

Benzothiazoles. XI. Nitration of 6-Substituted 2-Methylbenzothiazoles

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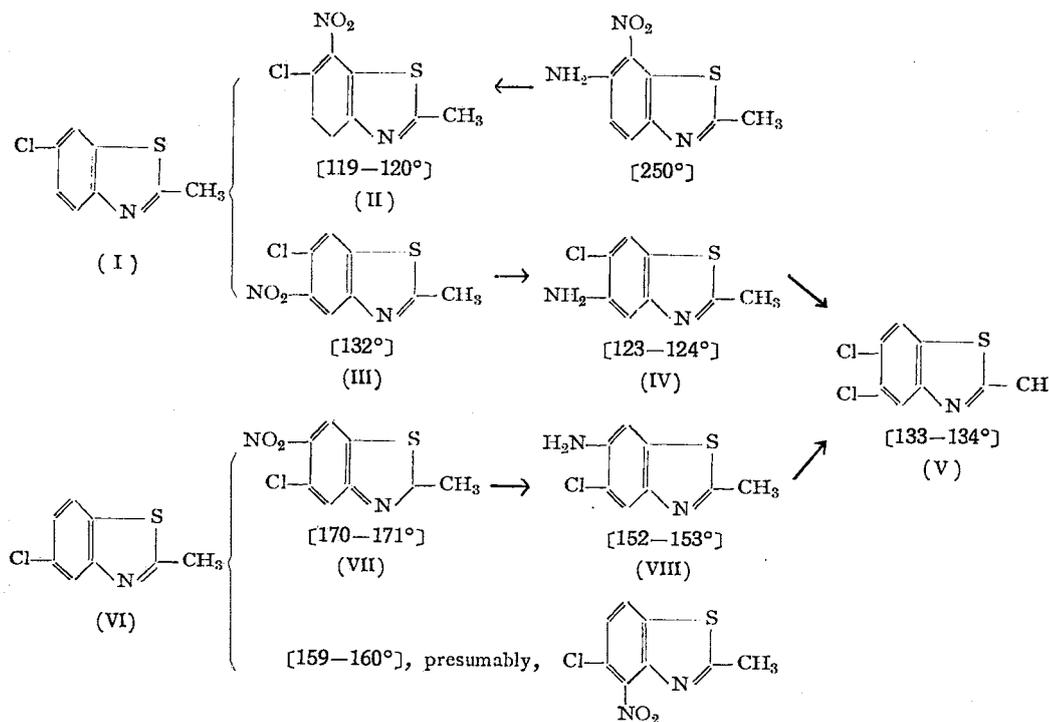
The literature appeared to indicate that 6-substituted benzothiazoles undergo nitration predominantly at seven position. Thus, nitration of 6-methoxybenzothiazole³⁾ gives rise to 6-methoxy-7-nitrobenzothiazole, and with 2-methyl-6-acethylaminobenzothiazole, nitration takes place exclusively at seven position. There are, however, no records of nitration which occurred at other position than seven.

A question which required further investigation was the apparent inconsis-

tency shown in the fact that nitration of 6-substituted benzothiazole took place at seven position, while Claisen rearrangement of the 6-allyloxybenzothiazole took place to both seven carbon and five carbon, with the former is predominating.^{3),4)}

It is our main concern in this place to examine whether or not the substitution at other position than seven, especially at five, position could occur in the case of nitration.

2-methyl-6-chloro- and 2-methyl-



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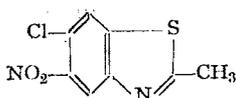
6-methoxybenzothiazole were subjected to nitration in conc. sulfuric acid at 0-20°, using 2.6 parts of fuming nitric acid.

In both cases we could afford to isolate the 5-isomer besides 7-substituted mononitroderivative.

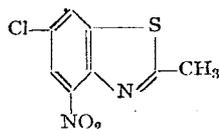
When a solution of 2-methyl-6-chlorobenzothiazole (I) in sulfuric acid was treated with a mixture of conc. sulfuric acid and fuming nitric acid at 10°. A mixture of mononitro-compounds which melted at 97-103° was obtained in almost quantitative yield. They were separated by fractional recrystallization from ethanol and by means of chromatography. The structure of the least

soluble product, m. p. 120°, in ethanol (yield, 70.5%) was established by comparison with an authentic sample prepared from 2-methyl-6-amino-7-nitrobenzothiazole to be 2-methyl-6-chloro-7-nitrobenzothiazole. (II). By evaporation of the mother liquor and by subjecting the residue to chromatography with alumina, the product (III), m.p. 132° was obtained in a small quantity (yield, 7.2%).

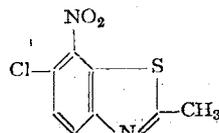
It may be either of two possible isomers (A) and (B), exclusive of 2-methyl-6-chloro-7-nitrobenzothiazole, m. p. 120°.



(A)



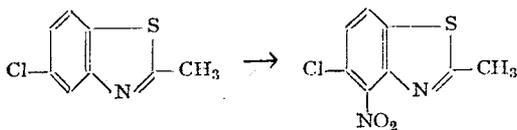
(B)



[120°]

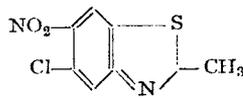
The structure of the compound, m. p. 132°, was established according to the following principle. In this place, conveniently we also consider the nitration

products of 2-methyl-5-chlorobenzothiazole (VI). There are three possible isomers (C), (D) and (E) which are derived from VI by nitration.

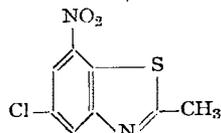


(VI)

(C)



(D)



(E)

Among these five chloronitro-2-methylbenzothiazole (A, B, C, D and E), (A) and (D) will give the same dichloroderivative, viz., 2-methyl-5,6-dichlorobenzothiazole (V), when they are converted to dichloroderivative by way of the aminoderivatives. There is no other possibility to afford the same dichloro 2-methylbenzothiazole. Therefore, compounds are (A) from I and (D) from VI respectively which will give the

dichloro-2-methylbenzothiazole V. The compound (III) of m. p. 132° and (VII) of m. p. 170-71° respectively gave the same dichloro-2-methylbenzothiazole (V) of m. p. 133-34° and therefore they are 5-nitro-6-chloro- and 5-chloro-6-nitro-2-methylbenzothiazole respectively.

Compound (IX) of m. p. 159-160° may presumably be 2-methyl-4-nitro-5-chlorobenzothiazole, but without adequate proof.

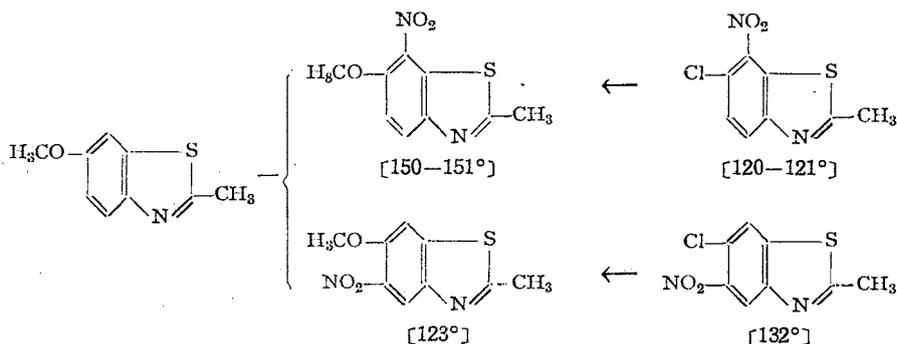
When 2-methyl-6-methoxybenzothiazole was nitrated in the similar condition (2.6 parts of nitric acid was employed at 0-2°), as described above.

And it gave dinitro-6-methoxy-2-methylbenzothiazole. Therefore a little more than equivalent amount of fuming nitric acid was employed in nitration.

In this cases, a mixture of mononitro-compounds, m. p. 115-142° was obtained in almost quantitative yield. They were easily separated by fractional recrystalli-

sation from ethanol.

The structure of the least soluble product, m. p. 150-151° (yield. 70.5%) was established by the mixed melting point with an authentic sample, prepared from 2-methyl-6-chloro-7-nitrobenzothiazole and sodium methylate. The structure of the compound of m. p. 123° was established to be 2-methyl-5-nitro-6-methoxybenzothiazole by a similar procedure.



From 2-methyl-6-nitrobenzothiazole, dinitroproducts could not be formed even under forcing conditions.

Yields obtained in nitration are shown in the following table.

Table I (Yields of Isomers)

Substituent at the position 6	4	5	7	ratio of 7 to 5
-NH-CO-CH ₃	0	0	quantitative	
-OCH ₃	0	8.2%	75%	9
-Cl	0	10.0	52-58%	5-6
-NO ₂	0	0	0	0

It is worth of note that ratios of 7-isomer to 5-isomer depend upon the

nature of substituents introduced into six position.

EXPERIMENTAL

I) Nitration of 2-methyl-6-chlorobenzothiazole: Experimental I: To the solution of a g. of 2-methyl-6-chlorobenzothiazole in b cc. of sulfuric

acid was added with stirring a mixture of c cc. of fuming nitric acid (d=1.54) and the equal volume of conc. sulfuric acid (98%) during 20 min. at 10°. After

the addition, the temperature was allowed to rise to room temperature. The clear, yellow solution, thus obtained, was then poured onto ice-water. The crude material separated was collected, air-dried and dried over conc. sulfuric acid under reduced pressure for 24 hrs. It weighed d g. The crude material was

recrystallized from e cc. of ethanol. Needle-like crystals separated. It weighed f g. and melted at g°. From the mother liquor h g. of product was recovered which melted at m°. and weighed n g. It was subjected to chromatography by means of alumina.

Table II

No. of Run.	(Results of experiment I)							Recovery from the mother liquor		
	a g.	b cc.	2c cc.	d g.	e cc.	f g.	g.	%	n g.	m.p.
(1)	4.0	20	8.0	4.4 (4.99)	100	2.1	109-113	42	1.9	80-90°
(2)	6.0	30	12.0	6.5 (7.30)	120	3.9	113-114	53	3.0	70-95°
(3)	3.6	20	10.0	4.54(4.54)	75	2.3	109-113	50	2.7	80-90°
(4)	8.0	40	16.2	8.60(10.0)	300	4.3	113-114	45	3.7	80-95°

a: material (base), b: sulfuric acid as solvent, 2c: nitrating mixture added, d: yield of crude material, e: ethanol used for recrystallization. numbers in parentheses show quantitative yield.

Experiment II: f g. was recrystallized again from ethanol to afford p g. of 2-methyl-6-chloro-7-nitrobenzothiazole (II), m. p. 118-119°, orange, silky platelete. Avaraged yield, 39.8%.

The m. p. did not depress when mixed with an authentic sample, prepared from 2-methyl-6-amino-7-nitrobenzothiazole according to Gattermann's procedure.

Table III (Results of Experiments II)

	f	P	Yield.
(1)	2.1g.	1.75 g.	35%
(2)	3.9g.	3.28 g.	45%
(3)	2.3g.	1.73 g.	38.3%
(4)	4.3g.	4.12 g.	41%

} average yield 39.6%

n and product recovred from also from the mother liquor in the experiment II was chromatographed by means of alumina and chloroform. The first eluate

did not give any residue when the chloroform was evaporated. From the subsequent run, the product of 2-methyl-5-nitro-6-chlorobenzothiazole was obtained.

The first run:

The 2nd eluate; m. p. 132°, 0.1g.
(6%)

the 3rd eluate: m. p. 110-115°, 0.3g.
0.5g. (12%)

the 4th eluate; m. p. 119-120°, 0.2g.

The second run: The eluate: no residue.

The 2nd one; m. p. 132°, 50 mg.

The 3rd one; m. p. 117-118°, 120-
121° after recryst. from ethanol.
0.1g.

0.5g. (12%)

The 4th one; m. p. 119-120°, 0.4g.

Average yield of the product of m. p. 120-121° was 0.5g (12.0%) and that of the product of m. p., 0.75g., 6%.

The total yield of product of m. p. 132° was 6% and that of the product of m. p., 119-120° amounted to 52-58%.

Structure-determination of the product of m. p., 132°:

Nitration of 2-Methyl-5-chlorobenzothiazole: To the solution of 1.5g of 2-methyl-5-chlorobenzothiazole in 10 cc. of conc. sulfuric acid was added with stirring a mixture of 2cc. of fuming nitric acid ($d=1.54$) and 2cc. of sulfuric acid (98%) at room temperature. The clear, red solution, thus obtained, was allowed to stand for 30 min. and then poured into ice water. The crude products separated was collected and air-dried. It weighed 2.1g., melted at 128-155°, which, after two recrystallization from ethanol, weighed 0.69g (28.3%), melted at 170°. From the mother liquor 0.15g. of mononitro-5-chloro-2-methylbenzothiazole was recovered. After several (four times) recrystallization, it weighed 1.0g., melted at 159-160° (41.4%).

Reduction of Product (VII) of m. p. 169-170°: A mixture of 1.30g. of 5-chloro-nitro-2-methylbenzothiazole

(VII), m. p. 169-170°, 11.2g. of hydrated stannous chloride, 28cc. of conc. hydrochloric acid and 10cc. of ethanol was heated on the water bath for 30 min. with shaking. On cooling, the double salt with stannous chloride separated. On rendering alkaline, 1.25g. of 5-chloro-6-amino-2-methylbenzothiazole, m. p. 143-146° was obtained, which, after one recrystallization from ethanol, weighed 1.15g. (quantitative yield), melted at 152-53°. Its acetyl derivative melts at 206°. Anal. Calcd. for $C_8H_7N_2S$ Cl: N, 14.57 Found: N, 14.83.

Reduction of 2-Methyl-5-Nitro-6-chlorobenzothiazole (III): A mixture of 0.13g. of 2-methyl-5-nitro-6-chlorobenzothiazole (III), 1.2g. of hydrated stannous chloride, 2cc. of conc. hydrochloric acid, and 1cc. of ethanol was heated on the water bath for 20 min. After rendering alkaline, the solution was extracted with ether. Ether was removed after drying with sodium carbonate. After one recrystallization of the residue from ethanol, it weighed 0.11g. and melted at 122-124° (platelet).

Chlorination of 5-chloro-6-Amino-(IV) and 5-Amino-6-Chloro-2-methylbenzothiazole (VIII): To a solution of 0.6g. of 2-methyl-5-amino-6-chlorobenzothiazole (IV), dissolved in 5 cc. of conc. hydrochloric acid and cooled to 0°, was added in drops 2cc. of sodium nitrite solution, prepared by dissolving 0.7g. of the nitrite in 6cc. of water, (potassium iodide-starch paper was used) The diazotized solution was converted to a dichloro-2-methylbenzothiazole (V), by adding it to a suspension of Gattermann copper. After diluting with water and neutralizing with conc. ammonia, an amorphous precipitate

was extracted with ether. After drying with sodium carbonate, the ether was removed and the residue was recrystallized from ethanol, and weighed 0.31g., m.p., 133-34°. In a similar procedure, 0.07 g. of 2-methyl-5-,6-dichlorobenzothiazole was obtained from 0.11g. of 2-methyl-5-amino-6-chlorobenzothiazole (VIII). The mixed melting point of V from IV and V from VIII did not depress. Anal. Calcd. for $C_8H_5N_2S_2Cl_2$: N, 6.42 Found, N, 6.51.

Nitration of 2-Methyl-6-Methoxybenzothiazole: To a solution of 5.0 g. of 2-methyl-6-methoxybenzothiazole in 20cc. of conc. sulfuric acid and cooled to 0°, was added dropwise a mixture of 2cc. of fuming nitric acid ($d=1.5$, one part) and 5cc. of conc. sulfuric acid at 0°. After the addition is over, the mixture was kept at 0° for 20 min., and then poured air-dried, it weighed 7.5 g. (75%), melted at 151°. 1.2g. of crude product was recovered from the mother liquor by removing the solvent. The crude material was chromatographed by means of alumina and chloroform. After removing the chloroform from the eluate, 0.8g. of the residue was obtained. After one recrystallization from ethanol, it weighed 0.5g., melted at 122-123°. Anal. Calcd. for $C_9H_9N_2O_3S$: C 48.21 H, 3.57 N, 12.50, Found: C, 48.42 H, 3.61 N, 3.61 N, 12.52.

Determination of the Structure of Product, m. p. 151° and Product of m. p. 122-3°.

2-Methyl-6-Methoxy-7-Nitrobenzothiazole from 2-methyl-6-Chloro-7-Nitrobenzothiazole: To a solution of 0.6g. of (VII) in 30cc. of warm methanol was added 11cc. of sodium methylate solution prepared by dissolving

0.8g. of sodium in 100cc. of absolute methanol. The solution was heated on the water bath for 15 min. After cooling, a crude material separated, which was recrystallized three times from ethanol and weighed 0.1g., melted at 150-51°. The mixed melting point did not depress with product, m. p. 151-153°, isolated from nitration-product of 2-methyl-6-nitrobenzothiazole.

2-Methyl-5-nitro-6-methoxybenzothiazole was prepared by the similar procedure.

Nitration of 2-Methyl-6-Nitrobenzothiazole: 2 g. of 2-methyl-6-nitrobenzothiazole was dissolved in 10cc. of conc. sulfuric acid (98%) and the solution was heated with 1g. of potassium nitrate for 4 hrs. on the water bath. After cooling, the solution was poured onto cracked ice. The crude material was recrystallized from ethanol. 1.6g. of the starting material was recovered.

Summary

1. Nitration of 6-chloro-2-methylbenzothiazole gave a mixture of 2-methyl-6-chloro-7-nitrobenzothiazole, m. p. 119-120°, (yield, 60.5%) and 2-methyl-6-chloro-5-nitrobenzothiazole, m. p. 132° (yield, 6%).

2. Nitration of 6-methoxy-2-methylbenzothiazole gave a mixture of 2-methyl-6-methoxy-7-nitro, m. p. 150-151°, (yield, 70.5%) and 2-methyl-6-methoxy-5-nitrobenzothiazole, m. p. 123°, (yield, 8.2%).

3. Nitration of 2-methyl-6-nitrobenzothiazole failed to give the dinitro products even under the forcing conditions.

4. It is worth of note that ratio of 7-isomer to 5-isomer is dependent on the nature of the substituent introduced

at six position.

5. The following new compounds were prepared : 2-methyl-6-chloro-7-nitro-, m. p. 119-120°, 2-methyl-5-nitro-6-chloro-m. p. 132°, 2-methyl-5-amino-6-chloro- m. p. 123-124°, 2-methyl-5-

chloro-6-amino- m. p. 152-153°, 2-methyl-6-methoxy-7-nitro-m. p. 150-151°, 2-methyl-5-nitro-6-methoxy-m. p. 123° and 2-methyl-5-chloro-6-acetylamino- and 2-methyl-5,6-dichlorobenzothiazole, m. p. 133°.

Literature

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