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SYNTHESIS OF DI- AND TRIALKYLAZULENES

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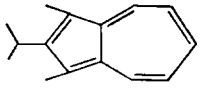
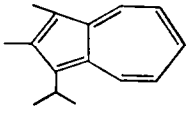
Abstract—The synthesis of 2-isopropyl-1,3-dimethyl, 1-isopropyl-2,3-dimethyl, 1-isopropyl-2-methyl and 5-isopropyl-6,8-dimethylazulenes are described.

IN continuation of the work on azulenes,[1–3] the syntheses of 2-isopropyl-1,3-dimethyl (I), 1-isopropyl-2,3-dimethyl (II) and 1-isopropyl-2-methyl (III) azulenes by the classical indan-diazoacetic ester method[4] and the synthesis of 5-isopropyl-6,8-di-methylazulene (IV) by the Ziegler-Hafner method[5] are reported.



I



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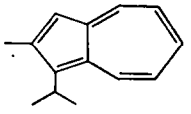

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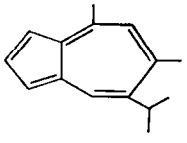
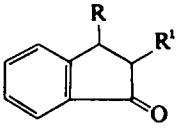


IV

2-Isopropyl-1,3-dimethylazulene. Treatment of diethyl isopropylmalonate[6] with 1-chloroethylbenzene[7] gave diethyl-α-isopropyl-α-(1-phenyl) ethylmalonate. Hydrolysis accompanied by decarboxylation yielded α-isopropyl-β-methyl-β-phenyl-propionic acid which was cyclized to give 2-isopropyl-3-methylindanone-1 (Va)



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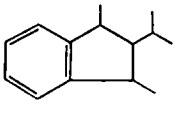

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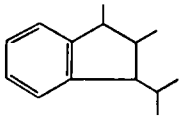
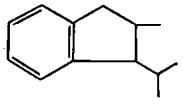


VII



VIII

a: R = Me; R¹ = –CH(Me)(Me)

b: R = R¹ = Me

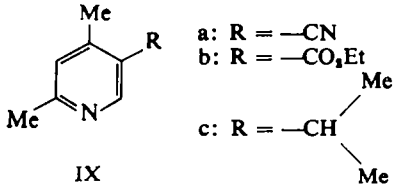
c: R = H; R¹ = Me

[1] T. R. Govindachari, S. Rajadurai and B. R. Pai, *Chem. Ber.* **91**, 908 (1958).
[2] T. R. Govindachari, K. K. Purushothaman and S. Rajadurai, *Chem. Ber.* **92**, 1662 (1959).
[3] T. R. Govindachari and P. S. Santhanam, *Ind. J. Chem.* **1**, 72 (1963).
[4] P. A. Plattner and J. Wyss, *Helv. Chim. Acta* **23**, 907 (1940).
[5] K. Ziegler and K. Hafner, *Angew. Chem.* **67**, 301 (1955).
[6] E. Fischer and F. Brauns, *Ber. Dtsch. Chem. Ces.* **47**, 3181 (1914).
[7] R. Grignard, *Bull. Soc. Chim. Fr.* **39**, 1589 (1926).

This was reacted with methylmagnesium bromide, dehydrated and reduced to 2-isopropyl-1,3-dimethyl-indan (VI). Treatment of the indan with diazoacetic ester followed by hydrolysis, decarboxylation and dehydrogenation yielded 2-isopropyl-1,3-dimethylazulene.

1-*Isopropyl*-2,3-*dimethylazulene* (II) *and* 1-*isopropyl*-2-*methylazulene* (III) were prepared similarly starting from 2,3-dimethylindanone-1[8] (Vb) and 2-methyl-indanone-1[9] (Vc) respectively.

5-*Isopropyl*-6,8-*dimethylazulene* (IV) was synthesized from 3-cyano-4,6-dimethyl-2(H)-pyridone.[10] The pyridone, on treatment with phosphorus oxychloride, gave 6-chloro-5-cyano-2,4-lutidine which was reduced to 5-cyano-2,4-lutidine (IXa). This



IX

was converted to 5-carbethoxy-2,4-lutidine (IXb). Reaction of the latter with excess methylmagnesium iodide followed by dehydration and reduction yielded 5-isopropyl-2,4-lutidine (IXc). Treatment of this with cyclopentadienyl sodium followed by pyrolysis gave 5-isopropyl-6,8-dimethylazulene.

All four new azulenes reported here have been characterized as their TNB derivatives.

EXPERIMENTAL*

2-*Isopropyl*-1,3-*dimethylazulene*

Diethyl α-isopropyl-α-(1-phenyl) ethylmalonate. Diethylisopropylmalonate (105 g) was added to a suspension of Na (12 g) in dry benzene (100 ml). 1-Chloroethylbenzene (70 g) was added during 1 hr and heating and stirring continued for 10 hr. The mixture then diluted with water, extracted with ether and the extract dried (Na_2SO_4). After removal of the solvent the residue was distilled *in vacuo* to yield the ester (80 g), b.p. 130–135°/0·5 mm. (Found: C, 70·3; H, 8·3. $C_{18}H_{26}O_4$ requires: C, 70·6; H, 8·5%.)

α-Isopropyl-β-methyl-β-phenylpropionic acid. The above diester (80 g) was refluxed with ethanolic KOH (50%; 200 ml) on a water-bath for 100 hr. After the removal of the solvent *in vacuo* it was diluted with water and extracted with ether to remove unsaponified ester and the clear aqueous soln acidified. The acid was extracted with ether, dried (Na_2SO_4) and ether removed. The residue was distilled *in vacuo* (50 g), b.p. 145°/0·5 mm. The anilide crystallized in white needles from EtOH m.p. 188°. (Found: C, 81·4; H, 8·1. $C_{19}H_{23}ON$ requires: C, 81·2; H, 8·2%.)

2-*Isopropyl*-3-*methylindanone*-1. A soln of the above acid (25 g) in dry Chf (100 ml) was mixed with $SoCl_2$ (20 ml) and left for 12 hr. The solvent was removed *in vacuo* and the acid chloride taken up in dry CS_2 and anhydrous $AlCl_3$ (20 g) was added gradually with ice cooling. After leaving at room temp for 12 hr it was poured onto crushed ice and extracted with ether. The extract was washed with $NaHCO_3$aq, water, dried (Na_2SO_4) and the solvent removed. The residue was distilled *in vacuo* (15 g), b.p. 130°/10 mm. The *semicarbazone* crystallized in white needles from EtOH, m.p. 218–219°. (Found: C, 68·7; H, 7·7. $C_{14}H_{19}N_3O$ requires: C, 68·6; H, 7·6%.)

* All m.ps are uncorrected. Visible spectra: Beckmann model D.U. spectrophotometer in pet. ether (b.p. 40–60°).

[8] A. D. Mitchell and J. F. Thorpe, *J. Chem. Soc.* 2275, 2724 (1910).

[9] W. Reid and A. Meyer, *Chem. Ber.* **90**, 2481 (1957).

[10] R. Grignard, *Bull. Soc. Chim. Fr.* **39**, 1589 (1926).

2-Isopropyl-1,3-dimethylindene-1. The above indanone (12 g) in dry ether was added to an ice cold soln of MeMgI (Mg 2·4 g, MeI 14 g) with stirring. After refluxing for 6 hr, it was decomposed with sat NH_4Claq (20 ml) and extracted with ether, ether removed and the residual indanol dehydrated with 30% H_2SO_4 (100 ml). The indene was then extracted with ether, washed with water, dried (Na_2SO_4), ether removed and the residue distilled *in vacuo* (10 g), b.p. 110°/10 mm. (Found: C, 90·3; H, 9·7. $C_{14}H_{18}$ requires: C, 90·3; H, 9·7%.)

2-Isopropyl-1,3-dimethylindan. A soln of the above indene was reduced to the indan in glacial AcOH in the presence of Adams catalyst under H press. of 55 lb/in². It was treated with $NaHCO_3$aq, extracted with ether, washed with water, dried (Na_2SO_4) and ether removed. The residue was distilled *in vacuo* (8 g), b.p. 110°/10 mm. (Found: C, 89·7; H, 10·8. $C_{14}H_{20}$ requires: C, 89·4; H, 10·6%.)

Addition of diazoacetic ester to 2-isopropyl-1,3-dimethylindan. To the above indan (5 g) in a 10 ml vigreux flask maintained at 130–140° was added diazoacetic ester (2 ml) during the course of 3 hr. The temp was then raised to 180° and the contents kept at the same temp for 2 hr. It was then fractionated *in vacuo*. The forerun which was mainly the starting material was subjected to this operation 5 times. The combined residues (4 g) were refluxed with alcoholic KOH (50%; 25 ml) for 10 hr, acidified, extracted with ether, dried (Na_2SO_4) and ether removed. The acid (2 g) was dehydrogenated and decarboxylated.

Dehydrogenation. The acid (150 mg) was mixed with PdC (30%; 50 mg) and heated for about 10 min at 320°. The product was cooled, extracted with pet. ether (b.p. 40–60°) and shaken with phosphoric acid (89%). The acid extract was diluted with water, extracted with pet. ether (b.p. 40–60°) and chromatographed over alumina in pet. ether (b.p. 40–60°) (20 mg).

Visible spectrum: 685(sh), 620, 605, 585(sh) and 565(sh) mμ. TNB adduct, m.p. 171°. (Found: C, 61·3; H, 5·0. $C_{21}H_{21}N_3O_6$ requires: C, 61·3; H, 5·1%.)

1-Isopropyl-2,3-dimethylazulene

1-Isopropyl-2,3-dimethylindene-1. A soln of 2,3-dimethyl-indanone-1 (12 g) in dry ether was added to an ice cold soln of isoPrMgBr (Mg 2·4 g, isoPrBr 13 g). It was worked up as before and dehydrated to the indene (10 g), b.p. 110°/8 mm. (Found: C, 90·1; H, 9·6. $C_{14}H_{18}$ requires: C, 90·3; H, 9·7%.)

1-Isopropyl-2,3-dimethylindan. A soln of the above indene (8 g) in glacial AcOH was reduced to give indan (7 g), b.p. 110°/8 mm. (Found: C, 89·6; H, 10·7. $C_{14}H_{20}$ requires: C, 89·4; H, 10·6%.)

Addition of diazoacetic ester to 1-isopropyl-2,3-dimethylindan. The addition product of diazoacetic ester and indan (5 g) was hydrolysed to the acid (4 g) which was dehydrogenated and decarboxylated.

Dehydrogenation of the acid to 1-isopropyl-2,3-dimethylazulene. The crude acid (4 g) was decarboxylated and dehydrogenated to the azulene and the latter purified as in the previous case. Visible spectrum: 685(sh), 630, 605 and 585(sh) mμ. TNB adduct, m.p. 150°. (Found: C, 61·5; H, 5·4. $C_{21}H_{21}N_3O_6$ requires: C, 61·3; H, 5·1%.)

1-Isopropyl-2-methylazulene

1-Isopropyl-2-methylindene-1. To an ice cold soln of IsoPrMgBr (Mg 2·4 g, isoPrBr bromide 13 g) in dry ether (80 ml) was added 2-methylindanone-1 (12 g). The product was dehydrated to the indene (10 g), b.p. 120°/10 mm. (Found: C, 90·7; H, 9·3. $C_{13}H_{16}$ requires: C, 90·7; H, 9·3%.)

1-Isopropyl 2-methylindan. A soln of the above indene (8 g) in glacial AcOH was reduced to indan (6 g), b.p. 110°/4 mm. (Found: C, 89·3; H, 10·6. $C_{13}H_{18}$ requires: C, 89·7; H, 10·3%.)

Addition of diazoacetic ester to the indan. The addition product of diazoacetic ester and indan (5 g) was hydrolysed to the acid (2 g) which was dehydrogenated and decarboxylated.

Dehydrogenation of the acid to 1-isopropyl-2-methylazulene. The crude acid (2 g) was dehydrogenated and the azulene purified. Visible spectrum: 630(sh), 585, 570, 555(sh) and 532 mμ. TNB adduct, m.p. 134°. (Found: C, 60·3; H, 5·0. $C_{20}H_{19}N_3O_6$ requires: C, 60·5; H, 4·8%.)

5-Isopropyl-6,8-dimethylazulene

6-Chloro-5-cyanol-2,4-lutidine. A mixture of 3-cyano-4,6-dimethyl-2(H)-pyridone (10 g), $POCl_3$ (25 g) and PCl_5 (25 g) was refluxed for 6 hr. Excess $POCl_3$ was removed *in vacuo* and the residue treated with crushed ice. The precipitated solid (8 g) was filtered off and crystallized from pet. ether (b.p. 60–80°, m.p. 102°. (Found: C, 57·6; H, 4·2. $C_8H_7N_2Cl$ requires: C, 57·5; H, 4·3%.)

5-Cyano-2,4-lutidine. The chloropyridine (5 g) was shaken in MeOH soln under a H press. of 30 lb/in² in the presence of $PaBaCO_3$ (5%; 5 g) and AcONa (30 g). It was filtered, solvent removed *in vacuo* and the residue diluted with water, basified with ammonia and the lutidine extracted with ether, washed with water, dried (Na_2SO_4) and solvent removed. The residue (3 g) was sublimed *in vacuo* and crystallized from pet. ether (b.p. 40–60°), m.p. 52°. (Found: C, 72·5; H, 6·1. $C_8H_8N_2$ requires: C, 72·7; H, 6·1%.)

5-Carbethoxy-2,4-lutidine. 5-Cyano-2,4-lutidine (10 g) was dissolved in abs. EtOH (150 ml) and saturated with dry HCl gas at room temp. It was refluxed for 2 hr, resaturated with HCl, refluxed, EtOH removed and basified with ammonia. The ester thus obtained was distilled *in vacuo* (7 g), b.p. 90°/3 mm. It formed a *picrate*, m.p. 161°. (Found: C, 47·1; H, 4·1. $C_{16}H_{16}N_4O_9$ requires: C, 47·1; H, 3·9%.)

2-(2,4-Dimethyl-5-pyridyl) propan-2-ol. A soln of 5-carbethoxy-2,4-lutidine (7 g) was added dropwise to an ice-cooled soln of MeMgI (Mg 5·2 g, MeI 12·5 ml), yield of the propanol (7 g), b.p. 110°/4 mm.

5-Isopropyl-2,4-lutidine. A soln of the propanol (3 g) in glacial AcOH (40 ml) and conc. H_2SO_4 (10 ml) was refluxed for 45 min, basified and the oil extracted with ether, washed with water, dried (Na_2SO_4) and ether removed. The residue was distilled *in vacuo* yielding the isopropenyl compound (2·5 g), b.p. 90°/10 mm. A soln of the isopropenyl compound (2·5 g) in MeOH (50 ml) was reduced in the presence of PaC (5%; 2 g) under H press of 40 lb/in² yielded the lutidine (2·5 g), b.p. 80–84°/8 mm. It formed a *picrate*, m.p. 168°. (Found: C, 50·9; H, 4·7. $C_{16}H_{18}N_4O_7$ requires: C, 50·8; H, 4·8%.)

5-Isopropyl-6,8-dimethylazulene. 5-Isopropyl-2,4-lutidine methiodide was prepared by mixing a soln of the lutidine in Chf (60 ml) and MeI (3 ml) and leaving it overnight. Removal of the solvent left the methiodide as a hygroscopic solid which was used as such for the next step.

To a suspension of the above methiodide in dry THF (20 ml) was added a soln of cyclopentadienyl sodium (Na 1·8 g and cyclopentadiene 10 g) in THF under N atm. at 0°. It was stirred at 0° for 2 hr, and at room temp for 2 hr, and the solvent removed *in vacuo*. The residue was heated at 280° for 8 min, cooled and extracted with pet. ether (b.p. 40–60°). The azulene thus obtained was purified Visible spectrum: 585 and 560 mμ. TNB adduct, m.p. 178°. (Found: C, 61·0; H, 5·4. $C_{21}H_{21}N_3O_6$ requires: C, 61·3; H, 5·1%.)

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