3,5-DI-*tert*-BUTYL-1,2-BENZOQUINONE CLEAVES A CC-BOND IN VICINAL AMINOBENZYL ALCOHOLS

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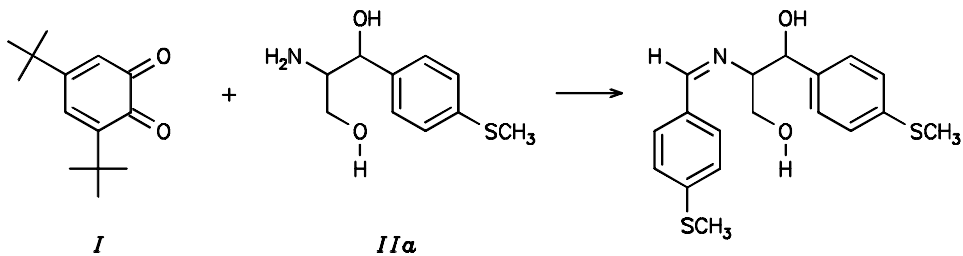
Dedicated to Dr Arnold Brossi on the occasion of his 70th birthday.

Two vicinal aminobenzyl alcohols, L-*threo*-1-(4-methylthiophenyl)-2-amino-1,3-propanediol (*IIa*) and 1-phenyl-2-amino-1,3-propanediol (*IIb*), underwent, under mild conditions, CC-bond cleavage with 3,5-di-*tert*-butyl-1,2-benzoquinone (*I*) producing in high yields 4-methylthiobenzaldehyde (*Va*) and benzaldehyde (*Vb*), respectively, and 2-hydroxymethyl-4,6-di-*tert*-butylbenzoxazole (*VII*). Ethanolamine (*VIII*) under identical conditions produced benzoxazole *VII*. The reported reaction is a second case in which quinone *I* mimics reactions of pyridoxal.

The Corey's reagent, 3,5-di-*tert*-butyl-1,2-benzoquinone (*I*), produces from *sec*-alkyl primary amines the respective ketones via an oxidative deamination mechanism[1,2]. The same reagent with L-*threo*-1-(4-methylthiophenyl)-2-amino-1,3-propanediol (*IIa*), an intermediate in the synthesis of the antibiotic Thiamphenicol, produced, when used in equimolar ratio, a Schiff base derived from *IIa* and 4-methylthiobenzaldehyde, L-*threo*-1-(4-methylthiophenyl)-2-(4-thiomethylbenzylidenimino)-1,3-dihydroxypropane (*III*) as the primary product (Scheme 1).



I *IIa* *III*

SCHEME 1

However, when *I* and *IIa* were used in 2 : 1 molar ratio, 4-methylthiobenzaldehyde (*Va*, 95%), 2-hydroxymethyl-4,6-di-*tert*-butylbenzoxazole (*VII*, 91%), and *I* (98%) were isolated as the products. Compounds *VII* and *I* were separated using chromato-

graphy on a preparative silica gel thin layer plate with hexane–methylene chloride (3 : 1). Compound *Va* was isolated and determined gravimetrically as 2,4-dinitrophenylhydrazone (m.p. 239 – 245 °C). In an analogous experiment 1-phenyl-2-amino-1,3-propanediol (*IIb*) produced *VII* (95%), *I* (93%), and benzaldehyde (*Vb*) (as 2,4-dinitrophenylhydrazone, 91%). Benzoxazole *VII* was the only product isolated in 54% yield when ethanolamine (*VIII*) was reacted with quinone *I*. Thus, unlike *sec*-alkyl primary amines, vic-amino alcohols *IIa* and *IIb* reacted with *I* under cleavage of a CC-bond (Scheme 2). Since ethanolamine (*VIII*) did not undergo such reaction, the benzylic character of the hydroxy group seems to be essential. In the experiment in which equimolar ratio of the reactants was used, the formation of the Schiff base *III* suggested competition between the quinone *I* and the benzaldehyde *Va*, formed in the early stages of the process, for the amino alcohol *IIa*. Trapping in form of a poorly soluble Schiff base allowed only portion (approximately 50%) of *IIa* to be reacted with *I*. Using twofold excess of the quinone, however, the competitive reaction involving the benzaldehyde is suppressed and the reaction with the quinone predominates providing quantitative yields of the cleavage products.

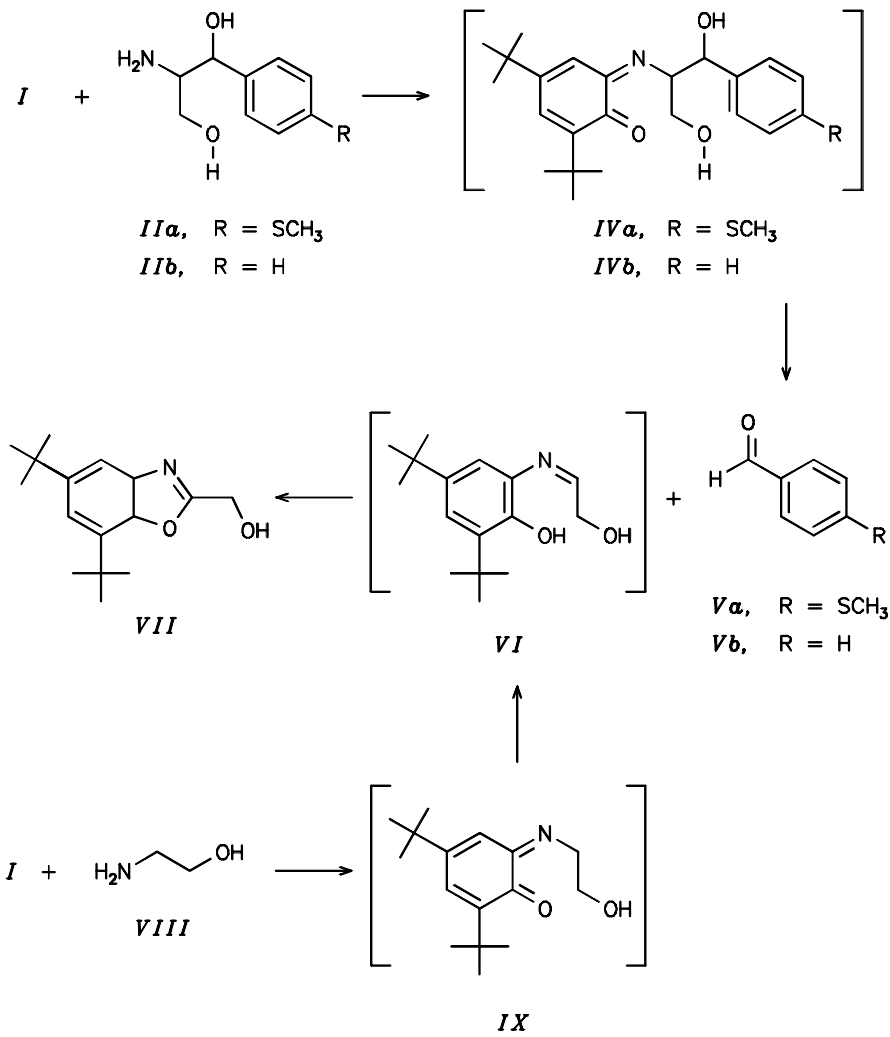
The likely second fragment of the cleavage reaction is a Schiff base *VI* which is derived from 2-hydroxy-3,5-di-*tert*-butylaniline and hydroxyacetaldehyde (Scheme 2). Followed by cyclization to a benzoxazoline intermediate and by dehydrogenation with the second mole of the quinone the Schiff base renders ultimately the substituted benzoxazole *VII*. The question about quinone *I* being found rather than the expected 3,5-di-*tert*-butylcatechol (*X*) was answered successfully when chromatography of *X* on a preparative thin layer silica gel plate rendered *I* in a quantitative yield. Evidently, the active surface of the silica gel catalyzed the autooxidation of *X* to *I*.

Unlike aminobenzyl alcohols *II*, the mechanism of the reaction of ethanolamine *VIII* with *I* involves a prototropic shift similar to that postulated for the mechanism of the oxidative deamination of *sec*-alkyl primary amines. This step is followed by a ring closure and dehydrogenation to produce benzoxazole *VII* as the final product (Scheme 2).

Together with the oxidative deamination of *sec*-alkyl primary amines the reported CC-bond cleavage (Scheme 2) is another reaction in which 3,5-di-*tert*-butyl-1,2-benzoquinone (*I*) mimics properties of pyridoxal[3]. In the latter application it complements other fine reagents which are used for cleavage of vicinal amino alcohols such as periodic acid[4] and lead tetraacetate[5]. The advantage of the newly reported process is in its selectivity that allows its application even in the presence of a sulfidic sulfur that is readily oxidized to a sulfoxide group with either the periodic acid or lead tetraacetate. On the other hand, the use of 3,5-di-*tert*-butyl-1,2-benzoquinone (*I*) reagent is limited to vicinal amino alcohols with the hydroxyl occupying the benzylic position.

EXPERIMENTAL

The melting points were determined on a Fisher–Johns melting point apparatus. The IR spectra (ν, cm^{-1}) were taken on a Mattson Instruments 2020 Galaxy Series FT-IR. The ^1H NMR spectra (δ, ppm) were collected on a Bruker 300 MHz NMR spectrometer in hexadeuteriodimethyl sulfoxide. For preparative layer chromatography Baker Silica Gel IB-F 20 × 20 cm plates were used. Amino alcohol *IIa* was kindly donated by Zambon Pharmaceutical Co., Milano, Italy. All other reagents were products of Aldrich Co.



SCHEME 2

Reaction of 3,5-Di-*tert*-butyl-1,2-benzoquinone (*I*)
with L-*threo*-1-(4-Methylthiophenyl)-2-amino-1,3-propanediol (*IIa*)

a) Equimolar amounts of *I* (1.10 g, 5 mmol) and *IIa* (1.05 g, 5 mmol) were reacted for 12 h in ethanol at room temperature. The separated solid, L-*threo*-1-(4-methylthiophenyl)-2-(4-thiomethylbenzylidenimino)-1,3-dihydroxypropane *III* (0.560 g, 26%) was collected by vacuum filtration and dried at laboratory temperature. White needles, m.p. 158 – 162 °C. ^{1}H NMR spectrum: 8.13 s, 1 H; 7.69 d, 2 H; 7.29 d, 2 H; 7.27 d, 2 H; 7.17 d, 2 H; 5.11 d, 1 H; 4.63 t, 1 H; 4.41 t, 1 H; 3.40 q, 1 H; 3.30 t, 2 H; 2.50 s, 3 H; 2.44 s, 3 H. IR spectrum: 3 450 (O–H); 3 010 (aromatic C–H); 2 900 (aliphatic C–H); 1 593 (C=N).

b) Two molar equivalents of *I* (0.440 g, 2 mmol) were reacted with *II* (0.210 g, 1 mmol), in ethanol for 12 h. The reaction mixture was chromatographed on a preparative silica gel thin layer plate using hexane–methylene chloride (3 : 1). From well separated zones 2-hydroxymethyl-4,6-di-*tert*-butylbenzoxazole *VII* (0.238 g, 91%) was isolated. Light yellow crystals, m.p. 104 – 107 °C. MS (*m*/*z*): 261 ($C_{16}H_{23}O_2N$). ^{1}H NMR spectrum: 7.27 s, 1 H; 7.27 s, 1 H; 5.86 t, 1 H; 4.69 d, 2 H; 1.45 s, 9 H; 1.34 s, 9 H. IR spectrum: 3 235 (O–H); 2 967, 2 900, 2 900 (aliphatic, *t*-butyl C–H); 1 485 (C=N); 1 244, 1 098 (asym, sym C–O–C); 1 002 (prim. unsat. alcohol C–O).

From the second zone, quinone *I* (0.216 g, 98%) was recovered by extraction with ethanol. In a separate experiment 4-methylthiobenzaldehyde *Va* was precipitated from the reaction mixture with 2,4-dinitrophenylhydrazine (0.315 g hydrazone, 95%).

Reaction of 3,5-Di-*tert*-butyl-1,2-benzoquinone (*I*)
with 1-Phenyl-2-amino-1,3-propanediol (*IIb*)

Two molar equivalents of *I* (0.440 g, 2 mmol) were reacted with *IIb* (0.165 g, 1 mmol) in ethanol for 12 h. Procedure used with *IIa* rendered 2-hydroxymethyl-4,6-di-*tert*-butylbenzoxazole *VII* (0.248 g, 95%), quinone *I* (0.205 g, 93%), and benzaldehyde (*Vb*) (0.273 g hydrazone, 91%).

Reaction of 3,5-Di-*tert*-butyl-1,2-benzoquinone (*I*) with Ethanolamine

Two molar equivalents of *I* (0.440 g, 2 mmol) were reacted with ethanolamine (0.061 g, 1 mmol) in ethanol for 12 h. Procedure used with *IIa* rendered 2-hydroxymethyl-4,6-di-*tert*-butylbenzoxazole (0.141 g, 54%) and 3,5-di-*tert*-butyl-1,2-benzoquinone (*I*) (0.180 g, 82%).

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