crystals, and did not depress the melting point of tetrahydrojatrorrhizine, m.p. 211~213°.

(3) F crystals, m.p. 169~171° (Tetrahydroberberine). Repeatedly recrystallized from methanol, they were obtained in light yellow needles or long plates, m.p. 169~171°; yield, approx. 3 g. They gave positive Gaebel's reaction, and did not depress by the mixed melting point determination with tetrahydroberberine, m.p. 169~171°. *Anal.* Calcd. for $C_{20}H_{21}O_4N$: C, 70.81; H, 6.25; N, 4.14. Found: C, 71.00; H, 6.25; N, 4.40.

(4) F' crystals, m.p. 169~171° (Tetrahydroberberine). Recrystallization from methanol yielded slightly yellow needles in minute quantities, m.p. 169~171°. Their properties quite agreed with those of F crystals.

(5) G crystals, m.p. 139~141° (Tetrahydroshobakunine). Repeated recrystallization from methanol gave clusters, m.p. 139~141°. They gave quite the same properties as tetrahydroshobakunine (a molecular compound of tetrahydroberberine and tetrahydropalmatine), and by the admixture of this substance with tetrahydroshobakunine, m.p. 139~141°, it shows no melting point depression.

Summary

The authors identified from domestic *Mahonia japonica* DC. isotetrandrine (I, R=CH₃) and berbamine (I, R=H) as the tertiary bases; berberine, palmatine and jatrorrhizine as the quaternary bases, and in addition a nitrogen-free neutral substance, m.p. 211~212.5°, in minute quantities. Although the Indian *Mahonia* usually yielded oxyacanthine, the authors showed that oxyacanthine was not to be found in the Japanese *Mahonia*, isotetrandrine being contained in large quantities instead. This is the first evidence of the occurrence of isotetrandrine in families other than the Menispermaceae.

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216. Yoshihisa Mizuno and Kikuo Adachi: Benzothiazoles. III. Synthesis of 2-Methylbenzothiazoles with Electron-attracting Groups.

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In one¹⁾ of the preceding papers of this series, the effect of para-nitro group in the benzene ring upon benzothiazole ring-formation of thioacyl-anilides by the action of potassium ferricyanide was examined. Based on the results obtained, we suggested that, in the case of *p*-nitro-thioacetanilide, enolization of thio-carbonyl group, which was essential to the ring formation, was so difficult owing to the considerable contribution of the structure (II) to resonance that the ring-formation of the thioacetanilide via the enol form was suppressed and the formation of *p*-nitro-acetanilide became favorable.

To check the general validity of this suggestion and also to study the scope and limitation of the improved procedure devised by one²⁾ of the present authors, other thioacetanilides with electron-attracting groups such as nitro, methyl, sulfonyl and cyano groups or with both nitro and methoxyl groups on the benzene ring were subjected to the

* Ohte-machi, Kanazawa. (水野義久, 足立亀久夫).

1) Annual Report of the Faculty of Pharmacy, Kanazawa University, **1**, 8 (1951).

2) This Journal, **70**, 540 (1950).

ring formation by similar procedures as reported before³⁾.

Although *m*-nitrothioacetanilide was cyclized to nitro-2-methylbenzothiazole in 33.2 % yield, para and ortho isomers failed to be cyclized. Other electron-attracting groups examined similarly exerted an inhibitory influence on the ring formation and the yield of benzothiazoles were poorer, than that of thioacetanilide (Table I). However, methylsulfonyl and cyano groups in the para position seem to have less influence than *p*-nitro group in hindering a ring formation. The increasing order of hindrance fall in with the increasing order of electron-attracting power of the group or superposed electron-attracting power of the groups (nitro and methoxyl) introduced (Table I)⁴⁾.

2-Nitro-4-methoxy- and *p*-methylsulfonyl-thioacetanilide are on the borderline between cyclizable and non-cyclizable thioacetanilides.

In the presently study, we could not effect cyclization of *p*-methylsulfonylthioacetanilide, but thioacetanilide may be a potential material for cyclization.

It is worthy of note in this place that the nitro-2-methylbenzothiazole obtained from *m*-nitrothioacetanilide in 33.2% yield was found to be 7-nitro-2-methylbenzothiazole. The 7-nitro structure was assigned to our compound (III) since it melted at 120° as compared to a melting point of 139° for the 5-nitro compound (IV) which was prepared from (V) according to Fries⁵⁾.

Table I. Yields of 2-Methylbenzothiazoles with Electron-Attracting Groups.

Material	m.p.	Product	m.p.	Yield %
(1) Thioacetanilide ⁶⁾	—	2-Methylbenzothiazole	—	71
(2) <i>m</i> -Nitrothioacetanilide ⁶⁾	—	7-Nitro-2-methylbenzothiazole	120°	33
(3) <i>p</i> -Cyanothioacetanilide	191~192° ^{b)}	2-Methyl-6-cyanobenzothiazole ⁹⁾	142~143°	32
(4) 4-Nitro-2-methoxythioacetanilide	95~96°	2-Methyl-6-nitro-4-methoxybenzothiazole	146~147°	24
(5) <i>p</i> -Methylsulfonylthioacetanilide	169~170°	(<i>p</i> -Methylsulfonylacetanilide) ^{a)}	—	(50)
(6) <i>o</i> -Nitrothioacetanilide ^{7,8)}	—	(Bisulfite)	—	(43)
(7) <i>p</i> -Nitrothioacetanilide	—	(<i>p</i> -Nitroacetanilide)	—	(95)
(8) <i>p</i> -Thioacetylaminobenzene	148°	(<i>p</i> -acetylaminobenzene)	—	(95)

a) Parentheses show that the ring-closure did not occur.

b) Only m.p.s of compounds which have not been reported before are listed.

3) This Journal, **68**, 247 (1948).

4) F. G. Bordwell, G. Cooper : J. Am. Chem.

Soc., **73**, 5184 (1951) ; J. F. Bunnett, A. Levitt : J. Am. Chem. Soc. **67**, 1944 (1945).

5) K. Fries, et al. : Ann., **527**, 61 (1937). 6) Y. Mizuno, K. Watanabe : This Journal, **68**, 250 (1948)

7) K. Fries, Reitz : Ann., **527**, 46 (1937). 8) G. Hopkin, L. Hunter : J. Chem. Soc., **1942**, 638 (1942).

9) A. I. Kiprianov : J. Gen. Chem. (U. S. S. R.), **15**, 200 (1945) ; C. A., **40**, 2309 (1946).

In the case of *p*-thioacetylaminobenzene, where electron-releasing groups ($-N : N - C H$) is introduced, the expected ring-formation was not effected and instead, *p*-acetylaminobenzene was formed.

Table II. Comparison of Melting Points of 5-Isomer and 7-Isomer of Nitro-, Amino-, and Acetyl-amino-2-methylbenzothiazoles.

Position	Nitro-	Amino-	Acetyl-amino-
7	120°	82~83°	94° from ethanol 129° from ethanol
5	130°	101~102°	159° from benzene

Experimental

(I) Preparation of Thioacetanilides.

The following thioacetanilides were prepared approximately by the similar procedure as reported before³⁾.

Table III.

Material	Xylene cc	K ₂ S g.	P ₂ S ₅ g.	Temp.	Product and Yield
<i>p</i> -Methylsulfonylacetyl-anilide (m.p. 185°) 3.8 g.	600	2.3	1.5	115°	<i>p</i> -Thioacetylaminophenyl methyl sulfone (m.p. 178°) 3.1 g.
4-Nitro-2-methoxyacetyl-anilide (m.p. 153~154°) 21.0 g.	200	10.0	7.3	120°	2-Methoxy-4-nitrothioacetyl-anilide (m.p. 96°) 22 g.
<i>p</i> -Cyanoacetanilide (m.p. 200°) 9.5 g.	220	5.3	3.7	120°	<i>p</i> -Cyanothioacetanilide (m.p. 191~192°) 9.2 g.
<i>p</i> -Acetylaminobenzene (m.p. 140~141°) 9.0 g.	300	3.86	2.62	120°	<i>p</i> -Thioacetylaminobenzene (m.p. 148°) 7.5 g.
<i>p</i> -Acetylaminophenyl methyl ketone (m.p. 167~168°) 5.2 g.	550	6.0	3.9	115°	All attempts to obtain the <i>p</i> -Acetylaminophenyl methyl ketone by the procedure proved futile.
2.6 g.	320	1.5	1.0	105°	
2.6 g.	200	3.0	2.0	120°	

(II) Oxidation of Thioacetanilides

(1) *p*-Methylsulfonylthioacetanilide.—2.31 g. of the thioacetanilide was dissolved in 16 cc. of 8% sodium hydroxide solution and the solution was added with stirring in small portions to the mixture of 8 g. of potassium ferricyanide and 14 cc. of water at a room temperature. During the addition, crystalline substance separated. After all the solution was added, the mixture was kept stirring for another 40 minutes. The crystals were collected and washed with water by which 2.2 g. of the substance melting at 145~160° was obtained. After two crystallizations from ethanol, it melted at 169~170°, and weighed 0.72 g. (32% yield of recovery). The substance was found to be the starting material, by mixed m.p.

From the mother liquor, 1.06 g. of *p*-methylsulfonylacetyl-anilide (m.p. 185°) was obtained. Yield, 50%.

(2) 6-Cyano-2-methylbenzothiazole.—3.4 g. of *p*-cyanothioacetanilide, dissolved in 30 cc. of 7% sodium hydroxide solution was added dropwise with stirring to a mixture of 18 g. of potassium ferricyanide and 28 cc. of water at a room temperature, during 30 minutes. After the addition was completed, the solution was kept stirring for another 30 minutes. Separated amorphous substance was extracted with 60 cc. of chloroform. After being dried with sodium carbonate, chloroform was evaporated and 4.5 g. of oily residue was obtained. On standing, a crystalline substance separated. The substance was filtered, and weighed 1.30 g. Recrystallization from ethanol yielded 1.0 g. of *p*-cyano-2-methylbenzothiazole, m.p. 142~143°. Picrate, m.p. 139~140°. Yield, 32%.

A mixture with an authentic sample⁹⁾ of 2-methyl-6-cyanobenzothiazole melted at 143~144°.

(3) **2-Methyl-4-methoxy-6-nitrobenzothiazole**—3.4 g. of 2-nitro-4-methoxythioacetanilide was dissolved in 30 cc. of 8% sodium hydroxide solution, and the solution was added dropwise with stirring to the mixture of 14.4 g. of potassium ferricyanide, and 25 cc. of water, during 30 minutes. After the addition was completed, the mixture was kept stirring for another 30 minutes at room temperature. The solution was extracted with two portions of 25 cc. of chloroform. The chloroform solution was dried over sodium carbonate for 2 days and concentrated to half its volume and chromatographed (aluminum oxide and chloroform as solvent). From the eluate, 1.0 g. of the material was obtained. After one crystallization from ethanol, it melted at 146~147° and weighed 0.85 g. Yield, 25%. *Anal.* Calcd. for $C_9H_8N_2O_3S$: N, 12.61. Found: N, 12.51.

(4) **2-Methyl-7-nitrobenzothiazole**.—The alkaline solution of *m*-nitrothioacetanilide, on standing, was readily converted to the alkaline-insoluble substance of unknown structure, and therefore, the procedure was slightly modified as follows: In a three-necked flask fitted with a mechanical stirrer was placed 30.0 g. of potassium ferricyanide (purity: 93%). To this mixture was added 320 cc. of 8% sodium hydroxide solution with stirring in the course of one hour at room temperature. During the addition, yellow amorphous substance separated which was collected and washed with water. The crude material was dissolved in 200 cc. of 20% hydrochloric acid and boiled on a water bath for 30 minutes. After cooling, the insoluble material was filtered off. The benzothiazole was precipitated by diluting the filtrate with three times its volume of water. Yield, 29.7 g. of m.p. 113~117°. Recrystallization from ethanol yielded 10 g. of 7-nitro-2-methylbenzothiazole, m.p. 120°. Yield, 33.6%. *Anal.* Calcd. for $C_8H_6N_2O_2S$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.32; H, 2.63; N, 14.92.

The hydrochloric acid solution obtained after the removal of 2-methyl-7-nitrobenzothiazole was neutralized carefully with concentrated ammonium hydroxide to give crude *m*-nitraniline. Weighed, 17 g. Crystallization from ethanol yielded 13 g. of pure *m*-nitraniline. The mixed melting point did not depress with an authentic sample of m.p. 113°. Yield of *m*-nitraniline, 61.6%.

(5) **2-Methyl-7-aminobenzothiazole**.—A mixture of 11 g. of 2-methyl-7-nitrobenzothiazole, 10 g. of tin, 120 cc. of concentrated hydrochloric acid and 90 cc. of methanol was heated on a water bath until a clear solution was obtained. It required four hours. The solution was concentrated to one-half its volume, neutralized and then made alkaline with concentrated sodium hydroxide solution. The amorphous substance separated, which was collected and washed with water, by which 10 g. of crude 7-amino-2-methylbenzothiazole was obtained. Crystallization from ethanol yielded 7.2 g. (78% yield) of pure 2-methyl-7-aminobenzothiazole, m.p. 82~83°.

2-Methyl-7-aminobenzothiazole was converted to 2-methyl-7-acetylaminobenzothiazole with acetic anhydride by the usual manner, m.p. 94° from ethanol. *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: N, 13.58. Found: N, 13.62.

Summary

(1) Thioacetanilides with electron-attracting groups in the benzene nucleus (thioacetanilide, *m*-nitro-, *p*-methylsulfonyl-, *p*-nitro-, *o*-nitro-, and 2-nitro-4-methoxy-thioacetanilides) were subjected to benzothiazole ring-formation. Among them, *m*-nitrothioacetanilide (33%), *p*-cyanothioacetanilide (32%), and 2-methoxy-4-nitrothioacetanilide (24%) underwent cyclization in a fair yield. *p*-Methylsulfonylthioacetanilide is on the borderline between cyclizable and non-cyclizable thioacetanilides. *p*-Nitro- and *o*-nitro-thioacetanilides did not undergo ring-closure under the conditions examined.

(2) The cyclized product obtained from *m*-nitrothioacetanilide was found to be 2-methyl-7-nitrobenzothiazole instead of the expected 2-methyl-5-nitrobenzothiazole.

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