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# Synthesis and characterization of some new ferrocene-containing rifamycins *

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**Abstract**

Eleven new ferrocene-containing rifamycins have been obtained by the condensation of 3-formylrifamycin SV with hydrazides of some *S*-modified, ferrocene-containing thioglycolic acids. The products were characterized by their UV spectra and TLC. The observed biological activity was lower than that of Rifampicin on Gram-positive bacteria, and insignificant towards Gram-negative ones.

## Introduction

Although many semisynthetic rifamycins, produced through various structural modifications, are known, the most significant results have been obtained by the transformation of the 3-formyl group from 3-formylrifamycin SV (Fig. 1). Among these species, special mention must be made of *N,N*-disubstituted hydrazones, characterized by their intense *in vitro* antibacterial activity towards Gram-positive bacteria and *Mycobacterium tuberculosis*.

Generally, such rifamycins are obtained through condensation reactions of 3-formylrifamycin SV with nucleophilic agents possessing an $NH_2$ group capable of reacting with the carbonyl group.

$$\text{Rif}-\text{CH}=\text{O} + \text{H}_2\text{N}-\text{R} \longrightarrow \text{Rif}-\text{CH}=\text{N}-\text{R} + \text{H}_2\text{O}$$

(Rif—CH=O : 3-formylrifamycin SV)

Nucleophilic agents, employed in obtaining 3-modified formylrifamycins, belong to the class of amines, hydrazines, hydroxylamines, semicarbazones, thiosemicarbazones, sulphonhydrazides etc., substituted with various radicals [1–9].

* Dedicated to Professor Cristofor Simionescu on the occasion of his 70th birthday on 17 July 1990.

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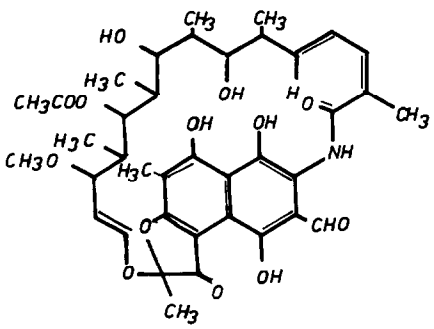


Fig. 1.

Although several compounds of this type are known, only one, i.e. 3-(4-methyl-1′-piperazinyliminomethyl)rifamycin SV, usually known as Rifampicin (D.C.I.), Rifadin (D.R.), Rifoldin or Rimactan, is applied therapeutically, exclusively as an antimicrobial agent, mainly in the treatment of tuberculosis.

The occurrence of secondary effects induced by prolonged utilization of Rifampicin has led to the necessity of producing new derivatives with superior characteristics.

Our investigations have mainly aimed at the synthesis of new rifamycins having a ferrocenyl or 1,1′-ferrocenylene group in the molecule, since the ferrocene nucleus is considered as an active agent in the improvement of the compound's biological properties.

**Results and discussion**

Ferrocene-containing rifamycins have been obtained through the reaction of 3-formylrifamycin SV with hydrazides of some *S*-modified, ferrocene-containing thioglycolic acids, according to the general reaction scheme:

$$\mathrm{Fc(\overset{R}{\overset{|}{C}}H-S-CH_2-CO-NH-NH_2)_x + x\ Rif-CH=O \longrightarrow}$$

(I, II)

$$\mathrm{Fc(\overset{R}{\overset{|}{C}}H-S-CH_2-CO-NH-N=CH-Rif)_x + x\ H_2O}$$

(III, IV)

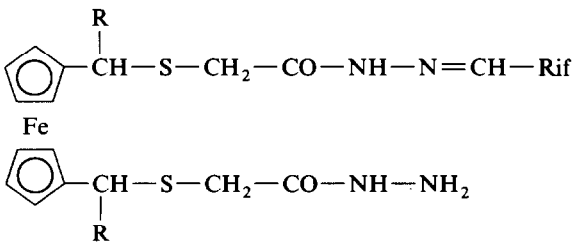
(Fc = ferrocenyl or 1,1′-ferrocenylene group;
I, III: $x = 1$, R = H, $CH_3$, $C_2H_5$, $C_3H_7$, $CH(CH_3)_2$, $C_6H_5$;
II, IV: $x = 2$, R = $CH_3$, $C_2H_5$, $C_3H_7$, $CH(CH_3)_2$, $C_6H_5$)

A 1 : 1 mixture of dichloromethane and absolute ethylic alcohol, offering optimal possibilities of reaction and separation, was selected as reaction medium.

The necessity of a complete transformation of 3-formylrifamycin SV, which is biologically inactive and difficult to remove from the reaction products, required the

chromatographic control of its presence in the reaction medium (Silicagel FG-254, $CHCl_3 : CH_3OH$ 9/1).

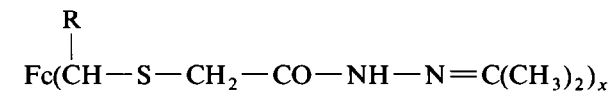
When employing hydrazides resulting from monosubstituted derivatives of ferrocene, I, a slight excess of hydrazide was used (3-formylrifamycin SV/hydrazide molar ratio = 1 : 1.05). In the case of hydrazides II, the molar ratio employed was 1 : 2, in order to restrict the formation of products with the structure V.



(V)

The condensation reaction occurs at 40 °C, the reaction time being up to 30 min.

In order to avoid the use of hydrazides (known to be oily products), a new method of synthesis was tested involving the corresponding hydrazones VI and VII as condensation compounds. (These are solid substances, easily split in an acid medium.).



(VI, VII)

(VI: $x = 1$, R = H, $CH_3$, $C_2H_5$, $C_3H_7$, $CH(CH_3)_2$, $C_6H_5$;
VII: $x = 2$, R = $CH_3$, $C_2H_5$, $C_3H_7$, $CH(CH_3)_2$, $C_6H_5$)

The new method of synthesis requires the reaction to be carried out in the presence of an acid catalyst (e.g. HCl, or $CH_3COOH$), a criterion which is based on the higher reactivity of 3-formylrifamycin SV versus the carbonylic group of acetone, as well as on the known stability of rifamycins in an acid medium [10].

Despite the disadvantage of a long reaction time (about 3 h at 40 °C) this method could be of interest in the case of certain condensation compounds that are difficult to isolate or purify through conventional methods.

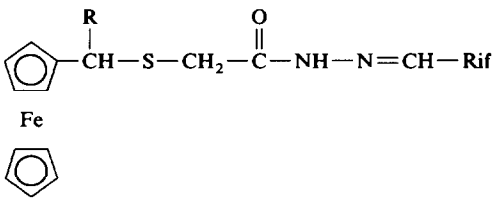
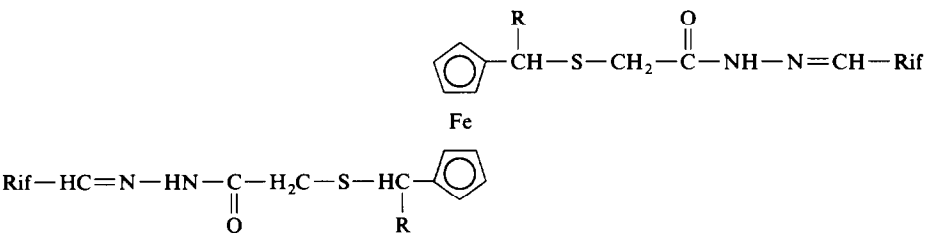
The products obtained were characterized through UV-VIS spectroscopy. Generally, semisynthetic rifamycins, obtained through the condensation of 3-formylrifamycin SV with compounds having an $NH_2$ group, show two characteristic maxima between 330–350 and 470–490 nm [1–10]. The values of the absorption maxima from the UV-VIS spectra are presented in Table 1.

The purity of the products was estimated through TLC, under conditions similar to those employed in the control of the synthesis process.

The antibacterial activity of the new ferrocene-containing rifamycins was tested through measuring the diameters of the inhibition zones. *Staphylococcus aureus, Klebsiela pneumonie, Escherichia coli* and *Pseudomonas aeruginosa* were used as test bacteria, the data obtained being compared with those of Rifampicin as reference sample. The synthesized derivatives showed a reduced activity for Gram-positive

Table 1

Characteristics of the ferrocene-containing rifamycins

| No. | R | Yield (%) (Method A) | UV λ (nm) | | $R_f$ |
|---|---|---|---|---|---|
|  | | | | | |
| 1 | H | 72.6 | 346 | 484 | 0.40 |
| 2 | $CH_3$ | 73.5 | 346 | 482 | 0.41 |
| 3 | $C_2H_5$ | 75.0 | 346 | 480 | 0.38 |
| 4 | $C_3H_7$ | 78.6 | 344 | 484 | 0.40 |
| 5 | $CH(CH_3)_2$ | 68.1 | 344 | 484 | 0.44 |
| 6 | $C_6H_5$ | 63.4 | 340 | 482 | 0.39 |
|  | | | | | |
| 7 | $CH_3$ | 78.5 | 344 | 484 | 0.35 |
| 8 | $C_2H_5$ | 71.4 | 342 | 484 | 0.30 |
| 9 | $C_3H_7$ | 66.7 | 344 | 484 | 0.33 |
| 10 | $CH(CH_3)_2$ | 74.6 | 340 | 486 | 0.31 |
| 11 | $C_6H_5$ | 62.8 | 340 | 484 | 0.29 |

bacteria and were inactive towards Gram-negative bacteria. The monosubstituted derivatives (III) show a biological activity higher than that of the disubstituted species IV, which may be explained through the complex molecular structure of IV (molecular weight about 2000).

## Experimental

*Instrumentation*

The UV-VIS spectra were recorded in methanol ($10^{-5}$ mol/l) on a VSU 2P spectrometer (Carl Zeiss).

*Starting materials*

Hydrazides I and II were obtained through the hydrazinolysis of the corresponding methylic esters, while hydrazones VI and VII were obtained through the reaction of hydrazides I and II with acetone [11].

*General procedures*

*Method A.* To a solution containing 1 mmol of hydrazide I or II in 8 ml of a 1 : 1 mixture of $CH_2Cl_2$ and absolute $C_2H_5OH$, a solution containing 3-formylrifamycin SV in 8 ml $CH_2Cl_2$ and absolute $C_2H_5OH$ (1 : 1) (molar ratios: I : Rif–CHO = 1.05 : 1, II : Rif-CHO = 1 : 2) was added. The mixture was maintained, under stirring, at 40 °C for 30 min, the complete transformation of 3-formylrifamycin SV beeing confirmed through TLC. The solution was concentrated at half volume and the reaction product was precipitated in 20 ml n-hexane.

*Method B.* The synthesis was performed under the same conditions as those described in method A. VI and VII hydrazones were employed as condensation compounds, the reaction occurring in the presence of two drops of acetic acid; the reaction time was 3 h.

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