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496. Studies on Sesquiterpenoids. Part VI.¹ Synthesis of 3,5,8-Trimethylazuleno[6,5-b] furan (Linderazulene).²

By Ken'ichi Takeda, Hitoshi Minato, and Makoto Ishikawa.

Zinc-dust distillation of linderene (I), isolated from the root of Lindera strychnifolia, Vill., yielded linderazulene. As this azulene was assumed to have structure (II), we have synthesised 3,5,8-trimethylazuleno[6,5-b]furan (II); it is identical with linderazulene.

STRUCTURE (I) has been suggested ³ for linderene, isolated from the root of Lindera strychnifolia Vill. Zinc-dust distillation of linderene yielded linderazulene⁴ which was the first azulenofuran identified and was assumed to be 3,5,8-trimethylazuleno[6,5-b]furan (II). Studies of linderazulene contributed greatly to the confirmation of the structures of sesquiterpenic lactones of the perhydroazulene type, and we have now synthesised it.

The sesquiterpenic alcohol, guaiol (III), seemed to be the most convenient starting material, since its two methyl groups are in positions similar to those of linderazulene. The $\alpha\beta$ -unsaturated ketone (IV)⁵ derived from guaiol was hydrogenated in ethanol with 5% palladium-barium carbonate, giving the hydroxy-ketone (V) which was easily dehydrated at the tertiary hydroxyl group. However, as we thought that the presence of a hydroxyl

³ Takeda and Ikuta, Tetrahedron Letters, 1964, 277.

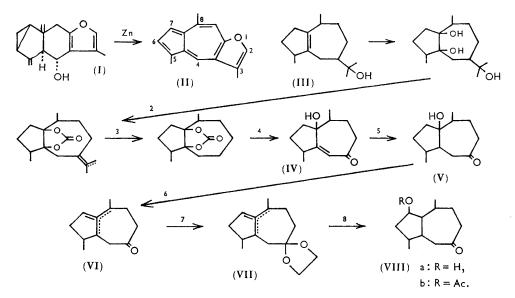
¹ Part V, Takeda, Minato, Nosaka, and Isizuka, Chem. and Pharm. Bull. (Japan), 1963, 11, 867.

² Preliminary communication, Tetrahedron Letters, 1963, 121.

⁴ Takeda and Nagata, Chem. and Pharm. Bull. (Japan), 1953, 1, 164.
⁵ Takeda and Minato, Tetrahedron Letters, 1960, No. 22, 33; Chem. and Pharm. Bull. (Japan), 1961, 9, 619.

Takeda, Minato, and Ishikawa:

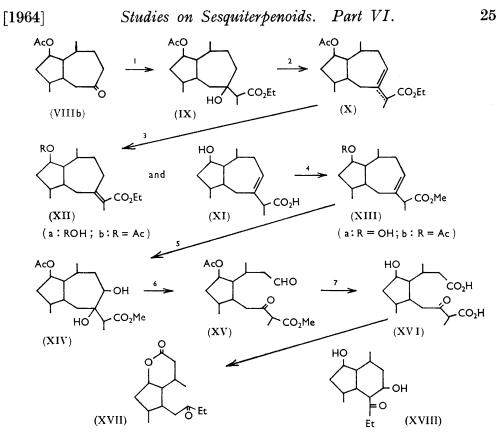
group in the five-membered ring right to the end of the reaction sequence would facilitate the dehydrogenation to give azulene, we decided to move the hydroxyl group of (V) to the adjacent position on the five-membered ring. Dehydration of (V) with phosphorus oxychloride-pyridine yielded a mixture of the double-bond isomers (VI) whose ethylene ketal derivative (VII) afforded the hydroxy-ketone (VIIIa) after hydroboration and deketalisation with 80% acetic acid.



Reagents: I, KMnO₄. 2, COCl₂. 3, O₃. 4, KOH. 5, H₂Pd-BaCO₃. 6, POCl₃-pyridine. 7, HO·CH₂·CH₂·OH-H⁺. 8, (i) B₂H₆, (ii) H₂O₂, (iii) H⁺.

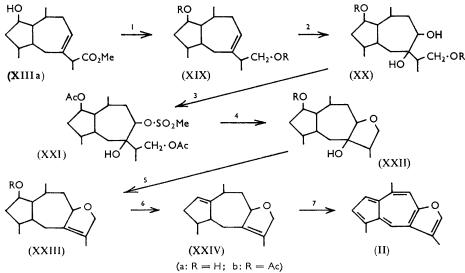
Reformatsky reaction of the acetoxy-ketone (VIIIb) with ethyl α -bromopropionate gave an oil (IX), which was dehydrated with thionyl chloride-pyridine to a mixture of the double-bond isomers (X). Separation of this mixture into the $\beta\gamma$ -unsaturated acid (XI) and $\alpha\beta$ -unsaturated ester (XIIa) was achieved by hydrolysis with potassium carbonate. The ester (XIIb), obtained by acetylation of (XIIa), had λ_{max} 230 m μ ($\alpha\beta$ -unsaturated ester) (ϵ 8900), whereas (XI) had a maximum at 206.5 m μ (ϵ 4910). Thus, it is evident that (XI) is a $\beta\gamma$ -unsaturated acid, but the position of the double bond has to be fixed. Esterification of (XI) with diazomethane followed by acetylation with acetic anhydridepyridine afforded a $\beta\gamma$ -unsaturated ester (XIIIb), whose n.m.r. spectrum shows a triplet centred at 4.31 τ (I = 6.6 c./sec.) corresponding to the hydrogen of a >C=CH- group, and its intensity shows that there is only one such hydrogen atom in the molecule. The triplet splitting indicates the existence of two protons on the adjacent carbon atom. On this basis the double bond in (XIIIb) is in the position shown. Moreover, oxidation of (XIIIb) with osmium tetroxide gave the dihydroxy-compound (XIV). A carbonyl derivative (XV) obtained by sodium periodate oxidation of (XIV) had v_{max} 2720 (aldehyde), 1738, and 1727 cm.⁻¹ (acetate, ester, aldehyde, and ketone). This compound (XV) formed a six-membered-ring lactone (XVII), ν_{max} , 1726 cm.⁻¹ (lactonic C=O), on silver oxide oxidation followed by ketonic hydrolysis of (XVI) with sulphuric acid. These results further confirm the situation assigned to the double bond in (XIIIb).

Lithium aluminium hydride reduction of (XIIIa) followed by acetylation with acetic anhydride-pyridine afforded a diacetoxy-compound (XIXb), which was oxidised with osmium tetroxide to an oily dihydroxy-derivative (XXb). Compound (XXIIa) was obtained by methanesulphonylation of (XXb) followed by ring-closure of (XXI) with



Reagents: 1, Me[•]CHBr[•]CO₂Et⁻⁻Zn. 2, SOCI₂⁻⁻pyridine. 3, K₂CO₃⁻⁻MeOH. 4, (i) CH₂N₂, (ii) (MeCO)₂O. 5, OsO₄. 6, NalO₄. 7, Ag₂O.

potassium hydroxide in methanol. Its monoacetate (XXIIb) was dehydrated with thionyl chloride-pyridine to give the unsaturated acetate (XXIIb) as a colourless unstable oil which was saponified by 4% potassium carbonate in methanol to yield (XXIIIa).



Reagents: I, LiAIH₄. 2, OsO₄. 3, MeSO₂CI-pyridine. 4, KOH. 5, SOCI₂-pyridine. 6, Me•C₆H₄•SO₂CIpyridine. 7, Pd-C.

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The position of the double bond in (XXIIIa) was established from its n.m.r. spectrum which shows a signal at 8.37 τ , corresponding to a methyl group on a double bond, and shows that there is no vinyl proton in the molecule.

The toluene-p-sulphonate of (XXIIIa) was dehydrated with pyridine to give an unstable colourless oil (XXIV), whose n.m.r. spectrum shows a multiplet centred at 4.65τ , corresponding to the vinyl proton; the intensity shows that there is only one such hydrogen atom in the molecule. From this result, another double bond in (XXIV) should be situated at the 7,7a-position. Dehydrogenation of (XXIV) yielded 3,5,8-trimethylazuleno[6,5-b]furan as lustrous violet-black plates, identical with linderazulene.

EXPERIMENTAL

Optical rotations are for dioxan solutions, and were obtained with a Rudolph Photoelectric Polarimeter model 200. Melting points were measured on a Kofler block ("Monoscope"; Hans Bock Co., Frankfurt) and are corrected.

7-Hydroxy-6,10-dimethylbicyclo[5,3,0]decan-3-one (V).—A mixture of 5% palladised barium carbonate (3.8 g.) in a solution of compound (IV) ⁵ (24.0 g.) in 95% ethanol (100 ml.) was hydrogenated at room temperature and atmospheric pressure; 1.17 equiv. of hydrogen were absorbed. The catalyst and the solvent were removed, the residue was extracted with ether, and the extract washed with water, dried (Na₂SO₄), and evaporated, leaving an oil (24.8 g.). After removal of the low-boiling fraction by distillation, the residue crystallised as the *product* (V) (16.1 g., 64%), plates, m. p. 103—104° (from acetone), $[\alpha]_D^{28} - 59.9°$ ($\pm 2^\circ$) (c 1.001) (Found: C, 73.8; H, 10.3. C₁₂H₂₀O₂ requires C, 73.4; H, 10.3%).

Dehydration of the Alcohol (V).—Phosphorus oxychloride (14·1 g.) was added with stirring during 20 min. to a solution of the alcohol (12·0 g.) in pyridine (120 ml.) in an ice-bath. The mixture was stirred at the same temperature for 20 min., at room temp. for 1 hr., and at 55—60° for 30 min., poured into ice-water, and extracted with ether. The extract was washed with 2N-sulphuric acid and 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, to give a colourless oil (VI) (9·17 g., 84%), b. p. 92—94°/1·2 mm.

Ketalisation of the Ketone (VI).—A solution of the ketone (9.17 g.) and toluene-p-sulphonic acid monohydrate (100 mg.) in ethylene glycol (250 ml.) was heated at 100° in an oil-bath for 40 min., and distilled at 130—135° (bath)/3 mm. during 2 hr., to leave 150 ml. of ethylene glycol in the flask. The distillate was extracted with light petroleum, washed with water, dried (Na₂SO₄), and evaporated, leaving a colourless oil (11·1 g.). Distillation gave the ketal (VII) as an oil (10·9 g., 96%), b. p. 87—89°/0·4 mm.

8-Hydroxy-6,10-dimethylbicyclo [5,3,0] decan-3-one (VIIIa).-Diborane, generated by the addition of a solution of sodium borohydride (1.02 g.) in diethylene glycol dimethyl ether (20 ml.) to a solution of boron trifluoride etherate (8.44 g.) in the same solvent (15 ml.), was passed into a flask containing the ketal (VII) (8.84 g.) in dry tetrahydrofuran (100 ml.) in a nitrogen atmosphere at 0-1° in an ice-bath during 1 hr. When the addition of sodium borohydride was complete, the diborane generator flask was warmed to $60-70^{\circ}$ and the residual diborane was driven into the reaction flask by the nitrogen. The mixture was stirred for another 2 hr. at 20-25°. To the mixture were added methanol (10 ml.) during 15 min., 3M-sodium hydroxide (10 ml.) during 20 min., and then 30% hydrogen peroxide (10 ml.) during 15 min., with stirring in an ice-bath. The mixture was stirred for 1 hr. at room temperature, evaporated in vacuo, and extracted with ether. The extract was washed with 2N-sodium thiosulphate, dried (Na_2SO_4) , and evaporated, leaving an oil (9.58 g.). The residue was dissolved in 80% acetic acid (75 ml.) and left for 3 hr. at room temperature. The solution was evaporated in vacuo, extracted with ether, washed with 2N-sodium carbonate, dried (Na2SO4), and evaporated, to give an oil (7.72 g.). The residue gave the product (VIIIa), prisms (2.93 g.), m. p. 102-103° (from ether), $[\alpha]_{n}^{27} - 59.9^{\circ} (\pm 2^{\circ})$ (c 1.102) (Found: C, 73.6; H, 10.3. $C_{12}H_{20}O_{2}$ requires: C, 73.4; H, 10.3%) and an oily mixture (4.86 g.). This mixture was acetylated, and chromatography on alumina gave the acetate (VIIIb), prisms (0.94 g.), m. p. 58-60° (from light petroleum), $[\alpha]_{D}^{22} - 17.3^{\circ} (\pm 2^{\circ})$ (c 1.048) (Found: C, 70.3; H, 9.55. $C_{14}H_{22}O_{3}$ requires C, 70.55; H, 9.3%). Acetylation of (VIIIa) gave the same acetate (3.38 g.) (total yield: 4.32 g., 46%).

Reformatsky Reaction of the Ketone (VIIIb).—A solution of ethyl α -bromopropionate (8.62 g.) in dry toluene (80 ml.) was added dropwise to a refluxing solution of the ketone (5.67 g.) in dry toluene (110 ml.) containing zinc dust (3.12 g.) and a piece of iodine, with stirring during 1 hr.,

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and this mixture was refluxed with stirring for another 2 hr. To the mixture were added water (30 ml.) and 2N-sulphuric acid (60 ml.). The toluene layer was washed with 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a yellow oil (7.76 g.). The residue was acetylated with acetic anhydride-pyridine to give the *ester* (IX), a colourless oil (5.94 g., 73%), b. p. 140—149°/0.05 mm., $[\alpha]_{\rm D}^{23}$ +38.6° (±2°) (c 1.043) (Found: C, 67.55; H, 9.45. C₁₉H₃₂O₅ requires C, 67.05; H, 9.45%).

Dehydration of the Alcohol (IX).—Thionyl chloride (800 mg.) was added dropwise to a solution of the alcohol (1·13 g.) in pyridine (10 ml.) in an ice-bath, and left for 1 hr. at the same temperature and for 2 hr. at room temperature. The solution was poured into ice-water and extracted with ether. The extract was washed with 2N-sulphuric acid and 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving an oil (1·0 g.). The residue was distilled to give the product (X) as a pale yellow oil (0·79 g., 74%), b. p. 121—125°/0·02 mm., $[\alpha]_{\rm D}^{23}$ +11·5° (±2°) (c 0·937), $\lambda_{\rm max}$ (in EtOH) 207 mµ (ε 4420) and 227 mµ (ε 4540), $v_{\rm max}$ (film) 1737 and 1710 cm.⁻¹ (Found: C, 70·75; H, 9·5. C₁₉H₃₀O₄ requires C, 70·8; H, 9·4%).

Separation of the $\beta\gamma$ -Unsaturated Acid (XI) and the $\alpha\beta$ -Unsaturated Ester (XIIa).—A solution of the ester (X) (4.2 g.) and potassium carbonate (5.0 g.) in 80% methanol was refluxed for 8 hr. on a steam-bath and evaporated. The residue was dissolved in water and extracted with ether. The extract gave the ester (XIIa) as an oil (1.59 g., 38%). Acetate (XIIb) was an oil, b. p. 162—163°/1.5 mm., $[\alpha]_{p}^{26} - 26.7^{\circ} (\pm 2^{\circ})$ (c 1.122), λ_{max} (in EtOH) 230 mµ (ϵ 8900), ν_{max} (film) 1736, 1712, and 1621 cm.⁻¹ (Found: C, 70.7; H, 9.4. C₁₉H₃₀O₄ requires C, 70.8; H, 9.4%).

The alkaline aqueous layer was acidified to Congo Red with 2N-sulphuric acid, extracted with ether, washed with water, dried (Na₂SO₄), and evaporated, leaving a crystalline substance (1.82 g., 43%), which was recrystallised from ether to give the *acid* (XI) as needles, m. p. 138—141°, $[\alpha]_{p}^{22} + 29.8^{\circ} (\pm 2^{\circ})$ (*c* 1.082), λ_{max} (in EtOH) 206.5 mµ (ε 4910) (Found: C, 71.25; H, 9.6. C₁₅H₂₄O₃ requires C, 71.4; H, 9.6%).

Esterification of the Acid (XI).— $\beta\gamma$ -Unsaturated acid (XI) was esterified with diazomethane in ether and acetylated with acetic anhydride-pyridine, to give the *ester* (XIIIb) as an oil, b. p. 118—120/0.05 mm., $[\alpha]_{D}^{22} + 54 \cdot 1^{\circ} (\pm 2^{\circ})$ (c 1.156), λ_{max} . (in EtOH) 206.5 m μ (ϵ 4450) (Found: C, 70.25; H, 9.25. $C_{18}H_{28}O_4$ requires C, 70.1; H, 9.15%).

Osmium Tetroxide Oxidation of the Ester (XIIIb).—A solution of osmium tetroxide (608 mg., 1·1 equiv.) in dry benzene (6 ml.), and then dry pyridine (0·6 ml.), were added to a solution of the ester (672 mg.) in dry benzene (14 ml.) in an ice-bath, and the mixture was left for 6 days at room temperature. Dioxan (15 ml.) was added, and the mixture was saturated with hydrogen sulphide. The black precipitate was filtered off and well washed with methanol. The filtrate and washings were evaporated *in vacuo*, and extracted with chloroform, and the extract was washed with 2N-sulphuric acid, water, 2N-sodium carbonate, and water, dried (Na₂SO₄), and evaporated, leaving a crystalline substance (712 mg.), which was recrystallised from acetone to give the *dihydroxy-ester* (XIV) (231 mg.), needles, m. p. 154–156°, $[\alpha]_{p}^{22}$ +88·7° (±2°) (c 1.054) (Found: C, 62·95; H, 8·85. C₁₈H₃₀O₆ requires C, 63·1; H, 8·8%), and a colourless oil (481 mg.), a mixture of (XIV) and a stereoisomer of (XIV).

Oxidation of the Ester (XIV) with Sodium Periodate.—A solution of sodium periodate (125 mg.) in water (8 ml.) was added to a solution of the ester (100 mg.) in methanol (5 ml.) and dioxan (5 ml.), and the mixture left at room temperature for 47 hr., evaporated *in vacuo*, and extracted with ether. The extract was washed with 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a colourless oil (XV) (98 mg.), $\nu_{max.}$ (film) 2720 (CHO), 1738, and 1727 cm.⁻¹.

Conversion of the Ester (XV) into the Lactone (XVII).—10% Sodium hydroxide (0.9 ml.) was added, with stirring, to a solution of silver nitrate (101 mg.) in water (1 ml.). To this mixture was added, with stirring, a solution of the ester (XV) (98 mg.) in dioxan (3 ml.) during 10 min., and stirring was continued for an additional 1 hr. at room temperature. The mixture was filtered and the filtrate extracted with ether. The aqueous layer was acidified with 2N-sulphuric acid, extracted with ether, washed with water, dried (Na₂SO₄), and evaporated, leaving an oil (79 mg.). The residue was dissolved in 10% sodium carbonate-methanol (2 ml.) and the mixture refluxed for 2 hr., acidified with 2N-sulphuric acid, refluxed for 1 hr., evaporated, and extracted with ether. The extract gave a lactone fraction, a colourless oil (XVII) (18 mg.), ν_{max} . (film) 1735 (lactone) and 1717 cm.⁻¹ (ketone), and a neutral fraction, prisms, m. p. 132—134° (XVIII) (39 mg.), ν_{max} . (in CHCl₃) 1707 cm.⁻¹ (C=O) (Found: C, 69·7; H, 10·0. C₁₄H₂₄O₃

requires C, 70·1; H, 10·1%). The oily lactone (XVII) gave a 2,4-dinitrophenylhydrazone, a reddish orange oil, ν_{max} (in CHCl₃) 1726 cm.⁻¹ (lactonic C=O).

Reduction of the Ester (XIIIa) with Lithium Aluminium Hydride.—A solution of the ester (3.14 g.) in dry ether (35 ml.) was added dropwise, with stirring, to a suspension of lithium aluminium hydride (670 mg.) in dry ether (70 ml.) and stirred for 3 hr. at room temperature. The mixture was decomposed by addition of ice-water and then 2N-sulphuric acid, in an ice-bath, and extracted with ether; the extract was washed with 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a colourless oil (XIXa) (2.84 g.), which was acetylated with acetic anhydride-pyridine to give an oil (XIXb), b. p. 118—120°/0.002 mm. (3.65 g., 96%).

Osmium Tetroxide Oxidation of the Acetate (XIXb).—A solution of osmium tetroxide (285 mg., 1·2 equiv.) in dry benzene (3 ml.), and then dry pyridine (0·3 ml.), were added to a solution of the acetate (XIXb) (300 mg.) in dry benzene (6 ml.) in an ice-bath, and the mixture was left for 41 hr. at room temperature. Benzene (10 ml.) was added, and the mixture was saturated with hydrogen sulphide, filtered, and the solid well washed with benzene. The filtrate and washings were washed with 2N-sulphuric acid, water, and 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a brown viscous oil (306 mg.). The residue was dissolved in light petroleum-benzene (1:1) (30 ml.) and chromatographed on alumina (10 g.), to give a colourless oil (XXb) (242 mg., 74%), which was saponified with 5% potassium carbonate-methanol, giving the *tetraol* (XXa), prisms, m. p. 153—154° (from ethyl acetate), $[\alpha]_{D^{23}} + 28\cdot7^{\circ} (\pm 4^{\circ})$ (c 0.519) (Found: C, 66·35; H, 10·4. C₁₅H₂₈O₄ requires C, 66·15; H, 10·4%).

Ring-closure of the Alcohol (XXb).—On treatment with methanesulphonyl chloride (37 mg.)– pyridine (2 ml.) at room temperature, (XXb) (93 mg.) afforded its oily methanesulphonate (XXI) (106 mg.). This was dissolved in 5% potassium hydroxide-methanol (5 ml.) and refluxed for 2 hr. The solution was evaporated, extracted with ether, and the extract washed with water, dried (Na₂SO₄), and evaporated, leaving an oil (65 mg.). The residue was dissolved in benzene (7 ml.) and chromatographed on alumina (2 g.). Elution with benzene-chloroform (7:3 and 5:5) and chloroform afforded the *furan derivative* (XXIIa) (33 mg., 50%), prisms, m. p. 169—170° (from acetone-ether), $[\alpha]_{\rm p}^{23} - 26 \cdot 1^{\circ} (\pm 2^{\circ})$ (c 1.036) (Found: C, 71.0; H, 10.45. C₁₅H₂₆O₃ requires C, 70.8; H, 10.3%). The monoacetate (XXIIb) formed prisms, m. p. 154·5—155·5°.

Dehydration of the Alcohol (XXIIb).—Thionyl chloride (361 mg.) was added dropwise, with stirring, to a solution of (XXIIb) (449 mg.) in pyridine (9 ml.) in an ice-bath and the mixture left for 2 hr. at room temperature, poured on to ice-water, and extracted with ether; the extract was washed with 2N-sulphuric acid, water, and 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a yellow oil (XXIIb) (411 mg.). The residue was dissolved in 4% potassium carbonate-methanol (10 ml.), refluxed for 3 hr. in a nitrogen atmosphere, evaporated, extracted with ether, washed with water, dried (Na₂SO₄), and evaporated, leaving the product (XXIIIa) (334 mg., 91%), needles, m. p. 92—94° (from ether) (Found: C, 76·1; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·25%).

Dehydration of the Alcohol (XXIIIa).—A solution of the alcohol (212 mg.) and toluenep-sulphonyl chloride (260 mg.) in pyridine (5 ml.) was heated at 95—100° for 1 hr. in a nitrogen atmosphere. The solution was poured on to ice-water, and extracted with ether; the extract was washed with 2N-sulphuric acid, water, and 2N-sodium carbonate, dried (Na₂SO₄), and evaporated, leaving a brown oil (200 mg.). The residue was dissolved in light petroleum (20 ml.) and chromatographed on alumina (6 g.), to give the *product* (XXIV) an unstable colourless oil (125 mg., 64%), v_{max} . (film) 3063, 1052, 845, and 810 cm.⁻¹.

Dehydrogenation of (XXIV).—When a mixture of (XXIV) (17.1 mg.) and 10% palladiumcharcoal (8.4 mg.) in a test tube (18 cm.) was heated at 300—310° for 3 min. in a nitrogen atmosphere, the violet azulene immediately condensed on the upper part of the tube and was extracted with light petroleum. The extract was evaporated, leaving a violet oil (15 mg.), ε_{562} 104 (linderazulene, ε_{562} 505). The residue was dissolved in light petroleum and chromatographed on neutral alumina ("Woelm," Activity II) (2.0 g.), to give violet needles (4.0 mg., 23%). Under the same conditions, (XXIV) (250 mg.) was dehydrogenated to give a violet oil (203 mg.), which was chromatographed, giving the violet needles (45 mg.). The crude azulene afforded a 2,4,6-trinitrobenzene adduct, violet-black needles, m. p. 154—155° (from ethanol), identical with that from linderazulene (mixed m. p.). The 2,4,6-trinitrobenzene adduct was dissolved in light petroleum and chromatographed on neutral alumina, to give 3,5,8trimethylazuleno[6,5-b]furan (II), lustrous violet-black plates, m. p. 106—107° (from isopropyl

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alcohol) (Found: C, 85.25; H, 7.0. $C_{15}H_{14}O$ requires C, 85.7; H, 6.7%), identical with linderazulene (mixed m. p., and ultraviolet, visible, and infrared spectra).

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