Synthesis and Properties of 1-Benzothiopyrano[2,3-*d*]-pyrimidine-2,4-(3*H*)diones (10-Thia-5-deazaflavins)

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Treatment of 6-arylthiouracils with the Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) gave the corresponding 6-arylthio-5-formyluracils, which could alternatively be prepared by the condensation of 6-chloro-5-formyluracils with thiophenols. Dehydrative cyclization of the above 5-formyluracils with polyphosphoric acid gave 1-benzothiopyrano[2,3-*d*]pyrimidine-2,4-(3*H*)diones (10-thia-5-deazaflavins). These 10-thia-5-deazaflavins oxidized alcohols to give the corresponding carbonyl compounds with the aid of strong base, and they were hydrogenated to 1,5-dihydro-10-thia-5-deazaflavins. Treatment of 10-thia-5-deazaflavins with concentrated aqueous potassium hydroxide led to the exclusive formation of 1,5-dihydro-10-thia-5-deazaflavins and 1,5-dihydro-10-thia-5-deazaflavin-5-ones *via* intermolecular oxidation-reduction (disproportionation) between initially formed 1,5-dihydro-5-hydroxy-10-thia-5-deazaflavins and unchanged 10-thia-5-deazaflavins.

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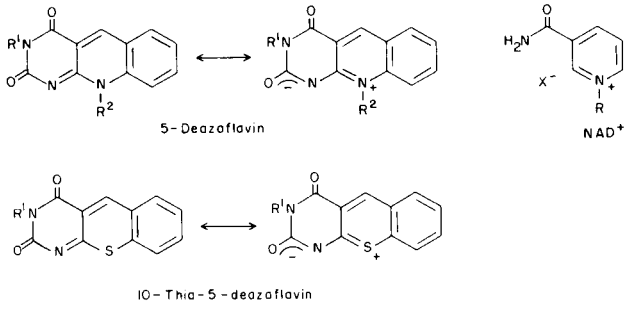
1-Benzothiopyrano[2,3-*d*]pyrimidine-2,4-(3*H*)dione (10-thia-5-deazaflavin) has an isosteric and isoelectronic structure of the biologically interesting 5-deazaflavin (1,2) which has been considered as a model not only of flavin nucleotide but also of nicotinamide nucleotide by annelation (that is, NAD^+ in flavin clothing) (3).

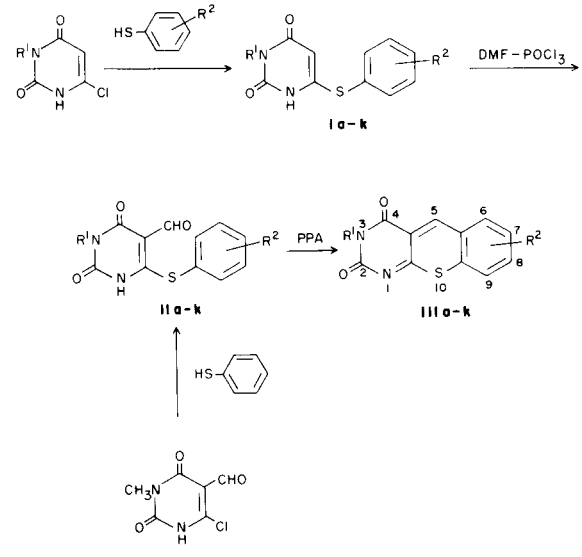
Scheme 1



Therefore, the 10-thia-5-deazaflavin would be expected to have some chemical and biological analogies to the 5-deazaflavin, however no report has been described on the synthesis of this ring system so far. This paper describes a synthetic approach to 10-thia-5-deazaflavin derivatives and their oxidizing ability toward alcohols and also their alkaline hydrolysis bringing about the disproportionation into oxidation-reduction products (4).

The starting materials, 6-arylthiouracils (Ia-k) were synthesized by refluxing of 6-chlorouracils with thiophenols in ethanol in the presence of potassium hydroxide (Method A) or by refluxing them in pyridine (Method B) (Table I).

Scheme 2



The 6-arylthiouracils (Ia-k) thus obtained were treated with a mixture of dimethylformamide and phosphorus oxychloride (Vilsmeier reagent) to give the corresponding 6-arylthio-5-formyluracils (IIa-k) (Table II). Furthermore, IId was obtained by refluxing of 6-chloro-5-formyl-3-methyluracil (2a) with thiophenol in ethanol in the presence of potassium carbonate.

Heating of the 5-formyluracil (IId) in polyphosphoric acid, followed by dilution with water, caused the dehydrative cyclization to give rise to the desired 3-methyl-10-thia-5-deazaflavin (IIId). The reaction is equally applicable to other 5-formyluracils (IIa-c and e-k)

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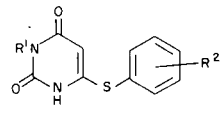
Table I

6-Arylthiouracils

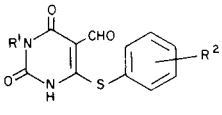


Compound No.	R^1	R^2	Method (a)	Yield (%)	Mp (b) (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	H	H	B	92	275	$C_{10}H_8N_2O_2S$	54.53	3.66	12.72	54.41	3.71	12.90
Ib	H	*p*-Cl	B	86	>300	$C_{10}H_7ClN_2O_2S$	47.16	2.77	11.00	46.96	2.71	11.32
Ic	H	*p*-CH_3	B	88	>300	$C_{11}H_{10}N_2O_2S$	56.39	4.30	11.96	56.52	4.43	12.17
Id	CH_3	H	A	95	222	$C_{11}H_{10}N_2O_2S$	56.39	4.30	11.96	56.27	4.35	11.88
Ie	CH_3	*p*-Cl	A	85	247	$C_{11}H_9ClN_2O_2S$	49.17	3.38	10.42	49.01	3.28	10.75
If	CH_3	*p*-CH_3	A	76	192	$C_{12}H_{12}N_2O_2S$	58.05	4.87	11.28	58.28	4.73	10.99
Ig	CH_3	*m*-CH_3	A	71	204	$C_{12}H_{12}N_2O_2S$	58.05	4.87	11.28	58.11	4.89	11.36
Ih	CH_3	*o*-CH_3	A	70	189	$C_{12}H_{12}N_2O_2S$	58.05	4.87	11.28	58.29	4.75	11.42
Ii	C_6H_5	H	A	87	223	$C_{16}H_{12}N_2O_2S$	64.85	4.08	9.45	64.98	4.01	9.31
Ij	C_6H_5	*p*-Cl	A	79	252	$C_{16}H_{11}ClN_2O_2S$	58.10	3.35	8.47	57.96	3.23	8.69
Ik	C_6H_5	*p*-CH_3	A	70	260	$C_{17}H_{14}N_2O_2S$	65.78	4.55	9.03	66.12	4.72	8.77

(a) Method A: condensation of a 6-chlorouracil with a thiophenol in ethanolic potassium hydroxide. Method B: condensation of a 6-chlorouracil with a thiophenol in pyridine. (b) All compounds were recrystallized from ethanol and were obtained as colorless needles.

Table II

6-Arylthio-5-formyluracils



Compound No.	R^1	R^2	Yield (%)	Mp (a) (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	H	H	96	>300	$C_{11}H_8N_2O_3S$	53.22	3.25	11.28	52.96	3.35	11.42
IIb	H	*p*-Cl	94	130	$C_{11}H_7ClN_2O_3S$	46.73	2.50	9.91	46.84	2.55	10.06
IIc	H	*p*-CH_3	86	243	$C_{12}H_{10}N_2O_3S$	54.96	3.84	10.68	54.77	3.68	10.51
IId	CH_3	H	93	207	$C_{12}H_{10}N_2O_3S$	54.96	3.84	10.68	54.83	3.81	10.82
IIe	CH_3	*p*-Cl	94	211	$C_{12}H_9ClN_2O_3S$	48.56	3.06	9.44	48.74	2.98	9.14
IIf	CH_3	*p*-CH_3	92	217	$C_{13}H_{12}N_2O_3S$	56.51	4.38	10.14	56.29	4.26	10.41
IIg	CH_3	*m*-CH_3	70	218	$C_{13}H_{12}N_2O_3S$	56.51	4.38	10.14	56.44	4.41	9.98
IIh	CH_3	*o*-CH_3	75	180	$C_{13}H_{12}N_2O_3S$	56.51	4.38	10.14	56.58	4.46	10.28
IIi	C_6H_5	H	67	127	$C_{17}H_{12}N_2O_3S$	62.95	3.73	8.64	62.81	3.85	8.53
IIj	C_6H_5	*p*-Cl	99	107	$C_{17}H_{11}ClN_2O_3S$	56.90	3.09	7.81	57.12	3.11	7.86
IIk	C_6H_5	*p*-CH_3	76	123	$C_{18}H_{14}N_2O_2S$	63.89	4.18	8.28	64.17	4.38	7.95

(a) All compounds were recrystallized from methanol and were obtained as light brown needles.

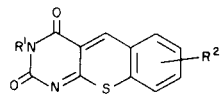
to afford the corresponding 10-thia-5-deazaflavins (IIIa-c and e-k) (Table III). The structures of III were established by the analytical and spectral data, particularly by the presence of characteristic C-5 proton signal at δ 10 ppm region in the nmr (in trifluoroacetic acid) (Table IV).

The light absorption spectra of III showed a pattern similar to those of typical 5-deazaflavins (2a, 5) except for their bathochromic shift (Table V).

The 10-thia-5-deazaflavins thus obtained did not show any strong oxidizing ability toward alcohols under weakly basic conditions, however with the aid of a strong base they oxidized alcohols to carbonyl compounds in stoichiometric yields. Thus, 3-methyl-10-thia-5-deazaflavin (IIId) oxidized benzyl alcohol to benzaldehyde (85%) in the presence of potassium *t*-butoxide, and IIId was reduced to the potassium salt of 1,5-dihydro-3-methyl-10-thia-5-deaza-

Table III

10-Thia-5-deazaflavins



Compound No.	R^1	R^2	Yield (%)	Mp (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	H	H	88	>300	red brown powder	$C_{11}H_6N_2O_2S$	57.37	2.63	12.17	57.58	2.83	12.53
IIIb	H	7-Cl	91	>300	red brown powder	$C_{11}H_5ClN_2O_2S$	49.98	1.90	10.58	50.12	1.98	10.33
IIIc	H	7-CH}	75	>300	red brown powder	$C_{12}H_8N_2O_2S$	59.00	3.30	11.47	59.22	3.26	11.79
IIId	CH_3	H	97	>300	yellow needles	$C_{12}H_8N_2O_2S$	59.00	3.30	11.47	59.08	3.19	11.50
IIIe	CH_3	7-Cl	98	>300	yellow needles	$C_{12}H_7ClN_2O_2S$	51.72	2.53	10.05	51.45	2.36	9.88
IIIf	CH_3	7-CH_3	87	>300	yellow needles	$C_{13}H_{10}N_2O_2S$	60.45	3.90	10.85	60.69	3.63	10.49
IIIg	CH_3	8-CH_3	86	264 dec	yellow needles	$C_{13}H_{10}N_2O_2S$	60.45	3.90	10.85	60.73	3.72	10.92
IIIh	CH_3	9-CH_3	94	>300	yellow needles	$C_{13}H_{10}N_2O_2S$	60.45	3.90	10.85	60.56	3.71	10.77
IIIi	C_6H_5	H	77	>300	dark green powder	$C_{17}H_{10}N_2O_2S$	66.65	3.29	9.15	66.38	3.30	8.83
IIIj	C_6H_5	7-Cl	97	>300	dark green powder	$C_{17}H_9ClN_2O_2S$	59.92	2.66	8.22	60.38	2.89	8.55
IIIk	C_6H_5	7-CH_3	89	293	yellow powder	$C_{18}H_{12}N_2O_2S$	67.48	3.78	8.74	67.61	3.69	8.51

(a) Compounds IIIa-h were recrystallized from dimethylformamide. Compounds IIIi-j were recrystallized from acetic acid.

Table IV

NMR Data for the 10-Thia-5-deazaflavins

Compound No.	δ (CF_3COOH) ppm
IIIa	7.99-9.02 (4H, ArH), 10.02 (1H, s, C_5-H)
IIIb	8.12-9.18 (3H, ArH), 10.04 (1H, s, C_5-H)
IIIc	2.82 (3H, s, C_7-CH_3), 7.98-8.72 (3H, ArH), 10.00 (1H, s, C_5-H)
IIId	3.68 (3H, s, N_3-CH_3), 8.05-8.85 (4H, ArH), 10.05 (1H, s, C_5-H)
IIIe	3.68 (3H, s, N_3-CH_3), 8.10-8.80 (3H, ArH), 9.95 (1H, s, C_5-H)
IIIf	2.80 (3H, s, C_7-CH_3), 3.68 (3H, s, N_3-CH_3), 8.11-8.69 (3H, ArH), 9.97 (1H, s, C_5-H)
IIIg	2.86 (3H, s, C_8-CH_3), 3.68 (3H, s, N_3-CH_3), 7.95-8.77 (3H, ArH), 9.94 (1H, s, C_5-H)
IIIh	2.93 (3H, s, C_9-CH_3), 3.68 (3H, s, N_3-CH_3), 7.95-8.82 (3H, ArH), 10.01 (1H, s, C_5-H)
IIIi	7.20-8.05 (5H, N_3-ArH), 8.05-8.92 (4H, ArH), 10.03 (1H, s, C_5-H)
IIIj	7.28-7.96 (5H, N_3-ArH), 8.23-8.84 (3H, ArH), 10.03 (1H, s, C_5-H)
IIIk	2.80 (3H, s, C_7-CH_3), 7.26-7.81 (5H, N_3-ArH), 8.28-8.68 (3H, ArH), 10.02 (1H, s, C_5-H)

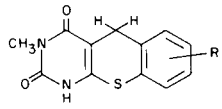
Table V

Visible and UV Maxima of Some 10-Thia-5-deazaflavins

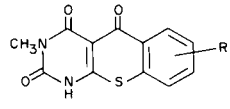
Compound No.	λ max (Chloroform) nm (log ε)
IIId	256 (4.29), 282 (4.47), 337 (4.17), 350 (4.20), 4llsh (4.06), 426 (4.14), 450 (4.06)
IIIe	266 (4.43), 273 (4.43), 285 (4.46), 332 (4.16), 344 (4.13), 421sh (4.02), 435 (4.08), 459 (4.01)
IIIf	262 (4.35), 286 (4.50), 345sh (4.21), 355 (4.24), 420sh (4.11), 436 (4.19), 460 (4.13)
IIIg	259 (4.32), 281 (4.42), 347sh (4.19), 358 (4.24), 411sh (4.15), 425 (4.24), 451 (4.17)
IIIh	243 (4.38), 283 (4.52), 351sh (4.21), 359 (4.23), 415 sh (4.09), 428 (4.16), 452 (4.09)
IIIi	256 (4.31), 284 (4.46), 342sh (4.24), 351 (4.25), 413sh (4.15), 428 (4.23), 452 (4.16)
IIIk	261 (4.38), 289 (4.50), 344sh (4.31), 355 (4.32), 416sh (4.20), 436 (4.29), 460 (4.24)

Table VI

1,5-Dihydro-3-methyl-10-thia-5-deazaflavins (IV) and 1,5-dihydro-3-methyl-10-thia-5-deazaflavin-5-ones (V)



IV



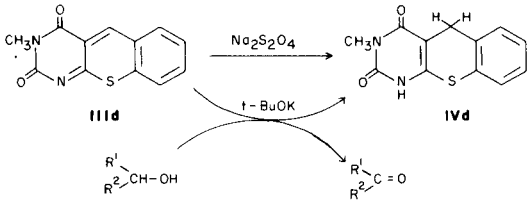
V

Compound No.	R	Yield (%)	Mp (°C) (a)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVd	H	47	>300	$C_{12}H_{10}N_2O_2S$	58.53	4.09	11.37	58.80	4.23	11.38
IVe	Cl	43	>300	$C_{12}H_9ClN_2O_2S$	51.34	3.23	9.98	51.54	3.42	9.87
Vd	H	46	>300	$C_{12}H_8N_2O_3S$	55.38	3.10	10.76	55.18	2.99	10.81
Ve	Cl	48	>300	$C_{12}H_8ClN_2O_3S$	48.90	2.39	9.51	48.73	2.58	9.80

(a) All compounds were recrystallized from ethanol and were obtained as colorless needles.

flavin (IVd), which was converted into the free IVd (90%) (*vide infra*) by treatment with acetic acid. Similarly, benzhydrol was oxidized by IIId in the presence of potassium *t*-butoxide to give benzophenone (81%).

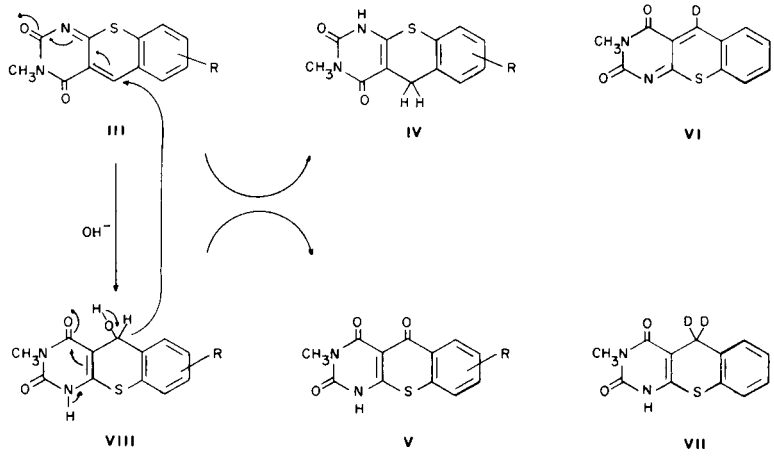
Scheme 3



Recently, the 5-deazaflavins have been found to undergo oxidation-reduction (disproportionation) in their hydrolysis with concentrated aqueous potassium hydroxide giving exclusively the corresponding 1,5-dihydro-5-deazaflavins and 1,5-dihydro-5-deazaflavin-5-ones (6). 10-Thia-5-deazaflavins (III) also showed behavior similar to 5-deazaflavins in their alkaline hydrolysis. Thus, heating of IIId in 20% aqueous potassium hydroxide gave a mixture of IVd and 1,5-dihydro-3-methyl-10-thia-5-deazaflavin-5-one (Vd) in the ratio about 1:1. Compound IVd was identical in all respects with the authentic sample obtained by sodium dithionite reduction of IIId. The structure of Vd was determined by mass spectrometry as well as nmr spectra (disappearance of the C-5 proton signal). Similarly, the hydrolysis of IIIe gave a mixture of 8-chloro-1,5-dihydro-5-methyl-10-thia-5-deazaflavin (IVe) and 6-chloro-1,5-dihydro-3-methyl-10-thia-5-deazaflavin-5-one (Ve).

Furthermore, treatment of 5-deuterio-3-methyl-10-thia-5-deazaflavin (VI) with 20% aqueous potassium hydroxide under the same conditions gave the corresponding 5,5-dideuterio-1,5-dihydro-3-methyl-10-thia-5-deazaflavin

Scheme 4



(VII) and the 5-ketone (Vd) in almost quantitative yields.

Therefore, this proportionation is rationalized in terms of initial nucleophilic attack of a hydroxide ion on the 5-position of the 10-thia-5-deazaflavins (III) giving the 5-hydroxy-1,5-dihydro-10-thia-5-deazaflavins (VIII). Subsequent transfer of a hydrogen equivalent from the 5-position of VIII to the 5-position of III affords the corresponding products IV and V.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Nmr spectra were determined with a JEOL JNM JH-60 spectrometer (tetramethylsilane as internal standard) and uv spectra were obtained with a JASCO UVIDEC-1 spectrometer (1-cm quartz cells). The identity of the compounds was confirmed by comparison of ir spectra determined in nujol with a JASCO IR-A1 spectrometer.

6-Arylthiouracils. General Procedure.

Method A (for Id-k).

A mixture of a 6-chlorouracil (0.01 mole) and a thiophenol (0.01 mole) was added to ethanolic potassium hydroxide including 0.01 mole of potassium hydroxide (50 ml) and the mixture was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was diluted with water to separate crystals, which were collected by filtration and recrystallized from ethanol to give colorless needles (Table I).

Method B (for Ia-c).

A mixture of a 6-chlorouracil (0.01 mole) and a thiophenol (0.01 mole) was refluxed in pyridine (30 ml) for 1 hour. After pyridine was evaporated *in vacuo*, the residue was treated with water to cause the separation of crystals, which were filtered off and washed with ether. Recrystallization from ethanol gave colorless needles (Table I).

6-Arylthio-5-formyluracils. General Procedure.

A 6-arylthiouracil (I) (0.01 mole) was added to a mixture of dimethylformamide (0.2 mole) and phosphorus oxychloride (0.02 mole) and the mixture was heated at 90° for 2 hours. Ice water was added to the reaction mixture and the resulting precipitates were filtered off. Recrystallization from ethanol yielded light brown needles (Table II).

5-Formyl-3-methyl-6-phenylthiouracil (IId). Alternative Procedure.

A mixture of 6-chloro-5-formyl-3-methyluracil (0.01 mole) and thiophenol (0.01 mole) was refluxed in ethanol (20 ml) in the presence of potassium carbonate (0.01 mole) for 3 hours. The reaction mixture was evaporated to dryness and the residue was treated with water to cause the separation of crystals, which were filtered off and recrystallized from ethanol to give IId in 80% yield.

1-Benzothiopyrano[2,3-*d*]pyrimidine-2,4-(3*H*)diones (10-Thia-5-deazaflavins) (IIIa-k). General Procedure.

A 6-arylthio-5-formyluracil (II) (0.005 mole) was suspended in polyphosphoric acid (3 ml) and the mixture was stirred at 120° for 2 hours. After cooling, the reaction mixture was diluted with water caused the separation of crystals, which were collected by filtration. Recrystallization from dimethylformamide or acetic acid gave colored crystals (see Table III).

Oxidation of Alcohols by 3-Methyl-10-thia-5-deazaflavin (IIId).

Compound IIId (0.002 mole) was added to benzyl alcohol (4 ml) including potassium *t*-butoxide (0.004 mole) and the mixture was heated at 80° for 2 hours in the dark. The reaction mixture was diluted with ether and the crystals which separated were filtered off to give the potassium salt of 1,5-dihydro-3-methyl-10-thia-5-deazaflavin (IVd). This salt was dissolved in water and neutralized with acetic acid to precipitate the free IVd, which was filtered off and recrystallized from ethanol to give colorless crystals, mp > 300°, in 90% yield.

To the filtrate was added 4-phenylsemicarbazide to precipitate benzaldehyde 4-phenylsemicarbazone, mp 181°, in 85% yield.

Similarly, benzhydrol was oxidized by IIId in the presence of potassium *t*-butoxide under the same conditions to give benzophenone (81% as the oxime, mp 140°) and 1,5-dihydro-10-thia-5-deazaflavin (IVd) (90%).

Oxidation-Reduction (Disproportionation) in the Alkaline Hydrolysis of 3-Methyl-10-thia-5-deazaflavins (IIId and e).

A 3-methyl-10-thia-5-deazaflavin (III) (0.01 mole) was added to 20% aqueous potassium hydroxide (3 ml) and the mixture was heated at 60° for 1 hour under stirring. After cooling, the precipitates were collected by filtration and then suspended in water. This suspended solutin was neutralized with acetic acid and the remaining 5-ketone (V) was filtered off. Recrystallization from ethanol gave V as colorless needles (Table VI).

The filtrate was acidified with acetic acid to cause the separation of 1,5-dihydro-10-thia-5-deazaflavins (IV). Recrystallization from ethanol gave IV as colorless needles (Table VI).

1,5-Dihydro-3-methyl-10-thia-5-deazaflavin (IVd).

A mixture of 3-methyl-10-thia-5-deazaflavin (IIId) (0.8 g, 0.0033 mole) and sodium dithionite (2.4 g, 0.013 mole) was added to a mixture of 25% aqueous ammonia (16 ml) and water (8 ml), and the mixture was heated at 90° for 40 minutes with stirring. After cooling, crystals which separated were collected by filtration and washed with water. Recrystallization from ethanol gave IVd as colorless needles (0.62 g, 77%); uv: λ max (ethanol) nm (log ε) 225 (4.07), 248.5 (3.97) and 296 (3.78); nmr (trifluoroacetic acid): δ ppm 1.33 (1H, s, NH), 3.53 (3H, s, N-CH_3), 3.87 (2H, s, C_5-H_2) and 7.29 (4H, s, aromatic protons); ir (nujol): ν max 3150 (NH), 1700s (carbonyl) and 1605s (carbonyl) cm^{-1}.

3-Methyl-10-thia-5-deaza[5-^2H]flavin (VI).

3-Methyl-6-phenylthiouracil (Id) (0.001 mole) was suspended in a mixture of ($^2H_7$)dimethylformamide (0.02 mole) and phosphorus oxychloride (0.002 mole) and the mixture was heated at 90° for 2 hours. After cooling, the reaction mixture was treated with ice water to precipitate crystals, which were filtered off and recrystallized from ethanol to give 5-[(^{2}H)formyl]-3-methyl-6-phenylthiouracil as light brown crystals, mp 207°; ms: m/e 263 (M^+), in 90% yield.

5-[(^{2}H)Formyl]-3-methyl-6-phenylthiouracil (0.005 mole) thus obtained was suspended in polyphosphoric acid (3 ml) and heated at 120° for 2 hours. The reaction mixture was treated with ice water to precipitate crystals, which were filtered off and recrystallized from dimethylformamide to give VI as yellow needles, mp > 300°; ms: m/e 245 (M^+), in quantitative yield.

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REFERENCES AND NOTES

(1) D. E. O'Brien, L. T. Weinstock and C. C. Cheng, *J. Heterocyclic Chem.*, **7**, 99 (1970).

(2a) F. Yoneda, Y. Sakuma, S. Mizumoto and R. Ito, *J. Chem. Soc. Perkin I*, 1805 (1976); (b) F. Yoneda, in "Method in Enzymology" Vol. 66, by D. B. McCormick and C. D. Wright eds., Academic Press, Inc., New York, 1980, p. 679; (c) F. Yoneda, K. Mori, Y. Sakuma and H. Yamaguchi, *J. Chem. Soc., Perkin Trans I*, 978 (1980).

(3) C. Walsh, *Acc. Chem. Res.*, **13**, 148 (1980).
(4) Preliminary report; F. Yoneda, M. Kawazoe and Y. Sakuma, *Tetrahedron Letters*, 2803 (1978).
(5) F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980).
(6) F. Yoneda and Y. Sakuma, *J. Chem. Soc., Perkin Trans. I*, 293 (1980).