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A FACILE PREPARATION OF RIFAMYCIN DERIVATIVES BY USE OF MANGANESE DIOXIDE

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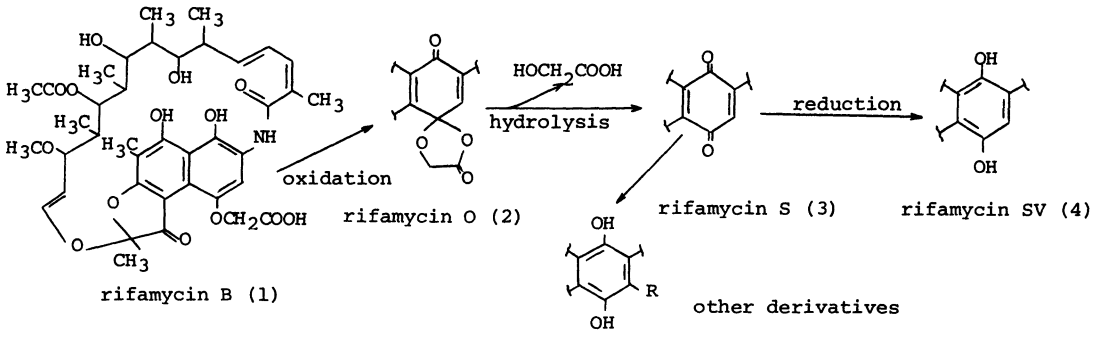
Rifamycin O, rifamycin S and rifamycin SV were prepared in good yields (88-94%) by the oxidation and hydrolytic cleavage of rifamycin B in the presence of manganese dioxide.

During the course of our work towards a synthesis of rifamycin derivatives, we developed a simple way to perform the conversion of rifamycin B to rifamycin O, rifamycin S, and rifamycin SV. Rifamycin S, especially among the above derivatives, has been of great commercial importance as the key intermediate for the synthesis of several hundreds of semisynthetic rifamycin S including rifampicin which is now used as an antituberculosic drug.[1] The key steps of chemical conversion from rifamycin B, a metabolic product of *Nocardia mediterranei*, are represented by the following scheme.[2]



The classical method for the preparation of rifamycin S involves reaction of rifamycin B with sodium nitrite or sodium persulfate.[3] In order to maintain substantial solubility of both the rifamycin B and the oxidant, the solvent is usually the mixture of acidic water and water miscible solvents. In this condition, however, the yield is relatively low (60-70%) due to the degradation of rifamycin S in the acidic polar milieu containing substantial amount of acidic water (50% V/V). The other disadvantage of this process is that the water soluble oxidants employed are very unstable at acidic pH and decompose with foaming.

We found in the continued work that manganese dioxide can effect the oxidation of rifamycin B very efficiently. Relatively non-polar solvents including chloroform, methylene chloride, ethyl acetate, and benzene are preferentially used for the preparation of rifamycin O. Polar solvents such as alcohols with catalytic amount of acidic water (1-5% V/V) can effect the oxidation and hydrolytic cleavage simultaneously to prepare rifamycin S. The use of solid manganese dioxide as an oxidizing agent is well documented for the preparation of unsaturated aldehydes and ketones from the corresponding allylic and benzylic alcohols.[4] It has also been found to oxidize N-alkylamines to form various products, depending on the nature of N-alkyl group.[5] The above application in oxidation reaction prompted us to use in rifamycin derivatives. We feel that the present application to rifamycin antibiotics will stimulate its use in other areas of synthetic organic chemistry. Definite advantages over the classical procedure are milder reaction conditions, simplified work-up operations. Besides, this process provides much high yield (up to 94%) compared with that of previously reported (60-70%).

The preparation of rifamycin derivatives by the manganese dioxide procedure is illustrated by the following examples :

Rifamycin O : 4 g of manganese dioxide is added to the solution of rifamycin B (H^+ form, 3.8 g, 0.005 mole) in 200ml of benzene and stirred for 5min at room temperature. The conversion to rifamycin O can be easily visualized by TLC using Eastman chromagram No. 13181 with the solvent system of chloroform/acetone (1:1). The complete disappearance of rifamycin B spot (Rf 0.1, yellow) accompanies with the appearance of rifamycin O spot (Rf 0.7, pale yellow). After filtration of manganese dioxide, concentration of benzene gave 3.7 g of yellowish product (yield 98%). It is recrystallized from methanol to give pure rifamycin O (3.3 g, yield 87%). Concentration of mother liquor gives additional 0.25 g of product raising the total yield to 94%. The IR spectrum coincided with that of standard rifamycin O. UV-visible spectrum (in methanol-acetate buffer, pH 4.6); 226nm ($E^{1\%}_{1cm}$365), 273nm($E^{1\%}_{1cm}$440), 370nm($E^{1\%}_{1cm}$60).

Rifamycin S : 6 g of manganese dioxide is added to the solution of rifamycin B (H^+ form, 5.3 g 0.007 mole) in 400ml of methanol and 20ml of 10% HCl. After stirring for 5 min manganese dioxide is removed by filtration. The filtrate is stood for 5 hr at room temperature. The tinge of yellow color gradually deepens as the hydrolysis proceeds. In TLC pattern, after initial disappearance of rifamycin B spot with the formation of rifamycin O spot, the rifamycin O spot redisappears with the development of rifamycin S spot (purple, Rf 0.4). After the hydrolysis reaction is completed, the solution is concentrated to 100ml. It is poured into ice cold water with stirring and the yellow precipitate is filtered and dried. It is recrystallized from methanol-water 1:1 mixture to give pure rifamycin S (4.44 g, yield 91%). The IR spectrum was identical with that of standard rifamycin S. UV-visible spectrum (in phosphate buffer pH 8.0); 224nm($E^{1\%}_{1cm}$478), 317nm($E^{1\%}_{1cm}$436), 525nm($E^{1\%}_{1cm}$68).

Rifamycin SV : After the hydrolysis reaction is completed in preparation of rifamycin S, it was concentrated to 200ml. To this, 200ml of 2% ascorbic acid in 0.1M phosphate buffer (pH 7.0) is added in portion with mild stirring maintaining the temperature to 50°C. Rifamycin S is instantaneously reduced to rifamycin SV by ascorbic acid with the color change to deep yellowish red. The solution is gradually chilled to 4°C and stored for 1 day. The red crystal of needle form is recovered after filtration and dried (3.82 g, yield 78%). The mother liquor is concentrated to 320ml, and the additional 0.5 g of crystal raises the total yield to 88%. The IR spectrum was identical with that of standard rifamycin SV. UV-visible spectrum (in phosphate buffer pH 7.4); 223nm($E^{1\%}_{1cm}$586), 314nm($E^{1\%}_{1cm}$322), 445nm($E^{1\%}_{1cm}$204).

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