415. Cyclic Dimers of Isoprene and Their Relation to Some Components of Tobacco Smoke.

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The cyclic dimers of isoprene are compared with similar substances isolated from cigarette smoke, and a mechanism is suggested for their origin during smoking. The synthesis and configurational isomerism of 1-ethyl-1,3- and -1,4-dimethylcyclohexanes, 1-chloro-1-ethyl-3- and -4-methylcyclohexanes, and 1-ethyl-3- and -4-methylcyclohexanols are described.

Thermal dimerisation of isoprene at temperatures below about 200° yields *m*- and *p*-mentha-1,8-diene, dimethylcyclo-octa-1,5-dienes, and a substance originally known as Lebedev's hydrocarbon.[1] The formulation of this last hydrocarbon as a mixture of 1,4- and 2,4-dimethyl-4-vinylcyclohexenes has been partly confirmed by oxidative degradation to 2-carboxy-2-methyladipic acid.[2] Reduction of Lebedev's hydrocarbon followed by dehydrogenation and oxidation of the resulting benzenoid hydrocarbons yielded a mixture of terephthalic, isophthalic, and trimellitic acid.[2] We have proved the structure more completely by synthesising *cis*- and *trans*-1-ethyl-1,3- and -1,4-dimethylcyclohexanes * and showing them to be identical with the four saturated hydrocarbons obtained by reduction of Lebedev's hydrocarbon. The route to 1-ethyl-1,3- and -1,4-dimethylcyclohexanes was similar to an earlier one used for the preparation of 1-ethyl-1-methylcyclohexane.[3] Treatment of 4-methylcyclohexanone with ethylmagnesium bromide yielded a mixture of two alcohols which were separated by fractional distillation into the epimeric 1-ethyl-4-methylcyclohexanols. Their infrared spectra showed strong C–O stretching bands, at 1170 cm.$^{-1}$ for the lower-boiling axial compound, and at 1125 cm.$^{-1}$ for the higher-boiling equatorial epimer. If we assume that the 4-methyl group takes up the equatorial position, the two alcohols are 1(*eq*)-ethyl-1(*ax*)-hydroxy-4(*eq*)-methylcyclohexane and 1(*ax*)-ethyl-1(*eq*)-hydroxy-4(*eq*)-methylcyclohexane, and are formed in an approximately 1 : 1 ratio. Consideration of non-bonded interactions in these alcohols suggests that *trans*-1-ethyl-4-methylcyclohexanol will have the first conformation assigned above but that *cis*-1-ethyl-4-methylcyclohexanol may also contain a considerable amount of 1(*eq*)-ethyl-1-(*ax*)-hydroxy-4(*ax*)-methylcyclohexane. The presence of a fairly strong absorption band at 1165 cm.$^{-1}$ supports this suggestion. Treatment of either alcohol with concentrated hydrochloric acid yielded the same proportions of *cis*- and *trans*-1-chloro-1-ethyl-4-methylcyclohexane. The lower-boiling *trans*-isomer, formed in greater amount, shows strong absorption at 837 cm.$^{-1}$, probably due to the axial chlorine atom. The conformation of the less stable *cis*-epimer is less certain. The tertiary chlorides were separated by fractional distillation into the pure *trans*-epimer and a 1 : 1 mixture of the latter and its *cis*-form. The action of thionyl chloride in pyridine or ether on either of the 1-ethyl-4-methylcyclohexanols gave the intermediate chlorosulphites which were distilled under reduced pressure to yield mainly unsaturated hydrocarbon with some of the epimeric tertiary chlorides. The proportions of the latter showed that some retention

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* In this paper, *cis* and *trans* refer only to the orientation of the ethyl group with respect to the 3- or 4-methyl of the cyclohexane ring.

[1] Lebedev and Mereshkovski, *J. Russ. Phys. Chem. Soc.*, 1913, **45**, 1249.

[2] Nazarov, Kuznetsova, and Kuznetsov, *Zhur. obshchei Khim.*, 1955, **25**, 307.

[3] Buck, Elsner, Forbes, Morrell, Smith, and Wallsgrove, *J. Inst. Petroleum*, 1948, **34**, 339.

of configuration had occurred. Treatment of the *trans*-chloride or the 1 : 1 mixture of the *cis*- and the *trans*-chloride with dimethylzinc yielded a mixture of *cis*- and *trans*-1-ethyl-1,4-dimethylcyclohexane [probably 1(*ax*)-ethyl-1(*eq*),4(*eq*)-dimethylcyclohexane and 1(*eq*)-ethyl-1(*ax*),4(*eq*)-dimethylcyclohexane respectively]. The proportions of these epimeric hydrocarbons were the same from either chloride, indicating a common reaction intermediate. The probably planar intermediate radical (or carbonium ion) would be attacked by a methyl radical (or methyl carbanion) faster from one side than the other, leading to a larger proportion of the less stable isomer, *cis*-1-ethyl-1,4-dimethylcyclohexane. The epimeric hydrocarbons were separated by preparative-scale gas chromatography.

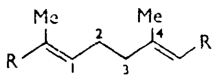
Similarly, the 1-ethyl-1,3-dimethylcyclohexanes were prepared from 3-methylcyclohexanone but the intermediate tertiary alcohols and chlorides were not separated into their epimers, although their relative proportions were obtained by gas chromatography. The steric effect of the 3-methyl group would be expected to influence the proportions of the epimeric tertiary alcohols produced in the Grignard reaction [4] more than a 4-methyl group, and in fact a greater proportion of the lower-boiling *cis*-1-ethyl-3-methylcyclohexanol was formed. Absorption bands at 1170 and 1125 cm.$^{-1}$ showed the presence of axial and equatorial forms of the tertiary hydroxyl group. The shielding effect of the 3-methyl group was evident in the reaction of dimethylzinc and 1-chloro-1-ethyl-3-methylcyclohexane since the proportions of the resulting *cis*- and *trans*-1-ethyl-1,3-dimethylcyclohexane were more nearly equal. Table 1 shows the proportions of epimers obtained in all cases (calculated from peak areas of gas chromatograms).

TABLE 1.

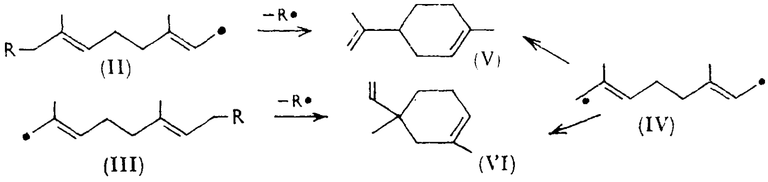
cis/*trans*	*cis*	*trans*
1-Ethyl-4-methylcyclohexanol	42%	58%
1-Ethyl-3-methylcyclohexanol	76	24
1-Chloro-1-ethyl-4-methylcyclohexane	34,[a] 50,[b] 23 [c]	66,[a] 50,[b] 77 [c]
1-Chloro-1-ethyl-3-methylcyclohexane	64 [a]	36 [a]
1-Ethyl-1,4-dimethylcyclohexane	84	16
1-Ethyl-1,3-dimethylcyclohexane	38	62

[a] Action of hydrochloric acid on either *cis*- or *trans*-alcohol. [b, c] Action of thionyl chloride on *cis*- and *trans*-alcohols respectively.

During our investigations of cigarette smoke we have isolated *p*-mentha-1,8-diene but not its *meta*-isomer. As isoprene is present in the smoke [5] it is possible that *p*-mentha-1,8-diene could be formed by dimerisation, but this reaction is known to produce the *meta*-isomer as well, so that another process must be sought for its formation. Similarly dimerisation of isoprene gives Lebedev's hydrocarbon, a mixture of dimethylvinylcyclohexenes, but we could isolate only 2,4-dimethyl-4-vinylcyclohexene from smoke. A likely precursor of the latter and *p*-mentha-1,8-diene is a polyisoprenoid chain compound of which there are considerable amounts in tobacco. Recent reports of experiments on Solanesol lend some support to this hypothesis.[6] In such a chain of this type (I) (R = continuation of chain), the bonds 2–3 have much lower dissociation energies than bonds 1–2 or 3–4.



(I)



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[4] Just and Nagarajan, *Experientia*, 1962, **18**, 404.

[5] Johnstone and Plimmer, *Chem. Rev.*, 1959, **59**, 890.

[6] Grossman, Deszyck, Ikeda, and Bavley, Paper delivered at the 16th Tobacco Chemists' Research Conference, Richmond, Virginia, Sept. 1962.

This can be estimated approximately by applying the known heats of formation[7] of the radicals (a) n-C_3H_7, (b) CH_2=CH, (c) CH_2=C(CH_3)·CH, and (d) CH_2=CH·CH_2 to the analogous

TABLE 2.

Bond split	1–2	2–3	3–4
Radicals analogous to fragments formed	a, b	c, d	a, b
$D + H$ (kcal./mole)	86	50	86

Heats of formation: (a) 22, (b) 64, (c) 20, (d) 30 kcal./mole.

fragments formed on splitting the bonds 1–2, 2–3, 3–4. Table 2 shows the estimated dissociation energies (D) for these bonds (H = heat of formation of polyisoprenoid). About 36 kcal./mole more of energy is required to break bonds 1–2 and 3–4 than 2–3, an estimate in good agreement with previous calculations on the pyrolysis of rubber.[8] The splitting of the polyisoprenoid on pyrolysis into $5n$ (n = integer) carbon-atom mono- (II, III) or bi-radicals (IV) is therefore to be expected. These radicals can readily cyclise to six-membered rings by attack of the radical at a suitably placed double bond to yield *p*-mentha-1,8-diene (V) and 2,4-dimethyl-4-vinylcyclohexene (VI). The latter is less likely to be formed as its formation involves attack at the highly substituted end of a trisubstituted double bond. The two hydrocarbons in cigarette smoke are present in the ratio 36 : 1. Six-centre internal reactions are well known.[9]

EXPERIMENTAL

Unless otherwise stated, all the compounds described are colourless liquids.

Preparative-scale Gas Chromatography.—Samples (0·5—10 ml.) of the hydrocarbons were placed on a 15′ × 1″ column packed with Celite brick-dust (Johns-Manville, 40—60 mesh) coated with 25% (w/w) of a silicone elastomer (E 301, Imperial Chemical Industries), and eluted at 130° with 200—300 ml./min. of nitrogen. Fractions were collected by cooling the effluent to −70°.

Analytical Gas Chromatography.—Nitrogen carrier gas used. Column 1, used for the hydrocarbons and tertiary chlorides, was a 200′ × 0·01″ Nylon capillary coated with squalane and operated at 70°. Column 2, for the tertiary alcohols, was a 100′ × 0·02″ Nylon capillary coated with polybutylene glycol and operated at 65°.

Ethylmethylcyclohexanols.—4-Methylcyclohexanone (42 g., 0·38 mole) was added slowly to an excess (0·57 mole) of ethylmagnesium bromide in ether at 0°, and the solution set aside overnight. Working up of this Grignard reaction mixture in the usual way gave a colourless oil (42 g.) which was fractionally distilled to yield trans-1-*ethyl*-4-*methylcyclohexanol*, b. p. 77°/12 mm., n_D^{20} 1·4592 (Found: C, 75·5; H, 12·7. $C_9H_{18}O$ requires C, 76·0; H, 12·75%), and colourless crystals, m. p. 23°, of cis-1-*ethyl*-4-*methylcyclohexanol*, b. p. 84°/12 mm., n_D^{20} 1·4644 (Found: C, 75·9; H, 12·9%). Similarly, from 3-methylcyclohexanone and ethylmagnesium bromide, was prepared 1-*ethyl*-3-*methylcyclohexanol*, b. p. 80°/15 mm. (Found: C, 76·2; H, 12·7%).

Ethylmethylcyclohexyl Chlorides.—Treatment of *cis*-1-ethyl-4-methylcyclohexanol (1 mol.) with thionyl chloride (1·2 mol.) in pyridine or ether at 20° yielded a chlorosulphite which decomposed on distillation at 120°/12 mm. Gas chromatography showed the distillate to contain 80% of unsaturated hydrocarbon and 20% of epimeric 1-chloro-1-ethyl-4-methylcyclohexanes. A similar result was obtained with *trans*-1-ethyl-4-methylcyclohexanol.

cis-1-Ethyl-4-methylcyclohexanol (0·15 mole) was shaken with concentrated hydrochloric acid (0·45 mole) and the acid layer saturated with anhydrous calcium chloride.[10] After 15 min., the organic layer was separated, cooled in ice, and saturated with dry hydrogen chloride. The

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[7] Trotman-Dickenson, " Gas Kinetics," Butterworths Scientific Publications, London, **1955**, p. 15.

[8] Bolland and Orr, *Trans. Proc. Inst. Rubber Ind.*, 1945, **21**, 133.

[9] Ref. 7, p. 133.

[10] Norris and Olmsted, *Org. Synth.*, 1932, Coll. Vol. 1, 138.

product, quickly washed with ice–water and dried ($CaCl_2$), was separated from residual alcohol by elution with petrol (b. p. 40—60°) from a short column of silica gel. Distillation gave the epimeric 1-chloro-1-ethyl-4-methylcyclohexanes, b. p. 74°/12 mm. (Found: C, 67·4; H, 10·5; Cl, 22·1. Calc. for $C_9H_{17}Cl$: C, 67·3; H, 10·7; Cl, 22·1%). Similarly, *trans*-1-ethyl-4-methylcyclohexanol yielded an identical mixture of these epimeric chlorides, and 1-ethyl-3-methylcyclohexanol gave 1-chloro-1-ethyl-3-methylcyclohexanes, b. p. 80°/12 mm. (Found: C, 67·35; H, 10·7; Cl, 22·0. Calc. for $C_9H_{17}Cl$: C, 67·3; H, 10·7; Cl, 22·1%).

Ethylmethylcyclohexanes.—Dimethylzinc, from methyl iodide (25 g.) and Zn–Cu couple (20 g.),[3] was dissolved in dry toluene (10 ml.) under dry carbon dioxide, and a solution of 1-chloro-1-ethyl-4-methylcyclohexane (18 g.) in dry toluene (20 ml.) was added slowly, the temperature being kept below 5°. The solution was set aside overnight, decomposed with water, acidified with dilute sulphuric acid, and the organic layer washed with aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). The toluene was distilled through a Vigreux column to leave a residue (14·5 g.) which, by preparative-scale gas chromatography, was separated into (i) a mixture of unsaturated hydrocarbons formed by dehydrochlorination of the tertiary chloride, (ii) trans-1-*ethyl*-1,4-*dimethylcyclohexane* (*A*), b. p. 167·7°, n_D^{20} 1·4411 (Found: C, 85·7; H, 14·5. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%), and (iii) cis-1-*ethyl*-1,4-*dimethylcyclohexane* (*B*), b. p. 168·5°, n_D^{20} 1·4398 (Found: C, 85·5; H, 14·4%). Similarly, from 1-chloro-1-ethyl-3-methylcyclohexane and dimethylzinc, were prepared cis-1-*ethyl*-1,3-*dimethylcyclohexane* (*C*), b. p. 166°, n_D^{20} 1·4410 (Found: C, 85·5; H, 14·3%), and trans-1-*ethyl*-1,3-*dimethylcyclohexane* (*D*), b. p. 168·5°, n_D^{20} 1·4425 (Found: C, 85·5; H, 14·4%).

Lebedev's Hydrocarbon.—This was prepared by dimerisation of isoprene, and hydrogenated at room temperature and atmospheric pressure in glacial acetic acid with platinic oxide, to yield a mixture of saturated hydrocarbons (*E*). Gas chromatography showed four components in the proportions 26 : 40 : 15 : 19 with retention volumes identical to those of *A*, *B*, *C*, and *D*, respectively. A mixture of *A*—*D* in these proportions had an infrared spectrum identical with that of *E*. The calculated refractive index (1·4408) of this mixture is in good agreement with the observed value for *E* (1·4405,[2] 1·4411 [1]).

2,4-*Dimethyl*-4-*vinylcyclohexene in Cigarette Smoke.*—A previously described fraction,[11] F.5 (1·7 g.), was chromatographed on the preparative column and the broad, indefinite zone of eluate was collected as five approximately equal fractions. The second and third fractions were combined, dissolved in petrol (5 ml.) (b. p. 30—40°, unsaturate-free) and extracted with 20% aqueous silver nitrate (6 × 5 ml.) to remove substances with *cis*-disubstituted double bonds. The petrol layer was extracted further with a 20% solution of silver nitrate in methanol–water (6 × 5 ml.) (2 : 1) to remove the remaining unsaturated material from aromatic and saturated hydrocarbons. These last extracts were treated with excess of concentrated ammonium hydroxide to yield an oil. On gas chromatography, the major component (*F*, 6 μg./g. of tobacco smoked) of this fraction had the same retention volume as Lebedev's hydrocarbon and a very similar infrared spectrum. Hydrogenation of *F* yielded a mixture of only two saturated hydrocarbons in the ratio 1 : 1 and retention volumes identical with those of *C* and *D*. A mixture of *C* and *D* in this ratio had an infrared spectrum identical with the mixture obtained by hydrogenation of *F*.

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THE UNIVERSITY, EXETER.
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[11] Johnstone, Quan, and Carruthers, *Nature*, 1962, **195**, 1267.