234. *Bridged Ring Systems. Part VI.*[1] *The Total Synthesis of (±)-Clovene.*[2]

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The synthesis of (±)-clovene (I) from bicyclo[3,3,1]nonane precursors is described.

The problem of the synthesis of the tricyclic sesquiterpenoid artefact clovene[3] (I) may be tackled in two ways. Construction of the carbon skeleton may be envisaged by elaboration of a suitable bicyclo[4,3,0]nonane containing the *gem*-dimethyl grouping but requiring stereospecific annellation to attach the third ring.[4] Alternatively, use of a bicyclo[3,3,1]-nonane precursor limits the stereochemical problems but necessitates unequivocal introduction of the *gem*-dimethyl group at a later stage.

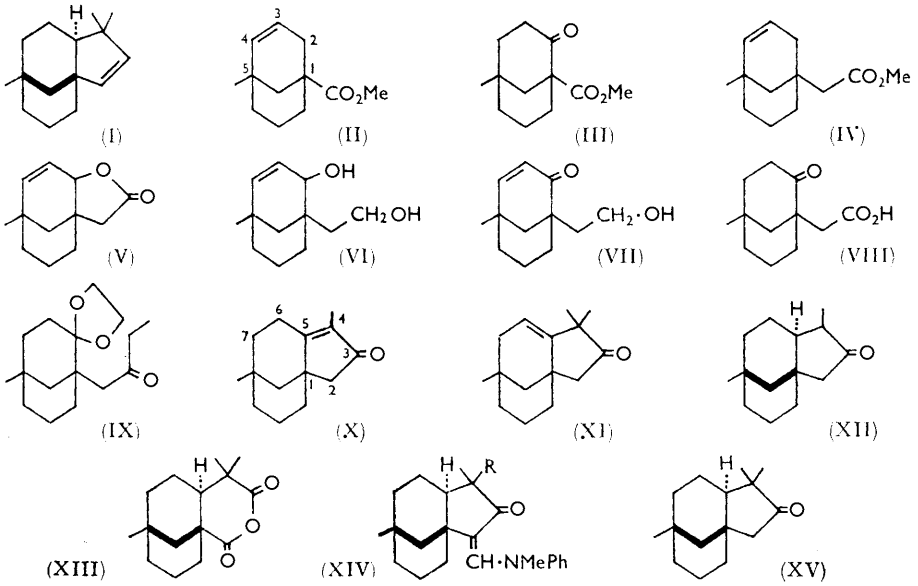
For this latter approach the previously described[5] 1-methoxycarbonyl-5-methylbicyclo[3,3,1]non-3-ene (II) was obviously a fruitful starting point. In an initial approach this ester was oxidised with selenium dioxide in acetic acid to give a mixture of epimeric acetates. Methanolysis followed by chromium trioxide oxidation furnished a homogeneous conjugated enone ($\lambda_{max.}$ 229 mμ, ε 8200) which was readily hydrogenated to the saturated keto-ester (III). The relative positions of the carbonyl and the ester groups were indicated by the smooth formation of a pyrazolone by treatment with hydrazine. This confirmed that the desired initial oxidation had been accomplished without the incursion of allylic rearrangement. Attempts were then made to exploit the 2-keto-function thus introduced to construct the clovene carbon framework by Reformatsky reaction of (III) with ethyl α-bromoisobutyrate. However, no useful product was isolable and another approach was therefore initiated.

Arndt–Eistert homologation of the acid corresponding to (II) by the Newman procedure[6] gave the required methyl ester (IV). Allylic oxidation of this compound with selenium dioxide in acetic acid produced, in a highly stereoselective manner, a good yield of a homogeneous crystalline product whose infrared spectrum (band at 1770 cm.$^{-1}$) showed it to be the γ-lactone (V). The γ-lactonic nature of the product established directly that the oxidation had proceeded in the desired manner. The next goal involved the transformation of lactone (V) into the saturated keto-acid (VIII). Because of the found susceptibility of the allylic C–O bond of (V) to hydrogenolysis this conversion was carried out by the following three-step operation. Lithium aluminium hydride reduction of lactone (V) gave the corresponding diol (VI) which, by allylic oxidation with specially prepared manganese dioxide[7] in light petroleum furnished the conjugated hydroxy-ketone (VII). [Oxidation of diol (VI) with commercial manganese dioxide surprisingly re-formed the lactone (V).] Oxidation of (VII) to the corresponding keto-acid was effected by chromium trioxide, and the product was catalytically hydrogenated to the required saturated keto-acid (VIII). This was then converted by esterification, ethylene glycol ketalisation, and hydrolysis into the corresponding ketal acid, which by treatment with ethyl-lithium gave the homologated ketal-ketone (IX). Mild acid hydrolysis of (IX) produced the corresponding 1,4-diketone. Attempts to obtain this diketone by a more

[1] Part V, G. Eglinton, J. Martin, and W. Parker, *J.*, 1965, , .
[2] Preliminary communication, P. Doyle, I. R. Maclean, W. Parker, and R. A. Raphael, *Proc. Chem. Soc.*, 1963, 239.
[3] A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsay, *J.*, 1954, 4659, and references therein.
[4] D. Becker and H. J. E. Loewenthal, preceding Paper.
[5] R. D. H. Murray, W. Parker, R. A. Raphael, and D. B. Jhaveri, *Tetrahedron*, 1962, **18**, 55.
[6] M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.
[7] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J.*, 1952, 1094.

direct route involving the interaction of the enol-lactone of (VIII) and ethylmagnesium bromide were unsuccessful.

Base-catalysed aldolisation of the 1,4-diketone corresponding to (IX) proceeded in the desired manner with the formation of the requisite cyclopentenone ring as shown by the development of strong absorption at 244 mμ. Methylation of the resulting 4-demethylclov-4-en-3-one (X) resulted in the expected α-methylation with deconjugation of the double bond [8] to give clov-5-en-3-one (XI) with the complete carbon skeleton of clovene. Unfortunately the 5,6-double bond in (XI) proved completely resistant to catalytic hydrogenation even under forcing conditions. However, the double bond in the conjugated precursor (X) was readily reduced by lithium–ammonia to give a saturated alcohol, oxidation of which yielded a homogeneous crystalline 4-demethylclovan-3-one (XII). This stereoselectivity of the reduction now posed the problem of determining the relative configuration at the newly created asymmetric centre at C-5 of ketone (XII). Recently the stereochemical course of such reductions of αβ-unsaturated ketones has been rationalised [9] by consideration of the relative stability of those most energetically favoured transition states for protonation of the intermediate carbanion in which the orbital at the β-carbon overlaps with the enolate carbon–carbon double bond. If the most favourable transition state can be unequivocally determined by inspection these concepts lead to predictions which are in harmony with the practical findings and which have clarified many seemingly anomalous results. Unfortunately, application of these ideas to the ketone (X) does not allow a clearcut decision in favour of a markedly more favoured transition state which would unambiguously predict whether or not the required *cis*-fusion of the five- and six-membered rings had resulted. A transition state leading to *cis*-fusion involving a boat shape for the cyclohexane ring certainly seems to necessitate less distortion of the five-membered ring than the corresponding *trans* transition state, but too literal interpretation from models is apt to be misleading.



To establish unequivocally the stereochemical relationship of clovene and the ketone (XII), the latter was converted into the 2-furfurylidene derivative which was then completely methylated at C-4. Oxidative degradation of the crystalline product gave a neutral substance (m. p. 76—78°) showing infrared absorption at 1760 and 1805 cm.$^{-1}$,

[8] Cf. H. J. Malhotra and S. K. Ringold, *J. Amer. Chem. Soc.*, 1962, **84**, 3402.
[9] G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, 1964, **86**, 1761.

typical of a glutaric anhydride. The solution infrared spectrum of this product was identical with that of (—) clovenic anhydride (m. p. 50—51°) obtained by oxidation of naturally derived clovene. This strongly indicated that the stereoselective reduction of (XI) had taken the desired course leading to the *cis*-fused ketone (XII). Direct methylation of (XII) to introduce the requisite *gem*-dimethyl grouping at C-4 gave an intractable mixture of products and the need for a blocking group at C-2 was indicated. Accordingly, (XII) was converted in the standard manner [10] into the 2-methylanilinomethylene derivative. Methylation followed by removal of the blocking group then furnished clovan-3-one (XV). Lithium aluminium hydride reduction of this ketone gave a crystalline mixture of the epimeric clovan-3-ols which was converted by treatment with ethyl chloroformate into the corresponding mixed carbonate. Pyrolysis of the carbonate in silicone oil gave an unsaturated hydrocarbon which was scrupulously purified through its crystalline dibromide.[11] Regeneration from this derivative gave (±) clovene indistinguishable from naturally derived (—)-clovene as evinced by the identity of their i.r., n.m.r., and mass spectra, and their gas chromatographic retention times.

Experimental

All melting points (corrected) were determined on a Kofler hot-stage apparatus; boiling points are uncorrected. Infrared spectra of liquid films and Nujol mulls were recorded on a Perkin-Elmer Infracord spectrometer, and solution spectra on a Unicam S.P. 100 spectrometer (only relevant bands are recorded). Ultraviolet spectra, measured on a Perkin-Elmer 137 U.V. spectrometer and a Unicam S.P. 500 spectrometer, refer to ethanol solutions. Mass spectra were determined on an A.E.I. M.S. 9 mass spectrometer, and n.m.r. spectra on the A.E.I. R.S. 2 spectrometer.

The neutral alumina (Woelm) was used in the condition in which it was obtained from the suppliers, and for ordinary usage neutral alumina was prepared from Spence H alumina, and graded according to Brockmann and Schodder.[12] Thin-layer chromatography was carried out on Silica Gel G (Merck), and gas chromatography on a Pye Argon Chromatograph with Celite 545 (120—150 mesh) acting as a support for Apiezon L stationary phase.

The term " light petroleum " refers to the fraction of b. p. 40—60°.

1-*Methoxycarbonyl*-5-*methyl*-2-*oxobicyclo*[3,3,1]*nonane* (III).—The ester [5] (II) (1·38 g.) was heated under reflux for 90 min. with a suspension of selenium dioxide (0·4 g.) in glacial acetic acid (10 ml.). The cooled mixture was diluted with light petroleum (100 ml.), filtered, and washed repeatedly with sodium hydrogen carbonate solution. Drying ($MgSO_4$) and evaporation gave a product which was purified by chromatography on alumina (Grade III; 30 g.) with benzene–light petroleum (1 : 1), to give an epimeric mixture (1·1 g.) of the corresponding 2-acetoxy-esters.

This product (4·36 g.) was solvolysed by heating under reflux with a solution of sodium methoxide (from sodium, 100 mg.) in methanol (50 ml.). The cooled solution was neutralised with carbon dioxide, evaporated to dryness, and the residue transferred to a silica gel column in light petroleum. Elution with chloroform afforded an epimeric mixture of the corresponding 2-hydroxy-esters (3·47 g.). To a cold (0°) solution of this product in acetone (35 ml.) was added a solution (8N) of chromium trioxide in dilute sulphuric acid until a red coloration persisted. The mixture was diluted with sodium chloride solution (10%; 150 ml.) and the whole extracted with light petroleum. Washing (NaCl soln.), drying ($MgSO_4$), evaporation, and distillation yielded 1-*methoxycarbonyl*-5-*methyl*-2-*oxobicyclo*[3,3,1]*non*-3-*ene* (3 g.), b. p. 94°/0·1 mm., n_D^{20} 1·4960, $\lambda_{max.}$ 229 mμ (ε 8200), $\nu_{max.}$ (thin film) 1735 (methoxycarbonyl), 1678 (conjugated ketone) cm.$^{-1}$ (Found: C, 68·7; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%). Treatment with Brady's reagent at room temperature gave two stereoisomeric 2,4-*dinitrophenylhydrazones* both crystallising from methanol in (a) orange needles, m. p. 168—170°, $\lambda_{max.}$ ($CHCl_3$) 260 (ε 9300), 380 mμ (ε 24,000) (Found: C, 55·5; H, 4·95; N, 14·55. $C_{18}H_{20}N_4O_6$ requires C, 55·65; H, 5·2; N, 14·45%); (b) yellow needles, m. p. 144—146°, $\lambda_{max.}$ ($CHCl_3$) 260 (ε 9500), 375 mμ (ε 27,000) (Found: C, 55·7; H, 5·45; N, 14·45%).

Catalytic reduction of the enone ester in ethyl acetate over 10% palladium–charcoal readily

[10] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223; A. J. Birch and R. Robinson, *J.*, 1944, 501; 1945, 582.

[11] A. W. Lutz and E. B. Reid, *J.*, 1954, 2265.

[12] H. Brockmann and H. Schodder, *Ber.*, 1941, **74**, 73.

gave the saturated product 1-*methoxycarbonyl*-5-*methyl*-2-*oxobicyclo*[3,3,1]*nonane* (III), b. p. 86—87°/0·15 mm., n_D^{20} 1·4870, $\nu_{max.}$ (thin film) 1735 (methoxycarbonyl), 1710 (saturated ketone) cm.$^{-1}$ (Found: C, 68·35; H, 8·5. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%). Brady's reagent in the cold gave the 2,4-*dinitrophenylhydrazone* as yellow needles (from methanol), m. p. 122—125° (Found: C, 55·65; H, 5·5; N, 14·25. $C_{18}H_{22}N_4O_6$ requires C, 55·4; H, 5·7; N, 14·35%); hot reagent gave the corresponding 2,4-*dinitrophenylpyrazolone* as pale yellow needles [from light petroleum (b. p. 60—80°)], m. p. 179—181° (Found: C, 57·05; H, 4·75; N, 15·55. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·05; N, 15·65%). Refluxing with hydrazine hydrate gave the *pyrazolone* as needles (from methanol), m. p. 114—115° (Found: C, 68·35; H, 8·25; N, 14·35. $C_{11}H_{16}N_2O$ requires C, 68·7; H, 8·4; N, 14·55%).

1-(*Methoxycarbonylmethyl*)-5-*methylbicyclo*[3,3,1]*non*-3-*ene* (IV).—Oxalyl chloride (19 ml.) was added cautiously to a solution of the acid [5] (30 g.) corresponding to (II) in dry benzene (300 ml.) containing dimethylformamide (0·1 ml.). After 3 hr. at room temperature the benzene and successive fresh portions of solvent (4 × 50 ml.) were evaporated under reduced pressure. The resulting acid chloride ($\nu_{max.}$ 1790 cm.$^{-1}$) was dissolved in dry ether (300 ml.) and added to an ethereal solution of diazomethane (6 equiv.). After 4 hr. at room temperature the solvent was removed under reduced pressure, to give the yellow crystalline diazo-ketone (32·3 g.). This product was dissolved in dry methanol (600 ml.) at room temperature and to it was added portionwise with stirring a saturated solution of silver benzoate in triethylamine (20 ml.; *ca.* 20%). When the brisk exothermic evolution of nitrogen had ceased (1½ hr.) ether (600 ml.) was added and the silver removed by filtration. After evaporation the residue was dissolved in light petroleum and the solution successively washed with dilute hydrochloric acid (N), sodium chloride solution, sodium hydrogen carbonate solution, and sodium chloride. Drying ($MgSO_4$) and careful evaporation of the solvent through a short Vigreux column gave the crude ester (31 g.). Purification was effected by chromatography on alumina (grade H, 800 g.) using light petroleum as eluant. Distillation gave the pure *ester*, b. p. 61—63°/0·01 mm., n_D^{24} 1·4838, $\nu_{max.}$ (thin film) 3300 (–CH=) 1730, 1260 (methoxycarbonyl), 705 (*cis* –CH=CH–) cm.$^{-1}$ (Found: C, 75·05; H, 9·45. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%). Base hydrolysis gave the corresponding *acid* which crystallised (light petroleum) in needles, m. p. 52—54° (Found: C, 74·15; H, 9·5. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%). The corresponding *amide* crystallised from light petroleum in needles, m. p. 87—88° (Found: C, 74·85; H, 9·65; N, 7·3. $C_{12}H_{19}NO$ requires C, 74·55; H, 9·90; N, 7·25%).

Lactone of 1-(*Carboxymethyl*)-2-*hydroxy*-5-*methylbicyclo*[3,3,1]*non*-3-*ene* (V).—The homologated ester (IV) (50 g.) was heated under reflux for 90 min. with a suspension of selenium dioxide (16·6 g.) in glacial acetic acid (400 ml.). The resulting mixture was diluted with light petroleum (800 ml.) and filtered into sodium chloride solution (10%; 1·6 l.). The aqueous layer was further extracted with light petroleum (4 × 250 ml.) and the combined petroleum solutions washed (sodium hydrogen carbonate solution and sodium chloride solution) and dried ($MgSO_4$). Evaporation under reduced pressure gave a waxy orange solid (45 g.) which was crystallised from light petroleum to give the pure *lactone* (V) (31·4 g.) as needles, m. p. 56—57°, $\nu_{max.}$ (CCl_4) 1770 cm.$^{-1}$ (Found: C, 75·15; H, 8·7. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). Chromatography of the mother-liquors (with silica gel and chloroform) gave a further quantity (3 g.) of pure lactone.

2-*Hydroxy*-1-(*hydroxyethyl*)-5-*methylbicyclo*[3,3,1]*non*-3-*ene* (VI).—A solution of the lactone (V) (31·4 g.) in dry ether (125 ml.) was added to a suspension of lithium aluminium hydride (6 g.) in ether (600 ml.) at a rate which maintained gentle reflux. After being heated under reflux for a further 2½ hr. the reaction mixture was treated with wet ether followed by hydrochloric acid (6N). The aqueous layer was repeatedly extracted with ether and the combined extracts washed with sodium chloride solution and dried ($MgSO_4$). Evaporation gave a solid residue (31 g.) which crystallised from light petroleum to give the *diol* (VI) as prisms, m. p. 61—62° (Found: C, 73·4; H, 10·1. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·25%).

1-(*Hydroxyethyl*)-5-*methyl*-2-*oxobicyclo*[3,3,1]*non*-3-*ene* (VII).—A solution of the diol (VI) (31 g.) in chloroform (2·5 l.) was shaken with specially prepared [7] manganese dioxide (310 g.) at room temperature for 20 hr. Filtration, evaporation, and crystallisation (light petroleum) gave the *hydroxy-ketone* (VII) (31 g.) as prisms, m. p. 45—47°, $\nu_{max.}$ (Nujol) 3400, 1650, 820 cm.$^{-1}$, $\lambda_{max.}$ 232 mμ (ε 8200) (Found: C, 74·1; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%).

1-(*Carboxymethyl*)-5-*methyl*-2-*oxobicyclo*[3,3,1]*non*-3-*ene*.—A solution (8N) of chromium trioxide in dilute sulphuric acid was added at 0° to a solution of the hydroxy-ketone (VII) (31 g.)

in acetone (300 ml.) until a permanent red coloration persisted. After 1½ hr. sodium chloride solution (500 ml.) was added to the mixture and the acetone carefully evaporated under reduced pressure before thorough ether extraction. The extract was washed with sodium chloride solution until colourless, and the acidic product then throughly extracted with sodium hydrogen carbonate solution. Acidification with sulphuric acid (6N) and isolation with ether gave almost pure enone acid (20·3 g.). The neutral fractions were reduced back to the diol (VI) by hydride and the two-stage oxidation repeated to give a further quantity of the enone acid (7 g.). By this recycling process the lactone could be converted into the enone acid in an overall yield of 80%. Crystallisation from benzene or sublimation at 140° gave prisms, m. p. 159—160°, of the pure enone *acid*, $\lambda_{max.}$ 232 mμ (ε 8200), $\nu_{max.}$ (Nujol) 1720, 1630, 820 cm.$^{-1}$ (Found: C, 69·15; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%).

1-(*Carboxymethyl*)-5-*methyl*-2-*oxobicyclo*[3,3,1]*nonane* (VIII).—The enone acid (4·72 g.) in ethyl acetate (100 ml.) rapidly absorbed one molecular proportion of hydrogen when shaken in the presence of palladium–charcoal (10%; 0·47 g.). Filtration and evaporation gave the saturated *keto-acid* (VIII) (4·7 g.), prisms, m. p. 138—139° (from benzene), $\nu_{max.}$ (Nujol) 1720, 1670 cm.$^{-1}$ (Found: C, 68·85; H, 8·45. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%). The corresponding enol-lactone was prepared by heating the keto-acid (1·6 g.) with acetic anhydride (24 ml.) containing sodium acetate (0·16 g.) for 20 hr. Removal of solvent, isolation with ether, and chromatography through alumina (Woelm grade I) with light petroleum gave the *enol-lactone* (1·06 g.), plates, m. p. 32—34° (from pentane), $\nu_{max.}$ (film) 1800, 1700 cm.$^{-1}$ (Found: C, 74·74; H, 8·1. $C_{12}H_{16}O_2$ requires C, 74·95; H, 8·4%). Base hydrolysis readily re-formed the parent keto-acid (VIII).

1-(*Carboxymethyl*)-2,2-*ethylenedioxy*-5-*methylbicyclo*[3,3,1]*nonane*.—The keto-acid (VIII) (5 g.) was treated with diazomethane and the resulting ester ketalised by heating it with ethylene glycol (7·8 ml.), ethyl orthoformate [13] (15·6 ml.), and toluene-*p*-sulphonic acid (0·05 g.) at 165° for 2 hr. The solution was taken up in light petroleum and washed with sodium chloride solution. Drying ($MgSO_4$), evaporation, and distillation gave the ketal *ester* (5 g.), b. p. 109—110°/0·17 mm, $\nu_{max.}$ (film) 1725, 1200—1100 cm.$^{-1}$ (Found: C, 66·9; H, 8·45. $C_{15}H_{24}O_4$ requires C, 67·15; H, 9·0%). The ketal-ester (5 g.) was heated under reflux with aqueous standard sodium hydroxide (60 ml.; N) until complete solution had occurred. The cooled solution was carefully acidified at 0° with hydrochloric acid (60 ml.; N) and extracted thoroughly with ether. Drying ($MgSO_4$) and evaporation gave the ketal *acid* (4·7 g.), prisms, m. p. 80—83° (from light petroleum) (Found: C, 66·15; H, 8·9. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%).

2,2-*Ethylenedioxy*-5-*methyl*-1-(2-*oxobutyl*)*bicyclo*[3,3,1]*nonane* (IX).—Ethyl-lithium was prepared by regular addition during 4 hr. of ethyl bromide (40 g.) in pentane (150 ml.) to a stirred suspension of lithium wire (6 g.) in pentane (100 ml.) maintained at gentle reflux in an atmosphere of nitrogen. The resulting violet suspension was added rapidly to a solution of the above ketal acid (11·6 g.) in pentane (120 ml.). After the addition the mixture was heated under reflux with stirring for 2 hr. After careful addition of ethanol to destroy excess of ethyl-lithium, ice-cold sodium chloride solution (100 ml.) was added and the aqueous layer extracted further with light petroleum. Drying and evaporation of the combined extracts gave the ketal ketone (IX). Careful acidification of the aqueous layer furnished unreacted ketal acid which was re-cycled with ethyl-lithium. A high overall yield (11·6 g.) of the almost pure ketal ketone (IX) was thus obtained. A sample was chromatographed over alumina (grade H) with light petroleum as eluant. Distillation then gave the pure ketal *ketone* (IX), b. p. 104°/0·07 mm., $\nu_{max.}$ (film) 1710, 1200—900 cm.$^{-1}$, shown to be homogeneous by thin-layer chromatography (Found: C, 72·05; H, 9·55. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%).

5-*Methyl*-2-*oxo*-1-(2-*oxobutyl*)*bicyclo*[3,3,1]*nonane*.—The ketal ketone (IX) (9·9 g.) was heated under reflux for 3 hr. with hydrochloric acid (0·5 ml.; 6N) in aqueous methanol (1 : 1; 250 ml.). The initially two-phase mixture became homogeneous and was then diluted with ice-cold sodium chloride solution and extracted thoroughly with light petroleum. The resulting *diketone* (8·2 g.) was purified by chromatography on silica gel with ether–light petroleum (1 : 9) as eluant, b. p. 100°/0·12 mm., $\nu_{max.}$ (film) 1710 cm.$^{-1}$ (Found: C, 75·7; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·65; H, 9·95%).

4-*Demethylclov*-4-*en*-3-*one* (X).—The above diketone (7·6 g.) was heated under reflux for 3 hr. with a solution of potassium hydroxide (8 g.) in methanol (120 ml.). Dilution with sodium chloride solution (250 ml.) and isolation with light petroleum gave a product which was

[13] A. Marquet, J. Jacques, *et al.*, *Bull. Soc. chim. France*, 1961, 1828; 1962, 91.

subjected to chromatography on alumina (grade H; 180 g.) using ether–light petroleum (1 : 9; 1 : 4; 1 : 1) as successive eluants. Distillation furnished the conjugated *ketone* (X) (4·17 g.), homogeneous as shown by thin-layer chromatography, b. p. 74—76°/0·05 mm., $\lambda_{max.}$ 244 mμ (ε 12,800), $\nu_{max.}$ (film) 1690, 1630 cm.$^{-1}$ (Found: C, 81·8; H, 9·6. $C_{14}H_{20}O$ requires C, 82·3; H, 9·85%). The 2,4-*dinitrophenylhydrazone* formed red plates, m. p. 223—225° [from benzene–light petroleum (b. p. 100—120°)], $\lambda_{max.}$ ($CHCl_3$) 393—397 mμ (ε 30,800) (Found: C, 62·6; H, 6·35; N, 14·45. $C_{20}H_{24}N_4O_4$ requires C, 62·5; H, 6·3; N, 14·6%).

Clov-5-en-3-one (XI).—The ketone (X) (180 mg.) was heated under reflux in nitrogen for 1 hr. with a suspension of potassium t-butoxide in benzene. Methyl iodide (2 ml.) was added to the cooled solution and the mixture heated under reflux for a further 2 hr. Isolation with light petroleum gave a crude product (168 mg.) which was purified by chromatography on alumina (Woelm grade I; 5 g.) with light petroleum as eluant, to give ketone (XI) (100 mg.), $\nu_{max.}$ (film) 1740 (cyclopentanone) 1385, 1365 (*gem*-dimethyl) cm.$^{-1}$, shown to be homogeneous by thin-layer chromatography. It formed a 2,4-*dinitrophenylhydrazone*, orange plates, m. p. 156—158° (from methanol) (Found: C, 62·9; H, 6·25. $C_{21}H_{26}N_4O_4$ requires C, 63·3; H, 6·6%). All attempts to hydrogenate this ketone using palladium–charcoal and Adams catalyst under normal and forcing conditions proved fruitless.

4-*Demethylclovan-3-one* (XII).—Complete reduction of the conjugated ketone (X) to the saturated alcohol was effected by the addition of a solution of the ketone (910 mg.) in ether (20 ml.) to a stirred solution of lithium (400 mg.) in liquid ammonia (80 ml.). After 2 hr. the excess lithium was destroyed with wet ether and dilute sodium chloride solution added. Extraction with light petroleum gave the crude alcohol, $\nu_{max.}$ (film) 3300 cm.$^{-1}$, which was dissolved in acetone and treated at 0° with excess of chromium trioxide (8N) in dilute sulphuric acid. The solution was diluted with sodium chloride solution and extracted with light petroleum. The crude product was purified by chromatography through alumina (Woelm grade I; 30 g.) by successive elution with light petroleum and ether–light petroleum (1 : 19). The desired *ketone* (XII) (630 mg.) was thus obtained as needles, m. p. 38—43° (from pentane), $\nu_{max.}$ (Nujol) 1740 cm.$^{-1}$ (Found: C, 81·85; H, 10·7. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%). The homogeneity of the ketone was shown by gas chromatography; on both 0·5% (125°) and 10% (150°) Apiezon L columns the ketone gave a single peak with retention times of 7·5 and 20·5 min., respectively. Thin-layer chromatography showed it to run as a single spot giving a characteristic wine-red colour with ceric sulphate spray. The 2,4-*dinitrophenylhydrazone* crystallised from ethanol–ethyl acetate in orange needles, m. p. 176—178° after preliminary melting and resolidification at 165—171° (Found: C, 62·2; H, 7·25; N, 14·2. $C_{20}H_{26}N_4O_4$ requires C, 62·15; H, 6·8; N, 14·5%).

(±)-*Clovenic Anhydride* (XIII).—The ketone (XII) (650 mg.) was treated with a solution of furfuraldehyde (2 ml.) in methanol (13 ml.) and potassium hydroxide solution (30%; 5 ml.) for 18 hr. at room temperature. The red reaction mixture was diluted with brine and the furfurylidene derivative (850 mg.), $\lambda_{max.}$ 334 mμ (ε 14,500), isolated with light petroleum. This derivative was heated under reflux in nitrogen for 16 hr. with three equivalents of sodium t-pentoxide in benzene.[14] Methyl iodide (4 ml.) was added to the cooled solution and reflux continued for a further 5 hr. Extraction with light petroleum gave 2-*furfurylideneclovan-3-one* (210 mg.) as pale yellow prisms, m. p. 108—110°, $\lambda_{max.}$ 334 mμ (ε 22,100) (Found: C, 80·55; H, 8·9. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%). This product (210 mg.) in ethyl acetate (10 ml.) at −70° was saturated with ozone until the liquid assumed a blue coloration. After concentration at 20° under reduced pressure the viscous residue was dissolved in acetic acid and treated with hydrogen peroxide (2 ml.; 30%) for 2 hr. on a steam-bath. Evaporation of the solvent and isolation with ether gave a crystalline product which was purified by chromatography on silica gel using light petroleum–ethyl acetate (49 : 1) as eluant. Crystallisation from light petroleum gave (±)-*clovenic anhydride* (XIII) as prisms, m. p. 76—78°, $\nu_{max.}$ (CCl_4) 1805, 1760 (six-membered anhydride ring), 1385, 1365 (*gem*-dimethyl) cm.$^{-1}$ (Found: C, 72·0; H, 8·75. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). The solution infrared spectrum of this material was superimposable on that of naturally derived (−)-clovenic anhydride, m. p. 50—51°. Hydrolysis of the racemic anhydride with aqueous sodium hydroxide gave (±)-clovenic acid which showed the same m. p., 180—184° (decomp.), as the naturally derived acid and was undepressed on admixture.

[14] J. Conia, *Bull. Soc. chim. France*, 1950, 537.

Clovan-3-one (XV).—A solution of ketone (XII) (2·4 g.) and ethyl formate (4·3 g.) in benzene (10 ml.) was added dropwise with stirring to a suspension of freshly prepared sodium methoxide (2 g.; dried at 180°/0·01 mm. for 3 hr.) in benzene (25 ml.) held at 0° under nitrogen. During 16 hr. the initial gelatinous mixture was transformed into a clear orange solution. The mixture was diluted with light petroleum (70 ml.) and ice-cold potassium chloride solution (150 ml.; 10%), and the water-soluble hydroxymethylene salt separated. The organic layer was extracted several times with small volumes of potassium chloride solution and the combined aqueous extracts acidified with dilute hydrochloric acid. Isolation with light petroleum gave crude 4-demethyl-2-hydroxymethyleneclovan-3-one (2·44 g.), $\nu_{max.}$ (film) 1675, 1610, 1210, 1030, 820 cm.$^{-1}$, free from starting ketone. This derivative (2·44 g.) was treated with a solution of *N*-methylaniline (1·5 g.) in methanol (15 ml.) for 16 hr. Concentration under reduced pressure gave the corresponding methylanilinomethylene derivative (XIV; R = H) (3·4 g.). This product was heated under reflux for 4 hr. under nitrogen with a suspension of sodamide (five equiv.) in benzene (25 ml.). Methyl iodide (5 ml.) was then added and heating continued for a further 16 hr. Ice-cold sodium chloride solution was then added, and the product, 2-methylanilinomethyleneclovan-3-one (XIV; R = Me) (3·3 g.) isolated with light petroleum. To remove the blocking group this compound was heated under reflux for 2 hr. with a solution of hydrochloric acid (25 ml.; 6N) in methanol (25 ml.), to give 2-hydroxymethyleneclovan-3-one which was isolated by light-petroleum extraction. This product was treated with aqueous potassium hydroxide (10 g. in 50 ml.) and the resulting solution subjected to prolonged steam-distillation. Light petroleum extraction of the steam distillate followed by distillation gave *clovan-3-one* (XV) (1·84 g.), b. p. 80°/0·03 mm., $\nu_{max.}$ (film) 1740, 1385, 1365 cm.$^{-1}$ (Found: C, 81·9; H, 10·9. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%). The *2,4-dinitrophenylhydrazone* crystallised in orange needles, m. p. 166—168° (from ethanol–ethyl acetate) (Found: C, 63·0; H, 7·05; N, 14·0. $C_{21}H_{28}N_4O_4$ requires C, 62·95; H, 7·05; N, 14·0%). The purification of clovan-3-one was considerably aided by the fact that the 4-demethyl compound was appreciably more steam-volatile and the small amount of this impurity was substantially removed in the first fraction of the steam-distillate. The homologues were also readily distinguishable in a clearcut manner by thin-layer chromatography; ceric sulphate development gave a royal-blue coloration with clovan-3-one, but a wine-red colour with the lower homologue.

Clovan-3-ol.—Clovan-3-one (244 mg.) was heated under reflux for 3 hr. with a suspension of lithium aluminium hydride (122 mg.) in ether. After addition of cold sodium chloride solution and dilute hydrochloric acid, isolation by ether and crystallisation furnished a crystalline mixture of epimeric *clovan-3-ols*, m. p. 70—85° (Found: C, 81·75; H, 11·4. $C_{15}H_{26}O$ requires C, 81·05; H, 11·8%).

Clovan-3-yl Ethyl Carbonate.—Ethyl chloroformate (2 ml.) was added dropwise to a cold (−10°) solution of clovan-3-ol (1 g.) in pyridine (3 ml.), and the mixture allowed to stand at 5° for 16 hr. Acidification with dilute hydrochloric acid and isolation with light petroleum gave the *carbonate* (1·32 g.), b. p. 120°/0·5 mm., $\nu_{max.}$ (film) 1740, 1385, 1365, 785 cm.$^{-1}$ (Found: C, 72·85; H, 9·85. $C_{18}H_{30}O_3$ requires C, 73·45; H, 10·25%).

(±)-*Clovene* (I).—A solution of clovan-3-yl ethyl carbonate (930 mg.) in silicone fluid (MS 200/1000 C.S.; 1·5 ml.) was heated for 2 hr. in a metal bath held at 300 ± 5°. After an initial vigorous reaction the yellow solution gently refluxed. The product was isolated by rapid distillation at 0·03 mm. into a trap cooled by liquid nitrogen. Distillation gave (±)-clovene (428 mg.), b. p. 48—52°/0·1 mm., free from starting material but contaminated with traces of silicone fluid. It was therefore scrupulously purified through the crystalline dibromide. To the crude clovene in carbon tetrachloride (5 ml.) at 0° was slowly added during 4 hr. a solution of bromine (370 mg.) in carbon tetrachloride (4 ml.) until the red coloration persisted. After 16 hr. at 5° and 4 hr. at room temperature a mixture of sodium chloride solution and sodium hydrogen carbonate solution (1 : 1; 20 ml.) was added and the product isolated by light petroleum. Trituration of the product with ethanol yielded a crystalline mixture of diastereoisomeric clovene dibromides (458 mg.), m. p. 61—75°; the product moved as one spot on subjection to thin-layer chromatography. The dibromide mixture (400 mg.) was heated under reflux for 16 hr. with a suspension of zinc dust (200 mg.) in ethanol (4 ml.). Dilution with light petroleum, filtration, washing, drying ($MgSO_4$), evaporation, and distillation gave (±)-*clovene* (I), b. p. 80°/0·15 mm., n_D^{21} 1·4911 (Found: C, 88·0; H, 11·75. $C_{15}H_{24}$ requires C, 88·15; H, 11·85%), $\nu_{max.}$ (CCl_4) 3000, 1385, 1365, 760, 745 cm.$^{-1}$. N.m.r. (CCl_4) τ 4·70, 4·75 (2 vinyl protons), 8·95, 9·05, 9·15 (3 methyl singlets). Mass spectrum: *m/e* (% of base

peak); 27 (17·1), 28 (2·7), 29 (17·1), 30 (0·5), 38 (0·7), 39 (22·8), 40 (4·2), 41 (50·5), 42 (3·0), 43 (7·0), 51 (7·0), 53 (16·6), 54 (2·0), 55 (22·9), 56 (1·6), 57 (1·1), 58 (0·4), 62 (0·4), 63 (2·5), 64 (1·2), 65 (13·1), 66 (2·9), 67 (14·8), 68 (1·7), 69 (10·5), 70 (0·7), 71 (0·5), 77 (26·0), 78 (7·2), 79 (23·2), 80 (3·0), 81 (12·9), 82 (1·5), 83 (1·2), 89 (1·3), 90 (0·5), 91 (43·0), 92 (7·3), 93 (19·2), 94 (2·7), 95 (15·2), 96 (1·6), 97 (0·8), 102 (1·1), 103 (5·4), 104 (2·6), 105 (37·5), 106 (6·1), 107 (13·8), 108 (3·5) 109 (4·5), 110 (0·5), 115 (7·2), 116 (3·1), 117 (9·7), 118 (2·4), 119 (7·6), 120 (9·5), 121 (5·3), 122 (1·0), 123 (0·5), 124 (0·1), 127 (1·3), 128 (3·7), 129 (3·5), 130 (1·9), 131 (8·3), 132 (2·6), 133 (17·5), 134 (3·2), 135 (1·4), 141 (0·9), 142 (0·5), 143 (0·9), 144 (0·7), 145 (5·7), 146 (3·7), 147 (10·5), 148 (1·9), 159 (1·5), 160 (1·3), 161 (100·0; base peak), 162 (14·1), 163 (1·2), 175 (2·1), 176 (0·6), 189 (50·3), 190 (8·2), 191 (0·8), 204 (5·7; parent peak), 205 (1·1), 206 (0·1). These spectroscopic properties and the behaviour on gas chromatography were identical with those of a sample of naturally derived (−)-clovene, n_D^{19} 1·4920, purified in a similar manner.

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