THE FORMATION OF SYMMETRICAL DIAMINOKETONES BY THE ACTION OF ACETIC ANHYDRIDE ON ACETYL-N-METHYLAMINO ACIDS

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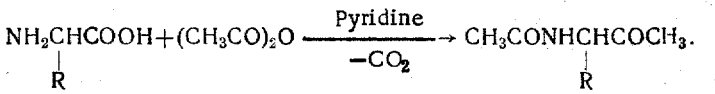
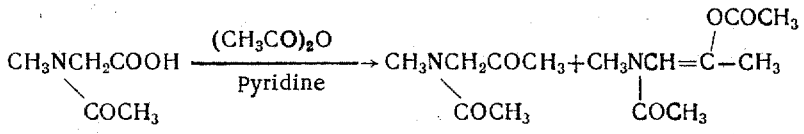
As reported previously [1], when tryptophans methylated at the NH_2 group react with acetic anhydride in glacial acetic acid solution, in addition to acetylamino acids the corresponding acetyldipeptides are formed. However, if abrine and 5-methoxyabrine are heated with pure acetic anhydride, more complex compounds of the peptide type are formed, the reaction being accompanied by the vigorous evolution of carbon dioxide. It might be assumed that in the latter case a transformation of the Dakin-West type takes place, i.e., the formation of acylaminoketones [2]:

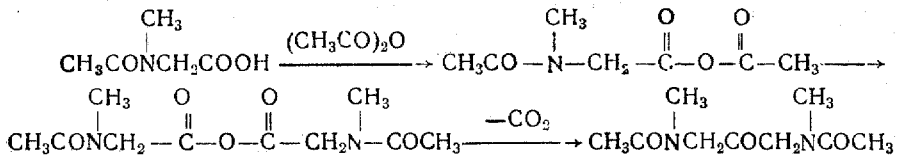


In actual fact, Wiley and Borum [3] have shown that, when it is heated with acetic anhydride in pyridine, acetylsarcosine is converted into a mixture of N-methylacetamidoacetone (I) and its enol acetate:



In the case of N-methylvaline and N-methylleucine, the homologs of N-methylacetamidoacetone are formed in low yields, and the bulk of the material is converted into a resin which has not been investigated [4].

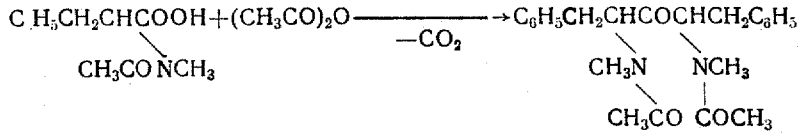
On repeating the reaction of acetylsarcosine with acetic anhydride, but in the absence of pyridine, we obtained a fraction with bp 117°-135° C/7 mm from which we have isolated N-methylacetamidoacetone (I), which was characterized by its IR spectrum, thin-layer chromatography on alumina, and the preparation of the 2, 4-dinitrophenylhydrazone. We did not detect the enol acetate of methylacetamidoacetone in our experiments. However, the reaction mixture contained a substance distilling at 200°-210° C/7 mm and crystallizing almost completely on standing, which proved to be N, N'-dimethyl-1, 3-di(acetamido)acetone (II), evidently formed by the following route:



A similar result was obtained with initially unacetylated sarcosine.

The formation of such symmetrical ketones in the Dakin-West reaction has not been reported previously, although the symmetrization of mixed anhydrides of acetylamino acids was recorded by Wieland et al. [5]. The aminoketone (II), in contrast to N-methylacetamidoacetone (I) and its enol acetate, is a colorless solid forming a 2, 4-dinitrophenylhydrazone. In the region of the carbonyl group absorption, the IR spectrum of this compound contains two bands, one of which (1732 cm^{-1}) is due to the stretching vibrations of the keto group while the other (1624 cm^{-1}) corresponds to the vibrations of a C=O group in an amide.

Similarly, by heating acetyl-N-methylphenylalanine with acetic anhydride we synthesized N, N'-dimethyl-2, 4-di-(acetamido)-1, 5-diphenylpentan-3-one (III), which was identified in the form of its 2, 4-dinitrophenylhydrazone:

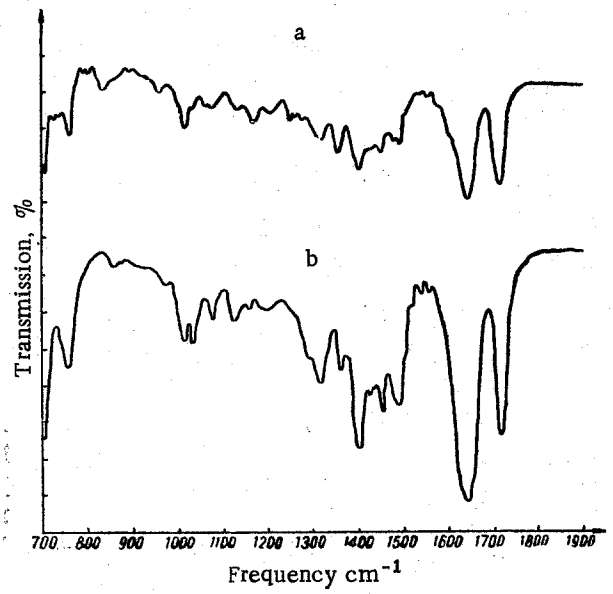


The reaction product, purified on a column of alumina, contained a small amount of an impurity whose R_f value was close to that of the main substance [0.42 and 0.49, respectively, Al_2O_3, benzene-acetone (5 : 1)]. By chromatographing 50 mg of this mixture in a thin layer of alumina it was possible to isolate in the form of noncrystallizing oils 27 mg of the aminoketone (III) and 7 mg of the by-product of the reaction. The IR spectrum of the ketone (III) (taken on a UR-10 instrument), as was to be expected, had two sharp peaks (figure a) corresponding to ketone (1715 cm^{-1}) and amide (1640 cm^{-1}) carbonyl groups. The spectrum of the by-product (figure b) was similar to the preceding one. It may be assumed that in this case in addition to symmetrization the formation of the unsymmetrical ketone takes place, or

else this second substance is a diastereomer of the aminoketone (III).

Thus, while in the reaction of acetylsarcosine with acetic anhydride the symmetrical and unsymmetrical ketones are formed in approximately equal amounts, in the case of acetylmethylphenylalanine the symmetrical ketone is the main reaction product (yield 80%).

The reaction that we have found is apparently characteristic for N-methylamino acids, since the nonmethylated amino acids form oxazolones on being heated with acetic anhydride [6]. This reaction may find application in the synthesis of difficultly accessible diaminoketones.



IR spectrum of N, N'-dimethyl-2, 4-di(acetamido)-1, 5-diphenylpentan-3-one (III) in KBr (a), and the by-product of the reaction of acetyl-N-methylphenylaniline with acetic anhydride in KBr(b).

Experimental

Acetylsarcosine. 26.7 g of sarcosine, 60 ml of glacial acetic acid, and 33.7 g of acetic anhydride were mixed. The reaction mixture became hot and the sarcosine gradually dissolved. The solution was heated with stirring for 1 hr at 100° C and was left to stand overnight. All the volatile substances were distilled off on a water bath in vacuum. The residue, which crystallized, was recrystallized from a mixture of ethyl acetate and alcohol (5 : 1) and was washed with ethyl acetate. This gave 28.8 g (73.3%) of acetylsarcosine with mp 130°–132° C. Literature data: mp 134°–134.5° C [3].

Reaction of acetylsarcosine with acetic anhydride. A mixture of 30 g of acetylsarcosine and 60 ml of acetic anhydride was boiled under reflux until the evolution of carbon dioxide ceased (1 hr; a check was made by bubbling the issuing gases through baryta water). The excess of acetic anhydride and the acetic acid were distilled off in vacuum on the water bath. The residue was fractionated in vacuum. Two fractions were isolated:

1. With bp 117°–135° C/7 mm, weight 9.6 g;
2. With bp 200°–210° C/7 mm (decomp.), weight 11.4 g.

The second fraction crystallized almost completely on standing. It was recrystallized from tetrahydrofuran to give 4.9 g (21.5%) of N, N'-dimethyl-1, 3-di(acetamido)acetone (II) with mp 105°–106° C. IR spectrum (paraffin oil): 1624 (amide C=O), 1732 (ketone C=O) cm^{-1}.

Found, %: C 54.19, 54.25; H 8.13, 7.95. Calculated for $C_9H_{16}N_2O_3$, %: C 54.05; H 8.05. When 0.2 g of 2, 4-dinitrophenylhydrazine and 0.2 g of the ketone (II) were boiled for 5 hr in 25 ml of absolute alcohol with the addition of three drops of concentrated hydrochloric acid, with subsequent evaporation to dryness in vacuum and recrystallization from 5 ml of absolute alcohol, 0.28 g (74%) of the 2, 4-dinitrophenylhydrazone with mp 123°–124° C was obtained.

Found, %: C 47.20, 47.36; H 5.56, 5.49. Calculated for $C_{15}H_{20}N_6O_9$, %: C 47.39; H 5.31.

The first fraction was distilled with steam until the water distilling over was neutral (to litmus) and then the substance remaining in the reaction flask, diluted with water, was extracted with ether in a liquid extractor for 15 hr. The

water was distilled off from the aqueous solution and the residue was distilled in vacuum. N-Methylacetamidoacetone (I) (4.1 g) was collected in the form of a colorless mobile liquid with bp 127°–128°C/10 mm, n_D^{20} 1.4632, R_f 0.28 [Al_2O_3, benzene-acetone (5:1)]. IR spectrum (paraffin oil): 1024, 1150, 1180, 1224, 1246, 1296, 1357, 1401, 1412, 1488; 1640 (amide C=O), 1723 (ketone C=O) cm^{-1}. Literature data: mp 98°–98.5°C/4 mm, n_D^{25} 1.4656 [3]. The ethereal extract, after the elimination of the solvent and the distillation of the residue in vacuum, gave another 1.7 g of the same substance with bp 127°–129°C/10 mm, n_D^{20} 1.4620, R_f 0.28 [Al_2O_3, benzene-acetone (5:1)], IR spectrum identical with the preceding one.

The total yield of pure ketone (I) was 5.8 g (19.6%). The 2,4-dinitrophenylhydrazone was obtained with a yield of 89–90%, mp 145°–147°C (from absolute alcohol). Literature data: mp 148°–149.5°C [3].

Acetyl-N-methylphenylalanine. With stirring, a solution of 1.5 ml of acetic anhydride in 5 ml of glacial acetic acid was added slowly to a solution of 1 g of N-methylphenylalanine [7] in 20 ml of glacial acetic acid heated to 50°–60°C. The clear colorless solution was left for a day. The acetic acid was distilled off in vacuum to dryness and the residue was dissolved in ether. The amino acid, which did not dissolve in the ether (0.42 g), was separated off and the filtrate was evaporated to dryness. The oily residue crystallized almost completely. After recrystallization from water, 0.36 g of colorless crystals of acetyl-N-methylphenylalanine was obtained. Evaporation of the filtrate gave another 0.05 g of the substance. The total yield was 0.41 g (57%, calculated on the N-methylphenylalanine that reacted), mp 144°–145°C (from alcohol). Literature data: mp 147°–148°C [9].

N,N'-Dimethyl-2,4-di(acetamido)-1,5-diphenylpentan-3-one (III). A solution of 4 g of acetylmethylphenylalanine in 10 ml of acetic anhydride was boiled for 40 min. The reaction was accompanied by vigorous evolution of carbon dioxide. The brown reaction mixture was diluted with 20 ml of water, carefully stirred, and left to stand overnight at room temperature. The solvent was distilled off in vacuum and the oily residue was dissolved in a small amount of benzene and adsorbed on a column of neutral alumina. Elution was carried out with a mixture of benzene and acetone (5:1), 15–20 ml fractions being collected and their composition being checked by thin-layer chromatography on alumina in the benzene–acetone (5:1) system. The fractions containing a substance with R_f values from 0.4 to 0.49 were combined and evaporated to dryness in vacuum. This gave 3.4 g of a yellow oil, part (1.4 g) of which was freed from colored impurities by preparative chromatography on plates of alumina and was then dissolved in 20 ml of absolute alcohol and boiled with 1 g of 2,4-dinitrophenylhydrazine and two drops of concentrated hydrochloric acid for 5 hr. The reaction mixture was cooled and the crystals which deposited were separated off. This gave 1.63 g of the 2,4-dinitrophenylhydrazone of N,N'-dimethyl-2,4-di(acetamido)-1,5-diphenylpentan-3-one with mp 129°–131°C (from a mixture of benzene and heptane). IR spectrum (paraffin oil): 676, 696, 700, 744, 760, 836, 840, 922, 1060, 1133, 1314, 1341, 1380, 1460, 1500, 1518, 1540, 1593, 1620, 1641 cm^{-1}.

Found, %: C 62.27, 62.17; H 5.73, 5.70; N 15.33, 15.43; mol. wt. 506 (modified Signer method [8]; solvent, methyl acetate; standard, di-n-octyl ketone). Calculated for $C_{29}H_{32}N_6O_6$, %: C 62.13; H 5.76; N 15.00; mol. wt. 560.

Summary

When acetyl-N-methylamino acids are heated with acetic anhydride, bis-acetyl derivatives of N,N'-dimethyl-α,α'-diaminoketones are formed.

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