The disulfide obtained by the both methods was identical by the mixed melting point determination and the comparison of the IR spectrum.

1,1'-Dibenzyl-3,3',5,5'-tetramethyl-4,4'-dithiodipyrazole (XVc)——By the method a) described for the synthesis of 1,1'-bis(*p*-nitrophenyl)-3,3',5,5'-tetramethyl-4,4'-dithiodipyrazole (XVb), colorless prisms were obtained in 77% yield, m.p. 104~105°. *Anal.* Calcd. for $C_{24}H_{26}N_4S_2$: C, 66.32; H, 6.03; N, 12.89. Found : C, 66.67; H, 6.24; N, 12.92.

General Method for Synthesis of 4-Carbamoylthiopyrazoles——To 5~10 times quantity of 90% H_2SO_4 was added 4-thiocyanatopyrazoles and the mixture was kept at 10° for 48 hr. The mixture was poured into ice-water and neutralized with 5% aq. NaOH. The separated solid was recrystallized from the solvent shown in Table VI.

Isomerization to Isothiocyanato Derivatives——Attempts were made to isomerize 1-(*p*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole (XIVb) to the isothiocyanato derivative under several conditions. Conditions employed were (1) refluxed for 10 hr. in toluene, (2) 180~190° for 10 hr. in toluene, (3) 170~180° for 10 hr. in toluene in the presence of anhyd. $ZnCl_2$, (4) 170~180° for 10 hr. in EtOH. In all cases the compound was recovered unchanged.

The authors express their deep gratitude to Dr. S. Kuwada, ex-Director of these Laboratories, for his encouragement and to Dr. T. Matsukawa for his helpful advice.

Thanks are also due to Dr. Y. Asahi for his aid in interpretation of the NMR spectra, to Mr. M. Kan for elemental analyses and to Messrs. T. Shima and H. Nakamachi and Miss T. Hiratsuka for optical measurement.

Summary

During the course of our synthetic approach to find out antifungal agents, new thiocyanatopyrazoles were synthesized by the direct thiocyanation reaction.

Some of the reactions of thiocyanatopyrazoles were also described.

(Received August 20, 1963)

Chem. Pharm. Bull. 12 (1) 33 ~ 40

UDC 547.841.64.07

6. Masao Tomita and Shin-ichi Ueda : Studies on the Dibenzo-*p*-dioxin (Diphenylene Dioxide) Derivatives. XXXVIII.[*1] The Color Reaction of Dibenzo-*p*-dioxin Derivatives in Concentrated Sulfuric Acid with Oxidizing Agents. The Detection by Electron Spin Resonance Spectra.[*2]

(*Faculty of Pharmaceutical Sciences, Kyoto University*[*3])

Tomita[1] discovered that all substances possessing a dibenzo-*p*-dioxin skeleton (I) gave blue to bluish green coloration in concentrated sulfuric acid with an oxidizing agent such as potassium nitrate, concentrated nitric acid, potassium bichromate, potassium permanganate, ferric chloride, potassium chlorate, manganese dioxide or hydrogen peroxide. This color reaction can be utilized for qualitative identification of dibenzo-*p*-dioxin derivatives.

However, octachlorodibenzo-*p*-dioxin (XIX) and octabromodibenzo-*p*-dioxin (XX) prepared by the present authors and a coworker[2] do not undergo this color reaction. In

---

[*1] Part XXXVII. S. Ueda : Yakugaku Zasshi, **83**, 805 (1963).

[*2] Preliminary communication : Tetrahedron Letters, No. 18, 1189 (1963).

[*3] Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 上田伸一).

1) M. Tomita : Yakugaku Zasshi, **52**. 889 (1932); *Ibid.*, **54**, 891 (1934).

2) M. Tomita, S. Ueda, M. Narisada : *Ibid.*, **79**, 186 (1959).

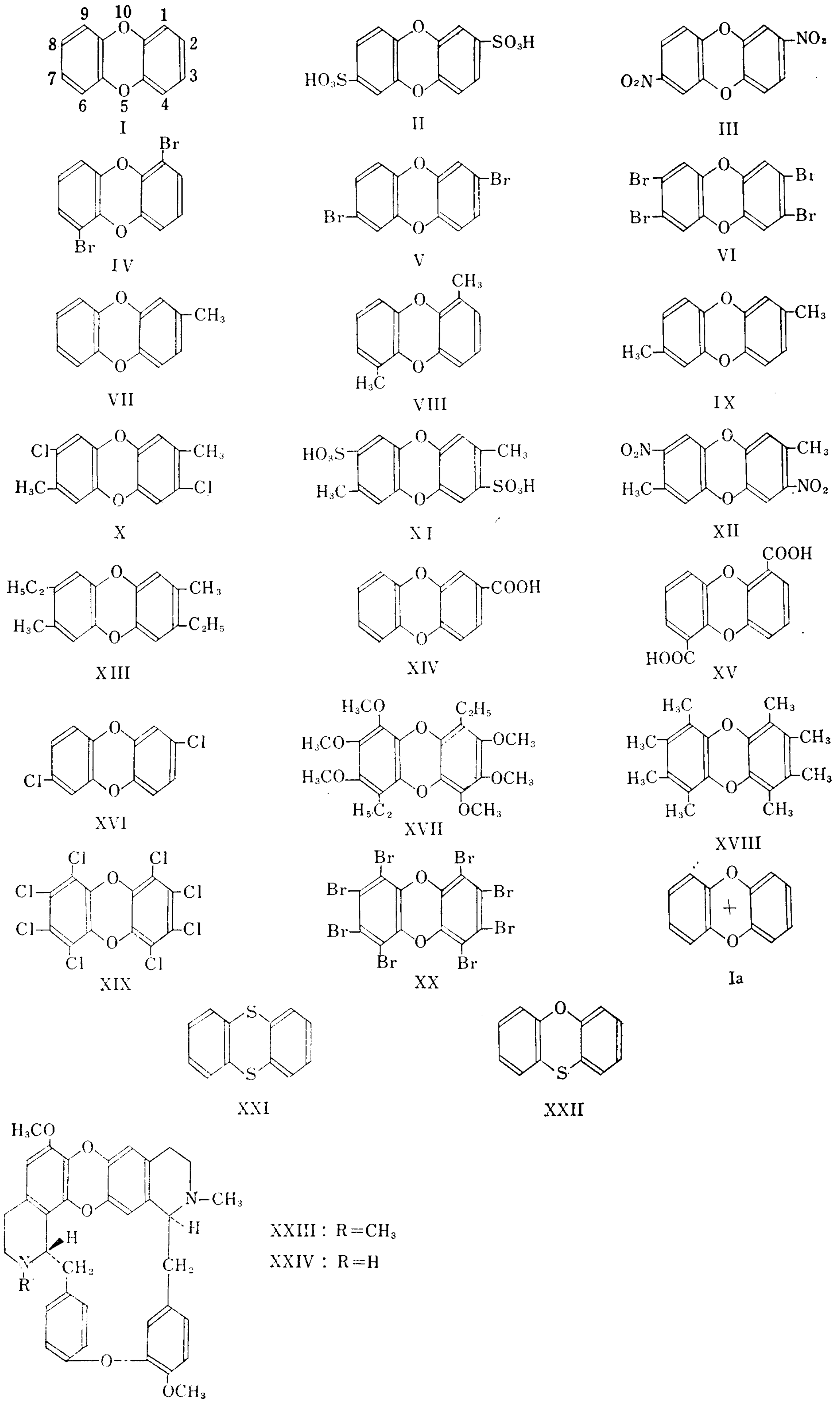
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
XVI
XVII
XVIII
XIX
XX
Ia
XXI
XXII
XXIII : R=CH₃
XXIV : R=H

Chart 1.

order to examine whether this failure is due to the insolubility of the octahalogeno derivatives in concentrated sulfuric acid or to the fact that these compounds can not take any quinoid form by substitution of all the hydrogens in the benzene ring for halogen atoms, 4,9-diethyl-1,2,3,6,7,8-hexamethoxydibenzo-*p*-dioxin (XVII)[3] and octamethyldibenzo-*p*-dioxin (XVIII)[4] were prepared.

Of these compounds, octamethyldibenzo-*p*-dioxin (XVIII) colored blue in concentrated sulfuric acid with potassium nitrate, but the compound (XVII) colored violet in this reaction, contrary to the usual dibenzo-*p*-dioxin coloration of blue, bluish green, or green.

Consequently, in the dibenzo-*p*-dioxin reaction, the quinoid formation was not considered since octamethyldibenzo-*p*-dioxin (XVIII) which could not take any quinoid form also gave the positive dibenzo-*p*-dioxin color reaction.

This color reaction was instantaneous and could be reversed by addition of water. For example, 1,6-dibromodibenzo-*p*-dioxin (IV)[2] gave blue color in concentrated sulfuric acid with potassium nitrate, then recovered quantitatively on pouring into ice water.[5] This coloring also took place in oxidizing, strong acidic media such as antimony pentachloride, fuming nitric acid, or trichloroacetic acid tegether with an usual oxidizing agent such as potassium nitrate.

From these results, the formation of the cation radicals such as Ia was expected, and an electron spin resonance (ESR) study seemed to reveal the reaction mechanism.

Therefore, the electron spin resonance spectra of dibenzo-*p*-dioxin derivatives in concentrated sulfuric acid with or without addition of potassium nitrate were measured. The spectrum of dibenzo-*p*-dioxin (I) in concentrated sulfuric acid consisted of five lines with the intensity ratios of 1:4:6:4:1, indicating a coupling of an unpaired electron spin with a set of four equivalent hydrogen nuclei in either 1,4,6,9- or 2,3,7,8-positions respectively. The g-value was 2.0044. The spectrum of thianthrene (XXI)[6] also gave five distinct lines with the intensity ratio 1:4:6:4:1, the g-value was 2.0080, whereas phenoxathiin (XXII) with less molecular symmetry gave considerably complex hyperfine structure contributed probably by all protons in the molecule. The electron spin resonance spectrum of dibenzo-*p*-dioxin in concentrated sulfuric acid with potassium nitrate also gave five lines but the spectrum changed gradually and sometimes showed the similar spectrum with that of 2,7-dinitrodibenzo-*p*-dioxin (III)[7] and finally the color disappeared. This colorless solution already gave no electron spin resonance absorption.

Dibenzo-*p*-dioxin-2,7-disulfonic acid (II)[8] in concentrated sulfuric acid gave no color and no electron spin resonance absorption. After the addition of potassium nitrate into the sulfuric acid solution, it colored blue and gave three-line spectrum in exactly 1:2:1 intensity ratios. In this case, when the air was removed from the sample solution, the color disappeared quickly.

2,3,7,8-Tetrabromodibenzo-*p*-dioxin (VI) in concentrated sulfuric acid with potassium nitrate gave only one band spectrum. Only in this case, the g-value was remarkably shifted up to 2.0135.

Therefore, there must be a strong contribution from 3,8-protons to give the major pattern of the spectrum of II and it was inferred that the contribution of 2,3,7,8-protons predominated over that of 1,4,6,9-protons in the case of I.

---

3) M. Tomita, S. Ueda : Yakugaku Zasshi, **81**, 724 (1961).
4) S. Ueda : *Ibid.*, **83**, 805 (1963).
5) *Idem* : *Ibid.*, **83**, 657 (1963).
6) H. Shine, L. Piette : J. Am. Chem. Soc., **84**, 4798 (1962); E. A. C. Lucken : J. Chem. Soc., **1962**, 4936.
7) M. Tomita : Yakugaku Zasshi, **55**, 1060 (1935).
8) M. Tomita, S. Ueda : *Ibid.*, **80**, 796 (1960).

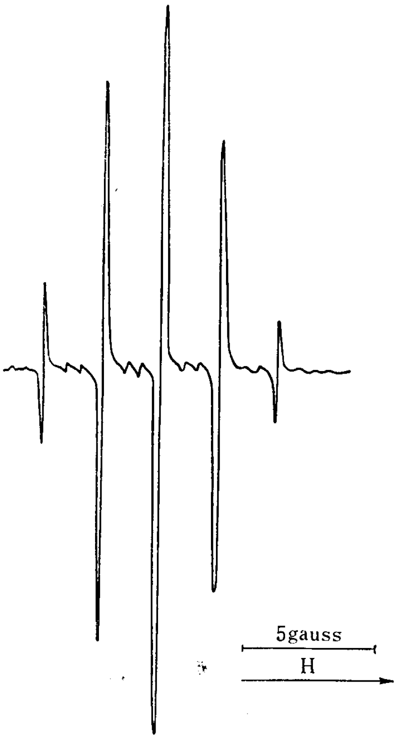

Fig. 1. Electron Spin Resonance Spectrum of Dibenzo-*p*-dioxin (I) in conc. Sulfuric Acid

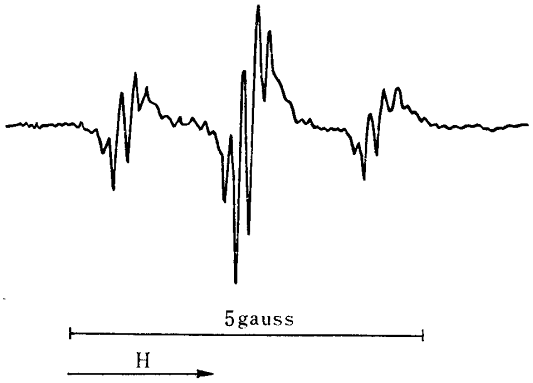

Fig. 2. Electron Spin Resonance Spectrum of Dibenzo-*p*-dioxin-2,7-disulfonic Acid (II) in conc. Sulfuric Acid with Potassium Nitrate

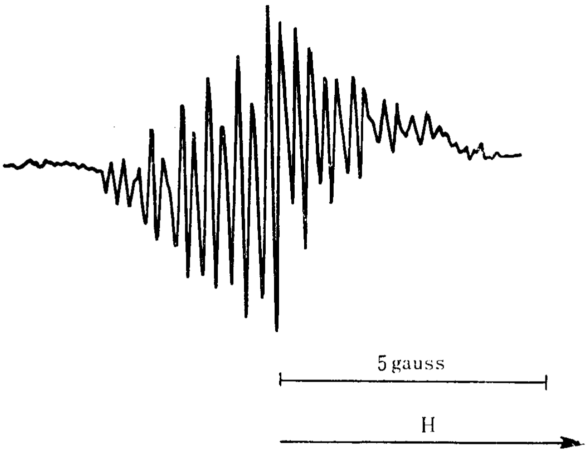

Fig. 3. Electron Spin Resonance Spectrum of 2,7-Dinitrodibenzo-*p*-dioxin (III) in conc. Sulfuric Acid with Potassium Nitrate

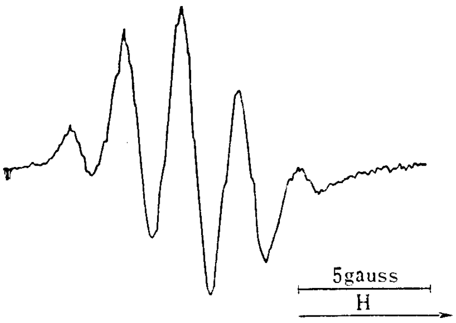

Fig. 4. Electron Spin Resonance Spectrum of Thianthrene (XXI) in conc. Sulfuric Acid

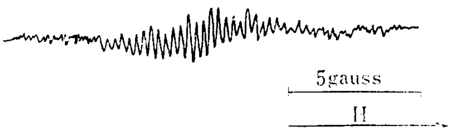

Fig. 5. Electron Spin Resonance Spectrum of Phenoxathiin (XXII) in conc. Sulfuric Acid

Fig. 6. Electron Spin Resonance Spectrum of 2,3,7,8-Tetrabromodibenzo-*p*-dioxin (VI) in conc. Sulfuric Acid with Potassium Nitrate

Fig. 7. Electron Spin Resonance Spectrum of 2,7-Dimethyl-3,8-dichlorodibenzo-*p*-dioxin (X) in conc. Sulfuric Acid with Potassium Nitrate

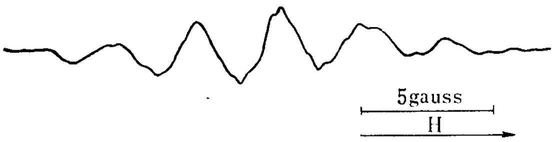

Fig. 8. Electron Spin Resonance Spectrum of 4,9-Diethyl-1,2,3,6,7,8-hexamethoxydibenzo-*p*-dioxin (XVII) in conc. Sulfuric Acid with Potassium Nitrate

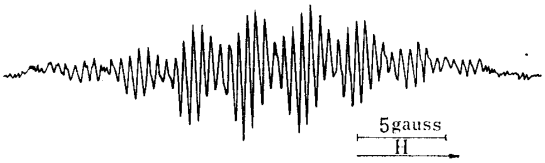

Fig. 9. Electron Spin Resonance Spectrum of Octamethyldibenzo-*p*-dioxin (XVIII) in conc. Sulfuric Acid

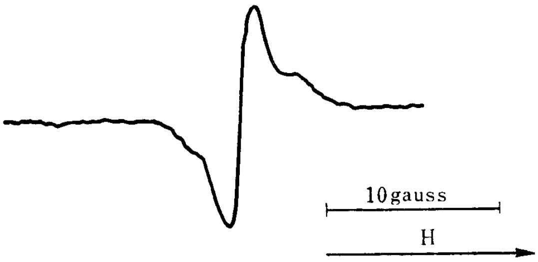

Fig. 10. Electron Spin Resonance Spectrum of 2,7-Dichlorodibenzo-*p*-dioxin (XVI) in conc. Sulfuric Acid with Potassium Nitrate

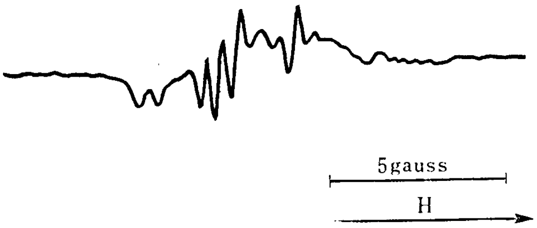

Fig. 11. Electron Spin Resonance Spectrum of 1,6-Dibromodibenzo-*p*-dioxin (IV) in conc. Sulfuric Acid with Potassium Nitrate

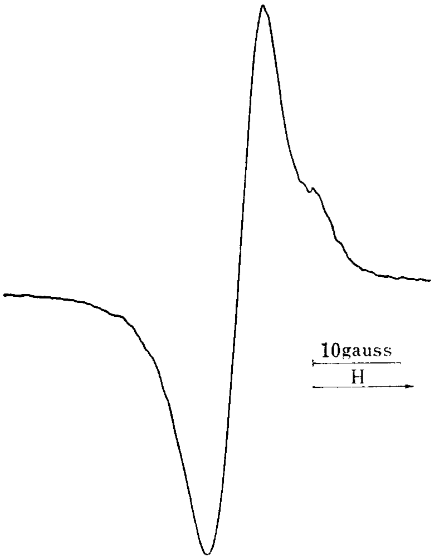

Fig. 12. Electron Spin Resonance Spectrum of 2,7-Dibromodibenzo-*p*-dioxin (V) in conc. Sulfuric Acid with Potassium Nitrate

Fig. 13. Electron Spin Resonance Spectrum of 2-Methyldibenzo-*p*-dioxin (VII) in conc. Sulfuric Acid with Potassium Nitrate

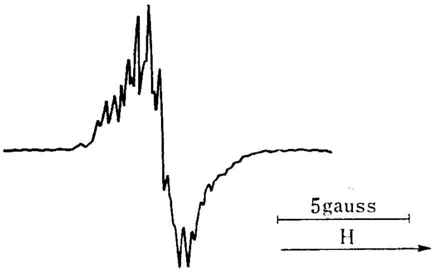

Fig. 14. Electron Spin Resonance Spectrum of Dibenzo-*p*-dioxin-2-carboxylic Acid (XIV) in conc. Sulfuric Acid with Potassium Nitrate

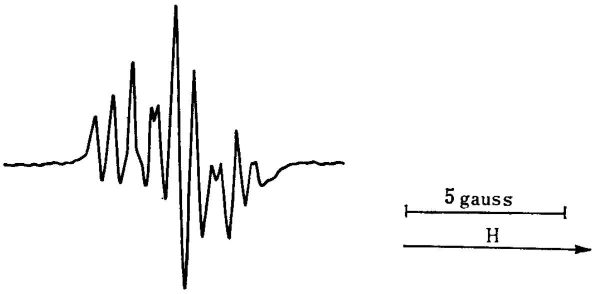

Fig. 15. Electron Spin Resonance Spectrum of 1,6-Dimethyldibenzo-*p*-dioxin (VIII) in conc. Sulfuric Acid with Potassium Nitrate

Fig. 16. Electron Spin Resonance Spectrum of Dibenzo-*p*-dioxin-1,6-dicarboxylic Acid (XV) in conc. Sulfuric Acid with Potassium Nitrate

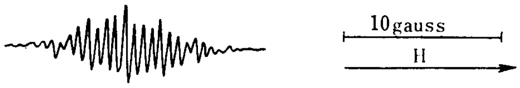

Fig. 17. Electron Spin Resonance Spectrum of 2,7-Dimethyldibenzo-*p*-dioxin (IX) in conc. Sulfuric Acid with Potassium Nitrate

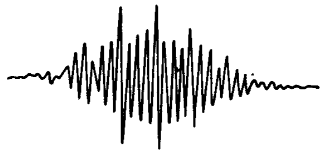

Fig. 18. Electron Spin Resonance Spectrum of 2,7-Dimethyl-3,8-dinitrodibenzo-*p*-dioxin (XII) in conc. Sulfuric Acid with Potassium Nitrate

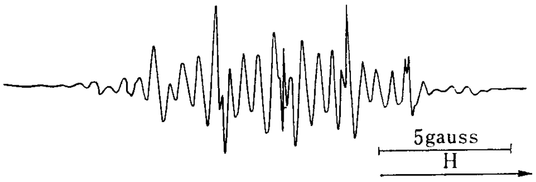

Fig. 19. Electron Spin Resonance Spectrum of 2,7-Dimethyldibenzo-*p*-dioxin-3,8-disulfonic Acid (XI) in conc. Sulfuric Acid with Potassium Nitrate

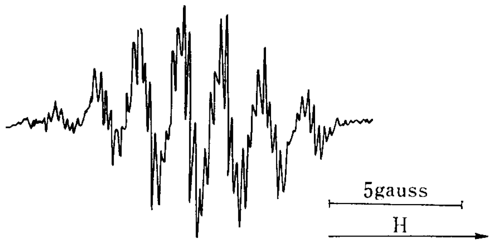

Fig. 20. Electron Spin Resonance Spectrum of 2,7-Dimethyl-3,8-diethyldibenzo-*p*-dioxin(XIII) in conc. Sulfuric Acid with Potassium Nitrate

Fig. 21. Electron Spin Resonance Spectrum of Trilobine (XXIV) in conc. Sulfuric Acid with Potassium Nitrate

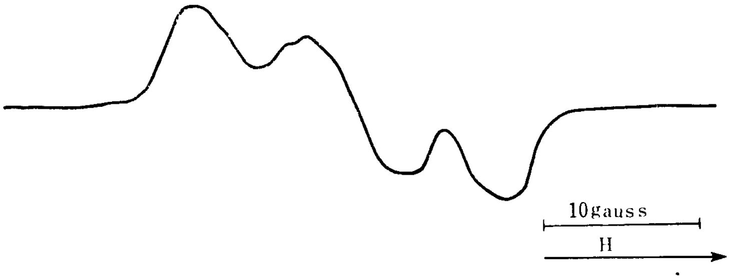

Fig. 22. Electron Spin Resonance Spectrum of Isotrilobine (XXIII) in conc. Sulfuric Acid with Potassium Nitrate

2,7-Dimethyldibenzo-*p*-dioxin (IX)[9] in concentrated sulfuric acid with potassium nitrate gave the same spectrum as that of 2,7-dimethyl-3,8-dinitrodibenzo-*p*-dioxin (XII)[10] under the same condition. This observation was supported by the fact that 2,7-dimethyldibenzo-*p*-dioxin (IX) was easily converted into 2,7-dimethyl-3,8-dinitrodibenzo-*p*-dioxin (XII) by treatment with sulfuric-nitric acid mixture.[5]

2,7-Dimethyl-3,8-dichlorodibenzo-*p*-dioxin (X)[10] gave seven line spectrum whose intensity ratios were about 1:6:15:20:15:6:1. Therefore, in this case, there must have been a contribution from six protons of two methyl groups.

1,6-Dibromodibenzo-*p*-dioxin (IV),[2] 2,7-dibromodibenzo-*p*-dioxin (V),[2] 2-methyldibenzo-*p*-dioxin (VII),[11] 1,6-dimethyldibenzo-*p*-dioxin (VIII),[12] 2,7-dimethyldibenzo-*p*-dioxin-3,8-disulfonic acid (XI),[8] 2,7-dimethyl-3,8-diethyldibenzo-*p*-dioxin (XIII),[13] dibenzo-*p*-dioxin-2-carboxylic acid (XIV),[14] dibenzo-*p*-dioxin-1,6-dicarboxylic acid (XV),[12] 2,7-dichlorodibenzo-*p*-dioxin (XVI),[2,15] 4,9-diethyl-1,2,3,6,7,8-hexamethoxydibenzo-*p*-dioxin (XVII) and octamethyldibenzo-*p*-dioxin (XVIII) in concentrated sulfuric acid with potassium nitrate all gave the electron spin resonance spectra. Among them, the concentrated sulfuric acid solution of octamethyldibenzo-*p*-dioxin (XVIII) gave blue color and electron spin resonance absorption without addition of potassium nitrate.

Trilobine (XXIV) and isotrilobine (XXIII),[16] the alkaloids of Menispermaceous plants, contain a dibenzo-*p*-dioxin skeleton and also gave the dibenzo-*p*-dioxin reaction. Each of them has a similar structure and gave a similar electron spin resonance spectrum in concentrated sulfuric acid with potassium nitrate. The g-values were 2.0033.

Furthermore, the ultraviolet and visible absortion spectra of dibenzo-*p*-dioxin (I) in sulfuric acid was measured. Dibenzo-*p*-dioxin (I) in concentrated sulfuric acid gave maximum absorptions at 240, 300, and 655 mμ and minimum absorptions at 215 and 260 mμ. After the addition of potassium nitrate to the concentrated sulfuric acid solution of I, the blue color was deepened. It gave maximum absorptions at 263 and 655 mμ and minimum absorption at 252 mμ. Therefore, it is possible to conclude that the blue color of dibenzo-*p*-dioxin color reaction originates from the absorption at 655 mμ.

Experimental

Electron Spin Resonance Spectra——A JES-3B-spectrometer (Japan Electron Optics Laboratory Co., Ltd.) was used with 100 Kc. field modulation. In all spectra, the field sweep increased in the same rate from left to right on the figures and a modulation amplitude of 0.1 gauss. An aqueous solution of potassium peroxylamine disulfonate[17] was used as a standard of the magnetic field and the g-value.

Ultraviolet and Visible Absorption Spectra——A Cary Model 15 recording spectrometer was used.

The authors wish to express their deep gratitude to Prof. H. Takaki, Dr. Y. Deguchi, and Mr. Y. Nakai, Faculty of Science, Kyoto University and Prof. K. Fukui, Faculty of Engineering, Kyoto University, for their kind guidance throughout the course of this investigation.

They are also indebted to Dr. S. Numa, Faculty of Medicine, Kyoto University, for the ultraviolet and visible absorption spectra measurement.

---

9) M. Tomita : Yakugaku Zasshi, **52**, 900 (1932).
10) M. Tomita, S. Ueda : *Ibid.*, **80**, 353 (1960).
11) M. Tomita : *Ibid.*, **56**, 814 (1936).
12) S. Ueda : *Ibid.*, **82**, 714 (1962).
13) C. Tani : *Ibid.*, **62**, 481 (1942).
14) M. Tomita : *Ibid.*, **57**, 609 (1937).
15) S. Uyeo : Bull. Chem. Soc. Japan, **16**, 177 (1941).
16) H. Kondo, M. Tomita : Ann., **497**, 104 (1932); M. Tomita, C. Tani : Yakugaku Zasshi, **62**, 468, 481 (1942); M. Tomita, Y. Inubushi, M. Kozuka : This Bulletin, **1**, 360, 368 (1953); M. Tomita, Y. Inubushi : *Ibid.*, **2**, 6 (1954); Y. Inubushi : *Ibid.*, **2**, 1, 11, 215 (1954); Y. Inubushi, K. Nomura, M. Miyawaki : Yakugaku Zasshi, **83**, 282 (1963); Y. Inubushi, K. Nomura : *Ibid.*, **83**, 288 (1963).
17) G.E. Pake, J. Townsend, S.I. Weissman : Phys. Rev., **85**, 682 (1952).

Summary

Compounds having a skeleton of dibenzo-*p*-dioxin (I) show a characteristic color (mostly blue or greenish blue and sometimes violet) in concentrated sulfuric acid with an oxidizing agent such as potassium nitrate. A series of electron spin resonance studies have revealed that the coloring was due to the formation of the cation radicals such as Ia.

(Received August 27, 1963)

[Chem. Pharm. Bull. 12 (1) 40～42]

UDC 547.841.64 : 543.422.25[539.124.143]

7. **Masao Tomita and Shin-ichi Ueda**: Studies on the Dibenzo-*p*-dioxin (Diphenylene Dioxide) Derivatives. XXXIX.*[1] Electron Spin Resonance Absorption Spectra of Dibenzo-*p*-dioxin Derivatives in Antimony Pentachloride.

(*Faculty of Pharmaceutical Sciences, Kyoto University**[2])

In the previous paper*[1] the authors reported that the blue colored sulfuric acid solutions of dibenzo-*p*-dioxin (I) derivatives always gave electron spin resonance (ESR) absorption spectra and the coloring was due to the formation of cation radicals such as Ia.

Dibenzo-*p*-dioxin derivatives in antimony pentachloride also gave a blue color and, therefore, the formation of the cation radicals was expected.

In order to confirm the existence of the cation radicals, the electron spin resonance spectra of dibenzo-*p*-dioxin derivatives in antimony pentachloride were measured.

Dibenzo-*p*-dioxin (I) in sulfuric acid gave five-line spectrum, whereas in antimony pentachloride it gave only one band spectrum with the g-value of 2.0054.

Dibenzo-*p*-dioxin-2,7-disulfonic acid (II),[1] 1,6-dibromodibenzo-*p*-dioxin (III)[2] and 2,3,7,8-tetrabromodibenzo-*p*-dioxin (V)[2] also gave one band spectra and their g-values were about the same as those in sulfuric acid with potassium nitrate.

2,7-Dimethyldibenzo-*p*-dioxin (VI),[3] soon after the addition of antimony pentachloride, gave an asymmetric spectrum. It evidently seemed to be the spectrum of the mixture but it gradually changed and after two and a half hours at room temperature it gave a symmetric spectrum. The shape of this spectrum was a little different from that of 2,7-dimethyl-3,8-dichlorodibenzo-*p*-dioxin (VII).[4]

2,7-Dibromodibenzo-*p*-dioxin (IV)[2] in antimony pentachloride gave an asymmetric spectrum which seemed to be the spectrum of the mixture. In this case chlorination of 2,7-dibromodibenzo-*p*-dioxin (IV) must have taken place, whereas the less reactive 1,6-dibromodibenzo-*p*-dioxin (III) gave a symmetric spectrum.

---

*[1] Part XXXVIII. M. Tomita, S. Ueda: This Bulletin, **12**, 33 (1964).

*[2] Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 上田伸一).

[1] M. Tomita, S. Ueda: Yakugaku Zasshi, **80**, 796 (1960).

[2] M. Tomita, S. Ueda, M. Narisada: *Ibid.*, **79**, 186 (1959).

[3] M. Tomita: *Ibid.*, **52**, 900 (1932).

[4] M. Tomita, S. Ueda: *Ibid.*, **80**, 353 (1960).