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

COMPOUNDS WITH POSSIBLE EFFECT ON POLYCYTHEMIA AND ERYTHREMIA. I. DERIVATIVES OF PYROGALLOL

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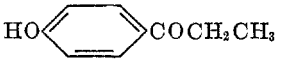
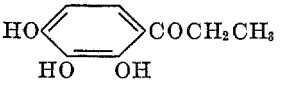
Polycythemia and erythremia are pathological conditions of the blood associated with an undue increase in the number of circulating red corpuscles Probably owing to the rarity of these diseases, no systematic efforts have yet been devoted to the chemotherapeutic aspect of the problem. The methods of treatment hitherto employed [use of inorganic arsenic derivatives, benzene, phenylhydrazine hydrochloride (1), radioactive phosphorus (2), x-rays, and surgical removal of bone-marrow tissue and of the spleen] are not without danger.

The present work is part of a research scheme on the chemotherapy of proliferative blood diseases including polycythemia and erythremia. In view of the outstanding results obtained by Haynal, Graf, and Matsch (3) in the treatment of these conditions with 4-hydroxypropiophenone (I), one line of research was the study of polyphenolic compounds which might theoretically be formed in the metabolism of this ketone, in the same way as tyrosine is converted into 3,4-dihydroxyphenylalanine *in vivo*.



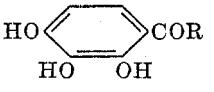
I



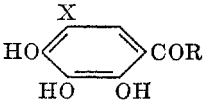
II

One such compound is 4-propionylpyrogallol (II), and this, along with the known ability of pyrogallol itself to reduce the oxygen consumption of tissues (4), prompted an investigation of this ketone, its analogs, and its derivatives.

4-Acylpyrogallols derived from aliphatic acids are generally prepared by the Nencki method, involving the heating of pyrogallol with the appropriate acid and zinc chloride; several ketones were prepared in that way by Hart and Woodruff (5), and more recently by Haworth and Woodcock (6). This series of ketones has now been widened by the similar preparation of 4-isobutyryl- (III), 4-*n*-decanoyl- (IV), 4-*n*-tridecanoyl- (V), and 4-*n*-pentadecanoyl-pyrogallol (VI). That the two last ketones and 4-*n*-valeroylpyrogallol were obtained



III R = *i*-C_3H_7 V R = *n*-$C_{13}H_{25}$
IV R = *n*-C_9H_{19} VI R = *n*-$C_{14}H_{29}$



VII

in excellent yield was proof that there is no difference in the behavior of aliphatic acids with an odd number of carbon atoms and those with an even num-

ber. Such a difference had been considered by Hart and Woodruff as a possible explanation for the poor yield of ketones obtained from *n*-valeric acid (14%) and *n*-heptoic acid (11%). In the case of 4-propionylpyrogallol, however, the

TABLE I

2,3,4,2′,3′,4′-HEXAHYDROXYDIPHENYLMETHANES (VIII)

SUBSTITUENT	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
5,5′-Dipropionyl-[a]	$C_{19}H_{20}O_8$	238	60.6	5.3	60.2	5.5
5,5′-Dibenzoyl-	$C_{27}H_{20}O_8$	232	68.6	4.2	68.4	4.5
5,5′-Di-(*n*-butyroyl)-	$C_{21}H_{24}O_8$	181–182	62.4	5.9	62.2	5.8
5,5′-Di-(*n*-valeroyl)-	$C_{23}H_{28}O_8$	173	63.9	6.5	63.8	6.3
5,5′-Dicaproyl-	$C_{25}H_{32}O_8$	171	65.2	7.0	65.0	7.3
5,5′-Di-(*n*-decanoyl)-	$C_{33}H_{48}O_8$	147–148	69.2	8.4	68.8	8.5

[a] Prepared in 90% yield by refluxing for 10 minutes a solution of 4 g. of 4-propionylpyrogallol and 2 ml. of a 35% aqueous solution of formaldehyde in 25 ml. of ethanol; the solid obtained on dilution with water was recrystallized from aqueous methanol. All the substances were silky, colorless, sublimable needles, which strongly retained water, and were dried in a vacuum at 100°.

TABLE II

2,3,4,2′,3′,4′-HEXAHYDROXYTRIPHENYLMETHANES (IX)

SUBSTITUENT	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
5,5′-Dipropionyl-[a]	$C_{25}H_{24}O_8$	162	66.4	5.3	66.3	5.6
4″-Chloro-5,5′-dipropionyl-	$C_{25}H_{23}ClO_8$	189–190	61.7	4.7	61.4	4.9
3″,4″-Dichloro-5,5′-dipropionyl-	$C_{25}H_{22}Cl_2O_8$	209–210	57.6	4.2	57.4	4.5
4″-Chloro-5,5′-diacetyl-	$C_{23}H_{19}ClO_8$	230–231	60.2	4.1	60.0	4.4
3″,4″-Dichloro-5,5′-diacetyl-	$C_{23}H_{18}Cl_2O_8$	259–260	56.0	3.7	55.9	3.8
5,5′-Dibenzoyl-	$C_{33}H_{24}O_8$	228	72.3	4.4	72.0	4.3
4″-Chloro-5,5′-dibenzoyl-[b]	$C_{33}H_{23}ClO_8$	255	68.0	3.9	67.6	4.0
3″,4″-Dichloro-5,5′-dibenzoyl-	$C_{33}H_{22}Cl_2O_8$	249–250	64.2	3.6	64.0	3.9

[a] This compound (and the two following ones) gave on heating with two moles of phenylhydrazine a *bis*-phenylhydrazone which could be indolized by the usual treatment with an acetic acid solution of hydrogen chloride (13), to give a product which formed with picric acid the deep brown-violet coloration characteristic of 2,3-disubstituted indoles. [b] The substance decomposed slowly above 240°.

Nencki method gave poor results, and this ketone was most easily prepared by heating pyrogallol with propionyl chloride, without solvent or dehydrating agent; in this case, the influence of heat and of the hydrogen chloride dissolved in pyrogallol propionate was enough to bring about a Fries rearrangement.

Chlorination and bromination of 4-acylpyrogallols in acetic acid with the

calculated amount of halogen readily gave 6-chloro- and 6-bromo-4-acylpyrogallols of the general formula VII; the new substances are listed in Table III. The position *ortho* to a hydroxyl and *meta* to the ketonic group, occupied by the halogen in these compounds, was assumed from analogy with similar halogenations in the literature (7), and was proven in the case of 6-bromo-4-acetylpyrogallol by its direct synthesis from acetyl chloride and 4-bromopyrogallol.

TABLE III

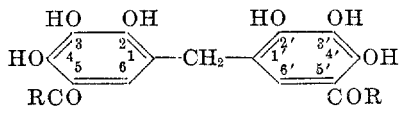
HALOGENATED 4-ACYLPYROGALLOLS

SUBSTITUENT[a]	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
6-Chloro-4-propionyl	$C_9H_9ClO_4$	126	49.9	4.1	49.5	4.3
6-Bromo-4-propionyl	$C_9H_9BrO_4$	131	41.4	3.4	41.1	3.5
6-Bromo-4-*n*-butyroyl	$C_{10}H_{11}BrO_4$	137	43.6	4.0	43.3	3.7
6-Bromo-4-isobutyroyl	$C_{10}H_{11}BrO_4$	135	43.6	4.0	43.5	4.2
6-Bromo-4-*n*-valeroyl	$C_{11}H_{13}BrO_4$	123–124	45.7	4.5	45.5	4.8
6-Chloro-4-*n*-caproyl	$C_{12}H_{15}ClO_4$	95–96	55.7	5.8	55.6	5.7
6-Bromo-4-*n*-caproyl	$C_{12}H_{15}BrO_4$	111	47.5	4.9	47.2	4.8
6-Bromo-4-*n*-decanoyl[b]	$C_{16}H_{23}BrO_4$	86–87	53.5	6.4	53.5	6.7
6-Bromo-4-*n*-pentadecanoyl	$C_{21}H_{33}BrO_4$	89–90	58.7	7.7	58.5	7.8
6-Bromo-4-palmitoyl	$C_{22}H_{35}BrO_4$	89–90	59.6	7.9	59.8	8.2
6-Chloro-4-benzoyl	$C_{13}H_9ClO_4$	147–148	58.9	3.4	59.0	3.5
6-Bromo-4-phenacetyl	$C_{14}H_{11}BrO_4$	164	52.0	3.4	51.9	3.4

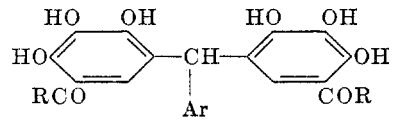
[a] All the substances were colorless needles, which darkened on exposure to air, and which gave a deep yellow coloration with aqueous alkalis; the halogen atom was firmly fixed and resisted the action of phenylhydrazine at 100°. [b] This ketone and the two following ones easily formed gelatinous precipitates on dilution of their solutions in alcohols or acetic acid with water.

The bromination of gallacetophenone had been performed by Rosenmund, Kuhnhenn, and Lesch (8), and that of 4-benzoylpyrogallol by Graebe and Eichengrün (9), but in neither case was the substituent assigned a position.

4-Propionylpyrogallol reacted readily with formaldehyde in the presence of hydrogen chloride, as does gallacetophenone (10), and gave 2,3,4,2′,3′,4′-hexahydroxy-5,5′-dipropionyldiphenylmethane (VIII; R = C_2H_5). This reac-



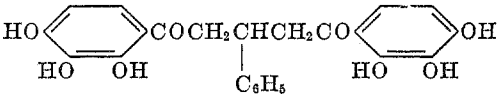
VIII



IX

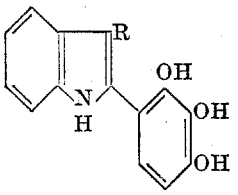
tion, suggestive of the high reactivity of the 4-position in the pyrogallol molecule, was also observed in the course of this work with several other 4-acylpyrogallols. The condensation of one molecule of benzaldehyde with two molecules of gallacetophenone had been performed by Blumstein and Kostanecki

(11), who assigned to the reaction-product the 1,5-diketone structure (X). This constitution is untenable in view of the fact that a similar acid-catalyzed condensation could be effected not only with homologs of gallacetophenone, but also with 4-benzoylpyrogallol; in the latter case, the reaction product must have been 2,3,4,2′,3′,4′-hexahydroxy-5,5′-dibenzoyltriphenylmethane (IX; R = Ar = C_6H_5). The triphenylmethane structure was more satisfactory because it made unnecessary the assumption that aliphatic and aromatic alde-

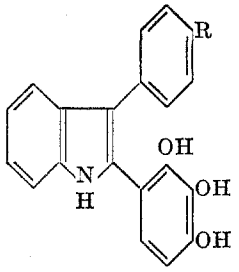


hydes would react differently from each other, and because under the experimental conditions used, benzaldehyde would not condense with non-phenolic propiophenones. A more rigid proof was furnished with the condensation products of benzaldehyde and 4-chlorobenzaldehyde with 4-propionylpyrogallol, by the indole character of the Fischer cyclization products of their *bis*-phenylhydrazones; no indolization could have occurred with the 1,5-diketone structure.

In view of the known ability of indole to induce lymphoadenosis and blood changes in mice through parenteral or intra-medullary injection (12), several indoles substituted at the 2-position by a pyrogallol residue were prepared by treating the phenylhydrazones of the appropriate 4-acylpyrogallols with hydrogen chloride in acetic acid (13). 2-(2,3,4-Trihydroxyphenyl)scatole (XI), 3-ethyl-2-(2,3,4-trihydroxyphenyl)indole (XII), and 3-*n*-butyl-2-(2,3,4-trihydroxyphenyl)indole (XIII) were thus obtained from 4-propionyl-, 4-*n*-butyryl-, and 4-caproyl-pyrogallol; 2-(2,3,4-trihydroxyphenyl)-3-phenylindole (XIV) and 2-(2,3,4-trihydroxyphenyl)-3-(4-chlorophenyl)indole (XV) were



XI R = CH_3
XII R = CH_2CH_3
XIII R = n-C_4H_9



XIV R = H
XV R = Cl

similarly obtained from 4-phenacetyl- and 4-(4-chlorophenacetyl)-pyrogallol. The two latter ketones are also of interest as potential anthelmintics, in view of the pronounced activity recently found in the parent 4-phenacetylresorcinol against oxyuriasis (14).

Both in animal experiments and in clinical trials, 4-propionylpyrogallol has shown anemia-producing activity; the 4-acylpyrogallols are also being tested for protective effects against lethal radiations, in view of the known influence of anoxemia upon radiation-resistance.

EXPERIMENTAL

Preparation of 4-propionylpyrogallol. To 25 g. of pyrogallol was added 25 g. of propionyl chloride at room temperature, in small portions so as to avoid an excessive reaction; the mixture gradually liquefied, and was heated on the water-bath for about 4 hours, until resolidification took place. After cooling, the reaction product was washed with benzene, and recrystallized from hot water, giving shiny colorless leaflets, m.p. 129°; yield, 75%. A similar procedure was found satisfactory for the preparation of gallacetophenone (15); applied to acetyl chloride and 4-bromopyrogallol [prepared according to Rosenmund and Kuhnhenn (16)], it yielded some *6-bromo-4-acetylpyrogallol*, m.p. 183°, identical with the bromination product of gallacetophenone (8). An attempt to condense pyrogallol with propionic acid with boron trifluoride failed to give 4-propionylpyrogallol in satisfactory yield. 4-Propionylpyrogallol gave a *2,4-dinitrophenylhydrazone*, which crystallized from acetic acid as silky red needles, m.p. 245–246°.

Anal. Calc'd for $C_{15}H_{14}N_4O_7$: N, 15.5. Found: N, 15.2.

As in the case of gallacetophenone (17), it formed with picric acid an *addition compound*, crystallizing from methanol as large, orange-yellow rhomboids, m.p. 123°.

2,3,4,2',3',4'-Hexahydroxy-5,5'-dipropionyltriphenylmethane (IX; Ar = C_6H_5, R = C_2H_5). A solution of 2 g. of benzaldehyde, 4 g. of 4-propionylpyrogallol, and 2 ml. of hydrochloric acid in 25 ml. of ethanol was refluxed for 30 minutes; the oily precipitate obtained on dilution with water solidified overnight, and gave on recrystallization from aqueous methanol silky colorless needles.

4-n-Valeroylpyrogallol. A mixture of 13 g. of pyrogallol, 12 g. of *n*-valeric acid, and 12 g. of finely powdered anhydrous zinc chloride was heated at 140–145° for 4 hours; after addition of water, the reaction product was taken up in ether, and gave on vacuum-distillation a 70% yield of a ketone, b.p. 202–204°/14 mm.

4-Caproylpyrogallol. This ketone, obtained in 70% yield as for the lower homolog, was found to melt at 86–87°, in accordance with Hart and Woodruff (5), and at variance with Haworth and Woodcock (7) who gave m.p. 72–74°.

4-Isobutyroylpyrogallol (III). Prepared in 40% yield, it had b.p. 198–200°/19 mm., and crystallized from aqueous methanol as colorless rhomboids, m.p. 118°.

Anal. Calc'd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.1.
Found: C, 61.2; H, 6.3.

4-n-Decanoylpyrogallol (IV). Obtained in 75–80% yield, it had b.p. 254–256°/13 mm., and crystallized from cyclohexane as silky colorless needles, m.p. 78–79°.

Anal. Calc'd for $C_{16}H_{24}O_4$: C, 68.6; H, 8.6.
Found: C, 68.3; H, 8.8.

4-n-Tridecanoylpyrogallol (V) crystallized from acetic acid as lustrous colorless leaflets, m.p. 84–85°.

Anal. Calc'd for $C_{19}H_{30}O_4$: C, 70.8; H, 9.3.
Found: C, 70.5; H, 9.5.

4-n-Pentadecanoylpyrogallol (VI) crystallized from a mixture of cyclohexane and ligroin as lustrous colorless leaflets, m.p. 87–88°.

Anal. Calc'd for $C_{21}H_{34}O_4$: C, 72.0; H, 9.7.
Found: C, 71.9; H, 9.9.

2-(2,3,4-Trihydroxyphenyl)scatole (XI). A mixture of 6 g. of 4-propionylpyrogallol and 5 g. of phenylhydrazine was heated at 120° until steam evolution had ceased. Then 50 ml. of acetic acid saturated with hydrogen chloride was added, and the mixture was refluxed for 5 minutes. The oil obtained on dilution with water solidified overnight, and gave on recrystallization from aqueous methanol fine colorless needles, m.p. 160°; yield, 80%. The compound gave a deep brown-violet coloration with picric acid.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.6; H, 5.1.
Found: C, 70.4; H, 5.3.

2-(2,3,4-Trihydroxyphenyl)-3-ethylindole (XII) was similarly prepared from 6 g. of 4-*n*-butyroylpyrogallol and 5 g. of phenylhydrazine; it crystallized from aqueous methanol as flat colorless prisms, m.p. 120°.

Anal. Calc'd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6.
Found: C, 71.1; H, 5.6.

3-n-Butyl-2-(2,3,4-trihydroxyphenyl)indole (XIII) crystallized from methanol as long, silky, colorless needles, m.p. 129–130°.

Anal. Calc'd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4.
Found: C, 72.5; H, 6.7.

2-(2,3,4-Trihydroxyphenyl)-3-phenylindole (XIV). 4-Phenacetylpyrogallol was prepared according to Noelting and Kadiera (18), and gave an indole, crystallizing from aqueous methanol as shiny colorless prisms, m.p. 189°, which darkened on exposure to air and light.

Anal. Calc'd for $C_{20}H_{15}NO_3$: C, 75.7; H, 4.7.
Found: C, 75.5; H, 4.9.

2-(2,3,4-Trihydroxyphenyl)-3-(4-chlorophenyl)indole (XV). The appropriate ketone (listed in Table III) was prepared from 4-chlorophenylacetic acid and pyrogallol as for 4-phenacetylpyrogallol; the indole crystallized from methanol as shiny colorless prisms, m.p. 192°.

Anal. Calc'd for $C_{20}H_{14}ClNO_3$: C, 68.3; H, 4.0.
Found: C, 68.0; H, 4.1.

4-Benzylpyrogallol. A mixture of 8 g. of 4-benzoylpyrogallol, 75 g. of amalgamated zinc, 200 ml. of hydrochloric acid, and 25 ml. of toluene was refluxed for 24 hours, and the toluene layer collected after cooling was washed with water and dried over sodium sulfate. After removal of solvent, the residue was vacuum-fractionated, giving 5 g. of a product, b.p. 252–255°/12 mm., crystallizing from a mixture of benzene and cyclohexane as very hygroscopic, colorless needles, m.p. 95–96°.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6.
Found: C, 71.9; H, 5.8.

4-(1-Naphthylacetyl)pyrogallol. Prepared from 1-naphthaleneacetic acid as for phenacetylpyrogallol, it crystallized from aqueous methanol as fine colorless prisms, m.p. 191–192°.

Anal. Calc'd for $C_{18}H_{14}O_4$: C, 73.5; H, 4.8.
Found: C, 73.2; H, 4.8.

Halogenation of 4-acylpyrogallols. To a water-cooled solution of one mole of the ketone in acetic acid, two moles of chlorine or bromine dissolved in acetic acid was added portionwise with stirring; after a few minutes, the halogenated product precipitated on dilution with water was collected, washed with water, recrystallized from aqueous methanol or acetic acid, and dried thoroughly in a vacuum.

SUMMARY

1. The synthesis and chemical properties of a wide series of 4-acylpyrogallols have been investigated, in view of certain possible biological effects of such substances.

2. The condensation of 4-acylpyrogallols with formaldehyde and aromatic aldehydes has been studied, and the structure of the resulting compounds is discussed.

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