32. On the Absolute Configuration of Indane-1-carboxylic Acid

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Summary

Doubts that have recently been expressed [1] about the currently accepted (+)-(*R*), (−)-(*S*) [2] absolute configuration of indane-1-carboxylic acid appear to be unwarranted. *Our ORD. values for 1-methylindane [12] are in error.*

In the case of indanes the conformational relationship between the aromatic ring and a substituent on the five-membered ring is fairly well-defined[1]); this makes indanes valuable in areas of research where such relationships matter. Thus, optically active indanes have figured in theoretical [3–11] and empirical [10–17] studies aimed at delineating the chiroptical properties of the dissymmetrically perturbed benzene chromophore. Comparisons of indane derivatives with open-chain analogs in stereo-differentiating reductions and esterifications produced results that led to a refining of our understanding of the steric requirements of phenyl groups [18–21] – once configurational relationships had been established. The biological activity of indane-1-carboxylic acid and other plant-growth stimulators is a function of absolute configuration [2] [22] [23] and chiral homologs and benzologs of this acid have been used in efforts to map out the size and shape of the active site for ester hydrolysis in chymotrypsin [24] [25]. Chiral indanols are formed in microbial reductions of indanones [26] [27], apparently in accord with *Prelog*'s rule [28]. Knowledge of absolute configurations has been important in all of these studies; errors in assignments of configuration to the chiral indane derivatives would therefore have widespread implications.

As seen in *Schemes 1a, 1b,* and *2*, indane-1-carboxylic acid (**1**) occupies a central position, rather like the hub of a wheel, in the pattern of configurational correlations in this series. It is important, then, to attribute neither more, nor less, certainty to the currently accepted configuration (+)-(*R*), (−)-(*S*) [2] for **1** than the available evidence warrants. For this reason we cannot let certain statements made recently in this journal [1] stand unchallenged. Specifically, and to quote:

'It is shown unequivocally by chemical correlations and *Raman* optical activity spectra that the (*R*)-configuration has to be attributed to (+)-1-methylindane

[1]) Some flexing of the saturated ring is possible but it seems likely that there is only one conformational energy minimum; the extent of noncoplanarity could be a function of the steric requirements of the substituents. Puckering has been explicitly invoked by several workers in efforts to account for chiroptical phenomena that seem difficult to explain otherwise [7] [8] [9] [11] [15].

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((+)-**3**)[2]). This is in contradiction to an earlier assignment of the (*R*)-configuration to (−)-**3**[2]) [12][2]), which was based on the (*R*)-configuration of (+)-indane-1-carboxylic acid[2]) [2].

'The (*S*)-configuration has to be attributed to (−)-**3**[2]) as well as to (+)-indane-1-carboxylic acid, provided there is no trivial mistake in *Brewster & Buta*'s work [12][2]). This, however, is at variance with *Fredga*'s correlation of (+)-indane-1-carboxylic acid with (−)-(*R*)-2-phenylsuccinic acid.'

It is further suggested, in footnote 6, that *Fredga*'s correlation is somewhat shaky because considerable racemization occurred in the ring closure step.

As can be seen by reference to *Scheme 1a*, *Hansen et al.* [1] are in effect, suggesting that one error (or an odd number of errors) has been made in relating (−)-**3** to (−)-**7** *via* the sequence: **7**→**1**→**2**→**3** and that this casts doubt on the configuration of **1**. But they themselves have reported that (*R*)-1-methylindane varies in sign of rotation with solvent, being dextrorotatory neat or in benzene and levorotatory in isooctane. They would appear to have overlooked the fact that we reported (*R*)-**3** to be levorotatory because we measured its rotation in isooctane. Thus one of the errors they are concerned about vanishes; (−)-(*R*)-**7** does indeed lead to (−)-(*R*)-**3** (isooctane) *via* **1** and **2** *(see Addendum)*. If errors remain, there must be two of them.

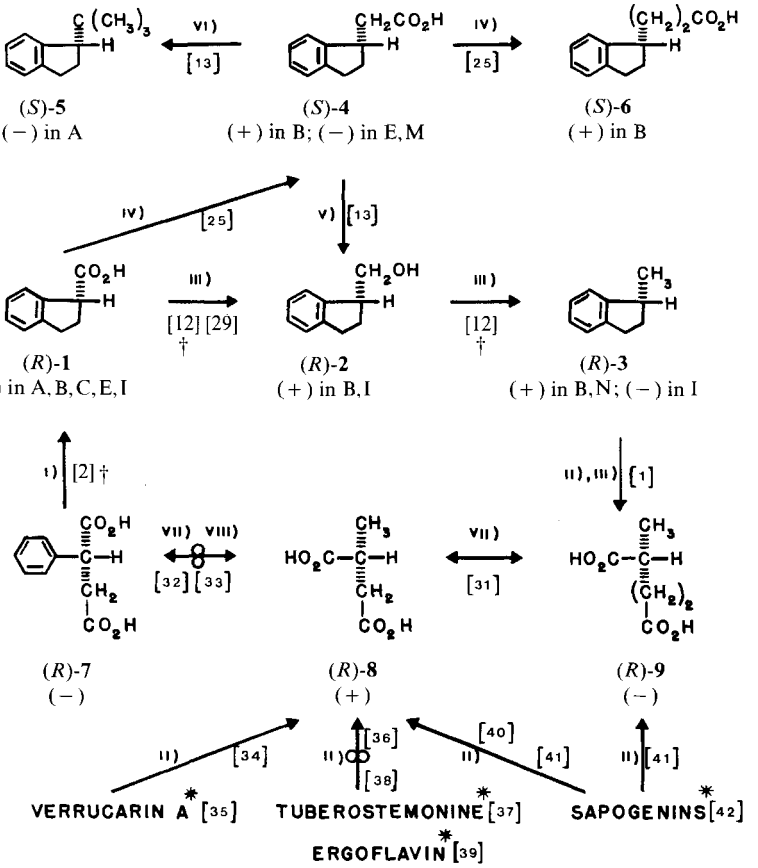
Of the three steps in the correlation, the second (**1**→**2**) seems most secure. Reduction of indane-1-carboxylic acid (**1**) to the alcohol **2** is unexceptional and has been carried out by two groups [12] [29]. Furthermore, these two compounds have each been correlated with 1-indanylacetic acid (**4**) – first, by *Baeyer-Villiger* degradation of the methyl ketone derived from **4** (**4**→**2**) [13] and second, by *Arndt-Eistert* synthesis of **4** from **1** [25], presumably with retention of configuration [30]. These compounds, along with those related to them (as, **5** and **6**), all stand together in configuration. Those configurations would be in jeopardy if, and only if, there were an error in *both* the first (**7**→**1**) and the third (**2**→**3**) step. It is our opinion that the occurrence of partial racemization in the first step – the conversion of phenylsuccinic acid (**7**) to indane-1-carboxylic acid (**1**) *via* cyclization and reduction – should occasion little alarm. The acid **1** forms a high-melting racemate [2]; a partially racemized sample would, therefore, be most unlikely to give the less abundant enantiomer on crystallization, even with seed *(see Addendum)*. On this basis, there exist no specific grounds *in print* for doubting that (+)-**1** is configurationally related to (−)-**7** and (+)-**3** (neat or benzene) ((−) in isooctane).

As summarized in *Schemes 1a* and *1b*, there is now abundant evidence, notably that provided by *Hansen et al.* [1] and *Smith et al.* [11], linking **7** and **3** to a host of substances with configurations established by the X-ray method. We know of no published contradictions of the configurational relationships developed in those schemes, except for the assertions of *Hansen et al.*, which we believe should be disregarded.

But doubts once raised are not so easily put down and it remains to link, by independent means, the central block of compounds (**1**, **2** and substances related to them) to compounds of known absolute configuration. Accordingly we present in *Scheme 2* two additional lines of evidence supporting the currently assigned con-

[2]) These numbers have been changed to accord with those used in this paper.

Scheme 1a



Methods: i) Cyclization and reduction; ii) oxidative degradation; iii) reduction; iv) *Arndt-Eistert* reaction; v) *Baeyer-Villiger* reaction; vi) alkylation and reduction; vii) quasiracemates; viii) ORD. and CD.
† *See addendum*

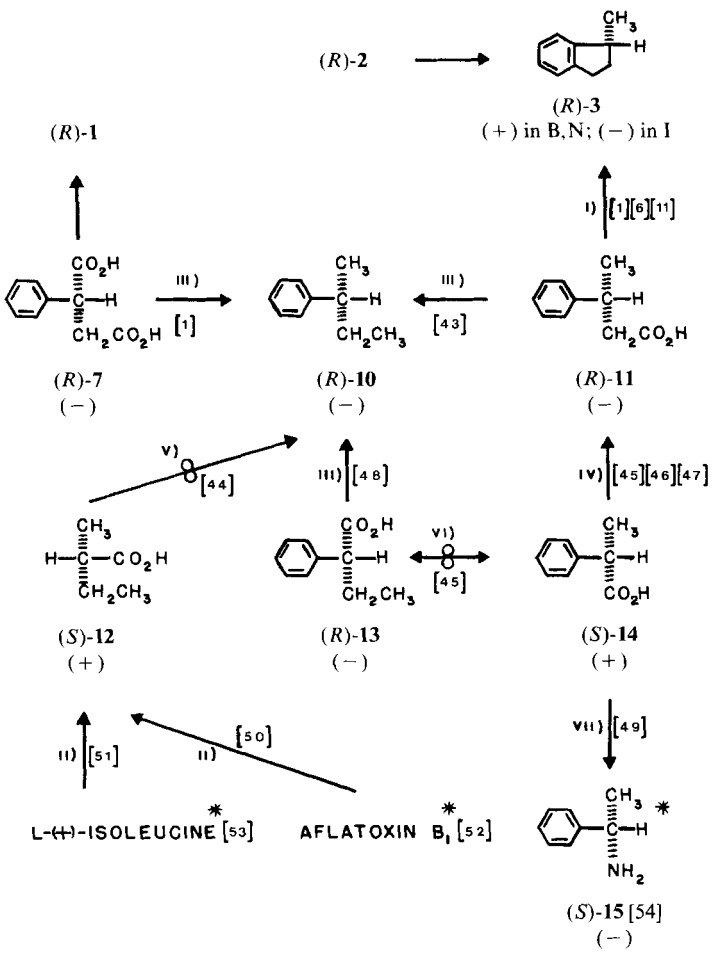
* Relative and/or absolute configuration by X-ray analysis; ⇔ Substances shown are related through enantiomers.

Solvents: A = acetone; B = benzene; C = chloroform; E = ethanol; I = iso-octane; M = methanol; N = none (neat).

figuration of indane-1-carboxylic acid (**1**). First, 1-indanamine (**16**) has been prepared from **1** by use of the *Curtius* reaction [12], which is believed to occur with retention of configuration [55]. This amine, fully characterized by ORD. and CD.[3]), has been degraded to glutamic acid [56], an amino acid of well-established configuration [57].

[3]) We had reported [12] that the hydrochloride of (*R*)-**16** was levorotatory at long wavelengths, as measured on an ORD. machine. This error, which was corrected by *Smith & Willis* [10], appears to have been the result of a mistake in setting an ORD. base-line. That error did not significantly affect the measurement of the ultraviolet *Cotton* effects (our main concern at the time) and these remain useful for enantiomer identification.

Scheme 1b

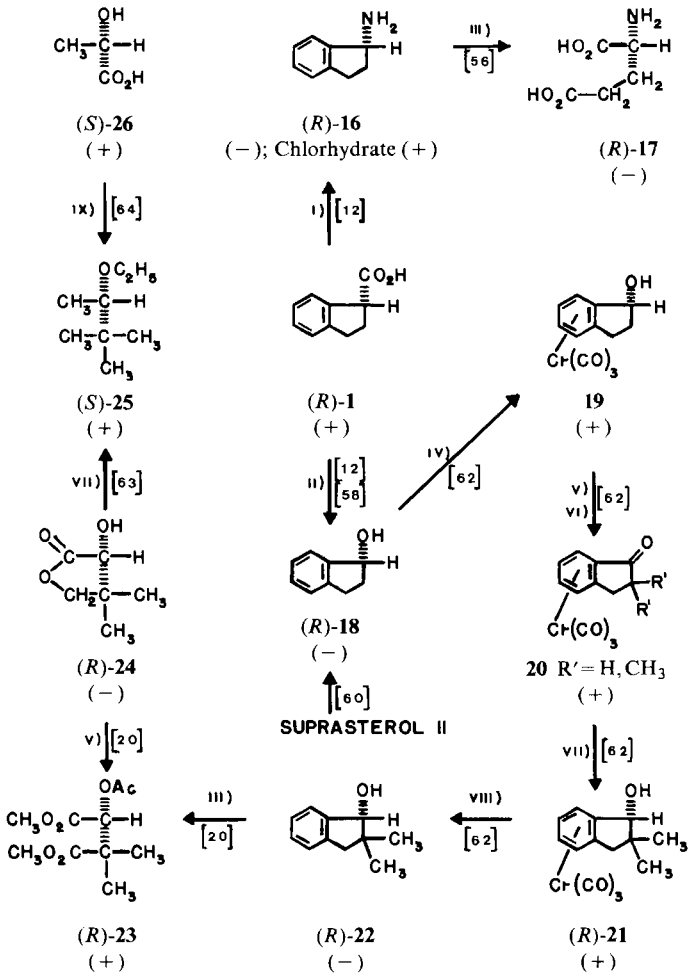


Methods: i) cyclization and reduction; ii) oxidative degradation; iii) reduction; iv) homologation *via* reduction, halogenation and carboxylation; v) *Grignard* ring closure; vi) quasiracemates; vii) *Curtius* reaction.

* Absolute configurations by X-ray analysis; ⇔ Substances shown are related through enantiomers. Solvents: B = benzene; I = iso-octane; N = none (neat).

Second, indanol (**18**) has been prepared [12] [58] by *Baeyer-Villiger* reaction of the methyl ketone derived from (**1**), again presumably with retention of configuration [59]. Indanol has been correlated with suprasterol II [60]; the internal configurational relationships of that substance have been established by X-ray analysis [61] and its absolute configuration rests on its preparation from ergosterol [60]. This configuration for indanol is supported by the correlation sequence shown in *Scheme 2*, a noteworthy example of one that relies on a surrogate chiral center to maintain configuration while the center of interest loses and regains its own

Scheme 2

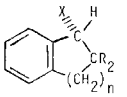


Methods: i) *Curtius* reaction; ii) *Baeyer-Villiger* reaction; iii) oxidative degradation; iv) metallation; v) oxidation; vi) alkylation; vii) reduction; viii) irradiation; ix) group elaboration *via Wittig* and *Simmonds-Smith* reactions.

chirality (**18** → **22**) [62]. The dimethylated indanol (**22**) has been degraded [20] to a product (**23**) that can be connected to pantolactone (**24**), in turn connected [63], *via* an ether of pinacolyl alcohol (**25**) [64], to (+)-(*S*)-lactic acid (**26**) [65].

There are, then, four separate strands of chemical evidence linking indane-1-carboxylic acid to substances with configurations assigned by the X-ray method. It would take an odd number of errors in each and every one of these separate correlations to reverse the current assignment of configuration for **1**. Additional support for these assignments is provided by a comparison of rotation values in the indane and tetralin series (where configurations have been assigned indepen-

Table. *Molecular rotations of indane and tetralin derivatives*[a])



((*R*)-Configuration)

R	X	$[M]_D$[b]) n = 1	n = 2
H	CO_2H	+70.3 (B) [2]	+112.4 (B) [66]
		+66.0 (I) [2]	+68.2 (I) [66]
		+46.8 (AA) [2]	+41.0 (AA) [66]
		+40.3 (W) [2]	+25.4 (W) [66]
		+24.9 (C) [2]	+25.4 (C) [66]
		+20.2 (E) [2]	+25.0 (E) [66]
		+5.2 (A) [2]	+18.6 (a) [66]
H	NH_2	−40.8 [56] (+CE) [12]	−62.5 [56] (+CE) [67]
	$NH_3^+Cl^-$	+5.3 [56] (+CE) [12]	
	NHAc	+239 [56] (+CE) [12]	
	$N(CH_3)_2$	−130 (+CE) [12]	−265 (B) (+CE) [67]
H	OH	−46.6 [20] (+CE) [12]	−44 [20] (+CE) [67]
	OAc	+228 [20] (+CE) [12]	+199 [20] (+CE) [67]
	OBz	+48.7 [20]	+88.3 [20]
CH_3	OH	−56 [20]	−43 [20]
	OAc	+447 [20]	+479 [20]
	OBz	+323 [20]	+413 [20]

a) Symbols: A = acetone, AA = acetic acid, B = benzene, C = chloroform, E = ethanol, W = water (neutral), CE = *Cotton* effect near 260 nm.

b) Corrected to presumed optical purity.

dently [23] [66] [67] *(Table)*. Although this conclusion may be tainted by the occurrence of chiral puckering of the saturated ring in the tetralin series [16], the general parallelism of the two series is striking and suggests that contributions from that effect are relatively small.

We conclude, then, that the absolute configuration [(+)-(*R*), (−)-(*S*)] originally assigned to indane-1-carboxylic acid by *Fredga* [2] is as secure as any based on lengthy chemical correlations and, perhaps, more secure than most. The only errors we know of are to be found in three theoretical papers [6–8] in which the (*R*)-configuration was assigned to samples of 1-methylindane that were levorotatory neat or in benzene – on the basis of our observation that the (*R*)-isomer is levorotatory in isooctane and, apparently, the assumption that the sign of rotation would not be sensitive to changes in solvent. The conclusions reached in those papers clearly require reconsideration.

Addendum. After our submission of this manuscript Professor *Hansen* provided us with unpublished information which confirms the conclusions presented above and which pinpoints the source of confusion as being *our own* ORD, data for 1-methylindane.

Hansen's unpublished ORD. curves for a sample of (*R*)-**3** prepared from (*R*)-**11** and for one of trideuteriomethylindane, prepared from (*R*)-**1** essentially by our

method, are closely parallel and establish the correctness of the connection between **1** and **3** shown in *Scheme 1a*. He has, in addition, confirmed *Fredga*'s correlation of **1** with **7**.

Hansen's ORD. curves for (*R*)-**3** show a strong positive trend with decreasing wavelength in the range of 600–300 nm and suggest an approach to a positive ORD. *Cotton* effect below 300 nm. *Smith et al.* [11] reported a positive CD. *Cotton* effect for (*R*)-**3** but did not report ORD. data. Our ORD. curve, taken on a *Bendix-Ericsson* spectropolarimeter, was nearly flat over this range, but showed a small negative bulge near 250 nm. The fact that *Hansen*'s ORD. and ours show opposite trends might suggest that we were working with the wrong enantiomer but a check of our records shows that this is not the case. All of our samples of 1-methylindane were prepared from (+)-alcohol whose rotation had been checked by use of a *Zeiss* visual polarimeter. Indeed, some of our raw data, from runs at concentrations high enough to give significant absorption, suggest positive *Cotton* effects of the sort shown by other members of this series. In view of the similar problem encountered with the weak long wavelength rotation of the hydrochloride of indanamine[3]) we conclude that our ORD. data for 1-methylindane is wrong and should be expunged from the literature. Our identification of (*R*)-**3** as (−) in isooctane, while correct, is therefore merely fortuitous; this voids our claim to a correlation with (*R*)-**2** (and, so, (*R*)-**1**). In view of the difficulties our ORD. data have caused for several groups of workers [1] [10] [11] [6] [7] [8] we would quarrel only with the charitable dismisal [1] of this mistake as 'trivial'.

Despite its inability to deal with samples of low rotation, the *Bendix* instrument used in our work [12] did give reasonably good *Cotton* effect data. It is of particular importance here that the ORD. *Cotton* effects of **1**, **2**, **16** (HCl), and **18** have all been confirmed in essential detail on a *Cary* instrument by *Lorentzen* [13] and so are believed to be reliable as means of enantiomer characterization.

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