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Pyrimidine Derivatives and Related Compounds. XXIX.[1] Photoreductive Cyclization of 5-Nitro-6-styryl(or anilino)uracil Derivatives to Pyrrolo[3,2-*d*]pyrimidine and Alloxazine Derivatives[2]

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Irradiation of 1,3-dimethyl-5-nitro-6-styryluracils (**1a**—**c**) principally gave 1,3-dimethyl-6-phenylpyrrolo[3,2-*d*]pyrimidines (**3a**—**c**) in 8—16% yields. Irradiation of 6-anilino-5-nitrouracils (**5a**—**c**) gave alloxazines (**6a,b**) and isoalloxazine (**6c**) in 14—18% yields. These products were formed by photoreductive cyclization of a nitro group with an *o*-substituted styryl or anilino group.

Keywords——photoreductive cyclization; 5-nitro-6-styryluracil derivatives; 5-nitro-6-anilinouracil derivatives; pyrrolo[3,2-*d*]pyrimidine derivatives; alloxazine derivatives

Many novel types of photochemical reactions of aromatic and olefinic nitro compounds have been found during the last few years.[4] This paper describes a photochemistry of 5-nitrouracil derivatives having a styryl group or an anilino group at the 6-position. This photochemical reaction involves a novel photoreductive cyclization of a nitro group with an *o*-substituent and also provides a synthetic route to biologically interesting condensed pyrimidines, *e.g.* the pyrrolo[3,2-*d*]pyrimidines and the alloxazines.

Photolysis of 1,3-dimethyl-5-nitro-6-styryluracil (**1a**) in isopropanol afforded two types of photoproducts, the benzo[*f*]quinazoline (**2a**) and the 6-phenylpyrrolo[3,2-*d*]pyrimidine (**3a**) in 8% and 16% yields, respectively. The structure of **2a** was confirmed by identification with the 1,3-dimethylated derivative of 1,3-dioxo-1,2,3,4-tetrahydrobenzo[*f*]quinazoline[5] prepared

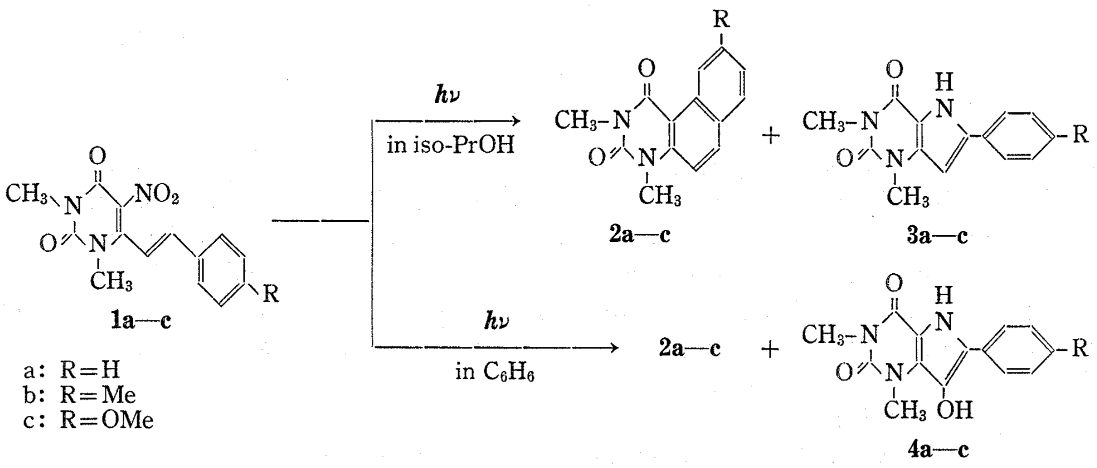

Chart 1

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[1] Part XXVIII: S. Senda, K. Hirota, and T. Asao, *Yakugaku Zasshi*, **95**, 1250 (1975).

[2] A part of this work was presented as a communication: S. Senda, K. Hirota, and M. Takahashi, *Heterocycles*, **4**, 461 (1976).

[3] Location: *5-6-1, Mitahora-higashi, Gifu.*

[4] For some examples see: J.T. Pinhey and E. Rizzardo, *Tetrahedron Letters*, **1973**, 4057; D. Döpp, D. Müller, and K. -H. Sailer, *ibid.*, **1974**, 2137; C.P. Joshua and P.K. Ramdas, *ibid.*, **1974**, 4359; P.M. Crosby, K. Salisbury, and G.P. Wood, *J. C.S. Chem. Commun.*, **1975**, 312; Y. Maki, T. Furuta, M. Kuzuya, and M. Suzuki, *ibid.*, **1975**, 616.

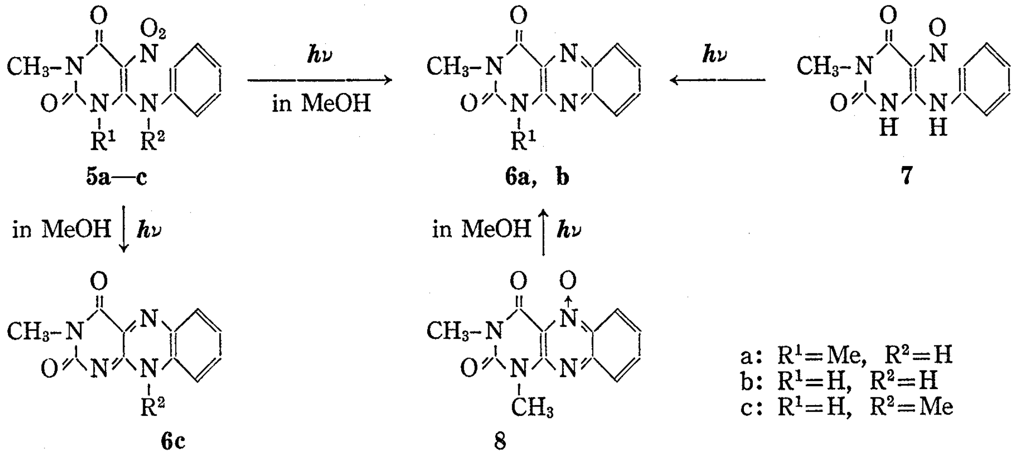
[5] A. Rosowsky and E.J. Modest, *J. Org. Chem.*, 31, 2607 (1966).

by Rosowsky's method. The pyrrolopyrimidine (**3a**) was identical in every respect with the authentic sample prepared by an alternative route.[6] Similar results were obtained by the photolysis of 5-nitro-6-styryluracil derivatives (**1b,c**), affording **2b,c** and **3b,c** in 3—8% yields.

A number of examples were reported on the photocyclization of a 6π-electron system, *e.g.* the photoconversion of *trans*-stilbenes to phenanthrenes.[7] Thus, the formation of the tricyclic pyrimidines (**2a—c**) could be explained in terms of the photo-electrocyclization similar to the case of *trans*-stilbenes, followed by a loss of nitrous acid.

The formation of the pyrrolopyrimidines (**3a—c**) greatly depends on the solvent used. Thus, the irradiation of 5-nitro-6-styryluracils(**1a—c**) in benzene resulted in no formation of **3a—c**, but instead, the benzo[*f*]quinazolines (**2a—c**) and 7-hydroxy-6-(*p*-substituted phenyl)pyrrolo-[3,2-*d*]pyrimidines (**4a—c**) were obtained in 9—12% and 6—8% yields, respectively. These results would imply that the key step in the formation of **3** from **1** is the deoxygenation of the nitro group[8] in an excited state by an alcoholic solvent. This implication could be supported by the following results. In the presence of benzaldehyde, known as a hydrogen donor to an excited nitro group,[9] the photolysis of **1** afforded **3** in 3—4% yields even in benzene.

On the other hand, the 7-hydroxypyrrolo[3,2-*d*]pyrimidines (**4**) may be formed by the direct addition of an excited nitro group to an ethylenic bond of a 6-styryl group in **1** as observed in the photochemistry of *o*-nitrostilbenes.[9]



a: R^1=Me, R^2=H
b: R^1=H, R^2=H
c: R^1=H, R^2=Me

Chart 2

An analogous photoreductive cyclization occurred on the photolysis of 6-anilino-5-nitrouracils (**5a-c**) in methanol affording the alloxazines (**6a,b**) and the isoalloxazine (**6c**) in 15%, 18%, and 14% yields. It has been demonstrated that the photochemistry of nitro compounds in an alcoholic solvent proceeds *via* the corresponding nitroso intermediates.[8] Therefore, we examined the photolysis of 5-nitroso-6-anilinouracil(**7**) in benzene and obtained the alloxazine (**6b**) in a 77% yield. These facts suggest a possible route to the alloxazines (or isoalloxazines) involving the 5-nitroso intermediates (**9**) in the photoreductive cyclization of the 6-anilino-5-nitrouracils (path a in Chart 3).

An alternative route to **6** *via* alloxazine-5-oxides (**8a,b**) and isoalloxazine-5-oxides (**8c**) (path b in Chart 3) was suggested by the following experiment. The photolysis of 1,3-dimethylalloxazine-5-oxide (**8a**) in methanol resulted in the formation of **6a** in a 96% yield. We are unable at present to obtain evidence (e.g. to detect any of possible intermediates, **8** or **9**) favoring any one route over the others.

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6) E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, **30**, 655 (1965).
7) For review, see W.E.V. Blackburn and C.T. Timmons, *Quart. Rev.*, **85**, 2186 (1963).
8) For review, see H.A. Morrison, "The Chemistry of the Nitro and Nitroso Groups," Part 1, ed. by H. Feuer, Interscience Publishers, New York, 1969, pp. 181—191.
9) J. Splitter and M. Carvin, *J. Org. Chem.*, **20**, 1086 (1955).

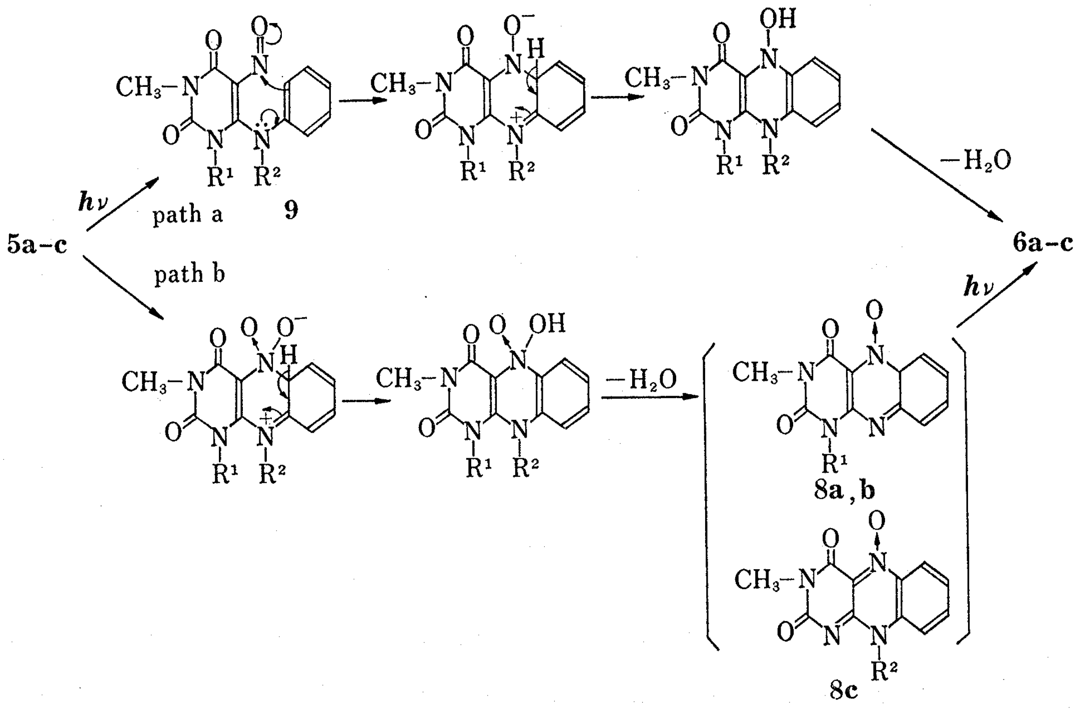


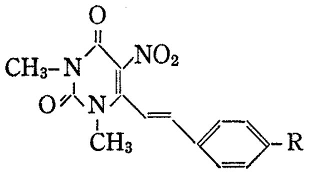
Chart 3

Although the present photoreductive cyclizations of the 5-nitrouracils do not proceed quantitatively, this type of photochemical reduction of the *o*-substituted nitro groups has been scarcely observed[10] even in the case of *o*-nitrostilbenes and *o*-nitrobiphenylamines which are proto-types of our compounds.

Experimental[11]

Materials——1,3-Dimethyl-5-nitro-6-styryluracils (**1a**—**c**) were prepared by the condensation of 5-nitro-1,3,6-trimethyluracil with benzaldehyde derivatives according to the procedure of Taylor, *et al.*[6] 6-Anilino-

Table I. 1,3-Dimethyl-5-nitro-6-(*p*-substituted)styryluracils (1)



Compd. No.	R	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
1a	H	196—198	AcOH-H_2O	85	$C_{14}H_{13}O_4N_3$	58.53 (58.59)	4.56 (4.48)	14.63 (14.60)
1b	Me	180—181	EtOH	78	$C_{15}H_{15}O_4N_3$	59.79 (59.68)	5.02 (5.00)	13.95 (13.88)
1c	OMe	187[a]	AcOH-H_2O	80	$C_{15}H_{15}O_5N_3$	56.78 (56.72)	4.77 (4.75)	13.24 (13.20)

a) lit.[6] mp 186—187°

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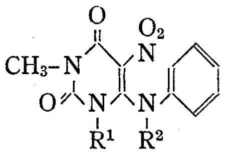
10) P.M. Preston and G. Tennant, *Chem. Rev.*, **72**, 627 (1972).

11) All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected.

Table II. 6-Anilino-3-methyl-5-nitrouracils (**5**)



Compd. No.	R^1	R^2	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
5a	Me	H	201[a)]	AcOH	90	$C_{12}H_{12}O_4N_4$	52.17 (52.10)	4.37 (4.35)	20.28 (20.25)
5b	H	H	291	AcOH	88	$C_{11}H_{10}O_4N_4$	50.38 (50.47)	3.84 (3.81)	21.37 (21.33)
5c	H	Me	236	AcOH	92	$C_{12}H_{12}O_4N_4$	52.17 (52.05)	4.37 (4.41)	20.28 (20.22)

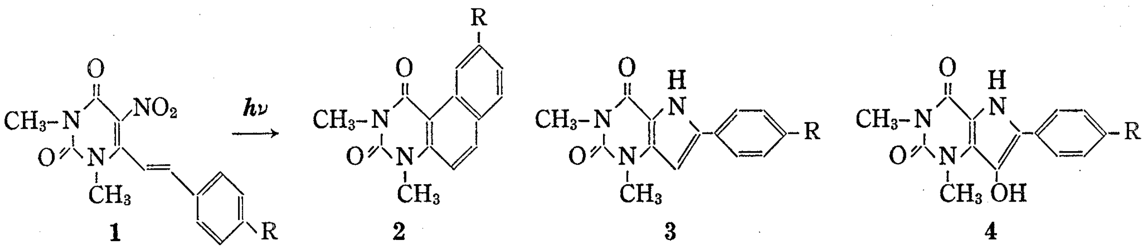
a) lit.[12)] mp 200°

5-nitrouracils (**5a**—**c**) were prepared by the treatment of 6-chloro-5-nitrouracils with aniline according to the procedure of Taylor, *et al.*[12)]

General Irradiation Procedure——Irradiations were carried out in a flask equipped with a Pyrex-jacketed immersion lamp. The light source was a Riko-UVL 100 W or 400 W high-pressure mercury lamp. Prior to irradiation the solution was flushed with nitrogen and nitrogen was bubbled through the solution constantly during irradiation.

Photolysis of 1,3-Dimethyl-5-nitro-6-styryluracils (1a—c)——A solution of **1a**—**c** was irradiated with a 100 W high-pressure mercury lamp, and the solvent was evaporated under reduced pressure. The residue was collected by filtration and washed with acetone to give pyrrolo[3,2-*d*]pyrimidine (**3a**—**c**) or 7-hydroxy-6-(*p*-substituted-phenyl)pyrrolo[3,2-*d*]pyrimidines (**4a**—**c**). From the acetone filtrate, the benzo[*f*]quinazolines (**2a**—**c**) were isolated by a preparative thin-layer chromatography (silica gel) using $CHCl_3$ as a developing

Table III. Photolysis of 1,3-Dimethyl-5-nitro-6-(*p*-substituted)styryluracils (**1**)



Starting materials No.	R	mg (mmole)	Solvent (ml)	Irradiation time (hr)	Yields of products (%) 2	3	4
1a	H	836(3.0)	iso-PrOH(300)	24	16	8	—
1b	Me	754(2.5)	iso-PrOH(700), MeOH(300)	24	8	3	—
1c	OMe	828(2.6)	iso-PrOH(1000)	24	8	3	—
1a	H	836(3.0)	C_6H_6(300)[a)]	24	12	3	—
1b	Me	604(2.0)	C_6H_6(300)[a)]	24	10	4	—
1a	H	573(2.0)	C_6H_6(250)	24	10	—	8
1b	Me	604(2.0)	C_6H_6(250)	24	12	—	8
1c	OMe	700(2.0)	C_6H_6(250)	24	9	—	6

a) Photolysis was carried out in the presence of benzaldehyde (1 g).

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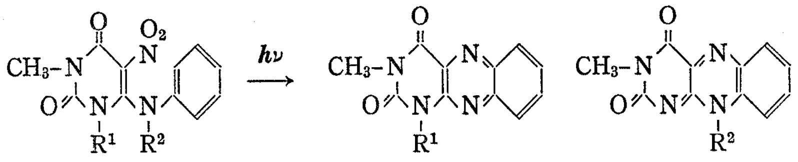
12) E.C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Am. Chem. Soc.*, **89**, 3369 (1967).

Table IV. Physical and Analytical Data of Products (**2**, **3**, and **4**)

Compd. No.	R	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	H	196	ligroin	$C_{14}H_{12}O_2N_2$	69.99 (70.03)	5.03 (5.53)	11.62 (10.85)
2b	Me	199	ligroin	$C_{15}H_{14}O_2N_2$	70.85 (70.84)	5.55 (5.53)	11.02 (10.85)
2c	OMe	232	AcOEt	$C_{15}H_{14}O_3N_2$	66.65 (66.62)	5.22 (5.22)	10.37 (10.26)
3a	H	>300	AcOH-H_2O	$C_{14}H_{13}O_2N_3$	65.87 (65.62)	5.13 (5.17)	16.46 (16.29)
3b	Me	>300	AcOH-H_2O	$C_{15}H_{15}O_2N_3$	66.90 (66.65)	5.61 (5.62)	15.02 (15.32)
3c	OMe	>300	MeOH	$C_{15}H_{15}O_3N_3$	63.15 (63.03)	5.30 (5.22)	14.73 (14.52)
4a	H	>300	AcOH	$C_{14}H_{13}O_3N_3$	61.98 (61.88)	4.83 (4.72)	15.49 (15.41)
4b	Me	>300	AcOH-H_2O	$C_{15}H_{15}O_3N_3$	63.15 (63.26)	5.30 (5.32)	14.73 (14.48)
4c	OMe	>300	AcOH-H_2O	$C_{15}H_{15}O_3N_3$	59.79 (59.85)	5.02 (4.65)	13.95 (13.87)

Table V. Photolysis of 6-Anilino-3-methyl-5-nitrouracils (**5**)



Starting materials No.	R¹	R²	mg (mmole)	Solvent (ml)	Irradiation time (hr)	Product	Yield (%)
5a	Me	H	520(2.0)	MeOH (250)	12	**6a**	15
5b	H	H	530(2.0)	MeOH(1000)	12	**6b**	18
5c	H	Me	533(2.0)	MeOH(1000)	5	**6c**	14

Table VI. Physical and Analytical Data of Alloxazines (**6a**, **b**) and Isoalloxazine (**6c**)

Compd. No.	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
6a	248	AcOH	$C_{12}H_{10}O_2N_4$	59.50 (59.38)	4.16 (4.14)	23.13 (22.89)
6b	>300	AcOH	$C_{11}H_8O_2N_4$	57.89 (57.77)	3.53 (3.53)	24.55 (24.56)
6c	>300	AcOH-H_2O	$C_{12}H_{10}O_2N_4$	59.50 (59.51)	4.16 (4.02)	23.13 (22.95)

solvent. The conditions of photolysis and the yields of products (**2**,**3** and **4**) are listed in Table III, and the physical and analytical data of products are given in Table IV.

Photolysis of 6-Anilino-5-nitrouracil (5a—c)——After irradiating a solution of **5a**—**c** with a 400 W high-pressure mercury lamp, the solvent was evaporated under reduced pressure. The residue was chromatographed on alumina using $CHCl_3$–ether (10: 1) as an eluent to give alloxazines (**6a**—**c**). The conditions of photolysis, and the physical and analytical data are given in Tavle V and VI, respectively.

Photolysis of 6-Anilino-3-methyl-5-nitrosouracil (**7**)[13]——A solution of **7** (248 mg, 1 mmole) in benzene (1000 ml) was irradiated with a 400 W high-pressure mercury lamp for 1.5 hr. The solvent was evaporated under reduced pressure, and the residue was collected by filtration, washed with ether and recrystallized from AcOH to give 3-methylalloxazine (**6b**), mp>300°, in 77% yield. **6b** was identical in every respect with the product obtained by the photolysis of **5b** in MeOH.

Photolysis of 1,3-Dimethylalloxazine-5-oxide (**8**)[13]——After the irradiation of **8** (500 mg, 1.85 mmole) in MeOH (1000 ml) with a 400 W high-pressure mercury lamp for 4 hr, the solvent was evaporated under reduced pressure. The residue was collected by filtration and recrystallized from AcOH to give 1,3-dimethylalloxazine (**6a**), mp 248°, in 96% yield. **6a** was identical in every respect with an authentic sample.[13]

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13) H. Goldner, G. Diets, and E. Carstens, *Ann.*, **694**, 142 (1969).