was evaporated to dryness. One ml. of Ac_2O was added and heated on a boiling water bath for 2 hr. The mixture was evaporated under reduced pressure to dryness and the residue was dissolved in benzene. It was purified by chromatography on Al_2O_3 column using benzene as the eluent. White prisms, 30 mg., m.p. $130\sim 131^\circ$, were obtained from benzene eluate. *Anal.* Calcd. for $\text{C}_{11}\text{H}_{12}\text{ON}_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.10; H, 6.50; N, 14.76. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 2250 ($\text{C}\equiv\text{N}$), 3360, 1650 and 1586 ($-\text{CONH}-$), 757 (*o*-substituted benzene). It was confirmed to be cyanoethyl-*o*-acetanilide by admixture and comparison of their IR spectra.

Fifty mg. of light brown needles, m.p. $180\sim 190^\circ$, was obtained from a part of CHCl_3 eluate of the silica-gel chromatography. Recrystallization from benzene gave colorless needles, m.p. $195\sim 196^\circ$. *Anal.* Calcd. for $\text{C}_9\text{H}_7\text{ON}$: N, 9.65. Found: N, 9.69. Mixed melting point determination and comparison of IR spectra established that this substance was identical with carbostyryl.

The author expresses his deep gratitude to Prof. Emeritus E. Ochiai and Prof. T. Okamoto of University of Tokyo for their kind guidances, to Prof. T. Kosuge of Shizuoka College of Pharmacy for his valuable advices, to President T. Owada, Vice-President T. Tanaka, Managing Director K. Oga, Director T. Sakata and Dr. H. Okeda of Nippon Soda Co., Ltd. for helpful encouragement. He is also indebted to Miss Y. Saito for elemental analyses.

Summary

In oxidation of 2-methylaminoquinoline with hydrogen peroxide, *cis*-2-nitrocinnamionitrile and a small amount of carbostyryl were obtained. And a reaction mechanism was proposed.

(Received January 12, 1961)

[Chem. Pharm. Bull.
12 (3) 352 ~ 356]

UDC 547.857'128 : 612.398.145

52. Takuzo Nishimura and Issei Iwai : Studies on Synthetic Nucleosides.

I. Trimethylsilyl Derivatives of Pyrimidines and Purines.

(Research Laboratories, Sankyo Co., Ltd.*¹)

Recently, a great attention has been drawn to the studies of organosilicon compounds containing the reactive Si-N linkage. Birkofer, *et al.*¹⁾ reported that N-acylated heterocyclic compound were easily obtained by the reaction of their N-trialkylsilyl derivatives with acylchlorides.

Authors developed a new synthetic method for nucleosides using trimethylsilyl derivatives of pyrimidines and purines, namely fusion of acylhalogeno sugars with these silyl compounds gave acylated nucleosides in good yields. These results will be reported in the following papers.

This paper describes the preparation and properties of trimethylsilyl derivatives of pyrimidines and purines.

Chart 1.

*¹ 1-888 Nishi-shinagawa, Shinagawa-ku, Tokyo. (西村卓三, 岩井一成).
1) L. Birkofer, H.P. Khlthau, A. Ritter : Chem. Ber., 93, 2804 (1960).

Generally, N-trialkylsilyl compounds are synthesized by treatment of trialkylhalosilane with amines or their metal salts,²⁻⁵⁾ or by exchange reaction of trialkylsilylamine with the other amines.^{6,7)} The authors prepared N-trimethylsilyl derivatives of pyrimidines and purines by a procedure of Birkofer, *et al.* which in past has been extensively used for the preparation of trimethylsilyl-N-heterocyclic compounds (IV).

The trimethylsilyl derivatives of the bases such as uracil, thymine, cytosine, N-acetylcytosine, adenine, N-benzoyladenine, guanine, hypoxanthine and xanthine were obtained in good yields, by treatment with hexamethyldisilazane (III)^{2,8)} or trimethylchlorosilane-triethylamine (II) in benzene or dioxane.

Pyrimidine and purine bases are sparingly soluble in organic solvents and have rather high melting points. On the other hand trimethylsilyl derivatives of these bases were distillable liquids or crystals with low melting points. Moreover, they were easily soluble in non polar solvents such as benzene, toluene and carbon tetrachloride. Fessenden and Crow⁵⁾ reported that N-trimethylsilylpyrrole was very stable in hot ethanol but it rapidly decomposed to recover the pyrrole by addition of catalytic amount of acids or bases. However, the silyl derivatives of pyrimidines and purines are completely decomposed with alcohol or water even under a neutral condition to regenerate the starting bases. The number of trimethylsilyl residues attached to the bases can be calculated from the results of the loss in weight on decomposition by aqueous ethanol. The results showed that these compounds were bis-trimethylsilyl derivatives except the guanine and xanthine which were tris-trimethylsilyl derivatives as shown in Table 1.

TABLE I. Physical Properties and Yields of the Trimethylsilylpyrimidines and -purines

Compound	b.p. (°C/mm. Hg)	m.p. (°C)	Yield ^{a)} (%)
Bis(trimethylsilyl)uracil	116/12	31~33	72
Bis(trimethylsilyl)thymine	124/14	63~65	89
Bis(trimethylsilyl)cytosine	168/30	122~123	69
Bis(trimethylsilyl)-N-acetylcytosine	137~139/6	62~68	71
Bis(trimethylsilyl)adenine	137/0.8	84~87	91
Bis(trimethylsilyl)-N-benzoyladenine	177~183/8 × 10 ⁻⁴	—	75
Bis(trimethylsilyl)hypoxanthine	135~142/0.8 ^{b)}	71~74	87
Tris(trimethylsilyl)guanine	167~168/1	—	88
Tris(trimethylsilyl)xanthine	163/1.5	87~90	77

a) Based on pyrimidines or purines reacted

b) Bath temperature

In the infrared spectra of silyl pyrimidines, the absorption bands at 1070~1050 cm⁻¹ caused by O-Si(CH₃)₃⁹⁾ were observed. Furthermore, the absorption spectrum in region of 1600~1500 cm⁻¹ was quite similar to that of 2,4-diethoxypyrimidine. On the basis of infrared data Birkofer, *et al.*¹⁰⁾ concluded that the silyl compound obtained by treating 5,6-

Chart 2.

- 2) R. O Sauer, R. H. Hasek : J. Am. Chem. Soc., **68**, 241 (1946).
- 3) R. M. Pike : J. Org. Chem., **25**, 232 (1961).
- 4) S. H. Langer, S. Connell, I. Wender : *Ibid.*, **23**, 50 (1958).
- 5) R. Fessenden, D. F. Crow : *Ibid.*, **25**, 598 (1960).
- 6) E. Larsson, C. G. Carlsson : Acta Chem. Scand., **4**, 45 (1950).
- 7) E. Larsson, R. E. I. Marion : *Ibid.*, **5**, 1173 (1951).
- 8) Inorganic Synthesis, vol. 5, p. 55.
- 9) G. R. Wilson, A. G. Smith, F. C. Ferris : J. Org. Chem., **24**, 1717 (1959).
- 10) L. Birkofer, H. P. Klthau, A. Ritter : Chem. Ber., **93**, 2810 (1960).

diaminouracil with hexamethyldisilazane has an aromatic ring system (V). This led that the structures for bis(trimethylsilyl)uracil and -thymine would be shown by VIIa and VIIb, respectively.

Chart 3.

In the case of bis(trimethylsilyl)cytosine and -N-acetylcytosine, their structural determination based on the infrared spectra was rather difficult because no conclusive assignment for the band due to Si-N linkage has been made.⁵⁾ Moreover, the band at 1750~1650 cm⁻¹ assigned for C=NH group of C-4 position was not observed. Therefore, bis(trimethylsilyl)cytosine and -N-acetylcytosine should be represented by the formulas VIc and VIId, respectively. In the case of purine derivatives, it appeared that one of the trimethylsilyl groups of the substituted purines would be attached to the N-9 of fused imidazole ring, because the absorption bands at 2700~2300 cm⁻¹ due to NH of imidazole ring were not observed and the silyl derivatives gave 9-glucoside by treatment of acyl-halogenose (following paper, Part III),¹¹⁾ and the other trimethylsilyl group(s) would be attached to hydroxy or amino groups because of absence of absorption bands at 1750~1650 cm⁻¹ caused by carbonyl or imino groups. Conclusively, trimethylsilyl purines have the structures as shown by Xa~e.

Fig. 1. Infrared Spectrum of Bis(trimethylsilyl)uracil (Liquid film)

Fig. 2. Infrared Spectrum of Bis(trimethylsilyl)adenine (Liquid film)

11) T. Nishimura, B. Shimizu : Agr. Biol. Chem., in press.

Chart 4.

As mentioned above, the silyl derivatives of pyrimidines and purines easily decomposed with alcohol and water to regenerate the original bases. Then it was shown that not only the Si-N but also Si-O linkage of the derivatives were easily cleaved even under the mild conditions without catalyst. The silyl compounds having these chemical properties are available for a new synthetic method of nucleosides which will be reported in following papers.

Experimental

Bis(trimethylsilyl)uracil (VIIa)—To a suspension of 11.3 g. of dry powdered uracil and [21.0 g. of trimethylchlorosilane in 100 ml. of dry dioxane was added dropwise the solution of 19.5 g. of triethylamine in dry dioxane with stirring under anhydrous condition at room temperature. After addition the stirring was continued for 7 hr. The precipitated mixture of triethylamine hydrochloride and uracil was filtered off and washed 3 times with each 20 ml. of dry dioxane. Filtrate and washings were collected and the solvent was removed. The resulting viscous oily residue was distilled under reduced pressure to give 15.7 g. of colorless oil VIIa, b.p. 116°/12 mm. Hg, m.p. 31~33°, IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 1255, 850, 758 (Si-C), 1070 (Si-O). UV: $\lambda_{\max}^{\text{dioxane}}$ 258 m μ . Treatment of the distillation residue and the filtered mixture with H₂O recovered 1.6 g. of uracil. *Anal.* Calcd. for C₁₀H₂₀O₂N₂Si₂: C, 46.79; H, 7.85; N, 10.92. Found: C, 46.68; H, 7.79; N, 11.36.

Bis(trimethylsilyl)thymine (VIIb)—To a suspension of 12.6 g. of dry powdered thymine and 21.7 g. of trimethylchlorosilane in 300 ml. of dry benzene was added dropwise the solution of 20.2 g. of triethylamine in benzene under mechanical stirring. By the similar procedure described above, oily product of bis(trimethylsilyl)thymine (VIIb, 22.2 g.) was obtained by distillation, b.p. 123~125°/13 mm. Hg, and the product crystallized on standing at room temperature, m.p. 63~65°, IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 1255, 850, 760 (Si-C), 1045 (Si-O). UV: $\lambda_{\max}^{\text{dioxane}}$ 266 m μ . *Anal.* Calcd. for C₁₁H₂₂O₂N₂Si₂: C, 48.83; H, 7.90; N, 10.35. Found: C, 48.37; H, 8.09; N, 10.74.

Bis(trimethylsilyl)cytosine (VIIc)—On the mixture of 5.0 g. of cytosine, 10.8 g. of trimethylchlorosilane and 10.0 g. of triethylamine, the similar procedure was applied as in the case of VIIb. Even after prolonged reaction period of 3 days, starting material cytosine remained unreacted. Oily product of VIIc (6.17 g.) was obtained, b.p. 168°/30 mm. Hg, m.p. 122~123°, IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 1255, 840, 754 (Si-C), 1063 (Si-O). UV: $\lambda_{\max}^{\text{dioxane}}$ 274 m μ . The unreacted cytosine (1.1 g.) was recovered. *Anal.* Calcd. for C₁₀H₂₁ON₃Si₂: C, 46.97; H, 8.28; N, 16.45. Found: C, 46.67; H, 7.99; N, 16.92.

Bis(trimethylsilyl)-N-acetylcytosine (VIIId)—From the mixture of 15.3 g. of N-acetylcytosine, 23.9 g. of trimethylchlorosilane and 22.0 g. of triethylamine, the crude product 25.6 g. was obtained, b.p. 143~165°/6 mm. Hg. Redistillation of the crude material at 137~138°/6 mm. Hg, afforded pure VIIId (18.1 g.) which crystallized at room temperature, m.p. 62~68°, IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 1260, 850, 760 (Si-C), 1070 (Si-O). UV: $\lambda_{\max}^{\text{dioxane}}$ 271 m μ . In this case also, 2.1 g. of N-acetylcytosine was recovered. *Anal.* Calcd. for C₁₂H₂₃O₂N₃Si₂: C, 48.40; H, 7.84; N, 14.17. Found: C, 48.18; H, 7.71; N, 14.11.

Bis(trimethylsilyl)adenine (IXa)—Dry powdered adenine (12.9 g.), trimethylchlorosilane (31.0 g.) and triethylamine (29.0 g.) were worked up in the similar way as VIIb. The reaction was continued for a day. The crude product (25.9 g.) was distilled at 128~138°/0.6~0.9 mm. Hg which was purified by redistillation, b.p. 134°/0.75 mm. Hg to yield 23.0 g. of colorless crystals, m.p. 84~87°, IR $\nu_{\max}^{\text{liquid}}$ cm⁻¹: 1260, 845, 760 (Si-C). UV: $\lambda_{\max}^{\text{dioxane}}$ 266 m μ . Adenine (0.7 g.) was recovered. *Anal.* Calcd. for C₁₁H₂₁N₅Si₂: C, 47.23; H, 7.57; N, 25.06. Found: C, 46.64; H, 7.39; N, 25.81.

Bis(trimethylsilyl)-N-benzoyladenine (IXb)—From 24.0 g. of N-benzoyladenine, 21.7 g. of trimethylchlorosilane and 20.2 g. of triethylamine, 25.3 g. of IXb was obtained by the same manner that described

for VIIb, b.p. $177\sim 184^{\circ}/8\times 10^{-4}$ mm. Hg. At room temperature, the product solidified, but not crystallized. On treatment of the distillation residue with aq. EtOH, 3.17 g. of N-benzoyladenine was recovered. IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 1260, 850, 762 (Si-C). UV: $\lambda_{\max}^{\text{dioxane}}$ 237 m μ . Anal. Calcd. for $\text{C}_{18}\text{H}_{25}\text{ON}_5\text{Si}_2$: C, 56.31; H, 6.57; N, 18.25. Found: C, 55.37; H, 6.47; N, 18.79.

Bis(trimethylsilyl)hypoxanthine (IXc)—The suspension of 4.2 g. of dry powdered hypoxanthine in 10.0 g. of hexamethyldisilazane was placed in 100 ml. round-bottom flask, and was refluxed for 12 hr. The crystals of hypoxanthine gradually dissolved and at the end of the reaction period, the mixture turned to homogeneous solution. After cooling the solvent was removed from the reaction mixture. A thick oily residue was distilled under reduced pressure to yield 7.5 g. of IXc, b.p. $113\sim 117^{\circ}/0.15$ mm. Hg. The product slowly crystallized at room temperature, m.p. $71\sim 74^{\circ}$, IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 1260, 850, 760 (Si-C). UV $\lambda_{\max}^{\text{dioxane}}$ m μ : 249, 252. Anal. Calcd. for $\text{C}_{11}\text{H}_{20}\text{ON}_4\text{Si}_2$: C, 47.06; H, 7.18; N, 20.08. Found: C, 46.60; H, 7.04; N, 20.35.

Tris(trimethylsilyl)xanthine (IXd)—Tris(trimethylsilyl) xanthine was prepared from xanthine using the 3.3 molar equivalents of trimethylchlorosilane and triethylamine for 3 days. From 5.0 g. of xanthine, 5.36 g. of IXd was obtained, b.p. $163^{\circ}/0.4$ mm. Hg, m.p. $86.5\sim 90^{\circ}$, IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 1260, 850, 760 (Si-C), 1070 (Si-O). UV $\lambda_{\max}^{\text{dioxane}}$ m μ : 237, 266. Unreacted xanthine (2.15 g.) was recovered. Anal. Calcd. for $\text{C}_{14}\text{H}_{28}\text{O}_2\text{N}_4\text{Si}_3$: C, 45.57; H, 7.67, N, 15.19. Found: C, 44.68; H, 7.38; N, 18.11.

Tris(trimethylsilyl)guanine (IXe)—Tris(trimethylsilyl)guanine was prepared from guanine using the 3 molar equivalents of trimethylchlorosilane and triethylamine for 4 days at 40° . From 10.0 g. of guanine, 18.2 g. of the product was obtained, b.p. $167\sim 168/1$ mm. Hg. and 1.9 g. of guanine was recovered. IR $\nu_{\max}^{\text{liquid}}$ cm^{-1} : 1260, 850, 760 (Si-C), 1060 (Si-O). UV $\lambda_{\max}^{\text{dioxane}}$ m μ : 250, 282. Anal. Calcd. for $\text{C}_{14}\text{H}_{29}\text{ON}_5\text{Si}_3$: C, 45.69; H, 7.96; N, 19.05. Found: C, 45.21; H, 7.90; N, 19.04.

Decomposition of Trimethylsilyl Derivatives—Above described trimethylsilyl derivatives were easily decomposed with aq. EtOH and all gave the starting pyrimidine and purine bases. After the decomposition of silyl derivatives, the weights of starting bases were measured.

From the decrease of the weight, the molecular weights of the derivatives and the number of trimethylsilyl residues were determined.

To the solution of the silyl derivatives in benzene was added aq. EtOH at room temperature. Immediately the decomposition occurred to deposit the crystals of the bases from the reaction mixture. For completion of the decomposition, the mixtures were heated in water bath at 70° for 1 hr. and then evaporated to dryness. The residual crystals were dried under reduced pressure at 110° for 1 hr. These results are summarized in Table II.

TABLE II.

Base	Weight of trimethylsilyl derivatives (g.)	Weight of deposited bases (g.)	Measured molecular weight	Number of trimethylsilyl groups attached
Thymine	0.4124	0.1910	272	2
Uracil	0.5018	0.2184	257	2
Cytosine	0.4025	0.1825	245	2
N-Acetylcytosine	0.2274	0.1184	294	2
Adenine	0.2289	0.1363	286	2
N-Benzoyladenine	0.1126	0.0683	393	2
Hypoxanthine	0.1856	0.0903	280	2
Guanine	0.2115	0.0894	358	3
Xanthine	0.6228	0.2582	367	3

The authors are indebted to Mr. M. Matsui, the director of this laboratory for his interest. The measurements of infrared spectra were carried out by Mr. H. Higuchi. Microanalyses were made by Dr. T. Onoe, Messrs. K. Ono, H. Nagashima and Misses K. Saito, N. Gonda, and H. Masuda.

Summary

Pyrimidine and purine bases were readily derived to trimethylsilyl derivatives by treatment with trimethylchlorosilane-triethylamine or hexamethyldisilazane. By the infrared investigation, it was clarified that the obtained derivatives possessed aromatic ring systems and physical properties of the product were reported.

(Received October 10, 1963)