Bridged Ring Systems. Part XVIII.[1] A Total Synthesis of (±)-Guaiol [2]

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Racemic guaiol [guai-1(5)-en-11-ol] has been synthesised from laevulinic acid and 2-methylcyclopentanone *via* 1-methyltricyclo[6.2.1.$0^{2,6}$]undec-2(6)-ene-5,11-dione. Bridge fission of this intermediate yielded an octahydroazulene keto-ester which has been elaborated to guaiol.

ALTHOUGH the structure [3] and stereochemistry [4] of the sesquiterpene alcohol guaiol (I) are both firmly established, the synthesis of this [5] or related polyhydroazulenes [6] presents special problems, namely (*a*) the construction of a suitably substituted seven-membered ring and (*b*) control of the stereochemistry. This paper describes a synthesis of (±)-guaiol which embodies a simple solution of problem (*a*).

Previously [7,8] we have explored a synthetic route to medium-sized rings involving bridge scission of bridged bicyclic intermediates, *e.g.* [8] (II) ⟶ (III) ⟶ (IV); the extension of this route to a synthesis of guaiol seemed feasible. In contrast to (II), the methyl derivative (V), which was conveniently available,[9] could be expected to yield three isomeric bridged bicyclic ketones (VI)—(VIII) under the same conditions. In fact only the first was encountered [τ 8·95 (3H, s)] and it was smoothly transformed into the ester mixture (IX) by methanolic hydrogen chloride. Since this ester incorporated substituents in two of the desired sites, attempts were then made to effect substitution at C-4, but both (IX) and its precursor (VI) afforded complex mixtures so this approach was abandoned in favour of one which would guarantee functionality at C-4.

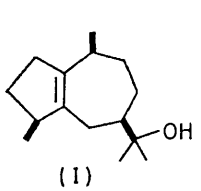
The Mannich base (X) [10] derived from laevulinic acid was esterified and the ester (XI) was treated with 2-methylcyclopentanone under thermal Michael conditions, this sequence affording the dione (XII) conveniently and in 68% yield. A by-product (XIV), isolated in 4% yield, arises *via* transaminomethylation from the Mannich base. Judged by the complexity of the n.m.r. methyl signal at τ 8·9 the diketo-ester (XII) was a mixture of isomers, although no g.l.c. separation was detected. The formation of the 2,2-disubstituted isomer (XV) was not expected [9,11] and indeed subsequent transformations corroborated this assumption.

The ring closure of (XII) to a bridged bicyclic ketone was more troublesome. The cyclisation of oxobutylcycloalkanones such as (XII) can conceivably lead to either of two systems, (XVII) and (XVIII), and it was important to us to understand the factors which govern a choice between them. Although it has been suggested [12] that the conformation of the side chain is all-important, we have postulated elsewhere [13] that the *reaction conditions* are the vital factor; *i.e.* that bridged ketones are the products of kinetic control, whereas the fused αβ-enones are formed under equilibrium conditions. It was therefore not surprising that ethanolic sodium ethoxide converted (XII) into the enone acid (XVI). This product showed two overlapping methyl doublets in the n.m.r. spectrum at τ 8·9 (*J* 7 Hz), indicating that it was a mixture of stereoisomers, but verifying too that the Michael product was (XII) rather than (XV). More

[1] Part XVII, G. L. Buchanan and G. A. R. Young, *J.C.S. Perkin I*, 1973, 732.
[2] Preliminary report, G. L. Buchanan and G. A. R. Young, *Chem. Comm.*, 1971, 643.
[3] E. H. Rodd, 'Chemistry of Carbon Compounds,' vol. IIB, Elsevier, London, 1953, p. 666.
[4] H. Minato, *Tetrahedron Letters*, 1961, 280.
[5] J. A. Marshall, A. E. Green, and R. Ruden, *Tetrahedron Letters*, 1971, 855.
[6] For leading references see C. H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, 1971, **93**, 1746.
[7] For a review, see G. L. Buchanan, *Topics Carbocyclic Chem.*, 1969, 227.
[8] G. L. Buchanan, A. C. W. Curran, J. McCrae, and G. W. McLay, *Tetrahedron*, 1967, **23**, 4729.
[9] H. L. Brown, G. L. Buchanan, A. C. W. Curran, and G. W. McLay, *Tetrahedron*, 1968, **24**, 4565.
[10] G. L. Buchanan, A. C. W. Curran, and R. T. Wall, *Tetrahedron*, 1969, **25**, 5503.
[11] E. M. Austin, H. L. Brown, and G. L. Buchanan, *Tetrahedron*, 1969, **25**, 5509; E. M. Austin, H. L. Brown, G. L. Buchanan, and R. A. Raphael, jun., *ibid.*, p. 5517.
[12] S. A. Julia, *Bull. Soc. chim. France*, 1954, 780; J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, 1965, **30**, 3462; R. D. Sands, *ibid.*, 1963, **28**, 1710.
[13] For a review, see G. L. Buchanan, *Topics Carbocyclic Chem.*, 1969, 205.

surprisingly, treatment with either boron trifluoride or toluene-*p*-sulphonic afforded the related ester (XVII), although these reaction conditions can usually be relied upon to give bridged products.[8,14] The latter reagent also yielded the keto-lactone (XIX) as a mixture of two

The mixture of lactones was converted by polyphosphoric acid at 100° into a single αβ-enone (XX), which showed the expected spectroscopic features. Thus far, lack of stereochemical control had not been a serious obstacle but it was now an important consideration in the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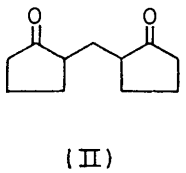
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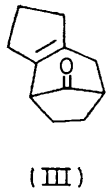
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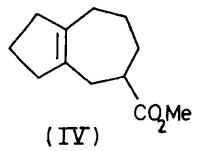
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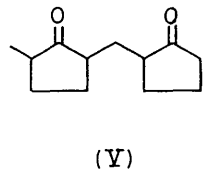
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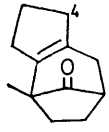
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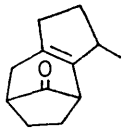
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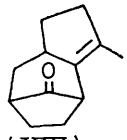
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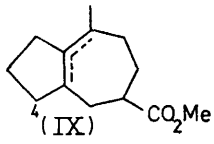
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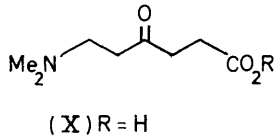
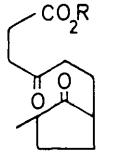
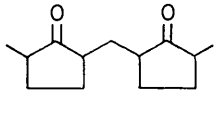

(X) R = H
(XI) R = Et

stereoisomers, and this prompted us to attempt to trap the intermediate aldol, by carrying out the cyclisation on the acid (XIII) rather than its ester. Indeed, stirring the ester with 10N-hydrochloric acid at room temperature caused hydrolysis and brought about cyclisation to (XIX) in 80% yield. As before, the product was a mixture of stereoisomers but the proportions differed substantially from that found before. The spirolactones were separated and independently characterised. They were

elaboration of (XX). The vinylogous β-diketone (XX) afforded the ester (XXI) on treatment with either acid or base and although the product in each case was homogeneous according to g.l.c. and t.l.c., the n.m.r. spectrum indicated that it was a 1 : 1 mixture of stereoisomers. In each spectrum the methyl signal was a clear doublet (J 7 Hz). However, a 70 : 30 enrichment was obtained by ' sacrificial ' crystallisation, in preparation for the final stage. The synthesis was completed by treatment


(XII) R = Et
(XIII) R = H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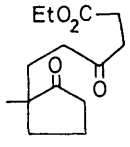
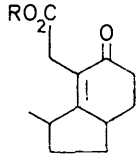
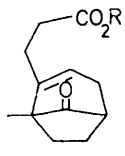

(XV)


(XVI) R = H
(XVII) R = Et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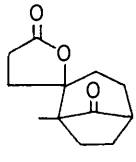
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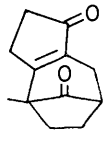
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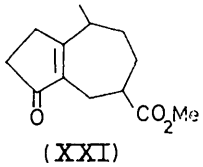
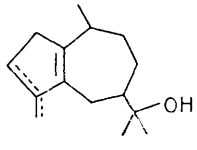

(XXI)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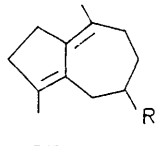
(XXIII)

also shown to equilibrate at 60° in the presence of polyphosphoric acid and are thus stereoisomers rather than structural isomers. These experiments appear to consolidate our proposition that the bridged bicyclic products are the first formed, in a rapid reversible step.

of the 1 : 1 mixture with an excess of methyl-lithium, mild dehydration of the resulting allylic alcohol, and catalytic reduction of the olefin mixture (XXII). The product was a mixture of four epimers which were separable by g.l.c. One of these, which constituted 10% of the mixture, was identical (g.l.c. and mass spectrum) with natural guaiol (I). The conversion (XXI) ⟶ (I) was then repeated on the enriched material, but the

[14] (*a*) E. J. Corey and S. Nozoe, *J. Amer. Chem. Soc.*, 1965, **87**, 5728; (*b*) for a review, see G. L. Buchanan, *Topics Carbocyclic Chem.*, 1969, 200.

product mixture was identical in composition with that obtained before, and it must be assumed that the reaction conditions are such that the equilibration of (XXI) is re-established. In one of a number of attempts to improve selectivity, the ester (XXI) was treated with 1 equiv. of methyl-lithium and the product was dehydrated. The final product showed $\lambda_{max.}$ 247 nm and vinylic absorption in the n.m.r. suggesting that the desired heteroannular diene of type (XXIII) was not the major intermediate.

EXPERIMENTAL

Microanalyses were performed by Miss F. Cowan, mass spectra were recorded on an A.E.I. MS12 instrument by Mr. A. Ritchie, and n.m.r. spectra were obtained by Mr. A. Haetzman on a Varian T60 instrument. G.l.c. mass spectral analysis was carried out on an LKB 9000 instrument under the direction of Dr. C. J. W. Brooks.

1-Methyltricyclo[6.2.1.0^{2,6}]*undec-2(6)-en-11-one* (VI).—The dione (V) (260 mg) and toluene-*p*-sulphonic acid (120 mg) in benzene (25 ml) were refluxed in a Dean–Stark water separator for 5 h, and after cooling anhydrous potassium carbonate (200 mg) was added. The benzene-soluble material was purified by preparative t.l.c. (20% ethyl acetate–petroleum) yielding the *tricyclic ketone* (182 mg, 65%) as a camphoraceous oil, b.p. 82—84° at 0·9 mmHg, t_R 2·9 min on 1% Apiezon L at 150°, $\nu_{max.}$ (CCl_4) 1758 cm^{-1} (CO), *m/e* 176, τ 8·95 (3H, s) (Found: C, 81·5; H, 8·4. $C_{12}H_{16}O$ requires C, 81·5; H, 8·15%).

Methyl 2-Methylbicyclo[5.3.0]*dec-1(7)-ene-5-carboxylate and its Isomer* (IX).—The tricyclic ketone (VI) (80 mg) in dry methanol (10 ml) containing concentrated sulphuric acid (1 ml) was boiled under reflux for 16 h; the mixture was cooled, concentrated, and dissolved in ether. The solution was washed ($NaHCO_3$; brine), dried, and concentrated. Preparative t.l.c. (20% ethyl acetate–petroleum) afforded the *ester* (42 mg, 50%) shown by g.l.c. to be a 1 : 1 mixture, $\nu_{max.}$ 1730 cm^{-1} (CO), τ 9·0 (d, *J* 7 Hz) and 8·36 (s) (Found: C, 74·8; H, 9·6. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·7%).

Ethyl 6-(3-*Methyl*-2-*oxocyclopentyl*)-4-*oxohexanoate* (XII).—6-Dimethylamino-4-oxohexanoic acid hydrochloride [10,15] (20 g) was refluxed overnight in dry ethanol (50 ml) containing concentrated sulphuric acid (1 ml). The solvent was removed *in vacuo* and the residue, dissolved in water, was basified and extracted with ether. The free base (13·2 g, 70%) obtained by evaporation *in vacuo* was added to 2-methylcyclopentanone (18 g) and refluxed for 16 g. On cooling, water (100 ml) and 6N-hydrochloric acid (10 ml) were added and the organic material was extracted into ether. Distillation removed the excess of methylcyclopentanone and the residue was chromatographed on silica (480 g). Elution with 2% ethyl acetate–petroleum yielded *2-methyl-5-(3-methyl-2-oxocyclopentylmethyl)cyclopentanone* (XIV) (500 mg), m.p. 44—52° (Found: C, 74·8; H, 9·6. $C_{13}H_{22}O_2$ requires C, 75·0; H, 9·7%), *m/e* 2·8, τ 8·9 (6H, overlapping doublets, *J* 6 Hz).

Elution with 10% ethyl acetate–petroleum afforded a mixture of epimeric *diketo-esters* (XII) (11·2 g, 68%), b.p. 131—132° at 0·2 mmHg, which were inseparable on g.l.c. (5% QF1) (Found: C, 66·4; H, 8·55. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%), *m/e* 254, $\nu_{max.}$ 1737 and 1728 cm^{-1} (CO), τ 8·8 (6H, m).

Cyclisations of the Diketo-ester (XII).—(*a*) The dione ester (100 mg) was stirred at room temperature for 2 h with sodium ethoxide [from sodium (30 mg)] in ethanol (20 ml). The mixture was then flooded with water, washed with ether, acidified, and extracted with ethyl acetate, affording an oil (68 mg) showing a broad CO_2H band in the i.r. spectrum, and $\lambda_{max.}$ 241 nm (ε 12,000). It was identical (i.r.) with the acid (XVI) obtained by hydrolysis) potassium hydroxide–ethanol) of (XVII).

(*b*) Boron trifluoride [16] was bubbled into a solution of the dione ester (100 mg) in dry methylene chloride (15 ml) until the solution turned yellow and became faintly turbid (10 min). Stirring was continued overnight at room temperature, and thereafter the solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The crude product (77 mg) showed three components on g.l.c. (5% QF1 at 175°; t_R 4·5, 8·5, and 9·9 min) in ratio 3 : 5 : 2. Preparative t.l.c. (40% ethyl acetate–petroleum) gave fractions 2 and 3 as an inseparable mixture of stereoisomers of *ethyl 2,3,5,6,7,7a-hexahydro-3-methyl-5-oxoinden-4-ylacetate* (XVII), b.p. 120° at 0·5 mmHg (Found: C, 71·3; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%), $\nu_{max.}$ (CCl_4) 1732 and 1664 cm^{-1} (CO), $\lambda_{max.}$ (EtOH) 243 nm (ε 12,100), *m/e* 236, τ 8·9 (6H, complex).

(*c*) The dione ester (340 mg) and toluene-*p*-sulphonic acid (350 mg) in benzene (25 ml) were refluxed in a Dean–Stark water separator for 4 h; the solution was then stored over potassium carbonate (400 mg) for 12 h. The benzene-soluble material (358 mg) obtained by evaporation was separated by preparative t.l.c. (40% ethyl acetate–petroleum) into the ester (XVII) (80 mg) and *1-methylbicyclo*-[3.2.1]*octane-2-spiro-2′-tetrahydrofuran-5′,8-dione* (XIX) (76 mg). The latter, purified by sublimation at 80° and 0·2 mmHg, had m.p. 106—107° (Found: C, 69·5; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%), $\nu_{max.}$ (CCl_4) 1780 and 1750 cm^{-1}, *m/e* 208, τ 9·0 (3H, s), t_R 16·5 min on 5% QF1 at 175°.

An isomeric spirolactone (XIX), t_R 32 min, was observed by g.l.c. of the crude product and was identical with that described in (*d*).

(*d*) The dione ester (5 g) was stirred for 12 h at room temperature with 10N-hydrochloric acid (60 ml). The opalescent solution was then diluted with water, and extracted with ethyl acetate. After washing ($NaHCO_3$) and drying, the solvent was removed, affording the *isomeric spirolactone* (XIX) (3·18 g) which solidified on trituration with ether and was purified by sublimation; m.p. 105—112° (Found: C, 68·95; H, 7·7%), $\nu_{max.}$ (CCl_4) 1772 and 1758 cm^{-1} (CO), *m/e* 208, τ 9·0 (3H, s), t_R 32 min on 5% QF1 at 175°.

G.l.c. of the crude product showed the presence of both spiro-lactones (t_R 16·5 and 32 min) in the ratio 1 : 5. Their mass spectra were almost identical.

1-Methyltricyclo[6.2.1.0^{2,6}]*undec-2(6)-ene-6,11-dione* (XX).—The mixture of spiro-lactones (3·6 g) was stirred with polyphosphoric acid (40 g) for 3 h at 100°, then poured on ice (100 g) and extracted with ethyl acetate. Removal of solvent left a dark red gum (1·9 g) which was purified by preparative t.l.c. (60% ethyl acetate–petroleum) and vacuum sublimation (110° at 0·3 mmHg) to give the *dione*, m.p. 100—102°, in 35% overall yield (Found: C, 75·7; H, 7·3. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%), $\nu_{max.}$ (CCl_4) 1760, 1705, and 1635 cm^{-1}, τ 8·9 (3H, s), $\lambda_{max.}$ (EtOH) 227 (ε 8100), 247 (9000), and 300 (300) nm, *m/e* 190, t_R 9·6 min on 5% QF1 at 175°.

[15] C. Mannich and M. Bauroth, *Ber.*, 1924, **57**, 1108.
[16] J. T. Adams, R. Levine, and C. R. Hauser, *Org. Synth.*, Coll. Vol. III, 1955, p. 405, Note 3.

Methyl 2-Methyl-8-oxobicyclo[5.3.0]*dec*-1(7)-*ene*-5-*carboxylate* (XXI).—(*a*) The enedione (XX) (110 mg) was refluxed for 60 h in methanol (15 ml) containing concentrated sulphuric acid (1 ml). The solvent was removed *in vacuo* and the residue was dissolved in ether and washed with aqueous sodium hydrogen carbonate. Evaporation yielded a yellow oil which was purified by preparative t.l.c. (60% ethyl acetate–petroleum), affording the *methyl ester*, b.p. 120° at 0·3 mmHg (58 mg) (Found: C, 70·1; H, 8·0. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%), $\nu_{max.}$ (CCl_4) 1735 and 1704 cm^{-1} (CO), $\lambda_{max.}$ (EtOH) 237 nm (ε 11,900), *m/e* 222, t_R 12·5 min on 5% QF1 at 175°; τ 8·8 (3H, two overlapping doublets, *J* 7 Hz) and 6·3 (3H, s).

(*b*) The enedione (950 mg) was refluxed for 2 h with sodium methoxide [from sodium (230 mg)] in methanol (40 ml). The solvent was removed, ether was added, and the organic phase was washed (2N-HCl; brine), dried, and evaporated, affording a yellow oil (916 mg) identical with that obtained in (*a*).

Some fractions from column chromatography on silica crystallised slowly, and were recrystallised (from light petroleum–ether) to give a 70 : 30 mixture of isomers (m.p. 48—74°) (based on n.m.r. integration at τ 8·8).

(±)-*Guaiol* (I).—The keto-ester (XXI) (106 mg, 0·48 mmol) in anhydrous ether (10 ml) was treated with ethereal methyl-lithium (4 mmol) and stirred overnight at room temperature. Saturated ammonium chloride solution was added and, after shaking for 5 min, the organic phase was washed, dried, and concentrated. The crude oily product was hydrogenated (5% Pd–C) in ethyl acetate, and re-isolated. T.l.c. indicated that it had the same R_F value as guaiol, but g.l.c. showed four components. Combined g.l.c.–mass spectroscopy revealed that these were isomers.

Fraction	%	t_R/min	Retention index	*m/e*
A	10	8·9	1715	222
B	25	9·7	1725	222
C	40	12·1	1775	222
D	25	12·9	1780	222
Guaiol		8·9	1715	222

• 1% OV17 at 125°.

The mass spectrum of fraction A was identical with that of natural guaiol, with significant peaks at *m/e* 222, 204, 189, 161, 107, 93, 81, and 59.

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