benzoyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (12 g, 0.026 mole) and MeI (80 ml) was heated in a sealed vessel at 100° for 3 hr. The collected precipitate was recrystallized from MeOH–EtOAc to yield a yellow crystalline solid (13.3 g, 76%), mp 241–242° dec.

1-(4-Chlorobenzoyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XVI).—Raney nickel (2 g) was added to a solution of XV (10.0 g, 0.022 mole) in MeOH (1200 ml) and the mixture was hydrogenated at atmospheric pressure; uptake of H_2 essentially ceased after 1 hr with uptake of 1.3 molar equiv. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was treated with 6 *N* HCl to yield a yellow solid which was filtered off and partitioned between $CHCl_3$ and 6 *N* NH_4OH. The organic layer was separated and the aqueous layer was extracted several more times with $CHCl_3$. The combined organic layers were washed (saturated NaCl) and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded an amorphous material which was crystallized from MeOH to give a white crystalline solid (3.1 g, 43%), mp 115–117°.

1-(4-Chlorobenzoyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XIV).—$NaBH_4$ (5.5 g 0.15 mole) was added to a refluxing solution of XII (3.5 g, 0.011 mole) in MeOH (500 ml). Heating was continued for an additional hour; H_2O (200 ml) was added, and the mixture was concentrated to *ca.* 150 ml *in vacuo*. The aqueous solution was extracted with $CHCl_3$, washed (saturated NaCl), and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a viscous oil which was crystallized as the corresponding hydrochloride (2.4 g, 65%). An analytical sample, mp 225–227°, was obtained by recrystallization from methanol.

1-(4-Chloro-α-hydroxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (XVII).—A mixture of XV (3.0 g, 0.0066 mole), $NaBH_4$ (5.0 g, 0.14 mole), and MeOH (400 ml) was boiled at reflux for 90 min. H_2O was added and the mixture was concentrated *in vacuo* to *ca.* 50 ml. The residue was extracted with $CHCl_3$ which was washed with saturated NaCl solution and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a colorless oil which crystallized (1.29 g, 50%) on treatment with ethereal HCl. An analytical specimen was obtained by recrystallization from MeOH–EtOAc.

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Synthesis and Pharmacology of Some α-Keto-, α-Hydroxy-, and α-Amino-1-benzylisoquinolines

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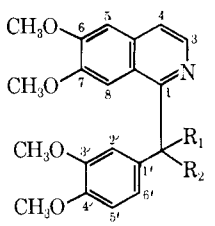
A number of α-keto, α-hydroxy, and α-amino-1-benzylisoquinolines related to papaveraldine and papaverinol have been prepared and examined pharmacologically. Testing covered dose-range studies in mice, examination for cardiovascular activity, and analgetic-antipyretic-antiedema studies. The pharmacological profile of the group, derivable from these data, is discussed.

The α-derivatized 1-benzylisoquinoline derivatives exemplified by papaveraldine (I), papaverinol (II), and papaverinylamine (III) are of general medicinal, chemical, and pharmacological interest because of their direct relationship to the clinically efficacious spasmolytic papaverine (IV). To date, however, there



I, $R_1R_2 = C{=}O$
II, $R_1 = OH$; $R_2 = H$
III, $R_1 = NH_2$; $R_2 = H$
IV, $R_1 = R_2 = H$

are only scattered reports of syntheses and biological testing in this area. Thus, 5′- and 6′-monomethylpapaveraldines,[1,2] as well as a number of variants in which one to four of the methoxyl groups have been replaced by methyl moieties, have been described.[3] In addition, the papaveraldine analogs having the 6,7- or 3′,4′-dimethoxy groups replaced by methylenedioxy,[4] the corresponding tetrahydroxy compound,[5] the 3′,4′,5,6-tetramethoxy isomer,[6] 6-bromopapaveraldine,[7] des-(tetramethoxy)papaveraldine (= 1-benzoylisoquinoline),[8] and several substituted 1-(4-pyridoyl)-6,7-dimethoxyisoquinolines[9] have been described. In the papaverinol series, only the 6-bromo[7] and the pyridoyl[9] analogs were prepared, and there is one publication devoted to synthesis of several α-amino compounds.[10]

On the biological side one finds only a few scattered observations in these series. Thus, papaveraldine and papaverinol are apparently in some respects biologically similar to papaverine, *i.e.*, they show activity against barium chloride and acetylcholine-induced spasm,[11] have protective action against histamine-induced bronchospasm,[12] but have little or no analgetic activity after oral administration in rats.[13,14] The corresponding 6′-bromo compounds as well as 6′-bromopapaverine are likewise antispasmodic at similar dosage levels.[7] Some other studies report the absence of any effect of papaveraldine on electrically stimulated laryngeal

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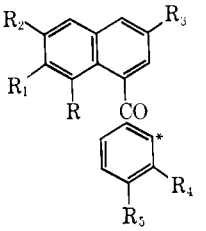
Table I[a]



No.	R	R1	R2	R3	R4	R5	Mp, °C	Formula[b]
1	H	OCH_2O		CH_3	H	H	135–137	$C_{18}H_{13}NO_3$
2	H	OCH_2O		CH_3	H	Cl	165–167	$C_{18}H_{12}ClNO_3$
3	H	OCH_2O		CH_3	H	OCH_3	138–140	$C_{19}H_{15}NO_4$
4	H	OCH_2O		CH_3	OCH_3	H	153–155	$C_{19}H_{15}NO_4$
5	H	OCH_2O		CH_3	OCH_3	OCH_3	189–191	$C_{20}H_{17}NO_5$
6	H	OCH_2O		H	H	H	142–144	$C_{17}H_{11}NO_3$
7	H	OCH_2O		H	H	Cl	160–162	$C_{17}H_{10}ClNO_3$
8	H	OCH_2O		H	H	OCH_3	158–159	$C_{18}H_{13}NO_4$
9	H	OCH_2O		H	OCH_3	H	126–127	$C_{18}H_{13}NO_4$
10	H	OCH_2O		H	OCH_3	OCH_3	211–212	$C_{19}H_{15}NO_5$
11	H	OCH_3	OCH_3	CH_3	H	H	140–142	$C_{19}H_{17}NO_3$
12	H	OCH_3	OCH_3	CH_3	H	Cl	185–188	$C_{19}H_{16}ClNO_3$
13	H	OCH_3	OCH_3	CH_3	H	OCH_3	135–137	$C_{20}H_{19}NO_4$
14	H	OCH_3	OCH_3	CH_3	OCH_3	H	164–166	$C_{20}H_{19}NO_4$
15	H	OCH_3	OCH_3	CH_3	OCH_3	OCH_3	155–157	$C_{21}H_{21}NO_5$
16	H	OCH_3	OCH_3	H	H	H	129–130	$C_{18}H_{15}NO_3$
17	H	OCH_3	OCH_3	H	H	Cl	161–162	$C_{18}H_{14}ClNO_3$
18	H	OCH_3	OCH_3	H	H	OCH_3	150–152	$C_{19}H_{17}NO_4$
19	H	OCH_3	OCH_3	H	OCH_3	H	160–162	$C_{19}H_{17}NO_4$
20	H	OCH_3	OCH_3	H	OCH_3	OCH_3	209–210	$C_{20}H_{19}NO_5$
21	H	OCH_2O		H	Cl	H	177–178	$C_{18}H_{12}ClNO_3$
22	H	H	OCH_3	H	H	Cl	125–126	$C_{17}H_{12}ClNO_2$
23	H	H	OCH_3	H	H	OCH_3	141–142	$C_{18}H_{15}NO_3$
24	H	H	OCH_3	H	OCH_3	H	123–124	$C_{18}H_{15}NO_3$
25	H	H	OCH_3	CH_3	H	H	144–145	$C_{18}H_{15}NO_2$
26	H	H	OCH_3	CH_3	H	Cl	117–119	$C_{18}H_{14}ClNO_2$
27	H	H	OCH_3	CH_3	H	OCH_3	114–116	$C_{19}H_{17}NO_3$
28	H	H	OCH_3	CH_3	OCH_3	H	93–95	$C_{19}H_{17}NO_3$
29	OCH_3	OCH_3	OCH_3	CH_3	H	H	133–134	$C_{20}H_{19}NO_4$
30	OCH_3	OCH_3	OCH_3	CH_3	H	Cl	122–124	$C_{20}H_{18}ClNO_4$
31	OCH_3	OCH_3	OCH_3	CH_3	H	OCH_3	133–134	$C_{21}H_{21}NO_5$
32	H	OCH_2O		CH_3	H	H, *CF_3	161–164	$C_{19}H_{12}F_3NO_3$
33	H	OCH_2O		CH_3	H	H, *CH_3	160–162	$C_{19}H_{15}NO_3$

[a] Yields obtained by treating the dihydrobenzoyl derivative with alcoholic base were usually in the 40–60% range. When these compounds were obtained directly from dihydrobenzyl derivatives with chromic acid, they were 10–25%. [b] All compounds were analyzed for C, H, N unless otherwise noted, and the analytical results obtained were within ±0.4% of the calculated values.

nerve cough reflex in cats[15] as well as the absence of anticonvulsant activity in the corresponding destetramethoxy compound.[8] No biological properties of the α-aminobenzyl series have been reported. Thus, it appears that to date there has been no systematic investigation of many of the biological parameters in the parent papaverine-derived series as well as an almost complete absence of any studies on related compounds.

As a result of an earlier study[16] in somewhat parallel series, a number of intermediates suitable for conversion to compounds of types I–III were available. These transformations were carried out by established techniques[3,4] as indicated in Scheme I to yield the compounds in Tables I–IV. The pharmacological profile of these substances is described below.

Pharmacology.—The series of α-keto-, α-hydroxy-, and α-amino-1-benzylisoquinolines was subjected to four basic screening procedures: the mouse dose range, an anesthetized-cat protocol for blood pressure effects, analgesia[17] and antipyretic activity in the rat, and edema-inhibiting[18] properties in the rat.

Ancillary pharmacological testing on some of the compounds was also carried out. It included measurement of blood glucose in fasted guinea pigs for hypoglycemic activity, inhibition of tonic extension in mice subjected to electroshock (25 mA, 0.2 sec),[19] inhibition of carrageenin-induced abscess formation,[20] inhibition of pleural fluid volume,[21] and diuretic activity

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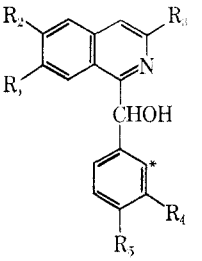
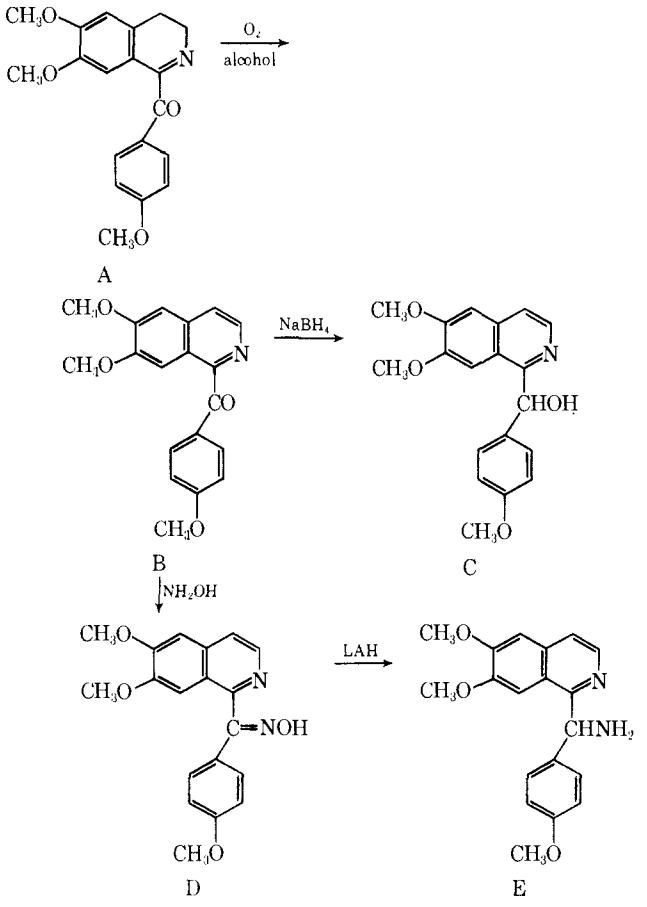
TABLE II



No.	R_2	R_3	R_4	R_5	R_6	Yield, %	Mp, °C	Formula[b]
34	OCH_2O		CH_3	H	Cl	35	169–170	$C_{18}H_{14}ClNO_3$
35	OCH_2O		CH_3	CH_3O	H	70	147–148	$C_{19}H_{17}NO_4$
36	OCH_2O		CH_3	CH_3O	CH_3O	64	140–141	$C_{20}H_{19}NO_5$
37	OCH_2O		H	H	H	50	167–169	$C_{17}H_{13}NO_3$
38	OCH_2O		H	H	Cl	48	145–146	$C_{17}H_{12}ClNO_3$
39	OCH_2O		H	H	CH_3O	67	121–123	$C_{18}H_{15}NO_4$
40	CH_3O	CH_3O	CH_3	H	H	90	144–145	$C_{19}H_{19}NO_3$
41	CH_3O	CH_3O	CH_3	H	Cl	34	159–161	$C_{19}H_{18}ClNO_3$
42	CH_3O	CH_3O	CH_3	H	CH_3O	77	137–138	$C_{20}H_{21}NO_4$
43	CH_3O	CH_3O	CH_3	CH_3O	H	87	127–129	$C_{20}H_{21}NO_4$
44	CH_3O	CH_3O	CH_3	CH_3O	CH_3O	72	149–150	$C_{21}H_{23}NO_5$
45	CH_3O	CH_3O	H	H	Cl	63	157–159	$C_{18}H_{16}ClNO_4$
46	CH_3O	CH_3O	H	H	CH_3O	87	145–146	$C_{19}H_{19}NO_4$
47	CH_3O	CH_3O	H	CH_3O	CH_3O	90	137–139	$C_{20}H_{21}NO_5$
48	OCH_2O		CH_3	H	H, *OCH_3	67	152–154	$C_{19}H_{17}NO_4$
49	H	CH_3O	H	H	Cl	50	142–143	$C_{17}H_{14}ClNO_2$
50	H	CH_3O	H	H	CH_3O	62	114–115	$C_{18}H_{17}NO_3$
51	OCH_2O		CH_3	Cl	H	65	146–147	$C_{18}H_{14}ClNO_3$
52	H	CH_3O	CH_3	H	Cl	55	123–125	$C_{18}H_{16}ClNO_2$
53	H	CH_3O	CH_3	H	CH_3O	83	147–148	$C_{19}H_{19}NO_3$
54	H	CH_3O	CH_3	CH_3O	H	80	219–220 dec[a]	$C_{19}H_{20}ClNO_3$

[a] HCl salt. [b] See footnote *b*, Table I.

SCHEME I



as measured by an increase in urine volume excretion in saline-loaded rats.

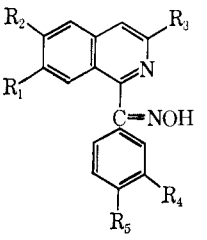
Discussion of Results

The majority of compounds tested in the mouse failed to produce overt side effects following administration of 300 mg/kg *po* (Table V). Only four compounds produced observable effects. They consisted mainly of decreased motor activity, low body posture, and, in several instances, dyspnea, tremors, or convulsions. Considering the high dose necessary to cause these effects (300 mg/kg *po*), the benzylisoquinolines appear to be relatively nontoxic substances. Only one compound (**63**) produced mild CNS stimulation.

Cardiovascular studies on various compounds yielded fairly uniform results (Table VI). Hypotension was generally transient at lower dose levels (0.5–5.0 mg/kg iv). Prolonged depressor effects often occurred after larger doses (5.0–10 mg/kg). Concurrent with the marked blood pressure lowering, there was also respiratory depression or cardiac slowing and arrest. Compounds **58** and **67** inhibited or reversed the pressor response to epinephrine and appeared to be adrenergic blocking agents. Compounds **61**, **63**, and **68** exhibited antihistaminic activity, while **61** also displayed weak parasympatholytic activity.

As shown in Table VII, a number of the benzylisoquinoline derivatives exhibited weak but significant analgetic and antipyretic activity. However, none of the compounds was as effective as phenylbutazone. Phenylbutazone was effective at approximately 30

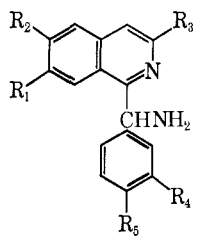
Table III



No.	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula[a]
55	OCH_2O		CH_3	CH_3O	H	65	196–197	$C_{19}H_{16}N_2O_4$
56	OCH_2O		CH_3	CH_3O	CH_3O	81	244–246	$C_{20}H_{18}N_2O_5$
57	CH_3O	CH_3O	H	H	CH_3O	80	229–231 dec	$C_{19}H_{18}N_2O_4$
58	CH_3O	CH_3O	H	CH_3O	CH_3O	90	256–257 dec	$C_{20}H_{20}N_2O_5$
59	H	CH_3O	CH_3	CH_3O	H	95	175–176	$C_{19}H_{18}N_2O_3$
60	CH_3O	CH_3O	CH_3	H	CH_3O	72	205–206	$C_{20}H_{20}N_2O_4$
61	CH_3O	CH_3O	CH_3	CH_3O	H	99	217–219	$C_{20}H_{20}N_2O_4$

[a] See Table I, footnote *b*.

Table IV



No.	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp,[a] °C	Formula[c]
62	OCH_2O		CH_3	OCH_3	H	32	233–235	$C_{19}H_{20}Cl_2N_2O_3$
63	OCH_2O		CH_3	OCH_3	OCH_3	58	223–225	$C_{20}H_{22}Cl_2N_2O_4$
64	OCH_3	OCH_3	H	H	OCH_3	35	219–220	$C_{19}H_{22}Cl_2N_2O_3$
65	OCH_3	OCH_3	H	OCH_3	OCH_3	48	212–214	$C_{20}H_{24}Cl_2N_2O_4$
66	H	OCH_3	CH_3	OCH_3	H	30	212–214	$C_{19}H_{22}Cl_2N_2O_2$
67	OCH_3	OCH_3	CH_3	H	OCH_3	28	223–224	$C_{20}H_{24}Cl_2N_2O_5$[b]
68	OCH_3	OCH_3	CH_3	OCH_3	H	42	217–218	$C_{20}H_{24}Cl_2N_2O_3$

[a] Recrystallized from MeOH–EtAc; decomposition points of the dihydrochloride salt. [b] $\cdot 0.5CH_3OH$. [c] See Table I, footnote *b*.

Table V

Summary of Pharmacological Activity in Dose-Range Studies in Mice

No.	Dose, mg/kg *po*	Observations
4, 5, 17, 38, 39, 45–47, 49, 50, 57, 58, 61, 62, 65, 67, 68	300	NOE[a]
37	300	Ataxia, hypothermia, loss righting reflex, loss corneal reflex, hypotonia, dyspnea
	75	Sl ↓ SMA,[b] dyspnea, lacrimation
63	300	Sl ↑ activity
	200	NOE
64	300	1/2 low body posture, 1/2 ↓ SMA, 1/2 intention tremors
66	300	↑ activity, convulsions, ataxia, mydriasis, exophthalmos, hypothermia
	200	Sl depression, low posture, dyspnea
	100	NOE

[a] No overt effects. [b] Spontaneous motor activity.

mg/kg *po* as an analgetic and antipyretic agent in control studies. Compounds **46**, **58**, and **68** exhibited the greatest degree of analgesia in this test procedure, whereas **62**, **63**, and **68** were the most potent in the reduction of skin temperature. Furthermore, Table VIII shows the summarized results on compounds which were tested for their effects against edema produced by carrageenin injected into the plantar surface of the hind foot of the rat. Compounds **8**, **23**, **45**, and **67** significantly reduced edema. In this test procedure, phenylbutazone exhibited an ED_{50} of 25 mg/kg *po* and is, therefore, significantly more potent than any of the benzylisoquinolines tested. It is of interest to note that one compound, *i.e.*, **58**, potentiated edema volume. Some of the compounds were also tested for hypoglycemic, anticonvulsant, antiinflammatory (inhibition of carrageenin abscess, pleural fluid volume), or diuretic activity but, for the most part, they were inactive. Only compound **67** showed significant inhibition of the carrageenin abscess test; however, this agent had an adrenergic blocking action in the anesthetized cat by reversing the pressor response to intravenously administered epinephrine. It may be speculated that this compound might cause peripheral vasodilation by virture of its adrenergic blocking action which could conceivably inhibit or relieve edema formation in the rat paw. This would produce a false positive antiinflammatory action in this test. Compounds **63** and **68** exhibited weak activity in inhibiting pleural fluid volume. The former was inactive in reducing foot edema produced by carrageenin, whereas **68**, which also

TABLE VI

SUMMARY OF ACTIVITY IN CARDIOVASCULAR STUDIES

No.	Dose, mg/kg iv	Result
37	0.5–10.0	Transient depressor
38	0.5–2.5	Transient depressor
	5.0	Lethal from respiratory paralysis
45	0.5–10	Transient depressor
46	0.5–5.0	Transient depressor
	10	Marked transient depressor
47	0.5–5.0	Transient depressor
	10.0	Marked prolonged depressor
49	0.5–10.0	Transient depressor
50	0.5, 2.5	Transient depressor
	5.0	Prolonged depressor
	10.0	Prolonged depressor, transient apnea
57	0.5–10.0	Transient depressor
58	0.5–5.0	Transient depressor
	10.0	Mod depressor, epinephrine inhibited
61	0.5, 1.0	Sl transient pressor
	2.5–10	Mod prolonged depressor, DMPP augmented, histamine and "Furmethide" inhibited
	0.5–10	No alteration of blood pressure or autonomic standards in anesthetized dog; histamine response unaltered
62	2.5	Marked transient depressor
	5.0	Lethal, cardiac arrest
63	1.0–2.5	Transient depressor
	5.0	Lethal, cardiac arrest, histamine response slightly reduced
64	0.5–2.5	Sl transient depressor
	5.0	Marked depressor, heart shows extrasystoles, bradypnea
65	0.5–2.5	Sl to mod depressor
	5.0	Marked depressor, heart beat erratic
	10	Lethal, cardiac arrest
66	0.5–2.5	Sl transient to mod prolonged depressor
	5.0	Lethal due to cardiac and respiratory arrest
67	1.0, 2.5	Sl transient depressor, epinephrine response reversed, norepinephrine pressor response inhibited
	10	Lethal due to cardiac arrest
68	2.5	Moderate depressor, histamine depressor response slightly inhibited
	5.0	Lethal, cardiac arrest

TABLE VII

SUMMARY OF ANALGETIC AND ANTIPYRETIC STUDIES[17]

No.	Dose, mg/kg *po*	% of animals showing positive response	
		Analgesia	Antipyresis
4, 5	100	0	0
17	200	30	40
37	100	30	10
38	100	20	10
39	100	20	0
45	100	40	0
46	100	50	0
47	100	30	0
49	100	10	20
50	100	20	10
57	100	10	0
58	100	70	20
	50	30	0
61	100	10	20
62, 63	100	40	80
64	100	30	40
65	100	40	20
66	100	20	10
67	100	30	40
68	100	50	60

TABLE VIII

SUMMARY OF ANTIEDEMA STUDIES[18]

No.	Dose, mg/kg *po*	Significant reduction in foot vol
8, 23, 45, 67	25	Yes
2, 9, 10, 12–16, 10–22, 28, 29, 31, 32, 35, 37–40, 43, 44, 47, 48, 50, 51, 53, 61, 63, 64, 66	25	No
58	25	Increases edema
	100	Increases edema

had weak antihistaminic activity, was not sufficiently interesting to warrant further testing.

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