The Synthesis of S-Guaiazulene from Hinokitiol

By Yoshio KITAHARA and Tadahiro KATO

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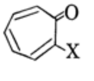
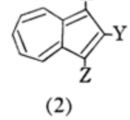
In recent years, a marvelous method of synthesizing azulenes have been developed by Nozoe and his co-workers.[1,2] This method is based on the reaction of tropolone methyl ether (1: X=OCH_3) or 2-halotropones (1: X=CI, Br) with malononitrile or ethyl cyanoacetate in the presence of sodium methoxide, and it is particularly useful for the synthesis of azulenes (2) having substituents (X, Y and Z) at their 1-, 2- and 3-positions.



(1)

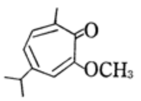


(2)

Thus, a number of azulene derivatives of this type were obtained and examined for their properties. Azulene itself (2: X, Y and Z= H) was successfully derived, by the same authors, from 1, 3-dicarboethoxy-2-aminoazulene (2: X and Z=CO_2Et, Y=NH_2), which might be recorded as one of the important azulene syntheses.

The syntheses of natural azulenes from tropolones by the above method have, however, so far been unsuccessful.

It was reported,[3] for instance, that in the reaction of 2-methoxy-4-isopropyl-7-methyltropone (3) and cyano ethyl acetate under similar conditions, the formation of an azulene nucleus (4) was impossible because of the steric interference of the methyl group at the 7 position.



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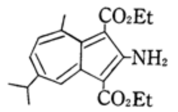
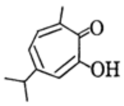


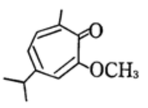
(4)

We tried to synthesize *S*-guaiazulene from hinokitiol although this compound had already been synthesized by Plattner and his co-workers.[4]

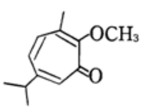
3-Methyl-6-isopropyltropolone (I)[5] gives its methyl ether almost quantitatively by reaction with diazomethane. This methyl ether is assumed to be a mixture of IIa and IIb, which are possible isomers to each other.



(I)

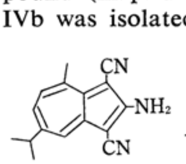


(IIa)

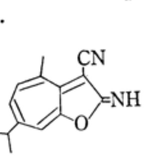


(IIb)

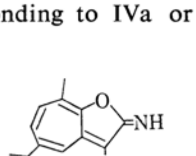
1, 3-Dicyano-2-aminoazulene derivative III was obtained in a 48% yield by the addition of malononitrile directly to the mixture of IIa and IIb in the presence of sodium methoxide. In this reaction a small amount of a compound (m. p. 140°C) corresponding to IVa or IVb was isolated.



(III)



(IVa)



(IVb)

It is known that cyano groups at the 1 and

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[1] T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem. & Ind.*, **1955**, 1257.

[2] T. Nozoe, S. Seto, S. Matsumura and Y. Murase, This Bulletin, **35**, 1179 (1962).

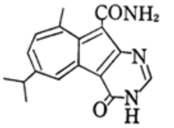
[3] T. Asano, Ph. D. Thesis, Tohoku University (1959).

[4] Pl. A. Plattner, A. Furst, L. Marti and H. Schmid, *Helv. Chim. Acta.*, **32**, 2137 (1949).

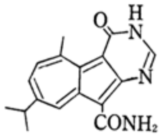
[5] See Experimental Section.

3 positions of the azulene nucleus are generally very stable and resist hydrolysis in acids and alkalis.[6-8] However, when III was heated in a mixture of concentrated sulfuric acid and formic acid, it gave a red crystalline compound, the infrared spectrum of which indicates the absence of a cyano group and which has multiple bands in the $3100\sim3400\ \text{cm}^{-1}$ region which are more complicated than those of III. This suggests the presence of a carbamoyl group.

This compound is deduced to have the structure Va from the results of micro analysis and from its behavior with relation to bases (it does not dissolve in a sodium bicarbonate solution although it does dissolve in a 2 N solution of sodium hydroxide, and the original substance is recovered on acidification).



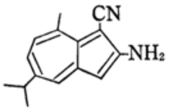
(Va)



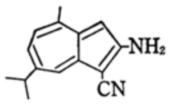
(Vb)

An attribution of the structure Vb to this compound is also possible, but, as will be mentioned later, the cyano group at the 1 position is more apt to be hydrolyzed than the other one. Therefore, Va rather than Vb seems to be more probable for this compound.

When III was heated in concentrated sulfuric acid for a considerable period, it blackened, evolving sulfur dioxide gas, and did not afford any clear product. However, when III was heated in 100% phosphoric acid[9] at 100°C, it gradually generated bubbles to yield a red crystalline compound in a 65% yield. Its infrared spectrum has a band of one cyano group ($2150\ \text{cm}^{-1}$); its micro analysis data fits either VIa or VIb.



(VIa)



(VIb)

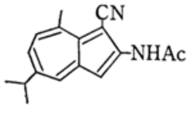
This hydrolysis is considered to proceed through the phosphoric acid ester formed with phosphoric acid and the cyano group. The formation of phosphoric acid ester from the cyano group at the 3-position might be difficult because of the steric interference of the methyl group at the peri position; accordingly, hydrolysis of the cyano group will also become difficult. Therefore, the obtained product is deduced to have the structure VIa. This deduction was finally proved to be true by the synthesis of *S*-guaiazulene from this compound.

We next tried to introduce a formyl group to the 1 position of VIa. It was already known[10] that the 1- and 3-positions of azulenes are easily formylated by the application of the Vilsmeier-Haack reaction.[11]

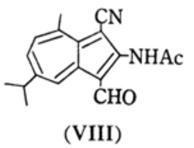
After the acetylation of the amino group at the 2-position of VIa, the acetylamino compound VII was treated with phosphorous oxychloride-dimethylformamide. Two compounds were produced, m. p. 176°C, and m. p. 232°C (decomp.), in a ratio of almost 3 : 1.

The infrared spectrum of the compound (m. p. 176°C) indicates the presence of a formyl group (2850 and $1626\ \text{cm}^{-1}$), and an acetyl group ($1708\ \text{cm}^{-1}$), and the results of its micro analysis are satisfactory for 1-cyano-2-acetylamino-3-formylazulene (VIII). The alkaline hydrolysis of VIII gave X, the formyl group of which reacts easily with hydrazine to give XI.

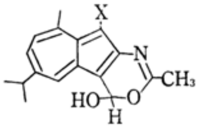
The red crystalline compound (m. p. 232°C (decomp.)) has the same composition ($C_{18}H_{18}NO_2$) as that of VIII; therefore, it is assumed to be an isomer of VIII. However, its infrared absorption spectrum has the broad band of a hydroxyl group ($3450\ \text{cm}^{-1}$) and the band of neither an acetyl group nor of a formyl group. From this infrared spectural date it may be concluded that the compound (m. p. 232°C (decomp.)) would have the structure IX. IX was easily hydrolyzed, when heated with 100% phosphoric acid, producing a red oil (XII):



(VII)



(VIII)



(IX) X=CN
(XII) X=H

In this way, it became clear that the cyano groups at both the 1 and 3 positions, the

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[6] T. Nozoe, T. Sato, S. Matsumura, T. Asano and H. Akino, Presented at the 9th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1956.

[7] T. Asano, Presented at the 12th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1959.

[8] W. Treibs, J. Hiebsch, and H. J. Neupert, *Chem. Ber.*, **92**, 606 (1959).

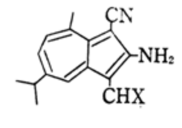
[9] R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York (1953), p. 412.

[10] K. Hafner, *Angew. Chem.*, **69**, 533 (1957); W. Treibs, *Chem. Ber.*, **92**, 141 (1959); K. Hafner and C. Bernhard, *Ann.*, **625**, 108 (1959).

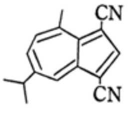
[11] A. Vilsmeir and A. Haach, *Chem. Ber.*, **60**, 119 (1927).

hydrolysis of which has hitherto been regarded as being difficult, could be hydrolyzed using 100% phosphoric acid. Since the yield of IX from VII was so low that it seemed difficult to obtain the last objective *S*-guaiazulene from IX, the preparation of 1, 3-dicyano-4-methyl-7-isopropylazulene (XIII) by the deamination of III, followed by its transformation into 4-methyl-7-isopropylazulene (XIV) was planned.

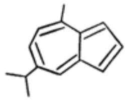
The diazotization of III is difficult by the usual manner. However, when a concentrated sulfuric acid solution of sodium nitrite was added to a solution of III in concentrated sulfuric acid and formic acid under ice cooling, III was easily diazotized, affording a bright violet solution, which was reductively decomposed, using hypophosphorous acid-copper powder, to give a crystalline compound in a 53% yield. The band of the amino group in the infrared spectrum of this compound disappears, and the ultraviolet absorption spectrum is very similar to that of 1, 3-dicyanoazulene.[12] When heated with phosphoric acid, XIII gave, under an evolution of gas, a small amount of blue oil and a green oil as the main products. The infrared spectrum of the green oil clearly indicates the presence of a hydroxyl group, which suggests that the hydration to the nucleus takes place. XIII can be hydrolyzed neither by sulfuric acid-formic acid nor by alkaline reagents, such as potassium hydroxide and sodium ethoxide, to recover the starting substance XIII. Therefore, the introduction of a methyl group to the 1-position of VIa was tried next.



(X) X=O
(XI) X=N·NH₂



(XIII)

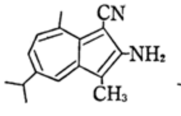


(XIV)

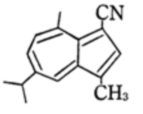
As has been mentioned before, the Vilsmeier reaction of VII produces a mixture of VIII and XI in a low yield; therefore, the above reaction was applied to VIa.

Since it was anticipated[13] that the formyl group at the 1-position of X would be very active in an acidic medium and would form an intermolecular Schiff's base with the amino group at the 2-position, X was directly subjected to Huang-Minlon reduction[14] without isolation and purification. As a result, a red crystalline compound was obtained in a 34% yield calculated from VIa. Its infrared spectrum has a band assigned to the cyano group at 2200 cm^{-1} and several bands at 3220, 3330 and 3450 cm^{-1} assigned to the amino group. The results of its micro analysis also fits the structure XV.

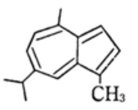
The diazonium salt of XV was reductively decomposed by ethanol, giving, in a 41% yield, a blue compound (m. p. 69~70°C) which is soluble in most organic solvents. The results of its micro analysis are satisfactory for XVI. The melting point, type of crystals, characteristic infrared absorption spectrum, and visible absorption curves of XVI[15] all coincide perfectly with those of 3-cyano-1, 4-dimethyl-7-isopropylazulene, which has already been prepared from *S*-guaiazulene by Stafford et al.[16]



(XV)



(XVI)



(XVII)

The phosphoric acid hydrolysis of XVI gave a blue oil in a 80% yield.[17] The oil was characterized by means of its trinitrobenzene complex (m. p. 147~148°C) and its picrate (m. p. 116~117°C), which were undepressed upon admixture with authentic samples[18] prepared from natural *S*-guaiazulene XVII. The infrared spectra of this oil and of natural *S*-guaiazulene are entirely identical.

Experimental

3-Methyl-6-isopropyltropolone (I).—To a mixture of hinokitiol (4-isopropyltropolone) (50 g.) and formaline (50 ml.), morpholine (50 ml.) was added. The generation of heat was observed. After being kept at room temperature for 1 hr., the mixture was heated at 60°C for 30 min. and then kept in a refrigerator overnight. 3-Morpholinomethyl-6-isopropyltropolone (m. p. 50°C) was obtained in a more than 90% yield.

The Reduction of 3-Morpholinomethyl-6-isopropyltropolone.—To a palladium chloride solution (30 ml.) prepared by Vogel's method[19] Norit (3 g.) was added; then hydrogen was absorbed to this mixture. When a sodium salt aqueous solution of 3-morpholinomethyl-6-isopropyltropolone (40 g.) was added to the palladium-carbon mixture and catalytically reduced at room temperature, a total of 4.2 l. of hydrogen was absorbed. With the progress of the reduction, sodium salt of the reduction product, 3-methyl-6-isopropyltropolone (I), was deposited.

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[12] W. Treibs, ibid., **92**, 606 (1959).

[13] K. Hafner and C. Bernhard, *Angew. Chem.*, **69**, 533 (1957); E. C. Kirby and D. H. Reid, *J. Chem. Soc.*, **1960**, 494.

[14] K. Hafner and C. Bernhard, *Ann.*, **625**, 108 (1959).

[15] D. H. Reid, W. H. Stafford and W. I. Stafford, *J. Chem. Soc.*, **1958**, 1118; W. Treibs, *Chem. Ber.*, **92**, 606 (1959).

[16] See Ref. 15.

[17] As a trinitrobenzene complex.

[18] Pl. A. Plattner, *Helv. Chim. Acta*, **25**, 581 (1942); **32**, 284, 2137 (1949).

[19] A. I. Vogel, "A Text-book of Practical Organic Chemistry," Longmans, Green and Co., New York (1951), p. 996.

The first 1 molar equivalent of hydrogen was rapidly absorbed, but the absorption of the second 1 molar equivalent of hydrogen was rather slow; a total of 2 molar equivalents of hydrogen were absorped. In methanol or acidic methanol solutions, however, hydrogen absorption did not stop even after 2 molar equivalents of hydrogen had been absorbed, so the reduction of the tropolone nucleus must have been taken place.

After the hydrogen absorption had ceased, 2 N sodium hydroxide (50 ml.) and water (200 ml.) were added to the reduction mixture, and then the crystals and palladium-carbon were filtered and dissolved in 2 N sulfuric acid. The solution was extracted with chloroform, and palladium-carbon was filtered off. On the other hand, the alkaline filtrate was acidified with 6 N sulfuric acid and extracted with chloroform. The extracts were combined with the former chloroform extracts, washed with water twice, and dried over magnesium sulfate. When the chloroform was removed and the remaining residue distilled under reduced pressure, 3-methyl-6-isopropyltropolone (I) (25.2 g.) was obtained as a yellow oil in a 91.5% yield.

The Tosylation of I. — *p*-Toluenesulfonyl chloride (4.6 g.) was added to a solution of 3-methyl-6-isopropyltropolone (3.65 g.) dissloved in absolute pyridine (10 ml.). After the mixture had been kept overnight and the pyridine removed under reduced pressure, colorless crystals were obtained on the addition of water. The recrystallization of these crystals from benzene-cyclohexane (1 : 1) gave colorless needles (m. p. 86~87°C) (3.7 g.).

Found: C, 65.08; H, 5.95. Calcd. for $C_{18}H_{20}O_4S$: C, 65.05; H, 6.07%.

The Methyl Ether of I.—To I (25.2 g.) dissolved in ether (100 ml.) an excess of a diazomethane ether solution was added, and the mixture was kept at room temperature overnight. This reaction prcceeded extremely slowly. After the ether had been removed and the residue had been distilled, the methyl ether, IIa and IIb, 26.8 g. was obtained in a 98% yield.

The Reaction of 2-Methoxy-4-isopropyl-7-methyltropone (IIa and IIb) with Malononitrile.—To a sodium methoxide solution prepared from absolute methanol (5 ml.) and sodium metal (100 mg.), malononitrile (360 mg.), and IIa and IIb, (400 mg.) were added successively; the mixture was kept at room temperature overnight. Then it was heated under reflux for 2.5 hr., and the resultant red solution was diluted with ethyl acetate and washed with a saturated sodium chloride aqueous solution three times and then dried over magnesium sulfate. After the removal of the solvent, there remained a red oil, which was then dissolved in benzene and chromatographed on alumina. From the benzene eluate, IVa or IVb (m. p. 140~141°C) was obtained in the form of yellow scales.

Found: C, 74.36; H, 6.63; N, 12.19. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.26; N, 12.38%.

UV λ_{max}^{MeOH} mμ (log ε): 242 (4.29), 295 (4.65).

From benzene - ethyl acetate (5 : 1), an eluate, III (250 mg., 48% yield) was obtained as orange prisms from ethanol. M. p. 184~185°C.

Found: C, 77.05; H, 6.19; N, 17.02. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86%.

UV λ_{max}^{MeOH} mμ (log ε): 235 (4.57), 315 (4.68), 325 (4.75), 390~400 (sh.).

The Hydrolysis of III. — *With Sulfuric Acid-Formic Acid.*—A mixture of III (350 mg.), 80% formic acid (2 ml.) and concentrated sulfuric acid (2 ml.) was heated at 85~95°C at 1 hr. The addition of water then afforded a red solution. A red crystalline substance (350 mg.) (m.p.>270°C) was obtained by neutralization (pH 4~5) with 2 N sodium hydroxide. Recrystallization from dimethylformamide gave Va (m.p.>270°C) in the form of red scales. The compound did not dissolve in a saturated sodium bicarbonate solution, but it did dissolve in 2 N sodium hydroxide.

Found: C, 69.29; H, 5.77; N, 14.23. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23%.

UV λ_{max}^{MeOH} mμ (log ε): 315 (4.61), 362 (3.84), 380 (3.85), IR 3370, 3270, 3170, 3070, 1655, 1605, 1585, 1510 cm^{-1}.

With 100% Phosphoric Acid. — 100% phosphoric acid (5 ml.) prepared by the addition of an excess quantity of phosphoric acid anhydride to 85% phosphoric acid was added to III (720 mg.), and the mixture was heated at 100°C for 3.5 hr. After water had been added to the reaction mixture, it was neutralized with sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate extract was washed with water and dried, and the solvent was removed, giving a red crystalline compound (420 mg.). Recrystallization from ethanol gave VIa (m. p. 157~158°C) as red prisms in a 65% yield.

Found: C, 80.39; H, 7.42; N, 12.79. Calcd. for $C_{15}H_{15}N_2$: C, 80.32; H, 7.19; N, 12.49%.

UV λ_{max}^{MeOH} mμ (log ε): 228 (4.30), 305 (4.76), 315 (4.82), 355 (3.91), IR 3400, 3300, 3200, 2150, 1640, 1540 cm^{-1}.

With 100% Phosphoric Acid at 120°C—A mixture of III and 100% phosphoric acid (3 ml.) was heated at 120°C for 5 hr., water was added, and the mixture was neutralized with sodium bicarbonate and extracted with benzene. The benzene extract was washed with water, dried, concentrated and chromatographed on alumina. The benzene eluate afforded a red oil. After this oil had been heated with acetic anhydride under reflux for 1 hr., the removal of the acetic anhydride gave a red crystalline compound. Recrystallization from dimethylformamide afforded blackish violet prisms (m. p. 250°C.)

Found: C, 88.48 (88.66); H, 8.13 (7.86); N, 3.85 (3.70). Calcd. for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67%.

The Acetylation of VIa.—A mixture of VIa (300 mg.) and acetic anhydride (4 ml.) was heated under reflux for 30 min.; the solvent was removed under reduced pressure, and then water was added. The filtered crystals were recrystallized from benzene (m. p. 182~184°C) VII as long red needles.

Found: C, 77.04; H, 6.88; N, 10.68. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52%.

UV λ_{max}^{MeOH} mμ (log ε): 240 (4.30), 307 (4.75), 317 (4.85), 355 (3.90), 370 (3.93).

The Vilsmeier Reaction of VII.—To VII (260 mg.) dissolved in dimethylformamide (10 ml.) phosphorus oxychloride (300 mg.) was added and the mixture was heated at 90°C for 1 hr. The reaction mixture was poured into water (100 ml.) yielding a crystalline compound IX. The filtrate was neutralized with 2 N sodium hydroxide and extracted with ethyl acetate. From the ethyl acetate extract, VIII was obtained. The recrystallization of VIII from ethanol gave orange prisms (130 mg.) (m. p. 175∼176°C).

Found: C, 73.88; H, 6.07; N, 9.85. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%.

UV λ_{max}^{MeOH} mμ (log ε): 232 (4.34), 252 (4.41), 287 (4.40), 322 (4.61).

The recrystallization of IX from dimethylformamide afforded red needles (50 mg.) (m. p. 232∼233°C (decomp.).

Found: C, 73.48; H, 5.53; N, 9.71. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%.

UV λ_{max}^{MeOH} mμ (log ε): 240 (4.46), 320 (4.66), 335 (4.70), 370 (3.83), 390 (4.02), 415 (4.17).

The Hydrolysis of IX with 100% Phosphoric Acid.—A mixture of IX (150 mg.) and 100% phosphoric acid (7 ml.) was heated at 120∼130°C for 5 hr., then it was diluted with water, neutralized with 2 N sodium hydoxide, and extracted with benzene. After the combined extract had been washed with water and dried, the removal of the solvent gave a reddish violet oil (XII). Picrate: m. p. >250°C, green needles.

Found: C, 55.74; H, 3.91; N, 11.34. Calcd. for $C_{23}H_{22}N_4O_9$: C, 55.42; H, 4.45; N, 11.24%.

The Hydrolysis of VIII. — To VIII (130 mg.) dissolved in methanol was added 2 N sodium hydroxide under reflux. After the methanol had been removed by heating on a water bath, a yellow crystalline compound was obtained on the addition of water. Recrystallization from methanol gave orange scales (X) (90 mg., m.p. 168∼169°C).

Found: C, 76.03; H, 6.55; N, 11.32. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10%.

UV λ_{max}^{MeOH} mμ (log ε): 230 (4.30), 252 (4.43). 282 (4.48), 335 (4.74).

The Condensation of X with Hydrazine.—An ethanol solution of XI and an excess quantity of hydrazine was heated for 10 min., and then water was added. After being kept overnight, a reddish crystalline product was obtained. Recrystallization from ethanol afforded XI as reddish brown needles (m. p. 158∼160°C (decomp.)).

Found: C, 71.73; H, 6.79; N, 21.03. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04%.

UV λ_{max}^{MeOH} mμ (log ε): 260 (4.41), 300 (4.45), 310 (4.45), 350 (4.76) 400 (sh.).

The Deamination of III. — III (1 g.) was dissolved in a mixture of 86% formic acid (50 ml.) and concentrated sulfuric acid (10 ml.). To this solution sodium nitrite (400 mg.) in concentrated sulfuric acid (20 ml.) was added. The solution turned a bright reddish violet. After the addition of the sodium nitrite solution, the mixture was allowed to stand for 30 min., then a small amount of copper powder and 38% hypophosphorous acid (8 g.) were added. When the resultant mixture was kept in a refrigerator overnight, the solution turned red. After the solution had been stirred at room temperature for 5 hr. to complete the reaction, water was added. The reaction mixture was neutralized with 2 N sodium hydroxide and extracted with benzene. The combined benzene extract was concentrated to a proper volume and chromatographed on alumina. From benzene eluate, a red crystalline compound (500 mg.) was obtained. Recrystallization from ethanol gave XIII (53% yield) as red needles (m. p. 145∼146°C).

Found: C, 82.11; H, 5.96; N, 11.80. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96%.

UV λ_{max}^{MeOH} mμ (log ε): 237 (4.71), 300 (4.55), 340 (3.89), 368 (4.02).

Attempts to Hydrolyze XIII. — a) XIII was dissolved in 100% phosphoric acid (1 ml.) and heated at 95∼100°C for 2 hr., but no gas evolution was noticed. After being heated at 120∼130°C for 2.5 hr., water was added. The reaction mixture was neutralized with 2 N sodium hydroxide and extracted with ethyl acetate. After the ethyl acetate had been removed, the residual oil was dissolved in benzene and chromatographed on alumina. From benzene eluate a blue oil was obtained. The infrared spectrum of this oil indicates the absence of a cyano group and this oil afforded its picrate of green needles, but its identity was not confirmed because of its small quantity. The ethyl acetate eluate gave a green oil, the infrared spectrum of which indicates the presence of a hydroxyl group (3400 cm^{-1}) and the absence of a cyano group. This oil gave a picrate, but its identity was not confirmed because of its small quantity.

b) XIII was dissolved in 10% sodium ethoxide-ethanol and heated at 95°C for 1 hr. The solvent was almost all removed. Water was then added to the residue, and it was extracted with ethyl acetate. From the ethyl acetate solution, the starting material was recovered.

c) A mixture of XIII, formic acid and concentrated sulfuric acid was heated for 1 hr. on a water bath. Only the starting substance was recovered.

The Synthesis of 1-Cyano-2-amino-*S*-guaiazulene (XV). — To VIa (550 mg.) dissolved in dimethylformamide (10 ml.), phosphorus oxychloride (1 g.) was added, and the mixture was kept overnight. Then the mixture was added to a heated ethanolic 2 N sodium hydroxide solution, ethanol (10 ml.) and hydrazine (2 ml.) were added, and the resultant mixture was heated for 30 min. on a water bath. After the addition of an ethylene glycol solution (5 ml.) of potassium hydroxide, which had been prepared by dissolving potassium hydroxide (5.6 g.) in ethylene glycol (25 ml.), the mixture was heated at 190∼200°C with reflux for 1.5 hr. Then it was diluted with water and extracted with ethyl acetate, and the combined ethyl acetate extract was washed with water and dried. After the ethyl acetate had been removed, it was chromatographed on alumina. From the benzene-ethyl acetate (1:1) eluate, a red crystalline substance was obtained. Recrystallization from methanol afforded red scales (m. p. 120∼121°C).

Found: C, 80.20; H, 7.63; N, 11.53. Calcd, for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76%.

UV λ_{max}^{MeOH} mμ (log ε) : 230 (4.25), 310 (4.78), 320 (4.82), 355 (3.95), 395∼400 (sh.), 420∼430 (sh.).

The Deamination of XV.—XV (230 mg.) was dissolved into a mixture of ethanol (10 ml.) and concentrated sulfuric acid (0.4 ml.). Isoamyl nitrite (130 mg.) was added to the mixture under ice cooling, and it was stirred for 30 min. Then the mixture was added to boiling ethanol (10 ml.) and heated for 30 min. After neutralization with 2 N sodium hydroxide, the mixture was extracted with benzene. The benzene extract was washed with water and dried, and the benzene was removed. When the resulting residue was dissolved in cyclohexane-ether (4 : 1) and chromatographed on alumina, a crystalline compound (90 mg.) (m. p. 64∼67°C) was obtained. Purification by sublimation gave XVI of bluish violet needles (m. p. 68.5∼69.5°C).

Found: C, 86.12; H, 7.99; N, 5.97. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.76; N, 6.27%.

UV λ_{max}^{MeOH} mμ (log ε) : 245 (4.44), 298 (4.58), 312 (4.47), 380 (3.98), 558 (2.75).

IR 2190, 1554, 1539, 1526, 1417, 1330, 1295 (doublet), 1208, 1160, 1123, 1097, 1055, 1020, 995, 953, 915 cm^{-1}.

The Hydrolysis of XVI.—A mixture of XVI (90 mg.) and 100% phosphoric acid (1 ml.) was heated at 98∼99°C°. It first became a clear solution, but then a compound, which might be carbamoyl-*S*-guaiazulene, was separated out. After this temperature had been maintained for an additional 4 hr., water was added. The resultant solution was neutralized with sodium bicarbonate and extracted with petroleum ether. The combined extract was washed with water and dried, and the solvent was removed. When the residual oil was chromatographed on alumina using petroleum ether, a blue oil was obtained. This oil was dissolved in ethanol (2 ml.), of which 0.5 ml. was used for the preparation of its picrate. The picrate (m. p. 116∼118°C) was obtained as blackish green needles. Similarly, from the ethanol solution (0.5 ml.), 1, 3, 5-trinitrobenzene complex (30 mg.) was obtained as green crystals. Recrystallization from ethanol afforded green needles (m. p. 147∼148°C). They were both identical with the authentic sample obtained from *S*-guaiazulene as determined by mixed melting point determination.

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