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.

INDIANAPOLIS, INDIANA RECEIVED OCTOBER 5, 1938

[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).

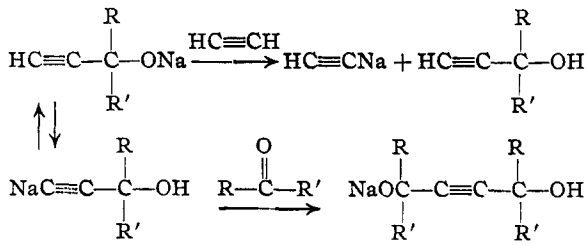
(4) Locquin and Sung, *ibid.*, [4] **35**, 597 (1924).

(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).



The preparation of the chloride from methylethylethynylcarbinol was investigated in some detail. Gaseous hydrogen chloride at 0° reacted only slightly with the alcohol, and little or no chloride was formed. Phosphorus trichloride in pyridine gave the chloride in fair yields, but the purification was difficult. Concentrated aqueous hydrochloric acid reacted with the carbinol at room temperature to give the chloride in about 40% yields, and purification was fairly simple. A more detailed study of the preparation and reactions of such acetylenic halides is in progress.

Experimental

Preparation of Alkylethynylcarbinols.—One mole of sodium acetylide was prepared[9] by adding 23 g. of sodium to about 1 liter of liquid ammonia, contained in a 2-liter, 3-necked round-bottomed flask fitted with a mechanical stirrer, while a rapid stream of dry acetylene was passing through the solvent. The acetylene was then shut off, and one mole of the aldehyde or ketone was added dropwise, with stirring, over a period of one hour. Stirring was continued for about three hours longer, with addition of liquid ammonia from time to time to keep the liquid level at about 1 liter. If acetylene gas is passed through the reaction mixture for the entire time, the yield of carbinol is in some cases, at least, higher and less glycol is formed. The reaction mixture may be hydrolyzed immediately, but generally the liquid ammonia was allowed to evaporate (overnight) and the resulting solid was hydrolyzed with ice and water. The hydrolysis mixture was made slightly acid, with cooling, with 50% sulfuric acid, the organic layer dissolved in ether, if viscous, washed with brine and dried over magnesium sulfate. The original aqueous layer and the wash water were extracted with ether in the case of the lower, water-soluble carbinols, and the extract added to the main product. The residue remaining after evaporation of the ether was distilled under reduced pressure through a small Vigreux column. In nearly all cases some high-boiling glycol was obtained after the carbinol had distilled over.

Preparation of Alkylalkynylcarbinols.—A liquid ammonia solution of sodamide was prepared[10] from 23 g. of sodium, 0.5 g. of ferric nitrate and 1.5 liters of liquid ammonia. To this was added 1.1 moles of alkylacetylene, dropwise, with stirring, in the course of fifteen minutes, and the mixture was stirred for an additional thirty minutes. Then 1 mole of aldehyde or ketone was added dropwise over a period of one hour. Stirring was continued for three hours and the mixture was allowed to stand overnight to evaporate the ammonia. The residue was hydrolyzed with ice and water and made slightly acid with 50% sulfuric acid. The organic layer was washed with water, dried over magnesium sulfate and distilled under reduced pressure through a small Vigreux column.

Preparation of Methylethylethynylcarbinol by Other Methods. Grignard Method.—An acetylenic Grignard reagent was prepared by treating ethylmagnesium bromide (made from 34 g. of magnesium and 166 g. of ethyl bromide) with a current of dry acetylene gas for several hours. The Grignard reagent was then cooled in an ice-bath, and a solution of 72 g. of methyl ethyl ketone in an equal volume of dry ether added over a period of three hours. The mixture was hydrolyzed and worked up in the usual way. There was obtained a 6% yield of carbinol, and a 65% yield of glycol.

Potassium *t*-Butylate Method.—The procedure of Gould and Thompson[5b] was followed. Considerable difficulty was found in purifying the product, as the *t*-butyl alcohol and the carbinol tended to distill together. A 40% yield of pure carbinol was obtained.

Sodium *t*-Butylate as Condensing Agent.—Sodium *t*-butylate was prepared by adding 23 g. of sodium to a liquid ammonia solution of 150 g. of *t*-butyl alcohol. The liquid ammonia was removed by allowing the mixture to stand overnight, and then heating it for two to three hours on a water-bath to drive off excess *t*-butyl alcohol and residual ammonia. The rest of the procedure was similar to that used with potassium *t*-butylate. A 53% yield of carbinol was obtained.

Conversion of Methylethylethynylcarbinol to the Chloride.—When 50 g. of the carbinol (b. p. 78° under 150 mm., $n^{20}D$ 1.4310) was saturated at 0° with dry hydrogen chloride, the product shaken with anhydrous potassium carbonate and distilled from fresh carbonate, no halogen-containing compound was obtained, and 26 g. of the carbinol, b. p. 74–78° under 150 mm., $n^{20}D$ 1.4330, was recovered.

The general procedure of Juvala[11] was tried. A mixture of 60 g. of carbinol and 11 g. of pyridine was added dropwise, with stirring, at 0°, to 33 g. of phosphorus trichloride. The liquid layer was decanted, the solid residue washed with a little dry ether and the liquid and ether combined and stored over anhydrous potassium carbonate. The material was distilled under reduced pressure through a small helix-packed column from fresh carbonate to give 20 g. of an impure chloride, b. p. 50–57° (135 mm.), $n^{20}D$ 1.4330–1.4386, d^{20}_4 0.9175.

Forty grams of the carbinol was shaken for a few minutes with 200 cc. of concentrated hydrochloric acid. The layers were separated, and the organic layer was stored in a refrigerator over anhydrous potassium carbonate. The light yellow liquid was distilled through a small helix-packed column from fresh carbonate to give 30 g. of material of b. p. 51–60° (137 mm.), $n^{20}D$ 1.4328–1.4390. Refractionation of this material yielded 20 g. of chloride of b. p. 51–52° (135 mm.), $n^{20}D$ 1.4328–1.4331, d^{20}_4 0.9140, MR_D obsd. 33.13, MR_D calcd. 32.71.

Anal. Calcd. for C_6H_9Cl: Cl, 30.41. Found: Cl, 30.36

(9) Vaughn, Hennion, Vogt and Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

(10) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(11) Juvala, *Ber.*, **63**, 1989 (1930).

TABLE I

YIELDS AND PHYSICAL CONSTANTS OF CARBINOLS

Acetylene	Carbonyl cpd.	Yield, %	B. p., °C.	Press., mm.	$n^{20}D$	d^{20}_4	*MR* obsd.	*MR* calcd.
Acetylene	Acetone	23	60	120	1.4207	0.8618	24.74	24.81
Acetylene	Acetone	55[a]						
Acetylene	Me Et ketone	60	78	150	1.4310	.8688	29.24	29.43
Acetylene	Me Et ketone	72[a]						
Acetylene	Me *n*-Pr ketone	50	58	26	1.4338	.8620	33.88	34.05
Acetylene	Me *n*-Am ketone	40	88	26	1.4396	.8547	43.20	43.28
Acetylene	Cyclohexanone	55	74	14	1.4820	.9873	36.35	36.47
Acetylene	Acetophenone	7[b]	101	14	1.5370	1.0314	44.26	44.30
Acetylene	Benzophenone	50	M. p. 49°					
Acetylene	Benzaldehyde	45	114	12	1.5508	1.0655	39.56	39.68
1-Hexyne	Me Et ketone	55	96	18	1.4487	0.8555	48.33	47.90
1-Hexyne	Acetaldehyde	21	88	40	1.4347	.8577	38.37	38.66
1-Hexyne	Me *n*-Pr ketone	65	106	20	1.4490	.8539	52.92	52.52
1-Heptyne	Me *n*-Pr ketone	65	120	19	1.4508	.8561	57.32	57.14

[a] Acetylene gas was passed through the mixture during the entire reaction. Mr. Froning has obtained 60% yields of dimethylethynylcarbinol and 15% yields of the glycol by this method, on 5-mole runs. See J. F. Froning, Master's Dissertation, University of Notre Dame, 1938. [b] Other workers have obtained poor yields from acetophenone. See Carothers and Coffman, THIS JOURNAL, **54**, 4071 (1932).

Summary

1. A general method has been described for the preparation of acetylenic carbinols from the sodium salt of acetylene or a monoalkylacetylene, and an aldehyde or ketone, in liquid ammonia solution.

2. Several new acetylenic carbinols have been prepared and characterized.

3. The preparation of the chloride from methylethylethynylcarbinol has been described.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, THE UNIVERSITY OF ROCHESTER]

Relation of Refractive Index to Density in Dental Hard Tissues[1]

BY RICHARD S. MANLY[2]

In certain biological mixtures and in many mineral series, the refractive index has become valuable because it is linearly related to the density. Since in previous work[3] a number of density fractions of pure enamel and dentine had been prepared, the mean refractive indices were determined to discover any similar relations in these tissues.

The reported values for the refractive indices of enamel are in good agreement. Von Ebner[4] and Hoppe[5] report a figure of 1.627 for the ordinary ray and the former, 1.6234 for the extraordinary ray. Taylor and Sheard[6] and Eisenberg[7] noted that the refractive index of enamel prisms ranges between 1.612 and 1.625. Wishart in 1933 (personal communication) examined a few specimens of enamel and found the refractive index to be less than 1.625, usually near 1.618, but appearing to vary somewhat from that number. For two samples of normal dentine Taylor and Sheard[6] found a refractive index of 1.577 ± 0.003. No values for the refractive index of cementum have been reported.

Experimental

A "mean refractive index" was estimated by the following interpolation procedure. A few milligrams of the 60-mesh enamel or dentine powder was stirred into a drop of liquid of known refractive index and placed on a constant temperature stage under a microscope. A "sodium" filter (Eastman Kodak Co. filters nos. 64 and 73) was used over the light source. Determination of the mean refractive index, *i. e.*, the refractive index at which half the particles were higher and half lower than the liquid, was made by interpolation from the counts obtained with 3 or 4 different liquids.

(1) This work was supported in part by the Rockefeller Foundation and in part by the Carnegie Corporation of New York.

(2) From a thesis submitted to the Division of Graduates Studies of the University of Rochester in partial fulfilment of the degree of Doctor of Philosophy, June, 1938.

(3) Manly, Hodge and Ange, *J. Dent. Research*, in press.

(4) Von Ebner, *Deut. Monatsh. Zahnhlk.*, **41**, 65 (1903).

(5) Hoppe, *Virchow's Arch. path. Anat.*, **24**, 13 (1892).

(6) Taylor and Sheard, *Proc. Soc. Exptl. Biol. Med.*, **26**, 257 (1928); *J. Biol. Chem.*, **81**, 479 (1929).

(7) Eisenberg, *Am. Dental Surg.*, **50**, 225 (1930).