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A Kinetic Study of Cyclodehydration of β-(*p*-Toluidino)acrolein. II.[1] Sulfonation of the Aromatic Ring as a Side Reaction of Cyclodehydration in Sulfuric Acid

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Sulfonation of the benzene ring of 3-(*p*-toluidino)-1-oxo-2-propene-2-sulfonic acid (III) (6.11×10^{-5} M) in 99.4% sulfuric acid at 25° was observed by following the UV spectral change of the solution. In a 9.51×10^{-1} M solution in 99.4% sulfuric acid, however, the bulk of III remained unchanged, and on dilution with 93.8% sulfuric acid, 6-methylquinoline (II) was formed.

Sodium 4-(3-oxo-1-propenylamino)benzenesulfonate (V), sodium 4-(3-oxo-1-propenylamino)-3-methylbenzenesulfonate (VI) and sodium 2-(3-oxo-1-propenylamino)-5-methylbenzenesulfonate (VII) were synthesized in connection with this investigation.

Keywords——sulfonation; cyclodehydration; 6-methylquinoline; β-(*p*-toluidino)-acrolein; sodium 4-(3-oxo-1-propenylamino)benzenesulfonate; sodium 4-(3-oxo-1-propenylamino)-3-methylbenzenesulfonate; sodium 2-(3-oxo-1-propenylamino)-5-methylbenzenesulfonate; sodium 2-(2-formyl-3-hydroxy-5,5-diethoxy-1-pentenylamino)-5-methylbenzenesulfonate

In the preceding paper[1] we reported a kinetic study of the cyclodehydration of β-(*p*-idino)acrolein (I) in sulfuric acid to form 6-methylquinoline (II). A reversible sulfonation of form 3-(*p*-toluidino)-1-oxo-2-propene-2-sulfonic acid (III) proceeded in parallel with the odehydration (Chart 1). The kinetic examination was carried out in the range of 88.0—% sulfuric acid. No side reactions were detected except for reversible sulfonation at α-position of I during cyclodehydration to form II in all concentrations of sulfuric acid nined.

In the present paper we report an irreversible sulfonation of the aromatic ring of III that irs in dilute solutions of III in high concentrations of sulfuric acid. This reaction did take place at high concentrations of III (about 1 M), so that the aromatic ring-sulfonated product could not be isolated from the reaction solution. Evidence for the aromatic ring sulfonation of III was obtained by examination of the ultraviolet absorption (UV) spectrum of the reaction solution.

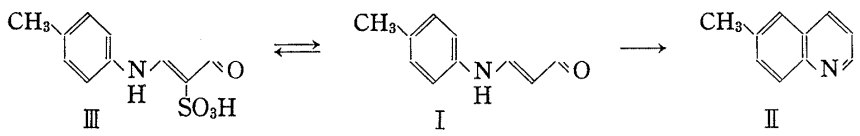

Chart 1

A 6.11×10^{-5} M solution of III in 99.4% sulfuric acid was allowed to stand for 24 hr at 25°, then diluted to 94.4% sulfuric acid by addition of 89.4% sulfuric acid. The UV spectrum of the resulting solution was measured at intervals. The optical density at 241 nm of the solution did not increase even after standing for 24 hr at 25°, suggesting that II was not formed in the solution.

1) Part I: S. Tamura, R. Imamura, and K. Ito, *Chem. Pharm. Bull.*, **26**, 930 (1978).
2) Location: *2-2-1, Miyama, Funabashi, 274, Japan.*

β-Anilinoacrolein does not undergo cyclodehydration to give quinoline but undergoes sulfonation at the *p*-position of the oxopropenylamino group in a sulfuric acid solution.[3] This means that sulfonated derivatives of β-arylaminoacrolein are resistant to cyclodehydration, and presumably III was sulfonated on the aromatic ring in dilute solution in 99.4% sulfuric acid. The synthesis of aromatic sulfo derivatives of β-arylaminoacrolein was attempted to substantiate sulfonation on the aromatic ring of III under the above-mentioned conditions.

The typical method of preparation of β-arylaminoacroleins is based on a reaction of arylamine and β-ethoxyacrolein (IV) in methanolic solution.[4] Sodium 4-(3-oxo-1-propenylamino)-benzenesulfonate (V) and sodium 4-(3-oxo-1-propenylamino)-3-methylbenzenesulfonate (VI) were prepared by the reaction of sodium sulfanilate and IV, and of sodium 3-methyl-2-aminobenzenesulfonate and IV in aqueous methanol, respectively.

The reaction of sodium 5-methyl-2-aminobenzenesulfonate and IV in aqueous methanol, however, gave a product other than the expected compound, sodium 2-(3-oxo-1-propenylamino)-5-methylbenzenesulfonate (VII). By recrystallization of the reaction product from methanol, pale yellow crystals were obtained. The results of elemental analysis were consistent with a molecular formula of $C_{15}H_{20}NO_7SNa$. The nuclear magnetic resonance (NMR) spectrum (dimethylsulfoxide-d_6) showed signals at δ 10.50 ppm (1H, NH, doublet, J=14 Hz), 9.07 ppm (1H, aldehyde, singlet), 7.67 ppm (1H, β-position, doublet, J=14 Hz), and no α-position signal was observed, suggesting that the α-position of the β-arylaminoacrolein skeleton is substituted. Signals were observed at δ 4.40—5.07 ppm (3H, multiplet), 3.23 ppm (6H, two methoxy groups, singlet), 2.25 ppm (3H, methyl group, singlet) and 1.57—2.03 ppm (2H, multiplet). The integrated intensity of the multiplet signal at δ 4.40—5.07 ppm decreased to the equivalent of 2H on addition of deuterium oxide to the solution. From the above results, the structure of this substance was estimated to be sodium 2-(2-formyl-3-hydroxy-5,5-dimethoxy-1-pentenylamino)-5-methylbenzenesulfonate (VIII). Another possible structure, sodium 2-(2-formyl-5-hydroxy-3,5-dimethoxy-1-pentenylamino)-5-methylbenzenesulfonate (IX), is not plausible because the signal of the two methoxy groups was observed as one singlet equivalent to 6H. In repeated experiments, the NMR spectrum (dimethylsulfoxide-d_6) of the product obtained under the conditions of preparation of VIII showed signals of an ethoxy group at δ 1.13 ppm (triplet, J=7 Hz) and 3.43 ppm (multiplet), suggesting that the ethoxy group of IV remains in the product. To avoid this complication, the reaction of sodium 5-methyl-2-aminobenzenesulfonate and IV was carried out in aqueous ethanol. The results of elemental analysis of the product (X) are consistent with a molecular formula of $C_{17}H_{24}NO_7SNa$, and the NMR spectrum (dimethylsulfoxide-d_6) showed a double quartet signal (4H) at δ 3.50 ppm (methylenes of two ethoxy groups) and a triplet signal (6H) at δ 1.10 ppm (methyls of two ethoxy groups.). The methylene group signal of aldehyde diethyl acetals (except for ethylal) shows a complex pattern (in many cases, it is observed as a double quartet) owing to the nonequivalence of the two protons of each methylene group.[5] The pattern of ethoxy group signals in the NMR spectrum of X suggests that a diethyl acetal group exists in X. The structure of X was, therefore, confirmed to be sodium 2-(2-formyl-3-hydroxy-5,5-diethoxy-1-pentenylamino)-5-methylbenzenesulfonate (Chart 2).

Preparation of VII was achieved by the reaction of sodium 5-methyl-2-aminobenzenesulfonate and IV in aqueous solution at room temperature. The compound VII was recovered unchanged when an ethanolic solution of VII and IV was refluxed for 5 hr. The route of formation of X in the reaction mixture of sodium 5-methyl-2-aminobenzenesulfonate and IV, therefore, remains unclear.

3) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **22**, 2982 (1974).
4) S. Tamura and E. Yabe, *Chem. Pharm. Bull.*, **21**, 2105 (1973).
5) J.S. Waugh and F.A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961); F. Kaplan and J.D. Roberts, *J. Am. Chem. Soc.*, **83**, 4666 (1961); L.S. Rattet, L. Mandell, and J.H. Goldstein, *J. Am. Chem. Soc.*, **89**, 2253 (1967).

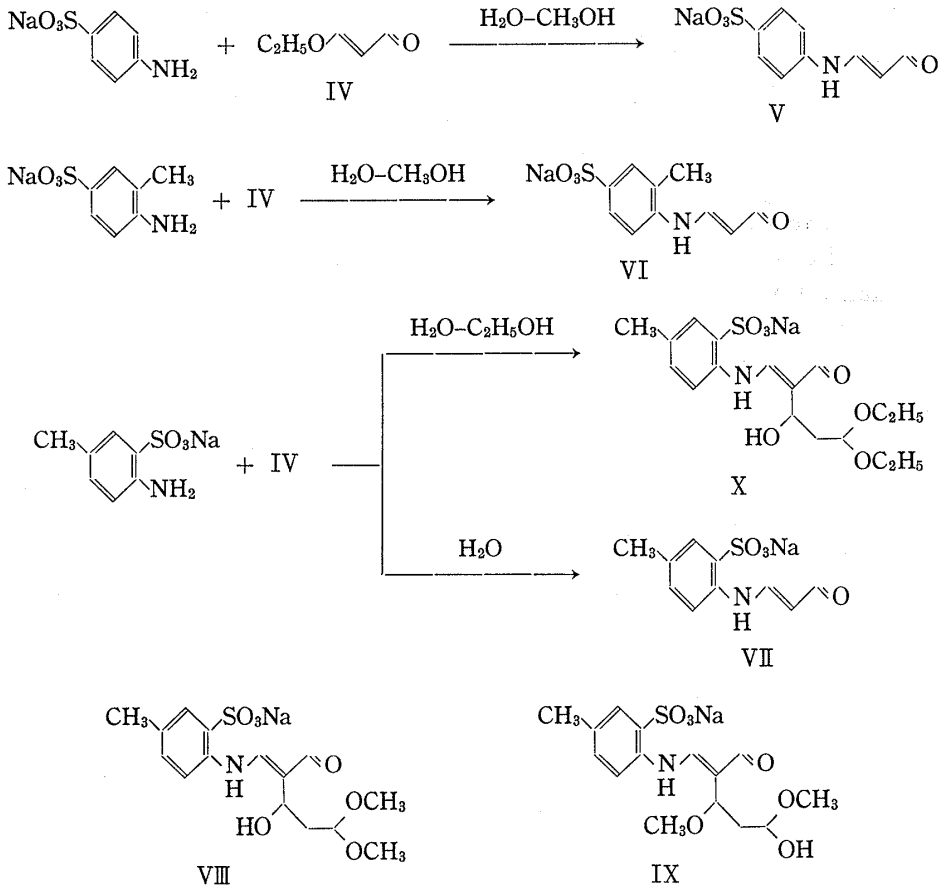

Chart 2

The NMR spectrum of VII in 82.3% sulfuric acid showed two signals of the 2-position of the oxopropenyl group at δ 7.10 ppm (triplet, J=11 Hz) and 6.69 ppm (triplet, J=11 Hz) suggesting that two conformational isomers exist in the solution. The signals of the 1- and 3-position of the oxopropenyl group were observed in the region of δ 8.8—9.4 ppm. The NMR spectrum of VII in 99.9% sulfuric acid showed signals of the 2-position of the oxopropenyl group at δ 7.00 ppm (triplet, J=11 Hz) and 6.51 ppm (triplet, J=11 Hz) and signals of the 1- and 3-position of the oxopropenyl group in the region of δ 8.6—9.3 ppm immediately after dissolution. After 2 hr, the signals of the 2-position of the oxopropenyl group disappeared and the signals of the 1- and 3-position of the oxopropenyl group shifted to the region of δ 8.9—9.7 ppm, suggesting that the 2-position was sulfonated in a manner similar to the case of I in concentrated sulfuric acid.[1] The preparation of 2-(3-oxo-2-sulfo-1-propenylamino)-5-methylbenzenesulfonic acid (XI) was achieved by allowing a solution of VII in a mixture of 99.5% sulfuric acid and 10% oleum to stand for 24 hr followed by pouring the reaction solution onto ice. The precipitate was collected and washed successively with acetic acid and ether (Chart 3).

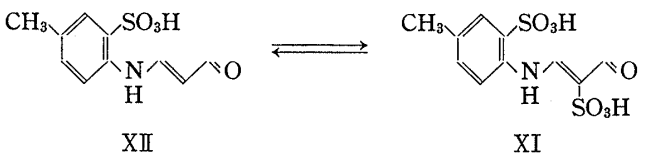

Chart 3

The NMR spectrum of XI in 82.3% sulfuric acid showed signals of the 1- and 3-position of the sulfonated oxopropenyl group in the region of δ 9.0—9.7 ppm, and no signal was observed

in the range of δ 4—8 ppm immediately after dissolution. After standing for 24 hr at 25°, the solution showed a small triplet signal (J=11 Hz) due to the 2-position of the oxopropenyl group of 2-(3-oxo-1-propenylamino)-5-methylbenzenesulfonic acid (XII) at 7.10 ppm, suggesting that the sulfo group at the 2-position of the sulfonated oxopropenyl group of XI had been partly hydrolyzed to form a small amount of XII in the solution. On heating the solution for 2 hr at 60°, the signals of the 2-position of the oxopropenyl group (δ 7.08 and 6.63 ppm) increased to reach one equivalent intensity and the signals of the 1- and 3-position shifted to the region of δ 8.8—9.4 ppm. Hydrolysis of XI to form XII is, therefore, much slower than that of III to form I in sulfuric acid of the same concentration: the latter hydrolysis was virtually complete within 24 hr at 25°.[1] The UV spectrum of XI in 82.3% sulfuric acid showed an absorption maximum at 330 nm immediately after dissolution. After standing for 67 hr at 25°, the absorption maximum shifted to 325 nm, and when the solution was heated for 2 hr at 60°, the absorption maximum shifted to 320 nm. This final pattern closely resembled that of VII in the sulfuric acid of the same concentration (Fig. 1). The minor difference between them is presumably a result of contamination by a small amount of an unkonwn impurity. This change of the UV spectrum of the solution of XI in 82.3% sulfuric acid is attributable to slow hydrolysis of XI to form XII in the solution and is consistent with the NMR spectral changes of XI in sulfuric acid of the same concentration.

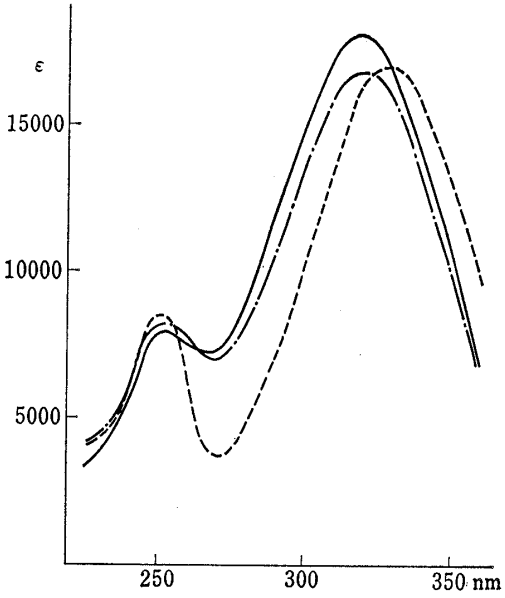

Fig. 1. UV Spectra of VII and XI in 82.3% H_2SO_4

———: VII,
– – – – – –: XI, immediately after dissolution,
———: XI, after standing for 67 hr at 25°, and heating for 2 hr at 60°.

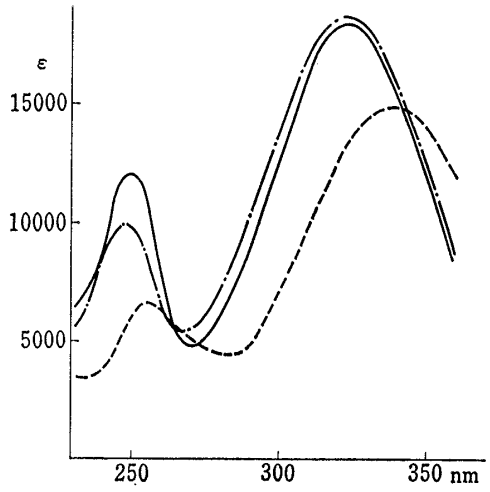

Fig. 2. UV Spectra of III, VII and XI in 99.4% H_2SO_4 Immediately after Dissolution

———: III, – – – – – –: VII, ———:XI.

The absorption maxima of the UV spectra of 99.4% sulfuric acid solutions of III, VII and XI were observed at 325, 337 and 325 nm immediately after dissolution (Fig. 2), respectively. The UV spectrum of each solution measured after standing for 24 hr at 25° showed only an absorption maximum at 325 nm (Fig. 3). The spectra closely resembled each other, suggesting that III was sulfonated at the *o*-position with respect to the sulfonated oxopropenylamino group and XII was sulfonated at the 2-position of the oxopropenyl group to give XI in either case upon standing.

As described earlier in this report, formation of II was not observed in terms of the UV spectrum of the solution when a 6.11×10^{-5} M solution of III in 99.4% sulfuric acid was allowed

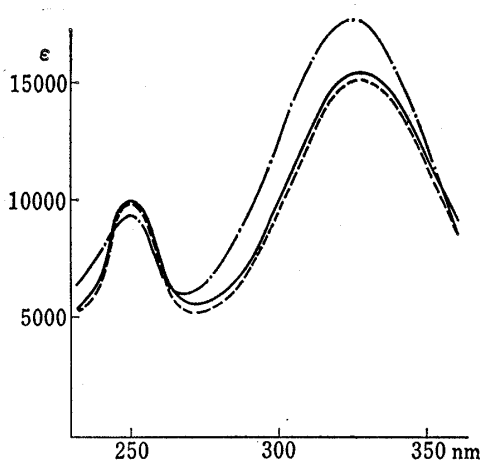

Fig. 3. UV Spectra of III, VII and XI in 99.4% H_2SO_4 at 24 hr after Dissolution

———: III, – – – – – –: VII, ———: XI.

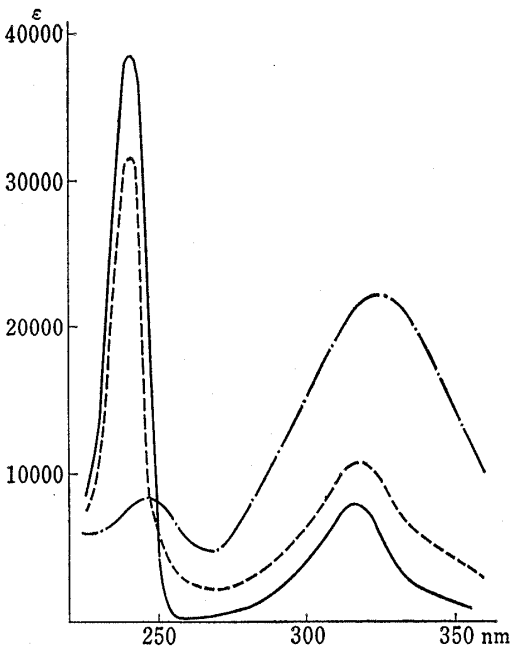

Fig. 4. UV Spectra of II in 93.8% H_2SO_4 and of the Reaction Solution of III in H_2SO_4

———: II.

– – – – – –: A 9.51×10^{-1} M solution of III in 99.4% H_2SO_4 was allowed to stand for 24 hr at 25°, and was then diluted with 93.8% H_2SO_4 to make a 4.29×10^{-5} M solution (the concentration of H_2SO_4 can be regarded as 93.8%). The solution was left to stand for a further 24 hr at 25°, then the UV spectrum was measured.

———: A 6.11×10^{-5} M solution of III in 99.4% H_2SO_4 was allowed to stand for 24 hr at 25°, and then diluted with 89.4% H_2SO_4 to 94.4% H_2SO_4 (the concentration of substrate was 3.05×10^{-5} M). The solution was left to stand for a further 24 hr at 25°, then the UV spectrum was measured.

to stand for 24 hr at 25°, and diluted to 94.4% sulfuric acid by addition of 89.4% sulfuric acid. The UV spectrum of the solution at 24 hr after dilution is shown in Fig. 4. However, when a 9.51×10^{-1} M solution of III in 99.4% sulfuric acid was allowed to stand for 24 hr at 25°, and then diluted to 4.29×10^{-5} M solution with 93.8% sulfuric acid (the concentration of sulfuric acid of the resulting solution can be regarded as 93.8%), the optical density at 241 nm of the solution gradually increased, suggesting that II was formed in the solution. The UV spectrum of the solution measured at 24 hr after dilution (Fig. 4) closely resembled that of II in sulfuric acid of the same concentration.

Thus, it was concluded that III is sulfonated at *o*-position with respect to the sulfonated oxopropenylamino group in 99.4% sulfuric acid at low concentrations of III, whereas it resists sulfonation at higher concentrations of III.

Kachurin and Mel'nikova[6] reported that addition of ammonium sulfate to aqueous sulfuric acid lowers the acidity of the latter: the H_0 value of 99.9% sulfuric acid is increased by 0.88 on addition of 1 mol of ammonium sulfate to 1 kg of sulfuric acid.

The compound III reduces the acidity of sulfuric acid when dissolved in it at high concentrations, so that sulfonation at its benzene ring dose not occur. The yield of II was nearly quantitative when I was treated with concentrated sulfuric acid.[3] This is attributable to the high concentration of I used in the preparative experiment.

Experimental

The UV spectra were measured on a Hitachi spectrophotometer, model 139, and the NMR spectra were recorded on a JNM-PMX 60 NMR spectrometer. The NMR spectra in sulfuric acid and in CD_3SOCD_3

6) O.I. Kachurin and L.P. Mel'nikova, *Izv. Vyssh. Ucheb. Zared., Khim. Khim. Tekhnol.*, **1968**, 11, 1079. [*C.A.*, **70**, 32128 (1969)].

were recorded using tetramethylsilane as an external and an internal standard, respectively. The following abbreviations are used: singlet (s), doublet (d), triplet (t), double doublet (dd), double quartet (dq) and multiplet (m).

Material——Compound I was prepared according to the previous paper.[4] The melting point of I was 122°.

Purification of III——The sodium salt of III[1] (0.40 g) was dissolved in 2.5 g of 80.0% H_2SO_4 and the solution was poured onto 2.0 g of ice under ice-cooling. The precipitate was collected and washed successively with AcOH and ether, then dried over KOH under reduced pressure to afford 0.26 g of III. mp 155° (dec.). *Anal.* Calcd for $C_{11}H_{10}NO_4S \cdot 1/2H_2O$: C, 47.99; H, 4.83; N, 5.60. Found: C, 48.12; H, 4.37; N, 5.56.

Preparation of V and of VI——A solution of 2.20 g (0.022 mol) of IV[7] in 20 ml of MeOH was added to a solution of 3.46 g (0.02 mol) of sulfanilic acid and 1.85 g (0.022 mol) of $NaHCO_3$ in 20 ml of H_2O. A clear yellow solution was initially obtained, and then a yellow crystalline mass (malonaldehyde dianil of sodium sulfanilate) precipitated from the solution. The precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH, affording 3.74 g (72.4%) of V. mp>220°. NMR (CD_3SOCD_3, δ): 9.27 ppm (1H, d, J=8 Hz, 3-position of oxopropenyl), 8.08 ppm (1H, d, J=13 Hz, 1-position of oxopropenyl) and 5.57 ppm (1H, dd, J=8, 12 Hz, 2-position of oxopropenyl). *Anal.* Calcd for $C_9H_8NNaO_4S \cdot 3/2H_2O$: C, 39.13; H, 4.01; N, 5.07. Found: C, 39.02; H, 3.53; N, 5.27.

Compound VI was obtained from 3-methyl-4-aminobenzenesulfonic acid (0.02 mol) and IV by a method similar to that used for the preparation of V. Yield, 2.43 g (43.2%). mp>220°. NMR (CD_3SOCD_3, δ): 9.20 ppm (1H, d, J=8 Hz, 3-position of oxopropenyl), 8.20 ppm (1H, d, J=12 Hz, 1-position of oxopropenyl), 5.67 ppm (1H, dd, J=8, 12 Hz, 2-position of oxopropenyl) and 2.27 ppm (3H, s, methyl). *Anal.* Calcd for $C_{10}H_{10}NNaO_4S \cdot H_2O$: C, 42.70; H, 4.30; N, 4.98. Found: C, 42.66; H, 4.34; N, 5.11.

Preparation of VII——Compound IV (4.40 g, 0.044 mol) was added to a solution of 8.23 g (0.044 mol) of 5-methyl-2-aminobenzenesulfonic acid and 4.06 g (0.048 mol) of $NaHCO_3$ in 50 ml of H_2O. A clear yellow solution was initially obtained, and then a yellow crystalline mass (malonaldehyde dianil) precipitated from the solution. The reaction mixture was allowed to stand overnight at room temperature. The precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to afford 8.68 g (72.5%) of VII. mp>290°. NMR (CD_3SOCD_3, δ): 9.98 ppm (1H, d, J=13 Hz, NH), 9.27 ppm (1H, d, J=8 Hz, 3-position of oxopropenyl), 8.08 ppm (1H, t, J=13 Hz, 1-position of oxopropenyl), 5.53 ppm (1H, dd, J=8, 13 Hz, 2-position of oxopropenyl) and 2.27 ppm (3H, s, methyl). *Anal.* Calcd for $C_{10}H_{10}NNaO_4S \cdot 1/2H_2O$: C, 44.12; H, 4.07; N, 5.14. Found: C, 44.17; H, 3.96; N, 5.05.

Preparation of X——A mixture of 5.23 g (0.025 mol) of sodium 5-methyl-2-aminobenzenesulfonate and 5.50 g (0.055 mol) of IV in 120 ml of EtOH was refluxed for 17 hr on a water bath. Undissolved starting material (2.58 g) was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH, affording 0.93 g (0.23%) of X. mp>250°. NMR (CD_3SOCD_3, δ): 10.45 ppm (1H, d, J=13 Hz, NH), 9.01 ppm (1H, s, formyl), 7.63 ppm (1H, d, J=13 Hz, 1-position of pentenyl), 4.47—5.00 ppm (3H, m, 3- and 5-position of pentenyl and OH), 3.50 ppm (4H, dq, J=2, 7 Hz, CH_2 of Et), 2.26 ppm (3H, s, methyl), 1.83 ppm (2H, m, 4-position of pentenyl) and 1.10 ppm (6H, t, J=7 Hz, CH_3 of Et). *Anal.* Calcd for $C_{17}H_{24}NNaO_7S$: C, 49.87; H, 5.91; N, 3.42. Found: C, 49.47; H, 5.80; N, 3.65.

Preparation of VIII——A mixture of 10.45 g (0.05 mol) of sodium 5-methyl-2-aminobenzenesulfonate and 5.25 g (0.0525 mol) of IV in 250 ml of MeOH was refluxed for 22 hr on a water bath. The undissolved starting material was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH to give 1.37 g of VIII. mp>300°. *Anal.* Calcd for $C_{15}H_{20}NNaO_7S$: C, 47.24; H, 5.29; N, 3.67. Found: C, 46.86; H, 5.28; N, 3.60.

Preparation of XI——Compound VII (2.72 g, 0.01 mol) was dissolved in a mixture of 12 g of 99.5% H_2SO_4 and 9 g of 10% oleum under ice-cooling, and the reaction mixture was allowed to stand for 24 hr at 25°. The reaction mixture was poured onto 9.5 g of ice under ice-cooling. The resulting mixture was allowed to stand for 1.5 hr to ensure complete precipitation. The precipitate was collected and washed successively with AcOH and ether to give 2.09 g (57%) of XI. mp 125° (dec.). *Anal.* Calcd for $C_{10}H_{11}NO_7S_2 \cdot 5/2H_2O$: C, 32.78; H, 4.40; N, 3.82. Found: C, 32.37; H, 4.02; N, 4.10.

7) S. Tamura and E. Takeda, *Chem. Pharm. Bull.*, **27**, 403 (1979).