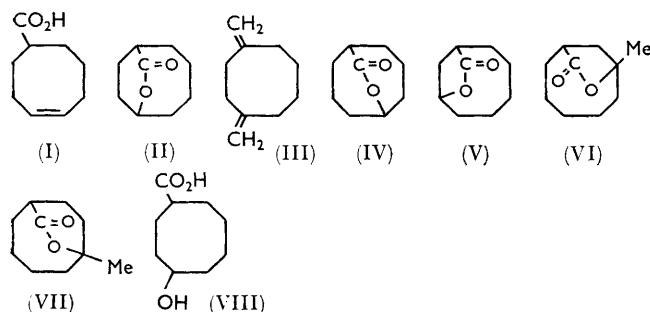


Studies on Cyclo-octanes. Part II.¹ 1,4-Disubstituted Cyclo-octanes.

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The reaction of cyclo-oct-4-enecarboxylic acid (I) with sulphuric acid is reported: an improved preparation of the lactone of 4-hydroxycyclo-octanecarboxylic acid and its conversion into 1,4-dimethylenecyclo-octane are described together with the chemical and light absorption properties of the latter.

THE lactone of 4-hydroxycyclo-octanecarboxylic acid (II), has been used for the preparation of *cis*-4-methylcyclo-octanol² but its preparation by the published procedure is tedious. The ready availability of cyclo-oct-4-enecarboxylic acid (I),³ makes it an attractive starting material for (II) and hence for various disubstituted cyclo-octanes; in particular a synthesis of 1,4-dimethylenecyclo-octane, (III), was required to extend our investigations on interactions between non-conjugated olefinic bonds.¹ While our work was in progress a report⁴ appeared on the reaction of (II) with acid, which in part duplicates our results.



The acid (I) reacted with 60% sulphuric acid to give two products together with traces of others. The principal product had the same g.l.c. retention time as (II) and (IV). (Mixtures of these could not be resolved on any stationary phase.⁴) However, separation of the product mixture by preparative g.l.c. gave (II) with the correct m.p. so that, at most, only very little (IV) can have been present. The structure of (II) was confirmed conversion of the compound into cyclo-octanecarboxylic

acid. The second component of the mixture was obtained contaminated with a further substance. Both were γ -lactones [$\nu(\text{C}=\text{O})$ 1770 cm^{-1}] and the ^1H n.m.r. spectrum was consistent with the major component being (V) and the minor component being (VI). These structures had been assigned to two of the isomerisation products of (II)⁴ and repetition of that work confirmed that the two γ -lactones formed from (I) had the same retention times as (V) and (VI). Pure (II) could be isolated from the mixture of lactones by alkaline hydrolysis and acidification, to give the hydroxy-acid (VIII) (the γ -hydroxy-carboxylates reformed lactone): it could also be obtained pure, with some loss, by recrystallisation of the mixture.

Reaction of (I) with 96% sulphuric acid gave a mixture of lactones, the composition of which is shown in the Table. Vapour-phase analysis of the mixture gave five peaks two of which corresponded to the lactones (V) and (VI), formed in the previous reaction, one (30% of the total) to (II) and (IV), and two others. To analyse for (II) and (IV) the lactone mixture was converted, in a number of stages [outlined in Scheme 1 for conversion of (IV) into (IX)] into a mixture of ketones and tertiary alcohols. The ketonic fraction consisted of three ketones having the same retention times as (IX)² (35%), (X)⁵ (28%), and (XI)² (37%). The method is obviously very approximate as much less (X) is obtained than expected (γ -lactones might reasonably be expected to give less good yields in the sequence of reactions used), but it does establish the presence of a substantial proportion of (IV) in the lactone mixture and an approximate figure of 15% is given in the Table. The tertiary

³ C. S. Dean, J. R. Dixon, S. H. Graham, and D. O. Lewis, *J. Chem. Soc. (C)*, 1968, 1491.

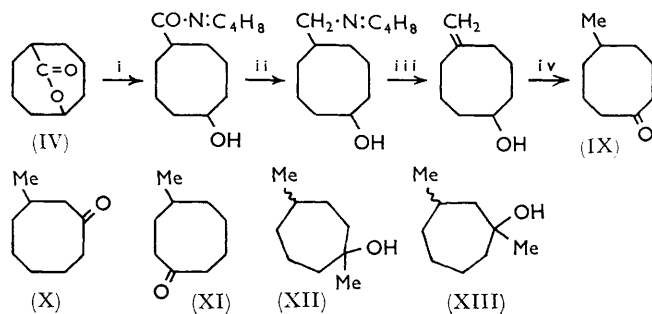
⁴ A. C. Cope, J. M. McIntosh, and M. A. McKerver, *J. Amer. Chem. Soc.*, 1967, **89**, 4020.

⁵ R. A. Appleton, K. H. Baggeley, C. Egan, J. M. Davies, S. H. Graham, and D. O. Lewis, *J. Chem. Soc. (C)*, 1968, 2032.

¹ Part I, K. H. Baggeley, W. H. Evans, S. H. Graham, D. A. Jonas, and D. H. Jones, *Tetrahedron*, 1968, **24**, 3445.

² A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.*, 1963, **85**, 3743.

alcohol fraction showed one main peak on g.l.c. (with a shoulder) which corresponded to 1,4-dimethylcycloheptanol, (XII); an authentic sample of this was synthesised from 4-methylcycloheptanone, and the same crystalline

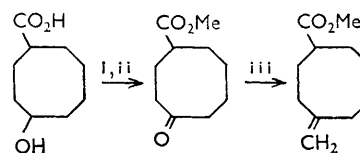


SCHEME 1

Reagents: i, $C_4H_9N, MgBr$; ii, AlH_4^- ; iii, pyrolysis of *N*-oxide; iv, H_2-Pt ; v, H_2CrO_4

hydrogen phthalate was obtained from both batches of alcohol. The configuration of this alcohol is not known, though apparently the same isomer of (XII) was formed

the mixture had the correct analysis for $C_9H_{15}BrO$ and showed no carbonyl or hydroxy-absorptions, and its 1H n.m.r. spectrum included two singlets (0.9H and 0.1H respectively) at τ 6.7 and 6.9, as well as an unresolved multiplet (1H) at about τ 5.6. On this basis the two compounds are formulated as (XV) and (XVI), formed as shown in Scheme 4.



SCHEME 2

Reagents: i, CH_2N_2 ; ii, H_2CrO_4 ; iii, $Ph_3P:CH_2$

The structure of the diene (III) was confirmed by i.r. and 1H n.m.r. spectral evidence (Experimental section). The u.v. spectrum showed very marked interaction between the two π -bonds; compound (III) was photochemically stable, for the spectrum was unchanged by prolonged exposure to light. Similar absorptions have

Lactonisation and rearrangement reactions in sulphuric acid

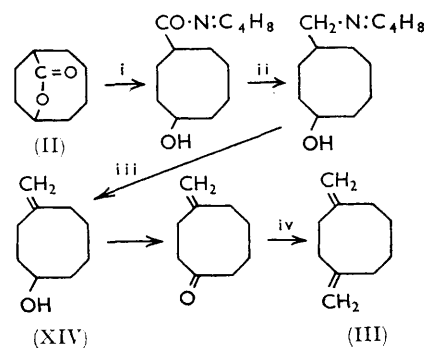
Substrate	Acid concn. (% v/v)	Time (hr.)	Temp.	Product distribution (%)					
				(II)	(IV)	(V)	(VI)	(VII)	Unknown
(I)	96	3	0°	15	15	28	14	14	14
(I)	60	4	20	65	0	35		Traces	
(II)	60	4	20		70	21	6	1	2
(II)/(IV) ⁴	33.3	4	85		33.5	43.5	8.8	4.9	9.8
(II)	33.3	12	85		13	72	7	3	5
(II)	33.3	42	85		2	59	13	10	16
(V)	33.3	42	85		2	85	8	1	4

predominantly both by the Grignard addition to methylcycloheptanone and by hydrogenation of 1-methyl-4-methylenecycloheptanol. This established (VII) as giving one of the two unidentified g.l.c. peaks; the sixth lactone has not yet been identified (though a possible structure has been suggested⁴). It was presumed that the second tertiary alcohol was (XIII), but very little was produced (see above).

A very similar mixture of lactones was obtained from (II) and from (IV) by Cope,⁴ who proposed mechanisms for the formation of (VI) and (VII); on the basis of i.r. spectra it was concluded that no (IV) was present, which is in strong contrast to our results described above. We have re-examined the rearrangement of (II) and have found, as is shown in the Table, that (V) also undergoes rearrangement, contrary to the earlier report.⁴ In these runs we did not attempt to analyse separately for (II) and (IV).

The lactone (II) was converted into 4-methoxycarbonylmethylcyclo-octane by the sequence of reactions shown in Scheme 2, but poor yields precluded the extension of the sequence to (III). This last was obtained as shown in Scheme 3. The oxidation of the enol (XIV) was carried out with pyridine-chromium trioxide. When (XIV) was treated with hypobromous acid a mixture of two products was obtained in the ratio 9:1.

been reported for *trans,trans*-cyclo-octa-1,5-diene⁶ and for germacrone.⁷ There has been some doubt in these cases as to whether the two olefinic bonds are crossed or



SCHEME 3

Reagents: i, $C_4H_9N, MgBr$; ii, AlH_4^- ; iii, pyrolysis of *N*-oxide; iv, $Ph_3P:CH_2$

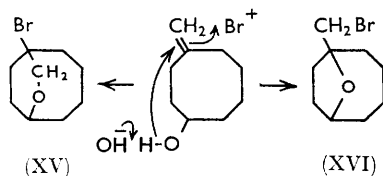
parallel; in the case of (III) examination of models shows that they must be parallel. These properties are in sharp distinction to the diene (XVII).¹ It had been suggested, on the basis of its 1H n.m.r. spectrum, that

⁶ G. M. Whitesides, G. L. Goe, and A. C. Cope, *J. Amer. Chem. Soc.*, 1967, **89**, 7136.

⁷ F. Sörm, *Pure Appl. Chem.*, 1961, **2**, 533.

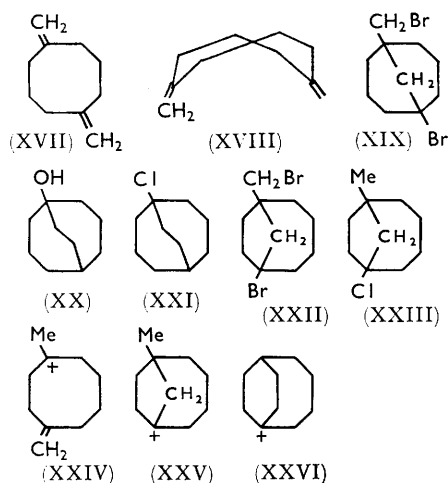
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it might principally populate a conformation such as (XVIII) with the olefinic bonds splayed slightly outwards. When the factors governing the transannular



SCHEME 4

interactions of chromophores are better understood it should become possible to decide if such a conclusion can be reconciled with the absence of u.v. absorption in the diene.



Like compound (XVII), compound (III) did not react with tetracyanoethylene. The diene (XVII) reacted with bromine to give (XIX), and with hydrochloric acid to give a mixture of (XX) and (XXI);¹ these results had been interpreted as meaning that (XVII) reacted with a proton to form a bicyclic carbonium ion in a concerted process and with bromine to give a methylenecyclo-octyl ion. Under similar conditions (III) gave a rather unstable dibromide, and reacted with hydrochloric acid to give a chloride but no alcohol. Neither of these products could be purified, but their ¹H n.m.r. spectra were consistent with the structures (XXII) and (XXIII) respectively; hence it would follow that reaction of (III) with proton gives initially the ion (XXIV) and that further reaction of this with nucleophile involves participation of the π -bond. {By analogy with the bicyclo[2,2,1]heptyl and the bicyclo[2,2,2]-octyl ions⁸ it may reasonably be assumed that (XXV) would be higher in energy than (XXVI)}.

EXPERIMENTAL

Lactone of 4-Hydroxycyclo-octanecarboxylic Acid (II).—Cyclo-oct-4-enecarboxylic acid (I) (5 g.) was shaken with 60% (v/v) sulphuric acid (7.5 ml.) for 4 hr.; the solution

was then poured on crushed ice (the use of larger quantities gave diminished yields). The products from eight batches were taken up in chloroform (3 \times 50 ml.), the extracts were washed with aqueous hydrogen carbonate [from the washings the acid (I) (8 g.) was recovered], and dried. Removal of solvent left an oil (30.7 g.) which showed two peaks, 35 and 65%, on g.l.c. (butanediol succinate at 130°). Preparative g.l.c., on a 7 ft. \times $\frac{3}{8}$ in. column packed with 25% butanediol succinate on 40–60 mesh Supasorb, gave the lactone (II), m.p. 123–124° (lit.,² 122.8–123.8°), ν_{\max} (CCl₄ solution) 1718 cm.⁻¹; together with an oil, b.p. 86–88°/0.2 mm., n_D^{20} 1.4915, ν_{\max} (film) 1770 cm.⁻¹, ¹H n.m.r. absorptions at τ 5.35 (0.7H, m), 7.3 (1H, m), and 8.75 (0.9H, s), g.l.c. analysis (butanediol succinate at 120°) showed two components in the ratio 7 : 3 (Found: C, 70.4; H, 9.0. C₉H₁₄O₂ requires C, 70.1; H, 9.1%). Five successive recrystallisations of the original lactone mixture (25 g.) from light petroleum gave (II), 97% pure (12 g.), m.p. 122–123°. The crude lactone mixture (25 g.) was dissolved in 3N-sodium hydroxide with warming and the solution was cooled in ice and acidified (Congo Red); it was extracted with chloroform (5 \times 25 ml.) and the combined extracts were washed with hydrogen carbonate solution, and dried. Evaporation of the chloroform gave a mixture (8 g.) which contained (II) (27%) and (V) (73%). Acidification of the hydrogen carbonate washings gave the hydroxy-acid (VIII), m.p. 89–90° (lit.,² 89.5–90.4°) (Found: C, 62.9; H, 9.2. Calc. for C₉H₁₆O₃: C, 62.8; H, 9.4%). The crude (VIII) was heated at 100–120° for 6 hr., and worked up to give (II), 96% purity (12 g.).

Action of Sulphuric Acid (96%) on Cyclo-octenecarboxylic Acid.—The acid (I) (5 g.) and 96% sulphuric acid (5 ml.) were stirred at 0° for 3 hr.; the mixture was then poured on crushed ice and worked up to give a mixture of lactones (4.5 g.). This showed five peaks on g.l.c. (butanediol succinate at 100°) with peak areas 14 : 14 : 28 : 14 : 30 (in order of increasing retention time); the third and fourth peaks corresponded to the major and minor γ -lactones isolated above, and the fifth peak to lactone (II) [and (IV)]. The mixture of lactones (20 g.) was subjected to the reactions described below for conversion of (II) into methylenecyclo-octanol. In this way was obtained successively a mixture of hydroxy-amides (23 g.) (not analysed), aminoalcohols (17 g.), b.p. 120–135°/0.5 mm. (Found: C, 73.6; H, 11.7; N, 6.4. C₁₃H₂₄NO requires C, 73.9; H, 11.8; N, 6.6%), and unsaturated alcohols (5 g.), b.p. 95–100°/10 mm. (Found: C, 77.3; H, 11.5. C₉H₁₆O requires C, 77.1; H, 11.3%). Hydrogenation of these over 5% Pd-C gave saturated alcohols (4.5 g.), b.p. 95–100°/10 mm. (Found: C, 75.7; H, 12.4. C₉H₁₈O requires C, 76.0; H, 12.7%). By oxidation of these alcohols (chromium trioxide in warm acetic acid) a mixture (4 g.) was formed which was separated into ketones (1.6 g.) and alcohols (2.4 g.) by chromatography on alumina (elution with CH₂Cl₂). The ketonic fraction consisted of (X) 29%, (XI) 36%, and (IX) 35% (in order of increasing g.l.c. retention time on tritoyl phosphate at 100°). The alcohol fraction, b.p. 90°/10 mm., showed two g.l.c. peaks, the smaller as a shoulder on the main peak (tritoyl phosphate at 100°); the ¹H n.m.r. spectrum included peaks at τ 8.85 (3H, s) and 9.18 (3H, d) with no signals below 7.8 (Found: C, 75.5; H, 12.5. C₉H₁₈O requires C, 76.0; H, 12.3%).

⁸ R. C. Fort and P. v. R. Schleyer, *Adv. Alicyclic Chem.*, **1966**, 299.

The *hydrogen phthalate*⁹ had m.p. 105–106° which was not depressed on admixture with the hydrogen phthalate of (XII) (Found: C, 70.6; H, 7.5. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.6%).

1,4-Dimethylcycloheptanol (XII).—4-Methylcycloheptanone (10 g.) was treated with the Grignard reagent from magnesium (2.5 g.) and methyl iodide (15 g.) to give the *alcohol* (XII) (9.7 g.), b.p. 78–80°/6 mm., n_D^{25} 1.4634 (Found: C, 75.9; H, 12.4%). The hydrogen phthalate had m.p. 105–106° (this resolidified on further heating and finally melted at 195°; the same behaviour was observed with both batches).

Isomerisation of Lactones.—The lactones (II) and (V) (0.5 g.) were heated with 33.3% sulphuric acid (2 ml.) on a water-bath at 80° for varying periods of time. The solutions were cooled and poured into water, and the lactones were extracted and analysed by g.l.c.: the components were identified by comparison of retention times with those of the lactones produced from (II) and sulphuric acid under the conditions specified by Cope.⁴

cis-4-Methoxycarbonylcyclo-octanol.—The hydroxy-acid (VIII) (10 g.) was treated with excess of ethereal diazomethane and a little methanol; the products after distillation (11.8 g., b.p. 110–115°/1 mm.) were chromatographed on alumina; elution with dichloromethane, gave compound (II) (6.1 g.) and the *hydroxy-ester* (5 g.), b.p. 112°/1 mm., n_D^{20} 1.4849, ν_{\max} (film) 3448br and 1733 cm^{-1} (Found: C, 64.5; H, 9.7. $C_{16}H_{18}O_3$ requires C, 64.5; H, 9.7%).

Methoxycarbonylcyclo-octane.—The above hydroxy-ester (0.5 g.) in ether (10 ml.) was boiled for 8 hr. with phosphorus pentoxide (1.5 g.) and worked up to give an oil (0.4 g.), b.p. 60–62°/0.5 mm., ν_{\max} (film) 3025 and 1733 cm^{-1} , no hydroxy-absorptions. The sample showed a distorted g.l.c. peak indicative of partially resolved components; the peak apex corresponded to the retention time of 5-methoxycarbonylcyclo-octene. The olefinic esters were hydrogenated over 5% Pd-C (theoretical uptake for 1 double bond) to give an oil, b.p. 67–71°/0.3 mm., the g.l.c. retention time and the i.r. spectrum of which were identical with those of an authentic sample of methoxycarbonylcyclooctane.

4-Methoxycarbonylcyclo-octanone.—4-Methoxycarbonylcyclo-octanol (5 g.) in ether (100 ml.) was stirred at 35° for 3 hr. with sodium dichromate (9 g.) and 96% sulphuric acid (10 ml.) in water (100 ml.); it was worked up to give the *keto-ester* (3.5 g.), b.p. 94°/0.4 mm., n_D^{20} 1.4710, ν_{\max} (film) 1730 and 1700 cm^{-1} (Found: C, 65.8; H, 8.8. $C_{16}H_{16}O_3$ requires C, 65.2; H, 8.8%).

4-Methoxycarbonylmethylenecyclo-octane.—4-Methoxycarbonylcyclo-octanone (5 g.) was boiled for 3 hr. with an ethereal solution of the Wittig reagent from methyltriphenylphosphonium bromide (9 g.) and phenyl-lithium (17 ml. of 1.46M-solution). The usual work up procedure and chromatography on alumina gave the unsaturated ester (2.5 g.) as an oil, ν_{\max} (film) 3077, 2645, 1728, and 880 cm^{-1} ; the sample was slightly contaminated with bromobenzene (g.l.c. analysis) and was not analysed. Reduction with lithium aluminohydride gave 4-hydroxymethylcyclo-octanol, b.p. 72°/0.5 mm., ν_{\max} (film) 3356br, 3077, and 880 cm^{-1} (Found: C, 77.5; H, 11.5. $C_{16}H_{18}O$ requires C, 77.9; H, 11.8%).

NN-Tetramethylene-(cis-4-hydroxycyclo-octyl)formamide.—Pyrrolidine (22.5 g.) in ether (100 ml.) was added to the Grignard reagent from magnesium (6.5 g.) and ethyl bromide (30 g.) after which the mixture was boiled for 1 hr.

and then allowed to cool. A solution of (II) (30 g.) in ether (30 ml.) and tetrahydrofuran (300 ml.) was added and the whole was stirred at room temperature for 2 days, boiled for 1 hr., and worked up to give the hydroxy-amide (4.2 g.) as a colourless gum which was used without further purification.

cis-4-(Pyrrolidin-1-yl)methylcyclo-octanol.—The above hydroxy-amide (26 g.) was boiled with lithium aluminium hydride (5.7 g.) in ether (400 ml.) for 24 hr., and worked up by using 6N-sodium hydroxide to dissolve the alumina. This gave the *amino-alcohol* (21.2 g.) as a viscous liquid, b.p. 120–125°/0.3 mm., n_D^{25} 1.5062 (Found: C, 73.7; H, 12.0; N, 6.7. $C_{13}H_{25}NO$ requires C, 73.9; H, 11.8; N, 6.6%).

4-Methylenecyclo-octanol (XIV).—The amine (50 g.) in methanol (100 ml.) was oxidised with 30% hydrogen peroxide (100 ml.), and the *N*-oxide was pyrolysed at 160°/0.2 mm. The products were partitioned into basic and neutral fractions, the latter being the *enol* (XIV) (8.1 g.), b.p. 75°/0.05 mm., ν_{\max} (film) 3360br, 3080, 1639, and 885 cm^{-1} (Found: C, 77.1; H, 11.4. $C_9H_{16}O$ requires C, 77.1; H, 11.5%). A solution of the enol (1 g.) and *N*-bromosuccinimide (1.3 g.) in dioxan (30 ml.) and water (3 ml.) was kept at room temperature for 30 min., and then worked up to give a mobile liquid (0.9 g.), b.p. 70°/18 mm., n_D^{25} 1.5166, ν_{\max} (film) 1075 and 1020 cm^{-1} and no olefinic, hydroxy, or carbonyl absorptions. The 1H n.m.r. spectrum included absorptions at τ 5.58 (1H, m), 6.60 (1.8H, s), and 6.88 (0.2H, s); g.l.c. (tricyanoethoxypropane at 100°) showed two components in the ratio 9:1 (Found: C, 49.4; H, 6.8. $C_9H_{15}BrO$ requires C, 49.3; H, 6.8%).

4-Methylenecyclo-octanone.—The enol (XIV) (3.5 g.) in pyridine (35 ml.) was added to the complex from chromium trioxide (7 g.) and pyridine (70 ml.), and the mixture was kept at room temperature overnight. The usual work up procedure, followed by chromatography on alumina (elution with dichloromethane) gave the unsaturated ketone (2.3 g.) as a mobile liquid, b.p. 75°/10 mm., ν_{\max} (film) 3080, 1703, 1639, and 890 cm^{-1} (Found: C, 78.1; H, 10.3. $C_9H_{14}O$ requires C, 78.2; H, 10.2%).

1,4-Dimethylenecyclo-octane (III).—The unsaturated ketone (2 g.) was boiled for 3 hr. with the Wittig reagent from methyltriphenylphosphonium bromide (6.4 g.) in ether (20 ml.) and phenyl-lithium (20 ml. of M-solution). The mixture was worked up without using acid, and the products were chromatographed on neutral alumina (elution with light petroleum) to give the diene (III) (1.2 g.) as a liquid, b.p. 52°/10 mm.; ϵ (212 m μ) 45,000, λ_{\min} 250 m μ (ϵ_{\min} 5700), λ_{\max} 255 m μ (ϵ 6900), ν_{\max} (film) 3080, 1639, and 885 cm^{-1} , 1H n.m.r. absorptions at τ 5.25 (4H, s), 7.8 (8H, singlet superimposed on multiplet), and 8.4 (4H, m) (Found: C, 87.7; H, 12.2. $C_{10}H_{16}$ requires C, 88.2; H, 11.8%). A solution of (III) (0.1 g.) and tetracyanoethylene (0.1 g.) in tetrahydrofuran (1 ml.) was kept at room temperature for some weeks, after which the starting materials were recovered unchanged.

Addition Reactions of the Diene (III).—A solution of (III) (0.5 g.) and bromine (1.5 g.) in carbon tetrachloride (5 ml.) was kept overnight at room temperature and then washed with alkali and dried. Removal of solvent left a pale yellow oil (0.68 g.) which decomposed on attempted distillation and was homogeneous (t.l.c. and g.l.c.), ν_{\max} (film) 790 and 740 cm^{-1} , no olefinic absorptions, 1H n.m.r.

⁹ A. G. Davies, J. Kenyon, and L. W. F. Salame, *J. Chem. Soc.*, 1957, 3148.

absorptions at τ 6.10 (2H, s) and 7—8.5 (14H). The diene (III) (0.5 g.) and 10N-hydrochloric acid (0.4 ml.) in glacial acetic acid (5 ml.) were kept at room temperature for 7 days and worked up to give an oil (0.61 g) which decomposed on attempted distillation and was homogeneous (t.l.c. and g.l.c.), ν_{\max} (film) 740 cm^{-1} , ^1H n.m.r. absorptions at τ 8.85 (3H, s) and 7.5—8.5 (14H).

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