[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE CHEMOTHERAPY OF CANCER. I. SOME ALKOXYMETHYLENE-1-TETRALONES[1]

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Received December 27, 1949

The alkaloid colchicine has long been known to be a mitotic poison, (1, 2) and as such, acts as a tumor-growth inhibitor in cancer. Although its high toxicity precludes its use in the treatment of human cancer, it is possible that simpler analogs of colchicine might retain some of the growth-inhibitory properties, while losing some of the toxicity of the alkaloid, and a good deal of work is being done in various laboratories on such analogs.

For many years the accepted structure for colchicine was that proposed by Windaus, I (3). On the basis of this structure, it was postulated (4) that the growth-inhibitory properties of colchicine are due to the diarylethylamine chain, and it has been found (4, 5) that simpler diaryl-ethyl- and -propylamines do have some growth-inhibitory action. It seemed to us, however, that the highly unsaturated "C" ring of colchicine might also be responsible, at least in part, for the mitotic poisoning activity. Many compounds with conjugated olefinic and carbonyl groups are growth-inhibitors in one degree or another; as examples may be cited the benzo- and naptho-quinones (6), the unsaturated lactones protoanemonin and hexenolactone (7, 8), and certain α, β-unsaturated ketones (8). It seemed of interest, therefore, to prepare compounds modeled after the "C" ring of colchicine for testing as tumor-growth inhibitors, and as the present work was started before the evidence in support of the tropolone structure of colchicine (II) (10) appeared, the compounds reported in this paper and the next are based on the Windaus structure (I).

In the present paper several derivatives of 2-hydroxymethylene-1-tetralone (III) are described.

Although 1-tetralone itself can be prepared (in rather poor yield) by oxidation of tetralin, the best route to bz-substituted 1-tetralones is by cyclization of the γ-arylbutyric acids. The 1-tetralones are readily converted, in 50–75% yields, to the 2-hydroxymethylene derivatives by condensation with ethyl formate in the presence of sodium ethoxide (11). The hydroxymethylene compounds are unstable to air, but may be purified by high-vacuum distillation.

[1] This investigation was supported (in part) by a research grant from the National Cancer Institute, U. S. Public Health Service, and the compounds are being tested at the Institute.

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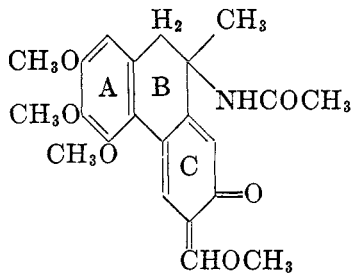
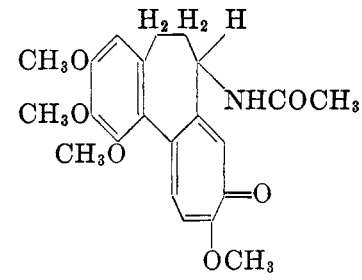
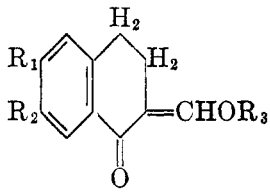


I



II



III

(a) $R_1 = R_2 = H; R_3 = C_2H_5$
(b) $R_1 = R_2 = H; R_3 = CH(CH_3)_2$
(c) $R_1 = H, R_2 = CH_3O, R_3 = C_2H_5$
(d) $R_1 = R_2 = CH_3O, R_3 = C_2H_5$

Alkylation of a hydroxymethylene ketone can occur either on the oxygen or on the carbon atom of the >C=CHOH system. Johnson and Posvic (12) have shown that methylation of these compounds with methyl iodide in the presence of potassium carbonate gives a high proportion of the C-methyl product. Since in the present work the O-alkyl derivative was the desired one, other methylating agents were investigated, including diazomethane, methyl sulfate under varying conditions, and methanol in the presence of a trace of acid, but we were unable to obtain appreciable yields of a stable O-methyl ether. As Johnson and Posvic have pointed out, isopropyl iodide gives a much higher proportion of O-alkylation. This has also been found true for ethyl iodide, and the O-ethyl ethers were obtained in fair yield by the action of ethyl iodide and potassium carbonate in anhydrous acetone, according to the general procedure of Claisen as described by Auwers (13). These ethers did not give an immediate color with ferric chloride but on standing with aqueous ferric chloride some hydrolysis to the free hydroxymethylene compound occurred, and the typical enol color developed.

Some of the compounds prepared in this work have been screened against sarcoma 37 in the mouse, at the National Cancer Institute. While they were found to be much less toxic than colchicine, they also showed much less growth-inhibitory action. The work is being continued, and compounds modeled after the recently proposed seven-membered "C" ring structure of colchicine (9, 10) are being synthesized.

EXPERIMENTAL[5, 6]

5-Tetralones. 1-Tetralone itself was prepared by air-oxidation of tetralin (14) but the best yield obtained was only 30%, instead of the 44–56% reported. γ-(*p*-Methoxyphenyl)-

[5] Analyses carried out by Mr. Charles Beazley, Micro-Tech Laboratories, Skokie, Illinois.

[6] All melting points are uncorrected.

butyric acid (15) was cyclized by phosphorus pentoxide in benzene to give a 32% yield of 7-methoxy-1-tetralone, m.p. 60–61° (16), and γ-(3′,4′-dimethoxyphenyl)butyric acid was cyclized to 6,7-dimethoxy-1-tetralone, m.p. 99°, in 58% yield by the procedure of Haworth and Marvin (17).

2-Hydroxymethylene-1-tetralones. The procedure was similar to that developed by Johnson and Shelberg (11) for related compounds. Ethyl formate (0.1 mole) was added to alcohol-free sodium ethoxide (from 0.1 gram-atom of sodium and 0.1 mole of absolute ethanol) in dry benzene and the resulting suspension was treated with 0.05 mole of the tetralone in an atmosphere of dry nitrogen. The reaction mixture was stirred at room temperature for 24 hours, evaporated to dryness under reduced pressure, and the residue dissolved in 10% aqueous sodium hydroxide and extracted with ether to remove non-acidic impurities. The aqueous layer was acidified with 2 *N* hydrochloric acid at 5–10° and repeatedly extracted with ether. The combined ether extracts were dried over magnesium sulfate, evaporated, and the residue distilled at *ca.* 0.1 mm. It was essential to avoid exposure to air throughout the preparation.

2-Hydroxymethylene-1-tetralone was obtained in 78% yield as a light yellow oil, b.p. 124–128°/4 mm., n_D^{20} 1.6232–1.6245. Auwers and Weigand (18) reported b.p. 153–154°/10 mm., n_α^{18} 1.6246.

2-Hydroxymethylene-7-methoxy-1-tetralone, formed a yellow oil, b.p. 115–120°/0.1 mm. The yield was 63%.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.37; H, 5.93.
Found: C, 70.16; H, 6.11.

2-Hydroxymethylene-6,7-dimethoxy-1-tetralone, was obtained in 75% yield as straw-colored crystals (from high-boiling petroleum ether) m.p. 147–150°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02.
Found: C, 66.08; H, 5.90.

Ethers of 2-hydroxymethylene-1-tetralones. The general procedure was similar to that described by Auwers (13). A mixture of 0.05 mole of the hydroxymethylenetetralone, 0.05 mole of anhydrous potassium carbonate, and 0.08 mole of alkyl iodide in 25 ml. of dry acetone was refluxed for 24 hours. The mixture was cooled, diluted with two volumes of dry ether, filtered from potassium iodide, the solvents removed, and the residue purified by molecular distillation; this did not permit determination of the boiling points. The products obtained gave slowly developing colors with ferric chloride, but only a very slight instantaneous color, indicating that they were largely, if not entirely, the O-alkyl ethers.

2-Ethoxymethylene-1-tetralone (IIIa) was obtained in 40% yield as a light yellow oil by distillation at 0.005 mm. (bath temperature 110–125°). It had n_D^{20} 1.5824. Auwers and Weigand (18) reported b.p. 170–171°/10 mm., n_α^{18} 1.5853. The material obtained in the present work appeared to be largely the O-ethyl ether.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98.
Found: C, 77.52; H, 7.30.

2-Isopropoxymethylene-1-tetralone (IIIb) distilled at 0.005 mm. (bath temperature 115–120°). The yield of oil, n_D^{20} 1.5847, was 79%.

Anal. Calc'd for $C_{14}H_{17}O_2$: C, 77.75; H, 7.46.
Found: C, 77.92; H, 7.68.

2-Ethoxymethylene-7-methoxy-1-tetralone (IIIc) was obtained as a yellow oil after two distillations at 0.008 mm. (bath temperature 95–120°). The oil solidified, and after recrystallization from petroleum ether (b.p. 30–60°) formed white crystals, m.p. 86–87.5°, which gave a slowly developing color with ferric chloride. The yield was 55%.

Anal. Calc'd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94.
Found: C, 72.38; H, 6.92.

2-Ethoxymethylene-6,7-dimethoxy-1-tetralone (IIId) was obtained as white needles, m.p. 98.5–100° from petroleum ether (b.p. 90–120°); yield, 40%.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92.
Found: C, 68.35; H, 6.92.

SUMMARY

Several alkoxymethylene derivatives of 1-tetralones have been prepared for testing as tumor-growth inhibitors.

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REFERENCES

(1) LUDFORD, *J. Natl. Cancer Inst.*, **6**, 89 (1945).
(2) STERN AND WILHUM, *Biochemistry of Cancer*, Academic Press, Inc., New York, 1947, p. 170.
(3) WINDAUS, *Ann.*, **439**, 59 (1924); GREWE, *Ber.*, **71**, 907 (1939).
(4) LETTRE AND FERNHOLZ, *Z. physiol. Chem.*, **278**, 175 (1943).
(5) LUTZ AND MURPHEY, *J. Am. Chem. Soc.*, **71**, 478 (1949).
(6) BEAUDET, *Helv. Chim. Acta*, **30**, 1804 (1947).
(7) SHAW, *J. Am. Chem. Soc.*, **68**, 2510 (1946); JOLY AND AMIARD, *Bull. soc. chim. France*, 139 (1947).
(8) RINDERKNECHT, *et al.*, *Biochem. J.*, **41**, 463 (1947).
(9) DEWAR, *Nature*, **155**, 141 (1945).
(10) TARBELL, *J. Am. Chem. Soc.*, **70**, 1669 (1948).
(11) JOHNSON AND SHELBERG, *J. Am. Chem. Soc.*, **67**, 1745 (1945).
(12) JOHNSON AND POSVIC, *J. Am. Chem. Soc.*, **69**, 1361 (1947).
(13) AUWERS, *Ber.*, **71**, 2082 (1938).
(14) THOMPSON, *Org. Syntheses*, **20**, 94 (1940).
(15) MARTIN, *J. Am. Chem. Soc.*, **58**, 1438 (1936).
(16) PLEMMER, SHORT, AND HILL, *J. Chem. Soc.*, 694 (1938).
(17) HAWORTH AND MAVIN, *J. Chem. Soc.*, 1485 (1932).
(18) AUWERS AND WIEGAND, *J. prakt. Chem.*, **134**, 82 (1932).