STUDIES IN RING FORMATION

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SUMMARY

PART I.

The previously reported acid catalysed conversion of 2-(3'-oxo-3'-phenylpropyl)-cyclopentanone to 4-phenylcyclohept-3-ene carboxylic acid has been studied. It has been shown that the cyclohept-4-ene carboxylic acid is also formed and that the reaction involves a bicyclo-(3,2,1)-octenone intermediate. The scope and mechanism of the process has been delineated by examining the effect of a range of substituents on the course and efficiency of the reaction.

PART II.

The mechanism of base catalysed bridge-fission of the epimeric 1-ethoxycarbonyl-4-tosyloxybicyclo-(3,2,1)-octan-8-ones has been shown to depend on the stereochemistry of the tosylate function. The equatorial epimer affords 1,1-diethoxycarbonylcyclohept-4-ene, while the axial epimer yields 1,5-diethoxycarbonylcyclohept-4-one.

CONTENTS.

PART I

INTRODUCTION

The scarcity of synthetic routes to seven-membered carbocycles attaches considerable importance to any new method of obtaining such compounds. The successful elaboration of bridged bicyclic systems to medium-sized rings in this department [1], led to the belief that bridge-fission of a suitably substituted bicyclo-(3,2,1)-octane molecule would afford a cycloheptane derivative, this being substantiated by the work of Stork[2] and Grob[3].

When this work was initiated in 1962, considerable investigation of the bicyclo-(3,3,1)-nonane system had been completed but much less was known both about the preparation and properties of bicyclo-(3,2,1)-octane compounds. A number of naturally occurring compounds incorporating this bridged ring system have been isolated and identified. No monoterpenes with the bicyclo-(3,2,1)-octane skeleton are known but the sesquiterpene helminthosporal (1)[4] and its parent hydrocarbon, sativene (2)[5], have been isolated and the former synthesised[6]. Sesquiterpenes of the cedrene group, the parent hydrocarbon (3)[7,8], cedrol (4)[7,8] and shellolic acid (5)[9, 10] are known and another example which has this structural feature is tricycloretivenal (6)[11]. A considerable number of diterpenes such as the gibberellins, typified by gibberellic acid (7)[12] and those related to phyllocladene (8)[13] and kaurene (9)[14] contain this bridged bicyclic system. The diterpenoid alkaloids of the Garrya group, e.g. garryine (10) and veatchine (11) also incorporate this skeletal feature [15, 16].

A number of methods of obtaining bicyclo-(3,2,1)-octane molecules have been reported but as the work described in this thesis concerns the possible elaboration of this system to seven-membered ring compounds by fission of the one-carbon bridge, only molecules with a functional group at C_8 are considered.

The first preparation of this type of compound was reported by Stobbe[17] in 1912, using dry HCl in ethanol to cyclise the δ-diketone (12) to 2,4-diphenylbicyclo-(3,2,1)-oct-2-en-8-one (13). Cyclisation of a cyclopent-

anone substituted with a three-carbon side chain has remained the most frequently used approach to the bicyclo-(3,2,1)-octan-8-one system. Treatment of cyclopentanone and benzalpyruvic acid using basic catalysis[18], led to the formation of (14) without isolation of the intermediate diketone.

Formation of the amino-ketone(15) from the pyrrolidine enamine of cyclopentanone and acrolein by Stork[2] provided the most widely used and versatile approach to this system. This molecule has proved to be suitable for elaboration to a number of related compounds. Thus the tedious procedure of Woodward and Foote[19, 20], involving pyrolysis of the N-oxide of the corresponding ketal(16), afforded bicyclo-(3,2,1)-oct-2-en-8-one(17) and thence the saturated analogue(18). LeSel[21] used mercuric acetate oxidation of the amino-alcohol(19) to prepare the enamine-alcohol(20) which was converted to the ketol(21) and then the diols (22) and (23).

A further example of cyclisation of a cyclopentanone substituted with a three-carbon side chain was the base catalysed reaction of the bromo-ketone(24)[22], from which bicyclo-(3,2,1)-octan-8-one(18) was isolated as a by-product(2-5%) of the desired spiran(25). A practical route to (18) was reported by Gutsche[23]. The cyano-ketone(26) was prepared by the enamine alkylation procedure[24], and converted to the nitroso-acetate(27) which decomposed in basic solution to yield the bicyclo-ketone via the diazo intermediate(28).

Dauben[25] obtained bicyclic molecules by treating the diketo-ester(29) or the related chloro compound(30) with concentrated sulphuric acid. The former yielded the ketol(31) and the latter gave the corresponding dehydrated product(32) and the chloro-acid(33). A further important procedure for the preparation of bicyclo-(3,2,1)-oct-2-en-8-one molecules using a 5-diketone, was not found in the literature until the practical work described in the thesis was completed. A paper published in 1959 by S. Julia[26] described the cyclisation of 2-cyclohexanonyl-2'-cyclopent-

anonyl-methane(34) and 2-(2'-oxocyclopentylmethyl)-1-tetralone(35) to the corresponding ketones(36) and (37) using anhydrous p-toluene sulphonic acid in acetic acid. Yields of 30-40% were obtained.

The second major approach to the preparation of these bridged compounds utilised the tendency of unsaturated ring systems to undergo transannular reactions. Thus Cope[27] has solvolysed cyclo-oct-4-ene brosylate(38) with trifluoroacetic acid to obtain the exo-alcohol(39) after hydrogenolysis. Similarly cyclo-octa-1, 5-diene(40) on treatment with concentrated sulphuric acid afforded a 75% yield of this compound. Oxidation yielded the ketone(18). A further example of formation of a compound with the desired bicyclic skeleton from a medium ring carbocycle has been investigated by LeBel[21]. Treatment of the bicyclic amino-ketone(15) with base yielded cyclohept-4-ene carboxylic acid (41)[2] which was reduced to cyclohept-4-ene carbaldehyde. Reaction of this compound with N-methyl hydroxylamine[28] followed by peracetic acid gave the nitrone(42) which was hydrolysed by acid to the ketol(43).

The final major approach involved rearrangement of more readily accessible bicyclic systems. Cope[29] converted anti-norbornen-7-ol to the tricyclic compound(44), which furnished the exo-acetate of bicyclo-(3,2,1)-octan-8-ol(39) on hydrogenation. A very low overall yield was obtained. Formolysis of bicyclo-(2,2,2)-octene was originally reported to yield trans-bicyclo-(2,2,2)-octane-2,3-diol(45)[30] but the structure of this product was subsequently shown to be exo-syn-bicyclo-(3,2,1)-octane-2,8-diol(23)[31]. LeBel[21] treated bicyclo-(2,2,2)-octene-oxide with peracetic acid and obtained only (23) but Grob[3], on hydrolysis of the same oxide, obtained both (23) and (45). Oxidation of the former resulted in the diketone(46). LeBel[32] obtained syn-8-bromobicyclo-(3,2,1)-oct-2-ene(47) and the dibromide(48) from reaction of bicyclo-(2,2,2)-octene with N-bromosuccinimide. The former was also obtained by Zaikov[33]. Hydrogenation of (47) yielded endo-8-bromobicyclo-(3,2,1)-octane(49) which was converted to exo-bicyclo-(3,2,1)-octan-8-ol(39) with aqueous

silver nitrate [32], demonstrating the possibility of converting such bromo-compounds to bridge carbonyl molecules. Grob[34] also obtained bicyclo-(3,2,1)-octane molecules by hydrolysing (50) and (51), the products of bromination of bicyclo-(2,2,2)-octadiene. The former afforded the unsaturated bromohydrin(52) while the latter gave a diol, converted by acid into a mixture of compounds from which the unsaturated diols(53) and (54) were obtained.

An important structural feature of bicyclo-(3,2,1)-octan-8-one molecules, which was expected to favour bridge-fission, was the apparent strain inherent in this system. This was evident from the high carbonyl frequencies in the infra-red spectra of the following compounds; the unsaturated ketones(17)[20] and (36)[26] showed absorption at 1758cm.$^{-1}$, the β-diketone(46)[3] at 1754cm.$^{-1}$ for the five-membered ring carbonyl and the keto-ester(32) at 1760cm.$^{-1}$. Again the difficulty experienced in converting a tetrahedral carbon atom at C_8 to the trigonal atom of a carbonyl, exemplified by the resistance of the alcohols(39) and (55)[19,29] and their Δ^2 unsaturated analogues[20] to oxidation and by the difficult conversion of the ketal(56) to the ketone(17)[19] was further supporting evidence.

An attempt by another worker[35] in this department to prepare 2-phenyl-bicyclo-(3,2,1)-oct-2-en-8-one(57) using hydrochloric and acetic acid treatment of the diketone(58), in a manner similar to that employed by Cope[36] for preparation of the bicyclo-(3,3,1)-nonane analogue(59), led to an excellent recovery of acidic material and a neutral compound identified spectroscopically as a γ-lactone. It was shown[35] that the acidic material was 4-phenylcyclohept-3-ene carboxylic acid(60) and the neutral product was the related lactone(61). The skeleton of the former was proved by hydrogenation and decarboxylation to phenylcycloheptane[37] and the relative positions of the double bond and carboxyl shown by oxidative cleavage. As shown in scheme (a) ozonolysis using an oxidative work up (H_2O_2) furnished acidic material

which, when treated with acetyl chloride, afforded a substituted succinic anhydride (62) isolated from the crude reaction mixture by crystallisation [35].

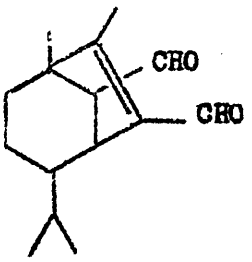
This reaction apparently offered a simple method of synthesis of substituted cycloheptene compounds from readily available substituted cyclopentanones, the acidic nature of the product affording a very convenient separation from by-products and starting material. The obvious novelty and potential usefulness of this reaction prompted investigation of a number of questions which it raised;

(a) the anticipated product of this reaction, 2-phenylbicyclo-(3,2,1)-oct-2-en-8-one(57), was not detected in the reaction mixture. It was assumed that this compound was formed initially but the considerable strain expected in this type of molecule had resulted in facile bridge-fission. However, this assumption could not be verified without isolation of (57), and at the time this study was initiated considerable effort by another worker[35] had been directed, without success, to synthesise this possible intermediate.

(b) if (57) was the intermediate in the reaction, acid catalysed bridge-fission, by protonation of the double bond, would be expected to yield 4-phenylcyclohept-4-ene carboxylic acid (63) as the product, as shown in scheme (b). However, oxidative cleavage had shown the product to be the Δ^3 isomer (60). It was therefore assumed that the Δ^4 acid (63) was formed initially and isomerised in the acidic medium to (60). Such isomerisations are well-known but in this case there appeared to be no driving force for complete migration of the double bond. It seemed likely that a mixture of both isomers was, in fact, present in the reaction product.

(c) if the bicyclo-(3,2,1)-oct-2-en-8-one system was the intermediate in the elaboration of a 1,5-diketone to a cycloheptene acid, was this facile cleavage a general property of such compounds or was the phenyl substituent an essential feature?

The purpose of the work described in this thesis was to investigate the scope and limitations of this reaction, to establish the bridged bicyclic compound as the intermediate and if possible, to elucidate the mechanism. A suitable starting point appeared to be investigation of the cyclisation of 2-(1',3'-diphenyl-3'-oxopropyl)-cyclopentanone(12) with hydrochloric and acetic acids since the expected intermediate in this particular reaction, the bicyclo-ketone(13), had been known since 1912[17]. Comparison of the products from similar treatment of (12) and (13) was regarded as the first step in establishing the possible mechanism.



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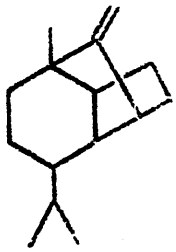

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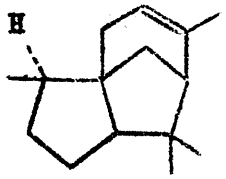

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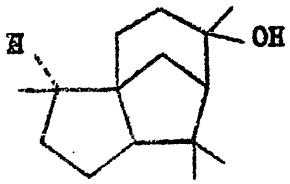

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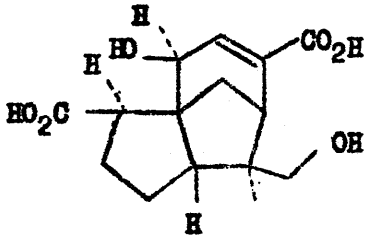

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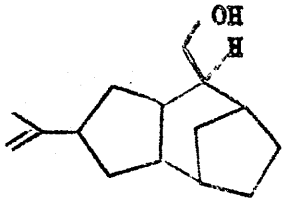

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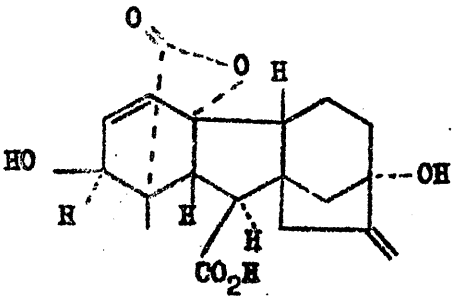

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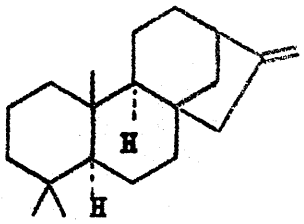

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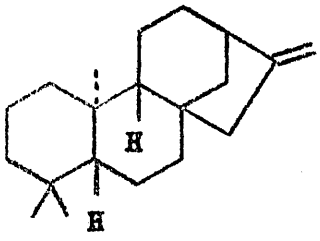

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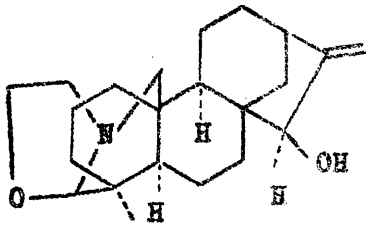

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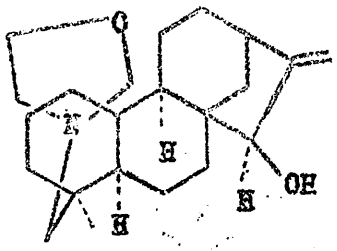

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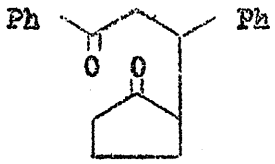

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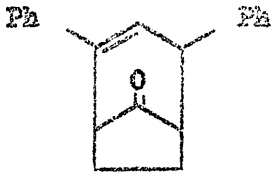

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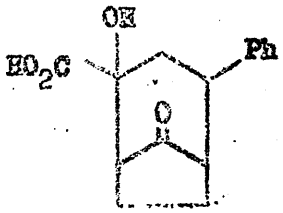

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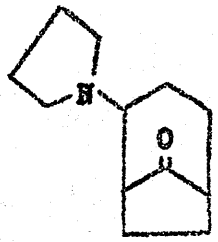

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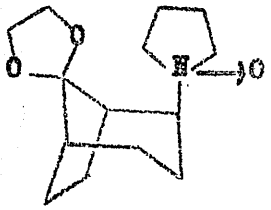

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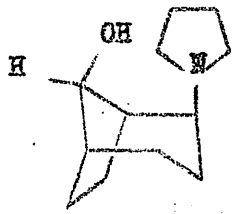

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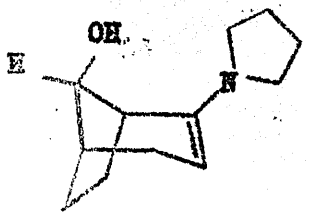

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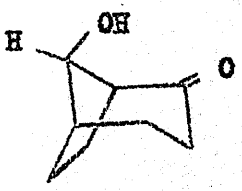

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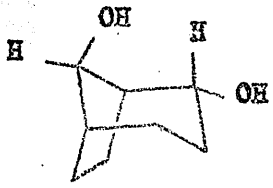

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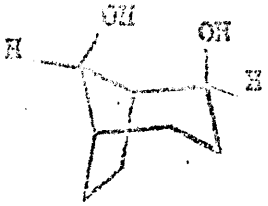

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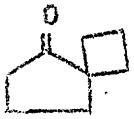

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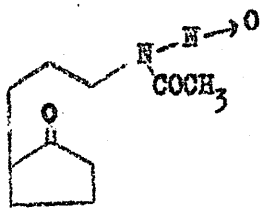

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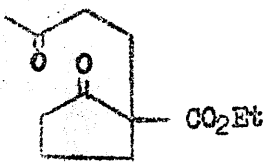

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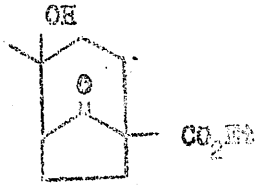

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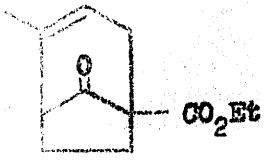

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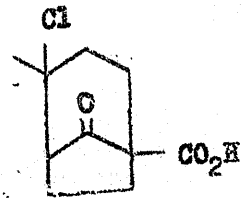

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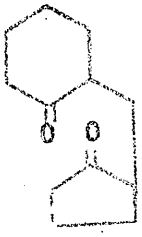

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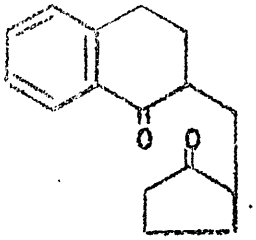

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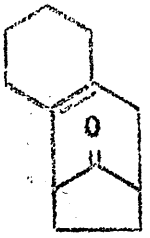

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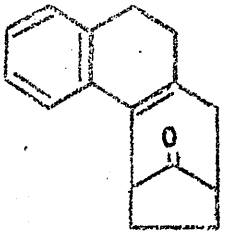

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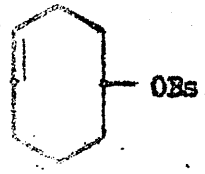

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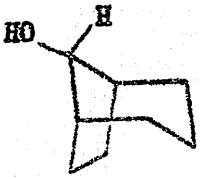

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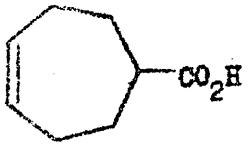

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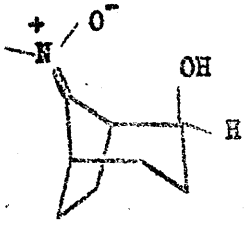

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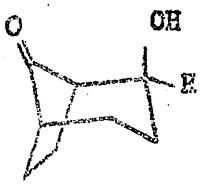

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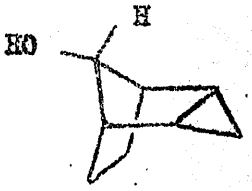

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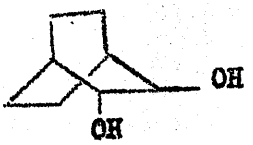

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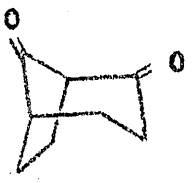

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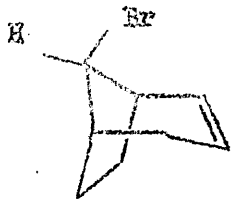

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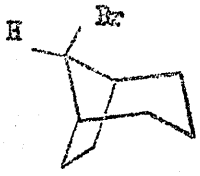

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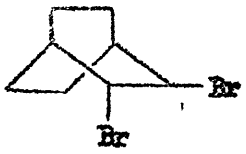

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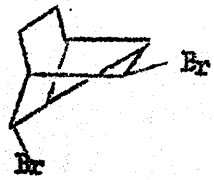

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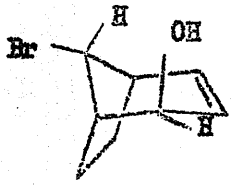

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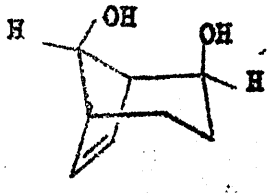

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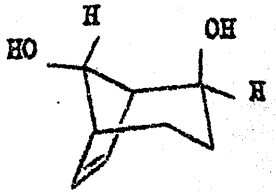

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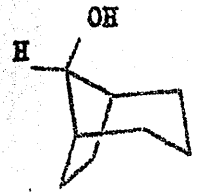

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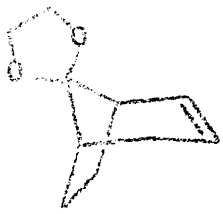

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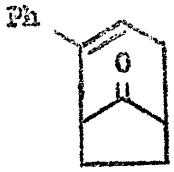

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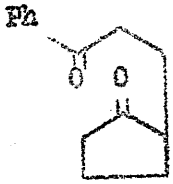

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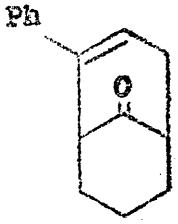

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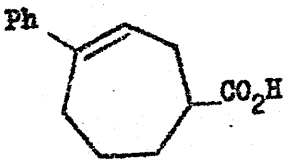

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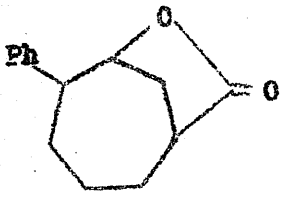

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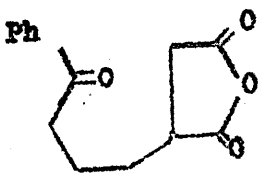

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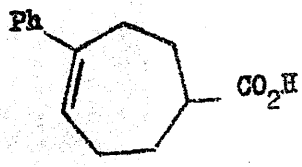
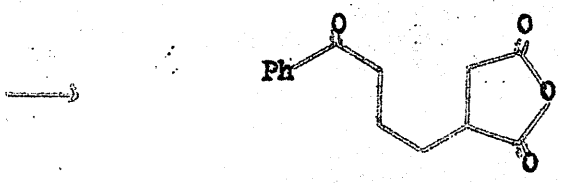


(63)

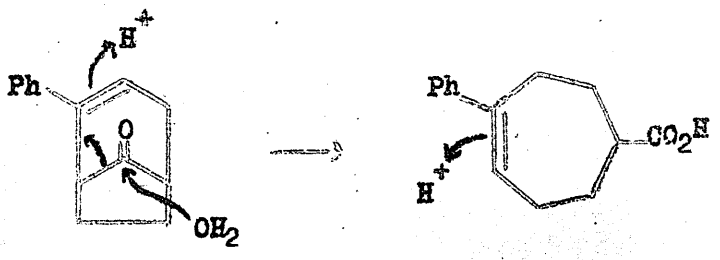
Scheme (a).

(60)



(62)

Scheme (b).



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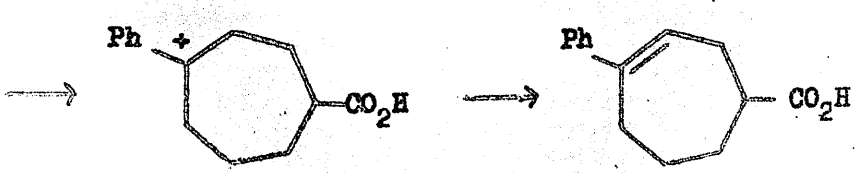

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REFERENCES.

1. Buchanan, McKillop and Raphael, J.C.S., 1965, 833.

2. Stork and Landesman, J. Amer. Chem. Soc., 1956, 78, 5128.

3. Grob and Hostynek, Helv. Chim. Acta, 1963, 46, 2209.

4. de Mayo, Spencer and White, Can. J. Chem., 1963, 41, 2996.

5. de Mayo and Williams, J. Amer. Chem. Soc., 1965, 87, 3275.

6. Corey and Nozoe, J. Amer. Chem. Soc., 1963, 85, 3527.

7. Stork and Breslow, J. Amer. Chem. Soc., 1953, 75, 3291.

8. Stork and Clarke, J. Amer. Chem Soc., 1955, 77, 1072.

9. Yates and Field, J. Amer. Chem. Soc., 1960, 82, 5764.

10. Cookson, Melera, and Morrison, Tetrahedron, 1962, 18, 1321.

11. Chiurdoglu and Decot, Tetrahedron, 1958, 4, 1.

12. Hartsuck and Lipscomb, J. Amer. Chem. Soc., 1963, 85, 3414.

13. Briggs, Cain, Cambie and Davis, J.C.S., 1962, 1840 and references therein.

14. Briggs, Cain, Cambie, Davis, Rutledge and Wilmshurst J.C.S., 1963, 1345 and references therein.

15. Weisner, Armstrong, Bartlett and Edwards, J. Amer. Chem. Soc., 1954, 76, 6068

16. Valenta, Weisner and Wong, Tetrahedron Letters, 1964, No. 36, 2437.

17. Stobbé, J. prakt. Chem., 1912, 86, 238.

18. Jung and Cordier, Compt. Rend., 1959, 249, 711 cf. C.A. 1960, 54, 4457d.

19. Foote and Woodward, Tetrahedron, 1964, 20, 687.

20. LeBel and Spurlock, Tetrahedron, 1964, 20, 215.

21. LeBel and Spurlock, J. Org. Chem., 1964, 29, 1337.

22. Meyer, Wenschuh and Tepelmann, Chem. Ber., 1958, 91, 1616.

23. Gutsche and Bailey, J. Org. Chem., 1963, 28, 607.

24. Stork, Brizzolara, Landesman, Szmuszkovicz and Terrell, J. Amer. Chem. Soc., 1963, 85, 207.

25. Dauben and McFarland, J. Amer. Chem. Soc., 1960, 82, 4245.

26. Julia and Varech, Bull. Soc. Chim. Fr., 1959, 1128.

27. Cope, Grisgar and Peterson, J. Amer. Chem. Soc., 1960, 82, 4299.

28. LeBel, Slusarczuk and Spurlock, J. Amer. Chem. Soc., 1962, 84, 4360.

29. Cope, Moon, Park and Woo, J. Amer. Chem. Soc., 1962, 84, 4865.

30. Walborsky and Lonczini, J. Amer. Chem. Soc., 1954, 76, 5396.

31. Kwart and Gatos, J. Amer. Chem. Soc., 1958, 80, 881.

32. LeBel, Huber and Zalkow, J. Amer. Chem. Soc., 1962, 84, 2226.

33. Zalkow and Oehlschlager, J. Org. Chem., 1964, 29, 1625.

34. Gagneux and Grob, Helv. Chim. Acta, 1959, 42, 1753.

35. Maxwell, Ph.D. Thesis, 1965, University of Glasgow.

36. Cope and Hermann, J. Amer. Chem. Soc., 1950, 72, 3405.

37. Henderson, B.Sc. Thesis, 1965, University of Glasgow.

DISCUSSION

Condensation of cyclopentanone and benzalacetophenone (1) in the presence of a catalytic quantity of piperidine as described by Stobbé [1], resulted in viscous oils from which 2-(1',3'-diphenyl-3'-oxopropyl)-cyclopentanone (2) could by crystallised only with difficulty. Investigation of the reaction employing varying quantities of catalyst and temperatures, resulted not only in improved yields and easier purification of the diketone (2) but from a reaction using an excess of piperidine, a 55% yield of a higher melting compound was isolated. Recrystallisation from commerical grade solvents induced decomposition of this material, the resultant oil smelling strongly of piperidine. The infra-red spectrum showed bands at 1691cm.$^{-1}$(aromatic ketone) and 1627cm.$^{-1}$(double bond) but no absorption for a five-membered ring ketone. This evidence together with analytical data which indicated the formula $C_{25}H_{29}NO$, suggested the enamine structure (3). Hydrolysis of this compound to the diketone (2) was readily accomplished by heating an ethanolic solution with dilute sulphuric acid and heating the enamine under reduced pressure for one hour also yielded the diketone.

The formation of this product in a reaction in which no attempt was made either to remove the water formed or to exclude atmospheric moisture (the reaction was carried out in a conical flask on a steam bath), is somewhat surprising. The very short reaction time and low temperature used is also surprising in view of the 5-8 hour reflux employed by Stork [2] for formation of the piperidine enamine of cyclopentanone, although this could, perhaps, be explained by

the absence of solvent. The mode of formation of the enamine (3) can be interpreted in two ways; (a) reaction of cyclopentenone and piperidine to form the enamine (4) and then alkylation with benzalacetophenone, or (b) Michael-type condensation to form the diketone (2) followed by reaction with piperidine to yield the enamine (3). The second postulation is rendered invalid by the observation that the diketone (2) treated under identical conditions with piperidine failed to yield the enamine.

The apparent establishment of an enamine alkylation mechanism in this reaction brings into doubt the assumption that secondary amine catalysed condensation of simple ketones and electrophilic olefins proceeds by formation of a carbenion or enolate of the former compound [3]. It is conceivable that, even in the presence of catalytic quantities of secondary amine, initial formation of an enamine occurs followed by condensation with the unsaturated compound and hydrolysis employing the water formed in the first step or traces present from the beginning. Formation of a quantity of the enamine using an excess of piperidine may be rationalised since decomposition of the product to recover the base for further reaction to take place is no longer necessary.

Treatment of the diketone (2) with concentrated hydrochloric acid and acetic acid at reflux yielded a crystalline acid. The mother liquor afforded further quantities of the acid together with a small yield of neutral material. It was anticipated that the acid was 2,4-diphenyl-cyclohept-3-ene carboxylic acid (5) by analogy with the mono-phenyl series previously investigated [4], but the n.m.r. spectrum of the methyl ester showed the olefinic proton signal (3.85 τ) as a triplet and not as the doublet expected. The ester was therefore assigned the structure (6) and the acid formulated as (7), the product expected from mechanistic considerations.

As discussed in the introduction, it was thought that in acidic solution the acid with the Δ^4 double bond (8), expected as the initial product, would equilibrate to a mixture of the Δ^3 and Δ^4 acids by protonation as shown in scheme (a), (8) $\rightleftharpoons$ (9). Evidence for this isomerisation and re-investigation of the acids obtained from the diketones (2) and (10) are discussed later(p.27).

Crystallisation of the neutral oil furnished a mixture consisting of two main components which were separated by chromatography. The less polar compound was assigned the lactonic structure (11) on the basis of its infra-red spectrum ($\nu_{C=O}^{CCl_4}$ 1778cm.$^{-1}$) and n.m.r. spectrum which showed a broad multiplet at 6.8-7.3τ(2H, C_1 and C_4), and singlets at 6.41τ(1H, C_2) and 5.0τ(1H, C_3). The conformation of the lactone shown (11a), may be deduced from the absence of splitting of the protons H_2 and H_3, which can only be explained if $\angle H_1H_2 = \angle H_2H_3 = \angle H_3H_4 = 90^\circ$.

The other component exhibited carbonyl absorption at 1750cm.$^{-1}$ in the infra-red spectrum. Analysis indicated the presence of two oxygen atoms and the absence of hydroxyl absorption and non-reducibility of the carbonyl group with sodium borohydride suggested a δ-lactone structure. The postulated structure (12) was supported by the absence of a signal ~ 5τ for the lactonic proton H-C-O-C=O and the presence of somewhat subsplit quartets centred at 6.5 τ(1H) and 7.02τ (2H) in the n.m.r. spectrum appeared consistent with an ABC system incorporating the protons on C_2 and C_3. This required a molecular conformation such as (12a), where little or no coupling occurred between the protons on C_1 and C_2.

The ring expansion reaction having been successfully applied to the diketone (2), it remained to prepare the bicyclo-ketone (13) for comparison. Stobbe[1] reported this compound and the bicyclo-(3,3,1)-nonenone analogue as the α,β-unsaturated ketones (14) with the double bond in the anti-Bredt position[5] at the bridgehead. The correct structure for the latter was established by

Cope [6] from a comparison of the ultra-violet spectrum of its 2,4-dinitrophenylhydrazone derivative with that of the hydrogenated ketone. Since the experimental details recorded by Stobbe were vague, a number of reactions using dry HCl in ethanol were undertaken. All yielded gums from which small quantities of a compound, subsequently shown to be the desired product, were isolated by chromatography. Dissolving the reaction mixture in ether and washing with aqueous base afforded improved yields but the quantity of unreacted diketone (2) made crystallisation of the product difficult. Substitution of acetic acid for ethanol as the reaction solvent failed to effect any improvement.

The difficulty in reproducting identical reaction conditions, caused by the use of dry HCl, made an alternative acidic catalyst desirable. Concentrated sulphuric acid at 0° caused sulphonation of the phenyl groups and polyphosphoric acid yielded partly reacted mixtures. Treatment of the diketone (2) with boron trifluoride etherate in refluxing benzene, however, yielded the bicyclo-ketone together with a considerable quantity of the cycloheptene acid (7).

At this stage it appeared obvious that, if the bicyclo-ketone was the intermediate in the formation of the cycloheptene acid, cleavage of the carbonyl bridge could only result if water or some other potential nucleophile was present. In the boron trifluoride reaction, which was carried out in strictly anhydrous conditions, only water formed in the initial aldol condensation of the diketone could have effected the cleavage to form the acid. Accordingly, the diketone was refluxed with anhydrous p-toluene sulphonic acid in benzene using a water separator to remove the water formed in the reaction. This resulted in an acceptable yield of 2,4-diphenylbicyclo-(3,2,1)-oct-2-en-8-one (15) easily separated from the starting material by crystallisation. The n.m.r. spectrum, which showed a quartet at 5.55 τ for the benzylic proton at C_4 and a doublet at 3.96 τ for the olefinic proton, proved the β,γ - position of the double bond. The infra-red spectrum absorption at

1755cm.$^{-1}$ for the carbonyl group was regarded as evidence of the strain inherent in the bicyclo-(3,2,1)-octene system with a trigonal carbon at C_8.

Treatment of the bicyclo-ketone (13) with hydrochloric acid in refluxing acetic acid for 6 hours yielded the expected diphenyl acid (7), affording confirmation that the ketone (13) was the probable intermediate in the acid catalysed ring expansion reaction.

Two possible approximate mechanisms were postulated at this stage, both involving protonation of the double bond of the bicyclo-compound. Scheme (b) then envisaged nucleophilic attack of the elements of water at the bridge carbonyl while scheme (c) visualised formation of a ketene intermediate suggested previously in the cleavage of a bicyclic α-diketone [7]. In the latter case this mechanism was later retracted [8].

With the establishment of this point, the technique used for preparing the ketone (13) was applied to the diketone (10) to obtain the elusive 2-phenylbicyclo-(3,2,1)-oct-2-en-8-one (15). Use of toluene as solvent afforded a solid mixture of starting material and the desired product, which was isolated by chromatography. The structure was confirmed by the high carbonyl frequency of 1758cm.$^{-1}$ in the infra-red spectrum and the presence of a triplet at 4.1 τ for the olefinic proton in the n.m.r. spectrum. This compound has subsequently been prepared in better yield using modified conditions [4].

During consideration of possible systems for use in determining the generality of the ring expansion procedure, it seemed that the effectiveness of this reaction might depend on the stability of the carbonium ion generated at C_2 of the bicyclo-intermediate, by protonation of the double bond. The excellent yield of cycloheptene acid formed with a phenyl substituent at this position, suggested that stabilisation of the carbonium ion by an aromatic system could be an important factor. As a result

thiophene, a heterocyclic exhibiting considerable aromatic character, was chosen as a suitable substituent to initiate this study.

Two methods of preparing the required diketone (16) seemed feasible, a general method for the formation of 1,5-diketones investigated by Gill et. al. [9] or reaction of the enol-lactone (17) with the appropriate Grignard reagent [10,11]. The former sequence was selected since it involved only two stages and a simple experimental procedure.

2-Acetylthiophene[12] was converted to the corresponding Mannich base hydrochloride (18) and the free base, 2-thienyl- β -dimethylaminoethyl ketone, refluxed with a three molar excess of cyclopentanone. Removal of the excess ketone and distillation furnished two fractions, the lower boiling being identified as 2-acetylthiophene (19). The higher boiling material which solidified, m.p. 163.5-164°, exhibited double carbonyl absorption at 1753cm.$^{-1}$ and 1670cm.$^{-1}$ in the infra-red spectrum, but the former value seemed too high a frequency for normal five-membered ring ketone absorption [13] and the melting point was very considerably greater than those of 1,5-diketones of comparable molecular weight. That this compound was not the desired diketone (16) was confirmed by analysis and, although it has not been identified, the isolation of 2-acetylthiophene suggested that formation of the diketone (16) had in fact taken place but that it had then undergone a retro-Michael reaction as shown in scheme (1), (16) - - → (19)[3,14].

This reversal of the condensation was thought to have arisen from the use of excessive heat during the reaction or, more probably, as a result of distillation of the product in the presence of traces of dimethylamine. In all subsequent preparations of this type, neutralisation of the reaction mixture prior to distillation prevented decomposition in this manner.

Repetition of the reaction at 90°-100° and neutralisation of the product with acetic acid, followed by ether extraction in the usual manner, yielded a solid mixture of two compounds. Crystallisation from ethanol yielded the more polar compound, $C_{19}H_{20}O_3S_2$, which showed $\nu_{C=O}^{CCl_4}$ 1735cm.$^{-1}$ and

1671cm.$^{-1}$, the latter peak being approximately twice the intensity of the cyclopentanone absorption. The fact that this compound resulted from condensation of two molecules of the thiophene compound with cyclopentanone was confirmed by the n.m.r. spectrum which showed a four-proton triplet for the methylene protons adjacent to the thienyl ketone function and six thienyl protons. Since the α-protons of the cyclopentanone ring were concealed in the methylene complex, n.m.r. spectroscopy could not be used to differentiate between the isomeric structures (20) and (21). At this stage, it was felt that the gem-disubstituted structure (20) was the more probable on the basis of the pattern known to result from Michael condensation with unsymmetrically substituted ketones, but this opinion is no longer held (see p.39).

Repeated recrystallisation of the reaction product failed to yield the less polar component in a pure state and it was used in subsequent reactions on the assumption that it consisted mainly of the desired diketone (16). It was later discovered that distillation using a Wood's metal bath provided a separation between the mono-and di-addition products of the reaction, since the high molecular weight material resisted distillation. In this manner a pure sample of the diketone (16) was obtained for characterisation.

While difficulty was being experienced in obtaining the diketone by this route, investigation of the alternative procedure using the enol-lactone (17) was undertaken. As a first step it was decided to prepare the known compound (10), since an authentic sample was available for comparison [4].

Condensation of methyl acrylate and the pyrrolidine enamine of cyclopentanone (22) [2] yielded the keto-ester (23), which was hydrolysed by base to the corresponding keto-acid (24). More concentrated solutions of base and longer reaction times resulted in decomposition to acrylic acid polymer. Attempted cyclisation of the keto-acid with acetic anhydride [39] yielded an oil $\nu_{C=O}$ 1825cm.$^{-1}$ and 1780cm.$^{-1}$, presumably mixed anhydride

(25) [16], and only a low yield of the enol-lactone (17) was obtained by distillation. Addition of a small quantity of fused sodium acetate to the reaction mixture [17], however, resulted in a 75% yield of an oil which showed two spots on t.l.c. The infra-red spectrum absorption at 1778cm.$^{-1}$ and the absence of an olefinic proton signal in the n.m.r. spectrum confirmed that the major product was 2-(2'-carboxyethyl)-1-hydroxycyclopent-1-ene-5-lactone (17a), the impurity being expected to have the isomeric structure (17b).

Treatment of the enol-lactone mixture with an ethereal solution of phenyl magnesium bromide yielded an oil which was distilled into two fractions, the lower boiling being rich in a compound which showed absorption at 1750cm.$^{-1}$ and possibly weak hydroxyl absorption in the infra-red spectrum. This was considered to be 2-hydroxy-2-phenylbicyclo-(3,2,1)-octan-8-one (26) by analogy with the products obtained from similar reactions [18,19,20]. The higher boiling, more polar compound solidified and was identified as the desired diketone (10). However, the recovery of pure diketone from this reaction was poor and since the thiophene substituted compound (16) had by this time been prepared, it was decided merely to establish the overall efficiency of the reaction from the enol-lactone to the cycloheptenone acid, by treating the crude Grignard product with hydrochloric acid and acetic acid, since it is expected that both products would react successfully under ring-expansion conditions. This procedure furnished a 54% yield of acidic material identified as 4-phenylcyclohept-3-ene carboxylic acid (27) by comparison of its infra-red spectrum with that of an authentic sample [4].

The mixture of thiophene substituted diketone (16) and triketone (20) or (21) was refluxed with concentrated hydrochloric acid and acetic acid yielding a very dark gum. This afforded acidic and neutral fractions, the latter being almost pure unreacted triketone (20) or (21), although the infra-red spectrum showed a weak absorption at 1780cm.$^{-1}$, attributed to the presence of a lactone. The acidic material showed absorption in the infra-red at 3500-2800cm.$^{-1}$ (acidic hydroxyl) and 1710cm.$^{-1}$ (carboxyl)

but attempts to distil this, resulted in frothing of the oil and crystallisation was also unsuccessful. Treatment with diazomethane yielded a dark viscous oil which showed absorption at 1730cm.$^{-1}$ (ester) in the infra-red spectrum and consisted of a major component with four more polar impurities (t.l.c.). Distillation afforded a deep yellow oil but further purification proved to be impracticable. Neither the acidic product nor the ester showed typical thiophene absorption bands [21] found in the infra-red spectra of their precursors and in view of these two points this reaction was abandoned. An attempt to use p-toluene sulphonic acid in undried benzene solution in place of concentrated hydrochloric acid and acetic acid, furnished a dark sludge which had a strong odour of hydrogen sulphide. Use of a catalytic quantity of the acid produced a cleaner product but the infra-red spectrum showed that the reaction was incomplete and t.l.c. indicated that a complex mixture of compounds had been formed. No further investigation of this reaction was undertaken, in spite of the fact that pure diketone (16) had become available, since the experience gained above suggested that the desired thiophene substituted cycloheptene acid was not produced.

Although this application was unsuccessful, valuable information concerning preparation of the diketone system was gained. Neutralisation of the crude product eliminated the retro-Michael reaction and distillation, even when solid material was obtained, was the most satisfactory method of purifying the diketone. This and subsequent results suggest that 1,5-diketones prepared by this route without purification by distillation, were in fact contaminated by a triketone when used for further reaction [9].

Attention was now turned to the synthesis of aliphatic substituted cycloheptene acids using the ring expansion reaction. If the mechanism proposed earlier was correct, then the tertiary carbonium ion, generated by protonation of the double bond in the bicyclic intermediate would be stabilised to a lesser extent by an aliphatic substituent than by the

phenyl group and as a result lower yields were anticipated.

The attempted preparation of 4-methylcyclohept-4-ene carboxylic acid (28), appeared at first sight, to be a suitable starting point, since the diketone (29) required as starting material was known [9]. Further consideration however, showed that this case was complicated by the possibility of cyclisation not only to the bicyclic system, but also between the side chain methyl group and the ring ketone function (30).

Study of the literature afforded little useful information concerning the favoured path of reaction of the diketone (29) or the analogous cyclohexanone compound (31), since neither had been isolated prior to Gill's preparation [9]. However, base catalysed reactions in which this type of 1,5-diketone system was an intermediate, led to the isolation of perhydroindanones or octalones [22,23,24,25], although in low yield and in some cases accompanied by ketols which may have had bridged bicyclic structures [26]. Molecules used in steroid syntheses, incorporating this diketone structure as an intermediate also yielded α,β-unsaturated ketones on cyclisation with base [10,11,17]. On the other hand, the related carbethoxylated compounds (32) and (33) could readily be prepared and although basic catalysis again resulted in cyclisation of the latter by the unwanted route [22], treatment of these compounds with concentrated sulphuric acid [27] yielded 1-ethoxycarbonyl-4-hydroxy-4-methylbicyclo-(3,2,1)-octan-8-one (34) and 1-ethoxycarbonyl-4-methylbicyclo-(3,3,1)-non-3-en-9-one (35) respectively. Dauben [27] also reported the isolation of the ethyl ester of 4-methylcyclohept-4-ene carboxylic acid (28), albeit in very low yield, together with 1-ethoxycarbonyl-4-methylbicyclo-(3,2,1)-oct-2-en-8-one (36) from similar treatment of 2-ethoxycarbonyl-2-(3'-chlorobut-2-ene)-cyclopentanone (37) which is believed to react by initial conversion to (32).

Consideration of this data suggested two factors which might influence the reaction path, (a) acidic catalysis and (b) introduction of a potential angular carbethoxy group which might inhibit formation of (38), an intermediate in the formation of the α,β-unsaturated ketone. Despite

the conclusion drawn by Dauben, that the formation of the bridged bicyclic system depended on the use of strong acid and the presence of a potential angular carbethoxy group, in the absence of evidence to the contrary it was felt that the use of acidic catalysis alone might be the important factor [28].

Accordingly, 2-(3'-oxobutyl)-cyclopentanone (29) was subjected to both hydrochloric/acetic acid reflux and concentrated sulphuric acid at room temperature but in both cases a negligible yield of acidic material was recovered and this was discarded without investigation because of the low yield. Both neutral fractions consisted of a mixture of compounds from which 5,6,7,8-tetrahydroindan-5-one (30) was isolated by distillation.

The failure of these reactions to cyclise in the desired manner led to acceptance of Dauben's conclusion that the carbethoxy grouping was essential. The diketo-ester (32) was therefore prepared [27] and treated with hydrochloric and acetic acids in the hope that the high reaction temperature might result in bridge-fission of the expected intermediate ketone (31). This procedure, however, yielded only 10% of crude acidic material which was not investigated because of the complexity of the mixture and the low recovery. Distillation of the neutral fraction yielded a mixture of two compounds which were separated by chromatography. The more polar was identified as the α,β-unsaturated ketone (30) and the other, which exhibited a carbonyl absorption of 1725cm.$^{-1}$ in the infra-red spectrum and showed no olefinic protons but a broad two-proton singlet at 7.27 τ in the n.m.r. spectrum, was tentatively assigned the isomeric structure (39) although satisfactory analytical figures could not be obtained.

The infra-red spectrum of this material retaken after it had been standing for a few days, showed absorption at 1685cm.$^{-1}$, attributed to formation of the α,β-unsaturated ketone (30) by double bond migration. The formation of these decarbethoxylated compounds was assumed to have occurred by initial hydrolysis and decarboxylation to yield the diketone (29), which then underwent ring closure.

A similar result has been reported by Wilds [29] using the same reagents to decarbethoxylate a related compound.

Since this had defeated the purpose of introducing the carbethoxy group it was decided to replace this function with a methyl group which would be retained during the cyclisation, for there is evidence that a methyl group can likewise favour bicyclic structures [30,31]. 2-Methylcyclopentanone was prepared by methylation of 2-carbethoxycyclopentanone [32] followed by hydrolysis and decarboxylation with hydrochloric acid [33]. Rigorous purification of the intermediate ensured that the product was free from cyclopentanone. β-Acetoethylation of this unsymmetrically substituted ketone by refluxing it with diethylaminobutan-3-one (40) yielded 40% of a diketone ($\nu_{C=O}^{CCl_4}$ 1739cm.$^{-1}$ and 1723cm.$^{-1}$) which exhibited a doublet at 8.94 τ for the ring methyl in the n.m.r. spectrum. This clearly indicated that the product was 2-(3'-oxobutyl)-5-methylcyclopentanone (41) and not 2-(3'-oxobutyl)-2-methylcyclopentanone (42) the product expected from a Michael-type condensation [3,22] of an unsymmetrically substituted ketone and an electrophilic olefin. The implications and possible mechanism of formation of this unexpected product will be discussed later (see p.37).

An alternative synthesis of the gem-disubstituted cyclopentanone (42) was now required. As mentioned previously, the strongly basic conditions required to generate the anion of cyclopentanone resulted not only in the initial condensation but also cyclisation to the perhydroindanone skeleton when reacted with methyl vinyl ketone or diethylaminobutan-3-one methiodide [22]. Ross and Levine [34] recently studied the condensation of methyl vinyl ketone with cyclohexanone and 2-methylcyclohexanone using lithamide, triton B and ethanolic potassium hydroxide as catalysts. All three induced cyclisation of the initially formed diketones, condensation with 2-methylcyclohexanone occurring as expected on the more substituted α-carbon.

These authors, however, attempted the condensation of methyl vinyl ketone and cyclopentanone using lithamide as catalyst and successfully isolated the uncyclised diketone (29). Thus it was anticipated that 2-methyl-cyclopentanone and methyl vinyl ketone would yield the suitably substituted diketone (42).

Application of the simpler experimental procedure using ethanolic potassium hydroxide as catalyst, afforded a mixture of products which was separated by chromatography to yield 2-(3'-oxobutyl)-2-methylcyclopentanone (42). The structure was confirmed by the infra-red spectrum ($\nu^{CCl_4}_{C=O}$ 1736cm.$^{-1}$ and 1720cm.$^{-1}$) and the n.m.r. spectrum which showed the ring methyl as a singlet at 9.03 τ .

Preparation of this compound enabled a final attempt to be made to evaluate the possibilities of successful application of the ring expansion reaction to this type of aliphatic substituted diketone.

Cyclisation of this diketone using hydrochloric acid-acetic acid, however, afforded an excellent recovery of 8-methyl-5,6,7,8-tetrahydroinden-5-one (43). The 2,4-dinitrophenylhydrazone derivative, recrystallised from ethyl acetate-ethanol mixtures had m.p. 158-160°, compared with the values of 153° quoted for this compound by Robinson [22] and 159-160° for the same derivative of 3-methyl-5,6,7,8-tetrahydroinden-5-one (44). The structure of the ketone was, however, confirmed by its n.m.r. spectrum which showed a singlet for the methyl group at 8.84 τ .

The failure of this reaction to lead to a cycloheptene acid or bicyclo-compound proved that the hydrochloric acid catalysed ring expansion could not be applied successfully to diketones with a methyl or methylene grouping at the 4' position of the side chain, since condensation between this carbon and the cyclopentanone carbonyl is preferred under these conditions

Use of a t-butyl ketone (45) would eliminate this side-reaction, and accordingly, the hydrochloride salt of dimethylamino-4,4-dimethyl-pentan-3-one (46) was prepared from pinacolone, the corresponding β-aminoketone was liberated in the usual manner and refluxed with excess cyclopentanone to yield 80% of the expected diketone (45). Attempts to react this compound with concentrated hydrochloric acid/acetic acid or to prepare the bicyclo ketone (47) using p-toluene sulphonic acid and toluene yielded only unchanged starting material, presumably on account of steric hinderance of the side chain carbonyl function by the bulky t-butyl group.

Only two other possible applications remained to be studied in the aliphatic field. If the side chain carbonyl function was aldehydic then the unwanted cyclisation could not occur and no steric problems could be envisaged. The other solution to these problems seemed to be the situation where both carbonyls of the 1,5-diketone system were sited in rings (48) and cyclisation by either pathway would lead to bridged bicyclic systems. (2,2'-Dicyclopentanonyl)-methane (48) offered the advantage of only one possible intermediate due to symmetry and if bridge fission occurred the product would have the perhydroazulene ring skeleton widely found in the sesquiterpene field. Indeed if the ring expansion reaction was successful then, without considering stereochemistry, a suitably substituted diketone of this type might be successfully converted to yield compounds such as guaiol (49) or bulnesol (50) since the carbonyl group is suitably situated and could readily be elaborated by a Grignard reaction.

Although (2,2'-dicyclopentanonyl)-methane (48) had been reported previously [35,36], it was decided to attempt its preparation by refluxing cyclopentanone and dimethylaminomethylcyclopentanone in the usual manner. This procedure afforded 71% of the desired diketone which solidified after distillation.

Treatment of this compound with concentrated hydrochloric acid in refluxing acetic acid for 24 hours yielded a small quantity of acidic material which was separated by distillation into a colourless oil and an intractible dark material. The oil exhibited carbonyl absorption at 1780cm.$^{-1}$ in the infra-red spectrum and it was assumed that this lactonic material had resulted either from poor separation or by thermal conversion of the acid. The neutral fraction was shown to consist of three components (t.l.c.) after distillation, and these were separated by chromatography. A small quantity of an oil which had a camphoraceous smell and exhibited carbonyl absorption at 1755cm.$^{-1}$ was initially obtained, followed by the major product, 1-hydroxybicyclo-(5,3,0)-decane-3-carboxylic acid lactone (51), identified by its infra-red spectrum ($\nu_{C=O}^{CCl_4}$ 1775cm.$^{-1}$) and by the absence of peaks below 7 τ in the n.m.r. spectrum, which showed that lactonisation had occurred on a fully substituted carbon atom. The final material obtained by chromatography was unreacted diketone.

To check the possibility that the compound eluted first on chromatography might be the bicyclo-ketone (52), a synthesis of this material was attempted by reaction of the diketone (48) with p-toluene sulphonic acid in benzene. Although this was unsuccessful, use of toluene as solvent effected reaction to yield two products. Chromatography furnished the more polar major component in a pure state (t.l.c.) and this was assigned the bicyclo-structure (52) on the basis of its analytical data ($C_{11}H_{14}O$) and infra-red spectrum ($\nu_{C=O}^{CCl_4}$ 1756cm.$^{-1}$). The n.m.r. spectrum showed a vestigial peak at 4.4 τ believed to be caused by the presence of an isomer (53) with a trisubstituted double bond. This material and the compound isolated from the hydrochloric acid reaction were shown to be identical (infra-red spectrum, t.l.c.). This observation of a small quantity of a bicyclo-ketone in a ring expansion reaction which had obviously not gone to completion (note the quantity of unreacted starting material), reinforced the concept of a bicyclic intermediate. A further interesting feature of this reaction was that the presence of a substituent on C_3 had apparently promoted a facile lactonisation of the cycloheptene acid (54) expected

as the major product. Since failure to prepare (54) would render this approach to the sesquiterpene skeleton useless, an attempt to cleave the lactone (51) was made using sodium methoxide. Only unchanged lactone was recovered.

A modified ring expansion technique, developed later, afforded bicyclo-(5,3,0)-dec-1(7)-ene-3-carboxylic acid (54) in greater than 50% yield.

The investigation of the ring expansion reaction in a system with a terminal aldehyde group required the synthesis of the keto-aldehyde (55). This compound could not be prepared by base catalysed condensation of cyclopentanone and acrolein due to polysubstitution or by alkylation of the enamine of cyclopentanone with acrolein since the bicyclic compound (56) resulted [37]. Conversion of 2-ethoxycarbonyl-2-(2'-formylethyl)-cyclopentanone (57) by hydrolysis and decarboxylation to the keto-aldehyde (55) appeared to be the best possible approach.

The aldehyde-ester (57) was prepared by triethylamine catalysed condensation of 2-carbethoxycyclopentenone and acrolein at room temperature. A small quantity of the isomeric ring-closed alcohol (58) was also produced. It was removed by chromatography since the boiling points of the two compounds were rather too close for distillation. The bulk of the aldehydic material was not purified in this manner since the alcohol was expected to be hydrolysed to the corresponding acid during decarboxylation of the aldehyde - ester and could thus be readily removed at that stage.

Treatment of the aldehyde-ester (57) with methanolic potassium hydroxide produced a neutral fraction of considerable complexity (t.l.c.) which was not investigated. The acidic material which accounted for 50% of the recovery appeared to be one compound, which was eventually identified as (59) (see Part II). An attempt to hydrolyse the ester function with lithium iodide and pyridine [38], and the related diethylene glycol ketal (60) with

sodium methoxide also failed. Efforts to preferentially hydrolyse the aldehyde function [39], thus retaining the β-keto-ester system to facilitate decarbomylation were not successful.

An alternative approach was now necessary. In the expectation that the aldehyde-ester would undergo decarbethoxylation prior to cyclisation, in a similar manner to the diketo-ester (32), yielding the bicyclo-ketol (61), olefin (62) or cycloheptene acid (63), this compound was refluxed for 24 hours with concentrated hydrochloric acid and acetic acid. The product was an intractable black tar and a similar result was obtained after 4 hours reflux. Stirring at room temperature with these reagents resulted in a negligible yield of acidic material but a reasonable recovery of a pale yellow, neutral oil which consisted of 4 compounds (t.l.c.). Chromatography afforded pure samples of the two least polar compounds, the two other compounds being eluted as a mixture. This polar mixture was shown to consist of the epimeric forms of the ring-closed alcohol-ester (58) identical to the by-product formed during preparation of the aldehyde-ester. The other two products were identified as the epimeric acetates (64a) and (64b) by comparison with authentic samples prepared from the alcohols after separation (see Part II). A possible mechanistic scheme for the formation of these acetylated products is outlined in scheme (e)

(57) - - - > (64)

The failure of the bridged bicyclic compounds to cleave under mild conditions and the formation of intractable material on more vigorous treatment caused the abandonment of the ring-expansion procedure on the aldehyde-ester (57). However, as discussed in Part II, an alternative reaction sequence yielded cycloheptene acids from this material.

The almost total lack of success of the acid catalysed ring-expansion reaction in the aliphatic field made further investigation of its scope in the aromatic field desirable. In addition it had not been possible to study how the stability of the carbonium ion, generated by protonation of the

double bond of the bicyclo-intermediate, affected the reaction by conjugation of aliphatic and aromatic substituents. A suitable alternative was considered to be investigation of the effect of both electron-releasing and electron-withdrawing substituents on a benzene ring. To this end, it was decided to apply the ring-expansion procedure to dibenzones substituted in the 3' position with p-tolyl, p-bromophenyl, p-methoxyphenyl and p-nitrophenyl groups.

The readily available ketone, p-methylacetophenone was converted via the corresponding Mannich base hydrochloride (65) [40] to 3-dimethylamino-4'-methylpropiophenone. High temperature reaction of the β-aminoketone and cyclopentanone yielded a solid product which consisted of a mixture of the desired diketone (66) and the triketo-compound (67) or (68). Both compounds were isolated, the former in 76% yield by distillation and the high molecular weight material by recrystallisation of the reaction mixture from hot ether.

Since the n.m.r. spectrum of the triketone did not distinguish between the structures (67) and (68), it was subjected to hydrochloric acid-acetic acid reflux in the anticipation that cyclisation to (69), (70) or (72) would occur. Treatment with ethanolic potassium hydroxide was also expected to yield the spiro-compound, if the gem-disubstituted structure was correct, but both reactions failed to effect any change. This evidence, and mechanistic considerations concerning the mode of formation, discussed later (see p. 37), favoured the 2,5-substitution pattern of structure (68).

Treatment of the diketone (66) under the usual conditions afforded 82% of solid acidic material and a low recovery of a neutral fraction consisting of starting material and a lactone ($\nu_{C=O}$ 1760cm.$^{-1}$). The lactone (72) was purified with difficulty by crystallisation from ethanol or more readily by treatment of the mixture with sodium borohydride followed by chromatography. The γ-lactone structure was confirmed by the infra-red spectrum absorption of 1760cm.$^{-1}$ and the presence of a doublet at 5.23τ, attributed to the

CH_2 protons, in the n.m.r. spectrum. An attempt to prepare this compound by surfacing the acidic material obtained from the same reaction with dilute acid, yielded 2% of a neutral fraction shown by infra-red spectroscopy and t.l.c. to consist of lactone (72), diketone (66) and some acidic material. This result confirms the reversibility of the reaction found with the phenylcycloheptene analogue [4].

Recrystallisation of the slightly coloured acidic material, m.p. 117-129°, from ethanol was difficult and failed to decolourise it or narrow the melting point range. Benzene-petrol mixtures, on the other hand, afforded a colourless crystalline solid, m.p. 127-129°, although the recovery was poor (~ 15%). This material was now readily recrystallised from ethanol. This behaviour, typical of a mixture, caused investigation of the homogeneity of the product. Samples of the crude reaction product and the purified material were esterified with diazomethane for analysis by t.l.c. and g.l.c. Although the former technique showed only one spot for both samples, g.l.c. analysis on 3% F-60 at 150° showed two peaks, 45% of the material having a retention time of 6.8 mins. and 55% with a retention time of 7.5 mins. for the crude product and one peak with a retention time of 6.8 mins. for the sharp melting compound. It was assumed, at this stage, that the mixture of acids obtained consisted of 4-(p-tolyl)-cyclohept-3-ene carboxylic acid (73) and 4-(p-tolyl)-cyclohept-4-ene carboxylic acid, formed by isomerisation of the double bond about the phenyl substituent.

The formation of this mixture focused attention on the conflicting evidence about the position of the double bond obtained from previous examples. Whereas the acidic material obtained from the diphenyl diketone (2) was identified as having the Δ^4 double bond position by its n.m.r. spectrum, the phenyl diketone (19) was believed to yield the Δ^3 double bond acid [4]. This had been proved by oxidative cleavage as previously described. (see p.4).

To reinvestigate the possible formation of isomers in both of these reactions, esterified samples of the crude reaction products were analysed by g.l.c. on a number of columns. The diphenyl acidic material consistently gave only one important peak but the monophenyl product exhibited two

pentin on all columns . This proves that the "phenyl cycloheptene carboxylic acid" formed from (10) by previous workers [4] was in fact a mixture. The fact that this mixture yielded a homogeneous product on reduction [4] suggests that the acids had the same carbon skeleton and differed only in the position of the double bond, about the phenyl substituent. It is therefore presumed that cleavage and cyclisation of this mixture, in fact yielded both a succinic (75) and a glutaric anhydride (76) only the former being isolated by crystallisation [4]. The apparent formation of only one acid in the diphenyl series is not fully understood but can presumably be attributed either to inability to achieve a separation of the isomers by analytical g.l.c. or to a steric-chemical effect of the phenyl substituent at C_2 which prohibits formation of the Δ^3 isomer (5). It is interesting to note that an excellent recovery of acidic material is obtained by recrystallisation from benzene-petrol mixtures in contrast to the results of the p-tolyl substituted and subsequent cases where a mixture has been proved. This suggests that only one major acid i.e. (6) is formed.

With the successful isolation of one of the p-tolylcycloheptene acids, efforts were directed at obtaining the other isomer by fractional crystallisation. Failure of this technique led to attempted separation of the corresponding esters by distillation and preparative scale g.l.c. without success.

The position of the double bond in the pure acid remained to be determined. This could not be established by n.m.r. spectroscopy, since an examination of models showed the expected splitting pattern of the olefinic proton in both isomers to be similar. The simplest solution to this problem appeared to lie in conversion of the mixture of acids to 1-methoxycarbonyl-3-oxo-4-(p-tolyl)-cycloheptane (77) and 1-methoxycarbonyl-4-(p-tolyl)-5-oxocyclo-heptane (78), the former being identifiable by comparison with a sample prepared from the lactone (72). The keto-ester obtained from the pure acid

could then be recognised and the position of the double bond in the starting material assigned accordingly.

The method proposed for preparation of the keto-esters involved hydroboration [41] of the acidic mixture followed by oxidation. In an effort to prevent reduction of the carbonyl function by diborane [42] generated during hydroboration, the mixture of acids was esterified but despite this precaution, some reduction of the ester function took place. The simpler process of using excess sodium borohydride and boron trifluoride etherate to achieve hydroboration and reduction of the ester group gave a good yield of a mixture of diols, which was treated with Jones reagent [43] affording a recovery of 70% acidic and 20% neutral material.

Treatment of the acidic material with diazomethane yielded a mixture of esters which was separated by chromatography, affording initially a liquid keto-ester, which showed absorption at 1745cm.$^{-1}$(ester) and 1712cm.$^{-1}$ (ketone) in the infra-red spectrum and the C_4 proton as a multiplet at 6.45 τ, partially concealed by the methyl ester protons, in the n.m.r. spectrum. Further elution yielded a solid keto-ester ($\nu_{c.c}$ 1715cm.$^{-1}$ and 1712cm.$^{-1}$) which showed a similar multiplet at 6.45 τ for the C_4 proton in the n.m.r. spectrum.

A further crystalline compound obtained from chromatography of the mixture showed absorption in the infra-red spectrum at 1744cm.$^{-1}$ (ester) and 1695cm.$^{-1}$ (aromatic ketone). The possible structures (79) or (80) were suggested for this material by the n.m.r. spectrum, which showed an AB quartet for the aromatic protons at 2.14 τ and 2.77 τ similar to that obtained from p-methylacetophenone, a six-proton singlet at 6.34 τ for the two carbomethoxyl groups and a triplet at 7.1 τ attributed to the methylene protons adjacent to the aromatic ketone. It appears that this material was formed by the Markownikoff addition of the elements of water to the unsaturated ester mixture during hydroboration [41], to yield the diol (81), which during the prolonged oxidation, dehydrated to reform the unsaturated material followed by oxidative cleavage of the double bond. In order to

prove that this product arose from cleavage of the ring, a sample of the mixture of esters (82) and (83) was treated with Jones reagent under identical conditions. Esterification (diazomethane), furnished a crystalline solid with identical infra-red spectrum, t.l.c. and g.l.c. retention times to the above. Although the material from both reactions appeared homogeneous it is difficult to understand why only one keto-diester should be formed, and no attempt was made to identify it as (79) or (80), or a mixture of both.

The principal products from the hydroboration-oxidation sequence were now examined to establish which of the keto-esters had the β-ketone function. A sample of the lactone (72) was cleaved with lithium aluminium hydride in refluxing tetrahydrofuran and the resultant diol oxidised with Jones reagent to yield acidic material which was esterified with diazomethane. Comparison of the infra-red spectrum of this sample of 1-methoxycarbonyl-3-oxo-4-(p-tolyl)-cycloheptane (77) with the spectra of the keto-esters obtained above, showed that it was identical to the liquid keto-ester and this was confirmed by t.l.c. and g.l.c.

Treatment of the pure acid obtained by crystallisation from the mixture of (73) and (74), under the conditions of hydroboration and oxidation used above, yielded acidic material which was esterified (diazomethane). Chromatography afforded initially an unidentified ester, then 1-methoxy-carbonyl-3-oxo-4-(p-tolyl)-cycloheptane (77) and the acyclic keto-diester (79) or (80) obtained previously. T.l.c. and g.l.c. confirmed the absence of the solid keto-ester and thus the structure of the pure acid was established as 4-(p-tolyl)-cyclohept-3-one carboxylic acid (73).

The solid keto-ester has, presumably the structure (78), but in the absence of reference compounds this could not be established rigorously. That the mixture of aryl cycloheptene carboxylic acids did in fact include a Δ^4 isomer, was established later.

If the ring expansion reaction did in fact involve a bicyclic intermediate, it was anticipated that treatment of the bicyclo-ketone (84) with hydrochloric acid-acetic acid would yield the same mixture of acids. To verify this, 2-(p-tolyl)-bicyclo-(3,2,1)-oct-2-en-6-one (84) was prepared from the diketone (66) using p-toluene sulphonic acid in benzene. The structure of this compound, obtained in 81% yield, was confirmed by the infra-red spectrum ($\nu_{C=O}$ 1757cm.$^{-1}$) and the n.m.r. spectrum which showed the olefinic proton as a triplet at 4.21 τ and a complex three-proton band at 7.1 τ - 7.4 τ attributed to the protons on C_1 and C_4. This compound was unstable and decomposed within a week to a yellow gum, even when stored under nitrogen. Similar decomposition occurred with all the bicyclo-(3,2,1)-octenone compounds of this type prepared, with the exception of the diphenyl system which remained unchanged indefinitely.

The ring expansion reaction, as expected, gave the lactone (72), a trace of the diketone precursor (66) and a mixture of the acids, (73) and (74) from which the former was isolated in 15% yield by recrystallisation from benzene-petrol mixtures.

To investigate the application of the ring expansion reaction to the second diketone of the series, 2-(3'-p-bromophenyl-3'-oxopropyl)-cyclopentanone (85), 3-dimethylamino-4'-bromopropiophenone hydrochloride (86) was prepared [44], and basified to yield the corresponding β-aminoketone. This was reacted in the usual manner, with cyclopentanone affording the desired diketone (85) in 62.5% yield. Hydrochloric acid-acetic acid treatment of this compound furnished a small neutral fraction, shown by t.l.c. to consist of the diketone together with a lactone ($\nu_{C=O}$ 1780cm.$^{-1}$) which was not isolated. An 80% recovery of acidic material was obtained and g.l.c. analysis of an esterified sample showed it contained two compounds, 45% with a retention time of 16.25 mins. and 55% with retention time 16.0 mins. on 1%SE-60 at 150°. By analogy with the p-tolylcycloheptene acids, the former was assigned the Δ^3 structure (87) and the latter the Δ^4 isomer (88).

Recrystallisation using benzene-petrol mixtures afforded a pure sample of the material with the shorter retention time and this was therefore regarded as pure 4-(p-bromophenyl)-cyclohept-3-ene carboxylic acid (87).

Application of the acid-catalysed bridge-fission reaction to the bicyclo-ketone (89), prepared from the diketone in the usual manner, furnished a similar mixture of the isomeric acids (87) and (88).

In order to investigate the effect of an electron releasing substituent, the p-methoxyacetophenone Mannich base hydrochloride (90) prepared from p-methoxyacetophenone using the general method described by Morrell [45], was treated with base to liberate 3-dimethylamino-4'-methoxypropiophenone. This compound, reacted with excess cyclopentenone at 140°, yielded a solid mixture of two compounds, from which 2-(3'-p-methoxyphenyl-3'-oxopropyl)-cyclopentenone (91) was isolated in 76% yield by distillation. Application of the standard conditions of the ring expansion reaction to this material afforded a 6% recovery of neutral and 88% of solid acidic material. The former consisted of starting material and a compound which exhibited absorption at 1780cm.$^{-1}$ in the infra-red spectrum to which the lactone structure (92) was assigned although it was not isolated. Attempts to recrystallise the acidic fraction from ethanol did not result in purification but, as with the acidic compounds obtained from the p-tolyl-diketone (66), benzene-petrol mixtures yielded a colourless compound which was readily recrystallised from ethanol. Samples of both the crude and purified material were esterified with diazomethane and analysed by g.l.c. The crude reaction product showed the existence of a mixture of two compounds, 45% with retention time of 14.5 mins. and 55% with retention time of 15.75 mins. on 3%SE-60 at 150°. On the basis of the results from the related p-tolylcyclo-heptene acids (73) and (74), the former material was assigned the structure of 4-(p-methoxyphenyl)-cyclohept-3-ene carboxylic acid (93) and the latter, 4-(p-methoxyphenyl)-cyclohept-4-ene carboxylic acid (94). The purified acid, which showed only one peak with a retention time of 15.75 mins., was thus identified as the Δ^4 isomer (94) since it was not foreseeable

that change of a group on the para position of a phenyl substituent would affect the relative retention times of double bond isomers on G.l.c.

With the satisfactory completion of the series of electron-releasing aromatic substituted diketones, the preparation of 2-(3'-p-nitrophenyl-3'-oxopropyl)-cyclopentanone (95) was undertaken. 3-Dimethylamino-4'-nitropropiophenone hydrochloride (96) was prepared using the method of Maxwell [45] and basification with 4N sodium hydroxide and ether extraction furnished a good recovery of a red oil assumed to be 3-dimethylamino-4'-nitropropiophenone since its infra-red spectrum showed the three bands at 2840cm.$^{-1}$, 2800cm.$^{-1}$ and 2750cm.$^{-1}$ characteristic of the dimethylamino tertiary amine group [46]. High temperature reaction of this β-amino-ketone and cyclopentanone yielded an oil which showed tendencies to crystallise, but efforts to encourage this were not successful. Chromatography afforded a red oil which eventually furnished an amorphous solid on trituration with petrol. Recrystallisation from ethyl acetate gave a low yield of a solid which showed absorption at 1745cm.$^{-1}$ (cyclopentanone carbonyl) and 1690cm.$^{-1}$ (aromatic ketone) in the infra-red spectrum. However, the intensity of the aromatic ketone absorption was considerably greater than that of the ring ketone and on this basis the mixture was considered to be rich in the di-condensation product (99) or (100), analogous to the impurities isolated from earlier reactions of this type. Subsequent efforts to repeat this preparation were largely unsuccessful, since satisfactory liberation of the β-aminoketone could not be achieved, but one condensation with cyclopentanone gave a reasonable recovery of crude product which was distilled in an effort to isolate the desired diketone. The distillate, however, was a black oil which had obviously undergone decomposition.

The inability to obtain uniformly acceptable yields of the free Mannich base was attributed to the instability of this material in basic solution [47], the normal tendency of this type of compound to decompose to the corresponding

vinyl ketone being enhanced by the electron-withdrawing influence of the nitro substituent. The use of an alternative approach to the diketone (95) involving dimethylaminomethylcyclopentanone and a three molar excess of p-nitro-acetophenone yielded a black gum which partially crystallised on standing. Attempts to crystallise the products from the excess ketone however, yielded only the latter and distillation was impracticable due to the previously observed decomposition of the diketone.

In an effort to obtain some information concerning the effect of the nitro substituent on the ring expansion reaction, the solid material isolated from the first attempt at preparation of the diketone (95) was subjected to 24 hrs. reflux with concentrated hydrochloric acid and acetic acid. A 5% recovery of acidic material, heavily contaminated by acetic acid, was obtained but this was not investigated because of the negligible amount available for purification of what, experience had shown, was almost certainly a mixture of isomers, (97) and (98).

The neutral fraction from the reaction consisted of both ether soluble and insoluble material. The infra-red spectrum of the former, which was also recovered in small quantities, showed absorption of equal intensity for both the ring ketone (1740cm.$^{-1}$) and the aromatic carbonyl (1690cm.$^{-1}$) and although t.l.c. showed two spots this was considered to be largely unreacted diketone (95). The ether insoluble compound had similar R_f on t.l.c. to the more polar material present in the ether soluble mixture, but showed increased intensity of the aromatic carbonyl band at 1690cm.$^{-1}$ relative to the ring ketone absorption at 1740cm.$^{-1}$ in the infra-red spectrum and consequently was regarded as unreacted triketone (99) or (100).

Interpretation of this reaction was difficult, but assuming that the triketone did not react, then it appears that conversion of the diketone (95) to cycloheptene acids was not as facile as that found in previous cases, since a larger quantity of unreacted diketone than acidic material was recovered and no lactonic carbonyl absorption was detected in the infra-red spectrum.

Assuming that the mixture of isomeric cycloheptene acids (8) and (9) arises by protonation of the double bond of the expected product, the Δ^4 isomer (8), to yield a carbonium ion of the type depicted by (101) as shown in scheme (a), it seemed likely that the introduction of a methyl substituent at C_3 would result predominantly in formation of the tetra-substituted double bond compound (102). Similarly it was expected that the diketone (103) would yield mainly 4-phenyl-5-methylcyclohept-4-ene carboxylic acid (104), as a result of the greater hyperconjugative stabilisation of the double bond [46]. These premises were now tested.

2-Methyl-3-dimethylaminopropiophenone hydrochloride (105) [44] was converted to the corresponding free base and reacted with cyclopentanone to yield an oil which was distilled into two fractions. The higher boiling fraction showed two spots, attributed to the diastereoisomeric forms of the diketone (106). This was confirmed by the n.m.r. spectrum which showed two overlapping doublets centred at 8.85 τ and 8.87 τ for the methyl group and a broad multiplet at 6.2 τ for the C_2, proton. Reaction with hydrochloric acid-acetic acid mixtures for 24 hrs. failed to yield any acidic material and investigation of the neutral material, by infra-red spectroscopy and t.l.c., showed that it consisted to a considerable extent of unreacted starting material. Prolonged reflux (8 days) afforded no acidic material and the neutral fraction was shown by t.l.c. to consist of three compounds including some starting material. The infra-red spectrum of this oil showed intense absorption at 1730cm.$^{-1}$ with a strong shoulder at 1750cm.$^{-1}$ and weak absorption at 1690cm.$^{-1}$. Since the major product of the reaction appeared to be lactonic, the reaction product was treated with sodium borohydride to facilitate chromatographic separation of this material from the diketone. However, the relatively non-polar third product also underwent reduction, to yield a compound of approximately similar R_f on t.l.c. to the lactone. Thus the following, somewhat lengthy, separation procedure was required. Chromatography of the crude reaction mixture afforded:-

(a) an oil which analysed for $C_{15}H_{16}O$ and showed absorption at 1755cm.$^{-1}$ in the infra-red spectrum. The bridged bicyclic structure (107),

postulated on the basis of this information, was confirmed by the n.m.r. spectrum which showed no olefinic proton, but instead a vinylic methyl singlet at 8.42 τ, a one-proton multiplet at 7.16 τ for the C_4 proton and a two-proton multiplet at 7.43 τ for the allylic protons on C_4.

(b) mixtures of the starting material and lactone which were separated by reduction with sodium borohydride and rechromatography to yield pure lactone (208) which showed absorption at 1770cm.$^{-1}$ in the infrared spectrum. The position of attachment of the lactone was shown to be at C_3 by the downfield shift of the methyl singlet to 8.82 τ and the absence of peaks at 5-6 τ in the n.m.r. spectrum.

The results of this reaction closely paralleled those obtained from (2,2'-dicyclopentanonyl)-methane (48) in that a small quantity of bridged bicyclic ketone was isolated and the major product of the reaction was lactonic and not acidic in nature. Further similarity was shown by the fact that both reactions appeared to require longer refluxes than usual.

The formation of a γ-lactone rather than the expected Δ^3 cycloheptene acid is not surprising in view of the tendency noted in the cycloheptene acids substituted only in the 4 position, to undergo lactonisation at C_3 by protonation of the double bond in the less favoured direction. In the tetra-substituted examples, formation of a carbonium ion at C_3 will occur more readily and hence lactone formation will be easier. It is also possible that the slower formation of the seven-membered ring product and isolation of the bicyclo-intermediate may be attributed to increased protonation of the double bond in the latter, in the direction contrary to that required for bridge fission.

The second case to be investigated was that in which the phenylcycloheptene acid was substituted in the 5-position and this required preparation of the 2,5-disubstituted cyclopentanone (203). The synthesis of the analogous diketone (41) by reaction of 2-methylcyclopentanone and diethylaminobuten-3-

one suggested that 3-dimethylaminopropiophenone, obtained from the corresponding hydrochloride (109) [45], and 2-methylcyclopentanone would yield the desired compound (103). Reflux of these compounds at 140° did, in fact, yield 76% of a solid diketone ($\nu_{C=O}$ 1759cm.$^{-1}$ and 1692cm.$^{-1}$), shown to have the desired substitution pattern by the presence of a doublet at 8.93 τ for the methyl protons in the n.m.r. spectrum. The formation of a 2,5-disubstituted cyclopentanone in this, and in the previous case, requires special comment.

It has long been known that electrophilic olefins, such as acrylonitrile or methyl vinyl ketone, condense with unsymmetrically substituted ketones under basic catalysis on the more substituted α-carbon atom [3]. Similarly, Mannich base methiodides were believed to decompose in the presence of strong bases to yield the corresponding vinyl ketone which condensed in Michael fashion to yield gem-disubstituted ketones [3,49]. Although this substitution pattern does indeed result, recent work [50] has shown that replacement of a vinyl ketone with the corresponding methiodide may produce different products, indicating that the mechanism is not necessarily identical in both cases. The formation of the diketones (41) and (103) as the products isolated from high temperature reaction of a Mannich base and 2-methylcyclopentanone, provided conclusive proof that this reaction does not take place by the accepted Michael reaction mechanism. While the assumption that the Mannich bases decompose thermally to yield free amine and the corresponding vinyl ketone, may be correct, the fact that condensation occurs on the least substituted α-carbon atom is reminiscent of enamine [2] and Schiff's base alkylation [51], and suggests that some such intermediate is involved. The isolation of an enamine in an earlier case (3), lends weight to this possibility. It was initially considered that the decomposition of the Mannich base occurred, the liberated secondary base condensed with the ketone to yield the enamine and alkylation with the vinyl ketone resulted in the product as shown in scheme (f).

This mechanism, however, failed to account for certain observations. As the reaction mixture was heated to reflux, evolution of dimethylamine commenced at 80° and continued throughout the reaction. It would therefore appear that as the Mannich base decomposed, considerable quantities of dimethylamine would be evolved before formation of the enamine occurred and the excellent yields obtained would not be expected if this was the case. In addition, distillation of the Mannich base derived from (109), under reduced pressure at temperatures considerably in excess of 80°, furnished mixtures of the base and phenyl vinyl ketone, while 3-diethylamino-butanone is stable to distillation, b.p. 76°/12mm. These facts suggest that these Mannich bases are not sufficiently unstable to decompose readily at 80°.

The alternative mechanism outlined in scheme (g) appears a more satisfactory postulate but further investigation is required to supply proof. It is envisaged that attack of the Mannich base on the carbonyl group occurs initially and this undergoes decomposition to yield the enamine and a vinyl ketone which condense in the normal manner. A rather similar decomposition of the enamine (110) and formation of (111) by refluxing in ethylene glycol has been reported [52].

Hydrolysis of the resultant enamine is thought to be effected by the mole of water formed earlier in the reaction.

The isolation of the uncyclised diketones (29) and (41) from this reaction in contrast to the enamine (112) of 5,6,7,8-tetrahydroindan-5-one obtained by treatment of the pyrrolidine enamine of cyclopentanone with methyl vinyl ketone [2], may be explained by consideration of a mechanism postulated recently [53]. This suggested that cyclisation of the initially formed enamine takes place by transfer of the base from the ring ketone to the side chain carbonyl as shown in scheme (h), (31) ---→ (113). If in this process the base becomes detached, then low boiling bases such as diethylamine and

dimethylamine may reasonably be assumed to evolve before formation of the side chain enamine takes place.

G.l.c. analysis of the reaction products of 2-methylcyclopentenone with diethylaminobutan-3-one and 3-dimethylaminopropiophenone showed that a small quantity of the gem-disubstituted isomers were formed in both cases.

The formation of this substitution pattern with an unsymmetrically substituted ketone is regarded as convincing evidence that the triketones obtained from this type of reaction have similar structures, e.g. (21) and (68).

Ring expansion conditions applied to the diketone (103), afforded a large recovery of starting material, uncontaminated by lactone or bicyclo-ketone and 10% of an acidic fraction. G.l.c. analysis of an esterified sample of this showed a purity of greater than 90%, the tetra-substituted double bond structure (104) being confirmed by the n.m.r. spectrum which showed no olefinic proton but a vinylic methyl signal at 8.33 τ. The low yield obtained obviously resulted from the increased difficulty of effecting condensation of the diketone in the presence of the methyl substituent.

These experiments demonstrate that the double bond in the aryl cyclo-heptene carboxylic acids is mobile, and can be trapped in either position by a suitable substituent.

A further position where a substituent might exert some influence on the products or effectiveness of the ring expansion was C_1. Investigation of the reaction on a diketone such as 2-methyl-2-(3'-oxo-3'-phenylpropyl)-cyclopentanone (114) was also of interest in testing the rather unlikely mechanism [scheme(c)] of bridge-fission involving a ketene intermediate rather than nucleophilic attack by water. As mentioned earlier such intermediates have been postulated in other circumstances [7], although

they were later repudiated [6].

Preparation of this gem-disubstituted cyclopentanone (114) was attempted initially by treatment of 2-methylcyclopentanone and 3-dimethylamino-propiophenone methiodide with sodamide [22], but the only product isolated from the black gum obtained, was a small quantity of a compound subsequently identified as the lactone (115), by comparison with a sample prepared in a more normal manner. Conversion of 3-dimethylaminopropiophenone hydrochloride (109) to phenyl vinyl ketone [54] by steam distillation and reaction with 2-methylcyclopentanone, using ethanolic potassium hydroxide as catalyst [34], afforded an acceptable yield of an oil which solidified after distillation. This low melting diketone (114) exhibited a singlet at 8.98 τ for the methyl protons in the n.m.r. spectrum. Hydrochloric acid-acetic acid treatment of the diketone afforded 64% recovery of neutral and 27% acidic material. G.l.c. analysis of esterified material showed that it consisted of two products, assumed to be 1-methyl-4-phenylcycloheyt-3-one carboxylic acid (116) and 1-methyl-4-phenylcyclohept-4-one carboxylic acid (117). Neither acid was obtained in a pure state since the mixture resisted efforts at crystallisation. T.l.c. and g.l.c. showed that the neutral material also consisted of a mixture to two compounds neither corresponding to starting material. Recrystallisation of the solid mixture from ethanol yielded the major component identified as the lactone (115) by its infra-red spectrum ($\nu_{C=O}$ 1777cm.$^{-1}$) and n.m.r spectrum which showed the methyl protons as a singlet at 8.74 τ and the C_3 proton as a cuisplit doublet at 5.18 τ. The benzylic proton at C_4 was visible as a multiplet at 7.25 τ. This compound was shown by t.l.c., infra-red spectroscopy and n.m.r. spectroscopy to be identical to the crystalline product obtained from the attempted preparation of the diketone (114) using Robinson's method.[22]

The comparative success of the ring expansion procedure in this case confirmed that the bridge-fission of the bicyclo-intermediate did not

proceed by a ketene mechanism. The formation of a considerable quantity of lactone results from replacement of the hydrogen on C_4 with the bulkier methyl group which forces the carboxyl function into the axial position required to achieve lactonisation.

The successful preparation and characterisation of the lactone(108) and the acid(104) permitted a rigorous proof of the positions of the double bonds in the phenyl cycloheptene acid mixture(27) and (118), obtained by a previous worker[4]. The scheme envisaged conversion of the acid mixture to the keto-esters(119) and (120), separation and treatment of each with methyl magnesium iodide. Decomposition of the Grignard complex under acidic conditions was expected to yield the lactone(108) from the Δ^3 isomer and the unsaturated acid(104) from the Δ^4 material.

Treatment of an esterified mixture of the acids(27) and (118) in diglyme with an excess of sodium borohydride and boron trifluoride etherate, afforded a mixture of diols which was subjected to prolonged oxidation with Jones reagent. The rather poor yield of neutral material obtained, was esterified with diazomethane and chromatographed twice to yield two keto-esters - a liquid and a solid. Both isomers exhibited the C_4 proton at 6.4τconcealed by the carbomethoxyl protons. Cleavage of the lactone(121)[4] with lithium aluminium hydride, oxidation of the resultant diol and esterification of the resulting keto-acid, afforded 1-methoxycarbonyl-3-oxo-4-phenylcycloheptane(119). The liquid had identical infra-red spectrum and g.l.c. retention times on a number of columns to the liquid keto-ester obtained above. The solid keto-ester was therefore assigned the 5-keto structure(120).

The rather poor yields and tedious chromatography required to separate these compounds from impurities made an alternative approach desirable. Epoxidation of the double bond and acid catalysed rearrangement offered

an alternative route, to the keto-esters.

Accordingly, the mixture of esters (122) and (123) was stirred for 1.5 hrs. with m-chloroperbenzoic acid in chloroform to yield an oil which exhibited a complex pattern on t.l.c.

Attempts to rearrange this mixture to the keto-esters(119) and (120) using boron trifluoride etherate in benzene, even at prolonged reflux temperatures, failed to effect any change.

Treatment of the mixture with concentrated sulphuric acid at 0° for 1.75 hrs. afforded a recovery of 27% of an oil which showed no hydroxyl absorption and twin carbonyl absorption at 1735cm.$^{-1}$ and 1710cm.$^{-1}$. G.l.c. analysis of the product showed that complete reaction had taken place, and chromatography afforded the keto-ester (119) and a small amount of the isomeric compound(120). The necessity of using sulphuric acid to rearrange the epoxides resulted in the yields of keto-esters obtained by this route showing little improvement over the hydroboration procedure, and the inexplicably small quantity of the 5-ketone compound(120) formed, was a definite disadvantage. However, sufficient material was obtained to carry out the Grignard reaction. Reaction of the keto-ester(119) with methylmagnesium iodide by inverse addition afforded a solid complex which was decomposed with dilute hydrochloric acid and refluxed overnight to give neutral and acidic fractions. The neutral material was shown to consist almost entirely of the lactone(108) identical in all respects with a sample prepared previously by another route.

The acidic material was esterified with diazomethane and g.l.c. analysis proved that it was unreacted keto-ester which had undergone hydrolysis in the acidic conditions.

Similar treatment of the isomer(120) also yielded acidic and neutral fractions the former being almost pure 4-phenyl-5-methylcycloheptan-1-one

carboxylic acid(104). Investigation of the rather large neutral product showed that it consisted mainly of two polar compounds which were thought to result from reaction of the ester functions with excess methylmagnesium iodide.

The isolation of the lactone and acid provided proof that the products from the ring-expansion reaction applied to the diketone(10) were, in fact, 4-phenylcyclohept-3-ene carboxylic acid(27) and 4-phenylcyclohept-4-ene carboxylic acid(118), and, by analogy, similar structures could be assigned to the products obtained from related diketones.

With the proof of the positions of the double bond in the products from the ring-expansion technique and the investigation of the effect of substituents in the cycloheptene ring on these products successfully completed, it can be stated that the reaction of the diketone(10) with strong acid passed through a bicyclic intermediate(15) to a mixture of the acids(27) and (118). Bridge fission is due to strain on the bicycle and presumably occurs by protonation of the double bond, and nucleophilic attack by water as outlined in scheme (b); double bond migration occurs as shown scheme (a). The alternative ketene mechanism shown in scheme (c), has been eliminated. The reaction fails in the absence of an aromatic substituent, except in one special case (48) - - → (51). As a practical method its value is diminished by double bond migration.

It was now of interest to examine the possibility of inducing bridge-fission in a bicyclo-(3,2,1)-octane to yield cycloheptene systems with functional groups other than carboxyl, or under conditions which would not isomerise the initially formed cyclohept-4-ene compound.

It was anticipated that in an acid medium the alcohol(124) could yield the cycloheptene aldehydes(125) and (126). In particular the anti-alcohol(124b) appeared, from an examination of models, to be suitably

aligned for facile bridge cleavage.

Reduction of the bicyclo-ketone(84), using sodium borohydride in methanol afforded a viscous oil which was transparent in the carbonyl region of the infra-red spectrum. Although efforts to crystallise this material were unsuccessful, t.l.c. and g.l.c. analysis appeared to indicate that the product was homogeneous. To verify that the product was not, in fact, a mixture of epimers, the ketone was also reduced using sodium borohydride in pyridine, a process reported [55,56] to give both epimers when applied to a closely related system. The oil obtained from the reduction also showed no carbonyl absorption in the infra-red spectrum, but contained two compounds, t.l.c. and g.l.c. indicating that the less polar of the components corresponded to that obtained from the initial reaction. The other compound was assumed, at this stage, to be the epimer.

Study of the infra-red spectrum of the product of reduction in methanol, showed intramolecular hydrogen bonding between the hydroxyl group and the double bond ($\Delta\nu$ = 39cm.$^{-1}$)[57], proving the relationship of these functions to be as shown in structure(124a).

An examination of models of both epimers showed that with the syn-epimer (124a), coupling of the bridgehead protons at C_1 and C_5 with the C_8 proton would be expected to produce a triplet for the latter, whereas in the anti-epimer (124b) no splitting would result and the C_8 proton would appear as a singlet. This conclusion has since been supported by n.m.r. studies on variously-substituted dibenzobicyclo-(3,2,1)-octadienes[58]. The identification of the pure alcohol as syn-2-(p-tolyl)-bicyclo-(3,2,1)-oct-2-en-8-ol (124a) was confirmed by the existence of a triplet at 5.93 τ for the C_8 proton in the n.m.r. spectrum.

Reflux of the alcohol(124a) with hydrochloric acid-acetic acid produced an oil which exhibited hydroxyl absorption and a carbonyl peak at 1730cm.$^{-1}$ in

the infra-red spectrum. T.l.c. showed three spots, a compound with large R_f and two others with similar R_f values to the syn and anti-epimers of the alcohol. Chromatography afforded the non-polar material, assumed to be a mixture of the aldehydes(125) and (126), but this was quickly disproved by analysis which suggested the formula $C_{17}H_{20}O_2$ and by the n.m.r. spectrum which showed a triplet at 4.36 τ for the olefinic proton, a one-proton singlet at 4.97 τ and a three-proton singlet at 8.03 τ. The last signal was typical of the methyl group of an acetate function and the lack of splitting of the peak at 4.97 τ suggested that the syn-alcohol had in fact undergone acetylation with inversion of configuration to yield the anti-acetate(127b) as the major product. G.l.c. analysis of the crude product from this reaction showed a mixture of four compounds, consisting of 13% of the syn-acetate(127a), 68% of the anti-acetate(127b) 4% of the syn-alcohol and 15% of the anti-alcohol. The structure of the syn-acetate was confirmed by acetylation of the syn-alcohol with acetic anhydride and pyridine, the product showing a triplet at 5.07 τ for the C_8 proton, and that of the anti-acetate (127b) by saponification to yield a crystalline alcohol with identical R_f on g.l.c. to that obtained as a minor product from reduction of the ketone(84) in pyridine. The n.m.r. spectrum of this alcohol showed the expected singlet at 5.88 τ for the C_8 proton and no intramolecular hydrogen bonding in the infra-red spectrum, confirming it to be anti-2-(p-tolyl)-bicyclo-(3,2,1)-oct-2-en-8-ol (124b).

Proof that the bicyclo-(3,2,1)-octane skeleton of the alcohols(124a) and (124b) had not undergone rearrangement was obtained by reaction of each with Jones reagent to reform the parent ketone(84).

Since it was still felt that the alignment of the anti-alcohol(124b) was favourable to acid catalysed bridge-fission, a satisfactory method of obtaining this compound was sought. The sodium borohydride/pyridine reduction of the ketone afforded only 25-30% of the anti-alcohol and 70-75% of the syn-epimer and separation was not feasible. Similar difficult-

ion existed with the hydrochloric acid treatment of the syn-alcohol in acetic acid where approximately 15% of the product consisted of the desired compound, but saponification of the crude reaction mixture would raise this to ~80%. However, the observation that this percentage of the product had the desired C_8 configuration, suggested that replacement of acetic acid with a solvent incapable of being incorporated in the product, i.e. not a potential nucleophile, would result in a satisfactory yield of the anti-alcohol(124b).

Treatment of the syn-alcohol(124a) with concentrated hydrochloric acid using dioxan as solvent afforded a mixture of the starting material and the anti-alcohol(124b). Recrystallisation of the solid product from acetone afforded 74% of the latter.

Application of the hydrochloric acid-acetic acid reaction to the anti-alcohol (124b), however, also failed to yield any bridge-cleaved products, a mixture of the epimeric acetates and alcohols resulting. G.l.c. analysis showed that the product distribution was, in fact, similar to that obtained from the syn-alcohol. Use of dioxan as solvent afforded a recovery of ~80% of the starting material and 20% of the syn-epimer.

The failure of both epimeric alcohols to undergo bridge-fission in acidic solution may be attributed to protonation of the hydroxyl function in preference to the double bond. The formation of the inverted products from the syn-alcohol(124a) suggests an Sn2 displacement mechanism, although such a process should be sterically difficult. On the other hand, a solvolysis study reported on the epimeric tosylates(128)[56] showed the formation of large amounts of rearranged products, arising from the formation of a carbonium ion at C_8. The absence of such products from (124) was shown by g.l.c. analysis of the crude reaction mixtures in the presence of n-pentadecane. It was expected that any unsaturated hydrocarbon with a C_{15} skeleton would have an R_t between that of n-pentadecane

and the acetates and alcohols. Since no rearrangement had occurred this was considered to rule out the possibility of formation of a carbonium ion at C_8, unless it is attacked by a nucleophile faster than it can undergo rearrangement. If this is so, the fact that the product from the syn-epimer (124a) has largely undergone inversion of configuration reflects the ease of approach of an incoming reagent over the five-membered ring [56], also demonstrated by the almost total formation of the syn-alcohol (124a) on reduction of the ketone (84).

The introduction of other groups at the C_8 position by changing the solvent was investigated by treating the syn-alcohol (124a) with hydrogen chloride gas in methanol. Two non-polar products resulted, which were transparent in the hydroxyl and carbonyl regions of the infra-red spectrum but which showed absorption at 2834cm.$^{-1}$, 2824cm.$^{-1}$ and 1105cm.$^{-1}$ (methoxyl)[59]. The n.m.r. spectrum of the main product showed a three-proton singlet at 6.70 τ and a one-proton singlet at 6.36 τ which proved that this was the expected anti-methyl ether (129b). The other component, although poorly resolved on g.l.c. was identified as the epimeric syn-methyl ether (129a) when it was fortuitously obtained as the major product from the syn-alcohol on treatment with p-toluene sulphonic acid in methanol. Chromatography and distillation separated this product from the anti-epimer and the epimeric alcohols, and its structure was confirmed by a triplet at 6.30 τ for the C_8 proton in the n.m.r. spectrum. An interesting observation was the decomposition of both methyl ethers on standing in a moist atmosphere to yield material which exhibited complex carbonyl absorption in the infra-red spectrum.

The possibility that the use of p-toluene sulphonic acid would yield a similar predominance of retention of configuration with other solvents was disproved when the syn-alcohol (124a), refluxed in acetic acid, afforded a similar product distribution to that obtained from concentrated hydrochloric acid.

Investigation of the reactions of the bridged bicyclic ketone (84), under

non-acidic conditions, was initiated by refluxing it with water, in view of the decomposition of this compound on standing. Treatment with water and water-dioxan mixtures, however, failed to produce any change, as did slow distillation. Reflux of the ketone in dioxan with 4% sodium hydroxide produced a mixture of solid and liquid material shown by t.l.c. to consist of starting material and a number of other inidentified products.

Refluxing the ketone (84) with methanolic sodium methoxide or potassium hydroxide yielded similar product mixtures containing no acidic material. The infra-red spectrum of the mixture of solid and liquid produced, was transparent in the hydroxyl region but showed a carbonyl peak at 1750cm.$^{-1}$ and intense absorption at 1120cm.$^{-1}$ and 1075cm.$^{-1}$. T.l.c. showed starting material and an unidentified product. The mixture was stable to basic hydrolysis conditions but reduction with sodium borohydride, to facilitate chromatographic separation, produced an oil transparent in the carbonyl region, which contained the unidentified product unchanged. Isolation of this compound confirmed the absence of hydroxyl and carbonyl absorption in the infra-red spectrum which showed a peak at 2830cm.$^{-1}$ (methoxyl) [59] and intense absorption at 1115cm.$^{-1}$ and 1068cm.$^{-1}$. The n.m.r. spectrum showed the olefinic proton as a triplet at 4.27 τ and the presence of two singlets at 6.85 τ and 6.78 τ attributed to two methoxyl groups in different environments. This evidence suggested that the product was the methyl ketal (130), and the structural assignment was confirmed by preparation of a sample under more normal acidic conditions. The formation of a ketal under basic conditions is unprecedented and defies rationalisation.

During the acid catalysed preparation of the ketal (130), g.l.c. analysis of the product showed the presence of the cycloheptene ester mixture (82) and (83). Hydrolysis of the esters afforded a sample of the ketal (130) identical in all respects with the product from the potassium hydroxide/methanol reaction. The structure (130) was further confirmed by reconversion to the ketone (84) by transketalisation using a catalytic quantity of p-toluene sulphonic acid in acetone.

The absence of starting material from the reaction mixture suggested that the mixture of esters noted above arose either by a competing mechanism or by direct conversion of methyl ketal(130) to the esters as outlined in Scheme (1),(130) - - → (82)(83). On extending the reflux time to 19 hrs. a reduced quantity of ketal was observed and after 38 hrs. only the esters were obtained, confirming the scheme shown. The initial formation of a tetrahedral C_8 carbon atom observed here suggested that under the aqueous conditions of the hydrochloric acid-acetic acid reaction, conversion of the bicyclo-ketone(84) to the cycloheptene acids might involve initial hydration of ketonic function to form (131), rather than the synchronous mechanism of scheme(b).

Reaction of the bicyclo-ketone(84) with concentrated sulphuric acid and methanol also furnished a mixture of equal quantities of the isomeric cycloheptene esters(82) and (83). Since the reaction was carried out in acidic conditions, no obstacle to the extension of this modification to the diketone(66) was envisaged and prolonged reflux (2 days), in fact, produced only the esters in equal quantities. Reflux for 19 hrs., however, yielded bicyclo methyl ketal(130) in addition to the esters, presumably by the same mechanism.

An attempt to use these modified conditions for the isolation of the acid(102) or its methyl ester, rather than lactone(108) from the diketone(106) was largely unsuccessful because of the exceptionally long reaction times required. As a modification, ethylene glycol seemed preferable to methanol because of its high boiling point and because the preparation of a ketal using p-toluene sulphonic acid and this solvent in a bicyclo-(3,2,1)-octane compound had already been described[55,56].

As an introductory exercise the bicyclo-ketone(84) was treated with p-toluene sulphonic acid in ethylene glycol on a steam bath in an effort to isolate the ketal(132). The oil obtained from this treatment showed absorption at

3500cm.$^{-1}$ (hydroxyl) and 1730cm.$^{-1}$ (ester) in the infra-red spectrum, the absence of the 1730cm.$^{-1}$ band indicating the complete reaction of the [illegible] material, despite the fact that the less polar of the two spots visible on t.l.c. had a similar R_f to the ketone(84). The reaction mixture was hydrolysed with methanolic potassium hydroxide, on the assumption that it contained the desired ketal(132) and a hydroxy-ester formed by bridge-fission. The neutral fraction afforded (132) identified by the absence of carbonyl and hydroxyl absorption in the infra-red spectrum and the presence of a four-proton singlet at 6.10τ in the n.m.r. spectrum for the methylene protons of the **ethylenedioxy** group.

Treatment of the diketone(66) with these reagents at reflux afforded a neutral fraction, which showed hydroxyl and ester carbonyl absorption in the infra-red spectrum. It seemed probable that this contained the isomeric cycloheptene ethylene glycol esters(133) and (134) since base hydrolysis afforded the corresponding acid mixture.

A short reflux (1 hr.) of the diketone(106) with *p*-toluene sulphonic acid and ethylene glycol afforded a mixture of compounds (t.l.c), chromatography of which furnished a 55% yield of the lactone (108). A quantity of a compound which showed absorption at 3500c.m.$^{-1}$(hydroxyl) and 1740cm.$^{-1}$(ester) in the infra-red spectrum was also obtained. This material was assigned the structure(136), since the n.m.r. spectrum exhibited no olefinic proton, but a vinylic methyl peak at 8.32τ and peaks at 6.27τ and 5.88τ for the methylene protons adjacent to the hydroxyl group and the ester function respectively.

Alternatively, base hydrolysis of the reaction mixture afforded a neutral **fraction** consisting of the lactone(108) and traces of a less polar compound believed to be the ketone(107) or corresponding ketal(135) and an acidic fraction of 48% containing 3-methyl-4-phenylcyclohept-3-one carboxylic acid(102) identified by its n.m.r. spectrum which showed no

olefinic proton but a vinylic methyl at 8.36 τ. G.l.c. analysis of an esterified sample indicated that the acidic product was homogeneous. An excellent recovery of almost pure lactone(108) was obtained by treatment of the diketone with ethylene glycol and p-toluene sulphonic acid followed by overnight reflux with hydrochloric acid.

Thus by varying the experimental conditions, the acid(102) - previously unobtainable, can be isolated in acceptable yield.

Another example in which the hydrochloric acid-acetic acid conditions afforded only lactone was that derived from (48). We had considered using the ring expansion reaction for the synthesis of naturally occurring sesquiterpenes with the perhydroazulene skeleton but this had been abandoned with the formation of the lactone(51) during efforts to prepare the model compound(54). The successful use of the modified procedure described above offered a possible solution to this problem. A short reflux of the diketone(48) with p-toluene sulphonic acid and ethylene glycol followed by basic hydrolysis furnished a yield of acidic material slightly in excess of 50% and a neutral fraction consisting mainly of the lactone(51). G.l.c. analysis of an esterified sample of the crude acidic material showed that it consisted of 80% of one component and two impurities. Distillation afforded a sample of greater purity which showed no olefinic proton signal in the n.m.r. spectrum confirming the tetra-substituted double bond structure(54).

The synthesis of this acid reopens the possibility of applying this procedure to a suitably substituted diketone system in a synthesis of a guaiol-type sesquiterpene.

The success of these forcing conditions in accelerating the formation and subsequent cleavage of the bicyclo-intermediate suggested that an improved yield of 4-phenyl-5-methylcyclohept-4-ene carboxylic acid(104) would result

from the diketone (103) under these conditions. This was confirmed by the isolation of 80% of this acid (104) after 17 hrs. reflux in ethylene glycol in the presence of p-toluene sulphonic acid. The neutral material recovered consisted only of the starting diketone.

MECHANISM

Throughout these investigations it has been demonstrated that the reaction under investigation proceeds via a strained bicyclic intermediate and two mechanisms have been considered. That involving a ketene intermediate has been eliminated, and that shown in scheme (b) appears to satisfy most of the evidence presented. However, it implies synchronous nucleophilic attack on the bridge carbonyl and C--C bond fission. A modified scheme was suggested by our study of the reaction products from concentrated sulphuric acid or p-toluene sulphonic acid in methanol. These experiments indicate that cleavage did not occur by nucleophilic attack of methanol at the carbonyl but apparently through the methyl ketal, as shown in scheme (i). It is, therefore, probable that the more standard reaction conditions (concentrated hydrochloric acid) involved the hydrated form of the bicyclo-ketone as outlined in scheme (j). This we believe is a satisfactory expression of the mechanism.

EXPERIMENTAL - GENERAL

Melting points were recorded on a Kofler microscope hot stage and are uncorrected. Routine infra-red spectra of liquid films and nujol mulls were recorded on Perkin Elmer 137 and Unicam S.P. 200 spectrophotometers. Infra-red spectra, where a solvent is given, were determined on a Unicam S.P. 100 double-beam spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum conditions. Ultra-violet absorption spectra were determined on a Unicam S.P. 800 spectrophotometer in ethanolic solution. Nuclear magnetic resonance spectra, recorded on a Perkin Elmer R.S.10 (60 megacycles) spectrometer, refer to solutions in carbon tetrachloride unless otherwise stated.

Gas-liquid chromatographic data were recorded with a Pye "Argon" Chromatograph equipped with a ^{90}Sr detector, using glass columns, 134cm. long and 4mm. internal diameter and an argon flow rate of 40 ml./min.

Column chromatography was carried out using B.D.H. silica or 100 mesh silica referred to as "fine silica". Thin-layer chromatography (t.l.c.) employed Kieselgel G silica using 20% ethyl acetate in petrol as the solvent system unless otherwise stated and iodine vapour for development.

Petrol refers to that fraction of petroleum ether, b.p. 60-80°.

EXPERIMENTAL

2-(1', 3'-Diphenyl-3'-oxopropyl)-cyclopentanone (2)

The procedure described by Stobbe [1] afforded a viscous oil, which after crystallisation, yielded 57% of the diketone (2). The modified method recorded below, resulted in an improved yield.

Benzalacetophenone (1) (100g., 0.48m.), cyclopentanone (50g., 0.59m.) and piperidine (5ml.) were mixed and heated on a steam bath for 3 hrs., then allowed to stand at room temperature overnight. The solid reaction mixture, recrystallised from petroleum ether, furnished the diketone (2) (110g., 75%) m.p. 79-81°. The infra-red spectrum showed absorption at 1740cm.$^{-1}$ (cyclopentanone) and 1680cm.$^{-1}$ (aromatic ketone). T.l.c. showed two spots attributed to the diastereoisomeric forms of the product.

1-Piperidino-2-(1', 3'-diphenyl-3'-oxopropyl)-cyclopentene(3).

Benzalacetophenone (2g., 0.012m.) (1), cyclopentanone (1g., 0.011m.) and piperidine (2g., 0.022m.) were mixed and heated on a steam bath for 15 mins. and then allowed to stand at room temperature. The reaction mixture solidified within 1 hr. and the product was washed with cold petroleum ether, cold ethanol and recrystallised from petroleum ether, yielding 2g. (55%) of the enamine (3), m.p. 113-116°. Recrystallised from$C_{25}H_{29}N$ O requires C, 83.52%, H, 8.06%, N, 3.90%). The infra-red $C_{25}H$spectrum (CCl_4) showed absorption at 1691cm.$^{-1}$ (aromatic ketone) and spec1627cm.$^{-1}$ (double bond). The n.m.r. spectrum ($CDCl_3$) showed a broad 1627cm.$^{-1}$ (double bond). The n.m.r. spectrum ($CDCl_3$) showed a broad unresolved peak at 5.97 τ attributed to the olefinic proton. Further interpretation of the spectrum was complicated by the partial decomposition of the sample, which occurred readily on successive recrystallisation from commercial grade solvents.

Concentration of the petroleum ether and ethanol washings and crystallisation of the resultant gum yielded the diketone (2) as a by-product.

Treatment of the diketone (2) with piperidine in the manner described above failed to yield any of the enamine (3).

Hydrolysis of the enamine (3)

The enamine (3) (0.35g.), dissolved in 6N sulphuric acid (5ml.) and ethanol (2ml.), was heated on a steam bath for 2 hrs. and allowed to cool. The solid product was filtered, washed with water and dried. Recrystallisation from petroleum ether yielded (0.24g.) of the diketone (2), m.p. 77-79°.

Thermal decomposition of the enamine (3)

The enamine (3) (0.5g.) was heated on a steam bath for 1 hr. under water-pump pressure. On cooling, the product solidified. The infra-red absorption spectrum was identical with that of the diketone (2).

2,4-Diphenylcyclohept-4-ene carboxylic acid (7)

A mixture of the diketone (2) (15g.), concentrated hydrochloric acid (30ml.) and acetic acid (70ml.) was refluxed for 18 hrs. The reaction mixture was cooled and the crystalline solid filtered off (11.7g.). The mother liquors were concentrated, diluted with water and extracted with ether. The organic solution was extracted with dilute sodium hydroxide, washed with brine and dried ($MgSO_4$). Acidification (6N HCl) of the basic extracts and filtration yielded a further 1g. of the crystalline solid affording a total yield of the acid (7), 12.7g. (85%).

Recrystallisation from benzene/petrol mixtures furnished 10.4g., m.p. 194-196°. (Found C, 82.37%, H, 6.86%. $C_{20}H_{20}O_2$ requires C, 82.16%, H, 6.89%). The infra-red spectrum showed absorption at 3500-2700cm.$^{-1}$ (acidic hydroxyl) and 1700cm.$^{-1}$ (carbonyl). Esterification of this material with diazomethane furnished an oil, b.p. 160°/0.03mm., which solidified after distillation. Recrystallisation afforded (6) m.p. 64-67°. (Found C, 82.43%, H, 7.70%. $C_{21}H_{22}O_2$ requires C, 82.34%, H, 7.25%). $\nu_{C=O}^{CCl_4}$ 1739cm.$^{-1}$. The n.m.r. spectrum showed a triplet at 5.85 τ for the olefinic proton confirming the Δ^4 position of the double bond.

Analytical g.l.c. of an esterified sample of the crude acidic product showed that it consisted of one major product and a number of minor impurities.

Concentration of the neutral fraction yielded a dark viscous oil which crystallised from ethanol affording 0.3g. of a colourless crystalline solid which consisted of two compounds (t.l.c.). The combined neutral fractions of several preparations were recrystallised twice from ethanol and chromatographed on silica. Elution with benzene afforded 2,4-diphenyl-3-hydroxycycloheptene carboxylic acid lactone (11), m.p. 182-183°. (Found C, 82.1%, H, 7.0%. $C_{20}H_{22}O_2$ requires C, 82.15%, H, 6.89%). The infra-red spectrum (CCl_4) showed absorption at 1778cm.$^{-1}$ and the n.m.r. spectrum ($CDCl_3$) exhibited a broad unresolved band at 6.8-7.3 τ(2H, C_1 and C_4), singlets at 6.41 τ (1H, C_2) and 5.0 τ (1H, C_3) and a finely split doublet at 2.66 τ(10H, phenyl protons). The existence of unsplit signals for the C_2 and C_3 protons indicates that the lactone has the conformation shown in structure (11a).

Elution with 5% and 15% mixtures of chloroform in benzene afforded the other component, tentatively addigned the δ-lactone structure (12), m.p. 142-145° (carbon tetrachloride and benzene-petrol mixtures). (Found C, 82.50%, H, 7.11%. $C_{20}H_{20}O_2$ requires C, 82.15%, H, 6.89%). The infra-

red spectrum (CCl_4) was transparent in the hydroxyl region but showed absorption at 1750cm.$^{-1}$. The n.m.r. spectrum ($CDCl_3$) had subsplit quartets centred at 6.5 τ (1H) and 7.05 τ (2H) which were assigned to the protons on C_2 and C_3. These protons appeared to constitute an ABC system, the simple nature of the A part at 6.05 τ requiring that little/ no coupling occurred between the protons on C_1 and C_2, i.e. $\angle H_1 H_2 \cong 90^\circ$ as in structure (12a).

The lactonic nature of the carbonyl function was verified by the failure of the compound to react with sodium borohydride in methanol.

2,4-Diphenylbicyclo-(3,2,1)-oct-2-en-8-one (13)

This compound, with the double bond drawn in the anti-Bredt position at the bridgehead, was reported by Stobbe[1] as being prepared from the diketone (2) by the action of hydrogen chloride in ethanol. A number of attempts to prepare this compound using variations of this method yielded gums from which unsatisfactory quantities of the desired ketone (13), $\nu_{C=O}$ 1750cm.$^{-1}$, m.p. 116-122°, were obtained, generally by chromatography. Modification of the work up, by dilution with ether, washing with saturated sodium bicarbonate and brine and drying ($MgSO_4$) resulted in improved but widely varying yields.

An alternative acidic catalyst was sought which could be subjected to more rigorous control. The use of concentrated sulphuric acid at 0° yielded a highly coloured, water-soluble solid which suggested that sulphonation of the phenyl groups had occurred. Reaction of the diketone (2) (1g.) with polyphosphoric acid (10g.) at 50° for 6 hrs. produced a mixture of the desired product and starting material which resisted purification by crystallisation.

Treatment of the diketone (2) (7g.) with boron trifluoride etherate (3.5ml.) in anhydrous benzene at reflux for 2 hrs. yielded a mixture of the desired bicyclo-ketone as a gum, with the solid diphenyl acid. Use of a water separator and a catalytic quantity of p-toluene sulphonic acid in benzene failed to produce reaction but the modification of this method described below proved to be satisfactory and has been adopted as the general synthetic procedure for a number of 2-aryl bicyclo- (3,2,1)-oct-2-en-8-one molecules.

p-Toluene sulphonic acid (10g.) and anhydrous benzene (200ml.) were refluxed with a water separator for 45 mins. When reflux subsided the water separator was drained and refilled with benzene and a solution of the diketone (2) (10g.) in benzene was added rapidly to the reaction mixture, which was then refluxed for 1 hr. After cooling, the solution was neutralised with anhydrous potassium carbonate and allowed to stand for 3 hrs. Filtration and concentration of the benzene solution furnished an oil which solidified on standing. Recrystallisation from ethanol gave 5.4g., (95%) of the desired ketone (13), m.p. 108-109°. (Found C, 87.68%, H, 6.55%. $C_{20}H_{18}O$ requires C, 87.52%, H, 6.61%). $\nu_{max}^{CCl_4}$ C=O 1759cm.$^{-1}$. In the n.m.r. spectrum a multiplet was shown at 2.8 τ for the bridgehead proton on C_1, and a poorly resolved quartet at 5.55 τ for the C_4 proton and a doublet at 3.96 τ (J = 3 cps.) for the vinyl proton at C_3. This material was unaffected by storage for long periods. Attempts to improve the yield by using ethyl orthoformate [60] to remove the water generated in the reaction in place of the water separator resulted in complete inhibition of the reaction.

The semicarbazone derivitive was made in the usual manner, m.p. 201-203° (ethanol) [1].

Treatment of the bicyclo-ketone (13) with concentrated hydrochloric acid-acetic acid.

The bicyclo-ketone (13) (5g.) was refluxed for 6 hrs. with concentrated hydrochloric acid (10ml.) in acetic acid (30ml.). On cooling the reaction mixture, a quantity of an acid (2g.) crystallised and was filtered. The mother liquor was subjected to the work up described for similar treatment of the diketone (2), yielding a further 1.2g. of acid and a neutral fraction which was shown by t.l.c. to consist of the starting ketone and the diketone (2). The acidic material was recrystallised from benzene/petrol mixtures, m.p. 193-196°, and had an infra-red spectrum identical with that of the cycloheptene acid (7).

2-Phenylbicyclo-(3,2,1)-oct-2-en-8-one (15)

p-Toluene sulphonic acid (3g.) and anhydrous toluene (120ml.) were refluxed for 1 hr. with a water separator. The source of heat was removed, the water separator drained and refilled with toluene and the diketone (16) (3g.), dissolved in toluene (50ml.), was run into the reaction mixture. The reflux was restarted and continued for 100 mins. and the reaction mixture cooled and neutralised with anhydrous potassium carbonate. After standing for 3 hrs. the solid was filtered, washed with hot benzene and discarded. The combined toluene solution and benzene washings were concentrated yielding an oil which solidified on standing. Attempts to purify the product by recrystallisation were unsuccessful and consequently chromatography on silica was employed. Elution with petrol furnished the desired ketone (15) which was readily recrystallised from petrol, m.p. 71-75° and 89-93°. (Found C, 85.06%, H, 7.13%. $C_{14}H_{14}O$ requires C 84.81%, H, 7.12%). $\nu_{C=O}^{CCl_4}$ 1756cm.$^{-1}$. The n.m.r. spectrum had a three-proton multiplet at 7.2 τ (C_1 and C_4) and a one-proton triplet at 4.1 τ (J=3.75 cps.) for the olefinic proton.

2-Thienyl- β -dimethylaminoethyl ketone hydrochloride (18).

A mixture of 2-acetylthiophene [12] (42.7g., 0.34m.), dimethylamine hydrochloride (28g., 0.34m.), paraformaldehyde (12.36g., 0.41 equiv), ethanol (100ml.) and concentrated hydrochloric acid (0.1ml) was refluxed for 2.5 hrs. then cooled and the solid product filtered off. Concentration of the mother liquors afforded a further two crops. Total yield of (18) after recrystallisation from ethanol was 43.3g. (58%), m.p. 178-180° with decomposition [14].

2-(3'-Oxo-3'-thienylpropyl)-cyclopentanone (16)

(1) Attempted preparation of (16) by the general procedure of Gill et.al.[3].

The hydrochloride (18) was dissolved in hot water, then cooled in ice and basified with 4N sodium hydroxide and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding 2-thienyl - β -dimethylaminoethyl ketone as an oil which was used without purification. The β-amino-ketone and cyclopentanone were mixed in a 1:3 molar ratio and refluxed for 30 mins. then the cyclopentanone was distilled out under water-pump pressure. The residual oil was then distilled at 0.05 mm. into two fractions, the lower boiling compound being identified as 2-acetylthiophene by comparison of its infra-red spectrum with that of an authentic sample. The high boiling material solidified and was recrystallised from benzene/petroleum ether mixtures to m.p. 165.5-166°. (Found C, 66.87%, H, 5.96%). $\nu_{C=O}^{CCl_4}$ 1753cm.$^{-1}$ and 1670cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1746cm.$^{-1}$ and 1664cm.$^{-1}$. This compound has not been identified.

(2) Preparation of (16) by a modified procedure.

2-Thienyl- β - dimethylaminoethyl ketone (14.6g., 0.08m.), liberated from the hydrochloride as described above, and cyclopentanone (20.1g. 0.24 m.) were stirred and heated at 90 - 100° for 45 mins. The

The reaction mixture was then cooled, neutralised with acetic acid, diluted with ether, washed with brine and dried ($MgSO_4$). Removal of the ether and excess cyclopentanone yielded an oil which solidified. Recrystallisation from benzene/petrol mixtures afforded 15g. of material, m.p. 40-43°, which was shown by t.l.c. to consist of two components. Further recrystallisation using this solvent mixture failed to purify the material and it was used in this state in subsequent reactions. However, distillation using a Woods metal bath afforded material, b.p. 146-152°/ 0.04m.m., which consisted only of the less polar component, identified as the desired dibotene (16), m.p. 52.5-53.5° (benzene/petrol mixtures). (Found C, 64.71%, H, 6.03%. $C_{12}H_{14}O_2S$ requires C, 64.85%, H, 6.35%). The infra-red spectrum ($CHCl_3$) showed absorption at 1734cm.$^{-1}$ (ϵ = 328) and 1662cm.$^{-1}$ (ϵ = 312).

Recrystallisation of the reaction mixture from ethanol furnished the more polar compound in a pure state, m.p. 109.5-110°. (Found C, 63.24%, H, 6.11%. $C_{19}H_{20}O_3S_2$ requires C, 63.33%, H, 5.59%). The infra-red spectrum (CCl_4) showed absorption at 1735cm.$^{-1}$ (ϵ = 318) and 1671cm.$^{-1}$ (ϵ = 638). The n.m.r. spectrum had peaks for the thiophene protons at 2.86 τ(2H, multiplet, C_4) and 2.24 τ(4H, multiplet, C_3 and C_5) and a peak at 6.89 τ(4H, triplet, methylenes adjacent to the thiophene carbonyl). On the basis of this spectral data the by-product was assigned the structure (20) or its isomer (21).

2-(2'-Methoxycarbonylethyl)-cyclopentanone (23)

Methyl acrylate (138g., 1.58m.) was added dropwise over 20 mins. to a solution of the pyrrolidine enamine of cyclopentanone (22) [2] (115g., 0.84m.) in dioxan (312ml.) and the reaction mixture stirred at room temperature for 15 hrs. Water (62ml.) was then added and the solution refluxed for 30 mins., the bulk of the volatiles removed under reduced pressure and the residual oil dissolved in ether. The organic solution was washed with 6N hydrochloric acid, water and dried over $MgSO_4$. Removal of the solvent and

distillation furnished (23) as a colourless oil, (67.6g., 47%), b.p. 138°/15 mm.[2]. $\nu_{C=O}^{CCl_4}$ 1743cm.$^{-1}$ (ketone and ester).

2-(2'-carboxyethyl)-cyclopentanone (24)

The keto-ester (23) (28g.) was added to a solution of potassium hydroxide (16.8g.) in methanol (1,400 ml.) and the mixture was allowed to stand for 2.75 hrs. The methanol was distilled off under reduced pressure, water added to the residue and the aqueous solution extracted with ether (these extracts were discarded). The alkaline solution was then acidified (6N HCl), extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Removal of solvent yielded (24) as an oil, (22.0g., 85%), which solidified after distillation, b.p. 150-152°/0.5 mm., m.p. 26-29°. Recrystallisation from benzene-petrol mixtures gave material, m.p. 34-36°[61], which showed absorption in the infra-red spectrum at 3500-2700cm.$^{-1}$ (acidic hydroxyl), 1740cm.$^{-1}$ (ketone) and 1720cm.$^{-1}$ (carboxyl). The semicarbazone derivative made in the usual manner had m.p. 213-215° (ethanol)[62].

Attempted hydrolysis of the keto-ester (23) by standing at room temperature for 18 hrs. with a 2% methanolic solution of potassium hydroxide yielded a white semi-solid which exhibited an intense peak at 1650cm.$^{-1}$ (double bond), together with broad bands at 3500-2700cm.$^{-1}$ (acidic hydroxyl) and 1740-1700cm.$^{-1}$ in the infra-red spectrum. This suggested that a retro-Michael reaction had taken place yielding acrylic acid polymer.

2-(2'-Carboxyethyl)-1-hydroxycyclopent-1-ene- δ -lactone (17a)

Refluxing the keto-acid (24) and acetic anhydride as described by Mannich[15] yielded an oil which showed absorption at 1825cm.$^{-1}$ and 1780cm.$^{-1}$ in the infra-red spectrum. Absorption at the higher frequency was attributed to mixed anhydride formation (25)[16] and distillation of the oil afforded

only a low yield of the enol-lactone. The improved procedure of Woodward [17] was used in subsequent preparations.

The keto-acid (24) (6g.) and acetic anhydride (30 ml.) were refluxed for 50 mins. then fused sodium acetate (20 mgm.) was added and the mixture refluxed for a further 3 hrs. The acetic anhydride was removed under water pump pressure and the residual oil dissolved in ether, washed with saturated sodium carbonate solution and brine and dried ($MgSO_4$). Removal of the solvent and distillation afforded the desired enol-lactone (17a) (4.1g., 78%); b.p. 114-117°/12 mm. (lit.[62,63] b.p. 118-119°/13 mm.). $\nu_{C=O}^{CCl_4}$ 1778cm.$^{-1}$. T.l.c. showed the presence of a more polar impurity believed to be the isomeric enol-lactone (17b), but the absence of a band for the olefinic proton in the n.m.r. spectrum indicated that it was a minor component of the mixture.

The material rapidly hydrolysed to the keto-acid (24) on standing in a moist atmosphere.

2-(3'-Oxo-3'-phenylpropyl)-cyclopentanone (10)

An ethereal solution of phenyl magnesium bromide [from magnesium (0.41g.) and bromobenzene (2.74g.) in anhydrous ether (25 ml.)] was added dropwise over 1 hr. to a stirred solution of the enol-lactone (17) (1.73g.) in anhydrous ether (25 ml.) and the reaction mixture refluxed for 4 hrs. After cooling and decomposition of the solid complex with mineral acid (6N HCl), ether was added and the organic layer was washed with saturated sodium carbonate solution and brine and dried ($MgSO_4$). Concentration and distillation furnished phenol and at higher temperatures an oil shown by t.l.c. to consist of two components. Redistillation of the oil afforded two fractions, b.p. 147-148°/0.15 mm. and b.p. 158-165°/0.15 mm. The lower boiling fraction, rich in the less polar compound, had absorption in the infra-red spectrum at 3500cm.$^{-1}$, 1750cm.$^{-1}$ and a shoulder at 3690 cm.$^{-1}$. This was considered to consist mainly of the bicyclo-(3,2,1)-

-octane ketol (26). The higher boiling fraction, consisting of the more polar compound, had absorption at 1740cm.$^{-1}$ and 1690cm.$^{-1}$ in the infra-red spectrum. This fraction solidified on standing, affording the diketone (10) (0.79g., 30%), m.p. 40-42° (benzene/petrol mixtures) [4,9]. The bis-2,4-dinitrophenylhydrazone, made in the usual manner, had m.p. 221-224° (xylene) [4,9].

Preparation of the mixture of acids (27) and (118) from the enol-lactone (17)

An ethereal solution of phenyl magnesium bromide [from magnesium (0.91g.) and bromobenzene (5.97g.) in anhydrous ether (42 ml.)] was added dropwise over 30 mins. to a stirred solution of the enol-lactone (17) (4g.) in anhydrous ether (50 ml.) and the reaction mixture refluxed for 3.5 hrs. The cooled reaction mixture was acidified with 6N hydrochloric acid, diluted with water and extracted with ether. The ethereal extracts were washed with 4N sodium hydroxide and brine and dried ($MgSO_4$). Concentration yielded 5g. of an oil which was refluxed with concentrated hydrochloric acid (10 ml.) and acetic acid (40 ml.) for 20 hrs. The bulk of the acetic acid was removed under reduced pressure and the residue flooded with water and ether extracted. The ethereal solution was extracted with dilute sodium hydroxide and the basic solution acidified with 6N hydrochloric acid and extracted with ether. Drying ($MgSO_4$) and concentration furnished 3.37g. of a viscous oil, b.p. 155°/0.03 mm., which showed absorption at 3500-2700cm.$^{-1}$ (acidic hydroxyl) and 1710cm.$^{-1}$ (carbonyl) in the infra-red spectrum. This spectrum was identical with that of the acidic product of the reaction of concentrated hydrochloric acid/acetic acid with the diketone (10)[4].

G.l.c. analysis of esterified samples (diazomethane) of the crude reaction product from the enol-lactone and from the diketone [4] showed

that both consisted of an identical mixture of two compounds (45%, R_t = 12.0 mins. and 55%, R_t = 12.8 mins. on 1%F-60 at 140°). These were subsequently identified as the methyl esters[8] of 4-phenylcyclohept-3-ene carboxylic acid (27) and 4-phenylcyclohept-4-ene carboxylic acid (118) respectively.

Treatment of the crude diketone (16) with concentrated hydrochloric acid and acetic acid.

The diketone (16), contaminated with the triketone (20) or (21), (6g.) was refluxed for 20 hrs. with concentrated hydrochloric acid (10 ml.) and acetic acid (30 ml.). Removal of the solvent gave a badly charred residue which was largely dissolved in ether and benzene. The combined organic solution was washed with water, extracted with 4N sodium hydroxide, washed with brine and dried ($MgSO_4$). Concentration afforded 0.32g. of a gummy solid consisting mainly of the triketone (20) or (21) (t.l.c. and i.r.). The infra-red spectrum however, also showed weak absorption at 1780cm.$^{-1}$ due to a lactone.

The basic layer was acidified with dilute mineral acid, extracted with ether and the organic solution washed with brine and dried ($MgSO_4$). Removal of the solvent afforded 3.5g. of a viscous oil which showed absorption at 3500-2800cm.$^{-1}$ and 1710cm.$^{-1}$ in the infra-red spectrum. However, no typical thiophene absorption bands[21] were present. Attempts to purify this material by distillation and crystallisation were unsuccessful.

Treatment of a methanolic solution of the acidic material with excess ethereal diazomethane furnished a dark oil which distilled, b.p. 180°/ 0.03 mm., to yield a yellow liquid. This material had a complex

t.l.c. pattern and showed absorption at 1730cm.$^{-1}$ in the infra-red spectrum but no thiophene absorption bands [21]. No attempt to purify or identify the products was made.

Treatment of the crude diketone (16) with p-toluene sulphonic acid in benzene.

The impure diketone (16) (2g.), p-toluene sulphonic acid (2g.) and wet benzene (55 ml.) were mixed and refluxed for 5 hrs. On cooling the reaction mixture, a black sludge settled, which had a strong odour of hydrogen sulphide. The solvent was decanted and the residue extracted with chloroform. Combination of the organic solutions, washing and drying, afforded a dark oil on concentration. This material had a complex t.l.c. pattern and was abandoned without further investigation.

Repetition of the reaction using a catalytic quantity of the acid furnished cleaner material, but a large amount of unreacted material remained and a number of products were formed (t.l.c. and i.r.).

2-(3'-Oxobutyl)-cyclopentanone (29)

This compound was synthesised from cyclopentanone and diethylamino-butan-3-one (40) [64] as described by Gill et.al. [9], as a colourless oil, b.p. 132°/11 mm., $\nu_{C=O}^{CCl_4}$ 1740cm.$^{-1}$ and 1720cm.$^{-1}$.

The bis-semicarbazone derivative was recrystallised from aqueous dioxan, m.p. 228-229° [9].

Treatment of (29) with hydrochloric acid/acetic acid.

A mixture of the diketone (29) (6g.), concentrated hydrochloric acid (10 ml.) and acetic acid (30 ml.) was refluxed for 6 hrs. and

then concentrated under reduced pressure. The residue was flooded with water, extracted with ether (2X) and the combined organic layers extracted with 4N sodium hydroxide, washed with brine and dried ($MgSO_4$). Distillation furnished 2.3g. of an oil, b.p. 113-115°/12 mm. The infra-red spectrum (CCl_4) showed absorption at 3500cm.$^{-1}$ (hydroxyl), 1720cm.$^{-1}$ (carbonyl) and 1680cm.$^{-1}$ (α,β-unsaturated ketone). Distillation afforded the major component of the mixture, the α,β-unsaturated ketone, 5,6,7,8-tetrahydroindanone-5 (30), confirmed by its ultra-violet absorption, λ max. 240 mμ(ϵ=10,800), lit.[2] $\lambda_{max.}$ 233mμ (ϵ=12,700) and deep red 2:4-dinitrophenylhydrazone derivative, m.p. 197.5-199° (dioxan-ethanol)[65]. (Found C, 57.29%, H, 5.31%, N, 17.40%. $C_{15}H_{16}N_4O_4$ requires C, 56.96%, H, 5.10%, N, 17.71%).

Acidification (6N HCl) and ether extraction of the basic solution afforded a negligible quantity of acidic material which was not investigated.

Treatment of (29) with concentrated sulphuric acid.

The diketone (29) (2g.), stirred and cooled in an ice bath was treated with concentrated sulphuric acid (4g.) by dropwise addition and then allowed to stand at room temperature overnight. The reaction mixture was poured onto ice, extracted with ether (5X) and the combined extracts washed with water and dried ($MgSO_4$). Removal of the solvent afforded an oil which showed practically similar absorption in the infra-red spectrum to the product obtained by treatment of the diketone with hydrochloric and acetic acids. 5,6,7,8-tetrahydroindanone-5 (30) was confirmed by its 2:4-dinitrophenylhydrazone, m.p. 197-199°, mixed m.p. 197-199°.

2-Ethoxycarbonyl-2-(3'-oxobutyl)-cyclopentanone (32)

This compound was prepared as described by Dauben [27] in 80% yield b.p. 136-140°/1 mm. $\nu_{C=O}^{CCl_4}$ 1750cm.$^{-1}$(cyclopentanone), 1730cm.$^{-1}$ (ester) and 1720cm.$^{-1}$ (chain ketone).

Treatment of the diketo-ester (32) with concentrated hydrochloric acid-acetic acid.

The diketo-ester (32) (15g.) was refluxed for 6 hrs. with concentrated hydrochloric acid (30 ml.) and acetic acid (90 ml.) and worked up in the usual manner. A recovery of 1.6g. of acidic material was obtained but this was not investigated because of the complexity of the product. The neutral fraction furnished 8.6g. of an oil which exhibited three spots on t.l.c. Distillation yielded 4.5g. of a colourless oil consisting of two compounds which were separated by chromatography on silica (120g.). Elution with 5% ethyl acetate in petrol afforded initially an oil with carbonyl absorption at 1725cm.$^{-1}$ in the infra-red spectrum and then an α,β - unsaturated ketone with carbonyl absorption at 1680cm.$^{-1}$. The more polar compound was identified as 5,6,7,8-tetrahydroindan-5-one (30) by formation of the 2,4-dinitro-phenylhydrazone derivative, m.p. 197-199.5°, mixed m.p. 197-199°. The less polar compound was considered to be 4,5,6,7-tetrahydroindan-5-one (39), b.p. 52°/0.004 mm. The n.m.r. spectrum showed no olefinic proton but a broad singlet (2H) at 7.27 τ attributed to the protons on C_4. The material rapidly decomposed, the infra-red spectrum (CCl_4) of a sample kept at room temperature for a few days showing absorption at 1725cm.$^{-1}$ and 1685cm.$^{-1}$. The latter value was attributed to formation of (30) by migration of the double bond into conjugation. Acceptable analysis figures for this material could not be obtained.

2-Methylcyclopentanone

2-Carbethoxy-cyclopentanone was converted to the sodium salt and alkylated with methyl iodide as described by Cornubert, [32]. The resultant 2-carbethoxy-2-methylcyclopentanone was hydrolysed and decarboxylated to yield 2-methylcyclopentanone [33], the purity of which was verified by g.l.c. analysis.

2-(3'-Oxobutyl)-5-methylcyclopentenone (41)

A stirred solution of diethylaminobutan-3-one (40) [64] (8.58g., 0.06 m.) in 2-methylcyclopentanone (17.3g., 0.177 m.) was refluxed for 1.25 hrs. at 140° then cooled, neutralised with acetic acid and diluted with ether. The ethereal solution was washed with brine and dried ($MgSO_4$), then concentrated and the excess 2-methylcyclopentanone removed by distillation on a water bath at water-pump pressure. The residue showed a major spot on t.l.c. with a trace of a slightly less polar material. Distillation, b.p. 122-126°/10 mm., afforded 4.01g., (40%) of a colourless oil, a sample (500 mgm.) of which was chromatographed on fine silica (10g.). Elution with 30% ether in petrol furnished pure diketone (41), (t.l.c. and g.l.c. analysis on 10% APL at 125°, R_t=15 mins.), b.p. 124-127°/mm. (Found C, 70.74%, H, 9.59%. $C_{10}H_{16}O_2$ requires C, 71.39%, H, 9.59%). $\nu_{C=O}^{CCl_4}$ 1739cm.$^{-1}$ and 1723cm.$^{-1}$. The n.m.r. spectrum showed a doublet at 8.94 τ (J=6cps.) for the methyl group on the cyclopentanone ring. G.l.c. analysis of the product prior to chromatography showed the presence of a trace of the 2, 2-substituted isomeric diketone (42) (10%APL at 125°, R_t=13.2 mins.).

An earlier reaction which was heated at 120° for 90 mins. yielded only 8% of an oil shown by g.l.c. analysis to consist of 70% of the diketone (41) together with 30% of the 2,2-substituted isomer (42) and an unidentified compound.

2-Methyl-2-(3'-oxobutyl)-cyclopentanone (42)

Preparation of this compound was undertaken using a procedure described by Ross and Levine [29]. A solution of 2-methylcyclopentanone (3.92g., 0.04 m.) in anhydrous ether (15 ml.) was cooled to 0° and treated with a solution of potassium hydroxide (0.17g., 0.003m.) in anhydrous ethanol (1.5 ml.). Methyl vinyl ketone (1.4g., 0.02 m.) dissolved in anhydrous ether (10 ml.), was added dropwise over a period of 30 mins. to the stirred reaction mixture then the ice bath was removed and the heterogeneous system stirred for 1 hr. After dilution with water and acidification (6N HCl.), the mixture was extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration and removal of the excess 2-methylcyclopentanone yielded 2.3g. of an oil which showed hydroxyl and complex carbonyl absorption in the infra-red spectrum. The oil was dissolved in petrol and chromatographed on silica (60g.), elution with 20% ether in petrol furnishing the desired diketone (42), b.p. 135°/11 mm. (Found C, 71.06%, H, 9.28%. $C_{10}H_{16}O_2$ requires C, 71.39%, H, 9.59%). $\nu_{C=O}^{CCl_4}$ 1736cm.$^{-1}$ and 1720cm.$^{-1}$. The n.m.r. spectrum showed the protons of the methyl group on the cyclopentanone ring as a singlet at 9.03 τ. G.l.c. retention time, 13.2 mins. (10% APL at 125°).

Further elution afforded material which showed hydroxyl absorption in the infra-red spectrum, but this was shown by g.l.c. analysis to be a mixture of three compounds.

G.l.c. analysis of the crude reaction product showed that two impurities with retention times of 15.9 mins. and 28.6 mins. (10% APL at 125°), were present in considerable quantities. Neither corresponded to the isomeric 2,5-substituted cyclopentanone (41) or the α,β-unsaturated ketone (43).

Treatment of the diketone (42) with concentrated hydrochloric acid-acetic acid.

The diketone (42) (540 mgm.), slightly contaminated with the hydroxylated impurity, was refluxed for 3 hrs. with concentrated hydrochloric acid (1 ml.) and acetic acid (4 ml.), then poured into water and extracted with ether. The extracts were washed with saturated sodium carbonate, brine and dried ($MgSO_4$), yielding 444 mgm. of an oil on concentration. Distillation of the oil, which showed one major spot on t.l.c. although the carbonyl region of the infra-red spectrum was rather complex, afforded 8-methyl-5,6,7,8-tetrahydroindan-5-one (43), b.p. 130-135°/10 mm. The infra-red spectrum (CCl_4) had absorption at 1676cm.$^{-1}$ and 1670cm.$^{-1}$ and the n.m.r. spectrum showed the methyl protons as a singlet at 8.84 τ and the olefinic proton as a very finely split triplet at 4.4 τ. G.l.c. retention time, 19.6 mins. (10% APL at 125°).

The deep red 2,4-dinitrophenylhydrazone derivative was made in the usual manner and recrystallised from ethanol-ethyl acetate mixtures, m.p. 158-160° (lit.[22] m.p. 153°).

Dimethylamino-4,4-dimethylpentan-3-one hydrochloride (46).

Pinacolone (7g., 0.08 m.), dimethylamine hydrochloride (6g., 0.074 m.), paraformaldehyde (2.3g., 0.076 m.), ethanol (10 ml.) and concentrated hydrochloric acid (0.5 ml.) were mixed and refluxed for 4.5 hrs. and then cooled, yielding a white solid. Filtration and recrystallisation from ethanol afforded 4.81g. (35.6%) of the desired hydrochloride (46), m.p. 127-132° (decomposition).

2-(3'-Oxo-4',4'-dimethylpentyl)-cyclopentanone (45)

Dimethylamino-4,4-dimethylpentan-3-one was obtained form the corresponding hydrochloride (46) in the usual manner. The β-amino-

ketone (13.4g., 0.085 m.) and cyclopentanone (21.6g., 0.255 m.) were stirred and refluxed for 2 hrs. at 140°. The usual work up yielded an oil which was distilled to give the desired diketone (45) (13.4g., 80%), b.p. 84-86°/0.02 mm.. The infra-red spectrum (CCl_4) showed absorption at 1740cm.$^{-1}$ (cyclopentanone) and 1699cm.$^{-1}$ (chain ketone) and the n.m.r. spectrum showed the methyl protons at 8.9 τ (singlet, 9H) and the protons on C_2' at 7.4 τ (triplet, J=7 cps., 2H).

This diketone was characterised as its mono-2,4-dinitrophenylhydrazone derivative (137), ($\nu_{C=O}$ 1700cm.$^{-1}$), recrystallised from methanol, m.p. 126.5-129°. (Found C, 57.66%, H, 6.17%, N, 14.79%. $C_{18}H_{24}N_4O_5$ requires C, 57.44%, H, 6.43%, N, 14.88%).

Treatment of the diketone (45) with hydrochloric acid/acetic acid.

The diketone (45) (5g.), concentrated hydrochloric acid (10 ml.) and acetic acid (30 ml.) were refluxed for 24 hrs. and worked up in the manner described previously. The neutral fraction furnished 4.74g. of unreacted diketone and the acidic material (200 mgm.) recovered from the reaction mixture consisted almost entirely of acetic acid.

Treatment of the diketone (45) with p-toluene sulphonic acid/ toluene

p-Toluene sulphonic acid (5g.) and anhydrous toluene (100 ml.) were refluxed with a water separator for 1 hr., then the reflux was allowed to subside, the water separator drained and refilled with toluene and the diketone (45) (4.5g.) in toluene (20 ml.) added rapidly to the reaction mixture. Reflux was restarted and continued for 3 hrs. The usual work up yielded only unreacted starting material.

2-Dimethylaminomethylcyclopentanone hydrochloride (138).

Cyclopentanone (84g., 1 m.), dimethylamine hydrochloride (90g., 1.11 m.), paraformaldehyde (35g., 1.16 equiv.), ethanol (250 ml.) and concentrated hydrochloric acid (2 ml.) were mixed and heated to reflux. The source of heat was removed until the resultant exothermic reaction subsided and the reaction mixture was then refluxed for 1.5 hrs. when a solid precipitated. The solid was filtered and the mother liquors concentrated to yield a further crop of the hydrochloride (138), 136.6g. (77.2%), m.p. 144-148°.

bis-Cyclopentan-2-onylmethane (48)

2-Dimethylaminomethylcyclopentanone was liberated from the corresponding hydrochloride (137) in the usual manner. The β-aminoketone (12.8g., 0.09 m.) and cyclopentanone (22g., 0.26 m.) were stirred and refluxed at 140° for 1.5 hrs., evolution of dimethylamine commencing at 80°. The cooled reaction mixture was neutralised with acetic acid, diluted with ether, washed with brine and dried ($MgSO_4$). Removal of the ether and excess cyclopentanone under reduced pressure yielded an oil which consisted of two components (t.l.c.). Distillation afforded the diketone (48), b.p. 92-98°/0.15 mm., (11.6g.) which solidified rapidly, m.p. 71.5-72.5° (petrol). (Found C, 73.53%, H, 8.64%, $C_{11}H_{16}O_2$ requires C, 73.30%, H, 8.95%). The infra-red spectrum (CCl_4) showed absorption at 1742cm.$^{-1}$. This compound has been reported by Nunn and Rapson [35] b.p. 129-130°/0.1 mm. and subsequently by Colonge et.al. [36] in two forms. Form A, m.p. 38° and form B, m.p. 70.5° (petrol).

Treatment of the diketone (48) with concentrated hydrochloric acid-acetic acid.

A mixture of the diketone (48) (3g.), concentrated hydrochloric acid (6 ml.) and acetic acid (18 ml.) was refluxed for 24 hrs. and worked

up in the normal manner, yielding a small quantity of acidic material contaminated by acetic acid. Distillation at water-pump pressure furnished initially a colourless oil whose infra-red spectrum showed carbonyl absorption at 1780cm.$^{-1}$, followed by a dark oil which could not be purified. The neutral fraction yielded 2.53g. of oil which showed three spots on t.l.c. Distillation failed to achieve a separation, the material boiling at 149-157°/11 mm. (1.5g.) being collected and chromatographed on silica (60g.). Elution with 5% ethyl acetate in petrol furnished initially 16 mgm. of an oil with a strong camphoraceous smell, identified as the bicyclo-ketone (52) by comparison of its infra-red spectrum with that of a sample prepared from the diketone by the action of p-toluene sulphonic acid. Further elution with this solvent mixture afforded 775 mgm. of an oil which showed a carbonyl frequency of 1780cm.$^{-1}$ in the infra-red spectrum, then mixtures of this compound and unreacted starting material and finally 350 mgm. of pure starting material. The main component was identified as 3-hydroxybicyclo-(3,3,0)-decane carboxylic acid lactone (51), b.p. 157°/12 mm. (Found C, 72.88%, H, 8.77%. $C_{11}H_{16}O_2$ requires C, 73.30%, H, 8.95%). $\nu_{C=O}^{CCl_4}$ 1775cm.$^{-1}$. The n.m.r. spectrum showed only a broad unresolved multiplet at 7.5-8.5 τ.

2,3-Cyclopentenobicyclo-(3,2,1)-oct-2-en-8-one (52)

Attempts to prepare this compound by refluxing the diketone (48) (4.5g.) with p-toluene sulphonic acid (2g.) in anhydrous benzene (100 ml.) for 5 hrs. in the usual manner failed to effect any change. Accordingly more vigorous conditions were employed. p-Toluene sulphonic acid (5g.) and anhydrous toluene (100 ml.) were refluxed with a water

separator for 2 hrs., then when reflux subsided the water separator was refilled with toluene and the diketone (48) (5g.) was added. The reaction mixture was then refluxed for 2 hrs., allowed to cool and neutralised with anhydrous potassium carbonate. After standing overnight the solid was filtered off and washed with hot benzene, the toluene solution and the washings combined and concentrated yielding 4.08g. of oil, which showed two spots on t.l.c. together with a trace of starting material. Chromatographic filtration afforded the more polar, major component as a pure compound identified as the desired ketone (52), b.p. 126-127°/18 mm. (Found C, 80.89%, H, 8.47%. $C_{11}H_{14}O$ required C, 81.44%, H, 8.70%). $\nu_{C=O}^{CCl_4}$ 1756cm.$^{-1}$. The n.m.r. spectrum showed a broad unresolved region from 8.2 τ - 7.5 τ together with a barely discernible peak at 4.4 τ attributed to the olefinic proton of a double bond isomer present as a minor impurity. This material was extremely unstable, rapidly decomposing to a brown oil.

Attempted hydrolysis of the lactone (51)

The lactone (51) (80 mgm.), dissolved in anhydrous methanol, (1 ml.) was added to a methanolic solution of sodium methoxide from sodium (100 mgm.) and anhydrous methanol (4 ml.) and the mixture refluxed for 24 hrs. The cooled solution was acidified with 6N hydrochloric acid and worked up in the normal manner yielding only unchanged starting material.

2-Ethoxycarbonyl-2-(2'-formylethyl)-cyclopentanone (57).

Redistilled acrolein (50 ml.) was added dropwise to a stirred solution of 2-carbethoxycyclopentanone (100g.) and triethylamine (7.5 ml.) in anhydrous benzene (500 ml.) at 0°. The reaction mixture was then

stirred at room temperature for 24 hrs., neutralised with acetic acid, washed with brine and dried ($MgSO_4$). Removal of the volatiles and distillation of the residue furnished the aldehyde-ester (57), (100.2g., 73.7%), b.p. 115-138°/0.2-0.5 mm., contaminated by small quantities of the isomeric ring-closed alcohol (58). Repeated distillation failed to effect a separation between the aldehyde-ester and the slightly higher boiling alcohol. Chromatography and re-distillation afforded a pure sample of (57), b.p. 75-78°/0.02 mm. (Found C, 61.93%, H, 7.46%. $C_{11}H_{16}O_4$ requires C, 62.25%, H, 7.60%). The infra-red spectrum (CCl_4) showed characteristic absorption at 2720cm.$^{-1}$ (aldehyde) and a carbonyl region with peaks at 1754cm.$^{-1}$ (ketone) and 1733cm.$^{-1}$ (aldehyde and ester). The n.m.r. spectrum (CCl_4) showed a singlet at 0.28 τ (1H), attributed to the aldehydic proton.

Treatment of the aldehyde-ester (57) with methanolic potassium hydroxide

The aldehyde-ester (57) (10g.) was dissolved in a solution of potassium hydroxide (6g.) in methanol (250 ml.) and allowed to stand at room temperature for 4 hrs. The methanol was evaporated and the residual oil dissolved in water and washed with ether. After acidification (6N HCl), the aqueous solution was extracted with ether. Concentration yielded a white solid which was recrystallised from ethanol to give 4.5g. (50%) of the diacid (59), m.p. 161-164°, identified by comparison with a sample prepared by another route (see Part II, p.137).

Treatment of the aldehyde-ester (57) with hydrochloric acid and acetic acid.

Treatment of the aldehyde-ester (57) with concentrated hydrochloric acid and acetic acid at reflux for 24 hrs. under the usual conditions

yielded an intractable, charred product. Reduction of the reflux time to 4 hrs. resulted in little improvement. The following milder conditions were therefore applied.

A mixture of the aldehyde-ester (57) (1g.), concentrated hydrochloric acid (1 ml.) and acetic acid (10 ml.) was stirred at room temperature for 4 hrs. The solvent was largely removed under reduced pressure, the residue flooded with water and extracted consecutively with ether and chloroform. The organic solutions were separately extracted with 4N sodium hydroxide then washed with brine and dried ($MgSO_4$). The basic extracts were combined, acidified (6N HCl), ether extracted and the organic solution washed with brine and dried ($MgSO_4$).

Base soluble material.

Concentration of the ethereal solution yielded 120mgm. of liquid, severely contaminated by acetic acid. Esterification with an excess of ethereal diazomethane to facilitate removal of the acetic acid, afforded an insignificant quantity of material.

Neutral Products.

Concentration of the ethereal solution yielded 450mgm. of an oil showing four spots on t.l.c. (40% ethyl acetate in petrol). Chromatography on a fine-mesh silica, using 20% ethyl acetate in petrol as eluant, furnished an initial sample of pure equatorial 1-ethoxycarbonyl-4-acetoxybicyclo-(3,2,1)-octan-8-one (64a) then mixtures of both epimers and finally pure axial epimer (64b). The structure of these epimeric acetates were assigned by comparison of their infrared spectra and g.l.c. retention times with authentic samples prepared from the corresponding alcohols using acetic anhydride in pyridine as described in Part II. Elution with more polar solvent mixtures afforded 1-ethoxycarbonyl-4-hydroxybicyclo-(3,2,1)-octan-8-one (58)

as a mixture of epimers. Concentration of the chloroform solution gave an additional quantity (100 mgm.) of these alcohols.

3-Dimethylamino-4'-methylpropiophenone hydrochloride (65)

This compound was synthesised as described by Adamson [40] in 67% yield, m.p. 160-168°, and used without purification.

2-(3'-Oxo-3'-p-tolylpropyl)-cyclopentanone (66).

Cyclopentanone (21g., 0.25 m.) and 3-dimethylamino-4'-methylpropiophenone (16g., 0.084 m.), liberated from the corresponding hydrochloride (65) in the usual manner, were stirred and refluxed at 140° for 20 mins., evolution of dimethylamine commencing at 80°. The cooled reaction mixture was neutralised with acetic acid, diluted with chloroform, washed with brine and dried ($MgSO_4$). Removal of the chloroform and excess cyclopentanone under reduced pressure furnished an oil which rapidly solidified. T.l.c. showed the presence of two compounds from which the desired diketone (66) (14.7g., 76%) was obtained by distillation using a Wood's metal bath, b.p. 160-170°/0.3 mm. The resultant solid had m.p. 71.5-73.5° (petrol). (Found C, 78.52%, H, 7.94%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1740cm.$^{-1}$ (ring ketone) and 1686cm.$^{-1}$ (aromatic ketone).

The mono-semicarbazone derivative (139) was made in the usual manner, m.p. 165-168° (acetic acid-water). (Found C, 66.92%, H, 7.02%, N, 14.67%. $C_{16}H_{21}N_3O_2$ requires C, 66.87%, H, 7.36%, N, 14.62%). $\nu_{C=O}$ 1690cm.$^{-1}$.

The impurity present in the crude reaction mixture was obtained by dissolving the product in hot ether and then cooling in ice. The solid which precipitated was recrystallised from ethanol, m.p. 139.5-141.5°. (Found C, 79.87%, H, 7.45%. $C_{25}H_{28}O_3$ requires C, 79.75%, H, 7.50%).

The infra-red spectrum (CCl_4) had absorption at 1735cm.$^{-1}$ (ϵ=338) and 1687cm.$^{-1}$ (ϵ= 752). The n.m.r. spectrum ($CDCl_3$) clearly indicated that the compound had two aromatic ketone side chains and one cyclopentanone ring. No spectral evidence could be obtained to differentiate between the 2,2-disubstituted cyclopentanone structure (67) and the 2,5-disubstituted isomer (68).

Treatment of the triketone (67) or (68) with hydrochloric acid-acetic acid.

The triketone (67) or (68) (1g.), concentrated hydrochloric acid (2 ml.) and acetic acid (6 ml.) were refluxed for 24 hrs. and worked up in the usual manner using chloroform as extracting solvent. Recovery of acidic material from the reaction mixture was negligible and the neutral fraction yielded 870 mgm. of unreacted starting material.

Attempted intramolecular Aldol condensation of the triketone (67)or (68).

The triketone (67) or (68) was refluxed for 11 hrs. with a solution of potassium hydroxide (0.6g.) in ethanol (80 ml.). On cooling a solid precipitated which had a similar infra-red spectrum and R_f on t.l.c. to starting material. Concentration of the mother liquor yielded further quantities of the unreacted triketone.

Treatment of the diketone (66) with concentrated hydrochloric acid-acetic acid.

A mixture of the diketone (66) (5g.), concentrated hydrochloric acid (10 ml.) and acetic acid (30 ml.) was refluxed for 24 hrs. and then the bulk of the solvent removed under reduced pressure, the residue

flooded with water and extracted with ether. The organic layer was extracted with 4N sodium hydroxide, washed with brine and dried ($MgSO_4$). Concentration furnished 500 mgm. of neutral material, shown by t.l.c. to consist of the starting material together with a more polar compound, believed to be the lactone (72) on the basis of its infra-red spectrum, ($\nu_{C=O}$ 1780cm.$^{-1}$). This product could be separated either by somewhat difficult recrystallisation from ethanol or more successfully by reduction of the diketone in the usual manner with sodium borohydride, followed by chromatography on silica. The lactone (72), thus obtained, was recrystallised from ethanol, m.p. 105-107°. (Found C, 78.25%, H, 8.04%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1781cm.$^{-1}$. The n.m.r. spectrum showed a doublet at 5.25τ (J=7 cps.) for the C_3 proton.

The basic extracts were acidified, extracted with ether and the organic layer washed with brine and dried ($MgSO_4$). Concentration yielded 4.1g. of an oil which rapidly solidified, m.p. 117-129°. Recrystallisation from ethanol was extremely difficult and the recovered material was coloured and of similar m.p. to the crude solid. Recrystallisation from benzene-petrol mixtures (42), however, afforded a low recovery (10-15%) of a colourless solid, which recrystallised readily from ethanol. G.l.c. analysis of the corresponding esterified material (diazomethane) showed that this was a pure acid (1% F-60 at 150°, R_t = 6.8 mins.), subsequently identified as 4-(p-tolyl)-cyclohept-3-ene carboxylic acid (73), m.p. 127-129°. (Found C, 77.98%, H, 8.05%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%. The infra-red spectrum showed absorption at 3300-2800cm.$^{-1}$ (acidic hydroxyl) and 1700cm.$^{-1}$ (carbonyl).

Esterification of a sample of the crude reaction product with diazomethane yielded an oil which showed one spot on t.l.c. but analysis by g.l.c. (3% F-60 at 150°) showed this to consist of 45% of the Δ^3 acid (73) (R_t = 6.8 mins.) and 55% of an acid subsequently shown to be 4-(p-tolyl)-cyclohept-4-ene carboxylic acid (74). Attempts to obtain a pure sample of the Δ^4 isomer by fractional crystallisation from a number of solvents failed.

Attempted lactonisation of the mixture of acids (73) and (74)

The mixture of acids (73) and (74) (1.5g.), 6N hydrochloric acid (15 ml.) and acetic acid (40 ml.) were refluxed for 14 hrs., then cooled, basified (4N NaOH) and extracted with ether. The extracts were washed with brine and dried yielding 300 mgms. of solid material. T.l.c. and the infra-red spectrum indicated that the bulk of this material was the acidic starting material together with some diketone (66) and traces of the lactone (72).

Attempted separation of 1-methoxycarbonyl-4-(p-tolyl)-cyclohept-3-ene (82) and 1-methoxycarbonyl-4-(p-tolyl)-cyclohept-4-ene (83)

A sample of the crude acidic product (700 mgm.) from hydrochloric acid-acetic acid treatment of the diketone (66) was esterified with excess ethereal diazomethane. Removal of the solvent afforded 720 mgm. of an oil which was distilled, b.p. 130-132°/0.03 mm. (Found C, 78.21%, H, 8.27%. $C_{16}H_{20}O_2$ requires C, 78.65%, H, 8.25%). $\nu_{C=O}^{CCl_4}$ 1740cm.$^{-1}$. The n.m.r. spectrum showed an olefinic proton at 4.03 τ. G.l.c. analysis (1% F-60 at 150°) indicated that the oil was a mixture of two isomeric products, (82) and (83).

Repeated distillation failed to effect a separation of these components and the apparent homogeneity of the product on t.l.c. indicated that column chromatography would also be ineffective. Preparative scale

g.l.c. using a 25 ft. 25% APL column at 240° provided a rather poor separation and the collected material was charred. Further efforts at separation were abandoned.

Attempted hydroboration of a mixture of esters (82) and (83).

The mixture of the esters (82) and (83) (2.4g.) was added to a suspension of sodium borohydride (840 mgm.) in anhydrous diglyme (12 ml.) and treated dropwise with a solution of distilled boron trifluoride etherate (5 ml.) in diglyme (6 ml.). The reaction mixture was stirred at room temperature for 1 hr., the excess hydride cautiously destroyed by the addition of water (8 ml.) and the boron complex decomposed by addition of 4N sodium hydroxide (5 ml.) followed by 30% hydrogen peroxide (6 ml.). This mixture was stirred for 1 hr. at 20° then ether was added and the organic layer washed with ferrous sulphate, brine and dried ($MgSO_4$). Concentration afforded 1.8g. of a colourless oil which exhibited hydroxyl absorption but was transparent in the carbonyl region and showed no peaks attributable to the tri-substituted double bond in the infra-red spectrum. This hydroboration of the double bond and reduction of the ester function had occurred yielding a mixture of diols.

Earlier attempts using smaller quantities of sodium borohydride and boron trifluoride etherate yielded mixtures of starting material, hydroxy esters and diols which were difficult to separate.

Oxidation of the mixture of diols.

The mixture of diols (1.8g.) formed by hydroboration of the esters

(82) and (83), was dissolved in acetone (70 ml.) and the stirred and cooled solution treated with an excess of Jones reagent [43]. The reaction mixture was stirred at room temperature overnight, poured into water (100 ml.) and extracted with ether. The ethereal solution was extracted with 4N sodium hydroxide, washed with brine and dried ($MgSO_4$), yielding 380 mgm. of an oil which partially solidified. Crystallisation from ethanol yielded a compound which had identical n.m.r. spectrum and g.l.c. retention times to the lactone (72). Efforts to obtain a pure sample by recrystallisation failed to provide sharp melting material and thus positive identification was not possible. Mechanistic considerations suggested that this was the epimer of the product product from the hydrochloric acid-acetic acid reaction.

Acidification of the basic extracts with 6N hydrochloric acid and ether extraction furnished, after drying ($MgSO_4$) and concentration 1.2g. of acidic material which was treated with excess diazomethane in the usual manner. The resultant oil was filtered through a short column of silica yielding 941 mgm. of material which showed three spots on t.l.c. Careful chromatography of the mixture on fine silica (10g.) using 15% ether in petrol as eluant, afforded 150 mgm. of 1-methoxycarbonyl-3-oxo-4-(p-tolyl)-cycloheptane(77), b.p. 174-176°/1.2 mm. (Found C, 73.55%, H, 7.77%. $C_{16}H_{20}O_3$ requires C, 73.82%, H, 7.74%). $\nu_{C=O}^{CCl_4}$ 1743cm.$^{-1}$ (ester) and 1712cm.$^{-1}$ (ketone). The n.m.r. spectrum showed the C_4 proton as a multiplet centred at 6.45 τ on which was superimposed the singlet for the carbomethoxyl protons at 6.32 τ (G.l.c., R_t = 20.6 mins. on 7% F-60/1% Z at 200°.

Elution using 20% ether in petrol yielded mixtures of the keto-ester (77) and the isomeric compound (78). 30% Ether in petrol afforded 260 mgm. of 1-methoxycarbonyl-4-(p-tolyl)-5-oxocycloheptane (78), m.p. 80-81.5° (petrol). (Found C, 73.84%,

H, 7.89%. $C_{16}H_{20}O_3$ requires C, 73.82%, H, 7.74%). $\nu_{C=O}^{CCl_4}$ 1742cm.$^{-1}$ (ester) and 1712cm.$^{-1}$ (ketone). The n.m.r. spectrum showed a multiplet centred at 6.49 τ for the proton on C_4 partially concealed by the singlet at 6.33 τ attributed to the carbomethoxyl protons. (G.l.c. R_t = 25.4 mins. on 7% F-60/1% Z at 200°).

More polar solvent mixtures yielded a further crystalline material which showed one spot on t.l.c. and which appeared to be homogeneous on g.l.c. This was tentatively assigned the structure (79) or (80) on the basis of spectral data. $\nu_{C=O}^{CCl_4}$ 1744cm.$^{-1}$ (ester) and 1690cm.$^{-1}$ (ketone). The n.m.r. spectrum showed peaks for the methylene protons adjacent to the aromatic ketone (7.1 τ, triplet, J=7 cps., 2H), the protons on the two carbomethoxyl groups (6.34 τ, singlet, 6H), the phenyl protons ortho to the methyl group (2.77 τ, doublet, 2H) and the phenyl protons adjacent to the ketone function (2.14 τ, doublet, 2H).

Identical Jones oxidation of 1g. of the mixture of the unsaturated esters (82) and (83), yielded 710 mgm. of acidic material which was esterified with diazomethane affording a product with identical infra-red spectrum and g.l.c. retention time to the diester isolated above.

Conversion of the lactone (72) to 1-methoxycarbonyl-3-oxo-4-(p-tolyl)-cycloheptane (77)

A solution of the lactone (72) (100 mgm.) in dry tetrahydrofuran (1 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (2 mgm.) in dry tetrahydrofuran (2 ml.) and the

mixture refluxed for 10 hrs. Saturated ammonium sulphate was added carefully, followed by dilute hydrochloric acid until the lithium salts dissolved. Extraction with ethyl acetate, washing and drying of the organic solution afforded material which showed hydroxyl absorption but which was transparent in the carbonyl region of the infra-red spectrum. Treatment of this product in acetone, with excess Jones reagent [43] for 20 hrs. afforded acidic material which was esterified with diazomethane to yield the liquid keto-ester (77). This compound had identical infra-red spectrum, t.l.c. and g.l.c. (R_t = 20.6 mins. on 7% E-60/1% Z at 200°) to the less polar keto-ester produced by hydroboration-oxidation of the mixture of esters (82) and (83).

Hydroboration and oxidation of the ester (82).

The acid (73), obtained by recrystallisation of the crude acidic product from hydrochloric acid-acetic acid treatment of the diketone (66), was converted to the methyl ester (82) by diazomethane. This sample (1.2g.) was hydroborated in diglyme using sodium borohydride and boron trifluoride etherate in the manner described above for the mixture of esters, except that the reaction mixture was stirred for 1.5 hrs. The excess hydride was destroyed by water and the organo-borane decomposed by the addition of 4N sodium hydroxide, then 30% hydrogen peroxide and the mixture stirred at 40° for 1 hr. The usual work up furnished a mixture of diols, (no carbonyl or double bond absorption in the infra-red spectrum), which was dissolved in acetone (50 ml.), cooled to 0° and the stirred solution treated with an excess of Jones reagent [43]. The reaction mixture was stirred at room temperature overnight and worked up as described above, yielding an acidic fraction which was

esterified with diazomethane to yield 720 mgm. of oil. G.l.c. analysis (7% F-60/1% Z at 200°) showed that the major component was 1-methoxycarbonyl-3-oxo-4-(p-tolyl)-cycloheptane (77), (R_t = 20.6 mins.) together with the acyclic keto-diester (79) or (80) and a significant quantity of an unidentified product. Chromatography on silica (10g.) using 15% ether in petrol as eluant, removed this by-product and 20% and 30% ether in petrol afforded the pure keto-ester (77).

The neutral fraction yielded a crystalline solid which was recrystallised from ethanol to yield a compound with comparable infra-red spectrum and identical g.l.c. retention times to the lactone (72).

2-p-Tolylbicyclo-(3.2.1)-oct-2-en-8-one (84).

p-Toluene sulphonic acid (4g.) and anhydrous benzene (200 ml.) were refluxed for 1.5 hrs. with a water separator. The source of heat was removed, the water separator drained and refilled with anhydrous benzene and the diketone (66) (10g.), dissolved in anhydrous benzene, added to the reaction mixture. The reflux was restarted and continued for 5 hrs., when the reaction mixture was cooled and neutralised with anhydrous potassium carbonate. After standing overnight the solid was filtered and washed with hot benzene and the filtrate concentrated to yield an oil which rapidly solidified. Recrystallisation from minimal quantities of ethanol yielded the desired product (84) (7.5g., 81%), m.p. 66-69.5°. (Found C, 85.07%, H, 7.51%. $C_{15}H_{16}O$ requires C, 84.87%, H, 7.60%). The infra-red spectrum (CCl_4) showed absorption

at 1757cm.$^{-1}$ and the n.m.r. spectrum had a complex region at 7.1-7.4 τ (3H) attributed to the protons on C_1 and C_4 together with a peak at 4.21 τ (triplet, J=3.75 cps., 1H), assigned to the olefinic proton at C_3. The corresponding semicarbazone derivative was recrystallised from aqueous acetic acid, m.p. 176-183°. (Found C, 71.22%, H, 6.88%, N, 15.50%. $C_{16}H_{19}N_3O$ requires C, 71.34%, H, 7.11%, N, 15.60%).

Treatment of the bicyclo-ketone (84) with hydrochloric acid-acetic acid.

The bicyclo-ketone (84) (2g.), concentrated hydrochloric acid (4 ml.) and acetic acid (10 ml.) were refluxed for 24 hrs. and worked up as described for the diketone (66). The neutral fraction yielded 610 mgm. of solid shown by t.l.c. to consist of the lactone (72) and a trace of the diketone (66). Recrystallisation from ethanol furnished pure lactone, m.p. 105-108°, identical in all respects to the sample obtained from similar treatment of the diketone. The acidic fraction yielded 1.4g. of solid with identical infra-red spectrum to the product obtained from reaction with the diketone. G.l.c. analysis (1% F-60 at 150°) of a sample of the unpurified reaction product, esterified by diazomethane, verified a mixture consisting of 45% of the cycloheptene acid (73) and 55% of the isomer (74).

3-Dimethylamino-4'-bromopropiophenone hydrochloride (86).

This material was synthesised as described by Knott [44] in 61% yield m.p. 190-192°. It was used without purification.

2-(3'-p-Bromophenyl-3'-oxopropyl)-cyclopentanone (85).

3-Dimethylamino-4'-bromopiophenone hydrochloride (86) was basified

and extracted with ether yielding the corresponding β-amino-ketone as a solid, on concentration.

3-Dimethylamino-4'-bromopropiophenone (20.2g., 0.078 m.) and cyclopentanone (20g., 0.238 m.) were stirred and refluxed at 140° for 20 mins., then cooled and neutralised with acetic acid. Addition of ether caused precipitation of a solid which was filtered off. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding an oil which solidified. T.l.c. indicated that the filtrate and the ether soluble material were both mixtures of two compounds which could not be purified by crystallisation. Combination and distillation, b.p. 166-176°/0.4 mm., yielded pure diketone (85) (14.4g., 62.5%), m.p. 69.5-72° (petrol). (Found C, 56.90%, H, 5.15%, Br, 27.23%. $C_{14}H_{15}O_2Br$ requires C, 56.94%, H, 5.12%, Br, 27.09%).

Treatment of the diketone (85) with concentrated hydrochloric acid-acetic acid.

The diketone (85) (4.1g.) was refluxed for 24 hrs. with concentrated hydrochloric acid (8 ml.) and acetic acid (25 ml.) and worked up in the manner described for the analogous reaction on the diketone (66), using benzene as extraction solvent. T.l.c. showed the neutral fraction to consist of the starting material and a more polar compound showing absorption in the infra-red spectrum at 1780cm.$^{-1}$. No separation was attempted.

Concentration of the acidic fraction yielded 3.3g. of a white solid which recrystallised from ethanol to give 2.8g., (67%) shown by

g.l.c. analysis of an esterified sample (diazomethane) to consist of 45% of 4-(p-bromophenyl)-cyclohept-3-ene carboxylic acid (87), and 55% of 4-(p-bromophenyl)-cyclohept-4-ene carboxylic acid (88), (1% F-60 at 150°, R_t = 16.25 mins. and 18.0 mins. respectively), the structures being assigned by analogy with the p-tolyl substituted cycloheptene acids.

Recrystallisation of the crude acidic product from benzene-petrol mixtures furnished a pure sample of 4-(p-bromophenyl)-cyclohept-3-ene carboxylic acid (87), m.p. 155-157.5°. (Found C, 57.23%, H, 5.17%, Br, 27.16%. $C_{14}H_{15}O_2Br$ requires C, 56.94%, H, 5.12%, Br, 27.09%). The infra-red spectrum showed absorption at 3300-2800 cm.$^{-1}$(acidic hydroxyl) and 1700cm.$^{-1}$ (carboxyl). The n.m.r. spectrum showed a triplet at 4.0 τ for the olefinic proton at C_3. The purity of this material was established by g.l.c. analysis of a sample esterified by diazomethane (1% F-60 at 150°, R_t = 16.25 mins.).

2-p-Bromophenylbicyclo-(3.2.1)-oct-2-en-8-one (89).

Using exactly the same procedure as for the preparation of the corresponding p-tolylbicyclo-ketone (84), p-toluene sulphonic acid (2g.) and the diketone (85) (3.11g.) furnished 2.95g. of crude reaction mixture as a solid, consisting of the desired product and unreacted starting material. Purification by re-crystallisation from ethanol or benzene/petrol mixtures failed. Filtration through a short column of silica using benzene as eluant yielded 2g., (68.5%), of the ketone (89), m.p. 75.5-76.5°

(ethanol). (Found C, 60.94%, H, 4.63%. $C_{14}H_{15}OBr$ requires C, 60.65% H, 4.69%). $\nu_{C=O}^{CCl_4}$ 1762cm.$^{-1}$. The n.m.r. spectrum had a broad, poorly resolved band at 7.1-7.4 τ (3H) assigned to the protons on C_1 and C_4 and a peak at 4.15 τ(triplet, J=3.75 cps., 1H) assigned to the olefinic proton at C_3.

Treatment of the bicyclo-ketone (89) with concentrated hydrochloric acid-acetic acid.

The bicyclo-ketone (89) (300 mgm.), concentrated hydrochloric acid (1 ml.) and acetic acid (2 ml.) were refluxed for 24 hrs. and worked up in the usual manner yielding 220 mgm. of acidic material. A sample, esterified by diazomethane, was subjected to g.l.c. analysis which showed the expected mixture of 45% 4-(p-bromophenyl)-cyclohept-3-ene carboxylic acid (87) and 55% 4-(p-bromophenyl)-cyclohept-4-ene carboxylic acid (88). (1% F-60 at 150°, R_t = 16.25 and 18.0 mins. respectively).

3-Dimethylamino-4'-methoxypropiophenone hydrochloride (90)

This compound was prepared using the general procedure of Maxwell [45] yielding 80% after recrystallisation from ethanol, m.p. 180-181° [66].

2-(3'-p-Methoxyphenyl-3'-oxopropyl)-cyclopentanone (91).

3-Dimethylamino-4'-methoxypropiophenone was obtained from the corresponding hydrochloride (90) in the usual manner by basification and ether extraction.

The β-aminoketone (20g., 0.08 m.) and cyclopentanone (20g., 0.24 m.) were stirred and refluxed at 140° for 30 mins. The cooled reaction mixture was neutralised with acetic acid, diluted with chloroform

washed with brine and dried ($MgSO_4$), removal of the solvent and excess cyclopentanone yielding a solid composed of two components (t.l.c.). Distillation, b.p. 196-198°/0.5 mm., furnished the pure diketone (91), (18.0g., 76%), m.p. 78-79.5° (ethanol). (Found C, 73.33%, H, 7.03%. $C_{15}H_{18}O_3$ requires C, 73.14%, H, 7.32%). $\nu_{C=O}^{CCl_4}$ 1740cm.$^{-1}$ and 1682cm.$^{-1}$.

Treatment of the diketone (91) with concentrated hydrochloric acid-acetic acid.

The diketone (91) (5g.) was refluxed with concentrated hydrochloric acid (10 ml.) and acetic acid (30 ml.) for 24 hrs. and worked up in a similar manner to the p-tolyl diketone (66) with the exception that the basic extracts were acidified and the solid acidic product filtered, yielding 4.4g., (88%). A sample of this crude product was esterified (diazomethane) for g.l.c. analysis which showed the existence of a mixture of 45% 4-(p-methoxyphenyl)-cyclohept-3-ene carboxylic acid (93) and 55% 4-(p-methoxyphenyl)-cyclohept-4-ene carboxylic acid (94), (1% F-60 at 150°, R_t = 14.5 and 15.75 mins. respectively), the structures being assigned by comparison of the g.l.c. retention times with those of the related p-tolylcycloheptene acids. Recrystallisation of the crude product from ethanol was not successful but two crystallisations from benzene-petrol mixtures furnished material which was readily recrystallised from ethanol. This treatment afforded an analytical sample of 4-(p-methoxyphenyl)-cyclohept-4-ene carboxylic acid (94), m.p. 137-139° (Found C, 72.80%, H, 7.18%. $C_{15}H_{18}O_3$ requires C, 73.14%, H, 7.32%) The infra-red spectrum showed absorption at 3300-2800cm.$^{-1}$ (acidic hydroxyl) and 1700cm.$^{-1}$ (carboxyl). The n.m.r. spectrum ($CDCl_3$) showed the olefinic proton at C_5 as a triplet at 3.92 τ. A sample was esterified (diazomethane) for g.l.c. analysis (1% F-60 at 150° R_t = 15.75 mins.).

The neutral fraction, consisting of 300 mgm. of oil, was shown to consist of unreacted diketone (91) and lactone (92) by t.l.c. and the infra-red spectrum, $\nu_{C=O}$ 1780cm.$^{-1}$, 1740cm.$^{-1}$ and 1680cm.$^{-1}$.

3-Dimethylamino-4'-nitropropiophenone hydrochloride (96)

This compound was prepared using the method of Maxwell [45], yielding 65.7% of the desired hydrochloride, m.p. 182-187° [67]. It was used without purification.

Attempted preparation of 2-(3'-p-nitrophenyl-3'-oxopropyl)-cyclopentanone (95)

The hydrochloride (96) was dissolved in hot water, then cooled in ice and basified with 4N sodium hydroxide. Ether extraction furnished a red oil after washing with brine, drying and concentration. This material showed the characteristic dimethylamino group absorptions [46] at 2840, 2800 and 2750cm.$^{-1}$ in the infra-red spectrum, and was assumed to be 3-dimethylamino-4'-nitropropiophenone. The β-amino-ketone (15g., 0.068 m.) and cyclopentanone (17.1g., 0.20 m.) were stirred and refluxed for 20 mins., evolution of dimethylamine commencing at 80°. The cooled reaction mixture was neutralised with acetic acid, diluted with ether, washed with water and dried ($MgSO_4$). Removal of the ether and excess cyclopentanone furnished a dark oil which showed signs of solidifying but efforts to crystallise it failed. Chromatographic filtration through silica provided material which formed an amorphous solid on trituration with petrol. Crystallisation from ethyl acetate gave a low recovery of a solid mixture which resisted further purification. The infra-red spectrum exhibited absorption at 1740cm.$^{-1}$ and 1690cm.$^{-1}$, the latter being considerably more intense. This suggested that the

mixture consisted largely of the triketone (99) or (100), together with some of the desired diketone (95). This material was used for further reaction (see below), without purification since distillation yielded a dark oil which had obviously decomposed.

Repetition of this preparation was largely unsuccessful due to unsatisfactory liberation of the free base from the hydrochloride (96). It is known that the Mannich bases of nitro-acetophenones are not stable to base [47, 68]. A number of alternative methods of liberation using milder basic conditions were also largely unsuccessful.

The use of dimethylaminomethylcyclopentanone and p-nitroacetophenone in a molar ratio of 1:3 at 100° for 2.5 hrs., furnished a dark viscous oil which crystallised on standing. The excess solid p-nitroacetophenone could not, however, be removed either by crystallisation or distillation, and this approach was abandoned.

Treatment of the crude mixture of (95) and the triketone (99) or (100) with concentrated hydrochloric acid in acetic acid.

The mixture of (95) and (99) or (100), (1g.) was refluxed for 24 hrs. with concentrated hydrochloric acid (2 ml.) and acetic acid (6 ml.) The usual work up using chloroform furnished an acidic fraction (50 mgm.) consisting of a gum, contaminated with acetic acid, which was not investigated. The neutral material consisted of ether soluble and insoluble material. The small amount of the former exhibited two spots on t.l.c. and had absorption of equal intensity at 1740cm.$^{-1}$ and 1690cm.$^{-1}$ in the infra-red spectrum. This apparently consisted mainly of unreacted diketone (95) together with some triketone.

The ether insoluble material was unreacted triketone (99) or (100) (t.l.c. and i.r.).

2-Methyl-3-dimethylaminopropiophenone hydrochloride (105).

This compound was prepared as described by Knott [44] in 79% yield, m.p. 137-139°, and used without purification.

2-(2'-Methyl-3'-oxo-3'-phenylpropyl)-cyclopentanone (106).

Basification of an aqueous solution of the hydrochloride (105) followed by ether extraction and drying ($MgSO_4$), yielded 2-methyl-3-dimethylaminopropiophenone.

This β-aminoketone (31.7g., 0.16m.) and cyclopentanone (40g., 0.48 m.) were stirred and refluxed at 140° for 20 mins., then cooled, neutralised with acetic acid and diluted with ether. The solution was washed with brine, dried ($MgSO_4$) and the ether and excess cyclopentanone distilled leaving 23.6g. of residual oil. Distillation resulted in two fractions, the lower boiling showing five spots on t.l.c., and the main fraction, b.p. 130-140°/0.25 mm., (17.98g., 50%), which showed two spots attributed to the diastereoisomeric forms of the desired diketone (106). A sample of the main fraction was redistilled, b.p. 125-127°/0.15 mm. (Found C, 77.76%, H, 8.18%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1741cm.$^{-1}$, (cyclopentanone) and 1686cm.$^{-1}$ (aromatic ketone). The n.m.r. spectrum had a broad multiplet centred at 6.2 τ for the proton on C_2 and two overlapping doublets (J=7 cps.) centred at 8.83 τ and 8.87 τ for the methyl group.

Treatment of the diketone (106) with concentrated hydrochloric acid-acetic acid

The diketone (106) (1g.), concentrated hydrochloric acid (2 ml.) and

acetic acid (5 ml.) were mixed and refluxed for 8 days. The usual work up furnished a neutral fraction (988 mgm.) which showed three spots on t.l.c., one corresponding to the starting material. Chromatography on fine silica (10g.) using 50% benzene in petrol as eluting solvent, resulted in a partial separation. The least polar material, 2-phenyl-3-methylbicyclo-(3,2,1)-oct-2-en-8-one (107) was obtained in a pure state in low yield, b.p. 100-105°/0.2 mm. (Found C, 84.26%, H, 7.80%. $C_{15}H_{16}O$ requires C, 84.87%, H, 7.60%). $\nu_{C=O}^{CCl_4}$ 1755cm.$^{-1}$. The n.m.r. spectrum showed no olefinic proton, a multiplet, (1H) at 7.16 τ for the proton on C_1, a multiplet, (2H) at 7.43 τ for the protons on C_4 and a singlet, (3H) for the methyl group at 8.42 τ.

Subsequent fractions contained the diketone and then mixtures with a compound which absorbed at 1780cm.$^{-1}$ in the infra-red spectrum. To facilitate chromatographic purification of this major lactonic component, the final fractions were combined and treated with sodium borohydride in methanol. The product was chromatographed on silica and elution with benzene furnished 3-hydroxy-3-methyl-4-phenyl cycloheptane carboxylic acid lactone (108) as a solid, m.p. 90-92° (petrol). (Found C, 78.23%, H, 7.83%. $C_{15}H_{16}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1778cm.$^{-1}$. The n.m.r. spectrum showed peaks at 7.3-7.5 τ (multiplet, 2H) for the protons on C_1 and C_4, and at 8.82τ (singlet, 3H) for the methyl protons.

Reflux of the reaction mixture for the usual 24 hrs. produced very little reaction (infra-red spectrum), and extension to three days also resulted in incomplete reaction.

In an early attempt to obtain the lactone (108) in a pure state the crude reaction product was reduced with sodium borohydride prior to chromatography. As above, this simplified separation of the diketone and lactone, but the reduction product of the bicyclo-ketone (107) could not be chromatographed apart from the lactone. This lactone can be obtained more readily by reaction of the diketone with p-toluene sulphonic acid and ethylene glycol, described below.

3-Dimethylaminopropiophenone hydrochloride (109)

This compound was prepared by the method of Maxwell [45] in 82% yield and used without purification.

2-(3'-Oxo-3'-phenylpropyl)-5-methylcyclopentanone (103)

3-Dimethylaminopropiophenone (3.5g., 0.02 m.), liberated from the corresponding hydrochloride (109) in the usual manner, was mixed with 2-methylcyclopentanone (5.8g., 0.06 m.) and the stirred solution refluxed at 140° for 30 mins. The cooled reaction mixture was neutralised with acetic acid, diluted with ether and washed with brine. After drying and concentration, the excess 2-methylcyclopentanone was distilled on a water bath, b.p. 30°/10 mm. and the residue crystallised from benzene/petrol mixtures. The solid material, however, showed two spots on t.l.c. (30% ethyl acetate in petrol) and consequently was subjected to distillation, b.p. 130-140°/0.05 mm., yielding diketone (103) 3.5g., (76%). Recrystallisation from ethanol afforded a sample, m.p. 68-70°. (Found C, 78.21%, H, 8.03%,

$C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1739cm.$^{-1}$ and 1692cm.$^{-1}$. The n.m.r. spectrum showed the methyl protons as a doublet at 8.93 τ (J=7 cps.) and the methylene protons adjacent to the aromatic ketone function as a triplet at 6.91 τ(J=7 cps.).

G.l.c. analysis (10% APL at 200°) of the distilled product showed that before crystallisation, the 2,5-disubstituted compound (103) (R_t = 22.8 mins.) contained traces of the isomeric diketone (114) (R_t = 20.2 mins.).

Treatment of the diketone (103) with concentrated hydrochloric acid-acetic acid

A mixture of the diketone (103) (830 mgm.), concentrated hydrochloric acid (2 ml.) and acetic acid (5 ml.) was refluxed for 24 hrs. in the usual manner, yielding 80 mgm. of acidic material and 740 mgm. of unreacted starting material. The acidic fraction was distilled and a sample esterified (diazomethane) for g.l.c. analysis which showed the presence of a major component (>80%) together with two impurities. Redistillation afforded 4-phenyl-5-methylcyclohept-4-ene carboxylic acid (104), b.p. 150-152°/0.25 mm. (Found C, 78.29%, H, 7.96%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). The infra-red spectrum showed absorption at 3300-2800cm.$^{-1}$ (acidic hydroxyl) and 1700cm.$^{-1}$ (carboxyl). The n.m.r. spectrum showed no olefinic proton but a vinylic methyl signal at 8.33 τ (3H, singlet).

Attempted preparation of 2-methyl-2-(3'-oxo-3'-phenylpropyl)-cyclopentanone (114)

(a) The method of Robinson[22]

A solution of 2-methylcyclopentanone (1.6g.) in anhydrous ether

(6 ml.) was added dropwise to a stirred suspension of sodamide (0.33g.) in anhydrous ether (10 ml.) and the mixture stirred for 3 hrs. at room temperature, under nitrogen. 3-Dimethylaminopropiophenone methiodide (3.0g.) was then added in small lots over 1 hr. and the suspension stirred for a further 17 hrs. at room temperature. The reaction mixture was then neutralised with 6N hydrochloric acid, diluted with water and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and concentrated, yielding a dark residue which was dissolved in benzene and filtered through a short column of silica (30g.). This treatment failed to decolourise the product but some of the resultant gum solidified and this material was washed with ether, distilled and recrystallised with difficulty from ethanol. The infra-red spectrum (CCl_4) showed absorption at 1777cm.$^{-1}$ and this compound was identical to a sample of the lactone (115) (t.l.c., g.l.c., n.m.r.) subsequently obtained from the diketone (114).

(b) <u>The method of Ross and Levine [34].</u>

3-Dimethylaminopropiophenone hydrochloride (109) was subjected to steam distillation and the distillate extracted with ether and dried ($MgSO_4$). Removal of the ether under reduced pressure on a steam bath yielded a hard polymeric glass. Concentration, however, by rotary evaporation afforded a 40% yield of phenyl vinyl ketone.

An ethereal solution of 2-methylcyclopentanone (3.92g., 0.04m.) was treated with a catalytic quantity of ethanolic potassium hydroxide followed by phenyl vinyl ketone (3.0g., 0.022m.) in

exactly the manner described for the preparation of the aliphatic analogue (42). Concentration and removal of the excess 2-methylcyclopentanone furnished 4.4g. of an oil which was distilled, b.p. 121-135°/0.01 mm. The distillate solidified on standing and was recrystallised to yield 2.04g. of the desired diketone (114), m.p. 40-42° (ethanol and petrol). (Found C, 77.87%, H, 7.78%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). $\nu_{C=O}^{CCl_4}$ 1736cm.$^{-1}$ and 1689cm.$^{-1}$. The n.m.r. spectrum showed a singlet at 8.98 τ(3H) for the methyl group.

G.l.c. analysis (10% APL. at 200°) of the distilled product showed that it consisted only of 2,2-disubstituted compound (114) (R_t = 20.2 mins.).

Treatment of the diketone (114) with concentrated hydrochloric acid-acetic acid.

The diketone (114) (500 mgm.), concentrated hydrochloric acid (1 ml.) and acetic acid (2.5 ml.) were mixed and refluxed for 24 hrs. The usual work up provided a neutral fraction of 320 mgm. which consisted of two compounds (t.l.c., g.l.c.). Recrystallisation afforded the less polar compound, identified as the lactone (115), m.p. 140-141.5°. (Found C, 78.14%, H, 8.05%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.86%). $\nu_{C=O}^{CCl_4}$ 1777cm.$^{-1}$. The n.m.r. spectrum showed a singlet for the methyl protons at 8.74 τ (3H), multiplets centred at 8.16 τ(6H), 7.73 τ(2H, C_2) and 7.22 τ (1H, C_4) and a subsplit doublet at 5.17 τ(1H, J=7 cps., C_3). This product was identical to that obtained by reaction of 2-methylcyclopentanone and phenyl vinyl ketone with sodamide.

The acidic material (137 mgm.), obtained from the reaction as an oil, was shown by g.l.c. analysis (10% APL. at 200°) of an esterified sample (diazomethane) to be a mixture of two compounds (R_t = 14.75 and 18.25 mins.). These were assigned the structures (116) and (117) by analogy with the p-tolylcycloheptene acids (73) and (74). The infra-red spectrum showed absorption at 3500-2800 $cm.^{-1}$ and 1700$cm.^{-1}$. The n.m.r. spectrum of this mixture had a singlet at 8.73 τ (3H) for the methyl protons and a triplet at 4.1 τ for the olefinic proton.

Hydroboration and oxidation of the mixture of esters (122) and (123)

The mixture of the esters (122) and (123) (2.4g.) was hydroborated in an identical manner to the p-tolylcycloheptene esters (82) and (83), yielding 1.5g. of a mixture of diols. This was oxidised with Jones reagent [43], as described previously, to yield 725 mgm. of acidic material, which was esterified with diazomethane. The resulting oil (653 mgm.) was chromatographed on fine silica (10g.). The fractions eluted with 40%, 45% and 50% ether in petrol were combined and rechromatographed. This furnished initially, a pure sample of 1-methoxycarbonyl-3-oxo-4-phenylcycloheptane (119), b.p. 136-138°/0.02 mm. (Found C, 72.57%, H, 7.43%. $C_{15}H_{18}O_3$ requires C, 73.15%, H, 7.37%) $\nu_{C=O}^{CCl_4}$ 1740$cm.^{-1}$ (ester) and 1711$cm.^{-1}$ (ketone). The n.m.r. spectrum showed the C_4 proton at 6.4 τ (1H, multiplet) on which was superimposed the methyl ester protons at 6.35 τ (3H, singlet). (G.l.c., R_t = 18.1 mins. on 7% F-60/1% Z at 200°). Further elution yielded 1-methoxycarbonyl-4-phenyl-5-oxocycloheptene (120), m.p. 72-73° (petrol). (Found C, 73.02%, H, 6.97%.

$C_{15}H_{18}O_3$ requires C, 73.15%, H, 7.37%). $\nu_{C=O}^{CCl_4}$ 1739cm.$^{-1}$ (ester) and 1710cm.$^{-1}$ (ketone). The n.m.r. spectrum showed the C_4 proton at 6.4 τ (1H, multiplet), partially concealed by the ester protons at 6.36 τ (3H, singlet). (G.l.c., R_t = 20.2 mins. on 7% F-60/1% Z at 200°).

Conversion of the lactone (121) to 1-methoxycarbonyl-3-oxo-4-phenyl-cycloheptane (119)

A solution of the lactone (121) [4] (100 mgm.) in dry tetrahydrofuran (1 ml.) was added to a stirred suspension of lithium aluminium hydride (2 mgm.) in dry tetrahydrofuran (2 ml.) and the mixture refluxed for 7.5 hrs. The work up described for reduction of the lactone (72), yielded an oil which showed hydroxyl but no carbonyl absorption in the infra-red spectrum. Treatment of this diol in acetone for 20 hrs. with an excess of Jones reagent [43] afforded an acidic fraction which was esterified with diazomethane to yield the liquid keto-ester (119) which had identical infra-red spectrum, t.l.c. and g.l.c. (7% F-60/1% Z at 200°, R_t = 18.1 mins.) to the liquid, less polar, keto-ester produced by the hydroboration procedure described above.

Attempted epoxidation of the mixture of esters (122) and (123).

A mixture of the esters (122) and 123) (1.8g.), dissolved in chloroform (60 ml.), was cooled to 0° and the stirred solution treated dropwise with m-chloroperbenzoic acid (1.8g.) in chloroform (20 ml.). The reaction mixture was stirred at room temperature for 1.5 hrs.,

then treated slowly with a 10% aqueous solution of sodium sulphite. The organic layer was separated, washed with sodium sulphite, sodium bicarbonate, brine and dried ($MgSO_4$). Concentration gave 2g. of an oil which showed absorption at 3500 $cm.^{-1}$ (hydroxyl) and 1730$cm.^{-1}$ (ester) in the infra-red spectrum and which had a complex t.l.c. pattern. The oil was distilled into three fractions; (a) b.p. 125-135°/0.03 mm., (b) 135-140°/0.03 mm. and (c) 140-160°/0.03 mm.

G.l.c. analysis of (a) showed that it contained the major product in 80% purity. The infra-red spectrum showed no hydroxyl absorption. Fraction (b) was a mixture of this compound and the keto-esters (119) and 120) and (c) consisted of these compounds and more polar materials. This fraction showed considerable hydroxyl absorption in the infra-red spectrum. Longer reaction times increased the amount of the higher boiling material at the expense of the lower boiling fraction. Thus it appeared that fraction (a) was largely a mixture of the epoxides (140) and (141).

The n.m.r. spectrum of fraction (a) confirmed the epoxide structure. The proton on the epoxide ring appeared at 7.15 τ (1H, multiplet), the ester protons at 6.37 τ (3H, singlet) and the aromatic protons at 2.77 τ (5H, singlet). No further attempts were made to characterise this mixture. Fractions (a) and (b) were combined for further reaction.

Attempted rearrangement of the product from the epoxidation of the esters (122) and (123).

(a) Boron trifluoride etherate.

Treatment of a solution of the distilled material from the previous reaction (500 mgm.) in benzene (5 ml.) with boron trifluoride etherate (3 ml.) at reflux for 17 hrs. was shown by g.l.c. anaylsis to have induced no reaction.

(b) Sulphuric acid.

The crude product from epoxidation of the esters (122) and (123) (5.8g.) was cooled in ice, stirred and treated over 20 mins. with concentrated sulphuric acid (58 ml.). The resultant solution was stirred at 0° for 105 mins., poured onto ice and water and extracted with ether. The extracts were washed with base (sat^{d}. $NaHCO_3$), brine and dried ($MgSO_4$), yielding 1.77g. of oil on concentration. G.l.c. analysis of the oil (7% F-60/1% Z at 200°) showed the predominant product was the keto-ester (119), (R_t = 18.1 mins.) and that a small quantity of the isomer (120) (R_t = 20.2 mins.) and a number of impurities were also present. An improved recovery was obtained by modifying the procedure in the following manner.

The crude epoxidation product (4.5g.) was dissolved in methanol (5 ml.) and the cooled and stirred solution treated dropwise with concentrated sulphuric acid (10 ml.) and the mixture stirred at room temperature. Aliquots removed after 5 and 10 hrs. were shown by g.l.c. analysis to contain increasing quantities of rearranged product but considerable starting material remained. After 27 hrs. the reaction mixture was poured onto ice and water and the aqueous solution stirred for 2 hrs., prior to extraction with ether. The extracts were washed with base (sat^{d}. $NaHCO_3$), brine and dried ($MgSO_4$), yielding 3.7g. of a dark coloured oil on concentration. This was distilled to yield 1.3g. of almost colourless oil, b.p. 125°/0.01 mm., which consisted mainly of the 3-keto-ester (119). A small quantity of the 5-keto-ester (120) and some unreacted starting material were also detectable by t.l.c. and g.l.c. analysis. Careful chroma-

tography on fine silica separated the rearranged products from starting material and rechromatography furnished pure 1-methoxycarbonyl-3-oxo-4-phenylcycloheptane (119) and a small quantity (100 mgm.) of 1-methoxycarbonyl-4-phenyl-5-oxocycloheptane (120), both identical with samples obtained from the hydroboration-oxidation sequence (t.l.c., g.l.c., infra-red spectrum).

Action of methyl magnesium iodide on 1-methoxycarbonyl-3-oxo-4-phenylcycloheptane (119).

A stirred solution of the keto-ester (119) (66 mgm.) in anhydrous ether (5 ml.), under nitrogen, was treated dropwise with an ethereal solution of methyl magnesium iodide [from magnesium (29 mgm.) and methyl iodide (220 mgm.) in anhydrous ether (2 ml.)] and then diluted with a further quantity of ether (5 ml.). The mixture was stirred and refluxed in a water bath for 45 mins., then cooled and treated with 6N hydrochloric acid (12 ml.). The two phase system was refluxed with vigorous stirring overnight, the ether rapidly evaporating. The cooled reaction mixture was extracted with ether and the organic solution extracted with 4N sodium hydroxide, washed with brine and dried ($MgSO_4$). Removal of the solvent yielded 39 mgm. of an oil which rapidly solidified. G.l.c. analysis showed the product consisted almost entirely of 3-hydroxy-3-methyl-4-phenylcycloheptane carboxylic acid lactone (108). Recrystallisation from benzene/petrol mixtures afforded a pure sample, m.p. 90-92°, identical in all respects to meterial prepared from the diketone (106).

The basic extracts were acidified (6N HCl), extracted with ether and the organic solution washed with brine and dried ($MgSO_4$). Concentration yielded 18 mgm. of acidic material which was esterified with diazomethane. G.l.c. analysis showed that this was identical to the starting compound (119).

Action of methyl magnesium iodide on 1-methoxycarbonyl-4-phenyl 5-oxocycloheptane

A stirred, ethereal solution of the keto-ester (120) (60 mgm.) was reacted with methyl magnesium iodide at reflux for 2.5 hrs., hydrolysed and worked up as described above for the isomeric compound, yielding 45 mgm. of neutral and 20 mgm. of acidic material. The neutral material was shown by g.l.c. analysis to be a complex mixture consisting mainly of two unidentified products. A sample of the acidic fraction was esterified with diazomethane to yield an oil shown by g.l.c. analysis to consist virtually entirely of the methyl ester of 4-phenyl-5-methyl-cyclohept-4-ene carboxylic acid (104). This acid had an identical infra-red spectrum to that of a sample prepared from the diketone (103) by reaction with hydrochloric and acetic acids.

Reduction of 2-p-tolylbicyclo-(3,2,1)-oct-2-en-8-one (84).

(a) Sodium borohydride/methanol

The ketone (84) (5.0g., 0.024 m.) dissolved in methanol (80 ml.) was treated with sodium borohydride (1.02g., 0.027 m).

and allowed to stand overnight at room temperature. The reaction mixture was acidified with 6N hydrochloric acid, diluted with water and ether extracted. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated to yield 5.05 g. of an oil which showed one spot on t.l.c. Analysis by g.l.c. (10% PEG A at 190°, R_t = 19.7 mins.) indicated that one pure epimer of 2-p-tolylbicyclo-(3,2,1)-oct-2-en-8-ol (124) was the only product formed. Distillation gave 4.3g., (86%), of the syn-isomer of the alcohol (124a) as an extremely viscous oil, b.p. 110°/0.06 mm., which resisted all efforts at crystallisation. (Found C, 83.97%, H, 8.39%. $C_{15}H_{18}O$ requires C, 84.07%, H, 8.47%). The infra-red spectrum (CCl_4) showed three absorption bands in the hydroxyl region, at 3626cm.$^{-1}$ (free hydroxyl), 3587cm.$^{-1}$ (intramolecularly bonded hydroxyl) and 3490cm.$^{-1}$ (intermolecularly bonded hydroxyl)[57] The n.m.r. spectrum showed peaks at 5.39 τ (triplet, J=4 cps., 1H) and 4.15 τ (multiplet, 1H) assigned to the protons at C_8 and C_3 respectively.

(b) Sodium borohydride/pyridine.

The ketone (84) (1.9g., 0.009 m.) and sodium borohydride (0.53g., 0.014 m.) in anhydrous pyridine (60 ml.) were reacted using the procedure described by Foote and Woodward [55], yielding 1.775g. of an oil which exhibited hydroxyl absorption in the infra-red spectrum and was transparent in the carbonyl region. T.l.c. showed the presence of two compounds, the less polar having similar R_f to that of the syn-isomer of the alcohol (124a). G.l.c. analysis of the mixture (10% PEG A at 190°)

confirmed that it consisted of 65% of the syn-isomer of 2-p-tolylbicyclo-(3,2,1)-oct-2-en-8-ol (124a) (R_t = 19.7 mins.) and 35% of another compound (R_t = 26.9 mins.) assigned the structure of the anti-isomer (124b) by comparison of its g.l.c. retention times with those of a pure sample prepared by another route.

Reaction of the syn-alcohol (124a) with concentrated hydrochloric acid.

(a) Acetic acid as solvent.

The syn-alcohol (124a) (720 mgms.), concentrated hydrochloric acid (2 ml.) and acetic acid (12 ml.) were mixed and refluxed for 5 hrs. then cooled, basified (4N NaOH), diluted with water and ether extracted. The ethereal solution was washed with 4N sodium hydroxide and brine and dried ($MgSO_4$). Removal of the solvent yielded 810 mgm. of an oil exhibiting hydroxyl absorption and a carbonyl peak at 1730cm.$^{-1}$ in the infra-red spectrum. G.l.c. analysis (10% PEG A at 190°) of the oil showed four components, 13% of the syn-acetate (127a) (R_t= 14.4 mins.), 68% of the anti-acetate (127b) (R_t=16.7 mins.), 4% of the syn-alcohol (124a) (R_t = 19.7 mins.) and 15% of the anti-alcohol (124b) (R_t = 26.0 mins.). The acetates were readily separated from the alcohol fraction by chromatography, and distillation furnished a sample rich in the anti-isomer (127b), b.p. 130-135°/0.5 mm. (Found C, 79.49%, H, 7.84%. $C_{17}H_{20}O_2$ requires C, 79.65%, H, 7.85%). The infra-red spectrum (CCl_4) showed absorption at 1736cm.$^{-1}$ and 1242cm.$^{-1}$. The n.m.r. spectrum had peaks at 8.03 τ (singlet, 3H), 4.97 τ (singlet, 1H) and 4.36 τ (triplet J=3.75 cps., 1H) attributed

to the protons on the acetate group, C_8 and C_3 respectively. The presence of the syn-acetate (127a) was confirmed by comparison of its retention times on a number of g.l.c. columns with those of an authentic sample prepared from the syn-alcohol as described below.

(b) Dioxan as solvent.

The syn-alcohol (124a) (2.95g.), concentrated hydrochloric acid (10 ml.) and dioxan (50 ml.) were refluxed for 19 hrs. then cooled, diluted with water, basified (4N NaOH) and extracted with ether. After washing with brine and drying ($MgSO_4$) the solvent was removed yielding 2.8g. of an oil which solidified on standing. G.l.c. analysis of the reaction mixture (10% PEG A at 190°) showed two components, 83% of the anti-alcohol (124b) (R_t = 26.9 mins.) and 17% of the syn-alcohol (124a) (R_t = 19.7 mins.). Recrystallisation from acetone and petrol gave 2.2g. (74%) of anti-2-p-tolylbicyclo-(3,2,1)-oct-2-en-8-ol (124b) m.p. 106-108.5°.

Hydrolysis of anti-8-acetoxy-2-(p-tolyl)-bicyclo-(3,2,1)-oct-2-ene. (127b).

The anti-acetate (127b) (60 mgm.), obtained from the syn-alcohol (124a) by hydrochloric acid/acetic acid reflux, was allowed to stand overnight at room temperature dissolved in a solution of potassium hydroxide (150 mgms.) in methanol (2 ml.). The solution was acidified (6N HCl), diluted with water and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding 50 mgm. of an oil which solidified on standing. Recrystallisation from

acetone furnished a sample of the anti-isomer of 2-p-tolyl-bicyclo-(3,2,1)-oct-2-en-8-ol (124b), m.p. 106-108.5°. (Found C, 83.71%, H, 8.41%. $C_{15}H_{18}O$ requires C, 84.07%, H, 8.47%). The infra-red spectrum (CCl_4) showed absorption at 3633cm.$^{-1}$ (free hydroxyl) and 3490cm.$^{-1}$ (intermolecularly bonded hydroxyl). The n.m.r. spectrum had peaks at 5.88 τ (singlet, 1H) and 4.38 τ (triplet J=3.75 cps., 1H) assigned to the protons on C_8 and C_3 respectively. This compound had identical g.l.c. retention times to the by-product of the sodium borohydride/pyridine reduction of (84) and to the product of hydrochloric acid-dioxan treatment of (124a).

Syn-8-acetoxy-2-p-tolylbicyclo-(3,2,1)-oct-2-ene (127a).

The syn-alcohol (124a) (450 mgm.), acetic anhydride (2.5 ml.) and anhydrous pyridine (6 ml.) were mixed and refluxed for 1.5 hrs., then allowed to cool and poured onto ice and water. The ethereal extracts of this aqueous solution were washed with 6N hydrochloric acid, brine, saturated sodium bicarbonate solution, brine and dried ($MgSO_4$). Concentration yielded 525 mgm. (97%) of an oil shown by g.l.c. (10% PMS A at 190°) to consist only of the desired syn-acetate (127a) (R_t = 14.4 mins.), its retention time being identical to the minor acetate component of hydrochloric acid/acetic acid treatment of the syn-alcohol (124a). Distillation furnished a sample for analysis, b.p. 118-126°/0.05 mm. (Found C, 79.49%, H, 7.99%. $C_{17}H_{20}O_2$ requires C, 79.65%, H, 7.85%). ν_{CCl_4} 1740cm.$^{-1}$ and 1244cm.$^{-1}$. The n.m.r. spectrum showed a singlet at 8.04 τ (3H), assigned to the acetate group, a triplet at 5.07 τ (J = 4cps., 1H) for the proton at C_8 and an ill-defined triplet at 4.21 τ (1H) for the olefinic proton at C_3.

Oxidation of the syn-alcohol (124a)

A stirred solution of the syn-alcohol (124a) (219 mgm.) in acetone (8 ml.), cooled to 0°, was treated dropwise with Jones reagent [43] until the red colouration persisted. The reaction mixture was then diluted with water and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding 170 mgm. of an oil which solidified on standing. This material was shown to be the expected ketone (84) by comparison of its infra-red spectrum and g.l.c. retention times with an authentic sample.

Oxidation of the anti-alcohol (124b).

Treatment of the anti-alcohol (124b) (460 mgm.) in acetone (50 ml.) with Jones reagent [43], in the usual manner resulted in a considerably slower oxidation than occurred with the syn-isomer. The ketone (84) (375 mgm.) was recovered, following the work up described above.

Reaction of concentrated hydrochloric acid with the anti-alcohol (124b).

(a) Acetic acid as solvent.

The anti-alcohol (124b) (360 mgm.), concentrated hydrochloric acid (1 ml.) and acetic acid (6 ml.) were refluxed for 5 hrs. The procedure described for the syn-isomer furnished 364 mgm. of an oil which g.l.c. analysis (10% PEG A at 190°) showed to consist of the four products obtained by similar treatment of the syn-isomer (124a) and in comparable ratios, i.e. the syn-and anti-epimeric alcohols (124a) and (124b) and the

correeponding acetates (127a) and (127b).

(b) Dioxan as solvent.

The anti-alcohol (124b) (200 mgm.) was dissolved in dioxan (5 ml.) containing concentrated hydrochloric acid (1.5 ml.) and refluxed for 19 hrs. The reaction mixture was then cooled, diluted with water, basified (4N NaOH) and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding 80 mgms. of oil which rapidly solidified. G.l.c. analysis (10% PMS A at 190°) indicated that the reaction mixture consisted of 80% of the starting alcohol and 20% of the syn-isomer (124a).

2-p-Tolyl-8-methoxybicyclo-(3.2.1)-oct-2-ene (129)

(a) Hydrogen chloride/methanol.

The syn-alcohol (124a) (330 mgm.) and a saturated solution of hydrogen chloride in methanol (10 ml.) were refluxed for 19 hrs., cooled, poured into water and extracted with ether. The organic solution was washed with brine and dried ($MgSO_4$), yielding 340 mgm. of an oil on concentration. T.l.c. (10% ethyl acetate in petrol) showed the presence of a major product with a slightly more polar impurity. Thick-layer chromatography of the mixture provided a separation and the major product, the anti-methyl ether (129b) was further purified by distillation, b.p. 140°/0.05 mm. (Found C, 84.86%, H, 8.78%. $C_{16}H_{20}O$ requires C, 84.16%, H, 8.83%). The infra-red spectrum (CCl_4)

showed absorption at 2834 and 1103cm.$^{-1}$ (methoxyl), and the n.m.r. had singlets at 6.70 τ (3H), and 6.36 τ (1H) attributed to the methoxyl protons and the proton on C_8 respectively. The olefinic proton showed as a poorly defined triplet at 4.37 τ.

The impurity was identified as the syn-methyl ether (129a) by comparison of its R_f on t.l.c. and retention times on g.l.c. with a sample obtained by treatment of the syn-alcohol with p-toluene sulphonic acid and methanol, described below.

(b) <u>p-Toluene sulphonic acid/methanol</u>.

The syn-alcohol (124a) (438 mgm.), p-toluene sulphonic acid (430 mgm.) and methanol (5 ml.) were mixed and refluxed for 4 hrs., cooled and poured into a solution of potassium hydroxide (500 mgm.) in water (30 ml.) and allowed to stand for 15 mins. The basic solution was then extracted with ether and the organic layer washed with brine and dried ($MgSO_4$). Concentration yielded 434 mgm. of oil which exhibited four spots on t.l.c. the most polar having similar R_f to the anti-alcohol. The oil was dissolved in petrol and chromatographed on fine silica (10g.). Elution with 5% ether in petrol yielded in the fourth fraction a mixture of an unidentified impurity and the anti-methyl ether (129b), in the fifth, a mixture of the anti-and syn-epimers and in the next three fractions pure syn-methyl ether (129a). Combination of these fractions and distillation furnished a pure sample of the predominant syn-epimer (129a), b.p. 120-122°/0.5 mm. (Found C, 83.95%, H,

8.19%. $C_{16}H_{20}O$ requires C, 84.16%, H, 8.83%). The infra-red spectrum (CCl_4) showed absorption at 2829 and 1122cm.$^{-1}$ (methoxyl). The n.m.r. spectrum showed a singlet at 6.70 τ for the methoxyl protons and triplets at 6.30 τ(J=4 cps.) and 4.20 τ(J=3.75 cps.) for the proton on C_8 and the olefinic proton respectively.

The fourth and fifth fractions from the column were re-chromatographed, elution with 2% ether in petrol furnishing a pure sample of the anti-epimer (129b) identical with the major product from the hydrogen chloride-methanol reaction described above.

Quantitive analysis of these mixtures by g.l.c. was not possible due to the small separation obtained between the peaks for the syn-and anti-epimers.

Rapid decomposition of both epimers occurred, ketonic absorption appearing in the infra-red spectrum.

Action of p-toluene sulphonic acid/acetic acid on the syn-alcohol (124a).

The syn-alcohol (124a) (20 mgm), p-toluene sulphonic acid (20 mgm) and acetic acid (2 ml.) were mixed and refluxed for 4 hrs., then cooled and poured into water and extracted with ether. The ethereal solution was washed with 4N sodium hydroxide, 5N hydrochloric acid and brine and dried ($MgSO_4$). Concentration yielded 18 mgm. of product which was analysed by g.l.c. (10% PEG A at 190°). A similar product distribution was obtained to that from the hydrochloric acid-acetic acid reaction, viz the predominant product was the anti-acetate (127b).

Attempted decomposition of the bicyclo-ketone (84) with water.

The bicyclo-ketone (84) (500 mgm.) and water (10 ml.) were mixed and refluxed for 26 hrs. then cooled and extracted with ether. The organic solution was extracted with 4N sodium hydroxide, washed with brine, dried ($MgSO_4$) and concentrated, yielding only unchanged starting material. Normal work up of the basic extract furnished no material of an acidic nature.

Similar treatment of the ketone with water (8 ml.) and dioxan (6 ml.) in a homogeneous solution failed to bring about any reaction.

Attempted decomposition of the bicyclo-ketone (84) by slow distillation.

Slow distillation of the ketone at 0.1 mm. resulted in a crystalline product on cooling. The infra-red spectrum and t.l.c. showed that the starting material had been recovered unchanged.

Treatment of the bicyclo-ketone (84) with 4N sodium hydroxide.

The bicyclo-ketone (84)(500 mgm.), 4N sodium hydroxide (5 ml.) and dioxan (10 ml.) were refluxed for 24 hrs. as a two phase system. The reaction mixture was diluted with water, acidified (6N HCl), extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration yielded a mixture of solid and liquid material shown by t.l.c. to consist of unchanged starting material with a number of unidentified impurities.

Action of methanolic potassium hydroxide on the bicyclo-ketone (84)

The bicyclo-ketone (84) (1g.) was dissolved in a solution of potassium hydroxide (1g.) in anhydrous methanol (25 ml.) and refluxed for 26 hrs. After cooling, dilution with water and acidification with mineral acid, the aqueous solution was extracted with ether, and the extracts washed with brine and dried ($MgSO_4$). Concentration yielded an oil (0.95g.) shown by t.l.c. and g.l.c. to consist of unreacted starting material and a less polar compound. Fractional distillation failed to separate the two components.

To facilitate chromatographic separation, a methanolic solution of the mixture was treated with sodium borohydride in the usual manner, the resultant oil showing no carbonyl absorption in the infra-red spectrum. G.l.c. indicated that the unidentified compound was unchanged by the reduction procedure. A sample of the oil was dissolved in petrol and chromatographed on fine silica. Elution with 5% ether in petrol initially afforded the new product and subsequently mixtures of this compound and the syn-alcohol (124a). Distillation of the combined early fractions yielded a pure sample of 2-p-tolyl-8,8-dimethoxybicyclo-(3,2,1)-oct-2-ene (130) positively identified by comparison of its infra-red and n.m.r. spectra, its R_f on t.l.c. and its retention times on a number of g.l.c. columns with an authentic sample prepared by the action of p-toluene sulphonic acid and methanol on the bicyclo-ketone (84).

Action of sodium methoxide on the bicyclo-ketone (84)

A solution of the bicyclo-ketone (84) (1g.) in anhydrous methanol (5 ml.) was added to a methanolic solution of sodium methoxide

[from sodium (1g.) and anhydrous methanol (30 ml.)] and the mixture refluxed for 26 hrs. The work up described above yielded 1g. of oil shown by t.l.c. and g.l.c. to be essentially similar to that obtained from potassium hydroxide in methanol. More concentrated sodium methoxide solutions and extended reflux times failed to increase the quantity of the ketal (130) formed.

Treatment of the bicyclo-ketone (84) with p-toluene sulphonic acid/methanol.

(a) Four hours reflux. 2-p-Tolyl-8,8-dimethoxybicyclo-(3,2,1)-oct-2-ene. (130)

The bicyclo-ketone (84) (1g.), p-toluene sulphonic acid (0.95g.) and methanol (10 ml.) were mixed and refluxed for 4 hrs., then cooled and poured into a stirred solution of potassium hydroxide (1g.) in water (10 ml.). The basic solution was extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration yielded 1.15g. of an oil showing absorption at 1730cm.$^{-1}$ in the infra-red spectrum and one spot on t.l.c. G.l.c. analysis (10% PEG A at 190°) of the product however indicated that it was a mixture consisting of the cycloheptene esters (82), (R_t = 14 mins.) and (83) (R_t = 15.75 mins.) and a new compound (R_t = 8 mins.).

The reaction was repeated on similar quantities and after 4 hrs. reflux a solution of potassium hydroxide (1g.) in water (2 ml.) was added and refluxed for 1.5 hrs. The usual work up yielded 425 mgm. of 2-p-tolyl-8,8-dimethoxy-bicyclo-(3,2,1)-oct-2-ene (130) after distillation, b.p. 110°/0.04 mm. (Found C, 78.91%, H, 8.41%. $C_{17}H_{22}O_2$

requires C, 79.03%; H, 8.58%). The infra-red spectrum (CCl_4) showed absorption at 2830cm.$^{-1}$, 1115cm.$^{-1}$ and 1068cm.$^{-1}$ (methoxyl) and the n.m.r. spectrum showed two singlets at 6.85 τ and 6.78 τ attributed to the protons on the methoxyl groups and a triplet at 4.27 τ (J=3.75 cps.) for the olefinic proton.

(b) Long reflux. The esters (82) and (83).

Bicyclo-ketone (84) (510 mgm.), p-toluene sulphonic acid (500 mgm). and methanol were refluxed for 19 hrs., cooled then poured into a stirred solution of potassium hydroxide (500 mgm.) in water, (10 ml.). The usual work up furnished an oil shown by g.l.c. analysis to consist of 85% of the mixture of esters (82) and (83) and 15% of the ketal (130). The oil was submitted to a further 19 hrs. reflux yielding 450 mgm. (76%) of a mixture of the cycloheptene esters (82) and (83).

Trans-ketalisation of the ketal (130).

The ketal (130) (110 mgm.), p-toluene sulphonic acid (20 mgm.) and acetone (10 ml.) were mixed and refluxed for 3 hrs., concentrated under reduced pressure and diluted with ether. The organic solution was washed with a saturated solution of sodium carbonate and brine and dried ($MgSO_4$). Concentration yielded 80 mgm., (89%), of the bicyclo-ketone (84) which solidified on standing. Recrystallisation from ethanol furnished a pure sample, m.p. 66-68°. Mixed melting point and comparison of g.l.c. retention times established the identity of the product.

Treatment of the bicyclo-ketone (84) with sulphuric acid/methanol

The bicyclo-ketone (84) (1g.), concentrated sulphuric acid (0.5 ml.) and methanol (15 ml.) were mixed and refluxed for 20 hrs., then cooled, diluted with water and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and concentrated yielding 1.03g. of an oil shown by g.l.c. analysis (10% PEG A at 190°) to consist of equal quantities of the cycloheptene esters (82) and (83).

Treatment of the diketone (66) with sulphuric acid/methanol.

Concentrated sulphuric acid (9 ml.) was added dropwise to a solution of the diketone (66) (18g.) in methanol (300 ml.) and the mixture refluxed for 60 hrs. The usual work up furnished an oil which was distilled, b.p. 128-130°/0.03 ml., (15.8g., 82.7%). G.l.c. analysis showed this to be a mixture of equal quantities of the cycloheptene esters (82) and (83).

G.l.c. analysis of a similar reaction refluxed for 19 hrs. showed the presence of the two esters together with a small quantity of the bicyclo-ketal (130).

Treatment of the diketone (106) with concentrated sulphuric acid in methanol.

The diketone (106) (2g.), dissolved in methanol (30 ml.), was treated with concentrated sulphuric acid (1.5 ml.) and the solution refluxed for 4 days when an aliquot was taken and worked up in the usual manner. T.l.c. indicated that the reaction had not gone to completion, some non-polar material assumed to be the cycloheptene methyl ester and the dimethyl ketal of the bicyclo-ketone (107) having been formed but large quantities of the

diketone remained unreacted. Reflux for 10 days failed to provide complete reaction and this method was abandoned.

Treatment of the bicyclo-ketone (84) with p-toluene sulphonic acid-ethylene glycol.

The bicyclo-ketone (84) (3g., 0.014 m.), p-toluene sulphonic acid (2.85g., 0.015 m.) and ethylene glycol (8.68g., 0.14 m.) were mixed and heated on a steam bath for 1.5 hrs., then cooled and poured into a vigorously stirred solution of potassium hydroxide (2.3g.) in ice and water (20g.) and left overnight. The basic solution was then extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration afforded an oil which showed two spots on t.l.c., a compound with similar R_f to the starting ketone and a very polar material. The infra-red spectrum showed absorption at 3500cm.$^{-1}$ (hydroxyl) and 1730cm.$^{-1}$ (carbonyl). The absence of the 1750cm.$^{-1}$ carbonyl absorption typical of the bicyclo-ketone suggested the least polar compound was the ethylene ketal (132) and the other material an ethylene glycol ester formed by bridge fission. Accordingly a sample of the reaction product was refluxed for 1 hr. with a methanolic solution of potassium hydroxide and worked up in the usual manner. The neutral fraction from this hydrolysis yielded only the less polar material as a solid, identified as 2-(p-tolyl)-8-ethylene-dioxy bicyclo-(3,2,1)-oct-2-ene (132), m.p. 67.5-69° (ethanol). (Found C, 79.36%, H, 7.91%. $C_{17}H_{20}O_2$ requires C, 79.65%, H, 7.86%). The infra-red spectrum was transparent in the hydroxyl and carbonyl regions and showed strong absorption at 1109cm.$^{-1}$ (ethylene-dioxy). The n.m.r. spectrum showed the olefinic proton at C_3 as a triplet at 4.30 τ (J = 3.75 cps.) and the methylene protons of the ethylene-dioxy group as a singlet at 6.10 τ.

The acidic material recovered from the hydrolysis was treated with diazomethane and analysed by g.l.c. which showed the product to be a mixture of the cycloheptene methyl esters (82) and (83). On the basis of this result and the infra-red spectrum of the crude reaction mixture, the polar product was considered to be a mixture of the ethylene glycol esters (133) and (134).

Treatment of the diketone (66) with p-toluene sulphonic acid-ethylene glycol.

A mixture of the diketone (66) (2g.) and p-toluene sulphonic acid (2g.) in ethylene glycol (10 ml.) was refluxed for 2 hrs., allowed to cool and poured into a solution of potassium hydroxide (2g.) in water (20 ml.). The basic solution was extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration yielded 1.7g. of an oil which showed three spots on t.l.c. Chromatography afforded a sample of each compound. The least polar was identified as the ketal (132) (t.l.c., i.r.). The other two components both showed absorption at 3500cm.$^{-1}$ (hydroxyl) and 1730cm.$^{-1}$ (ester) in the infra-red spectrum and both yielded a mixture of the esters (82) and (83) on basic hydrolysis and esterification with diazomethane. It was assumed that the less polar spot comprised the ethylene glycol esters (133) and (134) and the more polar the corresponding diethylene glycol esters.

Treatment of the diketone (106) with p-toluene sulphonic acid-ethylene glycol.

(a) A mixture of diketone (106) (1g.), p-toluene sulphonic acid (1g.) and ethylene glycol (5 ml.) was refluxed for 1 hr., then

cooled and poured into a solution of potassium hydroxide (1.3g.) in water (20 ml.) and allowed to stand at room temperature for 30 mins. The solution was diluted with water, extracted with ether and the extracts washed with brine and dried ($MgSO_4$). Concentration yielded 760 mgm. of an oil which showed three spots on t.l.c. Chromatography of a benzene solution of this material on fine silica (13g.) afforded 350 mgm. of the lactone (105), some starting material and then a compound which showed absorption in the hydroxyl region and at 1740cm.$^{-1}$ in the infra-red spectrum. This compound was identified as the ethylene glycol ester (136) although satisfactory analytical figures could not be obtained, due to a small impurity which could not be separated. The n.m.r. spectrum had peaks at 8.32 τ (singlet, 3H) for the methyl function, 6.27 τ (multiplet, 2H) for the methylene protons on the hydroxyl-bearing carbon and at 5.88 τ (multiplet, 2H) for the methylene protons adjacent to the ester group. Reflux of the reaction mixture for 16 hrs. furnished a 55% yield of lactone after chromatography.

(b) Acidic hydrolysis of the crude reaction product.

The diketone (106) (1g.) was refluxed for 1 hr. as described in (a) above and then cooled, treated with a solution of concentrated hydrochloric acid (1 ml.) in water (3 ml.) and the resulting two phase system refluxed for 17 hrs. After cooling, the reaction mixture was extracted with ether and the extracts washed with 4N sodium hydroxide and brine,

then dried. Concentration yielded 900 mgm. of contaminated lactone which was readily purified by recrystallisation from petrol to give 800 mgm., (80%) of the lactone (108), m.p. 90-92°.

(c) Basic hydrolysis of the crude reaction product.

Similar treatment of the diketone (106) (1g.) at reflux for 1 hr. followed by addition of potassium hydroxide (2g.) in water (4 ml.) and subsequent refluxing for 2 hrs., yielded 530 mgm. of neutral and 480 mgm. of acidic material. The neutral fraction was shown by t.l.c. and its infra-red spectrum to consist mainly of the lactone (108), together with some bicyclo-ketone (107) or ketal (135). The acidic material solidified and was recrystallised from petrol, m.p. 96-98°. (Found C, 77.93%, H, 7.55%. $C_{15}H_{18}O_2$ requires C, 78.23%, H, 7.88%). The infra-red spectrum showed absorption at 3500-2800cm.$^{-1}$ (acidic hydroxyl) and 1700cm.$^{-1}$ (carboxyl). The n.m.r. spectrum showed no olefinic proton signal but a vinylic methyl at 8.36 τ (singlet, 3H). G.l.c. analysis of an esterified sample established the purity of the acidic product.

Treatment of the diketone (48) with p-toluene sulphonic acid in ethylene glycol.

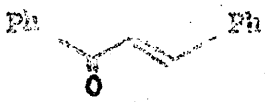
A mixture of the diketone (48) (1.2g.), p-toluene sulphonic acid (1.2g.) and ethylene glycol (6 ml.) was refluxed for 1 hr. A solution of potassium hydroxide (2g.) in water (4 ml.) was added and the basic solution refluxed for 2 hrs., then cooled, diluted with water, acidified (6N HCl) and extracted with ether. Extraction of the ethereal solution with dilute sodium hydroxide, furnished 645 mgm. of acidic material after the usual work up. G.l.c. analysis of an esterified sample (diazomethane), showed 80% of a major product contaminated by two compounds. Distillation furnished bicyclo-

(5,3,0)-dec-1 (7)-ene-3-carboxylic acid (54), b.p. 122-125°/ 0.15 mm. (Found C, 73.08%, H, 8.99%. $C_{11}H_{16}O_2$ requires C, 73.30%, H, 8.95%). The infra-red spectrum showed absorption at 3500-2800cm.$^{-1}$ and 1700cm.$^{-1}$. The n.m.r. spectrum confirmed the tetra-substituted position of the double bond by the absence of a signal for an olefinic proton.

A neutral fraction of 370 mgm. of an oil was recovered which consisted of the lactone (51), (infra-red spectrum, t.l.c., g.l.c.).

Treatment of the diketone (103) with p-toluene sulphonic acid in ethylene glycol.

The diketone (103) (1.4g.), p-toluene sulphonic acid (1g.) and ethylene glycol (10 ml.) were mixed and refluxed for 17 hrs. then allowed to cool and a solution of potassium hydroxide (1.5g.) in water (5 ml.) was added. This mixture was refluxed for 3 hrs. and after cooling was diluted with water, acidified (6N HCl) and extracted with ether. The extracts were washed with 4N sodium hydroxide, then brine and dried ($MgSO_4$) yielding 180 mgm. of unreacted starting material. The basic solution was acidified with mineral acid and worked up in the usual manner to yield 1.1lg. of the desired acid (104), identical to the product from the hydrochloric acid-acetic acid reaction.



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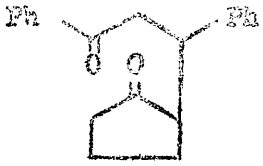

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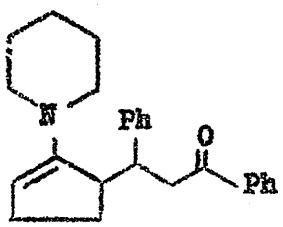

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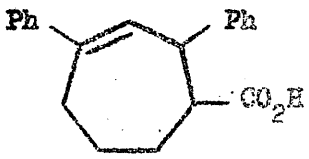

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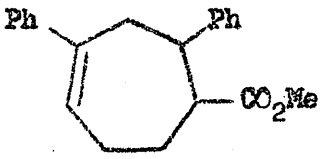

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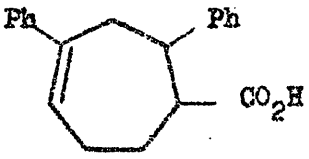

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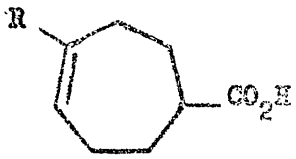

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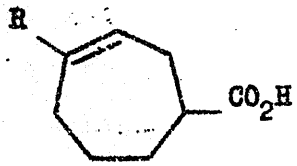

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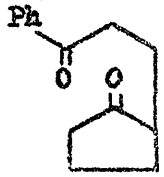

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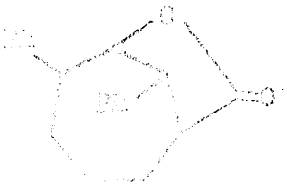

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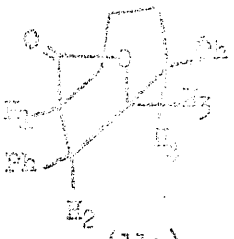

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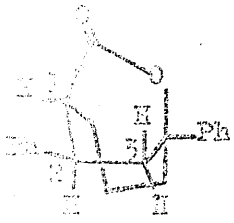

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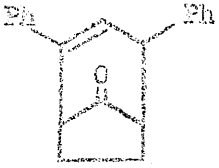

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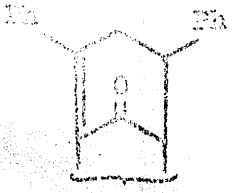

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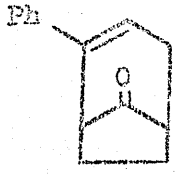

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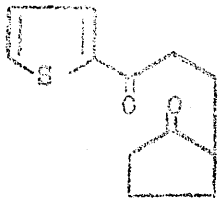

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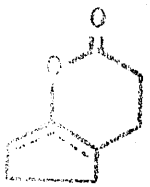

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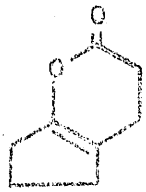

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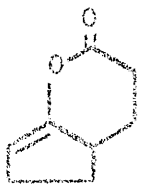

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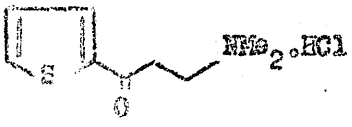

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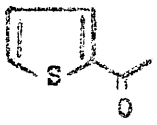

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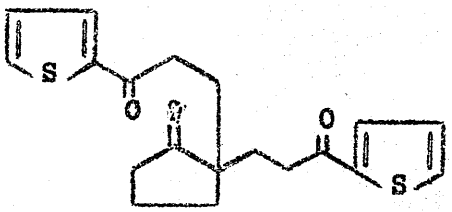

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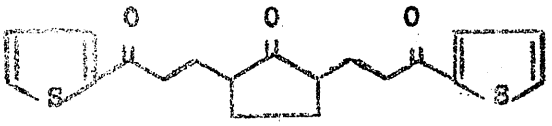

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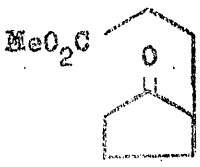

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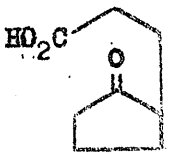

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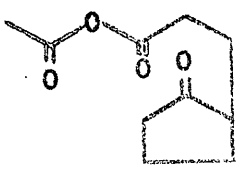

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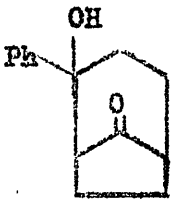

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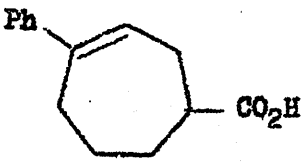

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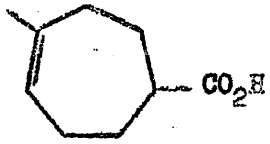

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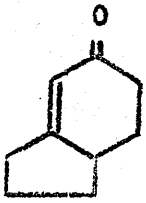

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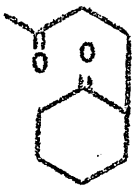

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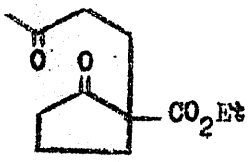

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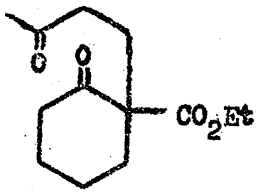

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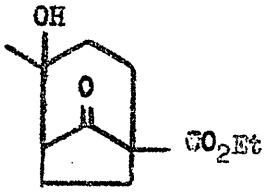

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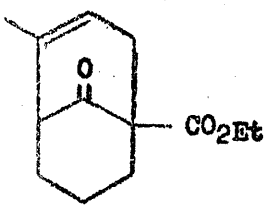

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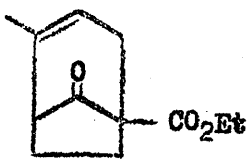

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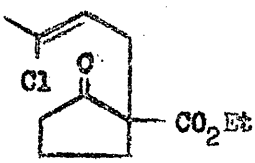

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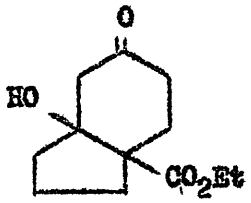

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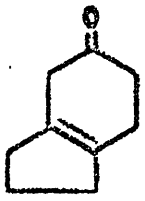


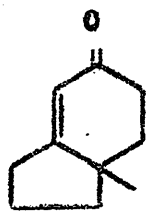
(39)

$CH_3COCH_2CH_2NEt_2$

(40)

(41)

(42)



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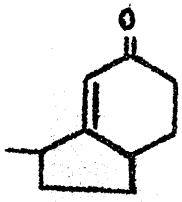

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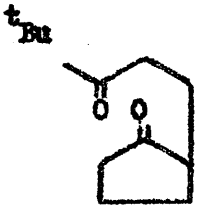
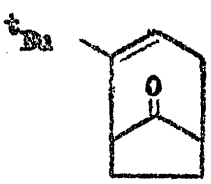


(45)

$^tBuCOCH_2CH_2NMe_2 \cdot HCl$.

(46)



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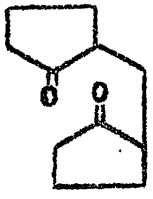

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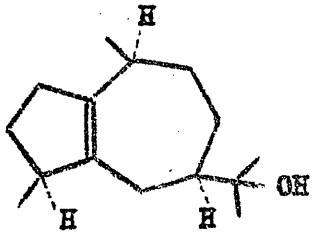

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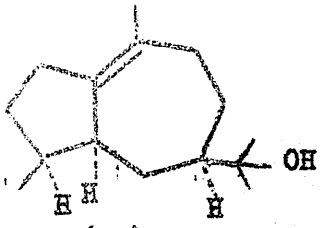

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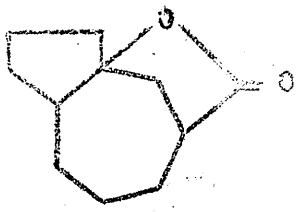

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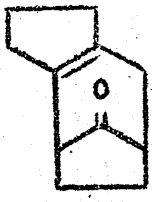

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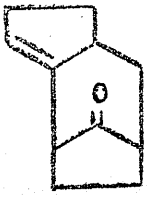

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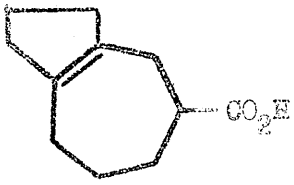

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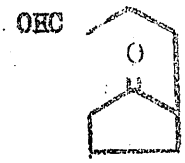

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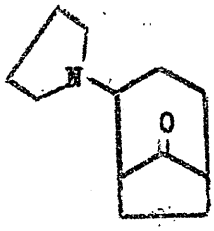

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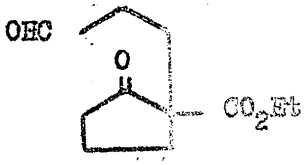

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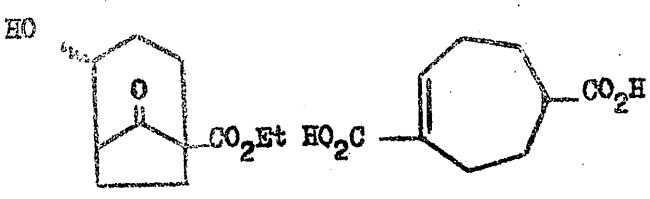

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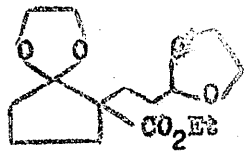

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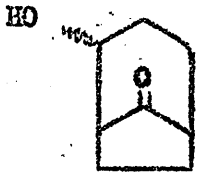

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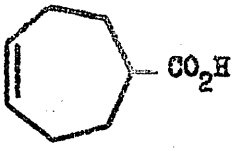

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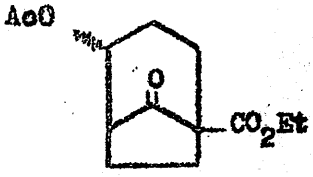

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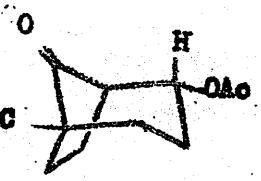

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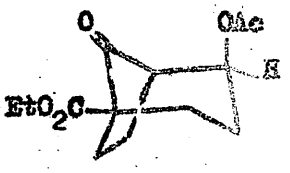

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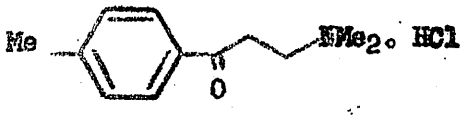

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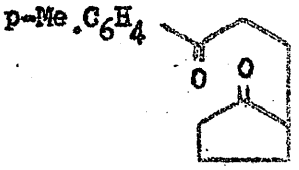

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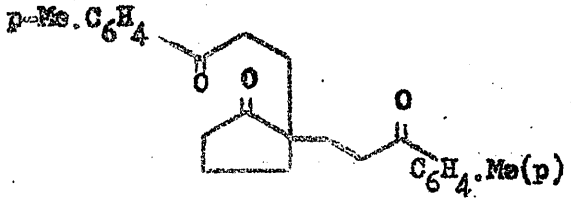

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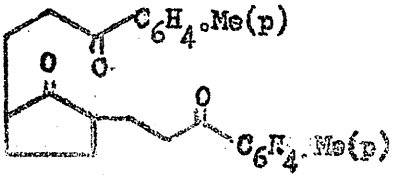

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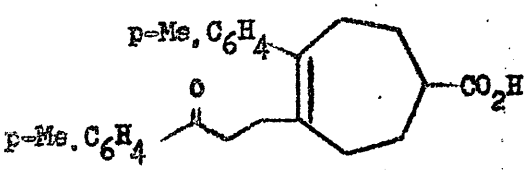

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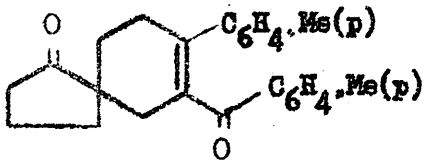

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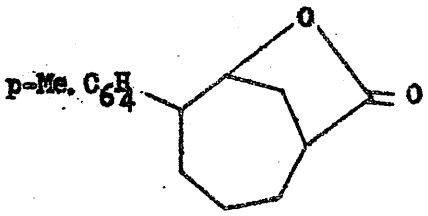

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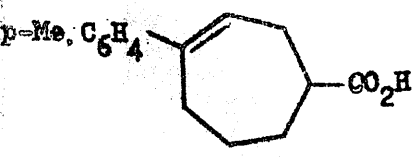

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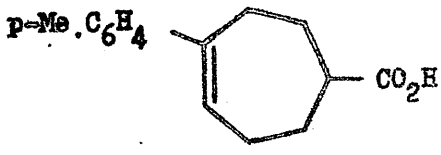

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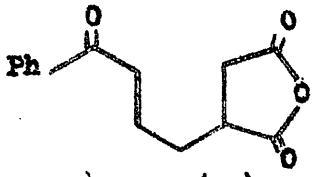

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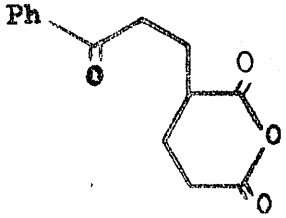

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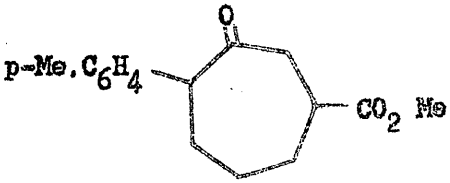

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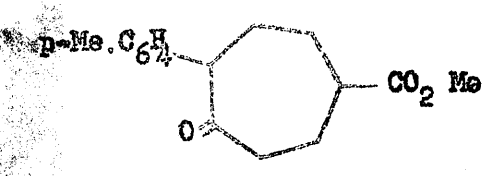

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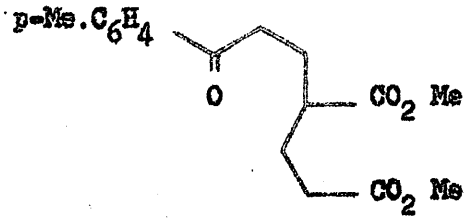

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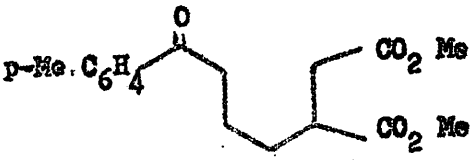

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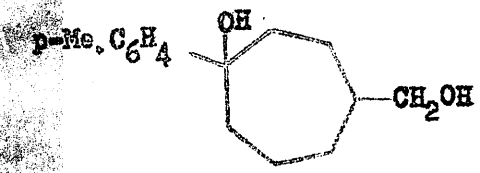

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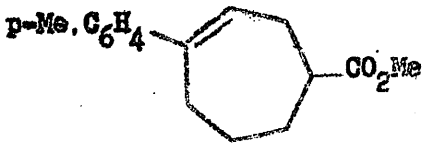

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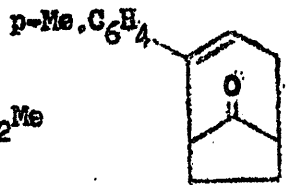

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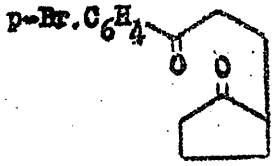

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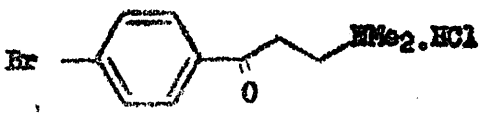

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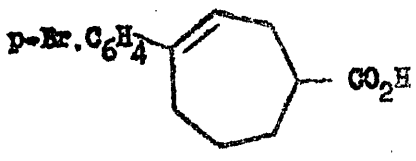

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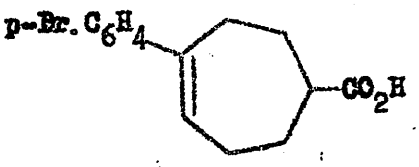

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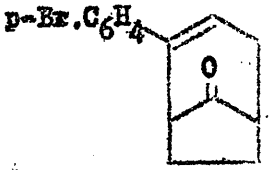

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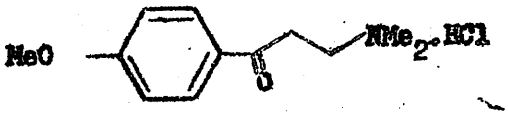

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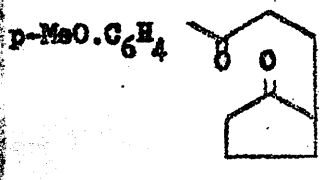

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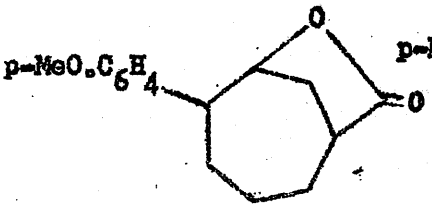

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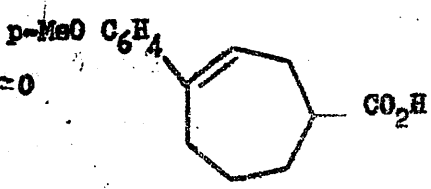

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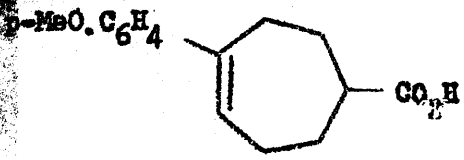

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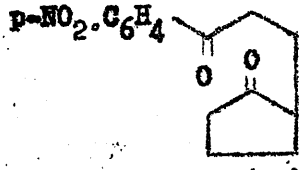

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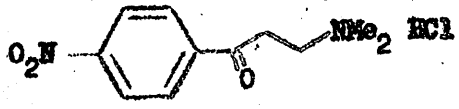

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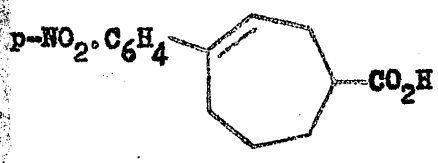

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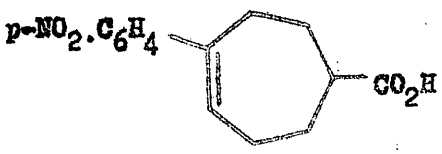

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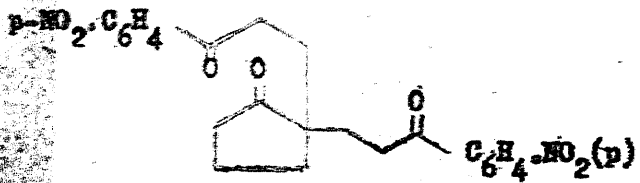

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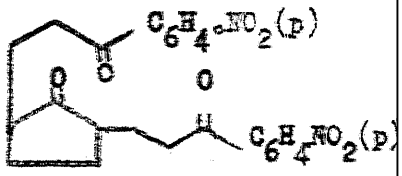

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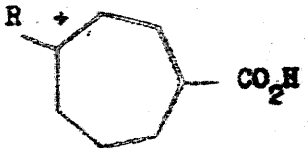

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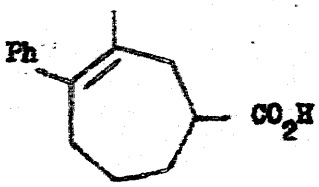

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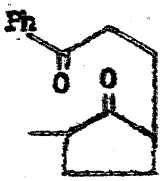

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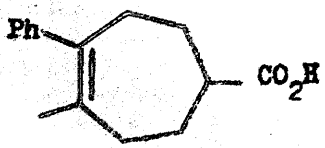

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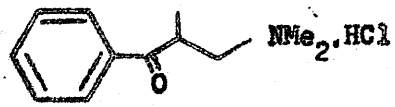

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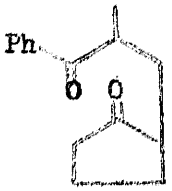

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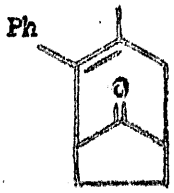

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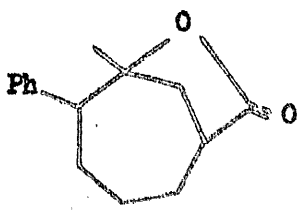

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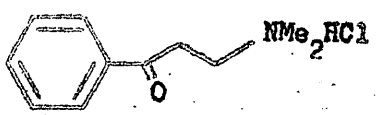

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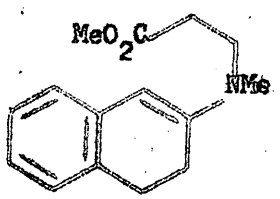

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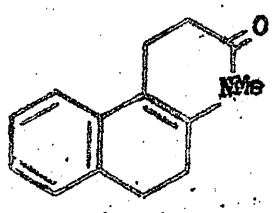

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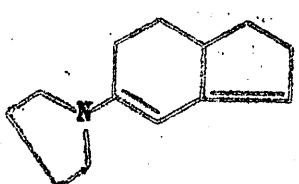

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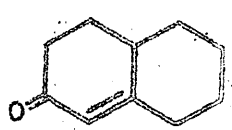

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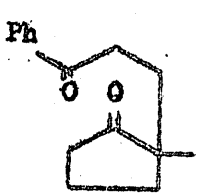

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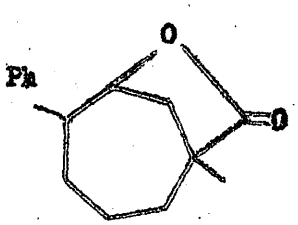

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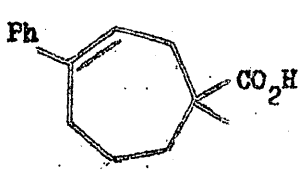

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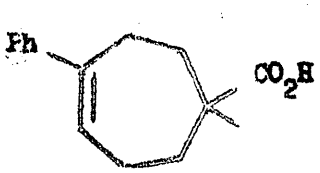

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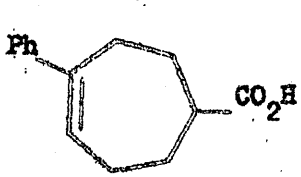

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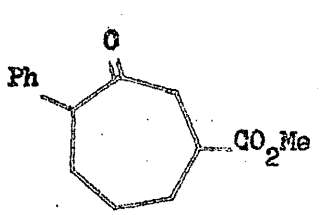

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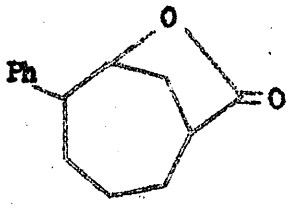

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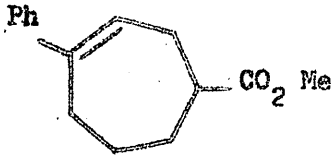

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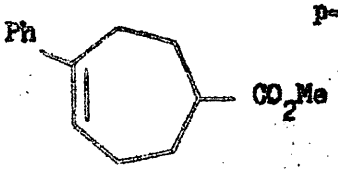

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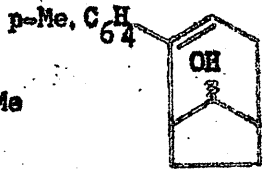

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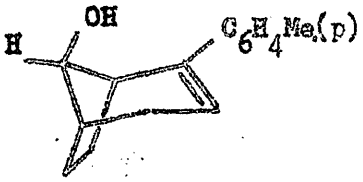

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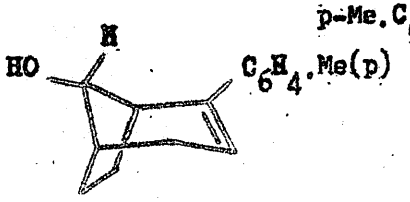

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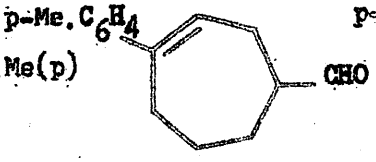

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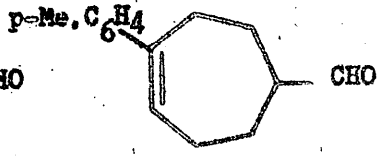

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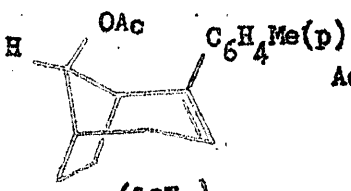

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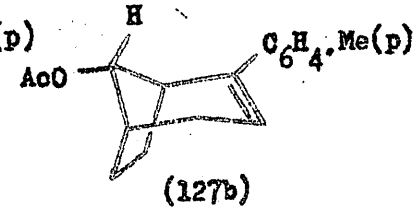

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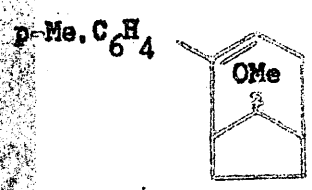

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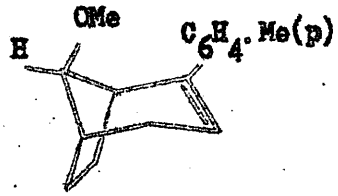

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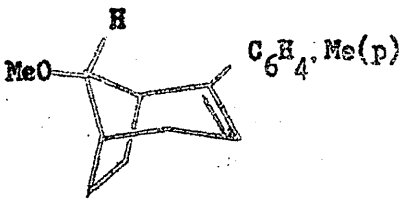

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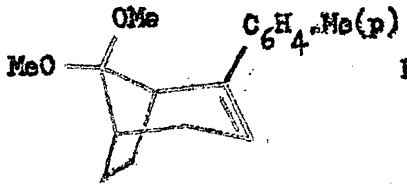

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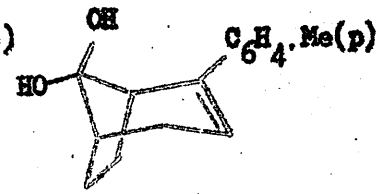

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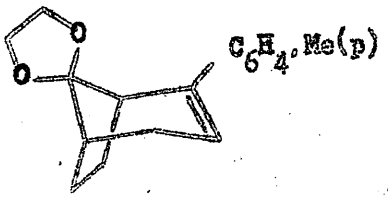

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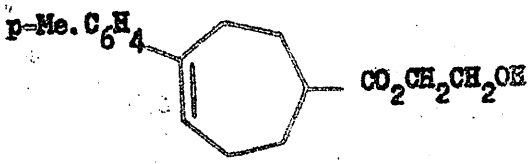

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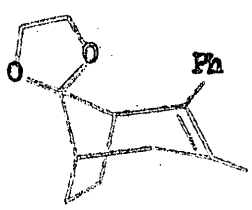

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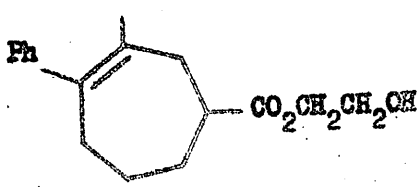

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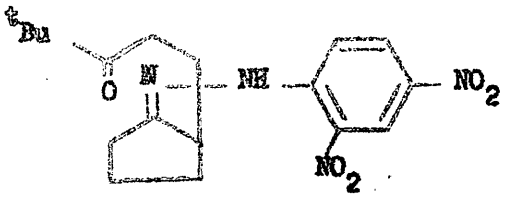

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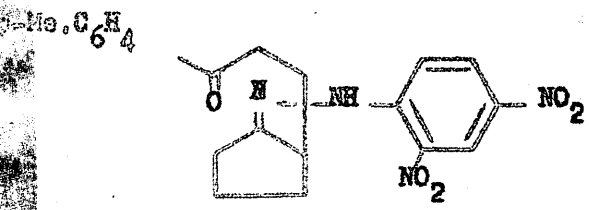

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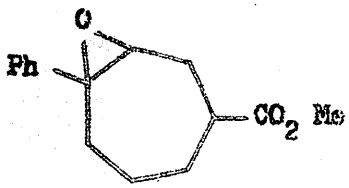

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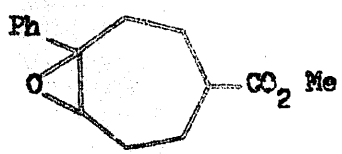

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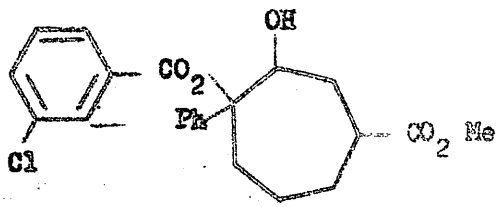

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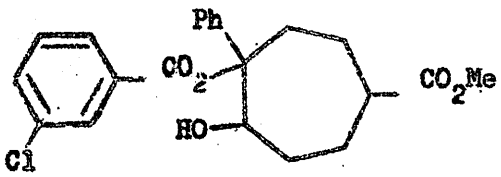
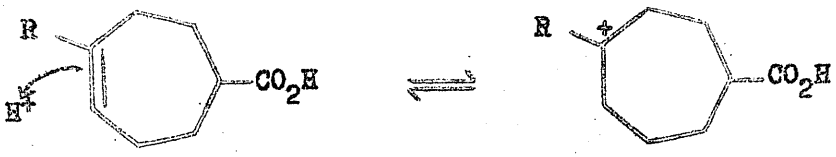
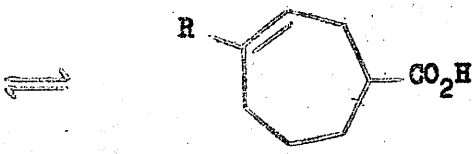


(143)

Scheme (a).

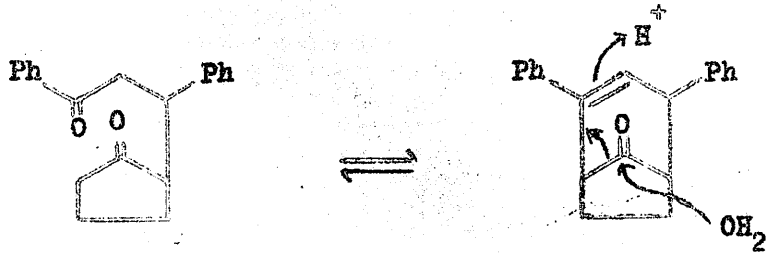


(8) (101)



(9)

Scheme (b).



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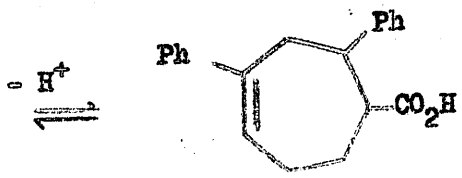
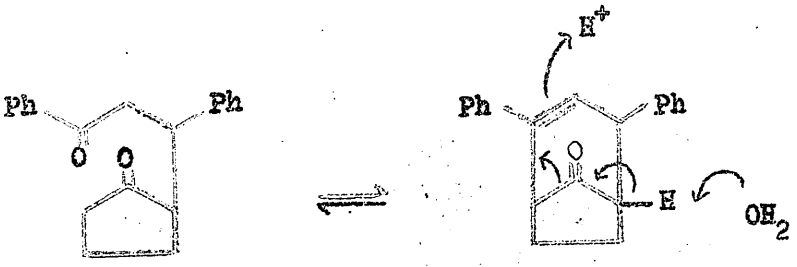
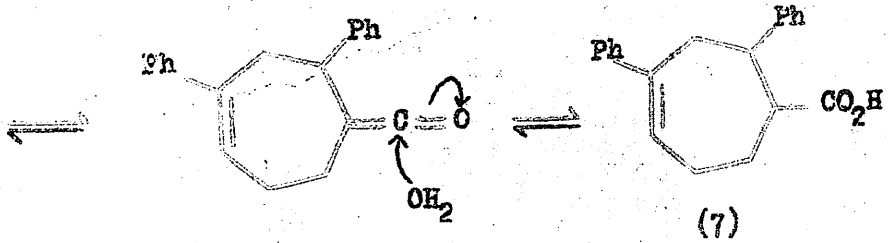


(7)

Scheme (c)



(2) (13)



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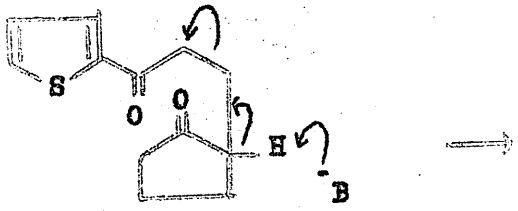
Scheme (d).



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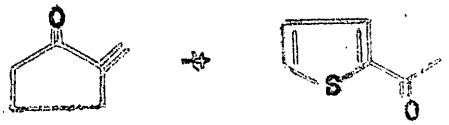
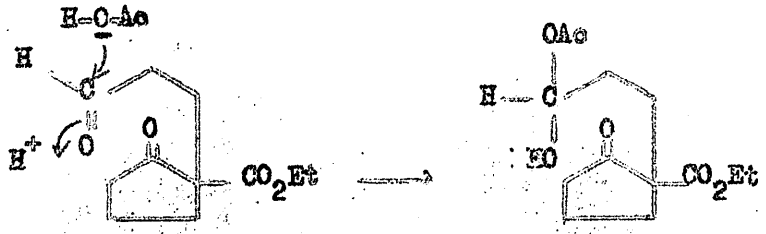


Scheme (e).



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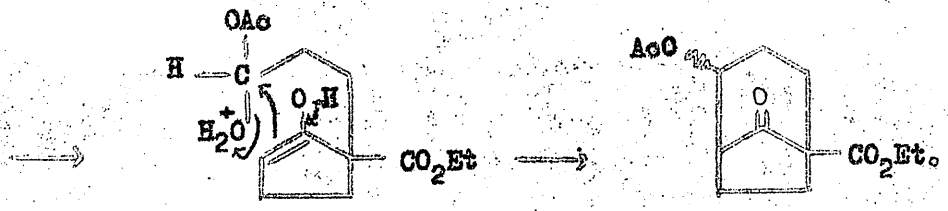
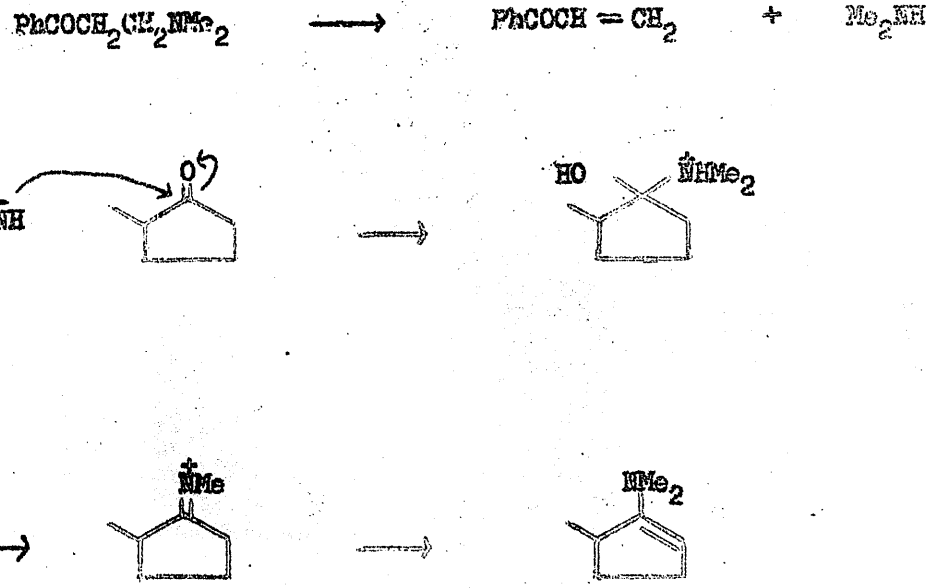
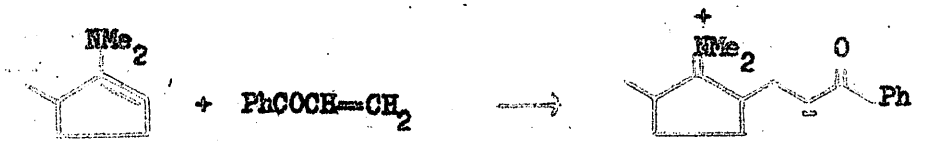
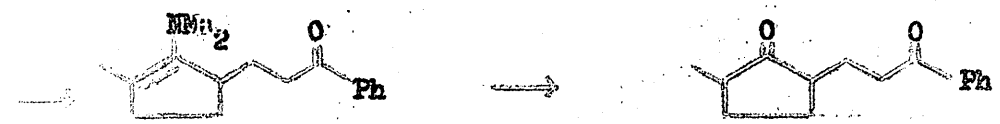


(64)

Scheme (f).

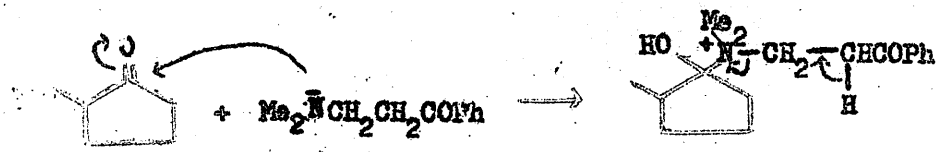


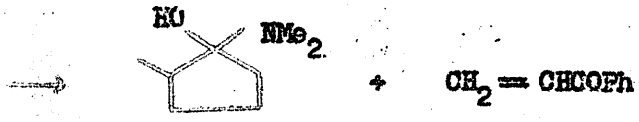


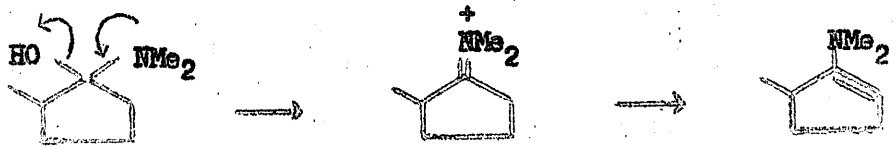


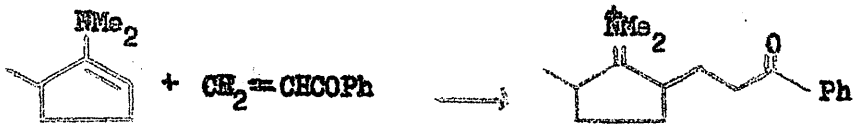
(103)

Scheme (g).



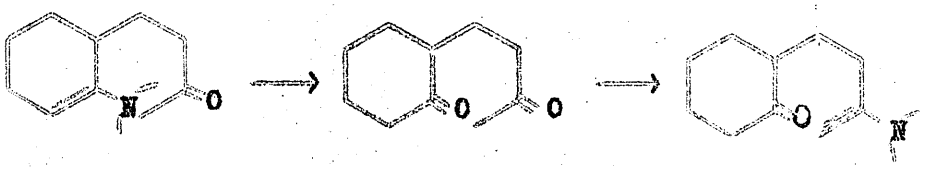


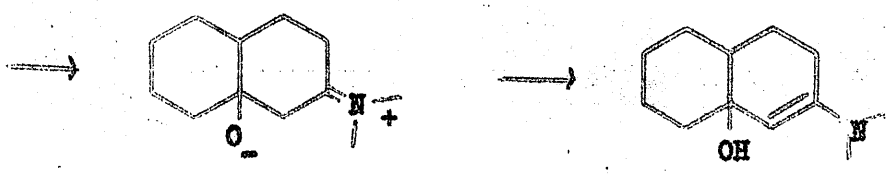




(103)

Scheme (h)





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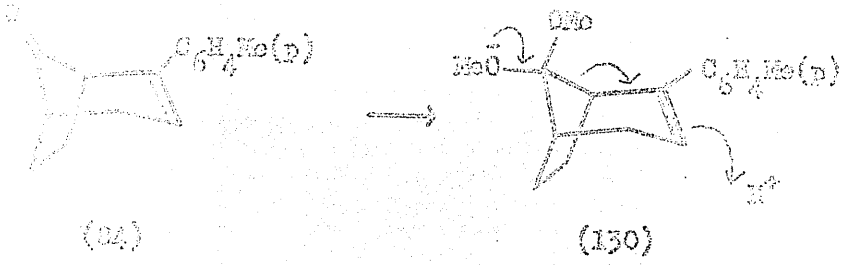
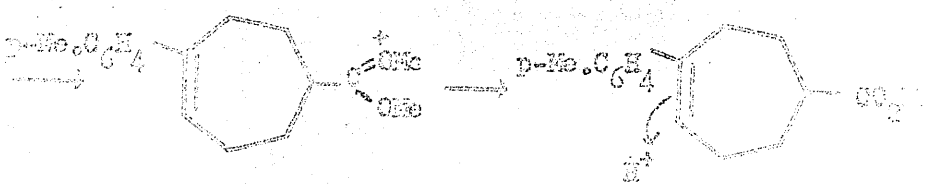


(24)

(130)



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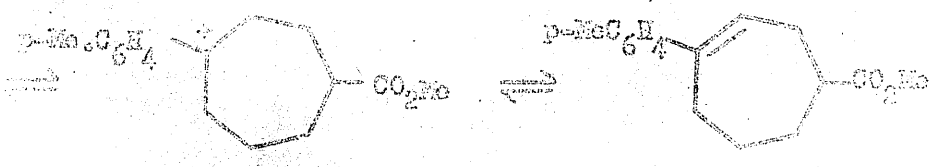
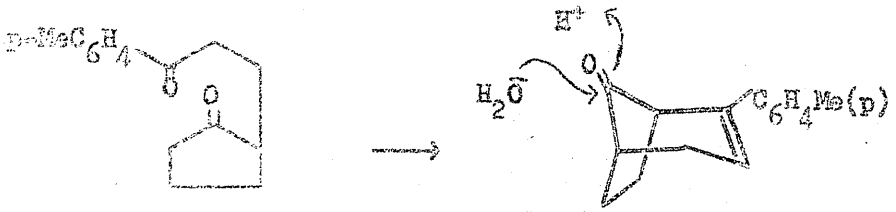


(98)

Scheme (1).



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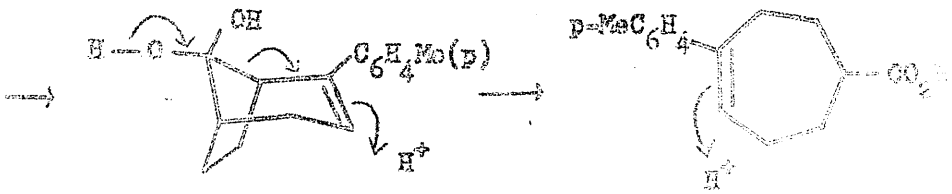

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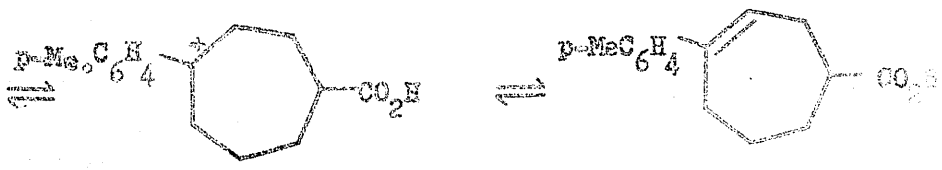


(73)

REFERENCES

1. Stobbé, J. prakt. Chem., 1912, 86, 232 and 238.

2. Stork, Kriszolara, Landesman, Szmuszkovez, and Terrell, J. Amer. Chem. Soc., 1963, 85, 207.

3. Bergmann, Ginsburg and Pappo, "Organic Reactions", Vol. 10, Wiley, 1959.

4. Maxwell, Ph.D. Thesis, 1965, University of Glasgow.

5. Bredt, Annalen, 1924, 437, 1.

6. Cope and Hermann, J. Amer. Chem. Soc., 1950, 72, 3405.

7. Burnell and Taylor, J.C.S., 1954, 3636.

8. Burnell and Taylor, J.C.S., 1955, 2054.

9. Gill, James, Lions and Potts, J. Amer. Chem. Soc., 1952, 74, 4923.

10. Fujimoto, J. Amer. Chem. Soc., 1951, 73, 1856.

11. Heard and Ziegler, J. Amer. Chem. Soc., 1951, 73, 4037.

12. Kosak and Hartough, Org. Syn., Coll. Vol. III, 14.

13. Bellamy, "The Infra-Red Spectra of Complex Molecules", Methuen and Co., 1954, p.128.

14. Julia, Eschenmoser, Heusser and Tarkoy, Helv. Chim. Acta, 1953, 36, 1885.

15. Mannich and Koch, Chem. Ber., 1942, 75, 803.

16. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, Inc., 1962, p. 45.

17. Woodward, Sondheimer, Taub, Heusler and McLamore, J. Amer. Chem. Soc., 1952, 74, 4223.

18. Zwahlen, Horton and Fujimoto, J. Amer. Chem. Soc., 1957, 79, 3131.

19. Fujimoto and Zwahlen, J. Org. Chem., 1960, 25, 445.

20. Dauben, Roswell and Templeton, J. Amer. Chem. Soc., 1961, 83, 5006

21. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, Inc., 1962, p. 52.

22. duFeu, McQuillin and Robinson, J.C.S., 1937, 53.

23. Hussey, Peng Liao, and Baker, J. Amer. Chem. Soc., 1953, 75, 4727.

24. Wilds, Hoffman and Pearson, J. Amer. Chem. Soc., 1955, 77, 647.

25. Crowley and Robinson, J.C.S., 1938, 2001.

26. Johnson, Korst, Clement and Dutta, J. Amer. Chem. Soc., 1960, 82, 614.

27. Dauben and McFarland, J. Amer. Chem. Soc., 1960, 82, 4245.

28. Corey and Nozoe, J. Amer. Chem. Soc., 1963, 85, 3527.

29. Wilds and Shunk, J. Amer. Chem. Soc., 1943, 65, 469.

30. Julia, Bull. Soc., Chim. Fr., 1954, 780.

31. Sands., J. Org. Chem., 1963, 28, 1710.

32. Cornubert and Borrel, Bull. Soc. Chim. Fr., 1930, 301.

33. Shive, Crouch and Lochte, J. Amer. Chem. Soc., 63, 2979.

34. Ross and Levine, J. Org. Chem., 1964, 29, 2341.

35. Munn and Rapson, J.C.S., 1949, 825.

36. Colonge, Dreux and Delplace, Bull. Soc. Chim. Fr., 1956, 1638.

37. Stork and Landesman, J. Amer. Chem. Soc., 1956, 78, 5128.

38. Schreiber, Leimgruber, Pesaro, Schudel, Threlfall and Eschenmoser, Helv. Chim. Acta, 1961, 44, 555.

39. Lednicer, J. Org. Chem., 1964, 29, 2481.

40. Adamson and Billinghurst, J.C.S., 1950, 1040.
Adamson, Barret, Billinghurst and Jones, J.C.S., 1958, 312.

41. Zweifel and Brown, "Organic Reactions", Vol. 13, Wiley, 1963.

42. Brown and Subba Rao, J. Amer. Chem. Soc., 1960, 82, 681.
Brown and Korytnyk, J. Amer. Chem. Soc., 1960, 82, 3866.

43. Bowden, Heilbron, Jones and Weedon, J.C.S., 1946, 39.

44. Knott, J.C.S., 1947, 1190.

45. Maxwell, Org. Syn., Coll. Vol. III, 305.

46. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, Inc., 1962, p. 46.40

47. Stamper and Aycock, J. Amer. Chem. Soc., 1954, 76, 2786.

48. Baker, "Hyperconjugation", Oxford Press, 1952.

49. Brewster and Eliel, "Organic Reactions", Vol. 7., Wiley, 1953.

50. Goldsmith and Hartman, J. Org. Chem., 1964, 29, 3524.

51. Stork and Dowd, J. Amer. Chem. Soc., 1963, 85, 2178.

52. Horii, Iwata and Tamura, J. Org. Chem., 1964, 29, 2768.

53. Spencer and Schmiegel, Chem. and Ind., 1963, 1765.

54. Blicke and Bruckhalter, J. Amer. Chem. Soc., 1942, 64, 451.

55. Foote and Woodward, Tetrahedron, 1964, 20, 687.

56. LeBel and Spurlock, Tetrahedron, 1964, 20, 215.

57. Schleyer, Trifan and Bacskai, J. Amer. Chem. Soc., 1958, 80, 6691.

58. Cristol, Mohrig and Florde, J. Org. Chem., 1965, 30, 1956.

59. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, Inc., 1962, p. 36.

60. Vogel and Schinz, Helv. Chim. Acta, 1950, 33, 116.

61. Dev and Rai, J. Indian Chem. Soc., 1957, 34, 266.

62. Shusherina, Levina, Lur'e and Zdanovich, Chem. Abs., 1956, 50, 13887 f.

63. Shusherina, Levina and Lur'e, Chem. Abs., 1959, 53, 2175 b.

64. Wilds, Nowak and McCaleb, Org. Syn., Coll. Vol. IV, 281.

65. Birch, J.C.S., 1944, 430.

66. Mannich and Lammering, Chem. Ber., 1922, 55, 3510.

67. Wheatley, Fitzgibbon and Chensy, J. Amer. Chem. Soc., 1954, 76, 4490.

68. Ginsberg, Lederman and Papa, J. Amer. Chem. Soc., 1953, 73, 4587.

PART II

INTRODUCTION AND DISCUSSION

A recent synthesis [1] of eight and nine membered carbocycles by cleavage of the one-carbon bridge of bicyclo-(3,3,1)-nonane and bicyclo-(4,3,1)-decane derivatives, utilised an extremely facile, base catalysed, β -elimination of the tosyloxy group of (1). Treatment of a mixture of the epimeric tosylates (2) with sodium ethoxide afforded the cyclo-octene diester (3) and unchanged starting material. Examination of models showed that the equatorial epimer was suitably aligned for β-elimination as shown in scheme (a), while the axial epimer was not, and it was assumed that a considerable difference in reactivity existed between the two forms, resulting in recovery of the axial epimer. This was verified by the failure of sodium ethoxide to promote any reaction of this epimer even on prolonged reflux.

It was felt that application of this reaction to the bicyclo-(3,2,1)-octane system might provide further information about the apparent disparity in reactivity between the epimers, in addition to affording an alternative route to a cycloheptene acid, such as (4). The previously prepared aldehyde-ester (5) (see Part I, p.24), was chosen as starting material and cyclisation to the alcohol (6) was studied by a number of methods.

Reaction of the aldehyde-ester (5) with concentrated hydrochloric acid, acetic acid and water on a steam bath for 4.5 hrs. yielded a mixture of acetate (7) and alcohol (6) similar to that obtained with concentrated hydrochloric acid-acetic acid mixtures at room temperature (see Part I). Concentrated sulphuric acid produced a complex mixture and concentrated sulphuric acid in ethanol

produced a mixture of the alcohol (6) with two less polar compounds, thought to be the corresponding epimeric ethyl ethers (8) [2]. p-Toluene sulphonic acid in benzene also produced the epimeric alcohols together with two other compounds tentatively identified as the corresponding tosylates (9) by comparison of their R_f on t.l.c. with that of authentic samples, prepared later.

Although these acid catalysed ring closures produced the desired compound, the formation of by-products required tedious chromatographic separation, since distillation at water-pump pressure resulted in partial decomposition of the alcohol (6) to the aldehydic precursor. The formation of small quantities of the desired alcohols in the preparation of the aldehyde-ester (5) suggested that more vigorous treatment with triethylamine would provide an alternative preparative method. Refluxing the aldehyde-ester (5) in benzene with triethylamine for 48 hrs. yielded mixtures of the alcohol and aldehyde after neutralising and washing the benzene solution. The rather poor recovery from the reaction led to chloroform extraction of the washings which afforded uncontaminated alcohol in reasonable quantities. Chromatographic filtration was used to purify this material. The total yield of alcohol was 60%. Comparable yields could be obtained by preparing the alcohol (6) directly from 2-carbethoxy-cyclopentanone without isolation of the aldehyde-ester. No estimation of the ratio of the epimers was possible nor were equilibration studies considered profitable since g.l.c. analysis like distillation, caused considerable retro-aldolisation.

Careful chromatography of the epimeric mixture on fine mesh silica afforded pure samples of each epimer. By analogy with the relative polarity on t.l.c. of the related epimeric alcohols (10),[2] the less polar was tentatively assigned the equatorial configuration (6a). This assignment was later confirmed (see p.132) by study of the n.m.r. spectra of these and derived compounds.

The infra-red spectrum of both epimers exhibited hydroxyl and carbethoxyl (1733cm.$^{-1}$) absorption together with the high $\nu_{C=O}$ (1760cm.$^{-1}$) typical of bicyclo-(3,2,1)-octanones with the ketonic function at C_8. The n.m.r. spectra provided further confirmation of the alcoholic structure. The ethyl ester appeared in both epimers as the typical triplet (8.72 τ), quartet (5.82 τ) pattern. The hydroxylic proton and the C_4 proton were found at 5.42 τ and 6.0 τ in the equatorial compound and at 6.57 τ and 5.7 τ in the axial epimer, the latter peak in both being partially obscured by the ester methylene.

Since analytical data for the alcohols were not obtained because of their thermal instability, the O-acetate of each was prepared by treatment with acetic anhydride in pyridine. These compounds were found to be identical with the acetates isolated from the reaction of the aldehyde-ester (5) with hydrochloric acid and acetic acid. (Infra-red spectrum, t.l.c., g.l.c.) (see Part I, p.25).

Treatment of a small quantity of each alcohol with p-toluene sulphonyl chloride in pyridine failed to yield crystalline products although the infra-red spectra and t.l.c. suggested that in both cases the tosylate had formed. However, treatment

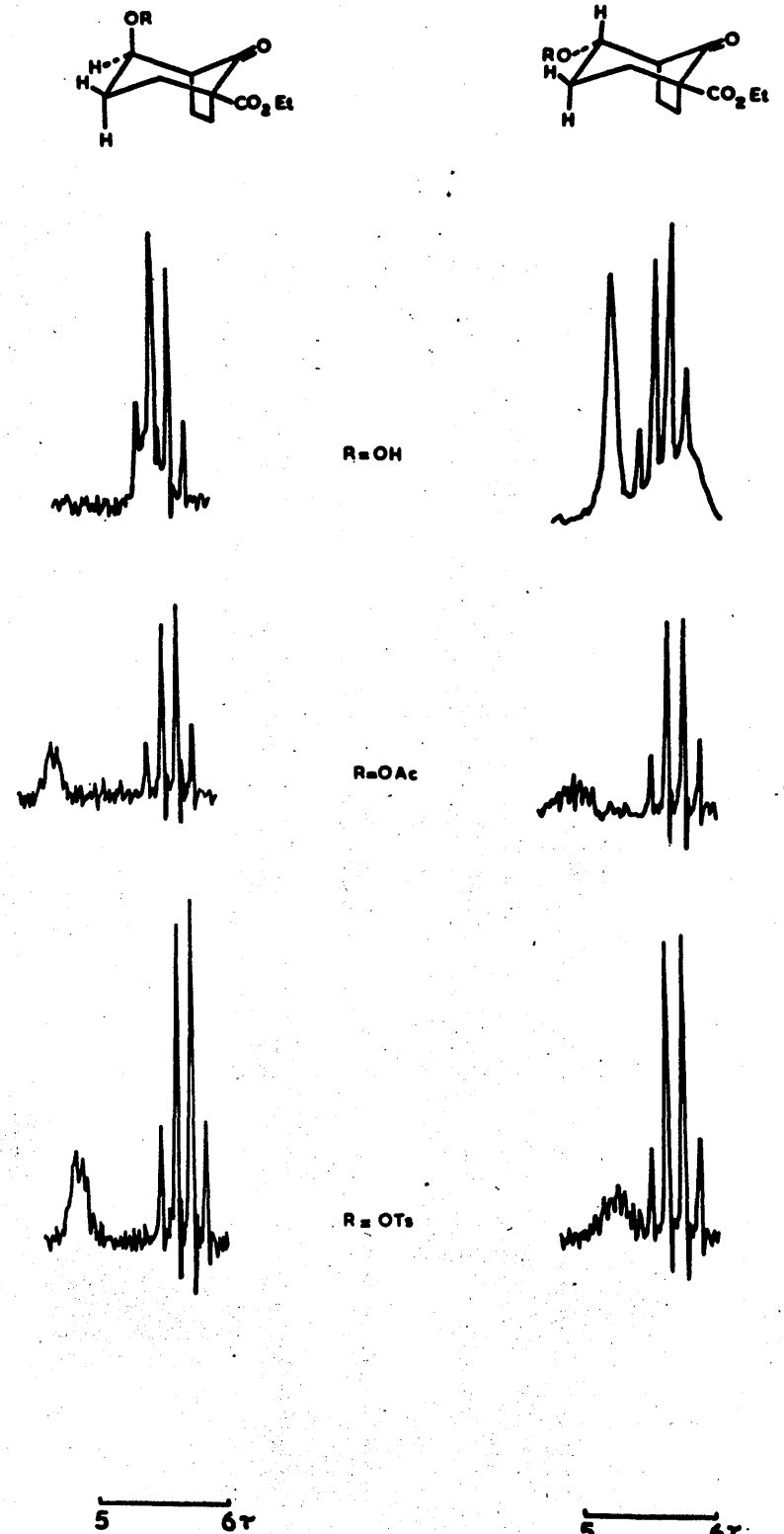


Fig.1.

of the aldehyde-ester (5) under these conditions, brought about both cyclisation and tosylation, and yielded a solid mixture of two compounds (t.l.c.) separated by chromatography. The infra-red spectra of these epimeric compounds showed that both had the tosylate structure (9) (ν 1375cm.$^{-1}$ and 1175cm.$^{-1}$). This was confirmed in each case by the n.m.r. spectrum which exhibited the typical AB quartet at 2.61 τ and 2.15 τ for the phenyl protons of the tosylate group and the tosylate methyl at 7.5 τ. The C_4 proton appeared at 4.94 τ in one epimer and 5.34 τ in the other.

Three related epimeric pairs were now available, the less polar alcohol having been converted into the less polar acetate and tosylate. The configurations of these compounds were established by examination of the C_4 proton signal in the n.m.r. spectra (see Fig. 1). In each epimeric pair, the C_4 proton of the less polar epimer absorbed at higher field than that of the more polar compound and in accordance with known principles [3], the former were identified as having the axial proton and thus the substituent was in the equatorial configuration. In addition to the considerations discussed by Jackman [3], in this case the axial proton also lies closer to the shielding cone of the C_8 ketone.

More conclusive evidence to support these configurational assignments in this rigid structure, was made available by inspection of the breadth of the multiplet for the C_4 proton. As discussed by Hassner [4], an axial proton, coupled with adjacent axial and equatorial protons, should result in a much wider band than an equatorial proton coupled with adjacent axial and equatorial protons. In the alcohols (6a) and (6b), although the C_4 proton was partially obscured by the ester methylene, this was found to

be the case and it was confirmed in the acetates (7a) and (7b) and tosylates (9a) and (9b) where the C_4 proton signal was clearly visible, as shown in Fig. 1. Measurement of the half-band widths ($W^{\frac{1}{2}}$) of the multiplets showed that they lay within the limits quoted [4] for axial and equatorial protons (See Table 1 below).

TABLE 1.	H>C<OR (4) signal (τ)	$W^{\frac{1}{2}}$ c.p.s.	C_4 proton assignment
Alcohols (6a)	~6.0	~30	a
(6b)	~5.7	~12	e
Acetates (7a)	5.07	20.4	a
(7b)	4.89	9.0	e
Tosylates (9a)	5.34	18.0	a
(9b)	4.94	9.0	e

The configurations of the alcohols and tosylates having been established, attention was directed to the preparation of the latter in quantity. Although the tosylates had been prepared from the alcohols and also from the aldehyde-ester (5), the simplest method of preparation was found to be direct conversion of 2-carbethoxycyclopentanone to the alcohols (6) and treatment of this crude reaction mixture with p-toluene sulphonyl chloride in pyridine. The dark viscous oil obtained by this procedure

was stored in a refrigerator until it solidified and then washed with cold ether to yield a crystalline mixture of the tosylates. Fractional crystallisation from ethanol afforded initially the equatorial (9a) and subsequently the axial epimer (9b).

An examination of models revealed that the equatorial tosylate group was suitably aligned to undergo base-catalysed β-elimination with simultaneous cleavage of the bridge at the C_8 position as shown in scheme (b), while it was thought that the axial would only yield the olefin (12) by expulsion of the tosylate group, outlined in scheme (c).

The equatorial tosylate reacted completely after 15 mins. reflux with a slight molar excess of ethanolic sodium ethoxide, to yield an oil which, after distillation, was shown by g.l.c. analysis to consist of not less than 90% of the gem-diester (11). This compound was identified by the absence of ultra-violet absorption, by the carbonyl absorption of 1732cm.$^{-1}$ and by double bond absorption at 3022 cm.$^{-1}$ (CCl_4) and 684cm.$^{-1}$ (CS_2) in the infra-red spectrum, the latter value being characteristic of a cis-disubstituted double bond. The extreme simplicity of the n.m.r. spectrum of this compound could only be explained by such a symmetrical molecule. The typical ethyl ester pattern of a 6-proton triplet at 8.77 τ and a 4-proton quartet at 5.88 τ was evident, together with a singlet for 8 protons at 7.83 τ and a finely split triplet at 4.37 τ for the two olefinic protons. The methylene protons on C_2 and C_7 have identical chemical shifts due to the symmetry of the molecule as do the protons on C_3 and C_6. The occurrence of all eight protons in a singlet, however, also requires the protons on C_2 and C_3 to have identical chemical shifts. Consideration of

Shoolery's Rules indicates that a methylene group appearing at 8.47 τ is moved downfield by the presence of two β - carbethoxy functions to ~7.95 τ. The allylic protons are also expected to appear in this region at ~8.0 τ. Thus on the basis of these empirical rules it appears feasible that all the methylene protons may have identical chemical shift. Examination of models confirms that the C_2 and C_7 protons lie only in the deshielding zones of the ester functions (13) and thus a downfield shift would be expected.

The only other compound formed (< 10%) was subsequently identified as the isomeric diester (14) by g.l.c. analysis.

Methanolic potassium hydroxide hydrolysed the gem-diester (11) to the corresponding diacid (15), which also had a simple n.m.r. spectrum showing a singlet for eight protons at 7.60 τ and a broad unresolved singlet at 4.20 τ for the olefinic protons.

Attempted thermal decarboxylation of the diacid (15) yielded an oil which appeared from study of the infra-red spectrum, to consist of an acidic compound and a lactone, presumably (16). A more satisfactory procedure involved refluxing the diacid with copper powder in pyridine for 40 mins., which yielded more than 80% of cyclohept-4-ene carboxylic acid (4). A slightly impure sample of this compound, supplied by Professor Stork[3], had similar m.p. and infra-red spectrum to this material and the corresponding methyl esters (diazomethane) had identical retention times on g.l.c. As a result of the destruction of the symmetry of the molecule, the n.m.r. spectrum showed a methylene complex from 8.4 τ - 7.4 τ and a finely split triplet at 4.23 τ for the olefinic protons.

The successful degradation of the gem-diester (11) to the known compound (4) confirmed the relationship of the carboxyl group and

the double bond suggested by the n.m.r. spectrum.

The isolation of both the equatorial and axial tosylates provided the opportunity of verifying the gross disparity in reactivity noted in the related epimeric tosylates (2) [1], under similar reaction conditions (see p.125).

Treatment of the axial tosylate (9b) with ethanolic sodium ethoxide at reflux for 15 mins., yielded 88% of the unsaturated diester (14), which showed double carbonyl absorption in the infra-red spectrum at 1739cm.$^{-1}$ (ester) and 1711cm.$^{-1}$ (α,β-unsaturated ester), absorption at λ_{max} 223mμ (ϵ=8,000) in the ultra-violet spectrum, and a slightly subsplit triplet at 2.93 τ (1H) for the olefinic proton in the n.m.r. spectrum. This also showed the different environments of the ester groups, the methyl protons occurring as two overlapping triplets at 8.77 τ and 8.74 τ and the methylenes as overlapping quartets centred at 5.91 τ and 5.87 τ.

Two possible mechanisms for the formation of this product can be visualised, (a) β-elimination of the tosylate group to yield the olefin (12), followed by bridge-fission and double bond migration in a manner similar to that described by Cope [6], as in scheme (d) or (b), cleavage of the β-keto-ester system followed by β-elimination of the tosylate group as outlined in scheme (e). The former path seems unlikely since the axial tosylate (2b) failed to react under similar conditions, thus scheme (e) represents the correct mechanism. The failure of (2b) to undergo any reaction can best be explained by assuming that bridge-fission did, in fact, occur but that the presence of the methyl group rendered β-elimination of the tosylate impossible. Consequently a transannular reaction of the type common in this eight membered ring system [1], resulted in reformation of the starting material, as indicated in scheme (f).

G.l.c. analysis of the products of base catalysed reaction of both the equatorial and axial tosylates showed that the impurity present in the former was, in fact, the diester (14), which was obtained as the only product from the latter. This may have resulted from traces of the axial epimer not detected by t.l.c. in the starting material or more probably by initial bridge-fission of the equatorial tosylate and β-elimination of the tosylate group occurring as a competing mechanism.

It should be pointed out at this stage that in theory, the equatorial tosylate could have yielded the same product as the axial epimer. That it did not, established the disparity in reactivity which was previously postulated [1]. However, it is now clear that the successful and uncomplicated conversion of the mixed tosylates (2)→(3) depended not so much on the gross disparity in reactivity between the axial and equatorial epimers as on the fact that the stereochemistry of each favoured separate reaction paths and that one of these paths was blocked by the presence of the bridgehead methyl function.

Hydrolysis of the α,β-unsaturated ester (14) with methanolic potassium hydroxide yielded the diacid (17), which was stable to the conditions that produced decarboxylation of the isomeric gem-diacid (15). It had absorption λ_{max} 223mμ (ϵ = 5,210) in the ultra-violet spectrum and showed an olefinic proton at 2.95 τ in the n.m.r. spectrum.

The acid was found to be identical to that obtained in 50% yield from the action of methanolic potassium hydroxide on the aldehyde-ester (5) (Part 1, p.76). This simple two stage synthesis of

1,5-dicarboxycyclohept-1-ene (17) from 2-carbethoxycyclopentanone can be envisaged mechanistically as occurring by ring closure and hydrolysis of the aldehyde-ester (5) to the alcohol (6) followed by cleavage of the bridge and β-elimination of the hydroxyl function. The poor leaving-group potential of the hydroxyl function in basic solution rendered unlikely the β-elimination of the equatorial hydroxyl with concomitant bridge-fission and it was considered that both epimers followed the same route. This would account for the absence of the gem-diacid (15) in the product (g.l.c.).

EXPERIMENTAL

1-Ethoxycarbonyl-4-hydroxybicyclo-(3.2.1)-octan-8-one (6)

(a) Dilute hydrochloric acid/acetic acid.

A solution of the aldehyde-ester (5) (15g.) and concentrated hydrochloric acid (15 ml.) in acetic acid (120 ml.) and water (40 ml.) was heated on a steam bath for 4.5 hrs. then allowed to stand at room temperature overnight. After neutralisation with a saturated solution of sodium bicarbonate, the aqueous solution was extracted with ether and chloroform. The organic solutions were separately washed with brine and dried ($MgSO_4$) before combination. Removal of the solvent gave a yield of 5.36g. of oil which had similar infra-red spectrum and t.l.c. to the crude product obtained using concentrated hydrochloric acid at room temperature (see Part 1), i.e. the reaction product consisted of a mixture of the desired epimeric alcohols (6) and the corresponding acetates (7).

(b) Concentrated sulphuric acid.

The aldehyde-ester (5) (5.7g.) was treated dropwise with concentrated sulphuric acid (11g.) at 0° and the resultant solution was allowed to stand overnight at room temperature. The solution was poured into ice and water, neutralised with sodium bicarbonate and extracted with ether. The ethereal solution was washed, dried ($MgSO_4$) and concentrated to yield 1.28g. of an oil which was shown to be a complex mixture containing the desired alcohols (t.l.c.).

(c) Sulphuric acid/ethanol

A stirred solution of the aldehyde-ester (5) (1g.) in ethanol (25 ml.) at 0° was treated with a solution of concentrated

sulphuric acid (1 ml.) in ethanol (25 ml.) and allowed to stand for 48 hrs. at room temperature. The reaction mixture was poured onto water and extracted with chloroform. The organic solution was washed with 4N sodium hydroxide and brine, dried ($MgSO_4$) and concentrated, yielding 1.02g. of an oil which was shown by t.l.c. to consist of the desired alcohol (6) as a mixture of epimers together with two less polar products. Chromatography on silica effected a separation of the alcohols from the less polar impurities which were tentatively identified as the corresponding ethyl ethers (8) because of the lack of hydroxyl absorption in the infra-red spectrum and by analogy with the results of Martin [2].

(d) p-Toluene sulphonic acid/toluene.

A mixture of p-toluene sulphonic acid (0.5g.) and sodium-dried toluene (25 ml.) was refluxed for 1.5 hrs. with a water separator. When reflux subsided the water separator was drained and refilled with toluene and the aldehyde-ester (5) (1g.) in toluene was rapidly added to the reaction mixture. Reflux was restarted and continued for 3 hrs., then cooled and the solution neutralised by the addition of anhydrous potassium carbonate. Filtration and removal of the toluene afforded a yellow oil shown by t.l.c. (40% ethyl acetate in petrol) to consist of the desired alcohol (6) as a mixture of epimers together with two less polar compounds which had similar R_f on t.l.c. to samples of the epimeric tosylates (9), prepared later.

(e) Triethylamine/benzene.

A solution of the aldehyde-ester (5) (20g.) and triethylamine

(20 ml.) in anhydrous benzene (200 ml.) was refluxed for 48 hrs., then cooled and neutralised with acetic acid. The reaction mixture was washed with brine, 4N sodium hydroxide, brine and dried ($MgSO_4$). The combined brine washes were extracted with chloroform and dried ($MgSO_4$). Removal of the benzene gave an oil shown by t.l.c. (40% ethyl acetate in petrol) to consist of the epimeric alcohols (6) and the aldehyde-ester (5). Chromatography on silica initially afforded mixtures of the three components and subsequently mixtures of the epimeric alcohols. The chloroform solution, on concentration yielded only the epimeric alcohols which were purified by chromatographic filtration. The total yield of the alcohols obtained was 12.5g. (62.5%).

Comparable yields of the alcohols were obtained by reacting 2-carbethoxycyclopentanone and acrolein as described in the synthesis of the aldehyde-ester (5) and then treating the crude reaction mixture with additional triethylamine for 48 hrs. at reflux in the manner detailed above. There appeared to be no advantage in isolating and purifying the aldehyde-ester.

Separation and identification of the epimeric alcohols (6a) and (6b).

A pure sample of each epimeric alcohol was obtained by careful chromatography. The epimeric mixture of alcohols (1g.) were dissolved in ether and chromatographed on fine mesh silica (30g.). Elution with ether afforded initially the pure equatorial isomer (6a), (280 mgm.) then mixtures of both epimers and finally the pure axial isomer (6b), (440 mgm.). Attempts to distil these compounds

for analysis resulted in each case in a mixture of both epimers, together with aldehyde-ester (5). Similar retro-aldolisation and isomerisation occurred during attempts at g.l.c. analysis. The equatorial epimer (6a) had absorption in the infra-red spectrum (CCl_4) at 3629cm.$^{-1}$ (free hydroxyl), a broad band at 3440-3540cm.$^{-1}$ (bonded hydroxyl), 1760cm.$^{-1}$ (ketone), 1733cm.$^{-1}$ (ester) and bands at 1294(m), 1268(s), 1252(m), 1198(m), 1175(s), 1095(m), 1070(s), and 1015cm.$^{-1}$(m). The n.m.r. spectrum had significant peaks at 5.42 τ(poorly defined singlet, 1H) assigned to the hydroxyl proton and 6.0 τ(multiplet, 1H) on which was superimposed the methylene protons of the ester function. This multiplet was assigned to the axially situated proton on C_4. The axial epimer (6b) showed absorption in the infra-red spectrum (CCl_4) at 3620cm.$^{-1}$ (free hydroxyl), a broad band at 3420-2540cm.$^{-1}$ (bonded hydroxyl) 1761cm.$^{-1}$ (ketone), 1733cm.$^{-1}$ (ester) and bands at 1295(m), 1272(s), 1241(m), 1198(s), 1174(m), 1111(m), 1096(m), 1066(m), 1044(m), 1017(m) and 943cm.$^{-1}$(m). The n.m.r. spectrum showed significant peaks at 5.7 τ (multiplet, 1H), largely concealed by the superimposed methylene protons of the ethyl ester group and a somewhat broadened singlet at 6.57 τ(1H). The former peak is attributed to the equatorially situated proton on the carbon substituted with the hydroxyl function, and the other to the hydroxyl proton. The peaks in the spectrum of both epimers attributed to the hydroxyl protons were verified by D_2O exchange.

Equatorial 1-ethoxycarbonyl-4-acetoxybicyclo-(3.2.1)-octan-8-one (7a)

The less polar equatorial alcohol (6a) (280 mgm.) was refluxed for 1 hr. with acetic anhydride (2 ml.) in pyridine (6 ml.). After

cooling, the reaction mixture was poured onto ice and water and extracted with ether. The ethereal solution was washed with 6N hydrochloric acid and brine and dried ($MgSO_4$). Removal of the solvent yielded 270 mgm. of the equatorial acetate (7a) which was distilled for analysis b.p. 122-128°/0.8 mm. (Found C, 61.35%, H, 7.21%. $C_{13}H_{18}O_5$ requires C, 61.41%, H, 7.14%). The infra-red spectrum (CCl_4) exhibited a broad carbonyl region with two peaks at 1762cm.$^{-1}$ and 1736cm.$^{-1}$. Other notable peaks occurred at 1302(m), 1298(m), 1270(s), 1233(s), 1221(s), 1187(m), 1173(s), 1052(s), 1028(m) and 1019cm.$^{-1}$(m). The n.m.r. spectrum showed peaks at 8.01 τ (singlet, 3H) for the acetate group, and a broad multiplet centred at 5.07 τ attributed to the proton on C_4. This peak had a half-band width of 20.4 cps. indicating the axial environment [4] of the proton thus proving that this compound is the equatorial acetate (7a). This compound had identical infra-red spectrum and R_f on t.l.c. to the less polar of the acetate products of hydrochloric acid-acetic acid treatment of the aldehyde-ester (5). G.l.c. analysis confirmed that these products were identical.

Axial 1-ethoxycarbonyl-4-acetoxybicyclo-(3,2,1)-octan-8-one (7b).

Similar treatment of the more polar axial alcohol (6b) (350 mgm.) furnished 180 mgm. of the axial acetate (7b). Recrystallisation of the solid reaction product from benzene-petrol mixtures gave an analytical sample m.p. 77-77.5°. (Found C, 61.76%, H, 7.35%. $C_{13}H_{18}O_5$ requires C, 61.41%, 7.14%). The infra-red spectrum (CCl_4) showed absorption in the carbonyl region as a broad band with three peaks at 1765cm.$^{-1}$, 1746cm.$^{-1}$ and 1735cm.$^{-1}$. Other bands were recorded at 1295(m), 1275(s), 1235(s), 1204(s), 1174(m), 1135(m), 1115(m), 1095(m), 1055(m), 1037(m) and 1009cm.$^{-1}$(s). The n.m.r. spectrum showed a singlet, (3H) at 7.98 τ for the acetate function

and a multiplet at 4.89τ for the proton on C_4. The half-band width of this peak was 9 c.p.s., typical [4] of an equatorial proton indicating the axial nature of the acetate function. This compound was identical (infra-red spectrum, t.l.c.) to the more polar acetate formed in the attempted hydrochloric acid-acetic acid ring closure of the aldehyde-ester (5). Similar g.l.c. retention times were recorded for both compounds.

1-Ethoxycarbonyl-4-tosyloxybicyclo-(3.2.1)-octan-8-one(9).

(a) From 2-ethoxycarbonylcyclopentanone

A stirred solution of 2-ethoxycarbonylcyclopentanone (100g.) and triethylamine (7.5 ml.) in anhydrous benzene at 0° was treated dropwise with acrolein (50 ml.) and stirring continued for 24 hrs. at room temperature. A further quantity of triethylamine (80 ml.) was added and the reaction mixture refluxed for 48 hrs. The dark solution was then cooled to 0° and a solution of p-toluene sulphonyl chloride (78g.) in anhydrous pyridine (150 ml.) added dropwise over 30 mins. After standing for 4 days the mixture was poured onto ice and left for 24 hrs., diluted with benzene and the organic layer washed repeatedly with 6N hydrochloric acid, then saturated sodium bicarbonate and brine and dried ($MgSO_4$). Removal of the volatiles yielded 180g. of a dark oil which solidified after storage in a refrigerator. Addition of ether furnished a colourless solid mixture of the epimeric tosylates (9). Fractional crystallisation from ethanol yielded substantial quantities of each epimer. The equatorial tosylate (9a) m.p. 95.5-96.5° (ethanol). (Found C, 59.05%, H, 6.21%. $C_{18}H_{22}SO_6$ requires C, 59.01%, H, 6.05%). The

infra-red spectrum (CCl_4) showed absorption at 1766cm.$^{-1}$ (ketone) 1733cm.$^{-1}$ (ester) 1375 and 1175cm.$^{-1}$ (tosylate). The n.m.r. spectrum had peaks constistant with the tosylate and ethyl ester functions together with a multiplet at 5.34 τ (half band width of 18 c.p.s.) attributed to the proton on C_4 in an axial environment [4].

The axial tosylate (9b) recrystallised from ethanol, m.p. 95-96.5° (Found C, 59.23%, H, 6.01%. $C_{18}H_{22}SO_6$ requires C, 59.01%, H, 6.05%). The infra-red spectrum (CCl_4) of this material showed absorption at 1766cm.$^{-1}$ (ketone), 1736cm.$^{-1}$ (ester), 1375 and 1175cm.$^{-1}$ (tosylate) and the n.m.r. spectrum showed a multiplet at 4.94 τ (half band width, 9 c.p.s.) assigned to the proton on C_4 which is equatorial [4].

The equatorial epimer (9a) is the less polar compound on t.l.c. (40% ethyl acetate in petrol).

(b) <u>From the aldehyde-ester (5).</u>

The aldehyde-ester (5) (4.24g., 0.02m.) was refluxed in pyridine for 4 hrs. then cooled to 0°, stirred and treated in a dropwise manner with a solution of p-toluene sulphonyl chloride (6.0g., 0.03m.) in pyridine (15 ml.) The reaction mixture was stirred for 4 days at room temperature then poured onto ice and water and left for 2 days. The crystalline tosylate mixture was filtered and washed with ether yielding 4.1g., 56%. Separation of the equatorial (9a) and axial (9b) epimers was achieved by chromatography on silica.

(c) <u>From the alcohols (6a) and (6b).</u>

Each epimer of the alcohol (6) (100 mgm.) was treated separately in the usual manner with p-toluene sulphonyl chloride in

pyridine. Neither reaction mixture afforded crystalline material but t.l.c. and infra-red spectroscopy confirmed that tosylation had taken place. The former technique showed that the less polar alcohol yielded the less polar tosylate.

1,1-Diethoxycarbonylcyclohept-4-ene (11).

A solution of the equatorial tosylate (9a) (1.83g., 0.005 m.) in hot anhydrous ethanol (10ml.) was added to a solution of sodium ethoxide [from sodium (0.15g., 0.0065m.) anhydrous ethanol (20 ml.)] at 60° and the reaction mixture stirred and refluxed for 15 mins., then cooled, poured onto ice, acidified (6N HCl) and extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$) and the solvent evaporated yielding 1.16g. of an oil consisting of the desired diester (11) together with <10% of the isomeric compound (14) identified by its g.l.c. retention time. Distillation afforded an analytical sample of (11), b.p. 120°/0.6 mm. (Found C, 64.55%, H, 8.09%. $C_{13}H_{20}O_4$ requires C, 64.98%, H, 8.39%). The infra-red spectrum (CCl_4) showed absorption at 3022cm.$^{-1}$ (double bond) and 1734cm.$^{-1}$ (ester) and in carbon disulphide solution at 684cm.$^{-1}$ (cis double bond). The n.m.r. spectrum showed peaks at 8.77 τ (6H, triplet, ester methyls), 7.83 τ(6H, singlet, C_2, C_5, C_6 and C_7 methylenes), 5.88 τ(4H, quartet, ester methylenes) and at 4.37 τ(2H, finely split triplet, olefinic protons).

1,1-Dicarboxycyclohept-4-ene (15).

The diester (11) (780 mgm.) was dissolved in a solution of potassium hydroxide (2g) in methanol (50 ml.) and allowed to stand for 18

hrs. at room temperature. The methanol was removed under reduced pressure, the residue diluted with water, washed with ether, acidified (6N HCl) and extracted with ether. The ethereal solution was washed with water and dried ($MgSO_4$) yielding 509 mgm. (81%) of the diacid (15) on concentration. Recrystallisation from ethanol afforded an analytical sample m.p. 152-159° (decomp.). (Found C, 58.92%, H, 6.62%. $C_9H_{12}O_4$ requires C, 58.69%, H, 6.57%). The infra-red spectrum (KCl disc) exhibited a broad band at 3500-2500cm.$^{-1}$ (acidic hydroxyl) and a broad carbonyl absorption with two peaks 1720 and 1700cm.$^{-1}$. The n.m.r. spectrum (trifluoroacetic acid) showed peaks at 7.60 τ (8H, singlet, ring methylenes) and 4.20 τ (2H, broad unresolved singlet, olefinic protons).

1-Carboxycycloheat-4-one (4).

Decarboxylation of the diacid (15) by heating at 180° with copper powder for 90 mins. yielded a dark oil showing absorption in the infra-red spectrum at 3300-2600cm.$^{-1}$ (acidic hydroxyl), 1740cm.$^{-1}$ and 1720cm.$^{-1}$. The carbonyl absorption at 1740cm.$^{-1}$ was intense and this was attributed to formation of a lactone expected to have the structure (16). Smaller quantities of this impurity were formed by the following procedure.

The diacid (15) (1.76g.), copper powder and pyridine (30 ml.) were refluxed for 40 mins. The pyridine was removed under reduced pressure, the residue diluted with ether and extracted with 4N sodium hydroxide. The basic extracts were acidified with mineral acid, extracted with ether and the organic solution washed with brine and dried ($MgSO_4$). Concentration afforded the acid (4) (1.1g., 83.3%). Recrystallisation from petrol furnished a sample m.p.

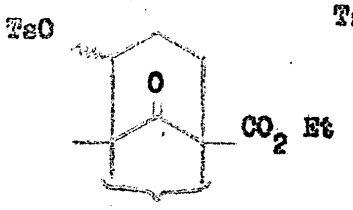
66.5-69.5° (lit.[7] m.p. 65-67°). (Found C, 68.60%, H, 8.85%. $C_8H_{12}O_2$ requires C, 68.55%, H, 8.63%). The infra-red spectrum (CCl_4) showed absorption at 3540 and 3300-2800cm.$^{-1}$ (acidic hydroxyl), 3022cm.$^{-1}$ (double bond), 1755 and 1707cm.$^{-1}$ (acid carbonyl). In carbon disulphide solution the carbonyl absorption showed a broad band at 1710-1700cm.$^{-1}$, and a peak at 682cm.$^{-1}$ for the double bond. The n.m.r. spectrum (CCl_4) showed peaks at 4.25 τ (triplet, 2H) for the olefinic protons, at -2.05 τ for the carboxyl proton and a complex band at 8.4-7.4 τ (9H). A slightly impure, authentic sample of this compound, kindly supplied by Professor Sykes[75] had an identical infra-red spectrum and its methyl ester had similar retention times on a number of g.l.c. columns to the above material.

1,5-Methoxycarbonylcycloheptan-1-one (14).

The axial tosylate (9b) (1.63g., 0.005m.) dissolved in hot anhydrous ethanol (10 ml.) was added to a solution of sodium ethoxide [from sodium (0.15g., 0.0065m.) in anhydrous ethanol (20 ml.)] at 60° and the resulting suspension stirred and refluxed for 15 mins. Using the procedure described for the preparation of the isomeric diester (11), 0.06g., (88.3%) of the pure diester (14) was obtained. Distillation gave a colourless oil b.p. 95°/0.5 mm. (Found C, 64.73%, H, 8.39%. $C_{13}H_{20}O_4$ requires C, 64.98%, H, 8.39%). The infra-red spectrum (CCl_4) showed absorption at 1739cm.$^{-1}$ (ester) and 1711cm.$^{-1}$ (α,β-unsaturated ester). The n.m.r. spectrum exhibited triplets for the protons of the methyl groups of the ester functions at 8.77 τ and 8.74 τ and quartets at 5.91 τ and 5.87 τ for the ester methylene protons. The olefinic proton appeared as a subsplit triplet at 2.93 τ. The ultra-violet spectrum showed absorption λmax. 225 mμ. (ϵ = 8,000).

1,5-Dicarboxycycloheptl-ene (17).

The α,β-unsaturated diester (14) (300 mgm.) was dissolved in a solution of potassium hydroxide (400 mgm.) in methanol (6 ml.) and water (2 ml.) and refluxed for 3.5 hrs. The usual procedure yielded 0.21g. of the diacid (17). Recrystallisation from ethanol and benzene-petrol mixtures gave an analytically pure sample, m.p. 162-165°. (Found C, 58.48%, H, 6.33%. $C_9H_{12}O_4$ requires C, 58.69%, H, 6.57%). The infra-red spectrum showed absorption at 3300-2800cm.$^{-1}$ (acidic hydroxyl) and an unresolved band at 1720-1680cm.$^{-1}$ (carboxyl). The n.m.r. spectrum (dimethyl sulphoxide) showed a triplet at 2.95τ for the olefinic proton and the ultra-violet spectrum had a maximum absorption of λ max = 223 mμ. (ϵ = 5,210).



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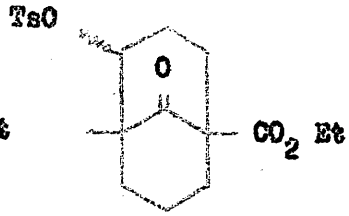

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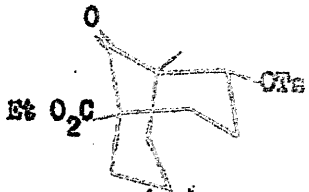

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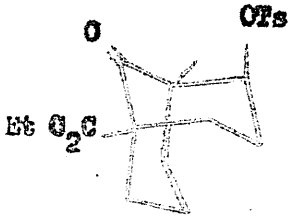

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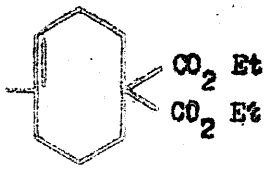

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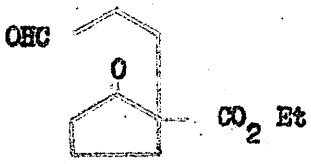

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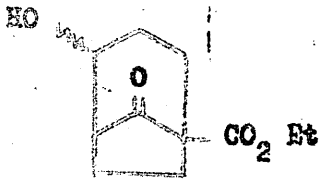

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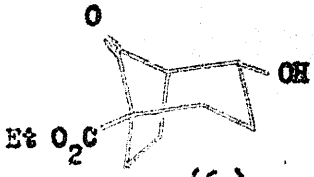

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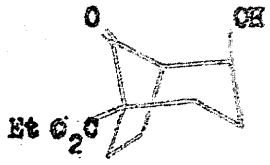

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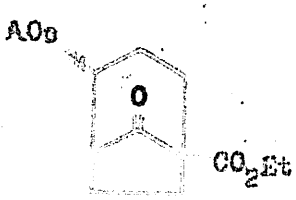

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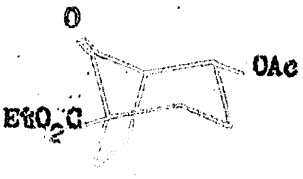

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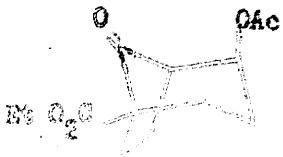

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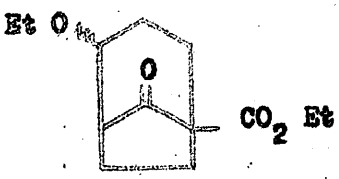

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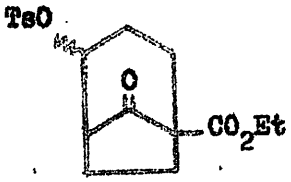

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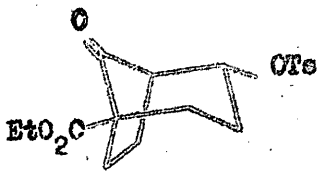
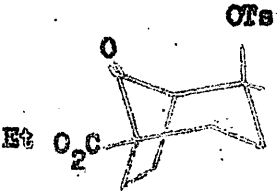
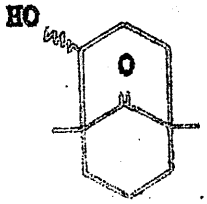


(9a)



(9b)



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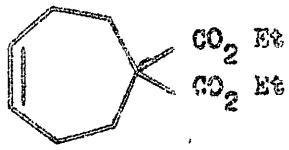

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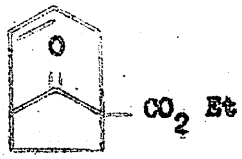

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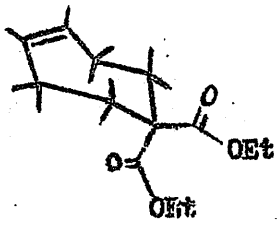

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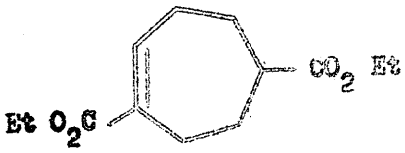
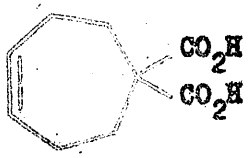


(14)



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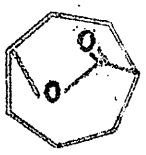
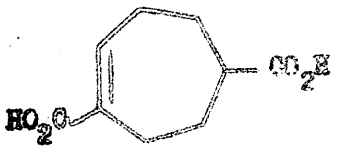
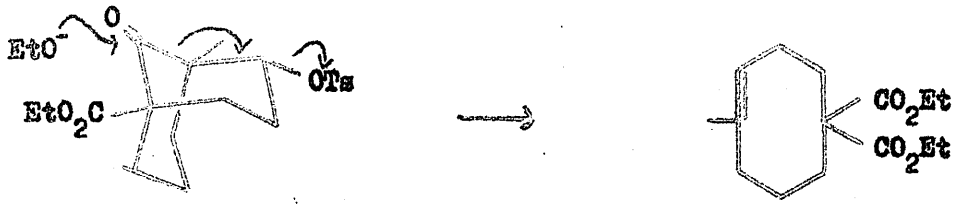


(16)



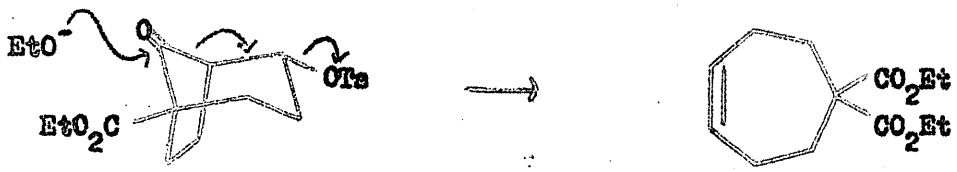
(17)

Scheme (a).



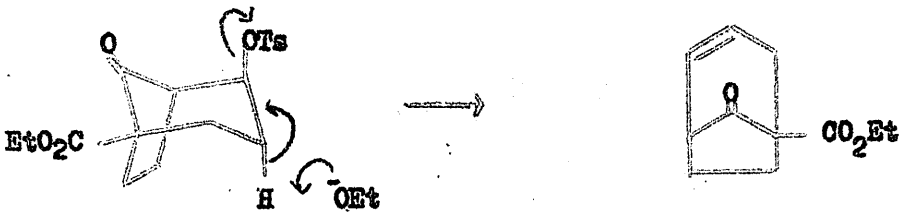
(2a) (3)

Scheme (b).



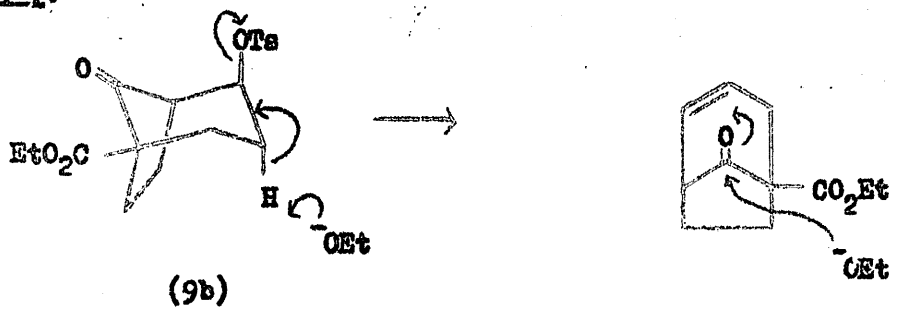
(9a) (11)

Scheme (c).

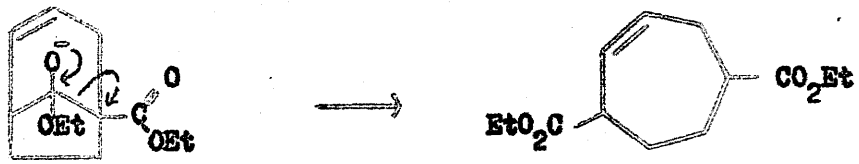


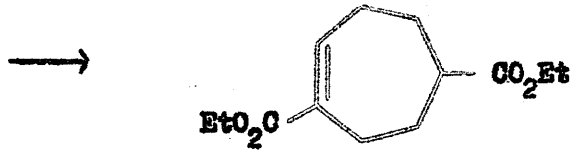
(9b) (12)

Scheme (d).



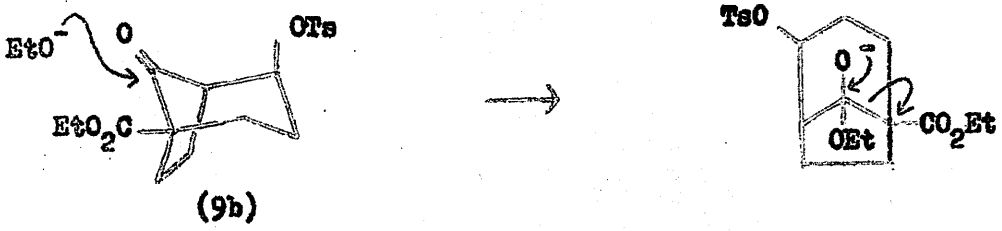
(9b)



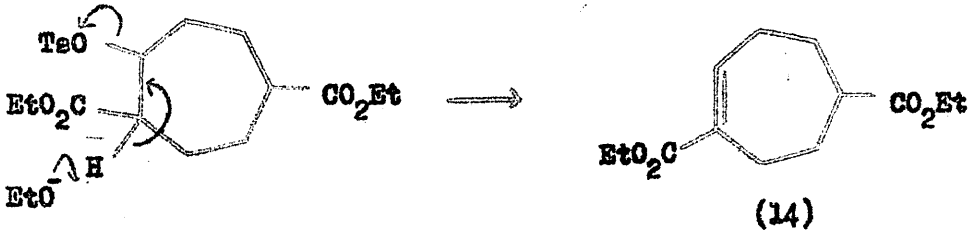


(14)

Scheme (e).

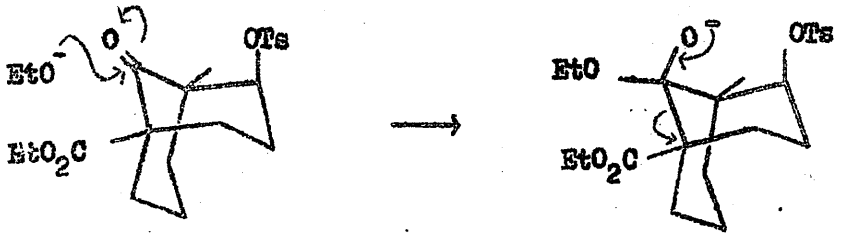


(9b)

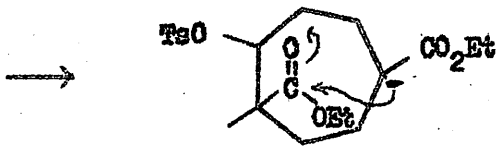


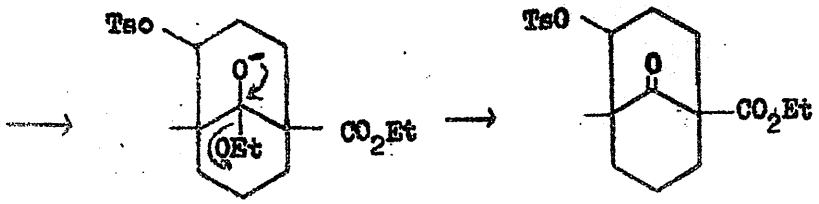
(14)

Scheme (f).



(2b).





(2b)

REFERENCES.

1. Buchanan, McKillop and Raphael, J.C.S., 1965, 833.

2. Martin, Ph.D. Thesis, 1964, University of Glasgow.

3. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, 1962, p.116.

4. Hassner and Heathcock, J.Org. Chem., 1964, 29, 1350.

5. Stork and Landesman, J. Amer. Chem. Soc., 1956, 78, 5129.

6. Cope, Graham and Marshall, J. Amer. Chem. Soc., 1954, 76, 6159.