dine was added 1.72 g. (9.0 mmole) of *p*-toluenesulfonyl chloride; the resulting solution was allowed to stand at refrigerator temperature for 2 days and was then diluted with 100 ml. of ice water and extracted with three 50-ml. portions of ether. The ethereal solution was washed with ice cold water, 10% hydrochloric acid, 10% sodium carbonate, and water until neutral and then dried over anhydrous sodium sulfate. The solution was filtered and concentrated to a volume of 5 ml., diluted with 10 ml. of hexane, and cooled in an ice bath to give 1.65 g. (60%) colorless fluffy crystals, m.p. 85–86°; IR (mineral oil) 8.55 μ (—SO_3—); NMR ($CDCl_3$) δ 2.32 (s, 3H, arom. —CH_3).

(+)-*cis*-2-(*o*-Bromophenyl)-1-azidocyclohexane (IX)—A vigorously stirred slurry of 1.5 g. (23 mmole) of dry sodium azide and 0.95 g. (2.3 mmole) of VIII in 50 ml. of dry *N*-methylpyrrolidone under nitrogen was slowly heated in an oil bath (4 hr.) at 90° and maintained at that temperature for 20 hr. The reaction mixture was cooled, diluted with 250 ml. of water, and extracted with three 100-ml. portions of petroleum ether (b.p. 40–50°) followed by three 100-ml. portions of ether. The combined petroleum ether and ether solutions were washed with water and dried over anhydrous sodium sulfate. Filtration and evaporation of solvent using a 40° water bath afforded 0.63 g. (98%) of an oil, which was chromatographed on silica gel, eluting with petroleum ether. A small amount of colorless oil, containing no azide stretching band in the IR, eluted first, followed by pure IX as a clear oil, IR (neat) 4.72 μ (—N_3); $[\alpha]_D = +123°$ (c 4, chloroform).

(+)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine (X)—An ether solution of 0.33 g. of IX, which had not been chromatographed, was stirred with 0.15 g. of powdered lithium aluminum hydride for 2 hr., decomposed by the addition of a few drops of water, and filtered through a sintered-glass funnel. Evaporation of solvent yielded 0.27 g. (90%) of colorless oil, $[\alpha]_D = +95°$ (c 4, methanol); IR (neat) 2.98 and 3.05 μ (N—H).

(+)-*cis*-2-(*o*-Bromophenyl)cyclohexyl Formamide (XI)—A mixture of a solution of 0.25 g. of X in 10 ml. of toluene and 3 ml. of 99% formic acid was heated at gentle reflux for 1 hr. and then at a slightly higher temperature for 18 hr. so that water and formic acid azeotroped into a Dean-Stark tube. The reaction mixture was cooled, diluted with 25 ml. of ether, and washed twice with water, twice with 10% sodium carbonate, and with water until neutral; then it was dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded a yellow oil, which was crystallized from a benzene–hexane mixture to give 150 mg. of off-white crystals, m.p. 159–160°; $[\alpha]_D = +119°$ (c 2, methanol); IR (mineral oil) 3.07 μ (N—H), 5.97 and 6.08 μ (C=O).

The formamide prepared in the same manner from (+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, which was resolved as its (−)-menthoxyacetamide (6), had the following physical properties: m.p. 158–159°; $[\alpha]_D = +120°$ (c 3, methanol). The IR and NMR spectra of the two formamides were identical.

Anal.—Calcd. for $C_{13}H_{16}BrNO$: C, 55.33; H, 5.72; N, 4.96. Found: C, 55.20; H, 5.72; N. 5.15.

REFERENCES

(1) D. R. Galpin and A. C. Huitric, *J. Org. Chem.*, **33,** 921 (1968).

(2) D. R. Galpin and A. C. Huitric, *J. Pharm. Sci.*, **57,** 447 (1968).

(3) A. Camerman, L. H. Jensen, T. G. Cochran, and A. C. Huitric, *ibid.*, **59,** 1675(1970).

(4) H. Shechter and F. T. Williams, *J. Org. Chem.*, **27,** 3699 (1962).

(5) F. Freeman, A. Yeramyan, and F. Young, *ibid.*, **34,** 2438 (1969).

(6) T. G. Cochran and A. C. Huitric, to be published.

(7) M. Raban and K. Mislow, in "Topics in Stereochemistry," vol. 2, N. L. Allinger and E. L. Eliel, Eds., Interscience, New York, N. Y., 1967, chap. 4, p. 199.

(8) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28,** 2772 (1963).

(9) A. C. Huitric, W. G. Clark, K. Leigh, and D. C. Staiff, *ibid.*, **27,** 715(1962).

(10) H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, **1962,** 954.

(11) C. Djerassi, A. Moscowitz, K. Ponsold, and G. Steiner, *J. Amer. Chem. Soc.*, **89,** 347(1967).

(12) H. C. Brown and C. P. Garg, *ibid.*, **83,** 2952(1961).

(13) A. C. Huitric, unpublished data.

(14) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83,** 4013(1961).

(15) A. Camerman, L. H. Jensen, T. G. Cochran, and A. C. Huitric, to be published.

(16) A. W. Ingersoll, in "Organic Reactions," vol. II, R. Adams, W. E. Bachman, L. F. Fieser, J. R. Johnson, and H. R. Snyder, Eds., Wiley, New York, N. Y., 1944, chap. 9, p. 376.

ACKNOWLEDGMENTS AND ADDRESSES

Received July 17, 1970, from the *College of Pharmacy, University of Washington, Seattle, WA 98105*

Accepted for publication September 8, 1970.

This investigation was supported in part by Grant 5 R01 NS08329 from the National Institutes of Health, U. S. Public Health Service.

* AFPE Manufacturers Association Fellow, 1967–1968; NIH Predoctoral Fellow, 1968–1970.

Azulene Analogs of Pharmacologic Agents I: Amides

PETER H. DOUKAS* and TULLY J. SPEAKER

Abstract □ The paper describes the synthesis of 15 azulene analogs of the benzenoid pharmacologic agent procainamide as part of a study of the pharmacodynamic effects of nonbenzenoid aromatic compounds. Three distinct series of compounds were prepared: azulene-1-carboxamides, 1-(3-nitroazulene)-carboxamides, and 1-(3-acetamidoazulene)-carboxamides. The preparation of 3-nitroazuloic acid, a new azulene intermediate, is also described.

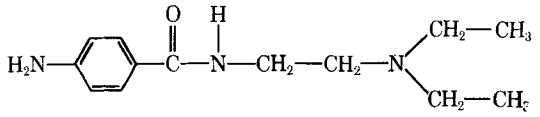
Keyphrases □ Procainamide azulene analogs—synthesis □ Azulene analogs, procainamide—synthesis □ Column chromatography—separation □ IR spectrophotometry—structure □ UV spectrophotometry—structure

It is recognized that the presence of aromatic moieties in pharmacodynamic entities of varying specific activity may be prerequisite for optimal activity. These aromatic functions are, for the most part, benzenoid in nature. Several cyclic systems exist which show aromaticity but which are not benzenoid in character (1). Among these, azulene (isomeric to naphthalene), by virtue of its totally hydrocarbon nature, closely resembles benzene and its derivatives but differs in that it has a dipole moment, is a nonalternant hydrocarbon, has a resonance energy

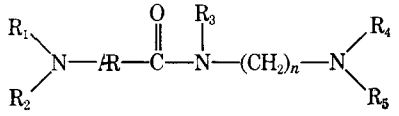
intermediate between that of benzene and naphthalene, and is considerably more reactive (2). The authors anticipate that these differences might alter the association of a pharmacophore with the biophase. Replacing the benzene moiety with the azulyl structure in pharmacodynamic systems requiring aromaticity in their pharmacophore affords the opportunity to study what effects this nonphysiologic, nonbenzenoid aromatic system might have upon the activity of a pharmacologically active molecule.

As a part of a continuing study (3) of the effects of nonbenzenoid aromatic systems on the activity of pharmacodynamic agents, a series of azulene analogs of procainamide (I), a known local anesthetic and antifibrillatory agent, was prepared. The synthesis of these materials is reported in this paper. Their biological evaluation is in process and will be reported in the near future.

Structure I may be reduced to the general formula II,



I

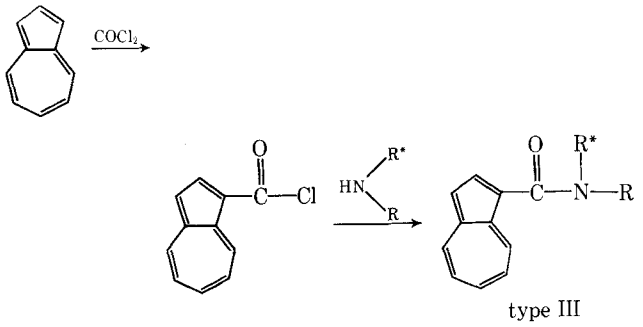


II

where AR indicates the presence of an aromatic group. In this series of 1,3-disubstituted azulenes (III, V, and VI), the structures and physical properties of which are given in Table I, the azulene nucleus would satisfy the aromatic prerequisite, R_2 would be a function altering the electronic distribution of the already polar azulene nucleus, and R_1 would be a substituted aminoalkyl side chain. Alteration of the electronic character of the aromatic system would be expected to impart different electrostatic properties to the variously substituted compounds and perhaps thereby alter affinity and/or intrinsic activity. Although resonance interactions may not occur between the electron-rich 1- and 3-positions of azulene, as they occur in *para*-substituted benzenoid pharmacologic agents, the inductive interactions are quite strong, and substitution at either position markedly affects the electron density of the other.

Type III compounds (azulene-1-carboxamides) were prepared *via* carboxychlorination of azulene, after the method of Treibs *et al.* (4), followed by reaction of the azulene acid chloride with the appropriate amine (Scheme I).

3-Nitroazuloic acid (IV), which would easily serve as a common intermediate in the synthesis of compounds of Types V and VI, has not been previously reported in the literature. The preparation of its methyl ester, *via* cupric nitrate nitration in low yield and a nonreproducible tetranitromethane nitration in good yield, was reported by Anderson *et al.* (5). A method requiring critical attention to reaction conditions was developed in this laboratory for the synthesis of 3-nitroazuloic acid in satisfactory yields (about 45–65%). The synthesis



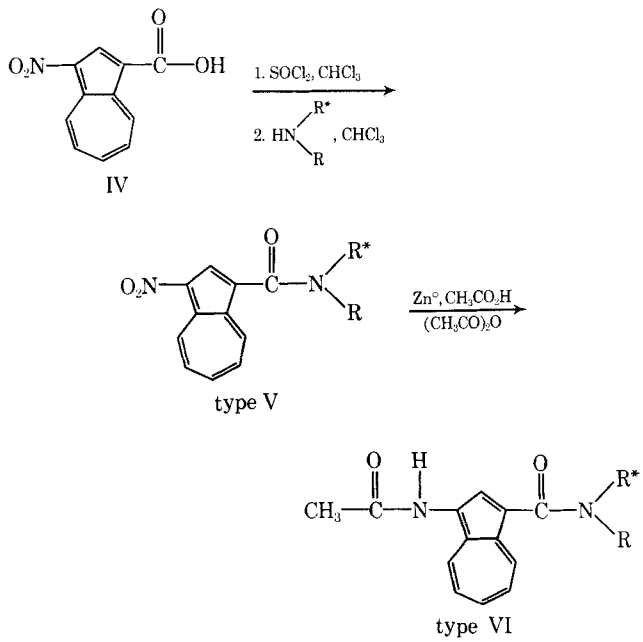
type III

R* may be H or R

Scheme I

requires a very slow addition of tetranitromethane in ethanol to a solution of azuloic acid in freshly distilled pyridine. The purity of the pyridine and the addition rate are essential, since alteration of either condition results in drastic reduction of yield and the production of intractable tars. The product displays a visible absorption maximum hypsochromic shift of 40–50 nm. from that of azuloic acid. It has been shown that a shift of this type occurs when a known azulene is substituted in the 3-position with a nitro group (5). Further structural proof was obtained by conversion of the acid to two known derivatives, methyl-3-nitroazuloate and methyl-3-acetamidoazuloate, for which physical data were reported previously. The preparation of 3-nitroazuloic acid affords an intermediate that will facilitate the synthesis of several 1,3-disubstituted azulyl systems, heretofore unattainable or attainable only through extended syntheses with poor yields.

Reacting the 3-nitro acid chloride with appropriate amines gave 3-nitroazulene-1-carboxamides (Type V compounds), as shown in Scheme II.



IV

type V

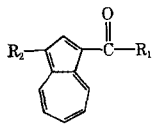
type VI

R* may be H or R

Scheme II

The 3-nitro group provided a strong electron-withdrawing substituent; in the interest of including a

Table I—Azulene Carboxamides



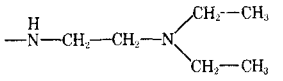
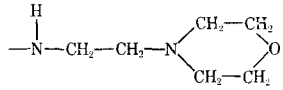
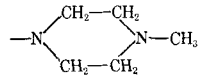
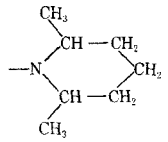
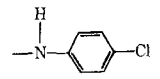
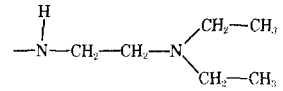
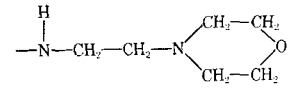
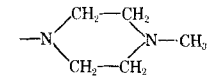
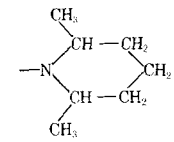
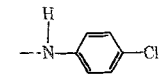
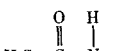
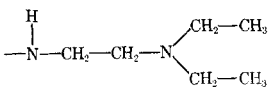
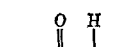
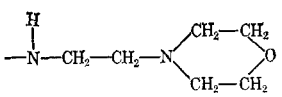
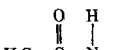
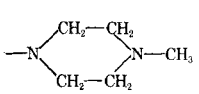
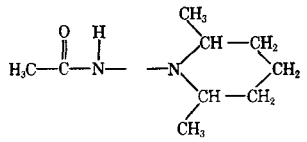
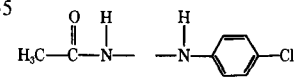
No.	R_2	R_1	M.p.	Formula	Anal., % Calcd.	Anal., % Found	Spectral Data IR Max., $cm.^{-1}$	Spectral Data UV-Vis. Max., nm.	Spectral Data Log ϵ
III-1	H—		Oil	$C_{17}H_{22}N_2O$	C, 75.47 H, 8.20 N, 10.36	C, 75.23 H, 7.97 N, 10.17	3240 1651	545 370 353 290 232	2.48 3.78 3.70 4.63 4.40 sh
III-2	H—		112–114°	$C_{17}H_{20}N_2O_2$	C, 71.80 H, 7.09 N, 9.85	C, 71.69 H, 7.13 N, 9.85	3250 1625	550 365 350 290 230	2.60 3.89 3.74 4.66 4.46 sh
III-3	H—		94.5–95.5°	$C_{16}H_{18}N_2O$	C, 75.56 H, 7.13 N, 11.02	C, 75.30 H, 7.17 N, 11.10	1610	560 360 342 285 230	2.54 3.61 3.65 4.61 4.39
III-4	H—		96°	$C_{17}H_{21}NO$	C, 79.95 H, 8.29 N, 5.48	C, 80.17 H, 8.01 N, 5.21	1615	570 355 340 286 282 230	2.34 3.29 3.45 3.40 sh 4.42 4.18
III-5	H—		182–183.5°	$C_{17}H_{12}ClNO$	C, 72.47 H, 4.29 N, 5.68	C, 72.35 H, 4.05 N, 5.54	3200 1625	543 365 300 260 235	2.67 4.17 4.67 4.21 4.35
V-1	O_2N—		99–100°	$C_{17}H_{21}N_3O_3$	C, 64.74 H, 6.71 N, 13.32	C, 64.57 H, 6.90 N, 13.11	3250 1640	495 382 310 285 235	3.01 4.03 4.18 sh 4.35 4.27
V-2	O_2N—		210–212°	$C_{17}H_{19}N_3O_4$	C, 61.99 H, 5.81 N, 12.76	C, 62.25 H, 5.69 N, 12.40	3250 1640	490 387 305 285 230	3.07 4.14 4.34 4.48 4.38
V-3	O_2N—		197–198°	$C_{16}H_{17}N_3O_0$	C, 64.20 H, 5.73 N, 14.04	C, 64.15 H, 5.94 N, 13.99	1610	502 395 308 280 235 220	2.95 3.04 3.23 3.34 3.28 sh 3.36
V-4	O_2N—		156–158°	$C_{18}H_{22}N_2O_3$	C, 69.21 H, 6.45 N, 8.97	C, 69.21 H, 6.56 N, 8.81	1635	510 398 310 278 220	2.92 4.01 4.20 4.30 4.35
V-5	O_2N—		>270°	$C_{17}H_{11}ClN_2O_3$	C, 62.49 H, 3.39 N, 8.57	C, 62.47 H, 3.57 N, 8.28	1650	390 295 240	0.55[a] 1.48 0.82
VI-1			125–128°	$C_{19}H_{25}N_3O_2$	C, 69.69 H, 7.70 N, 12.83	C, 69.40 H, 7.45 N, 12.72	3215 1640	598 375 298 238	2.60 3.76 4.57 4.39
VI-2			186–187°	$C_{19}H_{23}N_3O_3$	C, 66.84 H, 6.79 N, 12.31	C, 66.56 H, 6.86 N, 12.02	3200 1650	600 380 300 240	2.43 3.65 4.54 4.42
VI-3			157–159°	$C_{18}H_{21}N_3O_2$	C, 69.43 H, 6.80 N, 13.49	C, 69.30 H, 6.67 N, 13.27	3200 1650	615 378 295 235	2.53 3.71 4.54 4.34

Table I—*(Continued)*

No.	R_2	R_1	M.p.	Formula	Anal., % Calcd.	Anal., % Found	Spectral Data: IR Max., $cm.^{-1}$	Spectral Data: UV–Vis. Max., nm.	Spectral Data: Log ϵ
VI-4			144–145°	$C_{20}H_{24}N_2O_2$	C, 72.04 H, 7.56 N, 8.40	C, 71.99 H, 7.47 N, 8.40	3250 1675	620 383 370 295 236	2.56 3.76 3.74 sh 4.62 4.38
VI-5			144–146° dec.	$C_{19}H_{15}ClN_2O_2 \cdot H_2O$	C, 63.96 H, 4.80 N, 7.85	C, 64.28 H, 4.98 N, 7.82	3245 1650	590 373 305 240	2.50 3.80 4.07 4.00

[a] $OD_{max.}$

strong electron-donating group so as to encompass as wide a range of electronic effects as possible, the preparation of 3-amino-1-azulene carboxamides was investigated. The reduction of the 3-nitro compounds seemed to be a facile route to the production of the desired 3-amino compounds. In attempting to prepare these compounds, it was found that both the free amines and several of their acid salts were very unstable and decomposed readily. This property of azulyl amines was reported previously (6), but the extreme degree of instability was unexpected. In effect, the 3-amino compounds, although perhaps often prepared, could not be isolated in this study.

By contrast, the acetamidoazulenes are known to be stable systems and, recognizing that the acetamido function exerts a mild positive inductive effect, it was decided that this group might well be substituted for the apparently unavailable 3-amino function.

The 3-acetamidoazulene-1-carboxamides (Type VI compounds) were prepared from the 3-nitro carboxamides *via* a dissolving metal reduction utilizing zinc in acetic acid in the presence of acetic anhydride (Scheme II).

EXPERIMENTAL[1]

Materials and Instrumentation—All melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. UV and visible absorption spectra were obtained with a Cary model 15 recording spectrophotometer utilizing ethanol as the solvent. IR spectra were obtained with a Perkin-Elmer Infracord model 127 recording spectrophotometer utilizing potassium bromide disks unless otherwise indicated. Azulene,[2] phosgene,[3] tetranitromethane,[4] and ethanol[5] were used. Other solvents and other reagents were of reagent grade.[6] When necessary, solvents were freshly distilled prior to use.

General Chromatographic Procedure—Chromatographic separations employed Merck Reagent Aluminum Oxide (Alumina) No. 71707 in the following procedure: concentrated solutions containing starting materials, reaction products, and decomposition products were adsorbed on a small amount of alumina (5–15 g.). The alumina adsorbate was air dried with frequent stirring. The resulting free-flowing adsorbate was packed above a 2 × 10, 4 × 20, or 4 × 40-cm. column of fresh alumina and eluted with solvents of increasing polarity. The following solvents proved useful: petroleum ether, benzene, toluene, dichloromethane, chloroform, ethanol, and combinations of these.

General Method for the Preparation of Azulene-1-carboxamides (Type III Compounds)—A slow stream of gaseous phosgene was added with stirring to a solution of 0.500 g. (0.004 mole) of azulene in 70 ml. of freshly distilled toluene contained in a 300-ml. three-necked flask equipped with a gas inlet tube and gas trap. After an addition time of 30–40 min., during which the color of the mixture changed from blue to wine-red, the gas supply was removed, and the mixture was allowed to stir for another 40 min. At the end of this interval, the reaction mixture was flushed of phosgene. This was conveniently done at this scale by placing the reaction mixture in a 100-ml. sintered-glass funnel secured atop a filter flask into which gaseous nitrogen was being introduced (at a very low pressure) *via* the side arm. The nitrogen escaped through the sinter into the toluene in the form of numerous small bubbles. The system was flushed in this way with nitrogen for 3–4 hr. to remove excess HCl and phosgene. At the end of this interval the nitrogen flow was stopped, 0.02 mole of the appropriate amine in 10 ml. of dry toluene was placed at the bottom of the filter flask, and the acid chloride solution was added *via* suction through the sintered-glass funnel. Upon contact with the amine solution, the wine-red color of the acid chloride solution turned to dark blue with the liberation of HCl. After complete addition, the reaction mixture was stirred for 10 min., filtered to remove insoluble amine hydrochloride, and then worked up to give the azulene-1-carboxamides. The purification of the individual azulene-1-carboxamides is reported later. Unless otherwise indicated, the reaction mixture was extracted with dilute hydrochloric acid, and the aqueous phase was chilled in an ice bath and made alkaline with dilute aqueous ammonia. The aqueous phase was extracted with chloroform, and the resultant blue organic layer was dried over sodium sulfate, filtered, concentrated, and chromatographed on alumina. Typical yields ranged from 75–90%.

1-(2-Diethylaminoethyl)-azulenecarboxamide (III-1)—This material was prepared and isolated according to the general procedure for the preparation of azulene-1-carboxamides. Chloroform eluted a single blue band. Evaporation of the chloroform yielded a blue oil which could not be induced to crystallize. IR: 3240, 1650 $cm.^{-1}$; $\lambda_{max.}$ (log ϵ): 545(2.48), 370(3.79), 353(3.70), 290(4.63), 232(4.40 sh).

Anal.—Calcd. for $C_{17}H_{22}N_2O$: C, 75.47; H, 8.20; N, 10.36. Found: C, 75.23; H, 7.97; N, 10.17.

1-(2-Morpholinoethyl)-azulenecarboxamide (III-2)—This material was prepared and isolated according to the general procedure for the preparation of azulene-1-carboxamides. Chloroform eluted a single blue band. Partial evaporation of the chloroform at room temperature gave successive crops of blue crystals which were collected, washed with petroleum ether, and air dried, m.p. 112–114°. IR: 3250, 1625 $cm.^{-1}$; $\lambda_{max.}$ (log ϵ): 550(2.60), 365(3.89), 350 (3.74), 290(4.66), 230(4.46 sh).

Anal.—Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.69, H, 7.13; N, 9.85.

1-(*N*-Methylpiperazine)-azulenecarboxamide (III-3)—This material was prepared and chromatographically isolated according to the general procedures already described. The chloroform eluate

[1] Analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.
[2] Purchased from Henley & Co., Inc., New York, N. Y.
[3] Purchased from the Union Carbide Corp., Linde Div.
[4] Purchased from Aldrich Chemical Company as were all the amines utilized in the syntheses.
[5] Publiker Industries.
[6] B. A. Baker & Co. or Fisher Scientific Co.

was allowed to evaporate at room temperature to yield a blue oil. The oil was triturated with petroleum ether in a dry ice–acetone bath to yield a dark-blue solid, which was collected, air dried, and redissolved in chloroform. Slow evaporation of the chloroform gave dark-blue crystals, m.p. 94.5–95.5°. IR: 1610 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 560(2.54), 360(3.61), 342(3.65), 285(4.61), 230(4.39).

Anal.—Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13, N, 11.02. Found: C, 75.30; H, 7.17; N, 11.10.

1-(2,6-Dimethylpiperidine)-azulenecarboxamide (III-4)—This material was prepared according to the general procedure for the preparation of azulene-1-carboxamides. The reaction mixture was washed with 5% hydrochloric acid and dilute aqueous ammonia. The toluene layer was then dried over sodium sulfate, filtered, concentrated, and chromatographed on alumina. Petroleum ether eluted unreacted azulene and left a large blue band. The blue band was immobile in the usual solvents, so it was extruded and extracted in a continuous extraction apparatus with a mixture of equal parts of chloroform and carbon tetrachloride for 10 hr. The solvent was evaporated at room temperature to yield a blue solid which, upon recrystallization from hot aqueous ethanol, gave blue crystals, m.p. 96°. IR: 1615 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 570(2.34), 355(3.29), 340(3.45), 286 (3.40 sh), 282 (4.42), 230(4.18).

Anal.—Calcd. for $C_{17}H_{21}NO$: C, 79.95; H, 8.29; N, 5.48. Found: C, 80.17; H, 8.01; N, 5.21.

1-(*p*-Chloroaniline)-azulenecarboxamide (III-5)—This material was prepared according to the general procedure for the preparation of azulene-1-carboxamides. During this reaction, most of the product precipitated out of the reaction mixture. The resultant blue solid was taken up in chloroform, and the organic layer was washed with 5% hydrochloric acid and dilute aqueous ammonia; it was dried over sodium sulfate and allowed to evaporate at room temperature to give dark-blue crystals, m.p. 182–183.5°. IR: 3200, 1625 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 543(2.67), 365(4.17), 300(4.67), 260(4.21), 235(4.35).

Anal.—Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 5.68. Found: C, 72.35; H, 4.05; N, 5.54.

Preparation of Azuloic Acid—This material was prepared according to the method of Treibs *et al.* (4).

Preparation of 3-Nitroazuloic Acid (IV)—At room temperature a solution of 1.345 ml. (0.0112 mole, 40% molar excess) tetranitromethane in 3 ml. anhydrous ethanol was added dropwise to a solution of 1.360 g. (0.0079 mole) azuloic acid in 15 ml. of recently distilled pyridine contained in a 100-ml. three-necked flask equipped with dropping funnel, mechanical stirrer, and drying tube. Addition time was 2.5 hr. The reaction mixture was stirred for 16 hr., during which the color of the mixture changed from blue to reddish-brown, and then was filtered in a sintered-glass funnel. The yield of orange solid was repeatedly washed with petroleum ether until the washings showed no bluish color, indicative of unreacted azuloic acid. The solid was then washed with anhydrous ether, which removed all but the last traces of pyridine, and was allowed to air dry. The yield of crude 3-nitroazuloic acid was 1.10 g. (65.0% yield). When recrystallized from hot ethanol and water, the crude product gave orange needles, m.p. >270°. IR: 1690 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 483(2.87), 328(3.90), 312(4.17), 285(4.36), 215 (4.36).

Anal.—Calcd. for $C_{11}H_7NO_4 \cdot H_2O$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.65; H, 3.45; N, 6.22.

Preparation of Methyl Ester of 3-Nitroazuloic Acid—The acid chloride of 3-nitroazuloic acid was prepared according to the *in situ* method described later and used without further purification. The acid chloride was dissolved in 30 ml. of chloroform and then stirred at room temperature with an excess of methanol. The solvent mixture was allowed to evaporate at room temperature overnight to yield 0.320 g. of red crystals, m.p. 144–146° [lit. (5) 146°].

Preparation of Methyl Ester of 3-Acetamidoazuloic Acid—Powdered zinc, 0.500 g. (0.0077 g. atom), was added in divided portions over a 0.5-hr. interval to a solution of methyl-3-nitroazuloate, 0.150 g. (6.4 mmoles), and sodium acetate, 1.00 g. (0.012 mole), in a mixture of 2 ml. acetic acid and 15 ml. acetic anhydride. The reaction mixture was stirred for 0.5 hr. after complete addition of the zinc, during which the color of the solution changed from red to blue. The mixture was decanted from any unreacted zinc, diluted with 50 ml. of ice water, and extracted with chloroform. The blue chloroformic extract was dried over sodium sulfate, filtered, concentrated, and chromatographed on alumina. Benzene eluted a yellow band and chloroform eluted a brown band, closely followed by a blue band. The blue eluate was evaporated at room temperature to yield 0.105 g. of blue needles, m.p. 204–206° [lit. (5) 206°].

General Method for the Preparation of 1-(3-Nitroazulene)-carboxamides (Type V Compounds)—In Situ *Preparation of 3-Nitroazuloic Acid Chloride*—A solution of 0.960 g. (0.0081 mole) of thionyl chloride in 10 ml. of recently distilled chloroform was added dropwise to a refluxing suspension of 0.600 g. (0.0027 mole) 3-nitroazuloic acid in 100 ml. of recently distilled chloroform in a 250-ml. three-necked flask equipped with a heating mantle, dropping funnel, reflux condenser, and mechanical stirrer. Addition time was 30 min., after which the mixture was refluxed with stirring for 2.5 hr. During this interval, most of the solids dissolved. The mixture was filtered hot, and the filtrate was evaporated to dryness under reduced pressure and with the aid of gentle heat (50°) to yield a reddish-orange solid. This solid was suitable for use without additional purification.

Conversion of Acid Chloride to Amide—The solid acid chloride was dissolved in 100 ml. of recently distilled chloroform. A 3–5 molar excess of the appropriate amine in 10 ml. of chloroform was added dropwise to the resultant solution, over a period of 15 min., at room temperature. The mixture was stirred for an additional 30 min. at room temperature and then was successively washed with dilute aqueous ammonia and water. The chloroformic solution, after drying over sodium sulfate, was filtered and concentrated *in vacuo* to about one-tenth volume. The concentrate was then adsorbed onto alumina and chromatographed. The elution and crystallization procedures for the individual 1-(3-nitroazulene)-carboxamides are given later. The typical yields were 75–80%.

1-(2-Diethylaminoethyl)-3-nitroazulenecarboxamide (V-1)—This compound was prepared by the general method of preparation of 1-(3-nitroazulene)-carboxamides described above and chromatographed on alumina. Elution with petroleum ether separated a minor orange band. Dichloromethane–petroleum ether (50:50) eluted a minor orange band and a closely following greenish-brown band. Dichloromethane slowly eluted a large red band, leaving several bands yet uneluted. The dichloromethane eluate was allowed to evaporate spontaneously to yield a red oil. The red oil was dissolved in a chloroform–*n*-heptane mixture (50:50) which, on slow partial evaporation at room temperature, gave red needles, m.p. 99–100°. IR: 3250, 1640 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 495(3.01), 382(4.03), 310(4.18 sh), 285(4.35), 235(4.27).

Anal.—Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.57; H, 6.90; N, 13.11.

1-(2-Morpholinoethyl)-3-nitroazulenecarboxamide (V-2)—This compound was prepared by the general method described for 1-(3-nitroazulene)-carboxamides and was chromatographed on alumina. Elution with toluene gave a minor yellow band, and dichloromethane–chloroform (50:50) separated a large orange band from a faintly yellow band. The orange band was extruded, packed atop a fresh alumina column, and eluted with chloroform. The chloroform eluate was diluted with an equal amount of *n*-heptane, and the mixture was allowed to evaporate spontaneously to yield reddish-orange crystals, m.p. 210–212°. IR: 3250, 1640 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 490(3.07), 387(4.14), 305(4.34), 285(4.48), 230(4.38).

Anal.—Calcd. for $C_{17}H_{19}N_3O_4$: C, 61.99; H, 5.81; N, 12.76. Found: C, 62.25; H, 5.69; N, 12.40.

1-(N-Methylpiperazine)-3-nitroazulenecarboxamide (V-3)—This compound was prepared by the general method described for 1-(3-nitroazulene)-carboxamides and was chromatographed on alumina. Elution with toluene produced a faintly yellowish-orange band. Chloroform slowly eluted a major reddish-orange band, leaving a weak yellow band. The chloroform eluate was allowed to evaporate spontaneously to yield a red solid which was recrystallized from chloroform–*n*-heptane (50:50) to give reddish-maroon crystals, m.p. 197–198°. IR: 1610 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 502(2.95), 395(3.04), 308(3.23), 280(3.34), 235 (3.28 sh), 220(3.36).

Anal.—Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.73; N, 14.04. Found: C, 64.15; H, 5.94; N, 13.99.

1-(2,6-Dimethylpiperidine)-3-nitroazulenecarboxamide (V-4)—This compound was prepared by the general method described for 1-(3-nitroazulene)-carboxamides and was chromatographed on alumina. Dichloromethane eluted first a minor orange band and then a closely following major red band. Because these bands were difficultly resolved, this separation required a long column. The red eluate was collected and allowed to evaporate spontaneously, yielding a red glass. The glass was taken up in the minimum amount of chloroform, and the resultant solution was diluted with an equal

amount of *n*-heptane. Slow evaporation yielded reddish-maroon crystals, m.p. 156–158°. IR: 1635 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 510(2.92), 398(4.01), 310(4.20), 278(4.30), 220(4.35).

Anal.—Calcd. for $C_{18}H_{22}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.21; H, 6.56; N, 8.81.

1-(p-Chloroaniline)-3-nitroazulenecarboxamide (V-5)—This material separated out of the reaction mixture and was collected by filtration. It was found to be poorly soluble in most solvents. To purify the compound, 50-mg. aliquots were dissolved in 100 ml. of boiling anhydrous ethanol. The resultant solution was allowed to cool to room temperature to give red needles, which were collected by filtration and washed with cold ethanol, m.p. >270°. IR: 1650 cm.$^{-1}$; $\lambda_{max.}$ ($OD_{max.}$):[7] 390(0.55), 295(1.48), 240(0.82).

Anal.—Calcd. for $C_{17}H_{11}ClN_2O_3$: C, 62.49; H, 3.39; N, 8.57. Found: C, 62.47; H, 3.57; N, 8.28.

General Method for the Preparation of 1-(3-Acetamidoazulene)-carboxamides (Type VI Compounds)—Over an interval of 1 hr., 0.600 g. (0.0090 g. atom) of powdered zinc was gradually added to a stirred solution of 0.001 mole of the appropriate 1-(3-nitroazulene)-carboxamide and 0.600 g. (0.0074 mole) of sodium acetate in 30 ml. of a mixture of equal volumes of acetic acid and acetic anhydride. During the addition, the color of the solution gradually turned from red to blue. After complete addition, the mixture was stirred an additional 0.5 hr. and then decanted from any unreacted zinc into 100 ml. of ice water. The resulting aqueous solution was slowly made alkaline with 10% sodium hydroxide solution in an ice water bath and extracted with chloroform. The greenish-blue chloroform extracts were dried over sodium sulfate, filtered and concentrated. The purification procedures for the individual materials follow. Typical yields were 60–70%.

1-(2-Diethylaminoethyl)-3-acetamidoazulenecarboxamide (VI-1)—This material was prepared according to the general procedure for 1-(3-acetamidoazulene)-carboxamides and was chromatographed on alumina. Benzene eluted yellow and blue bands. A mixture of ethanol and toluene (5:95) eluted the product. Evaporation of the ethanol–toluene eluate gave a bluish-green solid, m.p. 125–128°. IR: 3215, 1640 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 598(2.60), 375(3.76), 298(4.57), 238(4.39).

Anal.—Calcd. for $C_{19}H_{25}N_3O_2$: C, 69.69; H, 7.70; N, 12.83. Found: C, 69.40; H, 7.45; N, 12.72.

1-(2-Morpholinoethyl)-3-acetamidoazulenecarboxamide (VI-2)—This material was prepared according to the general procedure for 1-(3-acetamidoazulene)-carboxamides and was chromatographed on alumina. Dichloromethane eluted a light-orange band. Ethanol–toluene (10:90) eluted a brown band closely followed by a greenish-blue band. The greenish-blue eluate was allowed to stand at room temperature, and partial evaporation gave green crystals, m.p. 186–187°. IR: 3200, 1650 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 600(2.43); 380(3.65), 300(4.54), 240(4.42).

Anal.—Calcd. for $C_{19}H_{23}N_3O_3$; C, 66.84; H, 6.79; N, 12.31. Found: C, 66.56; H, 6.86; N, 12.02.

1-(N-Methylpiperazine)-3-acetamidoazulenecarboxamide (VI-3)—This material was prepared according to the general procedure for 1-(3-acetamidoazulene)-carboxamides and was chromatographed on alumina. Dichloromethane eluted a small green band. A mixture of ethanol and toluene (10:90) eluted a greenish-blue band which, upon evaporation, gave a green solid (m.p. 154–156°) that could not be satisfactorily recrystallized. The crude solid was taken up in the minimum amount of chloroform and chromatographed on alumina. A mixture of ethanol and toluene (15:85) eluted the product and yielded greenish-blue needles upon slow evaporation, m.p. 157–159°. IR: 3200, 1650 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 615(2.53), 378(3.71), 295(4.54), 235(4.34).

Anal.—Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.30; H, 6.67; N, 13.27.

1-(2,6-Dimethylpiperidine)-3-acetamidoazulenecarboxamide (VI-4)—This material was prepared according to the general procedure for 1-(3-acetamidoazulene)-carboxamides and chromatographed on alumina. Toluene eluted yellow and red bands. A mixture of ethanol and toluene (10:90) eluted the product. Slow evaporation of the ethanol–toluene eluate yielded a blue solid which was recrystallized from hot aqueous ethanol, m.p. 144–146°. IR: 3250, 1675 cm.$^{-1}$: $\lambda_{max.}$(log ϵ): 620(2.56), 383(3.76), 370(3.74 sh), 295(4.62), 236(4.38).

Anal.—Calcd. for $C_{20}H_{24}N_2O_2$: C, 72.04; H, 7.56; N, 8.40. Found: C, 71.99; H, 7.47; N, 8.40.

1-(p-Chloroaniline)-3-acetamidoazulenecarboxamide (VI-5)—This material was prepared according to the general procedure for 1-(3-acetamido)-azulenecarboxamides and chromatographed on alumina. The nitroamide was initially insoluble in the reduction mixture, but as the zinc was added (and reduction began to take place) the material gradually dissolved. Petroleum ether eluted a yellow band, and toluene–chloroform (50:50) eluted a brown band. Chloroform slowly eluted the product. Evaporation of the chloroform yielded a crude solid which was recrystallized from hot aqueous ethanol to give yellowish-green crystals, m.p. 144–146° dec. IR: 3245, 1650 cm.$^{-1}$; $\lambda_{max.}$ (log ϵ): 590(2.50), 373(3.80), 305(4.07). 240(4.00).

Anal.—Calcd. for $C_{19}H_{15}ClN_2O_2 \cdot 1H_2O$: C, 63.96; H, 4.80; N, 7.85. Found: C, 64.28; H, 4.98; N, 7.82.

[7] A sufficient quantity of this material to give log ϵ data could not be dissolved; therefore, optical density values ($OD_{max.}$) are given.

REFERENCES

(1) "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959.

(2) E. Heilbronner, in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959, pp. 171–276, and references cited therein.

(3) T. J. Speaker and G. D. Redman, *J. Pharm. Sci.*, **55,** 479 (1966).

(4) W. Treibs, H. J. Neupert, and J. Heibsch, *Chem. Ber.*, **92,** 1216(1959).

(5) A. G. Anderson, Jr., R. Scotoni, Jr., E. J. Cowles, and C. G. Fritz, *J. Org. Chem.*, **22,** 1193(1957).

(6) J. Schulze and F. Heilbronner, *Helv. Chim. Acta*, **41,** 1492 (1958).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 29, 1970, from the *School of Pharmacy, Temple University, Philadelphia, PA 19140*

Accepted for publication August 27, 1970.

Abstracted from a thesis submitted by P. H. Doukas to the School of Pharmacy, Temple University, in partial fulfillment of Doctor of Philosophy degree requirements.

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