[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF RICHMOND]

Creatinine Derivatives. III. Alkylation with Methyl and Ethyl Sulfates. The Structure of Methylcreatinine

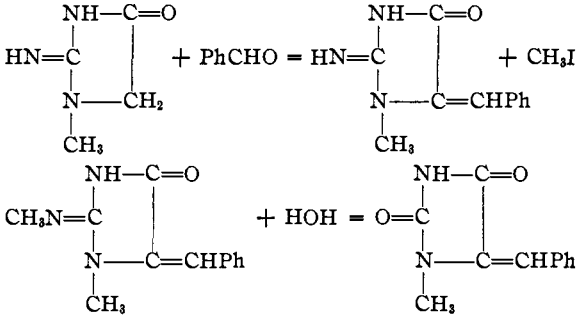
BY WM. R. CORNTHWAITE[1]

Methylcreatinine has been prepared by Korndorfer[2] and others by heating creatinine with methyl iodide in a sealed tube and treating the product with potassium carbonate or silver oxide. The use of other methylating agents has not been noted.

In attempting to prepare a quantity of methylcreatinine the use of methyl sulfate led to very gratifying results and yields as high as 80% of the theoretical calculated as sulfate have been obtained in this Laboratory.

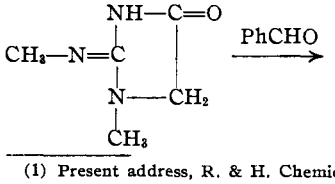
The structure of methylcreatinine has received considerable attention and has been discussed by Johnson and Nicolet.[3]

Nicolet and Campbell[4] in an effort to prove the position of the methyl group, methylated benzalcreatinine, then hydrolyzed the product to 1-methyl-5-benzalhydantoin, whose structure was proved, indicating the methyl group was attached to the 2 position.



The condensation of benzaldehyde with methylcreatinine was then tried with no success.

In the present work we have been able to condense benzaldehyde with methylated creatinine and find the product identical in properties with the 2-methyl-5-benzalcreatinine as described by Nicolet and Johnson. This would be evidence that the methyl group was actually in the 2 position.



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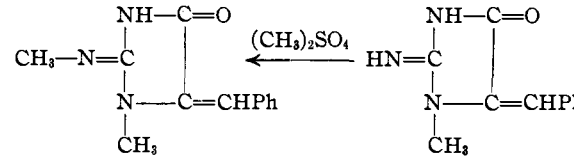
(2) Korndorfer, *Arch. Pharm.*, **242**, 641 (1904).

(3) Johnson and Nicolet, THIS JOURNAL, **37**, 2416 (1915).

(4) Nicolet and Campbell, *ibid.*, **50**, 1155 (1928).



In addition we have successfully methylated furfuralcreatinine using methyl sulfate, the product being identical with that from the condensation of furfural with methylcreatinine.[5]

It was not possible to obtain satisfactory results in ethylating creatinine with ethyl sulfate, creatinine ethyl sulfate being the chief product, ethylcreatinine sulfate being isolated from residual sirups with difficulty.

Thanks are due the Valentine Meat Juice Company for the creatine from which the creatinine used in these experiments was prepared.

Experimental Part

Preparation of Methylcreatinine Sulfate.—Ten cc. of distilled water was added to 15 g. of creatinine in an evaporating dish and placed on a steam-bath. Thirty cc. of methyl sulfate was then added over a period of one hour and the liquid allowed to digest for two hours on the steam-bath. An equal volume of 95% alcohol was then added and the mixture allowed to cool, whereupon it solidified to a solid mass. This was dissolved in hot 95% alcohol, allowed to crystallize and filtered with suction. On recrystallization from 95% alcohol white needle-shaped crystals were obtained of m. p. 118°; yield 60–80%. Methylcreatinine picrate was prepared from the sulfate, m. p. 178–181°. Aurichloride, m. p. 173–175°.

Methylcreatinine.—Six-tenths gram of methylcreatinine sulfate and 0.5 g. of sodium bicarbonate were dissolved in a small amount of water and the solution evaporated to dryness on the steam-bath. The methylcreatinine was extracted with absolute alcohol and evaporated to crystallization *in vacuo*. Recrystallization from acetone gave white needles, m. p. 80°, hygroscopic and very soluble in water.

Creatinine Ethyl Sulfate.—Thirty-five cc. of ethyl sulfate was added to 10 g. of creatinine on a boiling water-bath over a period of one hour. The mixture was allowed to remain on the bath for two more hours after which it was let stand overnight. A crystalline mass was obtained the next morning which was washed with acetone and ether, then recrystallized from absolute alcohol; m. p. 146°; yield, 5 g.

Anal. Calcd. for $C_4H_7ON_3 \cdot C_2H_5OSO_3H$: N, 17.57; SO_4, 40.15. Found: N, 17.23, 17.35; SO_4, 40.60.

(5) Cornthwaite and Jordan, *ibid.*, **56**, 2733 (1934).

Ethylcreatinine Sulfate.—Several residues left after crystallization of the creatinine ethyl sulfate were collected and after standing several days a crystalline mass appeared. This was recrystallized from absolute alcohol and proved to be ethylcreatinine sulfate, m. p. 168°. It was converted to the picrate, m. p. 96°, hydrochloride, m. p. 264°, aurichloride, m. p. 153°, chloroplatinate, m. p. 190–217°, dec., corresponding to data given in the literature.

Anal. Calcd. for $C_6H_{12}ON_3 \cdot H_2SO_4$: N, 17.57; SO_4, 39.98. Found: N, 16.68, 17.00; SO_4, 40.41.

N^2-Methyl-5-benzalcreatinine.—Eight grams of methyl creatinine sulfate was dissolved in the least amount of water. Five grams of sodium carbonate was added and the mixture evaporated to dryness on the water-bath. The methylcreatinine was taken up in hot absolute alcohol and the solution evaporated to a sirup. Five cc. of redistilled benzaldehyde was added and the mixture heated in an oil-bath at 140–150° for three hours. The resulting product was treated with dilute hydrochloric acid, which caused the gummy mass to become hard. It was then washed with ether and suspended in sodium bicarbonate solution to destroy any acidity and filtered immediately, washed with cold water, and recrystallized from hot water. Pale flat needle-shaped yellow crystals were formed. These were filtered, washed with cold water and dried in a vacuum desiccator, m. p. 126°; mixed melting point with N^2-methyl-5-benzalcreatinine prepared by methylating benzalcreatinine, 126°.

N^2-Methyl-5-furfuralcreatinine.—Three grams of furfuralcreatinine was added to 15 cc. of methyl sulfate on the steam-bath and allowed to remain for one hour. The product was washed with ether, recrystallized from hot water and air dried, m. p. 132°; mixed melting point with N^2-methyl-5-furfuralcreatinine prepared by condensing furfural with methylcreatinine, 132°.

Summary

1. Creatinine has been methylated in good yield by using methyl sulfate. The use of ethyl sulfate gave poor results in the ethylation of creatinine, creatinine ethyl sulfate being the main product.

2. Further proof is presented for the structure of methylcreatinine.

3. Methylcreatinine sulfate, ethylcreatinine sulfate and creatinine ethyl sulfate have been described for the first time.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FORDHAM UNIVERSITY]

The Use of Synthetic Zeolites in the Isolation of Vitamin B_1. I. Experiments with Rice Polishings[1,2]

BY LEOPOLD R. CERECEDO AND DOUGLAS J. HENNESSY

Organic bases of moderate strength have been shown by Whitehorn[3] to be removed from solution when passed through a bed of permutit, the process being that of base exchange. Whitehorn further showed that the reaction could be reversed by passing a solution of a salt such as potassium chloride through the permutit layer, whereupon the organic base is removed and is found in the filtrate.

As far as we are aware only naturally occurring silicates, such as acid clays,[4] and fuller's earth,[5] have been used heretofore in the isolation of vitamin B_1. The findings of Whitehorn suggested the idea of using permutit or other zeolites of a similar composition. Certain advantages in using synthetic. zeolites offered themselves, the most important being the use of neutral salts for the recovery of the vitamin from them, provided the base exchange principle were found to be applicable. Other factors were: the known composition of the material, the means of controlling the size of the particles, the possibility of modifying the composition of the zeolites if necessary, and the possibility of regenerating the material following its use.

A systematic investigation was carried out to determine the best conditions for the removal of the vitamin from extracts by means of the zeolites and the most suitable way of recovering the substance from the zeolites. Once these were established, it was found that a single silver precipitation, followed by a precipitation with silicotungstic acid, yielded highly potent concentrates, from which on recrystallization crystals of pure vitamin hydrochloride could be obtained.

(1) Presented at the Chapel Hill meeting of the American Chemical Society, April, 1937.

(2) This investigation was begun in the early part of 1932.

(3) Whitehorn, *J. Biol. Chem.*, **56**, 751 (1923).

(4) Jansen and Donath, *Mededeel. Dienst Volksgezondheit Nederland Indië*, pt. 1, 186 (1926); Ohdake, *Proc. Imp. Acad. Tokyo*, **7**, 102 (1931); Van Veen, *Rec. trav. chim.*, **50**, 610 (1931).

(5) Windaus, Tschesche, Ruhkopf, Laquer and Schultz, *Z. physiol. Chem.*, **204**, 123 (1932); Seidell and Smith, THIS JOURNAL, **55**, 3380 (1933); Williams, Waterman and Keresztesy, *ibid.*, **56**, 1187 (1934).