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The Anionoid Substitution Reaction of Diethyl 2-Acetamido-6-bromoazulene-1, 3-dicarboxylate

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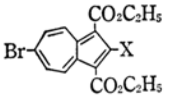
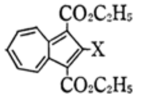
The bromine atom in diethyl 2-acetamido-6-bromoazulene-1, 3-dicarboxylate (I) is as reactive toward the anionoid reagents as in diethyl 6-bromoazulene-1, 3-dicarboxylate. Twenty-seven 6-substituted azulene derivatives have been synthesized from I by the nucleophilic substitution reaction. On one of them, diethyl 2-acetamido-6-diethylaminoazulene-1, 3-dicarboxylate, the removal of the 2-acetamido group has been carried out, giving diethyl 6-diethylaminoazulene-1, 3-dicarboxylate.

In a previous paper1) dealing with anionoid substitution reactions on diethyl 6-bromoazulene-1, 3-dicarboxylate (I), it was shown that the bromine atom of I was easily displaced with various anionoid reagents, such as amines, alkoxide and mercaptide. In more recent work,2) it was found that the bromine atom of diethyl 2-amino-6-bromoazulene-1, 3-dicarboxylate (II)3,4a,b) was also displaced with alkoxide or mercaptide, but this reaction required much more severe conditions than those with I, and II did not react with amines. Such differences between the reactivities of I and II toward anionoid reagents may be attributed to the existence or nonexistence of the electron-releasing amino group which enhances the electron density at Position 6. The author's interest in the activity of the bromine atom in I and II has led to the suggestion that the bromine atom of diethyl 2-acetamido-6-bromoazulene-1, 3-dicarboxylate (III) will be reactive toward the anionoid reagents. The present paper will deal with reactions of III with various anionoid reagents.



I: $X=H$
II: $X=NH_2$
III: $X=NHCOCH_3$
VII: $X=N(COCH_3)_2$



IV: $X=NH_2$
V: $X=NHCOCH_3$
VI: $X=N(COCH_3)_2$

It has been reported that the acetylation of diethyl 2-aminoazulene-1, 3-dicarboxylate (IV) was not achieved by heating IV in acetic anhydride for 3 hr.4a) However, the heating of IV in acetic anhydride for 7—10 hr. gave a monoacetyl derivative V and a diacetyl derivative VI. When it was treated with acetic anhydride under the same conditions, the amino compound II gave a mixture of a monoacetyl derivative III and a diacetyl derivative (VII). The further acetylation of III afforded VII, while the alkaline or the acidic hydrolysis of VII gave a mixture of III and II. The relation among IV, V and VI was similar to that among 6-bromoazulene derivatives, II, III and VII. The ultraviolet spectra of these acetates are shown in Fig. 1.

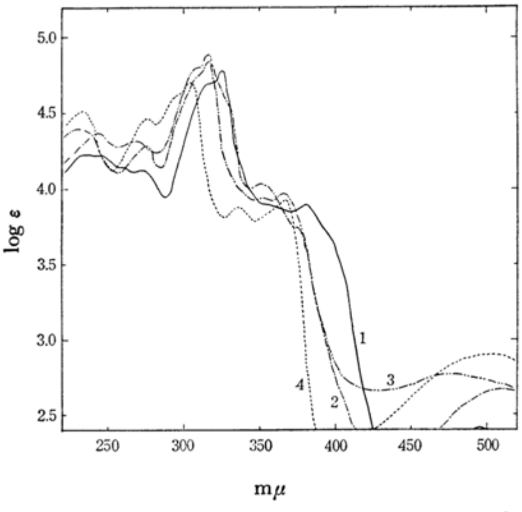


Fig. 1. Ultraviolet absorption spectra in methanol.

1. Diethyl 2-acetamido-6-bromoazulene-1, 3-dicarboxylate (III)
2. Diethyl 2-diacetylamino-6-bromoazulene-1, 3-dicarboxylate (VII)
3. Diethyl 2-acetamidoazulene-1, 3-dicarboxylate (V)
4. Diethyl 2-diacetylaminoazulene-1, 3-dicarboxylate (VI)

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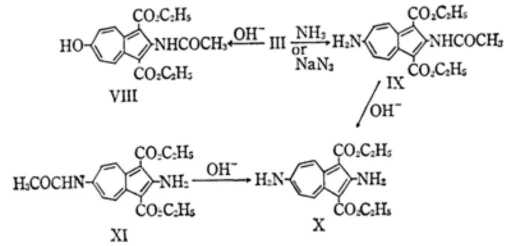
1) T. Nozoe, K. Takase and M. Tada, This Bulletin, **38**, 247 (1965).

2) T. Nozoe et al., unpublished data.

3) T. Nozoe, *Croat. Chem. Acta,* **29**, 20 (1957); T. Nozoe and S. Ito, *Chem. org. Naturstoffe,* **19**, 33 (1961).

4) a) T. Nozoe, S. Matsumura, Y. Murase and S. Seto, *Chem.* & *Ind.,* **1955**, 1257; T. Nozoe, S. Seto, S. Matsumura and Y. Murase, This Bulletin, **35**, 1179 (1962). b) T. Nozoe, S. Seto and S. Matsumura, ibid., **35**, 1990 (1962).

The treatment of III with aqueous ethanolic alkali afforded II and a hydroxyazulene derivative VIII, which in turn gave an acetoxy derivative ($\nu_{C=O}$ 1770 cm^{-1}) when heated with acetic anhydride. The treatment of III with ammonia or sodium azide (in the presence of dimethyl sulfoxide)⁵⁾ afforded diethyl 2-acetamido-6-aminoazulene-1, 3-dicarboxylate (IX). The alkaline hydrolysis of IX yielded diethyl 2, 6-diaminoazulene-1, 3-dicarboxylate (X), which had also been derived from diethyl 6-acetamido-2-aminoazulene-1, 3-dicarboxylate (XI).⁶⁾ The reaction of III with sodium ethoxide in ethanol afforded diethyl 2-acetamido-6-ethoxyazulene-1,3-dicarboxylate (XII), and the treatment of III in ethanol with an aqueous solution of sodium hydrosulfide afforded the 6-mercapto derivative (XIII). The ultraviolet spectra of these derivatives are shown in Fig. 2.



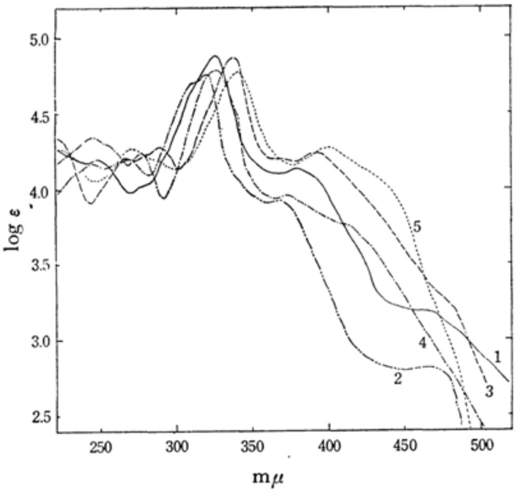
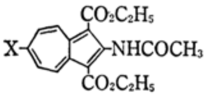


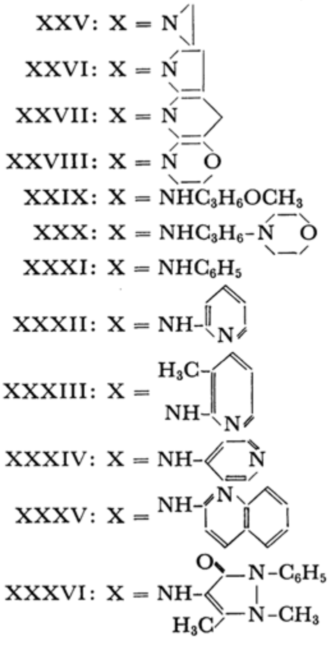
Fig. 2. Ultraviolet absorption spectra in methanol.

1. Diethyl 2-acetamido-6-hydroxyazulene-1, 3-dicarboxylate (VIII)
2. Acetate of VIII
3. Diethyl 2-acetamido-6-aminoazulene-1, 3-dicarboxylate (IX)
4. Diethyl 2-acetamido-6-ethoxyazulene-1, 3-dicarboxylate (XII)
5. Diethyl 2-acetamido-6-hydrazinoazulene-1, 3-dicarboxylate (XIV)

The reaction of III with hydrazine, phenylhydrazine, dimethylamine, diethylamine, 2-phenylethylamine, 2-hydroxyethylamine, di(2-hydroxyethyl)amine, 2-cyanoethylamine, di(2-cyanoethyl)amine, allylamine, diallylamine, ethyleneimine, pyrrolidine, piperidine, morpholine, 3-methoxypropylamine, 3-morpholinopropylamine, aniline, 2-aminopyridine, 3-methyl-2-aminopyridine, 4-aminopyridine, 2-aminoquinoline and 4-aminoantipyrine afforded, respectively, diethyl 2-acetamido-6-hydrazino- (XIV), -6-phenylhydrazino- (XV), -6-dimethylamino- (XVI), -6-diethylamino- (XVII), -6-(2-phenylethylamino)- (XVIII), -6-(2-hydroxyethylamino)- (XIX), -6-di(2-hydroxyethyl)amino- (XX), -6-(2-cyanoethylamino)- (XXI), -6-di(2-cyanoethyl)amino- (XXII), -6-allylamino- (XXIII), -6-diallylamino- (XXIV), -6-ethyleneimino- (XXV), -6-pyrrolidino- (XXVI), -6-piperidino- (XXVII), -6-morpholino- (XXVIII),



XII: X = OC_2H_5
XIII: X = SH
XIV: X = $NHNH_2$
XV: X = $NHNHC_6H_5$
XVI: X = $N(CH_3)_2$
XVII: X = $N(C_2H_5)_2$
XVIII: X = $NHC_2H_4C_6H_5$
XIX: X = NHC_2H_4OH
XX: X = $N(C_2H_4OH)_2$
XXI: X = NHC_2H_4CN
XXII: X = $N(C_2H_4CN)_2$
XXIII: X = $NHCH_2CHCH_2$
XXIV: X = $N(CH_2CHCH_2)_2$



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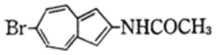
5) K. Hafner, H. Patzelt and H. Kaiser, *Ann.*, **656**, 24 (1962).

6) T. Nozoe, K. Takase and M. Tada, This Bulletin, **36**, 1006 (1963).

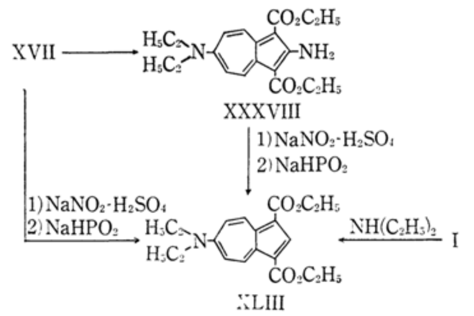
-6-(3-methoxypropylamino)- (XXIX), -6-(3-morpholinopropylamino)- (XXX), -6-anilino- (XXXI), -6-(2-pyridylamino)- (XXXII), -6-(3-methylpyridin-2-yl)amino- (XXXIII), -6-(4-pyridylamino)- (XXXIV), -6-(2-quinolylamino)- (XXXV), and -6-(4-antipyrinylamino)azulene-1, 3-dicarboxylate (XXXVI).

It was mentioned in the previous report[1] that the reaction of 2-acetamido-6-bromoazulene (XXXVII)[4b] with amines did not afford any 6-aminoazulene derivatives. Therefore, it can be understood that the activity of the bromo group at Position 6 of III is enhanced by the presence of two ethoxycarbonyl groups at Positions 1 and 3, by which III is invested with reactivity towards anionoid reagents, thus giving some 6-substituted azulene derivatives.



XXXVII

The acidic or the alkaline hydrolysis of XVII, XIX, XX, XXIV and XXVIII afforded 2-amino compounds XXXVIII, XXXIX, XL, XLI and XLII respectively; these deacetylations were more difficult than the deacetylation of the 6-acetamido-2-aminoazulene derivative XI.[6] The substituents were removed in XVII and XXXVIII; the diazotization reaction of XXXVIII was realized by sodium nitrite and an excess of sulfuric acid, while the decomposition of the diazonium salt formed was achieved on letting it stand in the presence of sodium hypophosphite. The reaction carried out in dioxane gave diethyl 6-diethylaminoazulene-1, 3-dicarboxylate (XLIII), which had also been derived from I.[1] An acetamido group in XVII, upon being hydrolyzed with the sulfuric acid, XLIII, was directly obtained from XVII. An attempt to derive 2-amino-6-diethylaminoazulene did not succeed. The ultraviolet spectra of XVII and XXXVIII are shown in Fig. 3.



Some compounds of these anionoid reaction products have been investigated in terms of the growth-inhibitory activity in relation to Crocker Sarcoma 180 and Bashford Carcinoma 63.[7]

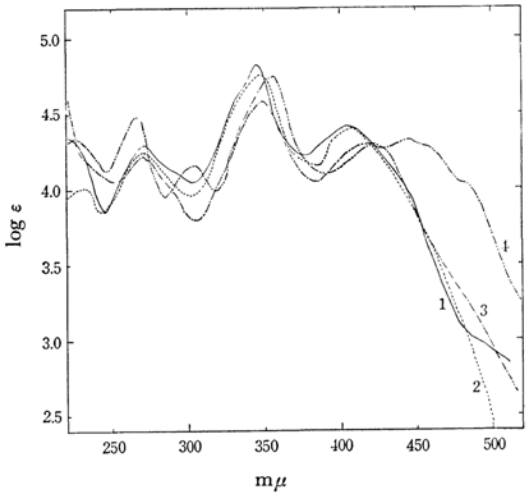


Fig. 3. Ultraviolet absorption spectra in methanol.

1. Diethyl 2-acetamido-6-diethylaminoazulene-1, 3-dicarboxylate (XVII)
2. Diethyl 2-acetamido-6-morpholinoazulene-1, 3-dicarboxylate (XXVIII)
3. Diethyl 2-acetamido-6-anilinoazulene-1, 3-dicarboxylate (XXXI)
4. Diethyl 2-amino-6-diethylaminoazulene-1, 3-dicarboxylate (XXXVIII)

Experimental[8]

The Reaction of Diethyl 2-Amino-6-bromoazulene-1, 3-dicarboxylate (II) and Acetic Anhydride.—A solution of II (5.0 g.) in acetic anhydride (8 ml.) was refluxed for 8 hr., and the residue produced by the evaporation of the excess of acetic anhydride under reduced pressure was dissolved in hot ethanol (60 ml.). The insoluble compound was recrystallized from ethyl acetate to give diethyl 2-acetamido-6-bromoazulene-1, 3-dicarboxylate (III) (m. p. 212—213°C; 4.0 g.) as pale red needles.

Found: C, 53.09; H, 4.37; N, 3.42. Calcd. for $C_{18}H_{18}O_5NBr$: C, 52.95; H, 4.44; N, 3.43%.

λ_{max}^{MeOH} $m\mu$ (log ε): 234 (4.23), 245 (4.22)sh, 272 (4.13), 314 (4.69)sh, 324 (4.78), 360 (3.87)sh, 379 (3.89), 496 (2.39).

IR (Nujol): 3270, 1718, 1658 cm^{-1}.

From the ethanol solution, brilliant red needles were obtained; these were recrystallized from ethanol to afford diethyl 2-diacetylamino-6-bromoazulene-1, 3-dicarboxylate (VII) (m. p. 141—142°C; 0.5 g.).

Found: C, 53.34; H, 4.42; N, 3.10. Calcd. for $C_{20}H_{20}O_6NBr$: C, 53.34; H, 4.48; N, 3.11%.

λ_{max}^{MeOH} $m\mu$ (log ε): 233 (4.39), 274 (4.28), 316 (4.83), 350 (4.03), 373 (3.75), 509 (2.69).

IR (Nujol): 1704, 1686 cm^{-1}.

Refluxing II (5.0 g.) in acetic anhydride for 12 hr. gave III (0.6 g.) and VII (4.1 g.), while refluxing III (50 mg.) in acetic anhydride for 1.5 hr. afforded VII (45 mg.).

The Hydrolysis of III.—a) A mixture of III (50

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[7] H. Endo and M. Tada, *Sci. Rep. Res. Inst. Tohoku Univ.(C)*, **11**, 377 (1964).

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

mg.) in ethanol (8 ml.) and 6 N sulfuric acid (2 ml.) was refluxed for 1.5 hr. After the mixture had been cooled, the crystals precipitated gave II (20 mg.).

b) A mixture of III (100 mg.) in ethanol (6 ml.) and a 10% potassium hydroxide alcohol solution (6 ml.) was stirred for 2 hr. at room temperature; by this procedure II (20 mg.) was obtained.

The Hydrolysis of VII.—a) A mixture of VII (150 mg.) in ethanol (5 ml.) and 6 N sulfuric acid (1.5 ml.) was refluxed for 30 min. After it had cooled, III (130 mg.) precipitated out.

b) To a suspension of VII (1.0 g.) in ethanol (30 ml.) concentrated ammonia water (10 ml.) was added, and the mixture was warmed on a water bath for 5 min. At once III (850 mg.) was precipitated.

c) A mixture of VII (50 mg.) in ethanol (5 ml.) and 6 N sulfuric acid (3 ml.) was refluxed for 2 hr.; by this procedure II (15 mg.) was obtained.

Diethyl 2-Acetamidoazulene-1, 3-dicarboxylate (V).—A solution of IV (0.6 g.) in acetic anhydride (2 ml.) was refluxed for 7 hr., and the residue produced by the evaporation of the solvent was dissolved in benzene. The solution was then passed through a column of alumina and eluted with benzene. From the effluent, IV (50 mg.) was recovered; when the column was then further eluted with ethyl acetate, crude crystals were obtained. Recrystallization from methanol afforded V (m. p. 141—142°C; 0.4 g.) as red prisms.

Found: C, 65.94; H, 5.69; N, 4.28. Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25%.

λ_{max}^{MeOH} mμ (log ε): 243 (4.37), 268 (4.32), 306 (4.80)sh, 315 (4.88), 351 (3.95), 366 (3.98), 480 (2.77).

IR (Nujol): 3330, 1706, 1664 cm⁻¹.

Diethyl 2-Diacetylaminoazulene-1, 3-dicarboxylate (VI).—A solution of IV (0.6 g.) in acetic anhydride (3 ml.) was refluxed for 10 hr. The residue produced by the evaporation of the solvent was recrystallized from methanol to give VI (550 mg.; m. p. 138—138.5°C) as red needles.

Found: C, 64.85; H, 5.70; N, 3.63. Calcd. for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77%.

λ_{max}^{MeOH} mμ (log ε): 234 (4.51), 275 (4.46), 304 (4.70), 337 (3.87), 366 (3.92), 505 (2.93).

IR (Nujol): 1727, 1689 cm⁻¹.

Diethyl 2-Acetamido-6-hydroxyazulene-1, 3-dicarboxylate (VIII).—A solution of III (0.2 g.) in ethanol (30 ml.) was added to a 10% potassium hydroxide aqueous solution (5 ml.), and the mixture was stirred for 1 hr. at room temperature. After the mixture had been allowed to stand overnight, the II (20 mg.) which precipitated was filtered off. The filtrate was diluted with water (20 ml.) and acidified with 6 N sulfuric acid. The crystals which separated were recrystallized from aqueous ethanol to give VIII (m. p. 217—218°C (decomp.); 0.1 g.) as dull yellow crystals.

Found: N, 4.14. Calcd. for $C_{18}H_{19}O_6N$: N, 4.06%.

λ_{max}^{MeOH} mμ (log ε); 234 (4.51), 275 (4.46), 304 (4.70), 337 (3.87), 366 (3.92), 505 (2.93).

IR (Nujol): 3410, 3155, 1706, 1647 cm⁻¹.

The Acetate of VIII: Obtained as reddish brown crystals by refluxing VIII in acetic anhydride for 15 min. (from aqueous ethanol); m. p. 137—138°C.

Found: N, 3.89. Calcd. for $C_{20}H_{21}O_7N$: N, 3.62%.

λ_{max}^{MeOH} mμ (log ε): 244 (4.18), 268 (4.20), 312 (4.72)sh, 318 (4.77), 368 (3.94), 465 (2.85).

IR (Nujol): 3270, 1770, 1715, 1664 cm⁻¹.

Diethyl 2-Acetamido-6-aminoazulene-1, 3-dicarboxylate (IX).—*a) From Liquid Ammonia.*—III (500 mg.) was added to an excess of liquid ammonia. After the mixture had stood for one week at room temperature, the residue obtained by the evaporation of the ammonia was dissolved in ethyl acetate. The solution was then passed through a column of alumina and eluted with ethyl acetate. From the first effluent, II (30 mg.) was obtained. From the second effluent, yellow crystals (310 mg.) were obtained; these were recrystallized from ethanol to give IX (m. p. 225—225.5°C) as yellow scales.

Found: C, 62.82; H, 5.54; N, 8.07. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%.

λ_{max}^{MeOH} mμ (log ε): 267 (4.20), 288 (4.27), 337 (4.85), 393 (4.23).

IR (Nujol): 3410, 3360, 3270, 1672, 1647 cm⁻¹.

The Picrate of IX: M. p. 155°C (decomp.); dull brown micro-prisms (from ethanol).

Found: N, 11.95. Calcd. for $C_{24}H_{23}O_{12}N_5$: N, 12.21%.

b) From Sodium Azide.—III (300 mg.) and sodium azide (1.0 g.) were added to dimethyl sulfoxide (10 ml.). The mixture was then heated on a water bath for 15 hr. After dilution with water (250 ml.), it was extracted with ethyl acetate. The extract was washed with 2 N acetic acid and water, and dried over anhydrous sodium sulfate. The extract was then passed through a column of alumina and eluted with ethyl acetate. From the effluent, IX (100 mg.) was obtained.

Diethyl 2, 6-Diaminoazulene-1, 3-dicarboxylate (X).—A mixture of IX (25 mg.) in ethanol (6 ml.) and 6 N sulfuric acid (1.5 ml.) was refluxed for 40 min., and the mixture was concentrated to half volume under reduced pressure. After the addition of water (6 ml.), the solution was neutralized with sodium hydrogen carbonate and the crystals thereby formed were recrystallized from benzene to give dull brown plates (m. p. 206—207°C; 10 mg.), which showed no depression of melting point on admixture with an authentic specimen[6] of X and which were identified with X by a comparison of their infrared spectra.

Diethyl 2-Acetamido-6-ethoxyazulene-1, 3-dicarboxylate (XII).—To a solution prepared from metallic sodium (20 mg.) and absolute ethanol (6 ml.), finely powdered III (200 mg.) was added. The mixture was then stirred for 5 hr. at room temperature. After it had stood overnight, it was diluted with water and the crystals thereby formed were recrystallized from aqueous ethanol to give XII (m. p. 116—117°C; 150 mg.) as yellow needles.

Found: C, 64.70; H, 6.58; N, 3.71. Calcd. for $C_{20}H_{23}O_6N$: C, 64.33; H, 6.21; N, 3.75%.

λ_{max}^{MeOH} mμ (log ε): 245 (4.34), 278 (4.24), 327 (4.79), 372 (3.97), 408 (3.77)sh.

IR (KBr): 3530, 3380, 1718, 1701, 1681, 1667 cm⁻¹.

Diethyl 2-Acetamido-6-mercaptoazulene-1, 3-dicarboxylate (XIII).—Into a suspension of III (50 mg.) in ethanol (10 ml.), a 27% sodium hydrosulfide aqueous solution (3 ml.) was added. The mixture was then stirred for 3 hr. at room temperature. After it had stood overnight, this mixture was diluted with water (40 ml.) and acidified with 6 N sulfuric acid. The acidic solution was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The residue obtained by the evaporation of the solvent was recrystallized from benzene to yield XIII (m. p. 220—221°C; 20 mg.) as red micro-prisms.

Found: C, 61.05; H, 4.96; N, 3.68. Calcd. for $C_{18}H_{19}O_5NS$: C, 59.82; H, 5.30; N, 3.88%.

IR (Nujol): 3400, 3280, 1709, 1684, 1650 cm^{-1}.

Diethyl 2-Acetamido-6-hydrazinoazulene-1, 3-dicarboxylate (XIV).—Eighty per cent hydrazine hydrate (5 ml.) was added to a suspension of II (100 mg.) in methanol (10 ml.), and the mixture was stirred for 3 hr. at room temperature. After it had stood overnight, the reaction mixture was concentrated to half volume and added with water. The crystals thereby formed were recrystallized from ethanol to afford XIV (m. p. 203—204°C (decomp.); 60 mg.) as yellow micro-needles.

Found: C, 60.16; H, 5.63; N, 11.48. Calcd. for $C_{18}H_{21}O_5N_3$: C, 60.16; H, 5.89; N, 11.69%.

λ_{max}^{MeOH} mμ (log ε): 222 (4.27), 271 (4.26), 288 (4.19)sh, 341 (4.77), 399 (4.26).

IR (Nujol): 3340, 3320, 1667, 1645 cm^{-1}.

The Acetate of XIV: M. p. 234.5—235°C, pale brown micro-needles (from ethanol).

Found: N, 10.58. Calcd. for $C_{20}H_{23}O_6N_3$: N, 10.47%.

Diethyl 2-Acetamido-6-phenylhydrazinoazulene-1, 3-dicarboxylate (XV).—Into a solution of phenylhydrazine (3 ml.) in ethanol (10 ml.), III (300 mg.) was added. The mixture was then refluxed for 1 hr. and concentrated to 1/4 volume. After the addition of water (50 ml.) and 2 N acetic acid (5 ml.), the crystals thereby formed were recrystallized from ethanol to give XV (m. p. 218—219°C; 190 mg.) as brownish yellow micro-prisms.

Found: C, 66.00; H, 5.71; N, 9.54. Calcd. for $C_{24}H_{25}O_5N_3$: C, 66.19; H, 5.79; N, 9.65%.

λ_{max}^{MeOH} mμ (log ε): 270 (4.21)sh, 285 (4.22), 342 (4.75), 402 (4.31).

IR (KBr): 3380, 3330, 3290, 1701, 1647 cm^{-1}.

Diethyl 2-Acetamido-6-dimethylaminoazulene-1, 3-dicarboxylate (XVI).—To a mixture of a 40% dimethylamine aqueous solution (10 ml.) in methanol (20 ml.), III (500 mg.) was added, and the mixture was refluxed for 30 min. After the addition of water (40 ml.), the crystals thereby separated were recrystallized from methanol to give XVI (m. p. 179—180°C; 300 mg.) as yellow silky needles.

Found: C, 64.77; H, 6.19; N, 7.42. Calcd. for $C_{20}H_{24}O_5N_2$: C, 64.50; H, 6.50; N, 7.52%.

λ_{max}^{MeOH} mμ (log ε): 223 (4.27), 270 (4.28), 344 (4.82), 402 (4.37).

IR (Nujol): 3260, 1695, 1637 cm^{-1}.

Diethyl 2-Acetamido-6-diethylaminoazulene-1, 3-dicarboxylate (XVII).—III (500 mg.) was added to a mixture of diethylamine (5 ml.) and ethanol (6 ml.), and the mixture was refluxed for 1 hr. After the addition of water (30 ml.), the crystals which separated were recrystallized from ethanol to give XVII (m. p. 165—166°C; 320 mg.) as yellow micro-prisms.

Found: N, 6.85. Calcd. for $C_{22}H_{28}O_5N_2$: N, 7.00%.

λ_{max}^{MeOH} mμ (log ε): 271 (4.28), 290 (4.11)sh, 345.5 (4.82), 403 (4.41).

IR (Nujol): 3260, 1701, 1669, 1642 cm^{-1}.

Diethyl 2-Acetamido-6-(2-phenylethylamino)-azulene-1, 3-dicarboxylate (XVIII).—To a mixture of β-phenylethylamine (300 mg.) in ethanol (20 ml.), III (300 mg.) was added. The mixture was refluxed for 1 hr. and then concentrated to 1/3 volume. After the addition of water (30 ml.) and 2 N hydrochloric acid (3 ml.), the crystals thereby formed were recrystallized from aqueous ethanol to afford XVIII (m. p. 163—164°C; 210 mg.) as yellow leaflets.

Found: C, 69.39; H, 6.33; N, 5.95. Calcd. for $C_{26}H_{28}O_5N_2$: C, 69.62; H, 6.29; N, 6.25%.

λ_{max}^{MeOH} mμ (log ε): 270 (4.22), 290 (4.15), 343 (4.83), 399 (4.32).

IR (KBr): 3340, 3300, 1701, 1684, 1650 cm^{-1}.

Diethyl 2-Acetamido-6-(2-hydroxyethylamino)-azulene-1, 3-dicarboxylate (XIX).—III (80 mg.) was added to a solution of ethanolamine (2 ml.) in ethanol (5 ml.). The mixture was then refluxed for 30 min. and concentrated to 1/3 volume. After the addition of water (20 ml.), the crystals thereby obtained were recrystallized from aqueous ethanol to afford XIX (m. p. 207—208°C; 45 mg.) as yellow needles.

Found: N, 7.01. Calcd. for $C_{20}H_{24}O_6N_2$: N, 7.21%.

λ_{max}^{MeOH} mμ (log ε): 220 (3.99), 269 (4.17), 290 (4.13), 342 (4.78), 399 (4.27).

IR (Nujol): 3330, 3270, 1695, 1664 cm^{-1}.

Diethyl 2-Acetamido-6-[di(2-hydroxyethyl)-amino]azulene-1, 3-dicarboxylate (XX).—III (0.8 g.) was added to a solution of diethanolamine (5 ml.) in ethanol (10 ml.). The mixture was then refluxed for 1 hr. and concentrated to half volume. After the addition of water, the crystals which separated were recrystallized from aqueous methanol to XX (m. p. 210—211°C; 500 mg.) in the form of brownish yellow needles.

Found: C, 60.98; H, 6.49; N, 6.97. Calcd. for $C_{22}H_{28}O_7N_2$: C, 61.10; H, 6.53; N, 6.48%.

λ_{max}^{MeOH} mμ (log ε): 225 (3.97), 270 (4.25), 347 (4.77), 404 (4.38).

IR (Nujol): 3300, 1704, 1658 cm^{-1}.

Diethyl 2-Acetamido-6-(2-cyanoethylamino)-azulene-1, 3-dicarboxylate (XXI). — III (200 mg.) was added to a mixture of β-aminopropionitrile (2 ml.) and triethylamine (2 ml.) in ethanol (15 ml.). The mixture was then refluxed for 2 hr. and concentrated to 1/4 volume. After the addition of water, the reaction solution was neutralized with 2 N hydrochloric acid. The crystals thereby formed were recrystallized from aqueous ethanol to afford XXI (m. p. 105—106°C; 110 mg.) as yellowish orange leaflets.

Found: N, 10.39. Calcd. for $C_{21}H_{23}O_5N_3$: N, 10.58%.

λ_{max}^{MeOH} mμ (log ε): 268 (4.20), 289 (4.13), 342 (4.74), 398 (4.24).

IR (KBr): 3530, 3410, 3280, 2257, 1695, 1661 cm^{-1}.

Diethyl 2-Acetamido-6-[di(2-cyanoethyl)amino]-azulene-1, 3-dicarboxylate (XXII).—III (300 mg.) was added to a mixture of 3, 3′-iminodipropionitrile (3 ml.) and triethylamine (3 ml.) in ethanol (10 ml.). The mixture was then refluxed for 2.5 hr. and concentrated to 1/4 volume. After the addition of water (50 ml.), the reaction mixture was extracted with benzene, and the extract was washed with 2 N hydrochloric acid and water. After being dried over anhydrous sodium sulfate, the benzene extract was passed through a column of alumina and eluted with benzene. From the effluent, III (80 mg.) was recovered; the column was then further eluted with a mixture of benzene and ethyl acetate. From the effluent, dull orange crystals were obtained; these were recrystallized from aqueous ethanol to give XXII (m. p. 136—138°C; 135 mg.) as brownish yellow micro-prisms.

Found: N, 12.60. Calcd. for $C_{24}H_{26}O_5N_4$: N, 12.44%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 270 (4.25), 288 (4.16)sh, 341 (4.83), 400 (4.32).

IR (KBr): 3510, 3360, 2247, 1689, 1656 cm^{-1}.

Diethyl 2-Acetamido-6-allylaminoazulene-1, 3-dicarboxylate (XXIII).—A mixture of III (200 mg.) and allylamine (2 ml.) in ethanol (10 ml.) was treated as in the case of XVII; by this procedure XXIII (m. p. 144—145°C; 110 mg.) was obtained as orangish yellow prisms (from ethanol).

Found: C, 65.47; H, 6.44; N, 7.19. Calcd. for $C_{21}H_{24}O_5N_2$: C, 65.61; H, 6.29; N, 7.29%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 270 (4.23), 289 (4.17), 342 (4.80), 399 (4.29).

IR (KBr): 3360, 1706, 1689 cm^{-1}.

Diethyl 2-Acetamido-6-diallylaminoazulene-1, 3-dicarboxylate (XXIV).—A mixture of III (200 mg.) and diallylamine (3 ml.) in ethanol (10 ml.) was treated as in the case of XVI; by this procedure XXIV (m. p. 158—159°C; 120 mg.) was obtained as orange needles (from methanol).

Found: N, 6.77. Calcd. for $C_{24}H_{28}O_5N_2$: N, 6.60%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 234 (3.99)sh, 248 (4.15), 257 (4.15), 275 (4.11), 324 (4.68), 342 (4.55), 389 (4.25).

IR (Nujol): 3250, 1721, 1701, 1678 cm^{-1}.

Diethyl 2-Acetamido-6-ethyleneiminoazulene-1, 3-dicarboxylate (XXV).—A mixture of III (60 mg.) and ethyleneimine (4 ml.) in methanol (4 ml.) was refluxed for 10 min. After the addition of water (40 ml.), the crystals thereby formed were recrystallized from methanol to give XXV (m. p. 164.5—165.5°C; 20 mg.) as orange micro-prisms.

Found: C, 64.68; H, 5.95; N, 7.43. Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.85; H, 5.99; N, 7.56%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 238 (3.95), 268 (4.10), 334 (4.77), 367 (4.13)sh, 399 (4.21), 445 (3.17)sh.

IR (Nujol): 3175, 1701, 1692, 1642 cm^{-1}.

Diethyl 2-Acetamido-6-pyrrolidinoazulene-1, 3-dicarboxylate (XXVI).—A mixture of III (200 mg.) and pyrrolidine (2 ml.) in ethanol (10 ml.) was treated as in the case of XVIII to form XXVI (m. p. 182—183°C (decomp.); 100 mg.) as brilliant yellow micro-scales (from aqueous ethanol).

Found: C, 66.19; H, 6.72; N, 6.70. Calcd. for $C_{22}H_{26}O_5N_2$: C, 66.31; H, 6.58; N, 7.03%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 272 (4.26), 292 (4.10)sh, 347 (4.78), 402 (4.40).

IR (KBr): 3410, 1709, 1669 cm^{-1}.

Diethyl 2-Acetamido-6-piperidinoazulene-1, 3-dicarboxylate (XXVII).—A mixture of III (200 mg.) and piperidine (10 ml.) in methanol (20 ml.) was treated as in the case of XIV to form XXVII (m. p. 141—142°C; 130 mg.) as yellow needles (from ethanol).

Found: C, 66.85; H, 6.43; N, 6.82. Calcd. for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84; N, 6.79%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 270.5 (4.32), 274 (4.32), 347.5 (4.77), 410 (4.42).

IR (Nujol): 3250, 1706, 1639 cm^{-1}.

Diethyl 2-Acetamido-6-morpholinoazulene-1, 3-dicarboxylate (XXVIII).—A mixture of III (200 mg.) and morpholine (4 ml.) in ethanol (10 ml.) was treated as in the case of XVI, thus forming XXVIII (m. p. 205.5—206°C; 135 mg.) as yellow needles (from methanol).

Found: C, 63.65; H, 6.56; N, 6.60. Calcd. for $C_{22}H_{26}O_6N_2$: C, 63.75; H, 6.32; N, 6.76%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 233 (4.01), 271 (4.25), 347 (4.74), 409 (4.40).

IR (Nujol): 3280, 1718, 1701, 1647 cm^{-1}.

Diethyl 2-Acetamido-6-(3-methoxypropylamino)-azulene-1, 3-dicarboxylate (XXIX).—A mixture of III (200 mg.) and 3-aminopropyl methyl ether (2 ml.) in ethanol (10 ml.) was treated as in the case of XVIII to give XXIX (m. p. 157—158°C; 90 mg.) as brownish yellow prisms (from aqueous ethanol).

Found: C, 63.56; H, 6.73; N, 6.62. Calcd. for $C_{22}H_{28}O_6N_2$: C, 63.44; H, 6.78; N, 6.73%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 269 (4.25), 290 (4.28), 342 (4.81), 397 (4.32).

IR (KBr): 3290, 1706, 1678, 1647 cm^{-1}.

Diethyl 2-Acetamido-6-(3-morpholinopropylamino)azulene-1, 3-dicarboxylate (XXX).—A mixture of III (200 mg.) and 3-aminopropylmorpholine (2 ml.) in ethanol (12 ml.) was refluxed for 2 hr. and then concentrated to 1/4 volume under reduced pressure. After the addition of water, the solution was extracted with ethyl acetate. The extract was washed with 2 N acetic acid and water, and dried over anhydrous sodium sulfate. The residue obtained by the evaporation of the solvent was recrystallized from aqueous ethanol to afford XXX (m. p. 67—68°C; 60 mg.) as yellow micro-needles.

Found: N, 8.68. Calcd. for $C_{25}H_{33}O_6N_3$: N, 8.91%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 269 (4.10), 286 (4.03)sh, 343 (4.69), 399 (4.19).

IR (KBr): 3400, 3330, 1695, 1684, 1653 cm^{-1}.

Diethyl 2-Acetamido-6-anilinoazulene-1, 3-dicarboxylate (XXXI).—A mixture of III (500 mg.) and aniline (5 ml.) in ethanol (10 ml.) was treated as in the case of XXX to give XXXI (m. p. 233—234°C; 380 mg.) as yellow leaflets (from aqueous ethanol).

Found: C, 68.82; H, 5.84; N, 6.48. Calcd. for $C_{24}H_{24}O_5N_2$: C, 68.56; H, 5.75; N, 6.66%.

$\lambda_{max}^{\mathrm{MeOH}}$ mμ (log ε): 270 (4.21), 274 (4.20)sh, 348 (4.58), 417 (4.30).

IR (KBr): 3250, 3215, 1701, 1669, 1642 cm^{-1}.

Diethyl 2-Acetamido-6-(2-pyridylamino)azulene-1, 3-dicarboxylate (XXXII).—A mixture of III (200 mg.), 2-aminopyridine (1 g.), and triethylamine (2 ml.) in ethanol (10 ml.) was refluxed for 7 hr. and then concentrated to half volume. After the reaction mixture had been cooled, the III (80 mg.) which had precipitated was filtered off. The filtrate was acidified with 2 N hydrochloric acid and extracted with benzene. After being washed with water and dried over anhydrous sodium sulfate, the extract was passed through a column of alumina and eluted with benzene. From the first effluent, III (30 mg.) was recovered, while from the second effluent, the crystals obtained were recrystallized from ethanol to give XXXII (m. p. 185—186°C; 15 mg.) as orange needles.

Found: 9.75. Calcd. for $C_{23}H_{23}O_5N_3$: N, 9.97%.

λ_{max}^{MeOH} mμ (log ε): 228 (4.27)sh, 271 (4.29), 303 (4.14)sh, 354 (4.69), 422 (4.57).

IR (KBr): 3360, 3230, 1701, 1669, 1647 cm^{-1}.

Diethyl 2-Acetamido-6-(3-methylpyridin-2-ylamino)azulene-1, 3-dicarboxylate (XXXIII).—A mixture of III (200 mg.), 2-amino-3-methylpyridine (2 ml.) and triethylamine (2 ml.) in ethanol (10 ml.) was treated as in the above experiment to form XXXIII (m. p. 110—112°C; 15 mg.) as yellow micro-prisms (from aqueous ethanol); III (20 mg.) was also recovered.

Found: N, 9.35. Calcd. for $C_{24}H_{25}O_5N_3$: N, 9.65%.

λ_{max}^{MeOH} mμ (log ε): 270 (4.23), 297 (4.16)sh, 344 (4.75), 400 (4.29).

IR (KBr): 3340, 3310, 1706, 1689, 1658, 1647 cm^{-1}.

Diethyl 2-Acetamido-6-(4-pyridylamino)azulene-1, 3-dicarboxylate (XXXIV).—A mixture of III (200 mg.), 4-aminopyridine (400 mg.) and triethylamine (2 ml.) in ethanol (10 ml.) was treated as in the case of XXXII to form XXXIV (m. p. 145—146°C; 35 mg.) as yellow needles (from ethanol); III (70 mg.) was also recovered.

Found: C, 65.56; H, 5.25; N, 9.69. Calcd. for $C_{23}H_{23}O_5N_3$: C, 65.54; H, 5.50; N, 9.97%.

λ_{max}^{MeOH} mμ (log ε): 232 (4.26), 278 (4.31), 324 (4.85), 369 (4.09), 439 (3.13).

IR (KBr): 3300, 1718, 1704, 1645 cm^{-1}.

Diethyl 2-Acetamido-6-(2-quinolylamino)-azulene-1, 3-dicarboxylate (XXXV).—A mixture of III (300 mg.), 2-aminoquinoline (300 mg.) and triethylamine (3 ml.) in ethanol (15 ml.) was treated as in the case of XXXII to form XXXV (m. p. 220—221°C; 20 mg.) as reddish yellow prisms (from ethanol); III (180 mg.) was also recovered.

Found: C, 68.53; H, 5.32; N, 8.66. Calcd. for $C_{27}H_{25}O_5N_3$: C, 68.78; H, 5.34; N, 8.91%.

λ_{max}^{MeOH} mμ (log ε): 230 (4.38)sh, 270 (4.33), 351 (4.66), 427 (4.51).

IR (KBr): 3340, 3280, 1695, 1664 cm^{-1}.

Diethyl 2-Acetamido-6-(4-antipyrinylamino)-azulene-1, 3-dicarboxylate (XXXVI).—A mixture of III (300 mg.), 4-aminoantipyrine (300 mg.) and triethylamine (3 ml.) in ethanol (15 ml.) was treated as in the case of XXXII to form XXXVI (m. p. 234—235°C; 80 mg.) as deep yellow micro-prisms (from ethanol).

Found: C, 65.55; H, 5.57; N, 10.38. Calcd. for $C_{29}H_{30}O_6N_4$: C, 65.65; H, 5.70; N, 10.56%.

λ_{max}^{MeOH} mμ (log ε): 277 (4.35), 282 (4.34)sh, 343 (4.69), 390 (4.36).

IR (KBr): 3230, 3165, 1709, 1689, 1672, 1661 cm^{-1}.

Diethyl 2-Amino-6-diethylaminoazulene-1, 3-dicarboxylate (XXXVIII).—A mixture of XVII (200 mg.) and 12 N sulfuric acid (1 ml.) in ethanol (5 ml.) was refluxed for 50 min. and then concentrated to half volume under reduced pressure. After the addition of water (40 ml.), the crystals thereby formed were dissolved in benzene. The benzene solution was passed through a column of alumina and eluted with benzene. From the effluent, crystals (80 mg.) were obtained; these crystals were recrystallized from ethanol to give XXXVIII (m. p. 153—154°C; 65 mg.) as brownish yellow prisms.

Found: C, 67.27; H, 7.00; N, 7.65. Calcd. for $C_{20}H_{26}O_4N_2$: C, 67.02; H, 7.31; N, 7.82%.

λ_{max}^{MeOH} mμ (log ε): 227 (4.33), 265.5 (4.49), 303 (4.16), 354.5 (4.74), 419 (4.28), 444 (4.32), 480 (4.05)sh.

IR (Nujol): 3530, 3370, 1715, 1678 cm^{-1}.

The Picrate of XXXVIII: M. p. 155—157°C, reddish brown prisms (from ethanol).

Found: C, 53.27; H, 4.56; N, 11.98. Calcd. for $C_{26}H_{29}O_{11}N_5$: C, 53.15; H, 4.98; N, 11.92%.

Diethyl 2-Amino-6-(2-hydroxyethylamino)azulene-1, 3-dicarboxylate (XXXIX).—A mixture of XIX (40 mg.) in ethanol (5 ml.) and 6 N sulfuric acid (1 ml.) was refluxed for 1 hr. After the addition of water, the crystals thereby precipitated were recrystallized from ethanol to yield XXXIX (m. p. 184—185°C; 15 mg.) as yellowish brown prisms.

Found: C, 62.17; H, 6.01; N, 7.84. Calcd. for $C_{18}H_{22}O_5N_2$: C, 62.41; H, 6.40; N, 8.09%.

λ_{max}^{MeOH} mμ (log ε): 252 (4.09), 297 (3.91)sh, 343 (4.76), 409 (4.24).

IR (Nujol): 3530, 3370, 3300, 1706, 1684, 1667, 1603 cm^{-1}.

Diethyl 2-Amino-6-[di(2-hydroxyethyl)amino]-azulene-1, 3-dicarboxylate (XL).—A 10% potassium hydroxide aqueous solution (1 ml.) was added to a solution of XX (100 mg.) in ethanol (5 ml.). The mixture was then refluxed for 10 min. and concentrated to half volume under reduced pressure. After the addition of water (30 ml.), the reaction solution was extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulfate. After the removal of the solvent, the crystals which remained were recrystallized from aqueous methanol to form XL (m. p. 146—147°C; 30 mg.) as orangish yellow prisms.

Found: N, 6.89. Calcd. for $C_{20}H_{26}O_6N_2$: N, 7.18%.

IR (Nujol): 3530, 3340, 1667, 1634 cm^{-1}.

Diethyl 2-Amino-6-diallylaminoazulene-1, 3-dicarboxylate (XLI).—A mixture of XXIV (150 mg.) in ethanol (6 ml.) and 6 N sulfuric acid (1 ml.) was treated as in the case of XXXVIII to give XLI (m. p. 123—124°C; 20 mg.) as brownish yellow micro-prisms (from a mixture of benzene and cyclohexane).

Found: N, 7.16. Calcd. for $C_{22}H_{26}O_4N_2$: N, 7.33%.

λ_{max}^{MeOH} mμ (log ε): 228 (4.31), 263 (4.47), 300 (4.13), 354 (4.72), 419 (4.22), 444 (4.24), 480 (3.98)sh.

IR (KBr): 3480, 3360, 1667, 1634 cm^{-1}.

Diethyl 2-Amino-6-morpholinoazulene-1, 3-dicarboxylate (XLII).—A solution of XXVIII (50 mg.) in ethanol (4 ml.) and 6 N sulfuric acid (1.5 ml.) was treated as in the case of XXXVIII to give XLII (m. p. 134—134.5°C; 10 mg.) as yellow needles (from methanol); then XXVIII (15 mg.) was also recovered.

Found: N, 7.13. Calcd. for $C_{20}H_{24}O_5N_2$: N, 7.52%.

λ_{max}^{MeOH} mμ (log ε): 260 (4.42), 293 (4.00), 349 (4.69), 428 (4.21), 480 (3.95)sh.

IR (Nujol): 3460, 3340, 1675, 1667, 1634 cm^{-1}.

The Picrate of XLII: M. p. 156—157°C, brownish black crystals (from ethanol).

Found: C, 52.12; H, 4.66; N, 11.50. Calcd. for $C_{26}H_{27}O_{12}N_5$: C, 51.91; H, 4.52; N, 11.64%.

Diethyl 6-Diethylaminoazulene-1, 3-dicarboxylate (XLIII).—*a) From XXXVIII.* — Into a solution of XXXVIII (180 mg.) and concentrated sulfuric acid (0.6 ml.) in dioxane (10 ml.), sodium nitrite (50 mg.) in water (2 ml.) was stirred at room temperature. After the mixture had been stirred for a further 30 min., sodium hypophosphite (1.5 g.) was added. The mixture was then stirred for a further 3 hr. and then allowed to stand overnight at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. It was then passed through a column of alumina and eluted with benzene. From the effluent, the crystals were obtained; they were then recrystallized from ethanol to give yellow needles (25 mg.), which showed no depression of melting point on admixture with an authentic specimen[1] of XLIII.

The water-layer was adjusted to a slightly alkaline state with a 10% potassium hydroxide aqueous solution and extracted with ethyl acetate. By the same purification, XLIII (5 mg.) was obtained.

b) From XVII.—A solution of XVII (200 mg.) and concentrated sulfuric acid (1 ml.) in dioxane (10 ml.) was warmed on a water bath for 15 min. and then treated as in a) to yield XLIII (35 mg.).

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