Azulene Analogs of Pharmacologic Agents

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The synthesis of a series of azulene-1-carboxylic acid esters is described. These esters are to be screened for pharmacologic activity.

AZULENE, with a resonance energy of about 46 Kcal./mole can be classified as aromatic with respect to resonance stability (1, 2) and is the only known bicyclic nonbenzenoid hydrocarbon of this type. Azulene has been unequivocally shown to undergo electrophilic substitution at the 1-position (3).

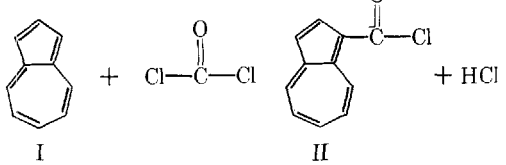
Until the development of an efficient method for the preparation of azulene in 1956 by Ziegler (4), utilization of this nonbenzenoid nucleus was severely restricted, at least in part by economic factors.

Investigation of the pharmacodynamic activity of azulene and azulene derivatives, principally hydrocarbons, has to date been restricted in the main to examination of the antiphlogistic (5, 6), antiallergic (7), and bacteriostatic (8) properties of these compounds or mixtures of them obtained from chamomile and similar oils.

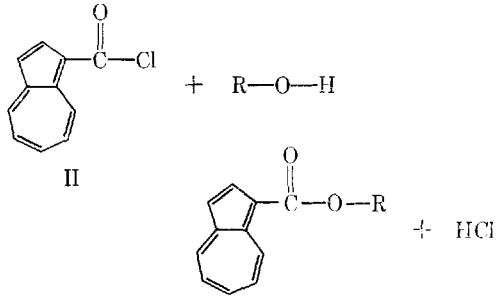
It seemed of importance, therefore, to undertake a systematic study of the effects of replacing benzenoid nuclei in structures known to exhibit pharmacologic activity with the nonbenzenoid aromatic nucleus of azulene.

Because the aromatic portions of local anesthetics are essential to a high level of local anesthetic activity, it seemed reasonable to initiate this study by preparing several azulene compounds which might be expected to be local anesthetics were their aromatic portions benzenoid rather than nonbenzenoid.

The room temperature reaction of azulene (I) with phosgene in the absence of Friedel-Crafts catalysts described by Triebs *et al.* conveniently provided the acid chloride of azulene-1-carboxylic acid (II), and this acid chloride on reaction with appropiate alcohols afforded the corresponding esters (III) in yields averaging about 90% of theoretical, based on azulene.



I II

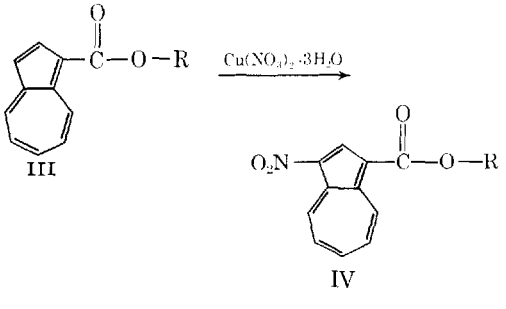


II III

The high π-electron density of the 1- and 3-positions of the azulene nucleus calculated by the linear combination of atomic orbitals-molecular orbital method of Hückel (10) suggests that a 3-substituent corresponds closely in electronic behavior to a *para* substituent in a phenyl nucleus.

Accordingly, it was of interest to prepare several 3-substituted esters for this study.

Treating an azulene-1-carboxylic acid ester with cupric nitrate in a mixture of acetic acid and acetic anhydride after the method of Anderson (11) provided a route to the corresponding 3-nitro ester (IV) and reduction of the 3-nitro



III IV

esters yielded the relatively unstable 3-amino esters (V).

Attempts to chlorocarboxylate 1-nitroazulene were unfruitful.

Some esters substituted in the alcohol-derived portion are poorly stable under even these mild nitration conditions, but the relative stability of the Ω-haloalkanol esters to these nitration conditions offered a method for introduction of more labile groups into the alcohol-derived portion of the 3-substituted esters.

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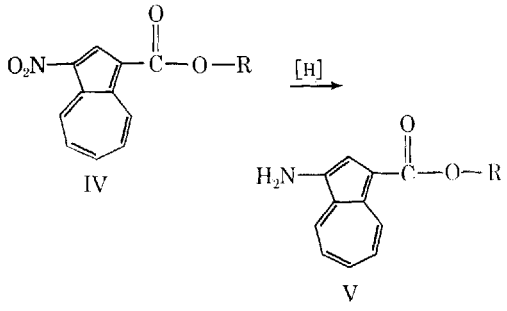


EXPERIMENTAL

Azulene for this study was at first prepared in this laboratory after the method of Ziegler (4) and was later obtained from Terra Chemicals, Inc.

Alcohols available from Distillation Products Industries, Division of Eastman Kodak Co., were obtained from that source. The others were prepared in this laboratory.

All melting points were determined using a Fisher-Johns melting point apparatus and are corrected.

All spectral data were obtained using a Beckman DB spectrophotometer and Distillation Products Industries spectro grade methanol as solvent.

Gases were obtained from the Matheson Co., Inc.

Chromatographic alumina was Fisher Scientific Co. No. A540.

Esters of Azulene-1-carboxylic Acid.—Each of the esters of unsubstituted azulene-1-carboxylic acid was prepared by the following procedure adapted from Triebs *et al.* (9). A solution of 1.282 Gm. (0.01 mole) of azulene in 50 ml. of dry toluene was saturated with phosgene while cooled in a bath of running tap water and allowed to stand 1 hr. (Failure to cool the solution increased the amount of tarry material formed and significantly lowered yields of ester.) During this time the solution changed from a dark blue color to a dark red-violet color. The excess phosgene was removed by gentle refluxing under a slight vacuum for about 30 min.

A solution of 0.010 mole of the appropriate alcohol in dry toluene was added dropwise to this solution of azulene-1-carboxylic acid chloride. The reaction mixture was allowed to stand 30 min., treated with 20 ml. of dilute ammonium hydroxide, and transferred to a separator. The reaction vessel was rinsed with an additional 10 ml. of toluene and the rinsings were added to the funnel. The reaction mixture was successively extracted with 10-ml. portions of ammonium hydroxide until the aqueous portion showed no blue color. The wet toluene was allowed to evaporate spontaneously in a stream of cool air. (Early experiments suggested that yields fall drastically if the esters are heated at steam bath temperatures.)

The residue was triturated with approximately 5 Gm. of alumina and packed above an alumina chromatography column (1.8 × 15 cm.), and the chromatogram was developed first with ligroin to remove any unreacted azulene and then with toluene. The red-violet eluates were collected, and solvent was allowed to evaporate spontaneously as before. Most of these esters were oils.

Alkanolamine esters were converted to their corresponding hydrochlorides in the usual manner. The amine hydrochlorides were hygroscopic.

3-Nitroazulene-1-carboxylic Acid Esters.—Each of the 3-nitroazulene-1-carboxylic acid esters was prepared by the following procedure adapted from the work of Anderson *et al.* (11). Increasing the quantity of reagents by a factor of 10 introduced no new difficulties.

A chilled slurry of 0.241 Gm. (0.001 mole) of finely powdered cupric nitrate, $Cu(NO_3)_2 \cdot 3H_2O$, in 3 ml. of acetic anhydride was added to a mechanically stirred solution of 0.001 mole of an azulene-1-carboxylic acid ester in a mixture of 5 ml. of acetic acid and 1 ml. of acetic anhydride maintained at temperatures below 5°. The transfer of the slurry was facilitated by the use of an additional 2 ml. of chilled acetic anhydride.

The mixture was stirred for 10 min. and poured into 50 ml. of ice water and extracted with three 10-ml. portions of chloroform. The combined chloroform extracts were washed 3 times with 10-ml. portions of water, evaporated to dryness in a stream of cool air, and the residue was triturated with about 5 Gm. of alumina.

This triturate was packed above an alumina chromatography column (1.8 × 15 cm.). Elution with toluene removed the unreacted ester as a red-violet band and slowly displaced an orange band from a closely following dark brown region. The column was extruded and the orange region packed above a fresh alumina column. The new column was eluted with 20% ether in toluene and evaporation of the orange eluate in a stream of cool air gave orange to red needles of the 3-nitro esters.

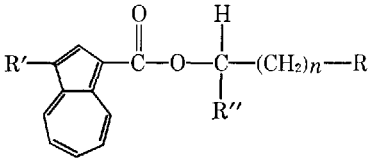
3-Aminoazulene-1-carboxylic Acid Esters.—Each of the 3-aminoazulene-1-carboxylic acid esters was prepared by the following procedure adapted from that of Anderson *et al.* (3). Over a 5-min. period 0.5 Gm. of zinc dust was added to a stirred solution of 0.001 mole of the appropriate 3-nitroazulene-1-carboxylic acid ester and 0.2 Gm. of sodium acetate in 10 ml. of acetic acid. The mixture was stirred 1 hr. and diluted with 30 ml. of distilled water. The resulting blue mixtures were decanted from any unreacted zinc and extracted with three 20-ml. portions of ether. The emerald-green ether extracts were combined and washed with aqueous sodium hydroxide (5% w/v) until free of acid. The ether solution was extracted with dilute hydrochloric acid until the aqueous extracts were colorless.

The combined acid extracts were neutralized with ammonium hydroxide and extracted with two 20-ml. portions of ether. The ether was allowed to evaporate spontaneously, and the residue was triturated with about 5 Gm. of alumina. The triturate was packed above an alumina chromatography column and eluted with 20% ether in toluene. It gave only a single red band. Spontaneous evaporation of the eluate in a stream of cool air gave the free 3-aminoazulene-1-carboxylic acid esters. The amines were converted to their hydrochlorides in the usual manner.

Alkanolamine Ester of 3-Nitroazulene-1-carboxylic Acid.—The Ω-halo ester of 3-nitroazulene-1-carboxylic acid was converted to the corresponding *N,N*-dialkylaminoalkanol ester of 3-nitroazulene-1-carboxylic acid by the following procedure.

A solution of 0.073 Gm. (0.001 mole) of diethylamine in 10 ml. of ether was added dropwise to a

TABLE I.—ESTERS OF AZULENE-1-CARBOXYLIC ACIDS



R	R′	R″	*n*	Yield, %	M. p., °C.	Formula	Anal. Calcd.	Anal. Found	λ_{max}	Log ε
H	H	H	1	93	Oil	$C_{13}H_{12}O_2$	C, 77.97 H, 6.04	77.82 6.40	232	4.70
Cl	H	H	1	86	60–61	$C_{13}H_{11}ClO_2$	C, 64.07 H, 4.55	64.21 4.37	310	4.63
Dimethylamino	H	H	1	92	105 dec.	$C_{15}H_{17}NO_2$. HCl	N, 5.00	4.89	304	4.74
Diethylamino	H	H	1	93	127	$C_{17}H_{21}NO_2$. HCl	N, 4.55	4.61	228	3.33
2-Methylpiperidino	H	H	2	87	122	$C_{20}H_{25}NO_2$. HCl	N, 4.02	3.98	240	3.11
Cyclohexylamino	H	CH_3	1	88	108	$C_{20}H_{25}NO_2$. HCl	N, 4.02	4.09	315	4.50
H	NO_2	H	1	64	150–152	$C_{13}H_{11}NO_4$	N, 5.71	5.66	292	4.61
Cl	NO_2	H	1	52	108–110	$C_{13}H_{10}ClNO_4$	N, 5.00	4.94	292	3.24
Diethylamino	NO_2	H	1	50	183–184	$C_{17}H_{20}N_2O_4$. 2HCl	N, 7.19	7.10	243	4.51
H	NH_2	H	1	83	190–191	$C_{13}H_{13}NO_2$	N, 5.56	5.55	219	4.60
Diethylamino	NH_2	H	1	78	163–165	$C_{17}H_{22}N_2O_2$. 2HCl	N, 7.79	7.74	240	4.62

mechanically stirred solution of 0.279 Gm. (0.001 mole) of the 2-chloroethanol ester of 3-nitroazulene-1-carboxylic acid in 20 ml. of ether, and the mixture was heated at reflux temperature for 1 hr. The ether was decanted from the resulting gummy blue solid, and the residue was dissolved in 20 ml. of distilled water. The solution was transferred to a separator, and the solution was made alkaline with ammonium hydroxide. The solution was extracted with 20-ml. portions of ether, and the combined ether extracts were washed with a little water. The ether extract was allowed to evaporate spontaneously, and the residue was triturated with about 3 Gm. of alumina. The triturate was packed above an alumina chromatography column and eluted with 20% ether in toluene. Only a single red-orange band appeared. It was eluted and spontaneous evaporation of the solvent in a stream of cool air gave the *N,N*-diethylamino derivative, which was converted to the corresponding hydrochloride in the usual manner.

The results are reported in Table I together with some of the physical properties of these new compounds.

Upon preliminary pharmacologic testing some of these compounds were found to exhibit local anesthetic activity.

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