[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WASHINGTON]

Azulene. VI. Synthesis and Properties of Some 1,3-Disubstituted Azulenes[1,2]

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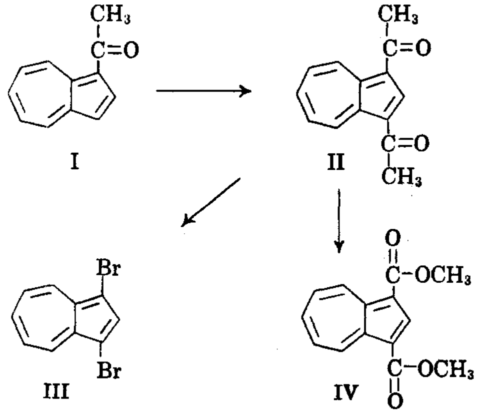
Received April 22, 1957

Improved procedures for the acetylation of azulene and for the conversion of 1-acetylazulene to a diacetylazulene have been found. Additional evidence has been obtained that the latter compound is the 1,3-derivative. An 81% yield of 1-nitroazulene has been realized by nitration with tetranitromethane. A number of new 1,3-disubstituted azulenes have been prepared and their visible absorption spectra examined with respect to the additive effect of the groups present.

In earlier papers in this series results establishing the electrophilic substitution of azulene in the 1-position and the orientation of a second substituent on to the 3-position by both *ortho, para-* and *meta*-directing groups were reported.[3,4]

One of the reactions investigated was Friedel-Crafts acetylation and from this were obtained 1-acetylazulene (I) and a diacetylazulene postulated to be II.[3] The 1-acetylazulene was best prepared (57%) using acetic anhydride and stannic chloride in methylene chloride. Further acetylation of I under these conditions or under those (acetic anhydride and aluminum chloride in carbon disulfide at room temperature) which gave the best (18%; 62% net) yield of diacetylazulene from azulene gave essentially none of the disubstituted product. We have now discovered that reaction of azulene with acetyl chloride and stannic chloride in carbon tetrachloride at reflux temperature gives an 83% yield of II from azulene and an 87% yield of II from I. The yields in these reactions were found to vary considerably (to as low as 5%) with changes in the relative amounts of reagents and solvent as well as in temperature and time.



Though the structure of I was firmly established,[3] there was no direct evidence for the structure of the diacetylazulene. Since all disubstituted azulenes formed by electrophilic substitution were found to be 1,3-derivatives, the structure represented by II was most probable. The displacement of the acetyl group by a positive chlorine had been noted in the formation of 1,3-dichloroazulene from 1-acetylazulene on reaction with alkaline hypochlorite.[5] Accordingly, a similar process was tried with hypobromite on the diacetylazulene and, as expected, the known 1,3-dibromoazulene (III)[3] was formed. Further evidence was provided by oxidation of II with sodium hypoiodite to the diacid which was characterized as the dimethyl ester (IV). The properties of this substance (red color and crystalline nature) corresponded to those reported[6] for diethyl azulene-1,3-dicarboxylate.

The mononitration of azulene was first accomplished in 63% yield with cupric nitrate and acetic anhydride.[3] Subsequently it was learned that Scheibli[7] had effected the reaction with tetranitromethane in comparable (59%) yield. Our further efforts to improve the former method did not succeed but conditions have now been found for the latter which give an 81% yield of 1-nitroazulene.

No dinitroazulene was produced with either of the above reagents, either from azulene directly or from 1-nitroazulene. Nitration of azulene with nitric acid and acetic anhydride, however, gave either a 43% (84% net) yield of 1-nitroazulene or a mixture of 1-nitroazulene (45%) and an orange crystalline dinitroazulene (13%) which was presumed to be the 1,3-derivative (V), depending on the conditions used. The latter product was also obtained in 35% (52% net) yield from 1-nitroazulene. The separation of the dinitroazulene from traces of 1-nitroazulene was very difficult and the dinitro compound when chromatographed on

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[1] Taken in part from the Ph.D. thesis of Charles G. Fritz.

[2] Support for a part of this work by contract DA-04-200-ORD-235 with the Office of Ordnance Research, U. S. Army, and by the Agnes H. Anderson Research Fund is gratefully acknowledged.

[3] A. G. Anderson, J. A. Nelson, and J. J. Tazuma, *J. Am. Chem. Soc.*, **75**, 4980 (1953).

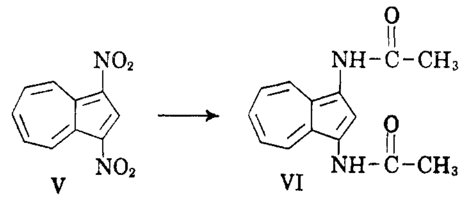
[4] A. G. Anderson, E. J. Cowles, J. J. Tazuma, and J. A. Nelson, *J. Am. Chem. Soc.*, **77**, 6321 (1955).

[5] Whether chlorination of the acetyl group occurred prior to displacement was not determined. Formation of a chloro ketone might be expected to aid the displacement reaction.

[6] T. Nozoe, S. Matsumura, and S. Seto, *Chemistry and Industry*, 1257 (1955).

[7] K. G. Scheibli, Doctoral Thesis, Eidgenössischen Technischen Hochschule, Zurich, Switzerland, 1952, p. 30.

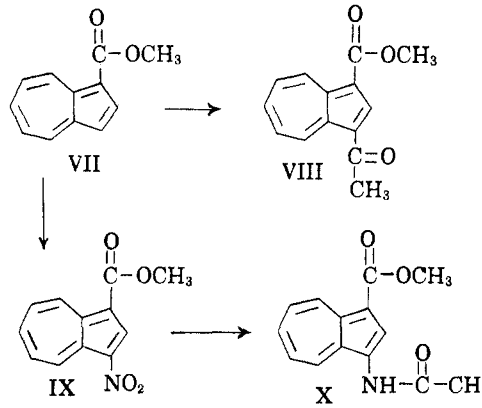
alumina changed completely into a yellowish green material which was strongly adsorbed and was not characterized. Purification was ultimately achieved through chromatography on specially prepared silica gel. Reductive acetylation of V gave the corresponding 1,3-diacetamidoazulene (VI).



V VI

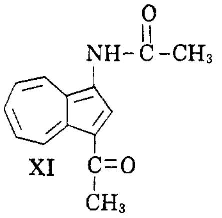
In connection with studies of the effect of substituents in the 1- and 3-positions on absorption in the visible region (see below), it was desired to prepare certain 3-substituted derivatives of methyl 1-azuloate (VII). Attempts to prepare VII directly by reaction of azulene with ethyl chlorocarbonate and stannic chloride or aluminum chloride were unsuccessful and it was prepared, therefore, as before[3] from 1-acetylazulene.

Attempts to couple VII with benzenediazonium chloride both under the conditions used for reaction with azulene[3] and by adding a large excess of the cold diazonium salt solution to a hot solution of the ester failed. The acetylation of VII, however, proceeded smoothly on addition of a slight excess of stannic chloride to a solution of the ester in acetic anhydride. The product, most probably VIII, was isolated as red crystals in 80% yield.



VII VIII IX X

Treatment of VII with nitric acid in acetic anhydride in the cold gave the nitro ester (IX) in low yield and the yield was not improved by increasing the concentration of nitric acid. The recovery of most of the starting material made the net yield 38%. Nitration with cupric nitrate trihydrate in acetic anhydride as previously performed[3] gave somewhat better results (44% net yield) and when this method was repeated with a much longer reaction time the actual yield was 36% and no starting material was recovered. In a single experiment a 62% net yield of IX was obtained by nitration with tetranitromethane and pyridine in ethanol but this result could not be duplicated. Reductive acetylation[3] of IX gave X (69%). Acetylation of 1-acetamidoazulene[3] gave the 3-acetyl derivative (XI) in 78% yield and thus provided an additional compound in the series.



XI

The additivity of the spectral shifts in the visible region caused by alkyl groups on the different positions of the azulene ring was first noted by Plattner[8] and has become known as Plattner's Rule. It has been very useful in the identification of many natural and synthetic alkylazulenes. In our work it was soon recognized that this rule could be applied, at least qualitatively, to 1- and 1,3-substituted azulenes having groups other than alkyl.

Cowles[9] has recently reported on a study of a number of these compounds and the present work affords several additional examples. Certain of the new compounds were not sufficiently soluble in the solvents previously used[9] and, therefore, all spectra were taken in alcohol. As this change in solvent caused an appreciable change in the shift caused by acetyl and nitro groups as compared to that observed in other solvents,[9] the diacetyl and dinitro compounds were also included. Although the more complex correlations using the squares of the frequencies or wave-length values determined by least squares[9] might give better agreement, it is seen (Table II) that when average shifts for either the wave lengths (mμ) or wave numbers (cm.$^{-1}$) are used the results are quite good.

TABLE I

AVERAGE SHIFTS (Mμ AND CM.$^{-1}$) OF PRINCIPAL PEAK CAUSED BY GROUPS ON THE 1-(3-) POSITION[a]

Group	$\Delta\lambda_{max}$	$\Delta 1/\lambda_{max}$
$-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3$[b]	−43	+1490
$-\overset{\displaystyle O}{\overset{\|}{C}}-OCH_3$[b]	−36	+1180
$-NO_2$[b]	−40	+1460
$-NH-\overset{\displaystyle O}{\overset{\|}{C}}-CH_3$	+41	−1330

[a] Average shift values were determined by successive iterations until reasonable self-consistency was achieved. The value for 1-nitroazulene was so divergent that it was not used. [b] Groups causing a marked hypsochromic shift also remove most of the fine structure and the highest point of the band was assumed to coincide with the maximum of the principal peak.

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(8) Pl. A. Plattner, *Helv. Chim. Acta*, **24**, 283E (1941); Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **30**, 1320 (1947).

(9) E. J. Cowles, *J. Am. Chem. Soc.*, **79**, 1093 (1957).

TABLE II

ABSORPTION MAXIMA (Mμ AND CM.$^{-1}$) OF 1,3-DISUBSTITUTED AZULENES[a]

Groups	λ_{max} (calcd.)	λ_{max} (obs.)	% dev.[b]	$1/\lambda_{max}$ (calcd.)	$1/\lambda_{max}$ (obs.)	% dev.[b]
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}, -\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}$	492	498	1.2	20280	20080	1.0
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{OCH_3}, -\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{OCH_3}$	506	511	1.0	19660	19570	0.9
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}, -\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{OCH_3}$	499	498	0.2	19970	20080	0.5
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{OCH_3}, -\mathrm{NO_2}$	502	503	0.2	19940	19880	0.3
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{OCH_3}, -\mathrm{NH}-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}$	583	583	0.0	17150	17150	0.0
$-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}, -\mathrm{NH}-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}$	576	575	0.2	17460	17390	0.4
$-\mathrm{NH}-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}, -\mathrm{NH}-\overset{\overset{\mathrm{O}}{\Vert}}{\mathrm{C}}-\mathrm{CH_3}$	660	653	1.1	14640	15310	4.4
$-\mathrm{NO_2}, -\mathrm{NO_2}$	498	488	2.0	20220	20490	1.1

[a] The calculated values were obtained by addition of the appropriate values in Table I to the observed values (max, 578 mμ or 17,300 cm.$^{-1}$) for azulene. [b] % deviation = difference ÷ λ_{max} (obs.) or $1/\lambda_{max}$ (obs.) × 100 to nearest 0.1.

EXPERIMENTAL[10,11]

1,3-Diacetylazulene (II). *A. From azulene.* A solution of 7.2 mg. (0.056 mmole) of azulene, 0.1 ml. (0.06 mmole) of stannic chloride, and 5 ml. (0.07 mole) of acetyl chloride in 8 ml. of carbon tetrachloride was refluxed for 20 min. on a steam bath. It was then shaken thoroughly with 200 ml. of water, during which process the blue solution turned red, and the mixture was extracted with ether. The residue remaining after removal of the solvent from the combined extracts was chromatographed (hexane then dichloromethane) on acid-washed alumina and the red eluate fraction yielded 10 mg. (83.6%) of product, m.p. 185–188°, identical (infrared absorption spectrum) with an authentic sample.[3]

B. From 1-acetylazulene (I). To a solution of 16.5 mg. (0.097 mmole) of 1-acetylazulene in 10 ml. of carbon tetrachloride was added 0.2 ml. (0.12 mmole) of stannic chloride. An immediate orange coloration resulted. Acetyl chloride (5 ml., 0.07 mole) was then added slowly, and during this process a yellow precipitate formed. The mixture was refluxed (steam bath) for 12 min. and then worked up as described above (A) to give 17.9 mg. (86.9%) of diacetylazulene, m.p. 186–188°.

Conversion of 1,3-diacetylazulene to 1,3-dibromoazulene (III). A solution of sodium hypobromite prepared by adding 0.5 g. of bromine to 10 ml. of 10% sodium hydroxide at 0° was added to 16.6 mg. (0.078 mmole) of the diacetylazulene dissolved in 11 ml. of dioxane. After 1 hr. the blue-green solution was diluted with 200 ml. of water. Extraction with ether, removal of the solvent from the combined extracts, and chromatography (petroleum ether then 1:10 dichloromethane–petroleum ether) of the residue on alumina gave 4.8 mg. (20.8%) of blue needles, m.p. 89–91°, identical (ultraviolet, visible and infrared absorption spectra) with an authentic sample[3] of 1,3-dibromoazulene.

Dimethyl azulene-1,3-dicarboxylate (IV). To a cooled (0°) solution of 215 mg. (1.0 mmole) of 1,3-diacetylazulene in 50 ml. of dioxane was added 40 ml. of 12% potassium hydroxide also at 0°. To this mixture was added dropwise with stirring 25 ml. of a solution of iodine (10%) and potassium iodide (20%) in water over a period of 1 hr. Stirring was continued for 30 min., the iodoform removed by filtration and the filtrate extracted with ether. The aqueous solution was then acidified and extracted with ether (only a portion of the water-insoluble material dissolved in the ether) and the ether extracts treated with an excess of diazomethane. Slow evaporation of the ether solution left a solid residue which was chromatographed (methylene chloride) on alumina. The main fraction of red crystals, m.p. 171°, amounted to 49.1 mg. (13.1%) and showed absorption maxima (mμ, D_{max}) at 234, 0.65; 271, 0.57; 284, 0.53; 290, 0.66; 295, 0.69; 301, 0.86; 357, 0.19: 367, 0.20, and 511.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.65; H, 4.96.

1-Nitroazulene. Method A. To a solution of 64 mg. (0.5 mmole) of azulene in 2 ml. of pyridine was added 1.2 ml. of a 0.5*M* ethanolic solution (0.6 mmole) of tetranitromethane. The color of the solution changed to red after 18 min. and the mixture was treated in a separatory funnel with 100 ml. of 10% hydrochloric acid and the whole extracted with dichloromethane. Evaporation of the organic extracts left a semicrystalline residue which was chromatographed (dichloromethane) on alumina to give 70.5 mg. (81%) of product identical (m.p. and absorption spectra) with an authentic sample.[3]

Method B. To a cooled (ice bath) solution of 128 mg. (1.0 mmole) of azulene in 9.9 ml. of acetic anhydride was added dropwise and slowly 0.082 ml. (1.3 mmole) of concentrated nitric acid. After 10 min. of continued cooling and occasional shaking, the mixture was diluted with 10 ml. of water and extracted with 20 ml. of chloroform. The red-brown chloroform extract was washed with small (5–10 ml.) portions of 1*N* ammonium hydroxide until the wash solution remained strongly alkaline, then with water and, finally, with saturated salt solution. Evaporation (air stream) of the solvent and chromatography (chloroform) on alumina gave 63 mg. (49%) of recovered azulene from the first violet blue band and 74 mg. (43%, 84% net) of crystalline 1-

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(10) Melting points were taken on a calibrated Fisher-Johns apparatus and are uncorrected. Ultraviolet and visible spectra were taken in ethanol on a Cary Model 11S recording spectrophotometer unless otherwise indicated.

(11) Microanalyses were performed by B. Nist and C. H. Ludwig.

nitroazulene having the same infrared spectrum (Nujol mull) as the product from Method A and an authentic sample.[3]

1,3-Dinitroazulene (V). A solution of 43 mg. (0.247 mmole) of 1-nitroazulene in 5 ml. of acetic anhydride was cooled to 0° and treated with a cold solution of 3 drops (1.2 mmole) of nitric acid in 3 ml. of acetic anhydride. After 1 min. the mixture was warmed to room temperature and then, after 5 min., it was poured into cold water. The solution was extracted with dichloromethane and then with chloroform and the combined extracts dried over sodium sulfate. The residue remaining after removal (air stream) of the solvent was chromatographed on silica gel which had been previously treated with *tert*-butyl alcohol, air-dried overnight and then poured into a column filled with hexane. The sample was applied with a minimal volume of benzene and the chromatograph developed with a 1:1 mixture of 80–120° petroleum ether and carbon tetrachloride until the eluate was colorless. From this eluate was recovered 15 mg. (33%) of 1-nitroazulene. The dinitroazulene remained on the column as a sharp band which was eluted with dichloromethane. The yield of orange needles which melted with slow decomposition at *ca.* 245° was 19 mg. (35%). The material showed absorption maxima (mμ) in ethanol at 237 (log ϵ 4.17); 297 (4.40); 306 (4.47); 376 (4.18) and 390 (4.14) and in dichloromethane at 452 (ϵ 1235); 472 (1480); 480 (1490); 487 (1460); 500 (1400); 528 (785) (shoulder); 538 (616) (shoulder); and 670 (12). The principal peak in the visible region was at 488 mμ with ethanol as the solvent.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 55.05; H, 2.77. Found: C, 54.95; H, 2.94.

1,3-Diacetamidoazulene (VI). To a solution of 20.7 mg. (0.0095) mmole) of 1,3-dinitroazulene and 1.5 g. of sodium acetate in 15 ml. of acetic anhydride and 2 ml. of glacial acetic acid heated to 100° was added 0.5 g. of powdered zinc. Heating was continued for 5 min. and the mixture then poured into 300 ml. of water. Extraction with chloroform (all of the blue color was not extracted from the aqueous layer) and removal (air stream) of the solvent from the extracts left a residue which was chromatographed on alumina. A greenish brown and a small blue fraction (1-N-acetylaminoazulene) were removed with chloroform. Elution with ethyl acetate then gave a yellow-green fraction and, finally, acetone was used to obtain a red and a larger blue-green fraction. The latter afforded 8 mg. (34.8%) of product as green needles, m.p. 251–253°. The substance showed absorption maxima (mμ, D_{max}) at 245, 0.79; 298, 1.46; 379, 0.25 and a single broad peak at 653 mμ.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.36; H, 5.83. Found: C, 69.20; H, 5.78.

Methyl 3-acetylazuloate (VIII). Stannic chloride (0.05 ml., 0.03 mmole) was added to a solution of 5.0 mg. (0.027 mmole) of methyl 1-azuloate in 1 ml. of acetic anhydride. After 20 min. the mixture was hydrolyzed with 150 ml. of water and the solution extracted with ether. The residue obtained by evaporation of the extract solution was chromatographed (alumina) with benzene as the eluent. Red, yellow, and blue zones developed. The red zone afforded 4.9 mg. (79.7%) of red crystals, m.p. 118–119°. Ultraviolet absorption maxima (mμ, D_{max}) were observed at 238, 1.6; 281, 2.1; 306, 1.75; 368, 0.51, and 378, 0.52. The visible spectrum had a single maximum at 498 mμ.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.74; H, 5.55.

Methyl 3-nitroazuloate (IX). A solution of 6.5 mg. (0.035 mmole) of methyl 1-azuloate in 1 ml. of acetic acid was treated with a suspension of 34 mg. (0.14 mmole) of cupric nitrate trihydrate in 1 ml. of acetic anhydride for 2 min. The reaction was quenched by hydrolysis with 200 ml. of water and the aqueous solution extracted with ether. Evaporation of the solvent and chromatography of the residue on Florisil with petroleum ether (70–120°), to remove unreacted ester, and then dichloromethane gave 2.9 mg. (35.8%) of product as red needles, m.p. 146°. The substance showed absorption maxima in the ultraviolet (mμ, D_{max}) at 220, 1.25; 286, 1.08; 374, 0.32; 390, 0.23, and a single peak in the visible at 503 mμ.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.29; H, 3.94. Found: C, 62.06; H, 3.91.

Methyl 3-acetamidoazuloate (X). A solution of 8.0 mg. (0.028 mmole) of the above nitro ester (IX) and 1 g. of sodium acetate in 2 ml. of acetic anhydride and 0.1 ml. of glacial acetic acid was treated with 0.5 g. of zinc dust for 10 min. The mixture was then diluted with 200 ml. of water and extracted four times with ether. The residue obtained by evaporation of the ether was chromatographed on alumina. Benzene eluted a yellow fraction and a green band was removed with benzene–dichloromethane. Chloroform eluted first a brown and then a violet fraction. The latter yielded 5.81 mg. (69%) of product as blue needles, m.p. 206°. Absorption maxima (mμ, D_{max}) in the ultraviolet were observed at 243, 0.97; 300, 1.45; 311, 1.29 and 380, 0.32. The visible spectrum had a single maximum at 583 mμ.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.11; H, 5.76. Found: C, 69.27; H, 5.51.

1-Acetamido-3-acetylazulene (XI). A solution of 0.08 ml. (0.4 mmole) of stannic chloride and 0.1 ml. (0.3 mmole) of acetyl chloride in 1 ml. of dichloromethane was added to a solution of 37.9 mg. (0.2 mmole) of 1-acetamidoazulene in 5 ml. of dichloromethane. The resulting suspension was shaken for 20 min., then hydrolyzed with 200 ml. of water and the hydrolyzate extracted with ether. Evaporation of the solvent from the combined extracts left a residue which was chromatographed on alumina. Elution with dichloromethane removed a small amount of starting material and the product was then removed with chloroform. The yield of green needles, m.p. 202° (dec.) was 36.4 mg. (78%). The substance exhibited absorption maxima in the ultraviolet (mμ, D_{max}) at 247, 0.75; 285, 0.85; 309, 0.90 and 398, 0.26. The visible spectrum had a single maximum at 575 mμ.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 73.96; H, 5.78. Found: C, 73.74; H, 6.03.

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