

Seiko Nan'ya*, Hirofumi Ishida, Kiyoshi Kanie, Noriyuki Ito and Yasuo Butsugan

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, 466 Nagoya, Japan
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o-Monobromoacetylacetylphenones, **3a** and **3b** reacted with hydroxylamine or hydrazine hydrate to produce heterocycles, 2,3-benzoxazine or phthalazine derivatives. The reaction of bromoacetyl group of **3a** and **3b** with several thioamides afforded thiazole derivatives in high yields. Whereas *o*-dibromoacetylbenzophenone **2a** reacted with aniline or cyclohexylamine to produce non-heterocycles, 2-substituted-aminophenylindanones and the mechanism for the formation of these non-heterocycles is proposed.

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o-Diacylbenzenes **1** are the interesting starting materials reacting with several primary amines to produce a variety of heterocycles, namely isoindole, benzoxazine and phthalazine derivatives [1-3]. To modify the reactivity of **1**, the bromination of acetyl group of **1** with some brominating reagents were carried out. When **1** was treated with bromine in acetic acid 2-bromo-3-substituted-inden-1-ones were obtained, whereas treating **1a** with bromine in tetrachloromethane under ultraviolet irradiation dibromoacetylbenzophenone **2a** was prepared [4,5]. Compound **1b** was reacted with bromine in anhydrous methanol to afford a new compound 1,3-di(bromomethyl)-1,3-dimethoxy-1*H*,3*H*-isobenzofuran. Carrying out the bromination of **1** in dry ether with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane(dibromo Meldrum acid) monobromoacetylacetylphenones **3** were obtained.

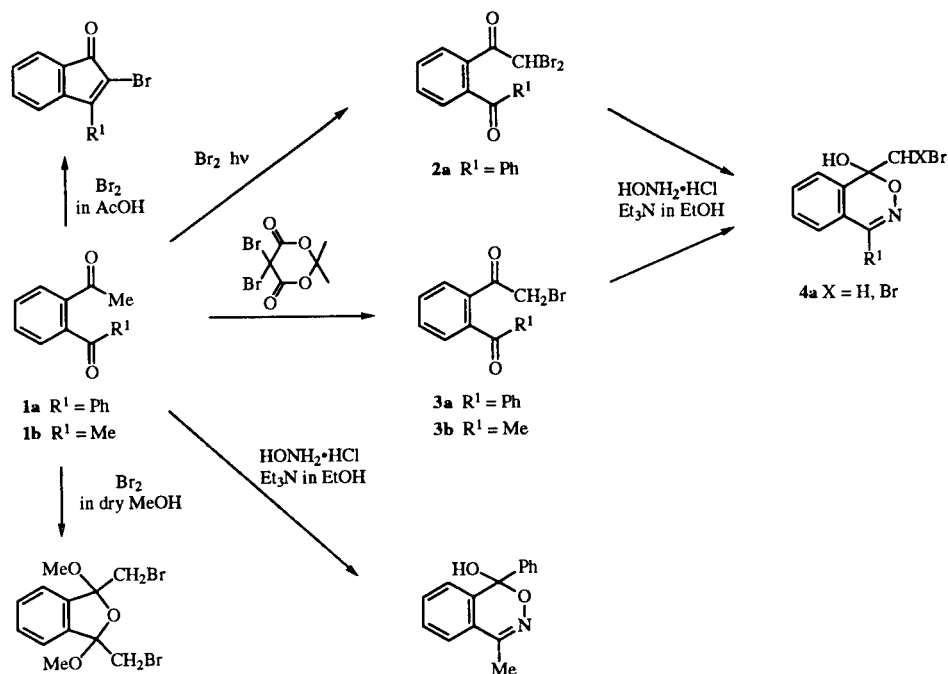
In this work we report the reactions of **3a,b** and **2a** with

hydroxylamine, hydrazine hydrate and thioamide derivatives.

The ethanol solution of **3a,b** and **2a** reacted with hydroxylamine hydrochloride in the presence of triethylamine to produce 1-bromomethyl-1-hydroxy-4-substituted-1*H*-2,3-benzoxazine **4**. In this reaction the amino group of hydroxylamine will attack the carbonyl carbon either of bromoacetyl or benzoyl (or acetyl) group. From their spectroscopic data the structure of the products were assigned structure **4** which were attacked on the carbonyl carbon of the bromoacetyl group by the amino group.

In the ¹H nmr spectra the singlet signals at δ 4.10 (**4a**, X = H), 4.18 (**4a**, X = Br) and 3.86 (**4b**, X = H) ppm assignable to hydroxyl-group shifted to a lower magnetic field than the signal of 1-hydroxy-1-phenyl-4-methyl-1*H*-2,3-benzoxazine (**5a**) (δ 3.48 ppm) which was formed from non-brominated **1a** and hydroxylamine [2]. The signals at 1-position in the ¹³C nmr spectra appeared at δ

Scheme 1



95.0 (**4a**, X = H), 96.6 (**4a**, X = Br) and 97.5 (**5a**) ppm respectively. The tendency of these chemical shifts is compatible with that of substituents attached to the carbon of the 1-position in **4** and **5a**.

The treatment of **3** in ether with hydrazine hydrate at -20° afforded 1-bromomethyl-4-substituted-phthalazine **6** in good yields. On the other hand, treating **2** in a similar manner some decomposition products were obtained. This reaction with **3** is a simple and useful route to prepare 1,4-disubstituted phthalazine derivatives.

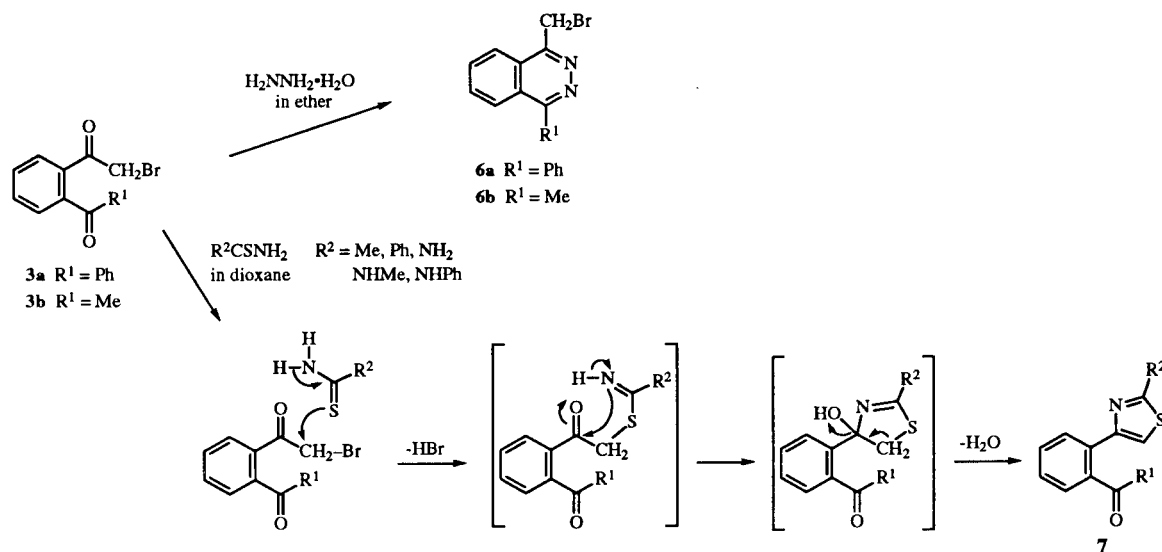
The bromoacetyl group of **3** reacted with several thioamides in dioxane at room temperature to produce thiazole derivatives in high yields. The cyclization proceeds as shown in Scheme 2.

two bromo substituents. The mechanism for the formation of phenylindanones is proposed as shown in Scheme 3.

EXPERIMENTAL

Melting points were determined on Yanaco micro-melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were measured on a Varian Gemini-200 or Varian XL-200 spectrometers, using tetramethylsilane as the internal standard. Mass spectra were obtained with a Hitachi M-2000 spectrometer. The infrared spectra were recorded with JASCO A-102 spectrometer using potassium bromide pellets. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh

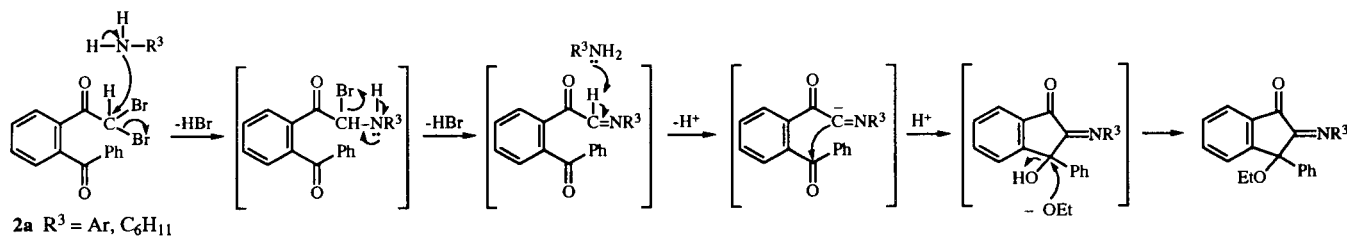
Scheme 2



The reaction of **2a** and aniline or cyclohexylamine in ethanol produced non-heterocycles, 2-substituted imino-3-ethoxy-3-phenylindan-1-ones, whereas **2a** and aqueous

ASTM and FL 60D, Fuji Silysia) were used. Elemental analyses were performed at Elemental Analysis Center in Kyoto University.

Scheme 3



ammonia afforded 3-phenylisoindolin-1-one [5,6]. In the former case, the attack of the amino group on the carbonyl carbon of dibromoacetyl was presumably hindered by the bulky phenyl or cyclohexyl group as well as the

o-Bromoacetylacetophenone (**3b**).

A mixture of *o*-acetylacetophenone **1b** (10 mmoles) in dry ether and dibromo Meldrum Acid [7] (5 mmoles) was stirred at room temperature for 2 days. After neutralization of the mixture

with sodium bicarbonate solution, the product was extracted with ether and washed with water. The extract was chromatographed on a silica gel column using benzene-ethyl acetate (95:5) as the eluent. From the first fraction 76% of **3b** was obtained and the next fraction 24% of **1b** was recovered.

Compound **3b** had mp 83-84° dec; ir: 1700 and 1665 cm⁻¹ (ν CO); ¹H nmr (deuteriochloroform): δ 7.88-7.36 (m, 4H), 4.24 (s, 2H, CH₂Br), 2.65 (s, 3H, CH₃); ms: m/z 242/240 (M⁺), 161 (M-Br)⁺, 147 (base peak, M-CH₂Br).

Anal. Calcd. for C₁₀H₉BrO₂ (241.08): C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.96; H, 3.82; Br, 33.00.

1,3-Di(bromomethyl)-1,3-dimethoxy-1*H*,3*H*-isobenzofuran (ISO).

To an anhydrous methanol solution (30 ml) of **1b** (2 mmoles) was added bromine (2 mmoles) and the mixture was stirred in an ice-salt bath for 13 hours. After dilution of the mixture with water (30 ml), concentrated sulfuric acid (1 ml) was added and stirred at 15° for 20 hours. The resulting mixture was shaken with water and ether [8]. After the usual work up the residue was chromatographed on a silica gel column using benzene-ethyl acetate (9:1) as the eluent to give colorless ISO in 49% yield.

Compound ISO had 131-135° dec; ir: 2840 (ν OCH₃), 1070 and 1060 cm⁻¹ (ν COC); ¹H nmr (deuteriochloroform): δ 7.52 (m, 4H), 3.86 (d, 2H, J = 11 Hz, CH₂Br), 3.69 (d, 2H, J = 11 Hz, CH₂Br), 3.32 (s, 6H, OCH₃); ¹³C nmr (deuteriochloroform): δ 138.5, 130.2, 123.4, 107.6 (OCO), 51.0 (OCH₃), 34.9 (CH₂Br); ms: m/z 337/335/333 (M-OCH₃)⁺, 273/271 (M-CH₂Br)⁺.

Anal. Calcd. for C₁₂H₁₄Br₂O₃ (366.05): C, 39.38; H, 3.86; Br, 43.66. Found: C, 39.34; H, 3.78; Br, 43.24.

1-Bromomethyl-1-hydroxy-4-phenyl-1*H*-2,3-benzoxazine (**4a**, X = H).

To an ethanol solution (5 ml) of **3a** (0.5 mmole) hydroxylamine hydrochloride (1 mmole) and triethylamine (1.2 mmoles) were added and stirred at room temperature for 1 hour. After evaporating the mixture under reduced pressure, acetone was added to the residue and the resulting precipitate (triethylamine hydrochloride) was filtered off. After concentrating the filtrate, the residue was chromatographed on a silica gel column using benzene-ethyl acetate (95:5) as the eluent to afford **4a**, X = H in 53% yield.

Compound **4a**, X = H had mp 121° dec; ir: 3150 (ν OH), 1605 (ν CN), 1100 and 1050 cm⁻¹ (ν CO); ¹H nmr (deuteriochloroform): δ 7.66-7.59 (m, 4H), 7.53-7.44 (m, 4H), 7.33 (m, 1H), 4.03 (d, 1H, J = 11.2 Hz, CH₂Br), 3.93 (d, 1H, J = 11.2 Hz, CH₂Br), 4.10 (br, 1H, OH); ¹³C nmr (deuteriochloroform): δ 159.5 (CN), 132.7, 132.5, 130.0, 129.6, 129.2, 129.1, 128.7, 127.7, 126.9, 123.5, 122.0, 95.0 (1-C), 36.0 (CH₂Br); ms: m/z 319/317 (M⁺), 224 (base peak, (M-CH₂Br)⁺).

Anal. Calcd. for C₁₅H₁₂BrNO₂ (318.17): C, 56.63; H, 3.80; N, 4.40. Found: C, 57.04; H, 3.76; N, 4.57.

1-Dibromomethyl-1-hydroxy-4-phenyl-1*H*-2,3-benzoxazine (**4a**, X = Br).

The mixture of **2a** (0.5 mmole), hydroxylamine hydrochloride (1 mmole) and triethylamine (1.2 mmoles) in ethanol was stirred at room temperature for 30 hours. Treating the mixture in a similar manner as described above, **4a**, X = Br was obtained in 31% yield.

Compound **4a** (X = Br) had mp 129° dec; ir: 3350 (ν OH), 1600 (ν CN), 1092 and 1040 cm⁻¹ (ν CO); ¹H nmr (deuteriochloroform): δ 7.81 (m, 1H), 7.71-7.62 (m, 3H), 7.55-7.47 (m, 4H), 7.33 (m, 1H), 6.11 (s, 1H, CHBr₂), 4.18 (s, 1H, OH); ¹³C nmr (deuteriochloroform): δ 160.0 (CN), 132.6, 132.2, 130.1, 129.2, 129.1, 128.9, 128.7, 127.7, 126.6, 126.1, 96.6 (1-C), 48.7 (CHBr₂); ms: m/z 399/397/395 (M⁺), 318/316 (M-Br)⁺, 224 (M-CHBr₂)⁺.

Anal. Calcd. for C₁₅H₁₁Br₂NO₂ (397.07): C, 45.37; H, 2.79; Br, 40.25; N, 3.53. Found: C, 45.50; H, 2.84; Br, 40.07; N, 3.26.

1-Bromomethyl-1-hydroxy-4-methyl-1*H*-2,3-benzoxazine (**4b**, X = H).

The ethanol solution of **3b** (1 mmole), hydroxylamine hydrochloride (2 mmoles) and triethylamine (2.4 mmoles) was stirred at room temperature for 45 minutes. Treating the mixture in a similar manner to that for **4a** using benzene-ethyl acetate (3:1) as the eluent, **4b** (X = H) was obtained in 26% yield.

Compound **4b** (X = H) had mp 110.5-112° dec; ir: 3150 (ν OH), 1615 cm⁻¹ (ν CN); ¹H nmr (deuteriochloroform): δ 7.62-7.45 (m, 4H), 3.91 (s, 2H), 3.68 (br, 1H, OH), 2.42 (s, 3H, CH₃); ¹H nmr (DMSO-d₆): δ 7.75-7.47 (m, 4H), 7.34 (br, 1H, OH), 4.16 (d, 1H, J = 10.8 Hz, CHBr), 3.84 (d, 1H, J = 10.8 Hz, CHBr), 2.32 (s, 3H, CH₃); ms: m/z 257/255 (M⁺), 239/237 (M-H₂O)⁺, 162 (base peak, (M-CH₂Br)⁺).

Anal. Calcd. for C₁₀H₁₀BrNO₂ (256.10): C, 46.90; H, 3.94; Br, 31.20. Found: C, 46.82; H, 3.90; Br, 30.96.

1-Hydroxy-4-methyl-1-phenyl-1*H*-2,3-benzoxazine (**5**) lit [2].

This compound had ¹³C nmr (deuteriochloroform): δ 154.3 (CN), 134.2, 132.1, 129.2, 128.9, 128.5, 128.1, 127.2, 125.7, 123.7, 121.5, 97.5 (1-C), 17.0 (CH₃).

1-Bromomethyl-4-phenylphthalazine (**6a**).

To an ether solution of hydrazine hydrate (0.84 mmole) an ether solution (5 ml) of **3a** (0.56 mmole) was added dropwise with stirring at -20° over 15 minutes and the mixture was stirred at -20° for 2 hours. After neutralization of the mixture with hydrochloric acid, the ether layer was washed with water and chromatographed on a silica gel column using benzene-ethyl acetate (9:1) as the eluent to afford **6a** in 55% yield.

Compound **6a** had mp 114° dec; ir: 2925 and 2850 cm⁻¹ (ν CH₂); ¹H nmr (deuteriochloroform): δ 8.33 (m, 1H), 8.14 (m, 1H), 8.04-7.84 (m, 2H), 7.78-7.73 (m, 2H), 7.61-7.56 (m, 3H), 5.18 (s, 2H, CH₂Br); ms: m/z 300/298 (M⁺), 219 (base peak, (M-Br)⁺).

Anal. Calcd. for C₁₅H₁₁N₂Br (299.17): C, 60.22; H, 3.71; N, 9.36. Found: C, 59.91; H, 3.75; N, 9.51.

1-Bromomethyl-4-methylphthalazine (**6b**).

The ether solution of **3b** (0.3 mmole) and hydrazine hydrate (0.46 mmole) was treated in a similar manner as described above. The residue was chromatographed using chloroform-methanol (99:1) as the eluent to give **6b** in 51% yield.

Compound **6b** had mp 60° dec; ir: 2925 (ν CH₂), 1388 cm⁻¹ (ν CH₃); ¹H nmr (deuteriochloroform): δ 8.28-8.23 (m, 1H), 8.17-8.12 (m, 1H), 7.96 (m, 2H), 5.07 (s, 2H, CH₂Br), 3.02 (s, 3H, CH₃); ms: m/z 238/236 (M⁺), 157 (M-Br)⁺.

Anal. Calcd. for C₁₀H₉N₂Br (237.10): C, 50.66; H, 3.83; N, 11.82. Found: C, 50.88; H, 3.95; N, 11.57.

General Procedure for Thiazole Derivatives 7.

The dioxane solution (15 ml) of **3a** or **3b** (0.5 mmole) was stirred with thioamide (R^2CSNH_2) (0.6 mmole) at room temperature for 2-6 hours. After neutralization of the mixture with sodium bicarbonate solution, the product was extracted with ethyl acetate. The extract was chromatographed on a silica gel column using benzene-ethyl acetate (9:1) or tetrachloromethane-chloroform (1:1) as the eluent.

4-(2-Benzoylphenyl)-2-methylthiazole (**7a**, $R^2 = Me$).

This compound was obtained in 98% yield and had mp 101-101.7°; ir: 1665 (v CO), 1595 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.79-7.65 (m, 3H), 7.60-7.39 (m, 4H), 7.33-7.29 (m, 2H), 7.05 (s, 1H, 5-H), 2.51 (s, 3H, CH_3); ms: m/z 279 (M^+), 251 (M-CO) $^+$, 202 (M-Ph) $^+$.

Anal. Calcd. for $C_{17}H_{13}NOS$ (279.36): C, 73.09; H, 4.69; N, 5.01. Found: C, 73.04; H, 4.81; N, 4.95.

4-(2-Benzoylphenyl)-2-phenylthiazole (**7a**, $R^2 = Ph$).

This compound was obtained as an orange oil in 98% yield; ir: 1667 (v CO), 1660 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.88-7.76 (m, 3H), 7.64-7.53 (m, 3H), 7.49-7.39 (m, 3H), 7.34-7.26 (m, 6H); ms: m/z 341 (M^+), 313 (M-CO) $^+$, 264 (M-Ph) $^+$.

Anal. Calcd. for $C_{22}H_{15}NOS$ (341.43): C, 77.39; H, 4.43; N, 4.10. Found: C, 77.31; H, 4.51; N, 4.14.

2-Amino-4-(2-benzoylphenyl)thiazole (**7a**, $R^2 = NH_2$).

This compound was obtained in 69% yield and had mp 199-200°; ir: 3385 and 3300 (v NH_2), 1640 (v CO), 1595 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.75-7.66 (m, 3H), 7.57-7.41 (m, 4H), 7.36-7.28 (m, 2H), 6.44 (s, 1H, 5-H), 4.76 (br, 2H, NH_2); ms: m/z 280 (M^+), 252 (M-CO) $^+$, 203 (M-Ph) $^+$.

Anal. Calcd. for $C_{16}H_{12}N_2OS$ (280.35): C, 68.55; H, 4.31; N, 9.99. Found: C, 68.64; H, 4.40; N, 9.90.

4-(2-Benzoylphenyl)-2-methylaminothiazole (**7a**, $R^2 = NHMe$).

This compound was obtained as an orange oil in 73% yield; ir: 3370 (v NH), 1665 (v CO), 1598 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.76-7.70 (m, 3H), 7.55-7.28 (m, 6H), 6.46 (s, 1H, 5-H), 4.98 (br, 1H, NH), 2.73 (m, 3H, CH_3); ms: m/z 294 (M^+), 265 (M-NMe) $^+$.

Anal. Calcd. for $C_{17}H_{14}N_2OS$ (294.38): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.05; H, 5.04; N, 9.14.

4-(2-Benzoylphenyl)-2-phenylaminothiazole (**7a**, $R^2 = NHPh$).

This compound was obtained in 67% yield and had mp 165-166°; ir: 3320 (v NH), 1650 (v CO), 1600 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.78-7.71 (m, 3H), 7.58-7.42 (m, 4H), 7.36-7.15 (m, 6H), 7.06 (br, 1H, NH), 6.98 (m, 1H), 6.60 (s, 1H, 5-H); ms: m/z 356 (M^+), 328 (M-CO) $^+$, 279 (M-Ph) $^+$.

Anal. Calcd. for $C_{22}H_{16}N_2OS$ (356.45): C, 74.13; H, 4.52; N, 7.86. Found: C, 74.06; H, 4.41; N, 7.63.

4-(2-Acetylphenyl)-2-methylthiazole (**7b**, $R^2 = Me$).

This compound was obtained in 79% yield and had mp 65-66.2°; ir: 1685 cm^{-1} (v CO); 1H nmr (deuteriochloroform): δ

7.59-7.43 (m, 4H), 7.18 (s, 1H, 5-H), 2.74 (s, 3H, CH_3), 2.26 (s, 3H, $COCH_3$); ms: m/z 217 (M^+), 202 (base peak, M-Me) $^+$.

Anal. Calcd. for $C_{12}H_{11}NOS$ (217.29) + 1/10 H_2O : C, 65.79; H, 5.15; N, 6.39. Found: C, 65.43; H, 4.96; N, 5.97.

4-(2-Acetylphenyl)-2-phenylthiazole (**7b**, $R^2 = Ph$).

This compound was obtained as brown oil in 59% yield; ir: 1683 cm^{-1} (v CO); 1H nmr (deuteriochloroform): δ 8.02-7.88 (m, 3H), 7.75-7.40 (m, 6H), 7.25 (s, 1H, 5-H), 2.33 (s, 3H, CH_3); ms: m/z 279 (M^+), 264 (M-Me) $^+$, 202 (M-Ph) $^+$.

Anal. Calcd. for $C_{17}H_{13}NOS$ (279.36): C, 73.09; H, 4.69; N, 5.01. Found: C, 72.88; H, 4.55; N, 4.89.

4-(2-Acetylphenyl)-2-aminothiazole (**7b**, $R^2 = NH_2$).

This compound was obtained in 76% yield and had mp 116-119°; ir: 3390 and 3290 (v NH_2), 1670 (v CO), 1630 cm^{-1} (v CN); 1H nmr (deuteriochloroform): δ 7.61-7.38 (m, 4H), 6.56 (s, 1H, 5-H), 5.13 (br, 2H, NH_2), 2.28 (s, 3H, CH_3); ms: m/z 218 (M^+), 203 (M-Me) $^+$.

Anal. Calcd. for $C_{11}H_{10}N_2OS$ (218.28): C, 60.53; H, 4.62; N, 12.83. Found: C, 60.47; H, 4.46; N, 12.72.

4-(2-Acetylphenyl)-2-aminomethylthiazole (**7b**, $R^2 = NHMe$).

This compound was obtained in 44% yield and had mp 125-128° dec; ir: 3350 (v NH), 1680 cm^{-1} (v CO); 1H nmr (deuteriochloroform): δ 7.65-7.33 (m, 4H), 6.54 (s, 1H, 5-H), 5.47 (br, 1H, NH), 2.93 (s, 3H, NCH_3), 2.28 (s, 3H, $COCH_3$); ms: m/z 232 (M^+), 217 (M-Me) $^+$.

Anal. Calcd. for $C_{12}H_{12}N_2OS$ (232.31) + 1/5 H_2O : C, 61.10; H, 5.30; N, 11.91. Found: C, 61.47; H, 5.08; N, 11.77.

4-(2-Acetylphenyl)-2-aminophenylthiazole (**7b**, $R^2 = NHPh$).

This compound was obtained as brown oil in 42% yield. ir: 3325 (v NH), 1680 cm^{-1} (v CO); 1H nmr (deuteriochloroform): δ 7.71-6.94 (m, 10H, aromatic H and NH), 6.69 (s, 1H, 5-H), 2.31 (s, 3H, CH_3); ms: m/z 294 (M^+), 279 (M-Me) $^+$.

Anal. Calcd. for $C_{17}H_{14}N_2OS$ (294.37): C, 69.36; H, 4.79; N, 9.52. Found: C, 69.13; H, 4.60; N, 9.24.

REFERENCES AND NOTES

- [1] S. Nan'ya and E. Maekawa, *Nippon Kagaku Kaishi*, 1953 (1974); 1535 (1975); 1747 (1977); S. Nan'ya, T. Fujii and Y. Butsugan, *J. Heterocyclic Chem.*, **27**, 1407 (1990).
- [2] S. Nan'ya, T. Kitahara and Y. Butsugan, *J. Heterocyclic Chem.*, **29**, 255 (1992).
- [3] S. Nan'ya, Y. Suzuki and E. Maekawa, *Bull. Nagoya Inst. Technology*, **34**, 157 (1982).
- [4] S. Nan'ya, T. Kitahara, K. Fujii, A. C. Bajji and Y. Butsugan, *J. Heterocyclic Chem.*, **29**, 1525 (1992).
- [5] S. Nan'ya, A. C. Bajji, H. Ishida, E. J. Moiji and Y. Butsugan, *J. Heterocyclic Chem.*, **31**, 401 (1994).
- [6] S. Nan'ya, H. Ishida and Y. Butsugan, *J. Heterocyclic Chem.*, **31**, 1725 (1994).
- [7] R. Bloch, *Synthesis*, 140 (1978).
- [8] M. Gaudry and A. Marquet, *Tetrahedron*, **26**, 5611 (1970).