acetic acid at *p*H 3–4 for approximately 1 day, and the solvent was evaporated in a stream of nitrogen. The solid residue was redissolved in aqueous solution and stirred at *p*H 6.4 for 3 hr. Evaporation of the water left a solid residue that gave a weakly positive Bratton-Marshall test. The solid was, therefore, redissolved in water, treated with activated carbon, and recrystallized from water. The colorless needles that separated gave ultraviolet and infrared spectra identical with those of 2,8-diazahypozanthine dihydrate prepared from 5-amino-*v*-triazole-4-carboxamide without isolation of the diazo derivative.

*Spectroscopic determinations.* Stock solutions of 5-diazoimidazole-4-carboxamide for the ultraviolet studies were prepared by adding the solvent in the dark to a specimen weighed to the nearest microgram. Each stock solution was stored in the dark during the determination of stability at a given *p*H. Initial concentrations of the diazoimidazole (II) were near 10 mg./l.

All ultraviolet spectra were recorded with a Beckman Model DK-2 spectrophotometer or with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer.

*Acknowledgment.* The authors are indebted to Mr. C. A. O'Dell for technical assistance; to Dr. W. J. Barrett, Dr. W. C. Coburn, Jr., and associates of the Analytical Section for spectral determinations; and to Mr. W. F. Fitzgibbon and associates of the Organic Preparations Section for large quantities of starting materials. Microanalyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

# Compounds with Potential Activity Against Lethal Radiations. VIII. Synthesis of Phenolic Ketones by Means of Boron Trifluoride

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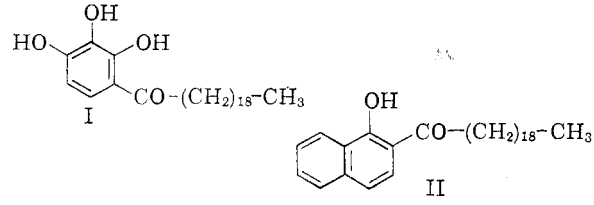
*Received September 1, 1960*

Boron trifluoride in the presence of hydrogen fluoride proved an excellent catalyst for the synthesis of phenolic ketones, prepared for evaluation of their protective action against lethal radiations. The naphthols and pyrogallol gave monoketones, while hydroquinone was disubstituted. 4-Acylcatechols were best prepared by acylation of guaiacol and subsequent demethylation.

In earlier papers,[1] we described how a number of phenolic ketones, especially those bearing a long-chain acyl group, possess significant protective properties against whole-body x-ray irradiation in mice. Continuing this research, we have now synthesized phenolic ketones derived from di- and triphenols and from $\alpha$- and $\beta$-naphthol.

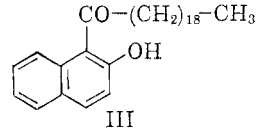
The most convenient method for these syntheses was the condensation of carboxylic acids with the phenols in presence of boron trifluoride mixed with some hydrogen fluoride (*i.e.*, the gas produced by the reaction of oleum on potassium fluorborate), the hydrogen fluoride enhancing the condensing qualities of boron trifluoride. In these conditions, a temperature of 70° was sufficient to complete the condensation. The procedure is particularly useful for preparing ketones with long chains, as the Nencki, Friedel-Crafts, or Fries reactions customarily used may lead to splitting or rearrangement of such chains. Thus, with pyrogallol, arachidic acid gave 4-arachidoylpyrogallol (I), and with $\alpha$- and $\beta$-naphthol, 2-arachidoyl-1-naphthol (II) and 1-arachidoyl-2-naphthol (III), all in excellent yields and without by-products. Similarly, 5-pentadecylresorcinol was easily converted with the appropriate acids, into 5-pentadecyl-4-resacetophenone (IV), 5-pentadecyl-4-respropiophenone



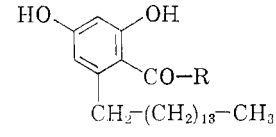

I




II




III




IV. R = $CH_3$
V. R = $C_2H_5$
VI. R = $CH_2$—$C_6H_5$

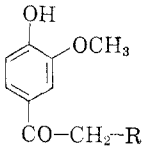
(V), and 5-pentadecyl-4-phenacetylresorcinol (VI), where in similar conditions the Nencki reaction gave but poor results.[2]

The acylation of catechol was far less easy to achieve (this lack of reactivity had already been noted in Nencki reactions[3]), and 4-acylcatechols were more readily accessible by boron trifluoride-catalyzed acylation of guaiacol and demethylation of the resulting 2-methoxy-4-acylphenols by means

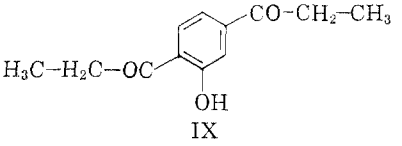
(1) A. Lacassagne, J. F. Duplan, and N. P. Buu-Hoï, *J. Natl. Cancer Inst.*, **15**, 915 (1955).

(2) *Cf.* R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 999 (1946).

(3) N. P. Buu-Hoï, *J. Org. Chem.*, 19, 1770 (1954).



VII. R = $CH_3$
VIII. R = $C_2H_5$



IX

of pyridine hydrochloride.[4] 4-Propionylcatechol and 4-butyrylcatechol were thus obtained in good yields *via* 2-methoxy-4-propionylphenol (VII) and 2-methoxy-4-butyrylphenol (VIII) respectively. This method also provides a convenient route to the 3-ethers of acylcatechols which otherwise are not easily accessible.[5]

Whereas in all the above instances only monoacylation was observed, in the case of hydroquinone propionylation gave 2,5-dipropionylhydroquinone (IX).

In biological tests of these ketones for their protective action against the lethal effects of whole-body x-ray irradiation in mice, 4-arachidoylpyrogallol, 2-arachidoyl-1-naphthol, and 1-arachidoyl-2-naphthol showed significant activity.

## EXPERIMENTAL

*4-Arachidoylpyrogallol* (I). The catalytic mixture of boron trifluoride and hydrogen chloride was produced by the reaction of oleum on potassium fluoroborate in a proportion of 8 l. of oleum to 7 kg. fluorborate; a mixture of 48 g. of arachidic acid, 30 g. of pyrogallol, and 30 ml. of anhydrous xylene was saturated, during 20 min., with the gas thus generated, and during the last 5 min. the flask was heated on a water bath at 70° to complete the condensation. After cooling, the product was treated with water and xylene was added; the xylene layer was washed first with aqueous sodium carbonate, then with water, and dried over sodium sulfate, and the solvent evaporated *in vacuo*. The solid remaining was recrystallized first from cyclohexane, then from acetone, giving fine colorless needles, m.p. 99°. Yield: 90%. The product was readily soluble in lipids and showed pronounced antioxidant activity (substrate, linseed oil). Its solution in ethanol gave a bright yellow coloration with sodium hydroxide.

*Anal.* Calcd. for $C_{26}H_{44}O_4$: C, 74.3; H, 10.6. Found: C, 74.3; H, 10.7.

*2-Arachidoyl-1-naphthol* (II). A mixture of 10 g. of α-naphthol, 15 g. of arachidic acid, and 15 ml. of anhydrous xylene was treated with boron trifluoride–hydrogen fluoride and the product worked up as above. After two recrystallizations from cyclohexane, the ketone was obtained in 70% yield as shiny pale yellow needles, m.p. 93°, very soluble in lipids and giving a yellow coloration in a solution of sodium hydroxide in ethanol.

*Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 81.3; H, 10.6. Found: C, 81.6; H, 10.4.

*1-Arachidoyl-2-naphthol* (*III*). Prepared in 80% yield from 10 g. of β-naphthol and 15 g. of arachidic acid in 15 ml. of xylene, this ketone crystallized from cyclohexane in shiny yellowish needles, m.p. 76°, with properties similar to its isomer.

*Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 81.3; H, 10.6. Found: C, 81.5; H, 10.5.

*5-Pentadecyl-4-resacetophenone* (IV). The 5-pentadecylresorcinol[6] used in this work (m.p. 95°) was prepared by catalytic hydrogenation of cardol. A mixture of 20 g. of this phenol, 30 ml. of xylene, and 30 ml. of acetic acid was saturated with the catalyst for 1 hr. at 50–60°, and the reaction product left to stand overnight. After decomposition with ice and neutralization with sodium carbonate, the solid obtained was recrystallized twice from ethanol, giving fine colorless needles, m.p. 63°. Yield: 75%.

*Anal.* Calcd. for $C_{23}H_{38}O_3$: C, 76.2; H, 10.6. Found: C, 76.0; H, 10.8.

*5-Pentadecyl-4-respropiophenone* (V). Prepared as above, and in similar yield, from propionic acid, this ketone crystallized from ethanol in fine colorless prisms, m.p. 76°.

*Anal.* Calcd. for $C_{24}H_{40}O_3$: C, 76.6; H, 10.7. Found: C, 76.4; H, 10.5.

*5-Pentadecyl-4-phenacetylresorcinol* (VI). Prepared with a 15% excess of phenylacetic acid, the product of the condensation was purified by treatment with a hot aqueous solution of sodium carbonate. Crystallization from ethanol gave yellowish needles, m.p. 105°. In this as in the two previous cases, the Nencki reaction (heating of 5-pentadecylresorcinol with the corresponding acid in presence of anhydrous zinc chloride) furnished several unidentified by-products.

*Anal.* Calcd. for $C_{29}H_{42}O_3$: C, 79.4; H, 9.6. Found: C, 79.1; H, 9.8.

*Preparation of 4-propionylcatechol.* A mixture of 20 g. of freshly redistilled guaiacol, 15 g. of glacial acetic acid, and 30 ml. of xylene was saturated with the catalyst at 60–70°, and the product kept overnight at room temperature. After the usual treatment and vacuum-distillation of the reaction product, *2-methoxy-4-propionylphenone* (VII) was obtained in almost theoretical yield as a pale yellow oil, b.p. 182°/12 mm., which readily solidified; recrystallization from hexane gave shiny colorless leaflets, m.p. 54°.

*Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7. Found: C, 66.5; H, 6.7.

A mixture of 5 g. of the foregoing ketone and 10 g. of redistilled pyridine hydrochloride was gently refluxed for 10 min.; after cooling and addition of dilute hydrochloric acid, the precipitate formed was washed with water, and recrystallized from aqueous ethanol, giving *4-propionylcatechol* in 80% yield, as shiny colorless prisms, m.p. 142.°

*Preparation of 4-butyrylcatechol. 2-Methoxy-4-butyrylphenol* (VIII), prepared from guaiacol and butyric acid as for the lower homolog, was purified by vacuum distillation; the pale yellow oil obtained, b.p. 202°/12 mm., readily solidified in hexane, to give fine colorless prisms, m.p. 45°.

*Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.7; H, 7.5.

Demethylation of 5 g. of this ketone with 10 g. of pyridine hydrochloride afforded *4-butyrylcatechol*, crystallizing from aqueous ethanol in fine colorless prisms m.p. 149°.

*2,5-Dipropionylhydroquinone* (IX). The condensation of hydroquinone with propionic acid in xylene was difficult to achieve and necessitated heating on a boiling water bath. Repeated crystallization of the reaction product from aqueous methanol afforded a 7% yield of this *diketone* as large yellowish prisms. m.p. 151–152°. This compound was sublimable and gave a yellow solution in sulfuric acid.

*Anal.* Calcd. for $C_{12}H_{14}O_4$:C,64.8; H, 6.3; O, 28.8. Found: C, 64.5; H, 6.0; O, 29.0.

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(4) *Cf.* N. P. Buu-Hoï, *Rec. trav. chim.*, **68**, 759 (1949).
(5) T. Reichstein, *Helv. chim. Acta*, **10**, 394 (1927).
(6) For further derivatives of this diphenol, see R. N. Chakravarti and N. P. Buu-Hoï, *Bull. Soc. chim. France*, 1498 (1959).