after treatment with charcoal, was evaporated to dryness *in vacuo*, and the white crystalline residue extracted with hot acetonitrile (25 ml.). The cooled extract deposited tiny white needles, which were recrystallized from acetonitrile and dried *in vacuo* over phosphorus pentoxide at 110° for 12 hr.; yield of 9-ethyl-7,8-dihydro-9*H*-imidazo[2,1-*i*]-purine (XI) 158 mg. (41%); m.p. 225°; mixed m.p. with XI from (a) undepressed; λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—268 (13.9); *p*H 7—274 (11.8); *p*H 13—230 (20.2), 278 (12.0); R_{Ad}[18]: A[19]—0.53; B—0.99; C—1.12; D—2.08.

Hydrogenolysis of 9-(2-chloroethyl)-7,8-dihydro-9H-imidazo-[2,1-i]purine (VI). A solution of 1.0 g. of 9-(2-chloroethyl)-7,8-dihydro-9*H*-imidazo[2,1-*i*]purine (VI) in 35 ml. of ethyl alcohol was shaken under a hydrogen atmosphere (50 p.s.i.) in the presence of 200 mg. of 5% palladium-on-charcoal at room temperature for 72 hr. The filtered reaction mixture, when evaporated to dryness under diminished pressure, left a white solid residue, which moved as two spots on paper chromatograms developed by water-saturated butyl alcohol; R_{Ad}[18]: A[19]—0.41, 0.61. The slower moving component moved as the hydrochloride of the expected product XI; and the faster-moving component, as the starting free base VI. At room temperature the hydrogenolysis of the chlorine atom was slow and incomplete after 3 days; when the reaction temperature was increased to 50°, some undesired ring reduction presumably occurred as evidenced by additional spots on the paper chromatograms.

Acknowledgment. The authors are indebted to the members of the Analytical Section of Southern Research Institute, who, under the direction of Dr. W. J. Barrett, performed the spectral and most of the microanalytical determinations reported. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Pyrimidines. VI. *N*-Methyl-*as*-triazine Analogs of the Natural Pyrimidines[1]

KWANG YUEN ZEE-CHENG AND C. C. CHENG

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N-Methyl substituted *as*-triazine analogs of the naturally occurring pyrimidines, uracil, thymine, and cytosine, have been prepared by unambiguous synthesis. Their physical and chemical properties have been studied.

It has recently been reported that 6-azauracil (3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine) inhibits the growth of a number of microorganisms and certain experimental tumors.[2] However, this compound is highly toxic and less effective in the treatment of human cancer than its riboside, 6-azauridine.[3,4] It was also found that 6-azathymidine is a more potent thymine antagonist than 6-azathymine (3,5-dioxo-6-methyl-2,3,4,5-tetrahydro-*as*-triazine) in DNA bisynthesis.[5] In certain clinical trials 5-fluoro-2′-deoxyuridine, 5-FUDR, has been reported to be superior to 5-fluorouracil.[6] These findings suggest that *as*-triazine analogs of the naturally occurring pyrimidines bearing substituents on the nitrogen which would normally bear the pentose moiety (in the *as*-triazine system, N-2) might possess interesting biological activity.

A methyl group was selected as the substituent group for this study since it is relatively easy to introduce. Simple *N*-alkyl substitution in other heterocyclic systems has resulted in favorable therapeutic indices when compared with the corresponding *N*-unsubstituted or *N*-aryl substituted compounds in certain test systems.[7] For the purpose of comparison, several 4-methyl- and 2,4-dimethyl-*as*-triazines have also been prepared.

The methylation of *as*-triazines to produce the

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[1] This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

[2] (a) F. Šorm and J. Škoda, *Czech. Chem. Commun.*, **21**, 487 (1956); (b) R. E. Handschumacher and A. D. Welch, *Cancer Research*, **16**, 965 (1956); (c) M. T. Hakata, L. W. Law, and A. D. Welch, *Proc. Am. Assoc. Cancer Res.*, **2**, 113 (1956); (d) F. Šorm, A. Jakubavic, and S. Šlechta, *Experientia*, **12**, 271 (1956); (e) J. Škoda and F. Šorm, *Chem. Listy*, **50**, 165 (1956); (f) S. Bieber, G. B. Elion, H. C. Natham, and G. H. Hitchings, *Proc. Am. Assoc. Cancer Res.*, **2**, 188 (1957); (g) J. Sablik and F. Šorm, *Neoplasma*, **4**, 113 (1957); (h) G. B. Elion, S. Bieber, H. C. Natham, and G. H. Hitchings, *Cancer Research*, **18**, 802 (1958).

[3] (a) J. J. Jaffe, R. E. Handschumacher, and A. D. Welch, *Yale J. Biol.*, **30**, 168 (1957); (b) R. Schinder and A. D. Welch, *Science*, **125**, 548 (1957); (c) F. Šorm and H. Keilova, *Experientia*, **15**, 1 (1958); (d) A. D. Welch, R. E. Handschumacher, S. C. Finch, J. J. Jaffe, S. S. Cardoso, and P. Calabresi, *Cancer Chemotherapy Reports*, **9**, 39 (1960).

[4] It has been shown that 6-azauridine is not cleaved by mammalian organisms. Thus, free azauracil is not formed metabolically from 6-azauridine. References are given in (3 (d)).

[5] (a) W. H. Prusoff and A. D. Welch, *J. Biol. Chem.*, **218**, 929 (1956); (b) W. H. Prusoff, L. G. Lajtha, and A. D. Welch, *Biochim. et Biophys. Acta*, **20**, 209 (1956).

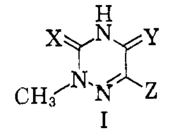
[6] F. J. Ansfield, *Proc. Am. Assoc. Cancer Res.*, **3**, 205 (1961).

[7] This is true in the pyrazolo[3,4-*d*]pyrimidine as well as the purine systems. see, for example, (a) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, *Cancer Research*, **17**, 579 (1957); (b) R. K. Robins, *J. Med. Chem.*, in press.

desired 2-methyl-*as*-triazines is rather impractical.[8] Furthermore, methylation of the mercury salt of 3,5-dioxo-6-methyl-2,3,4,5-tetrahydro-*as*-triazine with methyl iodide resulted in the isomeric 4-methyl derivative.[9] A direct synthetic method was devised in this laboratory by combining the methods of Cattelain[10] and Falco *et al.*[11] Thus, refluxing a mixture of 2-methyl-3-thiosemicarbazide[12] and diethyl oxomalonate gave ethyl 2-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylate (I-1). Aqueous ammonia converted I-1 readily to the amide (I-2). Hydrolysis of I-1 gave the corresponding acid (I-3). Oxidation of I-3 by either permanganate or dilute nitric acid gave the 3,5-dioxo compound (I-4). The desired 3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-*as*-triazine (1-methyl-6-azauracil, I-5) was obtained from I-4 by decarboxylation.

Treatment of I-4 with thionyl chloride resulted in the isolation of a stable acid chloride (I-6). The corresponding amide (I-7) and ethyl ester (I-8) were then prepared from I-6. Compound I-8 was alternately prepared by the direct condensation of 2-methylsemicarbazide[13] and ethyl oxomalonate in neutral solution. This condensation occurs readily at conditions much milder than the strong basic conditions utilized by other investigators.[14] Compound I-8 was readily converted to I-4 by basic hydrolysis.

2,6-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (1-methyl-6-azathymine, I-10) was prepared from the intermediate 2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (I-9). Compound I-9 was in turn prepared from the condensation of 2-methyl-3-thiosemicarbazide and pyruvic acid in ethanol. Refluxing I-10 with phosphorus pentasulfide in pyridine gave 2,6-dimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-*as*-triazine (I-11).


I

(1) $X = S; Y = O; Z = COOC_2H_5$
(2) $X = S; Y = O; Z = CONH_2$
(3) $X = S; Y = O; Z = COOH$
(4) $X, Y = O; Z = COOH$
(5) $X, Y = O; Z = H$
(6) $X, Y = O; Z = COCl$
(7) $X, Y = O; Z = CONH_2$
(8) $X, Y = O; Z = COOC_2H_5$
(9) $X = S; Y = O; Z = CH_3$
(10) $X, Y = O; Z = CH_3$
(11) $X, Y = S; Z = CH_3$
(12) $X, Y = S; Z = H$
(13) $X = S; Y = NH; Z = H$
(14) $X = S; Y = O; Z = H$
(15) $X = O; Y = S; Z = H$
(16) $X = O; Y = NH; Z = H$
(17) $X, Y = O; Z = CN$
(18) $X, Y = O; Z = Br$

Thiation studies of 3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-*as*-triazine (I-5) have yielded some interesting results. Compound I-5 and phosphorus pentasulfide in tetralin above 180° gave 2-methyl-3,5-dithioxo-2,3,4,5-tetrahydro-*as*-triazine (I-12). Ammonia replaced only one thioxo group of I-12 to yield 5-imino-2-methyl-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (I-13). The structure of I-13 was assigned by the following experiment: Dilute sodium hydroxide readily hydrolyzed I-13 to 2-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (I-14). The ultraviolet absorption spectra of compound I-14 (major peak at 262 mμ at *p*H 11) is identical to that of I-9. On the other hand, phosphorus pentasulfide in tetralin under 160° replaced only one oxo-group of I-5. The resulting product gave the same elementary analysis as I-14. However, the product exhibited ultraviolet absorption spectra (major peak at 332 mμ at *p*H 11) strikingly dissimilar to that of I-14. This evidence, together with the results of paper chromatographic comparison, established the structure for this product as 2-methyl-3-oxo-5-thioxo-2,3,4,5-tetrahydro-*as*-triazine (I-15), which is isomeric to I-14. Ammonia converted I-15 into the desired 5-imino-2-methyl-3-oxo-2,3,4,5-tetrahydro-*as*-triazine (1-methyl-6-azacytosine, I-16) in good yield.

Phosphorus oxychloride under various conditions failed to convert the oxotriazines (*e.g.*, I-5, I-10, etc.) to the corresponding chloro derivatives. This difficulty has also been noted by Chang and Ulbricht.[15] The attempted chlorination of I-7 with phosphorus oxychloride resulted only in the dehydration of the amide group, yielding the corresponding 6-cyano derivative (I-17).

Bromination of I-5 with bromine in acetic acid was not successful. Excess bromine in water, based on the procedure of Chang and Ulbricht,[15] converted I-5 to a monobrominated product. The structure of this product was assigned as 6-bromo-3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-*as*-triazine (I-18), as cuprous cyanide in pyridine readily converted I-18 to 6-cyano-3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-*as*-triazine (I-17), which was found to be identical to that prepared from the corresponding 6-carboxamide (I-7).

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(8) E. Cattelain, *Bull. soc. chim. France*, **12**, 53, 59 (1945).

NOTE ADDED IN PROOF: Gut and co-workers have recently reported the preparation of some *N*-methylated *as*-triazine derivatives by direct methylation of the corresponding *N*-unsubstituted compounds. Our unequivocal synthesis further substantiated their assignment of the position of the methyl groups. See J. Gut, M. Prystaš, J. Jonáš, and F. Šorm, *Coll. Czech. Chem. Commun.*, **26**, 974 (1961); J. Gut, M. Pryataš, and J. Jonáš, *ibid.*, **26**, 986 (1961).

(9) R. H. Hall, *J. Am. Chem. Soc.*, **80**, 1145 (1958).

(10) E. Cattelain, *Compt. rend.*, **210**, 301 (1940).

(11) E. A. Falco, E. Pappas, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 1938 (1956).

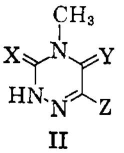
(12) A. H. Greer and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 874 (1950).

(13) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3286 (1908).

(14) (a) J. R. Bailey, *Am. Chem. J.*, **28**, 386 (1902); (b) P. K. Chang, *J. Org. Chem.*, **23**, 1951 (1958).

(15) P. K. Chang and T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).

Refluxing a mixture of diethyl oxomalonate and 4-methyl-3-thiosemicarbazide[16] in ethanol gave ethyl 4-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylate (II-1). The attempted hydrolysis and decarboxyltaion of II-1 in dilute base resulted in ring cleavage. By elementary analysis and ultraviolet absorption spectra the reaction product was found to be the 4-methyl-3-thiosemicarbazone of glyoxylic acid. Direct synthesis from glyoxylic acid and 4-methyl-3-thiosemicarbazide confirmed this structural assignment.



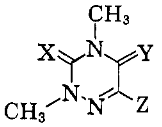
II

(1) X = S; Y = O; Z = $COOC_2H_5$
(2) X, Y = O; Z = COOH
(3) X, Y = O; Z = H
(4) X = S; Y = O; Z = CH_3
(5) X, Y = O; Z = CH_3
(6) X, Y = S; Z = CH_3

Nitric acid oxidation of II-1, which was found to be superior to permanganate oxidation, gave 4-methyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylic acid (II-2). It is interesting to note that chloroacetic acid also converted II-1 to II-2 but did not convert I-1 to I-4. This suggests that the tautomerization between >C=S and >C—SH forms at the 3 position of the *as*-triazine system can occur only when the nitrogen atom at the 2 position is unsubstituted. Decarboxylation of II-2 gave 3-methyl-6-azauracil (II-3).

Unlike the direct formation of 2,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (I-9) from pyruvic acid and 2-methyl-3-thiosemicarbazide, refluxing pyruvic acid and 4-methyl-3-thiosemicarbazide in ethanol gave only the uncyclized condensation product, the 4-methyl-3-thiosemicarbazone of pyruvic acid. Cyclization of this intermediate could not be achieved in aqueous acid or base. The desired compound, 4,6-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (II-4), was obtained when the semicarbazone was sublimed or refluxed in dimethylformamide. Chloroacetic acid converted II-4 to 4,6-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (3-methyl-6-azathymine, II-5), isomeric with I-10. Compound II-5 is identical to that prepared by Hall[9] from the methylation of the mercuric salt of 6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (6-azathymine). Our unequivocal synthesis thus confirmed his structural assignment. Thiation of II-4 with phosphorus pentasulfide in tetralin gave 4,6-dimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-*as*-triazine (II-6).

Ethyl 2,4-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylate (III-1) was readily obtained from 2,4-dimethyl-3-thiosemicarbazide[17] and diethyl oxomalonate in ethanol. Aqueous alkali at room temperature hydrolyzed III-1 to the corresponding carboxylic acid (III-2).



III

(1) X = S; Y = O; Z = $COOC_2H_5$
(2) X = S; Y = O; Z = COOH
(3) X, Y = O; Z = COOH
(4) X, Y = O; Z = H
(5) X = S; Y = O; Z = CH_3
(6) X, Y = S; Z = CH_3

On the other hand, when an alkaline solution of III-1 was heated on a steam bath for 1 hr., followed by acidification, a product, III-3 ,which contained no sulfur, was obtained. The ultraviolet absorption spectra of III-3 are similar to those of I-4 (3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylic acid). The structure of III-3 was therefore established as 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine-6-carboxylic acid. Compound III-3 was readily decarboxylated to yield 2,4-dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (1,3-dimethyl-6-azauracil, III-4).

The cyclized product, 2,4,6-trimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-*as*-triazine (III-5), was obtained directly from 2,4-dimethyl-3-thiosemicarbazide and pyruvic acid. It seems that the presence of an electron donating group at the 2 position of semicarbazide favors the process of spontaneous cyclization.

The dithiated derivative, 2,4,6-trimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-*as*-triazine (III-6), was prepared from III-5 and phosphorus pentasulfide in pyridine.

The melting points and ultraviolet absorption characteristics of *N*-methyl-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazines (*N*-methyl-6-azauracils and *N*-methyl-6-azathymines) and the corresponding ribosyl and unsubstituted derivatives are listed in Table I.

EXPERIMENTAL[18]

Ring closures. Ethyl 4-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxylate (II-1). To a boiling solution

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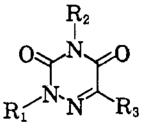
[16] G. Pulvermacher, *Ber.*, **27**, 622 (1894).

[17] M. Busch, E. Opfermann, and H. Walther, *Ber.*, **37**, 2320 (1904).

[18] All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2, and the infrared spectra were taken with a Perkin-Elmer Infracord. The R_f values in our paper chromatographic measurements were carried out at 25° (descending). The solvent systems used were (A) methanol–formic acid–water = 15:3:1; (B) 3% ammonium chloride; and (C) butanol saturated with 2*N* aqueous ammonia.

TABLE I

MELTING POINTS AND ULTRAVIOLET ABSORPTION CHARACTERISTICS OF 6-AZAURACIL DERIVATIVES


IV

R_1	R_2	R_3	M.P.	λ_{max} mμ; (log ε) pH 1	pH 7	pH 11	0.2 N NaOH
H	H	H	277–279	258 (3.79)	253 (3.77)	250 (3.77)	287 (3.67)
H	H	CH_3	217	263 (3.85)	—	252 (3.86)[a]	
CH_3	H	H	160–161	273 (3.88)	270 (3.84)	266 (3.81)	265 (3.79)
CH_3	H	CH_3	201–203	273 (3.83)	271 (3.81)	265 (3.79)	
Ribosyl	H	H	158–160	262 (3.83)	259 (3.84)	253 (3.87)	253 (3.89)[b]
Ribosyl	H	CH_3	—	262 (3.70)	262 (3.71)	251 (3.73)[c]	
H	CH_3	H	170–171	258 (3.76)	258 (3.76)	296 (3.90)	296 (3.83)
H	CH_3	CH_3	157–158	260 (3.73)	260 (3.73)	297 (3.85)	
H	Ribosyl	H	—	261 (–)	261 (–)	—	299 (–)[d]
H	Ribosyl	CH_3	164–165	264 (3.71)	304 (3.71)	304 (–)[c]	
CH_3	CH_3	H	67–68	272 (3.81)	272 (3.82)	273 (3.83)	272 (3.92)
CH_3	CH_3	CH_3	102–103	274 (3.84)	273 (3.81)	273 (3.80)[c]	

[a] Ref. 11. [b] Sample kindly provided by Professor R. E. Handschumacher of Yale University. [c] Ref. 9. [d] R. E. Handschumacher, *J. Biol. Chem.*, **235**, 764 (1960).

of 21 g. (0.2 mole) of 4-methyl-3-thiosemicarbazide[16] in 350 ml. of 95% ethanol was added a solution of 35 g. (0.2 mole) of diethyl oxomalonate in 70 ml.of ethanol. The solution was refluxed with stirring for 48 hr. and concentrated to one-third of its original volume. On cooling, light yellow plates of II-1 were obtained. The yield was 33.8 g. (78%), m.p. 197–199°. Recrystallization from a mixture of water and ethanol raised the melting point to 201–203°. The compound is soluble in ethanol and tetrahydrofuran, slightly soluble in ethanol and tetrahydrofuran, slightly soluble in ether and water. $\lambda_{max}^{pH\,1}$ 270 mμ (ε 42,000), 325 mμ (ε 13,800); $\lambda_{max}^{pH\,11}$ 266 mμ (ε 20,500), 345 mμ (ε 20,000). R_f(A) = 0.82, R_f(C) = 0.32.

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.1; H, 4.2; N, 19.5. Found: C, 39.1; H, 4.2; N, 19.4.

Ethyl 2-methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxylate (I-1) was prepared from 2-methyl-3-thiosemicarbazide[12] and diethyl oxomalonate, in 75% yield. M.p. 150–151°. $\lambda_{max}^{pH\,1}$ 267 mμ (ε 18,100), 333 mμ (ε 6,700); $\lambda_{max}^{pH\,7}$ 236 mμ (ε 12,800), 271 mμ (ε 34,000); $\lambda_{max}^{pH\,11}$ 238 mμ (ε 13,000), 267 mμ (ε 33,000). R_f (A) = 0.63, R_f (B) = 0.76.

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.1; H, 4.2; N, 19.5. Found: C, 39.0; H, 4.5; N, 19.7.

Ethyl 2,4-dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxylate (III-1) was prepared from 2,4-dimethyl-3-thiosemicarbazide[16] and diethyl malonate in 85% yield. Recrystallization from water gave long fluffy needles, m.p. 88–89°. $\lambda_{max}^{pH\,1,7}$ 225 mμ (ε 15,000), 267 mμ (ε 20,000), 330 mμ (ε 7,600); $\lambda_{max}^{pH\,11}$ 228 mμ (ε 9,800), 267 mμ (ε 16,500), 302 mμ (ε 8,500). R_f(A) = 0.88, R_f(B) = 0.80.

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.9; H, 4.8; N, 18.3. Found: C, 42.1; H, 5.1; N, 18.6.

2,6-Dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine (I-9) was prepared from 2-methyl-3-thiosemicarbazide and pyruvic acid in 51% yield. Recrystallization from water gave light yellow needles, m.p. 163–165°. $\lambda_{max}^{pH\,1}$ 264 mμ (ε 18,900); $\lambda_{max}^{pH\,11}$ 237 mμ (ε 14,100), 262 mμ (ε 26,300). R_f (A) = 0.79.

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.2; H, 4.5; N, 26.7. Found: C, 38.2; H, 4.3; N, 26.7.

2,4,6-Trimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine (III-5) was prepared in 80% yield by refluxing equivalent amounts of 2,4-dimethyl-3-thiosemicarbazide[13] and pyruvic acid in ethanol. Recrystallization from 50% ethano, gave white plates, m.p. 64–65°. $\lambda_{max}^{pH\,1,7}$ 224 mμ (ε 13,500), 264 mμ (ε 18,500); $\lambda_{max}^{pH\,11}$ 265 mμ (ε 16,500). R_f (A) = 0.82 R_f (B) = 0.83.

Anal. Calcd. for $C_6H_9N_3OS$: C, 42.1; H, 5.3; N, 24.5. Found: C, 41.9; H, 5.3; N, 24.6.

4,6-Dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine (II-4). To a boiling solution of 42 g. (0.4 mole) of 4-methyl-3-thiosemicarbazide in 800 ml. of ethanol was added dropwise a solution of 35. 2 g. (0.4 mole) of pyruvic acid dissolved in 80 ml. of ethanol. The mixture was refluxed for 30 hr. to give 67 g. (95%) of 4-methyl-3-thiosemicarbazone of pyruvic acid, m.p. 222–224° d. $\lambda_{max}^{pH\,1}$ 240 mμ (ε 67,000), 288 mμ (ε 17,300); $\lambda_{max}^{pH\,11}$ 278 mμ (ε 18,500).

Anal. Calcd. for $C_5H_9N_3O_2S$: C, 34.2; H, 5.2; N, 24.0. Found: C, 34.4; H, 5.2; N, 24.3.

A solution of 65 g. of 4-methyl-3-thiosemicarbazone of pyruvic acid and 300 ml. of dimethylformamide was refluxed for 4 hr. The solvent was evaporated and the residue was recrystallized from water to yield 27 g. (45%) of II-4 as white needles, m.p. 188–190°. $\lambda_{max}^{pH\,1,7}$ 268 mμ (ε 17,500), $\lambda_{max}^{pH\,11}$ 264 mμ (ε 11,200), 326 mμ (ε 5500). R_f (A) = 0.78, R_f (C) = 0.50.

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.2; H, 4.5; N, 26.7. Found: C, 38.6; H, 4.6; N, 26.6.

Hydrolysis. 2-Methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxylic acid (I-3). A mixture of 80 g. (0.37 mole) of I-1 and 750 ml. of 1*N* NaOH was heated on the steam bath for 6 hr. The solution was filtered and the filtrate was adjusted to *p*H 1 with concentrated hydrochloric acid. On cooling, 57 g. (81%) of I-3 was collected as yellow powder, m.p. 345–350° dec. (darkened at 283°). Recrystallization from water raised the melting point to 351–353° dec. (darkened at 283°). $\lambda_{max}^{pH\,1}$ 267 mμ (ε 18,200), 325 mμ (ε 5,800); $\lambda_{max}^{pH\,11}$ 238 mμ (ε 14,600), 265 mμ (ε 24,400). R_f (A) = 0.68, R_f (B) = 0.79.

Anal. Calcd. for $C_5H_5N_3O_3S$: C, 32.1; H, 2.7; N, 22.5. Found: C, 32.4; H, 2.9; N, 22.7.

2,4-Dimethyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine 6-carboxylic acid (III-2) was similarly prepared in 36% yield. M.p. 185–187° dec. $\lambda_{max}^{pH\,1}$ 287 mμ (ε 14,100); $\lambda_{max}^{pH\,7,11}$ 289 mμ (ε 21,000). This compound, although analyzed accordingly, could not give satisfactory results in all three paper chromatographic systems.

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.8; H, 3.5; N, 20.9; S, 15.9. Found: C, 35.5; H, 3.5; N, 20.8; S, 16.0.

Hydrolytic cleavage of II-1. A mixture of 8.6 g. of II-1 and 80 ml. of 1*N* sodium hydroxide was heated on a steam bath for 5 hr. A trace of insoluble substance was filtered and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. On cooling, 5.5 g. of yellow solid was collected, m.p. 132–137°. Recrystallization from a small amount of water gave light yellow needles, m.p. 175–177°.

From the elementary analysis (Found: C, 30.1; H, 4.5; N, 26.4), the structure of this hydrolyzed product was designated as 4-methyl-3-thiosemicarbazone of glyoxylic acid (Calcd. for $C_4H_7N_3O_2S$: C, 29.9; H, 4.3; N, 26.4). The structure was definitely proved by a direct synthesis from glyoxylic acid and 4-methyl-3-thiosemicarbazide. These products were found to be identical.

Decarboxylation. 3,5-Dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine (I-5). Five grams of I-4 were heated at 275–285° with agitation for 10 min. The solid melted with bubbling. The cooled solid mass was purified from a small amount of water followed by resublimation *in vacuo* to give 3 g. (81%) of I-5 as white crystals, m.p. 160–161°. The ultraviolet absorption maxima are listed in Table I. R_f (A) = 0.73, R_f (B) = 0.74.

Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.7; H, 4.0; N, 33.1. Found: C, 37.4; H, 4.1; N, 32.8.

3,5-Dioxo-4-methyl-2,3,4,5-tetrahydro-as-triazine (II-3) was similarly prepared in 93% yield. M.p. 170–171°. R_f (A) = 0.79, R_f (B) = 0.84, R_f (C) = 0.47.

Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.7; H, 4.0; N, 33.1. Found: C, 37.7; H, 3.9; N, 33.0.

2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-as-triazine (III-4): Two grams of powdered III-3 was sublimed at 200°/10 mm. followed by recrystallization from water and resublimation to give 1.2 g. of III-4 as a white powder, m.p. 67–68°. R_f (A) = 0.90.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.6; H, 5.0; N, 29.7. Found: C, 43.2; H, 5.0; N, 29.2.

Thiation. 2,6-Dimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-as-triazine (I-11). A mixture of 10 g. of finely powdered I-9 and 30 g. of purified[19] phosphorus pentasulfide was refluxed in 150 ml. of dry pyridine for 3 hr. The solvent was removed and the residue was decolorized with charcoal in boiling water. The orange solid was recrystallized from 50% ethanol to give 5.4 g. (50%) of I-11, m.p. 223–225°. $\lambda_{\max}^{\text{pH }1}$ 272 mμ (ϵ 24,700), 326 mμ (ϵ 11,600); $\lambda_{\max}^{\text{pH }11}$ 274 mμ (ϵ 21,400), 337 mμ (ϵ 14,300). R_f (C) = 0.46.

Anal. Calcd. for $C_5H_7N_3S_2$: C, 34.6; H, 4.1; N, 24.2. Found: C, 34.4; H, 4.2; N, 24.4.

2-Methyl-3,5-dithioxo-2,3,4,5-tetrahydro-as-triazine (I-12). To a finely ground mixture of 10 g. of I-5 and 30 g. of purified phosphorus pentasulfide was added 100 ml. of tetralin. The suspension, with stirring, was heated at 180–190° for 3 hr. The solid was filtered on cooling and washed with petroleum ether. It was then boiled in 1 l. of water with charcoal and filtered to give 10 g. (80%) of I-12 as orange crystals, m.p. 156–158°. $\lambda_{\max}^{\text{pH1}}$ 275 mμ (ϵ 26,200), 330 mμ (ϵ 11,000); $\lambda_{\max}^{\text{pH }11}$ 280 mμ (ϵ 21,900), 337 mμ (ϵ 14,500). R_f(A) = 0.80, R_f(B) = 0.73, R_f(C) = 0.18.

Anal. Calcd. for $C_4H_4N_3S_2$: C, 30.2; H, 3.2; N, 26.3. Found: C, 30.5; H, 3.4; N, 26.0.

2-Methyl-3-oxo-5-thioxo-2,3,4,5-tetrahydro-as-triazine (I-15) was prepared from I-5 and phosphorus pentasulfide in tetralin. Recrystallization from 95% ethanol and then from water gave 5.8 g. (52%) of I-14, as orange needles, m.p. 143–144°. $\lambda_{\max}^{\text{pH }1}$ 245 mμ (ϵ 5,900), 336 mμ (ϵ 14,400); $\lambda_{\max}^{\text{pH }11}$ 247 mμ (ϵ 7,200), 332 mμ (ϵ 12,800). R_f(A) = 0.78, R_f (B) = 0.76, R_f (C) tailing.

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.6; H, 3.5; N, 29.2. Found: C, 33.4; H, 3.5; N, 28.9.

4,6-Dimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-as-triazine (II-6) was prepared from II-4 and phosphorus pentasulfide in tetralin. Recrystallization from 50% ethanol gave 6.3 g. (60%) of II-6 as orange-red needles, m.p. 128–129°. $\lambda_{\max}^{\text{pH }1,7}$ 275 mμ (ϵ 25,000); $\lambda_{\max}^{\text{pH }11}$ 256 mμ (ϵ 18,100), 283 mμ (ϵ 15,200). R_f (A) = 0.80, R_f (C) = 0.51.

Anal. Calcd. for $C_5H_7N_3S_2$: C, 34.6; H, 4.1; N, 24.2. Found: C, 34.7; H, 4.1; N, 23.9.

2,4,6-Trimethyl-3,5-dithioxo-2,3,4,5-tetrahydro-as-triazine (III-6) was prepared by refluxing 10 g. of powdered III-5 and 30 g. of purified phosphorus pentasulfide in 250 ml. of dry pyridine. The crude product was recrystallized from ethanol to give 7 g. (65%) of bright red needles, m.p. 74–75°. $\lambda_{\max}^{\text{pH }1,7}$ 270 mμ (ϵ 22,500), 317 mμ (ϵ 13,000); $\lambda_{\max}^{\text{pH }11}$ 227 mμ (ϵ 13,500), 264 mμ (ϵ 18,200). R_f (A) = 0.85, R_f (C) = 0.90.

Anal. Calcd. for $C_6H_9N_3S_2$: C, 38.5; H, 4.8; N, 22.4. Found: C, 38.3; H, 5.0; N, 22.0.

Dethiation. 4-Methyl-3,5-dioxo-2,3,4,5-tetrahydro-as-triazine (II-2): A mixture of 7 g. of II-1 and 70 ml. of 8N nitric acid was stirred at 50–60° for 2 hr.[11] and evaporated *in vacuo* to dryness. The residue was purified from water to give 3.6 g. (65%) of white needles, m.p. 253–254° d. $\lambda_{\max}^{\text{pH }1}$ 272 mμ (ϵ 8,000); $\lambda_{\max}^{\text{pH }11}$ 306 mμ (ϵ 10,000). R_f (A) = 0.71, R_f(B) = 0.88.

Anal. Calcd. for $C_5H_6N_3O_4$: C, 35.1; H, 2.9; N, 24.5. Found: C, 35.2; H, 2.9; N, 24.3.

This compound was also prepared in 80% yield by refluxing II-1 with 20% chloroacetic acid for 6 hr.

3,5-Dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine-6-carboxylic acid (I-4) was prepared from either I-1 or I-3 by nitric acid or permanganate oxidation.[11] Recrystallization from water gave I-4 in 75–83% yield. M.p. 267–268° d. $\lambda_{\max}^{\text{pH }1}$ 289 mμ (ϵ 9,800); $\lambda_{\max}^{\text{pH }11}$ 275 mμ (ϵ 6,500). R_f (A) = 0.66, R_f (B) = 0.84.

Anal. Calcd. for $C_5H_5N_3O_4$: C, 35.1; H, 2.9; N, 24.5. Found: C, 35.3; H, 2.9; N, 24.1.

Refluxing a mixture of 6.5 g. of I-1 and 30 ml. of 20% chloroacetic acid for 6 hr. gave, instead of I-4, the hydrolyzed but not dethiated compound I-3, in 87% yield.

2,4-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxylic acid (III-3): A mixture of 11.5 g. of III-1 and 100 ml. of 1*N* sodium hydroxide was heated at 90–100° for 1 hr. The solution was cooled and acidified with hydrochloric acid. (Hydrogen sulfide was liberated during the process of acidification.) The product was isolated as a white solid, m.p. 220–221°. It gave a negative test for sulfur. Recrystallization from a small amount of water gave white, fine needles, m.p. 221–222°. The yield was 2 g. (21%). $\lambda_{\max}^{\text{pH }1}$ 288 mμ (ϵ 8,900); $\lambda_{\max}^{\text{pH }7,11}$ 282 mμ (ϵ 7400). R_f (A) = 0.78, R_f (B) = 0.91.

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.9; H, 3.8; N, 22.7. Found: C, 39.1; H, 3.9; N, 23.0.

2,6-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-as-triazine (I-10): This compound was made from 3.0 g. of I-9 and 30 ml. of 8*N* nitric acid by a similar procedure to the preparation of I-4. Recrystallization from ethanol gave 1.3 g. (50%), m.p. 201–203°. Ultraviolet absorption maxima are recorded in Table I. R_f (A) = 0.78, R_f (B) = 0.82.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.6; H, 5.0; N, 29.8. Found: C, 42.7; H, 4.8; N, 30.2.

4,6-Dimethyl-3,5-dioxo-2,3,4,5-tetrahydro-as-triazine (II-5). One gram of II-4 and 7 ml. of 20% chloroacetic acid was refluxed for 6 hr. During that time the solid dissolved gradually. The solution was then cooled and the product crystallized from the solution as white needles. The yield was almost quantitative; recrystallization from water yielded white needles which melted at 157–158°. It gave a negative test for sulfur. Ultraviolet absorption maxima are listed in Table I. R_f (A) = 0.87, R_1 (B) = 0.87, R_f (C) = 0.70.

Amination. 5-Imino-2-methyl-3-thioxo-2,3,4,5-tetrahydro-as-triazine (I-13). Four-tenths gram of I-12 was heated with 40 ml. of 20% ethanolic ammonia at 100° for 1 hr. The contents were then concentrated *in vacuo* to *ca.* 10 ml. to yield

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[19] H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 792 (1961).

0.45 g. of white crystalline product. It was recrystallized from water to give 0.31 g. (85%) of I-13 as white silky crystals, m.p. 258–259°. $\lambda_{max}^{pH\,1}$ 240 mμ (ε 19,500), 270 mμ (ε 40,000). No change in ultraviolet absorption at *p*H 11. R_f (A) = 0.78. R_f (C) = 0.65.

Anal. Calcd. for $C_4H_6N_4S$: C, 33.8; H, 4.2; N, 39.4. Found: C, 33.8; H, 4.5; N, 39.2.

5-Imino-2-methyl-3-oxo-2,3,4,5-tetrahydro-as-triazine (I-16) was similarly prepared from I-15 and ethanolic ammonia at 120°. The crude product was recrystallized from water to give 0.62 g. (70%) of I-16 as white cubic crystals, m.p. 328–329°. The product gave a negative test for sulfur. It hydrolyzed readily in both acid and base. $\lambda_{max}^{pH\,1}$ 290 mμ (ε 7,500), $\lambda_{max}^{pH\,7,11}$ 280 mμ (ε 6,500). R_f (B) = 0.75.

Anal. Calcd. for $C_4H_6N_4O$: C, 38.1; H, 4.8; N, 44.4. Found: C, 38.4; H, 4.7; N, 44.0.

Deamination. 2-Methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine (I-14). Two grams of I-13 in 50 ml. of 1*N* NaOH were stirred at room temperature. After 3 hr. a clear solution was obtained. The solution was allowed to stir overnight and then acidified to pH 2 with *ca.* 5 ml. of concentrated hydrochloric acid. The white solid that precipitated was filtered and washed with a small amount of cold water to yield 1.6 g. (80%), m.p. 220–222°. Recrystallization from water gave white crystals, m.p. 222–223°. This compound can be sublimed easily under reduced pressure. $\lambda_{max}^{pH\,1}$ 263 mμ (ε 16,500), 300 mμ (ε 3,600); λ_{max}^{pH11} 234 mμ (ε 13,300), 262 mμ (ε 22,400). R_f (A) = 0.77, R_f (B) tailing, R_f(C) = 0.16.

Anal. Calcd. for $C_4H_5N_3OS$: C, 33.6; H, 3.5; N, 29.2. Found: C, 33.4; H, 3.6; N, 29.3.

Preparation of acid chloride. 3,5-Dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine-6-carboxylic acid chloride (I-6). A mixture of 20 g. of powdered I-4 and 100 ml. of thionyl chloride was refluxed for 20 hr. Excess thionyl chloride was removed *in vacuo*. The residue was recrystallized from toluene to give a quantitative yield of I-6, m.p. 203–205°. The product is soluble in dioxane, hot benzene and toluene. It is insoluble in carbon tetrachloride and ether.

Anal. Calcd. for $C_5H_4ClN_3O_3$: C, 31.7; H, 2.1; N, 22.2. Found: C, 31.8; H, 2.1; N, 21.8.

Preparation of acid amides. 2-Methyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-as-triazine-6-carboxamide (I-2). To 300 ml. of concentrated aqueous ammonia was added with stirring, 16.2 g. of finely powdered I-1. All the solid dissolved and after a few minutes, a yellow precipitate was formed. The reaction mixture was stirred overnight at room temperature and filtered to give 10 g. of yellow solid, m.p. 290–292° dec. An additional 4 g. of less pure product, m.p. 280–283° dec., was obtained by concentrating the mother liquor. Recrystallization from water gave I-2 as fine yellow needles, m.p. 291–293° dec. The yield was almost quantitative. $\lambda_{max}^{pH\,1}$ 268 mμ (ε 20,000), 334 mμ (ε 7,100); $\lambda_{max}^{pH\,11}$ 234 mμ (ε 15,000), 271 mμ (ε 25,400). R_f (A) = 0.60, R_f (B) = 0.59.

Anal. Calcd. for $C_5H_6N_4O_2S$: C, 32.2; H, 3.3; N, 30.1. Found: C, 31.8; H, 3.1; N, 30.0.

The corresponding 6-*N*(*N'*,*N'*-diethylaminoethyl)carboxamide, m.p. 230–232°, was similarly prepared from I-1 and ethanolic *N*,*N*-diethylethylenediamine.

3,5-Dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine-6-carboxamide (I-7) was prepared in 92% yield from I-6 and ethanolic ammonia. It melted at 279–281° dec. after recrystallization from water. $\lambda_{max}^{pH\,1}$ 289 mμ (ε 9400), $\lambda_{max}^{pH\,7,11}$ 287 mμ (ε 7700). R_f (A) = 0.50, R_f (B) = 0.71.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.3; H, 3.5; N, 32.9. Found: C, 35.6; H, 3.5; N, 32.6.

The corresponding 6-*N*-methylcarboxamide, m.p. 171–172°, and 6-*N*(*N'*,*N'*-diethylaminoethyl)carboxamide, m.p. 212–213°, were similarly prepared from I-6 with ethanolic methylamine and *N*,*N*-diethylethylenediamine, respectively.

Preparation of carboxylic esters. Ethyl 3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine-6-carboxylate (I-8). *Method A.* A mixture of 3.7 g. of I-6 and 50 ml. of absolute ethanol was stirred at room temperature for 10 min. followed by gentle boiling for 15 min. The reaction mixture was reduced to 20 ml., treated with charcoal, and filtered. On cooling, 3.2 g. (92%) of I-8 was isolated which melted at 130–132°. $\lambda_{max}^{pH\,1}$ 289 mμ (ε 10,000), $\lambda_{max}^{pH\,11}$ 285 mμ (ε 6,800). R_f (A) = 0.84, R_f (B) = 0.84, R_f (C) = 0.22.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.5; N, 21.1. Found: C, 42.0; H, 4.4; N, 21.2.

The corresponding methyl ester was similarly prepared, m.p. 179–180°.

Method B. A solution of 87 g. (0.5 mole) of diethyl oxomalonate in 100 ml. of ethanol was added dropwise to 52.5 g. (0.5 mole) of 2-methylsemicarbazide[13] dissolved in 300 ml. of warm ethanol. The reaction mixture was refluxed with stirring for 2 days. On cooling, 73 g. (73%) of I-8 was isolated, m.p. 128–130°. It was recrystallized from water to give white needles, m.p. 130–132°. The product was found to be identical to that prepared by Method A.

Preparation of nitrile. 6-Cyano-3,5-dioxo-2-methyl-2,3,4,5-tetrahyro-as-triazine (I-17) A mixture of powdered 3.4 g. of I-7 and 50 ml. of phosphorus oxychloride was refluxed for 4 hr. with stirring. Excess phosphorus oxychloride was distilled *in vacuo* from the clear solution. The gray residue was extracted with ether. The ethereal extract was evaporated to leave the crude product as a white crystalline solid. It was recrystallized from toluene to give 2.3 g. (75%) of I-17 as white cubic crystals, m.p. 191–193°. A strong nitrile band was observed at 4.4 μ. $\lambda_{max}^{pH\,1}$ 295 mμ (ε 11,300); $\lambda_{max}^{pH\,7,11}$ 291 mμ (ε 8,700). R_f (A) = 0.79, R_f (B) = 0.85, R_f (C) = 0.20.

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.5; H, 2.6; N, 36.8. Found: C, 39.3; H, 2.6; N, 36.5.

This compound was also prepared by refluxing a mixture of 4.2 g. (0.02 mole) of I-18 and 2.7 g. (0.03 mole) cuprous cyanide in 50 ml. of dry pyridine for 2 hr. The solvent was removed *in vacuo* and the residue was boiled with 15% hydrochloric acid in the presence of charcoal for a few minutes. The crude product, isolated on cooling, was recrystallized with toluene to give white cubic crystals, m.p. 191–193°.

Preparation of bromo derivative. 6-Bromo-3,5-dioxo-2-methyl-2,3,4,5-tetrahydro-as-triazine (I-18). A solution of 5 g. of I-5, 80 ml. of water and 5 ml. of bromine was stirred at room temperature for 20 hr. A white solid separated gradually. It was filtered and washed with water to give 7.1 g. (87%) of I-18, m.p. 203–204°. Recrystallization from water raised the melting point of the product to 207–208°. This compound gave a negative test for ionizable halide. $\lambda_{max}^{pH\,1}$ 287 mμ (ε 8,000); $\lambda_{max}^{pH\,7,11}$ 280 mμ (ε 6,300). R_f (A) = 0.80, R_f (B) = 0.62.

Anal. Calcd. for $C_4H_4BrN_3O_2$: C, 23.3; H, 1.9; N, 20.4. Found: C, 23.2; H, 1.9; N, 20.3.

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