were determined at 25° in chloroform solution at 0.2–1.0% concentrations. Ultraviolet spectra were measured in methanol solution on a Cary recording spectrophotometer, and infrared spectra were determined in pressed KBr disks on a Perkin-Elmer spectrophotometer (Model 21). Solutions were dried with $Na_2SO_4$ and evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

**17α-Acetoxy-21-fluoropregna-4,6-diene-3,20-dione.**—Hydrogen chloride was bubbled vigorously over a 3–4 min. period (to saturation) into a well-stirred solution of 2.227 g. (5.71 mmoles) of 17-acetoxy-21-fluoroprogesterone[3] and 1.480 g. (6.52 mmoles) of recrystallized 2,3-dichloro-5,6-dicyanobenzoquinone[4] in 75 ml. of dioxane (purified according to Fieser[5]). Precipitation of hydroquinone began in about 1 min. (exothermic). The mixture was stirred 30 min. and filtered. The precipitate of hydroquinone was washed well with benzene, the entire filtrate was further diluted with benzene (200 ml. total), and the resulting solution was washed with two 50-ml. portions of water, two 75-ml. portions of 1% aqueous NaOH, and two 50-ml. portions of saturated aqueous NaCl. The solution was dried, the solvent was evaporated, and the residue crystallized on trituration in ether. Recrystallization from acetone–petroleum ether afforded 1.684 g. (76%) of product. The analytical sample (from acetone–hexane) had m.p. 205.5–206.5°; $[\alpha]D$ −10°; $\lambda_{max}$ 5.78, 6.02, 6.19, 6.31, 7.93, 9.52 μ; $\lambda_{max}$ 282 mμ (ε 25,200).

*Anal.* Calcd. for $C_{23}H_{29}FO_4$: C, 71.10; H, 7.53; F, 4.89. Found: C, 70.85; H, 7.45; F, 5.22.

**17α-Acetoxy-6α,7α-epoxy-21-fluoropregn-4-ene-3,20-dione.**—To a solution of 776 mg. (2 mmoles) of 17α-acetoxy-21-fluoropregna-4,6-diene-3,20-dione in 190 ml. of methylene chloride was added 53 ml. of an ethereal solution of monoperphthalic acid[5] in ether( containing 48 mg./ml., 14 mmoles of perphthalic acid), and the solution was stirred well and allowed to stand at room temperature for 68 hr. protected from atmospheric moisture. The solution was decanted from precipitated phthalic acid, washed with two 50-ml. portions of saturated aqueous $Na_2CO_3$, two 50-ml. portions of water, and two 50-ml. portions of saturated aqueous NaCl, and dried. The solvent was evaporated and the oily residue (711 mg.) crystallized on trituration with ether. The precipitate was washed several times with cold ether to afford 477 mg. of product, m.p. 228–232° dec. Recrystallization from methylene chloride–ether afforded 227 mg. of product, m.p. 240–243° dec. containing approximately 1% of 4,6-diene starting material (as estimated from the ultraviolet spectrum). The analytical sample (from ethyl acetate–petroleum ether) had m.p. 242–245° dec.; $[\alpha]D$ +3°; $\lambda_{max}$ 5.80, 6.03, 7.92, 8.08, 11.56 μ; $\lambda_{max}$ 240 mμ (ε 14,900).

*Anal.* Calcd. for $C_{23}H_{29}FO_5$: C, 68.29; H, 7.24; F, 4.70. Found: C, 68.48; H, 7.50; F, 5.21.

**17α-Acetoxy-6-chloro-21-fluoropregna-4,6-diene-3,20-dione (I).**—Hydrogen chloride was bubbled into a stirred solution of 195 mg. of 17α-acetoxy-6α,7α-epoxy-21-fluoropregn-4-ene-3,20-dione in 10 ml. of glacial acetic acid over a 10-min. period and the orange solution was allowed to stand 2 hr. loosely capped at room temperature. After resaturation with HCl, the solution was allowed to stand an additional 2 hr., and then was poured slowly with stirring into 100 ml. of ice–water. The aqueous mixture was extracted with $CH_2Cl_2$ and the extracts were combined, washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and dried. The solvent was evaporated and the residue crystallized on trituration with methanol. Chromatography on silica gel using 5% ether–benzene as eluent afforded the product (150 mg., m.p. 210–214°). Recrystallization from methanol gave the analytical sample: m.p. 217–219°; $[\alpha]D$ −8°; $\lambda_{max}$ 5.76, 6.00, 6.23, 6.30, 7.94, 8.11, 11.42 μ; $\lambda_{max}$ 284 mμ (ε 21,200).

*Anal.* Calcd. for $C_{23}H_{28}ClFO_4$: C, 65.36; H, 6.69; Cl, 8.31; F, 4.49. Found: C, 65.56; H, 6.95; Cl, 8.95; F, 4.32.

**Acknowledgment.**—We wish to thank Dr. I. Ringler for assistance in obtaining and interpreting the Clauberg assays, Mr. L. Brancone and staff for microanalytical data, and Mr. W. Fulmor and associates for the spectroscopic and polarimetric data.

(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed. (revised), D. C. Heath and Company, Boston, Mass., 1957, p. 285, method a.

## 2H-1,3,2-Oxazaphosphorine Derivatives[1]

CARL TABB BAHNER, HUGHLAN W. POPE, AND DAVID BROTHERTON

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

*Received January 19, 1965*

The widespread interest in Cytoxan, which may be considered as a nitrogen mustard derivative of 2H-1,3,2-oxazaphosphorine (I),[2] led us to prepare other derivatives of I, with a stilbene or benzylideneindene group. One compound showed marked antitumor activity against the Walker 256 tumor in rats (Table I).

TABLE I

BIOLOGICAL ACTIVITY

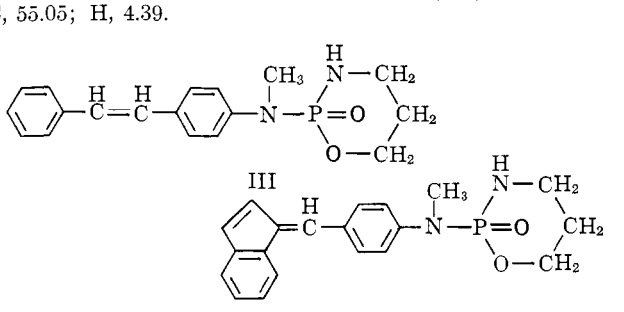
| Compd. | KB cell test[a] $ED_{50}$, mg./kg. | Tumor wt.[b] T/C @ mg./kg. | | Killed @ mg./kg. | |
|---|---|---|---|---|---|
| II | | 0.9 | 12 | 1/3 | 25 |
| III | 33 | 0.13 | 250 | 3/3 | 500 |
| | | 0.8 | 100 | 0/3 | 250 |
| V | 29 | 0.8 | 320 | 3/3 | 640 |

[a] Results of the standard *in vitro* KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center at the University of Miami Cell Culture Laboratory and Southern Research Institute. [b] We are grateful to Professor Alexander Haddow, Mr. J. E. Everett, and Mr. B. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single i.p. injection in Arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor bearing animals were sacrificed approximately 8 days later and the average weights of tumors in treated and untreated hosts are reported as the ratio *T/C*.

### Experimental

***p*-Styrylphenylmethylphosphoramidic Dichloride (II).**—A mixture of 13.6 g. of 4-N-methylaminostilbene[3] and 120 ml. of $POCl_3$ was refluxed 16 hr., then most of the $POCl_3$ was removed by distillation. Recrystallization of the solid product produced almost colorless crystals, m.p. 126–127° (cor.), yield 71%.

*Anal.*[4] Calcd. for $C_{15}H_{14}Cl_2NOP$: C, 55.24; H, 4.38. Found: C, 55.05; H, 4.39.



III



V

**2-(Styryl-N-methylanilino)tetrahydro-2H-1,3,2-oxazaphosphorine 2-Oxide Monohydrate (III).**—A mixture of 9.06 g. of II, 2.06 g. of 3-amino-1-propanol, 5.61 g. of triethylamine, and 300 ml. of anhydrous dioxane was allowed to stand for 12 hr. at room temperature then filtered to remove the triethylamine hydrochloride formed. (The 96% yield of triethylamine hydro-

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

(2) H. Arnold, F. Bourseaux, and N. Brock, *Nature*, **181**, 131 (1958); O. M. Friedman, E. Boger, V. Grubliauskas, and H. Sommer, *J. Med. Chem.*, **6**, 50 (1963).

(3) A. Haddow, R. J. C. Harris, T. A. R. Kon, and E. M. F. Roe, *Phil. Trans. Roy. Soc. London*, **A241**, 147 (1948).

(4) Analyses by Weiler and Strauss, Oxford, England.

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 $C_{26}H_{21}N_2O_2P$: 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

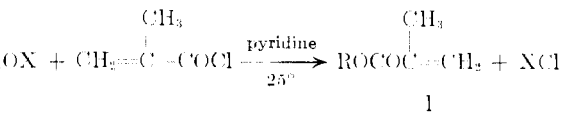
ROBERT J. CORNELL[1] AND L. GUY DONARUMA

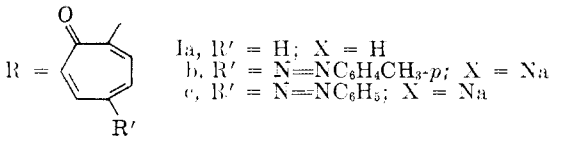
*Department of Chemistry, Clarkson College of Technology, Potsdam, New York*

*Received November 19, 1964*

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.

(2) P. L. Pauson, *Chem. Rev.*, **55**, 9 (1955).

(3) K. Sato, K. Akaishi, K. Kawmura, and Y. Nakamura, *Gann*, **44**, 356 (1953); K. Sato and K. Akaishi, *ibid.*, **43**, 150 (1952); S. Katasura, K. Sato, K. Akaishi, T. Nozoe, and Y. Kitahara, *Proc. Japan Acad.*, **27**, 31 36, 250 (1951); *Chem. Abstr.*, **46**, 2700, 11460 (1952); B. Wada, *Cytologia* (Tokyo), **17**, 279 (1952); J. Leiter, J. L. Hartwell, J. S. Kahler, I. Kline, and M. J. Shear, *J. Natl. Cancer Inst.*, **14**, 365 (1953).

(4) S. Katasura, K. Tamura, S. Hatori, and S. Maeda, *Tohoku J. Exptl. Med.*, **49**, 357 (1948); *Chem. Abstr.*, **43**, 5906 (1949); S. Maeda, *Igaku To Seibutsugaku*, **18**, 311 (1951); *Chem. Abstr.*, **45**, 9608 (1951); R. Meier, B. Schar, and L. Neipp, *Experientia*, **10**, 74 (1954); A. J. Baille, G. G. Freeman, J. N. Cook, and A. R. Somerville, *Nature*, **156**, 65 (1950); S. Katasura, *Zentr. Bakteriol. Parasitenk. Abt. I. Orig.*, **161**, 206 (1954), *Chem. Abstr.*, **48**, 12898 (1954); S. Yang, G. Nozawa, M. Yanagisawa, and I. Mishima, *Niigata Igakkai Zasshi*, **66**, 515, 826, 849, 853 (1952); S. Yang, T. Manabe, S. Maeda, and S. Watanabe, *ibid.*, **67**, 74, 113, 185, 447, 514, 938 (1953); S. Katasura, M. Yanagisawa, J. Kush, and S. Watanabe, *Klin. Wochschr.*, **31**, 405 (1953); *Chem. Abstr.*, **47**, 7586 (1953).

(5) A. J. Baille, G. G. Freeman, J. W. Cook, and A. R. Somerville, *Nature*, **166**, 65 (1950); H. Takahashi, *Nippon Naikagahkai Zasshi*, **47**, 212 (1958).

(6) S. Katasura and M. Tsuruma, *Zentr. Bakteriol., Parasitenk. Abt. I. Orig.*, **168**, 378 (1957); *Chem. Abstr.*, **51**, 16702 (1957).

(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.