

Registry No.—4,7-dimethyldihydrocoumarin, 18782-15-5; 4,7-dimethylchroman-2-ol, 24454-18-0; 4,7-dimethyl chroman-2-acetate, 24454-19-1; 2 semicarbazone, 24454-20-4; 4, 24454-21-5; 5, 24454-22-6; 6, 24454-23-7; 13, 24454-24-8; 14, 24454-25-9; 15, 24454-

26-0; chroman-3-ol, 21834-60-6; tetrahydropyran-3-ol, 19752-84-2; 19, 1481-82-9; 2, 24454-30-6.

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Configuration and Conformation of 3-Arylidene flavanones

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The stereochemistry of 3-arylidene flavanones has been established by the preparation of both *cis* (**3a-c**) and *trans* (**2a-c**) isomers. Configurations and conformations are assigned on the basis of nmr spectra. The products obtained by the acid-catalyzed condensation of flavanones and aromatic aldehydes have the *trans* configuration. Ultraviolet irradiation produces the *cis* isomers. Allylic coupling constants show that the *trans* isomers exist in the conformation with the 2-phenyl group axial. The *cis* isomers appear to exist in both conformations. In 2,2-diphenylchromanone (**4**) the steric effect of the second phenyl group causes formation of the *cis* product 2,2-diphenyl-3-benzylidenechromanone (**5**). *o*-Hydroxybenzaldehyde with flavanone does not give the benzylidene derivative but forms *o*-hydroxybenzylflavone.

Flavanones have been condensed with a number of aromatic aldehydes to form 3-arylidene flavanones (termed flavindogenides) in high yield.¹ Flavindogenides have also been isolated as coproducts during the preparation of flavanones by the acid-catalyzed condensation of aromatic aldehydes and substituted *o*-hydroxyacetophenones.² Interest in 6-nitro-3-benzylidene flavanones as bacteriostats led Széll and Zarandy to reinvestigate methods for their preparation.³ Recently two natural products, eucomin and eucomol, related in structure to flavindogenides, were isolated.⁴ Eucomin is the first member of the arylidenechromanone family to be found in nature.

Two geometrical isomers are possible for the product from the condensation of aromatic aldehydes and flavanones since the β -aryl groups of the flavindogenide may be either *cis* or *trans* to the carbonyl group. In the reported cases only one of the two possible geometrical isomers was obtained. The condensation of aryl aldehydes with methylene compounds normally yields unsaturated products which have the carbonyl function *trans* to the larger group at the β -carbon atom.^{5,6} However, as shown below, there was some evidence to suggest that 3-(2-nitrobenzylidene)flavanone prepared in the normal way had the *cis* configuration. Cromwell and coworkers⁷ prepared *trans*-2-(2-aminobenzylidene)-4,4-dimethyltetralone by the reduction of the corresponding nitro compound with iron and acetic

acid. This compound was cyclized by refluxing with hydrochloric acid or on treatment with hydrogen chloride to give 5,5-dimethyl-5,6-dihydrobenz[*c*]acridine. Algar and M'Cullagh⁸ were unable to isolate the corresponding amino compound by reduction of 3-(2-nitrobenzylidene)flavanone with stannous chloride in acetic acid saturated with hydrogen chloride but obtained 2,3-(2-phenylchromano-3,4)quinoline directly. This cyclized product was the only product obtained when the flavanone was treated under the conditions described by Bell and Cromwell for formation of the amino compound.⁹ These results tended to indicate a *cis* configuration for the 3-arylidene flavanones.

In view of the interest shown in flavindogenides we undertook the present work in order to assign their stereochemistry. The stereochemical assignment was also necessary for our further studies on the epoxidation reactions of flavindogenides.¹⁰ In this paper the results of our study on *cis*- and *trans*-3-arylidene flavanones are presented.¹¹

The stereochemistry of the 3-arylidene flavanones has now been unambiguously determined by the synthesis of both the *trans* (**2a-c**) and *cis* (**3a-c**) compounds. Condensation of flavanones (**1a,b**) with benzaldehyde or anisaldehyde forms *trans*-flavindogenides (**2a-c**) in yields approaching 90%. In our study, as in previous reports, only one isomer was obtained. An examination of the reaction mixture using thin layer chromatography showed no trace of a second isomer. The nmr spectra of the crude reaction product also indicated only one isomer.

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(2) (a) J. H. Adams, *J. Org. Chem.*, **32**, 3992 (1967); (b) M. K. Seikel, M. J. Lounsbury, and S. Wang, *ibid.*, **27**, 2952 (1962); (c) T. Széll and R. E. M. Unyi, *ibid.*, **28**, 1146 (1963).

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(9) J. R. Doherty, Ph.D. Thesis, National University of Ireland, 1962.

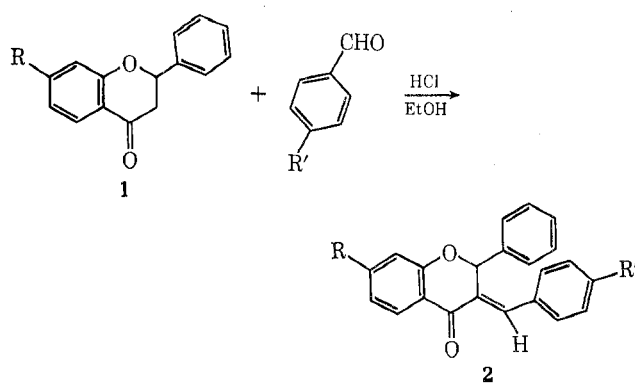
(10) (a) Flavanoid Epoxides. VI: D. D. Keane, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague, *Tetrahedron*, in press. (b) Flavonoid Epoxides. VII: J. R. Doherty, D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. B. Simons, and T. C. Teague, *ibid.*, in press.

(11) Preliminary communication: J. R. Doherty, D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons, and P. C. Teague, *Chem. Ind. (London)*, 1641 (1967).

TABLE I
PHYSICAL DATA ON FLAVINDOGENIDES

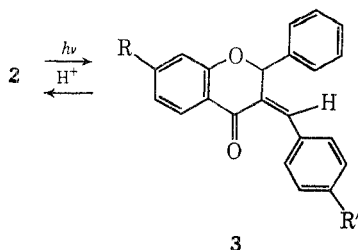
Configuration	Isomers		Isomers		Isomers	
	2a, <i>trans</i>	3a, <i>cis</i>	2b, <i>trans</i>	3b, <i>cis</i>	2c, <i>trans</i>	3c, <i>cis</i>
Yield, ^a %	80	82	83	44	81	38
Mp, °C (lit.)	104 (104 ^b)	96	147.5 (149 ^b)	<i>c</i>	145.5	108.5
UV, λ _{max} ^c (ε)	304 (16,600) ^d	307 (11,000) ^d	340 (16,900) 242 (13,600)	352 (14,500) 250 (18,100)	357 (21,800) 239 (16,600)	354 (19,400) 239 (17,900)
Ir, ^e ν _{C=O} , ν _{C=C}	1670, 1610	1670, 1610	1670, 1600	1670, 1600	1675, 1610	1675, 1610
Photochemical equilibration, %	8	92	8	92	20	80
Chemical equilibration, HCl, %	100	0	100	0	100	0
Anal., %						
Calcd C, H	84.6, 5.2	84.6, 5.2		80.7, 5.3	77.42, 5.38	77.42, 5.38
Found C, H	84.6, 5.2	84.4, 5.2		80.2, 5.5	77.41, 5.47	77.42, 5.30

^a Yields are for recrystallized products. ^b See ref 1b. ^c **3b** was not crystalline. ^d Determined in methanol. ^e Determined as 1% solution in CCl₄.



- a, R = H; R' = H
 b, R = H; R' = OCH₃
 c, R = OCH₃; R' = OCH₃

Irradiation of the *trans* compounds with ultraviolet light using a Corex or a Pyrex filter to screen out radiation below 260 mμ gave mixtures with a high percentage (80–92%) of the *cis* isomers (**3a–c**). No other products were detected. The pure *cis* isomers were isolated by either fractional crystallization or by column chromatography. The *cis* isomers are crystalline solids except for **3b** (a yellow glass) which resisted attempts at crystallization although thin layer chromatography indicated it to be pure. The structure of the *cis*-flavindogenides was inferred from elemental analyses, infrared, and electronic spectra (which were very similar to those of the *trans* compounds), nmr spectra, and the fact that they were completely and essentially quantitatively isomerized to the *trans*-flavindogenides when treated with acid. The properties of the isomeric flavindogenides are shown in Table I.



- a, R = H; R' = H
 b, R = H; R' = OCH₃
 c, R = OCH₃; R' = OCH₃

In order to assign the positions of the vinylic and the 2-proton signals in the nmr spectra of the isomeric

flavindogenides, **2a–c** were prepared with deuterium in the β position by condensation of **1a** and **1b** with the respective aldehydes-1-*d*. The products have physical, electronic, and infrared spectral properties essentially identical with those of the nondeuterated compounds. The nmr spectra of deuterated *trans*-flavindogenides lacked the signal at τ 1.9 and allowed unequivocal assignment of this signal to the vinyl proton. The singlet in the τ 3.9 region was not so broad. Irradiation of the *trans*-flavindogenides-β-*d* and product work-up as described above yielded the *cis*-flavindogenide-β-*d*. The nmr spectra of these *cis* derivatives were essentially identical with those of the nondeuterated isomers except for the absence of a signal of τ 3.3 and a sharpening of the singlet in the region of τ 3.9. Significant nmr data for the *cis*- and *trans*-flavindogenides are listed in Table II.

TABLE II
NMR DATA OF FLAVINDOGENIDES^{a,b}

Compound	Configuration	Chemical shifts, τ			
		Vinyl H	2 H	5 H	OCH ₃
2a	<i>trans</i>	1.92	3.37	2.14	
3a	<i>cis</i>	3.30	3.89	2.08	
2b	<i>trans</i>	1.98	3.34	2.14	6.30
3b	<i>cis</i>	3.32	3.89	2.10	6.28
2c	<i>trans</i>	1.95	3.33	2.12	6.28, 6.25
3c	<i>cis</i>	3.37	3.92	2.10	6.22

^a Determined as 10% solutions in CDCl₃. ^b Correct integrated area was obtained for the multiplets of the aromatic protons not listed.

Configuration.—Nuclear magnetic resonance spectroscopy has been most definitive in allowing the stereochemical assignment of *cis* and *trans* exocyclic α,β-unsaturated ketones. The deshielding effect resulting from the diamagnetic anisotropy of the carbonyl group causes the vinyl proton in the *trans* isomer (with the proton *cis* to the carbonyl group) to display a signal at a lower field than does that of the *cis* isomer.¹² This property has been used by Cromwell, *et al.*,⁶ in assignment of *cis* and *trans* configurations to benzylidenindanones and benzylidenetetralones and by Hassner and Mead¹³ in assignment of the geometrical isomers of benzylidenecyclohexanones. In each instance the vinylic proton in the *trans* isomer gives a signal at a

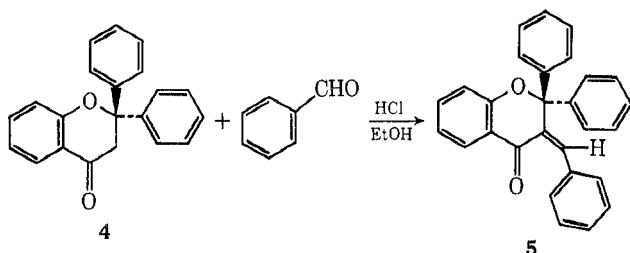
(12) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, p 124.

(13) A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

lower field (by *ca.* 1 ppm) than the *cis* isomer. With both the *cis*- and *trans*-3-arylidene flavanones available, the configuration of each pair could be established by determining the field position of the vinyl protons.

The nmr spectra of the *trans*-flavindogenides **2a-c** obtained in the acid-catalyzed condensation showed two broadened singlets (each corresponded to a single proton) at τ 1.9 and 3.3. The two singlets are due to the proton at C₂ and the vinylic proton. The observed broadening of the signal is attributed to a small long-range allylic coupling¹⁴ between the two protons. An absorption at τ 1.9 is much lower than expected for either 2 H or an ordinary vinyl proton and indicates the *trans* configuration for the flavindogenides **2a-c** in which the vinylic proton lies well in the deshielding zone of the carbonyl group. In support of this conclusion, the *cis*-flavindogenides **3a-c** obtained by ultraviolet irradiation do not display a signal at this low-field position. The 5-H protons of **3a-c** absorb at a lower field (τ 2.08–2.10) than the other aromatic protons. The 5-H protons of **2a-c** absorb at a similar field position (τ 2.12–2.14). The shift of the aromatic 5-H proton downfield arises from the deshielding effect of the carbonyl group and is characteristic of flavanone and flavone systems.

Compared with the preparation of flavindogenides, the condensation of benzaldehyde with 2,2-diphenyl-4-chromanone (**4**) requires a lengthy reaction period. When an ethanolic solution of the chromanone and benzaldehyde was saturated with hydrogen chloride and worked up after 12 or 24 hr, only starting materials were isolated. After a reaction period of 4 days a condensation product was obtained in 39% yield. Spectral data and elemental analysis are consistent with 2,2-diphenyl-3-benzylidenechromanone (**5**). In contrast to the flavindogenides obtained in the condensation reactions, **5** has a *cis* configuration as shown by an nmr signal at τ 3.70 for the β hydrogen.



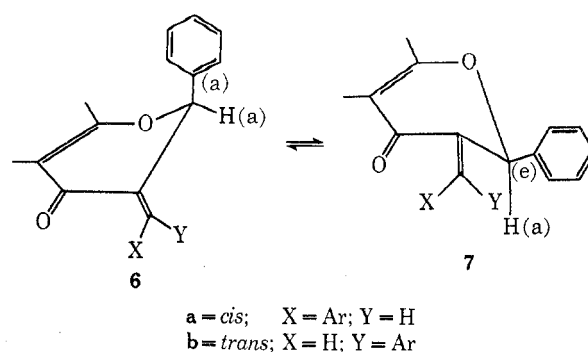
In view of the results obtained upon reduction of 3-(2-nitrobenzylidene)flavanone, it seemed of interest to prepare this compound and examine its nmr spectrum. The spectrum of this compound was consistent with a *trans* configuration since it showed a signal at τ 1.70 (assigned to the vinyl hydrogen) and a signal at τ 3.70 (assigned to the 2 hydrogen). Apparently the amino compound isomerizes under the mildly acid reduction conditions which then allow cyclization to occur.

Prior to the synthesis of the *cis*-flavindogenides an attempt was made to prepare 3-(2-hydroxybenzylidene)flavanone. It was anticipated that the presence or absence of hydrogen bonding between the hydroxyl group and the carbonyl group would allow assignment of *cis* or *trans* configuration, respectively. The product of the condensation of 2-hydroxybenzaldehyde

with flavanone did show hydrogen bonding as indicated by its infrared and nmr spectra. However an inspection of the spectral data showed that the endocyclic product, 3-(2-hydroxybenzyl)flavone had been obtained and not the expected flavindogenide.

Conformation.—The “sofa” conformation has been proposed by Philbin and Wheeler¹⁵ for flavanone-type molecules. This conformation allows a strainless chromanone molecule to have all the atoms, apart from C₂, coplanar. The infrared frequencies of a series of flavanones indicate that the carbonyl group and the fused benzene ring are conjugated in each case.¹⁶ Hence they are probably coplanar. This coplanarity is also indicated by the observation of Clark-Lewis, *et al.*,¹⁷ that the 2,3-coupling constants in flavanones are unaltered by the presence of a 5-hydroxyl group. An hydroxyl substituent in this position forms a strong intramolecular hydrogen bond with the carbonyl group and forces the coplanarity of this group with the aromatic A ring.

Inspection of models indicates that the flavindogenides may adopt the strainless “sofa” conformation in which all the atoms of the heterocyclic ring except C₂ are coplanar. As in the flavanones two conformers are possible in which the axial and equatorial bonds at C₂ are interchanged.



An examination of the model of *trans*-flavindogenides shows that in conformation **7b** there is severe nonbonded interaction between an equatorial 2-phenyl and the β -phenyl group. Such an interaction is not present in conformation **6b** which has the 2-phenyl group in the axial position. Whereas in cyclohexane and related structures a large group normally adopts the equatorial conformation to avoid 1,3 diaxial interaction, in the flavindogenides there are no axial groups to interact with an axial 2-phenyl.

Supporting evidence for an axial 2-phenyl group is provided from an examination of the long range allylic coupling between the 2-H and β proton. Sternhell, *et al.*,¹⁸ found that the magnitude of allylic coupling depends on the dihedral angle (ϕ) that the C–H bond of the allylic proton at position 2 makes with the plane of the double bond. The values¹⁹ are, for $\phi = 0-65^\circ$ and for $\phi = 110-180^\circ$, $J_{\text{allylic}} = 0-1.3$ cps; for $\phi = 65-110^\circ$, $J_{\text{allylic}} = 1.3-3.1$ cps.

(15) E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc. London*, 167 (1958).

(16) B. L. Shaw and T. H. Simpson, *J. Chem. Soc.*, 655 (1955).

(17) J. W. Clark-Lewis, L. M. Jackman, and T. M. Spotswood, *Aust. J. Chem.*, **17**, 632 (1964).

(18) D. J. Collins, J. J. Hobbs, and S. Sternhell, *ibid.*, **16**, 1030 (1963).

(19) G. R. Newseroff and S. Sternhell, University of Sidney, personal communication.

The nmr spectra of *cis*- and *trans*-benzylidenechromanones²⁰ show a doublet for the protons at C₂ (*cis*, $J_{\text{allylic}} = 1.27$ cps; *trans*, $J_{\text{allylic}} = 2.06$ cps) indicating that these protons become equivalent by rapid inversion of the two conformers. For the *cis*- and *trans*-benzylidenechromanones the observed splitting is the average value of the allylic coupling of the vinyl proton with an axial proton at C₂ and with an equatorial proton at C₂.

The low value of the allylic coupling constant for the *trans*-flavindogenide ($J_{\text{allylic}} = 0.95 \pm 0.5$ cps) confirms that these compounds exist in conformation **6b** in which the hydrogen at position 2 is equatorial $\phi = 2^\circ$.

Further support of conformation **6** is provided by the fact that *cis*-2,2-diphenyl-3-benzylidenechromanone (**5**) is formed on treatment of **4** with benzaldehyde (the vinyl proton of **5** is found at τ 3.70 showing little influence of the deshielding effect of the carbonyl group and thus indicates a *cis* configuration). With two phenyl groups at C₂, the steric effect prevents the formation of a *trans* isomer.

For *cis*-flavindogenides there appears to be little steric energy difference between the conformation in which the 2-phenyl group is axial (**6a**) and that in which it is equatorial (**7a**). Models indicate that some non-bonded interaction may exist in **7a** between the β hydrogen and 2-phenyl. The epoxidation reactions of *cis*-flavindogenides also seem to indicate an axial 2-phenyl group.¹⁰ However, the allylic coupling constant (1.23 ± 0.5 cps) of **1b** is very close to the average value (1.27 cps) observed for *cis*-3-benzylidenechromanone and suggests that the *cis*-flavindogenides exist in both conformations.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Elementary analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany, Galbraith Laboratories, Inc., Knoxville, Tenn., or in the departmental microanalytical laboratory of University College, Dublin. The infrared spectra were determined with either a Perkin-Elmer Model 337 or Beckman IR-5 spectrometer. Ultraviolet spectra were determined either on a Perkin-Elmer Model 202 or Bausch and Lomb Spectronic 505 spectrometer. The nmr spectra were recorded on a Varian A-60 or 60A spectrometer using tetramethylsilane (τ 10) as an internal standard. The measurements of the allylic coupling constants of *cis*- and *trans*-3-benzylidene flavanones were determined²¹ as 12% solutions in CDCl₃ on an HA-100 spectrometer using decoupled scans and were corrected by compensating for incomplete resolution.

The Preparation of Flavanone (1a) and 7-Methoxyflavanone (1b).—Benzaldehyde was condensed with 2'-hydroxyacetophenone (Eastman Organic Chemicals) or 2'-hydroxy-4'-methoxyacetophenone²² in ethanol in the presence of 50% sodium hydroxide solution to form the respective chalcones as previously described.²³ The 2'-hydroxychalcone was obtained as yellow needles in 78% yield, mp 87–89° (lit.²³ mp 88–89°). The 2'-hydroxy-4'-methoxyflavanone was obtained as yellow needles in 65% yield, mp 107.5–108.5° (lit.²⁴ mp 105°). The chalcones in turn were converted to the flavanones by ring closure in dilute aqueous sodium hydroxide as previously described:²⁵ **1a**, white needles (92% yield), mp 74–76° (lit.²⁵ 76°); **1b**, white plates (64% yield), mp 88–89° (lit.²⁴ mp 91°).

(20) M. Bennett, University College, Dublin, Ireland, personal communication.

(21) The authors are grateful to Professor S. Sternhell for determining the allylic coupling constants.

(22) R. Adams, *J. Amer. Chem. Soc.*, **41**, 247 (1919).

(23) W. Feuerstein and St. von Kostanecki, *Ber.*, **31**, 715 (1898).

(24) St. von Kostanecki and M. L. Stoppani, *ibid.*, **37**, 1180 (1904).

(25) K. Freudenberg and L. Orthner, *ibid.*, **55**, 1748 (1922).

The Preparation of *trans*-3-Arylidene flavanones (2a–c).—The following procedure for the preparation of *trans*-3-anisylidene flavanone (**2b**) illustrates the general procedure used.

A solution of 20 g of flavanone and 25 ml of anisaldehyde in 25 ml of ethanol was saturated with anhydrous hydrogen chloride capped, and allowed to stand for 24 hr. The mixture was then cooled in an ice bath. The solid was removed by filtration and washed with 25 ml of cold ethanol giving 27 g (91%) of product. Recrystallization from 700 ml of ethanol gave 25 g (83%) of pale yellow crystals, mp 146.5–147.5° (lit.^{1b} 148–149°).

Yield, physical, and spectral data of **2a–c** are recorded in Tables I and II.

trans-Flavindogenides- β -*d* **2a–c** were prepared by the above procedure from anisaldehyde-1-*d*²⁶ or benzaldehyde-1-*d*.²⁷

Photochemical Isomerization of *trans*-3-Arylidene flavanones (2a–c) to *cis*-3-Arylidene flavanones (3a–c).—The following is a typical example of the photochemical isomerization experiments. A solution of 5 g of *trans*-3-anisylidene-7-methoxyflavanone in 100 ml of benzene was irradiated at room temperature for 12 hr by a Hanovia 450-W mercury arc lamp contained in an immovable quartz probe. A Corex filter was utilized to screen out radiation below 260 m μ . At the end of a 12-hr irradiation period the benzene was removed and a yellow oil was left. The crude product was chromatographed over 60 g of silicic acid. The column was eluted with benzene and yielded earlier fractions of a yellow oil (3 g) and later fractions which were predominantly *trans* isomer. The yellow oil was again chromatographed over 60 g of silicic acid and eluted with 3:2 hexane–benzene. This procedure resulted in a series of fractions which were induced to crystallize. These fractions, when combined and recrystallized from hexane, gave 1.9 g (38%) of *cis*-3-anisylidene-7-methoxyflavanone. Yields and physical and spectral data of the *cis*-flavindogenides are recorded in Tables I and II.

cis-Flavindogenides- β -*d* (**3a–c**) were prepared from the deuterated *trans* isomers by the general procedure described above.

Acid-Catalyzed Isomerization of 3a–c to 2a–c.—A dilute solution of the *cis* isomer in ethanol was brought to reflux and 1 drop of concentrated hydrochloric acid was added. The solution was refluxed for 30 min. On removal of the solvent a solid was left (>90% yield) which had an nmr spectrum identical with that of the corresponding *trans* isomer. No *cis* isomer could be detected by nmr.

***trans*-3-(2-Nitrobenzylidene) flavanone.**—A solution of *o*-nitrobenzaldehyde (1.1 g), flavanone (1.1 g), and ethanol (10 ml) was saturated with anhydrous hydrogen chloride. After 48 hr the solvent was removed on a water bath at reduced pressure. The resulting oil was dissolved in 20 ml of hot ethanol and deposited a solid on cooling, 0.3 g, mp 144–156°. Recrystallization from 20 ml of ethanol gave 0.2 g of a cream colored solid: mp 156–157° (lit.⁸ mp 155.5–156.5°); nmr τ 3.7 (singlet, 1 proton assigned to 2 H), 1.7 (singlet, 1 proton assigned to β H), 3.2–2.8 (complex aromatic absorption, 13 protons).

2,2-Diphenyl-4-chromanone (4).—Concentrated hydrochloric acid (37 ml) was added to a refluxing solution of 5.5 g of 2'-hydroxy- β -phenylchalcone²⁸ in 180 ml of glacial acetic acid. The solution was refluxed for 5 hr, cooled in an ice bath, and 300 ml of water was added. The resulting solid was removed by filtration, washed thoroughly with water, dried, and recrystallized from 270 ml of hexane. The off-white crystals weighed 4.7 g (86%), mp 137–138.5° (lit.²⁸ 133–134°).

***cis*-2,2-Diphenyl-3-benzylidenechromanone (5).**—A solution of 1 g of **4**, 2 ml of benzaldehyde, and 3 ml of ethanol was saturated at room temperature with anhydrous hydrogen chloride, sealed, and allowed to stand for 4 days (previous reaction periods 12 and 24 hr had resulted in recovery of only starting material). The dark-colored reaction mixture was taken up in 100 ml of ether and washed successively with water, 5% sodium carbonate solution, water, 15% sodium bisulfite solution, and water. The ether was evaporated leaving a yellow oil which was dissolved in 20 ml of refluxing ethanol. The solution furnished 0.65 g (50%) of solid, mp 173–184°, upon cooling. The solid was recrystallized from 50 ml of ethanol and gave 0.5 g (39%) of yellow crystals, mp 190–191°. The infrared spectrum (CCl₄) shows significant absorptions at 1680 (C=O) and 1605 (C=C) cm⁻¹. The nmr spectrum (CDCl₃) has signals at τ 2.23 (pair of doublets,

(26) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(27) A. Streitwieser, Jr., and J. R. Wolfe, *J. Amer. Chem. Soc.*, **79**, 903 (1957).

(28) A. Schonberg and E. Singer, *Ber.*, **94**, 241 (1961).

1, $J = 2$ and 8 cps, 5 H), 2.32–3.33 (m, 18, Ar H), and 3.70 (s, 1, β H).

Anal. Calcd for $C_{25}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.44; H, 5.39.

3-(2-Hydroxybenzyl)flavone—A solution of 0.5 g of flavanone in 1 ml of salicylaldehyde was saturated with anhydrous hydrogen chloride, stoppered, and allowed to stand for 24 hr; 3 ml of methanol was then added. A crystalline solid separated. Recrystallization from ethanol gave 0.4 g (55%) of fine off-white crystals, mp 200–201°. The ultraviolet spectrum (EtOH) has λ_{max}^{sh} 307 m μ (ϵ 11, 600), 283 (13,800), and 241 (21,800). The infrared spectrum (CCl_4) shows significant absorptions at 3100 (bonded OH), 1640 (C=O), 1615 (C=C), and 1230 cm^{-1} (=COC-). The nmr spectrum ($CDCl_3$, very dilute owing to insolubility) has signals at τ 0.3 (singlet, bonded OH, wt 1), 1.65 (perturbed pair of doublets, $J = 8$ cps, 5 H, wt 1), 2.0–3.1 (complex multiplet, Ar H, wt 12), and 6.07 (singlet, CH_2 , wt 2). In deuterated dimethyl sulfoxide the signal at 0.3 is missing and is replaced by a singlet (wt 1) at τ 6.52.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.29; H, 5.11.

3-(2-Acetoxybenzyl)flavone—A solution of 0.5 g of 3-(2-hydroxybenzyl)flavone, 3 ml of acetic anhydride, and 2 drops of phosphoric acid was refluxed for 5 min and then poured into 5 ml of water. An oil separated which soon solidified. An additional 50 ml of water was added, and the solid was removed by filtration and washed thoroughly with water. The solid was recrystallized from 20 ml of ethanol and gave 0.4 g (71%) of small white crystals, mp 143–144°. The infrared spectrum (CCl_4) has characteristic absorptions at 1770 ($CH_3C=O$), 1650 (C=O), 1625 (C=C), and 1215, 1198 cm^{-1} (=COC- and -COC=O). The nmr spectrum ($CDCl_3$) has signals at τ 1.82 (perturbed pair of doublets, $J = 7.5$ cps, 5 H, wt 1), 2.42–3.16 (complex multiplet, Ar H, wt 12), 6.12 (singlet, CH_2 , wt 2), and 7.87 (singlet, CH_3CO , wt 3).

Registry No.—2a, 24467-41-2; 2b, 24467-42-3; 2c, 24467-43-4; 3a, 24467-44-5; 3b, 24467-45-6; 3c, 24467-46-7; 5, 24467-47-8; *trans*-3-(2-nitrobenzylidene)flavanone, 24467-48-9; 3-(2-hydroxybenzyl)flavone, 24467-49-0; 3-(2-acetoxybenzyl)flavone, 24467-50-3.

Oxidation of β -Carotene. Site of Initial Attack

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The reaction between β -carotene and molecular oxygen in toluene at 60° was investigated. A linear relation was found between the loss in β -carotene and time. The reaction rate increased with increasing temperature. The activation energy, E_a , for the oxidation of β -carotene was found to be 10.2 kcal/mol. Though free-radical initiators caused rate enhancement, the kinetics of the reaction and the light absorption characteristics of the reaction solution were altered. This indicated a difference in the mechanism of the reaction in the presence of free-radical initiators. The rate of loss of β -carotene was increased in the presence of cupric ions and decreased in the presence of diphenylamine. The products of the reaction were β -carotene 5,6-monoepoxide and its isomer, β -carotene 5,6,5',6'-diepoxide, and β -carotene 5,8-monoepoxide and its isomer, β -carotene 5,8,5',8'-diepoxide. A reaction mechanism was proposed.

In view of the fact that the oxidative reactivity of the β -carotene molecule may be influenced by both an electronic factor and a stereochemical factor, as was suggested by Zechmeister, *et al.*,² the size and reactivity of the oxidizing agent would be expected to play a predominant role. The reaction site would not only be a function of the inherent reactivity (electron density) of the β -carotene molecule but also a function of the size and reactivity (stability) of the attacking reagent. This is shown by the results of the oxidation reactions of β -carotene in the presence of the various metal oxides (and metal oxide catalysts)^{3–5} and by peroxides alone or with enzyme catalysis.^{6–8} The oxygen in metal oxides or in the form of peroxy radicals is in an activated (reactive) state and thus might nullify the inherent differences in reactivities in the various parts of the β -carotene molecule. From a stereochemical consideration oxidation with metal oxides, for example OsO_4 and H_2O_2 or $KMnO_4$, involves the transitory formation of a five-membered intermediate.⁹ The formation

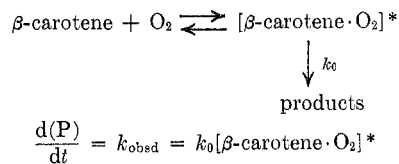
of such a space-requiring transition state would favor those sites of least steric hindrance. These might give the most stable transition state even though these sites may not be the centers of the highest electron density.

Oxidation of β -carotene with molecular oxygen has two unique characteristics. (1) Owing to the smaller size of the oxygen molecule, steric hindrance is not important. (2) Owing to the relative unreactivity of the oxygen molecule compared with peroxy radicals, the competitive reactivity between different carbon atoms could be retained.

The oxidation of β -carotene with molecular oxygen may therefore reflect the inherent reactivity of the β -carotene molecule. Also, the reaction of β -carotene with oxygen could illustrate the mechanism of the uncoupled enzymatic oxidation of β -carotene *in vivo*¹⁰ by way of model systems.

Results and Discussion

The rate of loss of β -carotene is shown in Figure 1. A straight line passing through the origin was obtained. This indicates an overall zero-order reaction kinetics. Thus



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