having the same charcoal to salicylate ratios, the fractions of salicylate adsorbed were 0.401, 0.711, 0.920, and 0.984, respectively. Clearly, these results show either zero effect, a very slight interference, or a very slight enhancement of adsorption. Overall, no effect of significance can be identified.

CONCLUSIONS

Whether results similar to those obtained using sodium salicylate would be found with other kinds of drugs is, of course, unproved. However, if simple adsorption of the test drug and of the pepsin or gastric mucin is all that occurs, results with other drugs should not be radically different.

However, the question of whether pepsin and/or mucin should be added to simulated gastric fluid to make evaluations more realistic is overshadowed by the implications of data obtained by Andersen (17). He carried out adsorption tests in actual gastric contents (pH 1.5, 60% solids) obtained by aspiration of the stomachs of human volunteers after test meals had been consumed. Values for the amounts of mercuric chloride, barbital, and strychnine adsorbed on charcoal were only about 50–60% of the amounts adsorbed from pH 1.5 hydrochloric acid solutions.

Since the reductions in adsorption were quite large and probably depend on a whole complex array of solid and dissolved materials present in the stomach, it appears that absolute similarity between simulated gastric fluid and actual gastric contents is not achieved simply by adding pepsin and/or mucin to the simulated gastric fluid recipe. Therefore, it is probably just as well to omit both pepsin and mucin in tests involving simulated gastric fluid and to figure, as a rule of thumb, that the amount of drug adsorbed *in vivo* will be roughly half of that adsorbed *in vitro*. The experimental results reported in this paper give one a feeling for the influence of two specific important constituents of actual gastric fluid and indicate that they, at least, are not crucial in affecting adsorption.

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Synthesis and Antiulcerogenic Evaluation of 2-(Substituted Phenylimino)-2*H*-quinolizines

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Received July 1, 1977, from the *Chemical Research Division and the Biological Research Division, Norwich-Eaton Pharmaceuticals, Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication November 22, 1977.

Abstract □ The synthesis and antiulcerogenic evaluation of a series of 2-(substituted phenylimino)-2*H*-quinolizines are described. The most active compound, the 4-chlorophenylimido derivative, inhibited ulcer formation by 98%.

Keyphrases □ Quinolizines, substituted phenylimino—synthesized, evaluated for antiulcerogenic activity □ Antiulcerogenic activity—various 2-(substituted phenylimino)-2*H*-quinolizines evaluated □ Structure–activity relationships—various 2-(substituted phenylimino)-2*H*-quinolizines evaluated for antiulcerogenic activity

The synthesis and preliminary pharmacological evaluation of a series of 2-(substituted amino)quinolizinium bromides were reported previously (1, 2). As a continuing part of this investigation, the synthesis and antiulcerogenic testing of a series of 2-(substituted phenylimino)-2*H*-quinolizines (II*a*–II*f*, Table I) are now described. Compounds II*a*–II*f*, when examined for antiulcerogenic action by the modified Shay procedure (2), inhibited ulcer formation as much as 98%.

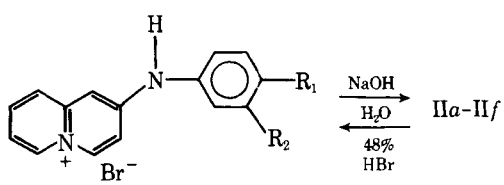
DISCUSSION

The syntheses of the intermediate compounds, I*a*–I*f*, were described previously (1–3). Their reaction with aqueous sodium hydroxide provided the phenylimino-2*H*-quinolizines (II*a*–II*f*) in high yield (Scheme I). Compounds II*a*–II*f* are the first reported examples of this class of compounds. The elemental analyses and IR and NMR spectra of II*a*–II*f* are consistent with the assigned structures.

For II*a* as an example, the IR spectrum showed strong absorption at 1640, 1560, and 1490 cm^{-1}. These absorptions are characteristic of all other phenylimino-2*H*-quinolizines as well.

The NMR spectral assignment of II*a* was made by use of homonuclear decoupling experiments. The NMR spectrum (dimethyl sulfoxide-d_6) of II*a* showed a *meta* split doublet at 6.22 ppm integrating for one proton, assigned to the proton at position 1. The proton at position 3 appeared as a split doublet (*ortho* and *meta* coupling) at 6.57 ppm. The proton at the 4-position of the quinolizine ring appeared as an *ortho* coupled doublet at 7.89 ppm. The proton at the 6-position appeared as a doublet at 7.85 ppm and showed *ortho* and *meta* splitting.

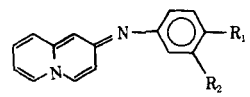
The proton at the 7-position of the quinolizine ring appeared as a split



I*a*–I*f*

Scheme I

Table I—Antiulcerogenic Evaluation and Physical and Analytical Data for New Compounds



Compound	R_1	R_2	Melting Point	Yield, %	Recrystallization Solvent	Formula		Analysis, % Calc.	Analysis, % Found	Gastric Antiulcerogenic Effect, Inhibition of Control Ulceration[a], %
IIa	Cl	Cl	153–155°	100	Ethyl acetate	$C_{15}H_{10}Cl_2N_2$	C	62.30	62.50	72 (n = 4)
							H	3.49	3.53	
							N	9.69	9.68	
IIb	Cl	H	183–184°	87	Ethanol–water	$C_{15}H_{11}ClN_2$	C	70.73	70.71	98 (n = 5)
							H	4.35	4.28	
							N	11.00	10.90	
IIc	H	CF_3	134–135°	97	Benzene–hexane	$C_{16}H_{11}F_3N_2$	C	66.66	66.79	30 (n = 5)
							H	3.85	3.89	
							N	9.72	9.58	
IId	H	Cl	97–100°	87	Ethanol–water	$C_{15}H_{11}ClN_2 \cdot 3/4\ H_2O$	C	67.16	67.27	48 (n = 5)
							H	4.70	4.80	
							N	10.45	10.30	
IIe	OCH_2CH_3	H	157–159°	100	Benzene–hexane	$C_{17}H_{16}N_2O$	C	77.25	77.23	74 (n = 5)
							H	6.10	5.96	
							N	10.60	10.49	
IIf	CH_3	CH_3	185–187°	89	Benzene–hexane	$C_{17}H_{16}N_2$	C	82.22	81.94	56[b] (n = 5)
							H	6.49	6.34	
							N	11.28	11.20	

[a] The nontreated control group consisted of 21 rats; n = number of rats per group. [b] The dose was 50 mg/kg po; all others were 150 mg/kg po.

triplet at 6.46 ppm with *ortho* and *meta* splitting. A pair of *ortho* split doublets, centered at 7.00 ppm and showing additional *meta* coupling, was assigned to the proton at the 8-position. An *ortho* coupled doublet with *meta* fine structure centered at 7.08 ppm was assigned to the proton at position 9. The protons of the dichloroaniline ring appeared as a *meta* coupled doublet at 6.98 ppm, which was assigned to the proton at the 2′-position. The proton at the 5′-position appeared as an *ortho* coupled doublet at 7.41 ppm, and the proton at the 6′-position appeared as an *ortho* split doublet with additional *meta* splitting.

The NMR spectra of the quinolizine compounds at 60 MHz were all similar and consistent with the assignment based on the decoupling experiments of IIa.

Reaction of the phenylimino-2*H*-quinolizines with 48% hydrobromic acid regenerated the corresponding quinolizinium bromides (Ia–If).

The antiulcerogenic activity of IIa–IIf was determined by use of a slightly modified procedure (1) of Shay *et al.* (4).

Male Sprague–Dawley rats[1], 175–250 g, were fasted 24 hr prior to the experiment; each was dosed with 150 mg of compound/kg po. It was necessary to lower the dose of IIf to 50 mg/kg po because of its toxicity at the higher dose. Ulcerogenesis in the rumen of the rat stomach was graded according to the following scale: 0, no ulceration; 0.5, gray discoloration and thinning of mucosa; 1, hemorrhagic spots; 2, hemorrhagic suffusion; 3, one to five small ulcers (<3 mm); 4, many small ulcers (or one marked ulcer); 5, many ulcers (marked size); and 6, perforated ulcer.

The degree of gastric ulceration in the presence of each compound was compared to the nontreated control and expressed as percent inhibition of control ulceration.

Compounds IIa, IIb, and IIe (Table I) caused marked inhibition of rumenal ulceration in the range of 72–98%. Less inhibition was elicited with IIc, IId, and IIf. The most active compound in inhibiting ulcer formation was IIb, the 4-chloro analog. There was a 50% reduction in antiulcerogenic action when the chlorine atom was in the 3-position. The dichloro-substituted compound (IIa) was somewhat less active than IIb, while the dimethyl-substituted compound (IIf) was not as effective as the 4-ethoxy derivative (IIe). In general, the compounds exerting the greatest inhibition were 3,4-disubstituted (IIa and IIf) or 4-monosubstituted (IIb and IIe). The 3-monosubstituted compounds (IIc and IId) were much less active.

[1] Charles River Breeding Laboratories.

EXPERIMENTAL[2]

A stirred suspension of 2-(3,4-dichloroanilino)quinolizinium bromide (Ia) (23 g, 0.062 mole) in water (1000 ml) was heated to 50°. To the aqueous mixture was added, in portions, a solution of 2 *N* NaOH (400 ml). The solution precipitated a yellow-orange product, and the aqueous mixture was warmed at 50° for 1 hr. After cooling and filtration, the air-dried product weighed 18 g (100%). Recrystallization from ethyl acetate provided analytically pure material (IIa), mp 153–155°; UV: λ_{max} 345 nm ($E^{1\%}_{1cm}$ 740) in 5% ethanol–water. Solubility in water was 180 mg/liter; pKa = 8.9.

All other 2-(substituted phenylimino)-2*H*-quinolizines (IIb–IIf) were prepared similarly. The analytical and physical data for all compounds are shown in Table I (5).

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[2] Melting points were determined in open capillary tubes using a Mel-Temp melting-point apparatus and are uncorrected. NMR spectra were obtained on a Varian A-60A instrument with tetramethylsilane as an internal standard. Peak assignments were based on homonuclear decoupling experiments performed on IIa using Bruker WH-270 at Bruker Instruments, Billerica, MA 01821. IR spectra were recorded on a Perkin-Elmer model 137 Infracord. UV spectra were determined on a Perkin-Elmer model 350 spectrophotometer.