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Structure of Leurocristine Methiodide Dihydrate by Anomalous Scattering Methods; Relation to Leurocristine* (Vincristine) and Vincaleukoblastine (Vinblastine)

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The complete molecular structure including the stereochemistry and the absolute configuration of leurocristine methiodide dihydrate, $(C_{47}H_{59}O_{10}N_4{}^+)I^-.2H_2O$, has been determined by the combination of two crystallographic methods based on the anomalous scattering of X-rays. The structures of the antileukemia agent leurocristine (Vincristine) and the oncolytic alkaloid vincaleukoblastine (Vinblastine) are, therefore, established.

The crystals used in the study were monoclinic in space group $P2_1$ with two molecules in the unit cell of dimensions $a=10{\cdot}96\pm0{\cdot}05$, $b=21{\cdot}89\pm0{\cdot}05$, $c=12{\cdot}68\pm0{\cdot}01$ Å and $\beta=124°\,53'\pm10'$. The final value of $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$ is 0·12 for 1378 reflections.

Several new crystallographic approaches to the determination of molecular structures employing anomalous scattering are proposed.

Vinca rosea Linn. of the family *Apocynaceae*, better known as Madagascar periwinkle, grows throughout the world, and has been known for centuries in the folk medicine of both civilized and uncivilized cultures as a cure or preventive for many assorted ailments (d'Sévigné, 1684;‡ Peckolt, 1910; Watt & Breyer-Brandwijk, 1962; Garcia, 1954; Johnson, Wright, Svoboda & Vlantis, 1960; Johnson, Armstrong, Gorman & Burnett, 1963; Schlittler, 1964). Its reputed activity in the treatment of diabetes prompted two groups in 1949 to begin systematic studies. However, both groups, one at the Eli Lilly Research Laboratories in Indianapolis, including Svoboda, Johnson, Neuss & Gorman, and the other at the Collip Laboratories of the University of Western Ontario, including Noble, Beer and Cutts, failed to observe any effect on the blood sugar content when laboratory animals were treated with extracts of this periwinkle. However, both groups noted the development of acute leukopenia when extracts of the leaf were administered, and finally in 1958 Beer succeeded in isolating a crystalline alkaloid, christened vincaleukoblastine, which produced severe leukopenia (Noble, Beer & Cutts, 1958). Since that time some sixty different alkaloids have been isolated from *Vinca rosea* Linn. Twenty of these have consisted of two alkaloids joined chemically, and four of these twenty exhibit antitumor activity. Clinical tests on (Svoboda, 1964) two of these four, vincaleukoblastine (VLB) and leurocristine (LCR) have proved activity against a large number of human tumors, and LCR has shown some effectiveness in the treatment of leukemia (Johnson, Wright, Svoboda & Vlantis, 1960). The effectiveness in many cases is restricted by the limit imposed on dosages by toxic side effects: chiefly acute leukopenia (Gorman, Neuss, Svoboda, Barnes & Cone, 1959; Frei, Franzino, Shnider, Costa, Colsky, Brindley, Halsey, Holland, Gold & Jonsson, 1961) when VLB is used, and neuromuscular abnormalities (but little or no leukopenia) when LCR is administered (Armstrong, Dyke, Fouts & Gahimer, 1961).

The molecular structures of these chemically joined alkaloids, especially of LCR and VLB, have been studied by several methods. Vindoline, which can be isolated

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* A.M.A. approved generic names are Vincristine (VCR) for leurocristine and Vinblastine (VLB) for vincaleukoblastine. VLB is supplied as Velban ® and VCR as Oncovin ® (Lilly).

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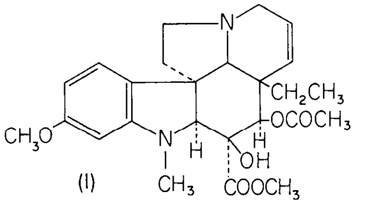
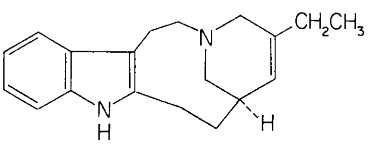
‡ '... guérissez-vous avec votre bonne pervenche, bien verte, bien amère, mais bien spécifique à vos maux, et dont vous avez senti de grands effets: refraîchissez-en cette poitrine enflammes; ...' from a letter from Mme d'Sévigné to Mme de Grignan, Nov. 5, 1684.

among the degradation products of these alkaloids, was assigned structure (I) primarily from nuclear magnetic resonance and mass spectrographic studies (Gorman, Neuss & Biemann, 1962). These methods do not, however, yield any evidence for the stereochemical assignments, but they led to the conclusion that vindoline is one of the two constituent alkaloids of VLB and LCR. Also these mass spectrographic studies supported the conclusion that the skeleton of vindoline is the same as that of aspidospermine (VI) for which a structure (but not the absolute configuration) was established by X-ray diffraction methods (Mills & Nyburg, 1960).



(I)



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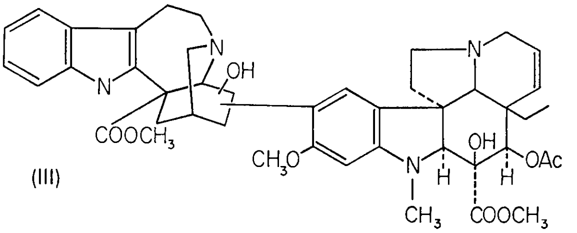

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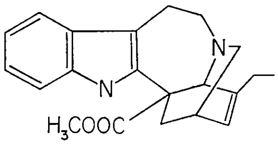

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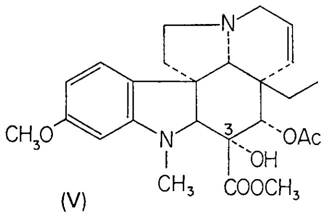

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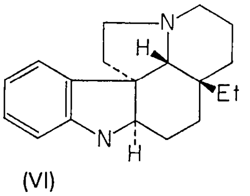


(VI)

The first proposal (III) of a complete structure for VLB and LCR was made by Neuss, Gorman, Boaz & Cone (1962), who concluded that catharanthrine (IV) was the partner of vindoline in LCR and VLB. The essential evidence was that cleavamine (II) resulted by similar treatment of either catharanthrine or leurosine, which is one of the four dimeric alkaloids exhibiting antitumor activity and is very closely related to LCR and VLB. Also the close relation between LCR and VLB was established, but evidence for the stereochemical assignments was still lacking. In the next proposal for the structures of VLB and LCR (Neuss, Gorman, Hargrove, Cone, Biemann, Büchi & Manning, 1964), the catharanthrine portion of the molecule was replaced by velbanamine, for which steric conformations at several positions were assigned with good chemical evidence (Fig. 1). In the vindoline portion, however, the stereochemistry at several positions was revised, but no chemical evidence was presented for these changes.

The absolute configuration of cleavamine (II) has been established by X-ray diffraction methods (Kutney, Trotter, Tabata, Kerigan & Camerman, 1963; Camerman & Trotter, 1964). Cleavamine has one asymmetric center in common with the nine asymmetric centers of VLB or LCR. In particular, cleavamine shares one asymmetric center with the three of velbanamine.

While the present study was in progress, Hargrove (1964) made an additional proposal for the structure of vindoline (V), particularly giving interesting reasons for the steric assignment of OH at position 3. After the completion of our study the absolute configuration of the *N*(*a*)-acetyl-7-ethyl-5-desethylaspidospermidine *N*(*b*)-methiodide structure was published (Camerman, Camerman & Trotter, 1965), but aspidospermine (VI) does not occur as one of the alkaloid residues of VLB and LCR, nor does it occur in the same plant, but the biogenetic relations are probably quite close.

Background of methods

The methods used here are based upon anomalous scattering, involving the collection of pairs $|F_{hkl}|^2$

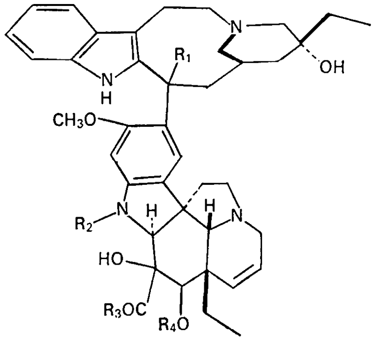


Fig. 1. Proposal by Neuss *et al.* (1964) for the structures of VLB and LCR. For VLB: $R_1 = COOCH_3$, $R_2 = CH_3$, $R_3 = OCH_3$ and $R_4 = COCH_3$. For LCR: $R_1 = COOCH_3$, $R_2 = CHO$, $R_3 = OCH_3$ and $R_4 = COCH_3$.

$|F_{\overline{hkl}}|^2$, which result from $f=f'+if''$ for the atomic scattering factor (Coster, Knol & Prins, 1930). Bijvoet (1949) developed the method for absolute molecular configuration determination, and extended the use of these related pairs of reflections to the resolution of phase ambiguities in isomorphous replacement methods (Bijvoet, 1954). The Fourier transforms led to the $P_c(\mathbf{u})$ and $P_s(\mathbf{u})$ functions (Okaya, Saito & Pepinsky, 1955; Pepinsky & Okaya, 1956). The $P_c(\mathbf{u})$ function has $n(n-1)$ non-origin peaks of height $f'_i f'_j + f''_j f''_j$, at positions of the usual centrosymmetric Patterson function, while the $P_s(\mathbf{u})$ function has peaks of height $f'_i f''_j - f'_j f''_i$ at $\mathbf{u}=\mathbf{r}_i-\mathbf{r}_j$. Hence $P_s(\mathbf{u})$ has a center of antisymmetry. If p of the n atoms in the unit cell are anomalous scatterers there are $p(n-p)$ positive and $p(n-p)$ negative peaks in $p_s(\mathbf{u})$, but their coincidence limits the power of this method.

One of the two methods used here is a further development of the $P_c(\mathbf{u})$ and $P_s(\mathbf{u})$ functions into a sum function $P_c(\mathbf{u})+bP_s(\mathbf{u})$ (Lipscomb, 1957), where b is a weighting constant or modification function. We choose b so that if $P_c(\mathbf{u})$ contains positive peaks at $\mathbf{u}=\mathbf{r}_i-\mathbf{r}_j$ and at $\mathbf{u}=\mathbf{r}_j-\mathbf{r}_i$, and if $P_s(\mathbf{u})$ contains positive peaks at $\mathbf{u}=\mathbf{r}_i-\mathbf{r}_j$ and negative peaks at $\mathbf{u}=\mathbf{r}_j-\mathbf{r}_i$, the sum function contains only positive peaks at $\mathbf{u}=\mathbf{r}_i-\mathbf{r}_j$. This procedure clearly preserves the absolute configuration. The present study is the first test of the power of this method.

The other of the two methods, here called the Bijvoet–Raman–Ramachandran (BRR) method, is based upon the use of anomalous scattering for single crystals (Peerdeman & Bijvoet, 1956) as further developed by Ramachandran & Raman (1956; also Raman, 1958, 1959). Here we refer specifically to the problem of two heavy atoms (at $y=\frac{1}{4}$ and $y=\frac{3}{4}$) per unit cell in the space group $P2_1$, in which the heavy atoms (H) are necessarily in a centrosymmetric array but the light atoms (L) are not. When anomalous scattering occurs

$$F=F_L+F'_H+iF''_H=F'+iF''_H\,.$$

Define the quantity $\Delta=|F|^2-|\bar{F}|^2$, where $F=F_{hkl}$ and $\bar{F}=F_{\overline{hkl}}$. If we write $F=A+iB$, $\bar{F}=\bar{A}+i\bar{B}$, $F'=A'+iB'$, $\bar{F}'=\bar{A}'+i\bar{B}'$, we find from Fig. 2 that $B'=\Delta/(4F''_H)$. From B' and the F''_H from the known heavy atom positions and scattering amplitude, it is thus possible to find $B=B'+F''_H$ for each reflection. We find $A=\pm\sqrt{-B^2+|F|^2}$. Bijvoet proposed that the ± ambiguity be resolved by taking the value closest to F_H. Therefore, $F_{hkl}=A_{hkl}+iB_{hkl}$ can then be found, and the structure solved (Hall & Maslen, 1965; Dale, Hodgkin & Venkatesan, 1963; Guertz, Peerdeman & Bijvoet, 1963).

We now show how these methods were used in the solution of the structure of leurocristine methiodide (Figs. 3 and 4) (Moncrief & Lipscomb, 1965).

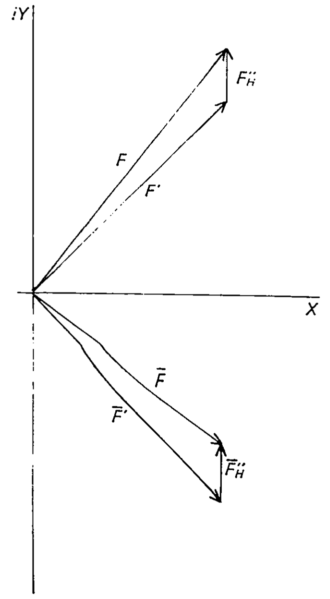
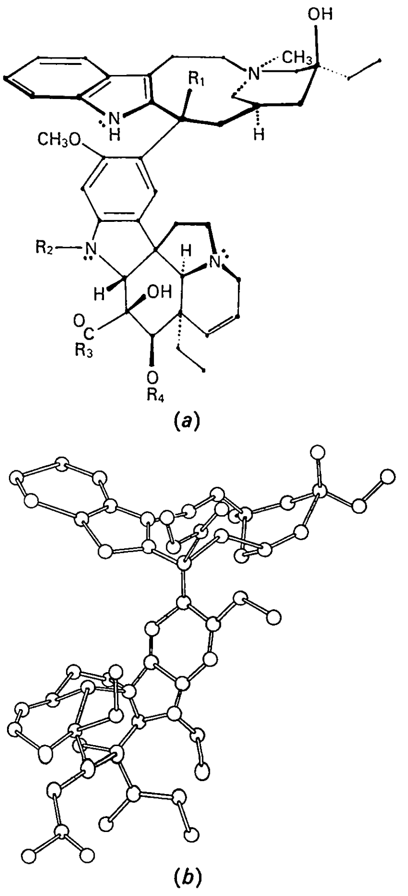


Fig. 2. Argand diagram indicating the vector relationships in the complex plane between the various components of the structure factors F and $\bar{F}$.



(a)

(b)

Fig. 3. (a) Structure of LCR methiodide as determined by X-ray crystallographic methods. LCR and VLB have no methyl group on 6′ (see Fig. 4 for the numbering system used). The R groups are defined under Fig. 1 and the bond linking 15 and 18′ (Fig. 4) has been rotated by 180° to facilitate comparison with Fig. 1. (b) The LCR methiodide molecule as it appears in the crystal. **a** is to the reader's right, **b** toward the top of the page, and **c** toward the reader.

Experimental

Crystals of leurocristine methiodide dihydrate $(C_{47}H_{59}O_{10}N_4)^+I^-.2H_2O$ are monoclinic. The extinction only of $0k0$ when k is odd and optical activity of this natural product fix the space group as $P2_1$. Unit-cell parameters are $a=10\cdot96\pm0\cdot05$, $b=21\cdot89\pm0\cdot05$, $c=12\cdot68\pm0\cdot01$ Å, and $\beta=124°53'\pm10'$. Flotation of the crystals in a mixture of dichloromethane and chloroform yielded a measured density of $1\cdot37\pm0\cdot02$ g.cm^{-3} in good agreement with the value of $1\cdot34\pm0\cdot02$ g.cm^{-3} computed from the unit-cell parameters and the assumption of two formula weights in the unit cell.

Three-dimensional data for hkl and $\bar{h}k\bar{l}$ reflections were collected from crystals mounted on **a** and on **c** with the use of the Buerger automated X-ray diffractometer. Weissenberg geometry, the ω-scan and Cu $K\alpha$ radiation ($\lambda=1\cdot5418$ Å) were employed. Owing to slow decomposition of the crystals by the X-ray beam an average of about 800 reflections were taken on each of five crystals, each of which was discarded when any one of the five selected check reflections decreased by ten per cent of its initial value. After the usual corrections for Lorentz and polarization factors, the data were correlated (Simpson, 1963) to a single list of 2356 independent reflections, which yielded 1378 independent reflections if averages were taken of $|F_{hkl}|$ and $|F_{\bar{h}k\bar{l}}|$. Standard deviations σ of the observed intensities $I\geq\sigma_c$ were taken as proportional to, actually 0·5% of, the number of net counts and inversely proportional to the number of times N that a reflection was observed, where σ_c is proportional to the total number of counts of reflection plus background. For $I<\sigma_c$ we chose $\sigma=K/N$, where K is 0·5% of I at the value of $I=2\bar{\sigma}_c$.

Structure determination

Coordinates of the two iodide ions of the unit cell were found easily from the three-dimensional Patterson function which had been sharpened so that the average intensity was independent of sin θ.

Unsharpened three-dimensional $P_c(\mathbf{u})$ and $P_s(\mathbf{u})$ functions were calculated. The twofold symmetry of each of these functions was eliminated by computation of a three-dimensional minimum function M after superposition of the Patterson functions at the iodide positions in the space group $P2_1$ (Simpson & Lipscomb, 1963). The sum of these two minimum functions, $MP_c(\mathbf{u})+bMP_s(\mathbf{u})$, was then taken, where b was found from the average heights of peaks in these two functions. This value of b is 1·9 times the theoretical value of f'_H/f''_H. Careful examination of this map did not reveal a substantial part of the structure, but it was later found that 43 peaks in the asymmetric unit of this map were within 0·75 Å of atomic positions in the actual structure, and that only 9 peaks did not correspond to atoms. Furthermore, 11 of the remaining atoms of the final structure fell on positive density of this map, but 10 more actually lay in negative regions. We feel that lack of resolution is the principal difficulty, and that sharpening of the $P_c(\mathbf{u})$ and $P_s(\mathbf{u})$ functions would have helped. But at this point we turned to another method.

Values of F''_H and Δ were used in the BRR method to calculate structure factors. The phase φ from the heavy-atom structure was used as a basis for choosing between the two possible values of A, for each reflection, and the structure factor found by this method was weighted by multiplication by cos $(|\varphi-\beta|)$. A three-dimensional electron density map from these structure factors was computed, and another map was also made from which the contributions of iodide ions were subtracted from the structure factors. No reasonable molecular structure could be found from either of these maps, although a possible position for an indole ring was noted in the map in which iodide ions were present. After solution of the structure we found that 62 peaks of this map were within 0·75 Å of correct atomic positions, and that the two remaining atoms were on diffuse positive density, but there were also 52 false peaks in this map. In the map from which iodide ions had been subtracted there were 58 peaks within 0·75 Å of the correct final positions, 3 more atoms on positive density and 2 missing atoms, but there were also 29 false peaks. The advantage of the smaller number of false peaks in the latter map seems to have been lost in the decreased resolution, as compared with the map before subtraction of iodide ions. Thus we did not solve the structure from the use of the BRR method alone.

At this stage a careful comparison of the $MP_c(\mathbf{u})+bMP_s(\mathbf{u})$ map and the BRR map yielded 37 peaks at positions differing in the two maps by less than 0·5 Å. When these 37 peaks and the one iodide ion of the asymmetric unit were used to compute phases, the resulting three-dimensional electron density map yielded seven additional peaks. After three additional cycles all atoms (except H) of the structure were located unambiguously, and we were able to show that only one of the original 37 atoms was incorrect.

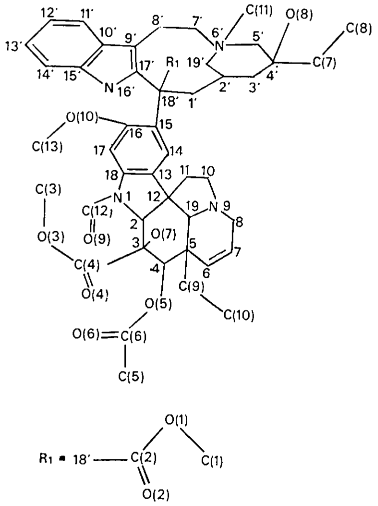


Fig. 4. The numbering system for the rings and the side-groups of leurocristine methiodide.

Refinement was carried out by least-squares procedures, starting from a rather satisfactory value of $R=\Sigma\,||F_o|-|F_c||/\Sigma\,|F_o|=0{\cdot}23$. One cycle of refinement in which only position parameters, except for the y coordinate of iodide, were varied followed by a cycle in which only the isotropic thermal parameters were varied yielded $R=0{\cdot}22$. Anisotropic refinement of I^- only yielded $R=0{\cdot}20$. Owing to limitations in the program and computer storage, we carried out six cycles in each of which three position parameters and six thermal parameters of different sets of 19 neighboring atoms were varied, while all others were held fixed. Off-diagonal terms were included only within each block. The value of $R=0{\cdot}12$, which then resulted was actually increased to $0{\cdot}12_4$ upon addition of H atoms, and fell only to $R=0{\cdot}12_1$ after three additional cycles of refinement of C, N and O parameters. In Table 1 we list these final parameters along with isotropic equivalents of the anisotropic thermal parameters for the 64 atoms excluding H. A final three dimensional electron density map from which all atoms including H were subtracted yielded no peaks greater than 1 e.Å^{-3} in height.

The absolute configuration is preserved in both the $MP_c(\mathbf{u})+bMP_s(\mathbf{u})$ method and the BRR method. Hence the structure as found [Fig. 3(*a*)] must have the correct absolute configuration. However, an additional test was made by comparison of the observed value of Δ for sixty randomly chosen related pairs of reflections with the value of Δ calculated from the absolute configuration shown in Fig. 3(*a*). All sixty pairs of reflections gave the same sign for Δ (observed) and Δ (calculated), thus confirming the absolute configuration.

Results and discussion

Bond lengths and angles (Tables 2 and 3) are reasonable, but have rather large average deviations of ±0·10 Å for distances and ±8° for angles from generally accepted values. Average bond lengths of recognized bond types, when several can be averaged, are in quite good accord with expected values. The two major reasons for these rather large deviations are the lack of complete refinement, and the incompleteness of X-ray data especially at high scattering angles. Position parameters were still shifting, towards generally accepted values of bond distances, when the block-diagonal least-squares refinement was terminated for financial reasons. Thus only a relatively small fraction of off-diagonal interactions have been included in these refinements. The X-ray data were taken from $h=-11$ to $+8$, $k=-25$ to $+25$ and $l=-10$ to $+10$, thus covering only some 35% of the Cu $K\alpha$ sphere. Furthermore, the somewhat rapid fall-off of intensities with angle of scattering, as shown by the somewhat high thermal parameters in Table 1, and the slow decomposition of the crystals in the X-ray beam have limited the high angle data and introduced inaccuracies beyond the counting statistics and the more usual systematic errors of structure determination. Under these circumstances we felt justified in terminating the refinements when we felt that the structure and absolute configuration had been established.

Table 1. *Final positional and thermal parameters*

Atom	x (Å)	y (Å)	z (Å)	Isotropic equivalent of anisotropic temperature factor
I^-	2·604	5·472	1·943	6·9
1	8·032	4·437	10·685	4·7
2	6·385	3·699	9·676	4·7
3	6·208	3·085	11·204	4·4
4	5·849	4·056	11·985	5·0
5	4·198	4·845	10·765	3·2
6	2·740	4·125	10·720	8·8
7	1·362	3·649	9·335	4·3
8	1·282	3·765	7·885	5·6
9	2·940	3·815	8·013	4·4
10	2·878	3·913	6·662	4·0
11	4·514	4·657	6·818	4·7
12	5·247	4·879	8·710	5·3
13	6·203	6·208	9·476	3·8
14	5·740	7·527	8·870	3·0
15	7·048	8·383	9·411	4·3
16	8·466	8·101	10·558	5·4
17	9·241	6·818	10·912	7·8
18	7·774	5·894	10·303	4·5
19	3·744	4·961	9·107	5·4
1′	6·707	9·850	7·287	5·5
2′	6·158	8·677	6·368	4·5
3′	6·584	8·562	5·124	3·8
4′	6·144	9·338	3·674	4·9
5′	4·268	9·244	2·723	7·1
6′	3·442	9·641	3·520	6·2
7′	3·539	11·007	4·246	8·7
8′	3·219	11·521	5·201	5·0
9′	3·543	11·021	6·656	4·5
10′	2·243	10·863	6·941	4·1
11′	0·518	11·430	5·863	6·5
12′	−0·323	11·167	6·607	7·3
13′	−0·068	10·872	8·179	6·1
14′	1·631	10·499	9·157	5·5
15′	2·472	10·495	8·472	5·6
16′	4·195	10·111	9·251	4·9
17′	4·714	10·280	8·203	4·0
18′	6·478	9·952	8·590	8·3
19′	4·171	8·578	5·177	5·2
C(1)	8·412	12·137	12·499	8·5
C(2)	7·501	11·041	9·913	3·8
C(3)	10·732	2·541	14·700	6·5
C(4)	7·686	2·348	12·301	8·7
C(5)	6·803	3·346	16·127	9·9
C(6)	6·876	3·914	14·757	5·1
C(7)	6·444	8·898	2·390	6·9
C(8)	5·952	9·423	0·896	10·8
C(9)	4·486	6·324	11·482	6·7
C(10)	2·823	7·056	10·679	6·6
C(11)	1·519	9·447	2·710	7·4
C(12)	9·272	3·845	10·822	9·0
C(13)	11·186	8·742	11·069	7·7
O(1)	7·575	10·929	11·251	4·6
O(2)	8·166	11·882	9·316	6·6
O(3)	8·890	3·097	13·423	6·5
O(4)	7·905	1·051	12·359	7·2
O(5)	6·012	3·471	13·275	5·0
O(6)	7·541	5·029	14·962	10·0
O(7)	4·945	2·139	10·119	5·1
O(8)	6·653	10·710	4·063	5·5
O(9)	9·437	2·611	10·635	5·6
O(10)	9·759	9·144	11·071	6·0
O(H_2O–1)	1·286	7·653	6·044	7·0
O(H_2O–2)	10·751	6·285	2·740	7·8

Possible hydrogen bonding distances are given in Table 4. The interesting short intramolecular distance of 2·54 Å between O(7) and N(9), as well as the relative conformations about these two atoms, indicate that a hydrogen bond is highly probable, thus supporting Hargrove's interesting conjecture in his proposal of a structure for vindoline. Other short intermolecular distances which do not correspond to hydrogen bonds are I$^-$ to 5′ of 4·01 Å, I$^-$ to 17 of 3·99 Å, O(H$_2$O – 1) to 10′ of 3·32 Å, 7′ to O(9) of 3·21 Å, 8′ to O(9) of

Table 2. *Bond distances*

C–C (benzene and indole)	
13–14	1·41 Å
13–18	1·33
14–15	1·39
15–16	1·24
16–17	1·44
17–18	1·53
9′–10′	1·49
9′–17′	1·50
10′–11′	1·53
11′–12′	1·43
12′–13′	1·47
13′–14′	1·44
14′–15′	1·36
10′–15′	1·46
Average	1·43
C$_{sp^3}$–C$_{sp^3}$	
2–3	1·75
2–12	1·54
3–4	1·42
4–5	1·59
5–19	1·45
12–19	1·73
11–12	1·61
10–11	1·72
1′–2′	1·40
2′–3′	1·53
2′–19′	1·63
3′–4′	1·47
4′–5′	1·55
7′–8′	1·28
5–C(9)	1·60
C(9)–C(10)	1·56
4′–C(7)	1·54
C(7)–C(8)	1·38
1′–18′	1·45
Average	1·54
C$_{\text{benzene}}$–O	
16–O(10)	1·50 Å
C$_{sp^3}$–N	
10–9	1·32
8–9	1·59
19–9	1·47
2–1	1·54
Average	1·48
C$_{sp^2}$–N	
C(12)–1	1·31
C$_{\text{benzene}}$–N	
18–1	1·49
C$_{sp^3}$–N7⊕	
7′–6′	1·52
19′–6′	1·74
5′–6′	1·49
C(11)–6′	1·62
Average	1·59
C–N (indole)	
15′–16′	1·47
17′–16′	1·42
Average	1·44
C$_{sp^3}$–C$_{sp^2}$	
18′–C(2)	1·56 Å
3–C(4)	1·44
C(5)–C(6)	1·52
8–7	1·41
5–6	1·60
Average	1·50
C$_{sp^2}$–C$_{sp^2}$	
6–7	1·36
C$_{sp^2}$–C$_{\text{benzene or indole}}$	
8′–9′	1·39
18′–17′	1·61
12–13	1·56
18′–15	1·71
Average	1·56
C=O	
C(6)–O(6)	1·25
C(4)–O(4)	1·31
C(12)–O(9)	1·27
C(2)–O(2)	1·40
Average	1·30
C$_{sp^3}$–O	
C(1)–O(1)	1·59
4–O(5)	1·34
C(3)–O(3)	1·63
3–O(7)	1·45
C(13)–O(10)	1·48
4′–O(8)	1·44
Average	1·48
C$_{sp^2}$–O	
C(2)–O(1)	1·30
C(4)–O(3)	1·31
C(6)–O(5)	1·29
Average	1·30

Table 3. *Bond angles*

1–2–3	102°
1–2–12	100
1–C(12)–O(9)	128
1–18–13	111
1–18–17	120
2–1–18	110
2–1–C(12)	116
2–12–13	109
2–12–11	108
2–12–19	108
2–3–4	115
2–3–O(7)	93
2–3–C(4)	106
3–2–12	114
3–4–5	113
3–4–O(5)	108
3–C(4)–O(4)	128
3–C(4)–O(3)	114
4–3–O(7)	118
4–3–C(4)	114
4–5–6	109
4–5–19	115
4–5–C(9)	106
4–O(5)–C(6)	126
5–4–O(5)	117
5–6–7	124
5–19–12	120
5–19–9	118
5–C(9)–C(10)	110
6–5–19	109
6–5–C(9)	111
6–7–8	116
7–8–9	118
8–9–10	119
8–9–19	101
9–10–11	117
9–19–12	88
10–11–12	86
5′–6′–C(11)	124
6′–7′–8′	138^0
7′–8′–9′	129
7′–6′–C(11)	95
7′–6′–19′	102
8′–9′–10′	122
8′–9′–17′	147
9′–10′–11′	126
9′–10′–15′	127
9′–17′–16′	115
9′–17′–18′	117
10′–11′–12′	109
10′–9′–17′	90
10′–15′–16′	93
10′–15′–14′	139
11′–10′–15′	106
11′–12′–13′	143
12′–13′–14′	101
13′–14′–15′	119
14′–15′–16′	127
15′–16′–17′	113
16′–17′–18′	128
17′–18′–C(2)	99
18′–C(2)–O(1)	116
C(1)–O(1)–C(2)	116
C(3)–O(3)–C(4)	123
C(5)–C(6)–O(6)	118
10–9–19	113°
11–12–13	116
11–12–19	113
12–13–14	129
12–13–18	106
13–14–15	114
13–18–17	129
13–12–19	102
14–15–16	123
14–13–18	118
14–15–18′	113
15–16–17	127
15–16–O(10)	118
15–18′–1′	101
15–18′–17′	109
15–18′–C(2)	111
16–17–18	101
16–O(10)–C(13)	117
16–15–18′	123
17–16–O(10)	107
18–1–C(12)	119
1′–2′–3′	114
1′–2′–19′	113
1′–18′–17′	121
1′–18′C(2)	117
2′–1′–18′	117
2′–3′–4′	134
2′–19′–6′	109
3′–2′–19′	101
3′–4′–5′	98
3′–4′–O(8)	112
3′–4′–C(7)	125
4′–5′–6′	120
4′–C(7)–C(8)	132
5′–4′–O(8)	110
5′–4′–C(7)	102
5′–6′–7′	126
5′–6′–19′	107

Table 3 (*cont.*)

C(5)–C(6)–O(5)	124
C(7)–4′–O(8)	107
C(9)–5–19	107
C(11)–6′–19′	98
O(1)–C(2)–O(2)	137
O(3)–C(4)–O(4)	119
O(5)–C(6)–O(6)	116
O(7)–3–C(4)	108

Table 4. *Possible hydrogen bonding contacts*

Molecule	at	x	y	z
1		x	y	z
2		$1-x$	$y+\frac{1}{2}$	$1-z$
3		$x-1$	y	z
4		x	y	$z-1$

Atom	in Molecule	to Atom	in Molecule	d
O(7)	1	9	1	2·54 Å
O(H_2O–1)	1	16′	1	3·76
O(8)	1	O(4)	2	3·63
O(8)	1	O(7)	2	2·68
O(H_2O–1)	1	O(H_2O–2)	3	3·06
I^-	1	O(H_2O–2)	3	3·43
O(H_2O–2)	1	O(6)	4	3·23

3·30 Å, 12′ to O(8) of 3·31 Å and C(10) to C(13) of 3·30 Å.

The chemical formula and bonds, except for aspects of stereochemistry, are in agreement with the latest of the chemical studies (Neuss *et al.*, 1964). On the other hand the chemical proposals of steric structure are somewhat more difficult to compare. The proposals based on good chemical evidence for two of the three asymmetric centers of the velbanamine portion are actually correct but the wrong absolute configuration was chosen. The chemical proposals for four of the six asymmetric centers of the vindoline portion are also correct guesses, without an explicit statement of chemi-

Table 5. *List of observed and calculated structure factors*

h	k	l	F_{obs}	F_{calc}
0	4	0	192	204
0	6	0	30	17
0	8	0	98	95
0	12	0	61	62
0	14	0	38	38
0	16	0	36	35
0	18	0	14	6
0	20	0	25	26
0	24	0	17	18
0	2	1	129	164
0	3	1	81	88
0	4	1	39	28
0	5	1	94	96
0	6	1	114	110
0	7	1	130	126
0	8	1	30	32
0	9	1	45	42
0	10	1	52	47
0	11	1	89	84
0	12	1	12	16
0	13	1	20	22
0	14	1	20	21
0	15	1	30	29
0	16	1	27	27
0	17	1	39	42
0	18	1	29	29
0	19	1	25	24
0	21	1	31	32
0	23	1	12	13
0	1	2	58	60
0	2	2	71	63
0	3	2	96	93
0	4	2	77	72
0	5	2	128	112
0	6	2	86	78
0	7	2	25	25
0	8	2	28	29
0	9	2	116	103
0	10	2	20	19
0	11	2	71	75
0	12	2	14	12
0	13	2	53	50
0	15	2	23	24
0	16	2	14	17
0	19	2	18	19
0	20	2	11	14
0	23	2	13	16
0	2	3	139	142
0	3	3	32	26
0	4	3	32	32
0	5	3	40	29
0	6	3	87	88
0	7	3	58	56
0	8	3	68	67
0	9	3	43	47
0	11	3	28	23
0	12	3	54	53
0	13	3	39	39
0	14	3	31	29
0	15	3	22	19
0	16	3	38	38
0	17	3	11	9
0	18	3	26	26
0	24	3	12	13
0	0	4	31	30
0	1	4	51	52
0	2	4	70	66
0	3	4	63	62
0	4	4	40	42
0	5	4	68	53
0	6	4	32	28
0	7	4	47	49
0	8	4	46	46
0	9	4	30	28
0	11	4	15	16
0	12	4	31	31
0	13	4	31	30
0	14	4	30	32
0	15	4	16	19
0	16	4	29	30
0	17	4	27	29
0	18	4	25	24
0	19	4	14	12
0	1	5	21	15
0	2	5	30	27
0	3	5	68	62
0	4	5	24	25
0	5	5	60	56
0	6	5	40	39
0	7	5	57	55
0	8	5	19	17
0	9	5	37	31
0	12	5	12	12
0	13	5	32	33
0	14	5	22	20
0	15	5	30	26
0	17	5	12	13
0	19	5	16	15
0	21	5	13	12
0	1	6	25	24
0	2	6	37	35
0	3	6	17	14
0	4	6	38	40
0	5	6	23	22
0	6	6	25	24
0	7	6	14	15
0	8	6	45	45
0	9	6	14	12
0	10	6	15	14
0	11	6	30	30
0	12	6	29	27
0	13	6	23	20
0	14	6	21	20
0	15	6	22	24
0	16	6	22	21
0	17	6	11	8
0	0	7	38	35
0	1	7	20	19
0	2	7	30	23
0	3	7	17	12
0	4	7	26	21
0	6	7	35	32
0	10	7	29	24
0	11	7	19	17
0	1	8	18	17
0	3	8	20	15
0	5	8	18	16
0	7	8	23	16
0	13	8	17	17
0	14	8	11	11
0	15	8	13	12
0	0	9	27	26
0	2	9	28	23
0	6	9	11	10
0	7	9	10	9
0	9	9	18	20
0	10	9	17	14
0	0	10	10	11
0	2	10	21	20
0	4	10	11	12
0	8	10	11	7
1	1	0	81	80
1	2	0	21	32
1	3	0	112	123
1	4	0	95	91
1	5	0	115	111
1	6	0	24	23
1	7	0	43	37
1	8	0	36	31
1	9	0	60	52
1	10	0	19	18
1	11	0	71	76
1	12	0	18	19
1	13	0	58	64
1	14	0	15	16
1	15	0	35	35
1	16	0	24	25
1	17	0	27	31
1	18	0	21	18
1	19	0	14	15
1	20	0	13	11
1	21	0	14	15
1	23	0	17	17
1	24	0	12	7
1	25	0	11	9
1	0	1	85	93
1	1	1	49	40
1	2	1	37	30
-1	2	1	88	98
1	3	1	153	148
1	4	1	108	101
-1	4	1	52	49
1	5	1	116	118
1	6	1	44	42
1	7	1	50	50
-1	7	1	73	59
1	8	1	67	70
-1	8	1	82	73
1	9	1	79	78
1	10	1	53	59
-1	10	1	62	54
1	11	1	50	48
-1	11	1	48	43
1	12	1	68	66
-1	12	1	20	21
1	13	1	33	32
-1	13	1	45	49
-1	14	1	34	37
-1	15	1	28	22
1	16	1	40	45
-1	16	1	55	51
-1	17	1	41	38
-1	18	1	19	22
1	19	1	17	19
1	20	1	22	26
-1	20	1	27	23
-1	21	1	19	17
1	0	2	76	82
1	1	2	11	10
1	2	2	93	88
-1	2	2	34	41
1	3	2	38	40
1	4	2	66	75
1	5	2	90	86
-1	5	2	87	87
1	6	2	50	48
-1	6	2	49	40
1	7	2	45	37
-1	7	2	31	20
1	8	2	64	65
-1	8	2	105	91
1	9	2	61	59
-1	9	2	45	43
1	10	2	47	43
-1	10	2	47	38
1	11	2	34	37
-1	11	2	29	23
1	12	2	47	47
-1	12	2	74	69
1	13	2	23	25
-1	13	2	21	14
1	14	2	47	45
-1	14	2	28	25
1	15	2	14	13
-1	15	2	20	23
1	16	2	45	50
-1	16	2	40	37
1	17	2	18	17
-1	17	2	20	15
1	18	2	28	21
-1	18	2	22	21
1	19	2	26	22
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-1	21	2	22	23
1	0	3	68	64
-1	0	3	56	47
1	1	3	64	65
1	2	3	22	24
-1	2	3	36	21
1	3	3	61	59
-1	3	3	78	69
1	4	3	28	30
-1	4	3	27	27
1	5	3	45	47
-1	5	3	73	56
1	6	3	24	21
-1	6	3	46	48
1	7	3	57	59
-1	7	3	35	36
1	8	3	34	35
-1	8	3	27	28
1	9	3	38	34
-1	9	3	77	71
1	10	3	30	30
1	11	3	41	43
-1	11	3	67	62
-1	12	3	22	21
1	13	3	45	39
1	14	3	15	14
-1	14	3	14	19
1	15	3	25	27
-1	15	3	26	27
-1	17	3	41	41
-1	18	3	14	11
1	19	3	15	17
-1	19	3	25	29
1	23	3	11	10
-1	24	3	11	5
1	0	4	32	27
-1	0	4	95	97
1	1	4	31	30
-1	1	4	55	46
1	2	4	33	32
-1	2	4	50	52
1	3	4	51	53
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1	4	4	45	40
-1	4	4	48	37
1	5	4	34	35
-1	5	4	38	39
1	6	4	14	24
-1	6	4	58	62
1	7	4	46	45
-1	7	4	62	54
1	8	4	47	44
-1	8	4	42	41
1	9	4	28	29
-1	9	4	31	35
1	10	4	40	43
-1	10	4	35	36
1	11	4	33	34
-1	11	4	18	17
-1	12	4	28	28
1	13	4	31	30
-1	13	4	30	35
-1	14	4	18	21
1	15	4	11	17
-1	15	4	37	39
1	16	4	12	14
-1	16	4	18	11
1	17	4	12	13
-1	17	4	18	17
1	18	4	22	23
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-1	19	4	19	14
1	0	5	52	52
-1	0	5	33	34
1	1	5	17	17
-1	1	5	30	34
1	2	5	59	54
-1	2	5	38	43
-1	3	5	11	15
1	4	5	52	53
-1	4	5	21	19
1	5	5	13	12
-1	5	5	12	10
1	6	5	32	36
-1	6	5	41	35
-1	7	5	23	26
1	8	5	50	44
-1	8	5	62	62
1	9	5	21	22
-1	9	5	12	14
1	10	5	34	30
-1	10	5	19	15
-1	11	5	24	21
1	12	5	24	22
-1	12	5	40	43
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-1	18	5	26	26
-1	20	5	18	21
1	0	6	23	21
1	1	6	17	18
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1	2	6	23	24
-1	2	6	29	32
-1	3	6	39	46
-1	4	6	13	12
1	5	6	26	32
-1	5	6	18	12
1	6	6	16	16
-1	6	6	13	10
1	7	6	20	22
-1	7	6	31	33
1	8	6	19	17
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-1	11	6	36	38
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1	13	6	31	21
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-1	4	7	11	13
1	5	7	32	26
1	6	7	19	15
1	7	7	29	26
1	10	7	26	23
1	11	7	18	15
1	13	7	12	13
-1	13	7	9	9
1	0	8	19	7
1	1	8	14	14
1	2	8	16	13
-1	4	8	13	16
1	8	8	23	21
1	9	8	16	13
-1	9	8	14	13
-1	12	8	10	16
1	0	9	11	5
2	0	0	130	104
2	1	0	47	49
2	2	0	77	76
2	3	0	35	35
2	4	0	129	131
2	5	0	31	32
2	6	0	69	63
2	7	0	32	27
2	8	0	53	56
2	9	0	67	66
2	10	0	69	72
2	11	0	25	29
2	12	0	38	41
2	13	0	25	25
2	14	0	49	50
2	16	0	55	61
2	18	0	25	26
2	20	0	18	17
2	22	0	11	5
2	0	1	106	98
2	1	1	73	63
-2	1	1	55	55
2	2	1	59	58
-2	2	1	13	11
2	3	1	36	38
-2	3	1	83	89
2	4	1	67	68
-2	4	1	99	81
2	5	1	56	52
-2	5	1	132	101
2	6	1	83	85
-2	6	1	28	28
2	7	1	57	54
-2	7	1	84	77
2	8	1	64	63
-2	8	1	48	49
2	9	1	59	67
-2	9	1	67	60
2	10	1	47	50
-2	10	1	43	38
2	11	1	44	40
-2	11	1	65	67
2	12	1	29	24
2	13	1	23	24
-2	13	1	32	33
2	14	1	27	26
-2	14	1	17	12
2	15	1	15	11
-2	15	1	27	32
-2	16	1	34	35
2	17	1	11	13
2	18	1	24	20
-2	18	1	15	9
2	19	1	23	23
-2	19	1	36	30
-2	20	1	22	21
2	0	2	27	26
2	1	2	63	62
-2	1	2	68	54
2	2	2	11	8
-2	2	2	79	73
2	3	2	78	76
-2	3	2	47	49
2	4	2	46	45
-2	4	2	79	70
2	5	2	54	56
-2	5	2	112	85
2	6	2	32	33
-2	6	2	55	48
2	7	2	74	67
-2	7	2	84	73
2	8	2	39	34
-2	8	2	26	15
2	9	2	60	63
-2	9	2	69	70
2	10	2	14	12
-2	10	2	25	25
2	11	2	39	42
-2	11	2	54	48
-2	12	2	29	26
2	13	2	51	51
-2	13	2	43	48
2	14	2	14	5
-2	14	2	35	39
2	15	2	13	19
-2	15	2	32	32
2	16	2	20	25
-2	16	2	19	22
2	17	2	32	35
-2	17	2	31	24
2	18	2	15	11
-2	19	2	28	27
2	0	3	59	51
2	1	3	26	30
2	2	3	68	59
-2	2	3	187	164
2	3	3	47	50
-2	3	3	14	18
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-6	9	2	23	18
6	10	2	10	7
-6	10	2	32	23
-6	11	2	19	17
-6	12	2	21	19
-6	13	2	35	29
-6	14	2	14	14
-6	15	2	32	28
-6	0	3	30	31
6	1	3	12	14
-6	1	3	25	24
6	2	3	25	24
-6	2	3	69	57
6	3	3	15	20
-6	3	3	34	34
6	4	3	11	6
-6	4	3	44	29
-6	5	3	28	21
-6	6	3	33	26
-6	8	3	26	23
-6	9	3	17	10
-6	10	3	41	31
-6	11	3	22	26
-6	12	3	18	19
6	15	3	12	6
-6	15	3	13	9
-6	0	4	11	19
-6	1	4	17	20
-6	2	4	23	29
-6	3	4	16	12
-6	4	4	16	27
-6	5	4	16	23
-6	7	4	26	39
-6	8	4	14	11
-6	9	4	18	23
-6	10	4	11	7
-6	11	4	19	16
-6	12	4	16	8
-6	15	4	13	8
-6	16	4	12	7
-6	0	5	11	11
-6	1	5	18	22
-6	2	5	15	16
-6	3	5	13	17
-6	5	5	11	14
-6	6	5	12	16
-6	7	5	27	27
-6	8	5	14	11
-6	11	5	18	17
-6	13	5	14	12
-6	8	6	10	17
7	0	0	13	24
7	1	0	37	32
7	2	0	14	16
7	3	0	29	27
7	4	0	12	11
7	6	0	19	17
7	8	0	13	17
7	9	0	18	18
7	10	0	11	14
7	11	0	18	13
7	12	0	15	9
7	13	0	12	13
7	14	0	10	4
7	15	0	16	5
7	16	0	10	8
7	18	0	10	2
-7	0	1	15	13
7	1	1	21	26
-7	1	1	15	20
7	2	1	10	5
-7	2	1	25	22
7	3	1	23	29
7	4	1	10	4
-7	4	1	17	15
7	5	1	19	21
-7	5	1	15	11
7	6	1	21	26
-7	6	1	43	39
7	7	1	14	8
-7	7	1	11	12
7	8	1	14	8
-7	8	1	23	22
7	9	1	17	17
-7	9	1	18	12
-7	10	1	27	19
-7	11	1	12	10
-7	12	1	18	9
-7	13	1	15	12
-7	14	1	10	18
-7	0	2	40	31
-7	1	2	22	21
7	2	2	13	15
-7	2	2	23	9
7	3	2	13	5
-7	4	2	14	10
-7	5	2	30	27
-7	7	2	15	23
-7	8	2	16	21
-7	9	2	16	9
-7	10	2	19	12
-7	11	2	25	17
-7	12	2	19	22
-7	13	2	18	10
-7	1	3	32	29
-7	2	3	16	13
-7	3	3	30	30
-7	4	3	22	21
-7	5	3	36	35
-7	9	3	25	24
-7	10	3	14	9
-7	11	3	25	17
-7	12	3	15	5
-7	13	3	17	3
-7	7	4	11	9
-7	8	4	15	16
-7	11	4	10	6
-7	12	4	10	17
-7	13	4	11	5
-7	1	5	10	13
-7	2	5	14	15
-7	4	5	12	19
-7	6	5	19	21
-7	8	5	16	15
-7	13	6	10	10
8	0	0	14	17
8	1	0	16	8
8	2	0	17	19
8	3	0	14	6
8	4	0	16	9
8	5	0	15	16
8	6	0	21	14
8	7	0	13	6
8	9	0	11	11
8	10	0	14	13
8	14	0	12	15
8	15	0	15	7
-8	0	1	14	1
-8	1	1	18	17
-8	3	1	20	22
8	4	1	14	9
-8	5	1	25	18
8	6	1	13	17
-8	6	1	10	4
-8	7	1	20	15
-8	8	1	13	4
-8	9	1	21	14
8	12	1	10	6
-8	0	2	26	22
-8	2	2	14	2
-8	6	2	27	8
-8	8	2	18	13
-8	10	2	17	8
-8	0	3	25	17
-8	1	3	14	14
-8	2	3	41	41
8	3	3	13	4
-8	3	3	15	10
-8	4	3	15	16
-8	5	3	11	9
-8	6	3	39	28
-8	7	3	19	13
-8	10	3	16	9
-8	18	3	10	9
-8	0	4	12	17
-8	2	4	18	7
-8	6	4	14	7
-8	9	4	21	14
-8	10	4	17	9
-8	12	4	16	19
-9	3	1	11	8
-9	1	2	18	15
-9	3	2	30	27
-9	4	2	15	4
-9	1	3	16	16
-9	3	3	23	11
-9	15	3	11	11
-9	0	4	15	6
-9	2	4	11	5
-9	4	4	16	12
-9	6	4	13	19
-11	6	3	12	8

cal evidence, but with the wrong absolute configuration. One more comparison of absolute configuration is possible: the two asymmetric centers of cleavamine established by Kutney *et al.* (1963) and Camerman & Trotter (1964) are in accord with the appropriate two out of ten in leurocristine methiodide found in the present study.

Table 6. *List of* $\Delta I = I_{hkl} - I_{\overline{hkl}}$ *for the* 636 *largest observed intensities,* I_{hkl}

The figures are, from left to right, *h*, *k*, *l*, *ΔI*

0	4	0	-8154	0	8	0	2018	0	12	0	139	0	14	0	-215
0	16	0	-577	0	20	0	-113	0	2	1	-751	0	3	1	4072
0	4	1	786	0	5	1	-1105	0	6	1	1390	0	7	1	2106
0	8	1	845	0	7	1	134	0	10	1	-530	0	11	1	-986
0	13	1	157	0	15	1	-215	0	16	1	-253	0	17	1	242
0	18	1	218	0	19	1	83	0	21	1	-120	0	1	2	-1230
0	2	2	824	0	3	2	-2220	0	4	2	-1040	0	5	2	-775
0	6	2	979	0	7	2	52	0	8	2	-318	0	9	2	-632
0	11	2	725	0	13	2	-527	0	15	2	-72	0	2	3	-140
0	3	3	78	0	4	3	-502	0	5	3	-2114	0	6	3	-1291
0	7	3	-168	0	8	3	713	0	9	3	-45	0	11	3	159
0	12	3	485	0	13	3	-314	0	14	3	-46	0	15	3	3
0	16	3	234	0	18	3	-181	0	1	4	760	0	2	4	314
0	3	4	1230	0	4	4	-647	0	5	4	-625	0	6	4	452
0	7	4	-23	0	8	4	-340	0	9	4	-219	0	12	4	106
0	13	4	-15	0	14	4	159	0	16	4	221	0	17	4	-60
0	1	5	99	0	2	5	-51	0	3	5	5	0	4	5	17
0	5	5	345	0	6	5	-110	0	7	5	-957	0	8	5	10
0	9	5	165	0	12	5	157	0	14	5	51	0	15	5	-82
0	1	6	-89	0	2	6	-150	0	4	6	12	0	5	6	80
0	6	6	-436	0	8	6	-367	0	11	6	343	0	12	6	105
0	13	6	2	0	14	6	207	0	15	6	-121	0	16	6	1
0	1	7	101	0	2	7	151	0	4	7	-94	0	6	7	-57
0	10	7	36	0	11	7	-21	0	1	8	122	0	5	8	89
0	7	8	-18	0	13	8	5	0	2	9	-160	0	9	9	1
0	10	9	51	0	2	10	-104	1	1	0	2002	1	2	0	-52
1	3	0	289	1	4	0	878	1	5	0	1084	1	6	0	88
1	7	0	-1740	1	8	0	181	1	9	0	-51	1	10	0	0
1	11	0	1106	1	13	0	484	1	17	0	-172	1	1	1	-1505
1	2	1	-613	-1	2	1	2590	1	3	1	4707	-1	3	1	2183
1	4	1	3065	-1	4	1	1429	1	5	1	1189	-1	5	1	-2102
1	6	1	-669	-1	6	1	-257	1	7	1	504	-1	7	1	2124
1	8	1	2027	-1	8	1	2067	1	9	1	-1125	1	10	1	-280
1	10	1	-1329	1	11	1	1232	-1	11	1	-227	1	12	1	2157
1	13	1	-429	-1	13	1	-36	-1	15	1	-116	1	16	1	48
1	16	1	251	-1	17	1	66	-1	20	1	90	-1	1	2	-1097
1	2	2	-1002	-1	2	2	202	1	3	2	305	1		2	-864
1	4	2	-1375	1	5	2	-187	-1	5	2	1852	1	6	2	340
1	6	2	47	1	7	2	424	-1	7	2	138	1	8	2	923
1	8	2	-714	1	9	2	-659	-1	9	2	237	1	10	2	1652
1	10	2	130	1	11	2	164	-1	11	2	-203	1	12	2	-390
1	12	2	391	1	14	2	309	1	16	2	-465	-1	16	2	-401
1	17	2	10	1	1	3	123	1	2	3	272	-1	2	3	-107
1	3	3	1743	-1	3	3	-43	1	4	3	85	1	5	3	-6
1	5	3	737	1	6	3	332	-1	6	3	62	1	7	3	263
1	7	3	30	1	8	3	-293	-1	8	3	-58	1	9	3	185
1	9	3	-939	1	10	3	-229	1	11	3	309	-1	11	3	28
3	6	1	-463	-3	6	1	164	3	7	1	321	3	8	1	-722
3	8	1	351	3	9	1	-82	-3	9	1	-397	-3	10	1	17
3	11	1	-140	-3	12	1	-120	3	13	1	-112	-3	13	1	99
3	14	1	54	3	15	1	115	-3	16	1	-76	-3	17	1	-130
3	1	2	-90	-3	1	2	589	3	2	2	242	-3	2	2	-116
3	3	2	182	-3	3	2	1028	3	4	2	1362	-3	4	2	427
3	5	2	110	-3	5	2	600	3	6	2	-46	-3	6	2	23
3	7	2	108	3	8	2	-349	-3	8	2	987	-3	9	2	925
3	10	2	815	-3	11	2	-423	-3	12	2	144	3	1	3	-172
3	1	3	-694	3	2	3	298	-3	2	3	184	3	3	3	312
3	3	3	-679	-3	4	3	128	3	5	3	-258	-3	5	3	1505
3	6	3	71	-3	6	3	-2	3	7	3	575	-3	7	3	1708
3	9	3	141	-3	9	3	748	3	11	3	-116	-3	11	3	-456
3	13	3	189	3	15	3	-135	3	1	4	391	-3	1	4	-368
3	2	4	-26	-3	2	4	412	3	3	4	-20	-3	3	4	-281
3	4	4	658	3	5	4	12	3	6	4	-265	-3	6	4	684
3	7	4	1022	3	8	4	-136	-3	8	4	87	3	9	4	-387
3	9	4	-352	-3	10	4	42	3	11	4	97	-3	11	4	146
3	13	4	-8	-3	1	5	74	3	2	5	124	-3	2	5	-126
3	3	5	-307	3	4	5	-17	-3	4	5	-188	3	6	5	-7
3	6	5	-946	3	8	5	-208	-3	8	5	-138	-3	10	5	60
3	12	5	-8	-3	12	5	60	-3	14	5	14	-3	16	5	-1381
3	18	5	-101	-3	3	6	-1064	-3	7	6	-311	-3	9	6	-99
3	13	6	-38	-3	15	6	7	-3	17	6	-148	4	2	0	-1739
4	3	0	65	4	4	0	2535	4	5	0	489	4	6	0	-957
4	7	0	-324	4	8	0	-8	4	10	0	204	4	12	0	271
4	18	0	136	4	1	1	-596	-4	1	1	-539	4	2	1	355
4	2	1	182	-4	3	1	419	-4	4	1	-34	-4	5	1	1061
4	6	1	-420	-4	6	1	-89	-4	7	1	513	-4	8	1	-228
4	9	1	-172	-4	9	1	-127	4	10	1	-91	-4	11	1	-158
4	13	1	-294	4	14	1	211	-4	15	1	-746	4	1	2	-31
4	1	2	-198	-4	2	2	969	-4	3	2	811	4	4	2	147
4	4	2	979	-4	5	2	620	-4	6	2	-567	4	7	2	-461
4	7	2	0	-4	8	2	-607	4	9	2	206	-4	9	2	384
4	10	2	-306	4	11	2	-206	-4	11	2	-517	4	1	3	52
4	2	3	44	-4	2	3	769	4	3	3	-269	4	4	3	104
4	4	3	-927	4	5	3	124	-4	6	3	100	4	8	3	232
4	8	3	-587	-4	9	3	87	-4	14	3	-481	-4	16	3	-272
4	2	4	42	-4	3	4	-312	-4	4	4	212	-4	5	4	-226
4	6	4	14	-4	7	4	58	4	8	4	-17	-4	8	4	18
4	10	4	95	-4	11	4	236	4	1	5	-63	-4	2	5	-290
4	3	5	-308	-4	4	5	55	4	5	5	47	4	7	5	-24
4	7	5	-449	-4	9	5	-669	-4	10	5	-162	-4	11	5	-346
4	13	5	-103	-4	15	5	-0	-4	17	5	-165	-4	6	6	-182
4	8	6	-186	-4	10	6	312	-4	14	6	191	5	3	0	-204
5	13	0	-335	-5	2	1	-1339	5	4	1	182	-5	4	1	970
5	7	1	-117	-5	10	1	-122	5	13	1	440	-5	2	2	-296
5	4	2	-717	-5	5	2	615	5	6	2	-239	-5	6	2	-621
5	1	3	-1008	-5	2	3	-128	-5	11	3	-382	-5	13	3	-293
5	15	3	-542	-5	1	4	-9	-5	4	4	-367	-5	1	5	133
5	2	5	-83	-5	2	5	-402	-5	4	5	-238	-5	6	5	-388
5	8	5	-175	-5	10	5	-115	-5	11	6	101	-5	13	6	394
5	17	6	91	6	2	0	-139	-6	1	1	218	-6	5	1	-14
6	11	1	-572	-6	2	3	-615	-6	4	3	-331	-6	10	3	-224
6	7	5	10	-6	11	5	-1	7	1	0	-229	-7	6	1	-146
7	7	3	-2001	-7	6	5	25	-8	2	3	-372	-8	6	3	-122

Table 6 (*cont.*)

1	13	3	-266	1	15	3	82	-1	15	3	92	-1	17	3	29
1	19	3	150	1	1	4	-424	-1	1	4	-824	1	2	4	204
1	2	4	74	1	3	4	-563	-1	3	4	569	1	4	4	81
1	4	4	-1620	1	5	4	668	-1	5	4	-964	-1	6	4	647
1	7	4	31	-1	7	4	411	1	8	4	225	-1	8	4	210
1	9	4	343	-1	9	4	436	1	10	4	400	-1	10	4	373
1	11	4	295	1	13	4	98	-1	13	4	-127	1	18	4	92
1	1	5	-6	-1	1	5	-20	1	2	5	457	-1	2	5	-44
1	4	5	-537	-1	4	5	-371	1	6	5	689	-1	6	5	284
1	7	5	148	1	8	5	-181	-1	8	5	409	1	9	5	-118
1	10	5	-222	-1	10	5	-101	-1	11	5	-7	1	12	5	-218
1	12	5	73	-1	14	5	-150	1	16	5	97	-1	16	5	158
1	18	5	-5	-1	1	6	290	1	2	6	1	-1	2	6	32
1	3	6	-104	1	5	6	86	1	7	6	53	-1	7	6	-127
1	8	6	71	-1	9	6	14	-1	10	6	-55	1	11	6	-11
1	11	6	-121	-1	12	6	-112	1	13	6	78	1	1	7	-90
1	2	7	105	1	3	7	-3	1	5	7	-202	1	6	7	-41
1	7	7	-312	1	10	7	70	1	11	7	18	1	2	8	-6
1	8	8	149	2	1	0	249	2	2	0	-2091	2	3	0	-64
2	4	0	1595	2	5	0	-72	2	6	0	-2028	2	7	0	99
2	8	0	281	2	9	0	950	2	10	0	773	2	11	0	168
2	12	0	84	2	13	0	142	2	14	0	384	2	16	0	490
2	1	1	189	-2	1	1	-1869	2	2	1	465	2	3	1	1115
2	3	1	-669	2	4	1	1010	-2	4	1	-338	2	5	1	-17
2	5	1	-1219	2	6	1	-401	2	7	1	976	-2	7	1	-769
2	8	1	-746	-2	8	1	513	2	9	1	-632	-2	9	1	-211
2	10	1	-760	-2	10	1	214	2	11	1	241	-2	11	1	-583
2	13	1	131	-2	13	1	-158	-2	15	1	52	-2	16	1	358
2	19	1	-158	2	1	2	-174	-2	1	2	-1781	-2	2	2	1167
2	3	2	-860	-2	3	2	1237	2	4	2	-79	-2	4	2	-1383
2	5	2	-573	-2	5	2	-807	2	6	2	-83	-2	6	2	-662
2	7	2	1568	-2	7	2	288	2	8	2	222	2	9	2	1756
2	9	2	-1288	2	11	2	-9	-2	11	2	111	2	13	2	204
2	13	2	187	-2	14	2	-47	-2	15	2	59	2	2	3	112
2	2	3	7744	2	3	3	121	2	4	3	-701	-2	4	3	-250
2	6	3	-80	2	7	3	308	-2	7	3	177	2	8	3	-526
2	8	3	-347	2	9	3	288	2	10	3	107	-2	10	3	915
2	11	3	47	-2	12	3	391	-2	16	3	-31	2	2	4	143
2	2	4	-130	-2	3	4	-699	-2	4	4	459	-2	5	4	606
2	6	4	-184	2	7	4	207	-2	7	4	-34	2	8	4	-151
2	9	4	-302	-2	11	4	370	-2	12	4	-32	2	13	4	259
2	14	4	11	2	1	5	148	-2	2	5	42	2	3	5	-362
2	3	5	-236	2	5	5	-64	-2	5	5	528	2	6	5	5
2	6	5	-76	2	7	5	115	-2	7	5	-79	2	9	5	15
2	9	5	34	2	10	5	72	2	11	5	-107	-2	11	5	-151
2	13	5	-97	-2	13	5	-142	2	15	5	-84	-2	17	5	22
2	1	6	-99	2	2	6	76	-2	2	6	89	2	3	6	155
2	4	6	-124	-2	4	6	-308	2	5	6	-76	-2	6	6	-170
2	9	6	-114	-2	9	6	-47	-2	10	6	79	-2	11	6	126
2	12	6	52	-2	14	6	130	-2	16	6	-193	2	4	7	119
3	1	0	768	3	2	0	-217	3	3	0	-1385	3	4	0	348
3	5	0	215	3	6	0	414	3	7	0	1903	3	8	0	-93
3	9	0	1800	3	10	0	206	3	11	0	27	3	13	0	816
3	15	0	370	3	17	0	-165	3	1	1	-360	-3	1	1	-741
3	2	1	28	-3	2	1	-1665	3	3	1	234	-3	3	1	-20
3	4	1	789	-3	4	1	221	3	5	1	-972	-3	5	1	-134

We now consider the methods which were used and possible improvements. It certainly seems to us that the sum function $MP_c(\mathbf{u}) + bMP_s(\mathbf{u})$ is considerably more powerful than the $P_s(\mathbf{u})$ function itself, and that the power of this sum function could be greatly improved by high angle data and judicious sharpening of the coefficients. A more explicit comparison of two sections of final electron density at $y = 11/60$ in Fig. 5(*a*) and at $y = 19/60$ in Fig. 5(*b*) with that obtained at an early stage from the $MP_c(\mathbf{u}) + MbP_s(\mathbf{u})$ function [Fig. 6(*a*) and (*b*)] indicates the resolution problem rather well. Also the problems of resolution in the BRR method are illustrated by the maps for these same sections in Fig. 8 for the complete structure factor, and in Fig. 7 when the contribution of the iodide ion has been subtracted from the structure factors. In retrospect, peaks were found for much of the structure in both maps, but it seems doubtful to us that either method alone would have yielded the structure from these X-ray diffraction data. Thus the key to the method was the peaks which were in common to both methods.

Inasmuch as the imaginary part B of the structure factor can be calculated uniquely from anomalous dispersion X-ray data, it may be worth exploring various methods for obtaining the real part A, so that it could be properly scaled by a constant k and then combined as $kA + iB$ to yield the structure factor and hence the structure. One method of calculating A would be based upon use of all unique peaks based upon the necessarily centrosymmetric electron density map based upon iodine phases alone. Another method for the A's

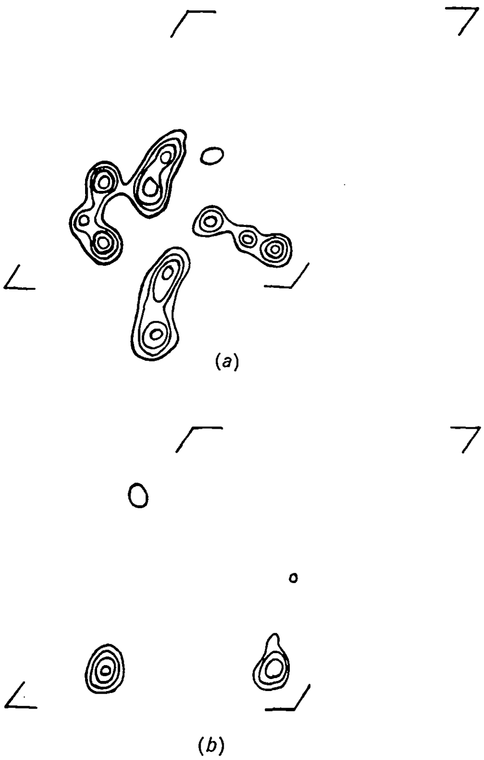

Fig. 5. Two-dimensional sheets from the final electron density map for LCR methiodide at (a) $y=11/60$ and (b) $y=19/60$.

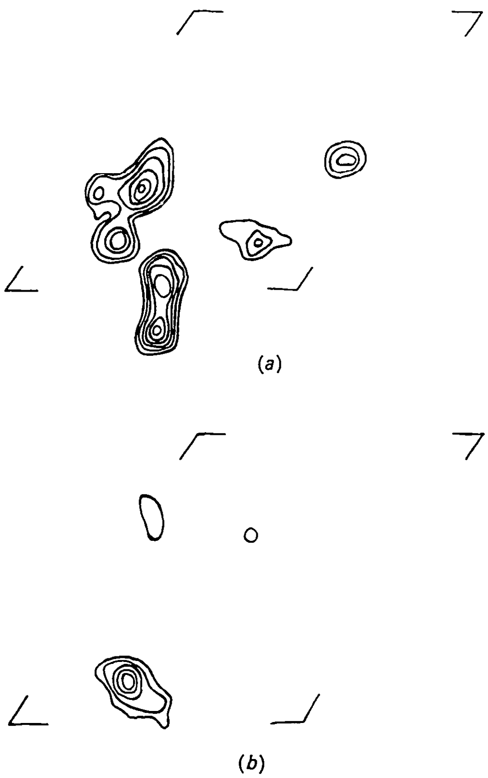

Fig. 6. Two-dimensional sheets from the $P_c(\mathbf{u})+bP_s(\mathbf{u})$ function at (a) $y=11/60$ and (b) $y=19/60$.

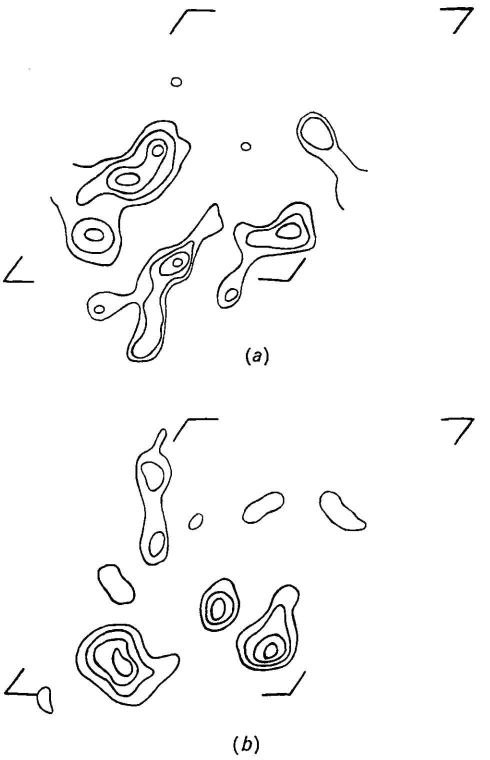

Fig. 7. Two-dimensional sheets from the electron density map calculated by the BRR method without the iodide contribution. In (a) $y=11/60$ and in (b) $y=19/60$.

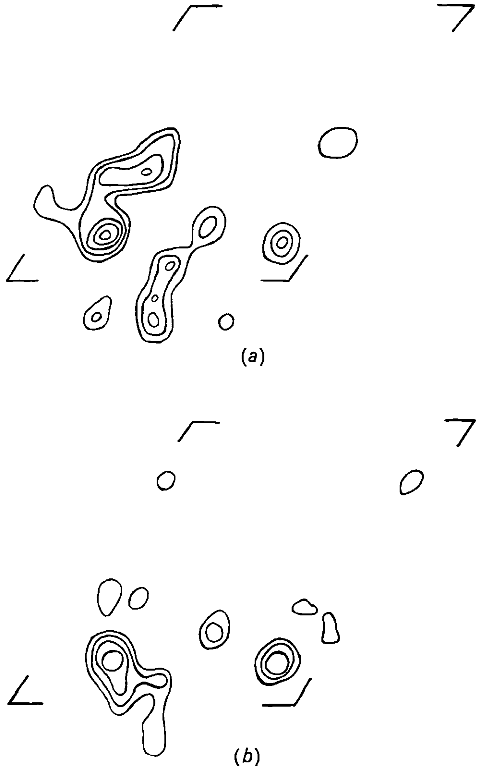

Fig. 8. Two-dimensional sheets from the electron density map calculated by the BRR method with the iodide contribution. $y=11/60$ in (a) and 19/60 in (b).

would be based upon the peaks of a three-dimensional minimum function calculated as outlined above from $MP_c(\mathbf{u})$, from $MP_s(\mathbf{u})$, or better yet from the $MP_c(\mathbf{u})+bMP_s(\mathbf{u})$ function. Still another method would be based upon molecular fragments which had been located by other methods. After this structure determination had been completed we tested one of these methods, the computation of A's from well-resolved peaks in a three-dimensional electron density map computed from the iodide phases only. An electron density map then computed from these A's and from the B's obtained by the BRR method yielded 17 peaks which also appeared in the 24 peaks of the iodine phased map and which were within 0·75 Å of atoms in the final structure. Unfortunately, the seven other peaks appeared within 0·75 Å of the mirror images of the proper atomic positions of the final structure. In addition, a number of other peaks were present, about equally divided among those at correct atomic positions, those at mirror images of correct atoms, and those which were not at either correct atomic or mirrored positions.

Alternatively, one might use only the signs of these A values as a basis for choice between the two possible values in the BRR method, particularly for those reflections having smallest $|\varphi-\beta|$, for which the heavy-atom phases gave signs which disagreed with those of the final structure in two of ten cases. We found that all of these ten signs of A's were correctly given by the peaks appearing in the electron density map based upon iodide ions only.

A third alternative is the use of A and B values from the above methods, but with the use of the sign of B as found in the BRR method. Of course, more input information than the iodide positions is required for the B values. Hopefully, the mirror plane of the iodide arrangement would then be destroyed. Together with the two approaches outlined above, this method might deserve further consideration.

In summary, this structure of leurocristine methiodide, together with the known chemical relationships establishes the structures of leurocristine, and vincaleukoblastine, including all asymmetric centers and the absolute configuration. It can be hoped that the syntheses of these and closely related compounds will lead to molecules which are more effective against tumors, with less toxic side-effects. Perhaps the three-dimensional structure will aid in the elucidation of mechanism of action of these compounds. Finally, the combination of methods of structure determination proved here to be effective, together with partially tested further proposals, may aid in structure studies of more complex molecules by anomalous dispersion techniques.

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