2,3-Dihydro-4*H*-1-benzopyran-4-one *O*-Carbamoyloximes, a Series of Gastric Antisecretory Agents

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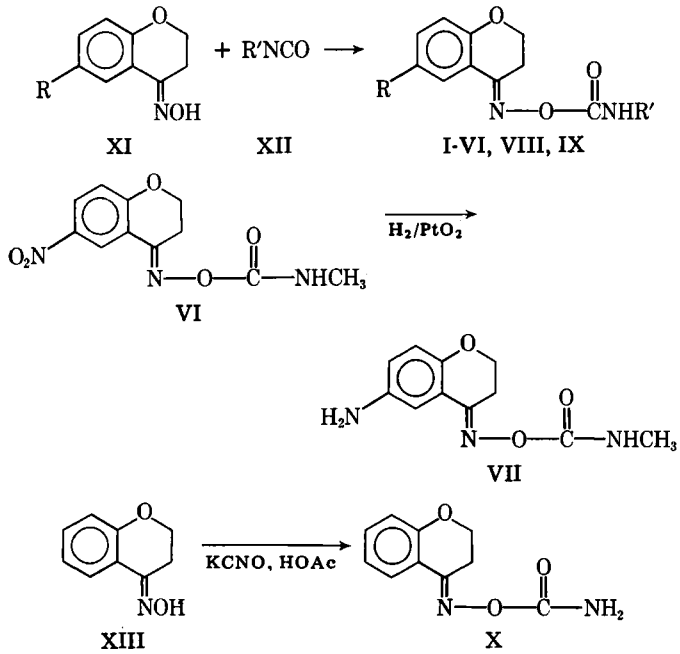
Abstract □ A series of 2,3-dihydro-4*H*-1-benzopyran-4-one *O*-carbamoyloximes were synthesized and evaluated for gastric antisecretory activity in a pylorus-ligated rat model. Various substituents in the 6-position did not afford any compounds more active than I.

Keyphrases □ 2,3-Dihydro-4*H*-1-benzopyran-4-one *O*-carbamoyloximes—synthesis, antisecretory activity, pylorus-ligated rats □ Antisecretory agents, gastric—potential, 2,3-dihydro-4*H*-1-benzopyran-4-one *O*-carbamoyloxime series, synthesis, evaluation in pylorus-ligated rats □ Synthesis—2,3-dihydro-4*H*-1-benzopyran-4-one *O*-carbamoyloxime series, gastric antisecretory activity, pylorus-ligated rats

To identify novel agents acting on the GI tract, 10 members of a series of 2,3-dihydro-4*H*-1-benzopyran-4-one *O*-carbamoyloximes were synthesized and evaluated for gastric antisecretory activity (1).

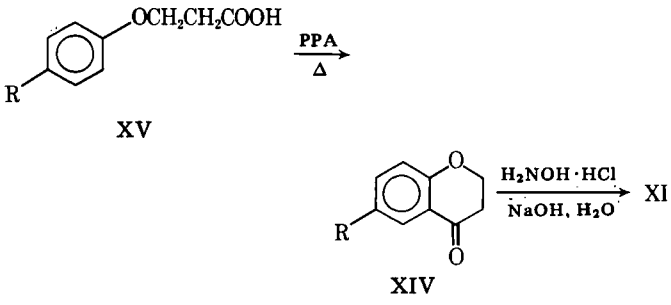
RESULTS AND DISCUSSION

Chemistry—Eight compounds (I–VI, VIII, and IX; Table I) were prepared by the reaction of the appropriate oxime XI with the isocyanate XII (Scheme I). The amine VII (Table I) was obtained by catalytic hydrogenation of the corresponding nitro compound VI (Table I, Scheme I), while acid-catalyzed reaction of XIII with potassium cyanate gave X (Scheme I).



Scheme I

The intermediate oximes XIa–d (Table II) were prepared from the corresponding 2,3-dihydro-4*H*-benzopyran-4-ones (XIV) (Scheme II), which were synthesized by ring closure of the corresponding 3-phenoxypropanoic acids (XV) with polyphosphoric acid, as described by Parham and Huestis (2).



Scheme II

Pharmacology—Compounds I–V and VII exhibited marked antagonism of total gastric acid output in pylorus-ligated rats. Compounds VIII–X showed moderate antagonism, while VI was inactive (Table III). Dose–response determinations of the 10 compounds revealed that I was most potent in inhibiting total gastric acid output as exemplified by a low ID_{50} value of 5.7 mg/kg p.o. Compounds II–V were also active in reducing gastric acid output with ID_{50} values of 22.1–22.7 mg/kg p.o. No evidence of toxicity was noted at their respective ID_{50} values.

EXPERIMENTAL[1]

Synthesis—*2,3-Dihydro-6-nitro-4*H*-1-benzopyran-4-one Oxime (XI d)*—To a solution of hydroxylamine hydrochloride (79 g, 1.14 moles) in water (770 ml) were added 10% NaOH (619 ml) and 2,3-dihydro-6-nitro-4*H*-benzopyran-4-one (150 g, 0.78 mole) (3, 4). Sufficient ethanol–ether (95:5) (750 ml) was added to give a solution at reflux. The mixture was refluxed for 25 min, cooled to 50° over 2 hr, and the resultant tan crystals were collected by filtration and washed with ethanol–ether (95:5) to give 60 g, mp 173–178°. Recrystallization from benzene gave material with a melting point of 185–186° in 27% yield.

*2,3-Dihydro-6-nitro-4*H*-1-benzopyran-4-one O-(Methylaminocarbonyl)oxime (VI)*—A mixture of XI d (19 g, 0.09 mole) and benzene was refluxed for 45 min in a flask equipped with a Dean Stark trap. Heating was discontinued and *N,N*-diethylethanamine (0.5 ml) was added, followed by a solution of methyl isocyanate (7.3 g, 0.10 mole) in benzene (30 ml). The mixture was refluxed for 3 hr and then stored at room temperature for 3 days. The material was collected by filtration, stirred in absolute ethanol (150 ml), and cooled overnight to give, after filtration, 16 g of VI.

An analytical sample was prepared by recrystallization from absolute ethanol (Table I); IR (mineral oil): 2.98 (NH) and 5.73 μm (C=O); ^{1}H-NMR: 2.80 (d, 3, CH_3, collapsed to singlet on exchange with D_2O), 3.10 and 4.45 (2 t, J = 6.4 Hz, 4, CH_2CH_2), 6.21 (d, J = 9.2 Hz, 1, aromatic), 7.27 (dd, $J_{5,7}$ = 2.7 Hz, $J_{7,8}$ = 9.2 Hz, 1, aromatic), 7.98 (d, J = 2.7 Hz, 1, aromatic), and 6.77 ppm (broad, 1, NH, exchanged with D_2O).

Similarly prepared were I–IV, VIII, and IX (Table I). In the case of V, filtration of the reaction mixture provided the product directly (Table I).

*6-Amino-2,3-dihydro-4*H*-1-benzopyran-4-one O-(Methylaminocarbonyl)oxime Hydrochloride (VII)*—A mixture of VI (4.0 g, 0.016 mole) and ethanol (400 ml) was shaken with hydrogen in the presence of platinum oxide (0.20 g) until the theoretical quantity of hydrogen was consumed (21 hr). The catalyst was removed by filtration, and the filtrate was cooled in an ice bath and treated with ethanolic hydrogen chloride.

[1] Melting points were determined on a Mel-Temp apparatus, and those below 230° were corrected. IR spectra were determined as Nujol mulls on a Perkin-Elmer 137B spectrophotometer, and NMR spectra were determined on a Varian A-60A spectrometer in dimethyl sulfoxide-d_6 with tetramethylsilane as an internal standard.

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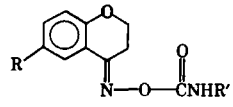
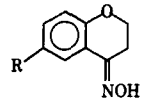
Table I—Physical and Analytical Data for 2,3-Dihydro-4*H*-1-benzopyran-4-one *O*-Carbamoyloximes



Compound	R	R′	Recrystallization Solvent	Melting Point	Yield, %	Formula	Elemental Analysis, % Calc.	Found
I	H	CH_3	2-propanol	125–126°	88	$C_{11}H_{12}N_2O_3$	C 59.99	59.76
							H 5.49	5.59
							N 12.72	12.69
II	CH_3O	C_2H_5	2-propanol	97–98°	83	$C_{13}H_{16}N_2O_4$	C 59.08	59.21
							H 6.10	6.16
							N 10.60	10.56
III	H	C_2H_5	2-propanol	110–111°	79	$C_{12}H_{14}N_2O_3$	C 61.53	61.44
							H 6.02	5.92
							N 11.96	11.98
IV	CH_3O	CH_3	2-propanol	119–120°	59	$C_{12}H_{14}N_2O_4$	C 57.59	57.55
							H 5.64	5.66
							N 11.20	11.20
V	Cl	CH_3	benzene	182–184	80	$C_{11}H_{11}ClN_2O_3$	C 51.68	51.50
							H 4.35	4.23
							N 11.00	10.80
VI	NO_2	CH_3	ethanol	204–207°	67	$C_{11}H_{11}N_3O_5$	C 49.81	49.80
							H 4.18	4.24
							N 15.85	15.65
VII	NH_2	CH_3	methanol	194–199°	58	$C_{11}H_{13}N_3O_3 \cdot HCl$	C 48.62	48.46
							H 5.19	5.18
							N 15.47	15.13
VIII	H	$CH_2CH{=}CH_2$	toluene	83–86°	73	$C_{13}H_{14}N_2O_3$	C 63.40	63.38
							H 5.73	5.81
							N 11.38	11.40
IX	H	$CH_2CH_2CH_3$	toluene	80–82°	68	$C_{13}H_{16}N_2O_3$	C 62.89	62.78
							H 6.50	6.67
							N 11.28	10.96
X	H	H	toluene	120–122°	44	$C_{10}H_{10}N_2O_3$	C 58.25	58.59
							H 4.89	4.77
							N 13.58	13.45

Table II—Physical and Analytical Data for 2,3-Dihydro-4*H*-1-benzopyran-4-one Oximes



Compound	R	Melting Point	Yield, %	IR, μm OH	^{1}H-NMR, ppm	Empirical Formula	Elemental Analysis, % Calc.	Found
XI a	H	140–142° (lit. 138°)[b]	97	3.10				
XI b	CH_3O	120–121° (lit. 120°)[b]	99	3.10				
XI c	Cl[a]	127–128°	55	3.15	2.85 and 4.25 (2 t, J = 6.4 Hz, 4, CH_2CH_2), 6.99 (d, J = 9.4 1, aromatic), 7.35 (dd, $J_{5,7}$ = 2,2 Hz, $J_{7,8}$ = 9.4 Hz, 1, aromatic), 7.78 (d, J = 2.2 Hz, 1, aromatic), 11.55 (s, 1, exchanged with D_2O)	$C_9H_8ClNO_2$	C 54.70	54.83
							H 4.08	4.06
							N 7.09	6.88
XI d	NO_2	185–186°	27	3.08	3.00 and 4.48 (2 t, J = 6.4 Hz, 4, CH_2CH_2), 7.30 (d, J = 9.4 Hz, 1, aromatic), 8.30 (dd, $J_{5,7}$ = 3.2 Hz, $J_{7,8}$ = 9.4 Hz, 1, aromatic), 8.77 (d, J = 3.2 Hz, 1, aromatic), 11.87 (s, 1, exchanged with D_2O)	$C_9H_8N_2O_4$	C 51.92	51.92
							H 3.87	3.79
							N 13.46	13.34

[a] For intermediate 6-chloro-2,3-dihydro-4*H*-1-benzopyran-4-one, see Ref. 3 and 4. [b] See Ref. 1.

The solution was concentrated to a volume of 70 ml and cooled. The product was removed by filtration. IR (mineral oil): 2.90 (NH_2) and 5.70 μm (C=O); ^{1}H-NMR: 2.73 (d, 3, CH_3, collapsed to singlet in D_2O), 3.00 and 4.30 (2 t, J = 6.4 Hz, 4, CH_2CH_2), 7.07 (d, J = 9.0 Hz, 1, aromatic), 7.48 (dd, $J_{5,7}$ = 2.7 Hz, $J_{7,8}$ = 8.8 Hz, 1, aromatic), 8.06 (d, J = 2.7 Hz, 1, aromatic), 7.7 (broad, 2, NH_2, exchanged with D_2O), and 6.82 ppm (broad, 2, NH and HCl).

*2,3-Dihydro-4*H*-1-benzopyran-4-one O-(Aminocarbonyl)oxime* (*X*)—To a solution of the oxime (XI a) (8.15 g, 0.05 mole) in glacial acetic acid (175 ml) at ambient temperature was added a solution of potassium cyanate (4.05 g, 0.05 mole) in water (20 ml). The solution was stirred at ambient temperature for 48 hr, diluted with 200 ml of water, and extracted with chloroform (2 × 150 ml). The combined extracts were dried (magnesium sulfate), concentrated to dryness *in vacuo*, and the residue was recrystallized from methylbenzene (40 ml) to give the product (Table I); IR (mineral oil): 2.83 and 2.90 (NH_2) and 5.67 μm (C=O); ^{1}H-NMR: 3.01 and 4.28 (2 t, J = 6.8 Hz, 4, CH_2CH_2), 7.27 (m, 4, aromatic and NH_2), and 8.22 ppm (d, J = 2.0 Hz, 2, aromatic).

Pharmacology—Male Sprague–Dawley rats, each weighing 180–210 g and previously fasted for 24 hr, were used in the modified, standard pylorus-ligated gastric secretory model. All compounds were given perorally, as suspensions in 0.5% methyl cellulose[2], 1 hr prior to pylorus

[2] Methocel.

Table III—Effect of Compounds I–X on Gastric Secretion in the Pylorus-Ligated Rat

	No. of Rats	Dose mg/kg p.o.	Volume of Gastric Secretions: ml/100 g Body Wt.	Volume of Gastric Secretions: Mean Percent of Control[b]	Total Gastric Acid Output: meq/100 g Body Wt.	Total Gastric Acid Output: Mean Percent of Control[b]	ID_{50}[c], mg/kg p.o. (95% Confidence Limits)
Control[a]	5		3.01 ± 0.79		0.18 ± 0.059		
I	3	50	1.99 ± 0.33	66	0.096 ± 0.028	53	5.7 (1.0–21.0)
Control[a]	5		3.44 ± 0.89		0.23 ± 0.076		
II	3	100	2.30 ± 0.50	67	0.097 ± 0.035	42	22.1 (11.7–37.0)
Control[a]	5		4.65 ± 0.71		0.31 ± 0.066		
III	3	100	1.78 ± 0.20	38	0.063 ± 0.0050	20	26.7 (19.2–31.0)
Control[a]	5		3.46 ± 0.60		0.21 ± 0.060		
IV	3	100	2.24 ± 0.63	65	0.12 ± 0.041	57	24.7 (19.2–31.0)
Control[a]	5		1.85 ± 0.62		0.095 ± 0.052		
V		100	0.83 ± 0.12	45	0.057 ± 0.012	60	25.9 (11.9–50.7)
Control[a]	5		5.00 ± 0.76		0.31 ± 0.083		
VI		100	4.07 ± 1.16	81	0.37 ± 0.12	121	—
Control[a]	5		5.00 ± 1.27		0.31 ± 0.083		
VII	3	100	1.78 ± 0.58	36	0.14 ± 0.064	45	>180
Control[a]	5		5.62 ± 0.18		0.61 ± 0.049		
VIII	3	100	1.34 ± 0.21	24	0.062 ± 0.010	10	57.4 (51.6–64.9)
IX	3	100	1.48 ± 0.29	26	0.073 ± 0.017	12	43.4 (24.4–111.3)
X	3	100	2.22 ± 0.055	39	0.014 ± 0.091	23	50.4 (30.1–127.1)

[a] The control values were obtained by peroral administration of 0.50% methylcellulose solution to a group of rats at 1 ml/100 g % body weight. [b] Compared to control (nondrug-treated) reading 4 hr after pylorus-ligation of rat stomach. [c] The dose eliciting 50% inhibition of total gastric acid output; calculated from data obtained at doses of 10, 30, and 100 mg/kg p.o., by method of linear regression analysis (5) of the dose–response curve.

ligation. Under light ether anesthesia, the rat stomach was ligated at the pylorus region. The conscious rat was sacrificed by a chloroform overdose 4 hr after ligation. The stomach was carefully excised and its contents drained into a centrifuge tube. Samples were centrifuged to separate secretions from debris, and gastric fluid volume was read and recorded. Titration was performed on a sample aliquot of 1 ml diluted to a volume of 5 ml using distilled water. The titrant used was 0.1 *N* NaOH. Acid concentration in the stomach was determined by titration to pH 7. Total gastric acid output was calculated as the product of volume of gastric secretions and acid concentration for each compound tested.

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Effect of Nutrient Depletion on the Sensitivity of *Pseudomonas cepacia* to Antimicrobial Agents

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Abstract □ *Pseudomonas cepacia* depleted of various nutrients showed marked variation in sensitivity to cetrimide, chlorhexidine, and benzalkonium chloride. In all cases cells depleted of magnesium were the most resistant. It is proposed that these observations may be due to alterations of the envelope of *P. cepacia* in response to changes in the growth environment. This may have profound implications for investigations of the resistance of this organism both *in vivo* and *in vitro*.

Keyphrases □ Nutrient depletion—effect of senstivity of *Pseudomonas cepacia* to antimicrobial agents □ Antimicrobial agents—effect of nutrient depletion on sensitivity of *Pseudomonas cepacia* □ *Pseudomonas cepacia*—effect of nutrient depletion on sensitivity to antimicrobial agents

Pseudomonas cepacia, previously considered as only a plant pathogen, has, in the last decade, been implicated in nosocomial infections with increasing frequency (1–3). The organism is more resistant to most useful antimicrobial agents than other Gram-negative bacteria. It is capable of survival and even multiplication in quaternary ammonium compounds (2, 4, 5) and will multiply in distilled or deionized water (6, 7).

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