*Synthesis of 2-Substituted Azulenes by Nucleophilic Substitution Reactions of 2-Haloazulene Derivatives**

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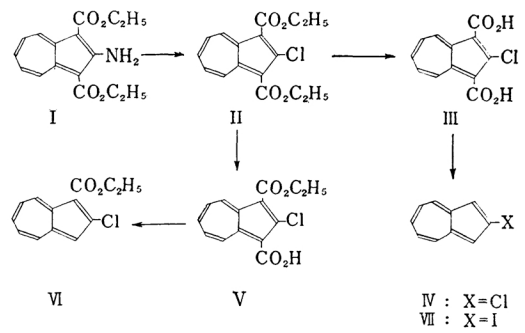
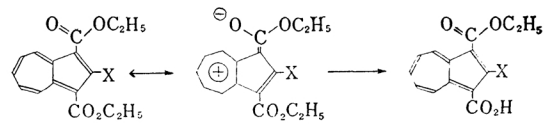
Quantum mechanical calculation as to the position of attack on azulenes by nucleophilic reagents, first made by Brown[1], showed that such reactions should result in substitution in the 4- (or 8-) and 6-positions. The susceptibility of the 4-position to nucleophilic attack was proved by an ether exchange reaction converting ethyl 4-methoxyazulenecarboxylate into 4-ethoxyazulenecarboxylate[2]. According to the result of the ground state electron density calculation made by Julg[3] using the SCF-method, it has been shown that the density in the 2-position has comparatively lower values.

In the preceding papers[4], we reported that the reaction of 2-halo- or 2-methoxytropone with ethyl cyanoacetate resulted in the novel condensation to form diethyl 2-aminoazulene-1, 3-dicarboxylate (I) and other related azulene derivatives. In the present series of experiments, we wish to report on nucleophilic substitution at 2-position in 2-haloazulene derivatives, obtained from the compound I by Sandmeyer reaction.

Passage of dry hydrogen chloride gas through the benzene solution of I precipitated reddish orange salt[4b], and addition of isoamyl nitrite to this suspension resulted in the color change from green, blue, violet, to red, and the reaction mixture afforded diethyl 2-chloroazulene-1, 3-dicarboxylate (II), m. p. 78°C, in over 90% yield. The use of hydrogen bromide in place of hydrogen chloride resulted in the formation of a small amount of deaminated product, diethyl azulene-1, 3-dicarboxylate, but not of the anticipated 2-bromo compound. Hydrolysis of II with an excess of 10% ethanol - water solution of potassium hydroxide afforded 2-chloroazulene-1, 3-dicarboxylic acid (III), very sparingly soluble in organic solvents, and its decarboxylation by heating at 265~270°C under a partially reduced pressure gave 2-chloroazulene (IV) as violet crystals of m. p. 92°C, in a fairly good yield. Hydrolysis of II with one molar equivalent of potassium hydroxide produced a crystalline monobasic acid (V), whose decarboxylation by heating at 250°C afforded ethyl 2-chloroazulene-1-carboxylate (VI) as reddish violet oil (picrate, m. p. 92°C). It is



interesting to note that one of two ethoxycarbonyl groups in II is somewhat more resistant to alkali, and monobasic acid (V) is obtained in a good yield. This probably means that one of two ethoxycarbonyl groups is stabilized by the resonance with the following ionic structure.



The halide interchange reaction was studied in connection with the preparation of 2-iodo- and 2-bromoazulene. 2-Iodoazulene (VII) as violet crystals of m. p. 126°C could be prepared conveniently form 2-chloro compound IV by treatment with potassium iodide in wet acetic acid. 2-Bromoazulene (VIII), however, could

* Presented at the 9th Annual Meeting of the Chemical Society of Japan, Kyoto, April, 1956; General outline of this paper is already described in some review articles. Cf. T. Nozoe, *Croat. Chem. Acta*, **29**, 201 (1957); T. Nozoe and T. Asao, in "Dai Yuki Kagaku (Comprehensive Organic Chemistry)", Vol. 13, Asakura Shoten, Tokyo (1960), p. 439; T. Nozoe and S. Ito, *Frotschr. Chem. org. Naturstoffe*, **19**, 33 (1961).

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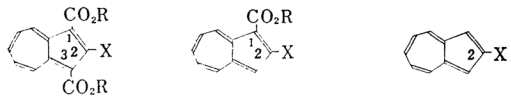
1) R. D. Brown, *Trans. Faraday Soc.*, **44**, 984 (1948).
2) D. H. Reid, W. H. Stafford and J. P. Ward, *J. Chem. Soc.*, **1958**, 1100.
3) A. Julg, *J. Chim. Phys.*, **52**, 377 (1955).
4) a) T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem. & Ind.*, **1955**, 1257; b) This Bulletin, **35**, 1179 (1962); c) T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.*, **32**, 339 (1956); d) T. Nozoe, S. Seto and S. Matsumura, *Chem. & Ind.*, **1961**, 1715; e) S. Matsumura, *Chem. Pharm. Bull.*, in press.

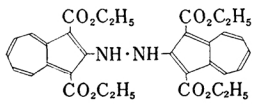
not be obtained by the action of potassium bromide in similar condition.

By the use of these compounds (II—VII), we had been able to synthesize various new azulene derivatives of the types A, B and C.



(A) (B) (C)

1, 2, 3,-Trisubstituted Azulene (A).—Reaction of II with sodium methoxide in methanol afforded dimethyl 2-methoxyazulene-1, 3-dicarboxylate (IX) and monomethyl ester of 2-methoxyazulene-1, 3-dicarboxylic acid (X). Ester group in azulene nucleus, in the presence of alkali or alcoholate, is easily exchanged by alcoholysis. Treatment of II with ammonia, methylamine, dimethylamine, aniline and *p*-bromoaniline, respectively afforded 2-amino- (I), 2-methylamino- (XI), dimethylamino- (XII), anilino- (XIII) and 2-(4'-bromoanilino)-azulene derivatives (XIV). Reaction of II with hydrazine hydrate afforded, besides diethyl 2-hydrazinoazulene-1, 3-dicarboxylate (XV), bis-1, 3-diethoxycarbonylazulen-2-yl) hydrazine (XVI).

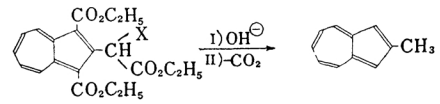


XVI

Treatment of II with sodiocompound of diethyl malonate, ethyl cyanoacetate, and ethyl acetoacetate respectively afforded the anticipated diethyl 2-diethoxycarbonylmethyl-(XVII), 2-(cyano-ethoycarbonylmethyl)- (XVIII), and 2-(acetyl-ethoxycabonylmethyl)-azulene-1,3-dicarboxylate (XIX).

1, 2-Disubstituted Azulenes (B).—Ethyl 2-chloroazulenl-1-carboxylate (VI) may be generally used to synthesize 1,2-disubstituted azulenes of the type (B). For example, reaction of VI with sodium ethoxide afforded ethyl 2-ethoxyazulene-1-carboxylate (XX), and reaction of VI with ethyl cyanoacetate, in the presence of sodium ethoxide, also afforded XX, besides a small amount of violet crystals (XXI) of unknown structure. Trisubstituted azulene (A) also could be converted to disubstituted derivatives (B) without difficulty. Thus, hydrolysis of XIII with one molar equivalent of potassium hydroxide afforded crystalline carboxylic acid, whose decarboxylation gave ethyl 2-anilinoazulene-1-carboxylate (XXII).

2-Substituted Azulenes (C).—2-Monosubstituted azulenes can be obtained as follows: 1) By saponification followed by decarboxylation of di- or trisubstituted derivatives, 2) by nucleophilic substitution of 2-iodoazulene (VII), or 3) more conveniently by nucleophilic substitution of 2-chloroazulene-1, 3-dicarboxylic acid (III) accompanied by simultaneous decarboxylation. Hydrolysis of IX, XX and XIII followed by decarboxylation respectively afforded 2-methoxy- (XXIII), 2-ethoxy- (XXIV) and 2-anilinoazulene (XXV). Heating of 2-chloroazulene (IV) with a methanolic solution of sodium methoxide in a sealed tube, however, gave only a trace of XXIII, while most of the original compound were recovered. Under the same condition, 2-iodoazulene (VII) afforded XXIII in a fairly good yield. Similarly, 2-cyanoazulene (XXVI) was obtained from VII by treatment with cuprous cyanide in pyridine over 85% yield. Heating of 2-chloroazulene-1, 3-dicarboxylic acid (III) with aniline, hydrazine and dimethylamine, respectively, resulted in facile substitution and simultaneous decarboxylation to form 2-anilino- (XXV), 2-hydrazino- (XXVII) and 2-dimethylaminoazulene (XXVIII). Hydrolysis of XVII and XVIII followed by decarboxylation produced 2-methylazulene (XXIX).



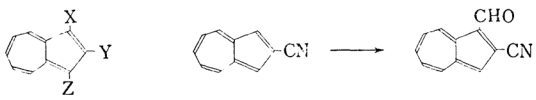
XVII : X=$CO_2C_2H_5$
XVIII : X=CN

XXIX

Cyano group in the 1- and 3-position is quite stable to attempted saponification with strong acid or alkali[4b], 2-cyanoazulene, however, are susceptible to such reagent, affording methyl azulene-2-carboxylate (XXX), on heating with absolute methanol containing hydrogen chloride. Hydrolysis of XXVI and XXX with alkali gave azulene-2-carboxylic acid (XXXI).

Further Substitution of Azulene Derivatives.—The fact that azulenes are liable to electrophilc substitution in the 1- and 3-positions is generally well known, and various azulene derivatives have been obtained by this method[5]. Combination of this electrophilic substitution and our nucleophilic substitution would give various azulene derivatives (D) having different substituents in the 1-, 2- and 3-positions. For example, application of Vilsmeier method to 2-cyanoazulene (XXVI) gave 2-cyano-1-formylazulene (2-cyanoazulene-1-carboxyaldehyde) (XXXII). This compound has been substituted further to give the compound of the type D[6].

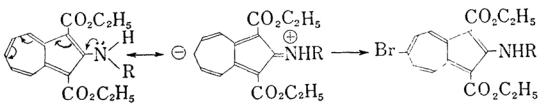
5) A. G. Anderson, Jr., J. A. Nelson and J. J. Tazuma, *J. Am. Chem. Soc.*, 75, 4980 (1953).
6) T. Nozoe and A. Sato, to be published.



(D) XXVI XXXII

Julg[3] predicted that the elctron density of the 5-position of azulene nucleus has the next highest values after 1- and 3-positions. More recently Anderson et al.[7] have reported that the acetylation of 1, 3-dichloroazulene by means of acetyl chloride in carbon tetrachloride in the presence of stannic chloride gave 5-acetyl-1, 3-dichloroazulene.

In the case of 2-amino- substituted azulenes

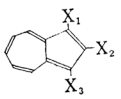


(E) (F)

R=H, CH_3, Ph.

(I, XI—XIII), the 4- (or 8-) and 6-positions would have higher electron density than the 5-position by the electron releasing mesomeric effect of the amino group in the 2-position. Accordingly, the electrophilic substitution of these compounds is likely to occur in the 4- (or 8-) and 6-positions, because 1- and 3-positions are already blocked by ethoxycarbonyl groups. Furthermore, it may be presumed that the 4- or 8-position is sterically hindered by the ethoxycarbonyl groups in the 1- and 3-positions and is less easily attacked than the 6-position. The bromination of 2-amino- (I), 2-methylamino- (XI) and 2-anilinoazulene derivatives (XIII) respectively afforded monobromo derivatives, XXXIII, XXXIV and XXXV (type F), while 2-dimethylaminoazulene derivative XII was inert to bromine. Diethyl 2-(4'-bromoanilino)azulene-1, 3-dicarboxylate (XIV) and the brominated product XXXV showed the closs melting point, but

TABLE I. SOME PROPERTIES OF THE REACTION PRODUCTS



Compd. No.	X_1	X_2	X_3	M. p., °C	Color
II	CO_2Et	Cl	CO_2Et	77～ 78	R
III	CO_2H	Cl	CO_2H	260～265(d)	R
IV	H	Cl	H	91～ 92	V
VI	CO_2Et	Cl	H	Oil (pic. 92)	R
VII	H	I	H	125～126	V
IX	CO_2Me	OMe	CO_2Me	61～ 62	O
X	CO_2H	OMe	CO_2Me	145(d)	O
XI	CO_2Et	NHMe	CO_2Et	Oil (TNB 102)	O
XII	CO_2Et	NMe_2	CO_2Et	81～ 82	O
XIII	CO_2Et	NHPh	CO_2Et	141～142	O
XIV	CO_2Et	NHPhBr	CO_2Et	166～168	O
XV	CO_2Et	$NHNH_2$	CO_2Et	Oil (acetate 132)	O
XVI	CO_2Et	NHNHAz	CO_2Et	163～164	O
XVII	CO_2Et	$CH(CO_2Et)_2$	CO_2Et	Oil	R
XVIII	CO_2Et	$CH(CN)CO_2Et$	CO_2Et	116～117	R
XIX	CO_2Et	$CH(Ac)CO_2Et$	CO_2Et	53～ 54	R
XX	CO_2Et	OEt	H	84～ 85	P
XXII	CO_2Et	NHPh	H	Oil (TNB 112)	O
XXIII	H	OMe	H	82～ 83	R.V
XXIV	H	OEt	H	Oil	R.V
XXV	H	NHPh	H	144～145	R.O
XXVI	H	CN	H	77～ 78	B
XXVII	H	$NHNH_2$	H	127～128	R.O
XXVIII	H	HMe_2	H	98～ 99	O
XXX	H	CO_2Me	H	110～111	B
XXXI	H	CO_2H	H	200～203	G
XXXII	CHO	CN	H	180～182	R.V

pic.=picrate, TNB=Trinitrobenzene compound, R=Red, V=Violet, P=Pink, O=Orange, B=Blue, G=Green, Az=1,3-Diethoxycarbonylazulen-2-yl

7) A. G. Anderson and L .L. Replogle, *J. Org. Chem.*, 25, 1275 (1960).

a distinct depression of the melting point occurred on their admixture. As the 2'- (or 6'-) position of benzene ring in XIII is sterically hindered by two ethoxycarbonyl groups in the 1- and 3-positions, the possibility of the substitution of benzene ring would be excluded. From these considerations, it was assumed that XXXIII, XXXIV and XXXV were likely to be 6-bromo derivatives of I, XI and XIII respectively. Resistance of dimethylamino compound XII in bromination reaction would be due to the steric interference between two ethoxycarbonyl groups and a dimethylamino group. More recently, one of us (Matsumura)[4e] established the structure of the compound (XXXIII) as diethyl 2-amino-6-bromoazulene-1, 3-dicarboxylate, by synthesizing this compound from 5-bromo-2-methoxytropone and ethyl cyanoacetate.

Visible Absorption Spectra.—The visible absorption spectra[8] of the compounds IV, VII, XXIII, XXVI, XXVIII, and XXX are shown in Fig. 1. It was found that substitution of *o, p*-directing group in the 2-position of azulene ring caused a shift toward shorter wavelengths and substitution of *m*-directing group in the same position, a shift toward longer wavelengths in the spectra.

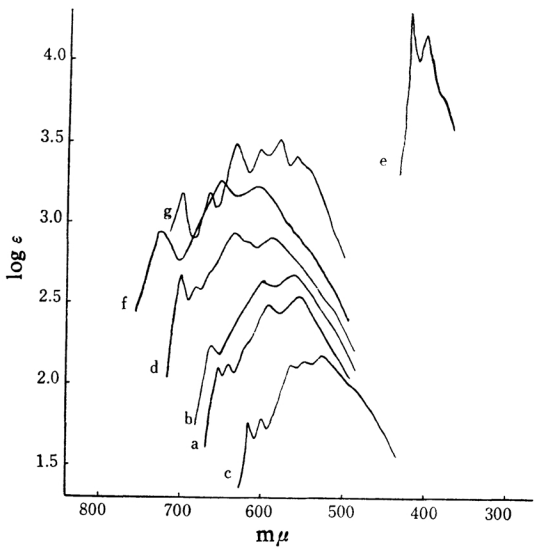


Fig. 1. Visible absorption spectra of IV, VII, XXIII, XXVI, XXVIII and XXX in cyclohexane.

IV(a) $Y = \log\varepsilon + 0$
VII(b) $Y = \log\varepsilon + 0.1$
XXIII(c) $Y = \log\varepsilon + 0$
XXVI(d) $Y = \log\varepsilon + 0.2$
XXVIII(e) $Y = \log\varepsilon + 0$
XXX(f) $Y = \log\varepsilon + 0.5$
Azulene(g) $Y = \log\varepsilon + 1.0$

8) Visible absorption spectra were measured with a Beckman DK spectrophotometer.

Experimental[9]

Diethyl 2-Chloroazulene-1, 3-dicarboxylate (II).—Dry hydrogen chloride gas passed through a solution of 6 g. of diethyl 2-aminoazulene-1, 3-dicarboxylate (I) dissolved in 200 ml. of dehydrated benzene under cooling and reddish orange precipitates began to separate out. Addition of 2.7 g. of isoamyl nitrite to this suspension resulted in the color change form green, blue, violet, to red gradually and the reaction mixture was allowed to stand overnight at room temperature. The solution was washed with water. After being dried over anhydrous sodium sulfate, the solvent was evaporated. The crystalline residue that formed was recrystallized from ethanol to afford 5.4 g. of II as red prisms, m. p. 77~78°C.

Found: C, 62.96; H, 4.91. Calcd. for $C_{16}H_{15}O_4Cl$: C, 62.54; H, 4.92%.

UV λ_{max}^{MeOH} mμ (logε): 237 (4.50), 272 (4.36), 296 (4.65), 306 (4.75), 310 (4.58), 344 (3.90), 349 (3.89), 357 (3.68).

Diethyl Azulene-1, 3-dicarboxylate.—To a solution of 600 mg. of I dissolved in 20 ml. of dehydrated benzene saturated with dry hydrogen bromide, 270 mg. of isoamyl nitrite was added at room temperature. The color of the mixture changed to reddish brown gradually. After allowing to stand overnight at room temperature, the solution was washed with water and dried over anhydrous sodium sulfate and the solvent was removed under a reduced pressure. The oily 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 ethanol to give 150 mg. of diethyl azulene-1, 3-dicarboxylate, m. p. 120~121°C

2-Chloroazulene-1, 3-dicarboxylic Acid (III).—A solution of 5 g. of II dissolved in 50 ml. of 10% ethanol-water (4 : 1) solution of potassium hydroxide was refluxed in a water bath for 15~30 min. The solution colored from red to reddish violet. After being cooled, the solution was acidified with 6 N nitric acid. The precipitate thereby formed was collected by filtration and repeatedly washed with water, by which 4 g. of sparingly soluble 2-chloroazulene-1, 3-dicarboxylic acid (III), m. p. 260 ~265°C (decomp.), was obtained.

2-Chloroazulene (IV).—Low-pressure (200 mmHg) sublimation of 1 g. of III by heating at 265~270°C produced violet crystals. The crystals were dissolved in petroleum ether (b. p. 50~60°C) and the solution was passed through a column of alumina. The column was eluted with petroleum ether and the solvent was cautiously removed. The crystalline residue was recrystallized from methanol to give 600 mg. of IV as violet needles, m. p. 91~92°C.

Found: C, 74.16; H, 4.13. Calcd. for $C_{10}H_7Cl$: C, 74.07; H, 4.32%.

9) All melting points are uncorrected. The microanalyses were carried out by Mr. S. Ohyama, Miss. A. Iwanaga and Mr. S. Azumi, to whom the authors are deeply indebted.

UV λ_{max}^{MeOH} mμ (logε): 226 (4.36), 275 (4.87), 284 (4.88), 290 (4.35), 328 (3.76), 343 (3.85), 350 (3.53); $\lambda_{max}^{Cyclohexane}$ mμ (logε): 552 (2.55), 593 (2.49), 619 (2.22), 638 (2.11), 653 (2.10).

Ethyl 2-Chloroazulene-1-carboxylate (VI).—To a solution of 200 mg. of potassium hydroxide dissolved in 10 ml. of ethanol-water (4:1) mixture, 1 g. of II was added and the mixture was refluxed in a water bath for 15 min., by which the color of solution turned clearly reddish violet. The solution was acidified with 6 N nitric acid. The precipitate was collected by filtration and repeatedly washed with water, by which 500 mg. of crude crystalline carboxylic acid (V), m. p. 193~195°C (decomp.), was obtained. Five hundred milligrams of V was decarboxylated by treatment as in the foregoing case. The oily substance thereby obtained was dissolved in petroleum ether (b. p. 50~60°C) and the solution was passed through a column of alumina, by which the product separated into violet and reddish violet bands. Elution of the violet band with petroleum ether afforded ca. 20 mg. of IV. Elution of the reddish violet band with benzene gave 300 mg. of reddish violet oil (VI).

Picrate of VI.—Red needles, m. p. 91~92°C, as recrystallized from ethanol. Found: C, 48.97; H, 3.15; N, 9.26. Calcd. for $C_{19}H_{14}O_9N_3Cl$: C, 49.20; H, 3.02; N, 9.07%.

2-Iodoazulene (VII).—A mixture of 10 g. of IV and 200 g. of potassium iodide in 600 ml. of acetic acid containing 50 ml. of water was refluxed at 130~140°C for 3.5 hr. and diluted with 1000 ml. of water. The violet crystals thet separated out were collected by filtration. The collected crystals were dissolved in benzene to separate from inorganic salt and the solution was passed through a column of alumina. The column was eluted with benzene and the solvent was removed. The violet crystals thereby obtained were recrystallized from a large quantity of methanol to afford 12 g. of violet needles (VII), m. p. 125~126°C.

Found: C, 47.08; H, 2.69. Calcd. for $C_{10}H_7I$: C, 47.24; H, 2.75%.

UV $\lambda_{max}^{Cyclohexane}$ mμ (logε): 558 (2.58), 601 (2.54), 660 (2.13).

Attempted Synthesis of 2-Bromoazulene (VIII).—A mixture of 100 mg. of IV and 1.5 g. of potassium bromide was refluxed with 6 ml. of glacial acetic acid and 0.5 ml. of water for 4 hr. The reaction mixture was diluted with 10 ml. of water. The black precipitates that separated out were collected by filtration. The precipitates were very sparingly soluble in organic solvents.

Action of Sodium Methoxide on II.—To a solution of 300 mg. of sodium methoxide dissolved in 3 ml. of absolute methanol, 200 mg. of II was added and the mixture was refluxed on a water bath for 2 hr. After evaporation of methanol, the residue was dissolved in water to separate into water-insoluble and soluble portions. The water-insoluble portion was recrystallized from methanol to give 120 mg. of orange needles (IX), m. p. 61~62°C.

Found: C, 65.53; H, 5.12. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15%.

The water-soluble portion produced, upon neutralization with dilute nitric acid, 20 mg. of orange precipitates and recrystallization from methanol afforded micro scales (X), m. p. 143~145°C (decomp.).

Found: C, 64.82; H, 4.58. Calcd. for $C_{14}H_{12}O_5$: C, 64.61, H, 4.65%.

Diethyl 2-Aminoazulene-1, 3-dicarboxylate (I).—A mixture of 100 mg. of II, 1 ml. of ethanol and 1 ml. of 28% ammonia water was sealed in a tube and heated at 100°C for 1 hr. The mixture was allowed to cool and crystals that formed were collected by filtration. The recrystallization from ethanol afforded 60 mg. of orange prisms (I), m. p. 93~94°C.

Diethyl 2-Methylaminoazulene-1, 3-dicarboxylate (XI).—To a solution of 200 mg. of II dissolved in 3 ml. of ethanol, 3 ml. of 10% aqueous solution of methylamine was added and refluxed on a water bath for 2 hr. After removal of ethanol, the reaction mixture was diluted with water and extracted with benzene and the benzene extract was passed through a column of alumina, by which the product separated into red and orange bands. Elution of the red band with benzene recovered 40 mg. of II. Further elution of the orange band with benzene-ethyl acetate mixture afforded 160 mg. of orange oil (XI).

UV λ_{max}^{MeOH} mμ (logε): 230 (4.13), 253 (4.25), 275 (4.23), 325 (4.62), 405 (3.82).

1, 3, 5-Trinitrobenzene Compound of XI.—Orange needles, m. p. 100~102°C, as recrystallized from ethanol.

Found: C, 53.92; H, 4.56; N, 10.76. Calcd. for $C_{23}H_{22}O_{10}N_4$: C, 53.70; H, 4.31; N, 10.89%.

Diethyl 2-Dimethylaminoazulene-1, 3-dicarboxylate (XII).—A mixture of 200 mg. of II, 3 ml. of 40% aqueous solution of dimethylamine and 3 ml. of ethanol was refluxed on a water bath for 2 hr. and the reaction mixture was diluted with water. The orange crystals that separated out were collected by filtration. The collected crystals were recrystallized from petroleum ether (b. p. 80~90°C) to afford 160 mg. of orange leaflets (XII), m. p. 81~82°C.

Found: C, 68.77; H, 6.49; N, 4.83. Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44%.

UV λ_{max}^{MeOH} mμ (logε): 223 (4.20), 265 (4.30), 323 (4.58), 430 (4.04).

Diethyl 2-Anilinoazulene-1,3-dicarboxylate (XIII).—A mixture of 100 mg. of II dissolved in 2 ml. of ethanol and 60 mg. of aniline was heated in a water bath for 3 hr. and the reaction mixture was diluted with water and extracted with benzene. After removal of the solvent, the residue was recrystallized from ethanol to give 70 mg. of orange needles (XIII), m. p. 141~142°C.

Found: C, 72.81; H, 5.83; N, 3.69. Calcd. for $C_{22}H_{21}O_4N$: C, 72.71; H, 5.82; N, 3.85%.

UV λ_{max}^{MeOH} mμ (logε): 230 (4.25), 237 (4.25), 260 (4.28), 270 (4.40), 310 (4.62), 327 (4.68), 420 (4.09).

Diethyl 2-(4'-Bromoanilino)-azulene-1, 3-dicarboxylate (XIV).—A mixture of 100 mg. of II dissolved in 2 ml. of ethanol and 100 mg. of *p*-bromoaniline was treated as in the foregoing case, by which 60 mg. of orange needles (XIV), m. p. 166~168°C was obtained.

Found: C, 59.58; H, 4.77; N, 3.16. Calcd. for $C_{22}H_{20}O_4NBr$: C, 59.73; H, 4.52; N, 3.16%.

Diethyl 2-Hydrazinoazulene-1, 3-dicarboxylate (XV).—To a solution of 100 mg. of II dissolved in 3 ml. of ethanol, 100 mg. of 80% aqueous solution of hydrazine hydrate was added and the mixture was refluxed for 2 hr. When cooled, crystals formed, they were collected by filtration and recrystallized from ethanol to give 30 mg. of orange scales of bis-(1, 3-diethoxycarbonylazulen-2-yl)hydrazine (XVI), m. p. 163~164°C.

Found: C, 67.37; H, 5.59; N, 4.68. Calcd. for $C_{32}H_{32}O_8N_2$: C, 67.12; H, 5.63; N, 4.89%.

The mother liquor after separation of above product was evaporated. The oily residue thereby formed was dissolved in benzene and the solution was passed through a column of alumina, by which the product separated into red, yellow and orange bands. Elution of the red band with benzene recovered II. Further elution of the orange band with benzene afforded 30 mg. of orange oil (XV).

Isopropylidine Compound of XV.—A solution of 30 mg. of XV dissolved in 0.3 ml. of acetone was warmed on a water bath for 10 min. After removal of the solvent, the residue was dissolved in benzene and chromatographically purified through a column of alumina. Isopropylidine compound was obtained as orange leaflets, m. p. 133~134°C.

Found: C, 67.15; H, 6.34; N, 8.33. Calcd. for $C_{19}H_{22}O_4N_2$: C, 66.65; H, 6.48; N, 8.18%.

Acetate of XV.—A solution of 50 mg. of XV dissolved in 0.5 ml. of acetic anhydride was warmed on a water bath for 50 min. Evaporation of excess acetic anhydride left crystals which were recrystallized from ethanol and acetate of XV, m. p. 130~132°C, was obtained.

Found: C, 62.61; H, 5.83; N, 8.25. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%.

Diethyl 2-(Diethoxycarbonylmethyl)-azulene-1, 3-dicarboxylate (XVII).—To a suspension of diethyl sodiomalonate prepared from 30 mg. of metallic sodium, 250 mg. of diethyl malonate and 1 ml. of absolute ethanol, 100 mg. of II was added and the mixture was warmed on a water bath for 1 hr. The color of reaction mixture turned into dark reddish violet. After removal of the solvent, the residue was dissolved in water and the solution was acidified with acetic acid and the dark red oil that formed was extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and passed through a column of alumina, by which the product separated into red and dark red bands. Elution of the red band with benzene afforded ca. 10 mg. of II. Further elution of the dark red band with ethyl acetate gave 60 mg. of red oil (XVII).

Found: C, 64.57; H, 6.83. Calcd. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09%.

Diethyl 2-(Cyano-ethoxycarbonylmethyl)-azulene-1, 3-dicarboxylate (XVIII).—To a suspension of ethyl sodiocyanoacetate prepared from 75 mg. of metallic sodium, 370 mg. of ethyl cyanoacetate and 5 ml. of absolute ethanol, 500 mg. of II was added and the mixture was heated at 90°C for 1 hr. and small amount of precipitate separated gradually. Ethanol was evaporated from the mixture, the residue was dissolved in water and the solution was acidified with 6 N nitric acid by which red crystalline precipitate was produced. The precipitate was dissolved in benzene and chromatographically purified through an alumina column. The crystals thereby obtained were recrystallized from ethanol to give 470 mg. of XVIII as red prisms, m. p. 116~117°C.

Found: C, 65.63; H, 5.68; N, 3.92. Calcd. for $C_{21}H_{21}O_6N$: C, 65.78; H, 5.52; N, 3.65%.

UV λ_{max}^{MeOH} mμ (logε): 235 (4.50), 277 (4.51), 300 (4.72), 335 (3.87), 355 (3.86), 363 (3.97).

Diethyl 2-(Acetyl-ethoxycarbonylmethyl)-azulene-1, 3-dicarboxylate (XIX).—To a suspension of ethyl sodioacetoacetate prepared from 50 mg. of metallic sodium, 400 mg. of ethyl acetoacetate and 4 ml. of absolute ethanol, 200 mg. of II was added and the mixture was warmed in a water bath for 1 hr. The reaction mixture changed the color from reddish purple to dark purple and the precipitates began to separate out gradually. After removal of the solvent, the residue was dissolved in water and the aqueous solution was acidified with 6 N nitric acid. The red oil thereby produced was extracted with benzene and the benzene extract was dried over anhydrous sodium sulfate. The solution was passed through a column of alumina. The column was eluted with ethyl acetate and 120 mg. of red crystals was obtained. Recrystallization from cyclohexane afforded 100 mg. of red prisms (XIX), m. p. 53~54°C.

Found: C, 66.03; H, 5.25. Calcd. for $C_{22}H_{24}O_7$: C, 65.98; H, 6.04%.

UV λ_{max}^{MeOH} mμ (logε): 235 (4.55), 267 (4.41), 305 (4.80), 340 (3.90).

Ethyl 2-Ethoxyazulene-1-carboxylate (XX).—To a solution of 100 mg. of sodium ethoxide dissolved in 3 ml. of absolute ethanol, 200 mg. of VI was added and the mixture was refluxed for 3 hr. After evaporation of ethanol, the residue was dissolved in benzene and the solution was passed through a column of alumina, by which the product separated into red and pink bands. Elution of the red band with benzene recovered 60 mg. of VI. Further elution of the pink band with benzene afforded 90 mg. of pink crystals. Recrystallization from ethanol afforded pink prisms (XX), m. p. 84~85°C.

Found: C, 73.68; H, 6.49. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%.

UV $\lambda_{max}^{Cyclohexane}$ mμ (logε): 464 (2.09), 488 (2.11), 527 (1.92), 574 (1.17).

Reaction of VI with Ethyl Cyanoacetate.—To a suspension of ethyl sodiocyanoacetate prepared from 40 mg. of metallic sodium, 200 mg. of ethyl cyanoacetate and 4 ml. of absolute ethanol, 150 mg. of VI was added and the mixture was heated at 120~130°C for 1.5 hr. The reaction occurred gradually and dark violet precipitate began to separate out. After removal of ethanol, the residue was dissolved in water and the solution was acidified with 6 N nitric acid. The dark oil thereby formed was extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and the solution was passed through a column of alumina, by which the product separated into red, pink and dark violet bands. Elution of the red band with

benzene recovered 90 mg. of VI. Further elution of the pink band with benzene afforded crystalline substance. Recrystallization from ethanol gave ca. 20 mg. of XX, m. p. 84~85°C. Further elution of the dark violet band with ethyl acetate afforded a small amount of violet needles (XXI), m. p. 115~116°C. The yield of XXI was so poor that further examination of this product was not made.

Ethyl 2-Anilinoazulene-1-carboxylate (XXII).—To a solution of 15 mg. of potassium hydroxide dissolved in 1.5 ml. of ethanol, 100 ml. of XIII was added and the mixture was refluxed in a water bath for 3 hr. After being cooled, the solution was acidified with 6N hydrochloric acid. The crystalline carboxylic acid thereby formed was collected by filtration and washed with water and benzene. The thermal decomposition of the carboxylic acid by heating at 160°C produced orange oil and the oil was dissolved in petroleum ether (b. p. 70~80°C). The solution was passed through a column of alumina. The column was eluted with benzene and 50 mg. of orange oil (XXII) was obtained.

Trinitrobenzene Compound of XXII.—Brownish orange needles, m. p. 111~112°C, as recrystallized from ethanol.

Found; C, 60.41; H, 3.52; N, 10.86. Calcd. for $C_{25}H_{20}O_8N_4$: C, 59.52; H, 4.00; N, 11.11%.

2-Methoxyazulene (XXIII).—a) A mixture of 50 mg. of VII and 100 mg. of sodium methoxide dissolved in 1 ml. of absolute methanol was sealed in a tube and heated at 100°C for 30 hr. The reaction occurred gradually and the color changed from violet to reddish violet. Evaporation of methanol left crystalline residue. The residue was dissolved in petroleum ether (b. p. 50~60°C) and the solution was passed through a column of alumina. The column was eluted with petroleum ether and a small amount of VII was recovered. Further elution of the column with petroleum ether-benzene (1:1) mixture afforded 20 mg. of reddish violet crystals which were crystallized from methanol to give reddish violet needles (XXIII), m. p. 82~83°C, with an aroma.

Found: C, 83.46; H, 6.21. Calcd. for $C_{11}H_{10}O$: C, 83.51; H, 6.37%.

UV λ_{max}^{MeOH} mμ (logε): 237 (4.07), 275 (4.76), 300 (4.72), 335 (3.87), 355 (3.86), 363 (3.97). $\lambda_{max}^{Cyclohexane}$ mμ (logε): 524 (2.19), 544 (2.14), 550 (2.13), 561 (2.12), 592 (1.77), 613 (1.75).

b) A mixture of 100 mg. of IV and 200 mg. of sodium methoxide dissolved in 2 ml. of absolute methanol was treated as in the foregoing case. One-hundred and seventy milligrams of IV was recovered and a small amount of XXIII was obtained.

c) To a solution of 50 mg. of IX dissolved in 0.5 ml. of ethanol, 1 ml. of 10% aqueous solution of potassium hydroxide was added and the solution was refluxed in a water bath for 2 hr. The color of the solution changed from orange to reddish violet. After cooling, the solution was acidified with 6N sulfuric acid and the precipitate was washed with water and 30 mg. of crude acid substance sparingly soluble in organic solvents was obtained. Low-pressure (100 mmHg) sublimation of the acid substance by heating at 200°C produced red oily substance. Purification by chromatography over alumina gave 10 mg. of XXIII.

2-Ethoxyazulene (XXIV).—To a solution of 50 mg. of XX dissolved in 1 ml. of 10% aqueous solution of potassium hydroxide was added and the mixture was treated as in the case of above procedure c). The oil thereby obtained was chromatographically purified through an alumina column, by which 20 mg. of reddish violet oil (XXIV) was obtained.

UV λ_{max}^{MeOH} mμ (logε): 237 (3.99), 275 (4.69), 285 (4.81), 315 (3.65), 340 (3.45), 355 (3.59), 370 (3.48).

2-Anilinoazulene (XXV).—a) A solution of 100 mg. of XIII dissolved in 2 ml. of 10% ethanol-water (4:1) solution of potassium hydroxide was warmed in a water bath for 2.5 hr. After cooling, the solution was acidified with 6N hydrochloric acid. The acid substance thereby formed was collected by filtration, washed with water and completely dried in a desiccator. The acid substance was heated at 160°C under a reduced pressure (10 mmHg) to effect decarboxylation, by which reddish orange crystals were obtained. The crystals were recrystallized from petroleum ether (b. p. 50~60°C) to give 40 mg. of XXV as reddish orange scales, m. p. 144~145°C.

Found: C, 87.53; H, 6.07; N, 6.43. Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39%.

UV λ_{max}^{MeOH} mμ (logε): 256 (4.14), 310 (4.75), 352(3.78), 420 (4.35).

b) To a solution of 50 mg. of III dissolved in 0.5 ml. of pyridine, 100 mg. of aniline was added and the mixture was heated at 120~130° for 1 hr. After removal of pyridine, the residue was dissolved in benzene and the solution was passed through a column of alumina, by which the product separated into yellow and brown bands. Elution of the yellow band with benzene recovered aniline. Further elution of the brown band with benzene afforded reddish orange crystals which were recrystallized from petroleum ether to give ca. 15 mg. of XXV, m. p. 144~145°C.

2-Cyanoazulene (XXVI).—a) A mixture of 5 g. of VII, 5 g. of cuprous cyanide and 50 ml. of pyridine, dried over solid potassium hydroxide, was heated at 140~150°C for 30 min. The color of the solution changed from violet to deep blue. Pyridine was distilled off under a reduced pressure and the residue was dissolved in benzene to separate from inorganic substance. Evaporation of benzene left deep blue crystalline solid. The crystalline solid was dissolved in a large quantity of cyclohexane and the solution was passed through a column of alumina, by which the product separated into violet and deep blue bands. Elution of the violet band with cyclohexane recovered 600 mg. of VII. Further elution of the deep blue band with benzene afforded 2 g. of blue crystals which were recrystallized from methanol to give deep blue leaflets (XXVI), m. p. 77~78°C.

Found: C, 86.31; H, 4.43; N, 9.36. Calcd. for $C_{11}H_7N$: C, 86.25; H, 4.61; N, 9.15%.

UV $\lambda_{max}^{Cyclohexane}$ mμ (logε): 586 (2.72), 621 (2.71), 635 (2.73), 660 (2.50), 679 (2.40), 697 (2.47).

b) A mixture of 500 mg. of IV, 500 mg. of cuprous cyanide and 5 ml. of pyridine was treated as in the foregoing case, by which 430 mg. of IV was recovered and 10 mg. of XXVI was obtained.

2-Hydrazinoazulene (XXVII).—A solution of 100 mg. of III dissolved in 3 ml. of 80% aqueous solution of hydrazine hydrate was heated in a water bath for 30 min. The leaflet crystals began to separate out. The crystals were collected by filtration and recrystallized from benzene to afford 30 mg. of reddish orange leaflets (XXVII), m. p. 127~128°C.

Found: C, 75.89; H, 6.54; N, 17.83. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71%.

UV λ_{max}^{MeOH} mμ (logε): 240 (4.12), 285 (4.82), 296 (4.92), 347 (3.76), 389 (3.94), 405 (3.86).

2-Dimethylaminoazulene (XXVIII).—A solution of 100 mg. of III dissolved in 3 ml. of 40% aqueous solution of dimethylamine was sealed in a tube and heated at 100°C for 3 hr. The leaflet crystals formed on cooling were collected by filtration and dissolved in benzene. The solution was passed through a column of alumina. The column was eluted with benzene and 50 mg. of orange crystals was obtained. Recrystallization from ethanol afforded 30 mg. of XXVIII as orange leaflets, m. p. 98~99°C.

Found: C, 84.21; H, 7.85; N, 8.43. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18%.

UV λ_{max}^{MeOH} mμ (logε): 247 (4.05), 292 (4.75); 302 (4.83), 335 (3.69), 355 (3.74), 400 (4.06), 424 (4.23).

2-Methylazulene (XXIX).—A solution of 200 mg. of XVII or XVIII dissolved in 30% ethanol-water (4:1) solution of potassium hydroxide was heated at 100°C for 6 hr. After cooling, the solution was acidified with 6 N hydrochloric acid. The precipitate thereby formed was collected by filtration and repeatedly washed with water. After being dried, low pressure sublimation (100 mmHg) of the precipitate by heating at 260~270°C produced violet oil with an odor of naphthalene. The oil was dissolved in petroleum ether (b. p. 50~60°C) and chromatographically purified through an alumina column, by which 70 mg. of the crystalline residue was obtained. Recrystallization from methanol-water mixture gave 50 mg. of violet needles (XXIX), m. p. 49~50°C. The ultraviolet and visible absorption spectra of XXIX and its melting point were in good agreement with those reported in the literature.

Methyl Azulene-2-carboxylate (XXX).—Hydrogen chloride gas was passed through the solution of 100 mg. of XXVI dissolved in 3 ml. of absolute methanol and the solution was heated on a water bath for 8 hr. Methanol was evaporated from the solution and residual crystals were dissolved in petroleum ether-benzene (1:1) mixture. The solution was passed through a column of alumina. The column was eluted with benzene-petroleum ether mixture and 60 mg. of blue crystals was obtained. Recrystallization from methanol afforded blue needles (XXX), m. p. 110~111°C.

Found: C, 77.19; H, 5.40. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41%.

UV $\lambda_{max}^{Cyclohexane}$ mμ (logε): 604 (2.71), 656 (2.73), 713 (2.37), 728 (2.42).

Azulene-2-carboxylic Acid (XXXI).—a) A solution of 100 mg. of XXVI dissolved in 2 ml. of 10% ethanol-water (4:1) solution of potassium hydroxide was warmed in a water bath for 3 hr. Black substance began to precipitate out. The filtrate obtained after isolation of the black substance was concentrated and the residue was dissolved in water. The solution was neutralized with dilute sulfuric acid, from which green precipitate was obtained. Recrystallization of this precipitate from benzene afforded 20 mg. of XXXI as green needles, m. p. 200~203°C (decomp.).

Found: C, 76.67; H 5.00. Calcd. for $C_{11}H_8O_2$: C, 76.73; H, 4.68%.

UV λ_{max}^{MeOH} mμ (logε): 610 (2.62), 661 (2.65), 732 (2.35).

b) A solution of 100 mg. of XXX dissolved in 2 ml. of 10% ethanol-water (4:1) solution of potassium hydroxide was treated as the above procedure, by which 40 mg. of XXXI was obtained.

2-Cyano-1-formylazulene (XXXII).—To a solution of 100 mg. of XXVI dissolved in 0.3 ml. of dimethylformamide, 120 mg. of phosphorus oxychloride was added under ice-cooling. The reaction mixture was poured into ice-water, by which reddish violet crystals began to precipitate out. The crystals were recrystallized from methanol to afford 80 mg. of XXXII as reddish violet scales, m. p. 180~182°C.

Found: C, 79.46; H, 4.05; N, 7.62. Calcd. for $C_{12}H_7ON$: C, 79.55; H, 3.89; N. 7.73%.

UV $\lambda_{max}^{Cyclohexane}$ mμ (logε): 543 (2.88), 583 (2.90), 629 (2.57), 645 (2.51).

Bromination of Diethyl 2-Aminoazulene-1, 3-dicarboxylate (I).—To a solution of 100 mg. of I dissolved in 2 ml. of chloroform, 60 mg. of bromine was added and the mixture was allowed to stand at room temperature for 2 hr. A large amount of orange crystals began to precipitate out. The crystals were collected by filtration and repeatedly washed with water. Recrystallization from benzene afforded 130 mg. of orange prisms (XXXIII), m. p. 163~164°C.

Found: C, 52.65; H, 4.23; N, 3.72. Calcd. for $C_{16}H_{16}O_4NBr$: C, 52.35; H, 4.37; N, 3.87%.

UV λ_{max}^{MeOH} mμ (logε): 245 (4.33), 320 (4.55), 332 (4.66), 410 (3.38), 473 (3.50).

Bromination of Diethyl 2-Methylaminoazulene-1, 3-dicarboxylate (XI).—To a solution of 100 mg. of XI dissolved in 1.5 ml. of acetic acid, 60 mg. of bromine was added, by which brownish red oil separated out and later crystallized. The mixture was allowed to stand overnight at room temperature. Acetic acid removed and the residual oil was extracted with chloroform. The chloroform extract was washed with an aqueous solution of sodium hydrogencarbonate and water. After removal of chloroform, the 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 brown oil which was crystallized from cyclohexane to crystals of melting point, 98~105°C.

Recrystallization from ethanol afforded 90 mg. of orange scales (XXXIV), m. p. 117~118°C.

Found: C, 53.79; H, 4.65; N, 3.46. Calcd. for $C_{17}H_{18}O_4NBr$: C, 53.54; H, 4.73; N, 3.67%.

Bromination of Diethyl 2-Anilinoazulene-1, 3-dicarboxylate (XIII).—To a solution of 100 mg. of XIII dissolved in 2 ml. of chloroform, 60 mg. of bromine was added and the mixture was allowed to stand at room temperature for 2 hr. The chloroform solution was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dissolved in benzene and the solution was passed through a column of alumina. The column was eluted with benzene and 60 mg. of orange crystals was obtained. Recrystallization from ethanol afforded orange scales (XXXV), m. p. 173~174°C, which showed a distinct depression of the melting point on admixture with XIV.

Found: C, 59.64; H, 4.82; N, 3.27. Calcd. for $C_{22}H_{20}O_4NBr$: C, 59.73; H, 4.52; N, 3.16%.

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