

EXPERIENCE IN THE DETERMINATION OF ABSOLUTE CONFIGURATION  
OF LIGHT ATOM COMPOUNDS BY X-RAY ANOMALOUS SCATTERING

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The absolute configuration of a chiral molecule whose relative configuration has been determined by X-ray crystal structure analysis can usually be determined by careful examination of the data or by further measurement. The procedures require the detection of the small intensity differences due to anomalous scattering. They have become standard practice for compounds containing Si or heavier atoms and have recently been extended to molecules with O as heaviest atom in the crystal making the method important for organic compounds (see ref. 1 for a list of such determinations).

The purpose of this note is to document the absolute configurations of seven C-H-O compounds as determined by anomalous scattering and to compare them with those deduced by other methods. Details of the techniques of measurement and evaluation will be published elsewhere<sup>2</sup>. A preliminary account of the determination of two of the structures has already appeared<sup>3</sup> and references to work by other authors on light atom compounds are given there.

Table 1 gives the names and formulae of the compounds investigated. (For further information on the substances see refs. 4-16) A "+" sign in the column headed Enantiomer indicates that the relative configuration obtained in the crystal structure analysis is the absolute configuration, a "-" sign indicates the mirror image. The sign is not of intrinsic chemical significance as the relative configuration initially obtained is fortuitous. P is the statistical significance of the enantiomer determination given as the probability that the absolute configuration has been incorrectly assigned. The statistical significance of such determinations can be extremely high as the information required is independently contained in each of a large number of X-ray reflections.

The compounds ingenol triacetate (ref. 4, Structure Ia and Fig. 1b), 6,20-epoxy lathyrol (ref. 5, Structure Ic and Fig. 1a) and lathyrol triacetate

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(ref. 6, Structure V and Fig. 1b) are biogenetically related, having all been derived from plants of the family Euphorbiaceae. Their absolute configurations can be referred to that of a structural unit which they have in common and which is shown in Fig. 1. The atoms 12, 13, 14 and 8 lie roughly in the same plane while atom 15 lies above it. The present measurements have shown that for all three compounds the absolute configuration of the structural unit is as shown in Fig. 1a. These determinations are also consistent with the absolute configuration of a related bromine derivative, neophorbol<sup>7</sup>, previously determined by anomalous scattering.

The relative configuration obtained in the crystal structure analysis of  $\gamma$ -rhodomycinone by Röhrl and Hoppe<sup>8</sup> is indicated in their Fig. 8 (ring A of molecule 1). The absolute configuration is obtained (our Fig. 1b) by reflecting the diagram in the plane of the paper. Brockmann et al.<sup>9</sup> have deduced the absolute configurations of a series of anthracyclonones from measurements of circular dichroism. Their diagram of  $\gamma$ -rhodomycinone (compound 4a, p. 4722) is consistent with the configuration illustrated in our Fig. 2.

The crystal structure of obtusifolin was solved by Narayanan et al.<sup>10,11</sup>. The present measurements have shown that the relative configuration obtained is absolute. The absolute configuration is illustrated in Fig. 1c. Previous chemical work on the structure has been done by Hänsel et al.<sup>12</sup>.

The stereochemistry of the compounds grayanotoxin-I, -II and -III has been extensively investigated by Kakisawa et al.<sup>13</sup> using optical rotatory dispersion and other techniques. On the basis of further measurements on grayanotoxin-II Iwasa et al.<sup>14</sup> modified the structure proposals with respect to the H atom at C1. This modified proposal was verified by the crystal structure analysis of grayanotoxin-7 (Narayanan et al.<sup>15</sup>). Our measurements have now also confirmed the absolute configuration.

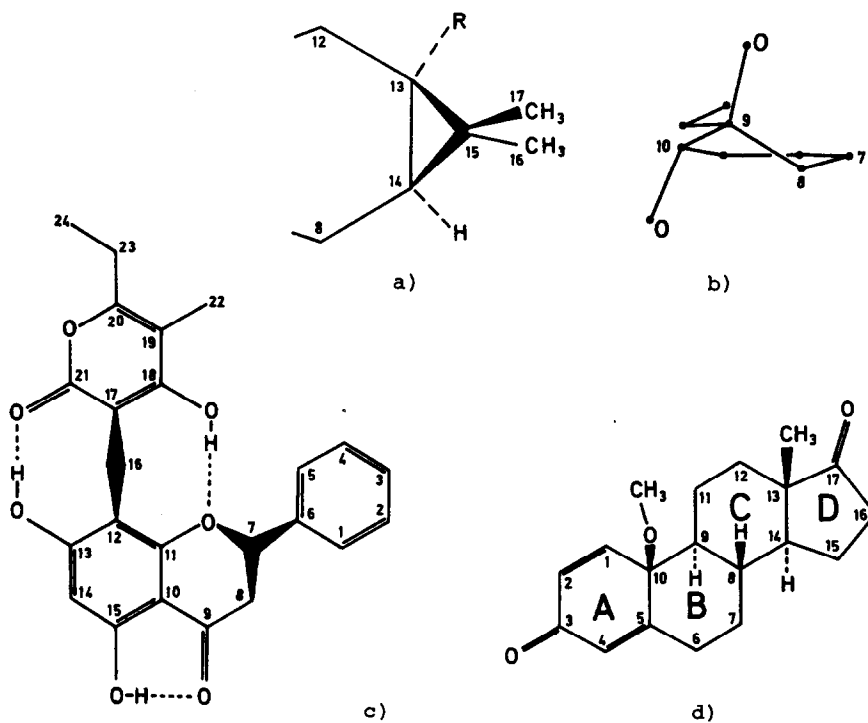
The crystal structure analysis of estro-p-quinol methyl ether was performed by Narayanan et al.<sup>16</sup> confirming a structure proposal by Hecker<sup>17</sup>. Our measurements now further confirm that the absolute configuration is consistent with that of all other steroids (the residue at C13 is in  $\beta$  position). The absolute configuration is shown in Fig. 1d. The absolute configurations of several heavy atom derivatives of steroids have also been determined by anomalous scattering<sup>1</sup>.

Summing up we find that for all substances our determinations confirm the absolute configurations proposed by analogy with related substances or on independent stereochemical evidence. For obtusifolin no previous proposal had been made for the absolute configuration. In all cases except  $\gamma$ -rhodomycinone<sup>8</sup> the diagrams (and atomic coordinates) already published correspond to the correct absolute configuration.

For light atom structures the intensity differences that have to be detected are very small. For C-H-O compounds the average magnitude of the diffe-

	Formula	Enantiomer	P
Lathyrol triacetate	$C_{26}H_{36}O_8$	+	<< 0.001
$\gamma$ -Rhodomycinone	$C_{20}H_{18}O_7$	-	<< 0.001
Obtusifolin	$C_{24}H_{22}O_7$	+	<< 0.001
Grayanotoxin-I	$C_{22}H_{37}O_7$	-	<< 0.001
Estro-p-quinol methyl ether	$C_{19}H_{24}O_3$	+	<< 0.001
6,20-Epoxy lathyrol	$C_{32}H_{40}O_8$	-	< 0.01
Ingenol triacetate	$C_{26}H_{34}O_8$	+	< 0.001

**Table 1.** Compounds whose absolute configurations have been determined. P is the significance of the determination.



**Fig. 7.** Absolute configuration of:-

- a) the structural unit common to the euphorbia compounds,
- b) ring A of  $\gamma$ -rhodomycinone,
- c) obtusifolin and d) estro-p-quinol methyl ether.

rences depends on the atomic ratio O:C, the optimum value being about 0,46. (see ref. 2). Significant determinations were, however, performed for substances with much lower atomic ratios (down to 0.16), showing that the method is quite generally applicable if care is taken with the measurements. Furthermore, it is not necessary to perform extremely accurate refinement<sup>2</sup>. In view of the high significance of the determinations with C-H-O compounds the determination should also be possible for C-H-N (and perhaps even C-H) compounds in favourable cases. Where necessary and feasible, crystallographers should, therefore, always attempt to complement their structure analysis by an enantiomer determination.

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