[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

HYPNOTICS AND ANTICONVULSANTS. II. HALOGENATED TERTIARY ACETYLENIC CARBINOLS

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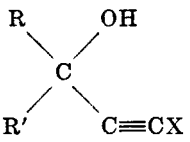
In connection with a research program on tertiary acetylenic carbinols as central nervous system depressants,[1] we were interested in determining the effect of halogen substitution on activity in this series. We therefore prepared and screened a number of halogenated acetylenic carbinols of different types.

The first class of compounds to receive attention was that of the haloethynyl carbinols of general structure I. A few members of this class (R and R′ = alkyl; X = Cl or Br) were prepared some years ago (1) and even studied pharmacologi-



I

cally (2). We have prepared other compounds of this type, including several in which one of the R groups is unsaturated or in which X = I. The published method (1) of preparation, involving treatment of the ethynyl carbinol with a strongly alkaline hypohalite solution, worked well in the simpler cases, but the chlorination of compounds in which one of the R groups is unsaturated had to be carried out with great care, since explosions were then usually encountered. The method failed where X = I, and the two iodo compounds were prepared by treatment of the sodium salts of the ethynyl carbinols in liquid ammonia with iodine (3).

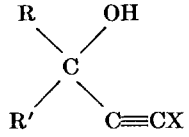
The ethynyl carbinols (I, X = H) used in this work are known; some of them were described in the preceding paper.[1] The pharmacology of the haloethynyl carbinols has been reported elsewhere (4), and the physical properties of the new compounds prepared are summarized in Table I. The infrared spectra of these haloethynyl carbinols all displayed the rather weak band at 4.5 μ characteristic of fully substituted acetylenes, rather than the band at 3.05–3.1 μ (mono-substituted acetylene) found in the spectra of the ethynyl carbinols.

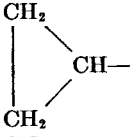
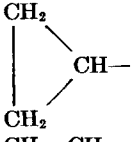
The next group of compounds to be investigated was that of the alkyl β-chlorovinyl ethynyl carbinols (II). The lowest homolog, II (R = CH_3), has been prepared in moderate yield by the addition of sodium acetylide to methyl β-chlorovinyl ketone in liquid ammonia (5, 6). We have prepared this compound in higher yield and several of its homologs by the addition of lithium acetylide to the appropriate alkyl β-chlorovinyl ketone in liquid ammonia. The physical and pharmacological properties of these carbinols are presented in Table II.

[1] For paper I in this series, see McLamore, Harfenist, Bavley, and P'an, *J. Org. Chem.*, **19**, 570 (1954).

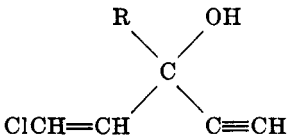
TABLE I

HALOETHYNYL CARBINOLS



R	R'	X	Yield, %	B. P.		n_D^t/t (°C.)	d_4^{20}	Formula	Analyses			
									Calc'd		Found	
				°C.	MM.				C	H	C	H
CH_3—	C_2H_5—	—Cl	74.2	64	17	1.4591/25	1.050	C_6H_9ClO	54.35	6.84	54.08	6.83
CH_3—	C_2H_5—	—I	22.2	49–51	0.08	[a]	[a]	C_6H_9IO	32.16	4.05	32.01	4.13
C_2H_5—	C_2H_5—	—Cl	61	69	13	1.4620/23.9	1.040	$C_7H_{11}ClO$	57.34	7.56	57.40	7.65
C_2H_5—	C_2H_5—	—I	13.7	58–59	0.3	[b]	[b]	$C_7H_{11}IO$	35.31	4.66	35.15	4.63
CH_3—		—Cl	74.7	76–76.5	18	1.4800/25	1.105	C_7H_9ClO	58.14	6.27	58.29	6.43
CH_3		—Br	71	89–90	12	[c]	[c]	C_7H_9BrO	44.47	4.80	44.35	4.81
CH_3—	CH_2=CH—	—Br	79	76–80	9	1.5068/26	1.450	C_6H_7BrO	41.17	4.03	39.86	3.93
C_2H_5—	CH_2=CH—	—Cl	29.5[d]	67–68	12	1.5735/23.8	1.050	C_7H_9ClO	58.14	6.27	58.35	6.38
C_2H_5—	CH_2=CH—	—Br	87	90–94	12	1.5000/25	1.375	C_7H_9BrO	44.47	4.80	44.19	4.81
i-C_3H_7—	CH_2=CH—	—Br	89	53–54	1.0	1.4972/25	1.312	$C_8H_{11}BrO$	47.31	5.46	46.92	5.42
n-C_4H_9—	CH_2=CH—	—Br	90.6	49–50	0.14	1.4934/23.9	1.250	$C_9H_{13}BrO$	49.79	6.03	49.66	6.02
CH_3—	CH_2=C(CH_3)—	—Br	44	89–90	15	1.5051/23.5	1.375	C_7H_9BrO	44.47	4.80	44.14	4.85

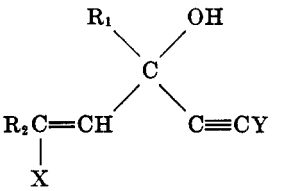
[a] M.p. 39.5–40.2°. [b] M.p. 34.4–35.2°. [c] M.p. 51.5–52.5°. [d] 46.5% yield based on recovery of starting material.



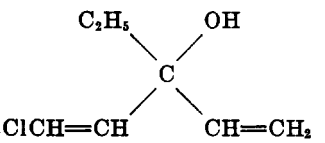
II

The required ketones were prepared by the addition of an acid chloride to either acetylene or vinyl chloride in the presence of aluminum chloride, as described by a number of investigators (7, 8). More consistent results and better yields were obtained by the use of vinyl chloride, but its use necessitates dehydrohalogenation of the intermediate alkyl β,β-dichloroethyl ketones (8).

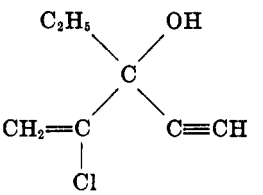
In view of the desirable pharmacological properties (Table II) of ethyl β-chlorovinyl ethynyl carbinol (II, R = C_2H_5), we have prepared, in addition to the simple homologs, the following related compounds:[2]



Compound	R_1	R_2	X	Y
III	C_2H_5	H	Cl	Br
IV	C_2H_5	H	Cl	CH_3
V	C_2H_5	H	Br	H
VI	CH_2=CH	H	Cl	H
VII	C_2H_5	n-C_3H_7	Cl	H



VIII



IX

The bromoethynyl carbinol III was prepared from II (R = C_2H_5) by the action of alkaline hypobromite as described above (1). Compound IV was obtained by addition of the lithium salt of propyne to ethyl β-chlorovinyl ketone. The β-bromovinyl analog V was made by the addition of lithium acetylide to ethyl β-bromovinyl ketone; the requisite ketone was prepared by addition of propionyl bromide to vinyl bromide (with aluminum chloride), followed by steam distillation (8). The highly unsaturated carbinol VI resulted from the action of two moles of lithium acetylide on β-chloroethyl β-chlorovinyl ketone (*cf.* Method B, Paper I[1]). This latter ketone was the product of addition of β-chloropropionyl chloride to acetylene in the presence of aluminum chloride

[2] After this work was completed, a paper [Julia, *Ann. chim.*, [12], **5**, 595 (1950)] came to our attention in which compounds closely related to our carbinols IV and VII are described.

TABLE II

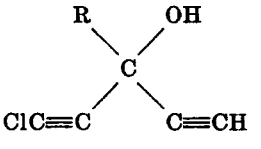
HALOGENATED TERTIARY ACETYLENIC CARBINOLS

No.	Yield, %	B.P.		n_D^{25}	d_4^{20}	Formula	Analyses				Activities[a]	
							Calc'd		Found		Hypnotic mg./kg.	Anticonvulsant mg./kg.
		°C.	MM.				C	H	C	H		
II, R = CH_3—	65	68	15	1.4758	1.068	C_6H_7ClO	55.19	5.40	55.34	5.52	~140	<50
II, R = C_2H_5—	80.2	28.5–30	0.1	1.4780	1.064	C_7H_9ClO	58.14	6.27	58.03	6.15	92	12
II, R = n-C_3H_7—	77	43–44	.5	1.4754	1.043	$C_8H_{11}ClO$	60.57	6.99	60.69	6.98	~180	~50
II, R = i-C_3H_7—	47.3[b]	38–38.5	.6	1.4781	1.038	$C_8H_{11}ClO$	60.57	6.99	60.40	6.94	108	24
III	84.8	54	.025	[c]	[c]	C_7H_8BrClO	37.61	3.61	37.31	3.57	~350	<100
IV	32.2	51	.5	1.4966	1.074	C_8H_1ClO	60.57	6.99	58.60[d]	6.55[d]	~300	<100
									58.51	6.57		
V	48	42.8–43	.11	1.5045	1.375	C_7H_9BrO	44.47	4.80	44.75	4.85	~120	<50
VI	64.9	33.5	.2	1.4960	1.103	C_7H_7ClO	58.96	4.95	58.70	4.95	140	43
VII	34.3	57.5–59.5	.07	1.4801	1.012	$C_{10}H_{15}ClO$	64.34	8.10	64.51	8.15	208	56
VIII	51.2	33	.03	1.4787	1.064	$C_7H_{11}ClO$	57.34	7.56	57.45	7.49	155	45
IX	13.8	32–33	.7	1.4718	1.047	C_7H_9ClO	58.14	6.27	59.42[d]	6.65[d]	~180	~45
X, R = CH_3—	29.9	37.5	2.6			C_6H_5ClO	56.05	3.92	55.49	3.98[e]	~350	~100
X, R = C_2H_5—	29	32.9–33.5	1.0	1.4823	1.114	C_7H_7ClO	58.96	4.93	58.61	5.04	~175	~100

[a] A preceding ~ sign indicates that the value is an estimate based on screening data; the < sign indicates that insufficient data were available below that dosage level for a significant estimate. [b] The low yield in this case is probably due to the fact that the ketone used proved to be largely isopropyl β,β-dichloroethyl ketone, and insufficient lithium acetylide was used to act as a dehydrohalogenating agent. [c] M.p. 41–42°. [d] This compound could not be obtained analytically pure in spite of repeated fractionation. [e] Calc'd: Cl, 27.58; found: Cl, 27.63.

(9,10). Compound VII was obtained in the usual way from 5-chloroöct-4-en-3-one, which was synthesized from propionyl chloride and pentyne-1 with aluminum chloride. Partial hydrogenation of II (R = C_2H_5) afforded the non-acetylenic carbinol VIII. Finally, the α-chlorovinyl analog IX was prepared by the reaction of two equivalents of lithium acetylide with ethyl α,β-dichloroethyl ketone; the required ketone was obtained by chlorination of ethyl vinyl ketone in carbon tetrachloride solution. The properties of compounds III–IX are given in Table II.

Some years ago it was reported that the reaction of sodium acetylide with methyl β,β-dichlorovinyl ketone fails to give the expected carbinol, although addition of alkynes and Grignard reagents to this ketone proceed normally (6). We prepared the ketone by the published procedure (6, *cf.* 11) from acetyl chloride, vinylidene chloride, and aluminum chloride. Treatment of the ketone with propynyl magnesium bromide produced what appeared to be the expected methyl β,β-dichlorovinyl propynyl carbinol, although it could not be obtained analytically pure. Addition of lithium acetylide to this ketone was then studied, and, in contrast to the reported result with sodium acetylide, an acetylenic carbinol was isolated. This material was not, however, the expected carbinol and proved to have the structure X (R = CH_3) as indicated by the relatively



X

low boiling point, analyses and infrared spectrum. The infrared spectrum was particularly conclusive, since it displayed strong bands at *both* 3.05 μ (mono-substituted acetylene) and 4.5 μ (fully substituted acetylene). Evidently, lithium acetylide acts as a base to remove the elements of hydrogen chloride from the molecule before or after addition to the carbonyl group. It was later found that this same product can be obtained from the ketone and sodium acetylide, although in much lower yield.

The homolog, X (R = C_2H_5), was obtained even more unexpectedly when ethyl α,β,β-trichloroethyl ketone was treated with two equivalents of lithium acetylide. Formation of this product obviously must involve the removal at some stage of the chloro substituent *alpha* to the carbonyl group as well as one of the *beta* halogen atoms. The trichloroketone used in the reaction was prepared by the aluminum chloride-catalyzed addition of propionyl chloride to dichloroethylene.

The halogenated carbinols II–X were all screened for hypnotic and anticonvulsant activities in mice by methods described elsewhere (4), and the results are included in Table II. Hypnotic activity is defined as the dose in mg. per kg. body weight which causes sleep in 50% of the mice used. Anticonvulsant activity is similarly determined by the amount of compound which protects 50% of the mice from metrazole-induced seizures. As indicated, some of the values are es-

timates based on a limited amount of screening data. It can be seen from Table II that the most active compound in this group is II (R = C_2H_5).

EXPERIMENTAL[3]

Chloro- and bromo-ethynyl carbinols (I, X = Cl or Br, and III). These compounds were prepared from the ethynyl carbinols and alkaline hypohalite solutions according to the published method (1), except that the reaction mixtures were stirred vigorously in a creased flask rather than shaken. Two attempts to prepare ethyl vinyl chloroethynyl carbinol by this method were unsuccessful owing to explosions after about 2 hours reaction time. This compound was finally obtained by interrupting the reaction after 1 hour and separating the product from unchanged ethynyl carbinol by fractional distillation. After separation from the reaction mixture, the chloroethynyl carbinol appeared to be quite stable and could be distilled at reduced pressure without any sign of decomposition. An attempt to apply this procedure to the preparation of methyl vinyl chloroethynyl carbinol failed, however, when a curious series of mild, repeating explosions began after about one-half hour and continued for several hours.

Iodoethynyl carbinols (I, X = I). Treatment of diethyl ethynyl carbinol with alkaline hypoiodite solution led only to recovery of the ethynyl carbinol, but this carbinol and methyl ethyl ethynyl carbinol were both successfully iodinated by the following procedure (which, however, failed when applied to ethyl vinyl ethynyl carbinol).

To a solution of sodium amide prepared from 25 g. of sodium in 1 l. of liquid ammonia (12) was added 0.50 mole of the ethynyl carbinol in 50 ml. of dry ether. The mixture was stirred at the reflux temperature (Dry-Ice condenser) for 1.5 hours and then slowly treated with 127 g. (0.5 mole) of iodine (I_2), partly as solid and partly in ether solution (750 ml.). Ammonia was allowed to evaporate overnight, and the residue was poured into a mixture of ice and water. The ether layer was separated, washed twice with saturated sodium chloride solution containing a little sodium bisulfite, and dried over sodium sulfate. Ether was removed and the residue was distilled twice. The iodoethynyl carbinol fraction was then crystallized from petroleum ether.

Alkyl β-chlorovinyl ethynyl carbinols (II). The four alkyl β-chlorovinyl ethynyl carbinols of structure II were prepared by very similar procedures, and therefore only the preparation of the ethyl homolog will be described in detail.

To a stirred suspension of 735 g. (5.5 moles) of anhydrous, powdered aluminum chloride in 1500 ml. of carbon tetrachloride was added 462.5 g. (5.0 moles) of propionyl chloride. This mixture was cooled to 0–5° and vinyl chloride introduced with stirring until it was no longer absorbed (2–3 hours). The reaction mixture then was poured into a slurry of ice and water and stirred to decompose the aluminum chloride complex. The organic layer was separated, washed with water, dried, and concentrated to remove carbon tetrachloride. The residue was subjected to steam-distillation, and the ketone was isolated from the distillate with the aid of ether. Ordinary distillation then gave 495.5 g. (83.6% yield) of ethyl β-chlorovinyl ketone, b.p. 50–54° at 15 mm. This material, although undoubtedly contaminated with the higher-boiling dichloroketone, was sufficiently pure for conversion to the carbinol.

To about 300 ml. of liquid ammonia in a 1 l., 3-neck flask, equipped with a stirrer, Dry-Ice condenser, and gas inlet tube, was added 3.05 g. (0.44 mole) of lithium metal in small pieces. Acetone-free acetylene was passed into the stirred solution at about 1 l. per minute until the blue color was discharged and the gray solid disappeared to give a clear solution. The gas inlet tube then was replaced by a dropping-funnel, and 47.4 g. (0.40 mole) of the above ketone was added in an equal volume of ether during about 20 minutes. The solution rapidly darkened in color through yellow to deep red. Ether (200 ml.) was added and the ammonia was allowed to evaporate overnight. The residual suspension was poured into a

[3] No attempt was made to obtain analytically pure samples of most of the intermediate ketones used in the preparation of carbinols II–X. Preparation of each ketone will, however, be described briefly under the preparation of the corresponding carbinol.

stirred mixture of ice and acetic acid (30 g.; 0.5 mole), and the aqueous layer was separated and re-extracted with ether. The combined ether extracts were washed with dilute sodium bicarbonate solution, dried with anhydrous magnesium sulfate, and concentrated. Two distillations of the residue afforded 46.3 g. (80.2% yield) of pure ethyl β-chlorovinyl ethynyl carbinol, b.p. 28.5–30° at 0.1 mm. (see Table II).

Ethyl β-chlorovinyl propynyl carbinol (IV). This carbinol was prepared from ethyl β-chlorovinyl ketone by the same method used for II (R = C_2H_5), with the substitution of propyne for acetylene. The compound could not, however, be obtained analytically pure, even after repeated fractional distillation (Widmer column).

Ethyl β-bromovinyl ethynyl carbinol (V). The required ethyl β-bromovinyl ketone was prepared from propionyl bromide (200 g.; 1.46 moles), vinyl bromide (excess), and aluminum chloride (144.5 g.; 1.08 moles) by the same method used for ethyl β-chlorovinyl ketone (above). The product was not homogeneous, possibly because of halogen exchange, and the best fraction (41.8 g.) from a fractional distillation (22 in. Widmer column) was used for preparation of the carbinol.

The carbinol V was prepared from the bromo ketone (41.8 g.) and lithium acetylide in the same manner as described above for II (R = C_2H_5). Fractional distillation (12 in. wire-spiral column) afforded 23.2 g. (48% yield) of essentially pure V, b.p. 40–43° at 0.11 mm.

Vinyl β-chlorovinyl ethynyl carbinol (VI). The intermediate β-chloroethyl β-chlorovinyl ketone was prepared from β-chloropropionyl chloride (127 g.; 1.0 mole), aluminum chloride (134 g.; 1.0 mole), and acetylene (9, 10) under essentially the same conditions described above for ethyl β-chlorovinyl ketone. Acetylene was not absorbed, however, until the temperature was raised from 0–5° to 20–25°. The product was not steam-distilled, but was subjected to two ordinary distillations to give 103.6 g. of ketone, which apparently (analysis) contained some vinyl β-chlorovinyl ketone.

The carbinol VI was prepared in the usual way from the above ketone and *two* equivalents of lithium acetylide (*cf.* Method B, Paper I[1]). Fractional distillation through an 18 in. packed column was necessary to obtain analytically pure carbinol.

Ethyl β-chloropent-1-enyl ethynyl carbinol (VII). The necessary ketone, 5-chloroöct-4-en-3-one, was prepared by addition of pentyne-1 (70.9 g.; 1.04 moles) to a stirred, cooled (10°) mixture of aluminum chloride (130 g.; 0.97 mole), carbon tetrachloride (125 ml.), and propionyl chloride (82.5 g.; 0.892 mole). Addition was extended over a period of 2 hours, and a further 1.5 hours was allowed for completion of the reaction. The reaction mixture was treated in the usual way, (without steam-distillation), and two distillations of the product afforded 80.5 g. of the ketone, b.p. 39–41° at 0.03 mm.; n_D^{24} 1.4696; d_4^{20} 0.999.

Anal. Calc'd for $C_8H_{13}ClO$: C, 59.81; H, 8.16.

Found: C, 60.45; H, 8.33.

The carbinol VII was prepared from the above ketone (40.2 g.; 0.25 mole) and lithium acetylide in the usual fashion. The carbinol was distilled, and then fractionated through a 12 in. wire-spiral column to give 16.0 g. (34.3% yield) of essentially pure material, b.p. 56–59.5° at 0.07 mm.

Ethyl vinyl β-chlorovinyl carbinol (VIII). Hydrogenation at atmospheric pressure and 29° of 28.92 g. (0.200 mole) of II (R = C_2H_5) in 200 ml. of absolute ethanol with 3 g. of a 5% palladium-on-calcium carbonate catalyst (a similar catalyst containing traces of lead was ineffective) was interrupted after absorption of 0.2 mole of hydrogen. The catalyst was filtered off and the solvent was removed under reduced pressure. Distillation, followed by fractionation through an 18 in. packed column (glass helices), afforded 15 g. (51.2% yield) of the dihydro carbinol VIII, b.p. 33° at 0.03 mm.

Ethyl α-chlorovinyl ethynyl carbinol (IX). Ethyl vinyl ketone[4] (40.6 g.; 0.483 mole) was

[4] The ethyl vinyl ketone required was prepared in 64.9% yield by steam distillation (8) of ethyl β-chloroethyl ketone (Paper I[1]). The yield could undoubtedly be improved, since an appreciable amount of the β-chloro ketone was recovered. This method is considerably more convenient and efficient than the methods previously used for this conversion (13, 14).

chlorinated in carbon tetrachloride (100 ml.) by addition of 34.2 g. (0.483 mole) of chlorine at −10 to −15°. The reaction mixture was subjected directly to steam-distillation, and the organic portion of the distillate was separated, dried, and distilled twice to give 52 g. (69.4% yield) of ethyl α,β dichloroethyl ketone, b.p. 73–76° at 18 mm., n_D^{25} 1.4580, d_4^{20} 1.199.

Anal. Calc'd for $C_5H_8Cl_2O$: C, 38.73; H, 5.20.

Found: C, 39.20; H, 5.29.

The ketone (46.5 g.; 0.30 mole) was treated with two equivalents of lithium acetylide under the usual conditions. The product, after two distillations (6.0 g.; 13.8% yield), was still not pure and was fractionated through a small wire-spiral column. The best fraction was not analytically pure, possibly due to the presence of a small amount of ethyl diethynyl carbinol (*cf.* formation of X, R = C_2H_5).

Methyl ethynyl chloroethynyl carbinol (X, R = CH_3). Methyl 2,2-dichlorovinyl ketone (6) (69.5 g.; 0.5 mole) was treated in the usual way with lithium acetylide from 7.0 g. (1.01 moles) of lithium. The product was distilled and then fractionated through a 12 in. Widmer column to give a total of 19.2 g. (29.9% yield) of X (R = CH_3), b.p. 37.5° at 2.6 mm. The structure of this carbinol was established by the low boiling point, analyses (Table II), and infrared spectrum (strong bands at 3 05 μ *and* 4.5 μ).

Ethyl ethynyl chloroethynyl carbinol (X, R = C_2H_5). To a stirred mixture of aluminum chloride (140 g.; 1.05 mole) and propionyl chloride (92.5 g.; 1.0 mole) was added 242.4 g. (2.5 moles) of dichloroethylene (*cis-trans* mixture) as rapidly as the temperature would permit (*ca.* 15 minutes). The mixture was refluxed on a steam bath for 3 hours, and decomposed with ice and water. The organic layer was separated with the aid of carbon tetrachloride, dried, and distilled to give 86.6 g. (45.6% yield) of ethyl α,β,β-trichloroethyl ketone, b.p. 47–49° at 0.1 mm. n_D^{25} 1.4740, d_4^{20} 1.333.

Anal. Calc'd for $C_5H_7Cl_3O$: C, 31.69; H, 3.72.

Found: C, 31.92; H, 3.72.

Treatment of the trichloro ketone (75.8 g.; 0.40 mole) with lithium acetylide from 5.83 g. (0.84 mole) of lithium as before afforded 16.5 g. (29% yield) of twice-distilled X (R = C_2H_5), b.p. 32–32.5° at 0.07 mm. The analytical sample was obtained by fractionation of this material through a small wire-spiral column. Structure X (R = C_2H_5) was assigned to this product on the basis of the low boiling point, analyses (Table II), and infrared spectrum (strong bands at 3.05 μ *and* 4.5 μ).

SUMMARY

Halogenated tertiary acetylenic carbinols of the following types have been prepared for evaluation as hypnotics and anticonvulsants:

1. Several new chloroethynyl and bromoethynyl carbinols, which were obtained by treatment of the ethynyl carbinols with alkaline hypohalite solutions.

2. Two iodoethynyl carbinols, which were prepared by the action of iodine on the sodium salts of the ethynyl carbinols in liquid ammonia.

3. Four homologous alkyl β-chlorovinyl ethynyl carbinols, made by the addition of lithium acetylide to the appropriate alkyl β-chlorovinyl ketones.

4. A group of carbinols related to ethyl β-chlorovinyl ethynyl carbinol.

None of the compounds prepared was as active pharmacologically as ethyl β-chlorovinyl ethynyl carbinol.

The reaction of lithium (or sodium) acetylide with methyl 2,2-dichlorovinyl ketone has been shown to yield methyl ethynyl chloroethynyl carbinol by an unexpected combination of dehydrohalogenation and addition. The higher homolog, ethyl ethynyl chloroethynyl carbinol was produced even more unexpectedly

when ethyl α,β,β-trichloroethyl ketone was treated with two moles of lithium acetylide.

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