Chemistry of Natural Compounds, Vol. 38, No. 5, 2002

CHEMICAL MODIFICATION OF PLANT ALKALOIDS. III. X-RAY DIFFRACTION AND NMR STUDIES OF THE STRUCTURE OF 1,3-DIMETHYL-5-ARYLMETHYL-5-CYTISYLMETHYLBARBITURIC ACIDS

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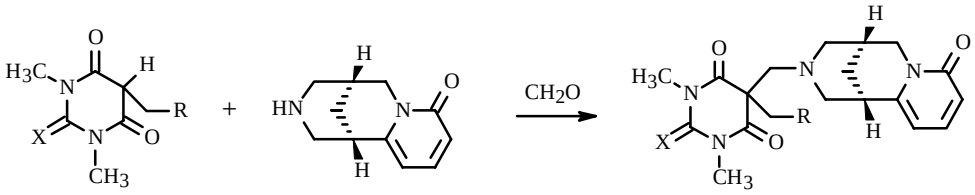
UDC 547.854+547.689.6+547.833.3

The three-dimensional structure of 1,3-dimethyl-5-(4-allyloxybenzyl)-5-cytisylmethylbarbituric acid was found by x-ray structure analysis. A conformation with proximal cytisine and 2,4,6-trioxopyrimidine moieties was observed. Analogous structures for other synthesized 1,3-dimethyl-5-arylmethyl-5-cytisylmethylbarbituric acids and their 2-thio analogs were proved and the intramolecular effects caused by mutual magnetic shielding of spatially proximal groups were studied using PMR.

Key words: 1,3-dimethyl-5-(4-allyloxybenzyl)-5-cytisylmethylbarbituric acid, three-dimensional structure, 1,3-dimethyl-5-arylmethyl-5-cytisylmethylbarbituric acids, X-ray, PMR.

5,5-Dialkyl derivatives of barbituric acid are well known as the basis of medicinal preparations [1]. A promising path for creating new effective pharmacological agents is the introduction of fragments of plant alkaloids into the 2,4,6-trioxopyrimidine ring.

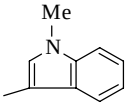


1a - o **2** **3a - j** (X = O) **3k - o** (X = S)

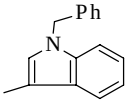
a - j: X = O
k - o: X = S

a: R = Ph
b: R = C_6H_4 (*n*-$OCH_2CH{=}CH_2$)
c: R = C_6H_4 (*n*-NO_2)
d: C_6H_4 (*n*-OMe)
e: R = α-Naphthyl
f: R = 9-Anthryl
g: R = 2-Thienyl
h: R = 2-Furyl

k: R = C_6H_4 (*n*-OMe)
l: R = C_6H_3 (3,4-OMe)
m: R = C_6H_3 (2,6-Cl)
n: R = α-Naphthyl
o: R = 9-Anthryl



i: R =



j: R =

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 0009-3130/02/3805-0450$27.00

TABLE 1. Bond Lengths (Interatomic Distances) (r, Å) for **3b**

Bond	r	Bond	r	Bond	r	Bond	r
N1-C6	1.380(3)	C5-C21	1.577(3)	C13-O13	1.244(3)	C23-C24	1.381(4)
N1-C2	1.381(3)	C6-O6	1.222(3)	C13-C14	1.431(4)	C24-C25	1.396(3)
N1-C1	1.470(3)	C7-N8	1.474(3)	C14-C15	1.357(4)	C25-O28	1.378(3)
C2-O2	1.215(3)	N8-C19	1.461(3)	C15-C16	1.400(4)	C25-C26	1.383(3)
C2-N3	1.393(3)	N8-C9	1.466(3)	C16-C17	1.378(4)	C26-C27	1.392(3)
N3-C4	1.376(3)	C9-C10	1.527(4)	C17-C18	1.493(3)	O28-C29	1.436(3)
N3-C3	1.466(3)	C10-C11	1.521(4)	C18-C20	1.531(3)	C29-C30	1.497(3)
C4-O4	1.212(3)	C10-C20	1.523(4)	C18-C19	1.538(4)	C30-C31	1.309(4)
C4-C5	1.511(3)	C11-N12	1.484(3)	C21-C22	1.501(3)		
C5-C6	1.510(3)	N12-C17	1.381(3)	C22-C23	1.390(3)		
C5-C7	1.536(3)	N12-C13	1.401(3)	C22-C27	1.399(3)		

TABLE 2. Valency Angles (ω, deg) for **3b**

Bond	ω	Bond	ω	Bond	ω	Bond	ω
C6-N1-C2	124.05(18)	C6-N1-C2	124.05(18)	N8-C7-C5	109.16(18)	N12-C17-C18	119.5(2)
C6-N1-C1	117.69(19)	C6-N1-C1	117.69(19)	C19-N8-C9	109.90(19)	C17-C18-C20	111.5(2)
C2-N1-C1	118.23(18)	C2-N1-C1	118.23(18)	C19-N8-C7	113.46(18)	C17-C18-C19	108.76(18)
O2-C2-N1	121.9(2)	O2-C2-N1	121.9(2)	C9-N8-C7	113.77(19)	C20-C18-C19	109.5(2)
O2-C2-N3	120.4(2)	O2-C2-N3	120.4(2)	N8-C9-C10	109.9(2)	N8-C19-C18	108.73(19)
N1-C2-N3	117.77(18)	N1-C2-N3	117.77(18)	C11-C10-C20	110.4(2)	C10-C20-C18	106.3(2)
C4-N3-C2	124.85(18)	C4-N3-C2	124.85(18)	C11-C10-C9	111.8(2)	C22-C21-C5	112.97(19)
C4-N3-C3	118.6(2)	C2-N3-C3	116.07(19)	C20-C10-C9	109.4(2)	C23-C22-C27	117.4(2)
C2-N3-C3	116.07(19)	O4-C4-N3	121.5(2)	N12-C11-C10	115.0(2)	C23-C22-C21	122.1(2)
O4-C4-N3	121.5(2)	O4-C4-C5	121.0(2)	C17-N12-C13	122.7(2)	C27-C22-C21	120.4(2)
O4-C4-C5	121.0(2)	N3-C4-C5	117.45(19)	C17-N12-C11	122.66(19)	C24-C23-C22	121.8(2)
N3-C4-C5	117.45(19)	C6-C5-C4	115.37(18)	C13-N12-C11	114.6(2)	C23-C24-C25	119.6(2)
C6-C5-C4	115.37(18)	C6-C5-C7	110.04(18)	O13-C13-N12	119.2(2)	O28-C25-C26	124.5(2)
C6-C5-C7	110.04(18)	C4-C5-C7	108.45(18)	O13-C13-C14	124.8(2)	O28-C25-C24	115.2(2)
C4-C5-C7	108.45(18)	C6-C5-C21	106.40(17)	N12-C13-C14	116.0(2)	C26-C25-C24	120.3(2)
C6-C5-C21	106.40(17)	C4-C5-C21	106.86(18)	C15-C14-C13	121.2(2)	C25-C26-C27	119.0(2)
C4-C5-C21	106.86(18)	C7-C5-C21	109.57(18)	C14-C15-C16	120.9(3)	C26-C27-C22	121.9(2)
C7-C5-C21	109.57(18)	O6-C6-N1	120.2(2)	C17-C16-C15	119.6(2)	C25-O28-C29	117.12(18)
O6-C6-N1	120.2(2)	O6-C6-C5	121.51(19)	C16-C17-N12	119.5(2)	O28-C29-C30	107.6(2)
O6-C6-C5	121.51(19)	N1-C6-C5	118.09(18)	C16-C17-C18	121.0(2)	C31-C30-C29	123.2(3)
N1-C6-C5	118.09(18)						

We previously found that aminomethylation of 1,3-dimethyl-5-arylmethylbarbituric acids (**1a**-**g**) by the alkaloid cytisine (**2**) in the presence of formaldehyde leads to the formation of 5-arylmethyl-5-cytisylmethylbarbituric acids (**3a**-**g**) [2, 3]. In continuation of these studies, we synthesized new derivatives of **3** that contain furan (**3h**) and indole (**3i** and **j**) heterocycles as the substituent R and also prepared for the first time the 2-thio analogs of this series (**3k**-**o**).

It has been hypothesized [2, 3] that derivatives of **3** and their analogs contain an intramolecular through-space interaction between the 2,4,6-trioxopyrimidine and 2-pyridone fragments that may generate a stable conformation with a plane-parallel orientation of these fragments. Compounds **3** with such an orientation of the rings become somewhat similar to sandwich complexes. Therefore, we used the term "intramolecular sandwich" to denote this conformation.

Considering the special importance of the three-dimensional structure of a molecule for explaining its properties and predicting the biological activity, we studied the crystal structure of 1,3-dimethyl-5-(4-allyloxybenzyl)-5-cytisylmethylbarbituric acid (**3b**) using x-ray structure analysis. This proved that the molecule exists in the intramolecular sandwich conformation (Fig. 1). Owing to the rarity of this conformation, we describe it completely including the bond lengths and valency angles (Tables 1 and 2).

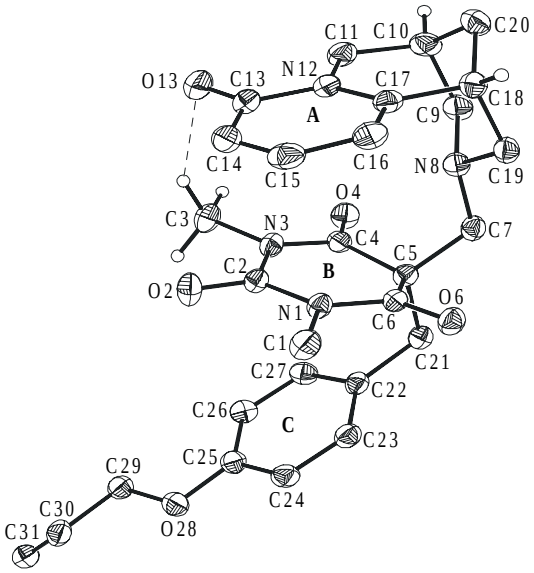
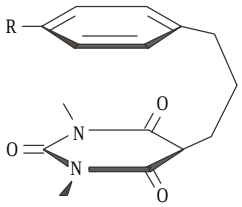
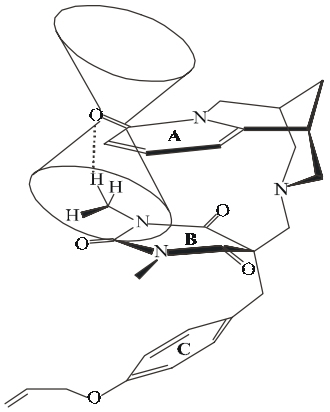


Fig. 1



4: R = H, CH_3, OCH_3, NO_2



3b

Fig. 2

Fig. 1. Molecular structure of **3b** with 50% anisotropic probability ellipsoids; dashed line, intramolecular H-bond.
Fig. 2. Hypothetical three-dimensional structure of **4** [6] and the structure of **3b** showing anisotropic magnetic effects found in PMR spectra.

Compound **3b** contains three planar parts that are denoted as the planes of rings A, B, and C in Figs. 1 and 2. Plane A includes atoms of the 2-pyridone ring of cytisine and atoms adjacent to it. Plane B includes 8 of 11 atoms of the 1,3-dimethyl-2,4,6-trioxopyrimidine system (C1, C2, C4, C6, N1, O2, O4, O6). Three atoms of this system deviate markedly from this plane: C5 (-0.240 Å), N3 (+0.137 Å), and C3 (+0.246 Å). The benzene ring and adjacent atoms form the third plane C.

It is interesting that planes A and B are spatially close and almost parallel. The angle between the planes is 12.3°. The dihydropyridine ring (A) is situated exactly over the pyrimidine (B). The distance between the centers of these rings is 3.901 Å. The minimal distance between the two heterocycles is 3.532 Å. These features indicate the existence of distant (the sum of the Van der Waals radii for two C atoms is 3.40 Å; for N and C, 3.25 Å [4]) attractive intramolecular interactions between the π-electron systems of these heterocycles. Compound **3b** is devoid of characteristics typical of charge-transfer complexes. It is colorless, displays no paramagnetism, etc.

Thus, the observed approach of planes A and B can be explained by a weak intramolecular π—π interaction between the 2-pyridone and 2,4,6-trioxopyrimidine systems, where the limited conformational flexibility of the aliphatic part of the methylcytisine fragment does not allow the planes to adopt the ideally parallel orientation. It should be noted that although interactions of this type are known between aromatic systems [5] they do not practically lead to the formation of stable structures like **3b** owing to the low energy. An exception might be 1,3-dimethyl-5-(3-phenylpropyl)barbituric acid and its analogs (**4**), the three-dimensional structures of which are shown in Fig. 2 and were proposed using PMR spectra and acid constants [6]. The intramolecular attractive interactions in **3b** and **4** might be similar in nature although the energy of this interaction is much lower in the latter.

The benzyl group in **3b** also has a somewhat unusual orientation. Substituents in 5,5-dialkylbarbituric acids are known to lie at angles greater than 90° to the plane of ring B [7]. However, not only the methylcytisine but also the benzene in **3b** is twisted toward the pyrimidine ring. The angle between planes B and C is 36.2°. It can be assumed that the orientation of the benzene ring also results from attractive interactions inherent to this system.

Another interesting feature that should be noted is the intramolecular H-bond between methyl proton H3a(C3) and O13 of the 2-pyridone. The measured parameters [C3...O13, 3.344(3); H3a...O13, 2.36(3) Å; angle C3–H3a...O13, 150(2)°] correspond to a weak but distinct H-bond, the presence of which creates a pseudoframework in **3b**. Additional confirmation of the participation of the N-3-methyl in H-bonding is its spatial orientation, which could avoid any intramolecular contacts by rotating by 60°, and the deviations of N3 and C3 from plane B (see above). The participation of the methyl in H-bonding to

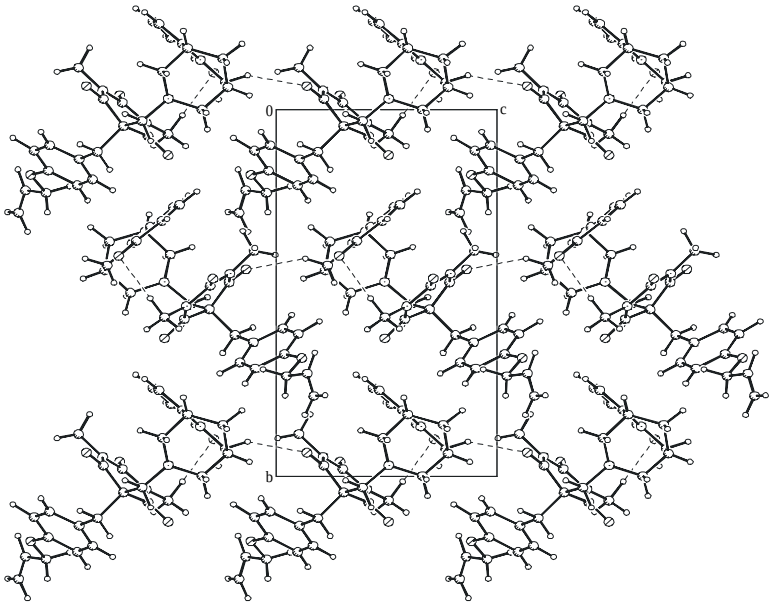


Fig. 3. Molecular packing of **3b** in the crystal; dashed lines, H-bonds.

the carbonyl oxygen does not contradict theoretical concepts because many instances are known where a methyl forms a C–H...O H-bond [8].

The presence of several intramolecular interactions in **3b** probably is largely responsible for the crystal packing and explains the high crystal density (1.344 g/cm^3), which is much higher than the values typical for organic compounds (1.00-1.20 g/cm^3). The **3b** molecules are stacked along the z axis in the crystal. Molecules in the stacks are joined by weak intermolecular H-bonds C11–H11b...O6 (x, y, -1+z) [C11...O6, 3.374(3); H11b...O6, 2.47(3) Å; angle C11–H11b...O6, 148(2)°] (Fig. 3).

After establishing the three-dimensional structure of **3b**, we were able to explain many features of the PMR spectra of this type of compounds. On the other hand, the existence of such spectral features enabled PMR spectroscopy to be used to investigate conformational phenomena of the intramolecular sandwich in solution.

It was found that a characteristic feature of the PMR spectra of all derivatives of **3** is the distinct magnetic nonequivalence of the N-methyl groups (CH_3–N1 and CH_3–N3). This is obviously due to the approach of plane B to the asymmetric cytisine ring. Features of the magnetic shielding of the N-methyls require a detailed discussion because they are directly related to the conformation of the intramolecular sandwich.

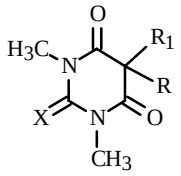
The signals of the N1 and N3 methyls coincide and form a 6H singlet at 3.30 ± 0.05 ppm in PMR spectra of model compounds that do not have asymmetric centers such as 1,3-dimethylbarbituric acid (**5a**), 5-benzyl- (**5b**), 5,5-dibenzyl- (**5c**), 5-benzyl-5-piperidinomethyl- (**5d**), and other 5-substituted 1,3-dimethylbarbituric acids (in $CDCl_3$, Table 3) [6, 7]. Theoretical spectra calculated using the program ACID LABS predict this same range of chemical shifts for the NMe groups. For 1,3-dimethyl-2-thiobarbituric acid (**5e**) and its derivatives, the only difference is that the N-Me singlet is shifted to weaker field by about 0.30 ppm (Table 3). However, one of the N-methyls (Me-N1) in **3b** has a shift of 3.04 ppm; the other (Me-N3), 2.80 ppm. The difference between these values ($\Delta\delta$) is 0.24 ppm. Such a significant strong-field shift of the signal for the latter can be explained only by the influence of the anisotropy cone of the asymmetric cytisine. According to the X-ray structure analysis, Me-N3 is expected to lie at the center of the magnetic cone of the C13=O13 bond (Fig. 3). This is possible only if the conformation is close to that of the intramolecular sandwich (Figs. 1 and 3). Using general concepts about the relation of the proton chemical shift to the distance from the center of a shielding cone [9] and taking the chemical shift of the first methyl (Me-N1, $CDCl_3$, δ 3.06) as the basis, we estimated the distance between the center of the Me-N3 (C-3) group and the center of the C13=O13 bond in the proposed conformation, obtaining a rough approximation of 3.7 ± 0.2 Å. This is close to the distance measured experimentally in the crystal by X-ray structure analysis [3.508(3) Å]. This indicates that the three-dimensional structure of **3b** is the same in the crystal and solution.

TABLE 3. Chemical Shifts (δ, ppm) and Spin—Spin Coupling Constants (J, Hz) in PMR Spectra of compounds **3a**, **b**, **e**, **f**, and **h—j**

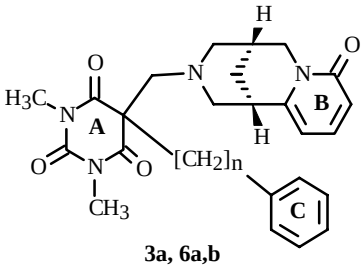
Compound	CH_3-N1 3H s	CH_3-N3 3H s	C20 AB-syst. (12.5, 2.5)	C10 br.s	C19 d+d (10.5)	C9 d+d (9.0)	C18 br.s	C7 AB-syst. (12.5)	C21 AB-syst. (13.5)	C11 m	C16 d (6.5)	C14 d (9.0)	C15 dd (6.5, 9.0)	Aromatic protons m	Other protons
3a	3.02	2.76	1.70	2.28	2.55+ 2.79	2.59+ 2.97	2.79	2.85	3.15	3.70	5.74	6.20	6.78	7.1(4H) 6.8 (1H)	-
3b	3.04	2.80	1.68	2.25	2.55+ 2.77	2.58+ 2.93	2.77	2.85	3.1	3.71	5.75	6.23	7.14	6.7 (4H)	4.41(2H, m, OCH_2); 5.23+5.32(1H+1H, d+ d, $=CH_2$); 5.95 (1H, m, -CH=)
3e	2.75	2.44	1.65	2.30	2.60+ 2.92	2.64+ 3.12	2.72	3.28	3.36	3.68	5.70	6.20	7.21	7.05 (2H), 7.42 (2H), 7.72 (3H)	-
3f	2.40	2.01	1.68	2.24	2.63+ 3.00	2.67+ 3.21	2.42	3.42	3.65	3.99	5.67	6.00	6.94	7.35-7.47(4H), 7.88-7.97(4H), 8.27(1H)	-
3h	3.15	2.90	1.69	2.28	2.54+ 2.9	2.57+ 2.77	2.76	2.96	3.06	3.74	5.79	6.30	7.17	5.87(1H), 6.13 (1H), 7.12(1H)	-
3i	2.95	2.67	1.70	2.29	2.57+ 2.81	2.61+ 2.96	2.78	3.11	3.17	3.75	5.79	6.23	7.00	6.60(1H), 7.09-7.17(3H), 7.29(H)	3.72(3H, s, NCH_3)
3j	2.85	2.59	1.69	2.28	2.57+ 2.81	2.61+ 2.96	2.77	3.13	3.17	3.71	5.77	6.23	7.01	6.66(1H), 6.89(2H), 7.07-7.34(7H)	5.14 (2H, NCH_2)
3k	3.42	3.18	1.68	2.29	2.57+ 2.85	2.59+ 3.01	2.76	2.85	3.16	3.72	5.70	6.15	7.09	6.65(4H, d+d, J 9.0)	3.69(3H, OCH_3)
3l	3.44	3.19	1.70	2.29	2.60+ 2.86	2.61+ 3.00	2.76	2.86	3.16	3.74	5.77	6.16	7.09	6.30-6.35(2H), 6.60(1H)	3.71(3H, OCH_3), 3.76(3H, OCH_3)
3m	3.57	3.30	1.66	2.23	2.55+ 2.91	2.57+ 3.02	2.74	3.21	3.26	3.68	5.77	6.18	7.10	7.09-7.13(1H), 7.21-7.25(2H)	-
3n	3.11	2.79	1.70	2.28	2.63+ 2.97	2.66+ 3.14	2.76	3.30	3.40	3.69	5.74	6.04	7.22	7.01(H), 7.41(2H)	-
3o	2.74	2.31	1.68	2.24	2.65+ 3.08	2.69+ 3.27	2.73	3.47	4.00	3.64	5.67	5.91	6.89	7.65-7.74(4H) 7.36-7.43(4H), 7.88-7.93(4H),	-
5e	3.16	3.16	-	-	-	-	-	3.07 (c)	3.13 (c)	-	-	-	-	8.28(1H) 7.04(2H), 7.16(3H)	1.29-1.33(6H, $(CH_2)_3$) 2.36(4H, m, 2×NCH_2) 3.16(6H, s, 2×NCH_3)

We made an attempt to estimate the stability of the intramolecular sandwich conformation using dynamic PMR methods. It was expected that any disruption of this conformation would be evident in the chemical shift of the shielded Me-N3 group. Using **3a-c** as examples, it was shown that heating their DMSO-d_6 solutions to 90°C produced no substantial changes in the spectra. Therefore, this conformation is retained. The energy barrier is evidently greater than 15 kcal/mol, which is much greater than in 1,3-dimethyl-5-(3-phenylpropyl)barbituric acids **4** (Fig. 3), in which the maximal energy of the intramolecular interaction was estimated in the range 1.8-2.4 kcal/mol [6].

A comparison of PMR spectra of **3a** and **3b**, **6a** and **6b**, and model compounds **5a-f** showed that not only the cytisine ring (A) but also the phenyl ring (C) influences the chemical shift of the methyls on N1 and N3. Judging from the deviations of the shifts of the NMe groups from the typical value of 3.30 ppm, both these groups in benzyl derivative **3a** are shielded by ring C (Figs. 1 and 4). Because the separation between planes C and B increases as the number of methylenes (n) separating them increases in **6a**, the effect of the phenyl substituent decreases and becomes practically insignificant in **6b** (with retention of the effect of ring A on the Me-N3 group).



5a - f



3a, 6a,b

	Me-N1 + Me-N3 (6H, d, ppm)
a: X = O, R = R_1 = H	3.30
b: X = O, R = H, R_1 = CH_2Ph	3.30
c: X = O, R = H, R_1 = CH_2CH_2Ph	3.22
d: X = O, R = H, R_1 = $CH_2CH_2CH_2Ph$	3.28
e: X = O, R = CH_2Ph, R_1 = $CH_2N(CH_2)_5$	3.16
f: X = S, R = R_1 = H	3.60

	Me-N1 (δ, ppm)	Me-N3 (δ, ppm)
3a: n = 1	3.02	2.76
6a: n = 2	3.14	2.97
6b: n = 3	3.25	3.00

Fig. 4. Chemical shifts of NMe groups in spectra of model compounds **5a-f** and 1,3-dimethyl-5-phenylalkyl-5-cytisylmethylbarbituric acids **3a** and **6a** and **6b**.

Substituting the phenyl ring (**3c** and **-d**) or replacing the aryl by a heterocycle (thiophene, furan, indole, **3g-j**) did not substantially change the signals of protons in the remaining part of the molecule (Table 3). The chemical shift of the first NMe group in PMR spectra of **3g-i**, like in **3a-d**, was located at 3.01-3.10 ppm whereas the signal of the second one (Me-N3) shifted to strong field by 0.2-0.3 ppm (Table 3). This indicated that the structures of these compounds are similar.

For the 2-thio derivatives of 1,3-dimethyl-5-arylmethyl-5-cytisylmethylbarbituric acids **3k-o**, the signals of the NMe groups shifted to weak field compared with the oxygen analogs. However, the magnetic nonequivalence of these groups in **3k-o** was nearly the same (Table 3). Therefore, it can be concluded that replacing the oxygen in the 2-position by sulfur does not significantly change the three-dimensional structure of intramolecular sandwiches.

Interesting changes in the nature of the shielding of the NMe groups was observed on going to the 5-naphthylmethyl- (**3e**) and 5-anthrylmethylbarbituric acids (**3f**). Signals of the N1 and N3 methyls in the spectrum of **3e** were observed at 2.75 and 2.44 ppm; for **3f**, at 2.40 and 2.00 ppm, respectively. Analogous changes in the position of the signals were observed for the series of 2-thio analogs on going to the naphtyl- and anthryl derivatives (**3n** and **-o**) (Table 3). Compared with **3b**, in which the difference of chemical shifts (Δδ) between Me-N1 and Me-N3 was 0.24 ppm, the magnetic nonequivalence of the methyls in fragment B of **3f** increased, reaching Δδ 0.40 ppm. It was noted above that Δδ can act as a criterion for estimating the distance between the center of the Me-N3 (C-3) and the center of the C13=O13 bond. Considering that the X-ray structure analysis of **3b** gives a value of 3.508(3) Å for this distance, a calculation of the corresponding distance in **3f** gives approximately 3.3-3.4 Å. This in turn is consistent with a closer approach of planes A and B in **3f** compared with **3a** and **b** and, probably, a greater stabilization energy for the intramolecular sandwich conformation on replacing the 5-benzyl group by 5-anthrylmethyl.

As mentioned above, the spatial approach of rings B and C leads to shielding of the aromatic NMe groups. This effect is especially evident for the 5-anthrylmethyl derivatives **3f** and **-o** due to the geometric and anisotropic parameters of the anthryl group. Thus, the chemical shift of Me-N1 in **3f** is 2.40 ppm, which is approximately by 0.90 ppm lower than the standard value in model compounds **5a-d**. Correspondingly, the second methyl (Me-N3), which is affected simultaneously by two anisotropy cones, is shifted to even weaker field (2.00 ppm).

Lowering the temperature produced characteristic changes in the PMR spectra of derivatives of **3**. Cooling has an especially strong effect on the position of the Me-N3 signal, which shifts at -60°C to strong field by 0.17 ppm whereas that of Me-N1 shifts by 0.05 ppm. Most of the other signals in the low-temperature spectrum either do not shift or are shifted to weak field by 0.01-0.10 ppm. This parameter clearly illustrates the intramolecular spatial effects in **3o**, where the specific strong-field shift of the Me-N3 signal at low temperature can be explained by the increased shielding of this group owing to closer approach of rings A and B and a decrease of vibrational processes in the intramolecular sandwich conformation.

Thus, the three-dimensional structure of 1,3-dimethyl-5-alkyl-5-cytisylmethylbarbituric acids, which involves the

intramolecular sandwich conformation and a pseudoframework, determines to a large extent the spectral and physicochemical properties of these compounds. The principal reason for the appearance of these structures is considered to be the existence of distant π—π interactions between the cytisine and 2,4,6-trioxopyrimidine parts of the molecule. It is expected that further study of 5-cytisylmethyl derivatives of barbituric acid and related compounds will shed further light on the nature of these interactions.

EXPERIMENTAL

PMR spectra were recorded on a Bruker AM-500 spectrometer at working frequency 500 MHz in $CDCl_3$. Signals were identified using standard NMR methods of HH-COSY and NOESY. Temperature dependences of proton spectra were investigated in the range 20 to -60°C in steps of 10°C.

The purity of the starting materials and products was monitored using TLC [on Silufol UV-254 plates using $CHCl_3$, $CHCl_3$:EtOAc (3:1), and $CHCl_3$:EtOAc:HOAc (3:2:0.1)], PMR (Table 3), and elemental analyses.

Cytisine (pharmacopoeic) isolated from willow thicket seeds of purity at least 99% was used in the experiments.

The syntheses and properties of compounds **3a-g** have been described [2].

X-ray Structure Analysis. Compound **3b** (0.1 g) was dissolved in $CHCl_3$ (1 mL) and treated with CCl_4 (3 mL) and heptane (5 mL) to grow crystals. The solution was placed in a cylinder and held at 20°C for 10 days, during which 3/4 of the initial solvent volume evaporated naturally. The resulting crystals were separated and washed with hexane.

Crystals of **3b** ($C_{28}H_{32}N_4O_5$, M = 504.58) are monoclinic, space group $P2_1$, a = 8.4590(12), b = 16.674(2), c = 9.0412(13) Å, β = 102.135(4)°, V = 1246.7(3) Å^3, Z = 2, d_c = 1.344 mg/cm^3, F(000) = 536, mk = 0.094 mm^{-1}.

Unit-cell constants and intensities of 8537 reflections were measured on an automated Bruker diffractometer SMART CCD 1000 (T = 110 K, λ MoKα, ω-scanning in steps of 0.3° and exposures of 10 sec per frame, Θ_{max} = 27°). The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms. Hydrogen atoms were located in difference Fourier syntheses and refined isotropically. The final agreement factors were R_1 = 0.0498 for 4566 independent reflections with I > 2 σ(I) and wR_2 = 0.1338 for all 5362 independent reflections. Calculations were made using the SHELXTL PLUS (Version 5.10) programs [10]. Atomic coordinates, bond lengths, bond and torsion angles, and anisotropic temperature factors for **3b** have been deposited in the Cambridge Structural Database.

Preparation of 1,3-Dimethyl-5-arylmethylbarbituric Acids (1h-j) and Their 2-Thio Analogs (1k-o). General Method. 1,3-Dimethylbarbituric acid (**5a**, 0.01 mole) or 1,3-dimethyl-2-thiobarbituric acid (**5f**, 0.01 mole) was dissolved in EtOH (30 mL), treated with the appropriate aldehyde (0.011 mole), heated to boiling, and cooled. The precipitate of 5-arylidene derivative was separated and washed with hot EtOH (70%). The crude precipitate was added to a mixture of isopropanol (70 mL) and water (20 mL), heated to 40-50°C, stirred, treated in small portions with $NaBH_4$ (0.02 mole) to produce a homogeneous solution, stirred at room temperature for 10 min, diluted with water (100 mL), and cooled to room temperature. The precipitate was filtered off. The filtrate was acidified with HCl to pH 1. The resulting precipitate was separated, washed with EtOH (30%), and recrystallized from aqueous alcohol.

This method produced the compounds:

1h. 1,3-Dimethyl-5-(2-furylmethyl)barbituric acid, 28%, mp 86-87°C;

1i. 1,3-Dimethyl-5-(1-methylindolyl-3-methyl)barbituric acid, 39%, mp 146-148°C;

1j. 1,3-Dimethyl-5-(1-benzylindolyl-3-methyl)barbituric acid, 43%, mp 117-118°C;

1k. 1,3-Dimethyl-2-thio-5-(4-methoxybenzyl)barbituric acid, 30%, mp 98-100°C;

1l. 1,3-Dimethyl-2-thio-5-(3,4-dimethoxybenzyl)barbituric acid, 42%, mp 102-104°C;

1m. 1,3-Dimethyl-2-thio-5-(2,6-dichlorobenzyl)barbituric acid, 27%, mp 96-98°C;

1n. 1,3-Dimethyl-2-thio-5-(α-naphyhylmethyl)barbituric acid, 29%, mp 163-165°C;

1o. 1,3-Dimethyl-2-thio-5-(9-anthrylmethyl)barbituric acid, 40%, mp 181-183°C.

Preparation of 1,3-Dimethyl-5-arylmethyl-5-cytisylmethylbarbituric Acids (3h-j) and 2-Thio Analogs (3k-o). General Method. A mixture of the appropriate 1,3-dimethyl-5-arylmethylbarbituric acid (**1h-o**, 0.01 mole) and cytisine base (**2**, 0.011 mole) was treated with alcohol (2 mL) and water (30 mL) and stirred with heating to less than 45°C until completely dissolved. The solution was cooled to room temperature, treated with stirring with formaldehyde (0.014 mole, 20% aqueous solution), and left for 6 h. The resulting precipitate was filtered off, washed with alcohol (40%), and dried in air.

The following compounds were prepared by this method:

3h. 1,3-Dimethyl-5-(2-furylmethyl)-5-cytisylmethylbarbituric acid. $C_{23}H_{26}N_4O_5$ (438.48), 30%, mp 184-186°C;

3i. 1,3-Dimethyl-5-(1-methylindolyl-3-methyl)-5-cytisylmethylbarbituric acid. $C_{28}H_{31}N_5O_4$ (501.58), 60%, mp 184-185°C;

3j. 1,3-Dimethyl-5-(1-benzylindolyl-3-methyl)-5-cytisylmethylbarbituric acid. $C_{34}H_{35}N_5O_4$ (577.67), 53%, mp 163-165°C;

3k. 1,3-Dimethyl-2-thio-5-(4-methoxybenzyl)-5-cytisylmethylbarbituric acid. $C_{26}H_{30}N_4O_4S$ (494.61), 26%, mp 141-143°C;

3l. 1,3-Dimethyl-2-thio-5-(3,4-dimethoxybenzyl)-5-cytisylmethylbarbituric acid. $C_{27}H_{32}N_4O_5S$ (524.63), 35%, mp 171-172°C;

3m. 1,3-Dimethyl-2-thio-5-(2,6-dichlorobenzyl)-5-cytisylmethylbarbituric acid. $C_{25}H_{26}C_{l2}N_4O_3S$ (533.47), 43%, mp 180-182°C;

3n. 1,3-Dimethyl-2-thio-5-(α-naphthylmethyl)-5-cytisylmethylbarbituric acid. $C_{29}H_{30}N_4O_3S$ (514.64), 47%, mp 215-217°C;

3o. 1,3-Dimethyl-2-thio-5-(9-anthrylmethyl)-5-cytisylmethylbarbituric acid. $C_{33}H_{32}N_4O_3S$ (564.70), 75%, mp 234-236°C;

6a. 1,3-Dimethyl-5-(2-phenylethyl)-5-cytisylmethylbarbituric acid. $C_{26}H_{30}N_4O_4$ (462.54), 50%, mp 194-196°C;

6b. 1,3-Dimethyl-5-(2-phenylpropyl)-5-cytisylmethylbarbituric acid. $C_{27}H_{32}N_4O_4$ (476.57), 15%, mp 55-57°C.

1,3-Dimethyl-5-(2-phenylethyl)barbituric Acid (5c). 1,3-Dimethylbarbituric acid (**5a**, 3.12 g, 0.02 mole) was mixed with $CHCl_3$ (5 mL), treated with an equivalent amount of triethylamine, stirred for 10 min at 40°C until homogeneous, treated with 2-phenylethylbromide (15 g), left for seven days at 70°C, and treated with aqueous ammonia (50 mL, 3%). The organic layer was separated and extracted again with aqueous ammonia. The combined aqueous extract was extracted with $CHCl_3$ (10 mL) to remove water-insoluble impurities. The basic aqueous solution was acidified with conc. HCl until the pH was 1. The separated oil was removed and reprecipitated from aqueous ammonia to give the product (0.51 g) as an oil, yield 10%.

1,3-Dimethyl-5-(3-phenylpropyl)barbituric Acid (5d) was prepared analogously. Yield 20%, mp 88°C (H_2O—EtOH).

ACKNOWLEDGMENT

We thank the Russian Foundation for Basic Research (Projects No. 00-03-32807a and 00-15-97359) for financial support.

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