The temperature at which the sulfur is kept affects the yields: at 300° the reaction was slow (5% conversion per passage) while at 400° the ultimate yield was 41% and an inconveniently large amount of sulfur distilled over. Dilution of the isoprene with carbon bisulfide (1:1) increased the yield of crude 3-methylthiophene at 350° to 51%.

Thiophene.—Crude 50% butadiene[6] yielded 6% of thiophene when bubbled through molten sulfur at temperatures ranging from 320 to 420°. The same yield was obtained when pure liquid butadiene (from the tetrabromide) was dropped into the apparatus from a chilled separatory funnel. The thiophene boiled at 82–84°, had a density d_{15}^{20} 1.05, gave a blue indophenin reaction, and with mercuric chloride yielded 2-chloro-mercurithiophene which did not depress the melting point of authentic material. Carbon bisulfide was again noted as a by-product.

2,3-Dimethylthiophene.—A distillate fraction boiling at 45–160° was obtained from the pyrolysis products of a mixture of crepe rubber and zinc oxide. This fraction had previously been shown to contain about 4% of 3-methyl-1,3-pentadiene[7] mixed with mono-olefins and hydromatic compounds. One hundred grams of this material was dripped into boiling sulfur and gave 48 g. of crude product. The thiophene homologs were isolated therefrom in a manner similar to that previously described[8] and there were obtained 0.3 g. of 3-methylthiophene and 0.15 g. of 2,3-dimethylthiophene. The 2,3-dimethylthiophene was identified as the mercurichloride, melting at 215° (alone, or mixed with authentic material) and the mercurithiocyanate which blackened but did not melt at 205°.[5]

3,4-Dimethylthiophene.—From 50 cc. of pure dimethylbutadiene which had reacted with sulfur at 400–420° were recovered 10 cc. of unconverted material and 12.5 g. (31% yield) of 3,4-dimethylthiophene, which boiled at 145.5–148.5°, had a density d_{15}^{25} 0.994, a refractive index n_{D}^{25} 1.5187 and gave a blue indophenin reaction. For identification, its mercurichloride (melting at 139–140.5°), mercuriiodide (melting at 140–141°) and *bis*-2-(3,4-dimethylthienyl) mercury (melting at 153–154°) derivatives were prepared.[5]

Summary

A procedure is described for the conversion of diolefins into thiophene homologs by interaction with molten sulfur.

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[6] We are indebted to Dr. B. T. Brooks for a generous supply of this material.

[7] Midgley and Henne, THIS JOURNAL, **53**, 204 (1931); **51**, 1215 (1929).

[8] Midgley, Henne and Shepard, *ibid.*, **54**, 2957 (1932).

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Caffeine Derivatives. I. The 8-Ethers of Caffeine

BY RALPH C. HUSTON AND WINSTON F. ALLEN[1]

The extensive investigations and syntheses of compounds in the purine group by Emil Fischer and his associates include the preparation of only two 8-monoethers of caffeine, namely, methoxy- and ethoxycaffeine. Fischer's method,[2] later repeated by W. Wislicenus[3] and H. Biltz,[4] consisted simply in heating 8-chloro- or 8-bromocaffeine in a methyl or ethyl alcohol solution containing an excess of sodium or potassium alcoholate (sodium or potassium added in the form of the metal or hydroxide). Isoamyloxycaffeine was later prepared by the same general procedure.[5] The preparation of fifteen 8-phenyl ethers of caffeine was accomplished by A. Baumann.[6] The methods involved heating 8-chlorocaffeine with a phenol in the presence of an equivalent amount of potassium hydroxide. The reaction took place in an aqueous solution with refluxing, or under pressure at a higher temperature. Xylene was used as the solvent instead of water in some cases.

General Methods of Preparation

Both 8-chloro- and 8-bromocaffeine were used in the preparation of the sixteen ethers described in this paper. The former was used in most cases because of the ease and economy of preparation.[7] Fairly good yields of 8-methoxy- and 8-ethoxycaffeine were obtained by using an excess of metallic sodium or sodium hydroxide, as in Fischer's method. Attempts to prepare the higher alkyl and aryl ethers by the same procedure met with little or no success. A more successful procedure was adopted whereby an exactly equivalent amount of sodium alcoholate or phenylate was used.

In preparing the alkyl ethers, clean metallic sodium was quickly weighed out to 0.02 g. and cut into small pieces.[8]

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[1] Abstract from a thesis presented in partial fulfilment of the requirements for the Ph.D. degree by W. F. Allen, W. K. Kellogg Fellow at Michigan State College, 1932.

[2] E. Fischer, *Ber.*, **17**, 1785 (1884); *ibid.*, **30**, 569 (1897); *Ann.*, **215**, 261 (1882); and "Untersuchungen in der Puringruppe," pp. 38, 95–96, 162.

[3] W. Wislicenus and H. Körber, *Ber.*, **35**, 1992 (1902).

[4] H. Biltz and M. Bergius, *Ann.*, **414**, 59 (1917).

[5] Magnanini, private communication.

[6] A. Baumann, *Arch. Pharm. Inst. Univ. Berlin*, **10**, 127–147 (1913); and *Chem. Zentr.*, II, 2036 (1913).

[7] E. Fischer and Reese, *Ann.*, **221**, 336 (1883).

[8] Sodium in the form of "bird shot" was used sometimes to an advantage when kept in a toluene solution and weighed out as needed.

The sodium was added to enough absolute alcohol to effect solution of the resulting caffeine ether while hot. The proportion was generally 50 g. of the chlorocaffeine to 300 cc. of alcohol. After disappearance of the sodium, an equivalent amount of 8-chlorocaffeine (dried at 120°) was added and shaken well. The mixture was refluxed, with occasional shaking, on a steam or oil bath for one-half to five hours, depending upon the speed of the reaction. The hot solution was filtered immediately to remove the sodium chloride, the flask and filter being washed with a small quantity of the absolute alcohol. Methoxy-, ethoxy-, normal propyloxy-, secondary propyloxy- and isoamyloxycaffeine crystallized out more or less completely when cooled. With the higher alkyl ethers, such as *n*-hexyloxy- and *n*-heptyloxycaffeine, it was necessary to concentrate the solution to a smaller volume by vacuum distillation. In order to secure a maximum yield, the mother liquor was diluted with about an equal volume of water. In case of the lower members of the series, merely concentrating the solution to a smaller volume was found sufficient.

Dilute (40–50%) ethyl alcohol was found very suitable for recrystallizing the alkyl ethers. The amounts and proportions varied because of the decreased solubility of successive members of the series in water. To secure a more nearly anhydrous compound, the first four members were also successfully recrystallized from carbon tetrachloride. The higher members were recrystallized from petroleum ether for the same reason.

The normal alkyl ethers were obtained in nearly quantitative yields and the reaction was usually completed within one-half an hour. The secondary caffeine ethers were formed rather slowly and gave from 40–50% yields. Only about 12% yield was obtained of *t*-butyloxycaffeine after several hours.

Benzyloxy- and phenylethoxycaffeine were prepared in the same manner as the alkyl derivatives. However, be-

TABLE I

PREPARATION AND PROPERTIES OF THE 8-ETHERS OF CAFFEINE

Name	Materials used			Heated, hrs.	Solvents of recryst.	Crystal structure, needles
	8-Cl-caff., g.	Alc., cc.	Na, g.			
Methoxycaffeine[2,3,4]	200	1000	20.12	0.75	H_2O, EtOH, CCl_4	Blunt
Ethoxycaffeine[2,3,4]	100	700	10.06	1.0	H_2O, EtOH, CCl_4	Blunt
n-Propyloxycaffeine	50	300	5.03	1.0	H_2O, EtOH, CCl_4	Blunt
s-Propyloxycaffeine	50	300	5.03	1.0	H_2O, dil. EtOH	Needles
n-Butyloxycaffeine	30	200	3.02	1.0	Dil. EtOH, CCl_4	Slender, or prisms
s-Butyloxycaffeine	30	125	3.02	3.5	Dil. EtOH	Slender
t-Butyloxycaffeine	30	125	3.02	6.0	H_2O, pet. ether	Slender
n-Amyloxycaffeine	20	65	2.02	1.0	Dil. EtOH	Very slender, or prisms
Isoamyloxycaffeine[5]	50	300	5.03	1.0	Dil. EtOH	Needles
n-Hexyloxycaffeine	20	60	2.02	1.0	Dil. EtOH, pet. ether	Very slender, or prisms
n-Heptyloxycaffeine	20	100	2.02	1.0	Dil. EtOH, pet. ether	Waxy, hairlike
Allyloxycaffeine	30	200	3.02	1.0	Dil. EtOH	Needles
Phenyloxycaffeine[6]	20	16.5	2.02	5.0	H_2O, EtOH	Lustrous
p-Hydroxyphenyloxycaffeine	20	10.0	2.02	5.0	EtOH, dil. EtOH	Clusters of short
Benzyloxycaffeine	30	200	3.03	4.0 (150–160°)	EtOH	Clusters of very small
Phenylethoxycaffeine	20	125	2.02	4.0 (160–170°)	EtOH	Clusters of blunt

Name	Soly. in water at		Yield, %	M. p., °C.	Formula	Analyses	
	25°	100°				Calcd.	Found
Methoxycaffeine[2,3,4]	0.29	4.59	90.7	172.5–174.0	$C_9H_{12}N_4O_3$	N, 25.00	24.39
Ethoxycaffeine[2,3,4]	.30	3.56	68.1	137.5–140.0	$C_{10}H_{14}N_4O_3$	N, 23.53	23.18
n-Propyloxycaffeine	.04	0.81	90.1	129.5–130.5	$C_{11}H_{16}N_4O_3$	N, 22.22	21.60
s-Propyloxycaffeine	.07	.65	39.9	153.5–154.7	$C_{11}H_{16}N_4O_3$	N, 22.22	21.77
n-Butyloxycaffeine	.04	.32	89.9	88.6– 90.0	$C_{12}H_{18}N_4O_3$	N, 21.06	20.53
s-Butyloxycaffeine	.03	.46	55.9	122.5–123.8	$C_{12}H_{18}N_4O_3$	N, 21.06	20.34
t-Butyloxycaffeine			12.3	158.0–161.6	$C_{12}H_{18}N_4O_3$	N, 21.06	21.11
n-Amyloxycaffeine	.02	.09	86.9	71.8– 72.6	$C_{13}H_{20}N_4O_3$	N, 20.00	19.49
Isoamyloxycaffeine[5]	.007	.100	91.3	125.0–127.0	$C_{13}H_{20}N_4O_3$	N, 20.00	19.52
n-Hexyloxycaffeine	.011	.04	74.3	52.5– 53.6	$C_{14}H_{22}N_4O_3$	N, 19.05	18.53
n-Heptyloxycaffeine	.005	.02	85.9	61.2– 63.6	$C_{15}H_{24}N_4O_3$	N, 18.18	18.01
Allyloxycaffeine	.47	1.02	83.5	124.0–126.0	$C_{11}H_{14}N_4O_3$	N, 22.40 C, 52.80 H, 5.64	22.02 52.69 5.66
Phenyloxycaffeine[6]	.022	0.21	72.0	140.4–143.0	$C_{14}H_{14}N_4O_3$	N, 19.58	20.03
p-Hydroxyphenyloxycaffeine	.015	.23	24.2	207.0–209.0	$C_{14}H_{14}N_4O_4$	N, 18.54	18.02
Benzyloxycaffeine	.005	.02	80.1	172.0–173.5	$C_{15}H_{16}N_4O_3$	N, 18.06 C, 60.0 H, 5.37	17.96 59.89 5.35
Phenylethoxycaffeine			85.8	142.0–144.5	$C_{16}H_{18}N_4O_3$	N, 17.83	17.49

cause of the high boiling point of the alcohols, the reaction temperature was held between 150 and 170°. A higher temperature caused decomposition.

Phenyloxy- and *p*-hydroxyphenyloxycaffeine were prepared by adding 1 mole of metallic sodium to slightly more than 2 moles of the phenol in a xylene solution and then 1 mole of 8-chlorocaffeine. The mixture was refluxed for five hours. In a second method, these two ethers were prepared by using the same proportions of reagents in an ethyl alcohol solution. The products were separated in the same manner as were the alkyl ethers. In the first procedure the xylene filtrate was distilled under reduced pressure to a small volume in order to secure a second crop of crystals. These methods differed from those of Baumann,[6] who used potassium hydroxide in an alcohol solution.

The last four ethers (table), containing phenyl groups, were most successfully recrystallized from 95% or dilute (40–50%) alcohol.

All of the caffeine ethers gave the murexide reaction. However, the phenyl derivatives gave a brick-red color instead of the usual bright red or scarlet. The stability of the ether-caffeine derivatives toward alkalies proved to be much greater than caffeine or most of the uric acid derivatives. Hot dilute hydrochloric acid readily converted all of the alkyl ethers to hydroxycaffeine. The same compound was formed when the ethers were heated alone at temperatures from 250–300°. On the other hand, it was found that the phenyl ethers were very stable toward boiling 10% hydrochloric acid or when heated alone at temperatures below decomposition.

In general, the branched chain alkyl ethers of caffeine possessed properties very similar to the straight chain compounds. However, the branched ethers were more readily converted to hydroxycaffeine by heating in dilute hydrochloric acid or heating alone at a high temperature. Evidently the substitution of alkyl groups for hydrogen on the carbon atom attached to the ethereal oxygen weakens the oxygen–carbon bond.

Summary

1. Sixteen 8-alkyl- and aryl ethers of caffeine have been prepared, twelve of which are new compounds.

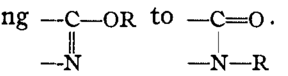
2. All of the alkyl ethers, benzyloxycaffeine and phenylethoxycaffeine are converted into hydroxycaffeine by heating in dilute hydrochloric acid or by heating alone at a high temperature. Phenyloxy- and *p*-hydroxyphenyloxycaffeine are not converted into hydroxycaffeine.

EAST LANSING, MICH. RECEIVED FEBRUARY 21, 1934

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

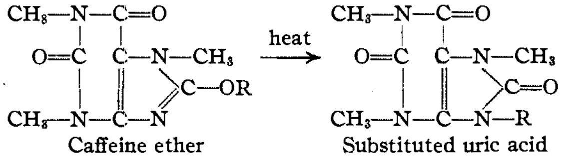
Caffeine Derivatives. II. Molecular Rearrangement of the 8-Ethers of Caffeine

BY R. C. HUSTON AND WINSTON F. ALLEN[1]

The molecular rearrangement of the nitrogen substituted ethers has been observed by Wheeler and Johnson,[2] Wislicenus and Körber[3] and others.[4] It involves the transformation of the grouping  $\begin{array}{c}-\mathrm{C}-\mathrm{OR}\\ \| \\ -\mathrm{N}\end{array}$ to $\begin{array}{c}-\mathrm{C}=\mathrm{O}\\ | \\ -\mathrm{N}-\mathrm{R}\end{array}$.

Rearrangement of several nitrogen substituted imino ethers was found to occur most easily under the catalytic influence of an alkyl iodide but also appeared to take place by simply heating.

In the rearrangement of the 8-ethers of caffeine to the corresponding uric acids, we are dealing with the same groupings as above.



In repeating the work of Biltz and his co-workers[5] on the molecular rearrangement of methoxy and ethoxycaffeine to tetramethyluric acid and trimethyl-9-ethyluric acid, respectively, it was found that the rearrangement took place fully as well, if not better, when the ethers were heated in an open tube contained in a paraffin bath. Tetramethyluric acid was obtained in yields as high as 95% (*Anal.* Calcd. for $C_9H_{12}N_4O_3$: N, 25.00. Found: N, 24.42.), while trimethyl-9-ethyluric acid was formed in about 50% yields (*Anal.* Calcd. for $C_{10}H_{14}N_4O_3$: N, 23.53. Found: N, 22.77).

The trimethyl-9-alkyluric acids were conveniently separated from hydroxycaffeine by forming the insoluble barium salts of the latter and extracting with chloroform.

All attempts to cause the molecular rearrangement of *n*-propyloxycaffeine to trimethyl-9-*n*-propyluric acid by heating in a closed tube were unsuccessful. However, by heating this ether in an open tube at 250–270° for eight hours, a 35% yield of trimethyl-9-*n*-propyluric acid was produced, melting at 138.8–140.6° *Anal.* Calcd. for $C_{11}H_{16}N_4O_3\cdot H_2O$: N, 20.74; C, 48.88; H, 6.66. Found: N, 20.87; C, 49.20, 49.09; H, 6.40, 6.34. The properties of this compound and the method of its preparation indicate its structure. However, further proof of its configuration would be desirable, as well as the explanation of the formation of intermediate products during the pyrolysis.

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(1) Abstract from a thesis presented in partial fulfilment of the requirements for the Ph.D. degree by W. F. Allen, W. K. Kellogg Fellow at Michigan State College, 1932.

(2) Wheeler and Johnson, *Am. Chem. J.*, **21**, 185 (1899).

(3) Wislicenus and Körber, *Ber.*, **35**, 164, 1991 (1903).

(4) Wislicenus and Goldschmidt, *ibid.*, **33**, 1467 (1900); Lander, *J. Chem. Soc.*, **83**, 406 (1903).

(5) Biltz and Strufe, *Ann.*, **413**, 199–200 (1916–1917); Biltz and Berguis, *ibid.*, **414**, 54–57 (1917).