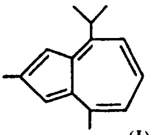
110. *The Structure of Zierone. Part. I. The Synthesis of Zierazulene and* 6-*Methylzierazulene.*

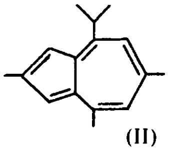
By D. J. Collins.

2 : 4-Dimethyl-8-*iso*propyl- (I) and 2 : 4 : 6-trimethyl-8-*iso*propyl-azulene (II) have been synthesised and shown to be identical with respectively zierazulene and a methyl derivative thereof.

In a preliminary communication [1] it was stated that reduction and dehydrogenation of the sesquiterpene ketone zierone, $C_{15}H_{22}O$, gave a new violet azulene, zierazulene, $C_{15}H_{18}$. Similarly, by reduction and dehydrogenation of hydroxymethylenezierone, $C_{16}H_{22}O_2$, was obtained a new tetra-alkylazulene, $C_{16}H_{20}$, in which the alkyl group was in a position next to that previously occupied by the keto-group. On the basis of visible spectra, the isoprene rule, and other chemical evidence,[2] the structures (I) and (II) were assigned to zierazulene and the methyl derivative, respectively. The synthesis of 2 : 4-dimethyl-8-*iso*propyl- (I) and 2 : 4 : 6-trimethyl-8-*iso*propyl-azulene (II) has confirmed these deductions.

The diazoacetic ester–indane ring-expansion, used by Pfau and Plattner [3] in their synthesis of vetivazulene (III), is often ambiguous with 5- or 6-substituted indanes (cf., *e.g.*, the synthesis of S-guaiazulene, in which 1 : 4-dimethyl-6-*iso*propylazulene was also formed [4]). With indanes (IV) substituted in the 4- or the 4 : 7-positions, this difficulty does not arise. 4 : 8-Disubstituted azulenes synthesised by this method include 2 : 4 : 8-trimethyl-,[5] 1 : 4 : 8-trimethyl-,[6] and 1 : 4-dimethyl-8-*iso*propyl-azulene.[6]


(I)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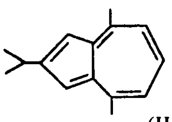
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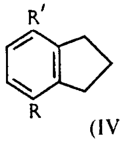
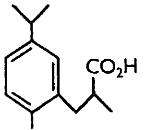


(IV)

Chloromethylation of *p*-cymene gave 2-chloromethyl-*p*-cymene,[7,8] which on condensation with ethyl methylmalonate, followed by hydrolysis and decarboxylation, gave α-methyl-β-(2-methyl-5-*iso*propylphenyl)propionic acid [7,9] (V). Friedel–Crafts cyclisation of the derived acid chloride gave 2 : 4-dimethyl-7-*iso*propylindan-1-one (VI), which was reduced by lithium aluminium hydride to the *cis-trans*-isomeric indanols (VII). Clemmensen reduction of the ketone (VI) afforded the indane (VIII). Treatment of the latter with diazoacetic ester in the usual way, and hydrolysis of the crude ester (IX; R = CO_2Et) obtained, gave the acid which with 10% palladium–charcoal at 250° underwent decarboxylation and dehydrogenation to 2 : 4-dimethyl-8-*iso*propylazulene (I). This hydrocarbon



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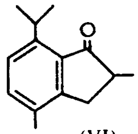

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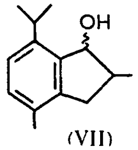

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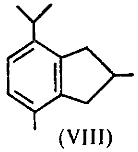
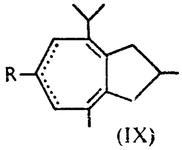

(VIII)



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[1] Birch, Collins, and Penfold, *Chem. and Ind.*, 1955, 1773.

[2] Unpublished work.

[3] Pfau and Plattner, *Helv. Chim. Acta*, 1939, **22**, 202.

[4] Plattner, Fürst, Marti, and Schmid, *ibid.*, 1949, **32**, 2137; Plattner, Fürst, and Marti, *ibid.*, p. 2452.

[5] Herz, *J. Amer. Chem. Soc.*, 1951, **73**, 4923.

[6] Herz, *ibid.*, 1952, **74**, 1350.

[7] Whittleston, *ibid.*, 1937, **59**, 825.

[8] Kadesch, *ibid.*, 1944, **66**, 1207.

[9] Rapson and Short, *J.*, 1933, 128.

was isolated by chromatography on alumina, purified by several successive extractions into syrupy phosphoric acid, and converted into its *s*-trinitrobenzene complex which after two recrystallisations from ethanol melted at 120°. The azulene was recovered by chromatography on alumina, again subjected to the phosphoric acid extraction procedure, and reconverted into its *s*-trinitrobenzene adduct which now melted at 122·5°, and did not depress the melting point of the corresponding zierazulene adduct. Likewise, the two picrates showed no depression of melting point. The visible spectrum of 2 : 4-dimethyl-8-*iso*propylazulene showed $\lambda_{max.}$ 545 mμ, $\lambda_{infl.}$ 582, 632 mμ, and is virtually identical with that of zierazulene[1] ($\lambda_{max.}$ 546 mμ, $\lambda_{infl.}$ 582, 634 mμ). The infrared spectra of 2 : 4-dimethyl-8-*iso*propylazulene and zierazulene, measured in chloroform solution, were identical. The proof that zierazulene has the structure (I) establishes it as the third known, fundamentally different, C_{15} natural azulene.

The visible spectrum of the above-mentioned methylzierazulene indicated that the new methyl group had entered the 6-position: reduction and dehydrogenation of the ester (IX; R = CO_2Et) should give 2 : 4 : 6-trimethyl-8-*iso*propylazulene, the proposed structure.

In every case so far reported, *e.g.*, 4 : 8-dimethyl-6-*iso*propylazulene[10] and 4 : 8-dimethylazulene-6-aldehyde,[11] diazoacetic ester has attacked the 5 : 6-positions of 4 : 7-disubstituted indanes (IV), and the resulting esters can be used to prepare 6-substituted azulenes. Reduction of the ester (IX; R = CO_2Et) with lithium aluminium hydride gave the hydroxymethyl compound (IX; R = $CH_2{\cdot}OH$), which on dehydrogenation with palladium–charcoal gave a reddish-violet oil. Isolation in the usual way gave an azulene fraction whose *s*-trinitrobenzene adduct, m. p. 130—138°, appeared to be heterogeneous. Paper chromatography[12] (see p. 534) of the crude azulene gave two spots whose R_F values were identical with those of pure zierazulene and the methylzierazulene. The presence of zierazulene must be due to partial elimination of the hydroxymethyl group during dehydrogenation. Repeated crystallisation of the crude adduct from ethanol gave the 2 : 4 : 6-trimethyl-8-*iso*propylazulene–*s*-trinitrobenzene complex, whose m. p., 155—157°, was undepressed on admixture with the methylzierazulene adduct. Pure 2 : 4 : 6-trimethyl-8-*iso*propylazulene (II), obtained by chromatography on alumina of its pure *s*-trinitrobenzene adduct in *cyclo*hexane, gave a picrate whose m. p. and mixed m. p. with the methylzierazulene picrate was 138—140°. The visible spectrum of 2 : 4 : 6-trimethyl-8-*iso*propylazulene (II) in *cyclo*hexane ($\lambda_{max.}$ 536 mμ, $\lambda_{infl.}$ 570, 623 mμ) was identical with that of the methylzierazulene ($\lambda_{max.}$ 534 mμ, $\lambda_{infl.}$ 570, 622 mμ); and the infrared spectra of the two hydrocarbons measured in chloroform solution were identical. The relatively intense band at 859 cm.$^{-1}$ shown by 2 : 4 : 6-trimethyl-8-*iso*propylazulene is not shown by 2 : 4-dimethyl-8-*iso*propylazulene.

EXPERIMENTAL

Visible spectra were measured for *cyclo*hexane solutions by using a Hardy recording spectrophotometer. Infrared spectra were measured with a Perkin-Elmer double-beam spectrophotometer. Light petroleum refers to the fraction of b. p. 60—90°.

α-Methyl-β-(2-methyl-5 iso*propyl)propionic Acid* (V).—To powdered sodium (2·3 g.) in dry xylene (40 ml.) was slowly added ethyl methylmalonate[13] (17·4 g.), and the mixture refluxed for 2 hr. To the vigorously stirred mixture (at room temperature) was added 2-chloromethyl-*p*-cymene[7] (18·2 g.; b. p. 143—147°/50 mm.) during 15 min. After refluxing for a further 6 hr., the mixture was cooled and acidified with a small amount of acetic acid, and water (100 ml.) was added. The product was isolated with ether. Fractional distillation gave a small forerun and then the malonic ester (18·8 g., 59%), b. p. 149—160°/1 mm. Rapson and Short[9]

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[10] Plattner and Roniger, *Helv. Chim. Acta*, 1943, **26**, 905.
[11] Arnold and Pahls, *Chem. Ber.*, 1954, **87**, 257.
[12] Knessl and Vlastiborová, *Coll. Czech. Chem. Comm.*, 1954, **19**, 782.
[13] "Organic Reactions," Coll. Vol. II, John Wiley and Sons, New York, 1955, p. 279.

give b. p. 181—185°/8 mm. The ester was hydrolysed for 3 hr. with a solution from sodium (28 g.) in refluxing 95% ethanol (550 ml.). Water (600 ml.) was added and the bulk of the ethanol removed by distillation. Working up in the usual way gave a brown oil which crystallised. Recrystallisation of a small amount from aqueous methanol gave the malonic acid as needles, m. p. 173°. Rapson and Short[9] record m. p. 170°. The bulk of the crude dicarboxylic acid was heated at 180°; distillation then gave the acid (V) (61·4 g., 93%), b. p. 159—160°/2 mm. Rapson and Short[9] record b. p. 190—195°/14 mm.

The *amide*, plates from ethanol, had m. p. 107·5° (Found: C, 76·7; H, 9·6. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6%).

2 : 4-*Dimethyl*-7-iso*propylindan*-1-*one* (VI).—The acid (V) (70 g.) and thionyl chloride (70 g.) were heated at 80—90° for ½ hr. Excess of thionyl chloride was removed by raising the bath-temperature to 160°, and distillation gave the acid chloride (73 g., 96%), b. p. 109—111°/1 mm. This (78·5 g.) was added dropwise with stirring to finely ground anhydrous aluminium chloride (47 g.) in pure dry benzene (80 ml.) during 1¼ hr. at ≯35°. After being stirred for a further 4 hr., the mixture was poured on ice (400 g.), concentrated hydrochloric acid (100 ml.) added, and the mixture shaken. Isolation with ether and distillation gave 2 : 4-*dimethyl*-7-iso*propylindan*-1-*one* (VI) (62·4 g., 94%), b. p. 111—114°/1 mm., n_D^{15} 1·5429 (Whittleston[7] records b. p. 147—150°/9 mm., but the ketone was not analysed or characterised) (Found: C, 83·3; H, 9·0. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 186°, was obtained as brilliant red hexagonal plates from ethanol (Found: C, 62·4; H, 5·6. $C_{20}H_{22}O_4N_4$ requires C, 62·8; H, 5·8%).

2 : 4-*Dimethyl*-7-iso*propylindan*-1-*ol* (cis *and* trans) (VII).—The foregoing indanone (2·0 g.) in dry ether (20 ml.) was added slowly to a suspension of lithium aluminium hydride (0·8 g.) in dry ether (60 ml.), and the mixture refluxed 1½ hr. Working up in the usual way gave a viscous oil, which was dissolved in light petroleum and adsorbed on alumina (30 g.). Elution with light petroleum (300 ml.) gave a viscous, colourless oil (620 mg.) which slowly crystallised. Recrystallisation from *n*-hexane gave 2 : 4-*dimethyl*-7-iso*propylindan*-1-*ol* (VII) as needles, m. p. 84·5° (Found: C, 82·3; H, 9·9. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%).

Elution of the column with ether–light petroleum (3 : 2) gave a further 70 mg. of viscous oil. Crystallisation from *n*-hexane gave the *isomer* as fleecy needles, m. p. 79·5° (Found: C, 82·3; H, 9·9%). A mixture of the *cis-trans*-isomers melted at 74°.

2 : 4-*Dimethyl*-7-iso*propylindane* (VIII).—To amalgamated zinc wool (150 g.), concentrated hydrochloric acid (150 ml.), and water (115 ml.) was added the indanone (VI) (58·4 g.), and the mixture was refluxed for 17 hr. (50 ml. portions of acid were added at 3 hr. intervals). The cooled mixture was decanted and the metal washed with ether. The ether washings, together with an ether extract of the aqueous suspension, were washed successively with water, 10% sodium hydroxide solution, and water, and dried (Na_2SO_4). After removal of the solvent, distillation from sodium gave 2 : 4-*dimethyl*-7-iso*propylindane* (VIII) (51·4 g., 95%), b. p. 94°/1·5 mm., n_D^{15} 1·5202 (Found: C, 89·7; H, 10·8. $C_{14}H_{20}$ requires C, 89·3; H, 10·7%).

2 : 4-*Dimethyl*-8-iso*propylazulene* (I).—The foregoing indane (15 g.) was heated at 135°, and diazoacetic ester (4 g.) added dropwise with shaking during 15 min. The temperature was then raised to 160° during 2 hr. and kept there for another hour. Evolution of nitrogen became vigorous at 140° and the mixture turned dark red above 145°.

Fractional distillation gave unchanged starting material (12·6 g.), b. p. 80—120°/1 mm., a dark red viscous oil (2·75 g.), b. p. 120—175°/1 mm., and a dark brown viscous residue (1·35 g.).

Recovered indane was recycled twice, giving a further 2·0 g. of the required ester (IX), b. p. 120—175°/1 mm., and a dark brown residue (4·5 g.). The total yield of the crude ester was 4·75 g. (23%). The dark brown residues from this and subsequent experiments were combined and distilled, giving more of the required ester.

The ester (9·4 g.) was refluxed in a solution from sodium (3·3 g.) in 95% ethanol (70 ml.) for 1 hr. Water (70 ml.) was added, refluxing continued for ½ hr., and the bulk of the alcohol removed. Isolation in the usual way gave 1 : 2 : 3 : 5(7)-tetrahydro-2 : 4-dimethyl-8-*iso*propylazulene-6-carboxylic acid as a brown viscous oil (4·6 g.).

The crude acid (4·6 g.) was heated under nitrogen with 10% palladium–charcoal (460 mg.) at 250° for 2 hr. Azulene formation began when the temperature had reached 230° and the mixture rapidly became deep violet. The cooled mixture was extracted with light petroleum and chromatographed on alumina. The violet eluate was purified by several successive extractions from light petroleum solution into cold syrupy phosphoric acid, which persistently became deep red. The deep violet oil (700 mg., 19·8%) thus obtained was treated with *s*-trinitrobenzene (720 mg.) in ethanol (30 ml.), giving an adduct (940 mg.), m. p. 119°. Two recrystallisations from ethanol gave a product of m. p. 120° which was dissolved in light petroleum and chromatographed on alumina. The violet eluate was extracted into phosphoric acid, which then became only pale yellow. The purified 2 : 4-dimethyl-8-*iso*propylazulene (I), recovered as before, was converted into its *s-trinitrobenzene adduct*, which crystallised from ethanol as fine maroon needles, m. p. 122·5°, undepressed on admixture with zierazulene–*s*-trinitrobenzene adduct (Found: C, 61·7; H, 5·2. $C_{21}H_{21}O_6N_3$ requires C, 61·3; H, 5·1%). The *picrate* crystallised as fine dark brown needles (from ethanol), m. p. 118°, undepressed on admixture with zierazulene picrate (Found: C, 58·9; H, 4·9. $C_{21}H_{21}O_7N_3$ requires C, 59·0; H, 4·9%).

For the measurement of spectra, 2 : 4-dimethyl-8-*iso*propylazulene was recovered from the pure *s*-trinitrobenzene adduct by chromatography on alumina in spectroscopically pure *cyclo*hexane: (*a*) Visible (in *cyclo*hexane): $\lambda_{max.}$ 545 mμ, $\lambda_{infl.}$ 582, 632 mμ (zierazulene showed [1] $\lambda_{max.}$ 549 mμ, $\lambda_{infl.}$ 582, 634 mμ). (*b*) Infrared (in $CHCl_3$): $\nu_{max.}$ 1575s, 1510s, 1475m, 1458m, 1393w, 1384w, 1371w, 1321s, 1192w, 1125w, 1032m cm.$^{-1}$ (identical with the spectrum of zierazulene).

2 : 4 : 6-*Trimethyl*-8-iso*propylazulene*.—The ester (IX; R = CO_2Et) (5·0 g.) in dry ether (10 ml.) was added to lithium aluminium hydride (1·5 g.) in dry ether (100 ml.). The mixture was refluxed for ½ hr., and the complex decomposed in the usual manner. After being washed with water and dried (Na_2SO_4), the ether solution gave the crude hydroxymethyl compound as a brown viscous oil (3·5 g.)

The alcohol (3·5 g.) and 10% palladium–charcoal (350 mg.) were heated to 240°. After the initial vigorous reaction, the temperature was raised to 255° for 1¼ hr., then to 290° for a further 15 min. The reddish-violet mixture was extracted with light petroleum and chromatographed on alumina, and the azulene fraction purified as before by several successive extractions into syrupy phosphoric acid. The azulene thus obtained (620 mg., 19·4%) was treated with *s*-trinitrobenzene (650 mg.) in ethanol (30 ml.), giving an adduct of m. p. 130—138°). Paper chromatography (see below) showed that it was a mixture, and that the contaminant was 2 : 4-dimethyl-8-*iso*propylazulene. After seven recrystallisations from ethanol the *s*-trinitrobenzene adduct of 2 : 4 : 6-*trimethyl*-8-iso*propylazulene* (II) was obtained as fine reddish-brown needles, m. p. and mixed m. p. with the methylzierazulene adduct, 155—157° (Found: C, 62·0; H, 5·3. $C_{22}H_{23}O_6N_3$ requires C, 62·1; H, 5·4%). The *picrate* was brown needles (from ethanol), m. p. and mixed m. p. 138—140° (Found: N, 9·5. $C_{22}H_{23}O_7N_3$ requires N, 9·5%). Spectroscopic samples were prepared in a similar manner to those of 2 : 4-dimethyl-8-*iso*propylazulene: (*a*) Visible (in *cyclo*hexane): $\lambda_{max.}$ 534 mμ, $\lambda_{infl.}$ 570, 622 mμ (methylzierazulene showed [1] $\lambda_{max.}$ 534 mμ, $\lambda_{infl.}$ 570, 622 mμ). (*b*) Infrared (in $CHCl_3$): $\nu_{max.}$ 1586s, 1510s, 1470m, 1458m, 1394m, 1384m, 1374w, 1334m, 1316w, 1204w, 1155w, 1087w, 1034w, 859m cm.$^{-1}$ (identical with the infrared spectrum of the methylzierazulene).

Paper Chromatography of Natural and Synthetic Zierazulenes.—The method used was that of Knessl *et al.*[12] Whatman No. 1 paper was impregnated with pure paraffin oil by soaking in a 20% (v/v) paraffin–light petroleum solution for a few min., then drying between filter papers. To determine the approximate paraffin content of the paper (which should be 1·8—2·4 mg./sq. cm.), a strip of paper of known area and weight was treated similarly and reweighed. The mobile phase was 55% (w/w) phosphoric acid. On paper with a paraffin content of 1·97 mg./sq. cm. and a development time of 48 hr., synthetic and natural zierazulene had R_F 0·33. Under the same conditions, the synthetic and the natural methylzierazulene had R_F 0·60.

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