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Preparation of 5-(cyclohexylmethyl)barbituric acid derivatives by acid-catalyzed reductive cyclohexylmethylation of barbituric acids with *p*-hydroxy or *p*-methoxybenzaldehydes

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Abstract—A very inexpensive, simple, and high yield procedure for the preparation of valuable pharmaceutical intermediates, 5-cyclohexylmethylbarbiturates, was developed starting from either *p*-hydroxy or *p*-methoxybenzaldehyde and barbituric acid. Although the reaction sequence involves several steps, such as selecting a suitable catalyst (5% Pd–C in 2% percent molar ratio) and solvent (methanol–hydrochloric acid 1:1) the preparation can be carried out in only one practical step (one-pot preparation).

In our search for new barbituric acid derivatives with more biological activity it came as a surprise that there is no available method for the preparation of simple barbituric acid derivatives such as 5-cyclohexylmethylbarbiturates. 5-Monoalkylated barbituric acids are very important intermediates in the preparation of asymmetric biologically active barbituric acid derivatives.[1] Therefore, these molecules can be of use for generating new more potent chiral barbituric acid derivatives, as discussed in Ref. 1. To be able to venture into this field of research more thoroughly, various derivatives of 5-(cyclohexylmethyl)barbiturates must be readily available or easily synthesized. To accomplish this target we have developed a very efficient synthetic procedure for the preparation of a wide variety of 5-(cyclohexylmethyl)barbituric acids.

The most general way to prepare barbituric acid derivatives is by urea condensation with malonic acid esters.[2] Direct 5-alkylation of barbituric acid and *N*-alkyl or *N*-aryl derivatives usually does not produce excellent results.[3] Nevertheless, barbituric acids have been alkylated with yields of more than 90%[4] by a combination of (triphenylmethyl) sodium or (triphenylmethyl) potassium and subsequent treatment with an alkyl halide. Recently, we developed a method for a reductive *C*-alkylation of barbituric acid derivatives.[5] The reaction involves barbituric acid condensation with the corresponding aldehyde or ketone, followed by the catalytic reduction of the newly formed C=C double bond.

Reductive *C*-benzylation of barbituric acids with benzaldehyde derivatives is a very efficient way to prepare mono- and in some cases di-benzylated barbiturates. The rate of the benzylation strongly depends on the nature of the substituents on the aromatic ring of the benzaldehyde. Electron-donating groups, such as dimethylamino, strongly increase the reactivity. We were able to achieve controlled benzylation by introducing the alkyl and benzyl together, as well as introducing two different benzyl groups in the 5-position of the barbituric acid ring.[5] Due to fact that *C*-benzylated barbiturates are easy to synthesize,[5] one can propose that through reduction of the aromatic ring, preparation of 5-cyclohexylmethylbarbiturates should be a straightforward process. The ideal precursors should be *p*-hydroxybenzaldehyde and *p*-methoxybenzaldehyde due to fact that water and methanol can be easily removed from the cyclohexane ring upon aromatic ring reduction.[6]

Condensation reactions with both *p*-hydroxybenzaldehyde and *p*-methoxybenzaldehyde with barbituric acids in methanol requires only several minutes in refluxing methanol. The condensation product **1** (Scheme 1) precipitates as yellow–orange solid from the methanol solution. The yields for these reactions are almost quantitative.[7] Reduction of these condensation products either with 5% Pd–C, 5% Pd–C in methanol or

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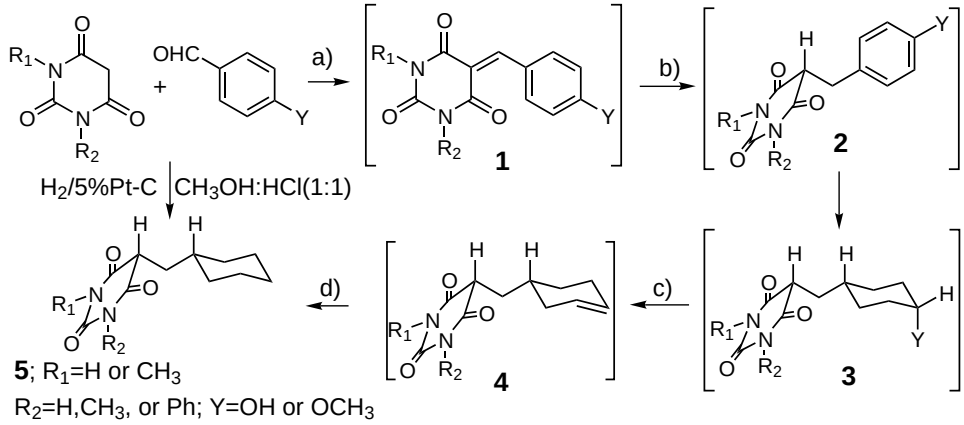

Scheme 1. Several reaction steps involved in the transformation of barbituric acid into 5-(cyclohexylmethyl)barbituric acid.

acetic acid suspension generates product **2** with reduction of isolated double bonds but not aromatic ring reduction. Using this method, product **2** can be isolated in almost quantitative yields. If the reduction is performed in a 0.01 M methanol suspension with PtO_2 as a catalyst at 80 psi hydrogen pressure and 70°C for several days, then the product of hydrogenation, compound **3**, can be isolated.[8] In acidic media compound **3** can be transformed into **4** and then it can be reduced into final product **5**. To avoid all of these steps, the reductive alkylation of barbituric acids with aromatic aldehydes were performed in various acidic solvents such as acetic acid, methanol-dilute sulfuric acid, methanol–trichloroacetic acid, aqueous hydrochloric acid, and methanol–hydrochloric acid. Considering the low solubility of the condensation product **2**, the combination of methanol–hydrochloric acid (1:1) as a solvent for the reductive alkylation of barbituric acids was proven to be the reaction media of choice. In many instances some amount of the product can be detected in the reaction mixture if 5% Pd-C with 50% of water was used, however, the best results were obtained with 5% Pd–C with 50% water as a catalyst.[9] Our isolated yields for these reactions are presented in Table 1.

To fully confirm the structure of our compounds one of the products of reductive cyclohexylmethylation of the above barbituric acids, product **5d**, was the subject of X-ray structural analysis[10] and proton and carbon NMR's were consistent with each of the products listed in Table 1.[11,12] The monoclinic, $P2_1/c$ crystals were grown from a methanol solution by allowing methanol to slowly evaporate at room temperature. The X-ray determined structure of 5-(cyclohexylmethyl)-1,3-dimethylbarbiturate (**5d**) is presented in Fig. 1. Both amide nitrogens of the barbituric acid ring are blocked with methyl groups, therefore strong hydrogen bonding interactions that are usually present in crystalline barbituric acids are not possible here. Actually, the barbituric acid ring is almost planar and it is almost perpendicular to the neighboring cyclohexane ring, which is in the chair conformation (Fig. 2). Other structural characteristics for compound **5d** are provided in supplementary materials.

Table 1. Synthesis of 5-(cyclohexylmethyl) barbiturates by reductive alkylation starting material

Entry	R_1	R_2	Y	Product	Yield (%)
1	H	H	OCH_3	**5a**	89.3
2	H	CH_3	OH	**5b**	84.0
3	H	C_6H_5	OCH_3	**5c**	93.3
4	CH_3	CH_3	OH	**5d**	88.0

In conclusion it can be stated that a very efficient one-pot synthetic procedure for 5-cyclohexylmethylation of barbituric acid under acidic and reductive reaction conditions was developed. The starting materials for this preparation are readily available, the yields of the reactions were very high, and purification of compounds involves simple crystallization from suitable solvents. As such, this method of preparation should be applicable to large-scale industrial application.[13]

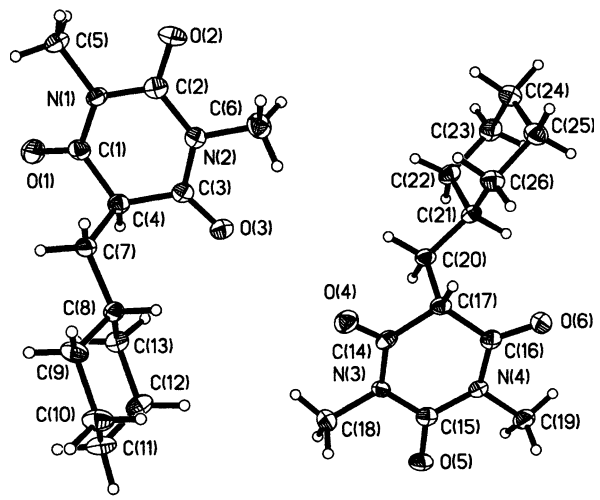

Figure 1. ORTEP drawing of two conformers of crystallographically unique structure of **5d** present in solid state. Thermal ellipsoids are at the 30% probability level.

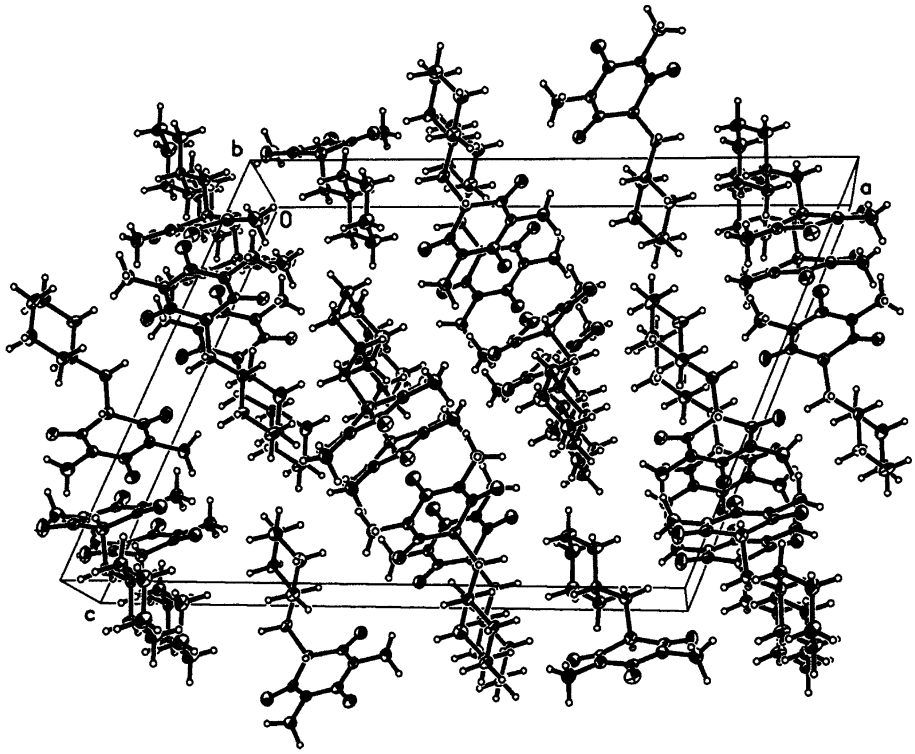

Figure 2. ORTEP drawing of the unit cell of **5d**.

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8. In the case where R_1 and $R_2 = CH_3$ and Y = OH, hydrogenation product was isolated, crystallized and characterized with X-ray analysis. The ratio of *cis–trans* isomer is 4:1.
9. **Preparation of 5-(cyclohexylmethyl)-1,3-dimethylbarbituric acid (5d)**: Into a methanol (100 ml) suspension of 1,3-dimethylbarbituric acid (1.27 g; 8.20 mmol) and 4-hydroxybenzaldehyde (1 g; 8.2 mmol) concentrated hydrochloric acid (100 ml) and 5% Pt on charcoal with 50% of water (1.3 g; 2 molar percent) were added. The resulting suspension was shaken under hydrogen pressure (70 psi) for 5 h. The catalyst was separated by filtration, the filtrate was concentrated to 50 ml and diluted with water ($\sim$100 ml). The formed white precipitate was separated by filtration and purified by crystallization from methanol. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.660 (t, 1H, J = 6.0 Hz, CH), 3.108 (s, 6H, N-CH_3), 1.796 (t, 2H, t, J = 6.6 Hz, CH_2), 1.636 (m, 4H, two CH_2 from cyclohexane), 1.450 (m, 1H, CH-cyclohexane), 1.121 (m, 4H, J = 4, two CH_2 from cyclohexane), 0.837 (m 2H, one CH_2 from cyclohexane). ^{13}C NMR (300 MHz, DMSO-d_6): δ 165 and 148 (two carbonyls from the barbituric acid ring), 42, 32, 31, 28, 24, 22, and 22 ppm. EIMS: m/z (%) 252 (M^+, 15), 169 ($M-C_6H_{11}^+$, 80), 157 (1,3-dimethylbarbituric acid $+1^+$, 100), 97 ($C_6H_{11}CH_3^+$, 30), and 83 ($C_6H_{11}^+$, 93)). Anal. calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.63; H, 5.11; N, 11.02.
10. X-Ray structure determination was performed on a Bruker SMART 1KCCD automated diffractometer. Crystals of compound **5d** were obtained by crystallization from methanol by allowing slow solvent evaporation. All reagents and solvents were purchased from Aldrich and used without prior purification. X-Ray single crystal structure determination of compound **5d** at 155(2) K. *Crystal data*: $C_{13}H_{20}N_2O_3$, M_r = 252.31, monoclinic, space group $P2_1$, a = 24.369(3), b = 6.3025(8), c = 18.301(2) Å, β = 111.449(2)°, V = 2616.0(6) Å^3, Z = 8, ρ_{calcd} 1.281 Mgm^{-3}, F_{000} = 1088, wavelength (λ) = 0.71073 Å, absorption coefficient (μ) = 0.091 mm^{-1}.

Data collection and reduction: Crystal size: 0.50×0.40×0.20 mm, θ range: 2.23 to 26.48°, index ranges: $-30 \leq h \leq 30, -7, \leq k \leq 7, -22 \leq 1 \leq 22$, reflections collected: 31129, independent reflections: 5367 [$R_{int} = 0.0993$], refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 537/0/485, final R indices [$I > 2\sigma(I)$]: $R_1 = 0.051$, $wR_2 = 0.1149$, goodness-of-fit on F^2: 0.828. R indices (all data) $R_1 = 0.1017$, $wR_2 = 0.1234$, largest diff. peak and hole: 0.253 and −0.288 e Å^{-3}.

Measurement computing and graphics: *SMART 1K CDD* (Bruker, 2000); cell refinement: *SMART*; data reduction *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure: *SHELXS 97* (Sheldrick, 1997); program(s) used to refine structure: *SHELX 97* (Sheldrick, 1997); molecular graphics: *SHELXTL 97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL 97*. (a) Bruker (2000). *SMART* (Version 5.060) and *SMART-Plus* (Version 6.02). Bruker AXS Inc, Madison, Wisconsin, USA. (b) Sheldick, G. M. (1997). *SHELXTL* DOS/Windows/NT. Version 5.1. Bruker AXS Inc, Madison, Wisconsin, USA. (c) Sheldrick, G. M. *SHELXL-97*, University of Göttingen, Göttingen, Germany, 1997.

11. NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer using DMSO-d_6 as solvent and solvent signals at 2.49 ppm in ^{1}H NMR and 36.0 ppm in ^{13}C NMR as references for chemical shift. Mass spectra were measured on a Hewlett–Packard GS–MS instrument by injecting samples dissolved either in chloroform or in methanol.
12. **NMR data: 5-(Cyclohexylmethyl)barbituric acid (5a)**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.137 (s, 1H, NH), 3.154 (t, 1H, $J = 6.0$ Hz, CH), 1.754 (t, 2H, $J = 5.7$ Hz, CH_2), 1.594 (m, 4H, $J = 5.1$ Hz, CH_2 cyclohexane), 1.310 (m, 1H, CH-cyclohexane), 1.095 (m, 4H, $J = 4.5$ Hz, CH_2 cyclohexane), 0.834 (m, 2H, CH_2 cyclohexane). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167 and 147 (barbituric acid carbonyls), 42, 31, 31, 28, 22, and 22 ppm. **5-(Cyclohexylmethyl)-1-methylbarbituric acid (5b)**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.319 (s, 1H, NH), 3.569 (t, 1H, $J = 6.0$ Hz, CH), 3.044 (s, 3H, CH_3), 1.767 (t, 2H, $J = 6.3$ Hz, CH_2), 1.605 (m, 4H, two CH_2 from cyclohexane), 1.460 (m, 1H, CH-cyclohexane), 1.098 (m, 4H, $J = 4.2$ Hz, two CH_2 from cyclohexane), 0.836 (m, 2H, $J = 9.9$ Hz, one CH_2 from cyclohexane). ^{13}C NMR (300 MHz, DMSO-d_6): δ 168, 167, and 146 (three barbituric acid ring carbonyls), 43, 30, 30, 28, 24, 22, and 22 ppm. **5-(Cyclohexylmethyl)-1-phenylbarbituric acid (5c)**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.700 (s, 1H, NH), 7.416, (t, 2H, $J = 7.5$ Hz, Ar), 7.197 (d of t, 3H, Ar), 3.735 (t, CH, $J = 5.9$ Hz, CH), 1.853 (t, 2H, $J = 6.6$ Hz, CH_2), 1.630 (m, 4H, two CH_2 from cyclohexane), 1.520 (m, 1H, CH-cyclohexane), 1.124 (m, 4H, $J = 4.4$ Hz, two CH_2 from cyclohexane), 0.855 (m, 2H, $J = 5.7$, one CH_2 from cyclohexane). ^{13}C NMR (300 MHz, DMSO-d_6): δ 167, 167, and 145 (barbituric acid carbonyls), 130, 124.9, 124.7, 124.4 (aromatic carbons), 42, 29, 28, 26, 21, and 21 ppm.
13. Patent application for reductive 5-cyclohexylmethylation of barbituric acid derivatives is in preparation.