[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

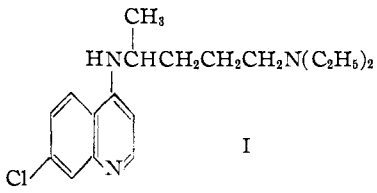
A New Synthesis of Chloroquine

BY WILLIAM S. JOHNSON AND BENNETT G. BUELL

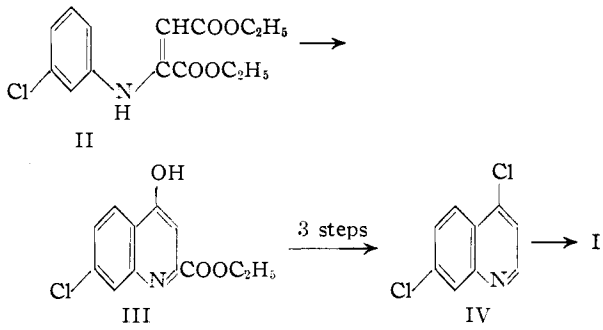
RECEIVED MARCH 15, 1952

The important antimalarial, chloroquine (I), has been synthesized by a new scheme. The adduct (V) from *m*-chloroaniline and methyl acrylate is tosylated and hydrolyzed to give the acid VI which on cyclization followed by detosylation affords 4-keto-7-chloro-1,2,3,4-tetrahydroquinoline (VII) as the exclusive product. Condensation of VII with 4-diethylamino-1-methylbutylamine preferably in the presence of an oxidizing agent like nitrobenzene yields chloroquine (I). Similar experiments in the parent series (lacking the 7-chloro group) are described. The condensation of the quinolone with β-phenylethylamine has also been studied.

Chloroquine (I) is an important antimalarial drug which is manufactured in large quantity[1] by the Surrey and Hammer process[2] consisting of the following steps: condensation of *m*-chloroaniline with ethyl oxaloacetate to give (II), pyrolytic cyclization (to III), saponification, thermal decarboxylation and reaction with phosphorus oxychloride giving 4,7-dichloroquinoline (IV), which is finally condensed with 4-diethylamino-1-methylbutylamine. The yields in this excellent synthesis leave little to be desired except for the cyclization step, II → III, in which the ring closes partly into the position ortho to the chloro group giving a mixture containing about 50% of the undesired 5-chloro isomer.

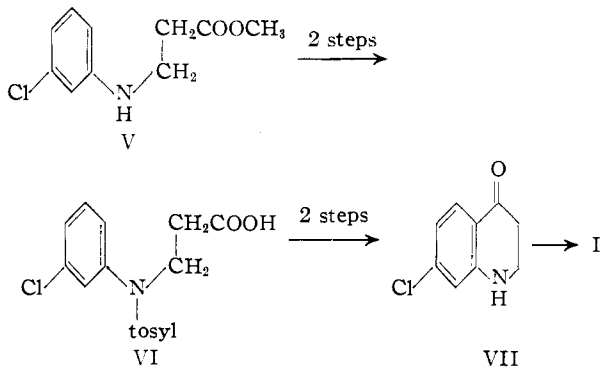


I



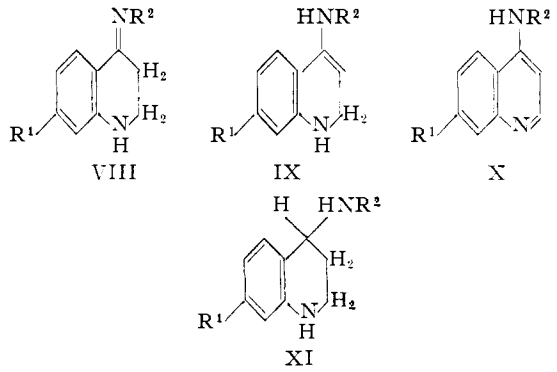
II III IV

In view of the more specific orientation in the cyclization of the acid VI (prepared by tosylation of the adduct V of *m*-chloroaniline and methyl acrylate, followed by hydrolysis of the ester) to give exclusively the desired 7-chloro isomer (formula VII, tosyl in place of H) in over 80% yield,[3,4] we considered it desirable to investigate the possibility of converting 4-keto-7-chloro-1,2,3,4-tetrahydroquinoline (VII) into chloroquine (I) with the hope of providing an improved synthesis. A description of such a study is reported herein.



V VI VII

In preliminary work we hoped to improve the conversion of VII to 4-amino-7-chloroquinoline (X, R^1 = Cl, R^2 = H) with a view to employing the latter in a reductive amination reaction with 1-diethylaminopentanone-4 analogous to the scheme used by Elderfield, Kreysa, Dunn and Humphreys[5] for the preparation of plasmochin. Attempts to improve the previously reported[3] 43% yield of the amine by dehydration of the oxime VIII (R^1 = H, R^2 = OH) failed. When the procedure of Horning and Horning[6] for the conversion of cyclohexenones into anilines was applied to 4-keto-1,2,3,4-tetrahydroquinoline, *i.e.*, heating the azine with palladium-on-carbon, crude 4-aminoquinoline, X (R^1 = R^2 = H), was produced in 85% yield. This product, however, was difficult to purify, and material of good quality was obtained in only 56% yield. Comparable results were obtained in the series carrying the 6-methoxy group.



VIII IX X XI

Our attention was finally directed to a study of the condensation of 4-ketotetrahydroquinolines (such as VII) with primary amines. It was hoped

(1) R. L. Kenyon, J. A. Wiesner and C. E. Kwartler, *Ind. Eng. Chem.*, **41**, 654 (1949).

(2) A. R. Surrey and H. F. Hammer, THIS JOURNAL, **68**, 113 (1946).

(3) W. S. Johnson, E. L. Woroch and B. G. Buell, *ibid.*, **71**, 1901 (1949).

(4) The procedure for this improved yield is described in the Experimental part of the present paper.

(5) R. C. Elderfield, F. J. Kreysa, J. H. Dunn and D. D. Humphreys, THIS JOURNAL, **70**, 40 (1948).

(6) E. C. Horning and M. G. Horning, *ibid.*, **69**, 1907 (1947).

that the Schiff base VIII would tautomerize to the eneamine IX which, being a 1,2-dihydroquinoline derivative, could in turn be aromatized readily to give X. Since Schiff bases are generally produced in better yield by condensing the amine with the ketal instead of the free ketone,[7,8] an attempt was made to prepare the diethyl ketal of 4-keto-1,2,3,4-tetrahydroquinoline by the conventional ethyl orthoformate method. The product, however, contained only one ethoxyl group and was identified as 4-ethoxyquinoline (yield 35–48%). The abnormal course of this reaction is undoubtedly due to the fact that the enol ether—which is surely present in the reaction mixture, at least in low concentration, by a reversible mechanism—has the 1,2-dihydroquinoline structure and like other members of this class[9] should undergo a facile and irreversible dehydrogenation. This reaction was not given further study, and our attention was turned to a consideration of the direct condensation of amines with the quinolones.

As a model, the condensation of 4-keto-1,2,3,4-tetrahydroquinoline with β-phenylethylamine was studied. These reagents were heated in benzene solution containing a trace of ammonium chloride with provision for removal of water by azeotropic distillation.[8] After about seven hours the calculated amount of water separated, and a nicely crystalline product was readily isolated by crystallization. Instead of the Schiff base, this substance proved to be 4-(β-phenylethylamino)-quinoline, X (R^1 = H, R^2 = $CH_2CH_2C_6H_5$), m.p. 159°, identified by analysis of the base and the picrate and by comparison with authentic material prepared by condensation of β-phenylethylamine with 4-chloroquinoline. Since the yields of the aromatic product from the amine–ketone condensation were invariably under 50% it was suspected that the reaction proceeded largely by a disproportionation to give equimolar amounts of X and XI (R^1 = H, R^2 = $CH_2CH_2C_6H_5$). Indeed the oily material remaining after separation of the crystalline product has been shown in the companion paper[9] to consist largely of the tetrahydro compound. When the condensation was carried out essentially as described above (in toluene) and after the water was separated the heating was continued with added palladium-on-carbon to promote dehydrogenation of the tetrahydro compound, the aromatic base X (R^1 = H, R^2 = $CH_2CH_2C_6H_5$) was obtained in 64% yield. When the palladium catalyst was introduced at the beginning of the condensation, the product was contaminated with a higher-melting substance which appeared to be 4-hydroxyquinoline, m.p. 198–200°. This compound evidently arose from direct dehydrogenation of the ketone; indeed when the latter was heated alone with palladium-on-carbon in xylene, 4-hydroxyquinoline was produced in 71% yield. Elderfield and Maggiolo[10] have carried out this type of dehydrogenation in 95–100% yield using palladium-black in aqueous solution containing potassium maleate.

The best yields of X (R^1 = H, R^2 = $CH_2CH_2C_6H_5$) were obtained by employing an oxidizing agent in the reaction mixture to dehydrogenate the intermediary dihydroquinoline IX (R^1 = H, R^2 = $CH_2CH_2C_6H_5$) before it undergoes disproportionation. Air alone will serve as the oxidizing agent, increasing the yield significantly, but a reagent like nitrobenzene is even more effective. The ammonium chloride catalyst is not required. Thus in an experiment carried out by William De Acetis, a mixture of 4-keto-1,2,3,4-tetrahydroquinoline, β-phenylethylamine and nitrobenzene was heated at 140–180° for seven hours, and the crude crystalline aromatic compound was isolated in 86% yield.

The use of 4-diethylamino-1-methylbutylamine in place of β-phenylethylamine in the condensation with 4-ketotetrahydroquinoline gave X (R^1 = H, R^2 = $CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$), isolated as the diphosphate, which was identified by comparison of the salt and the free base with authentic material obtained by an independent synthesis from 4-chloroquinoline. The ammonium chloride method (in toluene) gave the product in 38% yield. The additional palladium-on-carbon treatment did not raise the yield appreciably. When the condensation was carried out at higher concentrations in xylene and in the presence of air, yields as high as 60% were realized. With phenol as the solvent (without ammonium chloride) and reaction temperatures of 150–155°, the yields were 62–76% in air, and consistently 74% in the presence of nitrobenzene.

The condensation of 4-keto-7-chloro-1,2,3,4-tetrahydroquinoline (VII) with 4-diethylamino-1-methylbutylamine gave comparable results. Chloroquine (I) was isolated as the diphosphate and identified by comparison of the salt and the free base regenerated therefrom with authentic specimens made by the Surrey and Hammer method.[2] In the absence of any oxidizing agent the diphosphate was isolated in 40% yield, and in the presence of air the yield rose to 60–80%. With nitrobenzene yields as high as 89% have been realized. Experiments carried out by James Ackerman have resulted in a procedure whereby the diphosphate can be obtained consistently in 80% yields. The effect of concentration on yield was demonstrated by experiments at dilutions of 0.004–0.067 g. of ketone per ml. of solvent in which no chloroquine was obtained.

The over-all yield of chloroquine from *m*-chloroaniline by our best procedures is approximately 25%, which compares favorably with the Surrey and Hammer process.[2]

Acknowledgment.—It is a pleasure to thank Dr. A. R. Surrey of the Sterling-Winthrop Research Institute for helpful suggestions relating to the isolation and purification of chloroquine, and for supplying us with a number of compounds for comparison purposes.

Experimental[11]

Azine of 4-Keto-1,2,3,4-tetrahydroquinoline.—A mixture of 1.00 g. of the ketone,[3] m.p. 45–47.5°, 0.206 g. of 85% hydrazine hydrate, 15 ml. of alcohol and 1 drop of concentrated hydrochloric acid was boiled under reflux for 6.5 hours. The sparingly soluble azine which crystallized from the re-

(7) J. Hoch, *Compt. rend.*, **199**, 1428 (1934).
(8) R. H. Jones, Ph.D. Dissertation, University of Wisconsin, 1948.
(9) W. S. Johnson and B. G. Buell, THIS JOURNAL, **74**, 4517 (1952).
(10) R. C. Elderfield and A. Maggiolo, *ibid.*, **71**, 1906 (1949).
(11) All melting points are corrected for stem exposure.

action mixture as yellow needles amounted to 0.452 g. (46% yield), m.p. 175–177° with previous softening. Repeated recrystallization from methanol gave yellow needles, m.p. 179.7–180.7° (vac.).

Anal. Calcd. for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25. Found: C, 74.34; H, 6.22.

Azine of 4-Keto-6-methoxy-1,2,3,4-tetrahydroquinoline.—A mixture of 1.00 g. of the ketone,[3] m.p. 112–113°, 0.166 g. of 85% hydrazine hydrate, 14 ml. of alcohol and 0.70 ml. of concentrated hydrochloric acid was boiled under reflux for 4 hours. The crude product which crystallized in orange rods amounted to 0.841 g. (85% yield), m.p. 229.5–232° (vac.). Repeated recrystallization from ethyl acetate raised the m.p. to 233–233.8° (vac.).

Anal. Calcd. for $C_{20}H_{22}O_2N_4$: C, 68.55; H, 6.33. Found: C, 68.62; H, 6.42.

4-Aminoquinoline.—A mixture of 0.277 g. of the azine of 4-ketotetrahydroquinoline, m.p. 176–177.5° (vac.), and 0.139 g. of 20% palladium-on-carbon[12] was heated in a sublimation tube at 190–193° for 15 minutes at a pressure of 45–50 mm., then for an additional 15 minutes at 0.04 mm. The distillate, which came over at the lower pressure as a colorless oil that solidified, amounted to 0.235 g., m.p. 133.5–144.5°. Three recrystallizations from benzene removed some less soluble material and gave 0.156 g. (57% yield) of colorless crystals, m.p. 151.5–153° with previous softening. The melting point was not depressed on admixture with authentic 4-aminoquinoline[13] (m.p. 154–155.5°)[3] prepared from 4-chloroquinoline.

4-Amino-6-methoxyquinoline.—A mixture of 0.300 g. of the crude azine of 4-keto-6-methoxytetrahydroquinoline, m.p. 220–228°, and 0.150 g. of 20% palladium-on-carbon[12] was treated as described above at 198–200° for 15 minutes at 50 mm., then for 10 minutes at 0.03 mm. During the final 5 minutes, the temperature was raised to 213°. The yellowish distillate which solidified amounted to 0.255 g. (86% yield), m.p. 110–115° with presoftening. Crystallization from toluene followed by recrystallization from benzene gave 0.156 g. (52% yield) of colorless needles, m.p. 118.5–120°, undepressed on admixture with an authentic specimen[13] (m.p. 122–122.5°) prepared from the 4-chloro compound.

The acetyl derivative prepared by refluxing the amine with acetic anhydride was obtained from alcohol as colorless prisms, m.p. 243–245°. This m.p. was not depressed on admixture with the acetyl derivative, m.p. 245.5–246.5°, which was prepared in the same manner from the amine, m.p. 121–122°, obtained by dehydration of the oxime.[3]

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.60. Found: C, 67.09; H, 5.48.

Attempted Preparation of 4,4-Diethoxy-1,2,3,4-tetrahydroquinoline. Isolation of 4-Ethoxyquinoline.—The following procedure is adapted from that of Jones and Adkins[8] for the preparation of the ketal of 1-diethylaminopentanone-4. A mixture of 3.00 g. of 4-keto-1,2,3,4-tetrahydroquinoline, m.p. 45–47.5°, 5 ml. of ethanol, 11 ml. of ethanolic hydrogen chloride (2 *N*), and 4.3 ml. of ethyl orthoformate was allowed to stand for 11 days at room temperature. The solvent was then evaporated, and the red solid hydrochloride decomposed by treatment with a solution of 0.5 g. of sodium in 10 ml. of ethanol. After swirling for 30 minutes the salt was removed by filtration, and the solvent evaporated. Distillation of the residual oil gave 1.72 g., b.p. 139–146° (8 mm.), $n^{25}D$ 1.5940. A dark polymeric residue was left in the flask.

In another run carried out on exactly twice the above scale, there were obtained (1) 0.69 g., b.p. 75–105° (0.3 mm.), $n^{25}D$ 1.6025; (2) 2.49 g., b.p. 100–103° (0.1 mm.), $n^{25}D$ 1.5980; (3) 1.92 g. of brown polymeric residue.

Anal. of fraction 2. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; ethoxyl, 26.01. Found: C, 76.05; H, 6.47; ethoxyl, 25.73.

The analysis is in agreement with 4-ethoxyquinoline which is reported to boil at 186.5° (30 mm.).[14] The chloroplatinate prepared from fraction (2) and recrystallized from dilute hydrochloric acid melted at 212–213° (dec.). The chloroplatinate of 4-ethoxyquinoline is reported to melt at 213° (dec.).[14]

Condensation of β-Phenylethylamine with 4-Keto-1,2,3,4-tetrahydroquinoline. (a) Ammonium Chloride Method.—A mixture of 2.47 g. of freshly distilled amine, 3.01 g. of ketone (m.p. 43–45°), 21 mg. of ammonium chloride and 30 ml. of benzene was boiled under reflux in a system equipped with a water separator. After 7.5 hours approximately the calculated amount of water was removed. On concentration and cooling the solution deposited 1.39 g. of 4-(β-phenylethylamino)-quinoline as yellow crystals, m.p. 148–154°. Repeated recrystallization from benzene gave fine colorless rods, m.p. 159–159.5°.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50. Found: C, 81.95; H, 6.17.

This material was recovered unchanged after heating with 20% palladium-on-carbon[12] for 45 minutes at 179–218°. An authentic specimen of the product was prepared by the condensation of β-phenylethylamine with 4-chloroquinoline according to the general method of Surrey and Hammer.[2] It melted at 159–160° alone or on admixture with the specimen described above.

The picrate of the product obtained by the ketone–amine condensation was obtained, after repeated recrystallization from alcohol, as fine yellow needles, m.p. 198–199° (presoftening at 184–186°).

Anal. Calcd. for $C_{23}H_{19}O_7N_5$: C, 57.86; H, 4.01. Found: C, 57.89; H, 3.97.

The oil remaining after concentration of the filtrate in the ketone–amine condensation described above, continued to deposit crystalline material on standing over a period of several weeks. A total of 1.16 g. of 4-(β-phenylethylamino)-quinoline, m.p. ranging from 124–144° to 157–158.5°, was obtained in various crops by crystallization and finally by chromatography of the residual oils on alumina. The total yield of material of fair quality was 2.54 g. (50%). The nature of the residual oily material is described elsewhere.[9]

(b) **After-treatment with Palladium Catalyst.**—A mixture of 0.93 g. of the amine, 1.00 g. of ketone, 10 mg. of ammonium chloride and 12 ml. of toluene was refluxed for 5 hours with provision for removal of water (see above). About 60% of the solvent was then removed by distillation, xylene was added to replace the volume, 0.10 g. of 30% palladium-on-carbon[12] was introduced, and the mixture was refluxed for 11 hours (internal temperature 128°). After filtering and cooling, the mixture deposited 1.00 g. of the aromatized product, m.p. 156.5–159°. The second crop amounted to 0.08 g., m.p. 151–155.5° (with presoftening), bringing the total yield to 64%.

(c) **In the Presence of Palladium Catalyst (Isolation of 4-Hydroxyquinoline).**—A mixture of 0.42 g. of the amine, 0.50 g. of ketone, 6 mg. of ammonium chloride, 0.250 g. of 20% palladium-on-carbon[12] and 20 ml. of xylene was refluxed for 14 hours. After filtering and cooling, the mixture deposited 0.266 g. of crystals, m.p. 132–144°. Recrystallization from toluene gave a small, less soluble fraction which on recrystallization from methanol–benzene amounted to 0.02 g., m.p. 198–200° (presoftening).

A mixture of 0.100 g. of ketone, 0.100 g. of 20% palladium-on-carbon[12] and 5 ml. of xylene was boiled under reflux for 24 hours. After filtering and cooling, the solution deposited 0.009 g. of the product, m.p. 198–200°. The bulk of the material remained adsorbed on the carbon, and on elution with hot methanol, 0.061 g. of material, m.p. 190–194° (presoftening), was isolated. If the product is assumed to represent mainly 4-hydroxyquinoline, which is reported to melt at 201°,[15] the total yield of crude material was 71%.

(d) **Nitrobenzene Method.**—A mixture of 2.61 g. of the amine, 1.00 g. of ketone and 1.80 g. of nitrobenzene was heated in an atmosphere of nitrogen for 3 hours at 170–180°, then for 4 hours at 140–150°. The dark semi-solid residue was steam-distilled to remove excess amine and nitrobenzene; then the residue was dried and dissolved in benzene, the last traces of moisture being removed by boiling off a portion of the solvent. On cooling, the solution deposited 1.00 g. of tan 4-(β-phenylethylamino)-quinoline, m.p. 150–156°. A second crop obtained by the addition of petroleum ether (40–60°) to the filtrate amounted to 0.45 g. m.p. 153–155°, making the total yield 86%.

(12) Prepared by the procedure of R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

(13) Supplied by Dr. A. R. Surrey.

(14) F. Wenzel, *Monatsh.*, **15**, 453 (1894).

(15) R. Camps, *Ber.*, **34**, 2703 (1901).

Condensation of 4-Diethylamino-1-methylbutylamine with 4-Keto-1,2,3,4-tetrahydroquinoline. (a) In the Presence of Air.—A mixture of 0.412 g. of freshly distilled diamine ($n^{25}D$ 1.4406), 0.250 g. of ketone, 0.375 g. of phenol and 2 mg. of sodium iodide[16] in a flask fitted with an air condenser protected from moisture by a soda lime guard tube was heated in an oil-bath at 150–153° for 17 hours. After cooling, the solution was diluted with excess potassium hydroxide solution, and the mixture was extracted with ether. The ether solution was washed with water, then with 1 *N* hydrochloric acid. The combined aqueous acid solutions were made strongly alkaline with potassium hydroxide solution, and the liberated amine was taken up in ether, washed with water, saturated salt solution and dried over anhydrous potassium carbonate. Evaporation of the ether left 0.431 g. of a brown solid, m.p. 62–72° (presoftening). Treatment with phosphoric acid in methanol by the method of Surrey and Hammer[2] gave 0.627 g. (74% yield) of the diphosphate hydrate of 4-(4′-diethylamino-1-methylbutylamino)-quinoline as colorless micro crystals, m.p. 214.5–216.5° (vac.) (dec.) when inserted at 180°. The m.p. was not depressed on admixture with a specimen of authentic material, m.p. 213.5–214.5° (vac.) (dec.), prepared by condensation of the amine with 4-chloroquinoline according to the procedure of Steck, Hallock and Holland.[17] A sample of this authentic material was prepared for analysis by repeated recrystallization from alcohol, m.p. 216–217.5° (vac.) (dec.) with softening at 214.5°.

Anal. Calcd. for $C_{18}H_{27}N_3(H_3PO_4)_2 \cdot H_2O$: C, 43.28; H, 7.06. Found: C, 42.80; H, 7.29.

In another run carried out just as described above there was obtained from 0.200 g. of ketone, 0.429 g. (63% yield) of diphosphate, m.p. 213–216° (vac.) (dec.). This salt was treated with aqueous potassium hydroxide and the free amine isolated in 97% yield as a nearly colorless solid, m.p. 75.5–78° (reported[18] 75–77°). The free base was prepared also from the authentic diphosphate described above, m.p. 76–78.2°, undepressed on admixture with the specimen described above.

(b) **Nitrobenzene Method.**—A mixture of 0.825 g. of diamine, 0.500 g. of ketone, 0.50 g. of phenol and 0.168 g. of nitrobenzene was heated as described above (part a) at 150–156° for 7 hours and 15 minutes. The crude amine (about 1 g.) was dissolved in 7 ml. of methanol and 3 ml. of a solution containing 1 g. of phosphoric acid was added. After standing for 1 day, the solution deposited 1.243 g. (73% yield) of pale yellow diphosphate, m.p. 215–216.5° (vac.) (dec.).

In another run carried out exactly as described above except that the amount of nitrobenzene was increased to 0.90 g., the yield of tan diphosphate, m.p. 214–216° (vac.) (dec.), was 1.257 g. (74%).

Improved Procedure for Cyclization of N-Tosyl-β-*m*-chloroanilinopropionic Acid (VI).—The reaction was carried out as previously described[3] except that the proportion of reagents was altered somewhat. The acid chloride was prepared from 10.50 g. of the acid, m.p. 105.8–107°, and 6.50 g. (5% molar excess) of phosphorus pentachloride. The acid chloride dissolved in 160 ml. of thiophene-free benzene was added during 45 minutes to a stirred suspension of 5.00 g. (25% molar excess) of anhydrous aluminum chloride in 160 ml. of thiophene-free benzene at 5–8°. After stirring for 7 hours at 25° the reaction mixture was worked up as previously described.[3] The crude, cream-colored, solid, neutral material amounted to 9.94 g., m.p. 94.5–122°. A single crystallization from alcohol gave 8.16 g. (82% yield) of pale, cream-colored prisms, m.p. 128.5–130°. An additional 0.26 g., m.p. 125–128°, was obtained by recrystallization of the second crop of material.

On diluting the filtrate with water 0.415 g. of colorless material, m.p. 92–94°, was isolated. Two recrystallizations from alcohol gave colorless rods, m.p. 90.5–92°. The analysis indicates that this material is the product of intermolecular acylation (involving benzene), namely, **N-tosyl-β-*m*-chloroanilinopropionylbenzene.**

Anal. Calcd. for $C_{22}H_{20}O_3ClNS$: C, 63.84; H, 4.87. Found: C, 63.80; H, 4.49.

The hydrolysis of 8.09 g. of the cyclic ketone described above to 4-keto-7-chloro-1,2,3,4-tetrahydroquinoline (VII) was carried out with 20 ml. of acetic acid, 20 ml. of hydrochloric acid and 5 ml. of water by heating for 5 hours at 119–122° as described previously.[3] There was thus obtained 4.21 g. (96% yield) of VII, m.p. 129–131.5° (presoftening). Recrystallization from ethyl acetate gave material of excellent purity, m.p. 131–133°, in 84% recovery.

Condensation of 4-Diethylamino-1-methylbutylamine with 4-Keto-7-chloro-1,2,3,4-tetrahydroquinoline. (a) In the Presence of Air.—In a typical experiment a mixture of 0.165 g. of the diamine, 0.100 g. of crude ketone, m.p. 129–131.5°, and 0.15 g. of phenol[16] was heated in an oil-bath at 154° for about 6 hours. The reaction mixture was worked up as described above for the parent series (part a). Treatment of the crude product with methanolic phosphoric acid gave 0.192 g. (68% yield) of light cream-colored diphosphate, m.p. 185–195° (dec.). Phosphate preparations of authentic chloroquine[13] also melted in this range. The m.p., however, is not a good criterion of purity, since this property is quite variable.[19] A specimen of diphosphate, m.p. 187–196° (dec.)—obtained in a similar run (with ketone, m.p. 130–132°) in which the heating period was about 9 hours and 1.5 mg. of sodium iodide (probably ineffective) was also present (yield 83%)—was decomposed with potassium hydroxide solution. The chloroquine, isolated by ether extraction, was obtained in 93% recovery as an almost colorless solid, m.p. 86–89°, undepressed on admixture with an authentic specimen,[13] m.p. 87.2–89°.

(b) **In the Presence of Nitrobenzene.**—A mixture of 1.31 g. (0.0083 mole) of diamine, 1.00 g. (0.0055 mole) of ketone, m.p. 132–133°, and 0.57 g. (0.0046 mole) of nitrobenzene was heated under a nitrogen atmosphere for 5 hours in an oil-bath at 155–160°. The reaction mixture was worked up essentially as described above and the crude product, after treatment in ether solution with Norit, was obtained as a brown oil which solidified on scratching. The yield was 1.62 g. (92%), m.p. 76–83°. This product gave a yellow-orange diphosphate which was purified by digestion with boiling alcohol for three hours. The salt, which was then light tan in color, amounted to 2.30 g. (81% yield), m.p. 208–214° (dec.). The free chloroquine liberated from this salt was obtained as light tan crystals, m.p. 85.5–88°.

In another run with 0.33 g. of diamine, 0.200 g. of ketone, m.p. 131.5–133°, 0.30 g. of phenol and 0.114 g. of nitrobenzene and a 7-hour heating period, there was obtained 0.504 g. (89% yield) of pale yellow chloroquine phosphate, m.p. 184–192° (dec.).

MADISON, WISCONSIN

(16) Subsequent experiments indicated that this reagent was unnecessary.

(17) E. A. Steck, L. L. Hallock and A. J. Holland, THIS JOURNAL, **68**, 129 (1946).

(18) A. R. Surrey and R. A. Cutler, *ibid.*, **68**, 2570 (1946).

(19) N. L. Drake, H. J. Creech, D. Draper, J. A. Garman, S. Haywood, R. M. Peck, E. Walton and J. O. Van Hook, *ibid.*, **68**, 1214 (1946).