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Comparative Pharmacology of Some Thiomorpholine Derivatives.

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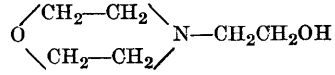
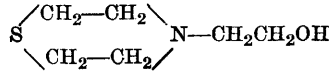
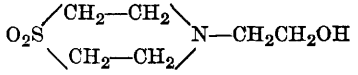
Gardner and Haenni[1] described a series of compounds containing the morpholine rings, which they claimed exhibited some local anesthetic activity. The general structure of their compounds is expressed by the formula,



Burrows,[2] under the direction of Professor E. Emmet Reid in the Laboratory for Organic Chemistry, Johns Hopkins University, prepared 2 series of analogous compounds, which the writer had the privilege of investigating pharmacologically. One series was composed of thiomorpholines. The first of these, labelled No. 0, is thiomorpholine ethanol and has the following structure,



In addition, 7 esters were prepared from this alcohol, namely, the acetate, propionate, butyrate, valerate, caproate, heptoate and benzoate. In this paper these are labelled Nos. 1 to 7, respectively. A second series of compounds, analogous to the thiomorpholines and containing 2 oxygen atoms attached to the sulphur, was also prepared. These may be termed sulphoxy-thiomorpholines, the first member of the series, sulphoxy-thiomorpholine ethanol, being labelled No. Ox; and the 7 other members, esters similar to those of the thiomorpholines, being labelled 1x to 7x, respectively. The structure of the first member of this series is as follows:



The action of aqueous solutions of these 2 series of compounds was studied on living seedlings of *Lupinus albus,* on tadpoles of *Rana pipiens,* on goldfish, *Carassius auratus,* and on cats under ether anesthesia.

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[1] Gardner and Haenni, *J. Am. Chem. Soc.*, 1931, **53**, 2763.

[2] Burrows and Reid, in press.

Effect on Plants. Seedlings of *Lupinus albus* were grown in plant-physiological solutions containing the drugs in concentrations of 1:500. The effect is shown in Table I. Both series of compounds inhibited the growth of the plants, the least toxic being Nos. O and Ox. The sulphoxy-thiomorpholines were in every case more toxic than the plain thiomorpholine compounds.

TABLE I.
Effect of thiomorpholine derivatives on growth of lupinus albus seedlings.

Thiomorpholine S 1:500 Concentration of	Phytotoxic Index	Thiomorpholine SO_2 1:500 Concentration of	Phytotoxic Index
Compound No. 0	87%	Compound No. 0x	59%
" " 1	77%	" " 1x	28%
" " 2	75%	" " 2x	38%
" " 3	64%	" " 3x	29%
" " 4	69%	" " 4x	33%
" " 5	51%	" " 5x	27%
" " 6	23%	" " 6x	21%
" " 7	59%	" " 7x	28%

Effect on Tadpoles. Tadpoles of *Rana pipiens,* 4 weeks old, were placed in solutions of the drugs, 1:1,000 and 1:500. The results obtained in the weaker solution were as follows:

	Tadpoles in Solution 1:1,000							
Thiomorpholine	No. 0	1	2	3	4	5	6	7
Killing time, hrs.	48	24	15	12	10	4½	3½	15

The toxicity increased progressively from compound 0 to ester 6. Compound 7, or the benzoic acid ester, however, was less toxic than some other aliphatic esters.

Toxicity for Goldfish. Small goldfish, 2 in. long, were placed in solutions of 1:250 of both series of compounds. Time of onset of muscular incoordination, indicated by floating on the side, and the time required to effect respiratory paralysis were both noted. The results are exhibited in Table II. Here again the esters were pro-

TABLE II.
Goldfish (Carassius Auratus) in solution 1:250

Thiomorpholine	0	1	2	3	4	5	6	7
Floating on side in	2 hr.	37 min.	39 min.	20 min.	9 min.	5 min.	4 min.	2 min.
Respiration paralyzed in	24 "	64 "	73 "	30 "	25 "	18 "	9 "	4 "
Sulphoxy-Thiomorpholine	0x	1x	2x	3x	4x	5x	6x	7x
Floating on side in	12 min.	4 min.	3 min.	13 min.	7 min.	3 min.	2 min.	4 min.
Respiration paralyzed in	24 "	13 "	16 "	22 "	14 "	10 "	5 "	7 "

gressively more toxic than the mother substance, or thiomorpholine ethanol. The sulphoxy compounds were all more toxic than the plain thiomorpholine compounds.

Anesthetic Effect. Solutions of both series of compounds varying from 0.1 to 1.0%, were tested for local anesthetic action on rabbits' eyes and frogskin. Contrary to the results obtained by Gardner and Haenni with morpholines, it was found that the thiomorpholines had very little local anesthetic effect, the only one producing definite local anesthesia being compound No. 7, or the benzoic acid ester. One per cent solutions of this ester, applied to the rabbit's eye, produce local anesthesia lasting from 5 to 10 minutes. None of the sulphoxy-thiomorpholines was found to produce any local anesthetic action.

Experiments on Blood Pressure and Respiration. Experiments were made with intravenous injections of the aqueous solutions of thiomorpholines in cats kept under ether anesthesia. When injected in doses of from 10 to 15 mg. per kg. weight of cat, it was found that all the compounds produced an immediate fall in blood pressure and a slight inhibition of the respiration. The depressant action on the blood pressure increased progressively from compound 0 to compound 7. This depressant effect was of short duration, however, and the circulation became normal after the lapse of a few minutes. The most depressant action on the respiration was exerted by compound 7. The sulphoxy-thiomorpholines acted in much the same way but were slightly more toxic.

Summary. 1. The pharmacology of thiomorpholine ethanol and 7 esters thereof was compared with that of sulphoxy-thiomorpholine ethanol and 7 esters thereof in respect to local anesthetic effect, toxicity and action on blood pressure and respiration. 2. Only the benzoic ester of thiomorpholine-ethanol showed any appreciable local anesthetic effect, and none of the sulphoxy-thiomorpholine compounds revealed any definite local anesthetic action. 3. The toxicity of both series of compounds is not very great but the sulphoxy-thiomorpholine derivatives are in general more toxic than the thiomorpholine derivatives.