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DIMERIZATION OF (+)-LYSERGIC ACID ESTERS[§]

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Abstract – Dimer isomer mixtures, characterized by a bridgehead C8-C8' bond, (**6a**-**7a**; **6b**-**7b**) were obtained from (+)-lysergic acid methyl or ethyl ester (**1b**; **1c**) in a solution of methanol or ethanol. The isomers were separated, and their structures were determined by detailed NMR measurements and X-ray analysis. Density functional theory was applied to provide insight into the reaction mechanism. Based on an extended examination and the theoretical calculations, a plausible reaction sequence leading to dimers is also presented. The proposed mechanism has been verified by detecting the formation of the superoxide radical anion ($O_2^{\bullet -}$).

INTRODUCTION

Studies on ergot alkaloids have been in the focus of interest for about two centuries.[1] Conscious applications of the natural products and their derivatives in the regular medicine[2] represented the first essential step. On the other hand, from a chemical point of view, the isolation and preparation of the first homogeneous ergot alkaloid performed by Sandoz's researchers[3] can be regarded as a milestone in this area. The majority of the ergot alkaloids contain (+)-lysergic acid **1a** or (+)-isolysergic acid **2a** as the principal constituent of the molecule (Figure 1).

[§]A few aspects of this work have been partly presented on "1st European Chemistry Congress" (27-31 August, 2006; Budapest Hungary; N-PO-183).

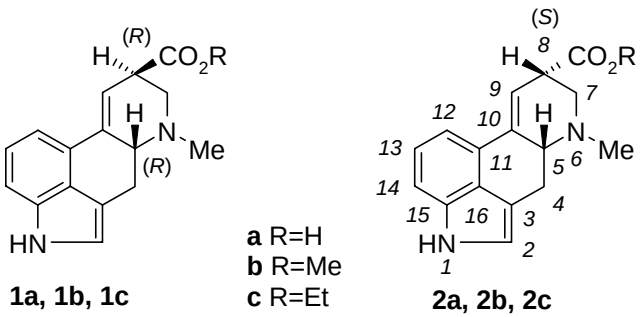


Figure 1 Structure of (+)-Lysergic acid (**1a**) and (+)-Isolysergic acid (**2a**) and their Esters.

After isolation of **1a** in 1934,[4] the preparation of a few simple derivatives, e.g. its methyl ester (**1b**)[4] was performed in the earlier years. The structure determination of **1a** and its derivatives, including the stereochemistry, was terminated in the early sixties years.[2] During the last seven decades, various special properties of **1a** and its derivatives have been presented. Isomerization to **2a** by heating a solution of **1a** in several types of solvents (water, alcohols) was first described by Wellcome's group.[5] Esters **1b** and **2b** were prepared from acids **1a** and **2a** by methylation.[5] Mutarotation of **1b** in MeOH[6] was also observed and was supposed to occur through a double bond migration.[7] The relationship between **1a** and **2a** and their derivatives was explained later as C8-epimerization via an "enolic intermediate" **3** (Figure 2).[8]

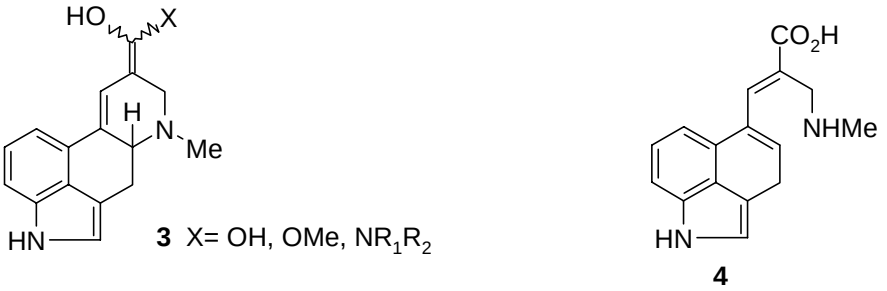


Figure 2 Structures of hypothetic compounds **3** and **4**.

Wellcome's group presented the second remarkable property of **1a** in 1936. On treating **1a** with aqueous barium hydroxide solution under harsh reaction conditions (sealed-tube, 150 °C, 4 h) racemic product (±)-**1a** was obtained.[6] The racemization was interpreted by Woodward as occurring via an achiral intermediate **4** (Figure 2), and his hypothesis inspired several groups to elaborate their total syntheses[2,9] or approaches[2,9] to (±)-**1a**, applying, however, 2,3-dihydroindole derivatives.

The third curiosity, the so-called indole-naphthalene isomerization, was described in 1953.[10] Acid (±)-**1a** was esterified with EtOH/HCl at 0 °C, then the solution of the (±)-**1c** obtained was heated in a sealed-tube. After then, the reaction mixture was acylated by Ac_2O, and at the end of the transformations naphthalene **5a** was isolated. The same result was obtained in MeOH. This irreversible isomerization was interpreted by simple energy calculations: naphthalenes proved to be more stable than indoles. This isomerization

highly influenced research groups dealing with the total synthesis of (±)-**1a**, the majority of them tried to avoid the approaches with indole derivatives, but rather they used dihydroindoles.

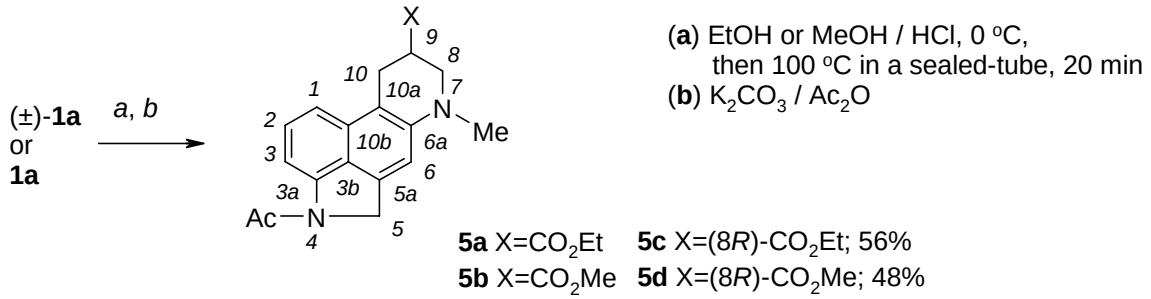


Figure 3 Indole-Naphthalene Isomerization.

Finally, we have to mention the formation of the so-called "lumi-derivatives"; C10-OH or C10-OMe compounds could be obtained from amides of **1a** in H_2O/H^+ or $MeOH/H^+$ under irradiation of the solutions with UV light.[11,12]

RESULTS AND DISCUSSION

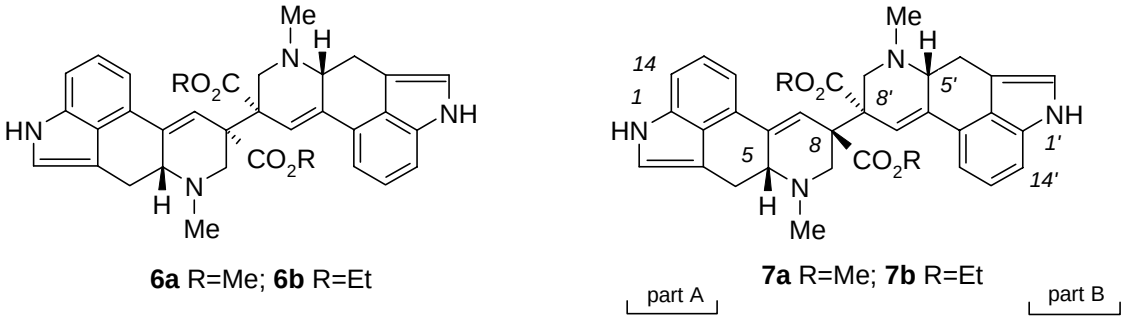
1) Synthetic aspects - Considering the above-presented extensive and lingering studies, one might hardly expect any new transformations in this field. Nevertheless, as a part of our continued interest in the reactions of the ergot derivatives, we have re-examined a few aspects of the above properties of **1a** and its derivatives. During this work an unexpected reaction of **1b** and **1c**, an unprecedented dimerization in the ergot alkaloids field was discovered under mild conditions.

To revisit and complete some of the earlier studies cited above, the indole-naphthalene isomerization was repeated starting with optically active **1a**. Naphthalene **5c** and **5d** were obtained *via* the Stoll's route reserved the optical activity {**5c**: $[\alpha]_D$ +62° (c 1.99, $CHCl_3$), **5d**: $[\alpha]_D$ +16° (c 0.25, $CHCl_3$)} showing that no racemization *via* C-8 epimerization occurred in the circumstances applied (Fig. 3). The absolute configuration of both **5c** and **5d** at C-8 must be (*R*). In the dominant conformation of *N*-Ac- naphthalenes (**5a-5d**) exists in a *quasi*-equatorial position, which is supported by the measured coupling constant value (9.8 Hz) between vicinal protons H-7_β and H-8, a characteristic value for *trans*-diaxial relative arrangement.

Next the racemization of **1a** was re-examined. Repeating the original procedure we found that (±)-**1a** did really formed in good yield when **1a** was heated in sealed-tube in barium hydroxide solution. Furthermore we found that barium hydroxide solution has no distinctive role; potassium hydroxide solution gave the same result (yield: 78%). During the recrystallization, a small crop (10%) of pure (±)-**2a** has also been isolated and characterized by spectroscopic methods. With pure (±)-**2a** in our hand, we tried to transform it into (±)-**2b** with diazomethane but the product obtained proved to be a mixture of (±)-**1b** and (±)-**2b** (ratio: ≈ 11:9).[#]

[#]In our first direct synthesis of **1a**, the structures of both **2a** and **2b** were determined by NMR spectroscopy in mixtures.[13] The formation of epimer mixture as end product under the alkylation can be rationalized in the following way: Acid (±)-**2a** dissolves poorly in acetone. The epimerization of (±)-**2a** into the equilibrium containing (±)-**2a** and (±)-**1a** is faster then the methylation.

As only epimerization of **1a** was investigated and published earlier,[5] we also tried a similar transformation of ester **1b** into **2b** in MeOH solution. On boiling a solution of **1b** (MeOH, overnight) or heating it at 40 °C for 48 h, completely unexpected dimer isomers (**6a** and **7a**) were formed. The same result was obtained when the solution of **1b** was allowed to react at room temperature for about 5-6 days.[ε]



6a R=Me; **6b** R=Et

7a R=Me; **7b** R=Et

Figure 4 Structure of Dimers **6a**-**7a** and **6b**-**7b**.

After purification the reaction mixture, an isomer mixture of **6a** and **7a** was obtained in a 68% yield (**6a**:**7a** ≈ 6:4). The separation of dimer isomers by a second chromatography afforded **6a** (30%) and **7a** (12%) in pure form. The ethyl ester analogs (**6b**, **7b**) were obtained in the same way, however in lower yields (**6b** + **7b**: 52%; ratio: ≈ 7:3; **6b**: 23%, **7b**: 15%). The bulkier ethyl ester group did not substantially affect the reaction sequence leading to dimer isomers. On the other hand, we found that the presence of an ester group is a requirement for the dimerization. The solution of **1a** in MeOH was refluxed for 2-3 days but only the earlier described epimerization at C8 was observed, and no traces of dimers could be detected. Alcohols as solvent were found essential for the formation of dimers. In all other solvents examined ($CHCl_3$, $CDCl_3$, CD_2Cl_2, DMSO-d_6, acetone, $CDCl_3$ + MeOD-d_4: 4:2), **1b** gave only epimer mixtures. It is worth mentioning here that the position of equilibrium significantly depends on the character of the ester group. While a 3:2 ratio of equilibrium between **1b** and **2b** can be measured by the NMR method after keeping the solution in $CDCl_3$ for two weeks at room temperature, at the same time the portion of **2c** in the **1c** ⇆ **2c** equilibration was found to be as small as 7%. A few entirely other types dimers in the ergot alkaloids field have been presented in the literature.[14]

[ε]All reactions were protected against the air, light and humidity applying the usual experimental protocol. The reaction was repeated about 6-7 times on different batches of MeOH. Compound **1b** was prepared several times and applied as starting material for the dimerization. The result was always the same. The reaction was also performed in a NMR tube to verify that the dimers did not form during the isolation.

2) Structure elucidation of dimers - *a) NMR-methods*: The formation of the dimer structures was assumed from the presence of a quaternary carbon at ca. 53 ppm and by the absence of vicinal couplings on the H-7 proton resonances in the ^{13}C and ^{1}H NMR spectra of compounds **6a**, **6b**, **7a**, and **7b**.

The NMR spectra displayed single sets of spectral parameters for **6a** and **6b**, which correspond to symmetrical dimer forms while for **7a** and **7b** we observed two chemically non-equivalent sets of ^{1}H and ^{13}C resonances. Consequently, asymmetric dimer structures were assigned to these compounds, where the two halves differ in the configuration at C-8. Decoupling and heterocorrelated NMR experiments helped to assign each set of protons and carbons of the two halves. However, the similarity of the spectral parameters did not afford a direct configurational assignment of the two halves.

The spectral parameters of one half of the asymmetric dimers (part B of **7a** and **7b**) are quite similar to those of the symmetric dimers **6a** and **6b**, while in the other half (part A) these parameters differ from their values of part B. It can be assumed that, similarly to diethyl amide derivatives of **1a** and **2a**, the C8-epimers exist in different conformations (Figure 5). [15]

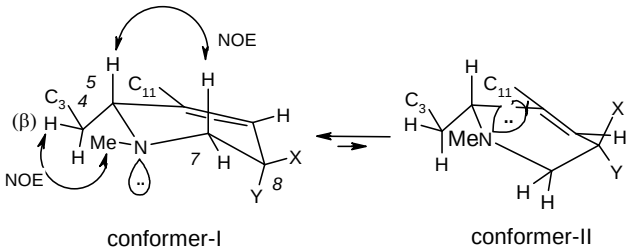


Figure 5 Relationships of Dimers in Ring D.

The upfield shift of C-7 and C-4 carbons of part A, relative to their values in part B, can be accounted for the γ-gauche interaction existing in the conformer II. The differences of the H-7 geminal couplings and some of the long-range couplings in the two halves of the above dimers can also be connected with slight conformational differences of ring D. However, the contribution of conformer II can not be significant, since no NOE's were found between H-4_α and H-7_α protons.

In the absence of vicinal proton-proton couplings in ring D, the alternative approach in assigning the C-8 configuration is to use the stereodependence of the vicinal carbon-proton coupling values. As follows from the Karplus-type dihedral angle relationship, maximum $^{3}J_{CH}$ values are expected for 0^{o} and 180^{o} while minimum (zero) values for the near 90^{o} dihedral angles.[16] In monomers **1b** and **1c**, according to molecular models, the dihedral angle between the carboxy carbon and H-9 proton is ca. 20^{o}. Consequently, this carbon correlated relatively strongly with the H-9 proton in the long-range heterocorrelated experiments. Similar long-range hetero-correlations were found between the H-9 proton and the carboxy carbon in part A of the asymmetric dimers **7a** and **7b**, while no such correlations were obtained between the in symmetric dimers **6a** and **6b** and in part B of the asymmetric dimers **7a** and **7b**.

In the symmetric dimers, and in part B of the asymmetric dimers, on the basis of the observed geometric dependence of $^3J_{(H9,COO)}$, it can be concluded that the orientation of the ester groups corresponds to that of the isolysergic acid while part A of the asymmetric dimers are displaced as in the lysergic acid. The preferred orientation about the C8–C8' bond in **7a** can also be established by the NOESY spectrum. The NOE connectivities of some ring D protons between the two halves reveal that **7a**, similarly to **6a**, exists preferably in an extended form. In particular, the H-9 proton of part A showed NOE correlations both with H-7$_\alpha$ and H-7$_\beta$ protons of part B, while the H-9 proton of part B correlated only with the H-7$_\alpha$ proton of part A. This difference is the consequence of the different C-8 stereochemistry of the two halves, where, according to the stereomodels, the H-7$_\beta$ proton of part A can not get into the vicinity of the part B protons. The relative arrangement of the two halves in **7a** is corroborated by the long-range connectivities observed between the protons and carbons of the two D rings. The molecular models of the suggested stereochemistry reflect a ca. 20^o dihedral angle between H-9(B) and C-8(A) and a ca. 90^o dihedral angle between H-9(A) and C-8(B). Accordingly, intense heterocorrelation was detected in the HMBC and INEPT-long-range spectra between H-9(B) and C-8(A), while no such correlation existed between H-9(A) and C-8(B).

b) X-Ray analysis: Tiny crystals of **6a**, suitable for single crystal X-ray analysis,[17] were obtained from a mixture of diisopropylether and acetone (7/3); despite several attempts we could not obtain single crystals of any of the asymmetric isomers (namely **6b** and **7b**) (Figure 6).

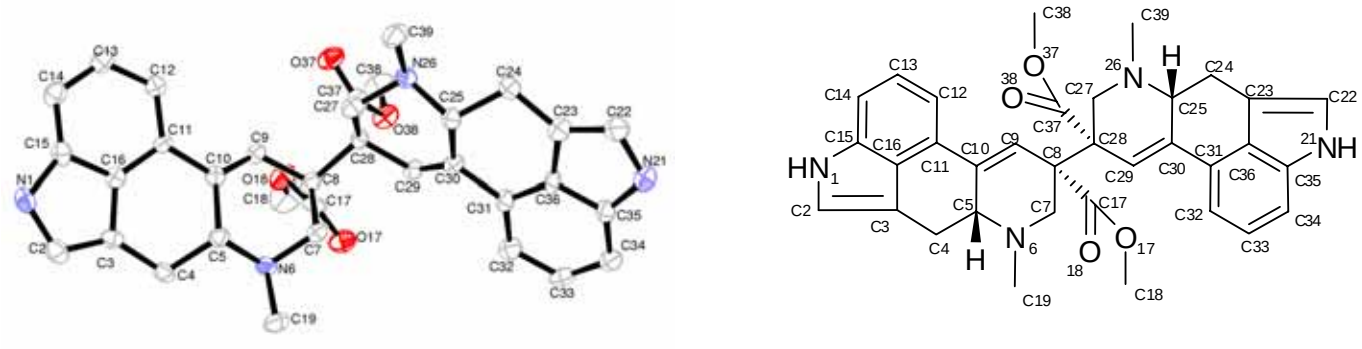


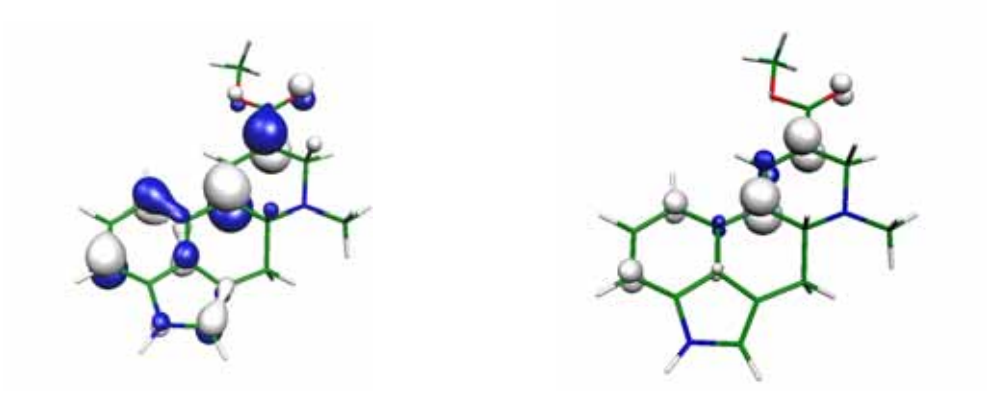
Figure 6 The ORTEP plot and crystallographic numbering scheme for the first of the independent molecules of **6a** (second molecule labelled with corresponding 40+n labels).

The obtained dimer has a unique structure. The search in the CSD[18] (Cambridge Structural Database) for a similar molecular structure, defined as two generic six-membered rings (with C, N or O atoms) joined together by an acyclic C(sp^3)-C(sp^3) bridgehead bond, indicates that none of such structure has been previously reported with ester functions attached to the bridgehead atoms. Also C(sp^3)-C(sp^3) bonds between tertiary (bonded to either C, N or O atoms) carbons substituted with an ester function are not very common in the CSD. In addition to the unique connection of the dimer parts, two other interesting structural features occur. The C(sp^3)-C(sp^3) bridgehead bond is very long and the molecule consists of

two symmetry equivalent parts (viz. 2 x **2b**). The crystallographic results for **6a** confirm the presence of symmetry within the dimer. The asymmetric unit of the unit cell (space group $P2_12_12_1$) contains two independent dimers having slightly different torsion angles between the ester groups, yet the same intramolecular symmetry persists. In each of the two independent dimers one half of the molecule is symmetry-equivalent with the other half, to which it is related by a non-crystallographic twofold axis. The twofold symmetry is unaffected by the conformational freedom around the bridgehead C–C bond of the dimer allowing the two independent molecules to adopt slightly different torsion angles around the bridgehead C–C bond. In this respect, crystallographic results confirm the NMR evidence. In addition to the intriguing molecular structure, the bridgehead C–C bond of the dimer manifests a striking feature of the molecular structure of **6a** and of the whole class of dimers described in this work. The two large parts of the dimer are structurally surprisingly unaffected by the close proximity of the ester groups. Even the very short intramolecular *cis*-conformational carbonyl carbon to carbonyl carbon [C(17)–C(37) and C(57)–C(77)] distances, 2.866(8) and 2.939(9) Å respectively, do not alter the normal sp^3 C–C and C–N bond distances and angles around the bridgehead carbons [C(8), C(28), C(48) and C(68)]. As the sum of van der Waals radii of carbon is 3.4 Å, the measured contact distances are 0.534/0.461 Å shorter. The bridgehead bond lengths, measured from the two independent dimers, are 1.603(9) Å and 1.612(9) Å [C(8)–C(28) and C(48)–C(68)], respectively. These apparently high values are not surprising considering that 86 examples of acyclic $C(sp^3)$–$C(sp^3)$ bonds between tertiary (bonded to carbon atom) carbons longer than 1.6 Å can be found in the CSD. As mentioned before, the value of the torsion angle between the ester functions across the bridgehead C–C bond is different in the two crystallographically independent molecules, being 51.2(7)° for the first molecule [C(17)–C(8) –C(28)–C(37)] and 59.3(7)° for the second [C(57)–C(48)–C(68)–C(77)].

3) A plausible interpretation of reaction mechanism leading to dimers – A few similar types of dimerization by oxidative coupling from more simple compounds in the presence of metal ions, can be found in the literature.[19] Furthermore, we have performed our original reaction with a few modifications to obtain details from the character of the dimerization. The solution of **1b** in MeOH was treated as described above (stirring at 40 °C) in the presence of a radical scavenger (3,5-di-*tert*-butylphenol, 1 equivalent). The scavenger completely altered the original result; no dimers were formed. This experience shows that the dimerization may be a radical process. In another run, $Na_2S_2O_4$ also inhibited the dimerization. This indicates that the traces of air-oxygen also may play a role in the reaction pathway. In both cases, the epimer mixture of **1b** and **2b** could be recuperated from the reaction mixture. When the mixture was directly irradiated with white light the dimerization took place perfectly for 20 h at 40 °C. This indicates that the light accelerated the dimerization. In the final experiment radical initiator 10 mol% of AIBN was added to the reaction mixture but it did not change the rate of the dimerization at all.

In order to provide further support for the radical mechanism, we examined the electronic structure and thermodynamical stability of the radical **1b**$^{\bullet}$ assumed to act as an intermediate in the dimerization reaction, by applying density functional theory at the B3LYP/6-31G* level.[20] As expected, the radical has a nearly planar equilibrium structure, which allows a high degree of delocalization of the unpaired electron. In Figure 7, we depicted the isodensity surface of the singly occupied molecular orbital of **1b**$^{\bullet}$ along with the spin density of the radical, which both indicate that the electron delocalization is extended almost to the entire molecular frame including the allylic unit, the COOMe group, and the two aromatic rings as well.



a) b)

Figure 7 Surface plots of a) singly occupied MO and b) spin density of radical **1b**$^{\bullet}$ (isodensity values are 0.05 and 0.01 e/bohr^3, respectively).

R$^{\bullet}$	D_{298} (calc)	D_{298} (exp)
$C_6H_5^{\bullet}$	110.6	111
$CF_3^{\bullet}$	102.7	107
$CH_2H_3^{\bullet}$	109.1	106
$CH_3^{\bullet}$	104.8	105
$CMe_3^{\bullet}$	93.4	95.8
$PhCH_2^{\bullet}$	88.2	88
$HCO^{\bullet}$	87.0	87
CH_2=CH-$CH_2^{\bullet}$	84.9	86
1b$^{\bullet}$	68.2	
Mean absolute deviation: 1.4 kcal/mol		

Table 1 Calculated and experimental C-H bond dissociation enthalpies (in kcal/mol) for a set of R-H compounds. Experimental data are taken from Ref. 21.

These results point to the enhanced stability of the **1b**$^{\bullet}$ radical; therefore, we estimated the homolytic bond dissociation enthalpy (BDE) of the C–H bond in **1b**. The BDE values of R–H compounds are generally considered to provide a reasonable measure of the relative stability of free radicals,[21] including stable radicals such as CH_2=$CHCH_2^{\bullet}$ or $PhCH_2^{\bullet}$, the experimental data range between 80-90 kcal/mol. Our calculations (Table 1) predict a significantly lower C–H bond dissociation enthalpy for **1b**, indicating that the associated radical might be unusually stable and probably long lived, allowing for dimerization.

Although the calculated BDE value falls into the energy range of UV-visible light, it is quite unlikely that radical **1b**$^{\bullet}$ is produced via direct photolytic excitation. We anticipate that the reaction pathways depicted in Figure 8 may represent a plausible mechanism.

On the basis of our findings that two isomers are produced in the reaction, we argue that an anionic species (***i***) formed via deprotonation of **1b** is a common intermediate in the epimerization (route a) and dimerization pathways. The former reaction route can proceed through the enolic form (***ii***) of **1b**, whereas the radical formation likely involves an oxidation process leading either directly to radical (**1b**$^{\bullet}$ = ***iv***) or involving a peroxo radical intermediate (***iii***). The relative rates along these reaction channels might be rather sensitive to the stability of the anionic intermediate, which should be closely related to the solvent medium. Our observation that the dimerization only takes place in protic solvents suggests that the presence of an H-bonded network might be a key factor for the preference of routes (b) or (c). Further theoretical and also kinetic studies were required to gain more insight into the mechanistic details.

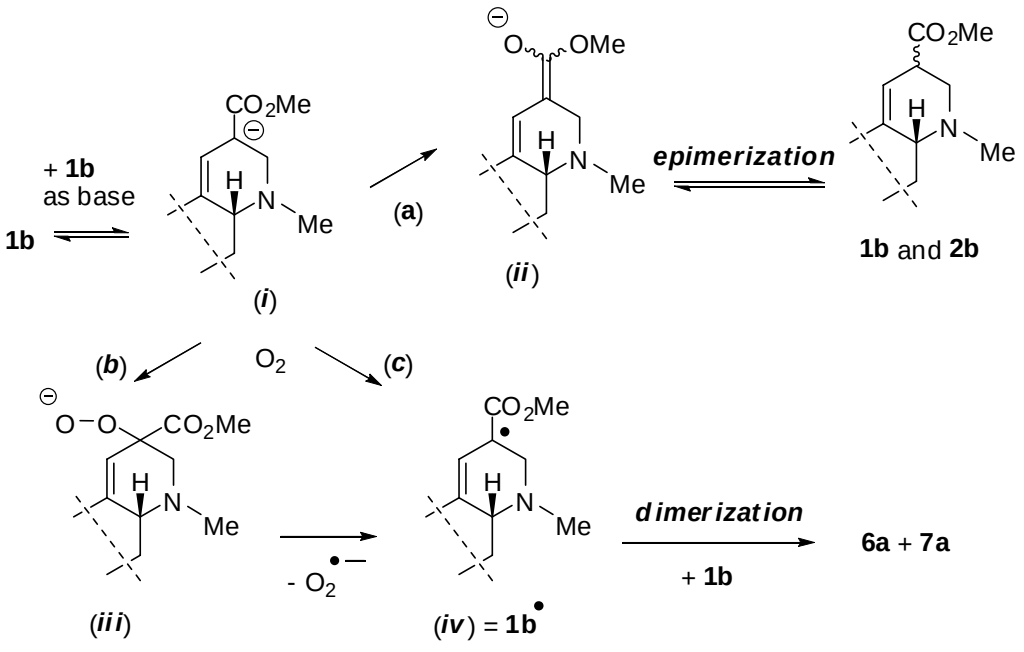


Figure 8 A plausible reaction sequence leading to dimers.

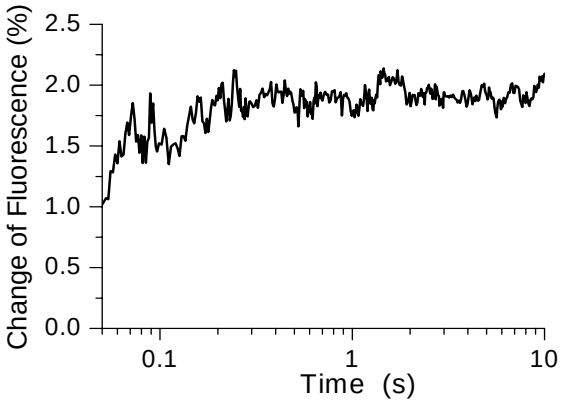


Figure 9 (+)-Lysergic acid methyl ester-induced formation of $O_2^{\bullet -}$ in MeOH. The time-course of ethidium fluorescence intensity changes (%) was recorded logarithmically, comprising 1000 data point acquired automatically. The concentration of (+)-**1b**: 0.1 mM.

To identify the primary reactive oxygen species requires a method with sufficient temporal resolution. Therefore measurements were conducted in the 0.05-10 s range of time applying the techniques of fast chemical kinetics in combination with fluorescence detection[22] (Figure 9). Hydroethidine, a blue fluorescent dye until oxidized to the red fluorescent ethidium was used to selectively monitor superoxide radical anion ($O_2^{\bullet -}$) formation.[23] These measurements helped us to choose pathway c as the more probable transformations leading to the dimers.

CONCLUSIONS

We have shown that the simple derivatives of (+)-lysergic acid, (+)-lysergic acid methyl or ethyl ester, afforded dimer isomers under mild reaction conditions in alcohols. The dimerization can be regarded as fourth special reaction in this field, beside the well-known discovered particular properties of ergot derivatives. An observation at the early stage – mutarotation of **1b** in methanol – has taken a final and correct explanation. The isomers of the dimer were separated and their structures were disclosed by detailed NMR examination and X-ray analysis. Our proposed reaction pathway leading to the dimers attempts to delineate the C8-epimerization and dimerization via a common intermediate, a carbanion species that is formed in the first step. In the following transformations unusually stable radical could be formed by catalysis of traces of air-oxygen, and their recombination can give the dimer product and a superoxide radical anion. Experimental data on (+)-lysergic acid methyl ester-induced superoxide radical anion formation provided evidence for the proposed mechanism. The feasibilities of the C8-epimerization and dimerization routes have been related to solvent effects.

EXPERIMENTAL

General: All reactions were carried out under an atmosphere of nitrogen or argon in dried glassware. Methanol and ethanol were dried Grignard-reaction and distillation or with a simple distillation. Chloroform and dichloromethane were distilled from phosphorous pentoxide. Acetone was distilled from potassium permanganate. Column chromatography was performed with Merck silica gel (0.040-0.063

mm). Analytical thin-layer chromatography was performed with commercial silica gel plates (Merck or Polygram of Macherey-Nagel, plastic sheets), and the plots were visualized under UV light or developed by iodine atmosphere and immersion in a solution of *o*-toluidine. Melting points were obtained on a Carl Zeiss apparatus equipped with microscope and are uncorrected. Elemental analyses (C, H, N) were carried out by Vario EL III (Elementar Analysen System Gmbh) automatic microanalyzer. IR data were recorded on potassium bromide plates on a Nicolet-7795 FT-IR spectrometer. Optical rotations were measured on an AA-10R automatic polarimeter (Optical Activity Ltd.) using 1.0 dm cells and the sodium D line (589 nm) at ambient temperature. MS spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos-MS-902 mass spectrometer. FAB-MS spectra were measured on a ZAB 2SEQ spectrometer. High resolution NMR measurements were carried out on a Varian Unity Inova 400 and Varian NMR System 600 spectrometers, equipped with 5 mm indirect detection probes, operating at 399.9 and 599.9 MHz for ^{1}H and at 100.5 and 150.9 MHz for ^{13}C nuclei. All spectra were acquired at 30 or 35 ^{o}C. The proton chemical shifts were measured relative to tetramethylsilane internal standard, and the carbon chemical shifts were reported using solvents as internal standards ($CDCl_3$ at 77.2 ppm, Py-d_5 at 150.0 ppm). The structural and spectroscopic assignments were made by the combined use of 1D and 2D experiments, such as HSQC and HMBC heterocorrelation techniques, using standard Varian software. One-dimensional long-range ^{1}H-^{13}C correlations were obtained in a sequence of selective INEPT-long-range experiments with delay values optimized for 3, 6, or 8 Hz couplings. Phase sensitive NOESY spectrum with 2048 x 128 blocks has been measured using 0.5 s mixing time. Data processing was performed using three-fold linear prediction. Rutin-like ^{1}H and ^{13}C measurements were carried out on a Varian Gemini 200 spectrometer.

1) Synthesis - Ester derivatives **1b** and **1c** were prepared applying the Sandoz's procedure[10] (HCl/alcohol) but using **1a** as starting material instead of (±)-**1a**. Physical constants and spectroscopic data of **1b** were in full agreement with the reported in our earlier publication.[13] Ester **1c** can be regarded as a new compound without physical and spectroscopic characterization. Similarly, naphthalene **5a** and **5b** has been known as racemic derivatives without any spectroscopic data. We have followed the official IUPAC rules for the name of dimers but for the NMR assignment the traditional ergoline-numbering was applied to a better comparison of dimers and monomers.

(±)-Isolysergic acid [(±)-**2a**] (Racemization of **1a**): A suspension of **1a** (3.0 g, 11.2 mmol) in aqueous KOH (1.5%, 50 mL) was passed into a steely sealed-tube and closed. The sealed-tube was putted into an oil-bath heated to 150 ^{o}C and kept steady for 4 h. After cooling to rt, the solution was put into a flask, the sealed-tube was washed with hot water (2 x 25 mL). The pH of the solution was adjusted to about 6 with aqueous HCl solution (20%, 25-30 mL). The precipitated dark crystals were filtered off, washed with

water to yield (±)-**1a** as grey semisolid crystals (2.34 g, 78%), which proved to be optically inactive. An analytical sample (0.5 g) was recrystallized from hot water with charcoal to afford (±)-**2a** (50 mg, 10%) beside the well known (±)-**1a**. Acid (±)-**2a**: mp 230-255 °C (tawny colour crystals, decomp.); TLC: R_f of (±)-**2a**: 0.21 ($CHCl_3$ + MeOH + NH_4OH, 5/5/0.1 mL); [TLC: R_f of (±)-**1a**: 0.28 ($CHCl_3$ + MeOH + NH_4OH, 5/5/0.1 mL)]. IR ν_{max} (KBr): 3415, 3117, 3055, 1600, 1450, 1378, 1344 cm^{-1}. HRMS (EI-MS): calcd for: $C_{16}H_{16}N_2O_2$; 268.1212, found 268.1216. ^1H NMR (Pyr-d_5, 400 MHz): δ 2.52 (s, 3 H, NCH_3), 2.80 (dd, *J* = 11.4, 4.2 Hz, 1 H, H-7$_\beta$), 2.90 (m, *J* = 14.4, 11.5, 1.6 Hz, 1 H, H-4$_\alpha$) 3.33 (m, 1 H, H-5), 3.52 (m, 1 H, H-8), 3.54 (dd, *J* = 14.4, 5.9 Hz, 1 H, H-4$_\beta$), 3.60 (dd, *J* = 11.4, 2.4 Hz, 1 H, H-7$_\alpha$), 7.01 (dd, *J* = 5.9, 2.2 Hz, 1 H, H-9), 7.20 (t, *J* = 1.6 Hz, 1 H, H-2), 7.33 (dd, *J* = 7.5, 7.3 Hz, 1 H, H-13), 7.40–7.45 (m, 1 H, H-12, H-14), 11.65 (d, *J* = 1.6 Hz, 1 H, NH) ppm. ^{13}C NMR (Py-d_5, 100 MHz): δ 27.7 (C-4), 42.4 (C-8), 43.5 (NCH_3), 54.5 (C-7), 63.6 (C-5), 110.6 (C-3), 110.6 (C-12), 111.3 (C-14), 119,7 (C-9), 120.0 (C-2), 123.6 (C-13), 127.5 (C-16), 129.2 (C-11), 135.4 (C-15), 137.1 (C-10), 175.1 (CO_2H) ppm.

(+)-Lysergic acid methyl ester (**1b**): Ester **1b** was prepared as described in the below examples. For the crystallization dry benzene was applied. The NMR spectra have been given to a better comparison of dimer subunits. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.59 (s, 3 H, NCH_3), 2.68 (m, *J* = 14.5, 11.5, 1.8 Hz, 1 H, H-4$_\alpha$), 2.69 (dd, *J* = 11.4, 10.7 Hz, 1H, H-7$_\beta$), 3.17 (m, *J* = 11.5, 5.6, 3.5, 2.1 Hz, 1 H, H-5), 3.26 (m, *J* = 11.4, 5.3, 1.2 Hz, 1 H, H-7$_\alpha$), 3.50 (dd, *J* = 14.5, 5.6 Hz, 1 H, H-4$_\beta$), 3.71 (m, *J* = 10.7, 5.3, 3.5, 2.3 Hz, 1 H, H-8), 3.77 (s, 3 H, OCH_3), 6.59 (m, *J* = 2.3, 2.1, 1.2 Hz, 1 H, H-9), 6.87 (t, *J* = 1.8 Hz, 1 H, H-2), 7.15–7.23 (m, 3 H, H-12, H-13, H-14), 8.12 (d, *J* = 1.8 Hz, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.4 (C-4), 42.4 (C-8), 43.9 (NCH_3), 52.2 (OCH_3), 55.1 (C-7), 63.1 (C-5), 109.9 (C-12), 111.0 (C-3), 112.7 (C-14), 118.2 (C-9), 118.5 (C-2), 123.5 (C-13), 126.5 (C-16), 128.3 (C-11), 134.2 (C-15), 136.4 (C-10), 173.0 (CO_2) ppm.

(+)-Lysergic acid ethyl ester (**1c**): A suspension of **1a** (3.0 g, 11.2 mmol) in dry EtOH (100 mL) was cooled with an ice-bath to –5 °C. Dry HCl gas was bubbled through the suspension, which gradually became to a dark solution for about 2-3 h while the temperature was kept on 0-5 °C. (The progress of the esterification was checked with TLC; eluent: a) $CHCl_3$+MeOH; 10/1; b) $CHCl_3$ + MeOH + NH_4OH, 5/5/0.1). The reaction mixture was poured into a mixture of $CHCl_3$ and ice-water (300 + 100 mL), then the pH was adjusted about 8 with NH_4OH solution (25%, 50 mL). The phases were separated and the organic layer was washed with water (2 x 50 mL), dried. The filtrate was evaporated under reduced pressure to yield brown oil (3.9 g). The oil obtained was crystallized (cyclohexane + AcOEt + acetone, 20/0.5/0.5 mL) to afford the title compound as tawny colour crystals (2.41 g, 73%); R_f 0.8 ($CHCl_3$ + MeOH, 10/1); mp 119-121 °C; $[\alpha]_D$ +62° (c 0.32, $CHCl_3$). IR ν_{max} (KBr): 3398, 2959, 1728, 1447, 1300, 1183 cm^{-1}. HRMS (FAB-MS; matrix: glycerol): calcd for $[M+H]^+$: 297.1603, found 297.1600; comp.:

M=296; $C_{18}H_{20}N_2O_2$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.59 (s, 3 H, NCH_3), 2.68 (dd, *J* = 11.4, 10.7 Hz, 1 H, H-7$_\beta$), 2.69 (m, *J* = 14.5, 11.6, 1.7 Hz, 1 H, H-4$_\alpha$), 3.16 (m, *J* = 11.6, 5.6, 3.4, 2.0 Hz, 1 H, H-5), 3.27 (m, *J* = 11.4, 5.4, 1.2 Hz, 1 H, H-7$_\alpha$), 3.50 (dd, *J* = 14.5, 5.6 Hz, 1 H, H-4$_\beta$), 3.70 (m, *J* = 10.7, 5.4, 3.4, 2.3 Hz, 1 H, H-8), 4.22 (q, *J* = 7.1 Hz, 2 H, OCH_2), 6.60 (m, *J* = 2.3, 2.0, 1.2 Hz, 1 H, H-9), 6.88 (dd, *J* = 1.8, 1.7 Hz, 1 H, H-2), 7.15–7.23 (m, 3 H, H-12, H-13, H-14), 8.13 (d, *J* = 1.8 Hz, 1 H, NH) ppm. ^{13}CNMR ($CDCl_3$, 100 MHz): δ 14.5 (CH_3), 27.4 (C-4), 42.5 (C-8), 43.9 (NCH_3), 55.1 (C-7), 61.1 (OCH_2), 63.2 (C-5), 109.9 (C-12), 111.0 (C-3), 112.7 (C-14), 118.5 (C-9), 118.5 (C-2), 123.5 (C-13), 126.4 (C-16), 128.3 (C-11), 134.2 (C-15), 136.3 (C-10), 172.6 (CO_2) ppm. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95, H, 6.80, N, 9.45. Found: C, 72.90, H, 6.87, N, 9.47.

(+)-4-Acetyl-7-methyl-4,5,7,8,9,10-hexahydroindolo[4,3-*fg*]quinoline 9-carboxylic acid ethyl ester (**5c**; Indole-Naphthalene Isomerization): Acid **1a** (0.75 g, 2.79 mmol) was transformed into ethyl ester as described above but the reaction mixture was transformed further in the following way. The ethanolic solution saturated with HCl was transfused into a sealed-tube, closed, and it was putted into an oil-bath heated to 100 ^{o}C and kept steady for 0.5 h. After cooling to rt, the reaction mixture was poured to a mixture of $CHCl_3$, ice water and saturated Na_2CO_3 solution (300 + 100 + 60 mL) while stirring and cooling the mixture. In the second step acetic anhydride (7.5 mL, 79 mmol) and potassium carbonate (15.0 g, 108 mmol) were added to the mixture and stirred further for 0.5 h. The phases were separated and the organic layer was washed with water (3 x 75 mL), dried. The filtrate was evaporated under reduced pressure to yield a black oil (787 mg) which was purified by column chromatography (hexane + AcOEt + $CHCl_3$; 300/300/6.0, then 400/400/12) to yield the title compound as black colour crystals (530 mg, 56%); R_f 0.42 ($CHCl_3$ + acetone, 20/1). An analytical sample was recrystallized from a mixture of benzene + diisopropyl ether + acetone applying charcoal; mp 178-180 ^{o}C (white crystals); $[\alpha]_D$ +61.8^o (c 1.99, $CHCl_3$). IR ν_{max} (KBr): 1734, 1661, 1659, 1628, 1600 1415 cm^{-1}. HRMS (EI-MS): calcd for $C_{20}H_{22}N_2O_3$; 338.1630, found 338.1632. ^{1}H NMR ($CDCl_3$, 400 MHz; two sets of amide rotamers): δ 1.30 (t, *J* = 7.1 Hz, 3 H, CH_2Me), 2.24, 2.43 (2 s, 3 H, COMe), 2.98, 3.02 (2 s, 3 H, NMe), 3.04–3.14, 3.25 (2 m, 3 H, H-9, H-10$_\alpha$, H-10$_\beta$), 3.36 (dd, *J* = 11.4, 9.8 Hz, 1 H, H-8$_\beta$), 3.49 (m, *J* = 11.4, 3.8, 1.8 Hz, 1 H, H-8$_\alpha$), 4.22 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.93 + 5.11 (2 s, 2 H, H-5), 6.69 + 6.80 (2 s,1 H,H-6), 6.68 + 7.63 (2 dd, *J* = 7.3, 0.5 Hz, 1 H, H-3), 7.18 + 7.20 (2 dd, *J* = 8.4, 0.5 Hz, 1 H, H-1), 7.31 + 7.34 (2 dd, *J* = 8.4, 7.3 Hz, 1 H, H-2) ppm.^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.5 (CH_2Me), 24.0 + 25.0 (COMe), 26.0 (C-10), 38.2 + 38.3 (C-9), 40.6 + 40.8 (NMe), 52.9 (C-8), 54.4 + 55.2 (C-5), 61.0 (OCH_2), 103.6 + 107.2 (C-3), 105.4 + 105.8 (C-6), 109.6 + 110.3 (C-10a), 114.2 + 114.4 (C-1), 123.9 + 124.3 (C-3b), 129.1 + 130.0 (C-2), 130.8 + 131.4 (C-10b), 134.2 + 134.4 (C-5a), 142.5-143.4 (C-6a), 145.7 + 146.3 (C-3a), 168.6 + 168.8 (NCO), 173.8 (CO_2) ppm. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99, H, 6.55, N, 8.28. Found: C, 70.90,

H, 6.48, N, 8.17.

(+)-4-Acetyl-7-methyl-4,5,7,8,9,10-hexahydroindolo[4,3-*fg*]quinoline-9-carboxylic acid methyl ester (**5d**): Naphthalene derivatives **5d** was prepared as described above. R_f 0.4 ($CHCl_3$ + acetone, 20/1); mp 155-157 °C (from diisopropyl ether); $[\alpha]_D$ +16° (c 0.25, $CHCl_3$). IR ν_{max} (KBr): 1734, 1661, 1659, 1628, 1600 1415; 1739, 1666, 1628, 1600, 1500, 1410 cm^{-1}. MS (EI-MS): 324 (M+, 100), 309 (5, M-Me), 293 (4), 282 (13), 263 (12), 221 (23). ^1H NMR ($CDCl_3$, 400 MHz): 2.29, 2.51 (2 s, 3 H, COMe), 3.00, 3.04 (2 s, 3 H, NMe), 3.03–3.15 + 3.27 (2 m, 3 H, H-9, H-10$_\alpha$, H-10$_\beta$), 3.37 (dd, *J* = 11.5, 9.8 Hz, 1 H, H-8$_\beta$), 3.48 (m, *J* = 11.5, 3.7, 1.6 Hz, 1 H, H-8$_\alpha$), 3.76 (s, 3 H, OMe), 5.05 + 5.15 (2 s, 2 H, H-5), 6.72 + 7.65 (2 dd, *J* = 7.3, 0.5 Hz, 1 H, H-3), 6.78 + 6.85 (2 s, 1 H, H-6), 7.20 + 7.21 (2 dd, *J* = 8.4, 0.5 Hz, 1 H, H-1), 7.33 + 7.36 (2 dd, *J* = 8.4, 7.3 Hz, 1 H, H-2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.1 + 25.0 (COMe), 26.0 (C-10), 38.2 + 38.3 (C-9), 40.6 + 40.7 (NMe), 52.2 (OMe), 52.9 + 53.0 (C-8), 54.4 + 55.3 (C-5), 103.6 + 107.2 (C-2), 105.4 + 105.8 (C-4), 109.5 + 110.2 (C-10), 114.2 + 114.4 (C-12), 124.0 + 124.4 (C-16), 129.2 + 130.1 (C-2), 130.9 + 131.5 (C-10b), 134.2 + 134.4 (C-5a), 142.6 + 143.5 (C-6a), 146.0 + 146.4 (C-3a), 168.6 + 168.8 (NCO), 174.2 (CO_2) ppm. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35, H, 6.21, N, 8.64. Found: C, 70.41, H, 6.19, N, 8.57.

(6a*R*,6'a*R*,9*R*,9'*R*)-Dimethyl-7,7'-dimethyl-4,4',6,6a,6',6a',7,7',8,8',9,9'-dodecahydro-9,9'-biindolo[4,3-*fg*]quinoline-9,9'-dicarboxylate (**6a**) and **(6a*R*,6'a*R*,9*R*,9'*S*)-dimethyl-7,7'-dimethyl-4,4',6,6a,6',6a',7,7',8,8',9,9'-dodecahydro-9,9'-biindolo-[4,3-*fg*]quinoline-9,9'-dicarboxylate** (**7a**): Ester **1b** (1.5 g, 5.3 mmol) was dissolved in dry MeOH (150 mL) under nitrogen atmosphere and the solution was stirred for 48 h at 40 °C then rt for 24 h. After evaporation of the solvent, the residue was purified by chromatography (eluent: $CHCl_3$+MeOH, 20/1; R_f of **6a**+**7a** > **1b** but differences could not be observed between **6a** and **7a** in this solvent mixture). The isomer mixture (1.01 g, 68%; ratio of **6a**:**7a** = 63/37%, determined by NMR integrals) was separated with a second chromatography (eluent: hexane +AcOEt + MeOH, 6/4/0.5; R_f of **7a** > **6a**).

Dimer **6a** (443 mg, 30%), R_f 0.385 (hexane + AcOEt + MeOH, 5/5/1); mp 173-177 °C (nearly white crystals from a mixture of diisopropyl ether + acetone, 7/3); $[\alpha]_D$ +170° (c 0.5, $CHCl_3$). IR ν_{max} (KBr): 3446, 3399, 2949, 1733, 1606, 1445, 1431, 1236 cm^{-1}. HRMS (FAB-MS; matrix: NOBA): calcd for $C_{34}H_{34}N_4O_4$ 562.2580, found 562.2610; $[M+H]^+$: 563.2678; ESIpoz (turbo spray) $[M+H]^+$: 563.4. ^1H NMR ($CDCl_3$, 400 MHz; to a better comparison, the chemical shifts of dimers are given applying the ergoline-numbering): δ 2.53 (s, 2 x 3 H, NCH_3), 2.63 (m, *J* = 14.6, 11.3, 1.6 Hz, 2 x 1 H, H-4$_\alpha$), 2.79 (d, *J* = 11.3 Hz, 2 x 1 H, H-7$_\beta$), 3.09 (m, *J* = 11.3, 5.7, 1.9 Hz, 2 x 1 H, H-5), 3.46 (dd, *J* = 14.6, 5.7 Hz, 2 x 1 H, H-4$_\beta$), 3.49 (dd, *J* = 11.3, 1.2 Hz, 2 x 1 H, H-7$_\alpha$), 3.69 (s, 2 x 3 H, OCH_3), 6.82 (dd, *J* = 1.9, 1.2 Hz, 2 x

1 H, H-9), 6.88 (dd, *J* = 1.6, 1.8 Hz, 2 x 1 H, H-2), 7.18 (dd, *J* = 6.7, 6.9 Hz, 2 x 1 H, H-13), 7.22 (dd, *J* = 6.7, 1.2 Hz, 2 x 1 H, H-12), 7.25 (dd, *J* = 6.9, 1.2 Hz, 2 x 1 H, H-14), 7.99 (d, *J* = 1.8 Hz, 2 x 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.3 (2 x C-4), 43.9 (2 x NCH_3), 52.5 (2 x OCH_3), 53.1 (2 x C-8), 57.2 (2 x C-7), 63.4 (2 x C-5), 110.0 (2 x C-12), 111.2 (2 x C-3), 112.7 (2 x C-14), 118.6 (2 x C-2), 119.9 (2 x C-9), 123.6 (2 x C-13), 126.7 (2 x C-16), 128.3 (2 x C-11), 134.2 (2 x C-15), 136.5 (2 x C-10), 173.3 (2 x CO_2) ppm. Anal. Calcd for $C_{34}H_{34}N_4O_4$: C, 72.58, H, 6.09, N, 9.96. Found: C, 72.61, H, 6.14, N, 9.91.

Dimer **7a** (176 mg, 12%), R_f 0.414 (hexane + AcOEt + MeOH, 5/5/1); mp 153-177 °C (decomp.; light brawn crystals; from a mixture of cyclohexane + AcOEt, 3/2); $[\alpha]_D$ +190° (c 0.263, $CHCl_3$). IR ν_{max} (KBr): 3414, 2950, 2848, 1728, 1604, 1447, 1230 cm^{-1}. HRMS (FAB-MS; matrix: NOBA): calcd for $C_{34}H_{34}N_4O_4$ 562.2580, found 562.2594; $[M+H]^+$: 563.2672; ESIpoz (turbo spray) $[M+H]^+$: 563.4. ^{1}H NMR ($CDCl_3$, 600 MHz,) *part A*: δ 2.49 (s 3 H, NCH_3), 2.73 (m, *J* = 14.6, 11.4, 1.4 Hz, 1 H, H-4$_\alpha$), 2.83 (d, *J* = 12.4 Hz, 1 H, H-7$_\beta$), 3.16 (m, *J* = 11.4, 5.4, 1.6 Hz, 1 H, H-5), 3.39 (dd, *J* = 14.6, 5.4 Hz, 1 H, H-4$_\beta$), 3.52 (dd, *J* = 12.4, 0.9 Hz, 1 H, H-7$_\alpha$), 3.61 (s, 3 H, OCH_3), 6.67 (dd, *J* = 1.6, 0.9 Hz, 1 H, H-9), 6.87 (dd, *J* = 1.8, 1.4 Hz, 1 H, H-2), 7.14–7.25 (m, 3 H, H-12, H-13, H-14), 7.90 (d, *J*=1.8 Hz, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 26.1 (C-4), 43.0 (NCH_3), 52.2 (OCH_3), 53.9 (C-8), 55.2 (C-7), 62.2 (C-5), 110.1 (C-12), 111.4 (C-3), 112.6 (C-14), 118.6 (C-2), 119.1 (C-9), 123.4 (C-13), 126.8 (C-16), 128.8 (C-11), 134.2 (C-15), 138.6 (C-10), 172.8 (CO_2) ppm, *part B*: 2.45 (s, 3 H, NCH_3), 2.59 (m, *J* = 14.3, 11.3, 1.7 Hz, 1 H, H-4$_\alpha$), 2.88 (d, *J* = 11.5 Hz, 1 H, H-7$_\beta$), 3.00 (m, *J* = 11.3, 5.7, 1.7 Hz, 1 H, H-5), 3.41 (dd, *J* = 14.3, 5.7 Hz, 1 H, H-4$_\beta$), 3.62 (dd, *J* = 11.3, 1.2 Hz, 1 H, H-7$_\alpha$), 3.72 (s, 3 H, OCH_3), 6.72 (dd, *J* = 1.7, 1.2 Hz, 1 H, H-9), 6.85 (dd, *J* = 1.7, 1.7 Hz, 1 H, H-2), 7.14–7.25 (m, 3 H, H-12, H-13, H-14), 7.91 (d, *J*=1.7 Hz, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 27.2 (C-4), 43.8 (NCH_3), 52.5 (OCH_3), 53.5 (C-8), 58.7 (C-7), 63. 4 (C-5), 109.9 (C-12), 111.3 (C-3), 112.7 (C-14), 118.6 (C-2), 121.3 (C-9), 123.5 (C-13), 126.7 (C-16), 128.6 (C-11), 134.2 (C-15), 136.1 (C-10), 173.4 (CO_2). Anal. Calcd for $C_{34}H_{34}N_4O_4$: C, 72.58, H, 6.09, N, 9.96. Found: C, 72.49, H, 6.00, N, 9.89.

(6a*R*,6'a*R*,9*R*,9'*R*)-Diethyl-7,7'-dimethyl-4,4',6,6a,6',6a',7,7',8,8',9,9'-dodecahydro-9,9'-biindolo[4,3-*fg*]quinoline-9,9'-dicarboxylate (**6b**) and

(6a*R*,6'a*R*,9*R*,9'*S*)-diethyl-7,7'-dimethyl-4,4',6,6a,6',6a',7,7',8,8',9,9'-dodecahydro-9,9'-biindolo[4,3-*fg*]quinoline-9,9'-dicarboxylate (**7b**): Ester **1c** (1.0 g, 3.37 mmol) was dissolved in dry EtOH under nitrogen atmosphere and the soluton was stirred for 4 days at 50 °C. After evaporation of the solvent, the residue was purified by chromatography (eluent: $CHCl_3$ + acetone, 20/1; R_f of **6b**+**7b** > **1c** but differences could not be observed between **6b** and **7b** in this solvent mixture). The isomer mixture (514 mg, 52%; ratio of **6b**:**7b** = 68/32%, determined by NMR integrals) was separated with a second chromatography

(eluent: hexane + AcOEt + MeOH, 6/4/0.5; R_f of **7b** > **6b**).

Dimer **6b** (227 mg, 23%), R_f 0.41 (hexane + AcOEt + MeOH, 5/5/1); mp 172-190 °C (pale brown crystals, from cyclohexane, 5 mL); $[\alpha]_D$ +59.8° (c 0.167, $CHCl_3$). IR ν_{max} (KBr): 3382, 1727, 1706, 1447, 1377, 1231 cm^{-1}. HRMS (FAB-MS; matrix: glycerol): calcd for $[M+H]^+$: 591.2971, found 591.2986; comp.: M=590; $C_{36}H_{38}N_4O_4$. ^1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz): δ 1.24 (t, *J* = 7.1 Hz, 2 x 3 H, CH_3), 2.50 (s, 2 x 3H, NCH_3), 2.62 (m, *J* = 14.6, 11.3, 1.7 Hz, 2 x 1 H, H-4$_\alpha$), 2.81 (d, *J* = 11.4 Hz, 2 x 1 H, H-7$_\beta$), 3.09 (m, *J* = 11.3, 5.7, 1.9 Hz, 2 x 1 H, H-5), 3.44 (dd, *J* = 14.6, 5.7, 2 x 1 H, H-4$_\beta$), 3.46 (dd, *J* = 11.4, 1.2, 2 x 1 H, H-7$_\alpha$), 4.12 + 4.22 (m, *J* = 10.8, 7.1 Hz, 2 x 2 H, OCH_2), 6.82 (dd, *J* = 1.9, 1.2 Hz, 2 x 1 H, H-9), 6.88 (dd, *J* = 1.7, 1.8 Hz, 2 x 1 H, H-2), 7.17 (dd, *J* = 6.9, 7.2 Hz, 2 x 1 H, H-13), 7.21 (dd, *J* = 6.9, 1.2 Hz, 2 x 1 H, H-12), 7.24 (dd, *J* = 7.2, 1.2 Hz, 2 x 1 H,H-14), 7.82 (d, *J* = 1.8 Hz, 2 x 1 H,NH) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 100 MHz): δ 14.5 (2 x CH_3), 27.4 (2 x C-4), 43.9 (2 x NCH_3), 52.7 (2 x C-8), 57.5 (2 x C-7), 61.2 (2 x OCH_2), 63.5 (2 x C-5), 109.8 (2 x C-3), 110.4 (2 x C-12), 111.9 (2 x C-14), 119.3 (2 x C-2), 120.1 (2 x C-9), 122.8 (2 x C-13), 126.7 (2 x C-16), 128.0(2 x C-11), 134.4 (2 x C-15), 136.5 (2 x C-10), 172.6 (2 x CO_2) ppm. Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20, H, 6.48, N, 9.48. Found: C, 73.36, H, 6.51, N, 9.35.

Dimer **7b**: (148 mg, 15%), R_f 0.49 (hexane + AcOEt + MeOH, 5/5/1 mL); mp 143-146 °C (decomp., pale brown crystals; from cyclohexane + Et_2O); $[\alpha]_D$ +134.5° (c 0.22, $CHCl_3$). IR ν_{max} (KBr): 3411, 2978, 2849, 1724, 1656, 1604, 1448, 1226 cm^{-1}. HRMS (FAB-MS; matrix: glycerol): calcd for $[M+H]^+$: 591.2971, found 591.2978; comp.: M=590; $C_{36}H_{38}N_4O_4$. ^1H NMR ($CDCl_3$, 400 MHz) *part A*: δ 1.18 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.49 (s, 3 H, NCH_3), 2.74 (m, *J* = 14.4, 11.3, 1.6 Hz, 1 H, H-4$_\alpha$), 2.87 (d, *J* = 12.4 Hz, 1 H, H-7$_\beta$), 3.20 (m, *J* = 11.3, 5.4, 1.8 Hz, 1 H, H-5), 3.35 (dd, *J* = 14.4, 5.4 Hz, 1 H, H-4$_\beta$), 3.46 (dd, *J* = 12.4, 0.7 Hz, 1 H, H-7$_\alpha$), 4.05–4.35 (m, 2 H, OCH_2), 6.65 (dd, *J* = 1.8, 0.7 Hz, 1 H, H-9), 6.85 (dd, *J* = 1.6, 1.7 Hz, 1 H, H-2), 7.13–7.24 (m, 3 H, H-12, H-13, H-14), 7.89 (d, *J* = 1.7 Hz, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3 (CH_3), 25.7 (C-4), 42.9 (NCH_3), 53.7 (C-8), 55.0 (C-7), 61.5 (OCH_2), 62.0 (C-5), 110.2 (C-12), 111.6 (C-3), 112.6 (C-14), 118.6 (C-2), 119.7 (C-9), 123.4 (C-13), 126.8 (C-16), 129.1 (C-11), 134.1 (C-15), 138.2 (C-10), 172.6 (CO_2). ^1H NMR ($CDCl_3$, 400 MHz) *part B*: δ 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.44 (s, 3 H, NCH_3), 2.56 (m, *J* = 14.2, 11.3, 1.6 Hz, 1 H, H-4$_\alpha$), 2.83 (d, *J* = 11.3 Hz, 1 H, H-7$_\beta$), 2.98 (m, *J* = 11.3, 5.6, 1.9 Hz, 1 H, H-5), 3.37 (dd, *J* = 14.2, 5.6 Hz, 1 H, H-4$_\beta$), 3.59 (dd, *J* = 11.3, 1.1 Hz, 1 H, H-7$_\alpha$), 4.05-4.35 (m, 2H, OCH_2), 6.71 (dd, *J* = 1.6, 1.1 Hz, 1 H, H-9), 6.81 (dd, *J* = 1.6, 1.7 Hz, 1 H, H-2), 7.13-7.24 (m, 3 H, H-12, H-13, H-14), 7.93 (d, *J* = 1.7 Hz, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4 (CH_3), 27.3 (C-4), 43.8 (NCH_3), 53.4 (C-8), 58.9 (C-7), 61.0 (OCH_2), 63.5 (C-5), 109.7 (C-12), 111.5 (C-3), 112.7 (C-14), 118.4 (C-2), 121.8 (C-9), 123.4 (C-13), 126.7 (C-16), 128.9 (C-11), 134.2 (C-15), 135.9 (C-10), 173.0 (CO_2). Anal. Calcd for $C_{36}H_{38}N_4O_4$: C, 73.20, H, 6.48, N,

9.48. Found: C, 73.29, H, 6.53, N, 9.41.

2) X-ray analysis - X-ray single-crystal data collection was performed on a BRUKER-NONIUS KAPPACCD diffractometer, geared with graphite-monochromated Mo Kα radiation (λ=0.71073 Å) and provided of an APEXII area detector and an OXFORD CRYOSTREAM cryogenic device. Data collection: COLLECT.[24] Cell refinement and data reduction: EVALCCD.[25] Structure solution and refinement: SHELXTL.[26]

Table 2 Crystal data and structure refinement for **6a**.

Chemical formula: $C_{34}H_{34}N_4O_4$
Formula weight: 562.66
Temperature: 173(2) K
Goodness-of-fit on F^2: 1.108
Largest and mean shift/su: 0.000 and 0.000
Largest diff. peak and hole: 0.70 and –0.45 e $Å^{-3}$
Crystal system, space group: monoclinic, $P2_1$
Unit cell parameters:
a = 10.798(2) Å α = 90°
b = 24.899(5) Å β = 93.97(3)°
c = 11.878(2) Å γ = 90°
Cell volume: 3185.8(11) $Å^3$
Z: 4
Calculated density: 1.284 g/cm^3
Absorption coefficient μ: 0.087 mm^{-1}
F(000):1308
Crystal colour and size:
colourless, 0.20 × 0.15 × 0.05 mm^3
Reflections for cell refinement:
Crystal colour and size:
colourless, 0.20 × 0.15 × 0.05 mm^3
Reflections for cell refinement:
2059 (θ range 2.5 to 27.5°)

Data collection method: Nonius KappaCCD diffractometer
ϕ and ω scans
θ range for data collection: 5.2 to 25.0°
Index ranges: h –12 to 12, k 0 to 29, l 0 to 14
Completeness to θ = 25.0° 97.0 %
Reflections collected: 5579
Independent reflections: 5579 (R_{int} = 0.0000)
Reflections with $F^2>2\sigma$: 3846
Absorption correction:
semi-empirical from equivalents
Min. and max. transmission: 0.9827 and 0.9956
R indices (all data): R1 = 0.1329, wR2 = 0.1566
Structure solution: direct methods
Refinement method:
Full-matrix least-squares on F^2
Weighting parameters a, b: 0.0031, 6.6266
Data / restraints / parameters: 5579 / 1465 / 820
Final R indices [$F^2>2\sigma$]: R1=0.0802, wR2=0.1305
R indices (all data): R1 = 0.1329, wR2 = 0.1566

3) Computational details - Geometry optimizations for **1b** and radical **1b•** were carried out at the B3LYP/6-31G* level of density functional theory[20] using the Gaussian 03 package.[27] The same

computational method was used to compute the harmonic vibrational frequencies to estimate the zero-point energy (ZPE) and thermal contributions to the gas phase enthalpies of the reaction components. The thermal corrections were calculated for standard conditions (T = 298 K and p = 1.0 atm). The homolytic C-H bond dissociation contributions to the gas phase enthalpies of the reaction components. The thermal corrections were calculated for standard conditions (T = 298 K and p = 1.0 atm). The homolytic C-H bond dissociation energy of **1b** was calculated as D_{298} = H(**1b**$^{\bullet}$) + H(H$^{\bullet}$) – H(**1b**), where H refers to the enthalpy of a given species at 298 K.

4) Detection of superoxide radical anion - Rapid mixing (<1 ms) of ice-cold reactants was performed in a micro-volume stopped-flow UV/fluorescence detection system (SF-61 DX2) supported by the Kynet-Asist2 software (HiTech Scientific). For monitoring ethidium formation, the end-product of hydroethidine (Molecular Probes) oxidation, the red ethidium fluorescence (610 nm) was detected using a 535 nm excitation filter (Molecular Probes). The time-course of ethidium fluorescence intensity changes (%) was recorded logarithmically, comprising 1000 data point acquired automatically. Ice-cold reactants, reactant 1 (0.2 mM dihydroethidium in methanol) and reactant 2 (methanol) or reactant 3 (0.2 mM (+)-lysergic acid methyl ester in methanol), were loaded into the reservoirs thermostatted at 30.0±0.1 ^{o}C. After 3 min, aliquots (75 μl) of reactant 1 were mixed with equal amount of reactant 2 or 3. Baseline reaction (reactant 1 with reactant 2) was repeated 8 times, and the 8 data sets were averaged to get one trace for the baseline reaction. Measurements on the effect of (+)-lysergic acid methyl ester on ethidium formation (reactant 1 with reactant 3) were repeated 8 times, also. Transformation of the percentile fluorescence data into the percent change of fluorescence was performed with subtraction of the trace of the baseline reaction.

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17. Crystal data for **6a**: $C_{34}H_{34}N_4O_4$ x ½ H_2O x ½ $C_4H_8O_2$, *FW* = 615.71, monoclinic $P2_1$, a = 10.798(2) b = 24.899(5), c = 11.878(2) Å, β = 93.97(3)°, d_c = 1.284 g/cm^3, Reflections collected 5579 of which 3846 independent, 820 parameters, R1 = 0.0802, wR2 = 0.1305, R1 = 0.1329, wR2 = 0.1566

(all data), GOF = 1.108, largest diff. peak and hole 0.705 and -0.450 e Å^3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 608116. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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