# The Synthesis of Azulene Derivatives Condensed with Several Heterocycles[1)]

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The reactions of ethyl 1,2-diaminoazulene-3-carboxylate with formic acid, nitrous acid, glyoxal sodium bisulfite, diacetyl, and benzil afforded the corresponding azulene derivatives condensed at the 1,2-position with nitrogen-containing heterocycles, namely, imidazole, triazole, and pyrazine rings. 2-Amino-1-formylazulene reacted with guanidine or thiourea to give 2-aminoazuleno[2,1-*d*]pyrimidine. The ultraviolet and visible absorption spectra of these azulenes are presented.

Azulene derivatives condensed with furans,[2,3)] pyrroles,[4)] thiophenes,[5)] pyridines,[6,7)] pyrazines,[8)] thiapyran,[9)] and azepine[9)] have already been synthesized.

During the course of an investigation of the reactions of 1,2-diaminoazulene derivatives and 2-amino-1-formylazulene, the present authors have synthesized azuleno[1,2-*d*]imidazole, azuleno[1,2-*d*]triazole, azuleno[2,1-*b*]pyrazine and azuleno[2,1-*d*]pyrimidine derivatives; the results will be reported in this paper.

The heating of 1,2-diacetamidoazulene (I)[10)] in acetic anhydride or acetic acid in anticipation of the formation of an azulenoimidazole derivative led to the complete recovery of the starting material, and the treatment of I in hydrochloric acid at the boiling point resulted in the formation of a resinous product besides the starting compound.

The reaction of the hydrochloride of ethyl 1,2-diaminoazulene-3-carboxylate (II)[10)] and 40% aqueous formic acid yielded yellow crystals (III) in a good yield. The results of the elemental analyses ($C_{14}H_{14}O_3N_2$) and the infrared spectrum (3420 and 3300 cm$^{-1}$ ($NH_2$)) indicate that Compound (III) is not the expected azulenoimidazole, but ethyl 2-amino-1-formamidoazulene-3-carboxylate. An alternative structure for III, ethyl 1-amino-2-formamidoazulene-3-carboxylate, may be excluded because an amino group at the 1-position is less sterically hindered and must be more basic than one at the 2-position.[10)]

The acetylation of III afforded the 2-acetamido derivative (IV), whose ultraviolet spectrum shows a curve very similar to that of ethyl 1,2-diacetamidoazulene-3-carboxylate.[10)]

The reaction of II with anhydrous formic acid yielded light purple crystals, the elemental analyses ($C_{14}H_{12}O_2N_2$) and the infrared spectrum of which show one sharp carbonyl band at 1680 cm$^{-1}$; the compound may, therefore, be assumed to be ethyl azuleno[1,2-*d*]imidazole-9-carboxylate (V).

The treatment of the solution of II in hydrochloric acid with sodium nitrite afforded orange crystals (VI) in a fairly good yield. From the analyses ($C_{13}H_{11}O_2N_3$) and the similarity of the ultraviolet spectrum (Fig. 1) to that of Compound (V), Compound (VI) is considered to be ethyl azuleno[1,2-*d*]triazole-9-carboxylate.

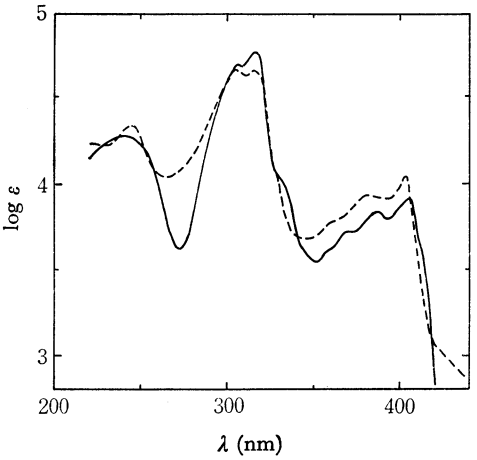

Fig. 1. UV absorption spectra of V (——) and VI (------) in methanol.

The attempted derivation of V and VI to azuleno[1,2-*d*]imidazole and azuleno[1,2-*d*]triazole respectively by alkaline hydrolysis, followed by thermal decarboxylation, resulted in the formation of a resinous substance; no objective compounds could be obtained.

The reactions of II and an aqueous solution of glyoxal or glyoxal sodium bisulfite under various conditions yielded resinous products; no pure products could be isolated. However, when unstable ethyl 1,2-diaminoazulene-3-carboxylate (IIa), obtained by passing a methanolic solution of II through an ion-exchange resin (Amberlite IRA-410), was reacted with glyoxal sodium bisulfite, ethyl azuleno[2,1-*b*]pyrazine-10-car-

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4) K. Matsui and T. Nozoe, *Chem. Ind.*, (London), **1960**, 1302; K. Matsui, *Nippon Kagaku Zasshi*, **82**, 1517, 1520, 1522, 1665, 1667 (1961); L. L. Replogle, K. Katsumoto, and H. L. Ammon, *J. Amer. Chem. Soc.*, **90**, 1086 (1968); H. L. Ammon, L. L. Replogle, D. H. Watts, Jr., K. Katsumoto, and J. M. Stewart, *ibid.*, **93**, 2196 (1971).

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8) T. Nozoe, P. W. Yang, H. Ogawa, and T. Toda, This Bulletin, **41**, 2095 (1968).

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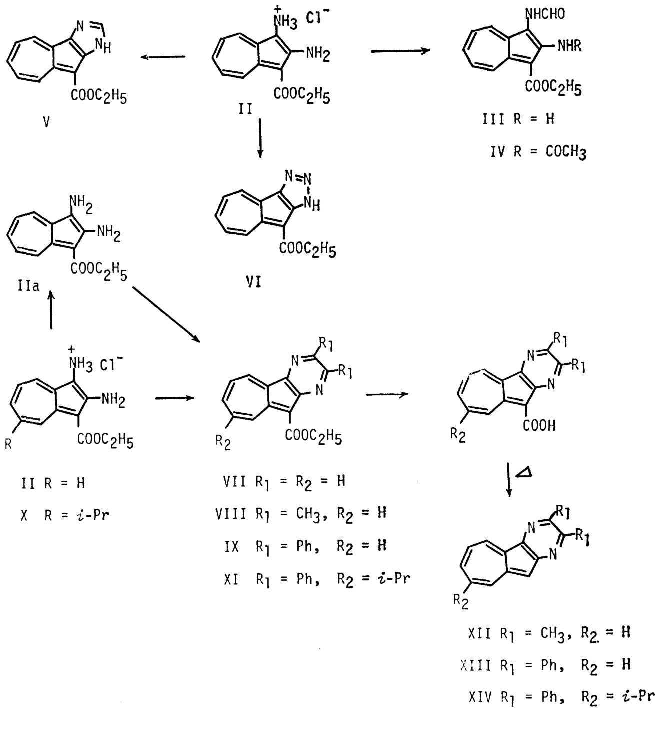
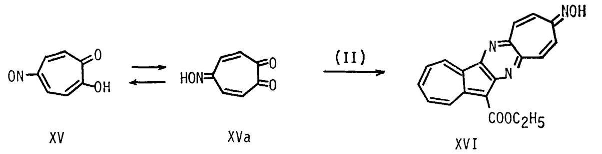
boxylate (VII) was obtained as greenish brown crystals in a low yield.

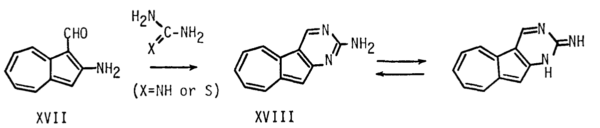
The reaction of II with diacetyl and benzil proceeded smoothly to give the corresponding products, 2,3-dimethyl and 2,3-diphenyl derivatives (VIII and IX respectively).

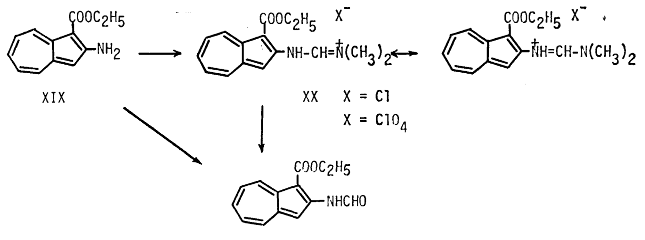
The hydrochloride of ethyl 1,2-diamino-5-isopropylazulene-3-carboxylate (X)[10] afforded the 8-isopropyl derivative (XI) by means of a reaction with benzil.

The hydrolysis of Compounds VIII, IX, and XI with ethanolic alkali gave the corresponding carboxylic acids, and the thermal decarboxylation yielded 2,3-dimethyl-, 2,3-diphenyl-, and 2,3-diphenyl-8-isopropylazuleno[2,1-*b*]pyrazine (XII, XIII, and XIV respectively).









It has been shown that 5-nitrosotropolone (XV) reacted with *o*-diamine derivatives *via* its tautometic *o*-diketone form (XVa) to give troponoids fused with pyrazine or quinoxaline rings.[11,12]

The reaction of II with XV gave yellowish-green crystals (XVI) as an insoluble precipitate. The infrared spectrum of XVI shows an OH band at 3400 cm$^{-1}$, and the permanganate oxidation of XVI, followed by methylation with diazomethane, afforded tetramethyl pyrazinetetracarboxylate;[12] therefore, Compound XVI must has the structure shown in the scheme.

2-Amino-1-formylazulene (XVII)[6] reacted with guanidine, and orange needles (XVIII) were obtained. The analyses of the compound accord with the $C_{12}H_9N_3$ formula, and the infrared spectrum displays bands at 3300 and 3100 cm$^{-1}$ similar to those of 2-aminopyrimidine;[13] thus, the compound may be considered to be 2-aminoazuleno[2,1-*d*]pyrimidine.

A similar reaction of XVII with thiourea gave the same compound (XVIII); this fact shows that the aza-nitrogen at the 1-position of XVIII came from an amino group at the 2-position of XVII in the reaction with thiourea.

The reactions of XVII with formamide and of 2-chloro-1-formylazulene with guanidine resulted in the recovery of the starting compounds in both cases.

The attempted formylation of ethyl 2-acetamidoazulene-1-carboxylate by the Vilsmeier method resulted in the complete recovery of the starting azulene. However, the similar formylation of ethyl 2-aminoazulene-1-carboxylate (XIX) afforded crystalline chloride (XX: X=Cl), which was easily converted to perchlorate (XX: X=$ClO_4$). The mild treatment of the chloride with sodium hydrogen carbonate yielded ethyl 2-formamidoazulene-1-carboxylate (XXI), which was also obtained by the direct formylation of XIX with formic acid. Therefore, Compound (XX) may be considered to have the structure shown in the scheme.

The unreactivity of the azulene attached by the ethoxycarbonyl group at the 1-position to the Vilsmeier reaction must be attributable to the electron-withdrawing effect of the ethoxycarbonyl group, as is observed in the diazo-coupling reaction of the same compound.[10]

## Experimental[14]

*Ethyl 2-Amino-1-formamidoazulene-3-carboxylate (III).* A solution of II (134 mg) in 40% formic acid (2 ml) was heated on a water bath for 30 min. After cooling, the crystals which separated out were filtered to yield 135 mg of yellowish-brown crystals; mp 200 °C. The crystals were chromatographed on alumina, using acetone as the solvent, and then recrystallized from ethyl acetate to give III as orange-yellow

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[11] T. Nozoe, M. Sato, and T. Matsuda, *Sci. Repts. Tohoku Univ.*, **I**, **37**, 407 (1953); S. Ito, *ibid.*, **42**, 236 (1958); T. Nozoe, S. Ito, S. Suzuki, and K. Hiraga, *Proc. Japan Acad.*, **32**, 344 (1956).

[12] T. Asao, This Bulletin, **34**, 151 (1961).

[13] L. N. Short and H. W. Thompson, *J. Chem. Soc.*, **1952**, 168.

[14] All melting points are uncorrected.

micro needles; mp 203—204 °C.

Found: C, 64.82; H, 5.45; N, 11.04%. Calcd for $C_{14}H_{14}O_3N_2$: C, 65.10; H, 5.46; N, 10.85%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$); 242 (3.94), 315.5 (4.46), and 355 (3.62).

*Ethyl 2-Acetamido-1-formamidoazulene-3-carboxylate (IV).* A solution of III (100 mg) in acetic anhydride (0.5 ml) was heated on a water bath for 50 min. The solvent was then removed to leave a violet residue, which was dissolved in chloroform, and passed through an alumina column; 70 mg of violet needles were thus obtained. Recrystallization from ethanol afforded IV as violet micro needles; mp 220—222 °C.

Found: C, 63.88; H, 5.64; N, 9.28%. Calcd for $C_{16}H_{16}O_4N_2$: C, 63.99; H, 5.37; N, 9.33%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$); 225$^{\text{sh}}$ (4.32), 248 (4.35), 314 (4.73), 360 (3.84) 375$^{\text{sh}}$ (3.70) and 535 (2.67).

*Ethyl Azuleno[1,2-*d*]imidazole-9-carboxylate (V).* A solution of II (196 mg) in anhydrous formic acid (1.5 ml) was heated on a water bath for 1 hr. To the solution we then added water (10 ml), after which the solution was neutralized with sodium hydrogen carbonate and extracted with chloroform. When the extract was dried and passed through an alumina column, violet crystals were obtained, recrystallization from benzene afforded light brownish-purple crystals (V); mp 202 °C.

Found: C, 70.13; H, 5.30; N, 10.93%. Calcd for $C_{14}H_{12}O_2N_2$: C, 69.99; H, 5.03; N, 11.66%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 243.5 (4.28), 305 (4.70), 317 (4.72), 332$^{\text{sh}}$ (4. 1), 370 (3.73), 386 (3.84), 405 (3.92), 475$^{\text{sh}}$ (2.27), 515 (2.36) and 550$^{\text{sh}}$ (2.32).

*Ethyl Azuleno[1,2-*d*]triazole-9-carboxylate (VI).* To a solution of II (134 mg) in acetic acid (60 mg), water (7 ml), and dioxane (2 ml), a solution of sodium nitrite (38 mg) in water (2 ml) was added under cooling. After the addition, the solution was stirred for 15 min at 60 °C and then for 2 hr at room temperature. After cooling with ice, an 80 mg portion of a brown product was obtained; it was recrystallized from benzene to give orange needles (VI); mp 178 °C (decomp.).

Found: C, 64.46; H, 4.72; N, 17.30%. Calcd for $C_{13}H_{11}O_2N_3$: C, 64.72; H, 4.60; N, 17.42%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$); 244 (4.35), 302 (4.68), 316 (4.71), 360$^{\text{sh}}$ (3.78), 380 (3.95), 402 (4.06), and 480 (2.50).

*Ethyl Azuleno[2,1-*b*]pyrazine-10-carboxylate (VII).* To a stirred solution of 200 mg of II in methanol (30 ml), ion-exchange resin (Amberlite IRA-410) was added in small portions to almost the neutral point, after which the resin was filtered off. To the solution, a solution of glyoxal sodium bisulfite (260 mg) in water (40 ml) was added drop by drop, after which the solution was kept at room temperature overnight. The methanol was removed under reduced pressure, and the residue was extracted with chloroform and dried. The evaporation of the solvent gave a greenish brown residue; when this residue was dissolved in benzene and passed through an alumina column, yellowish green crystals were obtained. Recrystallization from ethanol–petroleum ether gave VII as pale greenish crystals; mp 112—115 °C.

Found: C, 71.43; H, 4.46; N, 10.73%. Calcd for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 224 (4.32), 251 (4.36); 318 (4.63), 330 (4.64), 369 (3.79), 391 (3.96), 417 (4.03), 468 (2.39), 505 (2.46) 540 (2.47), and 585 (2.33).

*Ethyl 2,3-Dimethylazuleno[2,1-*b*]pyrazine-10-carboxylate (VIII).* A solution of II (300 mg) and diacetyl (200 mg) in ethanol (40 ml) was stirred for 3 hr at room temperature. Water (500 ml) was then added, and the solution was extracted with chloroform. After drying, the extract was passed through an alumina column; yellowish green crystals were thus obtained. Recrystallization from benzene–cyclohexane yielded 210 mg of VIII as greenish needles; mp 138—139 °C.

Found: C, 72.72; H, 5.46; N, 9.76%. Calcd for $C_{17}H_{16}O_2N_2$: C, 72.84; H, 5.75; N, 9.99%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 227 (4.34), 255 (4.39), 325 (4.68), 338 (4.74), 373 (3.85), 395 (3.89), 416 (3.89), 520 (2.38), 554 (2.41), 600$^{\text{sh}}$ (2.29), and 660$^{\text{sh}}$ (1.75).

*2,3-Dimethylazuleno[2,1-*b*]pyrazine (XII).* A solution of VIII (120 mg) in ethanol (6 ml) and a 1M sodium hydroxide solution (4 ml) was refluxed for 6 hr. The ethanol was removed, water was added, the solution was acidified with hydrochloric acid, and then the solution was extracted with chloroform. The dark brown product obtained by removing the solvent was heated under reduced pressure to afford a dark greenish product. Recrystallization from cyclohexane gave XII as violet prisms; mp 143 °C.

Found: C, 80.94; H, 5.70; N, 13.15%. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 470 (2.00), 505 (2.11), 550 (2.24), 595 (2.28), and 650 (2.16).

*Ethyl 2,3-Diphenylazuleno[2,1-*b*]pyrazine-10-carboxylate (IX).* When a solution of II (60 mg) and benzil (50 mg) in ethanol (7 ml) was heated on a water bath for 10 min, greenish needles were precipitated out. After cooling, 70 mg of crystals were obtained; recrystallization from ethanol then gave IX as yellowish green silky needles; mp 209—210 °C.

Found: C, 80.10; H, 5.00; N, 6.93%. Calcd for $C_{27}H_{20}O_2N_2$: C, 80.18; H, 4.98; N, 6.92%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 235 (4.41), 287 (4.50), 361 (4.71), 410$^{\text{sh}}$ (5.07), 520$^{\text{sh}}$ (2.51), 560 (2.58), and 604 (2.50).

*2,3-Diphenylazuleno[2,1-*b*]pyrazine (XIII).* A solution of IX (304 mg) in ethanol (50 ml) and a 1M sodium hydroxide solution (8 ml) was refluxed for 5 hr. The ethanol was then removed, water (30 ml) was added, the solution was acidified with hydrochloric acid, and the dark greenish crystals thus precipitated out were filtered and dried. The crystals were submitted to decarboxylation by heating under reduced pressure to afford greenish crystals, which were dissolved in chloroform, passed through an alumina column, and recrystallized from benzene–cyclohexane to give XIII as greenish crystals (75 mg); mp 180—181 °C.

Found: C, 86.90; H, 4.85; N, 8.33%. Calcd for $C_{24}H_{16}N_2$: C, 86.72; H, 4.85; N, 8.43%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 290.5 (4.37), 354 (4.63), 410$^{\text{sh}}$ (3.95), 510 (2.29), 555 (2.36), 605 (2.38), 660 (2.24), and 738 (1.88).

*Ethyl 2,3-Diphenyl-8-isopropylazuleno[2,1-*b*]pyrazine-10-carboxylate (XI).* A solution of ethyl 2-amino-5-isopropyl-1-(*p*-tolylazo)azulene-3-carboxylate in ethyl acetate was submitted to catalytic hydrogenation in the presence of 5% Pd-C. After two molar equivalents of hydrogen had been absorbed, the catalyst was removed, to the filtrate was added a solution of benzil (250 mg) in ethanol (5 ml), and the resulted solution was kept at room temperature overnight. The solvent was then removed, and the residue was dissolved in chloroform and passed through an alumina column. The product obtained from greenish effluents was recrystallized from cyclohexane and then from ethanol to give XI (100 mg) as yellowish green needles; mp 211 °C.

Found: C, 80.98; H, 5.73; N, 6.21%. Calcd for $C_{30}H_{26}O_2N_2$: C, 80.69; H, 5.87; N, 6.27%.

$\lambda_{\max}^{\text{MeOH}}$ nm (log $\varepsilon$): 237 (4.41), 291 (4.51), 364 (4.72), 410$^{\text{sh}}$ (4.15), 430$^{\text{sh}}$ (3.91), 565 (2.63), and 620 (2.55).

*2,3-Diphenyl-8-isopropylazuleno[2,1-*b*]pyrazine (XIV).* A solution of XI (140 mg) in ethanol (16 ml) and a 1M sodium hydroxide solution (4 ml) was refluxed for 5 hr. The ethanol was then removed, water was added, and the solution was acidified to give a dark brown solid. The solid was dried and decarboxylated by heating under reduced pressure, thus yielding a yellowish solid, which was subsequently purified by chromatography and repeated sublimation to afford yellowish green crystals, mp 61 °C.

Found: N, 7.64%. Calcd for $C_{27}H_{22}N_2$: N, 7.48%.

$\lambda_{\max}^{\mathrm{MeOH}}$ nm (log $\varepsilon$): 281 (4.30), 355 (4.51), $410^{\mathrm{sh}}$ (3.80), $440^{\mathrm{sh}}$ (3.39), $510^{\mathrm{sh}}$ (1.96), 560 (2.07), 605 (2.09), 660 (1.98), and $740^{\mathrm{sh}}$ (1.54).

*The Reaction of II and 5-Nitrosotropolone (XV).* To a solution of 150 mg of II in methanol (20 ml), a solution of XV (100 mg) in methanol (10 ml) was added, and the resulting solution was stirred at room temperature from 2 hr. After cooling, the precipitate (90 mg) was filtered and then recrystallized from diluted pyridine to give yellowish green micro crystals (XVI): the mp blackens from around 290 °C.

Found: C, 68.49; H, 4.02; N, 11.44%. Calcd for $C_{20}H_{15}O_3N_3$: C, 69.55; H, 4.38; N, 12.17%.

$\lambda_{\max}^{\mathrm{MeOH}}$ nm (log $\varepsilon$): 229 (3.41), 245 (4.35), 314 (4.55), 397 (4.58), 590 (2.80), 630 (2.79), and $690^{\mathrm{sh}}$ (2.56).

*Oxidation of XVI.* Into a solution of XVI (300 mg) in a 10% potassium hydroxide solution (40 ml), a solution of potassium permanganate (3.6 g) in water (110 ml) was added drop by drop at 70—80 °C. After 2 hr, a small amount of methanol was added, manganese dioxide was filtered out and washed with a dilute pottassium hydroxide solution, and the combined filtrate and washing were concentrated to about 20 ml. The solution was then acidified with hydrochloric acid and extracted with ether; 30 mg of pale yellow crystals (mp 191 °C) were thus obtained. The crystals were methylated with diazomethane, and the product was purified by chromatography to give colorless crystals (mp 181 °C), whose infrared absorption spectrum was superimposable upon that of authentic tetramethyl pyrazinetetracarboxylate.

*2-Aminoazuleno[2,1-d]pyrimidine (XVIII).* a) To a solution of guanidine hydrochloride (168 mg) in ethanol (3 ml) containing sodium ethoxide prepared from 42.8 mg of sodium, 2-amino-1-formylazulene (XVII) (250 mg) was added, and the resulting solution was refluxed for 15 hr. After cooling, the precipitate was filtered and washed with water to give 90 mg of crystals. Recrystallization from ethanol gave XVIII as brown needles; mp 283 °C (decomp.).

Found: C, 73.59; H, 4.36; N, 21.22%. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53%.

$\lambda_{\max}^{\mathrm{MeOH}}$ nm (log $\varepsilon$): 250 (4.09), 324 (4.82), 336 (4.78), 391 (3.50), 418 (3.16), 514 (3.62), 550 (2.43), and 610 (2.06).

b) A solution of 2-amino-1-formylazulene (300 mg) and thiourea (160 mg) in ethanol (10 ml) containing sodium ethoxide prepared from 50 mg of sodium was refluxed for 12 hr. The solvent was then removed, and the residue was washed with water. Crystallization from ethanol gave 80 mg of brown crystals, and the starting azulene (150 mg) was recovered from the filtrate. The recrystallization of the former crystals from ethanol gave brown needles (mp 282 °C (decomp.)), whose infrared spectrum was superimposable upon that of the XVIII obtained by means of Method a).

*Vilsmeier Reaction of Ethyl 2-Aminoazulene-1-carboxylate (XIX).* Into a solution of XIX (1 g) in dimethylformamide (20 ml), a solution of phosphorus oxychloride (2 g) in dimethylformamide (6 ml) was stirred under cooling with ice. After standing at room temperature overnight, the precipitate was filtered and washed with chloroform to give 1.19 g of crystals. Recrystallization from ethanol afforded orange crystals (XX: X=Cl); mp 205—206 °C (decomp.). Perchlorate (XX: $X=ClO_4$); pink crystals (from ethanol); mp over 280 °C.

Found: C, 51.98; H, 4.78; N, 7.11%. Calcd for $C_{16}H_{19}O_6N_2Cl$: C, 51.83; H, 5.17; N, 7.56%.

*Ethyl 2-Formamidoazulene-1-carboxylate (XXI).* a) A solution of chloride (XX) (100 mg) in water was made slightly alkaline by adding sodium carbonate solution, and then it was extracted with chloroform. The extract was dried, passed through an alumina column, and recrystallized from benzene to afford 50 mg of XXI as orange needles; mp 81—83 °C.

Found: C, 67.28; H, 5.31; N, 5.63%. Calcd for $C_{14}H_{13}O_3N\cdot 1/2H_2O$: C, 66.65; H, 5.59; N, 5.56%.

b) A solution of ethyl 2-aminoazulene-1-carboxylate (XIX) (100 mg) in formic acid (1 ml) and pyridine (0.5 ml) was allowed to stand at room temperature for 2 days. The precipitate which separated out was filtered; 108 mg of reddish brown crystals (mp 83 °C) were thus obtained. The infrared spectrum of the crystals was superimposable upon that of XXI obtained by means of Method a).

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