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SYNTHETIC ANTIMALARIALS

By

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fulfillment of the requirements for the
degree of Doctor of Philosophy

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INTRODUCTION

Therapeutic treatment of malaria up to 1942 involved in almost all cases the use of quinine or atebrin[1] or the two in conjunction. Activity had been found in other types of compounds, and particularly in quinolines basically substituted in the 8-position, but the active compounds carried so much toxicity as well that the compounds were impractical as drugs. Relatively recently, sulfadiazine was reported as effective in man.[2]

Consequently, the early part of the synthetic program of the Committee on Medical Research of the Office of Scientific Research and Development was devoted largely to the preparation of derivatives of sulfanilamide with the view of finding a causal prophylactic. The animal tests, however, were in almost all cases disappointing, and this line of approach was discontinued.

A number of quinolines bearing dialkylaminoalkylamino groups in the 4-position had been prepared by the Germans[3,4] and by the Russians[5,6] and after preliminary testing in the United States, an extensive synthetic program involving this type of compounds was initiated. This program resulted in the discovery of a number of compounds with significant activity as suppressives; several of these compounds are now used clinically in place of atebrin.[7]

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[1] H. Mauss and F. Mietzsch, German Patent 553,072 (1932).

[2] L. T. Coggeshall, et al., J. Am. Med. Assoc., 117, 1077 (1941).

[3] H. Andersag, S. Breitner and H. Jung, German Patent 683,692 (1939); C. A. 36, 4973 (1942).

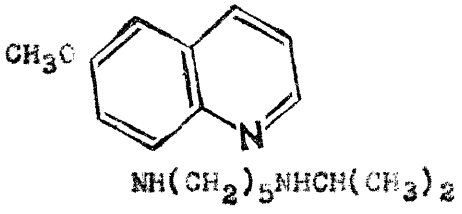
[4] H. Andersag, S. Breitner and H. Jung, U. S. Patent 2,233,970 (1941); C. A. 35, 3771 (1941).

[5] E. P. Hal'perin, Med. Parasitol. Parasitic Diseases (U.S.S.R.), 9, 44 (1940); C. A. 36, 1674 (1942).

[6] O. J. Magidson and M. V. Rubstov, J. Gen. Chem. (U.S.S.R.), 7, 1896 (1937); C. A. 32, 564 (1938).

[7] F. Y. Wiselogle, A Survey of Antimalarial Drugs 1941-1945 (Ann Arbor, Michigan: J. W. Edwards, 1930), Vol. I, pp. 378-406.

However, it soon became apparent that these 4-aminoquinolines qualitatively resembled atebrin in that they were not a parmanent cure for vivax malaria, although satisfactory as suppressives.[8] In the consequent search for a cure for relapsing vivax, attention turned to the derivatives of 8-aminoquinoline previously mentioned, which had been reported to have this property, although plasmochin (pamaquine),[9] the best of this type of compound available at that time, is too toxic to be used safely as a clinical cure, especially in the non-Caucasian races. A survey of several hundred new derivatives of 8-aminoquinoline, however, led to the discovery of a number of compounds possessing a more favorable ratio between activity and toxicity than that of plasmochin. At the present time, it is considered that two of the best of these are 8-(5-isopropylaminoamylamino)-6-methoxyquinoline (pentaquine) (I), and 8-(4-isopropylamino-1-methylbutylamino)-6-methoxyquinoline (II), although the clinical evaluation is a time-



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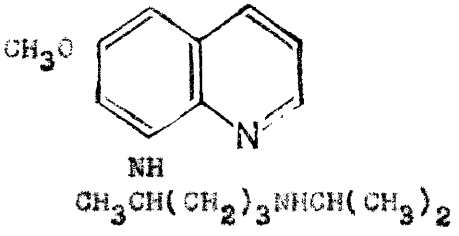

(II)

consuming procedure, and one of the compounds closely related to them may prove to be more useful as a cure when the testing is finally complete.

Concurrently with this work in the United States, an independent attack of the problem in Great Britain led to discovery of activity in a new type of compound. This work culminated in the synthesis and evaluation

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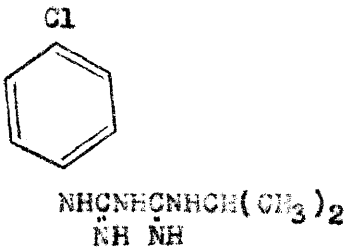
[8] Ibid., Vol. I, p. 106.

[9] Schuleman, Schonhofer and Zingler, U. S. Patent 1,747,531 (1930).

of the drug known as paludrine, 1-(p-chlorophenyl)-4-isopropylbiguanide



(III)

(III). This drug has now been tested in the United States, and is considered at the present time to have considerable value as a suppressive drug, but not as a curative drug in vivax malaria.[10]

The synthetic program in the United States, as integrated under the Committee on Medical Research, followed two paths: (1) the search for optimum activity in a known series of drugs, guided by the observed relation between structure of the compounds and activity in animal and human testing as found by the biological and pharmacological divisions of the program, and (2) the search for significant activity in compounds fundamentally different in structure from known active compounds, while possessing formal resemblance in structure. This thesis describes synthetic work on members of both classes of compounds; compounds of the first type synthesized include representatives of the 4-aminoquinoline and 8-aminoquinoline groups. Testing data on the compounds in this thesis will be found elsewhere, or will be listed in Table V where testing data has become available since publication of Wiselogle's Survey.[7]

In the 4-aminoquinoline group, the synthetic program was initially guided by the activity of two compounds. They are 7-chloro-4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline (IV), a drug used by the

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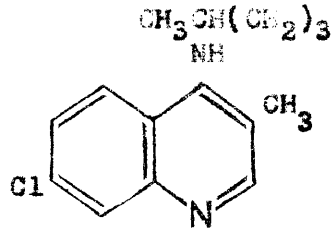
[10] F. Y. Wiselogle, op. cit., Vol. I, p. 252.

Germans, and 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (chloroquine) (V), one of the drugs in clinical use today.



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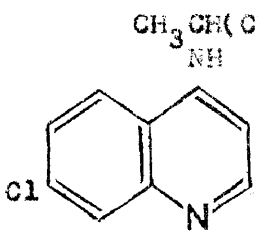
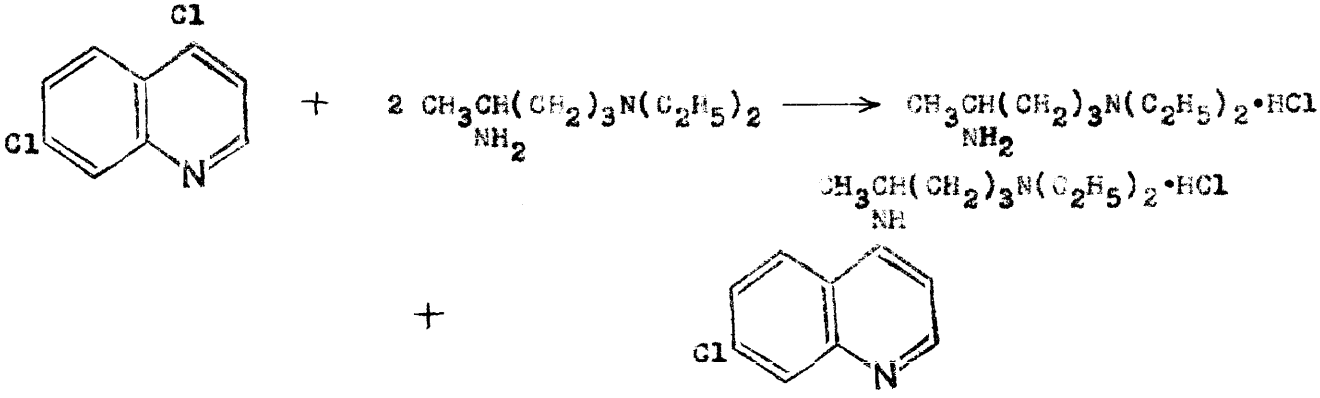


(V)

With attention centering on chloroquine, synthesis was directed to two types of compounds: (1) compounds in which the basic side chain was modified, and (2) compounds in which substitution in the quinoline nucleus was modified. Subsequent testing showed that compounds of the first type in general possess much greater activity.

Synthesis of the 4-aminoquinolines was accomplished without exception by an amination reaction involving the proper 4-chloroquinoline and substituted primary amines. This is possible even when other halogens are present in the benzenoid ring, since halogens α- and γ- to the nitrogen atom in a heterocyclic aromatic ring are strongly activated. In general, at least a two-fold excess of the alkylamine was used to take up the hydrogen chloride formed in the reaction. The reaction by which chloroquine is prepared, for example, is as follows:



The compounds of this class described in this thesis are listed in

Table I. The intermediates were obtained elsewhere. The reaction was in general carried out by heating the reactants without solvent slowly until an exothermic reaction could be noted by a positive temperature differential between the reaction mixture and the heating bath, and continuing heating at that approximate temperature until an appropriate test showed that no more of the original 4-chloroquinoline remained in the reaction mixture. After suitable isolation of the basic product, it was distilled in vacuo and crystallized either as the free base or as a suitable salt.

In some cases, and especially where the heterocyclic ring of the quinoline nucleus was heavily substituted, it was found necessary to add equimolecular quantities of phenol to the reaction mixture before a reaction would take place. In these cases, the reaction usually proceeded more difficultly and only at higher temperatures.

The compound in which the terminal amino group of the basic side chain is primary, 4-(3-aminopropylamino)-7-chloroquinoline, was synthesized as a result of metabolic studies in which it was shown that dealkylation of the terminal amino group in the basic side chain of the corresponding tertiary amine took place in the human body.[11]

In the reaction of 2,4-dichloroquinoline with 1-diethylamino-4-aminopentane,[12] a complicating factor of two activated halogen atoms led to a mixture of the two possible products. The bases could not be crystallized or separated satisfactorily by distillation; hence, testing was done on a mixture of the phosphates of the two compounds.

In the reaction of 4,7-dichloro-3-phenylquinoline with Noval diamine

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[11] F. Y. Wiselogle, op. cit., Vol. I, p. 104.

[12] Hereinafter called Noval diamine.

in the presence of phenol as a catalyst, evidence was observed of a preliminary reaction, presumably between the phenol and the activated halogen of the quinoline, and a crystalline compound was isolated in small amount from the reaction mixture which is believed to be this intermediate compound. This may be taken as evidence of the mode of action of the phenol catalyst.

Preparation of crystalline salts of the tri-acid bases often represented the most difficult part of the synthesis. Probably due to individual solubility characteristics, it was often impossible to predict how many of the basic groups would participate in salt formation. Phosphates were in most cases crystalline, but showed a marked tendency to form solvates. The most convenient method for salt preparation where applicable was that devised for the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline dihydriodide. In this procedure, a solution of a soluble salt of the base in a suitable medium was prepared, and a soluble neutral salt (here potassium iodide) of an acid forming a salt with the organic base insoluble in the medium used, was added, yielding a precipitate of the desired product.

Also in accordance with the first part of the synthetic program, that is, the search for optimum activity in a known series of drugs, a typical representative of the 8-aminoquinoline group, 8-(5-sec.-butylaminoamylamino)-6-methoxyquinoline, was synthesized. In this case, the object of the search was for a curative drug for vivax malaria; the synthesis is very similar to that of pentaquine.[13]

In connection with the second part of the synthetic program, the search

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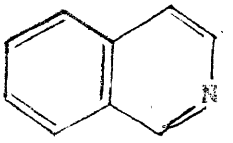
[13] N. Drake, et al., J. Am. Chem. Soc. 68, 1529 (1946).

for significant activity in compounds fundamentally different in structure, heterocyclic, aromatic nitrogen-containing compounds other than quinolines were logical subjects for testing. Therefore, basically substituted derivatives of isoquinoline (VI) and phthalazine (VII) were



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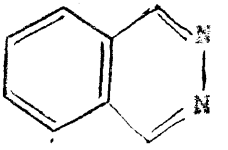

(VII)

prepared for screening tests. The 1-positions in the two nuclei were the most logical places to attach the Noval diamine side-chain with a view both toward formal structural resemblance to the 4-aminoquinoline group and toward ease of synthesis from a chemical viewpoint. These compounds were also made from the nucleus containing a halogen in the position desired for attachment of the Noval side-chain, and these α-halogens proved to possess, as predicted, activity similar to the α- and γ-halogen atoms placed on the quinoline nucleus, and sufficient to react with Noval diamine under comparable conditions. In the case of the 1-chlorophthalazines, the halogen is even more strongly activated than that in the 4-chloroquinolines. The preparation of the isoquinoline drugs closely paralleled that of the 4-aminoquinoline group; in the case of the phthalazine drugs, however, a complication was the fact that attempts to distil the products, even under high vacuum, led to decomposition before distillation would take place. This necessitated direct preparation of the salt without isolation of the pure base. The intermediate substituted 1-chloroisoquinolines[14] and 1-chlorophthalazines[15]

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[14] Supplied by Dr. R. L. Shriner, University of Indiana.

[15] R. R. Vaughan and W. L. Baird, J. Am. Chem. Soc. 68, 1314 (1946).

were obtained elsewhere. Tables II and III list respectively the 1-(4-diethylamino-1-methylbutylamino)isoquinolines and 1-(4-diethylamino-1-methylbutylamino)phthalazines prepared.

Also part of the search for activity in compounds not containing the quinoline nucleus was the synthesis of some N-isopropylaminoalkyl- and N-isopropylaminoalkanol- p-chloroanilines. The basis for the hope for activity in this type of compound lay in three lines of reasoning: (1) that such compounds contain the same aromatic nucleus (p-chloroaniline) as paludrine,[10] (2) that an essential requirement for antimalarial activity seems to be the presence of one strongly basic amino group and one weakly basic (aromatic) amino group, separated by an aliphatic chain and attached to an aromatic nucleus, and (3) significant activity, although coupled with high toxicity, was to be found in many aminoalcohols.[16] The compounds synthesized are to be found in Table IV. The alkylaminoalkylaminochlorobenzenes were made by essentially the same procedure as the 8-aminoquinoline group; that is, the appropriate alkylaminoalkyl halide was coupled with the aromatic amine in aqueous solution. Salts can also be prepared by a similar convenient method; that is, the distilled base was dissolved in aqueous acetic acid and the hydrohalogen acid salt was precipitated with the desired sodium halide.

Preparation of similar compounds containing a hydroxyl in the side-chain offered difficulties in preparation of the required aminohydroxyalkyl halide and in coupling with p-chloroaniline, particularly the latter. In the case of 1-(p-chloroanilino)-3-isopropylamino-2-propanol a synthesis useful only for a three-carbon side-chain was used,

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[16] F. Y. Wiselogle, op. cit., Vol. II, pp. 274-353.

the reaction of p-chloroaniline, isopropylamine, and epichlorohydrin. This gave the desired product in 6% yield together with several by-products which could be isolated, and a large amount of polymer. The by-products were an oil and a low-melting hygroscopic solid; the oil has been tentatively identified as 1,3-diisopropylamino-2-propanol. A probable empirical formula of $C_6H_{13}NO$ has been found for the solid; its structure has not been proved.

Preparation of 5-(p-chloroanilino)-1-isopropylamino-2-pentanol offered difficulties in the coupling of the side-chain with p-chloroaniline. The corresponding keto side-chain, 5-bromo-1-isopropylamino-2-pentanone hydrobromide, was made available by synthesis, but attempts to couple this with p-chloroaniline led only to high-melting insoluble material due to the complicating presence of the ketone group. Only one method of reduction to the alcohol, the Meerwein-Ponndorf method, seemed feasible, and this offered the possibility of ring formation. It was found possible to carry out this reduction and couple directly with p-chloroaniline, but the yield was quite low. However, the compound was isolated and identified.

Attempts to make the side-chain necessary for the isomeric 3-pentanol led uniformly to failure. It is not possible to make the Grignard reagent of 2-alkoxyethyl bromides, which could lead to an intermediate ketone.[17] In another approach, both the Thorpe[18] and Ziegler[19] reactions were found to be of no use in the case of β-methoxypropionitrile.

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[17] R. C. Tallman, J. Am. Chem. Soc., 56, 126 (1934).

[18] J. F. Thorpe, J. Chem. Soc., 95, 1901 (1909).

[19] K. Ziegler, H. Eberle, and H. Ohlinger, Ann., 504, 94 (1933).

The sodium ethoxide used as catalyst in the former had no action at all on the nitrile, and the lithium derivatives of secondary amines used in the latter led to a polymer and recovered starting material. In still another approach, the feasibility of the Reformatsky reaction using an aldehyde and α-bromoacetonitrile was investigated. It was found using benzaldehyde that the reaction proceeded in low yield but led to the unsaturated nitrile (cinnamic nitrile) rather than to the desired substituted β-hydroxynitrile.

Lack of time prevented investigation of several other approaches to the necessary intermediate side-chain. Perhaps the most promising approach would be the reaction of allyl magnesium bromide with β-methoxypropionitrile to give allyl 2-methoxyethyl ketone. Oxidation to the glycol and reduction of the ketone by a Meerwein-Ponndorf reaction followed by a periodic acid oxidation should lead to 3-hydroxy-5-methoxypentanal. If this compound could be obtained, a reductive isopropylamination should give a compound exactly analogous to the 1-isopropylamino-5-methoxy-2-pentanol used as an intermediate in the preparation of 5-(p-chloroanilino)-1-isopropylamino-2-pentanol (see Experimental).

Another possible method would start with investigation of a method for a catalytic transformation of β-methoxypropionic acid or one of its salts to 1,5-dimethoxy-3-pentanone. After cleavage with one molecular equivalent of hydrobromic acid, it should be possible to isolate 1-bromo-5-methoxy-3-pentanone, which, by an amination reaction with isopropylamine, should give 1-isopropylamino-5-methoxy-3-pentanol.

Still another possibility of making the same intermediates lay in the reactions of divinyl ketone. If one molecule of isopropylamine and

one molecule of methanol could be added stepwise, 1-isopropylamino-5-methoxy-3-pentanone could be prepared. Otherwise, addition of two molecules of methanol would lead to 1,5-dimethoxy-3-pentanone, after which the synthesis would be carried forward as described above.

EXPERIMENTAL

6-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline - Method I. - A mixture of 19.8 g. of 4,6-dichloroquinoline[20] and 34.8 g. of Noval diamine was stirred and heated at 155-160° for five hours and at 160-170° for two and one-half hours. The reaction mixture was taken up in aqueous acetic acid and the solution filtered to remove unreacted quinoline nucleus. The filtrate was made strongly alkaline with sodium hydroxide and extracted with ether. The product was obtained from the dried ether solution by distillation. The yield was 24.4 g.; the boiling point was 180-185° (0.1 mm.). The base was crystallized from benzene-Skellysolve F; the yield was 15.1 g. (48.8%), of crystals which melted at 71-73°. Anal. Calcd. for $C_{18}H_{26}N_3Cl$: C, 67.55; H, 8.19. Found: C, 66.16; H, 7.73.

6-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline Diphosphate Dihydrate. - To a solution of 12.8 g. of base in 9.2 g. of 85% phosphoric acid and 50 ml. of water were added 25 ml. of methanol and 140 ml. of 2-propanol. After the mixture had stood in the refrigerator for three days, the crystals were removed by filtration and washed with 2-propanol and ether. The yield of salt was 17.5 g. (79.5%); the melting point was 152.4-154.0°. Anal. Calcd. for $C_{18}H_{26}N_3Cl \cdot 2H_3PO_4 \cdot 2H_2O$: P, 11.21; moisture, 6.52. Found: P, 11.42; moisture, 6.26 (at 100°, no vacuum).

4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline[21] - Method II. A mixture of 49 g. of 4-chloro-2-phenylquinoline[22] and 63 g. of

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[20] D. S. Tarbell, J. Am. Chem. Soc., 68, 1277 (1946).

[21] U. P. Basu and P. K. Das-Gupta, J. Ind. Chem. Soc., 16, 301 (1939); C. A., 34, 1021 (1940).

[22] R. C. Elderfield, et al., J. Am. Chem. Soc., 68, 1272 (1946).

TABLE I

4-Aminoquinolines

Product	SN[a]	Reaction Temp., °C.[b]	Reaction Time, hr.	Method	B. p., °C.	B. p., Mm.	M. p., °C.	Yield, %
6-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline	11,046	155-170	7½	I	180-185	0.1	71-73	49
4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline	10,552	165-185	14	II	225-250	0.5	oil	85
7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline	10,555	155-187	5½	III	225-231	0.1	oil	44
2,2'-[3-(7-Chloro-4-quinolylamino)-propylimino]diethanol	10,562	95-105	6½	I	not distilled		110.5-111.4	63
4-(3-Aminopropylamino)-7-chloroquinoline	11,438	120-145	2½	II	195-200	0.3	87.8-89.8	44
7-Chloro-4-(5-diethylamino-1-methylamylamino)quinoline	10,961	170-180	6	II	235-238	0.5	80.5-82.0	72
2-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline plus isomer	10,963	150	6	I	200-210	0.5	oil	52
8-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline	11,407	158-173	4½	II	not distilled		122.9-123.5	36
7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-phenylquinoline	10,556	165-175	15	II	235-245	0.001	oil	80
4-(4-Diethylamino-1-methylbutylamino)-7-methoxyquinoline	11,421	160-180	3	II	230-240	0.5	101.0-101.7	77[c]
4-(4-Diethylamino-1-methylbutylamino)-8-methoxyquinoline	10,661	165-175[d]	2	II	220	0.5	138.3-139.7	35
4-(4-Diethylamino-1-methylbutylamino)-7-methoxy-2-phenylquinoline	10,549	161-166	12	III	238-242	0.2	oil	53

[a]These Survey Numbers identify the drugs in F. Y. Wiselogle, A Survey of Antimalarial Drugs, op. cit.

[b]Temperatures given are those of the reaction mixture.

[c]Yield of crude product.

[d]The temperature rose briefly to 215° due to heat of reaction.

Noval diamine was stirred and heated at 170-190° for fourteen hours. Strong alkali was added after cooling, and the mixture was extracted with ether. The dried extracts were concentrated and the residue was distilled in vacuo. The yield was 62.7 g. (85%); the boiling point was 225-250° (0.5 mm.). The base did not crystallize; it was converted to the salt for analysis.

4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline Triphosphate. - To a solution of 20.1 g. of the base in 78 ml. of water and 17.0 g. of 85% phosphoric acid were added 40 ml. of methanol and sufficient 2-propanol to cause turbidity. The turbid solution was seeded and cooled overnight in a refrigerator. The salt was removed by filtration and washed with 2-propanol and ether; it weighed 23.4 g. and melted at 168-171°. After recrystallization from water-methanol-2-propanol, the product weighed 19.5 g. (56%); the melting point was 174-176°. Anal. Calcd. for $C_{24}H_{31}N_3 \cdot 3H_3PO_4$: P, 14.2. Found: P, 14.4, 14.5.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline[3,4] - Method III. - A mixture of 25 g. of 4,7-dichloro-3-phenylquinoline,[23] 8.6 g. of phenol and 31.8 g. of Noval diamine was stirred and heated at 155° for one hour and at 185° for four and one-half hours. Aqueous acetic acid was added and the solution was decanted from non-basic impurities.[24] The supernatant liquid was extracted with ether and

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[23] R. C. Elderfield and J. B. Wright, ibid., 68, 1276 (1946).

[24] During the period of heating at 155°, an exothermic reaction took place; however, after this reaction was over, the reaction mixture was insoluble in 5% nitric acid, indicating that the desired reaction had not taken place. This evidence is supported by the isolation of a new compound, presumably the 4-phenoxyquinoline, by concentrating the ether solution of the non-basic material, washing with warm water to remove phenol, and recrystallizing the product from methanol. This procedure gave 2.7 g. of white crystals which melted at 141.5-143.5°.

the extracts were added to the original insoluble material. The aqueous phase was then made strongly basic and again extracted with ether. The product was obtained from the ether solution by distillation. The fraction collected boiled at 225-230° (0.1 mm.) and weighed 15.9 g. (44.1%). The base could not be recrystallized successfully; it was converted to the salt for analysis.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline Dihydriodide. - To a solution of 15.65 g. of base in a mixture of 50 ml. of water, 50 ml. of ethanol, and 9.11 g. of 85% phosphoric acid was added a solution of 13.1 g. of potassium iodide in 150 ml. of water. The yellow dihydriodide which formed was removed by filtration; it weighed 23 g. A composite from several experiments (29 g.) was recrystallized from methanol and then stirred for five hours with warm water (50°) and again separated by filtration and dried. The yield was 21 g.; the melting point was 263-273° d. Anal. Calcd. for $C_{24}H_{30}N_3Cl \cdot 2HI$: C, 44.2; H, 4.95. Found: C, 44.11; H, 4.78.

2,2'-[3-(7-Chloro-4-quinolylamino)-propylimino]diethanol. The preparation of this compound from 9.9 g. of 4,7-dichloroquinoline and 17.9 g. of 1-diethanolamino-3-aminopropane[25] was carried out by Method I. However, the oil which separated after the acetic acid solution was made alkaline was washed with water until it crystallized. After recrystallization, first from alcohol-water, and then from alcohol-ether, the yield of white crystals was 10.1 g. (63% overall); the melting point was 110.5-111.4°.

2,2'-[3-(7-Chloro-4-quinolylamino)-propylimino]diethanol Diphosphate. - To a solution of 6.48 g. of base in 4.62 g. of 85% phosphoric

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[25]Supplied by Dr. R. C. Elderfield, Columbia University.

acid and 20 ml. of water were added 12 ml. of methanol and 5 ml. of 2-propanol. The crystalline salt was removed by filtration and dried; the yield was 10.2 g. (98%); the melting point was 199.4-201.2°. Anal. Calcd. for $C_{16}H_{22}N_3O_2Cl \cdot 2H_3PO_4$: P, 11.92. Found: P, 11.86.

1-Acetamino-3-aminopropane. - A mixture of 28 g. of 1,3-diaminopropane and 33.3 g. of ethyl acetate was heated in a sealed tube at 100° for twelve hours.[26] Distillation yielded 16 g. (36%) of product which boiled at 130-140° (2.5 mm.).

4-(3-Aminopropylamino)-7-chloroquinoline. - The condensation of 16.0 g. of 1-acetamino-3-aminopropane and 12.4 g. of 4,7-dichloroquinoline was carried out by Method II, and the solid obtained on addition of alkali was then boiled seven hours with 20% hydrochloric acid to remove the acetyl group. The product crystallized on neutralization of the solution and was recrystallized from benzene-Skellysolve F. The crude product was distilled in vacuo; the boiling point was 195-200° (0.3 mm.). The compound was again recrystallized to give 6.53 g. (44%) of a product which melted at 87.8-89.8°. Anal. Calcd. for $C_{12}H_{14}N_3Cl$: C, 61.20; H, 5.97; N, 17.83. Found: C, 60.91, 60.73; H, 6.03, 5.90; N, 17.74, 17.37.

4-(3-Aminopropylamino)-7-chloroquinoline Diphosphate. Two molecular equivalents of 85% phosphoric acid were added dropwise with stirring to a refluxing solution of 6.33 g. of base in 150 ml. of ethanol. After one hour's stirring, the mixture was cooled and filtered, yielding 12.65 g. of a white powder (99% based on a diphosphate monoethanolate) which melted at 205.9-209.6°. Anal. Calcd. for $C_{12}H_{14}N_3Cl \cdot 2H_3PO_4 \cdot C_2H_5OH$:

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[26] S. R. Aspinall, J. Am. Chem. Soc., 62, 2160 (1940).

P, 12.98. Found: P, 13.02, 12.93. For some unknown reason it was impossible to obtain consistent alkoxyl analyses.

7-Chloro-4-(5-diethylamino-1-methylamylamino)quinoline. - The condensation of 28.4 g. of 4,7-dichloroquinoline and 1-diethylamino-5-aminohexane[27] was carried out by Method II. Vacuum distillation gave 38 g. of a product which crystallized in the receiver after boiling at 235-238° (0.5 mm.). Two recrystallizations from benzene-Skellysolve B gave 31.2 g. of crystals (72.3% overall); the melting point was 80.5-82.0°. Anal. Calcd. for $C_{19}H_{28}N_3Cl$: C, 68.3; H, 8.45. Found: C, 67.6, 68.0; H, 8.42, 8.19.

7-Chloro-4-(5-diethylamino-1-methylamylamino)quinoline Diphosphate. - To a solution of 12.1 g. of base in a mixture of 8.36 g. of 85% phosphoric acid and 48 ml. of water were added 24 ml. of methanol and 150 ml. of 2-propanol. Crystallization was allowed to proceed in a refrigerator for three days, whereupon the salt was removed by filtration and washed with 2-propanol and ether. The yield weighed 15 g. (78%); the melting point was 186.8-190.8°. Anal. Calcd. for $C_{19}H_{28}N_3Cl \cdot 2H_3PO_4$: P, 11.7. Found: P, 12.3.

2-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline and 4-Chloro-2-(4-diethylamino-1-methylbutylamino)quinoline. - The condensation of 30 g. of 2,4-dichloroquinoline[25] and 58 g. of Noval diamine was carried out by Method I. Vacuum distillation gave 25 g. (51.6%) of an oil which boiled at 200-210° (0.5 mm.). The isomers could not be crystallized or satisfactorily fractionated.

2-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline and 4-Chloro-

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[27] F. P. Anderson, J. V. Crawford, and E. L. Sherrill, ibid., 68, 1294 (1946).

2-(4-diethylamino-1-methylbutylamino)quinoline Diphosphate Trihydrates. - To 19.8 g. of base were added 14 g. of 85% phosphoric acid and 45 ml. of water. Dioxane was added to turbidity (100 ml.), and the mixture was seeded and allowed to stand for several hours, whereupon an additional 100 ml. of dioxane was added. After standing overnight the salt was removed by filtration, washed with 80% aqueous dioxane and redissolved in a small amount of water. This aqueous solution was added slowly to 250 ml. of 2-propanol while the mixture was seeded. The product was removed by filtration and washed with 2-propanol. The yield of salt was 48% of the calculated amount; the melting point was 95-99°. Anal. Calcd. for $C_{18}H_{26}N_3Cl \cdot 2H_3PO_4 \cdot 3H_2O$: P, 10.87. Found: P, 10.93.

8-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline. - The condensation of 9.9 g. of 4,8-dichloroquinoline[20] and 17.5 g. of Noval diamine was carried out by Method II. However, the product crystallized from the first two 30-ml. ether extracts of the alkaline mixture. It was removed by filtration and washed first with a third 30-ml. extract and then with 15 ml. of fresh ether. The yield of nearly white crystals was 5.7 g. (35.6%); the melting point was 123.0-123.7°. Recrystallization from benzene-Skellysolve F gave a 97% recovery of crystals which melted at 122.9-123.5°. Anal. Calcd. for $C_{18}H_{26}N_3Cl$: C, 67.6; H, 8.19. Found: C, 68.58; H, 7.96.

8-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline Diphosphate Trihydrate. - To a solution of 7.25 g. of base in 5.24 g. of 85% phosphoric acid and 29 ml. of water were added 15 ml. of methanol and 57 ml. of 2-propanol. After the mixture had stood in a refrigerator for two days, the solid was removed by filtration and washed with 2-propanol and ether. A second crop of crystals was obtained by

concentration of the filtrate. The yield of salt was 11.1 g. (86%); it melted at 119.5-120.8° with previous sintering at 116°. This material was heated under reflux in boiling ethanol for eight hours; the mixture was cooled and the solid removed by filtration. It weighed 10.7 g., and melted at 121.4-122.1°. Anal. Calcd. for $C_{18}H_{26}N_3Cl \cdot 2H_3PO_4 \cdot 3H_2O$: P, 10.87; moisture, 9.48. Found: P, 10.83; moisture 10.0 (at 100°, no vacuum).

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-phenylquinoline. - The condensation between 33 g. of Noval diamine and 26 g. of 4,7-dichloro-2-phenylquinoline[22] was carried out by Method II. Vacuum distillation gave 30 g. (80%) of a viscous oil which boiled at 235-245° (1 micron).

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-phenylquinoline Diphosphate. - A solution of 25.6 g. of base in 70 ml. of water containing 14.92 g. of 85% phosphoric acid was warmed with Darco and filtered. After the addition of 35 ml. of methanol to the filtrate, 2-propanol was added until the solution was turbid. The salt was allowed to crystallize overnight in a refrigerator, and was then removed by filtration and recrystallized from warm water and 2-propanol as before. The yield was 18.9 g. (46.5%); the melting point was 248-252°. Anal. Calcd. for $C_{24}H_{30}N_3Cl \cdot 2H_3PO_4$: P, 10.5. Found: P, 10.9, 11.0.

4-(4-Diethylamino-1-methylbutylamino)-7-methoxyquinoline. - The condensation of 52 g. of 4-chloro-7-methoxyquinoline[28] and 93.5 g. of Noval diamine was carried out by Method II. Vacuum distillation gave 65 g. (77%) of an oil which boiled at 230-240° (0.5 mm.). This material

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[28] A. M. Lauer, et al., ibid., 68, 1268 (1946).

was crystallized twice from Skellysolve B with use of Norit and seven more times without use of carbon. The yield was 28 g. (33.2% overall) of white crystals melting at 101.0-101.7°. Anal. Calcd. for $C_{19}H_{29}N_3O$: C, 72.35; H, 9.26; methoxyl, 9.85. Found: C, 71.70, 72.05; H, 8.71, 8.83; methoxyl, 9.61, 9.90.

4-(4-Diethylamino-1-methylbutylamino)-7-methoxyquinoline Diphosphate. - To a solution of 6.68 g. of base in 4.88 g. of 85% phosphoric acid and 27 ml. of water were added 14 ml. of methanol and 50 ml. of 2-propanol. After the mixture had stood overnight in a refrigerator, 10.0 g. of salt was obtained by filtration and drying, which melted, after sintering at 170°, at 198-200°. This substance was heated under reflux in boiling ethanol for six hours and allowed to stand overnight. The salt was then filtered from the solution and dried; the yield was 9.4 g. (86.7%); the melting point was 197.9-199.1°. Anal. Calcd. for $C_{19}H_{29}N_3O \cdot 2H_3PO_4$: P, 12.1 Found: P, 11.9.

4-(4-Diethylamino-1-methylbutylamino)-8-methoxyquinoline. - The condensation of 49.5 g. of 4-chloro-8-methoxyquinoline[28] and 89 g. of Noval diamine was carried out by Method II. However, the product crystallized from the ether extracts of the basic solution; a yield of 42 g. (52%) was obtained. Since crystallization failed to give a sample of analytical purity, the base was distilled, boiling at 220° (0.5 mm.), and again recrystallized (96% recovery) to give crystals melting at 138.3-139.7°. Anal. Calcd. for $C_{19}H_{29}N_3O$: C, 72.35; H, 9.26; methoxyl, 9.85. Found: C, 71.67; H, 8.77; methoxyl, 9.35.

4-(4-Diethylamino-1-methylbutylamino)-8-methoxyquinoline Diphosphate Trihydrate. - To 10.2 g. of base in 7.47 g. of 85% phosphoric acid and 40 ml. of water were added 20 ml. of methanol and 83 ml. of

2-propanol. After the mixture had been cooled in a refrigerator overnight, the salt was removed by filtration and washed with 2-propanol and ether. For purification the crude salt was heated under reflux in boiling alcohol for eight hours, cooled, and filtered. The yield was 14.7 g. (80%); the melting point was 127.5-128.4°. Anal. Calcd. for $C_{19}H_{29}N_3O \cdot 2H_3PO_4 \cdot 3H_2O$: P, 10.95; moisture, 9.55. Found: P, 10.90; moisture, 9.80 (at 100°, no vacuum).

4-(4-Diethylamino-1-methylbutylamino)-7-methoxy-2-phenylquinoline. - The condensation of 9.0 g. of 4-chloro-7-methoxy-2-phenylquinoline[22] and 12 g. of Noval diamine in the presence of 3.2 g. of phenol was carried out by Method III. However, the reaction mixture was taken up directly in base without acetic acid treatment. Vacuum distillation gave 6.95 g. (53%) of an oil boiling at 238-242° (0.2 mm.).

4-(4-Diethylamino-1-methylbutylamino)-7-methoxy-2-phenylquinoline Triphosphate. - The base (5.25 g.) was stirred thoroughly with a mixture of 4.54 g. of 85% phosphoric acid and 20 ml. of water. The solution was decanted from undissolved material, and to it were added 11 ml. of methanol and 52 ml. of 2-propanol; the mixture was then cooled for three hours. Filtration yielded 6.34 g. of salt which melted at 194.5-197.5°. Recrystallization from water-methanol-2-propanol produced 5.65 g. (62%) of nearly white crystals which melted at 195.0-197.5°. Anal. Calcd. for $C_{25}H_{33}N_3O \cdot 3H_3PO_4$: P, 13.56. Found: P, 13.21.

5-sec.-Butylamino-1-pentanol. - A mixture of 10.5 ml. of concentrated hydrochloric acid and 126 ml. of distilled water was cooled to 4°, the cooling bath was removed, and 42 g. of dihydropyrane was added with stirring. Stirring was continued for ten minutes after the mixture

became homogeneous, and then 74.3 ml. of sec.-butylamine was added while the temperature was held at 20°. The mixture was hydrogenated in a low-pressure apparatus in the presence of platinum. The filtered reduction mixture was made basic and extracted with Skellysolve C. The extracts were concentrated and the residue distilled in vacuo to give 59 g. (74.3%) of a low-melting solid which boiled at 107-109° (3.5 mm.).[13]

N-(5-Chloroamyl)sec.-butylamine Hydrochloride. To a stirred solution of 59 g. of the aminoalcohol in 370 ml. of Skellysolve C was added 49 g. of thionyl chloride in one portion. The suspension was stirred and refluxed for two hours, 100 ml. of solvent was distilled, and the product was removed by filtration and washed with ether. The yield was 75.5 g. (95%); the melting point was 146.0-148.3°. A sample purified for analysis by recrystallization from alcohol-ether melted at 145.5-147.0°. Anal. Calcd. for $C_9H_{20}ClN \cdot HCl$: C, 50.50; H, 9.89. Found: C, 50.28, 50.54; H, 9.82, 9.82.

8-(5-sec.-Butylaminoamylamino)-6-methoxyquinoline. - A mixture of 130.8 g. of crude N-(5-chloroamyl)sec.-butylamine hydrochloride, 213 g. of 8-amino-6-methoxyquinoline, and 150 ml. of water was heated with stirring at 80° for twenty hours and at 103° for four hours. The melt was poured into water, and alkali and sodium acetate were added until the pH, followed by a Beckman pH meter, rose to 5.0. The mixture was heated to 65-85° and extracted with toluene.[29] The hot suspension was cooled to 20° with stirring and the solid hydrochloride was removed by filtration. It was treated with aqueous alkali and extracted

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[29] The small amount of crystalline material that separated from the cooled toluene extracts was returned to the aqueous mixture, as was a 200-ml. aqueous extract of the combined toluene extracts. After concentration and distillation in vacuo, 100 g. of 8-amino-6-methoxyquinoline was recovered from the toluene extracts.

with ether. The product was obtained from the dried, concentrated ether solution by distillation *in vacuo*. The yield of oil boiling at 155-165° (3 microns) was 108 g., the refractive index was $n_D^{25} = 1.5708$. Redistillation of the forerun gave an additional 22 g.; the total yield was 130 g. (67.8%).

8-(5-sec.-Butylaminoamylamino)-6-methoxyquinoline Monohydrobromide. - A solution of 75 g. of the base in 50 ml. of ethanol was dissolved in a mixture of 1.5 l. of water and 28.6 g. of acetic acid, and 103 g. of sodium bromide dissolved in a small amount of water was added. The crystallized product was removed by filtration, washed with water, and dried. The yield was 93 g. (98%); the melting point was 164-165°. This was recrystallized from ethanol to give 81 g. of crystals which melted at 164.3-165.1°. Anal. Calcd. for $C_{19}H_{29}N_3O \cdot HBr$: C, 57.50; H, 7.63. Found: C, 57.67, 57.50; H, 7.62, 7.56.

The monohydrochloride, which melted at 150.0-151.5°, and the monohydriodide, whose melting point was 151.5-153.0°, were also prepared.

4-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline. - The condensation of 22.1 g. of 1,4-dichloroisoquinoline[14] and 39.0 g. of Noval diamine was carried out by Method I (p. 12). However, the acetic acid solution was extracted to remove unreacted isoquinoline nucleus. Vacuum distillation gave 21.5 g. (61%) of an oil boiling at 167-169° (0.2 mm.). Conversion to salts gave no compounds of definite composition; therefore the mixture of phosphates was reconverted to free base and the oil was analyzed after redistillation. Anal. Calcd. for $C_{18}H_{26}N_3Cl$: C, 67.6; H, 8.18. Found: C, 66.8, 66.9; H, 7.89, 8.33.

5-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline. - The condensation of 19.8 g. of 1,5-dichloroisoquinoline[14] and 34.8 g.

TABLE II

1-(4-Diethylamino-1-methylbutylamino)isoquinolines

Product	SN[a]	Reaction Temp., °C.[b]	Reaction Time, hr.	B. p., °C.	B. p., Mm.	Yield, % Base	Yield, % Salt	Salt Prepared	M. p., °C.
4-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline	14,038	160-165	1½	167-169	0.2	61	-	None	
5-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline	11,447	155-160	5½	200-218	0.4	65	49	Diphosphate	107-115
8-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline	13,806	160-170	1	162-167	0.2	69	82	Triphosphate	154.0-155.9

[a]These Survey Numbers identify the drugs in F. Y. Wiselogle, A Survey of Antimalarial Drugs, op. cit.

[b]Temperatures given are those of the reaction mixture.

TABLE III

1-(4-Diethylamino-1-methylbutylamino)phthalazines

Product	SN[a]	Reaction Temp., °C.[b]	Reaction Time, hr.	Salt Prepared	M. p., °C.	Yield, %
6-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine	11,614	87-100	3½	Diphosphate	235 d.	39
7-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine	11,615	95-100	4	Dihydriodide	164.6-165.8	16
1-(4-Diethylamino-1-methylbutylamino)phthalazine	11,069	100	3	Triphosphate Monohydrate	170-190	8

[a]These Survey Numbers identify the drugs in F. Y. Wiselogle, A Survey of Antimalarial Drugs, op. cit.

[b]Temperatures given are those of the reaction mixture.

of Noval diamine was carried out by Method II. Vacuum distillation gave 20.8 g. (65%) of an oil boiling at 200-216° (0.4 mm.).

5-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline Diphosphate. - The salt was precipitated from a solution of 12.72 g. of base in a mixture of 9.2 g. of 85% phosphoric acid and 25 ml. of water by the addition of 50 ml. of 2-propanol and prolonged cooling; the yield of a tan powder was 16.5 g. The salt was reconverted to base and the latter was taken up in benzene and washed with water whereupon the solvent was removed *in vacuo*. The residual oil was dissolved in ethanol and stirred while the appropriate amount of 85% phosphoric acid was added. The resulting suspension was stirred for several days at room temperature before filtration; the yield was 10.1 g. (49%) of a light tan salt dried to constant weight; the melting point was 107-115°. Anal. Calcd. for $C_{18}H_{26}N_3Cl \cdot 2H_3PO_4$: P, 12.01. Found: P, 12.35, 12.37.

8-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline. - The condensation of 19.8 g. of 1,8-dichloroisoquinoline[14] and 34.9 g. of Noval diamine was carried out by Method I. Vacuum distillation gave 22 g. (69%) of an oil boiling at 162-167° (0.3 mm.).

8-Chloro-1-(4-diethylamino-1-methylbutylamino)isoquinoline Triphosphate. - The triphosphate was precipitated twice from a stirred solution of the base in ethanol; the impure salt first obtained was reconverted to base, extracted with ether, washed, and freed from ether *in vacuo*. The product was converted to pure triphosphate in the same way. The crude salt (38 g., 91%, from 21.7 g. of base) melted at 153-155°. The purified salt (17.6 g., 90% from 10.2 g. of base) melted at 154.0-155.9°. Anal. Calcd. for $C_{18}H_{26}N_3Cl \cdot 3H_3PO_4$: C,

35.22; H, 5.75; F, 15.15. Found: C, 35.49, 35.71; H, 5.60, 5.83; F, 15.08, 15.04.

6-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine. - A mixture of 27.8 g. of 1,6-dichlorophthalazine[15] and 87 g. of Noval diamine was stirred and heated at 87-100° for three and one-half hours. The reaction was sufficiently exothermic so that an appreciable temperature differential was established between the oil-bath and the mixture of reactants. When the internal temperature dropped below the bath temperature, the reaction was assumed to be complete. The mixture was cooled and 200 ml. of ether and 50 ml. of 20% sodium hydroxide were added. The layers were separated and the ethereal solution was exhaustively extracted with water to remove excess side-chain. The ether was removed by distillation *in vacuo*, and the oily residue was slurried successively with two 100-ml. portions of Skellysolve F, which were decanted. The remaining oil, after heating under reduced pressure to remove petroleum ether, weighed 27 g. Attempts to purify the compound were unsuccessful; it was therefore converted to the diphosphate which was easier to purify.

6-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine Diphosphate. - To 25.2 g. of the crude base were added 26.0 g. of 85% phosphoric acid and 100 ml. of water. The suspension was centrifuged to remove a small amount of insoluble amorphous material, and the supernatant liquid was filtered and diluted to 150 ml. with water. To the solution was added 200 ml. of 2-propanol, and crystallization was allowed to proceed for two days in a refrigerator. The salt, after removal by filtration (27 g.), was redissolved in water and reprecipitated by 2-propanol. The yield was 23 g. (39% overall); the melting

point was 235° d. Anal. Calcd. for $C_{17}H_{25}N_4Cl \cdot 2H_3PO_4$: P, 12.00. Found: P, 12.11.

7-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine. - The condensation of 24.75 g. of 1,7-dichlorophthalazine[15] and 87 g. of Noval diamine was carried out by the method given for 1,6-dichlorophthalazine. However, after the ether solution was washed exhaustively with water, the ether was replaced by benzene and the solution was dried azeotropically before removal of solvent *in vacuo* and washing with Skellysolve. The residue weighed 23.4 g. (58.5%).

7-Chloro-1-(4-diethylamino-1-methylbutylamino)phthalazine Dihydriodide. - To 21.3 g. of base were added 29.8 g. of freshly distilled 57% hydriodic acid and 30 ml. of water. The suspension was stirred and filtered, and the insoluble material was washed with a little water. From the cooled filtrate 14.6 g. of salt was obtained; an additional 1.4 g. was obtained by concentration. The crude material was recrystallized in succession from alcohol-ether, water, and ethanol; the yield of yellow crystals melting at 164.6-165.8° was 10.4 g. (16% overall from 1,7-dichlorophthalazine). Anal. Calcd. for $C_{17}H_{25}N_4Cl \cdot 2HI$: C, 35.4; H, 4.71. Found: C, 35.18, 35.06; H, 4.82, 4.69.

1-(4-Diethylamino-1-methylbutylamino)phthalazine. - The condensation of 54.9 g. of 1-chlorophthalazine[15] and 116 g. of Noval diamine was carried out by the method described for 1,7-dichlorophthalazine. The solvent-free oil weighed 33.5 g.

1-(4-Diethylamino-1-methylbutylamino)phthalazine Triphosphate Monohydrate. - To the base were added 23.4 g. of 85% phosphoric acid and 100 ml. of water. After filtration from insoluble material, the volume of the solution was brought to 150 ml. with water and 200 ml.

of 2-propanol was added. Cooling overnight caused the crystallization of 18 g. of salt, which was recrystallized from water and 2-propanol; the yield was 13.4 g. (8% overall from 1-chlorophthalazine); the melting point was 170-190°. Anal. Calcd. for $C_{17}H_{26}N_4 \cdot 3H_3PO_4 \cdot H_2O$: P, 15.54; moisture, 3.0. Found: P, 14.89, 15.03; moisture, 2.87.

4-Isopropylamino-2-butanol. - A mixture of 37 g. of freshly distilled aldol, 24.8 g. of isopropylamine and 120 ml. of ethanol was hydrogenated in a low-pressure apparatus in the presence of platinum; the hydrogen uptake was about 25% in excess of the calculated. The filtered reduction mixture was concentrated and distilled *in vacuo*; everything boiling up to 90° (16 mm.) was collected. The distillate crystallized and, after decantation of a small amount of supernatant liquid, the residue was redistilled to give 27 g. (49%) boiling at 83-86° (12 mm.). The calculated neutral equivalent for $C_7H_{17}NO$ is 131.2. Found: 137.6.

3-Chloro-N-isopropylbutylamine Hydrochloride. To a vigorously stirred solution of 58 g. of the crude aminoalcohol in 450 ml. of Skellysolve C was added 58 g. of thionyl chloride. The suspension was refluxed for one hour and 150 ml. of solvent was distilled. The product was removed by filtration; the yield was 80 g. (97%); the melting point was 129-133°. A sample purified for analysis melted at 147.8-148.5°. Anal. Calcd. for $C_7H_{17}Cl_2N$: C, 45.15; H, 9.20. Found: C, 45.51, 45.40; H, 9.50, 9.32.

N^3-(p-Chlorophenyl)-N^1-isopropyl-1,3-butanediamine. - A mixture of 80 g. of 3-chloro-N-isopropylbutylamine hydrochloride, 138 g. of p-chloroaniline, and 54 ml. of water was stirred and heated at 70° for one hour, 80° for nineteen hours, and 103° for four hours. The

TABLE IV

N-Substituted 4-Chloroanilines

Product	M. p., °C.	B. p., °C.	B. p., Mm.	Yield, %	Salt Prepared	M. p., °C.
N^3-(p-Chlorophenyl)-N^1-isopropyl-1,3-butanediamine	oil	103-111	0.03	50	Monohydrobromide	138.6-139.8
N^5-(p-Chlorophenyl)-N^1-isopropyl-1,5-pentanediamine	oil	120-128	0.05	31[a]	Monohydrochloride	153-154
1-(p-Chloroanilino)-3-isopropylamino-2-propanol	104.8-105.6	115	0.03	6	Monohydrochloride	152.4-154.2
5-(p-Chloroanilino)-1-isopropylamino-2-pentanol	91-92	90[b]	0.0005	7	Monohydrochloride	149.5-150.5

[a]Yield of salt

[b]Sublimation temperature

mixture was diluted with 750 ml. of an aqueous solution containing 0.9 mole of sodium acetate, and extracted with a 2-l. portion of ether. An aqueous extract of the resulting ether solution was returned to the two-phase aqueous mixture, which was then further extracted with ether. The mixture was made alkaline and filtered through an asbestos mat, after which it was extracted with ether. The dried ether solution was concentrated and distilled *in vacuo* to give 52 g. (50%) of a very light yellow oil boiling at 103-111° (35 microns); the refractive index was $n_D^{25} = 1.5327$.

N^3-(p-Chlorophenyl)-N^1-isopropyl-1,3-butanediamine Monohydrobromide. - To a solution of 52 g. of the base in a mixture of 26 g. of acetic acid and 200 ml. of water was added a solution of 50 g. of sodium bromide in 100 ml. of water. The product separated as an oil which crystallized on seeding and stirring, and weighed 68 g. (98%) after removal by filtration and drying. This was recrystallized first from ethanol-ether and second from water to give 39 g. of white crystals melting at 138.6-139.8°. Anal. Calcd. for $C_{13}H_{21}N_2Cl \cdot HBr$: C, 48.60; H, 6.90; Br, 24.85. Found: C, 48.60, 48.59; H, 7.13, 7.19; Br, 24.90, 24.92. An inhomogeneity determination showed that the inhomogeneity is 3% ± 2%.[30]

N^5-(p-Chlorophenyl)-N^1-isopropyl-1,5-pentanediamine Monohydrochloride. - A mixture of 50 g. of 5-chloro-N-isopropylamylamine hydrochloride[13], 60 g. of p-chloroaniline and 65 ml. of water was stirred and heated at 80° for twenty hours and at 103° for four hours. The pH of the cooled reaction mixture was brought to 4.75 by the addition

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[30]Determined by the counter-current extraction process. See Craig, J. Biol. Chem., 155, 519 (1944); Craig, *et al.*, *ibid.*, 161, 321 (1945).

of 70 g. of sodium acetate trihydrate in 300 ml. of water, and p-chloroaniline was extracted with ether. The hydrochloride of the coupled product separated slowly from the aqueous solution on continued cooling. This was removed by filtration and washed with dilute sodium chloride solution.[31] After two recrystallizations from alcohol-ether, the yield was 23 g. (31%); the melting point was 153-154°. Anal. Calcd. for $C_{14}H_{23}N_2Cl \cdot HCl$: C, 57.80; H, 8.31. Found: C, 58.18, 57.98; H, 8.19, 8.14.

1-(p-Chloroanilino)-3-isopropylamino-2-propanol. - A mixture of 128 g. of p-chloroaniline and 250 ml. of water was held below 10° while 93 g. of epichlorohydrin was added dropwise. After stirring for one hour at room temperature and for one-half hour at 50°, the mixture was cooled and 59 g. of isopropylamine was added. The mixture was stirred until the heat of reaction subsided, and stirred with heating at 80° for eighteen and one-half hours and at 103° for three hours. The slightly acid solution was extracted with ether and the extracts discarded. The solution was made alkaline and extracted with ether, the dried ether extracts were concentrated, and the residue distilled *in vacuo* to give two fractions. The first consisted of everything distilling up to 120° (30 microns) and the second fraction was the product; it boiled at 120-130° (30 microns), with the oil bath heated

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[31] The filtrate was found to contain the salt corresponding to about 7 g. of a base boiling at 160° (10 microns). When the base was dissolved in an aqueous solution containing half its weight of acetic acid and saturated with sodium chloride, a hydrochloride precipitated which was recrystallized from water-acetone and from ethanol-acetone to give crystals melting at 186.0-187.0°. The analysis corresponded to N^1-(p-chlorophenyl)-N^5-isopropyl-N^5-(5-isopropylaminoamyl)-1,5-pentanediamine dihydrochloride. Anal. Calcd. for $C_{22}H_{40}N_3Cl \cdot 2HCl$: C, 58.15; H, 9.29, ionic Cl, 15.60. Found: C, 58.27, 58.10; H, 9.49, 9.55; Cl, 15.23, 15.22.

to 210°. The forerun was redistilled to give a mixture of two compounds; the first, lower-boiling fraction, crystallized to give a hygroscopic solid, "A". The second, slightly higher-boiling compound was an oil, "B". These compounds will be discussed below. The residue from the redistillation of these two compounds was combined with the original fraction which boiled at 120-130° (30 microns) and redistilled. A fraction which boiled at 115-120° (30 microns) and which later solidified was accepted as product. This was recrystallized from Skellysolve C to give 15 g. (6.2%) of a white crystalline solid whose melting point was 104.8-105.6° with softening at 101°. Anal. Calcd. for $C_{12}H_{19}N_2OCl$: C, 59.40; H, 7.88. Found: C, 59.51, 59.45; H, 8.09, 8.19.

1-(p-Chloroanilino)-3-isopropylamino-2-propanol Monohydrochloride. - To a solution of 2.43 g. of the crystalline base in an aqueous solution containing 1.20 g. of acetic acid was added 2 g. of sodium chloride. The desired salt crystallized and was removed by filtration and washed with cold water. It was recrystallized from absolute ethanol-anhydrous ether to give 2.1 g. of white crystals which melted at 152.4-154.2°. Anal. Calcd. for $C_{12}H_{19}ClN_2O \cdot HCl$: ionic Cl, 12.72. Found: Cl, 12.91, 12.95.

Compounds "A" and "B". - Both these compounds were also prepared by the reaction between isopropylamine and epichlorohydrin (Here too the yield was low; 5 g. of "A" and 10 g. of "B" were obtained from a 1-mole run.), and were shown to be identical with those originally isolated on the basis of boiling points, and on the basis of refractive indexes and neutral equivalent for "B" and on the basis of melting point and mixed melting point for "A". The boiling point of "A" is 91-95° (5.5 mm.); recrystallization from small amounts of petroleum

ether and sublimation *in vacuo* gave crystals which melted at 57.3-58.8°. *Anal.* Calcd. for $C_6H_{13}NO$: C, 62.6; H, 11.3; N, 12.17. Found: C, 63.07, 63.34; H, 11.53, 11.74; N, 11.87, 11.68. On the basis of boiling point, these analyses, and method of synthesis, a suggested structure is 3-hydroxy-1-isopropyltrimethyleneimine. The somewhat higher-boiling oil, compound "B", boiled at 103-104° (5.3 mm.), and the crude oil gave a neutral equivalent of 89.5 (the calculated value is 87.1); the refractive index was $n_D^{25} = 1.449$. The oil was dissolved in ether and alcoholic hydrogen chloride was added; it gave a hydrochloride melting at 266-269° after recrystallization from methanol-acetone. *Anal.* Calcd. for $C_9H_{22}N_2O \cdot 2HCl$: C, 43.7; H, 9.79. Found: C, 43.90, 44.00; H, 9.86, 9.66. On the basis of boiling point, analyses, and method of preparation, the compound is considered identified as 1,3-diisopropylamino-2-propanol.

Methyl 4-Pentenyl Ether.[32] - The preparation of 4-pentenol-1 reported in the literature was carried through as described from 582 g. of tetrahydrofurfuryl chloride and 217 g. of powdered sodium.[33] Instead of decomposing the alkoxide with water at the end of the two-hour stirring period, however, 630 g. of dimethyl sulfate was added slowly with stirring, while a very pasty precipitate separated. After stirring for fifteen minutes after the addition of the dimethyl sulfate, sufficient water was added to change the thick precipitate to a granular salt from which most of the ether solution could be decanted. The solid residue was then dissolved in water and the solution was extracted

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[32] R. Paul, Ann. chim., 18, 303 (1932).

[33] Org. Syn. 25, 84 (1945).

with ether. The combined ether solutions were dried and the whole distilled rapidly to separate the product from non-volatile matter. The distillate was then fractionated to give 400 g. (83%) of methyl 4-pentenyl ether which boiled at 96-97°; the refractive index was $n_D^{25} = 1.3967$.

1-Isopropylamino-5-methoxy-2-pentanol. - To a well-stirred solution of 150 g. (194 ml.) of methoxypentene in 750 ml. of purified dioxane was added slowly 2300 ml. of hypochlorous acid solution, prepared as reported in the literature.[34] The temperature was kept below 15° during the reaction. After addition was complete, the mixture was stirred for one hour, 70 g. of sodium bisulfite and 450 g. of sodium chloride were added and the mixture was extracted with three 600-ml. portions of ether. The dried extracts were concentrated to remove ether, and dioxane was removed under the vacuum of an aspirator.[35]

Two-thirds of the concentrate was dissolved in 375 ml. of anhydrous ether and 130 g. of isopropylamine was added. The mixture was shaken in a hydrogenation bomb at 110° for twenty-four hours. After removing from the bomb, the mixture was extracted with dilute hydrochloric acid. The acid solution was made strongly basic and extracted with ether. The basic ether extracts were dried and concentrated and the residue was distilled *in vacuo*. In the first distillation, about 5 g. of forerun was removed and then everything distilling up to 100° (50 microns) was collected. When the distillate was redistilled, 62.5 g. of a light

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[34] Org. Syn. Coll. Vol. I, p. 158.

[35] If the product of this reaction, 1-chloro-5-methoxy-2-pentanol,[32] is isolated at this point, a yield of 55.5% is obtained; the boiling point is 105-111° (16 mm.), $n_D^{25} = 1.4506$. It was found that better yields were obtained by the overall process without isolation.

yellow oil which boiled at 90-100° (1.2 mm.) (35.6% overall from methoxypentene) was collected.

1-Isopropylamino-5-methoxy-2-pentanol Hydrochloride. - Dry hydrogen chloride was passed over a solution of 62.5 g. of base in 1 l. of anhydrous ether with swirling. The equivalence point can be detected by the appearance of an orange color. The yield of crystalline hydrochloride was removed by filtration and weighed 69 g. Recrystallization from alcohol-ether gave 64 g. (85.5%) of a crude product (m.p. 91-96°), which was satisfactory for use in the next step. Recrystallization to constant melting point gave an analytical sample which melted at 104-105°. Anal. Calcd. for $C_9H_{21}NO_2 \cdot HCl$: C, 51.15; H, 10.47. Found: C, 50.77, 50.76; H, 10.37; 10.26.

1-Isopropylamino-5-methoxy-2-pentanone Hydrochloride. - To a stirred mixture of 31.8 g. of crude 1-isopropylamino-5-methoxy-2-pentanol hydrochloride, 25 g. of potassium dichromate, and 15 ml. of water was added a mixture of 16 ml. of sulfuric acid and 7.5 ml. of water.[36] The mixture was kept below 25° during the addition, which took several hours. The stirred mixture was kept between 20° and 26° for nineteen hours, then dissolved in water, and poured into a large excess of alkali. The organic material was extracted with ether, and the product was precipitated from the dried extracts with alcoholic hydrogen chloride. The crude material weighed 24.5 g. and was recrystallized from acetone to give 14.2 g. (45%) of white crystals melting at 134-139°. By concentration and dilution with ether, a second low-melting crop, which weighed

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[36]The procedure is that described in Org. Syn. Coll. Vol. I, 211.

8.6 g., was obtained.[37] A sample of the first crop was recrystallized to obtain an analytical sample; the melting point was 144-145°. Anal. Calcd. for $C_9H_{19}NO_2 \cdot HCl$: C, 51.60; H, 9.64. Found: C, 51.87, 51.83; H, 9.53, 9.74.

5-Bromo-1-isopropylamino-2-pentanone Hydrobromide. - Fifteen and eight-tenths grams of 1-isopropylamino-5-methoxy-2-pentanone hydrochloride was treated with aqueous alkali and extracted with ether. The solution was dried and the ether removed. The base was dissolved in 175 ml. of constant-boiling hydrobromic acid, and the solution was heated at 90-95° for one hour and at 100° for one-half hour. Excess hydrobromic acid was removed *in vacuo*, and the residue was heated up to 100° under the vacuum of an aspirator. The solid residue was recrystallized from acetone; 16.3 g. (71%) of crystals which melted at 162.6-164.6° were obtained.[38] A portion was recrystallized to constant melting point to obtain an analytical sample; the melting point was 164-165°. Anal. Calcd. for $C_8H_{16}BrNO \cdot HBr$: C, 31.7; H, 5.65. Found: C, 31.73, 32.01; H, 5.60, 5.69.

5-(p-Chloroanilino)-1-isopropylamino-2-pentanol. - To a refluxing solution of 3 g. of aluminum isopropoxide in 50 ml. of anhydrous 2-propanol was added 7 g. of 5-bromo-1-isopropylamino-2-pentanone hydrobromide. The solution was distilled through an efficient fractionating column

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[37] This material is a mixture of product and starting material; on reoxidation by the same procedure a similar yield of pure product is obtained.

[38] A simpler procedure in which the hydrochloride was dissolved in the hydrobromic acid gave an 84.5% yield of melting point 162.8-164.8°. However, this product was shown through analysis to contain some hydrochloride of the product as an impurity.

for thirty minutes and cooled.[39] To it was added 8 g. of p-chloroaniline and, after two hours at room temperature, the flask containing the mixture was placed in an oil bath which was heated at 50° for two hours, at 70° for two hours, at 80° for two hours, and at 100° (reflux) for thirty hours. The mixture was poured into excess alkali and extracted with ether. The ether solution was extracted with sufficient dilute hydrochloric acid to remove compounds containing aliphatic amino groups. The aqueous solution was neutralized and extracted with ether, and the ether solution was dried and concentrated. The residue was molecularly distilled at 10 microns, giving a small forerun of a basic oil and a sublimate which was recrystallized twice from Skellysolve B to give 0.44 g. (7%) of nearly white crystals melting at 90-92°. This compound could not be completely purified by recrystallization, and gave an analysis low in carbon. Therefore the hydrochloride of a small sample of this material was prepared by precipitation from ether solution with alcoholic hydrogen chloride. Recrystallization from acetone removed a small amount of insoluble material and gave a product which after another recrystallization melted at 149.0-150.5°. The carbon content of this compound was still slightly low, so the salt was dissolved in water and the free base was precipitated with dilute sodium hydroxide. The base was filtered, washed well with water, and dried. It was recrystallized from Skellysolve B and sublimed to give crystals which melted at 91-92°.

Anal. Calcd. for $C_{14}H_{23}ClN_2O$: C, 62.1; H, 8.56. Found: C, 61.92, 62.14; H, 8.61, 8.87.

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[39] In a similar experiment distilled for only ten minutes and worked up at this point by pouring on ice and alkali, extracting with ether, and adding dry hydrogen bromide, a mixture of salts was obtained from which a small amount of starting material could be isolated.

α-Valerylvaleronitrile. - To an ethereal solution of phenyllithium prepared from 1.9 g. of lithium and 20 g. of bromobenzene[40] was added 8.2 g. of diethylamine and then 18.7 g. of valeronitrile and the mixture was refluxed for one-half hour. The mixture was decomposed by shaking with 2 N hydrochloric acid, and then extracted with dilute alkali.[19] The basic solution was made acidic and extracted with ether. The product was obtained from the dried ether solution by concentration and distillation *in vacuo*. The yield was 10 g. (54%) of a colorless oil which boiled at 95-98° (2 mm.). A simultaneous run using β-methoxypropionitrile in an attempt to prepare the corresponding cyanoketone and from it 1,5-dimethoxypentanone gave only starting material and a small amount of a solid polymer. None of the products was soluble in alkali.

Cinnamic Nitrile. - A solution of 21 g. of benzaldehyde and 21 g. of α-bromoacetonitrile[41] in 80 ml. of dry benzene was added to 18 g. of granulated zinc over a period of two hours, during which time the mixture was refluxed and stirred. After the mixture was refluxed an additional two hours, it was decomposed with ice-cold 10% sulfuric acid and washed successively with 5% sulfuric acid, 5% potassium carbonate, and with saturated sodium chloride solution until the washings were neutral. The benzene solution was concentrated and the residue was distilled *in vacuo*. After a considerable forerun, an oil weighing 5.1 g. (20%) distilled at 115-125° (40 microns). The distillate was

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[40] H. Gilman, J. Am. Chem. Soc., 54, 1957 (1932).

[41] W. Steinkopf, Ber. 38, 2694 (1905). The yield of the precursor, α-bromoacetamide was raised to 71% by preparing it from bromoacetyl bromide and ammonia gas in anhydrous ether below -14°. The yield of α-bromoacetonitrile from purified amide was raised to 80% by distilling from phosphorus pentoxide in a bath heated to 150° at a pressure of 25 mm.

redistilled molecularly and a middle cut was analyzed. Anal. Calcd. for C_9H_9NO: C, 73.4; H, 6.16. Calcd. for C_9H_7N: C, 83.7; H, 5.47. Found: C, 82.57; H, 6.49. The distillate was hydrolyzed in boiling 10% sodium hydroxide. Ammonia was evolved during the hydrolysis, and a solid precipitate formed when the basic solution was acidified. This precipitate was recrystallized and identified as cinnamic acid by its melting point (133°) and by check neutral equivalents of 146.0 (calc. 148.1).

TABLE V

Testing Data[a]

Compound	Test	Evaluation
8-(5-*sec.*-Butylaminoamylamino)-6-methoxyquinoline	G-4	Q 200
	G-5	Q 80
	2-U	$\frac{1}{2}$ x 971; like pentaquine
N^3-(p-Chlorophenyl)-N^1-isopropyl-1,3-butanediamine	G-5	Q 0.21
1-(p-Chloroanilino)-3-isopropylamino-2-propanol	G-5	Q 0.21

[a]These data are for tests on compounds carried out since publication of F. Y. Wiselogle, *op. cit.* Description of the tests and meaning of the evaluation is described therein.