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REACTION OF RIFAMYCIN S WITH 1,3,5-TRI-t-BUTYLHEXAHYDRO-1,3,5-TRIAZINE

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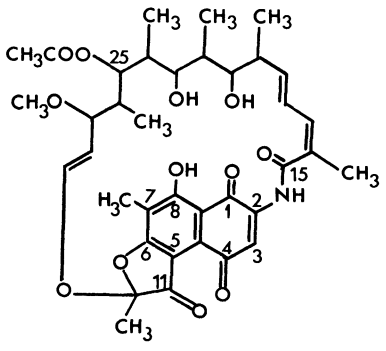
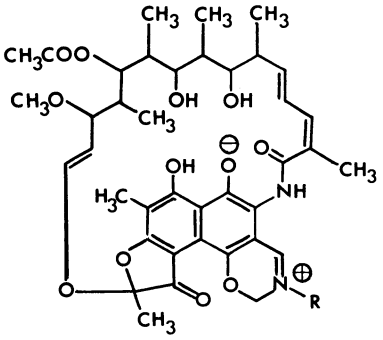
Rifamycin S and 25-O-desacetylrifamycin S were found to react with 1,3,5-tri-t-butylhexahydro-1,3,5-triazine to give deep-blue compounds. The structures of these compounds are discussed in comparison with those of " so-called deep-blue compounds" reported by earlier workers.

Recently, Marsili and Pasqualucci obtained a characteristic deep-blue colored compounds in satisfactory yields by treating rifamycin S with N,N-bis(alkoxymethyl)-alkylamines and assigned the structure (I).[1] Earlier, the deep-blue compounds were obtained in very low yields by oxidation with MnO_2 of 3-(dialkylamino)methyl-rifamycin SV and subsequent disproportionation, and were suggested to have the structure (II).[2-4] When we treated rifamycin S and 25-O-desacetylrifamycin S[5] with 1,3,5-tri-t-butylhexahydro-1,3,5-triazine, we also obtained the deep-blue colored compounds (A) and (B) in 32 and 30% yields respectively, however, have confirmed the structures of these compounds (A) and (B) to be (IIIa) and (IIIb) instead of (I) or (II).

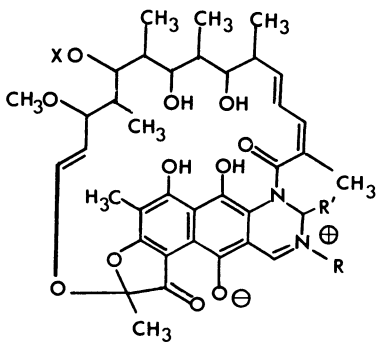


Rifamycin S



(I)

a: R= CMe_3

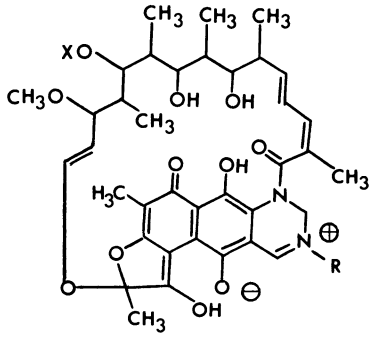


(II)

a: R= Et, R'= Me, X= H

b: R= CMe_3, R'= H, X= Ac

c: R= CMe_3, R'= X = H



(III)

a: R= CMe_3, X= Ac

b: R= CMe_3, X= H

To a solution of rifamycin S (1.0 g) in pyridine (6.0 ml) was added 1,3,5-tri-t-butylhexahydro-1,3,5-triazine (0.8 g). After stirring at 60°C for 1.5 hours the reaction mixture was poured into 10% acetic acid to separate dark-blue precipitates, which upon column chromatography on silica gel afforded a deep-blue compound (A) (367 mg). MS m/e : 792 (M^+). Found : C, 63.72; H, 7.02; N, 3.22%. Calcd for $C_{43}H_{56}O_{12}N_2 \cdot H_2O$: C, 63.69; H, 7.21; N, 3.45%. UV (pH 6.1 phosphate buffer) : λ_{max} 227 nm ($\log \varepsilon$ = 4.54), 272(4.30), 310(4.21), 356(4.22), and 568(4.05). A similar treatment of 25-O-desacetylrifamycin S (1.0 g) also afforded another deep-blue colored compound (B) (360 mg). Found : C, 64.09; H, 7.17; N, 3.67%. Calcd for $C_{41}H_{54}O_{11}N_2 \cdot H_2O$: C, 64.04; H, 7.34; N, 3.64%. UV (pH 6.1 phosphate buffer) : λ_{max} 227 nm ($\log \varepsilon$ = 4.54), 273(4.29), 311(4.21), 356(4.22), and 569(4.06). The IR spectra of (A) and (B) are shown in Fig.1.

At first, we considered[6] the deep-blue colored compound (A) to have the structure (Ia), since (A) was identical in all respects of UV, IR, and NMR spectra to the deep-blue colored compound, which was prepared from rifamycin S and N,N-bis(ethoxymethyl)-t-butylamine (bp 105-110°C/37 mmHg) according to the method of Marsili and Pasqualucci,[1] who assigned the structure (Ia) to the deep-blue colored compounds.

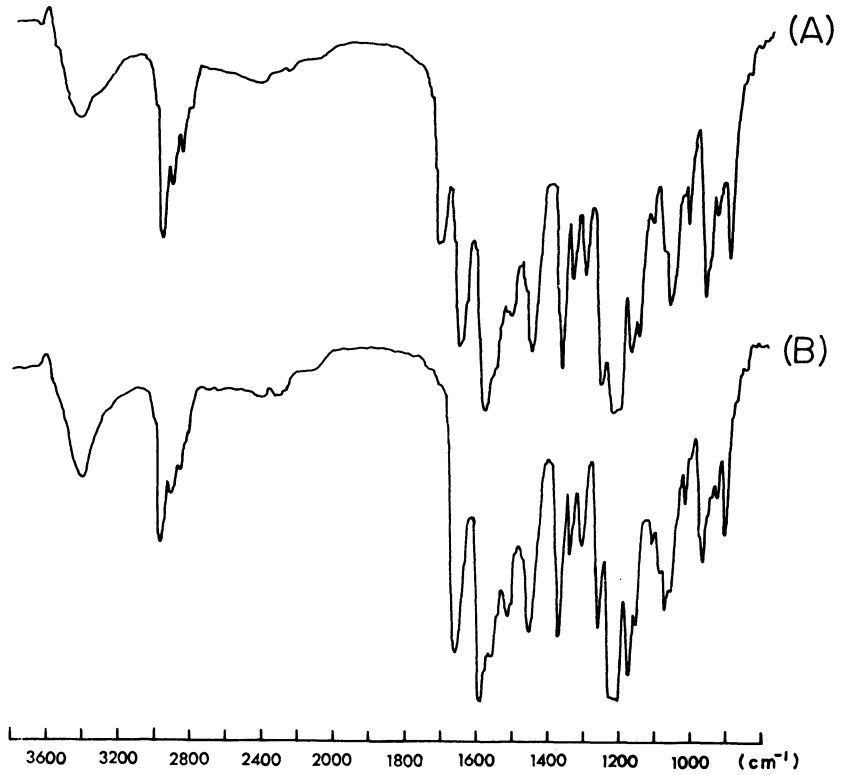


Fig.1 IR spectra of (A) and (B) in $CHCl_3$ solution.

The furanoic νC_{11}= O band has been known to appear at $\sim$1740 cm^{-1} in the IR spectra of the derivatives of rifamycin, when there is no intramolecular hydrogen-bonding between franoic C_{11}= O and C-4 hydroxyl.[7] This implies that, if the structure of (A) is represented by (Ia), no intramolecular hydrogen-bonding can be formed, and hence the IR spectrum of (A) should show a typical furanoic νC_{11}= O band at $\sim$1740 cm^{-1}. In the spectrum of (A), however, the typical furanoic νC_{11}= O band at $\sim$1740 cm^{-1} is small and quite obscure due to the presence of the acetyl νC=O band in the same region. Whereas, the IR spectrum of (B) clearly has no furanoic νC_{11}= O band at $\sim$1740 cm^{-1}. Hence, the assignment of the structure (Ia) to the compound (A) must be in error.

The NMR spectrum ($CDCl_3$, TMS) of (A) showed two doublet signals which couple each other with 13 Hz at δ 4.52 and δ 6.58 ($\underline{CH}_2$-$\overset{|}{N}^{\oplus}$=) and one singlet signal at δ 8.94 ($\underline{CH}$=$N^{\oplus}$<). The NMR spectrum of (B) also shows two doublet signals (δ 4.45 and δ 6.65, J= 13 Hz, $\underline{CH}_2$-$\overset{|}{N}^{\oplus}$=) and one singlet signal (δ 9.08, $\underline{CH}$=$N^{\oplus}$<). The chemical shifts of these signals are in very good agreements with those of proton signals which belong to the dihydropyrimidine ring of (IIa).[2] Further, the UV spectra of (A) and (B) closely resemble that of (IIa).[2]

All these spectroscopic observations suggest that (A) and (B) should be assigned to have structures (IIb) and (IIc). Meanwhile, Maggi et al. suggested[2] based on an investigation of polarographic oxidation wave of (IIa) that the two hydroquinonic hydroxyl groups in (IIa) are non-equivalent and one is ionized. The IR spectra of (A) and (B) show the amidic $\nu C_{15}=O$ bands appearing at $\sim$1660 cm^{-1}. This rather low frequency is known to indicate that there is an intramolecular hydrogen-bonding between the amidic $C_{15}=O$ and C-1 hydroxyl,[7] and hence, the ionized hydroxyl group must be the C-4 hydroxyl. In other words, the C-4 hydroxyl group is completely dissociated and hence possesses no hydrogen atom. These observations imply that the absence of the furanoic $\nu C_{11}=O$ band of (B) at $\sim$1740 cm^{-1} is not caused by the formation of an intramolecular hydrogen-bonding between the furanoic $C_{11}=O$ and C-4 hydroxyl while (A) also should show a similar phenomenon. Thus, we now would like to assign structures (IIIa) and (IIIb), in which the carbonyl $C_{11}=O$ of dihydrofuran ring is lacking, for the compounds (A) and (B) respectively. Therefore, the earlier structure (II) suggested by Maggi et al. should now be revised to (III). In a separate model reaction between 2-aminonaphthoquinone and N-methylene-t-octylamine, we found the resulting product to be 3-t-octylbenzo[g]-1,2,3,4-tetrahydro-5,8-quinazolindione which has a similar structure to the compound (III). A detailed report on this reaction and the structure for these deep-blue colored compounds will be reported in the near future.

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