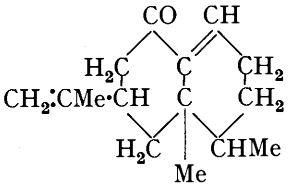
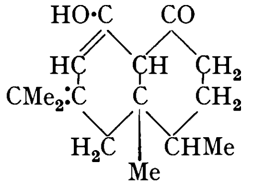
14. *The Constitutions of Eremophilone, Hydroxyeremophilone, and Hydroxydihydroeremophilone. Part IV.*

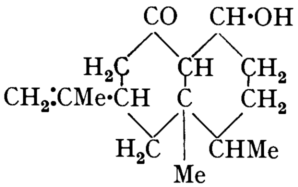
By A. E. Gillam, J. I. Lynas-Gray, A. R. Penfold, and J. L. Simonsen.

The product resulting from the action of methylmagnesium iodide on hydroxytetrahydroeremophilone methyl ether yields on dehydrogenation with selenium 1 : 6-dimethyl-7-*iso*propylnaphthalene. Structure (V; R = H) is now assigned to hydroxyeremophilone. The representation (I) previously given to eremophilone has been confirmed by the oxidation of this ketone to a tetrabasic acid (XIX). The absorption spectra of hydroxyeremophilone and related ketones have been studied and the results are discussed.

In Part III (J., 1939, 87) the suggestion was made that eremophilone, hydroxyeremophilone, and hydroxydihydroeremophilone are represented by (I), (II), and (III) respectively. The recognition of these ketones as derivatives of 1 : 9-dimethyl-7-*iso*propyldecalin has since received support from the synthesis by Copp and Simonsen (J., 1940, 415) of *d*-1 : 2-di-


(I.)

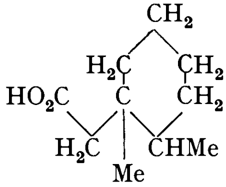

(II.)

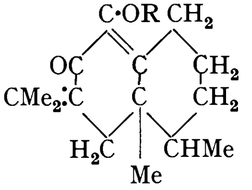

(III.)

methyl*cyclo*hexylacetic acid (IV), which has been shown to be identical with the *cyclo*hexyl acid derived from hydroxyeremophilone (J., 1938, 773).*

Whilst we can now advance additional evidence in support of the structure (I) assigned to eremophilone, we find (II) and (III) to be incorrect and they should be replaced by (V; R = H) and (VI).

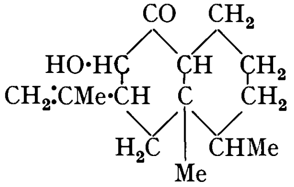
(IV.)

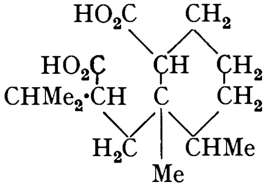




(V.)

(VI.)

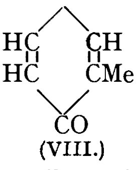




(VII.)

As noted previously (J., 1938, 767), many of the reactions of hydroxyeremophilone suggested that it was a potential 1 : 2-diketone and, since eremophilone oxide can be converted into the hydroxyketone (J., 1932, 2754), one of the carbonyl groups must be in position 5. With the object of establishing rigidly the position of the second (potential) carbonyl group hydroxyeremophilone methyl ether (J., 1938, 771) has been catalytically hydrogenated; the tetrahydro-ether was not obtained pure, but it was characterised by the preparation of its 2 : 4-*dinitrophenylhydrazone*, m. p. 145°. The ketone reacted readily with methylmagnesium iodide and dehydrogenation of the product with selenium gave 1 : 6-dimethyl-7-*iso*propylnaphthalene (J., 1936, 675), which was identified by the preparation of the picrate, m. p. 124—125°, and the styphnate, m. p. 140—141°. It follows, therefore, assuming no molecular rearrangement to occur during the dehydrogenation, that hydroxyeremophilone methyl ether must be represented by (V; R = Me). This structure is in accord with the fact previously recorded (J., 1939, 89) that the glycols prepared from hydroxyeremophilone and hydroxydihydroeremophilone by reduction with sodium and alcohol yield, on oxidation with lead tetra-acetate, followed by potassium permanganate, a dibasic acid, $C_{15}H_{26}O_4$, m. p. 193—194°, which we now consider to be (VII).

Whilst the structure (V; R = H) undoubtedly represents one of the tautomeric forms of the hydroxy-ketone, the bright yellow colour of the molten ketone and of its solutions suggests that it can exist also as the 1 : 2-diketone, although it has not proved possible to prepare any derivatives of this form. The structure (V; R = H) for hydroxyeremophilone contains a carbonyl group in crossed conjugation with two ethylene linkages. Chromophorically such a system might be expected to absorb similarly to that of a simple cyclic αβ-unsaturated ketone by analogy with three compounds having crossed-conjugated systems quoted by Ruzicka *et al.* (*Helv. Chim. Acta*, 1938, **21**, 1735), namely, $\Delta^{1:4}$-cholestadienone, santonin, and the hydroxy-ketone (VIII). These compounds all exhibit an intense absorption maximum between 2300 and 2420 A. The open-chain example in phorone is apparently exceptional in that the crossed conjugation causes a displacement of the maximum to longer wave-lengths ($\lambda_{\max.}$ 2650 A.) as compared with the simple open-chain αβ-unsaturated ketone, mesityl oxide, which is closely similar in absorption spectrum to the cyclic compounds referred to by Ruzicka *et al.* If we tentatively attribute the light absorption of hydroxyeremophilone to the chromophoric properties of a simple αβ-unsaturated ketone only, in the crossed conjugated system we can have either



(VIII.)

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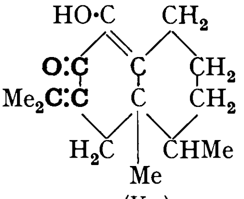
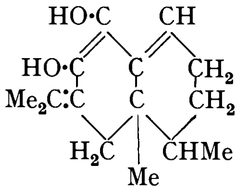
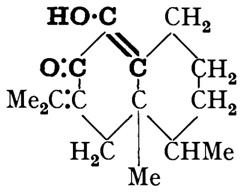
* The keto-acid, *dl*-6-keto-1 : 2-dimethyl*cyclo*hexylacetic acid, described by Copp and Simonsen, is probably structurally identical with the dextrorotatory keto-acid obtained by the oxidation of hydroxyeremophilone.

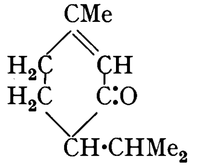
of two chromophoric groups C:C–C:O. Depending upon which of the two ethylene linkages forms part of the effective light-absorbing C:C–C:O group, the chromophore will contain either an *exo*cyclic or a cyclic ethylene linkage (V*a*) or (V*b*). When the ethylene linkage is cyclic, there is the added complication of a hydroxyl group in this particular conjugated system.

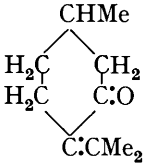

(V*a*.)

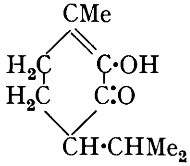

(XII.)


(V*b*.)

This raises the question as to whether the ethylene linkage being cyclic or *exo*cyclic affects the absorption due to the $\alpha\beta$-unsaturated ketone. We have submitted this question to direct test in the case of piperitone (IX) and pulegone (X) (Fig. 1). It will be


(IX.)

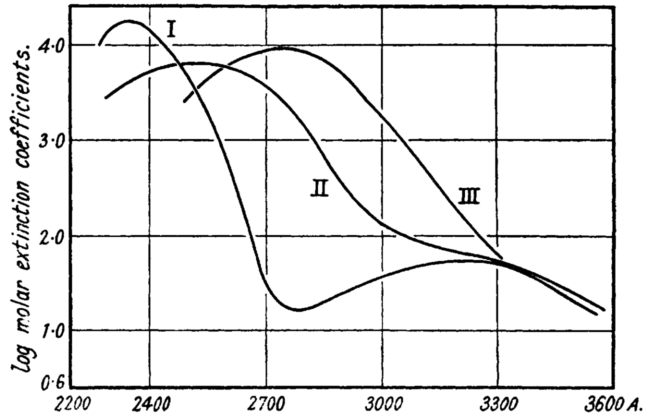

(X.)


(XI.)

seen that, whilst the low-intensity absorption band due to the carbonyl group is unaltered in the two cases, the high-intensity band due to the conjugated system is displaced from 2355 A. in piperitone to 2520 A. in pulegone, the displacement being presumably due to the change from a cyclic to an *exo*cyclic ethylene linkage. To complete the analogy, diosphenol (XI), which is identical with piperitone except that there is a hydroxyl group on one of the two carbon atoms in the ethylene linkage, has also been examined. It will be seen that the presence of the hydroxyl group causes a displacement of the ethylene band to longer wave-lengths (2355 to 2740 A.) and the disappearance (or masking) of the absorption band due to the carbonyl group. This property of the hydroxyl group in modifying

Fig. 1.

The effect of molecular environment on the absorption due to the $C=C-C=O$ *chromophore.*

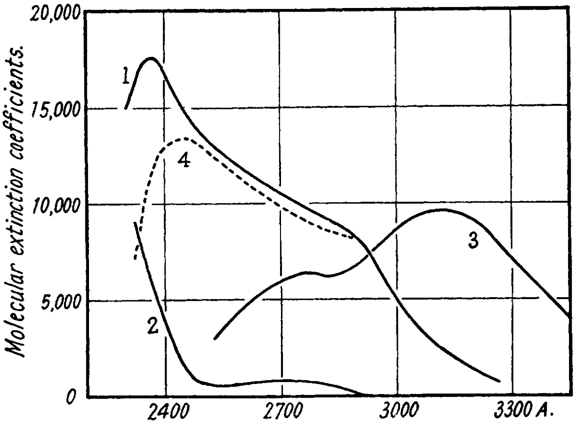


I *Piperitone.* II *Pulegone.* III *Diosphenol (solutions in alcohol).*

the absorption spectrum of $\alpha\beta$-unsaturated ketones is also shown in hydroxymethylenecamphor (Fig. 4), where the normal ethylene band is displaced to longer wave-lengths (*i.e.*, from *ca.* 2350 A. to 2645 A.). Other diosphenols showing the same effect have been recorded: Butenandt *et al.* (*Ber.*, 1936, **69**, 2779) found cholestane-3 : 4-dione-enol to absorb maximally at 2800 A. and Stiller and Rosenheim (J. 1938, 353) found that cholestane-2 : 3-dione exists in two enolic forms absorbing at 2720 (log $\varepsilon = 3{\cdot}70$) and 2700 (log $\varepsilon = 3{\cdot}93$). Heywood and Kon (J., 1940, 713) also have drawn attention to several cases of enolised diketones showing absorption maxima between 2640 and 2745 A. Thus the location to be expected for hydroxyeremophilone would be very similar to that of diosphenol, *i.e.*, 2740 A. In actual fact the main maximum is situated at 3125 A. with a subsidiary inflection at 2775 A. (Fig. 2). To explain this location necessitates a formula containing a longer chain of ethylene linkages and the most probable way to obtain this is to postulate a tautomerism of (V*a*) to (XII) in alcoholic solution.

FIG. 2.

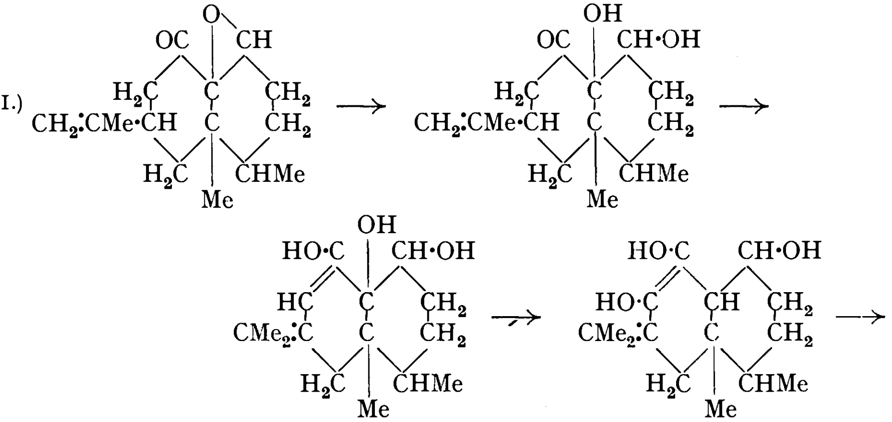
Absorption spectra in ethyl alcohol.



1. *Hydroxyeremophilone benzoate (observed).*
2. *Benzoic acid (observed).*
3. *Hydroxyeremophilone (observed).*
4. *Hydroxyeremophilone as present in the benzoate (by difference, curve 1 minus curve 2).*

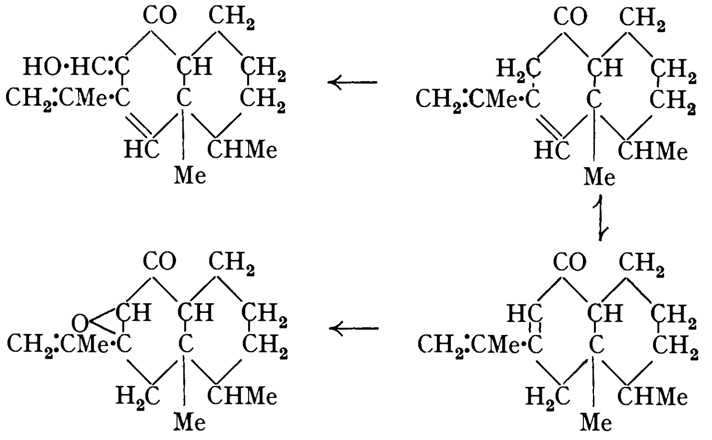
It is possible to test this hypothesis by examining the benzoyl derivative (V; R = Bz) of hydroxyeremophilone, in which the tautomeric change suggested could not occur. The absorption spectra concerned are shown in Fig. 2, where it will be seen that, after allowing for the absorption of the benzoate radical, the absorption of hydroxyeremophilone in the combined state is quite different from that of the free compound. The displacement to longer wave-lengths in the case of the free compound is consistent with an increase of the conjugated system such as is indicated in the postulated tautomeric form (XII). It was difficult at first to reconcile the constitution now assigned to hydroxyeremophilone with its formation from eremophilone oxide, which, if (I) correctly represents eremophilone, must be (XIII). We now venture to suggest that the mechanism of this reaction is that outlined in the scheme set out below, which involves an anionotropic rearrangement.

(XIII.)



(XII)

Before this mechanism was evolved it appeared to us possible that eremophilone might be an equilibrium mixture of (XIV) and (XV); hydroxymethylene-eremophilone (XVI) would then be derived from (XIV), and the oxide (XVII) from (XV). Although indirect evidence was already available (J., **1938**, 771) that the ethylene linkages in eremophilone were not conjugated, it was desirable to obtain further confirmation. This has now been obtained by the reduction of eremophilone by the Ponndorff method to *eremophilol.* The absorption spectrum of this liquid alcohol exhibited two maxima of very low intensity at 2440 and 2750 A. (ε = 193 and 188 respectively). This result completely rules out the possibility of the presence of two conjugated ethylene linkages in eremophilol (and therefore in eremophilone), since such dienes exhibit absorption bands of high intensity (ε of the order 5,000—35,000) situated between 2350 and 2650 A. (cf. Booker, Evans, and Gillam, J., 1940, 1453). The two bands of low intensity in the specimen of eremophilol are almost certainly due to traces of some strongly absorbing impurities in the oil, which had only been purified by distillation. Less than 2% of compounds containing C : C–C : C or C : C–C : O groups would be sufficient to account for the observed intensity, although only the 2440 A. band could be due to the most likely impurity, eremophilone.

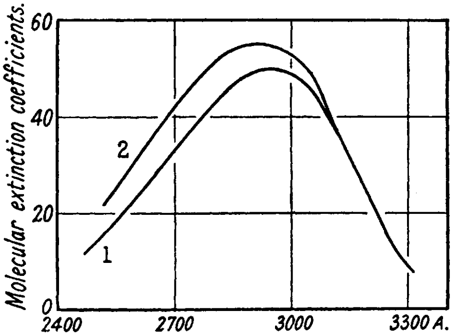


(XVI.) (XIV.) (XVII.) (XV.)

The absorption spectra of eremophilone oxide and of dihydroeremophilone oxide are shown in Fig. 3, the curves being typical, in both location and intensity, of compounds containing an isolated carbonyl group, and are sharply differentiated from the absorption curve of eremophilone itself (Fig. 4). This difference in absorption between eremophilone and eremophilone oxide is sufficient in itself to indicate that the oxygen atom in the oxide has attached itself to the ethylene linkage originally in conjugation with the carbonyl group.

FIG. 3.

Absorption spectra in ethyl alcohol.

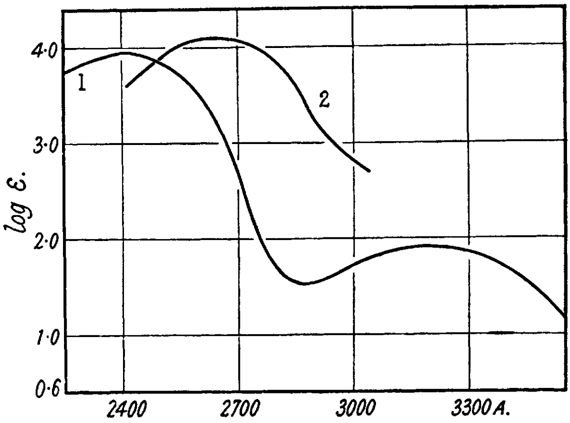


1. *Eremophilone oxide.*
2. *Dihydroeremophilone oxide.*

Although there was already available proof that eremophilone contained an *iso*propenyl side chain, the position of the second ethylene linkage had not been directly determined.

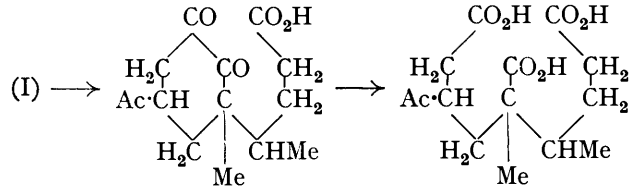
FIG. 4.

Absorption spectra in ethyl alcohol.

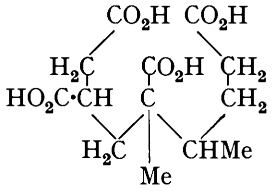


1. *Eremophilone (typical of most αβ-unsaturated ketones).*
2. *Hydroxymethylenecamphor (a typical hydroxylated αβ-unsaturated ketone).*

We have now oxidised eremophilone with ozone and have obtained as the main product of the ozonolysis (apart from formaldehyde) a polybasic keto-acid. On the basis of (I) the keto-acid would be (XVIII); neither the acid nor its methyl ester was obtained pure,



(XVIII.)



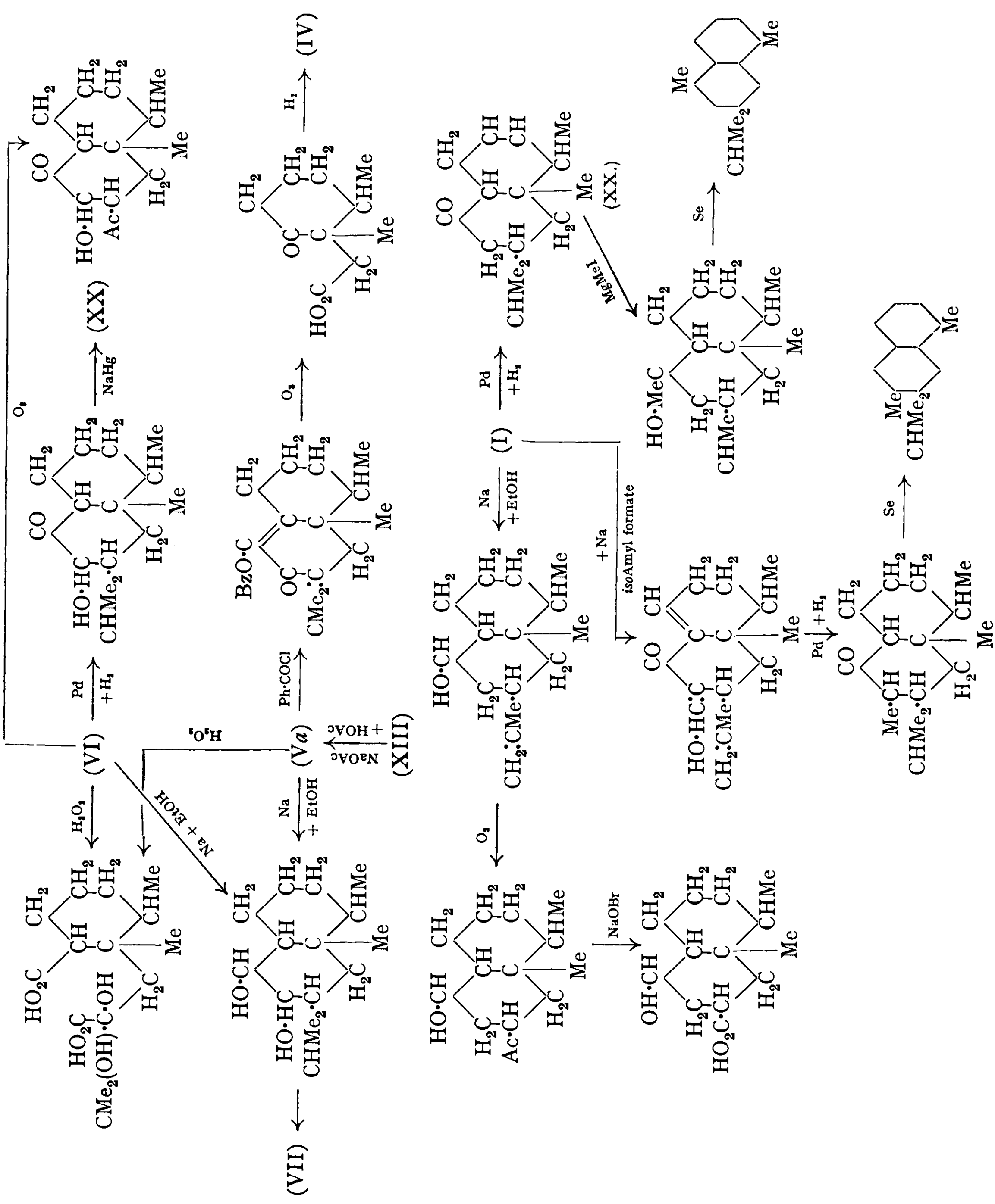
(XIX.)

nor did they give crystalline derivatives with the usual carbonyl reagents. On oxidation of the keto-acid with sodium hypobromite, bromoform and a liquid acid were obtained. Titration of the latter and an analysis of its *silver* salt indicated that it had the expected composition, $C_{13}H_{20}O_8$, and this was confirmed by an analysis of the *methyl* ester. There can be little doubt that the tetrabasic acid is (XIX), thus providing final proof of the structure of eremophilone.

During the course of the somewhat prolonged study of eremophilone and its congeners, which has formed the subject of this series of papers, a considerable number of degradation products have from time to time been described and incorrectly formulated. In so far as they have not been referred to above the more important reactions are shown schematically on p. 66.

EXPERIMENTAL.

Tetrabromoeremophilone.—Contrary to the results previously recorded (J., 1932, 2752) we have now succeeded in preparing a crystalline bromo-derivative of eremophilone. To a well-cooled solution of the ketone (0·5 g.) in chloroform (5 c.c.) a chloroform solution of bromine (1 c.c. equiv. to 1 g. of bromine) was slowly added. Bromination was complete after the addition of 0·8 c.c. and removal of the solvent under diminished pressure gave an oil from which hydrogen bromide was slowly evolved. On trituration with ligroin (b. p. 40—60°) a solid separated. *Tetrabromoeremophilone* was best purified by solution in cold benzene and precipitation by careful addition of ligroin; it then formed highly iridescent prisms, decomp. 116°



(Found : Br, 59·0. $C_{15}H_{22}OBr_4$ requires Br, 59·5%). The tetrabromide was somewhat unstable and decomposed if its solution in alcohol or ethyl acetate was warmed.

Eremophilol.—A mixture of eremophilone (10 g.), *iso*propyl alcohol (50 g.), and aluminium *iso*propoxide (3·5 g.) was distilled with an efficient column until acetone could no longer be detected in the distillate; during the distillation the volume was kept constant by the addition of *iso*propyl alcohol. The excess of *iso*propyl alcohol was removed by distillation, the cooled residue mixed with dilute sulphuric acid, and the oil which separated dissolved in ether. The dried ethereal extract gave on evaporation an oil (7·5 g.). *Eremophilol*, b. p. 164—165°/13 mm., n_D 1·5202, $[\alpha]_{5461}$ − 55·6° in methyl alcohol (*c*, 5·25) (Found : C, 81·6; H, 10·8. $C_{15}H_{24}O$ requires C, 81·8; H, 10·9%), was a somewhat viscid oil with a pleasant odour. The 3 : 5-*dinitrobenzoate*, prepared by treating the oil with 3 : 5-dinitrobenzoyl chloride in pyridine solution, was a gum which partly crystallised on trituration with methyl alcohol. The solid (2 g. from 5 g. of the alcohol) separated from methyl alcohol in needles, m. p. 88—89°, $[\alpha]_{5461}$ − 149·4° in ethyl acetate (*c*, 0·813) (Found : C, 63·6; H, 6·4. $C_{22}H_{26}O_6N_2$ requires C, 63·8; H, 6·3%).

Ozonolysis of Eremophilone.—Eremophilone (10 c.c.) in methyl acetate (50 c.c.) was ozonised at 0°. Formaldehyde was present in the issuing gases, but only a trace of acetone could be detected on decomposition of the ozonide. After completion of the ozonolysis the solvent was removed under diminished pressure, water (10 c.c.) added, and the resinous ozonide decomposed by heating on the water-bath. Addition of sodium carbonate to the aqueous solution left a neutral oil (1·6 g.) undissolved; this was removed by ether, the alkaline solution acidified, and the liquid keto-acid extracted with ether. Evaporation of the solvent from the dried extract gave a viscid oil (12 g.), which reacted rapidly with the ordinary carbonyl reagents, but the products were amorphous. The *methyl* ester, prepared by means of diazomethane, was a somewhat viscid, yellow oil, b. p. *ca.* 220°/18 mm., analysis showing it to be impure (Found : C, 60·7; H, 8·3. $C_{17}H_{28}O_7$ requires C, 59·3; H, 8·1%). For conversion into the tetracarboxylic acid, the keto-acid (12 g.) in aqueous sodium hydroxide was oxidised with aqueous sodium hypobromite (sodium hydroxide, 21 g.; water, 280 c.c.; bromine, 22·8 g.). Bromoform separated immediately and after 1 hour this was removed, the excess of sodium hypobromite destroyed with sulphur dioxide, and the tetra-basic acid extracted by ether from the acidified solution in a constant-extraction apparatus. The acid (12 g.) was a gum which on titration showed the presence of only three carboxyl groups (Found : *M*, 310. $C_{13}H_{20}O_8$ requires *M*, 304), and this was confirmed by the analysis of the *silver* salt (Found : Ag, 51·3. $C_{13}H_{17}O_8Ag_3$ requires Ag, 51·8%). The acid was esterified with diazomethane in ethereal solution, the *methyl* ester being an oil, b. p. 203—205°/5 mm., $[\alpha]_{5461}$ − 17·5° in methyl alcohol (*c*, 6·03) [Found : C, 56·4; H, 7·3; OMe, 41·3, 41·6. $C_{13}H_{16}O_4(OMe)_4$ requires C, 56·7; H, 7·8; OMe, 34·4%. The high methoxyl value is due probably to the partial elimination of the angle methyl group].

Conversion of Hydroxyeremophilone Methyl Ether into 1 : 6-*Dimethyl*-7-iso*propylnaphthalene*.—A solution of hydroxyeremophilone methyl ether (20 g.) in alcohol (100 c.c.) containing palladium–norit (1 g.; 10%) was shaken with hydrogen, absorption corresponding to approximately 2 molecules being complete in 15 hours. The resulting oil, b. p. 175—176°/19 mm., $d_{19\cdot8^\circ}^{19\cdot8^\circ}$ 0·9989, $n_D^{19\cdot8^\circ}$ 1·5045, $[\alpha]_{5461}$ + 47·9°, gave with alcoholic ferric chloride an intense blue colour, indicating that the hydrogenation had been accompanied by some hydrolysis [Found : C, 77·9; H, 10·6; OMe, 13·1. $C_{15}H_{25}(OMe)$ requires C, 76·2; H, 11·1; OMe, 12·3%]. The oil gave a gummy 2 : 4-dinitrophenylhydrazone. It was remethylated and on hydrogenation the methyl ether (12 g.) absorbed hydrogen (600 c.c.). The product, which now gave only a faint colour with ferric chloride, had b. p. 168°/16 mm., $d_{19\cdot8^\circ}^{19\cdot8^\circ}$ 0·9983, $n_D^{19\cdot8^\circ}$ 1·4848, $[\alpha]_{5461}$ + 17·2°, and was still impure (Found : 79·1; H, 10·6%). It gave, however, a crystalline 2 : 4-*dinitrophenylhydrazone*, separating from alcohol in fine yellow needles, m. p. 140° (Found : C, 61·0; H, 7·3. $C_{22}H_{32}O_5N_4$ requires C, 61·1; H, 7·4%).

The methyl ether (10 g.) in ether (500 c.c.) was added to an ethereal solution of methylmagnesium iodide (from 2 g. of magnesium). Interaction was vigorous and, after being kept overnight, the mixture was heated on the water-bath for ½ hour. Isolation of the product in the usual manner gave an oil (9·5 g.), b. p. 148—160°/16 mm., which did not react with Brady's reagent. The oil (5 g.) was heated with selenium (5 g.) at 270° for 12 hours and for a further 36 hours at 300—320°. The product was dissolved in ether, the ethereal extract washed with aqueous sodium hydroxide and water, and the solvent removed from the dried extract. The residual oil (2 g.) was distilled over sodium, b. p. 150—152°/14 mm. From the distillate the picrate was prepared, which crystallised from alcohol in orange-red needles, m. p. 124—125°, and at 124—126° in admixture with the picrate of 1 : 6-dimethyl-7-*iso*propylnaphthalene (Found : C, 59·1; H, 4·8. Calc. for $C_{15}H_{18},C_6H_3O_7N_3$: C, 59·0; H, 4·9%). The styphnate crystallised from alcohol in fine yellow needles, m. p. 140—141°, both alone and in admixture with 1 : 6-dimethyl-7-*iso*propylnaphthalene styphnate (Found : C, 57·4; H, 4·9. Calc. for $C_{15}H_{18},C_6H_3O_8N_3$: C, 56·9; H, 4·7%).

Absorption Spectra.—The determinations were made by standard methods, a Hilger E3 spectrograph being used with a Spekker photometer; unless otherwise stated, purified ethyl alcohol was the solvent.

Piperitone. This was obtained from a commercial specimen and was purified by conversion into its semicarbazone, from which it was regenerated by hydrolysis with oxalic acid. It exhibited an absorption spectrum of the most characteristic αβ-unsaturated ketone-type, the ketone band being exceptionally well defined and of good persistence (Fig. 1). The maxima were situated at 2355 and 3210 A., the values of ε being 17,780 and 54 respectively.

Diosphenol. The absorption spectrum of this compound has been determined by a semi-quantitative method (Mayer, *Atti R. Accad. Lincei*, 1914, **23**, *I*, 439), $\lambda_{max.}$ 2680 A. being recorded. Walker and Read (J., 1934, 230) record $\lambda_{max.}$ 2715 A., ε = 11,000, but give no absorption curve. We are indebted to Professor Read for a specimen of diosphenol, for which we have found $\lambda_{max.}$ = 2740 A., ε = 11,000 (Fig. 1).

Pulegone. Our thanks are due to Professor A. R. Todd and Mr. D. C. Wright for a pure specimen of this compound, prepared from oil of pennyroyal *via* the bisulphite compound and the semicarbazone. The product was free from *iso*pulegone. Absorption data have been recorded by Lowry, Simpson, and Allsopp (*Proc. Roy. Soc.*, 1937, *A*, **163**, 486) for *cyclo*hexane solution and by Savard (*Bull. Soc. chim.*, 1928, **43**, 524) for hexane solution. For alcoholic solution we have found $\lambda_{max.}$ 2520 A., ε = 6500 for the ethylene band and only an inflexion of negligible persistence for the >CO group ($\lambda_{max.}$ *ca.* 3250 A., ε = 63).

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