APPROVAL SHEET

Robert A. Hayes, PhD. 1948

Title of Thesis: Synthetic Antimalarials

Thesis and Abstract approved: Nathan S. Drake

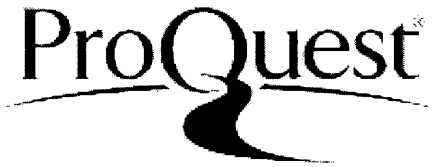
May 15, 1948

SYNTHETIC ANTIMALARIALS

By

Robert A. Hayes

Thesis submitted to the Faculty of the Graduate School
of the University of Marylani in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy
1948



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The author wishes to express his sincere appreciation to Dr. Nathan L. Drake for his continuous interest and counsel during the course of these researches.

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INTRODUCTION

The investigation of the antimalarial properties of 8-aminoquinoline began with the observation of Roehl that this substance had a definite but slight antimalarial effect. Exploitation of this discovery in the laboratories of I. G. Farbenindustrie resulted in the preparation of pamaquine, 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline and some similar compounds. Goldman has reviewed the early work done on these drugs.[1]

Studies in this country have shown that pamaquine effects a radical cure of relapsing vivax malaria when it is administered with quinine.[2] They also have shown that combined pamaquine-quinine therapy is too dangerous for broad practical use.

It became desirable, therefore, to investigate numerous derivatives of the 8-aminoquinolines in an attempt to discover a drug which has the desirable curative action but which has less severe toxic effects. Consequently, several hundred of these compounds have been prepared and examined by the groups working on the cooperative wartime malaria program. The results of these investigations are tabulated and evaluated in the comprehensive report of this work.[2]

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[1]Goldman, Thesis, University of Maryland, College Park, Maryland, 1943.

[2]Survey of Antimalarial Drugs, 1941-1945, Frederick Y. Wiselogle, Editor (J. W. Edwards, Ann Arbor, Michigan, 1946), Vol. I, p. 106 ff. The data on the individual compounds are recorded in Vol. II.

The usual methods of screening potential antimalarial drugs consist of pharmacological tests against various forms of avian malaria in chicks and ducks. These tests are all either for suppressive or prophylactic activity. Since the principle action of the 8-aminoquinolines is curative, it is not surprising that these tests fail to give reliable information as to the activity of the drugs. Recently, a test for the curative action of the 8-aminoquinolines against plasmodium cynomolgi in the rhesus monkey has been devised.[3] The results of this test closely parallel those obtained from clinical trial. Prior to the development of this test, toxicity data obtained from several experimental animals were used to determine whether or not the drug would be investigated clinically.

Toxicity tests have been carried out in the mouse, dog, rat, and rhesus monkey, but only the latter show any differentiation between those drugs which exert a primary effect on the blood and blood-forming organs and those which affect the central nervous system. Furthermore, the monkey reacts in much the same manner as does man in this respect. The toxicity data obtained from the rhesus monkey was therefore used to determine whether or not the drug would be examined clinically. A full description of this test is given in the Survey.[4]

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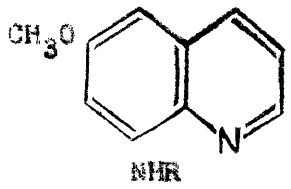
[3]Schmidt, Fradkin, Squires, and Genther, Federation Proceedings, 7, 221 and 253 (1948).

[4]Survey of Antimalarial Drugs, Vol. I, p. 508.

The investigation of 8-aminoquinolines has consisted chiefly of the variation of the side chain in quinolines containing a 6-methoxy substituent. Many variations of R in the structure



have been prepared and examined. A good many of these are recorded in the Survey.[2]

When R is a simple alkyl group, the resulting compounds are unpromising. Their toxicities are nearly as great as that of pamaquine and the suppressive tests indicate that these drugs are only slightly active. The activity is also very small when R is a 3-chloropropyl group.[5]

The introduction of oxygen or sulfur into the side chain as an alcohol, polyalcohol, ether, or thioether gives rise to compounds which are, perhaps, less toxic than pamaquine but which are only very slightly active when assayed against avian malaria.[5]

Snyder and Freier have prepared some compounds where R is some variation of an N-substituted aminopropionyl group.[6] These compounds are also reported to be inactive in avian malaria.

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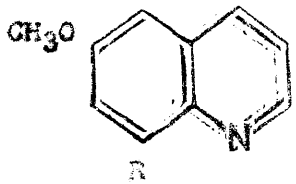
[5]Ibid., Vol. II. See SN 5237, SN 11,162, SN 12,173, SN 7672, and other similar compounds.

[6]Snyder and Freier, J. Am. Chem. Soc., 68, 2485 (1946).

Some ω-(6-methoxy-8-quinolylamino)alkylguanidines have been prepared.[7] These compounds are far less toxic than pamaquine. It is understood that they are to be subjected to clinical trial in the near future.

Funke and co-workers claim that an active and relatively non-toxic compound is obtained when R is a diethylaminobenzyl group.[8] They assayed the compound against plasmodium praecox in canaries.

Cerkovnikov and co-workers have prepared some compounds of the type



in which R is 2-quinuclidylmethylamino, 1-piperidyl, hexamethyleneimino, 4-morpholyl, 4-thiomorpholyl, 4-amino-1-piperidyl, 4-dimethylamino-1-piperidyl, and 4-(3-diethylamino-1-propyl)amino-1-piperidyl.[9] No pharmacological data is published on these compounds.

A great many compounds containing side chains of the types $NHCH(CH_3)(CH_2)_nNRR'$ and $NH(CH_2)_nNRR'$ have been prepared in which the terminal nitrogen is that of a primary, secondary, or tertiary amine. These are the only types of side chains which have been shown to be effective.

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[7]Garman, Thesis, University of Maryland, College Park, Maryland, 1948.

[8]Funke, Bovet, and Montezin, Ann. Inst. Pasteur, 72, 264 (1946). c.f. Chemical Abstracts, 41, 5880 (1947).

[9]Cerkovnikov, Prelog, and Stern, Helv. Chim. Acta, 26, 1180-5 (1943). Rajner, Cerkovnikov, Stern, Arch. Pharm. 281, 78-83 (1943). c.f. Chemical Abstracts, 39, 523 (1945).

The compounds resulting when R and R' are both hydrogen are usually less toxic than pamaquine. Clinical tests on 8-(3-aminopropylamino)-6-methoxyquinoline and the corresponding hexyl derivative have shown, however, that these drugs are probably not sufficiently active to be of general use.[10] It is understood that clinical trials are underway on SN 3851, 8-(5-aminoamylamino)-6-methoxyquinoline. This compound is less than one-tenth as toxic as pamaquine in the rhesus monkey.

When the terminal nitrogen on the side chain is that of a tertiary amine, the resulting drugs are probably too toxic to be of general use. Many variations of R and R' with varying numbers of carbon atoms between the nitrogens have been examined. Rajner and co-workers have examined some compounds of this type for prophylactic action.[11] They report that very little protection is afforded when the side chain is a 2-piperidinobutylamino, 2-piperidinopropylamino, or a 2-diethylaminobutylamino group.

Elderfield has reported that 8-(5-diethylamino-1-methylpentylamino)-6-methoxyquinoline has a suppressive action equal to that of pamaquine in ducks.[2] No toxicity data is available.

Clinical tests for curative action on three compounds, including pamaquine, in which the terminal nitrogen of the side chain is that of a

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[10]Survey of Antimalarial Drugs, 1941-1945, Vol. I, p. 414 and p. 430.

[11]Rajner, Gerkovnikov, and Stern, Arch. Pharm., 281, 78-83 (1943). C.f. Chemical Abstracts, 39, 523 (1945).

[12]Elderfield, Kremer, Kupchan, Birstein, and Cortes, J. Am. Chem. Soc., 69, 1258 (1947).

tertiary amine have been carried out. All of these drugs have shown quite severe toxic reactions when the dosage approaches that required for effective curative action.[13]

In general, the drugs showing the most promise as antimalarials are those in which the terminal nitrogen is that of a secondary amine. Some of these compounds show a toxicity of less than one-half that shown by pamaquine. The majority of them have been reported previously,[2] and their inclusion here would be needless repetition. Elderfield and co-workers have prepared 8-(5-isopropylamino-1-methylpentylamino)-6-methoxyquinoline and the corresponding n-propyl derivative.[12] He reports that the activity of these drugs is twice that of pamaquine in suppressive tests. No toxicity data are available.

Robinson and co-workers have prepared a large series of 6-methoxy-8-(3-alkylaminopropylamino)quinolines.[14] The alkyl group in this series is methyl, butyl, tert-butyl, heptyl, benzyl, phenylisopropyl, phenyl, furfuryl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 10-aminodecyl, and 2-hydroxyethyl. They have also prepared 8-(10-guanyldecylamino)-6-methoxyquinoline and 8-[10-(10-aminodecylamino)decylamino]-6-methoxyquinoline. None of these has been shown to be a promising antimalarial.

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[13]Survey of Antimalarial Drugs, Vol. I, p. 407 ff. See SN 971, SN 11,191, and SN 12,325.

[14]Quin and Robinson, J. Chem. Soc. 555-6 (1943). Glen and Robinson, ibid., 557-61 (1943). Crum and Robinson, ibid., 561-5 (1943).

Several of the compounds in which the terminal nitrogen is that of a secondary amine have been examined clinically.[15] Two of these, pentaquine, 8-(5-isopropylaminoamylamino)-6-methoxyquinoline, and isopentaquine, 8-(4-isopropylamino-1-methylbutylamino)-6-methoxyquinoline, have been shown to be superior antimalarials. Both show a high percentage of cures without too serious accompanying toxic reactions.

A relatively small amount of work has been done to date on the effect of nuclear substituents on the antimalarial action and toxicity of the 8-aminoquinolines. The 6-methoxy derivatives are the only ones that have been shown to be effective and all of the satisfactory drugs are in this series. These were used as a basis for the discussion of the effect of variations in the side chain and are not discussed in this section.

The 5,6-dimethoxy-8-aminoquinolines have been studied quite extensively since it was at first thought that these derivatives possessed certain advantages over the 6-methoxy compounds. Many of these are reported in the Survey.[2] Elderfield and co-workers have prepared 5,6-dimethoxy-8-(5-isopropylamino-1-methylpentylamino)quinoline and the corresponding n-propyl compound.[12] They report that these drugs have an activity equal to and twice that of pamaquine, respectively, in suppressive tests. No toxicity data are available. In general, the activity of the compound is retained or perhaps slightly increased when the quinoline

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[15] Survey of Antimalarial Drugs, Vol. I, p. 407 ff. See SN 12,451, SN 13,232, SN 13,233, SN 13,274, SN 13,276, SN 13,380, and SN 13,429.

has methoxyl groups in the five and six positions. However, the toxicity is probably greater for these drugs than it is for pamaquine.[16] Some of them have been subjected to clinical trial and have been shown to be unsatisfactory.[17] 5,6-dimethoxy-8-(5-isopropylaminoamylamino)-quinoline has also been examined clinically. This compound was prepared by Drake and co-workers.[18]

Schönhöfer claims that the introduction of a methoxyl group in the seven position is definitely distherapeutic.[19] To support this claim he reported that 5,6,7-trimethoxy-2-methyl-8-(4-diethylamino-1-methylbutylamino)quinoline, 5,7-dimethoxy-8-(4-diethylamino-1-methylbutylamino)quinoline, and 7-methoxy-8-(3-dimethylamino-1,1-dimethylpropylamino)quinoline are inactive. He assayed his compounds against canaries. Frisch and Bogert support this view in their report on the activities of several 5-amino-6,7-dimethoxy-8-(diethylaminoalkylamino)quinolines.[20]

The 2-methoxy and the 4-methoxy derivatives show very little activity in suppressive tests against p. lophurae in the duck.[21] Only two of these compounds have been made, and an evaluation of their action is impossible.

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[16]Ibid., Vol. I, p. 130.

[17]Ibid., Vol. I, p. 407 ff. See SN 8233, SN 9972, and SN 12,354.

[18]Drake, Van Hook, Garman, Hayes, Johnson, Kelley, Melamed, and Peck, J. Am. Chem. Soc., 68, 1531 (1946).

[19]Schönhöfer, Z. Physiol. Chem. 274, 1-8 (1942).

[20]Frisch and Bogert, J. Org. Chem., 9, 373-9 (1944).

[21]Survey of Antimalarial Drugs, Vol. I, p. 164.

The same situation exists with regard to the 5-methoxy compounds. One of these, 8-(6-diethylaminohexylamino)-5-methoxyquinoline shows a reasonable activity against p. lophurae in ducks.[20] No toxicity data are available.

Several compounds in which the quinoline has 5-chloro-6-methoxy substituents have been prepared. Most of these are recorded in the Survey.[2] Quin and Robinson have prepared 5-chloro-6-methoxy-8-(11-diethylaminohendecylamino)quinoline,[14] and Drake and co-workers have prepared 5-chloro-6-methoxy-8-(isopropylaminoamylamino)quinoline.[18] Toxicity tests have shown that the latter is far less toxic than pamaquine. These drugs appeared to be quite promising and some of them have been subjected to clinical trial. They were found to be inactive.[22]

The replacement of the methoxyl group in the six position by a hydroxyl group has been carried out in several instances. Schönhöfer prepared 8-(2-dimethylamino-1-methylpropylamino)-6-quinolinol and reported that this compound is less active than pamaquine in canaries.[19] Drake and co-workers have prepared 8-(5-isopropylaminoamylamino)-6-quinolinol.[18] Other compounds of this type are recorded in the Survey.[2] The low toxicity of the 6-quinolinols has prompted clinical trials in several instances. These drugs have been shown to be ineffective in the treatment of relapsing vivax malaria.[23]

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[22]Ibid., Vol. I, p. 449.

[23]Ibid., Vol. I, p. 450.

Some compounds containing acyloxy or benzoyloxy substituents in the six position have been prepared.[24] These have not shown any particular promise in the suppressive tests. Toxicity data are not available.

Some unsubstituted 8-aminoquinolines with varying side chains have been investigated. Robinson and co-workers have prepared 8-(10-guanyldecylamino)quinoline and the corresponding propyl compound.[14] Cerkovnikov and Prelog have described the preparation of 8-(4-amino-1-piperidyl)quinoline, 8-(1-piperazyl)quinoline, 8-(4-methyl-1-piperazyl)quinoline, and 8-(4-methylamino-1-piperidyl)quinoline.[25] No pharmacological data are available on these compounds. The data on the unsubstituted 8-aminoquinolines which are reported in the Survey indicate that their toxicity is not much different and that their activity is not so great as that shown by the corresponding 6-methoxyl compounds.[2]

A few 8-aminoquinolines with a methyl group in the two, four, five, six, or seven positions have been examined.[2] These drugs show uniformly low activity in the suppressive tests and varying toxicities. One of these, 2-methyl-8-(6-diethylaminohexylamino)quinoline has been tested clinically and shown to be inactive.[26]

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[24]Walton, Thesis, University of Maryland, College Park, Maryland, 1948.

[25]Cerkovnikov and Prelog, Ber. 74B, 1661-3 (1941).

[26]Survey of Antimalarial Drugs, Vol. I, p. 447.

Some of the 5-amino-6-methoxy and the 5-amino derivatives have toxicities of the order of one-fourth to one-half that of pamaquine. Suppressive tests have shown them to be only slightly active. These compounds are reported in the Survey.[27]

In general, there is insufficient data available on most of the drugs containing various nuclear substituents to properly evaluate their action as antimalarials. It is only in the cases of those drugs which have been examined clinically that any proper evaluation can be made. Of these only the 6-methoxy-8-aminoquinolines have been shown to be effective. The 5,6-dimethoxy derivatives are too toxic, and the 5-chloro-6-methoxy, the 6-hydroxy, and the 2-methyl compounds have been shown to be inactive or nearly so.

Much of the screening on the other derivatives was based exclusively on the results of suppressive tests which have since been shown to be inadequate for the evaluation of the 8-aminoquinolines. Furthermore, many of the compounds were made without regard to the effect of the side chain on their toxicity. This effect has been shown to be very definite, at least from a qualitative point of view, and is discussed in the following paragraphs.

The 8-aminoquinolines show three types of toxic reactions in the rhesus monkey. One of these is distinguished by an irreversible damage to the central nervous system which includes loss of vision and several other neurological effects. This type of toxic reaction is known as the plasmocid

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[27] Ibid., Vol. I, p. 169.

effect since it was first recognized in animals receiving plasmocid, 8-(3-diethylaminopropylamino)-6-methoxyquinoline. Compounds producing the plasmocid action are obviously contraindicated.

The second of these effects is characterized by a marked depression of all physical and mental activities, cyanosis, and circulatory and respiratory impairment. This is known as the pamaquine effect since it is a characteristic reaction of monkeys receiving pamaquine. These symptoms disappear when therapy is discontinued.

The third type of toxic reaction is known as the atypical effect and is characterized by cardiac failure and sudden death in relatively healthy monkeys. Fortunately this effect occurs with only a few compounds.

Nearly all compounds which have side chains with only two or three carbon atoms separating the nitrogens show the plasmocid effect. A few of them show the atypical reaction and only one, 8-(3-aminopropylamino)-6-methoxyquinoline exhibits the pamaquine effect. It is concluded, therefore, that all of these compounds are unsatisfactory antimalarials because of their toxicity.

Most of the compounds containing side chains with four or more carbon atoms separating the nitrogens show the pamaquine effect. One of these, 8-(4-isopropylaminobutylamino)-6-methoxyquinoline, produces an atypical reaction. It is in this group of compounds that the prospect of obtaining superior antimalarials is greatest. A detailed discussion of the effects of the side chain on toxicity is included in the survey.[28]

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[28]Ibid., Vol. I, p. 111 ff.

In the investigation of the effect of the variation of the basic side chain structure $NH(CH_2)_nNR$, attention has been directed principally to the variation of n while relatively little work has been done on the various modifications of the terminal alkyl group. This is especially true in those compounds where n is four or five. The researches described in this thesis were designed to investigate the effect of the various modifications of terminal amyl and butyl groups on the efficacy of the drugs. Seven compounds were prepared where n was five, two where n was four, and one each where n was two or three.

Those compounds in which n is two, three, and most of those in which n is five were prepared by condensation of the appropriate side chain chloride hydrochloride, or in one case the bromide hydrobromide, with 8-amino-6-methoxyquinoline. The condensation was carried out in much the same manner as that described for the preparation of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline.[29] Any variations from this procedure are discussed in the experimental section. The yields obtained in the preparation of these drugs are probably not the optimum since, in most cases, a sufficient quantity was obtained from one run and further work on the preparation was deemed unnecessary.

No attempt was made to prove conclusively the structure of the drugs. The method of synthesis, melting point, analysis, and homogeneity were considered as sufficient evidence to establish the structure and purity of the materials.

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[29]Drake, Van Hook, Garman, Hayes, Johnson, Kelley, Melamed, and Peck, J. Am. Chem. Soc., 68, 1529 (1946)

The side chains, with one exception, were made from the reaction of thionyl chloride and the appropriate aminoalcohol in refluxing 90-100° petroleum ether in much the same manner as that described for the preparation of 5-isopropylamino-1-chloropentane hydrochloride.[29] Neopentylaminopropylbromide hydrobromide was made by the demethoxylation of 3-methoxy-N-neopentyl-1-propylamine in an excess of 48% hydrobromic acid on a steam bath. Subsequent removal of the excess acid in vacuo resulted in the isolation of the desired bromide hydrobromide. Since the losses involved in purification of these materials are usually very high, the crude salts were used directly in the condensation. These salts can be purified by recrystallization from absolute ethanol and ether.

The preparation of 5-n-amylamino-1-pentanol and 5-n-butylamino-1-pentanol was achieved by the reductive alkylamination of an aqueous solution of 5-hydroxypentanal with n-amyl or n-butylamine at room temperature in a manner similar to that described by Drake and co-workers.[29] The slight changes from their procedure are reported in the experimental section of this thesis.

The remaining aminoalcohols were prepared by the reaction of the appropriate primary aminoalcohol or methoxyamine with the desired aldehyde or ketone in the presence of hydrogen and Adams catalyst at 90°. These compounds were isolated by distillation under reduced pressure. 3-methoxy-N-neopentyl-3-propylamine, neopentylaminoethanol, 5-(2-methyl-3-butylamino)-1-pentanol, 5-neopentylamino-1-pentanol and 5-isoamylamino-1-pentanol were prepared in this manner.

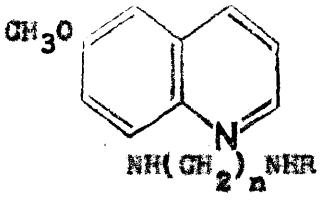
Both of the drugs in which n is four and two of those in which n is five were prepared by reductive alkylation of the corresponding 8-(ω-aminoalkylamino)-6-methoxyquinoline with the desired aldehyde or ketone in ethanol solution in the presence of Adams catalyst at room temperature.

Those aldehydes which were not commercially available were prepared by dehydrogenation of the corresponding alcohol over copper chromium oxide catalyst at 325-350°. A description of this procedure is given in the experimental section.

The results of the preliminary toxicity tests on these compounds are shown in Table 1.

Table 1*

The Toxicity of Some 8-aminoquinolines of the Type



R	n	Toxicity Quantitative[a]	Toxicity Qualtitative
$CH_2C(CH_3)_3$	2	2	plasmocid
$CH_2C(CH_3)_3$	3	0.5	plasmocid
$CH_2C(CH_3)_3$	4	0.5	pamaquine
$CH(CH_3)CH(CH_3)_2$	4		
$CH_2C(CH_3)_3$	5	<0.5	pamaquine
$CH_2CH(CH_3)_2$	5	<0.5	pamaquine
$CH_2CH(CH_3)C_2H_5$	5	0.5	pamaquine
$(CH_2)_3CH_3$	5	0.5	pamaquine
$(CH_2)_4CH_3$	5		
$CH_2CH_2CH(CH_3)_2$	5		
$CH(CH_3)CH(CH_3)_2$	5		

[a]The figures in this column are pamaquine equivalents, i.e.; the number two indicates that the compound is twice as toxic as pamaquine.

*The author wishes to express his appreciation to Dr. L. H. Schmidt, Christ Hospital, Mount Auburn, Cincinnati, Ohio, for the toxicity data recorded in this table.

EXPERIMENTAL PART *

Trimethylacetaldehyde.[30] Two hundred seventy-two grams of neopentyl alcohol was distilled slowly over copper chromium oxide catalyst at 325-350°. The product was distilled through a two-foot, helix-packed column. The yield of trimethylacetaldehyde, boiling at 74-75°, was 103 g. (41%). The residue was largely neopentyl alcohol and was used in subsequent runs. A tight roll of copper gauze served to support the catalyst.

3-methoxy-N-neopentyl-1-propylamine. A mixture of 59 g. (0.69 mole) of trimethylacetaldehyde and 61 g. (0.69 mole) of 3-methoxypropylamine[31] was hydrogenated over Adams catalyst at 1800 p.s.i. and 90°. The reduction required about one hour. The catalyst was removed by filtration and the product was distilled under reduced pressure. A yield of 75 g. (69%) of 3-methoxy-N-neopentyl-1-propylamine, boiling at 73-75°/20mm., was obtained.

Calculated for $C_9H_{21}NO$: N. E., 159.

Found: N. E., 159.

3-bromo-N-neopentyl-1-propylamine hydrobromide. A solution of 63 g. (0.40 mole) of 3-methoxy-N-neopentyl-1-propylamine in 420 g. of

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[30] This method of preparation is similar to that reported by Adkins, Kommes, Struss, and Dasler, J. Am. Chem. Soc., 55, 2992 (1933).

[31] Utermohlen, J. Am. Chem. Soc., 67, 1505 (1945).

*The author wishes to express his appreciation to Miss Eleanor Werble, Mrs. Mary Aldridge, and Mr. Byron Baer for the carbon and hydrogen determinations recorded in this section.

48% hydrobromic acid was warmed overnight on a steam bath. The solution was evaporated to dryness under reduced pressure, and the crude semi-solid residue was used directly in the next step. Recrystallization of a small portion from acetone yielded a white crystalline material which melted at 252-253° (dec).

Calculated for $C_8H_{19}NBr_2$: C, 33.22; H, 6.57.

Found: C, 33.42, 33.27; H, 6.61, 6.89.

8-(3-neopentylaminopropylamino)-6-methoxyquinoline monohydrobromide, UM 165 Q. The crude 3-bromo-N-neopentyl-1-propylamine hydrobromide was heated and stirred with 139 g. (0.8 mole) of 8-amino-6-methoxyquinoline and 50 ml. of water first at 70° for twenty hours and then at 100° for four hours. The resulting mixture was poured into 200 ml. of warm water and was buffered at pH 5.0 with sodium acetate trihydrate. The mixture was extracted four times with 200 ml. portions of hot benzene. The aqueous portion was made strongly alkaline with 25% sodium hydroxide solution and extracted with two 200 ml. portions of ether. The ether extracts were washed twice with 100 ml. portions of water and dried over anhydrous magnesium sulfate. The solution was concentrated and the residue was distilled under reduced pressure. The free base obtained weighed 21.5 g.; it boiled at 160-175°/100 μ. It was dissolved in 12 ml. of glacial acetic acid and 100 ml. of water. To the vigorously stirred solution was added 20 g. of solid sodium bromide. The crude monohydrobromide was removed by filtration. After two recrystallizations from water, it melted at 200.1-201.1° (dec.). The yield was 14 g. (10% overall from 3-methoxy-N-neopentyl-1-propylamine).

Calculated for $C_{18}H_{28}N_3OBr$: C, 56.54; H, 7.33.

Found: C, 56.57, 56.48; H, 7.30, 7.28.

Homogeneity:[32] >98 ± 2%. Figure 1, and Table 2.

N-neopentylethanolamine. This compound was prepared from 31 g. (0.5 mole) of ethanolamine and 43 g. (0.5 mole) of trimethylacetaldehyde in exactly the same manner as that described for 3-methoxy-N-neopentyl-1-propylamine. The product weighed 48.5 g. (74%), and boiled at 75-80°/10 mm.

Calculated for $C_7H_{17}NO$: N. E., 131.

Found: N. E., 132.

2-chloro-N-neopentylethylamine hydrochloride. To a stirred solution of 44 g. (0.33 mole) of N-neopentylethanolamine in 200 ml. of skellysolve C was added slowly 43 g. (0.36 mole) of thionyl chloride. The mixture was stirred and refluxed for three hours, or until the evolution of sulfur dioxide had stopped, and then was allowed to stand overnight. The crude 2-chloro-N-neopentylethylamine hydrochloride was removed by filtration and washed well with petroleum ether. It was used directly in the next step. Recrystallization of a small portion from 95% ethanol yielded a white crystalline material which melted at 263-266° (dec.).

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[32] Williamson, Holley, and Gallbreath, private communication. A mathematical discussion of the procedure is given by Williamson and Craig, J. Biol. Chem., 168, 687 (1947).

FIGURE 1

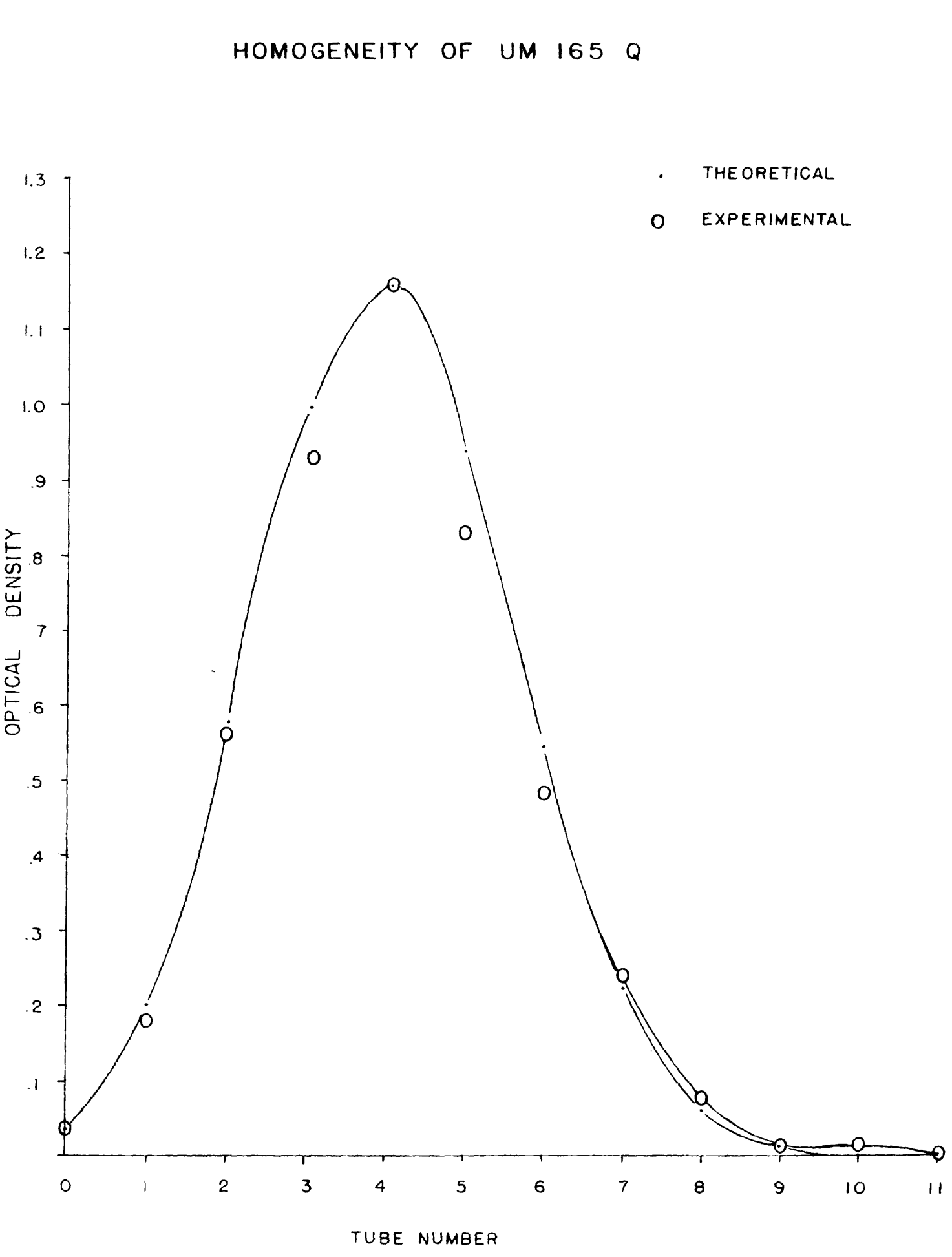
HOMOGENEITY OF UM 165 Q
THEORETICAL
EXPERIMENTAL
OPTICAL DENSITY
1.3
1.2
1.1
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
1
2
3
4
5
6
7
8
9
10
11
TUBE NUMBER

Table 2

Homogeneity of UM 165 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.034	0.032	
1	0.179	0.202	
2	0.561	0.578	0.63
3	0.930	0.998	0.55
4	1.160	1.160	0.62
5	0.830	0.940	0.51
6	0.480	0.545	0.58
7	0.242	0.223	
8	0.078	0.064	
9	0.022	0.012	
10	0.021	0.001	
11	0.000	0.000	
Sum	4.820[a]	4.755	Ave. K = 0.58

Homogeneity = $\frac{4.755}{4.820}$ = >98±2%.

Solvent: Cyclohexane. Buffer: 80% sodium acetate, 10% acetic acid. The experimental K's were calculated from the formula, $K = \frac{r}{n+1-r} \times \frac{E_r}{E_{r-1}}$, where r=tube number, n=number of plates, E_r and E_{r-1} = the optical density at tube r and r-1 respectively. The theoretical values for tube numbers above five were calculated from the formula, $T_r = \frac{n+1-r}{r} \times K \times T_{r-1}$. Those values for tube numbers below five were calculated from the formula, $Tr = \frac{r+1}{n-r} \times \frac{1}{K} \times T_{r+1}$. Tube five was the standard point.

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[a] When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

Calculated for $C_9H_{17}NCl_2$: C, 45.16; H, 9.14.

Found: C, 45.30, 45.20; H, 9.18, 9.08.

8-(2-neopentylaminoethylamino)-6-methoxyquinoline dihydrobromide, UM 166 [illegible]. The free base of this compound was prepared from 118 g. (0.66 mole) of 8-amino-6-methoxyquinoline and the crude 2-chloro-N-neopentylethylamine hydrochloride by a procedure essentially the same as that described for 8-(3-neopentylaminopropylamino)-6-methoxyquinoline. The only pertinent difference was that the preliminary heating was at 80° instead of 70°. The base was isolated by distillation; it boiled at 140-160°/40 μ. The dihydrobromide was prepared by the addition of 50 ml. of constant boiling hydrobromic acid to 37 g. of the base. The resulting mixture was cooled to 0° and filtered. After two recrystallizations from 95% ethanol, 10 g. of desired product, melting at 235.6-236.8° (dec.), was obtained (6% overall yield based on the aminoalcohol).

Calculated for $C_{17}H_{27}N_3OBr_2$: C, 45.43; H, 6.01.

Found: C, 45.76, 45.85; H, 6.22, 6.17.

Homogeneity:[32] 96[illegible]%. Figure 2, and Table 3.

5-neopentylamino-1-pentanol. This compound was prepared from 66 g. (0.77 mole) of trimethylacetaldehyde and 84 g. (0.82 mole) of 5-amino-1-pentanol[33] in exactly the same manner as that described for 3-methoxy-N-neopentyl-1-propylamine. The product weighed 100 g. (76%), and boiled at 126-131°/17 mm.

Calculated for $C_{10}H_{23}NO$: N. E., 173.

Found: N. E., 175.

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[33] Woods and Sanders, J. Am. Chem. Soc., 68, 2111 (1946)

FIGURE 2

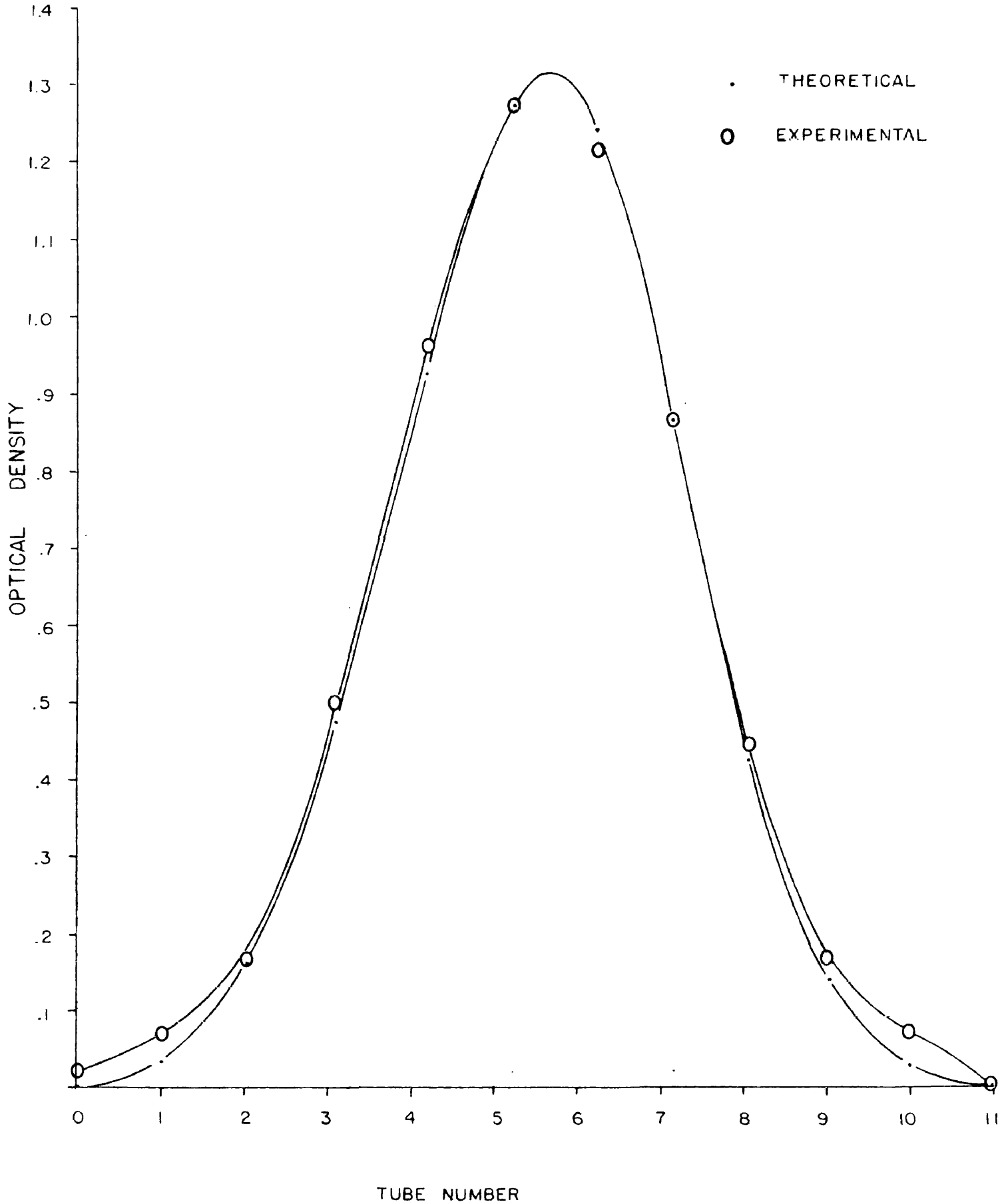
HOMOGENEITY OF UM 166 Q
THEORETICAL
EXPERIMENTAL
OPTICAL DENSITY
1.4
1.3
1.2
1.1
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
1
2
3
4
5
6
7
8
9
10
11
TUBE NUMBER

Table 3

Homogeneity of UM 166 2

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.021	0.003	
1	0.065	0.033	
2	0.163	0.160	
3	0.498	0.471	1.02
4	0.964	0.924	0.97
5	1.270	1.270	0.94
6	1.210	1.240	0.95
7	0.865	0.868	1.00
8	0.447	0.425	1.03
9	0.167	0.139	1.12
10	0.068	0.027	
11	0.003	0.002	
Sum	5.774[a]	5.562	

K = 0.98

Homogeneity = $\frac{5.562}{5.774}$ = 96±3%

Solvent: Cyclohexane. Buffer: 75% sodium acetate, 25% acetic acid.

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

5-chloro-N-neopentyl-1-amylamine hydrochloride. This compound was prepared from 100 g. (0.58 mole) of 5-neopentylamino-1-pentanol and thionyl chloride by exactly the same procedure as that described for 2-chloro-N-neopentylethylamine hydrochloride. The crude material was used directly in the next step. Three recrystallizations of a small portion from absolute ethanol and ether yielded a white, crystalline material melting at 180.7-183.7° (dec.).

Calculated for $C_{10}H_{23}NCl_2$: Ionic Cl, 15.6.

Found: Ionic Cl, 15.5, 15.7 (Volhard).

8-(5-neopentylaminoamylamino)-6-methoxyquinoline monohydrochloride, UM 170 g. The free base of this compound was prepared from 209 g. (1.20 moles) of 8-amino-6-methoxyquinoline and the crude 5-chloro-N-neopentyl-1-amylamine hydrochloride by exactly the same procedure as that described for 8-(2-neopentylaminoethylamino)-6-methoxyquinoline. The base was isolated by distillation; it boiled at 180-185°/50 μ. The monohydrochloride was prepared by essentially the same procedure as that described for the monohydrobromide of the corresponding propyl compound. Sodium chloride was substituted for sodium bromide in this procedure. After two recrystallizations from water, the salt melted at 188.9-189.5° (dec.), and weighed 56 g. (22% overall yield based on the aminoalcohol).

Calculated for $C_{20}H_{32}N_3OCl$: C, 65.75; H, 8.76.

Found: C, 66.00, 65.85; H, 8.75, 8.65.

Homogeneity:[32] 98±2%. Figure 3, and Table 4.

FIGURE 3

HOMOGENEITY OF UM 170 Q

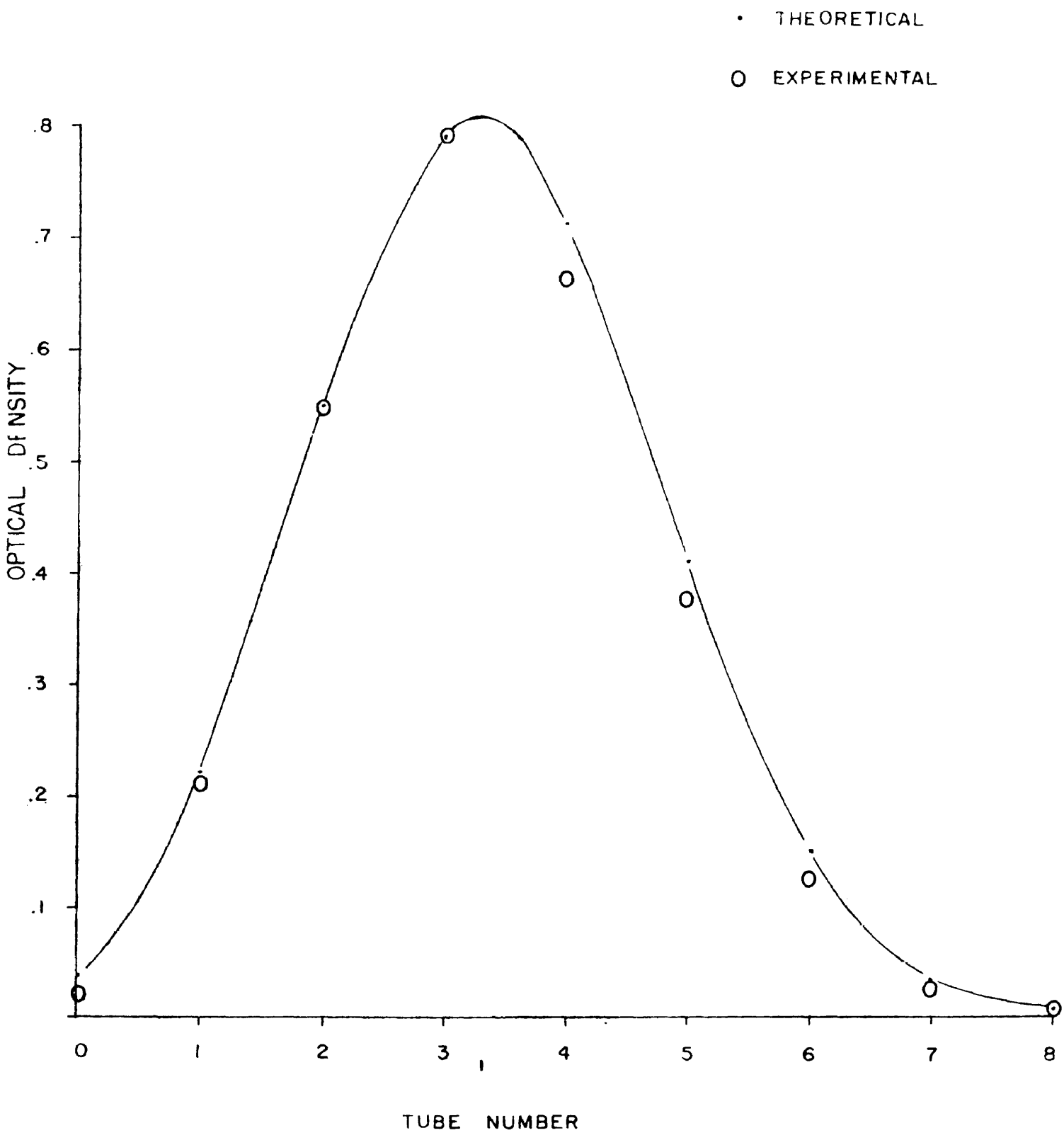

Table 4

Homogeneity of UM 170 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.022	0.038	
1	0.215	0.218	
2	0.545	0.549	0.72
3	0.790	0.790	0.72
4	0.660	0.710	0.67
5	0.375	0.409	0.71
6	0.124	0.147	0.66
7	0.027	0.030	0.76
8	0.009	0.003	
Sum	2.904[a]	2.894	

K = 0.72

Homogeneity = $\frac{2.894}{2.904}$ = >98±2%

Solvent: Cyclohexane. Buffer: 69% sodium acetate, 31% acetic acid.

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

8-(4-neopentylaminobutylamino)-6-methoxyquinoline monohydrochloride, UM 171 Q.[34] An aqueous solution of 28.5 g. (0.07 mole) of 8-(4-aminobutylamino)-6-methoxyquinoline dihydrochloride hemihydrate[34] was made strongly alkaline with 25% sodium hydroxide solution and extracted with two 100 ml. portions of chloroform. The chloroform was removed on a steam bath. The residue was dissolved in 75 ml. of absolute ethanol, 17.2 g. (0.20 mole) of trimethylacetaldehyde was added and the mixture was hydrogenated over Adams catalyst at 2000 p.s.i. The reduction required about one hour. After removal of the catalyst by filtration the solution was evaporated to dryness on a steam bath. The oily residue was dissolved in 12 ml. of glacial acetic acid and 100 ml. of water; 20 g. of solid sodium chloride was added and the mixture was stirred and scratched until crystallization occurred. The crude monohydrochloride was removed by filtration and recrystallized four times from water and finally from alcohol and ether. The product weighed 10 g. (41%), and melted at 197.2-198.6° (dec.).

Calculated for $C_{19}H_{30}N_3OCl$: C, 64.96; H, 8.55.

Found: C, 65.10, 65.02; H, 8.45, 8.55.

Homogeneity:[32] 91±5%. Figure 4, and Table 5.

8-(5-isobutylaminoamylamino)-6-methoxyquinoline monohydrobromide, UM 177 Q. The free base of this compound was prepared from 50 g. (0.13 mole)

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[34]This compound was prepared in a manner similar to that described by Cope in a private communication to Dr. Nathan L. Drake.

FIGURE 4

HOMOGENEITY OF UM 171 Q

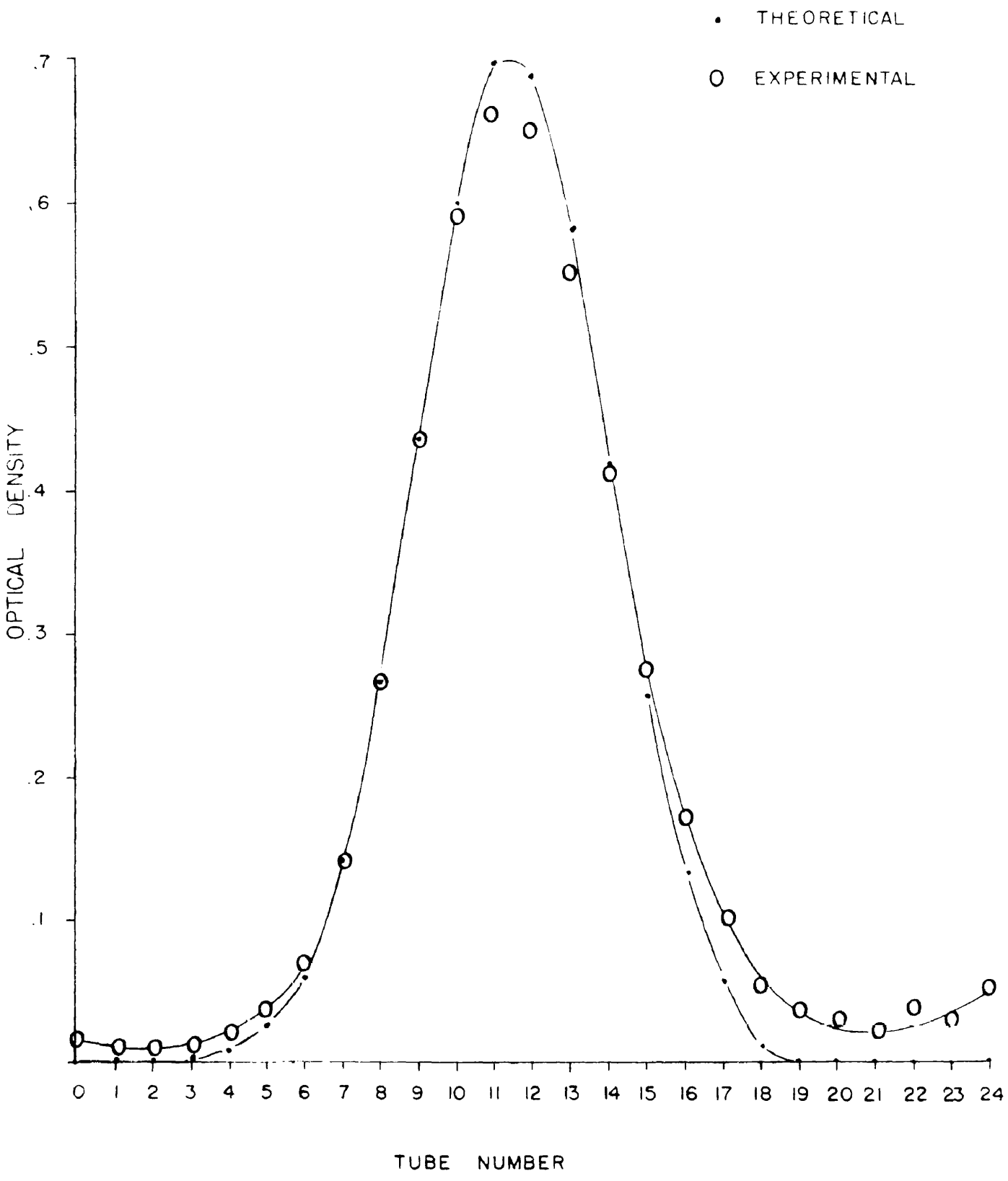

Table 5

Homogeneity of UM 171 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Tube No.	Optical Density Experimental	Optical Density Theoretical
0	0.017	0.000	13	0.550	0.580
1	0.008	0.000	14	0.413	0.417
2	0.009	0.000	15	0.274	0.254
3	0.012	0.002	16	0.171	0.130
4	0.020	0.007	17	0.100	0.056
5	0.035	0.024	18	0.056	0.012
6	0.067	0.059	19	0.036	0.000
7	0.140	0.138	20	0.029	0.000
8	0.265	0.268	21	0.022	0.000
9	0.435	0.435	22	0.023	0.000
10	0.590	0.597	23	0.027	0.000
11	0.660	0.694	24	0.048	0.000
12	0.650	0.686	Sum	4.761[a]	4.359

K = 0.91

Homogeneity = $\frac{4.359}{4.761}$ = 91±5%

Solvent: Cyclohexane. Buffer: Citrate.

[a] When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

of 8-(5-aminoamylamino)-6-methoxyquinoline dihydrochloride trihydrate[35] and 19 g. (0.27 mole) of isobutyraldehyde by a procedure essentially the same as that described for 8-(4-neopentylaminobutylamino)-6-methoxyquinoline. The free base was molecularly distilled (pot temperature 180-190°). To a solution of the distillate in an excess of 48% hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The crystalline monohydrobromide was removed by filtration, recrystallized once from water and twice from 95% ethanol. The product weighed 10 g. (20%), and melted at 175.7-176.9° (dec.).

Calculated for $C_{19}H_{30}N_3OBr$: C, 57.57; H, 7.57.

Found: C, 57.79, 57.70; H, 7.61, 7.81.

Homogeneity:[32] >98±2%. Figure 5, and Table 6.

2-methylbutanal. This compound was prepared from 202 g. (2.3 moles) of sec-butylcarbinol according to the same procedure as that described in the preparation of trimethylacetaldehyde. The product wieghed 59 g. (30%), and boiled at 91-93°.

8- 5-(2-methylbutylamino)amylamino -6-methoxyquinoline monohydrochloride, UM 178 Q. This compound was prepared from 50 g. (0.13 mole) of 8-(5-aminoamylamino)-6-methoxyquinoline dihydrochloride trihydrate[35] and 23 g. (0.27 mole) of 2-methylbutanal by a procedure essentially the same as that described for the preparation of 8-(4-neopentylaminobutylamino)-6-methoxyquinoline monohydrochloride. The free base was isolated

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[35] Garman, Thesis, University of Maryland, College Park, Maryland, 1948. Baldwin, J. Chem. Soc., 2959 (1929).

FIGURE 5

HOMOGENEITY OF UM 177 Q

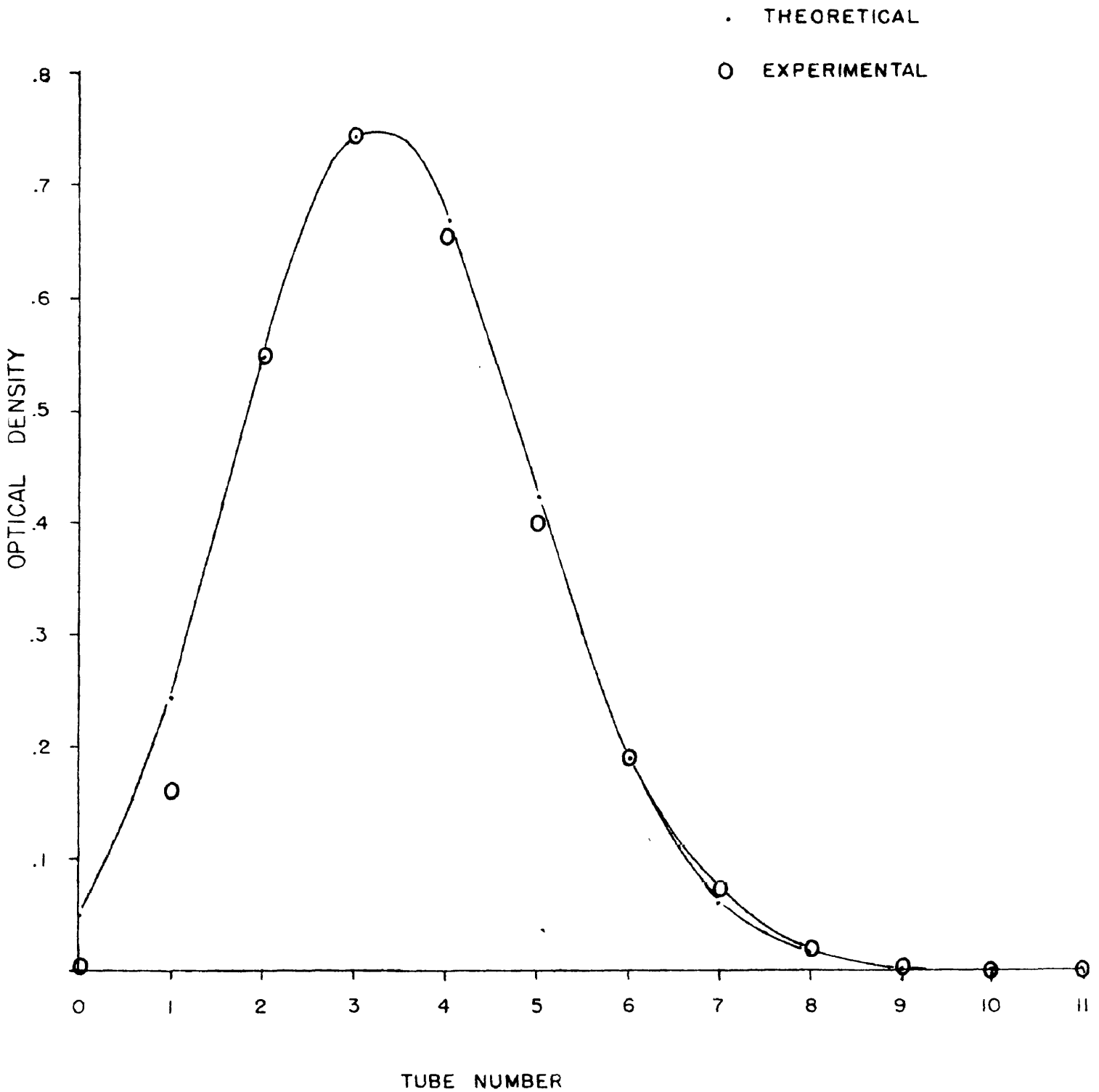

Table 6

Homogeneity of UM 177 [illegible]

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.002	0.049	
1	0.161	0.243	
2	0.545	0.548	
3	0.741	0.741	0.45
4	0.650	0.666	0.44
5	0.398	0.420	0.44
6	0.187	0.189	0.47
7	0.071	0.061	0.53
8	0.014	0.014	
9	0.000	0.002	
10	0.000	0.000	
11	0.000	0.000	
Sum	2.941[a]	2.933	

K = 0.46

Homogeneity = $\frac{2.933}{2.941}$ = >98±2%.

Solvent: Cyclohexane. Buffer: 90% sodium acetate, 10% acetic acid.

---

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

by molecular distillation (pot temperature 180-190°). The salt weighed 14 g. (26%), and melted at 149.6-150.5° (dec.).

Calculated for $C_{20}H_{32}N_2O_2Cl_2$: C, 65.75; H, 8.73.

Found: C, 65.52, 65.81; H, 9.02, 9.04.

Homogeneity;[32] 98±2%. Figure 6, and Table 7.

5-n-butylamino-1-pentanol. A solution of 31.5 ml. of concentrated hydrochloric acid in 375 ml. of distilled water was cooled to 0-5° in an ice bath. The ice bath was removed and 126 g. (1.5 moles) of dihydropyrane was added all at once. The resulting mixture was stirred until it became homogeneous, allowed to stand for ten minutes, and then cooled in an ice bath to 10-15°. To this solution was added slowly with cooling 139 g. (1.9 moles) of n-butylamine while the temperature was kept below 25°. The resulting mixture was hydrogenated over Adams catalyst at 25° and an initial pressure of 2000 p.s.i. The reduction was complete in about two hours. The catalyst was removed by filtration, and the solution was saturated with solid sodium hydroxide. The upper layer was separated and distilled under reduced pressure. A small forerun was obtained. The n-butylaminopentanol weighed 147 g. (62%), boiled at 150-152°/20 mm., and had a neutral equivalent of 167. A small portion was redistilled; it boiled at 155-156°/28 mm.

Calculated for $C_9H_{21}NO$: N. E., 159.

Found: N. E., 163.

N-n-butyl-5-chloro-1-amylamine hydrochloride. This compound was prepared from thionyl chloride and 117 g. (0.73 moles) of 5-n-butylamino-1-pentanol in exactly the same manner as that described for

FIGURE 6

HOMOGENEITY OF UM 178 Q

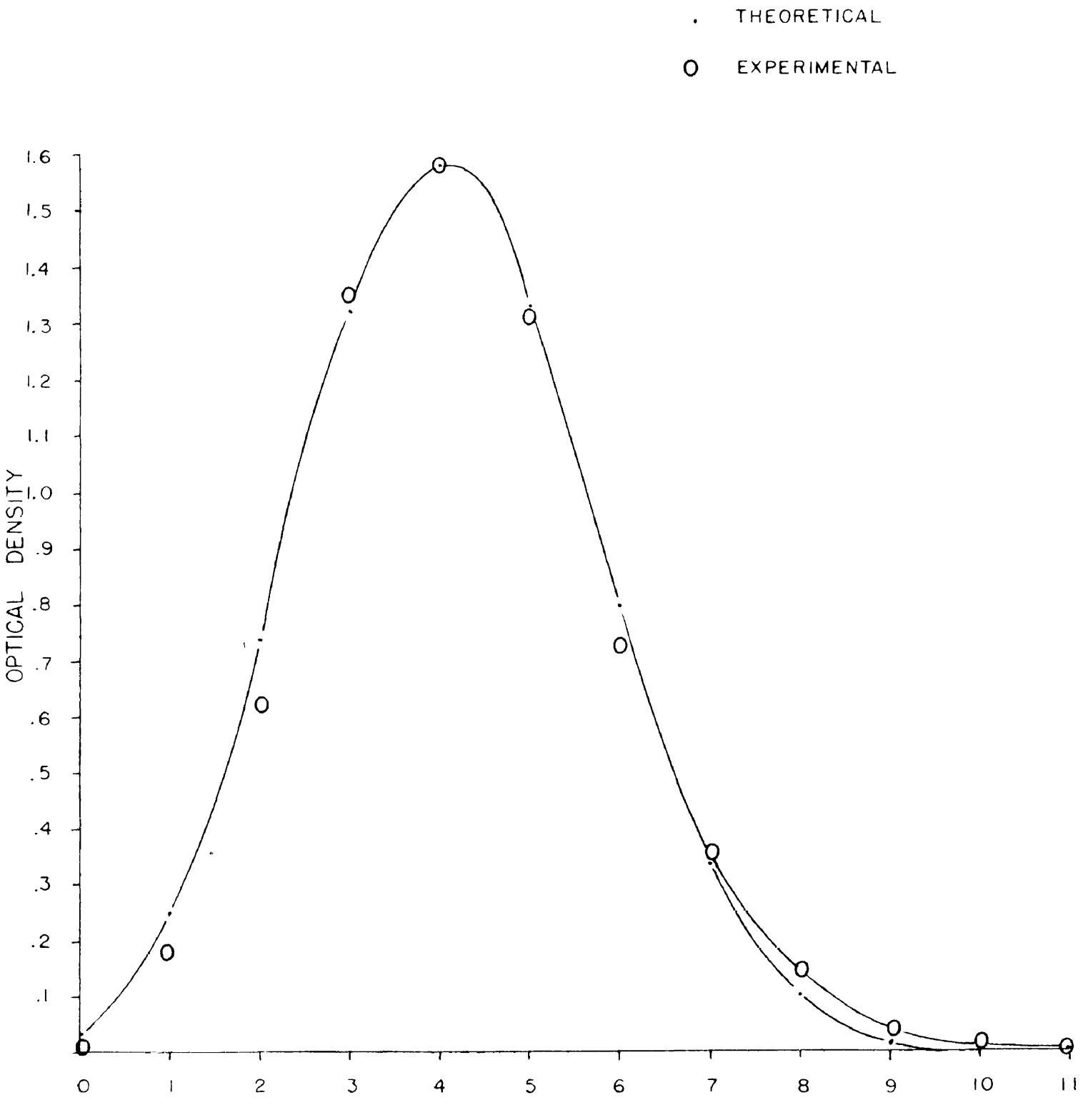

Table 7

Homogeneity of UM 178 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.014	0.037	
1	0.178	0.245	
2	0.618	0.735	
3	1.350	1.320	0.73
4	1.580	1.580	0.59
5	1.310	1.330	0.55
6	0.725	0.796	
7	0.355	0.341	
8	0.146	0.103	
9	0.040	0.021	
10	0.020	0.002	
11	0.007	0.000	
Sum	6.641[a]	6.510	

K = 0.60

Homogeneity = $\frac{6.510}{6.641}$ = 98±2%.

Solvent: Cyclohexane. Buffer: 80% sodium acetate, 20% acetic acid.

---

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

2-chloro-N-neopentylethylamine hydrochloride. The crude material was used directly in the next step. Recrystallization of a small portion from absolute ethanol and ether yielded a white crystalline material which melted at 222.2-225.2° (dec.).

Calculated for $C_9H_{21}NCl_2$: Ionic Cl, 16.6.

Found: Ionic Cl, 16.6, 16.6 (Volhard).

8-(5-n-butylaminoamylamino)-6-methoxyquinoline monohydrobromide, U.R. 179 $\frac{1}{2}$. The free base of this compound was prepared from 243 g. (1.4 moles) of 8-amino-6-methoxyquinoline and the crude N-n-butyl-5-chloro-1-amylamine hydrochloride by exactly the same procedure as that described for the preparation of 8-(2-neopentylaminoethylamino)-6-methoxyquinoline. It was isolated by distillation at 184-195°/100 μ. To a solution of the base in an excess of 48% hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The crude monohydrobromide, after two recrystallizations from water, melted at 135.6-136.8° (dec.); it weighed 38 g. (14% overall yield from the aminoalcohol).

Calculated for $C_{19}H_{30}N_3OBr$: C, 57.57; H, 7.57.

Found: C, 57.90, 57.62; H, 7.17, 7.28.

Homogeneity:[32] 94±3%. Figure 7, and Table 8.

5-n-amylamino-1-pentanol. This compound was prepared from 126 g. (1.5 moles) of dihydropyrane and 165 g. (1.9 moles) of n-amylamine in exactly the same manner as that described for the corresponding butyl compound. The product weighed 158 g. (61%), and boiled at 164-165°/30 mm.

Calculated for $C_{10}H_{23}NO$: N. E., 173.

Found: N. E., 174.

FIGURE 7

HOMOGENEITY OF UM 179 Q

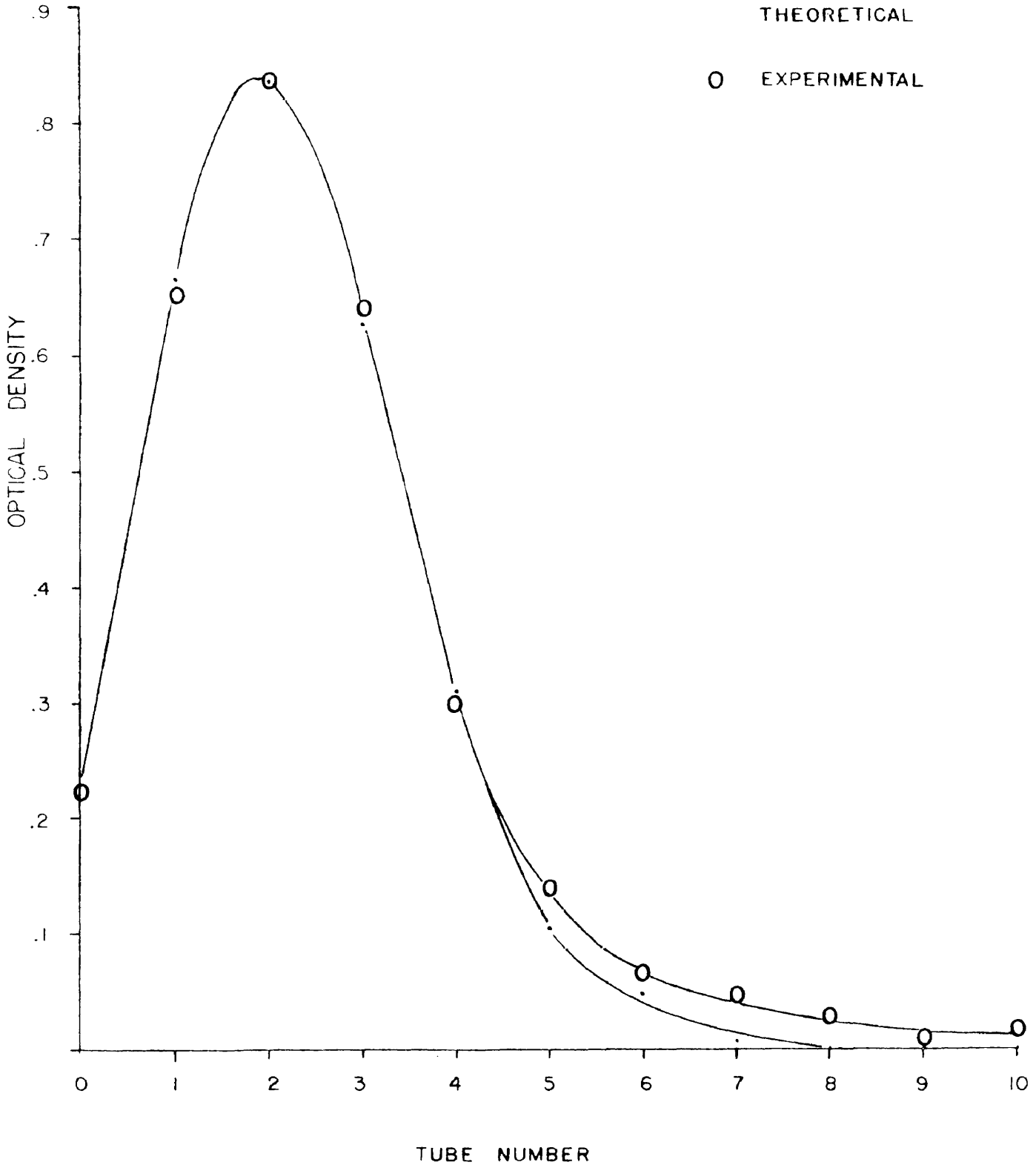

Table 8

Homogeneity of UM 179 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.223	0.238	
1	0.652	0.666	0.29
2	0.839	0.839	0.29
3	0.639	0.627	0.27
4	0.297	0.307	
5	0.140	0.103	
6	0.065	0.024	
7	0.049	0.004	
8	0.028	0.000	
9	0.007	0.000	
10	0.016	0.000	
Sum	2.994[a]	2.808	

K = 0.28

Homogeneity = $\frac{2.808}{2.994}$ = 94±3%.

Solvent: Cyclohexane. Buffer: 90% sodium acetate, 10% acetic acid.

---

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

N-n-amyl-5-chloro-1-amylamine hydrochloride. This compound was prepared from 129 g. (0.74 mole) of 5-n-amylamino-1-pentanol and thionyl chloride in exactly the same manner as that described for the preparation of 2-chloro-N-neopentylethylamine hydrochloride. The crude material was used directly in the next step. Recrystallization of a small portion from absolute ethanol and ether yielded a white crystalline material which melted at 229.0-231.6° (dec.).

Calculated for $C_{10}H_{23}NCl_2$: Ionic Cl, 15.6.

Found: Ionic Cl, 15.7, 15.9 (Volhard).

8-(5-n-amylaminoamylamino)-6-methoxyquinoline monohydrobromide, UM 180 μ. The free base of this compound was prepared from 244 g. (1.4 moles) of 8-amino-6-methoxyquinoline and the crude N-n-amyl-5-chloroamylamine hydrochloride by exactly the same procedure as that described for the preparation of 8-(2-neopentylaminoethylamino)-6-methoxyquinoline. The free base was isolated by distillation; it boiled at 210-220°/200 μ. To a solution of the base in an excess of 48% hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The crude monohydrobromide was removed by filtration and recrystallized once from water and twice from 95% ethanol. It weighed 77 g. (27% overall yield from the aminoalcohol), and melted at 123.5-124.9° (dec.).

Calculated for $C_{20}H_{32}N_3OBr$: C, 58.54; H, 7.80.

Found: C, 58.73, 58.89; H, 7.90, 7.94.

Homogeneity:[32] 94±3%. Figure 8, and Table 9.

FIGURE 8

HOMOGENEITY OF UM 180 Q

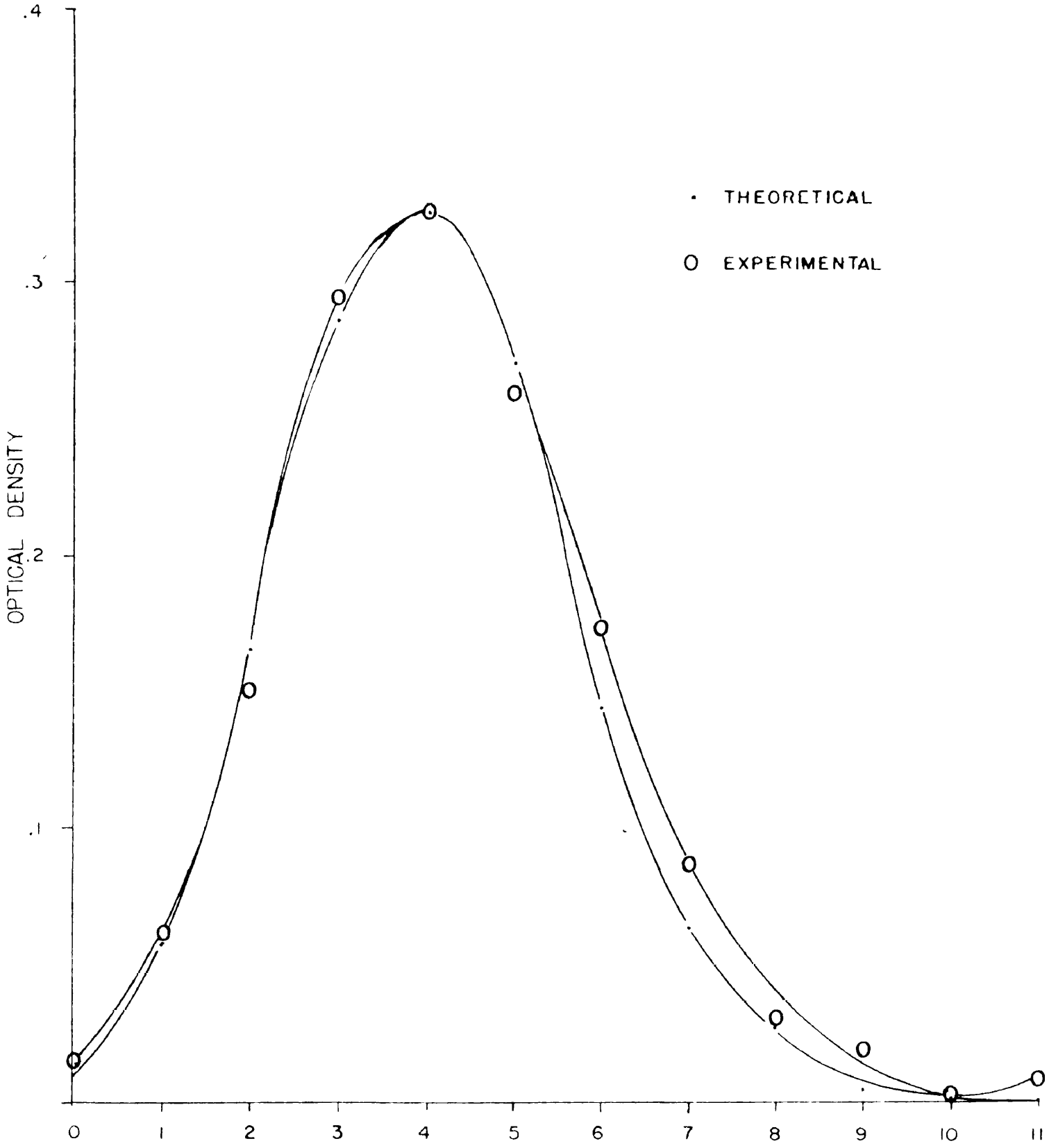

Table 9

Homogeneity of UM 180 Q

Tube No.	Optical Density		Experimental K
	Experimental	Theoretical	
0	0.014	0.009	
1	0.061	0.058	
2	0.150	0.166	
3	0.294	0.286	0.49
4	0.325	0.325	0.65
5	0.259	0.270	0.55
6	0.173	0.154	0.57
7	0.086	0.063	
8	0.030	0.018	
9	0.019	0.003	
10	0.000	0.000	
11	0.007	0.000	
Sum	1.445[a]	1.352	

K = 0.57

Homogeneity = $\frac{1.352}{1.445}$ = 94±3%

Solvent: Cyclohexane. Buffer: 85% sodium acetate, 15% acetic acid.

[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

Isovaleraldehyde. This compound was prepared from 176 g. (2.0 moles) of isoamylalcohol in exactly the same manner as that described for the preparation of trimethylacetaldehyde. The product weighed 43 g. (25%), and boiled at 90-92°.

5-isoamylamino-1-pentanol. This compound was prepared from 55 g. (0.53 mole) of 5-amino-1-pentanol[33] and 50 g. (0.58 mole) of isovaleraldehyde in exactly the same manner as that described for the preparation of 3-methoxy-N-neopentyl-1-propylamine. The desired aminoalcohol weighed 65 g. (70%), and boiled at 136-138°/10 mm.

Calculated for $C_{10}H_{23}NO$: N. E., 173.

Found: N. E., 175.

5-chloro-N-isoamyl-1-amylamine hydrochloride. This compound was prepared from 52 g. (0.3 mole) of 5-isoamylamino-1-pentanol and thionyl chloride in exactly the same manner as that described for the preparation of 2-chloro-N-neopentylethylamine hydrochloride. The crude material was used directly in the next step. Recrystallization of a small sample from absolute ethanol and ether yielded a white crystalline material which melted at 221.7-224.1° (dec.).

Calculated for $C_{10}H_{23}NCl_2$: Ionic Cl, 15.6.

Found; Ionic Cl, 15.7, 15.8 (Volhard).

8-(5-isoamylaminoamylamino)-6-methoxyquinoline monohydrobromide, UM 181 x. The free base of this compound was prepared from 104 g. (0.6 mole) of 8-amino-6-methoxyquinoline and the 5-chloro-N-isoamyl-1-amylamine hydrochloride by exactly the same procedure as that described

for the preparation of 8-(2-neopentylaminoethylamino)-6-methoxyquinoline. It was isolated by molecular distillation (pot temperature 160-180°). To a solution of the base in an excess of constant boiling hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The crude monohydrobromide was removed by filtration. After four recrystallizations from water, it melted at 143.3-144.6° (dec.), and weighed 6 g. (5% overall yield based on the aminoalcohol).

Calculated for $C_{20}H_{32}N_3OBr$: C, 58.54; H, 7.80.

Found: C, 58.74, 58.88; H, 7.92, 7.93.

Homogeneity:[32] >98±2%. Figure 9, and Table 10.

5-(2-methyl-3-butylamino)-1-pentanol. This compound was prepared from 88 g. (1.0 mole) of methylisopropylketone[36] and 78 g. (0.84 mole) of 5-aminopentanol[33] by exactly the same procedure as that described for the preparation of 3-methoxy-N-neopentyl-1-propylamine. The desired aminoalcohol weighed 85 g. (58%), and boiled at 130-132°/13 mm.

Calculated for $C_{10}H_{23}NO$: N. E., 173.

Found: N. E., 174.

5-chloro-N-(2-methyl-3-butyl)-1-amylamine hydrochloride. This compound was prepared from 75 g. (0.43 mole) of 5-(2-methyl-3-butylamino)-1-pentanol and thionyl chloride by exactly the same procedure as that described in the preparation of 2-chloro-N-neopentylethylamine hydrochloride. The crude material was used directly in the next step.

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[36]Organic Synthesis, Coll. Vol. II, p. 408.

FIGURE 9

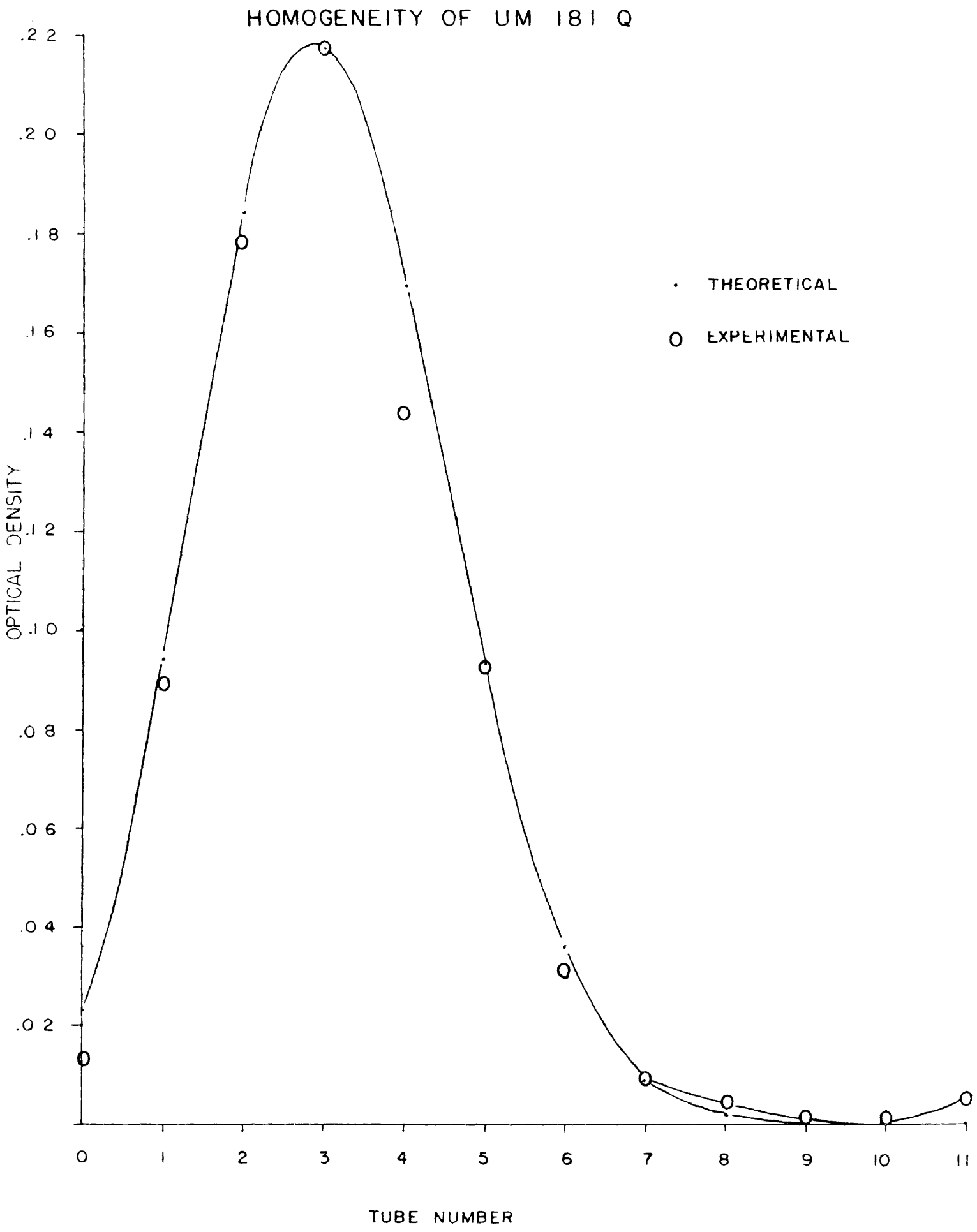
HOMOGENEITY OF UM 181 Q
.22
.20
.18
.16
.14
.12
.10
.08
.06
.04
.02
OPTICAL DENSITY
THEORETICAL
EXPERIMENTAL
0
1
2
3
4
5
6
7
8
9
10
11
TUBE NUMBER

Table 10

Homogeneity of UM 161 2

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.013	0.023	
1	0.089	0.094	
2	0.178	0.184	0.40
3	0.217	0.217	0.41
4	0.144	0.169	0.33
5	0.062	0.093	0.41
6	0.031	0.036	0.38
7	0.009	0.009	0.41
8	0.004	0.002	
9	0.000	0.000	
10	0.000	0.000	
11	0.005	0.000	
Sum	0.834[a]	0.827	

K = 0.39

Homogeneity = $\frac{0.827}{0.834}$ = >98±2%.

Solvent: Cyclohexane. Buffer: 75% sodium acetate, 25% acetic acid.

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[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

Recrystallization of a small sample from absolute ethanol and ether yielded a white crystalline material which melted at 137.4-138.9° (dec.).

Calculated for $C_{10}H_{23}NCl_2$: Ionic Cl, 15.6.

Found: Ionic Cl, 15.5, 15.6 (Volhard).

8-[5-(2-methyl-3-butylamino)amylamino]-6-methoxyquinoline monohydrobromide, UM 182 Q. The free base of this compound was prepared from the crude 5-chloro-N-(2-methyl-3-butyl)-1-amylamine hydrochloride and 139 g. (0.8 mole) of 8-amino-6-methoxyquinoline in exactly the same manner as that described for the preparation of 8-(2-neopentylaminoethylamino)-6-methoxyquinoline. It was isolated by molecular distillation (pot temperature 150-170°). To a solution of the free base in an excess of constant boiling hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The crude monohydrobromide was removed by filtration. After four recrystallizations from water, it weighed 11 g. (7% overall yield based on the aminoalcohol), and melted at 164.2-165.1° (dec.).

Calculated for $C_{20}H_{32}N_3OBr$: C, 58.54; H, 7.80.

Found: C, 58.54, 58.81; H, 7.68, 7.94.

Homogeneity:[32] 97±2%. Figure 10, and Table 11.

8-[4-(2-methyl-3-butylamino)butylamino]-6-methoxyquinoline monohydrobromide, UM 183 Q. The free base of this compound was prepared from 26 g. (0.3 mole) of methylisopropylketone[36] and 62 g. (0.15 mole) of 8-(4-aminobutylamino)-6-methoxyquinoline dihydrochloride hemihydrate[34] by essentially the same procedure as that described in the

FIGURE 10

HOMOGENEITY OF UM 182 Q

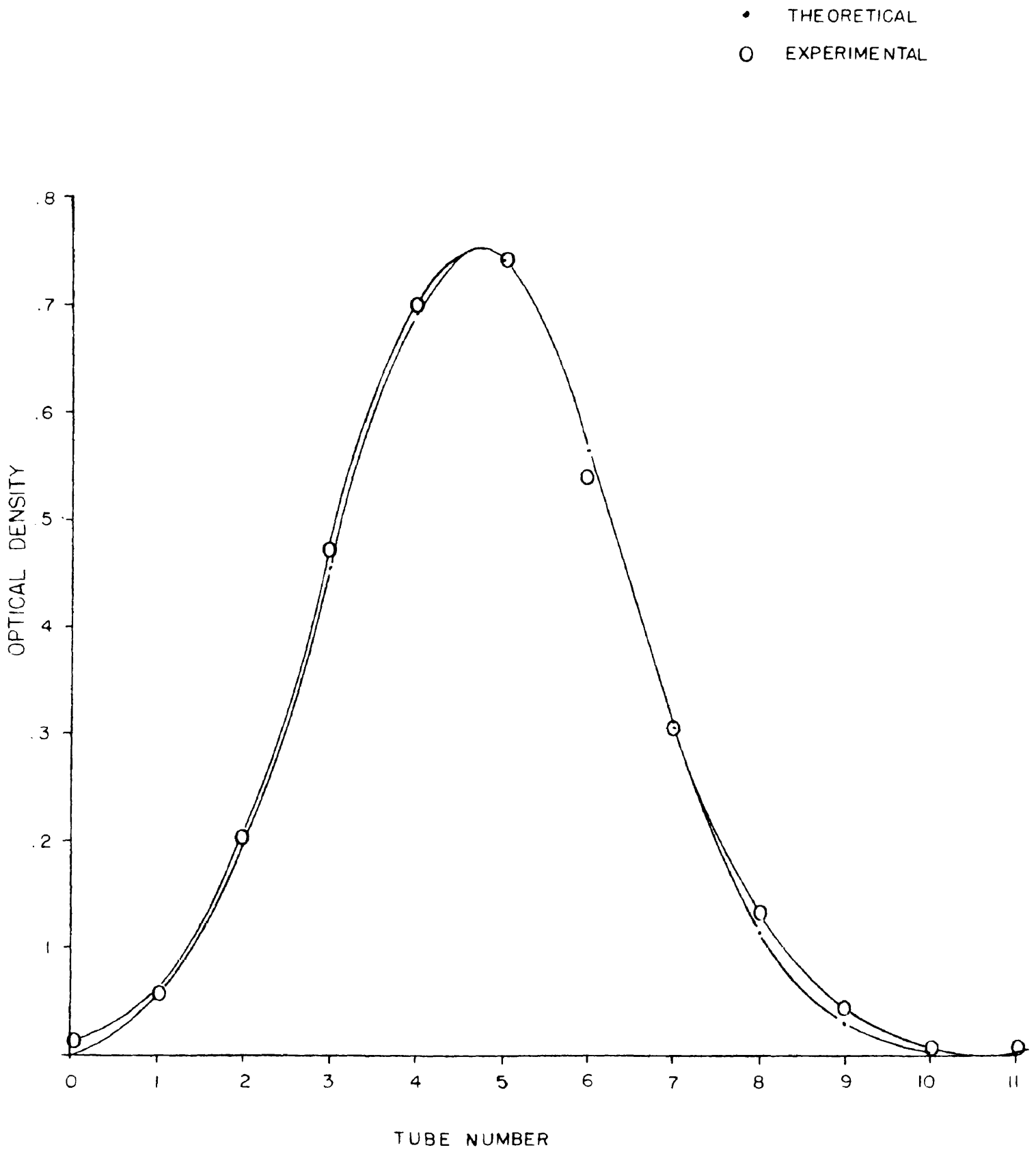

Table 11

Homogeneity of DM 182 Q

Tube No.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.013	0.006	
1	0.057	0.052	
2	0.203	0.198	0.71
3	0.407	0.454	0.78
4	0.700	0.691	0.74
5	0.740	0.740	0.75
6	0.539	0.562	0.73
7	0.304	0.305	0.79
8	0.133	0.116	
9	0.043	0.029	
10	0.015	0.004	
11	0.008	0.000	
Sum	3.242[a]	3.157	

K = 0.76

Homogeneity = $\frac{3.157}{3.242}$ = 97±2%.

Solvent: Cyclohexane. Buffer: 92% sodium acetate, 8% acetic acid.

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[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

preparation of 8-(4-neopentylaminobutylamino)-6-methoxyquinoline. It was isolated by molecular distillation (pot temperature 170-180°). To a solution of the base in an excess of 48% hydrobromic acid was added 20% aqueous sodium acetate solution until the mixture was at pH 5.0. The oily material obtained was allowed to stand overnight in a refrigerator. The now crystalline monohydrobromide was removed by filtration. After five recrystallizations from water, it melted at 173.4-175.0° (dec.), and weighed 4.5 g. (7%).

Calculated for $C_{19}H_{30}N_3OBr$: C, 57.57; H, 7.57.

Found: C, 57.55, 57.78; H, 7.65, 7.67.

Homogeneity: ^{32} >98±2%. Figure 11, and Table 12.

FIGURE 11

HOMOGENEITY OF UM 183 Q

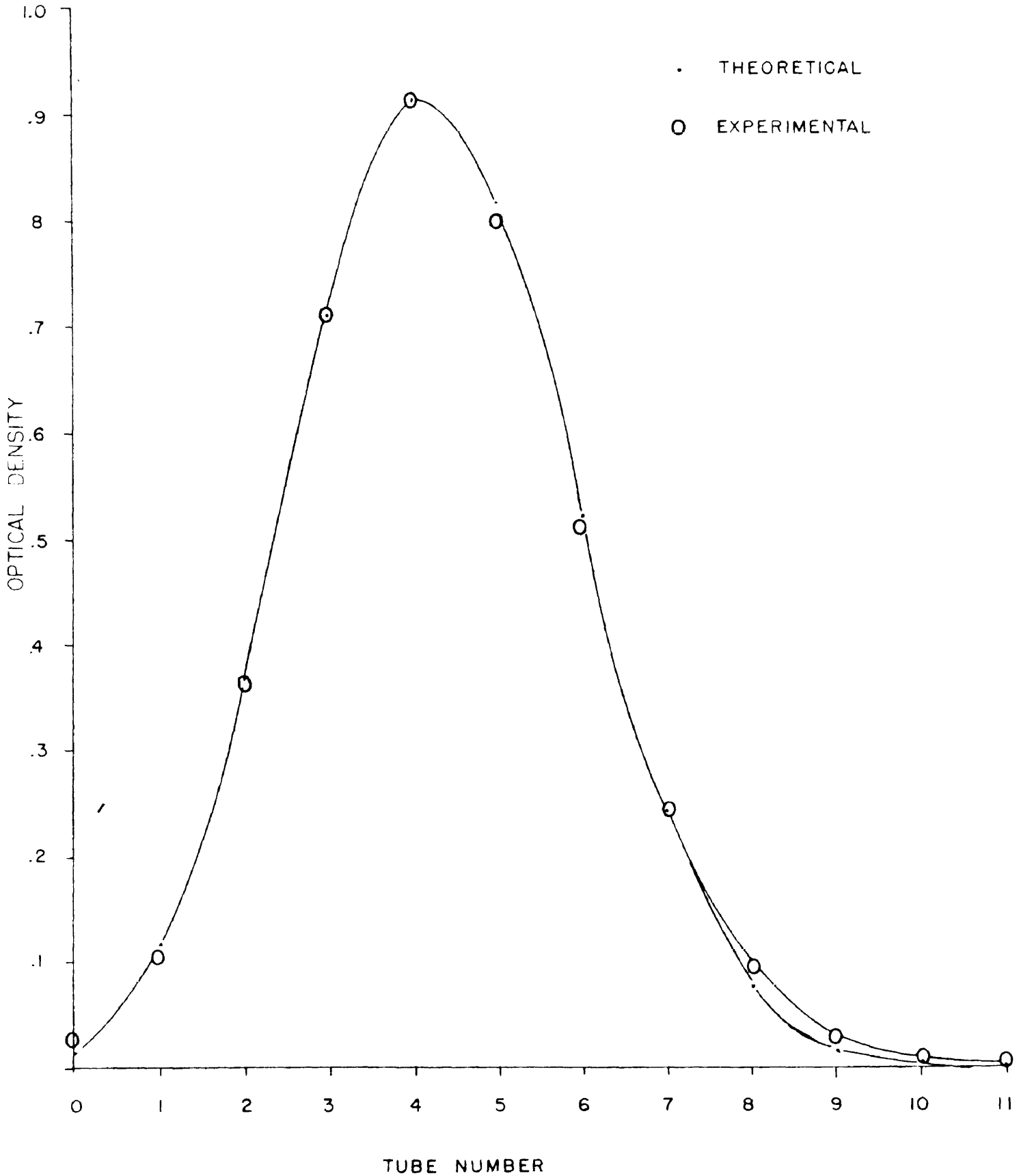

Table 12

Homogeneity of UM 183 Q

Tube no.	Optical Density Experimental	Optical Density Theoretical	Experimental K
0	0.029	0.016	
1	0.105	0.115	
2	0.363	0.369	0.69
3	0.710	0.709	0.65
4	0.910	0.910	0.64
5	0.796	0.814	0.63
6	0.510	0.521	0.64
7	0.242	0.238	0.66
8	0.093	0.076	0.67
9	0.028	0.016	
10	0.008	0.002	
11	0.000	0.000	
Sum	3.839[a]	3.786	

K = 0.64

Homogeneity = $\frac{3.786}{3.839}$ = >98±2%.

Solvent: Cyclohexane. Buffer: 81% sodium acetate, 19% acetic acid.

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[a]When this sum was calculated, the theoretical values were substituted for those experimental values which were lower than the theoretical.

ABSTRACT

Robert A. Hayes, Ph D. 1948 (B. A. College of Wooster)
Title of Thesis: Synthetic Antimalarials
Thesis directed by Professor Nathan L. Drake
Major: Organic Chemistry, Department of Chemistry
Minors: Physical and Inorganic Chemistry
Pages in thesis 52. Words in abstract 120.

The synthesis of eleven potential antimalarial drugs and fourteen new intermediate compounds is described. All of the drugs prepared are in the 8-aminoquinoline series.

Seven of the drugs were prepared by the condensation of the appropriate N-alkylaminoalkylhalide hydrohalide with 8-amino-6-methoxyquinoline. 8-(3-neopentylaminopropylamino)-6-methoxyquinoline, 8-(2-neopentylaminoethylamino)-6-methoxyquinoline, 8-(5-neopentylaminoamylamino)-6-methoxyquinoline, 8-(5-n-butylaminoamylamino)-6-methoxyquinoline, 8-(5-n-amylaminoamylamino)-6-methoxyquinoline, 8-(5-isoamylaminoamylamino)-6-methoxyquinoline, and 8-[5-(2-methyl-3-butylamino)amylamino]-6-methoxyquinoline were prepared in this manner. The other four drugs were prepared by the reductive alkylation of the appropriate 8-(ω-aminoalkylamino)-6-methoxyquinoline with the proper aldehyde or ketone. 8-(4-neopentylaminobutylamino)-6-methoxyquinoline, 8-(5-isobutylaminoamylamino)-6-methoxyquinoline, 8-[5-(2-methylbutylamino)amylamino]-6-methoxyquinoline and 8-[4-(2-methyl-3-butylamino)butylamino]-6-methoxyquinoline were prepared in this manner.

The following new compounds were prepared as intermediates for the synthesis of the above drugs: 3-methoxy-N-neopentyl-1-propylamine,

3-bromo-N-neopentyl-1-propylamine hydrobromide, 2-neopentylaminoethanol, 2-chloro-N-neopentylethylamine hydrochloride, 5-neopentylamino-1-pentanol, 1-chloro-N-neopentyl-5-amylamine hydrochloride, 5-n-butylamino-1-pentanol, N-n-butyl-5-chloro-1-amylamine hydrochloride, 5-n-amylamino-1-pentanol, N-n-amyl-5-chloro-1-amylamine hydrochloride, 5-isoamylamino-1-pentanol, 5-chloro-N-isoamyl-1-amylamine hydrochloride, 5-(2-methyl-3-butylamino)-1-pentanol, and 5-chloro-N-(2-methyl-3-butylamino)-1-amylamine hydrochloride.

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Publications

Cristol, Hayes, and Haller, Ind. Eng. Chem., An. Ed., 17, 470 (1945).

Schaeter, Soloway, Hayes, and Haller, ibid., 17, 704 (1945).

Haller, Bartlett, Drake, Newman, Cristol, Baker, Hayes, Kilmer, Wagerlein, Kueller, Schneider, and Keatley, J. Am. Chem. Soc., 67, 1591 (1945).

Drake, Van Hook, Garman, Hayes, Johnson, Kelley, Melamed, and Peck, ibid., 68, 1529, (1946).

Drake, Baker, Garman, Hayes, Haywood, Peck, Preston, Sterling, Van Hook, and Walton, ibid., 68, 1602 (1946).

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