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UNCONVENTIONAL RECYCLIZATION OF COTARNINE UNDER THE ACTION OF 1,3-DIMETHYLBARBITURIC ACID

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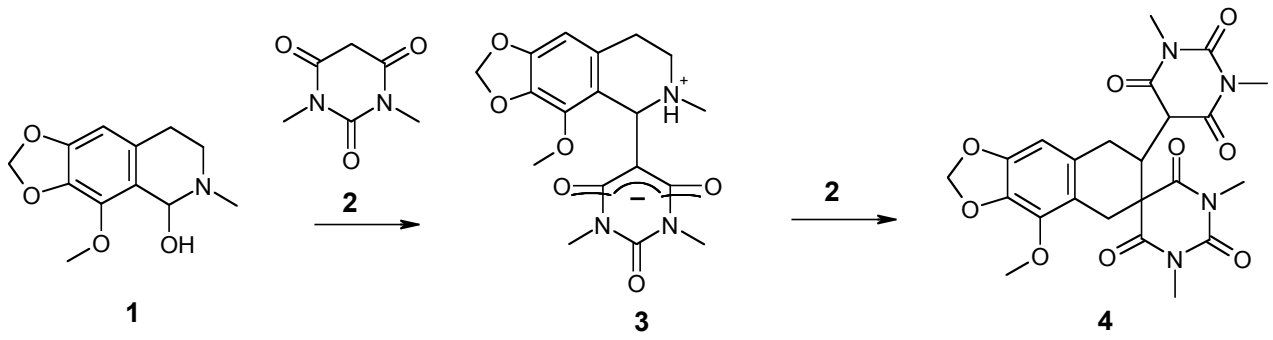
Abstract – The result of condensation of cotarnine with 1,3-dimethylbarbituric acid depends essentially on the temperature. In a harsh conditions (190° C, without solvent), an unconventional tandem rearrangement proceeds to give (5a*R**,9a*S**)-11-methoxy-6,8-dimethyl-7,9-dioxo-5,6,7,8,9,10-hexahydro-5a-*H*-1, 3-dioxa-6,8-diaza-cyclopenta[*b*]anthracene-9a-carboxylic acid methylamide. The structure of this compound was confirmed by XRD. The rearrangement proceeding via the [1,5] H-shift is similar to T-reactions.

INTRODUCTION

The chemistry of 1-hydroxy-8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline (**1**) (cotarnine) and related heterocyclic pseudo-bases draw attention in view of their versatile reactivity[1] and important biological and medicinal implications. Cotarnine chloride is being used in medicine as a hematostatic agent[2] while pseudo-base (**1**) (alkaloid from *Papaver pseudo-orientale)* is biogenetically related to isoquinoline alkaloids of *Papaver.*[3,4]

Recently, the interaction of **1** with 1,3-dimethylbarbituric acid (**2)** under mild conditions was found to yield a zwitter-ionic adduct, 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-quinolin-1-yl)-1,3-dimethylbarbituric acid (**3**), whereas subsequent treatment of **1** with excessive **2** at 150°C gave rise to an unconventional reaction leading to the spirocyclic derivative (**4**) (Scheme 1).[5]



Scheme 1

The XRD data for compound (**4**) and tentative mechanism for its formation were discussed in[6]. Nevertheless, such a recyclization does not seem trivial and is interesting from the academic point of view. Some details of the process (e.g. the mechanism of recyclization of intermediate (**3**) leading to formation of a new carbocyclic ring system) still wait for their rationalization.

RESULTS AND DISCUSSION

In continuation of our studies[5,6] on transformations of cotarnine (**1**) (shown in Scheme 1), we report here on a new unexpected reaction. Treatment of **1** with an equimolar amount of acid (**2**) in dimethylacetamide (DMAC) at 160°C was found to afford the methylenedioxyantracene derivative (**5**) in 10% yield. According to the XRD data (Figure 1), compound (**5**) is present in crystal in the form of the *rac*-*R**,*S**-diastereomer containing two asymmetric atoms (carbon **5a** and **9a**). The hydropyrimidine ring and the cyclohexene ring are *cis*-fused; the bridgehead hydrogen and the CONHMe group occur in staggered conformation. Bond distances and angles suggest a strained system as a result of steric effects.

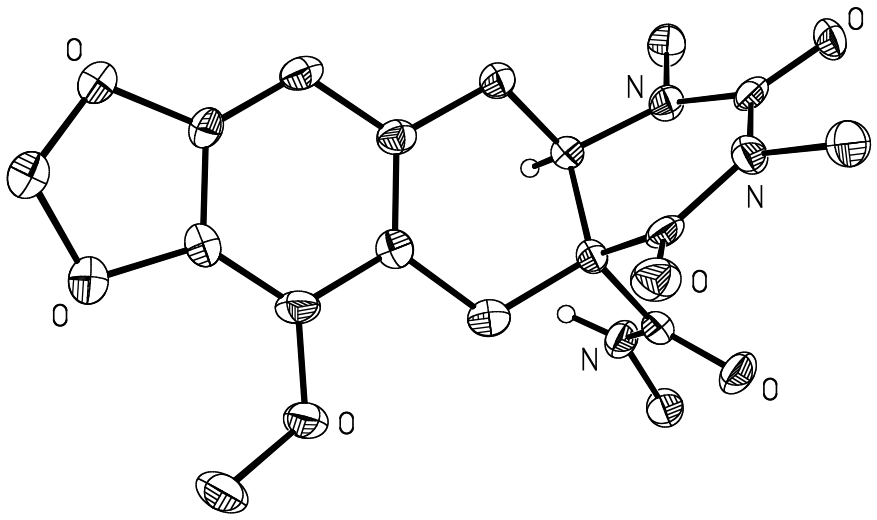
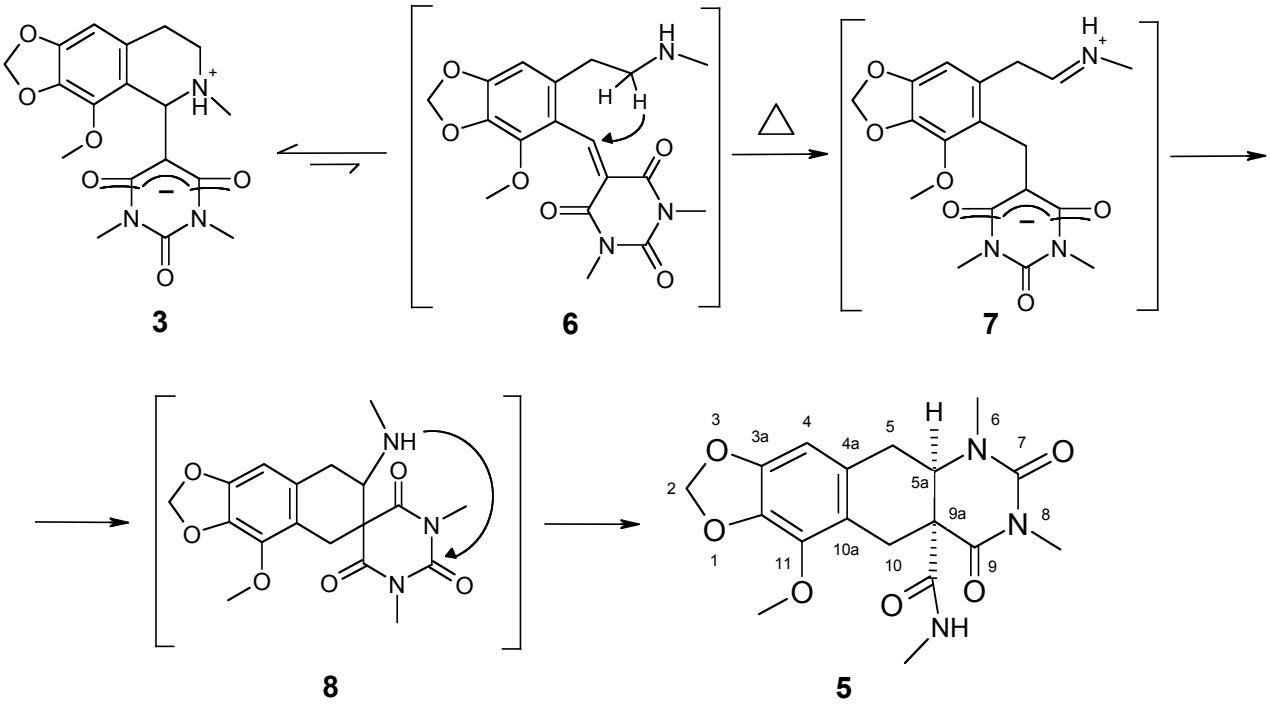


Figure 1. Molecular structure of compound (**5**).

The transformation of cotarnine (**1**) under the action of acid (**2**) initially afforded adduct (**3**). This was confirmed by the following experiments: holding adduct (**3**) in DMAC at 160°C (or without solvent at 190°C) gave product (**5**) in a yield of 16 and 35%, respectively. Without solvent, the process turned out to be even more efficient (despite harsher conditions). In both cases, compound (**5**) was obtained as a sole *R**,*S**-diastereomer, which was evidenced by ^{1}H and ^{13}C NMR measurements. We assume that the isomerization of **3** into compound (**5**) involves the steps depicted in Scheme 2.

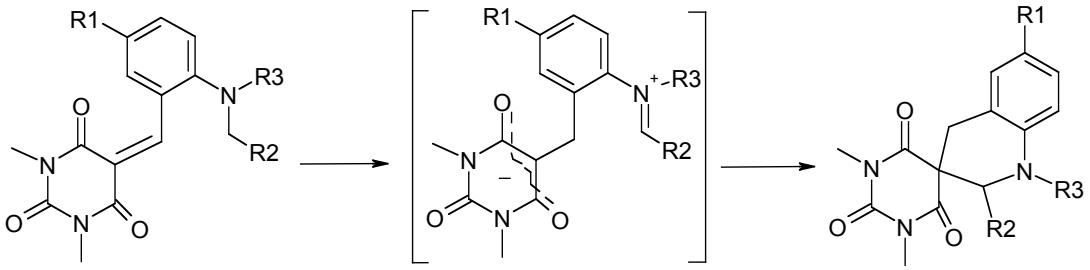


Scheme 2

Cotarnine (**1**) and its numerous derivatives are known to exhibit ring–chain tautomerism.[4] To rationalize this observation, adduct (**3**) can be assumed to exist in equilibrium with its opened form (**6**). We have also to keep in mind the analogy between system (**6**) and 5-(2-dialkylaminoarylidene)barbiturates (**9**) (Scheme 3). As is known, the latter ones readily undergo the so-called T-reaction leading to formation of spirocyclic derivatives (**10**) via the [1,5] H-shift.[7] Similar [1,5] H-shift in compound (**6**) (Scheme 2) results in formation of zwitter-ion (**7**) followed by cyclization to afford the spirosystem (**8**). We have to note that such a T-reaction of compound (**6**) is unconventional: the transformation involves a secondary amino group, but not a tertiary amino group. Also, to our knowledge, this is the first T-reaction that leads to closure of a carbocycle (all previous manifestations of the *tert*-amino effect were associated with closure of azaheterocycles[8]).

The spirocyclic intermediate (**8**) (Scheme 2) is unstable in the reaction conditions and for this reason could not be isolated. Tentatively, the end product (**5**) is formed upon followed rearrangement in **8**, which

also looks unexpected and interesting. We assume that this is an intramolecular rearrangement caused by the nucleophilic attack of the methylamino group in the carbamide-type carbonyl. Conformational lability of molecule (**8**) seems to be sufficient for initiation of the process. The alternative mechanism of recyclization via opening the barbiturate ring seems less likely in view of (*i*) absolute diastereomeric purity of compound (**5**) and (*ii*) the fact that the rearrangement in the solid state was more effective, whereas the alternative disclosure of the barbiturate ring must result in formation of side products (polyamides), which was not observed in experiment.



9 10

Scheme 3

The above conclusions about the mechanism for transformation of cotarnine (**1**) under the action of acid (**2**) shed new light on our previous results. Just as in the previously studied examples,[5,6] the key stage is the T-reaction of adduct (**3**) yielding the spirocyclic intermediate (**8**). In the presence of an excess acid (**2**),[5,6] compound (**8**) alkylated **2** and afforded **4**;[5,6] under the conditions of this work, the conversion of **3** into **5** occurred by tandem recyclization.

The new T-reaction may turn out of especial interest for the chemistry of isoquinoline alkaloids.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were taken with a Bruker AM-500 spectrometer, while the mass spectra, with an MKh-1303 instrument. Assignment of signals in NMR spectra was accomplished by D2 standard methods.

Cotarnine (**1**) was prepared from cotarnine chloride.[6] 5-(8-Methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric acid (**3**) (as a complex with $CHCl_3$) was prepared from **1** and 1,3-dimethylbarbituric acid (**2**).[9]

Single crystal of compound (**5**) was obtained upon slow evaporation of a solution of **5** in an EtOH–H_2O mixture (4 : 1). Crystal data for **5**: $C_{18}H_{21}N_3O_6$; monoclinic; space group *C*2/*c*; at 120 K: a = 36.73(2), b = 6.941(4), c = 13.420(9) Å, β = 99.36(1)°, z = 8. The data were collected with a Bruker three-circle diffractometer equipped with a SMART 1000 CCD detector. The structure was solved by direct methods

and refined by full-matrix least-square method on F^2 with anisotropic thermal parameters for non-hydrogen atoms. Hydrogen atoms were placed in calculated positions and refined in riding model with fixed thermal parameters [U_{iso}(H) = 1.5U_{eq}(C) for the CH_3 groups and U_{iso}(H) = 1.2U_{eq}(C) for other groups], exception for hydrogen atom of amino group which was objectively localized from the difference Fourier map and refined isotropically. The final *R*-factors are R_1 = 0.0513 for 1075 reflections with $I > 2y(I)$ and $wR_2 = 0.1141$ for all 2961 independent reflections. All calculations were carried out by using the SHELXTL (PC Version 5.10) program package.[10] CCDC 234702 contains the supplementary crystallographic data for this paper, see: www.ccdc.cam.ac.uk/conts/retrieving.html or Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk

Preparation of **(5a*R**,9a*S**)-11-Methoxy-6,8-dimethyl-7,9-dioxo-5,6,7,8,9,10-hexahydro-5a-*H*-1,3-dioxa-6,8-diazacyclopenta[*b*]anthracene-9a-carboxylic acid methylamide (5)**

Method 1. Cotarnine (**1**, 2.38 g, 10 mmol) was dissolved in dimethylacetamide (6 mL) and 1,3-dimethylbarbituric acid (**2**, 1.56 g, 10 mmol) was added. The solution was held at 160°C for 20 min. After cooling down, the reaction mixture was treated with 1% aq. ammonia (50 mL) and allowed to stay at 10°C for 2 days. The separated precipitate was washed with 50% EtOH and recrystallized from AcOH to obtain 0.37 g (10%) compound (**5**).

Method 2. Complex (**3**)·$CHCl_3$ (0.99 g, 2 mmol) was held (in an oil bath) at 190°C for 30 min in an inert atmosphere. The dark reaction mixture was cooled down and treated with 1% aq. ammonia (25 mL) for 1 h. A crystalline product was taken out, washed with 50% EtOH, and dried to obtain 0.26 g (35%) compound (**5**).

Compound (**5**) was obtained as a white powder, mp 288–289°C (from AcOH). ^{1}H NMR (500 MHz, $CDCl_3$, *J*, Hz), δ, ppm: 2.63 and 3.09 dd (1H+1H, AB-system, $C5H_2$, *J* 15.9), 2.68 and 3.60 d (1H+1H, AB-system, $C10H_2$, *J* 14.2), 2.77 and 2.79 s (3H, amide conformers N9a'Me), 3.14 and 3.17 s (3H+3H, N6Me+N8Me), 4.00 s (3H, OMe), 4.23 dd (1H, C5aH, J^1 10.1, J^2 6.0), 5.83 and 5.85 d (1H+1H, AB-system, OCH_2O, *J* 11.0), 6.00 br. s (1H, NH), 6.20 s (1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 26.93, 28.40 and 29.70 ($N6CH_3$, $N8CH_3$ and N9a'Me), 30.36 $C10H_2$, 34.88 $C5H_2$, 53.31 C5'H, 53.78 C9', 59,35 OMe, 100.72 OCH_2O, 101.80 $C_{arom}H$, 117.08 C10a, 125.77 C4a, 134.44 C1a, 140.52 C3a, 148.14 C11, 151.66 C7=O, 168.54 C9=O, 171.02 C9a'=O. MS: M^+ 375.

Anal. Calcd for $C_{18}H_{21}N_3O_6$ (%): C 57.59; H 5.64; N 11.19. Found: C 57.44; H 5.71; N 11.10.

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