The reaction mixture was added to 400 ml. of water and upon cooling a white precipitate appeared. This white solid was isolated by filtration and recrystallized from petroleum ether (b.p. 60–80°). The yield was essentially quantitative. An analytical sample was prepared by sublimation; m.p. 92–94°.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.98; H, 5.04.

3,3′-Diphenic acid was prepared by permanganate oxidation and was recrystallized from ethanol; m.p. 353–356° (lit. m.p. 330–332°,[20] 356–357°[17]).

3,3′-Di(3-keto-3-(3-bromophenyl)-1-propenylbiphenyl (XXII).—A mixture of XXI (0.02 mole) and IIb (0.04 mole) was dissolved in 60 ml. of ethyl acetate. This solution was saturated with hydrogen chloride gas and was allowed to stand for 3 days at room temperature. A tan-brown precipitate was isolated, washed with cold alcohol, and recrystallized from benzene; m.p. 180–182°. The filtrate was evaporated and more of the dichalcone product was isolated and combined with the initial crop of crystals. The over-all yield was 9.8 g. (94%). The infrared spectrum showed carbonyl absorption at 1665 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{20}Br_2O_2$: C, 62.93; H, 3.52. Found: C, 62.90; H, 3.80.

The 2,4-dinitrophenylhydrazone derivative was prepared by a Soxhlet technique and was recrystallized from dioxane; m.p. 266–268°.

Anal. Calcd. for $C_{42}H_{28}N_8O_8Br_2$: C, 54.08; H, 3.03. Found: C, 53.83; H, 3.30.

(20) H. R. Snyder, C. Weaver, and C. D. Marshal, *J. Am. Chem. Soc.*, **71**, 289 (1949).

3,3′-Di[2-carbethoxy-5-(3-bromophenyl)-3-keto-4-cyclohexenyl]biphenyl (XXIII).—A solution of sodium ethoxide in ethanol was prepared from sodium (0.002 g.-atom) and 100 ml. of ethanol. Ethyl acetoacetate (0.014 mole) was added to this solution, and 1 hr. later the dichalcone XXII (0.0034 mole) was added. The reaction mixture was refluxed for 3 hr. and while still hot was added to a cold solution of dilute hydrochloric acid. A yellow precipitate was isolated by filtration, washed with cold ethanol, and recrystallized from ethanol–benzene; m.p. 90–97°; yield, 1.8 g. (64%).

Anal. Calcd. for $C_{42}H_{36}O_6Br_2$: C, 63.32; H, 4.54. Found: C, 63.15; H, 4.33.

3,3′-Di[3-keto-5-(3-bromophenyl)-4-cyclohexenyl]biphenyl (XXIV).—The Michael addition product (XXIII) 0.00085 mole) was heated in a sealed tube with 22 ml. of acetic acid and 11 ml. of 20% hydrochloric acid. This tube was shaken for 4 hr. at 150°, cooled, opened, and the contents were extracted with benzene. The benzene layer was washed successively with water, 10% sodium hydrogen carbonate solution, and water. Drying of the benzene layer was done by magnesium sulfate and, after filtration of the drying agent, the solution was evaporated to approximately 20 ml. Ethanol was added and upon cooling a yellow-white solid appeared. This solid was isolated and recrystallized from ethanol–benzene; m.p. 95–98°; yield, 0.24 g. (43%); λ_{max}^{EtOH} 270 mμ (ε 49,200), 228 (39,900). The infrared spectrum showed carbonyl absorption at 1665 cm.$^{-1}$.

Anal. Calcd. for $C_{36}H_{28}Br_2O_2$: C, 66.26; H, 4.32. Found: C, 65.98; H, 4.44.

Acknowledgment.—The authors are grateful to Dr. Franz Kasler for the analytical determinations.

The Structure of a Cyclic C_{18} Acid from Heated Linseed Oil

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Received March 13, 1963

One of the cyclic fatty acids formed by heating linseed oil in the absence of air was isolated in pure form and was shown to be ethyl 11-(2-methylcyclohex-2-en-1-yl)undec-*trans*-9-enoate. A combination of chemical degradation, synthesis, and physical measurements was used to determine the structure.

Crampton and co-workers showed that heating of linseed oil at 275° under carbon dioxide produced substances which were toxic when fed to rats.[1–3] They found that the toxic materials were formed from linolenate esters and could be concentrated greatly by conversion to ethyl esters, distillation, and treatment with urea. The portion which formed an adduct with urea was harmless. Wells and Common suggested that the nonurea-adductable materials contained a nonterminal ring structure.[4] Others have obtained indirect evidence for a cyclic structure.[5]

Later, MacDonald obtained direct evidence that cyclic compounds were formed during the heating of linseed oil in the absence of oxygen.[6] He isolated phthalic anhydride after aromatization and oxidation of the distillable, nonurea-adductable fraction. He established that the distillable, nonurea-adductable fraction contained esters of C_{18}-monocarboxylic acids averaging two double bonds per molecule. More recently, MacDonald, *et al.*, have postulated specific structures for two compounds from heated linseed oil.[7] None of this structure work, however, was carried out with pure compounds.

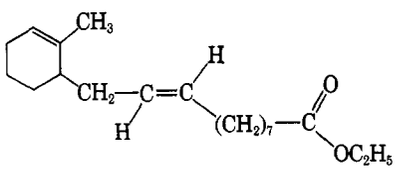
In the current investigation, one of the compounds in the distillable, nonurea-adductable material (DNUA) from anaerobically heated linseed oil was isolated in pure form and its structure was elucidated. The biological studies on this and similar materials from the DNUA of heated linseed oil is the subject of another study in these laboratories.

Although gas chromatography showed the DNUA from heated linseed oil to contain at least five unknown compounds, information for only one is presented. The compound discussed is called α 1.38. The α value is the ratio of the gas chromatography (g.c.) retention time of this material to the g.c. retention time of ethyl linoleate on a polyester column.

The α 1.38 was concentrated by distillation of the DNUA mixture on a spinning band column, and was isolated in pure form from the distillation fractions most concentrated in α 1.38 by preparative gas chromatography (Fig. 1). The resulting ester was proved to have the structure I. The analytical data were consistent with the empirical formula for I, $C_{17}H_{29}CO_2C_2H_5$.

The behavior of α 1.38 during isolation suggested that it was a monomeric cyclic compound. It distilled

(1) E. Crampton, F. Farmer, and F. Berryhill, *J. Nutr.*, **43**, 431 (1951).
(2) E. Crampton, R. Common, F. Farmer, F. Berryhil', and L. Wiseblatt, *ibid.*, **44**, 177 (1951).
(3) E. Crampton, R. Common, F. Farmer, A. Wells, and D. Crawford, *ibid.*, **49**, 333 (1953).
(4) A. Wells and R. Common, *J. Sci. Food Agr.*, **4**, 233 (1953).
(5) Matsuo, N., *J. Chem. Soc. Japan, Pure Chem. Sec.*, **81**, 469 (1960).
(6) J. MacDonald, *J. Am. Oil Chemists' Soc.*, **33**, 394 (1956).
(7) A. McInnes, F. Cooper, and J. MacDonald, *Can. J. Chem.*, **39**, 1906 (1961).



I

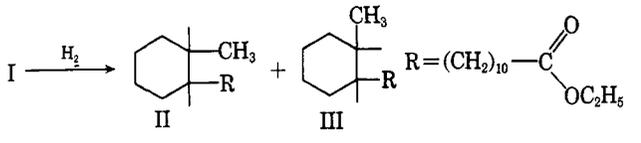
with linoleate and linolenate, suggesting that it was a monomer; it did not form an adduct with urea, which indicated a branched or a cyclic structure. Since this material originated from linseed oil, a cyclic structure was more likely.

The ultraviolet spectrum of α 1.38 indicated that it was not a conjugated diene or triene.

The infrared spectrum of α 1.38 showed bands at 5.72, 10.3, and 13.8 μ, which were assigned to ester, *trans* double bond, and tetramethylene groups, respectively.[8]

A comparison of the ratio of the intensities of the carbonyl band and the band at 10.3 μ in the infrared spectrum of α 1.38 with the ratio of the intensities of the corresponding bands in the infrared spectrum of elaidic acid showed that α 1.38 contained one *trans* double bond.

Microhydrogenation of α 1.38 showed an uptake of two moles of hydrogen per mole of α 1.38. Gas chromatography showed the hydrogenation product to be two compounds. This observation suggested the presence of a trisubstituted double bond; the *cis*-II and *trans*-III isomers would be obtained from the hydrogenation if α 1.38 (I) had a double bond in a ring adjacent to one of the side chains.[9]



II III

Azelaic acid was produced in the periodate–permanganate oxidation[10] of α 1.38 in 38% yield; this was 76% of the theoretical yield for a compound with structure I. Azelaic acid was identified by comparison of the gas chromatograms of authentic dimethyl azelate and the dimethyl esters of the oxidation products. The other major oxidation product (47% yield) had a retention time much longer than azelaic acid. The highly polar keto diacid formed by cleaving the double bond in the ring of α 1.38 (I) would be expected to have such a retention time. The oxidation products indicated that the tri-substituted double bond must be in the ring, and that the *trans* double bond was in the same chain as the ester group. The relative positions of the *trans* double bond and the ester group were also shown.

Dehydrogenation of α 1.38 over palladium on carbon at 250° produced an aromatic compounds (60% yield) which was shown to be ethyl 11-(2-tolyl)undecanoate.

The infrared spectrum of the dehydrogenated material showed bands at 6.22, 6.70, and 13.28 μ. All

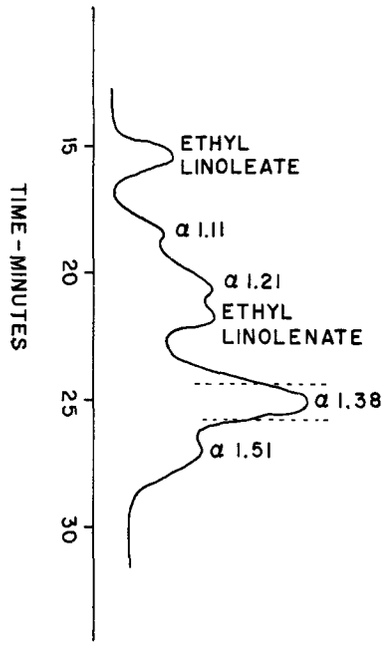


Fig. 1.—Gas chromatogram of a typical distillation fraction from DNUA which was used for the collection of α 1.38. The broken lines indicate the portion of the α 1.38 peak collected for use in structure studies. α = retention time of unknown peak/retention time of ethyl linoleate.

three bands are characteristic of aromatic compounds; the band at 13.28 μ is specific for 1,3-disubstituted benzene.[11]

The ultraviolet spectrum showed absorption maxima at 263, 272, and 277 mμ; this spectrum was consistent with an *ortho* substituted benzene.[12] The n.m.r. spectrum[13] showed a τ value of 2.9 p.p.m. which corresponded to four aromatic protons, thus confirming that the dehydrogenation product was a disubstituted benzene.

Mass spectroscopy was used to determine the carbon skeleton of aromatized α 1.38.[14] Peaks due to fragments from a substituted benzene ring were seen at 91, 105, 119, and 133 on the mass spectrum. The peak at 105, due to the *o*-xylyl ion, was the largest, as would be expected for a disubstituted benzene with a methyl side chain.[15]

The structure for aromatized α 1.38 was definitely established by an independent synthesis. 10-Undecenyl bromide (IV) was allowed to react with magnesium, and the resulting Grignard reagent was treated with cadmium chloride to give diundecenylcadmium (V). *o*-Toluyl chloride was added to the cadmium reagent to yield 11-(*o*-toluyl)-1-undecene (VII). The ketone was reduced by the Huang-Minlon modification of the Wolff–Kishner reaction,[16] and the double bond in the resulting hydrocarbon VIII was cleaved with ozone to produce 11-(*o*-tolyl)undecanoic acid (IX). Esterification of the acid by the Fisher proce-

(8) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 180; (b) p. 45; (c) p. 27.

(9) (a) R. Siegel and G. Smith, *J. Am. Chem. Soc.*, **82**, 6082 (1960); (b) **82**, 6087 (1960); (c) J. Sauvage, R. Baker, and A. Hussey, *ibid.*, **82**, 6090 (1960); (d) **82**, 3874 (1961).

(10) The author is indebted to D. F. Kuemmel of these laboratories for the periodate–permanganate oxidations.

(11) Ref. 8, pp. 64–83.

(12) (a) D. Tunnicliff, *et al.*, *Anal. Chem.*, **21**, 891 (1949); (b) American Petroleum Institute Research Project no. 44, Spectra no. 63, 71, 123, and 194.

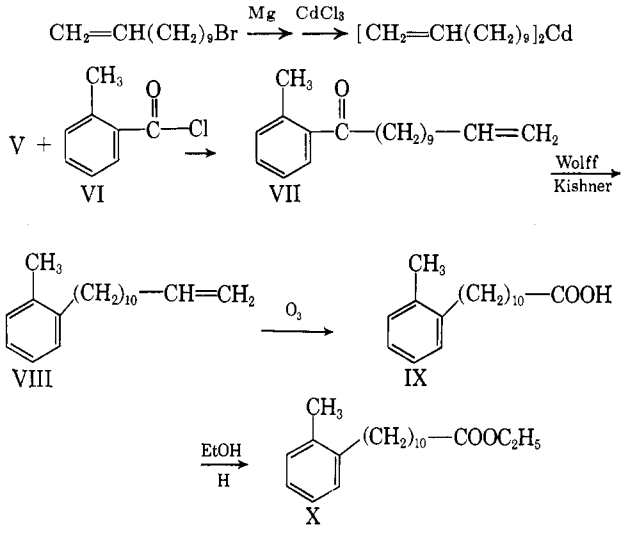
(13) The n.m.r. spectra were done by T. J. Flautt of these laboratories.

(14) The author is indebted to W. Courchene of these laboratories for the mass spectroscopy data.

(15) J. H. Beynon, "Mass Spectroscopy and Its Applications to Organic Chemistry," Elsevier Publishing Company, Amsterdam, Netherlands, 1960, pp. 340–345.

(16) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

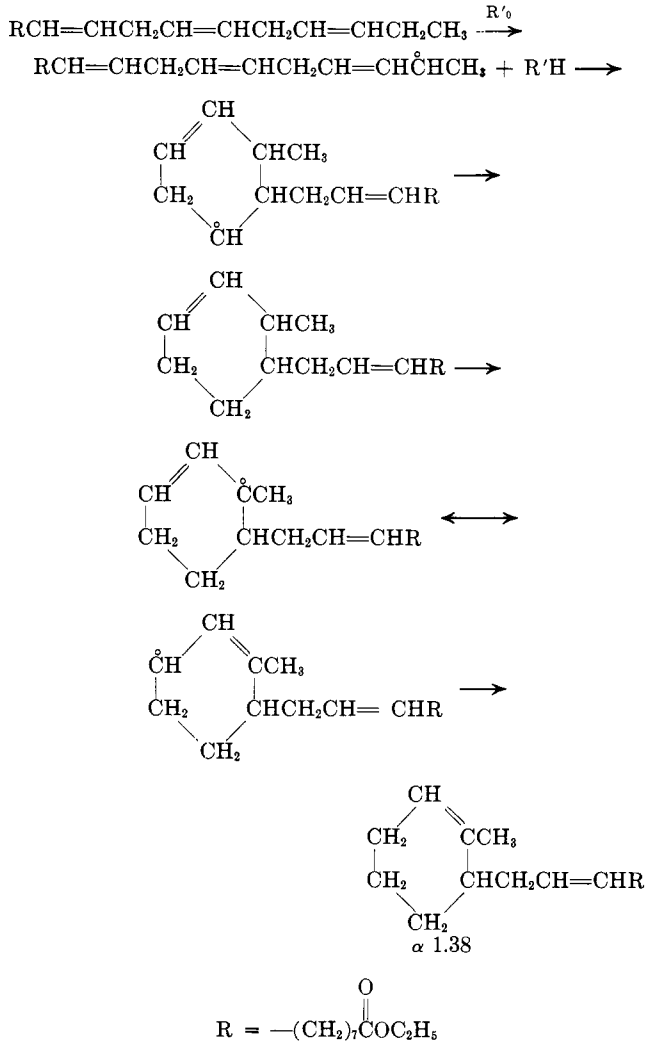
dure[17] gave the desired ethyl 11-(*o*-tolyl)undecanoate (X). The synthetic product was found, by comparison of g.c. curves and spectra, to be identical with the material obtained by dehydrogenation of α 1.38.



After the structure of aromatized α 1.38 was proved, it was necessary to show that a rearrangement had not occurred during the dehydrogenation of α 1.38 to give the aromatized material. This was shown by hydrogenating both α 1.38 and aromatized α 1.38 to the same products. The two saturated products were shown to be identical by gas chromatography and mass spectroscopy.

After the carbon skeleton of α 1.38 was established, assignment of the position of the trisubstituted double bond in α 1.38 was accomplished by elimination. There were three possible positions for a trisubstituted double bond. The ultraviolet, infrared, and n.m.r. spectra showed that the double bonds were not conjugated. Lack of a peak in the 7.0–7.3-τ region of the n.m.r. spectrum indicated that the two double bonds were not in a 1:4 relationship.[18] Alkali isomerization did not produce a conjugated product; this procedure would effect conjugation if the double bonds were in a 1:4 relationship.[19] The oxidation studies suggested that one of the double bonds was in the ring. Only if the ring double bond were in the Δ^2-position would all the foregoing conditions be satisfied.

No mechanistic studies have been carried out on this system. It was shown, however, that ethyl linolenate heated under the conditions used to prepare α 1.38 from linseed oil produced α 1.38 in 6% yield (16% of the ethyl linolenate was unaltered), and that ethyl linoleate heated under the same conditions did not produce any. Because the yield was low, this particular reaction accounted for a very small portion of the ethyl linolenate which was changed by the heating process. A pathway to α 1.38 from ethyl linolenate can be rationalized *via* a free radical allylic proton abstraction route. (see col. 2.)



Experimental

Isolation of α 1.38.—One liter of linseed oil was heated at 275° for 12 hr. with carbon dioxide bubbled through the oil during the entire heating period.

The heated linseed oil was saponified by heating under reflux for 45 min. with 200 g. of potassium hydroxide in 1500 ml. of water and 1200 ml. of ethanol. The reaction mixture was cooled, acidified, diluted with water, and extracted with hexane and ether. The solvent layers were washed with water, and the solvent was removed under vacuum (aspirator) on a rotary evaporator.

The fatty acids were heated under reflux for 45 min. with 10 ml. of concentrated sulfuric acid and 2 l. of anhydrous ethanol. The reaction mixture was cooled, diluted with water, and extracted with hexane and ether. The solvent layer was washed with water and the solvent was removed on a rotary evaporator.

The esters were distilled using a simple distillation apparatus. Everything boiling below 180° at 1 mm. was distilled.

Five hundred milliliters of distillate was mixed with 2 kg. of urea, 2 l. of ethanol, and 50 drops of Tenox II[20] and heated at 70° for 0.5 hr. The mixture was allowed to cool to room temperature, and stand at 0° overnight. The cold mixture was filtered, and most of the solvent was evaporated from the filtrate. About four volumes of water were added to the filtrate, and the resulting mixture was extracted with hexane and ether. The combined solvent layers were washed with water and dried over

(17) E. Fisher and Speier, *Ber.*, **28**, 3252 (1895).

(18) Varian Associates, "High Resolution NMR Spectra Catalog," 1962, Spectrum no. 337.

(19) J. Mitchell, Jr., H. Kraybill, F. Zscheile, *Anal. Chem.* **15**, 1 (1943).

(20) Tenox II is an Eastman Chemical Products, Inc., antioxidant with the following composition: 20% butylated hydroxy anisole, 6% propyl gallate, 4% citric acid, and 70% propylene glycol.

magnesium sulfate. The solvent was removed to leave 100 ml. of distillable nonurea adductable material (DNUA).

A 200-ml. charge of DNUA was distilled through a 36-in. Nester spinning band column at 1-mm. pressure and a reflux ratio of three. The temperature rise was gradual, with no apparent plateaus. The distillate was cut into 5-ml. fractions, which were analyzed by gas chromatography. None of the fractions contained α 1.38 free of other components, but some were appreciably concentrated in α 1.38.

The instrument used for the gas chromatography was an Aerograph Model A-100C with a 6-10 Varian recorder. Helium was the carrier gas. A $^3/_{16}$ in. (o.d.) × 10 ft. copper tube packed with Chromosorb W (30–60 mesh) containing 10% ethylene glycol adipate was used for the chromatography. The following operating conditions are representative: helium pressure, 20 p.s.i.g.; helium flow rate, 60–75 ml./min.; oven temperature, 205°; injection port temperature, 295°.

The fractions concentrated in α 1.38 were used to isolate the α 1.38 by preparative gas chromatography (Fig. 1).

The Aerograph unit was employed for the preparative work. For collection, a $^3/_8$ in. × 7 ft. copper tube packed with Chromosorb W (30–60 mesh) containing 25% ethylene glycol adipate was used. The following operating conditions are representative: helium pressure, 10 p.s.i.g.; helium flow rate, 200–275 ml./min.; oven temperature, 194–198°; injection port temperature, 295°; collection port temperature, 310°. The injection volume was 35 μl. The material was collected in a 16-mm. tube containing glass wool wet with methanol. The infrared spectrum of α 1.38 showed the following bands: 5.72, 8.50 μ (ester); 10.29 μ (*trans* double bond); 13.8 μ (tetramethylene). The ultraviolet spectrum of α 1.38 showed no appreciable absorption above 220 mμ. Analysis by n.m.r. gave the following τ values: 4.52–4.73 p.p.m. (vinyl protons); 5.84–6.19 p.p.m. (—OCH_2—); 7.78–8.02 p.p.m. (activated, methylene and methyl protons); 8.38 p.p.m. (vinyl methyl). Assuming that there were two protons on the methylene carbon of the ester group, the intensity of the peaks corresponds to 3.15 ± .17 vinyl protons and 26.81 ± 2.16 other protons.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.43; H, 11.11. Found: C, 77.73; H, 10.96.

Hydrogenation of α 1.38.—A 10-mg. quantity of α 1.38 in ethanol was hydrogenated using Adams catalyst at room temperature and 50 p.s.i. for 2 hr. in a Paar apparatus. Two moles of hydrogen were taken up per mole of α 1.38. The hydrogenation product showed two peaks on its gas chromatogram.

Oxidation of α 1.38.—Oxidation of α 1.38 was done with a periodate permanganate mixture.[10] The acids obtained from the oxidation were esterified for gas chromatography analysis.

The methyl esters of the oxidation products of α 1.38 showed two major peaks by gas chromatography. One of the peaks was identified as methyl azelate by comparison of gas phase retention times of the oxidation product and authentic methyl azelate. The other major peak was shown to be much more polar than methyl azelate and was not identified. Small amounts of pimelic, suberic, and sebacic esters were identified by comparison of their gas chromatography retention times with the gas chromatography retention times of authentic samples.

Aromatized α 1.38.—A 100-mg. (0.33 mole) quantity of α 1.38 was heated at 250° with 5 mg. of 10% palladium–charcoal for 12 hr. in a sealed tube. The reaction mixture was filtered to give a clear liquid. The dehydrogenation product was separated from low boiling fragments by preparative gas chromatography. The reaction gave the dehydrogenation product in 60% yield.

The infrared spectrum showed bands at 3.21, 6.22, 6.70 μ (aromatic); 13.28 μ (1,2-disubstituted benzene); 6.72, 8.48 μ (ester); and 13.75 μ (tetramethylene).

Ultraviolet analysis showed the following λ_{max} in mμ (log ϵ): 263 (2.30); 267 sh (2.23); 272 (2.24); 256 sh (2.25); and λ_{min} 269 (2.19).

The mass spectrum showed the following bands corresponding to aromatic fragments; 91 (tolyl ion), 105 most intense (*o*-xylyl ion), 119, 133, and a parent peak at 304.

Hydrogenation of Aromatized α 1.38.—A 50-μl. sample of aromatized α 1.38 in 2 ml. of methylcyclohexane was reduced with hydrogen and Raney nickel catalyst at 206° and 2500 p.s.i.

The hydrogenation product was filtered free of catalyst. The gas chromatogram of this material was identical with the gas chromatogram of hydrogenated α 1.38. The mass spectra of these hydrogenation products were identical.

Oxidation of Aromatized α 1.38.—Oxidation of aromatic α 1.38 with a periodate–permanganate mixture[10] gave no fragmentation products.

Ethyl 11-(o-tolyl)undecanoate (X).—A 10-g. (0.04 mole) quantity of 10-undecenyl bromide in 10 ml. of dry ethyl ether was added slowly to a three-necked flask containing 1.03 g. (0.04 g.-atom) of magnesium and 35 ml. of dry ethyl ether. The reaction was exothermic and the reaction flask was cooled in an ice bath. When the addition of the undecenyl bromide was complete, the reaction was stirred for 3 hr. at room temperature. The reaction was carried out in a nitrogen atmosphere.

The reaction flask was cooled in an ice bath and 3.9 g. (0.02 moles) of cadmium chloride was added over a period of 5–10 min. The reaction mixture was stirred and heated under reflux for 3 hr. The ether was distilled and 25 ml. of anhydrous benzene was added. A solution of 5 g. (0.03 mole) of *o*-toluyl chloride (VI) (prepared from *o*-toluic acid and thionyl chloride at 60°) in 30 ml. of anhydrous benzene was added over a period of 30 min. The reaction mixture was then heated under reflux for 24 hr. Approximately 30 g. of crushed ice and 50 ml. of 6 *N* sulfuric acid were added to the reaction mixture. The benzene and aqueous layers were separated and the aqueous layer was extracted with three 10-ml. portions of benzene. The benzene layers were combined and washed with water, with a saturated sodium bicarbonate solution, with water, and with a saturated sodium chloride solution. The benzene solution was dried over anhydrous sodium sulfate and the benzene was removed by distillation to leave 18 ml. of clear liquid. The infrared spectrum of the crude reaction products showed bands at 5.91, 6.26, and 6.72, 10.06, and 11.00, 13.4, and 13.8 μ which were assigned to aryl ketone, aromatic ring, terminal double bond, *o*-substituted benzene, and tetramethylene, respectively. This spectrum is consistent with the desired ketone, 11-(*o*-toluyl)-1-undecene (VII). The ketone was not purified for the next step.

The ketone VII (18 ml.) was heated under reflux with 10 g. of potassium hydroxide and 7.5 ml. of 85% hydrazine hydrate in 75 ml. of diethylene glycol for 1 hr. The water formed was removed by distillation and the temperature of the solution was allowed to rise to 150°; the reaction mixture was heated at this temperature for 16 hr. The reaction mixture was diluted with 7 ml. of water and the resulting mixture was extracted with ethyl ether (three times). The ether extracts were combined and washed with water. The solvent was removed on a rotary evaporator to leave a light yellow liquid (14 ml.). The infrared spectrum of the crude product was consistent with the structure of the desired hydrocarbon, 12-(*o*-tolyl)-1-dodecene (VIII). Bands were observed at 6.08, 6.26 and 6.70, 10.06 and 10.94, 13.3, and 13.8 μ which were assigned to double bond, aromatic ring, terminal double bond, *o*-substituted benzene, and tetramethylene, respectively.

A portion of the crude hydrocarbon VIII (4.0 ml.) was distilled through a spinning band column. The distilled hydrocarbon (0.5 ml., 0.002 mole), b.p. 60° (1.5 mm.), was dissolved in 5 ml. of chloroform and cooled to −60° in a Dry Ice–acetone bath. A stream of 0.6% ozone was bubbled through this solution for 5.8 min. (0.002 mole of ozone). The chloroform was evaporated in a nitrogen atmosphere, and 0.4 ml. of acetic acid was added to the ozonides. The acetic acid solution was added slowly to 0.8 ml. of a water solution containing 0.5 ml. of 30% hydrogen peroxide and 0.02 ml. of sulfuric acid. The resulting mixture was heated under reflux for 2 hr. The mixture was cooled and extracted with ether (three times). The ether extracts were extracted with a sodium hydroxide solution. The base extracts were acidified with hydrochloric acid and extracted with ether. The ether was removed on a rotary evaporator to leave 0.4 ml. of acids.

The acids (0.4 ml.) were heated under reflux with 1 ml. of ethanol and 0.05 ml. of sulfuric acid for 30 min. The esters were isolated in the usual manner to give 0.3 ml. of clear liquid. Gas chromatography showed one peak to be 60% of the mixture. This peak was collected by preparative gas chromatography (0.2 ml.) and was shown to be the desired ethyl 11-(*o*-tolyl)undecanoate (X). Based on the starting bromide, the yield of ethyl 11-(*o*-tolyl)undecanoate for the six-step synthesis was 5%.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78,95; H, 10.53. Found: C, 78.74; H, 10.42.

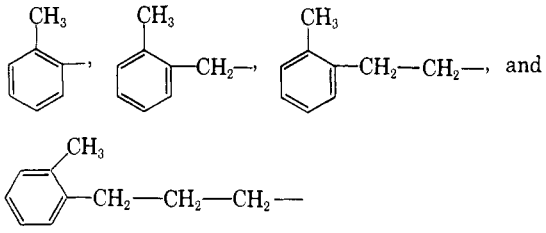
The infrared spectrum showed bands at 5.72 and 8.50, 6.25

and 6.71, 13.4 and 13.8 μ, which were assigned to ester, aromatic ring, "*o*-substituted" benzene, and tetramethylene, respectively.

The mass spectrum showed bands at 91, 105, 119, 133; the band at 105 was the most intense. These bands correspond, respectively, to the fragments shown in col. 2.

The parent peak was at 306.

The gas chromatogram and the spectra of synthetic ethyl 11-(*o*-tolyl)undecanoate were shown to be identical with the gas chromatogram and spectra of aromatized α 1.38.



Ozonolysis of Polycyclic Aromatics. XI.[1a] 3-Methylcholanthrene[2]

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Received February 11, 1963

Ozonization of the potent carcinogen 3-methylcholanthrene (**1**) (++++) in methylene chloride and 3:1 methylene chloride–methanol produced a mixture of unstable peroxides (**2**). Hydrogen peroxide oxidation of **2** led to a carboxylic acid mixture from which was isolated prehnitic acid (**6**) and 9-methylbenz[*a*]anthracene-7,12-dion-8-acetic acid (**3**). Decarboxylation of the carboxylic acid mixture led to 8,9-dimethylbenz[*a*]anthracene-7,12-dione (**7**), *via* **3**, and 1,2-dimethylanthraquinone (**8**) and biphenyl (**9**), from which is inferred the additional presence of 2-methyl-5,6-dicarboxyanthraquinon-1-acetic acid (**4**) and 2,2′,3,4,5-pentacarboxybiphenyl (**5**) in the original carboxylic acid mixture. Thus, to ozone, **1** reacts significantly as a 7,8,9-trisubstituted benz[*a*]anthracene derivative with predominant ozone attack occurring at the L-region. The conversion of **7** to 5,6-dimethylanthraquinone-1,2-dicarboxylic acid (**10**), and **8** to phthalic acid, with ozone, suggest the ozonolysis product sequence **3** → **4** → **6**.

Our continuing interest in the possible association between high carcinogenic potency of certain polycyclic aromatic hydrocarbons and their reactivity with ozone at specific sites relevant to the carcinogenic process, has led, among other hydrocarbons, to the ozonization of such lesser carcinogens as dibenz[*a*,*j*]- (+)[1b] and dibenz[*a*,*h*]anthracenes (++),[1c] and to the more strongly carcinogenic benzo[*a*]pyrene (++++),[1d] and 7,12-dimethylbenz[*a*]anthracene (++++).[1a]

The exact nature of this causative relationship, if any, is unclear. Thus, in dibenz[*a*,*h*]anthracene ozonolysis occurred predominantly at the K-region,[1c] experimentally demonstrated to be a primary site of both biological oxidation,[3a,4] and of involvement in the carcinogenic process.[3c,d] Further, in the series benz[*a*]anthracene (0), dibenz[*a*,*j*]- (+), and dibenz[*a*,*h*]anthracene (++), we have noted a decrease in reactivity at the L-region toward ozone as an electrophilic reagent which is accompanied by an increase in reactivity at the K-region toward ozone as a double bond reagent. This order, which corresponded to a progressive increase in carcinogenic activity and which would have been predicted from the Pullmans' K-region theory of carcinogenesis,[6] suggested that the potent carcinogen benzo[*a*]pyrene should react strongly with ozone at the K-region.

We have found, however, that benzo[*a*]pyrene is ozonized[1d] only at the L-region and at positions *adjacent* to the K-region, *i.e.*, the M-region,[7] which are also the sites of metabolic oxidation.[8] Thus in dibenz[*a*,*h*]anthracene and benzo[*a*]pyrene, the metabolic paralleling reactions which lead to products of ozone addition can also be considered as likely steps in the detoxification of these compounds,[9] with perhaps stronger evidence for loss of carcinogenicity.[11]

In their study of protein binding as a necessary, but not sufficient, prerequisite for hydrocarbon carcinogenesis, Heidelberger and Moldenhauer[3c] have experimentally demonstrated that benzo[*a*]pyrene, 7,12-dimethylbenz[*a*]anthracene, and 3-methylcholanthrene were bound to skin protein to a large and approximately equal extent. In this paper, we conclude our study of the trio by reporting on the ozonization of the potent carcinogen (++++), 3-methylcholanthrene (**1**).

Results

Ozonization of **1**, as in all our previous work, was conducted in methylene chloride, and 3:1 methylene chloride–methanol solvents at −78° with ozone–

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(2) This research was supported by a grant C-3325(C5) from the U. S. Public Health Service, National Cancer Institute.

(3) (a) C. Heidelberger, H. I. Hadler, and G. Wolf, *J. Am. Chem. Soc.*, **75**, 1303 (1953); (b) J. A. LaBudde and C. Heidelberger, *ibid.*, **80**, 1225 (1958); (c) P. M. Bhargava, H. I. Hadler, and C. Heidelberger, *ibid.*, **77**, 2877 (1955); (d) P. M. Bhargava and C. Heidelberger, *ibid.*, **78**, 3671 (1956); (e) C. Heidelberger and M. G. Moldenhauer, *Cancer Res.*, **16**, 442 (1956); (f) C. Heidelberger, M. E. Baumann, L. Griesbach, A. Ghobar, and T. M. Vaughn, *ibid.*, **22**, 78 (1962).

(4) In addition to 5,6-dibenz[*a*,*h*]anthracenedione (K-region oxidation product), six other metabolites of dibenz[*a*,*h*]anthracene are known: 7,14-dibenz[*a*,*h*]-anthracenedione,[3a] 2-hydroxy-,[3b] 2,9-dihydroxy-,[3b] and 4,11-dihydroxydibenz[*a*,*h*]anthracenes,[5] 4,11-dihydroxybenz[*a*]anthracene-7,14-dione,[3a] and 5-hydroxy-1,2-naphthalenedicarboxylic acid.[3a]

(5) J. Cason and L. F. Fieser, *J. Am. Chem. Soc.*, **62**, 2681 (1940).

(6) (a) A. Pullman and B. Pullman, "Cancérization par les Substances Chimiques et Structure Moléculaire," Masson et Cie, Paris, 1955; (b) A. Pullman and B. Pullman, *Advan. Cancer Res.*, **3**, 117 (1955).

(7) It should be noted that metabolic perhydroxylation does *not* always occur at the M-region, the Pullmans notwithstanding.[6b] *Cf.* ref. 36.

(8) A. H. Conney, E. C. Miller, and J. A. Miller, *J. Biol. Chem.* **228**, 753 (1957).

(9) Of all the known metabolites of polycyclic aromatic carcinogens, only two, dibenz[*a*,*h*]anthracene-7,14-dione and 2-phenylphenanthrene-3,2′-dicarboxylic acid,[3c,10] have ever been screened. Carcinogenic testing by subcutaneous injection and direct application of these metabolites to the skin of mice was negative.[3f]

(10) This dicarboxylic acid is also an oxidation product of our ozonolysis studies.[1c]

(11) Suggested by a referee of paper VIII.[1d]