Synthesis of *N*,*N*-Dialkyl-9-oxoacridine-10(9*H*)-carbothioamides *via* the Reaction of (2-Halophenyl)(2-isothiocyanatophenyl)methanones with Secondary Amines, Followed by Cyclization with NaH

by **Kazuhiro Kobayashi***, **Kazuhiro Nakagawa**, and **Shohei Yuba**

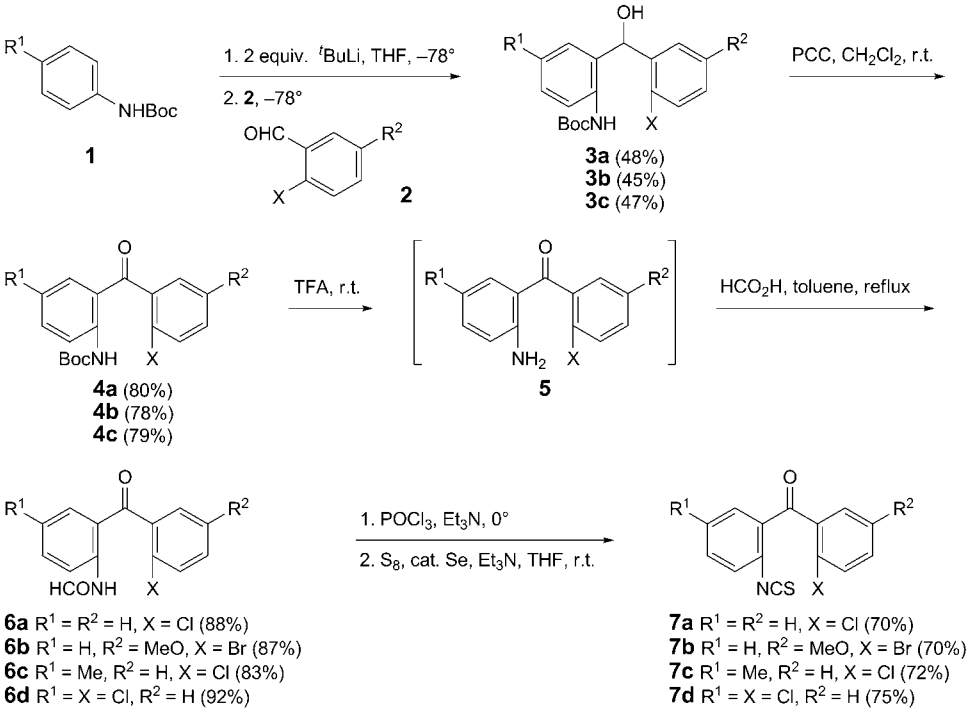
Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan (phone/fax: +81-857-315263; e-mail: kkoba@chem.tottori-u.ac.jp)

The first preparation of acridin-9(10*H*)-ones carrying a tertiary thiocarbamoyl group at C(10), *i.e.*, *N*,*N*-dialkyl-9-oxoacridine-10(9*H*)-carbothioamides **9**, is described. The method is based on the reaction of (2-halophenyl)(2-isothiocyanatophenyl)methanones **7**, prepared from (2-aminophenyl)(2-halophenyl)methanones **5** by a convenient three-step sequence, with secondary amines in DMF at room temperature to generate the corresponding thiourea derivatives **8** *in situ*, which are treated with NaH at 100–120° to provide the desired products in one-pot reactions in generally good yields.

Introduction. – There has been an increasing interest in the development of novel and efficient methods for the synthesis of acridin-9(10*H*)-one derivatives [1][2] because of their biological activities [2][3] and occurrence in nature [4]. In a previous article [2], we have described a simple method for the preparation of 10-aryl- or 10-(arylmethyl)acridin-9(10*H*)-ones, based on the reaction of (2-fluorophenyl)(2-halophenyl)methanones with benzenamines or arylmethanamines. Herein, we report a convenient method, which allows the preparation of a novel type of acridin-9(10*H*)-ones, *N*,*N*-dialkyl-9-oxoacridine-10(9*H*)-carbothioamides **9**, possessing a tertiary thiocarbamoyl substituent at N(10). The method relies on cyclization of the corresponding thiourea intermediates **8**, derived by the addition of secondary amines to the isothiocyanate C-atom of (2-halophenyl)(2-isothiocyanatophenyl)methanones **7**.

Results and Discussion. – As outlined in *Scheme 1*, the key precursors of our synthesis, (2-halophenyl)(2-isothiocyanatophenyl)methanones **7**, were prepared *via* six-step sequence starting with 1,1-dimethylethyl *N*-phenylcarbamates **1** and 2-halobenzaldehydes **2** in general. The reaction of 1,1-dimethylethyl *N*-lithio-*N*-(2-lithiophenyl)carbamates, generated from **1** and ^{t}BuLi by the method of *Muchowski* and *Venuti* [5], with **2** gave the corresponding alcohols **3** in moderate yields. These alcohols were oxidized with PCC (pyridinium chlorochromate) to produce the corresponding ketones **4** in good yields. De(*tert*-butoxycarbonylation) of **4** with TFA (CF_3COOH) allowed the quite easy formation of 2-aminophenyl 2-halophenyl ketones **5a**–**5c**. These ketones (without any purification) and the commercially available 2-amino-5-chlorophenyl 2-chlorophenyl ketone (**5d**) were treated with HCO_2H to give the corresponding formamides **6** in good yields. Dehydrations of **6** with $POCl_3$ gave the corresponding isocyanides, which, without any purification, on treatment with S_8 in the

Scheme 1



presence of a catalytic amount of Se under the conditions reported by *Fujiwara et al.* [6], afforded **7** in good overall yields.

The one-pot transformation of **7** into *N*,*N*-dialkyl-9-oxoacridine-10(9*H*)-carbothioamides **9** was conducted as outlined in *Scheme 2*. The reaction of **7** with secondary amines proceeded rapidly in DMF at room temperature to form the corresponding thiourea derivatives **8**. After complete consumption of **7** (TLC (SiO_2)), NaH was added at the same temperature. Cyclization took place generally by heating at 100° at an appropriate rate, and the desired products **9** were obtained, after aqueous workup and subsequent recrystallization of the residual solid, in generally good yields as compiled in the *Table*. When substrate **7b** was used, cyclization required somewhat higher temperature (120°), and the yield of the corresponding product **9d** was lower than those using the other substrates **7**, probably due to the electron-donating MeO substituent (*Entry 4*). It should be noted that the use of $^{i}Pr_2NH$ leads to the corresponding product **9g** in considerably lower yield than those of the others (*Entry 7*). This result may be attributed to the steric bulkiness due to two ^{i}Pr groups.

In conclusion, we have demonstrated that the method based on the reaction of (2-halophenyl)(2-isothiocyanatophenyl)methanones with secondary amines, followed by treatment of the resulting thiourea derivatives with NaH, provides the first and convenient route to *N*,*N*-dialkyl-9-oxoacridine-10(9*H*)-carbothioamides. Investigations toward the synthesis of related derivatives utilizing the present methodology are now in progress in our laboratory.

Scheme 2

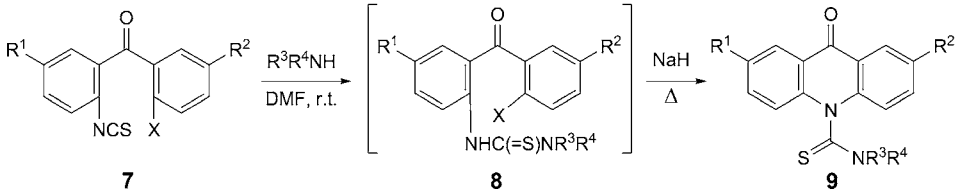


Table. *Preparation of* N,N-*Disubstituted 9-Oxo-9*H-*acridine-10-carbothioamides* **9**

Entry	**7**	R^3	R^4	Temp. [°]	Time [h]	**9**	Yield[a]) [%]
1	**7a**	Et	Et	100	1	**9a**	78
2	**7a**		$-(CH_2)_4-$	100	2	**9b**	77
3	**7a**		$-(CH_2)_5-$	100	2	**9c**	82
4	**7b**		$-(CH_2)_2O(CH_2)_2-$	120	8	**9d**	65
5	**7c**	Et	Et	100	1.5	**9e**	72
6	**7d**	Et	Et	100	2	**9f**	79
7	**7d**	^{i}Pr	^{i}Pr	100	5	**9g**	50
8	**7d**		$-(CH_2)_4-$	100	3	**9h**	95
9	**7d**		$-(CH_2)_5-$	100	2	**9i**	90
10	**7d**		$-(CH_2)_2O(CH_2)_2-$	100	2	**9j**	80
11	**7d**	Ph	Me	100	2	**9k**	82

[a]) Yields of isolated products.

Experimental Part

General. All of the org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals were commercially available. TLC: Silica gel *60 PF_{254}* (*Merck*). Column chromatography (CC): *Wako Gel C-200E*. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Perkin–Elmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *JEOL ECP500* FT-NMR spectrometer or *JEOL LA400* FT-NMR spectrometer (at 500 or 400 MHz, resp.) in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ^{13}C-NMR Spectra: *JEOL ECP500* FT-NMR spectrometer at 125 MHz in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard. EI-MS (70 eV): *JEOL JMS AX505 HA* spectrometer; in *m*/*z* (rel. %). HR-MS (DART, pos.): *Thermo Scientific Exactive* spectrometer; in *m*/*z*.

1,1-Dimethylethyl {2-[(2-Chlorophenyl)(hydroxy)methyl]phenyl}carbamate (**3a**). *Representative Procedure.* To a stirred soln. of 1,1-dimethylethyl (lithio)(2-lithiophenyl)carbamate in THF (6 ml) at −78°, generated from 1,1-dimethylethyl phenylcarbamate (**1**; 0.39 g, 2.0 mmol) and ^{t}BuLi (4.0 mmol) as described by *Muchowski* and *Venuti* [5], was added *2-chlorobenzaldehyde* (**2**; 0.28 g, 2.0 mmol). After 15 min, sat. aq. NH_4Cl (20 ml) was added, and the mixture was extracted with AcOEt (3 × 15 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by CC (SiO_2) to give **3a** (0.32 g, 48%). Yellow oil. R_f (THF/hexane 1:10) 0.18. IR (neat): 3366, 1704. ^{1}H-NMR (400 MHz): 1.52 (*s*, 9 H); 3.39 (br. *s*, 1 H); 6.23 (*d*, *J* = 3.9, 1 H); 6.92 (*d*, *J* = 7.8, 1 H); 7.02 (*t*, *J* = 7.8, 1 H); 7.27–7.38 (*m*, 4 H); 7.46 (br. *s*, 1 H); 7.62 (*d*, *J* = 7.8, 1 H); 7.72 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{18}H_{20}ClNO_3$ (333.81): C 64.77, H 6.04, N 4.20; found: C 64.58, H 6.17, N 4.24.

1,1-Dimethylethyl {2-[(2-Bromo-5-methoxyphenyl)(hydroxyl)methyl]phenyl}carbamate (**3b**). Pale-yellow solid. M.p. 109–112° (hexane/THF). IR (KBr): 3388, 3348, 1696. ^{1}H-NMR (400 MHz): 1.52 (*s*, 9 H); 3.45 (br., 1 H); 3.81 (*s*, 3 H); 6.12 (*d*, *J* = 3.9, 1 H); 6.76 (*dd*, *J* = 8.8, 2.9, 1 H); 6.93 (*dd*, *J* = 7.8, 2.0, 1 H); 7.03 (*dd*, *J* = 7.8, 6.8, 1 H); 7.21 (*d*, *J* = 2.9, 1 H); 7.26–7.31 (*m*, 1 H); 7.34 (br. *s*, 1 H); 7.43 (*d*, *J* = 8.8,

1 H); 7.68 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{19}H_{22}BrNO_4$ (408.29): C 55.89, H 5.43, N 3.43; found: C 55.80, H 5.44, N 3.14.

1,1-Dimethylethyl {2-[(2-Chlorophenyl)(hydroxyl)methyl]-4-methylphenyl}carbamate (**3c**). Yellow solid. M.p. 137–138° (hexane/THF). IR (KBr): 3470, 3298, 1695. ^{1}H-NMR (500 MHz): 1.50 (*s*, 9 H); 2.21 (*s*, 3 H); 3.52 (br. *s*, 1 H); 6.19 (*d*, *J* = 4.0, 1 H); 6.77 (*s*, 1 H); 7.09 (*d*, *J* = 8.0, 1 H); 7.14 (br. *s*, 1 H); 7.27 (*dd*, *J* = 8.0, 1.7, 1 H); 7.32–7.36 (*m*, 2 H); 7.48 (*d*, *J* = 8.0, 1 H); 7.64 (*d*, *J* = 7.4, 1 H). Anal. calc. for $C_{19}H_{22}ClNO_3$ (347.84): C 65.61, H 6.38, N 4.03; found: C 65.56, H 6.44, N 4.01.

Compounds **4** were prepared by the PCC oxidation of **3** under conditions reported in [7].

1,1-Dimethylethyl [2-(2-Chlorobenzoyl)phenyl]carbamate (**4a**). Yellow oil. R_f (THF/hexane 1:4) 0.52. IR (neat): 3284, 1732, 1642, 1606. ^{1}H-NMR (400 MHz): 1.57 (*s*, 9 H); 6.93 (*t*, *J* = 6.9, 1 H); 7.32–7.37 (*m*, 3 H); 7.44–7.47 (*m*, 2 H); 7.55 (*dd*, *J* = 7.8, 6.8, 1 H); 8.55 (*d*, *J* = 7.8, 1 H); 10.85 (br. *s*, 1 H). Anal. calc. for $C_{18}H_{18}ClNO_3$ (331.79): C 65.16, H 5.47, N 4.22; found: C 65.14, H 5.68, N 3.93.

1,1-Dimethylethyl [2-(2-Bromo-5-methoxybenzoyl)phenyl]carbamate (**4b**). White solid. M.p. 118–122° (hexane/AcOEt). IR (KBr): 3279, 1727, 1639, 1606. ^{1}H-NMR (500 MHz): 1.55 (*s*, 9 H); 3.80 (*s*, 3 H); 6.81 (*d*, *J* = 3.4, 1 H); 6.89–6.94 (*m*, 2 H); 7.35 (*dd*, *J* = 8.0, 1.1, 1 H); 7.51 (*d*, *J* = 8.6, 1 H); 7.55 (*ddd*, *J* = 8.6, 6.9, 1.8, 1 H); 8.55 (*d*, *J* = 8.6, 1 H); 10.82 (br. *s*, 1 H). Anal. calc. for $C_{19}H_{20}BrNO_4$ (406.27): C 56.17, H 4.96, N 3.45; found: C 56.02, H 5.07, N 3.37.

1,1-Dimethylethyl [2-(2-Chlorobenzoyl)-4-methylphenyl]carbamate (**4c**). Yellow oil. R_f (AcOEt/hexane 1:4) 0.53. IR (neat): 3287, 1731, 1640. ^{1}H-NMR (500 MHz): 1.54 (*s*, 9 H); 2.20 (*s*, 3 H); 7.09 (*s*, 1 H); 7.30 (*d*, *J* = 7.4, 1 H); 7.35–7.38 (*m*, 2 H); 7.43 (*d*, *J* = 8.0, 1 H); 7.47 (*dd*, *J* = 8.0, 7.4, 1 H); 8.43 (*d*, *J* = 8.6, 1 H); 10.71 (*s*, 1 H). Anal. calc. for $C_{19}H_{20}ClNO_3$ (345.82): C 65.99, H 5.83, N 4.05; found: C 66.05, H 6.06, N 4.01.

N-*[2-(2-Chlorobenzoyl)phenyl]formamide* (**6a**). *Representative Procedure.* Compound **4a** (0.40 g, 1.2 mmol) was dissolved in TFA (1.5 ml), and the soln. was stirred at r.t. for 10 min. TFA was removed under reduced pressure, and the residual crude *(2-aminophenyl)(2-chlorophenyl)methanone* (**5a**) [8] was used in the next step without any purification. The *N*-formylation of the crude compound with HCO_2H under conditions reported in [9] gave **6a** (0.27 g, 88%). Yellow solid. M.p. 93–94° (hexane/CH_2Cl_2). IR (KBr): 3317, 1698, 1643, 1604. ^{1}H-NMR (400 MHz): 7.06–7.64 (*m*, 7 H); 8.59–11.46 (*m*, 3 H). Anal. calc. for $C_{14}H_{10}ClNO_2$ (259.69): C 64.75, H 3.88, N 5.39; found: C 64.71, H 3.85, N 5.21.

N-*[2-(2-Bromo-5-methoxybenzoyl)phenyl]formamide* (**6b**). Beige solid. M.p. 125–127° (hexane/AcOEt). IR (KBr): 3300, 1696, 1644. ^{1}H-NMR (400 MHz): 3.81 (*s*, 3 H); 6.83 (*d*, *J* = 2.9, 1 H); 6.92 (*dd*, *J* = 8.8, 2.9, 1 H); 7.08 (*t*, *J* = 7.8, 1 H); 7.41 (*d*, *J* = 7.8, 1 H); 7.52 (*d*, *J* = 8.8, 1 H); 7.61 (*t*, *J* = 7.8, 1 H); 8.59 (*s*, 1 H); 8.80 (*d*, *J* = 7.8, 1 H); 11.41 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{12}BrNO_3$ (334.16): C 53.91, H 3.62, N 4.19; found: C 54.01, H 3.64, N 4.15.

N-*[2-(2-Chlorobenzoyl)-4-methylphenyl]formamide* (**6c**). Pale-yellow solid. M.p. 95–96° (hexane/Et_2O). IR (KBr): 3289, 1702, 1631. ^{1}H-NMR (500 MHz): 2.25 (*s*, 3 H), 7.15 (*s*, 1 H); 7.33 (*d*, *J* = 7.4, 1 H); 7.38–7.42 (*m*, 2 H); 7.45–7.50 (*m*, 2 H); 8.55 (*s*, 1 H); 8.69 (*d*, *J* = 8.6, 1 H); 11.32 (br. *s*, 1 H). Anal. calc. for $C_{15}H_{12}ClNO_2$ (273.71): C 65.82, H 4.42, N 5.12; found: C 65.82, H 4.43, N 5.09.

N-*[4-Chloro-2-(2-chlorobenzoyl)phenyl]formamide* (**6d**). Yellow solid. M.p. 103–105° (hexane/Et_2O). IR (KBr): 3300, 1697, 1646. ^{1}H-NMR (400 MHz): 7.33–7.58 (*m*, 6 H); 8.57 (*s*, 1 H); 8.81 (*d*, *J* = 8.8, 1 H); 11.30 (br. *s*, 1 H). Anal. calc. for $C_{14}H_9Cl_2NO_2$ (294.13): C 57.17, H 3.08, N 4.76; found: C 57.06, H 3.29, N 4.75.

(2-Halophenyl)(2-Isothiocyanatophenyl)methanones **7**. Compounds **6** were dehydrated with $POCl_3$ under conditions reported in [10] to give the corresponding ketones **7**. The crude isocyanides were treated with S_8 in the presence of a cat. amount of Se under conditions reported by *Fujiwara et al.* [6] to give **7**.

(2-Chlorophenyl)(2-isothiocyanatophenyl)methanone (**7a**). Reddish-brown oil. R_f (AcOEt/hexane 1:3) 0.52. IR (neat): 2091, 1672. ^{1}H-NMR (400 MHz): 7.30–7.57 (*m*, 7 H); 7.61 (*d*, *J* = 7.8, 1 H). Anal. calc. for $C_{14}H_8ClNOS$ (273.74): C 61.43, H 2.95, N 5.12; found: C 61.47, H 2.98, N 5.08.

(2-Bromo-5-methoxyphenyl)(2-isothiocyanatophenyl)methanone (**7b**). Reddish-brown oil. R_f (AcOEt/hexane 1:10) 0.24. IR (neat): 2106, 1674. ^{1}H-NMR (400 MHz): 3.83 (*s*, 3 H); 6.92 (*dd*, *J* = 8.8, 2.9, 1 H); 6.98 (*d*, *J* = 2.9, 1 H); 7.32–7.35 (*m*, 2 H); 7.50–7.56 (*m*, 2 H); 7.61 (*d*, *J* = 6.9, 1 H). Anal. calc. for $C_{15}H_{10}BrNO_2S$ (348.21): C 51.74, H 2.89, N 4.02; found: C 51.65, H 3.17, N 3.85.

(2-Chlorophenyl)(2-isothiocyanato-5-methylphenyl)methanone (**7c**). Reddish-brown oil. R_f (AcOEt/hexane 1:3) 0.55. IR (neat): 2110, 1672. ^{1}H-NMR (400 MHz): 2.37 (*s*, 3 H); 7.22 (*d*, *J* = 7.8, 1 H); 7.34 (*dd*, *J* = 8.8, 2.0, 1 H); 7.39–7.44 (*m*, 2 H); 7.45–7.50 (*m*, 3 H). Anal. calc. for $C_{15}H_{10}ClNOS$ (287.76): C 62.61, H 3.50, N 4.87; found: C 62.52, H 3.64, N 4.90.

(5-Chloro-2-isothiocyanatophenyl)(2-chlorophenyl)methanone (**7d**). Pale-yellow solid. M.p. 54–56° (hexane). IR (KBr): 2098, 1679. ^{1}H-NMR (400 MHz): 7.27 (*d*, *J* = 6.8, 1 H); 7.41–7.54 (*m*, 5 H); 7.57 (*d*, *J* = 2.0, 1 H). Anal. calc. for $C_{14}H_7Cl_2NOS$ (308.18): C 54.56, H 2.29, N 4.54; found: C 54.58, H 2.30, N 4.27.

N,N-*Diethyl-9-oxoacridine-10(9*H*)-carbothioamide* (**9a**). *Representative Procedure.* To a stirred soln. of **7a** (97 mg, 0.36 mmol) in DMF (1.2 ml) at r.t. was added Et_2NH (26 mg, 0.36 mmol) dropwise. After complete consumption of **7a** (TLC (SiO_2; AcOEt/hexane 1:3; within 5 min), NaH (60% in mineral oil; 14 mg, 0.36 mmol) was added, and the mixture was heated at 100° until disappearance of the thiourea intermediate **8a** (TLC (SiO_2; AcOEt/hexane 1:3; *ca.* 1 h). Sat. aq. NH_4Cl (10 ml) was added, and the mixture was extracted with AcOEt (3 × 10 ml). The combined extracts were washed with H_2O and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a residual solid, which was recrystallized from hexane/CH_2Cl_2 to give **9a** (87 mg, 78%). Pale-yellow solid. M.p. 159–161°. IR (KBr): 1646, 1605, 1255. ^{1}H-NMR (500 MHz): 0.97 (*t*, *J* = 7.4, 3 H); 1.62 (*t*, *J* = 6.9, 3 H); 3.28 (*q*, *J* = 7.4, 2 H); 4.24 (*q*, *J* = 6.9, 2 H); 7.34–7.40 (*m*, 4 H); 7.70 (*dd*, *J* = 8.0, 7.4, 2 H); 8.54 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR: 10.36; 13.26; 47.13; 47.77; 115.67; 121.78; 122.48; 127.55; 133.93; 139.02; 177.78; 180.31. MS: 310 (100, M^+). Anal. calc. for $C_{18}H_{18}N_2OS$ (310.41): C 69.65, H 5.84, N 9.02; found: C 69.63, H 5.64, N 9.22.

*10-(Pyrrolidin-1-ylcarbonothioyl)acridin-9(10*H*)-one* (**9b**). Pale-yellow solid. M.p. 163–164° (hexane/CH_2Cl_2). IR (KBr): 1640, 1604, 1257. ^{1}H-NMR (500 MHz): 1.96 (*quint.*, *J* = 6.9, 2 H); 2.17 (*quint.*, *J* = 6.9, 2 H); 3.20 (*t*, *J* = 6.9, 2 H); 4.14 (*t*, *J* = 6.9, 2 H); 7.34–7.38 (*m*, 4 H); 7.71 (*ddd*, *J* = 8.0, 6.9, 1.7, 2 H); 8.55 (*dd*, *J* = 8.0, 1.7, 2 H). ^{13}C-NMR: 24.76; 25.84; 51.21; 53.83; 115.15; 121.81; 122.43; 127.73; 134.19; 138.17; 177.55; 177.74. MS: 308 (100, M^+). Anal. calc. for $C_{18}H_{16}N_2OS$ (308.40): C 70.10, H 5.23, N 9.08; found: C 69.96, H 5.26, N 9.06.

*10-(Piperidin-1-ylcarbonothioyl)acridin-9(10*H*)-one* (**9c**). Pale-yellow solid. M.p. 186–188° (hexane/CH_2Cl_2). IR (KBr): 1637, 1605, 1251. ^{1}H-NMR (500 MHz): 1.44 (*quint.*, *J* = 5.7, 2 H); 1.72 (*quint.*, *J* = 5.7, 2 H); 1.98 (*quint.*, *J* = 5.7, 2 H); 3.30 (*t*, *J* = 5.7, 2 H); 4.51 (*quint.*, *J* = 5.7, 2 H); 7.35 (*dd*, *J* = 8.0, 7.4, 2 H); 7.40 (*d*, *J* = 8.5, 2 H); 7.70 (*ddd*, *J* = 8.5, 7.4, 1.1, 2 H); 8.54 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR: 23.64; 25.39; 26.50; 50.92; 51.74; 115.65; 121.73; 122.46; 127.58; 134.00; 138.66; 177.69; 179.24. MS: 322 (100, M^+). Anal. calc. for $C_{19}H_{18}N_2OS$ (322.42): C 70.78, H 5.63, N 8.69; found: C 70.81, H 5.80, N 8.72.

*2-Methoxy-10-(morpholin-4-ylcarbonothioyl)acridin-9(10*H*)-one* (**9d**). Yellow solid. M.p. 196–198° (hexane/CH_2Cl_2). IR (KBr): 1643, 1605, 1274. ^{1}H-NMR (400 MHz): 3.29 (*t*, *J* = 4.9, 2 H); 3.50 (*t*, *J* = 4.9, 2 H); 3.94 (*s*, 3 H); 4.00 (*t*, *J* = 4.9, 2 H); 4.52–4.56 (*m*, 2 H); 7.35–7.38 (*m*, 4 H); 7.68–7.72 (*m*, 1 H); 7.94 (br. *s*, 1 H); 8.55 (*dd*, *J* = 7.8, 2.0, 1 H). ^{13}C-NMR: 49.94; 50.38; 55.83; 66.02; 66.29; 106.82; 115.18; 117.12; 120.97; 122.40; 122.57; 124.83; 127.73; 133.40; 133.96; 138.18; 155.45; 177.15; 180.36. MS: 354 (100, M^+). Anal. calc. for $C_{19}H_{18}N_2O_3S$ (354.42): C 64.39, H 5.12, N 7.90; found: C 64.35, H 5.13, N 7.70.

N,N-*Diethyl-2-methyl-9-oxoacridine-10(9*H*)-carbothioamide* (**9e**). Pale-yellow solid. M.p. 157–158° (hexane/CH_2Cl_2). IR (KBr): 1648, 1604, 1258. ^{1}H-NMR (500 MHz): 0.96 (*t*, *J* = 7.4, 3 H); 1.60 (*t*, *J* = 7.4, 3 H); 2.48 (*s*, 3 H); 3.26 (*q*, *J* = 7.4, 2 H); 4.23 (*q*, *J* = 7.4, 2 H); 7.30 (*d*, *J* = 8.6, 1 H); 7.33–7.38 (*m*, 2 H); 7.52 (*dd*, *J* = 8.6, 2.3, 1 H), 7.67 (*ddd*, *J* = 8.6, 6.9, 1.7, 1 H); 8.32 (*s*, 1 H); 8.53 (*dd*, *J* = 8.0, 1.7, 1 H). ^{13}C-NMR: 10.38; 13.28; 20.72; 47.09; 37.74; 115.54; 115.66; 121.68; 121.70; 122.22; 126.87; 127.58; 132.27; 133.74; 135.34; 137.20; 138.91; 177.75; 180.57. MS: 324 (100, M^+). Anal. calc. for $C_{19}H_{20}N_2OS$ (324.44): C 70.34, H 6.21, N 8.63; found: C 70.17, H 6.21, N 8.60.

2-Chloro-N,N-*diethyl-9-oxoacridine-10(9*H*)-carbothioamide* (**9f**). Pale-yellow solid. M.p. 184–185° (hexane/CH_2Cl_2). IR (KBr): 1648, 1605, 1257. ^{1}H-NMR (400 MHz): 0.98 (*t*, *J* = 6.8, 3 H); 1.60 (*t*, *J* = 6.8, 3 H); 3.22–3.31 (*m*, 2 H); 4.15–4.31 (*m*, 2 H); 7.35–7.38 (*m*, 3 H); 7.63 (*dd*, *J* = 8.8, 2.9, 1 H); 7.71 (*dd*, *J* = 8.8, 6.9, 1 H); 8.49 (*d*, *J* = 2.9, 1 H); 8.51 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR: 10.36; 13.36; 47.17; 47.84; 115.68; 117.57; 121.60; 122.67; 122.86; 126.77; 127.65; 128.44; 134.00; 134.29; 137.45; 138.88; 176.70; 179.71. MS: 344 (100, M^+). Anal. calc. for $C_{18}H_{17}ClN_2OS$ (344.86): C 62.69, H 4.97, N 8.12; found: C 62.64, H 5.14, N 8.14.

2-Chloro-N,N-*bis(1-methylethyl)-9-oxoacridine-10(9*H*)-carbothioamide* (**9g**). Beige solid. M.p. 257–259° (hexane/CH_2Cl_2). IR (KBr): 1646, 1604, 1258. ^{1}H-NMR (500 MHz): 1.04 (*d*, *J* = 6.9, 6 H); 1.97 (br. *s*, 6 H); 3.83–3.89 (*m*, 1 H); 4.07 (br., 1 H); 7.36 (*dd*, *J* = 8.0, 7.4, 1 H); 7.41 (*d*, *J* = 8.6, 1 H); 7.43 (*d*, *J* = 8.0, 1 H); 7.63 (*dd*, *J* = 8.6, 1.1, 1 H); 7.72 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 8.50 (*d*, *J* = 1.1, 1 H); 8.52 (*dd*, *J* = 8.0, 1.1, 1 H). ^{13}C-NMR: 18.12; 20.34; 51.12; 56.38; 115.75; 117.50; 121.61; 122.66; 122.78; 126.79; 127.66; 128.34; 133.87; 134.10; 137.26; 138.75; 176.66; 177.48. HR-MS: 373.1139 ([*M* + H]$^+$, $C_{20}H_{22}ClN_2OS^+$; calc. 373.1141). Anal. calc. for $C_{20}H_{21}ClN_2OS$ (372.91): C 64.42, H 5.68, N 7.51; found: C 64.20, H 5.75, N 7.48.

*2-Chloro-10-(pyrrolidin-1-ylcarbonothioyl)acridin-9(10*H*)-one* (**9h**). Pale-yellow solid. M.p. 228–230° (dec.; hexane/CH_2Cl_2). IR (KBr): 1638, 1604, 1256. ^{1}H-NMR (400 MHz): 1.94–2.05 (*m*, 2 H); 2.14–2.20 (*m*, 2 H); 3.18 (*t*, *J* = 6.3, 2 H); 4.13 (*t*, *J* = 6.9, 2 H); 7.34–7.38 (*m*, 3 H); 7.63 (*dd*, *J* = 8.6, 2.3, 1 H); 7.72 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 8.50 (*d*, *J* = 2.3, 1 H); 8.52 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR: 24.74; 25.85; 51.26; 63.86; 115.22; 117.09; 121.63; 122.70; 122.79; 126.91; 127.78; 128.39; 134.25; 134.54; 136.62; 138.08; 176.65; 176.95. MS: 342 (100, M^+). Anal. calc. for $C_{18}H_{15}ClN_2OS$ (342.84): C 63.06, H 4.41, N 8.17; found: C 62.97, H 4.43, N 8.15.

*2-Chloro-10-(piperidin-1-ylcarbonothioyl)acridin-9(10*H*)-one* (**9i**). Pale-yellow solid. M.p. 177–178° (dec.; hexane/CH_2Cl_2). IR (KBr): 1640, 1602, 1257. ^{1}H-NMR (500 MHz): 1.42–1.47 (*m*, 2 H); 1.70–1.75 (*m*, 2 H); 1.95–2.00 (*m*, 2 H); 3.27–3.29 (*m*, 2 H), 4.44–4.54 (*m*, 2 H); 7.35–7.40 (*m*, 3 H); 7.63 (*dd*, *J* = 9.2, 2.3, 1 H); 7.71 (*ddd*, *J* = 8.6, 6.9, 1.7, 1 H); 8.49 (*d*, *J* = 2.3, 1 H); 8.52 (*dd*, *J* = 8.0, 1.7, 1 H). ^{13}C-NMR: 23.61; 25.41; 26.59; 50.98; 51.81; 115.75; 117.56; 121.58; 122.65; 122.83; 126.81; 127.68; 128.44; 134.09; 134.34; 137.11; 138.58; 176.61; 178.69. MS: 356 (100, M^+). Anal. calc. for $C_{19}H_{17}ClN_2OS$ (356.87): C 63.95, H 4.80, N 7.85; found: C 63.76, H 4.94, N 7.70.

*2-Chloro-10-(morpholin-4-ylcarbonothioyl)acridin-9(10*H*)-one* (**9j**). Pale-yellow solid. M.p. 255–257° (hexane/$CHCl_3$). IR (KBr): 1645, 1606, 1260. ^{1}H-NMR (500 MHz): 3.31–3.33 (*m*, 2 H); 3.50–3.53 (*m*, 2 H); 4.00–4.02 (*m*, 2 H); 4.53–4.55 (*m*, 2 H); 7.35–7.40 (*m*, 3 H); 7.65 (*dd*, *J* = 8.6, 2.9, 1 H); 7.74 (*ddd*, *J* = 8.0, 7.4, 1.7, 1 H); 8.50 (*d*, *J* = 2.9, 1 H); 8.52 (*dd*, *J* = 8.0, 1.7, 1 H). ^{13}C-NMR: 50.00; 50.42; 66.03; 66.29; 115.40; 117.19; 121.59; 122.68; 123.07; 127.01; 127.88; 128.72; 134.30; 134.55; 137.04; 138.52; 176.49; 179.65. MS: 358 (100, M^+). Anal. calc. for $C_{18}H_{15}ClN_2O_2S$ (358.84): C 60.25, H 4.21, N 7.81; found: C 60.04, H 4.29, N 7.76.

2-Chloro-N-*methyl-9-oxo*-N-*phenylacridine-10(9*H*)-carbothioamide* (**9k**). Pale-yellow solid. M.p. 184–185° (hexane/CH_2Cl_2). IR (KBr): 1645, 1603, 1254. ^{1}H-NMR (500 MHz): 3.98 (*s*, 3 H); 6.79 (*d*, *J* = 8.0, 1 H); 6.93 (*dd*, *J* = 8.0, 6.9, 1 H); 7.02 (*dd*, *J* = 6.9, 7.4, 1 H); 7.29 (*dd*, *J* = 8.0, 7.4, 2 H); 7.64–7.65 (*m*, 4 H); 7.73 (*dd*, *J* = 8.6, 6.9, 1 H); 8.30 (*s*, 1 H); 8.31 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR: 46.03; 116.42; 118.13; 121.13; 122.19; 122.59; 123.02; 126.55; 127.37; 128.14; 129.06; 129.18; 133.52; 133.76; 137.93; 139.42; 142.47; 176.45; 180.69. MS: 378 (100, M^+). Anal. calc. for $C_{21}H_{15}ClN_2OS$ (378.87): C 66.57, H 3.99, N 7.39; found: C 66.51, H 4.14, N 7.26.

This work was supported in part by a *Grant-in-Aid for Scientific Research* (*C*) 22550035 from the *Japan Society for the Promotion of Science*. We thank Mrs. *Miyuki Tanmatsu* at our university for recording mass spectra and performing combustion analyses.

REFERENCES

[1] A. I. S. Almeida, V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, *Synlett* **2012**, 889; Y. Fang, D. C. Rogness, R. C. Larock, F. Shi, *J. Org. Chem*. **2012**, *77*, 6262; A. V. Dubrovskiy, R. C. Larock, *J. Org. Chem*. **2012**, *77*, 11232.

[2] K. Kobayashi, K. Nakagawa, S. Yuba, T. Komatsu, *Helv. Chim. Acta* **2013**, *96*, 389.

[3] A. H. Abadi, S. M. Abou-Seri, Q. Hu, M. Negri, R. W. Hartmann, *Med. Chem. Commun.* **2012**, *3*, 663; V. Verones, N. Flouquet, M. Lecoeur, A. Lemoine, A. Farce, B. Baldeyrou, C. Mahieu, N. Wattez, A. Lansiaux, J.-F. Gossens, P. Berthelot, N. Lebegue, *Eur. J. Med. Chem*. **2013**, 59, 39.

[4] X.-L. Yang, Z.-H. Xie, X.-J. Jiang, Y.-B. Huang, J.-K. Liu, *Chem. Pharm. Bull*. **2009**, *57*, 734; R. M. Ngoumfo, J.-B. Jouda, F. T. Mousfo, J. Komguem, C. D. Mbazoa, T. C. Shiao, M. I. Choudhary, H.

Laatsch, J. Legault, A. Pichette, R. Roy, *Bioorg. Med. Chem.* **2010**, *18*, 3601; B. V. Tsassi, H. Hussain, A. Geagni, E. Dongo, I. Ahmed, M. Riaz, K. Krohn, *Helv. Chim. Acta* **2011**, *94*, 1035; D. Lacroix, S. Prado, D. Kamoga, J. Kasenene, B. Bodo, *J. Nat. Prod.* **2011**, *74*, 2286.

[5] J. M. Muchowski, M. C. Venuti, *J. Org. Chem.* **1980**, *45*, 4798.

[6] S. Fujiwara, T. Shin-Ike, N. Sonoda, M. Aoki, K. Okada, N. Miyoshi, N. Kambe, *Tetrahedron Lett.* **1991**, *32*, 3503.

[7] K. Kobayashi, T. Suzuki, *Heterocycles* **2012**, *86*, 403.

[8] G.-S. J. Chen, M. S. Gibson, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1138; E. Rizzetto, S. Castellano, C. Florio, M. Vadori, G. Stefancich, *Pharmazie* **2006**, *61*, 505.

[9] K. Kobayashi, K. Yoneda, K. Miyamoto, O. Morikawa, H. Konishi, *Tetrahedron* **2004**, *60*, 11639.

[10] Y. Ito, K. Kobayashi, N. Seko, T. Saegusa, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73.

Received June 17, 2013