mmoles of L-ascorbic acid and 6 mmoles of phosphate buffer, pH 6.3—9.0. After stirring for 2 hr at room temperature in air, oxygen or nitrogen atmosphere, the product was extracted into ethyl acetate several times. The combined extracts were dried over Na_2SO_4 and concentrated before separation by chromatography. Deuterium content in the phenolic product was determined by mass spectrometry using a direct probe inlet system on a Hitachi RMU7L mass spectrometer.

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Studies on Heterocyclic Compounds. XVII.[1] Reaction of 6-Mercapto-1,3-Dimethyluracil with Electrophilic Reagents[2]

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Attempts to prepare 5-oxothiopyrano[2,3-*d*]pyrimidine derivatives by the reaction of 6-mercapto-1,3-dimethyluracil (I) with various acetylenecarboxylates and ethyl ethoxymethylenecyanomalonate have led instead to the synthesis of substituted thiopyrimidine-2,4-dione. The condensation of (I) with diethyl ethoxymethylenemalonate yielded readily the corresponding 5-oxothiopyrano[2,3-*d*]pyrimidine-2,4-dione. Elimination of ethoxycarbonyl group in V obtained 1,3-dimethyl-5-oxothiopyrano[2,3-*d*]pyrimidine-2,4-dione.

Some pyrido[2,3-*d*]pyrimidines exhibit interesting antibacterial activities[4] and antitumor activities,[5] and compounds with this ring system have been extensively investigated.[6]

Little is known, however, of the chemistry of the 8-sulfur isostere, the thiopyrano[2,3-*d*]-pyrimidine system,[7] which may be of potential biological importance. This paper deals with a successful synthesis of 1,3-dimethyl-5-oxothiopyrano[2,3-*d*]pyrimidines by reaction of 6-mercapto-1,3-dimethyluracil (I) with electrophilic reagents.

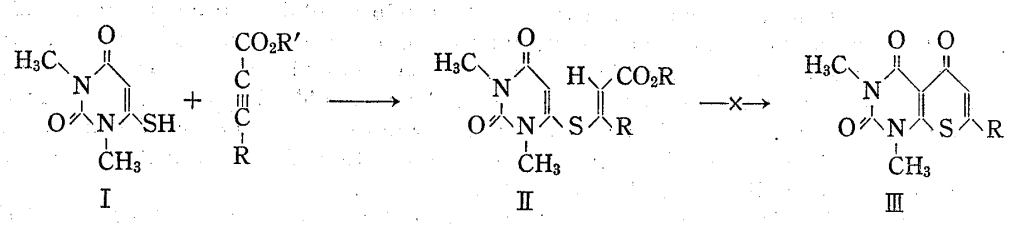

Chart 1

When compound I was treated with methyl propiolate in chloroform, a single product was obtained in good yield. Proton magnetic resonance (PMR), mass spectral and elementary

1) Part XVI: H. Ogura, K. Kikuchi, H. Takayanagi, K. Furuhata, Y. Iitaka, and R.M. Acheson, *J. Chem. Soc.* (I), **1975**, 2316.
2) Presented at the 91st annual meeting of Pharmaceutical Society of Japan, Fukuoka, 1971 Preliminary Reports, p. 670.
3) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
4) B.S. Hurlbert, R. Ferone, T.A. Herrmann, G.H. Hitchings, M. Barnett, and S.R.M. Busby, *J. Med. Chem.*, **11**, 711 (1968).
5) J.L. Shim, R. Niess, and A.D. Broom, *J. Org. Chem.*, **37**, 578 (1972).
6) For a comprehensive review, see (a) W.G. Irwin and D.G. Wibberley, *Adv. Heterocyclic Chem.*, **10**, 149 (1969).
7) To our best knowledge only two publications dealt with the compounds of this ring system. B.R. Baker, C.E. Morreal, and B.-T. Ho, *J. Med. Chem.*, 6, 658 (1963); H. Ogura and M. Sakaguchi, *Chem. Lett.*, **1972**, 657.

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analyses indicated that the product was the Michael-type adduct (II, R–H). The *trans* disposition of the olefinic protons in the side-chain was evidenced by a small coupling (10 Hz) between them.[5] This *trans* compound (II, R=H) failed to undergo cyclization to form 5-oxothiopyrano[2,3-*d*]pyrimidine (III, R=H) by treatment with polyphosphoric acid (PPA) or Dowtherm A. The *trans* configuration of the side-chain apparently impedes the cyclization, since the exocyclic carbonyl group cannot approach the C-5 position of the pyrimidine in II.

Other acetylenic compounds, dimethyl acetylenedicarboxylate also gave the corresponding Michael-type adduct II ($R=CO_2CH_3$), but the product II failed to cyclize to III, indicating the *trans* stereochemistry in the side-chain.

We, therefore, attempted to synthesize a compound analogous to II in which the terminal alkyloxycarbonyl group is *cis* to the pyrimidine (*e.g.* IV). Such a compound was expected to undergo cyclization. The reaction of I with diethyl ethoxymethylidene malonate in chloroform at reflux, indeed, gave directly the desired 5-oxothiopyrano[2,3-*d*]pyrimidine derivative V in excellent yield.

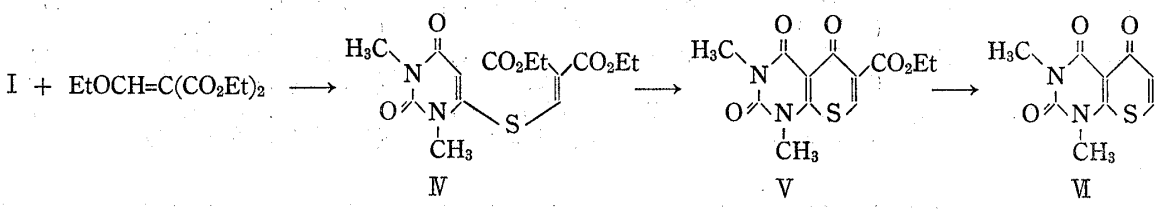

Chart 2

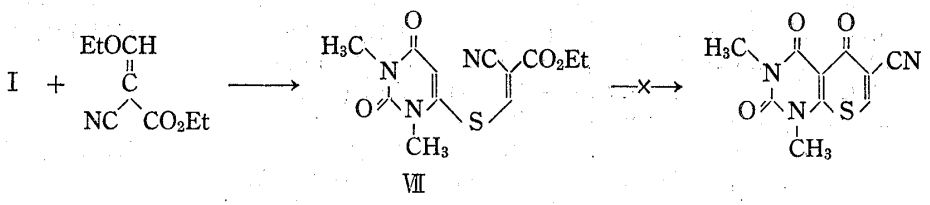

Chart 3

The open-chain intermediate IV could not be isolated when the reaction was carried out at room temperature. An analogous reaction I with ethyl ethoxymethylidenecyanoacetate gave an open-chain product which resisted cyclization to the thiopyrano[2,3-*d*]pyrimidine by heating in 6N HCl or with Dowtherm A, suggesting that the ethoxycarbonyl group is *trans* to the pyrimidine as in VII. The 6-ethoxycarbonyl derivative V could easily be converted into the 6-unsubstituted thiopyrano[2,3-*d*]pyrimidine (VI) by treatment with 6N HCl and PPA at 150—160°.

Experimental

All melting points are not corrected. PMR spectra were measured in $CDCl_3$ with a Varian T-60 spectrometer with tetramethyl silane as the internal standard. Mass spectra were measured with JEOL-OIS Spectrometer by a direct inlet system at 75 eV. The Ultraviolet spectra were taken with a Hitachi EPS-3T recording Spectrophotometer.

Methyl 6-(1,3-Dimethyluracilyl)-β-thioacrylate (IIa, R=H, R′=CH_3)——A solution of 1,3-dimethyl-6-mercaptouracil[8] (I, 1.72 g, 0.01 mole) and propiolate (0.84 g, 0.01 mole) in $CHCl_3$ (25 ml) was stirred overnight at room temperature. The solution was filtered and, after evaporate of the solvent, the residue was recrystallized from $CHCl_3$. Methyl 6-(1,3-dimethyluracilyl)-β-thioacrylate (IIa) was obtained as colorless crystals.

Hydrolysis of Methyl 6-(1,3-Dimethyluracilyl)-β-thioacrylate (IIa)——IIa (1.28 g, 0.005 mole) was dissolved in MeOH (5 ml) and 6N HCl (15 ml), and the solution was refluxed for 45 min. After evaporation of the solvents under reduced pressure, the residue was recrystallized from $CHCl_3$. 6-(1,3-Dimethyluracilyl)-β-thioacrylic acid (IIb, R=H, R′=H) was obtained as colorless crystals.

8) H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972).

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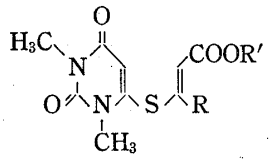
Methyl 6-(1,3-Dimethyluracilyl)-β-methoxycarbonyl-β-thioacrylate (IIc, R=CO_2CH_3, R′=CH_3)——IIc was also prepared analogously by reaction of and dimethylacetylene dicarboxylate.

The analytical and spectral data are summerized in Table I.

Table I. 6-(1,3-Dimethyluracilyl)-β-thioacrylates



No.	R	R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Mass spectrum *m/e* (M^+)
IIa	H	CH_3	158 ($CHCl_3$)	85.0	$C_{10}H_{12}O_4SN_2$ (256.21)	46.88 (46.76)	4.72 (4.71)	10.93 (11.09)	256
IIb	H	H	215 ($CHCl_3$)	46.8	$C_9H_{10}O_4SN_2$ (242.19)	44.63 (44.75)	4.16 (4.14)	11.57 (11.83)	242
IIc	CO_2CH_3	CH_3	116 (benzene)	47.7	$C_{12}H_{14}O_6SN_2$ (314.25)	45.86 (45.96)	4.49 (4.46)	8.92 (8.81)	314

No.	NMR δ (ppm) in $CHCl_3$	UV λ_{max}^{EtOH} nm (log ε)
IIa	3.30 (3H, singlet, CH_3), 3.53 (3H, singlet, CH_3), 3.78 (3H, singlet, CH_3 of ester), 5.87 (1H, singlet, 5-H) 6.17 (1H, doublet, $J=10$ Hz, *trans* –CH=CH–), 7.07 (1H, doublet, $J=10$ Hz, *trans* –CH=CH–).	264(4.14), 298(4.14)
IIb	3.20 (3H, singlet, CH_3), 3.46 (3H, singlet, CH_3), 6.06 (1H, singlet, 5-H), 6.20 (1H, doublet, $J=10$ Hz, *trans* –CH=CH–), 7.57 (1H, doublet, $J=10$ Hz, *trans* –CH=CH–),	254(3.85), 296(3.65)
IIc	3.20 (3H, singlet, CH_3), 3.57 (3H, singlet, CH_3), 3.77 (3H, singlet, CH_3), 3.80 (3H, singlet, CH_3), 5.70 (1H, singlet, 5-H), 7.06 (1H, singlet, =CH–),	280(4.13)

Reaction of 1,3-Dimethyl-6-mercaptouracil (I) with Diethyl Ethoxymethylidenemalonate——Compound I (5.24 g, 29 mmole) and diethyl ethoxymethylidenemalonate (6.49 g, 30 mmole) were dissolved in $CHCl_3$ (90 ml) and the solution was refluxed for 2 hr. After evaporation of the solvent, the residue was recrystallized from $CHCl_3$. 6-Ethoxycarbonyl-5-oxothiopyrano[2,3-*d*]pyrimidine (V, 6.3 g, 73%) was obtained as colorless crystals, mp 202.5°. *Anal.* Calcd. for $C_{11}H_{12}O_5N_2S$ (284.22): C, 46.48, H, 4.26, N, 9.86. Found: C, 46.32, H, 4.15, N, 9.71. Mass Spectrum *m/e*: 284. UV λ_{max}^{EtOH} nm (log ε): 243 (4.13), 314 (3.59). NMR ($CDCl_3$) δ ppm: 1.40 (3H, triplet, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 3.50 (3H, singlet, CH_3), 3.58 (3H, singlet, CH_3), 4.36 (2H, quartet, $J=7.0$ Hz, $C\underline{H}_2CH_3$), 8.46 (1H, singlet, =CH–S–).

Next, the reaction was carried out at room temperature and V was obtained instead of the open-chain intermediate IV.

Reaction of I with Ethyl Ethoxymethylidenecyanoacetate——A solution of I (850 mg, 4.9 mmole) and ethyl ethoxymethylidene cyanoacetate (920 mg, 5.4 mmole) in $CHCl_3$ (15 ml) was heated under reflux for 2 hr. The solvent was removed *in vacuo*, the residue was recrystallized from $CHCl_3$. Ethyl 6-(1,3-dimethyluracilyl) thiomethylenecyanoacetate (VII, 0.65 g, 44.6%) was obtained as colorless crystals, mp 163° (decomp.) *Anal.* Calcd. for $C_{12}H_{13}O_4N_3S$ (295.25): C, 48.81; H, 4.44, N, 14.23. Found: C, 48.53, H, 4.40, N, 13.98. Mass Spectrum *m/e*: 295 (M^+). UV λ_{max}^{EtOH} nm (log ε): 220 (5.13), 299 (4.74). NMR ($CDCl_3$) δ ppm: 1.40 (3H, quartet, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.50 (3H, singlet, CH_3), 3.64 (3H, singlet, CH_3), 4.40 (2H, quartet, $J=7.0$ Hz, $C\underline{H}_2CH_3$) 5.93 (1H, singlet, =CH–), 8.97 (1H, singlet, =CH–S–).

1,3-Dimethyl-5-oxothiopyrano[2,3-*d*]pyrimidine (VI)——A mixture of V (1.0 g, 3.5 mmole), conc. HCl (5 ml) and H_2O (5 ml) was heated under reflux for 3 hr. After cooling, the mixture was extracted with $CHCl_3$ (12 ml×3) and the combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue

9) H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2171 (1968).

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was added to PPA[9] (10 ml) and the mixture was heated at 150—160° with vigorous stirring for 2 hr, then diluted with H_2O (25 ml) and extracted with $CHCl_3$ (15 ml × 3). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to dryness to a colorless solid which was crystallized from $CHCl_3$ to give VI (400 mg, 51% yield), mp 160°. *Anal.* Calcd. for $C_9H_8O_3N_2S$ (224.17): C, 48.22, H, 3.60, N, 12.50, Found: C, 48.16, H, 3.48, N, 12.37. Mass spectrum *m/e*: 224 (M^+). UV λ_{max}^{EtOH} nm (log ε): 218 (4.34), 294 (4.15). NMR ($CDCl_3$) δ ppm, 3.50 (3H, singlet, CH_3), 3.62 (3H, singlet, CH_3), 6.32 (1H, doublet, J=12.5 Hz, cis –CH=CH–S–), 8.20 (1H, doublet, J=12.5 Hz, cis –CH=CH–S–).

Acknowledgement The authors are grateful to Dr. K.A. Watanabe of Sloan-Ketterin Institute for Cancer Research and Cornell University Medical College for his encouragement and his useful suggestions.

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The Synthesis of 3-Spirooxindole Derivatives. IX.[1] The Reactions of 2-Hydroxytryptamine with Hemiacetals

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The condensation of 2-hydroxytryptamine hydrochloride (IX) with the hemiacetals such as tetrahydropyran-2-ol (X) and morroniside (III), a member of the iridoids, was investigated.

A condensation of IX with X was carried out by standing a solution of IX, X, and sodium acetate in the molar ratio of 1: 1: 2 in an aqueous ethanol at room temperature or at reflux for 42 hr to give the amino-alcohol (XI) in 85% yield, which was further characterized as two isomeric diacetyl derivatives (XIIa, XIIb).

A condensation of IX with morroniside (III) was conducted under a similar condition only by heating a solution of the components at reflux for 42 hr to give the lactams (XIVa, b), which seemed to have been generated through the processes of the Mannich type of condensation like the preliminary work, followed by elimination of methanol.

Attempts to prevent the lactam formation and to isolate the Mannich base were unsuccessful in the latter case, but the condensations of 2-hydroxytryptamine with hemiacetals were proved to have smoothly proceeded to afford the Mannich bases in high yields.

The iridoid glucoside, loganin (I) occupies an important position in the biosynthesis of the indole alkaloids, *i.e.*, the *Corynanthe*, *Aspidosperma* and *Iboga* families.[3] The evidence made to date indicates that loganin becomes the C_9–C_{10} nontryptamine moiety incorporated into the skeleton of these alkaloids. Tracer experiments also show that loganin is a biogenetic precursor of a growing number of iridoid[4] and alkaloid glucosides.[5] Loganin is cleaved *in*

1) Part VIII: Y. Ban, N. Taga, and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **24**, 736 (1976). Inquiries should be addressed to Y. Ban.

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3) *a*) A.R. Battersby, *Pure and Appl. Chem.*, **14**, 117 (1967); *b*) A.I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970); *c*) H. Inouye, S. Ueda, and Y. Takeda, *Chem. Pharm. Bull.* (Tokyo), **19**, 587 (1971); *d*) H. Goeggel and D. Arigoni, *Chem. Comm.*, **1965**, 538; *e*) J.P. Kutney, "Lectures in Heterocyclic Chemistry," edited by R.N. Castle and E.F. Elslager, S-1 (1972). (A Supplementary Issue of the Journal of Heterocyclic Chemistry, Volume 9). (The lecture was presented at 3rd International Congress of Heterocyclic Chemistry, at Sendai, Japan, August 23–27, 1971).

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