Summary

3-(1-Hydroxyethyl)-S-guaiazulene (III) was prepared by reduction of 3-acetyl-S-guaiazulene (II) with lithium aluminum hydride. (III) was converted into 3-vinyl-S-guaiazulene (IV) by dehydration and further into 3-ethyl-S-guaiazulene (V) by catalytic hydrogenation. An isomeric carbinol (VIII) was also produced from S-guaiazulene-3-carboxaldehyde (VI) by its treatment with methylmagnesium iodide, and (VIII) was confirmed to be 3-(1-hydroxyethyl)-S-guaiazulene by its derivation to (V). The remarkably different stability against dehydration observed between the two isomeric 3-(1-hydroxyethyl)-S-guaiazulenes (III and VIII) is discussed from the structural point of view.

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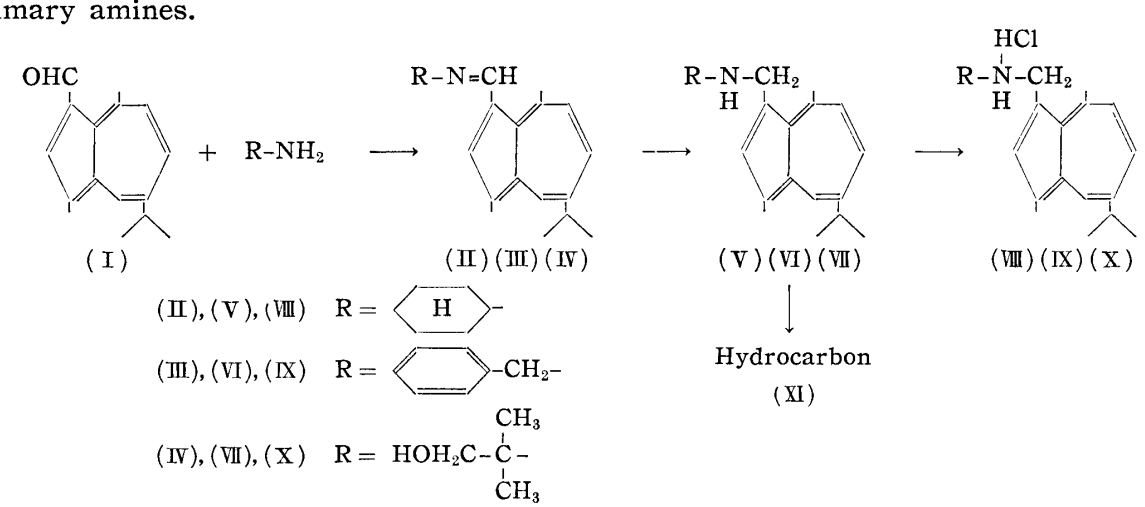
28. **Makoto Miyazaki**: Studies on Azulenes. X.*1 3-Aminomethyl-S-guaiazulenes.

(*Government Forest Experiment Station**2)

Although syntheses of several azulenes involving amino groups substituted in the ring[1] or contained in their side chains[2] have hitherto been reported, no attempt has been made to prepare 3-aminomethyl-S-guaiazulene derivatives from S-guaiazulene-3-carboxaldehyde (I) via the Schiff bases of the latter, a method which seems to be the simplest to introduce an amino group in the side chain of azulenoid compounds.

Recently, a brief communication[2] on aminomethylation of azulene appeared and it involves treatment of the latter with bis(dimethylamino)methane, paraformaldehyde, and acetic acid in benzene. This procedure, however, does not pass through the Schiff base as intermediate which is readily attainable from azulene-aldehyde with several primary amines.



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*1 Part IX: This Bulletin, 8, 140(1960).

*2 Shimomeguro, Meguro-ku, Tokyo (宮崎 信).

1) A.G. Anderson, Jr., J.A. Nelson, J.J. Tazuma: J. Am. Chem. Soc., **75**, 4980(1953); A.G. Anderson, Jr., R. Scotonii, Jr., E.J. Cowels, G.G. Fritz: J. Org. Chem., **22**, 1193(1957); T. Nozoe, S. Matsumura, Y. Murase, S. Seto: Chem. & Ind.(London), **1955**, 1257; D.H. Reid, W.H. Stafford, J.P. Ward: J. Chem. Soc., **1958**, 1100.

2) K. Nafner: Angew. Chem., **70**, 412(1958); Ann., **606**, 79(1957); K. Hafner, H. Weldes: Ann., **606**, 90(1957).

This paper deals with the preparation of several 3-aminomethyl-S-guaiazulenes by the above-mentioned procedure, as well as the properties of the isolated intermediates of the reactions.

S-Guaiazulene-3-carboxaldehyde (I) dissolved in a suitable solvent such as acetone or hexane was reacted with cyclohexylamine, benzylamine, or butanolamine (2-amino-2-methyl-1-propanol), and respective products were isolated as N-(S-guaiazulen-3-ylmethylene)cyclohexylamine (II) as blue plates, m.p. 121~122°(decomp.); N-(S-guaiazulen-3-ylmethylene)benzylamine (III) as blue plates, m.p. 68~69°(decomp.), and N-(S-guaiazulen-3-ylmethylene)-1,1-dimethyl-2-hydroxyethylamine (IV) as blue plates, m.p. 126~127°(decomp.). These compounds showed infrared absorptions characteristic to -N=C- group at 1605, 1610, and 1600 cm^{-1}, respectively, as shown in Fig. 1.

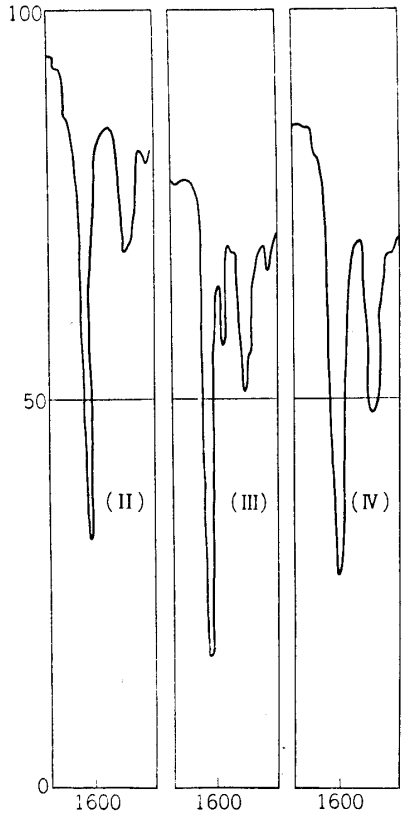

Fig. 1.
Infrared Absorption Spectra of (II)(in KBr), (III), and (IV) (in Nujol)

These Schiff bases are stable in the crystalline state or in nonpolar solvents, such as hexane, but unstable in polar solvents. The methanolic solution of (II), (III), and (IV) spontaneously changed color from blue to reddish orange and similar change for (III) was observed in ethanolic solution. (II), (III), and (IV) were readily soluble in slightly acid solutions such as in dil. acetic or hydrochloric acid, resulting in orange red solution. The strips of filter papers immersed in the blue solution of (II), (III), and (IV) in hexane, changed on exposure to the air in a few minutes to yellow and the original blue color of the paper was recovered by exposure to gaseous ammonia. In ammonia-alkaline ethanolic solution these bases were blue in color and gradually hydrolysed to (I). These observations suggest the occurrence of a reversible protonation of the Schiff bases to form azulenium ion in the acid solution.

Catalytic hydrogenation of (II), (III), and (IV) afforded the respective products, 3-cyclohexylaminomethyl-S-guaiazulene (V) as blue crystalline mass, 3-benzylaminomethyl-S-guaiazulene (VI) as a blue oil, and 3-(1,1-dimethyl-2-hydroxyethylaminomethyl)-S-guaiazulene (VII) as a blue oil, and were isolated as their respective hydrochlorides; 3-cyclo-

hexylaminomethyl-S-guaiazulene hydrochloride (Ⅷ) as blue needles, m.p. ca. 180°(decomp.); 3-benzylaminomethyl-S-guaiazulene hydrochloride (Ⅸ) as blue needles, m.p. ca. 130°(decomp.); and 3-(1,1-dimethyl-2-hydroxyethylaminomethyl)-S-guaiazulene hydrochloride (Ⅹ) as blue needles, m.p. 157~158.5°(decomp.).

An attempt to prepare *p*-toluenesulfonamide derivatives from (Ⅴ), (Ⅵ), and (Ⅶ) failed, giving a common crystalline product (Ⅺ) of blue plates, m.p. 191~192°. The elemental analysis and determination of molecular weight of this product revealed that (Ⅺ) was a hydrocarbon containing two S-guaiazulene moieties. Further, the bathochromic shift (by 22 mμ) of the absorption maximum of (Ⅺ) in the visible range compared with that of S-guaiazulene revealed an alkyl substitution at the 3-position of at least one of two S-guaiazulene moieties involved in (Ⅺ).

From these observations and the mode of formation of this compound (Ⅺ), it is presumed to be 3,3'-methylene-diguaiazulene, probably the same compound with that (m.p. 190~191°) reported by Arnold[3] as an unexpected product of chloromethylation of S-guaiazulene.

Experimental

N-(S-Guaiazulen-3-ylmethylene)cyclohexylamine (Ⅱ)—A solution of 200 mg. of (Ⅰ) and 250 mg. of cyclohexylamine in 1 cc. of acetone was warmed slightly on a water bath for 2 hr. and allowed to stand for 2 days at room temperature. Change in color of the solution from violet to blue, and gradual formation of blue crystalline product were observed. On filtration and recrystallization from hexane, 235 mg. of blue plates (Ⅱ), m.p. 121~122°(decomp.), was obtained. IR : ν_{max}^{KBr} 1605 cm^{-1}(C=N). Visible spectrum : $\lambda_{max}^{ligroine}$ mμ (ε) : 438(133), 604(437), 655(331). *Anal.* Calcd. for $C_{22}H_{29}N$: C, 85.94; H, 9.51. Found : C, 86.06; H, 9.38.

N-(S-Guaiazulen-3-ylmethylene)benzylamine (Ⅲ)—140 mg. of benzylamine was added into a warmed solution of 300 mg. of (Ⅰ) in 2 cc. of hexane, the mixture was kept at 50° on a water bath for 2 hr. and then at room temperature for 24 hr. whereby blue crystals appeared. Recrystallization from hexane gave 390 mg. of blue plates (Ⅲ), m.p. 68~69°(decomp.). IR : ν_{max}^{Nujol} 1610 cm^{-1}(C=N). Visible spectrum : $\lambda_{max}^{ligroine}$ mμ (ε) : 485(235), 604(469), 645(371). *Anal.* Calcd. for $C_{23}H_{25}N$: C, 87.59; H, 7.99. Found: C, 87.51, H, 7.85.

N-(S-Guaiazulen-3-ylmethylene)-1,1-dimethyl-2-hydroxyethylamine (Ⅳ)—To a solution of 200 mg. of (Ⅰ) in 1 cc. of acetone, 300 mg. of butanolamine (2-amino-2-methyl-1-propanol) and 0.5 cc. of hexane were added and the mixture was kept at room temperature over night, whereby blue crystals formed. The crystals were collected and recrystallized from hexane to 240 mg. of (Ⅳ) as blue plates, m.p. 126~127°(decomp.). IR : ν_{max}^{Nujol} 1600 cm^{-1}(C=N). Visible spectrum : $\lambda_{max}^{ligroine}$ mμ (ε) : 485(132), 604 (448), 660(434). *Anal.* Calcd. for $C_{20}H_{27}ON$: C, 80.76; H, 9.15. Found : C, 80.81; H, 9.01.

Hydrolyses of (Ⅱ), (Ⅲ), and (Ⅳ)—A solution of 30 mg. of (Ⅱ) in 0.5 cc. of ammoniacal EtOH (28% NH_4OH 30, H_2O 20, EtOH 50, in volume) was allowed to stand at room temperature for 24 hr. The color of the solution changed from blue to violet. Cooling of the resulting solution and filtration yielded 15 mg. of brown needles. It was recrystallized from hexane to brown needles, m.p. 83~84°, which showed no depression in a mixed fusion with (Ⅰ). Other Schiff bases (Ⅲ and Ⅳ) were also readily hydrolysed by the same treatment to give (Ⅰ) as the hydrolysed product.

3-Cyclohexylaminomethyl-S-guaiazulene (Ⅴ) and its Hydrochloride (Ⅷ)—200 mg. of (Ⅱ) was hydrogenated over 20 mg. of PtO_2 in 4 cc. of AcOMe containing 0.05 cc. of 28% NH_4OH, whereby the initial blue color of the solution changed to dark violet and then finally to blue. Removal of the solvent by distillation in N_2 gave a blue oily residue which was dissolved in hexane, adsorbed on an alumina column (1×20 cm.), and eluted with a mixed solvent of hexane and ether (1:1). After 2 cc. of initial blue eluate, 25 cc. of the main blue eluate was obtained. This was concentrated in N_2 to give a residual blue oil which was repurified through a short column of alumina to obtain 80 mg. of blue crystalline mass (Ⅴ).

Into a solution of (Ⅴ) in 4 cc. of ether 0.5 cc. of dil. HCl was added to form a blue crystalline salt in the ether layer. The salt was dissolved in a small amount of AcOMe and an excess of ether was added into the solution to complete precipitation of (Ⅷ) as blue needles, m.p. 180°(decomp.). UV: λ_{max}^{EtOH} mμ (log ε): 245(4.52), 291(4.71), 304(4.40), 3.50(3.82), 369(3.88); Visible spectrum : λ_{max}^{EtOH} mμ (ε): 590(585), 640(457). *Anal.* Calcd. for $C_{22}H_{32}NCl$: C, 76.39; H, 9.32; N, 4.05. Found : C, 76.41; H, 9.29; N, 4.16.

3) H. Arnold, K. Pahls : Chem. Ber., **89**, 121(1956).

3-Benzylaminomethyl-S-guaiazulene (VI) and its Hydrochloride (IX)—100 mg. of (III) was hydrogenated over 10 mg. of PtO_2 in 5 cc. of EtOH, whereby the blue color of the solution changed to a dark violet and finally to blue. The solution was treated similary as in the case of (V) to give 60 mg. of a blue oil (VI). It formed blue hydrochloride (IX) of m.p. 130°(decomp.). UV : λ_{max}^{EtOH} mμ (log ε): 244(4.59), 291(4.76), 303(4.33), 350(3.74), 365(3.74); Visible spectrum : λ_{max}^{EtOH} mμ (ε) : 586(438), 640(335). *Anal.* Calcd. for $C_{23}H_{28}NCl$: C, 78.04; H, 7.97; N, 3.96. Found : C, 77.89; H, 7.91; N, 4.23.

3-(1,1-Dimethyl-2-hydroxyethylaminomethyl)-S-guaiazulene (IV) and its Hydrochloride (X)—A solution of 250 mg. of (IV) in a mixed solvent of 3 cc. of acetone, 6 cc. of EtOH, and 0.24 cc. of 28% NH_4OH was added into a mixed solvent of 4 cc. of EtOH and 2 cc. of acetone containing 15 mg. of PtO_2. The mixture was hydrogenated and 20 cc. of hexane was added into the reaction solution. The resulting solution was washed with H_2O and the solvent was removed in N_2. The residual blue oil was purified in the same way as described above to give 85 mg. of blue oil (VII). It gave a hydrochloride (X) of blue needles, m.p. 157~158.5°(decomp.). UV : λ_{max}^{EtOH} mμ (log ε) : 246(4.56). 287(4.69), 292(4.71), 305(4.42), 352(3.87), 365(3.78); Visible spectrum : λ_{max}^{EtOH} mμ (ε) : 590(695), 640(590). *Anal.* Calcd. for $C_{20}H_{30}ONCl$: C, 71.51; H, 9.00; N, 4.18. Found : C, 71.62; H, 8.68; N, 4.20.

Hydrocarbon (XI)—Into a solution of 70 mg. of (V) in 0.5 cc. of pyridine, 280 mg. of *p*-toluenesulfonyl chloride was added, the mixture was warmed slightly on a water bath for 30 min., and a small amount of H_2O was added into the reaction mixture. Blue crystals formed were collected to 50 mg. of blue needles and recrystallized from acetone to blue plates (XI), m.p. 191~192°(decomp.). *Anal.* Calcd. for $C_{30}H_{34}$: C, 91.31; H, 8.67; mol. wt., 395. Calcd. for $C_{31}H_{36}$: C, 91.12; H, 8.88; mol. wt., 409. Found : C, 91.39; H, 8.33; mol. wt.(Rast, with 3-bromocamphor), 422, 431.

Summary

The Schiff bases, N-(S-guaiazulen-3-ylmethylene)cyclohexylamine (II), N-(S-guaiazulen-3-ylmethylene)benzylamine (III), and N-(S-guaiazulen-3-ylmethylene)-1,1-dimethyl-2-hydroxyethylamine (IV) were prepared in excellent yields by condensation of S-guaiazulene-3-carboxaldehyde (I) with corresponding primary amines. These bases were easily converted into secondary amino derivatives of S-guaiazulene, i.e. 3-cyclohexylaminomethyl-S-guaiazulene hydrochloride (VIII), 3-benzylaminomethyl-S-guaiazulene hydrochloride (IX), and 3-(1,1-dimethyl-2-hydroxyethylaminomethyl)-S-guaiazulene hydrochloride (X), by catalytic hydrogenation and salt formation with hydrochloric acid.

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