[Chem. Pharm. Bull. 19(10)2181—2183(1971)]

UDC 547.852.2.04

Studies on the Pyridazine Derivatives. XV.[1] On the Nucleophilic Reaction of 3-Ethoxy-4,6-dinitropyridazine 1-Oxide

Mitsuji Yanai, Toshio Kinoshita and Shigeko Takeda

Faculty of Pharmaceutical Sciences, Nagasaki University[2]

(Received March 4, 1971)

Many reports have been published on the nucleophilic reaction of nitro or alkoxy aromatic amine N-oxides,[3] though only few reports on the reaction of the compounds which contained both functional groups.[4] Previous paper[5] of this series, it was reported that transetherification was observed in pyridazine N-oxides. In this paper, 3-ethoxy-4,6-dinitropyridazine 1-oxide was taken up for the reaction material.

The nitration of 3-ethoxypyridazine 1-oxide (I) has been reported.[6] In this time, a mixture of mononitro compound II (14%) and dinitro compound III (24.5%) was obtained under slightly vigorous condition. These nitro compounds were converted with methanolic solution of sodium methoxide to 3,4-dimethoxy-[7] (IV) and 3,4,6-trimethoxypyridazine 1-

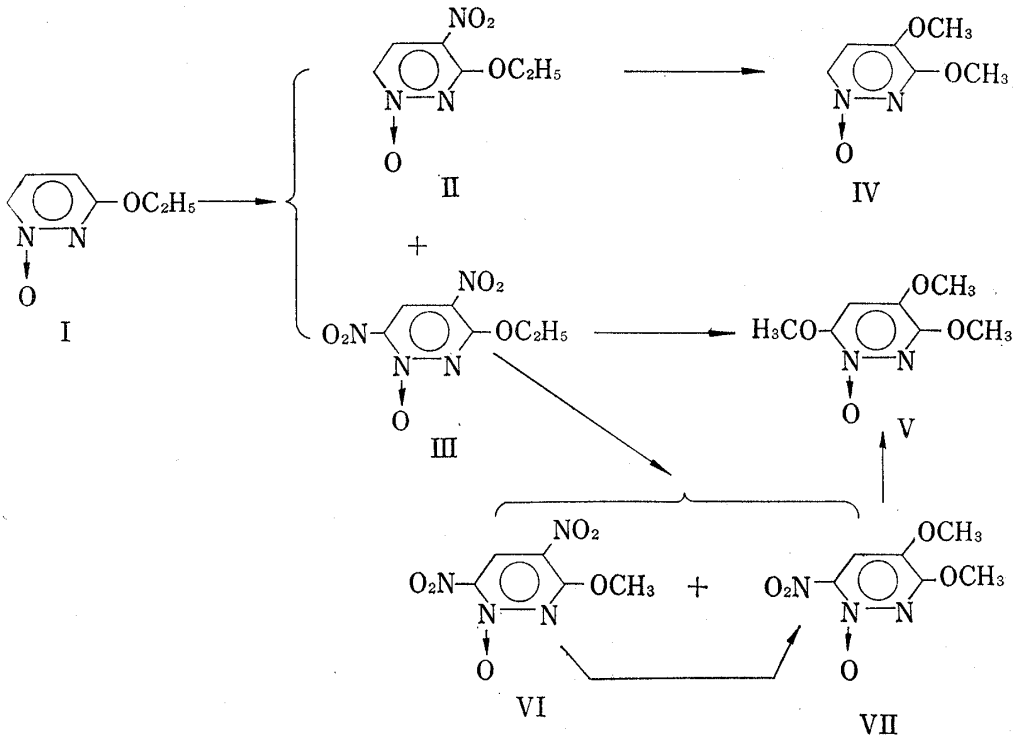

Chart 1

1) Part XIV: M. Yanai, T. Kinoshita, H. Watanabe and S. Iwasaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1849 (1971).
2) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*
3) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, p. 340.
4) M. Yanai and T. Kinoshita, *Chem. Pharm. Bull.* (Tokyo), **16**, 1221 (1968).
5) M. Yanai and T. Kinoshita, *Yakugaku Zasshi*, **87**, 114 (1967).
6) M. Yanai, T. Kuraishi and T. Kinoshita, *Yakugaku Zasshi*, **81**, 708 (1961).
7) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **8**, 550 (1960).

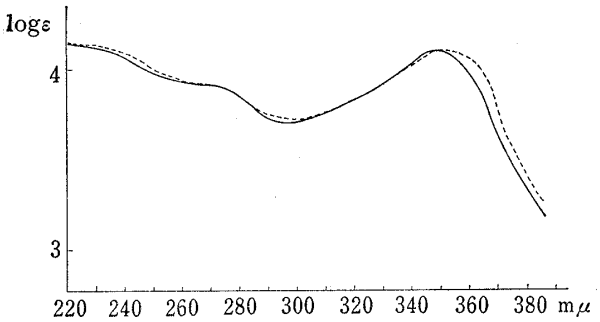

Fig. 1. Ultraviolet Spectra of VI (——) and III (------), (95% EtOH)

oxide[8] (V), respectively. In consideration of transetherification and comparison of ultraviolet spectrum with that of 3-methoxy-4,6-dinitropyridazine 1-oxide[7] (VI), the dinitro compound (III) was concluded to be 3-ethoxy-4,6-dinitropyridazine 1-oxide.

When III was treated with sodium methoxide of 1.1 equivalent at room temperature for 30 minutes, a mixture of VI and 3,4-dimethoxy-6-nitropyridazine 1-oxide[9] (VII) was obtained in 6.4% and 46.8% yield. Furthermore, it was found that VI was converted to VII, and VII to V with sodium methoxide. These results suggest that the reactive order of the functional groups in compound III is C_2H_5O-(position 3)>NO_2-(4)>NO_2-(6), towards the alkoxide ion. This order interests us in comparison with the following result, 3,6-dimethoxy-4-ethoxypyridazine 1-oxide[4] is obtained from 3,6-dimethoxy-4-nitropyridazine 1-oxide, indicating that the nitro group is more active than the methoxyl groups.

Experimental[10]

Nitration of 3-Ethoxypyridazine 1-Oxide (I)——To a solution of 55 g of I and 275 ml of conc. H_2SO_4, 130 ml of fuming HNO_3 (S.G. 1.52) was added dropwise at 60—65° during 4 hours. The mixture was heated at 70—75° for 4 hours. After the reaction, it was poured on crushed ice. The separated crystals were filtered and washed with water. The product was recrystallized from MeOH to give 22 g (24.5%) of yellow prisms, mp 113.5—115.5°. *Anal.* Calcd. for $C_6H_6O_6N_6$ (3-ethoxy-4,6-dinitropyridazine 1-oxide(III)): C, 31.31; H, 2.63; N, 24.35. Found: C, 31.56; H, 2.69; N, 23.99. The acidic filtrate was extracted with $CHCl_3$, the extract was washed with $NaHCO_3$ solution, dried over $MgSO_4$, evaporated to dryness. The residue was recrystallized from water to give 10 g (14%) of yellow prisms, mp 105—106°. This compound was identified with an authentic specimen of 3-ethoxy-4-nitropyridazine 1-oxide. From the mother liquor of recrystallization, 15 g of mixture of II and III was obtained. To the solution of 15 g of the mixture and 75 ml of concd. H_2SO_4, 30 ml of fuming HNO_3 was added dropwise, heated at 75—80° for 5 hours. The mixture was poured on crushed ice, separated crystals were collected, recrystallized from MeOH to give 7.2 g of yellow plates, mp 113.5—115.5° (III).

3,4-Dimethoxypyridazine 1-Oxide (IV)——A solution of 0.46 g of II and 5 ml of MeOH–NaOMe solution(Na; 0.057 g) was allowed stand at room temperature for 2 hours. The reaction mixture was evaporated to dryness *in vacuo*. Small amount of water was added to the residue, extracted with $CHCl_3$, dried over $MgSO_4$, evaporated to dryness. The residue was recrystallized from AcOEt to give 0.17 g(44%) of colorless prisms, mp 137—138° (hygroscopic, dried at 100° *in vacuo*). This compound was identified with an authentic specimen of 3,4-dimethoxypyridazine 1-oxide.

Reaction of III with MeOH–NaOMe Solution——i) A solution of 3 g of III and 15 ml of MeOH–NaOMe (Na; 0.65 g) was refluxed for one hour. The solvent was evaporated to dryness *in vacuo*, the residue was dissolved in water, extracted with $CHCl_3$, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from AcOEt to give 2.2 g(80%) of colorless needles, mp 117°. This compound was identified with an authentic specimen of 3,4,6-trimethoxypyridazine 1-oxide. This compound was obtained also by reaction of VII with MeOH–NaOMe solution: A solution of 0.5 g of VII and 5 ml of MeOH–NaOMe(Na; 0.068 g) was refluxed for one hour. The reaction mixture was treated same method of above, mp 117°. ii) To a solution of 2 g of III and 80 ml of dry MeOH, 10 ml of MeOH–NaOMe solution(Na; 0.22 g) was added with cooling, allowed stand at room temperature for 30 minutes. The reaction mixture was evaporated to dryness *in vacuo*, the residue was dissolved in small amount of water, extracted with $CHCl_3$ and dried over $MgSO_4$. The solvent was removed, the residue was recrystallized from MeOH to give 0.82 g(46.8%) of yellow scales, mp 155—156° (decomp.). *Anal.* Calcd. for $C_6H_7O_5N_3$ (VII): C, 35.83; H, 3.51; N, 20.89. Found: C, 35.92; H, 3.60; N, 20.68. From the mother liquor of recrystallization, 0.12 g(6.4%) of yellow scales were

8) T. Itai and H. Igeta, *Yakugaku Zasshi*, **75**, 966 (1955).
9) T. Nakagome, Japan patent 26 213 (1964) [*Chem. Abstr.*, **58**, 3426 (1963)].
10) The known products were identified with authentic specimens by mixed melting point test and infrared comparison, respectively.

obtained, mp 125—126°. *Anal.* Calcd. for $C_5H_4O_6N_4$(VI): C, 27.79; H, 1.87; N, 25.93. Found: C, 27.44; H, 1.85; N, 25.54. Compound VII was obtained also by reaction of VI with MeOH–NaOMe solution: To a suspension of 1 g of VI in 30 ml of dry MeOH, 5 ml of MeOH–NaOMe solution was added with cooling. The mixture was allowed stand at room temperature for 3.5 hours (crystals separated). The reaction mixture was treated same to above method, yield 0.38 g(42%), mp 155—156°. This compound was identified with an authentic specimen of VII.

[Chem. Pharm. Bull. 19(10)2183—2185(1971)]

UDC 547.92.04 : 547.918.057

Studies on Steroid Conjugates. VI. Synthesis of 17α-Estradiol 17-N-Acetylglucosaminide[1]

Toshio Nambara, Takako Anjyo, and Shujiro Goya

Pharmaceutical Institute, Tohoku University[2]

(Received March 26, 1971)

In 1964 Layne, *et al.* isolated first 17α-estradiol 17-N-acetylglucosaminide (IV) from the rabbit urine treated with β-glucuronidase after a large dosage of estrone benzoate.[3] As a series of our studies on the modified steroids the metabolic fate of 3-deoxyestrone in the rabbit has previously been investigated. In our experiment, however, it was found that 17α-estradiol, one of the principal metabolites, was excreted solely in the form of the 17-glucuronide, and no evidence was obtained for *in vivo* formation of steroidal N-acetylglucosaminide.[4] It was thereby assumed that the observed difference would be ascribable to the breed. In order to clarify the possible conjugation of N-acetylglucosamine with the estrogens in the domestic rabbit and the behaviors of the conjugate against the enzymatic hydrolysis, the availability of the authentic sample has become requisite. In this paper we wish to report the synthesis of the titled compound from estrone by an unequivocal route (see Chart 1).

For this purpose 17α-estradiol 3-benzyl ether (I), derivable from estrone in five steps,[5] was employed as a starting material. The Koenigs–Knorr reaction has already been used with success for the preparation of the steroidal N-acetylglucosaminides.[6] Consequently an introduction of the sugar moiety was attempted by the use of this reaction. When I and acetochloroglucosamine (1α-chloro-2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-D-glucopyranose) were stirred in dry toluene with cadmium carbonate as the condensing agent, the reaction proceeded with ease to give 3-benzyloxyestra-1,3,5(10)-trien-17α-yl-2′-acetamido-2′-deoxy-3′,-4′,6′-tri-O-acetyl-β-D-glucopyranoside (II) almost quantitatively. The formation of the β-glucoside linkage was verified by the inspection of the nuclear magnetic resonance (NMR) spectrum. The anomeric proton of the sugar moiety in II appeared at 4.62 ppm as doublet (J=7.8 cps) indicating a *trans*-diaxial relationship to the vicinal 2′-proton. The catalytic

1) This paper constitutes Part IL of the series entitled "Analytical Chemical Studies on Steroids"; Part XLVIII: T. Nambara, M. Nokubo, and Y.H. Bae, *Chem. Pharm. Bull.* (Tokyo), **19**, 2096 (1971).
2) Location: *Aobayama, Sendai.*
3) D.S. Layne, N.A. Sheth, and R.Y. Kirdani, *J. Biol. Chem.*, **239**, 3221 (1964).
4) T. Nambara and M. Numazawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 990 (1971).
5) T. Nambara, M. Numazawa, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1725 (1969).
6) R. Hirschmann, R.G. Strachan, P. Buchschacher, L.H. Sarett, S.L. Steelman, and R. Silber, *J. Am. Chem. Soc.*, **86**, 3903 (1964); G. Sauer, M. Matsui, R. Bloch, J.S. Liang, and D.K. Fukushima, *J. Org. Chem.*, **34**, 3525 (1969).