Table I

	Initial Assay, Per Cent	Storage Conditions	Reassays after Storage, Per Cent ½ Mo.	1½ Mo.	13½ Mo.	25½ Mo.
U. S. P. XI method	1.01	Room temp.	1.02	1.01	0.92	0.86
		105° F.	..	1.04	0.83	..
Experimental method	1.03	Room temp.	1.02	1.01	1.02	1.00
		105° F.	..	1.01	1.00	..

(90%), 5 parts. The resulting clear solution is treated with a rapid stream of hydrogen sulfide gas to precipitate the mercury; precipitation is complete within 10 minutes and the mercuric sulfide settles quickly in a granular form. Warm the beaker and its contents to about 50° C. Collect the mercuric sulfide on a dried, weighed, asbestos-prepared Gooch crucible using a filter pump. Rinse the hydrogen sulfide inlet tube, the beaker and the precipitate on the Gooch with hot benzene and then with a little alcohol. Any particles of mercuric sulfide adhering to the walls of the beaker are removed and transferred to the filter by a final rinse with warm water. Dry the precipitate to constant weight at 120° C. and weigh accurately (within 0.0005 Gm.). The weight of mercuric sulfide found multiplied by 0.9310 equals the weight of mercuric oxide.

DISCUSSION

The results are shown in Table I.

This tabulation shows clearly that after a period of approximately a year the U. S. P. XI method does not determine all of the mercury.

In addition it may be noted here that the experimental method offers greater ease of manipulation. There is some difficulty encountered in the U. S. P. XI method at the very beginning where the 10-Gm. sample has to be introduced into a separatory funnel and then mixed with the ether. Later after the hydrochloric acid and water have been added, vigorous shaking is directed to dissolve the mercuric oxide. This, in our hands, has resulted in emulsions which sometimes resist separation and, instead, forms a gelatinous intermediate layer interfering with the subsequent filtration and making the washing and draining long and tedious.

CONCLUSION

The modified assay method described herein measures the total mercury content of Ointment Mercury Oxide Yellow, U. S. P. XI, even after aging and even though some of the mercury oxide has undergone change to form something in which the mercury is in a different state of combination. It is superior to the U. S. P. XI method in speed and simplicity.

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Preliminary Antispasmodic Tests of a Series of Morpholino and Some Other Compounds*

By L. W. Rowe†

For more than two years a group of morpholino and some other compounds, which were synthesized by research chemists in our laboratories (1), have been subjected to preliminary pharmacological tests in an effort to select a very limited number of the most promising for more thorough investigation. The results of the detailed study on a more limited number of compounds will be reported later by another group (2).

The method used for determining relative antispasmodic action was that of Magnus (3, 4) in which excised intestinal strips from guinea pigs or rabbits were suspended in warm, oxygenated Locke-Ringer Solution and exposed alternately to definite concentrations of the unknowns and of

* Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

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papaverine hydrochloride or diphenylacetyl-diethyl-aminoethanol hydrochloride (Trasentin) which were both used as controls. The comparative relaxing action was determined directly on the same and different strips. Some work was done with the antagonistic effect against barium chloride but this will not be included in the report.

The relative toxicity was determined upon white mice dosed intraperitoneally by finding the amount of each compound in milligrams per gram which would produce a 60% mortality.

In the first table only the morpholino compounds will be given, together with the short symbol by which they will be referred to later and their toxicity to white mice.

In the second table compounds other than morpholines together with the short symbol by which they will be referred to and their toxicity to white mice are listed.

Table I

	Compound	Symbol	M. L. D., Mg. per Gm.
1.	*N*-β-Morpholine-ethyl diphenylchloroacetamide HCl	S-2	0.50
2.	β-4-Morpholine-ethyl diphenylacetate HCl	S-5	0.80
3.	Diphenyl acetic acid β-morpholine-ethyl amide HCl	S-6	0.30
4.	β-4-Morpholine-ethyl cinnamate HCl	S-8	1.50
5.	γ-4-Morpholine-propyl diphenylacetate HCl	S-9	0.35
6.	β-4-Morpholine-ethyl benzilate HCl	S-10	0.30
7.	ε-4-Morpholine-butyl diphenylacetate HCl	S-11	0.30
8.	β-Methyl-β-4-morpholine-propyldiphenylacetate HCl	S-12	0.70
9.	β-4-Morpholine-ethyl triphenylacetate HCl	S-13	0.40
10.	β-4-Morpholine-ethyl diphenylchloroacetate HCl	S-14	0.20
11.	γ-4-Morpholine-propyl diphenylacetate bromobenzylate	S-15	0.04
12.	β-4-Morpholine-ethyl dibenzylacetate HCl	S-16	0.60
13.	γ-Methyl-β-4-morpholine-ethyl diphenylacetate HCl	S-17	0.10
14.	β-4-Morpholine-ethyl cyclohexane carboxylate HCl	S-18	2.50
15.	β-Methyl-β-4-morpholine-1-propanol	S-20	0.70
16.	β-4-Morpholine-ethyl tertiary butylacetate HCl	S-22	1.0
17.	β-4-Morpholine-ethyl trimethylacetate sulfate	S-23	1.25
18.	β-4-Morpholine-ethyl phenylacetate HCl	S-24	1.50
19.	β-4-Morpholine-ethyl diphenyl propionate HCl	S-25	0.50
20.	β-4-Morpholine-ethyl-2-camphane carboxylate HCl	S-26	0.35
21.	Dimethyl-4-morpholine-propyl diphenylacetate HCl	S-28	1.20
22.	4-Morpholine-*N*-hexyl diphenylacetate HCl	S-29	0.40
23.	β-4-Morpholine-ethyl diphenylacetate HBr	S-30	0.80
24.	β-4-Morpholine-ethyl *N,N*-diphenylcarbamate HCl	S-32	0.35
25.	β-4-Morpholine-ethyl phenylcyclohexaneacetate HCl	S-35	0.40
26.	Phenylcyclohexaneacetate acid β-4-Morpholine ethylamide HCl	S-36	0.30
27.	Dimethyl-4-morpholine-propyl phenylcyclohexaneacetate HCl	S-37	0.50
28.	β-4-Morpholine-ethyl acetoxydiphenylacetate HCl	S-38	0.30
29.	Dimethyl-4-morpholine-propyl diphenylacetate sulfate	S-39	1.0
30.	Dimethyl-4-morpholine-propyl diphenylacetate benzyl hydrobromide	S-40	1.1
31.	Dimethyl-4-morpholine-propylbenzaote HCl	S-41	0.9
32.	Dimethyl-4-morpholine-propylcinnamate HCl	S-42	1.0

Table II

	Compound	Formula	Symbol	M. L. D., Mg. per Gm.
1.	Papaverine HCl	$C_{20}H_{21}O_4N.HCl$	Papaverine	0.15
2.	Diphenylacetyl-diethylaminoethanol HCl	$C_{20}H_{23}O_2N.HCl$	Trasentin	0.35
3.	Sodium diphenyl hydantoinate	$C_{15}H_{11}O_2N_2.Na$	Dilantin	0.15
4.	β-Diethylaminoethyl benzilate HCl	$C_{20}H_{25}O_3N.HCl$	S-1	0.10
5.	β-Diethylaminoethyl diphenylchloroacetate HCl	$C_{20}H_{24}O_2NCl.HCl$	S-3	0.18
6.	γ-Diethylaminopropyl diphenylchloroacetate HCl	$C_{21}H_{26}O_2NCl.HCl$	S-4	0.06
7.	*N*-Methyl cyclohexylamine HCl	$C_7H_{15}N.HCl$	S-7	0.40
8.	Diethylamino-hydroxy propyl diphenylacetate HCl	$C_{21}H_{27}O_3N.HCl$	S-27	0.18
9.	Dimethyl butyrylamino-pyridine HCl	$C_{11}H_{16}ON_2.HCl$	S-31	0.60
10.	β-Diphenyl acetamino-pyridine HCl	$C_{19}H_{16}ON_2.HCl$	S-33	0.40
11.	β-Ethyl phenylamino-ethyldiphenylacetate HCl	$C_{24}H_{25}O_2N.HCl$	S-34	0.40
12.	Methyl phenylpiperidine carbonic acid ethyl ester	$C_{15}H_{21}O_2N$	S-140	1.75

Table III.

Compound	Antispasmodic Activity, Per Cent of Papaverine	Effective Dilutions
1. S-2	50	1- 25,000 to 1- 50,000
2. S-5	75	1- 35,000 to 1- 75,000
3. S-6	20	1- 10,000 to 1- 20,000
4. S-8	40	1- 20,000 to 1- 40,000
5. S-9	75	1- 35,000 to 1- 75,000
6. S-10	25	1- 12,500 to 1- 25,000
7. S-11	60	1- 30,000 to 1- 60,000
8. S-12	60	1- 30,000 to 1- 60,000
9. S-13	25	1- 12,500 to 1- 25,000
10. S-14	75	1- 35,000 to 1- 75,000
11. S-15	50	1- 25,000 to 1- 50,000
12. S-16	60	1- 30,000 to 1- 60,000
13. S-17	60	1- 30,000 to 1- 60,000
14. S-18	10–20	1- 5,000 to 1- 20,000
15. S-20	5–10	1- 2,500 to 1- 10,000
16. S-22	5–10	1- 2,500 to 1- 10,000
17. S-23	5	1- 2,500 to 1- 5,000
18. S-24	10	1- 5,000 to 1- 10,000
19. S-25	50	1- 25,000 to 1- 50,000
20. S-26	60	1- 30,000 to 1- 60,000
21. S-28	200	1-100,000 to 1-200,000
22. S-29	150	1- 75,000 to 1-150,000
23. S-30	40	1- 20,000 to 1- 40,000
24. S-32	30	1- 15,000 to 1- 30,000
25. S-35	100	1- 50,000 to 1-100,000
26. S-36	50	1- 25,000 to 1- 50,000
27. S-37	10	1- 5,000 to 1- 10,000
28. S-38	25	1- 12,500 to 1- 25,000
29. S-39	200	1-100,000 to 1-200,000
30. S-40	100	1- 50,000 to 1-100,000
31. S-41	40	1- 20,000 to 1- 40,000
32. S-42	40	1- 20,000 to 1- 40,000

Table IV

Compound	Antispasmodic Activity, Per Cent of Papaverine	Effective Dilution
1. Papaverine	100	1-50,000 to 1-100,000
2. Trasentin	100	1-50,000 to 1-100,000
3. Dilantin	25	1-12,500 to 1- 25,000
4. S-1	50	1-25,000 to 1- 50,000
5. S-3	50	1-25,000 to 1- 50,000
6. S-4	75	1-35,000 to 1- 75,000
7. S-7	10	1- 5,000 to 1- 10,000
8. S-27	30	1-15,000 to 1- 30,000
9. S-31	20	1-10,000 to 1- 20,000
10. S-33	10	1- 5,000 to 1- 10,000
11. S-34	10	1- 5,000 to 1- 10,000
12. S-140	5	1- 2,500 to 1- 5,000

In Tables III and IV the relative antispasmodic activity of the compounds listed in Tables I and II, respectively, are given in terms of papaverine hydrochloride as the control or 100%. In most instances these percentages are the averages of several days' comparisons on a series of five or six intestinal strips each day. After each strip was subjected to a definite dilution of the drug until the maximum action of the dose was reached, the solution was withdrawn and fresh, warm Locke-Ringer Solution was added. The variation in dilution noted in the table was that used on different strips and on different days.

DISCUSSION

In the entire series S-28 and S-39 show up best and these are merely different salts of the same compound. Their activity by the Magnus method is fully twice that of papaverine hydrochloride and their toxicity is only about one-eighth or 12.5% as great. S-29, S-35 and S-40 are also quite active, but in the case of the first two the toxicities are somewhat nearer that of papaverine. Then there is a group of four compounds S-4, S-5, S-9 and S-14 whose activities are about three-fourths that of papaverine, but only S-5 of this group has a low toxicity.

Dilantin which is primarily a good anticonvulsant, is shown to have a rather weak antispasmodic action by the method used, namely, about 25% that of papaverine.

SUMMARY

1. One morpholine compound, dimethyl-4-morpholine propyl diphenylacetate, was found to be the most promising in the preliminary tests of a series of 32 experimental morpholine preparations.

2. Several others were found to be fully as good as papaverine but not as active as S-28.

3. Dilantin showed a definite but relatively weak antispasmodic action.

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