

This article was downloaded by:

On: 24 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Macromolecular Science, Part A

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597274>

The Tridimensional Structure of Polyflavonoid Tannins by Conformational Analysis

A. Pizzi^a; F. A. Cameron^a; N. J. Eaton^a

^a National Timber Research Institute Council for Scientific and Industrial Research, Pretoria., Republic of South Africa

To cite this Article Pizzi, A. , Cameron, F. A. and Eaton, N. J.(1985) 'The Tridimensional Structure of Polyflavonoid Tannins by Conformational Analysis', *Journal of Macromolecular Science, Part A*, 22: 4, 515 — 540

To link to this Article: DOI: 10.1080/00222338508056617

URL: <http://dx.doi.org/10.1080/00222338508056617>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

The Tridimensional Structure of Polyflavonoid Tannins by Conformational Analysis

A. PIZZI, F. A. CAMERON, and N. J. EATON

National Timber Research Institute
Council for Scientific and Industrial Research
Pretoria, Republic of South Africa

ABSTRACT

The conformations of minimum total energy of bi-, tri-, and polyflavonoids, constituting the polymeric condensed tannins, are elucidated. Maps of minimum total energy and spacial conformations are shown and discussed. The maps show the different conformations of rotational isomers for the different interflavonoid linkages. Considerations regarding the relative abundances of the various structures tie up with findings in both nature and by synthetic means. Van der Waals forces are predominant. H-bonds are present but have considerably lower importance in determining the conformations of minimum energy. H-bonds locations and values are reported. The helix confirmations of a few polyflavonoids are reported and discussed.

INTRODUCTION

The advances in condensed tannins chemistry have been extensive during the last decade. To the excellent and steady work of research groups dedicated to the fundamental aspects in this field [1-4, 8] has been added the impetus of research groups dedicated to elucidate, at

both basic and applied levels, the reactions and behavior of condensed tannins as a raw material for the manufacture of wood adhesives [5, 10]. These materials as well as their application reactions have mainly been approached from an organic chemistry angle, with perhaps a few exceptions [11].

This organic chemistry approach has been very successful indeed in elucidating the primary and secondary structure of polyflavonoid tannins as well as their characteristic reactions. However, a gap still remains in our knowledge of the tertiary structure of these materials; a gap that may be better investigated by a physicochemical, rather than organic chemistry, approach.

Conformational analysis is the tool used in this article to elucidate the tertiary structures of minimum energy of condensed flavonoids and polyflavonoids of which the secondary and primary structures were already known [1]. This is not an easy task as several flavonoid combinations are known. The investigation was limited to 4,6- and 4,8-linked polyflavonoids and to those condensed flavonoids which have started to be known as "angular" tannins [1]. All these types of condensed tannins had to be investigated as it is apparent from the applied research literature [7] that considerable differences in applied behavior exist according to the type of flavonoid linkages present.

The "ab initio" conformational analysis program used has already been reported in a recent series of articles on the structures of amorphous and crystalline cellulose I [12, 13]. It is based on the proven fact that the conformational energy of a biological molecule or macromolecule can be represented with good accuracy by a sum of four types of contributions, namely:

$$E_{(\text{tot})} = E_{(\text{VdW})} + E_{(\text{HB})} + E_{(\text{ele})} + E_{(\text{tor})}$$

where $E_{(\text{tot})}$ is the total energy of the system, $E_{(\text{VdW})}$ is the van der Waals energy, $E_{(\text{HB})}$ is the H-bonding energy contribution, $E_{(\text{ele})}$ is the electrostatic contribution, and $E_{(\text{tor})}$ is the bond torsional energy contribution (hindered rotation around skeletal bonds). A fifth energy value is also calculated, taking into account possible aromatic and etherocyclic ring deformations. The well-proven mathematical expressions as well as their functional coefficients for each of the forms of energy considered have already been extensively reported [12].

The present study takes into account not only the energy barriers to rotations around the interflavonoid C-C bonds but also those of side-group bonds which could contribute to the stabilization of the molecules in a conformation of minimum total energy.

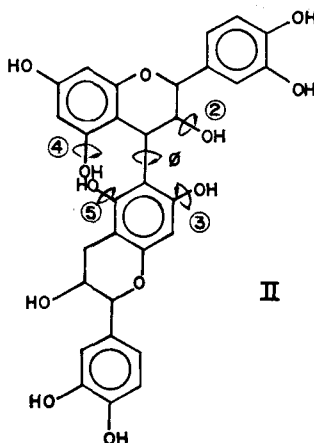
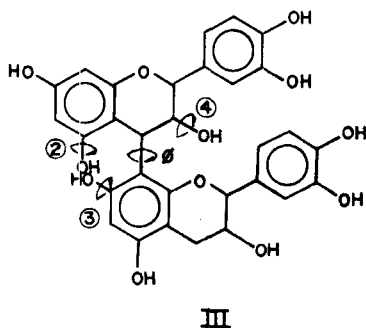
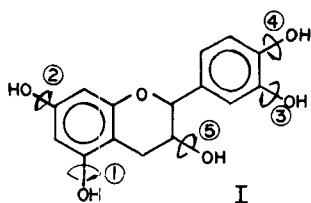
The original atom coordinates, bond angles, and distances of a monoflavonoid were obtained from a recent crystallographic study of the monoflavonoid catechin [14]. Electrostatic charges on the various atoms were calculated by MNDO and Geomo programs [15]. As the

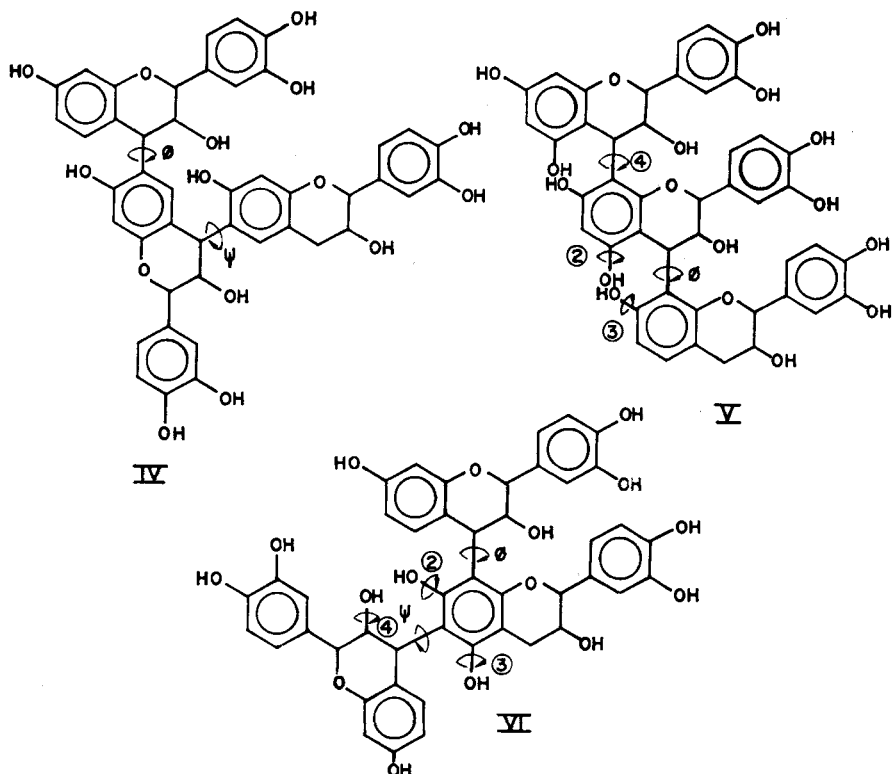
catechin bond lengths of the side groups obtained by x-ray diffraction [14] appeared to be very inaccurate, the molecule geometry was optimized by use of the Geomo program [15].

It was decided to use the original crystallographic coordinates anyhow as it appeared that on several initial experiments the conformational positions of minimum energy did not vary with the two sets of bond lengths. The absolute depths of the energy minima did, however, change, as expected. Since these are relative rather than absolute minima, it was felt that the x-ray-derived data, i.e., experimental results, should be used. A new, more accurate x-ray diffraction study was commissioned from another research group, and it is under way [16]. The conformational and relative energy results reported here are thus valid with both sets of side group bond lengths. The molecules studied in their trans and cis variations were (see below).

Tetramers derived from Structures II and III with the next dimer connected to Structure II and III with a 4,6- or 4,8-interflavonoid linkage, respectively, and tetramers of angular tannins as Structure VI obtained by linking Structure II to Structure III with 4,6- (4 for II, 6 for III) linkage were also studied.

In the case of Structure I it was decided to maintain the position of the B-rings in respect of the etherocyclic ring without rotation of the interconnecting bond and to maintain the relative positions as obtained from the x-ray diffraction data. Rotation of this bond showed that the position of minimum energy is identical to that obtained by x-ray diffraction. The B-ring was not rotated in any of the other structures as it is always located on the outside of the helix formed, and its

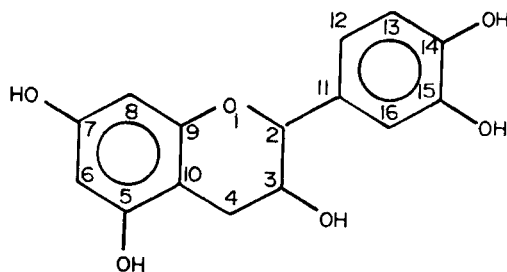




relative position in relation to the rest of the flavonoid unit does not change as a consequence of the rotation of the interflavonoid connecting bonds.

EXPERIMENTAL

The numbering of each monoflavonoid unit was done according to standard rules as follows:

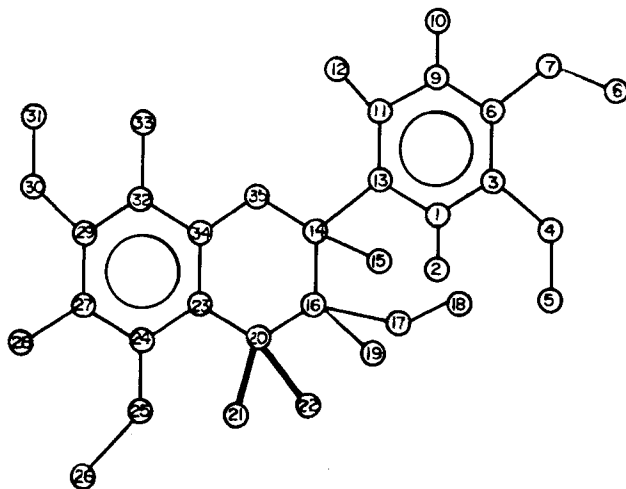


The methods used to determine the position of 0° from which each bond is rotated were:

- For the monomer (Structure I), 0° was taken as the positions obtained by x-ray crystallography [14].
- For dimers, trimers, and tetramers, from the position of minimum obtained in monomer, 0° for $-OH$ side chains was also taken as the positions obtained by x-ray crystallography in relation to the monoflavonoid skeleton the $-OH$ chain belongs to.
- The 0° position for the interflavonoid bond was taken as follows.

EXTENSION OF THE TANNIN CHAIN

The extension of the tannin chain from the basic monomer is explained by using the following example. Consider extending a monomer to a dimer with 4,8-linkage. The monomer is



After formation of the dimer, using 4,8-linkage, Atom 20 will be joined to the equivalent on the second monomer of Atom 32 (32', say). The method used to generate the coordinates of the second monomer uses the fact that the positions of the atoms of the second monomer relative to Bond 20-32' will be equivalent to the positions of the atoms of the first monomer relative to Bond 33-32. Therefore, to calculate the coordinates of the atoms of the second monomer, the matrices are obtained which transform Bond 20-21 to Bond 32-33. Then, Bond 20-21 is extended to its required length and Atom 21 is replaced by Atom

Phloroglucinol A-rings

Dimer II (4,6-linked)	3,4 cis	105	-	-72	-139	142	136	-	321.826	321.826
	All-trans	-46	-	-48	91	-113	-108	-	318.547	318.547
Dimer III (4,8-linked)	3,4-cis (Figs. 4 and 5)	-72	-	104	-52	-	-	-	331.056	331.056
	All-trans (Fig. 3)	-30	-	-108	103	-130	-	-	318.990	318.990
Trimer V (4,8-linked)	All-3,4-cis (Fig. 9)	-72	-	102	57	-	-	-163	660.974	329.918
	All-trans (Fig. 8)	-29	-	-109	62	-	-	-151	639.499	320.509
Tetramer (4,8-linked)	All-3,4-cis (Figs. 9 and 10)	-	-	102	57	-	-	-163	990.344	329.370
	All-trans	-	-	88	75	-	-	-96	1 180.100	540.601

Angular tannins

Trimer VI (4,8-, 6,4- linked) A rings: res/ phloro/res	All-3,4-cis	-75	-	170	111	-120	-	-137	655.645	-
	All-trans (Fig. 6)	-22	-	70	50	-129	-	-8	638.100	-
Tetramer (4,6-, 8,4-, 4,6-linked) A rings: res/ phloro/res/res	3,4-trans/3,4-cis (Fig. 7)	-29	-	74	80	-124	-	66	641.868	-
	3,4-cis/3,4-trans	-77	-	178	50	-130	-	-166	649.012	-
	All-trans	-78	-	-	-	-	-	-	992.829	-

32'. The transformation matrices are then applied to the coordinates of the atoms of the first monomer relative to Atom 32 to give the corresponding position of the atoms relative to Atom 32'. These positions give the coordinates for the atoms of the second monomer.

The coefficients of the van der Waals, H-bond, electrostatic, and torsional functions used have already been reported [12]. The atomic charges have been obtained using the Geomo program [15].

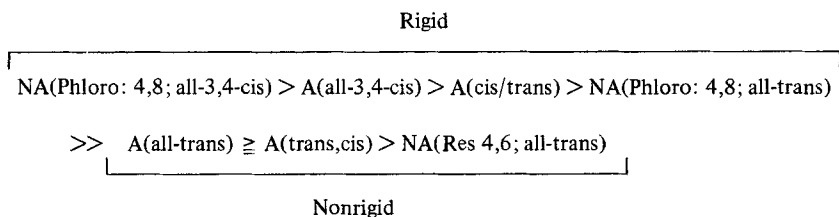
The conformations of minimum energy of I, II, III, IV, V, VI, and of the tetramers are expressed as a function of the rotational angles indicated according to the (a), (b), and (c) connections used. The rotational angles defining the conformations of minimum energy as well as the relative energy values are shown in Table 1. The H-bond contributions, in total, are shown in Table 1, and the localized H-bond interactions in Table 2.

DISCUSSION

The total energies of the conformations of minimum energy shown in Table 1 indicate that the order of stability obtained by conformational analysis is consistent with the yields found by synthetic means for (i) 4,6-linked resorcinol A-rings biflavonoids obtained by reaction of (-)-fisetinidol with (+)-mollisaccacidin, such as the 2,3-trans-3,4-cis: 2',3:trans (3,4-cis, Table 1, Figs. 1 and 2), and all-trans biflavonoids of Structure II [17]. (ii) The "angular" tannins trimers (VI), with the 4,8:4,6-linked all-trans (Figs. 5 and 13), only slightly more favorable than the 2,3-trans-3,4-trans:2',3'-trans:2'',3''-trans-3'',4''-cis-bi-(-)-fisetinidol-(+)-catechin (trans/cis, Table 1, Figs. 6 and 14) explaining the similar yields obtained by the synthetic route [18]. The $E_{(tot)}$ maps confirm the existence of four rotational isomers for both triflavonoids. (iii) The 4,8-linked biflavonoids (III) (Figs. 3 and 4) and derived triflavonoids (Figs. 7, 8, 11, and 12). However, two discrepancies are present in this case, namely, (a) the difference in the values of E_{min} for the all-trans and 3,4-cis conformations is larger than expected by the synthetic route results [17]; and (b) the decreasing yield order by the synthetic route of 4,8-linked all-trans; 4,8-linked trans, cis,trans; 4,6-linked all-trans is inconsistent with the $E_{(tot)}$ decreasing stability in which the last two conformations invert order. This shows that, while in many cases the relative values of minimum $E_{(tot)}$ are a good indication of which form is likely to be synthesized in higher yield, the relative conformation stabilities are only vaguely related to the proportions of compounds formed in the reactions.

There is definite evidence that, while the reactions determining the type of compound formed are predominantly kinetically controlled, the relative proportions of the stereoisomers formed also respond to a measure of thermodynamic control [19-21].

As regards "nonangular" tannins, the resorcinol A-ring 4,6-linked trimer IV, all-trans (Fig. 9), has wider allowed zones than the "angular" trimers VI. It is also capable of forming four rotamers (Fig. 10). The phloroglucinol A-ring 4,8-linked all-trans (Fig. 7) trimer V has wider allowed zones, lower rigidity, and much lower rotational barriers than the all-cis (3,4-cis) (Figs. 11 and 12). The all-3,4-cis has only three allowed rotamers (Fig. 12), two of which are energetically comparable, the third one being unfavorable energetically. The respective maximum values of the rotational barriers of all the nonangular (NA) and angular (A) trimers examined are, in decreasing order of barrier value,



where (NA(Res 4,6; all-3,4-cis) map was not generated but expected to be nonrigid but more rigid than the all-trans).

As regards the -OH side chains, the van der Waals forces allow some variation between +20° and -20° around the conformation of minimum energy. Energy variations due to the H-bond are small. For tannins, the van der Waal forces are preponderant in determining the conformations of minimum energy. Polyflavonoids then form helixes (i.e., the resorcinol 4,6-linked all-trans type forms a helix with approximately a four flavonoid units step for 360° rotation) (Figs. 8 and 9).

TABLE 2. Conformational Analysis, Tannins, H-Bonds Locations and Energy Constitution

Atoms	Phloroglucinol A-rings, E_{HB} , kcal/mol								
	Dimer 4,8-		Trimer 4,8-		Tetramer 4,8-		Dimer 4,6-		
	cis	trans	cis	trans	cis	trans	cis	trans	
H(03)-O(1')	-0.3176								
O(05)-H(07')	-0.2388						-0.2370	-0.0884	
O(7)-H(07')	-0.0923		-0.0923				-0.1218		
O(1)-H(07')	-0.3257		-0.3257				-0.2611	-0.1322	
H(05)-O(1')	-0.3440		-0.3440				-0.2611	-0.1322	
O(3)-H(97')		-1.680		-1.7695					
H(05)-O(7')		-1.111	-0.2388	-1.0561			-0.0735	-0.1868	
H(03)-O(1)		-0.118							
H(03)-O(7')		-0.085		-0.0829			-0.1536		
O(3)-H(05')							-1.6661	-2.6539	
H(05)-O(5')							-0.4495	-0.6245	

H(05)-O(5')				-0.1942	-0.2765
H(03')-O(1'')					
H(05')-O(1'')					
O(1')-H(07'')					
O(3)-H(07'')					
O(5)-H(07'')					
O(3')-H(07'')					
H(03')-O(7'')					
H(03')-O(7''')					
H(05')-O(3'')					
H(013'')-O(7''')					
	-0.3186	-0.0902	-0.3186		
	-0.2952	-1.2868	-0.2952	-0.2719	
	-0.7737	-0.0980	-0.7737		
	-3.3860		-3.3860		
		-1.7477			
					-1.2385
					-0.3812
					-0.2382
					-0.0350
					-0.3446

(continued)

TABLE 2 (continued)

Resorcinol A-rings, E_{HB} , kcal/mol									
Atoms	Dimer 4,6-		Trimer 4,6-		Tetramer 4,6-			trans-	trans-
	cis	trans	cis	trans	trans-	cis-	cis-		
O(3)-H(08')		-3.5447		-3.5447					
H(03)-O(7')	-2.5629	-0.1385	-2.7825	-0.1385					
O(1')-H(07'')				-0.4941					
O(3')-H(07'')			-0.9874	-0.0607					
H(03')-O(7'')			-0.3405						
O(13)-H(03'')			-0.8448						
O(13)-H(03''')							-0.3392		
O(3)-H(03''')							-0.2214		
H(03)-O(3''')							-1.5496		
O(7)-H(07''')								-0.1599	
O(13')-H(07''')								-0.2138	
H(013')-O(7''')								-0.3446	
H(013')-O(7''')									-0.0449
H(03)-O(8''')									-0.2237

Angular tannins, E_{HB} , kcal/moi

Atoms	$2^\circ, 3^\circ, 4^\circ, \Psi^\circ$ rotated Φ° fixed in dimer minimum				$2^\circ, 3^\circ, 4^\circ$ fixed in previous column's minimum			
	trans- trans	cis- trans	cis- cis	cis- cis	trans- trans	cis- trans	trans- cis	cis- cis
H(03)-O(1')	-0.3194			-0.3198				
O(3)-H(07')		-1.7185			-1.6334	-0.1785	-1.7199	
H(03)-O(7')		-0.0829						
H(05')-O(1'')				-0.2422				-0.2412
H(05')-O(3'')	-3.1514	-2.8632			-2.8632	-2.7473	-1.6689	
O(5')-H(03'')	-0.0960	-0.1027			-0.1027	-0.1036	-0.3396	
H(07)-O(7'')	-0.6816					-0.7623		
H(07')-O(1'')	-0.4792	-0.3356			-0.3356	-0.5367	-0.2529	
H(07')-O(3'')				-0.9795				-1.0078
H(03'')-O(1'')					-0.1211	-0.1183	-0.1345	-0.1446
H(07')-O(7'')								-0.0178

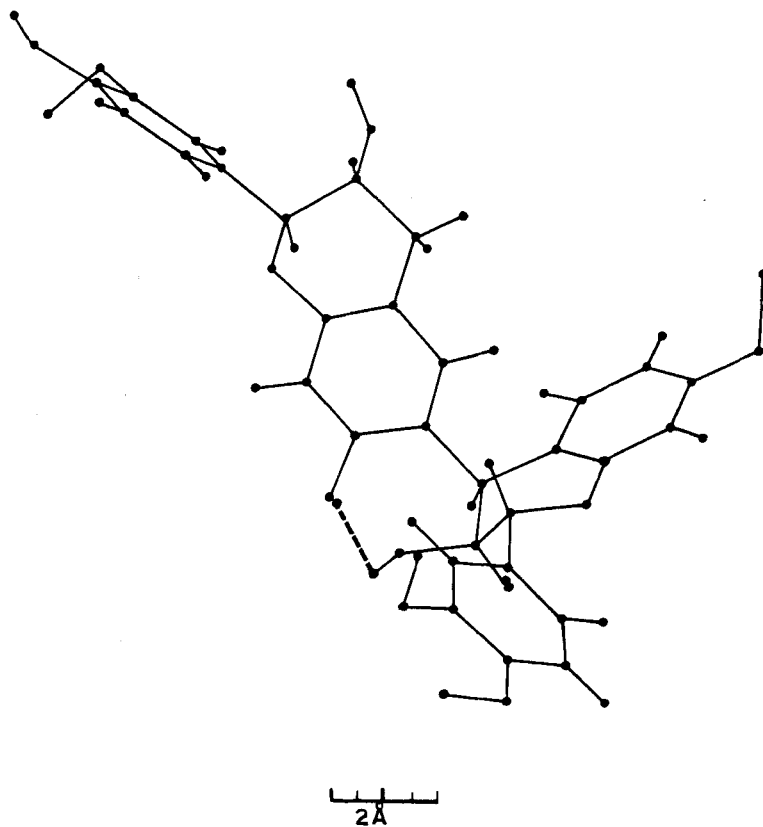


FIG. 1. Biflavonoid, resorcinol A-rings 4,6-linked; 3,4-cis at link.

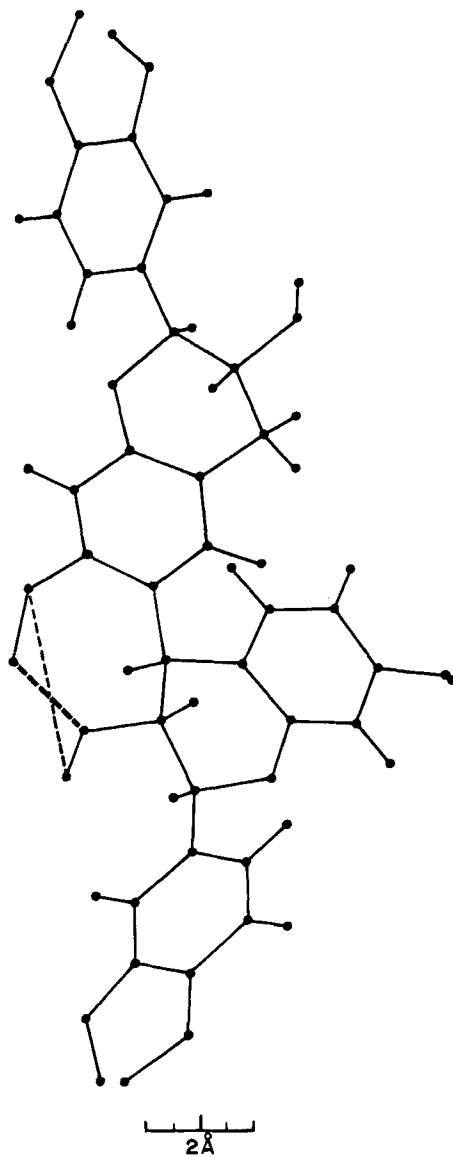


FIG. 2. Biflavonoid, resorcinol A-rings 4,6-linked; all-trans.

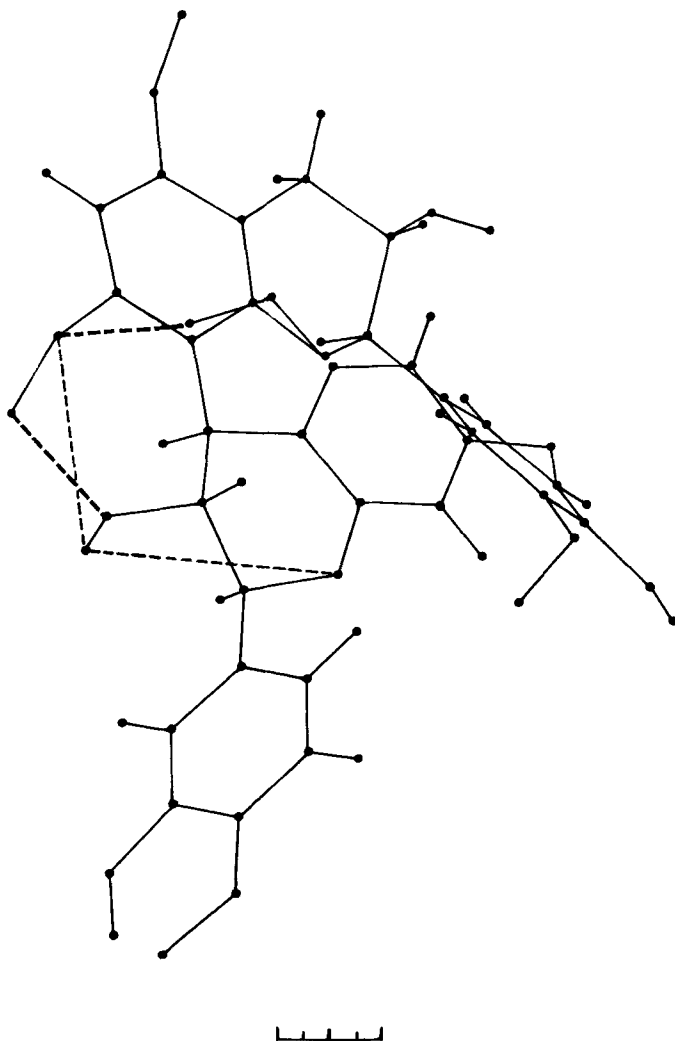


FIG. 3. Biflavonoid, phloroglucinol A-rings 4,8-linked; all-trans. The scale indicates 2 Å.

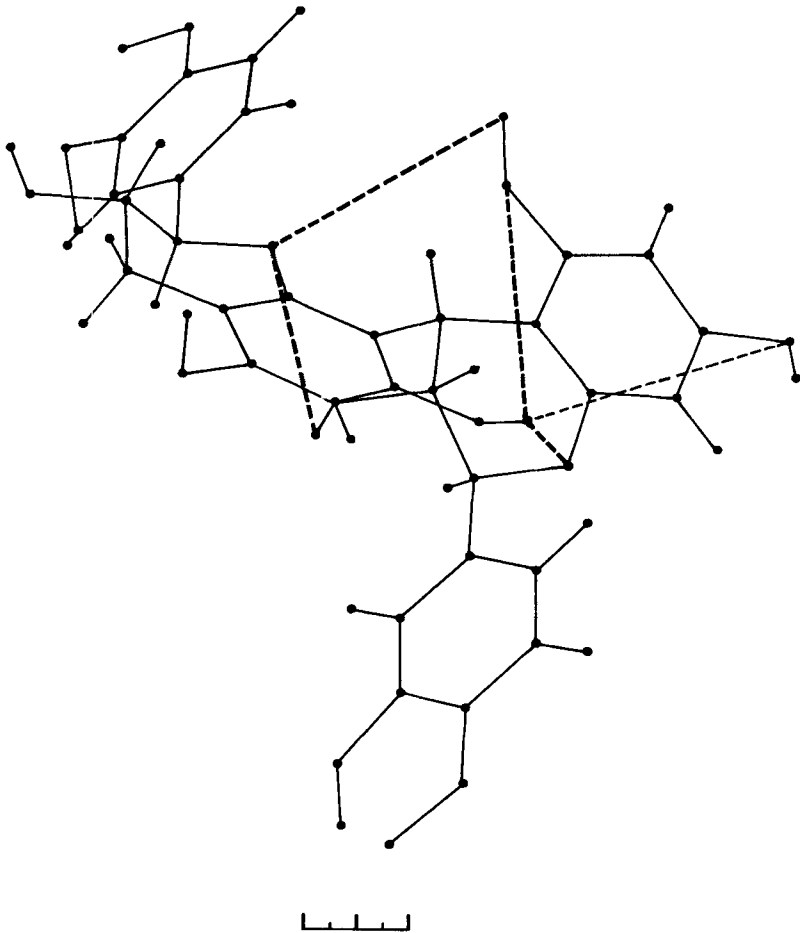
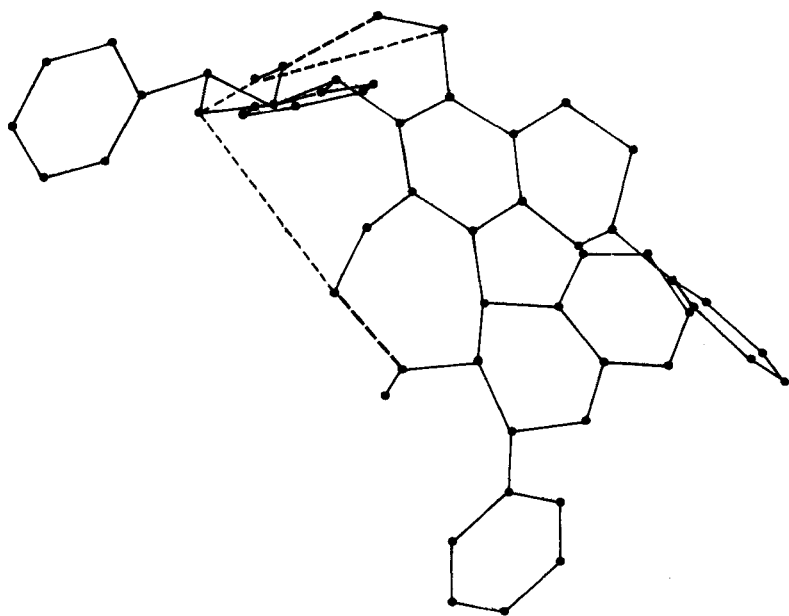


FIG. 4. Biflavonoid, phloroglucinol A-rings 4,8-linked; 3,4-cis at link (X,Y projection). The scale indicates 2 Å.



PLANE X

FIG. 5. Trifiavonoid, "angular tannin," all-trans [2,3-trans-3,4-trans: 2',3'-trans: 2'',3''-trans-3'',4''-trans-bi(-)-fisetinidol-(+)-catechin]. The scale indicates 2 Å.

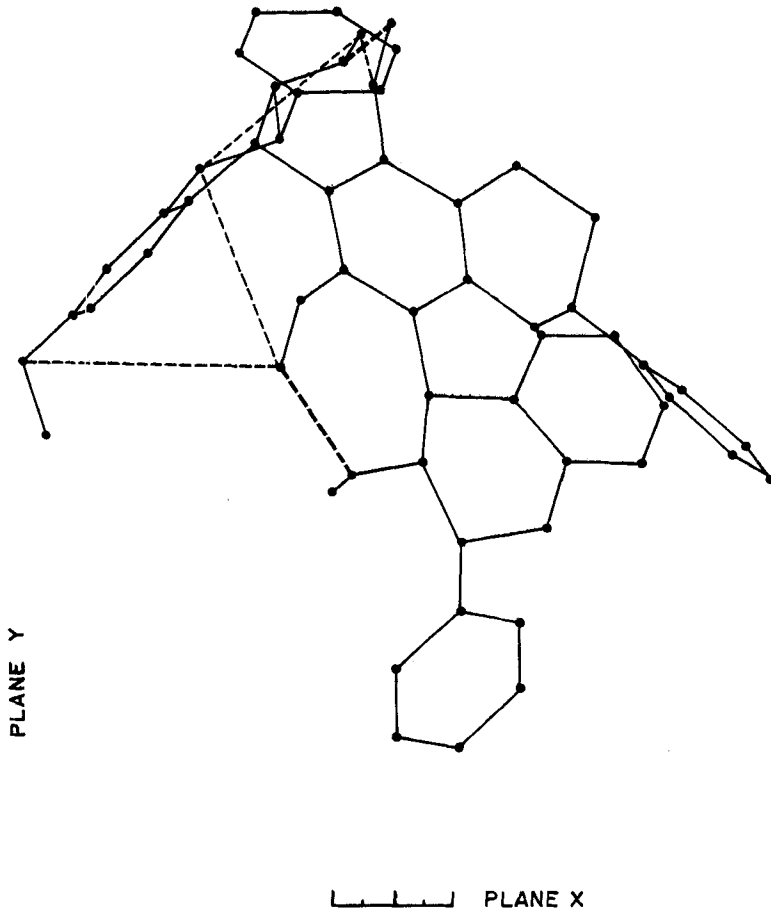


FIG. 6. Triflavonoid, "angular tannin," trans/cis[2,3-trans-3,4-trans; 2',3'-trans; 2'',3''-trans-3'',4''-cis-bi-(-)-fisetinidol-(+)-catechin]. The scale indicates 2 Å.

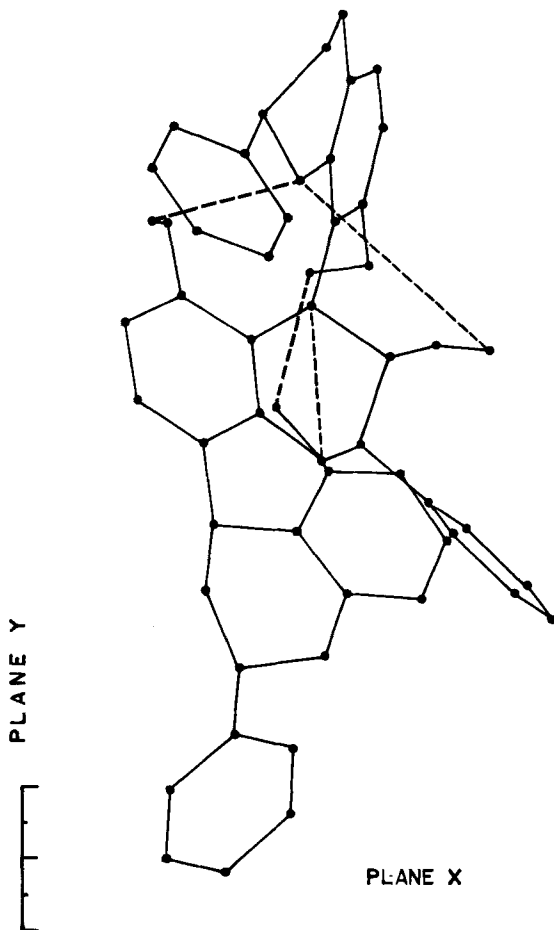


FIG. 7. Triflavonoid, nonangular tannin; all phloroglucinol A-rings; all 4,8-linked; all-trans. The scale indicates 2 Å.

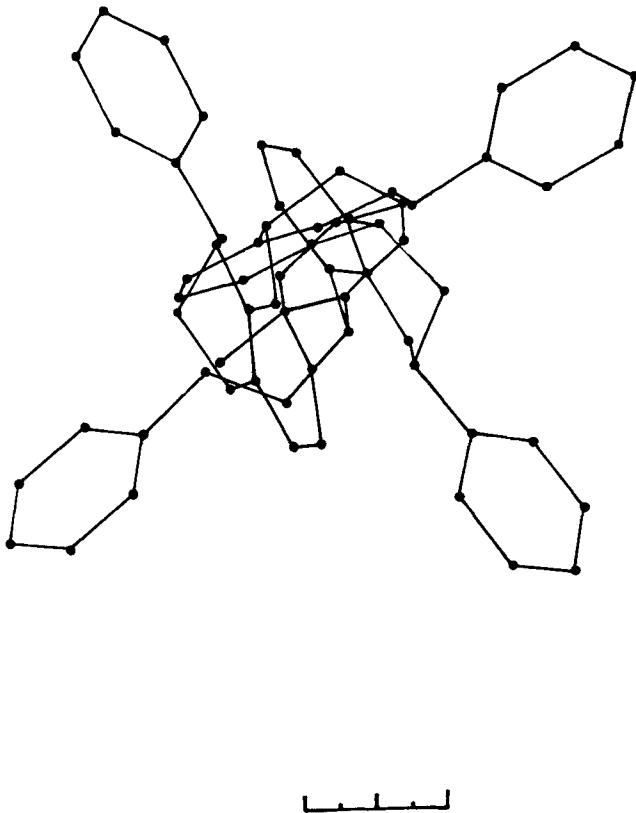


FIG. 8. Tetraflavonoid, phloroglucinol A-rings, 4,8-linked; all 3,4-cis; seen along helix axis. Note: B-rings all pointing outward from helix axis. The scale indicates 2 Å.

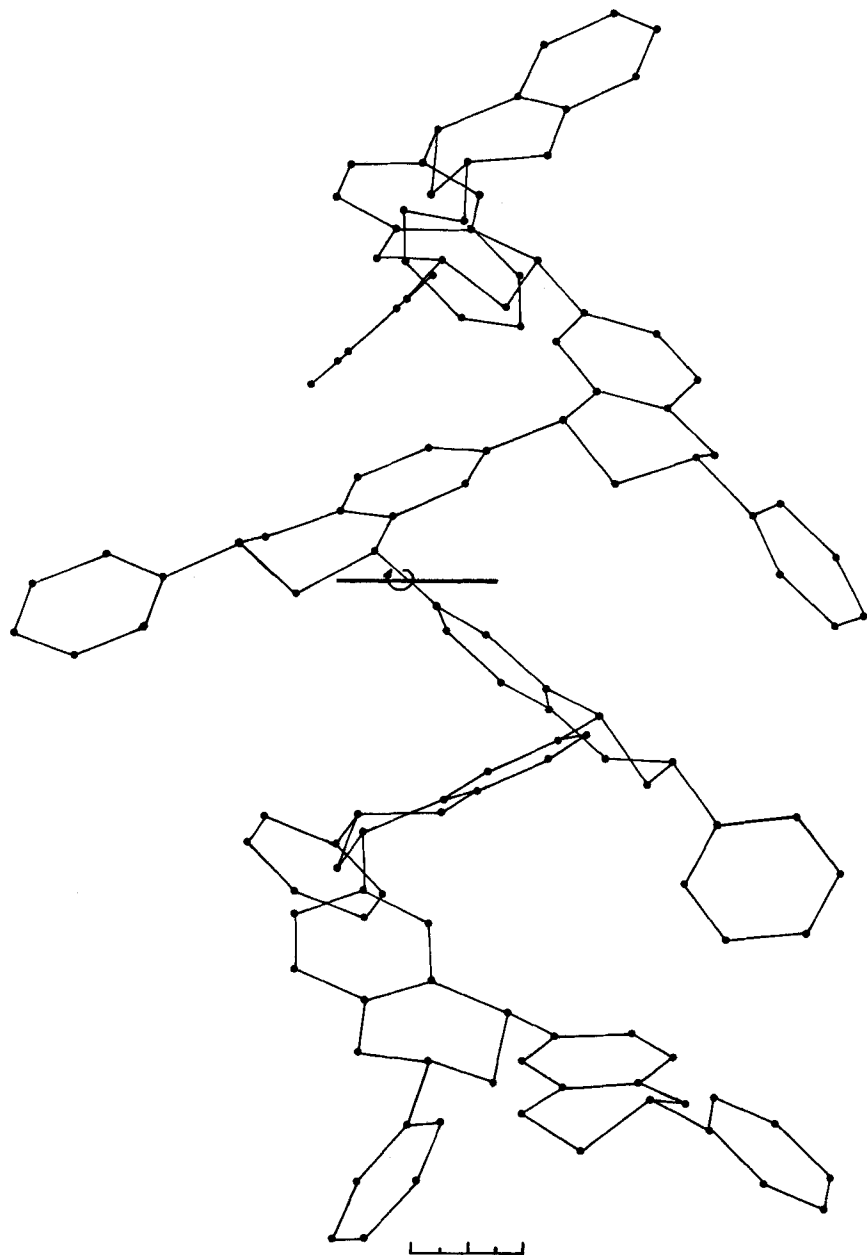


FIG. 9. Octamer; resorcinol A-rings; 4,6-linked; all-trans (formed by combination and minimization of two tetramers). B-rings effect as in Fig. 8 also present. H-bonds not shown in this figure. The scale indicates 2 Å.

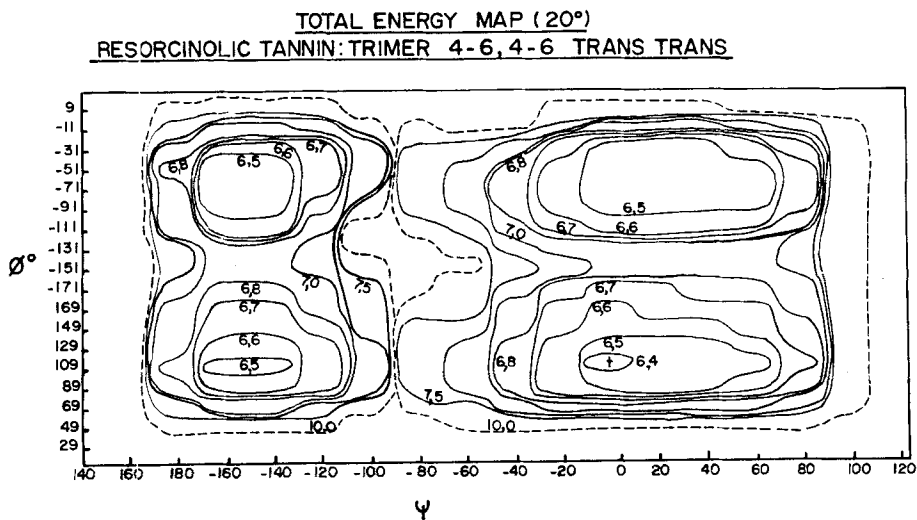


FIGURE 10.

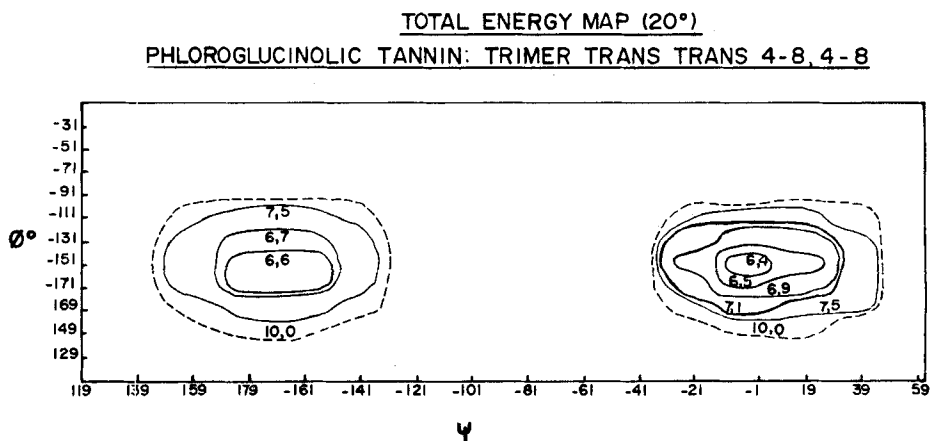


FIGURE 11.

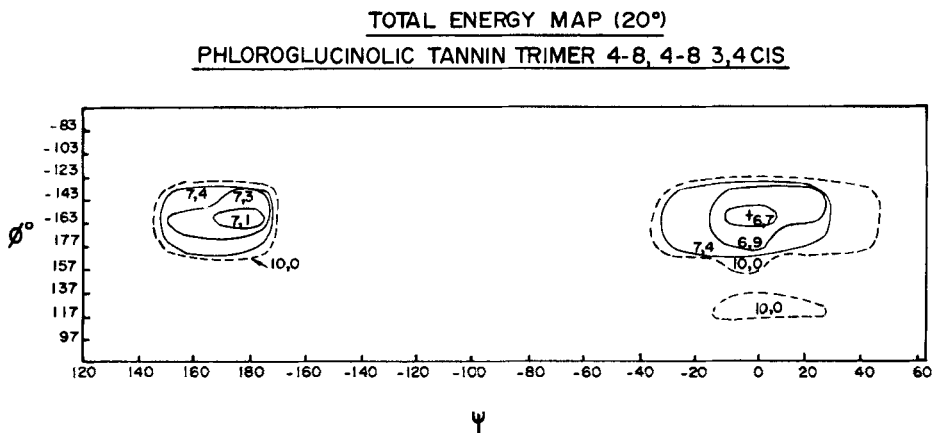


FIGURE 12.

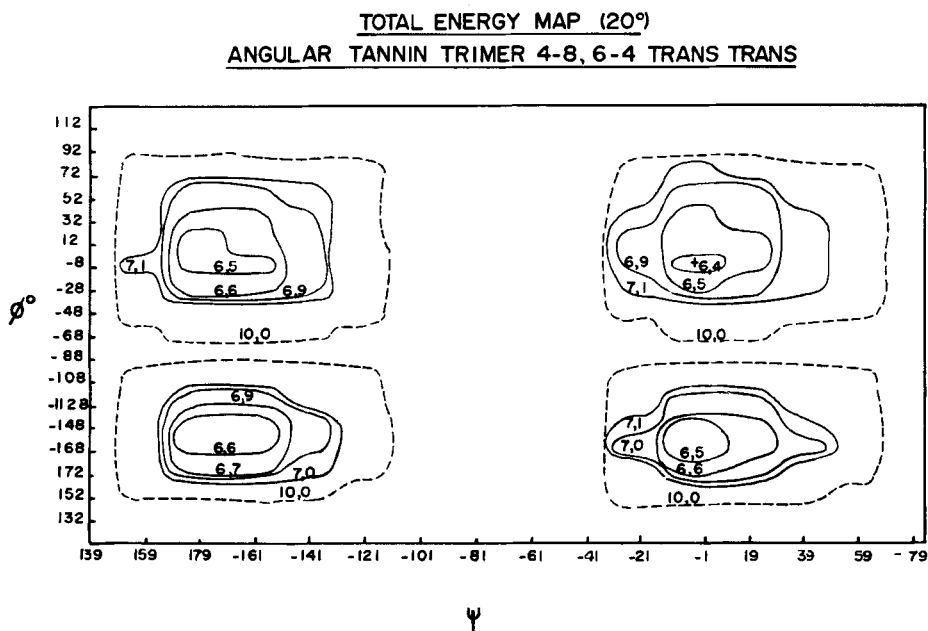


FIGURE 13.

TOTAL ENERGY MAP (20°)
ANGULAR TANNIN TRIMER 4-8, 6-4 TRANS CIS

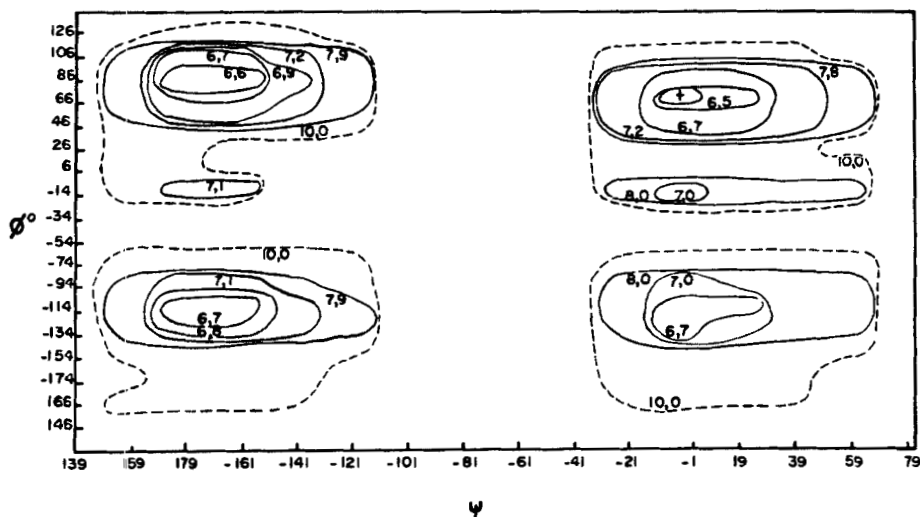


FIGURE 14.

REFERENCES

- [1] D. G. Roux, D. Ferreira, and J. J. Botha, J. Agric. Food Chem., **28**, 216 (1980).
- [2] E. Haslam, J. Chem. Soc. C., p. 1734 (1967) and other papers in this series; E. Haslam, Phytochemistry, **16**, 1625 (1977).
- [3] L. Y. Foo and L. J. Porter, J. Chem. Soc., Perkin Trans. 1, p. 1186 (1978); L. J. Porter, N. Z. J. Sci., **17**, 213 (1974).
- [4] J. W. Clark-Lewis and G. F. Katekar, J. Chem. Soc., p. 4502 (1962).
- [5] K. F. Plomley and A. M. Stashevski, CSIRO Aust. For. Prod. Newsl. 363 (1969).
- [6] W. E. Hillis and G. Urbach, J. Appl. Chem., p. 474 (1959); 665 (1959).
- [7] A. Pizzi, J. Macromol. Sci.-Rev. Macromol. Chem., **C18**, 247 (1980).
- [8] C. Ayla and Weissman, Holz Roh- Werkst., **40**, 13 (1982).
- [9] R. Hemingway and G. W. McGraw, Appl. Polym. Symp., **28** (1976); R. Hemingway and R. Kreibich, Ibid., **39** (1984).

- [10] R. Marutzky and Dix, Ibid., 39 (1984).
- [11] D. Du T. Rossouw, A. Pizzi, and G. McGillivray, J. Polym. Sci., Polym. Chem. Ed., 18, 3323 (1980); A. Pizzi and P. Van Der Spuy, Ibid., 18, 3447 (1980).
- [12] A. Pizzi and N. J. Eaton, J. Macromol. Sci.-Chem., A21, 1443 (1984).
- [13] N. J. Eaton and A. Pizzi, User Manual for BONDS-A Computer Programme to Perform the Conformational Analysis of Polysaccharides, CSIR Special report HOUT 323, Pretoria, South Africa, November 1983.
- [14] M. Hattingh, "Die Struktuuranalise van 8-broom-tetrametiel catechin deur middel van X-straaldiffraksie tegnieke," MSc Thesis, University of the Orange Free State, South Africa, January 1977; D. W. Engel, M. Hattingh, H. K. L. Hundt, and D. G. Roux, Chem. Commun., p. 695 (1978).
- [15] Quantum Chemistry Exchange Program, Programs Mindo and Geomo, Department of Chemistry, Indiana University, Bloomington, Indiana 47405, 1984.
- [16] C. Schutte, Private Communications, 1984.
- [17] J. J. Botha, D. Ferreira, and D. G. Roux, J. Chem. Soc., Chem. Commun., p. 700 (1978).
- [18] J. J. Botha, D. Ferreira, D. G. Roux, and W. E. Hull, Ibid., p. 510 (1979).
- [19] A. Pizzi, F. A. Cameron, and N. J. Eaton, The Tridimensional Structure of Polyflavonoid Tannins by Conformational Analysis, CSIR Special Report HOUT 379, Pretoria, South Africa, March 1985.
- [20] J. J. Botha, D. A. Young, D. Ferreira, and D. G. Roux, J. Chem. Soc., Perkin Trans. 1, p. 1213 (1981).
- [21] R. S. Thompson, D. Jacques, E. Haslam, and R. J. N. Tanner, Ibid., p. 1387 (1972).

Received December 15, 1984

Revision received April 2, 1985