*Chemistry of Natural Compounds, Vol. 37, No. 6, 2001*

# CHEMICAL MODIFICATION OF PLANT ALKALOIDS. 2. REACTION OF COTARNINE WITH BARBITURIC ACID DERIVATIVES AND STRUCTURE OF 5-DIHYDROCOTARNYLBARBITURIC ACIDS

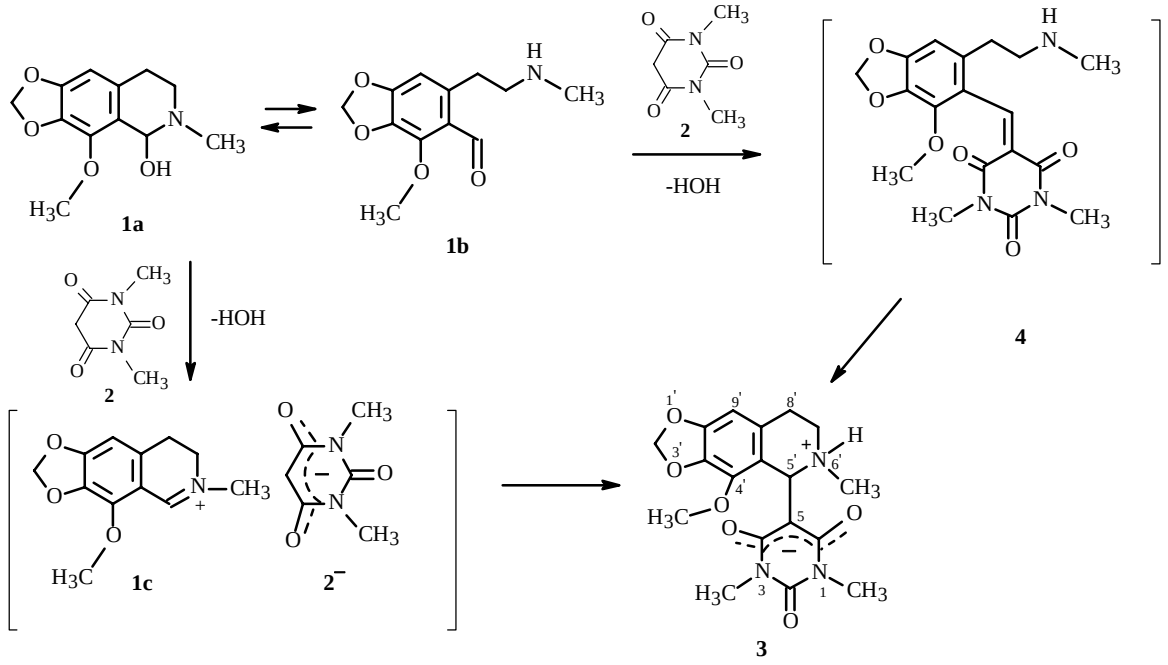
**K. A. Krasnov,[1] V. G. Kartsev,[2] and M. N. Yurova[1]**

UDC 547.854+547.689.6+547.833.3

*The reaction of barbituric acid and its N-substituted derivatives and 2-thio analogs with cotarnine forms 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-g]isoquinolinyl-1)barbituric acids, a new class of zwitter-ions, the structure of which was studied by $^{1}H$ and $^{13}C$ NMR spectroscopy and mass spectrometry. The prepared compounds exist in solution as stable intermolecular associates and have a complicated H-bonded structure.*

**Key words:** cotarnine, 5-dihydrocotarnylbarbituric acids, zwitter-ionic structure.

Cotarnine is a tetrahydroisoquinoline pseudo-base [1]. The free base can be represented as a mixture of two tautomers, cyclic **1a** and open **1b**, with the former predominating. Protonation induces dehydration and forms cation **1c**. The chemical properties of this compound have been reviewed in detail [2].




Therefore, cotarnine on one hand exhibits properties typical of aromatic aldehydes and, on the other, reacts with certain CH- and NH-acids to produce tetrahydroisoquinoline Mannich bases [2, 3]. Such a reaction can be used to synthesize compounds that are structurally related to isoquinoline alkaloids and other natural products [2-5].

1) I. I. Mechnikov St. Petersburg State Medical Academy, 195067, St. Petersburg, Piskarevskii pr., 47; 2) ZAO "InterBioScreen," 142432, Chernogolovka, Moscow District, Institutskii pr., 8. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 465-471, November-December, 2001. Original article submitted October 18, 2001.

0009-3130/01/3706-0543$25.00 

We previously found [6] that cotarnine (**1**) in $CHCl_3$ reacts with 1,3-dimethylbarbituric acid (**2**) to give 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy[4,5-*g*]isoquinolinyl-1)1,3-dimethylbarbituric (dihydrocotarnyl-1,3-dimethylbarbituric) acid (**3**). The structure and stereochemistry of this unusual zwitter-ion system was studied in the solid state by x-ray structural analysis and in solution by $^1H$ and $^{13}C$ NMR spectroscopy [6]. The mechanism of formation of **3** has not been discussed.

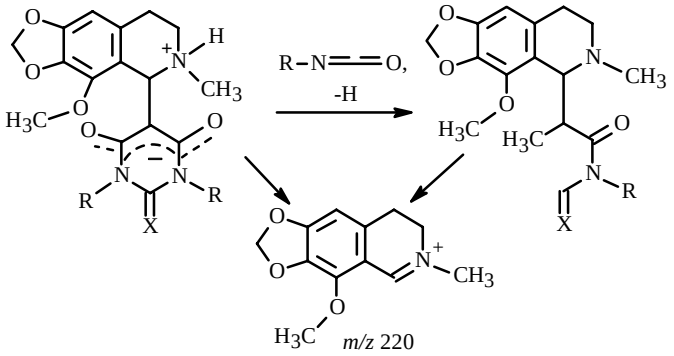
We assume that the reaction of **2** and the aldehyde tautomer **1b** produces arylidene derivative **4**, which is a typical reaction of barbituric acid with aromatic aldehydes [7]. Considering that the reactive C-5 double bond in 5-benzylidenebarbituric acids is susceptible to reversible addition of nucleophiles [8], intermediate **4** should add intramolecularly the secondary amine (Michael reaction) to form **3**. The appearance in the reaction mixture of an unstable colored product with an absorption maximum in the range 400-430 nm, which is characteristic of 5-alkoxybenzylidenebarbituric acid [7], should provide indirect evidence that **4** is involved in the reaction. The absorption maxima of the other components are found at shorter wavelengths.

However, a study of the reaction kinetics indicates that another formation mechanism of **3** is possible. We used UV spectra to show that the reaction at a concentration of $2\times10^{-5}$ M in $CHCl_3$ is ~50% complete after 70 min at 20°C. The reaction rate does not change if the starting concentrations are increased and obeys a first-order equation. Thus, the UV spectrum contains only 30 sec after mixing the reagents absorption bands characteristic of the acid anion **2** ($\lambda_{max}$ 260 nm) and cotarnine cation (**1c**) ($\lambda_{max}$ 335 nm). It can be proposed that a salt or ion pair [(**1c**$^+$)—(**2**$^-$)] forms in a first rapid step. Then it slowly adds carbanion $2^-$ to the electrophilic double bond of **1c** in a second step to form **3**.

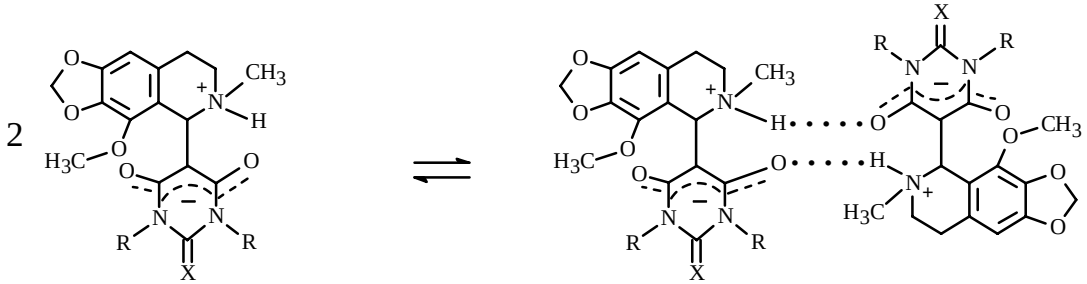
Considering the equilibrium nature of these reactions, both mechanisms could occur simultaneously. The first is more probable in polar solvating solvents; the second, in slightly polar aprotic media.

We established that 1,3-dimethyl-2-thiobarbituric (**5a**) and 1,3-diethyl-2-thiobarbituric (**5b**) acids react with cotarnine to form 1,3-dialkyl-2-thio-5-dihydrocotarnylbarbituric acids (**6a** and **b**). The structures of these were proved using mass spectra and $^1H$ and $^{13}C$ NMR spectra (Tables 1 and 2).

The mass spectra of **3** and **6a** and **b** contain peaks for the molecular ions with characteristic fragmentation into [M - RNCO] ions and an ion with *m*/*z* 220. This suggests a general pattern for the primary fragmentation of **3** and **6a** and **b** via electron impact:




Complicated differences are observed in the $^1H$ and $^{13}C$ NMR spectra of **3** and **6a** and **b** owing to the occurrence of slow tautomerism in their solutions. We determined earlier using an x-ray structural analysis and $^1H$ NMR spectra that 5-dihydrocotarnyl-1,3-dimethylbarbituric acid (**3**) tends to form associates (dimers) stabilized by intermolecular H-bonds [6]. Only the dimer is observed in the solid state; an equilibrium mixture of the monomer (A) and dimer (B), in solutions.




**3:** X = O, R = Me; **6a:** X = S, R = Me; **6b:** X = S, R = Et

TABLE 1. Chemical Shifts (δ, ppm) and Relative Content of Isomers (Monomer/Dimer) for **3**, **6a** and **b**, and **8a-r** in DMSO-$d_6$ at 20°C and 0.05 M

| Com-pound | Isomer content, % | Me-6′, s | 2H-7′, m 2H-8′, m | OMe-4′, s | H-5′, s | H-2′, s | H-9′, br.s | H-6′, s | H-1(3) br.s | Other aliphatic protons (J, Hz) | Other aromatic protons, m |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3** | B, 11 | 2.64 | 2.73-3.68 | 3.55 | 5.68 | 5.93 | 6.46 | 9.26 | - | 3.06(6H, s) | - |
| | A, 89 | 2.73 | 2.73-3.68 | 3.58 | 5.30 | 5.92 | 6.46 | 8.49 | - | 3.06(6H, s) | - |
| **6a** | B, 65 | 2.77 | 2.75-3.60 | 3.55 | 5.40+5.42 | 5.91 | 6.47 | 8.45 | - | 3.44(3H, s) | - |
| | A, 35 | 2.71 | 2.75-3.60 | 3.58 | 5.62 | 5.93 | 6.47 | 9.38 | - | 3.44(3H, s) | - |
| **6b** | B, 63 | 2.75 | 2.76-3.68 | 3.53 | 5.40+5.41 | 5.93 | 6.49 | 8.48 | - | 1.12(6H, t , J=6.1), 4.36(4H, m) | - |
| | A, 37 | 2.67 | 2.76-3.68 | 3.55 | 5.66 | 5.96 | 6.49 | 9.42 | - | 1.00(6H, m), 4.36(4H, m) | - |
| **8a** | B, 35 | 2.69 br.s | 2.81-3.48 | 3.65 | 5.53 | 5.93 | 6.46 | 8.88 | 9.25 | | - |
| | A, 65 | 2.69 br.s | 2.81-3.48 | 3.67 | 5.28 | 5.92 | 6.46 | 8.60 | 9.25 | | |
| **8b** | B, 25 | 2.73 br.s | 2.75-3.50 | 3.67 | 5.65 | 5.90 | 6.36 | 9.17 | 9.43 | 3.04(6H, m) | - |
| | A, 75 | 2.73 br.s | 2.75-3.50 | 3.67 | 5.25 | 5.90 | 6.36 | 8.65 | 9.43 | 3.04(6H, s) | - |
| **8c** | B, 36 | 2.66 | 2.75-3.60 | 3.55 | 5.58+5.62 | 5.91 | 6.46 | 9.22 | 9.48+9.85 | - | 7.20(5H) |
| | A, 64 | 2.72 | 2.75-3.60 | 3.57 | 5.33 | 5.94 | 6.46 | 8.53 | 9.80 | - | 7.20(5H) |
| **8d** | B, 39 | 2.71 | 2.66-3.48 | 3.70 | 5.59+5.66 | 5.95 | 6.42+6.49 | 9.25 | 9.63 | 4.74-4.96(m, $CH_2$) | 6.98-7.39(5H) |
| | A, 61 | 2.73 | 2.66-3.48 | 3.70 | 5.34 | 5.95 | 6.46 | 8.54 | 9.59 | 4.74-4.96(m, $CH_2$) | 6.98-7.39(5H) |
| **8e** | B, 40 | 2.79 | 2.70-3.49 | 3.79 | 5.62+5.71 | 5.92 | 6.30+6.37 | 9.35 | 9.24 | - | 6.98-7.20 |
| | A, 60 | 2.79 | 2.70-3.49 | 3.79 | 5.37 | 5.91 | 6.31 | 8.68 | 9.58 | - | 6.98-7.20 |
| **8f** | B, 37 | 2.77 | 2.68-3.45 | 3.77 | 5.59+5.67 | 5.92 | 6.35 | 9.22 | 9.36 | - | 7.02+7.28(2+2H) |
| | A, 63 | 2.77 | 2.68-3.45 | 3.77 | 5.34 | 5.90 | 6.35 | 8.62 | 9.70 | - | 7.10+7.35(2+2H) |
| **8g** | B, 38 | 2.75 | 2.70-3.50 | 3.77 | 5.60+5.68 | 5.92 | 6.32 | 9.20 | 9.26 | - | 6.94+7.43(2+2H) |
| | A, 62 | 2.78 | 2.70-3.50 | 3.77 | 5.35 | 5.91 | 6.32 | 8.65 | 9.63 | - | 7.05+7.47(2+2H) |
| **8h** | B, 30 | 2.76 | 2.70-3.50 | 3.77 | 5.61+5.67 | 5.93 | 6.32 | 9.18 | 9.05 | 2.35(3H, s) | 6.85+7.10(2+2H) |
| | A, 70 | 2.78 | 2.70-3.50 | 3.77 | 5.36 | 5.91 | 6.32 | 8.63 | 9.62 | 2.37(3H, s) | 6.96+7.13(2+2H) |
| **8j** | B, 36 | 2.73 | 2.70-3.52 | 3.74 | 5.57+5.66 | 5.93 | 6.34+6.40 | 9.21 | 9.15 | 3.78(3H, s) | 6.81-7.05(4H) |
| | A, 64 | 2.77 | 2.70-3.52 | 3.74 | 5.35 | 5.93 | 6.36 | 8.61 | 9.53 | 3.78(3H, s) | 6.81-7.05(4H) |
| **8k** | B, 55 | 2.71 br. s | 2.95-3.60 | 3.70 | 5.32 br.s | 5.90 | 6.39 | 8.75 | 10.53 | - | - |
| | A, 45 | 2.71 br.s | 2.95-3.60 | 3.70 | 5.55 br.s | 5.93 | 6.39 | 9.25 | 10.53 | - | - |
| **8i** | B, 62 | 2.75 | 2.97-3.50 | 3.64 | 5.33 | 5.90 | 6.42 | 8.61 | 10.80 | 3.42(3H, s) | - |
| | A, 38 | 2.68 | 2.97-3.50 | 3.69 | 5.60 | 5.94 | 6.42 | 9.31 | 10.56+10.8 | 3.42(3H, s) | - |
| **8l** | B, 55 | 2.73 | 2.55-3.50 | 3.63 | 5.28 | 5.92 | 6.40 | 8.54 | 10.45 | 1.10-1.76(10H, m), 5.50(1H, m) | - |
| | A, 45 | 2.66 | 2.55-3.50 | 3.63 | 5.57 | 5.90 | 6.40 | 9.40 | 10.45 | 1.10-1.76(10H, m), 5.50(1H, m) | - |
| **8m** | B, 59 | 2.76 | 2.70-3.55 | 3.75 | 5.35 | 5.94 | 6.40 | 8.62 | 10.96 | - | 7.05+7.36(2+3H) |
| | A, 41 | 2.76 | 2.70-3.55 | 3.75 | 5.50+5.62 | 5.94 | 6.40 | 9.35 | 10.67 | - | 7.01+7.27(2+3H) |
| **8n** | B, 56 | 2.77 | 2.90-3.50 | 3.75 | 5.33 | 5.95 | 6.40 | 8.62 | 10.92 | - | 7.00-7.20 |
| | A, 44 | 2.77 | 2.90-3.50 | 3.75 | 5.55+5.64 | 5.95 | 6.40 | 9.34 | 10.63 | - | 6.90-7.10 |
| **8o** | B, 61 | 2.80 | 2.75-3.55 | 3.78 | 5.35 | 5.91 | 6.36 | 8.67 | 10.88 | - | 7.05+7.33(2+2H) |
| | A, 39 | 2.80 | 2.90-3.63 | 3.78 | 5.57+5.67 | 5.91 | 6.36 | 9.26 | 10.55 | - | 6.90+7.25(2+2H) |
| **8p** | B, 61 | 2.79 | 2.74-3.50 | 3.77 | 5.37 | 5.93 | 6.35 | 8.64 | 10.79 | 2.38(3H, s) | 6.93-7.20 |
| | A, 39 | 2.72 | 2.74-3.62 | 3.80 | 5.55+5.67 | 5.93 | 6.32+6.40 | 9.26 | 10.64+10.9 | 2.35+2.40 (3H, s+s) | 6.93-7.20 |
| **8q** | B, 61 | 2.80 | 2.72-3.53 | 3.79 | 5.36 | 5.94 | 6.34 | 8.66 | 10.58 | 3.80(3H, s) | 6.75-7.00 |
| | A, 39 | 2.80 | 2.75-3.63 | 3.79 | 5.57+5.67 | 5.94 | 6.33+6.38 | 9.23 | 10.35+10.6 | 3.80(3H, s) | 6.75-7.00 |
| **8r** | B, 70 | 2.86 | 2.73-3.50 | 3.88 | 5.41+5.42 | 5.94 m | 6.33 | 8.61 | - | - | 7.05-7.37(10H, m) |
| | A, 30 | 2.81 | 2.73-3.50 | 3.89 | 5.68 | 5.94 m | 6.34 | 9.37 | - | - | 7.05-7.37(10H, m) |

———

Monomer (A) and dimer (B).

TABLE 2. $^{13}$C NMR Spectra (δ, ppm) for Monomer and Dimer of **3**, **6a**, and **8k** in DMSO-$d_6$ at 20°C

| Com-pound | Form | Me-1(3) | C-2 | C-4(6) | C-5 | C-1′ | C-2′ | C-3′ | C-4′ | OMe-4′ | C-4′a | C-5′ | Me-6′ | C-7′ | C-8′ | C-8′ | C-9′ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3** | A | | 152.76 | | 82.56 | 135.69 | 100.81 | 147.01 | 139.81 | 58.80 | 127.08 | 60.30 | 25.34 | 49.39 | 40.40 | 120.26 | 101.94 |
| | B | | 152.76 | | 78.46 | 134.83 | 100.73 | 147.44 | 138.81 | 59.02 | 126.55 | 56.92 | 24.97 | 47.13 | -* | 120.80 | 101.75 |
| **6a** | A | 26.66 | 176.55 | 161.78 | 84.02 | 135.68 | 102.64 | 148.16 | 139.73 | 59.61 | 127.10 | 57.05 | 26.90 | 50.25 | 41.33 | 121.10 | 102.61 |
| | B | | 176.03 | | 87.90 | 136.25 | 102.79 | 147.85 | 140.68 | 59.33 | 127.83 | 60.56 | 25.97 | 48.04 | 41.65 | 120.78 | 102.79 |
| **8k** | A | | 175.58 | | 82.93 | 134.49 | 100.85 | 147.61 | 138.78 | 59.26 | 126.63 | 56.40 | 26.41 | 47.35 | 40.61 | 119.77 | 101.74 |
| | B | | 175.41 | | 87.21 | 135.45 | 100.90 | 147.17 | 139.72 | 58.91 | 127.20 | 59.10 | 25.20 | 49.41 | -* | 119.36 | 101.99 |

*Overlaps DMSO signal (39.0-40.0 ppm); Monomer (A) and dimer (B).

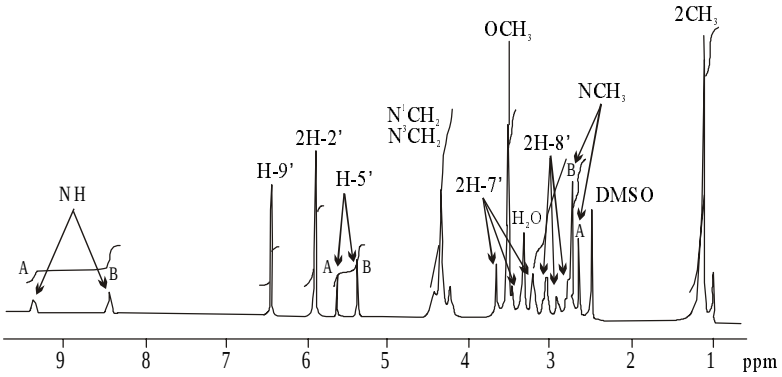



Fig. 1. $^1$H NMR spectrum of **6b** (DMSO-$d_6$, 20°C, 0.05 M). Separated signals of isomers: monomer (A) and dimer (B). In other instances, signals of isomers overlap.

The $^1$H NMR spectra of 2-thio derivatives **6a** and **b**, like that of **3** (Table 1), contain doubled sets of signals, the relative strength of which depends on the solution concentration. This is explained by the presence of an equilibrium mixture of the monomer and dimer (Fig. 1), the spectral properties of which differ and the exchange between which occurs slowly at 20°C (<1 per minute).

Figure 1 shows the spectrum of **6b**. Under these conditions, it contains 36% monomer and 64% dimer. The quantitative ratio of the isomers was found by integrating intensities of the most characteristic pairs of signals, which correspond with the $C^{1'}$–H and $N^{2'}$–H protons. Signals were assigned to the monomer and dimer based on a study of the concentration dependence of the spectra taking into account that dilution should shift the equilibrium in favor of the monomer owing to increased dissociation of the dimer.

A comparison with 5-dihydrocotarnyl-1,3-dimethylbarbituric acid (**3**) showed that **6a** and **b** exhibit an increased tendency to associate. The relative content of the dimer in solutions of these compounds under identical conditions was ~10 times greater than that for the oxygen analog **3** (Table 1). The predominance of the dimer indicates that intramolecular H-bonds in the monomers of **6a** and **b** are weaker than those in the dimers.

This fact can be explained by the fact that the planes of the pyrimidine and tetrahydroisoquinoline rings are perpendicular. This makes formation of intramolecular H-bonds unfavorable.

It is interesting to note that the degree of association of **3** and **6a** and **b** is practically independent of the solvent polarity. The ratio of isomers remained the same, within the uncertainty limits of integration, on going from DMSO to $CHCl_3$ at the same concentration (0.05 M).

The rate of the exchange processes was estimated using dynamic $^1$H NMR. Signals of the isomers coalesce in the $^1$H NMR of **3** in DMSO-$d_6$ at 44-45°C; of the thioanalogs **6a** and **b**, at 85-90°C (with decomposition). This indicates that the activation energy of the transition between dimer and monomer is much higher for **6a** and **b**. Apparently this is due to stronger H-bonds in dimers of **6a** and **b**.

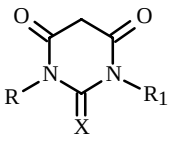
TABLE 3. Yield, Melting Point, and Elemental Analysis of **3**, **6a** and **b**, and **8a-r**

| Compound | Empirical formula | mp, °C | Yield, %, synthesis method |
|---|---|---|---|
| **3** | $C_{18}H_{21}N_3O_6$ | 201-203 | 86A |
| **6a** | $C_{18}H_{21}N_3O_5S$ | 210-211 | 92A |
| | | | 81B |
| **6b** | $C_{20}H_{25}N_3O_5S$ | 187-188 | 90A |
| | | | 73B |
| **8a** | $C_{16}H_{17}N_3O_6 \cdot H_2O$ | >200p | 65C |
| **8b** | $C_{17}H_{19}N_3O_6$ | 188-191 | 82A |
| **8c** | $C_{23}H_{23}N_3O_6$ | 220-221 | 68B |
| **8d** | $C_{22}H_{21}N_3O_6$ | 198-199 | 67B |
| **8e** | $C_{22}H_{20}FN_3O_6$ | 173-179 | 88B |
| **8f** | $C_{22}H_{20}ClN_3O_6$ | 153-157 | 50B |
| **8g** | $C_{22}H_{20}BrN_3O_6$ | 202-204 | 89B |
| **8h** | $C_{23}H_{23}N_3O_6$ | 174-177 | 63B |
| **8i** | $C_{23}H_{23}N_3O_7$ | 195-198 | 70B |
| **8j** | $C_{16}H_{17}N_3O_5S\ H_2O$ | >210p. | 28B |
| | | | 74C |
| **8k** | $C_{17}H_{19}N_3O_5S$ | 192-193 | 63B |
| **8l** | $C_{22}H_{27}N_3O_5S$ | 221-223 | 91B |
| **8m** | $C_{22}H_{21}N_3O_5S$ | 226-228 | 80B |
| **8n** | $C_{22}H_{20}FN_3O_5S$ | 221-225 | 79B |
| **8o** | $C_{22}H_{20}ClN_3O_5S$ | 194-196 | 68B |
| **8p** | $C_{23}H_{23}N_3O_5S$ | 206-208 | 59B |
| **8q** | $C_{23}H_{23}N_3O_6S$ | 241-243 | 71B |
| **8r** | $C_{28}H_{25}N_3O_5S$ | 183-184 | 85A |
| | | | 62B |

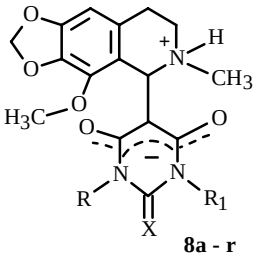
Analytical data for all compounds agreed with those calculated.

The $^{13}C$ NMR spectra of 5-dihydrocotarnylbarbituric acids are also consistent with the presence of two isomers. Using standard procedures, we identified all peaks (Table 2) and showed that each C atom correlates with two signals, the relative intensities of which correlate with the ratio of isomers found from the proton spectra.

We also investigated several other barbituric and 2-thiobarbituric acid derivatives (**7a-r**) and determined that they all react the same with cotarnine.



**7a - r**



**8a - r**

X: **a - i** O; **j - r** S
$R_1$ = **a - p** H; **r** Ph
R = **a, j** H; **b, k** Me; **c** $CH_2Ph$; **d, m** Ph; **e, n** $C_6H_4F$-*p*; **f, o** $C_6H_4Cl$-*p*; **g** $C_6H_4Br$-*p*; **h, p** $C_6H_4Me$-*p*; **i,q** $C_6H_4OMe$-*p*; **l** cyclohexyl; **r** Ph

Unsubstituted barbituric acid (**7a**), which has several potentially nucleophilic centers ($C^5$ and $N^{1(3)}$, reacted with cotarnine in only one direction to form 5-dihydrocotarnylbarbituric acid (**8a**). Owing to the low solubility of the starting material and final product, the reaction could be performed only in DMSO. Compound **8a** was extremely insoluble in organic solvents and very soluble in water. This was consistent with a zwitter-ionic structure.

TABLE 4. Acid Constants (pKa) of Barbituric and 2-Thiobrabituric Acid Derivatives

| Compound | pKa | Ref. |
|---|---|---|
| **2.** 1,3-Dimethylbarbituric acid | 4.68 | 9 |
| **7b.** 1-Methylbarbituric acid | 4.34 | 9 |
| **7a.** Barbituric acid | 4.03 | 9 |
| **7c.** 1-Benzylbarbituric acid | 4.00 | 10 |
| **7d.** 1-Phenylbarbituric acid | 3.85 | 10 |
| **5a.** 1,3-Dimethyl-2-thiobarbituric acid | 2.60 | 11 |
| **7k.** 2-Thiobarbituric acid | 2.60 | 11 |

1-Methyl-5-dihydrocotarnylbarbituric acid (**8b**) was prepared by heating cotarnine and 1-methylbarbituric acid (**7b**) in $CHCl_3$.

The most effective method for preparing 1-benzyl- and 1-aryl-5-dihydrocotarnylbarbituric acids (**8b-k**) (Table 3) was treatment of the corresponding barbituric acid derivatives **7b-k** with cotarnine in methanol. We note that 1-methyl- (**7b**) and 1,3-dimethylbarbituric (**2**) acids under these conditions reacted poorly and formed mixtures of the starting materials and final products.

On the other hand, 2-thiobarbituric acid (**7k**) and its N-substituted derivatives **7l-r** reacted well with cotarnine in methanol to form the corresponding 2-thio-5-dihydrocotarnylbarbituric acids **8k-r**. The rate of formation of **8k-r** and their yields were, as a rule, greater than those for the oxygen derivatives.

The $^1$H NMR spectra of **8a-r** exhibited the same common features that were noted above for the zwitter-ions **3** and **6a** and **b**, although the observed signal pattern was still more complicated for the derivatives with an unsymmetrically substituted pyrimidine ring. We found that all these compounds exist as mixtures of exchanging monomers and dimers, the quantitative ratios of which were determined using $^1$H NMR spectra (Table 1).

The 5-dihydrocotarnylbarbituric acids are partially hydrolyzed in solutions containing water to the starting barbituric acids and cotarnine. We estimated the degree of hydrolysis by comparing the $^1$H NMR spectra in dry DMSO-$d_6$ with those of the same samples taken one day after adding 3% $H_2O$. The stability to hydrolysis of 5-dihydrocotarnylbarbituric acids increased in the following order: **3** ≤ **8b** < **8a** ≤ **8c** < **8d** < **8l** < **8i** ≤ **8k** < **8m**.

Thus, the least hydrolytically stable oxygen derivatives are the 1-alkyl substituted 5-dihydrocotarnylbarbituric acids; the most stable, 1-arylsubstituted ones, which are inferior to the 2-thio analogs.

The relationship of the structure and hydrolytic stability of 5-dihydrocotarnylbarbituric acids can be explained by effects of N-substituents on the acidity of the 2,4,6-trihydroxypyrimidine ring.

Table 4 shows that replacing the protons on $N^1$ and $N^3$ in barbituric acid by methyls reduces the acidity; by aryls, increases it. The acid constants increase by about two orders of magnitude on changing from 2,4,6-trihydroxy to 2-thio compounds. Increasing the acidity of the proton-donating moiety should correspondingly lead to an additional energy gain on forming the zwitter-ion.

It is also interesting to note that the hydrolytic stability of 5-dihydrocotarnylbarbituric acids correlates with the relative content of dimers of this zwitter-ion.

These data indicate that the important factors determining the relative stability of 5-dihydrocotarnylbarbituric acids are the stabilization energy of the anionic moiety and the strength of H-bonds in the dimer.

In conclusion, it should be stated that 5-dihydrocotarnylbarbituric acids are theoretically interesting and promising subjects for biological investigations as structural analogs of natural isoquinolines.

## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM-500 spectrometer at working frequency 500 MHz; mass spectra, on an MX-1303 instrument with a direct probe into the ion chamber at 150°C and 70 eV ionization potential. The purity of the products was monitored using TLC on Silufol UV-254 plates and solvent systems $CHCl_3$—ethylacetate—acetic

acid (3:2:0.1) or DMF (the $R_f$ values are not given because the final products, in contrast with the starting materials, form elongated bands in the chromatograms), $^1$H NMR (Table 1), and elemental analysis.

The purity of the starting materials was monitored using TLC and systems $CHCl_3$ and $CHCl_3$—ethylacetate (3:1).

The starting N-substituted barbituric and 2-thiobarbituric acids (**5a** and **b**, **7b-j**, and **7i-r**) were prepared by the literature method [12] from diethylmalonate and the corresponding urea and thiourea derivatives.

**4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolin-5-ol (1).** Cotarnine chloride monohydrate (pharm., 27.1 g, 0.1 mole) was dissolved in water (100 mL), stirred, treated with aqueous KOH (10%, 0.11 mole), and held at 15°C for 6 h. The precipitate was filtered off, washed with water, and dried in a vacuum desiccator at 45°C over KOH to give **1**, 18.9 g (80%), mp 130-132°C (lit. 130°C [3]).

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1,3-dimethylbarbituric (5-dihydrocotarnyl-1,3-dimethylbarbituric) acid (3). Method A.** A mixture of **2** (1.56 g, 0.01 mole) and dry cotarnine (**1**, 2.36 g, 0.01 mole) was treated with $CHCl_3$ (20 mL), heated to dissolve the solids, and boiled for another 2 min. The hot solution was filtered through filter paper to remove solids. The resulting solution was kept for one day at room temperature. The precipitate was separated, washed with $CHCl_3$ and $CCl_4$, and dried in a vacuum desiccator to give **3**, 3.45 g, as colorless needle-like crystals.

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-methylbarbituric (5-dihydrocotarnyl-1-methylbarbituric) acid (8b).** This was prepared by method A from cotarnine (**1**) and 1-methylbarbituric acid (**7b**).

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1,3-dimethyl-2-thiobarbituric (5-dihydrocotarnyl-1,3-dimethyl-2-thiobarbituric) acid (6a). Method B.** 1,3-Dimethyl-2-thiobarbituric acid (**5a**, 1.72 g, 0.01 mole) and cotarnine (**1**, 2.59 g, 0.011 mole) were dissolved in anhydrous methanol (20 mL) and filtered through filter paper to remove solids. The resulting solution was kept for 3 h at 40°C and for 1-3 days at room temperature. The crystalline precipitate was separated, washed with methanol, and dried in a vacuum desiccator to give **6a**, 3.17 g.

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1,3-diethyl-2-thiobarbituric (5-dihydrocotarnyl-1,3-diethyl-2-thiobarbituric) acid (6b)** was prepared by methods A and B from cotarnine (**1**) and 1,3-diethyl-2-thiobarbituric acid (**5b**).

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-benzylbarbituric (5-dihydrocotarnyl-1-benzylbarbituric) acid (8c), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-phenylbarbituric (5-dihydrocotarnyl-1-phenylbarbituric) acid (8d), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-fluorophenylbarbituric (5-dihydrocotranyl-1-*p*-fluorophenylbarbituric) acid (8e), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-chlorophenylbarbituric (5-dihydrocotarnyl-1-*p*-chlorophenylbarbituric) acid (8f), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-bromophenylbarbituric (5-dihydrocotarnyl-1-*p*-bromophenylbarbituric) acid (8g), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-methylphenylbarbituric (5-dihydrocotarnyl-1-*p*-methylphenylbarbituric) acid (8h), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-methoxyphenylbarbituric (5-dihydrocotarnyl-1-*p*-methoxyphenylbarbituric) acid (8j), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-methyl-2-thiobarbituric (5-dihydrocotarnyl-1-methyl-2-thiobarbituric) acid (8i), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-cyclohexyl-2-thiobarbituric (5-dihydrocotranyl-1-cyclohexyl-2-thiobarbituric) acid (8l), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-phenyl-2-thiobarbituric (5-dihydrocotarnyl-1-phenyl-2-thiobarbituric) acid (8m), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-fluorophenyl-2-thiobarbituric (5-dihydrocotarnyl-1-*p*-fluorophenyl-2-thiobarbituric) acid (8n), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-chlorophenyl-2-thiobarbituric (5-dihydrocotarnyl-1-*p*-chlorophenyl-2-thiobarbituric) acid (8o), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-methylphenyl-2-thiobarbituric (5-dihydrocotarnyl-1-*p*-methylphenyl-2-thiobarbituric) acid (8p), 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1-*p*-methoxyphenyl-2-thiobarbituric (5-dihydrocotarnyl-1-*p*-methoxyphenyl-2-thiobarbituric) acid (8q), and 5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)1,3-diphenyl-2-thiobarbituric (5-dihydrocotarnyl-1,3-diphenyl-2-thiobarbituric) acid (8r)** were prepared by method B from cotarnine (**1**) and the corresponding derivatives of barbituric (**7c-j**) or 2-thiobarbituric

(**5b**, **7i-r**) acid.

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)barbituric (5-dihydrocotarnylbarbituric) acid (8a). Method B.** Barbituric acid (**7a**, 1.28 g, 0.01 mole) was dissolved in anhydrous DMSO (10 mL) at 40°C, stirred and treated with cotarnine (2.36 g, 0.01 mole). The resulting solution was left for one day at room temperature. The precipitate was separated, washed with hot $CHCl_3$ and $CCl_4$, and dried in a vacuum desiccator over KOH to give **8a**, 1.9 g, as white crystals.

**5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2H-1,3-methylenedioxy-[4,5-*g*]isoquinolinyl-1)2-thiobarbituric (5-dihydrocotarnyl-2-thiobarbituric) acid (8k)** was prepared by method B from cotarnine (**1**) and 2-thiobarbituric acid (**7k**).

Table 1 contains PMR spectra of the synthesized compounds; Table 3, yields and properties.

## REFERENCES


1. A. P. Orekhov, *Alkaloid Chemistry* [in Russian], ONTI, Moscow (1938), p. 622.
2. D. Beke, in: *Advances in Heterocyclic Chemistry*, (1963), A. R. Katritzky, ed., Academic Press, New York (1963), Vol. 1, p. 167.
3. H. Mohrle and B. Grimm, *Arch. Pharm. (Weinheim),* **319**, 835 (1986).
4. M. Chrzanovska and A. Sulma, *Pol. J. Chem.*, **72**, 2202 (1998).
5. K. W. Bentley, *Nat. Prod. Rep.*, **9**, 555 (1992).
6. K. A. Krasnov, M. N. Yurova, and V. G. Kartsev, in: *Nitrogen-Containing Heterocycles and Alkaloids,* V. G. Kartsev and G. A. Tolstikov, eds., Iridium Press, Moscow (2001), Vol. 2, p. 152.
7. B. A. Ivin, A. D. D′yachkov, I. M. Vishnyakov, N. A. Smorygo, and E. G. Sochilin, *Zh. Org. Khim.*, **11**, 1337 (1979).
8. E. Haslinger, M. Reithmaier, W. Robien, and P. Wolschann, *Monatsh. Chem.*, **115**, 375 (1984).
9. A. I. Biggs, *J. Chem. Soc.*, 2485 (1956).
10. K. A. Krasnov and V. I. Slesarev, *Zh. Org. Khim.*, **4**, 601 (1997).
11. H. G. Mantner and E. M. Clauton, *J. Am. Chem. Soc.*, **23**, 6270 (1959).
12. E. Fisher and A. Diltey, *Liebigs Ann. Chem.*, **335**, 334 (1904).