Experimental

2′,3′,5′-Tri-O-acetyladenosine (IV)—Five g. of adenosine[4] (dried over P_2O_5 for 5 hr. at 3 mm./Hg) was added to 70 cc. of pyridine under vigorous stirring. When 5 g. of Ac_2O was added at room temperature, suspended adenosine dissolved gradually to form a yellow solution. After 1.5 hr. of stirring, the insoluble amorphous solid was removed by filtration (recovered as adenosine) and the filtrate was evaporated below 50° *in vacuo*. Residual syrup was taken up in $CHCl_3$, dried (Na_2SO_4), evaporated *in vacuo*, and recrystallized from EtOH to 4.1 g. of (IV), m.p. 166～167°. λ_{max}^{EtOH} 258.0 mμ (λ_{max} of 6-acetamino compound, 283～284 mμ).

2′,3′,5′-Tri-O-acetylinosine (V)—A clear solution was obtained from 1.5 g. of (IV) dissolved in AcOH (4 cc.)-H_2O (15 cc.) mixture, 0.5 g. of $NaNO_2$ was dissolved into this and the mixture was set aside at room temperature for 48 hr. Gentle bubbling of the yellow reaction mixture almost ceased at the end of this period. UV absorption spectrum after 20 hr. showed λ_{max} at 244.9 mμ. The solvent was removed *in vacuo* and the residue was extracted with hot dehyd. EtOH. Small, white needles, m.p. 236～238°, were obtained (800 mg.), which was identical with a sample derived from inosine. When recrystallization was difficult, $CHCl_3$-extraction was employed for total removal of AcOH and pyridine.

2′,3′,5′-Tri-O-acetylthioinosine (VI)—300 mg. of (IV) was dissolved in dry pyridine and 800 mg. of P_2S_5 was added. The whole was refluxed for 4 hr. until two layers, upper yellow and lower orange, separated. Both were poured into boiling water in order to destroy P_2S_5. Granular precipitate was collected by decantation, triturated with EtOH-H_2O, and filtered. Recrystallization from EtOH-Me_2CO gave 250 mg. of (VI), m.p. 214～216°. Mixed fusion with (V) melted at 205～208°. *Anal.* Calcd. for $C_{16}H_{18}O_7N_4S$: C, 46.88; H, 4.64; N, 13.67. Found: C, 47.26; H, 4.65; N, 13.21. λ_{max}^{EtOH} 315 mμ, λ_{min}^{EtOH} 250 mμ.

Deacetylation of (VI) with MeOH-NH_3—A solution of 100 mg. of (VI) dissolved in 20 cc. of MeOH was saturated with dry NH_3 at 0°. The whole was kept standing for 24 hr. at room temperature. Evaporation of the solvent under reduced pressure afforded a syrup containing colorless crystals (i) (10 mg.). When the syrup was triturated with MeOH, 35 mg. of (VI) was recovered. From the mother liquor, 20 mg. of thioinosine (VII) was obtained, which was confirmed by direct comparison with an authentic sample. (i) was found to be triacetyladenosine, m.p. 166°, λ_{max} 259 mμ.

Deacetylation of (VI) with NaOMe—2.5 g. of (VI) was dissolved in 185 cc. of anhyd. MeOH and 4 cc. of *N* NaOMe was added. On refluxing for 4.5 hr., a slightly yellow solution formed. The solvent was removed by evaporation *in vacuo*, 15 cc. of H_2O was added, and adjusted to pH 8.5 with AcOH. This solution was extracted with $CHCl_3$ and pH was adjusted to 4～5 (at this stage ca. 15 cc.). Brownish white precipitate which appeared was collected and dried. Recrystallization from EtOH gave cream-colored crystals, m.p. 208～210° (800 mg.), which was identified as thioinosine by direct comparison with an authentic sample.

(Received November 30, 1959)

4) Y. Mizuno, K. Nakamura, T. Ueda: Yakugaku Zasshi, **77**, 683(1957).

UDC 547.852.2.07

Hiroshi Igeta: Syntheses of Pyridazine Derivatives. IV.[1] Reaction of 3,6-Dimethoxypyridazine 1-Oxide with Phosphoryl Chloride.

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As reported in Part III[1] of this series, the reaction of 3-methoxypyridazine 1-oxide, in which the neighboring position of the N-oxide group is unsubstituted, with phosphoryl chloride yielded 3-methoxy-6-chloropyridazine. The present paper is a report on the reaction of 3,6-dimethoxypyridazine 1-oxide, in which *ortho* position of the N-oxide group is substituted with methoxyl group, with phosphoryl chloride.

When 3,6-dimethoxypyridazine 1-oxide[2] (I) was treated with phosphoryl chloride at room temperature, a chloro-dimethoxyl compound (II) was obtained. This chloro-dimethoxypyridazine was reacted with sodium methoxide in methanol and produced a trimeth-

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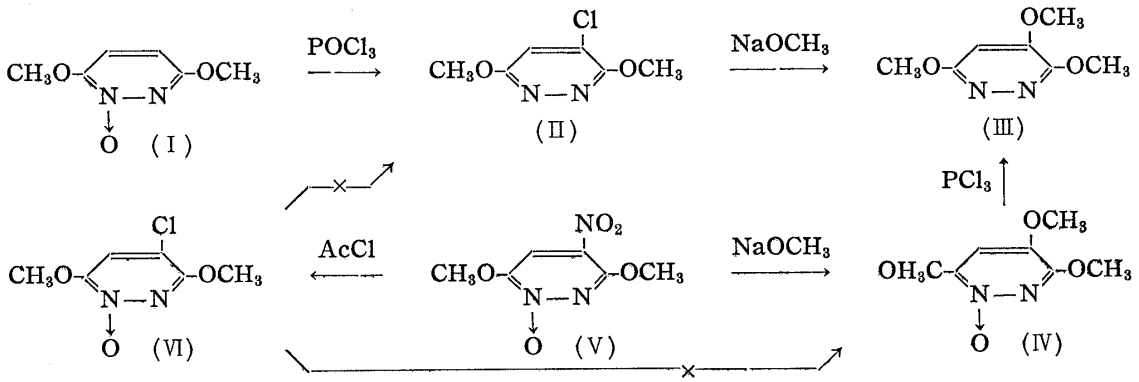
1) Part III: This Bulletin, **7**, 938(1959).

2) Part II. T. Itai, H. Igeta: Yakugaku Zasshi, **75**, 996(1955).



oxyl compound, which was proved to be identical with 3,4,6-trimethoxypyridazine[2] (III).

The nitro group of 3,6-dimethoxy-4-nitropyridazine 1-oxide[2] (V) was converted into the methoxyl group with sodium methoxide and 3,4,6-trimethoxypyridazine 1-oxide (IV) so obtained was reduced with phosphorus trichloride to 3,4,6-trimethoxypyridazine (III). The reaction of 3,6-dimethoxy-4-nitropyridazine 1-oxide (V) with acetyl chloride yielded 4-chloro compound[2] (VI), but neither deoxygenation of this with Raney nickel or phosphorus trichloride to form 3,6-dimethoxy-4-chloropyridazine (II) nor substitution of chlorine atom of (VI) with methoxyl group to produce the trimethoxyl N-oxide compound (IV) was successful.

Thus, when *ortho* position of the N-oxide group in pyridazine N-oxides is substituted, the reaction with phosphoryl chloride seems to give a chloro compound which has chlorine atom at a position *para* to the N-oxide group.

Experimental

3,6-Dimethoxy-4-chloropyridazine (II)—To a solution of 1 g. of (I) dissolved in 15 cc. of $CHCl_3$, 2 cc. of $POCl_3$ was added dropwise, the mixture was cooled for a short time, and then allowed to stand for 4 hr. The reaction mixture was poured on ice, neutralized with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was passed through a column of activated alumina and $CHCl_3$ was evaporated from the effluent. The white residue (1.08 g.) was recrystallized from petr. benzine and 0.8 g. (72%) of white rhomboprismatic crystals, m.p. 86°, was obtained. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.27; H, 4.03. Found: C, 41.27; H, 3.95.

Reaction of 3,6-Dimethoxy-4-chloropyridazine (II) with $NaOCH_3$; Formation of 3,4,6-Trimethoxypyridazine (III)—To a solution of $NaOCH_3$, prepared from 75 mg. of Na and 5 cc. of MeOH, a solution of 500 mg. of (II) dissolved in 5 cc. of MeOH was added and the mixture was refluxed for 2 hr. After evaporation of MeOH, the white residue was extracted with ether, the ether extract was dried over anhyd. K_2CO_3, and ether was evaporated to dryness. The white residue (420 mg.) was recrystallized from water and 300 mg. (60%) of white needles, m.p. 120°, was obtained. This showed no depression on admixture with authentic specimen.

The author wishes to express his gratefulness to Prof. S. Shibata and to Prof. T. Okamoto of the University of Tokyo for their kind and helpful guidances, and to Dr. T. Kariyone of this Laboratory for his encouragement. He is also indebted to Mr. T. Oba of this Laboratory for the determination of infrared spectra, and to Miss S. Nakamura of this Laboratory for elemental microanalyses.

Summary

Treatment of 3,6-dimethoxypyridazine 1-oxide (I) with phosphoryl chloride at room temperature gave a chloro-dimethoxyl compound (II), m.p. 86°, and reaction of (II) with sodium methoxide yielded a trimethoxyl compound (III), which was proved to be identical with 3,4,6-trimethoxypyridazine. This shows that, when *ortho* position of the N-oxide group in pyridazine N-oxides is substituted, the reaction with phoshoryl chloride seems to give a chloro compound which has chlorine atom at a position *para* to the N-oxide group.

(Received December 19, 1959)