[CONTRIBUTION FROM THE U. S. VITAMIN CORPORATION RESEARCH LABORATORIES]

Hypnotic Activity of Some Tertiary Alcohols[1]

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A series of tertiary alcohols has been prepared to evaluate the structural features which contribute to hypnotic activity. In addition to the ethynyl group, the cyclopropyl, pentamethylene, tetramethylene and *o,o'*-diphenylene groups attached to the carbinol carbon improve hypnotic activity. Maximum activity was associated with the compound 9-ethynyl-9-hydroxyfluorene. The synthesis of trichloromethylethynylcarbinol is described.

Considerable published work[2,3] has demonstrated that the incorporation of the ethynyl and vinyl group in tertiary alcohols produces desirable hypnotic activity. These groups attached to the carbinol carbon appear to augment the hypnotic activity of the saturated carbinol, tertiary amyl alcohol (TAA).

Our interest was in the factors modifying the TAA structure which contribute to hypnotic activity. More desirable effects are noted (Table I) upon structural modification of TAA so that one methyl group is replaced by a cyclopropyl group (I), or two methyl groups by a tetramethylene group (III) or a pentamethylene group (V), than when one methyl group is replaced by the ethynyl group (VIII).

Replacement of the ethyl group in I, III and V by the ethynyl group to give II, IV and VI, respectively, considerably lengthened the duration of hypnosis although the effective dose levels were not altered. Ethynyl structures showed better therapeutic indices in groups B and C (Table I). In group A the ethyl compound was superior and this observation was investigated with additional cyclopropylcarbinols (group E) with unfavorable results.

Investigation of 9-ethynyl-9-hydroxyfluorene yielded effective hypnosis for 1.5 hours at 0.6 mmoles/kg. with a therapeutic index of 1.7. No hypnosis or toxicity was noted when this compound was tested orally in rats. This may be due to its low solubility or to sensitivity to hydrochloric acid.[4]

The non-fused ring structure[5] derived from benzophenone, diphenylethynylcarbinol,[6] was ineffective as a hypnotic at 2.8 mmoles/kg.

The low solubility of 9-ethynyl-9-hydroxyfluorene was improved by preparation of the corresponding 4-carboxylic acid but hypnotic activity was lost. A similar effect of the carboxyl group was noted upon testing γ-ethynyl-γ-valerolactone[7] and the γ-ethynyl-γ-hydroxyvaleric acid derivable from this compound. No hypnotic activity was observed at levels as high as 3.2 and 3.3 mmoles/kg., respectively.

TABLE I

		Effective dose, mmoles[a]	Duration of hypnosis (hr.)	Toxic dose[g] / Effective dose
Group A.	Carbinol			
I.	Cyclopropylmethylethyl[b]	1.5	2	2.6
II.	Cyclopropylmethylethynyl[c]	2.1	6	2.2
Group B				
III.	1-Ethylcyclopentanol[d]	1.7	1	1.7
IV.	1-Ethynylcyclopentanol[c]	1.8	3	2.3
Group C				
V.	1-Ethylcyclohexanol[e]	1.3	0.5	1.8
VI.	1-Ethynylcyclohexanol[c]	1.45	3.5	2.5
VII.	1-Ethynyl-4-methylcyclohexanol[c]	1.3	1	2.3
Group D.	Carbinol			
VIII.	Ethynylmethylethyl[c]	3.1	1	1.7
IX.	Ethynylmethylvinyl[f]	2.1	0.75	2.5
Group E.	Carbinol			
X.	Cyclopropylmethylallyl	1.6	6	1.7
XI.	Cyclopropylmethylbenzyl	2.8	5	1.2
XII.	Cyclopropylmethylphenyl[b]	5.6	..	1.0

[a] Tertiary amyl alcohol, 6.3 mmoles effective dose. [b] Ref. 15. [c] Ref. 3. [d] O. Wallach and K. v. Martens, *Ann.*, **365**, 276 (1909). [e] P. Sabatier and A. Mailhe, *Compt. rend.*, **138**, 1321 (1904). [f] Ref. 2b. [g] Compounds tested intraperitoneally in guinea pigs, using as the criterion a dosage inducing sleep of about 30 minutes. Superficially, the hypnosis is the same in all compounds, with respiratory rate not materially affected and animals alert upon awakening. About 10–15 guinea pigs were used to establish critical points for each compound.

The preparation of other 9-ethynyl-9-hydroxyfluorenecarboxylic acids was not achieved due to failure of sodium acetylide to add to the corresponding 2- and 3-fluorenonecarboxylic acids. No product was obtained upon condensing sodium acetylide with 2-indanone. Similar difficulties[8] and poor yields have been reported in preparation of ethynyl tetralols.

The course of hypnosis with trichloromethyldimethyldimethylcarbinol[9] and trichloromethylethynylcarbinol involved profound central nervous system depression. These compounds probably function by a pattern other than that of the halogen-free alcohols described herein.

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(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Cincinnati, Ohio, April, 1955.

(2) (a) W. M. McLamore, M. Harfenist, A. Bavley and S. Y. P'An, *J. Org. Chem.*, **19**, 570 (1954); (b) S. Y. P'An, J. F. Gardocki, M. Harfenist and A. Bavley, *J. Pharmacol. Exptl. Therap.*, **107**, 460 (1953).

(3) D. Papa, F. J. Villani and H. F. Ginsberg, THIS JOURNAL, **76**, 4446 (1954).

(4) G. F. Hennion and B. Raymond, Abstracts of Papers, Division of Organic Chemistry, American Chemical Society, New York, N. Y., Sept. 12, 1954, pp. 71–80.

(5) H. L. Friedman, National Research Council, Publ. 206, Washington, D. C., 1951, p. 295. Compares a variety of structures bearing *gem*-diphenyl groups with 9-fluorenyl derivatives.

(6) A. I. Zakarova, *J. Gen. Chem. (U.S.S.R.)*, **11**, 939 (1941); *C. A.*, **37**, 355 (1943).

(7) O. R. Kreimeier, U. S. Patent 2,122,719 (July 5, 1938).

(8) M. W. Goldberg, U. S. Patent 2,524,787 (October 10, 1950).

(9) C. Weizmann, E. Bergmann and M. Sulzbacher, THIS JOURNAL, **70**, 1189 (1948).

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Experimental

9-Ethynyl-9-hydroxyfluorene.—A solution of 36 g. (0.2 mole) of fluorenone in 150 ml. of dimethylacetal was added rapidly to a suspension of sodium acetylide prepared from 9.2 g. (0.4 g. atom) of sodium,[10] in 400 ml. of liquid ammonia. A slow stream of acetylene was passed through the reaction mixture for 3 hours while stirring and cooling, and then 32 g. (0.6 mole) of ammonium chloride was added. After one hour, the ammonia was distilled out, 300 ml. of ether added, and the mixture stirred for 30 minutes. The ether was filtered off, the filter cake re-extracted and the filtrates dried with potassium carbonate. Filtration and evaporation yielded 41.2 g. of crude product. Recrystallization from methanol–water (charcoal) gave 30.9 g. (75%) of white crystals, m.p.[11] 109–110°.

Anal.[12] Calcd. for $C_{15}H_{10}O$: C, 87.35; H, 4.89. Found: C, 87.45; H, 4.89.

9-Ethynyl-9-hydroxyfluorene-4-carboxylic Acid.—A suspension of 33.6 g. (0.15 mole) of fluorenone-4-carboxylic acid[13] in 200 ml. of methylal was added to sodium acetylide which had been prepared from 8.1 g. (0.35 g. atom) of sodium in 500 ml. of liquid ammonia. After stirring 5 hours, the cooled mixture was allowed to stand overnight. The ammonia was evaporated and dilute hydrochloric acid added with cooling until the mixture was decidedly acid. The insoluble solid (30.5 g.) was separated and dissolved in saturated sodium bicarbonate. Cautious acidification yielded the product (12%) which melted with darkening at 170° and completely decomposed at 282°.

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.84; H, 4.16.

Trichloromethylethynylcarbinol.—Sodium acetylide was prepared from 13.8 g. (0.6 g. atom) of sodium in 500 ml. of liquid ammonia. The ammonia was replaced by 300 ml. of dry ether, the mixture cooled in a Dry Ice–acetone bath and 73.7 g. (0.5 mole) of trichloroacetaldehyde added over one hour with stirring. The reaction mixture was cooled and stirred overnight. Upon reaching room temperature, water (300 ml.) was added slowly with rapid stirring. The ether layer was separated and the aqueous fraction re-extracted. The extracts were combined and dried with magnesium sulfate.

Filtration, removal of the ether and distillation yielded 23.4 g. (27%), b.p. 77–81° (16 mm.), $n^{22}D$ 1.5029, d^{25} 1.467. Titration of the ethynyl hydrogen by the method of Hanna and Siggia[14] yielded 60% of the theoretical yield; molar refraction found 34.91, calcd. 34.61 (the value for trichloromethyl group was calculated from trichloroethanol).

Anal. Calcd. for $C_4H_3OCl_3$: C, 27.70; H, 1.74; Cl, 61.32. Found: C, 27.52; H, 1.78; Cl, 61.4.

The *p*-nitrophenylurethan, m.p. 150–153°, was prepared in the usual manner.

Anal. Calcd. for $C_{11}H_7N_2O_4Cl_3$: C, 39.15; H, 2.09. Found: C, 39.41; H, 2.21.

An attempt to prepare diethynylmethylcarbinol from ethyl acetate and sodium acetylide by a similar procedure resulted in reddish oils, apparently extremely susceptible to air oxidation, which resisted purification by distillation.

Allylcyclopropylmethylcarbinol.—The compound prepared from allylmagnesium bromide and methylcyclopropyl ketone following the procedure of Favorskaya[15] was obtained in 31% yield, b.p. 113–117° (193–195 mm.).

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.56; H, 10.80.

The phenylurethan m.p. 48–49.5° (pentane), was prepared in the usual manner.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.45; H, 7.74.

Benzylcyclopropylmethylcarbinol.—Prepared as above in 47% yield, b.p. 112–115° (8 mm.).

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.18; H, 9.05.

The phenylurethan, m.p. 95–97° (pentane), was prepared in the usual manner.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 77.14; H, 7.23.

(10) C. D. Hurd and W. D. McPhee, THIS JOURNAL, **69**, 240 (1947).

(11) Melting points are not corrected.

(12) Analyses by Drs. Weiler and Strauss, Oxford, England.

(13) E. R. Atkinson and H. J. Lawler, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 222.

(14) J. C. Hanna and S. Siggia, *Anal. Chem.*, **21**, 1469 (1949).

(15) T. A. Favorskaya, *et al.*, *J. Gen. Chem.* (*U.S.S.R.*), **20**, 855 (1950); *C. A.*, **44**, 9358 (1950).

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A Non-enzymatic Duplication of the "Fatty Acid Cycle"[1]

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The "fatty acid cycle," which governs fat metabolism *in vivo*, has been duplicated using simplified model compounds containing the structural elements which are considered important to the activity of coenzyme A. The reactions include Claisen-type self-condensation of N,S-diacetylthioethanolamine (I) to N-acetyl-S-acetoacetylthioethanolamine (III), reduction of the latter to N-acetyl-S-β-hydroxybutyrylthioethanolamine (IV), dehydration of IV to N-acetyl-S-crotonylthioethanolamine (V), and hydrogenation of V to N-acetyl-S-butyrylthioethanolamine (VI). The structures of III, V and VI were ascertained by independent syntheses. The compounds prepared are of interest as models of intermediates involved in the enzymatic cycle.

The role of coenzyme A (CoA) in fat metabolism has been the object of numerous investigations. Recently, the combined efforts of Lynen[3] and Lipmann[4] have resulted in the formulation of a "fatty acid cycle," in part anticipated by Barker,[5] consisting of four reversible, enzyme-catalyzed steps. In the first of these, two molecules of S-acetylCoA (Ia) are condensed by β-ketothiolase to give one molecule of S-acetoacetylCoA (IIIa) and one molecule of CoA (IIa). The acetothioacetate (IIIa) is reduced by β-ketohydrase to S-β-hydroxybutyryl-CoA (IVa). Dehydration catalyzed by crotonase

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(2) Abstracted from part of the Ph.D. Dissertation of Curt W. Beck, January, 1955.

(3) F. Lynen, Acetyl-coenzyme A and the "fatty acid cycle," Harvey Lectures, Series XLVIII, 1952–1953, p. 210, 1953.

(4) F. Lipmann, "Biosynthetic Mechanisms," Harvey Lectures, Series XLIV, 1948–1949, p. 99, 1950.

(5) H. A. Barker in "Phosphorus Metabolism," edited by W. D. McElroy and B. Glass, The Johns Hopkins Press, Baltimore, Md., 1951, Vol. I, pp. 241 ff.