[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Some Barbituric Acids Containing the 2-Methylallyl Group

BY WILBUR J. DORAN AND H. A. SHONLE

The introduction of the allyl group into the barbituric acid nucleus at the 5-position has led to the production of several therapeutically useful barbituric acids. Barbituric acids containing unsaturated aliphatic groups such as the crotyl, propinyl, cyclohexenyl, and cyclopentenyl groups are known. Shonle and Waldo[1] found that alkenyl ethyl barbituric acids containing the secondary pentenyl and hexenyl groups not only had less hypnotic action than the corresponding barbituric acids with saturated alkyl groups but also caused convulsions at low doses.

The recent availability of 2-methylallyl chloride[2] led us to prepare and investigate a series of barbituric and thiobarbituric acids containing the 2-methylallyl group. Three thiobarbituric acids containing this group have been reported.[3] Pharmacological studies of the first few 2-methylallyl-alkylbarbituric acids prepared indicated the desirability of making and studying an extended series of barbituric acids containing the 2-methylallyl group.

Since it had been observed in this Laboratory[4] that disubstituted barbituric acids containing a non-cyclic alkyl group having 6 carbon atoms or more tend to hemolyze red blood cells with comparative rapidity, we attempted the synthesis of but two barbituric acids containing a hexyl group.

The malonic esters were prepared in the usual manner by condensing the alkyl halides with sodiomalonic ester or sodioalkylmalonic ester and were purified by fractional distillation *in vacuo*.

The 2-methylallylalkylbarbituric acids and thiobarbituric acids were prepared in some instances by condensing the disubstituted malonic ester with urea or thiourea in the presence of sodium ethylate. Others were prepared by treating the 5-alkylbarbituric acid with 2-methylallyl chloride in dilute caustic solution. 2-Methylallylphenylbarbituric acid was prepared from the interaction of 2-methylallyl chloride and phenylbarbituric acid in dilute caustic solution.

(1) Shonle and Waldo, THIS JOURNAL, **55**, 4694 (1933).

(2) Supplied through the courtesy of the Shell Development Company, Emeryville, California.

(3) Tabern and Volwiler, THIS JOURNAL, **57**, 1961 (1935); English Patent 457,762.

(4) Powell and Swanson, unpublished report.

The pharmacological studies on this series of barbituric acids have been reported.[5]

The thiobarbituric acids were not as satisfactory as the corresponding barbituric acids, since some of them had a tendency to produce convulsions along with the sedative effect, while others produced no anesthesia and had a pure convulsive type of reaction. Gruhzit[6] has reported that liver damage occurs following the administration of certain thiobarbituric acids.

Table I summarizes the physical properties of the new malonic esters. Table II covers the new barbituric acids and includes a pharmacological summary. The minimum anesthetic dose (M.A.D.) and minimum lethal dose (M.L.D.) were determined in white rats by the intraperitoneal administration of dilute solutions of the sodium salts of the barbituric acids. Table III similarly describes the thiobarbituric acids prepared.

TABLE I

Substituted 2-methylallyl ethyl malonate	B. p., °C.[b]	Mm.	$n^{25}D$
n-Propyl	99	2	1.4406
1-Methylethyl	126–127	9–10	1.4451
n-Butyl	131–132	3	1.4414
1-Methylpropyl	102–104	1.5	1.4481
2-Methylpropyl	110–113	1	1.4446
n-Pentyl	112–114	1	1.4435
1-Methylbutyl	142–144	8–9	1.4483
2-Methylbutyl	135–137	7	1.4443
3-Methylbutyl	115–116	2.5	1.4419
n-Hexyl	127-131	1	1.4441
2-Ethylbutyl[a]	129–133	1	1.4487
Allyl	124–127	6	1.4492
2-Methylallyl	114–116.5	1	1.4532
Hydrogen	113–116	14–17	1.4341

[a] The 2-ethylbutyl bromide used boiled at 147–148°.
[b] Anschütz thermometer used.

We wish to thank J. H. Waldo for the preparation of several of the barbituric acids and E. E. Swanson and W. E. Fry for the pharmacological assays.

(5) Swanson and Fry, *J. Am. Pharm. Assn.*, **26**, 317–319 (1937). Clinical studies have been under way for some time and will be reported by Dr. G. F. Kempf and his colleagues.

(6) Gruhzit, "Thio-barbiturates: Toxicity and Histopathology," Fed. Am. Soc. Exp. Biol., Washington, March 25–28, 1936.

TABLE II

Substituted 2-methylallyl-barbituric acid	M. p., °C.[f]	% Nitrogen Calcd.	% Nitrogen Found		M. A. D.,[h] mg./kg.	M. L. D., mg./kg.	Average duration of M. A. D., min.
Ethyl[a]	165–167	13.34	13.38	13.40	125	300	360
n-Propyl[b]	173.5–174.5	12.50	12.62	12.51	120	280	300
1-Methylethyl[b]	163–164	12.50	12.35	12.34	100	220	210
n-Butyl[a]	125–126	11.76	11.87	11.81	100	235	110
1-Methylpropyl[a]	140–142	11.76	11.74	11.82	90	200	150
2-Methylpropyl[a,b]	179.8–180.5	11.76	11.77	11.92	105	240	115
n-Pentyl[a,b,c]	111–112	11.11	11.18	11.17	140	330	63
1-Methylbutyl[a,b]	141.5–143	11.11	11.08	11.14	60	140	90
2-Methylbutyl[b]	142–143.5	11.11	11.23	11.31	115	290	80
3-Methylbutyl[a,b]	143.6–144.4	11.11	11.27	11.32	110	260	87
1-Ethylpropyl[a,d]	181.5–183	11.11	10.90	10.97	80	160	90
n-Hexyl[b]	127–129	10.52	10.42	10.51	175	500	60
2-Ethylbutyl[b]	148–150	10.52	10.56	10.60	150	350	90
Allyl[b,e]	165–167	12.61	12.65	12.56	80	180	380
2-Methylallyl[b]	207–209	11.86	11.93	11.87	100	130	105[i]
Cyclopentyl[a]	159–161	11.20	11.24	11.27	100	250	115
Phenyl[a]	203–205	10.85	10.73	10.58	150	200	340
Hydrogen	187–189	15.38[g]			inert	...	...

[a] Prepared by treating 2-methylallyl chloride with the monosubstituted barbituric acid in dilute caustic. [b] Prepared by condensing the disubstituted malonic ester with urea. [c] When prepared from methallyl chloride and *n*-pentylbarbituric acid, it melted 94–95.5°. [d] The 1-ethylpropylethylmalonate used boiled 111–112° at 5.5 mm., $n^{20}D$ 1.42914, and the 1-ethylpropylbarbituric acid melted 197.5–198°. [e] On treating allyl bromide with monomethallyl barbituric acid in dilute caustic some N-allylation occurred, resulting in a mixture of the desired product and N-allyl-allyl-methallyl-barbituric acid, which melted at 149–150°. Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.61. Found: N, 10.36, 10.24. [f] Anschütz thermometer used. [g] This barbituric acid contained water of crystallization after prolonged drying in vacuum. *Anal.* Calcd. for $C_8H_{10}N_2O_3 \cdot 0.5H_2O$: C, 50.3; H, 5.76; N, 14.66. Found: C, 50.0, 50.2; H, 6.06, 6.16; N, 14.43, 14.32. [h] Over a thousand rats were used in this pharmacological investigation. [i] The animals had convulsions.

TABLE III

Substituted 2-methylallylthio-barbituric acid	M. p., °C.[b]	% Nitrogen Calcd.	% Nitrogen Found		M. A. D., mg./kg.	M. L. D., mg./kg.	Average duration of M. A. D., min.
n-Propyl	157–158	11.66	11.60	11.72	200	400	900[c]
n-Butyl	137–137.5	11.02	11.08	11.21	250	400	600[c]
1-Methylpropyl	138–139	11.02	11.00	10.92	None	100	Convulsions
1-Methylbutyl[a]	214.5–215	10.44	10.42	10.47	None	100	Convulsions

[a] Prepared by treating 2-methylallyl chloride with 1-methylbutylthiobarbituric acid in dilute caustic. The 1-methylbutylthiobarbituric acid used melted at 146.5–148°. *Anal.* Calcd. for $C_9H_{14}N_2O_2S$: N, 13.08. Found: N, 13.11, 13.10. [b] Anschütz thermometer used. [c] Convulsions were observed in most animals.

Summary

A series of thirteen new malonic esters containing the 2-methylallyl group is described. In addition, eighteen new barbituric acids and four new thiobarbituric acids containing the 2-methylallyl group have been prepared, and some of their physical and pharmacological properties summarized.

INDIANAPOLIS, IND. RECEIVED JULY 6, 1937