[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

5,5-Crotyl Alkyl Barbituric Acids[1]

BY WILBUR J. DORAN AND H. A. SHONLE

A recent report from this Laboratory described a series of barbituric acids containing the unsaturated 2-methylallyl.[2] Since some of these derivatives produced an anesthesia of brief duration, we believed that the isomeric 5,5-crotyl alkyl and 5,5-(1-methylallyl) alkyl barbituric acids might also be of short duration.

Crotyl substituted barbituric acids described in the literature are 5,5-dicrotyl,[3] 5,5-crotyl allyl[4] and, since the preparation of the barbituric acids herein described was completed, 5,5-crotyl isopropyl[5] and 5,5-crotyl isobutyl barbituric acids.[5]

A representative group of 5,5-crotyl alkyl barbituric acids, prepared by treating the sodium salts of 5-monoalkyl barbituric acids with crotyl bromide, is described in this paper. The treatment of 5-monoethyl barbituric acid with crotyl bromide gave two 5,5-crotyl ethyl barbituric acids, which we believe to be the *cis* and *trans* isomers. Our crotyl isopropyl and crotyl isobutyl barbituric acids differ in melting points from those described in the I. G. Farbenindustrie patent.[5] These may also be cases of *cis* and *trans* isomers.

A barbituric acid containing the isomeric 1-methylallyl group in the 5-position, and a 2-crotyl thiobarbituric acid were included in this study.

Pharmacological results, in Table I, give the minimum anesthetic dose (M. A. D.), the minimum lethal dose (M. L. D.) and the average duration of anesthesia determined by the intraperitoneal administration of dilute solutions of the sodium salts of the barbituric acids in white rats. With few exceptions the 5,5-crotyl alkyl barbituric acids produce an anesthesia of shorter duration than the isomeric 2-methylallyl barbituric acids. 5,5-(1-Methylallyl) ethyl barbituric acid has a duration of anesthesia twice as long as that of the isomeric *cis*- and *trans*-crotyl ethyl barbituric acids, while 5-*n*-butyl 2-crotyl thiobarbituric acid produced only convulsant effect.

(1) Presented before the Division of Medicinal Chemistry at the 96th meeting of the American Chemical Society, Milwaukee, Wisconsin, September 5 to 9, 1938.

(2) Doran and Shonle, THIS JOURNAL, **59**, 1625 (1937).

(3) Braun and Schirmacher, *Ber.*, **56**, 538 (1923).

(4) Taub, Schutz and Meisenberg, U. S. Patent 1,511,919, Oct. 14, 1924.

(5) I. G. Farbenindustrie A.-G., British Patent 475,948, Nov. 29, 1937.

Experimental

The crotyl alkyl barbituric acids were prepared either by condensing the crotyl alkyl ethyl malonate with urea, or by condensing crotyl bromide with the alkyl barbituric acid, using the usual procedure for the introduction of the allyl group.

Since the action of phosphorus tribromide on crotyl alcohol produces an equilibrium mixture of crotyl and 1-methylallyl bromide (consisting of 87% of the primary isomer), it is necessary to separate these isomers by distillation procedures just prior to use.[6] Instead of using vacuum, we used atmospheric pressure for the fractionation of the crotyl bromide from this isomeric mixture. Fractionating 222 g. through a 30-cm. Widmer column during a period of two hours, we obtained as a final fraction 31.5 g. boiling at 106–108° (uncorr.) and possessing $n^{25}D$ 1.47936. It was therefore almost pure crotyl bromide.

FRACTIONATION OF 222 G. OF AN ISOMERIC MIXTURE OF CROTYL BROMIDE

Fraction	B. p., °C. (uncorr.)	Wt., g.	$n^{25}D$	% crotyl bromide
1	98–100	8.8	1.46228	11.0
2	100–101	25.3	1.47003	51.0
3	101–103	30.0	1.47218	61.5
4	103–105	33.8	1.47479	75.0
5	105–103	41.6	1.47677	86.5
6	105–106	36.3	1.47872	96.0
7	106–108	31.5	1.47936	99.5
8 Residue		10.0		
		217.3		

1-Methylallyl bromide was obtained from the equilibrium mixture of crotyl and 1-methylallyl bromides by slow fractionation through a long column at atmospheric pressure.[6] The fraction boiling at 88–90° which was used contained less than 10% of the primary bromide.

To dilute alcoholic solutions of the sodium salts of the various pure monosubstituted barbituric acids, were added molecular proportions of the freshly distilled crotyl bromide. In some instances a small amount of a copper salt was added. The reaction was completed usually after several hours of warming. The crude 5,5-crotyl alkyl barbituric acids which separated at the end of the reaction, after the alcohol solvent was removed under vacuum, were dissolved in chloroform and were freed from unreacted 5-mono alkyl barbituric acids by extracting with dilute sodium bicarbonate solution. The disubstituted barbituric acids were freed from chloroform and then recrystallized from dilute alcohol until a constant melting point was obtained.

In the case of 5,5-crotyl ethyl barbituric acid two fractions were obtained on recrystallizing from dilute alcohol, each of which had a constant melting point. The final purification of the lower melting isomer was effected by

(6) Winstein and Young, THIS JOURNAL, **58**, 104 (1936).

TABLE I

5,5-Crotyl alkyl barbituric acid	M. p., °C.[a]	% Nitrogen Calcd.	% Nitrogen Found		M. A. D. mg./kg.	M. L. D., mg./kg.	Average duration of M. A. D., min.
Ethyl	108–110	13.34	13.43	13.34	100	280	372
Ethyl	120–121	13.34	13.36	13.38	100	240	300
n-Propyl	160–161	12.50	12.58	12.60	130	340	120
1-Methylethyl	144–145[b]	12.50	12.46	12.76	70	180	200
n-Butyl	142–143	11.76	11.79	11.82	110	320	40
1-Methylpropyl	130–131	11.76	11.93	11.94	80	220	120
2-Methylpropyl	126–127[b]	11.76	11.92	11.77	100	300	45
1-Methylbutyl	110–113[c]	11.11	11.15	11.19	90	200	66
3-Methylbutyl	147–148	11.11	11.22	11.29	120	180	40

Ethyl 1-methylallyl barbituric acid had a M. A. D. of 125 mg./kg. and a M. L. D. of 175 mg./kg. The average duration of M. A. D. was seven hundred and twenty minutes.

[a] Anschütz thermometer used. [b] British Patent 475,948 gives a melting point of 137–138° for 1-methylethyl crotyl barbituric acid and 115° for 2-methylpropyl crotyl barbituric acid. [c] Also obtained in a hydrated form melting at 88–90°, calcd. for $C_{13}H_{20}N_2O_3 \cdot H_2O$: N, 10.37%; found: N, 10.58 and 10.65%.

recrystallization from hot water. That these are isomeric crotyl ethyl barbituric acids and not a mixture of crotyl ethyl and 1-methylallyl ethyl barbituric acids was proved by the catalytic hydrogenation of each isomer. Using Adams platinum catalyst, each isomer, after reduction, gave butyl ethyl barbituric acids which had identical melting points, and which showed no depression in melting point when mixed with each other or when mixed with a known sample of *n*-butyl ethyl barbituric acid. From this it is evident that they were isomeric crotyl ethyl barbituric acids, presumably of the *cis–trans* type. Some evidences of similar isomers were obtained with some of the other barbituric acids, but the amounts were so small that products of constant melting point were not obtained.

1-Methylallyl bromide, obtained as described above, was added immediately to a solution of a molecular amount of sodium ethylate and ethyl ethylmalonate in absolute alcohol. The solution was kept cold during the addition. It was then stoppered and allowed to come to room temperature and to stand at room temperature for two days. It was desired to avoid the use of heat during this reaction, because of the rapid isomerization rate of 1-methylallyl bromide. The crude 1-methylallyl ethyl ethyl malonate was freed from alcohol and sodium bromide, dried, and fractionated under vacuum. Two fractions were obtained, the first being 1-methylallyl ethyl ethyl malonate, boiling at about 104–108° (uncorr.) at 6 mm. and possessing $n^{25}D$ 1.4333, and the second, crotyl ethyl ethyl malonate, boiling at 114–118° (uncorr.) at 6 mm. and possessing $n^{25}D$ 1.4390. The identification of these malonic esters was established from the structures of the barbituric acids obtained by condensing the esters in the usual manner with urea in the presence of sodium ethylate.

The lower boiling ester gave a barbituric acid which melted at 146.5–148.0°. The anal. calcd. for $C_{10}H_{14}O_3N_2$: N, 13.34; found: N, 13.36 and 13.16. When it was reduced catalytically using Adams catalyst, a reduced barbituric acid was obtained which after crystallization melted at 165.5–166.0°. Since there was no depression of the melting point when mixed with a known sample of 5,5-secondary butyl ethyl barbituric acid, it was evident that we originally had 5,5-(1-methylallyl) ethyl barbituric acid. Crystals of the two forms of crotyl ethyl barbituric acid melting at 107° and 118–119° were obtained when the higher boiling ester fraction was condensed with urea.

5,5-Crotyl *n*-propyl, 5,5-crotyl 1-methylethyl, 5,5-crotyl *n*-butyl, 5,5-crotyl 1-methylpropyl, 5,5-crotyl 2-methylpropyl, 5,5-crotyl 1-methylbutyl, and 5,5-crotyl 3-methylbutyl barbituric acids were prepared by treating freshly fractionated crotyl bromide with the sodium salt of the appropriate monosubstituted barbituric acid.

5,5-Crotyl 1-methylbutyl barbituric acid was also prepared from urea and crotyl 1-methylbutyl ethyl malonate, which was prepared by condensing crotyl bromide with 1-methylbutyl ethylmalonate in the presence of sodium ethylate. Crotyl 1-methylbutyl ethyl malonate boiled at 140–145° (uncorr.) at 10 mm. and possessed $n^{25}D$ 1.4450.

A solution of the sodium salt of 5-*n*-butyl thiobarbituric acid was treated with crotyl bromide with the expectation of obtaining 5,5-*n*-butyl crotyl thiobarbituric acid. After several hours of refluxing, part of the alcohol was taken off under vacuum and the reaction product filtered off and washed with sodium bicarbonate solution. The resulting disubstituted thiobarbituric acid was purified by several recrystallizations from dilute alcohol and had a melting point of 238–239°. The anal. calcd. for $C_{12}H_{18}N_2O_2S$: N, 11.02; found: N, 11.09 and 11.14.

Since the injection of a sodium salt of this thiobarbituric acid produced only convulsions, the possibility of substitution on an atom other than the methylene carbon had to be considered.

A portion of the *n*-butyl crotyl thiobarbituric acid was refluxed for about twenty hours in dilute alcoholic hydrochloric acid solution. The alcohol was evaporated off and the residue filtered off and recrystallized from dilute alcohol. A product melting at 203–205° (uncorr.) was obtained. When it was mixed with 5-*n*-butyl barbituric acid (m. p. 204–207°. uncorr.) there was no depression of the melting point. From these facts, it was evident that the crotyl group was attached to the sulfur and that the disubstituted thiobarbituric acid melting at 238–239° was 5-*n*-butyl 2-crotyl thiobarbituric acid.

The reaction of crotyl bromide with 5-*n*-butyl thiobarbituric acid is therefore different from its reaction with 5-*n*-butyl barbituric acid.

A similar reaction had been reported previously for alkyl, allyl and benzyl halides and 5-methyl thiobarbituric acid.[7]

Table I covers some of the physical properties of the

(7) Nishikawa, *J. Chem. Soc. Jap.*, **56**, 1487 (1935); *ibid.*, **58**, 97 (1937).

crotyl alkyl barbituric acids described and includes a brief summary of their pharmacological response.

Summary

Crotyl ethyl, crotyl 1-methylbutyl and 1-methylallyl ethyl ethyl malonates have been prepared and characterized. A series of eight crotyl alkyl barbituric acids has been prepared, and some of their physical and pharmacological properties are described. Also 5,5-(1-methylallyl) ethyl barbituric acid and 5-*n*-butyl-2-crotyl thiobarbituric acids have been prepared and pharmacologically studied.

The presence of *cis–trans* isomers has been observed in 5,5-crotyl alkyl barbituric acids.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Preparation of Acetylenic Carbinols[1]

BY KENNETH N. CAMPBELL, BARBARA K. CAMPBELL AND LAWRENCE T. EBY

Acetylenic alcohols have been prepared, in general, through the Grignard reaction[2] or by condensing an acetylene with an aldehyde or ketone in an anhydrous solvent such as ether. In some cases the latter reaction has been carried out using the sodium derivative of the acetylene,[3] in others the sodium enolate of the carbonyl compounds has been used,[4] while in still other cases use has been made of condensing agents such as sodamide,[5a] potassium *t*-butylate[5b] and potassium hydroxide.[5c] None of these methods is entirely satisfactory.

Since large amounts of acetylenic alcohols were needed for other work, we investigated the preparation of these alcohols from sodium acetylide and a carbonyl compound, using liquid ammonia as a solvent. Such a method would have considerable advantages over the older methods in simplicity and ease of manipulation. At the time this work was started, there was but one reference in the literature to the use of liquid ammonia as a solvent for the reaction.[6] Later, McGrew and Adams[7] reported the preparation of ethynylethylcarbinol by a method similar to ours, and a recent series of patents[8] describes the preparation of some acetylenic carbinols in liquid ammonia solution.

We have shown that sodium acetylide in liquid ammonia will condense with many aldehydes and ketones to give the corresponding carbinols in good yields (see Table I) and the method is a general one. Comparatively small amounts of the glycols, formed by the condensation of two molecules of the carbonyl compound with one of acetylene, were obtained. The yield of the acetylenic carbinols can be increased, and that of the glycol decreased, by passing acetylene gas into the mixture during the entire course of the reaction. The reaction has been extended successfully to include the sodium derivatives of monoalkyl acetylenes. Several of the carbinols prepared in this work have not been described before. These include: 1-phenyl-3-propyn-1-ol, 3-methyl-4-nonyn-3-ol, 4-methyl-5-decyn-4-ol, 4-nonyn-3-ol and 4-methyl-5-undecyn-4-ol.

In the case of methylethylethynylcarbinol, this method of preparation was compared with others. The liquid ammonia method was found to be the most satisfactory, as it gave better yields and was carried out more easily. Although a direct comparison of methods was not carried out in other cases, the short time required, and the ease of manipulation, in the liquid ammonia method would seem to make it preferable even if, in certain cases, other methods gave better yields.

The condensation of sodium acetylide with a carbonyl compound does not seem to involve an enol form of the latter, since benzophenone and benzaldehyde will undergo the reaction. The following mechanism is suggested to explain the glycol formation, and the effect of excess acetylene gas.

$$HC{\equiv}CNa + R{-}\underset{\underset{O}{\|}}{C}{-}R' \longrightarrow$$

(1) Paper XXIX on the chemistry of substituted acetylenes; previous paper, THIS JOURNAL, **60**, 1717 (1938).

(2) Iotisch, *Bull. soc. chim.*, [3] **34**, 181 (1905).

(3) Nef, *Ann.*, **308**, 264 (1899); Moureu and Desmots, *Bull. soc. chim.*, **27**, 360 (1902).

(4) Locquin and Sung, *ibid.*, [4] **35**, 597 (1924).

(5) (a) Ruzicka, *Helv. Chim. Acta*, **2**, 182 (1919); (b) Gould and Thompson, THIS JOURNAL, **57**, 340 (1935); (c) Favorsky, *Bull. soc. chim.*, **26**, 284 (1901).

(6) Bayer and Co., German Patent, 285,770; *Friedländer*, **12**, 57–58 (1914–16).

(7) McGrew and Adams, THIS JOURNAL, **59**, 1499 (1937).

(8) Kreimeier, U. S. Patents 2,106,180–2,106,182 (1936); *C. A.*, **32**, 2547 (1938).