



UDC 547.783

THE STRUCTURE OF 1-ETHOXY-3A,8A-DIHYDROXY-3-(1-NAPHTHYL)METHYL-1,3,3A,8A-TETRAHYDROINDENO[1,2-d]IMIDAZOLE-2,8-DIONE

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Received 11 May 2021; accepted 4 July 2021; available online 20 July 2021

Abstract

Aim. Definition of the structure of 1-ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione. **Methods.** XRD study of the structure, mass spectrometry, ¹H and ¹³C NMR spectroscopy. **Results.** It has been found that ninhydrin reacts with *N*-ethoxy-*N'*-(1-naphthyl)methylurea yielding only one of the possible diastereomers of 1-ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione such as the diastereomer. The structure of 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione has been analyzed by XRD study. The formation of alternative trans-3a(HO),8a(HO)-diastereomer has not been observed. **Conclusions.** In 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione the 3a- and 8a-hydroxyl groups are *cis*-oriented to each other. There are two independent molecules of the compound 15 (15A and 15B) in the asymmetric part of the unit cell. The length of the N–O bond is also different for both molecules 15A and 15B. In the molecule 15A the length of the N(2)–O(5) bond is 1.396(7) Å, in the molecule 15B the length of the N(4)–O(10) bond is 1.405(7) Å. It has found the new case of the existence of urea derivatives as a mixture of the two forms which differ by the pyramidal degree of the nitrogen atom and the lengths of the nitrogen atom bonds. In the both independent molecules the imidazolidinone cycle adopt the envelope conformation. In the both independent molecules the similar elongation of the C(3a)–C(8a) and C(8)–C(8a) bonds has been found.

Keywords: 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione; structure; *cis*-isomer; elongated C–C bond; ninhydrin; *N*-alkoxyureas.

СТРУКТУРА 1-ЕТОКСИ-3А,8А-ДИГІДРОКСИ-3-(1-НАФТІЛ)МЕТИЛ-1,3,3А,8А-ТЕТРАГІДРОІНДЕНО[1,2-*D*]ІМІДАЗОЛ-2,8-ДІОНУ

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Анотація

Мета. Синтез та встановлення будови 1-етокси-3a,8a-дигідрокси-3-(1-нафтіл)метил-1,3,3a,8a-тетрагідроіндено[1,2-*d*]імідазол-2,8-діону. **Метод.** РСА аналіз отриманих структур. **Результати.** У молекулі 1-етокси-3a*S*,8a*R*-дигідрокси-3-(1-нафтіл)метил-1,3,3a,8a-тетрагідроіндено[1,2-*d*]імідазол-2,8-діону гідроксильні групи в положеннях 3a- і 8a- знаходяться в цисоїдній орієнтації. Спостерігається подовження зв'язків C(3a)–C(8a) і C(8)–C(8a).

Ключові слова: 1-етокси-3a,8a-дигідрокси-3-(1-нафтіл)метил-1,3,3a,8a-тетрагідроіндено[1,2-*d*]імідазол-2,8-діон; структура; *cis*-ізомер; подовжений C–C зв'язок; нінгідрин; *N*-алкоксисечовини.

СТРУКТУРА 1-ЭТОКСИ-3А,8А-ДИГИДРОКСИ-3-(1-НАФТИЛ)МЕТИЛ-1,3,3А,8А-ТЕТРАГИДРОИНДЕНО[1,2-*D*]ИМИДАЗОЛ-2,8-ДИОНА

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Аннотация

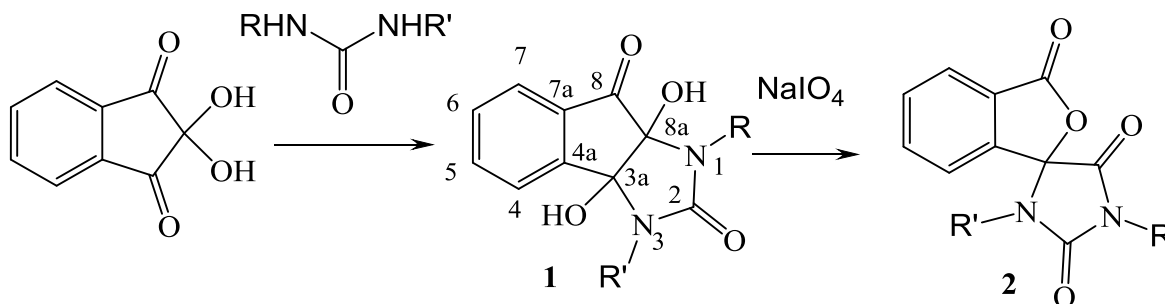
Цель. Синтез и установление структуры 1-этокси-3а,8а-дигидрокси-3-(1-нафтил)метил-1,3,3а,8а-тетрагидроиндено[1,2-*d*]имидазол-2,8-диона. **Метод.** РСА анализ полученных структур. **Результаты.** В молекуле 1-этокси-3а,8а-дигидрокси-3-(1-нафтил)метил-1,3,3а,8а-тетрагидроиндено[1,2-*d*]имидазол-2,8-диона гидроксильные группы в положениях 3а- и 8а- находятся в цисоидной ориентации. Наблюдается удлинение связей С(3а)–С(8а) и С(8)–С(8а).

Ключевые слова: 1-этокси-3а,8а-дигидрокси-3-(1-нафтил)метил-1,3,3а,8а-тетрагидроиндено[1,2-*d*]имидазол-2,8-дион; структура; цис-изомер; удлиненная С–С связь; нингидрин; *N*-мочевины.

Introduction

Ninhydrin interacts with urea and *N,N'*-dialkylureas giving adducts **1** [1–5] (Scheme 1).

During oxidation of the adducts **1** with NaIO₄ the disruption of the C(8)–C(8a) bond occurs yielding spirohydandoin **2** (Scheme 1) possessing the anticonvulsant activity [6–9].

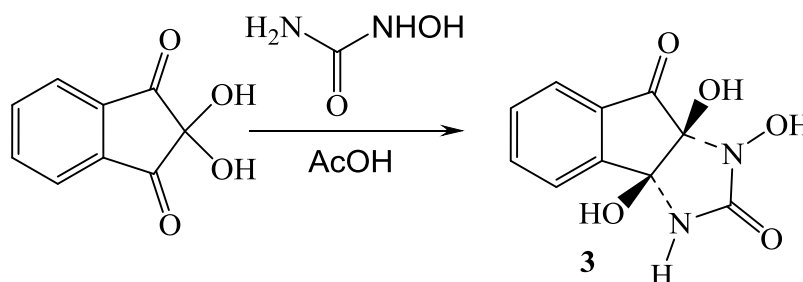


Scheme 1. The interaction of ninhydrin with urea and *N,N'*-dialkylureas and the standard numeration of the ring atoms in adducts **1** and the relative compounds [**3**]

The creation of the innovative approach to the imidazolidin-2-ones derivatives is an actual task of organic synthesis [10–14]. The ninhydrin interaction with the derivatives of *N*-hydroxyurea [15; 16] is one of the most innovative routes to the imidazolidin-2-ones.

The ninhydrin interaction with *N*-hydroxyurea

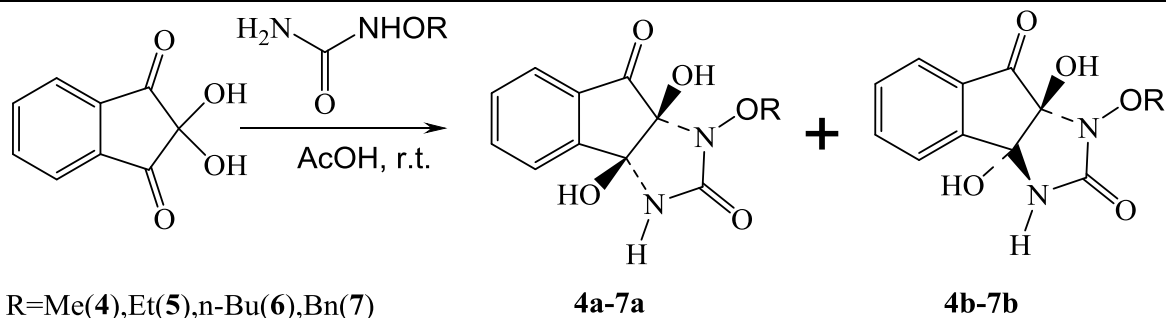
in acetic acid at the room temperature gives 1,3а,8а-trihydroxy-1,3,3а,8а-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **3** as single *cis*-3а(HO),8а(HO)-diastereomer with high yield [15] (Scheme 2). The alternative *trans*-3а(HO),8а(HO)-diastereomer formation has not been observed.



Scheme 2. The synthesis of 1,3а,8а-trihydroxy-1,3,3а,8а-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **3** [15]

In the same conditions ninhydrin reacts with *N*-alkoxyureas producing mixtures of diastereomers of 1-alkoxy-3а,8а-*R*-dihydroxy-1,3,3а,8а-

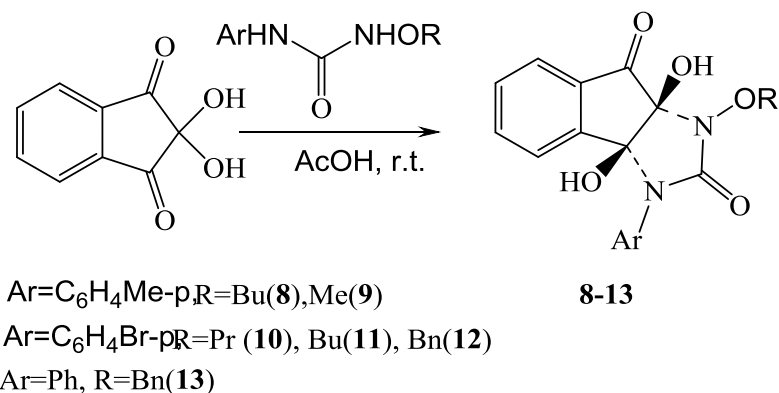
tetrahydroindeno[1,2-*d*]imidazole-2,8-diones **4–7** [15] (Scheme 3).



Scheme 3. The synthesis of 1-alkoxy-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-diones 4-7 [15]

In these mixtures the diastereomers **4a-7a** are the main component. The diastereomers **4a-7a** have the *cis*-orientation of the C(3a)-OH and C(8a)-OH hydroxyl groups each to other. The diastereomers **4b-7b** with *trans* orientation of 3a-HO and 8a-HO-groups have been observed in the trace amounts of the reaction mixtures, the *cis/trans* ratio is 10 : 1 [15]. The structures of compounds **3** and **6a** had been proved by XRD study [15].

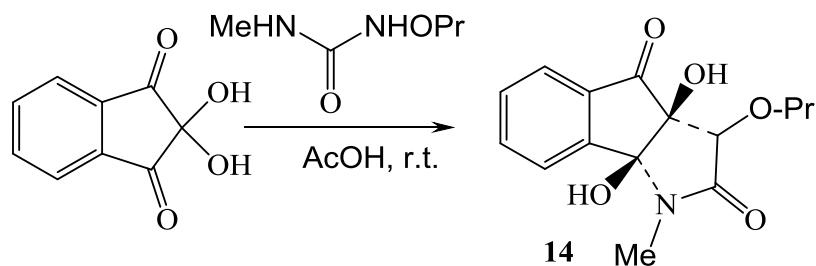
Ninhydrin reacts with *N*-alkoxy-*N'*-arylyureas in acetic acid at room temperature selectively forming only one of the possible diastereomers of 1-alkoxy-3-aryl-3a*S*,8a*R*-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones such as the diastereomer **8-13** with the mutual *cis*-orientation of the C(3a)-OH and C(8a)-OH hydroxyl groups, too [16] (Scheme 4). The formation of alternative *trans*-3a(HO),8a(HO)-diastereomer has not been observed.



Scheme 4. The synthesis 1-alkoxy-3-aryl-3a,8a-dihydroxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones 8-13 [16]

Ninhydrin reacts with *N*-propyloxy-*N'*-methylurea in the same conditions giving only one of the possible diastereomers of 3a*S*,8a*R*-dihydroxy-3-methyl-1-propyloxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-diones

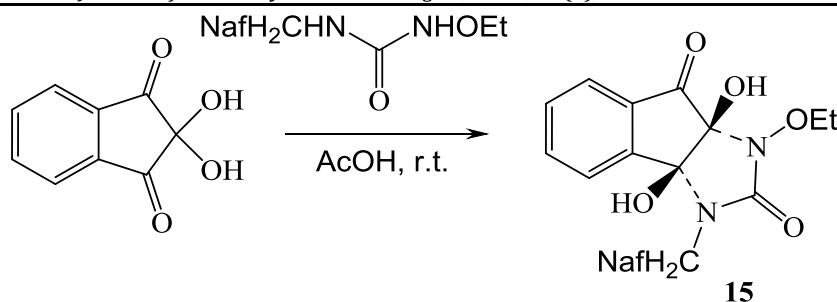
such as the diastereomer **14** [16] (Scheme 5). The compound **14** has the mutual *cis*-orientation of the C(3a)-OH and C(8a)-OH hydroxyl groups. It has been proved by the XRD study of the diastereomer **14**.



Scheme 5. The synthesis of 3a*S*,8a*R*-dihydroxy-3-methyl-1-propyloxy-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **14**

It has been found that ninhydrin reacts with *N*-ethoxy-*N'*-(1-naphthyl)methylurea yielding only one of the possible diastereomers of 1-ethoxy-

3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione such as the diastereomer **15** [16] (Scheme 6).



Scheme 6. The synthesis of 1-ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione **15** [16]

The structure of compound **15** has been proposed by analogy with the previous case. But this assumption must be checked by XRD study. This work is focused on the XRD study of 1-ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione **15** structure.

Experimental

1-Ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione (15) [16]. Ninhydrin (70.3 mg, 0.395 mmol) was dissolved in the solution of *N*-ethoxy-*N'*-(1-naphthyl)methylurea [17] (96.4 mg, 0.395 mmol) in acetic acid (4 mL) at stirring at 20°C during 2h, the obtained reaction solution was frozen, then acetic acid was evaporated under vacuum (3 mmHg) at 17°C, the residue was extracted by water (6 mL) at 8 °C during 19 h, the formed precipitate was filtered out, washed by water (2 mL), dried under vacuum (3 mmHg), giving 148 mg (92 %) 1-ethoxy-3a,8a-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-d]imidazole-2,8-dione **15**, *cis*-3a,8a-dihydroxy diastereomer, colorless crystals, mp 157–159 °C (with decomp.). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 1.152 (3H, t, *J* = 7.0 Hz, NOCH₂Me); 3.860–4.001 (2H, m, NOCH₂Me); 5.091 (1H, d, ²*J* = 16.8 Hz, NCH₂); 5.159 (1H, d, ²*J* = 16.8 Hz, NCH₂); 7.091 (1H, d, *J* = 7.2 Hz, Ar); 7.198 (1H, d, *J* = 7.2 Hz, Ar); 7.320 (1H, s, C(3a)-OH); 7.348 (1H, d, *J* = 8.0 Hz, Ar); 7.472–7.601 (4H, m, C₁₀H₇); 7.764 (1H, s, C(8a)-OH); 7.805 (2H, t, *J* = 7.6 Hz, C₁₀H₇); 7.918–7.990 (1H, m, Ar); 8.135–8.218 (1H, m, Ar). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 13.70 (Me); 40.42 (NCH₂); 71.91 (NOCH₂); 87.67 (C-OH); 88.79 (C-OH); 123.07 C(H) C₁₀H₇; 123.73 C(H) C₁₀H₇; 124.60 C(H) C₆H₄; 125.12 C(H) C₆H₄; 125.32 C(H) C₁₀H₇; 125.68 C(H) C₁₀H₇; 126.18 C(H) C₁₀H₇; 127.25 C(H) C₁₀H₇; 128.49 C(H) C₁₀H₇; 130.51 C_q C₁₀H₇; 130.56 C(H) C₆H₄; 132.32 C_q C₆H₄; 133.06 C_q C₁₀H₇; 133.09 C_q C₁₀H₇; 136.11 C(H) C₆H₄; 148.81 C_q C₆H₄; 155.69 [N(C=O)N]; 195.16 (C=O). MS (FAB) *m/z* 404 [M+H]⁺(25); 203

(9); 141 (100). Anal. Calc. for C₂₃H₂₀N₂O₅: C 68.31; H 4.98; N 6.93. Found: C 68.46; H 4.94; N 6.76.

Crystal data for compound **15** : from CH₂Cl₂, C₂₃H₂₀N₂O₅, *M* = 404.41, monoclinic, space group **P2₁/n**, *a* = 7.0451(13), *b* = 23.191(4), *c* = 25.893(5)Å, β = 92.855(9)°, *V* = 4225.3(13)Å³, *Z* = 8, *d_c* = 1.271, μ 0.091 mm⁻¹, *F*(000) 1696, crystal size ca. 0.02 × 0.06 × 0.38 mm. All crystallographic measurements were performed at 173K on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected for reflections within θ_{max} ≤ 25.0° using Mo-K_α radiation (λ = 0.71078Å). The intensities of 39335 reflections were collected (7414 unique reflections, *R*_{merge} = 0.2185). The structure were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package [18]. All hydrogen atoms were placed at calculated positions and refined as 'riding' model. There were significant regions of disordered electron density detected in the residual Fourier difference map after refinement of all frameworks atoms. None of these lattice solvent molecules could be reasonably modeled, and the remaining electron density had its contribution to the diffraction data accounted for with the SQUEEZE routine within PLATON. Analysis of the voids from SQUEEZE results in a total electron count of 222 e⁻ within the voids per unit cell, with a void volume of 531 Å³. An estimation of the nature of the solvent was unable to be determined. Convergence was obtained at *R*₁ = 0.1035 and *wR*₂ = 0.2632 for 3015 observed reflections with *I* ≥ 2σ(*I*), *R*₁ = 0.2408 and *wR*₂ = 0.3558, *GOF* = 0.928 for 7414 independent reflections, 541 parameters, the largest and minimal peaks in the final difference map 0.48 and -0.55 e/Å³.

The atomic coordinates, molecular geometry parameters, and crystallographic data of compound **15** were deposited to the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ UK [fax: +44-1223-336033, e-mail:

deposit@ccdc.cam.ac.uk] and is available on request quoting the deposit number CCDC 2076259.

Results and discussion

The earlier proposed structure of 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **15** has been proved by XRD study (Fig. 1, 2, Table).

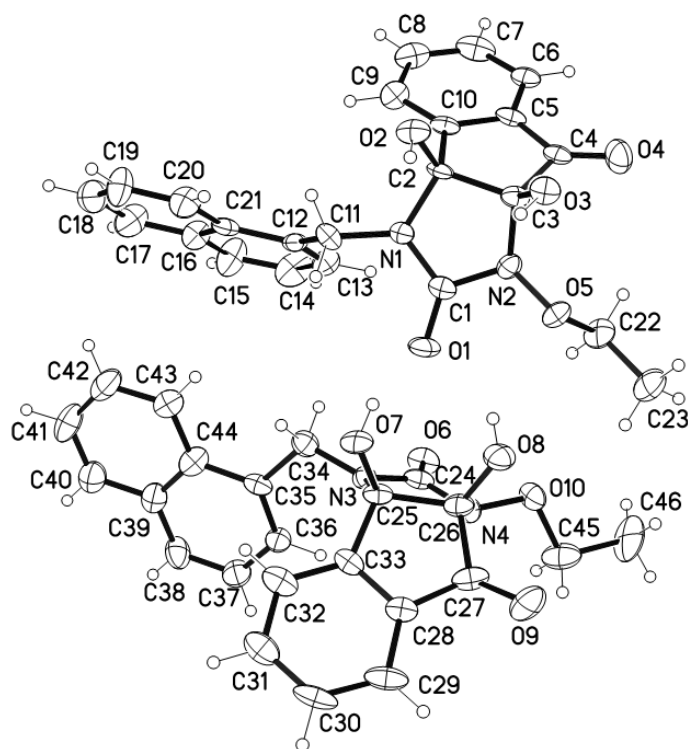


Fig. 1. Molecular structure of 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **15** with atoms represented by thermal vibration ellipsoids at 50 % probability level

There are two independent molecules of the compound **15** (**15A** and **15B**) in the asymmetric part of the unit cell (Figure 1). The molecular structure of compound **15** contains *cis*-fused indane and imidazolidinone moiety (Fig. 1,2) with the angle between the indane and imidazolidinone planes is 60.0° (**15A**), 59.3° (**15B**) for these two independent molecules. At these molecules the C(2)–O(2)H and C(3)–O(3)H in the molecule **15A** and C(25)–O(7)H and C(26)–O(8)H in the molecule **15B** are *cis*-oriented to each other. In the molecule **15A** the O(2)–C(2)–C(3)–O(3) torsion angle is 10.7(8)°, in the molecule **15B** the O(7)–C(25)–C(26)–O(8) torsion angle is 9.9(8)°.

The imidazolidinone cycle adopt the envelope conformation. The C(1), N(1), C(2), and C(3) atoms in the molecule **15A** and, respectively, the C(24), N(3), C(25), and C(26) atoms in the molecule **15B** are situated in the same plane with the mid-square deviation of these atoms 0.0097 Å in the molecule **15A** and 0.0073 Å in the molecule **15B**), whereas the C(2), N(2), C(3) atoms plane in the molecule **15A** and the C(24), N(4), C(26) atoms plane in the molecule **15B** form with this plane the two-sided corner which is equal 13.6(7)°

in the molecule **15A** and 24.3(7)° in the molecule **15B**.

The N(1) atom in the molecule **15A** and the N(3) atom in the molecule **15B** have a planar configuration. In these atoms the sum of bond angles ($\Sigma\beta$) is 358.0(6)° in the molecule **15A**, 357.2(6)° in the molecule **15B**. The N(2) atom in the molecule **15A** and the N(4) atom in the molecule **15B** have a pyramidal configuration. For the N(2) atom $\Sigma\beta$ is 341.2(5)°(the molecule **15A**), for the N(4) atom $\Sigma\beta$ is 342.9(5)°(the molecule **15B**).

The length of the N–O bond is also different for both molecules **15A** and **15B**. In the molecule **15A** the length of the N(2)–O(5) bond is 1.396(7) Å, in the molecule **15B** the length of the N(4)–O(10) bond is 1.405(7) Å. This existence of urea derivatives as a mixture of the two forms which differ by the pyramidity degree of the nitrogen atom and the lengths of the nitrogen atom bonds is known for *N*-chloro-*N*-ethoxyurea [19], *N*-chloro-*N*-methoxy-*N'*-4-nitrophenylurea [20] and *N*-[(benzoyl)-(hydroxy)methyl]-*N*-benzyloxy-*N'*-(2-bromophenyl)urea [21].

In the molecule **15A** the N(1)–C(1) bond is shorter (1.350(9) Å) than the N(2)–C(1) bond (1.387(9) Å); in the molecule **15B** the N(3)–C(24) bond is shorter (1.355(9) Å) than the N(4)–C(24) bond (1.384(9) Å) too. This length differences indicate on the stronger conjugation between the lone pair of the N(1) atom and the C(1)=O(1) carbonyl in the molecule **15A** and the lone pair of the N(3) atom and the C(24)=O(6) carbonyl in the molecule **15B** as compared to conjugation between the lone pair of the N(2) atom and the C(1)=O(1) carbonyl in the molecule **15A** and the lone pair of the N(4) atom and the C(24)=O(6) carbonyl in the molecule **15B**. Earlier this phenomenon had been established for compounds **3**, **6a** [15], **9,10,13,14** [16].

The endocyclic C(2)–C(3) bond (1.566(10) Å) in the molecule **15A** and the similar endocyclic C(25)–C(26) bond (1.593(10) Å) in molecule **15B** are elongated as compared to the average length of C(sp³)–C(sp³) ordinary bond (1.540 Å) [22]. These bonds are corresponded to the C(3a)–C(8a) bond at the standard numeration of this fused polycyclic system [3] (see Scheme 1). Also the

some elongations of the endocyclic C(3)–C(4) bond in molecule **15A** and the similar C(26)–C(27) bond in the molecule **15B** take place. The length of C(3)–C(4) bond is 1.565(10) Å, the length of C(26)–C(27) bond is 1.564(10) Å. But the average length of C(sp³)–C(sp²) bond is 1.510 Å [22]. These elongated bonds correspond to the C(8)–C(8a) bond at the standard numeration of this fused polycyclic system [3] (see Scheme 1). The elongated C–C bond may be recognized as the potential reaction central in the chemical interactions of the compound **15**.

Earlier the similar elongation of the C(8)–C(8a) bond had observed in the similar fused polycyclic system [23; 24].

And vice versa, the exocyclic C(22)–C(23) bond (1.515(11) Å) and the C(45)–C(46) bond (1.498(11) Å) are shortened to the average length of the C(sp³)–C(sp³) ordinary bond.

In the crystal the molecules of the compound **15** are connected in the chains by O–H...O hydrogen bonds (Figure 2) which are oriented toward the crystalline axis *a* (Table).

Table

The hydrogen bonds in the crystal of compound **15**

D–H...A (symmetry operation)	d(D–H), Å	d(H...A), Å	d(D...A), Å	angle(DHA), degree
O(7)–H(7A)...O(1)	0.84	1.98	2.760(7)	154.4
O(8)–H(8A)...O(1)	0.84	2.16	2.910(7)	149.0
O(2)–H(2)...O6\$1#1	0.84	1.97	2.752(6)	154.0
O(3)–H(3)...O6\$1#1	0.84	2.17	2.925(7)	150.0

Symmetrical transformations used to generate equivalent atoms: #1 x+1,y,z

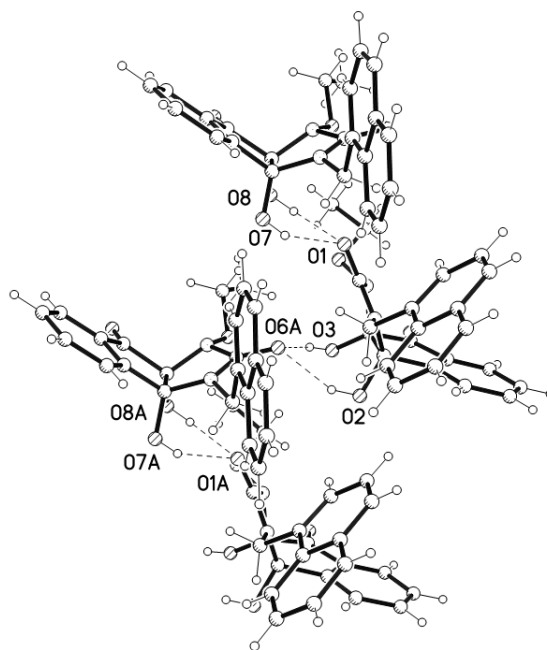


Fig. 2. Molecular packing of 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione **15** with molecules connected in H-bonded chains along *0a* direction in the crystal

Conclusions

The structure of 1-ethoxy-3a*S*,8a*R*-dihydroxy-3-(1-naphthyl)methyl-1,3,3a,8a-tetrahydroindeno[1,2-*d*]imidazole-2,8-dione 15 has been proved by the XRD study. In this compound the 3a- and 8a-hydroxyl groups are *cis*-oriented to each other. Similar elongation of the C(3a)-C(8a) and C(8)-C(8a) bonds has been found.

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