cubic crystals, m.p. 146–147°; $\lambda_{max}^{CHCl_3}$ 5.64, 6.82, 7.73, 8.60, 10.32, and 11.00 μ; λ_{max}^{EtOH} 272.5 mμ (log ε 2.95) and 280.8 mμ (log ε 2.95).

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.64; H, 8.26. Found: C, 78.50; H, 8.44.

b. **By Sodium Borohydride Reduction of IV.**—To a stirred, refluxing solution of 26.0 g. (0.10 mole) of keto acid IV, neutralized to the phenolphthalein end point, in 200 ml. of 50% methanol was added 1.25 g. (0.033 mole) of sodium borohydride over 0.5 hr. The reaction mixture was refluxed for 22 hr., decomposed with 6 *N* hydrochloric acid, and worked up in the usual fashion to give 12.15 g. of unchanged acid IV and 12.35 g. (47.5%) of lactone XXIII, m.p. 136–138°. Recrystallization from hexane-acetone afforded colorless microcrystals of XXIII, m.p. 146–147°, identical in all respects to the lactone prepared by catalytic reduction (see method a preceding).

Optical Rotatory Dispersion Studies. LXXXII.[1a] Conformational Analysis. XXXVII.[1b] Determination of the Stereochemistry and Conformation of the Four Isomeric Cyanodihydrocarvones by Optical Rotatory Dispersion and Dipole Moment Measurements[2]

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Of the four possible cyanide addition products of (−)-carvone (I), three have now been isolated in pure form and the presence of the fourth one demonstrated chromatographically. Through a combination of chemical transformations, optical rotatory dispersion measurements, and dipole moment data, it has been possible to assign the correct stereochemistry to the two newly generated asymmetric centers and to assign plausible conformations to the four isomeric 3-cyano-2,3-dihydrocarvones.

Many years ago, Lapworth[4] studied the 1,4-addition of cyanide to (+)-carvone (antipode of I[5]) and isolated two crystalline, isomeric nitriles, both of which exhibited mutarotation. Their chemistry was studied *in extenso*, but no stereochemical assignments were made, and no further work appears to have been done on these substances during the past fifty years. In the cyanide addition to carvone, two new asymmetric centers are generated, thus creating the possibility of four stereoisomers (II–V). Furthermore, since we are dealing here with a flexible ring system, eight conformers (IIA or B–VA or B) must be considered, if we restrict ourselves to chair forms; and many more, if boat and twist forms are also brought into play. It was decided, therefore, to attack this interesting stereochemical problem by attempting the isolation of as many of the dihydrocarvone isomers as possible and to subject them to optical rotatory dispersion scrutiny[6] in the light of the octant rule.[7] The latter has been shown[8] to be of considerable utility in the solution of conformation problems, and it was of interest to examine its applicability to the present cases and to confirm the conformational conclusions by dipole moment measurements.[9]

In the present work, (−)-carvone of known absolute configuration (I)[10] was employed and duplication of Lapworth's conditions[4a] (potassium cyanide in ethanol–water–acetic acid at room temperature) yielded about 70% of the highest melting isomer II (m.p. 95.5°) of 3-cyano-2,3-dihydrocarvone, the physical constants being in reasonable agreement with those reported by Lapworth[4a] for the antipode. Thin-layer chromatography on silica gel was found to be an excellent method for determining the purity of the dihydrocarvones, since a solvent system was used that effected separation of all four isomers. In fact, this method showed that the crude cyanodihydrocarvone prepared by Lapworth's first[4a] procedure consisted principally of isomer II, contaminated with some IV and traces of III.

By conducting the cyanide addition in refluxing aqueous ethanol—in the absence of acetic acid—Lapworth[4b] encountered a second isomer (m.p. 84°, now shown to be III) in high yield. Attempts in our hands to duplicate quantitatively these results failed, since thin-layer chromatography always demonstrated the existence of approximately equal amounts of isomers II and III, as well as traces of IV. By means of gradient elution chromatography, it was possible to isolate the pure second isomer III (m.p. 86.5°), with constants in reasonable agreement with those recorded[4b] for its antipode.

The question then arose whether the two cyanodihydrocarvones (now known to be II and III) of m.p. 95.5 and 86.5° were isomeric at C-2 and/or at C-3, since both these centers are invertible. In order to gain information on this point, each pure isomer was subjected to equilibration in ethyl acetate solution in the presence of *p*-toluenesulfonic acid, the course of the reaction being followed by thin-layer chromatography. Complete equilibration was reached at room tempera-

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[1] (a) For preceding paper see C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, in press; (b) for preceding paper see J. M. Conia, J. L. Ripoll, L. A. Tushaus, C. L. Neumann, and N. L. Allinger, *J. Am. Chem. Soc.*, **84**, 4982 (1962).

[2] Financial support was provided by the National Cancer Institute (grant no. CRTY-5061) of the National Institutes of Health to Stanford University, and by the National Science Foundation (grants no. 19981 and G-10346) to Wayne State University.

[3] Recipient of an undergraduate research fellowship at Stanford University from the National Science Foundation.

[4] (a) A. Lapworth, *J. Chem. Soc.*, **89**, 945, 1819 (1906); (b) A. Lapworth and V. Steele, *ibid.*, **99**, 1877 (1911).

[5] All structural formulas in this paper represent correct absolute configurations according to the steroid notation.

[6] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1960.

[7] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

[8] For pertinent discussion and earlier references see C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962); *Proc. Natl. Acad. Sci., U. S.*, **48**, 1093 (1962); *J. Chem. Soc.*, 2390 (1963).

[9] For discussion and earlier references of the use of dipole moment studies in conformational analysis, see N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegeli, *J. Org. Chem.*, **28**, 780 (1963).

[10] See A. J. Birch, *Ann. Reports Progr. Chem.*, **47**, 192 (1951).

ture in about one week, at which time the equilibration mixture of isomer II (m.p. 95.5°) consisted of two spots, corresponding to II and a new isomer (IV) (15%), but none of isomer III (m.p. 86.5°). When this experiment was conducted on a larger scale and separation was effected by partition chromatography on Celite impregnated with formamide, the new pure isomer was obtained in 13% yield as a low-melting (m.p. 13.5°) solid, which proved to be homogeneous by thin-layer chromatography. Conversely, equilibration of pure III (m.p. 86.5°) did not show any spot attributable to II or IV, but did exhibit a faint spot due to a fourth isomer (V), which, unfortunately, was formed in such small quantity as to preclude preparative isolation.

Previously discussed equilibration experiments suggested strongly that the two readily available cyanodihydrocarvones (II and III) are isomeric at C-3 and are thermodynamically more stable than their epimers at C-2, since equilibration led only to small (II → IV) or negligible (III → V) amounts of new isomers. To substantiate this conclusion, the substituent at C-3 in both II and III was altered in such a manner as to prevent further epimerization at that center. The pure higher melting (m.p. 95.5°) 3-cyano-2,3-dihydrocarvone (II) was reduced with lithium aluminum hydride to a crystalline mixture (VI) of epimeric amino alcohols, which was transformed to the corresponding benzamide mixture VII and oxidized with chromium trioxide in acetone solution.[11,12] The resulting 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (VIII) was a sharp melting (m.p. 180.5°) solid, homogeneous by thin-layer chromatography, in which only C-2 was now equilibratable.

By the same sequence of reactions, the lower melting (m.p. 86.5°) 3-cyano-2,3-dihydrocarvone (III) was transformed *via* the amino alcohol (X) and benzamido alcohol (XI) mixtures into a crystalline, chromatographically homogeneous, 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (XII) of m.p. 145°. Most importantly, while this amide was largely unaffected by methanolic potassium hydroxide, identical base treatment of the m.p. 180.5° benzamide VIII (derived from II) gave preponderantly (65%) a new 2-methyl-3-benzamidomethyl-5-isopropenylcyclohexanone (IX) of m.p. 104°. Since only C-2 is invertible in all of the benzamidocyclohexanones, it follows that the amides VIII (m.p. 180.5°) and XII (m.p. 145°), and, hence their precursor 2-cyano-2,3-dihydrocarvones (II and III), must differ in configuration at C-3.

This crucial point could also be settled by another method in which epimerization at C-2 was made impossible, while equilibration at C-3 could be examined. Thus it was found that sodium borohydride reduction of the highest melting isomer II produced an alcohol, which on reoxidation regenerated essentially pure II, thin-layer chromatography indicating the presence of a trace of its C-2 epimer IV. On the other hand, when the alcohol, produced by sodium borohydride reduction of II, was heated with methanolic potassium hydroxide—conditions which could epimerize only the C-3 center—and the resulting mixture reoxidized, thin-layer chromatography now demonstrated the existence of two strong spots corresponding to the original 2-cyano-2,3-dihydrocarvone (II, m.p. 95.5°) and its C-3 epimer III (m.p. 86.5°). Thus it has been conclusively established that the original 2-cyano-2,3-dihydrocarvone (II, m.p. 95.5°) and its m.p. 86.5° epimer III differ in configuration at C-3 and are of the same orientation at C-2, while II and IV must differ at C-2 but be the same at C-3. With the relative configurations of these compounds established on the basis of chemical evidence, it is now possible to consider the optical rotatory dispersion curves of these ketones and to derive stereochemical assignments from them.

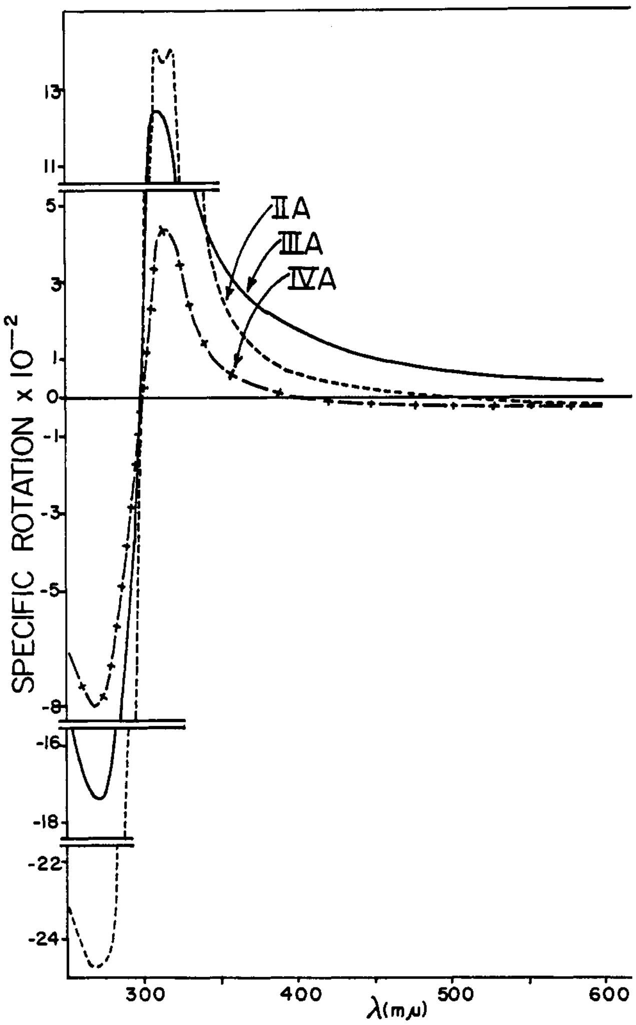

Figure 1

From a qualitative standpoint, consideration of chair forms is probably sufficient and that conformation, labelled A in the formula flow sheet, is considered to be energetically favored over its "flipped" conformer B. A decision between a given conformer pair, A-B, was made by the use of the following energetic parameters. The energy of an axial methyl group adjacent to a carbonyl group in a simple cyclohexanone is of the order of 1.6 kcal./mole[13]; that of an axial cyano group β to a carbonyl group is unknown, but must be quite small as an axial cyano group in a cyclohexane has an energy of only 0.2 kcal./mole.[14] Finally, the energy of an axial iso-

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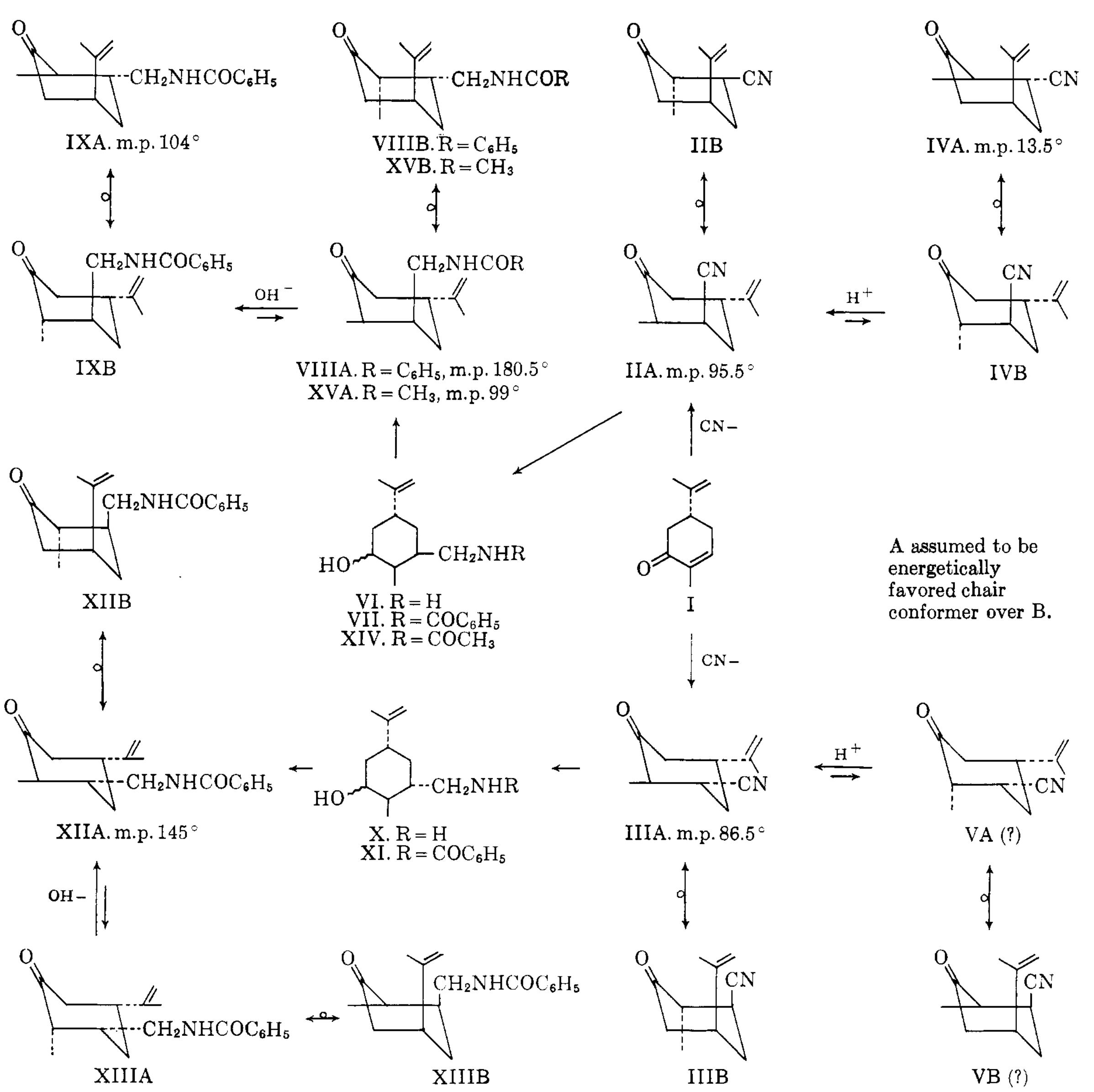
[11] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

[12] This procedure does not cause any perceptible epimerization of the adjacent asymmetric center [see ref. 1 as well as G. Ohloff, J. Osiecki, and C. Djerassi, *Ber.*, **95**, 1400 (1962)].

[13] (a) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); (b) B. Rickborn, *ibid.*, **84**, 2414 (1962).

[14] (a) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962); (b) B. Rickborn and F. Jensen, *ibid.*, **27**, 4606 (1962).



A assumed to be energetically favored chair conformer over B.

propylidene function is not known with certainty, but is probably somewhat lower than that (2.1 kcal./mole) of an axial isopropyl substituent.[15]

The acid-catalyzed equilibration experiments demonstrated that the two cyanodihydrocarvones of m.p. 95.5 and 86.5° are more stable than their epimers at C-2. Both ketones exhibit positive Cotton effects of appreciable molecular amplitude (*a* as defined in ref. 8), that (Fig. 1) of the higher melting isomer exhibiting $a = +69$ and that (Fig. 1) of the lower melting one, $a = +53$. While these amplitude values cannot be employed to differentiate securely between the two alternative representations IIA and IIIA, there is available also the rotatory dispersion curve (Fig. 1) of the C-2 epimer (IV) of the m.p. 95.5° (II) cyanodihydrocarvone. Its amplitude ($a = +22$) is considerably lower than that of its more stable epimer, thus eliminating immediately the possibility that we are dealing with the pair IIIA → VA, since the axial methyl group in VA would have resulted in a more positive (rather than more negative) Cotton effect, the molecular amplitude increment[1] being nearly +70. We suggest, therefore that the m.p. 86.5° isomer of 2-cyano-2,3-dihydrocarvone should be represented by stereoformula IIIA, since the alternate conformer IIIB possesses three axial substituents. In view of the known[1,13] equilibrium position between an axial and equatorial 2-methylcyclohexanone (over 90% in favor of the latter), it is not surprising that thin-layer chromatography indicated the presence of only trace quantities of VA in the acid-catalyzed equilibration of IIIA.

If expression IIIA is associated with the m.p. 86.5° isomer, then the principal conformer of the higher melting one (m.p. 95.5°) must be represented by stereoformula IIA, the alternate conformer (IIB) again being less stable because of the additional axial substituents. It will be noted from an inspection of Fig. 1 that the molecular amplitude *dropped* [+69 (IIA) → +22 (IVA)] upon epimerization at C-2. If conformation IVB were the correct representation for this C-2 epimer (m.p. 13.5°), then its molecular amplitude should be approximately +136 (due to the +67 contribution[1] of the axial 2-methyl group). Since the amplitude actually decreased, we conclude that the principal conformer of the third isomer (m.p. 13.5°) of 2-cyano-2,3-

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[15] (a) N. L. Allinger and S. Hu, *J. Org. Chem.*, **27**, 3417 (1962); (b) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

dihydrocarvone should probably be represented by the stereoformula IVA.[16]

Next, dipole moment studies were undertaken to substantiate the conformational conclusions derived from the optical rotatory dispersion measurements. Such independent confirmation was desired since the rotatory dispersion arguments are based in part on the assumption that conformation VA represents the predominant rotational contributor in the equilibrium VA ⟷ VB, an assumption which may not necessarily be justified. The geometry of cyclohexanone is known fairly accurately, the coordinates of all the atoms being available.[17] The cyanodihydrocarvones contain three functionalities—the olefinic linkage, the ketone and the cyano group—which contribute to the resultant dipole. The directions of the moments of the carbonyl and cyano groups are known and the magnitudes of these group moments may be approximated by those of cyclohexanone (3.06 D.)[18] and of isobutyronitrile (3.6 D.).[19] The magnitude of the moment of the olefin can be taken as 0.4 D.,[20] but as the isopropylidene group rotates, the vector sweeps out a cone which will add in an uncertain way to the resultant of the other groups. If free rotation is assumed, then the olefin contributes a component of 0.4 D. acting along the line from the ring carbon (to which it is bound) to the attached olefinic carbon atom. Since the moment is small, it seems a good approximation to consider the group as freely rotating, even though this is a physically unreasonable assumption.

Having a set of dipole vectors, specified in magnitude and in direction, for conformations IIA, IIIA, IVA, IVB, VA, and VB (the most plausible chair conformations for the four possible isomeric 3-cyano-2,3-dihydrocarvones), it was possible to calculate the dipole moment of each isomer with an IBM 650 computer and the previously described[9] program. The dipole moments of the two principal isomers, II and III, were then determined by dielectric constant measurements, the calculations being carried out by essentially the method of Halverstadt and Kumler,[21] except that an IBM 650 computer and a previously described program[22] were utilized. Comparison of the calculated moments (Table I) with those found experimentally for the two predominant cyanodihydrocarvone isomers of m.p. 95.5° and m.p. 86.5° fully confirm the stereochemical assignments IIA and IIIA.

Previous stereochemical conclusions automatically apply to the derived benzamidomethyl derivatives VIIIA, IXA, and XIIA. The optical rotatory dispersion curve (Fig. 2) of VIIIA differs substantially from that (Fig. 1) of its derived cyanodihydrocarvone (IIA), the negative background, upon which the positive Cotton effect is superimposed, apparently being associated with the amide absorption in the far ultraviolet. This is supported by the observation that the corresponding acetamido analog XVA exhibits a similar dispersion curve (Fig. 2) and that the corresponding benzamido (VII) and acetamido (XIV) precursor alcohols show plain negative dispersion curves. The benzamidomethyl ketone IXA possesses a stronger positive Cotton effect (Fig. 2) than does (Fig. 1) the corresponding cyanodihydrocarvone (IVA); a comparison of the cyanodihydrocarvone (IIIA) optical rotatory dispersion curve (Fig. 1) with that (Fig. 2) of its benzamidomethyl derivative XIIA actually demonstrates an inversion in the sign of the Cotton effect. These apparently contradictory observations are easily accommodated by the assumption that the rotational con-

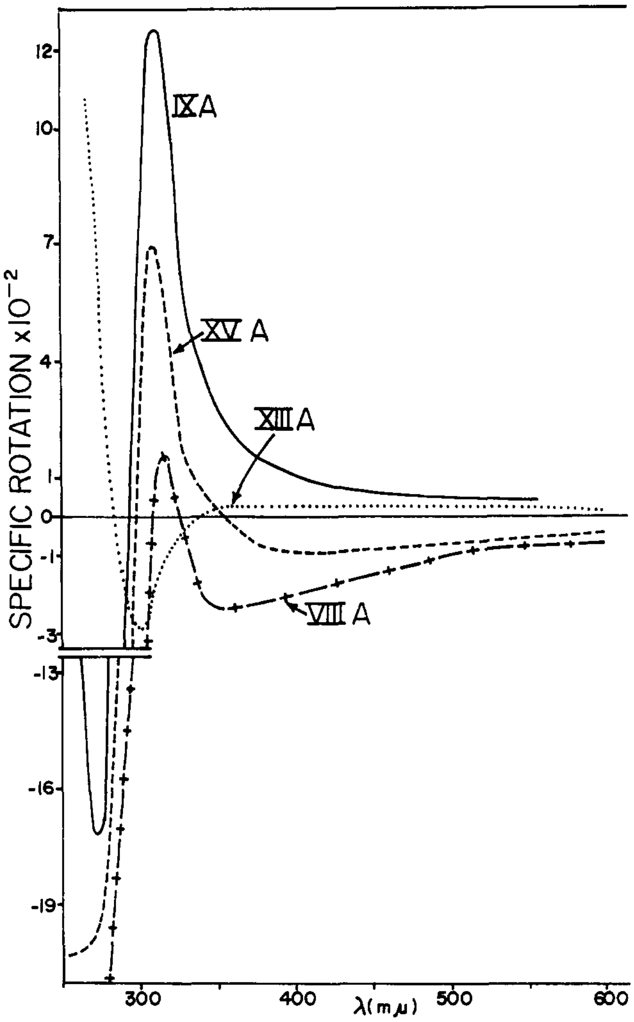

Fig. 2.—Dotted curve marked XIIIA should be marked XIIA.

TABLE I

VALUES FOR RESULTANT DIPOLE MOMENTS (DEBYE UNITS)

Structure	Calculated	Found
IIA	5.30	5.16 (m.p. 95.5° isomer)
IIB	3.13	
IIIA	2.74	2.88 (m.p. 86.5° isomer)
IVA	3.13	
IVB	5.30	
VA	2.74	
VB	5.84	

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(16) A twist form of IVB would be expected (ref. 8) to give a strongly positive Cotton effect. In order to explain the stronger positive Cotton effect of IIA over IVA, one must assume that an isopropenyl group (axial or equatorial) β to a carbonyl group makes a stronger rotatory contribution than an equatorial or axial β-cyano substituent. The limited available examples [C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390, (1963); J. Osiecki, Ph.D. thesis, Stanford University, 1960] are in complete accord with this conclusion.

(17) (a) N. L. Allinger and J. Allinger, *Tetrahedron*, **2**, 64 (1958); (b) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955); (c) see also footnote 10 in ref. 7.

(18) N. L. Allinger, J. Allinger, M. A. DaRooge, and S. Greenberg, *J. Org. Chem.*, **28**, in press.

(19) M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 457 (1947).

(20) L. G. Wesson, "Tables of Electric Dipole Moments," The Technology Press, Cambridge, Mass., 1947.

(21) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(22) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

tribution of the hitherto not studied benzamidomethyl grouping is larger than that of a cyano as well as that of an isopropenyl substituent [$\text{—CH}_2\text{NHCOC}_6\text{H}_5 > \text{—C(=CH}_2\text{)CH}_3 > \text{CN}$].

One last point must be emphasized. While the stereochemistry of the isomeric 3-cyano-2,3-dihydrocarvones can be considered as completely settled, the conformational assigments made in this paper to those ketones, where no dipole moment measurements could be performed for lack of material, should be considered to be only of qualitative significance, especially since we do not take into consideration the possible (minor) contributions of nonchair forms. Whether electrostatic repulsion between the C=O and CN dipoles in an axially oriented 3-cyanocyclohexanone plays a significant role is a moot point; it should be noted, however, that the difference in molecular amplitude of the Cotton effect of the axially oriented cyano ketone IIA in methanol *vs.* isooctane solution (see Experimental) is somewhat larger than the difference observed between these two solvents in the equatorial epimer IIIA.

Experimental[23]

2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (II).[24]—Following the procedure of Lapworth,[4a] 15.0 g. of (−)-carvone (I)[25] in 40 cc. of 95% ethanol was mixed with 9.0 g. of potassium cyanide in 20 cc. of water, followed by the dropwise addition of 6 g. of glacial acetic acid over a 30-min. period, with continuous stirring but without external cooling. After a further 30 min., fine crystals had appeared, whereupon 20 cc. of water was added and after an additional 30 min., precipitation was completed by the addition of 40 cc. of water and cooling in ice. The resulting crystals were collected (12.75 g., m.p. 87–91.5°) and were found by thin-layer chromatography to consist largely of II, contaminated with some IV and traces of III. Recrystallization from aqueous ethanol provided 8.76 g. of chromatographically homogeneous II, m.p. 93.5–95°, while the analytical sample [after sublimation at 70° (0.1 mm.)] exhibited m.p. 95–95.5°, $[\alpha]^{24}\text{D}$ −6.2° (*c* 2.75), (lit.[4] m.p. 93.5–94.5°, $[\alpha]^{12}\text{D}$ +13.5° for antipode). The relevant infrared bands are listed in Table II, while the rotatory dispersion curve is reproduced in Fig. 1. R.D. in methanol (*c* 0.103): $[\alpha]_{589}$ −12°, $[\alpha]_{318}$ +1400°, $[\alpha]_{314}$ +1360°, $[\alpha]_{310}$ +1400°, $[\alpha]_{270}$ −2490°, $[\alpha]_{250}$ −2300°. The molecular amplitude $a = +69$ was reduced to +54 in isooctane solution.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.75; H, 8.81.

2β-Methyl-3α-cyano-5α-isopropenylcyclohexanone (III).[24]—To a refluxing mixture of 12.0 g. of (−)-carvone (I) and 7.5 cc. of ethyl acetate was added a hot solution of 6.0 g. of potassium cyanide in 15 cc. of water and 17 cc. of 95% ethanol and heating continued for 20 min., two phases remaining during this period. The cooled solution was extracted with ether, dried, and evaporated to yield 13.2 g. of a yellowish, pasty mass of crystals, which by thin-layer chromatography was shown to contain approximately equal amounts of II and III, as well as traces of IV and less intense spots of very low R_f value (presumably acids and/or amides). Separation was not feasible by gas phase chromatography, three very closely overlapping peaks being observed, and recourse had to be taken to gradient elution chromatography on 850 g. of neutral alumina (activity II), starting with hexane–benzene (3:1) and adding benzene–hexane (3:1). Fractions of 50 cc. each were collected, using an automatic fraction collector, and were divided into three groups on the basis of thin-layer chromatographic analysis. Fractions 1–47 contained only traces (40 mg.) of carvone (I), while fractions 48–70 consisted largely of the desired isomer III (2.28 g., m.p. 30–79°), the remaining fractions representing varying proportions of II, III, and IV. One recrystallization from aqueous ethanol provided 1.58 g. of III, m.p. 78.5–84.5°, raised to 85.5–86.5° (0.96 g.) upon recrystallization from hexane–benzene. The analytical specimen was sublimed at 85° (0.1 mm.), whereupon it showed m.p. 86–86.5°, $[\alpha]_D$ +47° (*c* 1.72) (lit.[4b] m.p. 84°, $[\alpha]_D$ −42.1° for antipode). R.D. (Fig. 1) in methanol (*c* 0.104): $[\alpha]_{589}$ +42° $[\alpha]_{310}$ +1250, $[\alpha]_{270}$ −1740°, $[\alpha]_{250}$ −1580°, the molecular amplitude being practically unchanged in isooctane solution. The characteristic infrared peaks are listed in Table II.

TABLE II

INFRARED MAXIMA (CHLOROFORM) OF 2-METHYL-3-CYANO-5-ISOPROPENYLCYCLOHEXANONES[a]

Wave length	Compound II	Compound II	Compound IV
4.47	s	s	s
5.85	s	...	...
5.86	...	s	s
6.10	m	m	m
7.47	w	...	...
7.56	min	m	m
7.61	w	...	...
7.75	min	min	w
8.00 (broad)	...	m	...
8.33 (broad)	m	...	m
8.71	m	...	...
8.75	...	...	m
8.81	...	m	...
8.95	w	...	w
9.20	...	w	...
9.87	w	min	...
10.06	min	m	m
10.29	m	min	...
10.46	min	m	min
10.68	min	min	w
11.07	...	...	s
11.17	s	s	...

[a] Listed are maxima of important functional groups and maxima which are not the same for all three isomers.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.38; H, 8.52.

2α-Methyl-3β-cyano-5α-isopropenylcyclohexanone (IV).[24]—A solution of 2.37 g. of 2β-methyl-3β-cyano-5α-isopropenylcyclohexanone (II) in 30 cc. of benzene and 15 cc. of ethyl acetate containing 2.4 g. of *p*-toluenesulfonic acid was kept at room temperature for 4 days and then washed with sodium bicarbonate solution and water. Evaporation left a residue, which by thin-layer chromatography was found to consist of a mixture of II and IV with the former predominating. Separation was effected by hexane elution from a column of 170 g. of Celite,[26] impregnated with 75 cc. of formamide. The first fractions (0.34 g.) were combined and recycled to furnish 0.31 g. of a colorless oil, which was virtually pure IV as demonstrated by thin-layer chromatography. Recrystallization from hexane–ethyl acetate between −8° and −22° led to colorless needles, chromatographically homogeneous, which were distilled at 90° (0.1 mm.) to give the analytical sample of IV with m.p. 11.5–13.5°. R.D. (Fig. 1) in methanol (*c* 0.082): $[\alpha]_{589}$ −10°, $[\alpha]_{3\ 15}$+446°, $[\alpha]_{270}$ −806°,

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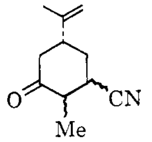
[23] All melting points were taken in capillaries and are corrected. Rotations were measured in 95% ethanol and infrared spectra in chloroform solution. The optical rotatory dispersion curves were determined by Mrs. Ruth Records with a Nippon Bunko (Japan Spectroscopic Co.) automatically recording spectropolarimeter (Model ORD-2); while the microanalyses are due to Messrs. E. Meier and J. Consul. Thin-layer chromatograms were performed on silica gel G (E. Merck, Darmstadt) plates, 10% ethyl acetate in benzene being used as the developing agent. The approximate R_f values were: II (0.37), III (0.52), IV (0.42), and V (0.40).

[24] In order to simplify the nomenclature and, since the absolute configuration of all products is known, we are employing the steroid notation (ref. 5) based on the following representation.



[25] The material [$[\alpha]_D$ −60.7° (neat), $n^{25}\text{D}$ 1.4968] was purchased from Farmer's Chemical Co., Kalamazoo, Mich., and was homogeneous according to gas-phase chromatography.

[26] Commercial Celite 545 was washed overnight with concentrated hydrochloric acid, then successively with dilute acid, water, sodium bicarbonate solution, and finally water. The material was dried at 110° for 20 hr. before use.

$[\alpha]_{250}$ −649°, the characteristic infrared bands being listed in Table II.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.13; H, 8.56.

Epimerization Experiments at C-2.—A solution of either isomer II or III and an equal weight of *p*-toluenesulfonic acid in ethyl acetate solution produced in each case two spots in a thin-layer chromatogram: II → II + IV; III → III + V. Within 1 week at room temperature, the ratio of intensities for a given pair (II and IV, or III and V) ceased to change and, even after 3 months, no spot corresponding to the other pair appeared. In the equilibration of III, the spot corresponding to its C-2 epimer (V) was so faint that isolation of this isomer was not attempted.

Under more forceful conditions, such as alcoholic potassium hydroxide, the same effects were noted in a matter of seconds, but epimerization also occurred at C-3 as demonstrated by the appearance of all four spots after a very short while.

Epimerization Experiments at C-3.—In a model experiment, 128 mg. of II was dissolved in methanol and left for 1 hr. with a solution of 33 mg. of sodium borohydride in 2 cc. of 50% aqueous methanol. After acidification, the product was isolated with ether and shown to lack completely any infrared carbonyl absorption. The entire alcohol (124 mg.) was oxidized in 10 cc. of acetone at 0° with 8 *N* chromic acid solution,[11,12] small quantities of anhydrous magnesium sulfate being added simultaneously. Thin-layer chromatography of the oxidation product showed that it consisted virtually of only the starting ketone II, contaminated with nonoxidized alcohol and traces of IV.

The sodium borohydride (10 mg.) reduction of 20 mg. of II was repeated but, prior to reoxidation, the alcohol was heated under reflux for 20 min. with 10% aqueous–methanolic potassium hydroxide solution. Thin-layer chromatography of this oxidation mixture demonstrated the presence of strong spots due to II and III, as well as a trace of IV. Conversely, when this sequence was repeated with pure III, thin-layer chromatography clearly showed the production of II, weak spot) in addition to a strong spot corresponding to III, but no indication of spots associated with IV or V.

2β-Methyl-3β-benzamidomethyl-5α-isopropenylcyclohexanone (VIII).[24]—2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (II) (1.02 g.) was reduced with 0.6 g. of lithium aluminum hydride by heating under reflux for 30 min. in ether (150 cc.) solution and decomposing the reaction mixture by the sodium sulfate technique. The resulting mixture of alcohols (VI) [0.99 g., m.p. 63–84°, $[\alpha]_D$ −10° (*c* 1.19), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.77, 2.95, 6.10, and 11.2 μ, but no bands between 4.0–6.0 μ] was used directly in the next step.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.55. Found: C, 72.25; H, 11.55.

The amino alcohol (1.25 g. of VI) was dissolved in a mixture of 100 cc. of chloroform and 15.8 cc. of 2% sodium hydroxide solution and benzoyl chloride (0.87 cc.) in 15 cc. of chloroform was added with vigorous stirring at room temperature over a period of 30 min. After 1.5 hr., the basic aqueous solution was separated and the organic layer washed to neutrality, dried, and evaporated. The crystalline benzamido alcohol mixture VII (1.85 g.), m.p. 105–130°, $[\alpha]_D$ −22° (*c* 1.35). R.D. in methanol (*c* 0.10): plain negative curve, $[\alpha]_{500}$ −76°, $[\alpha]_{400}$ −102°, $[\alpha]_{300}$ −218°, $[\alpha]_{280}$ −384°, showed two spots in a thin-layer chromatogram (2:3 ethyl acetate–benzene) and was oxidized without further separation.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 74.85; H, 8.80.

A portion (133 mg.) of this mixture (VII) was oxidized at room temperature in acetone solution with 8 *N* chromic acid solution,[11,12] and the quantitatively produced ketone VIII (m.p. 176–179.5°) was recrystallized twice from benzene and sublimed at 150° (10^{-5} mm.), whereupon the analytical specimen exhibited m.p. 179–180.5°, $[\alpha]_D$ −68° (*c* 0.59), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.87, 6.05, and 11.22 μ. R.D. (Fig. 2) in methanol (*c* 0.071): $[\alpha]_{589}$ −62°, $[\alpha]_{317}$ +160°, $[\alpha]_{254}$ −5130°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.73; H, 8.13.

2α-Methyl-3β-benzamidomethyl-5α-isopropenylcyclohexanone (IX).[24]—The above-described 2β-methyl isomer VIII (174 mg.) was left at room temperature for 1 hr. in 25 cc. of methanol containing 350 mg. of potassium hydroxide. The solution was neutralized, the methanol evaporated, and the product (168 mg.) extracted with methylene chloride. Recrystallization from benzene provide 30 mg. of the starting material (VIII), m.p. 175–179°, and, since chromatography on alumina did not effect any good separation of the mother liquor material, it was subjected to fractional crystallization from acetone–hexane. From the less soluble portion an additional 23 mg. of VIII (m.p. 171–174°) could be isolated, while the more soluble material yielded in three crops a total of 81 mg. of IX. Two additional recrystallizations from acetone–hexane and one from benzene–hexane gave colorless needles of IX which were homogeneous by thin-layer chromatography; m.p. 102–104°, $[\alpha]_D$ +19° (*c* 0.05), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.87, 6.05, and 11.19 μ. R.D. (Fig. 2) in methanol (*c* 0.098): $[\alpha]_{589}$ +24°, $[\alpha]_{310}$ +1260°, $[\alpha]_{273}$ −1730°, $[\alpha]_{265}$ −1020°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.30; H, 8.17.

On the basis of the weights of the isolated substances in the base-catalyzed epimerization reaction, the equilibrium composition is approximately 39% VIII *vs.* 61% IX. In order to obtain an independent value, 13 mg. each of pure VIII and of pure IX was allowed to stand at room temperature for 30 min. in 1% methanolic potassium hydroxide solution. Each mixture was worked up under identical conditions and in each instance a melting point of 96–145° was encountered for the total crude product (12 mg.). The rotatory dispersion curves were determined in methanol solution (*c* 0.10) and the equilibration mixture of VIII exhibited a peak at $[\alpha]_{303}$ +1000°, while that of IX showed $[\alpha]_{304}$ +930°. Using the rotations observed at 310 mμ (VIII, +210°; IX, +1260°; equilibrium mixtures, +925°), one arrives at a 32% (VIII)–68% (IX) equilibrium composition.

2β-Methyl-3α-benzamidomethyl-5α-isopropenylcyclohexanone (XII).[24]—The lithium aluminum hydride reduction of 2β-methyl-3α-cyano-5α-isopropenylcyclohexanone (III) was performed exactly as described for II and the crude alcohol mixture (X), representing a viscous liquid, was benzoylated in 92% yield to produce the benzamide mixture XI, m.p. 161–173°. R.D. in methanol (*c* 0.107): $[\alpha]_{589}$ +47°, $[\alpha]_{400}$ +94°, $[\alpha]_{300}$ +140°, $[\alpha]_{260}$ +210°.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 74.88; H, 8.84.

Oxidation of XI in acetone solution provided 97% of colorless crystals, m.p. 124.5–133.5°, which after two recrystallizations from acetone–hexane led to the analytical specimen of XII m.p. 143.5–145°, $[\alpha]_D$ +23° (*c* 1.37), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.87, 6.05, and 11.22 μ. R.D. (Fig. 2) in methanol (*c* 0.10): $[\alpha]_{589}$ +19°, $[\alpha]_{303}$ −280°, $[\alpha]_{255}$ +1070°.

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.64; H, 8.21.

Base-catalyzed equilibration of this amide XII in an attempt to prepare the 2α-epimer XIII yielded a product, m.p. 135–140°, [R.D. in methanol (*c* 0.107): $[\alpha]_{589}$ +9°, $[\alpha]_{360-320}$ +35° (broad plateau), $[\alpha]_{293}$ −170°, $[\alpha]_{276}$ 0°] which showed two spots in a thin-layer chromatogram, the new spot (corresponding to XIII) being very faint. Attempts to isolate the new epimer by fractional crystallization proved unsuccessful.

TABLE III

DIPOLE MOMENT DATA, BENZENE SOLUTION, 25° (EXPERIMENTAL ERROR ±0.03 D.)

2β-Methyl-3β-cyano-5α-isopropenylcyclohexanone (IIA)[24]

N_2	d_{12}	ϵ_{12}
0.00000000	0.873322	2.2762
.00079446	.873541	2.3051
.00151767	.873732	2.3319
.00230825	.873982	2.3610
.00299230	.874170	2.3870
$\alpha = 37.029$	$\epsilon_1 = 2.2759$	$d_1 = 0.87332$
$\beta = 0.285$	$P_{2\infty} = 595.3$	$\mu = 5.16$ D.

2β-Methyl-3α-cyano-5α-isopropenylcyclohexanone (IIIA)[24]

N_2	d_{12}	ϵ_{12}
0.00000000	0.873345	2.2763
.00043163	.873407	2.2812
.00088528	.873526	2.2868
.00113033	.873513	2.2892
.00162884	.873730	2.2947
$\alpha = 11.374$	$\epsilon_1 = 2.2764$	$d_1 = 0.87331$
$\beta = 0.243$	$P_{2\infty} = 222.0$	$\mu = 2.88$ D.

2β-Methyl-3β-acetamidomethyl-5α-isopropenylcyclohexanone (XV).[24]—To a vigorously stirred and ice-cold solution of 626 mg. of the 2β-methyl-3β-aminomethyl-5α-isopropenylcyclohexanol mixture (VI) in 200 cc. of pyridine and 30 cc. of dry benzene, 349 mg. of acetic anhydride in 150 cc. of benzene was added dropwise over a period of 4 hr. After one additional hour at ice-bath temperature, the mixture was poured into water, the product isolated in the usual manner with ether, then chromatographed on 10 g. of neutral alumina (activity III), elution being effected first with 250 cc. of methylene chloride, followed by 150 cc. of ethyl acetate. The desired acetamido alcohol mixture (XIV) was obtained as a colorless oil (135 mg.), which crystallized spontaneously; m.p. 70–96.5°. R.D. in methanol (*c* 0.12): $[\alpha]_{589}$ $-21°$, $[\alpha]_{500}$ $-29°$, $[\alpha]_{400}$ $-50°$, $[\alpha]_{300}$ $-134°$, $[\alpha]_{260}$ $-183°$. This material was directly oxidized with chromium trioxide in acetone solution[11,12] and recrystallized from acetone–hexane to give the desired, chromatographically homogeneous ketone XV, m.p. 98–99°, $\lambda_{\max}^{\mathrm{CHCl_3}}$ 2.90, 5.87, 6.00 and 11.20 μ. R.D. (Fig. 2) in methanol (*c* 0.105): $[\alpha]_{589}$ $-48°$, $[\alpha]_{308}$ $+704°$, $[\alpha]_{240}$ $-2280°$.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.72; H, 9.58.

Dipole Moment Measurements.—The dipole moments were measured in benzene solution at 25°, using the previously described[27] apparatus, the data being summarized in Table III. References to the method of calculation are given in the Discussion. The molar refractivity (50.25 cc.) was calculated from tables[28] and atomic polarization was neglected.

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The Constitution of Otobain

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A new lignan, otobain, for which the structure 5,6-methylenedioxy-2,3-dimethyl-4-(3′,4′-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene (VI) is proposed, has been isolated from the fruit of *Myristica otoba*.

The fat expressed from the fruit of *Myristica otoba* is reputedly used in Colombia as a medicament for skin diseases of domestic animals. It was first examined over one hundred years ago by Uricoechea,[2] who isolated a product which he named "otobite" and to which he attributed the empirical formula $C_{24}H_{26}O_5$. A more extensive examination was performed by Baughman and co-workers,[3] who reported the isolation of isomers, $C_{20}H_{20}O_4$, which they named otobite and isootobite, and suggested that the previously isolated product was a mixture. From a sample of otoba fat collected in 1960 in the Departmento of Tolima, Colombia,[4] we have isolated a lignan for which the name otobain was proposed in a preliminary communication.[5] Gilchrist, Hodges, and Porte[6] since have described work on the isolation and structure elucidation of the same product to which they have fortunately assigned the same name in conformance with lignan nomenclature. The assumption that otobite and otobain are identical[6] we regard as questionable on the basis of reported differences of behavior (*e.g.*, Zeisel determination, action of bromine).[3,5]

Empirical analyses and molecular weight determination established that otobain had a molecular formula, $C_{20}H_{20}O_4$. The absence of absorption bands in the infrared spectrum characteristic of hydroxyl and carbonyl groups indicated that all four oxygen atoms were present as ether functions. The absence of methoxyl groups, established by Zeisel determination, suggested the likelihood that the oxygen functions were two methylenedioxy groups. That at least one such group was present was apparent from the infrared spectrum (potassium bromide disk) which showed a strong band at 928 cm.$^{-1}$, with a weak overtone at 1850 cm.$^{-1}$, considered most characteristic for methylenedioxy groups[7]; the presence of strong bands at 1362, 1242, 1130, and 1045 cm.$^{-1}$, particularly in the demonstrated absence of aromatic methoxyl groups, supports this assignment. Chemical evidence for the presence of two methylenedioxy groups was obtained by treatment of otobain with phosphorus pentachloride followed by sodium carbonate. The isolated product, $C_{20}H_{16}O_6$, had an infrared absorption band at 1830 cm.$^{-1}$ characteristic of five-membered ring strained carbonyl systems[8] of which the derived benzenoid cyclic carbonate is typical.

Kuhn–Roth C-methyl determination indicated the presence of two such groups, leaving unaccounted only two carbon atoms to be incorporated in a ring. This preliminary characterization strongly suggested that otobain is a lignan[9,10] of the phenyltetralin class, of which structure I based on unexceptional biogenetic considerations,[11–13] is the most obvious possibility. Integration of the nuclear magnetic resonance spectrum of otobain established the presence of five aromatic protons, and the ultraviolet absorption spectrum was also consistent with this formulation. Closely related to I are the lignans, isolated from *Himantandra* species by Hughes and Ritchie,[14] named galbulin (II) and galcatin (III), the absolute stereochemical assignments being proposed by two independent groups.[15,16]

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