75. The Synthesis of *N, N*-Dimethyl-2-(1-phenyl-2,5-cyclohexadien-1-yl)-ethylamine and of Mesembrine-Like Metabolites of this Potential Analgesic

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Dedicated to Prof. Dr. *A. Hürlimann* on the occasion of his 60th birthday

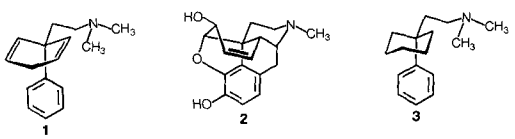
(7.1.83)

Summary

The synthesis of the analgesic compound *N, N*-dimethyl-2-(1-phenyl-2,5-cyclohexadien-1-yl)ethylamine (**1**) is described. Its structural relation to morphine and its pharmacological activity is shortly discussed. The isolation of three mesembrine-like metabolites of **1** from the plasma of rats is reported along with synthetic work permitting the determination of the relative configuration of these metabolites.

Introduction. – The main reasons for synthesizing *N, N*-dimethyl-2-(1-phenyl-2,5-cyclohexadien-1-yl)ethylamine (**1**) as a potential analgesic compound were: *a)* the structural similarity of the achiral compound **1** and morphine (**2**) (basic N-atom separated by three bonds from a phenyl-substituted quaternary C-atom in accordance with the classical minimum requirements for opiate-type analgesic activity [1]); *b)* the assumption that the conformational flexibility of **1** might lead to fast on- and off-rates in the reaction of drug and receptor and to a reduced physical dependence liability in comparison to morphine (**2**)[1]; *c)* the expectation that the morphine-like conformation depicted for **1** would be less disfavored by steric strain than the analogous conformation of the known weak analgesic compound **3** [3] *(Scheme 1)*[2], and *d)* the obviously good synthetic accessibility of **1** from cheap starting materials[3]).

Scheme 1



[1]) It was discussed for some time, whether the complexed receptor might undergo slow changes which would affect its affinity for opiates and influence the development of tolerance and physical dependence (*cf.* [2]).

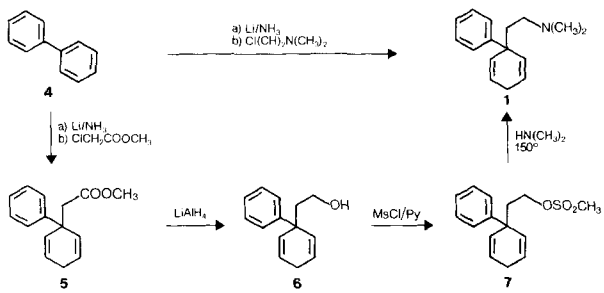
[2]) This expectation has recently been confirmed by a conformational study of 1-phenyl-substituted 2,5-cyclohexadienes [4].

[3]) *Cf.* the synthesis of 1-methyl-1-phenyl-2,5-cyclohexadiene [5].

Synthesis and pharmacological activity of 1. – It was possible to obtain **1** directly in 20–30% yield by treatment of biphenyl (**4**) with an excess of Li in liquid ammonia and subsequently with 2-chloro-*N*,*N*-dimethyl-ethylamine *(Scheme 2)* [6]. However, the four-step procedure **4** → **5** → **6** → **7** → **1** shown in *Scheme 2* turned out to be more advantageous; it is, therefore, described in the *Exper. Part* [6]. Methyl chloroacetate was used in excess in this procedure, as one equivalent of it is probably serving as the acid which is mono-protonating the dianion resulting from the reaction of biphenyl (**4**) with an excess of Li.

The maleic acid salt **1a** of the free amine **1** could easily be crystallized. This water-soluble salt was submitted to the biological tests. It displayed mild and probably central analgesic activity on test animals [7] *(Table)* and was essentially free of unwanted side-effects. The absence of physical dependence liability in monkeys is especially noteworthy [8].

Scheme 2



Table

Test[a])	**1a**[b]) ED_{50}[d]) mg/kg *p.o.*	**2** ED_{50}[d]) mg/kg *p.o.*	**3a**[c]) ED_{50}[d]) mg/kg *p.o.*
Acetic acid writhing test, mouse, 1 h [7] [9]	106	2	54
Hot plate test, mouse, 1 h [7] [10]	63	43	100
Phenylquinone writhing test, rat, 1 h [7] [11]	121	2	13
Dental pulp test, monkey, 1 h [7] [8]	29	6	–

a) Modified test procedures according to the references given in the *Table*. Compare the pharmacological literature with respect to standard errors *etc.*

b) Maleate of **1** (1:1).

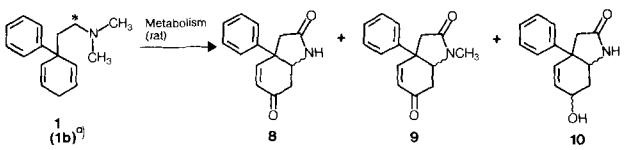
c) Hydrochloride of **3**.

d) Dose which is effective in 50% of the animals; oral administration.

Metabolic studies. – The ^{14}C-labelled maleic acid salt **1b** was used for the metabolic studies [12]. It had been obtained from biphenyl (**4**) and methyl bromo[1-^{14}C]acetate in analogy to the reaction sequence described in *Scheme 2* [13]. Plasma and urine of male *Füllinsdorf*-albino rats to which **1b** had been

administered intravenously and orally, respectively, was collected, adjusted to pH 9, extracted with CH_2Cl_2, and separated by TLC. Unchanged **1** (**1b**) was found, along with a complex mixture of metabolites in the urine, and along with the three main metabolites **8**–**10** *(Scheme 3)* in the plasma. These three metabolites were also present in the urine. They were examined by *Fourier*-transform ^{1}H-NMR. and by GC./MS. of the trimethylsilylated derivatives, and the constitutions depicted in *Scheme 3* could be assigned to them.

Scheme 3



1 (1b)[a] 8 9 10

[a]) Maleic acid salt (1:1), ^{14}C-labelled at the position indicated by the asterisk

The extraction of the urine of a male Swiss beagle dog to which **1b** had been orally administered led again to the observation of a rather complex mixture of metabolites, which differed significantly from the mixture extracted from the rat urine, and pharmacokinetic studies in volunteers showed a rather high, though variable bioavailability of unchanged **1** in humans [14].

Relative configuration and synthesis of 8–10. – The remaining open questions concerning the configuration of the plasma metabolites **8**–**10** (their metabolic formation involves several unknown steps), their pharmacological activity, and their structural relation with mesembrine and related alkaloids were the motives for the synthetic work[4]).

The ketone **8** was our first synthetic target. The ester **5** was, therefore, converted to the acid **11**, and *via* the acyl chloride to the amide **12**, in the hope that **12** might be oxidized and cyclized to **8** *(Scheme 4)*. Analogously, **9** was expected to be accessible *via* the *N*-methylated amide **13**. As the initial oxidation experiments failed, we decided to synthesize the iodolactone **14**, hoping that it might be converted to **8** in a series of classical reactions. This sequence was unsuccessful, but the ^{1}H-NMR. spectra of **14**, its dehydrohalogenation product **15**, and the bromination product **16** of the latter turned out to be valuable for the unambiguous assignment of the relative configuration of the metabolites **8**–**10**.

We finally found that an excess of MnO_2 in CH_2Cl_2 converted **12** smoothly to **17**. The diene **15** was a by-product of this reaction. Heating of **17** in the presence of 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) led quantitatively to **8a** which was in complete agreement with the isolated metabolite **8** with respect to the measured scalar physical properties. The amide **13** was converted to **18** and **9a** analogously, the latter being again in good agreement with the isolated metabolite **9**. Reduction of **8a** with $NaBH_4$ yielded the two alcohols **10a** and **19** in a ratio of *ca.* 1:10; the minor product **10a** corresponded to the isolated metabolite **10**.

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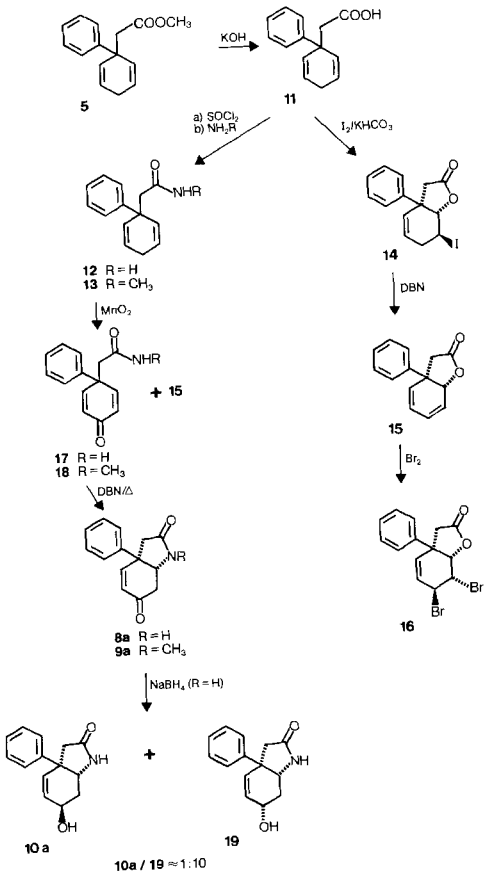
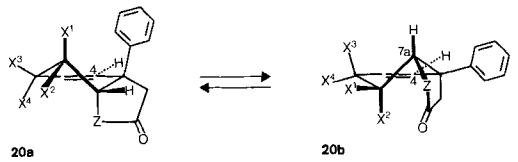
[4]) It turned out that the synthesized (racemic) metabolites are practically devoid of analgesic activity in the test animals [7].

Scheme 4



It can reasonably be expected that the cyclization reactions **17** → **8a**, **18** → **9a** and **11** → **14** are leading to *cis*-fused rings, and it is, furthermore, not unexpected that the *endo*-hydroxy compound **19** is formed as the main product of the borohydride reduction of **8a**. These expectations are confirmed by comparison of the ^{1}H-NMR. data of **8a**, **9a**, **10a**, **14**, **16** and **19**. Two conformations (**20a** and **20b**) can be drawn for the *cis*-fused ring system **20**, whereas only one conformation can be drawn for the *trans*-fused **21** *(Scheme 5)*. The crucial difference between the ring systems **20** and **21** is that only *cis*-fusion allows a conformation (**20a**) in which H–C(4) and H–C(7a) are arranged almost ideally for a W-type long-range coupling. No such coupling is observed in the ^{1}H-NMR. spectrum of the iodolactone **14**. This compound must exist preferentially in the conformation **20b** which avoids the unfavorable steric repulsion between the axial substituent X^1 (= I) and the pseudo-axial phenyl ring present in **20a**. The expected long-range coupling between H–C(4) and H–C(7a) is, however, visible in the ^{1}H-NMR.-spectrum of the dibromo compound **16**, derived from **14** in a sequence of reactions which is hardly

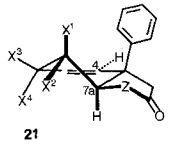
Scheme 5



20a **20b**

($X^1 = X^2 = H$, $X^3, X^4 = =O$, $Z = NH$: **8a**; $X^1 = X^2 = H$, $X^3, X^4 = =O$, $Z = NCH_3$: **9a**; $X^1 = X^2 = X^4 = H$, $X^3 = OH$, $Z = NH$: **10a**; $X^1 = X^4 = H$, $X^2 = X^3 = Br$, $Z = O$: **16**; $X^1 = X^2 = X^3 = H$, $X^4 = OH$, $Z = NH$: **19**)

($X^1 = I$, $X^2 = X^3 = X^4 = H$, $Z = O$: **14**)



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expected to lead to inversion at C(7a). The long-range coupling between H–C(4) and H–C(7a) is also visible in the ^{1}H-NMR. spectra of **8a**, **9a**, **10a** and **19** which, therefore, are *cis*-fused and assume preferentially the conformation **20a**. Further details of the ^{1}H-NMR. data can be found in the *Exper. Part.* They allow the differentiation of the *endo*- and *exo*-hydroxy compounds **19** and **10a** and fully support the proposed structure assignments.

Experimental Part

General remarks. Melting points (m.p.) were determined on a *Büchi-SMP-20* apparatus and are not corrected. *Kieselgel F_{254} (Merck)* plates were used for thin layer chromatography (TLC.). – IR. spectra (in cm^{-1}): *Beckman IR 9* or *Nicolet FTIR-system 7199; s* = strong, *m* = medium, *w* = weak. – ^{1}H-NMR. spectra: *Varian A-60D* and *EM-360* (60 MHz), *Bruker-Spectrospin WP 80 CW* (80 MHz), *HX-90/15* (90 MHz), *HX-270* (270 MHz) and *WM-400* (400 MHz). Chemical shifts in ppm relative to TMS (= 0 ppm), coupling constants *J* in Hz; the chemical shifts of *AB*- and *XY*-systems, resp., are calculated (first-order), the shift of doublets (*d*) and triplets (*t*) refers to the centre of the respective multiplets (*m*); br. = broad; the *XX'YY'*-part of the *ABXX'YY'*-systems of the 2,5-cyclohexadiene moiety of **1a**, **6**, 7, and **13** has the appearance of the *XY*-part of an *ABXY*-system and is interpreted accordingly. – Mass spectra (MS.; in *m/z*, intensities in parenthesis): *MS 9* (*AEI*, Manchester). – Correct elemental analysis (C,H,N,S, halogen) were obtained for all crystalline substances described. Spectra and analysis were measured and carried out by our Central Research Department. RT. = room temperature.

Preparation of methyl 2-(1-phenyl-2,5-cyclohexadien-1-yl)acetate (**5**). Biphenyl (**4**; 15.4 g, 0.1 mol) was dissolved in 300 ml of dry ether and added to 600 ml of dry NH_3 at $-33°$. After cooling to $-70°$, Li-wire (1.67 g, 0.24 mol) was added in portions. The mixture was stirred for 1 h at $-33°$. It was cooled again to $-70°$, and freshly distilled methyl chloroacetate (26.0 g, 0.24 mol) in 100 ml of dry ether was added within 5 min. The color of the mixture changed from dark red to yellow. NH_4Cl (13.0 g, 0.24 mol) was added and NH_3 distilled. The remaining ether layer was washed with water, aq. HCl-, and aq. Na_2CO_3-solutions, dried, evaporated, and chromatographed with ether/hexane 1:5 on 800 g of silica gel giving **5** (14.8 g, 65%) as oily product. – IR. (neat): 1745*s*, 1635*w*, 1597*w*, 1581*w*, 1491*m*, 1237*s*, 1159*s*, 765*m*, 734*m*, 697*s*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.62 (*s*-like *m*, 2 H, 2 H–C(4)); 2.83

(*s*, 2 H, CH_2CO); 3.52 (*s*, 3 H, CH_3O); 6.81 (*s*-like *m*, 4 H, 4 olef. H); 6.90–7.60 (*m*, 5 H, 5 arom. H). – MS.: 228 (1, M^+), 185 (1), 167 (6), 155 (100), 154 (51), 115 (6), 91 (15), 77 (13).

Preparation of 2-(1-phenyl-2,5-cyclohexadien-1-yl)ethanol (**6**). The ester **5** (68.5 g, 0.3 mol) was dissolved in 250 ml of ether and added to a stirred suspension of $LiAlH_4$ (11.4 g, 0.3 mol) in 1150 ml of ether. After 1 h, 50 ml of EtOH were added followed by 50 ml of water. The mixture was filtered, the precipitate washed with ether, and the org. layers were combined, dried, and evaporated. The resulting crude alcohol (60 g) was recrystallized from benzene/hexane, and colorless **6** (52.6 g, 88%) was obtained, m.p. 58–59°. – IR. (KBr): 3374*s*, 3290*m*, 1631*w*, 1596*w*, 1492*m*, 1026*s*, 763*m*, 745*s*, 698*s*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 1.98 (br. *s*, 1 H, HO); 2.14 (*t*, J=7, 2 H, CH_2CH_2OH); 2.60–2.90 (*m*, 2 H, 2 H–C(4)); 3.75 (*t*, J=7, 2 H, CH_2CH_2OH); 5.70 (X-part of $ABXY$-systems, $J_{AX}\approx J_{BX}\approx 2$, J_{XY}= 12, slightly br., 2 H, 2 olef. H); 5.85 (Y-part of $ABXY$-systems, $J_{AY}\approx J_{BY}\approx 3$, J_{XY}= 12, 2 H, 2 olef. H); 7.05–7.50 (*m*, 5 H, 5 arom. H). – MS.: 200 (0.5, M^+), 155 (100), 154 (17), 153 (7), 152 (6), 128 (5), 115 (6), 91 (10), 77 (19), 51 (8), 39 (5).

Preparation of 2-(1-phenyl-2,5-cyclohexadien-1-yl)ethyl methanesulfonate (**7**). Methanesulfonyl chloride (18.6 g, 0.16 mol) was added at 0–5° to a solution of **6** (27 g, 0.135 mol) in 270 ml of pyridine. The mixture was stirred for 3 h at RT. Upon the addition of 250 ml of water, the product precipitated. Filtration, washing with water, and recrystallization from benzene/hexane led to colorless **7** (26.2 g, 70%), m.p. 65–67°. – IR. (KBr): 1631*w*, 1597*w*, 1494*m*, 1351*s*, 1175*s*, 772*m*, 761*m*, 745*m*, 721*m*, 694*m*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.32 (*t*, J=8, 2 H, CH_2CH_2OS); 2.55–2.85 (*m*, 2 H, 2 H–C(4)); 2.95 (*s*, 3 H, CH_3S); 4.32 (*t*, J=8, 2 H, CH_2CH_2OS); 5.65 (X-part of $ABXY$-systems, $J_{AX}\approx J_{BX}\approx 1.5$, J_{XY}= 11, 2 H, 2 olef. H); 5.94 (Y-part of $ABXY$-systems, $J_{AY}\approx J_{BY}\approx 3$, J_{XY}= 11, 2 H, 2 olef. H); 7.00–7.50 (*m*, 5 H, 5 arom. H). – MS.: 182 (5, $M^+ - CH_3SO_3H$), 167 (7), 155 (100), 154 (38), 153 (5), 115 (5), 105 (6), 91 (9), 81 (10), 77 (15), 69 (22).

Preparation of N,N*-dimethyl-2-(1-phenyl-2,5-cyclohexadien-1-yl)ethylammonium maleate* (**1a**). Condensed dimethylamine (140 ml, *ca.* 2.3 mol) was added to a solution of **7** (200 g, 0.72 mol) in 1300 ml of toluene, and the mixture was heated under pressure (*ca.* 40 atm) to 150° for 16 h. After cooling, the excess dimethylamine was distilled, and the toluene solution was washed with water and evaporated. The residue was dissolved in ether and extracted into dil. aq. HCl-solution. The acidic aq. phase was treated with an excess of 28% NaOH-solution and extracted with ether. The resulting ether layer was washed with water, dried, and evaporated to give the amine **1** as an oil (151 g, 97.8% pure according to GC.). It was dissolved in 200 ml of EtOH and added to maleic acid (72 g, 0.62 mol) in 300 ml of EtOH. The resulting solution was boiled shortly with active carbon, filtered, and evaporated. Recrystallization of the residue from EtOH/ether yielded **1a** (196 g, 79.5%), m.p. 129°. – IR. (KBr): 2652*m*, 2440*m*, 1719*m*, 1620*s*, 1546*s*, 1502*s*, 1388*s*, 772*m*, 736*m*, 708*m*, 695*m*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.05–2.40 (*m*, 2 H, CH_2CH_2N); 2.60–2.80 (*m*, 2 H, 2 H–C(4)); 2.82 (*s*, 6 H, $(CH_3)_2N$); 2.90–3.25 (*m*, 2 H, CH_2CH_2N); 5.59 (X-part of $ABXY$-systems, $J_{AX}\approx J_{BX}\approx 2$, J_{XY}= 10.5, slightly br., 2 H, 2 olef. H); 5.95 (Y-part of $ABXY$-systems, $J_{AY}\approx J_{BY}\approx 3$, J_{XY}= 10.5, slightly br., 2 H, 2 olef. H); 6.25 (*s*, 2 H, 2 olef. H of maleate); 7.05–7.45 (*m* with *s*-like signal at 7.30, 5 H, 5 arom. H); *ca.* 15 (br., 2 H, COOH, HN^+). – MS.: 227 (14, M^+), 156 (12), 155 (34), 154 (14), 77 (18), 72 (42), 71 (39), 58 (100).

Preparation of 2-(1-phenyl-2,5-cyclohexadien-1-yl)acetic acid (**11**). The ester **5** (2.38 g, 0.01 mol) was heated for 1 h at 80° in a solution of KOH (2.4 g, 0.043 mol) in ethylene glycol. After cooling, addition of water and ether, and extraction, the aq. layer was acidified and again extracted with ether. Drying and evaporation of the latter ethereal layer gave **11** which solidified upon standing. Recrystallization from ether/hexane afforded pure **11** (1.7 g, 80%), m.p. 92°. – IR. (KBr): 3090*s*, 3050*s*, 2682*w*, 2640*w*, 1713*s*, 1646*m*, 1491*w*, 1236*s*, 761*m*, 738*m*, 706*s*. – ^{1}H-NMR. (60 MHz, $(CD_3)_2SO$): 2.55–2.70 (*m*, 2 H, 2 H–C(4)); 2.80 (*s*, 2 H, CH_2CO); 5.60–6.10 (*m* with strong *s*-like signal at 5.87, 4 H, 4 olef. H); 7.10–7.50 (*m*, 5 H, 5 arom. H); 12.0 (br. *s*, 1 H, COOH). – MS.: 214 (3, M^+), 169 (4), 167 (5), 165 (3), 155 (100), 154 (53), 115 (7), 91 (20), 77 (16), 51 (6).

Preparation of 2-(1-phenyl-2,5-cyclohexadien-1-yl)acetamide (**12**). The acid **11** (10.7 g, 0.05 mol) was heated to reflux for 2 h in a mixture of thionyl chloride (13.75 ml) and $CHCl_3$ (125 ml). The mixture was concentrated and fully evaporated after the addition of toluene. The resulting acyl chloride was dissolved in ether and added to 300 ml of condensed NH_3 at −70°. The cooling-bath was removed, the mixture allowed to warm-up, and NH_3 slowly distilled. Aqueous workup led to solid **12.** Recrystallization from ether/hexane yielded pure **12** (7.67 g, 72%), m.p. 105°. – IR. (KBr): 3464*s*, 3137*m*, 1681*s*, 1656*s*, 1608*m*, 1595*m*, 1488*m*, 757*m*, 739*m*, 699*m*. – ^{1}H-NMR. (60 MHz, $CDCl_3$): 2.60–

2.80 (*m*, 2 H, 2 H–C(4)); 2.81 (*s*, 2 H, CH_2CO); 5.40–6.20 (*m* with strong *s*-like signal at 5.90, 6 H, H_2N and 4 olef. H); 7.05–7.45 (*m*, 5 H, 5 arom. H). – MS.: 213 (1, M^+), 212 (3), 167 (8), 155 (100), 154 (38), 91 (25), 77 (25), 59 (90).

Preparation of N-*methyl-2-(1-phenyl-2,5-cyclohexadien-1-yl)acetamide* (**13**). Substitution of NH_3 by methylamine in the procedure described above and chromatography of the product with CH_2Cl_2/MeOH 10:1 on silica gel led to 42% of crude **13** (0.9 g from 2 g of **11**) which was recrystallized from CH_2Cl_2/ether, m.p. 130–132°. – IR. (KBr): 3342*s*, 1640*s*, 1600*m*, 1556*s*, 1493*m*, 768*m*, 722*m*, 697*m*. – ^{1}H-NMR. (80 MHz, $(CD_3)_2SO$): 2.48 (*d*, $J=5$, 3 H, CH_3N); *ca.* 2.50–2.70 (*m*, 2 H, 2 H–C(4)); 2.67 (*s*, 2 H, CH_2CO); 5.79 (*X*-part of *ABXY*-systems, $J_{AX}\approx J_{BX}\approx 2.5$, slightly br., $J_{XY}=10.5$, 2 H, 2 olef. H); 5.92 (*Y*-part of *ABXY*-systems, J_{AY} and J_{BY} leading only to br. signals, $J_{XY}=10.5$, 2 H, 2 olef. H); 7.05–7.45 (*m*, 5 H, 5 arom. H); 7.45–7.75 (*m*, 1 H, HN). – MS.: 227 (4, M^+), 226 (12), 167 (10), 155 (80), 154 (19), 153 (17), 152 (13), 115 (9), 91 (17), 77 (20), 73 (100).

Preparation of 2-(4-oxo-1-phenyl-2,5-cyclohexadien-1-yl)acetamide (**17**). MnO_2 (1.74 g, 20 mmol) was added to a solution of **12** (426 mg, 2 mmol) in 30 ml of CH_2Cl_2. Stirring for 24 h at r.t. under exclusion of light, filtration, evaporation, and chromatography with CH_2Cl_2/MeOH 10:1 on 20 g of silica gel yielded crystalline **17** (196 mg, 43%; TLC.: Rf 0.35, CH_2Cl_2/MeOH 10:1), dienelactone **15**[5]) (103 mg, 22%; TLC.: Rf 0.75), and slightly impure **12** (122 mg, 28%; TLC.: Rf 0.45).

Data of **17**. M.p. 140–142°. – IR. (KBr): 3410*m*, 3320*m*, 3219*m*, 1685*s*, 1652*s*, 1615*s*, 1597*s*, 1493*m*, 863*s*, 735*m*, 698*s*. – ^{1}H-NMR. (80 MHz, $(CD_3)_3SO$): 2.95 (*s*, 2 H, CH_2CO); 6.26 (*AA'*-part of *AA'BB'*-system, $J_{AB}=10.5$, 2 H, 2 olef. H); 6.90 (br., 1 H, H–N); 7.35 (*BB'*-part of *AA'BB'*-system, $J_{AB}=10.5$, 2 H, 2 olef. H); 7.35–7.60 (*m*, 6 H, 5 arom. H and HN). – MS.: 227 (70, M^+), 210 (19), 185 (28), 184 (30), 183 (31), 182 (30), 170 (43), 169 (36), 157 (36), 156 (52), 155 (100), 154 (56), 153 (38), 141 (70), 128 (64), 115 (67), 77 (38), 70 (43).

Preparation of N-*methyl-2-(4-oxo-1-phenyl-2,5-cyclohexadien-1-yl)1-acetamide* (**18**). Treatment of **13** (1.1 g, 4.85 mmol) with MnO_2 (3.8 g, 44 mmol) as described above led to solid **18** (300 mg, 26%; TLC.: Rf 0.35, CH_2Cl_2/MeOH 10:1), which was recrystallized from CH_2Cl_2/ether. No pure **15** was isolated in this experiment.

Data of **18**. M.p. 140–140.5°. – IR. (KBr): 3292*s*, 1661*s*, 1636*s*, 1596*m*, 1565*m*, 1493*m*, 854*m*, 750*m*, 698*m*. – ^{1}H-NMR. (80 MHz, $(CD_3)_2SO$): 2.48 (*d*, $J=5$, 3 H, CH_3N); 2.95 (*s*, 2 H, CH_2CO); 6.22 (*AA'*-part of *AA'BB'*-system, $J_{AB}=10.5$, 2 H, 2 olef. H); 7.33 (*BB'*-part of *AA'BB'*-system, $J_{AB}=10.5$, 2 H, 2 olef. H); 7.30–7.50 (*m*, 5 H, 5 arom. H); 7.68–8.00 (br., 1 H, HN). – MS.: 241 (100, M^+), 184 (15), 183 (23), 170 (22), 169 (30), 156 (22), 155 (35), 141 (38), 128 (26), 115 (30), 84 (31), 77 (17).

*Preparation of (3a*RS,*7a*SR*)-3a-phenyl-6,7-dihydro-2,6(3a*H*)-indolinedione* (**8a**). Heating of **17** (500 mg, 2.2 mmol) to reflux in 50 ml of toluene in the presence of 1,5-diazabicyclo[4.3.0]-5-nonene (0.13 ml, 1.1 mmol), evaporation, and chromatography with CH_2Cl_2/MeOH 10:1 on 20 g of silica gel led to **8a** (480 mg, 96%; TLC.: Rf 0.37, CH_2Cl_2/MeOH 10:1), which crystallized upon concentration of the eluted solution. The product was recrystallized from CH_2Cl_2/ether, m.p. 202°. – IR. (KBr): 3200*m*, 3092*m*, 1685*s*, 1496*m*, 790*m*, 760*m*, 725*m*. – ^{1}H-NMR. (80 MHz, $CDCl_3$): 2.60 (*A*-part of *AB*-system, slightly br., $J_{AB}=17$, 1 H, H–C(3)); 2.65 (*d*, $J=3.5$, slightly br. because of coupling with $J<1$ to H–C(5), 2 H, H_{exo}–C(7), H_{endo}–C(7)); 3.28 (*B*-part of *AB*-system, slightly br., $J_{AB}=17$, 1 H, H–C(3)); 4.36 ($t\times d$, $J_{7a,7exo}=J_{7a,7endo}=3.5$, $J_{7a,4}\approx 1.5$, slightly br. because of additional coupling i.a. with HN, 1 H, H–C(7a)); 6.33 (*d*, $J_{5,4}=10.5$, slightly br. because of coupling with $J<1$ to H–C(7), 1 H, H–C(5)); 6.80 (*d*, $J_{4,5}=10.5$, with coupling to H–C(7a), $J\approx 1.5$, and additional coupling with $J<1$, 1 H, H–C(4)); 6.91 (br., 1 H, HN); 7.25–7.65 (*m*, 5 H, 5 arom. H). – MS.: 227 (73, M^+), 185 (78), 184 (49), 157 (83), 156 (85), 129 (29), 128 (75), 115 (20), 77 (23), 70 (100).

*Preparation of (3a*RS,*7a*SR*)-1-methyl-3a-phenyl-6,7-dihydro-2,6(3a*H*)-indolinedione* (**9a**). The cyclization of **18** (2 g, 8.3 mmol) was achieved in full analogy to the cyclization of **17**. Recrystallization from CH_2Cl_2/ether/hexane yielded pure **9a** (1.3 g, 65%), m.p. 129–130°. – IR. (KBr): 1682*s*, 1622*m*, 1601*w*, 1495*m*, 794*m*, 768*m*, 703*m*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 2.68 (*A*-part of *AB*-system, slightly br., $J_{AB}=17$, 1 H, H–C(3)); 2.73 (*d*, slightly br., $J=4$, 2 H, H_{exo}–C(7), H_{endo}–C(7)); 2.83 (*s*, 3 H, CH_3N); 3.22 (*B*-part of *AB*-system, slightly br., $J_{AB}=17$, 1 H, H–C(3)); 4.11 ($t\times d$, $J_{7a,7exo}=J_{7a,7endo}=4$, $J_{7a,4}=1.7$, 1 H, H–C(7a)); 6.23 (*d*, slightly br., $J_{5,4}=10$, 1 H, H–C(5)); 6.74 ($d\times d$, $J_{4,5}=10$, $J_{4,7a}=1.7$,

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[5]) Dienelactone **15** was obtained as the main product (60%) by analogous treatment of the acid **11** with MnO_2.

1 H, H–C(4)); 7.25–7.50 (*m*, 5 H, 5 arom. H). – MS.: 241 (100, M^+), 213 (13), 212 (11), 189 (31), 184 (21), 170 (18), 157 (45), 156 (33), 141 (18), 129 (19), 128 (44), 127 (15), 115 (17), 84 (85), 42 (41).

*Preparation of (3a*RS,*6*SR,*7a*SR*)-6-hydroxy-3a-phenyl-3a,6,7,7a-tetrahydro-2-indolinone* (**10a**) *and (3a*RS,*6*RS,*7a*SR*)-6-hydroxy-3a-phenyl-3a,6,7,7a-tetrahydro-2-indolinone* (**19**). $NaBH_4$ (0.5 g, 13.2 mmol) was added to a solution of **8a** (2 g, 8.8 mmol) in 350 ml of MeOH at 0°. After 2 h at r.t., water was added, and the mixture was evaporated. The residue was dissolved in CH_2Cl_2, washed with water, dried, evaporated and chromatographed with CH_2Cl_2/MeOH 10:1 on 100 g of silica gel. Practically pure **19** (0.8 g) and a mixture **10a**/**19** (0.7 g) were obtained. Pure **10a** (130 mg, 3.2%, from two combined analogous experiments; TLC.: Rf 0.35, CH_2Cl_2/MeOH 10:1) could be obtained from the mixture by fractional crystallization from CH_2Cl_2, and pure **19** (1.4 g, 35%, from two combined analogous experiments; TLC.: Rf 0.40) crystallized from an ether solution of the combined practically pure fraction from the chromatography and the mother liquour which was obtained after the crystallization of **10a**.

Data of **10a**. M.p. 168–170°. – IR. (KBr): 3273*m*, 1677*s*, 1598*w*, 1496*w*, 1063*m*, 1047*m*, 754*m*, 699*m*. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 1.555 (*d*, J = 6.5, 1 H, HO); 1.715 ($d\times d\times d$, $J_{7exo,7endo}$ = 14, $J_{7exo,6endo}$ = 9, $J_{7exo,7a}$ = 3, 1 H, H_{exo}–C(7)); 2.17 ($d\times t\times d$, $J_{7endo,7exo}$ = 14, $J_{7endo,6endo}$ = $J_{7endo,7a}$ = 5, $J_{7endo,5}$ = 1, 1 H, H_{endo}–C(7)); 2.51 (*A*-part of *AB*-system, J = 17, 1 H, H–C(3)); 3.085 (*B*-part of *AB*-system, J = 17, 1 H, H–C(3)); 4.075 ($d\times d\times d$, $J_{7a,7endo}$ = 5, $J_{7a,7exo}$ = 3, $J_{7a,4}$ = 1.3, 1 H, H–C(7a)); 4.45 ($d\times d\times d\times d\times d$, $J_{6endo,7exo}$ = 9, $J_{6endo,OH}$ = 6.5, $J_{6endo,7endo}$ = 5, $J_{6endo,5}$ = 2.5, $J_{6endo,4}$ = 1.3, 1 H, H_{endo}–C(6)); 5.50 (br., 1 H, HN); 5.70 ($d\times t$, $J_{4,5}$ = 10, $J_{4,6endo}$ = $J_{4,7a}$ = 1.3, 1 H, H–C(4)); 6.04 ($d\times d\times d$, $J_{5,4}$ = 10, $J_{5,6endo}$ = 2.5, $J_{5,7endo}$ = 1, 1 H, H–C(5)); 7.27–7.45 (*m*, 5 H, 5 arom. H); the assigned couplings were confirmed by irradiation at 1.555, 2.17, 4.075, 4.45, 5.50, 5.70, and 6.04 ppm. – MS.: 229 (1.5, M^+), 227 (1), 211 (13), 187 (9), 186 (10), 185 (11), 172 (22), 170 (22), 159 (100), 158 (26), 157 (12), 142 (13), 141 (11), 130 (18), 129 (15), 128 (16), 115 (20), 91 (16), 77 (13).

Data of **19**. M.p. 138–140°. – IR. (KBr): 3373*s*, 3195*m*, 1686*s*, 1598*w*, 1495*m*, 765*m*, 741*m*, 725*m*, 697*s*. – ^{1}H-NMR. (90 MHz, $CDCl_3$): 1.88 (*A*-part of *AB*-system with additional coupling, J_{AB} = $J_{7exo,7endo}$ = 15, $J_{7exo,7a}$ = 4, $J_{7exo,6exo}$ = 3.5, 1 H, H_{exo}–C(7)); 2.08 (*B*-part of *AB*-system with additional coupling, J_{AB} = $J_{7endo,7exo}$ = 15, $J_{7endo,7a}$ = $J_{7endo,6exo}$ = 4, $J_{7endo,5}$ < 1, 1 H, H_{endo}–C(7)); 2.53 (*A*-part of *AB*-system, J_{AB} = 17, 1 H, H–C(3)); 3.11 (*B*-part of *AB*-system, J_{AB} = 17, 1 H, H–C(3)); 3.48 (*d*, J = 7, slightly br., 1 H, HO); 3.99 (*t*, $J_{7a,7exo}$ = $J_{7a,7endo}$ = 4, br. because of coupling with $J\approx 1$ to H–C(4), 1 H, H–C(7a)); 4.26 ($d\times t\times d\times d$, not fully resolved, $J_{6exo,OH}$ = 7, $J_{6exo,5}$ = $J_{6exo,7endo}$ = 4, $J_{6exo,7exo}$ = 3.5, $J_{6exo,4}\approx 1$, 1 H, H_{exo}–C(6)); 5.76 ($d\times t$-like, $J_{4,5}$ = 10, $J_{4,6exo}\approx J_{4,7a}\approx 1$, 1 H, H–C(4)); 6.17 ($d\times d$, $J_{5,4}$ = 10, $J_{5,6exo}$ = 4, slightly br. because of small coupling to H_{endo}–C(7), 1 H, H–C(5)); 7.10–7.50 (*m*, 6 H, HN and 5 arom. H). – MS.: 229 (10, M^+), 211 (4), 186 (13), 185 (24), 172 (27), 159 (100), 158 (38), 157 (15), 142 (18), 130 (16), 129 (17), 128 (16), 115 (19), 91 (15), 77 (11), 43 (18).

*Preparation of (3a*RS,*7*RS,*7a*RS*)-7-iodo-3a-phenyl-3a,6,7,7a-tetrahydro-2(3*H*)-benzo[b]furanone* (**14**). The acid **11** (3.21 g, 15 mmol) was dissolved in 90 ml of aq. 0.5N $NaHCO_3$. A solution of I_2 (7.62 g, 30 mmol) and KI (15.24 g, 92 mmol) in 45 ml of water was added, and the mixture was allowed to stand for 24 h. A dark precipitate formed. The solution was decanted, and the precipitate was dissolved in $CHCl_3$, washed with water, Na_2SO_3- and $NaHCO_3$-solution, and again with water, dried, filtered, and evaporated. Solid **14** (3.67 g, 72%) was obtained and recrystallized from CH_2Cl_2/ether/hexane, m.p. 140–142°. – IR. (KBr): 1766*s*, 1654*w*, 1595*w*, 1496*m*, 1176*s*, 759*m*, 700*s*. – ^{1}H-NMR. (270 MHz, $CDCl_3$): 2.78(*A*-part of *AB*-system with additional coupling, J_{AB} = $J_{6exo,6endo}$ = 18.5, $J_{6exo,7endo}$ = 8, $J_{6exo,H(olef.)}\approx 3$ and $J'_{6exo,H(olef.)}\approx 1$, 1 H, H_{exo}–C(6)); 2.84 (*A*-part of *AB*-system, J = 18, 1 H, H–C(3)); 2.96 (*B*-part of *AB*-system with additional coupling, J_{AB} = $J_{6endo,6exo}$ = 18.5, $J_{6endo,7endo}$ = 5.5, $J_{6endo,H(olef.)}\approx 4$, $J'_{6endo,H(olef.)}\approx 1$, 1 H, H_{endo}–C(6)); 3.10 (*B*-part of *AB*-system, J = 18, 1 H, H–C(3)); 4.32 ($t\times d$, $J_{7endo,6exo}$ = $J_{7endo,7a}$ = 8, $J_{7endo,6endo}$ = 5.5, 1 H, H_{endo}–C(7)); 4.88 (*d*, $J_{7a,7endo}$ = 8, 1 H, H–C(7a)); 5.86–5.99 (*m*, 2 H, H–C(4) and H–C(5); $J_{4,5}$ = 10 can be determined, a complete first order interpretation of the signal is, however, not possible); 7.25–7.42 (*m*, 5 H, 5 arom. H). – MS.: 340 (7, M^+), 213 (91), 195 (15), 185 (11), 171 (81), 167 (28), 155 (36), 154 (54), 153 (25), 152 (23), 143 (100), 141 (36), 129 (33), 128 (61), 115 (48), 91 (53), 77 (34).

*Preparation of (3a*RS,*7a*SR*)-3a-phenyl-3a,7a-dihydro-2(3*H*)-benzo[b]furanone* (**15**). Heating of **14** (2.7 g, 7.9 mmol) in 70 ml of hexamethylphosphoric triamide in the presence of 1,5-diazabicyclo-[4.3.0]-5-nonene (1.89 ml, 15.8 mmol) to 70° for 16 h led to a dark brown mixture. Cooling to r.t., dilution with ether, washing with aq. NH_4Cl-solution, drying, and evaporation afforded solid **15** (1.5 g, 89%). The anal. sample was recrystallized from ether/hexane, m.p. 82–84°. – IR. (KBr): 1760*s*, 1749*s*,

1493*m*, 1210*s*, 950*s*, 768*m*, 748*m*, 724*m*, 702*m*. – ^{1}H-NMR. (80 MHz, $CDCl_3$): 2.94 (*A*-part of *AB*-system, $J = 17.5$, 1 H, H–C(3)); 3.28 (*B*-part of *AB*-system, $J = 17.5$, 1 H, H–C(3)); 5.21 (*d*, $J = 5$, slightly br. because of long-range coupling to olef. H, 1 H, H–C(7a)); 5.82 (*d*-like, $J \approx 9$, br. because of long-range coupling, 1 H, H–C(4)); 5.90–6.45 (*m*, 3 H, 3 olef. H); 7.20–7.45 (*m*, 5 H, 5 arom. H). – MS.: 212 (98, M^+), 184 (65), 170 (57), 167 (65), 165 (48), 156 (44), 155 (82), 154 (59), 153 (51), 152 (59), 142 (100), 141 (72), 128 (37), 115 (57), 91 (38), 81 (54), 77 (47).

Preparation of (3aRS,6RS,7RS,7aRS)-6,7-dibromo-3a-phenyl-3a,6,7,7a-2(3H)-benzo[b]furanone (**16**). Bromine (0.18 ml, 3.5 mmol) was added at 0° to a solution of **15** (750 mg, 3.5 mmol) in 80 ml of CCl_4. The mixture was stirred at r.t. for 2 h. Addition of 10% aq. $Na_2S_2O_3$-solution and CH_2Cl_2, extraction, drying, and evaporation afforded 1.6 g of a mixture which contained one main product according to TLC. (Rf 0.60, ether). Chromatography of this mixture with ether/hexane 3:1 on silica gel gave solid **16** (900 mg, 69%). An anal. sample was obtained by recrystallization from CH_2Cl_2/ether/hexane, m.p. 140–143°. – IR. (KBr): 1793*s*, 1596*w*, 1497*m*, 1168*s*, 765*m*, 699*m*. – ^{1}H-NMR. (400 MHz, $CDCl_3$): 2.88 (*A*-part of *AB*-system, $J = 17.5$, 1 H, H–C(3)); 3.30 (*B*-part of *AB*-system, $J = 17.5$, 1 H, H–C(3)); 4.37 ($d \times d$, $J_{7exo,6endo} = 8$, $J_{7exo,7a} = 2.5$, 1 H, H_{exo}–C(7)); 4.90 ($d \times d \times d$, $J_{6endo,7exo} = 8$, $J_{6endo,5} = 2.5$, $J_{6endo,4} = 1.5$, 1 H, H_{endo}–C(6)); 4.93 ($d \times d$, $J_{7a,7exo} = 2.5$, $J_{7a,4} = 1.2$, 1 H, H–C(7a)); 5.77 ($d \times t$, slightly br., $J_{4,5} = 10$, $J_{4,6endo} = 1.5$, $J_{4,7a} = 1.2$, 1 H, H–C(4)); 6.27 ($d \times d$, $J_{5,4} = 10$, $J_{5,6endo} = 2.5$, 1 H, H–C(5)); 7.34–7.51 (*m*, 5 H, 5 arom. H); the assigned couplings were confirmed by irradiation at 4.37, 4.90, 4.93, 5.77, and 6.27 ppm. – MS.: 370 ($\ll 1$, M^+), 292 (6), 290 (6), 211 (100), 184 (65), 183 (40), 170 (59), 167 (71), 165 (59), 156 (43), 155 (90), 154 (72), 153 (54), 152 (61), 142 (99), 141 (70), 128 (35), 115 (58), 91 (36), 81 (60), 77 (48).

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