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The Synthesis of 5- and 6-Aminoazulene Derivatives from 5- and 6-Acetylazulene Derivatives

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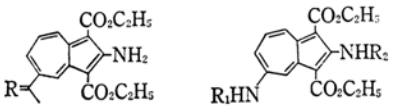
The Schmidt reactions on diethyl 5-acetyl-2-aminoazulene-1, 3-dicarboxylate and diethyl 6-acetyl-2-aminoazulene-1, 3-dicarboxylate afforded diethyl 2, 5-diaminoazulene-1, 3-dicarboxylate (I) and diethyl 2, 6-diaminoazulene-1, 3-dicarboxylate respectively. A preferential formation of the 5-acetamido-2-amino compound upon the mild acetylation of I, which contrasted with the preferential diazotization of the 2-amino group, was observed.

In a previous paper,[1] it was reported that 5- and 6-aminoazulene derivatives were synthesized by the reaction of 5-acetamidotropolone derivatives and ethyl cyanoacetate. 6-Aminoazulene derivatives were also synthesized from 6-bromoazulene derivatives by nucleophilic displacement with ammonia or amines.[2,3] In the present paper, the authors will described a third route of synthesizing aminoazulene derivatives, in which the aminoazulenes are synthesized from 5- and 6-acetylazulene derivatives[4] by the Schmidt reaction.

The treatment of diethyl 5-acetyl-2-aminoazulene-1, 3-dicarboxylate (I)[4] or its ethylene ketal (II)[4] with sodium azide in concentrated sulfuric acid gave two compounds, III and IV. One of these, III, was identical with the diethyl 5-acetamido-2-aminoazulene-1, 3-dicarboxylate which had already been obtained.[1] The other one, IV, was confirmed

1) T. Nozoe, K. Takase and M. Tada, This Bulletin, **36**, 1006 (1963).
2) T. Nozoe, K. Takase and M. Tada, ibid., **38**, 247 (1965).
3) M. Tada, ibid., **39**, 1954 (1966).
4) T. Nozoe, K. Takase and M. Tada, ibid., **36**, 1010 (1963).

to be diethyl 2, 5-diaminoazulene-1, 3-dicarboxylate from the facts that the acetylation of IV gave III and the mild alkaline hydrolysis of III gave IV. The further acetylation of III afforded a diacetamido compound V.



I: R=O III: R_1=$COCH_3$; R_2=H

II: R= IV: R_1=R_2=H

V: R_1=R_2=$COCH_3$

The same treatment of diethyl 5-acetylazulene-1, 3-dicarboxylate (VI)[4] with sodium azide and concentrated sulfuric acid afforded diethyl 5-aminoazulene-1, 3-dicarboxylate (VII). The acetylation of VII gave an acetamido compound VIII, which was also derived from III by deamination with isoamyl nitrite and sulfuric acid. When treated with isoamyl nitrite and sulfuric acid, the diamino compound IV gave the amino compound VII, in which the amino group at Position 2 was only deaminated. This fact shows that the basicity of the 2-amino group of IV is greater than that of the 5-amino group. The ultraviolet absorption spectra of the compounds, IV, V, VII and VIII, are shown in Fig. 1.

In an attempt to synthesize 2, 5-diaminoazulene

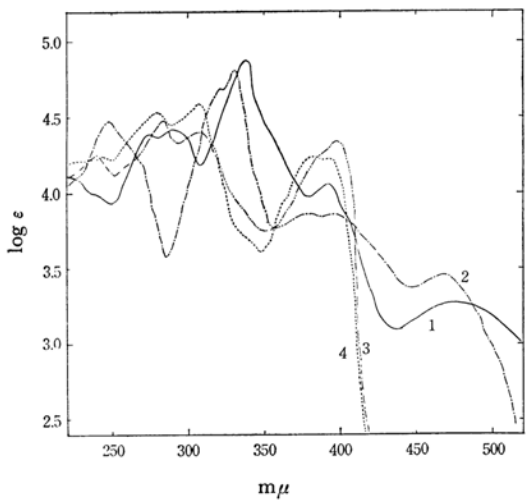
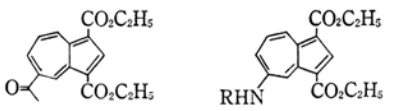


Fig. 1. Ultraviolet absorption spectra in methanol.

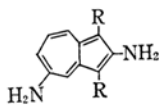
1. Diethyl 2, 5-diaminoazulene-1, 3-dicarboxylate (IV)
2. Diethyl 2, 5-diacetamidoazulene-1, 3-dicarboxylate (V)
3. Diethyl 5-aminoazulene-1, 3-dicarboxylate (VII)
4. Diethyl 5-acetamidoazulene-1, 3-dicarboxylate (VIII)



VI VII: R=H

VIII: R=$COCH_3$

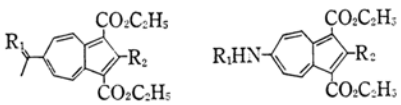
(IX), the corresponding dicarboxylic acid X obtained by the alkaline hydrolysis of III or IV was submitted to thermal decarboxylation, thus forming a dark tarry material from which none of the desired product was isolated.



IX: R=H

X: R=COOH

The preferential formation of 5-acetamido-2-amino compound III on the mild acetylation of 2, 5-diamino compound IV, 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. Similar phenomena are also observed in the case of diethyl 2, 6 - diaminoazulene - 1, 3 - dicarboxylate (XI).[1] The Schmidt reactions on diethyl 6-acetyl-2-aminoazulene-1, 3-dicarboxylate (XII)[4] and its ethylene ketal (XIII)[4] afforded 2, 6-diaminoazulene derivative (XI). The reaction of diethyl 6-acetylazulene-1, 3-dicarboxylate (XIV)[4] gave both the 6-amino compound (XV) and the 6-acetamido compound (XVI).[1]



XII: R_1=O; R_2=NH_2 XI: R_1=H; R_2=NH_2

XV: R_1=R_2=H

XIII: R_1= ; R_2=NH_2 XVI: R_1=$COCH_3$; R_2=H

XIV: R_1=O; R_2=H

Experimental[5]

The Schmidt Reaction of Diethyl 5-Acetyl-2-aminoazulene-1, 3-dicarboxylate (I). — Into a solution of I (1.0 g.) in concentrated sulfuric acid (4 ml.), sodium azide (240 mg.) was added in small portions with stirring at room temperature. After having been stirred for 2 hr., the mixture was diluted with water (30 ml.), made slightly alkaline with 2 N sodium hydroxide, and allowed to stand in a cold place. The solid

5) All melting points are uncorrected. Shoulders in the UV spectral data are designated by "sh."

(600 mg.) which precipitated out was collected by filtration, washed with water, and recrystallized from ethanol to give yellow needles (300 mg.; m. p. 184—185°C), which showed no depression of melting point on admixture with diethyl 5-acetamido-2-aminoazulene-1, 3-dicarboxylate (III).[1]

The residue obtained by the evaporation of the filtrate was dissolved in benzene, and the benzene solution was passed through a column of alumina. The column was eluted with benzene. The crude crystals (50 mg.) obtained from the effluent, were recrystallized from ethanol to give diethyl 2, 5-diaminoazulene-1, 3-dicarboxylate (IV) (40 mg.; m. p. 145—146.5°C) as dull orange micro-prisms.

Found: N, 9.32. Calcd. for $C_{16}H_{18}O_4N_2$: N, 9.27%.

λ_{max}^{MeOH} mμ (log ε): 220.5 (4.11), 235 (3.99) sh, 289 (4.43), 335 (4.88), 389 (4.07), 476 (3.28).

IR (Nujol): 3535, 3365, 3255, 1667, 1626 cm^{-1}.

The Dipicrate of IV.—Dark yellowish green micro-prisms (from ethanol); m. p. 147—148°C.

Found: C, 44.47; H, 3.17; N, 14.69. Calcd. for $C_{16}H_{18}O_4N_2$-$C_{12}H_6O_{14}N_6$: C, 44.22; H, 3.18; N, 14.74%.

When it was refluxed in acetic anhydride for 30 min., IV was acetylated to give III. This III (100 mg.) was then heated under reflux with potassium hydroxide (100 mg.) in 80% aqueous ethanol (5 ml.) for 3 hr.; by this procedure IV (20 mg.) was obtained.

The Schmidt Reaction of Diethyl 2-Amino-5-(1, 1-ethylenedioxyethyl)azulene-1, 3-dicarboxylate (II).—Into a solution of II (100 mg.) in concentrated sulfuric acid (1 ml.), sodium azide (25 mg.) was added in small portions with stirring at room temperature; the reaction mixture was then treated as in the above-mentioned method to give both III (35 mg.) and IV (4 mg.).

Diethyl 2, 5-Diacetamidoazulene-1, 3-dicarboxylate (V).—A solution of III (30 mg.) in acetic anhydride (1 ml.) was refluxed for 1 hr. The residue obtained by the evaporation of the solvent was recrystallized from aqueous ethanol to give V (20 mg.; m. p. 132—133°C) as brown micro-needles.

Found: C, 62.20; H, 5.71; N, 7.31. Calcd. for $C_{20}H_{20}O_6N_2$: C, 62.16; H, 5.74; N, 7.25%.

λ_{max}^{MeOH} mμ (log ε): 247.5 (4.47), 319 (4.70), 329 (4.82), 378 (3.86), 394 (3.86), 465 (3.46).

IR (Nujol): 3470, 3345, 1712, 1704, 1672 cm^{-1}.

By the same treatment, IV was acetylated to give V.

Diethyl 5-Aminoazulene-1, 3-dicarboxylate (VII).—*a) From Diethyl 5-Acetamido-2-aminoazulene-1, 3-dicarboxylate (III).*—A solution of III (200 mg.) in dioxane (12 ml.) and concentrated sulfuric acid (0.8 ml.) was warmed on a water bath for 10 min. and chilled. Into the solution, a solution of sodium nitrite (100 mg.) in water (4 ml.) was added with stirring without cooling. After the mixture had been stirred for 3 hr., a solution of sodium hypophosphite (1.6 g.) in water (10 ml.) was added. The mixture was stirred for a further 2 hr. and then allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted with benzene. The extract was washed with water, dried over anhydrous sodium sulfate, and passed through a column of alumina. The column was eluted with benzene. From the effluent, the crude crystals (30 mg.) were obtained. Recrystallization from ethanol afforded VII (m. p. 157—158°C) as purple scales.

Found: C, 66.66; H, 5.69; N, 4.78. Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88%.

λ_{max}^{MeOH} mμ (log ε): 240 (4.24), 282 (4.47), 305 (4.40), 395 (4.32), 565 (3.20).

IR (Nujol): 3390, 3320, 3215, 1684, 1647 cm^{-1}.

b) From Diethyl 2, 5-Diaminoazulene-1, 3-dicarboxylate (IV).—To the diazotized solution of IV (200 mg.) with sodium nitrite (100 mg.), sodium hypophosphite (1.6 g.) was added, and the reaction mixture was treated as in a); VII (45 mg.) was thus obtained.

c) From Diethyl 5-Acetylazulene-1, 3-dicarboxylate (VI).—Into a mixture of VI (150 mg.) in chloroform (3 ml.) and concentrated sulfuric acid (2 ml.), sodium azide (70 mg.) was stirred in small portions without cooling. After the mixture had been stirred for 20 min., the acid layer was diluted with water and extracted with benzene. The extract was then washed with water, dried over anhydrous sodium sulfate, and passed through a column of alumina. The crystals obtained from the effluent were recrystallized from ethanol to give VII (8 mg.).

Diethyl 5-Acetamidoazulene-1, 3-dicarboxylate (VIII).—*a) From Diethyl 5-Acetamido-2-aminoazulene-1, 3-dicarboxylate (III).*—Into a solution of III (200 mg.) in dioxane (12 ml.) and concentrated sulfuric acid (1.2 ml.), a solution of sodium nitrite (100 mg.) in water (4 ml.) was gradually dropped with stirring under ice-water cooling. After the mixture had been stirred for 40 min. at room temperature, a solution of sodium hypophosphite (1.6 g.) in water (10 ml.) was added. The mixture was treated as in the case of VII-a) and gave reddish violet crystals (30 mg.). Recrystallization from a mixture of benzene and cyclohexane afforded VIII (20 mg.; m. p. 191—192°C) as pale purple scales.

Found: C, 65.58; H, 5.79; N, 4.30. Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25%.

λ_{max}^{MeOH} mμ (log ε): 235 (4.22) sh, 242 (4.23), 277 (4.53), 306 (4.59), 380 (4.24), 391 (4.23), 522 (2.96).

IR (Nujol): 3185, 1686, 1639 cm^{-1}.

b) From Diethyl 5-Aminoazulene-1, 3-dicarboxylate (VII).—A solution of VII (20 mg.) in acetic anhydride was warmed on a water bath for 5 min. The residue produced by the evaporation of the solvent was then recrystallized from aqueous methanol to give VIII (15 mg.).

2, 5-Diaminoazulene-1, 3-dicarboxylic Acid (X).—To a solution of III (200 mg.) in ethanol (6 ml.), a 10% potassium hydroxide aqueous solution (2 ml.) was added. The mixture was refluxed for 4 hr., concentrated to 2/3 volume under reduced pressure, diluted with water (20 ml.), and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The brownish black residue (45 mg.) obtained by the evaporation of the solvent was recrystallized from a mixture of benzene and cyclohexane to give X (30 mg.; m. p. above 285°C) as fine black crystals.

Found: N, 11.07. Calcd. for $C_{12}H_{10}O_4N_2$: N, 11.38%.

IR (Nujol): 3470, 3355, 3225, 1650, 1621 cm^{-1}.

IV was hydrolyzed to give X by the same treatment.

Diethyl 2, 6-Diaminoazulene-1, 3-dicarboxylate (XI).—Into a solution of diethyl 6-acetyl-2-aminoazulene-1, 3-dicarboxylate (XII) (1.0 g.) in concentrated sulfuric acid (4 ml.), sodium azide (240 mg.) was added in small portions with stirring without cooling; the reaction mixture was then treated as in the case of I to give the crude crystals (400 mg.). Recrystallization from benzene gave dull brown plates (290 mg.; m. p. 207—208°C), which showed no depression of melting point on admixture with XI[1]; the infrared spectrum was identical with that of XI.

XI (30 mg.) was also derived from diethyl 2-amino-6-(1, 1-ethylenedioxyethyl)azulene-1, 3-dicarboxylate (XIII) (100 mg.) by the same treatment.

The Schmidt Reaction of Diethyl 6-Acetylazulene-1, 3-dicarboxylate (XIV).—Into a mixture of XIV (70 mg.) in chloroform (3 ml.) and concentrated sulfuric acid (1.5 ml.), sodium azide (30 mg.) was added in small portions with stirring without cooling. After the mixture has been stirred for 30 min., the acid layer was diluted with ice-water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and passed through a column of alumina. The column was eluted with ethyl acetate, and from the first effluent, XIV (3 mg.) was recovered. Orange leaflets (15 mg.; m. p. 220—221°C) from the second and orange scales (20 mg.; m. p. 235—236°C) from the third were obtained. The former showed no depression of melting point on admixture with diethyl 6-acetamidoazulene-1, 3-dicarboxylate (XVI),[1] and the latter showed no depression of melting point on admixture with diethyl 6-aminoazulene-1, 3-dicarboxylate (XV).[1]

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