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BRIDGED RING SYSTEMS—I
SYNTHETIC APPROACHES TO CLOVENE

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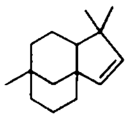
Abstract—Details are given for the synthesis of 5-methyl-1-(ketoisobutenyl) bicyclo [3:3:1] nonan-3-one (X) and its attempted conversion into a clovene precursor (XI) is described.

One product of the acid-catalysed rearrangement of caryophyllene is the isomeric tricyclic hydrocarbon clovene (I), the structure of which has been rigorously established in a noteworthy series of papers by Barton *et al.*[1] As part of a more extensive study of the bicyclo [3:3:1] nonane system, which makes up part of the clovene skeleton, synthetic approaches to this interesting sesquiterpene have been initiated.



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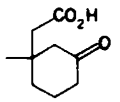

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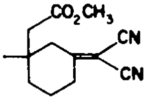

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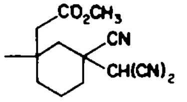

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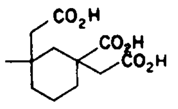

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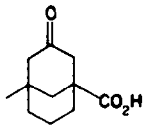

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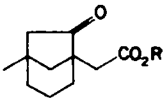

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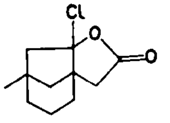

VIII

Michael addition of diethyl malonate to 3-methylcyclohex-2-enone produced, after hydrolysis and decarboxylation, the crystalline keto-acid (II).[2] Condensation of its methyl ester with malononitrile under Knoevenagel conditions furnished the conjugated dinitrile (III). Addition of hydrogen cyanide to the activated double bond of III employing the usual conditions[3] were uniformly unsuccessful, but acceptable yields of the required trinitrile (IV) were eventually obtained by the use of sodium cyanide in dimethylformamide. The mixture of stereoisomers thus obtained was hydrolysed with fuming hydrochloric acid to the tricarboxylic acids (V). High dilution Dieckmann cyclization of the corresponding methyl esters followed by acid hydrolysis and decarboxylation furnished a mixture of the two bicycloketoacids (VI) and (VII, R = H). From this mixture the required crystalline 5-methylbicyclo [3:3:1]-nonan-3-one-1-carboxylic acid (VI) could be separated by solvent trituration. A more efficient method of separation involved reaction of the mixture of acids with

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[1] A. Aebi, D. H. R. Barton, A. W. Burgstahler and A. S. Lindsey, *J. Chem. Soc.* 4659 (1954), and references cited therein; cf. H. W. Lutz and E. B. Reid, *J. Chem. Soc.* 2265 (1954), and A. Eschenmoser and H. H. Gunthard, *Helv. Chim. Acta* **34**, 2338 (1951).

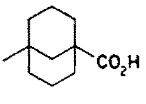
[2] E. H. Farmer and J. Ross, *J. Chem. Soc.* 2358 (1925).

[3] A. Lapworth and J. A. McRae, *J. Chem. Soc.* 2741 (1922).

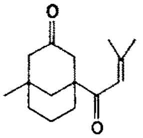
oxalyl chloride followed by treatment of the acid chloride mixture with aluminium chloride. Under these conditions the acid chloride of VII was converted into the chloro-lactone (VIII), the acid chloride of VI remaining unaffected. Chromatography on alumina readily separated the crystalline chlorolactone (VIII), while the acid chloride of VI was readily hydrolysed *in situ* by the alumina to the free acid (VI) which was strongly adsorbed.

The structure of the crystalline acid (VI) thus obtained was confirmed by the strong absorption of its methyl ester at 1710 cm^{-1} (six-ring C═O) and 1733 cm^{-1} (methyl ester) and by its conversion through Wolff–Kishner reduction to the crystalline 5-methylbicyclo [3:3:1] nonane-1-carboxylic acid (IX), identical with a specimen-prepared by an alternative route.[4] For further elaboration of the ketoacid (VI) it was at first deemed desirable to protect the carbonyl function. However, the grouping proved unexpectedly resistant to ketalization, even under forcing conditions,[5] and the synthesis was therefore continued with the ketoacid (VI) itself. The corresponding acid chloride was treated with isobutene in the presence of stannic chloride[6] and the crude reaction product filtered through alumina. This not only served to remove the polyisobutene formed, but also effected dehydrochlorination to yield the required enedione (X) which could be eluted with ether. Purification of this product was tedious because of a persistent impurity consisting of the t-butyl ester of VI, but repeated chromatography on silica gel finally yielded a product showing the expected maximal light absorption at 241 mμ (ε 12,800) 1710 cm^{-1} (six-ring C═O) and 1685 cm^{-1} (conjugated C═O) with only a trace of absorption at 1740 cm^{-1} (t-butyl ester).

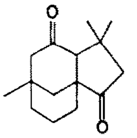
It was confidently expected that the enedione (X) would undergo an internal Michael condensation to yield the tricyclic compound (XI) containing the complete carbon skeleton of clovene, but all the reaction conditions tried to effect this ring closure were unsuccessful. Either the enedione (X) was recovered unchanged, or a retro-aldol cleavage occurred to give the methyl ketone (XII). This failure may be bound up with the presence of the *gem*-dimethyl function of X which could act as an effective "distance piece" to prevent formation of the required carbon–carbon bond.



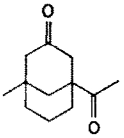
IX



X



XI



XII

It was found that the side-chain carbonyl group of the enedione (X) could be selectively reduced by sodium borohydride in anhydrous methanol to give the enolone (XIII). This alcohol was treated with *p*-bromobenzenesulphonyl chloride in pyridine in an attempt to form the corresponding *p*-bromobenzenesulphonate which, it was hoped, would undergo an intramolecular S$_N$2′ displacement[7] to give the clovenone (XIV) by treatment with base. However the main product from this reaction was the conjugated diene (XV).

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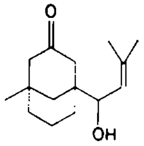
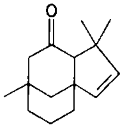
[4] D. Jhaveri, R. D. H. Murray, W. Parker and R. A. Raphael, *Tetrahedron* in press.
[5] H. J. Dauben, B. Löken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).
[6] J. Colonge and K. Mostafavi, *Bull. Soc. Chim. Fr.* **6**, 335 (1939).
[7] G. Stork and W. N. White, *J. Amer. Chem. Soc.* **78**, 4609 (1956).

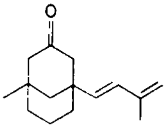
In view of the unpromising nature of the above intermediates, alternative routes to clovene are now being actively explored.



XIII



XIV



XV

EXPERIMENTAL

Ultra-violet absorption spectra refer to ethanol solutions and were measured with a Unicam S.P. 500 spectrophotometer. Melting points (corrected) were determined on a Kofler block. Boiling points are uncorrected. The alumina used for chromatography (Spence, type H) was acid-washed and activated and graded according to the method of Brockman and Schodder. Light petroleum refers to the fraction b.p. 40–60° unless stated otherwise.

3-*Methylcyclohex-2-enone*. Ethyl acetoacetate and paraformaldehyde were condensed in the presence of piperidine.[8] Hydrolysis with 20% sulphuric acid afforded 3-methylcyclohex-2-enone which was fractionally distilled before use.

3-*Methylcyclohexanone*-3-*acetic acid* (II). This is a modification of the method employed by Farmer and Ross.[2] Freshly distilled diethyl malonate (480 g) was added dropwise over 1 hr to a stirred solution of sodium (70 g) in absolute ethanol (3 l.) at room temp and the stirring continued for a further hour. 3-Methylcyclohex-2-enone (330 g) was added dropwise and the reaction mixture stirred at room temp for 5 days. The dark red solution was then poured onto crushed ice, carefully acidified with hydrochloric acid (10%) and extracted with ether (3 × 1·5 l.). The product, after evaporation of solvent and starting materials by distillation under reduced press (15 mm) in an oil bath at 180°, was a thick red oil (550 g) which was heated under reflux with 10% hydrochloric acid (3 l.) for 2 days. The acidic material (220 g) from this reaction was distilled to give the required keto-acid (II) as a colourless oil (100 g) b.p. 145°/0·5 mm, n_D^{20} 1·4840. (Found: C, 63·25; H, 8·2. Calc. for $C_9H_{14}O_3$: C, 63·55; H, 8·25%). Trituration with light petroleum afforded the keto-acid as a solid which crystallized from ether–light petroleum in prisms m.p. 51–53° (lit,[8] m.p. 37°). (Found: C, 63·45; H, 8·2%).

The corresponding methyl ester was a mobile oil b.p. 90–91°/0·5 mm, n_D^{20} 1·4666. (Found: C, 64·95; H, 8·85. $C_{10}H_{16}O_3$ requires: C, 65·2; H, 8·75%). The semicarbazone of the keto-methyl ester crystallized from methanol as colourless needles m.p. 150–151·5°. (Found: C, 55·0; H, 8·15. $C_{11}H_{19}O_3N_3$ requires: C, 54·75; H, 7·95%).

3-*Methoxycarbonylmethyl*-3-*methylcyclohexylidenemalononitrile* (III). Methyl 3-methylcyclohexanone-3-acetate (50 g), redistilled malononitrile (25 g), dry benzene (1 l.), dry ammonium acetate (7·5 g) and glacial acetic acid (10 ml) were refluxed for 12 hr under a Dean and Stark apparatus. Ammonium acetate (1·5 g) and acetic acid (2 ml) were then added and the solution refluxed for a further 24 hr. Silica gel was placed in the water separator to ensure complete removal of water from the reaction mixture. The crude product was fractionally distilled to give 3-methoxycarbonylmethyl-3-methylcyclohexylidene-malononitrile as a clear oil (57·2 g) b.p. 122–123°/0·1 mm, n_D^{19} 1·5068. (Found: C, 67·35; H, 7·0; N, 12·15. $C_{13}H_{16}O_2N_2$ requires: C, 67·2; H, 6·95; N, 12·05%).

The product exhibited I.R. maxima at 2200, 1728 and 1597 cm^{-1} with a U.V. maximum at 239 $m\mu$ (ϵ 13,500).

3-*Methoxycarbonylmethyl*-3-*methyl*-1-*cyano*-1-*dicyanomethylcyclohexane* (IV). A solution of III (35 g) and sodium cyanide (12 g) in dimethylformamide (1·75 l.) was allowed to stand at room temp for 4 days. Acetic acid (100 ml) was then added, the reaction mixture left overnight in a fume-cupboard, then diluted with water (5 l.) and extracted with ether (2 × 500 ml). The aqueous liquors were further diluted with water (2 l.) and re-extracted with ether (500 ml). The product was a thick oil (35 g) which was dissolved in benzene and chromatographed on silica (200 g). Elution with benzene (2 × 500 ml) afforded unreacted starting material (10 g) and further elution with benzene (6 × 500 ml) gave the *trinitrile* (IV) as a mixture of stereoisomers (26 g) m.p.

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[8] M. W. Cronyn and G. H. Riesser, *J. Amer. Chem. Soc.* 75, 1664 (1953).

106–120°. Repeated recrystallization from aqueous methanol afforded one isomer as colourless plates m.p. 120·5–122°. (Found: C, 64·65; H, 6·6; N, 15·95. $C_{14}H_{17}O_2N_3$ requires: C, 64·85; H, 6·6; N, 16·2%). Hydrolysis and decarboxylation of this isomer to the corresponding tricarboxylic acid, followed by Dieckmann cyclization of the trimethyl ester gave a mixture of β-keto-esters, which on hydrolysis and decarboxylation yielded 5-methylbicyclo [3:3:1] nonan-3-one-1-carboxylic acid(VI) as the sole product. This demonstrates unambiguously the stereochemistry of this isomer.

1-*Carboxyl*-3-*methylcyclohexane*-1:3-*diacetic acid* (V). The trinitrile-ester, (IV; 26 g) and fuming hydrochloric acid (1 l.) were refluxed for 72 hr and then concentrated to 500 ml. The cooled solution was saturated with ammonium sulphate and extracted with ether (3 × 250 ml). The combined ethereal extracts were washed with saturated ammonium sulphate solution, dried and the solvent removed under reduced press. Trituration of the residual oil with ether furnished the *tricarboxylic acid* (V; 23·5 g) as a mixture of stereoisomers m.p. 157–175°. (Found: C, 55·7; H, 7·05. $C_{12}H_{18}O_6$ requires: C, 55·8; H, 7·05%). On sublimation, the tricarboxylic acid (V; m.p. 157–164°) furnished an anhydride as a mixture of stereoisomers which crystallized from ether–hexane in prisms m.p. 118–136°. (Found: C, 60·25; H, 6·55. Calc. for $C_{12}H_{16}O_5$: C, 60·0; H, 6·7%). This product exhibited I.R. absorption at 1850 and 1770 cm^{-1} (5-ring anhydride).

Treatment of the mixture of isomers (V) with an excess of diazomethane gave *dimethyl* 1-*methoxycarbonyl*-3-*methylcyclohexane*-1:3-*diacetate* as a colourless oil b.p. 135°/0·1 mm, n_D^{20} 1·4708. (Found: C, 60·15; H, 8·15. $C_{15}H_{24}O_6$ requires: C, 60·0; H, 8·05%).

5-*Methylbicyclo* [3:3:1] *nonan*-3-*one*-1-*carboxylic acid* (VI). A solution of the trimethyl ester of V (30 g) in xylene (500 ml) was added from a Herschberg dropping funnel over 24 hr to a vigorously stirred refluxing solution of potassium t-butoxide (from potassium 8 g) in xylene (2 l.). Refluxing was continued for a further 8 hr with periodic removal of the liberated t-butanol by fractional distillation. The cooled reaction mixture was poured onto ice, acidified with dil hydrochloric acid and the xylene layer separated. The aqueous layer was extracted with ether and the combined extracts washed with water and dried. Distillation afforded a thick oil (19·2 g) b.p. 122–150°/0·01 mm, which exhibited I.R. absorption typical of an enolizable β-ketoester and also showed an U.V. maximum at 250 mμ (ε, 2,300) changing to 284 mμ (ε, 5,650) in ethanol containing 1% of N NaOH. The β-ketoester (19·2 g) was refluxed with 6N HCl (100 ml) for 6 hr and then saturated with ammonium sulphate and extracted with ether, Removal of the solvent, after the usual work-up procedure, yielded a mixture of the keto-acids VI and VII (R=H) as a thick oil which partially solidified on trituration with ether-light petroleum. Recrystallization of this solid (6 g) from ethyl acetate gave 5-*methylbicyclo* [3:3:1] *nonan*-3-*one*-1-*carboxylic acid* m.p. 127–129°. (Found: C, 67·4; H, 8·1. $C_{11}H_{16}O_3$ requires: C, 67·3; H, 8·2%). The product exhibited I.R. absorption at 1728 and 1690 cm^{-1} (Nujol) and 1748 and 1705 cm^{-1} (CCl_4 solution, 5·0 mm cells).

Methyl 5-*methylbicyclo* [3:3:1] *nonan*-3-*one*-1-*carboxylate*. This prepared from VI in the usual manner, was clear oil b.p. 90°/0·05 mm, n_D^{25} 1·4835. (Found: C, 68·2; H, 8·6. $C_{12}H_{18}O_3$ requires: C, 68·55; H, 8·65%). The product showed I.R. maxima at 1733 and 1710 cm^{-1}, with a distinctive band at 1121 cm^{-1}. The corresponding semicarbazone crystallized from aqueous methanol in needles m.p. 193–194°. (Found: C, 58·4; H, 7·75; N, 15·65. $C_{13}H_{21}O_3N_3$ requires: C, 58·4; H, 7·9; N, 15·7%).

Methyl 5-*methylbicyclo* [3:2:1] *octan*-7-*one*-1-*acetate* (VII, R=CH_3). The liquid mixture of acids (VI) and (VII, R=H) (4·1 g), remaining after solvent trituration, was treated with oxalyl chloride (10 ml) in dry benzene. The product which showed I.R. maxima at 1790, 1740 and 1710 cm^{-1}, was warmed on a steam bath for 30 min with a catalytic amount of aluminium chloride; the neutral product, isolated in the usual fashion, was then adsorbed on alumina (Grade III) from pet ether (60–80°). Elution with the same solvent afforded the *chlorolactone* (VIII; 2·1 g) which crystallized from pentane in prisms m.p. 49–51°. (Found: C, 61·85; H, 7·2; Cl, 16·3. $C_{11}H_{15}O_2Cl$ requires: C, 61·55; H, 7·0; Cl, 16·5%). The I.R. spectrum showed a maximum at 1811 cm^{-1} (CCl_4 solution, 5·0 mm cells).[9] Further elution with chloroform yielded a mixture of the bicyclo [3:3:1] nonane acid (VI) and the corresponding acid chloride which, by hydrolysis gave the pure acid (VI).

A solution of the chlorolactone VIII (1·72 g) in dry methanol was refluxed with one equivalent of sodium methoxide (from sodium 0·18 g) for 3 hr. Distillation of the crude product afforded *methyl* 5-*methylbicyclo* [3:2:1] *octan*-7-*one*-1-*acetate* (0·943 g) as a colourless oil b.p. 60°/0·02 mm, n_D^{5} 1·4719. (Found: C, 68·85, H, 8·85. $C_{12}H_{18}O_3$ requires: C, 68·55; H, 8·65%). The product exhibited a

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[9] W. Brügel, G. Stengel, F. Reicheneder and H. Suter, *Angew. Chem.* **68**, 441 (1956).

characteristic I.R. spectrum, markedly different from that of the methyl ester of VI with one band at 1743 cm^{-1} (CCl_4 solution, 5·0 mm cells) and a distinctive peak at 1108 cm.$^{-1}$

5-Methylbicyclo [3:3:1] *nonane-*1*-carboxylic acid* (IX). A mixture of the keto-acid VI (50 mg), sodium (100 mg), ethanol (2 ml) and hydrazine hydrate (0·5 ml) was heated at 185° in a sealed tube for 18 hr. Sublimation of the crude product gave 5-methylbicyclo [3:3:1] nonane-1-carboxylic acid (40 mg) m.p. 141–143°. (Found: C, 72·9; H, 9·7. $C_{11}H_{18}O_2$ requires: C, 72·5; H, 9·9%).

5-Methylbicyclo [3:3:1] *nonan-*3*-one-*1*-carboxylic acid chloride.* A solution of the keto-acid VI (2·95 g) and oxalyl chloride (5 ml) in dry benzene (25 ml) was allowed to stand at room temp overnight. Distillation of the crude product gave the *acid chloride* (2·7 g) as a colourless oil b.p. 88°/0·04 mm, n_D^{23} 1·5082. The product showed I.R. maxima at 1790 and 1710 cm^{-1}.

1*-Acetyl-*5*-methylbicyclo* [3:3:1] *nonan-*3*-one* (XII). The acid chloride of VI (511 mg) in dry ether (50 ml) was added dropwise to a stirred ethereal solution of diazomethane (large excess) and the reaction mixture allowed to stand at room temp for 24 hr. The crude product on trituration with light petroleum gave the diazoketone (162 mg) as a yellow solid m.p. 60–85° (decomp). This material was shaken with 55% hydroiodic acid in chloroform (20 ml) for 5 min and then washed with water, dil sodium thiosulphate solution, water and dried. Distillation of the residual oil, after removal of the solvent, gave 1*-acetyl-*5*-methylbicyclo* [3:3:1] *nonan-*3*-one* (140 mg) as a colourless oil b.p. 50°/0·01 mm, n_D^{23} 1·4951. (Found: C, 74·65; H, 9·35. $C_{12}H_{18}O_2$ requires: C, 74·2; H, 9·35%). The product gave a positive iodoform test and also furnished a bis-2:4-dinitrophenylhydrazone which crystallized from chloroform–methanol in yellow needles m.p. 248–250°. (Found: N, 19·7. $C_{24}H_{26}O_8N_8$ requires: N, 20·2%).

1*-(Ketoisobutenyl)-*5*-methylbicyclo* [3:3:1] *nonan-*3*-one* (X). Pure isobutene was passed through a tower of potassium hydroxide pellets, then condensed by cooling to −10° and a large excess (25 ml) added to a mixture of the acid chloride of VI (6·0 g) and freshly distilled stannic chloride (1 g) in pure dry methylene chloride (120 ml). The reaction mixture (in a stoppered flask) was set aside at −5° for 42 hr and the product isolated in the normal manner. It exhibited a band at 1790 cm^{-1} in the infra-red corresponding to unreacted acid chloride (ca. 30%). A solution of this oil in methylene chloride (150 ml) was again treated with isobutene (25 ml) and stannic chloride (1 g), set aside at −5° for 72 hr and then worked up. The product (33 g) which exhibited I.R. maxima at 1710, 1740, 1650 cm^{-1} with a weak band at 1790 cm^{-1}, was adsorbed on alumina (Grade III, 90 g) from light petroleum. Elution with the same solvent removed polymeric isobutene, and subsequent elution with ether furnished the crude enedione (X) (4·25 g).* This material was adsorbed on silica (225 g) from benzene and the percentage of ether in the eluting solvent increased until elution with 2% ether–benzene followed by repeated fractional distillation afforded 1*-(ketoisobutenyl)-*5*-methylbicyclo* [3:3:1] *nonan-*3*-one* (2·13 g) as a colourless oil b.p. 108°/0·007 mm, n_D^{20} 1·5165. (Found: C, 76·65; H, 9·7. $C_{15}H_{22}O_2$ requires: C, 76·9; H, 9·45%). The product exhibited I.R. absorption at 1710, 1685 and 1620 cm^{-1} with a U.V. maximum at 241 mμ (ε 12,800). The corresponding *bis*-semicarbazone crystallized from methanol as needles m.p. 253–254°. (Found: N, 24·15. $C_{17}H_{28}O_2N_6$ requires: N, 24·15%).

Attempted cyclization of the enedione (X). The enedione (X) was recovered unchanged after treatment with the following reagents; naphthalenesulphonic acid/benzene, stannic chloride/methylene chloride, borontrifluoride/acetic acid, potassium acetate/acetic acid, potassium t-butoxide/xylene and *p*-toluenesulphonyl chloride/pyridine.

Treatment of the enedione (X) with dil sulphuric acid, potassium hydroxide/methanol, sodium methoxide/methanol or N-benzyltrimethylammonium methoxide/methanol gave mainly the retro-aldol product viz. 1-acetyl-5-methylbicyclo [3:3:1] nonan -3-one (XII) together with a trace of the keto-acid (VI) from the corresponding t-butyl ester present as an impurity in the enedione. Refluxing the enedione (X) with sodamide/benzene, sodium t-amylate/benzene or sodium t-amylate/t-amyl alcohol caused extensive degradation of the molecule.

1*-(Hydroxyisobutenyl)-*5*-methylbicyclo* [3:3:1] *nonan-*3*-one* (XIII). Sodium borohydride (126 mg) was added to a solution of the enedione X (1·64 g) in dry methanol (10 ml) and the reaction mixture held at 0° for 5·5 hr. The crude product was adsorbed from benzene on a short column of silica (50 g). Elution with 5% ether-benzene gave the ketol (XIII; 1·45 g) which was purified by short path distillation b.p. 130°/0·01 mm. (Found: C, 76·9; H, 10·25. $C_{15}H_{24}O_2$ requires: C, 76·3; H, 10·25%). The product exhibited I.R. maxima at 3500, 1710 and 1635 cm^{-1}. When

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* After 72 hr, elution of this column with chloroform afforded 1-acetyl-5-methylbicyclo [3:3:1]-nonan-3-one (XII; 0·45 g) identical with an authentic sample.

the ketol was distilled at 0·1 mm pressure the distillate was contaminated with the dienone (XV) formed by pyrolytic dehydration of the ketol (XIII).

1-(3-*Methylbutadienyl*)-5-*methylbicyclo* [3:3:1] *nonan*-3-*one* (XV). *p*-Bromobenzenesulphonyl chloride (665 mg), the ketol XIII (305 mg) and dry pyridine (2 ml) were warmed on a steam bath for 2 hr. The liquid product (295 mg) was adsorbed on alumina (Grade I, 13 g) from 25% benzene–light petroleum (60–80°). Elution with the same solvent gave the *dienone* (*XV*) as a sweet-smelling oil (210 mg) b.p. 70°/0·01 mm, n_D^{23} 1·5197. (Found: C, 82·2; H, 9·95. $C_{15}H_{22}O$ requires: C, 82·5; H, 10·15%). The product exhibited I.R. absorption at 3050, 1710, 1645, 1610, 973 and 888 cm^{-1} with an U.V. maximum at 230 mμ (ε 23,900).

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