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SHORT COMMUNICATIONS

Unusual Reaction of Alkaloid Cotarnine with 1,3-Dimethylbarbituric Acid

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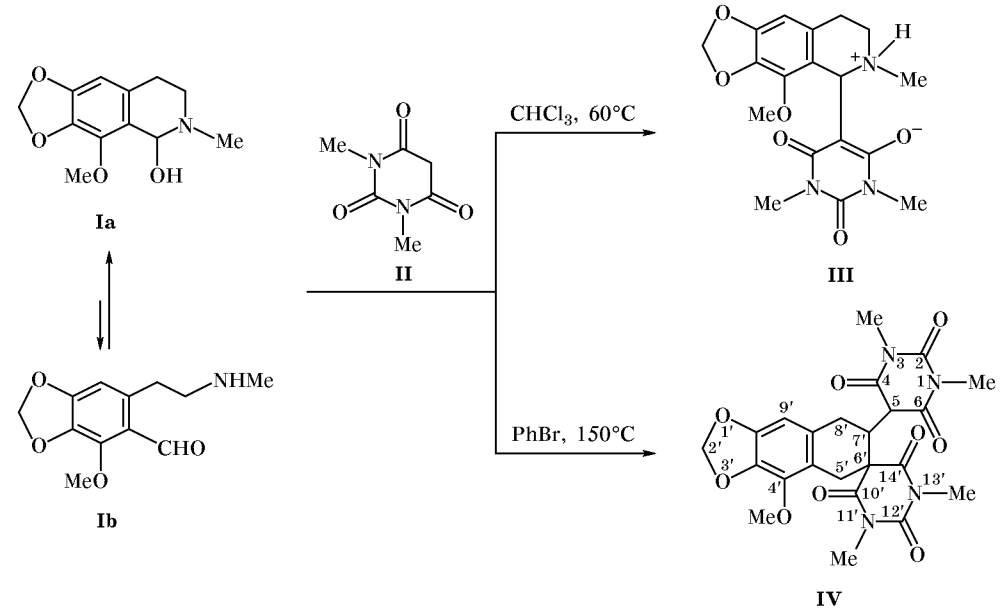
Cotarnine is a natural pseudobase of the isoquinoline series, which is capable of undergoing ring–chain transformations [1]. Its structure may be represented as two isomeric forms occurring in equilibrium: bicyclic **Ia** and monocyclic **Ib** [2]. Monocyclic isomer **Ib** is responsible for formation of derivatives at the aldehyde (e.g., oxime [3]) or amino group (amides [4]). In the other cases cotarnine behaves as cyclic semiaminal **Ia**, which is readily dehydrated to give iminium ion, and reacts with some CH and NH acids following the Mannich reaction pattern and yielding the corresponding tetrahydroisoquinoline bases [2, 5, 6]. The reaction of cotarnine with 1,3-dimethylbarbituric acid (**II**) on heating in chloroform leads to formation of 6-hydroxy-1,3-dimethyl-5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-1,2,3,4-tetrahydropyrimidine-2,4-dione (**III**) as inner salt [7]. When the same reaction was performed with 2 equiv of barbituric acid **II** under more severe conditions, we isolated an unusual product, spiropyrimidine derivative **IV** (Scheme 1). The structure of **IV** was derived from the data of mass spectrometry and NMR spectroscopy (^{1}H and ^{13}C; the spectra were recorded in a standard mode and also using COSY, DEPT, and INADEQUATE techniques).

Presumably, elevated temperature favors formation of cotarnine tautomer **Ib** which react with 1,3-dimethylbarbituric acid (**II**) to give adduct **V**. Such products are typical of reactions of barbituric acids with aromatic aldehydes [8]. Compound **IV** is likely

Scheme 1.



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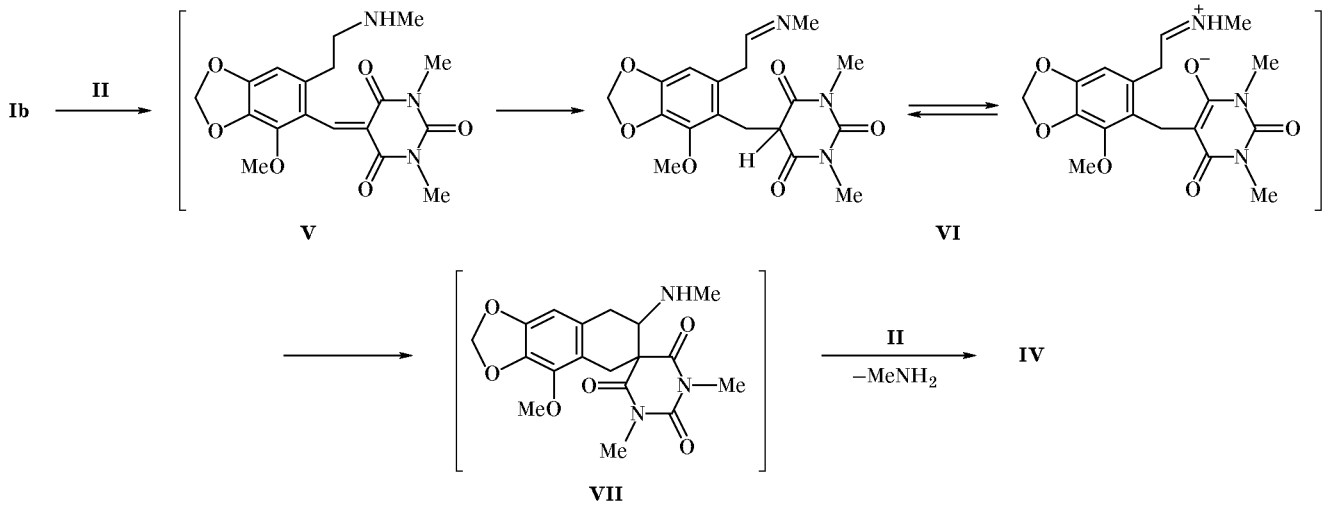
Scheme 2.



to be formed as a result of a series of subsequent transformations shown in Scheme 2. Disproportionation of **V** involves oxidation of the amino group and reduction of the double C=CHAr benzylidene bond to give intermediate **VI**. The possibility for such reaction follows from the properties of 5-benzylidenebarbituric acids in which the active C=CHAr bond is readily reduced; e.g., on heating with formic acid in the presence of trimethylamine the corresponding 5-benzylbarbiturates are obtained [9]. Intramolecular cyclization of **VI** via carbanion addition at the double C=N bond should lead to formation of amine **VII**. In the final stage compound **VII** reacts with the second molecule of barbituric acid **II** in such a way that the anion derived from **II** displaces methylamine molecule, yielding final product **IV**. Analogous processes have been reported in the literature. An example is alkylation of 1,3-dimethylbarbituric acid with triethylamine and other alkylamines, described in [10]. As a result, the corresponding 5-alkyl derivatives of acid **II** were obtained. We hope that our further study will refine the mechanism of the above process.

1,3-Dimethyl-2,4,6-trioxoperhydropyrimidine-5-spiro-6′-[7′-(1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-4′-methoxy-5′,6′,7′,8′-tetrahydro[1,3]-dioxolo[4,5-*g*]naphthalene] (IV). To a solution of 0.02 mol of 1,3-dimethylbarbituric acid (**II**) in 15 ml of bromobenzene we added 0.01 mol of cotarnine, and the mixture was heated to the boiling point over a period of 10 min and was refluxed for an additional 10 min. The mixture was cooled and treated with 100 ml of a 3% solution of ammonia, and the aqueous solution was washed with chloroform (2 × 20 ml) and acidified with hydrochloric acid to pH 1. The precipitate was filtered off and treated over a period of 1 h with 100 ml of a 3% solution of sodium acetate on stirring. The undissolved material was separated, the solution was acidified with hydrochloric acid to pH 1, and the precipitate was filtered off, washed with water, and dried. Yield of **IV** 1.8 g (36%), colorless crystals, mp 234–235°C (from CCl_4). ^{1}H NMR spectrum, δ, ppm: 2.71 d.d (1H, *exo*-5′-H), 2.86 d (1H, *exo*-8′-H), 3.19 s (6H, 1-CH_3, 3-CH_3), 3.20 d (1H, *endo*-5′-H), 3.27 s and 3.36 s (3H each, 11′-CH_3, 13′-CH_3), 3.37 m (1H, *endo*-8′-H), 3.45 m (1H, 7′-H), 3.78 d (1H, 5-H), 3.90 s (3H, OCH_3), 5.80 s and 5.84 s (1H each, OCH_2O), 6.26 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 28.42, 28.56, 28.59, 29.05 (1-Me, 3-Me, 11′-Me, 13′-Me); 29.69 ($C^{8'}$); 36.71 ($C^{5'}$); 41.45 ($C^{7'}$); 49.25 ($C^{6'}$); 50.85 (C^5); 59.27 (MeO); 100.74 ($C^{2'}$); 101.94 ($C^{9'}$); 114.22 ($C^{1'}$), 128.63 ($C^{3'}$); 133.92 ($C^{4'}$); 140.10 ($C^{4a'}$); 148.36 ($C^{9a'}$); 151.30 (C^2, C^2); 167.94, 168.18 (C^4, C^6); 169.40, 171.81 ($C^{10'}$, $C^{14'}$). Mass spectrum, *m*/*z* (I_{rel}, %): 500 (3) M^+, 344 (100), 327 (11), 259 (2), 229 (5), 189 (1), 157 (2), 143 (1). Found, %: C 55.13; H 4.77; N 11.15. $C_{23}H_{24}N_4O_9$. Calculated, %: C 55.20; H 4.83; N 11.19.

The NMR spectra were measured on a Bruker AM-500 spectrometer at 500 MHz for ^{1}H or 200 MHz for ^{13}C from solutions in $CDCl_3$. The mass spectra (70 eV) were recorded on an MKh-1303 instrument with direct sample admission into the ion source heated to 150°C.

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