[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

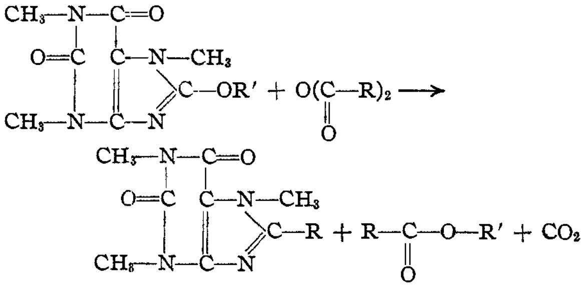
Caffeine Derivatives.[1] III. The Preparation of 8-Methyl- and 8-Ethylcaffeine

BY R. C. HUSTON AND W. F. ALLEN[2]

The methylation of caffeine in the eighth position has never met with success when the usual methylating agents were used. It was established that 1,3,7,8-tetramethylxanthine (8-methylcaffeine) could not be obtained from caffeine, but only from 8-methylxanthine by the Böhringer method.[3]

The xanthines and isoxanthines differ in that only the latter can be methylated[4] directly in the eighth position. According to Biltz and Sauer, 1,3,9-trimethylisoxanthine is readily methylated in the eighth position with methyl sulfate. This is probably effected by addition of methyl and monomethyl sulfate radicals at the 7–8 double bond, and subsequent elimination of methyl hydrogen sulfate. Apparently the 8–9 double bond in caffeine does not favor the addition of methyl and monomethyl sulfate radicals.

The work described in this article is an application of the acid anhydride method of Böhringer and Söhne[5] to the preparation of 8-alkylcaffeines from caffeine. The hydrogen in the eighth position was first replaced by an oxygen-containing group by forming the ether or hydroxy derivative. This was heated in a closed tube with a slight excess of acid anhydride. A much higher temperature was found to be necessary than for the preparation of 8-methylxanthine from uric acid. We were not able to bring about the reaction by heating under atmospheric pressure in the presence of an organic base such as pyridine.



Experimental

8-Methylcaffeine.—From two to five grams of anhydrous alkyl ether of caffeine was heated at 260 to 270° in a closed tube in the presence of 5 cc. of redistilled (b. p. 137–138°) acetic anhydride. After cooling, the somewhat discolored contents of the tube were washed out with hot alcohol and evaporated to dryness on a steam-bath. The residue was then dissolved in about 100 cc. of hot water and clarified with animal charcoal. After filtering, the solution was concentrated to 10 to 15 cc. Crystals of 8-methylcaffeine separated out upon cooling in the form of clusters of very small needles or sometimes platelets. The product was recrystallized from 95% alcohol, forming lustrous white platelets. It was dried at 110°. Yields obtained from five different caffeine ethers are summarized in the following table:

	Yield, %
8-Methoxycaffeine	10.8
8-Ethoxycaffeine	45.9
8-*n*-Propyloxycaffeine	53.3
8-*n*-Butyloxycaffeine	44.9
8-Isoamyloxycaffeine	67.5

Anal. Calcd. for $C_9H_{12}N_4O_2$: N, 26.92. Found: N, 26.83. The melting point agrees with that of 8-methylcaffeine prepared by the Böhringer[3] method; 207.0–208.5°.

At 25° the solubility in water is approximately 0.74 g. per 100 g. water; and 32.5 g. at the boiling point. It is quite soluble in hot alcohol, acetone, benzene and chloroform. 8-Methylcaffeine is very stable toward acids but, like caffeine, is readily decomposed by alkali, forming methylamine and other decomposition products.

8-Ethylcaffeine. (a) From 8-Alkyl Ethers of Caffeine (except Methoxycaffeine).—From two to five grams of anhydrous 8-alkyl ether of caffeine was reheated at 295 to 320° in a closed tube with 5 to 10 cc. of redistilled propionic anhydride (b. p. 162.0–165.5°). The contents were washed out with hot alcohol and the solvent evaporated. The discolored residue was taken up in water and clarified with animal charcoal. Because of the fact that some hydroxycaffeine was present, the filtrate (about 50 cc.) was neutralized with barium hydroxide solution and evaporated to dryness. The residue was extracted with five or six 25-cc. portions of hot chloroform. After removing the solvent, the product was crystallized twice from hot alcohol.

The following yields were obtained: 7.2% from ethoxycaffeine, 17.0% from isopropyloxycaffeine and 13.9% from isoamyloxycaffeine; melting point (after three crystallizations) 186.0 to 187.5°.[3]

Anal. Calcd. for $C_{10}H_{14}N_4O_2$: N, 25.22. Found: N, 25.09.

(b) From Hydroxycaffeine.—Two grams of anhydrous hydroxycaffeine was heated in a closed tube with 5 cc. of redistilled propionic anhydride. When the temperature reached 360° the furnace was immediately shut off. The contents of the tube were treated as in (a); yield 0.4 g. (19%).

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[1] THIS JOURNAL, **56**, 1356, 1358 (1934).

[2] 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.

[3] Böhringer and Söhne, German Patent 128,212, *Chem. Zentr.*, I, 549 (1902); von Ernst Waser, "Synthese der organischen Arznei-mittel," Ferdinand Enke, Stuttgart, pp. 204–205.

[4] H. Biltz and J. Sauer, *Ber.*, **64B**, 752–766 (1931).

[5] Böhringer and Söhne, German Patent 121,224, *Chem. Zentr.*, II, 71 (1901).

When heated at or above its melting point, 8-ethylcaffeine sublimes, forming fine interwoven needles. Like 8-methylcaffeine, it is quite stable toward acids but is easily decomposed in alkalies. Solubility in 100 cc. of water is 0.6 g. at 25° and 2.0 g. at 100°. It is moderately soluble in cold alcohol and quite soluble in boiling alcohol. The crystals came down from either a water or alcohol solution as bundles of very small colorless needles.

Attempts to prepare 8-*n*-propylcaffeine and 8-*n*-butylcaffeine by this method were unsuccessful. When heated in a closed tube at temperatures ranging from 260 to 360°, the materials recovered were unchanged caffeine ether and hydroxycaffeine. Higher temperatures gave decomposition products.

Summary

1. 8-Methylcaffeine has been prepared by heating the 8-alkyl ethers of caffeine with acetic anhydride.

2. 8-Ethylcaffeine has been prepared by heating the 8-alkyl ethers of caffeine (except methoxycaffeine) or hydroxycaffeine with *n*-propionic anhydride.

3. Attempts to prepare 8-*n*-propyl- and 8-*n*-butylcaffeine by the same general procedure have been unsuccessful.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

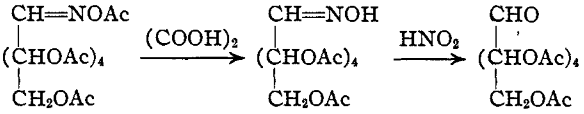
A New Synthesis of Aldehydo Sugar Acetates[1]

BY M. L. WOLFROM, L. W. GEORGES AND S. SOLTZBERG

A number of open chain or *aldehydo* sugar acetates have been synthesized in this Laboratory by the controlled hydrolysis of acetylated sugar mercaptals with mercuric chloride and cadmium carbonate. We wish to report a new method of synthesis for these substances, which may present advantages over the above in certain cases.

Wolfrom and Thompson[2] have shown that *aldehydo*-glucose oxime hexaacetate is formed in low yield by the rather vigorous acetylation of glucose oxime, mild acetylation producing the ring or β-glucose oxime hexaacetate. Acetylation of galactose oxime[3] produces a small amount of β-galactose oxime hexaacetate and a large amount of an approximately equal mixture of *aldehydo*-galactose oxime hexaacetate and galactononitrile pentaacetate, from which it is impossible to separate the former in good yield.

The above work shows that it might be possible to use the sugar oximes as a source for acetylated open chain oximes. We have now found that the latter compounds may be deoximated with the formation of the *aldehydo* sugar acetates. It is first necessary to remove the O-acetyl group of the oxime hexaacetate and this is readily effected with a methanol solution of oxalic acid. The deoximation is then produced with nitrous acid, a reagent first used by Claisen and co-workers.[4]



$$\begin{array}{l}CH{=}NOAc\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array} \xrightarrow{(COOH)_2} \begin{array}{l}CH{=}NOH\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array} \xrightarrow{HNO_2} \begin{array}{l}CHO\\ |\\ (CHOAc)_4\\ |\\ CH_2OAc\end{array}$$

When the mixture of acetylated oxime and nitrile obtained from galactose oxime is carried through the above reactions, the resultant mixture of acetylated nitrile and *aldehydo*-galactose pentaacetate is easily separated. The acetylation of glucose oxime does not produce a sufficient amount of the *aldehydo*-glucose oxime hexaacetate to make this reaction a practical source for the compound. However, further acetylation of the oxime of β-glucose tetraacetate produced the above substance as the sole crystalline reaction product.

We have found that the semicarbazones of the *aldehydo*-acetates of glucose and galactose readily undergo oxygen replacements of their semicarbazide part by means of nitrous acid. Acetylation of the semicarbazones of these two sugars produced a good yield of the *aldehydo*-semicarbazone pentaacetates. In the case of glucose, this substance (m. p. 155°; $[\alpha]_D$ + 97°, $CHCl_3$) was accompanied by three other products which were isolated in crystalline condition. One was an isomeric pentaacetate (m. p. 236°; $[\alpha]_D$ −16°, $CHCl_3$). Another was a tetraacetate (m. p. 171°; $[\alpha]_D$ −9°, $CHCl_3$) which produced the pentaacetate melting at 236° on further acetylation

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[1] Presented before the Section of Chemistry at the Forty-fourth Meeting of the Ohio Academy of Science, Columbus, Ohio, March 30, 1934.

[2] M. L. Wolfrom and A. Thompson, THIS JOURNAL, **53**, 622 (1931).

[3] V. Deulofeu, M. L. Wolfrom, P. Cattaneo, C. C. Christman and L. W. Georges, *ibid.*, **55**, 3488 (1933).

[4] L. Claisen and O. Manasse, *Ber.*, **22**, 530 (1889).