A New Class of Hypnotics: Unsaturated Carbinols

In the course of a general investigation of the synthesis and pharmacological properties of unsaturated carbinols and derivatives, it was noted that compounds of the general formula $R\gtrless\overset{\overset{|}{OH}}{C}-C\equiv CH$ **(I)** and $R\gtrless\overset{\overset{|}{OH}}{C}-CH=CH_2$ **(II)**, wherein R is an aliphatic, mono- or bicyclic residue, exhibited hypnotic activity in several species of experimental animals.[1] Having established that the effect of several aliphatic ethinyl carbinols was characterized by high hypnotic activity and low toxicity on oral or parenteral administration, we prepared diverse types of compounds with the unsaturated alcohol moiety in an effort to correlate this pharmacodynamic action with chemical structure.

In general, the simpler aliphatic ethinyl carbinols showed a hypnotic potency from one-half to three-quarters that of phenobarbital in the experimental animals, without any toxic side effects. Of particular interest was the complete absence of "hangover" in the animals at the therapeutic dose.

The aliphatic, alicyclic, and aryl carbinols of formula **I** were prepared by the conventional ethination of the appropriate ketones or aldehydes with sodium acetylide in liquid ammonia (2). The corresponding vinyl compounds were readily secured in good yield by catalytic reduction of the ethinyl carbinols with palladium on calcium carbonate in pyridine solution (3).

The following representative types of compounds of formulas **I** and **II** have been prepared and tested[2]: 2-methyl-3-butyne-2-ol; 3-methyl-1-pentyne-3-ol; 4-methyl-1-pentyne-3-ol; 3,4-dimethyl-1-pentyne-3-ol; 3,3,4-trimethyl-1-pentyne-3-ol; 3-ethyl-4-methyl-1-hexyne-3-ol, b.p. 77–79° (30 mm.). Calcd. for $C_9H_{16}O$: C 77.04, H 11.43. Found: C 76.89, H 11.56; 3,5-dimethyl-1-hexyne-3-ol; 3-*n*-butyl-1-octyne-3-ol, b.p. 126–127° (27 mm.). Calcd. for $C_{12}H_{22}O$: C 79.04, H 12.19. Found: C 79.69, H 11.96; 1-ethinyl-1-cyclohexanol; 2-, 3-, and 4-methyl-1-ethinyl-1-cyclohexanol; 3,3,5-trimethyl-1-ethinyl-1-cyclohexanol, b.p. 91–93° (15 mm.). Calcd. for $C_{11}H_{18}O$: C 79.46, H 10.91. Found: C 79.36, H 11.40; 2-isopropyl-5-methyl-1-ethinyl-1-cyclohexanol, b.p. 109–110° (15 mm.). Calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18. Found: C 80.52, H 11.25; 1-ethinyl-1-cyclopentyl acetate, b.p. 95–96° (29 mm.). Calcd. for $C_9H_{12}O_2$: C 71.03, H 7.95. Found: C 70.99, H 8.21; 2-cyclohexyl-3-butyne-2-ol, b.p. 106–110° (23 mm.). Calcd. for $C_{10}H_{16}O$: C 78.88, H 10.61. Found: C 78.82, H 11.07; 2-(1′-

[1] For a preliminary report of the general pharmacological tests for these compounds and the results of extended potency, toxicity, metabolic and clinical studies with 3-methyl-1-pentyne-3-ol, see Ref. (1).

[2] The physical properties of those compounds for which analyses are not given can be found in Ref. (2).

methylcyclohexyl)-3-butyne-2-ol, b.p. 110–113° (20 mm.). Calcd. for $C_{11}H_{18}O$: C 79.33, H 10.92. Found: C 79.28, H 11.35; 2-(2′-methylcyclopentyl)-3-butyne-2-ol, b.p. 80–82° (12 mm.). Calcd. for $C_{10}H_{16}O$: C 78.88, H 10.61. Found: C 79.19, H 10.79; 2-(2′,3′-dimethylcyclopentyl)-3-butyne-2-ol, b.p. 80–82° (8 mm.). Calcd. for $C_{11}H_{18}O$: C 79.45, H 10.93. Found: C 79.71, H 11.36; 2-phenyl-3-butyne-2-ol, m.p. 50–51°; 3-phenyl-1-pentyne-3-ol, b.p. 110–113° (11 mm.). Calcd. for $C_{11}H_{12}O$: C 82.45, H 7.57. Found: C 82.88, H 8.15; 2-(*p*-chlorophenyl)-3-butyne-2-ol, b.p. 120–121° (7 mm.), m.p., 40–41°. Calcd. for $C_{10}H_9OCl$: C 66.48, H 5.03. Found: C 66.90, H 5.29; 3-*t*-butyl-5-phenyl-4-penten-1-yne-3-ol, m.p. 64–65°. Calcd. for $C_{15}H_{18}O$: C 84.05, H 8.48. Found: C 83.85, H 8.76; 1-ethinyl-1-decalol; 3,4-dimethyl-1-penten-3-ol, b.p. 131–135°. Calcd. for $C_7H_{14}O$: C 73.61, H 12.31. Found: C 83.85, H 8.76; 3,4,4-trimethyl-1-penten-3-ol, b.p. 144–146°. Calcd. for $C_8H_{16}O$: C 74.92, H 12.60. Found: C 74.47, H 12.48.

In addition, other types of unsaturated alcohols which have been prepared and tested include diethinyl glycols, heterocyclic ethinyl carbinols, and alkyl and alicyclic acetylenic glycols. Complete experimental details for all the compounds in this study will be published shortly.

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Preliminary Investigations on the Role of Salts in the Polymerization of Actin [1]

The present paper gives a short account of our earlier investigations on the polymerization of actin under the influence of added salt, as far as confirmed with purified preparations (1,2).

Polymerization was followed quantitatively by measurements of viscosity and light scattering.

We find that the addition of salt has two effects: an immediate and a delayed one. In the viscosity test, addition of salts causes an instantaneous drop, which we ascribe to the electroviscous effect, followed by a strong rise due to polymerization. The addition of salts also causes an immediate drop in pH, not followed by any pH change during polymerization. These observations suggest that the addition of salt effects a depression of the negative charges carried by the protein in the neutral or weakly alkaline pH range in which these experiments were done.

The same point is shown with particular clarity by our light-scattering measurements. Addition of salts instantaneously raises the turbidity about twofold, after

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