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Racemic estrone methyl ether is the lamellar conglomerate

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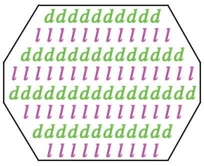
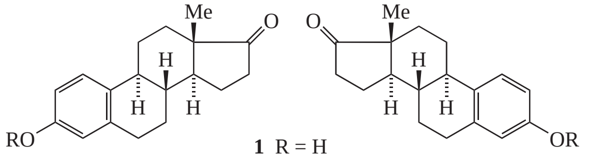
Methyl ether of racemic estrone, the long-known steroid, crystallizes in the form of a lamellar conglomerate. This form exhibits many properties of the ordinary conglomerates, however it requires special methods for the enantiomer separation due to pseudoracemic composition of the crystals.



Estrone and its derivatives are known as human and animal estrogenic hormones as well as useful medicaments. Preparation of estrone **1** is only possible by a multistage chemical synthesis. In the most of many dozens of such syntheses published by now,[1] the immediate precursor of estrone is its methyl ether **2**. The simplest syntheses that do not involve homochiral starting materials or reactants result in the methyl ether of racemic estrone *dl*-**2**.[2–4] Because only one enantiomer of estrone, namely *d*-**1**, possesses the desired hormonal activity, separation of enantiomers must be carried out and has already been made in the first syntheses.[2,3] The separation stage was performed by crystallization of diastereomeric pair of *l*-menthoxyacetate of racemic estrone *dl*-**1** obtained from ether *dl*-**2**.

On the other hand, it was found in the same studies[3] that racemic ether *dl*-**2** is a conglomerate,[†] that is a rare (less than 10% for nonionic compounds) occasion of racemate crystalline form with a property of spontaneous enantiomer separation on crystallization. The conglomerate form of ether *dl*-**2** was proved by the complete coincidence of its solid state IR spectrum with a spectrum for the individual enantiomer *d*-**2** obtained from 'natural' estrone *d*-**1**. Additional confirmations were the identity of the crystallographic characteristics and the lack of mixed melting point depression of *d*-**2** with *dl*-**2** (somewhat peculiar property).[6] Nevertheless, crystallization of ether *dl*-**2** in the form of a conglomerate is not mentioned in reviews and in the most comprehensive list of the known conglomerates.[5,‡]



d-(+)-**1**,**2** **1** R = H **2** R = Me *l*-(–)-**1**,**2**

Main crystalline forms of racemates are racemic compounds, solid solutions and conglomerates.[5] The latter form is of particular interest since only conglomerates can be easily separated into individual enantiomers by a preferable crystallization, or, in case of small quantities, even by a manual triage of enantiomer crystals.[5,7] The simplest last method was first used by Pasteur[8] and is still used in practical work.[9,10] Nevertheless, the authors of the first and the subsequent syntheses of estrone did not exploit this opportunity, without specifying the reason.

The potential possibility of easy separation of the enantiomers of racemic ether *dl*-**2** is attractive to simplify the synthesis of *d*-estrone *d*-**1** and to make more available its 'unnatural' enantiomer *l*-**1**, which has interesting biological properties.[11] However, for this purpose, it was necessary to confirm the conglomerate nature of ether *dl*-**2**.

Enantiopure ether *d*-**2** crystallizes easily at a slow evaporation of its (1.0 g) solution in dichloromethane at room temperature to give well-designed crystals with a weight in the range from 42 to 241 mg. Similarly, about a dozen of perfect monocrystals weighing from 2 to 7.8 mg was produced from 40 mg of racemic *dl*-**2** after evaporation of its solution in EtOAc–CH_2Cl_2 mixture. Crystals of *d*-**2** and *dl*-**2** seem to be morphologically identical (Figure 1). Further work was carried out with these monocrystals.

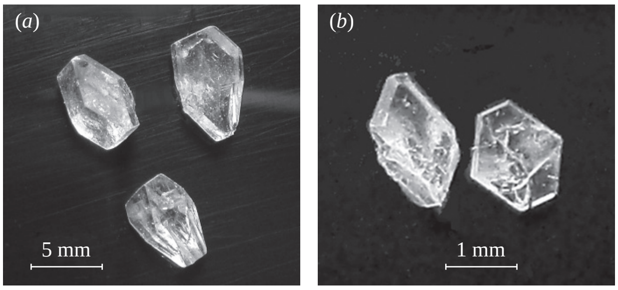


Figure 1 Crystals of methyl ethers of (*a*) *d*-estrone (*d*-**2**, 42–46 mg) and (*b*) *dl*-estrone (*dl*-**2**, 3.3 and 5.5 mg).

[†] Until otherwise stated (see below), the term 'conglomerate' is used in a classical meaning: a racemate which crystallizes as a mixture of separate crystals of two enatiomers.[5]

[‡] One possible reason is the usage of several dissimilar terms for conglomerates ('*dl*-mixture', '*dl*-crystalline mixture', 'racemic mixture'[3] and 'mixed crystals'[6]) in early publications. This rendered it impossible for searching machines to find many published examples of conglomerates.

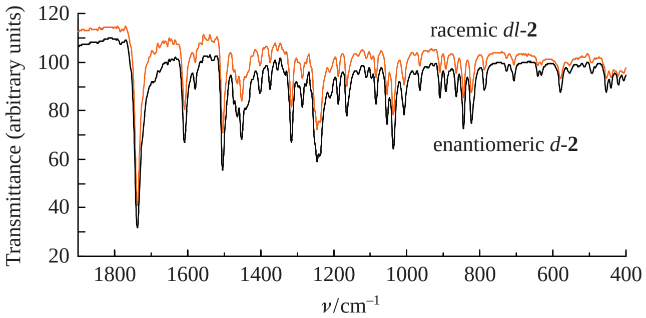


Figure 2 Fingerprint areas of IR spectra (KBr pellets). For the full spectra, see Figure S1 in Online Supplementary Materials.

Measured in this work, mp of racemate *dl*-**2** (mixture of crystals!) was 143.5–147 °C that was much lower as compared with mp 173.5–174.0 °C for the enantiomer *d*-**2**, while the rich solid state IR spectra of both samples are practically identical (Figure 2). These two properties correspond to published data[2,3] and are convincing but not absolute evidence of racemate crystallization in the form of conglomerate.

Crystal structure of *dl*-**2** was determined by single crystal X-ray diffraction (XRD) as asymmetric spatial group $P2_12_12_1$, $Z = 4$ (Figure 3).[§] Unit cell parameters of *dl*-**2** coincide with the published ones[12] of XRD for an individual enantiomer *d*-**2**. The presence of four molecules of the same enantiomer in the crystal unit cell convincingly proves the conglomerate nature of *dl*-**2**, but this proof is applicable only to the level of the unit cell sizes.

A unique property of conglomerates is a very significant difference in some properties of a mixture and of single crystals of the conglomerate. These properties of single crystals are the melting point, optical rotation and some other, that in the case of a conglomerate are identical with those of enantiomers. Unexpectedly we have found that the melting points of single crystals of *dl*-**2** and their smallest fragments are exactly the same as for the mixture of crystals (see above). Moreover, the optical rotation of monocrystal solutions is indistinguishable from zero in the measurements on the devices available to us,[¶] and the Flack parameter[13] has a value of 0.4. All these properties prove the presence of both enantiomers in each single crystal in a ratio close to 1 : 1, which contradicts the usual conglomerate.

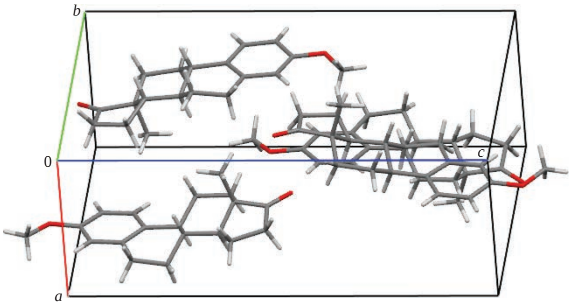


Figure 3 Unit cell of *dl*-**2** single crystal.

The accumulation of the properties found indicates the crystallization of *dl*-**2** as a conglomerate, but with participation of the process called in the recent publications as lamellar racemic twinning[9] or epitaxial lamellar twinning.[14,††] This process results in a crystal consisting of many layers of extensive flat areas (lamellae) of unit cells containing the same enantiomer throughout the lamella. Configuration of enantiomers in adjacent lamellae alternates. The experimentally found thickness of these lamellae is up to 50 μm, *i.e.* tens of thousands of unit cells.[15–18]

It is necessary to dwell on and to establish the terminology. A number of names has been used for the process described above and even there are discussions.[9,16] For the result of this process, there are also several names for the crystalline form of the respective racemates.[18–23,‡‡] In this paper we will use the name ‘lamellar conglomerate’ (LC). The racemates that crystallize with the lamellar racemic twinning process are still conglomerates, but at the micrometer rather than millimeter level of the crystals. More simply organized and widespread conglomerates for clarity can be called ‘plain conglomerate’ (PC). These two types of conglomerates are closely related and there are cases when the same racemate crystallizes as LC or PC depending on crystallization conditions.[16,24] The term ‘conglomerate’ will now generalize LC with PC and can be defined as ‘crystalline racemate with a single enantiomer only in each unit cell’.

Although the above method of LC identification (optical rotation in combination with XRD) is quite reliable, it is desirable to have another method based on some unique property of LC. This property can be the enantiomer composition of single crystals. For racemates in the forms of racemic compounds and solid solutions, the ratio of enantiomers in a single crystal is strictly 1 : 1 and for PC is 1 : 0. Crystals of LC are constructed from almost equal (±1) numbers of alternating lamellae of the one and the other enantiomers. However, lamellae can have very different sizes (and numbers of molecules), so the ratio of *d*- and *l*-enantiomeric molecules in a single crystal may differ markedly from 1 : 1, and this difference be the larger, the smaller is the size of the crystal. This unique property of LC has already been used

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[§] Crystals of steroid *dl*-**2** were grown by slow evaporation of the solution in CH_2Cl_2 at room temperature. Crystal data for *dl*-**2** at 100(2) K: $C_{19}H_{24}O_2$ ($M = 284.38$), orthorhombic, space group $P2_12_12_1$, $a = 6.8557(14)$, $b = 11.719(2)$ and $c = 18.421(4)$ Å, $V = 1480.0(5)$ Å^3, $Z = 4$, $d_{\text{calc}} = 1.276$ g cm^{-3}, $\mu = 0.104$ mm^{-1}, $F(000) = 616$, the final $R = 0.0329$, $wR = 0.0892$ and $S = 1.039$ for 3214 observed reflections with $I > 2\sigma(I)$, absolute structure parameter 0.4(2), crystal size 0.10 × 0.07 × 0.07 mm^3. The measurements were performed on the ‘Belok’ beamline ($\lambda = 0.80246$ Å) of the National Research Center ‘Kurchatov Institute’ (Moscow, Russian Federation) using a MAR CCD detector. Semi-empirical absorption corrections were applied using the SCALA program. The structure was solved by the direct method and refined by full-matrix least squares against F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms of the carbon-containing ligands were set in geometrical positions and refined using the riding model. All calculations were carried out with the SHELX97 program package.

CCDC 1858853 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

[¶] The accuracy of the readings of the polarimeter used is ±0.005°, which for solutions of monocrystals with a weight of 3–4 mg in 1 ml of solvent in 1 dm cuvette responds with an error $[\alpha]_D$ ±1.5°.

[††] Process of lamellar racemic twinning manifests itself during the crystallization of supersaturated solutions of the racemate conglomerate with slow or absent stirring. In addition, the necessary prerequisite for the process is the possibility for crystals of any enantiomer to serve as a seed for the crystallization of another enantiomer. Crystallization of the first enantiomer leads to a drop in the concentration of this enantiomer in the solution near the crystal, but this solution remains supersaturated with the second enantiomer. Now second enantiomer begins to grow further on the same crystal, and in the solution around the crystal, the concentration of the second enantiomer decreases and the concentration of the first enantiomer increases (due to diffusion from the rest of the solution). After some time, the first enantiomer becomes again growing on the crystal, and so on. For more detailed description of lamellar racemic twinning mechanism, see refs. 9,15–18.

[‡‡] For the racemic crystalline forms obtained with the participation of twinning, the names ‘pseudoracemic conglomerate’ (in original German ‘pseudo-racemisches Konglomerat’)[19] and ‘pseudoracemate’[20] have firstly been proposed, that are sometimes used at present.[21] The popular name is ‘epitaxial racemic conglomerate’ (ERC).[18,22,23] However, this name reflects the composition and origin of the form, but not its structure and the following properties.

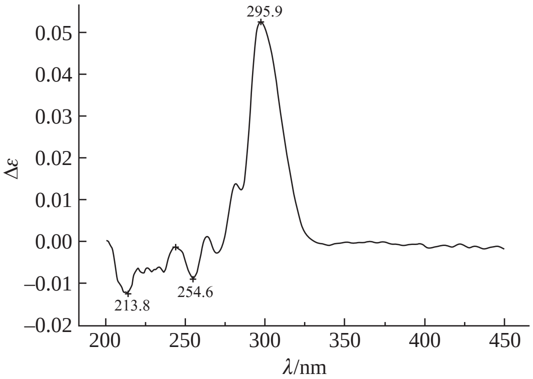

Figure 4 Circular dichroism spectrum of *dl*-**2** monocrystal (weight 4.2 mg, solution in 1 ml MeOH).

in the separation of enantiomers of helicenes[25] and can be applied to identify new LC.

The measurment of the small enantiomeric excess (*ee*) in single crystals is easily solved in the presence of a chromophore in the structure of the molecule, which allows the optical circular dichroism (CD) to be used. Sensitivity of CD method may be, in favorable cases, many times higher than the sensitivity of optical rotation measurement. One such case is 17-keto steroids, to which *dl*-**2** belongs.

A solution of *dl*-**2** monocrystal weighing 4.2 mg gave a clear maximum (Figure 4) in the CD spectrum at a wavelength (295.9 nm) coinciding with a maximum for *d*-**2**. Maximum height ($\Delta\varepsilon$ +0.053; for *d*-**2** under the same conditions $\Delta\varepsilon$ +3.4[26]) demonstrates *ee* 1.5% in the selected monocrystal of *dl*-**2** and confirms once again that it has the structure of LC.

The crystallization of some organic racemates in the form of LC is still little known, despite the fact that probably the first case was discovered and correctly interpreted in 1915.[19] To the authors' knowledge, about only fifteen more LCs are published by now.[9,15,16,18,22,25,27,28] However, there is an opinion that the formation of LC is common in the conglomerate crystallizations[9] but remained unidentified for some compounds described as ordinary conglomerates, that is as PC. There exists the first example of re-identification of the long-known PC as LC,[9] our example is the second. Since racemic steroid compounds are rare, the existence of the steroid *dl*-**2** as LC is highly untypical. The closely related homologous D-homo-*dl*-**2** crystallizes as a racemic compound.[29,30,§§]

Crystallization of a racemate as LC makes impossible the separation of its enantiomers by most of the methods effectively applied to PC, including a manual triage[7–9] of the crystals as well as the entrainment or preferential crystallization.[7] However, a method of enantiopure 'tailor-made' additives increasingly used for deracemization of PC has been successfully applied to LC.[14,22,28] Due to a close relationship between these two types of conglomerates seemingly the simplest method could be the conversion of LC into PC. Indeed, depending on the conditions of crystallization or solvent, sometimes the same racemate can be crystallized as LC or PC.[16,24] Insufficiency of the experimental material does not allow one to judge about the generality of this technique. Our attempts to obtain *dl*-**2** in the PC form by crystallization from other solvents (methanol, ethanol, *n*-hexane) did not lead to a success, and an LC form has been obtained in all cases.

In summary, the impossibility of the enantiomer separation of racemic estrone methyl ester *dl*-**2** by conventional crystallization is explained, and another example is added to a short list of identified lamellar conglomerates, this time the long-known steroid.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.005.

[§§] This conclusion is based on the much higher melting point of the racemic D-homo-*dl*-**2** (from 155–157 to 162–163 °C[29]) in comparison with the corresponding *d*-enantiomer (mp from 131–134 to 140–141 °C[30]).

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