

Although compound I showed activity against adenocarcinoma 755 when tested in these laboratories, none of the analogs showed any appreciable activity against this tumor, sarcoma 180, or leukemia L-1210.²

EXPERIMENTAL³

Procedure A. To a solution of 1.12 g. (9.2 mmoles) of 3,4-xylylene in 20 ml. of anhydrous ether was added 0.50 g. (2.4 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. The reaction mixture was allowed to stand overnight at room temperature protected from moisture, then the precipitated 3,4-xylylene hydrochloride was removed by filtration. Evaporation of the filtrate to dryness *in vacuo* gave a solid, which was recrystallized from absolute ethanol to give 0.70 g. (77%) of white crystals of V, m.p. 128–130°. Further recrystallizations raised the melting point to 132–133°. The analytical data are recorded in Table I.

Procedure B. A flask containing a mixture of 26.4 g. (0.207 mole) of *o*-chloroaniline and 10.0 g. (0.048 mole) of phenylphosphonothioic dichloride was placed in an oil bath at room temperature and the temperature raised to 165° over 15–20 min., then held at that temperature for 1 hr. The mixture was cooled, then dissolved in 150 ml. of chloroform. Treatment of the chloroform solution with 100 ml. of 1*N* hydrochloric acid caused the precipitation of *o*-chloroaniline hydrochloride. After the removal of the hydrochloride by filtration, the layers were separated and the chloroform layer was washed with two 60-ml. portions of 2*M* aqueous ammonia and 100 ml. of water. The chloroform layer was dried over magnesium sulfate, then concentrated to dryness *in vacuo* to yield 14.8 g. of a white solid. Recrystallization from absolute ethanol gave 9.6 g. (52%) of III as white crystals, m.p. 112–114°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 113–114°. The analytical data are recorded in Table I.

Procedure C. To a mixture of 12.98 g. (0.094 mole) of *p*-nitroaniline and 7.44 g. (0.094 mole) of pyridine in 400 ml. of dry benzene was added 10.0 g. (0.047 mole) of phenylphosphonothioic dichloride dropwise with stirring over a period of about 10 min. After the addition was complete, the reaction was heated at reflux for 7 hr., then cooled and concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ethyl acetate and washed with two 100-ml. portions of 1*N* hydrochloric acid, 150 ml. of 2*M* aqueous ammonia, and finally with two 100-ml. portions of water. The ethyl acetate solution was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The solid residue was dissolved in 200 ml. of acetone, then water (approximately 50 ml.) was added until the solution became slightly turbid. The solution was cooled to 0° overnight, then filtered to yield 5.95 g. (30%) of pale yellow crystals of VII, m.p. 196–200°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 198–200°. The analytical data are recorded in Table I.

Procedure D. To 40 ml. of concentrated ammonium hydroxide was added 2.0 g. (9.5 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. An oily layer separated which slowly crystallized on standing. The reaction was heated on a steam bath for 0.5 hr., then concentrated to dryness *in vacuo* and the residue was taken up in 20 ml. of water. The aqueous layer was extracted with two 10-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, then evaporated to dryness.

(2) These tests were performed at Stanford Research Institute by Dr. Joseph Greenberg and staff under a contract with the Cancer Chemotherapy National Service Center.

(3) Melting points were taken on a Fisher-Johns block and are uncorrected.

in vacuo to yield 0.91 g. (57%) of an oil. Crystallization from absolute ethanol gave 0.80 g. (50%) of IX as white crystals, m.p. 30–35°. Recrystallization from absolute ethanol raised the melting point to 38–40°. The analytical data are recorded in Table I.

Procedure E. A solution of 7.3 g. (0.078 mole) of phenol and 6.2 g. (0.078 mole) of pyridine in 20 ml. of anhydrous ether was added dropwise with stirring to a solution of 13.2 g. (0.078 mole) of thiophosphoryl chloride in 20 ml. of anhydrous ether over a period of about 10 min. The reaction mixture was heated at reflux for 1 hr., then cooled to 0° and the precipitated pyridine hydrochloride was removed by filtration. The filtrate was concentrated to dryness *in vacuo* to yield 15.6 g. (88%) of crude *o*-phenylphosphorothioic dichloride as an oil.

To a cold (5–10°) solution of 15.6 g. of this dichloride in 10 ml. of dry benzene was added 28.1 g. (0.30 mole) of aniline in 30 ml. of benzene dropwise with stirring. The reaction mixture was stirred for 2 hr. in an ice bath, then filtered to remove aniline hydrochloride. The filtrate was concentrated to dryness *in vacuo* to yield a solid, which was recrystallized from absolute ethanol to give 17.4 g. (74%) of XIV as white crystals, m.p. 118–120°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 122–123°. The analytical data are recorded in Table I.

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(4) E. J. Kohn, U. E. Hanninen, and R. B. Fox, Naval Research Laboratory Rept. C-3180, 1947.

(5) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23**, 1889 (1958).

(6) A. Michaelis, *Ann.*, **293**, 215 (1896).

Selective Oxidation of Alkyl Groups

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Previous workers² have shown that the oxidation of *p*-dialkylbenzenes with nitric acid will yield alkylbenzoic acids, but no generalization has been expressed concerning the relative ease of oxidation of the alkyl groups. Cullis³ reported the relative rates of oxidation of some monoalkylbenzenes by permanganate. However, other than with *t*-butyl groups, the literature reveals that permanganate oxidizes dialkylbenzenes to benzene dicarboxylic acids. It would be useful sometimes in organic synthesis to be able to oxidize selectively only one alkyl group of dialkylbenzenes. For this reason,

(1) Taken from the M.S. Thesis of Andrew I. Wims, Howard University, 1959. Present position: Teaching Assistant, Pennsylvania State University.

(2) Cf. W. F. Tuley and C. S. Marvel, *Org. Syntheses, Coll. Vol. III*, Wiley and Sons, N. Y., 1955, p. 822; G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12**, 1102 (1952).

(3) C. F. Cullis and J. W. Ladbury, *J. Chem. Soc.*, 555 4186 (1955).

and to seek some principle for predicting the relative ease of oxidizing alkyl groups, a study was made of the selective oxidation of dialkylbenzenes with nitric acid. The identity and purity of the products were verified by mixed melting points and infrared spectra.

EXPERIMENTAL

Preparation of compounds. Those dialkylbenzenes not readily available commercially were prepared by the Wurtz-Fittig reaction.⁴ Of the required substituted benzoic acids, only *p*-ethylbenzoic acid had to be synthesized, which was prepared by carbonating *p*-ethylphenylmagnesium bromide.⁵

The melting or boiling points of the compounds used in this study are listed in Table I. All liquids were distilled at reduced pressures and a constant boiling fraction taken. The boiling point of a small sample was then determined at atmospheric pressure. All solids were recrystallized from ethanol to constant melting points.

Oxidations with nitric acid. A typical oxidation with nitric acid can be described for *p*-cymene. A mixture of 15 g. of *p*-cymene, 70 ml. of water, and 20 ml. of concentrated nitric acid was placed in a flask. The mixture was allowed to reflux gently for 8 hr. After cooling, the solid was collected and dissolved in 60 ml. of 1*N* sodium hydroxide. The alkaline solution was distilled over zinc dust until the distillate ran clear, in order to reduce any nitrated products. The solution was then acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol to a constant melting point of 180°. The literature value for *p*-toluic acid is 181°. A mixed melting point with an authentic sample of *p*-toluic acid was 180–180.5°. Its infrared spectrum in spectro grade dimethylformamide had the characteristic band of *p*-toluic acid at 13.14 μ , while the characteristic band of cumic acid at 12.88 μ was absent.

Other dialkylbenzenes were oxidized similarly. Little attention was given to per cent yields, although the yields were sufficiently large to make the reactions suitable for a preparation. In all cases, only one of the two potential acids was recovered, and it was identified by mixed melting point with an authentic sample and infrared spectra.

Permanganate oxidations. A few attempts were made to use potassium permanganate for oxidizing one alkyl group of a given dialkylbenzene, but except when a *t*-butyl group was one of the alkyl groups, only the respective dicarboxylic acid was obtained. For example, *p*-*t*-butyltoluene yielded *p*-*t*-butylbenzoic acid, whereas *p*-cymene gave terephthalic acid. Experiments were made using a 10:1 molar ratio of hydrocarbon to permanganate at temperatures of 60–70°.

Infrared spectra. Spectra of the substituted benzoic acids were measured in spectro grade *N,N*-dimethylformamide in a Perkin Elmer spectrophotometer 12C using a rock salt optical system. Characteristic bands for the acids were found as follows: *p*-Toluic acid 13.14 μ ; *p*-ethylbenzoic acid 13.04 μ ; *p*-cumic acid 12.88 μ ; *p*-*t*-butylbenzoic acid 12.80 μ .

DISCUSSION

Nitric acid oxidation of *p*-methyl-, *p*-ethyl-, and *p*-isopropyl-*t*-butylbenzenes always gave *p*-*t*-butylbenzoic acid as the only isolated product. This inertness of the *t*-butyl group to oxidation has been observed previously. For example, Ligge⁶ attempted

(4) Cf. E. Wertheim, *A Laboratory Guide for Organic Chemistry*, 3rd ed., McGraw-Hill, N. Y., 1948, p. 128.

(5) Cf. H. Gilman, N. B. St. John, and F. Schulze, *Org. Syntheses*, Coll. Vol. II, Wiley and Sons, N. Y., 1943, p. 425.

(6) D. I. Ligge, *J. Am. Chem. Soc.*, **69**, 2088 (1947).

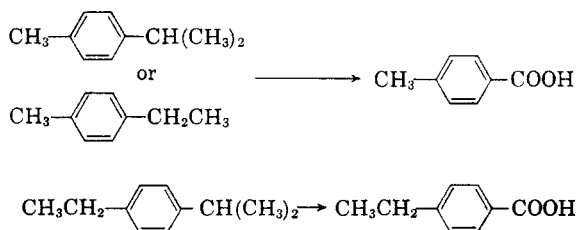
TABLE I
PHYSICAL PROPERTIES OF COMPOUNDS USED IN THIS STUDY

Compound	Observed	Literature
		B.P.
<i>p</i> -Ethylcumene	194–194.5	194 ^a
<i>p</i> - <i>t</i> -Butylethylbenzene	206–206.5	205.4 ^b
<i>p</i> - <i>t</i> -Butylcumene	222–222.5	220 ^c
<i>p</i> - <i>n</i> -Propylethylbenzene	204	202–206 ^d
<i>p</i> -Isobutylethylbenzene	211	210 ^e
<i>p</i> -Ethyltoluene ^f	162.5	161–162 ^g
<i>p</i> -Cymene ^h	176	177 ⁱ
<i>p</i> - <i>t</i> -Butyltoluene ^h	191.5	192–193 ^j
<i>p</i> -Bromoethylbenzene ^f	187–188	188–189 ^k
Isopropyl bromide ^h	60	59.4 ^l
<i>t</i> -Butylbromide ^h	74	73.3 ^m
<i>p</i> -Bromocumene ^f	218	216 ⁿ
<i>n</i> -Propylbromide ^h	70	71 ^l
Isobutyl bromide ^h	92	91 ^p
<i>o</i> -Ethyltoluene ^f	164–165	164.8–165 ^q
		M.P.
<i>p</i> -Toluic acid ^h	180.5	181 ^r
Cumic acid ^h	118–119	117–118 ^s
<i>p</i> - <i>t</i> -Butylbenzoic acid ^h	165.5	164 ^t
<i>p</i> -Ethylbenzoic acid	111–112	110–111 ^t
<i>o</i> -Toluic acid ^h	104–105	102–103 ^u
		n_D
<i>p</i> -Methylbenzyl methyl ether	1.4991	1.4990 ^v

^a D. Todd, *J. Am. Chem. Soc.*, **71**, 1356 (1949). ^b G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12**, 1102 (1952). ^c V. N. Ipatev, N. A. Orlov, and A. D. Petrov, *Chem. Zentr.*, **1**, 2081 (1930). ^d Ng. Ph. Bun-Hou, Ng. Hoan, and Ng. D. Xuong, *Rec. trav. chim.*, **71**, 285 (1952). ^e O. Wallach, *Ann.*, **414**, 210 (1917). ^f Purchased from Aldrich Chemical Co. ^g F. Richter and W. Wolff, *Ber.*, **63**, 1723 (1930). ^h Purchased from Eastman Kodak Co. ⁱ K. T. Serijan, H. F. Hipsher, and L. C. Gibbons, *J. Am. Chem. Soc.*, **71**, 873 (1949). ^j P. S. Varma, *J. Indian Chem. Soc.*, **14**, 157 (1937). ^k E. L. Skaw and R. MacCulloch, *J. Am. Chem. Soc.*, **57**, 2439 (1935). ^l R. S. Schwartz, B. Post, and I. Fankuchen, *J. Am. Chem. Soc.*, **73**, 4490 (1951). ^m J. W. Copenhauer, M. F. Roy, and C. F. Marvel, *J. Am. Chem. Soc.*, **57**, 1311 (1935). ⁿ A. L. Soloman and H. C. Thomas, *J. Am. Chem. Soc.*, **72**, 2028 (1950). ^p K. Auwers, *Ann.*, **419**, 109 (1919). ^q O. Herb, *Ann.*, **258**, 10 (1890). ^r L. Bert, *Bull. soc. chim.*, **37**, 1400 (1925). ^s *Org. Synthesis*, Coll. Vol. III, 822 (1955). ^t M. J. Schlatter and R. D. Clark, *J. Am. Chem. Soc.*, **75**, 361 (1953). ^u R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, p. 250 (1957). ^v C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

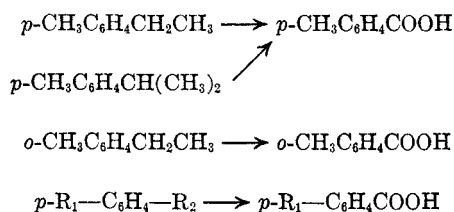
to oxidize *p*-di-*t*-butylbenzene with chromic oxide, aqueous potassium permanganate, and several concentrations of nitric acid. Only 50% nitric acid at 180° brought about a significant oxidation of the *p*-di-*t*-butylbenzene.

Initial experiments on the oxidation of diethylbenzenes with 15% nitric acid gave the following results:



It can be seen that, exclusive of the *t*-butyl groups, the preferential oxidation of these respective alkyl groups decreases in the order, isopropyl, ethyl, methyl. This is the order of increasing electronegativity of the groups and also of the increasing number of *alpha* hydrogens. Hence, to explore further the selectivity shown, groups were chosen which have the same number of *alpha* hydrogens but a third group of varying electronegativity. For example, *p*-isobutylethylbenzene, has a methyl group and an isopropyl group, attached to the *alpha* carbons. In this case, oxidation produced *p*-ethylbenzoic acid. Thus, it appears that the relative ease of oxidation of the alkyl groups, provided there is at least one α -hydrogen atom, is determined by the relative electronegativity of the alkyl groups attached to the *alpha* carbon atoms. To test this idea, *p*-*n*-propylethylbenzene, was oxidized. *p*-Ethylbenzoic acid was obtained, again supporting the idea expressed above. In all cases, mixed melting points and infrared spectra of the oxidation products showed no sign of other *p*-alkylbenzoic acids being present.

The nitric acid oxidations in this study can be summarized as follows:



R₁ = ethyl; R₂ = *n*-propyl, isopropyl, and isobutyl

R₁ = *t*-butyl; R₂ = methyl, ethyl, isopropyl

This generalization about the relative ease of oxidation of carbon-attached side chains only applies to hydrocarbon groups. Once a carbon-oxygen, carbon-nitrogen, or carbon halogen bond is formed, the carbon is easily oxidized. For example, the CH₂OH, CH=O, and CH₂Cl groups are probably much more easily oxidized than alkyl groups in spite of the fact that there are highly electronegative atoms attached to the α -carbon. To test this idea, *p*-methylbenzyl methyl ether was prepared and oxidized with 15% nitric acid. As expected, the product was *p*-toluic acid.

In summary, it can be generalized that 15% nitric acid will oxidize dialkylbenzenes to alkylbenzoic acids, and with groups containing at least one α -hydrogen atom, the relative ease of oxidation increases with decreasing electronegativity of the groups attached to the α -carbon.

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Oxidation of a Secondary Alkyl Tosylate by Dimethyl Sulfoxide

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In the course of a study of the thermal decomposition of tosylates of secondary alcohols as a route to olefins, we had occasion in one instance to examine the modification reported by Nace.¹ In his procedure dimethyl sulfoxide is used as a medium and sodium hydrogen carbonate is optionally used to protect the olefin formed from the action of the liberated sulfonic acid.

When the tosylate (I) of 1,3-diphenoxy-2-propanol (II) was heated with dimethyl sulfoxide and sodium bicarbonate for six hours at a maximum temperature of 103°, the only product recovered was unchanged starting material. When the reaction temperature was allowed to rise to 150°, 10% of the input of I was recovered as its saponification product II; the remainder was converted to a yellow oil which, after distillation followed by crystallization of the distillate, was found to be 1,3-diphenoxy-2-propanone (III). III showed carbonyl absorption in the infrared; its melting point and that of its 2,4-dinitrophenylhydrazone agreed with the values reported in the literature.²

While the oxidation by dimethyl sulfoxide of phenacyl³ and benzyl halides⁴ and of tosylates of benzyl alcohols⁵ to aldehydes has been reported,⁶ the oxidation of a secondary alkyl tosylate to the corresponding ketone seems not to have been noted before.

Attempts to oxidize II directly by dimethyl sulfoxide were unsuccessful.

EXPERIMENTAL⁷

Dimethyl sulfoxide was obtained from the Stepan Chemical Co. and used without purification.

1,3-Diphenoxy-2-propyl *p*-toluenesulfonate (I) was prepared from the alcohol and *p*-toluenesulfonyl chloride in pyridine according to the usual procedure. The crude yield was 95%, m.p. 117–119°. After recrystallization from 2-propanol the product melted at 121°.

Anal. Calcd. for C₂₂H₂₂O₃S: C, 66.32; H, 5.57. Found: C, 66.08; H, 6.08.

(1) H. R. Nace, *Chemistry & Industry (London)*, 1629 (1958).

(2) J. Munch-Petersen, *Acta Chem. Scand.*, 5, 519 (1951).

(3) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, 79, 6562 (1957).

(4) H. R. Nace, U. S. Patent 2,888,488, May 26, 1959.

(5) N. Kornblum, *et al.*, *J. Am. Chem. Soc.*, 81, 4113 (1959).

(6) I. M. Hunsberger and J. M. Tien, *Chemistry & Industry (London)*, 88 (1959) also report the oxidation of ethyl bromoacetate to ethyl glyoxylate and propose a mechanism for the reaction.

(7) Melting points were taken on a Fisher-Johns block and are uncorrected.