
VII. Chlorination of 2-Alkyl-6-Nitro- and 2-Alkylbenzothiazoles.

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With a view to preparing benzothiazole analogs (I) of chloramphenicol, possible routes to (I) were examined. In the first place, chlorination of 2-methyl- (II), 2-ethyl- (III), 2-methyl-6-nitro- (IV), and 2-ethyl-6-nitro-benzothiazole (V) was carried out to find suitable intermediates of (I) among these chlorinated compounds. In this respect, Hammick2) has shown that trichloro-α-picoline is produced when α-picoline is chlorinated in glacial acetic acid containing excess of potassium acetate. We adopted the procedure in our chlorination of (II), (III), (IV), and (V).

Chlorination of 2-methylbenzothiazole in glacial acetic acid in the presence of sodium acetate at 75~80°C gave trichloromethylbenzothiazole. No other chlorinated compounds, i.e., neither monochloromethyl- nor dichloromethylbenzothiazole, were detected in the reaction mixture, even when the amount of chlorine necessary for monosubstitution was passed in. That is, 2-methylbenzothiazole behaved as did picoline2) or quinaldine3) under analogous conditions. The trichlorinated compound was converted into benzothiazolyl-2-carboxylic acid, m.p. 108~109°C, and then into benzothiazolyl-2-carboxyhydrazide, m.p. 170~171°C, through 2-carbethoxybenzothiazole, m.p. 70~71°C.

Chlorination of 2-ethylbenzothiazole was carried out by passing the amount of chlorine necessary for disubstitution through a mixture of the base, sodium acetate, and acetic acid. Dichloroethylbenzothiazole was obtained, which afforded a carbonyl compound, m.p. 107~108°C (its semicarbazone, m.p. 258°C (decomp.), when treated with alcoholic silver nitrate. It is probable that the carbonyl compound is 2-acetylbenzothiazole, but the structure was established by mixed melting with synthetic specimen, prepared from 2-ethylbenzothiazole by oxidation with selenium dioxide.

Chlorination of 2-methyl-6-nitrobenzothiazole, m.p. 165°C, prepared from 2-methyl-
benzothiazole by nitration, proceeded in absorbing three moles of chlorine to form trichloromethyl-6-nitrobenzothiazole, m.p. 113°. It gave 6-nitrobenzothiazolyl-2-carboxylic acid when treated with alcoholic silver nitrate.

Chlorination of 2-ethyl-6-nitrobenzothiazole (VI) gave dichloroethylbenzothiazole (VII), m.p. 93~94°, in a yield of 63%, which was converted to 2-acetyl-6-nitrobenzothiazole (X). The 2-acetyl-6-nitro compound (X) was also obtained by the mononitration of 2-acetylbenzothiazole (IX) in a 11% yield. Mixed melting point of these two carbonyl compounds did not depress. 2-Acetyl-6-nitrobenzothiazole was brominated with chloroform solution of bromine to form 2-bromoacetyl-6-nitrobenzothiazole (XI), m.p. 147°, in a fair yield.

**Experimental**

**Chlorination of 2-methylbenzothiazole**—Through a solution of 10 g. of 2-methylbenzothiazole in 60 cc. of glacial acetic acid mixed with 20 cc. of acetic anhydride, was passed a stream of dried chlorine gas at 80~85° in the presence of 20 g. sodium acetate, until A (A=4.5, 9.0, and 14.0) g. of increase in weight was observed. Then the mixture was poured into ice-water and an oily product separated. After neutralizing with conc. ammonia carefully, extracting with ether, and removing the solvent, B (B=8.2, 9.5, and 14.0) g. of crude material was obtained.

**Hydrolysis of the chlorinated benzothiazole**—A g. of the oily chlorinated product was heated with 20 g. of sodium carbonate and 100 cc. of 50% methanol for five hours on a boiling water bath. On removing the methanol, C (C=2.0, 3.5, and 8.0) g. of sodium 2-benzothiazolylcarboxylate was obtained and besides, D (D=6.0, 4.2, and 1.2) g. of the starting material was recovered. It was converted into its picrate, m. p. 153°, which did not lower the m. p. of the picrate of 2-methylbenzothiazole.

The sodium carboxylate was transformed into the free acid with 85% phosphoric acid. It melted at 108° under decompn. and was converted to 2-carbethoxybenzothiazole, m.p. 70~71°, and to benzothiazolyl-2-carbonyldrazide, m.p. 171°, needle-like crystals. Anal. Calcd. for C₉H₇O₆N₃: N, 21.75. Found: N, 21.68.

**Chlorination of 2-ethylbenzothiazole**—Through a solution of 25 g. of ethylbenzothiazole in 150 cc. of acetic acid and 50 cc. of acetic anhydride was passed a stream of dried chlorine gas in the presence of 50 g. of sodium acetate at 80~85°, until 22 g. (2 moles) of increase in weight was observed. It required 2 hours. The reaction mixture was poured into ice-water and after neutralizing with conc. ammonia, the solution was extracted with ether. On removing the solvent, after drying with sodium sulfate, 28 g. of oily product remained.

**Hydrolysis with silver nitrate**—28 g. of the dichloroethylbenzothiazole was heated with a solution of 50 g. of silver nitrate in 20 cc. of 96% ethanol for five hours on a steam bath. After removing silver chloride, the ethanol was distilled off. The residue, rendered alkaline with sodium carbonate, was subjected to steam distillation. 4.5 g. of 2-acetylbenzothiazole was obtained from the distillate, which melted at 105~106°. After one recrystallization from ligroine, it melted at 107~108°. Its semicarbazone melted at 258°. The hydrolysis was also effected with either sodium acetate or silver acetate to yield similar results. Anal. Calcd. for C₁₀H₁₀O₄N₄S: C, 51.26; H, 4.30; N, 23.83. Found: N, 51.62; H, 4.74; N, 23.81.

**Oxidation of 2-ethylbenzothiazole with selenium oxide**—To a solution of 11.0 g. (0.1 mole) of sublimated selenium dioxide dissolved in 100 cc. of 95% alcohol, was added a solution of 16.3 g. (0.1 mole) of 2-ethylbenzothiazole in 30 cc. of 95% ethanol. The mixture was boiled for 7 hours on a water bath. After removing selenium by filtration and the alcohol under reduced pressure, the residue was subjected to steam distillation. As a forerun, unreacted 2-ethylbenzothiazole was recovered. Then, 2.0 g. of 2-acetylbenzothiazole was obtained. Yield, 11%.

To a solution of selenium dioxide dissolved in 50 cc. of dioxane and a small amount of water by heating at 45~50°, was added a solution of 7.5 g. of 2-ethylbenzothiazole in 20 cc. of 97% dioxane
and the mixture was heated for three hours on a steam bath, during which selenium separated. After removing the selenium and the solvent, the residue was subjected to steam distillation. No starting material was recovered in this case. 3.6 g. of 2-acetylbenzothiazole was obtained, which melted at 107°–108° (44.2% yield), after one recrystallisation from ethanol.

**Nitration of 2-acetylbenzothiazole**—To a solution of 2 g. of 2-acetylbenzothiazole in 10 cc. of conc. sulfuric acid was added a mixture of 2 cc. conc. sulfuric acid and 2 cc. of fuming nitric acid (d = 1.54) at 0° to 2°. The mixture was allowed to stand for 30 minutes at room temperature. It was then poured into ice-water to separate a sludgy substance, which was extracted with chloroform. After removing the chloroform, the residue was recrystallized from ethanol. Fine needle-like crystals of orange yellow color separated, weighed 0.7 g., m. p. 191°. Anal. Calcd. for C₉H₆O₃N₂S: C, 48.56; H, 2.72; N, 12.61. Found : C, 48.65; H, 2.99; N, 12.72

**Chlorination of 2-methyl-6-nitrobenzothiazole**—Through a solution of 5 g. of 2-methyl-6-nitrobenzothiazole in 2.3 g. of acetic anhydride and 50 cc. of glacial acetic acid was passed a stream of dried chlorine gas in the presence of 7.4 g. of sodium acetate at 75°–80°, until 3.4 g. of increase in weight was observed. After that, the mixture was poured onto ice to separate the chlorinated products. 7.4 g. of products, which melted at 113° after three recrystallizations from ethanol, weighed 5.6 g. (73%). It was converted to 2-carboxy-6-nitrobenzothiazole, m. p. 181°–182°.

**Chlorination of 2-ethyl-6-nitrobenzothiazole**—Through a solution of 5 g. of 2-ethyl-6-nitrobenzothiazole in 50 cc. of glacial acetic acid and 2.34 g. of acetic anhydride was passed a stream of dried chlorine gas in the presence of 7 g. of sodium acetate at 75°–80°, until 3.41 g. of increase was obtained. After that, the mixture was poured onto ice. 5.3 g. of a product which melted at 65°–85° was obtained. It melted at 93°–94° after three recrystallizations from ethanol. It weighed 3.2 g., yield, 63%.

**Hydrolysis of 2-dichloroethyl-6-nitrobenzothiazole**—A solution of 2.8 g. of 2-dichloroethyl-6-nitrobenzothiazole and 3.5 g. of silver nitrate in 50 cc. of ethanol was heated for 2 hours on a water bath, during which silver chloride separated. After removing the silver chloride and the ethanol (under reduced pressure), the residue was crystallized from acetone. It weighed 1.6 g., melted at 191°–192° (small sandy crystals). It did not lower the m. p. of the sample, prepared from (IX) by nitration.

**Bromination of 2-acetyl-6-nitrobenzothiazole**—To a solution of 4.5 g. of 2-acetyl-6-nitrobenzothiazole in 100 cc. of chloroform was added a solution of 2.3 g. of bromine in 16 cc. of chloroform at 55°. It required 2 hours. The mixture was allowed to stand under the direct sunlight for one hour. After washing the mixture with water, it was dried with sodium sulfate. On removing the chloroform, 5.3 g. of brominated compound, which melted at 120°–138°, remained. After two recrystallizations from 40 cc. of a mixture of ethanol and chloroform (1:1), it weighed 3.2 g., melted at 146°–147°. Anal. Calcd. for C₉H₅O₃SN₂Br: N, 9.30. Found : N, 9.41.

**Hexamine complex of (XI)**—To a solution of 3.2 g. of 2-bromoacetyl-6-nitrobenzothiazole in 15 cc. of chloroform was added a solution of 1.4 g. of hexamine in 12 cc. of chloroform. The mixture was kept in an ice-box overnight and the precipitate was filtered, washed with chloroform, and dried at 80° to yield 3.0 g. of the hexamine complex, which melted at 187° under decomposition.

**Summary**

1) Possible routes of preparing benzothiazole analogs of chloramphenicol were examined, one of which was proved to be promising. The route is as follows: 2-Ethyl-, 2-ethyl-6-nitro-, 2-dichloroethyl-6-nitro-, 2-acetyl-6-nitro- (X), and to 2-α'-bromoacetyl-6-nitrobenzothiazole. Overall yield of (X) by the present route was found to be 18%.

2) During the present investigation, following new compounds were prepared: Benzothiazolyl-2-carbohydrazide, m. p. 171°; 2-acetylbenzothiazole, m. p. 107°–108°, its semicarbazone, m. p. 258° (decomp.); 2-acetyl-6-nitrobenzothiazole, m. p. 191°–192°; 2-α',α''-dichloro-6-nitrobenzothiazole, m. p. 93°–94°; 2-bromoacetyl-6-nitrobenzothiazole, m. p. 146°–147°.

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