chloride indicated that reaction was practically complete.) The filtrate was evaporated to dryness at 20 mm. pressure. The solid was dissolved in benzene, and the solution was shaken with aqueous NaCl, then dried ($MgSO_4$). The product was precipitated by addition of isohexane. After drying, the white crystals melted at 160–161°.

*Anal.* Calcd. for $C_{18}H_{23}N_2O_3$: C, 62.41; H, 6.69; N, 8.09. Found: C, 62.38; H, 6.78; N, 7.96.[4]

**(α-Inden-1-ylidene-*p*-tolyl)methylphosphoramidic Dichloride (IV).**—A mixture of 5.0 g. of 1-(4-N-methylaminobenzylidene)-indene[5] and 50 ml. of $POCl_3$ was refluxed for 1.25 hr. under anhydrous conditions then poured into 1300 ml. of boiling isohexane with stirring. The precipitate which formed after cooling to −10° was recrystallized from isohexane; yield 5.0 g. (65%); yellow crystals, m.p. 90–92°.

*Anal.*[6] Calcd. for $C_{17}H_{14}Cl_2NOP$: C, 58.30; H, 4.03. Found: C, 58.31; H, 4.10.

**Tetrahydro-2-(α-inden-1-ylidene-N-methyl-*p*-toluidino)-2H-1,3,2-oxazaphosphorine 2-Oxide (V).**—A solution of 5.0 g. of IV in 50 ml. of nitrobenzene and a solution of 1.07 g. of 3-amino-1-propanol in 50 ml. of nitrobenzene were added simultaneously through separate dropping funnels, dropwise during 35 min., to a stirred solution of 2.89 g. of triethylamine in 400 ml. of nitrobenzene. After 2.5 hr. more stirring, the amine hydrochloride was removed by filtration, and the nitrobenzene was removed by distillation at 1–2 mm. The oily residue was washed with one 100-ml. portion of boiling isohexane and four 250-ml. portions of boiling isooctane, then recrystallized by dissolving in hot benzene and adding isohexane and cooling; yield 3.2 g. (64%) of yellow crystals, m.p. 138–140°.

*Anal.*[6] Calcd. for $C_{20}H_{21}N_2O_2P$: C, 68.18; H, 6.01; N, 7.95. Found: C, 68.10; H, 6.04; N, 7.89.

(5) C. T. Bahner, H. Kinder, D. Brotherton, J. Spiggle, and L. Gutman, *J. Med. Chem.*, **8**, 390 (1965).

(6) Analyses by Alfred Bernhardt, Mülheim (Ruhr), Germany.

## 2-Methacryloxytropones. Intermediates for the Synthesis of Biologically Active Polymers

ROBERT J. CORNELL[1] AND L. GUY DONARUMA

*Department of Chemistry, Clarkson College of Technology, Potsdam, New York*

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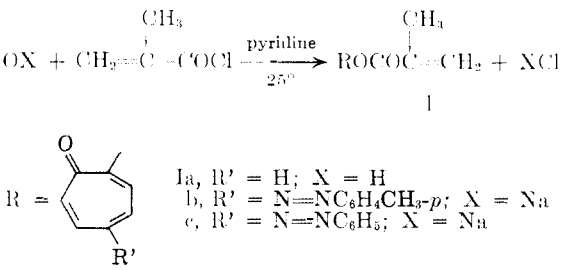
The antimitotic and antineoplastic effects of the naturally occurring troponoid, colchicine, are well known, and extensive work has been done on both the chemistry and the biological activity of colchicine.[2] A few tropolones also are known to exhibit the same effects.[2,3] In addition, tropolones are known to possess activity against bacteria,[4] fungi,[5] and viruses.[6] Some tropolones also exhibit hyperglycemic,[7] diuretic,[7] nerve-stimulating,[8] and intestinal-paralytic[8] effects.

In our laboratories we have undertaken a program aimed at investigating the effects of polymerization on the activity of biologically active monomers. To carry out such studies it was necessary to prepare polymerizable active monomers. Since tropolone and some simple acylation products of tropolone appear to show a broad spectrum of biological activity, it was thought that perhaps suitable vinyl monomers might be prepared by the reaction of methacrylyl chloride with tropolone and its derivatives.



When such reactions were carried out, as indicated above, the corresponding 2-methacryloxytropones were obtained in good yields (50–65%). Of the potential monomers prepared (Ia–Ic), only Ia was found to polymerize easily. All polymerization procedures tried to date on Ib and Ic have failed. Compounds Ia–Ic showed activity against cancer in tissue culture tests.[9] The homopolymer prepared from Ia[10] was more active than the monomer.[10] Compounds Ia and Ib were also screened for antibacterial activity.[11] These results are shown in Table I. As can be seen from Table I, Ia showed a good broad spectrum of antibacterial activity, but Ib showed almost no activity at all. The homopolymer of Ia also showed a broad spectrum of antibacterial activity.[10]

TABLE I

ANTIBACTERIAL ACTIVITY OF SOME 2-METHACRYLOXYTROPONES

| Bacterial species | Zone of inhibition, width in mm. Ia | Ib |
|---|---|---|
| *Staphylococcus aureus* 6538 | 15 | 1 |
| *Salmonella typhosa* 6539 | 22 | 0 |
| *Salmonella chloraesuis* 10708 | 17 | 0 |
| *Escherichia coli* 11229 | 16 | 0 |
| *Streptococcus pyogenes* 624 | 17 | 1 |

A number of other tropolone esters also were prepared employing methods similar to those used to prepare Ia–Ic. The structures of these compounds are shown below. Of the acyloxytropones (II–VI) shown

(1) This paper was taken in part from the thesis submitted by R. J. Cornell in partial fulfillment of the requirements for the degree of Master of Science.

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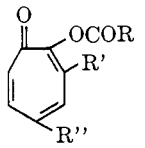
(7) A. Akiharu, *Nippon Yakurigaku Zasshi*, **55**, 352 (1959); *Chem. Abstr.*, **54**, 10137 (1960).

(8) S. Katsura, *Naunyn-Schmiedebergs Arch. Exptl. Pathol. Pharmakol.*, **221**, 215 (1954); *Chem. Abstr.* **48**, 6572 (1954).

(9) Tests performed by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md.

(10) R. J. Cornell and L. G. Donaruma, *J. Polymer Sci.*, in press.

(11) Testing carried out by the Wisconsin Alumni Research Foundation, Madison, Wis.; agar plate test, U.S.D.A. Circular No. 198, 1931. Each sample was tested at 100% concentration for activity against five representative bacteria species. Results are expressed as width of zone (in mm.) of growth inhibition of the organism. Those compounds showing wide zones were worthy of further testing by serial dilution technique over a larger number of species. This procedure provides good leads for the screening of chemicals for more specific activity by other techniques.



II, R = $C_6H_4NO_2$-*p*; R' and R'' = H
III, R = $C_6H_4NHOH$-*p*; R' and R'' = H
IV, R = $C_6H_4OCH_3$-*p*; R' and R'' = H
V, R = $C_6H_4NO_2$-*p*; R' = I; R'' = H
VI, R = *n*-hexyl; R' = H; R'' = $NHCO(CH_2)_5CH_3$

above, only VI showed activity against cancer in a tissue culture screen.[9]

## Experimental[12]

Tropolone was purchased from the Biddle–Sawyer Corp., New York, N. Y.

**2-Methacryloxytropone (Ia).**—Ten grams (0.083 mole) of tropolone, 0.10 g. of hydroquinone, 14.0 g. of dry pyridine, and 150 ml. of dry benzene were mixed under nitrogen, and 8.52 g. (0.083 mole) of methacrylyl chloride was added dropwise with vigorous stirring. Stirring was continued for 1 hr. after the addition of methacrylyl chloride was complete. The reaction mixture was washed successively with water, dilute HCl, water, and finally dried ($CaCl_2$). The benzene was evaporated leaving a white solid. Recrystallization from hexane gave 12.4 g. (65%) of white needles, m.p. 78–79°. A positive Baeyer test for unsaturation was obtained; infrared data (cm.$^{-1}$): 790 w, 825 m, 850 w, 912 w, 1000 m, 1050 w, 1080 m, 1150 s, 1250 s, 1270 m, 1350 m, 1400 w, 1480 m, 1530 m, 1600 s, 1620 s, 1650 s, 1750 s, 3020 m, 3450 w.

*Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.49; H, 5.29. Found: C, 69.71; H, 5.16.

**2-Methacryloxy-5-*p*-tolylazotropone (Ib).**—5-*p*-Tolylazotropolone was prepared by a previously reported procedure.[13] The bright red sodium salt was made by dissolving 5-*p*-tolylazotropolone in ethanol and adding an equimolar quantity of $NaOCH_3$. Ten grams (0.038 mole) of the sodium salt of 5-*p*-tolylazotropolone, 6.0 g. of dry pyridine, 0.10 g. of hydroquinone, and 150 ml. of dry benzene were mixed under nitrogen. An equimolar amount of methacrylyl chloride (3.9 g.) was added dropwise with vigorous stirring. After 1 hr., the reaction mixture was washed successively with water, dilute HCl, water, and finally dried ($CaCl_2$). The benzene was evaporated off leaving 6.0 g. (51%) of crude product. Recrystallization from ethanol–water gave red-orange needles with m.p. 168–169°; infrared data (cm.$^{-1}$): 732 w, 800 w, 825 m, 842 w, 868 m, 890 m, 935 w, 952 m, 1070 m, 1100 s, 1120 s, 1160 w, 1175 s, 1210 m, 1290 w, 1320 w, 1390 w, 1460 w, 1600 s, 1630 m, 1750 s, 2900 w.

*Anal.* Calcd. for $C_{14}H_{12}N_2O_2$: C, 70.11; H, 5.23. Found: C, 70.35; H, 5.27.

**2-Methacryloxy-5-phenylazotropone (Ic).**—5-Phenylazotropolone was prepared by the procedure of Nozoe, *et al.*,[14] or by the coupling of phenyldiazonium chloride with tropolone according to the procedure employed to prepare 5-*p*-tolylazotropolone.[13] Eight grams (0.032 mole) of the sodium salt of 5-phenylazotropolone, 0.10 g. of hydroquinone, and 5.0 g. of dry pyridine were mixed with 150 ml. of dry benzene under nitrogen. An equimolar amount of methacrylyl chloride (3.3 g.) was added dropwise with vigorous stirring. After 1 hr. the reaction mixture was washed successively with water, dilute HCl, water, and finally dried ($CaCl_2$). The benzene was evaporated off leaving 5.2 g. (55%) of crude product. Recrystallization from ethanol–water gave orange plates with m.p. 135–137°; infrared data (cm.$^{-1}$): 728 m, 772 s, 808 m, 838 w, 868 s, 890 m, 945 m, 958 m, 1010 w, 1065 m, 1120 s, 1145 w, 1165 s, 1200 m, 1220 w, 1260 w, 1285 m, 1315 s, 1340 w, 1370 w, 1385 w, 1420 w, 1440 m, 1475 m, 1535 w, 1580 w, 1600 s, 1620 s, 1720 s.

*Anal.* Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79. Found: C, 69.49; H, 5.04.

**2-*p*-Nitrobenzoxytropone (II).**—Three grams (0.02 mole) of the sodium salt of tropolone and 3.2 g. of dry pyridine, were added to 100 ml. of dry benzene. With vigorous stirring, 3.7 g. (0.02 mole) of *p*-nitrobenzoyl chloride was added in small portions. The mixture was stirred for 1 hr. with the formation of a white solid which was filtered and dried. Recrystallization from ethanol gave long white needles with m.p. 175–176°; a yield of 4.8 g. (88%) was obtained from the reaction; infrared data (cm.$^{-1}$): 713 s, 728 w, 755 w, 785 s, 835 m, 860 m, 878 m, 948 w, 980 w, 1020 m, 1045 w, 1070 s, 1135 w, 1180 w, 1220 m, 1250 s, 1275 s, 1280 s, 1350 s, 1395 m, 1475 m, 1540 s, 1600 s, 1620 s, 1650 m, 1760 s, 3100 w, 3500 w.

*Anal.* Calcd. for $C_{14}H_9NO_5$: C, 62.00; H, 3.34. Found: C, 62.00; H, 3.60.

**2-*p*-Hydroxylaminobenzoxytropone (III).**—Ten grams (0.037 mole) of the nitro derivative was added to a mixture of 200 ml. of methanol and 0.5 g. of palladium on carbon. Reduction was performed by bringing the reaction into contact with hydrogen at 2.81 kg./cm.$^2$. After taking up 0.08 mole of hydrogen, the mixture was filtered to remove the used catalyst. The methanol was evaporated leaving 7.6 g. (80%) of crude 2-*p*-hydroxylaminobenzoxytropone. An oil formed when recrystallization was attempted from ethanol. The oil eventually solidified and upon repeating this process several times purification of the product was achieved; m.p. 158–159°. A positive Tollens test was obtained; infrared data (cm.$^{-1}$): 760 m, 775 m, 825 w, 865 m, 1000 w, 1020 w, 1060 w, 1145 s, 1165 w, 1225 m, 1250 s, 1265 m, 1285 m, 1470 m, 1510 m, 1540 m, 1605 s, 1725 s, 3100 m, 3280 s.

*Anal.* Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.30. Found: C, 65.16; H, 4.36.

**2-*p*-Methoxybenzoxytropone (IV).**—Tropolone (10 g., 0.083 mole) and 14 g. of dry pyridine were dissolved in 150 ml. of dry benzene. An equimolar amount (14.6 g.) of anisoyl chloride was added dropwise with stirring. Stirring was continued for 1 hr. after the addition of anisoyl chloride was complete. The reaction mixture was washed with water, dilute HCl, water, and finally dried ($CaCl_2$). The benzene was evaporated leaving 18.7 g. (88%) of crude product. Recrystallization from ethanol gave white needles with m.p. 147–148°; infrared data (cm.$^{-1}$): 760 s, 775 m, 790 w, 850 s, 875 w, 945 w, 1010 m, 1020 s, 1062 s, 1120 m, 1140 s, 1170 s, 1180 m, 1250 s, 1275 s, 1385 m, 1425 m, 1435 w, 1460 m, 1510 s, 1575 s, 1605 s, 1630 m, 1725 s, 2830 w.

*Anal.* Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.33; H, 4.79.

**3-Iodo-2-*p*-nitrobenzoxytropone (V).**—The potassium salt of 3-iodotropolone was prepared by the procedure of Kitahara and Arai.[15] Ten grams (0.036 mole) of this salt and 5.7 g. of dry pyridine were mixed with 200 ml. of dry benzene. The mixture was stirred with the addition of 6.7 g. (0.036 mole) of *p*-nitrobenzoyl chloride in small portions, heated to 60° with a water bath, and maintained at that temperature for 1 hr. with stirring. The precipitate was filtered off, washed with water, 5% NaOH, and finally with water. The crude product weighed 2.85 g. (20%) and was recrystallized from ethanol giving pale yellow needles with m.p. 181–183°; infrared data (cm.$^{-1}$): 710 s, 736 m, 765 s, 778 w, 845 m, 865 w, 875 m, 885 w, 955 w, 1015 m, 1030 w, 1075 s, 1150 s, 1170 w, 1210 m, 1250 s, 1265 s, 1310 m, 1330 s, 1365 w, 1395 w, 1450 w, 1475 w, 1510 s, 1560 m, 1580 s, 1715 s, 3300 w.

*Anal.* Calcd. for $C_{14}H_8INO_5$: C, 42.30; H, 2.03. Found: C, 41.88; H, 2.33.

**2-Heptanoyloxy-5-heptanamidotropone (VI).**—Five grams (0.036 mole) of 5-aminotropolone and 5.5 g. of dry pyridine were dissolved in 100 ml. of dry benzene. Two molar equivalents (11.8 g.) of heptanoyl chloride was added dropwise with stirring. After 1 hr., the reaction mixture was washed successively with water, dilute HCl, and water and finally dried ($CaCl_2$). The benzene was removed by evaporation leaving 2.8 g. (22%) of crude product. Recrystallization from ethanol–water gave a white powder with m.p. 112–113°; infrared data (cm.$^{-1}$): 852 m, 858 s, 882 w, 908 w, 970 w, 1090 m, 1110 w, 1145 m, 1169 m,

(12) Melting points were taken on a Reichert apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer Model 237 as KBr wafers. Legend for the interpretations of infrared data: s, strong absorbance; m, medium absorbance; w, weak absorbance.

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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

JOHN L. ARCHIBALD

*Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania*

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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.); $\lambda_{max}^{film}$ 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]

CARL TABB BAHNER, HAROLD KINDER, DAVID BROTHERTON, JOHN SPIGGLE, AND LEE GUTMAN

*Carson-Newman College, Jefferson City, Tennessee 37760*

*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

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

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