Azulene Analogs of Pharmacologic Agents II: Amides

PETER H. DOUKAS* and TULLY J. SPEAKER

Abstract □ The paper describes the synthesis of nine azulene analogs of the benzenoid pharmacologic agent lidocaine, as part of a study of the pharmacodynamic effects of nonbenzenoid aromatic compounds. Two series of compounds were prepared: 1-azulyl amides and 1-amido-3-acetyl azulenes.

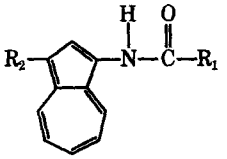
Keyphrases □ 1-Azulyl amides (lidocaine analogs)—synthesis □ 1-Amido-3-acetyl azulenes (lidocaine analogs)—synthesis □ Lidocaine analogs—synthesis, 1-azulyl amides, 1-amido-3-acetyl azulenes □ Column chromatography—separation

To study further (1) the pharmacological effects of replacing a benzenoid moiety by a nonbenzenoid, nonphysiologic azulyl structure, several azulyl amides (Types I and II) related to lidocaine (III) were synthesized as shown in Scheme I.

The 1-azulyl amides (Type I compounds) were prepared from 1-nitroazulene by reduction to 1-aminoazulene which, upon extraction from the reduction medium, was immediately reacted with the appropriate Ω-halo acid chloride in a Schotten–Baumann-type (2) synthesis to yield Ω-haloazulyl amides. It was essential that the aminoazulene be reacted immediately upon extraction, since even when kept cold, it underwent substantial decomposition. Once purified, the Ω-haloazulyl amides were reacted with the appropriate amines to yield the desired amino amides.

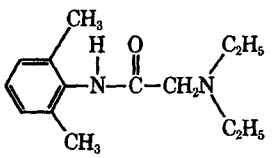
To introduce an electron-withdrawing substituent in the 3-position, various attempts to nitrate the azulyl amides were undertaken, all of which produced large amounts of amorphous decomposition products. Similar results were reported (3) for the nitration of the analogous *S*-acetyl thioazulene. It was subsequently decided to utilize the acetyl function in the 3-position as an electron-withdrawing function.

Attempts to prepare 1-amido-3-acetyl azulenes (Type II compounds) utilizing Friedel–Crafts conditions gave very poor yields of the desired intermediates due to difficulty in breaking the complex formed between the azulene and the Friedel–Crafts catalyst. The use of the Vilsmeier reaction was reported for the preparation of several azulyl ketones (4), and this approach gave satisfactory yields (about 40–50%) of appropriate intermediates. These amidoketones were very difficult to purify and required repeated chromatographic separation and recrystallization. Analytical data and NMR spectra indicated that the Vilsmeier product obtained

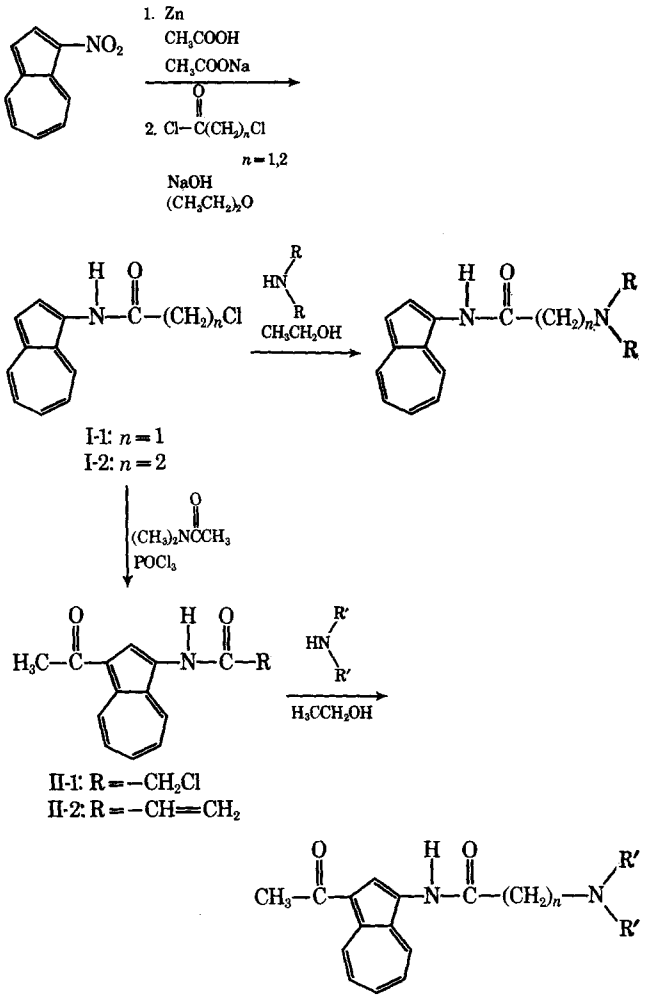


Type I: $R_2 = H$

Type II: $R_2 = CH_3C(=O)-$



III



Scheme I

from 1-(3-chloropropionamido)-azulene (I-2) had lost HCl to give 1-propenamido-3-acetylazulene (II-2).

The 1-propenamido-3-acetyl azulene was utilized in a Michael addition reaction to give the desired product. Acetylation of chloracetamido azulene (I-1) gave the expected 1-chloracetamido-3-acetylazulene (II-1). The biological properties of these compounds will be reported shortly.

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. NMR spectra were obtained with Varian A-60 and Jeolco C-60H spectrometers, utilizing tetramethylsilane as the internal standard. The azulene used in this study was purchased[2],

[1] Analyses were performed by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

[2] Henley and Co., Inc., New York, N. Y.

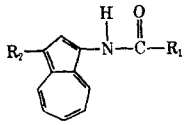


Table I—Azulylamides

Number	R_2=	R_1 =	M.p.	Formula	Percent Calcd.	Percent Found	Spectral Data: $IR_{max.}$ cm.$^{-1}$	Spectral Data: $UV_{max.}$/ Vis., nm.	Spectral Data: log e	Percent Yield	Recrystallization Solvent
I-1	H—	$-CH_2-Cl$	132.5–133.5°	$C_{12}H_{10}NOCl$	C, 65.58 H, 4.59 N, 6.37	C, 65.42 H, 4.60 N, 6.01	3200 1650	620 378 352 345 285 235	2.41 3.64 3.59 3.44sh 4.39 4.00	63.0	Chloroform–hexane
I-2	H—	$-CH_2-CH_2-Cl$[a]	112–113°	$C_{13}H_{12}NOCl$[a]	C, 66.81 H, 5.18 N, 5.99	C, 66.58 H, 4.80 N, 5.42	3200 1645	620 377 360 345 285 235	2.46 3.57 3.53 3.43sh 4.59 4.23	61.0	Chloroform–hexane
I-3	H—	$-CH_2-N(CH_2-CH_3)_2$	99[b]–100°	$C_{22}H_{23}N_5O_7$[b]	C, 56.28[b] H, 4.94 N, 14.92	C, 56.22[b] H, 4.98 N, 14.74	3200 1650	625 382 355 348 295 285	2.53 3.73 3.55 3.50sh 4.32sh 4.45	42.7	Ethanol
I-4	H—	$-CH_2-CH_2-N(CH_2-CH_3)_2 \cdot HCl$	187–189°	$C_{17}H_{22}N_2O$ HCl	C, 66.54 H, 7.55 N, 9.13	C, 66.52 H, 7.51 N, 8.90	3200 1650	625 385 368 355 295 288	2.60 3.73 3.71 3.60sh 4.46 4.54	68.6	Ethanol–ether
I-5	H—	$-CH_2-CH_2-N(CH_2-CH_2)_2O \cdot HCl$	243–245° dec.	$C_{17}H_{20}N_2O_2$ HCl	C, 63.64 H, 6.59 N, 8.73	C, 63.88 H, 6.86 N, 8.70	3210 1650	625 376 358 345 295 286	2.54 3.71 3.68 3.57sh 4.54 4.55	75.0	Ethanol–ether
II-1	$CH_3-C(=O)-$	$-CH_2-Cl$	180–183°	$C_{14}H_{12}NO_2Cl$	C, 64.25 H, 4.62 N, 5.35	C, 64.40 H, 4.58 N, 5.45	3200 1675 1645	570 395 300 245	2.68 3.81 4.43 4.23	64.2	Chloroform–benzene
II-2	$CH_3-C(=O)-$	$-CH=CH_2$[c]	187–189° (char 168°)	$C_{15}H_{13}NO_2$[c] H_2O	C, 70.02 H, 5.88 N, 5.44	C, 70.18 H, 6.00 N, 5.49	3150 1710 1650	575 402 305 240	2.69 3.82 4.50 4.07	49.0	Aqueous ethanol
II-3	$CH_3-C(=O)-$	$-CH_2-N(CH_2-CH_3)_2$	102–104°	$C_{18}H_{22}N_2O_2$	C, 72.45 H, 7.45 N, 9.39	C, 72.63 H, 7.31 N, 9.29	3250 1690	575 400 305 285 245	2.72 3.83 4.46 4.44 4.30	69.1	Ethyl acetate–*n*-heptane
II-4	$CH_3-C(=O)-$	$-CH_2-CH_2-N(CH_2-CH_3)_2$	93–95°	$C_{19}H_{24}N_2O_2$	C, 73.04 H, 7.74 N, 8.97	C, 72.99 H, 7.64 N, 9.06	3125 1675	575 400 305 245 245	2.71 3.88 4.58 4.58 4.45	70.0	Ethyl acetate–*n*-heptane

[a] NMR ($CDCl_3$): δ to (m, 7 protons), 3.7 (t, 2 protons), 2.7 (t, 2 protons). [b] Values are for the trinitrobenzene complex. [c] NMR (deuteroacetone): δ 7 to 10 (m, 6 protons), 6.5 (m, 2 protons), 5.75 (q, 1 proton), 2.65 (s, 3 protons).

and 1-nitroazulene was prepared after the method of Anderson *et al.* (5).

General Chromatographic Procedure—Chromatographic separations were done on Merck reagent aluminum oxide (alumina) No. 71707, utilizing 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 and combinations thereof were used: petroleum ether, benzene, toluene, dichloromethane, chloroform, and ethanol.

General Method for Ω-Chloroacylamidoazulenes—Powdered zinc, 1.600 g. (0.024 g. atom), was added over a 0.5-hr. period to a mechanically stirred solution of 0.500 g. (0.0029 mole) of 1-nitroazulene and 0.700 g. (0.0086 mole) of sodium acetate in 30 ml. of glacial acetic acid in a 100-ml. beaker at room temperature. After complete addition of the zinc, during which the color of the solution slowly changed from red to violet, the reaction mixture was allowed to stir for an additional 20 min. The solution was diluted with 50 ml. of cold water, and the resulting mixture was decanted from the unreacted zinc. The mixture was exhaustively extracted with 30-ml. aliquots of peroxide-free ether; the combined green ether extracts were washed free of acid with 5% sodium hydroxide solution and then were washed with successive 50-ml. aliquots of water until the washings were substantially free of yellow color The ether solution was placed in a 500-ml. three-necked flask containing 50 ml. of 5% sodium hydroxide solution, and the whole mixture was placed in an ice bath. The biphasic mixture was stirred, and 0.0031 mole of the appropriate Ω-chloroacyl chloride in 10 ml. of ether was added dropwise. After complete addition, the mixture was allowed to stir for 20 min. (during which the color of the solution changed from green to blue). The phases were separated, and the ether layer was washed once with 50 ml. of 5% hydrochloric acid and twice with 50-ml. portions of water, dried over sodium

sulfate, and allowed to evaporate at room temperature. The resulting solids were recrystallized from chloroform–hexane to yield dark-green needles. Compounds I-1 and I-2 were prepared by this method. Percentage yields and physical and spectral properties of these compounds are presented in Table I.

General Method for 1-(Ω-Dialkylaminoacylamido)-azulenes—A solution of 0.50 mmole of the appropriate Ω-haloacylamidoazulene and 1.0 mmole of the appropriate secondary amine in 30 ml. of anhydrous ethanol was refluxed overnight, diluted to opacity with water, and extracted with chloroform. The chloroformic extract was extracted with dilute mineral acid; the resultant aqueous solution was basified and reextracted with chloroform. The organic phase was washed with water, dried over sodium sulfate, filtered, and allowed to evaporate at room temperature to yield a green oil. The oils prepared by this method were converted to their respective crystalline derivatives, I-3, I-4, and I-5, the physical and spectral properties of which are presented in Table I.

General Method for 1-(Acylamido)-3-acetylazulenes—A 10-fold molar excess (0.250 g.) of phosphorus oxychloride dissolved in 10 ml. of dimethylacetamide was added dropwise to a stirred solution of 0.22 mmole 1-chloracylamidoazulene in 15 ml. of dimethylacetamide. During the addition, the color of the solution gradually turned from blue to green. After completion of the addition, the stirred reaction mixture was heated in an 80° water bath for 1 hr., another 10-fold molar excess of $POCl_3$ was added, and the stirred mixture was kept in the 80° water bath for a 2nd hr. The flask was then removed from the water bath, and the stirred mixture was allowed to come slowly to room temperature. During this cooling, a large amount of crystalline white material separated from the green liquid. The mixture was chilled in an ice bath, 50–60 ml. of cold water was added, and the stirred resultant red solution was gradually made alkaline (pH 10) by the cautious addition of small portions of solid sodium carbonate.

The basic solution was exhaustively extracted with chloroform, and the combined green organic extracts were dried over sodium sulfate, filtered, concentrated, and chromatographed on alumina in accord with the general procedure previously described. Specifically, petroleum ether–dichloromethane (50:50) separated a blue band of starting material, leaving behind a slow moving green band which was extruded and packed atop a fresh column of alumina. Sequential development of the green band from the reaction mixture for II-1 with benzene and chloroform–benzene (30:70) separated a light-orange band and then II-1 as a dark-green band, leaving behind a faint yellowish-green band. Sequential development of the green band from the reaction mixture for II-2 with petroleum ether–dichloromethane (50:50) and chloroform eluted a faint-green band and then II-2 as a dark-green band. Evaporation of the eluting solvents gave solid or semisolid products which, after recrystallizing twice, gave crystals. The physical and spectral properties and yields of these compounds are given in Table I.

General Method for 1-(Ω-Diethylaminoacylamido)-3-acetylazulenes—A solution of 1.0 mmole of the appropriate 1-(Ω-haloacylamido)-3-acetylazulene and 2.0 mmoles of diethylamine in 15 ml. of anhydrous ethanol was refluxed overnight, diluted with 50 ml. of water, and exhaustively extracted with chloroform. The green organic phase was counterextracted with dilute hydrochloric acid, and the resultant red aqueous phase was made alkaline with dilute sodium hydroxide and chilled in an ice bath to give a green precipitate. The green precipitates were chromatogrammed on alumina with benzene to remove minor orange, yellow, and light-green bands and with chloroform to elute II-3 and II-4 as major dark-green zones. Spontaneous evaporation of the chloroform gave a green semisolid or oil, which solidified after standing for several days and which gave II-3 and II-4 as green crystals from ethyl acetate–*n*-heptane (50:50) when the solvent mixture was allowed to evaporate spontaneously. The physical and spectral properties and yields of these compounds are given in Table I.

REFERENCES

(1) P. H. Doukas and T. J. Speaker, *J. Pharm. Sci.*, **60**, 184(1971).

(2) V. Migrdichian, "Organic Synthesis," vol. 1, Reinhold, New York, N. Y., 1957, p. 483.

(3) A. G. Anderson, Jr., *J. Amer. Chem. Soc.*, **81**, 5669(1959).

(4) K. Hafner and K. L. Morita, in "Friedel–Crafts and Related Reactions," vol. 4, G. A. Olah, Ed., Interscience, New York, N. Y., 1965, pp. 148–150, and references cited therein.

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

ACKNOWLEDGMENTS AND ADDRESSES

Received May 21, 1970, from the *School of Pharmacy, Temple University, Philadelphia, PA 19140*

Accepted for publication September 24, 1970.

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

The authors thank Dr. R. John Stedman for his invaluable assistance in obtaining and interpreting the NMR spectra.

* Temple University Predoctoral Fellow, 1967–1969.