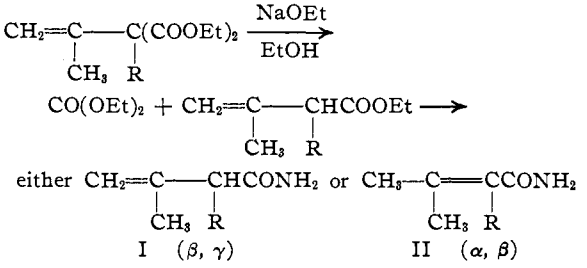
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Substituted Vinyl Barbituric Acids. I. Isopropenyl Derivatives

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

Intensive search for efficient hypnotics and anesthetics has led to the synthesis of hundreds of 5,5-dialkylbarbituric acids. The saturated and unsaturated alkyl groups with from three to five carbon atoms have been introduced into the barbituric acid nucleus as the necessary alcohols became available, by way of the alkyl halides and the corresponding malonic or cyanoacetic esters.

This method fails for the introduction of vinyl and alkyl substituted vinyl groups because of the inactivity of the halogen in vinyl halides $\left(\rangle C{=}CX\right)$. The recent development of a practical indirect method for the introduction of 1-methylvinyl or isopropenyl groups into malonic ester[1] has furnished the intermediates necessary for the preparation of isopropenyl alkyl barbituric and thiobarbituric acids, which are described in this communication.



amides, which are formed from the monocarboxylic esters produced by alcoholysis, were all solids which could be purified readily. Their structure is of some interest, since after the loss of a carbethoxy group the double bond can migrate from the β,γ- to the α,β-position. By analogy with vinylethylmalonic ester, which under similar conditions gives the known α,β-unsaturated compound α-ethylcrotonamide,[2] the α,β-unsaturated structure (II) was regarded as more likely.

TABLE I

5-ISOPROPENYL 5-ALKYLBARBITURIC ACIDS

5-Alkyl group	M. p., °C. (uncorr.)	Yield, %	Formula	Nitrogen, % Calcd.	Found[d]
Methyl	181–181.5	75	$C_8H_{10}O_3N_2$	15.22	15.13
Ethyl	184–184.2	75	$C_9H_{12}O_3N_2$	14.28	14.24
Propyl	149–150[a]	60	$C_{10}H_{14}O_3N_2$	13.33	13.53
Allyl	144.5–145	60	$C_{10}H_{12}O_3N_2$	13.46	13.40
Butyl	156–157	70	$C_{11}H_{16}O_3N_2$	12.51	12.64
Isobutyl	161.5–162.5	65	$C_{11}H_{16}O_3N_2$	12.51	12.51
Amyl	123–124	73	$C_{12}H_{18}O_3N_2$	11.76	11.88
Isoamyl	128–129	60	$C_{12}H_{18}O_3N_2$	11.76	11.99
Benzyl[b]	231.5–232.5	24[c]	$C_{14}H_{14}O_3N_2$	10.85	10.73
Ethyl N-methyl	125.5–126	50	$C_{10}H_{14}O_3N_2$	13.33	13.37
Ethyl N-ethyl	67–68[e]	15	$C_{11}H_{16}O_3N_2$	12.51	12.62
Ethyl N-allyl	65–66[e]	15	$C_{12}H_{16}O_3N_2$	11.86	11.92

[a] Also obtained in a less stable polymorphic form of m. p. 158.5–159.5°. *Anal.* N calcd. 13.33, found 13.52. [b] Prepared from ethyl benzyl isopropenyl malonate which contained a small amount of a solid impurity; b. p. of the ester 141–142° (1 mm.); $n^{25}D$ 1.4981; d^{25}_{25} 1.0579. [c] Using one equivalent of sodium ethoxide in the condensation. Approximately half of the ester was recovered. With three equivalents of sodium ethoxide the yield was 13%, and 40% of the theoretical amount of α-benzyl-β-methyl-crotonamide was obtained. [d] We are indebted to Mr. C. S. Miller for all nitrogen analyses by a semimicro Kjeldahl procedure. [e] Recrystallized from a mixture of ether and pentane.

Some difficulty was anticipated in condensing the malonic esters with urea and its derivatives, since the alcoholic sodium ethoxide used as a condensing agent produces alcoholysis of these substituted vinyl esters to ethyl carbonate and monocarboxylic esters. Actually, good yields of barbituric acids were obtained in most cases, although small amounts of monocarboxylic esters and amides were obtained as by-products. The Structure II was proved to be correct by ozonization of two of the amides, which gave acetone but no formaldehyde. The structures of the barbituric acids follow from those of the corresponding malonic esters, which were determined previously.[1] In addition the methyl isopropenyl barbituric acid was reduced quantitatively to the known methyl isopropyl derivative,[3] m. p. and mixed m. p. 188–189°.

(1) Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938).

(2) Cope and McElvain, *ibid.*, **54**, 4311 (1932).

(3) Preiswerk, *Helv. Chim. Acta*, **6**, 192 (1923).

TABLE II

α-ALKYL β-METHYL CROTONAMIDES

α-Alkyl group	M. p., °C. (uncorr.)	Formula	Nitrogen, % Calcd.	Found
Ethyl	151–151.5	$C_7H_{13}ON$	11.02	10.82
Butyl	115–116	$C_9H_{17}ON$	9.04	9.15
Isobutyl	128–128.2	$C_9H_{17}ON$	9.04	8.88
Amyl	111–112	$C_{10}H_{19}ON$	8.28	8.46
Isoamyl	108–109	$C_{10}H_{19}ON$	8.28	8.39
Benzyl	122–122.5	$C_{12}H_{15}ON$	7.41	7.34

TABLE III

5-ISOPROPENYL 5-ALKYL THIOBARBITURIC ACIDS

5-Alkyl group	M. p., °C. (uncorr.)	Yield, %	Formula	Nitrogen, % Calcd.	Found
Methyl	154–155	15	$C_8H_{10}O_2N_2S$	14.14	14.32
Ethyl	191–192	80	$C_9H_{12}O_2N_2S$	13.20	12.96
Propyl	184–185	90	$C_{10}H_{14}O_2N_2S$	12.39	12.59
Allyl	176.5–177	75	$C_{10}H_{12}O_2N_2S$	12.49	12.23
Butyl	160–161	70	$C_{11}H_{16}O_2N_2S$	11.68	11.84
Isobutyl	164–165	70	$C_{11}H_{16}O_2N_2S$	11.68	11.88
Amyl	139–140	90	$C_{12}H_{18}O_2N_2S$	11.02	11.17
Isoamyl	165.5–166.5	60	$C_{12}H_{18}O_2N_2S$	11.02	11.26
Benzyl	157–158	70	$C_{14}H_{14}O_2N_2S$	10.22	10.18

Experimental Part

Barbituric Acid Condensations.—The synthesis of 5-butyl 5-isopropenyl barbituric acid will serve as a typical example. To a solution of 13.8 g. (0.60 mole) of sodium in 200 cc. of absolute alcohol was added 19.2 g. (0.32 mole) of urea and 51.2 g. (0.20 mole) of ethyl butyl isopropenyl malonate. The mixture was refluxed from a bath at 105° for twelve hours, after which it was cooled and the alcohol removed by distillation in vacuum. The solid residue was dissolved in 150 cc. of water and extracted 3 times with ether. The ether extract was washed with water and set aside to evaporate. The water washings were added to the main portion of the aqueous solution, which was then acidified dropwise with a 50% excess of concd. hydrochloric acid with stirring and cooling in ice. The crystalline barbituric acid was filtered, washed with ice water, and recrystallized from dilute alcohol. The properties of the barbituric acids, prepared in this manner, are recorded in Table I. N-Alkyl barbituric acids were prepared similarly from the corresponding N-alkyl ureas.

The ether extract on evaporation left a mixture of a liquid ester and a solid amide. The mixture was filtered and the ester distilled in vacuum; 12 g., b. p. 110–126° (10 mm.), was obtained. The low boiling point proves that this ester was almost completely the monocarboxylic ester produced by alcoholysis, but it was not further purified or analyzed because of its contamination with solid amide. The amide (2.0 g.) was purified by recrystallization from a mixture of ether and pentane. The proper-

TABLE IV

5-ISOPROPENYL 5-ALKYL BARBITURIC ACIDS

RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a]

5-Alkyl group	Administration[b]	AD 50[c] mg./kg.[e]	AD 100 mg./kg.	LD 50[d] mg./kg.	Ratio, LD 50/AD 50	Duration at AD 100 Induction, min.[f]	Anesthesia, hours[g]
Methyl	I. P.	1375	1500	1850	1.3	67	1.0
Ethyl	I. P.	240	260	650	2.7	40	2.5
Ethyl	Oral	285	300	720	2.5	55	>5.0
Propyl	I. P.	190	200	540	2.8	20	2.8
Propyl	Oral	220	240	440	2.0	25	>6.0
Allyl	I. P.	180	200	360	2.0	60	1.7
Butyl	I. P.	105	120	365	3.5	12	1.5
Butyl	Oral	170	180	420	2.5	14	1.0
Isobutyl	I. P.	120	140	280	2.3	14	1.5
Amyl	I. P.	115	130	350	3.0	1	0.5
Amyl	Oral	130	160	470	3.6	4	2.0
Isoamyl	I. P.	130	150	320	2.5	6	0.3
Isoamyl	Oral	150	180	450	3.0	6	0.5
Benzyl	I. P.	Convulsions		100	...	..	...
Ethyl N-methyl	I. P.	85	100	420	4.9	5	>4.0
Ethyl N-methyl	Oral	120	160	420	3.5	2	>4.0
Ethyl N-ethyl	I. P.	120	160	570	4.8	2	0.7
Ethyl N-allyl	I. P.	120	140	420	3.5	4	1.0
5-Ethyl 5-isoamyl barbituric acid[h]	I. P.	55	65	205	3.7	7	0.3
5-Ethyl 5-isoamyl barbituric acid[h]	Oral	90	100	345	3.8	3	.3

[a] We are indebted to Mr. Harry J. Pratt for technical assistance in making these determinations. Five or more mice (females) were used at each dose level. From fifty to one hundred mice were used for each sample and each method of administration. [b] Clear aqueous solutions, made by dissolving the dry sodium salts in water, were administered within thirty minutes after the solutions were prepared. Administration was made either by stomach tube (oral) or by intraperitoneal injection (I. P.). [c] AD 50 designates the dose at which 50% of the animals were anesthetized, as evidenced by loss of the righting reflex. Similarly, AD 100 is the lowest dose at which all of the animals lost the righting reflex. [d] LD 50 designates the dose which killed 50% of the animals. The method of computation of AD 50 and LD 50 is the one devised by Behrens and described in Burn, "Biological Standardization," Oxford University Press, London, 1937. [e] The values refer to weights of the free barbituric acids. [f] Time elapsing between injection and loss of the righting reflex. [g] Time elapsing between loss and regaining of the righting reflex. [h] Given as a standard for purpose of comparison.

ties of the amides, which were obtained from both the barbituric and thiobarbituric acid syntheses, are recorded in Table II.

The thiobarbituric acids, with one exception, were prepared in an exactly similar fashion using thiourea. Their properties are recorded in Table III. Ethyl methylisopropenylmalonate under these conditions gave no thiobarbituric acid. Instead a good yield of methylisopropenylmalonic acid,[4] m. p. 132–133° (dec.), was isolated.

Methyl isopropenyl thiobarbituric acid was obtained in poor yield by using one equivalent of sodium ethoxide in the volume of alcohol ordinarily employed with 3 equivalents and refluxing the mixture only nine hours.

Structure of the Amides.—Saturated solutions of 0.3 to 0.5 g. of the butyl and isoamyl substitute amides (Table II) in carbon tetrachloride were treated with a rapid stream of ozonized oxygen at 0 to −5° for one and one-half hours. After removal of the solvent in vacuum, the ozonides were decomposed with zinc dust, water and catalysts, essentially as described by Whitmore and Church.[5]

The volatile products were removed by a rapid steam distillation of a total volume of 75 cc. There was no formaldehyde in the distillate, according to the very sensitive color tests with gallic acid and resorcinol.[6] The more volatile portion of the distillate was removed by distilling 2 cc. and treated with dinitrophenylhydrazine and hydrochloric acid. The dinitrophenylhydrazone of acetone, m. p. and mixed m. p. 124–125°,[7] was formed in each case.

Pharmacological Data.—Results of a preliminary pharmacological assay of the barbituric acid derivatives are recorded in Tables IV and V. The effectiveness of the isopropenyl barbituric acids increases as the size of the other alkyl group increases, reaching a maximum with the butyl and amyl derivatives. The latter are also short in action and induction period, and have high therapeutic ratios.

Substitution of an alkyl group in the 1-position (on nitrogen) increases the effectiveness and therapeutic ratio and shortens the duration and induction period.

The thiobarbituric acids show a similar variation in effectiveness. They have the advantage of a shorter induction period, but all of them produce convulsions to varying degrees.

TABLE V

5-ISOPROPENYL 5-ALKYL THIOBARBITURIC ACIDS, RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a]

5-Alkyl group	AD 50[b] mg./kg.	AD 100 mg./kg.	LD 50 mg./kg.	Ratio, LD 50/AD 50	Duration at AD 100: Induction, min.	Duration at AD 100: Anesthesia, hours
Methyl	560	600	700	1.3	20	1.0
Ethyl	200	250	300	1.5	11	1.5
Propyl	150	200	380	2.5	10	2.0
Allyl	175	200	260	1.5	6	3.0
Butyl	125	150	340	2.7	4	2.6
Amyl	150	165	300	2.0	4	0.1
Isoamyl	140	180	280	2.0	4	.5
Benzyl	...	...	15	...	..	...

[a] By intraperitoneal administration in each case.
[b] For explanation of symbols, see footnotes in Table IV.

Summary

The preparation, properties and preliminary pharmacological assay of several new barbituric and thiobarbituric acid derivatives containing the isopropenyl or 1-methylvinyl group are described. Some alcoholysis of the isopropenyl alkyl malonic esters from which the barbituric acids are prepared occurs during their condensation with urea and thiourea, leading to a series of α-alkyl β-methyl crotonamides.

BRYN MAWR, PENNSYLVANIA

RECEIVED OCTOBER 24, 1938

(4) Kon and Speight, *J. Chem. Soc.*, 2727 (1926).

(5) Whitmore and Church, THIS JOURNAL, **54**, 3710 (1932).

(6) As described in Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1914, Vol. I, p. 24.

(7) Campbell, *Analyst*, **61**, 393 (1936).