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The Crystal Structure of Euphenyl Iodoacetate

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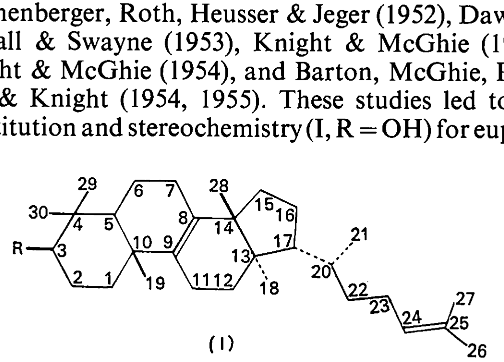
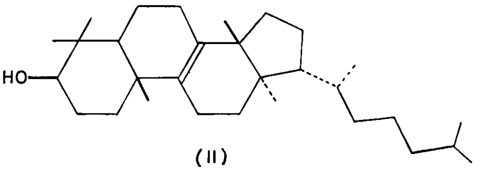
The crystal structure of euphenyl iodoacetate has been determined by the heavy-atom technique and refined by Fourier and least-squares analyses of the three-dimensional data. It has the unit-cell dimensions $a=7{\cdot}260\pm0{\cdot}003$, $b=11{\cdot}547\pm0{\cdot}005$, $c=19{\cdot}217\pm0{\cdot}008$ Å, $\beta=94{\cdot}07\pm0{\cdot}08°$, with $Z=2$; space group $P2_1$. The stereochemistry of euphenol, 24,25-dihydroeuphol, has been confirmed: in particular, both the side chain and the C(21) methyl group are α oriented. The side chain is not fully extended with respect to the rest of the molecule.

Introduction

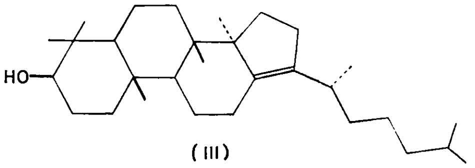
Euphol was isolated in a state of purity first by Newbold & Spring (1944). Subsequently, it has been the subject of detailed chemical investigations by Vilkas (1950), Barbour, Bennett & Warren (1951), Christen, Dünnenberger, Roth, Heusser & Jeger (1952), Dawson, Halsall & Swayne (1953), Knight & McGhie (1953), Knight & McGhie (1954), and Barton, McGhie, Pradhan & Knight (1954, 1955). These studies led to the constitution and stereochemistry (I, R = OH) for euphol.



(I)



(II)



(III)

The configurations at C(17) and C(20), favoured by Barton *et al.* (1955) on the basis of molecular rotation measurements, were α and β respectively. Arigoni, Viterbo, Dünnenberger, Jeger & Ruzicka (1954), from a study of the acid-catalysed rearrangement of euphenol (II) to isoeuphenol (III), concluded that the side chain was α oriented. Further degradative studies on the side chain (Riniker, Arigoni & Jeger, 1954) resulted in the isolation of D(−)-methyl-2,6-dimethyl heptanoate. Since this compound has been correlated with D(+)-glyceraldehyde by Cornforth, Youhotsky & Popjak (1954), its formation suggested that the configuration of the methyl group at C(20) was α, or *trans* to the C(19) methyl group. Several detailed reviews discuss fully the chemistry of euphol and related triterpenes: Simonsen & Ross (1957), Gascoigne & Simes (1954) and Ourisson, Crabbé & Rodig (1964).

Experimental

A number of crystalline derivatives of euphol were prepared by Dr J. F. McGhie of Chelsea College of Science and Technology. The preliminary measurements made on these compounds are summarized in Table 1. Cu $K\alpha$ radiation was used throughout.

Euphenyl iodoacetate was selected for detailed study. The crystals of this compound exhibited a pinacoidal habit with the order of prominent development {001} > {010} > {100}. The material was recrystallized from a 1:1 mixture of methanol and methylene chloride; the melting point of the purified compound was 97°C. The density was determined by flotation in aqueous sodium bromide solution with the result: $D_m=1{\cdot}26\pm0{\cdot}01$ g.cm^{-3}. An optical examination revealed the orientation: $Y\|\mathbf{a}$ (approximately); $X\|\mathbf{b}$; Z lay at 5° to $\mathbf{c}$ in the obtuse β angle. A more accurate determination of the unit-cell dimensions, using a calibrated Weissenberg camera, gave the results: $a=7{\cdot}260\pm0{\cdot}003$, $b=11{\cdot}547\pm0{\cdot}005$, $c=19{\cdot}217\pm0{\cdot}008$ Å, $\beta=94{\cdot}07\pm0{\cdot}08°$. For recording the reflexions, crystals were prepared of about $0{\cdot}2\times0{\cdot}2$ mm^2 cross-section and about 2 mm in length. Weissenberg photographs were taken by the equi-inclination technique with packs of four films in the camera. The relative intensities were estimated visually and an intensity range of 1 to 2000 was covered. The intensities were corrected for Lorentz and for polarization effects but not for absorption; a correction

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was applied for spot shape (Phillips, 1954, 1956). Altogether, 947 independent measured reflexions were used for the structure analysis.

The intensities were scaled approximately and an average isotropic temperature factor of 6 Å^2 was deduced, by the method of Wilson (1942). The average standard deviation of the structure amplitudes was estimated as 0·19, with the use of the statistics of small samples (Tippett, 1925; Ibers, 1956). The only systematic absences were $0k0$ for $k=2n+1$, and since the unit cell contained two asymmetrical molecules, the space group $P2_1$ was chosen. The molecular formula was confirmed as $C_{32}H_{53}O_2I$ to 1 in 10^6 by mass spectrometry.

Structure determination

The Patterson projection on (010) and the Patterson section at $V=\frac{1}{2}$ were computed with the use of sharpened coefficients. The former [Fig. 1(*a*)] displays three peaks, *A*, *B* and *C*, of about equal weight. Subsequently, the Patterson section $P(U\frac{1}{2}W)$ [Fig. 1(*b*)] showed peak *B* to be due to the iodine–iodine vector. The initial stages of the structure determination were based on the heavy-atom technique. The phase angles were calculated from the iodine atoms situated at $\pm(0{\cdot}433, \frac{1}{4}, 0{\cdot}142)$, these x and z coordinates being deduced from the Patterson maps (Fig. 1).

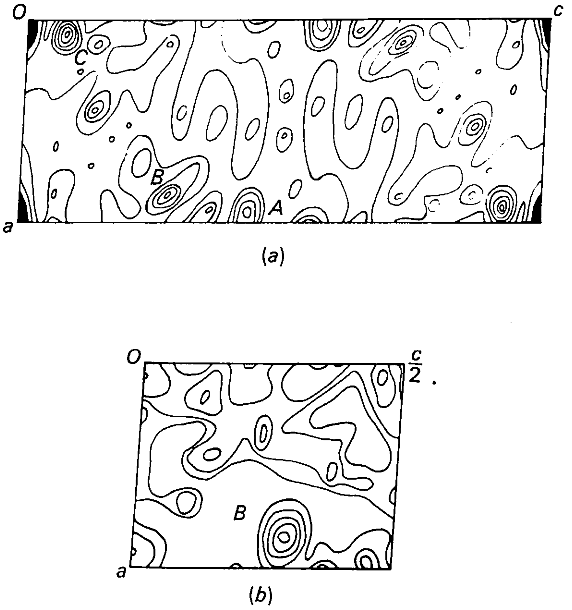


Fig. 1. (*a*) Patterson projection on (010). (*b*) Patterson section on $V=\frac{1}{2}$.

The electron-density projection on (010) (Fig. 2) indicated appreciable overlap of the two molecules in the unit cell, and some difficulty was experienced in placing the atoms of the side chain and of the angular methyl groups. In spite of the poor resolution in this projection Fourier and least-squares analyses yielded a residual (*R*) of 0·25, indicating that the structure was probably correct.

Three-dimensional studies involved the selection of a molecule from its mirror image, in the asymmetric unit. By successive Fourier syntheses, using coefficients for which $\left||F_o|-|F_c|\right|<\frac{1}{2}|F_o|$, the residual was reduced from 0·50 to 0·37. Least-squares analyses improved the refinement to $R=0{\cdot}25$, using anisotropic temperature factors for the iodine atoms and isotropic temperature factors otherwise. At this stage, two atoms of the side chain were not clearly resolved. A sharpened F_o synthesis revealed the carbon atom C(23) but the position of C(24) had to be inferred from stereochemical considerations.

The variations in electron density on difference Fourier sections were less than 1 e.Å^{-3} at this stage. The final least-squares refinements did not include C(32). Previous cycles moved this carbon atom into a stereochemically unfavorable position which was due possibly to diffraction effects associated with the iodine atom. The final value of the residual was 0·22, calculated with only the observed reflexions. The atomic coordinates and temperature factors, bond lengths and bond angles are recorded in Tables 2 to 4 and a composite electron density map of the molecule is shown in Fig. 3 (dashed lines indicate peaks due to atoms in superposition in this aspect).

Estimation of accuracy

Although the stereochemistry of euphenyl iodoacetate was confirmed, the analysis did not justify detailed estimates of accuracy. Estimated standard deviations

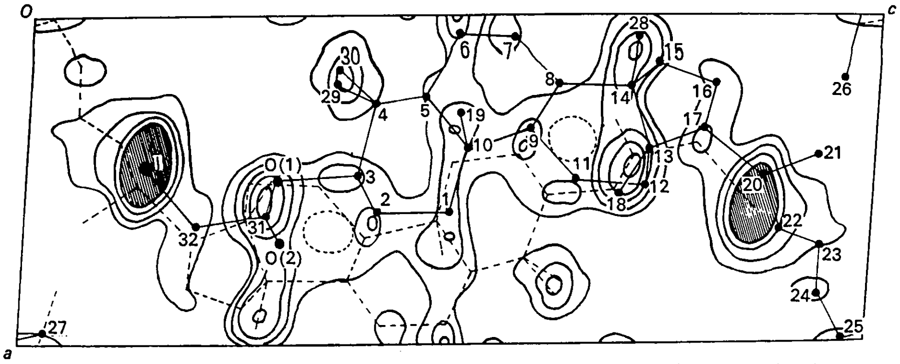


Fig. 2. The electron density map of euphenyl iodoacetate projected on (010).

Table 1. *Preliminary measurements on derivatives of euphol*

	a (Å)	*b* (Å)	*c* (Å)	*β* (°)	D_m (g.cm^{-3})	D_c (g.cm^{-3})	*Z*	Space group
Euphadienyl benzoate	7·30	11·20	41·05		1·07	1·06	4	$P2_12_12_1$
Euphenyl benzoate	7·30	11·20	41·05		–	1·06	4	$P2_12_12_1$
Euphadienyl *p*-iodobenzoate	11·20		46·6		–	1·30	6	$P6_3$
Euphenyl chloroacetate	7·26	11·51	18·47	94·8	1·07	1·09	2	$P2_1$
Euphenyl iodoacetate	7·25	11·54	19·23	94·1	1·26	1·24	2	$P2_1$

Table 2. *Final atomic parameters*

	x	*y*	*z*	*B*
I	0·427	0·245	0·143	*
O(1)	0·480	0·334	0·317	7·0
O(2)	0·708	0·196	0·308	6·7
C(1)	0·561	0·408	0·505	3·0
C(2)	0·567	0·426	0·420	3·9
C(3)	0·468	0·320	0·383	5·4
C(4)	0·267	0·325	0·396	3·7
C(5)	0·244	0·311	0·469	5·5
C(6)	0·056	0·296	0·495	3·6
C(7)	0·067	0·247	0·570	6·5
C(8)	0·216	0·298	0·627	5·5
C(9)	0·350	0·350	0·593	3·3
C(10)	0·351	0·401	0·516	3·6
C(11)	0·493	0·425	0·642	3·5
C(12)	0·507	0·413	0·729	3·5
C(13)	0·393	0·283	0·736	1·9
C(14)	0·207	0·280	0·700	5·8
C(15)	0·117	0·167	0·724	6·6
C(16)	0·209	0·146	0·803	2·8
C(17)	0·334	0·250	0·807	5·0
C(18)	0·503	0·188	0·708	4·0
C(19)	0·275	0·532	0·508	2·2
C(20)	0·500	0·208	0·863	8·8
C(21)	0·417	0·150	0·925	9·5
C(22)	0·667	0·283	0·883	10·8
C(23)	0·617	0·383	0·925	12·1
C(24)	0·783	0·450	0·952	14·8
C(25)	0·950	0·383	0·975	13·2
C(26)	0·967	0·450	0·050	11·3
C(27)	0·133	0·417	0·933	12·5
C(28)	0·063	0·380	0·713	2·2
C(29)	0·182	0·217	0·362	6·3
C(30)	0·156	0·422	0·360	3·8
C(31)	0·589	0·268	0·282	3·8
C(32)	0·633	0·303	0·208	10·5

* β_{11}	β_{22}	β_{33}
0·113	0·060	0·006
β_{23}	β_{13}	β_{12}
−0·004	−0·003	0·029

Table 3. *Bond lengths*

I———C(32)	2·00 Å
C(32)–C(31)	1·53
O(1)—C(31)	1·31
O(2)—C(31)	1·27
O(1)—C(3)	1·30
C(1)—C(2)	1·64
C(2)—C(3)	1·56
C(3)—C(4)	1·50
C(4)—C(5)	1·43
C(5)—C(10)	1·54
C(10)–C(1)	1·56
C(5)—C(6)	1·49
C(6)—C(7)	1·54
C(7)—C(8)	1·59
C(8)—C(9)	1·34
C(9)—C(10)	1·60
C(9)—C(11)	1·60
C(11)–C(12)	1·67
C(12)–C(13)	1·72
C(13)–C(14)	1·48 Å
C(14)–C(8)	1·43
C(14)–C(15)	1·54
C(15)–C(16)	1·63
C(16)–C(17)	1·50
C(17)–C(13)	1·51
C(4)—C(30)	1·52
C(4)—C(29)	1·52
C(10)–C(19)	1·62
C(13)–C(18)	1·48
C(14)–C(28)	1·59
C(17)–C(20)	1·62
C(20)–C(21)	1·54
C(20)–C(22)	1·52
C(22)–C(23)	1·47
C(23)–C(24)	1·49
C(24)–C(25)	1·48
C(25)–C(26)	1·63
C(25)–C(27)	1·65

Table 4. *Bond angles*

I———C(32)–C(31)	107°
C(32)–C(31)–O(2)	111
C(32)–C(31)–O(1)	119
O(2)—C(31)–O(1)	127
C(17)–C(16)–C(15)	98°
C(16)–C(15)–C(14)	105
C(15)–C(14)–C(13)	106
C(15)–C(14)–C(8)	118

Table 4 (*cont.*)

C(31)–O(1)—C(3)	121
O(1)—C(3)—C(2)	107
O(1)—C(3)—C(4)	107
C(10)–C(1)—C(2)	104
C(1)—C(2)—C(3)	108
C(2)—C(3)—C(4)	109
C(3)—C(4)—C(5)	110
C(4)—C(5)—C(10)	114
C(5)—C(10)–C(1)	115
C(4)—C(5)—C(6)	121
C(5)—C(6)—C(7)	112
C(6)—C(7)—C(8)	119
C(7)—C(8)—C(9)	109
C(8)—C(9)—C(10)	131
C(9)—C(10)–C(5)	105
C(10)–C(5)—C(6)	109
C(9)—C(10)–C(1)	103
C(10)–C(9)—C(11)	107
C(9)—C(11)–C(12)	122
C(11)–C(12)–C(13)	100
C(12)–C(13)–C(14)	115
C(13)–C(14)–C(8)	111
C(14)–C(8)—C(9)	128
C(8)—C(9)—C(11)	116
C(14)–C(8)—C(7)	123
C(12)–C(13)–C(17)	118
C(13)–C(17)–C(16)	111
C(14)–C(13)–C(17)	96
C(3)—C(4)—C(30)	116
C(3)—C(4)—C(29)	106
C(5)—C(4)—C(30)	115
C(5)—C(4)—C(29)	105
C(30)–C(4)—C(29)	103
C(1)—C(10)–C(19)	105
C(9)—C(10)–C(19)	114
C(5)—C(10)–C(19)	115
C(12)–C(13)–C(18)	110
C(17)–C(13)–C(18)	109
C(14)–C(13)–C(18)	108
C(8)—C(14)–C(28)	97
C(15)–C(14)–C(28)	106
C(13)–C(14)–C(28)	120
C(13)–C(17)–C(20)	115
C(16)–C(17)–C(20)	103
C(17)–C(20)–C(21)	109
C(17)–C(20)–C(22)	123
C(21)–C(20)–C(22)	113
C(20)–C(22)–C(23)	112
C(22)–C(23)–C(24)	112
C(23)–C(24)–C(25)	118
C(24)–C(25)–C(26)	92
C(24)–C(25)–C(27)	114
C(26)–C(25)–C(27)	108

of the atomic coordinates and of the bond lengths are listed in Table 5 for groups of atoms. The average C–C single bond distance was 1·55 Å and the average tetrahedral angle was 110°. The atoms of the double bond and acetate systems form planar configurations with average estimated standard deviations of 0·03 Å and 0·02 Å respectively.

Table 5. *Average estimated standard deviations* (Å) *for groups of atoms*

	$\bar{\sigma}(x)$	$\bar{\sigma}(y)$	$\bar{\sigma}(z)$	$\bar{\sigma}(l)$
O(1), O(2), C(1) to C(19) C(28) to C(32) (non-side-chain atoms)	0·04	0·04	0·04	0·06
C(20) to C(27) (side-chain atoms)	0·08	0·08	0·07	0·11
I	0·02	0·02	0·02	0·04

The data listed in Table 2 include large temperature factors for the carbon atoms in the side chain. It seems improbable that these temperature factors represent thermal vibrations alone; they reflect, perhaps, some uncertainty in the atomic positions for the atoms of the side chain. Such uncertainty could arise from either rigid-body vibrations of the side chain or from a partially disordered arrangement of those atoms. The second of these hypotheses was examined but no better agreement between $|F_o|$ and $|F_c|$ was obtained.*

The stereochemistry of the molecule

Two aspects of a model of euphenyl iodoacetate are illustrated by Fig. 4. The ring systems *A*/*B* and *C*/*D* are *trans* fused. Ring *A* is in the chair configuration but the C(8), C(9) double bond confers a degree of planarity upon the *B*/*C* ring system. Ring *D* is strained, presumably by *trans* fusion to ring *C*; this may explain the ready acid-catalysed isomerization of euphenol (II) to isoeuphenol (III).

The side chain is not fully extended with respect to the ring system. Such an extension would lead to an interaction between the methyl groups at C(18) and C(21). In lanostenyl iodoacetate (Fridrichsons & Mathieson, 1953) and cholesteryl iodide (Carlisle & Crowfoot, 1945), the C(18) methyl group and the side chain are in the β orientation but the C(21) methyl group retains the α configuration. Thus, the side chain in these molecules can be extended without the interaction of methyl groups, and indeed such an extension occurs. Non-extension of the side chain has been noted for calciferyl 4-iodo-3-nitrobenzoate (Crowfoot Hodgkin, Rimmer, Dunitz & Trueblood, 1963), but the side chain in this compound contains a C(22), C(23) double bond. The configuration of the paraffinic side chain in euphenyl iodoacetate is a direct consequence of the orientation at C(17), C(18) and C(20). The structure of the closely related epilimonol iodoacetate has been determined (Arnott, Davie, Robertson, Sim & Watson, 1961), but in this compound the side chain is replaced by a furan ring so that a direct comparison is not possible.

The packing of the molecules

As already discussed, the projection on (010) exhibits considerable overlap of the two molecules in the unit cell. In this respect, the structure resembles the *A* form of cholesteryl iodide (Carlisle & Crowfoot, 1945); the

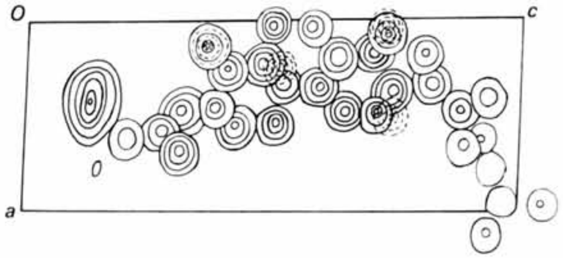
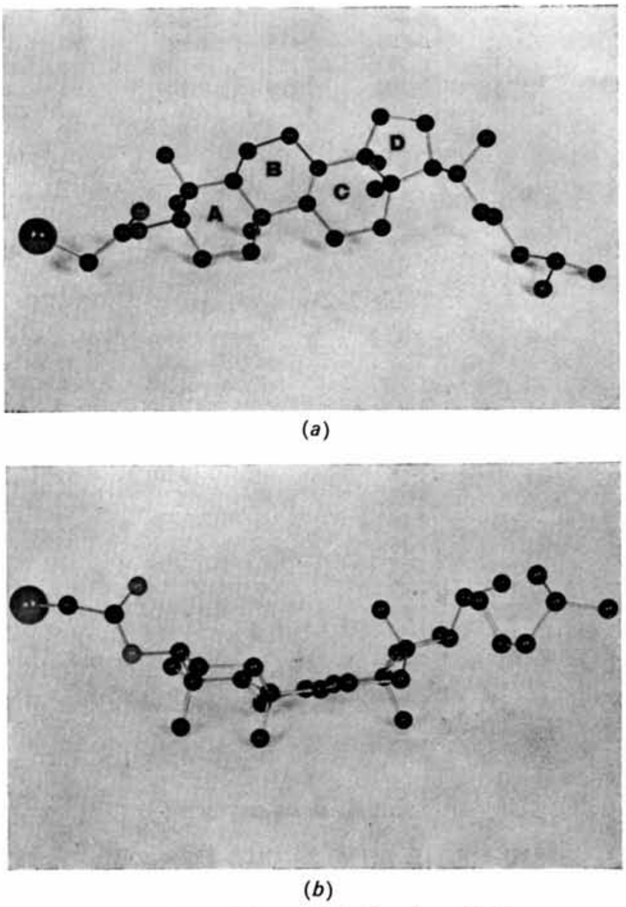


Fig. 3. A composite electron density map of the molecule of euphenyl iodoacetate. (Several contours for the iodine atom have been omitted for the sake of clarity).



(*a*)

(*b*)

Fig. 4. Two views of the model of euphenyl iodoacetate.

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* The observed and calculated structure factors may be had on request from Dr M. F. C. Ladd.

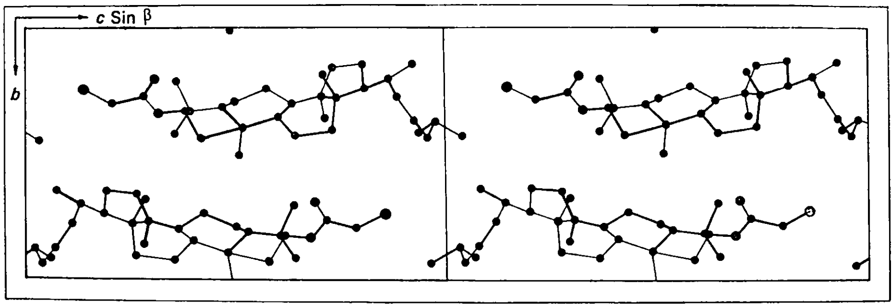

Fig. 5. The packing of the euphenyl iodoacetate molecules as seen along [100].

ring system in euphenyl iodoacetate is more inclined to (010), however, than is the case with cholesteryl iodide.

It is difficult to fit euphenyl iodoacetate into the classification of Bernal, Crowfoot & Fankuchen (1940). This may be due to the peculiar property of the side chain and, perhaps, to the presence of the iodoacetate group. Euphenyl iodoacetate resembles most closely the structure of ergotetraene and may thus be described as approximating to a *b*121 classification. Fig. 5 shows a view of the molecules in adjacent unit cells, projected on to (100).

Conclusions

The biogenesis of triterpenes has received detailed study during past years. Recent reviews have been given by Clayton (1965*a*, *b*). In connexion with this crystal structure determination, it is interesting to note that the implied biogenetic mechanism determines the configuration at C(17) but not that at C(20).

The absolute configuration of euphenyl iodoacetate has not been determined. However, since euphol can be described as 13-*iso*-14-*iso*-17-*iso*lanosterol, and since lanosterol has been related to cholesterol, the absolute configuration in euphenyl iodoacetate corresponds to the atomic coordinates as listed in Table 2.

The authors acknowledge with thanks the use of a structure-factor least-squares program written for 'Atlas' by Dr R. D. Diamand of the Royal Institution, London.

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