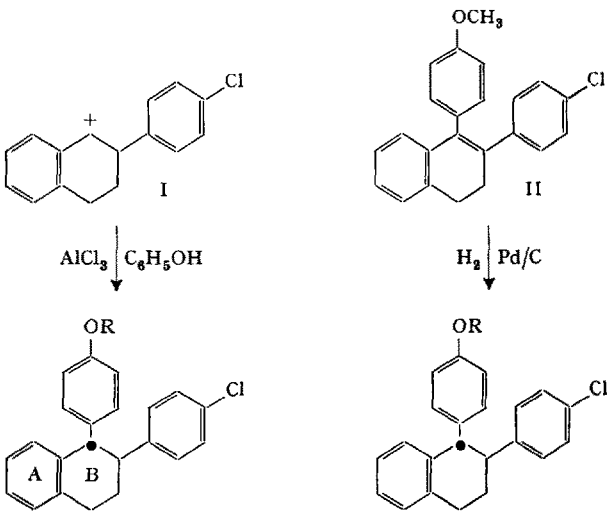
Synthetic Estrogens and Implantation Inhibitors

Several years ago a program was initiated in our laboratories which had as its goal the synthesis of selective hydroxylase inhibitors. One aspect of this work involved the preparation of dihydro- and tetrahydronaphthalene derivatives which preferentially blocked the 11β- or the 17α- hydroxylase systems in the biosynthesis of adrenal cortical and gonadal steroid hormones[1]. More recently we have reported on the uterotrophic activity of a series of phenolic 3,4-dihydro-1,2-diarylnaphthalenes[2]. It is the purpose of this communication to outline the synthesis and biological activity of selected *cis* and *trans* isomers of 1,2,3,4-tetrahydro-1,2-diarylnaphthalene derivatives.

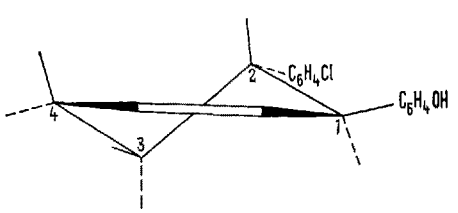
Friedel-Crafts type alkylation of phenol by means of the carbonium ion produced by the action of a Lewis acid (e.g. $AlCl_3$) on 1-hydroxy-2-*p*-chlorophenyl-1,2,3,4-tetrahydronaphthalene (I) resulted in a mixture of phenolic products from which the *trans* form of the desired phenolic substance III was isolated. The *cis* compound IV was more conveniently accessible by demethylation of compound VI which, in turn, was obtained by catalytic reduction of the dihydronaphthalene derivative II[3].

The stereochemical assignment of IV (*cis* configuration) was made on the basis of its mode of formation, i.e. *cis* addition of hydrogen by catalytic reduction of an olefin. Moreover, the NMR-spectrum of this compound gave a coupling constant of 5 c/s for the C_2 hydrogen which was a broad doublet at 4.35 δ. This is indicative of an axial equatorial relationship, although a strict conformational assignment for this isomer is not unequivocal. On the other hand, NMR was very useful in determining the conformation of the *trans* compound III. The C_1 hydrogen for this substance is a broad doublet at 4.12 δ. The coupling constant, $J_{1,2}$, for III is approximately 10 c/s, which establishes the *trans* diaxial relationship of the $C_{1,2}$ hydrogens for which there is ample evidence[4]. Assuming ring B to be in the pseudo-chair form, then the conformation of *trans* compound III is as illustrated in the Figure[5].



III R = H
V R = CH_3
VII R = $CH_2CH_2N(C_2H_5)_2$

IV R = H
VI R = CH_3
VIII R = $CH_2CH_2N(C_2H_5)_2$



Conformation of Compound III

Etherification of phenol III, m.p. 141–142°, in a mixture of dimethylformamide toluene 1:1 at room temperature with methyl iodide furnished the methyl ether V, m.p. 140–141°. The basic ether VII, m.p. 78–79°, was obtained via alkylation of III with diethylaminoethylchloride.

The action of the Grignard reagent, *p*-methoxyphenylmagnesiumbromide on 2-*p*-chlorophenyl-1-tetralone yielded, on dehydration, II, m.p. 160–162°. Its extended conjugation was indicated in the UV-absorption spectrum λ_{max} 232 and 305 mμ (ε 18,160 and 16,060 in ethanol). Catalytic reduction of II in ethyl acetate at atmospheric pressure yielded compound VI, m.p. 108–110°, which was demethylated in pyridine hydrochloride at 230–250° to afford phenol IV, m.p. 150–153°. An admixture of the *trans* (III) and *cis* (IV) isomers melted at 134–152°. The basic ether VIII, b.p. 305–310°/760 mm (uncorrected) was prepared from the *cis* phenol IV according to the above outlined procedure.

Biological activity. Phenols III and IV elicited a marked uterotrophic response in immature female rats, the *trans* form III being active at a dose of 2 γ/rat. The basic ether VII offered complete protection against pregnancy at an oral dose of 20 γ/kg/day (approximately 4 γ/rat/day) given to female rats for four consecutive days starting with the day of mating. Only partial antifertility effect was demonstrable when the compound was given as a single oral dose (200 γ/kg) on the fourth day after mating. This pattern of activity is suggestive of inhibition of nidation of the fertilized ovum. Two 3,4-dihydronaphthalene derivatives were reported to inhibit implantation in the rat by DUNCAN et al.[6].

Zusammenfassung. Ausgewählte *cis*- und *trans*-Isomere, Derivate des 1,2,3,4-Tetrahydro-1,2-diphenylnaphthalins, wurden beschrieben. Der basische Äther VII blokkierte die Nidation in der Ratte bei einer täglichen Dosis von 20 γ/kg per os.

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CIBA Pharmaceutical Company, Summit (New Jersey USA), January 11, 1965.

[1] W. L. BENCZE and L. I. BARSKY, J. Med. Pharm. Chem. *5*, 1298 (1962).

[2] W. L. BENCZE, L. I. BARSKY, W. P. SOPCHAK, A. A. RENZI, N. HOWIE, and J. J. CHART, J. Med. Pharm. Chem. *8*, 213 (1965).

[3] In the series in which the 2-phenyl group was unsubstituted, it was possible to isolate the *cis* isomer from the alkylation reaction mother liquor. This isomer is identical to the *cis* isomer obtained by catalytic reduction of 1-(*p*-methoxyphenyl)-2-phenyl-3,4-dihydronaphthalene. Its NMR spectrum corresponded very closely to the spectrum of IV.

[4] T. GILCHRIST, R. HODGES, and A. L. PORTE, J. chem. Soc. *1962*, 1780.

[5] The possible conformation of the *cis* compound IV will be discussed in detail in a forthcoming publication.

[6] G. W. DUNCAN, S. C. LYSTER, J. J. CLARK, and D. LEDNICER Proc. Soc. exp. Biol. Med. *112*, 439 (1963).