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Stability of Thiabenzenes[1]

It has been reported the instability of 1,2,4,6-tetraphenylthiabenzene (**1**) would be considerably due to the steric hindrance by the bulky of 2- and 6-phenyl groups, in contrast to the lesser hindrance in other S-arylthiabenzenes by Price and his coworkers.[2] However, in this communication, we found that the stability of thiabenzenes is effected not only by the steric hindrance of the substituents but rather by the electronic structure of those molecules during the course of the studies on the application of thiabenzene derivatives to medicinal chemistry.[1]

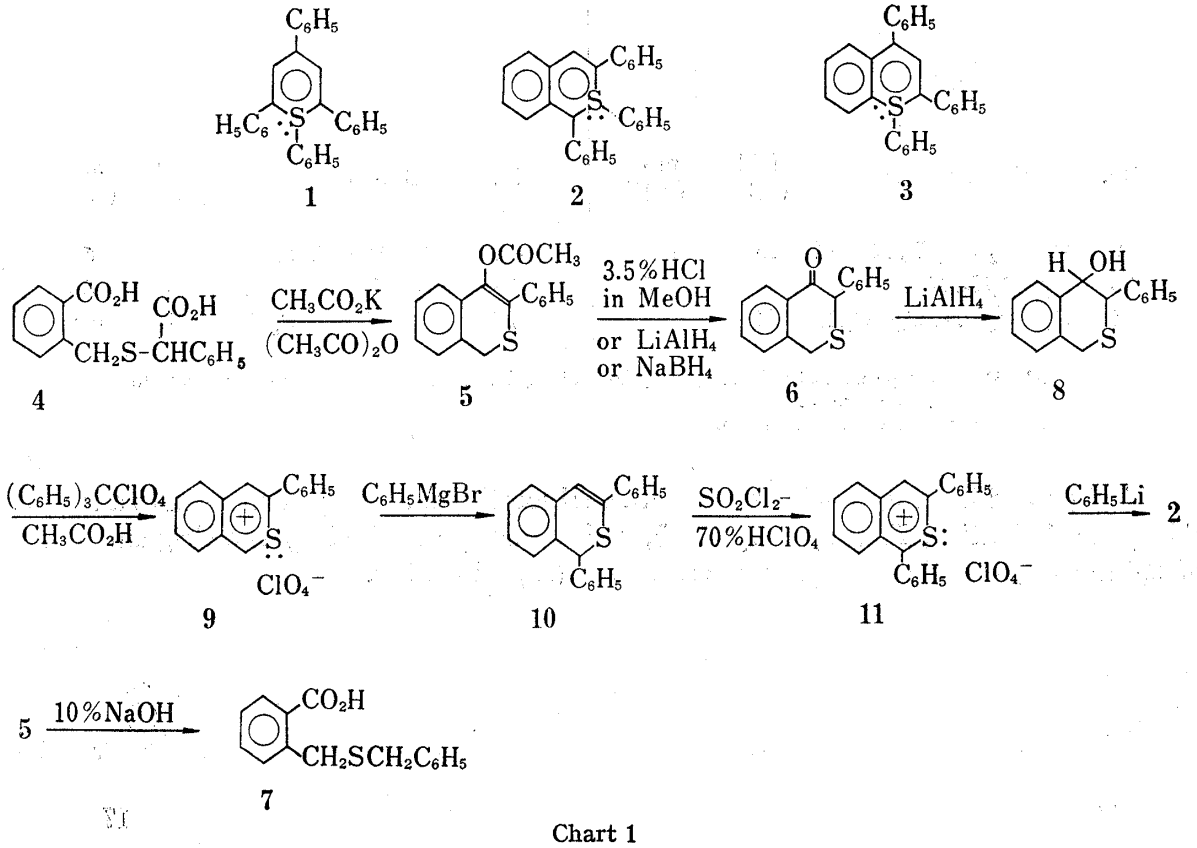


Chart 1

1) M. Hori, T. Kataoka, H. Shimizu, and S. Yoshimura, *Yakugaku Zasshi*, submitted.
2) *a*) G. Suld and C.C. Price, *J. Am. Chem. Soc.*, **83**, 1770 (1961); *idem, ibid.*, **84**, 2090, 2094 (1962); *b*) C.C. Price, M. Hori, T. Parasaran, and M. Polk, *ibid.*, **85**, 2278 (1963); *c*) M. Polk, M. Siskin and C.C. Price, *ibid.*, **91**, 1206 (1969).

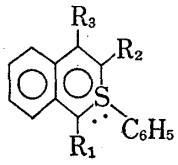
This paper deals with the synthesis of 1,2,3-triphenyl-2-thianaphthalene (**2**), 1,2,4-triphenyl-1-thianaphthalene (**3**), and their related compounds, and further with the stability of thiabenzenes.

(*o*-Carboxybenzylthio)mandelic acid (**4**)[3] was cyclized by treatment with $(CH_3CO)_2O$ and anhydrous CH_3CO_2K to the isothiochromene derivative, **5** (57%, mp 98°) and then hydrolyzed with 3.5% HCl in MeOH to give the isothiochromanone derivative, **6** (71%, mp 72°). Reduction of **5** with $NaBH_4$ in MeOH or with $LiAlH_4$ in ether, yielded also **6** in 71% or 76%, respectively. However, **5** was saponified with 10% NaOH to form (*o*-benzylthiomethyl)-benzoic acid, **7** (77%, mp 110°). Reduction of **6** with $LiAlH_4$ in ether gave the corresponding isothiochromanol, **8** (97%, mp 95°), which was converted to 3-phenyl-2-thianaphthylium perchlorate, **9** (53%, mp 200° (decomp.)) by treatment with trityl perchlorate in CH_3CO_2H. After Grignard reaction of **9** in ether, product, **10** (65%, mp 80°) was further treated with SO_2Cl_2–70% $HClO_4$ to derive 1,3-diphenyl-2-thianaphthylium perchlorate, **11** (60%, mp 232° (decomp.)).

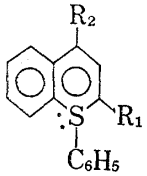
Finally, **2**, which is the same steric structure with the unstable **1**, was successfully prepared by the usual thiabenzene synthesis from **11** with phenyllithium as a very stable compound on exposure to air at room temperature.

On the other hand, many stable S-arylthiabenzenes as shown in Table I was also synthesized in usual way except **3**.

Table I. 2-Thianaphthalene and 1-Thianaphthalene Derivatives[a]



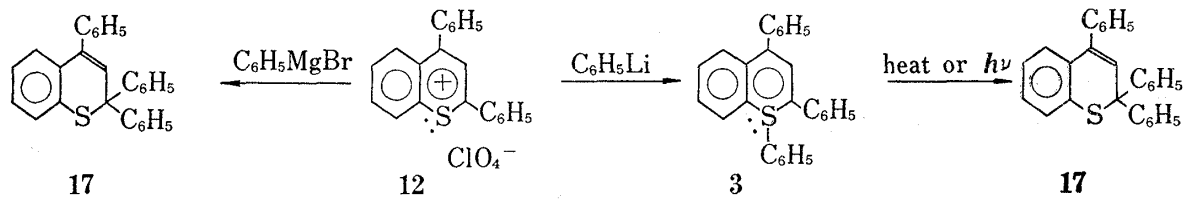
No.	Substituents	Yield (%)	mp (°C)[b]
2	$R_1=R_2=C_6H_5$, $R_3=H$	73	100
13	$R_1=C_6H_5$, $R_2=R_3=H$	68	87
14	$R_1=R_2=H$, $R_3=C_6H_5$	54	90



No.	Substituents	Yield (%)	mp (°C)[b]
3	$R_1=R_2=C_6H_5$	85	60
15	$R_1=C_6H_5$, $R_2=H$	96	85
16	$R_1=H$, $R_2=C_6H_5$	65	104

a) All new compounds had satisfactory analytical and IR, UV, NMR and Mass spectroscopic data to support the assignment.
b) Were melted with decomposition.

To light and heating, **3** in benzene or ethereal solution was easily isomerized to an isomeric thiopyran derivative, **17** (83%, mp 186°), which was synthesized by the Grignard reaction of 2,4-diphenyl-1-thianaphthylium perchlorate (**12**)[4] in ether.



17 **12** **3** **17**

Chart 2

3) For synthesis of **4** and mechanism for the formation of **7**: M. Hori, T. Kataoka, and H. Shimizu, the 90th Annual Meeting of the Pharmaceutical Society of Japan, 1968, Abstracts of Papers, p. 96.
4) A. Lüttringhaus, N. Engelhard, and A. Kolb, *Ann.*, **654**, 189 (1962).

In connection with synthesis of extremely unstable S-alkylthiabenzenes,[5] further studies on the electronic structure and stability of thiabenzenes are now in progress.

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5) A.G. Hortmann and R.L. Harris have recognized the generation of an unstable 1-methyl-3,5-diphenyl thiabenzene by the treatment of 1-methyl-3,5-diphenyl-2*H*-thiinium tetrafluoroborate with *t*-butyllithium in DMSO-d_6 in a standard NMR tube under nitrogen stream but were not able to isolate it (*J. Am. Chem. Soc.*, **92**, 1803 (1970)).

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Ultra-microdetermination of Amino Acids by Microbioassay, Applying Lactic Acid Assay with Lactate Dehydrogenase[1]

A new ultra-micro microbioassay method proposed in this paper was proved to be approximately 300 times as sensitive as the conventional method for glycine. The principle of Hohorst's analytical method[2] was applied to this method, which assays the lactic acid produced during the growth of lactic acid bacteria with the aid of lactate dehydrogenase (LDH) [L-lactate: NAD oxidoreductase, EC 1.1.1.27] from rabbit muscle.

In order to compare the assayable range of the conventional titrimetry,[3] which assays the lactic acid resulted from the growth of the bacteria, with that of our method (hereinafter referred to as the LDH method), the growth response of *Leuconostoc mesenteroides* p-60 to various concentration of glycine were determined as shown in Fig. 1.

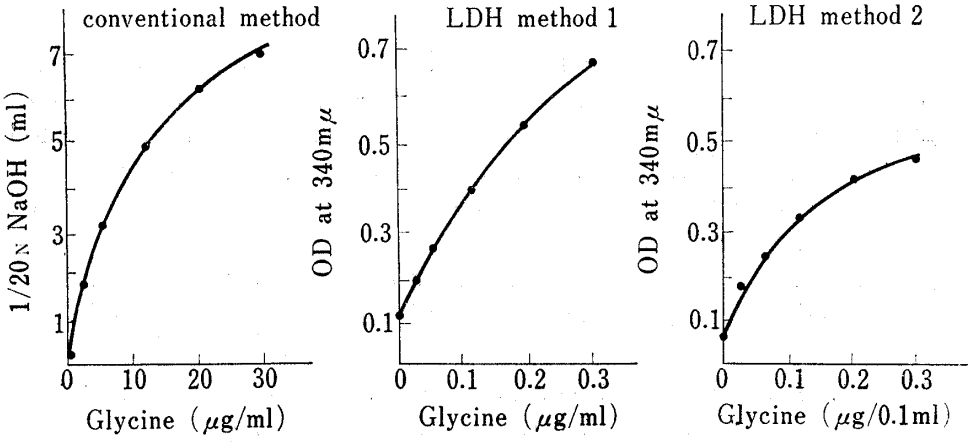

Fig. 1. Growth Responses of *Leuconostoc mesenteroides* p-60 to Various Concentrations of Glycine as Determined by the Conventional Method, LDH Method 1 and LDH Method 2

1) This work was presented at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974.
2) H.-J. Hohorst, "Method of Enzymatic Analysis," ed. by H-U. Bergmeyer, Academic Press, London/New York, 1963, p. 378.
3) G. Tamura, T. Tsunoda, J. Kirimura, and S. Miyazawa, *Nippon Nogeikagaku Kaishi*, **26**, 464 (1952).