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AZULENES AND RELATED SUBSTANCES—XI*

A NEW AZULENE SYNTHESIS—AZULENE, 1-METHYL†-2-METHYL‡- AND 1, 3-DIMETHYLAZULENE†

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Abstract—The polyphosphoric acid induced intramolecular acylation of lactones has been applied to the synthesis of the bicyclo [0,3,5] decane system, and the preparation of azulene, 1-methyl-, 2-methyl- and 1,3-dimethylazulene is reported.

A NUMBER of syntheses of azulenes have been summarized in review articles.[1] The present method which is based on the polyphosphoric acid-induced intramolecular acylation of lactones,[2–4] reported in a preliminary communication,[5] is now recorded in detail and an extension of the method serves to illustrate the generality of the synthetic route.

The general method of synthesis is outlined in Fig. 1. The ethyl cycloheptanone-2-carboxylate (I), may be obtained by a modification of Prelog and Hinden's method[6] or more conveniently by the carbethoxylation of suberone with diethyl carbonate in the presence of sodium hydride.[7]

The Michael addition of ethyl cycloheptanone-2-carboxylate to ethyl acrylate, ethyl crotonate or methyl methacrylate proceeds smoothly in the presence of potassium t-butoxide in t-butanol[8] to furnish the addition products (II, III, IV) in yields of 90–93, 70–75 and 70–75% respectively. The condensation product (II) was obtained earlier[9] by the interaction of ethyl β-chloropropionate and I in 66% yield.

After hydrolysis and decarboxylation of the Michael condensation products (II, III and IV), distillation of the resulting crude β-2-oxocycloheptylpropionic acids (V, VI, VII) led, invariably, to the formation of some enol lactone, hence, it was found

* Part X: *J. Indian Chem. Soc.* **36**, 693 (1959).

† T. M. Jacob, Ph.D thesis, Madras University (1956).

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[1] W. Keller-Schierlein and E. Heilbronner in *Non-benzenoid Aromatic Compounds* (Edited by D. Ginsburg) p. 277–322, Interscience, New York (1959); and earlier Refs recorded therein.

[2] C. Rai and Sukh Dev, *Experientia* **11**, 114 (1955); *J. Indian Chem. Soc.* **34**, 178 (1957).

[3] Sukh Dev and C. Rai, *J. Indian Chem. Soc.* **34**, 266 (1957).

[4] T. M. Jacob and Sukh Dev, *J. Indian Chem. Soc.* **36**, 429 (1959).

[5] T. M. Jacob and Sukh Dev, *Chem. and Ind.* 576 (1956).

[6] V. Prelog and W. Hinden, *Helv. Chim. Acta* **27**, 1856 (1944).

[7] This method [V. H. Wallingford, A. H. Homeyer and D. M. Jones, *J. Amer. Chem. Soc.* **63**, 2252 (1941)] has recently been applied to a number of cyclanones [S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler and M. J. Urbigkit, *Tetrahedron* **19**, 1625 (1963)].

[8] Sukh Dev, *Sci. & Cult.* **16**, 31 (1950).

[9] Pl. A. Plattner, A. Fürst and K. Jirasek, *Helv. Chim. Acta* **29**, 730 (1946).

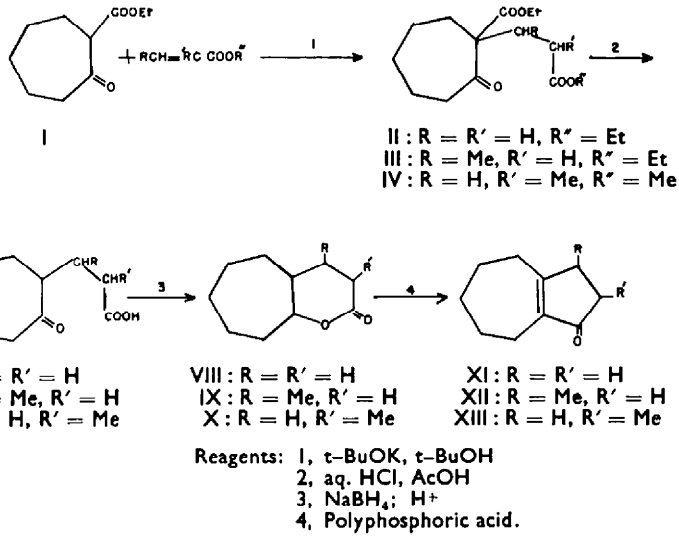
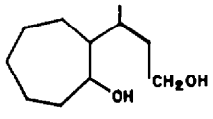


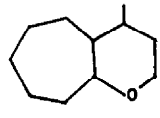
FIG. 1

more profitable to isolate these as their esters. However, for the next step the crude keto acids could be utilized.

Reduction followed by lactonization of the keto acids could be accomplished in high yields (90–95%) under specified conditions. When the ethyl ester of VI was subjected to this treatment with sodium borohydride considerable amounts of the corresponding glycol (XIV) was obtained;[10] this readily cyclized to $\alpha\beta$-tetramethylene-γ-methyltetrahydropyran (XV) by thermal treatment.



XIV



XV

When the δ-lactones were treated with polyphosphoric acid, the corresponding cyclopentenones (XI, XII, XIII) resulted in excellent yields. However, the conditions for optimum yield varied considerably and had to be worked out for each case separately. This four-step reaction sequence, starting from ethyl 2-oxocycloheptane carboxylate, makes the bicyclic ketones (XI, XII, XIII) available in $\sim$ 80, 55 and 60% overall yields respectively. The preparation, by other methods, of Δ^9-octahydro-1-oxoazulene (XI)[11–13] and Δ^9-octahydro-1-oxo-3-methylazulene (XII)[11,12] has been reported.

[10] Esters are usually resistant to $NaBH_4$, however some cases of reduction have been reported; for a summary see N. G. Gaylord, *Reduction with Complex Metal Hydrides* pp. 500–506, Interscience, New York (1956).

[11] E. A. Braude and W. F. Forbes, *J. Chem. Soc.* 2208 (1953), and Refs cited there.

[12] A. M. Islam and R. A. Raphael, *J. Chem. Soc.* 2247 (1953).

[13] Sukh Dev, *J. Indian Chem. Soc.* **32**, 255 (1955).

Azulene[11,14] and 1-methylazulene[11] have been prepared from XI and XII respectively by the standard reduction-dehydration-dehydrogenation sequence and the synthesis of 2-methylazulene from XIII by this method has been carried out. Action of methylmagnesium iodide on XII, followed by dehydration and S-dehydrogenation furnished 1, 3-dimethylazulene.

The preparation of a variety of 1-alkyl-, 1, 2-dialkyl-, 1, 3-dialkyl- and 1, 2, 3-trialkylazulenes by the route discussed is apparently feasible.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Solvent extracts were finally washed with brine and then dried (Na_2SO_4). Pet. ether refers to the fraction of b.p. 40–60°. The UV and visible spectral measurements were made on a Beckman D U spectrophotometer.

2-Carbethoxycycloheptanone. In a 3-necked flask carrying a dropping funnel, a stirrer and a condenser, NaH (4·8 g, 0·2 mole) was at once covered with a mixture of dry ether (30 ml) and diethyl carbonate (23·63 g, 0·2 mole). The mixture was gently refluxed and stirred, while cycloheptanone (11·2 g, 0·1 mole) in ether (20 ml) was slowly added during 4 hr. The reaction mixture was stirred and refluxed for another 2 hr and then left overnight (15 hr). The viscous product was chilled and cautiously treated with gl. acetic acid (20 ml) and ice (40 g); the solvent layer was separated and washed with ice-water (20 ml), and the aq. part extracted with pet. ether (20 ml × 2). The combined extracts were dried and the solvent flashed off; the residue, on fractionation, gave the desired keto ester: b.p. 116°/4 mm, n_D^{24} 1·4720, yield 15·5–16·5 g (85–90%).

Michael addition products

Ethyl (2-carbethoxy-cycloheptanone)-2-β-propionate (II). To a solution of K (0·1 g) in t-BuOH (15 ml), contained in a 3-necked flask carrying a stirrer, a dropping funnel, a thermometer and an outlet connected to a guard-tube (SiO_2-gel), 2-carbethoxysuberone (23·0 g, 0·125 mole) was added in one lot; t-BuOH (10 ml) was used for washing in the last traces of the keto ester. To the above stirred mixture, ethyl acrylate (16·65 g, 0·15 mole) was added with external cooling (cold water ~15°), at a rate such that the reaction temp did not exceed 30° (~½ hr). The reaction mixture was stirred for another 10 min and then set aside at room temp (22–25°) for 24 hr. The pale-coloured product was acidified with gl.AcOH (2 ml), diluted with benzene (50 ml), washed with brine (50 ml × 2) and dried. The solvent was removed and the residue fractionated to give the required product as a colourless liquid, b.p. 156–157°/1 mm, n_D^{26} 1·4660, yield 33 g (93%).

Ethyl (2-carbethoxy-cycloheptanone)-2-β-butyrate (III). The condensation of 2-carbethoxycycloheptanone (9·57 g) and ethyl crotonate (6·06 g) was carried out in the presence of t-BuOK (from 0·39 g K) as detailed above for II, except that the reaction mixture after having stood at room temp for 24 hr was refluxed for 10 hr and then worked up. The required compound was collected as a colourless oil, b.p. 170–175°/3·5 mm, n_D^{24} 1·4695, yield 11 g (71%). An analytical sample had: b.p. 160–161°/1·5 mm, n_D^{25} 1·4690, d_4^{25} 1·0740, M_D 77·31 (Calc: 77·21), (Found: C, 64·44; H, 8·70. $C_{16}H_{26}O_5$ requires: C, 64·40; H, 8·78%).

Methyl (2-carbethoxycycloheptanone)-2-β-isobutyrate (IV). A solution of K (0·025 g) in t-BuOH (10 ml) was chilled to 0° and a mixture of ethyl cycloheptanone carboxylate (1·84 g, 0·01 mole) and methyl methacrylate (1·2 g, 0·012 mole) was added and swirled till the mixture became clear. After leaving aside at room temp for 15 hr, the mixture was refluxed for 2 hr and then worked up as under II to furnish IV: b.p. 145–146°/0·8 mm, n_D^{25} 1·4682, yield 2·03 g, 71·5%. (Found : C, 63·70; H, 8·75. $C_{16}H_{24}O_5$ requires: C, 63·36; H, 8·51%).

Hydrolysis of Michael adducts

The hydrolysis products were best purified through their ethyl esters, which are described below.

Ethyl cycloheptanone-2-β-propionate (ester of V). The condensation product II (33 g) was mixed with water (33 ml) and conc. HCl (66 ml) and refluxed for 24 hr. The excess of aq. acid was, next, distilled off under suction (water-pump) from a stream-bath. The residue was diluted with ethanol

[14] Sukh Dev, *J. Indian Chem. Soc.* **32**, 325 (1955).

(33 ml), benzene (66 ml) and sulphosalicylic acid (0·5 g) added and the mixture refluxed with continuous removal of water (modified Dean-Stark apparatus).[15] The product was cooled, washed with water, dried and fractionated to yield the ester of V: b.p. 145°/5 mm, n_D^{28} 1·4660, yield 23·5 g, 95·5% (cf. Plattner *et al.*)[9] The 2,4-*dinitrophenylhydrazone* was obtained as reddish-orange prismatic plates from alcohol, m.p. 91–92°. (Found : N, 14·49. $C_{18}H_{24}O_6N_4$ requires: N, 14·28%).

Ethyl cycloheptanone-2-β-butyrate (ester of VI). The compound III proved resistant to hydrolysis by the above method, but the following modification proved effective. The condensation product (12·9 g) was mixed with acetic acid (26 ml) and conc. HCl (65 ml) and the mixture refluxed for 65 hr. This was worked up as detailed above to furnish the desired ethyl ester: b.p. 132°/1·5 mm, n_D^{28} 1·4680, d_4^{28} 1·022, M_D 61·53 (Calc: 61·70), yield 6·7 g, 68%. (Found: C, 68·94; H, 9·69. $C_{13}H_{22}O_3$ requires: C, 68·99; H, 9·80%). The 2,4-*dinitrophenylhydrazone* crystallized as yellow leaflets (dil. ethanol), m.p. 89°. (Found: N, 13·81. $C_{19}H_{26}O_6N_4$ requires: H, 13·79%).

Methyl cycloheptanone-2-β-isobutyrate (ester of VII). The Michael product IV (2·67 g), mixed with acetic (5 ml) and conc. HCl (13 ml), was refluxed for 24 hr and then freed of aq. acid as described previously. The residue was diluted with methanol (3 ml), benzene (12 ml) and 0·5 ml conc. H_2SO_4 added, and refluxed for 12 hr. The reaction mixture was worked up to yield the methyl ester of VII: b.p. 111–112°/1 mm, n_D^{28} 1·4630, d_4^{28} 1·023, M_D 57·14 (Calc: 57·1), yield 1·72 g, 86·5%. (Found: C, 68·40; H, 9·70. $C_{12}H_{20}O_3$ requires: C. 67·89; H, 9·50%).

δ-Lactones

The crude acids obtainable from the hydrolysis of the above esters (1 part ester, 2 parts conc. HCl and 1 part water were mixed and refluxed for 5 hr for the propionic ester and 15 hr for the butyric and isobutyric esters, and then worked up by removing the aq. acid under suction from a steam-bath) were used as such for the next step.

γδ-Cycloheptano-δ-valerolactone (VIII). The keto acid V (from 10·6 g, 0·05 mole ester) was dissolved in cold NaOHaq. (3 g in 50 ml water), and while being heated and stirred at 50 ± 2°, was treated with a solution of $NaBH_4$ (0·95 g, 0·025 mole) in water (25 ml containing a drop of 10% NaOHaq), during 15 min. The stirring was discontinued, but the heating was continued for a total of 5 hr. The reaction mixture was cooled to room temp, acidified with conc. HCl aq (10 ml) and left aside for 15 hr, after which it was saturated with NaCl and extracted with ether (20 ml × 4), washed with brine and then with sat. $NaHCO_3$aq (15 ml × 2); after drying the solvent was flashed off and the residue fractionated to give the lactone (VIII): b.p. 136–138°/2 mm, n_D^{30} 1·4965, yield 7·8 g, 92·6%. An analytical sample had b.p. 137°/2 mm, n_D^{25} 1·4960, d_4^{25} 1·076, M_D 45·64; Calc: 45·65. (Found: C, 71·10; H, 9·70. $C_{10}H_{16}O_2$ requires: C, 71·39; H, 9·59%).

β-Methyl-γδ-cycloheptano-δ-valerolactone (IX). The keto acid VI (from 3·08 g ester) was reduced and lactonized as described above for VIII to furnish the required compound: b.p. 130°/1 mm, n_D^{28} 1·4910, d_4^{22} 1·049, M_D 50·25; Calc: 50·25, yield 2·65 g, 86%. (Found: C, 72·59; H, 9·81. $C_{11}H_{18}O_2$ requires: C, 72·49; H, 9·96%).

In another experiment the ethyl ester of VI (3·08 g) was reduced with $NaBH_4$ (0·6 g) in ethanol (22 ml), first at room temp (20–25°) for 18 hr, and later at reflux for 1 hr. To the reaction mixture NaOH (3 g) dissolved in water (10 ml) was added and refluxed for 10 hr. The reaction mixture was diluted with water (20 ml) and extracted with ether to yield a gum (1·95 g), which could be evaporately distilled under high vacuum at a temp not exceeding 100° to yield the glycol (XIV) as a colourless syrup. (Found: C, 71·45; H, 11·23. $C_{11}H_{22}O_2$ requires: C, 70·92; H, 11·90%). When the distillation was conducted at a higher press., a mobile liquid, b.p. 80–85°/2 mm, n_D^{24} 1·4865 and analysing for *αβ-tetramethylene-γ-methyltetrahydropyran* (XV) was obtained. (Found: C, 79·03; H, 11·46. $C_{11}H_{20}O$ requires: C, 78·51; H, 11·98%). The aq. alkaline part could be worked up to yield 0·63 g of lactone (IX).

α-Methyl-γδ-cycloheptano-δ-valerolactone (X). The keto acid VII (from 5·6 g ester) on reduction and lactonization, as detailed for VIII, yielded X: b.p. 127–128/°1 mm, n_D^{25} 1·4906, yield 4·5 g, 90·5%. (Found: 72·80; H, 9·90; $C_{11}H_{18}O_2$ requires: C, 72·49; H, 9·96%).

Cyclopentenones

Δ⁹-Octahydro-1-oxoazulene (XI). To polyphosphoric acid (PPA; from 7 g P_2O_5 and 3 ml syrupy H_3PO_4; Sukh Dev[16]) contained in a test tube (6″ × 1″) and maintained at 60 ± 2°, the lactone VIII

[15] Sukh Dev, *J. Indian Chem. Soc.* **30**, 447 (1953).

[16] Sukh Dev, *J. Indian Chem. Soc.* **32**, 262 (1955).

(0·84 g, 0·005 mole) was added in one lot and well-mixed with a glass rod, and the resulting light brownish mixture heated at the above temp for 4½ hr under anhydrous conditions. The reddish-brown product was, next, diluted with cooling with ice-water to ~50 ml, saturated with $(NH_4)_2SO_4$ (20 g), and the whole extracted continuously with pet. ether. From the extract, the solvent was fractionated off and the residue distilled to furnish the ketone as a colourless liquid: b.p. 135–137°/13 mm, n_D^{29} 1·5215, yield 0·72 g, 96%. An analytical sample had: b.p. 132–133°/10 mm, n_D^{26} 1·5240, d_4^{26} 1·031, M_D 44·46; Calc: 43·54; $E\Sigma_D$ 0·61, $\lambda_{max}^{ethanol}$ 241 mμ, ε, 13690. The 2,4-*dinitrophenylhydrazone* crystallized from acetic acid in dark red lustrous leaflets, m.p. 233–234°, undepressed by an authentic[3] sample.

Δ⁹-*Octahydro*-1-*oxo*-3-*methylazulene* (XII). To PPA (from 15 g P_2O_5 and 9 ml syrupy phosphoric acid; 3-necked flask) maintained at 80 ± 2°, the lactone IX (2·73 g, 0·015 mole) was added all at once with stirring. The stirring was stopped after 3 min, but the heating was continued for a total of 60 min. The deep-red reaction mixture was diluted with water (100 ml) and worked up as above to yield the required product as a colourless liquid (80%), b.p. 100–102°/1 mm, n_D^{24} 1·5130, d_4^{24} 1·006, M_D 49·00; Calc: 48·16; $E\Sigma_D$ 0·51, $\lambda_{max}^{ethanol}$ 240 mμ, ε, 11620. The 2,4-*dinitrophenylhydrazone* was obtained as red needles (benzene), m.p. 234–235°, undepressed by an authentic[11] sample.

Δ⁹-*Octahydro*-1-*oxo*-2-*methylazulene* (XIII). The lactone X (10·18 g, 0·055 mole) was rapidly added with stirring to PPA (from 75 g P_2O_5 and 31 ml syrupy phosphoric acid) maintained at 60 ± 2° and contained in a 3-necked flask. The stirring was stopped after 15 min but the heating at the above temp was continued, with occasional 5-min stirring, for a total of 24 hr. The reddish brown product was worked up as detailed for XI to yield the ketone (XIII) as a colourless liquid (8·83 g, 97%), b.p. 110–111°/4 mm, n_D^{27} 1·5188, d_4^{27} 1·000, M_D 49·28; Calc: 48·16; $E\Sigma_D$ 0·68, $\lambda_{max}^{ethanol}$ 242 mμ, ε, 10430. (Found: C, 80·90; H, 9·90. $C_{11}H_{16}O$ requires: C, 80·44; H, 9·83%). The 2,4-*dinitrophenylhydrazone* crystallized from benzene–hexane as red crystals, m.p. 208–210°. (Found: N, 16·30. $C_{17}H_{20}O_4N_4$ requires: N, 16·27%).

2-Methylazulene

Δ⁹-*Octahydro*-1-*oxy*-2-*methylazulene*. The ketone XIII (2·2 g) in ether (15 ml) was reduced in the usual manner with a slurry of $LiAlH_4$ (0·72 g) in ether (40 ml), first at ~ −10° (1 hr) and later at room temp (25°) for ½ hr. The reaction mixture was treated with water, 10% H_2SO_4 (20 ml), at below 0°, the solvent layer was washed with water, and finally with brine containing $NaHCO_3$. After drying, the solvent was flashed off and the residue distilled from a flask, which had been freed of any acid film on its surface (by treatment with Na_2CO_3aq): b.p. 82–84°/4 mm, n_D^{26} 1·5098, d_4^{26} 0·9913, M_D 50·1; Calc: 49·56, yield 1·98 g, 85·4%. (Found: C, 79·42; H, 10·91. $C_{11}H_{18}O$ requires: C, 79·46; H, 10·92%).

Hexahydro-2-methylazulene. To freshly fused and powdered $KHSO_4$ (100 mg) contained in a flask, immersed in an oil bath (130–140°), and arranged for vacuum distillation (2–3 mm), the above alcohol (1·36 g) was added dropwise during 1 min. By the time the addition was over, all the dehydrated material had distilled over; the distillate was redistilled over Na to give the pure diene: b.p. 70–72°/3 mm, n_D^{25} 1·5170, d_4^{25} 0·9133, M_D 49·09; Calc: 47·66; $E\Sigma_D$ 0·75, $\lambda_{max}^{ethanol}$ 245 mμ, ε, 10690, yield 0·58 g, 48%. (Found: C, 88·65; H, 10·91. $C_{11}H_{16}$ requires: C, 89·12; H, 10·88%).

The diene gave positive colour reactions with Sabetary's[17] and Ehrlich-Muller[18] reagents for azulene precursors.

2-Methylazulene. The above diene (1·3 g) was dehydrogenated with S (0·85 g) at 220°/400 mm for 1·5 hr. The product was directly distilled off *in vacuum* and then redistilled over freshly precipitated Cu powder. The blue-violet distillate was taken up in pet. ether and chromatographed over Al_2O_3 (Basic/I, 15 cm × 1·5 cm); pet. ether (10 ml × 4) eluted a total of 0·37 g of colourless material, while pet. ether–ether (4:1; 10 ml × 4), next, eluted 90 mg (7% on diene) of the required crude azulene as a blue-violet solid (m.p. 40–42°). The azulene (146 mg) was treated with 100 mg trinitrobenzene in 3 ml ethanol to yield 200 mg (m.p. 123–125°) deep brown needles, which after recrystallization from ethanol yielded the pure *trinitrobenzene complex* as deep brown needles, m.p. 138–139° (Lit. m.p.: 140–141°[19], 135–136°[20]). The azulene was further characterized by its UV and visible light absorption; for this purpose a known weight of the complex was decomposed on Al_2O_3

[17] S. Sabetary and H. Sabetary, *C. R. Acad. Sci. Paris* **199**, 313 (1934).
[18] A. Muller, *J. Prakt. Chem.* **151**, 233 (1938).

using n-heptane as eluent: $\lambda_{max}^{heptane}$ 240, 274, 283, 301, 330, 345, 526, 532, 552, 563, 567, 592, 612, 651 and 674 mμ; the values are in accord with those reported in the literature.[19,20]

1,3-*Dimethylazulene*

The ketone XII (1·7 g, in 30 ml ether) was reacted with an ethereal solution of MeMgI (from 304 mg of Mg) in the usual manner and then worked up with NH_4Cl aq to yield the crude methyl carbinol (1·6 g), which was directly dehydrated with $KHSO_4$ (40 mg), as detailed above, to furnish the diene: b.p. 120–125°/28 mm, n_D^{32} 1·5110, yield 0·68 g. The diene (0·55 g) was dehydrogenated with S (0·35 g) at 220–250° under slight suction for 1 hr and worked up as described for 2-methylazulene; the crude azulene (90 mg) was taken up in heptane, and after rechromatography over alumina, was directly identified by its visible absorption: $\lambda_{max}^{heptane}$ 640, 705, 750, and 772 mμ (Lit.[21]: 638, 705, 750 and 770 mμ).

[19] Pl. A. Plattner and E. Heilbronner, *Helv. Chim. Acta* **30,** 910 (1947); **31,** 804 (1948).
[20] W. Herz, *J. Amer. Chem. Soc.* **78,** 1485 (1956).
[21] Pl. A. Plattner, A. Furst and K. Jirasek, *Helv. Chim. Acta* **30,** 1320 (1947).