551. *A Quantitative Study of the Nitration of Benzothiazole.*

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The mononitration of benzothiazole in nitric–sulphuric acid, at 10° and 35°, has been quantitatively investigated. All four mononitrobenzothiazoles are produced, the 5-isomer being detected for the first time as a nitration product. The orientation of the four isomers has been unequivocally established, use being made of the relation between dipole moment and elution behaviour in chromatography on alumina as supporting evidence. A procedure is described for isolating the nitro-compounds in quantity.

IN view of recent interest in benzothiazole it was surprising to find no comprehensive investigation of its mononitration. In 1883 Mylius [1] isolated 6-nitrobenzothiazole as a nitration product and established its structure by conversion into *p*-phenylenediamine. Later investigators have confirmed the 6-isomer as the major product but have made conflicting claims about the remainder. Nishizawa [2] claimed that he obtained, by nitration at room temperature or 60°, a quantitative yield, which he separated into 6-isomer and a supposed molecular compound (m. p. 138°) of the 6- and the 7-isomer, converted by catalytic reduction into the corresponding amines. However we have now shown that all four mononitro-derivatives are formed, with the 4- and the 7-isomer in about equal amount; the supposed molecular compound was shown by a mixed m. p. diagram not to exist, and the m. p. quoted for it does not correspond to that (m. p. 123°) of the eutectic mixture of 6- and 7-isomers; furthermore, 7-aminobenzothiazole had not been authenticated at the time.

Mizuno *et al.*[3] isolated the 6-isomer and what they presumed to be the 7-isomer. Peticolas *et al.*[4] isolated the 6-isomer and a small amount of a compound (m. p. 135°), which they presumed (possibly correctly) to be the 4-isomer. Veltman [5] was able to separate the nitration product by fractional crystallisation from methanol, ethanol, and benzene into 6-nitrobenzothiazole, 7-nitrobenzothiazole, and a substance, m. p. 106°, which he thought to be the 4-isomer, but which was obviously not pure, as can be seen from its low m. p. and the m. p. discrepancies of the derived amino- (123°) and 2-aminonitrobenzothiazole (235°) with those recorded for 4-amino- (94° [6]) and 2-amino-4-nitrobenzothiazole (254°,[6] 248° [7]).

We nitrated benzothiazole in nitric–sulphuric acid and from the product removed most of the predominant 6-isomer by means of solvent. The remainder was separated into its four components by column chromatography on alumina, using the technique that had been successful for separation of polynitronaphthalenes.[8] Our results are summarised in the Table.

Nitration of benzothiazole in sulphuric (*d* 1·84) *and nitric acid* (*d* 1·5).

		Product composition (%)			
Temp.	Yield (%) *	4-NO_2	5-NO_2	6-NO_2	7-NO_2
10° ± 2°	83	22·8	6·4	49·5	21·3
35° ± 2°	91·6	21·4	8·5	50·1	20·0

* Total yield of pure mononitrobenzothiazoles.

The nitro-compounds were eluted in the order 7-, 6-, 5-, 4-; good separation was

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[1] Mylius, Dissertation, Berlin, 1883.

[2] Nishizawa, *J. Pharm. Soc. Japan*, 1942, **62**, 47.

[3] Mizuna, Adachi, and Nakamura, *J. Pharm. Soc. Japan*, 1952, **72**, 1266.

[4] Peticolas, Sureau, Frenkiel, and Goupil, *Bull. Soc. chim. France*, 1949, 111.

[5] Veltman, *J. Gen. Chem. U.S.S.R.*, 1960, **30**, 1363.

[6] Erlenmeyer and Ueberwasser, *Helv. Chim. Acta*, 1940, 328.

[7] Elderfield and Short, *J. Org. Chem.*, 1953, **18**, 1092.

[8] (*a*) Ward, Johnson, and Day, *J.*, 1959, 487; (*b*) Johnson, Thesis, London, 1960; (*c*) Ward and Johnson, *J.*, 1961, in the press.

achieved between the last three isomers but only partial separation between the 7- and the 6-isomer (see also the discussion below of the relation between dipole moment and elution behaviour). The composition of mixtures of 6- and 7-isomers was therefore determined from the mixed m. p. diagram (accuracy *ca.* $\pm 1\%$). The accuracy of the chromatographic separations is estimated at $\pm 2\%$ but may be better. The absence of other isomers in the individual nitro-compounds or in the mixture of 6- and 7-isomers was confirmed by infrared spectroscopy.

The chromatographic method is not suitable for the preparation of the nitrobenzothiazoles in quantity, so we devised an alternative procedure. Most of the 6-isomer (*ca.* 85% of it) is readily obtained by simple solvent separation. The residue is steam-distilled, yielding a mixture (A) of the 6- and the 7-isomer, and a non-volatile residue (B) of the 4- and the 5-isomer. 7-Nitrobenzothiazole (*ca.* 55% of it) is obtained from mixture (A) by destruction of the 6-isomer with methanolic sodium hydroxide (cf. Mizuno [3]). Crystallisation of mixture (B) from methanol and then from xylene yields the 4-isomer (*ca.* 40%); and the 5-isomer (*ca.* 25%) can be obtained from the residue by destroying the 4-isomer as above; alternatively, but more laboriously, the 4- and the 5-isomer can be separated by column chromatography. The original steam-distillation is tedious owing to the low volatility of the 6- and the 7-isomer, and satisfactory separation by solvents only was impossible.

Before this work the orientation of the 5-isomer had been established by synthesis [9] and that of the 6-isomer by Mylius [1] and Colonna and Anderson.[10] The identity of our products with these, together with the orientation of the other isomers has been shown by melting points, infrared spectra, calculated and measured dipole moments, and the relation of the last to elution behaviour on alumina. The infrared spectra of all four isomers show peaks which can be allocated (*a*) to those considered by O'Sullivan [11] to be characteristic of a benzene ring fused to a five-membered ring, and (*b*) to the hydrogen ring patterns in the benzene ring [12] [801 cm.$^{-1}$ (hydrogen pattern 1,2,3) for the 4- and the 7-isomer; 813 cm.$^{-1}$ (5-) and 818 cm.$^{-1}$ (6-) (hydrogen pattern 1,2), 922 cm.$^{-1}$ (5-) and 899 cm.$^{-1}$ (6-) (hydrogen pattern 1) for the 5- and the 6-isomer].

With isomeric molecules, which contain the same number and same type of functional groups, the elution sequence in column chromatography is often indirectly proportional to the order of dipole moments for the compounds.[8,13] The elution order for the nitrobenzothiazoles was $7 \geqslant 6 > 5 > 4$. This order is consistent with the dipole moments calculated for these (7-nitro-, 2·3; 6-nitro-, 2·9; 5-nitro-, 4·8; 4-nitro-, 5·7 D). Further, the dipole moments of the 4- and the 7-isomer were measured by us, being about 5·2 and 2·5 D respectively, giving reasonable agreement with the calculated values. The dipole moments were calculated by using values of 4·0 D for the nitro-group and 1·45 D for benzothiazole.[14] The direction of the latter was derived by vector addition of the calculated π- and σ-moments of benzothiazole.[15] When the charge-density diagram of Metzger and Pullmann [16] and an " exageration factor " of 10/3 (calculated from the similarly obtained pyridine diagram) were used, the π-moment found was 2·41 D, θ $353\frac{1}{2}$°. Using C–H + 0·40, C–N − 0·45, and a formal C–S moment of −1·0 D (calculated from the similarly obtained thiophen diagram) we found the σ-moment to be 1·02 D, θ $126\frac{1}{2}$°. This gives a resultant angle of 18° (bisecting the C–N–C angle) for benzothiazole; the calculated magnitude of 1·87 D is in fair agreement with experiment, and shows that some reliance can be attached to the calculations. Further, the sequence of calculated dipole moments is not altered when

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[9] Brand, *Z. angew. Chem.*, 1928, **41**, 614; Spieler and Prijs, *Helv. Chim. Acta*, 1950, **33**, 1429.

[10] Colonna and Andrisano (*Publ. Ist. chim. Univ. Bologna*, 1943, *No.* 3, 3; *Chem. Abs.*, 1947, **41**, 754).

[11] O'Sullivan, *J.*, 1960, 3278.

[12] Hawkins, Ward, and Whiffen, *Spectrochim. Acta*, 1957, **10**, 106.

[13] Franc and Latinak, *Coll. Czech. Chem. Comm.*, 1955, **20**, 817.

[14] Oesper, Lewis, and Smyth, *J. Amer. Chem. Soc.*, 1942, **64**, 1131.

[15] Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113.

[16] Metzger and Pullmann, *Compt. rend.*, 1948, **226**, 1614.

the direction of the benzothiazole moment is varied by ±15° (the accuracy claimed for the method of calculation [15] is ±10°).

EXPERIMENTAL

Dipole moments were measured by Dr. S. Walker and Mr. A. N. Sharpe, B.Sc., by the method described previously.[9] Ultraviolet spectra were recorded with a Unicam S.P. 500 spectrophotometer for cyclohexane solutions. The infrared spectra were measured for Nujol mulls by Dr. K. Morgan (University of Birmingham).

Nitration of Benzothiazole.—Benzothiazole (31·5 g.) was dissolved in sulphuric acid (*d* 1·84; 50 ml.) by portionwise addition, with vigorous stirring, below 20°. Nitric acid (*d* 1·5; 25 ml.) was added dropwise so that the temperature was maintained at 10° ± 2° (or 35° ± 2°), and this temperature was then maintained for a further hr. The mixture was poured on ice (250 g.) with stirring, and aqueous ammonia (*d* 0·88) added, below 25°, till the solids became slightly orange (pH 2). The solids were collected, washed by agitation with dilute aqueous ammonia and water, and dried at 80° *in vacuo*. Yields were 49 g. (10°) and 47 g. (35°).

Analysis of the Nitration Product.—The product obtained by nitration at 10° was crystallised from hot ethanol (700 ml.), and the solids obtained on cooling were again dissolved in hot ethanol [550 ml. recovered from the original filtrate (used to prevent possible losses of volatile material in concentration of this filtrate) plus 150 ml. of fresh solvent]. The inorganic residue (8·2 g.) was removed from the hot solution which was set aside to crystallise slowly. Filtration gave 6-nitrobenzothiazole, m. p. 177° (14·78 g.). The combined filtrates were evaporated to dryness and the residue was dried *in vacuo* at 120° (25·6 g.). A portion (2·0 g.) of this residue was passed in benzene (200 ml.)–light petroleum (b. p. 40—60°; 25 ml.) through an alumina (B.D.H.) column (90 × 2·5 cm.) prepared in a similar solvent. Elution was with this solvent mixture (1700 ml.), followed by benzene (200 ml.) and 9 : 1 v/v benzene–ethyl acetate (400 ml.). When the product front had nearly reached the bottom of the column, 20-ml. fractions were collected. These were each evaporated to dryness and quickly dried *in vacuo* at 80°. The separation was followed from the appearance, weights, and m. p.s of the recovered solids. The column was finally washed with ethanol but this only afforded by-products. Before the product front reached the base of the column the eluent contained only by-products (0·1160 g.). Fractions 1—10 also contained by-products (0·0838 g.). After this 7-nitrobenzothiazole began to appear (fractions 11—17), followed by a mixture of this with 6-nitrobenzothiazole (18—31) and finally almost pure 6-isomer (32—36) (fractions 11—36 contained 0·7464 g.). The next fraction (37) was pure eluent. 5-Nitrobenzothiazole was collected from fractions 38—50 (0·1712 g.), again followed by pure solvent (51—52). 4-Nitrobenzothiazole was in fractions 53—73 (0·6124 g.). The combined yield of nitrobenzothiazoles was 1·5300 g. The ethanol elution gave more by-products (0·1155 g.) (total recovery of solids 1·8453 g., *ca.* 92%).

The mixture of 6- and 7-nitrobenzothiazoles was analysed by mixed m. p. diagram, based on the following values:

6-Nitro-compd. (%)	0	10	20	30	35	40	60	70	100
M. p.	153°	147°	138°	128·5°	123°	126°	148°	157°	177°

The product obtained by nitration at 35° was analysed similarly.

Preparation of the Nitrobenzothiazoles.—The yields given below are the amount of each isomer recovered in relation to the total amount of this in the nitration product, as indicated by the chromatographic analysis. Almost pure 6-nitrobenzothiazole (m. p. 177°; *ca.* 83%) was obtained by crystallization from hot ethanol as described above. The product (30 g.) obtained by evaporation of the ethanol filtrates (containing *ca.* 8·3 g. of 7-, 4·2 g. of 6-, 3·1 g. of 5-, and 9·3 g. of 4-isomer; cf. Table) was steam-distilled. After being kept at 0° overnight the distillates were filtered, yielding a mixture of 6- and 7-nitrobenzothiazole (9·8 g., *ca.* 80%). This mixture was dissolved in warm methanol (700 ml.) and treated with a solution of sodium hydroxide (5 g.) in methanol (100 ml.) at 25° (cf. Mizuno [3]); stirring was continued for 4 hr., the mixture was kept overnight at 0°, and the solids were collected and washed with ethanol, affording almost pure 7-nitrobenzothiazole, m. p. 154—155° (4·6 g., *ca.* 55%). The products (9·4 g., *ca.* 76% calc. on 4- and 5-isomers) not volatile in steam were collected from the residual aqueous suspension after this had been kept overnight at 0°. They were dissolved in hot methanol (350 ml.) (charcoal), concentrated to 140 ml., and set aside to crystallise. The solid (4·65 g.;

m. p. 131—133°) that separated was crystallised from hot xylene (30 ml.; charcoal), yielding the 4-nitro-isomer (3·7 g., *ca.* 40%; m. p. 135°). The xylene filtrate was evaporated and the residue dissolved in the methanol filtrate. This was then stirred with a solution of sodium hydroxide (1 g.) in methanol (20 ml.) for 2 hr., and the solids were collected after being kept at 0° overnight (1·9 g.). 5-Nitrobenzothiazole (0·8 g., *ca.* 25%; m. p. 161°) was recovered from this material by chromatography on alumina (100 × 2·5 cm.) in benzene, elution being with benzene until the faintly reddish-brown band (due to this isomer) nearly reached the base of the column, and then with benzene–ethyl acetate (19:1 v/v).

The products had the following properties:

4-*Nitrobenzothiazole*, greenish needles (from xylene), m. p. 137°, discoloured in air (Found: C, 47·0; H, 2·3; N, 15·6. $C_7H_4N_2O_2S$ requires C, 46·6; H, 2·2; N, 15·5%). Dipole moment, 5·20 ± 0·05 D at 25° in C_6H_6. $\lambda_{max.}$ 234sh, 240sh, 280 mμ (ε 11,390, 10,640, 5830), $\nu_{max.}$ 1609m, 1559m, 1514s, 1450s, 1410s, 1344s, 1318s, 1286s, 1218m, 1193m, 1118m, 1076m, 974w, 869s, 863m, 804s, 801s, 758w, 746m, 735s, 720m, 681w, 663w cm.$^{-1}$.

5-Nitrobenzothiazole, yellowish needles (from xylene), m. p. 164° (Brand [9] gives 162°) (Found: C, 46·8; H, 2·0; N, 15·7%), $\lambda_{max.}$ 235, 240, 283, 319sh mμ (ε 22,970, 23,980, 8560, 860), $\nu_{max.}$ 1600m, 1570m, 1511s, 1470m, 1429m, 1421m, 1408m, 1348s, 1281m, 1258m, 1194w, 1143m, 1088w, 1053m, 1038m, 931m, 922m, 847m, 833m, 813m, 796m, 736m, 685w, 662w cm.$^{-1}$.

6-Nitrobenzothiazole, yellowish needles (from ethanol), m. p. 178° (Jacobson and Kwaysser [17] give 176—177°), $\lambda_{max.}$ 220, 228sh, 281, 316sh, 329sh mμ (ε 20,810, 19,500, 12,000, 3780, 2150), $\nu_{max.}$ 1603m, 1572m, 1542w, 1510s, 1481m, 1456m, 1436s, 1406m, 1396m, 1344s, 1336s, 1296s, 1291s, 1254m, 1200m, 1141w, 1126m, 1117s, 1034m, 906s, 899m, 851s, 847s, 818w, 800s, 749s, 746s, 716m, 656w cm.$^{-1}$.

7-Nitrobenzothiazole, white leaflets (from xylene), m. p. 155° (Found: C, 47·0; H, 2·2; N, 15·7%). Dipole moment 2·46 ± 0·05 D at 25° in C_6H_6. $\lambda_{max.}$ 231sh, 236, 304, 324sh, 340sh mμ (ε 11,420, 11,790, 6500, 5900, 2730), $\nu_{max.}$ 1616m, 1567m, 1528s, 1514s, 1487s, 1460m, 1407m, 1350s, 1317s, 1286m, 1218m, 1198m, 1186s, 1155m, 1096m, 1057m, 988w, 971w, 910w, 857s, 841s, 806m, 801m, 735s, 710m, 665w cm.$^{-1}$.

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[17] Jacobson and Kwaysser, *Annalen*, 1893, **277**, 244.