

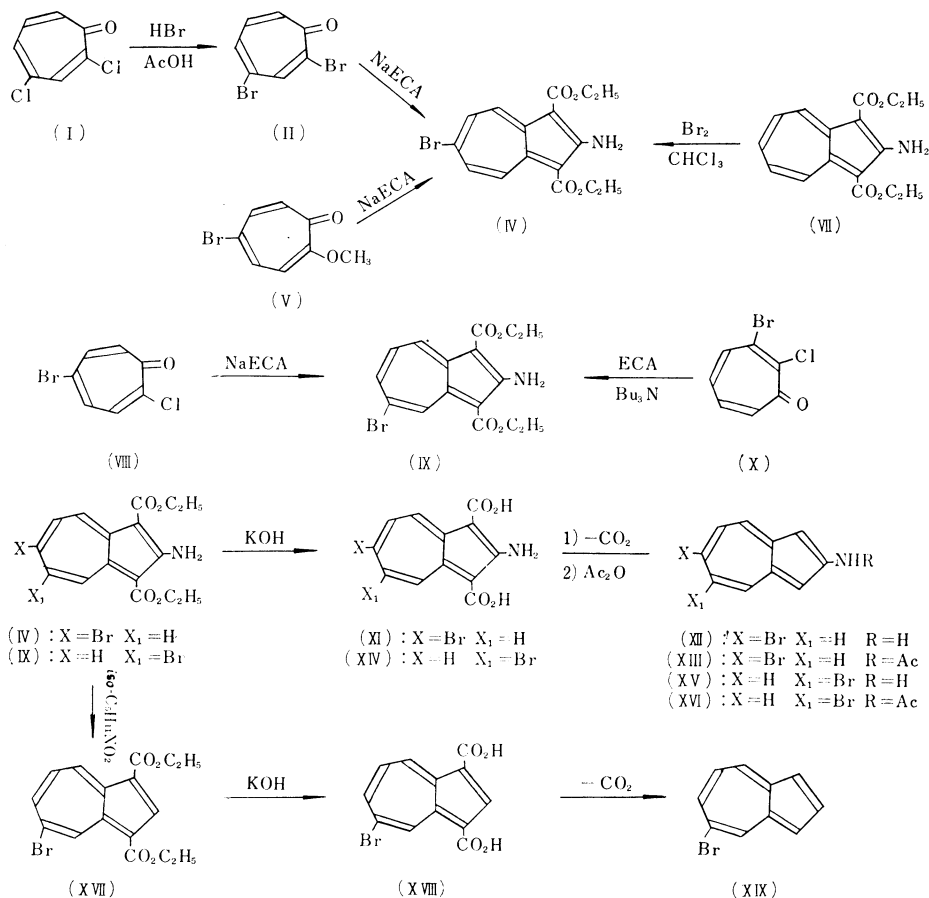
163. Shingo Matsumura : Syntheses of Bromoazulene Derivatives.

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Nozoe and his co-workers reported that condensation of troponoids and cyanoacetic ester in the presence of a base afforded 2-amino- and 2-hydroxyazulene derivatives in a fairly good yield which could be used as the useful starting materials for preparation of a variety of azulene derivatives.^{1,2)}

The present paper describes the syntheses of 5-bromo- and 6-bromoazulene derivatives by a new synthetic procedure.

When 2,4-dichlorotroponone (I) was treated with hydrogen bromide, 2,4-dibromotroponone (II), m.p. 145°, was obtained. A mixture of (II) and two molar equivalents of ethyl cyanoacetate (III) in absolute ethanol, in the presence of two molar equivalents of sodium ethoxide, was allowed to stand at room temperature, and (IV) was obtained as orange crystals, m.p. 164°.



ECA = Ethyl cyanoacetate

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1) T. Nozoe, S. Matsumura, Y. Murase, S. Seto : Chem. & Ind. (London), 1955, 1257.

2) T. Nozoe, S. Seto, S. Matsumura, T. Asano : Proc. Japan Acad., 32, 339 (1956).

Condensation of 2-methoxy-5-bromotropone (V) and (III), in the presence of one molar equivalent of sodium ethoxide, afforded (IV) and (VI) (orange crystals, m.p. 183°). As is apparent from the ultraviolet absorption spectra*² of (IV) and (VI) given in Fig. 1, the curve of (IV) is similar to that of diethyl 2-amino-1,3-azulenedicarboxylate type.

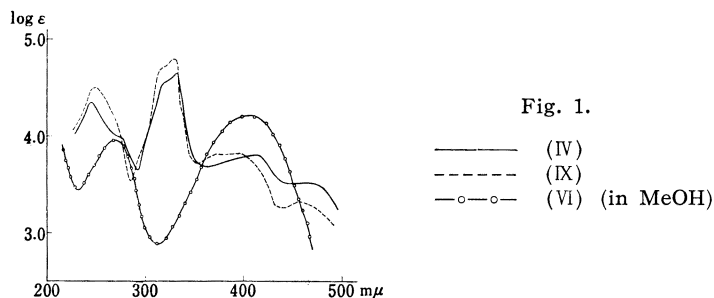
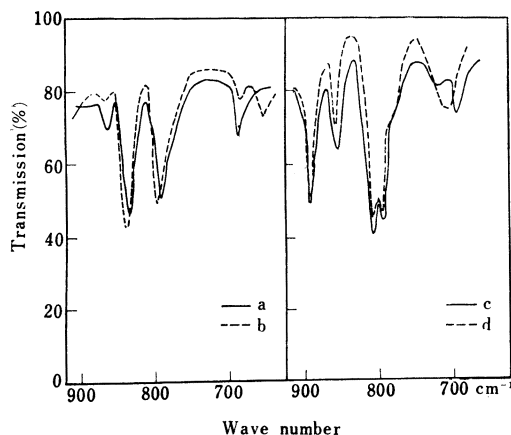


Fig. 1.

(IV) showed no depression in the melting point on admixture with the monobromo-compound, m.p. 164°, obtained by the bromination of diethyl 2-amino-1,3-azulenedicarboxylate (VIII) in chloroform.³⁾ The infrared absorption spectrum*³ of (IV), as shown in Fig. 2, exhibits absorption bands at 855, 835, and 790 cm^{-1} due to the C-H out-of-plane vibration of diethyl 2-amino-1,3-azulenedicarboxylate derivatives substituted in the 6-position.⁴⁾ These facts suggest that (IV) is diethyl 2-amino-6-bromo-1,3-azulenedicarboxylate.

Fig. 2. IR Spectra of (IV) and (IX) in KBr disk (900~650 cm^{-1})

- a : (IV)
- b : diethyl 2-amino-6-isopropyl-1,3-azulenedicarboxylate
- c : (IX)
- d : diethyl 2-amino-5-isopropyl-1,3-azulenedicarboxylate

It was found that condensation of (II) and (III) underwent abnormal (cine) reaction to form (IV). This tendency is observed in the reaction of troponoids and this kind of abnormal reaction seems to occur preferentially in 2-halotropones.⁵⁾ Reaction of 2-chloro-5-bromotropone (VIII) and (III) in dehyd. benzene, in the presence of two molar equivalents of sodium ethoxide, afforded (IX) as orange crystals, m.p. 117°. Reaction of 2-chloro-3-bromotropone (X) and (III), in the presence of tributylamine, afforded (VI)

*² UV absorption spectra were measured with the Hitachi EPS-2 Type Recording Spectrophotometer.

*³ IR absorption spectra were measured with the Perkin-Elmer Model 21 double beam Spectrophotometer.

3) T. Nozoe, S. Seto, S. Matsumura : This Bulletin in press.

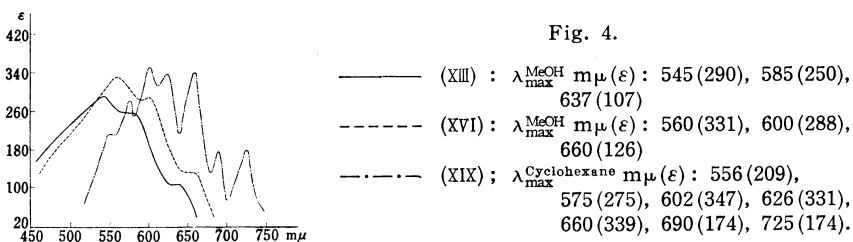
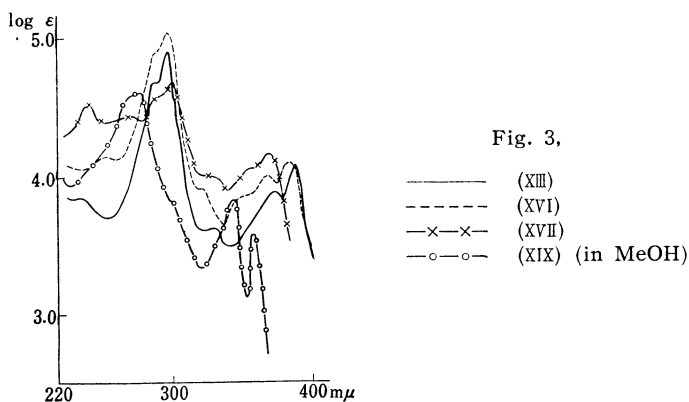
4) S. Matsumura : This Bulletin in press.

5) T. Nozoe : Croatica Chem. Acta, 29, 207 (1957).

and (IX). (IX) shows the ultraviolet absorption spectrum similar to that of diethyl 2-amino-1,3-azulenedicarboxylate type (Fig. 1). The infrared absorption spectrum of (IX) (Fig. 2) exhibits absorption bands at 880, 803, and 787 cm^{-1} due to the C-H out-of-plane vibration of diethyl 2-amino-1,3-azulenedicarboxylate derivatives substituted in the 5-position.⁴⁾ These facts indicate clearly that the abnormal reaction occurs in the condensation of (VIII) and (X) with (III).

(IV), upon hydrolysis, afforded 2-amino-6-bromo-1,3-azulenedicarboxylic acid (XI), m.p. 270° (decomp.). Decarboxylation by heating in pyridine gave unstable 2-amino-6-bromoazulene (XII) as red crystals, m.p. 135°, in good yield, whose acetylation with acetic anhydride afforded 2-acetamido-6-bromoazulene (XIII) as violet crystals, m.p. 189°. Application of nitrous acid to (IV) could not give rise to any pure product.

Hydrolysis of (IX) afforded 2-amino-5-bromo-1,3-azulene dicarboxylic acid (XIV), m.p. 270° (decomp.), which on decarboxylation produced unstable 2-amino-5-bromoazulene (XV) as red crystals, m.p. 83°, whose acetylation with acetic anhydride gave 2-acetamido-5-bromoazulene (XVI) as blue crystals, m.p. 173°. The ultraviolet absorption spectra of (XIII) and (XVI) are shown in Fig. 3. Deamination of (IX) by isopentyl nitrite in an ethanolic solution, in the presence of conc. sulfuric acid, gave diethyl 5-bromo-1,3-azulenedicarboxylate (XVII) as reddish violet crystals, m.p. 125°, in a poor yield. Hydrolysis of (XVII) afforded 5-bromo-1,3-azulenedicarboxylic acid (XVIII), which was decarboxylated by heating at 270~280° to 5-bromoazulene (XIX), blue crystals, m.p. 50°. The ultraviolet absorption spectra of (XVII) and (XIX), and the visible spectra of (XIII), (XVI) and (XIX) are given in Fig. 3 and Fig. 4, respectively.



The visible absorption maximum of (XIX) shifts to a longer wave length by 22 $m\mu$ than in the case of azulene and the maximum of (XVI) undergoes a shift to a longer wave length by 12 $m\mu$ than in the case of 2-acetamidoazulene. In (XIII), however, there is observed a shift of 3 $m\mu$ to a shorter wave length as compared with 2-acetamidoazulene.

It was found that the introduction of a bromine in the odd-number position of azulene ring caused a shift of the maximum to a longer wave length, whereas the introduction in the even-number position brought about a shift to a shorter wave length.

Experimental**

2,4-Dibromotropone (II)—A solution of 200 mg. of 2,4-dichlorotropone (I) in 10 cc. of AcOH was placed in a sealed tube, saturated with HBr. gas, and heated at 100° for 5 hr. The solvent was removed under reduced pressure and a colorless oily substance was obtained. This oil was dissolved in benzene, and the solution was passed through a column of alumina. The column was eluted with benzene and 150 mg. of colorless crystals was obtained. Recrystallization from a benzene-cyclohexane mixture afforded (II) as colorless needles, m.p. 144~145°. *Anal.* Calcd. for C₇H₄OBr₂: C, 31.83; H, 1.53. Found: C, 31.76; H, 1.29.

Diethyl 2-Amino-6-bromo-1,3-azulenedicarboxylate (IV)—a) To a suspension of ethyl sodiocyanoacetate prepared from 40 mg. of Na, 250 mg. of ethyl cyanoacetate and 1 cc. of abs EtOH, a solution of 150 mg. of (II) in 5 cc. of abs. EtOH was added dropwise under ice-cooling, and the mixture was stirred vigorously. The reaction occurred immediately, and the color of the solution changed from yellow to orange, when a small amount of orange crystals began to separate out. After standing overnight at room temperature, the most part of the solvent was distilled off under reduced pressure. The orange residue was dissolved in benzene and the solution was passed through a column of alumina. The column was eluted with benzene and the solvent was evaporated. The crystalline residue was recrystallized from EtOH and 70 mg. of orange prisms (IV), m.p. 163~164°, was obtained. *Anal.* Calcd. for C₁₆H₁₆O₄NBr: C, 52.35; H, 4.37; N, 3.87. Found: C, 52.65; H, 4.12; N, 3.56. UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (log ϵ): 245 (4.33), 320 (4.55), 332 (4.66), 410 (3.38), 473 (3.50).

b) To a suspension of ethyl sodiocyanoacetate prepared from 100 mg. of Na, 720 mg. of ethyl cyanoacetate and 4 cc. of abs. EtOH, a solution of 500 mg. of 2-methoxy-5-bromotropone (V) dissolved in 30 cc. of dehyd. benzene was added with stirring under ice-cooling. The mixture was allowed to stand at room temperature for 10 hr. and the solvent was completely evaporated. The orange residue was dissolved in benzene and the solution was washed with H₂O. The solvent was removed and the crystalline orange substance was repeatedly recrystallized from EtOH, and 140 mg. of (IV) and 100 mg. of orange crystals (A), m.p. 169~173°, were obtained. The orange crystals (A) was dissolved in benzene and the solution was passed through a column of alumina. The column was eluted with benzene and 20 mg. of (V) was recovered. Further elution of the column with AcOEt afforded 50 mg. of orange crystals. Recrystallization from EtOH afforded orange needles (VI), m.p. 182~183°. *Anal.* Calcd. for C₁₉H₂₀O₅N₂: C, 64.03; H, 5.66; N, 7.86. Found: C, 63.76; H, 5.07; N, 7.54. UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ : 268, 408.

Diethyl 2-Amino-5-bromo-1,3-azulenedicarboxylate (IX)—a) To a suspension of ethyl sodiocyanoacetate prepared from 40 mg. of Na, 250 mg. of ethyl cyanoacetate and 1 cc. of abs. EtOH, a solution of 250 mg. of 2-chloro-5-bromotropone (VIII) dissolved in 10 cc. of dehyd. benzene was added dropwise under ice-cooling. After standing overnight at room temperature, the solvent was completely evaporated. The orange residue was dissolved in benzene and the solution was passed through a column of alumina. The column was eluted with benzene and 120 mg. of orange crystals, m.p. 107~109°, was obtained. Four recrystallizations from EtOH afforded (IX) as orange scales, m.p. 117~118°. *Anal.* Calcd. for C₁₆H₁₆O₄NBr: C, 52.35; H, 4.37; N, 3.87. Found: C, 52.48; H, 4.16; N, 3.65. UV $\lambda_{\text{max}}^{\text{MeOH}}$ m μ (log ϵ): 250 (4.58), 319 (4.76), 331 (4.88), 396 (3.95), 460 (3.40).

b) To a solution of 200 mg. of 2-chloro-3-bromotropone (X) and 250 mg. of ethyl cyanoacetate in 4 cc. of dehyd. benzene, 170 mg. of tributylamine was added under stirring. The mixture was allowed to stand overnight at room temperature and the solution was washed with dil. HNO₃ and H₂O. After being dried over Na₂SO₄, the solution was passed through a column of alumina. The column was eluted with benzene and 80 mg. of orange crystals was obtained. Recrystallization from EtOH afforded (IX). Further elution of the column with AcOEt gave 20 mg. of (VI).

2-Amino-6-bromoazulene (XII)—To a solution of 200 mg. of KOH in 5 cc. of EtOH-H₂O, 500 mg. of (IV) was added and the mixture was refluxed on a water bath for 3 hr., after which the solution colored orange yellow. The solution was acidified with dil. HNO₃, and the deposited precipitate was collected by filtration and washed with H₂O, yielding 450 mg. of 2-amino-6-bromo-1,3-azulenedicarboxylic acid (XI). A suspension of 450 mg. of (XI) in 2 cc. of pyridine was heated at 120~130° for 15 min. to effect decarboxylation. The residue obtained by evaporation of the excess pyridine was dissolved in benzene and the solution was passed through a column of alumina. The column was

** All melting points are uncorrected.

eluted with benzene, and evaporation of the solvent from the effluent afforded red crystals. Recrystallization from a benzene-cyclohexane mixture afforded 250 mg. of red needles (XII), m.p. 135~136°. *Anal.* Calcd. for $C_{10}H_8NBr$: C, 54.05; H, 3.60; N, 6.31. Found: C, 54.01; H, 3.42; N, 6.55.

2-Acetamido-6-bromoazulene (XIII)—Two hundred milligrams of (XII) was added to 0.2 cc. of Ac_2O and the mixture colored violet immediately. After standing at room temperature for 2 hr., the violet crystals that separated out were collected by filtration and recrystallization from benzene afforded 200 mg. of violet needles (XIII), m.p. 188~189°. *Anal.* Calcd. for $C_{12}H_{10}ONBr$: C, 54.54; H, 3.79; N, 5.30. Found: C, 54.39; H, 3.52; N, 5.35. UV λ_{max}^{MeOH} $m\mu$ (log ϵ): 237 (3.89), 289 (4.68), 300 (4.93), 330 (3.61), 374 (3.89), 392 (4.08).

2-Amino-5-bromoazulene (XV)—To a solution of 40 mg. of KOH in 1 cc. of EtOH- H_2O (4:1), 100 mg. of (IX) was added and the mixture was refluxed on a water bath for 3 hr. The solution was neutralized with dil. HNO_3 , whereby 60 mg. of 2-amino-5-bromo-1,3-azulenedicarboxylic acid (XVI) was obtained. A suspension of 60 mg. of (XIV) in 0.5 cc. of pyridine was treated as in the preparation of (XII) and 30 mg. of (XV) was obtained as red needles, m.p. 82~83°. *Anal.* Calcd. for $C_{10}H_8NBr$: C, 54.05; H, 3.60; N, 6.31. Found: C, 54.23; H, 3.56; N, 6.52.

2-Acetamido-5-bromoazulene (XVI)—A mixture of 30 mg. of (XV) and 0.2 cc. of Ac_2O was treated as in the preparation of (XIII) and 30 mg. of (XVI) was obtained as blue needles, m.p. 172~173°. *Anal.* Calcd. for $C_{12}H_{10}ONBr$: C, 54.54; H, 3.79; N, 5.30. Found: C, 54.28; H, 3.65; N, 5.53. UV λ_{max}^{MeOH} $m\mu$ (log ϵ): 250 (4.17), 290 (4.91), 297 (5.06), 323 (3.91), 352 (3.84), 368 (4.01), 386 (4.10).

Diethyl 5-Bromo-1,3-azulenedicarboxylate (XVII)—To a solution of 200 mg. of (IX) in 20 cc. of EtOH containing 150 mg. of conc. H_2SO_4 , 100 mg. of isopentyl nitrite was added at room temperature and the mixture was warmed at 60~70° on a water bath for 30 min. The solution gradually colored reddish brown. The solvent was evaporated under a reduced pressure, and the residue was neutralized with 10% $NaHCO_3$ solution. The oily residue that separated out was extracted with benzene, and the extract was passed through a column of alumina. The column was eluted with benzene and the solvent was removed. The crystalline residue was recrystallized from cyclohexane and 30 mg. of reddish violet granular crystals (XVII), m.p. 124~125°, was obtained. *Anal.* Calcd. for $C_{18}H_{16}O_4Br$: C, 54.70; H, 4.27. Found: C, 54.86; H, 4.38. UV λ_{max}^{MeOH} $m\mu$ (log ϵ): 243 (4.54), 273 (4.45), 305 (4.68), 330 (3.99), 382 (4.17).

Further elution of the column with a mixture of benzene- $AcOEt$ (1:1) gave a dark brown oil together with ca. 10 mg. of (IX).

5-Bromoazulene (XIX)—To a solution of 30 mg. of (XVII) in 1 cc. of EtOH, 1 cc. of 10% KOH solution was added and the solution was refluxed on a water bath for 30 min. The solution changed its color from reddish violet to violet. After being cooled, the solution was acidified with 6N H_2SO_4 and the precipitate was washed with H_2O , and 20 mg. of 5-bromo-1,3-azulenedicarboxylic acid (XVIII), sparingly soluble in organic solvents, was obtained. Sublimation of 20 mg. of (XVIII) at 270~280° under reduced pressure (100 mm. Hg.) produced blue leaflets. The crystals were dissolved in petr. ether (b.p. 50~60°) and the solution was passed through a column of alumina. The column was eluted with petr. ether and the solvent was cautiously evaporated. The residue was crystallized from $MeOH-H_2O$ (2:1) to yield ca. 10 mg. of (XIX), m.p. 48~50°. *Anal.* Calcd. for $C_{10}H_7Br$: C, 57.97; H, 3.38. Found: C, 58.23; H, 3.16. UV λ_{max}^{MeOH} $m\mu$ (log ϵ): 280 (4.62), 302 (3.82), 343 (3.81), 359 (3.56).

The author expresses his deep gratitude to Professors Tetsuo Nozoe and Shuichi Seto for their kind and unflinching guidances throughout the course of the present work. The author is indebted to Messrs. S. Aono and H. Sato for measurement of the infrared and ultraviolet spectra, and to Miss Y. Endo and Mr. S. Ohyama for elemental analyses.

Summary

5-Bromo- and 6-bromoazulene derivatives were synthesized by the application of a new synthetic method to azulene derivatives.

(Received August 25, 1961)