2-Bromo-1-hydroxyquinolizinium Bromide Substituted Anilinium Salts: A New Class of Anti-inflammatory Agents

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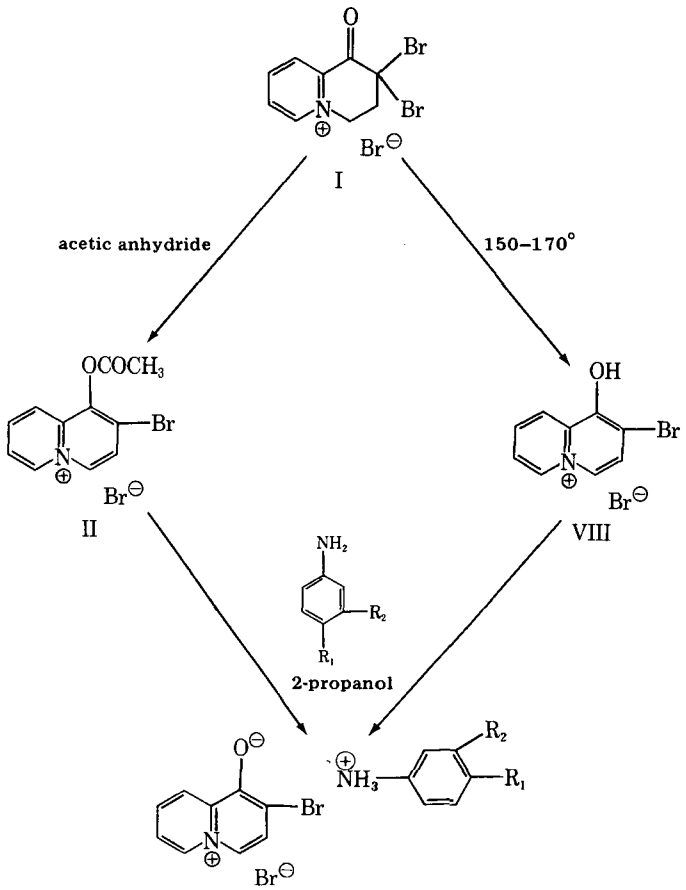
Received October 6, 1981, from the *Chemical and ‡Biological Research Divisions, Norwich Eaton Pharmaceuticals, Inc., Norwich, NY 13815. Accepted for publication January 28, 1982.

Abstract □ A series of 2-bromo-1-hydroxyquinolizinium bromide substituted anilinium salts have been prepared by reaction of 1-acetoxy-2-bromoquinolizinium bromide with an appropriately substituted aniline. The resulting anilinium derivatives exhibited a moderate to high degree of anti-inflammatory activity in the carrageenin-induced rat paw edema assay. The most active anilinium salt of the series was evaluated for antiarthritic activity in the adjuvant induced arthritis rat model.

Keyphrases □ Anti-inflammatory agents—2-bromo-1-hydroxyquinolizinium bromide substituted anilinium derivatives, antiarthritic activity, rat □ 2-Bromo-1-hydroxyquinolizinium bromide—anti-inflammatory agents, substituted anilinium derivatives, antiarthritic activity, rat □ Derivatives, anilinium—2-bromo-1-hydroxyquinolizinium bromide, anti-inflammatory agents, antiarthritic activity, rat

As part of an investigation of the chemistry of quinolizinium salts, a number of 2-bromo-1-hydroxyquinolizinium bromide substituted anilinium salts were prepared and screened for biological activity. These anilinium compounds exhibited a moderate to high degree of anti-inflammatory activity in the carrageenin-induced rat paw edema assay. No structure–activity relationships, however, were found.



Scheme I

EXPERIMENTAL[1]

Chemistry—2-Bromo-1-hydroxyquinolizinium bromide-*p*-phenetidinium salt (III) was prepared by adding *p*-phenetidine (24 g, 0.18 mole) to a solution of 1-acetoxy-2-bromoquinolizinium bromide (30 g, 0.09 mole) (II) (1–3) in 2-propanol (600 ml). The stirred mixture was boiled under reflux for 4 hr, then chilled and filtered. The yellow crystalline product was washed thoroughly with ether and weighed 37 g (97%).

The remaining compounds in Table I were prepared in a similar manner from II and the appropriately substituted aniline. The reaction of 2-bromo-1-hydroxyquinolizinium bromide (VIII) (3) with the appropriate aniline under similar conditions provided the corresponding substituted anilinium compound III–VII in comparable yields (4). The microanalytical data for compounds III–VII are given in Table II.

Pharmacologic Testing—The compounds were tested for anti-inflammatory activity according to the carrageenin method as described previously (5). Each compound was suspended in distilled water by sonification and administered orally, 300 mg/kg in three male Wistar rats, 1 hr before subplantar injection of 0.05 ml of a 1% solution of carrageenin[2] into the left hind foot. The percentage reduction in edema formation (as compared to a nondrug-tested control) of the rat foot was recorded 4 hr after carrageenin administration.

Examination of VI for antiarthritic activity was determined by use of the adjuvant-induced arthritis model described previously (6). Ten male Wistar rats per treatment group were used in the antiarthritic evaluation. Three principal areas were considered in determining the efficacy of a drug: edema formation, body weight changes, and arthritic scores.

The arthritic lesion scores are based on a modification of previous procedures (6), in which a maximum lesion score of 27 is possible. The results are given in Table III.

RESULTS AND DISCUSSION

The 1-hydroxy-2-(substituted anilino)quinolizinium bromides (III–VII) (Table I) were readily prepared by the reaction of the known 1-acetoxy-2-bromoquinolizinium bromide (II) (1–3) or 2-bromo-1-hydroxyquinolizinium bromide (VIII) (3) with an appropriately substituted aniline in 2-propanol as shown in Scheme I (4). The preparation of the intermediate (II or VIII) proceeded through 2,2-dibromo-1,2,3,4-tetrahydro-1-oxo-quinolizinium bromide (I) either by reaction with acetic anhydride or by heating at 150–170° as shown in Scheme I. The synthesis of I has been described earlier (3).

Since II was more readily available synthetically than VIII, the procedure for the preparation of III–VII involving the use of II was favored. The yields of the final products III–VII were comparable, proceeding through either intermediate. The spectra of compounds III–VII (IR, NMR, UV), as well as the microanalytical data were consistent with the assigned structures. Further confirmation of the structure assignment was obtained when the starting material VIII was regenerated and the corresponding aniline hydrobromide salt isolated during treatment of III–VII with 48% hydrogen bromide.

These quinolizinium anilinium salts (III–VII) were evaluated for anti-inflammatory activity in the carrageenin-induced rat paw edema assay (5). The results are shown in Table I. The reference drug phenylbutazone (IX) is included for purposes of comparison. No apparent un-

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

[2] Viscarin, Algin Corporation of America.

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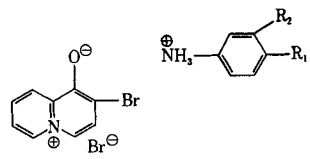
Table I—Anti-Inflammatory Evaluation and Physical Data for New Compounds



No.	R_1	R_2	Melting Point	Yield, %	Recrystallization Solvent	Formula[a]	Inhibition of Edema Formation, %[b,c]
I	OC_2H_5	H	161–162°	97	Ethanol–Ether	$C_{17}H_{18}Br_2N_2O_2$	31.4
IV	OCH_3	H	129–133°	74	2-Propanol–Ethyl Acetate	$C_{16}H_{16}Br_2N_2O_2$	44.1
V	OC_6H_5	H	123–125°	65	2-Propanol–Ether	$C_{21}H_{18}Br_2N_2O_2$	37.0
VI	$OCH_2CH{=}CH_2$	H	125–127°	77	2-Propanol	$C_{18}H_{18}Br_2N_2O_2$	63.0
VII	OCH_3	OCH_3	160–162°	76	Ethanol	$C_{17}H_{18}Br_2N_2O_3$	46.4
IX	Phenylbutazone						58.5[d]

[a] Analytical results for C, H, N, and Br are within ±0.24% of the theoretical values and shown in Table II. [b] Dosed at 300 mg/kg orally 60 min before carrageenin injection. [c] Compared to control (nondrug treated) hind paw 4 hr after carrageenin injection. [d] Dosed at 100 mg/kg orally.

Table II—Microanalytical Data

No.	Formula	Calc. C	Calc. H	Calc. N	Calc. Br	Found C	Found H	Found N	Found Br
I	$C_{17}H_{18}Br_2N_2O_2$	46.18	4.10	6.34	36.15	46.20	4.30	6.42	35.92
IV	$C_{16}H_{16}Br_2N_2O_2$	44.88	3.77	6.54	37.33	44.70	3.70	6.57	37.16
V	$C_{21}H_{18}Br_2N_2O_2$	51.45	3.70	5.72	32.61	51.42	3.74	5.72	32.77
VI	$C_{18}H_{18}Br_2N_2O_2$	47.60	3.99	6.17	35.19	47.69	4.09	6.12	35.26
VII	$C_{17}H_{18}Br_2N_2O_3$	44.56	3.96	6.12	34.89	44.80	4.01	5.96	34.88

Table III—Antiarthritic Evaluation of Compound VI

Compound	Dose, *per os* mg/kg (21-day)	Inhibition of Primary Lesion Injected Paw, % (22-day)	Inhibition of Secondary Lesion Noninjected Paw, % (22-day)	Increase in Body Weight, % (22-day)	Mean Arthritic Score
VI	50	0	10	22	13
	200	20	30	33	12
Aspirin	300	36	39	27	14
Phenylbutazone IX	100	78	82	40	8
Adjuvant control 0.5% methylcellulose	—	0	0	22	17

toward gross signs of drug action were observed for compounds III–VII.

The most active member of the series (VI) was examined for antiarthritic activity by use of the adjuvant-induced arthritis model (6). The results of the study were grouped into three principal areas: edema formation, body weight changes, and arthritic scores. All three areas are equally important in determining the anti-inflammatory efficacy of a drug. The results indicate that VI is at least as active as aspirin but less active than phenylbutazone. The results are presented in Table III.

The anti-inflammatory activity of compounds III–VII as revealed by the percent inhibition of edema formation was less than that elicited by several of the 2-(substituted amino)quinolizinium bromides reported previously (7).

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ACKNOWLEDGMENTS

The authors acknowledge the technical assistance of Miss Yvonne Miller in the preparation of chemical intermediates and the evaluation of these compounds for anti-inflammatory activity by Mr. Arthur C. Ilse, Jr. Microanalytical data were provided by Mr. Marvin Tefft and Mr. Grant Gustin.