Mannich and Braun[6] stated that the hydrochloride is hygroscopic; no melting point was reported by them.

Analysis of Amine Hydrochlorides.—We found the Fajans method[7] very suitable and advantageous for the determination of chlorine in many of our amine hydrochlorides. Since the method requires some modification in the case of an amine salt, the whole procedure is described below.

In order to carry out the analysis successfully the liberated amine must be extracted with ether. In the event that the amine base is very insoluble in water, ether can be added to the neutralized solution and titration performed without removal of the ether later. If the base is somewhat soluble, as is the case with methylcyclohexylmethylamine, the amine must be extracted and the ether layer removed, otherwise enough of the amine remains in the aqueous layer to obscure the end-point. When an amine was found to be very soluble in water it was so difficult to remove it completely from the water layer that the Fajans method was not used.

A mixture of the amine hydrochloride, which weighed 0.2–0.3 g., 15 cc. of water and one drop of phenolphthalein indicator was made alkaline with 2% chloride-free sodium hydroxide solution. If the amine hydrochloride is insoluble in water, sufficient alcohol may be added to effect solution or the alkali may be added in portions and the mixture agitated or warmed until the red color has disappeared before each addition of the alkali. The liberated amine is extracted three times with 50-cc. portions of ether, the ether layer removed carefully by decantation and the slight amount of solvent which remains can be evaporated on a steam-bath. The cold solution is neutralized with 1:50 nitric acid and diluted to about 75 cc. Ten drops of dichlorofluorescein indicator and 5 cc. of 2% dextrin solution are added and the solution titrated with 0.1 *N* silver nitrate. Calcd. for $C_{23}H_{33}NCl$ (benzyldi-β-cyclohexylethylamine hydrochloride): Cl, 9.75. Found: Cl, 9.73, 9.76.

(7) See Willard and Furman, "Elementary Quantitative Analysis," D. Van Nostrand Co., New York, 1935, p. 138.

Summary

A number of mixed amines of the general type CH_3NRR' have been described in which R and R′ represent alkyl, cycloalkylalkyl and arylalkyl groups. Eleven of the amines were found to be strong antispasmodics.[8]

(8) A very recent contribution to the field of antispasmodics is the paper by Buth, Külz and Rosenmund (*Ber.*, **72**, 19 (1939)).

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 2, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

Substituted Vinyl Barbituric Acids. III. Derivatives Containing a Dialkylvinyl Group Having Five or More Carbon Atoms

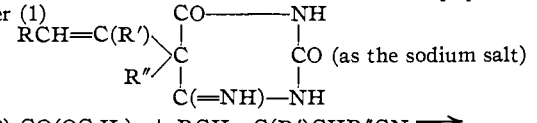
BY ARTHUR C. COPE AND EVELYN M. HANCOCK

The recent syntheses of a number of (dialkylvinyl) alkyl cyanoacetic esters in which the substituted vinyl groups contain five, six and seven carbon atoms,[1] furnished the intermediates necessary for the syntheses of corresponding barbituric acids, which are described in this paper.

The substituted vinyl alkyl cyanoacetic esters condense with urea readily, giving imino barbituric acids which can be hydrolyzed to the barbituric acids. In each case a side reaction occurs during the condensation, in which part of the ester undergoes alcoholysis and loses a carbethoxy group as ethyl carbonate, forming a nitrile.

$$RCH{=}C(R')C(R'')(CN)COOC_2H_5 + H_2NCONH_2 + NaOC_2H_5 \longrightarrow$$

either (1)



(as the sodium salt)

or (2) $CO(OC_2H_5)_2 + RCH{=}C(R')CHR''CN \rightleftharpoons$

I (β,γ) $RCH_2C(R'){=}C(R'')CN$ II (α,β)

(1) Cope and Hancock, THIS JOURNAL, **60**, 2903 (1938).

The nitriles which are produced may have structures corresponding to either I or II, or may be composed of mixtures of the α,β- and β,γ-unsaturated isomers. After loss of a carbethoxy group the double bond can shift through the migration of hydrogen. Nitriles similar in structure to these have been observed to reach equilibrium in the presence of sodium ethoxide as a catalyst.[2] The structures of the nitriles and their synthesis by the alcoholysis of substituted vinyl alkyl cyanoacetic esters will be the subject of a future communication.

In order to produce barbituric acid derivatives according to equation (I) in good yield, it is essential that the alcoholysis (equation II) be minimized. One method by which this may be accomplished is by the substitution of sodium isopropoxide in isopropyl alcohol for the sodium ethoxide in ethyl alcohol usually employed as a condensing agent. Another method which was employed in some cases was to substitute guani-

(2) *Cf.* Kandiah and Linstead, *J. Chem. Soc.*, 2139 (1929); Letch and Linstead, *ibid.*, 443 (1932); Letch and Linstead, *ibid.*, 612 (1933).

TABLE I

5-(DIALKYLVINYL)-5-ALKYL BARBITURIC ACIDS

5-(Dialkylvinyl) group	5-Alkyl group	M. p., °C. (uncorr.)	Yield, %	Yield of nitrile, %	Formula	Nitrogen, % Calcd.	Found[e]
1-Methyl-1-butenyl, $CH_3CH_2CH=C(CH_3)-$	Methyl	160–161	55[b]	20	$C_{10}H_{14}O_3N_2$	13.33	13.28
	Ethyl[g]	162–163	48[a], 51[i]	20	$C_{11}H_{16}O_3N_2$	12.50	12.51
	Propyl[g]	129.5–130.5	50[a], 41[i]	25	$C_{12}H_{18}O_3N_2$	11.76	11.79
	Isopropyl	120–120.5	15[a]	60	$C_{12}H_{18}O_3N_2$	11.76	11.83
	Methyl N-methyl[d]	75–76	30[b]	30	$C_{11}H_{16}O_3N_2$	12.50	12.43
	Ethyl N-methyl[d]	53–55	21[b]	20	$C_{12}H_{18}O_3N_2$	11.76	11.77
1-Ethylpropenyl, $CH_3CH=C(C_2H_5)-$	Methyl	188.5–189.5	60[a]	15	$C_{10}H_{14}O_3N_2$	13.33	13.44
	Ethyl	174.5–175.5	45[a]	30	$C_{11}H_{16}O_3N_2$	12.50	12.37
	Propyl	152.5–153.5	40[a]	[f]	$C_{12}H_{18}O_3N_2$	11.76	11.85
	Isopropyl	125–126	10[a]	60	$C_{12}H_{18}O_3N_2$	11.76	11.76
	Propyl N-methyl[d]	75–76	30[a]	20	$C_{13}H_{20}O_3N_2$	11.11	11.12
1-Methyl-1-pentenyl, $CH_3CH_2CH_2CH=C(CH_3)-$	Methyl	161.5–162.5	50[b]	25	$C_{11}H_{16}O_3N_2$	12.50	12.57
	Ethyl[h]	127–128	40[b]	45	$C_{12}H_{18}O_3N_2$	11.76	11.48
1,3-Dimethyl-1-butenyl, $(CH_3)_2CHCH=C(CH_3)-$	Methyl	195–196	41[c]	15	$C_{11}H_{16}O_3N_2$	12.50	12.39
	Ethyl	188–188.5	47[c]	40	$C_{12}H_{18}O_3N_2$	11.76	11.82
1-Methyl-1-hexenyl, $CH_3CH_2CH_2CH_2CH=C(CH_3)-$	Methyl	159.5–160	38[c], 53[a]	50	$C_{12}H_{18}O_3N_2$	11.76	11.65
	Ethyl	113.5–114	44[c]	40	$C_{13}H_{20}O_3N_2$	11.11	11.02
1-Propyl-1-butenyl, $CH_3CH_2CH=C(C_3H_7)-$	Ethyl	138–139	31[c]	35	$C_{13}H_{20}O_3N_2$	11.11	10.93

[a] Using two equivalents of sodium isopropoxide in isopropyl alcohol. [b] Using two equivalents of sodium ethoxide in ethyl alcohol. [c] Using three equivalents of sodium ethoxide in ethyl alcohol. [d] Recrystallized from a mixture of ether and pentane. [e] We are indebted to Mr. C. S. Miller for all nitrogen analyses by a semi-micro Kjeldahl procedure. [f] Not isolated. [g] Ozonization produced propionaldehyde, m. p. and mixed m. p. of the 2,4-dinitrophenylhydrazone with a known sample 154–155° (uncorr.), *cf.* Campbell, *Analyst*, **61**, 393 (1936). [h] Ozonization produced butyraldehyde, m. p. and mixed m. p. of the 2,4-dinitrophenylhydrazone with a known sample 121–121.5° (uncorr.). [i] By the guanidine procedure.

dine for urea. Guanidine condenses with the esters much more rapidly than does urea, so that there is little time during which alcoholysis can occur. The diiminobarbituric acids which are the products of the guanidine condensations may be hydrolyzed to barbituric acids, although the hydrolysis is slower than that of corresponding mono-imino barbituric acids.

The rates of condensation (equation I) and alcoholysis (equation II) vary according to the structure of both the substituted vinyl group, RCH=C(R')-, and the alkyl group, R''. Particularly extensive alcoholysis occurred in two cases in which R'' was the isopropyl group. Apparently the presence of two branched groups attached to the central or methylene carbon atom of the substituted cyanoacetic ester so retarded the condensation that alcoholysis became the principal reaction.

In contrast to the results obtained in preparing 1-methylpropenyl barbituric acids,[3] these derivatives containing higher substituted vinyl groups were relatively pure as precipitated, and were readily brought to constant melting points by recrystallization. Two geometric isomers should exist for each of the compounds described in Table I, but only one product was isolated in each case. The structures of these products follow from those of the substituted cyanoacetic esters from which they were prepared. In addition, direct proof that the structures of the products are those indicated in Table I was obtained in representative cases. Three of the compounds were ozonized, and in each case the identity of the aldehyde formed served to establish the position of the double bond in the substituted vinyl group. Moreover, the 5-methyl, ethyl and propyl 5-(1-methyl-1-butenyl) derivatives were hydrogenated quantitatively and the products identified as the corresponding 5-alkyl-5-(1-methylbutyl)-barbituric acids.

Experimental Part

The barbituric acid syntheses in which the esters were condensed with urea in the presence of sodium ethoxide were performed in the manner previously described.[3] Sodium isopropoxide was used in a similar manner. The following preparation illustrates the use of guanidine in the condensations.

5-Ethyl-5-(1-methyl-1-butenyl)-barbituric Acid.—A solution of sodium ethoxide was prepared by dissolving 82.8

(3) Paper II, Cope and Hancock, THIS JOURNAL, **61**, 353 (1939).

TABLE II

5-(DIALKYLVINYL)-5-ALKYL BARBITURIC ACIDS. RESULTS OF PHARMACOLOGICAL TESTS IN WHITE MICE[a,b]

5-(Dialkylvinyl) 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	Duration at AD 100 Anesthesia hours
1-Methyl-1-butenyl, $CH_3CH_2CH{=}C(CH_3)$—	Methyl	I. P.	130	140	500	3.8	16	1.0
	Methyl	Oral	220	240	600	2.7	16	>7.0
	Ethyl	I. P.	50	60	180	3.6	9	0.4
	Ethyl	Oral	55	80	190	3.5	6	2.0
	Propyl	I. P.	65	70	270	4.2	7	0.3
	Propyl	Oral	80	100	320	4.0	4	.5
	Isopropyl	I. P.	25	30	100	4.0	4	.3
	Isopropyl	Oral	35	40	120	3.4	3	1.0
	Methyl N-methyl	I. P.	45	50	170	3.8	2	0.3
	Methyl N-methyl	Oral	45	60	190	4.2	4	.2
	Ethyl N-methyl	I. P.	45	50	140	3.1	2	.3
	Ethyl N-methyl	Oral	35	50	125	3.6	3	1.5
1-Ethylpropenyl, $CH_3CH{=}C(C_2H_5)$—	Methyl	I. P.	185	200	580	3.1	21	1.0
	Methyl	Oral	260	350	860	3.3	15	>3.0
	Ethyl	I. P.	90	100	280	3.1	12	0.7
	Ethyl	Oral	120	140	380	3.2	8	1.7
	Propyl	I. P.	90	110	270	3.0	6	0.4
	Propyl	Oral	140	160	340	2.4	5	.4
	Isopropyl	I. P.	45	50	155	3.4	5	.3
	Isopropyl	Oral	55	70	230	4.2	4	.4
	Propyl N-methyl	I. P.	110	120	480	4.4	4	.1
	Propyl N-methyl	Oral	170	180	570	3.4	2	.1
1-Methyl-1-pentenyl, $CH_3CH_2CH_2CH{=}C(CH_3)$—	Methyl	I. P.	120	140	375	3.1	6	1.0
	Methyl	Oral	200	220	620	3.1	7	0.8
	Ethyl	I. P.	55	80	160	2.9	3	1.2
	Ethyl	Oral	60	80	210	3.5	3	0.7
1,3-Dimethyl-1-butenyl, $(CH_3)_2CHCH{=}C(CH_3)$—	Methyl[c]	I. P.	140	150	200	1.4	6	.6
	Ethyl[c]	I. P.	...	...	25	...	..	...
1-Methyl-1-hexenyl, $CH_3CH_2CH_2CH_2CH{=}C(CH_3)$—	Methyl	I. P.	100	120	360	3.6	6	.4
	Methyl	Oral	225	240	820	3.6	6	.7
	Ethyl	I. P.	45	50	130	2.9	8	.1
	Ethyl	Oral	80	100	180	2.3	3	.3
1-Propyl-1-butenyl, $CH_3CH_2CH{=}C(C_3H_7)$—	Ethyl	I. P.	45	50	130	2.9	8	.1
	Ethyl	Oral	80	100	220	2.8	3	1.0

[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; Cope and Hancock, THIS JOURNAL, **61**, 96 (1939). [c] Produced convulsions.

g. of sodium (3.6 moles) in 1200 cc. of absolute alcohol in a two-liter three-necked flask. Guanidine carbonate, 144 g. (0.8 mole), was added to the hot solution with stirring. The sodium ethoxide and guanidine carbonate reacted rapidly, forming guanidine and sodium carbonate. Two moles of sodium ethoxide remained to catalyze the condensation. The mixed ethyl and isopropyl ester of ethyl-(1-methyl-1-butenyl)-cyanoacetic acid, 209 g. (1.0 mole, calculated as the ethyl ester) was added to the mixture during twenty minutes. The heat of reaction was sufficient to keep the solution refluxing during this period. The mixture was refluxed from a bath at 105° for fourteen hours. The alcohol was then removed in vacuum and the residue dissolved in 1200 cc. of water. The solution was made acid to Congo red by adding concd. hydrochloric acid. The volume of the acidified solution was measured, and an equal volume of concd. hydrochloric acid was added in order to make the acid concentration approximately 20%. The resulting solution was refluxed for six hours. After cooling, the crystalline barbituric acid was separated by filtration and washed with a small volume of ice water. One recrystallization from dilute alcohol was sufficient to purify the product; m. p. 162–163°, yield 114 g. (51%). During the hydrolysis with hydrochloric acid the diiminobarbituric acid is at first completely soluble in the hot acid; after about five minutes of refluxing a voluminous crystalline precipitate of a monoimino barbituric acid separates. This precipitate slowly goes back into solution, and after one and one-half to two hours of refluxing the barbituric acid suddenly starts to crystallize. Since the hydrolysis of the corresponding 4-iminobarbituric acid, obtained by condensing the same ester with urea, is complete in one hour or less, while this hydrolysis requires six hours, presumably in the hydrolysis of the diimino derivative the imino group in the 4 position is removed rapidly, and the 2-imino group much more slowly.

The properties of eighteen substituted vinyl alkyl barbituric acids, prepared by one of the three condensation procedures, and the yields of purified products, are recorded in Table I. The yields of nitriles formed as by-products are given as a rough indication of the amount of alcoholysis which occurred in each case. The nitriles were distilled and had relatively constant boiling points, but the amounts available in most cases did not permit the careful fractionation necessary to obtain pure samples for analysis.

Ozonizations.—The barbituric acids designated by footnotes (*g*) and (*h*), Table I, were ozonized by the procedure previously used for (1-methylpropenyl) alkyl barbituric acids.[3] The volatile aldehydes produced on the decomposition of the ozonides were identified by converting them to the 2,4-dinitrophenylhydrazones, whose melting points are recorded in the footnotes. Traces of formaldehyde detectable by color tests also were formed in the ozonizations but, as pointed out previously,[3] this does not necessarily indicate the presence of traces of the isomeric compounds in which the substituted vinyl group has the structure $CH_2{=}C(R)—$, since even saturated barbituric acids give traces of formaldehyde on ozonization.

Quantitative Reductions.—Samples of methyl, ethyl and propyl (1-methyl-1-butenyl) barbituric acids (the first three compounds in Table I) were dissolved in alcohol and reduced with hydrogen in the presence of a palladinized charcoal catalyst. In each case one molar equivalent of hydrogen was absorbed, within experimental error. The catalyst was separated by filtration and the reduction product purified by one or two crystallizations. The methyl derivative gave 5-methyl-5-(1-methylbutyl)-barbituric acid,[4] m. p. 179–180°. The ethyl derivative gave 5-ethyl-5-(1-methylbutyl)-barbituric acid,[4] m. p. and mixed m. p. with a known sample 129–130°. The propyl derivative gave 5-propyl-5-(1-methylbutyl)-barbituric acid,[4] m. p. 85–87°.

Pharmacological Data

The results of preliminary pharmacological tests made on the new substituted vinyl barbituric acids are recorded in Table II. The (1-methyl-1-butenyl) and (1-ethylpropenyl) derivatives are effective hypnotics which have high therapeutic ratios. In both of these groups of compounds the substituted vinyl group contains five carbon atoms. The majority of the remaining compounds, in which the substituted vinyl groups have six and seven carbon atoms, have somewhat lower therapeutic ratios. The compounds containing a (1-methyl-1-butenyl) group, with the exception of the methyl derivative, are effective in practically the same dosage when administered orally to white mice as when administered intraperitoneally. This indicates unusually efficient absorption of the (1-methyl-1-butenyl) compounds following administration by mouth. The presence of two branches in the chain of the substituted vinyl group appears to be undesirable, since both of the (1,3-dimethyl-1-butenyl) compounds produced convulsions, and the ethyl derivative had no narcotic action whatever.

Summary

A number of 5-(dialkylvinyl)-5-alkyl barbituric acids have been prepared by condensing substituted vinyl alkyl cyanoacetic esters with urea or guanidine, and hydrolyzing the resulting imino barbituric acids. Several of the barbituric acids, particularly those in which the substituted vinyl group contains five carbon atoms, are effective hypnotics with high therapeutic ratios.

BRYN MAWR, PENNSYLVANIA

RECEIVED JANUARY 20, 1939

(4) Volwiler and Tabern, *ibid.*, **56**, 1139 (1934).

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

The Action of Barium Hydroxide on the Monobasic Sugar Acids. III

BY FRED W. UPSON, WILLIAM K. NOYCE AND WALTER D. ALBERT

This paper is a continuation of the work of Bonnett and Upson[1] and Albert and Upson,[2] and presents the results of a quantitative study of the products resulting from the action of barium hydroxide on several aldonic acids at a temperature of 140° for twenty-four hours. The compounds studied were glycolic acid, *dl*-erythronic acid, α-*d*-glucoheptonic acid, *l*-rhamnonic acid and α-*l*-rhamnohexonic acid. We now have information concerning the alkali decomposition of aldonic acids containing from two to seven carbon atoms including two methyl aldonic acids and also glycolic acid.

(1) Bonnett and Upson, THIS JOURNAL, **55**, 1245 (1933).
(2) Albert and Upson, *ibid.*, **57**, 132 (1935).

Experimental

Materials.—The various materials used in this study either were prepared in this Laboratory by known methods or obtained from commercial sources. The *dl*-erythronic lactone was supplied by Dr. J. W. E. Glattfeld of the University of Chicago. The different substances were purified where necessary. Analysis, specific rotation