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The Synthesis of 1,2-Diamino- and 1,2,3-Triaminoazulene Derivatives[1]

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The diazo coupling reaction of 2-amino- (I), 2-acetamido-, and 2-amino-1-ethoxycarbonyl-azulene with *p*-toluene diazonium salt gave the corresponding 1-(*p*-tolylazo)azulene derivatives, II, V, and VIII respectively, in good yield; 2-amino-1,3-di(*p*-tolylazo)azulene (III) was also obtained by the reaction of I and two molar equivalents of *p*-toluene diazonium salt. The catalytic reduction of V and VIII afforded 2-acetamido-1-aminoazulene and ethyl 1,2-diaminoazulene-3-carboxylate as hydrochloride. The similar reduction of II and III yielded only a resinous product, and 1,2-diamino- or 1,2,3-triaminoazulene could not be isolated, not even as their salts. However, the reductive acetylation of II and III afforded the corresponding polyacetamidoazulenes. The ultraviolet and visible absorption spectra of these azulenes are indicated.

1-, 2-, 4-, and 6-aminoazulenes have been synthesized[2] by several groups all as unstable compounds except for 2-aminoazulene,[2c] and detailed investigation of 1-aminoazulene concerning to its basicity and spectroscopic properties have been reported.[2b] Syntheses of polyaminoazulenes have also been attempted, but none of the polyaminoazulene have been reported except for their derivatives, 1,3-diacetamidozaulene[3] and diethyl 2,5- and 2,6-diaminoazulene-1,3-dicarboxylate.[2e]

In the present investigation, the syntheses of 1,2-diamino- and 1,2,3-triaminoazulene were attempted in order to compare their stabilities, basicities, and spectroscopic properties with those of aromatic amines and other aminoazulenes; our results will be reported herein.

Among the synthetic courses of these polyaminoazulenes, the reduction of 2-amino-1(or 1,3-di)-arylazoazulene derivatives was chosen.

The reaction of 2-aminoazulene (I)[2c] and one molar equivalent of *p*-toluene diazonium salt in ethanol easily afforded 2-amino-1-(*p*-tolylazo)azulene (II) in a good yield, besides a small amount of 2-amino-1,3-di-(*p*-tolylazo)azulene (III). Compound (III) was also obtained by the reaction of I and two molar equivalents of the diazonium salt. The structure of the products

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[1] Presented at the Tohoku Local Meeting of the Chemical Society of Japan, Yamagata, October, 1961; M. Kobayashi, Master Thesis, Tohoku University, Sendai, March, 1962.

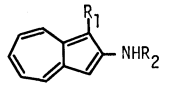
[2] a) A. J. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *J. Amer. Chem. Soc.*, **75**, 4980 (1953). b) J. Schulze and E. Heilbronner, *Helv. Chim. Acta*, **41**, 1492 (1958). c) T. Nozoe, S. Matsumura, Y. Murase, and S. Seto, *Chem. & Ind.*, **1955**, 1257; T. Nozoe, S. Sato, S. Matsumura, and T. Asano, *Proc. Japan Acad.*, **32**, 339 (1956). d) D. H. Reid, W. H. Stafford, and J. P. Ward, *J. Chem. Soc.*, **1958**, 1100. e) T. Nozoe, K. Takase, and M. Tada, This Bulletin, **36**, 1006 (1963).

[3] A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22**, 1193 (1957); A. G. Anderson, Jr., C. G. Fritz, and R. Scotoni, Jr., *J. Amer. Chem. Soc.*, **79**, 6511 (1957).

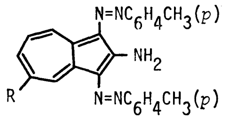
[4] T. Nozoe, S. Seto, T. Asano, and T. Asao, to be published.

are assumed from the general reactivity of azulenes.[2a] By a similar method, 2-acetamidoazulene (IV)[2c] gave 2-acetamido-1-(*p*-tolylazo)azulene (V), and ethyl 2-aminoazulene-1-carboxylate (VI)[2c] and its 7-isopropyl derivative (VII)[4] afforded the corresponding 3-*p*-tolylazo derivatives (VIII and IX respectively). 2-Amino-5-isopropyl-1,3-di(*p*-tolylazo)azulene (X) was also obtained from 2-amino-5-isopropylazulene.[2c]

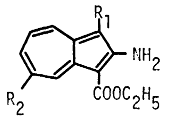
In contrast with the cases of Compounds IV, VI, and VII, the azo-coupling reactions of ethyl 2-acetamidoazulene-1-carboxylate[2c] and its 7-isopropyl derivative[4] were unsuccessful, and the starting materials were recovered.



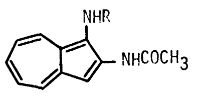
I $R_1 = R_2 = H$
II $R_1 = N{=}NC_6H_4CH_3(p)$
$R_2 = H$
IV $R_1 = H$, $R_2 = COCH_3$
V $R_1 = N{=}NC_6H_4CH_3(p)$
$R_2 = COCH_3$



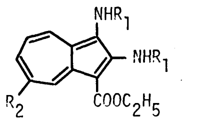
III R = H
X R = *i*-Pr



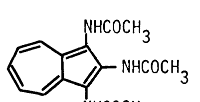
VI $R_1 = R_2 = H$
VII $R_1 = H$, $R_2 = i\text{-Pr}$
VIII $R_1 = N{=}NC_6H_4CH_3(p)$
$R_2 = H$
IX $R_1 = N{=}NC_6H_4CH_3(p)$
$R_2 = i\text{-Pr}$



XI R = $COCH_3$
XIII R = H

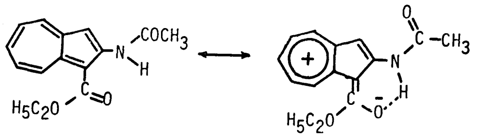


XIV $R_1 = R_2 = H$
XV $R_1 = H$, $R_2 = i\text{-Pr}$
XVI $R_1 = COCH_3$, $R_2 = H$
XVII $R_1 = COCH_3$, $R_2 = i\text{-Pr}$



XII

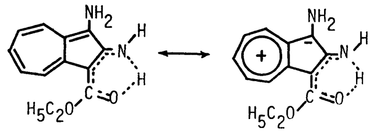
It is considered that such an unreactivity of the 2-acetamidoazulene derivatives for the electrophilic attack may be attributable to a contribution of the resonance form shown below caused by the electron-attractive effect of the ethoxycarbonyl group. This assumption is supported by the following spectroscopic data: ethyl 2-acetamidoazulene-1-carboxylate shows ν_{co} at the low frequency of 1650 cm^{-1}, and NMR signals at a lower field (δ 7.3—7.6 (m, H_5—H_7), 8.06 (s, H_3), 8.27 (d, J=9 Hz, H_4), 9.03 (d, J=9 Hz, H_8), 11.45 (bs, NH), and 2.33 (NCH_3)) than the corresponding signals of 2-acetamidoazulene (δ 7.0—7.6 (m, H_1, H_3, H_5—H_7), 7.90 (NH), 8.15 (d, J=9 Hz, H_4, H_8) and 2.28 (NCH_3)).

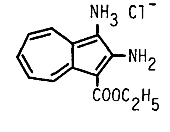


In the reduction of II in ethyl acetate using 5% Pd-C as the catalyst, two molar equivalents of hydrogen were consumed, but the product was very unstable and was rapidly decomposed to a black resinous compound and could not be isolated even as hydrochloride or picrate. Therefore, the reductive acetylation of II was attempted in acetic anhydride; 1,2-diacetamidoazulene (XI) was thus obtained in a good yield as stable violet crystals. 1,2,3-Triaminoazulene also could not be isolated in the free state by the reduction of III; however, the reductive acetylation of III afforded 1,2,3-triacetamidoazulene (XII) as yellowish-green crystals. The 2-acetamido-1-aminoazulene (XIII) obtained by the reduction of V was also so unstable that it was isolated only as hydrochloride. Various attempts to isolate the free amino compound (XIII) from the hydrochloride failed. The acetylation of the hydrochloride or the reductive acetylation of V yielded the previously-obtained 1,2-diacetamidoazulene (XI).

From the reduction mixture of ethyl 2-amino-3-(*p*-tolylazo)azulene-1-carboxylate (VIII), ethyl 2,3-diaminoazulene-1-carboxylate (XIV) could not be isolated; however, monohydrochloride of XIV was obtained in a good yield as golden yellow crystals. In a similar manner, monohydrochloride of ethyl 1,2-diamino-5-isopropylazulene-3-carboxylate (XV) was obtained from the azo compound (IX). These hydrochlorides are considerably stable, but are gradually changed to black resin, and the attempted isolations of the free amines, XIV and XV, from the hydrochlorides resulted in resinification. The acetylation of these hydrochlorides or the reductive acetylations of VIII and IX afforded the corresponding diacetates (XVI[5] and XVII respectively).

In view of the facts that the 2-amino group may form a stable hydrogen bonding with the ethoxycarbonyl group and that the 1- and 3-positions of the azulene nucleus have the highest electron densities, the 1-amino group in XIV must have a higher basicity than the 2-amino group; therefore, it is considered that hydrogen chloride may form a salt with the 1-amino group, as is shown below.





The ultraviolet and visible absorption maxima of the aminoazulene and *p*-tolylazoazulene derivatives obtained above are shown in Table 1.

The visible absorption maxima shown in Table 1, together with that of 2-acetamidoazulene [$\lambda_{\max}^{\text{MeOH}}$ nm

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[5] 1,2-Diacetamidoazulene (XVI) has also been obtained by the reduction of ethyl 2-amino-3-nitrosoazulene-1-carboxylate; T. Nozoe, P.W. Yang, H. Ogawa, and T. Toda, This Bulletin, **41**, 2095 (1968).

Table 1. Ultraviolet and visible absorption maxima

Compounds	λ_{max}^{MeOH} nm (log ε)		
II	238 (4.27),	285 (4.29),	316 (4.28),
	375^{sh} (4.64),	388 (4.66),	535^{sh} (3.69)
III	254 (4.19),	355^{sh} (4.43),	414 (4.72),
	548 (3.85)		
VIII	254 (4.23),	295^{sh} (4.42),	328 (4.51),
	345^{sh} (4.35),	385 (4.54),	510 (4.04)
IX	259 (4.16),	328 (4.56),	345^{sh} (4.40),
	390 (4.54),	500 (4.05)	
X	235^{sh} (4.20),	256 (4.24),	345^{sh} (4.33),
	355^{sh} (4.42),	418 (4.75),	542 (3.86)
XI	242 (4.25),	297 (4.81),	345^{sh} (3.63),
	360 (3.79),	380 (3.81),	395^{sh} (3.32),
	560 (2.50)		
XII	246 (4.34),	307 (4.72),	320^{sh} (4.36),
	365 (3.69),	375 (3.55),	600 (2.54)
XVI	235^{sh} (4.31),	248 (4.33),	314 (4.72),
	360 (3.82),	370^{sh} (3.77),	395^{sh} (3.21),
	535 (2.68)		
XVII	255 (4.33),	318 (4.72),	357 (3.85),
	540 (2.80)		

(log ε); 540 (2.44) and 580^{sh} (2.38)] indicate that the acetamido groups at the 1- and 3-positions cause the absorption maxima to shift to longer wavelengths, according to the expanded Plattner rule.[3,6]

Experimental[7]

Coupling Reaction of 2-Aminoazulene with p-*Toluene Diazonium Chloride.* To a stirred solution of 2 g of 2-aminoazulene in a mixture of 30 ml of ethanol and 10 ml of dioxane, a solution of *p*-toluenediazonium chloride prepared from 1.79 g of *p*-toluidine was added at once under cooling with ice. After stirring for 2 hr, the solution was allowed to stand at room temperature overnight. A deep brown solid (3.4 g) was then filtered out; to the filtrate water (150 ml) was added, and it was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated, leaving a deep reddish semi-solid. A benzene solution of the combined solids was chromatographed on an alumina column and eluted with benzene. The first effluent gave brown crystals (mp 180—195 °C), which were recrystallized from ethyl acetate to give 2-amino-1-3-di(*p*-tolylazo)azulene (III) (400 mg) as deep brown needles (mp 199—200 °C).

Found: C, 75.80; H, 5.66; N, 18.19%. Calcd for $C_{24}H_{21}N_5$: C, 75.96; H, 5.58; N, 18.46%.

The second effluent gave brown crystals (mp 150—160 °C), which were recrystallized from ethyl acetate to afford 2-amino-1-(*p*-tolylazo)azulene (II) (3.1 g) as brown crystals (mp 162—163 °C).

Found: C, 78.00; H, 5.78; N, 15.74%. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08%.

*2-Acetamido-1-(*p*-tolylazo)azulene (V).* a) To a stirred solution of 185 mg of 2-acetamidoazulene in 4 ml of ethanol, a solution of *p*-toluene diazonium chloride prepared from 120 mg of *p*-toluidine was added at once under cooling with ice. After stirring for 2 hr, the solution was made slight alkaline by the addition of sodium hydrogen carbonate. Brown precipitate was then filtered out, dried, and dissolved in benzene, and the solution was chromatographed on an alumina column. The recrystallization of the crystals obtained from the effluent from ethanol gave 136 mg of V as reddish violet needles (mp 185—186 °C).

Found: C, 74.79; H, 6.01; N, 13.85%. Calcd for $C_{19}H_{17}ON_3$: C, 75.22; H, 5.65; N, 13.85%.

b) The acetylation of 50 mg of 2-amino-1-(*p*-tolylazo)-azulene with acetic anhydride gave 40 mg of V (mp 185—186 °C, undepressed on admixture with a sample prepared by Method a)).

Hydrochloride of 2-Acetamido-1-aminoazulene (XIII). A solution of 210 mg of V in 15 ml of ethyl acetate was submitted to catalytic hydrogenation in the presence of 50 mg of 5% Pd-C. After two molar equivalents of hydrogen had been uptaken, the catalyst was filtered off; the filtrate was shaken with 5 ml of concentrated hydrochloric acid, thus affording 110 mg of precipitate. Recrystallization from water gave 95 mg of black-violet needles (mp over 280 °C).

Found: C, 60.80; H, 5.22; N, 11.57%. Calcd for $C_{12}H_{12}ON_2 \cdot HCl$: C, 60.89; H, 5.11; N, 11.84%.

1,2-Diacetamidoazulene (XI). A solution of 1.22 g of 2-amino-1-(*p*-tolylazo)azulene in 190 ml of acetic anhydride was submitted to catalytic hydrogenation in the presence of 500 mg of 5% Pd-C. After two molar equivalents of hydrogen had been uptaken, the catalyst was filtered and the filtrate was evaporated, leaving a dark yellow residue, from which 55 mg of acetotoluidide were obtained. After the catalyst had been washed thoroughly with acetic acid, the washings were evaporated to give 540 mg of violet crystals. Recrystallization from acetic acid gave 1,2-diacetamidoazulene as violet crystals (mp 278 °C (decomp.)).

Found: C, 69.25; H, 5.61; N, 11.46%. Calcd for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.83; N, 11.56%.

The same compound was also obtained in a good yield by the acetylation of the hydrochloride of 2-acetamido-1-aminoazulene with acetic anhydride.

1,2,3-Triacetamidoazulene (XII). A solution of 500 mg of 2-amino-1,3-di(*p*-tolylazo)azulene (III) in 100 ml of acetic anhydride was submitted to catalytic hydrogenation in the presence of 250 mg of 5% Pd-C. After four equivalents of hydrogen had been uptaken, the catalyst was filtered and washed with acetic acid. The combined filtrate and washing was concentrated to a small volume, thus affording yellowish-orange crystals; these crystals were recrystallized from ethanol to gave 276 mg of 1,2,3-triacetamidoazulene as yellowish-green crystals (mp 271—272 °C).

Found: C, 64.11; H, 5.63; N, 13.97%. Calcd for $C_{16}H_{17}O_3N_3$: C, 64.20; H, 5.72; N, 14.04%.

*Ethyl 2-Amino-3-(*p*-tolylazo)azulene-1-carboxylate (VIII).* To a solution of 215 mg of ethyl 2-aminoazulene-1-carboxylate in 4 ml of ethanol, a solution of *p*-toluenediazonium chloride prepared from 118 mg of *p*-toluidine was added under cooling with ice. After having been allowed to stand overnight, the solution was made slight alkaline; the precipitate was filtered and washed with water. A solution of the solid in benzene was chromatographed on an alumina column; subsequent recrystallization from ethanol gave 240 mg of ethyl 2-amino-3-(*p*-tolylazo)azulene-1-carboxylate as deep reddish crystals (mp 120—121 °C).

Found: C, 71.98; H, 5.34; N, 12.76%. Calcd for $C_{20}H_{19}O_2N_3$: C, 72.05; H, 5.74; N, 12.61%.

Hydrochloride of Ethyl 2,3-Diaminoazulene-1-carboxylate (XIV). A solution of 200 mg of ethyl 2-amino-3-(*p*-tolylazo)azulene-

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[6] *Cf.* E. Heilbronner, "Non-Benzenoid Aromatic Compounds," ed. by D. Ginsbrug, Interscience Publ., New York (1959), pp. 218—254; T. Nozoe, and T. Asao, "Dai-Yuki Kagaku (Comprehensive Organic Chemistry)," **13**, Asakura Shoten, Tokyo (1960), pp. 450—456.

[7] All melting points are uncorrected.

1-carboxylate in 15 ml of ethyl acetate was submitted to catalytic hydrogenation in the presence of 50 mg of 5% Pd-C. After two molar equivalents of hydrogen had been uptaken, the catalyst was filtered and washed with ethyl acetate; the combined filtrate and washing was shaken with concentrated hydrochloric acid to give yellowish-orange crystals. Recrystallization from dilute hydrochloric acid gave 170 mg of XIV as golden yellow needles (mp over 260 °C).

Found: C, 58.33; H, 5.33; N, 10.91%. Calcd for $C_{13}H_{14}O_2N_2\cdot HCl$: C, 58.45; H, 5.67; N, 10.51%.

Picrate of ethyl 2,3-diaminoazulene-1-carboxylate. Mp changed to black from around 215 °C.

Found: C, 49.67; H, 3.67; N, 15.28%. Calcd for $C_{19}H_{17}O_9N_5$: C, 49.67; H, 3.73; N, 15.25%.

Ethyl 2,3-Diacetamidoazulene-1-carboxylate (XVI). A solution of 150 mg of hydrochloride of XIV in acetic anhydride (1 ml) was heated on a water bath for 30 min. The excess acetic anhydride was then removed to leave a violet residue, which was dissolved in benzene; the solution was then chromatographed on an alumina column. Recrystallization from benzene gave 160 mg of XVI as light purple needles (mp 216—218 °C).

Found: C, 65.20; H, 5.57; N, 8.66%. Calcd for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91%.

Ethyl 2-Amino-5-isopropyl-1-(p-tolylazo) azulene-3-carboxylate (IX). To a stirred solution of 210 mg of ethyl 2-amino-5-isopropylazulene-3-carboxylate in 3 ml of ethanol, a solution of *p*-toluene diazonium chloride prepared from 150 mg of *p*-toluidine was added under cooling with ice. After stirring for 2 hr, the solution was allowed to stand at room temperature overnight. The precipitate was filtered, and dissolved in benzene, and the solution was chromatographed on an alumina column. The effluent afforded reddish crystals, which were recrystallized from ethanol to give ethyl 2-amino-5-isopropyl-1-(*p*-tolylazo)azulene-3-carboxylate (220 mg) as reddish-brown crystals (mp 118—120 °C).

Found: C, 73.35; H, 6.51; N, 11.04%. Calcd for $C_{23}H_{25}O_2N_3$: C, 73.57; H, 6.71; N, 11.19%.

2-Amino-1,3-di(p-tolylazo)-5-isopropylazulene (X). To a stirred solution of 92 mg of 2-amino-5-isopropylazulene in 2 ml of ethanol, a solution of *p*-toluene diazonium chloride prepared from 120 mg of *p*-toluidine was added. After standing for a day, water was added and then extracted with benzene; the solution was subsequently chromatographed on an alumina column, 110 mg of 2-amino-1,3-di(*p*-tolylazo)-5-isopropylazulene as yellow-brown crystals (mp 170—171 °C (from ethyl acetate)) being thus obtained.

Found: C, 76.86; H, 6.15; N, 16.43%. Calcd for $C_{27}H_{27}N_5$: C, 76.93; H, 6.46; N, 16.62%.

Hydrochloride of Ethyl 1,2-Diamino-5-isopropylazulene-3-carboxylate (XV). A solution of 1 g of IX in 80 ml of ethyl acetate was submitted to catalytic hydrogenation in the presence of 300 mg of 5% Pd-C. After two molar equivalents of hydrogen had been uptaken, the catalyst was filtered; the filtrate was shaken with 10 ml of concentrated hydrochloric acid to give 380 mg of hydrochloride of XV as yellow crystals; the mp changed to black from around 250 °C, after washing with ethyl acetate.

Found: C, 62.03; H, 6.48; N, 8.71%. Calcd for $C_{16}H_{20}O_2N_2\cdot HCl$: C, 62.23; H, 6.85; N, 9.07%.

Ethyl 1,2-Diacetamido-5-isopropylazulene-3-carboxylate (XVII). A solution of 50 mg of hydrochloride of XV in 0.3 ml of acetic anhydride was heated on a water bath for 30 min. The solvent was then removed; the residue was purified by chromatography (alumina, benzene) and then recrystallized from cyclohexane to give 30 mg of XVII as light purple needles (mp 162—164 °C).

Found: N, 7.62%. Calcd for $C_{20}H_{24}O_4N_2$: N, 7.86%.

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