(Bios II). Magnesium chloride or nitrate does not show the above phenomenon while potassium or ammonium sulfate gives some increase in activity. Combinations of magnesium chloride or nitrate with potassium or ammonium sulfate give about the same increase in growth in the presence of the bios preparation as does magnesium sulfate.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Di- and Trialkyl Barbituric Acids

BY H. A. SHONLE AND WILBUR J. DORAN

During the past several years, a number of new dialkyl substituted barbituric acids have been prepared in this Laboratory for the purpose of studying the relationship of the pharmacological action to the chemical structure.[1] Since the intermediate malonic esters were available, it seemed advantageous to extend this study to include certain trialkyl substituted barbituric acids. During the course of the preparation of the trialkyl barbituric acids, several undescribed dialkyl barbituric acids were prepared.

A considerable number of 1-alkyl-5,5-dialkyl barbituric acids have been described since Fischer and Dilthey[2] prepared N-methyldiethylbarbituric acid.[3]

The various malonic esters were made in the usual manner by adding the alkyl halide, usually the bromide, to an absolute alcoholic solution of sodiomalonic ester or sodioalkylmalonic ester, refluxing until the reaction was completed and purifying the malonic ester by fractional distillation *in vacuo*. Table I summarizes some of the physical properties of the malonic esters.

Most of the barbituric acids were prepared by condensing the di-substituted malonic ester with urea, methyl urea, or ethyl urea, in the presence of an alcoholic solution of sodium ethoxide, after which they were precipitated and purified, usually by recrystallization from dilute alcohol. In some instances, however, the barbituric acid was an oil which would not readily crystallize, so that its purification had to be effected by fractional distillation *in vacuo*. Table II summarizes the properties of the various barbituric acids prepared.

TABLE I

	Ethyl malonate	B. p., °C.	Mm.	$n^{25}D$
1	3-Methylbutylmethyl[a]	103–104	3	1.4248
2	*n*-Hexylmethyl	125	3.5	1.4280
3	1-Methylpentylmethyl	126	6	1.4323
4	1-Methylpentylallyl	139	5	1.4442
5	2-Ethylhexylmethyl	126	1.5	1.4353
6	*n*-Pentylmethyl	99	8	1.4254
7	1-Methylbutylmethyl	124	10	1.4288
8	*n*-Propyl-2-methylbutyl	100	1	1.4319

[a] Sommaire [*Bull. soc. chim.*, **33**, 189–95 (1923)] describes this ester as boiling at 242–247°.

The di- and trialkyl barbituric acids were converted into their sodium salts by the addition of a 50% solution of sodium hydroxide to an alcoholic solution of the barbituric acid, followed by the removal of the alcohol by vacuum distillation. Solutions of the sodium salts of these barbituric acids were studied pharmacologically on several varieties of laboratory animals. The results obtained by the intraperitoneal injection into white rats are summarized in Table II, wherein the minimum anesthetic dose (M. A. D.) and the minimum lethal dose (M. L. D.) are reported. The detailed pharmacological study will be reported elsewhere.[4] From the pharmacological data, it appears, in general, that the introduction of a third alkyl group lessens the duration of the action. In some instances, alkylating the nitrogen group made the barbituric acids less effective.

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(1) Swanson, *Proc. Soc. Exptl. Biol. Med.*, **31**, 961 (1934); U. S. Patent, 1,996,627; Shonle, Waldo, Keltch and Coles, THIS JOURNAL, **58**, 585 (1936).

(2) Fischer and Dilthey, *Ann.*, **335**, 334 (1904); U. S. Patent, 782,742.

(3) Among the various investigators who have reported in this field are: Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927); Hjort and Dox, *ibid.*, **35**, 155 (1929); Dox and Jones, THIS JOURNAL, **51**, 316 (1929); Kleiderer and Shonle, *ibid.*, **56**, 1772 (1934); Tabern and Volwiler, Kansas City Meeting, American Chemical Society, April 16, 1936.

(4) Swanson, *in press*.

TABLE II

Compounds numbers 9, 14, 15 and 18 were reported by Tabern and Volwiler, Kansas City Meeting, American Chemical Society, April 16, 1936. The nitrogen determinations were obtained by the micro-Dumas method.

	Barbituric acid	M. p., °C.	%, Nitrogen Calcd.	Found		M. A. D. mg./kg.	M. L. D. mg./kg.	Av. duration of symptoms of surviving rats, min.
1	3-Methylbutylmethyl[a]	124.5–125.2	13.20	12.96	12.76	1000	1500	447
2	*n*-Hexylmethyl	168–169	12.38	12.57	12.58	150	450	260
3	1-Methylpentylmethyl	173–174	12.38	12.50	12.41	150	400	227
4	1-Methylpentylallyl[b]	Oil	11.11	11.47	11.41	60	150	108
5	2-Ethylhexylmethyl	132–132.5	11.02	11.14	11.06	125	250	223
6	*n*-Propyl-2-methylbutyl	129–130.5	11.67	11.58	11.55	110	220	165
7	N-methyl *n*-propylethyl	94.5–95.0	13.20	13.03	13.02	140	200	570
8	N-methyl 2-methylpropylethyl	90–91	12.38	12.48	12.24	140	200	228
9	N-methyl 1-methylpropylethyl[c]	94–95	12.38	12.44	12.44	90	120	764
10	N-methyl *n*-pentylmethyl	108–109	12.38	11.82	11.69	1000	None	...
11	N-methyl *n*-pentylethyl[d]	Oil	11.67	11.40	11.42	90	190	191
12	N-methyl 3-methylbutylmethyl	106–107	12.38	12.01	12.03	None	2000	...
13	N-ethyl 3-methylbutylethyl[e,f]	Oil	11.02	11.33	11.45	150	300	68
14	N-methyl 1-methylbutylmethyl	116–117	12.38	12.58	12.55	150	350	240
15	N-methyl 1-methylbutylethyl[c,g]	Oil	11.67	11.75	11.87	70	140	205
16	N-methyl 1-methylbutylallyl[h]	Oil	11.11	11.08	11.15	60	120	133
17	N-ethyl 1-methylbutylethyl[e,h]	Oil	11.02	10.87	10.88	150	340	224
18	N-methyl 1-methylpentylmethyl[i]	Oil	11.67	11.75	11.61	150	400	152
19	N-methyl 1-methylpentylallyl	Oil	10.53	10.18	10.13	80	170	313
20	N-methyl *n*-hexylmethyl[j]	Oil	...	...	...	...	...	...
21	N-methyl 2-ethylhexylmethyl[k]	Oil	...	...	...	...	...	...
22	N-methyl 2-ethylhexylethyl[c]	Oil	...	...	...	...	...	...

[a] Sommaire [*Bull. soc. chim.*, **33**, 189–195 (1923)] gives the m. p. of this barbiturate as 108°. [b] B. p. 218–220° at 7 mm. [c] Prepared by the action of dimethyl sulfate on the sodium salt of the corresponding 5,5-dialkylbarbituric acid. All of the other N-methylbarbiturates were prepared by condensation of the dialkylmalonic esters and methyl urea. [d] B. p. 155–156° at 1 mm. [e] Prepared from ethyl urea and the dialkylmalonic ester and also by the action of diethyl sulfate on the sodium salt of the corresponding 5,5-dialkylbarbituric acid. [f] B. p. 192–194° at 13 mm. [g] B. p. 188–190° at 7 mm. [h] B. p. 148–150° at 1 mm. [i] B. p. 180° at 3 mm. [j] The barbituric acid was obtained as an oil which decomposed on distillation with the formation of the acetyl urea, b. p. 189° at 3 mm., m. p. 63–64°. Kropp and Taub (German patent 606,499, Dec. 4, 1934) give 183–185° at 1.5 mm. as the b. p. of the barbituric acid. % nitrogen for *n*-hexylmethylacetylmethyl urea, calcd., 13.08, found, 13.24 and 13.18. The acetyl urea exhibited no demonstrable hypnotic action. [k] The barbituric acid was obtained as an oil which on standing at room temperature decomposed into 2-ethylhexylmethylacetylmethyl urea, m. p. 65–70°. % nitrogen, calcd., 11.57, found, 11.63 and 11.89. 750 mg. per kg. produces ataxia only in rats. Kropp and Taub (German patent 606,499) report the preparation of this barbituric acid.

Summary

The preparation of a number of new dialkyl malonic esters and di- and trialkyl barbituric acids has been described, and the pharmacological action of the latter summarized.

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