Synthesis and Insecticidal Activity of 4-(Aminomethyl)-2*H*-1-benzothiopyran-2-ones (Thiocoumarins) and Related Compounds

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Bromination of 4-methyl-2*H*-1-benzothiopyran-2-ones (4-methylthiocoumarins) with bromine under irradiation of high-pressure mercury lamp gave 3-bromo-4-methylthiocoumarin, which reacted with secondary amine to give 4-(aminomethyl)thiocoumarins. The structure was determined by X-ray crystallographic analysis. A series of 4-methylthiocoumarin and related compounds were tested for insecticidal activity, and 4,6-dimethylthiocoumarin shows the most significant insecticidal activity against *Nilaparvata lugens* and *Aphis gossypii*. An introduction of an aminomethyl group in thiocoumarin results in improvement of activity against *Tetranychus urticae* and *Spodoptera litura*.

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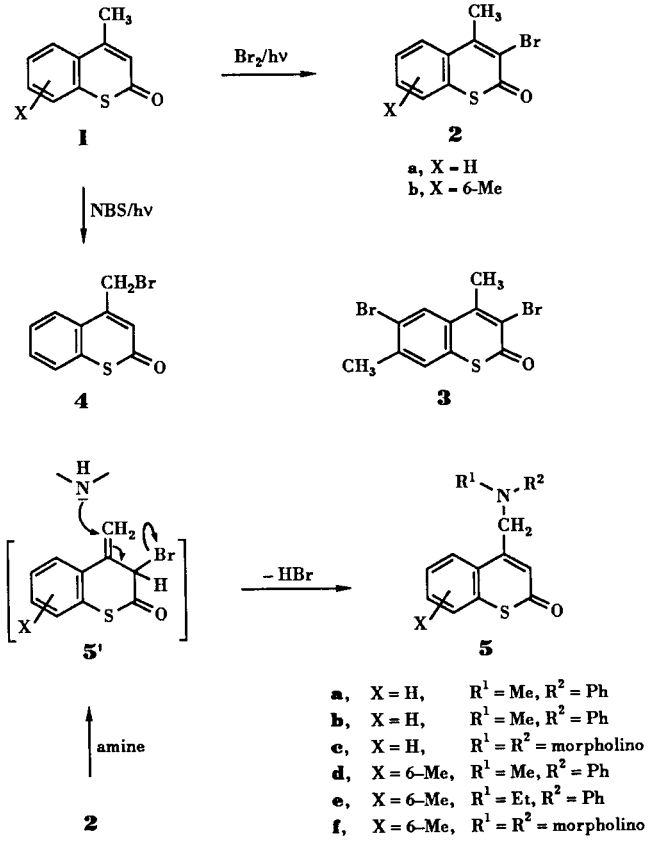
4*H*-1-Benzothiopyran-4-ones (thiochromones) and thioflavones have been tested for antimicrobial activity and antitumor activity [1,2]. Some 2*H*-1-benzothiopyran-2-ones (thiocoumarins), isomer of thiochromones, have exhibited anti-vitamin K activity, and plant and animal growth arrest activity [3].

We attempted to prepare novel thiocoumarins and related compounds as potential insecticidal active compounds. In this study, we prepared novel 4-(aminomethyl)-thiocoumarins, and examined insecticidal activities of a series of thiocoumarins, compared with related compounds.

Scheme I



4-Methylthiocoumarins **1** were prepared by a previously reported method [4]. The reaction of **1a** with bromine at room temperature under a high-pressure mercury lamp gave only a brominated product **2a** in 67% yield. Compared with ^{1}H nmr of **1a**, the singlet resonance at 6.6 ppm which corresponds to the proton at the 3-position disappeared and the methyl protons at the 4-position in **2a** were still observed. These results suggest that the bromination occurs at the 3-position of **1**. 3-Bromo derivative **2b** from 4,6-dimethylthiocoumarin was similarly prepared, but only the 3,6-dibromo derivative **3** from 7,4-dimethylthiocoumarin was obtained.

The reaction of **1a** with *N*-bromosuccinimide (NBS) under a high-pressure mercury lamp gave the 4-bromomethyl derivative **4** assigned from the ^{1}H nmr spectra, but no 3-bromo derivative was obtained. In the former bromi-

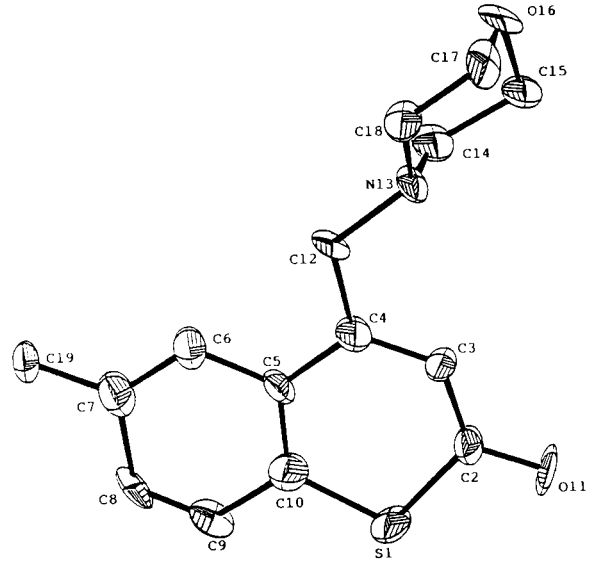


Figure 1. ORTEP view of **5f** showing the atom numbering scheme and thermal ellipsoids at the 50% probability level

nation, electrophilic attack of the bromine cation at the 3-position of **1** might occur initially, as it is well known that electrophilic substitution in thiocoumarin takes place preferentially at the 3-position [5].

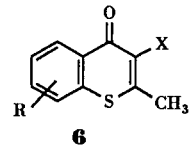
We now found that 4-(aminomethyl)thiocoumarin **5**, not the 3-amino derivative, was prepared by reaction of 3-bromo-4-methylthiocoumarin **2** with a secondary amine in DMF under refluxing for 1 hour. Based on the ^{1}H nmr spectra, the following structure of **5** is assigned. Compared with the ^{1}H nmr of **2a**, the singlet proton at the 3-position and the methylene proton appeared at 6.6 ppm and 4.7 ppm in the ^{1}H nmr spectra of **5a**. These results suggest that an aminated product is not the 3-substituted derivative, but the 4-aminomethyl derivative. In other amino products, similar observations were made in the ^{1}H nmr spectra of **5**. In this amination, first, the 1,3-shift of the methyl proton at the 4-position in **2** takes place and then nucleophilic attack of a secondary amine to the methylene group and loss of an hydrogen bromide might give 4-aminomethyl derivative **5** (Scheme I). This amination is limited to secondary amines at present. Similar reaction of an oxo analogue has been proposed [6].

Table I

Selected Bond Lengths/Å in Two Independent Molecular Units of **5f**

S1	– C2	1.758	S21	– C22	1.758
S1	– C10	1.728	S21	– C30	1.763
C2	– C3	1.390	C22	– C23	1.513
C2	– O11	1.247	C22	– O31	1.200
C3	– C4	1.391	C23	– C24	1.306
C4	– C5	1.462	C24	– C25	1.466
C4	– C12	1.536	C24	– C32	1.521
C5	– C6	1.453	C25	– C26	1.342
C5	– C10	1.386	C25	– C30	1.411
C6	– C7	1.380	C26	– C27	1.400
C7	– C8	1.533	C27	– C28	1.249
C7	– C19	1.418	C27	– C39	1.599
C8	– C9	1.248	C28	– C29	1.505
C9	– C10	1.428	C29	– C30	1.372
C12	– N13	1.526	C32	– N33	1.422
N13	– C14	1.412	N33	– C34	1.485
N13	– C18	1.439	N33	– C38	1.482
C14	– C15	1.552	C34	– C35	1.564
C15	– O16	1.500	C35	– O36	1.362
O16	– C17	1.469	O36	– C37	1.344
C17	– C18	1.480	C37	– C38	1.515

The structure of **5f** was also confirmed by X-ray crystallographic analysis. Figure 1 shows the molecule with atomic labelling and the bond lengths are shown in Table I. Bond angles, positional parameters, and thermal parameters are given in supplemental tables. Compound **5f** included two crystallographically independent molecular units at the original position which showed different bond lengths, and the mean C–S bond length in **5f** is *ca.* 1.75 Å. The heterocyclic ring in **5f** lies on the same plane of the benzene ring with dihedral angles of 2.5°. The morpholino group at the 4-position is in the chair form, as shown in Figure 1



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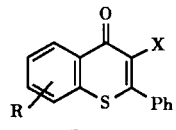

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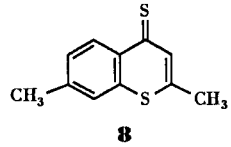

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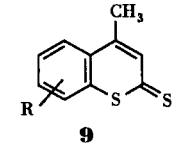

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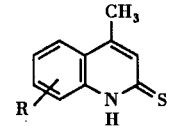

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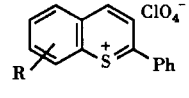

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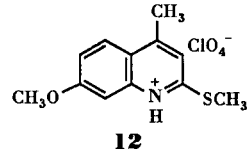

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Table II

Insecticidal Activity of Thiocoumarins

Compound	X, R^1, R^2	Mortality of Insects/% [a] *N.l.*	*T.u.* [b]	*S.l.*
1a	H	80	30	0
1b	7-Me	100	0	0
1c	6-Me	100	10	0
1d	7-Cl	40	20	0
1e	6-Cl	30	20	0
1f	6-Br	0	30	0
1g	7-OMe	0	40	0
5a	R^1 = Me, R^2 = C_6H_5	10	50	0
5b	R^1 = Et, R^2 = C_6H_5	10	40	10
5d	R^1 = Me, R^2 = C_6H_5, X = 6–Me	0	30	20
5e	R^1 = Et, R^2 = C_6H_5, X = 6–Me	10	60	40
5f	R^1 = R^2 = morphorino, X = 6–Me	0	30	30
2a	H	0	60	0
2b	6-Me	0	30	20
3	–	0	50	20

[a] *N.l.*, *Nilaparvata lugens*; *T.u.*, *Tetranychus urticae*; *S.l.*, *Spodoptera litura*. [b] Decreased % of *T.u.*.

Table III

Insecticidal Activity of Benzothiopyran Related Compounds

Compound	R, X, Y	Mortality of Insects/% [a] *N.l.*	*T.u.* [b]	*S.l.*
6a	R = X = H	10	40	0
6b	R = 7-Me, X = H	0	60	0
6c	R = 6-Me, X = H	20	50	0
6d	R = 6-Cl, X = H	0	20	0
6e	R = H, X = CH_2Cl	10	40	0
7a	X = H, R = 7-OH	0	40	0
7b	X = H, R = 8-OH	0	50	10
7c	X = H, R = 8-OMe	10	50	0
7d	X = CH_2OH, R = H	10	20	0
7e	X = CH_2OAc, R = H	0	70	0
7f	X = CH_2Cl, R = H	0	40	0
7g	X = CH_2Cl, R = 6-Me	0	70	0
8	–	0	40	0
9a	R = H	30	50	0
9b	R = 7-Me	0	10	0
9c	R = 7-MeO	50	40	0
10a	R = H	10	30	0
10b	R = 7-MeO	40	20	0
11a	R = 6-MeO	10	40	0
11b	R = 7-MeO	10	60	0
12	–	100	30	0

[a] All insects are explained as footnote [a] in Table II. [b] Decreased % of *T.u.*.

Insecticidal activities of thiocoumarins and related compounds are summarized in Tables II and III. We now found that 4-methylthiocoumarin derivative **1** exhibited significant insecticidal activity against *Nilaparvata lugens (N.l.)*, whereas the corresponding thiochromones **6** are inactive against *N.l.* and show weak activity against *Tetranychus urticae (T.u.)*. The most active 4-methylthiocoumarins are **1b** and **1c** against *N.l.* Comparison between the activities of **1b** or **1c** and the reference insecticide, dimethoxo(4-nitro-3-methylphenoxy)phosphine sulfide (Sumichion), shows that the mortalities of *Aphis gossypii (A.g.)* in concentration of 20 ppm of **1b** and **1c** are 70% and 15%, respectively, relative to 95% in same concentration of Sumichion, and proliferous rate of *A.g.* are 7.7% and 48%, respectively, relative to 2.2% in Sumichion.

An introduction of a aminomethyl group in the 4-position of thiocoumarin results in decrease in activity against *N.l.*, but leads to improvement of activity against *T.u.* and *Spodoptera litura (S.l.)*. An introduction of bromine at the 3-position results similarly in a decrease in activity.

Thioflavone derivative **7** which showed antimicrobial activity exhibits [1,2] weak insecticidal activity only against *T.u.* Comparison between the activities of **1** and **9** shows that replacement of a carbonyl group of **1** by the thiocarbonyl group results in decrease in activity against *N.l.*, except for **9c**. Aza analogue **10** shows similar activity. Though benzothiopyrylium salts **11** is inactive against *N.l.*, its aza analogue **12** exhibits significant activity against *N.l.* Compounds **6-12** shows similar activities against *T.u.*

EXPERIMENTAL

All melting points are uncorrected. The ^1H nmr spectra were recorded with a JEOL JNM-GX 270 spectrometer at 270 MHz. All spectra employed tetramethyl silane as the internal standard. The mass spectra were obtained with a Shimadzu LKB-9000 spectrometer operating 70 eV. The ir spectra were recorded with a Shimadzu IR-420 spectrometer using potassium bromide pellets.

Table IV

^1H-NMR, Mass, and IR Spectral Data of 4-(Aminomethyl)thiocoumarin **5**

Compound	^1H-NMR, (deuteriochloroform) (δ ppm)	Mass m/z (relative intensities)	IR (cm^{-1}) CO
5a	3.09 (s, 3H), 4.72 (s, 2H), 6.61 (s, 1H), 6.65-6.79 (m, 3H), 7.20-7.26 (m, 2H), 7.40-7.56 (m, 3H), 7.82 (d, 1H, J = 7.9 Hz)	281 (M^+, 100), 237 (57)	1630
5b	1.27 (t, 3H, J = 7.2 Hz), 3.49 (q, 2H, J = 7.3 Hz), 4.69 (s, 2H), 6.61-6.65 (m, 3H), 6.73 (t, 1H, J = 7.3 Hz), 7.17-7.23 (m, 2H), 7.44-7.55 (m, 3H), 7.85 (d, 1H, J = 7.9 Hz)	295 (M^+, 100), 281 (22) 252 (44)	1630
5c	2.56 (t, 4H, J = 4.6 Hz), 3.69 (s, 2H), 3.73 (t, 4H, J = 4.6 Hz), 6.77 (s, 1H), 7.40-7.50 (m, 3H), 8.10 (d, 1H, J = 7.9 Hz)	261 (M^+, 97), 186 (100) 184 (47)	1600
5d	2.46 (s, 3H), 3.09 (s, 3H), 4.72 (s, 2H), 6.59-6.79 (m, 3H), 7.34-7.45 (m, 5H), 7.61 (s, 1H)	295 (M^+, 100), 266 (65)	1625
5e	1.26 (t, 3H, J = 7.3 Hz), 2.48 (s, 3H), 3.50 (q, 2H, J = 6.9 Hz), 4.68 (s, 2H, 6.60-6.75 (m, 3H), 7.17-7.45 (m, 5H), 7.64 (s, 1H)	309 (M^+, 100), 294 (67) 282 (47)	1625
5f	2.46 (s, 3H), 2.57 (t, 4H, J = 4.9 Hz), 3.68 (s, 2H), 3.74 (t, 4H, J = 4.9 Hz), 6.80 (s, 1H), 7.30-7.39 (m, 2H), 7.84 (s, 1H)	275 (M^+, 65), 274 (67) 246 (70), 245 (100)	1620
5g	2.50 (s, 3H), 3.09 (s, 3H), 4.67 (d, 2H, J = 1.6 Hz), 6.58 (d, 1H, J = 1.6 Hz), 7.20-7.64 (m, 6H), 7.96 (s, 1H)	375 (M^+ +2, 68), 373 (M^+, 76) 344 (100), 342 (85)	1640

Table V
Analytical Data and MP of 4-(Aminomethyl)-thiocoumarins **5**

Compound	Yield %	Mp°C	Formula	Analysis (%) Calcd./Found C	H	N
5a	63	146-148	$C_{17}H_{15}NOS$	72.57	5.37	4.98
				72.36	5.46	5.04
5b	65	115-117	$C_{18}H_{17}NOS$	73.19	5.80	4.74
				73.10	6.02	4.68
5c	51	120-122	$C_{14}H_{15}NO_2S$	64.34	5.79	5.36
				64.48	5.80	5.28
5d	39	207-209	$C_{18}H_{17}NOS$	73.19	5.80	4.74
				72.87	5.55	4.68
5e	66	154-155	$C_{19}H_{19}NOS$	73.75	6.19	4.53
				73.54	5.92	4.59
5f	79	141-144	$C_{15}H_{17}NO_2S$	65.43	6.22	5.09
				65.78	6.24	4.97
5g	57	180-183	$C_{18}H_{16}NOSBr$	57.76	4.31	3.74
				58.04	4.20	3.66

Bromination of 4-Methylthiocoumarin **1** with Bromine.

Bromine (43 ml, 86.5 mmoles) was added to a solution of 4-methylthiocoumarin **1** (3.05 g, 17.3 mmoles) in dichloroethane (50 ml), and then the mixture was irradiated by a high-pressure mercury lamp for 4 hours at room temperature. After the mixture was kept over night, the resulting solid was filtered, and washed with aqueous solution of sodium sulfite. Recrystallization from ethanol-water gave compound **2a** in 67% yield.

Compounds **2b** and **3** were similarly prepared in yields of 88 and 93%, respectively.

3-Bromo-4-methyl-2*H*-1-benzothiopyran-2-one (**2a**).

This compound was obtained as colorless needles, mp 138-140°; ms: m/z 256 ($M^+ + 2$, 70), 254 (M^+, 68), 283 (73), 226 (70), 175 (100); ir: ν CO 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.90 (s, 3H), 7.42-7.56 (m, 3H), 7.95 (d, 1H, J = 8.1 Hz).

Anal. Calcd. for $C_{10}H_7OSBr$: C, 47.08; H, 2.77. Found: C, 47.11; H, 2.56.

3-Bromo-4,6-dimethyl-2*H*-1-benzothiopyran-2-one (**2b**).

This compound was obtained from 4,6-dimethylthiocoumarin, mp 127-129°; ms: m/z 270 ($M^+ + 2$, 68), 268 (M^+, 65), 242 (65), 240 (63), 189 (100); ir: ν CO 1625 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.48 (s, 3H), 2.87 (s, 3H), 7.27-7.39 (m, 2H), 7.75 (s, 1H).

Anal. Calcd. for $C_{11}H_9OSBr$: C, 49.09; H, 3.37. Found: C, 48.82; H, 3.08.

3,6-Dibromo-4,7-dimethyl-2*H*-1-benzothiopyran-2-one (**3**).

This compound was obtained from 4,7-dimethylthiocoumarin, mp 169-172°; ms: m/z 350 ($M^+ + 4$, 38), 348 ($M^+ + 2$, 69), 346 (M^+, 38), 320 (100), 318 (100); ir: ν CO 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.47 (s, 3H), 2.83 (s, 3H), 7.33 (s, 1H), 8.09 (s, 1H).

Anal. Calcd. for $C_{11}H_8OSBr_2$: C, 37.96; H, 2.32. Found: C, 38.12; H, 2.22.

4-Bromomethyl-2*H*-1-benzothiopyran-2-one (**4**).

N-Bromosuccinnimide (2.53 g, 14.2 mmoles) was added to a solution of **1a** (0.3 g, 1.7 mmoles) in dichloromethane (20 ml), and then the mixture was irradiated by a high-pressure mercury lamp for 10 hours at room temperature. The mixture was filtered, and the product was chromatographed on a silica gel (Wacogel C-300) with benzene and recrystallized from ethanol-water to give a pure compound **4** (yield 11%), mp 172-174°; ms: m/z 256 ($M^+ + 2$, 100), 254 (M^+, 100), 228 (26), 226 (51), 175 (84); ir: ν CO 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.61 (s, 2H), 6.71 (s, 1H), 7.46-7.54 (m, 3H), 8.00 (d, 1H, J = 7.3 Hz).

Anal. Calcd. for $C_{10}H_7OSBr$: C, 47.08; H, 2.77. Found: C, 47.21; H, 2.59.

General Reaction of 3-Bromo-4-methylthiocoumarin **2** with Amines.

N-Methylaniline (0.304 g, 2.84 mmoles) was added dropwise to a solution of 3-bromo-4-methylthiocoumarin **2a** (0.18 g, 0.71 mmole) in 20 ml of *N*,*N*-dimethylformamide. The solution was stirred for 1 hour at reflux. After cooling, the reaction mixture was poured into water, and dilute hydrogen chloride was added. The resulting solid was filtered and the product was chromatographed on silica gel with benzene or benzene-acetone (10:1 v/v) and recrystallized from ethanol-water to give pure 4-(*N*-methyl-*N*-phenylaminomethyl)-2*H*-1-benzothiopyran-2-one **5a**. Compounds **5b-5f** were similarly prepared from **2** and *N*-ethylaniline or morpholine. 7-Methyl-6-bromo-4-(*N*-methyl-*N*-phenylaminomethyl)-thiocoumarin **5g** also was obtained from **3** and methylaniline. The physical properties of compounds **5a-5g** are summarized in Tables IV and V.

X-Ray Crystallography of **5f**.

The crystal of **5f** was obtained by slow recrystallization from a saturated ethanol-water. All data were collected at 23° on Rigaku AFC-6R diffractometer with graphite-monochromated Mo-Kα radiation in the range $2\theta < 50°$ of the ω-2θ scan mode. 1489 Reflections had $F > 3\sigma(F)$ and were used in the structure refinement. The structure was solved by the Direct method of MULTAN 78 and completed by block-diagonal least-squares method using the UNICS program [7] in Osaka University.

The non-hydrogen atoms in **5f** were assigned anisotropic thermal parameters. All hydrogen atoms were placed in calculated

positions and included in structure factor. The final conventional index R is 0.065. Though two crystallographically independent molecular units at original position were included, only an ORTEP drawing for the molecular is shown in Figure 1.

Crystallographic data of **5f** is $C_{15}H_{17}NO_2S$: M = 275.37, monoclinic, spacing group Pc, a = 11.336(4), b = 16.871(7), c = 7.287(5) Å, β = 80.748(42)°, V = 1375.5(12) Å^3, Z = 4, D_d = 1.33 g cm^{-3}; crystal size: 0.08 x 0.2 x 0.7 mm^3. Tables of final atomic parameters including hydrogen atoms, anisotropic parameters, bond angles, and Fo-Fc table are available on request from the authours.

Insecticidal Activity.

Insecticidal activities of thiocoumarins and related compounds were determined by mortality or decreased percentage of insects when these compounds were sprayed. The decreased percentage of *Tetranychus urticae* was determined after 7 days when a standardized suspension of the test substrate (500 ppm) was sprayed on *Tetranychus urticae* on the seedlings of the kidney bean. The mortality of *Nilaparvata lugens* was determined after 7 days when *Nilaparvata lugens* on rice seedlings were dipped in the solution of the test substrate (50 ppm).

The mortality of *Spodoptera litura* was determined after 5 days when the suspension of the test substrate (500 ppm) was sprayed on *Spodoptera litura* on soybeans.

Insecticidal activities of **1b** and **1c** against *Aphis gossypii* were determined by mortality and proliferous rate after 2 and 6 days, respectively, when a suspension of **1b** or **1c** (20 ppm) was sprayed on *Aphis gossypii* on cucumber seedlings.

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