Syntheses and Properties of 4,6-Dimethyl[1,2,5]oxadiazolo[3,4-*d*]-pyrimidine-5,7(4*H*,6*H*)dione 1-Oxide

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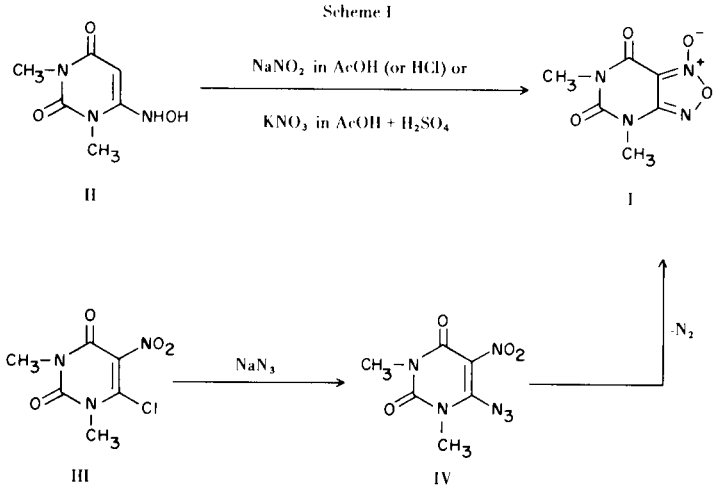
New convenient syntheses of 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione 1-oxide (I) from 1,3-dimethyl-6-hydroxylaminouracil by means of nitrosative and nitrative cyclizations are described. Compound I was converted into 4,6-dimethyl[1,2,5]oxadiazolo-[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)dione [4,6-dimethyl-5,7(4*H*,6*H*)furazano[3,4-*d*]pyrimidinedione] by refluxing in dimethylformamide. Transformation of I to 1,3,7,9-tetramethyl-2,4,6,8(1*H*,3*H*,-7*H*,9*H*)pyrimido[5,4-*g*]pteridinetetrone and/or 1,3,6,8-tetramethyl-2,4,7,9(1*H*,3*H*,6*H*,8*H*)pyrimido[4,5-*g*]pteridinetetrone is described.

The syntheses and reactions of benzofurazan oxides and their related compounds have been the subject of an extensive investigation in recent years (1). The reactions of oxadiazolo[3,4-*d*]pyrimidine *N*-oxide, the pyrimidine series of benzofurazan oxide, remain to be studied, although two synthetic procedures for this ring system have been reported. These procedures involve the reaction of a 6-chloro-5-nitropyrimidine with sodium azide and the nitrosation of a 6-hydrazino-5-nitropyrimidine, both of which apparently proceed *via* both the intermediate 4-azido-5-nitropyrimidine and tetrazolo[1,5-*c*]pyrimidine (2). The aim of the present study is to investigate new convenient syntheses of 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)dione 1-oxide (I) (3) and some transformation reactions of I.

Results and Discussion.

1,3-Dimethyl-6-hydroxylaminouracil (II) (4) in aqueous acetic acid or dilute hydrochloric acid was stirred with a slight excess of equimolar sodium nitrite under cooling at 3-5° for 1 hour, during which time yellow crystals gradually separated. The crystals were collected by filtration, washed with water and recrystallized from ethanol to give 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,-6*H*)dione 1-oxide (I). The assignment of structure I is based on satisfactory elemental analysis, and the presence of the parent ion (m/e 198) and a remarkable M+2 ion in its mass spectrum (Figure 1). It is known that powerful acceptors such as *o*-benzoquinone-type compounds including benzofuroxan and pyridofuroxan exhibit intense M+2 peaks and water is the probable origin of the hydro-

Scheme I



II I III IV

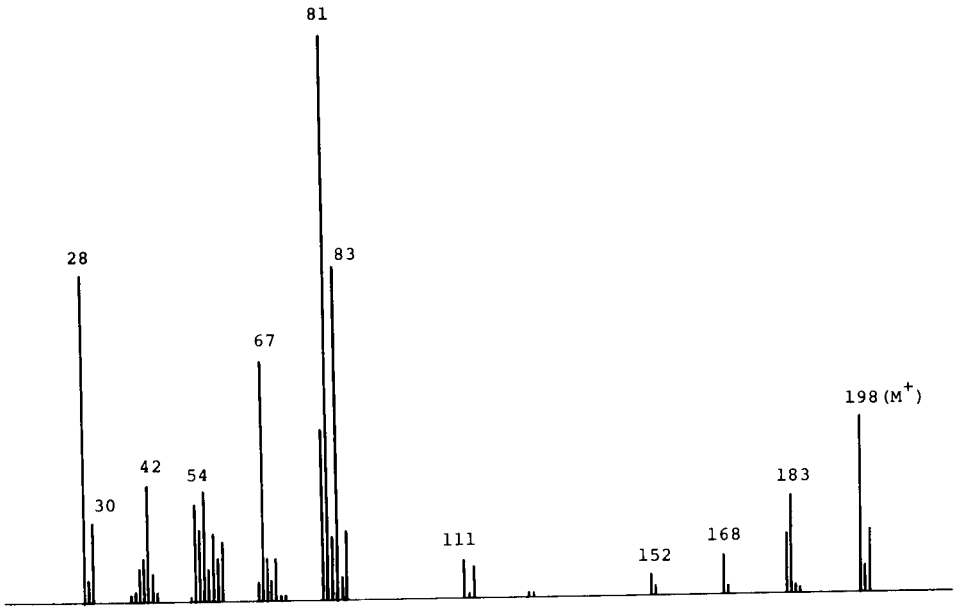
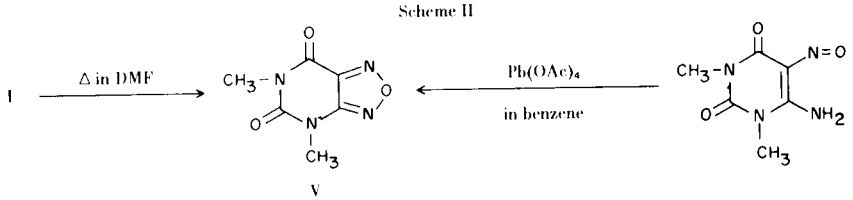


Fig. 1 Mass Spectrum of I (75 eV)

Scheme II



gen molecule responsible for the M+2 peak (5); this also appears to be the case in the above M+2 peak of I.

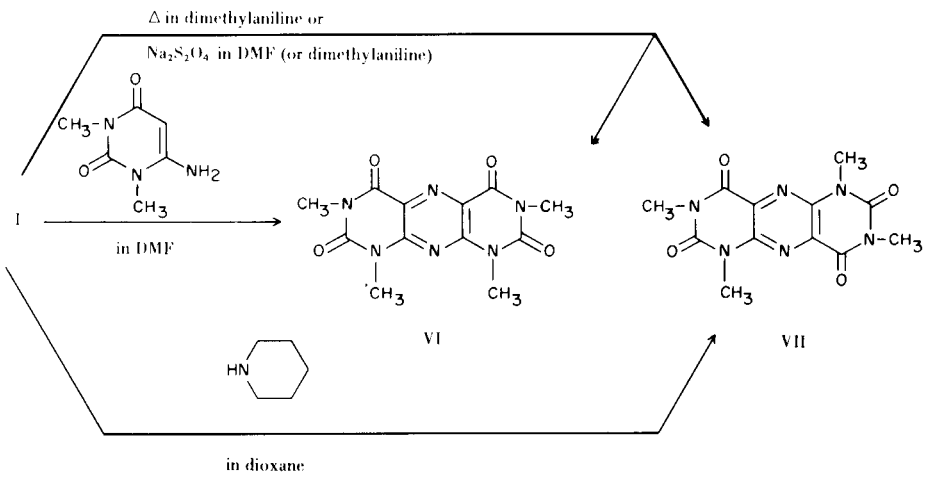
Next, the nitrative cyclization of II to obtain compound I was attempted. A mixture of II and equimolar potassium nitrite in acetic acid including excess sulfuric acid (about 3 moles) was stirred at 90° for 1 hour, followed by removal of the solvent by evaporation *in vacuo* and dilution with water to give I. It is known that a similar type of reaction occurs in several substituted 6-amino-uracils to give alloxazine *N*-oxides, isoalloxazine *N*-oxides, purine *N*-oxides and fervenulin *N*-oxides (6). This reaction is a useful addition to *N*-oxide synthesis by nitrative cyclization.

The structure of I was finally established by comparison with an authentic sample prepared by an unequivocal synthesis as follows. Reaction of 6-chloro-1,3-dimethyl-5-nitrouracil (III) (7) with sodium azide in tetrahydrofuran at room temperature gave 6-azido-1,3-dimethyl-5-nitrouracil (IV), which revealed a strong azide absorption at 2170 cm^{-1} in the infrared spectrum. Compound IV was converted on heating in dimethylformamide or without solvents into I, identical with the foregoing product prepared by nitrosative and nitrative cyclizations.

Although the removal of the oxide oxygen of I was attempted with triphenylphosphine in tetrahydrofuran or dioxane under various conditions, starting material was recovered. However, it was found that heating I in dimethylformamide alone under reflux results in the formation of 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)dione [4,6-dimethyl-5,7(4*H*,6*H*)furazano[3,4-*d*]pyrimidinedione (V)], which was identical in all respects with an authentic sample obtained by lead tetraacetate oxidation of 6-amino-1,3-dimethyl-5-nitrosouracil in benzene (8). This reaction appears to be an additional example of the participation of dimethylformamide alone as the reducing agent (9).

Heating of I with equimolar 6-amino-1,3-dimethyluracil in dimethylformamide under reflux for 8 hours gave 1,3,7,9-tetramethyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)pyrimido[5,4-*g*]pteridinetetrone (VI). This reaction virtually may involve 6-amino-1,3-dimethyluracil and V, which was formed by reduction of I with dimethylformamide de-

Scheme III



scribed above. When the reaction of I with 6-amino-1,3-dimethyluracil in dioxane was carried out, the starting materials were recovered.

On the other hand, heating I with excess piperidine in dioxane for 8 hours gave isomeric 1,3,6,8-tetramethyl-2,4,7,9(1*H*,3*H*,6*H*,8*H*)pyrimido[4,5-*g*]pteridinetetrone (VII), which was identical in all respects with an authentic sample (10,11), along with a small amount of VI.

It is interesting to note that refluxing of I in dimethylaniline only for 8 hours resulted in the formation of a nearly equimolar mixture of VI and VII.

Next, we have examined the reaction of I with sodium dithionite. Treatment of I with sodium dithionite in dimethylformamide yielded a mixture of VI and VII, whereas the reaction in water did not proceed, with the starting material being recovered. Treatment of I with sodium dithionite in dimethylaniline also gave a mixture of VI and VII.

EXPERIMENTAL (12)

4,6-Dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)dione 1-Oxide (I).

A.

A mixture of 0.85 g. (0.005 mole) of 1,3-dimethyl-4-hydroxylaminouracil (II) and 0.39 g. (0.0055 mole) of sodium nitrite in 40 ml. of water was stirred under cooling with salt-ice bath. To this suspension 0.9 ml. of glacial acetic acid (or 1 ml. of concentrated hydrochloric acid) was added dropwise while maintaining the mixture at 3-5°, whereupon II dissolved at once and the solution turned brown. After stirring for 2 hours under ice cooling, the yellow crystals which separated were collected by filtration, washed with water and recrystallized from ethanol to give 0.59 g. (60%) of pale yellow prisms, m.p. 245° dec.; uv λ max (ethanol): 268 nm (11,350), 317 (1,550); ir spectrum (see Figure II).

Anal. Calcd. for $C_6H_6N_4O_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.51; H, 2.98; N, 28.41.

B.

To a mixture of 0.85 g. (0.005 mole) of II and 0.51 g. (0.005 mole) of potassium nitrate in 20 ml. of acetic acid was added 1.57 g. (0.015 mole) of sulfuric acid and then the mixture was heated under stirring at 90° for 1 hour. After evaporation of the solvent, the residue was diluted with 30 ml. of water to give 0.64 g. (65%) of I.

C.

A mixture of 0.23 g. (0.001 mole) of 6-azido-1,3-dimethyl-5-nitrouracil (IV) (prepared by the procedure described below) in 5 ml. of dimethylformamide was refluxed gently for 30 minutes, during which time violent evolution of nitrogen was observed. The solution was evaporated *in vacuo* and the resulting residue was washed with water and recrystallized from ethanol to give 0.09 g. (45%) of I, which compared in all respects with the product prepared by nitrosative and nitrative cyclizations.

6-Azido-1,3-dimethyl-5-nitrouracil (IV).

To a solution of 0.22 g. (0.001 mole) of 6-chloro-1,3-dimethyl-5-nitrouracil (III) in 30 ml. of tetrahydrofuran was added 0.2 g. (0.003 mole) of sodium azide and the mixture was stirred for 5 hours at room temperature. The precipitate was collected by filtration and washed with water to remove sodium azide and sodium chloride to give crude IV. The filtrate was concentrated *in vacuo* to separate additional IV. The combined crude IV was recrystallized from tetrahydrofuran to yield 0.18 g. (80%) of colorless crystals, m.p. 148-149° dec.

Anal. Calcd. for $C_6H_6N_6O_4$: C, 31.86; H, 2.67; N, 37.16. Found: C, 31.87; H, 2.78; N, 36.82.

4,6-Dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)dione [4,6-Dimethyl-5,7(4*H*,6*H*)furazano[3,4-*d*]pyrimidinedione] (V).

A solution of 0.2 g. (0.001 mole) of I in 10 ml. of dimethylformamide was refluxed for 8 hours, and allowed to stand overnight in the refrigerator. The crystals thus separated were collected by filtration and washed with ether. Recrystallization from acetone gave 0.15 g. (83%) of colorless plates, m.p. 225°. The product was identical in all respects with an authentic sample (8).

1,3,7,9-Tetramethyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)pyrimido[5,4-*g*]pteridinetetrone (VI).

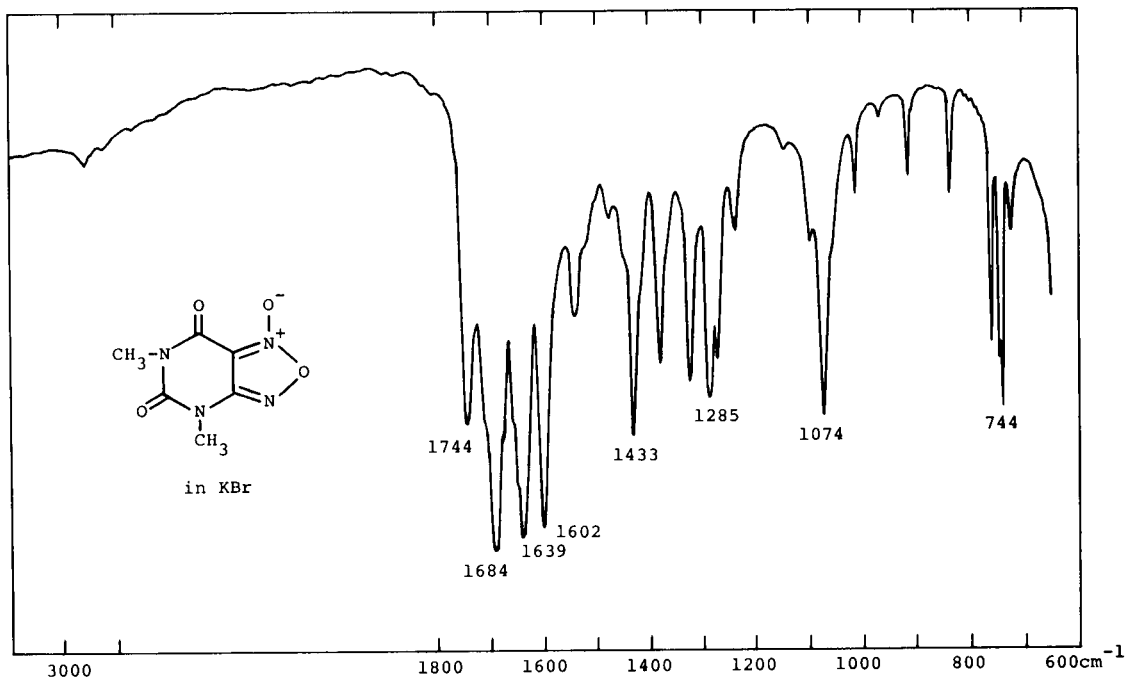


Fig. 2

A mixture of 0.2 g. (0.001 mole) of I and 0.16 g. (0.001 mole) of 6-amino-1,3-dimethyluracil in 10 ml. of dimethylformamide was refluxed for 8 hours and allowed to stand overnight at room temperature. The crystals which separated were collected by filtration and washed with ether to give 0.2 g. (67%) of VI, m.p. 385°, which was identical in all respects with an authentic sample (10).

1,3,6,8-Tetramethyl-2,4,7,9(1*H*,3*H*,6*H*,8*H*)pyrimido[4,5-*g*]pteridinetetrone (VII).

A mixture of 0.1 g. (0.0005 mole) of I with 0.1 g. (0.001 mole) of piperidine in 10 ml. of dioxane was refluxed for 8 hours, and the solvent was evaporated *in vacuo*. The resulting residue was washed with ether to give 0.07 g. of crude VII, contaminated with VI. Recrystallization from dimethylformamide gave 0.5 g. (67%) of VII, m.p. 350°. The product was identical in all respects with an authentic sample (10,11).

Reductive Dimerization of I.

A.

A mixture of 0.1 g. (0.0005 mole) of I with 0.17 g. (0.001 mole) of sodium dithionite in 10 ml. of dimethylformamide was refluxed for 8 hours and allowed to stand overnight at room temperature to precipitate 0.05 g. (66%) of a nearly equimolar mixture of VI and VII, which were easily distinguished by their crystalline forms (VI: almost colorless plates, VII: yellow prisms).

B.

A mixture of 0.1 g. (0.0005 mole) of I with 0.17 g. (0.001 mole) of sodium dithionite in 10 ml. of dimethylaniline was stirred at room temperature for 6 days. The crystals thus separated were collected by filtration and washed with ether to give 0.06 g. (79%) of a nearly equimolar mixture of VI and VII.

C.

A mixture of 0.1 g. (0.0005 mole) of I in 10 ml. of dimethylaniline was refluxed for 8 hours and allowed to stand overnight at room temperature to cause separation of 0.05 g. (66%) of a nearly equimolar mixture of VI and VII.

REFERENCES

(1) For reviews, see (a) A. J. Boulton and P. B. Ghosh, *Advan. Heterocyclic Chem.*, **10**, 1 (1969); (b) P. N. Preston and Tennant, *Chem. Rev.*, **72**, 649-651 (1972).

(2) C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **33**, 2086 (1968).

(3) A part of this paper has been reported in a preliminary form: F. Yoneda, Y. Sakuma, and M. Ueno, *J. Heterocyclic Chem.*, **10**, 415 (1973).

(4) W. Pfleiderer and H. Ferch, *Ann. Chem.*, **615**, 52 (1958).

(5) R. T. Aplin and W. T. Pike, *Chem. Ind.*, 2009 (1966).

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

(7) T. K. Liao and C. C. Cheng, *J. Heterocyclic Chem.*, **1**, 212 (1964).

(8) E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, **37**, 1601 (1972).

(9) E. C. Taylor and E. E. Garcia, *J. Am. Chem. Soc.*, **80**, 4721 (1964).

(10) F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1060 (1971).

(11) W. Pfleiderer, K.-H. Schundehutte, and H. Ferch, *Ann. Chem.*, **615**, 57 (1958).

(12) All melting points were uncorrected. Infrared spectra were obtained on a Japan Spectroscopic Co. Ltd. spectrophotometer, Model IR-I. The mass spectra (75 eV) were recorded on a Hitachi RMU-6D spectrometer.