[Chem. Pharm. Bull. 23(8)1885—1888(1975)]

UDC 547.854.4.04

Cyclization Reactions of Some 5-Nitro- and 5-Nitroso-6-benzylidenehydrazinouracils

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(Received December 25, 1974)

The treatment of 6-(benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil (I) with sulfuric acid in acetic acid gave a mixture of 1,6-dimethyl-5,7-dioxo-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo[4,3-*c*]pyrimidine (III) and 1,5-dimethyl-3-phenylpyrazolo-[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione. The reaction in the presence of potassium nitrate under the same conditions gave exclusively III. The reaction of 6-(benzylidene-1′-methylhydrazino)-3-methyluracil with potassium nitrate in acetic acid in the presence of sulfuric acid gave a mixture of 3-phenyltoxoflavin and 3-phenyl-1-demethyltoxoflavin. The treatment of 6-benzylidenehydrazino-3-methyl-5-nitrouracil with potassium nitrate in acetic acid (with or without sulfuric acid) gave 5,7-dioxo-6-methyl-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo[4,3-*c*]pyrimidine. The treatment of 6-benzylidenehydrazino-3-methyluracil with sodium nitrite in acetic acid at low temperature gave the corresponding 5-nitroso derivative, which was converted into 3,6-dimethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-pyrimido[5,4-*g*]pteridinetetrone by treatment with a mixture of acetic acid and sulfuric acid.

It is known that the heating of 6-benzylidenehydrazino-1,3-dimethyl-5-nitrouracil in dimethylformamide causes the cyclization to give 5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione.[2] This paper describes the cyclization reactions of some 5-nitro- and 5-nitroso-6-benzylidenehydrazinouracils.

In a previous report,[3] it was shown that both the fusion of 6-(benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil (I) and the refluxing of I in dimethylformamide gave 1,5-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (II) in moderate yields respectively. Now it was found that the treatment of I with sulfuric acid in acetic acid gave another cyclization product, 1,6-dimethyl-5,7-dioxo-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo-[4,3-*c*]pyrimidine (III) and II in 54 and 19% yields, respectively. The structure of III was determined by elemental analysis, mass spectrometry (molecular weight) and infrared (IR) spectra (presence of nitro group). To avoid the displacement of the nitro group, this reaction was carried out in the presence of potassium nitrate in a mixture of acetic acid and sulfuric acid (or in acetic acid alone), whereby III was exclusively formed in 65% yield as expected. It is noted that III belongs to a type of compounds observed previously.[4,5,6]

On the other hand, the treatment of 6-(benzylidene-1′-methylhydrazino)-3-methyluracil (IV)[3] with potassium nitrate in acetic acid in the presence of sulfuric acid gave 3-phenyltoxoflavin 4-oxide (V)[7] along with 3-phenyl-1-demethyltoxoflavin (VI),[8,9] but II and III

1) Location: *Oe-honmachi, Kumamoto 862, Japan.*
2) Y. Maki, K. Izuta, and M. Suzuki, *Chem. Commun.*, **1971**, 1442.
3) *a*) F. Yoneda and T. Nagamatsu, *Synthesis*, **1973**, 300; *b*) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 1484 (1975).
4) T.K. Liao, F. Baiocchi, and C.C. Cheng, *J. Org. Chem.*, **31**, 900 (1966).
5) M.E.C. Biffin, D.J. Brown, and T. Sugimoto, *J. Chem. Soc.* (*C*), **1970**, 139.
6) D.J. Brown and J.R. Kershaw, *J. Chem. Soc. Perkin I*, **1972**, 2316.
7) F. Yoneda, S. Nishigaki, and K. Shinomura, *Chem. Pharm. Bull.* (Tokyo), **19**, 2647 (1971).
8) F. Yoneda and T. Nagamatsu, *J. Am. Chem. Soc.*, **95**, 5735 (1973).
9) The formation of VI is ascribed to the demethylation of the preformed V with acetic acid, followed by deoxygenation.

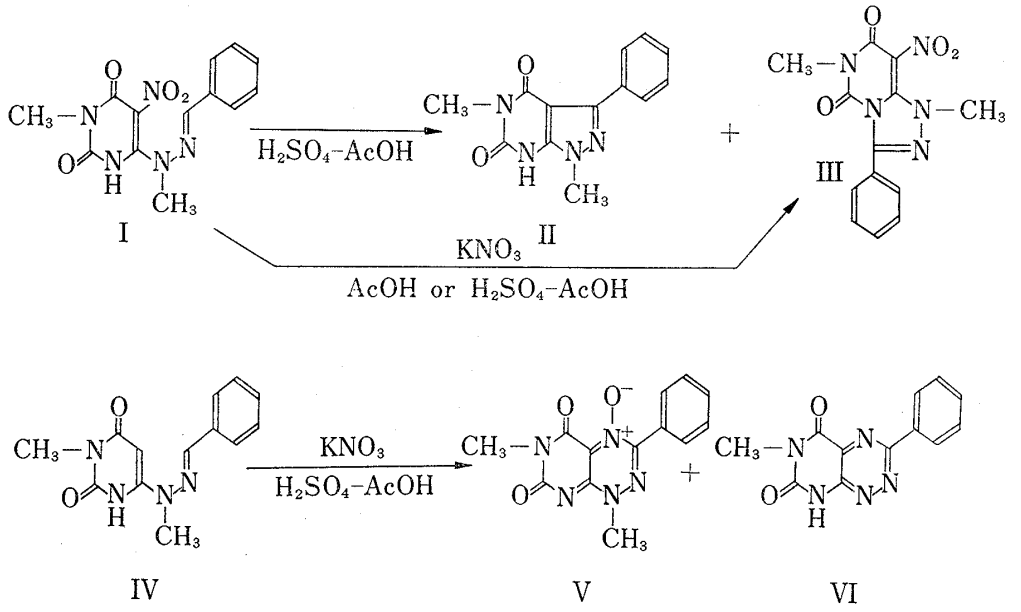

Chart 1

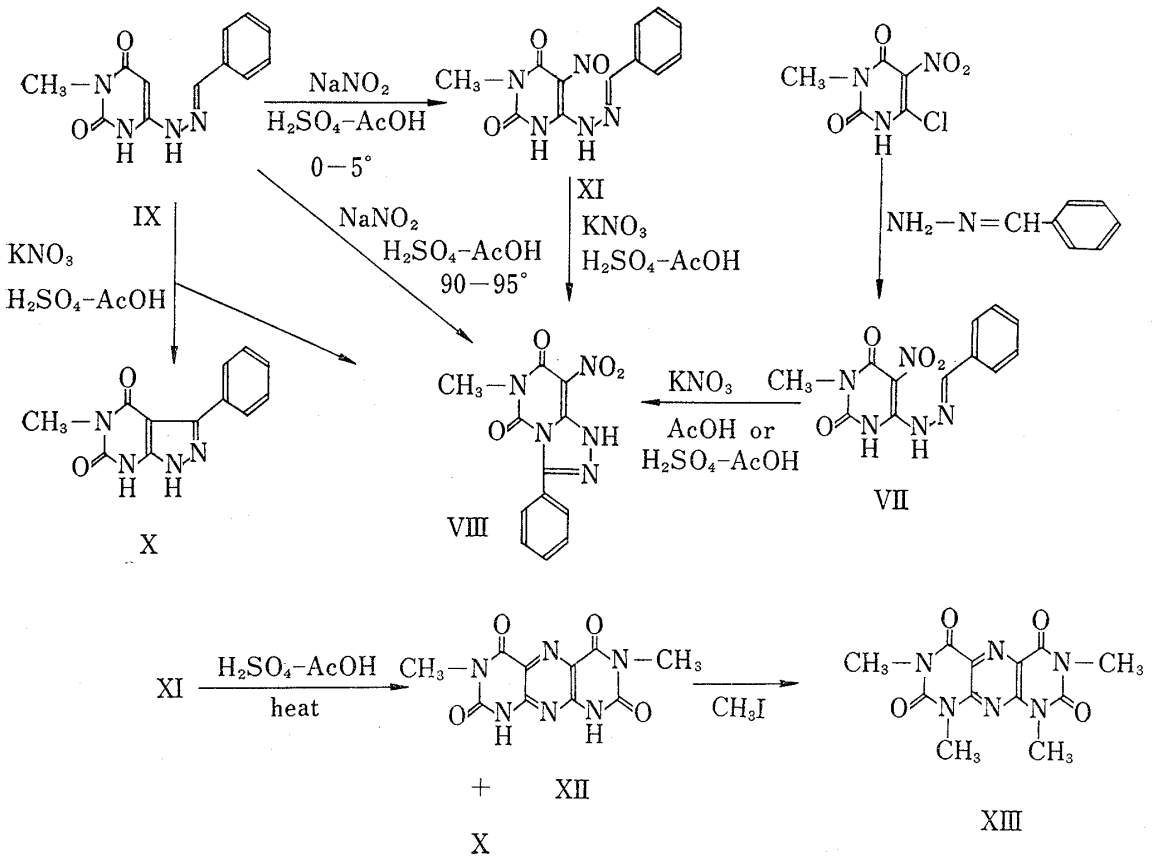

Chart 2

were not detected. This is an additional example of the nitrative cyclization of substituted 6-aminouracils leading to the heterocycle-N-oxides.[10]

Refluxing of 6-benzylidenehydrazino-3-methyl-5-nitrouracil (VII), which was prepared by treatment of 6-chloro-3-methyl-5-nitrouracil[4] with benzaldehyde hydrazone, in dimethyl-

10) F. Yoneda and Y. Sakuma, *Chem. Pharm. Bull.* (Tokyo), **21**, 448 (1973).

formamide or in a mixture of acetic acid and sulfuric acid gave no definite compounds, but only decomposed products. However, the treatment of VII with potassium nitrate in a mixture of acetic acid and sulfuric acid (or in acetic acid alone) gave 5,7-dioxo-6-methyl-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo[4,3-*c*]pyrimidine (VIII) in 65% yield.

Next, several cyclization reactions of 6-benzylidenehydrazino-3-methyluracil (IX)[3] were carried out. As described in a previous paper.[3b] heating IX with potassium nitrate in acetic acid in the presence of sulfuric acid gave 5-methyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (X) and VIII in 32 and 15% yields, respectively. This result is in contrast to the formation of toxoflavins from 6-(benzylidene-1′-methylhydrazino)-3-methyluracil (IV) under the same conditions. The heating of IX with sodium nitrite in acetic acid in the presence of sulfuric acid at 90—95° gave also VIII in 50% yield.

The treatment of IX in acetic acid with saturated aqueous solution of sodium nitrite at 0—5° gave exclusively 6-benzylidenehydrazino-3-methyl-5-nitrosouracil (XI). Heating XI with potassium nitrate in acetic acid in the presence of sulfuric acid gave VIII in 45% yield. Heating XI in a mixture of acetic acid and sulfuric acid gave interestingly a tricyclic pyrimidopteridine, 3,6-dimethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)pyrimido[5,4-*g*]pteridinetetrone (XII), and X in 35 and 20% yields respectively. XII was methylated with methyl iodide in dimethylformamide in the presence of potassium carbonate to yield 1,3,6,8-tetramethyl-2,4,5,7-(1*H*,3*H*,-6*H*,8*H*)pyrimido[5,4-*g*]pteridinetetrone (XIII).[11]

Experimental[12]

1,5-Dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (II) and 1,6-Dimethyl-5,7-dioxo-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo[4,3-*c*]pyrimidine (III)——A solution of 6-(benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil (I) (0.5 g, 0.0017 mole) in a mixture of H_2SO_4 (0.3 g) and AcOH (20 ml) was heated at 90—95° for 2 hr. The reaction mixture was diluted with H_2O (100 ml) to precipitate crystals which were collected by filtration and recrystallized from EtOH to give 0.08 g (19%) of II.[3]

The filtrate was evaporated *in vacuo* to dryness and the residue was recrystallized from EtOH to give 0.27 g (54%) of III as yellow needles, mp 163.5—165°. Mass Spectrum *m/e*: 301 (M^+). UV λ_{max}^{EtOH} nm (log ε): 225 (4.17), 260 (4.02), 350 (3.90). IR (Nujol) cm^{-1}: 1740 s, 1673 s, 1597 s, 1310 s (NO_2). NMR (CF_3COOH) ppm: 3.54 and 4.16 (each 3H, each s, $NCH_3 \times 2$), 7.63 (5H, C_6H_5). *Anal.* Calcd. for $C_{13}H_{11}O_4N_5$: C, 51.83; H, 3.68; N, 23.25. Found: C, 51.71; H, 3.71; N, 23.24.

Exclusive Formation of III—A mixture of I (1.5 g, 0.005 mole) and KNO_3 (1.0 g, 0.01 mole) in AcOH (50 ml) was heated at 90—95° for 4 hr. The reaction mixture was concentrated under reduced pressure and diluted with H_2O to separate crystals which were collected by filtration and recrystallized from EtOH to give 0.96 g (65%) of pale yellow needles.

3-Phenyltoxoflavin 4-Oxide (V)[7] and 3-Phenyl-1-demethyltoxoflavin (VI)[8]——To a mixture of 6-(benzylidene-1′-methylhydrazino)-3-methyluracil (IV) (2.58 g, 0.01 mole) and KNO_3 (1.5 g, 0.015 mole) in AcOH (100 ml) was added H_2SO_4 (1 g) and the mixture was heated at 90° for 1 hr. The reaction mixture was concentrated to a small volume under reduced pressure and diluted with H_2O to cause the separation of crystals which were collected by filtration. Fractional recrystallization from EtOH gave 1.6 g (56%) of V as yellow powder and 0.26 g (10%) of VI as pale yellow prisms. These are in all respects identical with the authentic samples.[7,8]

6-Benzylidenehydrazino-3-methyl-5-nitrouracil (VII)——To a stirred solution of 6-chloro-3-methyl-5-nitrouracil[4] (3 g, 0.015 mole) in EtOH (90 ml) were added hydrazine hydrate (0.74 g, 0.015 mole) and benzaldehyde (1.56 g, 0.015 mole). After stirring at room temperature for 2 hr, the crystals which separated were collected by filtration and recrystallized from EtOH to give 4 g (95%) of VII as pale yellow prisms, mp 259.5—261°. *Anal.* Calcd. for $C_{12}H_{11}O_4N_5$: C, 49.83; H, 3.83; N, 24.21. Found: C, 50.03; H, 3.78; N, 24.05.

5,7-Dioxo-6-methyl-8-nitro-3-phenyl-1,5,6,7-tetrahydro-*s*-triazolo[4,3-*c*]pyrimidine (VIII)[3b]——A) A mixture of VII (1.5 g, 0.0052 mole) and KNO_3 (1.0 g, 0.01 mole) in AcOH (50 ml) was heated at 90—95° for 4 hr. The reaction mixture was evaporated to dryness and the residue was diluted with H_2O to precipitate

11) *a*) E.C. Taylor, G.K. Cain, and H.M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954); *b*) F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1060 (1971).

12) All melting points were uncorrected. Infrared spectra (IR) were determined on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-I A, from samples mulled in Nujol. Nuclear magnetic resonance (NMR) spectra were determined at 60 MHz using tetramethylsilane as the internal standard.

crystals, which were collected by filtration and recrystallized from EtOH to give 0.97 g (65%) of VIII as pale yellow plates, mp 148—149°.

B) To a solution of 6-benzylidenehydrazino-3-methyluracil (IX)[3] (0.5 g, 0.002 mole) and $NaNO_2$ (2.11 g, 0.003 mole) in AcOH (20 ml) was added H_2SO_4 (0.3 g) and the mixture was heated at 90—95° for 2 hr. The reaction mixture was evaporated to a small volume and diluted with H_2O to separate crystals, which were collected by filtration. Recrystallization from EtOH gave 0.29 g (50%) of VIII.

C) To a mixture of 6-benzylidenehydrazino-3-methyl-5-nitrosouracil (XI) (0.4 g, 0.0015 mole) and KNO_3 (0.296 g, 0.003 mole) in AcOH (20 ml) was added H_2SO_4 (0.3 g) and the mixture was treated as described above to give 0.19 g (45%) of VIII.

6-Benzylidenehydrazino-3-methyl-5-nitrosouracil (XI)——To a stirred solution of 6-benzylidenehydrazino-3-methyluracil (IX)[3] (12 g, 0.049 mole) in acetic acid (180 ml) was added little by little a saturated aqueous solution of $NaNO_2$ (6 g, 0.087 mole) under cooling at 0—5°. After stirring for 2 hr at room temperature, the crystals which separated were collected by filtration, washed with H_2O and dried. The filtrate was diluted with H_2O to precipitate more crystals which were collected by filtration, washed with H_2O and dried. The combined crystals were recrystallized from EtOH to give 11.6 g (92.5%) of XI as pale green crystals, mp 205—206°. Mass Spectrum *m/e*: 273 (M^+). IR (Nujol) cm^{-1}: 3265, 1738 m, 1690 s, 1622 m, 1587 m, 1563 w, 1524 m. *Anal.* Calcd. for $C_{12}H_{11}O_3N_5$: C, 52.74; H, 4.06; N, 25.63. Found: C, 52.70; H, 4.11; N, 25.60.

3,6-Dimethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)pyrimido[5,4-*g*]pteridinetetrone (XII)——A mixture of XI (2 g, 0.007 mole) and H_2SO_4 (0.4 g) in AcOH (40 ml) was heated at 90—95° for 2 hr. After cooling, the crystals which separated were collected by filtration, washed with H_2O, dried and recrystallized from EtOH to give 2.1 g (35%) of XII as pale yellow crystals, mp>350°. Mass Spectrum *m/e*: 276 (M^+). UV $\lambda_{max}^{dioxane}$ nm (log ε): 266, 285 sh, 360 (ε could not be determined because of its insolubility, however the spectrum showed a similar pattern with that of XIII). IR (Nujol) cm^{-1}: 1739 s, 1660 s, 1583 s. *Anal.* Calcd. for $C_{10}H_8O_4N_6$: C, 43.48; H, 2.92; N, 30.43. Found: C, 43.48; H, 2.99; N, 30.38.

The filtrate was evaporated under reduced pressure to dryness and the residue was diluted with H_2O to separate crystals, which were recrystallized from EtOH to give 2.4 g (20%) of 5-methyl-3-phenylpyrazolo-[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)dione (X).[3]

1,3,6,8-Tetramethyl-2,4,5,7(1*H*,3*H*,6*H*,8*H*)pyrimido[3,4-*g*]pteridinetetrone (XIII)[11]——A mixture of XII (0.5 g, 0.0018 mole), CH_3I (1.28 g, 0.009 mole) and K_2CO_3 (2 g) in dimethylformamide (DMF) (40 ml) was refluxed for 2 hr. After removing inorganic substances by filtration, the filtrate was evaporated *in vacuo* and the residue was diluted with H_2O to precipitate crystals. Recrystallization from EtOH gave 0.2 g (36.4%) of XIII as pale yellow crystals, mp>360°, which was in all respects identical with an authentic sample.[11]