[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Substituted Vinyl Barbituric Acids. II. (1-Methylpropenyl) Derivatives

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

Syntheses of disubstituted malonic[1] and cyanoacetic esters[2] in which one substituent is the 1-methylpropenyl group, $CH_3CH{=}C(CH_3)$—, have been reported recently. These esters have been converted into barbituric acid derivatives, which are described in the present communication.

The condensation of (1-methylpropenyl)-alkylmalonic esters with urea gave samples of 5-(1-methylpropenyl)-5-alkylbarbituric acids which were analytically pure after one recrystallization but which required several more crystallizations to reach constant melting points. The same barbituric acids prepared from the corresponding cyanoacetic esters required fewer crystallizations to reach the same melting points. This is of interest because both the malonic and cyanoacetic esters in question were proved by ozonization[1,2] to contain very little of the isomeric derivatives substituted with a 1-ethylvinyl group, $CH_2{=}C(C_2H_5)$—, in place of the 1-methylpropenyl group.

We believe that the difficulty in obtaining constant melting products in this series is due to the presence of geometric rather than structural isomers. The higher melting points obtained initially when the barbituric acids were prepared from the cyanoacetic esters can be attributed to a difference in the ratio of geometric isomers present in the substituted malonic and cyanoacetic esters.

Evidence of the structural homogeneity of 5-ethyl-5-(1-methyl-propenyl)-barbituric acid was obtained by ozonization. Decomposition of the ozonide produced acetaldehyde, which was identified as the 2,4-dinitrophenylhydrazone. Traces of formaldehyde, sufficient in quantity for detection only by sensitive color tests, were obtained from the ozonization. However, the formation of a trace of formaldehyde has no significance in this case, for similar ozonizations of two barbituric acid derivatives substituted with saturated alkyl groups, namely, 5-ethyl-5-butylbarbituric acid and 5-ethyl-5-(1-methylbutyl)-barbituric acid, also produced traces of formaldehyde. In the latter two cases, the formaldehyde must come from general oxidation of the barbituric acid derivatives by ozone, so that traces of formaldehyde produced by the ozonization of any barbituric acid derivative cannot be regarded as structurally significant.

(1) Cope and Hancock, THIS JOURNAL, **60**, 2901 (1938).

(2) Cope and Hancock, *ibid.*, **60**, 2903 (1938).

Experimental Part

In the syntheses of (1-methylpropenyl)-barbituric acids from the malonic esters, the conditions previously used in preparing isopropenyl-alkylbarbituric acids[3] were employed. No amides were obtained from the condensations, since the ether extract containing the neutral products yielded only a small amount of unreacted disubstituted malonic ester in each case. This indicates a smaller susceptibility of the (1-methylpropenyl)-alkylmalonic esters to alcoholysis, as compared to the isopropenyl alkyl derivatives. The following example will illustrate the conditions used in the syntheses from the cyanoacetic esters.

A solution of sodium ethoxide was prepared from 3.68 g. (0.16 mole) of sodium and 100 cc. of absolute alcohol in a 200-cc. round-bottomed flask. Urea, 7.7 g. (0.128 mole), and ethyl *n*-butyl-(1-methylpropenyl)-cyanoacetate, 17.9 g. (0.08 mole), were added and the mixture refluxed for twelve hours from a bath at 105°. The alcohol was then removed in vacuum, the residue dissolved in 100 cc. of water and extracted three times with ether. The ether extract was washed with water and distilled in vacuum; 5 g. of the nitrile formed from the ester by loss of a carbethoxy group through alcoholysis was obtained, b. p. 89–92° (9 mm.). The nitriles obtained in this manner were not purified or analyzed, because of the small quantities which were available. The aqueous solution remaining after the ether extraction was neutralized with concd. hydrochloric acid; considerable carbon dioxide was evolved, and an insoluble imino barbituric acid was precipitated. The imino derivative was hydrolyzed without isolation by adding an equal volume of concd. hydrochloric acid and refluxing for one hour. The mixture was cooled and the crystalline barbituric acid filtered and washed with ice water. As precipitated, it melted at 160–162°, and three recrystallizations brought it to a constant melting point of 166–167°. The crude product weighed 6.5 g. (34%) and the purified product 4.2 g. (22%).

The same barbituric acid prepared from ethyl butyl-(1-methylpropenyl)-malonate melted at 147–150° as precipitated (crude yield 84%) and required six recrystallizations to arrive at the constant melting point of 166–167° (47% yield pure). The barbituric acids prepared from the malonic and cyanoacetic esters, together with a thiobarbituric acid prepared in a similar manner from thiourea and a N-methyl-barbituric acid prepared from methyl urea, are described in Table I.

(3) Cope and Hancock, *ibid.*, **61**, 96 (1939).

TABLE I

5-(1-METHYLPROPENYL)-5-ALKYLBARBITURIC ACIDS

5-Alkyl group	M. p., °C. (uncorr.)	Yield, % (purif.)	Formula	Nitrogen, % Calcd.	Found[a]
Methyl	189.5–190.5	33	$C_9H_{12}O_3N_2$	14.29	14.33
Ethyl[b,c]	154–155	60[d]	$C_{10}H_{14}O_3N_2$	13.33	13.43
Ethyl-1-methyl	103–104	50	$C_{11}H_{16}O_3N_2$	12.50	12.52
Propyl	157–159	60	$C_{11}H_{16}O_3N_2$	12.50	12.30
Propyl-2-thio	163–165	80	$C_{11}H_{16}O_2N_2S$	11.67	11.59
Allyl	126–127	36	$C_{11}H_{14}O_3N_2$	12.61	12.42
Butyl[b]	166–167	47[d]	$C_{12}H_{18}O_3N_2$	11.76	11.62

[a] We are indebted to Mr. C. S. Miller for semi-micro Kjeldahl analyses. [b] Prepared both from the malonic and the cyanoacetic esters. [c] The crude product, melting at 143–144° after one recrystallization, was analytically pure. % N found, 13.29. [d] From the malonic ester.

has been made by administration of their sodium salts to white mice, and the results are recorded in Table II. The compounds as a group have higher therapeutic ratios than the isopropenylalkylbarbituric acids.[3] The most effective of the 5,5-disubstituted compounds is the allyl derivative, which also has the highest therapeutic ratio. This is surprising because in the series of isopropenylbarbituric acids previously studied, the allyl derivative was decidedly inferior to the propyl and butyl compounds. Substitution of methyl on nitrogen, as in 1-methyl-5-(1-methylpropenyl)-5-ethylbarbituric acid, leads to a compound more effective and shorter in action than the corresponding derivative not substituted in the 1-position.

TABLE II

5-(1-METHYLPROPENYL)-5-ALKYLBARBITURIC ACIDS. RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a]

Alkyl group	Administration	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
5-Methyl	I. P.	450	500	1100	2.4	30	2.0
5-Ethyl	I. P.	150	160	490	3.3	20	3.0
5-Ethyl	Oral	150	200	550	3.7	11	>7.0
5-Ethyl-1-methyl	I. P.	55	80	210	3.8	2	1.0
5-Ethyl-1-methyl	Oral	80	100	285	3.6	2	1.2
5-Propyl	I. P.	115	130	460	4.0	14	0.5
5-Propyl	Oral	210	250	665	3.1	20	2.0
5-Propyl-2-thio	I. P.	130	160	475	3.7	5	1.0
5-Propyl-2-thio	Oral	200	240	540	2.7	4	0.3
5-Allyl	I. P.	90	100	380	4.2	20	.5
5-Allyl	Oral	120	160	525	4.4	18	3.0
5-Butyl	I. P.	105	120	330	3.1	4	1.0
5-Butyl	Oral	180	200	600	3.3	7	0.5

[a] We are indebted to Mr. Harry J. Pratt for technical assistance in making these determinations. The conditions of the tests were the same as those described previously.[3] [b] Terms are defined in the previous work.[3]

Ozonizations.—Approximately 1-g. samples of 5-ethyl-5-(1-methylpropenyl)-barbituric acid, 5-ethyl-5-butylbarbituric acid and 5-ethyl-5-(1-methylbutyl)-barbituric acid were dissolved in 20 cc. of ethyl acetate and treated with a rapid stream of ozonized oxygen at −15 to −10° for one and one-half hours. The solvent was removed in vacuum, the residues were decomposed with zinc dust, water and catalysts, and the volatile products removed by distillation as previously described.[1] The aqueous distillates from the decomposition of the ozonides of all three barbituric acids gave positive ring tests for formaldehyde with resorcinol and gallic acid, and a very weak test with resorcinol and sodium hydroxide (see references in Ref. 1). The most volatile portion of the distillate from the ozonization of 5-ethyl-5-(1-methylpropenyl)-barbituric acid on treatment with 2,4-dinitrophenylhydrazine and hydrochloric acid gave the 2,4-dinitrophenylhydrazone of acetaldehyde, m. p. and mixed m. p. with a known sample 166–168° (corr.).[4]

Pharmacological Data.—A pharmacological assay of the (1-methylpropenyl)-barbituric acids

(4) Campbell, *Analyst*, **61**, 391 (1936).

The low melting but analytically pure samples of the 5-ethyl- and 5-butyl-5-(1-methylpropenyl)-barbituric acids obtained after one crystallization were also converted into sodium salts and tested. They proved to be pharmacologically indistinguishable from the constant melting products obtained after several more crystallizations.

Summary

Several barbituric acid derivatives containing the 1-methylpropenyl group in the five-position have been prepared from the corresponding (1-methylpropenyl)-alkylmalonic and cyanoacetic esters. Chemical and pharmacological properties of these new substituted vinyl barbituric acids are reported.

BRYN MAWR, PENNA. RECEIVED DECEMBER 8, 1938