tration of daily doses of 5-50 mg per kg; and in mice and rats with the feeding of 0.01-1% Dicumarol in food. The majority of rabbits can tolerate daily doses of 0.1-0.5 mg per kg by vein for 6 weeks, and a few mice and rats can survive 30 days on a diet containing 0.005% Dicumarol. (3) Most animals dying from Dicumarol develop hemorrhage into various tissues and organs, and pulmonary edema. Central necrosis of the liver has been observed in about one-half of the rats examined, and occasionally in rabbits, mice, and dogs.

13755

Anesthetic Activity of Some New Derivatives of Barbituric Acid.*

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This is a study of 7 barbituric acids which, so far as we are aware, have not previously been referred to in the literature.

We have found all of these compounds to be anesthetic in mice. The anesthetic and lethal doses are shown in Table I. The corresponding data for two familiar drugs, pentobarbital and evipal, are included for comparison.

Methods. Animals. Male white mice were used in all of the experiments.

Administration of Drugs. All drugs were given as freshly prepared solutions of the sodium salts. (The doses shown in Table I are expressed in terms of the acid form.) The concentrations of the solutions were such that the mice received about 0.012 cc of solution per gram of body weight for the intravenous doses, about 0.017 cc per gram for the intraperitoneal anesthetic doses, and about 0.025 cc per gram for the intraperitoneal lethal doses. In the determination of the intravenous anesthetic doses, the injection occupied a period of ½ minute.

* This work was aided by a grant from Mallinckrodt Chemical Works. The first five compounds listed in Table I were kindly made for us by Mallinckrodt Chemical Works. The other two new compounds were synthesized in this laboratory.

TABLE I.
Anesthetic Doses, Lethal Doses, and Recovery Times as Determined in Mice by Injection of Solutions of Sodium Salts.

Barbituric acid	Melting point °C, corr.	Intravenous AD 50* mg/kg	Intraperitoneal AD 50 mg/kg	Intraperitoneal LD 50† mg/kg	Recovery‡ time, min
5-isopropyl-5-isobutyl	160-161	63.5 ± 1.5	76.0 ± 1.8	231 ± 4	25
5-*n*-butyl-5-*sec*-butyl	135-138	46.6 ± 0.9	63.8 ± 1.2	204 ± 9	16
5-*n*-butyl-5-isoamyl	170-172	23.7 ± 1.2	116.4 ± 4.8	600 ± 35	1
5-*sec*-butyl-5-isoamyl	132-133	32.5 ± 0.7	83.6 ± 2.7	243 ± 8	2
5-*n*-propyl-5-*n*-amyl	124-128	40.8 ± 0.5	88.6 ± 2.7	232 ± 10	4
5-*n*-propyl-5-*n*-hexyl	114-116	48.4 ± 2.6	111.0 ± 2.6	302 ± 13	1
5-*n*-propyl-5-*n*-heptyl	112-114	92.4 ± 3.1	132.0 ± 5.7	269 ± 16	15
pentobarbital		33.3 ± 1.9	42.3 ± 0.7	121 ± 2	28
evipal		29.2 ± 1.0	62.5 ± 1.1	286 ± 4	1

* AD 50—Median anesthetic dose.
† LD 50—Median lethal dose.
‡See *Methods*.

Median Doses. The median anesthetic doses (AD 50) and median lethal doses (LD 50) were estimated by interpolation on the assumption that the curve relating log dose and proportion anesthetized or killed is the integrated normal frequency curve. In Table I the median doses are accompanied by their standard errors, calculated by the equations given by Bliss.[1]

Criterion of Anesthesia. A mouse was considered anesthetized if it could not gain and maintain the standing position after stimulation by repeated pinching of the tail.

Recovery Times. A dose 1.25 times the previously determined AD 50 was given intravenously. The interval between the end of the injection and the recovery of the degree of righting ability described above was measured. The value shown in Table I is the median recovery time observed in a series of 11 mice.

The anesthesia produced in mice by all of the new compounds except isopropyl-isobutyl-barbituric acid is as quiet as that produced in this animal by any of the well known barbituric acids. Except for a fine rapid tremor of the legs which is sometimes seen in the light stages of anesthesia, the mice are well relaxed. The anesthesia with isopropyl-isobutyl-barbituric acid is not so smooth. Clonic spasms of the legs are much more pronounced, and occasionally a brief generalized convulsion can be elicited by stimulation. These convulsive movements are more conspicuous with small doses, large doses producing a rather quiet anesthesia. In mice the convulsive effects of this drug are no more intense than those of some of the widely used barbituric acids (*e. g.*, dial and evipal).

[1] Bliss, C. I., *Quart. J. Pharm. and Pharmacol.*, 1938, **11**, 192.

The recovery times shown in Table I, which furnish a rough index of the relative persistence of action of the compounds, indicate that they are all rather short acting. The longest acting of the new compounds has a duration of action of the same order as that of pentobarbital; the shortest acting, of the same order as that of evipal.

The first 3 of the new compounds show a brief delay in the full development of anesthesia after an intravenous injection. In the mice receiving the dose 1.25 times the AD 50, the mean lag for these three compounds was, respectively, 3 min, ½ min, and 5 sec. The other 4 new compounds had no appreciable lag.

Early work with the barbituric acids led to certain inferences regarding the relation between structure and activity. It is these generalizations, doubtless, that have discouraged further investigation of derivatives of the type presented here. For example, the generalizations arrived at by one worker in this field[2] included these: (1) That the sum of the carbon atoms in the 2 substituent groups in the 5-position is 7 in the most effective compounds; (2) that the greatest dissimilarity in the 2 groups gives the greatest activity; (3) that if both groups are larger than ethyl, less effective compounds result. The activity of the compounds studied here shows that none of these rules is generally applicable.

Summary. The anesthetic activity in mice of seven new 5,5-dialkyl-barbituric acids has been studied. Intravenous anesthetic doses, intraperitoneal anesthetic doses, intraperitoneal lethal doses, and duration of action were measured.

13756

Nature of the X-ray Effect in CO Recovery.*

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Rapid recovery from severe carbon monoxide poisoning under X-ray treatment[1, 2] and spectrographic evidence of the reduction of

2 Shonle, H. A., *Ind. Eng. Chem.*, 1931, **23**, 1104.

* This study was aided by a grant from the Research Council of the University of Missouri.

1 Cameron, John A., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 29.

2 Cameron, John A., *Radiology*, 1941, **36**, 486.