a consequence of the coupling between the vibrations of adjacent methylene groups.

In the spectrum of tetradecane where six bands are observed between 1187 and 1305 cm.$^{-1}$, Brown, Sheppard and Simpson tentatively assign the two of lowest frequency to the twisting mode and the other four to the wagging mode. In the fatty acids, where the spacing and relative intensities of the bands are very uniform there would seem to be no justification, at present, to assign individual bands specifically to wagging or twisting modes. Possibly, as a consequence of the polar end group one of these modes may have become very weak relative to the other and the whole series of bands observed may be due to one of these modes of vibration only. Both types of vibration may be active in the spectra of the alcohols, each accounting for one of the two progressions observed.

The existence of band progressions such as these, arising from interactions between the vibrations of neighboring methylene groups in linear polymethylene chains is predicted by recent theoretical work of Deeds and Shaffer,[8] although these investigators did not limit their occurrence to the solid phase only.

In the above discussion it has been tacitly assumed that in the crystalline state each *n*-paraffin hydrocarbon or fatty acid molecule behaves as an independent vibrating unit. However, the possibility that intermolecular forces play a part in generating these bands must also be considered,[9,10] and they might alternatively have their origin in a combination of internal vibrations with lattice vibrations.[11,12] It has recently been observed that the bands in stearic and eicosanoic acid exhibit a very strong polarization[13] effect, and a careful study of such polarization effects on single crystals may aid in their interpretation.

Acknowledgments.—The technical assistance of Mr. R. Lauzon and Mr. D. S. Keir is gratefully acknowledged. The investigation was aided by a grant from the Ontario Cancer Treatment and Research Foundation.

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(8) W. E. Deeds and W. H. Shaffer, Asbtracts of Symposium on Molecular Structure and Spectroscopy, The Ohio State University, June, 1951, p. 54.

(9) R. Newman and R. S. Halford, *J. Chem. Phys.*, **18**, 1276 (1950).

(10) R. S. Halford, Abstracts of the American Chemical Society Meeting, Boston, Mass., April, 1951, p. 1P.

(11) D. F. Hornig, *Discussions of the Faraday Society*, **9**, 115 (1950).

(12) R. D. Mair and D. F. Hornig, *J. Chem. Phys.*, **17**, 1236 (1949).

(13) A. R. H. Cole and R. N. Jones, *J. Optical Soc. Am.*, in press.

OTTAWA, CANADA RECEIVED NOVEMBER 1, 1951

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL OF CANADA, AND THE DEPARTMENTS OF CHEMISTRY AND BIOCHEMISTRY, QUEEN'S UNIVERSITY]

The Infrared Absorption Spectra of Unsaturated Fatty Acids and Esters[1]

BY R. G. SINCLAIR, A. F. McKAY, G. S. MYERS AND R. NORMAN JONES

The infrared absorption spectra of several unsaturated fatty acids, methyl esters and brominated derivatives have been determined at room temperature and when cooled with liquid nitrogen. The absorption bands characteristic of the unsaturated linkages are described and discussed. A spectrographic method is proposed for the determination of the degree of unsaturation of mixtures of *cis*-unsaturated acids, based on the measurement of the optical densities of the absorption bands at 3020 and 2920 cm.$^{-1}$. The spectra of liquid films or solutions of stearic, oleic, linoleic and linolenic acids do not differ sufficiently to permit the spectrographic analysis of the individual acids in complex mixtures. However, cooled solid films of binary mixtures of oleic and linoleic acids show large and progressive changes with concentration, especially between 680 and 750 cm.$^{-1}$ and the quantitative analysis of pairs of the above unsaturated acids from solid film measurements would appear to be feasible.

The identification and quantitative analysis of the unsaturated fatty acids present in extracts of biological material is a problem of particular interest in view of the essential part played by linoleic acid in animal metabolism. A comparative study of the infrared spectra of unsaturated fatty acids and esters has been undertaken in order to evaluate the extent to which infrared spectrometry might be applied to this problem. When these investigations were commenced, it was known from the work of McCutcheon, Crawford and Welsh,[2] that the *cis-trans* configuration of the ethylenic linkage modifies the infrared spectra of unsaturated fatty acids in a characteristic manner, and this has subsequently been confirmed by other investigators.[3-6] Recently Shreve, Heether, Knight and Swern[6] have described the infrared spectra of some monounsaturated fatty acids and methyl esters, but little has been published concerning the spectra of the more highly unsaturated fatty acids.

Experimental

The methods employed in measuring the spectra have been described in a preceding paper.[7] Most of the compounds were prepared at Queen's University, and unless already reported[7] their characteristics are summarized in Table I.

Results and Discussion

The absorption bands associated with the methylene groups of the chain, the terminal methyl group, and the carboxy and carbomethoxy groups are similar to those of the saturated acids and methyl esters. These have been discussed in preceding papers,[7,8] and this communication will be concerned only with those features of the infrared

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(1) Published as Contribution No. 2682 from The Laboratories of the National Research Council of Canada.

(2) J. W. McCutcheon, M. F. Crawford and H. L. Welsh, *Oil and Soap*, **18**, 9 (1941).

(3) J. A. Anderson and W. D. Seyfried, *Anal. Chem.*, **20**, 998 (1948).

(4) H. W. Lemon and C. K. Cross, *Can. J. Research*, **27B**, 610 (1949).

(5) P. C. Rao and B. F. Daubert, THIS JOURNAL, **70**, 1102 (1948).

(6) O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *Anal. Chem.*, **22**, 1498 (1950).

(7) R. G. Sinclair, A. F. McKay and R. N. Jones, THIS JOURNAL, **74**, 2570 (1952).

(8) R. N. Jones, A. F. McKay and R. G. Sinclair, *ibid.*, **74**, 2575 (1952).

TABLE I

CHARACTERISTICS OF COMPOUNDS

Compound	B.p., °C.	B.p., Mm.	M.p. (cor.) °C.	Iodine value Obsd.	Iodine value Calcd.
Oleic acid	.....		13.3 ± 0.05[b]	89.90	89.86
Elaidic acid	.....		43.7–44.5	89.70	89.86
Linoleic acid[a]	.....		−9 to −8	....	....
Linolenic acid[a]	.....		−16	....	....
Arachidonic acid	169–171	0.15	....	332	333.5
cis-2-Octadecenoic acid[c]	.....		50.5–51	....	....
trans-2-Octadecenoic acid[c]	.....		58.2–58.5	....	....
Methyl oleate	.....		−20.2 ± 0.05[b]	85.6	85.6
Methyl elaidate	162	5	13.0–13.5	....	....
Methyl linoleate	.....		....	173.0	172.6
Methyl linolenate	.....		....	258.6	260.4
Methyl *trans*-2-octadecenoate	.....		34–35	....	....
Methyl arachidonate[a]	159	0.2	....	316	318.8
2-Bromostearic acid	.....		57–57.5	....	....
9,10,12,13-Tetrabromostearic acid	.....		115.5	....	....
9,10,12,13,15,16-Hexabromostearic acid	.....		182.8	....	....
5,6,8,9,11,12,14,15-Octabromoeicosanoic acid (octabromoarachidonic acid)	.....		233 dec.	....	....

[a] An additional sample was supplied also by Dr. J. B. Brown. [b] Setting point. [c] See reference 11.

spectra which are associated with the ethylenic linkages.

Absorption specific to the ethylenic bond occurs in three regions of the spectrum. (a) 3000–3100 cm.$^{-1}$. Stretching vibrations of C═C—H carbon-hydrogen bonds; (b) 1580–1650 cm.$^{-1}$. Stretching vibrations of C═C bonds; (c) 690–980 cm.$^{-1}$. Out-of plane bending vibrations of C═C—H carbon-hydrogen bonds.

In order to obtain the maximum of information, prisms of lithium fluoride, calcium fluoride and sodium chloride were used in these respective regions, and each region will be considered separately.

C–H Stretching Vibrations.—The spectra of several unsaturated acids between 2500 and 3200 cm.$^{-1}$ are compared with the spectrum of stearic acid in Fig. 1. The unsaturated acids possess a band (A) at 3020 cm.$^{-1}$ attributable to the carbon hydrogen bonds of the unsaturated linkage. This band is similar in shape and position in oleic, linoleic, linolenic and arachidonic acids and its

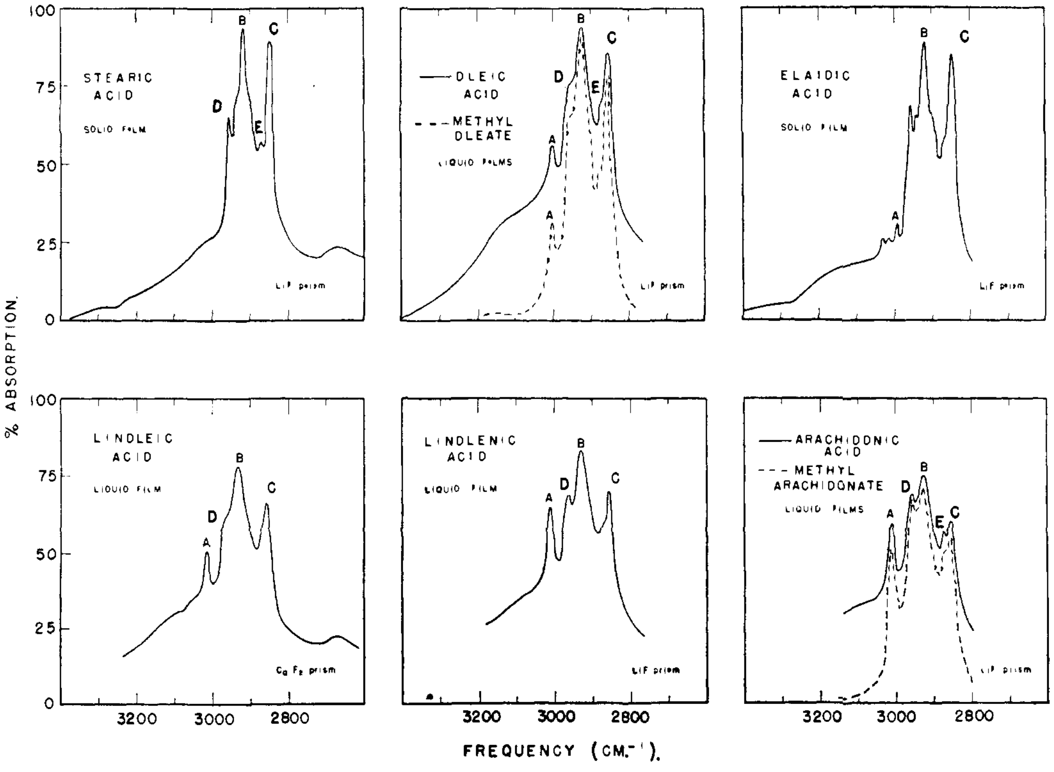


Fig. 1.—Infrared spectra of fatty acids and methyl esters in the C–H stretching region, as determined with CaF_2 or LiF prisms.

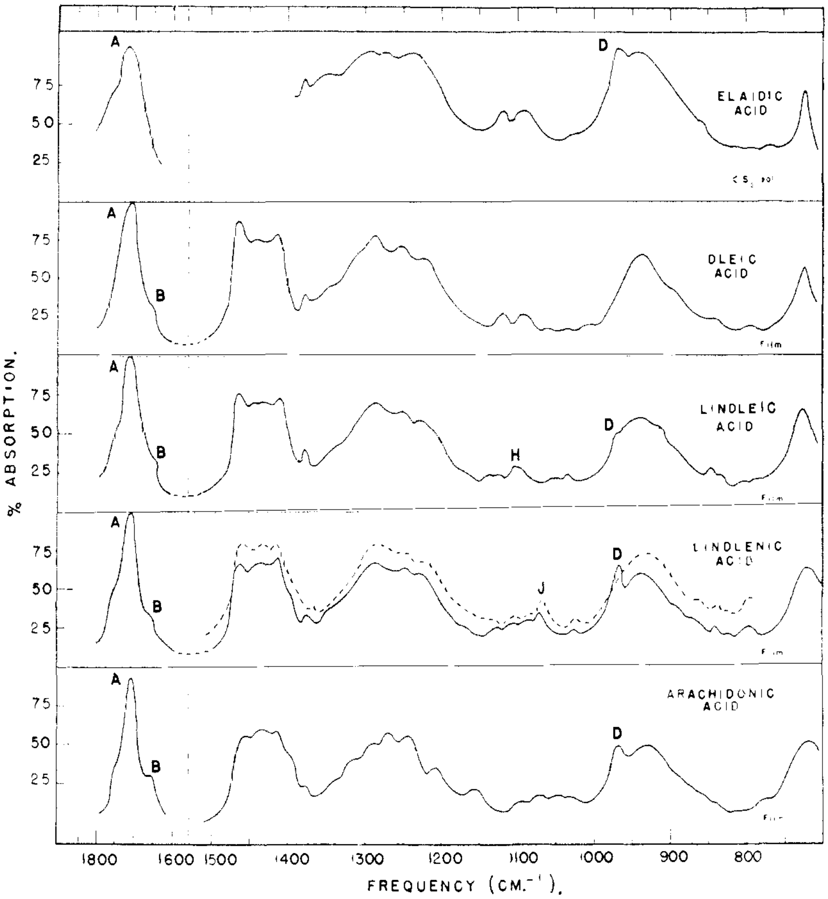


Fig. 2.—Infrared spectra of liquid films or carbon disulfide solutions of unsaturated fatty acids; NaCl prism.

intensity relative to the methylene C–H stretching band B increases with the degree of unsaturation. In elaidic acid bands occur at 2995, 3015 and 3033 cm.$^{-1}$ and the difference from the spectra of the other unsaturated acids may be due to the *trans*-ethylenic bond. The 3020 cm.$^{-1}$ band stands out more clearly in the spectra of the methyl esters than in the free acids as it is not superimposed on hydroxyl absorption.

With increasing unsaturation the number of methylene groups in the fatty acid chain diminishes and this produces an observable effect on the spectrum. Bands B and C (2920 and 2850 cm.$^{-1}$) which are due to methylene vibrations[7] diminish in intensity relative to the bands D and E (2920 and 2870 cm.$^{-1}$) of the terminal methyl group. The changes in the relative intensities of bands A and B with the degree of unsaturation are discussed further on page 2584 with reference to analytical applications.

C=O and C=C Stretching Vibrations.—The C=C stretching band can be detected at 1660 cm.$^{-1}$ in the spectra of liquid films of oleic, linoleic, linolenic and arachidonic acids (Fig. 2, band B), but it occurs on the shoulder of the strong carbonyl band (max. at 1708 cm.$^{-1}$) and is not resolved. In the spectra of liquid films of the methyl esters the C=C stretching band also occurs at 1660 cm.$^{-1}$ (Fig. 3, band B) but is better resolved as there is less overlap with the ester carbonyl band at 1741 cm.$^{-1}$ (Fig. 3, band A).

It was anticipated that the C=O and C=C bands of the free unsaturated acids would be separated better in the spectra of cooled solid films. However the contrary proved to be the case, as on solidification and cooling the carbonyl maximum shifts from 1708 to 1682 cm.$^{-1}$ (Fig. 4, band A), and the C=C band is totally obscured.[8a]

Although a weak band at 1660 cm.$^{-1}$ is observed for methyl oleate, a careful search failed to reveal any C=C stretching band in the spectrum of methyl elaidate in carbon disulfide solution. This is in accord with the observation of McCutcheon, Crawford and Welsh[2] that the band is weak or absent in the spectra of *trans*-unsaturated acids and esters. This conclusion, which is based on symmetry considerations, may not apply if the *trans*-ethylenic bond is near the end of the chain. Wotiz and Miller[9] have observed that the C≡C stretching vibration in linear acetylene compounds varies greatly in intensity with the position of the ethynyl group and is weak or absent if the ethynyl group is near the center of the chain. The *trans*-ethylenic group might be expected to behave similarly.

In the *cis*- and *trans*-2-octadecenoic acids (I, II; R_1 = COOH, R_2 = $C_{15}H_{31}$) the double bond is

[8a] On cooling a solid film of stearic acid with liquid nitrogen the carbonyl band is not appreciably displaced (see Fig. 5 of reference 7). It is inferred that in the unsaturated acids it is the change of phase and not the change of temperature *per se*, which is primarily responsible for the carbonyl frequency shift.

[9] J. H. Wotiz and F. A. Miller, This Journal, **71**, 3441 (1949).

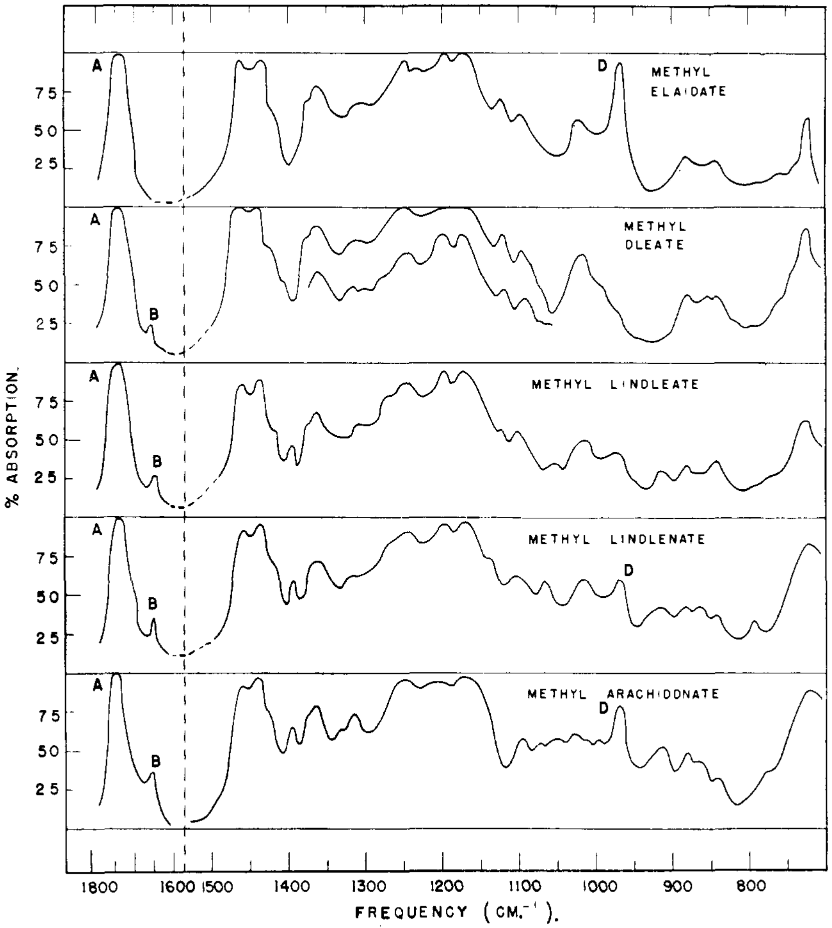
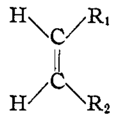


Fig. 3.—Infrared spectra of liquid films of unsaturated fatty acid methyl esters: 1800-1600 cm.$^{-1}$, $\mathrm{CaF_2}$ prism; 1500-700 cm.$^{-1}$, NaCl prism.

conjugated with the carboxylic acid group. In the spectra of both stereoisomers (Fig. 5) the carbonyl



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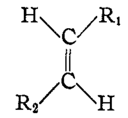

II

maximum is at 1695 cm.$^{-1}$ (band A) in carbon disulfide solution, the displacement from 1708 cm.$^{-1}$ in stearic acid being a normal effect of conjugation. The C═C stretching band is at 1653 cm.$^{-1}$ (band B) for the *trans*-isomer and 1645 cm.$^{-1}$ for the *cis*-isomer. The intensities of these bands are greatly enhanced by conjugation, as has been noted previously in the spectra of unsaturated steroids.[10] In the *trans*-methyl ester the carbonyl band (band A′) is at 1720 cm.$^{-1}$ in a nujol mull (*cf.* 1741 cm.$^{-1}$, for methyl stearate), and the C═C band at 1660 cm.$^{-1}$.

The higher frequency of the C═C stretching band in the *trans*- than in the *cis*-isomer has been cited in support of the steric configurations assigned for these two compounds,[11] as there is a body of evidence, based largely on Raman spectra[12] which indicates that the frequency of the C═C stretching band is 10–20 cm.$^{-1}$ higher for the *trans* than for the *cis* member of various types of ethylenic compounds. This may also be a factor in the failure to detect the C═C stretching band in methyl elaidate, as overlap with the carbonyl band will be greater than in methyl oleate if the C═C band is at a higher frequency.

Ethylenic C-H Bending Vibrations.—The association of a *prominent* band at 965–975 cm.$^{-1}$ with the *trans*-substituted ethylene structure II is well established[13–16] and has been used to differentiate between *cis*- and *trans*-substituted unsaturated fatty acids and esters.[4–6] This band is indicated in the accompanying spectra of elaidic acid and methyl elaidate (Figs. 2–4, band D).

The association of a band near 690 cm.$^{-1}$ with the analogous vibration of the *cis*-substituted ethylenic group (II) has been suggested[13,15] but the position of this band is more variable.[6] In a liquid film of oleic acid no prominent absorption band occurs between 650 cm.$^{-1}$ and the methylene wagging band near 720 cm.$^{-1}$ (Fig. 7), but when the film is cooled and solidified a strong peak appears at 704

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[10] R. N. Jones, P. Humphries, E. Packard and K. Dobriner, *ibid.*, **72**, 86 (1950).

[11] G. S. Myers, *ibid.*, **73**, 2100 (1951).

[12] See "The Raman Effect and its Chemical Applications," by J. H. Hibben, Reinhold Publishing Corp., New York, N. Y., 1939, p. 17.

[13] D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

[14] H. W. Thompson and D. H. Wiffen, *ibid.*, 1412 (1948).

[15] R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120, 131, 135 (1947).

[16] J. E. Kilpatrick and K. S. Pitzer, *J. Research Natl. Bur. Standards*, **38**, 191 (1947).

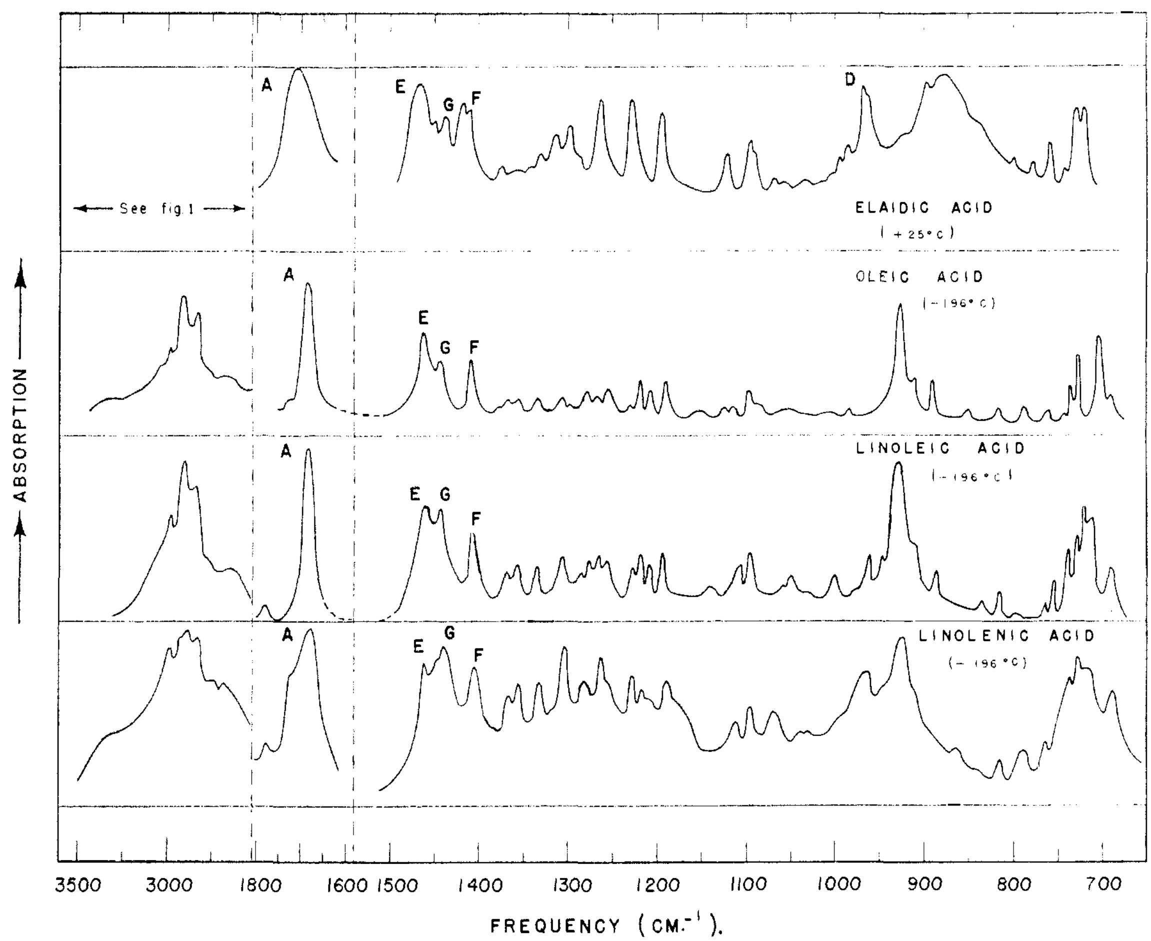

Fig. 4.—Infrared spectra of solid films of unsaturated fatty acids; NaCl prism.

cm.$^{-1}$ and this has been assigned tentatively to the *cis*-ethylenic hydrogen vibration.[17] Prominent absorption bands are also observed near 700 cm.$^{-1}$ in solid films of linoleic and linolenic acids (Fig. 4) but the assignment of these bands to *cis*-ethylenic hydrogen vibrations must be treated circumspectly since cooled films of stearic acid also show structure in the same region (see Fig. 5 of reference 7).

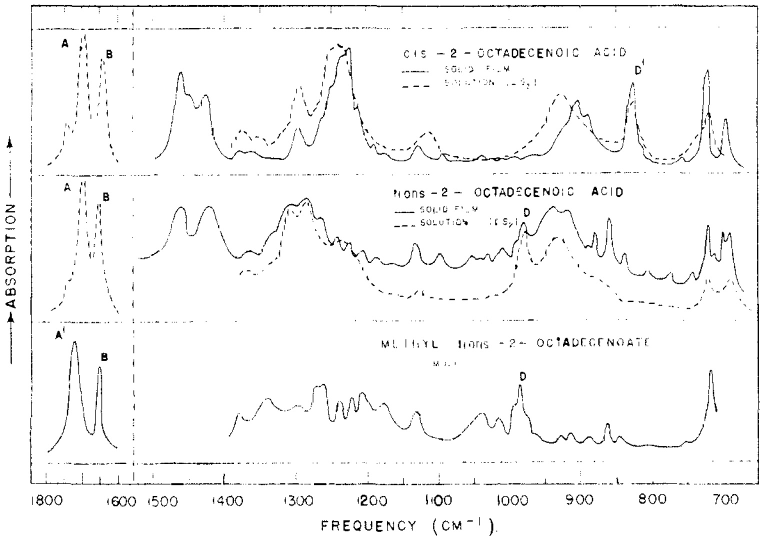

Fig. 5.—Infrared spectra of stereoisomeric 2-octadecenoic acids and *trans*-methyl ester; NaCl prism.

It is generally conceded that linoleic acid occurs naturally as the *cis–cis*-isomer. In the spectrum of linoleic acid the weak band at 966 cm.$^{-1}$ (Fig.

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(17) R. N. Jones, This Journal, **72**, 5322 (1950).

2, band D) may indicate a small quantity of a *trans*-isomer. Of the two samples of linolenic investigated (Fig. 2) one contained appreciable quantities of a *trans*-isomer, while the second showed no maximum near 970 cm.$^{-1}$ and was presumably pure "all *cis*" material. These two samples showed no other significant differences elsewhere in the spectrum. The methyl linolenate sample also possessed weak absorption at 970 cm.$^{-1}$ (Fig. 3, band D) while in the spectrum of methyl arachidonate the band at 970 cm.$^{-1}$ was strong enough to suggest a large proportion of a *trans*-isomer.

In *trans*-2-octadecenoic acid and its methyl ester, the prominent band at 980 cm.$^{-1}$ may be assigned tentatively to the ethylenic out-of-plane hydrogen vibration (Fig. 5, band D). This band is lacking from the spectrum of the *cis*-stereoisomer. The latter contains instead a band at 825 cm.$^{-1}$ (band D′) which may be the *cis*-ethylenic hydrogen bending band. The spectrum of the *trans*-stereoisomer is more sensitive to change of state than that of the *cis*-acid. In the solid state the 980 cm.$^{-1}$ band is weaker than in solution and a band at 860 cm.$^{-1}$ becomes prominent.

Other Absorption between 600 and 1500 Cm.$^{-1}$.—In the spectra of all fatty acids a strong band occurs near 1460 cm.$^{-1}$ (Fig. 4, band E) which has been assigned to an unperturbed methylene bending vibration.[7] The band at 1410 cm.$^{-1}$ (Fig. 4, band F) is attributed to the bending vibration of the methylene group adjacent to the carboxyl group.[7,18]

In the unsaturated acids there is a band at 1435 cm.$^{-1}$, the intensity of which increases progressively with the degree of unsaturation (Fig. 4, band G); this may be assigned tentatively to a bending vibration of a methylene group adjacent to a double bond, by analogy with a band at the same position observed in the spectra of unsaturated steroids.[19]

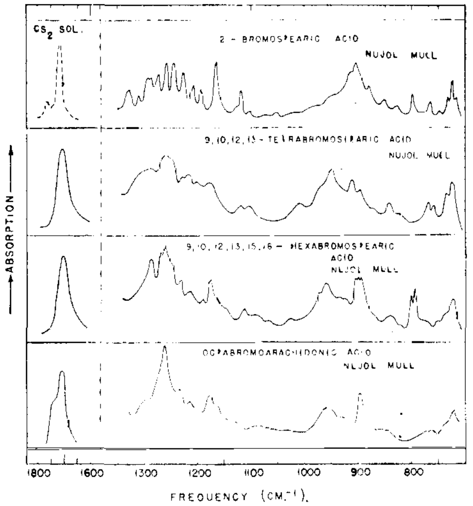

Fig. 6.—Infrared spectra of brominated fatty acids. Solid curves obtained from nujol mulls with NaCl prism. Dotted curve obtained from carbon disulfide solution with CaF_2 prism.

The remaining bands in the spectra of the unsaturated acids and esters correspond for the most part with bands in the spectra of the saturated compounds. Minor differences are observed in the weak absorption between 1000 and 1200 cm.$^{-1}$ which are probably associated with skeletal C–C stretching vibrations.

Spectra of the Brominated Acids.—The spectra of several brominated fatty acids are shown in Fig. 6. In 2-bromostearic acid the α-bromine substituent displaces the carbonyl band to 1716 cm.$^{-1}$ from 1708 cm.$^{-1}$ in stearic acid. A similar shift has been observed in the spectra of other α-bromoacids and α-bromoketones.[20,21] In other brominated fatty acids the bromine atom is remote from the carboxylic acid group and has no effect on the carbonyl frequency. Between 700 and 1350 cm.$^{-1}$ the spectra of the brominated acids show quite

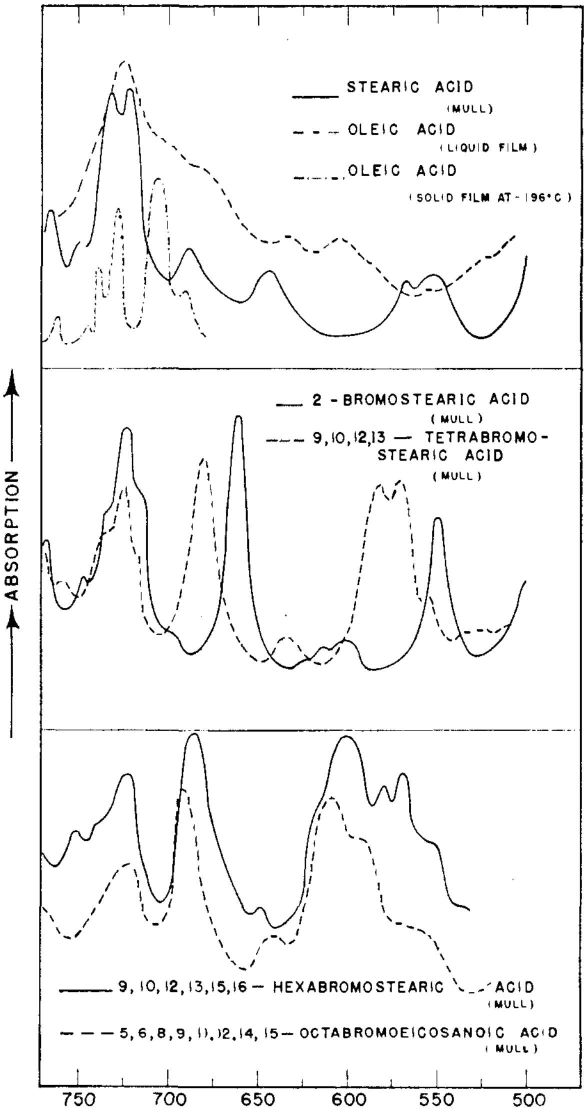

Fig. 7.—Infrared spectra of fatty acids below 800 cm.$^{-1}$ KBr prism.

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[18] Note that the 1410 cm.$^{-1}$ is absent from the spectra of both *cis* and *trans*-2-octadecenoic acids which have no α-methylene group (Fig. 5).

[19] Unpublished observation from this laboratory.

[20] E. J. Hartwell, R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1437 (1948).

[21] R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950).

marked differences from one another. Measurements have been extended down to 500 cm.$^{-1}$ using a potassium bromide prism (Fig. 7) and strong bands occur between 550 and 700 cm.$^{-1}$ which may be associated with C–Br stretching vibrations.

Analytical Applications of the Spectra

In the C–H stretching region it has been shown that the band at 3020 cm.$^{-1}$ increases with the number of *cis*-double bonds present, while the relative intensity of the methylene peak at 2920 cm.$^{-1}$ diminishes. These observations provide a basis for the evaluation of the degree of unsaturation. From an analysis of the curves shown in Fig. 1, it is found empirically that if d_A is the optical density at 3020 cm.$^{-1}$ and d_B the optical density at 2920 cm.$^{-1}$ then a plot of $d_B/(d_B - d_A)$ against the number of double bonds is approximately linear for oleic, linoleic, linolenic and arachidonic acids, while stearic and palmitic acids also fall on the same curve (Fig. 8). Analytical working curves similar to Fig. 8 can be established for suitable mixtures of saturated and *cis*-unsaturated acids, and as these measurements are based on determinations of intensity ratios only, the sample concentration or sample thickness is not required. In conjunction with an infrared microscope a method based on this principle should permit the determination of the degree of unsaturation of suitable fatty acid mixtures on microgram amounts. Divergencies from the linearity of the analytical working curve may be anticipated if the acid mixtures contain appreciable quantities of *trans*-ethylenic linkages or if the chain length varies considerably among the samples. Since palmitic and stearic acids give almost coincident points on the curve small changes in chain length would not appear to effect the results seriously.

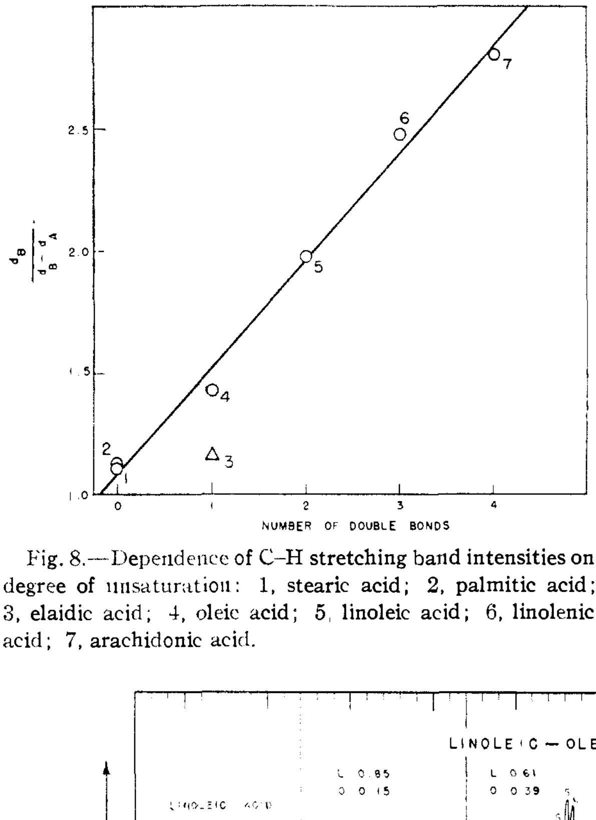

Fig. 8.—Dependence of C–H stretching band intensities on degree of unsaturation: 1, stearic acid; 2, palmitic acid; 3, elaidic acid; 4, oleic acid; 5, linoleic acid; 6, linolenic acid; 7, arachidonic acid.

The problem of the identification and estimation of individual unsaturated acids in mixtures is less promising of solution. The quantitative analysis of pairs of *cis-trans*-isomers from the intensity of the band at 965–970 cm.$^{-1}$ is well established, but the conditions for the analysis of mixtures of *cis*-unsaturated acids are much less favorable.

In solution and in liquid films, the spectra of oleic, linoleic and linolenic acids are very similar. It has been found possible to prepare working curves for the analysis of mixtures of linoleic and linolenic acids from measurements of the ratios of the optical densities of the peaks at 1120 cm.$^{-1}$ in linoleic and 1067 cm.$^{-1}$ in linolenic acid (Fig. 2, bands H and J). Small differences can also be observed between the liquid phase spectra of oleic and linoleic acids and between methyl linoleate and methyl linolenate but these bands are all of low intensity and unsuitable for the analysis of mixtures.

More favorable conditions for the analysis of binary mixtures of unsaturated fatty acids may be found in the solid phase low temperature spectra. The solid phase spectra of oleic and linoleic acids differ considerably, especially between 660 and 760 cm.$^{-1}$. In Fig. 9 are shown the spectra of a series of mixtures of these two acids. The bands marked S are present also in the spectrum of stearic

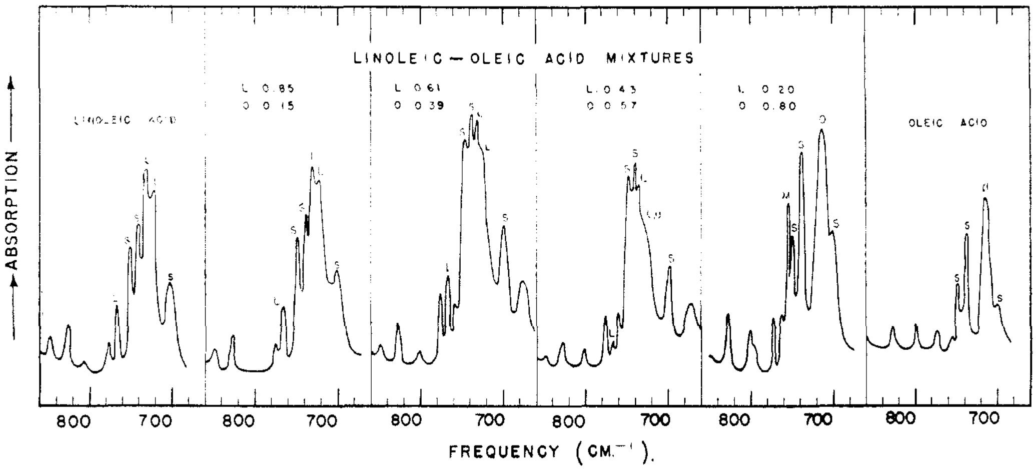

Fig. 9.—Infrared spectra of cooled solid films of mixtures of oleic and linoleic acids; concentrations expressed in mole fractions.

acid and persist throughout the series of mixtures. The three bands marked L diminish as the linoleic acid concentration decreases and the strong band O increases with the concentration of oleic acid.

The technique of low temperature infrared spectrometry does not lend itself easily to accurate measurements of band intensity, but mixtures of oleic and linoleic acids might be analyzed by matching the solid phase spectra with an atlas of the spectra of standard mixtures. For this purpose it would probably be sufficient to solidify the samples with solid carbon dioxide, as it is observed that on warming a sample cooled with liquid nitrogen the sharp characteristic structure persists until the compound approaches the melting point. Attention has been drawn previously to the effects of polymorphism on fatty acid spectra[7] and precautions must be taken in the preparation of samples to avoid complications due to polymorphism or compound formation and to recognize such if they should occur.[22]

The spectra of the solid brominated acids derived from oleic, linoleic and linolenic acids also exhibit large differences, especially between 450 and 700 cm.$^{-1}$ which could provide a basis for the analysis of mixed unsaturated acids, but while such a procedure would avoid the necessity of working at low temperature it would introduce the same uncertainties concerning the yields of brominated acids as complicate the interpretation of polybromide numbers.

Acknowledgments.—The authors wish to thank Dr. J. B. Brown of the Ohio State University for supplying samples of linoleic acid, linolenic acid and methyl arachidonate, and Mr D. S Keir and Mr. R. Lauzon for technical assistance in the determination of the spectra. The investigation was supported by a grant from The Ontario Cancer Treatment and Research Foundation, which is gratefully acknowledged.

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[22] In Fig. 9 the mixture containing 0 2 mole fraction of linoleic acid possesses a band (M) not present in either of the constituent acids which may indicate complex formation although this would not be anticipated on the basis of melting point data. See K. S. Markley, "Fatty Acids," Interscience Publishers, Inc., New York, N. Y., 1947, p. 126.

OTTAWA, CANADA RECEIVED NOVEMBER 1 1951

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Cortisone Intermediates. I. A New Preparation of 12α-Bromo-24,24-diphenylchol-23-en-3α-ol-11-one Acetate

BY E. B. HERSHBERG, HERSHEL L. HERZOG, STEPHEN B. COAN, LOIS WEBER AND MARGARET JEVNIK

A method derived from Gallagher's synthesis of dimethyl 12α-bromo-3α-succinoxy-11-ketocholanate from desoxycholic acid is applied to the synthesis of 12α-bromo-24,24-diphenylchol-23-en-3α-ol-11-one acetate, an intermediate in the Kendall synthesis of cortisone. The preparation and some reactions of the 12-phosphite and 12-sulfite esters of 24,24-diphenylchol-23-en-3α,12β-diol-11-one 3-acetate are described.

In common with all of the partial syntheses of cortisone from desoxycholic acid (I), that devised by Kendall and co-workers suffers from the multiplicity of steps required to shift the oxygen function from C-12 to C-11.[1] After eleven steps, by way of a Δ^{11}-system,[2] the hydroxyl group at C-12 is transformed into the ketone group at C-11, in 12α-bromo-24,24-diphenylchol-23-en-3α-ol-11-one acetate (IX). The same approach was used by Reichstein and co-workers,[3] in their synthesis of dehydrocorticosterone.

Gallagher and co-workers[4] developed a simpler process for transferring the oxygen from C-12 to C-11 which, starting with desoxycholic acid, led to dimethyl 12α-bromo-3α-succinoxy-11-ketocholanate (III) in seven steps. While methods have been suggested for incorporating this product into several schemes for the synthesis of cortisone, its use has not been reported. It is significant that the reaction of methyl 12α-bromo-3α,9α-epoxy-11-ketocholanate[1b,5] with excess phenylmagnesium bromide results in the reductive removal of bromine at C-12. From this it may be inferred that an attempt to prepare IX from III by reaction with phenylmagnesium bromide, followed by acetylation, also would result in the reductive loss of the C-12 bromine. In our laboratory it has been found advantageous to retain the bromine at C-12 since in the subsequent, modified Meystre–Miescher degradation of the side-chain[6] the desired C-20 ketone is isolated with comparative ease when bromine is present, and only with considerable difficulty when bromine is absent

We have applied Gallagher's approach in such a way that starting with desoxycholic acid, compound IX, an intermediate in the Kendall synthesis, is obtained. The number of steps has been reduced to seven, although our studies have not resulted in better than 10% over-all yield of IX from IV.

3α-Succinoxy-12-ketocholanic acid (IV), which is prepared readily from desoxycholic acid,[7] was brominated with bromine at 60° in glacial acetic acid solution to give a mixture of 11α- and 11β-bromo-3-succinoxy-12-ketocholanic acids (V). This mixture was then refluxed for several hours with a

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[1] (a) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946); (b) V. R. Mattox and E. C. Kendall, *ibid.*, **185**, 589 (1950); (c) E. C. Kendall, U. S. Patent 2,541,074, Feb. 13, 1951.

[2] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 452.

[3] (a) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946); (b) A. Lardon and T. Reichstein, *ibid.*, **26**, 747 (1943).

[4] (a) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 521 (1946); (b) T. F. Gallagher, *ibid.*, **162**, 539 (1946); (c) E. Borgstrom and T. F. Gallagher, *ibid.*, **177**, 951 (1949).

[5] E. P. Kohler and M. Tishler, THIS JOURNAL, **54**, 1594 (1932).

[6] Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **30**, 1037 (1947).

[7] E. Schwenk, B. Riegel, R. B. Moffett and E. Stahl, THIS JOURNAL, **65**, 549 (1943).