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Isomerization of Uroporphyrinogen I octamethyl ester through spiro-pyrrolenine intermediate

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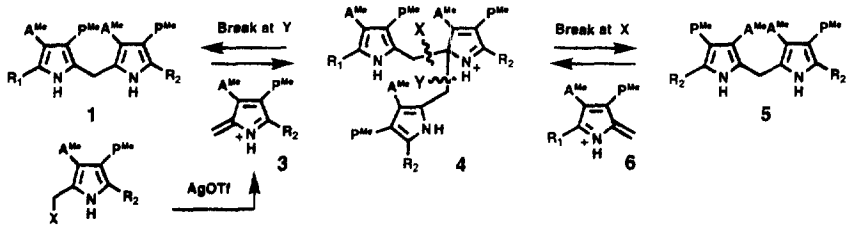
Abstract

Treatment of uroporphyrinogen I octamethyl ester with 2-mercaptobenzothiazolylmethyl pyrrole derivative in the presence of silver (I) trifrate under anaerobic condition in dichloromethane for 20 h, followed by aerial oxidation of the products, gave a statistical mixture of uroporphyrin I ~ IV octamethyl esters. It was proposed that this transformation proceeds through a spiro-pyrrolenine as a key intermediate.

keywords: coupling reaction; uroporphyrinogens; rearrangement; spiro compounds

We have recently reported that the coupling reaction of pyrromethane **1** with azafulvenium ion **3**, generated from 2-mercaptobenzothiazolylmethyl pyrrole derivative **2** and AgOTf in dry benzene at room temperature, gave a symmetric pyrromethane **5** in high yield. We proposed that this product **5** could be provided by coupling of **1** with **3** first to yield bis-(pyrrolylmethyl)pyrrolenine **4**, followed by cleavage at site x as shown in Scheme 1 [1].



Scheme 1

Looking at this rearrangement from **1** into **5** through pyrrolenine intermediate **4**, we were fascinated by the extensive studies on the reaction of azafulvenium ion **3** as an electophilic

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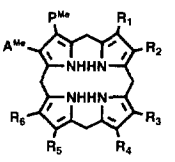
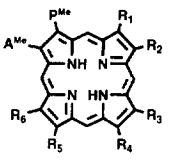
reagent with tetrapyrrole macrocyclic compounds, connecting to the attractive biosynthetic mechanism of uroporphyrinogen III [2,3]. We therefore decided to use uroporphyrinogen I octamethyl ester, shortened to uro'gen I Me ester, as a macrocyclic substrate instead of pyrromethane **1**, because of easy availability of it and the other three isomers [4,5,6].

Catalytic hydrogenation of uroporphyrin I octamethyl ester in EtOAc-MeOH-AcOH-H_2O (6:2:2:1) over 10% Pd-C for 1 h at room temperature provided uro'gen I Me ester, after filtration on Hyflo super-cel under Ar and followed by evaporation of the solvent under vacuum, which was contaminated with about 15% of uroporphyrin I octamethyl ester. Crude uro'gen I Me ester thus obtained was used without any purification in the next reaction, because of its high sensitivity for aerial oxidation.



Uroporphyrinogen octamethyl ester Type I ~ IV

I: $R_1=R_3=R_5=A^{Me}$ $R_2=R_4=R_6=P^{Me}$
II: $R_2=R_3=R_6=A^{Me}$ $R_1=R_4=R_5=P^{Me}$
III: $R_1=R_3=R_6=A^{Me}$ $R_2=R_4=R_5=P^{Me}$
IV: $R_1=R_4=R_6=A^{Me}$ $R_2=R_3=R_5=P^{Me}$



Uroporphyrin octamethyl ester Type I ~ IV

I: $R_1=R_3=R_5=A^{Me}$ $R_2=R_4=R_6=P^{Me}$
II: $R_2=R_3=R_6=A^{Me}$ $R_1=R_4=R_5=P^{Me}$
III: $R_1=R_3=R_6=A^{Me}$ $R_2=R_4=R_5=P^{Me}$
IV: $R_1=R_4=R_6=A^{Me}$ $R_2=R_3=R_5=P^{Me}$

To a solution of uro'gen I Me ester (85% purity: 4.7 mg, 5.8 μmol) and 2-mercaptobenzothiazolylmethylpyrrole derivative **3** (5.5 mg, 11.6 μmol) in dry degassed dichloromethane (2.0 ml) were added AgOTf (3.6 mg, 14.0 μmol) and powdered Na_2HPO_4 (10.0 mg, 70 μmol). The mixture was stirred under Ar at room temperature for 20 h. After dilution with dichloromethane (2ml), NaOAc (100 mg) was added to the mixture which was vigorously stirred under oxygen atmosphere for 1 h to oxidize the products. Then, the reaction mixture was poured into water (10 ml) and extracted with chloroform (10 ml x 4). The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified on silica gel TLC using a mixture of CH_2Cl_2-MeOH (100:5) as a solvent, giving rise to a mixture of porphyrin like products (3.0 mg). ^{1}H-NMR spectrum of the product was similar to that of the mixture of uroporphyrin I, II, III and IV.

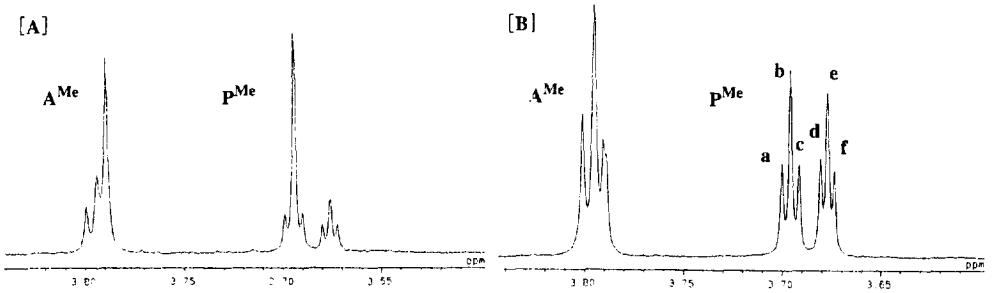
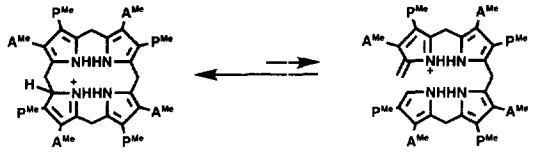


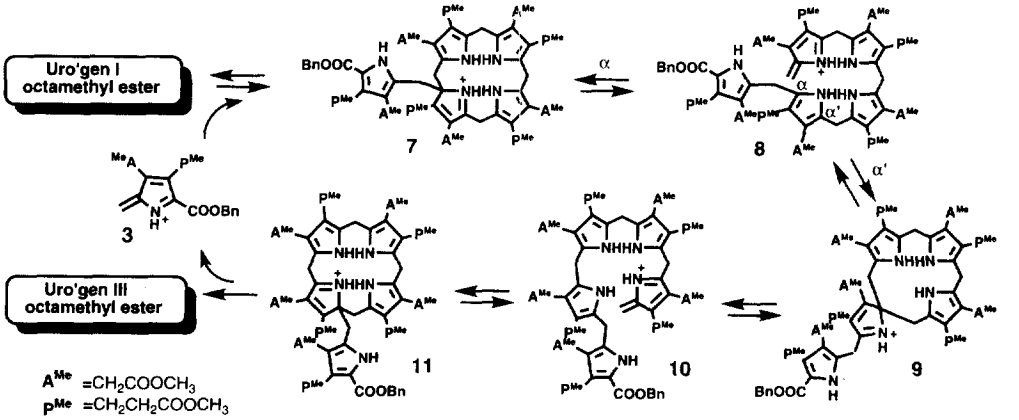
Fig. 1. The Me ester regions of acetic acid (A^{Me}) and propionic acid (P^{Me}) side chain of the 400 MHz NMR spectra ($CDCl_3$), involved in the isomers of uroporphyrin octamethyl ester, are described. [A] is the spectrum of the isomerized mixture of uroporphyrin octamethyl esters and [B] is the spectrum of a statistical mixture of uroporphyrin octamethyl esters of type I, II, III and IV (1:1:4:2): marked a=III (1.5H); b=I (1.5H) + IV (1.5H); c=III (1.5H); d=IV (1.5H); e=III (3H); f=II (1.5H).

We required evidence for the characterization of the uroporphyrin involved in the mixture by unambiguous assignment of the signals corresponding to each isomer in the ^{1}H-NMR spectrum and found that methyl signals of methyl propionate side chain, appeared at the region between 3.67-3.70 ppm (12H), were successfully characterized to each isomer of uroporphyrin octamethyl ester I~IV by comparison with authentic specimens (I, II, III) as summarized in Fig. 1. In addition, it was confirmed that the above reaction mixture consists of four isomers of uroporphyrin octamethyl ester in the ratios of about 2.5:1:4:2, corresponding to the isomers of type I:II:III:IV, which was calculated from HPLC peak areas (I,II,III+IV) by using Scott's method [7] and ^{1}H-NMR spectum. Highly enhanced signal of type I isomer in the ^{1}H-NMR spectrum, compared to the spectrum of statistical mixture of I~IV, should be due to contamination with starting material (about 15%) as mentioned above. Similar reaction of uro'gen I Me ester with AgOTf in the absence of **2** gave pure uroporphyrin I Me ester, indicating that the isomerization reaction requisites azafulvenium reagent **3**. We also confirmed that the uro'gen I Me ester did not isomerize to the mixture of four isomers by the aid of p-TsOH even in a long period. Mechanistically, the cyclic ring of uro'gen I Me ester should be opened by protonation at α-position of the pyrrole, but recyclization is so rapid and the cyclized molecule, namely uroporphyrinogen chromophore, is much more stable than the chain molecule as demonstrated in Scheme 2.



Scheme 2

In the case of the reaction of uro'gen I Me ester and **3**, the adduct **7** isomerizes to acyclic pentapyrrole **8**. However, recyclization of **8** is possible by two ways as illustrated in Scheme 3.



Scheme 3

Namely, cyclization at α position provides initial adduct **7**, but the other cyclization at the α' position provides the spiro-pyrrolenine intermediate **9** which might be followed by subsequent reactions of ring opening, recyclization and elimination of azafulvenium ion **3**, providing uro'gen III Me ester.

Similarly, it is proposed that uro'gen III reacts with **3** to yield a statistically equilibrated mixture of I, II III and IV as shown in Fig. 2 in a ratios of 1:1:4:2. Obviously, the observed ratios (2.5:1:4:2) of the mixture of four uroporphyrin I~IV octamethyl ester isomers, obtained from isomerization reaction of uro'gen I Me ester (contaminated with 15% uroporphyrin I octamethyl ester) with **3**, are good agreement with the statistically expected ratios (I:II:III:IV=25.6:10.6:42.5:21.3 %).

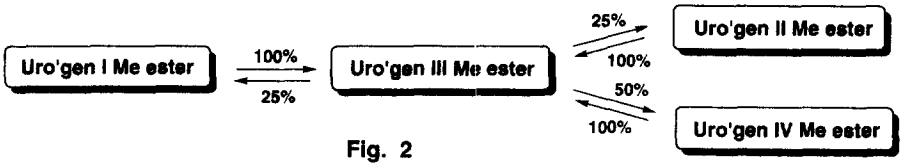


Fig. 2

Thus, it was concluded that uro'gen I Me ester was transformed into a statistical mixture of four uro'gen I~IV Me ester isomers by means of azafulvenium ion **3** through spiro-pyrrolenine intermediate such as **9**, which is very close to the remarkable rearrangement reaction demonstrated by Battersby as a model for the biosynthesis of uroporphyrinogen III [8,9,10,11].

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