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72. Makoto Miyazaki,* Hiroshi Watanabe,** Mieko Hashi,* and Tyunosin Ukita***: Studies on Azulenes. V.**** S-Guaiazulene-3-sulfonic Acid.

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Of the bicyclic non-benzenoid aromatic hydrocarbons, azulene is the most important, because it has considerably more stability than other possible groups of this type and it is the only known hydrocarbon of these groups which occurs in nature. Its resonance energy is considerble, though less than that of naphthalene, and so it is interesting to investigate its chemical properties especially with regard to aromatic substitution reactions.

Electrophilic substitution of azulene, such as methylation, halogenation, nitration, acetylation, diazonium coupling, and sulfonation have already been reported by Plattner,[1] Treibs,[2] and Anderson.[3] These substitutions are known to take place preferentially at 1- and 1,3-positions at which the π-electron density is the largest.

As for the sulfonation of S-guaiazulene, there has been a detailed paper reported by Treibs.[2] The sulfonated S-guaiazulene obtained by him readily coupled with both benzenediazonium chloride and diazotized sulfanilic acid under simultaneous elimination of the sulfonic acid group. These azo-S-guaiazulenes thus obtained were identified with 3-phenylazo- and 3-*p*-sulfophenylazo-S-guaiazulene, respectively, which were derived from S-guaiazulene by direct coupling of these diazonium salts.

From these observations, Treibs concluded that on sulfonation the sulfonic acid group must be introduced in the 3-position of S-guaiazulene, because, from his earlier studies, diazo coupling on azulene was proved to occur at its 1- or 3-position.

However, the results of these reactions do not exclude a possibility that the sulfonic acid group introduced into positions other than 3 was eliminated with simultaneous azo coupling at the 3-position of S-guaiazulene, because the latter is known to suffer direct azo coupling at 3-position.

This paper deals with a more detailed research for the structure of sulfonated S-guaiazulene. S-Guaiazulene-sulfonic acid was prepared from S-guaiazulene (I) by the action of sulfur trioxide complex of dioxane (D. S. reagent*****), according to the method reported by Treibs[2] and the product was isolated as its barium salt (III) in a yield of 70%. Spectra of the barium salt are shown in Figs. 1 and 2. The barium salt was further converted to benzylthiuronium salt, m.p. 153~154°, via the sodium sulfonate (IV).

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**** Part IV: J. Japan Wood Research Soc., **1**, 64(1955).
***** In order to have some informations on the sulfonation reaction of aromatic compounds with this reagent (D.S.), naphthalene and *p*-cymene were sulfonated under similar condition, and the respective products were isolated and proved to be 1-naphthalene- and *p*-cymene-2-sulfonic acid.

1) Pl. A. Plattner: Abstracts of Papers, 120th Meeting of American Chemical Society, New York, September 4, 1951.
2) W. Treibs: Die Phrmazie, **2**, 66(1952); Ann., **586**, 194, 202(1954).
3) A.G. Anderson, Jr., Jerry A. Nelson: J. Am. Chem. Soc., **72**, 3824(1950); A.G. Anderson, Jr., Jerry A. Nelson, James J. Tazuma: *Ibid.*, **75**, 4980(1953).

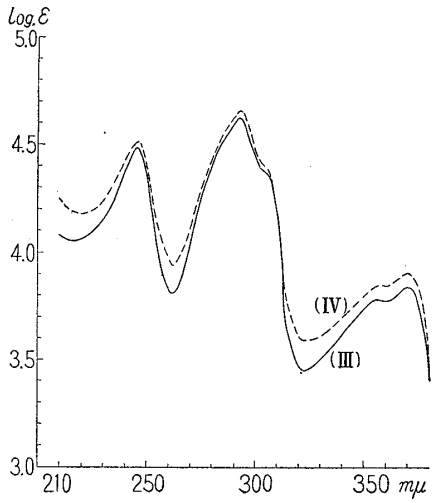


Fig. 1.
Ultraviolet Absorption Spectra of Barium S-Guaiazulene-sulfonate (III) and Sodium S-Guaiazulene-sulfonate (IV) (in H_2O)

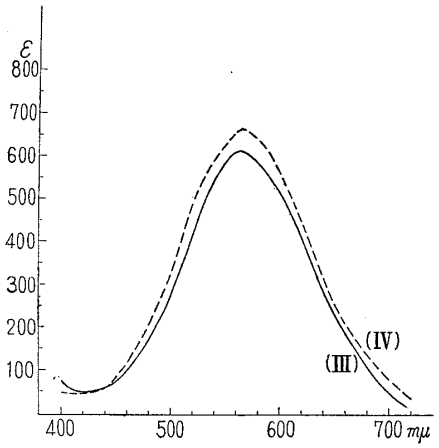
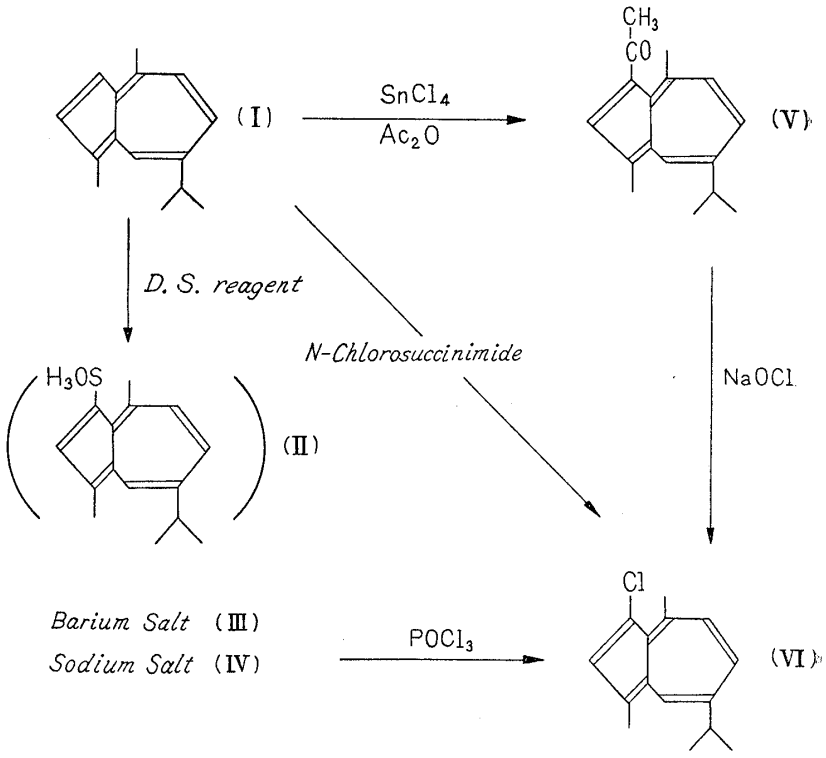


Fig. 2.
Visible Absorption Spectra of Barium S-Guaiazulene-sulfonate (III) and Sodium S-Guaiazulene-sulfonate (IV) (in H_2O)



On treatment with phosphoryl chloride (IV) gave an unstable monochloro-S-guaiazulene (VI) (trinitrobenzene complex, m.p. 123~124°), the spectra of which are shown in Figs. 3 and 4. Because S-guaiazulene (I), under the same condition and with the same reagent, did not give any chloro derivative, the conversion of (IV) to (VI) evidently did not involve S-guaiazulene as an intermediate. However, the same chloro-S-guaiazulene as (VI) was obtained from S-guaiazulene (I) by its chlorination with N-chlorosuccinimide.

Anderson[3] has already explained that N-halosuccinimide selectively attacks 1- and 3-positions of azulene to give the chlorine derivatives which exhibit a bathochromic shift of the maximum in its visible absorption spectrum by +28 mμ, for one chlorine compared with that of azulene. The spectrum of the chloro-S-guaiazulene (VI) also showed a bathochromic shift of the absorption maximum from that of the parent compound, S-guaiazulene (I), in a comparable order of magnitude (+26 mμ). Thus, the spectrometric evidence supports the possibility of the 3-position for chlorine substitution in the compound (VI).

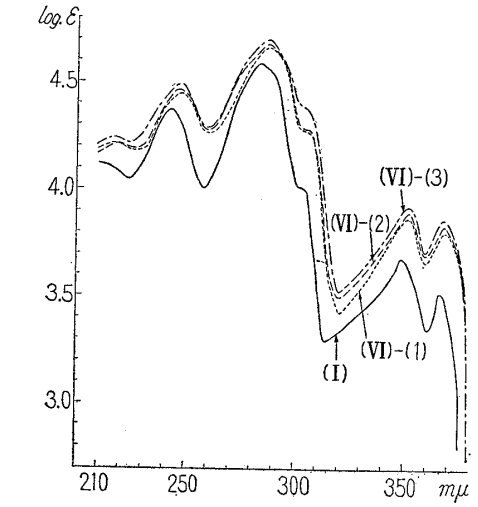


Fig. 3.
Ultraviolet Absorption Spectra of S-Guaiazulene (I) and Chlorinated S-Guaiazulenes (VI) (in EtOH)
(VI)-(1) from sodium S-guaiazulene-sulfonate with $POCl_3$
(VI)-(2) from S-guaiazulene with N-chlorosuccinimide
(VI)-(3) from 3-acetyl-S-guaiazulene with NaOCl

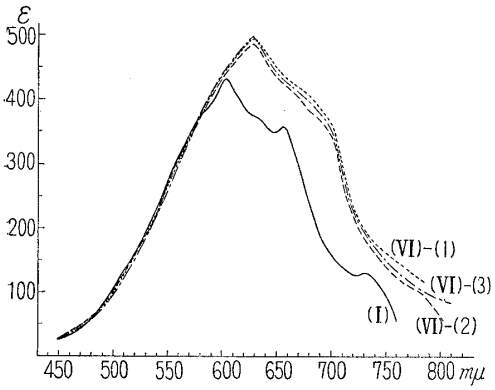


Fig. 4.
Visible Absorption Spectra of S-Guaiazulene (I) and Chlorinated S-Guaiazulenes (IV) (in ligroine)
(VI)-(1) from sodium S-guaiazulene-sulfonate with $POCl_3$
(IV)-(2) from S-guaiazulene with N-chlorosuccinimide
(VI)-(3) from 3-acetyl-S-guaiazulene with NaOCl

Further support for the position of chlorine which was substituted in (VI) was obtained from a reaction that the latter was also derived from 3-acetyl-S-guaiazulene, the structure of which had already been confirmed by us in the preceding paper of this series.[4] Thus on treatment of 3-acetyl-S-guaiazulene (V) with sodium hypochlorite, a monochloro-S-guaiazulene was formed, which was identical with the chlorinated S-guaiazulene (VI). In this case also this reagent, sodium hypochlorite, did not convert S-guaiazulene (I) into any chlorinated S-guaiazulene under the same condition. As

4) Tyunosin Ukita, Hiroshi Watanabe, Makoto Miyazaki : J. Am. Chem. Soc., **76**, 4584(1954).

shown in Figs. 3 and 4, the observed visible and ultraviolet spectra of the chlorinated S-guaiazulenes (VI) obtained by the three different routes described above were in good agreement.

Therefore, the product (VI) must be 3-chloro-S-guaiazulene. From the results of these reactions, it is concluded that the sulfonated S-guaiazulene is S-guaiazulene-3-sulfonic acid.

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Experimental

Sulfonation of S-Guaiazulene (I)—For the preparation of D.S. reagent, the procedure described by Suter[5] and Treibs[2] was applied with a slight modification, CCl_4 being used instead of ethylene chloride as a solvent and the white crystalline dioxane-SO_3 formed was removed by centrifugation. Before sulfonation, the reagent was titrated with an aq. $Ba(OH)_2$ to estimate the amount of SO_3 involved. To a solution of 1 g. of (I) in 12 cc. of CCl_4 was added dropwise the D.S. reagent until blue color disappeared under stirring and cooling with ice to below 0°. 62 cc. of the reagent, which was estimated to contain 0.837 g. of SO_3 (2 molar equivalent to 1 mole of (I) used), was required. After additional stirring for 30 mins. at 0°, the solution was poured into 200 g. of ice water and the CCl_4 layer was separated. After washing twice with petroleum ether, and addition of 20 cc. of EtOH the violet-colored solution thus obtained was neutralized by titration with saturated aq. $Ba(OH)_2$ to pH 7. $BaSO_4$ formed was removed by filtration and the filtrate was dried on a water bath at 30° to give 1.23 g. of the barium sulfonate (III) in 70.7% yield. Recrystallization of this salt from water gave blue needles, which were somewhat unstable. (III) $\lambda_{max}^{H_2O}$ mμ(log ε): 246(4.48), 293(4.63), 356(3.79), 370(3.84); and 568 mμ (ε 617.7)(Figs. 1 and 2). *Anal.* Calcd. for $C_{30}H_{34}O_6S_2Ba$: C, 52.06; H, 4.96. Found : C, 51.21; H, 5.23. To a solution of 0.6 g. of (III) in a minimum amount of hot water was added a slight excess of dil. NaOH solution. Blue precipitate of Na salt (IV) was filtered. After recrystallization from hot water, 0.42 g. of blue needles or blue plates were obtained in 80.8% yield. (IV) $\lambda_{max}^{H_2O}$ mμ (log ε) : 246(4.52), 293(4.66), 356(3.85), 370(3.91); and 568 (ε 667.5). For analysis, Na S-guaiazulene-sulfonate was dried over P_2O_5 at 128° for 2 hrs. in vacuum. *Anal.* Calcd. for $C_{15}H_{17}O_3SNa$: C, 59.98; H, 5.70. Found : C, 59.91; H, 5.67.

S-Guaiazulene-sulfonic Acid Benzylthiuronium Salt—To a solution of 50 mg. of (IV) in 5 cc. of water, 35 mg. of benzylthiuronium chloride dissolved in 3 cc. of EtOH was added and the blue violet crystals precipitated were filtered. Recrystallization from dil. EtOH gave 65 mg. of benzylthiuronium salt of S-guaiazulene-sulfonic acid as blue violet needles, m.p. 153~154°, in 87% yield. *Anal.* Calcd. for $C_{23}H_{28}O_3N_2S_2$: C, 62.16; H, 6.31; N, 6.30. Found : C, 62.17; H, 6.50; N, 6.30.

3-Chloro-S-guaiazulene (VI)—(1) From Na S-Guaiazulene-sulfonate (IV): A mixture of 850 mg. of $POCl_3$ and 70 mg. of (IV) was cooled in ice water for 50 mins. The violet color of the mixture turned to dark blue. It was poured into 100 cc. of ice water, extracted with 50 cc. of Et_2O, and washed with dil. NaOH solution and water. The ether layer was dried over Na_2SO_4 and the solvent was removed by distillation under reduced pressure in N_2 gas. The solution of the residue in petr. ether was passed through a column of activated alumina (1 i.d. × 10 cm.) and the elution was made with same solvent. 50 cc. of the first blue fraction was taken. After removal of the solvent from the fraction under reduced pressure in N_2 gas, the residue was purified by repeated chromatography using a column (0.8 i.d. ×20 cm.) of activated alumina with petr. ether. On removal of the solvent from 10 cc. of the first blue fraction by distillation under reduced pressure in N_2 gas, 18 mg. of blue oily chloro-S-guaiazulene (VI) was obtained in 33.3% yield. The product was so unstable that it gave resinous material on exposure to atmosphere. On treatment with trinitrobenzene in EtOH, it gave trinitrobenzene complex (T.N.B.) as violet needles, m.p. 123~124°. U.V. λ_{max}^{EtOH} mμ (log ε) : 248(4.46), 288(4.67), 307(4.29), 352(3.87), 369(3.82); $\lambda_{max}^{ligroine}$ 629 mμ (ε 496.1)(Figs. 3 and 4.) *Anal.* Calcd. for $C_{21}H_{20}O_6N_3Cl$: C, 56.57; H, 4.52. Found : C, 56.74; H, 4.62.

On removal of solvent from 25 cc. of the second blue fraction obtained by preliminary chromatography, 10 mg. of blue oil was obtained which gave T.N.B. as dark violet needles, m.p. 147~149°, showing no depression on mixed fusion with authentic S-guaiazulene T.N.B., m.p. 147~149°.

(2) From S-Guaiazulene with N-Chlorosuccinimide : 310 mg. of (I) was treated with 210 mg. of N-chlorosuccinimide in 30 cc. of benzene under refluxing for 45 mins. The succinimide formed was removed by filtration, the benzene layer was washed with water, and dried over Na_2SO_4. The residue obtained after removal of solvent by distillation similary as in the case of (I), was purified by repeated chromatography in the same way as above. From 60 cc. of the first blue eluate, 80 mg.

5) C.M. Suter, P.B. Evans, James M. Kiefer : J. Am. Chem. Soc., **60**, 538(1938).

of unstable blue oil was obtained in 22.0% yield. It gave the same T.N.B., m.p. 123~124°, as that obtained in (1). (VI) U.V. λ_{max}^{EtOH} mμ (log ε) : 248(4.48), 288(4.69), 307(4.30), 352(3.90), 369(3.84); $\lambda_{max}^{ligroine}$ 629 (ε 488.2)(Figs. 3 and 4). *Anal.* Calcd. for $C_{21}H_{20}O_6N_3Cl$: C, 56.57; H, 4.52. Found : C, 56.44; H, 4.36.

From 50 cc. of the second blue eluate from chromatography, 30 mg. of S-guaiazulene was recovered.

(3) From 3-Acetyl-S-guaiazulene (V) : For the preparation of 3-acetyl-S-guaiazulene (V), improved method was applied which gave better yield than that reported in earlier paper.[4] To a mixture of fused $SnCl_4$ and 65 cc. of pure Ac_2O a solution of 4.5 g. of (I) dissolved in 210 cc. of CCl_4 was added under stirring and the mixture was kept at 54~57° for 2 hrs. To the solution, 270 cc. of 2*N* HCl was added under cooling with ice at 10~20° and the mixture was shaken. The aq. solution was extracted with CCl_4 and the lower layer formed was washed with dil. Na_2CO_3 solution and water. After drying over $CaCl_2$ and removal of the solvent by distillation in N_2 gas, the residue was purified by chromatography using a column (25 i.d. × 24 cm.) of activated alumina and petr. ether as solvent. 500 cc. of blue violet effluent was taken and the solvent was removed by distillation in N_2 gas to give 3.32 g. of 3-acetyl-S-guaiazulene (V) in a 54.6% yield. Recrystallization from hydr. MeOH gave violet plates, m.p. 85~86.5°. *Anal.* Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found : C, 85.13; H, 8.45.

A solution of NaOCl was prepared from 4 g. of NaOH dissolved in 15 cc. of water containing 30 g. of ice, and 3.5 g. of Cl_2. 1.0 cc. of the solution thus prepared was added dropwise under cooling with ice and stirring to 10 cc. of aq. solution containing 1.0 g. of $MgSO_4$ which was covered with a solution of 100 mg. of (V) dissolved in 5 cc. of Et_2O. After stirring the mixture for 2 mins., Et_2O layer was separated and chromatographed through a column (2 i.d. × 15 cm.) of activated alumina using petr. ether as eluting solvent. 30 cc. of the first blue fraction was treated in the same way as in the case of (1) and rechromatographed. On removal of solvent from 13 cc. of first blue fraction, a few mg. of unstable blue oil was obtained. It gave T.N.B. complex as dark violet needles, m.p. 123~124°, which showed no depression on mixed fusion with that of chloro-S-guaiazulene obtained in experiments (1) and (2). U.V. λ_{max}^{EtOH} mμ (log ε) : 248(4.50), 288(4.71), 305(4.38), 352(3.93), 369(3.87); $\lambda_{max}^{ligroin}$ 629 (ε 497.0) (Figs. 3 and 4). *Anal.* Calcd. for $C_{21}H_{20}O_6N_3Cl$: C, 56.57; H, 4.52. Found : C, 56.41; H, 4.27.

Treatment of S-Guaiazulene (I) with Phosphoryl Chloride—A mixture of 50 mg. of (I) and 600 mg. of $POCl_3$ was kept cooling in an ice-water bath for 50 mins., during which the blue color of the solution did not change, the mixture was poured into 100 cc. of ice-water, extracted with 50 cc. of Et_2O, and washed with dil. NaOH solution and water. Et_2O layer, after drying over Na_2SO_4, was passed through an activated alumina column (1 i.d. × 20 cm.) and the column was eluted with petr. ether. Removal of solvent from 50 cc. of the only blue effluent gave 37 mg. of blue oil, which showed negative Beilstein's halogen test. It gave T.N.B. as dark violet needles, m.p. 148~149°, which showed no depression on mixed fusion with T.N.B. of S-guaiazulene, m.p. 147~149°.

Treatment of S-Guaiazulene (I) with Sodium Hypochlorite—100 mg. of (I) was treated with the same reagent described in (3) under the same condition. After the reaction was over, Et_2O layer was chromatographed through a column (2 i.d. × 15 cm.) of activated alumina using petr. ether as the eluting solvent. 30 cc. of the blue fraction was distilled under reduced pressure in N_2 gas to give 85 mg. of blue oil, which showed negative Beilstein's halogen test.

Summary

S-Guaiazulene-sulfonic acid (II), prepared from S-guaiazulene (I) by treatment with sulfur trioxide-dioxane complex was converted into the sodium salt. Treatment of the sodium salt (IV) with phosphoryl chloride gave a monochloro-S-guaiazulene (VI). The same chloro derivative was obtained from 3-acetyl-S-guaiazulene (V) with sodium hypochlorite. However, these chlorination conditions did not give any chloro derivative when applied to S-guaiazulene (I). The chloro derivative thus obtained was identified with a product obtainable from S-guaiazulene (I) by its treatment with N-chlorosuccinimide.

Since the structure of 3-acetyl-S-guaiazulene (V) had been confirmed in the preceding paper of this series and as the two chlorination reactions which gave the chloro derivative from the two substituted S-guaiazulenes, (II) and (V), did not give the former directly from S-guaiazulene, it is concluded that the chloro derivative produced from (II) and (V) is 3-chloro-S-guaiazulene and the sulfonated S-guaiazulene (II) is S-guaiazulene-3-sulfonic acid.

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