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Nitrosative Cyclization of 1,3-Dimethyl-6-(α-methylalkylidenehydrazino)-uracils by Means of N-Nitrosodimethylamine-Phosphorus Oxychloride Mixture. A New Route to 2-Vinyl-*v*-triazolo[4,5-*d*]pyrimidines

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A new synthetic method of 2-vinyl-*v*-triazolo[4,5-*d*]pyrimidines, which consists of the nitrosative cyclization of 1,3-dimethyl-6-(α-methylalkylidenehydrazino)uracils with a mixture of N-nitrosodimethylamine and phosphorus oxychloride (NDA+$POCl_3$) is described. The reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil with acetophenone gave 1,3-dimethyl-6-phenyl-7-azalumazine (3-phenylfervenulin) (X). The nitrosation of 6-benzylidenehydrazino-1,3-dimethyluracil with NDA+$POCl_3$ also gave X.

The antitumor activity of certain *v*-triazolo[4,5-*d*]pyrimidines has stimulated considerable interest in this area.[2] This ring system has generally been prepared by two principal routes: one involving the ring closure of suitably-substituted pyrimidine derivatives, and the other involving the utilizing of the *v*-triazole precursors and annelating the condensed pyrimidine ring.[3]

We now describe a new route to the synthesis of 2-vinyl-*v*-triazolo[4,5-*d*]pyrimidines consisting of the nitrosative cyclization of 1,3-dimethyl-6-(α-methylalkylidenehydrazino)-uracils with a mixture of N-nitrosodimethylamine (NDA) and phosphorus oxychloride (referred hereafter as NDA+$POCl_3$) which has first been introduced by us as a new type of nitrosating reagent.[4]

The key intermediates, 1,3-dimethyl-6-(α-methylalkylidenehydrazino) uracil (IIa—e), were prepared by the treatment of 1,3-dimethyl-6-hydrazino uracil (I)[5] with respective ketones (Table I).

Refluxing of 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)uracil (IIa)[6] with two equivalents of NDA+$POCl_3$ in benzene for 15 min afforded a good yield of 4,6-dimethyl-2-(1-phenylvinyl)-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (IVa). The structure of IVa was assigned on the basis of its spectral data and elemental analysis. In particular, the nuclear magnetic resonance (NMR) spectrum (DMSO-d_6) of IVa revealed two protons attributable to the olefinic protons of 1-phenylvinyl group at the position 2, which ruled out the possibility of 1,3-dimethyl-7-phenyl-9H-pyrimido[4,5-*c*][1,2,5]triazepine-2,4(1H,3H)-dione (VI)[7] as an alternative structure for IVa. Additional support for the structure of IVa was provided by its

1) Location: *a*) *35, Shinanomachi, Shinjuku-ku, Tokyo*; *b*) *5-1, Oe-honmachi, Kumamoto.*
2) The antitumor activity of *v*-triazolo[4,5-*d*]pyrimidines has been reviewed by R.K. Robins: *J. Med. Chem.*, **7**, 186 (1964).
3) R.K. Robins, "Heterocyclic Compounds," Vol. 8, ed. by R.C. Elderfield, John Wiley and Sons, 1967, p. 162, and references cited therein.
4) F. Yoneda, K. Senga, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 260 (1973).
5) W. Pfleiderer and K-H. Schündehütte, *Ann.*, **612**, 158 (1958).
6) S. Senda and K. Hirota, *Chem. Pharm. Bull.* (Tokyo), **22**, 1459 (1974).
7) The 6-amino-5-nitrosopyrimidine derivatives carrying methyl or methylene substituents on the 6-amino group have been known to undergo thermally induced intramolecular dehydration. For example, H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **691**, 142 (1969) and G.P.G. Dick, H.C.S. Wood, and W.R. Logan, *J. Chem. Soc.*, **1956**, 2131.

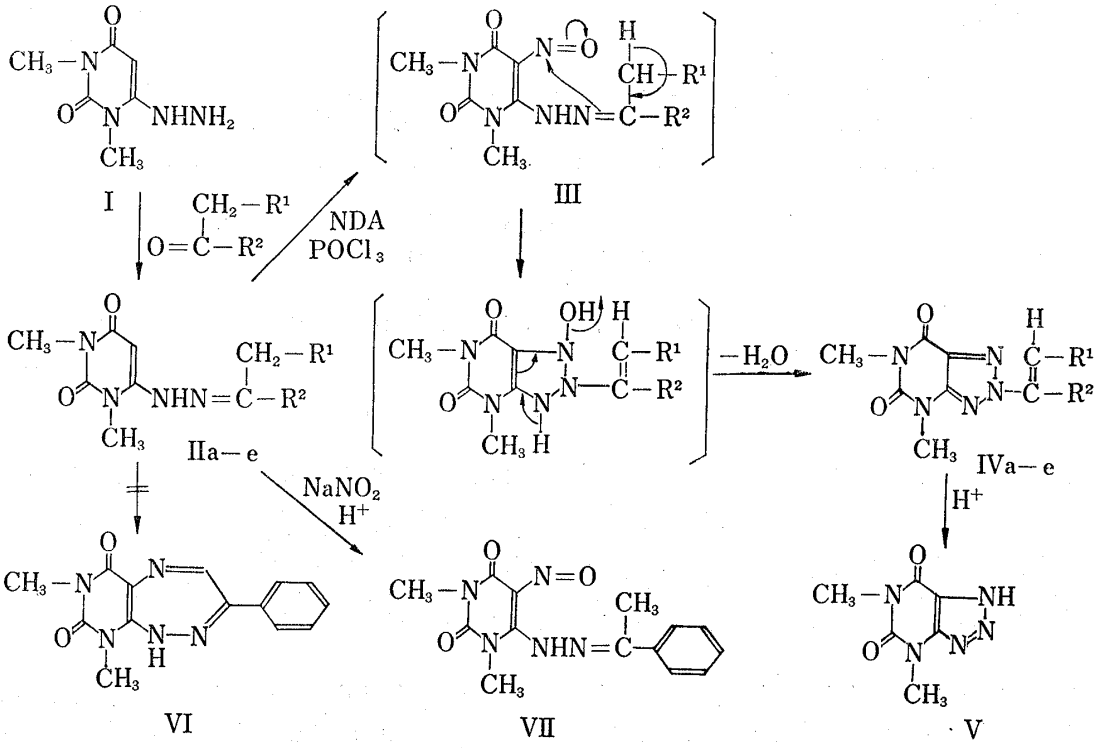
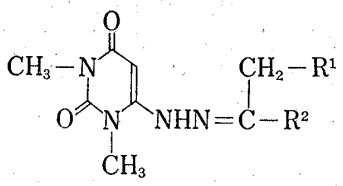


Chart 1

Table I. 1,3-Dimethyl-6-(α-methylalkylidenehydrazino)uracils



Compd. No.	R^1	R^2	mp (°C) Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	H	Ph	203—205[6] EtOH	72	$C_{14}H_{16}O_2N_4$	61.75	5.92	20.58	61.48	5.90	20.75
IIb	H	*p*-ClPh	214—216 DMF–EtOH	52	$C_{14}H_{15}O_2N_4Cl$	54.79	4.93	18.27	54.65	4.88	18.41
IIc	H	*p*-MePh	166—168 DMF–EtOH	50	$C_{15}H_{18}O_2N_4$	62.92	6.34	19.57	62.81	6.30	19.46
IId	H	Me	146—148[6] EtOH	84	$C_9H_{14}O_2N_4$	51.42	6.71	26.65	51.71	6.49	26.63
IIe	H	Et	130—131 EtOH	77	$C_{10}H_{16}O_2N_4$	53.55	7.19	24.99	53.58	7.20	25.25

acid cleavage to the known 4,6-dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (V).[8]

As depicted in the Chart 1, this reaction involves without doubt the intermediacy of a 5-nitroso derivative (III), whose dehydrative cyclization to the 2-vinyl-*v*-triazolo[4,5-*d*]pyrimidine is apparently facilitated by the presence of phosphorus oxychloride in the reaction medium. It should be noted here that the usual nitrosation of IIa with sodium nitrite and

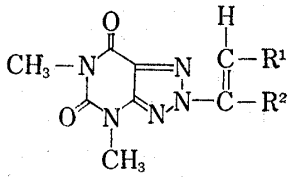
8) F.F. Blicke and H.C. Godt Jr., *J. Am. Chem. Soc.*, **76**, 2798 (1954).

acetic acid or hydrochloric acid did not give the corresponding *v*-triazolo[4,5-*d*]pyrimidine but 1,3-dimethyl 6-(α-methylbenzylidenehydrazino)-5-nitrosouracil (VII)[9] in good yield.

In complete analogy with the above result, 2-[1-(4-chlorophenyl)vinyl]-(IVb) and 2-[1-(4-methylphenyl)vinyl]-4,6-dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (IVc) were prepared by the reaction of the corresponding 1,3-dimethyl-6-(α-methylbenzylidenehydrazino)-uracils with NDA+$POCl_3$ (Table II).

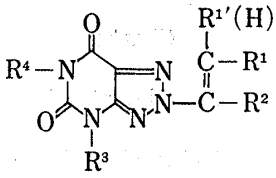
When the reaction was applied to 1,3-dimethyl-6-isopropylidenehydrazino uracil (IId),[6] the expected 4,6-dimethyl-2-isopropenyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (IVd)

Table II. 2-Substituted 4,6-Dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H, 6H)-diones



Compd. No.	R^1	R^2	mp (°C) Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa	H	Ph	188.5—190 EtOH	65	$C_{14}H_{13}O_2N_5$	59.35	4.63	24.72	59.37	4.74	24.53
IVb	H	*p*-ClPh	149.5—152 BzH–*n*-hexane	31	$C_{14}H_{12}O_2N_5Cl$	52.87	3.80	22.04	53.14	3.77	21.75
IVc	H	*p*-MePh	164—166 BzH–*n*-hexane	52	$C_{15}H_{15}O_2N_5$	60.59	5.09	23.56	60.84	5.00	23.69
IVd	H	Me	157—159 *n*-hexane	57	$C_9H_{11}O_2N_5$	48.86	5.01	31.66	48.76	4.97	31.59
IVe	Me	Me	124—125.5 *n*-hexane	44	$C_{10}H_{13}O_2N_5$	51.05	5.57	29.77	51.24	5.50	29.65

Table III. NMR Data of 2-Substituted 4,6-Dimethyl-*v*-triazolo[4,5-*d*]-pyrimidine-5,7(4H, 6H)-diones[a]



Compd. No.	δ (DMSO-d_6) R^1	$R^{1'}$ (H)	R^2	R^3 (CH_3)	R^4 (CH_3)
IVa	5.70 (d, 1H, $J_{R^1R^{1'}}$=1.5) 5.93 (d, 1H, $J_{R^1R^{1'}}$=1.5)		7.39 (s, 5H)	3.42 (s, 3H)	3.28 (s, 3H)
IVd	5.18 (br. s, 1H) 5.77 (s, 1H)		2.34 (s, 3H)	3.38 (s, 3H)	3.22 (s, 3H)
IVe	1.83 (tt, 3H, $J_{R^1R^{1'}}$=7, $J_{R^1R^2}$=1.5)	6.47 (qt, 1H, $J_{R^{1'}R^1}$=7, $J_{R^{1'}R^2}$=1.5)	2.24 (t, 3H, $J_{R^{1'}R^2}$= $J_{R^1R^2}$=1.5)	3.39 (s, 3H)	3.22 (s, 3H)

a) Coupling constant *J* given in Hertz.

9) This compound is extremely unstable, therfore the purification was unsuccessful. The structure and properties of VII will be covered in a later communication.

was obtained. However, 1,3-dimethyl-6-[(1-methylpropylidene)hydrazino]uracil (IIe) gave 4,6-dimethyl-2-(1-methylpropenyl)-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (IVe) instead of an isomeric 1-ethylvinyl derivative. The structures of these products were elucidated by the NMR spectroscopy. The NMR data for the *v*-triazolo[4,5-*d*]pyrimidines prepared in this study were summarized in Table III.

In connection with above study, we have investigated a following reaction to seek an alternative route to the *v*-triazolo[4,5-*d*]pyrimidines. For example, the reaction of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (VIII)[10] with acetophenone was carried out in expectation of the formation of IVa, however, the product was found to be 1,3-dimethyl-6-phenyl-7-azalumazine (3-phenylfervenulin) (X).[11] Compound X was alternatively obtained by the nitrosative cyclization of 6-benzylidenehydrazino-1,3-dimethyluracil (IX)[12] using NDA+$POCl_3$.

A possible mechanism for the formation of X from VIII and acetophenone is indicated in in Chart 2. A postulated intermediate would be 5,6-dihydro-1,3-dimethyl-5-hydroxy-6-methyl-6-phenyl-7-azalumazine (XI), which could give rise to the observed product X by loss of the element of methanol. An analogous aromatization was reported in the pteridine synthesis from a 6-amino-5-nitrosopyrimidine and 2-phenylpropionitrile.[13]

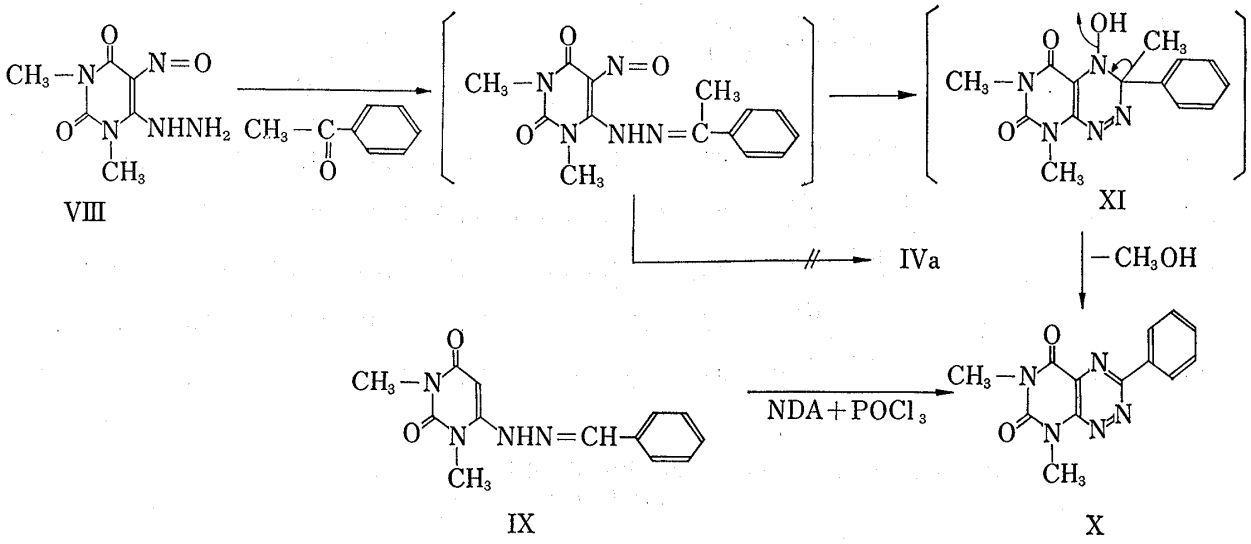


Chart 2

Experimental[14]

1,3-Dimethyl-6-(α-methylalkylidenehydrazino)uracils (IIa—e in Table I)——A mixture of 1,3-dimethyl-6-hydrazinouracil (I)[5] (1.7 g, 0.01 mole) and an equimolar amount of the respective ketone in AcOH (30 ml) was heated at reflux for 2 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from appropriate solvent to give the corresponding pure product. In the case of IId and IIe, the ketone itself was used as solvent.

2-Substituted 1,3-Dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-diones (IVa—e in Table II)——A mixture of 1,3-dimethyl-6-(α-methylalkylidene hydrazino)uracil (0.005 mole), NDA (0.74 g, 0.01 mole), and $POCl_3$ (1.54 g, 0.01 mole) in C_6H_6 (30 ml) was heated at reflux for 15—30 min. The reaction mixture was evaporated to dryness *in vacuo*. The residue was extracted with hot *n*-hexane (*ca.* 500 ml) and the extract

10) W. Pfleiderer and K-H. Schündehütte, *Ann.*, **615**, 42 (1958).
11) *a*) F. Yoneda, M. Kanahori, K. Ogiwara, and S. Nishigaki, *J. Heterocyclic Chem.*, **7**, 1443 (1970); *b*) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 2884 (1975).
12) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 1484 (1975).
13) J. Weinstock, J.P. Rosenbloom, and P.S. Hines, *J. Org. Chem.*, **33**, 3339 (1968).
14) All melting points were uncorrected. IR, NMR, and Mass spectra of all new compounds were consistent with the proposed structures. The NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-20 (60 MHz) spectrometer using tetramethylsilane as an internal standard.

was concentrated *in vacuo*. The residue was recrystallized from proper solvent to give the corresponding pure product (IVa—e).

4,6-Dimethyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (V)——A suspension of IVa (0.283 g, 0.001 mole) in HCOOH (5 ml) was refluxed for 10 hr. The solution was evaporated to dryness *in vacuo* and the residue was recrystallized from H_2O to give the product (V) (0.12 g, 67%), mp 254—257°, identified with an authentic sample.[8]

1,3-Dimethyl-6-phenyl-7-azalumazine (3-Phenylfervenulin) (X)——Method A: A mixture of 1,3-dimethyl-6-hydrazino-5-nitrosouracil (VIII)[10] (0.398 g, 0.002 mole) and acetophenone (0.216 g, 0.002 mole) in EtOH (10 ml) was refluxed for 10 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was triturated with EtOH and the insoluble solid was filtered. Recrystallization from EtOH afforded the pure product (X) (0.06 g, 11%), mp 267—270°, which is identical in all respects with the authentic sample.[11]

Method B: A mixture of 6-benzylidenehydrazino-1,3-dimethyluracil (IX)[12] (0.77 g, 0.003 mole), NDA (0.44 g, 0.006 mole) and $POCl_3$ (0.94 g, 0.006 mole) was heated at 90° for 15 min. The reaction mixture was triturated with H_2O and the insoluble solid was recrystallized from EtOH to give the product (X) (0.27 g, 35%) which is identical in all respects with the compound prepared by Method A.

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Studies on Tetrahydroisoquinolines. XII.[1] An Alternative Synthesis of (±)-Bracteoline, (±)-Isoboldine, (±)-N-Methyllaurotetanine, and Their Related Aporphines

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By the treatment of the *p*-quinol acetate (Xa) and (Xb) with trifluoroacetic acid, (±)-10-benzyloxy-1-hydroxy-2,9-dimethoxyaporphine (XIa) and (±)-9-benzyloxy-1-hydroxy-2,10-dimethoxyaporphine (XIb) were given in good yield, respectively. Furthermore, XIa and XIb were converted to (±)-bracteoline (XIIa) and (±)-isoboldine (XIIb) by catalytic debenzylation, or to (±)-10-hydroxy-1,2,9-trimethoxyaporphine (XIVa) and (±)-N-methyllaurotetanine (XIVb) by methylation and successive debenzylation, respectively.

Previously, a simple synthesis[1] *via* a *p*-quinol acetate of aporphines having alkoxyl groups in the D ring, such as (±)-thaliporphine (I), (±)-domesticine (II), and (±)-1-hydroxy-2,9,10,-11-tetramethoxyaporphine (III), has been achieved in our laboratory.

As an extension of the method, synthesis of aporphines having a hydroxyl group in the D ring was undertaken and we report here an improved synthesis of (±)-bracteoline (XIIa),[3] (±)-isoboldine (XIIb),[4] and (±)-N-methyllaurotetanine (XIVb).[5]

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1) Part XI: H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 262 (1976).
2) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
3) *a*) T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 2446; T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5375 (1971); *b*) P. Kerekes, K. Délenk-Heydenreich, and S. Pfeifer, *Chem. Ber.*, **105**, 609 (1972).
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