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Orientation in Friedel-Crafts Acetylation of Neroline and Its 6-Alkyl Homologues

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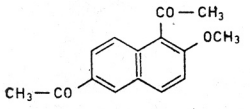
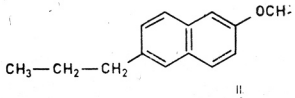
The Friedel-Crafts acetylation of neroline in nitrobenzene medium is shown to result predominantly either in 1- or in 6-substitution, depending on the experimental conditions; as a by-product, 1,6-diacetyl-2-methoxynaphthalene is obtained. Further, it is shown that 6-alkylated nerolines such as 6-propyl-2-methoxynaphthalene, are acetylated in position 1, even in nitrobenzene medium, and that 1,6-dialkylated nerolines such as 6-ethyl-2-methoxy-1-methylnaphthalene, can also be acetylated, whilst 1,6-dialkyl-2-naphthols are unable to undergo Nencki acylation reactions. In the course of this work, certain errors in the literature have been corrected.

It has generally been assumed that 2-methoxynaphthalene undergoes Friedel-Crafts acylation with acetyl chloride and aluminium chloride to give 2-methoxy-1-acetonaphthone when carbon disulphide[1] or benzene[2] is used as solvent, and 2-methoxy-6-acetonaphthone when nitrobenzene is the solvent.[3] It is therefore interesting to record that we have now found that in nitrobenzene medium, the acetylation occurs predominantly at position 1 when aluminium chloride is added to the solution of acetyl chloride and β-methoxynaphthalene, whilst 2-methoxy-6-acetonaphthone is the main product when acetyl chloride is added to a nitrobenzene solution of aluminium chloride and β-methoxynaphthalene. This difference is demonstrative of the influence of Perrier complexes on orientation in Friedel-Crafts acylations, and indicates positions 1 and 6 as being the most reactive in the molecule of neroline. As a by-product in the preparation of 2-methoxy-6-acetonaphthone, we isolated small amounts of a diketone, which must therefore be 1,6-diacetyl-2-methoxynaphthalene (I).

It was also to be expected that 6-alkylated nerolines would undergo Friedel-Crafts acetylation in position 1, regardless of the solvent used for the reaction. This has now been rigidly proved in the case of 6-propyl-2-methoxy naphthalene (II). This ether reacted with acetyl chloride and aluminium chloride to give 2-methoxy-6-propyl-1-acetonaphthone (III), in either nitrobenzene

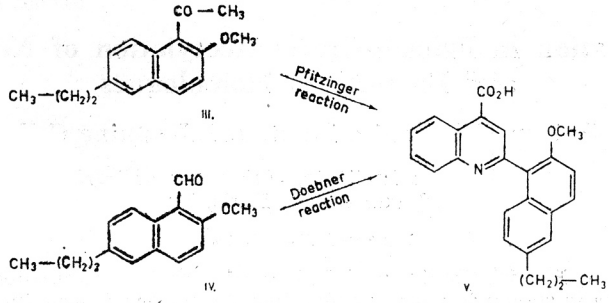


I.

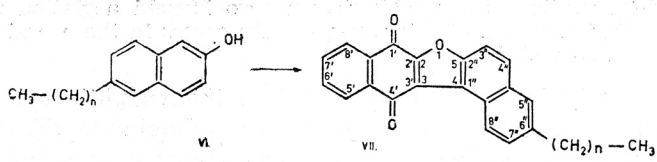


II.

or carbon disulphide medium. The constitution of this latter ketone was established by a Pfitzinger reaction[4] with isatin to give a *cinchoninic acid* (V), which was identical with the product of a Doebner condensation of pyruvic acid and aniline with 2-methoxy-6-propyl-1-naphthaldehyde (IV).

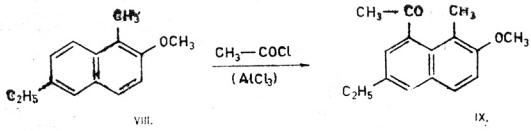


It is worth mention that the 6-propyl-2-naphthol (VI; n = 2) used in the present work had properties (m. p. 97°) different from those reported in the literature[5] for a substance prepared in another way, and whose m. p. (120—121°) suggests that it was probably *β-naphthol* (m. p. 122°) formed by a side-



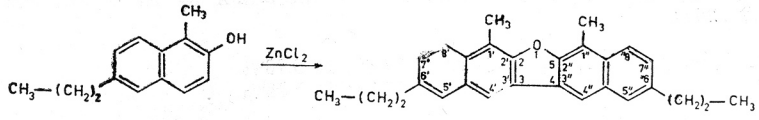
reaction. Conversely, 6-butyl-2-naphthol (VI; n = 3) was found to have a higher m. p. (105°) than the one given in the literature (97—98°). Both naphthols were characterised by condensation with 2,3-dichloro-1,4-naphthoquinone in pyridine medium to give the brasanquinones of formula VII.

A point of interest was to ascertain whether 1,6-dialkylated nerolines could still undergo Friedel-Crafts acetylation, and in which position. The answer to the first half of the question is in the affirmative, as 6-ethyl-2-methoxy-1-methylnahthalene (VIII) was found to react readily with acetyl chloride and aluminium chloride in nitrobenzene medium to give a ketone, for which the constitution of 6-ethyl-2-methoxy-1-methyl-8-acetonaphthone (IX) is tentatively proposed, in view of the known ability of position 8 to undergo substitution in the case of 2-methylnaphthalene;[6] this ketone underwent a Pfitzinger reaction to give a product, tentatively designated as 2-(6-ethyl-2-methoxy-1-methyl-8-naphthyl) cinchoninic acid.



In contrast with the facility, demonstrated above, with which 1,6-disubstituted nerolines undergo Friedel-Crafts acylations, 1,6-dialkyl-2-naphthols

were found to be resistant to Nencki acylation reactions. Thus, when 1-methyl-6-propyl-2-naphthol (X) was heated with octanoic acid in the presence of zinc chloride, the only homogeneous reaction-product isolated was a high-melting, non-ketonic, alkali-insoluble compound which, on the grounds of its analysis



and properties, was assigned the constitution of 1′, 1″-dimethyl-6′, 6″-dipropyl-dinaphtho (2′, 3′-2,3) (2″, 3″-5,4) furan (XI).

EXPERIMENTAL

Friedel-Crafts acetylation of neroline

a) To an ice-cooled, stirred solution of neroline (200 g.) and acetyl chloride (115.6 g.) in redistilled nitrobenzene (800 cc.), finely powdered aluminium chloride (187.3 g.) was added in small portions, and the mixture left overnight at room temperature. After decomposition with ice and removal of the nitrobenzene by steam distillation, the reaction-product was taken up in benzene, the benzene solution washed with a 5% aqueous solution of sodium hydroxide, then with water, dried (Na_2SO_4), the solvent removed, and the residue fractionated *in vacuo*. The portion boiling at 190—200°/11 mm. gave on fractional crystallisation first from methanol, then from petroleum ether, *2-methoxy-1-acetonaphthone*, as fine, colourless prisms (70 g.), m. p. 59—60° (lit., m. p. 59°); a further quantity (6 g.) of the same compound was obtained by a similar fractional crystallisation of the portion boiling at 205—215° 15 mm., from which *2-methoxy-6-acetonaphthone* was also isolated, as colourless prisms (6 g.), m. p. 110° (lit., m. p. 107°). The constitution of both isomers was ascertained by demethylation with boiling pyridine hydrochloride[7] to 2-hydroxy-1-acetonaphthone (m. p. 65°) and 2-hydroxy-6-acetonaphthone (m. p. 172°) respectively.

b) To an ice-cooled, stirred solution of aluminium chloride (200 g.) and neroline (192 g.) in nitrobenzene (1200 cc.), acetyl chloride (120 g.) was aded over a period of 20 minutes, and the reaction mixture left overnight at room temperature, then worked up as above. The yield was 80 g. of pure 2-methoxy-6-acetonaphthone, m. p. 109—110°. The higher-boiling residue b. p. 230—260°/17 mm.) gave on fractional recrystallisation from ethanol, *1,6-diacetyl-2-methoxynaphthalene* (I), as shiny, colourless needles (4 g.), m. p. 155°.

Anal. $C_{15}H_{14}O_3$ (242.26) calc'd: C 74.36; H 5.83%
found: C 74.10; H 5.89%

2-Methoxy-6-propyl-1-acetonaphthone (III)

To an ice-cooled, well-stirred solution of 2-methoxy-6-propylnaphthalene (17.8 g.; prepared by a Kishner-Wolff reduction of 2-methoxy-6-propionaphthone) and acetyl chloride (7.8 g.) in nitrobenzene (150 cc.), aluminium chloride (13 g.) was added in small portions, and the mixture left overnight at room temperature. After the usual treatment, the *ketone* obtained, b.p. 214°/15 mm., was recrystallised from petroleum ether, giving fine, colourless needles (15 g.), m.p. 52°.

Anal. $C_{16}H_{18}O_2$ (242.30) calc'd: C 79.31; H 7.49%
found: C 79.26; H 7.36%

The same product was obtained when carbon disulphide was used as solvent in place of nitrobenzene.

2-(2-Methoxy-6-propyl-1-naphthyl) cinchoninic acid (V)

a) A mixture of the foregoing ketone (2 g.), isatin (1.33 g.) and potassium hydroxide (1.38 g., dissolved in 1 cc. of water) in ethanol (10 cc.) was gently refluxed for 24 hours. After dilution with water and removal of the neutral impurities by ether extraction, the aqueous layer was acidified with acetic acid, giving a precipitate which crystallised from methanol as fine yellowish needles (2 g.), m. p. 209°.

Anal. $C_{24}H_{21}O_3N$ (371.42) calc'd: C 77.60; H 5.70%
found: C 77.33; H 5.95%

b) A solution of 2-methoxy-6-propyl-1-naphthaldehyde (3 g.), aniline (1.34 g.) and pyruvic acid (1.27 g.) in ethanol (30 cc.) was gently refluxed for 24 hours, and the reaction mixture diluted with water and kept overnight in the refrigerator; the solid formed was recrystallised from methanol, giving yellowish needles (0.8 g.), m. p. 209° (this m. p. was not depressed on admixture with a sample of the foregoing cinchoninic acid). Thermal decarboxylation yielded *2-(2-methoxy-6-propyl-1-naphthyl) quinoline,* which did not crystallise; it was characterised by its *picrate,* which formed silky, deep yellow needles, m. p. 214° (decomp.), from ethanol.

Anal. $C_{29}H_{24}O_8N_4$ (556.51) calc'd: N 10.07%
found: N 9.78%

6-Ethyl-2-methoxy-1-methyl-8(?)-acetonaphthone (IX)

To an ice-cooled, well stirred solution of 6-ethyl-2-methoxy-1-methylnaphthalene (28 g.) and acetyl chloride (12.1 g.) in nitrobenzene (150 cc.), aluminium chloride (20.5 g.) was added in small portions. The reaction mixture was worked up in usual way, yielding a single *ketone,* b. p. 212°/11 mm., which crystallised as fine, colourless needles (9.5 g.), m. p. 64°, from petroleum ether.

Anal. $C_{16}H_{18}O_2$ (242.30) calc'd: C 79.31; H 7.49%
found: C 79.46; H 7.62%

Nencki reaction with 1-methyl-6-propyl-2-naphthol

A mixture of 1-methyl-6-propyl-2-naphthol (15 g.), octanoic acid (10.8 g.), and freshly fused, finely powdered zinc chloride (10.2 g.) was heated for 28 hours at 165—175°; after cooling, the reaction mixture was kneaded with water and hot benzene, the benzene solution washed with water and dried over sodium sulphate, the solvent distilled off, and the residue fractionated *in vacuo.* The portion b. p. 320°/0.5 mm. yielded on repeated recrystallisation from cyclohexane, compound (XI) in the form of fine, pale yellow needles (0.5 g), m. p. 207°, insoluble in aqueous alkalis.

Anal. $C_{28}H_{28}O$ (380.50) calc'd: C 88.38; H 7.42%
found: C 88.05; H 7.80%

The lower-boiling portions consisted of recovered octanoic acid and 1-methyl-6-propyl-2-naphthol, and undefined products.

6-Propyl-2-naphthol

A mixture of 2-methoxy-6-propylnaphthalene (42 g.) and redistilled pyridine hydrochloride (170 g.) was refluxed for 30 minutes; after cooling, dilute hydrochloric acid was added, and the demethylation-product taken up in benzene, the benzene solution washed with water and dried over sodium sulphate, the solvent removed, and the residue fractionated *in vacuo. 6-Propyl-2-naphthol,* b. p. 185°/12 mm., formed shiny, colourless leaflets (30 g.), m. p. 96°, from cyclohexane.

Anal. $C_{13}H_{14}O$ (186.24) calc'd: C 83.83; H 7.58%
found: C 83.60; H 7.76%

6″-Propyldinaphtho(2′,3′ : 2,3) (1″,2″ : 4,5)furan-1′,4′-quinone (VII; n=2)

A mixture of 2,3-dichloro-1,4-naphthoquinone (0.5 g.), 6-propyl-2-naphthol (0.4 g.), and anhydrous pyridine (5 cc.) was refluxed for one hour; after cooling, ethanol was added, and the precipitate (0.7 g.) collected and washed with water. Recrystallisation from xylene afforded golden yellow needles, m. p. 222°, giving a greenish-blue halochromy with sulphuric acid.

Anal. $C_{23}H_{16}O_3$ (340.36) calc'd: C 81.16; H 4.74%
found: C 81.05; H 4.54%

6″-Butyldinaphtho(2′,3′ : 2,3) (1″,2″ : 4,5)furan-1′,4′-quinone (VII; n=3)

6-Butyl-2-naphthol, prepared by demethylation of 6-butyl-2-methoxynaphthalene, crystallised as shiny, colourless leaflets, m. p. 105° (lit., m. p. 97—98°); condensation with 2,3-dichloro-1,4-naphthoquinone, effected as above, yielded a compound crystallising as silky, golden yellow needles, m. p. 223°.

Anal. $C_{24}H_{18}O_3$ (354.38) calc'd: C 81.34; H 5.12%
found: C 81.30; H 5.25%

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IZVOD

Orijentacija kod acetilacije nerolina i njegovih 6-alkil homologa po Friedel-Craftsovoj metodi

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Acetilacijom nerolina u nitrobenzenu, po Friedel-Craftsovoj metodi dolazi uglavnom do supstitucije u položaju 1- ili 6-, što ovisi o eksperimentalnim uvjetima; kao nusprodukt dobiven je 1,6-diacetil-2-metoksinaftalen. Nadalje je utvrđeno, da se 6-alkil nerolini, kao na pr. 6-propil-2-metoksinaftalen, acetiliraju u položaju 7- i uz nitrobenzen kao otapalo. 1,6-Dialkilnerolin, kao na pr. 6-etil-2-metoksi-1-metilnaftalen, mogu se još acetilirati, ali 1,6-dialkil-2-naftoli ne mogu se acetilirati po Nenckijevoj metodi.

Za vrijeme rada ispravljeni su neki krivi navodi iz literature.

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