33. On the Absolute Configuration of (+)-Indane-1-carboxylic Acid

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Summary

The *(R)*-configuration, attributed to (+)-indane-1-carboxylic acid ((+)-**1**) by *Fredga* [1], is unequivocally confirmed *(Scheme 1)*. Configurational doubts, raised by an erroneous ORD. curve of (–)-1-methylindane ((–)-**4**) published by *Brewster & Buta* [2], are unfounded (*cf.* the following paper of *Brewster* [3] and the corrections in [4]). This was further verified by preparing deuteriated 1-methylindanes starting with (–)-*(R)*-3-phenylbutyric acid ((–)-*(R)*-**5**) as well as with (+)-*(R)*-**1** or (–)-*(S)*-**1** *(Scheme 2)*. The ORD. curves of the optically active **4** thus obtained were (disregarding deuterium isotope effects) identical or antipodal, respectively (*cf. Fig. 1, 2,* and *7a–e*).

Optically active methyl indane-1-carboxylates ((–)-*(R)*-**14** or (+)-(*S*)-[1-^{2}H]-**14**) show a strong solvent dependence of their ORD. and CD. spectra with a sign inversion occuring in going from isooctane to methanol or benzene. The observed changes can be explained by a change in the population of conformations where the ester carbonyl group is eclipsed either with the C(1), C(2)- or C(1), H-bond, with the n,π^*-transition having a slightly different energy and the ester group an essentially enantiomeric environment with respect to its orientation relative to the benzene moiety.

1. Introduction. – In connection with our work on vibrational *Raman* optical activity spectroscopy (VROA.) we proved by chemical and VROA. correlation, that (+)-1-methylindane ((+)-**4**)[2]) has the *(R)*-configuration [5]. This was in contradiction to the assignment of the *(R)*-configuration to (–)-**4** set up by *Brewster & Buta* [2]. Furthermore we pointed out that based on *Brewsters* correlation (+)-indane-1-carboxylic acid ((+)-**1**) which is correlated with (+)-**4** by reduction should consequently have the *(S)*-configuration. This, however, was in contradiction to the *(R)*-configuration of (+)-**1** established in 1956 by *Fredga* [1].

On the other hand extensive racemization observed in *Fredga*'s reactions and seeding with crystals of optically pure (+)-**1** could probably have been the reason for an erroneous correlationship in linking (–)-*(R)*-2-phenylsuccinic acid ((–)-**3**) with

[1]) Part of the planned thesis of *H.-R. Sliwka.*

[2]) All signs of rotation refer to the sodium D-line; for solvents see experimental part.

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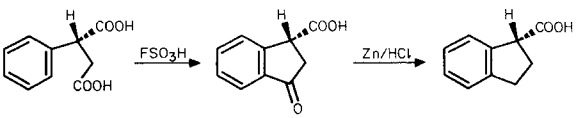
(+)-**1**. To derive once more the absolute configuration of (+)-**1** we repeated the correlation of (–)-(R)-**3** with (+)-**1** according to *Fredga* [1] by changing slightly the conditions.

2. Absolute configuration of (+)-indane-1-carboxylic acid. – A well-established procedure to cyclize phenylalkylcarboxylic acids like **3** is the $AlCl_3$ catalyzed reaction of the corresponding acid chlorides (*cf.* [6]–[8]). It is known, however, that reactions with acid chlorides occur with extensive racemization. In checking *Fredga*'s route we found that treatment of (–)-*(R)*-**3** with thionylchloride at 100° C, followed by base-catalyzed hydrolysis of the formed acid chloride of (–)-*(R)*-**3**, gave back (–)-*(R)*-**3** with 13% racemization. Thus, to avoid any misleading and keep racemization as low as possible, we chose to repeat *Fredga*'s pathway with slight modifications *(Scheme 1)*. Reaction of (–)-**3**, prepared according to [9] and [10], with fluorosulfonic acid [cf. 11] afforded (–)-*(R)*-indane-3-one-1-carboxylic acid ((–)-*(R)*-**2**[3]) in 60% yield and with of 77% over-all racemization.

Scheme 1



(–)-*(R)*-**3** (–)-*(R)*-**2** (+)-*(R)*-**1**

Fredga's method was applied in the following *Clemmensen* reduction to (+)-*(R)*-**1**. In contrast to *Fredga* we avoided any optically active seed crystals and obtained after workup, albeit in bad chemical yield (*cf. Exper. Part*), chemically pure (+)-*(R)*-**1**. ^{1}H-NMR.-shift experiments with Eu(hfc)$_3$[4]) of the methyl ester of (+)-(R)-**1** showed the same enantiomeric shifts as the ester of independently prepared (+)-**1**, and ORD. measurements gave the same positive plain curve.

Thus, the absolute configuration of (+)-**1** is well-established and in connection with the information collected in the foregoing paper of *Brewster* [3], and in the *Atlas of Stereochemistry* [12], no contradictions are left with respect to it. This means that in our statement in [5] "that the *(S)*-configuration has to be attributed to (–)-1-methylindane ((–)-**4**[5]) as well as to (+)-**1**[5]), provided there is no trivial mistake in *Brewster & Buta*'s work" [2], only the second possibility remains.

3. Configurational correlation of (–)-*(R)*-2-phenylsuccinic acid ((–)-*(R)*-3) with (–)-*(R)*-3-phenylbutyric acid ((–)-*(R)*-5) *via* (+)-*(R)*-1-methylindane ((+)-*(R)*-4). – For the assignment of vibrational modes in the VROA. spectra of (+)-*(R)*-1-methylindane ((+)-*(R)*-**4**) [5] [13] we needed deuteriated 1-methylindane derivatives (see *Scheme 2*). Starting with (–)-*(R)*-3-phenylbutyric acid ((–)-*(R)*-**5**) we were able to prepare by standard methods (*cf. Exper. Part* and [5]) the specifically at C(2) and C(3) deuteriat-

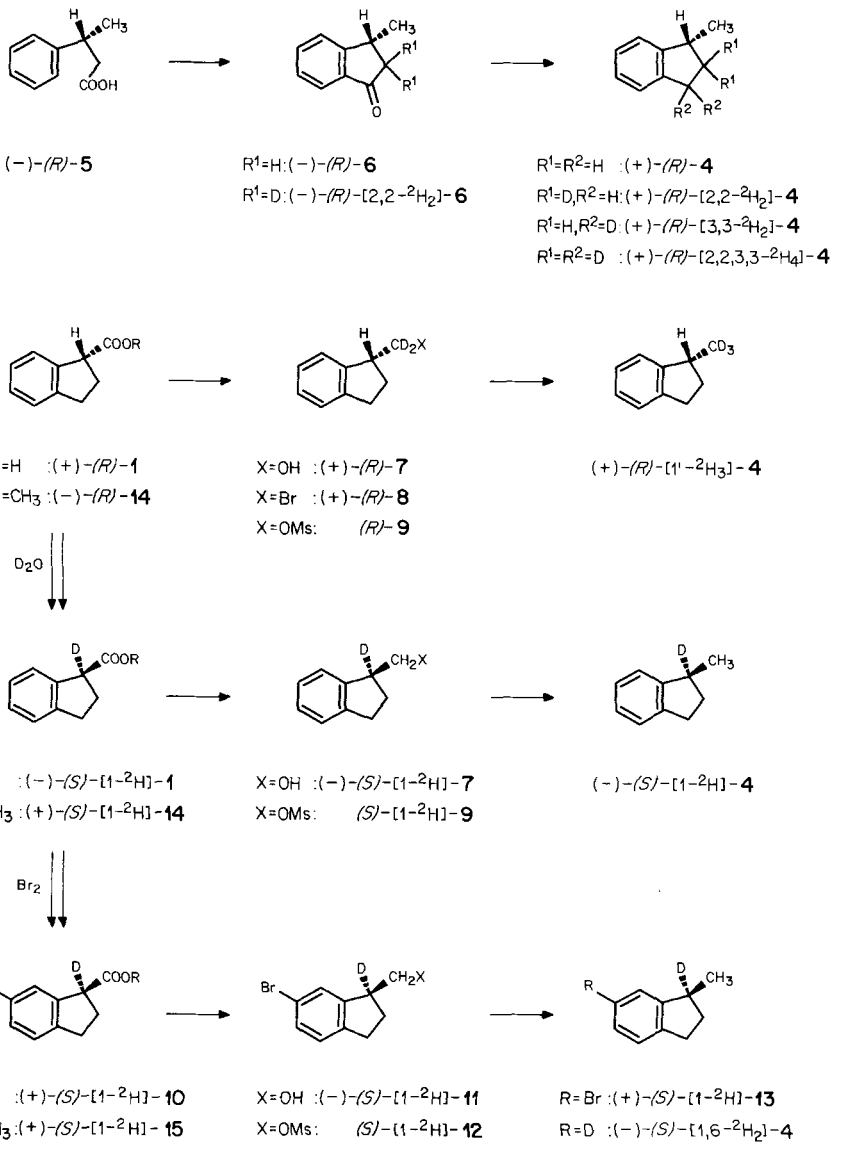
[3]) With respect to the small quantities and the low optical purity we were not able to derive accurately the solvent dependence of the optical activity of this compound.

[4]) Tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]-europium.

[5]) These numbers have been changed according to those used in this paper.

ed, optically and isotopically pure (+)-*(R)*-1-methyl-indanes shown in *Scheme 2.* On the other hand, to synthesize (+)-*(R)*-[1′-$^2H_3$]-**4** and (–)-*(S)*-[1-^{2}H]-**4** *(Scheme 2)* we had to start with (+)-*(R)*-indane-1-carboxylic acid ((+)-*(R)*-**1**) resp. (–)-*(S)*-[1-^{2}H]indane-1-carboxylic acid ((–)-*(S)*-[1-^{2}H]-**1**, by using essentially the procedures described by *Brewster & Buta* [2] for the protio compound. By bromination of racemic [1-^{2}H]-**1** (*cf.* [14]) and resolution of the formed bromo derivate we obtained pure (+)-[1-^{2}H]-**10** which again was transformed *via* **11** and **12** into (+)-6-bromo-1-me-

Scheme 2



thyl[1-^{2}H]-indane ((+)-[1-^{2}H]-**13**). The exchange of the bromo substituent by deuterium was achieved by deuteriolysis of the corresponding *Grignard* compound. Since we obtained by this route (–)-*(S)*-[1,6-$^2H_2$]-**4** the absolute configuration of (+)-[1-^{2}H]-**13** and (+)-[1-^{2}H]-**10** must also be *(S)*. The ORD. curves of (+)-*(R)*-**4** (prepared from (–)-*(R)*-**5**) and of all deuteriated 1-methylindanes are depicted in *Figures 1–2* (see also *Fig. 7a–e, Exper. Part*). Disregarding small deuterium isotope effects all

Ms = CH_3SO_2

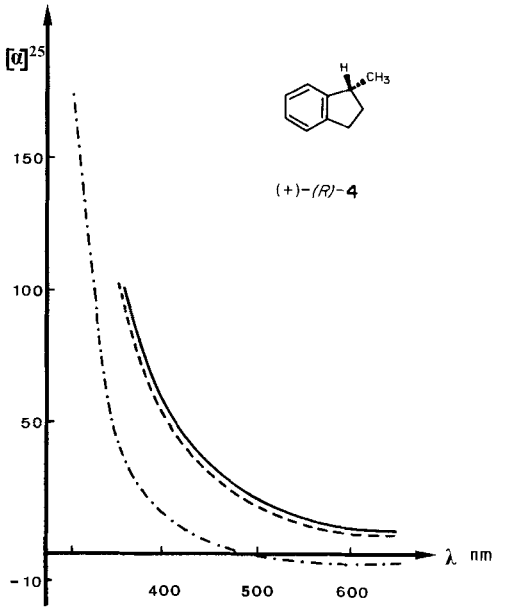


Fig. 1. *ORD. of (+)-*(R)-*1-methylindane ((+)-*(R)-**4**), neat (——), benzene (– – – –), isooctane (–·–·–·–), *prepared from (–)-*(R)-*3-phenylbutyric acid* ((–)-*(R)*-**5**) [5]

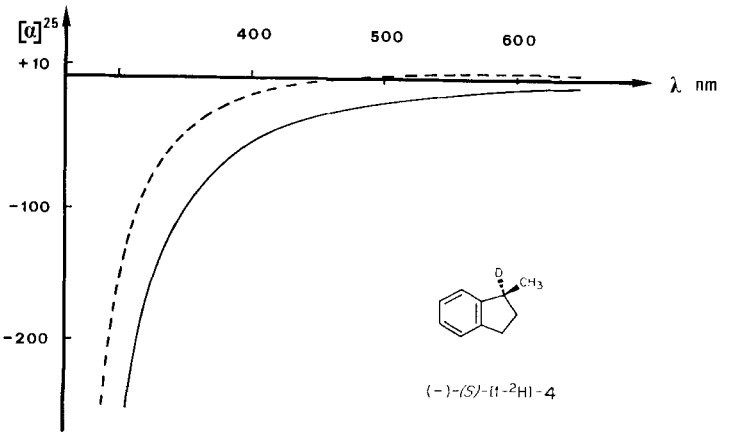


Fig. 2. *ORD. of (–)-*(S)-*1-methyl[1-^{2}H]indane* (–)-*(S)*-[1-^{2}H]-**4**), neat (——), isooctane (– – – –), *prepared from (–)-*(S)-*[1-^{2}H]indane-1-carboxylic acid* ((–)-*(S)*-**1**)

curves agree nicely, irrespective of the synthetic pathway, *i.e.* as expected from the correlations discussed above, (–)-*(R)*-**5** is correlated with (+)-*(R)*-**1** and hence with (–)-*(R)*-**3**. This again demonstrates that the ORD. curve of (–)-**4** published by *Brewster & Buta* [2] in 1966 was erroneous.

The solvent dependence of the ORD. curve of optically active 1-methylindane *(Fig. 1)* which was unfortunately not noticed in all cases led to further confusions (see [15] and literature cited in [3] and [5]). The chirally perturbed indane system therefore appears susceptible to solvent effects possibly due to a shift in the conformational equilibrium between a pseudoaxial and a pseudoequatorial position of the methyl group. These effects are to be distinguished from the solvent effects discussed below for the methyl ester of indane-1-carboxylic acid, ((–)-(R)-**14**) (*Fig. 3* and *4*), where changes in the observed chiroptical properties of transitions on the carboxyl group are important.

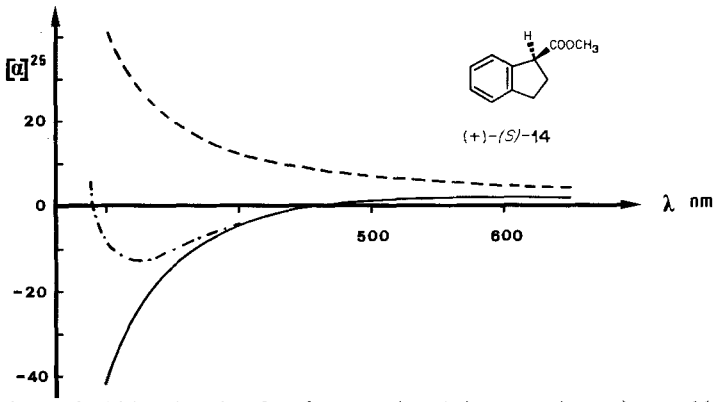


Fig. 3. *ORD. of methyl (+)*-(S)-*indane-1-carboxylate*, neat (——), isooctane (– – – –), tetrachloromethane (–·–·–·–) (Data taken from the (–)-*(R)*-compound)

4. Solvent and temperature dependence of the CD. spectra of optically active methyl indane-1-carboxylate. – 4.1. *The conformers of indane-1-carboxylic acid.* Indane-1-carboxylic acid comprises the same chromophoric system as phenylacetic acid. For α-substituted optically active phenylacetic acids it was shown from the solvent- and temperature-dependence of the CD. spectra that two strongly overlapping bands are often present in the 220–240 nm region, and that both bands stem from the n,π^*-transition of the carboxyl chromophore [16]. The experimental data can be explained by assuming an opposite sign and a slight difference in energy for the electronic transition in different conformers. The origin of the energy difference, not discussed in [16], must be due to the local electronic environment of the carboxyl group as determined by the rotational angle about the C(1'),C(1)-bond, and to differences in the degree of homoconjugation between the carboxyl and the phenyl group. The three conformers about the C(1'),C(1)-bond have the C,O-double bond eclipsed to the C(1),C(2)-, the C(1),C(7a)-, or the C(1), H-bond, with C(1),C(2 or 7a) preferred over C(1), H [17] as long as all other factors are equal. The carboxyl group itself is known to assume the single *trans*-conformation [17]. The homoconjugation between the π-systems in addition depends on the conformation about the C(1),C(7a)-bond.

As compared to the α-substituted phenylacetic acids one has the favorable situation in indane-1-carboxylic acid that the rotation about the (C1),C(7a)-bond is restricted by the limited conformational freedom of the five-membered ring of the

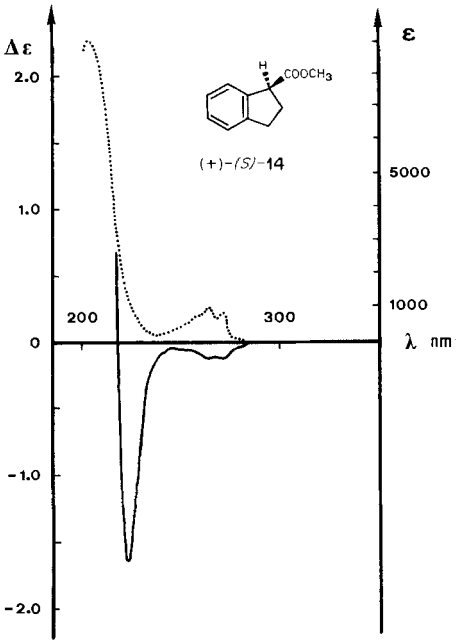


Fig. 4a. *UV.* (.....) and *CD.* (——) *of methyl (+)-*(S)*-indane-1-carboxylate in methanol* (Data taken from the (–)-*(R)*-compound, measured at +20° C)

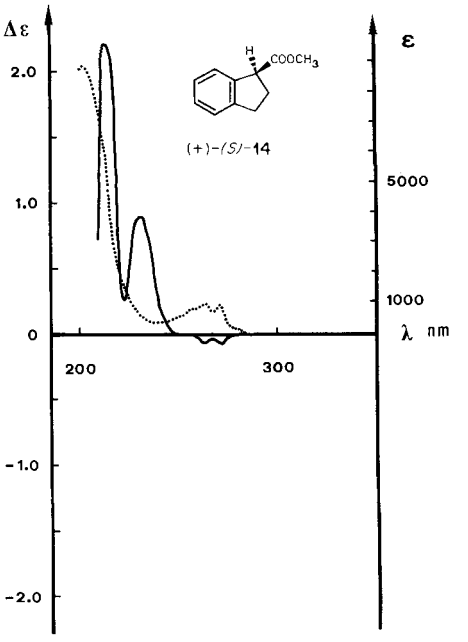


Fig. 4b. *UV.* (.....) *and CD.* (——) *of methyl (+)-*(S)*-indane-1-carboxylate in isooctane* (Data taken from the (–)-*(R)*-compound measured at +20° C; the CD. is averaged over night in order to improve the s/n)

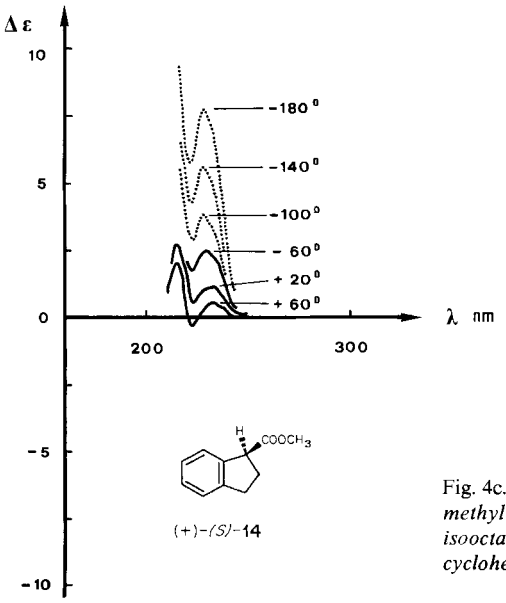


Fig. 4c. *Temperature dependent CD. of methyl (+)-*(S)*-indane-1-carboxylate in isooctane* (———) *and isopentane/methylcyclohexane 4:1* (.....)

indane system. For 1-methylindane we have found that the substituent slightly prefers a pseudoaxial over a pseudoequatorial position [13] due to steric interaction with the *peri*-H-atom of the aromatic ring. To judge from *Stuart-Briegleb* models this result likely also holds for the three conformers about the C(1'),C(1)-bond of indane-1-carboxylic acid. In the conformer where the carbonyl group is eclipsed with the C(1), H-bond the energy difference between the pseudoaxial and pseudoequatorial position of the carboxyl group appears to be lowest and the carbonyl group in the most favorable situation for interacting with surrounding molecules.

4.2. *The sign of the n,π** Cotton *effect.* In [16] the sign of the *Cotton* effect of the n,π^*-transition of α-substituted phenylacetic acids has been rationalized by the extended octant rule [18]. The advantage of such a treatment is that the octant, and therefore the inferred sign, is solely determined by the rotational angle about the C(1'),C(1)-bond. The notion of an octant rule appears inappropriate, however, for the chromophore dealt with. A sector rule basically considers electrostatic perturbations [19] and does moreover not assume the character of a regular octant rule for the carboxyl group [20]. The group theoretical sector rule for the carboxyl group is a planar rule as indicated in *Figure 5*. For a planar rule an electrostatic perturber placed at the center of the benzene ring assumes the 3 indicated positions for the conformers about the C(1'),C(1)-bond.

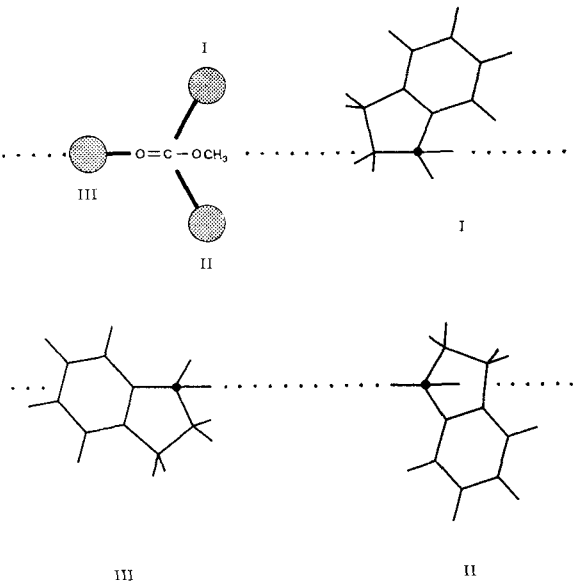


Fig. 5. *The positions of the benzene ring relative to the plane of the carboxyl group for the rotamers about the C(1'),C(1)-bond, with the carboxyl group in a pseudoaxial position.* The drawings are computer drawn projections

For the benzene ring instead of an electrostatic perturber the optical activity might be formally considered to arise through two mechanisms, namely *i)* an electrostatic perturbation contribution, assumed to be roughly isotropic and therefore dependent on the position only of the benzene ring, and *ii)* an overlap contribution

due primarely to the interaction of the benzene π-orbitals with the n- and the π-orbitals of the carboxyl group, and thus dependent on the position of the benzene ring as well as on its orientation. If the benzene ring is reflected through the π-plane of the carboxyl group the overlap contribution changes its sign exactly in the same way as the electrostatic contribution does in going from position I to position II (while the signs of the two contributions need not be the same, of course). Displacing the benzene ring from I to II by a *rotation* about the C(1'),C(1)-bond is not, however, equivalent to this cover operation of the point group C_s of the carboxyl group. No sign-change therefore is guaranteed to occur for the overlap contribution upon going from conformer I to II unless *a)* the plane of the benzene ring eclipses the C(1'),C(1)-bond or is perpendicular to it, or *b)* it is also rotated about the C(1),C(7a)-bond in a way which creates the required enantiomeric situation with respect to the interacting chromophores.

In indane-1-carboxylic acid *a* is approximately fulfilled for a pseudoaxial but not for a pseudoequatorial position of the carboxyl group, while *b* is impossible. For the α-phenylacetic acids discussed in [16] *a* and *b* are possible but not guaranteed. The authors indeed assume that opposite observed signs of CD. curves correspond to conformations with enantiomeric chromophores, due to their requirement for an appropriate geometrical disposition of the π-system of the benzene ring in the far octant occupied. As two rear octants only are geometrically accessible to the benzene ring in α-phenylacetic acids a *planar* rule is actually used, and not an octant rule. This, and the probably limited range of orientations of the benzene ring which lead to large optical activity explains why few exceptions (*e. g.* methyl α-cyclohexylmandelate) only are found. The fact that the empirical signs for positions I and II agree with those of the extended octant rule does not follow from symmetry considerations alone, however, and in this sense it is accidental. If the two geometrically inaccessible rear octants could have served as starting points, signs at variance with the octant rule would possibly have been obtained.

4.3. *Solvent- and temperature-dependence.* The CD. spectrum of the methylester of *(S)*-indane-1-carboxylic acid recorded in isooctane *(Fig. 4c)*, shows a large positive band at 232 nm and a smaller negative one at 222 nm at $+60°$ C. If the temperature is lowered *(Fig. 4c)* the size of the positive band increases and the maximum moves towards lower wavelengths, while the negative band disappears. The two bands therefore belong to different conformers, similarly as found for α-phenylactic acids, with the positive long wavelength band associated with the conformer of lowest energy in isooctane.

As outlined in 4.1 the lowest energy conformer is expected to have the (C,O)-double bond eclipsed to one of the two C(1),C-bonds. In the C(1),C(7a)-conformer, III in *Figure 5*, the benzene ring is almost bisected by the symmetry plane of the carboxyl group, and still more important, this plane is very nearly perpendicular to the π-plane of the benzene ring for the sterically favored pseudoaxial position of the substituent. The combined homoconjugated chromophore, therefore, deviates very little from an achiral situation, and this conformation can therefore not be responsible for the observed large positive CD. The C(1),C(2)-conformer I on the other hand shows a strongly chiral arrangement of the carboxyl-benzene π-system. The observed positive sign is in agreement with the results on α-phenyl carboxylic acids

[16]. The higher energy conformer with a negative sign then would have the (C,O)-double bond eclipsed to the C,H-bond and correspond to II in *Figure 5*.

The above considerations are supported by the solvent-dependence of the CD. spectrum. In a solvent like methanol or benzene one expects a stabilization of conformation II, for which the carbonyl group is most easily accessible to solvation. This should then lead to an increase in size of the negative band at shorter wavelength. A strong increase of this band and the disappearance of the positive band belonging to conformer I is indeed observed *(Fig. 4a)* in methanol. The negative band in methanol does not reach, however, the size of the positive band found in isooctane at low temperatures. This either means that a sizable amount of conformer I is also present in methanol, that the influence of the hydrocarbon frame apart from the aromatic chromophore cannot be entirely neglected, or that part of conformer II is present with a five-ring conformation which does not have the near enantiomeric chromophores associated with I and II for the substituent in a pseudoaxial position. The pseudoequatorial position, only little disfavored in II, might, if the arguments stay valid as used to explain the size of the optical activity of β,γ-unsaturated ketones [21], yield a lower optical activity than the pseudoaxial position, which entails an orientation of the benzene ring relative to the carbonyl group closely resembling that of 3,4:5,6-dibenzo-cyclohepta-3,5-dienone [21].

The conformation-dependence of the n,π^*-transition energy can be explained from the overlap between the carbonyl and benzene π-systems, though, as stated in 4.1, π-overlap need not be the only contribution. Conformer I has the two π-systems slightly more favorably arranged for interaction with the π-planes at a somewhat shallower angle than conformer II, and in agreement with this its n,π^*-transition energy is the lower one. The difference in wavelength does not correspond, of course, to the difference of the position of the observed positive and negative CD. band but is of the order of a couple of nanometers only [22].

(–)-Indane-1-carboxylic acid shows a behavior different from that of its methyl ester. For the methylester the ORD. plane curve changes from positive in isooctane to negative in substance or benzene *(Fig. 3)*, in accordance with the changes in the CD. spectrum, but for the acid it is negative in both solvents. Conformation II, therefore, appears to be the prefered one for the acid also in isooctane. This very likely is due to the fact that carboxylic acids tend to be present as dimers in a nonpolar environment. Dimer formation, though, is possible for indane-1-carboxylic acid in conformation I and II, with little direct steric preference being obvious from models for conformation II. In the dimer with conformation I, however, the two benzene rings are placed roughly on top of each other, with their centers at a distance of 7.5 to 8 Å. Subtracting 3.2 Å for the thickness of the aromatic systems one is left with a space of 4.5 Å to be occupied by the solvent molecules of isooctane. This might be a unfavorable situation for steric or entropic reasons. Yet, we do not want to imply by these considerations that electronic changes due to the H-bond to the carbonyl group could be disregarded in a more detailed analysis.

4.4. *6-Bromo[1-^{2}H]indane-1-carboxylic acid and the nature of the electronic transitions.* So far our discussion has been based on different conformers and a single electronic transition of the n,π^*-type on the carboxyl group, with the benzene moiety considered as a perturbation by weak orbital overlap and electrostatic interaction.

The strong temperature dependence with sign reversal of the chiroptical data of methyl indane-1-carboxylate as observed in isooctane are clear proof that different conformers are indeed involved. It does not prove, in contrast, that a single electronic transition only is responsible for the whole of the CD. data in the 215–240 nm region. Certain electronic states for even the simplest chromophores in organic chemistry, like the C,C-double bond, are still being debated, and in the light of this we do not pretend to decide the case for the carboxyl group with the limited data presented.

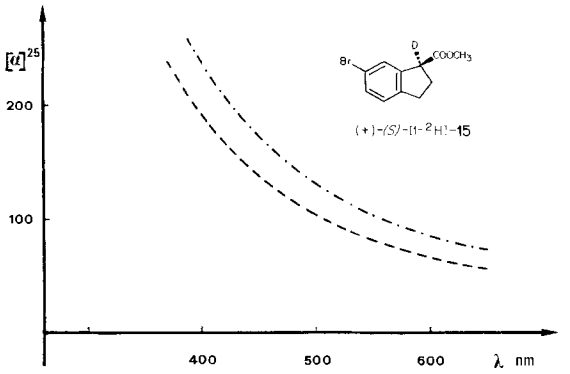


Fig. 6a. *ORD. of methyl (+)-(S)-6-bromo[1-²H]indane-1-carboxylate in benzene* (–·–·–·–) *and isooctane* (– – – –)

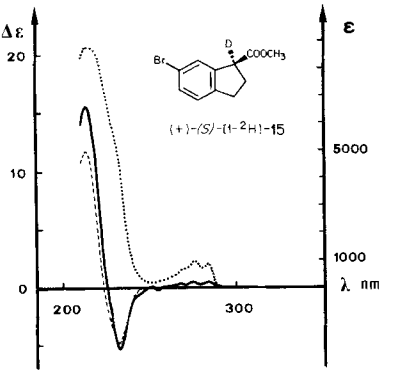


Fig. 6b. *UV.* (……) *and CD.* (——) *of methyl (+)-(S)-6-bromo[1-²H]indane-1-carboxylate in isooctane and CD.* (– – – –) *in methanol*

The sign and wavelength-dependence with respect to temperature and solvents gives a coherent picture, however, with a single n,π^*-transition at wavelengths longer than about 220 nm. The general claim as touted in [17b] that a CD. band in the 235 nm region, where observed in carboxylic acids and their esters, is always due to a transition other than the n,π^*-transition and not to different conformers, is certainly not well-founded. It may apply to cases where appropriate substituents carry lone pairs and possibly give rise to charge transfer transitions. This is exemplified by the fact that all long wavelength bands in [17b] disappear upon protonation of a lone pair.

A test on a number of our conclusions can be obtained by substituting the benzene ring of indane-1-carboxylic acid in position 6 by a strong electronic perturber like a Br-atom. In this case conformer I and II no longer present chromophorically enantiomeric situations, the benzene B_{1u}-type transition should move towards longer wavelengths, and charge transfer transitions possibly do occur between the Br-substituted aromatic system and the carboxyl group. The CD. spectrum of the methyl ester of *(S)*-6-bromo-[1-²H]indane-1-carboxylic acid ((+)-[1-²H]-**15**) *(Fig. 6b)* shows a negative band at 233 nm and a positive band at 214 nm in isooctane as well as in methanol, with little solvent dependence. The size of the *Cotton* effect at 233 nm is roughly seven times that of the molecule without the Br-atom as observed in isooctane at room temperatue. The molar extinction is much higher, too, and the transition leading to the 233 nm CD. band consequently is no longer identical to the

transition observed in the unsubstituted compound. The drastic changes in the optical and chiroptical properties, and in their solvent dependence, upon bromination therefore indirectly support the assumption of a single, only slightly perturbed carboxyl n,π^*-transition in indane-1-carboxylic acid and its ester.

We are indebted to Dr. *K. Noack*, Central Research Units, *F. Hoffmann–La Roche*, Basle, for his patience in measuring the CD. spectra which provided the key to the interpretation of the solvent dependance we had observed for the ORD. data of **14**. We thank Mr. *F. Nydegger* and Dipl. Chem. *W. Bernhard*, Institute of Organic Chemistry of the University of Fribourg for elemental analyses and mass spectra, respectively, and the *Chemische Werke Hüls AG*, Marl, for a gift of 3-phenylbutyric acid.

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Experimental Part

General Remarks. See [5]. Polarimetric measurements (c=g/ml) were performed with a *Perkin-Elmer* polarimeter, model 241 MC; optical purity=p. Determination of enantiomeric purity (e) by ^{1}H-NMR. using Eu(hfc)$_3$ (=tris-[3-(heptafluoropropyl-hydroxy-methylene)-d-camphorato]-europium, *Aldrich*) as shift reagent. All substances were characterized by their IR.-, ^{1}H-NMR.-, and mass spectra (MS.). Chemical purities were also determined by gas chromatography (GC.).

1. *Preparation of (+)-*(R)*-indane-1-carboxylic acid* ((+)-**1**) *from (–)-*(R)*-2-phenylsuccinic acid* ((–)-**3**). – 1.1. *Preparation of (–)-*(R)*-2-phenylsuccinic acid* ((–)-**3**). The racemic acid *(Fluka AG)* was resolved *via* its brucine salt [9] [10]. Decomposition of the salt with diluted HCl-solution afforded (–)-*(R)*-**3**. $[\alpha]_{589}^{25}=-79.2°$ (c=0.0483, acetone; $[\alpha]_{589}^{25}=+171.1°$, c=0.02, acetone [23], *i. e.* p=0,46).

1.2. *Preparation of (–)-*(R)*-indane-3-one-1-carboxylic acid* ((–)-**2**). To 7.5 g (0.039 mol) (–)-**3** [24] 18 ml fluorosulfonic acid was carefully added. After stirring for 1 h at 50° and for an additional h at 20° the mixture was poured to 50 ml ice/water. Extraction with ether gave 6.5 g of a yellow viscous oil which crystallized after 5 days at 5°. Recrystallization from hexane/benzene 1:1 afforded 4.1 g (60%) of (–)-**2**; m. p. 96–99° (m. p. of (±)-**2**: 75–78° [7] and 120° [8]), $[\alpha]_{589}^{25}=-13.5°$ (c=0.08, acetone).

1.3. *Preparation of (–)-*(R)*-Methyl indane-3-one-1-carboxylate.* After treating 0.35 g of (–)-**2** with an excess of diazomethane (*cf.* [25]) in ether at 0°, distillation gave 6,3 g (80%) (–)-methyl ester of **2**, m. p. 34,5–35° (m. p. of the racemic ester: 35–38° [7]). – $[\alpha]_{589}^{25}=-1.9°$ (c=0.05, acetone), $[\alpha]_{589}^{25}=-3.8°$ (c=0.059, benzene). – ^{1}H-NMR. ($CDCl_3$): 8.9–7.3 (*m*, 4H); 4.32 ($d\times d$, 1H, J_{vic}=4.1 und 7.8, H–C(1)); 3.80 (*s*, 3H, OCH_3); 3.18 ($d\times d$, 1H, J_{vic}=4.1, J_{gem}=18.9, H–C(2)); 2.85 ($d\times d$, 1H, J_{vic}=7.8, J_{gem}=18.9, H–C(2)). In the presence of Eu(hfc)$_3$ in $CDCl_3$ 2 signals for $COOCH_3$ were observed; e=0.106±0.005, *i. e.* cyclization of **3** to **2** had occured with 77% racemization.

1.4. *Preparation of (+)-*(R)*-indane-1-carboxylic acid* ((+)-**1**). According to *Fredga* [1] (*cf.* [7] [8]) 3.53 g (0.02 mol) of (–)-**2** were reduced with amalgamated zinc in diluted HCl-solution at RT. for 7 h. An orange-red oil was obtained which was thoroughly extracted with petrol ether (b. p. 60–80°). Purification of the extract on TLC. (silica gel; benzene/methanol/acetic acid 11.2:2:1) [26] and sublimation (90°/12 Torr) led to 78 mg (2.4%) of (±)-**1**. Further extraction of the orange-red oil gave after TLC. and sublimation 130 mg (3.5%) of (+)-**1**, $[\alpha]_{589}^{25}=4.8°$ (c=0.078, benzene) ([1]; $[\alpha]_{589}^{25}=+43.3°$, c=0.026, benzene, *i. e.* p=0.11).

1.5. *Preparation of (–)-*(R)*-methyl indane-1-carboxylate(–)-***14**). Esterification of 0.12 g (+)-**1** (p=0.11) with diazomethane yielded 0.11 g (88%) of (–)-*(R)*-**14**, $[\alpha]_{350}^{25}=+2.2°$ (c=0.023, benzene; e=0.12, ^{1}H-NMR. with Eu(hfc)$_3$), $[\alpha]_{365}^{25}=-2.0$ (c=0.025, isooctane). GC., IR., NMR., and MS. were identical with the data of an authentic sample of (±)-**14**. The ester showed with Eu(hfc)$_3$ in CCL_4 (e=0.12±0.01, *i. e.*: racemization must have occurred also in the reduction step) the same enantiomeric shift of the ester methyl group as the enantiomeric pure ester (–)-**14** (see 3.2).

2. *Preparation of the chloride of (–)-*(R)*-phenylsuccinic acid(–)-***3**) *and its hydrolysis.* Treatment of 1.0 g (5.2 mmol) of (–)-**3** (p=0.46) with an excess of thionyl chloride under reflux according to [1] and distillation in a "Kugelrohr" (120/0.03 Torr) provided 0.67 g (57%) colorless crystals, $[\alpha]_{589}^{25}=-18.4°$ (c=0.022, $CHCl_3$). Hydrolysis of this acid chloride with an aqueous 3% NaOH-solution led after usual workup to (–)-**3**, $[\alpha]_{589}^{25}=-68.8°$ (c=0.042, acetone; p=0.40), *i. e.* 13% racemization had occurred.

3. *Preparation of (+)-*(R)*-1-([$^2H_3$]methyl)indane* ((+)-*(R)*-[1'-$^2H_3$]-**4**).

3.1. *Preparation of (+)-indane-1-carboxylic acid* ((+)-**1**). Indene-1-carboxylic acid [27] was hydrogenated in ethanol in the presence of 10% Pd/C at 3.4 atm for 8 h [28]. Recrystallization of the crude material gave (±)-**1**; m. p. 55–55.8° (55–56°, 56.5–57° [29]). The salt of (±)-**1** with (+)-α-phenylethylamine [28] was recrystallized 9 times from benzene/ethanol 1:4 and provided after decomposition of the salt with diluted sulfuric acid and recrystallization of the acid (hexane) pure (+)-**1**; m. p. 45.4° (44–45° [28]), $[\alpha]_{589}^{25} = +43.6°$ ($c = 0.024$, benzene) ([28]: 43.6° (cf. [1]), *i. e.* p = 1,0); $[\alpha]_{589}^{25} = +40.2°$ ($c = 0.023$, isooctane ([1]: 40.7°)).

ORD.[a] nm	$[\alpha]^{25}$ $c = 0.024$ benzene	$[\alpha]^{25}$ $c = 0.023$ isooctane	ORD.[a] nm	$[\alpha]^{25}$ $c = 0.024$ benzene	$[\alpha]^{25}$ $c = 0.023$ isooctane
650		+31.8°	400	+128.7°	+113.0°
600	+41.5°	+38.4°	350	+204.7°	+173.9°
589	+43.6°	+40.2°	334		+206.1°
550	+51.7°	+47.7°	302		+315.1°
500	+66.7°	+60.5°	289		+395.4°
450	+89.7°	+80.3°			

[a] For ORD. in methanol see [30].

3.2. *Preparation of (–)-*(R)*-methyl indane-1-carboxylate* ((-)-**14**). Esterification of (+)-**1** (p = 1.0) with diazomethane in ether gave after distillation in a "Kugelrohr" (50°/0.04 Torr) pure (–)-**14**; m. p. 27–27.2° ([28]: 27–28°, [31]: 26–27°). – $\alpha_{589}^{35} = -1.4°$ (neat); $[\alpha]_{589}^{25} = +1.1°$ ($c = 0.038$, benzene); $[\alpha]_{589}^{25} = -5.2°$ ($c = 0.027$, isooctane); $[\alpha]_{589}^{25} = 0.0°$ ($c = 0.0128$, CCl_4) ([31]: $[\alpha]_{589}^{25} = -2.11°$ (c = 0.0265, ethanol)).

ORD.[a] nm	α^{35} neat	$[\alpha]^{25}$ $c = 0.038$ benzene	$[\alpha]^{25}$ $c = 0.027$ isooctane	$[\alpha]^{25}$ $c = 0.0128$ CCl_4	ORD.[a] nm	α^{35} neat	$[\alpha]^{25}$ $c = 0.038$ benzene	$[\alpha]^{25}$ $c = 0.027$ isooctane	$[\alpha]^{25}$ $c = 0.0128$ CCl_4
650	−1.6	+0.3	−4.1	0.0	400	+ 4.6	+ 9.2	−12.7	+ 3.9
600	−1.5	+0.9	−5.0	0.0	350	+14.1	+19.4	−19.8	+ 9.4
589	−1.4	+1.1	−5.2	0.0	334	+19.9	+24.9	−23.9	+11.7
550	−1.2	+1.6	−6.0	0.0	313				+12.5
500	−0.6	+2.6	−7.5	0.0	302	+41.0	+42.5	−41.7	+ 9.4
476	0.0				297		+46.2		+ 6.3
450	+0.9	+5.0	−9.3	+0.8	289			−55.9	− 4.7

[a] See *Fig. 3*.

^{1}H-NMR. (CCl_4): 7.4–6.95 (*m*, 4H); 3.93 (*d* × *d*, 1H, $J_{vic} = 6.3$ and 7.8, H–C(1)); 3.65 (*s*, 3H, OCH_3); 3.3–2.7 (*m*, 2H, 2H–C(3)); 2.65–2.1 (*m*, 2H–C(2)). – ^{1}H-NMR. (C_6D_6): 7.5–7.3 (*m*, 1H, H–C(7)); 7.15–7.03 (*m*, 3H, H–C(4), H–C(5) and H–C(6)); 3.83 (*d* × *d*, *J* = 7.2, 1H, H–C(1)); 3.33 (*s*, 3H, OCH_3); 3.13–2.17 (*m*, 3H, 2H–C(3) and 1H-C(2)); 2.17–1.7 (m, 1H, 1H–C(2)).

3.3 *Preparation of (+)-*(R)*-1-indanyl([1,1-$^2H_2$]methanol* (+)-**7**). This compound was prepared from (+)-**1** (p = 1.0) with $LiALD_4$ in ether (*cf.* [2]). Distillation of the crude product (131°/15 Torr) afforded pure (+)-**7** as a colorless liquid, $\alpha_{589}^{25} = +27.3°$ (neat). – ORD. (neat, 25°, nm in parentheses): 20.4° (650), 25.8° (600), 34.0° (550), 46.9° (500), 68.7° (450), 110.4° (400), 205.6° (350), 262.8° (334), 385.9° (313). – IR. (film): 2190, 2090 (C–D).

3.4. *Preparation of (–)-*(R)*-1-indanyl-([1,1-$^2H_2$]methyl)bromide* ((–)-**8**). To 2.6 g (17.3 mmol) (+)-**7** in 5 ml benzene 1.6 g phosphorus tribromide was added dropwise at 0°. The reaction mixture was stirred overnight at RT. and then for 2 h at 80°. Ice/water was added and the organic layer extracted with ether. After evaporation of the ether the residue was distilled in a "Kugelrohr" (60°/0.05 Torr.) and 1.72 g (47%) (–)-**8** were obtained as a colorless liquid. Purification over *Alox* (hexane) gave the bromide (GC. purity 94%) with $\alpha^{25}_{589} = -53.7°$ (neat). – ORD. (neat, 25°, nm in parentheses): –43.9° (650), –51.7° (600), –61.7° (550), –74.8° (500), –91.6° (450), –113.2° (400), –131,9° (350). – IR. (film): 2160 (C–D).

3.5. *Preparation of* (R)*-1-indanyl([1,1-$^2H_2$]methyl) methanesulfonate* (*(R)*-**9**). According to the *Cross-land* method [32] 1.59 g (11 mmol) methanesulfonyl chloride was added dropwise to a solution of 1.5 g (10 mmol) (+)-**7** and 1.52 g triethylamine at –12°. This mixture was stirred for 2 h at –5° and 1 h at RT. Workup and drying under reduced pressure (0.05 Torr) for 4 h at RT. led to *(R)*-**9** in quantitative yield.

3.6. *Preparation of (+)-*(R)*-1-([$^2H_3$]methyl)indane* ((+)-*(R)*-[1'-$^2H_3$]-**4**) *from* (–)-**8**. Reduction of 1.06 g (5 mmol) (+)-**8** with 0.23 g $LiAlD_4$ in ether in the presence of catalytic amounts of $CoCl_2$ [33] occurred by refluxing this mixture for 6 h. Usual workup and purification by preparative TLC. (hexane/ether 1:1) and GC. gave 70 mg (10%) (+)-[1'-$^2H_3$]-**4**; isotopic purity ≥91% (NMR.). ORD., IR.-, NMR.-, and MS. were identical with that of the sample described under 3.7.

3.7. *Preparation of (+)-*(R)*-1-([$^2H_3$]methyl)indane* ((+)-[1'-$^2H_3$]-**4** *from* (R)-**9**. After dissolving 2.4 g (10.2 mmol) freshly prepared *(R)*-**9** (see 3.5) in THF under N_2 21.4 ml of a *ca.* 1M "Super-Deuteride" in THF *(Aldrich)* was added by using a syringe [34]. After stirring for 15 min at RT. the solution was refluxed for 4 h and again stirred at RT. overnight. Workup according to [34] led to crude (+)-[1'-$^2H_3$]-**4**. Purification over *Alox* (act. III) and distillation ("Kugelrohr", 80°/15 Torr.) afforded 0.98 g (72%) pure (+)-[1'-$^2H_3$]-**4**; isotopic purity ≥97% (NMR.). – $\alpha^{25}_{589} = +13.4°$ (neat); $[\alpha]^{25}_{589} = +13.0°$ ($c = 0.022$, benzene); $[\alpha]^{25}_{589} = +0.5°$ ($c = 0.021$, isooctane).

ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ $c = 0.022$ benzene	$[\alpha]^{25}$ $c = 0.021$ isooctane	ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ $c = 0.022$ benzene	$[\alpha]^{25}$ $c = 0.021$ isooctane
650	+ 9.8	+ 9.0	– 0.2	350	+114.3	+117.8	+ 56.7
600	+12.6	+12.1	+ 0.3	334		+154.2	+ 79.9
550	+17.0	+16.6	+ 1.6	313		+231.0	+131.3
500	+24.0	+23.4	+ 4.1	302		+296.6	+177.8
450	+36.3	+35.9	+ 9.7	297		+333.5	
400	+60.4	+60.2	+22.3				

[a]) See *Fig. 7d.*

IR. (film): 2220, 2120, 2070 (C–D). – ^{1}H-NMR. (CCl_4): 7.03 (*s*, 4H); 3.1 (br. *t*, 1H); 2.95–2.7 (*m*, 2H, 2H–C(3)); 2.4–2.05 (*m*, 1H, H–C(2)); 1.8–1.4 (*m*, 1H, H–C(2)).

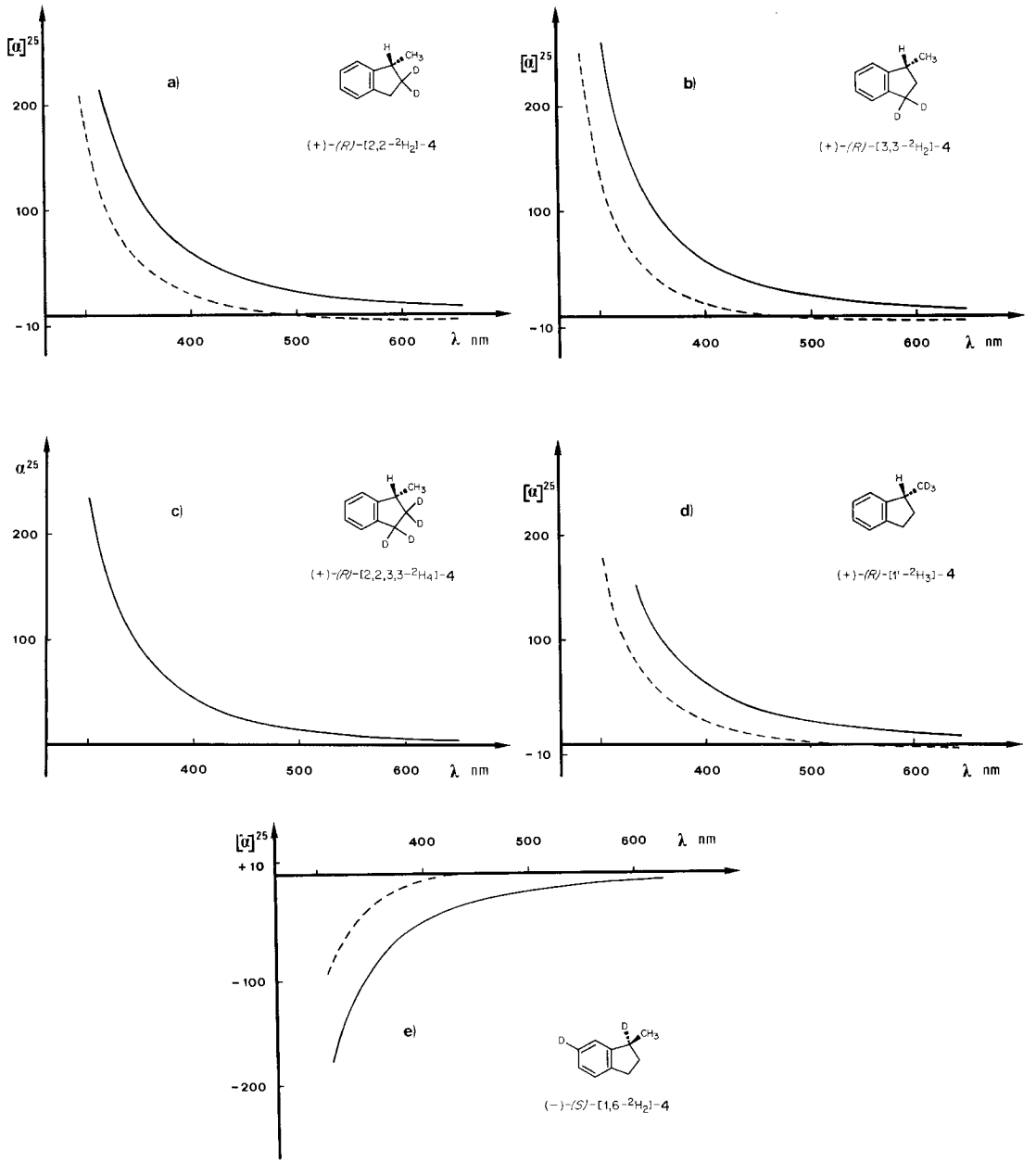

Fig. 7a–e. *ORD. of deuteriated 1-methylindanes,* neat (——), isooctane (– – – –)

4. *Preparation of (–)-*(S)*-1-methyl[1-*^{2}*H]indane* ((–)-*(S)*-[1-^{2}H]-**4**. – 4.1. *Preparation of (–)-*(S)*-[1-*^{2}*H] indane-1-carboxylic acid* ((–)-[1-^{2}H]-**1**). The sodium salt of (±)-**1** was deuteriated with D_2O in dimethoxyethane at 85–90°. The exchange was several times repeated with fresh D_2O. The acid was isolated and showed in the ^{1}H-NMR. a deuterium incorporation of ≥96% at C(1). Resolution with (–)-α-phenylethylamine (5 recrystallizations of the salt; *cf.* 3.1) gave pure (–)-[1-^{2}H]-**1**, m. p. 45.2°. – $[\alpha]_{589}^{25} = -41.6°$

(c=0.024, benzene). – ORD. (c=0.024, benzene, nm in parentheses): –33.1° (650), –39.9° (600), –49.7° (550), –64.2° (500), –85.8° (450), –122.8° (400), –195.0° (350), –234.1° (334), –371.7° (302), –466.5° (289). IR. (film): 2140 (C–D) – ^{1}H-NMR. ($(CD_3)_2CO$): 7.45–7.0 (*m*, 4H); 3.3–2.6 (*m*, 2H, 2H–C(3)); 2.6–2.1 (*m*, 2H, 2H–C(2)).

4.2. *Preparation of (+)-(S)-methyl [1-^{2}H]indane-1-carboxylate* ((+)-[1-^{2}H]-**14**). As described under 3.2; m. p.: 26.4°–26.8°. – $\alpha_{589}^{25} = +1.6°$ (neat); $[\alpha]_{589}^{25} = -1.1°$ (c=0.026, benzene); $[\alpha]_{589}^{25} = +5.2°$ (c=0.029, isooctane); $[\alpha]_{589}^{25} = 0.0°$ (c=0.010, methanol).

ORD. nm	α^{35} neat	$[\alpha]^{25}$ c=0.026 benzene	$[\alpha]^{25}$ c=0.029 isooctane	$[\alpha]^{25}$ c=0.010 methanol	ORD. nm	α^{35} neat	$[\alpha]^{25}$ c=0.026 benzene	$[\alpha]^{25}$ c=0.029 isooctane	$[\alpha]^{25}$ c=0.010 methanol
699				–1.0	400	– 3.8	–11.1	+12.8	– 5.0
650	+1.7	–0.4	+4.1		365				– 11.0
600	+1.6	–1.2	+4.8		350	–12.4	–21.9	+21.0	
550	+1.4	–1.9	+5.9		334	–18.0	–28.0	+25.9	
546				–1.0	302	–37.7	–49.1	+43.5	
500	+0.9	–3.5	+7.2		297	–42.9	–53.3		
463	0.0				289			+57.9	
450	–0.5	–5.8	+9.3		279				–172.0
436				–2.0					

4.3. *Preparation of (–)-(S)-(1-[1-^{2}H]indanyl)methanol* ((–)-[1′-^{2}H]-**7**). Reduction of (–)-[1-^{2}H]-**1** with $LiAlH_4$ was performed as described (3.3) and afforded after distillation ("Kugelrohr", 60°/0.05 Torr) pure (–)-[1′-^{2}H]-**7**. – $\alpha_{589}^{25} = -24.4°$ (neat). – ORD. (neat, 25°, nm in parentheses): –18.1 (650), –23.0 (600), –30.5 (550), –42.5 (500), –63.0 (450), –102.3 (400), –192.8 (350), –248.4 (334), –367.0 (313), –465.6 (302), –518.4 (297). IR. (film): 2190–2110 (C–D). – ^{1}H-NMR. (CCl_4): 7.0 (*s*, 4H); 3.7–3.4 (br. *s*, 3H, $-CH_2OH$); 2.8 (*t*, 2H, 2H–C(3)); 2.4–1.6 (*m*, 2H, 2H–C(2)).

4.4 *Preparation of* (S)-*(1-[1-^{2}H]indanyl)methyl methanesulfonate* (*(S)*-[1′-^{2}H]-**9**). Following the procedure described under 3.5 [1-^{2}H]-**9** was obtained and immediately reduced.

4.5. *Preparation of (–)-*(S)*-1-methyl[1-^{2}H]indane* ((–)-*(S)*-[1-^{2}H]-**4**). After dissolving 2.3 g (9.77 mmol)) of [1-^{2}H]-**9** under N_2 in THF 20.5 ml of *ca.* 1M "Super-Hydride" in THF *(Aldrich)* was added. After work-up (3.6.2) 0.9 g (70%) pure (–)-[1-^{2}H]-**4** was obtained with an isotopic purity ≥94% (NMR.). – $\alpha_{589}^{25} = -10.6°$ (neat); $[\alpha]_{589}^{25} = +2.3°$ (c=0.022, isooctane); $[\alpha]_{589}^{25} = -10.1°$ (c=0.022, benzene).

ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ c=0.022 benzene	$[\alpha]^{25}$ c=0.022 isooctane	ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ c=0.022 benzene	$[\alpha]^{25}$ c=0.022 isooctane
650	– 7.5	– 6.4	+ 2.8	350	–104.7	–103.2	– 43.7
600	– 9.9	– 9.2	+ 2.5	334	–137.6	–135.7	– 63.7
550	–13.6	–12.8	+ 1.6	313	–209.0	–207.2	–110.7
505			0.0	302	–271.6	–269.6	–154.9
500	–19.7	–19.3		297	–309.4	–312.2	–186.0
450	–30.6	–29.8	– 4.5	289			–248.4
400	–52.4	–51.4	–14.9				

[a]) See *Fig. 2*.

IR. (film): 2130, 2120 (C–D). – ^{1}H-NMR. (CCl_4): 7.03 (*s*, 4H); 2.95–2.7 (*m*, 2H, 2H–C(3)); 2.45–2.1 (*m*, 1H, 1H–C(2)); 1.8–1.4 (*m*, 1H, 1H–C(2)); 1.27 (*s*, 3H, CH_3–C(1)).

5. *ORD. and CD. Data of (+)-*(R)*-1-methylindane* ((+)-**4**). Prepared in [5].

ORD.[a] nm	α^{25} neat	$[\alpha]^{25}$ [b] neat	$[\alpha]^{25}$ $c=0.014$ benzene	$[\alpha]^{25}$ $c=0.019$ isooctane	ORD.[a] nm	α^{25} neat	$[\alpha]^{25}$ [b] neat	$[\alpha]^{25}$ $c=0.014$ benzene	$[\alpha]^{25}$ $c=0.019$ isooctane
650	+ 7.86	+ 8.38	+ 7.1	−3.2	480	+ 24.20	+ 25.79		
625	+ 8.99	+ 9.58			475				+ 1.1
600	+10.36	+11.04		−2.9	460	+ 28.91	+ 30.81		
589	+11.06	+11.79	+ 9.9	−2.6	450			+ 30.0	+ 3.7
580	+11.69	+12.46			440	+ 34.93	+ 37.22		
579	+11.75	+12.52			436	+ 36.42	+ 38.81		
550			+12.9	−2.1	420	+ 43.05	+ 45.88		
546	+14.59	+15.55			400	+ 54.00	+ 57.54	+ 51.9	+ 13.7
540	+15.24	+16.24			380	+ 69.59	+ 74.16		
520	+17.58	+18.73			350	+107.48	+114.54	+106.6	+ 43.7
500	+20.53	+21.88	+18.5	−0.5	297			+308.5	+177.4
490				0.0					

[a]) See *Fig. 1.* [b]) d_4^{25}: 0.9384 [35].

CD.: *cf.* [36] [37].

6. *Preparation of (+)-*(R)*-1-methyl[2,2-$^2H_2$]*indane ((+)-*(R)*-[2,2-$^2H_2$]-**4**). – 6.1. *Preparation of (−)-*(R)*-3-methyl-1-[2,2-$^2H_2$]indanone* ((−)-*(R)*-[2,2-$^2H_2$]-**6**). (−)-*(R)*-3-Methyl-1-indanone (p = 1,0 [5]) was treated two times with D_2O in dimethoxyethane in the presence of anhydrous K_2CO_3 following the procedure of *Almy & Cram* [38]. After distillation (52°/0.03 Torr) (−)-[2,2-$^2H_2$]-**6** was obtained in 84% yield and with an isotopic purity of ≥97% (NMR.). – $\alpha_{589}^{25} = -4.2°$ (neat).

6.2. *Reduction of (−)-[2,2-$^2H_2$]-**6** to (+)-[2,2-$^2H_2$]-**4**.* A mixture of 0.8 g (5.4 mmol) of the deuteriated ketone (−)-[2,2-$^2H_2$]-**6** and 0.72 g (5.4 mmol) anhydrous $AlCl_3$ was treated (2.5 h) with a mixture of 0.26 g (6.75 mmol) $LiAlH_4$ and 0.9 g (6.75 mmol) anhydrous $AlCl_3$ in boiling ether (*cf.* method 3 in [39]; see also [40]). The crude (+)-[2,2-$^2H_2$]-**4** was contaminated with about 20% of deuteriated 1-methylindene. Chromatography with hexane on silica gel + 5% $AgNO_3$ and distillation (65°/15 Torr) gave 0.54 g (75%) pure (+)-[2,2-$^2H_2$]-**4** with an isotopic purity of ≥95% (NMR.). – $\alpha_{589}^{25} = +12.5°$ (neat); $[\alpha]_{589}^{25} = +11.9°$ ($c=0.02$, benzene); $[\alpha]_{589}^{25} = -1.0°$ ($c=0.02$, isooctane). – IR. (film): 2215, 2120, 2160 (C–D).

ORD.[a] nm	α^{25} neat	$[\alpha]^{25}$ $c=0.02$ benzene	$[\alpha]^{25}$ $c=0.02$ isooctane	ORD.[a] nm	α^{25} neat	$[\alpha]^{25}$ $c=0.02$ benzene	$[\alpha]^{25}$ $c=0.02$ isooctane
650	+ 9.0	+ 8.4	− 1.4	350	+114.5	+116.8	+ 51.2
600	+11.7	+11.4	− 1.0	334	+149.9	+154.0	+ 73.2
550	+15.9	+15.3	− 0.1	313	+226.4	+231.7	+124.6
547			0.0	302	+293.9	+300.5	+171.1
500	+22.8	+21.8	+ 1.9	297	+340.4	+347.5	+204.7
450	+34.7	+34.2	+ 7.1	289		+420.3	+270.6
400	+58.4	+58.4	+18.4				

[a]) See *Fig. 7a.*

^{1}H-NMR. (CCl_4): 7.05 (*m*, 4H); 3.11 (*qa*, $J=6.9$, 1H, H–C(1)); 2.81 (*s*, 2H, 2H–C(3)); 1.26 (*d*, $J=6.9$, 3H, CH_3–C(1)).

7. *Preparation of (+)-*(R)*-1-methyl[2,2,3,3-$^2H_4$]indane* ((+)-*(R)*-[2,2,3,3-$^2H_4$]-**4**). *Clemmensen* reduction of 1.6 g (1.08 mmol) (−)-[2,2-$^2H_2$]-**6** (see 6.1) with 13 g amalgamated zinc and 36 ml conc. deuterium chloride in D_2O (three 12 ml portions) in 75 ml benzene yielded, after 50 h reflux and chromatography on silica gel +5% $AgNO_3$ with hexane, 0.82 g (56%) (+)-[2,2,3,3-$^2H_4$]-**4** with an isotopic purity of ≥96% at C(2) and ≥90% at C(3) (NMR.). – $\alpha_{589}^{25} = +8.3°$ (neat). – IR. (film): 2220, 2150, 2140, 2105, (C–D). –

^{1}H-NMR. (CCl_4): 6.95 (*s*, 4H); 3.14 (br. *qa*, J=7, 1H, H–C(1)); 1.29 (*d*, J=7, 3H, CH_3–C(1)). – ORD. (neat, 25°, nm in parentheses) (see *Fig. 7c*): 5.7 (650), 7.7 (600), 10.9 (550), 16.2 (500), 25.8 (450), 45.4 (400), 92.7 (350), 122.5 (334), 239.7 (302).

8. *Preparation of (+)-(*R*)-1-methyl[3,3-$^2H_2$]indane* ((+)-*(R)*-[3,3-$^2H_2$]-**4**). Treatment of 1.46 g (10.0 mmol) (–)-*(R)*-3-Methyl-1-indanone (p = 1.0 [5]) with $LiAlD_4/AlCl_3$ as described in section 6.2 (*cf.* [41]) and purification over silica gel + 10% $AgNO_3$ with hexane yielded 0.99 (67%) pure (+)-[3,3-$^2H_2$]-**3** with an isotopic purity of ≥96% (NMR.). – $\alpha^{25}_{589} = +11.0$ (neat); $[\alpha]^{25}_{589} = +8.6°$ (c=0.021, benzene); $[\alpha]^{25}_{589} = -1.5°$ (c=0.02, isooctane). – IR. (film): 2200, 2130, 2095 (C–D).

ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ c=0.021 benzene	$[\alpha]^{25}$ c=0.02 isooctane	ORD.[a]) nm	α^{25} neat	$[\alpha]^{25}$ c=0.021 benzene	$[\alpha]^{25}$ c=0.02 isooctane
650	+ 7.8	+ 6.0	– 2.0	334	+138.5	+120.6	+ 56.6
600	+ 10.3	+ 8.1	– 1.7	313		+184.5	+ 97.0
550	+ 14.1	+11.0	– 1.0	302	+274.0	+237.4	+134.5
504			0.0	297	+317.8	+274.1	+161.1
500	+ 20.3	+16.3	+ 0.2	289			+208.4
450	+ 31.2	+25.9	+ 3.9	280			+275.9
400	+ 53.2	+45.0	+12.8				
350	+105.5	+91.2	+38.4				

[a]) See *Fig. 7b.*

^{1}H-NMR. (CCl_4): 7.03 (*s*, 4H); 3.10 (*sextet*, J~7.2, 1H, H–C(1)); 2.4–2.1 (*m*, 1H, H–C(2)); 1.7–1.35 (*m*, 1H, H–C(2)); 1.27 (*d*, J=7.2, 3H, CH_3–C(1)).

9. *Preparation of (–)-(*S*)-1-methyl[1,6-$^2H_2$]indane* ((–)-*S*-[1,6-$^2H_2$]-**4**. – 9.1. *Preparation of (+)-*(S)*-bromo[1-^{2}H]indane-1-carboxylic acid* ((+)-*(S)*-[1-^{2}H]-**10**). To a suspension of 38.5 g (0.236 mol) of (±)-[1-^{2}H]-**1** (see 4.1) in 1000 ml water, 37.7 g (0,236 mol) bromine was added dropwise at 60° within 1 h, and stirring continued for another 2 h [14]. After filtration the residue was twice recrystallized from CCl_4 (140 ml): 20.4 g colorless crystals. The filtrated solution was extracted with ether and the extract combined with the mother liquors of the recrystallization. Solvent evaporation and sublimation of the residue (150°/180 Torr) gave 10.7 g [1-^{2}H]-**10**; total yield: 31.3 g (54%); m. p. 141–142°. Isotopic purity 90% (NMR.). Resolution with (+)-α-phenylethylamine (5 recrystallization of the salt; (*cf.* 3.1 and 4.1)) afforded 3.1 g (+)-[1-^{2}H]-**10**, isotopic purity 84% (NMR.), m. p.: 140.4–140.8° – $[\alpha]^{25}_{589} = +65.5°$ (c=0.013, benzene), p = 1.0 (see 9.2). – ^{1}H-NMR. (CCl_4): 7.53 (*d*, J_m=1.8, 1H, H–C(7)); 7.33 (*d* × *d*, J_m=1.8, 1H, H–C(5)); 7.13 (*d*, J_o=8, 1H, H–C(4)); 4.07 (br. *s*, OH); 3.1–2.8 (*m*, 2H, 2H–C(2)); 2.33 (*t*, J=7.1, 2H, 2H–C(3)).

9.2. *Preparation of (+)-(*S*)-methyl 6-bromo[1-^{2}H]indane-1-carboxylate* ((+)-*(S)*-[1-^{2}H]-**15**). Preparation as described under 3.2. Distillation in a "Kugelrohr" (100°/0.06 Torr) gave pure (+)-[1-^{2}H]-**15**; m. p.: 63.0–63.8°. – $[\alpha]^{25}_{589} = +89.5°$ (c=0.016, benzene), p = 1.0 (checked by determination of e with Eu(hfc)$_3$ in 1,1,2-trichlorofluoromethane by ^{1}H-NMR.). – $[\alpha]^{25}_{589} = +69.9°$ (c=0.015, isooctane). – IR. (KBr): 2140 (C–D).

ORD.[a]) nm	$[\alpha]^{25}$ c=0.016 benzene	$[\alpha]^{25}$ c=0.015 isooctane	ORD.[a]) nm	$[\alpha]^{25}$ c=0.016 benzene	$[\alpha]^{25}$ c=0.015 isooctane
650	+ 71.6	+ 57.3	450	+172.5	+138.3
600	+ 86.0	+ 67.9	436	+187.5	+150.8
589	+ 89.5	+ 71.0	400	+237.2	+191.9
579	+ 94.7	+ 74.1	365	+316.1	+254.2
550	+104.1	+ 83.5	350	+356.7	+289.7
546	+106.6	+ 84.7	334	+424.7	+345.2
500	+131.3	+105.3			

[a]) See *Fig. 6a.*

9.3. *Preparation of (–)-(S)-{1-(6-Bromo-[1-^{2}H]indanyl)}methanol* ((–)-*(S)*-[1-^{2}H]-**11**). Reduction of (+)-[1-^{2}H]-**10** with $LiAlH_4$ was performed as described (3.3 and 4.3) and afforded after distillation ("Kugelrohr", 130°/0.01 Torr) pure (–)-[1-^{2}H]-**11**. – $\alpha_{589}^{40} = -6.4°$ (neat). – ORD. (neat, 40°, nm in parentheses): –3.7° (650), –5.7° (600), –9.4° (550), –16.2° (500), –29.1° (450), –57.1° (400), –131.6° (350), –183.1° (334). – IR. (film): 2140 (C–D). – ^{1}H-NMR. (CCl_4): 7.37 (*s*, 1H, H–C(7)); 7.2–6.9 (*m*, 2H, H–C(5) and H–C(4)); 3.63 (*s*, 2H, CH_2OH); 3.27 (*s*, 1H, O*H*); 2.87 (*t*, 2H, 2H–C(3)); 2.4–1.6 (*m*, 2H, 2H–C(2)).

9.4. *Preparation of* (S)-{*1'-(6-bromo[1-^{2}H]indanyl)}methyl methanesulfonate* (*(S)*-[1-^{2}H]-**12**). Following the procedure described under 3.5 *(S)*-[1-^{2}H]-**12** was obtained and immediately reduced.

9.5. *Preparation of (+)-(S)-6-bromo-1-methyl[1-^{2}H]indane* ((+)-*(S)*-[1-^{2}H]-**13**). Reduction of 2.57 g *(S)*-[1-^{2}H]-**12** with "Super-Hydride" following the procedure described under 4.5 afforded after workup (3.7) and distillation ("Kugelrohr", 130°/10 Torr.) 1.68 g (95%) (+)-[1-^{2}H]-**13** with an isotopic purity = 80% (NMR). – $\alpha_{589}^{25} = +2.9°$ (neat); $[\alpha]_{589}^{25} = +9.4°$ (*c* = 0.014, benzene); $[\alpha]_{589}^{25} = +17.8°$ (*c* = 0.014, isooctane).

ORD. nm	α^{25}	$[\alpha]^{25}$ *c* = 0.014 benzene	$[\alpha]^{25}$ *c* = 0.014 isooctane	ORD. nm	α^{25}	$[\alpha]^{25}$ *c* = 0.014 benzene	$[\alpha]^{25}$ *c* = 0.014 isooctane
650	+3.6	+ 8.8	+14.8	400	– 27.2	+ 2.8	+27.4
600	+3.1	+ 9.1	+17.0	390		0.0	+26.7
589	+2.9	+ 9.4	+17.8	380	– 41.9		+26.3
550	+1.7	+ 9.8	+19.6	370		– 8.1	
519	0.0			360	– 65.3		+22.4
500	–1.5	+10.1	+23.2	350	– 80.8	– 22.1	+17.4
450	–8.9	+ 9.1	+25.9	334	–122.1	– 41.1	+ 5.6
440			+27.1	313		– 92.3	–31.4
410			+28.2	302		–146.0	–78.0

IR. (film): 2120 (C–D). – ^{1}H-NMR. (CCl_4): 7.17 (*d* × *d*, J_m2, 2H, H–C(5) and H–C(7)); 6.93 (*d*, J_o = 8, 1H, H–C(4); 2.77 (*m*, 2H, 2H–C(3)); 2.45–2.0 (*m*, 1H, H–C(2)); 1.8–1.3 (*m*, 1H, H–C(2)); 1.23 (*s*, 3H, CH_3).

9.6. *Preparation of (–)-(S)-1-methyl[1,6-$^2H_2$]indane* ((–)-*(S)*-[1,6-$^2H_2$]-**4**). After agitating 0.19 g (7.68 mmol) magnesium turnings with a teflon stirrer under heating in an oxygen free N_2 atmosphere for 24 h, a few ml of a solution of 1.55 g (7.68 mmol) (+)-[1-^{2}H]-**13** in 10 ml ether was added at RT. under continuous stirring. After refluxing for 1 min the reaction started and the bromide solution was slowly added at RT. After refluxing for 2 h the cooled (–15°) mixture was quenched with 4 ml D_2O. Usual workup gave after distillation ("Kugelrohr", 70°/10 Torr) 0.62 g (60%) of pure (–)-[1,6-$^2H_2$]-**4** with an isotopic purity of 80% at C(1) and 92% at C(6) (NMR.). – $\alpha_{589}^{25} = -8.2°$ (neat); $[\alpha]_{589}^{25} = -7.8°$ (*c* = 0.015, benzene); $[\alpha]_{589}^{25} = +4.1°$ (*c* = 0.015, isooctane). – IR. (film): 2265, 2115 (C–D). – ^{1}H-NMR. (CCl_4): 7.03 (*s*, 3H, H–C(4), H–C(5) and H–C(7)); 2.83 (*m*, 2H, 2H–C(3)); 2.45–2.0 (*m*, 1H, H–C(2)); 1.8–1.3 (*m*, 1H, H–C(2)); 1.27 (*s*, 3H, H_3C–C(1)).

ORD.[a] nm	α^{25}	$[\alpha]^{25}$ *c* = 0.015 benzene	$[\alpha]^{25}$ *c* = 0.015 isooctane	ORD.[a] nm	α^{25}	$[\alpha]^{25}$ *c* = 0.015 benzene	$[\alpha]^{25}$ *c* = 0.015 isooctane
650	– 5.6	– 5.5	+4.1	440			0.0
600	– 7.6	– 7.1	+4.1	400	– 44.7	– 43.5	– 6.9
589	– 8.2	– 7.8	+4.1	350	– 91.8	– 89.5	–29.9
550	–10.7	–10.4	+4.1	334	–122.3	–118.7	–46.5
500	–16.0	–15.6	+2.9	313	–187.4	–182.6	–85.0
450	–25.6	–24.3	+0.4				

[a]) See *Fig. 7e*.

REFERENCES

[1] *A. Fredga,* Chem. Ber. *89,* 322 (1956).
[2] *J. H. Brewster & J. G. Buta,* J. Am. Chem. Soc. *89,* 2233 (1966).
[3] *J. H. Brewster,* Helv. Chim. Acta *65,* 317 (1982).
[4] *J. H. Brewster,* J. Am. Chem. Soc. *102,* 7618 (1980).
[5] *H.-J. Hansen, H.-R. Sliwka & W. Hug,* Helv. Chim. Acta *62,* 1120 (1979).
[6] *W. Baker & W. G. Leeds,* J. Chem. Soc. *1948,* 974.
[7] *K. Mori, M. Matsui & Y. Sumiki,* Agric. Biol. Chem. *27,* 27 (1963).
[8] *S. C. Lahiri & H. K. Gupta,* J. Indian Chem. Soc. *53,* 1041 (1976).
[9] *H. Wren & H. Williams,* J. Chem. Soc. *109,* 572 (1916).
[10] *D. Biquard,* Ann. Chim. *20,* 97 (1933).
[11] *R. K. Hill & D. A. Cullison,* J. Am. Chem. Soc. *95,* 1229 (1973).
[12] Atlas of Stereochemistry, W. Klyne & J. Buckingham, 2nd edition, Chapman and Hall, London 1978.
[13] *W. Hug, A. Kamatari, K. Srinivasan, H.-J. Hansen & H.-R. Sliwka,* Chem. Phys. Lett. *76,* 469 (1980).
[14] *G. Kirsch, C. Rufer, F. Bahlmann, H. Simon & E. Stiebing,* Lieb. Ann. Chem. *1976,* 1914; *T. Aono, S. Kishimoto, Y. Araki & S. Noguchi,* Chem. Pharm. Bull. *25,* 3198 (1977).
[15] *S. D. Allen & O. Schnepp,* Chem. Phys. Lett. *29,* 210 (1974).
[16] *G. Barth, W. Voelter, H. S. Mosher, E. Bunnenberg & C. Djerassi,* J. Am. Chem. Soc. *92,* 875 (1970).
[17] a) *H. Dale,* «Stereochemie und Konformationsanalyse», Verlag Chemie, Weinheim 1978, p. 65 ff.; b) *T. Połonski,* Tetrahedron *31,* 347 (1975).
[18] *A. Moscowitz, K. Mislow, M. A. W. Glass & C. Djerassi,* J. Am. Chem. Soc. *84,* 1945 (1962).
[19] *J. A. Schellman,* J. Chem. Phys. *44,* 55 (1966) and Acc. Chem. Res. *1,* 144 (1968).
[20] *W. Klyne & P. W. Scopes* in "Optical Rotatory Dispersion and Circular Dichroism", F. Ciardelli and P. Salvadori, eds., Heyden & Son Ltd. London 1973, p. 126 ff.; *E. C. Ong, L. C. Cusachs & O. E. Weigang,* J. Chem. Phys. *67,* 3289 (1977).
[21] *K. Mislow* in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry" G. Snatzke, ed., Heyden & Son Ltd. London 1967, p. 153 ff.
[22] *K. N. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz & C. Djerassi,* J. Am. Chem. Soc. *87,* 66 (1965).
[23] *A. Fredga & M. Matell,* Bull. Soc. Chim. Belges *62,* 47 (1953).
[24] *R. K. Hill & D. A. Cullison,* J. Am. Chem. Soc. *95,* 1229 (1973).
[25] *M. Mousseron & G. Manon,* C. R. Hebd. Séances Acad. Sci. *226,* 1989 (1948).
[26] *E. Stahl,* «Dünnschichtchromatographie», Springer-Verlag, Berlin 1970, p. 620.
[27] *N. H. Cromwell & D. B. Capps,* J. Am. Chem. Soc. *74,* 4448 (1952).
[28] *H. M. Schwartz, W.-S. Wu, P. M. Marr & J. B. Jones,* J. Am. Chem. Soc. *100,* 5199 (1978).
[29] *W. Wunderlich,* Arch. Pharm. *286,* 512 (1953); *M. Tiffeneau & A. Orexhoff,* Bull. Soc. Chim. Fr. *27,* 789 (1920).
[30] *B. Sjöberg,* Acta Chem. Scand. *14,* 273 (1960).
[31] *T. N. Pattabiraman & W. B. Lawson,* J. Biol. Chem. *247,* 3029 (1972).
[32] *R. K. Crossland & K. L. Servis,* J. Org. Chem. *35,* 3195 (1970).
[33] *E. C. Ashby & J. J. Lin,* Tetrahedron Lett. *1977,* 4481.
[34] *R. W. Holder & M. G. Matturo,* J. Org. Chem. *42,* 2166 (1977).
[35] *J. Entel, C. H. Ruof & H. C. Howard,* Anal. Chem. *25,* 1303 (1953).
[36] *H. E. Smith, B. G. Padilla, J. R. Neergaard & F.-M. Chen,* J. Am. Chem. Soc. *100,* 6035 (1978).
[37] *S. D. Allen & O. Schnepp,* J. Chem. Phys. *59,* 4547 (1973).
[38] *J. Almy & D. J. Cram,* J. Am. Chem. Soc. *92,* 4316 (1970).
[39] *R. F. Nystrom & C. R. A. Berger,* J. Am. Chem. Soc. *80,* 2896 (1958).
[40] *M. E. C. Biffin, L. Crombie & J. A. Elvidge,* J. Chem. Soc. (B), *1965,* 7500.
[41] *M. E. C. Biffin, L. Crombie, T. M. Connor & J. A. Elvidge,* J. Chem. Soc. (B), *1967,* 841.