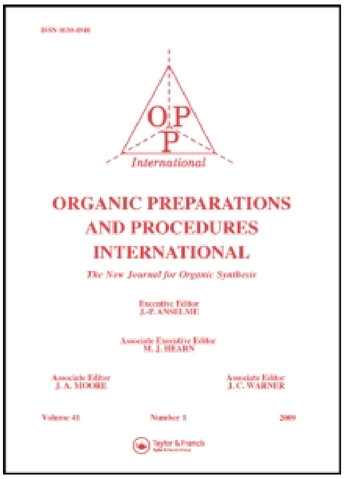

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CHLOROFORM-MEDIATED DDQ OXIDATION OF N-METHOXYSEPTORINOL, A SUBSTANCE ISOLATED FROM THE FUNGUS *SEPTORIA NODORUM* BERK

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CHLOROFORM-MEDIATED DDQ OXIDATION OF N-METHOXYSEPTORINOL, A SUBSTANCE ISOLATED FROM THE FUNGUS *SEPTORIA NODORUM* BERK

Submitted by
(06/14/93)

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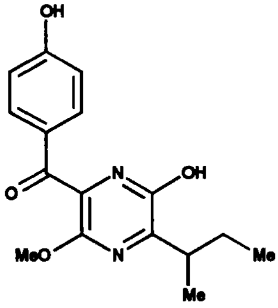
A group of three related metabolites, namely septorine (**1**), N-methoxyseptorine (**2**) and N-methoxyseptorinol (**3**), were isolated from the fungus *Septoria (Phaeosphaeria) nodorum* Berk, a common parasite of wheat. Compound **1** causes decoupling of mitochondria isolated from wheat coleoptile.[4] Total syntheses of *p*-O-methylseptorine[5] and of (+) **1**[6] were reported. Compound **2** was shown to be more potent biologically *in vitro* than **1**. Recently, **3** was isolated and a biosynthetic scheme was proposed according to which this substance was the precursor of **1** and **2**. Compound **3** is by far the most abundant of these three metabolites in the culture medium of *Septoria nodorum*. In order to obtain sufficient amounts of **2** for biological studies, a method for the oxidation of the benzylic alcohol portion of **3** to the carbonyl group was needed.



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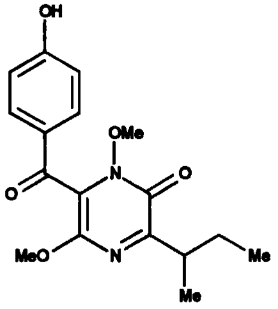
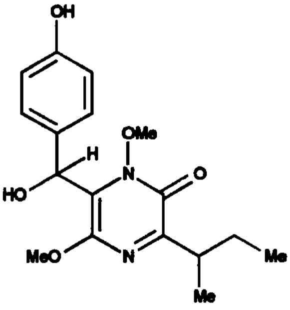


2



3

This oxidation became a real challenge due to the facile elimination of *p*-hydroxybenzaldehyde from **3**, thus making impossible to apply the classical methods of transformation of secondary alcohols into ketones. Among these methods, oxidation by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), appeared to be more amenable. However,attempts to carry out this reaction with THF or benzene as solvents under reflux only gave decomposition products. Poor yields accompanied by predominant formation of *p*-hydroxybenzaldehyde were observed for these reactions conducted at room temperature.

Previous works on the oxidation of benzylic alcohols by DDQ proposed a mechanism of dehydrogenation occurring through an intermediate charge transfer complex (CT).[7,8] In this scheme, chloroform was thought to produce a stabilizing effect on this charge transfer complex,thus increasing the yield of the oxidized substrate.

$$\text{DDQ} \quad + \quad \text{substrate} \quad \rightleftharpoons \quad [\text{CT}] \quad \longrightarrow \quad \text{DDQH}_2 \quad + \quad \text{substrate}^{ox}$$

Consequently,chloroform was choosen as solvent for the oxidation of **3** to **2** by DDQ at room temperature. To our surprise, slow but clean oxidation of **3** to **2** was observed. The yield of **2** after 4 days at 20° was 64% (isolation by preparative SiO_2 TLC, identification by comparing the physico-chemical data with those of the natural product). This result represents an argument in favour of the hypothesis concerning the mechanism of action of DDQ. Very likely, the oxidation of **3** occurs slowly at room temperature because of the steric hindrance of the secondary alcohol. This is supported by the rapid oxidation under the same conditions of 2-hydroxymethylindole to 2-indolecarboxaldehyde in a few minutes with a 100% yield.

In conclusion, it appears that the chloroform-mediated DDQ oxidation of benzylic alcohols to aldehydes or ketones may be an efficient and smooth method for conducting these reactions at room temperature. However,according to other authors ,the choice of a solvent for such DDQ oxidations depends essentially on the structure of the substrate, a relationship which is said to be ruled by still unknown factors.

EXPERIMENTAL SECTION

Mps were determined on a Kofler apparatus using a microscope and are corrected. The MS (electron impact) were determined on an AEI MS 50 spectrometer and the ^{1}H NMR spectra on a Bruker 300 MHz apparatus, ppm from zero TMS. Thin layer chromatography (TLC) was carried out on Schleicher-Schull SiO_2 fluorescent films for analytical purposes, and on 1 mm thickness plates for preparative isolation, UV observation at 254 nm with a Desaga lamp and extraction from the scraped layer with ethyl acetate.The reagents were all purchased from Aldrich Europe Chemie.

N-methoxyseptorine (2).- Compound **3** isolated from cultures of the fungus *Septoria nodorum* (100 mg, 0.3 mM) and DDQ (300 mg, 1.32 mM) were dissolved in anhydrous chloroform (200 mL, freshly distilled over $CaCl_2$). The reaction mixture was kept 4 days at 20° in the dark, then the reagent was destroyed by addition of water (100 mL) with stirring. The chloroform layer was repeatedly stirred with water until the aqueous layer became nearly colorless and the final organic phase was dried over Na_2SO_4 previous to concentration. Compound **2** was isolated from this extract by preparative SiO_2 TLC (CH_2Cl_2-AcOEt 7:3, Rf 0.65, yellow band (UV), 63 mg, 64% yield) and crystallized from ethyl acetate-pentane to give a pale yellow solid, mp. 163-167°, lit.[2] 167° (50 mg, 51%). MS, m/z (%): 332 M^+ (40), 302 $(M\text{-}HCHO)^+$ (15), 121 $(M\text{-}p\text{-}OH\text{-}benzoyl)^+$ (100); high resolution MS, calc.for $C_{17}H_{20}N_2O_5$ 332.13721, found 332.1387; ^{1}H NMR, $CDCl_3$, δ 9.10 (s, 1H, phenolic 0H), 4.05 (s, 3H, $NOCH_3$), 3.85 (s, 3H, OCH_3), 7.70 and 6.90 (d, 2H, J = 9 Hz each, aromatic), 3.40 (sext., J = 6 Hz, CH), 1.60 and 1.86 (m, 1H,J = 6 Hz, each, CH_2), 1.27 (d, 3H , J = 6 Hz, CH_3), 0.98 (t, 3H, J = 6 Hz, CH_3).

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SYNTHESIS OF CARBENOXOLONE ANALOGS FROM ARGENTATIN B[†]

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The triterpenes of the cyclolanostane type named argentatins are one of the principal components of the resin of the Mexican rubber plant, guayule (*Parthenium argentatum*), a common desert shrub in North Mexico and Southwestern USA.[1] Guayule has been intensively studied as a renewable native source of natural rubber,[2] and it is known that for each pound of natural rubber obtained, there also is produced one pound of a by-product named resin.[3] Taking into account that the annual production of guayule rubber is expected to be 500-1500 million pounds by the year 2000 [4] and that the argentatins comprise 27% of the resin,[5] then at the predicted levels of guayule rubber production,