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METALATION REACTIONS

III *. THE ACTION OF n-BUTYLLITHIUM ON 1,3-BENZODIOXOLE AND 1,3-BENZOXATHIOLE DERIVATIVES

S. CABIDDU, A. MACCIONI, P.P. PIRAS and M. SECCI
Istituto Chimico and Istituto di Chimica Farmaceutica e Tossicologica, Università, 09100 Cagliari (Italy)

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Summary

The reaction of n-butyllithium with 1,3-benzodioxole, 1,3-benzoxathiole, and their 2,2-dimethyl derivatives has been investigated. Except with 1,3-benzoxathiole there is competition between metalation and cleavage of the ether bond. Metalation occurs *ortho* to the oxygen, while cleavage gives substitution, elimination and reduction products.

Introduction

We previously showed that metalation of alkoxyalkylthiobenzenes takes place *ortho* to the alkoxyl group [2]. With 1-methoxy-2-(methylthio)benzene, however, side-chain metalation occurs [2].

We have now studied the reaction between n-butyllithium and 1,3-benzodioxole and 1,3-benzoxathiole derivatives in order to extend our previous studies on these compounds [3,4] and to throw light on conflicting reports in the literature [5,6]; thus while Gensler and Stouffer report that metalation of 1,3-benzodioxole is impossible because of the cleavage of both of the ether bonds with formation of 1,2-dihydroxybenzene [5], Ranade et al. report 5-substituted 1,3-benzodioxoles readily undergo metalation *ortho* to the oxygen atom [6].

Results and discussion

Treatment of 1,3-benzodioxole (I) with n-butyllithium (Scheme 1) gives, after carbonation, a mixture of 1,3-benzodioxole-4-carboxylic acid (V), 1,2-di-

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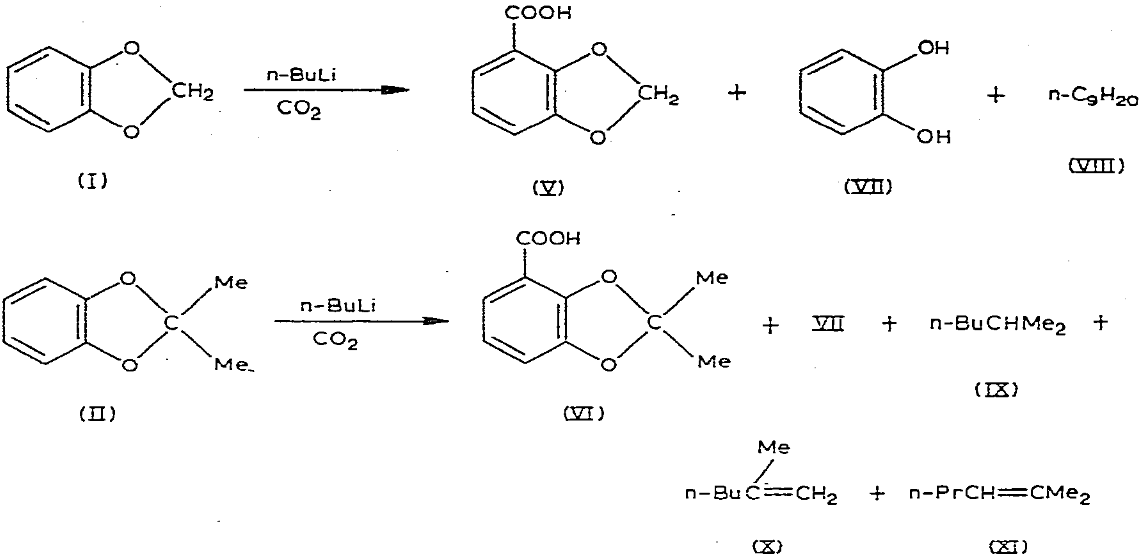
[*] For Part II see ref. 1.

hydroxybenzene (VII) and n-nonane (VIII) (VII and VIII being in equimolar amounts).

SCHEME 1



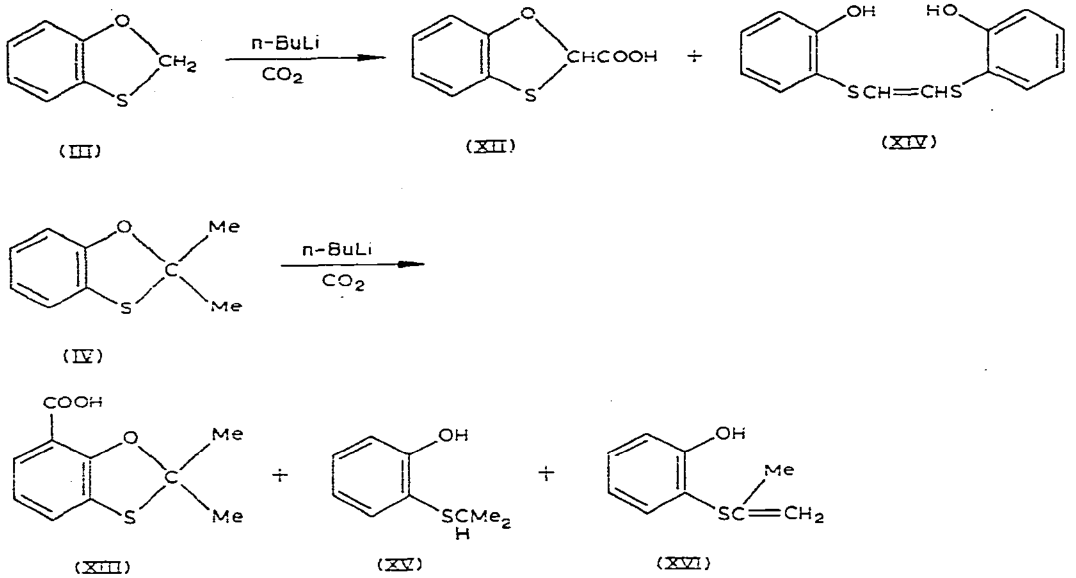
Similar results were obtained with 2,2-dimethyl-1,3-benzodioxole (II): 2,2-dimethyl-1,3-benzodioxole-4-carboxylic acid (VI) is the main product, along with smaller amounts of VII and an equimolar amount of a mixture of 2-methylhexane (IX), 2-methyl-1-hexene (X), 2-methyl-2-hexene (XI).

The simultaneous occurrence of addition and cleavage products is understandable since n-butyllithium can behave either as a Lewis acid [7] or as a metalating agent [2,8]. In the former case the ether bonds of the benzodioxole ring are attacked with formation of VII and hydrocarbons [3], while in the latter the aromatic ring is metalated. The products confirm that metalation mainly occurs at positions *ortho* to electron-withdrawing groups [8,9]. The behaviour of the organolithium reagent as a nucleophile, base, or hydride ion donor, accounts for the formation of hydrocarbons, as already noted for organomagnesium compounds [3].

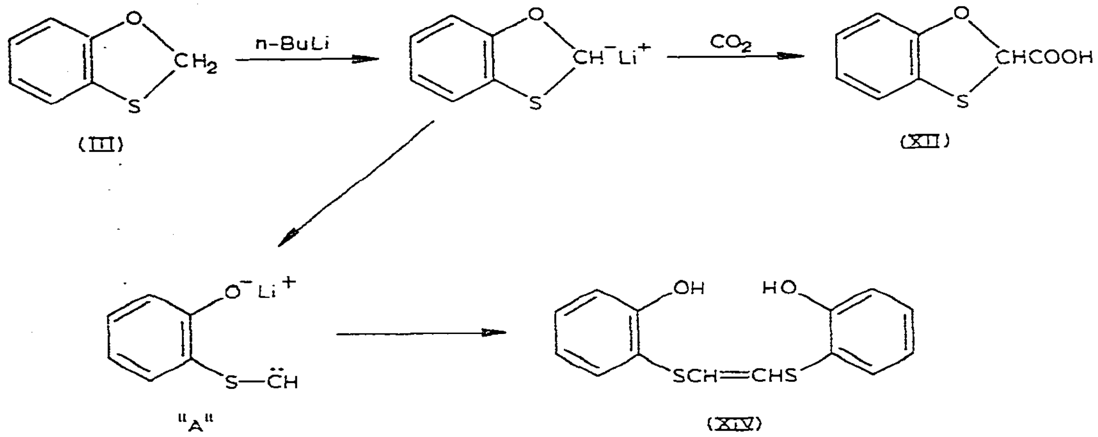
Metalation of 2,2-dimethyl-1,3-benzoxathiole (IV) (Scheme 2) gave after carbonation two fractions; only 2,2-dimethyl-1,3-benzoxathiole-7-carboxylic acid (XIII) was detected in the first fraction, while in the second 2-isopropylthiophenol (XV) and 2-isopropylidenethiophenol (XVI) were identified among several phenolic products.

Metalation of 1,3-benzoxathiole (III) (Scheme 2) gave 1,3-benzoxathiole-2-carboxylic acid (XII) and 1,2-bis[(*o*-hydroxyphenyl)thio]ethylene (XIV). The absence of products of carboxylation at the ring positions can be explained by assuming (Scheme 3) that the first step is the metalation of the methylene carbon of III. The lithium salt can than either react with carbon dioxide or undergo conversion into "A" and dimerization of "A" then gives the alkene XIV [10]. The metalation at the methylene position of compound III is consistent with

SCHEME 2



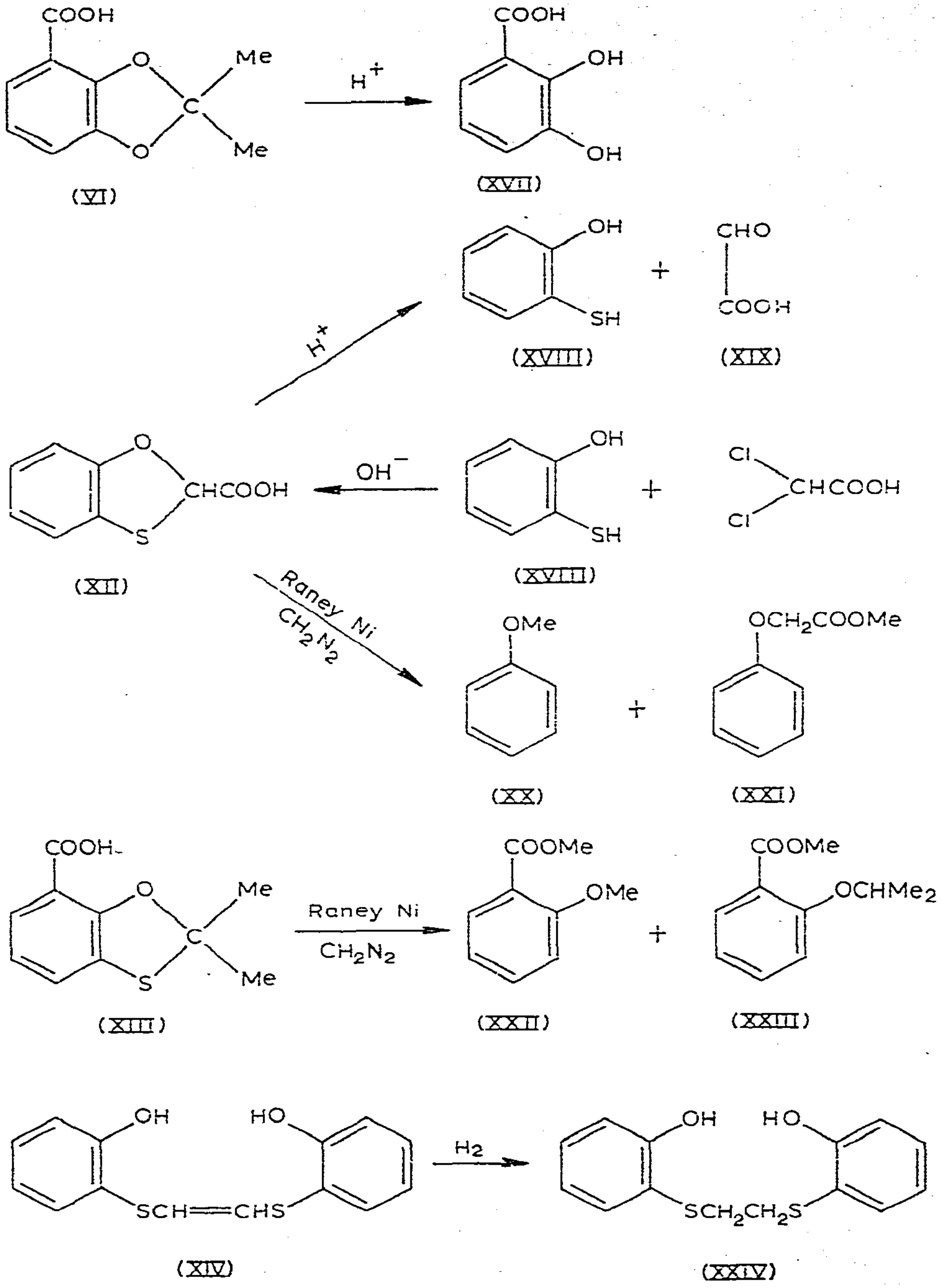
SCHEME 3



results from reaction of n-butyllithium with 1-methoxy-2-(methylthio)benzene [2].

The acid V is a well-characterized compound [11], and the structures of VI, XII, XIII and XIV have been determined from elemental analysis, spectroscopic data and by transforming them in known compounds (Scheme 4). Hydrolysis of VI gives 2,3-dihydroxybenzoic acid (XVII). Hydrolysis of XII gives 2-hydroxythiophenol (XVIII) and glyoxylic acid (XIX), while hydrogenolysis with Raney nickel [12] followed by treatment with diazomethane gives anisole (XX) and phenoxyacetic acid methyl ester (XXI). XII was also obtained by reaction of XVIII with dichloroacetic acid. Hydrogenolysis of XIII and subsequent treat-

SCHEME 4



ment with diazomethane, leads to 2-methoxybenzoic acid methyl ester (XXII) and 2-isopropoxybenzoic acid methyl ester (XXIII). Catalytic hydrogenation of XIV gives 1,2-bis[(*o*-hydroxyphenyl)thio]ethane (XXIV).

Experimental

General

Solutions of n-butyllithium in hexane were obtained from EGA-Chemie. All metalations were carried under dry, oxygen-free nitrogen [13]. Melting points were determined on a Tottoli apparatus and are uncorrected. Infrared spectra were recorded on a Perkin—Elmer Model 325 spectrophotometer using potassium bromide mulls. NMR spectra were recorded in deuteriochloroform on a JEOL C-60 HL spectrometer with hexamethyldisiloxane as internal standard. Mass spectra were measured with an Hitachi—Perkin—Elmer RMU-6D spectrometer at 70 eV. GLC analyses were performed with a Perkin—Elmer Model 881 gas-chromatograph, equipped with a flame ionization detector and a polyethylene glycol 20 M column, with N_2 as the carrier gas. Microanalysis for C and H were carried out on a Perkin—Elmer Model 240 Elemental Analyzer; analyses for S were by a published procedure [14,15].

Starting materials

1,3-Benzodioxole (I), 2,2-dimethyl-1,3-benzodioxole (II), 1,3-benzoxathiole (III) and 2,2-dimethyl-1,3-benzoxathiole (IV), were prepared by published methods [16—19].

Authentic samples

1,3-Benzodioxole-4-carboxylic acid (V), 2-isopropylthiophenol (XV), 2-isopropylidenethiophenol (XVI), 2-hydroxythiophenol (XVIII), phenoxyacetic acid methyl ester (XXI), 2-isopropoxybenzoic acid methyl ester (XXIII) and 1,2-bis[(*o*-hydroxyphenyl)thio]ethane (XXIV) were prepared by published methods [3,11,19—22]. 1,2-Dihydroxybenzene (VII), n-nonane (VIII), 2-methylhexane (IX), 2-methyl-1-hexene (X), 2-methyl-2-hexene (XI), 2,3-dihydroxybenzoic acid (XVII), glyoxylic acid (XIX), anisole (XX) and 2-methoxybenzoic acid methyl ester (XXII) were commercial products (EGA-Chemie).

1,3-Benzoxathiole-2-carboxylic acid (XII)

A solution of XVIII (80 mmol) and sodium hydroxide (200 mmol) in water (40 ml) was added dropwise with stirring to dichloroacetic acid (100 mmol). The mixture was heated for 10 h at 70—80° C, cooled, poured into water, and acidified with 10% hydrochloric acid. After extraction with chloroform, the chloroform solution was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was chromatographed on a silica gel column, using benzene/acetone (3/1) as eluent. Evaporation of the solvent gave compound XII; yield 25%, m.p. 119° C. (Found: C, 51.51; H, 3.31; S, 17.43. $C_8H_6O_3S$ calcd.: C, 52.74; H, 3.32; S, 17.60%.) ^1H NMR: δ 7.15 (m, 4H arom and 1H —C$\underline{H}$COOH) and 6.50 ppm (s, 1H, COOH, D_2O exchanged). IR: 3400 (OH), 1710 cm^{-1} (C=O).

Metalation of 1,3-benzodioxole (I)

A solution of I (32 mmol) in dry diethyl ether (50 ml) was treated dropwise at —10° C with 1.6 *M* n-butyllithium in hexane (35 mmol, 22 ml). When the addition was complete, the mixture was stirred under reflux for one hour. After cooling, it was added to crushed solid carbon dioxide, and after 24 h the residue was treated successively with 10% aqueous sodium bicarbonate and diethyl ether. The alkali layer was separated, washed with diethyl ether, acidified with cold concentrated hydrochloric acid, and extracted with chloroform. The combined extracts were dried over sodium sulphate, filtered, and concentrated in vacuo. The crude product was crystallized from ethanol, and identified as V by comparison (TLC, IR data and m.p.) with an authentic sample. Yield 41%; m.p. 230—233°C.

The ether phase was extracted with 10% aqueous sodium hydroxide, washed with water, dried (Na_2SO_4) and evaporated. The residue was identified as VIII by comparison (GLC) with an authentic sample; yield 45%. The sodium hydroxide layer was treated with 10% hydrochloric acid, extracted with diethyl ether and dried with sodium sulphate. After removal of the solvent under reduced pressure, the residue was identified as VII by comparison with an authentic sample. VII and VIII were obtained in equimolar amounts. The remaining component was the starting material.

Metalation of 2,2-dimethyl-1,3-benzodioxole (II)

A solution of II (32 mmol) in dry diethyl ether (50 ml) was treated dropwise at room temperature with n-butyllithium in hexane (35 mmol, 22 ml). The mixture was stirred under reflux for one hour and then worked up as described above.

From the bicarbonate phase the acid VI was obtained in 36% yield and was crystallized from ethanol, m.p. 158—159°C. (Found: C, 61.67; H, 5.14. $C_{10}H_{10}O_4$ calcd.: C, 61.85; H, 5.19%). ^{1}H NMR: δ 11.5 (s, 1H, COOH, D_2O exchanged), 7.10 (m, 3H arom) and 1.70 ppm (s, 6H, Me—C—Me). IR: 3100 (OH), 1690 (C=O), 740 cm^{-1} (1,2,3-trisubstituted benzene). From the ether phase a mixture of hydrocarbons was obtained, and these were identified by GLC as IX, X and XI, respectively, by comparison with authentic samples.

From the sodium hydroxide phase, VII was obtained in 31% yield. The combined yield of hydrocarbons IX, X and XI obtained was equal in molar terms to that of VII. The remaining component was unchanged starting material.

Hydrolysis of VI

A mixture of VI (10 mmol) and concentrated sulphuric acid (5 ml) was heated on a steam bath for 15 minutes and then poured into ice water. The precipitate was dried and identified as XVII; yield 90%, m.p. 215—216°C, undepressed on admixture with an authentic (commercial) sample.

Metalation of 1,3-benzoxathiole (III)

A solution of III (36 mmol) in dry diethyl ether (60 ml) was treated with n-butyllithium in hexane (39 mmol, 25 ml). The mixture was stirred at room temperature for 2 h and then added to crushed solid carbon dioxide. After 24 h the residue was diluted with diethyl ether and extracted with 10% aqueous sodium bicarbonate. The alkali layer was separated, washed with diethyl ether, acidified with cold concentrated hydrochloric acid and extracted with chloroform. After drying with sodium sulphate, the solvent was evaporated in vacuo and the crude product was crystallized from ethanol and identified as XII by comparison with an authentic sample. Yield 28%; m.p. 118—120°C.

The diethyl ether solution was extracted with 10% aqueous sodium hydroxide. The basic extract was treated with 10% sulphuric acid and extracted with diethyl ether, and the extract was dried over sodium sulphate. After solvent evaporation, the product was identified as 1,2-bis[(*o*-hydroxyphenyl)thio]ethylene (XIV). Yield 20%; crystallized from ethanol, m.p. 133—135°C. (Found: C, 60.50; H, 4.45; S, 23.01. $C_{14}H_{12}O_2S_2$ calcd.: C, 60.84; H, 4.38; S, 23.20%). ^{1}H NMR: δ 7.10 (m, 8 H arom), 6.10 (s, 2 H, OH, D_2O exchanged) and 5.70 ppm (s, 2 H, $C\underline{H}{=}C\underline{H}$). IR: 3410 (OH), 1675 cm^{-1} ($>C{=}C<$). Mass spectrum: *m/e* 276 $(M)^+$, 166, 151, 137, 126, 121. The remaining material was unchanged III.

Hydrolysis of XII

A mixture of XII (10 mmol), dimethyl sulfoxide (50 ml) and concentrated hydrochloric acid (12 ml) was gently refluxed for 30 minutes. After cooling, the solution was poured into water and extracted with diethyl ether. The ethereal layer was dried (Na_2SO_4) and evaporated to give pure XVIII in almost quantitative yield.

The aqueous phase was distilled in vacuo to give a viscous oil, which crystallized on standing, and was identified as glyoxylic acid (XIX), yield 85%; 2,4-dinitrophenylhydrazone, m.p. 190—191°C (dec.) [lit. [23]: m.p. 190°C (dec.)].

Action of Raney nickel catalyst on XII

A solution of XII (10 mmol) in 95% ethanol (10 ml) was refluxed for 2 h with 2 g of Raney nickel [12]. The mixture was filtered and evaporated. The residue was diluted with diethyl ether and treated with diazomethane. The GLC analysis showed two peaks with the same retention time as XX and XXI, respectively.

Hydrogenation of XIV

Compound XIV (5 mmol) in 95% ethanol (10 ml) was hydrogenated at atmospheric pressure over 5% palladium/carbon as catalyst. After filtration, the ethanol was evaporated in vacuo and the residue was identified as XXIV by comparison (IR and NMR) with an authentic sample. Yield 90%, m.p. 106—107°C.

Metalation of 2,2-dimethyl-1,3-benzoxathiole (IV)

A solution of IV (32 mmol) in dry diethyl ether (50 ml) was treated dropwise at room temperature with n-butyllithium in hexane (35 mmol, 22 ml). The mixture was worked up as described for I.

From the bicarbonate solution the acid XIII was obtained in 38% yield and was crystallized from ethanol; m.p. 138—140°C. (Found: C, 56.95; H, 4.65; S, 15.03. $C_{10}H_{10}O_3S$ calcd.: C, 57.12; H, 4.79; S, 15.25%). ^{1}H NMR: δ 13.55 (s, 1 H, COOH, D_2O exchanged), 7.40 (m, 3 H arom) and 2.00 ppm (s, 6 H, $\mathrm{Me}-\overset{\diagdown\,\diagup}{\mathrm{C}}-\mathrm{Me}$). IR: 3100 (OH), 1700 (C=O), 760 cm^{-1} (1,2,3-trisubstituted benzene).

The GLC analysis of the mixture from the sodium hydroxide phase showed several peaks, from which those of XV and XVI were identified. Starting material was recovered from the ether phase.

Action of Raney nickel catalyst on XIII

A solution of XIII (10 mmol), 95% ethanol (10 ml) and Raney nickel catalyst (2 g) was worked up as described above. GLC analysis of the products showed two peaks with the same retention times as XXII and XXIII.

Acknowledgement

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