[Chem. Pharm. Bull. 22(6)1265—1268(1974)]

UDC 547.783.03.09

Studies on the Smiles Rearrangement. XIV.[1] Novel Reactions of 1,3-Dimethyl-5-nitro-6-chlorouracil with 2-Aminothiophenol

Yoshifumi Maki, Tokiyuki Hiramitsu, and Mikio Suzuki

Gifu College of Pharmacy[2]

(Received September 7, 1973)

The reaction of 1,3-dimethyl-5-nitro-6-chlorouracil with 2-aminothiophenol in benzene containing an excess of triethylamine gave 1,3-dimethyl-10H-pyrimido(5,4-*b*)(1,4)benzothiazine-2,4(1H,3H)dione quantitatively *via* the Smiles rearrangement. The reaction in acetic acid, however, resulted in the formation of 2-methyl-4-nitropyrimido(4,3-*b*)benzothiazoline-1,3(2H,10H)-dione in 78% yield, involving an unusual uracil-ring cleavage which appears to occur in a benzothiazoline intermediate in the course of the acid-catalized Smiles rearrangement.

Recent articles from our laboratory have described the remarkable efficacy of 1,3-dimethyl-5-nitro-6-chlorouracil (I)[3] for the synthesis of pyrimidopteridine N-oxides,[4] pyrazolopyrimidines[5] and triazolopyrimidine N-oxides.[6]

We report here novel reactions of I with 2-aminothiophenol (II) leading to 1,3-dimethyl-10H-pyrimido(5,4-*b*)(1,4)benzothiazine-2,4(1H, 3H)-dione (III) and 2-methyl-4-nitropyrimido-(4,3-*b*)benzothiazoline-1,3(2H,10H)-dione (V), which is a hitherto unknown system, in excellent yields respectively.

Occurrence of both the reactions depends upon the reaction medium employed: While the reaction in the basic medium caused the Smiles rearrangement to give III, that in the acidic medium led to the formation of V *via* the cleavage of the uracil ring which is unexpected and unprecedented. It is worthwhile noting that the ring cleavage suggests the presence of a benzothiazoline intermediate (σ-complex intermediate), (XIII) in the acid-catalized Smiles rearrangement. Much attention has been directed towards the synthesis and chemistry of III[7–11] from the potential pharmacological interest. The present result also provides a convenient one-step synthesis of III.

In the presence of an excess of triethylamine, a mixture of I and II in benzene gave III at room temperature in 90% yield. Desulfurization of III with Raney nickel afforded 1,3-dimethyl-6-anilinouracil (IV), identical with a sample obtained by the reaction of 1,3-dimethyl-6-chlorouracil with aniline.[12] III was also identical in every respect with a sample prepared unequivocally by condensation of 1,3-dimethyl-5-bromobarbituric acid with II followed by dehydration.[7] Thus the alternative structure (III') was eliminated.

1) Part XIII: Y. Maki and M. Suzuki, *Yakugaku Zasshi*, **93**, 171 (1973).
2) Location: *492–36, Mitahora, Gifu, Japan.*
3) T.K. Liao and C.C. Cheng, *J. Hetero. Chem.*, **1**, 212 (1964).
4) Y. Maki, M. Sako, and E.C. Taylor, *Tetrahedron Letters*, **1971**, 4271.
5) Y. Maki, K. Izuta, and M. Suzuki, *Chem. Commun.*, **1971**, 1142.
6) Y. Maki, K. Izuta, and M. Suzuki, *Tetrahedron Letters*, **1972**, 1673.
7) H. Fenner, *Arzneim. Forsch.*, **20**, 1815 (1970).
8) H. Fenner, *Tetrahedron Letters*, **1970**, 617.
9) S.L. Jain, M.M. Mahandra, and K.S. Narang, *Ind. J. Chem.*, **1969**, 301.
10) J.M. Goldman and E.G. Andrews, as quoted in *Chem. Eng. News*, 44, (July 10, 1967): Abstract of Papers, 1st International Congress of Heterocyclic Chemistry, New Mexico, 1967.
11) J.P. Schaefer and L.L. Read, *J. Am. Chem. Soc.*, **94**, 908 (1972).
12) W. Pfleiderer and H. Ferch, *Ann.*, **615**, 52 (1958).

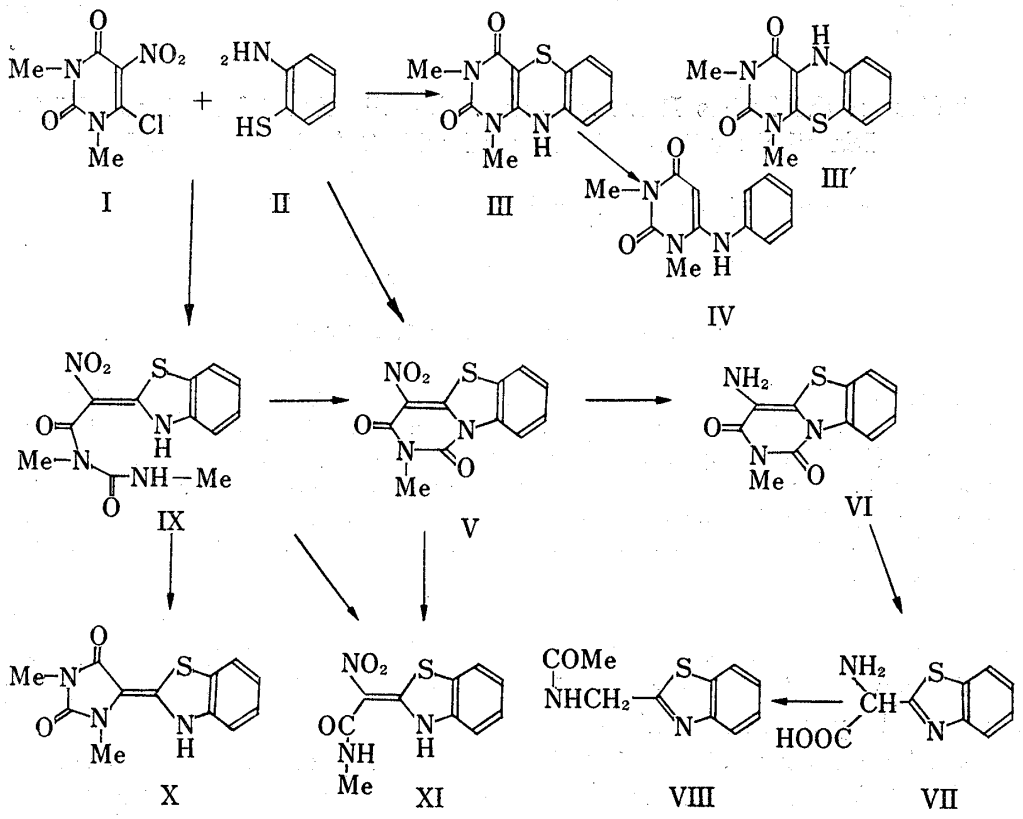

Chart 1

On the other hand, the reaction of I with II in acetic acid at 90° for 10 min afforded V in 78% yield. Mass spectral and microanalytical data on V established the molecular formula, $C_{11}H_7O_4N_3S$. The nuclear magnetic resonance (NMR) spectrum of V (in CF_3COOH) reveals only a singlet signal attributed to an N–Me group at 6.27 τ other than aromatic proton signals. Those data clearly indicate the loss of an N–Me group in the 1,3-dimethyluracil ring during the reaction. V does not have any NH stretching band, but carbonyl and nitro stretching bands at 1730, 1670, 1540 and 1380 cm^{-1} in its infrared (IR) spectrum.

Reduction of V with hydrosulfite to an amino derivative (VI) was effected in refluxed aqueous methanol in 82% yield. Hydrolysis of VI by using 1% sodium hydroxide led to the corresponding amino acid (VII). Purification of VII was unsuccessful and its acetylation (pyridine–acetic anhydride) resulted in the formation of 2-acetamidomethylbenzothiazole (VIII) (40%) accompanied with decarboxylation.

The structure of VIII was confirmed by its spectral data, *e.g.*, the NMR spectrum showed a doublet signal at 5.15 τ (2H, J=6 Hz, collapsed to a sharp singlet by deuterium exchange) assignable to methylene protons of an acetamidomethyl moiety($CH_3CONHC\underline{H}_2$–). The ultraviolet (UV) spectrum of VIII (UV λ_{max}^{EtOH} mμ (ε): 218 (21900), 254 (8500), 284 (1900), 294 (1400)) was superimposable on that of 2-methylbenzothiazole.

The facile decarboxylation of VII is explicable in terms of the electron withdrawing effect of the benzothiazole C=N bond situated at the β-position to the carboxyl group.

When I was allowed to react with II in refluxed benzene without addition of any catalyst, an unstable benzothiazoline derivative (IX) was obtained in 90% yield. IX showed two NH stretching bands at 3350 and 3275 cm^{-1} in its IR spectrum. The NMR spectrum of IX well demonstrated the presence of an –NHMe grouping (7.25 τ, 3H, doublet, J=4 Hz, collapsed to a singlet by deuterium exchange) and an –NMe grouping (6.77 τ, 3H, singlet), indicating the unexpected uracil-ring cleavage.

Upon treatment of IX with 10% sodium hydroxide at room temperature, 2-(1,3-dimethyl-4-hydantoinylidene)benzothiazoline (X) was produced as a result of the loss of nitrous acid in 80% yield. Its IR spectrum showed the presence of carbonyl bands characteristic of 1,3-dimethylhydantoin (1770 and 1700 cm^{-1}).

In contrast to this, the reaction of IX with 1% sodium hydroxide gave a simply hydrolyzed product (XI) which was also obtained by the alkaline hydrolysis of V.

When IX was heated in acetic acid, its smooth conversion to V took place. Thus, the structure of IX was established and IX must be an intermediate, which cyclizes to V as a result of the loss of methylamine.

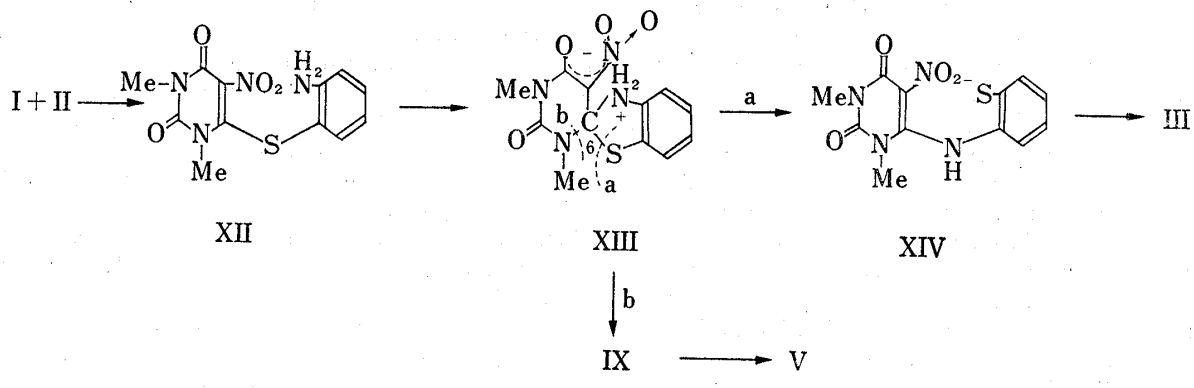

Chart 2

In both the acidic and basic media, the sulfide intermediate (XII) initially formed could be converted into a transient benzothiazoline intermediate (XIII) (see Chart 2). The base-catalyzed Smiles rearrangement is generally considered to proceed *via* the σ-complex intermediate.[13] The analogous intermediate is also predicted in the acid-catalized Smiles rearrangement.

The cleavage of the C_6–S bond of XIII in the basic medium causes the Smiles rearrangement. Thiol anion (XIV) thus formed spontaneously cyclizes to III by intramolecular displacement of a labile nitro group on the C_5-position. The base-catalyzed Smiles rearrangement of 2-amino-2′-nitrodiphenyl sulfides is usually accomplished by conversion of the amino function into an acetamido or benzamido function[13] which is acidic. The present Smiles rearrangement in the free amino compound (XII) belongs rather to exceptional cases.[14,15]

The formation of V in the acidic medium is best explained in terms of the C_6–N bond cleavage of XIII, presumably by virtue of protonation on the C_2-carbonyl oxygen, followed by an intramolecular cyclization. Thus, occurence of the novel ring cleavage can be ascribed to the unique feature of a benzothiazoline intermediate (XIII) proposed in the expected acid-catalyzed Smiles rearrangement.

Experimental[16]

Reaction of 1,3-Dimethyl-5-nitro-6-chlorouracil (I) with 2-Aminothiophenol (II) in Acetic Acid——A solution of I (1.1 g) and II (1.2 g) in HOAc (40 ml) was heated with stirring at 90° for 10 min. After cooling, the precipitated colorless solid was collected and recrystallized from dimethylsulfoxide (DMSO) to give 2-methyl-4-nitropyrimido(4,3-*b*)benzothiazoline-1,3(2H,10H)-dione (V) (1.1 g) as colorless needles,

13) J.F. Bunnett and R.E. Zahler, *Chem. Rev.*, **49**, 364 (1951); Th. J. de Boer and I.P. Dirkx, "The Chemistry of the Nitro Groups," ed. by H. Feuer, Wiley-Interscience, New York, Part 1, 1969, p. 587.
14) Y. Maki, M. Suzuki, and T. Masugi, *Chem. Pharm. Bull.* (Tokyo), **16**, 559 (1968).
15) H.L. Sharma, V.N. Sharma, and R.L. Mital, *Tetrahedron Letters*, **1959**, 1657.
16) All melting points are uncorrected. IR spectra were run on a Hitachi R-215 spectrometer. NMR spectra were recorded at 60 MHz with a Hitachi R-20B using TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet.

mp above 300°. *Anal.* Calcd. for $C_{11}H_7O_4N_3S$: C, 47.66; H, 2.55; N, 15.16. Found: C, 47.81; H, 2.67; N, 14.91. IR(KBr) cm^{-1}: 1730, 1670(CO), 1540, 1380(NO_2). NMR (CF_3COOH) τ: 0.90—2.30 (4H, m, aromatic protons), 6.27 (3H, s, $-NCH_3$). Mass Spectrum *m/e*: 277 (M^+).

Reactlon of 1,3-Dimethyl-5-nitro-6-chlorouracil (I) with 2-Aminothiophenol (II) in Benzene——A solution of I (1.1 g) and II (1.2 g) in benzene (50 ml) was refluxed for 1 hr. After cooling, the precipitated yellow solid was collected and washed with cold H_2O. After drying, the solid was washed with ether and recrystallized from acetone to give benzothiazoline derivative (IX), mp about 140°, as pale yellow crystals. IR (KBr) cm^{-1}: 3350, 3275(NH), 1700(CO), NMR(DMSO-d_6) τ: 1.62 (1H, q, J=4 Hz, $-NHCH_3$), 1.80—2.70 (4H, m, aromatic protons), 6.77 (3H, s, $-NCH_3$), 7.25 (3H, d, J=4 Hz, $-NHCH_3$). *Anal.* Calcd. for $C_{12}H_{12}O_4N_4S$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.81; H, 3.96; N, 18.14.

IX was easily converted into V by heating it in acetic acid at 90° for 20 min.

Reaction of 1,3-Dimethyl-5-nitro-6-chlorouracil (I) with 2-Aminothiophenol (II) in the Presence of Triethylamine——To a well stirred solution of I (1.1 g) and triethylamine (1.0 g) in benzene (50 ml) was added II (0.63 g) in benzene (10 ml) in portions at room temperature. After stirring for 20 min, the precipitated solid was collected, washed with MeOH and recrystallized from DMSO to give 1,3-dimethyl-10H-pyrimido-(5,4-*b*)(1,4)benzothiazine-2,4(1H,3H)-dione (III) (1.2 g) as pale yellow needles, mp 185° (decomp.), which was identical in every respect with a sample prepared unequivocally by condensation of 1,3-dimethyl-5-bromobarbituric acid with II followed by dehydration.[7] III gave 1,3-dimethyl-6-anilinouracil (IV)[12] upon treatment with excess Raney nickel in boiling EtOH in 15% yield.

Reduction of 2-Methyl-4-nitropyrimido(4,3-*b*)benzothiazoline-1,3(2H,10H)dione (V) with Sodium Hydrosulfite——A suspension of V (1.1 g) and sodium hydrosulfite (5.0 g) in 90% aqueous MeOH (400 ml) was refluxed for 3 hr. After evaporation of the solvent, the residue was washed with H_2O and recrystallized from EtOH to give an amino derivative (VI) (0.8 g), mp 201°, as colorless needles. IR (KBr)cm^{-1}: 3390, 3300(NH), 1680, 1640(CO). NMR (DMSO-d_6) τ: 1.40—2.75 (4H, m, aromatic protons), 5.90 (2H, broad, NH_2), 6.67 (3H, s, N-CH_3). Mass Spectrum *m/e*: 247 (M^+). *Anal.* Calcd. for $C_{11}H_9O_2N_3S$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.37; H, 3.72; N, 16.96.

Conversion of 2-Methyl-4-aminopyrimido(4,3-*b*)benzothiazoline-1,3(2H,10H)-dione (VI) into 2-Acetamidomethylbenzothiazole (VIII)——A suspension of VI (1.0 g) in 1% NaOH (100 ml) was heated with stirring at 90° for 3 hr. After cooling, the clear solution was neutralized with 1% HCl. The powdery mass thus separated was collected, washed with H_2O and MeOH to give an amino acid (VII) (0.5 g), mp about 130°. IR (KBr)cm^{-1}: 2950(NH_3^+) and 1660(COO^-). Mass Spectrum *m/e*: 164($M-CO_2^+$).

A suspension of VII (0.5 g) in a mixture of pyridine (15 ml) and $(MeCO)_2O$ (5 ml) was allowed to stand at room temperature for 24 hr. The resulting solution was poured into ice H_2O and extracted with $CHCl_3$. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel (solvent: $CHCl_3$) to isolate VIII (0.2 g), mp 133° (from ether), as colorless crystals. IR (KBr)cm^{-1}: 3280(NH), 1660(CO). NMR($CDCl_3$) τ: 1.90—2.70 (4H, m, aromatic protons), 3.35 (1H, broad, NH), 5.15 (2H, d, J=6 Hz, $-NHCH_2-$), 7.90 (CH_3CO). UV λ_{max}^{EtOH} mμ (ε): 218(21900), 254(8500), 284 (1900), 294(1400). Mass Spectrum *m/e*: 206 (M^+). *Anal.* Calcd. for $C_{10}H_{10}ON_2S$: C, 58.25; H, 4.89; N, 13.58. Found: C, 57.94; H, 4.86; N, 13.42.

2-(1,3-Dimethyl-5-hydantoinylidene)benzothiazole (X)——A solution of IX in 10% NaOH was allowed to stand at room temperature for 20 min. The precipitated solid was collected, washed well with H_2O and recrystallized from MeOH to give X (0.24 g), mp 228°, as colorless prisms. IR (KBr)cm^{-1}: 3470(NH), 1770, 1700(CO). NMR ($CDCl_3$) τ: 1.80—2.70 (4H, m, aromatic protons), 6.78 (3H, s, N-CH_3), 6.82 (3H, s, N-CH_3), *Anal.* Calcd. for $C_{12}H_{10}O_2N_3S$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.15; H, 3.96; N, 15.89. Mass Spectrum *m/e*: 261 (M^+).

N-Methyl-(α-nitro-2-benzothiazolylmethyl)carboxamide (XI)——A suspension of V (1.0 g) in 5% NaOH (100 ml) was heated with stirring at 90° for 2 hr. After cooling, the alkaline solution was acidified with dil. HCl. The solid thus deposited was collected and recrystallized from MeOH to give XI (0.5 g), mp 234°, as pale yellow needles. IR (KBr)cm^{-1}: 3350 (NH), 1620(CO), 1510. 1340(NO_2). NMR (DMSO-d_6) τ: 0.55 (1H, broad, $NHCH_3$), 1.70—2.70 (4H, m, aromatic protons), 7.07 (3H, d, J=5 Hz, $-NHCH_3$). *Anal.* Calcd. for $C_{10}H_9O_3N_3S$: C, 47.81; H, 3.61; N, 16.73. Found: C, 47.74; H, 3.55; N, 16.58. Mass Spectrum *m/e*: 237 (M^+). Analogously, XI (0.7 g) was also obtained from IX upon treatment with 1% NaOH at room temperature.

Acknowledgement The authors wish to thank Professor H. Fenner of Berlin Free University for kindly providing a sample of pyrimidobenzothiazine. This work was supported by the Grant for Scientific Research from the Ministry of Education.