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TRANSFORMATION OF BATRIDENE

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Transformations of 1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-5,5′-diisopropyl-2,2′-dinaphthylidene-8,8′-dibarbituric acid (batridene) in DMSO are studied.

Key words: 1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-5,5′-diisopropyl-2,2′-dinaphthylidene-8,8′-dibarbituric acid, transformation, DMSO.

The aldehyde groups in gossypol (GP) can be utilized in condensation reactions with C–H acids to produce arylidene derivatives, several of which have been found to have physiological activity [1]. One of these compounds is batridene, which is prepared via the reaction of GP with barbituric acid (BA) and is used as an immunosuppressor during kidney transplants, chronic glomerulonephritis, and allergodermatosis.

It has been reported that BA condenses readily and quantitatively with aromatic aldehydes without a hydroxyl group in the *o*-position [2]. If the starting aldehyde contains a hydroxyl or amino group in the *o*-position (for example, salicylaldehyde), the reaction produces *bis*-barbituric acid [3]. Derivatives of the diazacridine type are formed with *o*-aminobenzaldehyde and 2-amino-4-nitrobenzaldehyde [4].

Pharmaceutical-grade batridene is prepared by boiling alcoholic solutions of GP and BA in a 1:2 ratio. The precipitate that forms on cooling is bright red. It is filtered off, washed with ethanol and diethylether, and dried. The structure 1,1′,6,6′,7,7′-hexahydroxy-3,3′-dimethyl-5,5′-diisopropyl-2,2′-dinaphthylidene-8,8′-dibarbituric acid was proposed for batridene on the basis of elemental analysis and spectral data (**1**, Fig. 1). Data indicating that batridene behaves irregularly on dissolution were noticed during the preparation of the regulatory documentation for a batridene preparation. The work was further complicated by the fact that batridene is practically insoluble in water and most organic solvents. Sharp and informative absorption spectra could only be obtained by dissolving batridene in DMSO and a DMSO—ethanol mixture (1:9) during development of a quantitative analytical method for determining the batridene content of the substance and in tablets. The UV spectra of freshly prepared batridene solutions exhibit a strong absorption maximum at 320 nm ($D = 0.45$) and a very strong maximum at 495 nm ($D = 0.73$). However, the optical density of the long-wavelength maximum decreased on storage of the solutions. After awhile, the maximum at 495 nm disappeared [5]. Additional experiments were carried out to elucidate the reasons for such behavior.

The PMR spectrum of a freshly prepared solution of pharmaceutical-grade batridene in DMSO exhibits signals characteristic of batridene that are easily assigned. A 6-proton doublet (J = 6.5 Hz) at 1.54 ppm belongs to the methyl protons of the isopropyl group; a 3-proton singlet at 2.07 ppm; the aromatic methyl group on C3; a signal at 7.87 ppm, the aromatic proton on C4 (the quantity of protons refers to one half of the molecule because batridene is symmetric).

Exchange with deuterium showed that broad singlets at 9.3 and 10.15 ppm belong to the hydroxyl protons of GP. A very weak signal at 11.18 ppm arises from the amide proton of barbituric acid. The arylidene proton on C11 resonates in the characteristic region at 10.42 ppm. A peculiarity of the PMR spectrum is the presence of one signal for the two amide NH protons instead of two, as suggested by the formula of **1**. This is explained by the facts that two water molecules are immediately lost from the NH and *o*-OH groups of batridene upon dissolution in DMSO and another ring forms (**2**, Fig. 1). Additional signals appear within 2 h if the spectrum of this sample is recorded. The PMR spectra change completely after 3 d. The spectral parameters are consistent with a structural change of batridene.

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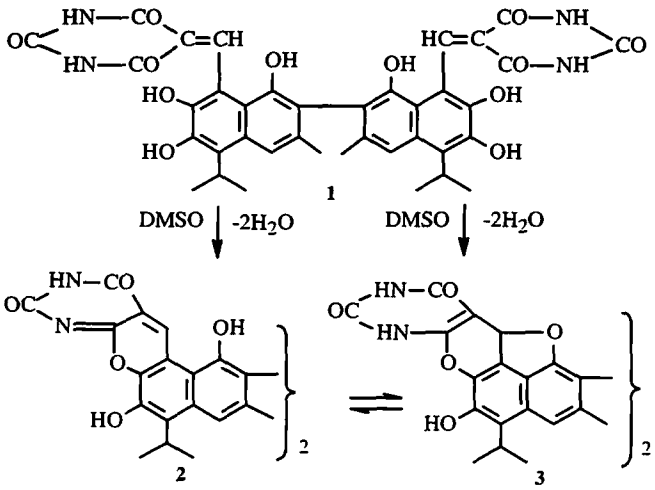

Fig. 1

Although the signals of the methyls in the transformed spectrum undergo a slight shift to higher field [*iso*-$(CH_3)_2$, to 1.45 ppm; Ar–CH_3, to 1.98 ppm], the changes in the weak-field part of the spectrum are substantial. The aromatic proton on C4 gives a signal at 7.1 ppm. The methine proton on C11 shifts sharply to strong field and resonates at 6.38 ppm. The signals of the amide groups are located at 11.25 and 11.08 ppm. The protons of the hydroxyls appear as structureless signals in the range 8.0-10.0 ppm. Apparently batridene in DMSO undergoes a tautomeric transformation because the signals do not change quantitatively but are qualitatively redistributed.

Primarily the lactol form (**3**, Fig. 1) is proposed for batridene in DMSO. We have previously demonstrated that GP itself in DMSO exists primarily in the lactol form [6]. This is also consistent with the PMR spectral parameters for a solution of batridene in DMSO that is stored for a long time at room temperature.

It is interesting that, like for GP, the batridene transformation in DMSO is reversible. If ethanol is added to batridene (**3**) stored in DMSO and the precipitate is washed and dried, the parameters of the resulting PMR spectrum correspond completely to form **2** of batridene. It should also be noted that the barrier to conversion of forms **2** and **3** is apparently high because differences in the properties of batridene in both forms can be found in the solution. Thus, **2** gives a blue color in 0.1 N NaOH. An absorption maximum is observed in the UV spectrum at 495 nm. The R_f value is 0.78. For **3**, the solution in 0.1 N NaOH is green. There is no long-wavelength maximum. The R_f value in the same TLC system is 0.87.

Batridene behaves similarly in DMF. The behavior of batridene in other solvents could not be studied owing to the exceedingly low solubility.

EXPERIMENTAL

TLC was performed on UV-254 plates using acetone and a chamber saturated with acetone vapor. UV spectra were recorded on a SF-26 spectrophotometer (c = 0.002%). PMR spectra were recorded on an XL-100 (Varian, USA) NMR spectrometer.

Batridene was prepared by the literature method [7].

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