CHLOROQUINE MANUFACTURE

Bottling Aralen Tablets

A Staff-Industry Collaborative Report . . .

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in collaboration with

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THE cost to society of malaria with its sustained annual toll of human lives has caused it to be ranked as one of the foremost medical problems of our civilization. There was no known remedy for the disease before the discovery of the New World. The use of cinchona bark as a specific remedy for malaria began in the sixteenth century when Peru began exporting it to Europe (*12*). The demand for cinchona bark was so great that accessible South American forests were soon stripped, and the British and Dutch initiated production in the East Indies. The British failed under the burden of over-production, while the Dutch succeeded.

By 1933 the Dutch East Indies annual production of cinchona bark was about 22,000,000 pounds (*12*), or more than 80% of the world's production. The procurement of sufficient quinine for antimalarial use was a serious problem for many countries. However, the United States was able to maintain an ample supply by importation from the East Indies. The possibility of a Japanese monopoly of cinchona bark in the event of war was realized here and was reflected in the increase of imports by the United States from the Netherlands Indies from less than 1,500,000 pounds to almost 5,500,000 pounds in 1940 (*21*). Soon after its entry into the war, Japan seized the natural sources of about 90% of all quinine produced, leaving the rest of the world dependent on other resources for combatting malaria. At that time the annual world production of quinine was about 2,000,000 pounds, whereas the production of synthetic materials for antimalarial use was comparatively small. Germany was the only country which had shown concerted attention to the synthetic antimalarial problem previous to the war (*18*).

[1] The businesses formerly conducted by Winthrop Chemical Company, Inc., and Frederick Stearns & Company are now owned by Winthrop-Stearns Inc.

THE AMERICAN MALARIA PROBLEM—WORLD WAR II

One of the greatest problems facing the medical division of the armed forces during World War II was the establishment of a program for the chemoprophylaxis and chemotherapy of malaria. The high incidence of malaria in many of the battle areas influenced the granting of a high priority to the antimalarial program. Despite the early recognition of the problem and considerable success in the development of agents and methods for combatting it, there were about 500,000 cases of malaria in the United States armed forces during the war (*8*).

At the time of the American entry into the war, there was available for the treatment and suppression of malaria, a drug, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine dihydrochloride, given the name quinacrine hydrochloride; this is produced by Winthrop-Stearns Inc., as Atabrine dihydrochloride. The method of manufacture for this compound was worked out in detail (*18*) and the Winthrop Chemical Company had already embarked on an expanded production schedule. At government request this was increased further and the manufacturing procedures developed at the Winthrop Chemical Company were given to other large pharmaceutical manufacturers, who also prepared the drug. By this means production was made to meet the armed forces' requirements and it became possible to institute a prophylactic campaign for the control of malaria in civilian population as well as in the armed forces; these procedures minimized the possible sources of reinfection.

During the prophylactic compaign some disadvantages associated with the use of quinacrine were uncovered. These included side effects characterized by nausea, vomiting, and diarrhea and the appearance of a yellow color in the skin or eyes of some subjects receiving repeated doses. It was shown subsequently that these side effects are not permanent reactions. It was known at that time that the yellow color receded and disappeared from the skin or eyes when the drug was withdrawn. However, these side effects and the propaganda, spread by the Japanese (that the drug rendered men sterile), made troops reluctant to take it and it was necessary to issue orders for rigidly controlled administration of the drug. It was found that proper administration of quinacrine reduced markedly the incidence of malaria.

An antimalarial program under government supervision was undertaken with the object of preparing more effective antimalarial drugs and determining the proper method for their administration. It was desired that the new drugs be more effective than quinacrine, produce fewer, if any, side effects, and preferably be colorless solids. The work was coordinated by the Office of Scientific Research and Development (OSRD) and several associated groups. A thorough description of the organization of the participating groups is contained in the monograph edited by Wiselogle (*22*), and the OSRD program has been summarized by Elderfield (*10*).

The OSRD assigned projects on the synthesis of compounds to universities and to chemical and pharmaceutical manufacturers. With the realization of the necessity for rapid screening and testing of the great number of compounds to come from these projects, there was developed an efficient program directed toward this end. During the period 1941 to 1946, approximately 14,000 materials were screened, including pure chemical compounds and natural products. About one third of these were synthesized especially for the OSRD program. Approximately seventy groups showed antimalarial action and further investigation narrowed the field to four or five chemical groups (*10*). The highly successful application of American scientific ingenuity by this group of workers, which led to the adoption of the effective drugs now in use, is deserving of more recognition than has generally been given.

One of the compounds submitted early by the Winthrop Chemical Company and reported by the OSRD to have good antimalarial action was 3-methyl-4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline, which was called Sontochin and was designated by the OSRD as SN-183. Strong interest in this compound and others in the same series did not develop until Sontochin tablets which were found in the possession of German prisoners captured in Tunisia, were identified in laboratories in the United States. Then, for security reasons, the original SN-183 was changed to SN-6911.

Interest in compounds of the Sontochin type was revived and one of the related compounds suggested for testing was 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinoline. A sample was submitted by Winthrop and it was assigned the number SN-7618. Later it was named chloroquine and is now manufactured by Winthrop-Stearns Inc., as Aralen.

Both Sontochin and chloroquine were first made by the German chemists Andersag, Breitner, and Jung (*2*, *3*). Apparently both had been tested by German workers and they had concluded that Sontochin was the more effective drug (*7*), so it was the antimalarial of German choice for field use. However, the screening and testing procedures developed under the OSRD showed SN-7618 (chloroquine) to be superior to Sontochin. It was a better prophylactic, produced more effective remedies with fewer side effects, and was a better suppressive—that is, allowed fewer relapses.

Studies by Pullman *et al.* (*17*), comparing chloroquine with quinacrine and quinine, have shown that chloroquine cleared the blood of parasites most rapidly and that while the relapse rate was about the same for the strain of vivax malaria parasite studied, the latent period following therapy and preceding relapse was greatest for chloroquine. Chloroquine was also shown superior to quinacrine and quinine for treatment of acute attacks of vivax malaria. Berliner and co-workers (*6*) compared a number of 4-aminoquinolines and reported chloroquine superior in that it has a margin of efficacy because of its greater activity and consistency. The findings of the OSRD have been substantiated and amplified further by the work done in 1946 by Berberian and Dennis (*4*) who demonstrated and reported the results of their field studies in Lebanon with chloroquine. They found it highly satisfactory for the control of clinical attacks of malaria caused by any one of the three common species of plasmodia. A 10-tablet (2.5 grams) regimen of chloroquine diphosphate, given in 3 days, cured 53 proved cases of *Plasmodium falciparum* malaria without relapse. It was found that when therapy of vivax malaria was followed by weekly suppressive medication for 4 to 6 months, the relapse rate was greatly reduced; no relapses were observed following the recommended dosage regimen. A single weekly dose of chloroquine diphosphate (0.5 gram) taken regularly throughout malaria transmission season was adequate to suppress malaria. Chloroquine diphosphate was found dispensable with impunity to infants and during the course of pregnancy.

Studies by Alving *et al.* (*1*) have indicated chloroquine to be a safe antimalarial in recommended doses.

Berberian and Dennis (*5*) also have described the high efficacy or prolonged chloroquine diphosphate treatment on malarial splenomegaly. The weekly administration of suppressive doses (0.5 gram) of chloroquine diphosphate, without recourse to antimosquito measures, reduced the splenic index in Saideh, a village in Lebanon, from 59 to 6 within an average treatment period of 26 weeks.

As a result of the OSRD findings, Winthrop Chemical Company began gearing production facilities to plant scale manufacture of chloroquine diphosphate (Aralen diphosphate) to be furnished to the American armed forces. While the patent literature indicated a method of synthesis, it furnished few details for the preparation of the necessary intermediates. A research program was instituted which led to the development by Surrey and Hammer (*20*) of a synthesis for Aralen. Other methods of synthesis developed under contract with the OSRD were those by Price and Roberts. The first of these (*15*) involved the use

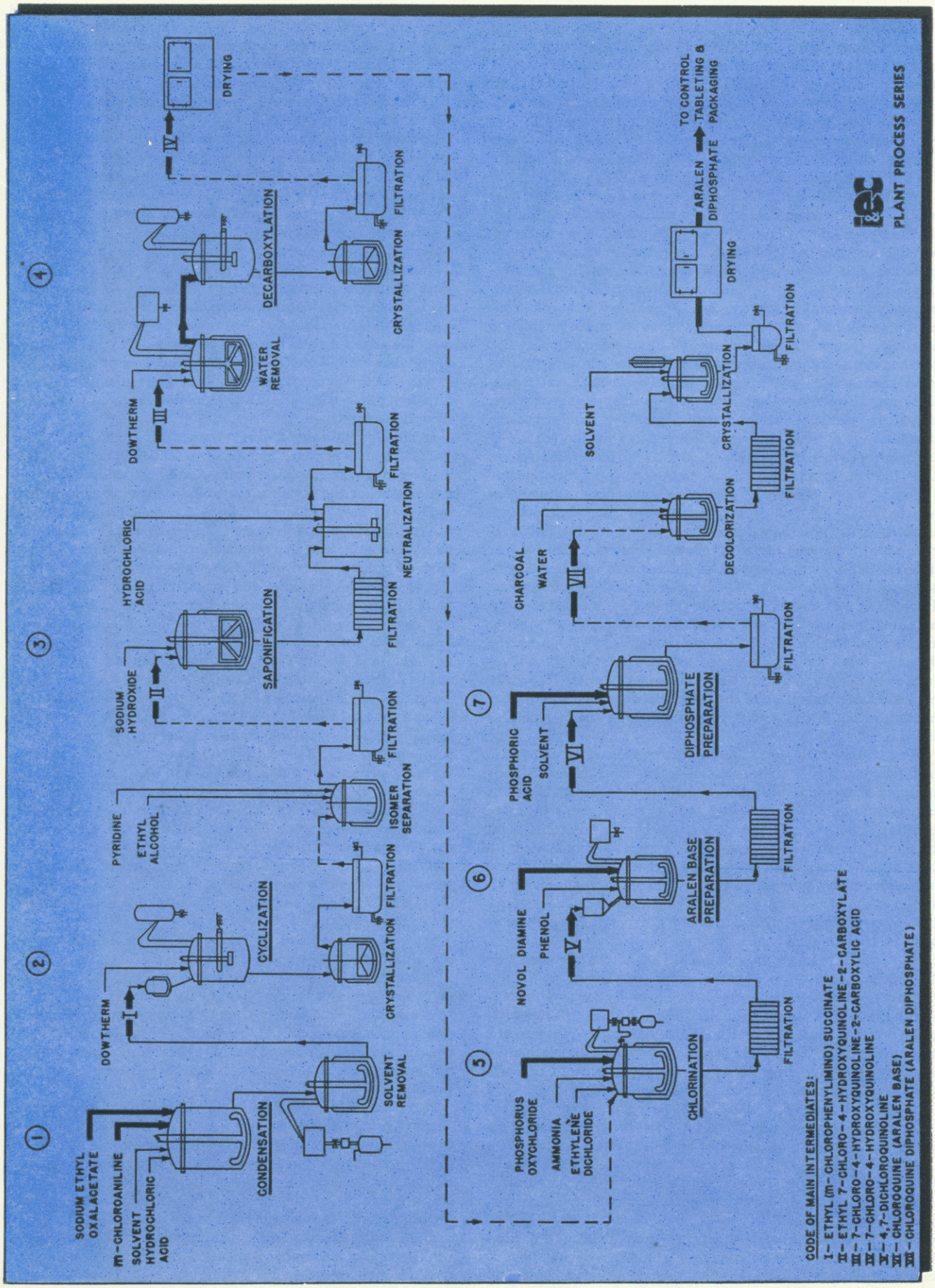


Figure 1. Process Flow Sheet

of ethoxymethylenemalonic ester and became known as the EMME synthesis. The other method (*16*) used *bis*(*m*-chlorophenyl)formamide as an intermediate. These methods and others were studied and the initial method herein described (*2, 3, 20*) was chosen for application on a production scale. Process and development work led to a simplification of the process which made it practical for plant manufacturing techniques.

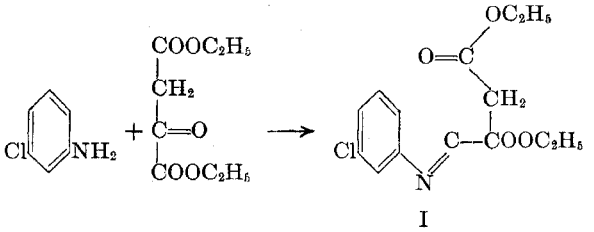
Under the pressure of wartime conditions it was imperative that production of this drug proceed at the greatest possible speed to supply the OSRD with sufficient material for controlled clinical tests. Regardless of the economics involved, it was necessary to begin with the research laboratory methods as guides for plant manufacture and to carry on development to simplify and improve the process as plant production proceeded. Operations could not await the design and fabrication of special equipment: production and development had to follow the direction dictated by the available plant equipment, in August 1944, which was pressed into immediate service.

During the early development period, assistance was contributed to the relief of pressure of immediate demands for clinical testing by the collaborative manufacture of chloroquine by batch laboratory methods in a number of universities. Dichloroquinoline was made at Columbia University, University of Illinois, Northwestern University, and the University of Virginia. The side chain was attached to the combined batches at the University of Maryland and the product was delivered to Winthrop for tableting. In addition to this a quantity of dichloroquinoline was manufactured by the Price method (*15*) by the National Aniline Division of the Allied Chemical and Dye Corporation which converted some of this to chloroquine.

A point of particular interest in this phase of the work is the specific system employed for the coordination of plant production and process development. At Winthrop-Stearns Inc., each manufacturing division has its own associated process development laboratory under the head of the division. Thus each process laboratory is devoted entirely to a specific and unified operation. The results of progress in both plant and laboratory are coordinated immediately and continuously through the division head; there is no great time lag between an improvement found in the laboratory and its practical application in the plant. The results of this system were particularly gratifying in the speed with which the Aralen process was carried from research laboratory through process development to a successful plant operation.

PROCESS DEVELOPMENT

Ethyl(*m*-chlorophenylimino)succinate (I). Step 1 of the synthesis was carried out in the laboratory by adding ethyl sodium oxalacetate to a cold acetic acid solution of 1.6 molar parts of *m*-chloroaniline, followed, after 16 to 20 hours of stirring, by neutralization with sodium hydroxide, then ether extraction. The product was recovered from the ether solution by distillation after removing unreacted *m*-chloroaniline by extraction with dilute hydrochloric acid. Low and erratic yields resulted from the factory application of this method. A detailed stepwise analytical control system revealed that the succinate was formed in good yield but decomposed on further processing, indicating that it was not sufficiently stable to withstand factory manipulation under these conditions. It has been shown by Surrey and Cutler (*19*) that the presence of *m*-chloroaniline in the succinate had to be avoided because a complex was formed which interfered with subsequent reactions.

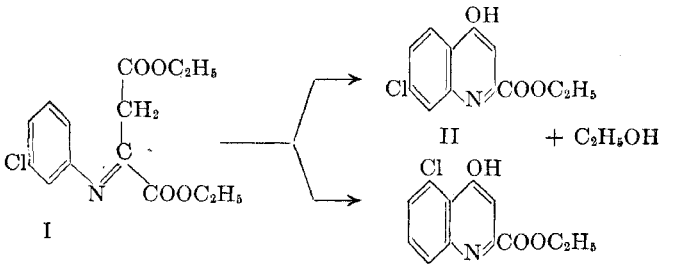


I

Neither reduction of the proportion of *m*-chloroaniline nor the removal of the excess from a solvent solution of product as a solid sulfate proved a satisfactorily sufficient step to remedy the problem on a plant scale.

Optimum conditions were achieved by the extraction of ethyl oxalacetate from its acidified sodium salt with a solvent and using this solution for reaction with *m*-chloroaniline under rigidly controlled conditions. The necessary speed and mildness were achieved and a good yield and quality were realized. With the equipment available it was then possible to manufacture 9000 pounds of the intermediate per month, enough to produce 2500 pounds of Aralen.

Ethyl-7-chloro-4-hydroxyquinoline-2-carboxylate (II). In step 2 the succinate is cyclized. Two isomers result, with the chlorine in the 5- as well as the 7-position.



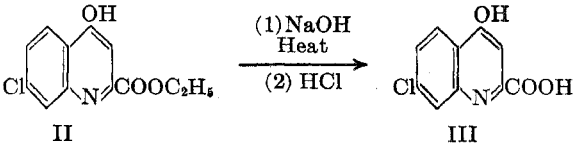
They are formed in nearly equal proportions and must be separated, as only the 7-isomer is useful in this process.

In the laboratory, the succinate was added to mineral oil at 250° C. and stirred until nearly the theoretical amount of alcohol distilled off. On cooling the mixture of isomers of the cyclized product solidified. The mixture was washed with petroleum ether to remove the oil, then dissolved in 4 parts of hot pyridine, followed by the addition of 4 parts of ethyl alcohol. On cooling to room temperature only the desired isomer crystallized and it was collected by filtration.

In the plant it was found that mineral oil had to be discarded because of its low flash point and tendency to carbonize. The substitution of another oil of higher flash point presented difficulties in that it was so viscous as to require preheating for handling and was difficult to free from the crystallized product. Fortunately, it was learned (*11*) that Dowtherm could be substituted for mineral oil in a high temperature reaction later in the process and the application of this idea to the cyclization reaction proved highly successful in solving the problem at hand.

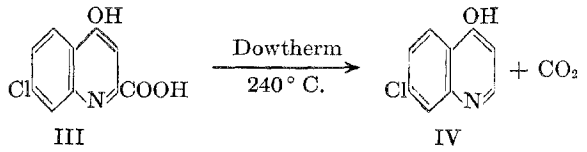
The isomer mixture separated from the Dowtherm on cooling as well as it did from the mineral oil originally recommended. After washing out the Dowtherm with acetone, the isomer mixture was separated as described above.

7-Chloro-4-hydroxyquinoline-2-carboxylic Acid (III). The third step in the synthesis was readily adapted to plant scale with virtually no modifications of the laboratory procedure.



The product of the previous procedure was hydrolyzed with aqueous sodium hydroxide solution in good yields to give the acid (III), which was isolated by treating the hydrolysis solution with hydrochloric acid followed by simple filtration.

7-Chloro-4-hydroxyquinoline (IV). Step 4, decarboxylation



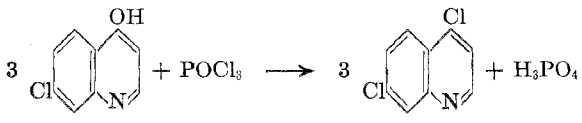
III IV

had been effected in the laboratory by simply adding the crude acid to mineral oil, with stirring, at 270° C. and stirring for 5 minutes at that temperature. On cooling the solid decarboxylated product was filtered off and washed with petroleum ether.

Once again mineral oil had to be discarded in the plant. Dowtherm was substituted. The rapid evolution of carbon dioxide produced excessive foaming and offered a potential danger of overflow from the reaction vessel. This was overcome by adding the acid to the Dowtherm at room temperature and raising the temperature slowly through the critical stage. Decarboxylation begins at 195° C. By raising the temperature at the rate of 1° per minute to 240° C., the evolution of carbon dioxide is steady and can be maintained under control. Maintenance at that temperature for 40 to 45 minutes finishes the reaction.

Control tests on the plant product prepared in this manner showed traces of acid (III) in about 50% of the product batches. Its removal with bicarbonate solution added an extra step with a consequent increase in cost. Longer heating periods or higher temperatures caused a darkening in the color and a decrease in yield of the product. Large and varied particle size, produced in drying and grinding the acid was a responsible factor for this difficulty. To solve the problem the crude wet acid was mixed with Dowtherm and the water distilled off in an agitated steam-jacketed kettle attached to a condenser; after this the slurry was blown directly into the decarboxylation kettle. In this way the particle size originally formed by the precipitation of the free acid was retained and the decarboxylation proceeded to completion without damage to the product.

4,7-Dichloroquinoline (V). Replacement of the hydroxyl group with chlorine, step 5, was originally accomplished in the laboratory by refluxing 7-chloro-4-hydroxyquinoline with an excess of phosphorus oxychloride for 2 hours, distilling off most of the phosphorus oxychloride in vacuum, and pouring the residue into ice



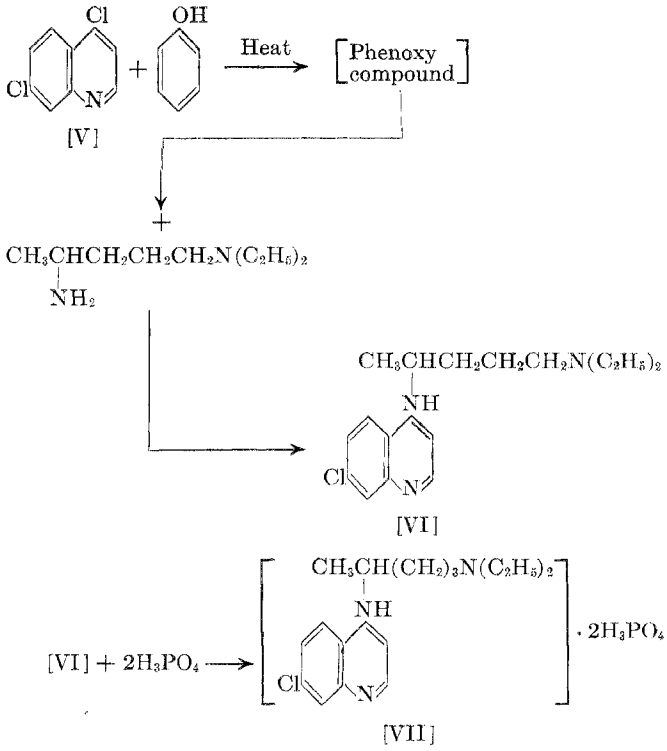
IV V

water. Alkalization with ammonium hydroxide precipitated the product, which was taken up in methylene chloride. The dichloroquinoline was then obtained by vacuum distillation.

This procedure had obvious disadvantages for plant application. Use of an excess of phosphorus oxychloride as a solvent not only increased costs, but its distillation in vacuo corroded equipment and its destruction, in large quantities, with water is a reaction to be avoided in plant operations. It was desirable to avoid the excessive operations involved in precipitation of the product, then redissolving in a large quantity of solvent preparatory to distillation. Dichloroquinoline sublimes easily and vacuum distillation with the simple equipment necessary in a large scale operation promised difficulties.

Adaptation of a method of chlorination used in Atabrine manufacture allowed reduction of the amount of phosphorus oxychloride used, eliminating the necessity for its recovery by vacuum distillation and the destruction of large amounts at the end of the reaction. This was effected by the use of ethylene dichloride as a solvent for the reaction and continuation of its use as the extractant for the product. This procedure allowed the entire step to be carried out in a single kettle and also allowed milder reaction conditions. Furthermore, the isolation of the 4,7-dichloroquinoline was not carried out; thus the possibility of dermatitis resulting from handling of the irritating compound was avoided.

Aralen[7-Chloro-4-(4-dimethylamino-1-methylbutylamino)-quinoline diphosphate] (VII). The final step in the process combines reactions 6 and 7, the synthesis of the Aralen base (VI) and preparation of the diphosphate (VII).



Chloroquine diphosphate
(Aralen diphosphate)

In the laboratory procedure, 0.5 mole of 4,7-dichloroquinoline is heated, with stirring, with 1 mole of novol diamine (N^1,N^1-diethyl-1,4-pentanediamine) for 3 to 7 hours at 160° to 170°, until test indicates completion. The mixture is dissolved in acetic acid solution then made alkaline with sodium hydroxide and the separated oil extracted with ether. The ether and unreacted novol diamine are removed by distillation and vacuum distillation. The crude base is dissolved in methanol and phosphoric acid–methanol solution is added. On chilling, the product solidifies and is collected by filtration and purified by recrystallization in water-methanol–isopropyl alcohol mixture.

The use of excess novol diamine constituted an excessive drain on the stocks of this important intermediate for Atabrine and its recovery entailed considerable time and labor. The conditions of the initial condensation required a temperature just above that obtained with the available steam supply.

In investigations directed to the relief of the raw materials problem, knowledge developed in the production of Atabrine was again drawn upon. It had been found there that a phenoxy derivative of the chloroacridine was so much more reactive than the chloroacridine itself that mole for mole reaction with the aliphatic amine could be effected completely at a considerably lower temperature. Likewise, it was found that when 4,7-dichloroquinoline was first treated with molten phenol, then with novol diamine, the desired reaction proceeded at a temperature attainable with the available steam supply and went to completion in the presence of only slightly more than one mole of the aliphatic amine.

With the recovery of novol diamine no longer necessary, the Aralen base need not be isolated before preparing the phosphate.

As a result a method was developed for the direct formation of the phosphate in the original reaction mixture and its isolation therefrom.

A problem arose in connection with the solvents used in purification. Not only was there objection to the cost of water-methanol-isopropyl alcohol solvent, but also to the cost of recovery of its constituents.

Because of the economic necessity for the reclamation of both the Aralen and the solvents from the mother liquors from filtration, it was necessary to devise a method of recovery. This was made complicated by the fact that the three original solvent components, water, methanol, and isopropyl alcohol, as well as acetone from the wash, were present. In addition to these plant objections the control laboratory objected to the presence of methanol in the final product as alcohol of crystallization. A compound of this constitution is described in the literature (*9*).

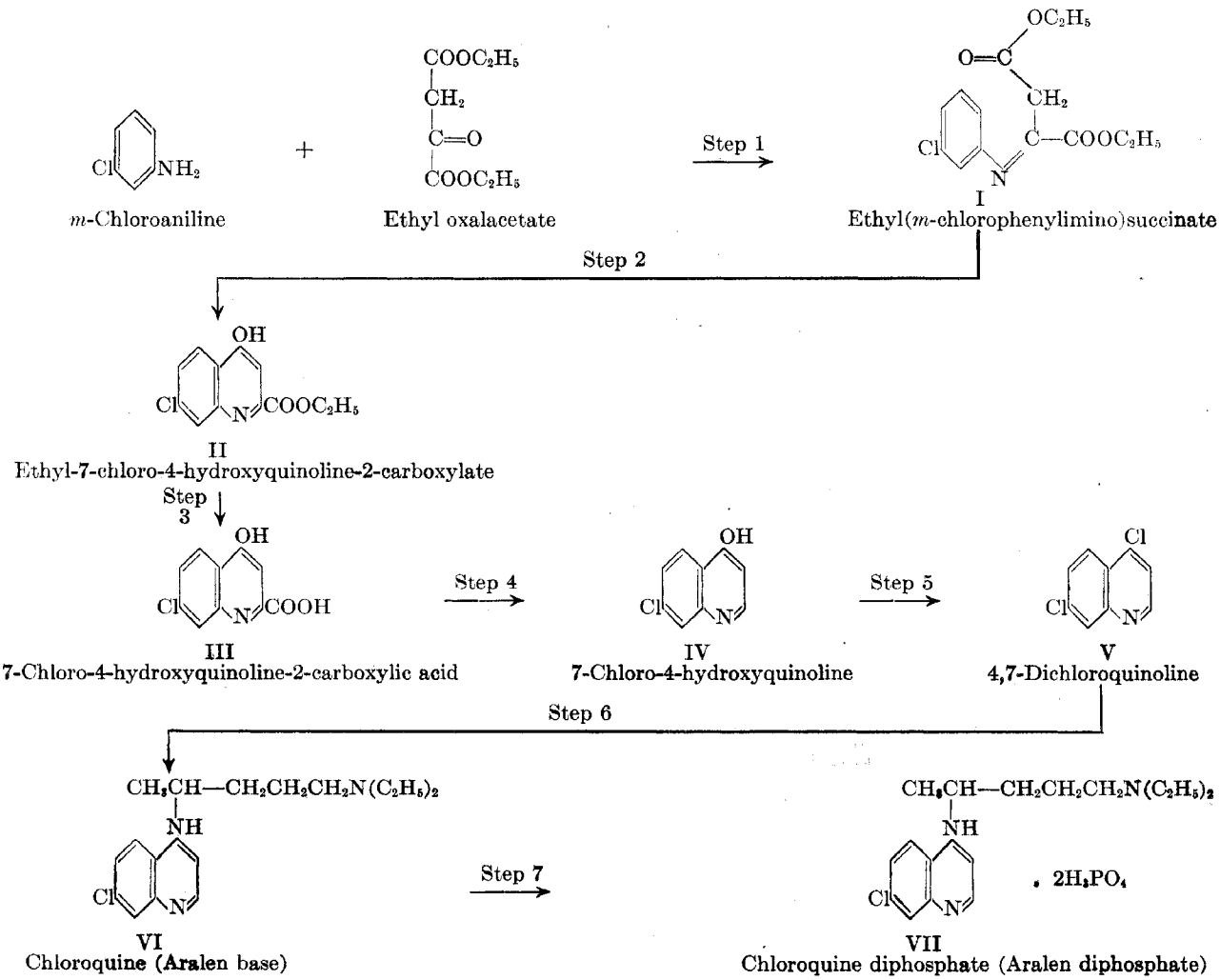
A simplified system of purification was devised. The crude Aralen was dissolved in water, treated with charcoal and filtered. A selected solvent was added at reflux temperature and cooling was regulated with extreme care to obtain the proper crystalline structure for satisfactory filtration. It was indicated in early development work that chloroquine exists in dimorphic forms. The easily filtered macrocrystalline form melts at 194° to 196° C. The microcrystalline form melts at 224° to 226° C. This observation was confirmed by Mason (*13*). The crystalline form can be influenced by rate of crystallization. This fact is used in the process described to secure the macrocrystalline form.

PLANT PROCESS

Condensation. To an aqueous solution of 240 pounds of sodium ethyl oxalacetate in a 500-gallon glass-lined kettle with an anchor stirrer, there is added an excess of aqueous hydrochloric acid. Ice is added to maintain moderate temperature. On completion of its liberation, the ethyl oxalacetate is extracted by vigorous agitation with solvent. The solvent layer is permitted to separate on standing and the aqueous layer is drained off. To the separated solvent layer is added the calculated amount of *m*-chloroaniline and the mixture is stirred at room temperature. After the relatively rapid reaction is finished, the solvent is distilled off, leaving 520 pounds of product which is forced, by means of compressed air, through a pipe to the drop tank connected to the cyclization kettle.

Cyclization. The cyclization kettle is a closed, unjacketed, 50-gallon carbon steel kettle, lagged with asbestos and equipped with a turbine agitator. Four 4-kw. stainless steel–sheathed immersion heaters protrude into the reaction chamber. A steam-jacketed steel drop tank is attached to the top of the vessel, as is a distillation column leading to a 200-gallon steel flash tank in which Dowtherm vapors condense while alcohol vapors are vented to the outdoors through a lead-off pipe.

Five parts of Dowtherm are heated to 250° C. in the reaction kettle and 1 part of the succinate product from the previous step is added from the drop tank at about 80° C. in a steady



Synthesis of Aralen Diphosphate Showing Intermediates

stream and at a rate to avoid a temperature drop to below 235° C. Heating and stirring are continued until alcohol is no longer distilled off. The solution is then piped by gravity to a water-jacketed, iron cooling kettle, with a paddle stirrer. Here it is cooled to about 70° C. and blown with compressed air to a wooden Nutsche suction filter covered with canvas duck where the solidified mixture of 5-chloro and 7-chloro isomers is filtered off. The solid is washed with acetone. The yield is about 475 pounds.

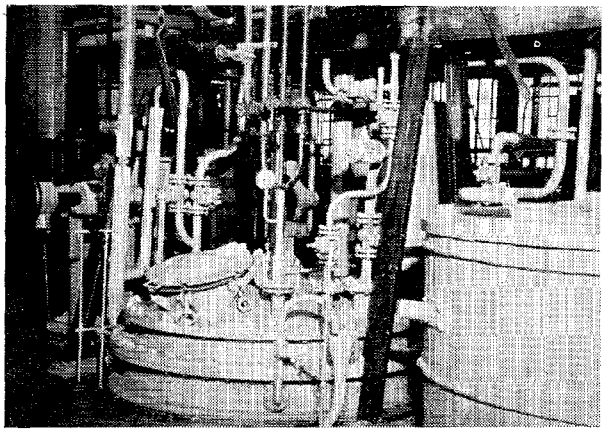


Figure 2. Saponification Kettle, Filter Press (Background), and Precipitation Kettle

The Dowtherm filtrate is distilled in a steel vacuum fractionating still for re-use. The still column is 5 feet tall by 14 inches in diameter and is packed to a height of 3.5 feet with No. 18-8 stainless steel Raschig rings. The still is operated at a pressure of 20 mm. of mercury; the pressure reduction is supplied by a three-stage steam jet ejector.

Isomer Separation. The isomer mixture is shoveled by hand to a carbon steel kettle with a reflux condenser. Here it is stirred with 4 parts of pyridine at reflux temperature until dissolved. Four parts of ethyl alcohol are added and the solution is allowed to cool, with stirring. After 12 hours at room temperature the 7-chloro isomer has crystallized. The slurry is blown to a wooden Nutsche suction filter where the solid is collected, washed with acetone, and allowed to dry. An average yield of the 7-isomer is about 245 pounds.

Saponification. The 7-chloro isomer is then saponified by shoveling it directly into a 10% solution of caustic soda contained in a carbon steel jacketed kettle with gate stirrer, in which it is heated, with stirring, at 90° C. for about 1 hour. The solution is then run through a plate-and-frame filter press into a 750-gallon wooden tank equipped with a paddle agitator. The acid is precipitated from the reaction mixture by neutralization with hydrochloric acid. The mixture is piped by gravity to a wooden Nutsche filter where the acid is collected and washed with water.

Decarboxylation. One part of wet acid is added to 5 parts of Dowtherm in a steam-jacketed steel kettle having a gate stirrer, where it is heated to 160° C. with agitation until all of the water is removed. The slurry is then blown to the decarboxylation kettle, which is constructed on the same pattern as the cyclization unit previously described. Here the slurry is heated as rapidly as possible to 195° C. where evolution of carbon dioxide begins. Thereafter the temperature rise is continued, with stirring, at the rate of 1° per minute, to 240° C., where the temperature is held 40 to 45 minutes to complete the decarboxylation. The contents of the kettle are run by gravity to a 75-gallon, jacketed, cooling kettle with a gate stirrer, where the product crystallizes. It is then transferred to a wooden Nutsche suction filter, washed with acetone, and dried by drawing air through the mass. Drying is then completed in a heated air oven at 50° C. About 140 pounds of the 7-chloro-4-hydroxyquinoline are obtained.

Chlorination. Preparation of the dichloroquinoline from the decarboxylated product is carried out in a 150-gallon glass-lined, steam-jacketed kettle, equipped with an anchor stirrer and a lead distilling column with a condenser for reflux. This kettle is charged with ethylene dichloride and the product from the previous step is added. The mixture is stirred, with heating, until the distillate contains no water. There is then added, slowly, the phosphorus oxychloride. The mixture is refluxed to complete the reaction, after which it is cooled and ice water is added until there is no further vigorous reaction. The mixture is neutralized with 26° Bé. aqua ammonia, brought to reflux, then passed through a plate-and-frame filter press and into a 150-gallon, 18-8 stainless steel, covered gravity separator. The ethylene dichloride layer is transferred to a 150-gallon dropping tank which is connected to a 50-gallon, glass-lined kettle equipped for distillation. The ethylene dichloride solution is fed into the kettle at the same rate at which the solvent is distilled off. The residual product of 150 pounds of dichloroquinoline remains. The collected solvent is ready for re-use. Azeotropic distillation at the beginning of the step eliminates the necessity for removal of water from the reclaimed solvent.

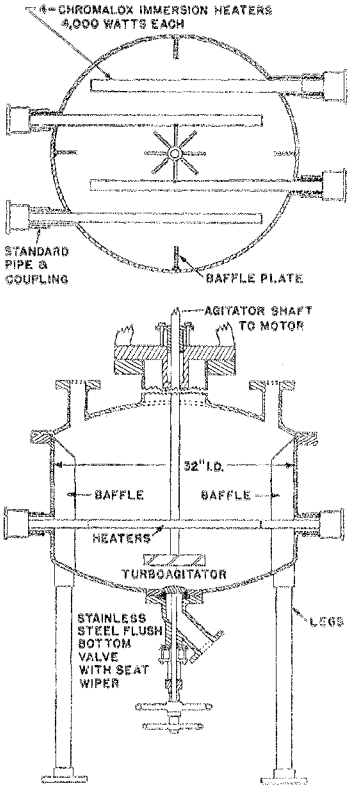


Figure 3. Decarboxylation Kettle

Aralen Base Synthesis. The residue is stirred, in the same kettle, with 48 pounds of molten phenol to form the phenoxy compound in a rapid reaction; after this there is added, with stirring, the calculated amount of novol diamine at 135° C. Completion of this reaction yields the Aralen base.

Diphosphate Preparation. The Aralen base is dissolved in methanol, passed through a plate-and-frame filter press into a 200-gallon, glass-lined kettle equipped with an anchor stirrer

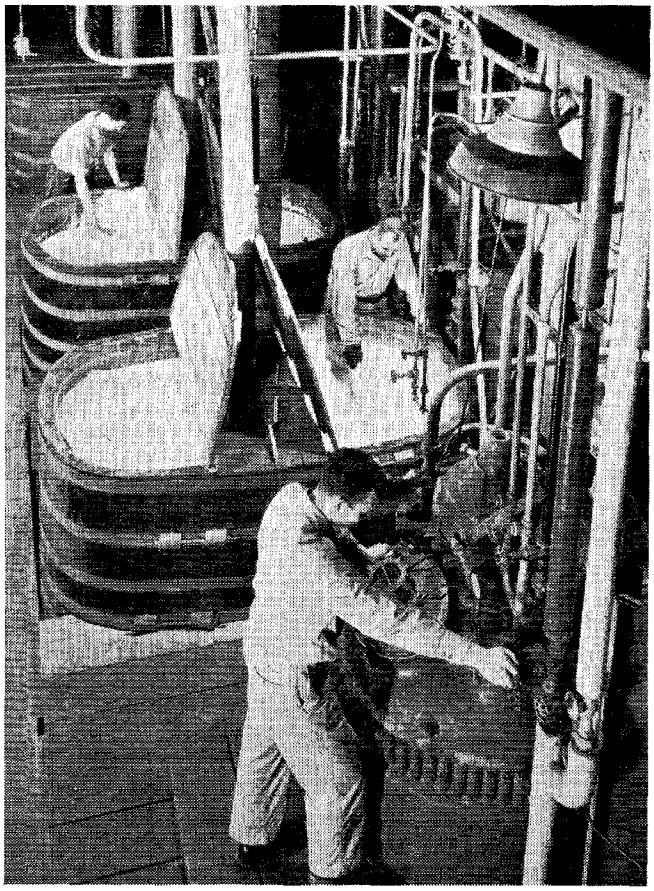


Figure 4. Filters and Reaction Kettle Used in Preparation of Diphosphate

where a methanol solution containing a slight excess of phosphoric acid is added. The diphosphate crystallizes from this mixture on cooling.

The slurry is piped by gravity to a wooden Nutsche suction filter where the crude diphosphate (Aralen) is collected and washed with methanol. The mother liquor is concentrated by distillation; the methanol is collected for re-use and the residue is treated with aqueous alkali to recover the Aralen base which is again passed through the preceding step. The crude Aralen (310 pounds) is then dissolved in hot water and treated with decolorizing charcoal. The mixture is filter-pressed and a selected solvent added at reflux temperature. On cooling, the purified Aralen crystallizes and is collected on a ceramic Nutsche suction filter and washed. It is then dried in a heated air oven at 50° C. and is ready for submission to the control laboratory for analysis. The final product weighs about 260 pounds.

PRODUCT HANDLING

Tableting. Aralen is tableted by the dry slugging method, which consists of reducing the drug to a fine powder and mixing it intimately with binders, fillers, and lubricating ingredients, then pressing this mixture into slugs. Slugs are actually tablets 1 inch in diameter by 0.25 inch thick, pressed to bring about cohesion of the tablet components. The slugs are reduced, in an oscillating granulator, to a powder which can be pressed into the final tablet containing either 250 mg. or 500 mg. of the Aralen diphosphate. Standard Stokes rotary tableting machines are used.

Each tablet is inspected for mechanical flaw by visual examination by trained inspectors. The tablets are poured onto a shallow metal tray which is shaken until all tablets lie flat and visible. After inspection on one side the tablets are turned over for inspection on the reverse side by covering with a tray and inverting. Mechanically defective tablets are removed and reworked for recovery of the active ingredient. The perfect tablets are poured into deep trays and sent to the bottling department.

Bottling. In the bottling department tablets are counted by means of a counting paddle. This instrument is a flat paddle about 5 × 7 inches. Of the same area and hinged to the handle so as to cover the surface of the paddle, is a board with 50 round perforations of diameter slightly larger than that of a tablet. The paddle is thrust into a deep tray of tablets, withdrawn and shaken horizontally. One tablet is held in each perforation. The tablets are released, by raising the perforated board, into funnels directing them into a bottle. Where production requirements permit, counting is done in this manner. With large scale production, a standard counting machine is employed.

The bottles then are fed manually into a machine which stuffs cotton into the top and drops them on a moving belt. Caps are screwed on manually and the bottles are fed into a labeling machine which drops them on an endless belt running to the boxing department where the bottles are placed in cartons by hand operation.

Because the use of this antimalarial drug is world-wide, it is necessary to label those bottles destined for export in the language of the country of destination. The text of each label must conform with the laws of the country of destination as well as those required by the United States Pure Food and Drug Law. At present the language requirements are met by printing the labels in Spanish, European Portuguese, and Brazilian Portuguese; for some countries an English language label is supplemented by a French language circular.

CONTROL

Control is of the highest importance in pharmaceutical production. Starting materials and finished products are all subjected to rigorous testing before release.

Starting Materials. Sodium ethyl oxalacetate is tested for total alkalinity by titration with hydrochloric acid and assayed by quantitative precipitation of the 2,4-dinitro-phenylhydrazine derivative. Minimum purity of 90% is required for acceptance.

m-Chloroaniline is checked for purity by freezing point determination. A freezing point within the range −10° to −12° C. is required for acceptance.

Novol diamine is assayed by use of the Van Slyke method for determination of amino nitrogen. A purity of at least 98% is required.

Finished Crystalline Powder. Chloroquine diphosphate (Aralen diphosphate) (*14*) is a white crystalline powder possessing a bitter taste. Melting point range is 193° to 195° C. It is freely soluble in water and practically insoluble in alcohol, benzene, chloroform, and ether. The pH of a 1% aqueous solution is about 4.5.

Before the finished product is released for tableting, it is subjected to control tests for moisture, melting point, Aralen content, phosphoric acid, and all other tests prescribed (*14*). Freedom from heavy metals, chlorides, and sulfates is determined by the tests as described in the United States Pharmacopoeia. An aqueous solution is also examined to determine its freedom from dirt and lint.

MOISTURE. A sample is dried over phosphorus pentoxide, in vacuo, at room temperature for 48 hours; the loss in weight must not exceed 2.0%.

ARALEN CONTENT. A sample is dissolved in distilled water and the solution made alkaline to litmus with ammonium hydroxide solution, then extracted 5 times with chloroform. The chloroform extracts are filtered, evaporated, heated 30 minutes at 100° C., and weighed. The product weight is calculated as chloroquine diphosphate. A minimum of 98% is acceptable.

Figure 5. Operators Removing Aralen from Drying Oven

In addition to the above tests, a spectrum absorption curve method is now being developed, using light of 3430 Å. wave length. Curves determined from measurements of absorption by highly purified samples of Aralen have been developed for use as standards in checking the acceptability of the product from the plant.

PHOSPHORIC ACID. Bismuth oxynitrate in dilute nitric acid solution is added to an aqueous solution of the product. The resultant precipitate is filtered off, washed, dried, and weighed as bismuth phosphate. The phosphorus content is calculated therefrom and must be within the range 11.8 to 12.25%.

TABLETS. After the crystalline powder has been tested and accepted it is delivered to the finished stock warehouse from which it is requisitioned by the pharmacist in charge of tableting. The tablet mixture is made up and assayed to a tolerance of 2.5% and the accepted material is given a release for pressing into tablets.

Finished tablets are examined and tested for appearance, fragility, weight (single and average), and disintegration time, and then submitted to those tests already described for the finished crystalline powder.

Single tablets must be within ±5% of the specified gross weight and ±5% of the specificed Aralen content; these are determined on a composite of 20 tablets.

COST FACTORS IN PRODUCTION

For a scheduled production of 5000 pounds of Aralen, from which 9,000,000 250-mg. tablets can be made with the equipment and process described, it would be necessary to manufacture and process 41,800 pounds of intermediates, obtained by the consumption of 140,000 pounds of raw materials.

If this production were to be effected in 1 month, in the plant described, services and labor as follows would be required:

A.	Services	
	Steam, lb.	1,300,000
	Water, gal.	220,000
	Electric power, kw. hr.	11,000
B.	Supervision	
	Foremen	3 (each 8 hr./day, 6 days/wk.)
C.	Direct labor	
	Operators (including materials handling)	16 (each 40 hr./wk. to provide continuous shifts 6 days/wk.)
	Control (men)	2 (40 hr./wk.)
	Tableting (men)	2 (40 hr./wk.)
	Packaging (women)	14 (40 hr./wk.)

SUMMARY AND FUTURE OUTLOOK

The process described for Aralen diphosphate manufacture is one which was brought into being through an intensive development program. Carried on under wartime secrecy and scarcities of raw materials, equipment, and personnel, this development yielded a successful plant process and a plant which produced on a commercial scale the chloroquine required by the Government. The plant described is capable of producing Aralen diphosphate at the rate of at least 5000 pounds per month. Since the beginning of the development, constant attention has been given to process improvement leading to the shortening or omission of steps and improvement of efficiency. Improvements of this nature are now being implemented, while others are still in the research stage.

Aralen was indicated by the OSRD program to be the most desirable antimalarial screened. At the present time, reports on its efficacy are favorable and no more desirable drug is being produced. However, research directed toward the finding of better drugs is continuing. The prediction of future production trends is difficult because of the continuing progress in the field and the possibility of finding new and more effective drugs.

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