[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORIES OF SCHERING CORPORATION]

A New Class of Hypnotics. Unsaturated Carbinols.[1] Part I

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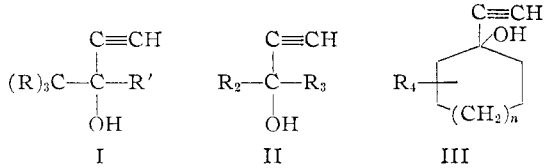
A series of unsaturated carbinols was prepared and examined for hypnotic action. The compounds derived from simple ketones and acetylene exhibited hypnotic activity in several species of animals. Several modifications of the basic structure $(R)_2C(OH)C{\equiv}CH$ were made in an attempt to enhance the hypnotic effect. Structure activity relationships were studied in the course of this investigation.

In the course of a study on the synthesis of relatively simple compounds related to the antiarthritic steroids,[2] pharmacological evaluation of various intermediates in these syntheses indicated that unsaturated carbinols exhibit hypnotic activity in several species of experimental animals.[3] Although the literature is replete with examples of the hypnotic effect of alcohols, little pharmacological work has been done with these substances in the past 50 years. The hypnotic effect of ethanol has been known since antiquity; however, only in the latter part of the nineteenth century were investigations on alcohols as a family carried out.[4] These studies indicated that branching of the alcohol, for example from primary to secondary to tertiary, increases the hypnotic activity of the alcohols, the maximum activity being obtained with the compounds containing 6–8 carbon atoms for the primary alcohols and a somewhat lower carbon content for the branched chain compounds. It was established also that unsaturation in the molecule enhanced hypnotic effect. Around 1890, tertiary amyl alcohol was introduced into clinical medicine as a hypnotic under the trade name Amylene Hydrate. Since then, little has appeared in the literature on the hypnotic activity of alcohols until the announcement from our laboratories on the simple, highly unsaturated tertiary carbinols.[5]

The ethinyl tertiary carbinols prepared in the course of the first phase of this study are of general formulas I–III

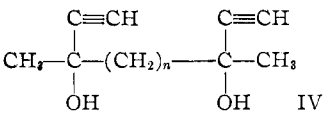


I II III

wherein R is hydrogen or alkyl, R_1 is alkyl, cycloalkyl or aryl, R_2 is aryl, R_3 is aryl or heterocyclic, R_4 is hydrogen, alkyl or an additional cyclic moiety forming a bicyclic ring and n is 0 or 1. In the tables are listed the ethinyl compounds of formulas I–III which were prepared from the appropriate ketone with either sodium acetylide in liquid ammonia[6] or potassium acetylide in *t*-amyl alcohol.

On the basis of the preliminary pharmacological studies it soon was apparent that the carbinols of formulas I and III, particularly those having a total of six to nine carbon atoms, were the compounds combining hypnotic effect in several species of animals with minimal toxicity. Thus, initial structural variations of the basic formula were, in general, confined to this group of compounds. The inherent risks of such a limited survey were, of course, recognized but were waived in favor of establishing early in the study the effect of: (a) the presence of a second acetylenic-tertiary alcohol group; (b) degree of unsaturation; (c) replacement of the acetylenic hydrogen; and (d) derivatives of the hydroxyl group.

The diethinyl glycols which were studied were of general formula IV. The compounds derived from diacetyl (n = 0) and acetonylacetone (n = 2) were prepared by the conventional sodium acetylide method. The bis compound



IV

derived from acetylacetone (n = 1) could not be obtained probably due to the ease of tautomerism of the active methylene hydrogens. Although the two glycols showed hypnotic effect in mice the compounds were devoid of either hypnotic or sedative effect in dogs and monkeys even at substantially high doses.

The increase in hypnotic activity in the transition from saturated to unsaturated alcohols was confirmed in a comparison of two of the more active ethinyl alcohols with the corresponding vinyl and saturated analogs. In both cases, the 3-methyl-1-pentyne-3-ol and the 3-ethyl-4-methyl-1-hexyne-3-ol, there was a very marked decrease in hypnotic effect for the vinyl and saturated compounds. The vinyl alcohols were prepared by reduction of the ethinyl-carbinols using a palladium-on-calcium carbonate catalyst in pyridine solution,[7] the saturated tertiary alcohols by reduction of the ethinyl compounds with Raney nickel or by the action of ethylmagnesium bromide on the appropriate ketone.

(1) Presented in abstract before the Division of Medicinal Chemistry, American Chemical Society Meeting, Atlantic City, N. J., September 15, 1952.

(2) D. Papa, H. F. Ginsberg and F. J. Villani, THIS JOURNAL, **76**, 4441 (1954).

(3) (a) D. Papa, F. J. Villani and H. F. Ginsberg, *Arch. Biochem. Biophys.*, **33**, 482 (1951); (b) S. Margolin, P. Perlman, F. J. Villani and T. H. McGavick, *Science*, **114**, 394 (1951).

(4) For a brief review of this subject, see Berger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, pp. 114, 129–130; and Goodman and Gilman, "Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1951.

(5) Recently the Dissertation of H. Bock "Zur Pharmakologie ungesättiger Alkohole," Breslau, 1930, has come to our attention. This Dissertation, which apparently has not been published in any journal, reports the hypnotic action in dogs of ethinyl alcohols and the bromo substituted ethinyl alcohols.

(6) A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Vol. I, Edward Arnold and Co., London, 1946.

(7) L. Ruzicka and P. Muller, *Helv. Chim. Acta*, **22**, 756 (1939).

Further unsaturation of the alcohols of formula I did not appreciably alter hypnotic activity. The two representative substances prepared were derived from allylacetone and hepten-1-one-5, both compounds having a total number of carbon atoms within the optimum range and a terminal unsaturation in one of the R quantities of formula I.[8]

Substitution of the acetylenic hydrogen by methyl, *n*-butyl, phenyl, hydroxyalkyl and carbethoxy resulted in substantial loss of hypnotic activity. Halogen substitution of the acetylenic hydrogen in the few cases studied did not alter appreciably the hypnotic effect over that of the parent alcohol. In these few cases the increase in activity was accompanied by an increase in toxicity.[9]

The methyl substituted acetylenic carbinols were obtained by the conventional sodium–liquid ammonia reaction with methylacetylene whereas the *n*-butyl and phenyl substituted compounds were prepared by treating the monosubstituted acetylenic Grignard, *i.e.*, phenylacetylenemagnesium bromide with the appropriate ketone. The hydroxyalkyl compounds were obtained by treating the Grignard complex of the ethinylcarbinol, with an aldehyde such as formaldehyde or acetaldehyde or a ketone, such as methyl ethyl ketone.

The derivatives of the tertiary hydroxy group, acyl and aryl ester, alkyl ethers, dialkylaminoalkyl ethers, carbonates, carbamates and allophanates were the most interesting group of compounds of this study from the standpoint of structure–activity relationship. The preparation of and pharmacological data for these compounds will appear in a forthcoming publication from these laboratories.

Pharmacology.—The hypnotic activity of the compounds of Tables I–III was evaluated as previously described.[3b] Compound 3, "Dormison," was the standard for comparison. Of the aliphatic ethinyl alcohols of formula I, no. 2–8, 10–14, 16 and 17 were the most active and substantially equivalent in hypnotic effect to the standard. Compound 18, containing eleven carbon atoms, showed one-half of the activity of the standard. Compounds 9, 15 and 23, representing further unsaturation in the molecule, showed no increase in activity over the parent compound.

The carbinols of formula I in which R = aryl, no. 19–21, were active in mice, but inactive in dogs. The cycloalkyl compounds of formula I, no. 24–29, were quite active, no. 24, 25 and 29, being the most active of this group.

In general, the compounds of formula II were relatively inactive in dogs, although in the mouse test potentiation of Evipal hypnosis was noted in all cases and was pronounced in the case of compounds no. 30–32.

In mice and dogs, the compounds of formula III, Table II, were comparable in activity to the standard. In the dog, no. 40 was the most active compound.

The remaining structural variations showed little hypnotic effect even in the Evipal potentiation test.

Acknowledgment.—The authors wish to express their appreciation to Dr. S. Margolin for the pharmacological data, to Mrs. Florence Villani, Miss Margaret Sherlock and Mrs. Virginia De Camp for their assistance in the preparation of many of the compounds and to Mr. Edwin Conner of our Microanalytical Laboratories for the analyses.

Experimental

Materials.—The ketones used in this work were, in most cases, obtained from commercial sources. Those not commercially available were prepared as follows: 1-Methylhexahydroacetophenone was prepared by the pinacolone rearrangement according to the procedure of Meerwein[10]; 2-methyl-1-acetylcyclopentane and 2,3-dimethyl-1-acetylcyclopentane were obtained by the Friedel–Crafts ring contraction of the cyclohexanes[11]; heptene-6-one-3 was prepared in 49% yield by the addition of diethylcadmium to γ-penteneoic acid chloride, b.p. 143–149°, $n^{32}D$ 1.4256, previously reported[12] b.p. 46–47° (12 mm.), $n^{18}D$ 1.4254; benzalpinacolone was prepared by the reaction of benzaldehyde with pinacolone.[13] The benzoylpyridines, N-methylbenzoyl-piperidines[14] and 7-methoxy-α-decalone[15] were prepared by methods previously described. The ketones 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone were obtained from the corresponding alcohols by dichromate oxidation as described for menthone.[16] The trimethylcyclohexanone also was prepared from isophorone by reduction with palladium chloride in ethanol.[17] 4-Methoxycyclohexanone was obtained from hydroquinone monomethyl ether. A mixture of 1 mole of hydroquinone monomethyl ether in 150 cc. of absolute ethanol and 15 g. of alkali-free Raney nickel was hydrogenated at 1,500 p.s.i. at 90–100°. The hydrogenation proceeded rapidly and within one hour the theoretical amount of hydrogen was absorbed. The catalyst was filtered, the solvent evaporated and the residue, 4-methoxycyclohexanol, distilled; yield 90%, b.p. 92–94° (8 mm.), $n^{22}D$ 1.4670; literature[18] b.p. 102–103° (15 mm.), $n^{19}D$ 1.4671. Oxidation with sodium dichromate in sulfuric acid gave the 4-methoxycyclohexanone, yield 50%, b.p. 84–85° (11 mm.), $n^{24}D$ 1.4550.

Ethination Procedures.—This incorporates features of several published methods and was found to give consistently good results. Into a 3-liter, three-necked flask equipped with a stirrer, gas inlet tube, a Dry Ice condenser and a dropping funnel, there was added one liter of anhydrous ammonia. A rapid stream of dry acetylene was passed through the system while 27.6 g. (1 mole plus 20% excess) of sodium was added slowly in small portions, with vigorous stirring. After stirring for one to two hours, the dark blue-black solution changed to a grayish-white mixture containing the monosodium acetylide and one mole of the ketone was added dropwise. Stirring was continued for an additional 6 hours in an atmosphere of acetylene. The mixture was kept overnight, during which time most of the ammonia evaporated. Ice-water was cautiously added and the resulting solution made strongly acid by the addition of dilute sulfuric acid. The acidified mixture was extracted with ether, the ether extracts washed with saturated salt solution, dried over sodium sulfate and distilled.

(8) S. Y. P'an, J. F. Gardocki, M. Harfenist and A. Vavley, *J. Pharmacol. Exptl. Therap.*, **107**, 459 (1953), have reported on the hypnotic effect and toxicity of two vinylethynylcarbinols, 3-methyl- and 3-ethyl-4-penten-1-yne-3-ol. In general, their data confirm our findings as reported herein and in ref. 3a.

(9) In an extensive study on the effect of halogenation on the hypnotic and anticonvulsant activities of acetylenic carbinols, S. Y. P'an, L. Markarian, W. M. McLamore and A. Bavley, *J. Pharmacol. Exptl. Therap.*, **109**, 268 (1953), have reported that, with few exceptions, no significant change in activity or toxicity was noted; *cf.* W. M. McLamore, S. Y. P'an and A. Bavley, Abstract of Papers, Kansas City Meeting, A.C.S., March 25, 1954.

(10) H. Meerwein, *Ann.*, **396**, 225 (1913).

(11) C. D. Nenitzescu, E. Cioranescu and I. P. Canterniari, *Ber.*, **70**, 277 (1937).

(12) B. Helferich, *ibid.*, **52**, 1809 (1919).

(13) G. A. Hill and G. M. Bramann, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 81.

(14) F. J. Villani, M. S. King and D. Papa, *J. Org. Chem.*, **17**, 249 (1952).

(15) F. J. Villani, M. S. King and D. Papa, to be published.

(16) L. T. Sandborn, ref. 13, p. 340.

(17) A. Skita, *Ber.*, **42**, 1630 (1909).

(18) L. Helfer, *Helv. Chim. Acta*, **7**, 960 (1924).

TABLE I

COMPOUNDS OF THE FORMULA $\begin{matrix} R & R' \\ \diagdown & \diagup \\ C & \\ | & \\ OH & \end{matrix}-C\equiv CH$

No.	R	R'	Yield, %	B.p.[a] °C.	Mm.	$n^{t}D$	t, °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$(CH_3)_2CH$[b]	H	34	131–135		1.4316	27					
2	CH_3	CH_3	47	102–105		1.4182	24					
3	C_2H_5	CH_3	80	120–122		1.4287	25					
4	$(CH_3)_2CH$	CH_3	70	131–133		1.4340	25					
5	C_3H_5[c]	CH_3		[d]								
6	$(CH_3)_3C$	CH_3	75	143–145		1.4382	28					
7	$(CH_3)_2CHCH_2$	CH_3	28	147–149		1.4328	24					
8	n-C_5H_{11}	CH_3	30	90–92	25	1.4375	25					
9	$CH_2{=}CHCH_2CH_2$	CH_3	28	160–161		1.4505	25	$C_8H_{12}O$	77.42	77.23	9.82	9.72
10	C_2H_5	C_2H_5	72	136–140		1.4352	26					
11	$(CH_3)_2CH$	C_2H_5	66	151–152		1.4380	26	$C_8H_{14}O$	76.14	76.47	11.18	11.70
12	$C_2H_5CH(CH_3)$	C_2H_5	76	163–170		1.4421	26	$C_9H_{16}O$	77.04	76.89	11.43	11.56
13	$C_3H_7CH(CH_3)$	C_2H_5	68	96–98	28	1.4449	25	$C_{10}H_{18}O$	77.86	77.46	11.76	12.12
14	$(C_2H_5)_2CH$	C_2H_5	72	89–92	25	1.4461	26	$C_{10}H_{18}O$	77.86	78.17	11.76	11.49
15	$CH_2{=}CHCH_2CH_2$	C_2H_5	61	89–91	31	1.4508	27	$C_9H_{14}O$	78.21	78.01	10.21	9.78
16	$(CH_3)_2CH$	$(CH_3)_2CH$	51	160–162		1.4420	25					
17	n-C_4H_9	C_2H_5		[e]								
18	n-C_4H_9	n-C_5H_{11}	71	126–127	27	1.4434	28	$C_{12}H_{22}O$	79.04	79.69	12.19	11.96
19	C_6H_5	CH_3	48	101–105	13	1.5345	25					
20	C_6H_5	C_2H_5	80	110–113	11	1.5258	28	$C_{11}H_{12}O$	82.45	82.88	7.57	8.15
21	p-ClC_6H_4	CH_3	56	120–121[f]	7	1.5458	26	$C_{10}H_9OCl$	66.48	66.90	5.03	5.29
22	C_6H_5	C_6H_5	35	139–143[g]	2	1.5991	24					
23	$C_6H_5CH{=}CH$	$(CH_3)_3C$	90	[h]				$C_{15}H_{18}O$	84.05	83.75	8.48	8.76
24	2-$CH_3C_5H_8$[i]	CH_3	38	80–82	12	1.4670	26	$C_{10}H_{16}O$	78.88	79.69	10.61	10.79
25	2,3-$(CH_3)_2C_5H_7$[i]	CH_3	41	80–82	8	1.4660	26	$C_{11}H_{18}O$	79.45	79.71	10.93	11.63
26	C_6H_{11}[j]	CH_3	77	106–110	23	1.4792	23	$C_{10}H_{16}O$	78.88	78.82	10.61	11.07
27	1-$CH_3C_6H_{10}$[j]	CH_3	69	110–113	20	1.4870	25	$C_{11}H_{18}O$	79.33	79.27	10.92	11.35
28	C_5H_9[i]	C_2H_5	71	104–106	25	1.4668	23	$C_{10}H_{16}O$	78.89	78.78	10.59	10.92
29	C_6H_{11}[j]	C_2H_5	50	117–118	20	1.4756	31	$C_{11}H_{18}O$	79.46	78.86	10.92	11.36
30	C_6H_5	2-C_5H_4N	62	[k]				$C_{14}H_{11}ON$	80.35	80.64	5.31	5.29
31	C_6H_5	3-C_5H_4N[l]	71	[m]				$C_{14}H_{11}ON$	80.35	80.74	5.31	5.66
32	C_6H_5	4-C_5H_4N[l]	50	[n]				$C_{14}H_{11}ON$	80.35	80.49	5.31	5.63
33	C_6H_5	1-CH_3-3-C_5H_9N	44	[o]				$C_{15}H_{19}ON$	78.55	78.45	8.37	8.23
34	C_6H_5	1-CH_3-4-C_5H_9N	42	[p]				$C_{15}H_{19}ON$	78.55	78.71	8.37	8.57
35	$C_2H_5C(CH_3)OH$	CH_3	30	105–109	25	1.4660	26	$C_8H_{14}O_2$	67.56	67.54	9.94	9.96
36	1-HOC_6H_{10}[j]	CH_3	61	[q]				$C_{10}H_{16}O_2$	71.43	71.83	9.53	9.78
37	$CH_3C(OH)(C\equiv CH)$	CH_3	13	108–110[r]	23	1.4773	26	$C_8H_{10}O_2$	69.46	69.43	7.24	7.51
38	$CH_3C(OH)(C\equiv CH)(CH_2)_2$	CH_3	51	[s]								

[a] The compounds for which no analysis is given are known substances reported in reference 6, the physical properties being listed since in many instances the ethinylcarbinols were contaminated by ketonic material. The latter impurity was removed by fractionation through a four-foot Todd column. [b] Unless otherwise noted the compounds were prepared by the sodium acetylide–liquid ammonia method. [c] C_3H_5 = cyclopropyl. [d] We are indebted to the Air Reduction Co., Inc., Murray Hill, N. J., for a generous supply of this compound and several of those listed in Table III. [e] We are indebted to Dr. F. E. Cislak of Reilly Tar and Chemical Corporation, Indianapolis, Indiana, for a generous supply of this compound and some of those listed in Table III. [f] M.p. 42–43°, recrystallized from hexane. [g] M.p. 47–48°, recrystallized from petroleum ether. [h] M.p. 65–66°, recrystallized from ethanol–water. [i] Cyclopentyl. [j] Cyclohexyl. [k] M.p. 67–68°, recrystallized from petroleum ether. [l] Prepared by the potassium acetylide–*t*-amyl alcohol method. [m] M.p. 142–143°, recrystallized from benzene. [n] M.p. 167–168°, recrystallized from benzene. [o] M.p. 135–136°, recrystallized from petroleum ether. [p] M.p. 133–134°, recrystallized from petroleum ether. [q] M.p. 76–77°, recrystallized from petroleum ether. [r] N. A. Milas, R. J. Brown and O. Phillips, THIS JOURNAL, **70**, 2862 (1948), report b.p. 76–78° (3 mm.), $n^{20}D$ 1.4852. [s] M.p. 93–94°, recrystallized from benzene–petroleum ether. Reference *r* reports m.p. 92–95°.

The use of methylacetylene in place of acetylene in this procedure gave compound 59 (Table III).

The procedure of Marvel, *et al.*,[19] was modified as follows: Four and three-tenths grams (0.11 mole) of potassium metal was dissolved in 125 ml. of anhydrous *t*-amyl alcohol contained in a 500-ml., three-necked flask equipped with stirrer, gas inlet tube, dropping funnel and condenser. After solution of the potassium, 250 ml. of anhydrous ether was added and the mixture cooled to −5°. A slow stream of acetylene was passed into the mixture, while a solution containing one-tenth of a mole of the ketone dissolved in about 100 ml. of anhydrous ether was added dropwise. The addition required about three hours. Stirring was continued for an

(19) C. S. Marvel, D. E. Pearson and L. A. Patterson, THIS JOURNAL, **62**, 2661 (1940).

TABLE II

COMPOUNDS OF THE FORMULA R(C≡CH)(OH)

No.	R	Yield, %	B.p.[a] °C.	Mm.	n'_D	t, °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
39	Cyclopentyl[b]	78	78–79	28	1.4721	23					
40	Cyclohexyl	86	69–70	10	1.4791	26					
41	2-Methylcyclohexyl	92[c]	103–106	46							
42	3-Methylcyclohexyl	94	76–79	10	1.4720	24					
43	4-Methylcyclohexyl	74	76–80	11	1.4701	24					
44	3,3,5-Trimethylcyclohexyl	40[d]	89–91	15	1.4534	28	$C_{11}H_{18}O$	79.46	79.86	10.91	11.40
45	4-Methoxycyclohexyl	46	112–114[e]	12	1.4860	20					
46	1-Decalyl[f]	23	79–82[g]	2	1.5033	26					
47	7-Methoxy-1-decalyl[f]	65	[h]				$C_{13}H_{20}O_2$	74.96	74.93	9.68	9.61
48	1-Octahydroindanyl[f]		97–102	9	1.4970	27	$C_{11}H_{16}O$	80.45	80.83	9.82	10.07
49–51[i]											

[a] See footnote *a*, Table I. [b] Unless otherwise noted the compounds were prepared by the sodium acetylide–liquid ammonia method. [c] The yield and physical constant given are for the mixture of isomers. The *cis* and *trans* isomers were separated by the procedure of N. A. Milas, N. S. MacDonald and D. M. Black, THIS JOURNAL, **70**, 1824 (1948). The solid isomer, recrystallized from petroleum ether, melted at 57–59° (reported m.p. 61°); the liquid isomer b.p. 139–142° (45 mm.), $n^{27}D$ 1.4724 (reported b.p. 84° (17 mm.)). [d] Yield of pure product obtained after separation of unreacted ketone *via* the bisulfite addition complex; purification through rectification unsatisfactory. [e] B.p. 120–124° (22 mm.), $n^{20}D$ 1.4871, reported by C. S. Marvel and W. L. Walten, *J. Org. Chem.*, **7**, 88 (1942). [f] Prepared by the potassium acetylide–*t*-amyl alcohol method. [g] B.p. 74–76° (1.5 mm.), $n^{26}D$ 1.5018, C. S. Marvel, D. E. Pearson and L. A. Patterson, THIS JOURNAL, **62**, 2661 (1940). [h] Recrystallized from petroleum ether m.p. 130–131°. [i] These compounds appear in the Experimental section.

TABLE III

COMPOUNDS OF THE FORMULA RR'R"C–OH

No.	R	R'	R"	Yield, %	B.p. °C.	Mm.	n'_D	t, °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
52	C_2H_4[a]	C_2H_5	CH_3	62	120–122[b]								
53	C_2H_5	C_2H_5	$(CH_3)_2CH$	57	158–160[c]		1.4350	22					
54	$C_2H_5CH(CH_3)$	C_2H_5	C_2H_5	66	69–70[d]	10	1.4410	18					
55	C_6H_5	C_2H_5	C_2H_5	72	85–88[e]	1	1.5128	25					
56	C_2H_5	CH_2=CH	CH_3	70	116–119[f]		1.4260	24					
57	$(CH_3)_2CH$	CH_2=CH	CH_3	71	131–133		1.4338	24	$C_7H_{14}O$	73.61	73.41	12.38	12.31
58	$C_2H_5CH(CH_3)$	CH_2=CH	C_2H_5	76	170–173		1.4439	27	$C_9H_{18}O$	75.99	75.56	12.68	12.93
59	CH_3—C≡C	C_2H_5	CH_3	13	147–151[g]		1.4405	27					
60	C_6H_5C≡C	C_2H_5	CH_3	93	96–99	22	1.4440	27	$C_{10}H_{18}O$	77.82	78.51	11.69	11.95
61	C_6H_5C≡C	C_2H_5	CH_3	88	135–138[h]	15	1.5446	24					
62	C_6H_5C≡C	C_2H_5	C_2H_5	73	138–142	12	1.4389	29	$C_{13}H_{16}O$	82.97	83.24	9.04	9.08
63	CH_2OHC≡C	C_2H_5	CH_3	68	108–109	3	1.4766	23	$C_7H_{12}O_2$	65.59	65.67	9.44	9.77
64	$CH_3OH(OH)C$≡C	C_2H_5	CH_3	45	134–137	24	1.4682	22	$C_8H_{14}O_2$	67.57	67.26	9.92	9.72
65	$(C_2H_5)(CH_3)(OH)C$—C≡C	C_2H_5	CH_3	60	102–103[g,i]	2							
66	1-$HOC_6H_{10}C$≡C[j]	C_2H_5	CH_3	55	121–124	1.5	1.4894	26	$C_{12}H_{20}O_2$	73.41	73.96	10.27	10.60
67	$(C_6H_5)_2C(OH)C$≡C	C_2H_5	CH_3	20	[k]				$C_{19}H_{20}O_2$	81.42	81.15	7.14	7.05
68	$(CH_3)_2C(OH)(C$≡C$)_2$	CH_3	CH_3	[l]									
69	$(C_2H_5)_2NCH_2C$≡C	C_2H_5	CH_3	[l]									
70	$C_5H_{10}NCH_2C$≡C	C_2H_5	CH_3	[l]									
71	C_3H_3	BrC≡C	CH_3	[m]									
72	$(CH_3)_2CHCH_2$	BrC≡C	CH_3	[m]									

[a] The known compounds appear in this table since the physical constants reported are for very pure samples specially purified for pharmacological tests. [b] M. Willcox and R. Brunel, THIS JOURNAL, **38**, 1838 (1916), report b.p. 120–122°. [c] J. Stas, *Bull. soc. chim. Belg.*, **35**, 384 (1926). [d] V. Prelog and E. Zalan, *Helv. Chim. Acta*, **27**, 547 (1944), report b.p. 63–65° (11 mm.). [e] A. Klages, *Ber.*, **36**, 3692 (1903), report b.p. 223–224°. [f] H. Rupe and F. Vonaesch, *Ann.*, **444**, 81 (1925), report b.p. 114–116°. [g] See reference 6. [h] A. F. Thompson and C. Margnetti, THIS JOURNAL, **64**, 573 (1942), report b.p. 138–140° (15 mm.). [i] M.p. 54–55° recrystallized from petroleum ether. [j] Cyclohexyl. [k] M.p. 66–67°, recrystallized from hexane. [l] Air Reduction Co., Inc. [m] Reilly Tar and Chemical Corporation.

additional hour, the reaction mixture then decomposed with ice-water and ether extracted. The ethinyl alcohols were isolated as described above.

Saturated Tertiary Carbinols.—Compounds 52, 53, 54 and 55 were prepared by the reaction in anhydrous ether of the appropriate Grignard reagent and ketone in a 5:3 ratio. Decomposition of the Grignard complex with dilute ammonium chloride solution, followed by ether extraction and distillation of the residue from the dried extracts afforded the pure products.

Vinylcarbinols.—The ethinylcarbinol (0.2 mole) was dissolved in 100 ml. of anhydrous pyridine and reduced in the Parr hydrogenator in the presence of 0.5 g. of 5% palladium-on-calcium carbonate catalyst. Absorption of the theoretical amount of hydrogen was complete in 10 minutes. After filtration of the catalyst, the filtrate was made strongly acid with dilute hydrochloric acid and extracted with ether. The ether extracts were combined, washed with saturated salt solution, dried and the residue distilled. In addition to compounds 56, 57 and 58 (Table III), the following cyclic vinyl compounds were prepared by this procedure: 1-vinyl-2-methyl-1-cyclohexanol, yield 68%, b.p. 65–72° (13 mm.), literature[20] b.p. 86–90° (30 mm.); 1-vinyl-3-methyl-1-cyclohexanol, yield 72%, b.p. 75–78° (10 mm.). *Anal.* Calcd. for $C_9H_{16}O$: C, 77.11; H, 11.50. Found: C, 76.50; H, 11.39.

1-Vinyl-4-methyl-1-cyclohexanol, yield 63%, b.p. 76.5–78.5° (12 mm.). *Anal.* Calcd. for $C_9H_{16}O$: C, 77.11; H, 11.50. Found: C, 77.36; H, 11.95.

Compounds 60, 61 and 62 (Table III).—To a solution of 0.38 mole of phenylacetylenemagnesium bromide (prepared from phenylacetylene- and ethylmagnesium bromide) in 250 ml. of anhydrous ether there was added slowly with stirring, 0.3 mole of the appropriate ketone. The reaction mixture

(20) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938).

was refluxed an additional 2 hours on the steam-bath then decomposed with cold dilute sulfuric acid. The acid solution was extracted with ether, the extracts dried and evaporated and the residue distilled. Compounds 61 and 62 (Table III) were prepared by this procedure. Substitution of phenylacetylene by *n*-butylacetylene afforded compound 60 (Table III).

Acetylenic Glycols.—To a solution of 0.6 mole of ethylmagnesium bromide in 500 ml. of anhydrous ether there was added dropwise 0.3 mole of the ethinyl carbinol in 100 ml. of anhydrous benzene. The mixture was refluxed with stirring for 3 hours, cooled in an ice-bath and 0.3 mole of the appropriate aldehyde or ketone in 50 ml. of anhydrous ether added dropwise with vigorous stirring. Stirring was continued for an additional 6 hours at 5–10° and the mixture kept overnight at room temperature. The Grignard complex was decomposed with dilute sulfuric acid and extracted with ether. The residue of the ethereal extract was purified by distillation or recrystallization. Compounds 63, 64, 65, 66 and 67 of Table III were prepared by this procedure.

Ethyl β-(1-Hydroxy-1-cyclohexyl)-propiolate (No. 49).—A solution of 40 g. of β-(1-hydroxycyclohexyl)-propiolic acid[21] in 200 ml. of anhydrous ethanol containing 1% concentrated sulfuric acid was refluxed 16 hours. After neutralization with aqueous potassium carbonate, the reaction mixture was extracted with ether, the ethereal solution dried and the residue distilled; yield 70%, b.p. 135.5–140° (2.5 mm.), $n^{27}D$ 1.4889. *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.09; H, 8.42.

1,2-Bis-(1-hydroxycyclohexyl)-acetylene (No. 50).—Ethination of cyclohexanone in ether in the presence of powdered potassium hydroxide[22] afforded a 90% yield of product, m.p. 103–104°,[5] after recrystallization from carbon tetrachloride.

γ-Ethinyl-γ-valerolactone (No. 51).—To a solution of 1 mole of sodium acetylide in 1 liter of liquid ammonia there was added over a period of 2 hours a solution of 58 g. (0.5 mole) of levulinic acid in 100 ml. of anhydrous ether. The reaction mixture was worked up as described under the ethination procedures. After evaporation of the ammonia, the residue was acidified and the aqueous solution saturated with salt and extracted with ether in a continuous extractor for 10 hours. The ether extract was dried, evaporated and the residue distilled; yield 46 g. (74%), b.p. 93–94° (5 mm.), $n^{23}D$ 1.4550. *Anal.* Calcd. for $C_7H_8O_2$: C, 67.76; H, 6.49. Found: C, 68.00; H, 6.83.

(21) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503 (1946).

(22) A. Babayan, *Bull. Armenian Branch Acad. Sci. U.S.S.R.*, 121 (1941); *C. A.*, **40**, 3394 (1946).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Synthesis and Properties of the 5-Phenyl-2- and 3-thiophene-ols[1]

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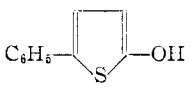
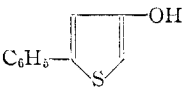
5-Phenyl-2-thiophene-ol has been synthesized by the oxidation of 2-phenyl-5-thienyl Grignard reagent or the corresponding lithium derivative, and by cyclization of β-benzoylpropionic acid. The chemical reactions of this thiophene-ol and of the 3-ol isomer demonstrate that these compounds exist in both keto and enol forms. The spectral data indicate that the enol structures predominate in alcohol solution and the keto tautomers in chloroform solution.

This paper is concerned with the synthesis and properties of 5-phenyl-2-thiophene-ol and 5-phenyl-3-thiophene-ol (I, II).



I



II

II was synthesized by the method of Friedländer and Kielbasinski[3]; a number of modifications are noted in the Experimental section.

The preparation of I was effected both by oxidation of the corresponding organometallic compound and by sulfuration and cyclization of β-benzoylpropionic acid (III). Dehydrogenation of 2-(1-cyclohexenyl)-thiophene[4] (IV) with chloranil[5] produced 2-phenylthiophene (V) in 79% yield. Both N-bromosuccinimide and bromine brominated V in the 5-position in comparable yields, and the derived Grignard reagent was oxidized in the presence of isopropyl- or cyclohexylmagnesium bromide.[6,7] Together with a 30% yield of I, there was obtained a small amount of 5,5′-diphenyl-2,2′-dithienyl (VI). The oxidation is very sensitive to slight changes in conditions; in some runs the quantity of I isolated was negligible, continued oxidation to bis-(β-mercaptostyryl)-maleic acid di-γ-lactone (VII) having taken place.

The formation of VI occurs primarily in the oxidation step rather than by a Fittig-type reaction between Grignard reagent and halide during the preparation of the organometallic, since when one-half of a solution of phenylthienyl Grignard reagent was oxidized we obtained VI in 10% yield, whereas carbonation of the remainder of the solution gave 2-phenylthiophene-5-carboxylic acid in 61% yield without any isolable VI. Numerous examples of the formation of coupled products R–R during the oxidation of organometallics RM are recorded in the literature.

We were also able to oxidize the lithium derivative of V in the presence of excess cyclohexylmagnesium bromide to I in 30% yield. In our second synthesis III was smoothly converted to I in pyridine–chloroform solution in 22% yield.[8] This one-step synthesis of I from readily available materials may be formulated as involving thiation of the car-

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(3) P. Friedländer and S. Kielbasinski, *Ber.*, **45**, 3389 (1912).

(4) (a) L. F. Fieser and J. Szmuszkovicz, THIS JOURNAL, **70**, 3352 (1948); (b) J. Szmuszkovicz and E. Modest, *ibid.*, **72**, 571 (1950).

(5) R. T. Arnold and C. J. Collins, *ibid.*, **61**, 1407 (1939).

(6) (a) C. D. Hurd and K. L. Kreuz, *ibid.*, **72**, 5543 (1950); (b) C. D. Hurd and H. J. Anderson, *ibid.*, **75**, 5124 (1953).

(7) M. S. Kharasch and W. B. Reynolds, *ibid.*, **65**, 501 (1943).

(8) *Cf.* E. Klingsberg and D. Papa, *ibid.*, **73**, 4988 (1951).