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THE ORIENTATION OF SOME DERIVATIVES OF β-*tert*-BUTYLNAPHTHALENE

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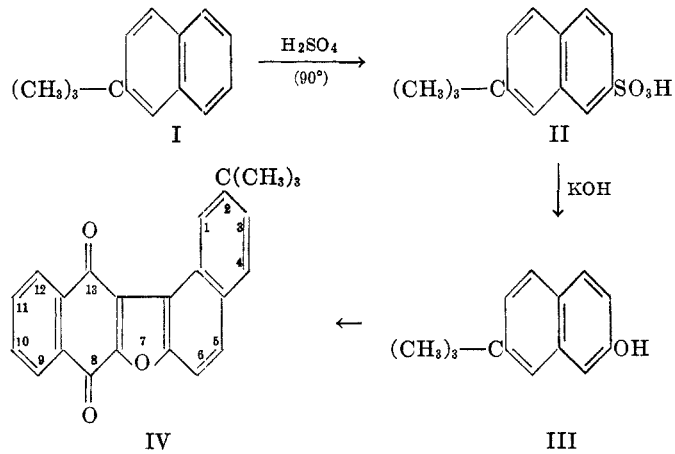
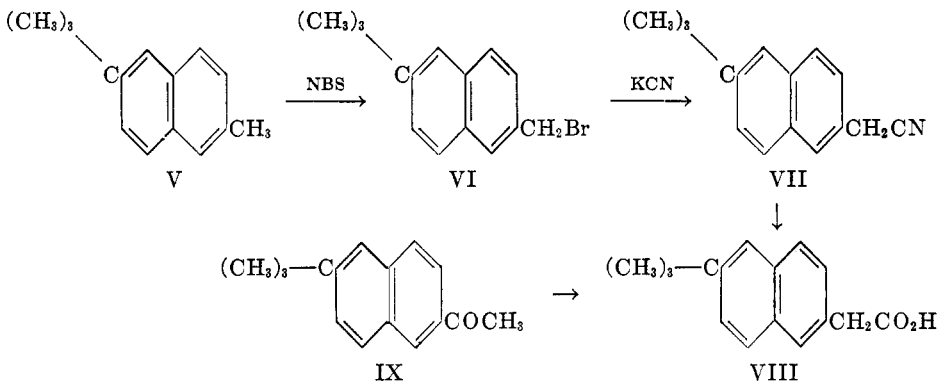
The study of β-*tert*-butylnaphthalene (I) offers an inviting field, both for pure chemistry research, and for the quest of substances of practical value, particularly in pharmacology. One of its derivatives, 6-*tert*-butyl-1-chloro-2-naphthol, has recently found use as a powerful anthelmintic against tapeworm (1); alkali salts of *tert*-butylnaphthalenesulfonic acid are used as detergents; and the bechic properties of its sodium salt have received pharmaceutical application as an ingredient in cough mixtures. From the theoretical viewpoint, it was of interest to study the directing power of the *tert*-butyl group in the naphthalene nucleus, and to determine the structure of several derivatives of β-*tert*-butylnaphthalene which had not yet been oriented unequivocally.

Under experimental conditions similar to those used for converting β-methylnaphthalene into 6-methylnaphthalene-2-sulfonic acid (2), β-*tert*-butylnaphthalene yielded a sulfonic acid which Contractor, Peters, and Rowe (3) presumed, by reason of analogy, to be 6-*tert*-butylnaphthalene-2-sulfonic acid. Alkaline fusion of this compound gave a liquid naphthol presumed to be 6-*tert*-butyl-2-naphthol. This structure has recently been discounted by the non-identity of that liquid naphthol with the well-crystallized, high-melting 6-*tert*-butyl-2-naphthol prepared synthetically in two different ways (1); the corresponding sulfonic acid could not therefore be 6-*tert*-butylnaphthalene-2-sulfonic acid. The other conceivable sites of sulfonation are the positions 1, 7, and 8. The position 1 was discarded in view of the ready condensation of the liquid *tert*-butylnaphthol with 2,3-dichloro-1,4-naphthoquinone to a derivative of brazanquinone, a reaction which excluded the presence of the *tert*-butyl group in *ortho* position (4). The position 8 was discarded because this brazanquinone derivative (IV) gave with



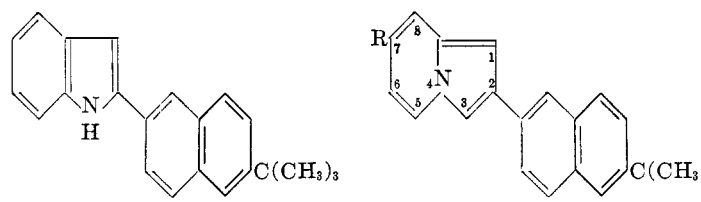
sulfuric acid the bluish-green coloration characteristic of similar compounds prepared from β-naphthols, and quite distinct from the coloration obtained with similar condensation products from α-naphthols (5). The noncrystalline naphthol studied was therefore 7-*tert*-butyl-2-naphthol (III), and the parent sulfonic acid, 7-*tert*-butylnaphthalene-2-sulfonic acid (II). This sulfonation at the position 7 of a 2-alkylnaphthalene is not without precedence in the literature, as β-methylnaphthalene is known to yield predominantly 7-methylnaphthalene-2-sulfonic acid when the reaction takes place at high temperature (6).

Another interesting structure problem was the orientation of the *tert*-butylation product of β-methylnaphthalene. This reaction was found to proceed more smoothly than with naphthalene, and gave in excellent yield a monobutylated product from which a sharp-melting picrate could be prepared. This hydrocarbon proved to consist mainly, if not entirely, of 6-*tert*-butyl-2-methylnaphthalene (V), as side-chain bromination with N-bromosuccinimide gave good yields of the solid 6-*tert*-butyl-2-bromomethylnaphthalene (VI); this was converted into 6-*tert*-butyl-2-naphthaleneacetonitrile (VII), hydrolysis of which gave an acid identical with 6-*tert*-butyl-2-naphthaleneacetic acid (VIII), prepared by

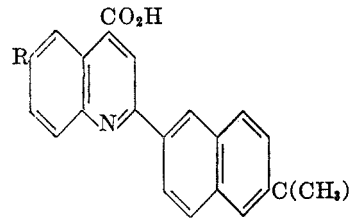


submitting the known 6-*tert*-butyl-2-acetonaphthone (IX) to a Willgerodt-Kindler reaction. This same ketone, reduced by Huang-Minlon's modification of the Kishner-Wolff method, yielded a homolog of V, 6-tert-*butyl*-2-ethylnaphthalene, as a low-melting, well-crystallized hydrocarbon.

The outstanding lipoid-solubility and tensioactive properties attached to the presence of a β-*tert*-butylnaphthyl group led us to prepare, for biological exami-



nation, several nitrogen-containing heterocyclic compounds derived from the readily accessible 6-*tert*-butyl-2-acetonaphthone. Fischer cyclization of the latter's phenylhydrazone yielded 2-(6-*tert*-butyl-2-naphthyl)indole (X); Tschitschibabin condensation (7) of 6-*tert*-butyl-2-ω-bromoacetonaphthone with α-picoline and 2,4-lutidine gave highly tensioactive quaternary pyridinium compounds which readily underwent cyclization to 2-(6-*tert*-butyl-2-naphthyl)pyrrocoline (XI) and 7-methyl-2-(6-*tert*-butyl-2-naphthyl)pyrrocoline (XII) respectively. Pfitzinger reactions with ketone IX yielded 2-(6-*tert*-butyl-2-naphthyl)cinchoninic acid (XIII) and its 6-substituted derivatives; the alkali salts of these atophan-like acids formed soapy aqueous solutions, and were readily soluble in organic solvents. They are being tested as less toxic substitutes for atophan.



XIII R = H
XIV R = CH_3
XV R = Br

EXPERIMENTAL

Preparation of intermediates. β-*tert*-Butylnaphthalene was prepared according to the literature (8), and sulfonated at about 90° as for the preparation of 6-methyl- and 6-ethylnaphthalene-2-sulfonic acid from β-methyl- and β-ethyl-naphthalene (2, 9). Sodium 7-*tert*-butylnaphthalene-2-sulfonate thus obtained formed a colorless microcrystalline powder with a bitter taste; its alkaline fusion was performed according to Contractor, Peters, and Rowe (3), and yielded *7-tert-butyl-2-naphthol* (III), in the form of a thick, pale yellow oil, b.p. 195°/20 mm., with properties corresponding to those reported by the foregoing authors for their "6-*tert*-butyl-2-naphthol."

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.0.
Found: C, 83.7; H, 8.2.

2-tert-Butyldinaphtho[2,1,2',3']furan-8,13-dione (IV). A mixture of 2 g. of the foregoing naphthol, 2 g. of 2,3-dichloro-1,4-naphthoquinone, and 20 ml. of pyridine was refluxed for six hours. The precipitate (3.2 g.) obtained on cooling crystallized from benzene as silky, orange-yellow needles, m.p. 283°, giving a greenish-blue coloration with sulfuric acid.

Anal. Calc'd for $C_{24}H_{18}O_3$: C, 81.4; H, 5.1.
Found: C, 81.6; H, 5.3.

tert-Butylation of β-methylnaphthalene. To a mixture of 395 g. (2.78 moles) of β-methylnaphthalene and 262 g. (2.88 moles) of *tert*-butyl chloride, 12 g. of finely powdered aluminum chloride was added in small portions with shaking. When the reaction had subsided, the mixture was poured onto ice, and the organic layer was taken up in benzene, washed with dilute hydrochloric acid, and dried over sodium sulfate. Vacuum-fractionation yielded 435 g. of a colorless hydrocarbon, b.p. 158–160°/14 mm., n_D^{24} 1.5799, giving a picrate which crystallized from ethanol as silky, orange-yellow needles, m.p. 112°.

Anal. Calc'd for $C_{15}H_{18}$: C, 91.0; H, 9.1.
Found: C, 91.3; H, 9.2.

6-tert-Butyl-2-bromomethylnaphthalene (VI). A mixture of 19.8 g. of the foregoing hydrocarbon, 17 g. of N-bromosuccinimide, and 0.5 g. of benzoyl peroxide in 250 g. of dry carbon tetrachloride was refluxed for 15 hours. After cooling and filtration, the filtrate was washed twice with a dilute aqueous solution of sodium hydroxide, then with water, and dried over sodium sulfate. After removal of the solvent, the residue was vacuum-fractionated, yielding 21 g. of a portion boiling at 135–145°/0.75 mm., which crystallized from methanol as silky, colorless, lachrymatory needles, m.p. 90–91°.

Anal. Calc'd for $C_{15}H_{17}Br$: C, 65.0; H, 6.1.

Found: C, 65.1; H, 6.4.

6-tert-Butyl-2-naphthaleneacetonitrile (VII). A solution of 9.5 g. of 6-*tert*-butyl-2-bromomethylnaphthalene in 100 ml. of acetone was mixed with a solution of 5.6 g. of potassium cyanide and 1 g. of sodium iodide in 8 ml. of water. After 20 hours' refluxing, the solvent was distilled off, the residue treated with water, and the nitrile taken up in benzene and purified by vacuum-distillation. Yield: 5 g. of a product, b.p. 216–218°/14 mm., crystallizing from cyclohexane as shiny colorless prisms, m.p. 72°.

Anal. Calc'd for $C_{16}H_{17}N$: C, 86.1; H, 7.6.

Found: C, 86.3; H, 7.7.

6-tert-Butyl-2-naphthaleneacetic acid (VIII). (*a*) A mixture of 4 g. of the foregoing nitrile and 100 ml. of a 10% solution of potassium hydroxide in aqueous ethanol was refluxed for 60 hours. After removal of the solvent, water was added, the neutral impurities were removed by extraction with ether, and the aqueous layer was acidified with hydrochloric acid. Yield, 4 g. of a product crystallizing from benzene as slim, colorless needles, m.p. 173°.

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

Found: C, 79.2; H, 7.4.

(*b*) A mixture of 22 g. (0.1 mole) of 6-*tert*-butyl-2-acetonaphthone, 15 g. (0.17 mole) of morpholine, and 5.5 g. (0.17 g.- atom) of sulfur was gently refluxed for 16 hours. The reaction product was poured into cold ethanol, and the precipitated resinous material refluxed for 18 hours with a 10% solution of potassium hydroxide in aqueous ethanol. After the usual treatment, 17 g. of an acid was obtained, crystallizing from benzene as colorless prisms, m.p. 173°. No depression of the m.p. was observed on admixture with a sample of the acid prepared as in the foregoing section.

2-(6-tert-Butyl-2-naphthyl)indole (X). A mixture of 5 g. of 6-*tert*-butyl-2-acetonaphthone and 5 g. of phenylhydrazine was heated at 140–150° until no more water evolved; the crude solid phenylhydrazone thus obtained was treated with 10 g. of freshly fused powdered zinc chloride, and the mixture cautiously was heated above 200°, until a vigorous reaction set up. After cooling, the reaction product was treated with an aqueous solution of acetic acid, and the indole formed was taken up in benzene. The residue from the evaporation of benzene (7 g.) crystallized from a mixture of ethanol and benzene as silky, colorless, sublimable leaflets, m.p. 237°.

Anal. Calc'd for $C_{22}H_{21}N$: C, 88.3; H, 7.1.

Found: C, 88.3; H, 7.2.

6-tert-Butyl-2-ω-bromoacetonaphthone. A cooled solution of 5 g. of 6-*tert*-butyl-2-acetonaphthone in 50 ml. of dry chloroform was treated dropwise with 3.5 g. of bromine (dissolved in chloroform) in the presence of traces of aluminum chloride. The chloroform solution was washed with dilute aqueous hydrochloric acid, then with water, and dried over sodium sulfate. After removal of the solvent, the solid obtained was recrystallized from methanol, giving colorless prisms (7 g.), m.p. 86°.

Anal. Calc'd for $C_{16}H_{17}BrO$: C, 63.0; H, 5.6.

Found: C, 63.2; H, 5.8.

2-(6-tert-Butyl-2-naphthyl)pyrrocoline (XI). A solution of 3 g. of the foregoing bromo ketone and 3 g. of α-picoline in 10 ml. of ethanol was heated at 60–70° for one hour; after cooling, ether was added, which caused the precipitation of the quaternary picolinium derivative as an oil which dissolved in water to give a foamy solution. To this solution, 5 g. of sodium hydrogen carbonate was added, and the mixture was brought to the boil. After

cooling, the precipitate formed was collected, dried, and recrystallized from a mixture of ethanol and benzene. Yield, 3.5 g. of shiny colorless leaflets, m.p. 178°.

Anal. Calc'd for $C_{22}H_{21}N$: C, 88.3; H, 7.1; N, 4.7.

Found: C, 88.1; H, 7.0; N, 4.5.

7-Methyl-2-(6-tert-butyl-2-naphthyl)pyrrocoline (XII) was similarly prepared in almost quantitative yield from 2,4-lutidine; it formed from benzene shiny colorless leaflets, m.p. 175°, sparingly soluble in ethanol.

Anal. Calc'd for $C_{23}H_{23}N$: C, 88.2; H, 7.3; N, 4.5.

Found: C, 88.1; H, 7.5; N, 4.4.

2-(6-tert-Butyl-2-naphthyl)cinchoninic acid (XIII). A solution of 4.6 g. of the ketone, 3 g. of isatin, and 3.4 g. of potassium hydroxide (dissolved in 2 ml. of water) in 20 ml. of ethanol was refluxed for 12 hours. The reaction product was diluted with 200 ml. of water and acidified with acetic acid; the yellow precipitate formed was collected, washed with water, and recrystallized from ethanol. Yield, 6 g. of silky colorless prisms, m.p. 250–251°, giving soapy solutions in aqueous alkaline solutions.

Anal. Calc'd for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.9; N, 3.9.

Found: C, 81.0; H, 6.1; N, 4.0.

6-Methyl-2-(6-tert-butyl-2-naphthyl)cinchoninic acid (XIV) was similarly obtained in 90% yield from 4.6 g. of ketone IX, 3.3 g. of 5-methylisatin, and 3.4 g. of potassium hydroxide in ethanol. It crystallized from ethanol as shiny colorless needles, m.p. 241°. The alkali salts of this acid were highly soluble in ether and chloroform.

Anal. Calc'd for $C_{25}H_{23}NO_2$: C, 81.3; H, 6.2.

Found: C, 81.1; H, 6.3.

6-Bromo-2-(6-tert-butyl-2-naphthyl)cinchoninic acid (XV) was prepared in 80% yield from 4.6 g. of ketone IX, 4.5 g. of 5-bromoisatin, and 3.4 g. of potassium hydroxide in ethanol. It formed from a mixture of ethanol and benzene shiny, pale yellow prisms, m.p. 273°.

Anal. Calc'd for $C_{24}H_{20}BrNO_2$: C, 66.4; H, 4.6.

Found: C, 66.1; H, 4.8.

6-tert-Butyl-2-ethylnaphthalene. A mixture of 18 g. of ketone IX, 30 g. of 85% hydrazine hydrate, and 50 ml. of diethylene glycol was refluxed for 15 minutes; after cooling, 30 g. of potassium hydroxide was added, and the mixture was heated with removal of water up to 200°, and refluxed for a further two hours. After cooling and dilution with water, the hydrocarbon formed was taken up in benzene, washed with dilute hydrochloric acid, and purified by vacuum-distillation. Yield, 15 g. of a colorless hydrocarbon, b.p. 171–172°/16 mm., $n_D^{21.5}$ 1.5733, which crystallized from petroleum ether as long prisms, m.p. 33°.

Anal. Calc'd for $C_{16}H_{20}$: C, 90.6; H, 9.4.

Found: C, 90.3; H, 9.6.

The corresponding *picrate* crystallized from ethanol as silky, orange-yellow needles, m.p. 82°.

Anal. Calc'd for $C_{22}H_{23}N_3O_7$: N, 9.5. Found: N, 9.8.

SUMMARY

1. *β-tert*-Butylnaphthalene is shown to be sulfonated at position 7 under conditions which bring about sulfonation at position 6 in the case of β-methyl- and β-ethyl-naphthalene

2. *tert*-Butylation of β-methylnaphthalene in the presence of aluminum chloride is shown to yield predominantly 6-*tert*-butyl-2-methylnaphthalene

3. In the course of this research, several derivatives of *β-tert*-butylnaphthalene of potential pharmacological interest have been prepared.

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REFERENCES

(1) BUU-HOÏ, LE BIHAN, AND RAYET, *J. Org. Chem.*, **15**, 1060 (1950).
(2) DZIEWONSKI, SCHOENOWNA, AND WALDMANN, *Ber.*, **58**, 1213 (1925).
(3) CONTRACTOR, PETERS, AND ROWE, *J. Chem. Soc.*, 1993 (1949).
(4) BUU-HOÏ, *J. Chem. Soc.*, 489 (1952).
(5) BUU-HOÏ AND DEMERSEMAN, *J. Chem. Soc.*, (1952), *in press*.
(6) SHREVE AND LUX, *Ind. Eng. Chem.*, **35**, 306 (1943).
(7) TSCHITSCHIBABIN, *Ber.*, **60**, 1607 (1927).
(8) FIESER AND PRICE, *J. Am. Chem. Soc.*, **58**, 1841 (1936); BUU-HOÏ AND CAGNIANT, *Rev. sci.*, **80**, 271 (1942).
(9) LEVY, *Compt. rend.*, **202**, 1679 (1936).