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

THE CHEMOTHERAPY OF CANCER. II. SOME ARYL-SUBSTITUTED ALKOXYMETHYLENE CYCLOHEXENONES[1, 2]

KENNETH N. CAMPBELL, ALBERT SCHRAGE[3], AND BARBARA K. CAMPBELL[4]

Received December 27, 1949

In continuation of our work (1) on chemotheraputeic agents for cancer, it seemed of interest further to explore compounds related to the unsaturated C ring of colchicine, since this ring may be responsible, in part at least, for the mitotic-poisoning activity of the alkaloid. The Windaus structure (I) for colchicine can be regarded as that of a methoxymethylene aryl-substituted cyclohexadienone where the two rings are linked together by a saturated two-carbon chain. It appeared worthwhile to prepare compounds as closely related to this structure as possible. Meyer and Reichstein (2) have prepared 3-methoxymethylene-4-ketotetrahydrophenanthrene (II) and 2-methoxymethylene-1-ketotetrahydrophenanthrene, but their synthesis did not appear to be easily adaptable to derivatives with one or more alkoxyl groups on the benzene ring. Neither did it seem feasible to prepare hydroxymethylenecyclohexadienones, since these would probably exist almost entirely in the isomeric salicylaldehyde form and therefore could not be alkylated in the desired way.

The method of Horning and Field (3), however, provided an excellent route to a variety of aryl cyclohexenones of the general structure III, starting from readily available aldehydes. These 3-methyl-5-aryl-2-cyclohexen-1-ones were condensed with ethyl formate and the resulting hydroxymethylene ketones, which were usually obtained as non-crystallizable dark red oils, were etherified directly to IV with ethyl iodide and potassium carbonate in dry acetone.

Some of these compounds have been tested against mouse sarcoma 37 at the National Cancer Institute, and have shown little or no activity. Steinegger and Lavan (4) who tested the Meyer-Reichstein compounds for anti-mitotic action found that 3-hydroxymethylene-4-ketotetrahydrophenanthrene showed activity, but the methyl ether did not.

EXPERIMENTAL[5, 6]

3-Methyl-5-aryl-2-cyclohexen-1-ones. These were prepared from the aromatic aldehydes by condensation with acetoacetic ester, cyclization, and decarboxylation without isolation of any of the intermediates, using the procedure described by Horning and Field (3) for the 5-*p*-methoxyphenyl compound.

---

[1] Abstracted from Ph.D. thesis of Albert Schrage, University of Notre Dame, June, 1949.

[2] 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 National Cancer Institute.

[3] Reilly Fellow, 1947–1949. Present address: Wellcome Research Laboratories, Tuckahoe, New York.

[4] Present address, Indiana University, South Bend, Indiana.

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

[6] All melting points are uncorrected.

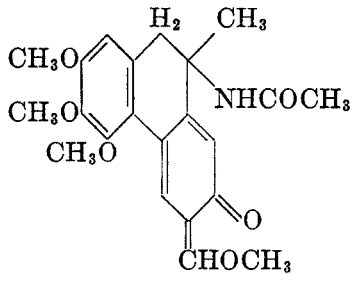
3-Methyl-5-(p-methoxyphenyl)-2-cyclohexen-1-one (IIIa) was obtained in 66% yield, b.p. 168–170°/0.8 mm., m.p. 63° (3).

3-Methyl-5-(3',4'-dimethoxyphenyl)-2-cyclohexen-1-one, (IIIb) b.p. 190°/1.2 mm., was obtained as a light yellow solid, m.p. 90–91° after recrystallization from ethyl acetate-petroleum ether (b.p. 30–60°) mixture. The yield was 22%.

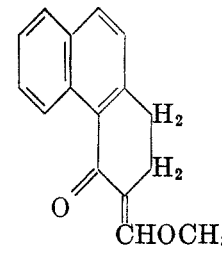
Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.39.

Found: C, 73.11; H, 7.45.

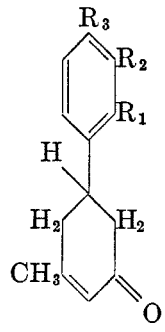
3-Methyl-5-(3',4'-methylenedioxyphenyl)-2-cyclohexen-1-one (IIIc) was obtained in 11% yield from piperonal. It had b.p. 201°/2 mm., m.p. 84°, in agreement with Knoevenagel and Hoffmann's value (5).



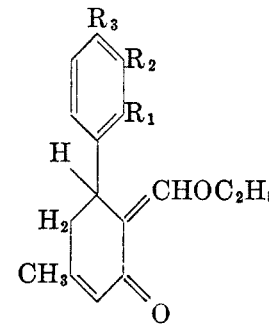
I



II



III



IV

(a) $R_1, R_2 = H; R = CH_3O$
(b) $R_1 = H; R_2$ and $R_3 = CH_3O$
(c) $R_1 = H; R_2—R_3 = —OCH_2O—$
(d) $R_1, R_2, R_3 = CH_3O$

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-2-cyclohexen-1-one (IIId). 2,3,4-Trimethoxybenzaldehyde was prepared in 90% yield from pyrogallol trimethyl ether as described by Slotta and Heller (6); b.p. 150–155°/10 mm., m.p. 26–28°. It was condensed with acetoacetic ester and converted to the cyclohexenone in 40% yield. The product boiled at 175–180°/0.5 mm. and solidified to light yellow crystals which melted at 101–102° after recrystallization from ethyl acetate-pretroleum ether.

Anal. Calc'd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30.

Found: C, 69.40; H, 7.47.

3-Methyl-5-aryl-6-ethoxymethylene-2-cyclohexen-1-ones. The cyclohexenones were condensed with ethyl formate in the presence of sodium ethoxide as described previously (1) except that the hydroxymethylene ketones could not be distilled even in a high vacuum, without decomposition. With one exception they could not be crystallized, either, and

therefore the crude red oils were etherified without purification by treatment with ethyl iodide and potassium carbonate in anhydrous acetone. The ethoxymethylene compounds were purified by molecular distillation. They did not give an immediate color with aqueous ferric chloride, but on long standing with the reagent the typical enol color developed.

3-Methyl-5-(p-methoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVa) was obtained as light yellow oil which was purified by distillation at 10^{-5} mm.; the yield was 20%.

Anal. Calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40.
Found: C, 74.97; H, 7.29.

3-Methyl-5-(3',4'-dimethoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVb). This was obtained in 21% yield as a light yellow oil.

Anal. Calc'd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34.
Found: C, 71.1; H, 7.36.

3-Methyl-5-(3,4-methylenedioxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVc). This was prepared as described previously; the yield of light yellow oil was 20%.

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.34.
Found: C, 71.07; H, 6.50.

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-6-hydroxymethylene-2-cyclohexen-1-one. This was the only hydroxymethylene compound which crystallized. It formed yellow prisms, m.p. 97.5–99.5° from hexane; yield 76%.

Anal. Calc'd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62.
Found: C, 67.05; H, 6.37.

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVd). This was obtained in 75% yield as a light orange oil which solidified on treatment with ethyl acetate-hexane mixture to yellow needles, m.p. 105–106°.

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28.
Found: C, 68.80; H, 7.47.

SUMMARY

Several 3-methyl-5-aryl-6-ethoxymethylene-2 cyclohexen-1-ones have been prepared as possible tumor-growth inhibitors.

NOTRE DAME, INDIANA

REFERENCES

(1) CAMPBELL, SCHRAGE, AND CAMPBELL, *J. Org. Chem.*, preceding article.
(2) MEYER AND REICHSTEIN, *Pharm. Acta Helv.*, **19**, 128 (1944) [*Chem. Abstr.*, **39**, 516 (1945)].
(3) HORNING AND FIELD, *J. Am. Chem. Soc.*, **68**, 384 (1946).
(4) STEINEGGER AND LAVAN, *Heriditas*, **34**, 193 (1948) [*Chem. Abstr.*, **42**, 7839 (1948)].
(5) KNOEVENAGEL AND HOFFMANN, *Ann.*, **303**, 230 (1898).
(6) SLOTTA AND HELLER, *Ber.*, **63**, 3029 (1930).