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THE NUCLEOPHILIC AROMATIC PHOTOSUBSTITUTION IN PHOTOAFFINITY LABELLING. A MODEL STUDY OF A CYCLOHEXIMIDE DERIVATIVE.

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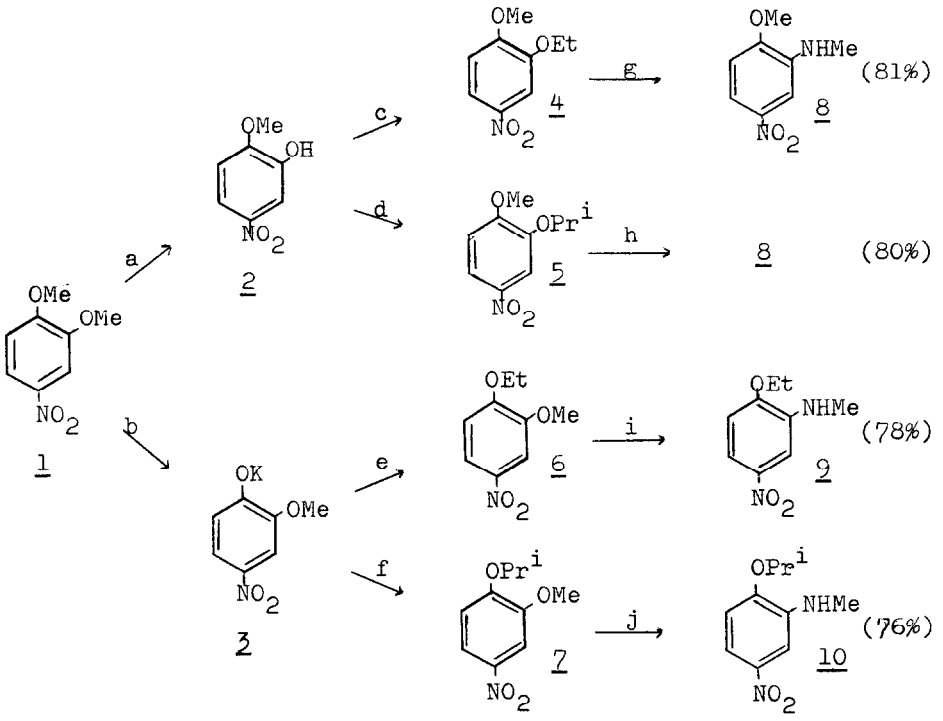
Summary: The photoreactions of several 4-nitrocatechol ethers with the relatively hard nucleophile methylamine occurs at the meta position respect to the nitro group. A derivative of the antibiotic cycloheximide carrying a 4-nitrocatechol ether moiety reacts with methylamine affording an in vitro model for photoaffinity labelling.

Photoaffinity labelling has been extensively used in the study of biological receptor sites[1], aryl azides, diazocompounds and aromatic ketones being the classical reagents used as photolabile moieties. Cantor et al.[2] suggested the use of nitrophenyl ethers[3]. These compounds are inert in the dark at room temperature, but under UV light (>300 nm) they react with nucleophiles in the so called aromatic nucleophilic photosubstitution, which has been extensively studied by Cornelisse and Havinga[4]. Recently, two rationalizations of the orientation in such photoreactions have appeared[5,6]. The orientation of the nitro group depends on the nucleophile hardness. Hard nucleophiles prefer to attack at the meta position while soft nucleophiles including aromatic amines, react at the para position[5-13].

We want now to report that 4-nitrocatechol ethers, namely 2-ethoxy-1--methoxy-4-nitrobenzene, 4 (m.p. 98-99°)[14], 2-isopropoxy-1-methoxy-4-nitrobenzene, 5 (m.p. 77-78°, Lit[15] m.p. 83°), 1-ethoxy-2-methoxy-4-nitrobenzene, 6 (m.p. 85-88° Lit[16] m.p.85°), and 1-isopropoxy-2-methoxy-4-nitrobenzene, 7 (m.p. 48-50°, Lit[15] m.p. 53°), react with the relatively hard methylamine under irradiation (400W medium pressure Hg lamp and pyrex filter) at the meta position respect to the nitro group. The ethers were prepared as

indicated in scheme 1. The starting material was 4-nitroveratrole, 1, which under irradiation in an aqueous solution of sodium hydroxide gave 2-hydroxy--1-methoxy-4-nitrobenzene 2.[17] The salt 3 was prepared as previously described[18].

Scheme 1



a.- hν/NaOH/H_2O/15h. b.- KOH/H_2O/ref./19h. c.- BrEt/Na_2CO_3/acetone/ref. d.- $BrPr^i$/Na_2CO_3/acetone/ref. e.- BrEt/DMF/ref./4h. f.- $BrPr^i$/DMF/ref./4h. g,h,i,j.- H_2O/MeOH/hν/4h/$MeNH_2$

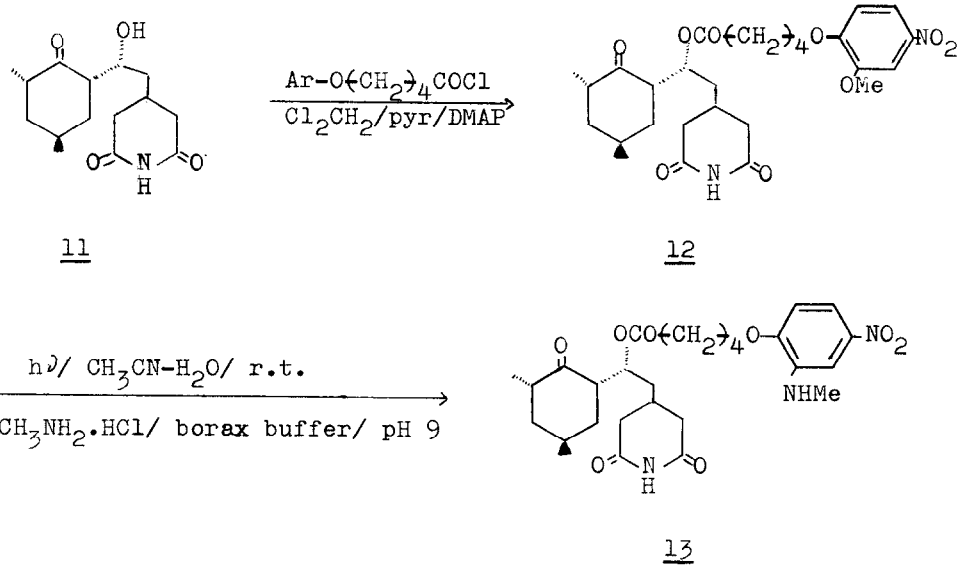
The photosubstitutions occurred in high yields to afford N-methyl-2--methoxy-5-nitroaniline, 8 (m.p. 84-85°, Lit[19] m.p. 86-87°), N-methyl-2-ethoxy-5-nitroaniline, 9 (m.p. 110°)[14] and N-methyl-2-isopropoxy-5-nitroaniline, 10 (m.p. 38°)[14]. Minor amounts of products arising from para--substitution (methylamine as nucleophile) and phenols from meta-substitution due to hydroxide ion acting as nucleophile, were also observed. According with the results of the scheme 1, the leaving group has no influence either on the orientation or on the yield.

However, although dimethylamine and other secondary amines (softer reagents than methylamine) reacted with 4-nitroveratrole at the para position [6], preliminary results indicate that with 4, 5, 6, and 7 as substrates a

dramatic drop in the yield is observed, which makes irrelevant any discussion on the orientation effect in these reactions. It must be pointed out that the excited states of aromatic rings are not planar[20], the deviation from planarity being larger for the triplet states, postulated intermediates in the nucleophilic aromatic photosubstitution reaction[4b], than for the corresponding singlets.

Cycloheximide, 11, is an antibiotic of the glutarimide family that acts at the ribosome level[21]. We have prepared cycloheximide 5-(2-methoxy-4--nitro)phenoxypentanoate, 12 (m.p. 114-116°)[14] as indicated in scheme 2. We can assume that once an antibiotic is fixed in the active site, the local concentration of nucleophiles should be high. Therefore we have irradiated 12 with a large excess of methylamine under the conditions shown in scheme 2.

Scheme 2



The reaction gave, among other minor products, a 56% yield of cycloheximide 5-(2-methylamino-4-nitro)phenoxypentanoate, 13 (m.p. 144-147°)[14], a sample of which was isolated and fully characterized. This experiment demonstrates the potentiality of nitrophenyl ethers as photoaffinity probes to identify biological receptor sites.

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