Polycyclic Systems. Part 19.[1] Synthesis of 8-Isobutyl-10-methyl-11*H*-indeno[2,1-*a*]phenanthrene (Second Diels Hydrocarbon), a Minor Dehydrogenation Product of Cholesterol

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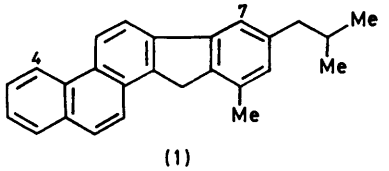
The structure of the second Diels hydrocarbon, a dehydrogenation product of cholesterol, has been confirmed as 8-isobutyl-10-methyl-11*H*-indeno[2,1-*a*]phenanthrene (1) by an unambiguous synthesis. 4-Isobutyl-2-methyl-1-bromobenzene (5) prepared from *m*-acetotoluidide was converted by a series of standard reactions into 2,4-dimethyl-6-isobutylindan-1-one (10) which on condensation with 2-(1-naphthyl)ethylmagnesium bromide followed by cyclisation and dehydrogenation afforded the desired hydrocarbon (1), identical with the second Diels hydrocarbon in all respects.

THE structure of the second Diels hydrocarbon, $C_{26}H_{24}$, first isolated from the dehydrogenation products of cholesterol [2] as a minor component, was the subject of controversy for a long period.[3-6] Recently, the structure was accepted to be 8-isobutyl-10-methyl-11*H*-indeno[2,1-*a*]phenanthrene (1), mainly on the basis of n.m.r. studies.[7] In view of a recent synthetic report of a somewhat contrary nature,[8] we thought it desirable to confirm the structure by a rational synthesis.

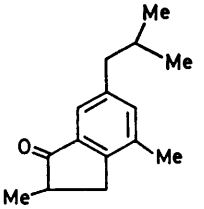
RESULTS AND DISCUSSION

The key intermediate in the synthesis was 2,4-dimethyl-6-isobutylindan-1-one (10) which was prepared as follows. *m*-Acetotoluidide was brominated and hydrolysed to 4-bromo-3-methylaniline (2).[9] The latter on Sandmeyer reaction with cuprous cyanide afforded 4-bromo-3-methylbenzonitrile (3) contaminated with a little of 2,4-dibromo-5-methylbenzonitrile which was readily removed by distillation and crystallisation. The bromonitrile (3) on treatment with isopropylmagnesium bromide [10] furnished 4-bromo-3-methyl-1-phenyl isopropyl ketone (4), easily convertible into 4-isobutyl-2-methyl-1-bromobenzene (5) by Clemmensen reduction. An alternative synthesis of the bromo-compound (5) was effected from *o*-cresol by acylation with isobutyryl chloride, Clemmensen reduction of the resultant ketone (6), and replacement of the phenolic OH by Br using triphenylphosphine and bromine.[11] The last reaction gave the desired bromide in extremely poor yield (*ca.* 10—15%) which appears to be characteristic of *o*-alkylated phenols.[12] Nevertheless, its identity with the bromide described above (superimposable i.r. and n.m.r. spectra) dispelled any doubt regarding the orientation of the bromine atom in the latter. Moreover, 4-bromo-3-methylbenzonitrile (3) and 2,4-dibromo-5-methylbenzonitrile were hydrolysed into the known 4-bromo-3-methylbenzoic acid,[13] and 2,4-dibromo-5-methylbenzoic acid [14] respectively, prepared by entirely different methods.

The structure of the bromo-compound (5) being thus assured, it was converted into 4-isobutyl-2-methylbenzaldehyde (7) through Grignard reaction with ethyl orthoformate,[15] and thence into the corresponding benzyl alcohol and benzyl bromide (8). Condensation of the latter with diethyl malonate, followed by methylation, hydrolysis, and decarboxylation afforded 3-(4-isobutyl-2-methyl-1-phenyl)-2-methylpropionic acid (9). Cyclisation of this with polyphosphoric acid, or of the derived acid chloride with stannic chloride, furnished 2,4-dimethyl-6-isobutylindan-1-one (10). The structure of the ketone was confirmed by the n.m.r. spectrum with the



(1)



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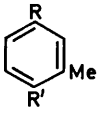

(2) R = NH_2, R' = Br
(3) R = CN, R' = Br
(4) R = CO·$CHMe_2$, R' = Br
(5) R = CH_2·$CHMe_2$, R' = Br
(6) R = CO·$CHMe_2$, R' = OH
(7) R = CH_2·$CHMe_2$, R' = CHO
(8) R = CH_2·$CHMe_2$, R' = CH_2Br
(9) R = CH_2·$CHMe_2$, R' = CH_2·CHMe·CO_2H

two aromatic protons appearing as two singlets at δ 7.33 and 7.13 (7-H and 5-H, respectively). Finally, 2-(1-naphthyl)ethylmagnesium bromide was allowed to react with the ketone (10), the resultant alcohol cyclised with polyphosphoric acid, and the product dehydrogenated with selenium to give 8-isobutyl-10-methyl-11*H*-indeno[2,1-*a*]phenanthrene (1), m.p. 225—226 °C, identical in all respects with the second Diels hydrocarbon.

4-Isobutyl-2-methylbenzaldehyde (7) was found to resemble a compound described by Rao *et al.*[8] as 2-isobutyl-4-methylbenzaldehyde (identical semicarbazone and dinitrophenylhydrazone), and used for the synthesis

of an 11-oxoindenophenanthrene supposedly identical with the ketone derived from natural Diels hydrocarbon. The structure (7) for this aldehyde seems more likely from its method of preparation, which consists of a Friedel–Crafts reaction of 3-isobutyltoluene with chloromethyl methyl ether, and Sommelet reaction of the resultant benzyl chloride. The chloromethyl group is expected to take up the position next to methyl rather than next to isobutyl in the benzene ring, which means that these two groups are interchanged in all subsequent products described by these workers.[8] This probably explains the non-identity of their final ketone, m.p. 192—193 °C with 7-isobutyl-9-methyl-11-oxoindeno[2,1-*a*]-phenanthrene, m.p. 187 °C, which we had synthesised earlier.[6]

EXPERIMENTAL

^{1}H N.m.r. spectra were taken with a Varian EM-390 90-MHz spectrometer for solutions in [^{2}H]chloroform unless otherwise stated. Chemical shifts (p.p.m.) are reported relative to tetramethylsilane as internal standard. Petroleum refers to the fraction of b.p. 40—60 °C. The m.p.s are all corrected. Organic extracts were dried over sodium sulphate. The homogeneity of compounds were checked by t.l.c. on silica gel, and in a few cases by g.l.c.

4-Bromo-3-methylaniline (2).—4-Bromo-3-methylaniline was prepared by bromination of *m*-acetotoluidide and subsequent hydrolysis of the recrystallised bromo-acetotoluidide, m.p. 79—81 °C (lit.,[9] m.p. 81—81.5 °C).

4-Bromo-3-methylbenzonitrile (3).—The above bromoaniline (30.0 g) was dissolved in aqueous hydrochloric acid (150 ml, 1 : 1), cooled to 0 °C, and diazotised with a solution of sodium nitrite (11.0 g) in water (30 ml). The excess of acid was neutralised by cautious addition of solid sodium carbonate. Meanwhile an aqueous solution of cuprous cyanide was prepared from copper sulphate (50.0 g) according to the standard procedure.[16] The neutralised diazotised solution was slowly added to this in the cold with vigorous stirring. The temperature was kept at 0—5 °C for 30 min, then brought to ambient, and finally the reaction was warmed to 50 °C on a water-bath. The separated oil was taken up in benzene and the benzene solution steam-distilled. *4-Bromo-3-methylbenzonitrile* (3) was obtained from the distillate as a crystalline solid (14.3 g, 45%), b.p. 100 °C at 0.5 mmHg, m.p. 55 °C (from petroleum) (Found: C, 48.6; H, 3.3; N, 7.3. C_8H_6BrN requires C, 49.0; H, 3.1; N, 7.1%); $\nu_{max.}$(KBr) 2 240 cm^{-1} (CN); δ 7.70 (1 H, d, *J* 9 Hz, 6-H), 7.53 (1 H, s, 2-H), 7.37 (1 H, d, *J* 9 Hz, 5-H), and 2.47 (3 H, s, 3-Me).

The high-boiling fraction, b.p. 140—145 °C at 0.5 mmHg (1.0 g), m.p. 140 °C (from petroleum) was found to be *2,4-dibromo-5-methylbenzonitrile* (Found: C, 35.3; H, 1.8; N, 5.1; Br, 57.5. $C_8H_5Br_2N$ requires C, 34.9; H, 1.8; N, 5.1; Br, 58.2%); $\nu_{max.}$(KBr) 2 240 cm^{-1}; δ 7.90 (1 H, s, Ar*H*), 7.53 (1 H, s, Ar*H*), and 2.40 (3 H, s, Me). The monobromo- and dibromo-nitriles were hydrolysed by ethanolic sodium hydroxide to furnish 4-bromo-3-methylbenzoic acid, m.p. 208 °C (lit.[13] m.p. 209 °C) and 2,4-dibromo-5-methylbenzoic acid, m.p. 184 °C (lit.,[14] 185 °C) respectively.

4-Bromo-3-methylphenyl Isopropyl Ketone (4).—To a Grignard solution prepared from isopropyl bromide (22.1 g, 0.16 mol), magnesium (4.32 g, 0.18 mol), and ether (100 ml), was added 4-bromo-3-methylbenzonitrile (15.0 g, 0.075 mol) in ether (60 ml) with stirring over a period of 1 h. The mixture was refluxed for 10 h, ether was distilled out, and the residual semi-solid mass decomposed with ice and 4N sulphuric acid. The resultant ketimine was hydrolysed by heating the solution in a water-bath for 1 h. The product, on the usual work-up, afforded *4-bromo-3-methylphenyl isopropyl ketone* (4) as a colourless oil (15.2 g, 82.5%); b.p. 140 °C at 1 mmHg (Found: C, 54.6; H, 5.5. $C_{11}H_{13}BrO$ requires C, 54.8; H, 5.4%); $\nu_{max.}$($CHCl_3$) 1 678 cm^{-1}; δ 7.83 (1 H, s, 2-H), 7.63 (2 H, s, 5-H + 6-H), 3.50 (1 H, m, C*H*Me$_2$), 2.47 (3 H, s, 3-Me), and 1.20 (6 H, d, *J* 7 Hz, CH*Me*$_2$); the *dinitrophenylhydrazone* had m.p. 152 °C (Found: C, 48.3; H, 4.2; N, 13.5. $C_{17}H_{17}BrN_4O_4$ requires C, 48.5; H, 4.0; N, 13.3%).

4-Isobutyl-2-methyl-1-bromobenzene (5).—The foregoing ketone (14.0 g), amalgamated zinc (140.0 g), concentrated hydrochloric acid (120 ml), and water (120 ml) were refluxed for 28 h with occasional addition of hydrochloric acid. *4-Isobutyl-2-methyl-1-bromobenzene* (5) was obtained as a colourless oil (8.7 g, 65%); b.p. 100 °C at 1 mmHg; n_D^{32} 1.5391; d^{32} 1.2374 g cm^{-3} (Found: C, 58.0; H, 6.9%; *m/e* 226, 228. $C_{11}H_{15}Br$ requires C, 58.15; H, 6.6%; *M*, 227); δ 7.40 (1 H, d, *J* 8 Hz, Ar-H), 7.00 (1 H, s, Ar-H), 6.90 (1 H, d, *J* 8 Hz, Ar-H), 2.45 (2 H, d, *J* 7 Hz, 4-CH$_2$), 2.40 (3 H, s, 2-Me), 1.90 (1 H, m, C*H*Me), and 0.92 (6 H, d, *J* 7 Hz, CH*Me*$_2$). The i.r. showed no carbonyl absorption.

4-Isobutyryl-2-methylphenol (6).—Isobutyryl chloride (20.0 g, 0.18 mol) was condensed with *o*-cresol (18.36 g, 0.17 mol) in the presence of anhydrous aluminium chloride (50.0 g, 0.37 mol) in nitrobenzene (150 ml) at 5—10 °C according to the usual procedure.[17] After decomposition with ice and hydrochloric acid, the nitrobenzene layer was separated and extracted repeatedly with aqueous 10% sodium hydroxide. *4-Isobutyryl-2-methylphenol* (6) was obtained, by acidification of the alkaline solution, as a crystalline solid (30.0 g, 99%); m.p. 124—125 °C (ethanol) (Found: C, 74.2; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.2; H, 7.9%); δ (60 MHz) 7.82 (1 H, s, 3-H), 7.72 (1 H, d, *J* 8 Hz, 5-H), 7.20 (1 H, s, 1-OH, exchangeable with D_2O), 6.90 (1 H, d, *J* 8 Hz, 6-H), 3.57 (1 H, m, *J* 7 Hz, C*H*Me$_2$), 2.32 (3 H, s, 2-Me), and 1.21 (6 H, d, *J* 7 Hz, CH*Me*$_2$); the *dinitrophenylhydrazone* had m.p. 115—117 °C (from methanol) (Found: N, 15.8. $C_{17}H_{18}N_4O_5$ requires N, 15.6%).

4-Isobutyl-2-methylphenol.—The foregoing phenolic ketone (10.0 g) was reduced by heating with amalgamated zinc (85.0 g) in concentrated hydrochloric acid (75 ml) and water (75 ml) for 25 h. The product, on the usual work-up, afforded *4-isobutyl-2-methylphenol* (6.0 g, 65%), b.p. 115 °C at 1 mmHg (Found: C, 80.2; H, 10.0. $C_{11}H_{16}O$ requires C, 80.5; H, 9.8%). The i.r. spectrum showed no carbonyl absorption.

4-Isobutyl-2-methyl-1-bromobenzene (5).—The above phenol (10.0 g, 0.06 mol) was heated with the complex prepared from triphenylphosphine (26.0 g, 0.09 mol) and bromine (16.0 g) in acetonitrile (25 ml) following the method of Schaefer and Higgins.[11] In spite of repeated efforts, the yield never exceeded 15% [reported yields are 72 (ref. 11) and 10% (ref. 12)]. The bromide had b.p. 100—102 °C at 1 mmHg, and superimposable i.r. and n.m.r. spectra with the specimen described earlier.

4-Isobutyl-2-methylbenzaldehyde (7).—To the Grignard reagent prepared from 4-isobutyl-2-methyl-1-bromobenzene (8.5 g, 0.037 mol), ethyl iodide (2.0 g), magnesium (1.4 g, 0.058 mol), and ether (80 ml) was added ethyl orthoformate (9.06 g, 0.061 mol). The mixture was refluxed for 5 h and

ether removed as far as possible. Towards the end, a vigorous reaction set in which subsided on cooling. The product was decomposed with 5N hydrochloric acid (40 ml), heated under nitrogen for 30 min in a water-bath, and the organic matter steam-distilled in a current of nitrogen. Extraction with ether and removal of solvent furnished an oil, which was converted into the sodium bisulphite adduct. The latter was decomposed with acid and 4-*isobutyl*-2-*methylbenzaldehyde* (7) was obtained as an oil (2.5 g, 38%), b.p. 90—92 °C at 0.2 mmHg (Found: C, 81.7; H, 9.4. $C_{12}H_{16}O$ requires C, 81.8; H, 9.1%); δ 10.28 (1 H, s, C*H*O), 7.75 (1 H, dd, *J* 2 and 7 Hz, 6-H), 7.30—7.00 (2 H, m, Ar-H), 2.67 (3 H, s, 2-Me), 2.48 (2 H, d, *J* 7 Hz, 4-CH_2), 1.90 (1 H, m, C*H*Me_2), and 0.90 (6 H, d, *J* 7 Hz, CH*Me*$_2$). It formed a *semicarbazone*, m.p. 212 °C (ethanol) (Found: C, 66.7; H, 8.2; N, 17.8. $C_{13}H_{19}N_3O$ requires C, 66.95; H, 8.15; N, 18.0%) and a *dinitrophenylhydrazone*, m.p. 168 °C (acetic acid) (Found: C, 60.5; H, 5.8; N, 15.4. $C_{18}H_{20}N_4O_4$ requires C, 60.7; H, 5.6; N, 15.7%). The reported m.p.s of the derivatives of an aldehyde [8] (supposed to be 2-isobutyl-4-methylbenzaldehyde) are 211 and 168 °C, respectively; the mixed m.p. of the semicarbazones was not depressed.

4-*Isobutyl*-2-*methylbenzyl Bromide* (8).—The preceding aldehyde (2.5 g) was reduced with an ethereal solution of lithium aluminium hydride to give 4-*isobutyl*-2-*methylbenzyl alcohol* (2.2 g, 87%), b.p. 105 °C at 0.5 mmHg (Found: C, 88.9; H, 10.5. $C_{12}H_{18}O$ requires C, 88.9; H, 10.1%). This was treated with phosphorus tribromide (2.0 g) in carbon tetrachloride (10 ml) at 60 °C for 1 h. 4-*Isobutyl*-2-*methylbenzyl bromide* (8) was obtained as a heavy oil (2.75 g, 92.3%), b.p. 94—96 °C at 0.2 mmHg (Found: C, 59.4; H, 7.3. $C_{12}H_{17}Br$ requires C, 59.75; H, 7.05%).

3-(4-*Isobutyl*-2-*methyl*-1-*phenyl*)-2-*methylpropionic Acid* (9).—The above bromide (2.7 g) was condensed with diethyl malonate in the presence of sodium ethoxide in ethanol to give diethyl 4-isobutyl-2-methylbenzylmalonate (3.0 g, 82%), b.p. 168—170 °C at 0.6 mmHg. This was methylated in the usual way with methyl iodide and sodium ethoxide and the crude product was directly hydrolysed by alkali to furnish the malonic acid as a semisolid mass, which was decarboxylated by heating at 180—185 °C for 1 h under nitrogen. 3-(4-*Isobutyl*-2-*methyl*-1-*phenyl*)-2-*methylpropionic acid* (9) thus obtained was distilled to give a viscous oil (1.63 g), b.p. 140 °C at 0.1 mmHg (Found: C, 77.0; H, 9.3; equiv., 235. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.4%; equiv., 234).

2,4-*Dimethyl*-6-*isobutylindan*-1-*one* (10).—(*a*) The foregoing acid (1.50 g, 6 mmol) in benzene (30 ml) was treated with phosphorus pentachloride (1.5 g) at room temperature for 1 h. To it was added dropwise a solution of stannic chloride (2.4 ml) in benzene (6 ml) at 5—10 °C. Stirring was continued for 1 h at room temperature and for 1 h at 45 °C, after which it was decomposed with ice and hydrochloric acid and the product worked-up in the usual way. The neutral organic matter was chromatographed through an alumina column using petroleum–benzene as eluant, to give 2,4-*dimethyl*-6-*isobutylindan*-1-*one* (10) as a gum, which was sublimed at 150—160 °C and 0.01 mmHg to give a colourless oil (0.9 g, 60%) (Found: C, 83.0; H, 9.5. $C_{15}H_{20}O$ requires C, 83.3; H, 9.3%); $\nu_{max.}$ (Nujol) 1 698 cm^{-1}; δ(CCl_4) 7.33 (1 H, s, 7-H), 7.13 (1 H, s, 5-H), 3.20 (1 H, m, 2-H), 2.45 (4 H, m, 3-H_2 + 6-CH_2), 2.27 (3 H, s, 4-Me), 1.85 (1 H, m, C*H*Me_2), 1.23 (3 H, d, *J* 8 Hz, 2-Me), and 0.91 (6 H, d, *J* 7 Hz, CH*Me*$_2$). The ketone afforded a red *dinitrophenylhydrazone*, m.p. 232 °C (from methanol–benzene) (Found: C, 63.4; H, 6.4; N, 14.5. $C_{21}H_{24}N_4O_4$ requires C, 63.6; H, 6.1; N, 14.1%).

(*b*) The acid (9) (0.1 g) was heated with polyphosphoric acid (4.0 g) at 100 °C for 1 h. The product was worked-up as usual and the ketone purified by chromatography over an alumina column. The oil (0.7 g) afforded a dinitrophenylhydrazone, m.p. 232 °C, identical with that in (*a*).

8-*Isobutyl*-10-*methyl*-11H-*indeno*[2,1-a]*phenanthrene* (1).—The preceding ketone (0.35 g) in benzene (10 ml) was treated with an excess of Grignard reagent prepared from 2-(1-naphthyl)ethyl bromide, magnesium, and ether. The resultant alcohol, without further purification, was heated with polyphosphoric acid (4.0 g) at 100—120 °C for 3 h. The product, on the usual work-up and distillation, afforded a semi-solid mass (0.72 g), b.p. 215—220 °C at 0.2 mmHg. This was intimately mixed with selenium powder (1.5 g) and heated in a metal-bath at 300—320 °C for 10 h. The dark solid was powdered, taken up in hot benzene, and the mixture passed through a column of neutral alumina using petroleum as eluant. 8-*Isobutyl*-10-*methyl*-11H-*indeno*-[2,1-a]*phenanthrene* (1) was obtained as a white solid, which crystallised from benzene–petroleum as colourless plates (110 mg), m.p. 226 °C (Found: C, 92.7; H, 7.3. Calc. for $C_{26}H_{24}$: C, 92.9; H, 7.1%). The i.r., u.v., and n.m.r. spectra of this hydrocarbon were identical with those of the second Diels hydrocarbon isolated from cholesterol.[6,7] It afforded an 11-oxo-derivative, m.p. 194 °C (Found: C, 89.1; H, 6.5. Calc. for $C_{26}H_{22}O$: C, 89.1; H, 6.3%) and a trinitrofluorenone complex,[18] m.p. 203 °C (Found: N, 6.4. Calc. for $C_{26}H_{24}{\cdot}C_{13}H_5N_3O_7$: N, 6.3%). The m.p.s of the second Diels hydrocarbon and its derivatives are 226, 194, and 202—203 °C respectively,[6] and no depression was observed in the mixed m.p.s.

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