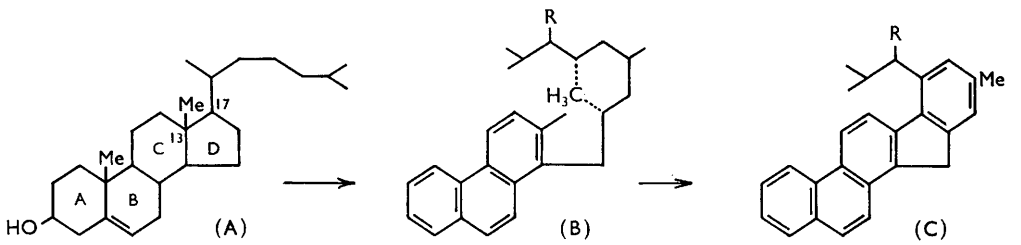
824. *Polycyclic Systems. Part X.*[1] *Structure of the* C_{26} *Hydrocarbon from Cholesterol: a Synthesis of 4′-Isobutyl-6′-methylindeno(2′,3′:1,2)-phenanthrene.*

By D. Nasipuri.

4′-Isobutyl-6′-methylindeno(2′,3′:1,2)phenanthrene has been synthesised. It differs from a hydrocarbon, $C_{26}H_{24}$ (or $C_{25}H_{22}$), which was isolated as a minor product on dehydrogenation of cholesterol and related compounds and to which this formulation was ascribed.

Cholesterol or cholesteryl chloride on dehydrogenation with selenium [2] afforded a number of hydrocarbons of which two are of particular importance. One, commonly known as the Diels hydrocarbon, is 3′-methyl-1,2-cyclopentenophenanthrene,[3] but the other,[4] of molecular formula $C_{26}H_{24}$ (or $C_{25}H_{22}$), m. p. 225—226°, has been the subject of much discussion [5] and is not still conclusively identified. Of the various plausible mechanisms of the formation of indeno(2′,3′:1,2)phenanthrene derivatives from the steroids, *e.g.*, $C_{26}H_{24}$ from cholesterol, $C_{27}H_{26}$ from ergosterol,[6] and $C_{28}H_{28}$ from phytosterols,[7] that involving initial fission of the steroid ring D followed by cyclisation of the side chain to give a new five-membered ring (A ⟶ C) (see also the formation of chrysene from cholic

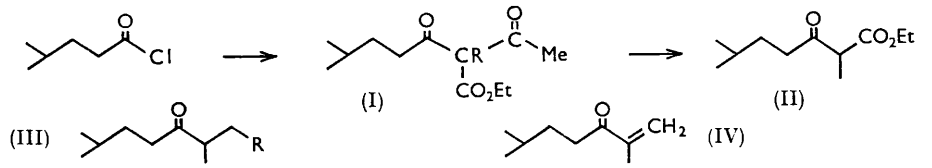


acid [8]) seems attractive. This implies structure (C; R = H) for the hydrocarbon from cholesterol and (C; R = Me or Et) for those from ergosterol and phytosterols respectively.[9] These structures, however, have not been confirmed by synthesis. In the previous paper,[1] we described a new unambiguous synthesis of indeno(2′,3′:1,2)phenanthrene. We now report the synthesis of its derivative (C; R = H) by that route. The synthetic hydrocarbon differs from that obtained from cholesterol.

The requisite Mannich base (III; R = piperidino) for the present synthesis was prepared from the keto-ester (II) by Mannich and Curtaz's procedure.[10] This ester was obtained from isohexanoyl chloride (*a*) by condensation with ethyl sodioacetoacetate followed by methylation of the resultant dioxo-ester (I; R = H), or (*b*) by condensation with ethyl α-methylacetoacetate and ammonolysis of the product (I; R = Me). The structure of the amino-ketone (III; R = piperidino) was confirmed by conversion into the keto-acid (III; R = $CH_2 \cdot CO_2H$) and comparison of the latter with a specimen prepared from the keto-ester (II) by treatment with ethyl β-bromopropionate and hydrolysis.

[1] Part IX, *J.*, 1961, 3361.
[2] Diels, Gädke, and Körding, *Annalen*, 1927, **459**, 1; Diels, *Ber.*, 1933, **66**, 487, 1122.
[3] Bergmann and Hillemann, *Ber.*, 1933, **66**, 1302; Harper, Kon, and Ruzicka, *J.*, 1934, 124.
[4] Cook, Hewett, Mayneord, and Roe, *Chem. and Ind.*, 1934, **53**, 569.
[5] Rosenheim and King, *Chem. and Ind.*, 1933, **52**, 299; Cook, Hewett, Mayneord, and Roe, *J.*, 1934, 1727; Bernal and Crowfoot, *J.*, 1935, 93.
[6] Diels and Karstens, *Annalen*, 1930, **478**, 129; Ruzicka, Goldberg, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 812; Diels and Stephan, *Annalen*, 1937, **527**, 279; and also ref. 7.
[7] Ruzicka and Goldberg, *Helv. Chim. Acta*, 1937, **20**, 1245.
[8] Raudnitz, Petru, and Stadler, *Ber.*, 1933, **66**, 879; Cook and Hewett, *J.*, 1933, 1098; see also ref. 1 and Ruzicka, Thomann, Brandenberger, Furter, and Goldberg, *Helv. Chim. Acta*, 1934, **17**, 200.
[9] Bergmann, *J. Amer. Chem. Soc.*, 1938, **60**, 2306
[10] Mannich and Curtaz, *Arch. Pharm.*, 1926, **264**, 741.

The methiodide of the amino-ketone was next condensed with potassio-derivative of the β-oxo-ester [1] (V), affording the dioxo-ester (VI; R = $\cdot CO_2Me$) in about 50% yield,



and, a by-product, whose dinitrophenylhydrazone gave correct analyses for the diketone (VI; R = H) and which was converted into the ketone (VII) by acid. The total product was, therefore, heated with acetic acid and concentrated hydrochloric acid under carbon

FIG. 1.

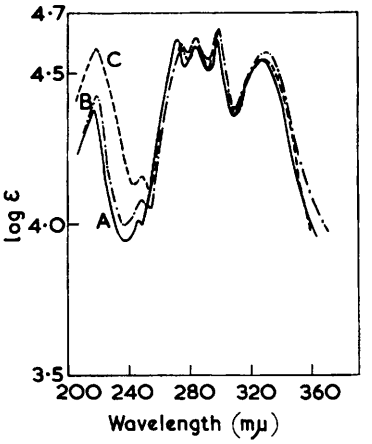
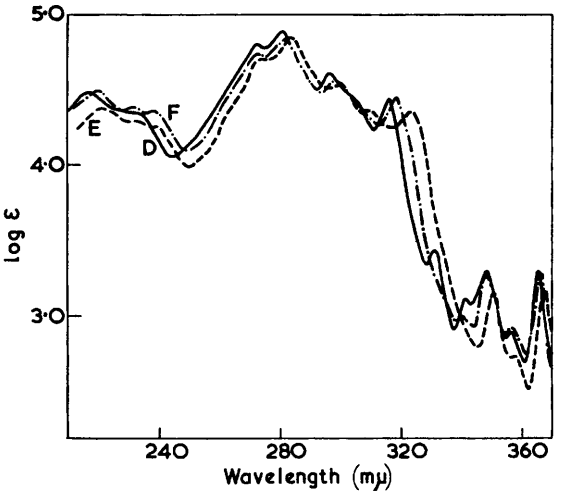
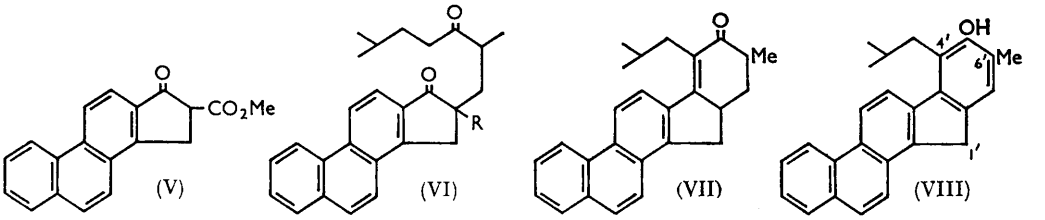


FIG. 2.



Absorption spectra of indeno(2′,3′:1,2)phenanthrenes: (A) 5′,6′,7′,7′a-*tetrahydro-5′-oxo-*; (B) 4′-*methyl derivative of* (A); (C) 4′-*isobutyl-6′-methyl derivative of* (A), i.e., (VII); (D) *indeno(2′,3′:1,2)phenanthrene*; (E) 4′-*isobutyl-6′-methyl derivative of* (D); (F) *Diel's hydrocarbon*, $C_{26}H_{24}$, *from cholesterol.*

dioxide,[11] the unsaturated ketone (VII) was then isolated in about 60% yield. Its infrared absorption spectrum is consistent with structure (VII); the ultraviolet absorption curves of this and two related ketones [1] are shown in Fig. 1. When during the hydrolysis air



was not fully excluded, *ca.* 10% of a phenolic compound (VIII), m. p. 231°, was isolated along with the ketone (VII); this compound gave an acetate, had infrared absorption due to an unassociated hydroxyl group, and was recovered unchanged on treatment with lithium aluminium hydride and subsequent dehydrogenation.

The ketone (VII) was reduced by lithium aluminium hydride and the crude alcohol dehydrogenated with 30% palladium–charcoal [12] at 300—320°. The product (C; R = H),

[11] Wilds and Werth, *J. Org. Chem.*, 1952, **17**, 1149.
[12] Linstead and Thomas, *J.*, 1940, 1127.

when purified, had m. p. 212·5° and ultraviolet absorption (Fig. 2) resembling that of the indenophenanthrene system (cf. Cook *et al.*[5]) with the characteristic slight bathochromic shift of the parent spectrum observed throughout. It gave a 2,4,7-trinitrofluorenone complex, m. p. 214—215°, and a 1′-ketone, m. p. 187°. The melting point of the hydrocarbon could not be raised further by repeated chromatography over alumina. It depressed the melting point of the Diels hydrocarbon from cholesterol, and similar depressions were observed with the derivatives. The synthetic hydrocarbon thus differs from the Diels hydrocarbon, m. p. 226° (ketone, m. p. 194°; trinitrofluorenone complex, m. p. 202—203°). The ultraviolet absorption spectra of the two (Fig. 2) are similar in the region 220—300 mμ., but different in the region 310—340 mμ. It should be noted that the elemental analysis of Diels hydrocarbon, isolated by us on dehydrogenation of cholesterol corresponds more closely to the molecular formula, $C_{25}H_{22}$.

Experimental

M. p.s are corrected. Ultraviolet absorption spectra were recorded for ethanolic solutions on a Beckmann spectrophotometer, unless otherwise stated.

Ethyl 2,6-*Dimethyl*-3-*oxoheptanoate* (II).—(*a*) A solution of isohexanoyl chloride, b. p. 142° (40 g.), in ether (100 ml.) was added gradually with stirring to a cooled suspension of ethyl sodioacetoacetate (from sodium, 7·2 g.); ethyl acetoacetate, 40 ml.) in ether (400 ml.). The mixture was left overnight at the room temperature, then refluxed for 30 min., cooled, and decomposed with an excess of cold dilute sulphuric acid. The aqueous layer was extracted once with ether. The combined ethereal solutions were washed with water, dried (Na_2SO_4), and evaporated, and the residue distilled, to yield *ethyl* 7-*methyl*-2,4-*dioxo-octane*-3-*carboxylate* (I; R = H) (46 g.), b. p. 95—100°/1·5 mm. A middle fraction was analysed (Found: C, 63·2; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

This product (45 g.) was added to a cooled solution of sodium (4·6 g.) in absolute ethanol (100 ml.) and was refluxed with an excess of methyl iodide for 10 hr. Most of the alcohol was then removed at the water-pump and the residue diluted with water and thoroughly extracted with ether. The ethereal extracts were washed with dilute sodium hydroxide solution, then with water, and dried ($MgSO_4$), and the ether was removed. The residue yielded *ethyl* 2,6-*dimethyl*-3-*oxoheptanoate* (II) (17 g.), b. p. 90—92°/5 mm. (Found: C, 66·1; H, 10·2. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%), n_D^{30} 1·4283.

(*b*) A solution of isohexanoyl chloride (47 g.) in ether (100 ml.) was added to a cooled suspension of sodio-derivative from sodium (8 g.), ethyl α-methylacetoacetate [13] (50 g.), and ether (450 ml.). After the initial reaction at the room temperature (12 hr.), the mixture was refluxed for 1 hr., and the product worked up as usual, to give *ethyl* 3,7-*dimethyl*-2,4-*dioxo-octane*-3-*carboxylate* (I; R = Me) (63 g.), b. p. 110—115°/5 mm. (Found: C, 64·7; H, 9·3. $C_{13}H_{22}O_4$ requires C, 64·5; H, 9·1%).

This ester (60 g.), in dry ether (100 ml.), was cooled in a freezing mixture while a rapid stream of dry ammonia was passed into it. After 1 hr., the solution was left overnight. It was then repeatedly shaken with cold 3N-hydrochloric acid, the ethereal layer separated, and the acid layer was extracted thrice with ether (100 ml.). The combined ether extracts were washed with water, dried (Na_2SO_4), and evaporated. The ester was obtained (30 g.), with b. p. 85—90°/5 mm., n_D^{31} 1·4281 (Found: C, 59·8; H, 10·0%). It showed an intense ferric reaction.

2,6-*Dimethyl*-1-*piperidinoheptan*-3-*one* (III; R = NC_5H_{10}).—The ester (II) (20 g.) was shaken with a solution of potassium hydroxide (6·5 g.) in water (250 ml.) at 0° for 48 hr. Some neutral matter separated and was removed in ether. To the cold alkaline solution, piperidine hydrochloride (12·2 g.) was added. The solution was kept acidic to Methyl Red by gradual addition of concentrated hydrochloric acid. 40% Formaldehyde solution (10 ml.) was next added and the mixture stirred in the cold with occasional addition of concentrated hydrochloric acid, then left overnight at 0°. The acidic solution was once extracted with ether and then basified with concentrated potassium hydroxide solution. The liberated *amino-ketone* was extracted with ether, dried (K_2CO_3), and distilled. 2,6-*Dimethyl*-1-*piperidinoheptan*-3-*one* (III;

[13] Cardwell, *J.*, 1949, 715.

R = ·NC_5H_{10}) was obtained as an oil (11·2 g., 50%) at b. p. 103—105°/2 mm. (Found: C, 74·6; H, 11·8; N, 6·8. $C_{14}H_{27}NO$ requires C, 74·7; H, 12·0; N, 6·2); it had n_D^{30} 1·4580.

4,8-*Dimethyl-5-oxononanoic Acid* (III; R = CH_2·CO_2H).—(*a*) The above amino-ketone (5 g.) was kept in with methyl iodide (1·5 ml.) at 0° for 1 hr. and then at the room temperature for 6 hr. The gummy methiodide was once washed with dry ether, then dissolved in dry methanol (15 ml.), added to a solution of ethyl sodiomalonate (from diethyl malonate, 4 ml., sodium, 0·6 g., and ethanol, 15 ml.), and heated under reflux for 4 hr. The product was worked up in the usual way, and organic matter taken up in ether, and finally distilled, to give ethyl 3,7-dimethyl-4-oxo-octane-1,1-dicarboxylate (3 g.), b. p. 180°/12 mm. This was boiled with concentrated hydrochloric acid (10 ml.) for 10 hr. The acid (III; R = CH_2·CO_2H) was obtained as a gum (1·2 g.), b. p. 140—150°/5 mm. Its *semicarbazone* (from ethanol) had m. p. 146° (Found: C, 56·05; H, 9·0; N, 16·3. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 8·95; N, 16·3%).

(*b*) The ester (II) (5 g.) was heated with ethyl β-bromopropionate (5 g.) and ethanolic sodium ethoxide (sodium, 0·6 g.; ethanol, 20 ml.). The product (4·8 g.), b. p. 180—185°/10 mm., was hydrolysed with concentrated hydrochloric acid as before and the acid (III; R = CH_2·CO_2H) was obtained as a gum (2 g.), b. p. 150°/3—4 mm. (semicarbazone, m. p. and mixed m. p. 146° (Found: C, 56·3; H, 9·0; N, 16·4%)].

(*c*) An ethanolic solution of the unsaturated ketone (IV) (see below) was condensed with diethyl malonate in presence of a trace of sodium ethoxide; the product, b. p. 180°/12 mm., on hydrolysis with concentrated hydrochloric acid afforded the same acid [semicarbazone, m. p. and mixed m. p. 146° (Found: N, 16·4%)].

Methyl 4′-(2,6-*Dimethyl*-3-*oxoheptyl*)-3′-*oxo*-1,2-*cyclopentenophenanthrene* 4′-*carboxylate* (VI; R = CO_2Me).—Methyl β-(2-methoxycarbonyl-1-phenanthryl)propionate [1] (6·3 g.), finely divided potassium (0·85 g.), dry thiophen-free benzene (50 ml.), and two drops of absolute methanol were refluxed for 4 hr. Meanwhile, 2,6-dimethyl-1-piperidinoheptan-3-one (III) (10 g.) was converted into the methiodide by treatment with methyl iodide (3·5 ml.), first in the cold for 1 hr. and then at the room temperature for 4—5 hr. The semisolid methiodide was once washed with dry ether, dissolved in absolute methanol (30 ml.), and added dropwise to the cooled mixture of the above product, with shaking. The whole was left at room temperature overnight, then refluxed for 1 hr., treated with cold dilute sulphuric acid, and extracted with benzene. After washing of the benzene extract with dilute acid, dilute alkali, and water, the solvent was removed and the residue distilled at oil-pump vacuum up to a temperature of 100° to separate a low-boiling fraction (3·5 g.), b. p. 60—80°/10 mm., which was identified as 2,6-dimethylhept-1-en-3-one (IV) by formation of a red *dinitrophenylhydrazone*, m. p. 112° (Found: C, 56·0; H, 6·4; N, 18·0. $C_{15}H_{20}N_4O_4$ requires C, 56·25; H, 6·25; N, 17·5%). This ketone converted into the acid (III; R = CH_2·CO_2H).

The residual gum (7·3 g.) was separated by chromatography over alumina in benzene–light petroleum (b. p. 60—80°) into two fractions: Fraction A (4·1 g., 50%), m. p. 100—110°, crystallised from ethyl acetate in needles, m. p. 115° and was the *dioxo-ester* (VI; R = CO_2Me) (Found: C, 78·0; H, 6·85. $C_{28}H_{30}O_4$ requires C, 78·1; H, 7·0%). Fraction B (0·8 g.), m. p. 110—120°, crystallised from ethyl acetate as plates, m. p. 128°, of the *diketone* (VI; R = H) (Found: C, 83·85; H, 7·7. $C_{26}H_{28}O_2$ requires C, 83·9; H, 7·5%). Since both the fractions yielded the same unsaturated ketone (VII) on acid cyclisation, they were not separated in later experiments.

5′,6′,7′,7′a-*Tetrahydro*-4′-*isobutyl*-6′-*methyl*-5′-*oxoindeno*(2′,3′:1,2)*phenanthrene* (VII).—(*a*) The dioxo-ester (VI; R = CO_2Me) (4 g.) was refluxed with acetic acid (100 ml.), concentrated hydrochloric acid (50 ml.), and water (5 ml.) under carbon dioxide for 20 hr. On cooling, the solution deposited crystals, m. p. 155—170°, which were collected, passed in a solvent through alumina, and crystallised from benzene in plates (2 g., 60%), m. p. 176° (Found: C, 87·98; H, 7·33. $C_{26}H_{26}O$ requires C, 88·13; H, 7·34%), $\lambda_{max.}$ (Fig. 1) 220, 250, 275, 286, 300, and 330 mμ (log ε 4·59, 4·16, 4·60, 4·61, 4·64, and 4·54 respectively), $\lambda_{min.}$ 245, 255, 280, 293, and 310 mμ (log ε 4·13, 4·12, 4·57, 4·51, and 4·36 respectively), $\lambda_{max.}$ (in $CHCl_3$) 6·08 and 6·20 μ. In a subsequent reaction, the crude gummy product (6·5 g.) consisting of a mixture of the dioxo-ester (VI; R = CO_2Me) and the diketone (VI; R = H) was heated with acetic acid (150 ml.), concentrated hydrochloric acid (75 ml.), and water (10 ml.). The mixture, on cooling, afforded the crude unsaturated ketone (VII) (5 g.), m. p. 150—165°, which on several crystallisations from benzene gave the pure ketone (3·6 g.), m. p. 176°.

(*b*) Cyclisation of the dioxo-ester (VI; R = CO_2Me), m. p. 115°, by dilute sodium hydroxide solution according to the method of Wilds and Close [14] failed almost completely, the dioxo-ester being recovered unchanged. This is presumably due to extremely low solubility of the dioxo-ester in aqueous alkali.

5'-Hydroxy-4'-isobutyl-6'-methylindeno(2',3'-1,2)phenanthrene (VIII).—When the dioxo-ester (VI; R = CO_2Me) (4 g.) was refluxed with acetic acid (100 ml.) concentrated hydrochloric acid (50 ml.), and water (5 ml.) in presence of air for 15 hr., a brown solid (3·8 g.) was obtained. This was adsorbed on alumina and eluted with benzene to yield two fractions: (*a*) the unsaturated ketone (VII) (2·3 g.), m. p. 160—165° which after a few crystallisations from benzene gave the pure ketone (2·0 g.), m. p. 176°; (*b*) a fraction (0·5 g.), m. p. 190—210°, which after repeated crystallisations from benzene afforded colourless flakes (0·3 g.), m. p. 231°. The latter had a strong absorption at 2·8 μ (OH group) and was the *phenol* (VIII) (Found: C, 88·5; H, 6·7. $C_{26}H_{24}O$ requires C, 88·6; H, 6·8%), $\lambda_{max.}$ 221·5, 242, 285, 300, 316, 325, 350, and 368 mμ (log ε 4·5, 4·26, 4·83, 4·50, 4·36, 4·37, 3·43, and 3·31 respectively), $\lambda_{min.}$ 238, 246, 295, 310, 320, 348, and 363 mμ (log ε 4·24, 4·25, 4·49, 4·34, 4·34, 3·37, and 2·99 respectively). With acetic anhydride (3 ml.) and a drop of pyridine (6 hr.) it (100 mg.) gave an *acetate*, needles (50 mg.), m. p. 260° [from benzene–light petroleum (40—60°)] (Found: C, 85·3; H, 6·6. $C_{28}H_{26}O_2$ requires C, 85·3; H, 6·6%). The phenol was recovered unchanged after treatment with lithium aluminium hydride followed by heating with 30% palladium–charcoal at 300—320° for 1 hr.

4'-Isobutyl-6'-methylindeno(2',3'-1,2)phenanthrene (C; R = H).—The unsaturated ketone (VII) (650 mg.), m. p. 176°, was stirred with lithium aluminium hydride (800 mg.) in tetrahydrofuran (50 ml.) at room temperature for 4 hr. and then refluxed for 1 hr. The product was worked up as usual and the crude gummy alcohol (600 mg.) was heated with 30% palladium–charcoal (250 mg.) at 300—320° for 1 hr. Repeated extraction with hot benzene and evaporation of the extracts gave a solid that crystallised from benzene–light petroleum (b. p. 40—60°) as plates (350 mg.), m. p. 200—205°. This sublimed at 280—290°/0·01 mm. and the sublimate crystallised several times as above and finally from pyridine to afford the *hydrocarbon* in needles, m. p. 212—212·5° (Found: C, 93·0, 92·8; H, 7·0, 7·2. $C_{26}H_{24}$ requires C, 92·9; H, 7·1%). The m. p. of the hydrocarbon was not raised further by crystallisation or chromatography over alumina. The ultraviolet absorption spectra (Fig. 2) showed maxima at 220·5, 232, 240, 274, 284, 300, 310, 324, 350, 358, and 367 mμ (log ε 4·38, 4·30, 4·26, 4·71, 4·86, 4·54, 4·37, 4·37, 3·18, 2·74, and 3·18 respectively), $\lambda_{min.}$ 229, 238, 250, 276, 296, 308, 318, 345, 356, and 362 mμ (log ε 4·28, 4·25, 3·98, 4·70, 4·52, 4·36, 4·26, 2·80, 2·71, and 2·51 respectively). The m. p. was depressed to 180—187° on admixture with Diels hydrocarbon, m. p. 226°, prepared from cholesterol according to the method of Ruzicka *et al.*[6] The latter hydrocarbon (Found: C, 93·3; H, 6·7. Calc. for $C_{26}H_{24}$: C, 92·9; H, 7·1. Calc. for $C_{25}H_{22}$: C, 93·2; H, 6·8%) had $\lambda_{max.}$ 220, 232, 239, 273, 282, 298, 319, 340, 348, 357, and 366 mμ (log ε 4·49, 4·38, 4·35, 4·74, 4·83, 4·54, 4·45, 2·99, 3·27, 2·92, and 3·31 respectively), $\lambda_{min.}$ 228, 236, 249, 275, 293, 314, 338, 344, 354, and 361 mμ (log ε 4·35, 4·33, 4·10, 4·73, 4·48, 4·27, 2·97, 2·93, 2·88, and 2·75 respectively) (cf. Fig. 2).

The synthetic hydrocarbon (C; R = H) afforded a 2,4,7-*trinitrofluorenone complex* which crystallised from benzene–ethanol in red needles, m. p. 214—215° (decomp.) Found: C, 71·55; H, 4·6; N, 6·3. $C_{26}H_{24},C_{13}H_5N_3O_7$ requires C, 71·9; H, 4·45; N, 6·45%). The Diels hydrocarbon from cholesterol likewise formed a *trinitrofluorenone complex* (red), m. p. 202—203° (Found: C, 71·5; H, 4·6; N, 6·3. $C_{26}H_{24},C_{13}H_5N_3O_7$ requires C, 71·9; H, 4·45; N, 6·3%). The mixed m. p. of these two was 185—200°.

4'-Isobutyl-6'-methyl-1'-oxoindeno(2',3'-1,2)phenanthrene.—The synthetic hydrocarbon (C; R = H) (130 mg.) was heated with sodium dichromate (400 mg.) in acetic acid (10 ml.) for 15 min., cooled, and diluted with water. The precipitate was filtered off and crystallised from acetic acid as orange needles (90 mg.), m. p. 184—186°. These were adsorbed on alumina and eluted with benzene. The triketone which was formed in small quantity was completely adsorbed at the top of the column and the *monoketone* was eluted in benzene. The orange compound left after the removal of benzene was twice crystallised from ethyl acetate and obtained as orange-red needles (50 mg.), m. p. 187° (Found: C, 89·1; H, 6·2. $C_{26}H_{22}O$ requires C, 89·1; H, 6·2%). The corresponding ketone obtained by the oxidation of the Diels hydrocarbon, m. p. 226°, was yellow and had m. p. 194° (Found: C, 88·8; H, 6·4. Calc. for $C_{26}H_{22}O$:

[14] Wilds and Close, *J. Amer. Chem. Soc.*, 1946, **68**, 83.

C, 89·1; H, 6·3%). Both ketones gave intense violet colours in concentrated sulphuric acid solution.

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