[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

COMPOUNDS WITH POTENTIAL ACTIVITY AGAINST LETHAL RADIATIONS. II.[1] POLYPHENOLIC KETONES AND INDOLES DERIVED FROM HIGHER FATTY ACIDS

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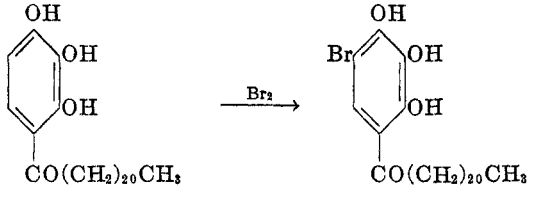
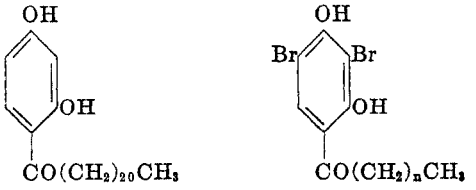
A number of lipid-soluble 4-acylpyrogallols prepared as potential drugs against polycythemia and erythremia (1) have recently been shown to display considerable protective activity against lethal radiations in mice (2). This protection, which was far more lasting than with compounds hitherto used such as cysteine (3) and cysteinamine (4), could be related to the reducing properties of 4-acylpyrogallols and their ability to antagonize the formation of peroxides and free radicals, especially in lipids.

Lipid-soluble derivatives of pyrogallol and other polyphenols having a high molecular weight have now been prepared for biological testing, with a view to obtaining substances whose metabolism and protective effects against lethal radiations would be even more protracted.



I II

Behenic acid was particularly considered as an intermediate for the present syntheses in view of its high molecular weight and its easy preparation by hydrogenation of erucic acid (5). Nencki condensation of behenic acid with pyrogallol in the presence of zinc chloride readily afforded 4-behenylpyrogallol (I); bromination of this ketone in acetic acid medium gave 6-bromo-4-behenylpyrogallol (II). On the other hand, 4-behenylresorcinol (III), prepared in the usual way from behenic acid and resorcinol, underwent disubstitution with



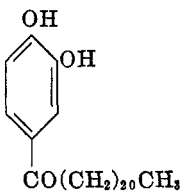
III

IV n = 20
V n = 14
VI n = 26

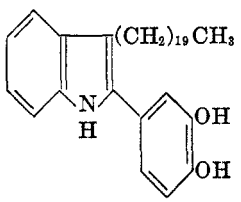
[1] Part I: Buu-Hoï, *J. Org. Chem.*, **18**, 1723 (1953).

bromine to give 2,6-dibromo-4-behenylresorcinol (IV). This easy dihalogenation is a general characteristic of 4-acylresorcinols, for resacetophenone (6) and respropiophenone (7) behave similarly, and 4-palmityl- and 4-stearyl-resorcinol have now been found to give readily 2,6-dibromo-4-palmityl- (V) and 2,6-dibromo-4-stearyl-resorcinol (VI).

The Nencki reaction was less satisfactory in the case of catechol, and 4-behenylcatechol (VII) was best prepared by using boron trifluoride as a condensation catalyst; this reagent has recently been used for the preparation of some ketones derived from quinol and resorcinol (8).

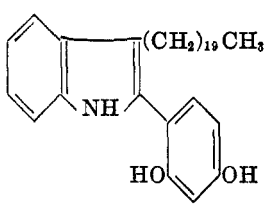


VII

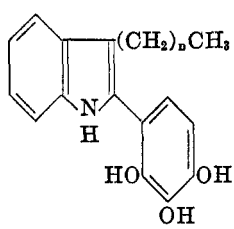


VIII

The known ability of certain 2,3-disubstituted indoles to undergo autoxidation with formation of peroxides (9) prompted the preparation of some high molecular polyphenolic indoles for testing for anti-radiation activity. 2-(3′,4′-Dihydroxyphenyl)- (VIII), 2-(2′,4′-dihydroxyphenyl)- (IX), and 2-(2′,3′,4′-trihydroxyphenyl)-3-*n*-docosylindole (X) were prepared by cyclization of the phenylhydrazones of ketones (VII), (III), and (I) respectively, by means of



IX



X n = 19
XI n = 13

hydrogen chloride in acetic acid; 2-(2′,3′,4′-trihydroxyphenyl)-3-*n*-tetradecylindole (XI) was similarly obtained from 4-palmitylpyrogallol (10).

The derivatives from pyrogallol and catechol were lipid-soluble compounds whose solutions underwent rapid oxidation on exposure to the air, especially in alkaline medium. In tests performed in this Institute by Professor Lacassagne and Dr. Duplan, 4-behenylpyrogallol showed notably protracted protective activity in mice against lethal X-rays.

EXPERIMENTAL

4-Behenylpyrogallol (I). A mixture of 50 g. of behenic acid (prepared by catalytic hydrogenation of pure erucic acid), 30 g. of pyrogallol, and 25 g. of finely ground anhydrous zinc chloride was heated at 150–160° for four hours; after addition of hot water, the reaction prod-

uct was dissolved in benzene, and purified by high vacuum distillation (the portion boiling above 250°/0.2 mm. was collected) and recrystallization from cyclohexane. The ketone was obtained in 70% yield as colorless microscopic needles, m.p. 100–101°, soluble in alcoholic potassium hydroxide solution with a bright yellow color.

Anal. Calc'd for $C_{28}H_{48}O_4$: C, 75.0; H, 10.7.
Found: C, 74.9; H, 10.9.

6-Bromo-4-behenylpyrogallol (II). A solution of 4.5 g. of 4-behenylpyrogallol in 1000 ml. of acetic acid was treated at room temperature with a solution of 1.6 g. of bromine in acetic acid; the precipitate obtained on dilution with water was recrystallized from acetic acid, giving silky, colorless needles, m.p. 99°; yield, 4.5 g.

Anal. Calc'd for $C_{28}H_{47}BrO_4$: C, 63.8; H, 8.9; Br, 15.2.
Found: C, 63.6; H, 8.8; Br, 15.5.

4-Behenylresorcinol (III) was prepared from 50 g. of behenic acid, 30 g. of resorcinol, and 25 g. of zinc chloride as for the preceding ketone. This ketone crystallized from cyclohexane as colorless needles, m.p. 103°, which gave with benzene and analogous solvents sorption phenomena, with formation of gelatinous masses. The coloration in ethanolic potassium hydroxide was yellow.

Anal. Calc'd for $C_{28}H_{48}O_3$: C, 77.8; H, 11.1.
Found: C, 77.5; H, 11.0.

2,6-Dibromo-4-behenylresorcinol (IV). A solution of 2 g. of 4-behenylresorcinol in 350 ml. of acetic acid was treated at 37–38° with a solution of 1.6 g. of bromine in acetic acid; the precipitate obtained after a few minutes was collected and recrystallized from acetic acid. Yield, 2.5 g. of silky, colorless needles, m.p. 110°.

Anal. Calc'd for $C_{28}H_{46}Br_2O_2$: C, 58.5; H, 8.0; Br, 27.9.
Found: C, 58.4; H, 7.8; Br, 27.5.

2,6-Dibromo-4-palmitylresorcinol (V), similarly prepared from 3.6 g. of 4-palmitylresorcinol (11) and 3.2 g. of bromine, crystallized from acetic acid as colorless leaflets, m.p. 104°.

Anal. Calc'd for $C_{22}H_{34}Br_2O_3$: C, 52.2; H, 6.7; Br, 31.6.
Found: C, 52.0; H, 6.8; Br, 31.4.

2,6-Dibromo-4-stearylresorcinol (VI), prepared from 3.8 g. of 4-stearylresorcinol (this ketone crystallized from cyclohexane as shiny colorless needles, m.p. 99°) and 3.2 g. of bromine, crystallized from acetic acid as colorless leaflets, m.p. 105°.

Anal. Calc'd for $C_{24}H_{38}Br_2O_3$: C, 53.9; H, 7.1; Br, 30.0.
Found: C, 54.0; H, 7.3; Br, 29.6.

4-Behenylcatechol (VII). Catechol was found to be far less reactive than pyrogallol and resorcinol in the Nencki reaction, and the yield of 4-behenylcatechol obtained by this method was only about 10%. This ketone was better prepared by saturating with boron trifluoride a mixture of 50 g. of behenic acid and 30 g. of catechol kept at about 80°; the reaction product was extracted with hot water, taken up in benzene, and recrystallized from cyclohexane. Yield, 75% of fine, colorless prisms, m.p. 103°. The solutions rapidly turned violet on exposure to the air.

Anal. Calc'd for $C_{28}H_{48}O_3$: C, 77.8; H, 11.1.
Found: C, 77.7; H, 11.3.

2-(3',4'-Dihydroxyphenyl)-3-n-docosylindole (VIII). A mixture of 2 g. of 4-behenylcatechol and 2 g. of phenylhydrazine was heated for a few minutes at 120° with removal of water; 200 ml. of acetic acid saturated with hydrogen chloride was added, and the mixture was refluxed for ten minutes. The precipitate obtained on addition of water was collected, washed with water, dried, and crystallized from cyclohexane. Yield, 1.7 g. of fine colorless needles, m.p. 98–99°, giving a brown color in a benzene solution of picric acid.

Anal. Calc'd for $C_{34}H_{51}NO_2$: C, 80.8; H, 10.1; N, 2.8.
Found: C, 80.5; H, 10.1; N, 2.5.

2-(2',4'-Dihydroxyphenyl)-3-n-docosylindole (IX) was prepared from 2 g. of phenylhydrazine and 2 g. of 4-behenylresorcinol as above, and with the same yield; it crystallized from cyclohexane as fine, colorless prisms, m.p. 109°.

Anal. Calc'd for $C_{34}H_{51}NO_2$: C, 80.8; H, 10.1; N, 2.8.
Found: C, 80.6; H, 10.3; N, 2.6.

2-(2',3',4'-Trihydroxyphenyl)-3-n-docosylindole (X) was prepared as in the case of VIII. This indole was highly soluble in benzene, and crystallized from ligroin as colorless prisms, m.p. 94°. The solutions of this substance in ethanol or benzene rapidly oxidized on exposure to the air, with the formation of dark resins.

Anal. Calc'd for $C_{34}H_{51}NO_3$: C, 78.3; H, 9.8; N, 2.7.
Found: C, 78.2; H, 9.7; N, 2.5.

2-(2',3',4'-Trihydroxyphenyl)-3-n-tetradecylindole (XI) was prepared as for VIII. This indole crystallized from ligroin as colorless leaflets, m.p. 90°, giving a brown picrate with picric acid in benzene medium. The solutions of this compound are also highly oxidizable.

Anal. Calc'd for $C_{28}H_{39}NO_3$: C, 76.9; H, 8.9; N, 3.2.
Found: C, 76.9; H, 9.2; N, 3.3.

SUMMARY

1. A series of polyphenolic ketones derived from behenic acid has been prepared for biological testing as compounds with potential protecting effects against lethal radiations.

2. From these ketones, polyphenolic 2,3-disubstituted indoles have been prepared for the same purpose.

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