

A STUDY OF THE PREPARATION AND PROPERTIES OF  
8-(5-iso-PROPYLAMINOAMYLAMINO)-6-METHOXYQUINOLINE  
AND SOME OF ITS SALTS

By

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

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## TABLE OF CONTENTS

	Page
INTRODUCTION .....	1
DISCUSSION .....	4
Preparation of 1-halo-5- <u>iso</u> -propylaminopentane hydrohalide .....	6
1-Bromo-5- <u>iso</u> -propylaminopentane hydrobromide .....	6
1-Chloro-5- <u>iso</u> -propylaminopentane hydrochloride .....	8
Purification of 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride .....	9
Condensation of 1-bromo-5- <u>iso</u> -propylaminopentane hydrobromide with 8-amino-6-methoxyquinoline .....	11
Condensation of 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline .....	13
An alternate method of condensation .....	20
Preparation and properties of some salts of SN-13,276 ...	22
EXPERIMENTAL .....	25
1-Halo-5- <u>iso</u> -propylaminopentane hydrohalide .....	26
1-Bromo-5-methoxypentane .....	26
1-Amino-5-methoxypentane .....	26
1-Methoxy-5- <u>iso</u> -propylaminopentane .....	28
1-Bromo-5- <u>iso</u> -propylaminopentane hydrobromide .....	29
1-Hydroxy-5- <u>iso</u> -propylaminopentane .....	30
1-Bromo-5-isopropylaminopentane hydrobromide .....	31
1-Chloro-5- <u>iso</u> -propylaminopentane hydrochloride .....	32
Purification of 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride .....	36
Condensations .....	38
Condensation of 1-bromo-5- <u>iso</u> -propylaminopentane hydrobromide with 8-amino-6-methoxyquinoline .....	40

In ethanol . . . . .	40
In buffered cellosolve-water . . . . .	45
Condensation of crude 1-chloro-5- <u>iso</u> -propylaminopentane . hydrochloride with 8-amino-6-methoxyquinoline . . . . .	46
In ethanol . . . . .	46
In dioxane . . . . .	48
In buffered cellosolve-water . . . . .	48
In water . . . . .	49
Condensation of purified 1-chloro-5- <u>iso</u> -propylamino- pentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media . . . . .	52
Attempted preparation of 8-(5-hydroxyamylamino)-6-methoxy- quinoline . . . . .	57
Salts of SW-13,276 . . . . .	60
Salts of SW-13,276 from undistilled SW-13,276 . . . . .	66
LITERATURE CITED . . . . .	73

## LIST OF TABLES

### Table

I	Condensation of 1-bromo-5- <u>iso</u> -propylaminopentane hydrobromide with 8-amino-6-methoxyquinoline in ethanol . . .	12
II	Condensations of 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media . . . . .	16
III	Condensations of purified 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media for twelve hours; temperature variations .	17
IV	Condensations of purified 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media at 80°; time variations . . . . .	19
V	Preparation of some salts of SN-13,276 . . . . .	23
VI	Properties of some salts of SN-13,276 . . . . .	24
VII	Condensation of 1-bromo-5- <u>iso</u> -propylaminopentane hydrobromide with 8-amino-6-methoxyquinoline in ethanol . . .	42
VIII	8-(5- <u>iso</u> -propylaminoamylamino)-6-methoxyquinoline monophosphate . . . . .	44
IX	Condensations of purified 1-chloro-5- <u>iso</u> -propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media; time, temperature and concentration variations . . . . .	56
X	Preparation of some salts of SN-13,276 . . . . .	62
XI	Recrystallization of some salts of SN-13,276 . . . . .	63
XII	Analysis of some salts of SN-13,276 . . . . .	64
XIII	pH and solubilities of some salts of SN-13,276 . . . . .	65

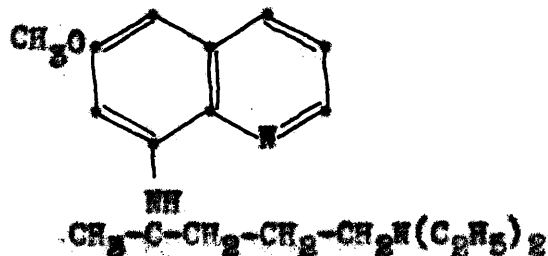
LIST OF FIGURES

Figure

1.	Plot of percent composition of 6-amino-6-methoxyquinoline and SW-13,276 vs. refractive index . . . . .	19
2.	Titration of an acid solution of SW-13,276 with standard alkali . . . . .	52

## INTRODUCTION

Plasmochin, (Pamaquine), 8-(4-diethylamino-1-methylbutylamino-6-methoxyquinoline (15P) I, when administered concurrently with a suppressive drug



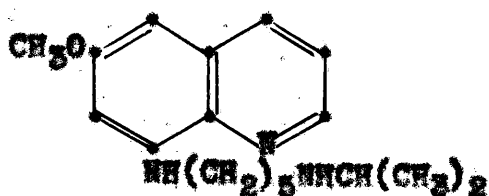
### I Plasmochin

such as quinine exerts a curative action against vivax malaria. When administered at curative dosage levels, however, Plasmochin causes serious toxic manifestations, the most serious of which are hemolytic episodes, including hemolytic anemia, which constitutes so serious a hazard to life as to require immediate cessation of the drug and prompt initiation of vigorous measures to combat these adverse symptoms. Plasmochin therapy is, therefore, used in the treatment of human vivax malaria only in very rare instances and under the most carefully controlled conditions.

Consequently, an intensive search has been undertaken in the past decade, and particularly during the recently terminated world war, to find a derivative or modification of Plasmochin which will retain the curative action of Plasmochin, but which will be less toxic.

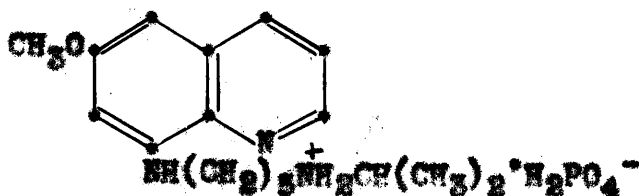


A number of variations of Plasmochin, particularly with variances in the 8-alkylaminoalkylamino group have been prepared at the University of Maryland under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland (4,5). One of the compounds synthesized was 8-(5-iso-propylaminoamylamino)-6-methoxyquinoline, designated SN-13,276 II, which was submitted to the Survey Office for test-



II. SN-13,276

ing as the monophosphate salt, SN-13,276-5 III.



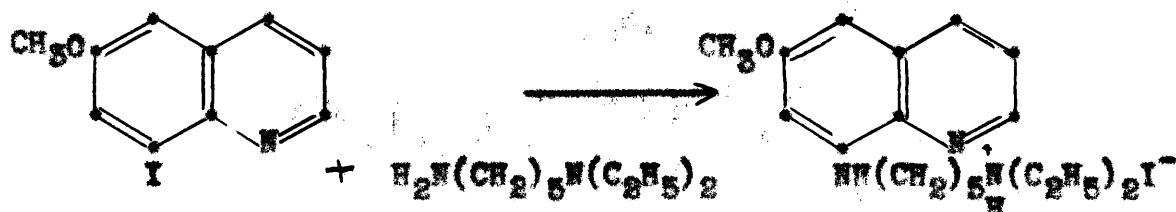
III. SN-13,276-5

The compound SN-13,276 was originally prepared with the primary intention of obtaining a sample of the pure compound for screening tests and little attention was given to refinements of preparative methods such that would lead to the optimum yields. When the Pharmacological and Clinical tests (18) indicated that the compound might be superior to Plasmochin as a curative drug against vivax malaria, it was decided to study the preparation and properties of this drug and its

salts in detail with the intention of determining what would be the optimum conditions for the preparation of the drug. It was also decided to work out, if possible, conditions which would be applicable to large scale production.

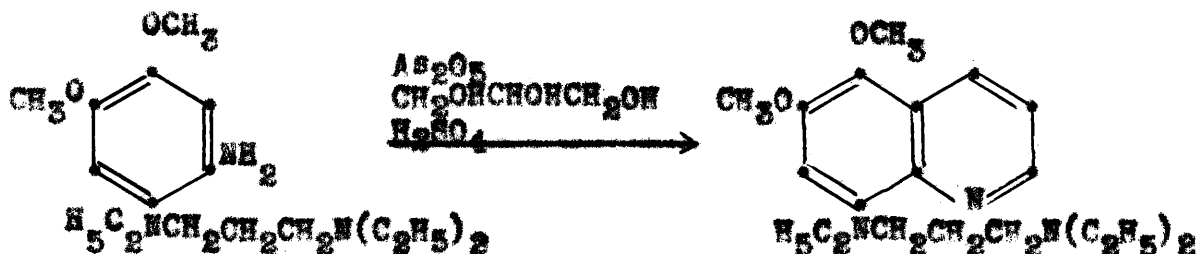
## DISCUSSION

N-alkyl derivatives of 8-aminoquinolines have been prepared in a variety of ways. Knunyantz (9) alkylated an alkylamino compound with an 8-iodoquinoline:



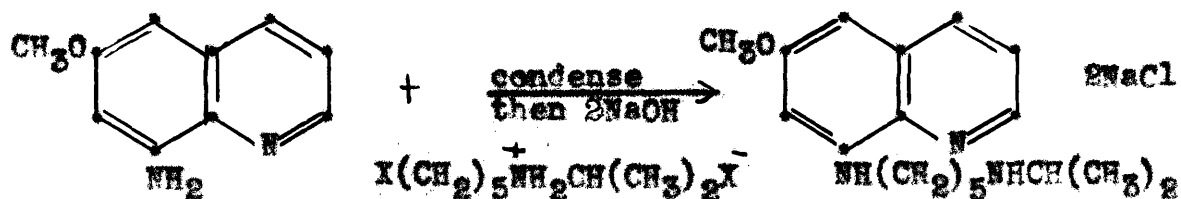
The halogen on the 8 position of quinoline is not sufficiently active to permit the use of bromine or chlorine in place of the iodine.

Schonhofer and Andersag (14P) have prepared 8-alkylaminoquinolines by the use of the Scaup reaction on properly substituted benzene compounds:

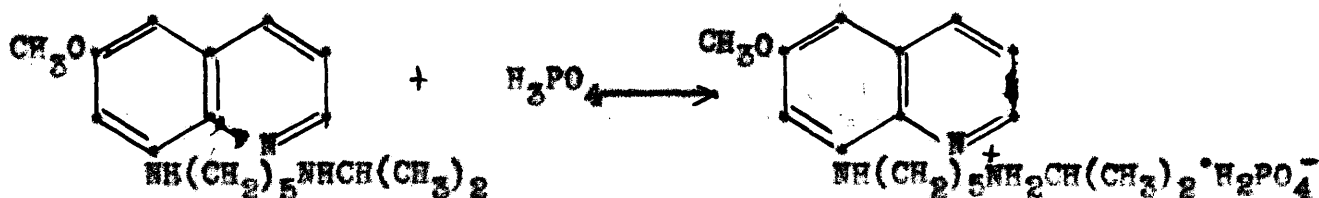


This method has not, however, found extensive application.

Extensive reports in the literature (8, 13) and our own experience (4, 5) have shown that N-alkyl derivatives of 8-aminoquinolines are best prepared by treating an 8-aminoquinoline with a suitable alkylating agent, usually an alkyl halide. Thus we would have with SN-13,276:



The products are usually sensitive to air oxidation, and they are rendered stable by converting them into suitable salts. Thus with SN-13,276-5:



Our problem then, can conveniently be separated into three sections:

1. Preparation of 1-halo-5-iso-propylaminopentane hydrohalide<sup>1</sup>
2. Condensation of 1-halo-5-iso-propylaminopentane hydrohalide with 8-amino-6-methoxyquinoline<sup>2</sup>
3. Preparation and properties of some salts of SN-13,276

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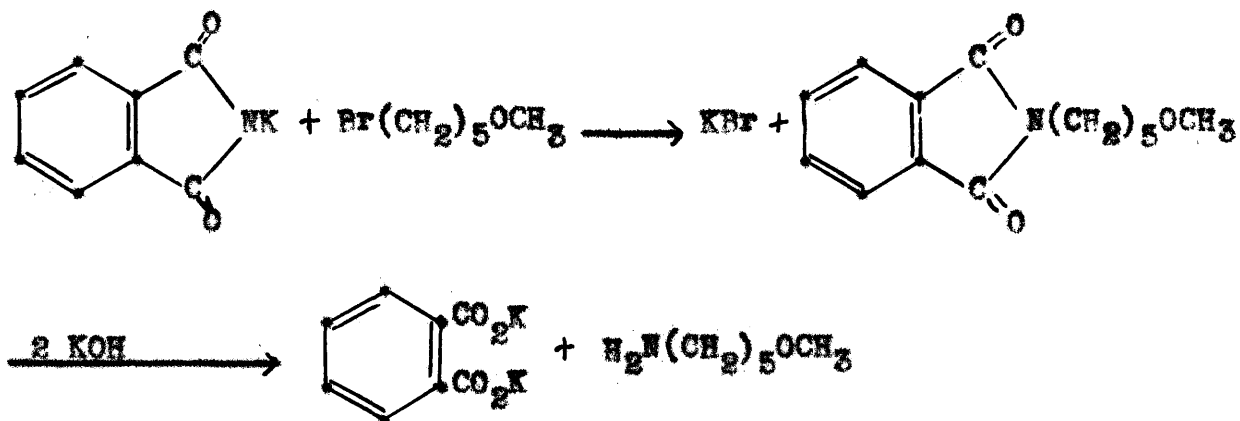
1. In this paper, when there is no danger of confusion, the 1-halo-5-iso-propylaminopentane hydrohalide will be referred to as "side chain".

2. 8-Amino-6-methoxyquinoline will frequently, hereafter, be referred to as "nucleus".

PREPARATION OF 1-HALO-5-iso-PROPYLAMINOPENTANE HYDROHALIDE

1-Bromo-5-iso-propylaminopentane hydrobromide. This compound was prepared by two general methods. The first proceeded through the intermediate 1-bromo-5-methoxypentane, which was transformed to 1-amino-5-methoxypentane by two different methods:

1. By the Gabriel synthesis in twelve percent yield;



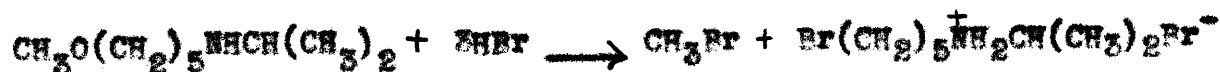
2. By the sodamide synthesis in thirty-nine percent yield;



1-Amino-5-methoxypentane was alkylated reductively in ninety percent yield by the method of Cope (2) to 1-methoxy-5-iso-propylaminopentane which was converted to 1-bromo-5-iso-

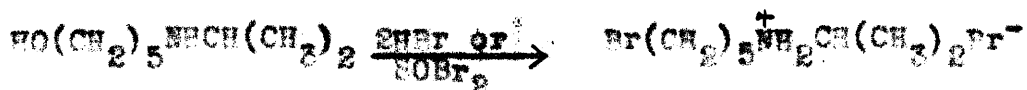


propylaminopentane hydrobromide by the action of forty-seven percent hydrobromic acid.



5-Hydroxypentanal, obtained from the acid hydrolysis of dihydropyran, according to the method of Paul (1<sup>o</sup>,19), was the starting compound for the second method of preparation of 1-bromo-5-iso-propylaminopentane hydrobromide. 5-Hydroxypentanal was reductively alkylated with iso-propylamine, according to the method of Cope (2), to 1-hydroxy-5-iso-propylaminopentane. The product, as obtained in ninety percent yield, was impure and hygroscopic, and did not give the correct neutral equivalent. However, a sample was converted to 1-bromo-5-iso-propylaminopentane hydrobromide which did give the correct analysis.

1-Hydroxy-5-iso-propylaminopentane was converted to 1-bromo-5-iso-propylaminopentane hydrobromide through the use of forty-seven percent hydrobromic acid at 100<sup>o</sup>, or thionyl bromide in benzene at 10<sup>o</sup>.



In all the above cases the 1-bromo-5-iso-propylaminopentane hydrobromide, remaining as a semi-solid or oil after removal of solvent, was used without further purification in subsequent condensations. A purified sample yielded the correct analysis.

There was no tar formed in the bromination of 1-methoxy-5-iso-propylaminopentane. There was considerable tar formed in each bromination of 1-hydroxy-5-iso-propylaminopentane. This tar was removed from the product of the aqueous acid reaction

either by decantation from the tar or through treatment with "Parco". The tar was not removed from the reaction using thionyl bromide.

Although the 1-bromo-5-iso-propylaminopentane hydrobromide obtained from 1-hydroxy-5-iso-propylaminopentane was more impure than that obtained from 1-methoxy-5-iso-propylaminopentane, the ease of preparing 1-hydroxy-5-iso-propylaminopentane as compared with 1-methoxy-5-iso-propylaminopentane, makes the former the preferred method.

The reaction of 1-hydroxy-5-iso-propylaminopentane with hydrobromic acid is preferred to its reaction with thionyl bromide because of the difficulties involved in the preparation and purification of thionyl bromide and because of the quality of products obtained from the respective bromination reactions.

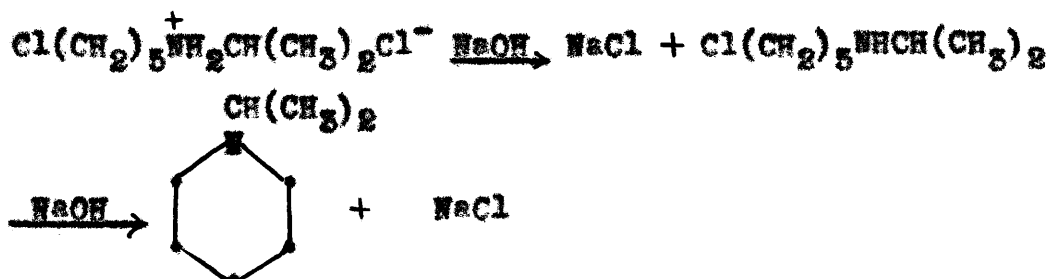
1-Chloro-5-iso-propylaminopentane hydrochloride. This compound was prepared by the action of thionyl chloride in chloroform or benzene on 1-hydroxy-5-iso-propylaminopentane hydrochloride. Low melting products were obtained in each case.



Another group working at the University of Maryland had succeeded in preparing high melting 1-chloro-5-iso-propylaminopentane hydrochloride in excellent yield, by reacting 1-hydroxy-5-iso-propylaminopentane hydrochloride with purified thionyl chloride in petroleum ether (90-100°) (5). This then, is the preferred method.

In our earlier work with this side chain, no attempt was made to purify the materials prior to condensation. It became apparent, however, that if the course of the condensation was to be studied in detail, it would be necessary to use starting materials of known purity. It was also felt that the processing of the condensation products would be facilitated by the use of pure starting materials.

Purification of 1-chloro-5-iso-propylaminopentane hydrochloride. It is necessary when working with 1-chloro-5-iso-propylaminopentane to keep its medium acid. In neutral or basic media, the compound will alkylate itself to form the cyclic compound, N-iso-propylpiperidine. This manifestation was proven by an experiment whereby an attempt was made to distill 1-chloro-5-iso-propylaminopentane. There was formed in the distilling pot a considerable amount of crystalline solid, one of the components of which was identified as N-iso-propylpiperidine hydrochloride. Also, 1-chloro-5-iso-propylaminopentane hydrochloride was converted to N-iso-propylpiperidine in eighty-two percent yield by the action of sodium hydroxide solution.



Purified 1-chloro-5-iso-propylaminopentane hydrochloride was prepared from the crude material in about seventy-five percent yield by recrystallizations using "Darce" from



ethanol-ether, benzene-petroleum ether, or acetone-ether.

CONDENSATIONS OF 1-BROMO-5-iso-PROPYLAMINOPENTANE HYDRO-  
WITH 8-AMINO-6-METHOXYQUINOLINE

Alkylation of 8-amino-6-methoxyquinoline with 1-bromo-5-iso-propylaminopentane hydrobromide was carried out by a method which was essentially that described by Rohrman and Schonle (13), whereby the reactants were allowed to condense in boiling ethanol. An excess of 8-amino-6-methoxyquinoline did not appear to be necessary. The unreacted nucleus was separated from the SW-13,276 by fractional distillation. It was not possible in this was to get a clean cut separation. The results of these condensations are summarized in table I.

SW-13,276 from the first condensation contained a large amount of nucleus. This accounts for the high yield of SW-13,276, and the low yield of SW-13,276-5 obtained from this. SW-13,276 from the third, fourth, and fifth condensation was twice distilled. There was evidence of decomposition during the first distillation. The low yields in the fifth condensation were due to the poor quality of the side chain.

A variation of the Rohrman Schonle method, whereby cello-solve and water, plus some sodium acetate added as a buffer, was used in place of the ethanol, did not cause alkylation. The preferential reaction in this buffered mixture seemed to be hydrolysis of the 1-bromo-5-iso-propylaminopentane.

TABIE I

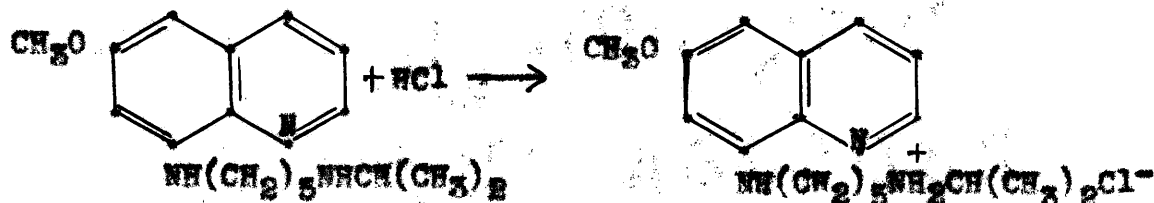
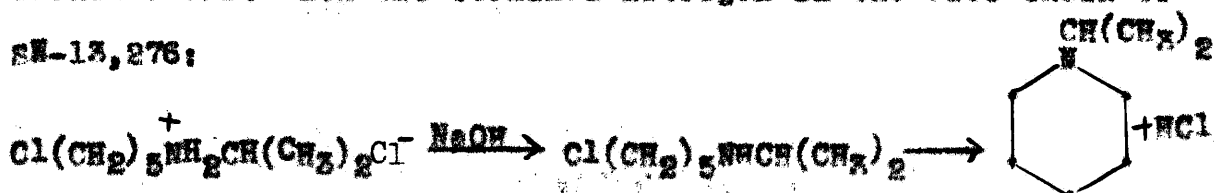
CONDENSATION OF 1-BROMO-5-iso-PROPYLAMINOPENTANE HYDRO-  
BROMIDE WITH 8-AMINO-8-METHOXYQUINOLINE IN ETHANOL

Cond. No.	Side chain	Nucleus moles	SW- 13,276	SW-13,276-5		
	Source			moles	from: SW- 13,276	Side Chain
I	$\text{CH}_3\text{O}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + HBr	0.175	0.35	48	46	21
II	$\text{CH}_3\text{O}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + HBr	0.84	1.00	41	54	22
III	$\text{HO}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + HBr	0.50	0.50	31	67	21
IV	"	4.10	4.10	38	64	23
V	$\text{HO}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + SOBr <sub>2</sub>	0.50	0.50	23	51	12

CONDENSATION OF 1-CHLORO-5-iso-PROPYLAMINOPENTANE HYDRO-  
CHLORIDE WITH 8-AMINO-8-METHOXYQUINOLINE

The first condensation in this series was run according to the method of Rohrman and Schonle. There was formed in the dried ether extracts of the condensation mixture a large amount of the monohydrochloride of SN-13,276, which was isolated as a tan crystalline solid. The conditions responsible for the formation of this salt in the dried ether extracts were believed to be as follows:

When the condensation was terminated, there was still a considerable quantity of unreacted 1-chloro-5-iso-propylaminopentane hydrochloride present. When this was made basic, 1-chloro-5-iso-propylaminopentane was taken up in the ether extract. This compound, in time, cyclized, forming N-iso-propylpiperidine, and liberating hydrogen chloride, which formed a salt with the terminal nitrogen in the side chain of SN-13,276:



Credulance was imparted to this belief by an experiment whereby a mixture of 1-chloro-5-iso-propylaminopentane and SN-13,276 in dry ether solution produced in a few weeks a fifty-six percent yield of the monohydrochloride of SN-13,276.

modifications of the Rohrsman Schonle procedure whereby boiling ethanol was replaced by dioxane in one case and with a fifty percent mixture of cellosolve and water, buffered with sodium acetate in the other case did not yield any appreciable amount of SW-13,276.

Condensations of crude 1-chloro-5-iso-propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline in aqueous media were effected by heating the mixture at successively higher temperatures, until the mixture was eventually heated at 100-105° (inside t.) for several hours. Excess 8-amino-6-methoxyquinoline hydrochloride was separated by pouring the mixture into excess hydrochloric acid solution, removing the 8-amino-6-methoxyquinoline hydrochloride formed by filtration, buffering the filtrate to pH 5, and removing the remainder of the 8-amino-6-methoxyquinoline by extraction with ether. An alternate, and more satisfactory method, was to omit the formation and filtration of the 8-amino-6-methoxyquinoline hydrochloride, and simply extract the buffered solution with ether or benzene. The aqueous portion, made basic, yielded SW-13,276 which was isolated by extraction followed by high vacuum distillation.

There was obtained as a forerun from the distillation of SW-13,276 a considerable quantity of 1-hydroxy-5-iso-propylaminopentane. It was not known whether this came from the crude side chain or whether it was formed in the condensation. Consequently, all subsequent condensations employed

purified starting materials.

A condensation was run identically as those above with the exception that purified materials were used. There was obtained a higher yield of SW-13,276, and a much lower yield of 1-hydroxy-5-iso-propylaminopentane.

To determine if heating the condensations at the lower temperatures was necessary, condensations were run identically with the one above, with the exception that they were heated at 103° (inside t.) for six and for ten hours respectively.

The results of the condensations of 1-chloro-5-iso-propylaminopentane hydrochloride with 8-amino-6-methoxyquinoline are summarized in table II.

The SW-13,276 from the tenth condensation was twice distilled. This accounts in part for the low yield.

By comparing condensations number twelve and thirteen it is apparent that some alkylation occurred below 103°. In an effort to determine at what temperature alkylation did occur appreciably, a series of condensations of purified materials in aqueous media were run for twelve hours at 60, 70, 80, and 90°. The procedure was essentially that used in the condensations above. From each there was obtained, as a low boiling forerun in the distillation of SW-13,276, some N-iso-propylpiperidine, and only traces of 1-hydroxy-5-iso-propylaminopentane. This series of condensations is summarized in table III.

Alkylation occurred to an appreciable extent in twelve hours at 80°. A series of condensations were then run at

TABLE II

CONDENSATIONS OF 1-CHLORO-5-iso-PROPYLAMINOPENTANE HYDRO-  
CHLORIDE WITH 8-AMINO-8-METHOXYQUINOLINE IN AQUEOUS MEDIA

Cond. No.	Side chain M. P. °C	Moles	Nucleus M. P. °C	Moles	Conditions Time Hrs.	Temp. °C	% SW-15,276 from side chain	
X	45-60	0.2	49-50	0.4	$\left\{ \begin{array}{l} 5 \\ 2 \\ 6 \end{array} \right.$	50	50	
						50-103		
						103		
XI	"	2.0	"	4.0	"	"	59	
XII	121-3	0.2	49.5- 50.0	0.4	"	"	67	
XIII	"	"	"	"	8	103	63	
XIV	"	"	"	"	10	103	67	

TABLE III

CONDENSATION OF PURIFIED 1-CHLORO-5-iso-PROPYLAMINOPENTANE  
 HYDROCHLORIDE WITH 8-AMINO-8-METHOXYQUINOLINE IN AQUEOUS  
 MEDIA FOR TWELVE HOURS; TEMPERATURE VARIATIONS

Cond. No.	Temp. °C	% SN-13276 from: Side chain	% Recovered Nucleus (a)	% Recovered Nucleus (b)	% Crude N- <u>iso</u> -propyl-piperidine
XV	60	19	44	87	50
XVI	70	35	48	75	29
XVII	80	50	70	86	20
XVIII	90	65	76	85	10

(a) Percent SN-13276 from nucleus is based on the amount of 8-amino-8-methoxyquinoline that was not recovered.

(b) Percent recovered nucleus is based on the amount of 8-amino-8-methoxyquinoline that was not transformed into the SN-13276 obtained.



80° for eighteen, twenty-four, and thirty hours to determine the time required to effect complete alkylation at that temperature. The results of these experiments are summarized in table IV. The condensation at 80° for twelve hours is added for comparison.

It was apparent that the reaction did not proceed to any appreciable extent at 80° after it had run for twenty-four hours. There was present at this time, however, some unreacted 1-chloro-5-iso-propylaminopentane as evidenced by the eight percent of N-iso-propylpiperidine obtained in working up the products. Consequently, a condensation was run for twenty hours at 80° and then for four hours at 103°. There was obtained from this condensation, SN-13,276 in eighty-one percent yield based on the quantity of 1-chloro-5-iso-propylaminopentane hydrochloride and eighty percent based on the quantity of 8-amino-6-methoxyquinoline not recovered. The yield of crude N-iso-propylpiperidine was three percent.

The purity of the SN-13,276 obtained and the 8-amino-6-methoxyquinoline recovered in most of these condensations was estimated from the refractive index. A graph, (fig. 1) plotting refractive index against percent composition of SN-13,276 and 8-amino-6-methoxyquinoline was constructed. Assuming these are the only components, we could estimate the amount of either component in any mixture. The SN-13,276 obtained from the alkylation of 8-amino-6-methoxyquinoline with purified 1-chloro-5-iso-propylaminopentane hydrochloride in aqueous media was generally over ninety-five percent pure.

TABLE IV

CONDENSATION OF PURIFIED 1-CHLORO-5-iso-PROPYLAMINOPENTANE  
 HYDROCHLORIDE WITH 8-AMINO-6-METHOXYQUINOLINE IN AQUEOUS  
 MEDIA AT 80°; TIME VARIATIONS

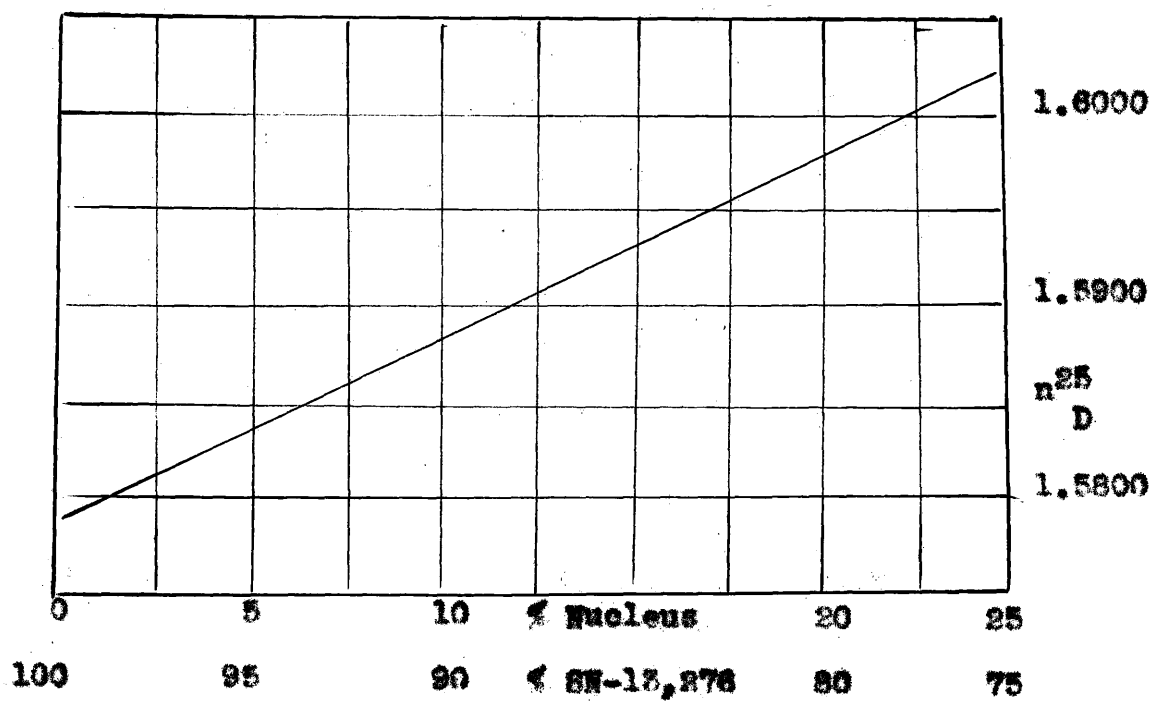
Cond. No.	Time Hrs.	% SN-13276 from: Side chain	% Recovered Nucleus <sup>(a)</sup>	% Recovered Nucleus <sup>(b)</sup>	% Crude N- <u>iso</u> -propyl- piperidine
XVIII	12	50	70	86	20
XIX	18	70	79	86	14
XX	24	78	78	82	8
XXI	30	78	81	85	8

(a) Percent SN-13276 from nucleus is based on the amount of 8-amino-6-methoxyquinoline that was not recovered.

(b) Percent recovered nucleus is based on the amount of 8-amino-6-methoxyquinoline that was not transformed into the SN-13276 obtained.

FIGURE 1

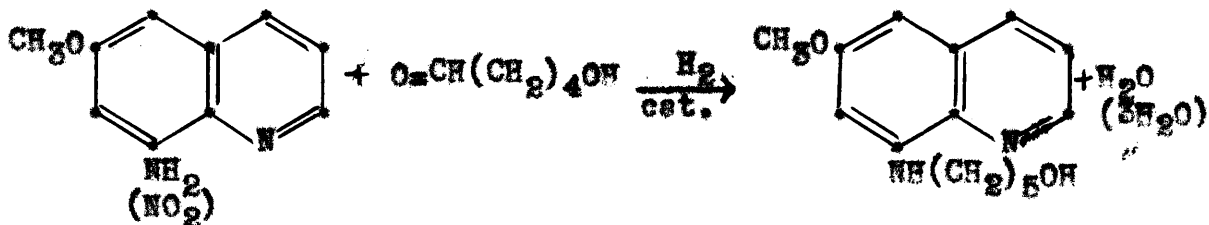
PLOT OF PERCENT COMPOSITION OF 6-AMINO-6-METHOXYQUINOLINE  
AND SN-13,276 vs. REFRACTIVE INDEX



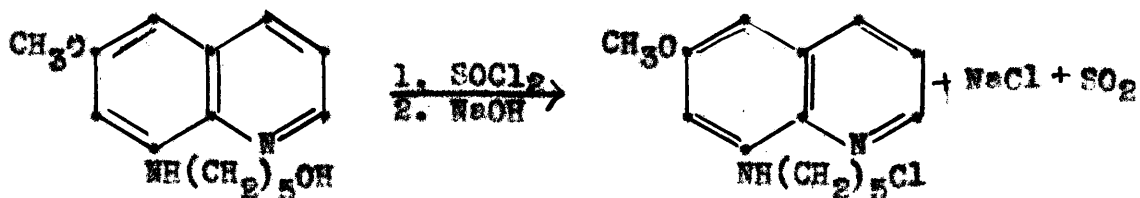
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## AN ALTERNATE METHOD OF CONDENSATION

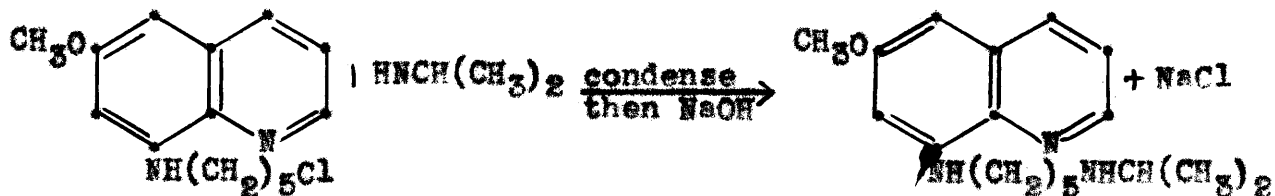
An alternate method of condensation was attempted by the reductive alkylation of 8-amino-6-methoxyquinoline or 6-methoxy-8-nitroquinoline with 5-hydroxypentanal.



It was believed that this product would react with thionyl chloride to yield 8-(5-chloromethylamino)-6-methoxyquinoline,



which could then be reacted with iso-propylamine to give FN-13,276.



An ethanolic solution of 5-hydroxypentanal and 8-amino-6-methoxyquinoline was reduced by hydrogen in the presence of platinum; pentamethylene glycol and 8-amino-6-methoxyquinoline were obtained.

Emerson and Walters (7) report the preparation of N-ethylaniline in forty-one percent yield by the reductive alkylation, with hydrogen and platinum, of aniline with

acetaldehyde in the presence of sodium acetate.



An ethanolic solution of 5-hydroxypentanal and 8-amino-6-methoxyquinoline, containing some sodium acetate as condensing agent, was shaken with hydrogen and platinum. There was a negligible uptake of hydrogen.

Emerson and Wohrmann (6) obtained secondary amines in good yields by reducing aromatic nitro compounds and aldehydes together with hydrogen in the presence of Raney nickel with sodium acetate as a condensing agent.

An ethanolic solution of 5-hydroxypentanal and 6-methoxy-8-nitroquinoline, containing some sodium acetate was reduced by hydrogen in the presence of Raney nickel. 8-Amino-6-methoxyquinoline, and a fraction for which, from the data obtained, it was not possible to assign a structure, were obtained by acidifying the mixture with hydrochloric acid.

The possibilities of this method have by no means been exhausted. However, in view of the doubtful success obtained, and the good yields obtained by the alkylation of 8-amino-6-methoxyquinoline with 1-chloro-5-iso-propylaminopentane hydrochloride in aqueous media, the method of reductive alkylation was abandoned.

## PREPARATION AND PROPERTIES OF SOME SALTS OF SN-13,276

A number of salts of SN-13,276 were prepared and their properties were determined, with the intention of further characterizing the compound. It was also felt that a study of these salts would provide information which might enable us to prepare SN-13,276 by a better method or in better yields. Only those salts were considered which were prepared easily in good yield, and which were easily purified. The general method of preparation was to dissolve SN-13,276 in ethanol, add the required amount of acid, and cool. The salts were usually recrystallized from ethanol.

SN-13,276 is a tri-acid base, and could theoretically react with three equivalents of acid. Practically, one or two equivalents of acid were employed in salt formation. The mono acid salts were in general the easier to prepare. The halides and phosphate salts were the only ones that were prepared without difficulty. Of the organic salts attempted, the oxalate was the only one that was obtained easily in fairly good yield. A summary of the salts formed is listed in table V.

The monohydriodide was prepared by adding potassium iodide to an aqueous solution of the monohydrochloride. The product analyzed a little high for carbon, indicating possible that there was not complete conversion from the monohydrochloride to the monohydriodide.

The properties of these salts are listed in table VI.

TABLE V

## PREPARATION OF SOME SALTS OF CN-15,276

Salt	% Yield	m. p. °C
monohydrochloride	84	151-2
monohydrobromide	95	166-7
monohydriodide	98	187-8
monophosphate	95	188-90
dihydrochloride	90	212-3d sinters 115
dihydrobromide	97	225-7d

TABLE VI

## PROPERTIES OF SOME SALTS OF SN-13,276

Salt	Color	M. P. °C	Solubility in water	Solubility in 95% ethanol at 5°	pH of aqueous sol at 20°
Monohydrochloride	off-white	152-3	0.012 g./ml. at 10°	0.026 g./ml.	8.05 (sat. soln. at 10°)
Monohydrobromide	off-white	166-7	0.0055 g./ml. at 25°	0.020 "	6.40 (sat. soln.)
Monohydriodide	off-white	166-8	0.0055 "	0.055 "	6.45 "
Monophosphate	pale yellow	189-90	0.067 "	0.0025 "	5.10
Dihydrochloride	orange	218-9 d sinter 216	0.5 g./ml. at 10°	0.017 "	2.00 (3 g./25 ml.)
Dihydrobromide	orange	225-7 d	0.1 g./ml. at 25°	0.025 "	1.90 (sat. soln.)



The study of these salts yielded information which both certified some previous methods of preparing SN-13,276 and SN-13,276-5 and suggested new ways of doing the same.

As a result of this study, a method of preparing pure SN-13,276-5 was developed whereby the high vacuum distillation of SN-13,276 was eliminated. This was particularly advantageous if the method was to be applied to large scale production.

The condensation products, in a small amount of water were buffered to pH 5 and extracted hot with benzene to remove excess nucleus. The monohydrochloride of SN-13,276, which precipitated from the cooled aqueous portion, was removed by filtration to leave most of the impurities in the aqueous filtrate. The monohydrochloride was made basic, and the liberated SN-13,276 was extracted with ether. The residue, remaining after distillation of ether, was precipitated as the monophosphate from ethanol. The yield of SN-13,276-5 was seventy percent, based on either the side chain or nucleus.

EXPERIMENTAL<sup>3</sup>

1-Bromo-5-methoxypentane. A solution of 4 moles of sodium methoxide in 2.5-l. of anhydrous methanol was added over a two hour period to a stirred, refluxing solution of 920 g. (4.0 moles) of 1,5-dibromopentane in 1.3-l. of anhydrous ethyl ether. The mixture was boiled under reflux for three hours, whereupon the condenser was adjusted for downward distillation and 4-l. of distillate was removed. The precipitated sodium bromide was filtered and washed with 2-l. of ether. The combined filtrate and washing were washed, until neutral to litmus, with water and dried over calcium chloride. The ether was distilled and the residue was fractionally distilled through a three foot Widmer column under reduced pressure. The following fractions were obtained:

dimethoxypentane 85 g. 92-6°/110 mm.

bromomethoxypentane 350 g. 96-128°/110 mm.

dibromopentane 90 g. residue

The second fraction was refractionated through the column to yield 274 g. (38% yield, based on the sodium methoxide) of 1-bromo-5-methoxypentane which boiled at 124-6°/100 mm.

1-Amino-5-methoxypentane. This compound was prepared by two methods.

1. By the Gabriel synthesis. Potassium phthalimide

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3. All melting points are corrected. Boiling points are not corrected. We are indebted to Miss Fleanor Werble for the C, H, and P microanalyses.

(280 g.; 1.5 moles) and 1-bromo-5-methoxypentane (274 g.; 1.51 moles) were stirred together at 150-170° for eighteen hours and then extracted with three 500-ml. portions of boiling ethanol. The residual potassium bromide was eighty-nine percent of the theoretically expected amount. The ethanol extracts were concentrated to 500-ml. by distillation, diluted with a solution of 560 g. of potassium hydroxide in 500-ml. of water and refluxed for five hours. The cooled mixture was extracted with 3-l. of ether; the extracts were dried and distilled to yield 29 g. of liquid boiling at 175-85°. A solution of this liquid in 25-ml. of twelve normal hydrochloric acid was extracted with three 25-ml. portions of ether. The ether extracts left no appreciable residue on distillation. The aqueous portion was made strongly basic with fifty percent potassium hydroxide solution and extracted with three 300-ml. portions of ether. The extracts were dried and distilled to yield 22 g. (12% yield) of 1-amino-5-methoxypentane boiling at 167-70°. Analysis calculated for  $C_6H_{15}NO$ : neutral equivalent, 117.2; found, neutral equivalent, 120.0.

2. By the sodamide synthesis. This method was essentially that outlined by Shreve and Purtsfield (17). A 1-l. three-necked flask, equipped with a stirrer with rubber sleeve, a drying tube, a thermometer, which dipped into the liquid, and a dropping funnel, was cooled to -50° in a dry ice-alcohol bath. Four hundred grams of liquid ammonia and 300 mg. of ferric nitrate was added, the stirrer was started, the cooling bath was removed, and 25.4 g. (1.10 moles) of sodium was added

in 1 g. pieces. The sodium reacted vigorously with the ammonia and care was taken that each piece had completely reacted before the next piece was added. The solution appeared blue-black while the sodium was reacting. The mixture was then cooled to  $-50^{\circ}$  in the dry ice-alcohol bath and 200 g. (1.10 moles) of 1-bromo-5-methoxypentane was added at a rate that permitted the temperature to be kept below  $-50^{\circ}$ . About two hours was required. The mixture was stirred at  $-50^{\circ}$  for two hours, the cooling bath was removed, and the ammonia was allowed to evaporate with stirring. A solution of 100 g. of sodium hydroxide in 600-ml. of water was added, the mixture was stirred for thirty minutes, and then extracted with five 200-ml. portions of ether. The ether extracts were extracted with one 300-ml. and two 100-ml. portions of ten percent hydrochloric acid solution. The acid extracts were made strongly basic by the addition of thirty-three percent sodium hydroxide solution and extracted with five 400-ml. portions of ether. The ether extracts were dried over anhydrous potassium carbonate and distilled. There was obtained 53 g. (41%) of 1-amino-5-methoxypentane which boiled at  $165-7^{\circ}$ . Analysis, neutral equivalent, 121.0.

1-Methoxy-5-iso-propylaminopentane. This compound was prepared by reductive alkylation of acetone with 1-amino-5-methoxypentane according to the method of Cope (2). A suspension of 35 mg. of Adams' platinum oxide catalyst<sup>4</sup> in 10-ml.

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4. The Adams' platinum oxide catalyst was purchased from the American Platinum Works.

of commercial absolute ethanol was shaken in a low-pressure hydrogenation apparatus (1) under one to two atmospheres of hydrogen for half an hour, whereupon a solution of 22 g. (0.19 mole) of 1-amino-5-methoxypentane and 19 g. (0.19 mole) of redistilled acetone in 30-ml. of commercial absolute ethanol was added and the mixture was shaken under one to two atmospheres of hydrogen pressure. The solution became warm when reduction commenced. Most of the 0.2 mole of hydrogen that was absorbed was taken up in the first hour and reduction was complete in three hours. The catalyst was filtered and washed with 10 ml. of benzene and the solvents were distilled from the combined filtrate and wash. The residue was fractionated through a one-foot Claisen column under reduced pressure to yield 27.3 g. (94%, based on the 1-amino-5-methoxypentane) of 1-methoxy-5-iso-propylaminopentane which boiled at  $93^{\circ}/20$  mm. Analysis, calculated for  $C_9H_{21}NO$ : neutral equivalent, 159; found, neutral equivalent, 161, 163.

1-Bromo-5-iso-propylaminopentane hydrobromide. A solution of 134 g. (0.84 mole) of 1-methoxy-5-iso-propylaminopentane in 900-ml. (8.0 moles) of forty-nine percent hydrobromic acid solution was heated on a steam bath for four hours. The evolution of methyl bromide had ceased after three hours. The excess water and hydrogen bromide were removed by distillation at  $100^{\circ}$  under the vacuum of a good water pump. The last traces were removed by heating at  $100^{\circ}$  at 2 mm. for two hours. The tan, semi-solid residue was used without further purification in subsequent condensations.

1-Hydroxy-5-iso-propylaminopentane. A suspension of Adams' platinum oxide catalyst<sup>5</sup> in 20-ml. of anhydrous ethanol was reduced in a low-pressure hydrogenation apparatus (1). A solution of 20 g. (0.2 mole) of 5-hydroxypentanal<sup>6</sup> in 18 g. (0.2 mole) of iso-propylamine was added to the reaction flask and rinsed in with 20-ml. of anhydrous ethanol. The mixture was then shaken under two to three atmospheres of hydrogen pressure for two hours, at which time the adsorption of hydrogen ceased; the theoretical pressure drop was observed. The reaction mixture was filtered and the flask and catalyst were rinsed with a little benzene. The combined filtrate and wash was distilled, first at atmospheric pressure to remove the benzene, alcohol and water, and then under reduced pressure. There was obtained 27 g. (93%) of 1-hydroxy-5-iso-propylaminopentane which boiled at 95-7°/1 mm. which collected as a white crystalline solid in the receiver. This material had a neutral equivalent of 156. The theoretical neutral equivalent, required for  $C_8H_{19}NO$ , is 145. The material (52 g., from several collected runs) was dissolved in 200-ml. of ether and extracted with 100-ml. of six normal hydrochloric acid. The acid extracts were made basic, extracted with ether, and the

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5. The Adams' platinum oxide catalyst was purchased from the American Platinum Works.

6. We are indebted to Dr. G. F. Woods for this sample of 5-hydroxypentanal. It boiled at 64-6°/6-7 mm. and had  $n_D^{20}$  1.4515. See (19).

extracts were dried over anhydrous potassium carbonate. The mixture was filtered, the ether was distilled, and the residue was distilled under reduced pressure to yield 42 g. (81% recovery) of 1-hydroxy-5-iso-propylaminopentane which boiled at 87-90°/1 mm., with the bath temperature at 120-5°. This product had a neutral equivalent of 151. The material is hygroscopic; a small sample of the solid placed in air gradually formed a melt. A sample in dry ether solution was converted to 1-hydroxy-5-iso-propylaminopentane hydrobromide by the action of dry hydrogen bromide. The product, recrystallized from acetone-ether, melted at 80-1° with previous sintering at 78°. Analysis, calculated for  $C_8H_{20}NOBr$ :  $Br^-$ , 35.3; found,  $Br^-$ , 35.4, 35.2 (Volhard).

1-Bromo-5-iso-propylaminopentane hydrobromide. This compound was prepared from 1-hydroxy-5-iso-propylaminopentane by two different methods.

1. By action of hydrobromic acid. A solution of 116 g. (0.80 mole) of 1-hydroxy-5-iso-propylaminopentane (neutral equivalent = 151) in 880-ml. (8.0 moles) of forty-eight percent hydrobromic acid solution was heated at 100° for four hours. The black solution, containing some tar, was heated with 40 g. of "Darco" for fifteen minutes and filtered. The straw-colored filtrate was concentrated by heating at 100° under the vacuum of a good water pump. The last traces of water were removed by heating at 100° at 2 mm. pressure for two hours. The tan, semi-solid residue weighed 200 g. (86%)/

It was used without further purification in subsequent condensations. A sample of this crude material was dissolved in hot ethanol, treated with Sparco<sup>®</sup>, and filtered. The filtrate was diluted with anhydrous ether to turbidity and cooled. The solid obtained (m.p. 108-116<sup>°</sup>) was dissolved in boiling acetone, treated with Sparco<sup>®</sup> and filtered. The filtrate was diluted to turbidity with ether and cooled. The resulting solid melted at 119-9<sup>°</sup>. Analysis, calculated for C<sub>8</sub>H<sub>13</sub>NBr: Br<sup>-</sup>, 27.7; found, Br<sup>-</sup>, 28.2, 27.8 (Volhard).

8. By action of thionyl bromide in benzene. A solution of 73 g. (0.50 mole) of 1-hydroxy-5-iso-propylamino-pentane (neutral equivalent 151) in 300-ml. of dry benzene was stirred and cooled to 10<sup>°</sup> and 114 g. (0.55 mole) of freshly distilled thionyl bromide was added at a rate that permitted the temperature to be kept below 10<sup>°</sup>. The black mixture was allowed to warm to room temperature slowly and to remain at that temperature overnight. It was then heated at 60<sup>°</sup> under the vacuum of a good water pump to remove most of the benzene and excess thionyl bromide, and was finally heated at 60<sup>°</sup> for two hours at 2 mm. pressure. The black residue was used without further purification in a subsequent condensation.

1-Chloro-5-iso-propylamino-pentane hydrochloride. This compound was prepared by several different methods.

1. By action of thionyl chloride in chloroform. A solution of 95 g. (0.80 mole) of redistilled thionyl chloride (Fastman Kodak Co., purified, redistilled from linseed oil) in 100-ml. of dry chloroform was added over a forty minute



period to a stirred, ice-cold solution of 180 g. (0.72 mole) of 1-hydroxy-5-iso-propylaminopentane hydrochloride<sup>7</sup> in 1200-ml. of dry chloroform. The pale orange mixture was stirred and heated at 40° for forty minutes, boiled under reflux for thirty minutes, and allowed to stand overnight. The solvents were distilled under the vacuum of a good water pump and the residue was poured into 1-l. of stirred anhydrous ether. The resulting oily, tan solid was dried to constant weight in a vacuum oven at 40°. It weighed 142 g. (98%) and melted at 102-7°.

2. By action of thionyl chloride in benzene. A solution of 66 g. (0.55 mole) of redistilled thionyl chloride (Eastman Kodak Co., purified, redistilled from linseed oil) in 100-ml. of dry benzene was added, over a thirty minute period, to a stirred solution of 91 g. (0.5 mole) of 1-hydroxy-5-iso-propylaminopentane hydrochloride in 500-ml. of dry benzene maintained at 10°. The stirred mixture was allowed to warm to room temperature, remain at this temperature for two hours and finally was boiled under reflux for one hour. The mixture was dark brown at room temperature, but turned black when boiled. The residue, remaining after the solvents were distilled, crystallized on cooling. It weighed 70 g. and melted at 90-110°. The yield (70%) was not representative, because the mixture bumped while boiling, and some of the

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7. This sample of 1-hydroxy-5-iso-propylaminopentane hydrochloride melted at 97.3-98.1°. It was prepared in the Laboratories of the University of Maryland (5).

product was 1 st. The procedure, however, was not repeated, because another group, working at the University of Maryland had succeeded in preparing 1-chloro-5-iso-propylaminopentane hydrochloride, melting at 112-120°, in 97% yield by reacting purified thionyl chloride with 1-hydroxy-5-iso-propylaminopentane hydrochloride in boiling petroleum ether (90-100°) (5). The last is the preferred method.

Purification of 1-chloro-5-iso-propylaminopentane hydrochloride. An attempt was made to distil 1-chloro-5-iso-propylaminopentane. An ice-cold solution of 100 g. (0.50 mole) of 1-chloro-5-iso-propylaminopentane hydrochloride (m.p. 45-60°)<sup>8</sup> in 200-ml. of water was made basic by the addition of sodium hydroxide solution. The temperature was kept below 10°. The basic mixture was extracted with 500-ml. of ether; the extracts were washed with water and dried over "Drierite". The "Drierite" was filtered and the ether was distilled from the filtrate under vacuum. The residue was distilled at 1-mm. pressure, while the heating bath was kept at as low a temperature as possible. There was obtained 27 g. of a liquid which boiled at 30-40°/1 mm. with the bath at 60-80°. A quantity of white crystalline solid remained in the pot. The 27 g. of liquid was redistilled and yielded 10 g. of liquid which boiled at 27-35°, leaving a white crystalline solid in the pot. The solid from the second distillation was dissolved in 20-ml. of ethanol and poured into 300-ml. of

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8. A quantity of 1-chloro-5-iso-propylaminopentane hydrochloride was purchased from the Sharples Chemical Co., as a brown, tacky solid that melted at 45-60°.

anhydrous ether. The solid that formed melted, when dry, at 100-140° and weighed 6 g. This solid was dissolved in 10 ml. of ethanol, anhydrous ether was added to turbidity, and the mixture was allowed to stand for two hours. The solid obtained (ca. 0.5 g.) was recrystallized from ethanol-ether to yield 0.2 g. of crystalline solid. An attempt was made to melt this in a silicone-oil bath. The solid darkened and started to shrink at about 200° but had not melted at 265°. A sample of authentic N-iso-propylpiperidine hydrochloride behaved in the same manner. The solid, dissolved in water, was made basic, and extracted with ether; the ether was distilled. The residue was dissolved in 5-ml. of ethanol and 2-ml. of a saturated solution of picric acid in ethanol was added. The cooled mixture yielded yellow crystals which melted at 151-2°. The filtrate from the 0.5 g. of N-iso-propylpiperidine hydrochloride was diluted with ether to yield an additional 5 g. of white crystalline solid, which melted at 100-140°. Attempts to fractionally crystallize this from ethanol-acetone, ethanol-ether, and acetone-ether did not yield any additional pure fractions.

N-iso-propylpiperidine. A solution of 20 g. (0.1 mole) of 1-chloro-5-iso-propylpiperidine hydrochloride in 20-ml. of water was neutralized with ten percent sodium hydroxide solution, and then 6 g. of solid sodium hydroxide was added. The mixture was boiled under reflux for three hours, and extracted with 100-ml. of ether. The ether extracts were dried over solid sodium hydroxide and distilled to yield 10.4 g.



(82%) of N-iso-propylpiperidine which boiled at 150°.

Analysis, calculated for  $C_8H_{17}N$ : neutral equivalent, 127.2; found, neutral equivalent, 128.1, 127.7. It had  $n_D^{25}$  1.4450, and gave a picrate which melted at 152-152.5°. Landenburg (10) reports a boiling point of 149-50°, and Schwoegler and Adkins (15) report a picrate melting point of 153°.

Recrystallization of 1-chloro-5-iso-propylaminopentane hydrochloride. This was carried out in several different mixtures of solvents.

1. Ethanol-ether. A solution of 100 g. of 1-chloro-5-iso-propylaminopentane hydrochloride (m.p. 45-60°) in 500-ml. of anhydrous ethanol was boiled under reflux with 15 g. of "Darco" for fifteen minutes, and filtered. The filtrate was distilled until 350-ml. of distillate was collected. The residue was poured into 1-l. of anhydrous ether and cooled. The solid that formed was filtered, washed with anhydrous ether and dried to constant weight in a vacuum oven at 40°. It weighed 74 g. and melted at 121-24°. Attempts to process the mother liquors resulted in an oil which could not be induced to crystallize.

2. Benzene petroleum ether. A solution of 50 g. of 1-chloro-5-iso-propylaminopentane hydrochloride (m.p. 46-60°) in 250-ml. of anhydrous ethanol was boiled under reflux with 5 g. of "Darco" for fifteen minutes and filtered. All of the ethanol was distilled from the filtrate. The residue, in 400-ml. of benzene, was distilled until 300-ml. of distillate

was collected. Petroleum ether (90-100°) was added to the residue to turbidity and the mixture was cooled. The resulting solid was filtered and dried to constant weight in a vacuum oven at 40°. It weighed 38 g. (76% recovery) and melted at 117-121°. The filtrates were diluted with petroleum ether to yield an additional 4 g. (8%) of solid which melted at 100-110°.

3. Acetone-ether. 1-Chloro-5-iso-propylaminopentane hydrochloride (470 g., m.p. 112-120°; prepared at the University of Maryland (5)) was dissolved in 1.5-l. of boiling acetone. The black solution was boiled under reflux with 50 g. of "Darco" for fifteen minutes, and filtered hot. The "Darco" was washed with 500-ml. of boiling acetone. The combined filtrate and washing were diluted to turbidity with anhydrous ether and cooled. The resulting white crystalline solid was filtered, washed with anhydrous ether and dried to constant weight in a vacuum oven at 40°. It weighed 350 g. (75% recovery) and melted at 120-123°. Analysis, calculated for  $C_8H_{19}NCl_2$ :  $Cl^-$ , 17.72; found,  $Cl^-$ , 17.68, 17.54. Attempts to process the mother liquors produced an oil that could not be induced to crystallize.

Ten grams of the solid, which melted at 120-23°, was dissolved in 10-ml. of acetone and the solution was diluted to turbidity with anhydrous ether. The solid obtained melted at 124.5-5.5°. Analysis, calculated for  $C_8H_{19}NCl_2$ : C, 48.00, H, 9.57. Found: C, 48.29, 48.14; H, 10.05, 9.85.

## CONDENSATIONS

The 1-halo-5-iso-propylaminopentane hydrohalide employed in these condensations was that described in the individual subsequent sections.

8-Amino-6-methoxyquinoline was purchased from the Winthrop Chemical Company. It was distilled in an atmosphere of nitrogen from von Braun flasks with wide tubes at low pressures. The boiling range of the product depended on the pressure, the height of the column and the temperature of the heating bath. Some of the recorded boiling ranges, with their accompanying pressures and bath temperatures were:

97-115<sup>o</sup>/2 microns, bath at 135-150<sup>o</sup>

120-130<sup>o</sup>/0.5 mm., bath at 150-170<sup>o</sup>

140-160<sup>o</sup>/1.0 mm., bath at 170-190<sup>o</sup>.

The once distilled product, when recrystallized from methanol (1 g. of base/0.4-ml. methanol) yielded a product which melted at 49-50<sup>o</sup>. This product was generally contaminated with some small amount of an unidentified material which caused the product to take on a purple-black color when exposed to air. 8-Amino-6-methoxyquinoline purified by this method, was, however, satisfactory for most condensations. Its homogeneity as estimated by the counter-current extraction process (3) was 98 ± 2%.<sup>9</sup> A cream-colored, crystalline solid, which melted at 49.5-50.00<sup>o</sup> and which would not discolor on

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9. We wish to thank Dr. R. C. Elderfield for his kindness in having this analysis carried out for us.

relatively long exposure to air, was obtained by a subsequent crystallization from methanol. The refractive index of this twice recrystallized material as a supercooled oil at 25° was  $n_D^{25}$  1.6750. This quality material was used when specified in the following sections.

8-(5-iso-propylaminoamylamino)-6-methoxyquinoline (SK-13,276) was isolated by distillation in an atmosphere of nitrogen at high vacuum from von Braun flasks with wide tubes. The boiling range depended on the pressure, the height of the column and the temperature of the heating bath. Some recorded boiling ranges, pressures, and bath temperatures were:

150-157°/2 microns, bath at 170-195°  
 165-170°/20 microns, bath at 200-210°  
 180-190°/0.5 mm., bath at 220-230°.

When pure, SK-13,276 is a pale yellow, viscous oil. It darkens on exposure to air. The pure material, distilled to constant refractive index had  $n_D^{25}$  1.5785, and gave the analysis: C, 71.13; H, 9.39. The theoretical analysis, required for  $C_{18}H_{27}N_3O$ , is C, 71.73; H, 9.02.

The material is hygroscopic. When preparing a sample for analysis, it was necessary to remove it from the still, weigh it and place it in the analytical combustion chamber as quickly as possible. A period of about five minutes was taken for these operations in this case.

CONDENSATION OF 1-BROMO-5-1SC-PROPYLAMINOPENTANE HYDRO-  
BROMIDE WITH 8-AMINO-6-METHOXYQUINOLINE

In ethanol. A series of five condensations using these materials was run by a method that was essentially that outlined by Rohrman and Schenle (11). The 8-amino-6-methoxyquinoline used melted at 49-50°. The 1-bromo-5-1sc-propylaminopentane hydrobromide was obtained from different sources and was of different quality as indicated in each case. There were variations in the ratio of the side chain to nucleus. The ratio of side chain to ethanol was constant in all cases. With the exception of the above noted discrepancies and some that will be shown later, the procedure employed was the same in each case. It will be sufficient, therefore to outline only one procedure in detail.

A solution of 0.84 mole of 1-bromo-5-1sc-propylaminopentane hydrobromide and 174 g. (1.0 mole) of 8-amino-6-methoxyquinoline in 1.2-l. of absolute ethanol was boiled under reflux for sixty hours. The reactants were completely in solution when refluxing commenced. Some orange solid appeared in a few minutes and the quantity of the solid increased during the remainder of the time. The mixture was poured on 500 g. of ice, made strongly basic by the addition of thirty-three percent sodium hydroxide solution, and extracted with one 2-l. and three 800-ml. portions of chloroform. The chloroform was distilled from the extracts. The residue in a 500-ml. von Braun flask was distilled in an atmosphere of nitrogen



under reduced pressure, first under the vacuum of a good water pump, and then under 2 mm. pressure to remove excess solvents and side chain or side chain degradation products. The residue was then distilled in a high vacuum. The fraction which boiled at 110-160°/4 microns, which consisted mainly of unreacted nucleus weighed 95 g. The fraction which boiled at 160-70°/7 microns (bath t., 190-210°) which consisted mainly of SN-13,276 weighed 103 g., which represented a yield of 41% based on the quantity of side chain used.

These first five condensations are outlined in table VII.

The distillation of SN-13,276 from the third, fourth, and fifth condensations terminated when the material started to decompose and it was no longer possible to keep a high vacuum. There was present at this time a considerable residue, which when cooled, formed a solid tar. The SN-13,276 obtained was somewhat colored and it was necessary to redistill it. SN-13,276 from the second distillation was pale yellow and left no appreciable residue in the pot.

It was not possible to get a quantitative separation of SN-13,276 and nucleus by fractional distillation, and the product as obtained was contaminated with nucleus. The product was converted to the monophosphate. The amount of monophosphate obtained, and the difficulty in purifying it, were the means by which the purity of the SN-13,276 was estimated. For this reason, we will include the conversion to the monophosphate salt and its purification here. A continuation of the above condensation will be used as the example. Discrepancies

TABLE VII

CONDENSATION OF 1-BROMO-5-iso-PROPYLAMINOPENTANE HYDROBROMIDE  
WITH 8-AMINO-6-METHOXYQUINOLINE IN ETHANOL

Cond. No.	Side chain Source	Moles	Nucleus moles	SW-13,276
I	$\text{CH}_3\text{O}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + HBr	0.175	0.35	48
II	"	0.84	1.00	41
III	$\text{HO}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + HBr	0.50	0.50	31
IV	"	4.10	4.10	38
V	$\text{HO}(\text{CH}_2)_5\text{NHCH}(\text{CH}_3)_2$ + SOBr <sub>2</sub>	0.50	0.50	23

from this procedure will be listed.

Two liters of ethanol was added to a solution of 103 g. (0.342 mole) of SW-13,276 and 39.6 g. (0.342 mole) of eighty-five percent phosphoric acid heated to 60°. The mixture was seeded and cooled in a refrigerator overnight. The yellow crystals that formed were filtered, washed with ice-cold ethanol and dried to constant weight in a vacuum oven at 40°. They weighed 117 g. and melted at 183-5°. After two recrystallizations from 8-1. of ninety-five percent ethanol the dried crystals weighed 74 g., representing a yield of 54% based on the quantity of SW-13,276, and 22% based on the side chain; the recrystallized salt melted at 187.5-8.5°. An alternate and better method of recrystallization was to employ methanol as the solvent.

Forty-nine grams of SW-13,276-5, m.p. 185-6°, in 1.2-1. of methanol was boiled under reflux until complete solution was effected, whereupon the condenser was set for downward distillation and 600-ml. of distillate was collected. The residue was cooled and 33 g. of yellow crystals, which melted at 188.5-189.5°, were obtained by filtration.

The monophosphates of SW-13,276 from the first five condensations are listed in table VIII.

The first attempt was to prepare the diphosphate of SW-13,276. There was present in the SW-13,276 from the first condensation a considerable amount of nucleus. A given weight of nucleus requires more phosphoric acid than does an

TABLE VIII

8-(5-iso-PROPYLAMINOAMYLAMINO)-6-METHOXYQUINOLINE  
MONOPHOSPHATE

Cond. No.	Salt Formation		Recrystallization <sup>(a)</sup>		from:		
	% from SW-13276	M. P. °C	Solvent	%	M. P.	SW-13276 side chain	
I	87	180-60	ethanol	48	188-90	46	82
II	85	183-5	"	54	187.5- 8.5	54	82
III	87	185-6	methanol	67	188.5- 9.5	67	81
IV			"	64	188-9	64	83
V	81	184-5	ethanol	51	185-6	51	12

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(a) The salts from condensations I and II were recrystallized twice.

equal weight of SN-13,276. Consequently, in this first experiment there was too little phosphoric acid to form the diphosphate of SN-13,276; formation of the monophosphate resulted. The low yield in the fifth condensation was due to the poor quality of the side chain.

In buffered cellosolve-water. A solution of 200 g. (0.69 mole) of 1-bromo-5-iso-propylaminopentane hydrobromide and 122 g. (0.70 mole) of 8-amino-6-methoxyquinoline in 350-ml. of fifty percent cellosolve-water, containing 190 g. (1.40 moles) of sodium acetate trihydrate was boiled under reflux for seventy hours. The mixture, which appeared to be entirely in solution, was poured into 2.1-l. of water, whereupon a black oil layer formed beneath the water layer. The mixture (pH 5.0) was extracted with three 400-ml. portions of chloroform. The chloroform extracts were distilled to yield 113 g. (93% recovery) of unreacted nucleus which boiled at 115-120°/2 microns.

The aqueous portion was made strongly basic by the addition of sodium hydroxide solution and extracted with five 400-ml. portions of chloroform. The extracts were distilled to yield 34 g. (34%) of 1-hydroxy-5-iso-propylaminopentane, which boiled at 70-80°/1 mm. Dry hydrogen chloride gas was blown over the surface of a solution of a sample of this material in anhydrous ether until the solution no longer gave a basic test with moist universal indicator paper. The solid that had formed was recrystallized from ethanol-acetone-

ether. It melted at 98.5-99.5°. A mixture of this with authentic 1-hydroxy-5-iso-propylaminopentane hydrochloride (m.p. 97.2-98.5°) melted at 97.5-98.5°.

CONDENSATION OF CRUDE 1-CHLORO-5-iso-PROPYLAMINOPENTANE  
HYDROCHLORIDE WITH 8-AMINO-8-METHOXYQUINOLINE

In ethanol. This condensation was run according to the method of Rohrsen and Schonle (11). A solution of 100 g. (0.5 mole) of 1-chloro-5-iso-propylaminopentane hydrochloride (m.p. 45-60°) and 87 g. (0.5 mole) of 8-amino-8-methoxyquinoline (m.p. 49-50°) in 500-ml. of ethanol was boiled under reflux for seventy-two hours, whereupon the condenser was adjusted for downward distillation and 300-ml. of distillate was collected. The residue was made basic by the addition of excess sodium hydroxide solution and extracted with four 500-ml. portions of ether. The ether extracts were dried over anhydrous calcium sulfate.

Some cream-colored crystalline solid appeared in the dried ether extracts. These crystals were separated mechanically from the drying agent, removed by filtration from adhering liquid and dried. They weighed 7 g. and melted at 148-50°. The calcium sulfate was removed by filtration from the dried ether extract; the filtrate was concentrated to 500-ml. by distillation, seeded and cooled in an ice-bath. The resulting solid was removed by filtration and dried. It melted at 151-2° and weighed 13 g. The ether was distilled from the filtrate; the residue was dissolved in 2-l. of ben-

zene and 1-l. of benzene was distilled to remove any water which might have been present. The residual benzene solution was seeded and cooled. The solid that formed was removed by filtration. It melted at 148-150° and weighed 10 g. The filtrate was distilled to yield 50 g. (58% recovery) of nucleus which boiled at 110-20°/8 microns.

The following evidence proved that the solid that formed in the dried ether extracts was the monohydrochloride of SW-13,276:

1. An aqueous solution of the solid gave a chloride ion test.
2. A solution of 20 g. of the solid in water was made basic and extracted with ether. The extracts were dried and distilled to yield 10 g. of an oil which boiled at 180-90°/0.5 mm. This oil was converted to a monophosphate which melted at 187.5-8°.
3. The solid, recrystallized from methanol-ether, melted at 151-2°. Authentic monohydrochloride of SW-13,276 melted at 152-3°.
4. Analysis, calculated for the monohydrochloride of SW-13,276,  $C_{18}H_{27}N_3O^+Cl^-$ : C, 63.98; H, 8.35. Found, C, 64.01, 63.83; H, 8.56, 8.51.

That this salt could be formed from a mixture of SW-13,276 and 1-chloro-5-iso-propylaminopentane was shown by the following experiment:

A solution of 5 g. (0.025 mole) of 1-chloro-5-iso-propyl-

aminopentane hydrochloride in 20-ml. of water was made basic and extracted with ether. The extracts were dried briefly over anhydrous magnesium sulfate and filtered. The filtrate was added to a solution of 7.5 g. (0.084 mole) of SN-13,276 in 25-ml. of anhydrous ether. In five hours, some solid had appeared. After three weeks, the solid was filtered, washed with ether, and dried. It weighed 4.8 g. (54%) and melted at 150-2°. A mixture of this with authentic monohydrochloride of SN-13,276 melted at 151-2°.

In dioxane. A mixture of 40 g. (0.2 mole) of 1-chloro-5-iso-propylaminopentane hydrochloride (m.p. 45-60°) and 35 g. (0.2 mole) of 8-amino-6-methoxyquinoline in 200-ml. of purified dioxane was boiled under reflux for seventy-two hours. The mixture was entirely in solution when boiling commenced. Some brown solid appeared in twelve hours, and the quantity of the solid increased during the remainder of the time. The mixture was poured into 500-ml. of water; the solution was made basic by the addition of excess sodium hydroxide solution and extracted with four 500-ml. portions of ether. The extracts were dried over anhydrous calcium sulfate. A few grams of cream-colored crystals formed in the dried ether extracts. The mixture was filtered and the filtrate was distilled to yield 30 g. (75% recovery) of nucleus which boiled at 110-20°/3 microns. No SN-13,276 was obtained.

In buffered cellosolve-water. A mixture of 40 g. (0.2 mole) of 1-chloro-5-iso-propylaminopentane hydrochloride



(m.p. 45-60°), 70 g. (0.4 mole) of 8-amino-6-methoxyquinoline (m.p. 49-50°) and 50 g. (0.4 mole) of sodium acetate trihydrate in 100-ml. of fifty percent cellosolve-water was boiled under reflux for sixty-five hours. The mixture was in solution during the entire time. It was poured into 600-ml. of water; and oil layer settled below the water. The mixture (pH 4.7) was extracted with three 300-ml. portions of ether. The extracts were dried and distilled to yield 60 g. (86% recovery) of nucleus which boiled at 130-40°/1mm. The aqueous portion was made basic and extracted with ether. The ether distilled from the dried extracts and left no appreciable residue.

In water. A 250-ml. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a thermometer, which extended into the reaction mixture, was charged with 70 g. (0.4 mole) of 8-amino-6-methoxyquinoline, 40.0 g. (0.2 mole) of 1-chloro-5-isopropylaminopentane hydrochloride (m. p. 45-60°) and 50-ml. of water. The mixture was stirred and heated:

5 hours at 50° (inside t.)

1 hour at 60° "

1 hour at 70° "

6 hours at 103° "

and poured into 500-ml. of hot water. The solution was made acid to Congo Red indicator by the addition of concentrated hydrochloric acid and cooled to 10°, whereupon 8-amino-6-methoxyquinoline hydrochloride precipitated. The mixture was centrifuged; the solid was washed with 50-ml. of cold water,

and dissolved in 100-ml. of hot water. Excess sodium hydroxide solution was added; the strongly alkaline mixture was cooled and extracted with ether.

The decanted aqueous portion and the washing from the nucleus hydrochloride were made basic to Congo Red indicator by the addition of solid sodium acetate trihydrate; an additional 80 g. of sodium acetate trihydrate was added and dissolved with stirring. The buffered mixture separated into two layers, a light-colored upper aqueous layer, and a dark oily lower layer. The mixture was extracted with one 500-ml. portion of ether to remove the remainder of the unreacted nucleus. This extract was combined with the before mentioned extracts containing nucleus; the mixture was dried and distilled to recover 35 g. of nucleus which boiled at 110-130°/0.5 mm.

The aqueous portion which still contained a large oily layer, was made strongly basic by the addition of sodium hydroxide solution and the alkaline mixture was extracted with four 250-ml. portions of ether.<sup>10</sup> The extracts were dried over anhydrous potassium carbonate, the mixture was filtered and the

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10. A black emulsion formed between the ether and water layers. This was removed during the first extraction and filtered by suction. A thin layer of black tar remained on the filter paper. The filtrate was added to the aqueous portion for subsequent extractions. The tar was soluble in chloroform. When the previous extractions were made with chloroform, this tar was taken up. It was believed that the tar was the material that decomposed when SN-13,278, extracted with chloroform, was distilled. When SN-13,278 was extracted with ether, and the tar was removed, the SN-13,278 distilled without any evidence of decomposition, leaving no appreciable residue.

ether was distilled from the filtrate. The residue was distilled in an atmosphere of nitrogen from a 100-ml. von Braun flask under reduced pressure, first under the vacuum of a good water pump to remove excess solvents and then under the vacuum of a "Wycac" oil pump. There was obtained first about 2 g. of 1-hydroxy-5-iso-propylaminopentane boiling at 90-110°/1 mm. followed by 34 g. of SN-13,276, boiling at 180-90°/0.5 mm. The SN-13,276 was redistilled from a 100-ml. von Braun flask and yielded 30 g. of product (50% based on the side chain) which boiled at 158-62°/2 microns (bath at 210°).

The SN-13,276 was converted to 37 g. of SN-13,276-5. This product melted at 187-8°; after it had been recrystallized from methanol, it weighed 31 g. and melted at 188.5-189.5°. Analysis, calculated for  $C_{18}H_{27}N_3O \cdot H_3PO_4$ : C, 54.13; H, 7.59. Found: C, 53.84, 54.05; H, 7.58, 7.58. The 31 g. of SN-13,276-5 represents a yield of 78% from SN-13,276, and 39% from side chain.

In a similar experiment, in which 400 g. (2.0 moles) of 1-chloro-5-iso-propylaminopentane hydrochloride and 700 g. (4.0 moles) of 8-amino-6-methoxyquinoline were used, the yield of once-distilled SN-13,276 was 59%. This was converted into SN,13-276-5, which after two recrystallizations from methanol, melted at 188.8-189.5°, and represented a yield of 63% based on SN-13,276, and 37% based on side chain. Analysis: C = 54.36, 54.34; H, 7.59, 7.72. The inhomogeneity of this sample as estimated by the counter-current extraction process (3) was  $2 \pm 2\%$ .<sup>11</sup>

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11. We wish to express our thanks to Dr. R. C. Elderfield for his kindness in having this analyses carried out for us.

CONDENSATIONS OF PURIFIED 1-CHLORO-5-iso-PROPYLAMINOPENTANE  
HYDROCHLORIDE WITH 8-AMINO-8-METHOXYQUINOLINE IN AQUEOUS MEDIA

In all of the following condensations, purified materials were used. The 1-chloro-5-iso-propylaminopentane hydrochloride melted at 120-30°. The 8-amino-8-methoxyquinoline melted at 49.5-50°. The condensation technique employed in all was the same. The ratio of side-chain to nucleus to water, with one exception was constant. An example of one condensation will suffice for them all.

A 250-ml. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a thermometer, which extended into the reaction mixture, was charged with 69.6 g. (0.40 mole) of 8-amino-8-methoxyquinoline 40.0 g. (0.20 mole) of 1-chloro-5-iso-propylaminopentane hydrochloride and 50-ml. of water. The mixture was stirred and heated at the specified temperatures for the specified lengths of time.

The methods of processing the condensation products varied. Examples, arranged in order of increasing efficiency, are given for each method as continuations of the above condensation.

Method A. The condensation melt was poured into 450-ml. of hot water, the flask was rinsed with 50-ml. of hot water and the rinsings were added to the main portion. The solution was made acid to Congo Red indicator by the addition of concentrated hydrochloric acid, and cooled to 10°, whereupon the hydrochloride was removed by filtration (or centrifugation) and washed with 50 ml. of ice-cold water. The nucleus hydrochloride, dissolved

in hot water, was made basic by the addition of excess sodium hydroxide solution; the nucleus was extracted from the alkaline mixture with three 200-ml. portions of ether.

The combined filtrate and washing from the nucleus hydrochloride was made basic to Congo Red indicator by the addition of sodium acetate trihydrate; an additional 89 g. of sodium acetate trihydrate was added and dissolved by stirring. The buffered mixture separated into two layers, an upper light-colored aqueous layer, and a lower dark organic layer. The mixture was extracted with three 200-ml. portions of ether to remove the remaining unreacted 8-amino-6-methoxyquinoline. Some solid usually precipitated during the extraction; it was then necessary to filter the mixture to permit a clean cut separation of the ether and aqueous layers. The ether extracts, combined with the previously obtained ether extracts containing nucleus were dried and distilled to recover the unreacted 8-amino-6 methoxyquinoline.

The solid (if it had formed) was added to the buffered aqueous portion. The mixture was heated to effect solution, and made basic by the addition of excess sodium hydroxide solution. The alkaline mixture was warmed to effect a complete conversion of unreacted 1-chloro-5-iso-propylaminopentane to N-iso-propylpiperidine, and extracted with four 400-ml. portions of ether. The tar was removed as mentioned previously. The ether extracts were washed with two 50-ml. portions of water, dried over anhydrous calcium sulfate, and filtered; the ether was distilled from the filtrate. The residue was distilled

under an atmosphere of nitrogen, in a 100-ml. von Braun flask at reduced pressure, first under the vacuum of a good water pump, then at 0.5-1.0 mm. pressure. There was obtained first, crude N-iso-propylpiperidine, boiling below 40° at about 20 mm. pressure, then a trace of 1-hydroxy-5-iso-propylaminopentane boiling somewhere between 80-100° at 0.5-1.0 mm., and finally SN-18,276 distilled without appreciable decomposition, as a pale yellow oil. There was no appreciable residue.

Method B. This is a variation of method A whereby the hydrochloride of 8-amino-6-methoxyquinoline was not filtered but was converted to 8-amino-6-methoxyquinoline which was extracted.

The melt was poured into 450-ml. of hot water; the flask was rinsed with 50 ml. of hot water and the rinsings were added to the main portion. The mixture was acidified with 35 ml. of concentrated hydrochloric acid, buffered until basic to Congo Red indicator by the addition of sodium acetate trihydrate, whereupon an additional 30 g. of sodium acetate trihydrate was added and dissolved by stirring. The buffered mixture was extracted with five 200-ml. portions of ether to remove the unreacted 8-amino-6-methoxyquinoline. The extracts were dried and distilled to recover the unreacted nucleus. The buffered aqueous portion was treated in the same manner as in method A.

Method C. This was a variation of method B whereby the unreacted 8-amino-6-methoxyquinoline was extracted from the buffered aqueous condensation products with benzene in place of ether. In this method the extraction was carried out at a higher temperature thus preventing the troublesome precipitation of solid during the extraction. In all other respects method C was identical with method B.

The purity of the 8-amino-6-methoxyquinoline recovered and the SN-13,276 obtained was estimated by the refractive index. By assuming the nucleus and SN-13,276 were the only components present, the composition of any fraction of known refractive index could be obtained from figure I.

The experimental detail of the condensations of 1-chloro-5-iso-propylaminopentane hydrochloride (m. p. 120-125°) with 8-amino-6-methoxyquinoline (m. p. 49.5-50.0°) is summarized in table IX.

The crude N-iso-propylpiperidine from the 60, 70, 80 and 90° condensations was redistilled. The boiling points, in that order, were 149-9.5°, 147.5-9°, 148-9°, 149-50°. They had  $n_D^{25}$  1.4447, 1.4454, 1.4451, 1.4447.

TABLE IX

CONDENSATIONS OF PURIFIED 1-CHLORO-5-iso-PROPYLAMINOPENTANE HYDROCHLORIDE  
WITH 8-AMINO-6-METHOXYQUINOLINE IN AQUEOUS MEDIA; TIME,  
TEMPERATURE AND CONCENTRATION VARIATIONS

Cond. No.	Time Hrs.	Temp °C	Method of Processing	% SW-13,276 from: side chain	% Nuc <sup>(a)</sup> 13,276 leus	n <sub>D</sub> <sup>25</sup> SW-13,276	% Rec'd Nucleus <sup>(b)</sup>	n <sub>D</sub> <sup>25</sup> Nuc-leus	% Crude N- <u>iso</u> -propyl-piperidine
XII	5	50	A	67					
	2	50-103							
	6	103							
XIII	6	103	A	63	60	1.5792	79	1.6672	
XIV	10	103	A	67	65	1.5790	79	1.6680	
XV	12	60	B	19	44	1.5842	87	1.6675	50
XVI	12	70	B	35	46	1.5840	75	1.6692	29
XVII	12	80	B	50	70	1.5830	86	1.6670	20
XVIII	12	90	B	65	76	1.5792	85	1.6690	10
XIX	18	80	C	70	79	1.5800	86	1.6690	14
XX	24	80	C	78	78	1.5798	82	1.6685	8
XXI	30	80	C	78	81	1.5792	85	1.6715	8
XXII	20	80	C	81	80	1.5785	83	1.6684	3
	4	103							
XXIII <sup>(c)</sup>	24	80	C	47	71	1.5786	65	1.6645	40

(a) Percent SW-13,276 from nucleus is based on the amount of 8-amino-6-methoxyquinoline that was not recovered.

(b) Percent recovered nucleus is based on the amount of 8-amino-6-methoxyquinoline that was not transformed into the SW-13,276 obtained.

(c) This condensation employed 0.2 mole of side chain and 0.2 mole of nucleus.



## ATTEMPTED PREPARATION OF 8-(5--HYDROXYAMYLAMINO)

## -6-METHOXYQUINOLINE

Trial 1. A suspension of 0.2 g. of platinum oxide<sup>12</sup> in 20-ml. of anhydrous ethanol was reduced by hydrogen in a low-pressure hydrogenation apparatus (1). A solution of 35 g. (0.2 mole) of 8-amino-6-methoxyquinoline and 20 g. (0.2 mole) of 5-hydroxypentanal<sup>13</sup> in 50 ml. of anhydrous ethanol was added and rinsed in with 20-ml. of anhydrous ethanol. The mixture was shaken under two to three atmospheres pressure of hydrogen until the uptake of hydrogen ceased. In twenty-four hours, 0.19 mole of hydrogen was absorbed.

The catalyst was removed from the mixture by filtration and the liquids were distilled under reduced pressure. After removal of the ethanol, there was obtained 24 g. of liquid which boiled at 80-100°/1 mm. and 29 g (83% recovery) of 8-amino-6-methoxyquinoline, which boiled at 110-20°/1 mm.

The fraction which boiled at 80-100° was carefully fractionated under reduced pressure through a one-foot modified Claised column to yield 14 g. of liquid which boiled at 95-7°/1 mm. It had  $n_D^{20}$  1.4506. 1, 5-dihydroxypentane has  $n_D^{20}$  1.4499.

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<sup>12</sup> The platinum oxide was purchased from the American Platinum Works.

<sup>13</sup> We are indebted to Dr. G. F. Woods for this sample of 5-hydroxypentanal. It had  $n_D^{25}$  1.4515, and boiled at 64-6°/6-7mm. See (19).

Trial 2. A mixture of 20.4 g. (0.1 mole) of 8-amino-6-methoxyquinoline and 30 g. (0.3 mole) of 5-hydroxypentanal<sup>14</sup> in 150-ml. of anhydrous ethanol and 2 g. of sodium acetate was added and the mixture was shaken under two to three atmospheres of hydrogen. In forty-four hours, only 0.026 moles of hydrogen was absorbed, so the reduction was abandoned.

Trial 3. A mixture of 20.4 g. (0.1 mole) of 6-methoxy-8-nitroquinoline, 30 g. (0.3 mole) of 5-hydroxypentanal,<sup>15</sup> 2 g. of sodium acetate trihydrate and 4 g. of Raney nickel (11) in 150 ml. of anhydrous ethanol was shaken under two to three atmospheres of hydrogen. The mixture became warm when reduction commenced; in fifty minutes, 0.33 mole of hydrogen was absorbed. The rate of reduction then decreased considerably, and in the next twenty hours, only 0.1 mole of hydrogen was absorbed.

The catalyst was filtered and washed with 10-ml. of ethanol. The combined filtrate and washing were heated to boiling and 8.4-ml. (0.1 mole) of concentrated hydrochloric acid was added. The mixture was cooled in a refrigerator overnight. The orange crystals that had formed were removed by filtration, washed with 10-ml. of cold ethanol and dried

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<sup>14</sup> We are indebted to Dr. G. F. Woods for this sample of 5-hydroxypentanal. It had  $n_D^{25}$  1.4515 and boiled at 64.6°/6-7 mm. See (19)

<sup>15</sup> 6-methoxy-8-nitroquinoline was purchased from the Winthrop Chemical Co. After recrystallization from ethanol, it melted at 160-160.5°.

to constant weight in a vacuum oven at 40°. They weighed 5.7 g. and melted at 220-4°d.; 8-amino-6-methoxyquinoline monohydrochloride melts at 225-8°d. A mixture of the product with 8-amino-6-methoxyquinoline monohydrochloride melted at 223-5°d.

The filtrate from the 8-amino-6-methoxyquinoline monohydrochloride was boiled under reflux, 1.2-l. of acetone was added so that the mixture was just turbid at reflux temperature; the turbid mixture was cooled in a refrigerator overnight. The red-brown crystals that had formed were removed by filtration, washed with acetone, and dried to constant weight in a vacuum oven at 40°. They weighed 6.2 g. and melted at 187-90°. They were dissolved in 100-ml. of ethanol; the solution was filtered hot. The filtrate was cooled to yield 4.3 g. of red-brown crystals which melted at 190-1°. An additional recrystallization from ethanol did not change the melting point. Analysis: C, 62.93, 62.97; H, 6.89, 6.85; neutral equivalent, 394, 395. 8-(5-Hydroxyamylamino)-6-methoxyquinoline hydrochloride requires for  $C_{13}H_{21}N_2O_2Cl$ : C, 60.7; H, 7.15; neutral equivalent, 297.

## SALTS OF SN-13,276

The mono and di hydrochloride and hydrobromide, the sulfate, disulfate, oxalate, and di primary phosphate salts of SN-13,276 were prepared in the following manner:

To a solution of 9 g (0.03 mole) of SN-13,276 ( $n_D^{25}$  1.5787) in 20-ml. of ethanol was added the required amount of acid, whereupon the solution became warm. On cooling the solution, crystals formed (in some cases, scratching the inside of the container with a glass rod was required to induce crystallization) and crystallization was promoted by cooling the mixture in a refrigerator overnight. The salt that had crystallized was removed by filtration by suction, washed with ether, and dried to constant weight in a vacuum oven at 40°.

Attempts were made to prepare the mono and di acetate and lactate by the same method. The salts did not crystallize from solution even on prolonged cooling.

The monohydriodide of SN-13,276 was prepared in the following manner:

To a solution of 5.07 g. (0.015 mole) of the monohydrochloride of SN-13,276 (m. p. 152-3°) in 15-ml. of water was added 2.49 g (0.015 mole) of analytical grade potassium iodide in 5-ml. of water. The resulting mixture, which partially crystallized, was heated at 80°, and ninety-five percent ethanol was added until a complete solution was effected. The solution was cooled until crystallization commenced;

crystallization was promoted by cooling the mixture in a refrigerator overnight. The resulting solid was removed by filtration by suction, and dried to constant weight in a vacuum oven at 50°.

The preparation of these salts is listed in table X.

The mono and di hydrochloride and hydrobromide, oxalate and mono hydriodide salts were recrystallized from ethanol. The melting points were not improved appreciably. The recrystallization of the salts is tabulated in table XI. Their analyses are listed in table XII.

From the amount of salt not recovered in the recrystallization with ethanol, i.e., that remaining in the ethanol, the solubility of the salt in ethanol was calculated.

To be assured that a saturated solution was obtained when determining the solubility of the salts in water, a slight excess of the salt was dissolved in water at 30°. The solution was seeded and allowed to remain at 25° overnight. In each case, a trace of solid had crystallized.

The pH of the solutions was determined with a Beckman pH meter, laboratory model G, with a glass electrode and a saturated calomel electrode.

The solubilities and pH of aqueous solutions are listed in table XIII.

TABLE X

## PREPARATION OF SOME SALTS OF SN-13,276

Quality	Acid added		Name of Salt	Color	Yield		V. P. °C
	Quantity g.	Quantity eq.			g.	%	
20.2% HCl	5.42	0.03	Monohydrochloride	tan	9.5	84	151-2
"	10.8	0.06	Dihydrochloride	orange	10.0	90	212-9 d (sinter 216)
46.8% HBr	5.20	0.03	Monohydrobromide	tan	10.8	95	106-8
"	10.4	0.06	Dihydrobromide	orange	13.5	97	226-8 d
96% H <sub>2</sub> SO <sub>4</sub>	1.53	0.03	Sulfate	brown	9.0	86	105-15
"	3.06	0.06	Disulfate	red-brown (oil)	10.7	89	oil
anhyd. oxalic	1.35	0.03	Oxalate	yellow	7.6	74	162-4
"	2.70	0.06	Dioxalate	yellow	10.4	93	140-60
85% H <sub>3</sub> PO <sub>4</sub>	6.90	0.06 (mole)	Diphosphate	orange	12.0	80	125-200
KI HCl	--		monohydriodide	grey-white		99	167-8.5

TABLE XI

RECRYSTALLIZATION OF SOME SALTS OF SN-13,276

Salt	Solvent	% Recovery	M. P. °C
Monohydrochloride	95% ethanol	87	152-3
Dihydrochloride	"	88	218-9 d minter 216
Monohydrobromide	"	89	166-7
Dihydrobromide	"	87	225-7 d
Oxalate	"	79	161-3
Monohydriodide	85% ethanol	75	167-8

TABLE XII

## ANALYSIS OF SOME SALTS OF SN-13,276

Salt	Calc'd for	Theory		Found	
		C	H	C	H
1-HCl	$C_{18}H_{27}N_3O \cdot HCl$	63.98	8.55	64.17 64.44	8.52 8.25
2-HCl	$C_{18}H_{27}N_3O \cdot 2HCl$	57.75	7.80	57.73 57.94	7.75 7.74
1-HBr	$C_{18}H_{27}N_3O \cdot HBr$	56.55	7.36	56.49 56.57	7.46 7.66
2-HBr	$C_{18}H_{27}N_3O \cdot 2HBr$	46.67	6.31	47.13 46.85	6.58 6.40
Oxalate	$C_{18}H_{27}N_3O \cdot CHO_2$ ( $H_2O$ )	62.62	8.29	62.54 62.37	8.54 8.37
1-HI	$C_{18}H_{27}N_3O \cdot HI$	50.76	6.57	50.96 50.95	6.47 6.74



TABLE XIII

pH and SOLUBILITIES OF SOME SALTS OF SN-13,276

Salt	Solubility in 95% ethanol at 5°	Solubility in water	pH of aqueous soln. at 20°
1-HCl	0.026 g./ml.	0.012 g./ml. at 10°	6.95 (sat. soln. at 10°)
2-HCl	0.017 "	0.50 "	2.00 (3 g./25 ml.)
1-HBr	0.020 "	0.0085 g./ml. at 25°	6.40 (sat. soln. at 20°)
2-HBr	0.025 "	0.10 "	1.20 "
Oxalate	0.045 "	0.0045 "	6.30 "
1-HI	0.055 " (25% ethanol)	0.0055 "	6.45 "
1-H <sub>2</sub> PO <sub>4</sub>	0.0025 g./ml.	0.067 "	5.10 "

## SALTS OF SN-13,276 FROM UNDISTILLED SN-13,276

A number of methods were tried in an attempt to prepare a pure salt of SN-13,276 without previously distilling the free base. The operations of each through the condensation and extraction of excess nucleus were the same in each case, and one example will suffice for them all.

A melt of 0.2 mole of 1-chloro-5-iso-propylaminopentane hydrochloride (m. p. 120-3°) and 0.4 mole of 8-amino-6-methoxyquinoline (m. p. 42.5-50.0°) in 50-ml. of water was stirred and heated at 80° (inside t.) for twenty hours and at 103° (inside t.) for four hours. The condensation products were poured into 200-ml. of water; the pH of the resulting solution was 3.9. Enough concentrated sodium hydroxide solution was added to the mixture to bring its pH to 4.5 and then sodium acetate trihydrate was added until the pH was 5.0.

The mixture, which then contained a considerable amount of dark-brown oil, was heated to 65° and extracted at that temperature with four 200-ml. portions of benzene to remove the excess nucleus. The benzene extracts were washed with one 20-ml. portion of hot water and the aqueous layer was added to the extracted aqueous solution. The benzene extracts were dried over anhydrous magnesium sulfate and then distilled from a von Braun flask with wide tubes. After the benzene was removed, 8-amino-6-methoxyquinoline distilled at 130-40°/0.5 mm. The recovered nucleus weighed 35 g.

The combined aqueous portions were processed in a variety of ways. Each will be described as a continuation of the above condensation.

Method 1. Preparation of SN-13,276-5 from SN-13,276 obtained by extraction only. The aqueous portion was made basic by the addition of 40 g. of fifty percent sodium hydroxide solution and extracted with four 200-ml. portions of ether. There was a small amount of black emulsion between the layers when this extraction was carried out. The emulsion layer was removed during the first extraction and filtered by suction; the filtrate was added to the water layer for further extraction. A very thin layer of black tar remained on the filter paper.

The combined ether extracts were washed with three 50-ml. portions of water and dried over anhydrous magnesium sulfate. The ether was removed from the filtered anhydrous solution by distillation on a steam bath. The residue was transferred to a 125-ml. Erlenmeyer flask, washed in with a small amount of ethanol, and cooled. It weighed 67.4 g. An aliquot (ca 0.5 g.) was dissolved in an excess of standard N/10 hydrochloric acid and back-titrated with standard alkali. The sharpest break in the ml. alkali vs. pH curve (Fig. 2) occurred at about pH 6.8. From this titration the amount of base in the residue was calculated to be 0.176 moles.

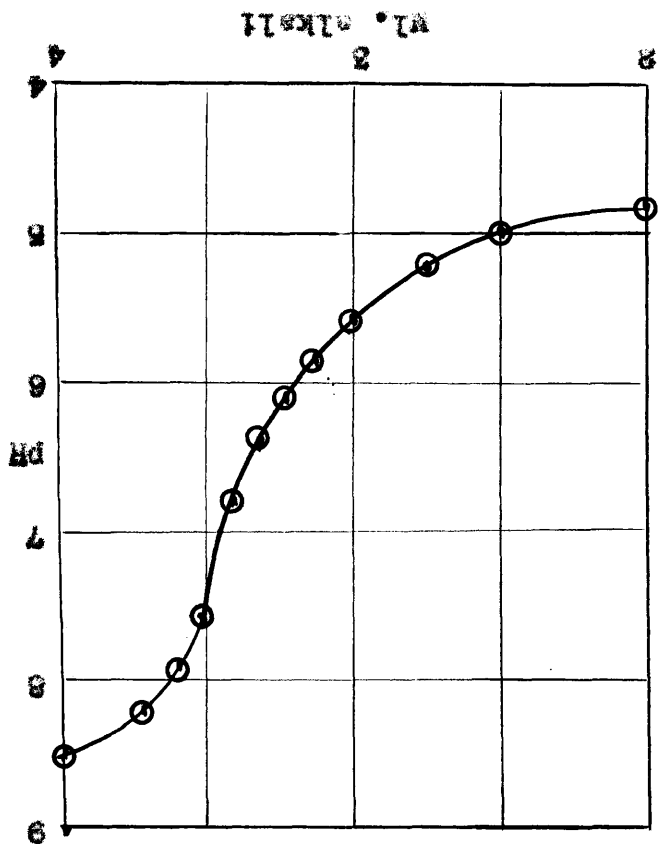


FIGURE 2  
 TITRATION OF AN ACID SOLUTION OF 3N-12, 276  
 WITH STANDARD ALKALI

The base was then dissolved in 550-ml. of ninety-five percent ethanol in a flask provided with a stirrer, a reflux condenser, and a funnel for addition of acid. The mixture was stirred and boiled under reflux, while a solution of 17.0 g. (0.176 mole) of eighty-five percent phosphoric acid in 30 ml. of ninety-five percent ethanol was added over a period of about five minutes. Yellow crystals of the mono-phosphate soon appeared; the mixture was heated under reflux for fifteen minutes and allowed to cool with stirring for an hour. It was finally cooled with stirring in an ice-bath for two hours and then filtered. The yellow crystals were washed with 50-ml. of ice-cold ninety-five percent ethanol and dried to constant weight in a vacuum oven at 50°. They weighed 57 g. and melted at 186.5-188°. Analysis, calculated for  $C_{18}H_{27}N_3O \cdot H_2PO_4$ : C, 54.13; H, 7.58. Found: C, 53.89, 53.82; H, 7.74, 7.93. The yield was 71% based on either side chain or nucleus.

Method 2. Preparation of the monohydrochloride of SW-13,276 and its purification. The combined aqueous portions were allowed to cool. The monohydrochloride of SW-13,276 started to crystallize at 50°, and the crystallization was completed on cooling the mixture in a refrigerator overnight. The light-grey solid was removed by filtration by suction and pressed dry on the funnel. After drying in a vacuum oven at 40° for twenty hours, the solid weighed 57 g. and melted at 141-5°, with previous sintering at 100°. It probably still contained some moisture. Pure hydrochloride of SW-13,276 melts at 152-30.

The black filtrate (pH 4.75) was made strongly basic and extracted with three 100-ml. portions of ether; the extracts were dried over anhydrous magnesium sulfate. The ether was distilled from the filtered, dry extracts and the residue was distilled in an atmosphere of nitrogen from a 100-ml. von Braun flask under reduced pressure. There was obtained 0.5 g. of N-iso-propylpiperidine which boiled below 40°/20 mm., less than 0.5 g. of 1-hydroxy-5-iso-propylaminopentane which boiled at 80-90°/0.5 mm. and 4.4 g. of SN-13,276 which boiled at 170-90°/0.5 mm. The SN-13,276 and  $n_D^{25}$  1.5790.

The following attempts were made to purify the monohydrochloride salt:

A. Ten grams of the salt, dissolved in 50-ml. of boiling absolute ethanol, was filtered to remove a small amount of suspended inorganic material and cooled in an ice bath. The grey-white crystalline solid that had formed was filtered, washed with anhydrous ether, and dried to constant weight in a vacuum oven at 40°. It weighed 7.0 g. and melted at 150-1°.

B. Ten grams of the salt, dissolved in 50-ml. of boiling methanol was cooled to 30°, and diluted with 20-ml. of anhydrous ether; the resulting turbid mixture was filtered. The filtrate was diluted with 100-ml. of anhydrous ether and the mixture was cooled in a refrigerator overnight. The resulting solid, when dry, melted at 151-2° and weighed 6.7 g.

C. Ten grams of the salt dissolved in 40-ml. of water at 60° was cooled in an ice bath. The grey-white solid that

had formed, was filtered and dried in a vacuum oven at 45° for sixty hours. It weighed 8.4 g. and melted at 149-50.5°.

Method 3. Preparation of SN-13,276-5 from the filtered monohydrochloride of SN-13,276. The combined aqueous portions were allowed to cool. The monohydrochloride of SN-13,276 started to crystallize at 50°, and the crystallization was completed on cooling the mixture in a refrigerator overnight. The light-grey solid was removed by filtration by suction, pressed dry on the funnel, and dissolved in 800-ml. of water at 50°. A solution of 20 g. of sodium hydroxide in 20-ml. of water was added; the strongly alkaline mixture was treated in the manner outlined in method 1. SN-13,276 was obtained in 70% yield (based on either side chain or nucleus) as a pale yellow finely crystalline solid which melted at 189.5-9.5°.

Method 4. Preparation of SN-13,276-5 from the filtered monohydroiodide of SN-13,276. The combined aqueous portions were heated to 85°, and a solution of 0.2 mole of potassium iodide in 20-ml. of water was added. A large amount of dark-brown, semi-solid material settled out of solution, leaving a clear orange upper aqueous layer. The mixture was boiled under reflux, whereupon 100-ml. of ethanol was added to effect solution. The mixture was cooled in a refrigerator overnight. The monohydroiodide came out of solution as an oil, which crystallized on cooling. The resulting tan solid was removed by filtration by suction, pressed dry on the funnel, and

dissolved in 1-1. of water at 80°. A solution of 10 g. of sodium hydroxide in 20-ml. of water was added; the cooled, strongly alkaline mixture was treated in the manner outlined in method 1. SN-13,276 was obtained in 71% yield (based on either side chain or nucleus) as a yellow, finely crystalline solid which melted at 188-9°.

Two identical check runs, employed 0.4 mole of 1-chloro-5-iso-propylaminopentane hydrochloride (m. p. 120-3°) and 0.3 mole of 8-amino-6-methoxyquinoline (m.p. 49.5-50.0°) were made according to the procedure outlined in method 3. SN-13,276-5 was obtained from each, as a pale-yellow-finely crystalline solid which melted at 189-90°. The yields, based on either side chain or nucleus were 69 and 71% respectively.



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## ABSTRACT

John O'Neill Van Hook, Doctor of Philosophy 1946. W. S.  
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Title of thesis: A study of the preparation and properties  
of 8-(5-iso-propylaminoamylamino)-6-methoxyquinoline and some  
of its salts.

Thesis directed by Professor Nathan L. Drake

Major: Organic Chemistry, Department of Chemistry

Minors: Physical and Inorganic Chemistry

Pages in thesis, 74. Words in abstract, 411.

8-(5-iso-propylaminoamylamino)-6-methoxyquinoline (SM-  
13,876) has been prepared by the alkylation of 8-amino-6-  
methoxyquinoline (nucleus) with 1-bromo-5-iso-propylamino-  
pentane hydrobromide and with 1-chloro-5-iso-propylamino-  
pentane hydrochloride (side chain).

1-Bromo-5-iso-propylaminopentane hydrobromide was pre-  
pared by two methods. The first proceeded through the inter-  
mediate 1-bromo-5-methoxypentane, which was converted by either  
the Gabriel or Sodamide synthesis to 1-amino-5-methoxypentane.  
This compound was reductively alkylated with acetone to give  
1-methoxy-5-iso-propylaminopentane, which reacted with hydro-  
bromic acid to give the desired compound.

According to the second method, iso-propylamine was re-  
ductively alkylated with 5-hydroxypentanal to give 1-hydroxy-  
5-iso-propylaminopentane which was converted to the desired  
compound by the action of thionyl bromide or hydrobromic acid.

1-Chloro-5-iso-propylaminopentane hydrochloride was prepared by reaction between 1-hydroxy-5-iso-propylaminopentane hydrochloride and thionyl chloride. The best medium employed for this reaction was petroleum ether (90-100°).

1-Bromo-5-iso-propylaminopentane hydrobromide was condensed with 8-amino-6-methoxyquinoline in boiling ethanol to yield a quantity of SN-13276 corresponding to 30-40% of the calculated amount.

1-Chloro-5-iso-propylaminopentane hydrochloride was condensed with 8-amino-6-methoxyquinoline in a variety of media, the most effective of which was water. A study of time, temperature and concentration variations showed that the optimum conditions were as follows:

A melt of 1 mole of 1-chloro-5-iso-propylaminopentane hydrochloride and 2 moles of 8-amino-6-methoxyquinoline in a small amount of water was heated at 80° for twenty hours, and then at 103° for four hours.

The condensation products were best processed in the following manner:

The melt was poured into a small amount of water and the solution was buffered at pH 5; the buffered mixture was heated to 80° and extracted at that temperature with benzene to remove excess nucleus. The aqueous portion was treated in either of two ways:

1. The solution was made basic and the liberated SN-13276 was extracted and distilled. It was obtained in 80%

yield (based on either side chain or nucleus) as a pale-yellow viscous oil, boiling somewhere between 160-90°/5 microns-1 mm., having, if pure,  $n_D^{25}$  1.5795. A solution of this in ethanol, when treated with the required amount of phosphoric acid, yielded the monophosphate of SN-13,276 (m.p. 189-90°); the yield was 90% of the calculated amount.

E. The solution was cooled, whereupon the monohydrochloride of SN-13,276 precipitated. This solid was removed by filtration and dissolved in water. The solution was made basic, and the liberated SN-13,276 was extracted with ether. The residue, remaining after distillation of the ether, was dissolved in ethanol. This solution, when treated with the required amount of phosphoric acid yielded the monophosphate of SN-13,276; the yield was 70%, based on either the side chain or nucleus.

Of the salts of SN-13,276 that were prepared, the mono and di hydrochloride and hydrobromide and mono phosphate and hydriodide were the only ones that were obtained in good yields.

APPROVAL SHEET

John O'Neill Van Hook, Doctor of Philosophy 1948

Title of thesis: A study of the preparation and properties of 8-(5-iso-propylaminoamylamino)-6-methoxyquinoline and some of its salts.

Thesis and abstract approved: \_\_\_\_\_  
Professor in charge of thesis

Date