I. THE ATTEMPTED FORMATION OF 8-ALKYL CAFFEINES BY THE PYROLYSIS OF CAFFEINE ETHERS WITH ALKYL ETHERS

II. THE PREPARATION AND MOLECULAR REARRANGEMENT OF TWO ETHERS OF CAFFEINE

Thesis for the Degree of M. S.

Kenneth D. Bacon

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Submitted as Part of the Requirements
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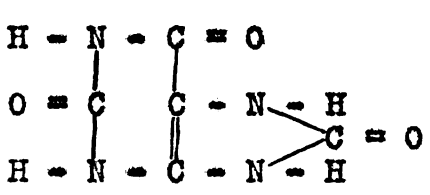
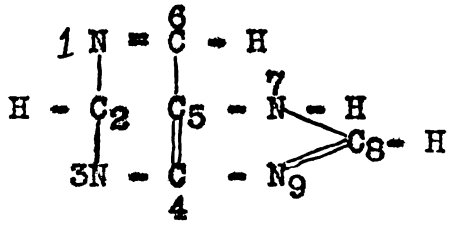
CONTENTS

INTRODUCTION

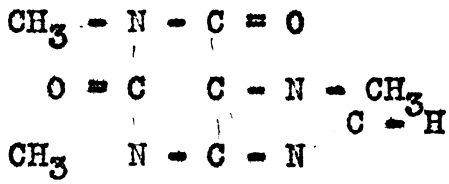
It was Emil Fischer and his associates that carried out the first extensive work on compounds containing the purine nucleus. His investigations led to the final decision regarding the structure of uric acid, both by its synthesis and by its reactions. He synthesized all of the mono, di, and trimethyl derivatives of uric acid that are possible by the theory of structure expressed by the formula suggested by Medicus in 1875, and proven by Fischer himself later. Finally he converted uric acid into purine, which contains the nucleus common to caffeine and related compounds.



Uric Acid



Purine



Caffeine

Caffeine is of interest to study, because of its occurence in the two most common beverages, tea and coffee, and its physiological effect when taken internally. It has a pronounced effect on the nervous system, it stimulates the heart action and it is a strong diuretic. It is possible, by comparing the physiological action of theobromine, theophylline and caffaine, to show that their different effects on

the system are due to introduction of alkyl groups, in this case methyl, into the purine nucleus.

It is not caffeine itself that interests us in this work, but rather certain derivatives of caffeine, particularly the 8-ethers of caffeine. The purpose of this thesis will be to accomplish the following aims:

1. The attempted formation of 8-alkyl caffeines by a process reported by Winston F. Allen from this laboratory.

2. The preparation and properties of certain new caffeine ethers.

3. The attempted molecular rearrangement of those prepared ethers.

HISTORICAL

A. Early work on caffeine-ethers.

In the course of Fischer's extensive, experimental work on compounds of the purine type, he prepared only two of the 8-ethers of caffeine, 8-methoxy, and 8-ethoxy-caffeine.[1] Fischer prepared these ethers by heating 8-chloro, or 8-bromo-caffeine in a methyl or ethyl alcohol solution containing an excess of sodium or potassium alcoholate. The alcoholate was made by adding either the metal or the hydroxide to the alcohol. Later W. Wislicenus[2], and H. Biltz[3] repeated this work.

A. Baumann[4] went farther than this in preparing fifteen 8-substituted-phenyl ethers of caffeine. His method consisted in heating 8-chlorocaffeine with a substituted phenol in the presence of an equivalant amount of potassium hydroxide. He was able to carry out the reaction in aqueous solution with refluxing and under pressure at high temperatures. In some cases he found that xylene was more satisfactory as a solvent, in place of the water.

B. The work of Huston and Allen[5].

1. General methods of preparation of the 8-ethers of caffeine.

In 1932 the work on the preparation of sixteen 8-ethers of caffeine was completed in this laboratory. Many of these ethers were new compounds. The use of both 8-chloro

and 8-bromo-caffeine was employed, with 8-chloro-caffeine being preferred in most cases due to its ease and economy of preparation.

Clean metallic sodium was cut into small pieces and added to enough absolute alcohol to permit the resulting alcoholate to readily dissolve. The proportion was generally about 1 gram of sodium to 6 mls. of the alcohol. When the sodium had entirely disappeared an equivalent amount of the 8-chloro-caffeine was added and shaken well. This mixture was refluxed on a steam or oil bath for one-half to five hours, depending upon the speed of the reaction. The sodium chloride was removed from the hot solution by immediate filtration. Some of the lower alkyl caffeine ethers crystallized out of the alcohol solution very satisfactorily when cooled. However, some of the higher ethers would not give good crystallization unless the solution was concentrated to a smaller volume. This was done by vacuum distillation, in order to keep the temperature at a minimum. In some cases it was necessary to add an equal volume of water to the concentrated solution to obtain complete crystallization. Recrystallization was best carried out from 40 to 50 per cent ethyl alcohol. Each ether seemed to offer its own particular problem where the higher alkyl groups were concerned. Those ethers which Allen prepared will be taken up in detail later.

2. Reactions of the 8-ethers of caffeine.

(a) Formation of hydroxy caffeine or 1-3-7 trimethyl-uric acid(5)

It was found that the 8-ethers of caffeine would form hydroxy-caffeine by two methods:

(1) By heating the ether in a closed tube at high temperatures. Using this method it was possible to obtain hydroxy-caffeine from all of the ethers to some extent except 8-phenyloxy-caffeine and 8-para-hydroxy-phenyloxy-caffeine. 8-Methoxy, 8-benzyloxy, and 8-phenyl-ethoxy-caffeine gave very small amounts of hydroxy-caffeine.

(2) By heating the ether with dilute hydroc chloric acid[6]. Hydroxy-caffeine was formed by the treatment of the caffeine ether with five parts by weight of 10 per cent hydrochloric acid in a flask, heating the mixture on a steam bath for twenty to thirty minutes. The ether gradually went into solution, and when the reaction had gone well toward completion the hydroxy-caffeine separated out while the solution was still hot. Upon cooling long slender needles in clusters formed. These crystals were filtered off, the filtrate made almost neutral, and concentrated down to nearly one-fifth of the original volume, thus a second crop of crystals were obtained. The entire product of crystals was recrystallized again from hot HOH or alcohol.

This reaction seemed to be typical of the 8-alkyl ethers of caffeine. The basis for this statement lies in the fact that hydroxy-caffeine was formed from the alkyl ethers up to and including n. heptyloxy-caffeine, in some cases readily. It was further found that the two phenyl alkyl

ethers of caffeine prepared by Huston and Allen would form hydroxy-caffeine in the same manner. Phenyloxy and p. hydroxy-phenyloxy-caffeine would not be converted into hydroxy-caffeine by any method however.

(b) Molecular rearrangement of the 8-ethers of caffeine to tetra-alkyl-uric-acids[5].

The second reaction that Huston and Allen found in the caffeine ethers was a less general reaction. It consisted of the molecular rearrangement of some of the 8-alkyl caffeine ethers to the corresponding alkyl substituted uric acid. It was reported, however, that only five of the prepared ethers would give this rearrangement.

In repeating the work of Biltz and his co-workers[7] on the molecular rearrangement of 8-methoxy and 8-ethoxy caffeine to tetra methyl, and trimethyl 9-ethyl-uric acids, it was found that the rearrangement would take place as reported in a closed tube at temperatures up to 250°C. Huston and Allen went further, however, and found that this rearrangement would take place better in an open tube heated in a paraffin bath.

The general procedure followed was as follows: From two to five grams of the caffeine ether was heated in either a closed or an open tube at temperatures from 240° to 305°C. for anywhere from 4 to 18 or more hours. In the course of the reaction it was found that the tube contents often formed a solid mass and a readily vaporized liquid after the heating had been continued for two to three hours. The solid

substance was thought to be hydroxy-caffeine. Varying amounts of hydroxy-caffeine were formed with the rearranged product.

The trimethyl 9-alkyl-uric acids were separated from hydroxy-caffeine as well as any unchanged caffeine ether by boiling the product with 10 per cent HCl, and then after evaporating to dryness the residue was dissolved in a small quantity of hot water. The solution was carefully neutralized with barium hydroxide solution, forming the insoluble barium salt of the hydroxy-caffeine. Once more the solution was evaporated to dryness. The residue was extracted with several small portions of hot chloroform. The soluble trimethyl 9-alkyl-uric acid was thus taken off, leaving the barium salt of hydroxy-caffeine. After distilling off the chloroform, the tetra methyl uric acid remained in a very pure state.

Those ethers which would rearrange follow:

1 - 8-methoxy-caffeine. Up to 95 per cent rearrangement either in the presence of a small quantity of absolute methyl alcohol, or without it, in a closed tube, or better in an open tube, at temperatures up to 360°. The best conditions for rearrangement were in an open tube at 240-250° for a period of four hours.

2 - 8-ethoxy-caffeine. Equal amounts of the dry ethoxy-caffeine and absolute ethyl alcohol were heated in an open tube at 245-255° for eight hours. These were the conditions for optimum yield of the rearranged product, which amounted

to 51.2 per cent of the theoretical.

3 - 8-n. propyloxy-caffeine. To obtain optimum rearrangement, this ether had to be heated for ten hours at 260-270° in an open tube. At the end of this period the oily liquid residue was removed with hot water, clarified with animal charcoal, and then any hydroxy-caffeine or unchanged ether was removed by the barium hydroxide method. A 35.5 per cent yield was obtained.

4 - 8-allyloxy-caffeine. Due to the fact that this was an unsaturated ether, it rearranged readily. By heating in an open tube at 170-185° for four hours, a maximum yield of 53.8 per cent trimethyl 9-allyl-uric acid was obtained. Higher temperatures or longer heating lowered the yield.

5 - Benzyloxy-caffeine. The ether was heated in a closed tube at 200-205° for ten hours for a maximum rearrangement of 50.0 per cent to the trimethyl 9-benzyl-uric acid.

These five caffeine ethers were the only ones that Huston and Allen could cause to rearrange. By using more drastic heating, over longer periods of time, it was found that the result was either the formation of more hydroxy-caffeine, or else decomposition of the ether into unrecognizable substances. Thus there seemed to be a temperature at which there was a maximum of the rearranged product formed, and at which there was a minimum of decomposition products and hydroxy-caffeine formed.

The five rearranged products were more soluble

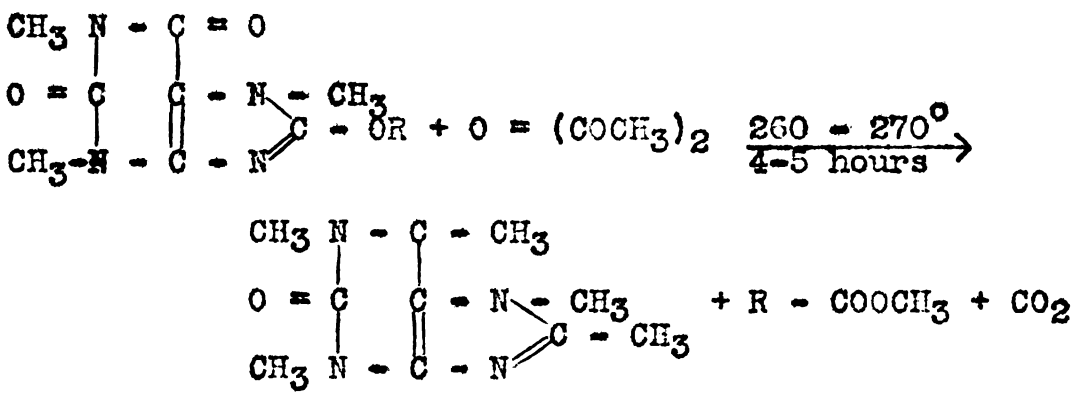
in alcohol and water than were the original ether compounds. All of them melted at temperatures higher than did the corresponding ethers. All except trimethyl 9 benzyl-uric acid sublimed when heated above their melting points. They possessed a more bitter taste than the ethers. In contrast to the original ether compounds, they were very stable toward hot dilute HCl, but very easily decomposed by dilute alkali. All gave a pronounced murexide reaction.

They report it impossible to bring about a rearrangement in the ethers having a phenyl group attached directly to the oxygen on the eighth caffeine position, or having two carbons between the benzene nucleus and that oxygen.

(c) Formation of the 8-alkyl-caffeines[13].

In this laboratory Allen reported on the preparation of certain of the 8-alkyl-caffeines by two methods. Each procedure consisted in the pyrolysis of caffeine compounds. They are as follows:

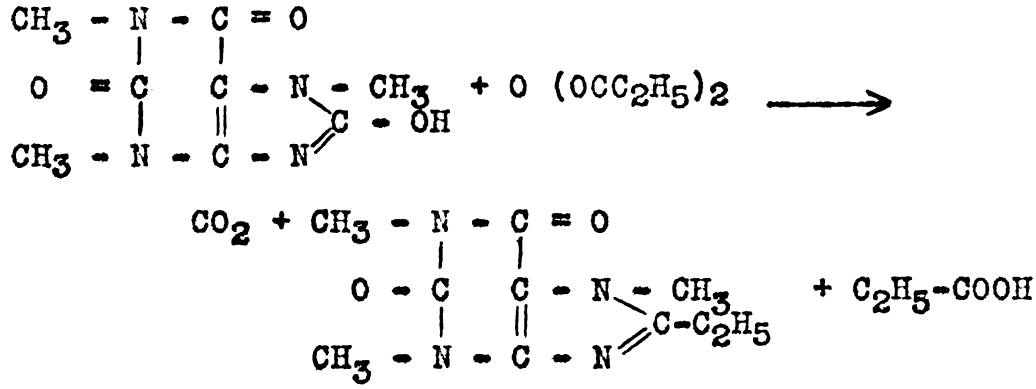
(1) The conversion of the 8-alkyl ethers of caffeine to 8-methyl and 8-ethyl caffeine by heating in the presence of alkyl acid anhydrides. The probable equation for the reaction is



The 8-methyl-caffeine was prepared by heating 2 gr. anhydrous alkyl-caffeine ether with an excess of acetic anhydride. This was done in a sealed tube at 260 to 270° for from 4 to 5 hours. After cooling, the dissolved contents of the tube were washed out with hot alcohol and evaporated to dryness on a steam bath. The residue was dissolved in 100 mls. of hot water and then clarified by boiling with animal charcoal. The filtrate was concentrated to 10-15 mls. and on cooling, the 8-methyl-caffeine would separate out. The product was recrystallized out of 95 per cent alcohol. The resulting white, thin platetets were then dried at room temperature and finally at 100° for five hours.

8-Ethyl-caffeine was prepared using the same procedure as for 8-methyl-caffeine. However, it was necessary to heat the reaction mixture at a considerably higher temperature to obtain the desired product. As a result of this high temperature considerable amounts of hydroxy-caffeine were found. This was separated from 8-ethyl caffeine by the barium hydroxide method, precipitating the hydroxy-caffeine as the barium salt, and extracting the residue with hot chlorofrom. This solvent was removed and finally the product was recrystallized from alcohol.

(2) The formation of 8-ethyl-caffeine from hydroxy-caffeine.



Anhydrous hydroxy-caffeine was heated with an excess of propionic anhydride. The temperature was raised to 360°, at which time the furnace was shut off. The blackened contents of the tube were washed out with hot alcohol and evaporated to dryness. The dissolved product was clarified by boiling with animal charcoal in water, from which after filtration the 8-ethyl-caffeine was crystallized. Allen reported that a temperature lower than 360° was not sufficient to convert the hydroxy-caffeine to ethyl-caffeine. Further, he found that allowing the reaction to take place in the inert gas, nitrogen, did not result in an increased yield. In fact the yield was decreased.

He concluded then that a temperature of 350° maintained for thirty minutes, or 355° for twenty minutes resulted in a maximum yield of 8-ethyl-caffeine.

(3) Formation of 8-alkyl-caffeines by pyrolysis of 8-propyloxy-caffeine with alkyl ethers.

Allen reported that by heating n. propyloxy-caffeine with an excess of n. propyl ether in a closed tube at 300-305° for eight hours, he obtained 8-ethyl-caffeine with a 37.5 per

cent yield. Here again he followed the procedure of clarifying the water solution of the dissolved product with animal charcoal, and then crystallizing from water.

Secondary propyloxy-caffeine was heated with an excess n. propyl ether at 295-300° for eight hours. The contents of the tube were treated as before. After recrystallizing out of hot alcohol he reports a 52.5 per cent yield.

Allen, in his report, says that the mechanism of this reaction can be explained on the basis of an intermediate formation of propionaldehyde. The pyrolysis of an ether to an aldehyde is reported by Hurd[8] and by Hinschelwood and Askey[9]

$$C_3H_7OC_3H_7 \xrightarrow{300^\circ} C_2H_5C(=O)H + C_3H_8$$

At this high temperature the aldehyde reacts with the caffeine ether to form the 8-alkyl-caffeine.

$$\text{Caffeine} - O - R + O = C(H) - C_2H_5 \longrightarrow$$

$$\text{Caffeine} - C_2H_5 + R\text{-}COOH$$

There is no report on the attempted formation of 8-alkyl-caffeines, using other others than n. propyl ether. There was an attempt made to prepare 8 n. butyl-caffeine by heating hydroxy-caffeine with n. bytyric, and n. valeric anhydride. Heating was done in a closed tube from 260-358°. In each attempt some of the hydroxy-caffeine was recovered, but the remainder had decomposed.

EXPERIMENTAL

A. The attempted formation of 8-Alkyl-caffeines by the pyrolysis of caffeine ethers with alkyl ethers.

1. Preparation of 8-chloro-caffeine.

8-Chloro-caffeine was prepared by the method of Fischer and Reese[1]. Fifty grams of caffeine, dried at 120° for at least five hours, was dissolved in four hundred grams of anhydrous chloroform. This was placed in a flask fitted with mercury seal stirrer, reflux condenser with calcium chloride tube and a delivery tube to bottom of flask. Chlorine gas, dried by passing through concentrated sulfuric acid, and finally phosphorous pentoxide, was bubbled through the mixture at the boiling point of the solvent, while stirring. The solution first became very cloudy, but after about thirty minutes or so it cleared up, and at that point the action was complete. The solvent was distilled off on a water bath, leaving behind the 8-chloro-caffeine as a white precipitate. This was digested with a small quantity of water, and then allowed to air dry. Finally it was dried at 120° for five hours. Before using any of the chloro-caffeine it was always dried at that temperature, to give an anhydrous compound.

Trial	1	2	3
Material - grs.	50	50	50
Actual Yield - grs.	46	44	51
Theoretical Yield - grs.	58	58	58
Per cent "	79.4	76	88
Melting Pt. determined	186-188	186-187	187
" " (Fischer)		188°	
Nitrogen - determined		24.27%	
" calculated		24.05%	

2. The preparation of 8-propyloxy-caffeine.

The 8-propyloxy-caffeine was prepared after the manner of Huston and Allen[5]. The propyl alcohol was dried with a few pieces of sodium, and then distilled, the fraction boiling from 97-98° being used. Two grams of freshly cut sodium were dissolved in one hundred grams of the alcohol. To this sodium alcoholate solution, twenty grams of anhydrous 8-chloro-caffeine were added. The mixture was refluxed on an oil bath, with stirring, for one hour.

While the reacted solution was hot it was filtered to remove the salt, washing the filter with a small quantity of absolute alcohol. On cooling the propyloxy-caffeine crystallized out. This first crop was filtered and the filtrate concentrated down to obtain a maximum yield of the ether. The 8 propyloxy-caffeine was recrystallized from 95 per cent alcohol.

Trial	1	2
N. propyl alcohol - grs.	100	100
Sodium - grs.	2	2
8-Chloro-caffeine	20	20
Yield - actual	18.2	17.6
Yield - theoretical	22.1	22.1
Yield - percentage	82.1	80.0
M.P. - determined	129-130°	
M.P. - correct.	129.5/130.5°	

3. Preparation of alkyl ethers.

a. Preparation of di-n. propyl ether[11].

N. propyl ether was prepared by the action of sulfuric acid on n. propyl alcohol. Thirty grams of redi-

stilled n. propyl alcohol was mixed carefully with forty grams of concentrated sulfuric acid. This mixture was put in a round bottom flask fitted with thermometer, mercury stirrer, and dondenser set for distillation. The flask was heated on an oil bath, keeping the solution at 135° while seventy grams of propyl alcohol were dropped slowly on the hot solution. The distillate was collected surrounded by ice, and then treated with potassium hydroxide pellets to remove traces of acid. It was next distilled over calcium oxide, collecting that portion boiling at 85-90° (correct 89°). The n. propyl ether was finally allowed to stand over sodium to remove the last traces of moisture.

b. Preparation of di-isopropyl ether.

Iso propyl alcohol was redistilled, B.P. 80-82°. The same proportions of alcohol and sulfuric acid were used as in the preparation of the n. propyl ether. The mixture was kept at 120° while the alcohol was being dropped into the acid mixture. During the reaction there was considerable SO_2 gas given off. The distillate was dissolved in concentrated sulfuric acid, and then separated by the addition of water. This removed any unsaturated compounds that may have been formed in the reaction. The ether was then dried and neutralized with anhydrous sodium carbonate. A few pieces of sodium were added and it was allowed to stand over night before distilling over sodium to remove all the moisture. B.P. 65-70 (correct Beilstein 68.5-69°).

c. Preparation of di n. butyl ether.

This ether was prepared by Williamson's method. Forty-six grams of freshly cut sodium were dissolved in 160 grams of absolute n. butyl alcohol. It was necessary to use heat and stirring to complete the reaction. The sodium alcoholate solution was refluxed with 270 grams of redistilled n. butyl bromide, B.P. 100°, for three hours. The mixture was then distilled, the fraction boiling from 135-140° being collected. The ether was redistilled over sodium, before being used, to insure an anhydrous product. (B.P. 140.5° Beilstein).

The proof of the structures of these alkyl ethers lies in the method of their preparation. Both methods used are typical for the preparation of ethers.

4. Pyrolysis of 8-alkyl-caffeine ethers with alkyl ethers.

The procedure followed for all these reactions was the same as was used by Allen in his report on work done in this laboratory[12].

The carefully weighed sample of anhydrous caffeine ether was put in a bomb tube with an accurately measured quantity of the alkyl ether. The bomb tube was sealed, put in the Carius furnace, and heated for the prescribed time at a certain temperature. When the tube had cooled, it was opened, the contents washed out with hot alcohol, and evaporated to a dark, tarry mass. This product was dissolved in hot water, and boiled with animal charcoal to clarify it. The filtrate was evaporated down in the attempt to obtain

crystals, but in each attempt crystallization was impossible. On evaporating off all the water there remained a tarry, brown decomposition product which would not crystallize from any common solvent, or at temperatures below 0°C. Attempts were made to bring about crystallization from absolute, 95 per cent and dilute alcohol, carbon disulfide, chloroform, carbon tetrachloride, acetone, petroleum ether, di-ethyl ether, benzene, and xylene.

We were forced to conclude that it was impossible to prepare the 8-alkyl-caffeines from alkyl-caffeine ethers and alkyl ethers by a pyrolysis reaction. Low temperatures gave the unchanged caffeine ether, while high temperatures resulted in decomposition of the ethers to a tarry, brown mass of no definite boiling point. The unchanged ether was successfully recrystallized from 95 per cent alcohol by adding a very small amount of water to it. Its identity was proved by melting points and by determination of the nitrogen content.

1. N. propyloxy-caffeine with n. propyl ether.

Trials	1	2	3	4
Grams caffeine ether	2	2	2	2
Cc's. alkyl ether	2	5	2	2
Temperature	250	300	300	325
Hours	8	5	8	8
No. of trials	2	2	4	1
Product	Caffeine ether		Decomposed	
Grams Product	1.2			

2. Isopropyloxy-caffeine with n. propyl ether.

Grams caffeine ether	2
Cc's. alkyl ether	2
Temperature	300
Hours	8
No. of trials	2
Product	Decomposed

3. Propyloxy-caffeine with isopropyl ether.

Grams caffeine ether	2	2
Cc's. alkyl ether	2	2
Temperature	250	300
Hours	8	8
No. of trials	2	2
Product	Decomposed	Decomposed

4. Propyloxy-caffeine with n. butyl ether

Grams caffeine ether	2	2
Cc's. alkyl ether	2	2
Temperature	300	300
Hours	4	8
No. of trials	1	1
Product	Decomposed	Decomposed

B. Preparation of two new 8-ethers of caffeine.

1. 8-Phenyl propyloxy-caffeine. $C_{17}H_{20}O_3N_4$.

After the manner of Huston and Allen[1], these caffeine ethers were prepared from the reaction of the sodium alcoholate on 8-chloro-caffeine.

1.51 Grams of bird shot sodium were quickly weighed out and dropped into 90 grams of redistilled phenyl propyl alcohol, B.P. 116-120° at 12 mm. This was heated with stirring and refluxing on an oil bath until all the sodium had reacted with the alcohol. To the sodium alcoholate solution were added 15 grams of anhydrous 8-chloro-caffeine. Stirring was continued while the mixture was heated for five hours at 140° on an oil bath.

At the end of this period the alcohol was distilled off under reduced pressure to avoid excessive heating with consequent decomposition of the product. The residue was dissolved in alcohol, and filtered hot to remove the salt. On cooling the phenyl propyloxy-caffeine separated out as fine needles. The product was recrystallized from dilute alcohol, the filtrate being concentrated to bring about a maximum yield.

The compound consisted of very small, needle-like crystals which were practically insoluble in cold water and cold alcohol. In hot water it melted to oily drops that were comparatively insoluble. The product melted at 110-111° and sublimed at higher temperatures. It gave a pronounced murexide test, with a bright vermilion color.

EXPERIMENTAL DATA ON PHENYL-PROPYLOXY-CAFFEINE

$C_{17}H_{20}O_3N_4$ M.W. (calc.)	328.08
Phenyl propyl alcohol, grams	90.0
Sodium, grams	1.15
8-Chloro-caffeine, grams	15.0
Temperature heated	140°
Hours heated	5
Recrystallized from	Dilute alcohol
Yield - actual	14
" - theoretical	24.3
" - percentage	57.5

Analysis:	Determined	Calculated
Carbon	62.02	62.18
Hydrogen	6.15	6.13
Nitrogen	16.85	17.07

Solubility:	Cold	Hot
Water	Pract. Ins.	Melts to oily drops
Alcohol	Very slight	9.2 gr./100 mls.
$CHCl_3$	Very sol.	Very soluble
CCl_4	Slightly	Moderately

2. 8-Phenyl-butyloxy-caffeine - $C_{18}H_{22}O_3N_4$.

It was necessary to prepare the phenyl butyl alcohol to be used in this synthesis. This was done by making phenyl propyl bromide from phenyl propyl alcohol, forming the Grignard, reacting the Grignard compound with dry formaldehyde gas, and finally hydralyzing the addition compound to the desired alcohol. The exact procedure is as follows.

An equivalent amount of phosphorus tribromide, 185 grams, was slowly dropped into 265 grams of phenyl propyl alcohol being stirred in a cooled flask protected from moisture. It was then washed with water, dried with anhydrous sodium carbonate, and finally distilled at 16 mm., collecting the fraction boiling between 120-125°(13). The yield amounted to 185 grams, or about 62 per cent of theoretical.

A Grignard reagent was prepared from the 185 grs. of the halide after the manner of Whitmore(14). The halide was diluted with six times its volume of anhydrous ether. A crystal of iodine was heated with 25 grams of magnesium metal dried in a desiccator. Ten mls. of the ether halide solution were added direct to start reaction. Then the solution was added one drop a second without cooling, the completed Grignard being allowed to stand over hight.

The flask was then fitted with as wide a delivery tube as possible, and through this tybe into the Grignard

solution was passed formaldehyde gas generated by heating anhydrous paraformaldehyde(15). The solution was stirred very rapidly and was cooled with a freezing mixture. The reaction was considered to have reach completion when a clear ether layer formed on top of the mixture when stirring was stopped. This took about thirty-five minutes.

The mixture was then hydrolized with ice and HCl, the ether layer separated, and aqueous part extracted with more ether. This ether solution was dried with calcium chloride and then the ether distilled off on a steam bath.

Finally the phenyl butyl alcohol was distilled off at reduced pressure. B.P. 138-142° at 14 mm. (Correct - Beilstein 140° at 14 mm.). The yield amounted to 65 grams or 22.4 per cent theoretical.

To prepare the phenyl-butyl-caffeine-ether, 85 grams of phenyl butyl alcohol were heated to 130° with 1.51 grams of bird shot sodium with stirring. When the sodium had completely reacted, 15 grams of anhydrous 8-chloro-caffeine were added. The mixture was refluxed with stirring for 5 hours at 150°. The alcohol was then distilled off at reduced pressure. The remaining solid was dissolved in hot 95 per cent alcohol, filtered to remove the salt, and finally cooled to crystallize, the filtrate being evaporated down to complete the crystallization. By redissolving the products twice in alcohol, each time adding water to cause crystallization, a very pure, white, crystalline compound was obtained. The

crystals were dried at 80°, and finally in a desiccator over sulfuric acid.

8-Phenyl-butyloxy-caffeine melted at 132-133°. It sublimed fairly easily above that temperature. The fluffy white crystals were comparatively insoluble in cold or hot water. The compound gave more of a red colored murexide test, than did the phenyl propyloxy-caffeine.

EXPERIMENTAL DATA ON PHENYL-BUTYLOXY-CAFFEINE

$C_{18}H_{22}O_3N_4$	M.W. (calc.)	342.00
Sodium, grams		1.15
Phenyl butyl alcohol, grams		85
8-Chloro-caffeine, grams		15
Temperature heated		130°
Hours heated		5
Recrystallized from		Dilute alcohol
Yield - actual		16
" - theoretical		26.1
" - percentage		61.2
Melting point		132-133°

Analysis:	Determined	- Calculated
Carbon	63.9	63.16
Hydrogen	6.69	6.42
Nitrogen	16.29	16.33

EXPERIMENTAL DATA (Continued)

Solubility:	Cold	Hot
Water	Very slightly	Slightly
Alcohol	Very "	7.13 gr./100 mls.
$CHCl_3$	Very "	Very soluble
CCl_4	Slightly sol.	Very "

3. Attempted formation of phenyl-amyloxy-caffeine.

It was attempted to prepare this compound by the same procedure used in the preparation of phenyl butyloxy-caffeine. However we only had 65 grams of phenyl butyl alcohol with which to prepare the phenyl amyl alcohol needed. This was recovered from the preceding preparation.

Phenyl butyl bromide was prepared from this alcohol, and the Grignard reagent from it was reacted with dry formaldehyde gas. On hydrolysis there was obtained 8.6 grams of phenyl amyl alcohol - B.P. 150-160° at 12 mm. (Correct B.P. Beilstein 155° at 12 mm.

1.12 Grams of sodium were dissolved in the alcohol which was in solution with 100 grams of anhydrous xylene. To the alcoholate solution were added 11.5 grams of anhydrous 8-chloro-caffeine. This mixture was heated on an oil bath at the boiling point of the solvent for 5 hours. Care was used to exclude moisture throughout the entire procedure. The solvent was evaporated under reduced pressure and the residue dissolved in alcohol. Upon recrystallization from dilute alcohol, there was obtained 5.2 grams of a white crystalline

compound, melting at 185-187°. On analysis it yielded 23.42 per cent nitrogen. It was found to contain chlorine.

From these results it was concluded that 5.2 grams of 8-chloro-caffeine had been recovered unchanged. Evidently the boiling point of the xylene was not high enough to bring about the desired reaction.

EXPERIMENTAL DATA

Materials in grams:	
Phenyl amyl alcohol	8.6
Xylene solvent	100
Sodium	1.12
8-Chloro-caffeine	11.5
Recovered 8-chloro-caffeine	5.2
Melting point - determined	185-187°
" " - correct	188°
Analysis - nitrogen	23.42%
Calculated - "	24.05%

4. Conversion of phenyl propyloxy-caffeine and phenyl butyloxy-caffeine to hydroxy-caffeine.

One gram of each of these two new caffeine ethers was heated on a steam bath with 10 mls. of 10 per cent hydrochloric acid. In each case the ether dissolved, and there was formed a small amount of what was assumed by the odor to be the phenyl propyl and phenyl butyl chloride. The volume of liquid was concentrated to about four mls. and on cooling

there separated out a batch of white fluffy needle-like crystals. On recrystallizing from hot water, there was obtained a good yield of hydroxy-caffeine, melting to a dark brown liquid at 330-340°. The proof of structure lies in the method of preparation and in the physical properties.

EXPERIMENTAL DATA

Materials used	Phenyl propyloxy-	Phenyl butyloxy-
Caffeine compound - grams	1	1
10 Per cent HCl - mls.	10	10
Time heated on steam bath	20 min.	35 min.
Hydroxy-caffeine - grams	.58	.62
M.P. - determined	330-340	
" correct	345	

5. The attempted molecular rearrangement of phenyl propyloxy-caffeine and phenyl butyloxy-caffeine.

It was attempted to rearrange these ethers by heating in open and closed tubes. After heating the contents of the tubes were washed out with hot alcohol. On evaporation to a smaller volume there was obtained in some cases a crop of crystals, each time proving to be the unchanged caffeine-ether. In other cases, where the temperature had been higher, there was more decomposition and discoloration, resulting in the recovery of less of the caffeine ether. The structure of the recovered product was proven to be the ether by its phys-

ical properties, and by the fact that it formed hydroxy-caffeine on treatment with hydrochloric acid.

EXPERIMENTAL DATA ON ATTEMPTED REARRANGEMENT

1. Phenyl-propyloxy-caffeine

Trials	1	2	3	4
Ether used - grams	.5	.5	.5	.5
Temperature	150	225	250	325
Hours heated	8	8	8	8
Open or closed tube	open	open	closed	closed
Recovered ether, grams	.35	.19	.11	decomposed

2. Phenyl-butyloxy-caffeine

Ether used	1.0	.5	1.0	.5
Temperature	150	225	250	325
Hours heated	8	8	8	8
Open or closed tube	open	open	closed	closed
Recovered ether, grams	.75	.12	.16	decomposed

SUMMARY AND DISCUSSION

The first purpose of this thesis has been to discuss the methods whereby it was attempted to prepare the 8-alkyl-caffeines. This was done by the pyrolytic reaction between 8-caffeine ethers and three of the alkyl ethers.

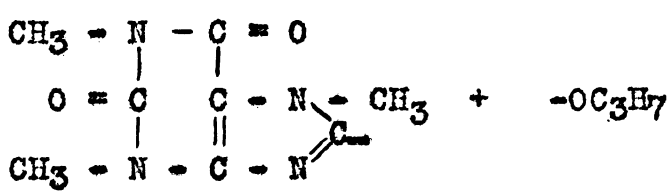
It has been shown by Hurd[1], that an alkyl ether will yield on pyrolysis, an aldehyde. It has been explained that the probable reaction between the aldehyde and the caffeine ether is as follows:

$$\text{Caffeine} - OC_3H_7 + O = \overset{H}{C} - C_2H_5 \xrightarrow{300^\circ}$$

$$\text{Caffeine} - C_2H_5 + C_3H_7COOH$$

An examination of the equation will show that the reaction involves:

1. The formation of a caffeine radical and a propyloxy radical.



2. The breaking down of the aldehyde is as follows:

$$C_2H_5 - \overset{H}{C} = O \quad \text{to} \quad C_2H_5 \text{ and } -\overset{H}{C} = O$$

3. Finally the 8-alkyl-caffeine is formed. But there is involved a migration of hydrogen from carbon to oxygen, and a migration of oxygen from carbon to carbon before the acid can be formed.

The very complicated mechanism of the whole reaction is

probably the reason for failure here in preparing any of the 8-alkyl caffeines by this method. It would be interesting to heat propyloxy-caffeine with propionaldehyde, as a check on the above explanation.

It must be concluded then, that it is impossible to prepare the 8-alkyl-caffeines by the pyrolysis of the 8 ethers of caffeine with alkyl ethers.

Secondly, two new caffeine ethers have been prepared from the action of a sodium alcoholate on 8-chloro-caffeine:

1. 8-Phenyl propyloxy-caffeine, a white, fine, needle-like crystalline compound, melting at 110-111°, practically insoluble in cold water, and melting to insoluble oily droplets in boiling water.

2. 8-Phenyl butyloxy-caffeine, a white, fluffy, crystalline compound when crystallized from dilute alcohol, melting at 132-133° and very slightly soluble in cold and hot water.

Both phenyl propyl and phenyl butyloxy-caffeine when heated in an excess of 10 per cent hydrochloric acid, will form hydroxy-caffeine. The murexide test is given by each of these ethers.

It is interesting to note that up to phenyl propyloxy-caffeine the melting point of the ether is lowered by the introduction of a methylene group into the chain. Phenyl butyloxy-caffeine however has a higher melting point.

Compound	M.P.
Phenyl benzyloxy-caffeine	172-173.5°
Phenyl ethoxy-caffeine	142-144.4°
Phenyl propyloxy-caffeine	110-111°
Phenyl butyloxy-caffeine	132-133°

A possible explanation for this might be that up to and including phenyl propyloxy-caffeine, the aliphatic characteristic is predominant, but beyond this point the ether character becomes more evident.

Finally, it was attempted to bring about the molecular rearrangement of the ethers to the 9-alkyl-uric acids. This was done in both open and closed tubes at varying high temperatures over different periods of time. However either some of the unchanged ether was recovered or else there was decomposition.

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