[CONTRIBUTION FROM KENT CHEMICAL LABORATORY, UNIVERSITY OF CHICAGO]

BENZALCREATININE AND RELATED COMPOUNDS

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Creatine and creatinine have recently[2] become much more available for synthetic work. As one of us[3] has shown the suitability of the condensation products of glycocyamidines with benzaldehyde as tools in the study of the methylation of glycocyamidine, it seemed desirable to attempt to extend this method to creatinine derivatives. It also seemed likely that the aldehyde condensation products of creatinine might provide a convenient means of obtaining α-methylamino acids.

Although the alkylation of glycocyamidine and of creatinine has received considerable attention, the two methods of proof that have been offered for the structures of the derivatives obtained seem to be quite without value. For a detailed discussion of this point, reference may be made to the paper by Johnson and Nicolet already cited.

An outline of the synthetic work involved may well accompany the discussion of its application to these problems. The method of Erlenmeyer, Jr.,[4] for the preparation of acetyl-5-benzalcreatinine (I),[5,6] was improved to give an 80% yield. Hydrolysis with acids readily gave 5-benzalcreatinine (II), but (I) may be used directly for many purposes. For instance, reduction (and hydrolysis) of (I) with hydriodic acid (tin and hydrochloric acid can also be used) gave 5-benzylcreatinine (III) in 66% yield.

Intensive hydrolysis of (III) with hot barium hydroxide solution gave N-methylphenylalanine (yield, 44%); the hydrolysis could also be so controlled as to give a good yield of 1-methyl-5-benzylhydantoin (IV),

[1] The material here presented was used by Edward D. Campbell in partial satisfaction of the requirements for the degree of Doctor of Philosophy at the University of Chicago, 1924.

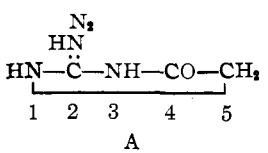
[2] Graham Edgar, *Chem. Met. Eng.*, **24**, 485 (1922).

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

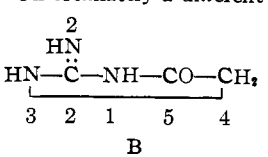
[4] Erlenmeyer, Jr., *Ann.*, **284**, 49 (1895).

[5] No direct evidence is available for the position assigned to the acetyl group.

[6] The numbering system used here for the glycocyamidine ring is that adopted by *Chemical Abstracts*, and is illustrated in Formula A. Unfortunately a different system

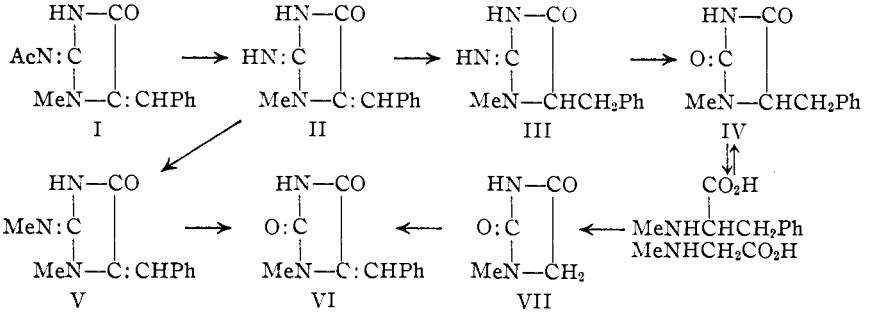


A



B

(Formula B) has been used in many publications, particularly in the numerous publications of Johnson and his co-workers, so that one must guard against confusion of names.



which was also synthesized from methylphenylalanine for comparison. The isolation of (IV), rather than the corresponding hydantoic acid, in this gentler hydrolysis, although no acid stronger than carbonic acid was used in working up the product, indicates that the hydrolysis took place without opening of the ring.

The preparation of N-methylphenylalanine just described gives an over-all yield of 22% from creatine in three steps. Considering the present availability of the starting material, this procedure may be found to compare favorably with the other methods available.[7] There seems little doubt that equal success would be attained in the use of other aromatic aldehydes in the preparation of analogous methylamino acids.[8]

The methylation of (II) with methyl iodide and alkali gave the methylbenzalcreatinine (V), the structure of which seems to follow definitely[9] from the fact that hydrolysis converted it nearly quantitatively to 1-methyl-5-benzalhydantoin (VI), with the liberation of methylamine apparently unaccompanied by any ammonia. The formation of (V) was unexpected, since the analogous alkylation of 5-benzalglycocyamidine resulted[3] in the formation of 3-methyl-5-benzalglycocyamidine. It seems, however, to be well established that it is a matter of somewhat extreme difficulty to open the ring in any of the unreduced aldehyde condensation products of hydantoins or of glycocyamidines by the action of alkali and, on the other hand, fairly intensive action of acids is in general necessary to close such rings. We therefore do not consider the evidence here offered for the structure of this derivative as open to the same ob-

[7] (a) Friedmann and Gutmann, *Biochem. Z.*, **27**, 491 (1911); (b) Fischer and Lipschitz, *Ber.*, **48**, 360 (1915).

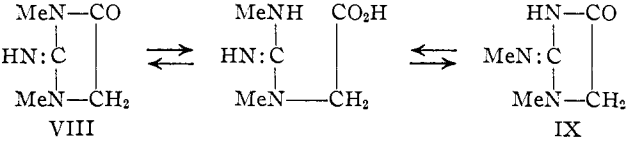
[8] Johnson and Nicolet, *Am. Chem. J.*, **47**, 459 (1912), recommended the synthesis of such compounds from hydantoin, and used N-methyltyrosine as an illustration. The substitution of creatine for hydantoin as a starting material eliminates the necessity for the introduction of two methyl groups.

[9] There is one bit of contrary evidence. The substance (V) is practically insoluble in cold aqueous alkali, which would suggest replacement of the hydrogen in position 3; but benzalcreatinine is itself only slightly soluble under the same conditions, and the evidence based on hydrolysis accordingly appears to us conclusive.

jections as have been raised[3] against the use, in otherwise similar cases, of evidence of structure from the alkaline hydrolysis of the glycocyamidine derivatives themselves.

The identity of (VI) was confirmed by its synthesis from the 1-methylhydantoin (VII) prepared from sarcosine. It was also obtained by the hydrolysis of (I) or (II).[10]

The methylation of creatinine by the method used by Korndörfer[11] and by Kunze[12] gave a methylcreatinine (VIII) or (IX) with the properties described by them. Unfortunately, all efforts to condense this product with benzaldehyde for comparison with (V) failed. As it has been shown[13] that N^2-methylglycocyamidine, when the ring is opened by treatment with alkali and then closed again by digestion with acid, gives a considerable amount of the isomeric 3-methylglycocyamidine, and as there was still reason to hope that at least one of the methylcreatinines would be capable of condensation with benzaldehyde, an attempt was made to "rearrange" our methylcreatinine in the sense indicated:



VIII IX

The product obtained after opening and again closing the ring still failed to condense with benzaldehyde under any of the conditions tried. It was, therefore, impossible to obtain any direct evidence as to the structure of the methylation products of creatinine itself by the method planned.

The failure of the methylcreatinines to undergo condensation, while rather unexpected, is not at all without precedent. Thus, Wheeler and Hoffman[14] obtained easy condensation with 3-phenylhydantoin, but none at all with the 1-phenyl and 1,3-diphenyl derivatives. Similarly, Biltz[15] was unable to carry out the reaction with 1,3-dimethylhydantoin, and in the case of 1-methylhydantoin we obtained less than half the usual yield. For some reason not yet adequately understood the accumulation of substituents on the nitrogens interferes more or less completely with this type of condensation.

[10] This hydrolysis method is the best available for the preparation of 1-methylated aldehyde condensation products of hydantoin, as these derivatives cannot be directly alkylated in position 1 until after the hydrogen in position 3 is replaced. On the other hand, 1-methylhydantoin requires sarcosine for its synthesis, and gives poor yields on subsequent condensation.

[11] Korndörfer, *Arch. Pharm.*, **242**, 641 (1904).

[12] Kunze, *ibid.*, **248**, 578 (1910).

[13] Ref. 3, p. 2426.

[14] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368 (1911).

[15] Biltz, *Ber.*, **45**, 1673 (1912).

Experimental Part

N-Acetyl-5-benzalcreatinine (I).—A mixture of 5 g. of creatine, 4 g. of benzaldehyde, 15 g. of fused sodium acetate, 50 cc. of glacial acetic acid and 15 cc. of acetic anhydride was refluxed in an oil-bath for an hour and the warm solution then poured into 1 liter of water. Seven grams (80%) of the acetyl-benzalcreatinine separated. It formed golden yellow needles from alcohol and melted at 208–209°. The same product was obtained in smaller yield by the method of Erlenmeyer, Jr.,[4] but his m. p. of 213° could not be attained.

Anal. Calcd. for $C_{13}H_{13}O_2N_3$: N, 17.28. Found: 17.19, 17.38, 17.27.

Dihydrochloride of 5-Benzalcreatinine.—The acetyl derivative was digested for two hours with an excess of 30% hydrochloric acid on the steam-bath and the solution then evaporated to dryness. From water containing a considerable amount of hydrochloric acid, the product separated in bright yellow crystals as the dihydrochloride.

Anal. Calcd. for $C_{11}H_{11}ON_3.2HCl$: N, 15.33. Found: 15.67, 15.82.

A portion of the second mole of hydrochloric acid is very easily lost by hydrolysis.

5-Benzalcreatinine (II).—The hydrochloride was dissolved in 40 parts of water and precipitated with excess of ammonium hydroxide. The product crystallized from alcohol in yellow flakes which darkened near 225° and melted with effervescence at 244°. It retained water tenaciously.

Anal. Calcd. for $C_{11}H_{11}ON_3$: N, 20.89. Found: 20.62, 20.51.

5-Benzylcreatinine (III).—Five grams of acetylbenzalcreatinine, 2 g. of red phosphorus, and 25 cc. of hydriodic acid (sp. gr. 1.7) were boiled for five hours under reflux; 6.8 g. of iodine was then added and boiling continued for five hours. The solution was evaporated nearly to dryness, the residue extracted with 100 cc. of hot water, and the resulting solution filtered. Concentration and cooling of the filtrate caused almost no separation of solid. Ammonium hydroxide in excess precipitated 2.9 g. (66%) of benzylcreatinine. From the filtrate 0.3 g. additional could be isolated, but this is not recommended. The substance crystallized from alcohol or water in white flakes melting with some decomposition at 282°.

Anal. Calcd. for $C_{11}H_{13}ON_3$: N, 20.68. Found: 20.54, 20.68.

The same substance was obtained when acetylbenzalcreatinine was boiled for six hours with 40 parts of 20% hydrochloric acid and a three-fold excess of tin. The solution was evaporated nearly to dryness, the residue taken up in 100 cc. of boiling water, excess of ammonium hydroxide added, and the solution filtered hot from precipitated tin compounds. The filtrate yielded benzylcreatinine (52%).

Hydrolysis of 5-Benzylcreatinine; N-Methylphenylalanine.—In an apparatus similar to that used for Kjeldahl distillations, except that provision was made for the continuous addition of water to replace that which distilled, 5 g. of benzylcreatinine and 40 g. of barium hydroxide in 50 cc. of water were boiled for ten hours. The ammonia, which was evolved continuously, was collected in standard acid, and at this time amounted to 2 molar proportions for the material used. The reaction mixture was diluted to 400 cc., and carbon dioxide was passed in until no more barium carbonate precipitated. When the solution was filtered and the filtrate concentrated to 10 cc., 1.8 g. of N-methylphenylalanine separated on cooling as clusters of fine, white needles. It sublimed with very little decomposition at 252–254°.[16]

Partial Hydrolysis of 5-Benzylcreatinine; 1-Methyl-5-benzylhydantoin (IV).—Using the same apparatus as in the preceding hydrolysis, 5 g. of benzylcreatinine was

[16] Friedmann and Gutmann, *Biochem. Z.*, **27**, 491 (1910), also report sublimation with slight decomposition, 252–254°.

heated with 3 g. of barium hydroxide in 50 cc. of water until 1 molar proportion of ammonia had collected in the distillate (four hours). The mixture, worked up as before, gave 3.0 g. of 1-methyl-5-benzylhydantoin, which after purification melted at 106°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.72. Found: 13.63, 13.80.

The same substance was prepared in 50% yield by the action of potassium cyanate on an acidified solution of N-methyl phenylalanine and subsequent digestion with hydrochloric acid. A mixture of the two products also melted at 106°.

1-Methyl-5-benzalhydantoin (VI).—By a similar hydrolysis procedure, 5 g. of acetylbenzalcreatinine and 35 g. of barium hydroxide in 50 cc. of water required ten hours' boiling for the evolution of 1 mole of ammonia. The solution yielded 4.0 g. of 1-methyl-5-benzalhydantoin as light yellow flakes melting at 193–194°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.87. Found: 13.66, 13.88, 13.70.

When sarcosine was converted to 1-methylhydantoin (m. p. 156°) and the latter condensed with benzaldehyde by the usual method, the same substance was obtained. A mixture of the two products also melted at 193–194°. It is of interest that, in three experiments, the average yield of benzal derivative from 1-methylhydantoin was only 32%.

1,3-Dimethyl-5-benzalhydantoin.—The methylation of 2 g. of 1-methyl-5-benzalhydantoin with methyl iodide and sodium hydroxide in hot alcohol gave 1.0 g. of the dimethyl derivative, which, recrystallized from hot water, melted at 92°. It was not soluble in aqueous alkali.

N^3-Methyl-5-benzalcreatinine (V).—A solution of 5 g. of benzalcreatinine, 1.1 g. of sodium hydroxide and 5 g. of methyl iodide in 200 cc. of alcohol was heated until it became neutral (ten hours) and then evaporated to dryness. Extraction with 300 cc. of cold 5% sodium hydroxide solution dissolved 1.8 g. of unmethylated benzalcreatinine, which separated on acidification. The residue, insoluble in cold alkali, was crystallized from hot water and gave 2.9 g. of methylbenzalcreatinine as light yellow flakes melting at 129°.

Anal. Calcd. for $C_{12}H_{13}ON_3$: N, 19.53. Found: 19.75, 19.62.

The same product was obtained when 1.5 g. of benzalcreatinine, 1.3 g. of methyl iodide and 3 cc. of methyl alcohol were heated for three hours at 100° in a bomb tube. In this case no alkali-soluble material remained.

Hydrolysis of N^3-Methyl-5-benzalcreatinine.—When a solution of 6 g. of the methylated benzalcreatinine just described and 40 g. of barium hydroxide in 60 cc. of water was boiled for two hours, 1 mole of amine appeared in the distillate. This was shown to be methylamine by its practically quantitative conversion to dimethyloxamide. No oxamide which would indicate the initial presence of ammonia could be detected.

The hydrolysis mixture was diluted with water and filtered hot. The filtrate, after removal of barium salts and concentration, gave 0.1 g. of 1-methyl-5-benzalhydantoin. The original insoluble portion was treated with warm dilute hydrochloric acid until solution was complete; excess of ammonium hydroxide then precipitated 4.5 g. of the methylbenzalhydantoin.

Methylation of Creatinine.—A mixture of 2 g. of creatinine, 2.6 g. of methyl iodide and 3 cc. of methyl alcohol (when the latter was omitted practically no reaction took place) was heated in a bomb tube for three hours at 100°. When the resulting solution was slightly concentrated, 2.0 g. of methylcreatinine hydriodide separated. This salt crystallized from alcohol in pale yellow needles which melted at 211–212°, and was presumably identical with the product similarly obtained by Korndörfer[11] and by Kunze.[12]

This salt was dissolved in water and shaken with an excess of precipitated silver

chloride. The methylcreatinine hydrochloride thus obtained melted with slight decomposition at 234–236°, as reported. All attempts to condense this product with benzaldehyde, either by the usual procedure or with longer heating and increased proportions of sodium acetate and of acetic anhydride, were completely unsuccessful.

At this stage it was thought worth while to show that the methylation could not have taken place with the introduction of a second methyl group on the 1-nitrogen. The methylcreatinine was accordingly hydrolyzed and found to yield sarcosine and methylamine. Since it was thus clear that the substance must have one of the two structures represented by VIII and IX, it was sought to convert it into a mixture of these two isomers (see discussion) in the hope that at least one of them might be condensed with benzaldehyde. The mixture obtained, however, gave no benzal derivative.

Summary

1. Benzalcreatinine and a number of new compounds derived from it have been described.

2. N-Methylphenylalanine may conveniently be prepared by the reduction and subsequent hydrolysis of benzalcreatinine.

3. Methylation of benzalcreatinine takes place first on the nitrogen atom in position 2. N-Methylcreatinine does not condense with benzaldehyde.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MCGILL UNIVERSITY]

THE POLYMERIZATION OF INDENE, CINNAMAL FLUORENE AND SOME DERIVATIVES OF INDENE

BY GEORGE STAFFORD WHITBY AND MORRIS KATZ

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Indene is known to be polymerizable by concentrated sulfuric acid, heat and other means.[1] The polymerizing agencies used in the present work were heat, antimony pentachloride and stannic chloride. The two latter were found to yield polymers higher than any previously obtained.[2] The molecular weight of the $SbCl_5$ product corresponded approximately to that of a molecule derived by the union of 15 indene molecules, while that of the $SnCl_4$ product corresponded approximately to the union of 25 indene molecules. Although these polymers are thus comparatively high, they do not show the properties of lyophilic colloids. Further, they do not represent chemical individuals but, rather, as was shown by fractionation, mixtures representing widely different degrees of polymeri-

[1] (a) Krämer and Spilker, *Ber.*, **23**, 3276 (1890); (b) **33**, 2260 (1900); (c) Weger, *Z. angew. Chem.*, **22**, 345 (1909); (d) Weger and Billmann, *Ber.*, **36**, 640 (1903); (e) Weissgerber, *Ber.*, **44**, 1438 (1911); (f) Guntz and Minguin, *Compt. rend.*, **152**, 373 (1911); (g) Ciamician and Silber, *Ber.*, **46**, 420 (1913); (h) Stobbe and Färber, *Ber.*, **57**, 1838 (1924); (i) Staudinger, *Ber.*, **59**, 3019 (1926); (j) Bruson, *Diss.*, Zürich (1925); (k) *Ber.*, **60**, 1094 (1927).

[2] Since the present work was complete some data on the polymeric product obtained from indene by $SnCl_4$ have been published by Staudinger, ref. 1 i.