1225 w, 1250 w, 1265 m, 1350 w, 1370 w, 1400 m, 1450 m, 1500 m, 1530 s, 1580 w, 1620 m, 1690 s, 1745 s, 1800 m, 1850 s, 1980 w, 3230 m.

Anal. Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65. Found: C, 69.76; H, 8.64.

Acknowledgment.—We are indebted to the Research Corporation for the partial financial support of this work.

Improved Synthesis of Oxotremorine

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Received January 21, 1965

Tremorine (1,4-dipyrrolidin-1-ylbut-2-yne) has been widely employed in the search for agents active against Parkinson's disease in man. The generalized tremor and spasticity caused in laboratory animals by tremorine is antagonized by drugs that are effective in the treatment of Parkinson's disease.[1,2] It has recently been suggested[3] that the pharmacological actions of tremorine may be entirely due to oxotremorine, an active metabolite[4] which Cho, *et al.*, isolated, identified as 1-(2-oxopyrroldin-1-yl)-4-pyrrolidin-1′-ylbut-2-yne, and synthesized.[5] Leslie and Maxwell[3] found that whereas some compounds of no clinical value in the treatment of Parkinson's disease were tremorine antagonists, anti-Parkinson drugs antagonized the actions of both tremorine and oxotremorine. The former compounds were presumed to have inhibited the oxidation of tremorine to oxotremorine which clearly has no bearing on central antitremor activity. These findings indicate that antagonism to oxotremorine should be a more discriminating test for anti-Parkinson agents, and a satisfactory practical source of oxotremorine would therefore seem to be of value.

Attempts to repeat the published synthesis[5] led to erratic results and the over-all yield of about 6% could not be duplicated. However, by conducting the reaction between pyrrolidone and propargyl chloride in liquid ammonia with sodamide as the condensing agent, N-propargyl-2-pyrrolidone was obtained in 83% yield. A Mannich reaction between this intermediate, formaldehyde, and pyrrolidine was carried out under the conditions described by Halsall and Thomas[6] for the preparation of 6-diethylaminohex-4-yn-1-ol. This provided a 61% yield of oxotremorine.

Experimental

N-Propargyl-2-pyrrolidone.—Sodamide was prepared from sodium (51 g., 2.2 g.-atoms) in about 2000 ml. of liquid NH_3. Pyrrolidone (170 g., 2.0 moles) was added dropwise to the stirred suspension. One hour later, 163 g. (2.2 moles) of propargyl chloride was added dropwise and stirring was continued a further 5 hr. After the NH_3 was allowed to evaporate overnight, the residue was stirred with ether and filtered (under N_2 to minimize fire hazard). Evaporation of the ether *in vacuo* and distillation of the residual oil gave the product as an almost colorless liquid: 204.7 g.; 83%; b.p. 76–86° (0.3 mm.); λ_{max}^{film} 3.13 (C≡C—H), 4.74 (C≡C), 5.92 μ (C=O).

1-(2-Oxopyrrolidin-1-yl)-4-pyrrolidin-1′-ylbut-2-yne (Oxotremorine).—A mixture of N-propargyl-2-pyrrolidone (12.3 g., 0.1 mole), 10 ml. of water, 7.4 g. (0.105 mole) of pyrrolidine, 6.3 g. (0.105 mole) of acetic acid, 8.5 g. (0.105 mole) of 37% aqueous formaldehyde solution, and 0.25 g. of cuprous chloride was stirred under nitrogen at 38–40° for 15 hr. The mixture was then extracted with ether followed by chloroform, and the combined extracts were dried and evaporated *in vacuo*. Distillation of the residue under reduced pressure and collection of the fraction boiling at 129–131° (0.1 mm.) provided 12.6 g. (61%) of oxotremorine. Pharmacological activity: maximal peripheral and central effects were observed in mice at a dose of 0.1 mg./kg. intraperitoneally.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.70; H, 8.66; N, 13.24.

Acknowledgment.—The author is indebted to Dr. Meier E. Freed for valuable advice and encouragement.

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Benzylidene Derivatives of Indene and Cyclopentadiene[1,2]

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Received January 19, 1965

In the search for compounds which would have the antitumor activity of 4-(4-dimethylaminostyryl)quinoline without its toxicity to normal animals,[3] we have synthesized the series of benzylidene derivatives of indene and of cyclopentadiene listed in Table I. Haddow, *et al.*,[4] have reported antitumor activity of 9-(4-dimethylaminobenzylidene)fluorene and the greater activity of 4-dimethylaminostilbene. The stilbene structure is a part of the benzylidene derivatives of fluorene and indene but not of cyclopentadiene. It is interesting that none of the cyclopentadiene derivatives reported here showed strong antitumor effects, but several indene derivatives did. The minimum single i.p. dose required for clear-cut effect against Walker 256 tumors was about 40 mg./kg. for the NH_2, $NHCH_3$, and $N(CH_3)_2$[5] compounds, but the maximum tolerated dose was more than 15 times as large for the $N(CH_3)_2$ compound as for the other two. Lengthening the alkyl groups on the nitrogen increased the minimum effective dose. The presence of a CH_3 at the 3-position on the benzylidene group did not change the minimum effective antitumor dose, but lowered the maximum tolerated dose. A CH_3 group on the 3-position of the indene ring lowered the maximum tolerated

(1) This investigation was supported by Public Health Service Research Grants No. CA 03717-05-7 from the National Cancer Institute.

(2) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Charleston, W. Va., Oct. 16, 1964.

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