CONCLUSION.

1. An accurate method has been developed for the assay of theophylline, which is considerably less involved than the method described in the U. S. P. XI.

2. Its applicability to the assay of Theophylline Monoethanolamine and Theophylline with Ethylene Diamine has been demonstrated.

3. Evidence is presented to show that the method described gives accurate results in the presence of monoethanolamine, ethylene diamine and starch.

The authors wish to express their appreciation to Dr. Edward J. Hughes for his friendly criticisms and advice.

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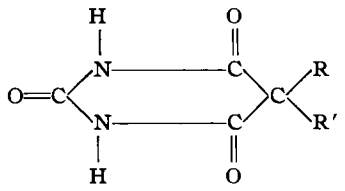
2-METHYL-ALLYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.*

BY EDWARD E. SWANSON AND WILLIAM E. FRY.[1]

As previously observed (1), there is a distinct relationship between the pharmacological action and chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds, with an increasing number of C-atoms in the alkyl substituted group, both the minimal anesthetic dose (M. A. D.) and the minimal lethal dose (M. L. D.) become relatively smaller, but when the alkyl radical is longer than 5 C-atoms, the amount required to produce anesthesia or death in rats again increases. Furthermore, as the alkyl chain lengthens, the ratio between the M. L. D. and M. A. D., or therapeutic index, appears to be gradually greater, and the duration of action becomes shorter. More recently, it has been reported (2) that the substitution of a methyl or an ethyl group on the nitrogen (nitrogen alkyl substituted barbituric acid derivatives) also obviously reduces the duration of action, and this shorter duration of action is independent of the quantity of drug administered.

The present investigation deals with the evaluation of a number of new methallyl (2-methyl-allyl) substituted barbituric acid derivatives synthesized by Doran and Shonle (3), with the general formula:



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* Scientific Section, A. PH. A., Dallas meeting, 1936.

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COMPARISON OF THE PHARMACOLOGIC ACTION OF 22 2-METHYL-ALLYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.

C = Convulsions

Number of Compound.	Barbituric Acids (Methallyls).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Average Duration of M. A. D. (Min.).	M. L. D. / M. A. D.	Barbituric Acids (Parent Compound).	Number of Rats.	M. A. D. Mg. per Kg.	M. L. D. Mg. per Kg.	Average Duration of M. A. D. (Min.).	M. L. D. / M. A. D.
1	*β-Brom-allyl-methallyl	12	None	500	...	−C	β-Brom-allyl-ethyl	..	...	...	..	..
2	Allyl-methallyl	33	80	180	380	2.25	Allyl-ethyl	..	..	..	..	..
3	Phenyl-methallyl	18	150	200	340	1.33	Phenyl-ethyl	21	150	250	1692	1.66
4	Ethyl-methallyl	33	125	300	360	2.40	Ethyl-ethyl	39	340	480	1400	1.41
5	*n*-Propyl-methallyl	60	120	280	300	2.33	*n*-Propyl-ethyl	49	150	210	1140	1.40
6	1-Methyl-ethyl-methallyl	30	100	220	210	2.20	1-Methyl-ethyl-ethyl	27	170	220	1520	1.37
7	*n*-Butyl-methallyl	90	100	235	110	2.35	*n*-Butyl-ethyl	40	80	200	450	2.44
8	1-Methyl-propyl-methallyl	18	90	200	150	2.22	1-Methyl-propyl-ethyl	35	60	130	600	2.16
9	2-Methyl-propyl-methallyl	67	105	240	115	2.30	2-Methyl-propyl-ethyl	35	120	220	540	1.83
10	*n*-Amyl-methallyl	126	140	330	63	2.35	*n*-Amyl-ethyl	50	70	210	180	3.00
11	1-Methyl-butyl-methallyl	123	60	140	90	2.33	1-Methyl-butyl-ethyl	27	50	110	200	2.20
12	2-Methyl-butyl-methallyl	145	115	290	80	2.52	2-Methyl-butyl-ethyl	48	80	230	190	2.87
13	3-Methyl-butyl-methallyl	106	110	260	87	2.30	3-Methyl-butyl-ethyl	60	80	200	210	2.50
14	1-Ethyl-propyl-methallyl	42	80	160	90	2.00	1-Ethyl-propyl-ethyl	28	65	110	420	1.69
15	*n*-Hexyl-methallyl	36	175	500	60	3.00	*n*-Hexyl-ethyl	95	100	240	80	2.40
16	2-Ethyl-butyl-methallyl	24	150	350	90	2.21	2-Ethyl-butyl-ethyl	..	..	..	..	..
17	Cyclopentyl-methallyl	30	100	250	115	2.50	Cyclopentyl-ethyl	..	..	..	..	..
18	Methallyl-methallyl	36	100	130	105	1.30C	Methallyl-ethyl	33	125	300	360	2.40
19	*n*-Propyl-methallyl-thio	21	200	400	900	2.00C	*n*-Propyl-ethyl-thio	..	..	..	..	..
20	*n*-Butyl-methallyl-thio	18	250	400	600	1.60C	*n*-Butyl-ethyl-thio	..	..	..	..	..
21	1-Methyl-propyl-methallyl-thio	36	None	100	..	−C	1-Methyl-propyl-ethyl-thio	..	..	..	..	..
22	1-Methyl-butyl-methallyl-thio	22	None	100	..	−C	1-Methyl-butyl-ethyl-thio	..	..	..	..	..

* Structure of this compound is doubtful.

wherein R-alkyl radical may be an allyl, β-brom-allyl, phenyl, cyclopentyl, a primary, or secondary alkyl radical with 2 to 6 C-atoms; and R′, a methallyl radical (2-methyl-allyl). Some of these compounds have been prepared by Tabern and Volwiler (4).

Albino rats weighing 77 to 128 Gm. (average, 98 Gm.) were used in this study. Solutions of the sodium salts of the compounds were injected intraperitoneally. The M. A. D., duration of action and the M. L. D. were determined by using 5 animals for each dose level.

As shown in Table I, these barbituric acid derivatives have a distinctly shorter duration. Thus, the substitution of a methallyl (2-methyl-allyl) radical in barbituric acid derivatives, similar to the nitrogen alkyl barbituric acid compounds, produces a change (shorter) in the duration of action. Compounds numbered 19, 20, 21 and 22 (Table I), derivatives of methallyl thiobarbituric acid, cause convulsions with little or no hypnotic or anesthetic properties. There is evidence (5) that certain thiobarbituric acid compounds show pathological changes, and when administered by vein in man (6), thrombosis and soreness of the arm may result.

CONCLUSIONS.

1. A number of methallyl (2-methyl-allyl) barbituric acid derivatives have been synthesized and studied pharmacologically.

2. The substitution of a methallyl radical in barbituric acid derivatives distinctly shortens the duration of action.

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DRUG EXTRACTION. XIII. THE EXTRACTION OF IPOMEA.*[1]

BY WILLIAM J. HUSA[2] AND PAUL FEHDER.

The U. S. P. X specified alcohol as the menstruum for the preparation of resin of ipomea. The N. F. VI changed the menstruum to a mixture of 9 volumes of alcohol and 1 volume of water. In the present paper a report is made of experiments which were carried out to determine the relative value of the U. S. P. X and N. F. VI menstrua from the standpoint of rate of extraction, purity and yield of resin.

EXPERIMENTAL DATA.

Effect of Variation in Solvents on Rate of Extraction.—Percolation experiments were conducted using ipomea, in moderately coarse powder, containing 21.1 per cent of resin by the N. F.

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* Scientific Section, A. PH. A., Dallas meeting, 1936.

[1] This paper is based on part of a dissertation presented to the Graduate Council of the University of Florida by Paul Fehder, in partial fulfilment of the requirements for the degree of Doctor of Philosophy. [2] Head Professor of Pharmacy, University of Florida.