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

COMPOUNDS WITH POTENTIAL ACTIVITY AGAINST LETHAL RADIATIONS. III.[1] BORON TRIFLUORIDE-CATALYZED SYNTHESIS OF HYDROXY ARYL KETONES

NG. PH. BUU-HOÏ AND JEAN SÉAILLES, JR.

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Recent studies have shown that a large number of long chain polyphenolic ketones possess considerable protective properties against lethal radiations in mice (1). These observations warranted a broad investigation of the relationship between this type of biological activity and chemical structure in the series of hydroxy aryl ketones, and a survey of the various methods for preparing these substances was therefore undertaken.

Of these methods, that of Nencki, which consists of heating an acid with a phenol in the presence of a dehydrating agent (zinc chloride), generally affords very low yields, except in the case of pyrogallol (2), and cannot be applied to sensitive acids such as the halogenated fatty acids. The Fries procedure (3) gives much better yields in the case of monohydric phenols, but is far less satisfactory with polyphenols; furthermore, the use of aluminum chloride often leads to isomerizations or splitting of radicals (4), and hydrogen fluoride, which has been advocated as an alternative catalyst, produces the Fries migration with acceptable yields only at high temperatures (5). The synthesis of hydroxy aryl ketones by demethylation of the corresponding ethers (usually easily accessible through Friedel-Crafts reactions) cannot be extended to long-chain ketones, which generally undergo fission under the influence of dealkylating agents (6). The Hoesch synthesis (7) requires the preliminary preparation of nitriles, and its applications are limited.

Direct condensation of phenols with acids in the presence of boron trifluoride has been used in several instances (8), but no systematic evaluation of the advantages of this procedure had yet been made. This study has now been undertaken, and, of the methods tried, that of boron trifluoride has proven by far the most satisfactory. In particular, a large number of long-chain hydroxy aryl ketones not easily accessible have been readily prepared; and halogenated acids underwent the condensation without decomposition. Furthermore, the brief duration of the condensation, the easy working-up of the reaction products, and the excellent yields recorded, combine to make the boron trifluoride-catalyzed reaction of acids on phenols and naphthols the method of choice, especially when hydroxy aryl ketones are required in quantity.

As regards the site of condensation, the acyl radical enters preferentially the *para* position when this is free, except in the case of α-naphthol, which reacts exclusively at the *ortho* position.

In the Table there is reported a selection of condensations leading to ketones which are less easily obtainable through other methods.

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[1] Part II: Buu-Hoï, *J. Org. Chem.*, **19**, 1770 (1954).

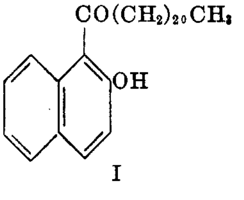
TABLE I

SYNTHESIS OF KNOWN KETONES BY THE BORON TRIFLUORIDE METHOD

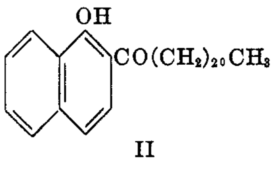
Organic acid	Phenol Used	Resulting Ketone	M.P., °C.
Acetic	*o*-Hydroxydiphenyl	3-Acetyl-6-hydroxydiphenyl[a]	173
Chloroacetic	Catechol	4-ω-Chloroacetylcatechol	173
Chloroacetic	Pyrogallol	ω-Chlorogallacetophenone	167
Chloroacetic	Resorcinol	ω-Chlororesacetophenone[b]	132
Propionic	Catechol	4-Propionylcatechol[c]	148
Propionic	*o*-Hydroxydiphenyl	3-Propionyl-6-hydroxydiphenyl[a]	154
Propionic	α-Naphthol	2-Propionyl-1-naphthol[d]	82
Propionic	β-Naphthol	1-Propionyl-2-naphthol[e]	72
n-Butyric	Catechol	4-*n*-Butyrylcatechol[c]	147
Caproic	Resorcinol	4-Caproylresorcinol[f]	58
Lauric	Pyrogallol	4-Lauroylpyrogallol[g]	78
Palmitic	Phenol	4-Hydroxypalmitophenone[h]	80
Palmitic	Resorcinol	4-Palmitoylresorcinol[i]	95
Palmitic	Pyrogallol	4-Palmitoylpyrogallol	92
Palmitic	α-Naphthol	2-Palmitoyl-1-naphthol[j]	82
Stearic	Phenol	4-Hydroxystearophenone[k]	89
Stearic	Resorcinol	4-Stearoylresorcinol[l]	99
Stearic	Pyrogallol	4-Stearoylpyrogallol	93
Stearic	Phloroglucinol	2-Stearoylphloroglucinol[m]	126
Stearic	α-Naphthol	2-Stearoyl-1-naphthol[n]	82

[a] Auwers and Wittig [*J. prakt. Chem.*, **108**, 106 (1925)] gave m.p. 172–173° for 3-acetyl-6-hydroxydiphenyl, and m.p. 148° for its homolog. [b] Obtained only in 30% yield; Sonn [*Ber.*, **50**, 1267 (1917)] gave m.p. 131°. [c] Rosenmund and Lohfert [*Ber.*, **61**, 2605 (1928)] gave m.p. 146–147° for 4-propionylcatechol, and m.p. 146° for its homolog. [d] Goldzweig and Kaiser [*J. prakt. Chem.*, **43**, 95 (1891)] gave m.p. 81°. [e] Gulati and Venkataraman [*J. prakt. Chem.*, **137**, 47 (1933)] gave m.p. 70–71°. [f] Twiss [*J. Am. Chem. Soc.*, **48**, 2209 (1926)] gave m.p. 56–57°. [g] Haworth and Woodcock (*loc. cit.*) gave m.p. 76–77°. [h] Auwers [*Ber.*, **36**, 3891 (1903)] gave m.p. 78°. [i] Adam [*Proc. Roy. Soc.* (*London*), [A]**119**, 643 (1928)] gave m.p. 94–95°. [j] Desai [*Proc. Indian Acad. Sci.*, [A]**13**, 33 (1941)] gave m.p. 83–84°. [k] Bell and Driver [*J. Chem. Soc.*, 835 (1940)] gave m.p. 90–90.5°. [l] Adam (*loc. cit.*) gave no m.p. [m] Karrer and Rosenfeld [*Helv. Chim. Acta*, **4**, 714 (1921)] gave m.p. 126°. [n] Desai (*loc. cit.*) gave m.p. 81–82°.

The biological evaluation of various types of hydroxy aryl ketones, performed in this Institute, showed that protective activity against lethal doses of X-rays is present only in readily oxidizable ketones (derivatives of catechol, pyrogallol, and naphthols), and not in ketones derived from monophenols or from resorcinol (9). An interesting observation was that whereas 1-behenoyl-2-naphthol (I) proved highly active, 2-behenoyl-1-naphthol (II) was much less so.



I



II

EXPERIMENTAL

Technique for boron trifluoride-catalyzed condensations. In the case of liquid or low-melting organic acids and phenols, no solvent was required for the condensation, and a mixture of the acid (1 mole) and the phenol (1.25 moles) was slowly saturated (2 to 3 hours) with boron trifluoride at temperatures ranging from 65 to 85°. The reaction product was treated with water, and the ketone was obtained in yields ranging from 70% (monophenols) to 95–98% (polyphenols or naphthols), recrystallized from the appropriate solvent, or purified by vacuum-distillation. With high-melting acids (behenic acid) or phenols (polyhydric phenols, β-naphthol), a solvent was used for the condensation, generally trichloroethylene or carbon tetrachloride. In the case of phenol and *o*-hydroxydiphenyl, there was evidence of the formation of some *o*-hydroxyketones, which were easily eliminated by recrystallization.

4-Behenoylphenol. The condensation was performed with a large excess of phenol, so as to avoid the recovery of any substantial amount of unreacted behenic acid. The ketone crystallized from cyclohexane or ligroin as shiny, colorless leaflets, m.p. 96–97°. Yield, 75%. This ketone and all the following ones gave a yellow coloration in sulfuric acid.

Anal. Calc'd for $C_{28}H_{48}O_2$: C, 80.8; H, 11.5.
Found: C, 80.6; H, 11.6.

2-Behenyl-4-methylphenol. The condensation of behenic acid (1 mole) with *p*-cresol (2 moles) was effected with an even higher yield (90–95%), probably because only one site for substitution was possible; the *ketone* crystallized from ligroin as large colorless leaflets, m.p. 80–81°.

Anal. Calc'd for $C_{29}H_{50}O_2$: C, 80.9; H, 11.6.
Found: C, 80.8; H, 11.6.

Similar results were recorded in the synthesis of *2-palmitoyl-4-methylphenol,* crystallizing from petroleum ether as silky needles, m.p. 61°.

Anal. Calc'd for $C_{23}H_{38}O_2$: C, 79.8; H, 11.0.
Found: C, 79.8; H, 11.3.

2-Stearoyl-4-methylphenol also crystallized from petroleum ether as lustrous leaflets, m.p. 69°.

Anal. Calc'd for $C_{25}H_{42}O_2$: C, 80.2; H, 11.2.
Found: C, 80.0; H, 11.3.

Condensation of higher fatty acids with 4-chloro-m-cresol. Excellent yields (90%) were also recorded in the preparation of the following ketones derived from 4-chloro-*m*-cresol, which, like *p*-cresol, has no free *para* position:

2-Myristoyl-4-chloro-5-methylphenol, silky needles, m.p. 81°, from methanol.

Anal. Calc'd for $C_{21}H_{33}ClO_2$: C, 71.5; H, 9.4.
Found: C, 71.4; H, 9.5.

2-Palmitoyl-4-chloro-5-methylphenol, lustrous leaflets, m.p. 86°, from petroleum ether.

Anal. Calc'd for $C_{23}H_{37}ClO_2$: C, 72.5; H, 9.7.
Found: C, 72.2; H, 9.8.

2-Stearoyl-4-chloro-5-methylphenol, lustrous leaflets, m.p. 88°, from ethanol or ligroin.

Anal. Calc'd for $C_{25}H_{41}ClO_2$: C, 73.4; H, 10.0.
Found: C, 73.3; H, 10.3.

2-Behenoyl-4-chloro-5-methylphenol, silky needles, m.p. 92–93°, from a mixture of ethanol and benzene.

Anal. Calc'd for $C_{29}H_{49}ClO_2$: C, 74.9; H, 10.5.
Found: C, 74.6; H, 10.4.

2-Myristoyl-1-naphthol was obtained in 90% yield from α-naphthol and myristic acid; it crystallized from a mixture of ethanol and benzene as shiny, yellowish leaflets, m.p. 80–81°.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.4; H, 9.6.
Found: C, 81.5; H, 9.6.

2-Behenoyl-1-naphthol was crystallized from acetic acid as silky, yellowish needles, m.p. 94°, giving a yellow coloration in a solution of sodium hydroxide in ethanol.

Anal. Calc'd for $C_{32}H_{50}O_2$: C, 82.4; H, 10.7.
Found: C, 82.2; H, 11.0.

Treatment with bromine (1 mole) in acetic acid afforded in quantitative yield *2-behenoyl-4-bromo-1-naphthol*, which crystallized from acetic acid as yellowish needles, m.p. 91–92°.

Anal. Calc'd for $C_{32}H_{49}BrO_2$: C, 70.5; H, 9.0.
Found: C, 70.1; H, 9.2.

1-Behenoyl-2-naphthol crystallized from cyclohexane as silky, colorless needles, m.p. 79–80°, giving a yellow coloration in a solution of sodium hydroxide in ethanol.

Anal. Calc'd for $C_{32}H_{50}O_2$: C, 82.4; H, 10.7.
Found: C, 82.5; H, 10.5.

4-(γ-Cyclohexylcaproyl)phenol. The condensation of phenol with γ-cyclohexylcaproic acid gave in 70% yield a *ketone* which crystallized from petroleum ether as shiny, colorless prisms, m.p. 99°.

Anal. Calc'd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5.
Found: C, 78.7; H, 9.5.

Halogenation in 60% aqueous acetic acid with bromine (2 moles) gave in 95% yield *2,6-dibromo-4-(γ-cyclohexylcaproyl)phenol*, crystallizing from petroleum ether as yellowish prisms, m.p. 67–68°.

Anal. Calc'd for $C_{18}H_{24}Br_2O_2$: Br, 37.0. Found: Br, 37.3.

SUMMARY

1. The synthesis of hydroxy aryl ketones by means of the boron trifluoride method has been extensively investigated.

2. A large number of ketones derived from mono- and poly-hydric phenols and naphthols have been prepared by this method, for testing as potential protective agents against lethal radiations.

PARIS V^e, FRANCE

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(3) See literature in BLATT, *The Fries Reaction* in *Org. Reactions*, **1**, 342 (1947); HAWORTH AND WOODCOCK, *J. Chem. Soc.*, 1001 (1946).

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