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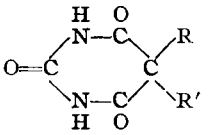
CROTYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.*

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

In a previous communication (1), it was observed that there is obvious relationship between the pharmacological action and the chemical structure of certain barbituric acid derivatives. In the primary or secondary alkyl substituted compounds, with an increase in the number of C-atoms in the alkyl group, both the minimal anesthetic dose (M. A. D.) and the minimal lethal dose (M. L. D.) grow 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. As the alkyl chain lengthens, the therapeutic index, or ratio between M. L. D. and M. A. D., appears to be gradually greater. The duration of action becomes shorter. More recently, it has been reported that the substitution of a methyl or an ethyl group on the nitrogen (nitrogen alkyl substituted barbituric acid derivatives) (2), or the substitution of an allyl or methallyl (2-methyl-allyl) (3) on one of the 5-5 positions, or a sulfur atom (4) in place of the 2 C-atom obviously reduces the duration of action. This shorter duration of action is independent of the quantity of drug administered.

The present investigation deals with the study of a number of new crotyl (3-methyl-allyl) substituted barbituric acid derivatives synthesized by Doran and Shonle (5), with the general formula:



wherein R-alkyl radical may be a primary or secondary alkyl radical with 2 to 5 C-atoms; and R′, a crotyl (3-methyl-allyl) radical.

Albino rats weighing 80 to 125 Gm. (average 99 Gm.) were used in this study. Solutions of the sodium salts of the compounds were injected intraperitoneally. The M. A. D., the 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 much shorter duration of action. Thus, the substitution of a crotyl (3-methyl-allyl), similar to the nitrogen alkyl barbituric acids and methallyl (2-methyl-allyl) compounds, produces a change (shorter) in the duration of action. Compound number 6, Crotyl-*n*-butyl-thio barbituric acid, shows convulsions with little or no hypnotic or anesthetic properties.

* Presented before the Scientific Section, A. PH. A., Minneapolis meeting, 1938.

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TABLE I.—COMPARISON OF THE PHARMACOLOGIC ACTION OF 10 CROTYL SUBSTITUTED BARBITURIC ACID DERIVATIVES.

No. of Compound.	Barbituric Acids (Crotyls).	No. of Rats.	M. A. D. Mg. per Kg.	Average Duration of M. A. D. Min.	M. L. D. Mg. per Kg.	M. L. D. / M. A. D.
1	Cis-crotyl-ethyl	50	100	372	280	2.80
2	Trans-crotyl-ethyl	40	100	300	240	2.40
3	Crotyl-*n*-propyl	60	130	120	340	2.60
4	Crotyl-iso-propyl	54	70	200	180	2.57
5	Crotyl-*n*-butyl	64	110	40	320	2.90
6	Crotyl-*n*-butyl-thio	15	*	...	...	...
7	Crotyl-sec-butyl	54	80	120	220	2.75
8	Crotyl-iso-butyl	55	100	45	300	3.00
9	Crotyl-iso-amyl	36	120	40	180	1.50
10	Crotyl-sec-amyl	51	90	66	200	2.22

No. of Compound.	Barbituric Acids (Parent Compound).	No. of Rats.	M. A. D. Mg. per Kg.	Average Duration of M. A. D. Min.	M. L. D. Mg. per Kg.	M. L. D. / M. A. D.
1						
2	Ethyl-ethyl	39	340	1400	480	1.41
3	Ethyl-*n*-propyl	49	150	1140	210	1.40
4	Ethyl-iso-propyl	27	170	1520	220	1.37
5	Ethyl-*n*-butyl	40	80	450	200	2.44
6	.....	..	...	...	...	...
7	Ethyl-sec-butyl	35	60	600	130	2.16
8	Ethyl-iso-butyl	35	120	540	220	1.83
9	Ethyl-iso-amyl	60	80	210	200	2.50
10	Ethyl-sec-amyl	27	50	200	120	2.40

* Convulsions.

CONCLUSIONS.

1. A number of crotyl (3-methyl-allyl) barbituric acid derivatives have been synthesized and studied pharmacologically.

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

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NATIONAL ASSOCIATION OF RETAIL DRUGGISTS.

At the Sherman Hotel, on October 10th, the N. A. R. D. will hold its fortieth annual convention. Among the speakers will be: Congressman Wright Patman, of Texas; Senator John E. Miller, of Arkansas; and Commissioner of Narcotics, H. J. Anslinger. It is expected that three thousand druggists will attend, and "Nothing is being left undone to really make this event long remembered in the history of drugdom."