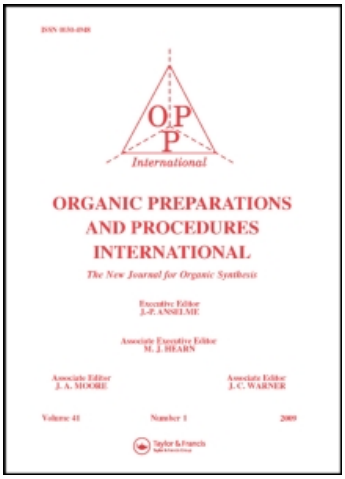

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PREPARATION OF AZULENE DERIVATIVES: AN AMINOACID, DICARBOXYLATES, AN ISOTHIOCYANATE, AND RELATED COMPOUNDS

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PREPARATION OF AZULENE DERIVATIVES: AN AMINOACID, DICARBOXYLATES, AN ISOTHIOCYANATE, AND RELATED COMPOUNDS

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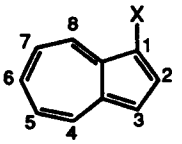
The unusual ultraviolet and fluorescence spectral properties of azulene (**1a**),[1,2] as well as its polar nature (μ = 1.08 D),[3] are well known. We now report syntheses of three types of azulene derivatives which may serve as fluorescent probes in biochemical systems: an azulylalanine (**1f**), derivatives of azulene-4,5-dicarboxylic acid (**4** and **5**) and an isothiocyanato compound (**6d**). The structural and regiochemical similarities of azulene



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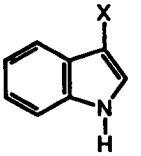


2

a, X = H

b, X = CH_2NMe_2

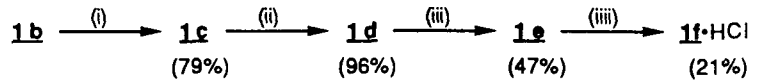
c, X = $CH_2C(CO_2Et)_2$ | NO_2

d, X = CH_2CHCO_2Et | NO_2

e X = CH_2CHCO_2Et | NH_2

f, X = CH_2CHCO_2H | NH_2

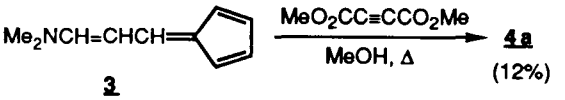
and indole (**2a**, μ = 2.05 D)[4] were exploited by application of known steps to prepare tryptophan (**2f**) from gramine (**2b**) (via **2c**, **2d**, and **2e**)[5] to the conversion of **1b**[6] into **1f** (Eq. 1), but by using DMSO instead of toluene in the first step. The low yield of aminoester **1e** is ascribed to attendant hydrolysis of the ester group in the third step plus the loss of hydrolysate during removal of tin salts. The hydrochloride of **1f** is purified, albeit in low yield, by sublimation *in vacuo* away from its mixture with inorganic salts. All compounds **1a**-**1f** are dark blue.



(Eq. 1)

(i) $O_2NCH(CO_2Et)_2$, DMSO (ii) NaOEt, EtOH
(iii) Sn, HCl (iiii) NaOH, H_2O; HCl; evaporate; sublime

Synthesis of dimethyl ester 4a (blue) from fulvene 3 (Scheme II) follows a brief note in the literature.[7] As expected, saponification of 4a occurs readily to produce a blue solution. On acidification, however, green anhydride 5a (82%) immediately forms.[7] A similar color change is noted on treatment of 5a with 1-aminobutane in benzene. The green solution becomes blue upon addition of the amine (probably by formation of a half acid-half amide), but the color reverts to green (formation of the imide



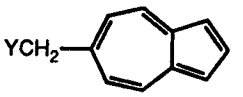
(Eq. 2)

a, R = Me b, R = $(CH_2)_{15}Me$ a, X = -O- b, X = -N-$(CH_2)_3Me$

5b, 84%) after one hour of refluxing. The color change (green to blue) also serves to indicate progress of the slow transformation 5a to 4b (72%), which occurs on refluxing 5a with excess 1-hexadecanol in toluene and tetrabutyl orthotitanate (catalyst)[8] for 6 days. It is apparent that coplanarity of the chromophoric system azulene-4,5-dicarbonyl (as in 5a and 5b) is associated with a green color, while non-coplanarity of the chromophore in 4a and 4b and in reaction intermediates in the conversion 5a to 5b results in a blue color. A similar structural relationship may also prevail in diester 4b, which remains blue in solution in toluene or as a viscous liquid, but which crystallizes as bright green needles.

Isothiocyanate 6d is prepared either directly from 6b[9] by reaction

with potassium thiocyanate in toluene/DMSO at 120 °C (30%) or by rearrangement (36%) of the thiocyanate 6c (also derived from 6b)[9] by means of zinc



6

a, Y = H b, Y = Cl c, Y = -SCN

d, Y = -N=C=S e, Y = -NHCNHPh (S)

chloride in refluxing toluene. While 6d was not obtained analytically pure it does react with aniline at room temperature to give chemically pure thiourea 6e (34%). All compounds 6a-6e are blue.

EXPERIMENTAL SECTION

Infrared spectra were determined by means of a Sargent-Welch 3-200 spectrophotometer; ^{1}H NMR spectra, by means of a Varian Associates XL-100A or, as noted in two cases, a Nicolet 360 MHz instrument. Electron-impact mass spectra were recorded by Dr. Richard Wielesek of this laboratory with a CEC model 21-110 apparatus at 70 eV. Elemental analyses were obtained by Desert Analytics, Tucson, Arizona.

Ethyl 2-Carboethoxy-2-nitro-3-(1-azulyl)propanoate (1c).- A rapid stream of nitrogen was passed through a vigorously stirred, heated (117 ± 5°) mixture of 1.4 g. (7.5 mmol) of 1-dimethylaminomethylazulene (1b),[6] 1.7 g. (8.3 mmol) of diethyl nitromalonate,[5] and 20 ml. (volume maintained constant) of reagent grade dimethyl sulfoxide for 12 hr. until evolution of dimethylamine ceased. Most of the solvent was removed by means of a Kugelrohr. A solution of the residue in chloroform (20 ml.) was extracted repeatedly with 20-ml. portions of saturated, aqueous sodium chloride solution and twice with water, dried (Na_2SO_4), concentrated, and chromatographed on silica gel (J. T. Baker, 300 g.)/chloroform. The first band (intensely blue) gave 2.07 g. (79%) of dark blue, viscous 1c. Molecular distillation (60°/0.005 mm.) gave an analytically pure sample. IR (neat): 1750 (C=O), 1560 and 1350 (NO_2) cm^{-1}. ^{1}H NMR (acetone-d_6, 360 MHz): δ 1.12 (t, J = 7 Hz, 6H, 2 CH_3), 4.24 (q, 4H, 2 CH_2), 4.35 (s, 2H, AzCH_2), 7.25 and 7.28 (2 overlapping t, J = 11 Hz, 2H, H-5 and H-7), 7.36 (d, J = 4 Hz, 1H, H-3), 7.70 (t, 1H, H-6), 7.87 (d, 1H, H-2), 8.41 (2 overlapping d, 2H, H-4 and H-8). MS m/e (relative intensity): 345 (M^+, 7), 300 (10), 299 (9), 226

(10), 153 ($AzC_2H_2^+$, 26), 141 ($AzCH_2^+$, 100).[10]

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06

Found: C, 62.83; H, 5.41; N, 4.06

Ethyl 2-Nitro-3-(1-azulyl)propanoate (1d).- A solution of 1.12 mmol of sodium ethoxide in 5 ml. of absolute ethanol was added dropwise to a vigorously stirred solution of 0.39 g. (1.12 mmol) of 1c in 20 ml. of the same solvent in an atmosphere of nitrogen. After 12 hr., the mixture was acidified (pH 6) with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated to yield 0.29 g. (96%) of bright blue, viscous 1d, purified by molecular distillation at 50°. IR (neat): 1750 (C=O), 1560 and 1370 (NO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 1.16 (t, J = 7 Hz, 3H, CH_3), 4.05 (m) and 4.22 (q, 4H total, 2 CH_2), 5.85 (t, J = 8 Hz, 1H, CH), 7.1-7.5 (m, 3H, H-3, H-5, and H-7), 7.71 (t, J = 11 Hz, 1H, H-6), 7.87 (d, J = 4 Hz, 1H, H-2), 8.43 (2 overlapping d, J = 11 Hz, 2H, H-4 and H-8). MS m/e (relative intensity): 273 (M^+, 50), 153 ($AzC_2H_2^+$, 78), 141 ($AzCH_2^+$, 94), 91 ($C_7H_7^+$, 100).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13

Found: C, 66.15; H, 5.62; N, 4.86

Ethyl 2-Amino-3-(1-azulyl)propanoate (1e).- A mixture of 0.46 g. of 1d, 1.19 g. of granulated tin, 15 ml. of ethanol, and 3 ml. of concentrated hydrochloric acid was stirred at 38° in an atmosphere of nitrogen for 18 hr. The cooled mixture was diluted with 15 ml. of water and treated with hydrogen sulfide gas in order to precipitate tin salts. The filtered solution was basified (pH 8) and extracted with ether. This extract was washed with water, dried (Na_2SO_4), and evaporated to give dark blue, viscous 1e, yield 0.19 g. (47%), purified by molecular distillation (35°). IR (neat): 3370 and 3300 (NH_2), 1725 (C=O), 1570 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (t, J = 7 Hz, 3H, CH_3), 1.60 (s, NH_2), 3.45 (m, 2H, $AzCH_2$), 3.81 (dd, 1H, CH), 4.13 (q, 2H, CH_2), 7.04 and 7.08 (2 t, J = 11 Hz, 2H, H-5 and H-7), 7.31 (d, J =

4 Hz, 1H, H-3), 7.51 (t, 1H, H-6), 7.77 (d, 1H, H-2), 8.26 (2 overlapping d, 2H, H-4 and H-8). MS m/e (relative intensity): 243 (M^+, 6), 141 ($AzCH_2^+$, 100).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76

Found: C, 73.76; H, 6.90; N, 5.55

2-Amino-3-(1-azulyl)propanoic Acid (**1f**).- A solution of 59 mg. of **1e** in 2 ml. of dichloromethane was stirred with 7 ml. of 2% aqueous sodium hydroxide solution in an atmosphere of nitrogen for 36 hr. until all of the blue color was transferred from the organic layer to the aqueous layer. The aqueous layer was separated, concentrated by rotoevaporation, acidified (pH 4) with 18% aqueous hydrochloric acid, and evaporated to dryness in a stream of nitrogen gas. The residue was sublimed at 135°/0.005 mm. to give 12.5 mg. (21%) of **1f**·HCl as a dark blue solid. IR (KBr): 3450, 2590, 2000, 1740 (C=O), 1580, 1485 cm^{-1}. ^1H NMR (D_2O, 360 MHz): δ 3.58 (ddd, J = 5, 8, 15 Hz, 2H, $AzCH_2$), 3.83 (dd, 1H, CH), 7.14 (2 overlapping t, J = 10 Hz, 2H, H-5 and H-7), 7.30 (d, J = 4 Hz, 1H, H-3), 7.58 (t, 1H, H-6), 7.73 (d, 1H, H-2), 8.28 and 8.31 (2 d, 2H total, H-4 and H-8). MS (inlet 280°) m/e (relative intensity): 215 (M^+ - HCl, 3), 141 ($AzCH_2^+$, 100), 128 (11).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56

Found: C, 62.28; H, 5.94; N, 5.55

Dimethyl Azulene-4,5-dicarboxylate (**4a**).- A mixture of 1.98 g. (20 mmol) of 3-dimethylamino-2-propen-1-al (Fluka), 1.64 g. (22 mmol) of dimethylammonium chloride, and 5 ml. of 1-butanol was refluxed for 1 hr. The cold solution deposited yellow crystals of *N*,*N*-dimethyl-*N*-(3-dimethylaminoprop-2-en-1-ylidene)ammonium chloride (**7**),[11] which were washed with acetone and stored in a desiccator, yield 3.2 g. (98%), mp. 79-80°, highly hygroscopic. ^1H NMR (DMSO-d_6): δ 3.10 and 3.28 (2 s, 6H each, 4 CH_3), 5.45 (t, J = 11 Hz, 1H, H-2), 7.80 (d, 2H, H-1 and H-3).

Reaction of 2.25 g. of 7 with sodium cyclopentadienide was conducted by the method of Arnold and Zemlicka[12] to form the unstable, bright orange intermediate fulvene 3 (0.93 g., 6.3 mmol). Compound 3 was dissolved in 100 ml. of ice-cold methanol, treated dropwise with a solution of 0.86 ml. (7 mmol) of dimethyl acetylenedicarboxylate in 5 ml. of methanol, and stirred at 22° for 36 hr. The mixture was concentrated and chromatographed on silica gel with dichloromethane as eluent. The first colored band (intensely blue) yielded 0.19 g (12%) of 4a as a dark blue solid, mp. 116-116.5°, lit.[7] mp. 116-117°. Recrystallization (50% ethanol) and sublimation (65°/0.005 mm.) gave an analytically pure sample. IR ($CDCl_3$, CaF_2 cell): 3080-2960, 1720 (C=O), 1300-1230 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.95 and 4.09 (2 s, 3H each, 2 CH_3), 7.20 (pseudo t, J = 10 Hz, 1H, H-7), 7.56 (d, J = 4 Hz, 2H, H-1 and H-3), 7.96 (t, 1H, H-2), 8.41 and 8.43 (2 overlapping d, J ≃ 9, 11 Hz, 2H, H-6 and H-8). MS m/e (relative intensity): 245 (15), 244 (M^+, 100), 213 (34), 170 (16), 127 (17).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95; m/e, 244.074

Found: C, 68.93; H, 5.07; m/e, 244.074

Azulene-4,5-dicarboxylic Anhydride (5a).- A solution of 30 mg. of ester 4a in 3 ml. of dichloromethane was stirred vigorously with 5 ml. of 3% aqueous potassium hydroxide for 5 days. The blue, aqueous layer was acidified with 2% aqueous hydrochloric acid to give a green product, which was extracted into benzene. The benzene solution was washed with water, dried (Na_2SO_4), and evaporated to give 20 mg. (82%) of 5a as green, hair-like crystals, mp. 180-181°, lit.[7] mp. 189°. Sublimation at 30° (0.005 mm.) produced dark green needles. IR ($CHCl_3$, CaF_2 cell): 1860, 1825, 1770, 1600, 1250 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.53 (pseudo t, J = 10 Hz, 1H, H-7), 7.80 (d, J = 4 Hz, 1H, H-1), 8.24 (d, J = 11 Hz, H-8) which overlaps 8.32 (d, 2H total, H-2), 8.5-8.7 (m, 2H, H-3 and H-6). MS m/e (relative intensity): 198 (M^+, 100), 126 (86).

Anal. Calcd for $C_{12}H_6O_3$: C, 72.73; H, 3.05. Found: C, 72.87; H, 3.11

N-Butyl Azulene-4,5-dicarboxylic Imide (5b).- To a solution of 93 mg. of anhydride 5a in 13 ml. of benzene was added 0.05 ml. (0.5 mmol) of freshly distilled 1-aminobutane. The green color immediately changed to blue, but the former color was restored after refluxing for 1 hr. The residue from evaporation of the solvent was sublimed at 70° (0.005 mm.) to give 100 mg. (84%) of short, bright green needles, mp. 60-61°. IR($CHCl_3$, CaF_2 cell): 1765, 1705 cm^{-1}. ^1H NMR (acetone-d_6): δ 0.96 (t, J = 6.5 Hz, 3H, CH_3), 1.2-1.9 (m, 4H, CH_2CH_2), 3.73 (t, J = 6-7 Hz, 2H, NCH_2), 7.43 (t, 1H, H-7), 7.68 (d, J = 4 Hz, 1H, H-1), 8.12 (d, J = 9 Hz, 1H, H-8), 8.16 (t, 1H, H-2), 8.46 (d, J = 4 Hz, 1H, H-3), 8.57 (d, J = 9 Hz, 1H, H-6). MS m/e (relative intensity): 253 (M^+, 100), 211 (29), 210 (28), 197 (45), 127 (32), 126 (32).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; m/e, 253.110
Found: C, 76.01; H, 5.78; N, 5.56; m/e, 253.110

Dihexadecyl Azulene-4,5-dicarboxylate (4b).- A green mixture of 112 mg (0.57 mmol) of anhydride 5a, 15 ml. (excess) of a saturated solution of 1-hexadecanol (Aldrich) in toluene, and 24 mg. (0.07 mmol) of tetrabutyl orthotitanate monomer (Fluka) was refluxed for 6 days until the solution turned blue. Evaporation of the solvent left a blue residue which was chromatographed (silica gel/carbon tetrachloride-dichloromethane, 5:1) once or twice to remove all 1-hexadecanol. The first blue band was collected and checked by ^1H NMR to see that the alcohol had been removed. The residue from evaporation of this band was then subjected to molecular distillation at 190° (0.025 mm.) to give a viscous, blue liquid (remains blue in solvents) which solidified to 273 mg. (72%) of green, hairy needles, mp. 50-51°. IR ($CDCl_3$, CaF_2 cell): 2910, 2840, 1710 (C=O), 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.87 (t, 6H, 2 CH_3), 1.26 (s, 52H, 26 CH_2), 1.80 (broad signal, 4H, 2 OCH_2CH_2), 4.35 and 4.51 (2 t, J = 6-7 Hz, 4H, 2 OCH_2), 7.20 (t, J ≃

10 Hz, 1H, H-7), 7.58 (2 overlapping t, 2H, H-1 and H-3), 7.96 (t, J = 4 Hz, 1H, H-2), 8.3-8.5 (2 overlapping d, J = 9, 11 Hz, 2H, H-6 and H-8). MS m/e (relative intensity): 664 (M^+, 34), 200 (74), 199 ($M^+ - C_{32}H_{65}O$, 100), 198 (38).

Anal. Calcd for $C_{44}H_{72}O_4$: C, 79.46; H, 10.91. Found: C, 79.67; H, 11.22

6-Isothiocyanatomethylazulene (6d) from 6-Chloromethylazulene (6b).- A solution containing 307 mg. of a mixture of 6b (75 mol %) and 6-methylazulene (6a),[9] 271 mg. of potassium thiocyanate, 10 ml. of toluene, and 12 ml. of dimethyl sulfoxide was heated at 120° in an atmosphere of nitrogen gas for 19 hr. The cooled mixture was poured into water. An ether extract of this mixture was washed repeatedly with saturated, aqueous sodium chloride solution (to remove DMSO) and then with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed (silica gel/carbon tetrachloride) to give recovered 6a from the first band (purplish blue) and 83 mg. (30%) of 6d, obtained as blue needles from the second blue band, mp. 90-91°, not obtained analytically pure. IR($CHCl_3$, CaF_2 cell): 2190 and 2100 (-N=C=S),[13] 1585, 1400, 1335 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.84 (s, 2H, CH_2), 7.09 (d, J = 10 Hz, 2H, H-5 and H-7), 7.42 (d, J = 4 Hz, 2H, H-1 and H-3), 7.92 (t, 1H, H-2), 8.30 (split d, 2H, H-4 and H-8). MS m/e (relative intensity): 199 (M^+, 82), 141 ($AzCH_2^+$, 100), 115 (27).

Rearrangement of 6-Thiocyanatomethylazulene (6c).- A solution of 31.4 mg. of 6c[9] and 76.4 mg. of anhydrous zinc chloride in 10 ml. of toluene was refluxed in a nitrogen atmosphere for 30 hrs. The residue from evaporation of the solvent was chromatographed (silica gel/carbon tetrachloride) and 6d (11.4 mg., 36%) was collected from the first blue band. This product was identical with that obtained from 6-chloromethylazulene.

N-(6-Azulylmethyl)-N'-phenylthiourea (6e).- A solution of 83 mg. of 6d and 0.2 ml. (excess) of aniline in 5 ml. of benzene was stirred for 12 hr. The bright blue precipitate 6e was collected and rinsed with benzene, yield 41

mg. (34%), mp. 190-192° dec., sublimed at 140°/0.003 mm to give a blue solid. IR (KBr): 3320 (NH), 1535 (C=S) cm^{-1}. MS m/e (relative intensity): 292 (M^+, 4), 258 (27), 141 ($AzCH_2^+$, 100), 115 (28).

Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58; m/e, 292.103

Found: C, 73.89; H, 5.26; N, 9.17; m/e, 292.103

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