The Condensation Products of 2,3,6-Trisubstituted-1,4-naphthoquinones with 2-Aminothiophenol

W. B. Kang, Seiko Nan'ya*, Yasushi Yamaguchi, Eturô Maekawa and Yoshio Ueno

Department of Applied Chemistry, Nagoya Institute of Technology,
Gokiso, Showa-ku, Nagoya-shi 466, Japan

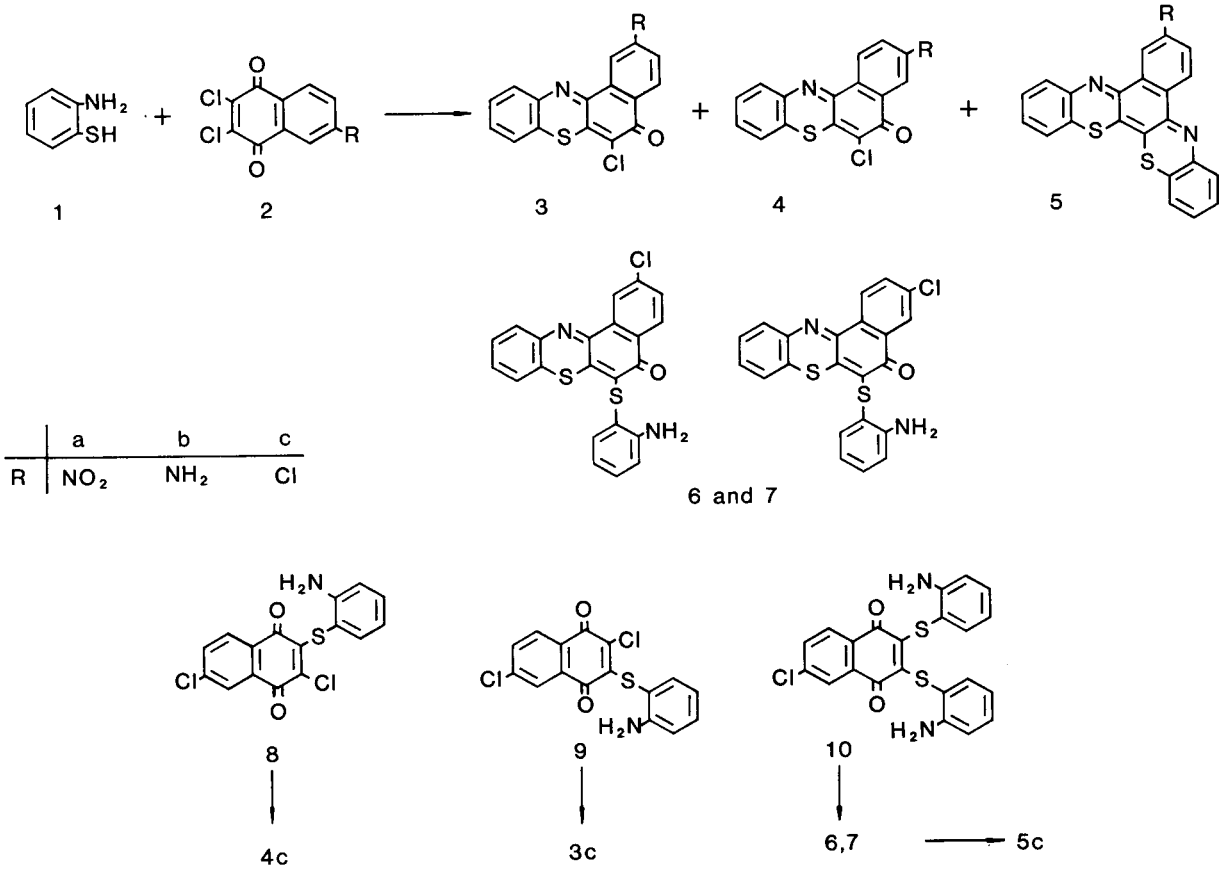
Received June 16, 1986

The 2,6-disubstituted-, 3,6-disubstituted-5*H*-benzo[*a*]phenothiazin-5-one derivatives and 7-substituted-benzo[*a*][1,4]benzothiazino[3,2-*a*]phenothiazine derivatives were prepared by the condensation of 2,3,6-trisubstituted-1,4-naphthoquinones with 2-aminothiophenol. The resulting compounds were subjected to reduction, dehalogenation and condensation with aniline. Some of the condensation intermediates were isolated and the reaction mechanism was also investigated.

J. Heterocyclic Chem., **24**, 91 (1987).

The phenothiazine and phenoxazine ring systems have been extensively studied and many such compounds have been used as drugs, dyestuffs and indicators [1-7]. As a part of our studies [8-12] on the synthesis and the chemical properties of iminoquinones, we now report the synthesis of 2,6-disubstituted and 3,6-disubstituted-5*H*-benzo[*a*]-phenothiazin-5-one derivatives using 2,3,6-trisubstituted-1,4-naphthoquinones [13] as starting materials.

In the previous papers [9-11] of this series we reported the synthesis of 1,6-disubstituted and 4,6-disubstituted-5*H*-benzo[*a*]phenothiazinone derivatives. In this work, 2-or 3-substituted-6-chloro-5*H*-benzo[*a*]phenothiazin-5-ones were prepared by the condensation of 2,3,6-trisubstituted-1,4-naphthoquinones **2a-c** with 2-aminothiophenol (**1**) in ethanol in the presence of hydrochloric acid (Scheme 1). The structures of the resulting compounds were identified by the reaction described below and from their spectroscopic data. Condensing **2a** and **2c** with **1**, 6-chloro-2-nitro-5*H*-benzo[3,4-*a*]phenothiazin-5-one (**3a**), 6-chloro-3-nitro-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**4a**) and 2,6-



Scheme 1

dichloro-5*H*-benzo[3,4-*a*]phenothiazin-5-one (**3c**) and 3,6-dichloro-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**4c**) were obtained as the main products respectively. However the condensation of **2b** with **1** produced 7-aminobenzo[*a*][1,4]-benzothiazino[3,2-*a*]phenothiazine (**5b**) as the main product together with the trace amounts of 2-amino-6-chloro-5*H*-benzo[3,4-*a*]phenothiazin-5-one (**3b**) and 3-amino-6-chloro-5*H*-benzo-[4,3-*a*]phenothiazin-5-one (**4b**) under the same conditions. Compounds **3a** and **4a** were isolated by column chromatography and reduced to **3b** and **4b** respectively using stannous chloride in acetic acid at 50-70°.

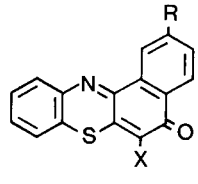
From the reaction mixture of **2c** with **1** intermediates **6** and **7** were separated in the yield of 10% and their ir and ms spectra were recorded. In solution or on a silica gel column, **6** and **7** were partly cyclized to **5c** and could not be obtained as purified crystals. In the ir spectra of **6** and **7**, there are vibrations at 3415 and 3325 cm^{-1} (NH_2), 1610 or 1605 cm^{-1} (C=O). The ms spectra of both **6** and **7** showed m/e = 420 (m^+). From these data we inferred that **6** and **7** should have the structures showed in Scheme 1. Compounds **3c** and **4c** did not condense with **1** under the same conditions as with the reaction of **1** and **2c**. It appears that the reaction of **2c** with **1** proceeds in the following manner: i) One of the thiophenoxide anions attacks one of C-2 and C-3 of **2c** giving the presumed intermediates **8** and **9** and subsquent ring closure to yield **3c** and **4c**. ii) Two thiophenoxide anions attack C-2 and C-3 of **2c** at the same time to give the presumed intermediate **10** followed by the rapid cyclization to **6** and **7** which partly cyclized to **5c** with dehydration (Scheme 1).

The dehalogenation of the compounds **3b** and **4b** in the presence of sodium hydrosulfite dissolved in pyridine, dioxane and water under a nitrogen atomosphere gave 2-amino-5*H*-benzo[3,4-*a*]phenothiazine-5-one (**12**) and 3-amino-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**11**) respectively.

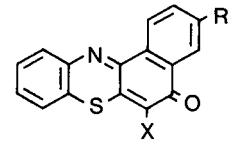
Treating **12** with aniline and hydrochloric acid in dimethyl sulfoxide at 100°, 2-amino-6-anilino-5*H*-benzo-[3,4-*a*]phenothiazin-5-one (**14**) was obtained in moderate yield and identified by comparing its ir, uv and ms spectra

Table 1

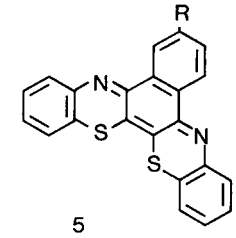
Physical and Analytical Data of Compounds **3**, **4**, **5**, **11**, **12** and **14**



3,12,14



4,11



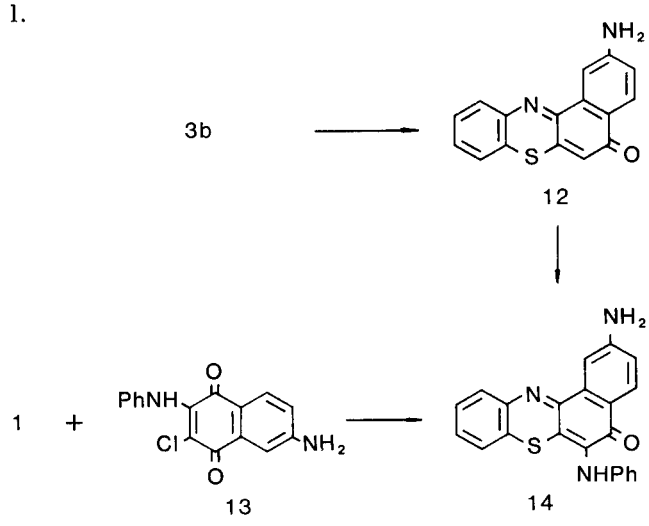
5

Compound	R	X	MP (°C)	Molecular formula	Mass (M^+) (relative intensity %)	Elemental Analysis (%) Found/(Calcd.) C	H	N
3a	NO_2	Cl	267-268 [a]	$C_{16}H_7ClN_2O_3S$ (342.8)	342/344 (100) (38)	56.31 (56.07)	1.90 (2.06)	8.33 (8.17)
4a	NO_2	Cl	351-352.5 [a]	$C_{16}H_7ClN_2O_3S$ (342.8)	342/344 (100) (39)	56.15 (56.07)	1.86 (2.06)	8.07 (8.17)
3b	NH_2	Cl	338-340 [a]	$C_{16}H_9ClN_2OS$ (312.8)	312/314 (100) (33)	61.54 (61.44)	2.76 (2.90)	8.56 (8.96)
4b	NH_2	Cl	325.5-327 [b]	$C_{16}H_9ClN_2OS$ (312.8)	312/314 (100) (40)	61.51 (61.44)	2.86 (2.90)	8.63 (8.96)
3c	Cl	Cl	286-288 [b]	$C_{16}H_7Cl_2NOS$ (332.2)	331/333 (100) (76)	57.62 (57.85)	1.96 (2.12)	4.33 (4.22)
4c	Cl	Cl	268-270 [b]	$C_{16}H_7Cl_2NOS$ (332.2)	331/333 (100) (73)	58.19 (57.85)	2.06 (2.12)	4.44 (4.22)
5c	Cl	–	354.5-356 [b]	$C_{22}H_{11}ClN_2S_2$ (402.9)	402/403/404 (100) (38) (56)	65.68 (65.58)	2.61 (2.75)	6.99 (6.95)
5b	NH_2	–	329-331 [b]	$C_{22}H_{13}N_3S_2$ (383.5)	383/384/385 (100) (34) (16)	69.15 (68.90)	3.31 (3.42)	10.67 (10.96)
11	NH_2	H	276-278.5 [b]	$C_{16}H_{10}N_2OS$ (278.3)	278/279 (96) (14)	69.41 (69.05)	3.46 (3.62)	9.84 (10.06)
12	NH_2	H	279-282 [a]	$C_{16}H_{10}N_2OS$ (278.3)	278/279 (100) (22)	69.39 (69.05)	3.56 (3.62)	10.01 (10.06)
14	NH_2	NHph	340-343 [a]	$C_{22}H_{15}N_3OS$ (369.4)	369/371 (100) (6)	71.61 (71.52)	4.10 (4.09)	11.53 (11.37)

[a] From benzene-ethyl acetate. [b] From benzene.

and mixed melting point with an authentic sample prepared by the reaction of 6-amino-2-anilino-3-chloro-1,4-naphthoquinone (**13**) and **1**. By this way, the structures of **3** and **4** were determined.

The structures of **3c** and **4c** were also identified by comparing their ir, uv spectra with the samples prepared by the diazotization of **3b** and **4b** followed by the Sandmyer reaction respectively (Scheme 2). Some of the physical and analytical data of the compounds are summarized in Table 1.



Scheme 2

EXPERIMENTAL

Melting points were determined with a Yanaco micromelting point apparatus and uncorrected. The ir spectra were recorded on a JASCO A-102 spectrometer using potassium bromide pellets. The uv spectra were obtained with a JASCO UV1DEC-505 spectrometer using 1 cm quartz cells. The absorption maxima are reported in nanometers. The ^{1}H-nmr spectra were obtained in dimethyl sulfoxide-d_6 using a Varian XL-200 spectrometer operating in an FT mode. Chemical shifts are reported in ppm from TMS used as internal standard and are given in δ units. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, d = doublet and m = multiplet. The ms spectra were recorded on a ESCO EMD-05B mass spectrometer. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh ASTM) and aluminium oxide (activated 300, Nakarai chemicals, Ltd.) were used.

Condensation of 2,3-Dichloro-6-nitro-1,4-naphthoquinone (**2a**) with 2-Aminothiophenol (**1**).

To a stirred suspension of **2a** (545 mg, 2 mmoles) in ethanol (50 ml) at room temperature was added slowly a solution of **1** (225 mg, 1.8 mmoles) in 20 ml of 15% hydrochloric acid over 20 minutes. After an additional 30 mintues of stirring, the precipitate was collected and column chromatographed on aluminium oxide using benzene as the eluent. From the first blue fraction 20 mg of 7-nitrobenzo[*a*][1,4]benzothiazino[3,2-*c*]-phenothiazine (**5a**) were obtained, then from the second red fraction 137 mg of 6-chloro-2-nitro-5*H*-benzo[3,4-*a*]phenothiazin-5-one (**3a**) and from the third red fraction 118 mg of 6-chloro-3-nitro-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**4a**). The total yield of the products based on **1** was 44% in the ratio of 8.5:7.1:1.0 (**3a**:**4a**:**5a**).

Compound **3a**.

This compound had ir: 1630 (C=O), 1520 and 1350 (NO_2) cm^{-1}; ^{1}H nmr (DMSO-d_6): 80°, δ 9.48 (s, 1H), 8.58 (d, 1H), 8.43 (d, 1H), 8.15 (m, 1H), 7.93 (m, 1H), 7.68 (m, 2H); uv (chloroform): λ max, nm (log ϵ), 247 (4.57), 317 (4.22), 372 (4.04), 388 (4.02), 498 (4.14).

Compound **4a**.

This compound had ir: 1635 (C=O), 1525 and 1340 (NO_2) cm^{-1}; ^{1}H nmr [14]; uv (chloroform): λ max, nm (log ϵ), 270 (4.40), 287 (4.36), 330 (4.33), 390 (4.01), 503 (4.07).

Compound **5a**.

This compound had ms: m/e = 413 (m$^+$) and was reduced to **5b** without another analysis.

Reduction of **3a**, **4a** and **5a**.

To a stirred suspension of **3a** (171 mg, 0.5 mmole) in 20 ml of acetic acid was added a solution of stannous chloride dihydrate (460 mg, 2 mmoles) in 4 ml hydrochloric acid at 50-70° over 5 minutes. After stirring for 1 hour, the resulting precipitate was suspended in water (200 ml), and treated with a solution of ferric chloride (500 mg) in 5 ml of water. After stirring for 1 hour, the resulting 2-amino-6-chloro-5*H*-benzo[3,4-*a*]-phenothiazin-5-one (**3b**) was collected in the yield of 90%.

Similarly, **4a** and **5a** were reduced to 3-amino-6-chloro-5*H*-benzo[4,3-*a*]-phenothiazin-5-one (**4b**) and 7-aminobenzo [*a*] [1,4]benzothiazino[3,2-*c*]-phenothiazine (**5b**) in 90% and 85% yield respectively.

Compound **3b**.

This compound had ir: 3330 and 3220 (NH_2), 1580 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 80°, δ 7.97 (m, 3H), 7.83 (m, 1H), 7.63 (m, 2H), 7.01 (m, 1H), 6.24 (s, 2H, NH_2); uv (chloroform): λ max, nm (log ϵ), 254 (4.53), 286 (4.17), 299 (4.24), 323 (4.37), 384 (4.03), 422 (4.03), 500 (3.84).

Compound **4b**.

This compound had ir: 3470 and 3360 (NH_2), 1600 (C=O) cm^{-1}; ^{1}H nmr [14]; uv (chloroform): λ max, nm (log ϵ), 274 (4.5), 311 (4.45), 460 (4.38).

Compound **5b**.

This compound had ir: 3440 and 3360 (C=O), 1610 (C=N) cm^{-1}; uv (chloroform): λ max, nm (log ϵ), 270 (4.72), 311 (4.42), 385 (4.10), 432 (4.17), 536 (4.27), 566 (4.25); ^{1}H nmr [14].

Condensation of 6-Amino-2,3-dichloro-1,4-naphthoquinone (**2b**) with **1**.

Compound **2b** (121 mg, 0.5 mmole) was treated with **1** (125 mg, 1 mmole) in the same way as the condensation of **2a** with **1**. The product was chromatographed on a column of silica gel eluting with benzene. From the first red-violet fraction 150 mg of 7-aminobenzo[*a*] [1,4]benzothiazino[3,2-*c*]phenothiazine (**5b**) were obtained in the yield of 80%. From the second and third red fractions 2-amino-6-chloro-5*H*-benzo-[3,4-*a*]phenothiazin-5-one (**3b**) and 3-amino-6-chloro-5*H*-benzo[4,3-*a*]-phenothiazin-5-one (**4b**) were obtained in about 3%.

Dehalogenation of **3b** and **4b**.

To a stirred suspension of **3b** (161 mg, 0.5 mmole) in the mixture of benzene (20 ml), 1,4-dioxane (8 ml) and water (20 ml) were added 890 mg of sodium hydrosulfite (5 mmoles) and 20 ml of pyridine under nitrogen atmosphere. The mixture was refluxed for 30 minutes and extracted with benzene. After the benzene layer was washed with 5% hydrochloric acid and water, the residue was chromatographed on a silica gel column eluting with benzene. From the red-orange fraction 2-amino-5*H*-benzo-[3,4-*c*]phenothiazin-5-one (**12**) was obtained in the yield of 89%.

Compound **12**.

This compound had ir: 3330 and 3220 (NH_2), 1580 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 70°, δ 7.87 (m, 3H), 7.62 (m, 1H), 7.53 (m, 2H), 6.98 (m, 1H), 6.74 (s, 1H, iminoquinone H), 6.12 (s, 2H, NH_2); uv (chloroform): λ

max, nm (log ε) 252 (4.55), 287 (4.26), 300 (4.33), 318 (4.13), 380 (4.07), 423 (4.06), 490 (3.89).

Compound **4b** was dehalogenated in the same way (refluxed for 2 hours) to give 3-amino-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**11**) in the yield of 47%.

Compound **11**.

This compound had ir: 3440 and 3330 (NH_2), 1580 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 70° δ 8.55 (d, 1H), 7.87 (d, 1H), 7.66 (d, 1H), 7.50 (m, 2H), 7.30 (d, 1H), 7.06 (d, 1H), 6.88 (s, 1H, iminoquinone H), 6.14 (s, 2H, NH_2); uv (chloroform): λ max, nm (log ε) 273 (4.56), 308 (4.48), 343 (3.88), 456 (4.40).

Synthesis of 2-Amino-6-anilino-5*H*-benzo[3,4-*a*]phenothiazain-5-one (**14**). Route A.

The Condensation of 6-Amino-2-anilino-3-chloro-1,4-naphthoquinone (**10**) with **1**.

To a stirred solution of **10** (150 mg, 0.5 mmole) in 20 ml of pyridine was added a solution of **1** (82 mg, 0.65 mmole) in 2 ml of ethanol. The mixture was refluxed for 2 hours and poured into water. The resulting precipitate was filtered giving 148 mg of **14** in the yield of 80%.

Route B.

To a stirred suspension of **12** (70 mg, 0.25 mmole) in 40 ml of dimethyl sulfoxide was added aniline (5 ml) and hydrochloric acid (5 ml) at room temperature. After stirring for 1 hour at 100°, the mixture was cooled and poured into water. The product was filtered giving 60 mg of **14** in 64% yield.

Compound **14**.

This compound had ir: 3480, 3370 and 3295 (NHPh and NH_2), 1600 (C=O) cm^{-1}: ^1H nmr (DMSO-d_6): 80°, δ 8.00-7.77 (m, 3H), 7.54-7.37 (m, 3H), 7.22 (m, 2H), 7.00-6.82 (m, 3H), 6.75 (s, 1H), 6.71 (s, 1H), 6.16 (s, 2H, NH_2): uv (chloroform): λ max, nm (log ε), 257 (4.46), 299 (4.40), 353 (4.24), 556 (3.78).

The Diazotisation and Sandmeyer Reaction of **3b** and **4b**.

To a stirred suspension of **3b** (94 mg, 0.3 mmole) in 20 ml of hydrochloric acid and 10 ml of water was added a solution of sodium nitrite (42 mg, 0.6 mmole) in 3 ml of water keeping the temperature below 10° by cooling with ice. After 1 hour, sulfamic acid was added to eliminate the excess sodium nitrite and the resulting diazonium solution was added dropwise to a solution of copper(I) chloride (89 mg, 0.6 mmole) in hydrochloric acid (7 ml) and water (7 ml) with stirring below 10°. After the addition of the diazonium solution, the mixture was heated to 50° and stirred for 1 hour. The resulting prepicitate was chromatographed on a silica gel column eluting with benzene. From the first reddish orange fraction 50 mg of 2,6-dichloro-5*H*-benzo[3,4-*a*]phenothiazin-5-one (**3c**) was obtained in 50% yield.

Compound **3c**.

This compound had ir: 1630 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 100°, δ 8.90 (d, 1H), 8.21 (d, 1H), 8.10 (m, 1H), 8.00 (d, 1H), 7.94 (m, 1H), 7.69 (m, 2H); uv (chloroform): λ max, nm (log ε), 260 (4.41), 316 (4.21), 391 (4.07), 484 (4.07).

In the same way, 3,6-dichloro-5*H*-benzo[4,3-*a*]phenothiazin-5-one (**4c**) was obtained in 67% yield from **4b**.

Compound **4c**.

This compound had ir: 1638 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 80°, δ 8.82 (s, 1H), 8.27 (d, 1H), 8.15 (m, 1H), 7.94 (m, 2H), 7.70 (m, 2H); uv (chloroform): λ max, nm (log ε), 260 (4.46), 320 (4.28), 368 (4.04), 385 (4.02), 485 (4.06).

Condensation of 2,3,6-Trichloro-1,4-naphthoquinone (**2c**) with **1**.

Compound **2c** (131 mg, 0.5 mmole) was condensed with **1** (75 mg, 0.6 mmole) in the same way as the reaction of **2a** and **1**. The product was chromatographed on a silica gel column eluting with benzene. From the first reddish violet fraction 48 mg of 7-chlorobenzo[*a*][1,4]benzothiazino-[3,2-*c*]phenothiazine (**5c**) were obtained in 24% yield (all the yields of compounds were based on the amount of **2c** used). From the second red fraction 50 mg of **3c** (30%) and from the third red fraction 42 mg of **4c** (25% yield) were obtained. From the forth and the fifth red fractions **6** and **7** were obtained in 10% yield.

Compound **5c**.

This compound had ir: 1585, 1560, 1515, 1485 cm^{-1}; ^1H nmr [14]; uv (chloroform): λ max, nm (log ε), 276 (4.67), 360 (4.20), 378 (4.24), 545 (4.23), 575 (4.22).

Compound **6**.

This compound had ir: 3415 and 3325 (NH_2), 1610 (C=O) cm^{-1}; ms: 420 (m^+).

Compound **7**.

This compound had ir: 3405 and 3320 (NH_2), 1605 (C=O) cm^{-1}; ms: 420 (m^+).

Acknowledgement.

This work was partly supported by a Grant-in-Aid for Scientific Research (No. 60470086) from the Ministry of Education.

REFERENCES AND NOTES

[1] S. P. Massie, *Chem. Rev.*, **54**, 797 (1954).

[2] D. E. Pearson, in "Heterocyclic Compounds", R. C. Elderfield, Vol. **6**, John Wiley and Sons, NY, 1957, p 624.

[3] C. R. Thompson, *Ind. Eng. Chem.*, **42**, 922 (1950).

[4] E. Schenker and H. Herbest, *Progr. Drug Res.*, **5**, 269 (1963).

[5] F. Mietzsch, *Angew. Chem.*, **66**, 363 (1954).

[6] H. B. Collier and S. C. Mcrae, *Can. J. Med. Sci.* **31**, 195 (1953).

[7] M. Ashikaga, *Okayama Igakkai Zasshi*, **66**, 977 (1954).

[8] S. Nan'ya, E. Maekawa, H. Hayakawa, Y. Kitaguchi and Y. Ueno, *J. Heterocyclic Chem.*, **22**, 1483 (1985).

[9] S. Nan'ya, E. Maekawa, W. B. Kang and Y. Ueno, *ibid.*, **23**, 589 (1986).

[10] Y. Ueno, S. Nan'ya, H. Hayakawa, W. B. Kang and E. Maekawa, *Monatsh. Chem.*, in press.

[11] Y. Ueno, *Pharmazie*, **39**, 355 (1984).

[12] S. Nan'ya, E. Maekawa, W. B. Kang and Y. Ueno, *J. Heterocyclic Chem.*, in press.

[13] T. Kasai and R. Kurabayashi, *Yuki Gosei kagaku kyokai shi*, **28**, 70 (1970).

[14] No ^1H nmr data were recorded for its poor solubility even in a dimethyl sulfoxide-d_6 solution at 80° in an FT mode.