[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XXIV.[1] Effect of Distance of a Single Asymmetric Center from an Aliphatic Carbonyl Function[2]

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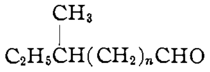
A series of optically active aliphatic aldehydes and methyl ketones has been synthesized for optical rotatory dispersion measurements. The single asymmetric center was always the same (S) since it was derived from (−)-2-methylbutanol-1 ("optically active amyl alcohol") which has been related to L-glyceraldehyde. The series of methyl ketones consisted of members in which the carbonyl function was separated by 0, 1, 2, 3 and 4 carbon atoms while the aldehydes covered the range 0–3 carbon atoms. In agreement with earlier work on aldehydes by Levene and Rothen, it was found that the sign of the Cotton effect curve is inverted in going from $n = 0$ to $n = 1$ (see type formulas I and II) and then reverts to the sign of the $n = 0$ aldehyde in the higher members, except that where $n = 2$, there exists a weak negative Cotton effect superimposed upon a positive "background" rotation. Furthermore, the anomalous character of the dispersion curve becomes less pronounced as the distance between the carbonyl chromophore and the asymmetric center is increased. Attention is called to the bearing of these observations upon the determination of absolute configuration.

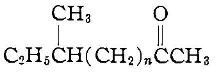
One of the important applications of the optical rotatory dispersion studies carried out in our laboratory[4] has been the determination of absolute configuration. Except in the case of α-halocyclohexanones,[1,5] where reference compounds are not required, this has been accomplished[6] by comparing the shape and sign of the dispersion curve of the unknown aldehyde or ketone with that of a steroid or bicyclic or polycyclic carbonyl compound of established absolute configuration. In view of the sensitivity of the rotatory dispersion method to changes in the immediate asymmetric environment,[7] it is important that comparison of rotatory dispersion curves be carried out between substances of identical conformation, thus limiting this approach, for the time being, largely to bi- or polycyclic substances. In monocyclic ketones, especially cyclohexanones, conformational mobility[8] may complicate the picture and a considerable number of model compounds of known absolute configuration have first to be synthesized.[9] The effect of ring size has already been examined[10] in a series of model 3-methylcycloalkanones and we should now like to turn to a consideration of aliphatic ketones and aldehydes which have so far been neglected in our studies.

The basic information which has to be secured is to determine the effect upon the rotatory dispersion curve of separating a single asymmetric center from the carbonyl chromophore by one or more carbon atoms. The only pertinent work in the literature is that of Levene and Rothen who synthesized[11] a series of aldehydes I, where $n =$ 0, 1, 2 and 3 and measured[12] their rotations in the visible and ultraviolet regions. They made the important observation that the aldehyde I ($n =$ O) exhibited a positive, and the configurationally related higher homolog I ($n = 1$) a negative Cotton effect curve.[13] The experimental data of Levene and Rothen[12] demonstrate that the other two aldehydes (I, $n = 2, 3$) show again a positive dispersion curve, but it is not possible to determine directly from their data whether this is characterized by a Cotton effect since only one reading was taken below 345 mμ; calculation[12] of the appropriate Drude equation, however, indicated that this was the case. Consequently, it was decided to repeat the synthesis of this series of optically active aldehydes (I, $n = 0 - 3$) and to carry out the dispersion measurements with a modern photoelectric spectropolarimeter[14] rather than by the earlier photographic technique.[15] Furthermore, it was desirable to extend this work also to ketones and for that purpose a series of optically active methyl ketones (II) was synthesized, where n ranged from 0–4.



$$C_2H_5\overset{\overset{\displaystyle CH_3}{|}}{C}H(CH_2)_nCHO$$

I



$$C_2H_5\overset{\overset{\displaystyle CH_3}{|}}{C}H(CH_2)_n\overset{\overset{\displaystyle O}{\|}}{C}CH_3$$

II

Synthesis of Aldehydes (I).—Since the Cotton effect curves[13] of a homologous series of configurationally related cyclic ketones[10] or aliphatic aldehydes[12] may show an inversion in sign at some stage, it is indispensable that the synthetic work involve

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[1] Paper XXIII, C. Djerassi, I. Fornaguera and O. Mancera, THIS JOURNAL, **81**, 2383 (1959).

[2] This investigation was supported by the National Cancer Institute (grant No. CY-2919) of the National Institutes of Health, U. S. Public Health Service.

[3] Taken from Part II of the Ph.D. Thesis of L. E. G.

[4] See C. Djerassi, *Bull. soc. chim. France*, 741 (1957), for pertinent references and general introduction.

[5] (a) C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957); (b) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

[6] (a) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956); (b) C. Djerassi and W. Klyne, *Chemistry & Industry*, 988 (1956); (c) C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957); (d) C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957).

[7] See C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958).

[8] For a pertinent example see C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958).

[9] This subject, which is being investigated with E. J. Eisenbraun, J. Osiecki and F. Burian, will form the subject of a future communication.

[10] C. Djerassi and G. W. Krakower, THIS JOURNAL, **81**, 237 (1959).

[11] P. A. Levene and A. Rothen, *J. Biol. Chem.*, **111**, 739 (1935).

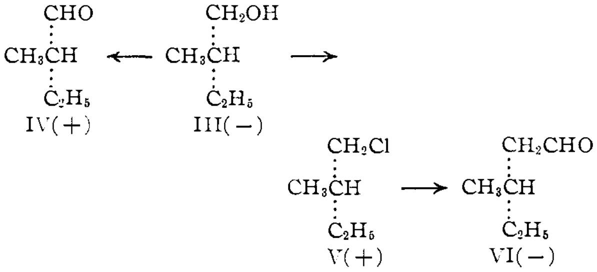
[12] P. A. Levene and A. Rothen, *J. Chem. Phys.*, **4**, 48 (1936).

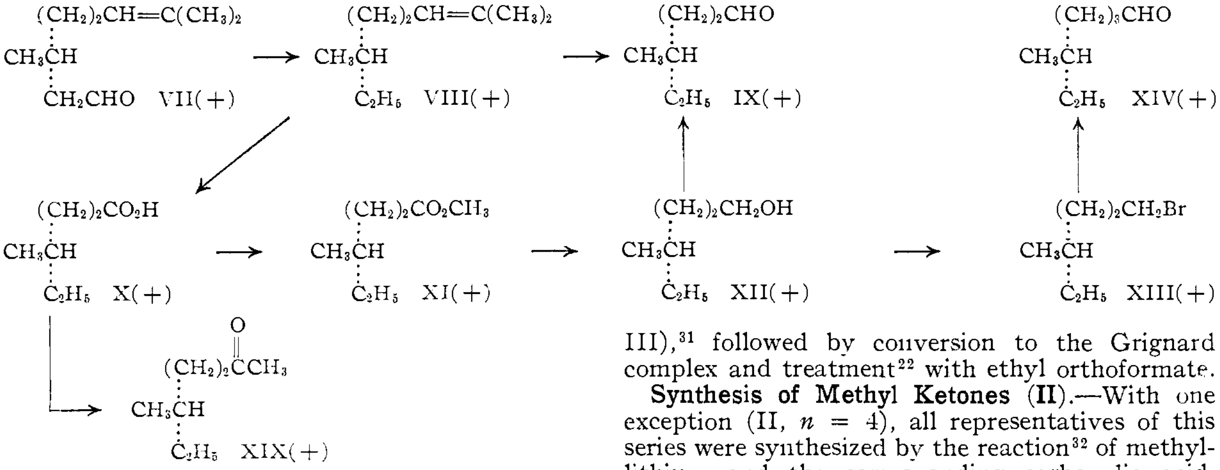
[13] For nomenclature and method of recording experimental data see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

[14] H. Rudolph, *J. Opt. Soc. Amer.*, **45**, 50 (1955); *Proc. Instr. Soc. Amer.*, Sept. 1956 (paper No. 56-3-1); E. Brand, E. Washburn, B. F. Erlanger, E. Ellenbogen, J. Daniel, F. Lippmann and M. Scheu, THIS JOURNAL, **76**, 5037 (1954).

[15] P. A. Levene, A. Rothen and R. E. Marker, *J. Chem. Phys.*, **1**, 662 (1933). The photographic measurements usually extend over a period of several days and since we have found that the aldehydes of series I are readily oxidized in air to the corresponding acids (showing plain rather than anomalous (see ref. 13) dispersion curves), it seemed very important to repeat the measurements by the photoelectric technique which requires less than two hours.

intermediates of known absolute configuration[16] rather than resolution of the final product. In the present investigation, the starting material was (−)-2-methylbutanol-1 ("optically active amyl alcohol") (III),[17] whose absolute configuration (S)[18] has been related to L-glyceraldehyde.[19] In our hands, the synthesis of the first member of the series (I, $n = 0$), (+)-2-methylbutanal (IV), proceeded more satisfactorily by oxidation of (−)-2-methylbutanol-1 (III) with potassium dichromate[20] rather than with chromium trioxide in pyridine solution.[21] The next higher homolog (I, $n = 1$), (−)-3-methylpentanal (VI), was prepared by a modification of the Tschitschibabin procedure[11,22] from (+)-2-methyl-1-butyl chloride (V),[23] since the lithium aluminum hydride reduction[24] of the N-methylanilide of (+)-3-methylpentanoic acid (XVII) did not give good results.


IV(+) III(−) V(+) VI(−)


VII(+) VIII(+) IX(+) XIV(+) X(+) XI(+) XII(+) XIII(+) XIX(+)

(+)-4-Methylhexanal (IX) (I, $n = 2$) has been synthesized earlier[11] by the Tschitschibabin reaction[22] on (+)-3-methylamylmagnesium bromide, but we have found the following procedure from (+)-citronellal (VII) far superior. The determination of the latter's absolute configuration (R)[18] has already been summarized[25] and Huang-Minlon reduction[26] afforded (+)-2,6-dimethyl-2-octene (VIII),[27] which should now be assigned[28] the (S) notation, identical with that of our earlier starting material (III). Ozonolysis[27] of VIII and careful decomposition of the ozonide with ferrous sulfate provided the desired aldehyde (+)-4-methylhexanal (IX). An alternate approach involving chromium trioxide–acetone oxidation[29] of (+)-4-methylhexanol-1 (XII) gave inferior results. The alcohol XII required for this oxidation was prepared by lithium aluminum hydride reduction of the methyl ester XI of (+)-4-methylhexanoic acid (X),[30] obtained by ozonization of (+)-2,6-dimethyl-2-octene (VIII) and treatment of the intermediate ozonide with hydrogen peroxide. .

The synthesis of the last member of this series (I, $n = 3$), (+)-5-methylheptanal (XIV), followed the route described by Levene and Rothen[11] and proceeded *via* (+)-4-methylhexyl bromide (XIII),[31] followed by conversion to the Grignard complex and treatment[22] with ethyl orthoformate.

Synthesis of Methyl Ketones (II).—With one exception (II, $n = 4$), all representatives of this series were synthesized by the reaction[32] of methyllithium and the corresponding carboxylic acid. The first three members of this series (II, $n = 0, 1, 2$) have already been described earlier in optically active form,[33–35] and our syntheses of (+)-3-methylpentanone-2 (XVI), (+)-4-methyl-

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[16] This problem has already been encountered in the synthesis of bicyclic ketones: C. Djerassi and D. Marshall, THIS JOURNAL, **80**, 3986 (1958); C. Djerassi, D. Marshall and T. Nakano, *ibid.*, **80**, 4853 (1958).

[17] We are greatly indebted to Prof. Harry S. Mosher of Stanford University for a generous supply of this alcohol obtained by fractionation of fusel oil.

[18] According to the convention of R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

[19] L. Crombie and S. H. Harper, *J. Chem. Soc.*, 2685 (1950), have summarized the chain of reactions establishing the configurational link between (−)-2-methylbutanol-1 (III) and L-glyceraldehyde. See also J. A. Mills and W. Klyne in "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, Vol. 1, Chapter 5.

[20] F. Ehrlich, *Ber.*, **40**, 2538 (1907); P. A. Levene and M. Kuna, *J. Biol. Chem.*, **110**, 323 (1935).

[21] J. T. Gruver and J. G. Calvert, THIS JOURNAL, **78**, 5208 (1956).

[22] A. E. Tschitschibabin, *Ber.*, **37**, 186 (1904).

[23] For preparation and constants see H. C. Brown and C. Groot, THIS JOURNAL, **64**, 2563 (1942); K. B. Wiberg and B. I. Rowland, *ibid.*, **77**, 1159 (1955).

[24] F. Weygand, G. Eberhard, H. Linden, F. Schäfer and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

[25] A. J. Birch, *Ann. Repts. Progr. Chem.*, **47**, 192 (1950).

[26] Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

[27] M. D. Sutherland, *ibid.*, **75**, 5944 (1953), and references cited therein.

[28] In the case of (+)-2,6-dimethyl-2-octene (VIII), the large substituent bearing the double bond (as well as all transformation products derived by cleavage of that double bond) should be labeled "a" according to the Cahn–Ingold–Prelog system (ref. 18) and the configuration of the substance should be referred to as (S).

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

[30] See P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **95**, 153 (1932), who prepared the acid X by another method.

[31] P. A. Levene and R. E. Marker, *ibid.*, **91**, 77 (1931).

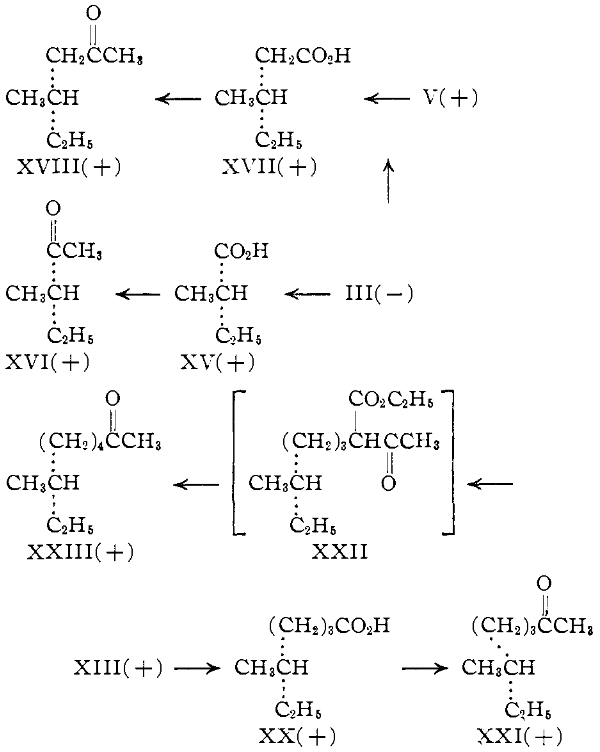
[32] See C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

[33] P. D. Bartlett and C. H. Stauffer, THIS JOURNAL, **57**, 2582 (1935).

[34] F. Nerdel and E. Henkel, *Ber.*, **86**, 1002 (1953).

[35] M. Rupe and S. Wild (*Ann.*, **414**, 117 (1918)) prepared XIX by alkylation of acetoacetic ester with (+)-2-methyl-1-butyl bromide (derived from III).

hexanone-2 (XVIII)[36] and (+)-5-methylheptanone-2 (XIX) are apparent from the flow sheet. Optically impure (+)-6-methyloctanone-2 (XXI) has already been obtained by Sutherland[27] from the ozonolysis of (+)-2,6-dimethyl-1-octene and we have now prepared it by the action of methyllithium upon (+)-5-methylheptanoic acid (XX).[30] The last member (II, n = 4) of this series, (+)-7-7-methylnonanone-2 (XXIII), was synthesized by alkylation of acetoacetic ester with (+)-4-methylhexyl bromide (XIII)[31] and ketonic hydrolysis of the intermediate β-keto ester XXII which was not isolated.



Optical Rotatory Dispersion Results.[37]—In contrast to the cyclic ketones studied earlier,[4] which exhibited very high rotations in the ultraviolet, the presently examined series of aliphatic ketones and aldehydes showed only low rotations (generally below 100°). Since the measurements had to be carried out in very dilute solution, the reported values are often subject to an error of 10–30%, which does not, however, affect any of the conclusions drawn from the dispersion curves.

Since hemiketals and hemiacetals show[38] only plain dispersion[13] curves, all aldehydes were examined in octane solution (in order to avoid acetal formation in methanol) and their molecular[37] rotatory dispersion curves are collected in Fig. 1. The most important conclusion to be drawn from Fig. 1 is that while the first member (I, n = 0) of the series, (+)-2-methylbutanal (IV), exhibits a positive Cotton effect,[13] that of the higher homolog (I, n = 1), (−)-3-methylpentanal (VI), is characterized by a negative one. We were thus able to confirm completely the earlier observation[12] of Levene and Rothen. The next aldehyde (I, n = 2), (+)-4-methylhexanal (IX), shows a weak negative Cotton effect superimposed on a positive "background"[13] curve, while that of the last member, (+)-5-methylheptanal (XIV), demonstrates only slight irregularities, its shape approaching that of a plain[13] curve.

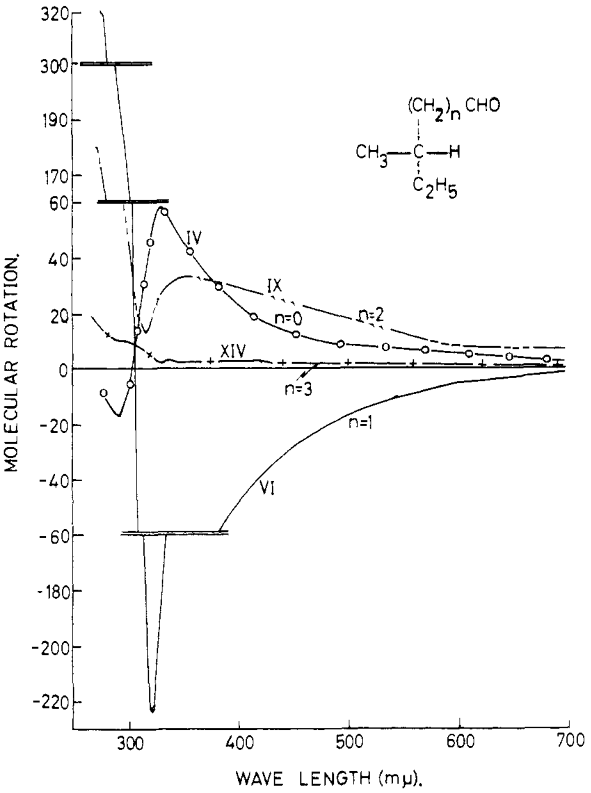


Fig. 1.—Molecular optical rotatory dispersion curves (octane solution) of (+)-2-methylbutanal (IV), (−)-3-methylpentanal (VI), (+)-4-methylhexanal (IX) and (+)-5-methylheptanal (XIV).

The relevant data[39] for the methyl ketones (II, n = 0–4) are collected in Fig. 2 and the same conclusions can be drawn as above for the aldehydes I: when one carbon atom is interposed between the asymmetric center and the carbonyl function, there is noted a reversal in sign of the Cotton effect, while all other members of the series show the same sign as the first member.[40] This reversal in sign (IV *vs.* VI in Fig. 1; XVI *vs.* XVIII in Fig. 2) can probably be associated with the preponderance

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[36] The ketone is listed as (+)-4-methylhexanone-2 (XVIII) because it shows a weak positive rotation when measured neat or in chloroform solution at the sodium D line. Its rotatory dispersion curve, however, is characterized by a negative Cotton effect (see Fig. 2).

[37] All values pertaining to the homologous series I and II are reported as molecular rotations ([α] × mol. wt./100).

[38] C. Djerassi, L. A. Mitscher and B. Mitscher, THIS JOURNAL, 81, 947 (1959).

[39] The few rotatory dispersion measurements which have been carried out in the earlier literature (ref. 34, 35) on such ketones were not performed far enough in the ultraviolet region to indicate the presence or absence of a Cotton effect.

[40] It seems that the ketone (II, n = 2) also possesses a weak negative Cotton effect (actually demonstrated with the aldehyde IX in Fig. 1) superimposed upon a positive plain curve, as indicated by the broad plateau between 360–332 mμ, which does not represent a peak (see ref. 13 as well as footnote 19 in C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, 77, 4354 (1955)). Unfortunately, it was impossible to carry out measurements below 305 mμ in either octane or methanol and the actual trough was not observed.

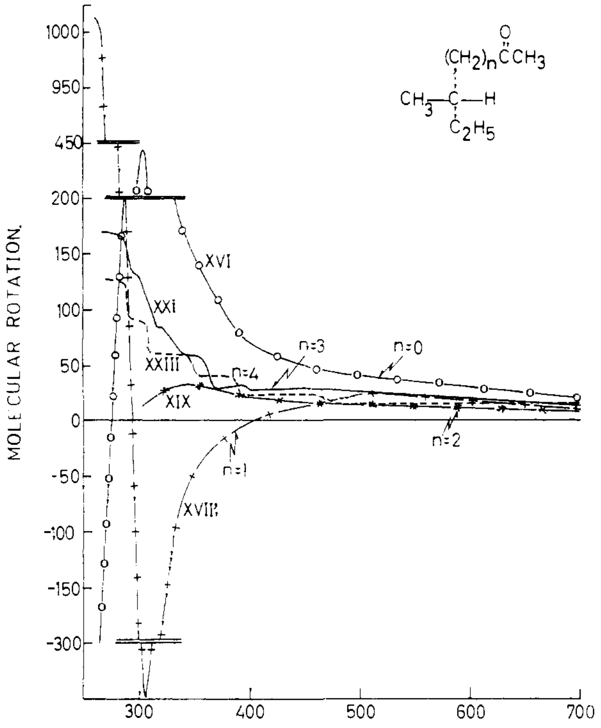


Fig. 2.—Molecular optical rotatory dispersion curves of (+)-3-methylpentanone-2 (XVI) (methanol), (+)-4-methylhexanone-2 (XVIII) (methanol), (+)-5-methylheptanone-2 (XIX) (methanol), (+)-6-methyloctanone-2 (XXI) (octane) and (+)-7-methylnonanone-2 (XXIII) (octane).

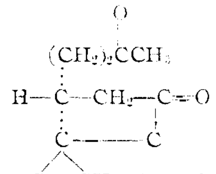
of a given free-rotational isomer in solution, similar to the explanation offered recently[1] with certain steroidal 17-halo-20-ketones. A detailed discussion of this point is not yet warranted and should await the accumulation of more experimental data.

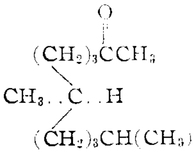
It is interesting to note that in the case of $n = 1$—in contrast to the corresponding aldehyde VI—the negative Cotton effect of the ketone XVIII does not make itself felt in the visible region to a marked extent and the rotation at the sodium D line is still positive.[36] This represents a further illustration of the disadvantage of utilizing only sodium D line rotations since the characteristic dispersion features are often masked partially or completely at that "insensitive" wave length. As is to be anticipated, the anomalous nature of the dispersion curve becomes less pronounced as the distance between the asymmetric center and the ketonic chromophore is increased and the last two representatives (II, $n = 3, 4$) show only a plain curve with minor irregularities.

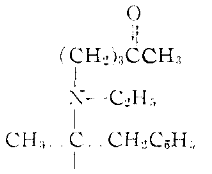
As far as the application of these results to the determination of absolute configuration is concerned, two general comments can be made:

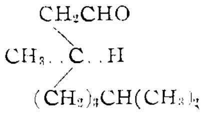
(a) The "distance factor"–tendency of anomalous Cotton effect curve to become plain when three or four carbon atoms are placed between the asymmetric center and the carbonyl function—probably varies in different systems and cannot be used as a very good criterion, although the sign of the curve still seems to be meaningful. Thus (+)-homoterpenyl methyl ketone (XXIV) ($n = 2$), hexahydro-ψ-ionone (XXV) ($n = 3$) and (+)-5-(N-ethyl-α-methylphenethylamino)-2- pentanone (XXVI)[41] all show positive dispersion curves which appear to be plain within the limits of error of the measurements.

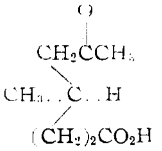
(b) The sign of the Cotton effect curves of ketones or aldehydes where none or one carbon atom is interposed ($n = 0$ or 1) is significant and, provided there is no other asymmetric center in close vicinity, the ethyl group attached to the asymmetric center in the model compounds I and II can be replaced by other substituents. Thus (+)-citronellal (VII) and its reduction product (+)-dihydrocitronellal (XXVII) show positive Cotton effect curves[10] and can be considered aldehydes equivalent to I, $n = 1$. The latter (VI) has a negative Cotton effect curve but upon inspection of representation XXVII for (+)-dihydrocitronellal (and the corresponding representation for (+)-citronellal), it will be seen that these compounds (VI *vs.* XXVII) belong to antipodal series and that their Cotton effect curves should, therefore, be of opposite sign. The utility of this conclusion is exemplified by the positive Cotton effect curve[42] of the keto acid XXVIII derived[42] from the antibiotic actidione. Equating the propionic acid side chain to the ethyl group of II ($n = 1$), then it will be seen that the sign of its Cotton effect (positive) is opposite to that (negative)[36] of the reference ketone XVIII and that the two substances should, therefore, belong to antipodal series in terms of absolute configuration. Proof by classical degradation means[42] has borne out this prediction.


XXIV


XXV


XXVI


XXVII


XXVIII

Work is now under way in this Laboratory to utilize the conclusions outlined under (b) for the determination of absolute configuration of aliphatic natural products, and the alcohol phytol—so common in nature and yet of undetermined absolute configuration—appears to be a suitable test case.

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[41] N. J. Leonard, J. A. Adamcik, C. Djerassi and O. Halpern, THIS JOURNAL, **80**, 4858 (1958).

[42] E. J. Eisenbraun, J. Osiecki and C. Djerassi, *ibid.*, **80**, 1261 (1958).

Experimental[43]

(+)-**2-Methylbutanal** (IV).[11,20]—A solution of 14.2 g. of potassium dichromate in 20 cc. of sulfuric acid and 75 cc. of water was added dropwise over a period of 45 min. to 25 g. of boiling (−)-2-methybutanol-1 (III).[17] During this addition and for a further 30 min., the solution was distilled slowly, the distillate being collected in 30 cc. of water containing 15 g. of sodium bisulfite. This receiving flask was shaken periodically during the distillation and the bisulfite solution was then extracted with ether to remove 22 g. of unreacted alcohol (III). Sodium bicarbonate (15 g.) was added to the aqueous bisulfite layer and the aldehyde was extracted with ether and distilled carefully after drying over magnesium sulfate; yield 0.125 g., b.p. 91.5°, $[\alpha]^{25}_{\mathrm{D}}$ +7.2° (*c* 0.32 in heptane), $\lambda_{\max}^{\mathrm{CHCl_3}}$ 5.80 μ; R.D. (*c* 0.143) in octane (Fig. 1): $[M]_{700}$ +2.3°, $[M]_{589}$ + 7.4°, $[M]_{317.5}$ +58.8°, $[M]_{292.5}$ −17.5°, $[M]_{280}$ −7.5°.

A **2,4-dinitrophenylphenylhydrazone** was prepared in aqueous sulfuric acid, passed over Fischer activated alumina in benzene solution and recrystallized from ethanol and ethanol–ethyl acetate; m.p. 127–128.5°, $[\alpha]^{25}_{\mathrm{D}}$ +1.4° (*c* 0.78 in chloroform).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04; O, 24.04. Found: C, 49.06; H, 5.42; N, 21.36; O, 23.98.

(−)-**3-Methylpentanal** (VI).—To an ethereal solution of (+)-2-methyl-1-butylmagnesium chloride, prepared from 15.0 g. of (+)-2-methyl-1-butyl chloride (V),[44] 3.4 g. of magnesium turnings and 200 cc. of dry ether, was added 16.6 g. of ethyl orthoformate over a period of 20 min. The mixture was heated under reflux with stirring for 6 hr., most of the ether was removed and 84 cc. of 6% hydrochloric acid was added. The organic layer was separated and distilled from a solution of 11.2 cc. of concd. sulfuric acid and 78 cc. of water into 11.2 g. of sodium bisulfite dissolved in 33 cc. of water. The bisulfite solution was shaken until the odor of aldehyde disappeared and it was then steam distilled. To the residual solution was added 9 g. of sodium bicarbonate and 22 cc. of water and this mixture was steam distilled to recover the aldehyde, which was separated, dried over magnesium sulfate and distilled; yield 5.5 g., b.p. 119°; $\lambda_{\max}^{\mathrm{capill.}}$ 5.75 μ, n^{25}_{D} 1.4014, $[\alpha]^{26}_{\mathrm{D}}$ −5.2° (*c* 0.71 in heptane), lit.[11] b.p. 122°, $[\alpha]_{\mathrm{D}}$ −2.46° (heptane); R.D. (*c* 0.086) in octane solution (Fig. 1): $[M]_{700}$ −1.5°, $[M]_{589}$ −6.2°, $[M]_{320}$ −221°, $[M]_{280}$ +328°.

The **semicarbazone** was prepared at room temperature in aqueous solution with semicarbazide hydrochloride and sodium acetate. Recrystallization from methanol and then from isopropyl alcohol afforded colorless crystals, m.p. 128–130°, $[\alpha]_{\mathrm{D}}$ +4° (*c* 2.75 in chloroform).

Anal. Calcd. for $C_7H_{15}N_3O$: C, 53.47; H, 9.62; N, 26.73; O, 10.18. Found: C, 53.91; H, 9.69; N, 26.46; O, 9.74.

(+)-**2,6-Dimethyl-2-octene** (VIII).—A mixture of 50 g. of (+)-citronellal (VII) (b.p. 115° at 26 mm., α^{26}_{D} +9.46°), 35 cc. of 85% hydrazine hydrate, 40 g. of potassium hydroxide and 300 cc. of diethylene glycol was heated with stirring to 130° for one hour. The flask was arranged for distillation and water, unreacted aldehyde (VII) and olefin (VIII) were allowed to distil from the mixture until the temperature rose to 175°. The upper layer of the distillate was separated, dried, returned to the reaction flask and heating and stirring were continued for 3.5 hr. at 175°. The upper layer was decanted, washed with water until neutral, dried over magnesium sulfate and distilled at 162–163° to give 29.5 g. of the desired olefin VIII,[27] $n^{26.5}_{\mathrm{D}}$ 1.4280, $[\alpha]_{\mathrm{D}}$ +9.1° (ethanol), no carbonyl band in the infrared.

(+)-**4-Methylhexanal** (IX).[11,27]—A current of 4–5% ozone was passed for 4 hr. through a solution of 28.8 g. of (+)-2,6-dimethyl-2-octene (VIII) in 150 cc. of methylene dichloride while cooling in an acetone–Dry Ice-bath, and the reaction mixture was then added to 10 g. of ferrous sulfate dissolved in 100 cc. of water and stirred overnight at room temperature. The methylene dichloride was removed first by distillation followed by steam distillation to give a volatile fraction which was washed with bicarbonate solution, dried and distilled; yield 16 g., b.p. 85–95° at 85 mm. This fraction was added to 16 g. of semicarbazide hydrochloride and 24 g. of sodium acetate in 130 cc. of water and after stirring at room temperature for one hour, the **semicarbazone** was collected and recrystallized four times from dilute ethanol; yield 13.1 g., m.p. 116–119°, $[\alpha]^{26}_{\mathrm{D}}$ +14.5° (*c* 0.47 in chloroform).

Anal. Calcd. for $C_8H_{17}N_3O$: C, 56.11; H, 10.01; N, 24.54; O, 9.34. Found: C, 55.84; H, 9.96; N, 23.99; O, 9.99.

The aldehyde was regenerated from 13 g. of semicarbazone by steam distillation in the presence of 10 g. of oxalic acid and after redistillation there was obtained 10 g., b.p. 87° at 97 mm., $[\alpha]^{25}_{\mathrm{D}}$ +7.9° (*c* 1.07 in heptane), n^{25}_{D} 1.4138, $\lambda_{\max}^{\mathrm{capill}}$ 5.75 μ; lit.[11] $[\alpha]_{\mathrm{D}}$ +1.73° (heptane); R.D. (*c* 0.243) in octane (Fig. 1): $[M]_{700}$ + 7.4°, $[M]_{589}$ +9.4°, $[M]_{340-345}$ +32.5° (plateau), $[M]_{317.5}$ +12.5°, $[M]_{275}$ +162°. Only a positive plain curve was observed in methanol solution.

(+)-**4-Methylhexanoic Acid** (**X**).[30]—The ozonolysis of 7.35 g. of (+)-2,6-dimethyl-2-octene (VIII) was performed exactly as described above except that the decomposition of the ozonide was performed by stirring overnight at room temperature with 50 cc. of 10% sodium bicarbonate and 50 cc. of 30% hydrogen peroxide. Distillation of the acid fraction provided 4.27 g. of (+)-4-methylhexanoic acid (X), b.p. 112° at 9 mm., n^{25}_{D} 1.4232, $[\alpha]^{25}_{\mathrm{D}}$ +8.12° (*c* 4.44 in chloroform).

A 0.5-g. sample of the acid was heated under reflux with 1 cc. of thionyl chloride for 15 min., 1.5 cc. of aniline in 15 cc. of benzene was added and the solution was filtered. The benzene filtrate was washed well with dilute sodium hydroxide and water, evaporated to dryness and the resulting **anilide** was recrystallized twice from dilute methanol; yield 0.5 g., m.p. 74–75°, $[\alpha]^{25}_{\mathrm{D}}$ +9.6° (*c* 0.445 in chloroform).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.32; N, 6.82. Found: C, 75.45; H, 8.97; N, 6.91.

(+)-**Methyl 4-methylhexanoate** (**XI**) was obtained in nearly quantitative yield by methylation of the acid X with diazomethane in ether solution; b.p. 165–166°, $[\alpha]^{25}_{\mathrm{D}}$ +8.03° (*c* 1.03 in chloroform).

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18; O, 22.19. Found: C, 66.12; H, 10.84; O, 22.22.

Reduction of the methyl ester XI with lithium aluminum hydride or of the aldehyde IX with sodium borohydride proceeded in high yield to give (+)-**4-methylhexanol**-1-(**XII**),[31] b.p. 74–76° at 10 mm., n^{26}_{D} 1.4231, $[\alpha]^{25}_{\mathrm{D}}$ +8.5° (*c* 1.16 in chloroform).

Anal. Calcd. for $C_7H_{16}O$: C, 72.35; H, 13.88. Found: C, 71.98; H, 13.58.

(+)-**5-Methylheptanal** (**XIV**) was prepared exactly as described by Levene and Rothen[11] and exhibited $[\alpha]^{25}_{\mathrm{D}}$ +5.66° (*c* 0.57 in heptane); R.D. (*c* 0.158) in octane (Fig. 1): $[M]_{700}$ +0.64°, $[M]_{589}$ +0.81°, $[M]_{350-342.5}$ +2.8° (broad), $[M]_{330}$ +2.2°. $[M]_{300-292}$ +9.8° (broad), $[M]_{260}$ +18.1°.

The yellow **2,4-dinitrophenylhydrazone** was filtered in benzene solution through a column of alumina and was then recrystallized from ethanol, m.p. 72–73.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.26; H, 6.83; N, 18.00.

(+)-**3-Methylpentanone-2** (**XVI**).[33]—Methyllithium[32] (0.104 mole in 84 cc.of ether) was added dropwise at room temperature to a stirred solution of 5.3 g. of (+)-2-methylbutanoic acid (XV)[45] in 100 cc. of dry ether and the mixture

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[43] Melting points and boiling points are uncorrected. We are indebted to Mrs. A. James, Mrs. T. Nakano and Mrs. C. Wilkinson for the rotatory dispersion curves which were measured with a Rudolph photoelectric spectropolarimeter. For details on experimental procedure see ref. 4, 6 and 13. As indicated in the discussion section, in view of the low rotation readings, the limit of error may reach 30% although this does not affect the conclusions to be drawn from the rotatory dispersion curves. All rotation and rotatory dispersion measurements were performed in 1-dm. tubes; in the case of the aldehydes, all measurements were performed on the same day as the sample was synthesized.

[44] Prepared in 83% yield from (−)-2-methylbutanol-1 (III) according to the procedure of Brown and Groot (ref. 23); b.p. 96°, n^{27}_{D} 1.4092, α^{27}_{D} +1.33°

[45] Prepared by permanganate oxidation (W. E. Doering and T. C. Aschner, THIS JOURNAL, **75**, 393 (1953)) of (−)-2-methylbutanol-1 (III); b.p. 174–176°, $[\alpha]_{\mathrm{D}}$ +17.97° (neat). The anilide (see R. H. Baker and L. E. Linn, *ibid.*, **70**, 3721 (1948)), prepared by Dr. T. Nakano in this Laboratory exhibited m.p. 96–97°, $[\alpha]^{22}_{\mathrm{D}}$ +40.2° (*c* 0.95 in acetone).

was then heated under reflux for 15 min. Water was added, the ether extract was washed, dried over magnesium sulfate and distilled. The crude ketone (b.p. 116–120°, $[\alpha]^{25}_{D}$ +25.4° (chloroform)) showed hydroxyl absorption in the infrared in addition to the 5.82 μ (liquid capillary) carbonyl band and it was, therefore, purified by chromatography on 20 g. of Merck acid-washed alumina. Elution with pentane afforded 0.8 g. of the ketone lacking hydroxyl absorption, b.p. 116–117°, n^{22}_{D} 1.3982, $[\alpha]_{D}$ +24.9° (*c* 0.57 in chloroform); R.D. (*c* 0.296 in octane): $[M]_{700}$ +5°, $[M]_{589}$ +9°, $[M]_{317.5}$ +139°, $[M]_{307.5}$ +102°; R.D. (*c* 0.317 in methanol) (Fig. 2): $[M]_{700}$ +15.2°, $[M]_{589}$ +26.2°, $[M]_{302.5}$ +439°, $[M]_{265}$ −205°.

(+)-**4-Methylhexanone-2** (**XVIII**)[34] was synthesized by the same procedure used above for the lower homolog from (+)-3-methylpentanoic acid (XVII)[46] and methyllithium. Purification was accomplished *via* the semicarbazone (m.p. 124–126° after recrystallization from hexane–acetone, $[\alpha]^{25}_{D}$ −1.27° (*c* 0.63 in chloroform)) followed by steam distillation in the presence of oxalic acid. The recovered ketone had b.p. 137°, $\lambda^{\text{capil.}}_{\text{max}}$ 5.80 μ, $[\alpha]^{25}_{D}$ +7.9° (*c* 0.632 in chloroform); R.D. (*c* 0.114 in octane): $[M]_{700}$ +10°, $[M]_{589}$ +10°, $[M]_{425-400}$ +10.8° (plateau), $[M]_{320}$ −6°, $[M]_{295}$ +16.5°; R.D. (*c* 0.205 in methanol) (Fig. 2): $[M]_{700}$ +7.1°, $[M]_{589}$ +7°, $[M]_{305}$ −350°, $[M]_{265}$ +1032°.

(+)-**5-Methylheptanone-2** (**XIX**).[35]—(+)-4-Methylhexanoic acid (X) (6.63 g.) was treated in the above-described manner with methyllithium in ether and the resulting ketone was purified *via* its bisulfite addition compound; yield 1.0 g., b.p. 167–168°. The substance proved to be identical in every respect with the product obtained from (+)-4-methylhexanoic acid chloride (prepared from 4.0 g. of X and 4.7 g. of thionyl chloride) and dimethylcadmium (prepared from 5.63 g. of cadmium chloride and methylmagnesium bromide derived from 5 g. of methyl bromide and 1.48 g. of magnesium) in ether solution (25 min. reflux time); purification was also accomplished through the bisulfite addition compound, affording 0.78 g. of ketone, b.p. 165–166°, $[\alpha]^{25}_{D}$ +9.9° (*c* 0.88 in chloroform); lit.[35] b.p. 167–168°, $[\alpha]^{20}_{D}$ +8.2° (neat); R.D.[47] (*c* 0.425 in octane): $[M]_{700}$ + 3.84°, $[M]_{589}$ +7.7°, $[M]_{370-337.5}$ +23° (plateau), $[M]_{315}$ +7.7°, $[M]_{305}$ −8.95°; R.D. (*c* 0.498 in methanol) (Fig. 2): $[M]_{700}$ +4.4°, $[M]_{589}$ +8.7°, $[M]_{360-332}$ +31.7° (plateau), $[M]_{308}$ +2.65°. No further readings could be obtained even upon diluting the solution or setting the symmetrical angle at 10°.

The **semicarbazone** was recrystallized from ethanol, m.p. 135–138°, $[\alpha]^{26}_{D}$ +10.9° (*c* 0.53 in chloroform).

Anal. Calcd. for $C_9H_{19}N_3O$: C, 58.34; H, 10.34; N, 22.68. Found: C, 58.62; H, 10.38; N, 22.84.

(+)-**6-Methyloctanone-2** (**XXI**).—When 8.6 g. of (+)-5-methylheptanoic acid (XX)[48] was treated with methyllithium in the above-described manner and the product subjected to fractional distillation, there was obtained 3.5 g. of the desired ketone, b.p. 84° at 12 mm., n^{23}_{D} 1.4212, $[\alpha]^{24}_{D}$ +12° (*c* 1.1 in chloroform); R.D. (*c* 0.033 in octane (Fig. 2)): $[M]_{700}$ +18°, $[M]_{589}$ +21°, $[M]_{500}$ +25° (infl.), $[M]_{450-400}$ +30° (plateau), $[M]_{370}$ +34° (infl.), $[M]_{355-340}$ +60° (plateau), $[M]_{325}$ +68° (infl.), $[M]_{300}$ +138° (infl.), $[M]_{280-260}$ +172° (plateau); R.D. (*c* 0.224 in methanol): $[M]_{700}$ +4.26°, $[M]_{589}$ +4.3°, $[M]_{450}$ +16° (infl.), $[M]_{345-340}$ +38° (plateau), $[M]_{315}$ +21.9°, $[M]_{305}$ +60.2°.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 75.60; H, 12.66.

The **semicarbazone** was recrystallized from aqueous ethanol, whereupon it exhibited m.p. 129–131°, $[\alpha]_{D}$ +1.9° (*c* 0.83 in chloroform); reported[27] for the semicarbazone of optically impure ketone prepared by another method, m.p. 130.5–131.5°.

Anal. Calcd. for $C_{10}H_{21}N_3O$: C, 60.26; H, 10.62; N, 21.08. Found: C, 60.17; H, 10.65; N, 21.38.

The yellow **2,4-dinitrophenylhydrazone** was prepared in aqueous sulfuric acid, filtered in benzene solution through a column of alumina and recrystallized from ethanol–ethyl acetate, m.p. 58–60°, $[\alpha]_{D}$ +3.5° (*c* 2.29 in chloroform) lit.[27] m.p. 61–62° (for derivative of optically impure material).

Anal. Calcd. for $C_{15}H_{22}N_4O_4$: C, 55.88; H, 6.88. Found: C, 56.18; H, 6.99.

(+)-**7-Methylnonanone-2** (**XXIII**).—To a gently refluxing solution of 1.72 g. of sodium and 9.5 cc. of ethyl acetoacetate in 50 cc. of absolute ethanol was added over a period of 45 min. 15 g. of (+)-4-methyl-1-hexyl bromide (XIII).[31,48] After heating for 10 hr. and letting stand at room temperature overnight, the solution was decanted from the precipitated sodium bromide and the latter washed with some ethanol. The solvent was removed by distillation and the crude ester XXII was stirred for 4 hr. at room temperature with 75 cc. of water containing 3.75 g. of sodium hydroxide. The upper oily layer was discarded, 7.5 cc. of 50% sulfuric acid was added and the mixture was distilled. The distillate was rendered basic and distilled again yielding 5.0 g. of the ketone XXIII (positive iodoform test, negative ferric chloride test), b.p. 97° at 12 mm., $\lambda^{\text{capil.}}_{\text{max}}$ 5.80 μ, n^{25}_{D} 1.4254, $[\alpha]_{D}$ +11.4° (*c* 0.92 in chloroform); R.D. (*c* 0.034 in octane) (Fig. 2): $[M]_{700}$ +17°, $[M]_{589}$ +17°, $[M]_{450-390}$ +26° (plateau), $[M]_{370}$ +45° (infl.), $[M]_{350-325}$ +55° (plateau), $[M]_{305}$ +92° (infl.), $[M]_{290-267.5}$ +128° (plateau); R.D. (*c* 0.017 in methanol): $[M]_{700}$ +32°, $[M]_{589}$ +32°, $[M]_{350}$ +66°, $[M]_{305-295}$ +164° (plateau), $[M]_{285-265}$ +229° (plateau).

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90; O, 10.24. Found: C, 76.31; H, 12.79; O, 10.86.

The **semicarbazone** was recrystallized from ethanol, m.p. 122–124°, $[\alpha]_{D}$ +9.8° (*c* 0.63 in chloroform).

Anal. Calcd. for $C_{11}H_{23}N_3O$: C, 61.93; H, 10.87; N, 19.70; O, 7.50. Found: C, 62.01; H, 11.12; N, 19.54; O, 7.69.

The yellow **2,4-dinitrophenylhydrazone** (m.p. 39–41°) was recrystallized from isopropyl alchohol.

Anal. Calcd. for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.68; H, 7.39; N, 16.40.

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(46) Prepared by carbonation of (+)-2-methylbutylmagnesium chloride (see K. J. Sax and W. Bergmann, *ibid.*, **77**, 1910 (1955); K. B. Wiberg and B. I. Rowland, ref. 23) and distilled at 140° and 100 mm.; n^{245}_{D} 1.4144, $[\alpha]^{25}_{D}$ +8.68° (neat).

(47) The maximum error in these measurements was [α] ±2.0° from 700 to 315 mμ and [α] ±4.5° below 315 mμ. This is based on a maximum error in the actual readings of ±0.011° with a 5° symmetrical angle setting and of ±0.016° with a symmetrical angle of 10°.

(48) Prepared (see ref. 30) by carbonation of the Grignard complex of (+)-4-methyl-1-hexyl bromide (XIII) (b.p. 86° at 46 mm., $[\alpha]_{D}$ +9.4° (*c*, 1.40 in chloroform)—see ref. 31); b.p. 139° at 25 mm., $[\alpha]^{22}_{D}$ +5.51° (c, 0.47 in chloroform). *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18; O, 22.19. Found: C, 66.52; H, 10.98; O, 22.25.