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Syntheses of Thiazolo[2,3-*f*]theophyllines and Their Mass Spectrometry

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Thiazolo[2,3-*f*]theophyllines were synthesized by ring closure of 8-(acylmethyl)-thiotheophyllines. And their structures were determined by desulfurization with Raney Ni. Their Mass Spectrum fragmentations were also described.

In the preparation of purine nucleosides, relative activities of 7- and 9-nitrogen of purine ring system are very important. In order to obtain some informations on structural features of purines, which control relative activities of 7- and 9-nitrogen, the cyclization of some 8-(acylmethyl)thiopurines have been investigated. When 8-(acylmethyl)thioadenines, which have an amino group at 6-position of purine ring, were cyclized in polyphosphoric acid or in ethanolic hydrogen chloride, the cyclization took place to 9-nitrogen to give thiazol[3,2-*e*]-adenines.[2] While cyclizations of 8-acetonylthioxanthine and 8-acetonylthiohypoxanthine, which have an oxo group at 6-position of purine ring, occured at 7-nitrogen and gave thiazolo-[2,3-*f*]xanthine and thiazolo[2,3-*f*]hypoxanthine, respectively.[3]

Theophylline is known to give only 7-substituted derivatives in glycosilations and alkylations. So it was expected that cyclization of 8-(acylmethyl)thiotheophyllines might take place to 7-nitrogen of purine. Thiazolotheophylline was synthesized by Ochiai[4] and described to be thiazolo[2,3-*f*]theophylline. But any proof for its structure was not described.

In this paper, the syntheses of thiazolo[2,3-*f*]theophyllines and their structural elucidations were described. Mass-spectrometric fragmentations of these compounds were also described.

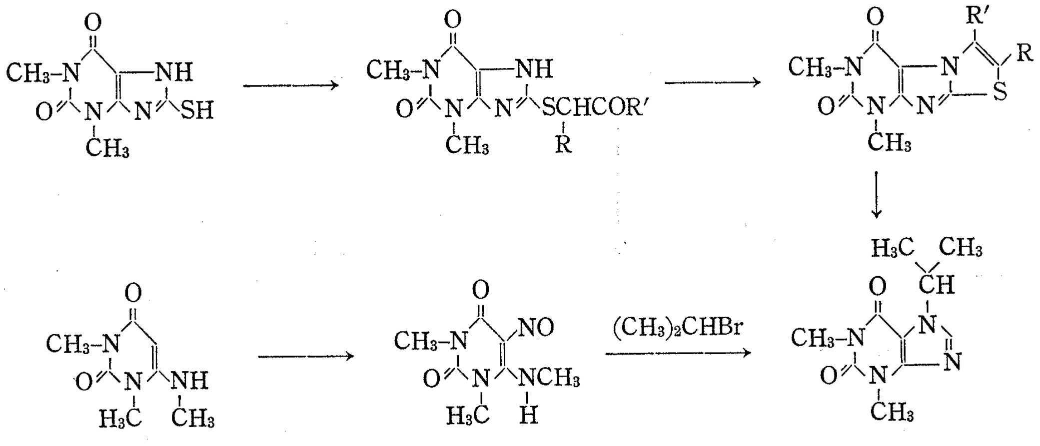

Chart 1

Thiazolo[2,3-*f*]theophyllines were prepared according to the procedure of Ochiai[4] with some modifications. Sodium salt of 8-thiotheophylline[5] were reacted with α-halocarbonyl compounds and resulting intermediates, 8-(acylmethyl)thiotheophyllines, were cyclized by

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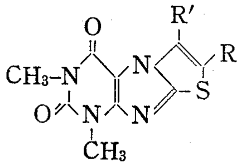
[1] Location: *33-94, Enokicho, Suita City, Osaka.*
[2] H. Uno, A. Irie and K. Hino, *Chem. Pharm. Bull.* (Tokyo), in press.
[3] H. Uno, A. Irie, and K. Hino, *Chem. Pharm. Bull.* (Tokyo), in press.
[4] E. Ochiai, *Chem. Ber.*, **69**, 1650 (1936).
[5] K.W. Merz and P.H. Stahl, *Chem. Abstr.*, **63**, 4296 (1965).

heating in polyphosphoric acid. Compounds thus obtained were summarized in Table I. Their ultraviolet (UV) spectra were resembled each other and it was suggested that they had the same ring system.

TABLE I



No.	R	R′	mp (°C)	(solvent)	Yield %	Method	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
I	H	CH_3	265—270	(EtOH)	80.2	A	$C_{10}H_{10}O_2N_4S$	47.99	4.03	22.39	12.81	47.74	4.27	22.25	13.01
II	H	C_2H_5	224—226	(EtOH)	50.6	A	$C_{11}H_{12}O_2N_4S$	49.98	4.58	21.20	12.13	50.09	4.72	21.35	12.27
III	CH_3	CH_3	244—246	(EtOH)	76.2	A	$C_{11}H_{12}O_2N_4S$	49.98	4.58	21.20	12.13	50.10	4.69	20.92	12.16
IV	H	$C(CH_3)_3$	234—236	(EtOH)	40.6	B	$C_{13}H_{16}O_2N_4S$	53.41	5.52	19.16	10.97	53.60	5.51	19.40	10.91
V	H	C_6H_5	285—289	(EtOH)	56.3	B	$C_{15}H_{12}O_2N_4S$	57.68	3.87	17.94	10.27	57.68	3.87	17.94	10.27

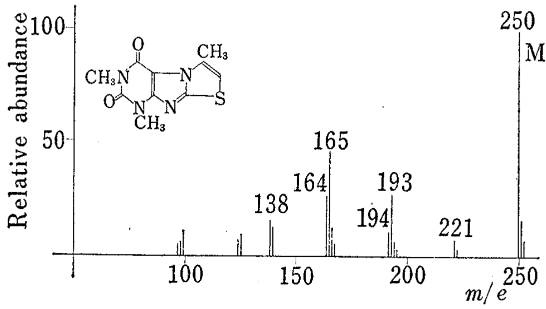


Fig. 1-a

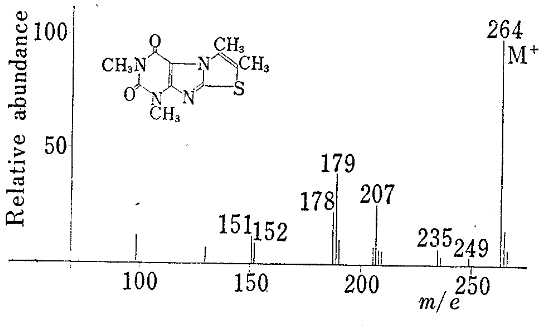


Fig. 1-b

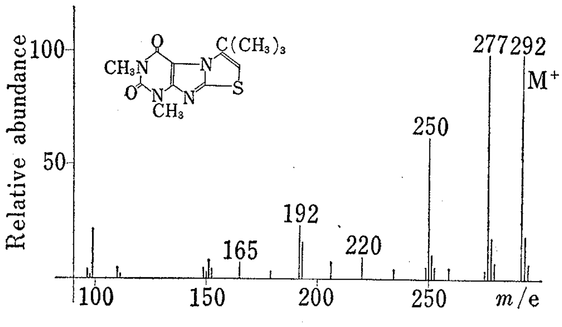


Fig. 1-c

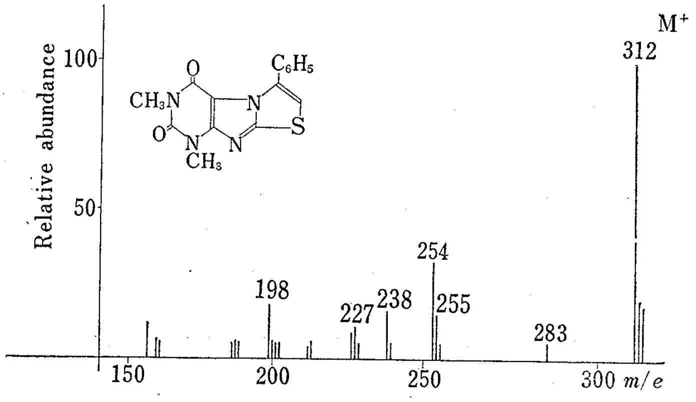


Fig. 1-d

The structure of these cyclization products was determined by Raney Ni desulfurization. I was refluxed in ethanol with Raney Ni and gave isopropyltheophylline, mp 175—177°. The UV spectra of this isopropyltheophylline was identified with that of caffeine (7-methyltheophylline)[6] and its mp and IR spectrum were identical with those of 7-isopropyltheophylline prepared according to the procedure of Goldner, *et al.*[7] Thus this isopropyltheophylline was determined to be 7-isopropyltheophylline derived from 6-methylthiazolo[2,3-*f*]theophylline.

The mass-spectra of thiazolo[2,3-*f*]theophyllines were shown in Fig. 1. The molecular ion peak of all compounds was the base peak. As shown in Fig. 1a and 1b, four main fragment peaks (M-29, M-57, M-85, and M-112) were observed. Moreover Fig. 1a and 1b were very similar to the mass-spectrum of theophylline.[8] Thus, the characteristic fragmentation of thiazolo[2,3-*f*]theophylline can be represented by an analogy of those of theophylline. The plausible fragmentation scheme of thiazolo[2,3-*f*]theophylline were shown in Chart 2. On the other hand, M-15 (*m/e* 249, M-CH_3) peak was found in the spectrum of 6-*tert*-butyl derivative (Fig. 1d) as expected. Small M-15 (*m/e* 249, M-CH_3) peak was found in the spectrum of 6,7-dimethyl derivative (Fig. 1b). This fragment may be represented by the structure of VI.

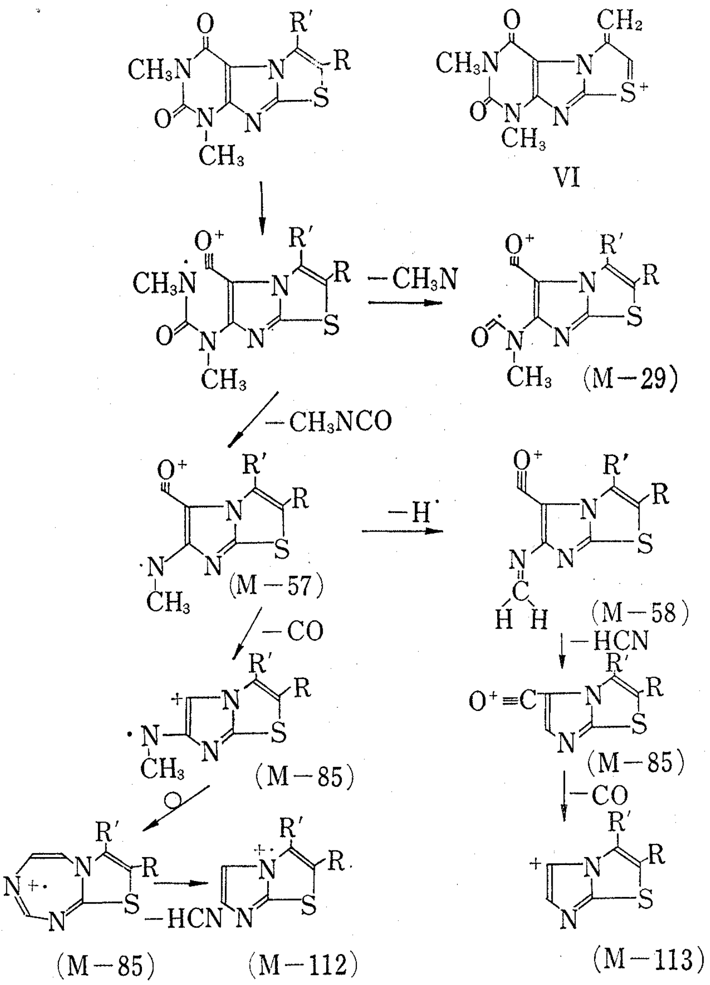


Chart 2

Experimental[9]

General Procedure for the Synthesis of 8-(Acylmethyl)thiotheophylline Derivatives——8-Thiotheophylline[5] (0.02 mole) was dissolved in 50 ml of 0.4N NaOH. To this solution was added dropwise α-halocarbonyl compound (0.02 mole) in 2 ml of EtOH under stirring for 30 min. Resulting precipitates were collected, washed with H_2O and recrystallized from suitable solvent. Results are summerized in Table II.

General Procedure for the Synthesis of Thiazolo[2,3-*f*]theophylline Derivatives——Method A: 8-(Acylmethyl)thiotheophylline (2 g) was dissolved in anhydrous EtOH (100 ml) and dry HCl was introduced into this solution at room temperature for about 10 min. The reaction mixture was refluxed for 3 hr and resulting precipitates were collected and recrystallized from suitable solvent.

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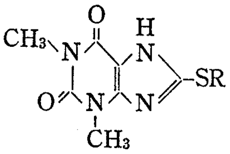
6) E. Buhler, *Chem. Ber.*, **100**, 492 (1967).
7) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **698**, 147 (1966).
8) G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.*, **93**, 632 (1962).
9) All melting points were uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Varian A-60 spectrometer using TMS as internal standard and UV spectra with Hitachi-2U spectrophotometer.

TABLE II.



No.	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
I	$-CH_2COCH_3$	198—200	$C_{10}H_{12}O_3N_4S$	44.76	4.51	20.88	11.95	44.81	4.65	20.97	12.20
Ⅱ	$-CH_2COCH_2CH_3$	192—194	$C_{11}H_{14}O_3N_4S$	46.79	5.00	19.85	11.36	46.73	5.12	19.76	11.52
Ⅲ	$-CH(CH_3)COCH_3$	188—190	$C_{11}H_{14}O_3N_4S$								
Ⅳ	$-CH_2COC(CH_3)_3$	230	$C_{13}H_{18}O_3N_4S$	50.31	5.85	18.05	10.33	50.45	6.02	18.26	10.59
Ⅴ	$-CH_2COC_6H_5$	234—236	$C_{15}H_{14}O_3N_4S$	54.53	4.27	16.96	9.71	54.32	4.41	16.88	9.93

Method B: 8-(Acylmethyl)thiotheophylline (2 g) was mixed with polyphosphoric acid (10 g) and heated for 3 hr at 140—150° under stirring. To the cooled reaction mixture was added cold H_2O (100 ml), and precipitates were collected, washed with H_2O and recrystallized from suitable solvent.

Desulfurization of 6-Methylthiazolo[2,3-*f*]theophylline (I)——I (2 g) and Raney Ni[2] (prepared from 20 g of Ni-alloy) were added to the mixture of H_2O (20 ml) and EtOH (120 ml). The reaction mixture was refluxed for 3 hr. After Ni was filtered off, solvents were evaporated *in vacuo* and the residue was recrystallized from EtOH–ether, yielding 0.2 g of 7-isopropyltheophylline, mp 175—177°. UV $\lambda_{\max}^{\text{EtOH}}$ 273 mμ. *Anal.* Calcd. for $C_{10}H_{14}O_2N_4$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.68; H, 6.35; N, 24.95. NMR ($CDCl_3$) δ: 7.69 (1H, s), 5.07 (1H, double q, $J=7$ Hz), 3.60 (3H, s), 3.41 (3H, s), 1.58 (3H, d, $J=7$ Hz).

Mass Spectral Measurements——The spectra were measured by the direct sample inlet technique on a Hitachi RMU-6L.

Mass Spectrum of I——*m/e* (Relative abundance), 250 (100, M), 221 (9), 193 (27), 192 (11), 166 (13), 165 (46), 164 (27), 139 (12), 138 (15).

Mass Spectrum of III——*m/e* (Relative abundance), 264 (100, M), 249 (3), 235 (7), 207 (26), 180 (11), 179 (40), 178 (22), 152 (9), 151 (12).

Mass Spectrum of IV——*m/e* (Relative abundance), 292 (100, M), 277 (100), 263 (5), 251 (11), 250 (63), 220 (9), 206 (8), 193 (16), 192 (23), 165 (8).

Mass Spectrum of V——*m/e* (Relative abundance), 312 (100, M), 283 (6), 255 (15), 254 (32), 238 (16), 227 (11), 226 (9), 198 (18).

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