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CIRCULAR DICHROISM—XLVI[1]

RULES FOR BENZENE COTTON-EFFECTS

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Abstract—For a benzenoid compound with chiral second sphere this chirality determines the sign of the Cotton-effects. Sector rules for third (fourth, . . .) sphere contributions are proposed, whose nodal planes are composed of the nodal planes of the corresponding transitions plus those additional planes, which are required by the symmetry of the molecule.

SEVERAL rules have been proposed in recent years[2] for the correlation of circular dichroism (CD) with absolute configuration of chiral benzenoid compounds. On general considerations Schellman[3] proposes a sector rule with twelfthfold symmetry for benzene derivatives lacking polar substituents attached to the ring, whereas, e.g. a monosubstituted derivative with a polar group should follow a rule with C_{2v}-symmetry (a quadrant rule). Kuriyama *et al.*[4] put forward such a quadrant rule for the ^1L_b ($^1B_{2u}$)-band CD (Fig 1A), DeAngelis and Wildman[5] used a somewhat other direction of projection and apply their rule to the ^1L_a($^1B_{1u}$)-band CD (Fig 1**B**). Both rules have mainly been applied to the same Amaryllidaceae alkaloids. In many cases ^1L_b- and ^1L_a-Cotton-effects have opposite signs, so tentatively the first mentioned rule can also be applied to the ^1L_a-band CD, the latter to the ^1L_b-band CD.

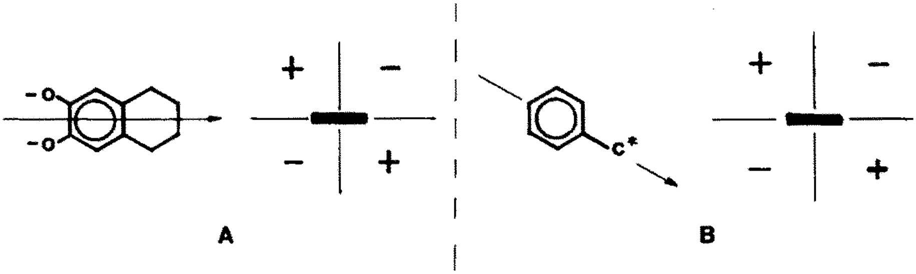


FIG 1. Quadrant rule of Kuriyama *et al.*[4] for ^1L_b-band CD (A) and of DeAngelis and Wildman[5] for ^1L_a-band CD (**B**)

General approach to the Cotton effect of aromatic chromophores

We[1,6–8] have used another approach which will be summarized and refined in the following. According to a general hypothesis[9,10] that chiral sphere of a molecule which is nearest to the chromophore determines mainly the Cotton-effect (sign and even magnitude). For a tetralin or tetrahydroisoquinoline the aromatic ring forms the first sphere, the cyclohexene (piperideine) ring the second, groups or rings attached to this second sphere build up the third sphere, etc.

Chiral first spheres are present, e.g. in hexahelicenes[11] (with chiral σ-skeleton) or in the vespirenes[12] (chiral interaction of two locally achiral fluorene systems). Such a chirality of the first sphere ("inherently dissymmetric chromophore" according to Moscowitz[13]) leads to $\Delta\varepsilon$-values of 100 and more.

The chiral second sphere

Examples for compounds with a chiral second sphere are tetralin or tetrahydroisoquinoline derivatives. The chirality of the cyclohexene or piperideine ring is determined by the configuration of the attached groups or rings. On the basis of experiment we proposed[6,8] that in a compound not further substituted in the aromatic ring, or substituted with two oxygen functions in 6,7-position, a negative CD within the ^1L_b-band is obtained with the conformation shown in Fig 2. We have proven this rule now by synthesis of the compound **12** with unambigous chirality (*viz* that shown in Fig 2) and conformation of the second sphere. **12** indeed shows a negative ^1L_b-band CD. The CD within the ^1L_a-band is also negative. The rule of the Japanese workers[4] leads also to a correct prediction of the CD, the other rule[5] cannot be applied here because it is defined only for benzene rings attached directly to a centre of chirality.

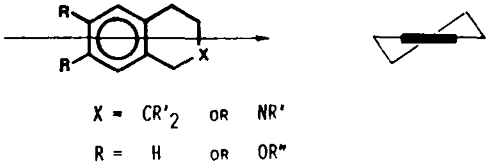
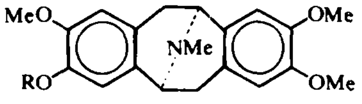
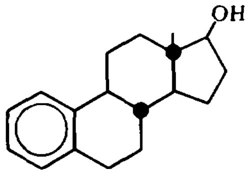


FIG 2. Chirality of second sphere leading to a negative ^1L_b-band Cotton-effect

A test of these different rules is possible, however, on the basis of the published[14,15] CD data of argemonine (**1**) and some of its analogs. The (−)-compound, whose absolute configuration is known, shows a small negative CD at about 291–298 nm, a positive one at 275–278 nm, a stronger negative one at 235–236 nm, and a still



1: R = Me
2: R = H



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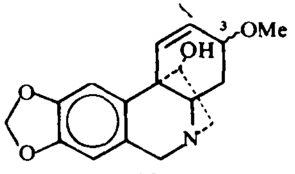
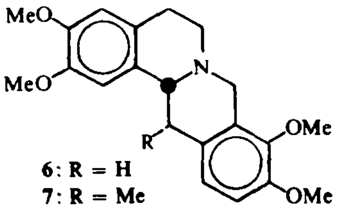


4: 3β − OMe
5: 3α − OMe



6: R = H
7: R = Me

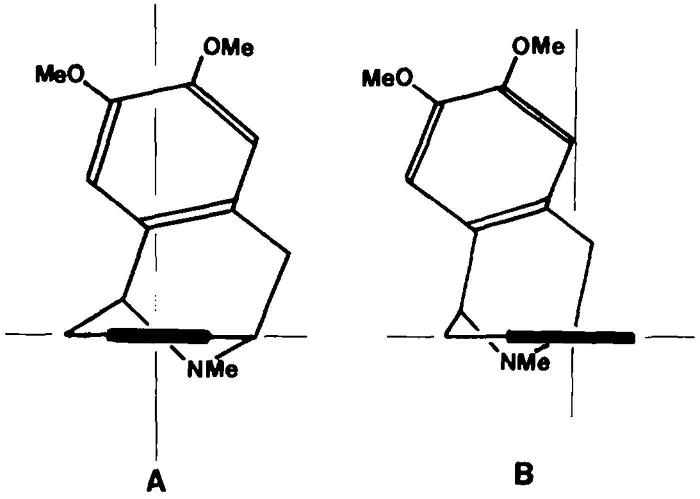


FIG 3. Projections of one chromophore of (−)-argemonine (1) according to Kuriyama *et al.*[4] (A) and DeAngelis and Wildman[5] (B)

stronger one, which was found positive[14] with one instrument but negative with another.[15] Mason *et al.*[14] have explained the two bands of opposite signs within the ^1L_b-absorption as being due to exciton splitting, though they differ appreciably in magnitude. We would rather assume, that they are due either to differently solvated species or to an allowed and forbidden series of vibronic bands,[16] as, e.g. for both (−)-argemonine hydrochloride and (−)-norargemonine (2) (in ethanol solution) only positive CD-bands were found.[15]

Assuming thus the presence of two identical chromophores, whose CD spectra are merely additive, we can predict the sign of the Cotton effect on the basis of the different rules. Fig 3 shows one projection along the C_2-axis of the pyrocatechol chromophore[4] (A) and one according to DeAngelis and Wildman[5] (B). Contributions from the second benzene ring more or less compensate each other in projection A, thus Kuriyama's rule[4] predicts a small positive CD within the ^1L_b-band, as found. Projection B (Fig 3) on the other hand predicts,[5] that the ^1L_a-band CD should be strongly positive, which is, however, in disagreement with the measured values.[14, 15]

Our argumentation is the following. Each benzene ring of (−)-argemonine is incorporated into two rings, a 6-membered and an 8-membered. Thus there exist two second chiral spheres at the same time, which lead to positive (6-membered ring) and negative (8-membered ring) Cotton effects within the ^1L_b-absorption, respectively. Usually the smaller ring determines the CD (see, e.g. ketonic examples from gibberellic acid series,[17] kaurene series,[17] or camphor series[18]), which leads in the case of (−)-argemonine correctly to a positive sign of the ^1L_b-band CD.

As mentioned above, the ^1L_a-band CD very often has the opposite sign to that within the ^1L_b-band. The ^1L_a-band lies at shorter wavelengths, and mixing with other transitions than the pure $^1A_{1g} \rightarrow {}^1B_{1u}$ (e.g. $\pi \rightarrow \sigma^*$, or other benzene transitions) is already more probable. It is therefore not surprising that exceptions from any proposed rule will be found much more often for the ^1L_a-band CD than for the

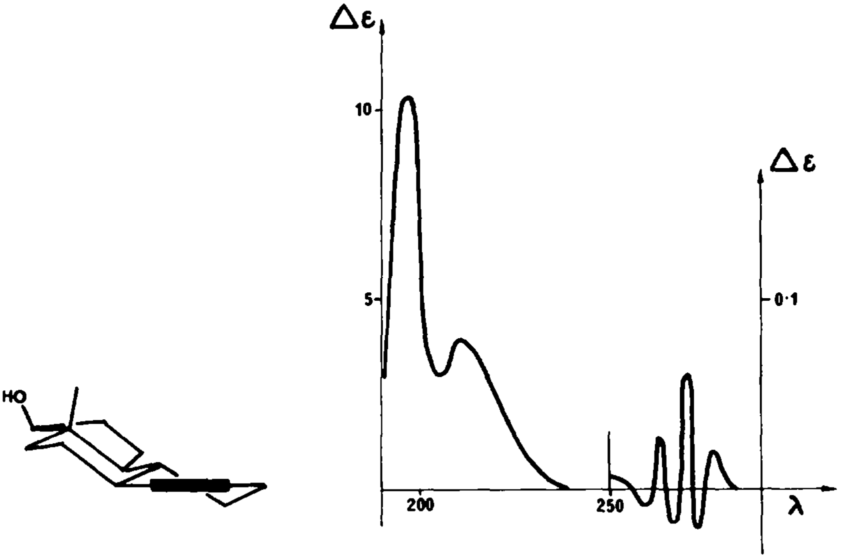


FIG 4. CD (in ethanol) and projection of 3

${}^1L_b$-band Cotton effect. The deviation from the rule for olefine $\pi \rightarrow \pi^*$ Cotton effects[19] found for simple methylene steroids[20] may be attributed to the same fact.

The sign of the Cotton effect can not always be unequivocally obtained from the CD-spectrum.$\Delta^{1,3,5(10)}$-estratrien-17β-ol (3), e.g. shows pronounced fine structure within the ${}^1L_b$-band CD with positive and negative partial bands.* This is again ascribed here to vibronic coupling.[16] From the chirality of the second sphere a positive CD is expected (Fig 4).

The chiral third sphere

Third (fourth, . . .) sphere contributions in general are only important for the sign of the CD, if first and second sphere are achiral, they will, however, influence somewhat the magnitude of the Cotton effects. In an earlier paper[6] we have assumed that the rule for these third-sphere contributions should mirror the state symmetry of the transition in question. The ${}^1A_{1g} \rightarrow {}^1B_{2u}$-transition has nodes at all corners of the benzene ring, the ${}^1A_{1g} \rightarrow {}^1B_{1u}$-transition antinodes.[21] For the ${}^1L_b$-band CD we have therefore proposed[6] a sector rule, whose nodal planes pass through the corners of the benzene ring, whereas for the ${}^1L_a$-band sector rule the nodal planes go through the midpoints of the six benzene bonds. The plane of the benzene ring was added as a further nodal plane. Such sector rules explain, e.g. why the ${}^1L_b$-band Cotton effects of the two epimers haemanthamine (4) and crinamine (5) are practically identical, whereas there is a large difference for the ${}^1L_a$-band CD (4: 289(+3·42), 244(−3·96); 5: 290 (+3·51), 245 (−2·84).** The OMe group lies in a nodal plane of the ${}^1L_b$-sector rule and should therefore give no contribution to the 290 nm band CD, whereas this is not the case for the ${}^1L_a$-sector rule. Similarly the more negative ${}^1L_b$-band CD of (+)-corydaline (7) compared to that of (+)-tetrahydropalmatine (6) has been

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* We thank Dr. M. Legrand, Paris, also here for informing us of his unpublished results.

** Values taken from Ref. 4. Somewhat other values have been given in Ref. 5.

explained with the same sector rule.[8] Kuriyama's rule[4] leads in this case to the wrong sign for the contribution of the methyl group, the rule of DeAngelis and Wildman[5] cannot be applied again for formal reasons.

These sector rules in the form as put forward earlier[6, 8] are, however, not always compatible with the local symmetry of the chromophore. We want to modify them therefore in the following way. A 6,7-dioxygenated tetralin (tetrahydroisoquinoline, if one disregards the substitution of one carbon atom by nitrogen in the nonbenzenoid ring) contains a C_2-axis, identical with the "long axis" of the molecule. A rotation around this axis must leave unchanged the signs of (second and) third sphere contributions. This requires a C_2-axis in the same direction for the corresponding sector rule, i.e. besides the plane of the ring (which is not a nodal plane either for the $^1A^1{}_g \rightarrow {}^1B_{2u}$- or for the $^1A_{1g} \rightarrow {}^1B_{1u}$-transition) there must be added one more nodal plane, which contains this C_2-axis and is perpendicular to the plane of the aromatic ring. The ^1L_a-sector rule has already the right symmetry for such a tetralin (tetrahydroiso-quinoline) and needs therefore no additional nodal plane (*cf* Fig 5**A** and **B**).

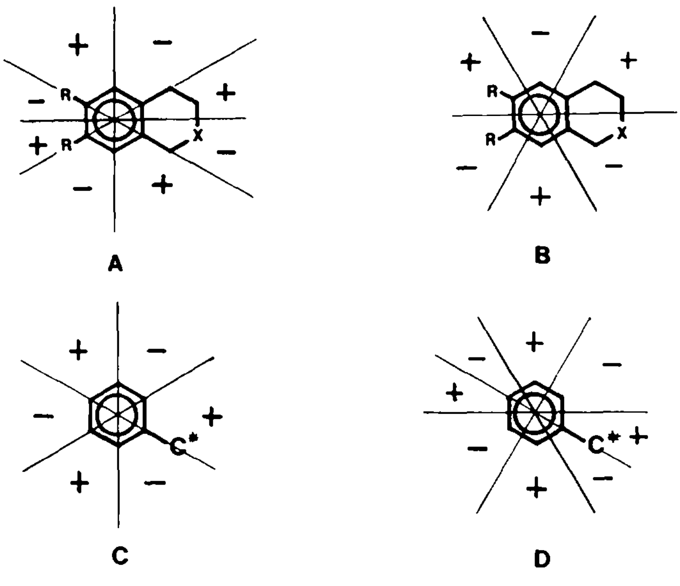


Fig 5. Modified sector rules for third sphere contributions to CD. Signs refer to upper sectors. Meaning of X and R as in Fig 2

A. ^1L_b-band CD of tetralins and similar compounds (e.g. tetrahydroisoquinolines)

B: ^1L_a-band CD of same compounds as in **A**. The sign pattern is tentative.

C: ^1L_b-band CD of monosubstituted benzene chromophores

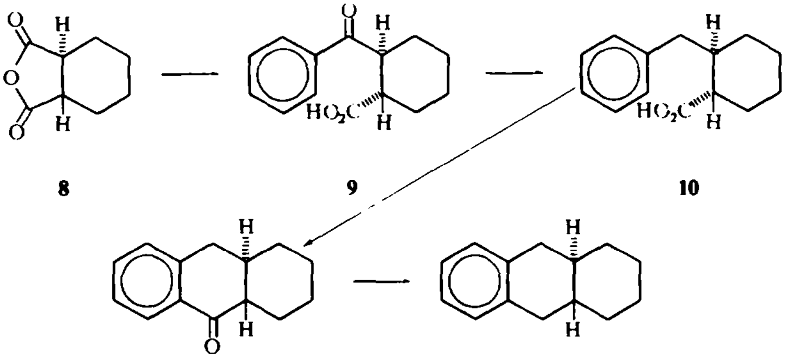
D: ^1L_a-band CD of same compounds as in C. Sign pattern tentative

The contrary is true for benzene derivatives monosubstituted by a chiral group. Now a C_2-axis lies in the direction of the C_{ar}—C^*— bond, so that the fifth nodal plane has to be added in case of the ^1L_a-sector rule, but not for the ^1L_b-band CD (Fig 5C and D). The signs are taken from experiment and are provisional for the ^1L_a-transitions. Within small sectors containing the direction of projection (Fig 1) the signs are the same for our sector rules and those of Kuriyama *et al.*[4] and DeAngelis and Wildman.[5]

One other advantage of these modified rules is the fact, that for a tetralin (tetrahydroisoquinoline) the direct contributions of the atoms at 2- and 3-position to the ^1L_b-band Cotton effect (taken now as third-sphere contributions) have formally the same signs as is predicted from the chirality of the second sphere. This is an analogy to cyclic ketones in the twist conformation: if the chiral second sphere gives e.g. rise to a positive CD,[22] than the sum of octant contributions[23] of the ring atoms would also be positive.

Synthesis of (−)-(4aR,9aR)-trans-1,2,3,4,4a,9,9a,10-*octahydroanthracene* (**12**) and *chiroptical properties of related compounds*

Starting from the optically active anhydride of (+)-*trans*-hexahydro phthalic acid, whose absolute configuration is known to be *S*,[24,25] **12** has been synthesized in optically active form. The corresponding racemic compounds have already been described, our synthesis does, however, not always follow these lines. For details see Experimental.



8 **9** **10** **11** **12**

Anhydrides give two Cotton effects around 220 nm.[26] The CD-curve of **8** shows that both bands are of equal magnitudes but opposite signs. In agreement with published ORD data[26] the couplet is of the positive type* for the *S*-anhydride **8**. Such a couplet is indeed expected from exciton splitting.

The ketoacid **9** gives a positive CD within the *R*-band of the Aryl-C(=O) chromophore, a positive CD which is relatively strong (+0·62) for such a type of compound in the region of the ^1L_b-absorption, and a strong negative *K*-band CD. The CD of the benzyl derivative **10** is virtually independent of the solvent. Within both the ^1L_b- and the ^1L_a-band the Cotton effects are of the same sign, *viz* negative. Both spectra can be explained by applying the sector rules, assuming reasonably preferred conformations for the two compounds.

In the benzoyl derivative **9** the carbonyl can be assumed to be in the plane of the aromatic ring. If furthermore the same carbonyl is also eclipsed to one of the ring C—C-bonds (the cyclohexane ring being in the chair conformation with two equatorial substituents), as suggested, e.g. by microwave spectra of simple oxocompounds,[27,28] we arrive at a preferred conformation as given in Fig 6. If we arrange the signs for the individual third sphere contributions for the ^1L_b-band CD as given in Fig 5C, a positive Cotton effect is predicted, as is found. The ^1L_a-band Cotton effect cannot be

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* For the definition of the sign of a couplet see Ref. 12.

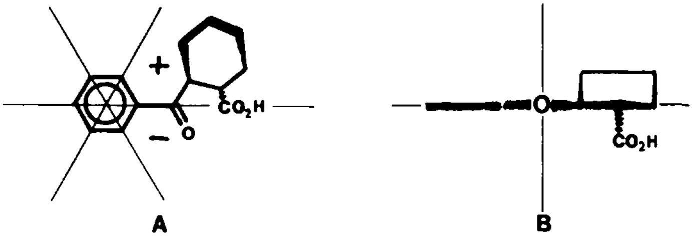

FIG 6. Projections of preferred conformation of **9**:
A: for ^1L_b-band CD
B: from O to C of carbonyl group

identified with certainty because of the strong K-band CD at 236 nm. Fig 6**B** gives a projection from the O to the C of the CO group. The carboxyl group extends into a front octant. By applying naively the octant rule for saturated ketones[23] one would predict from this projection a negative *R*-band CD. We have however found empirically[9, 10] that for a cyclohexenone with coplanar C═C—C═O-system, which necessarily possesses an achiral first but a chiral second sphere, the usual rule for twisted saturated ketones[22] has to be inverted. If the same inversion is also true for third sphere contributions of such coplanar conjugated ketones the sign of the Cotton effect will be predicted correctly.

For the benzyl compound **10** it may be assumed, that the $C(H_2)$—C(cyclohexane) bond is arranged perpendicularly to the plane of the benzene ring. With all reservations, which have to be taken into account for a comparison between crystal structure and conformation in solution, X-ray studies of, e.g. ephedrine hydrochloride[29] or dopamine hydrochloride[30] suggest also such an arrangement, which is the most favourable for p—π-conjugation. Assuming that staggered conformation around the $C(H_2)$—C(cyclohexane) bond, which leads to least steric interaction, the preferred conformation of **10** will be then that of Fig 7, in which the cyclohexane ring is above the plane of the benzene ring, and the carboxylic group very close to it. With the signs allotted in Fig 5C and **D** we expect then a negative Cotton effect for both the ^1L_b- (Fig 7A) as well as the ^1L_a-band (Fig 7**B**), in agreement with experiment.

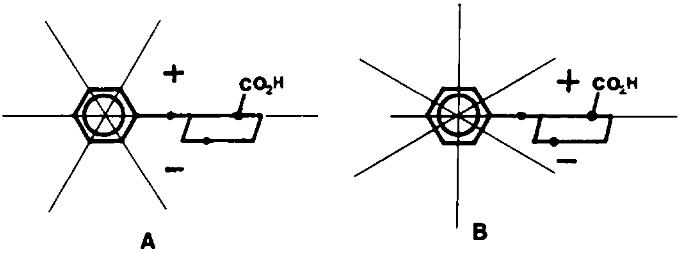

FIG 7. Projections of preferred conformation of **10**:
A: for ^1L_b-band CD
B: for ^1L_a-band CD

In the cyclic ketone **11** the conformation of the noncoplanar arylketone moity is nearly rigid, its chirality determines correctly the negative sign for the *R*-band CD according to the corresponding rule.[9, 10] The ^1L_b-band CD is more strongly positive; though the second sphere is chiral in this compound nevertheless the aforementioned rule cannot be applied here because of the conjugation with the CO group.

TABLE 1. CD DATA

Compound	Solvent	$\lambda_{max}(\Delta\varepsilon)$
8	acetonitril	241(+0·73), 214(−0·59). $[R_{241}] = +1{\cdot}20$, $[R_{214}] = -1{\cdot}56$
9	isooctane	370(+0·01), 362(−0·04), 351(+0·15), 337(+0·39), 325(+0·46), 315(+0·33), 278(+0·62), 236(−6·98), positive at shorter wavelengths
10	isooctane	269(−0·07), 263(−0·10), 256(−0·07), 223(−0·62)
	ethanol	269(−0·08), 263(−0·10), 257(−0·07), 223(−0·74)
11	isooctane	370(−0·36), 362(+0·08), 353(−0·57), 345(+0·18), 339(−0·48), 332(+0·15), 325(−0·29), 313(−0·21), 305(−0·10), 293(+1·69), 286(+1·69), 241(−1·88), 219(+1·65), 202(−15)
	acetonitril	362(−0·39), 347(−0·72), 333(−0·76), 320(−0·63), 310(−0·41), 290(+2·12), 240(−0·73), 218(+1·60), 203(−6·5)
12	isooctane	275(−0·16), 268(−0·19), about 215(−1·1)

EXPERIMENTAL

For details of measurements and preparations see Ref. 31.

(+)-(1S,2S)-trans-2-*Benzoyl-cyclohexanecarboxylic acid* (**9**)

(+)-(S)-*Hexahydrophthalic acid* was prepared according to Werner and Conrad[32] and showed $[\alpha]_D^{20} = +19{\cdot}2°$ (c = 4·1, acetone):[32] +18·2°). To a soln of 14 g (0·09 mole) of its anhydride,[32] and dissolved in 120 ml dry thiophene-free benzene, 60 g (0·45 mole) anhyd $AlCl_3$ were added at once at 0° (*cf* Jucker and Süess[33]). The mixture was then refluxed until no more HCl was evolved (*ca* 3 hr). Decomposition after cooling with a mixture of 100 g ice and 40 ml conc HCl, separation of the two layers and evaporation of the benzene *in vacuo* gave the crude acid. It was dissolved in 100 ml 12% Na_2CO_3aq and heated on the waterbath (60°) for about 10 min. After filtration 2 g charcoal were added and after stirring for 4 min the soln was filtered again. The colourless filtrate was acidified with conc HCl, and the precipitated acid filtered off, washed with water and dried *in vacuo*: 16 g (76%) acid **9**, m.p. 81–82° (racemate: 148–149°;[33] 151–152°), $[\alpha]_D^{20} = +11{\cdot}9°$ (c = 1·5, chloroform).

(+)-(1S,2R)-trans-*Benzylcyclohexane carboxylic acid* (**10**)

A solution of **9** (5 g, 0·022 mole) in 50 ml glacial AcOH was hydrogenated with 0·5 g of 10% Pd/C and 15 drops of 70% $HClO_4$ (conditions analogous to Ref. 34) for about 8 hr at room temp and 1 atm. After filtration from the catalyst about half of solvent was removed by distillation *in vacuo*, the remainder was heated to 75° and diluted with water until it became cloudy. After storage in the cold 3·6 g of crude acid **10** were obtained, which were purified by chromatography on a silicagel column with benzene/EtOAc (10:1) to give 2·9 g (62%) colourless prisms (from AcOH/water): m.p. 71–72° (racemate: 137°;[35] 133–134°), $[\alpha]_D^{20} = +23{\cdot}1°$ (c = 0·73, chloroform).

(−)-(4aR,9aS)-trans-*Hexahydroanthrone* (**11**). To an icecold soln of **10** (4 g, 0·018 mole) in 40 ml dry thiophene-free benzene 4·2 g (0·02 mole) PCl_5 were added slowly. Then the mixture was refluxed until no more HCl was evolved (about 5 min). After cooling in an icesalt bath 4·8 ml (0·04 mole) anhyd stannic chloride were added, then the soln was heated to 50° until no more HCl was evolved (about 1 hr). Decomposition was done with 8 g ice followed by 8 ml conc HCl. The two-phase mixture was refluxed for about 1 hr, cooled, and separated. The aqueous phases were extracted 3 times with benzene and the combined organic layers were worked up as usual. Purification was achieved by chromatography on silicagel with benzene to give 2·8 g (= 79%) colourless prisms (from EtOH): m.p. 109·5–110·5° (racemate: 110°:[35] 109–110°), $[\alpha]_D^{20} = -49{\cdot}4°$ (c = 0·69, chloroform).

(−)-(4aR,9aR)-trans-1,2,3,4,4a,9,9a,10-*Octahydroanthracene* (**12**). A soln of **11** (2 g, 0·01 mole) in 50 ml glacial AcOH was hydrogenated with 0·2 g of 10% Pd/C and 10 drops of 70% $HClO_4$ at room temp and about 1 atm for 20 hr. After usual work-up and chromatography on silicagel with benzene 1·5 g (= 81%) oily material was obtained, which crystallized by storing in the ice-box (colourless needles from AcOH/water), m.p.: 41–43° (racemate: 64°:[36] 63–64°), $[\alpha]_D^{20} = -61{\cdot}2°$ (c = 2·89, chloroform). $C_{14}H_{18}$(186), molecular ion found: 186.

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