665. *An Open-chain Analogue of Ethyl 7-Methylbisdehydrodoisynolic Acid.*

By Edward R. Clark.

Ethyl 3-ethyl-4-(*p*-methoxyphenyl)hex-4-ene-1-carboxylate (XII) has been synthesised and found to possess appreciable œstrogenic activity. This is the first known record of a substance possessing only one ring in its structure having more than a trace of such activity. The essential structural requirements for activity, postulated by Schueler, are discussed and a modification is suggested.

Schueler (*Science*, 1946, **103**, 221) has suggested that "a given substance may be œstrogenic if it consists of a rather large, rigid and inert molecular structure with two active hydrogen-bond-forming groups (*e.g.*, phenolic –OH) located at an optimum distance of 8·55 A. from one another." More recent work has to a certain extent borne out this hypothesis for most very active compounds. Among the exceptions are, of course, the triphenylethylenes. Schueler has discussed chlorotriphenylethylene (I) and pointed out that the chlorine group is essential for high activity and that its inductive effect increases the hydrogen-bond-forming power of the *para*-hydrogen atoms. Whether, in fact, hydrogen bonding of the *para*-hydrogen atoms is directly responsible for the activity of (I) or whether positions of low electron density are required for the attack of a nucleophillic reagent *in vivo*, producing the active compound, is a matter of conjecture. It appears to the present author that the latter hypothesis is the more likely in view of the prolonged activity of the compound and its slow elimination from the body.

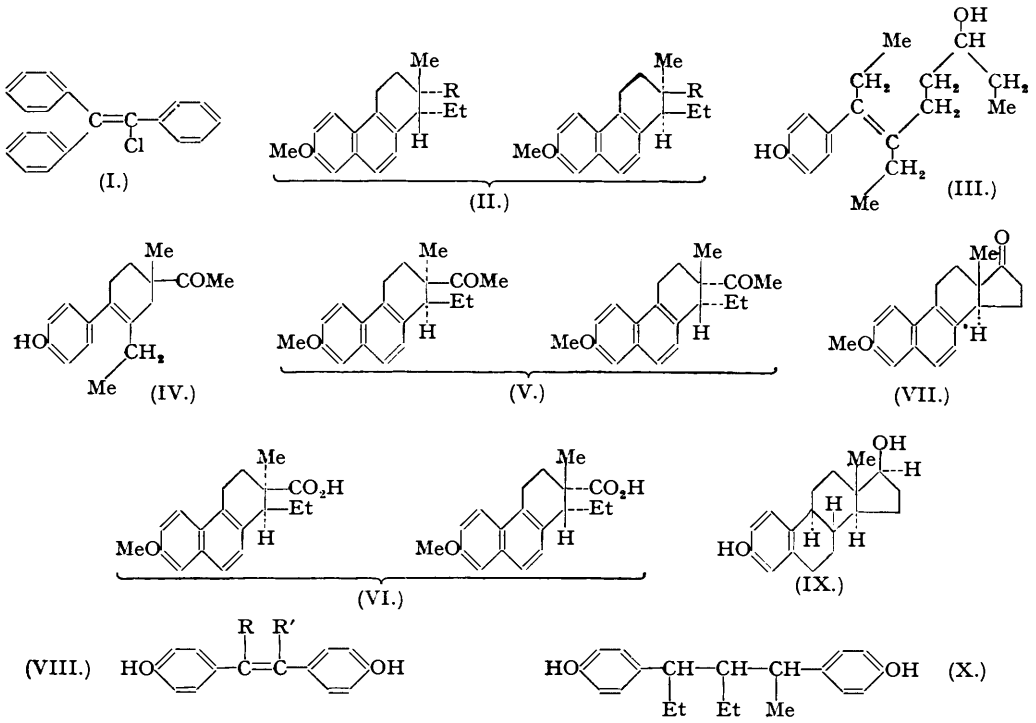
A further active œstrogenic agent not possessing two active hydrogen-bond-forming groups is the racemic phenanthrol methyl ether (II; R = Me) (Heer and Miescher, *Helv. Chim. Acta*, 1947, **30**, 777). It is difficult, however, to reconcile its reported high activity with the slight activity of its ethyl homologue (II; R = Et) (Anner, Heer, and Miescher, *ibid.*, 1946, **29**, 1071), and the question whether (II; R = Me) is itself the active agent or whether it is modified *in vivo* is pertinent, particularly having regard to its reported prolonged action in the body.

Of the compounds possessing two active, or potentially active, hydrogen-bond-forming groups at the required distance apart, several have been reported to possess little, if any, œstrogenic activity. Lack of rigidity may explain the comparative inactivity of (III) (Clark and Linnell, *J. Pharm. Pharmacol.*, 1949, **1**, 211); but the structures (IV) (Rubin and Wishinsky *J. Amer. Chem. Soc.*, 1946, **68**, 338) and (V) (Anner, Heer, and Miescher, *Helv. Chim. Acta*, 1946, **29**, 1071) would appear to conform to all of Schueler's requirements and yet (IV) is reported to be inactive and (V) to be 7,000—10,000 times less active than (±)-*cis*-7-methylbisdehydrodoisynolic acid (VI) from which it is obtained [or 20 times less active than (+)-equilenin methyl ether (VII) to which it is obviously closely related]. It should be added that Schueler suggests that ketone groups become hydrogen-bond-forming groups *in vivo*, either by enolisation or by reduction. The fission of ether groupings *in vivo* is a well-established fact (Stroud, *Nature*, 1940, **146**, 166).

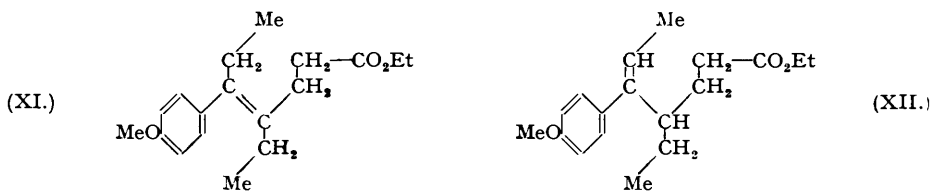
The low activities of (IV) and (V) make it obvious that Schueler's postulate is not sufficiently stringent in its requirements.

Rideal and Schulman (*Nature*, 1939, **144**, 100) demonstrated that the peak of activity in a series of αβ-dialkylstilbœstrols (VIII) coincided with the peak of adsorption on to a unimolecular layer. It is unfortunate that this correlation of œstrogenic activity and molecular adsorption has not been extended but it seems reasonable to assume that for high activity a compound must be capable of a high degree of adsorption at the receptor organ. Factors influencing the degree of adsorption are (*a*) that due to the functional groups and (*b*) adsorption due to Van der Waals forces, depending upon complimentary stereochemical structure of the receptor and substance. The importance of the latter requirement is well illustrated by the large divergence in activity between (+)-œstrone and lumiœstrone (Butenandt and Poschmann, *Ber.*, 1944, **77**, 392) which differ only in the linkage between the C and the D ring. At the same time it must be recognised that the hydrocarbon structures of diethylstilbœstrol (VIII; R = R′ = Et) and benzœstrol (X) are vastly different from that of œstra(17β)diol (IX), and yet these compounds are highly active œstrogens. Adsorption at the receptor, and hence their high activities, must therefore be due mainly to the functional groups. They differ from œstradiol in the possession of two phenolic hydroxyl groups instead of one phenolic and one alcoholic hydroxyl group, *i.e.*, in the possession of two acidic or strong hydrogen-bond-forming groups in place of one strong (acidic) and one weak (neutral) hydrogen-bond-forming group.

Similarly, the highly active (VI) has one acidic and one potentially acidic group, whilst the comparatively inactive (V) has one potentially acidic and one neutral group.



It appears probable, therefore, that increased hydrogen-bond-forming power of the functional groupings, or possibly the formation of an ionic bond between the carboxyl and a basic group of the receptor in the case of the œstrogenic carboxylic acids, may compensate for a low degree of Van der Waals adsorption of the hydrocarbon structure. Thus benzœstrol would be expected to have a low degree of adsorption since a particular orientation in space is necessary for the molecule to conform with the dimensional requirements of an œstrogen (Martin, *Chem. and Ind.*, 1944, 94), yet the possession of the two phenolic groups apparently compensates for the low degree of Van der Waals adsorption.



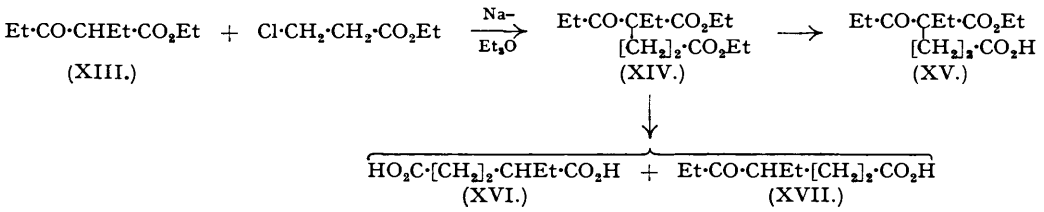
It seemed probable, therefore, that a compound such as (XI) might have appreciable activity despite its lack of rigidity, the potential carboxyl group " anchoring " the compound at the receptor and thereby enabling it to become correctly orientated to fit the receptor. (The ester was chosen since it is more easily administered and might, by analogy with the bisdehydrodoisynolic acid series, be expected to be only 5—10 times less active than the free acid. Similarly the methoxy-compound would be expected to be almost as active as the free phenol.) While the choice of the structure (XI), which may, as shown, be drawn so as to bear a formal resemblance to œstrone, was intentional, it is undesirable that too much weight should be put on this property as a criterion for œstrogenic activity. Rather should it be looked on as a useful hypothesis which has brought many results in this field. The important structural property of (XI) is that it possesses two potential, strong hydrogen-bond-forming groups at approximately the required distance apart. The use of a hydrocarbon skeleton similar to

that of (III) enables a direct measure of the influence of the carbethoxy-group in this type of structure to be determined.

The fact that the product of synthesis is mainly ethyl 3-ethyl-4-(*p*-methoxyphenyl)hex-4-ene-1-carboxylate (XII) does not invalidate the thesis, since, by analogy with diethylstilbœstrol the shift of the double bond would be expected to reduce the activity only slightly (Wessely *et al.*, *Naturwiss.*, 1939, **27**, 567). In a uterus-stimulating test on mice, (XII) has been found to have 1/500th of the activity of diethylstilbœstrol, *i.e.*, to have more than eighty times the activity of (III), and thus to be appreciably more active than any previously recorded monocyclic compound (Masson, *Rev. Canadian Biol.*, 1944, **3**, 491; Kaikini and Linnell, *Quart. J. Pharm. Pharmacol.*, 1947, **20**, 113).

Test substance.	Total dose/mouse.	Mean uterine weight.
Diethylstilbœstrol	1 γ	21·2 mg.
	2 γ	38·2 mg.
(XII)	250 γ	7·0 mg.
	500 γ	24·1 mg.
Controls	—	6—7 mg.

In previous attempts to synthesise (XI) as an intermediate in the production of (III) (Clark and Linnell, *loc. cit.*) by treating ethyl 3-*p*-methoxybenzoylpentane-1-carboxylate or the corresponding acid with ethylmagnesium iodide, the starting material was recovered quantitatively. The action of *p*-methoxyphenylmagnesium bromide on 3-ethyl-4-ketohexane-1-carboxylic acid (XVII) and its ethyl ester was therefore investigated.



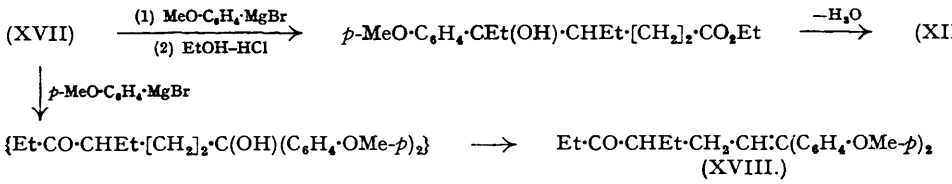
Ethylation of ethyl propionylacetate by ethyl iodide and sodium ethoxide gave ethylated and non-ethylated products, which could only be separated by careful fractionation using a 100-cm. column with a stainless-steel gauze packing. The resulting ethyl α-propionylbutyrate (XIII) was found to give no green copper complex when shaken with copper acetate solution and this proved a useful test for the purity of the distillate. An attempt to purify the mixed product by repeatedly shaking it with copper acetate solution was unsuccessful.

The use of sodium ethoxide in alcohol, and of sodium ethoxide alone, for the condensation of (XIII) with ethyl β-chloro- or β-iodo-propionate resulted in yields of only 22—27% of diethyl 3-ethyl-4-ketohexane-1 : 3-dicarboxylate (XIV). Powdered sodium in dry ether led to consistent yields of *ca.* 50%.

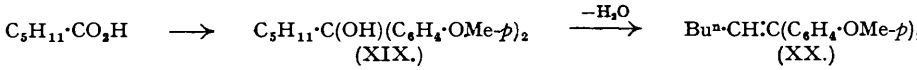
Some difficulty was experienced in hydrolysing (XIV) to a ketone. The mild conditions used by Lions (*Proc. Roy. Soc., N.S.W.*, 1938, **71**, 192) for the hydrolysis of diethyl 4-keto-3-methylpentane-1 : 3-dicarboxylate to 4-keto-3-methylpentane-1-carboxylic acid (81%) were found in this case to give mainly 3-carbethoxy-3-ethyl-4-ketohexane-1-carboxylic acid (XV). Various conditions of concentration, temperature, and time, and use of hydrochloric and hydrobromic acids were tried, the best yield of 3-ethyl-4-ketohexane-1-carboxylic acid being obtained by heating under reflux with dilute hydrochloric acid for 110 hours. In all the experiments using hydrochloric acid a small amount of high-boiling viscous oil was obtained. This was not investigated, but when constant-boiling hydrobromic acid was used for the hydrolysis, it represented as much as one-third of the starting material. Further heating under reflux with hydrobromic acid and glacial acetic acid as solvent yielded the same viscous oil and *ca.* 18% of α-ethylglutaric acid (XVI). In a later experiment 43% of (XVI) was obtained. The three acids (XV), (XVI), and (XVII) were identified as their benzylthiuronium salts. (XV) and (XVII) are colourless oils; (XVII) did not yield a crystalline semicarbazone or 2 : 4-dinitrophenylhydrazone.

In a further attempt to avoid the tedious fractionation of the mixture obtained on ethylation of ethyl propionylacetate, the mixture was converted into a mixture of (XIV) and diethyl 4-ketohexane-1 : 3-dicarboxylate and this was hydrolysed; however, the method was unsuccessful (see Experimental).

p-Methoxyphenylmagnesium bromide (4 equivalents) and (XVII) gave an acidic and (mostly) a neutral product. The acidic fraction was esterified without previous purification. The ester decolourised alkaline permanganate and bromine water, and analysis agreed with its formulation as (XI) or (XII). The neutral fraction, a viscous oil, decolourised alkaline permanganate and bromine water and contained no active hydrogen. It gave only a semi-solid red product on treatment with 2 : 4-dinitrophenylhydrazine. Analysis and ozonolysis to 4 : 4′-dimethoxybenzophenone in good yield indicated that it was (XVIII).



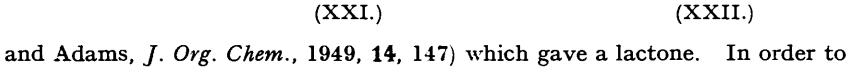
The only reports of the attack of an aromatic Grignard reagent on an acid group are those by Petrov *et al.*, who always used the sodium salt of the acid and phenylmagnesium bromide. In one paper (*Bull. Acad. Sci. U.S.S.R., Classe Sci. math. nat., Sér. Chim.*, 1938, 347) it is stated that no reaction occurs with salts of fatty acids higher than butyric, but in another (*J. Gen. Chem. U.S.S.R.*, 1938, **8**, 199) that with salts of higher fatty acids diphenyl compounds were formed and no phenyl ketones. The formation of (XVIII), and also the product of reaction between *p*-methoxyphenylmagnesium bromide and pentane-1-carboxylic acid, are consistent with the latter result.



The product of the last reaction, a pale yellow viscous oil, gave evidence of unsaturation and also of the presence of a hydroxyl group, *i.e.*, it was a mixture of (XIX) and (XX). Heating it with iodine gave a pure sample of 1 : 1-di-*p*-methoxyphenylhex-1-ene (XX).

Though the amount of material available was small, an attempt was made to decide between the alternative structures (XI) and (XII) for the unsaturated ester. Experience (Clark and Linnell, *loc. cit.*) has shown that *p*-methoxypropiophenone can be isolated as its 2 : 4-dinitrophenylhydrazone when present in quite small amounts. It could not however be isolated from the ozonolysis products on this occasion, nor could ethyl 3-ketopentane-1-carboxylate 2 : 4-dinitrophenylhydrazone : a red viscous oil was formed, possibly the 2 : 4-dinitrophenylhydrazone of ethyl 3-(*p*-methoxybenzoyl)pentane-1-carboxylate (Clark and Linnell, *loc. cit.*), but lack of material prevented isolation of this ester in a state of purity; probably, however, the substance is mainly, if not entirely, (XII).

Esterification of (XVII) by the Fischer method was more rapid than that normally used for γ- and δ-keto-acids and gave comparable yields. Ethyl 4-ketopentane-1-carboxylate (XXI) was obtained similarly in 68% yield (cf. Ruzicka, *Helv. Chim. Acta*, 1919, **2**, 144). Ethyl 3-ethyl-4-ketohexane-1-carboxylate was recovered after treatment with *p*-methoxyphenylmagnesium bromide (1 equivalent); this is similar to the lack of attack of allylmagnesium bromide on ethyl lævulate (Shchritza, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1853) but differs from the reaction of *n*-tetradecylmagnesium bromide on ethyl lævulate (Carson, Wolfhagen,



Torpey, and Adams, *J. Org. Chem.*, 1949, **14**, 147) which gave a lactone. In order to compare the reaction of a straight-chain δ-keto-ester the action of *p*-methoxyphenylmagnesium bromide on (XXI) was investigated; 4-hydroxy-4-*p*-methoxyphenylpentane-1-carboxylic lactone (XXII) was obtained in small yield.

Experimental.

(M. p.s are uncorrected. Microanalyses by Drs. Weiler and Strauss.)

Diethyl 3-Ethyl-4-ketohexane-1 : 3-dicarboxylate.—Ethyl α-propionylbutyrate (52 g.) (Anderson, Helverstadt, Miller, and Roblin, *J. Amer. Chem. Soc.*, 1945, **67**, 2197) was added during 1½ hours to powdered sodium (6·8 g.) in dry ether (300 c.c.), which was gently heated under reflux and stirred. After a further 1½ hours' refluxing all the sodium had reacted. Ethyl β-chloropropionate (50 g.) was added to the refluxing mixture during 1 hour, and the mixture stirred at room temperature overnight

and then, with refluxing, for a further 9 hours. The sodium chloride was centrifuged off from the cold ethereal solution, distillation of which yielded *diethyl 3-ethyl-4-ketohexane-1 : 3-dicarboxylate* (41 g.), b. p. 108—111°/0·4 mm. (Found : C, 62·2; H, 9·0. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%).

Hydrolysis of Diethyl 3-Ethyl-4-ketohexane-1 : 3-dicarboxylate.—(a) *Dilute hydrochloric acid.* (i) The ester (8 g.) was heated under reflux with concentrated hydrochloric acid (17 c.c.) and water (50 c.c.) for 3 hours. The cooled aqueous layer was saturated with ammonium sulphate and extracted with ether. The major product, on distillation, was 3-carbethoxy-3-ethyl-4-ketohexane-1-carboxylic acid (4·1 g.), b. p. 138—146°/0·3 mm., giving a *benzylthiuronium* salt, m. p. 121—122° (Found : C, 58·6; H, 7·3; N, 6·8; S, 7·6. $C_{20}H_{30}O_5N_2S$ requires C, 58·6; H, 7·3; N, 6·8; S, 7·8%).

(ii) The ester (16 g.), concentrated hydrochloric acid (40 c.c.), and water (80 c.c.) were heated under reflux, with stirring, for 110 hours. Working up as above yielded 3-ethyl-4-ketohexane-1-carboxylic acid (5·5 g.), b. p. 121—126°/0·3 mm., giving a *benzylthiuronium* salt, m. p. 111—111·5° (Found : C, 60·5; H, 7·9; N, 8·4; S, 9·4. $C_{17}H_{26}O_3N_2S$ requires C, 60·3; H, 7·7; N, 8·3; S, 9·5%).

(b) *Constant-boiling hydrobromic acid.* The ester (28·5 g.) and hydrobromic acid (*d* 1·49; 100 c.c.) were heated under reflux, with stirring, for 40 hours. Dilution and working up as above yielded 3-ethyl-4-ketohexane-1-carboxylic acid (2·0 g.), a fraction, b. p. 130—140°/0·5 mm. (4·5 g.), which gave a small amount of the benzylthiuronium salt of this acid, and a viscous oil, b. p. 140—153°/0·5 mm. (8·2 g.), which on treatment with hydrobromic and acetic acids gave α-ethylglutaric acid (3 g.), b. p. 150°/0·3 mm. Recrystallised from benzene–*cyclo*hexane (1 : 1), this had m. p. 59—60° (Found : C, 52·3; H, 7·6. Calc. for $C_7H_{20}O_4$: C, 52·5; H, 7·5%), and gave a *di*(*benzylthiuronium*) salt, m. p. 131·5—132° (Found : C, 56·5; H, 6·55; N, 11·3; S, 13·0. $C_{23}H_{32}O_4N_4S$ requires C, 56·3; H, 6·1; N, 11·4; S, 13·1%).

Further hydrolyses conducted in a similar manner to those described above gave the results shown in the table.

Reagent.	Temp.	Hrs.	Yield (%) of (XVII).	(XV).	(XVI).
1 : 2 HCl–H_2O	150° *	5	38	43	—
1 : 3 HCl–AcOH	Reflux	6	5	49	—
HBr (*d* 1·49)	,,	20	0	23	43

* Sealed tube.

Hydrolysis of Diethyl 3-Ethyl-4-ketohexane-1 : 3-dicarboxylate contaminated with Diethyl 4-Ketohexane-1 : 3-dicarboxylate.—The mixed glutarates (12 g.) obtained from ethyl α-propionylbutyrate contaminated with ethyl propionylacetate were heated under reflux with concentrated hydrochloric acid for 90 hours with stirring, and yielded, when worked up as above, an oil (4·7 g.), b. p. 114—124°/0·1 mm., which on storage deposited crystals of 4-ketohexane-1-carboxylic acid, m. p. 49·5—50·5° (Found : C, 58·1; H, 8·7. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%), yielding a semicarbazone, m. p. 188—189° (Found : C, 48·0; H, 7·5; N, 20·7. Calc. for $C_8H_{15}O_3N_3$: C, 47·8; H, 7·5; N, 20·9%). A further quantity of this semicarbazone could be isolated from the supernatant oil, which afforded also the benzylthiuronium salt of 4-keto-3-ethylhexane-1-carboxylic acid.

Ethyl 3-Ethyl-4-ketohexane-1-carboxylate.—Hydrogen chloride was passed into a solution of 3-ethyl-4-ketohexane-1-carboxylic acid (5 g.) in boiling absolute alcohol (40 c.c.) for 4 hours. Working up in the normal manner gave the ethyl ester (4·5 g.), b. p. 124—126°/14 mm., yielding a *phenylsemicarbazone*, m. p. 96·5—97·5° (Found : C, 65·4; H, 8·3; N, 12·5. $C_{18}H_{27}O_3N_3$ requires C, 64·9; H, 8·2; N, 12·7%).

Reaction between p-*Methoxyphenylmagnesium Bromide and 3-Ethyl-4-ketohexane-1-carboxylic Acid.*—To a cooled ethereal solution of *p*-methoxyphenylmagnesium bromide [from *p*-methoxyphenyl bromide (23 g.) and magnesium (3·0 g.) in dry ether (75 c.c.)] was added a solution of 3-ethyl-4-ketohexane-1-carboxylic acid (5 g.) in ether (25 c.c.), and the mixture was heated under reflux and stirred for 48 hours. The complex was decomposed with ice and dilute hydrochloric acid, the ethereal layer separated, and the aqueous layer extracted with ether. The combined ethereal extracts were washed with dilute sodium hydroxide solution and finally with water. Distillation of the dried ethereal solution yielded dianisyl (0·75 g.), m. p. 173—174° (mixed m. p. with a genuine sample, 173—174°), and *4-ethyl-5-keto-1 : 1-di-p-methoxyphenylhept-1-ene* (3·5 g.), an extremely viscous, pale yellow oil, distilling at 215—225° (air-bath)/0·03 mm. (Found : C, 78·6; H, 8·0. $C_{23}H_{28}O_3$ requires C, 78·4; H, 8·0%).

Acidification, followed by ethereal extraction of the alkaline washings and evaporation, yielded a viscous brown residue. This was heated under reflux for 3 hours with absolute alcohol (50 c.c.), with passage of hydrogen chloride through the solution. The excess of alcohol was removed under reduced pressure, water added, the oil taken into ether, and the ethereal solution washed with dilute sodium carbonate solution and finally dried. Distillation yielded *ethyl 3-ethyl-4-p-methoxyphenylhex-4-ene-1-carboxylate* (1 g.), b. p. 140—144° (air-bath)/0·03 mm. (Found : C, 74·7; H, 9·1. $C_{18}H_{26}O_3$ requires C, 74·5; H, 9·0%).

Ozonolysis of 4-Ethyl-5-keto-1 : 1-di-p-methoxyphenylhept-1-ene.—Ozonised oxygen was passed through a cold solution of 4-ethyl-5-keto-1 : 1-di-*p*-methoxyphenylhept-1-ene (0·5 g.) in chloroform (25 c.c.) for 6 hours, the chloroform distilled off under reduced pressure, and the ozonide decomposed with ice-water. The semi-solid mass obtained was crystallised from alcohol, giving 4 : 4′-dimethoxybenzophenone, m. p. 142·5—143·5° (mixed m. p. with a genuine sample, 142·5—143·5°) (Found : C, 74·3; H, 5·5. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%).

1 : 1-Di-p-methoxyphenylhex-1-ene.—To a cold solution of *p*-methoxyphenylmagnesium bromide, prepared from *p*-methoxyphenyl bromide (74·8 g.) and magnesium (9·7 g.) in dry ether (225 c.c.), was

added a solution of pentane-1-carboxylic acid (11·6 g.) in ether (25 c.c.). The mixture was heated under reflux, with stirring, for 48 hours, and decomposed with ice and dilute hydrochloric acid, the ethereal layer was separated, and the aqueous layer further extracted with ether. The combined ethereal solutions were washed with dilute sodium hydrogen carbonate solution and dried (Na_2SO_4). Evaporation gave a residue from which dianisyl (0·45 g.) crystallised, having m. p. 172·5—173° (Found: C, 78·1; H, 6·6; MeO, 28·2. Calc. for $C_{14}H_{14}O_2$: C, 78·4; H, 6·5; MeO, 29·0%). Distillation of the liquid portion gave a further quantity of dianisyl and finally a viscous almost colourless oil (10 g.), b. p. 177—182°/0·2 mm. This oil (2 g.) was distilled with iodine (0·15 g.), and the distillate dissolved in ether, washed with dilute sodium thiosulphate solution, and dried. Distillation yielded 1 : 1-*di*-p-*methoxyphenylhex*-1-*ene* (1·2 g.), b. p. 175—180°/0·2 mm. (Found: C, 80·8; H, 8·5. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·1%).

Ethyl 4-*Ketopentane*-1-*carboxylate*.—Hydrogen chloride was passed into a solution of 4-ketopentane-1-carboxylic acid (W. H. Perkin, jun., *J.*, 1896, **69**, 1510) (10 g.) in boiling absolute alcohol (30 c.c.) for 6 hours. The ester, isolated in the normal way, had b. p. 97—98°/8·5 mm. (Found: C, 60·8; H, 9·1. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%). It yielded a *semicarbazone*, m. p. 107·5—108·5° (Found: C, 50·2; H, 7·9; N, 19·9. $C_9H_{17}O_3N_3$ requires C, 50·0; H, 7·9; N, 19·55%).

Ethyl 3-*Ketopentane*-1-*carboxylate*.—Prepared according to the method of Friedmann (*J. pr. Chem.*, 1936, **146**, 159), this had b. p. 88—89°/7 mm. It yielded a 2 : 4-*dinitrophenylhydrazone*, m. p. 70·5—71° (Found: C, 49·5; H, 5·3; N, 16·25. $C_{14}H_{18}O_6N_4$ requires C, 49·6; H, 5·3; N, 16·55%).

4-*Hydroxy*-4-p-*methoxyphenylpentane*-1-*carboxylic Lactone*.—To a cold, stirred, ethereal solution of *p*-methoxyphenylmagnesium bromide, prepared from *p*-methoxyphenyl bromide (6·5 g.) and magnesium (0·8 g.) in dry ether (20 c.c.), was added, during 5 minutes, a solution of ethyl 4-ketopentane-1-carboxylate (5 g.) in dry ether (15 c.c.). The reaction mixture was stirred at room temperature for 1 hour and then at the b. p. for a further 3 hours. The product was poured on ice and dilute hydrochloric acid, the ethereal layer separated, and the aqueous layer further extracted with ether. The combined ethereal extracts were washed thoroughly with dilute sodium carbonate solution, and finally dried. Distillation gave 3 g. of unchanged ethyl 4-ketopentane-1-carboxylate. Acidification of the sodium carbonate washings and extraction with ether yielded a wax-like solid (1·0 g.), b. p. 155—157°/0·2 mm. Recrystallisation from benzene–*cyclo*hexane (1 : 1) yielded 4-*hydroxy*-4-p-*methoxyphenylpentane*-1-*carboxylic lactone*, m. p. 79·5—80·5° (Found: C, 71·3; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

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