and this was refluxed in acetic acid for 6 hours with 0.8 g. of zinc dust. The product was 0.3 g. of (XVI), b.p_6 150°, which gave a picrate of m.p. 133°, and was identical with one of the monobenzyl compound obtained as the reaction product of β-picoline and benzyl chloride.

Summary

Pyridine, α-, β-, and γ-picoline, and 2,6- and 2,4-lutidine form salts when heated with benzyl chloride at 100~150°. Raising of this temperature to 240~270° results in the formation of compounds in which the benzyl group has entered the pyridine nucleus or the side-chain methyl. By the examination of the structure of these benzyl compounds formed, following conclusions were drawn. The chief reaction product is a monobenzyl compound in which the benzyl group has been substituted in the 2- or 4-position, and the dibenzyl compound is obtained as the by-product in around 5% yield. This dibenzyl compound is the one with the benzyl group substituted in the 2- and 4-positions of the pyridine nucleus in the case of pyridine and β-picoline. In the case of α- and γ-picoline, and 2,6- and 2,4-lutidine, one of the benzyl groups is substituted in the nuclear carbon and the other in the side-chain methyl carbon.

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75. Yoshihisa Mizuno, Kikuo Adachi, and Kaname Nakamura: Benzothiazoles. XII[1]. Studies on Reaction between 2-Chlorobenzothiazoles and Compounds possessing Reactive Methylene Groups.

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It has been well established that diethyl malonate readily reacts with alkyl halides in the presence of sodium, sodium amide, or sodium triphenylmethylate to give alkylated diethyl malonate, and this reaction is called malonic ester synthesis. It is also well known that the halogen atom at 2-position of benzothiazole is as reactive as that of saturated aliphatic halide toward nucleophilic reagents such as ammonia[2], sodium alkoxides[3], and piperidine[4].

It has been our main objective to examine whether or not the malonic ester synthesis could be effected in 2-chlorobenzothiazole, using it as the reactive halide. A few investigations have been made in this direction by König and Fulda[5], Doering[6], Surrey[7], Hartmann[8], Kato[9], and Nakayama[10]. Some of them reported successful results of the malonic ester synthesis, involving the nitrogenous aromatic halogen compounds chiefly using phenylacetonitrile as the reactive methylene compound. No reports, however, have been found dealing with the reaction involving 2-halobenzothiazoles, showing that it would be worth to try the malonic ester synthesis involving them.

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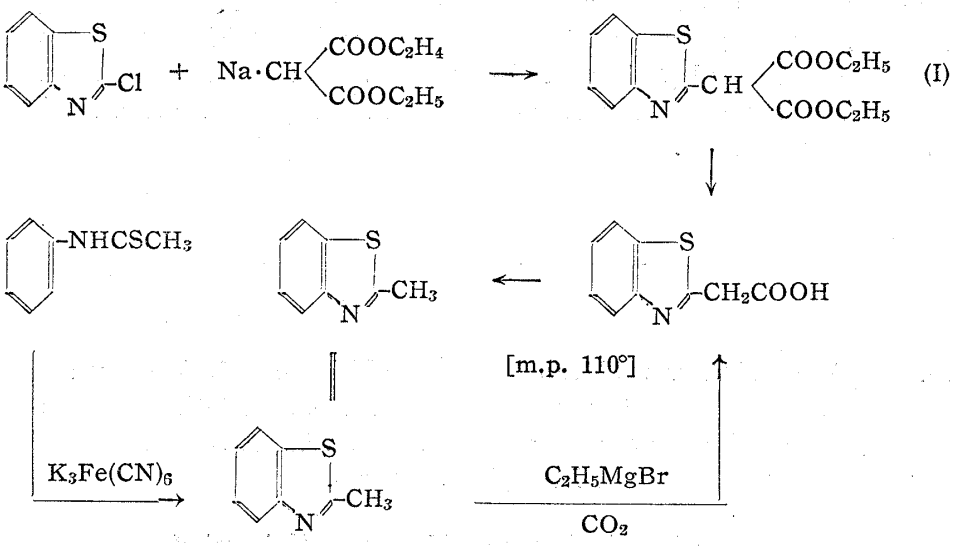
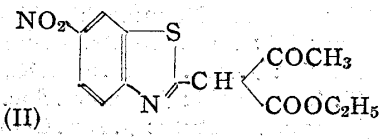
In the present paper, we report the successful synthesis of 2-diethylmalonylbenzothiazoles.

According to the usual procedure of malonic ester synthesis, sodium diethyl malonate was prepared and it was heated for several hours with 2-chlorobenzothiazole at the boiling point of the solvent used. The solvent, unreacted 2-chlorobenzothiazole, and ethyl malonate were removed. On adding water to the residue, crystals of 2-diethylmalonylbenzothiazole, m.p. 148°, was obtained from a mixture of benzene and benzine. It was converted to picrate of 2-methylbenzothiazole by way of 2-benzothiazolylacetic acid[11], m.p. 110°. The mixed melting point did not depress with the picrate of a synthetic specimen prepared from thioacetanilide.



It was also found that the yield of 2-diethylmalonylbenzothiazole varied according to the reaction conditions adopted. Therefore, further experiments were carried out to find out optimal conditions to obtain a good yield of 2-diethylmalonylbenzothiazole. Effects of the solvent employed, reaction temperature, reaction time, and molar ratio of sodium malonate to 2-chlorobenzothiazole upon the yield were examined. The satisfactory experimental conditions to give a good yield of 2-malonylbenzothiazole are described in the experimental part.

In addition to experiments to determine the optimal condition, effect of substituents on the benzene moiety of 2-chlorobenzothiazole upon the yield of 2-diethylmalonylbenzothiazole was also examined. In this case, it was assumed that electron-attracting group at 6-position would favor the formation of 2-diethylmalonylbenzothiazole while electron-releasing group at the same position would hinder the formation. Unexpectedly, however, the yields in both cases did not vary. 6-Nitro- and 6-amino-2-chlorobenzothiazoles were treated with sodium diethyl malonate to form the corresponding 2-diethylmalonylbenzothiazole derivatives in yield of 16% and 34%, respectively. When 2-bromobenzothiazole in place of 2-chloro derivative, was treated with sodium diethyl malonate, the yield of 2-diethylmalonylbenzothiazole was not any better. It was found that sodium ethyl acetoacetate instead of ethyl 2-sodiomalonate reacted successfully with 2-chlorobenzothiazole to give ethyl α-(6-nitro-2-benzothiazolyl)-acetoacetate (II).



(II)

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Experimental

(1) **2-Chlorobenzothiazole**—2-Chlorobenzothiazole was prepared by a modified procedure reported in the literatures given in Footnotes (3) and (12). A mixture of 50 g. of crude 2-mercaptobenzothiazole, 80 g. of phosphorus pentachloride, and 10 cc. of phosphoryl chloride was heated on a water bath for 2 to 3 hours. Phosphorus chloride was removed from the reaction mixture under a reduced pressure (15~20 mm.). The fraction, of $b.p_{21}$ 132~134° was collected (at atmospheric pressure, b.p 248°). Yield, 36 g.

(2) **2-Bromobenzothiazole**—To a solution of 15 g. of 2-aminobenzothiazole in 100 cc. of phosphoric acid (85%) was added 40 cc. of nitric acid (d=1.4) at 5° and the solution of the nitrate of 2-aminobenzothiazole thus formed was cooled to −5° and diazotized with a solution of 7 g. of sodium nitrite in 30 cc. of water at −15°. It required 2 hours' stirring at −15°. The diazotized solution was poured into a suspension of Gatterman's copper prepared from 80 g. of hydrated cupric sulfate and 100 cc. of 48% hydrobromic acid. The resultant solution was rendered alkaline with ammonia and extracted with ether. After drying the ether solution with sodium carbonate, the ether was removed and the residue was distilled. Yield, 5.0 g. of $b.p_7$ 125°.

(3) **Preparation of 2-diethylmalonylbenzothiazole**—1) Effect of the reaction time upon the yield, employing toluene as a solvent: A mixture of 0.01 mole of 2-chlorobenzothiazole and sodium diethyl malonate, prepared from 0.01 mole of sodium and 0.01 mole of diethyl malonate was heated for 20 hours at 120°, employing toluene as a solvent. A large amount of resinous material formed and the yield was poor.

Table I
Effect of Reaction Time on Yield.

Reaction time (hrs.)	Yield(%)
3	13.6
10	16.7
20	6.6

Table II

Molar ratio of sodium malonate to 2-chlorobenzothiazole	Yield (%)
1.0	23.9
2.5	20.2
5.0	57.0

2.) Effect of molar ratio of sodium diethyl malonate to 2-chlorobenzothiazole upon the yield, employing benzene or toluene: A similar condition was adopted in this case, except that benzene was used as a solvent. The molar ratio of sodium diethyl malonate to 2-chlorobenzothiazle was varied from 1 to 5. When toluene was used as a solvent, the molar ratio of sodium diethyl malonate to 2-chlorobenzothiazole was 5 to 1 and the mixture was heated for 10 hours, and the product was obtained in 11% yield, with the formation of a large amount of resinous material of unknown structure. These experiments have shown that toluene was not so satisfactory a solvent.

(4) **Optimal condition of synthesis of (I)**—To a solution of 10 cc. of diethyl malonate in 200 cc. of benzene was added 1.0 g. of metallic sodium and the solution was heated on a water bath for about 3 hours or until the sodium was completely dissolved. To this solution was added a solution of 1.7 g. (0.01 mole) of 2-chlorobenzothiazole in 10 cc. of benzene and the mixture was heated on a water bath for 20 hours, while sodium chloride separated. Benzene and diethyl malonate were removed from the reaction mixture but 2-chlorobenzothiazole was not recovered. On adding water to the residue an oily substance separated and solidfied on standing. It was collected by filtration and recrystallized from a mixture of benzene and benzine (b.p. 80~100°) to 1 g. of colorless needles, m.p. 148°. Yield, 57%. *Anal.* Calcd. for $C_{14}H_{15}O_4NS$: N, 4.78. Found: N, 4.96.

(5) **Preparation of 2-methylbenzothiazole from 2-diethylmalonylbenzothiazole**—A mixture of 1.0 g. of 2-diethylmalonylbenzothiazole in 5 cc. of hydrochloric acid (1: 1) was refluxed for 30 minutes on direct flame. After cooling, some crystals separated on the addition of water to the mixture. The crystals melted at 95° under decomposition and weighed 0.3 g. The filtrate was extracted with chloroform, the chloroform was removed, and the residue was converted to its picrate of m.p. 154°, which did not depress on admixture with a synthetic specimen prepared from thioacetanilide. The product of m.p. 95~110°(decomp.) was dissolved in a solution of sodium bicarbonate under evolution of carbon dioxide. On trying to crystallize it from methanol, it was converted into 2-methylbenzothiazole. Even on standing at room temperature it was converted into 2-methylbenzothiazole.

(6) **2-Diethylmalonyl-6-nitrobenzothiazole**—A mixture of 2 g. of diethyl malonate, 0.28 g. of metallic sodium, and 200 cc. of toluene was heated until the sodium was completely dissolved. To this was added 2.0 g. of 6-nitro 2-chlorobenzothiazole and heated for 2 hours at the boiling point of toluene. The toluene was removed and water was added to the residue. An amorphous substance of reddish brown color separated. It was recrystallized from acetone several times to needle crystals, m.p. 215~217°. It weighed 0.5 g. (16%). *Anal.* Calcd. for $C_{14}H_{14}O_6N_2S$: C, 49.70; H, 4.14. Found: C, 49.39; H, 4.51.

(7) **2-Diethylmalonyl-6-aminobenzothiazole**—A solution of sodium diethyl malonate, prepared from 2.0 g. of diethyl malonate and 0.15 g. of sodium in 50 cc. of xylene was heated with 0.9 g. of 2-chloro-6-aminobenzothiazole at the boiling point of xylene for 2 hours. An oily substance separated on adding water to the solution, and was extracted with a large amount of ether. After drying with sodium carbonate, ether was removed, and the residue was recrystallized from a mixture of benzene and benzine(b.p. 80~100°). It melted at 136° and weighed 0.5 g. (34%). *Anal.* Calcd. for $C_{14}H_{16}O_4N_2S$: N, 9.09. Found: N, 9.28.

(8) **Reaction between 2-chloro-6-nitrobenzothiazole and ethyl acetoacetate**—A solution of sodium ethyl acetoacetate, prepared from 2.0 g. of ethyl acetoacetate and 0.3 g. of sodium in 200 cc. of toluene, was heated with 2.0 g. of 6-nitro-2-chlorobenzothiazole for 1 hour at 100°. Toluene was removed and on adding water to the residue an amorphous substance separated. After air-drying it weighed 2.6 g. It was recrystallized from glacial acetic acid to afford a yellow amorphous substance and weighed 2.0 g. Yield, 70%. *Anal.* Calcd. for $C_{13}H_{12}O_5N_2S$: C, 49.60; H, 3.89; N, 9.09. Found: C, 49. 73; H, 4.03; N, 8.80.

(9) 2-Bromobenzothiazole was employed instead of 2-chlorobenzothiazole. The procedures similar to the case of 2-chlorobenzothiazole were carried out.

Summary

Malonic ester synthesis and related reactions in heterogenous aromatic series were carried out, involving 2-halobenzothiazole, diethyl malonate, and ethyl acetoacetate from which following new compounds were prepared. 2-Diethylmalonylbenzothiazole, m.p. 148°, ethyl α-(6-nitro-2-benzothiazolyl)-acetoacetate, m.p. 215~217°(decomp.), and 6-amino-2-diethylmalonylbenzothiazole, m.p. 211°.

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76. Takeo Ueda, Isao Nakata, and Shin-ya Ito: Studies on Electrolytic Reduction of Streptomycin.

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Dihydrostreptomycin has been prepared by hydrogenation of streptomycin, especially by means of catalytic reduction[1]. Although several methods of reduction with chemical reducing agents have been proposed, none has been taken up for the preparation of dihydrostreptomycin[2]. In view of the importance of this drug, we were prompted to try another method, *viz.*, electrolytic reduction of streptomycin. Though a similar method has already been published in the patent proposed by E. R. Squibb & Sons[3], the methods described there were somewhat ambiguous and some differences were observed between the claims made therein and the results obtained by us. This paper describes the important factors found for the electrolytic reducion of streptomycin.

Streptomycin is considered structurally as a kind of a glycoside, and therefore, its reduction might be referred to that of aldose, since dihydrostreptomycin is obtained by the reduction of the formyl group in the streptose portion of streptomycin to alcoholic group. On electrolytic reduction of aldoses, it has been shown by many authors[4] that aldoses should be electrolyzed in alkaline catholyte to increase molecules susceptible to reduction, and with cathode possessing higher hydrogen overvoltage to approach the vulger reduction potential of aldose to the electrode potential.

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