Tetrahedron, 1966, Vol. 22, pp. 621 to 628. Pergamon Press Ltd. Printed in Northern Ireland

NUCLEAR MAGNETIC RESONANCE SPECTRA AND STEREOCHEMISTRY OF 4-SUBSTITUTED FLAVANS

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(*Received* 9 *June* 1965; *in revised form* 10 *August* 1965)

Abstract—The NMR spectra of the 4α and β-benzoyloxyflavans have been completely analyzed, and the relative configurations deduced from coupling constant values. A simplified method of deducing relative stereochemistry of 4-substituted flavans from NMR spectra has been applied to these and other derivatives. The same dependence of vicinal coupling constants on the configuration of electronegative groups as exists in chair cyclohexanes has been found in 4-substituted flavans and has been tentatively interpreted as indicating a half-chair conformation for the dihydropyran ring.

DETERMINATION of the stereochemistry for the dihydropyran ring of flavans has been a difficult problem in the past, as many of the rules for conformational analysis of cyclohexanes are not valid for flavans. For example, the flavan-3,4-diols form cyclic derivatives such as carbonates regardless of whether the hydroxyl groups are *cis* or *trans* to one another,[1] and the α-halogen atom of the 3-bromoflavan-4-ones have little effect on the carbonyl stretching frequencies for these derivatives.[2] The application of NMR has afforded a quick and definitive answer to many of the stereochemical problems in flavan chemistry. Clark-Lewis *et al.* have recently published a very thorough account of applications of NMR in flavan chemistry,[3] but they mentioned 4-substituted flavans only briefly.

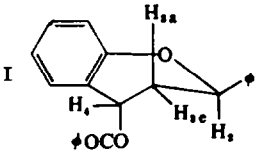
Before the advent of NMR, assignment of relative stereochemistry to 4-substituted flavans was an uncertain process at best.[4] No chemical data could distinguish between the 2,4-*cis* and 2,4-*trans* configurations in a completely unambiguous fashion. In the absence of certain knowledge of relative configurations an α,β designation of isomers was adopted.[5] Bogner *et al.*[6] assigned the *quasi-axial* conformation to the hydroxyl group of flavan-4β-ol produced by hydrogenation of 4-flavanone in acetic acid with PtO_2 catalyst making this the 2,4-*trans* isomer, as Huckel *et al.*[7] had found that this method produces *axial* alcohols in the cyclohexane series.[8] Mitsui and Kasahara[9] and

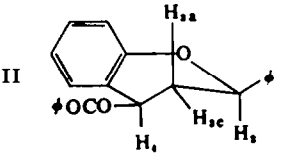
[1] R. Bognar, M. Rakosi, H. Fletcher, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters* 4 (1959).
[2] J. W. Clark-Lewis, T. McL. Spotswood and L. R. Williams, *Austr. J. Chem.* **16**, 107 (1963).
[3] J. W. Clark-Lewis, L. M. Jackman and T. McL. Spotwood, *Austr. J. Chem.* **17**, 632 (1964).
[4] J. W. Clark-Lewis, *Rev. Pure Appl. Chem.* **12**, 135 (1962).
[5] P. Karrer, Y. Yen and I. Reichstein, *Helv. Chim. Acta* **13**, 1308 (1930).
[6] R. Bognar, M. Rakosi, H. Fletcher, D. Kehoe, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **18**, 135 (1962).
[7] W. Huckel, M. Maier, E. Jordon, W. Seeger, *Liebig's Ann.* **616**, 46 (1958).
[8] See however S. Siegel, *J. Amer. Chem. Soc.* **75**, 1317 (1953) for a trenchant discussion on stereochemical assignments based on hydrogenation of cyclohexanones. We would like to thank a referee for calling this reference to our attention.

Roux and Paulus[10] also assigned the 2,4-*trans* configuration to several flavan-4β-ols.

Clark-Lewis *et al.*[11] used NMR measurements to determine the relative stereochemistry of the 3-bromo-4'-methoxy-6-methylflavan-4-ols and reductively debrominated them to the corresponding 4'-methoxy-6-methyl-flavan-4-ols. Their work, independent of our studies on the benzoylated 4-alcohols themselves,[12] clearly demonstrated that the early stereochemical assignments for flavan-4β-ols had to be reversed.

The 4-benzoyloxy flavans. We undertook an NMR study of the α and β isomers of 4-benzoyloxy flavan, I and II which are epimeric at C_4 in order to establish the relative configurations of these compounds unequivocally.[12] The aliphatic protons of these compounds have ABMX-type spectra ($J_{MX} \sim 0$) in $CDCl_3$ (Figs. 1 and 2). The lowest-





field signal was assigned to H_4 and the one slightly upfield to H_2, as is the case for flavan-3,4-diol derivatives for which these assignments have been verified by deuterium labeling experiments.[12] Assignment of the axial proton at C_3 as the high-field proton of the H_{3e}, H_{3a} pair agrees with results obtained in cyclohexanes[13] and was confirmed by calculations. The H_2 and H_4 signals in this system are closely analogous to X signals of ABX systems; thus one cannot determine exact coupling constant values from line positions of these signals alone.[14] Accordingly, the spectra were analyzed using IBM 7090 FORTRAN computer programs.[15] J. D. Swalen's programs, NMREN and NMRIT,[16] were used for the *beta* isomer. The spectral parameters thus determined are listed in Table 1. Proton-4 of the *alpha* isomer gave a triplet consisting of lines of 1:2:1 intensity ratio at 3·0 c/s intervals. Of the two possible sets of coupling constants, $J_{3a,4} = J_{3e,4} = 3{\cdot}0$ c/s and $J \sim 6{\cdot}0$, $J' \sim 0$,[17] both were tried; but only the former was found to be part of a self-consistent set of parameters.

The coupling constant values in Table 1 can be used to deduce the relative configurations and substituent conformations of the 4-benzoyloxyflavans by making use of the Karplus relationship of vicinal coupling constants and dihedral angles.[18] A

[9] S. Mitsui and A. Kasahara, *J. Chem. Soc., Japan* **81**, 1583 (1960).

[10] D. G. Roux and E. Paulus, *Biochem. J.* **84**, 416 (1962), and D. G. Roux, *Chem. & Ind.* 278 (1962).

[11] J. W. Clark-Lewis, T. M. Spotwood and L. R. Williams, *Proc. Chem. Soc.* 20 (1963).

[12] The results of this study have been the subject of a preliminary communication, C. P. Lillya, D. Kehoe, E. M. Philbin, M. A. Vickars and T. S. Wheeler, *Chem. & Ind.* 84 (1963).

[13] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* pp. 115–119. Pergamon Press, London (1959).

[14] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 135. McGraw-Hill, New York (1960).

[15] Computing was done at the M.I.T. Computation Center, Cambridge, Massachusetts.

[16] C. A. Reilly and J. D. Swalen, *J. Chem. Phys.* **37**, 21 (1962). We would like to thank Dr. Swalen for sending us copies of his programs.

[17] J. D. Roberts, *An Introduction to the Analysis of Spin-Spin Splitting in High Resolution Nuclear Magnetic Resonance* pp. 71 and 77. W. A. Benjamin, New York (1961).

[18] M. Karplus, C. F. Conroy in *Advances in Organic Chemistry* Vol II; pp. 308–311, Interscience. New York (1960).

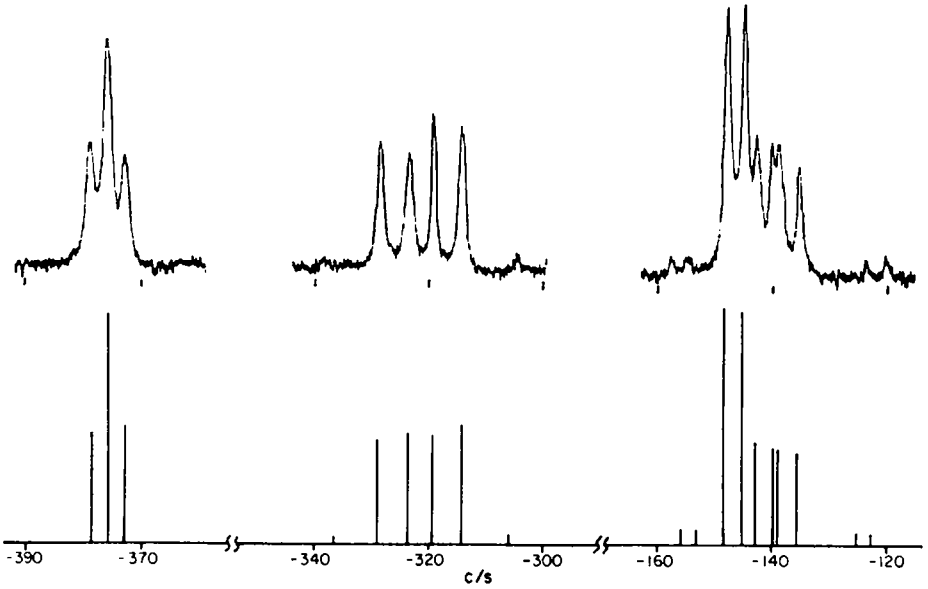


FIG. 1. NMR Spectrum of 4α-Benzoyloxyflavan (H_2, H_3 and H_4). Above-observed, below-calc.

TABLE 1. SPECTRAL PARAMETERS FOR α AND β 4-BENZOYLOXYFLAVANS CHEMICAL SHIFTS (C/S)[a]

	H_2	H_{3e}	H_{3a}	H_4	
alpha	−321	−146	−139	−376	
beta	−323	−168	−148	−393	
		J in c/s[b]			
	2,3e	2,3a	3e,4	3a,4	3e,3a
alpha	3·0	11·9	3·0	3·0	13·0
beta	2·2	11·5	6·2	10·2	13·3

[a] Chemical shifts are expressed in cycles per second relative to tetramethylsilane as an internal standard. The negative direction is downfield.

[b] Coupling constants are accurate to ±0·2 c/s.

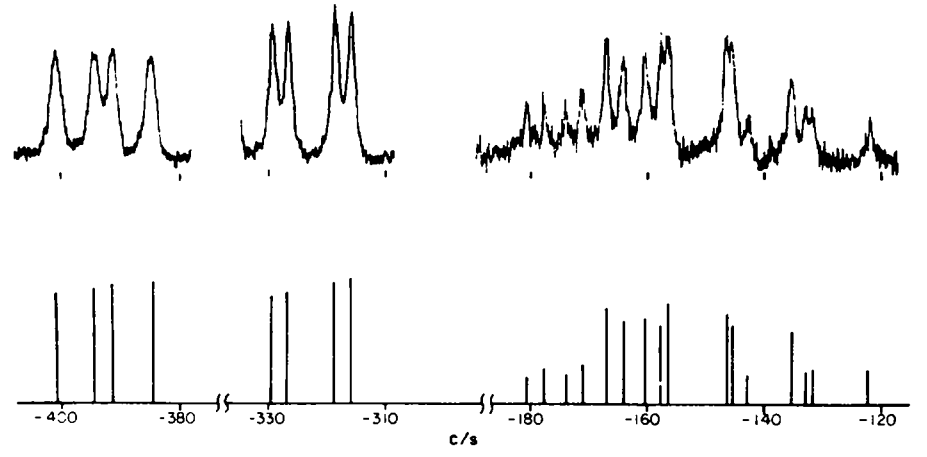


FIG. 2. NMR Spectrum of 4β-Benzoyloxyflavan (H_2, H_3 and H_4). Above-observed, below-calc.

half-chair conformation (see I and II) has been assumed for the dihydropyran ring in the following discussion, but assumption of a sofa conformation[19] in which all the atoms of the ring excepting C_2 are coplanar would not change our conclusions. The 11·9 c/s value of $J_{2,3a}$ for the *alpha* isomer is so large that it can only arise from a *trans-diaxial* coupling: thus H_2 is *axial*. $J_{3e,4} = J_{3a,4} = 3{\cdot}0$ c/s is reasonable if the C_4–H_4 bond approximately bisects the H_{3e}–C_3–H_{3a} angle when projected down the C_3–C_4 bond.[20] Accordingly, H_4 is *quasi-equatorial*; and 4α-benzoyloxyflavan has the 2,4 *trans* structure (I) with the 2-phenyl group *equatorial*. In the case of the *beta* isomer the large values of $J_{2,3a}$ and $J_{3a,4}$ require H_2 and H_4 to be *axial* and *quasi-axial* respectively. Thus 4β-benzoyloxyflavan has the 2,4-*cis* structure (II) with both substituents occupying *equatorial* positions. These data reverse the original assignments made on the basis of hydrogenation experiments.[6]

Other 4-substituted flavans. Lillya *et al.*[21] have used a simplified method for stereochemical analysis of 4-substituted flavan spectra based on the sums $|J_{2,3a} + J_{2,3b}|$ and $|J_{3a,4} + J_{3b,4}|$. These sums are easily obtained as the distances between the outermost lines of H_2 and H_4 multiplets.[14] Thus, one avoids the time-consuming analysis of the

TABLE 2[a]. SPECTRAL PARAMETERS FOR 4-SUBSTITUTED FLAVANS 2,4-*cis* COMPOUNDS

Flavan Derivative	H_2	H_4	$J_{2,3a} + J_{2,3e}$	$J_{3e,4} + J_{3a,4}$
4-Benzoyloxy (II)	−323	−393	13·7	16·2
3′,4,4′,7-Tetraacetoxy (III)[b]			12·8 ± 0·5	12·8 ± 0·5
3′,4,4′,5′,7-Pentaacetoxy (IV)[b]	−313	−365	12·8 ± 0·5	12·8 ± 0·5
4-Phthalimido (V)	−315	−353	13·9	18·0
4-Acetoxy-4′-methoxy-6-methyl (VI)	−304	−368	13·7	16·5
4-Acetoxy-6-bromo (VII)	−316	−373	14·4	17·0
	2,4-*trans* Compounds			
4-Benzoyloxy (I)	−321	−376	14·9	6·0
4-Acetoxy-4′-methoxy-6-methyl (VIII)	−307	−358	14·3	5·8
4-Acetoxy-6-bromo (IX)	−315	−376	15·4	6·1
4,6-Dibromo (X)	−324	−333	13·5	6·0

[a] Chemical shifts are expressed as in Table 1 and are accurate to ±2 c/s. Coupling constants are accurate to ±0·2 c/s except where noted.

[b] Ref. 21.

[c] Ref. 23.

complex H_{3a},H_{3e} multiplet. Often, as in the case of acetoxy derivatives, complete analysis is impossible due to the fact that other signals obscure parts of the H_{3a},H_{3e} multiplet. If it is assumed that 2-phenyl substituent is in the *equatorial* position (as in 4α and β-benzoyloxyflavan) on a half-chair or sofa dihydropyran ring and that all the vicinal J's have the same sign,[22] the Karplus relationship predicts that $J_{3a,4} + J_{3e,4}$ will be significantly smaller for 2,4-*trans* than for 2,4-*cis* isomers. This expectation is borne out by the data in Table 2. The close correspondence between the values of

[19] E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.* 167 (1958).

[20] These data can also be interpreted in terms of two rapidly equilibrating conformations. This would not change our conclusions on relative stereochemistry.

[21] C. P. Lillya, S. E. Drewes and D. G. Roux, *Chem. & Ind.* 783 (1964).

[22] There seems to be ample evidence for assigning positive signs to all vicinal coupling constants. See for example, M. Karplus, *J. Amer. Chem. Soc.* **84**, 2458 (1962); P. C. Lautenbur and R. J. Kurland, *Ibid.* **84**, 3405 (1962); F. A. L. Anet, *Ibid.* **84**, 3767 (1962).

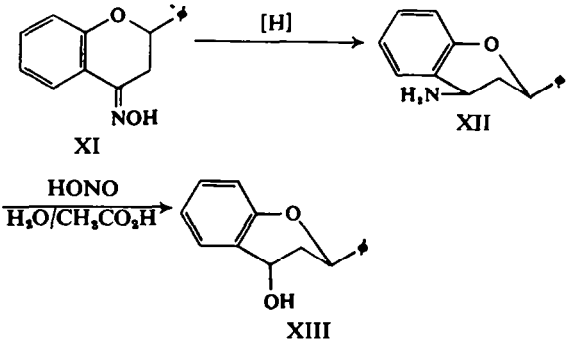
[23] R. Merten and G. Muller, *Chem. Ber.* **97**, 682 (1964).

these sums for the additional derivatives and those for the 4-benzoyloxyflavans, the stereochemistry of which is firmly established, increases our confidence on this method.

In all these compounds chemical shifts of the hydrogens on C_3 are from -130 to -170 c/s (7·2 to 7·8τ). For the 2,4-*cis* isomers all of the 16 predicted lines are observed for compounds II and V while parts of this region are obscured by acetate methyl signals for the others. The signals for the hydrogens on C_3 of 2,4-*trans* isomers are considerably simpler. The chemical shift between the hydrogens on C_3 is generally larger for the 2,4-*cis* isomers. H_4 consistently appears at lower field (3·45 to 4·12 τ for esters) than H_2 (4·62 to 4·94 τ for esters). The H_2 signal is a quartet in all these compounds with the exception of 2,4-*cis*-4-acetoxy-4′ methoxy-6-methylflavan (VI) for which it is a triplet. The shape of the H_4 signal is characteristic of relative configuration, being a quartet for all the 2,4-*cis* compounds and a 1:2:1 triplet for all those which are 2,4-*trans*. Our limited results indicate that the H_4 signal is the key to rapid stereochemical analysis of 4-substituted flavans, as both the distance between its outer lines and its shape are characteristic of a compound's relative configuration.

In view of these stereochemical assignments it would seem reasonable to reserve henceforth the designation *alpha* for 2,4-*trans* 4-substituted flavans and *beta* for 2,4-*cis* compounds. This convention will mean a reversal of many of the earlier stereochemical assignments; but this is inevitable. It will leave most of the compounds now described in the literature with the same designations however, a most fortunate result.

Determination of the stereochemistry of 4α-benzoyloxyflavan and 4β-phthalimidoflavan which were prepared from flavan-4α-ol[6] and 4β-aminoflavan[6] respectively clarifies the steric course of the reactions comprising the stereospecific synthesis of flavan-4α-ol reported by Bognar *et al.*[6] Reduction of 4-oximinoflavan (XI) with hydrogen and Pd/C or Pt_2O in acetic acid, with LAH, or with AlHg affords the 4β-amine (XII). The same steric course is followed in the reduction of 4-flavanone with the first two reagents;[6,24] however reduction of this ketone with AlHg gives the 4α-alcohol.[5,25] Nitrous acid deamination of the 4β-amine (XII) proceeds with inversion



of configuration at C_4 to give flavan-4α-ol (XIII). Recent investigations show that amine deaminations proceed with concurrent inversion and retention of configuration in a variety of solvents.[26]

[24] M. M. Bokadia, B. R. Brown and W. Cummings, *J. Chem. Soc.* 3308 (1960).
[25] K. Freudenberg and L. Orthner, *Ber. Dtsch. Chem. Ges.* **55**, 1748 (1922).
[26] W. Huckel and K. D. Thomas, *Liebig's Ann.* **645**, 177 (1961); W. Huckel, *Chem. Ber.* **96**, 220 (1963); E. H. White and F. W. Bachelor, *Tetrahedron Letters* 77 (1965).

Configuration of electronegative groups and vicinal coupling constants. Recently a correlation of vicinal coupling constants with the configuration of electronegative substituents in chair cyclohexanes was reported by Williams and Bhacca.[27] Their investigations of steroids having hydroxy and acetoxy substituents in rings A and C revealed that for the proton on the carbinol carbon, vicinal coupling constants were $J_{ae} = 5{\cdot}5 \pm 1{\cdot}0$ c/s and $J_{ea} = 2{\cdot}5$–$3{\cdot}2$ c/s.[28] The values for the analogous coupling constants in 4-substituted flavans are very close to these values as the data in Table 3 show.

TABLE 3. J_{ae} and J_{ea} VALUES FOR 4-SUBSTITUTED FLAVANS

β-Compounds	$J_{ae}(J_{3e,4})$	α-Compounds	$J_{ea}(J_{3a,4})$
II	6·2	I	3·0
III	6·0 ± 0·5	VIII	3·0
IV	6·0 ± 0·5	IX	2·9
V	6·6	X	3·0
VI	6·5		
VII	6·8		

The coupling constants in Table 3 were estimated from the line positions of the H_4 signal, a procedure which is accurate only when the chemical shift between H_{3e} and H_{3a} is relatively large. Williams and Bhacca's criterion for the validity of a first-order analysis, that $\delta_{3e3a} \geqq 20$ c/s, is almost certainly satisfied by all of the β compounds. In listing J_{ea} values it has been assumed that the H_4 triplets arise because of two equal vicinal coupling constants as was demonstrated in the case of 4α-benzoyloxyflavan.

In view of the great differences between the dihydropyran ring of flavans and chair cyclohexanes, the agreement between our values and those of Williams and Bhacca is striking; and such a correlation appears to exist for 3-substituted flavans as well. Clark-Lewis *et al.*[3] quote the following values for vicinal coupling constants ($J_{3,4}$) for flavan-3-ols (catechins), $J_{ae} = 5{\cdot}6$ and $J_{ea} = 4{\cdot}4$.[29] These data suggest that correlations of this type may be quite general for rigid and conformationally-anchored systems. Our data do not seem to be affected by the heterocyclic oxygen trans to H_{3e}. Although this should attenuate J_{ae} more than J_{ea}, our J_{ae} values are somewhat larger than the mean reported by Williams and Bhacca for carbocycles. Booth has recently reported evidence for such a stereospecific effect of heterocyclic oxygen in 1,3-dioxanes and morpholines.[30]

Conformation of the dihydropyran ring. Two conformations for the dihydropyran ring have received serious consideration, the half-chair (XIV) and the sofa (XV). Other possible conformations have been mentioned by Whalley.[31] The energy difference between the half-chair and sofa should be small; and if they both represent free energy minima, they would almost certainly be in rapid equilibrium with one another. The substitution pattern of the dihydropyran ring may determine its conformation, so

[27] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.* **86**, 27 42 (1964).

[28] We are using the notation of Williams and Bhacca in which the configuration of the proton on the carbon which bears the electronegative substituent is given first.

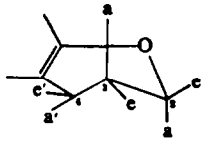
[29] It is not clear whether these represent average values or those obtained from the analysis of one representative spectrum.

[30] H. Booth, *Tetrahedron Letters* 411 (1965).

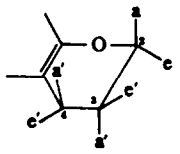
[31] W. B. Whalley, *The Chemistry of Flavanoid Compounds* (Edited by T. A. Geissman) p. 441. Pergamon Press, London (1962).

any conclusions drawn from our data can apply only to 4-substituted flavans. For the same reason evidence indicating that the dihydropyran ring in 4-flavanones is a sofa[3] has little bearing on the case of 4-substituted flavans.

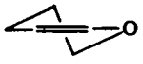
Clark-Lewis *et al.*[3] have pointed out that the accuracy of the Karplus equation is insufficient to allow a decision to be made between sofa and half-chair conformations for substituted flavans on the basis of coupling constant values. However, the conformational dependence of the effect of electronegative groups on vicinal coupling



III



iii



XIV

XV

constants is strikingly similar in 4-substituted flavans and chair cyclohexanes. This suggests that the conformation about the C_3–C_4 bond of the dihydropyran ring is similar to the staggered conformation in chair cyclohexanes. The conformation about the C_3–C_4 bond is significantly closer to being staggered in the half-chair than in the sofa. For this reason we favor a half-chair conformation for the dihydropyran ring or a preponderance of the half-chair should it exist in equilibrium with the sofa. A definitive answer to the conformational questions discussed here must await further data.

EXPERIMENTAL

The NMR spectra were measured on Varian Associates A-60 and DP-60 instruments at 60 and 56·4 mc. respectively in concentrations from 0·2M to 0·6M in $CDCl_3$. Chemical shifts were determined relative to tetramethylsilane as an internal standard. In the cases of the 4α and β-benzoyloxyflavans the spectra were calibrated with side bands of the TMS signal from an audio oscillator and the peak positions taken as the average of several sweeps upfield and downfield.

4α- and β-benzoyloxyflavans were prepared by benzoylation of the corresponding alcohols prepared as described in the literature (Ref. 6).

4 β-phthalimidoflavan

4 β-aminoflavan hydrochloride[6] m.p. 268–270° (0·5 g) in suspension in aqueous sat. Na_2CO_3aq (5%) was added to a solution of ethyl chloroformate in chloroform (2 ml:5 ml) and the mixture shaken for 15 min. The $CHCl_3$-layer yeilded on evaporation 4-carbethoxyaminoflavan which crystallized from EtOH in needles (0·4 g), m.p. 151° (Lit,[23] m.p. 142°). (Found: C, 72·8; H, 6·3; N, 4·9. Calc. for $C_{18}H_{19}NO_3$: C, 72·7; H, 6·4; N, 4·8%.) The carbethoxy derivative on treatment with phthalic anhydride as previously described[23] gave 4β-phthalimidoflavan m.p. 178° (lit.,[23] m.p. 158–159°*).

That no epimerization occurred in the above reaction was confirmed when hydrogenolysis of 4β-phthalimidoflavan with hydrzaine[23] regenerated 4β-aminoflavan characterized as its hydrochloride[6] identical with the starting material (mixed m.p.).

*Comparison of the NMR spectra of 4β-phthalimidoflavan m.p. 178° with that of a sample (m.p. 163°) kindly supplied by Dr. Müller showed the two compounds to be identical.

4-Acetoxy-4'-methoxy-6-methylflavans

(a) Acetylation of 4'-methoxy-6-methylflavan-4 β-ol[32] by the pyridine–acetic anhydride method yielded 4 β-acetoxy-4'-methody-6-methylflavan, needles, m.p. 152° from aq. EtOH. (Found: C, 73·1; H, 6·3. $C_{19}H_{20}O_4$ requires: C, 73·1; H, 6·4%.)

(b) *The isomeric* 4 α-*acetoxy-4'-methody-6-methylflavan* was formed as follows: 4'-methoxy-6-methylflavan-4 β-ol (2 g) was covered with $SOCl_2$ (2 ml) and allowed to stand for 5 min. Addition of pet. ether (b.p. 60–80°) followed by evaporation on a water pump removed excess $SOCl_2$. The residue was dissolved in pyridine (10 ml) containing water (2 ml) and the solution kept overnight. Addition of water precipitated 4'-methoxy-6-methyl-flavan-4α-ol, which separated from EtOH in crystals (0·7 g), m.p. 135° (lit.,[32] m.p. 127°), the *acetate* (acetic anhydride–pyridine) needles, m.p. 118° from aq. EtOH. (Found: C, 73·0; H, 6·4 Calc. for $C_{19}H_{20}O_4$: C, 73·1; H, 6·4%.)

4β-Acetoxy-6-bromoflavan

Sodium borohydride (40 mg) was added to a solution of 6-bromoflavanone[33] (200 mg) in MeOH. After 24 hr addition of water precipitated *6-bromoflavan-4β*-ol, which separated as needles (130 mg), m.p. 116°, from benzene–pet. ether, b.p. 60–80°. (Found: C, 59·4; H, 4·3; Br, 25·8. $CL_9H_{13}BrO_2$ requires C, 59·0; H, 4·3; Br, 26·3%.) *Acetate* (acetic anhydride–pyridine) needles, m.p. 119–120° from pet. ether, b.p. 60–80° (Found: C, 58·4; H, 4·4; Br, 23·1. $C_{17}H_{15}BrO_3$ requires: C, 58·8; H, 4·3; Br, 23·1%.)

4α,6-Dibromoflavan

A solution of 6-bromoflavan-4 β-ol (0·3 g) in dry ether (100 ml) was treated with PBr_3 (0·3 g) at 0°. After 5 hr the ether layer was washed with aqueous sodium acetate (5%). Removal of the ether and crystallization of the residue from pet. ether (b.p. 60–80°) gave 4α,6-*dibromoflavan*, m.p. 123°. Found C, 48·7, H, 3·5; Br, 43·6. $C_{15}H_{12}Br_2O$ requires: C, 48·9; H, 3·3; Br, 43·4%.)

4α-Acetoxy-6-bromoflavan

A mixture of silver acetate (0·4 g) and 4α,6-dibromoflavan (0·4 g) in acetic acid (7 ml) was refluxed for 30 min. After removal of AgBr, addition of water precipitated 4α-*acetoxy-6-bromoflavan* (0·2 g), m.p. 125–127°, cubes from pet. ether, b.p. 60–80°. (Found: C, 58·4; H, 4·4; Br, 22·8. Calc. for $C_{17}H_{15}BrO_3$: C, 58·8; H, 4·3; Br, 23·1%.)

Acknowledgements—We would like to thank Dr. Thomas R. Stengle for running some of our NMR spectra. One of us, C. P. L., would like to thank the National Science Foundation (U.S.A.) for predoctoral fellowship support from 1959 to 1963 during which some of this work was completed. The encouragement and advice of Prof. E. J. Corey during this period is also gratefully acknowledged. Parts of this paper have been abstracted from the thesis of C. P. L. presented to Harvard University in partial fulfillment of the requirements for the Ph.D. degree.

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