Reactions of 5-dihydrocotarnyl-1,3-dimethylbarbituric acid and other cotarnine derivatives with 1,3-dimethylbarbituric acid. X-ray diffraction analysis of a 5,5-spiro derivative of 1,3-dimethylbarbituric acid

K. A. Krasnov,[a] V. G. Kartsev,[b] and V. N. Khrustalev[c]*

[a]I. I. Mechnikov St.-Petersburg State Medical Academy,
47 Piskarevskii prosp., 195067 St.-Petersburg, Russian Federation.
Fax: +7 (812) 350 4428. E-mail: veselkoff@mail.ru
[b]"Interbioscreen" Company,
8 Institutskii prosp., 142432 Chernogolovka, Moscow region, Russian Federation.
Fax: +7 (095) 913 2114. E-mail: screen@ibscreen.ru
[c]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul. Vavilova, 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5085. E-mail: vkh@xrlab.ineos.ac.ru

6-Methyl-4-methoxy-5,6,7,8-tetrahydro-2*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-ol (cotarnine) and its derivatives, namely, 5-dihydrocotarnyl-1,3-dimethylbarbituric acid, dihydrocotarnylnitromethane, and dihydrocotarnylphenylacetonitrile, react with an excess of 1,3-dimethylbarbituric acid to give its 5,5-spiro derivative. The structure of the latter was proved by X-ray diffraction analysis. A possible reaction mechanism was discussed.

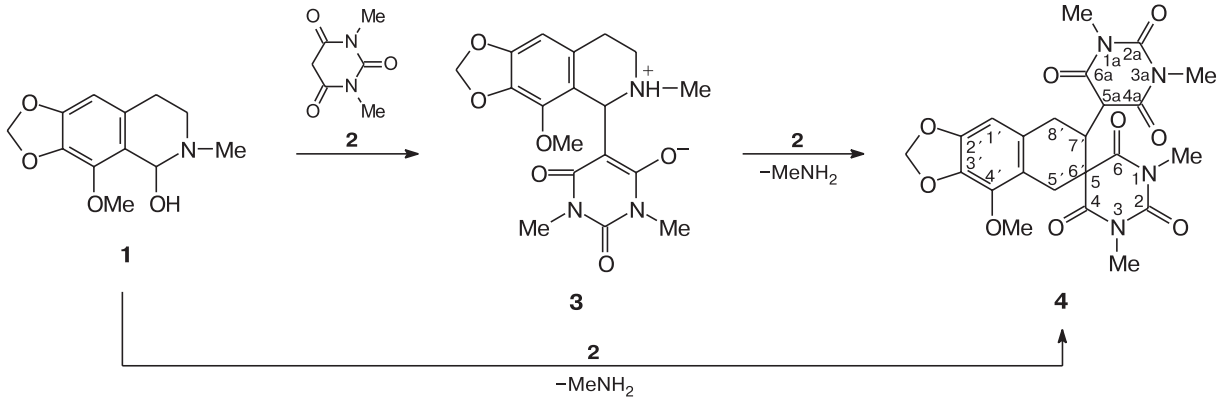
Key words: cotarnine, 1,3-dimethylbarbituric acid, 5-dihydrocotarnyl-1,3-dimethylbarbituric acid, 5,5-spiro derivatives of barbituric acid, X-ray diffraction analysis, NMR spectroscopy.

Earlier,[1,2] it has been found that heating of 4-methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-ol (cotarnine, **1**) with 1,3-dimethylbarbituric acid (**2**) in chloroform yields 5-(8-methoxy-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-1,3-dimethylbarbituric (5-dihydrocotarnyl-1,3-dimethylbarbituric) acid (**3**). The structure of the compound obtained was determined using X-ray diffraction analysis and ^{1}H NMR spectroscopy.

When heating compound **3** and acid **2** under drastic conditions, we found that methylamine is eliminated and that the reaction product is a 5,5-spiro derivative of barbituric acid (**4**), which can also be obtained directly from cotarnine and acid **2**. In the latter case, the reaction probably proceeds through intermediate **3** (Scheme 1).

According to the X-ray diffraction data (Fig. 1), crystal **4** is a racemate. Two crystallographically independent molecules (**A** and **B**) in its unit cell are linked by a

Scheme 1



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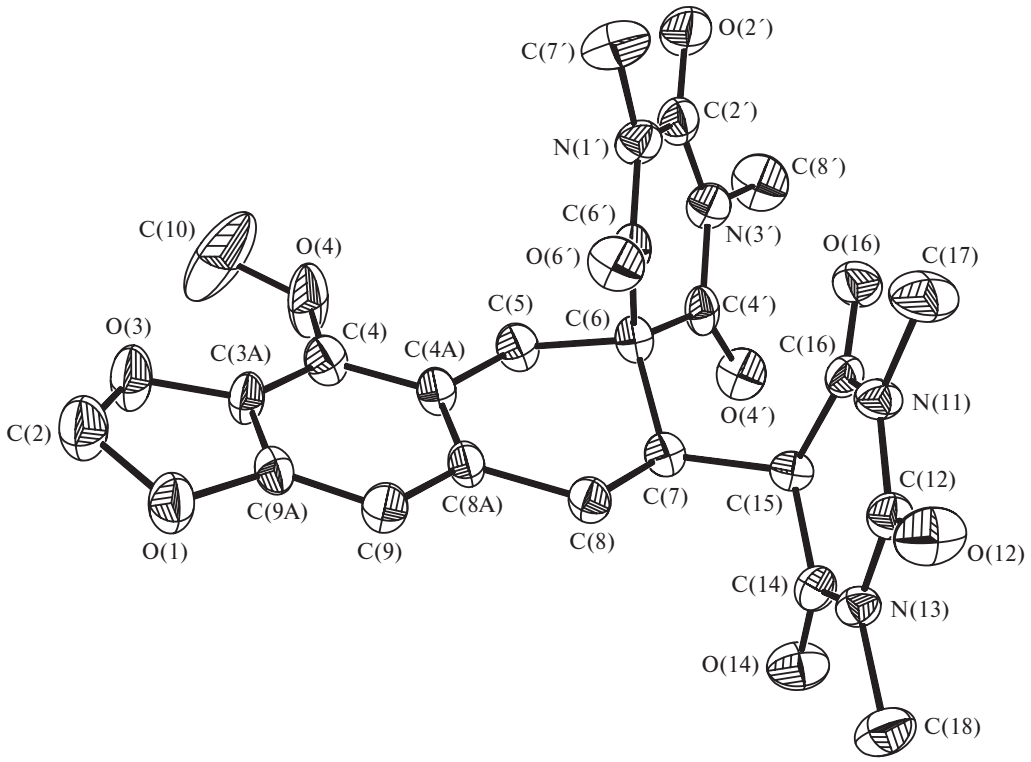
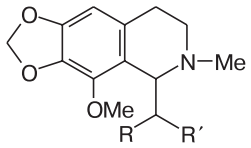


Fig. 1. Molecular structure of compound **4** (one of the two crystallographically independent molecules is shown with anisotropic thermal displacement ellipsoids (50% probability)).

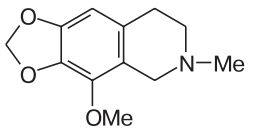
pseudocenter of inversion with the following coordinates: 0.2480, 0.8223, and 0.2651. Both independent molecules have virtually the same geometry, except for the torsion angle of the Me fragment in the methoxy group (the C(3A)—C(4)—O(4)—C(10) angle in **A** is –83.5(8)°, while the analogous C(3AA)—C(4AB)—O(4A)—C(10A) angle in **B** is 10.6(12)°). For this reason, only structure **A** will be considered in the discussion that follows. The bond lengths and angles in compound **4** have standard values. The trioxopyrimidine rings exist in a "sofa" conformation; the C(6) and C(15) atoms deviate from the plane of the other atoms in the corresponding heterocycle by 0.397 and 0.224 Å, respectively. The cyclohexene fragment has the same conformation (the C(6) atom extends 0.711 Å from the plane of the other ring atoms). The conformation of the 1,3-dioxolane ring is an "envelope" with the C(2) atom deviating from the plane of the heterocycle by 0.205 Å. The dihedral angles between the C(5)—C(4A)—C(8A)—C(8)—C(7) plane in the cyclohexene ring and the C(16)—N(11)—C(12)—N(13)—C(14) and C(6′)—N(1′)—C(2′)—N(3′)—C(4′) planes in the trioxopyrimidine rings are 89.7° and 63.7°, respectively. The molecules are stacked along the *Y* axis; the molecular stacks are united into layers linked by axis 2_1 and running parallel to the *XY*0 plane.

The yield of spiro derivative **4** from the reaction of compound **1** (or **3**) with acid **2** significantly depends on the solvent nature (Table 1), being higher in more polar solvents.

Like cotarnine, dihydrocotarnylnitromethane (**5**) and dihydrocotarnylphenylacetonitrile (**6**) react with acid **2** to give spiro derivative **4**. Apparently, these reactions also proceed through intermediate **3**.



5: R = H, R′ = NO_2
6: R = CN, R′ = Ph



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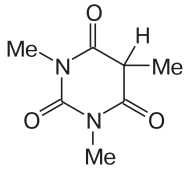

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Apart from spiro derivative **4**, the reactions studied afford 4-methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-[1,3]dioxolo[4,5-*g*]isoquinoline (**7**) (5—8%), 1,3,5-trimethylbarbituric acid (**8**) (2—5%), and unidentified compounds with molecular masses >700 (50—70%).

Table 1. Reaction conditions for cotarnine (**1**) and its derivatives (**3**, **5**, and **6**) with 1,3-dimethylbarbituric acid (**2**) and the yields of compound **4**

Starting reagents (number of moles)	Solvent	Yield of **4** (%)
1 (1) + **2** (2)	—	6
1 (1) + **2** (2)	*n*-Decane	9
1 (1) + **2** (2)	PhBr	16
3 (1) + **2** (1)	PhBr	17
1 (1) + **2** (2)	$MeCONMe_2$	22
3 (1) + **2** (1)	$MeCONMe_2$	24
1 (1) + **2** (3)	$MeCONMe_2$	28
1 (1) + **2** (3) + Et_3N (1)	$MeCONMe_2$	44
3 (1) + **2** (2) + Et_3N (1)	$MeCONMe_2$	48
5 (1) + **2** (2)	$MeCONMe_2$	33
6 (1) + **2** (2)	$MeCONMe_2$	35

The mechanism of the reaction under discussion remains the most difficult problem. We assumed that the formation of compound **4** includes four steps (Scheme 2).

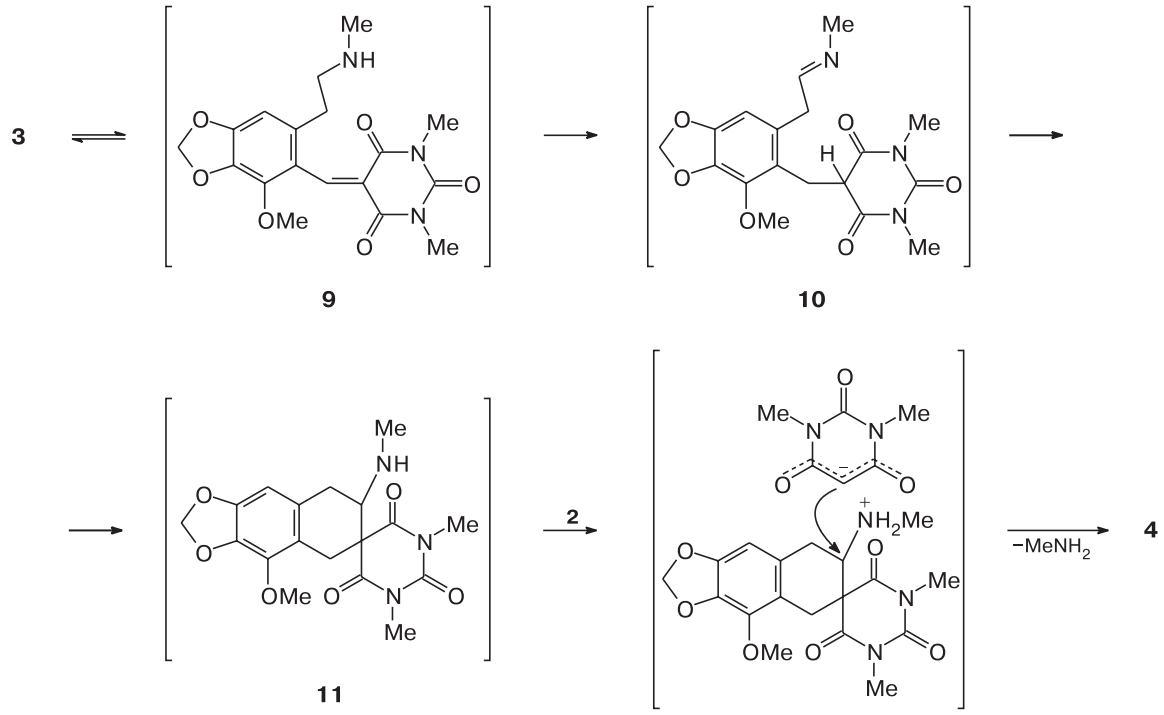
Step *1* (3 → 9). It is known that ring-chain tautomerism is possible for cotarnine and some of its derivatives.[3,4] We thus believe that there is an equilibrium in solution between compound **3** and a corresponding 5-arylidene-1,3-dimethylbarbituric acid **9**, which accounts for no higher than 0.1% of the tautomeric mixture. The opening of the tetrahydropyridine ring in compound **3**, which is colorless in the solid state, is indirectly confirmed by its yellow color in aprotic solvents (λ_{max} = 408—412 nm). Such a color is characteristic of 5-alkoxybenzylidenebarbituric acids;[5] its intensity is enhanced with heating and returns to the starting level upon cooling.

Step *2* (9 → 10). 5-Benzylidenebarbituric acids are known to show oxidative properties since their active C=CHAr double bond can easily be reduced, *e.g.*, by heating with formic acid in the presence of Me_3N.[6] We assumed that tautomer **9** disproportionates *in situ* (its amino group undergoes intramolecular oxidation, while the arylidene double bond is reduced) to give intermediate **10**. Taking into account that redox reactions of 5-benzylidenebarbituric acids are catalyzed by bases,[6] we carried out the reaction of compound **3** with acid **2** in the presence of Et_3N and, as expected, significantly increased the yield of product **4** (see Table 1).

Step *3* (10 → 11). The intramolecular Michael cyclization of compound **10** seems to be quite obvious.

Step *4* (11 + 2 → 4). Apparently, the final step of this process should be regarded as analogous to the known[7] alkylation of barbituric acids with alkylamines. In this case, intermediate amino derivative **11** can be assumed to be protonated with an excess of acid **2**. The resulting nucleophilic carbanion $\mathbf{2}^-$ attacks the secondary C atom of the CH^+NH_2Me fragment in substrate $\mathbf{11}^+$ to give, upon elimination of neutral methylamine, compound **4**. An alternative attack of carbanion $\mathbf{2}^-$ on the ^+NMe group of the same substrate results in the splitting of the Me

Scheme 2



group; this can account for the formation of compound **8** by methylating the starting acid **2**. Insofar as the molar ratio of derivative **4** to compound **8** in the final reaction mixture is ~7—8 : 1, one can state that substrate $\mathbf{11}^+$ undergoes selective splitting. Intermediate **11** was not isolated, probably because of its substantially higher reactivity under these conditions compared to, *e.g.*, Et_3N, which is dealkylated with acid **2** at a noticeable rate only at $T > 170$ °C.

It should be noted in conclusion that the aforesaid unusual multistep process yielding the new spiroheterocyclic system **4** calls for further investigation aimed at extending the discovered reactions to other derivatives of barbituric acid and cotarnine analogs.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer (500 and 125 MHz, respectively). Mass spectra were recorded on an MX-1303 instrument (direct inlet of a sample into the ion source at 150 °C, ionizing voltage 70 eV). The purity of the reaction products was checked by TLC on Silufol UV-254 plates in $CHCl_3$—AcOEt (4 : 1), $CHCl_3$—AcOEt—AcOH (3 : 2 : 0.1), Pr^iOH—water (4 : 1), or DMF—NH_4OH (25%) (3 : 1).

Cotarnine (**1**) was isolated from cotarnine hydrochloride according to the known procedure.[8] Dihydrocotarnylnitromethane (**5**) and dihydrocotarnylphenylacetonitrile (**6**) were prepared by the reactions of cotarnine (**1**) with nitromethane or phenylacetonitrile, respectively.[9] 5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-[1,3]dioxolo[4,5-*g*]isoquinoline (**7**) was synthesized by reducing cotarnine;[10] 1,3,5-trimethylbarbituric acid (**8**) was obtained by methylation of acid **2**.[6]

4´-Methoxy-1,3-dimethyl-7´-(1,3-dimethyl-2,4,6-trioxoperhydropyrimidin-5-yl)-2,4,6-trioxospiro[perhydropyrimidine-5,6´-(5´,6´,7´,8´-tetrahydro[1,3]dioxolo[4,5-*g*]naphthalene)] (4) (general procedure). Cotarnine **1** or its derivatives **3**, **5**, and **6** (1 mmol) was mixed with acid **2** (2 or 3 mmol). The reaction was carried out either in 10 mL of a solvent or without any solvent (see Table 1). The reaction mixture was refluxed in an oil bath at 160 °C for 20 min, cooled, and treated with aqueous 5% NH_3 (50 mL). The precipitate that formed was filtered off, and the organic material was extracted from the aqueous solution with $CHCl_3$ (3×20 mL). The extracts were combined (fraction *1*). The aqueous solution was acidified with HCl to pH 1, and the precipitate that formed was filtered off and washed with water. The organic material was extracted from the resulting aqueous acid solution with $CHCl_3$ (3×20 mL), and the extracts were combined (fraction *2*). The precipitate was transferred from the filter to a flask and treated with 3% AcONa (100 mL) while stirring it for 1 h. The undissolved portion was separated, the solution was acidified with HCl to pH 1, and the precipitate that formed was filtered off, washed with water, and dried to give compound **4** as colorless crystals, m.p. 234—235 °C (from CCl_4). The yield of **4** is given in Table 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. ^{1}H NMR ($CDCl_3$), δ: 2.71 (dd, 1 H, *exo*-H(8´), J = 14.0 Hz, J = 6.0 Hz); 2.86 (d, 1 H, *exo*-H(5´), J = 15.5 Hz); 3.19 (s, 6 H, N(1a)Me + N(3a)Me); 3.20 (d, 1 H, *endo*-H(5´), J = 15.5 Hz); 3.27, 3.36 (both s, 3 H each, N(1)Me, N(3)Me); 3.37 (dd, 1 H, *endo*-H(8´), J = 14.0 Hz, J = 6.0 Hz); 3.45 (m, 1 H, H(7´)); 3.78 (d, 1 H, H(5´), J = 7.0 Hz); 3.90 (s, 3 H, OMe); 5.82 (AB system, 2 H, OCH_2O, J = 19.0 Hz); 6.26 (s, 1 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 28.4, 28.5, 28.6, 29.1 (N(1)Me, N(3)Me, N(1a)Me, N(3a)Me); 29.7 (C(5´)); 36.7 (C(8)); 41.5 (C(7)); 49.3 (C(5)); 50.9 (C(5a)); 59.3 (MeO); 100.7 (OCH_2O); 101.9 (C(1´)); 114.2 (C(2´)); 128.6 (C(4´)); 133.9 (C(3´)); 140.1 (C(4″)); 148.4 (C(8″)); 151.3 (C(2), C(2a)); 167.9, 168.2, 169.4, 171.8 (C(4), C(6), C(4a), C(6a)). MS, m/z (I_{rel} (%)): M^+ 500 (3), 344 (100), 327 (11), 259 (2), 229 (5), 189 (1), 157 (2), 143 (1).

4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-[1,3]dioxolo[4,5-*g*]isoquinoline (7). A solution of fraction *1* in chloroform (see above) was treated with 5% HCl (20 mL). An aqueous acid extract was separated and washed with pure chloroform (10 mL). Then the aqueous solution was alkalified with aqueous NH_3, and the organic material was extracted with ether (2×20 mL). The combined ethereal solutions were washed with water, dried with Na_2SO_4, and saturated with dry HCl at 0 °C. The precipitate that formed was washed with ether, dried, dissolved in 5 mL of water, and alkalified with KOH. The resulting oil was extracted with ether, and the extract was washed with water and concentrated *in vacuo* to give compound **7** (100—200 mg, 5—8%) as a light yellow oil. Product **7** is identical with an authentic sample obtained in an independent way (TLC and ^{1}H NMR data).[10] The oil crystallized within one to two days, m.p. 51—52 °C (*cf.* Ref. 10: m.p. 55 °C). ^{1}H NMR ($CDCl_3$), δ: 2.41 (s, 3 H, NMe); 2.57 (t, 2 H, $ArCH_2$, J = 5.5 Hz); 2.77 (t, 2 H, NCH_2, J = 5.5 Hz); 3.40 (s, 2 H, CH_2); 2.57 (s, 3 H, OMe); 5.83 (s, 2 H, OCH_2O); 6.27 (s, 1 H, ArH).

1,3,5-Trimethylbarbituric acid (8). A solution of fraction *2* in chloroform (see above) was evaporated to dryness to give a mixture of acids **2** and **8** (0.5—1.3 g). The mixture was analyzed using TLC and ^{1}H NMR spectroscopy as described earlier.[7] The yield of compound **8** was 30 to 80 mg (5—8%).

X-ray diffraction analysis of compound 4. Crystals of compound **4** were grown from $CHCl_3$—heptane, 1 : 5 ($C_{23}H_{24}N_4O_9$, M = 500.46). The crystals are monoclinic, space group $P2_1/c$, at T = 293 K: a = 23.274(4) Å, b = 12.966(3) Å, c = 15.395(3) Å, β = 98.714(15)°, V = 4591.9(17) Å^3, Z = 8, d_{calc} = 1.448 g cm^{-3}, $F(000)$ = 2096, μ = 0.113 mm^{-1}. The unit cell parameters and the intensities of 5963 reflections were measured on a Siemens P3/PC automated four-circle diffractometer (T = 293 K, λ-Mo$K\alpha$ radiation, graphite monochromator, θ/2θ scan mode, θ_{max} = 23°). The structure was determined by the direct method and refined by the full-matrix least-squares method in the anisotropic approximation for nonhydrogen atoms. The H atoms were located geometrically and refined in the isotropic approximation with fixed coordinates (riding model) and thermal parameters (U_{iso}(H) = 1.5U_{eq}(C) for the Me group and U_{iso}(H) = 1.2U_{eq}(C) for the other groups). The final discrepancy factors are R_1 = 0.0696 for 3067 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.1536 for all 5784 independent reflections. All calculations were performed with the use of the SHELXTL PLUS program package (Version 5.10).[11]

Tables of atomic coordinates, bond lengths and angles, torsion angles, and anisotropic thermal parameters for compound **4** have been deposited with the Cambridge Crystallographic Database.

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