**A New Synthesis of 2,5-Diamino-7-hydroxythiazolo[4,5-*d*]pyrimidine
and a New Aspect on the Reactivity of 5-Bromopyrimidines**

Only one method has so far been published on the synthesis of thiazolo[4,5-*d*]pyrimidine series.¹⁾ In the course of the investigation of nucleophilic displacement of 5-bromopyrimidines, the writer found a new reaction to yield 2,5-diamino-7-hydroxythiazolo[4,5-*d*]pyrimidine (II) in a good yield.

2,6-Diamino-4-hydroxy-5-bromopyrimidine (I), m.p. 244° (decomp.), was added to a solution of thiourea in ethanol, and after refluxing for half an hour the solid was separated and treated with alkali. To this solution, diluted acetic acid was gradually added and light yellow crystals precipitated, m.p. >300°, U.V. λ_{max} (in 0.1N NaOH) 271, 345 m μ (log ϵ 3.94, 3.61) (*Anal.* Calcd. for $\text{C}_5\text{H}_5\text{ON}_5\text{S} \cdot 2\text{H}_2\text{O}$: C, 27.40; H, 4.15; N, 31.95. Found: C, 27.20; H, 4.21; N, 31.59). Yield, 91.3%.

This compound was confirmed to be 2,5-diamino-7-hydroxythiazolo[4,5-*d*]pyrimidine (II) through the comparison of I.R. spectrum and analytical data with those of the authentic sample prepared by the method of Maggiolo, *et al.*¹⁾

It has been generally concluded in pyrimidine chemistry that halogens at C-5 of pyrimidines are quite stable and difficult to displace by nucleophilic reagents^{2,3)} except in a few examples.⁴⁾ Above-mentioned 2,6-diamino-4-hydroxy-5-bromopyrimidine (I) was reported to be entirely inactive for popular nucleophilic reagents,³⁾ but from the experiments recently carried out by the writer it became clear that this 5-bromopyrimidine (I) reacts smoothly with morpholine or thiosalicylic acid to give 2,6-diamino-4-hydroxy-5-morpholinopyrimidine (III), m.p. >300°, U.V. λ_{max} (in 0.1N NaOH) 269 m μ (log ϵ 4.00), I.R. λ_{max} 1116 cm^{-1} (C-O-C) (*Anal.* Calcd. for $\text{C}_8\text{H}_{13}\text{O}_2\text{N}_5 \cdot \text{H}_2\text{O}$: C, 42.00; H, 6.62; N, 30.59. Found: C, 42.45; H, 6.96; N, 30.83), or 2,6-diamino-4-hydroxy-5-(2-carboxyphenylthio)pyrimidine (IV), m.p. >300°, U.V. λ_{max} (in 0.1N NaOH) 262 m μ (log ϵ 3.24)

1) A. Maggiolo, *et al.*: J. Am. Chem. Soc., **73**, 4426(1951).

2) G.W. Kenner, A. Todd: "Pyrimidines and Its Derivatives," 301. (R.C. Elderfield: "Heterocyclic Compounds," Vol. VI, 1957. John Wiley & Sons, Inc., New York); B. Lythgoe: Quart. Revs. (London), **3**, 199(1949); A. Bendich: "Chemistry of Purines and Pyrimidines," 128. (E. Chargaff, J.N. Davidson: "The Nucleic Acids," Vol. I, Academic Press Inc., New York, 1955); E. Ochiai, Y. Ito: Yakugaku Zasshi, **57**, 579(1937); M. Yanai: Yakugaku Zasshi, **62**, 99 (1942) (in German); M. P. V. Boarland, J. F. W. McOmie: J. Chem. Soc., **1952**, 3726; J. Chesterfield, *et al.*: J. Chem. Soc., **1955**, 3478.

3) A. Bendich, *et al.*: Biochim. et Biophys. Acta, **12**, 462(1953).

4) E. Ochiai, M. Yanai: Yakugaku Zasshi, **63**, 25(1943); C.C. Price, *et al.*: J. Am. Chem. Soc., **68**, 766(1946); A.P. Phillips: J. Am. Chem. Soc., **75**, 4092(1953).

(*Anal.* Calcd. for $C_{11}H_{10}O_3N_4S$: C, 47.50; H, 3.59; N, 20.12; S, 11.52. Found: C, 47.54; H, 3.68; N, 19.98; S, 11.10), respectively.

These results suggest the possibility of the use of 5-bromopyrimidines for the syntheses of new derivatives of amino- or hydroxy-pyrimidines. The details of these reactions and further examples in other pyrimidines will be published later.

The writer expresses his cordial acknowledgement to Dr. K. Takeda, Managing Director, and Dr. Y. Sawa of this Laboratory for their encouragements.

Research Laboratory,
Shionogi & Co., Ltd.,
Imafuku, Amagasaki,
Hyogo-ken.

Mahiko Horiuchi (堀内真彦)

March 10, 1959

UDC 547.92

Synthesis of the Ethynylated Steroids (Studies on Acetylenic Compounds)

Recently, several works on the alkylated steroids bearing methyl group at the 1-,¹⁾ 2-,²⁾ 4-,³⁾ 6-,⁴⁾ 7-,⁵⁾ 11-,⁶⁾ 14-,⁷⁾ or 16-⁸⁾ position have been reported. Some of these alkylated steroids, especially, 6- and 16-methyl compounds are significant in enhancing hormonal activity as compared with the mother steroids.

Considering that 17-ethynylated steroid is more important in variety of its actions, the following steroids ethynylated at 6-, 7-, or 16-position have been prepared from the corresponding oxosteroids.

Addition of 16-oxo-5-androstene-3 β ,17 α -diol 3-methyl ether⁹⁾ to lithium acetylide ($LiC\equiv CH$) in liquid ammonia and subsequent stirring at -40° for 5 hr. yielded 16 α -ethynyl-5-androstene-3 β ,16 β ,17 α -triol 3-methyl ether (I) of m.p. $191\sim 194^\circ$, $[\alpha]_D^{25} -66^\circ$ (in $CHCl_3$), which was converted into 16,17-acetonide by the action of acetone and hydrochloric acid at room temperature.

Analogously 7 ξ -ethynyl-5-cholestene-3 β ,7 ξ -diol 3-acetate (III) of m.p. $152.5\sim 154^\circ$, $[\alpha]_D^{25} -104.3^\circ$ (in $CHCl_3$), was prepared from 7-oxocholesterol¹⁰⁾ by the action of lithium acetylide and subsequent acetylation.

- 1) H. J. Ringold, *et al.*: J. Am. Chem. Soc., **78**, 2477(1956); C. Djerassi, *et al.*: *Ibid.*, **78**, 2479(1956).
- 2) J. A. Hogg, *et al.*: *Ibid.*, **77**, 6401(1955); H. J. Ringold, *et al.*: J. Org. Chem., **21**, 1333(1956).
- 3) H. J. Ringold, *et al.*: J. Org. Chem., **22**, 602(1957).
- 4) J. A. Campbell, *et al.*: J. Am. Chem. Soc., **80**, 4717(1958); G. P. Spero, *et al.*: *Ibid.*, **78**, 6213(1956); H. J. Ringold, *et al.*: J. Org. Chem., **22**, 99(1957); J. C. Bobcock, *et al.*: J. Am. Chem. Soc., **80**, 2904(1958); A. David, *et al.*: J. Pharm. Pharmacol., **9**, 929(1957).
- 5) C. H. Robinson, *et al.*: J. Am. Chem. Soc., **81**, 408(1959); J. A. Zderic, *et al.*: *Ibid.*, **81**, 432(1959); C. H. Robinson, *et al.*: J. Org. Chem., **24**, 121(1959).
- 6) H. J. Ringold, *et al.*: Tetrahedron, **2**, 164(1958); G. S. Fonken, *et al.*: *Ibid.*, **2**, 365(1958); G. S. Fonken: J. Org. Chem., **23**, 1075(1958).
- 7) W. Vosea, *et al.*: Helv. Chim. Acta, **36**, 299(1953).
- 8) A. Wettstein: *Ibid.*, **27**, 1803(1944); H. Mori, *et al.*: Yakugaku Zasshi, **78**, 813(1958); G. E. Arth, *et al.*: J. Am. Chem. Soc., **80**, 3160, 3161(1958); E. P. Oliveto, *et al.*: *Ibid.*, **80**, 4428, 4431(1958); D. Taub, *et al.*: *Ibid.*, **80**, 4435(1959).
- 9) M. N. Huffman, M. H. Lott: J. Biol. Chem., **172**, 789(1948).
- 10) A. Windaus: Ann., **520**, 98(1935); K. Heusler, A. Wettstein: Helv. Chim. Acta, **35**, 284(1952).