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Substituted Vinyl Barbituric Acids. IV. Derivatives Containing a Primary 1-Alkenyl Group

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Previous papers in this series have described the preparation and properties of barbituric acids substituted in the 5-position by (1-alkylvinyl) groups, RCH=C(R')—. This paper concerns barbituric acids containing "primary 1-alkenyl" groups, RCH=CH—, or R_2C=CH, in the 5-position.

The 5-(primary 1-alkenyl)-5-alkylbarbituric acids were prepared by condensing (primary 1-alkenyl)-alkylmalonic esters[3] with urea in the presence of alcoholic sodium ethoxide. Appreciable quantities of the substituted malonic esters underwent cleavage during the condensation, producing monocarboxylic esters and amides derived from them.[4] The yields of purified barbituric acid derivatives, which are recorded in Table I, were low in several cases, due partly to the occurrence of cleavage as a side reaction during the condensations, and partly to difficulties encountered in purification of the products. Most of the substituted barbituric acids did not crystallize readily, and in several cases a number of recrystallizations were required. Only one of the two possible geometric isomers was isolated in each case.

The structures of the barbituric acid derivatives must be those indicated in Table I, since there is no other position in the alkenyl groups which the double bond can take, unless the extremely improbable assumption is made that the double bond can migrate farther into the carbon chain. In the case of the first three compounds listed in Table I, which are 5-propenyl-5-alkyl-barbituric acids, such a migration would produce the corresponding 5-allyl-5-alkyl-barbituric acids, which are known.[5]

The three 5-propenyl-5-alkyl-barbituric acids (Table I) were proved to be different from the corresponding 5-allyl-5-alkyl derivatives by direct comparison in two cases, and by a divergence of physical properties in the third. Moreover, the position of the double bond in 5-propenyl-5-butyl-barbituric acid was definitely established by ozonization, which produced acetaldehyde.

The purity of two of the (primary 1-alkenyl)-alkyl-barbituric acids was established by quantitative reduction. One of the compounds reduced was 5-(1-butenyl)-5-ethyl-barbituric acid, and the reduction product was proved to be 5-butyl-5-ethyl-barbituric acid by direct comparison with a commercial sample of the latter (Neonal).

Experimental Part

The barbituric acid condensations were carried out in the manner previously described.[4a] The properties of the products and the yields of material purified by recrystallization to constant melting point are recorded in Table I.

In each preparation the neutral by-products were separated by ether extraction of the aqueous alkaline solutions containing the substituted barbituric acids, before acidification (as in ref. 4a). In all but two cases, distillation of these extracts gave a mixture of the original substituted malonic ester, the monocarboxylic ester formed by cleavage of a carbethoxy group from the dicarboxylic ester (see ref. 4a), and a small quantity of a solid amide. The quantity of this mixture varied from 10 to 30% of the weight of the original substituted malonic ester.

The amide formed as a by-product in the preparation of 5-isopropyl-5-(1-butenyl)-barbituric acid was present in sufficient quantity to permit isolation and purification, by washing free from ester with hexane and recrystallization from ether and hexane; m. p. 123–124°. Analysis indicated that this amide was 2-isopropyl-2-hexenamide, as expected by analogy with similar cases (ref. 4; the position of the double bond is assumed by analogy).

Anal. Calcd. for $C_9H_{17}ON$: N, 9.03. Found: N, 8.92.

Approximately 40% of the substituted malonic esters, free from cleavage products, were recovered from the condensations which produced 5-(1-isobutenyl)-5-ethyl-barbituric acid and 5-propenyl-5-isopropyl-barbituric acid, respectively.

Structure of 5-(Primary 1-alkenyl)-5-alkyl-barbituric Acids. Quantitative Reductions.—5-(1-Butenyl)-5-ethyl-barbituric acid (3.00 g.) was dissolved in 25 cc. of alcohol and shaken with hydrogen in the presence of 1 g. of palladinized charcoal catalyst. Reduction was complete in thirty minutes, and 98.5% of the theoretical quantity of hydrogen was required (within experimental error of one molar equivalent). The reduction product was isolated by filtering the catalyst and crystallizing from dilute alcohol; yield 2.6 g. (87%); m. p. 122–123°. It was proved to be

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(4) Analogous to the cleavage (or alcoholysis) previously observed in similar cases: (a) Cope and Hancock, *ibid.*, **61**, 96 (1939); (b) Cope and McElvain, *ibid.*, **54**, 4311 (1932).

(5) Their melting points are recorded by Volwiler, *ibid.*, **47**, 2236 (1925).

TABLE I

5-(PRIMARY 1-ALKENYL)-5-ALKYL-BARBITURIC ACIDS

5-(Primary 1-alkenyl) group	5-Alkyl group	M. p., °C. (uncor.)	Yield, %	Formula	Nitrogen, % Calcd.	Found[k]
Propenyl $CH_3CH{=}CH-$	Propyl	150.5–151[a]	40[i]	$C_{10}H_{14}O_3N_2$	13.33	13.38
	Isopropyl	140–141[a]	40[i]	$C_{10}H_{14}O_3N_2$	13.33	13.45
	Butyl	127.5–128.5[b]	50[i]	$C_{11}H_{16}O_3N_2$	12.50	12.49
1-Butenyl $CH_3CH_2CH{=}CH-$	Ethyl	109–110[b]	30[j]	$C_{10}H_{14}O_3N_2$	13.33	13.39
	Propyl	83–84[c]	20	$C_{11}H_{16}O_3N_2$	12.50	12.42
	Isopropyl	107–108[b]	70	$C_{11}H_{16}O_3N_2$	12.50	12.55
	Isopropyl-N-methyl	Liquid[c]	33[i]	$C_{12}H_{18}O_3N_2$	11.76	12.01
	Isopropyl-2-thio	109–110[b]	30	$C_{11}H_{16}O_2N_2S$	11.66	11.68
	Butyl	111–112[b]	12	$C_{12}H_{18}O_3N_2$	11.76	11.71
1-Isobutenyl $(CH_3)_2C{=}CH-$	Ethyl[f]	161.5–162[d]	22[j]	$C_{10}H_{14}O_3N_2$	13.33	13.33
1-Pentenyl $CH_3CH_2CH_2CH{=}CH-$	Ethyl	96.5–98[d]	18	$C_{11}H_{16}O_3N_2$	12.50	12.66
	Isopropyl	94–95[b]	28	$C_{12}H_{18}O_3N_2$	11.76	11.82
1-Isopentenyl $(CH_3)_2CHCH{=}CH-$	Ethyl	126.5–127[a]	30	$C_{11}H_{16}O_3N_2$	12.50	12.36
	Propyl	101–102[d]	12	$C_{12}H_{18}O_3N_2$	11.76	11.72
	Isopropyl	121.5–122[a]	70	$C_{12}H_{18}O_3N_2$	11.76	11.72
1-Methyl-1-butenyl[g] $CH_3CH_2CH{=}C(CH_3)-$	Ethyl-2-thio	150–152[a]	43[j]	$C_{11}H_{16}O_2N_2S$	11.67	11.59
	Propyl-N-methyl	50.5–52.5[h]	18[i]	$C_{13}H_{20}O_3N_2$	11.10	11.11

[a] Recrystallized from dilute alcohol. [b] Recrystallized from benzene and pentane. [c] Distilled in vacuum; b. p. 185–190 (1.5 mm.); then crystallized from benzene and pentane. [d] Recrystallized from ether and pentane. [e] Distilled in vacuum; b. p. 138–142 (1.5 mm.) [f] Geometric isomerism is not possible for this compound. [g] These two compounds are 5-(secondary 1-alkenyl)-5-alkyl-barbituric acids, related in structure to a series previously described in THIS JOURNAL, **61**, 776 (1939). They were prepared by the method used for their homologs, from esters described in THIS JOURNAL, **60**, 2903 (1938). [h] Distilled in vacuum, b. p. 154–158 (1 mm.), then crystallized from ether and pentane. [i] Using two equivalents of sodium ethoxide in a procedure otherwise similar to that described in ref. 4a. [j] Using one equivalent of sodium ethoxide. [k] We are indebted to Mr. C. S. Miller for semi-micro Kjeldahl analyses.

5-butyl-5-ethyl-barbituric acid by determining the mixed m. p. with a commercial sample of Neonal, which gave no depression.

A similar reduction of 3.00 g. of 5-(1-butenyl)-5-isopropyl-barbituric acid required 99.0% of one molar equivalent of hydrogen, and 2.8 g. (93%) of 5-butyl-5-isopropyl-barbituric acid, m. p. 154–155°, was isolated as the reduction product in the same manner.

Anal. Calcd. for $C_{11}H_{18}O_3N_2$: N, 12.39. Found: N, 12.37.

The identity of this sample of 5-butyl-5-isopropyl-barbituric acid was established by the fact that it did not depress the m. p. of a known sample (m. p. also 154–155°) prepared by the reduction of 5-butyl-5-isopropenyl barbituric acid.[4a] Another known sample prepared by the condensation of ethyl butyl-isopropylmalonate with urea had the same m. p.[6]

Comparison of Propenyl and Allyl Alkyl-barbituric Acids.—A mixed m. p. of 5-propenyl-5-isopropyl-barbituric acid (m. p. 140–141°) and 5-allyl-5-isopropyl-barbituric acid (m. p. 136–137°) was 121–127°. A mixture of 5-propenyl-5-butyl-barbituric acid (m. p. 127.5–128.5°) and 5-allyl-5-butyl-barbituric acid (m. p. 126–127°) had m. p. 106–120°.

Ozonization.—The ozonization of 5-propenyl-5-butyl-barbituric acid[7] produced acetaldehyde, m. p. of the 2,4-dinitrophenylhydrazone and mixed m. p. with a known sample 166–168° (cor.).[8]

Pharmacological Data

The results of pharmacological tests of the 5-(primary 1-alkenyl)-5-alkyl-barbituric acids are recorded in Table II. The 1-butenyl and 1-isopentenyl derivatives, particularly those in which the total number of carbon atoms in the groups attached to the barbituric acid nucleus is seven or eight, are the most effective hypnotics with the highest therapeutic ratios of the series. The compounds in which isopropyl is the alkyl group substituted in the 5-position are particularly effective.

The most noteworthy fact about the pharmacological action of these barbiturates is the very short duration of narcosis produced by several of them, particularly the 5-(1-butenyl)-5-isopropyl and 5-(1-isopentenyl)-5-isopropyl derivatives. These substances are short acting even at relatively high dose levels. We have observed similar durations of action heretofore only with N-substituted barbituric acids.

(6) The m. p. of 209–210° recorded by Shonle and Moment, THIS JOURNAL, **45**, 248 (1923), for 5-butyl-5-isopropyl-barbituric acid must be in error.

(7) By a procedure described by Cope and Hancock, *ibid.*, **61**, 353 (1939).

(8) Campbell, *Analyst*, **61**, 392 (1936).

TABLE II

5-(PRIMARY 1-ALKENYL)-5-ALKYL-BARBITURIC ACIDS—RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a,b]

5-(Primary 1-alkenyl) group	5-Alkyl group	Administration	AD 50 mg./kg.	AD 100 mg./kg.	LD 50 mg./kg.	Ratio, LD 50/AD 50	Duration at AD 100 Induction, minutes	Anesthesia, hours
Propenyl	Propyl	I.p.	160	180	420	2.6	8	1.0
$CH_3CH{=}CH{-}$	Propyl	Oral	215	240	550	2.6	22	1.5
	Isopropyl	I.p.	110	120	425	3.9	7	0.6
	Isopropyl	Oral	140	160	520	3.7	10	.5
	Butyl	I.p.	110	120	320	2.9	8	.2
	Butyl	Oral	200	260	480	2.4	9	3.0
1-Butenyl	Ethyl	I.p.	90	110	225	2.5	9	0.3
$CH_3CH_2CH{=}CH{-}$	Ethyl	Oral	130	150	320	2.5	16	>3.0
	Propyl	I.p.	110	125	340	3.1	6	0.3
	Isopropyl	I.p.	60	75	250	4.2	3	.6
	Isopropyl	Oral	100	120	300	3.0	3	.3
	Isopropyl-N-methyl	I.p.	75	80	350	4.7	3	.1
	Isopropyl-2-thio	I.p.	45	60	180	4.0	3	.3
	Isopropyl-2-thio	Oral	55	80	180	3.3	1	>3.0
	Butyl	I.p.	65	80	225	3.5	6	0.3
	Butyl	Oral	160	180	450	2.8	9	.8
Isobutenyl $(CH_3)_2C{=}CH{-}$	Ethyl	I.p.	575	800	1100	1.9	20	>4.0
1-Pentenyl	Ethyl	I.p.	80	100	210	2.6	4	1.6
$CH_3CH_2CH_2CH{=}CH{-}$	Ethyl	Oral	120	140	290	2.4	6	2.0
	Isopropyl	I.p.	75	100	225	3.0	3	0.3
	Isopropyl	Oral	150	160	380	2.5	2	1.0
1-Isopentenyl	Ethyl	I.p.	70	80	260	3.7	7	0.2
$(CH_3)_2CHCH{=}CH{-}$	Ethyl	Oral	100	120	360	3.6	4	1.0
	Propyl	I.p.	115	140	310	2.7	6	0.3
	Isopropyl	I.p.	50	70	200	4.0	5	.2
	Isopropyl	Oral	70	80	280	4.0	4	.2
1-Methyl-1-butenyl[c]	Ethyl-2-thio	I.p.	45	50	170	3.8	6	.3
$CH_3CH_2CH{=}C(CH_3){-}$	Propyl-N-methyl	I.p.	80	90	300	3.8	3	.2

[a] We are indebted to Mr. Harry J. Pratt for technical assistance in making these determinations. [b] The method of testing and the meaning of terms and symbols are described in the first paper of this series (ref. 4a) [c] See footnote "g," Table I.

Summary

A series of fifteen substituted vinyl alkyl barbituric acids has been prepared in which the substituted vinyl groups are of the type RCH=CH— or $R_2C{=}CH{-}$. The chemical and pharmacological properties of the compounds are recorded.

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