Table I—Concentration of Cocaine in Nine Species of *Erythroxylum* as Determined by GLC

Species	Collector	Specimen Number	Locality	Herbarium[a]	Collection Date	Cocaine[b], %
E. campestre A. St. Hil.	P. Dusen	16421	Brazil	MO	?	0.00014
E. citrifolium A. St. Hil.	W. H. Lewis *et al.*	254	Panama	MO	1966	n.d.
E. deciduum A. St. Hil.	L. O. Williams	7424	Brazil	MO	1945	n.d.
E. deciduum A. St. Hil.	L. B. Smith & Klein	7452	Brazil	NY	1956	0.00080
E. novogranatense (Morris) Hieron	R. E. Schultes	—	Cuba	NY	1955	0.00882
E. novogranatense (Morris) Hieron	Br. Daniel	15584	Colombia	OA	1961	0.00216
E. panamense Turcz.	T. B. Croat	5519	Canal Zone	MO	1968	0.00121
E. panamense Turcz.	T. B. Croat	4879	Canal Zone	MO	1968	0.00141
E. pelleterianum A. St. Hil.	Y. Mexia	4364	Brazil	MO	1930	0.00123
E. pulchrum A. St. Hil.	Riedel	390	Brazil	MO	?	0.00008
E. rufum Cav.	E. L. Ekman	11609	Santo Domingo	AA	1929	n.d.
E. rufum Cav.	R. A. Howard	12247	Dominican Republic	AA	1950	n.d.
E. coca Lam.[c]	J. A. Duke	—	—	—	1974	0.53
E. coca Lam.	—	—	—	—	<1930	0.03

[a] MO = Missouri Botanical Gardens, NY = New York Botanical Gardens, OA = Oaks Ames Economic Herbarium, Harvard University; and AA = Arnold Arboretum Herbarium, Harvard University. [b] Single leaves were analyzed, with data being expressed as the mean percent of two determinations; n.d. = cocaine not detected. [c] Leaf material from a 2-year-old living plant was collected and analyzed within 48 hr.

A sample of *E. coca* leaf analyzed within 2 days from the time of removal from the living plant contained 0.53% of cocaine, whereas a dried and stored sample at least 44 years old still contained 0.03% cocaine.

Studies are currently in progress to determine the decomposition rate of cocaine in stored *E. coca* leaves, as well as the natural variability of this alkaloid in various populations of *E. coca*.

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Synthesis and Anti-Inflammatory Evaluation of 2-(Substituted Amino)quinolizinium Bromides

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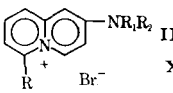
Abstract □ The synthesis and anti-inflammatory evaluation of a number of 2-(substituted amino)quinolizinium bromides, including some previously unreported analogs, are described. The more active compounds in inhibiting carrageenin-induced edema formation are those containing a *p*-alkoxyanilino group in the 2-position of the quinolizinium ring.

Keyphrases □ Quinolizinium bromides, 2-(substituted amino)—synthesis and anti-inflammatory evaluation □ Aminoquinolizinium bromides (2-substituted)—synthesis and anti-inflammatory evaluation □ Anti-inflammatory activity—evaluation of 38 2-(substituted amino)quinolizinium bromides

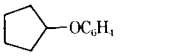
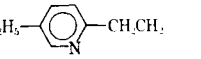
Previously, the synthesis and antiparasitic screening of a series of 2-(substituted amino)quinolizinium bromides were reported (1). Many of these compounds (III–XL) exhibited a significant degree of anthelmintic activity. The primary anti-inflammatory evaluation of this series of compounds, including some previously unpublished analogs, is reported herein. Compounds III–XL, when examined in the carrageenin-induced rat paw edema assay, inhibited edema formation as much as 76%.

The previously reported (1) synthesis involves the reaction of an appropriately substituted amine with either of the two intermediates, 2-bromoquinolizinium bromide (I) or 2-bromo-6-methylquinolizinium

Table I—Anti-Inflammatory Evaluation of Certain Quinolizinium Bromides



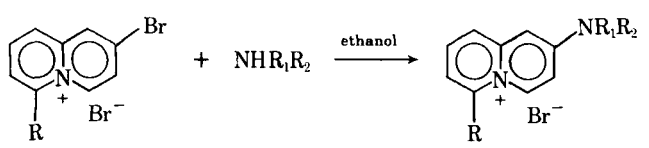
III–XXXIV: R = H
XXXV–XL: R = CH_3

Compound	R_1	R_2	Inhibition of Edema Formation[a], %
III	H	C_6H_5	59
IV	H	4-BrC_6H_4	26
V	H	4-$C_6H_5N{=}N{-}C_6H_4$	39
VI	H	4-$(CH_3)_2NC_6H_4$	62
VII	H	4-$(C_2H_5)_2NC_6H_4$	58
VIII	H	4-$C_2H_5OC_6H_4$	44
IX	H	4-$CH_3CH_2CH_2OC_6H_4$	68
X	H	4-$(CH_3)_2CHOC_6H_4$	41
XI	H	4-$(CH_3)_2CHCH_2OC_6H_4$	76
XII	H	4-$CH_3(CH_2)_3OC_6H_4$	26
XIII	H	4-$CH_3(CH_2)_7OC_6H_4$	44
XIV	H	4-$HC{\equiv}CCH_2OC_6H_4$	17
XV	H	4-$CH_2{=}CHCH_2OC_6H_4$	67
XVI	H	4-$C_6H_5OC_6H_4$	31
XVII	H		67
XVIII	H	3-$CH_3CHOHC_6H_4$	0
XIX	H	2-$CH_3OC_6H_4$	9
XX	H	2-$C_2H_5OC_6H_4$	21
XXI	H	3,4-$(CH_3)_2C_6H_3$	50
XXII	H	3,4-$(CH_3O)_2C_6H_3$	8
XXIII	H	2,4-$(CH_3O)_2C_6H_3$	29
XXIV	H	2-CH_3—4-$CH_3OC_6H_3$	46
XXV	H	2,4,6-$(CH_3O)_3C_6H_2$	19
XXVI	H	2,4-$(CH_3O)_2$—5-ClC_6H_2	0
XXVII	H	2,5-$(CH_3O)_2$—4-ClC_6H_2	2
XXVIII	H	2,5-$(C_2H_5O)_2C_6H_3$	34
XXIX	H	2-CH_2O—5-$CH_3C_6H_3$	51
XXX	H	$HOCH_2CHOHCH_2$	41
XXXI	$HOCH_2CH_2$	$HOCH_2CH_2$	0
XXXII	$CH_3CH_2OCH_2CH_2$	$CH_2CH_2OCH_2CH_2$	3
XXXIII	NH_2		22
XXXIV	H	3-$CF_3C_6H_4$	53
XXXV	H	4-$CH_3OC_6H_4$	12
XXXVI	H	4-$C_2H_5OC_6H_4$	44
XXXVII	H	4-$CH_3SC_6H_4$	9
XXXVIII	H	2,4-$(CH_3O)_2C_6H_3$	22
XXXIX	NH_2	$HOCH_2CH_2$	34
XL	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	34
XLI	Phenylbutazone[b]		59

[a] Compared to control (nondrug treated) hindpaw 4 hr after carrageenin administration. Compounds administered at 300 mg/kg. [b] Phenylbutazone administered at 100 mg/kg.

bromide (II) (Scheme I).

The compounds were tested for anti-inflammatory activity according to the carrageenin method reported by Winter *et al.* (2). Each compound was suspended in distilled water by sonification and administered perorally, 300 mg/kg in three male Wistar rats, 1 hr prior to subplantar injection of 0.05 ml of a 1% solution of carrageenin[1] into the left hindfoot. The percentage reduction of edema formation (as compared to a nondrug-treated control) in the rat hindpaw was recorded 4 hr after carrageenin administration. For comparison, the reference anti-inflammatory drug phenylbutazone (XLI) was tested (Table I).



I: R = H
II: R = CH_3

III–XXXIV: R = H
XXXV–XL: R = CH_3

Scheme I

The more active compounds exhibiting a high degree of reduction of the carrageenin-induced edema formation had a substituted anilino group in the 2-position of the quinolizinium ring. The presence of the methyl group in the 6-position (XXXVI and XXXVIII) did not appear to alter the degree of anti-inflammatory activity when compared with the corresponding demethyl compounds (VIII and XXIII).

Substitution on the anilino ring with alkoxy or dialkylamino groups in the 4-position resulted in the highest degree of anti-inflammatory activity (VI, VII, IX, XI, XV, and XVII), and the active quinolizinium compounds did not exhibit overt signs of toxicity, central depression, or lethality in doses that exerted marked anti-inflammatory activity.

[1] Viscarin.

Table II—Analytical and Physical Data for New Compounds

Compound	Melting Point	Yield, %	Recrystallization Solvent	Formula	Analysis, % Calc.	Found
V	239–240°	90	C_2H_5OH	$C_{21}H_{17}BrN_4$	C 62.23	62.07
					H 4.23	4.29
					Br 19.72	19.67
XXX	166–168°	60	C_2H_5OH	$C_{12}H_{15}BrN_2O_2$	C 48.17	48.42
					H 5.05	5.01
					Br 26.71	26.64
XXXIX	209–210°	92	C_2H_5OH	$C_{12}H_{16}BrN_3O$	C 48.33	48.48
					H 5.41	5.28
					Br 26.80	26.81

EXPERIMENTAL[2]

2-(*m*-Trifluoromethylanilino)quinolizinium bromide (XXXIV) was prepared as follows. To a solution of 2-bromoquinolizinium bromide (I) (1) (45 g, 0.15 mole) in ethanol (600 ml) was added *m*-trifluoromethylaniline (50 g, 0.30 mole). The stirred mixture was boiled under reflux for 5 hr, then treated with charcoal, and filtered. The product was precipitated from the filtrate by the addition of anhydrous ether.

The crude product weighed 42 g (76%). Recrystallization from isopropanol–ether provided analytically pure material, mp 229–230°.

Anal.—Calc. for $C_{10}H_{12}BrF_3N_2$: C, 52.03; H, 3.28; N, 7.59. Found: C, 51.96; H, 3.25; N, 7.61.

All other 2-(substituted amino)quinolizinium bromides were prepared similarly. Compounds V, XXX, XXXIV, and XXXIX have not been reported previously; the analytical and physical data for V, XXX, and XXXIX are shown in Table II. Analytical and physical data for all other compounds (Table I) were reported previously (1).

[2] Melting points were determined in open capillary tubes using a Mel-Temp melting-point apparatus and are uncorrected.

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Halothane Uptake by Coacervate Systems

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Abstract □ Two aggregated coacervae systems (acacia–gelatin and gelatin–benzalkonium chloride) were analyzed for gas sorption of halothane with a gas chromatograph, using a modified tonometer as an absorption chamber. Similar studies were performed on each system after the coacervate had been broken or "dissolved." Differences in absorption or solubilizing effect between coacervates and dissolved coacervates were noted. A significant halothane gas uptake was observed in the highly structured coacervate system.

Keyphrases □ Halothane—uptake by acacia–gelatin and gelatin–benzalkonium chloride aggregated coacervate systems, uptake compared to broken coacervate systems □ Coacervate systems—halothane uptake by acacia–gelatin and gelatin–benzalkonium chloride systems and similar broken systems □ Acacia–gelatin coacervate system—halothane uptake, compared to similar broken system □ Gelatin–benzalkonium chloride system—halothane uptake, compared to similar broken system

The importance of solvent abilities in structured systems as well as a renewed interest in liquid crystalline states suggested that it would be of value to investigate the solvent abilities of a coacervate in contrast to the solvent abilities of an analogous "broken" coacervate. Coacervates may be considered to be coagulated systems, while "dissolved" or broken coacervates can be considered noncoagulated systems. In this study, a unique ability of coacervate systems to attract and solubilize nonpolar gases in a polar medium is discussed.

The term coagulation, as used here, refers to a type of aggregate characterized by film–film bonded particulates. The term coacervation denotes the formation of a liquid precipitate by the mutual coagulation of hydrophilic colloids (1). The definition of coacervation has been more elaborately discussed (2) as a phenomenon of the separation of colloidal solutions into two or more immiscible liquid phases. The electrostatic and thermodynamic properties of a colloidal solution can be varied in such a way that the system separates into two amorphous liquid layers. One layer contains most of the colloid (the coacervate), while the second layer is colloid poor (the equilibrium liquid). The coacervate appears in the form of