The authors express their thanks to Mr. I. Iijima for his technical assistance.

Summary

Doebner reaction of naphthalene- or 3,4-dihydro-1,2-naphthalenedicarboxylic anhydride with malonic acid in pyridine provided a convenient method for 2-acetyl-1-naphthoic- or 2-acetyl-3,4-dihydro-1-naphthoic acid. The structures of the products were also established.

(Received November 28, 1963)

[Chem. Pharm. Bull. 12 (4) 497 ~ 499]

UDC 547.495.9 : 547.491

Takeo Ueda, Kiyoshi Takahashi, and Sachiko Kobayashi : Reaction of 1,1-(2,2'-Oxydiethyl)biguanide with Dicyanodiamide.

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Melander[1] reported that 1,1-(2,2'-oxydiethyl)biguanide hydrochloride (ABOB) showed a protective *in vivo* effect on mouse-adapted influenza A (PR 8) and B (Lee 1). However, the re-examination[2] with this reagent have proved that ABOB did not show any antiviral activity on influenza viruses in both experimental and clinical investigations. These conflicting results suggested that the effect of ABOB might be due to by-products and admixtures, which were formed in the course of reactions for synthesis of ABOB. Namely, on the supposition that when either dicyanodiamide or morpholine hydrochloride was in excess, either of those reactants possibly further reacted with the product (ABOB), afforded by the reaction of dicyanodiamide with morpholine hydrochloride, the reactions of ABOB with dicyanodiamide and ABOB with morpholine hydrochloride were investigated.

This paper is concerned with the reaction of ABOB with dicyanodiamide and that of ABOB with morpholine hydrochloride.

Reaction of 1,1-(2,2'-Oxydiethyl)biguanide with Dicyanodiamide

Under the same conditions as the synthetic procedure of ABOB from dicyanodiamide and morpholine hydrochloride,[3] a mixture of equimolar amounts of ABOB and dicyanodiamide was heated for 6 hr. at 160~180° in an oil bath. The reaction mixture, once melted to fluid, gradually solidified as a viscous mass, evolving ammonia gas. After reacting, the fusion mixture was divided into two parts, alcohol-soluble and alcohol-insoluble, in approximately equal quantities. From the former, ABOB and dicyanodiamide were obtained, while from the latter, a compound shaped in colorless needles, m.p. 242~244.5° (I).

The elementary analysis of the compound (I) gave an empirical formula, $C_7H_{12}ON_6$.

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1) B. Melander : Toxicology and Applied Pharmacology, **2**, 474 (1960); B. Melander : Antibiotics and Chemotherapy, **10**, 34 (1960).
2) G. G. Jackson, R. L. Muldon, L. W. Akers, O. Liu, G. C. Jhonson, C. Engel : "Antimicrobial Agents and Chemotherapy", 883 (1961).
3) S. L. Shapiro, V. A. Parrino, L. Freedman : J. Am. Chem. Soc., **81**, 3728 (1959).

Inspecting the infrared spectra of I shown in Fig.1, there exists the absorption, probably assigned to R-O-R bond, CH_2 group in moiety of morpholine, and several NH_2 groups.

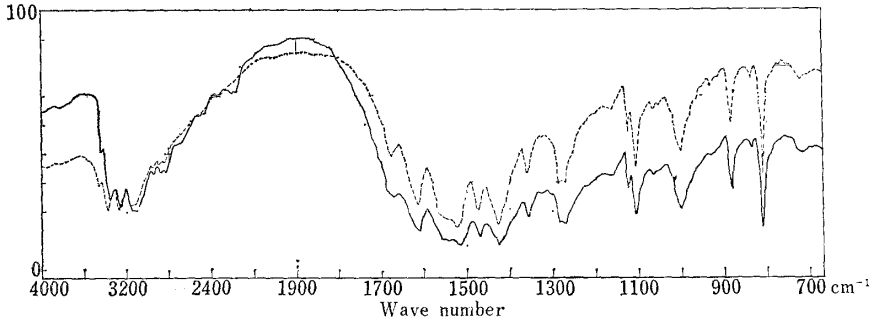

Fig. 1. Infrared Absorption Spectra of 2-Morpholino-4,6-diamino-*s*-triazine (in KBr disc)

——— authentic sample
– – – – – a compound obtained by reacting ABOB with dicyanodiamide.

From the above empirical formula, the assignment in the infrared absorption, and the other chemical properties of I, it can be reasonably assumed that I might be 2-morpholino-4,6-diamino-*s*-triazine.

On the other hand, 2-morpholino-4,6-diamino-*s*-triazine (II) was synthesized in conventional manner[4] from cyanuric chloride, ammonia, and morpholine as illustrated in Chart 1. In comparing the analytical data, infrared spectra, and chemical properties of I with those of II, they were completely superposed. Consequently, I was identified to be 2-morpholino-4,6-diamino-*s*-triazine.

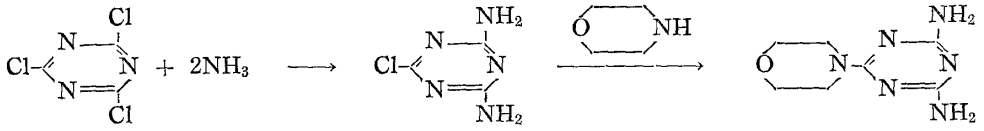

Chart 1.

Reaction 1,1-(2,2'-Oxydiethyl)biguanide with Morpholine Hydrochloride

By a method similar to that described in the reaction of ABOB with dicyanodiamide, a mixture of ABOB and morpholine hydrochloride was heated, but it was observed that any reaction did not take place, and the both reactants recovered almost quantitatively.

Antiviral Activity of 2-Morpholino-4,6-diamino-*s*-triazine

2-Morpholino-4,6-diamino-*s*-triazine was examined as to its activity on the PR-8 strain of influenza A virus in mice. The experimental procedures were the same to those described in the previous report.[5] This agent, however, did not show any effect on the virus. Therefore, it may be said that some compound other than 1,1-(2,2'-oxydiethyl)biguanide and 2-morpholino-4,6-diamino-*s*-triazine should be searched, if ABOB had truly exerted an antiinfluenzal effect.

Experimental

Thermal Reaction of 1,1-(2,2'-Oxydiethyl)biguanide with Dicyanodiamide——A mixture of 10.0 g. (0.05 mole) of ABOB and 4.3 g. (0.05 mole) of dicyanodiamide was heated with stirring for 6 hr. in an oil bath kept at 160~180°, until to solidify as a viscous mass. After cooling, the reaction mass was dissolved

4) D.F. Walker, Y. J. L'Italien, W.M. Pearlman, C.K. Banks : J. Am. Pharm. Assoc., **39**, 393 (1950).
5) K. Takahashi, M. Muraoka, T. Ueda : This Bulletin, **11**, 601 (1963).

in EtOH. The EtOH-insoluble material was collected by filtration, and the recrystallization from hot water yielded 2.7 g. of colorless needles, m.p. 242~244.5°, not depressed by mixture with the authentic sample synthesized from cyanuric chloride. *Anal.* Calcd. for $C_7H_{12}ON_6$: C, 42.85; H, 6.12; N, 42.85. Found: C, 42.43; H, 6.32; N, 43.01.

Synthesis of 2-Morpholino-4,6-diamino-*s*-triazine

2-Chloro-4,6-diamino-*s*-triazine——To 70 ml. of 12% NH_3-H_2O, 9.2 g. of cyanuric chloride suspended in hot Me_2CO was added with agitation. The reaction mixture was warmed at 40~45° for 4 hr. under stirring. After reacting, the precipitate was collected, washed with cold H_2O until no more Cl^- ion appeared, recrystallized from hot H_2O, and submitted to the next reaction without further purification.

2-Morpholino-4,6-diamino-*s*-triazine——To 1.7 g. of morpholine in 10 ml. of H_2O, 1.5 g. of 2-chloro-4,6-diamino-*s*-triazine was added and refluxed at 130~140° in an oil bath during 3 hr. The product was collected by filtration, and recrystallized from hot H_2O to give colorless needles, melted at 243~245°. *Anal.* Calcd. for $C_7H_{12}ON_6$: N, 42.85. Found: N, 42.95.

Summary

Thermal reaction of equimolar amounts of 1,1-(2,2'-oxydiethyl)biguanide with dicyanodiamide afforded a compound (I) other than the both reactants. The analytical data, infrared spectra, and chemical properties of I agreeded closely with those of 2-morpholino-4,6-diamino-*s*-triazine, synthesized by conventional manner from cyanuric chloride, ammonia, and morpholine. Consequently, I was verified to be 2-morpholino-4,6-diamino-*s*-triazine.

(Received September 11, 1963)

[Chem. Pharm. Bull. 12 (4) 499 ~ 501]

UDC 547.464.2 : 547.457.1

Teiichiro Ito: Reactions of Trifluoroacetic Acid with N-Benzyloxycarbonyl-tetra-O-acetyl-D-glucosamine.

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In the field of aminosugar chemistry, the carbobenzyloxy group has often been used to protect the amino group and it is usually removed by catalytic hydrogenation.[1] In our studies on sulfur-containing aminosugars,[2] some of the catalytic hydrogenation of carbobenzyloxy to remove the protective group was unsuccessful, and other methods were studied.

In 1959, F.Weygand and W. Steglich[3] described that the benzyloxycarbonyl groups of amino acids or peptides could be cleaved by refluxing in trifluoroacetic acid in good yield. Therefore this reaction was chosen in the decarbobenzyloxylation of 2-benzyloxycarbonylamino-2-deoxy-1,3,4,6-tetra-O-acetyl-β-D-glucopyranose (N-benzyloxycarbonyl-1,3,4,6-tetra-O-acetyl-β-D-glucosamine) (I), as a model compound.

By the treatment of the compound (I) with trifluoroacetic acid at 70° for 15 minutes, the reaction product was isolated as needle crystals, which, however, was not the expected

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1) cf. *a*) C. G. Greig, D. H. Leaback, P. G. Walker: J. Chem. Soc., **1961**, 879. *b*) C. L. Stevens, K. Nagarajan: J. Med. Pharm. Chem., **5**, 1124 (1962). *c*) J. D. Dutcher, D. R. Walters, O. Wintersteiner: J. Org. Chem., **28**, 995 (1963).
2) The previous report. T. Ito, T. Ishii: Agr. Biol. Chem., **27**, 423 (1963).
3) F. Weygand, W. Steglich; Z. Naturforsch., **14b**, 472 (1959).