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5-Ethyl-5-(1,3-Dimethyl-2-Butenyl)Barbituric Acid, A Potent Central Nervous System Stimulant*

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The pharmacological properties of 5,5-disubstituted barbituric acids may vary from sedative to stimulant action. The nature of the substituent groups in the 5-position has a profound effect on the type of pharmacological activity. For example, while 5-ethyl-5-(1-methylbutyl)barbituric acid (pentobarbital) (I), and 5-ethyl-5-(3-methylbutyl)barbituric acid (amobarbital) (II), are well known sedatives, the closely related 5-ethyl-5-(1,3-dimethylbutyl)barbituric acid (DMBB) (III), is a stimulant.[1] TAYLOR and NOBLE[2] reported that 5-ethyl-5-(3-methyl-2-butenyl)barbituric acid (IV) is a stimulant rather than a sedative like the corresponding saturated derivative, amobarbital (II).

It has been found that the combination of the two structural features of the substituted butyl groups which appear to confer stimulant properties, namely, methyl groups on carbon atoms 1 and 3 (see formula III) and a double bond between carbon atoms 2 and 3 (see formula IV) in a single molecule (formula V), produces stimulant action five or more times greater than that of III or IV. It is noteworthy that the position of the double bond in the butenyl group has a remarkable effect as shown by the lower potency of the 1-butenyl isomer[3] (VI). The structure of the substituted butyl group appears to be the predominant factor in determining activity. When the ethyl group of V is replaced by an allyl group, the resulting compound (VII) shows little change in pharmacological action. Table I shows the dose of each of these compounds required to cause deaths from convulsions in 50 per cent of one species (mice) of animals tested and provides one measure of relative stimulant activity.

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Table I. Intraperitoneal LD50 in mice of stimulant barbituric acids

Barbituric acid	LD50, mg/kg
III	17
IV	17
V	3·5
VI	21
VII	5

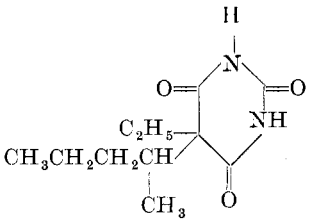
Table II shows data in several species of V and its saturated analogue III.

Table II. LD50 in various species of compounds V and III

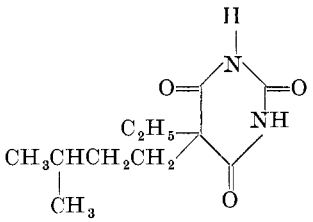
Species	Route	LD50, mg/kg	
		compound V	compound III
Mice	I.P.	3–4	12·5–25
Mice	Oral	17·5–20	70–75
Rats	I.P.	3–5	—
Rats	Oral	20–25	75–125
Dogs	I.V.	0·1–0·2	2·5–5
Dogs	Oral	1–2	10–15

The synthesis of V was accomplished by the following scheme: mesityl oxide → 4-methyl-3-pentene-2-ol → 4-bromo-2-methyl-2-pentene→diethyl ethyl(1,3-dimethyl-2-butenyl)malonate→V. The reduction of mesityl oxide to the pentenol was carried out by the aluminium alkoxide method, or, more conveniently, using sodium borohydride. The condensation of the disubstituted malonic ester with urea by the usual procedure gave a low yield. Somewhat better results were obtained by carrying out the condensation using solid sodium methoxide in the absence of a solvent, removing the alcohol formed in the reaction by distillation under reduced pressure.

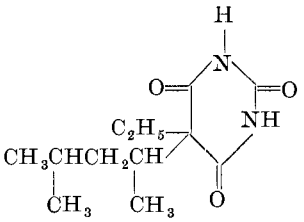
Confirmation of the structure of V was obtained by non-identity with VI and by conversion of V to III by catalytic hydrogenation.



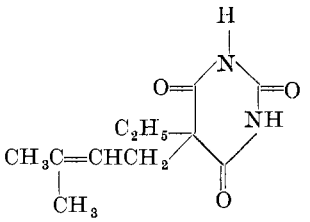
I



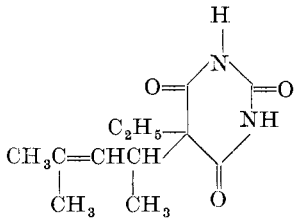
II



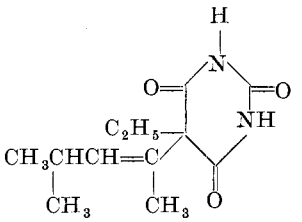
III



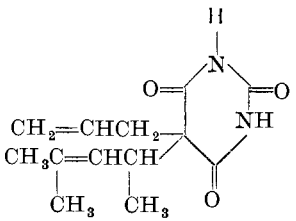
IV



V



VI



VII

Experimental

4-*Methyl*-3-*Pentene*-2-*ol*

(*a*) *Aluminium alkoxide method.* The directions of MILLS[4] were used to give a 73 per cent yield, b.p. 135–140°. The 3,5-dinitrobenzoate derivative was prepared, m.p. 76–78°. MACBETH and MILLS[5] report a b.p. of 139–140° for the alcohol and a m.p. of 82–84° for the 3,5-nitrobenzoate.

(*b*) *Sodium borohydride reduction.* A stirred, cooled solution of 588 g (6 moles) of mesityl oxide in 2 l. of methanol was treated with a total of 147·3 g (3·9 moles) of sodium borohydride, added in portions of 47·3, 75 and 25 g, respectively. The reaction was followed by ultraviolet absorption analysis after each addition until all the mesityl oxide had reacted. The mixture was stirred for 2 h longer, treated with 1,500 ml of water, refluxed for 2 h and poured into a precipitating jar containing 2,000 ml of water and 1,000 g of salt. The solution was extracted with petroleum ether. The petroleum ether extract was evaporated and the residue distilled; yield, 469·6 g (78 per cent), b.p. 133–146°.

4-*Bromo*-2-*Methyl*-2-*Pentene*

This material was prepared in 71 per cent yield by the method of ROUVÉ and STOLL.[6]

Diethyl Ethyl(1,3-*Dimethyl*-2-*Butenyl*)*Malonate*

A mixture of 161 g (0·86 mole) of diethyl ethylmalonate and a solution of sodium ethoxide (prepared from 400 ml of absolute ethanol and 19·78 g (0·86 mole) of sodium) was cooled and treated with 140 g (0·86 mole) of 4-bromo-2-methyl-2-pentene with stirring. The bromide was added over a period of 4 h. After all the bromide had been added, the mixture was allowed to come to room temperature by standing overnight. The alcohol was then removed by vacuum distillation and the resulting residue dissolved in water. The oil layer was collected and the water layer extracted with three portions of ether. The oil layer and ether extracts were combined, dried with sodium sulphate, the ether evaporated and the residue distilled; yield, 119 g (53 per cent), b.p. 77–82°/0·35–0·3 mm, $n_D^{24\cdot5}$ 1·4462.

Diethyl(1,3-Dimethyl-2-Butenyl)Malonate

Treatment of 99·2 g (0·62 mole) of diethyl malonate with 101 g (0·62 mole) of 4-bromo-2-methyl-2-pentane by the method described above gave 83 g (55 per cent) of product, b.p. 134–160°/55 mm, n_D^{26} 1·4395.

Diethyl Allyl(1,3-Dimethyl-2-Butenyl)Malonate

Prepared by the same procedure in 48 per cent yield, the product boiled at 104–108°/0·4 mm, n_D^{26} 1·4537.

5-Ethyl-5-(1,3-Dimethyl-2-Butenyl)Barbituric Acid

A mixture of 100·5 g (0·37 mole) of diethyl ethyl(1,3-dimethyl-2-butenyl)malonate, 44·4 g (0·74 mole) of urea and 40·0 g (0·74 mole) of sodium methoxide was stirred and heated on a steam bath for 5 h. A vacuum line was attached and the mixture was heated at reduced pressure for an additional hour. The residue was cooled and dissolved in crushed ice and water, and the cold basic solution was extracted with methylene chloride. The basic solution was then poured into excess dilute hydrochloric acid. The acid solution was treated with 300 ml of heptane and allowed to stand at room temperature overnight. The oily solid which formed was collected, washed with heptane, dried and recrystallized from the mixture of benzene and heptane; yield, 88·2 g (50 per cent), m.p. 137–139°. Evaporation of the methylene chloride extract and distillation of the residue gave 33 g (33 per cent) of recovered malonate.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60·5; H, 7·6; N, 11·8. Found: C, 60·6; H, 7·7; N, 11·8.

The infrared spectrum showed $\lambda_{max.}^{KBr}$ 2·94, 3·12, 3·25, 3·38, 3·44, sH 3·47, sH 5·77, 5·86, 6·68, 6·97 mμ.

Catalytic Hydrogenation of 5-Ethyl-5-(1,3-Dimethyl-2-Butenyl)Barbituric Acid (V)

A solution of 10 g (0·042 mole) of 5-ethyl-5-(1,3-dimethyl-2-butenyl)barbituric acid in 150 ml of methanol was shaken at room temperature with hydrogen and platinum catalyst. After absorption of hydrogen had ceased, the catalyst was removed by filtration and the filtrate evaporated. Crystallization of the

residue from aqueous methanol gave 10 g of 5-ethyl-5-(1,3-dimethylbutyl)barbituric acid (III), identified by m.p., mixed m.p. and ultraviolet and infrared absorption spectra.

5-*Allyl*-5-(1,3-*Dimethyl*-2-*Butenyl*)*Barbituric Acid* (*VII*)

The procedure described for the ethyl analogue was followed. The product was crystallized from a mixture of acetone and petroleum ether, m.p. 143–145°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: N, 11·2. Found: N, 11·1.

Summary. The effect on central nervous system stimulant activity of certain structural changes in the 5-alkyl groups of disubstituted barbituric acids has been studied by the preparation of 5-ethyl- and 5-allyl-5-(1,3-dimethyl-2-butenyl)barbituric acids (V and VII). These compounds are five to ten times as potent as the closely related, previously reported compounds III, IV and VI.

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