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AZULENES AND RELATED SUBSTANCES—XII

A NEW AZULENE SYNTHESIS—GUAIAZULENE* AND Se-GUAIAZULENE†

T. M. JACOB, P. A. VATAKENCHERRY and SUKH DEV‡
Department of Organic Chemistry, Indian Institute of Science, Bangalore, India

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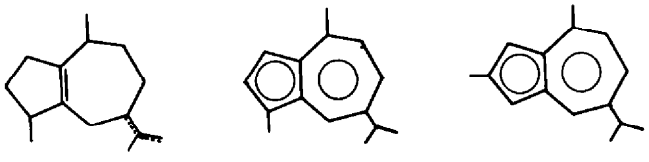
Abstract—The new method of azulene synthesis, described in the preceding communication, has been extended to the synthesis of guaiazulene and Se-guaiazulene.

THE preceding paper described the synthesis of azulenes with alkyl substituents on the 5-membered ring, the present work extends this general synthesis to azulenes having alkyl substituents on the 7-membered ring as well.

The sesquiterpene guaiene (I) is known to give rise to different azulenes depending on the conditions of dehydrogenation.[1–4] Thus, dehydrogenation with sulphur[1] at ~220° yields a bright blue azulene—guaiazulene[5]—which was formulated[6] as 1,4-dimethyl-7-isopropylazulene (II); on the other hand dehydrogenation with selenium at 300–320° furnishes[2] a mixture of azulenes in which a violet azulene, termed Se-guaiazulene, predominates and on the basis of its visible spectra characteristics was assigned[7] the structure III.



I II III

Guaiazulene

The first unambiguous synthesis, confirming the structure II for guaiazulene was reported by Sorm *et al.*,[8] this was followed by the present simpler route,[9,10] first reported in a preliminary form in 1956; and now described in detail.

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

† P. A. Vatakencherry, Ph.D thesis, Bombay University (1958).

‡ Present address: Division of Organic Chemistry, National Chemical Laboratory, Poona 8, India.

[1] L. Ruzicka, S. Pontalti and F. Balas, *Helv. Chim. Acta* **6**, 855 (1923).

[2] L. Ruzicka, A. J. Haagen-Smit, *Helv. Chim. Acta* **14**, 1104 (1931).

[3] F. Sorm, L. Dolejs, O. Knessl and J. Pliva, *Coll. Czech. Chem. Comm.* **15**, 82 (1950).

[4] W. T. House and M. Orchin, *J. Amer. Chem. Soc.* **82**, 639 (1960).

[5] This has often been referred to as S-guaiazulene.

[6] Pl. A. Plattner and L. Lemay, *Helv. Chim. Acta* **23**, 897 (1940).

[7] Pl. A. Plattner, *Helv. Chim. Acta* **24**, 283E (1941).

[8] F. Sorm, J. Gut, J. Hlavnicka, J. Kucera and L. Sedivy, *Coll. Czech. Chem. Comm.* **16**, 168 (1951).

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

[10] Another unpublished synthesis [W. Meier, Dissertation, Fed. Inst. Tech. (Zurich), No. 2098 (1954)] has been cited by W. Keller-Schierlein and E. Heilbronner in *Non-benzenoid Aromatic Compounds* (Edited by D. Ginsburg), pp. 298–299, Interscience, New York (1959).

The new synthetic route (Fig. 1), required the β-keto ester, 2-carbethoxy-4-isopropyl-7-methylsuberone (VII). This was readily obtained from α-methyl-δ-isopropylsuberic acid[11] (IV; Fig. 1), the method of choice being the Dieckmann cyclization of the ester V under high dilution conditions.[12] The β-keto ester (VII) gave only a weak greenish-blue coloration with alcoholic ferric chloride; in the UV it showed only a weak absorption (λ_{max}^{EtOH} 266 mμ, ε 560) and further its enolate

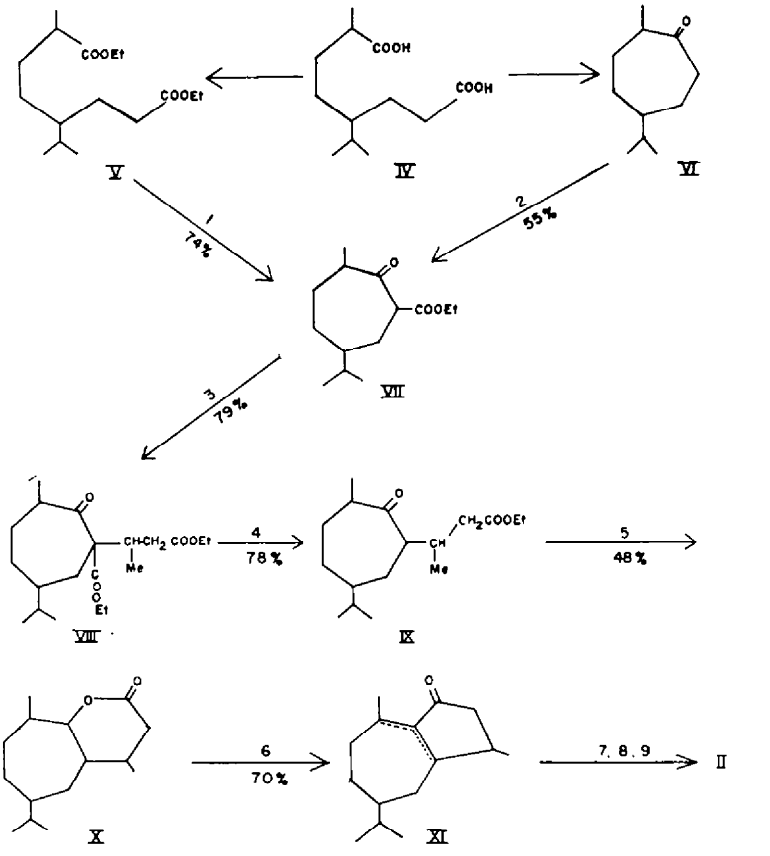


FIG. 1

($\lambda_{max}^{alc.NaOH}$ 275 mμ, ε 398) did not show the large bathochromic shift, as is known for enolic 2-oxo-cyclohexylcarboxylates.[13] Since, it is known[14,15] for cyclic β-keto esters

[11] T. M. Jacob and Sukh Dev, *J. Indian Chem. Soc.* **34**, 327 (1957).

[12] For Dieckmann cyclization of suberic and higher acid esters see: F. F. Blicke, J. Azuara, J. Doorenbos and E. B. Hotelling, *J. Amer. Chem. Soc.* **75**, 5418 (1953); N. J. Leonard and C. W. Schimelpfenig, *J. Org. Chem.* **23**, 1708 (1958).

[13] Enolic 2-oxo-cyclohexylcarboxylates in alcoholic solution show λ_{max} around 260 mμ having log ε of the order of 4; in alcoholic alkaline solution a bathochromic shift of ~27 mμ has been considered. average: B. Belleau, *J. Amer. Chem. Soc.* **73**, 5150 (1951).

[14] W. Dieckmann, *Ber. Dtsch. Chem. Ges.* **55**, 2470 (1922).

[15] G. Schwarzenbach, M. Zimmerman and V. Prelog, *Helv. Chim. Acta* **34**, 1954 (1951).

that the enol-content and acidity are dependent on ring-size, it was argued that this difference in the spectral characteristics could stem from the change in ring-size. To gather evidence on this point, the UV absorption of simple 2-carbethoxycyclanones[16] was studied and the results (Table 1) clearly supported the above contention, and are in accord with the structure VII for the Dieckmann product.

TABLE 1. ULTRAVIOLET ABSORPTION CHARACTERISTICS FOR SOME 2-CARBETHOXYCYCLANONES

Compound	λ_{max}^{EtOH} (mμ)	ε	$\lambda_{max}^{EtOH-NaOH}$ (mμ)	ε	$\Delta\lambda_{max}$
2-Carbethoxy-					
-cyclopentanone	254	495	286	16980	32
-cyclohexanone	256	7620	283	5818	27
-cycloheptanone	263	1660	280	1549	17
VII	266	560	275	398	9

The elaboration of the δ-lactone (X) from the keto ester (VII) proceeded smoothly, following the procedure (Fig. 1) discussed in the preceding paper. The polyphosphoric acid (PPA) induced intramolecular acylation of X can conceivably yield[17] two cyclopentenones (as depicted in XI); in practice the product, which was obtained in a yield of ~70%, showed two maxima in the UV (λ_{max} 232 mμ $\varepsilon = 7160$; λ_{max_2} 243 mμ $\varepsilon = 6580$), which indicated a mixture (XI). However, since both cyclopentenones would lead to the same final product, the separation of ketones was not attempted[18] and the mixture was reduced with $LiAlH_4$, the crude alcohol mixture dehydrated and the product (λ_{max} 246 mμ, ε 11600) dehydrogenated with sulphur to yield an azulene, identified as guaiazulene by its spectral characteristics, paper chromatography and preparation of complex with trinitrobenzene.

Se-guaiazulene

The formulation of Se-guaiazulene as III, was proved experimentally, when it was synthesized by Sorm *et al.*[19,20] A new synthesis, following the method described above for guaiazulene, is now reported.

The keto ester (VII) was condensed with methyl methacrylate to give XII in almost quantitative yield. The product was converted into the required lactone (XIII) in 85% overall yield by the route described under guaiazulene. The action of PPA on the lactone yielded a product (75%), which in the UV displayed a broad maximum at 235–240 mμ (ε 8620) and is thus represented as a mixture of the two ketones (XIV). As in the case of guaiazulene, the ketone mixture was reduced, dehydrated and dehydrogenated[20] with sulphur at ~220° to yield a purple azulene, identified as Se-guaiazulene by standard methods.

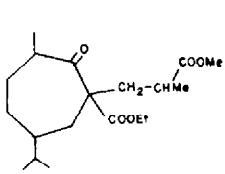
[16] Recently a detailed paper on the UV and IR spectra of 2-carbethoxycyclanones has appeared: S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron* **19**, 1625 (1963).

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

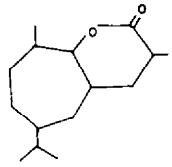
[18] In connection with another investigation, this aspect of PPA-induced intramolecular acylation of lactones, is being studied.

[19] F. Sorm, J. Kucera and J. Gut, *Coll. Czech. Chem. Comm.* **16**, 184 (1951).

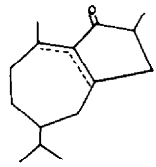
[20] It may be pointed out that the last step of dehydrogenation in the synthesis by Sorm *et al.*[19] had to be carried out at ~300°, a temp at which alkyl shifts may occur. However, as pointed out by these authors, their synthetic 2,9-dimethyl-5-isopropyl bicyclo-[0,3,5]-decane was identical (IR) with decahydro-Se-guaiazulene.



XII



XIII



XIV

TABLE 2. LIGHT ABSORPTION CHARACTERISTICS OF Se-GUAIAZULENE

Region	Present sample (in n-heptane)		Lit[19]* (in cyclohexane)	
	λ_{max}	ε	λ_{max}	ε
UV	244	13930	243	14450
	279	33880	278	34280
	288	40760	286	40740
	307	5620	308	6030
	319	1510	318 (inflection)	1580
	333	2340	332	2340
	347	3350	346	3310
			Lit[7]	
Visible	562	260	561	—
	598	230	606	—
	666 (shoulder).	80	667	—

* Values taken from the graph.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet. ether refers to the fraction b.p. 40–60°. All solvent extracts were finally washed with brine, before drying (Na_2SO_4). UV and visible spectra were taken on a Beckman DU spectrophotometer.

Guaiazulene

2-Carbethoxy-4-isopropyl-7-methylsuberone (VII)

(i) *By Dieckmann condensation.* Sodium hydride (4·5 g, 0·187 mole) was placed in a 1-litre flask and immediately covered with dry xylene (500 ml); the flask was fitted to a dilution apparatus,[21] a dropping funnel and condenser, and attached to a set-up for carrying reaction under N_2. A few drops of absolute ethanol were added to the flask, and a solution of diethyl α-methyl-δ-isopropylsuberate[11] (21·45 g, 0·075 mole) in 100 ml dry xylene was placed in the dropping funnel. The system was flushed with N_2 and the xylene heated to vigorous boiling; to this the ester solution was let in during 14 hr and the reaction mixture further refluxed for a period of 8 hr. The product was cooled, treated with 14 ml gl. acetic acid with ice-cooling, and slowly shaken for 3–4 hr intermittently; water (12 ml) was then added and after seeding with a crystal of sodium acetate, all the sodium acetate crystallized out, and was removed by filtration. The xylene solution was washed with water, then with $NaHCO_3$ aq and dried. The solvent was flashed off at ~100° under suction and the residue fractionated to yield the required compound as a colourless liquid, b.p. 139–140°/2 mm, n_D^{35} 1·4645, yield 13·2 g, 74%. An analytical sample had: n_D^{34} 1·4650, d_4^{34} 0·9940, M_D 66·77; Calc. for VII: 66·34. (Found: C, 70·02; H, 10·02. $C_{14}H_{24}O_3$ requires: C, 69·96; H, 10·07%).

(ii) *By diethyl carbonate condensation.* To NaH (1·2 g, 0·05 mole), contained in a suitable 3-necked flask, and covered with anhydrous ether (20 ml), diethyl carbonate (5·9 g, 0·05 mole) was added. This was stirred and refluxed and 2-methyl-5-isopropylsuberone[11] (VI; 4·2 g, 0·025 mole) added during

[21] A. C. Cope and E. C. Herrick, *J. Amer. Chem. Soc.* **72**, 983 (1950); N. J. Leonard and R. C. Sentz, *J. Amer. Chem. Soc.* **74**, 1704 (1952).

6 hr. The refluxing was continued for a further period of 2 days and then worked up with acetic acid to furnish 3·3 g (55%) of the required keto ester: b.p. 121–23°/0·9 mm, n_D^{30} 1·4655.

Ethyl (2-carbethoxy-4-isopropyl-7-methylsuberone)-2-β-butyrate (VIII)

To a solution of t-BuOK in t-BuOH (0·39 g K in 60 ml t-BuOH), chilled to 0°, a mixture of the β-keto ester VII (12·0 g, 0·05 mole) and ethyl crotonate (11·4 g, 0·1 mole) was added, and swirled and warmed under tap water till the mixture became homogenous, when it was left aside at room temp (22–25°) overnight (15 hr). The reaction mixture was, next, refluxed for 2 hr, cooled, treated with gl. acetic acid (1 ml), diluted with benzene (50 ml), and worked up to give the required product as a colourless oil, b.p. 183°/2·5 mm, n_D^{25} 1·4690, d_4^{25} 1·0350, M_D 95·81; Calc: 95·71, yield 13·9 g, 79%. (Found: C, 67·91; H, 9·64. $C_{20}H_{34}O_5$ requires: C, 67·76; H, 9·67%).

Ethyl (4-isopropyl-7-methylsuberone)-2-β-butyrate (IX)

The above diester (VIII; 4·47 g) was refluxed with HCl aq (90 ml) and acetic acid (35 ml) for 140–150 hr. The product was cooled, extracted with benzene (40 ml × 3) and worked up to yield the crude acid which was mixed with ethanol (5 ml), benzene (10 ml) and sulphosalicylic acid (0·25 g) and refluxed with continuous removal of water and, then, worked up in the usual manner to yield the ester IX: b.p. 150°/1 mm, n_D^{28} 1·4675, d_4^{28} 0·9819, M_D 79·73; Calc: 80·20, yield 2·8 g, 78%. (Found: C, 72·05; H, 10·66. $C_{17}H_{30}O_3$ requires: C, 72·30; H, 10·71%).

3-*Methyl-6-isopropyl-2-oxycycloheptyl-β-butyric acid δ-lactone* (X)

The keto ester IX (5·0 g) was mixed with HCl aq (10 ml) and water (5 ml) and refluxed for 20 hr. The HCl aq and water were removed under red. press. (30 mm) from a water-bath and the residual crude acid dissolved in NaOH aq (1·5 g NaOH in 20 ml water). To this alkaline solution, maintained at 50 ± 2°, a solution of 0·55 g $NaBH_4$ in 12 ml water containing a drop of 10% NaOH aq was added during 30 min; the heating and stirring were continued for 5 hr and the reaction mixture left overnight. The product was acidified with 6 ml of conc. HCl aq, heated for 2 hr at ~50° and again left overnight (24 hr). The reaction mixture was saturated with $(NH_4)_2SO_4$ and extracted with ether (15 ml × 4). The combined ether extracts were washed with sat. $NaHCO_3$ aq (15 ml × 2) and dried; the solvent was removed and the residue distilled to yield the required lactone X: b.p. 160°/1 mm, n_D^{28} 1·4870, d_4^{28} 0·9991, M_D 68·55; Calc: 68·75, yield 2·0 g, 47·6%. (Found: C, 75·44; H, 10·61. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

3,8-*Dimethyl-5-isopropyl-1-oxobicyclo*[5,3,0] *decene* (XI)

The above lactone (2·2 g) was treated with PPA (14 g P_2O_5 and 6 ml syrupy phosphoric acid) at 65 ± 2° for a total of 3 hr and then worked up[22] to give the unsaturated ketone XI: b.p. 120–125°/1 mm, n_D^{25} 1·5050, yield 1·5 g, 70%. (Found: C, 81·87; H, 10·88. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·91%).

A small amount of the ketone mixture was fractionated and the central cut converted into its 2,4-*dinitrophenylhydrazone* which after repeated crystallizations from ethyl acetate gave dark-red plates, m.p. 164–165°. (Found: N, 13·66. $C_{21}H_{28}O_4N_4$ requires: N, 13·99%).

Hexahydroguaiazulene

The ketone XI (1·25 g) in ether (10 ml) was reduced with $LiAlH_4$ (0·5 g in 25 ml ether) in the usual manner and worked up to give the crude alcohol (1·2 g), which was mixed with $KHSO_4$ (50 mg, freshly fused and powdered) and rapidly distilled at 4–5 mm press. The distillate was refractionated over Na to furnish the diene as a colourless liquid, b.p. 135°/12 mm, n_D^{24} 1·5070, yield 0·75 g, 65%. (Found: C, 88·23; H, 11·78. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84%).

Guaiazulene (II)

The above diene (220 mg) was mixed with S (100 mg) and heated at 215–220° for 1 hr under mild suction. The product was taken up in pet. ether (15 ml) and the blue solution extracted with 80% phosphoric acid (3 ml × 2). The acid phase was diluted with ice-water and extracted with ether (10 ml × 3), and the extracts washed and dried. The solvent was removed and the residue (15 mg)

[22] For further details see: Sukh Dev and Charanjit Rai.[17]

treated with trinitrobenzene (10 mg) in alcohol (1 ml) to give the complex which was twice recrystallized from ethanol to give black needles of the *trinitrobenzene complex*, m.p. 147–148°, mixed m.p. with an authentic sample (m.p. 150–151°) was 149–150°.

In another experiment, the crude azulene (10 mg) obtained from phosphoric acid extract was chromatographed over Al_2O_3 (Basic/1; 10 cm × 0·6 cm) in pet. ether and the blue eluterates combined and the solvent removed. The product on paper chromatography[23] showed a single spot and had the same R_F value as an authentic sample of guaiazulene, which was run side by side. The product in n-heptane showed λ_{max} 246, 285, 351, 369, 605, 660 and 735 mμ, which were identical with the values obtained for an authentic sample.

Se-Guaiazulene

Methyl (2-carbethoxy-4-isopropyl-7-methylsuberone)-2-β-isobutyrate (XII)

The β-keto ester (VII; 12 g, 0·05 mole) and methyl methacrylate (6·5 g, 0·065 mole) were condensed in the presence of t-BuOK (0·12 g K in 25 ml t-BuOH) in t-BuOH exactly in the manner described for VIII, and worked up in the same manner to yield the product XII as a colourless oil, b.p. 162–164°/2 mm, n_D^{28} 1·4675, d_4^{28} 1·037, M_D 91·18; Calc: 91·1. (Found: C, 67·21; H, 9·60. $C_{19}H_{32}O_5$ requires: C, 67·03; H, 9·47%).

Methyl (4-isopropyl-7-methylsuberone)-2-β-isobutyrate

The above diester (11·5 g) was hydrolysed with HCl aq (220 ml) and acetic acid (90 ml) at reflux during 150–160 hr. The reaction mixture was worked up by extraction with benzene to yield the crude hydrolysate, which was mixed with benzene (24 ml), anhydrous methanol (18 ml) and conc. H_2SO_4 (3 ml), and refluxed for 12 hr. Usual work up furnished the required product: b.p. 122–126°/1 mm, n_D^{25} 1·4666–1·4678, yield 8·43 g, 93%. An analytical sample had: b.p. 126°/1 mm, n_D^{26} 1·4660, d_4^{26} 0·9837, M_D 75·6; Calc: 75·58. (Found: C, 71·32; H, 10·53. $C_{16}H_{28}O_3$ requires: C, 71·60; H, 10·52%).

3-*Methyl-6-isopropyl-2-oxycycloheptyl-β-isobutyric acid δ-lactone* (XIII).

By following the procedure detailed for the isomeric lactone X, the above ester (8 g, 0·023 mole) was converted to the lactone XIII, which was obtained as a colourless, viscous liquid, b.p. 145–150°/1 mm, n_D^{25} 1·4852–1·4880, yield 6·6 g (93%). This was used as such in the next step.

The above product slowly crystallized out, when it was treated with pet. ether and the solid (1·0 g) filtered off and recrystallized from pet. ether; white needles, m.p. 110–111°. (Found: C, 75·90; H, 10·85. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%). The liquid part was redistilled: b.p. 163–165°/2 mm, n_D^{26} 1·4870, d_4^{26} 0·9995, M_D 68·61; Calc: 68·75. (Found: C, 75·25; H, 10·92. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

2,8-*Dimethyl-5-isopropyl-1-oxobicyclo* [5,3,0] *decene* (XIV)

To PPA (25 g P_2O_5 and 10 ml syrupy phosphoric acid) maintained at 50 ± 2° in a 3-necked flask, 3·0 g of the above lactone was added with stirring in one lot; the stirring was discontinued after 10–15 min, but the heating was continued for a total of 10 hr. The product was worked up as detailed elsewhere[22] to give the unsaturated ketone as a liquid, b.p. 123–128°/2 mm, n_D^{26} 1·5061–1·5100, yield 2·2 g, 78%. An analytical sample had: b.p. 113–114°/0·8 mm, n_D^{26} 1·5060, d_4^{26} 0·9594, M_D 67·95; Calc: 66·64, $E\Sigma_D$ 0·6. (Found: C, 81·95; H, 11·0; $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

The 2,4-*dinitrophenylhydrazone* after repeated crystallization from benzene–hexane mixture was obtained as red crystals, m.p. 128–130° (Found: N, 14·30. $C_{21}H_{28}O_4N_4$ requires: N, 13·99%).

2,8-*Dimethyl-5-isopropyl-1-oxybicyclo* [5,3,0] *decene*

The above ketone (2·0 g in 15 ml ether) was reduced with a slurry of $LiAlH_4$ (0·13 g) in 20 ml ether at ice-temp. (1 hr) and later at room temp (15 min). Usual work up gave the alcohol as a viscous liquid: b.p. 132–135°/2 mm, n_D^{24} 1·5005, yield 1·78 g, 87%. (Found: C, 81·00; H, 11·72. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

[3] O. Knessl and A. Vlastiborova, *Coll. Czech. Chem. Comm.* **19**, 782 (1954).

Hexahydro-Se-guaiazulene

In a modified Claisen flask (3 ml, column 3″) was placed 50 mg freshly fused and powdered $KHSO_4$. This was arranged for distillation at 140° (bath temp) at 1–2 mm, and 0·85 g of the above alcohol was let in during 1 min. The distillate was redistilled over a little Na to yield the diene: b.p 98–100°/1·2 mm, n_D^{28} 1·5080, d_4^{26} 0·9135, M_D 66·62; Calc: 66·16, $\lambda_{max}^{ethanol}$ 249 mμ (ε, 6902), yield 0·5 g 62%. (Found: C, 88·21; H, 11·70. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84%)

Se-guaiazulene (III)

By following the procedure detailed for guaiazulene, dehydrogenation of the above diene (1·2 g) with S (0·56 g) at 210–220°/80 mm, yielded 0·27 g (23%) of a violet-blue azulene. This was converted into the *trinitrobenzene complex*, which after two recrystallizations from alcohol furnished dark reddish-brown needles, m.p. 150–151° (Lit[19]: m.p. 150, 152°).

The product was further characterized by its UV and visible absorption (Table 2). For this purpose a known weight of the pure complex was decomposed on a short column of Al_2O_3 (Basic/I) using heptane as the eluent.