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COMPOUNDS WITH POTENTIAL ACTIVITY AGAINST LETHAL RADIATIONS. IV.[1] KETONES DERIVED FROM α- AND β-NAPHTHOL. A REVISION OF THE LITERATURE

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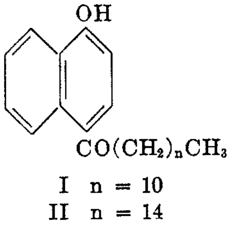
Received January 31, 1955

During a systematic investigation of compounds which might be protective against the biological effects of lethal radiations, the chemistry of the 4-acyl-1-naphthols has been studied. This approach was indicated because of the activity already found in some ketones derived from α- and β-naphthol (1).

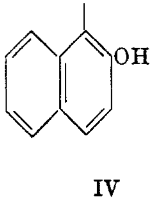
Few 4-acyl-1-naphthols have as yet been described in the literature. Witt and Braun (2) obtained 4-acetyl-1-naphthol in the Friedel-Crafts reaction of acetyl chloride with 1-ethoxynaphthalene in the presence of aluminum chloride, and Houben prepared the same ketone by the reaction of acetonitrile on α-naphthol (3); 4-propionyl-1-naphthol was prepared in good yield by Buu-Hoï through demethylation of the corresponding methyl ether with pyridine hydrochloride (4).

Alleged higher homologs were reported by Desai and Waravdekar (5), who reacted lauroyl, palmitoyl, and stearoyl chloride with α-naphthol in the presence of zinc chloride in nitrobenzene; the main reaction-products, described as 4-lauroyl-, 4-palmitoyl-, and 4-stearoyl-1-naphthol, had m.p. 146–147°, 180–181°, and 160–161° respectively. Methylation of these three products afforded compounds melting at 111–112°, 129–130°, and 125–126°, supposedly 4-lauroyl-, 4-palmitoyl-, and 4-stearoyl-1-methoxynaphthalene, and claimed to be identical with the ketones obtained by direct Friedel-Crafts reactions on 1-methoxynaphthalene (6).

It has now been found that none of these compounds correspond to the structure assigned to them. Lauroyl, palmitoyl, and stearoyl chloride reacted smoothly with 1-methoxynaphthalene in the presence of aluminum chloride in nitrobenzene (7) to give authentic 4-lauroyl-, 4-palmitoyl-, and 4-stearoyl-1-methoxynaphthalene, whose melting points were considerably lower than those reported, and more in line with those of long-chain compounds. Demethylation with



I n = 10
II n = 14
III n = 16



IV

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[1] Part III, Buu-Hoï and Seailles, J. Org. Chem., **20**, 606 (1955).

pyridine hydrochloride yielded the authentic 4-lauroyl-, 4-palmitoyl-, and 4-stearoyl-1-naphthol, whose melting points were likewise considerably below the recorded ones. The constitution of these ketones was ascertained through contrast with the corresponding 2-acyl-1-naphthols, the only alternatives possible. Further, in a repetition of Desai and Waravdekar's experiments, α-naphthol and the starting aliphatic acids were largely recovered, and no simple ketonic compound was obtained.

It ensures that the following substances, which Desai and Waravdekar (5) prepared from their ketones, cannot have the postulated constitution:

2-Bromo-4-lauroyl-1-naphthol
2-Nitro-4-lauroyl-1-naphthol
4-*n*-Dodecyl-1-naphthol and its methyl ether
2-Bromo-4-palmitoyl-1-naphthol
2-Nitro-4-palmitoyl-1-naphthol
4-*n*-Hexadecyl-1-naphthol and its methyl ether
2-Bromo-4-stearoyl-1-naphthol
2-Nitro-4-stearoyl-1-naphthol
4-*n*-Octadecyl-1-naphthol and its methyl ether.

Bhumgara, Desai, and Waravdekar (8) reacted phenacetyl chloride with α-naphthol and zinc chloride in nitrobenzene, and obtained a substance m.p. 92–93°, considered as 4-phenacetyl-1-naphthol, and identified with a product from a Fries rearrangement of α-naphthol phenylacetate. Authentic 4-phenacetyl-1-naphthol has now been prepared by demethylation of 4-phenacetyl-1-methoxynaphthalene (9), and found to have m.p. 187°, in agreement with Houben and Fischer (10), who prepared it from α-naphthol, benzyl cyanide, and hydrogen chloride in the presence of zinc chloride. 2-Bromo-4-phenacetyl-1-naphthol, prepared by halogenation of this ketone, was a colorless compound, m.p. 103°; a substance to which Bhumgara, Desai, and Waravdekar assigned that constitution was described as red needles, m.p. 76–78°. In the present work, 4-caproyl-, 4-*n*-decanoyl-, and 4-hexahydrobenzoyl-1-naphthol were also prepared by demethylation of the corresponding methyl ethers with pyridine hydrochloride, a reaction with became increasingly difficult with the lengthening of the chain.

In the β-naphthol series, Desai and Waravdekar (11) obtained from a Nencki reaction with stearic acid and zinc chloride, a substance m.p. 125–126°, described as 1-stearoyl-2-naphthol (IV). Authentic 1-stearoyl-2-naphthol, now prepared either by a boron trifluoride-catalyzed condensation of stearic acid with β-naphthol, or by a Fries rearrangement of β-naphthol stearate (12), melted at 64–65°. Further proof that the substance m.p. 125–126° (methyl ether, m.p. 72–73°) was not 1-stearoyl-2-naphthol, is that the alleged ethyl 1-stearoyl-2-naphthoxacetate obtained by condensation with ethyl bromacetate boiled at 279°, a temperature clearly too low for a compound of that structure; the same observation applies to "2-carbethoxy-3-*n*-heptadecyl-β-naphthacoumarone", described as boiling at 265°. Repetition of Desai and Waravdekar's procedure led to recovered β-naphthol (m.p. 125°; methyl ether m.p. 72°) and stearic acid.

The present work included the preparation of 4-acetyl-2-allyl-1-naphthol by

Claisen rearrangement of 4-acetyl-1-allyloxynaphthalene. A noteworthy difference observed between 4-acetyl-1-naphthol and 2-acetyl-1-naphthol as regards Pfitzinger reactions with isatin was that the former ketone did not react, even after three days, whereas the latter gave under the same conditions a substantial amount of 2-(1-hydroxy-2-naphthyl)cinchoninic acid. This is in line with earlier observations that *o*-hydroxy ketones react with isatin far more rapidly than do the *p*-isomers (13).

EXPERIMENTAL

Synthesis of 4-lauroyl-1-naphthol (I). To a cooled solution of 28 g. of 1-methoxynaphthalene and 38.5 g. of lauroyl chloride in 100 ml. of nitrobenzene, 26 g. of aluminum chloride was added portionwise with stirring. The mixture was kept overnight at room temperature, poured on ice, the nitrobenzene and the 1-methoxynaphthalene in excess removed by steam-distillation, and the reaction product taken up in benzene. The benzene solution was washed with dilute sodium hydroxide, dried over sodium sulfate, the solvent removed, and the residue fractionated *in vacuo.* Yield: 51 g. (85%) of *4-lauroyl-1-methoxynaphthalene,* b.p. 286–288°/13 mm., crystallizing from petroleum ether in shiny colorless needles, m.p. 53°, which gave an intense yellow coloration with sulfuric acid. In this and similar preparations, emulsions formed during the working up of the ketones were broken by addition of sodium chloride.

Anal. *Calc'd for* $C_{23}H_{32}O_2$: C, 81.1; H, 9.4.
Found: C, 81.0; H, 9.3.

A mixture of 5 g. of 4-lauroyl-1-methoxynaphthalene and 50 g. of redistilled pyridine hydrochloride was refluxed for two hours; water was added after cooling, and the precipitate was collected and purified by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid. Crystallization several times from ligroin yielded 1 g. of fine colorless needles, m.p. 88°, giving an intense yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 81.0; H, 9.2.
Found: C, 80.7; H, 9.3.

Synthesis of 4-palmitoyl-1-napthol (II). Friedel-Crafts condensation of 14 g. of 1-methoxynaphthalene with 24 g. of palmitoyl chloride and 13 g. of aluminum chloride in 100 ml. of nitrobenzene yielded 27 g. of *4-palmitoyl-1-methoxynaphthalene,* b.p. 315–317°/13 mm., crystallizing from petroleum ether in colorless prisms, m.p. 68°.

Anal. Calc'd for $C_{27}H_{40}O_2$: C, 81.8; H, 10.1.
Found: C, 81.7; H, 10.3.

Demethylation of 2 g. of this ketone by two hours' refluxing with 50 g. of pyridine hydrochloride yielded 0.50 g. of *4-palmitoyl-1-naphthol,* crystallizing from ligroin in colorless needles, m.p. 89°.

Anal. Calc'd for $C_{26}H_{38}O_2$: C, 81.7; H, 9.9.
Found: C, 81.4; H, 9.9.

Synthesis of 4-stearoyl-1-naphthol (III). Friedel-Crafts reaction of 5 g. of 1-methoxynaphthalene, 9 g. of stearoyl chloride, and 5 g. of aluminum chloride in 50 ml. of nitrobenzene, gave 9 g. of *4-stearoyl-1-methoxynaphthalene,* b.p. 327–330°/14 mm., crystallizing from petroleum ether in silky, colorless needles, m.p. 72–73°.

Anal. Calc'd for $C_{29}H_{44}O_2$: C, 82.1; H, 10.4.
Found: C, 82.2; H, 10.5.

4-Stearoyl-1-naphthol, obtained in 15% yield on demethylation with pyridine hydrochloride, crystallized from cyclohexane in fine, colorless prims, m.p. 90–91°.

Anal. Calc'd for $C_{28}H_{42}O_2$: C, 82.0; H, 10.2.
Found: C, 82.0; H, 10.5.

Synthesis of 4-n-decanoyl-1-naphthol. From 11 g. of 1-methoxynaphthalene, 13 g. of *n*-decanoyl chloride, and 10.2 g. of aluminum chloride, 17 g. of *4-n-decanoyl-1-methoxynaph-*

thalene was obtained. This ketone had b.p. 265°/13 mm., and crystallized from light petroleum ether in colorless needles, m.p. 41°.

Anal. Calc'd for $C_{21}H_{28}O_2$: C, 80.8; H, 9.0.
Found: C, 80.6; H, 9.1.

Demethylation gave a 30% yield of *4-n-decanoyl-1-naphthol*, which crystallized from cyclohexane in fine colorless prisms, m.p. 89°.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.7.
Found: C, 80.2; H, 8.7.

Synthesis of 4-n-caproyl-1-naphthol. From 12 g. of 1-methoxynaphthalene, 10 g. of caproyl chloride, and 11 g. of aluminum chloride, 14 g. of *4-caproyl-1-methoxynaphthalene* was obtained; this ketone had b.p. 237°/14 mm., n_D^{21} 1.5983, and crystallized from light petroleum ether in colorless needles, m.p. 38°.

Anal. Calc'd for $C_{17}H_{20}O_2$: C, 79.7; H, 7.8.
Found: C, 79.8; H, 7.9.

The corresponding *semicarbazone* crystallized from ethanol in colorless prisms, m.p. 197°.

Demethylation of this ketone gave a 50% yield of *4-caproyl-1-naphthol*, which crystallized from benzene in colorless prisms, m.p. 141°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.4.
Found: C, 79.0; H, 7.3.

Synthesis of 4-hexahydrobenzoyl-1-naphthol. From 11 g. of 1-methoxynaphthalene, 10 g. of hexahydrobenzoyl chloride, and 10 g. of aluminum chloride, there was obtained 12 g. of *4-hexahydrobenzoyl-1-methoxynaphthalene*, b.p. 255°/13 mm., crystallizing from ethanol in colorless prisms, m.p. 95°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 80.5; H, 7.6.

Demethylation gave a 50% yield of *4-hexahydrobenzoyl-1-naphthol*, which crystallized from acetic acid in colorless prisms, m.p. 184°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.0; H, 7.3.

4-Myristinoyl-1-methoxynaphthalene. Prepared from 11 g. of 1-methoxynaphthalene, 17 g. of myristinoyl chloride and 10 g. of aluminum chloride, this ketone (21 g.), b.p. 300–302°/15 mm., crystallized from ligroin in colorless leaflets, m.p. 61°.

Anal. Calc'd for $C_{25}H_{36}O_2$: C, 81.5; H, 9.8.
Found: C, 81.5; H, 10.0.

2-Bromo-4-phenacetyl-1-naphthol. 4-Phenacetyl-1-naphthol, m.p. 186°, was prepared in 60% yield by refluxing for 10 minutes a mixture of 6 g. of 4-phenacetyl-1-methoxynaphthalene and 20 g. of pyridine hydrochloride. To a solution of 1.7 g. of this hydroxyketone in 100 ml. of acetic acid and 40 ml. of water, a solution of 1 g. of bromine in acetic acid was added portionwise with stirring. The precipitate of *2-bromo-4-phenacetyl-1-naphthol* obtained on dilution with water, crystallized from aqueous acetic acid in shiny colorless prisms, m.p. 103°. Yield: 1.5 g.

Anal. Calc'd for $C_{18}H_{13}BrO_2$: Br, 23.5. Found: Br, 23.2.

2-(4-Methoxy-1-naphthyl)-3-phenylindole. 1-Methoxy-4-phenacetylnaphthalene was further characterized by the formation of this indole. A mixture of 2 g. of 1-methoxy-4-phenacetylnaphthol and 1.5 g. of phenylhydrazine was heated at 150–160° until water ceased to evolve, and the crude phenylhydrazone treated with a boiling solution of hydrogen chloride in acetic acid (14). The reaction mixture was poured on water, and the solid obtained was collected and recrystallized from ethanol. Yield: 2 g. of colorless needles, m.p. 231°.

Anal. Calc'd for $C_{25}H_{19}NO$: N, 4.0. Found: N, 4.1.

Repetition of Desai and Waravdekar's experiments. A mixture of 15 g. of α-naphthol, 15 g. of stearoyl chloride, and 14 g. of zinc chloride in 80 ml. of nitrobenzene was treated according to the cited authors. The main products isolated were α-naphthol and stearic acid; higher-boiling portions consisted of small amounts of complex substances with much higher carbon contents than the postulated stearoylnaphthol.

2-Bromo-4-caproyl-1-naphthol, prepared similarly from 4-caproyl-1-naphthol, crystallized from ligroin in colorless needles, m.p. 65°.

Anal. Calc'd for $C_{16}H_{17}BrO_2$: Br, 24.9. Found: Br, 25.1.

2-Allyl-4-acetyl-1-naphthol. 4-Acetyl-1-allyloxynaphthalene was prepared in 90% yield from 9 g. of 4-acetyl-1-naphthol, 7 g. of allyl bromide, and 2.5 g. of sodium hydroxide in ethanol; it crystallized from ligroin in shiny colorless prisms, m.p. 68°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2.
Found: C, 79.5; H, 6.5.

A solution of 2.7 g. of this ketone in 10 ml. of dimethylaniline was refluxed for 12 hours; after cooling, the mixture was poured into dilute hydrochloric acid, and the precipitate was collected, washed with water, and recrystallized from benzene. Yield: 1.5 g. of *2-allyl-4-acetyl-1-naphthol*, colorless, sublimable needles, m.p. 186°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2.
Found: C, 79.3; H, 6.2.

2-(1-Hydroxy-2-naphthyl)cinchoninic acid. A solution of 2 g. of 2-acetyl-1-naphthol, 1.7 g. of isatin, and 2.4 g. of potassium hydroxide in 15 ml. of ethanol was refluxed for 3 days; the precipitate obtained on acidification with aqueous acetic acid gave on recrystallization from benzene 0.5 g. of fine, yellowish needles, m.p. 302°.

Anal. Calc'd for $C_{20}H_{13}NO_3$: N, 4.4. Found: N, 4.5.

A similar reaction, performed with 4-acetyl-1-naphthol, gave no sizable trace of cinchoninic acid.

1-Stearoyl-2-naphthol (IV). In a mixture of 25 g. of β-naphthol and 25 g. of stearic acid heated at 80–85°, boron trifluoride was bubbled for three hours; the reaction mixture was treated with water, and the ketone obtained was taken up in benzene and purified by distillation *in vacuo*. Yield: 30 g. of *1-stearoyl-2-naphthol*, b.p. 310–312°/13 mm., which crystallized from petroleum ether in colorless prisms, m.p. 64–65°.

Anal. Calc'd for $C_{28}H_{42}O_2$: C, 82.0; H, 10.2.
Found: C, 81.9; H, 10.4.

1-Stearoyl-2-methoxynaphthalene, prepared from the foregoing ketone, dimethyl sulfate, and potassium hydroxide in ethanol, crystallized from ethanol in shiny colorless leaflets, m.p. 60–61°. Desai and Waravdekar (11) gave m.p. 72–73° for the methyl ether of their "1-stearoyl-2-naphthol".

Anal. Calc'd for $C_{29}H_{44}O_2$: C, 82.1; H, 10.4.
Found: C, 82.3; H, 10.5.

Repetition of the cited experiment (11) afforded no identifiable compound except recovered β-naphthol and stearic acid.

SUMMARY

1. A series of 4-acyl-1-naphthols has been prepared by demethylation of the corresponding 4-acyl-1-methoxynaphthalenes, for biological testing against lethal radiations.

2. The 4-lauroyl-, 4-palmitoyl-, and 4-stearoyl-1-naphthol and their derivatives reported in the literature, do not have the constitution assigned to them.

3. 1-Steroyl-2-naphthol has been prepared, and found to be different from the compound recorded in the literature under this name.

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