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Studies on Sulfenamides. II.[1] Oxidation of 2- and 4′-Substituted Benzenesulfenanilides with Lead Dioxide

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2- and 4′-Substituted benzenesulfenanilidyl radicals were generated by the oxidations of benzenesulfenanilides (4′-OMe (**1a**), 4′-Me (**1b**), 4′-Cl (**1c**), 4′-H (**1d**)) and 2-nitrobenzenesulfenanilides (4′-OMe (**3a**), 4′-Me (**3b**), 4′-Cl (**3c**), 4′-H (**3d**)) with lead dioxide, and their electron spin resonance (ESR) and visible spectra were investigated. The radicals generated from **1a**, **1b**, **3a**, and **3b** in benzene were fairly stable and gave well-resolved ESR spectra, whereas those from **1c**, **1d**, **3c**, and **3d** were less stable and decomposed thoroughly in an hour. The oxidations of **1a** and **1b** in benzene gave the corresponding 2,7-disubstituted phenazines as the final products, whereas those of **1c**, **1d**, **3a**—**d** did not. The oxidations of **3a**—**d** in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$ gave the corresponding phenazines and N-(2-nitrophenylthio)acetamide (**6**). The formation of **6** was interpreted in terms of acetamidation of the sulfenylium ion.

Keywords——benzenesulfenanilides; oxidation of benzenesulfenanilides; oxidation with lead dioxide; electron spin resonance; benzenesulfenanilidyl radicals; nitrene; nitrenium ion; synthesis of phenazines; 2-nitrobenzenesulfenylium ion; acetamidation

In the previous paper[1a] we reported the results on the controlled potential electrolyses of benzenesulfenanilides (4′-OMe (**1a**), 4′-Me (**1b**), 4′-Cl (**1c**), 4′-H (**1d**)) in acetonitrile. Electrolyses of **1a**—**c** gave 2,7-dimethoxyphenazine (**2a**), 2,7-dimethylphenazine (**2b**), and 2,7-dichlorophenazine (**2c**), respectively, whereas that of **1d** did not. Intermediacy of nitrenes was suggested for the formation of the phenazines.

In order to elucidate the mechanism of the formation of the phenazines more clearly, we have now studied the oxidations of benzenesulfenanilides (**1a**—**d**) and 2-nitrobenzenesulfenanilides (4′-OMe (**3a**), 4′-Me (**3b**), 4′-Cl (**3c**), 4′-H (**3d**)) with lead dioxide both in benzene and acetonitrile. Oxidation of Benzenesulfenanilides have been attempted with various oxidizing agents.[3] However, phenazines were not identified as the products except for the reaction of NN-bis-*p*-methoxyphenylbenzenesulfenamide in liquid sulfur dioxide,[4] in which 5,10-dihydro-2,7-dimethoxy-5,10-bis-*p*-methoxyphenylphenazine was obtained in yield of 1%.

Results

Electron Spin Resonance (ESR) Studies

A benzene solution of **1** and **3** was degassed by three freeze-and-thaw cycles and then treated with PbO_2. ESR spectrum of the mixture was recorded. The radicals generated from **1a**, **1b**, **3a**, and **3b** had half-lives of several hours, whereas those from **1c**, **1d**, **3c**, and **3d** decomposed thoroughly in an hour. The coupling constants are summarized in Table I,

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[1] *a*) Part I: H. Sayo, K. Mori, A. Ueda, and T. Michida, *Chem. Pharm. Bull.* (Tokyo), **26**, 1682 (1978); *b*) Preliminary report: H. Sayo and K. Mori, *ibid.*, **25**, 1489 (1977).

[2] Location: *Ikawadani-cho, Tarumi-ku, Kobe 673, Japan.*

[3] *a*) J. Barber, Brit. Patent 550446 (1943) [*C.A.*, **38**, 1850 (1944)]; *b*) S.I. Burmistrov and V.I. Glazkov, *Zh. Obshch. Khim.*, **22**, 1862 (1952); *c*) N. Capron, R. Sasin, and G.S. Sasin, *J. Org. Chem.*, **21**, 362 (1956); *d*) Y. Miura and M. Kinoshita, *Bull. Chem. Soc. Japan*, **50**, 1142 (1977); Y. Miura, Y. Katsura, and M. Kinoshita, *Chem. Lett.*, **1977**, 409.

[4] T. Ando, M. Nojima, and N. Tokura, *J. Chem. Soc. Perkin I*, **1977**, 2227.

Table I. ESR Spectral Data of 2- and 4′-Substituted Benzenesulfenanilidyl Radicals in Benzene

Radical		Coupling constants (G)								g-Value
4′-X	2-Y[a]	A_N	$A_{2\text{-H}}$	$A_{3,5\text{-H}}$	$A_{4\text{-H}}$	$A_{6\text{-H}}$	$A_{2'\text{-H}}$	$A_{3'\text{-H}}$	$A_{4'\text{-X}}$	
OCH_3	NO_2	9.30	—	0.21	0.68	0.68	4.00	1.06	0.68	2.0050
OCH_3	H	9.50	0.60	0.20	0.625	0.60	3.85	1.10	0.65	2.0055
CH_3	NO_2	9.42	—	0.22	0.68	0.68	3.98	1.24	5.20	2.0050
CH_3	H	9.50	0.725	0.225	0.75	0.725	3.75	1.20	4.70	2.0059
Cl	NO_2	9.38	—	0.26	0.72	0.72	3.90	1.36	0.52	2.0057
Cl	H	9.40	0.775	0.30	0.80	0.775	3.65	1.275	0.325	2.0062
H	NO_2	9.48	—	0.24	0.78	0.78	3.90	1.32	4.48	2.0049
H	H	9.45	0.775	0.275	0.80	0.775	3.70	1.25	4.20	2.0061

a) No splittings have been observed from 2-nitro nitrogen.

together with g-values. The values of A_H in the aniline part are larger than those in the phenylthinyl part. The unpaired electron is, therefore, distributed mainly on the aniline part. The coupling constants of 2-nitrobenzenesulfenanilidyl radicals are nearly equal to those of the corresponding benzenesulfenanilidyl radicals. The g-values of the former radicals are somewhat smaller than those of the latter. No splittings have been observed from 2-nitro nitrogen. The small splittings observed from 4′-chlorine atoms are in disagreement with the reported results.[3d] Such a small splitting of chlorine atom was reported on the radical cation of 1,3-benzodioxoles.[5]

The benzenesulfenanilidyl radicals and 2-nitrobenzenesulfenanilidyl radicals were also generated in acetonitrile, and their ESR spectra were recorded. The radicals generated from **1a**, **1b**, **3a**, and **3b** showed poorly resolved spectra, and had half-lives of several minutes, whereas those from **1c**, **1d**, **3c**, and **3d** had half-lives of less than a minute and did not give distinct spectra. The radicals generated from **3a** and **3b** in acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride were unstable and decomposed thoroughly in a minute.

Spectrophotometric Studies

A benzene solution of **1a** (1mM, 10 ml) was deoxygenated by passage of nitrogen through the solution and then PbO_2 (25 mg) was added. The reaction mixture was stirred with a magnetic stirrer, and 0.5 ml portions of the reaction mixture were taken out at regular time intervals, filtered, and diluted 50 times with benzene. At first a visible spectrum of the filtrate showed a λ_{max} at 593 nm, which is responsible for the blue color. The absorbance at 593 nm decreased gradually during the course of the reaction with a half-life ($t_{1/2}$) of *ca.* 90 min, while new λ_{max}'s appeared at 405 and 427 nm and their absorbances increased with the reaction time. The λ_{max}'s at 405 and 427 nm indicated the presence of **2a**.[6] The oxidations of **1b** and **1c** in benzene also gave blue solutions, λ_{max} 594 ($t_{1/2}=$ *ca.* 30 min) and 606 nm ($t_{1/2}=$ *ca.* 2 min), respectively. On the other hand, a green color observed on the oxidation of **1d** was so transient that the λ_{max} could not be determined. After a day the reaction mixture of **1b** showed a new λ_{max} at 364 nm, which indicated the presence of **2b**. On the other hand, the reaction mixtures of **1c** and **1d** showed new λ_{max}'s at 458 and 454 nm, respectively, which did not correspond to those of the corresponding phenazines. Acetonitrile solutions of **1a**—**d** were also treated with PbO_2. The reaction mixtures of **1a** and **1b** showed λ_{max}'s which corresponded to those of the phenazines, respectively, whereas those of **1c** and **1d** did not.

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5) W.T. Dixon and D. Murphy, *J. Chem. Soc. Perkin II*, **1976**, 1823.
6) P. Walker and W.A. Waters, *J. Chem. Soc.*, **1962**, 1632.

Benzene solutions of **3a**—**d** were treated with PbO_2 in a similar manner as above, but the visible spectra of the reaction mixtures gave no indication of the presence of the corresponding phenazines even after a day. Acetonitrile solutions of **3a**—**d** were also treated with PbO_2, but the visible spectra of the reaction mixtures did not show λ_{max}'s which corresponded to those of the phenazines. Since the anodic oxidations of **3a**—**c** in acetonitrile, in which the anolyte becomes acidic with a progress of electrolysis, gave **2a**—**c**,[7] the effect of an acid on the oxidation was investigated. Acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride was used as solvent. The latter was added to the solution in order to reduce the water content in the solution. Although **1** decomposed immediately in the solution, **3** did not decompose in the solution within 6 hours. The ultraviolet (UV) and visible (VIS) spectra of the reaction mixtures of **3a**—**c** in the solution indicated the presence of the corresponding phenazines, whereas that of **3d** did not.

Products Studies

The results of the oxidations of **1** and **3** are summarized in Table II. Although the oxidations of **1a** and **1b** gave the corresponding phenazines as the final products, those of **1c** and **1d** did not. The rate of formation of **2b** from **1b** was much slower than that of **2a** from **1a**. The oxidations of **1a** and **1b** in acetonitrile also gave the corresponding phenazines as the final products, and the rate of formation of **2a** and **2b** was faster in acetonitrile than in benzene. Thus the oxidation of an equimolar mixture of **1a** and **1b** was carried out in acetonitrile.

TABLE II. Results of Oxidation of 2- and 4′-Substituted Benzenesulfenanilides with PbO_2

Compd. No.	Conc. (mg/ml)	Solvent	PbO_2 g	Temp. °C	Time hr	Products identified	Yield	
							mg	%
1a	116/50	C_6H_6	0.53	30	2	2,7-Dimethoxyphenazine	33.1	54.0
						Diphenyl disulfide	36.9	67.3
1b	160/74	C_6H_6	1.28	35	22	2,7-Dimethylphenazine	26.7	33.9
						Diphenyl disulfide	46.4	57.3
1c	25/10	C_6H_6	0.05	40	4	*a*)		
1d	20/10	C_6H_6	0.05	40	4	*a*)		
1a+**1b**	(187+172)/160	CH_3CN	1.00	40	15	2,7-Dimethoxyphenazine	19.7	
						2,7-Dimethylphenazine	6.4	
						2-Methoxy-7-methylphenazine	15.3	
3a	140/50	*b*)	0.25	40	0.67	2,7-Dimethoxyphenazine	27.3	44.3
						N-(2-Nitrophenylthio)acetamide	15.7	14.6
						2,2′-Dinitrodiphenyl disulfide	14.0	17.9
3b	157/60	*b*)	0.31	40	0.67	2,7-Dimethylphenazine	38.6	60.9
						N-(2-Nitrophenylthio)acetamide	15.6	12.2
						2,2′-Dinitrodiphenyl disulfide	5.5	5.9
3c	171/60	*b*)	0.31	40	0.67	2,7-Dichlorophenazine	31.1	40.7
						N-(2-Nitrophenylthio)acetamide	37.7	29.2
3d	247/100	*b*)	0.61	40	0.67	Phenazine *ca.*	1	0.5
						N-(2-Nitrophenylthio)acetamide	21.9	10.3
						2,2′-Dinitrodiphenyl disulfide	7.1	4.6

a) Products were not identified.
b) CH_3CN containing 1% CF_3COOH and 1% $(CF_3CO)_2O$.

The oxidation of **3** was carried out in acetonitrile containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride, because the formation of the phenazines was negligible in benzene and in acetonitrile. The yield of 2,2′-dinitrodiphenyl disulfide was much lower than

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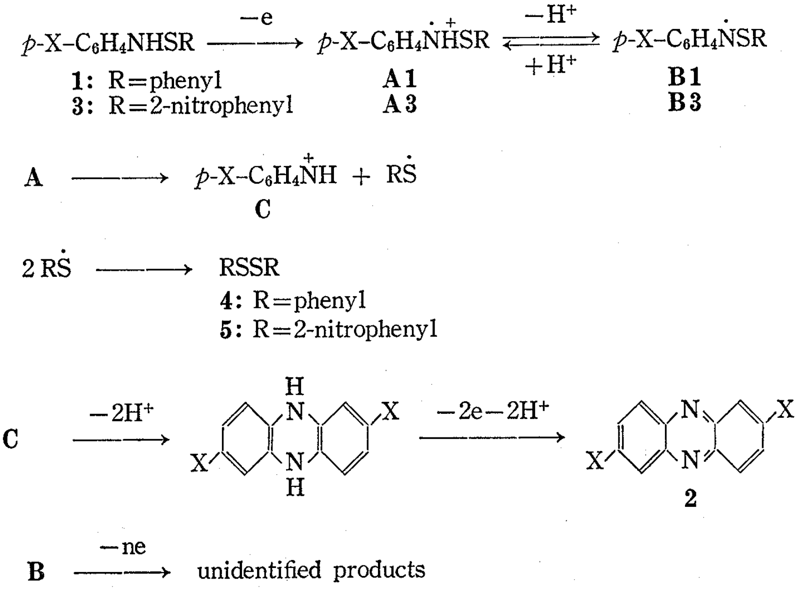
[7] H. Sayo, K. Mori, and A. Ueda, *Chem. Pharm. Bull.* (Tokyo), **25**, 525 (1977).

that of diphenyl disulfide, whereas N-(2-nitrophenylthio)acetamide was obtained from the oxidation of **3**.

Discussion

The following schemes are suggested for the oxidations of **1a** and **1b** (Chart 1). The formation of 2,7-disubstituted phenazines through intermediacy of nitrenes was reported on the pyrolysis of *p*-methoxyphenylazide in cumene[6] and on the rearrangement of azobenzenes to phenazines.[8] Since the observation of crossover products was claimed to favor the nitrene pathway in the latter reaction, the formation of 2-methoxy-7-methylphenazine on the oxidation of an equimolar mixture of **1a** and **1b** is considered to give an evidence, although not conclusive, for the nitrene pathway.



a: X=OMe, b: X=Me, c: X=Cl, d: X=H

Chart 1

As to the oxidation of **3** in acetonitrile, the effect of an acid has to be considered. The nitrogen atom of **A3** is considered to be less basic than that of **A1** because of electronegativity of 2-nitro group, and hence in the absence of CF_3COOH **A3** is immediately deprotonated and oxidized further to unidentified products. ESR experiments showed that **B3** is unstable in the presence of PbO_2. In the presence of CF_3COOH, a part of **A3** undergoes homolytic cleavage of the S–N bond, and most of **A3** are oxidized further to **D** without deprotonation,

$$\underset{R=\text{2-nitrophenyl}}{\mathbf{A3}} \xrightarrow{-e} \underset{\mathbf{D}}{p\text{-X-}C_6H_4\overset{\cdot +}{N}H\text{-}\overset{\cdot +}{S}R}$$

$$\mathbf{D} \longrightarrow \mathbf{C} + RS^+$$

$$2\mathbf{C} \xrightarrow{-2e-4H^+} \mathbf{2}$$

$$RS^+ + CH_3CN \longrightarrow RSN^+{\equiv}CCH_3 \xrightarrow{+H_2O} \underset{\mathbf{6}:\ R=\text{2-nitrophenyl}}{RSNHCOCH_3}$$

Chart 2

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8) R.A. Abramovitch and B.A. Davis, *J. Heterocycl. Chem.*, **1968**, 793.

and the S–N bond in **D** is immediately cleaved to form **C** and the sulfenylium ion. Nucleophilic attack of acetonitrile on the sulfenylium ion followed by hydrolysis yield **6** (Chart 2).

The sulfenylium ion has been suggested as a possible reaction intermediate in various electrophilic reactions.[9] Detailed kinetic analyses failed, however, to support such a mechanism. The strong evidence supporting the existence of sulfenylium ions so far available is the ionic behavior of sulfenyl chloride–Lewis acids adducts and results from conductivity, spectroscopic, and cryoscopic studies of 2,4-dinitrobenzenesulfenyl chloride in sulfuric acid solutions.[10] However, the recent study on the nuclear magnetic resonance (NMR) and conductimetric behavior of methane- and ethane-sulfenyl chloride in liquid sulfur dioxide gave no indication of the presence of sulfenylium ion.[11] Our result on the formation of N-(2-nitrophenylthio)acetamide can be considered to be a conclusive evidence for the intermediacy of sulfenylium ion. Nucleophilic attack of acetonitrile on carbonium ions was reported by Eberson and Nyberg for the anodic oxidations of pivalic acid and polymethylbenzenes in acetonitrile.[12]

The relationship between the stability of the sulfenanilidyl radicals and the formation of the phenazines is not clear at present. As to the oxidation of **3** the phenazines are formed most efficiently in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$, in which the 2,4-dinitrobenzenesulfenanilidyl radicals are most unstable. On the other hand, the oxidation of **3d**, which gives the most unstable radical, yields only a negligible amount of phenazine. Detailed studies are required on this.

Experimental

Materials——Benzenesulfenanilides were prepared as described previously.[1a] 2-Nitrobenzenesulfenanilides were prepared from 2-nitrobenzenesulfenyl chloride and the corresponding anilines by a known method.[13] Acetonitrile was purified as described previously. The purified acetonitrile contained 5—10 mM of water as determined by the method of Hogan *et al.*[14] Lead dioxide, trifluoroacetic acid, and trifluoroacetic anhydride were reagent grade chemicals and were used without further purification.

Apparatus——ESR spectra were recorded on a JES-FE 1X spectrometer, equipped with 100 kHz field modulation, at room temperature. Computer simulation of the spectrum was carried out using a JEOL EC-100 computer system. UV, IR, and NMR spectra were obtained as described previously.[1a]

Isolation of Products——Typical examples of the procedure are given below.

a) In a flask **1a** (116 mg) was dissolved in benzene (50 ml), and PbO_2 (530 mg) was added to the solution. The flask was placed in a thermobath (30°) and the mixture was stirred with a magnetic stirrer. After 2 hr the reaction mixture was filtered and the filtrate was extracted with HCl solution (10%). When the HCl solution was made slightly alkaline with NH_3 solution, yellow crystals separated out, which were collected and subjected to column chromatography on neutral alumina with benzene as eluant. The yellow crystals (30.8 mg, mp 249—250°) obtained from the first effluent were identified as **2a** from its UV, visible, IR, and NMR spectra in comparison with those of an authentic sample.[1a] The benzene layer which had been extracted with HCl solution was subjected to column chromatography on alumina with CCl_4 as eluant. The white crystals obtained from the first fraction were identified as diphenyl disulfide (**4**) (36.9 mg, mp 61—62°). After **4** was eluted completely, the eluant was changed to $CHCl_3$. The yellow crystals obtained from the effluent were identified as **2a** (2.3 mg).

b) **1a** (187 mg) and **1b** (172 mg) were dissolved in acetonitrile (160 ml) and treated with PbO_2 (997 mg) at 40°. After 15 hr the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in benzene and the benzene solution was extracted with HCl solution

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9) C.R. Russ and I.B. Douglass, "Sulphur in Organic and Inorganic Chemistry," ed. by A. Senning, Dekker, New York, 1971, Vol. 1, pp. 239—259; N. Kharasch, "Organic Sulfur Compounds," Vol. 1, ed. by N. Kharasch, Pergamon, New York, 1961, pp. 375—398.

10) *a*) S.N. Nabi and M.A. Khaleque, *J. Chem. Soc.*, **1965**, 3626; *b*) N. Kharasch, C.M. Buess, and W. King, *J. Am. Chem. Soc.*, **75**, 6023 (1953).

11) G. Capozzi, V. Lucchini, G. Modena, and F. Rivetti, *J. Chem. Soc. Perkin II*, **1975**, 361.

12) *a*) L. Eberson and K. Nyberg, *Acta Chem. Scand.*, **18**, 1567 (1964); *b*) *Idem*, *Tetrahedron Lett.*, **1966**, 2389.

13) J.H. Billman and E. O'Mahony, *J. Am. Chem. Soc.*, **61**, 2340 (1939).

14) J.M. Hogan, R.A. Engel, and H.F. Stevenson, *Anal. Chem.*, **42**, 249 (1970).

(20%). When the HCl solution was made slightly alkaline with 20% NaOH, a yellow precipitate separated out, which was collected and subjected to column chromatography on alumina with CCl_4 as eluant. The yellow crystals obtained from the effluent were subjected to preparative thin-layer chromatography on alumina with benzene as the developing solvent. Three yellow bands were obtained, and each band was scraped off and extracted with $CHCl_3$. From the top band **2b** (6.4 mg, mp 162.5—163°) was obtained. Yellow crystals obtained from the middle band was recrystallized from *n*-hexane (15.3 mg, mp 167.5—168.5°) and identified as 2-methoxy-7-methylphenazine by elemental analysis, UV, and NMR spectra. *Anal.* Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.40; N, 12.49. Found: C, 74.72; H, 5.43; N, 12.58. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 258 (97000), 352 (8380), 392 (8400), 410 (7420). NMR ($CDCl_3$) δ[15]: 2.63 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 7.35—7.75 (3H, m, aromatic protons), 7.9—8.15 (3H, m, aromatic protons). From the lowest band **2a** (19.7 mg) was obtained.

c) **3a** (140 mg) was dissolved in acetonitrile containing 1% CF_3COOH and 1% $(CF_3CO)_2O$ (50 ml) and treated with PbO_2 (250 mg) at 40°. After 40 min solid Na_2CO_3 (100 mg) was added to the reaction mixture. The mixture was filtered and the filtrate was evaporated to dryness. The residue was subjected to preparative thin-layer chromatography on alumina with $CHCl_3$–benzene (1:2) as the developing solvent. Three bands were obtained, and each band was scraped off and extracted with $CHCl_3$. 2,2'-Dinitrodiphenyl disulfide (14.0 mg) and **2a** (27.3 mg) were obtained from the top and the middle bands, respectively. From the lowest band yellow crystals (15.7 mg, mp 179—180°) were obtained and identified as N-(*o*-nitrophenylthio)acetamide (**6**) by elemental analysis, IR, NMR and Mass spectra. *Anal.* Calcd. for $C_8H_8N_2O_3S$: C, 45.25; H, 3.79; N, 13.20; S, 15.11. Found: C, 44.70; H, 3.79; N, 13.21; S, 14.98. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1660 and 1560 (CO, amide), 1560 and 1335 (NO_2), 1300 and 1240 (S–N). NMR ($CDCl_3$) δ: 2.16 (3H, s, CH_3), 7.3—7.5 (2H, m, aromatic protons), 7.65—7.9 (1H, m, aromatic proton), 8.25—8.45 (1H, m, aromatic proton), 9.68 (1H, s, NH). Mass Spectrum *m/e*: 212 (M^+). **6** was synthesized separately from 2-nitrobenzenesulfenyl chloride and acetamide, which was identical with **6** obtained from the oxidation of 3.

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15) Tetramethylsilane was used as the internal standard.