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SYNTHESIS OF OPTICALLY ACTIVE 1,3-DIMETHYLALLANTOINS VIA (-)-MENTHYL ETHERS OF THEIR BICYCLIC TAUTOMERS

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Summary – Availability of both diastereomers of 1-(-)-menthoxy-2,4-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane (**5**) through decarboxylative rearrangement of 5-(-)-menthoxy-1,3-dimethyl-isouric acid (**1**) allowed the access to both enantiomers of 1,3-dimethylallantoin (**6**); circular dichroism spectra of the related homologues (-)-**6a** and (-)-allantoin proved their corresponding *R*-configurations.

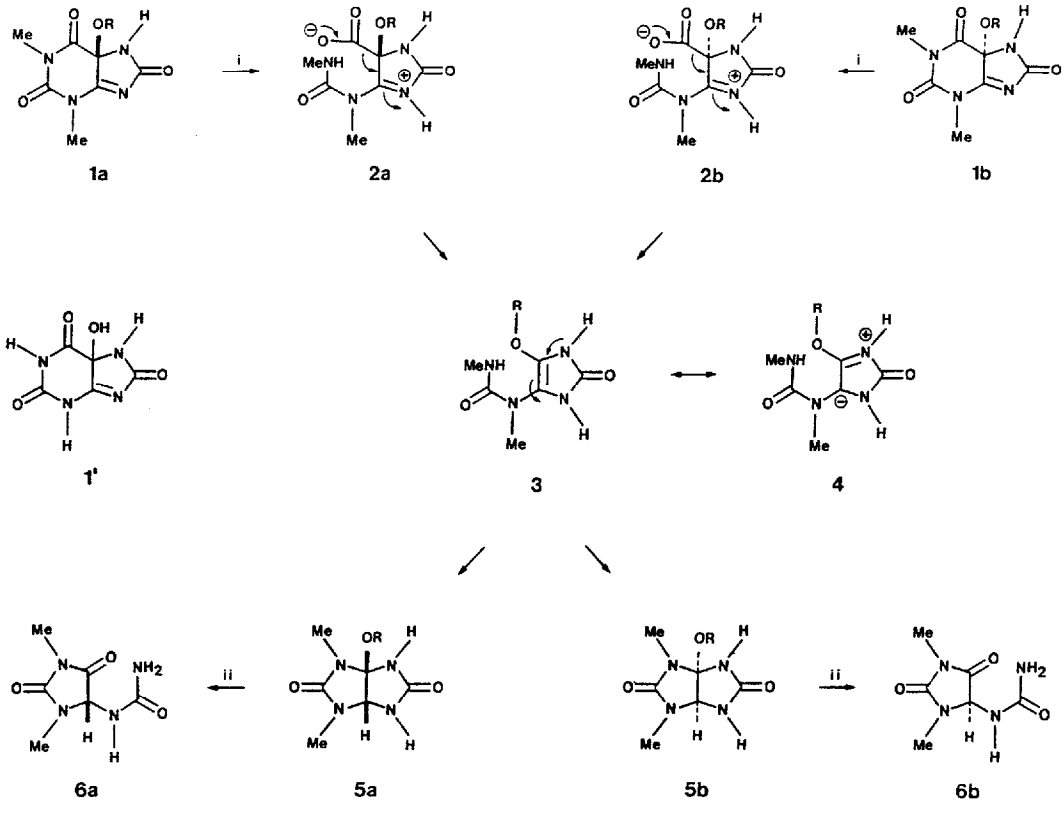
In 1934, Fosse and his coworkers obtained (-)-allantoin by allantoinase-mediated destruction of racemate which, besides the examples of isolation of the dextrorotatory natural product, thenceforth became the exclusive access to optically active allantoins.[1] These pioneering studies set the stage for a number of subsequent investigations dealing with the stereochemistry of the uricase reaction.[2-5] However, mechanistic ambiguities in uricolysis to allantoin and chiral elaboration of this small molecule represent substantial challenges. A strategy emerges from the possibility that a 5-adduct of uric acid, such as 5-hydroxy-isouric acid (**1'**), may be a precursor of allantoin.[6] This suggestion led us to consider a sequence starting from an appropriate chemical model bearing (-)-menthyl ether unit as a chiral auxiliary. Diastereomeric 5-(-)-menthoxy-1,3-dimethyl-isouric acids (**1a**/**1b**) have been prepared by reaction of 5-chloro-1,3-dimethyl-isouric acid[7] with (-)-menthol in pyridine.[8]

We have now developed a route which converts **1** into optically active 1,3-dimethylallantoins (**6**) in two simple steps (Scheme 1). Gradual addition of water (15ml) to a solution of **1** (5.0g, 14 mmol) in dioxane (10ml), with boiling at reflux for 1h, provided **5a**/**5b** (4.1-4.4g, 90-97%) in a 7:3 ratio.[9] This ratio was independent of the diastereomeric composition of the starting (-)-menthyl ether **1**, pure **1a** giving rise to an identical mixture of products. The bulk of the dominant isomer crystallized from the hot solution and recrystallization from alcohol gave the pure **5a** as colourless prisms; m.p. 277-8°, $[\alpha]_D^{25}$ -28° (c1.6, DMSO). ^{1}H NMR (DMSO-d_6), δ 8.21 (s,1H), 7.54 (bs,1H), 4.84 (d,1H,J=1.8), 3.50 (m,1H), 2.68 (s,3H), 2.62 (s,3H), 2.4 - 0.7 (um,18H). ^{13}C NMR (DMSO-d_6), δ 158.7 (s), 156.4 (s), 98.9 (s), 73.0 (d), 71.8 (d), 47.7 (d), 41.8 (t), 33.6 (t), 30.6 (d), 27.0 (q), 24.7 (d), 24.5 (q), 22.6 (t), 21.7 (q), 20.8 (q), 15.7 (q).[10]

Mixture **5a**/**5b**, obtained on cooling, was readily separated by recrystallization from alcohol to yield the remainder of **5a**. Evaporation of the solvent and recrystallization from ether/light petroleum afforded the minor isomer **5b**: m.p. 213-4°, $[\alpha]_D^{25}$ -72° (c2.6, DMSO). ^{1}H NMR (DMSO-d_6), δ 8.42 (s,1H), 7.74 (bs,1H), 4.75 (d,1H,J=0.9), 3.30 (m,1H), 2.68 (s,3H), 2.62 (s,3H), 2.3 - 0.7

(um,18H). ^{13}CNMR (DMSO-d_6), δ 158.7(s),156.3(s), 99.0(s), 72.7(d), 71.9(d), 47.4(d), 42.7 (t), 33.6(t),30.8(d),27.3(q),24.9(d),24.5(q),22.4(t),22.1(q),21.2(q),15.8(q).[10]

Preliminary X-ray data confirm the structure of **5a** (Figure 1),[11] being the first example of a derivative of the putative bicyclic tautomeric form in allantoin series. A possible mechanism for conversion **1**→**5**, based on related uricolytic transformations,[6] is shown in Scheme 1. That the product distribution is independent of configuration of **1** constitutes strong evidence for the common, enolic intermediate **3**. The stereoselectivity observed suggests that the chiral auxiliary influences the direction of approach of the neighbouring urea to the diastereotopic faces of **3**. The facile ring closure can be looked at as a 5-*Exo-Trig* allowed process,[12] due to the resonance structure **4**; whether a true iminol ether or a urea-assisted oxazolium variant of **4** could intervene in the hydrogen shift reaction is an unanswered but important question.[13] It would be expected, however, that the ring-chain tautomeric equilibria could be drastically affected by N-substituents.[14] Further evidence on this point is furnished by regiospecific cleavage of the ester aminal function of **5** which completed the sequence to optically active allantoins **6**.



Scheme 1. R = (-)-menthyl. (i) H_2O / dioxane, Δ; (ii) HCl/55%EtOH, Δ.

A typical procedure is as follows: to a boiling EtOH (120ml) solution of **5a** (3.24g, 10mmol), 5%HCl (100ml) was gradually added. After 10 min, the solution was concentrated, extracted with chloroform to remove menthol, and evaporated *in vacuo*. The residue was recrystallized from ethanol to yield (*R*)-(-)-1,3-dimethylallantoin (**6a**, 1.82g, 98%) as colourless prisms; m.p. 210-1°, $[\alpha]_D^{25}$ -75° (c3, H_2O). ^{1}H NMR (DMSO-d_6), δ 6.90 (bs, 1H), 5.93 (s, 2H), 5.19 (d, 1H, J=8.0), 2.83 (s, 3H), 2.72 (s, 3H). Similarly, reaction of **5b** provided cleanly the dextrorotatory (*S*)-enantiomer **6b**; m.p. 210-1°, $[\alpha]_D^{25}$ +75° (c2, H_2O).[15]

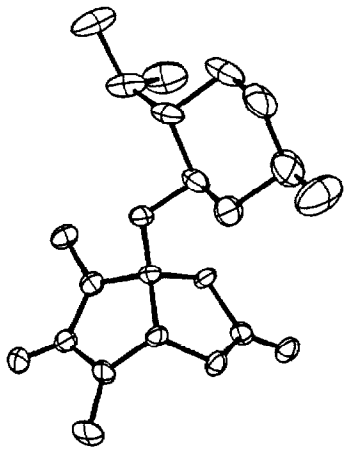


Figure 1. The skeletal array of **5a** (at R=0.106),[11] showing the (*R*,*R*)-configuration of the bicyclic system.

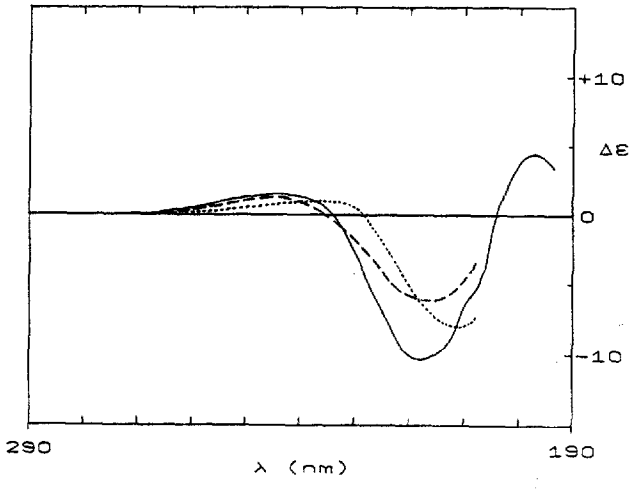


Figure 2. The CD spectra of (-)-**6a** in MeOH (———) and (-)-allantoin: pH 8.32 (----); pH 3.38 (·····), shown on a Δε scale.[4]

As a corollary, the availability of the *R*-configurational standard (-)-**6a** permitted an independent assignment of the absolute configuration of (-)-allantoin. A tentative, and, as it now turns out, correct, assignment of the *R*-configuration has already been made on the basis of chirospectral correlations with (*R*)-carbamoylalanine and (*S*)-hydantoin-5-acetic acid.[4,16] In a protic solvent like MeOH (-)-**6a** exhibits three CD Cotton effects: 242.0 (Δε=+1.3), 216.5 (Δε=-10.3), and ∿196 (Δε=+4.5) nm; comparison with the CD spectra reported for the laevorotatory allantoin[4] (Figure 2) provides an unambiguous evidence of its corresponding *R*-configuration.

Acknowledgement – We thank the Research Council of Croatia for support of this work.

References and Notes

[1] R. Fosse, P. E. Thomas, and P. de Graeve, *Compt. Rend.* **198**, 689, 1374, 1953 (1934); P. E. Thomas and P. de Graeve, *Ibid.* **198**, 2205 (1934).

[2] For reviews, see H. R. Mahler, in *The Enzymes*, Vol. 8, P. D. Boyer *et al.*, Eds., Academic Press, New York, 1963, p. 285; G. D. Vogels and C. van der Drift, *Bacteriol. Rev.* **40**, 403 (1976). It is now generally accepted that uricase catalyses only the interaction of urate with molecular oxygen; the nature of the initial intermediate and its non-enzymic breakdown to (+)-allantoin are still obscure.

[3] G. D. Vogels, F. E. de Windt, and W. Bassie, *Recl. Trav. Chim. Pays-Bas* **88**, 940 (1969).

[4] E. J. 's Gravenmade, G. D. Vogels, and C. van Pelt, *Ibid.* **88**, 929 (1969); the CD results have been expressed in terms of molecular ellipticity, using the relationship $[\theta] \cong 3300\Delta\varepsilon$.

[5] G. P. A. Bongaerts and G. D. Vogels, *Biochim. Biophys. Acta* **567**, 295 (1979).

[6] M. Poje and L. Sokolić-Maravić, *Tetrahedron* **42**, 747 (1986); *Ibid.* **44**, 6723 (1988).

[7] H. Biltz, *Liebigs Annln Chem.* **413**, 159 (1916).

[8] N. Modrić, A. Palković, I. Perina, and M. Poje, *Croat. Chem. Acta*, in press; there is thus obtained a 65% yield of **1a**/**1b**; successive recrystallizations from ether afforded the pure **1a**; m.p. 211-2°, $[\alpha]_D^{25}$ +63° (c 2, MeOH). Configurations were assigned using NMR methods.

[9] As judged by ^{1}H NMR and conversion **5a**/**5b** → **6a**/**6b**; $[\alpha]_D^{25}$ -30° (c 2, H_2O): *de* = *ee* = 40%.

[10] M.ps. are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a JEOL FX-100 spectrometer. Chemical shifts are given in δ units (ppm) relative to an internal TMS, and coupling constants are expressed in Hz (b, broad; s, singlet; d, doublet; t, triplet; q, quartet; um, unresolved multiplet). CD spectra were obtained with a Jasco J40CS spectropolarimeter. Satisfactory IR spectroscopic data, together with microanalytical (±0.3%) and MS data, were obtained for all new compounds.

[11] Further refinement is in progress; for complete X-ray data, see N. Modrić, M. Poje, I. Vicković, and M. Bruvo, to be submitted to *Acta Cryst. C*.

[12] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 734 (1976). Accordingly, the ring closure in **3** can be considered as a disfavourable 5-*Endo*-*Trig* process, and the 5-*Exo*-*Trig* mode in situations, of which **6** is a prototype, is sterically improbable.

[13] Interestingly, the (*Z*)-form of the urea side-chain, enabling its oxygen atom to achieve the required 5-*Exo*-*Trig* alignment at a short distance of 2.7 Å, can be discerned from the X-ray structure of (±)-allantoin: D. Mootz, *Acta Cryst.* **19**, 726 (1965). This interaction can be taken as a model for the transition state in stereospecific decarboxylation to (+)-allantoin (*cf.* ref. 2).

[14] The effect of N-substituents on the position of ring-chain equilibria can be understood by analysing them in relation to the conformation and the relative stability of the (*Z*)- and (*E*)-forms of the urea side chain. A few scattered observations are consistent with this view; both 1- and 7-methyluric acid afford 3-methylallantoin and the 3- and 9-methyl analogues 1-methylallantoin on oxidation: *cf.* E. Fischer, *Untersuchungen in der Puringruppe*, pp. 535-40, Springer, Berlin, 1907; E. Fischer and F. Ach, *Chem. Ber.* **32**, 2721 (1899); and refs 6 and 15.

[15] J. Abblard and A. Meynaud, *Bull. Soc. Chim. Fr.* 924 (1971) obtained (±)-1,3-dimethylallantoin (**6**), m.p. 214-5°, by reaction of 5-chlorohydantoin with *sym*-dimethylurea.

[16] The argument is tenuous at best because of the uncertainty in assignments in this wavelength region in amides and related chromophores: H. Basch, M. D. Robin, and N. A. Kuebler, *J. Chem. Phys.* **47**, 1201 (1967).

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