The Synthesis of 5- and 6-Aminoazulene Derivatives

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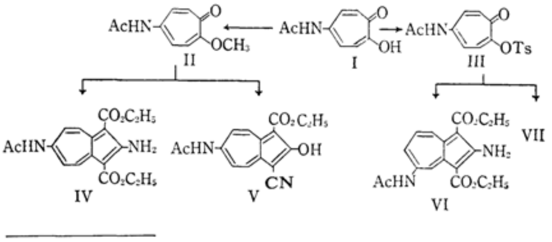
In our laboratory, we have made an effort to synthesize azulenes by the action of such active methylenes as malononitrile and ethyl cyanoacetate on troponoids[1-4]. Although this method, using substituted troponoids as the starting material, should provide a suitable method for the synthesis of azulenes with a functional group on the seven-membered ring, very few instances have been reported. We report herein the synthesis of 5- and 6-aminoazulene derivatives from 5-acetamidotropolone (I)[5].

The application of ethyl cyanoacetate, in the presence of one mole of sodium ethoxide, to 5-acetamido-2-methoxytropone (II) afforded two compounds, diethyl 6-acetamido-2-aminoazulene-1,3-dicarboxylate (IV) and ethyl 6-acetamido-3-cyano-2-hydroxyazulene-1-carboxylate (V), while 5-acetamido-2-(*p*-tolylsulfonyloxy)tropone (III) afforded diethyl 5-acetamido-2-aminoazulene-1,3-dicarboxylate (VI) and yellow crystals (VII) (m.p. above 270°C). The ultraviolet spectra of these compounds are shown in Figs. 1 and 2.

The structural proof of IV, V and VI was based on the analysis and on a comparison of the ultraviolet and infrared spectra with those of known compounds. The validity of the structures proposed was also supported by the well-established general concept that 2-halo- and 2-(*p*-tolylsulfonyloxy)tropones undergo condensation at the 1- and 7-positions of the troponoids, whereas 2-methoxytropones give rise to azulene derivatives derived by condensation at the 1- and 2-positions. The yellow compound (VII), $C_{14}H_{14}O_5N_2$, was shown by ultraviolet spectral evidence not to be an



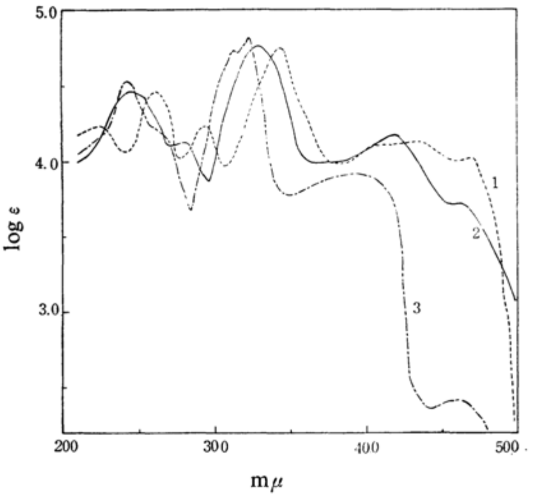


Fig. 1. Ultraviolet absorption spectra in methanol.

1 Diethyl 6-acetamido-2-aminoazulene-1,3-dicarboxylate (IV)
2 Diethyl 2,6-diaminoazulene-1,3-dicarboxylate (VIII)
3 Diethyl 2,6-diacetamidoazulene-1,3-dicarboxylate (IX)

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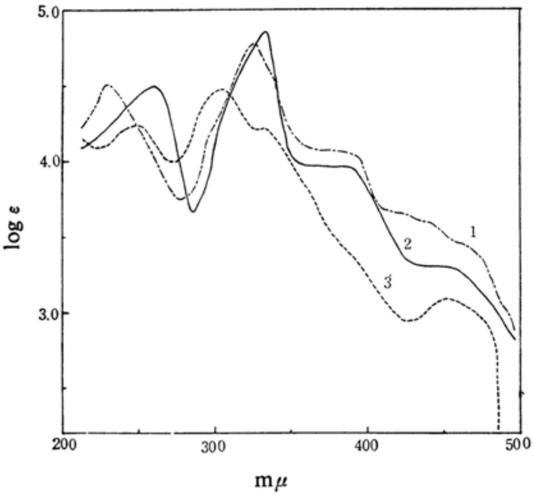
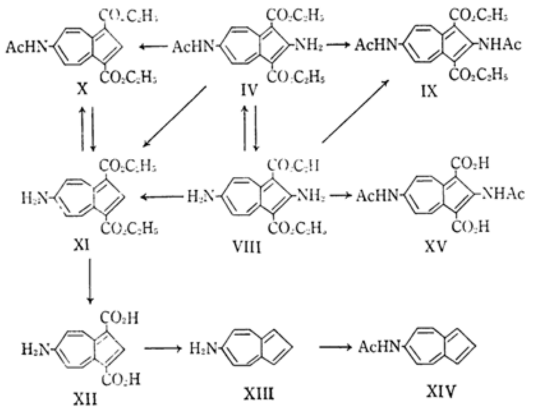


Fig. 2. Ultraviolet absorption spectra in methanol.

1 Ethyl 6-acetamido-3-cyano-2-hydroxyazulene-1-carboxylate (V)
2 Diethyl 5-acetamido-2-aminoazulene-1, 3-dicarboxylate (VI)
3 VII

azulene derivative; its precise structure will be reported on in another paper.

The alkaline hydrolysis of IV afforded a dull brown 2, 6-diamino compound VIII, the acetamido group being predominantly attacked; acetylation of the latter, in turn, gave first IV and then diacetate IX, which was also obtained by the acetylation of IV. Mono Schiff's base was obtained from VIII by the action of benzaldehyde. The diazotization of IV was realized by isoamyl nitrite or sodium nitrite and an excess of sulfuric acid, and decomposition of the diazonium salt formed was carried out by either leaving it standing at room temperature or treating it with active copper and sodium hypophosphite. The reactions carried out in dioxane gave the deaminated product, diethyl 6-acetamidoazulene-1, 3-dicarboxylate (X), while these carried out in aqueous ethanol gave diethyl 6-aminoazulene-1, 3-dicarboxylate (XI), the hydrolysis product of the acetamido group. The acetylation of XI gave X, and the acidic hydrolysis of X afforded XI. XI was obtained also by deamination of the diamino compound VIII, which showing the greater basicity of C_2-amino between the two amino groups. 6-Amino compound XI gave, on alkaline hydrolysis, a dicarboxylic acid XII, the decarboxylation of which in pyridine furnished 6-aminoazulene (XIII) in the form of red prisms (ultraviolet spectrum Fig. 3). XIII is rather unstable and darkens on being left in air for a long time, while its blueish acetate XIV is quite stable (ultraviolet spectrum Fig. 3).



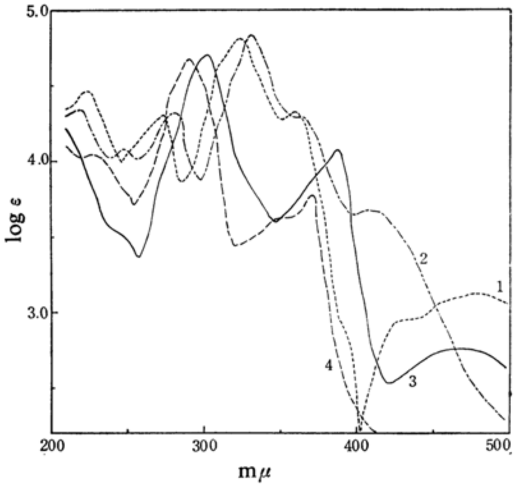


Fig. 3. Ultraviolet absorption spectra in methanol.

1 Diethyl 6-acetamidoazulene-1, 3-dicarboxylate (X)
2 Diethyl 6-aminoazulene-1, 3-dicarboxylate (XI)
3 6-Aminoazulene (XIII)
4 6-Acetamidoazulene (XIV)

In an attempt to derive 2, 6-diaminoazulene, the corresponding dicarboxylic acid XV was obtained from VIII. An attempt to decarboxylate XV on heating, however, resulted in a dark tarry material from which none of the desired product was isolated.

The preferential formation of a 6-acetamido derivative IV on the mild acetylation of 2, 6-diaminoazulene VIII, which contrasts with the preferential diazotization of the 2-amino group, can be explained by the operation of a steric hindrance caused by the presence of the two ethoxycarbonyl groups adjacent to the 2-amino group.

Experimental[6]

The Reaction of 5-Acetamido-2-methoxytropone (II) and Ethyl Cyanoacetate. — To a sodium ethoxide solution prepared from sodium (375 mg.) and absolute ethanol (30 ml.) were added ethyl cyanoacetate (3.6 g.) and then a suspension of II (3.12 g.) in absolute ethanol (50 ml.). The mixture was stirred for 4 hr. and then allowed to stand for 2 days at room temperature. The solvent was removed in vacuo, and water was added. The crystals which separated (2.5 g.) were recrystallized from ethanol to afford IV as yellow needles; m.p. 216~217°C.

Found: C, 62.95; H, 5.42; N, 8.28. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 245 (4.49), 280 (4.14), 335 (4.79), 420 (4.14), 462 (3.71). IR (Nujol): 3490, 3335, 1694, 1650, 1637 cm^{-1}.

The Picrate of IV.—M. p. 178~179°C (decomp.); black micro-prisms (from ethanol).

Found: C, 49.90; H, 4.09; N, 12.63. Calcd. for $C_{24}H_{23}O_{12}N_5$: C, 50.26; H, 4.04; N, 12.21%.

The aqueous mother liquor, after the separation of crystals, was extracted with benzene, by which a further crop of IV (0.20 g.) was obtained. The water layer was acidified with 6 N sulfuric acid, and the crystals (m. p. 220~230°C (decomp.)) thereby formed were collected by filtration and recrystallized from ethyl acetate to give V as yellowish brown micro-prisms; m. p. 234~236°C (decomp.); 70 mg.

Found: C, 63.70; H, 4.48; N, 9.02. Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.42; H, 4.73; N, 9.39%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 232 (4.51), 330 (4.86), 395 (4.01), 420 (3.65) sh, 460 (3.35) sh. IR (Nujol): 3460, 2232, 1781, 1709, 1692 cm^{-1}.

The Reaction of 5-Acetamido-2-(*p*-tolylsulfonyloxy)tropone (III) and Ethyl Cyanoacetate.—The reaction and the working-up of the reaction mixture were carried out in exactly the same way as in the previous section, using sodium (85 mg.), absolute ethanol (12 ml.), ethyl cyanoacetate (0.75 g.) and III (1.00 g.) in absolute ethanol (20 ml.). The crystals which separated (400 mg.) were recrystallized from ethanol to give pale yellow leaflets (VII); m. p. above 270°C.

Found: C, 57.74; H, 5.07; N, 9.54. Calcd. for $C_{14}H_{14}O_5N_2$: C, 57.93; H, 4.86; N, 9.65%.

$\lambda_{\max}^{\mathrm{MeOM}}$ mμ (log ε): 247 (4.25), 306 (4.49), 336 (4.23), 454 (3.13).

The mother aqueous liquor give a crystalline substance, 150 mg. of VI, which, after recrystallization from ethanol, gave yellow needles; m. p. 184~185°C.

Found: C, 62.74; H, 5.87; N, 8.06. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 263 (4.51), 336 (4.89), 392 (3.98), 450 (3.24) sh. IR (Nujol): 3500, 3370, 3220, 1669 cm^{-1}.

The Picrate of VI.—M. p. 150~151°C (decomp.); pale yellow crystals (from ethanol).

Found: N, 14.28. Calcd. for $C_{30}H_{26}O_{19}N_8$: N, 14.09%.

Diethyl 2,6-Diaminoazulene-1,3-dicarboxylate (VIII).—IV (200 mg.) was heated under reflux for 4 hr. with potassium hydroxide (200 mg.) in ethanol (12 ml.); by this procedure 100 mg. of brownish green crystals were precipitated. Recrystallization from benzene afforded VIII as dull brown plates with a metallic luster; m. p. 207~208°C.

Found: C, 63.76; H, 5.56; N, 9.20. Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.00; N, 9.27%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 224 (4.25), 262 (4.47), 296 (4.24), 346 (4.74), 430 (4.09), 472 (3.98). IR (Nujol): 3470, 3410, 3320, 3205, 1637 cm^{-1}.

VIII was acetylated to give IV by warming it in acetic anhydride on a water bath for 4 hr.

The Picrate of VIII.—M. p. 180~181°C (decomp.); black needles (from ethanol).

Found: C, 49.89; H, 3.88; N, 13.01. Calcd. for $C_{22}H_{21}O_{11}N_5$: C, 49.71; H, 3.99; N, 13.18%.

The Benzylidene Derivative of VIII.—A solution of VIII (90 mg.), a drop of acetic acid, and benzaldehyde (100 mg.) in ethanol (2 ml.) was warmed on a water bath for 15 min. After the solution had been allowed to stand overnight at room temperature, the crystals (70 mg.) deposited were recrystallized from benzene to recover 20 mg. of VIII. The filtrate was evaporated to dryness, and recrystallization from cyclohexane afforded a benzilidene derivative as orange prisms; m. p. 140~141°C, 15 mg.

Found: C, 70.97; H, 5.58; N, 7.25. Calcd. for $C_{23}H_{22}O_4N_2$: C, 70.75; H, 5.48; N, 7.18%.

IR (Nujol): 3500, 3370, 1686, 1664 cm^{-1}.

Diethyl 2,6-Diacetamidoazulene-1,3-dicarboxylate (IX).—A solution of IV in acetic anhydride, in the presence of pyridine, was refluxed on an oil bath for 3 hr. The crystalline residue produced by the evaporation of the solvent was recrystallized from ethanol to give IX as orange needles; m. p. 188~189°C.

Found: C, 62.66; H, 5.74; N, 7.27. Calcd. for $C_{20}H_{22}O_6N_2$: C, 62.16; H, 5.74; N, 7.25%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 345 (4.56), 316 (4.75), 327 (4.83), 378 (3.90), 398 (3.94), 470 (3.43). IR (Nujol): 3495, 3330, 1714, 1667 cm^{-1}.

The Deamination of IV.—*a) The Formation of Diethyl 6-Acetamidoazulene-1,3-dicarboxylate (X).*— Into a solution of IV (200 mg.) and concentrated sulfuric acid (0.4 ml.) in dioxane (6 ml.) was added sodium nitrite (50 mg.) in water (2 ml.) with stirring. After the mixture had been stirred for a further 30 min., active copper powder (100 mg.) and sodium hypophosphite (0.8 g.) were added. The mixture was stirred for a further 3 hr. and then allowed to stand overnight at room temperature. The reaction mixture was diluted with water (200 ml.) and extracted with ethyl acetate, and the extract was passed through a column of alumina, yielding X (130 mg.). Recrystallization from ethanol formed orange leaflets; m. p. 221~221.5°C.

Found: C, 65.27; H, 5.57; N, 4.06. Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 227 (4.46), 276 (4.30), 329 (4.80), 366 (4.29), 475 (3.04). IR (Nujol): 3320, 1706, 1695, 1667 cm^{-1}.

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[6] All melting points are uncorrected. Shoulders in the UV spectral data are by sh.

b) The Formation of Diethyl 6-Aminoazulene-1, 3-dicarboxylate (XI).—i) Into a solution of IV (200 mg.) and concentrated sulfuric acid (1.2 ml.) in 60% aqueous ethanol (20 ml.), isoamyl nitrite (180 mg.) was added with stirring while the mixture was being ice-cooled. After the mixture had been stirred for a further 30 min., ethanol (8 ml.) was added and the mixture was allowed to stand overnight at room temperature. The mixture was extracted with ethyl acetate after the addition of water (200 ml.), and the extract was passed through a column of alumina to give XI (10 mg.). The water-layer was adjusted to a slightly alkaline state and extracted with ethyl acetate. By the same purification, XI (90 mg.) was obtained. Recrystallization from ethanol formed orange scales; m. p. 236～237°C, 85 mg.

Found: C, 66.98; H, 6.01; N, 4.87. Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 225 (4.34), 252 (4.04), 284 (4.34), 335 (4.82), 365 (4.28), 410 (3.65). IR (Nujol): 3410, 3320, 3205, 1650 cm^{-1}.

The Picrate of XI.—M. p. 209～210°C (decomp.); orangish brown scales (from ethanol).

Found: C, 51.40; H, 4.17; N, 11.20. Calcd. for $C_{22}H_{20}O_{11}N_4$: C, 51.16; H, 3.90; N, 10.85%.

ii) To the diazotized solution of IV (200 mg.) with isoamyl nitrite (180 mg.), active copper powder (100 mg.) and sodium hypophosphite (0.8 g.) were added. The mixture was stirred for 2 hr. and then allowed to stand overnight at room temperature. After removal of the copper powder, the reaction mixture was treated as in i) to obtain XI (145 mg.).

iii) Into a solution of IV (200 mg.) in dioxane (8 ml.) and concentrated sulfuric acid (0.2 ml.), a solution of sodium nitrite (50 mg.) in water (2 ml.) was added with stirring while the mixture was being cooled. After the mixture had been stirred for 15 min., ethanol (5 ml.) and active copper powder (100 mg.) were added, and the mixture was warmed in a water bath for 1 hr. The solution was concentrated to half volume under a reduced pressure and treated as in i) to obtain XI (105 mg.).

The acetylation of XI with acetic anhydride by refluxing it for 10 min. gave X. The hydrolysis of X by refluxing it with 6 N sulfuric acid in ethanol gave XI.

The Deamination of VIII.—A solution of VIII (100 mg.) in 60% aqueous ethanol (10 ml.) and concentrated sulfuric acid (0.6 ml.) was diazotized with isoamyl nitrite (90 mg.) and treated as in the case of the deamination of IV, b-i); XI (20 mg.) was obtained.

6-Aminoazulene-1, 3-dicarboxylic Acid (XII).—A solution of XII (120 mg.) and potassium hydroxide (90 mg.) in 60% aqueous ethanol (15 ml.) was refluxed for 4 hr. The solution was concentrated to half volume under a reduced pressure, and this was then diluted with water (15 ml.) and acidified with 6 N sulfuric acid. The precipitate thereby formed was collected by filtration and repeatedly washed with water, by which process dicarboxylic acid (XII) was obtained as black crystalline powder; m. p. above 275°C; 80 mg.

6-Aminoazulene (XIII).—A solution of XII (80 mg.) in pyridine (2 ml.) was heated at 140～150°C to effect decarboxylation. The residue produced by evaporation of the excess of pyridine was dissolved in benzene and passed through a column of alumina, while the crude material obtained by the concentration of the effluent was recrystallized from ethanol to give XIII (m. p. 106～107°C; 10 mg.) as red scales.

Found: C, 84.12; H, 6.80; N, 9.32. Calcd. for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 306 (4.70), 390 (4.07), 465 (2.70). in EtOH; 470 (2.71). IR (Nujol): 3420, 3330, 3200 cm^{-1}.

6-Acetamidoazulene (XIV).—A solution of XIII (20 mg.) in acetic anhydride was warmed on a water bath for 5 min. The crystalline residue produced by the evaporation of the solvent was recrystallized from ethanol to give XIV (10 mg.) as blue needles.

Found: C, 78.26; H, 6.07; N, 7.46. Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56%.

$\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 230 (4.02), 291 (4.65), 355 (3.60), 374 (3.74). in EtOH; 570 (2.57). IR (Nujol): 3270, 1664 cm^{-1}.

2, 6-Diacetamidoazulene-1, 3-dicarboxylic Acid (XV).—A solution of VIII (20 mg.) and potassium hydroxide (100 mg.) in 60% aqueous ethanol (9 ml.) was refluxed for 7 hr. The solution was concentrated to 1/3 volume under a reduced pressure and diluted with water (20 ml.). The mixture was then extracted with ethyl acetate, and the extract passed through a column of alumina. From the effluent, a reddish, oily substance was obtained. This was warmed with acetic anhydride on a water bath for 3 hr. The product was crystallized from aqueous ethanol to give XV as a violet brown powder (m. p. 212～213°C; 10 mg.).

Found: N, 8.05. Calcd. for $C_{16}H_{14}O_6N_2$: N, 8.48%.

IR (Nujol): 3470, 3290, 1669, 1650 cm^{-1}.

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