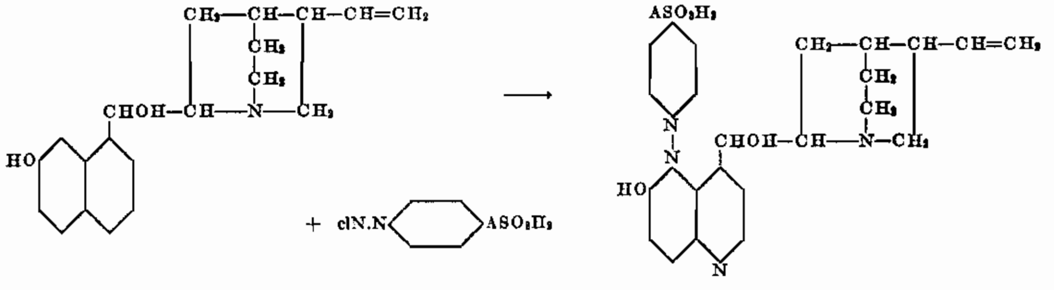
(2) If para amino phenyl arsine is diazotised in the usual manner and bound to apoquinine, crystals of reddish orange brown color of the melting point of 225–230° C. are obtained.

(3) By diazotising 3-amino-4-oxyphenyl 1-arsinic acid and binding it to hydro cupreine, crystals of reddish orange color of the melting point of 215° C. are obtained. In the similar way, if it is bound to apoquinine, crystals of the melting point of 174° C. are obtained.

(4) If 4-amino azo benzol 4-arsinic acid is diazotised in the usual manner and bound to apoquinine, crystals of orange color of the melting point of 165° C. are obtained.

Further, if 1 molecular weight of amino oxyphenyl arsen oxide, amino phenyl arsen oxide, amino thio-phenol, amino phenyl stibinic acid, amino oxyphenyl stibinic acid, amino oxyphenyl stibine oxide, amino phenyl arseno chlor-stibine, amino phenyl arseno chlor-bismuth and amino arsen phenyl stibinic acid are diazotised by the ordinary process and caused to act upon the before-mentioned cinchona alkaloids, for instance, hydrocupreine, anti-bacterial azo compound of orange color is obtained.

The formula of the typical reaction in this example is as follows:



Apoquinine

Apoquinine azo phenyl arsenic acid

Example VII

If cyclic amine belonging to amino diphenyls, amino naphthalenes, amino anthracenes, amino phenanthranes, amino pyridines, amino quinolines, amino pyrazolones, amino iso quinolines and amino acridines is diazotised and made to act upon the before-mentioned cinchona alkaloid and its derivative, antibacterial azo compound is obtained.

(1) If 20 grams of benzidine, 15 grams of sodium nitrite and 50 cubic centimeters of hydrochloric acid are diazotised in the usual manner and added to a solution consisting of 64 grams of apoquinine and 35 grams of caustic soda and combined with it, crystals of reddish purple color of the melting point of 185–190° C. are produced. In the similar way, from hydrocupreine is obtained crystals of dark reddish purple color of the melting point of above 200° C.

(2) 25 grams of ortho dianisidine, 15 grams of sodium nitrite and 50 cubic centimeters of hydrochloric acid are diazotised by the ordinary process and added to a solution consisting of 64 grams of apoquinine and 35 grams of caustic soda and combined with it, crystals of reddish purple color are obtained.

(3) If 20 grams of para amino diphenyl amine, 7 grams of sodium nitrite and 50 cubic centimeters of hydrochloric acid are diazotised in the usual manner and bound to apoquinine, crystals of darkish purple color of the melting point of 158° C. are obtained.

(4) If 15 grams of β-naphthyl amine, 7 grams of sodium nitrite and 50 cubic centimeters of hydrochloric acid are diazotised and added to a solution consisting of 32 grams of apoquinine and 35 grams of caustic soda and combined with it, crystals of light dark red color of the melting point of 128° C. are obtained.

(5) Similarly, from α-naphthyl amine is obtained crystals of dark red color of the melting point of 128° C.

(6) If 25 grams of 1-amino-2-naphthol-4-sulphonic acid is diazotised in the usual manner and made to act upon 32 grams of apoquinine, crystals of dark grey color of the melting point of 172° C. are produced.

(7) By diazotising 23 grams of naphthionic acid in the usual way and combining it with apoquinine, crystals of the melting point of above 200° C. are obtained.

(8) If 20 grams of β-nitronaphthyl amine is diazotised in the usual manner and combined with 32 grams of apoquinine, crystals of light bluish green color of the melting point of 165° C. are obtained.

(9) By diazotising 23 grams of β-amino anthraquinone in the usual way and binding it with 32 grams of apoquinine, crystals of greyish orange color of the melting point of 161° C. are obtained.

(10) If 10 grams of α-amino pyridine is diazotised by the usual process and caused to act upon 32 grams of apoquinine, crystals of greyish red color of the melting point of 157° C. are obtained.

(11) If 18 grams of amino antipyrine is diazotised and made to act upon hydro cupreine, azo compound of dark grey color is produced.

(12) If 15 grams of amino quinoline and amino iso quinoline are diazotised in the usual way and caused to act upon 32 grams of hydro cupreine, brown crystals are obtained.

(13) If 27 grams of 3,6 diamino 10 methyl acridinium chloride, 50 cubic centimeters of hydrochloric acid and 7 grams of sodium nitrite are diazotised and made to act upon 32 grams of hydrocupreine, crystals of dark purple color of the melting point of above 200° C. are obtained.

(14) Similarly, from apoquinine are obtained crystals of the melting point of above 200° C.

(15) If 27 grams of 2. ethoxy 6.9 diamino acridine is diazotised in the usual way and made to act upon 32 grams of hydrocupreine, crystals of dark purple color of the melting point of above 200° C. are produced.

(16) In the similar way, from apoquinine are obtained crystals of the melting point of above 200° C.

TAKEO TAKAYANAGI.