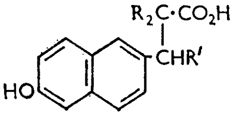
753. *Œstrogenic Carboxylic Acids. Part II.* Open-chain Analogues of Doisynolic Acid.*

By Edward R. Clark and R. D. Robson.

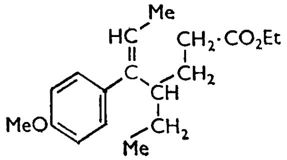
A number of alkyl-substituted 5-*p*-methoxyphenyl-pentanoic and -pentenoic acids have been synthesised. None was superior in œstrogenic activity to the previously reported ethyl 3-ethyl-4-*p*-methoxyphenylhex-4-ene-1-carboxylate.

Jacques and Horeau [1] have shown that, whereas allenolic acid [β-(6-hydroxy-2-naphthyl)-propionic acid] (I; R = R′ = H) is inactive, β-ethyl-αα-dimethylallenolic acid (I; R = Me, R′ = Et) is a potent œstrogen. Similarly in the bisdehydrodoisynolic acid series, absence of alkyl groups at positions 1 and 2 markedly decreases the potency.[2] It was hoped, therefore, that introduction of alkyl groups at positions 1 and 2 of ethyl 3-ethyl-4-*p*-methoxyphenylhex-4-ene-1-carboxylate [3] (II) would enhance the œstrogenic activity.

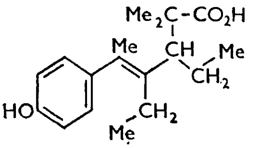
One of the two possible optical isomers of the acid (III) bears a particularly close formal resemblance to bisdehydrodoisynolic acid. Its synthesis could, we believed, be achieved by a Reformatsky reaction between ethyl α-bromoisobutyrate and 4-ethyl-5-*p*-methoxyphenylhexan-3-one (V; R = R′ = Et, R″ = Me), the double bond of the derived hexene (VII) being expected to migrate into conjugation with the ring.



(I)



(II)



(III)

For a preliminary investigation the most readily available ketone of type (V) appeared to be 3-ethyl-4-*p*-methoxyphenylhexan-2-one (V; R = Me, R′ = R″ = Et) which has been prepared by the action of ethylmagnesium bromide on α-ethyl-4-methoxystyryl methyl ketone [4] (IV; R = Me, R′ = Et). Use of methylmagnesium bromide and iodide in this reaction, in attempts to obtain the analogue (V; R = R″ = Me, R′ = Et) was not successful; the butadiene (VIII; R = H), $\lambda_{max.}$ 275 mμ (ε 13,700) in alcohol, formed by 1,2-addition, was the only isolable product when the bromide was used; only a very small amount of the required 1,4-addition product was obtained by using methylmagnesium iodide in the presence of cuprous chloride, which is stated to promote 1,4-addition.[5] Shukis and Ritter [4] state that some 1,2-addition also occurs with ethylmagnesium bromide. Our product was shown by infrared analysis to be a saturated ketone ($\nu_{max.}$ 1709 cm.$^{-1}$), there being no absorption due to hydroxyl or αβ-unsaturated ketone groups, but presence of the diene (VIII; R = Me) in the product was demonstrated by the ultraviolet absorption of an alcohol solution, a peak occurring at 277 mμ ($E^{1\%}_{1\,cm.}$ 403); the absence of a peak or inflexion at 296·5 mμ confirmed the absence of the original unsaturated ketone. Fractional distillation failed to separate the saturated ketone from the diene, which, however, would not be expected to interfere with a Reformatsky reaction. None of the required products were obtained, however, on treating this mixture with ethyl α-bromoisobutyrate, α-bromopropionate, or α-bromoacetate. Examination of molecular models demonstrated that the carbonyl group of 3-ethyl-4-*p*-methoxyphenylhexan-2-one (V;

---

* *J.*, 1950, 3397 is to be considered as Part I.

[1] Jacques and Horeau, *Bull. Soc. chim. France*, 1948, 711.

[2] Heer and Miescher, *Helv. Chim. Acta*, 1945, **28**, 1506.

[3] Clark, *J.*, 1950, 3397.

[4] Shukis and Ritter, *J. Amer. Chem. Soc.*, 1950, **72**, 1488.

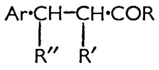
[5] Kharasch and Tawney, *ibid.*, 1941, **63**, 2308.

$R = Me, R' = R'' = Et$) is shielded but that the absence of either of the two ethyl groups makes it more accessible.

Catalytic hydrogenation of the styryl ketone (IV; $R = Me, R' = Et$) and oxidation of the product with chromic acid gave 3-4'-methoxybenzylpentan-2-one (V; $R = Me, R' = Et, R'' = H$) which reacted in the expected manner with ethyl α-bromopropionate, and α-bromoisobutyrate in the presence of zinc. The ethyl 3-hydroxy-4-4'-methoxybenzyl-3-methylhexane-2-carboxylate (IX) formed from the α-bromopropionate was partly dehydrated during isolation to the αβ-unsaturated ester (X), and dehydration was completed with potassium hydrogen sulphate. The position of the double bond was established by the infrared spectrum (strong band at 1730 cm.$^{-1}$). Dehydration of the crude product of reaction between the pentanone (V; $R = Me, R' = Et, R'' = H$) and ethyl α-bromoisobutyrate gave ethyl 2,3-dimethyl-4-4'-methoxybenzylhex-3-ene-2-carboxylate (VII; $R = Me, R' = Et, R'' = H$), the absence of an absorption peak at *ca.* 250 mμ showing that the double bond was not in conjugation with the aromatic ring, and this was confirmed by the weakness of the infrared absorption at *ca.* 1575 cm.$^{-1}$.

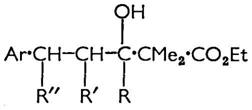
$\text{Ar}\cdot\text{CH}\text{:}\text{CR}'\cdot\text{COR}$

(IV)



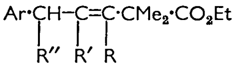
$\text{Ar}\cdot\underset{R''}{\text{CH}}-\underset{R'}{\text{CH}}\cdot\text{COR}$

(V)



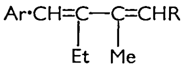
$\text{Ar}\cdot\underset{R''}{\text{CH}}-\underset{R'}{\text{CH}}-\overset{OH}{\underset{R}{\text{C}}}\cdot\text{CMe}_2\cdot\text{CO}_2\text{Et}$

(VI)



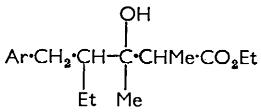
$\text{Ar}\cdot\underset{R''}{\text{CH}}-\underset{R'}{\text{C}}=\underset{R}{\text{C}}\cdot\text{CMe}_2\cdot\text{CO}_2\text{Et}$

(VII)



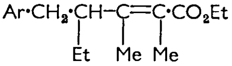
$\text{Ar}\cdot\text{CH}=\underset{Et}{\text{C}}-\underset{Me}{\text{C}}=\text{CHR}$

(VIII)



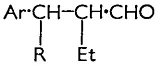
$\text{Ar}\cdot\text{CH}_2\cdot\underset{Et}{\text{CH}}-\overset{OH}{\underset{Me}{\text{C}}}\cdot\text{CHMe}\cdot\text{CO}_2\text{Et}$

(IX)



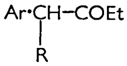
$\text{Ar}\cdot\text{CH}_2\cdot\underset{Et}{\text{CH}}-\underset{Me}{\text{C}}=\underset{Me}{\text{C}}\cdot\text{CO}_2\text{Et}$

(X)



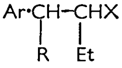
$\text{Ar}\cdot\underset{R}{\text{CH}}-\underset{Et}{\text{CH}}\cdot\text{CHO}$

(XI)



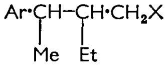
$\text{Ar}\cdot\underset{R}{\text{CH}}-\text{COEt}$

(XII)



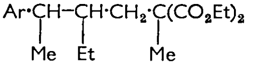
$\text{Ar}\cdot\underset{R}{\text{CH}}-\underset{Et}{\text{CHX}}$

(XIII)



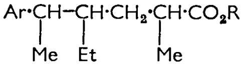
$\text{Ar}\cdot\underset{Me}{\text{CH}}-\underset{Et}{\text{CH}}\cdot\text{CH}_2\text{X}$

(XIV)



$\text{Ar}\cdot\underset{Me}{\text{CH}}-\underset{Et}{\text{CH}}\cdot\text{CH}_2\cdot\underset{Me}{\text{C}}(\text{CO}_2\text{Et})_2$

(XV)



$\text{Ar}\cdot\underset{Me}{\text{CH}}-\underset{Et}{\text{CH}}\cdot\text{CH}_2\cdot\underset{Me}{\text{CH}}\cdot\text{CO}_2\text{R}$

(XVI)

$\text{Ar} = p\text{-MeO}\cdot\text{C}_6\text{H}_4$

Even in the successful Reformatsky reactions the yields were poor. It was hoped that better yields of related compounds (*e.g.*, VII; $R = H, R' = R'' = Et$) would be obtained from the aldehydes (XI).

Various approaches were tried for synthesis of these aldehydes. Darzens glycidic ester condensations of the ketones (XII; $R = Me$ and Et), with either ethyl chloroacetate in the presence of sodium methoxide or ethyl dichloroacetate in the presence of magnesium–mercury amalgam, were unsuccessful, as was an attempt to prepare ethyl αβ-epoxy-α-ethyl-β-*p*-methoxyphenylbutyrate and hence 2-*p*-methoxyphenylpentan-3-one from 4-methoxyacetophenone and ethyl α-bromobutyrate. These ketones (XII; $R = Me$ and Et) were obtained from 1-*p*-methoxyphenylbutan-2-one [6] (XII; $R = H$).

The ketones (XII; $R = Et$ or Me) were converted *via* the alcohols into the halides (XIII; $R = Et, X = Br$; and $R = Me, X = Cl$). The derived Grignard reagents were then treated with ethyl orthoformate, and the products were hydrolysed. None of the expected aldehyde was obtained from the bromohexane (XIII; $R = Et, X = Br$), and

---

[6] Myers, Pratt, Morgan, O'Donnell, and Jensen, *J. Amer. Chem. Soc.*, 1955, **77**, 5655.

only a very small amount of the aldehyde (XI; R = Me) (as its 2,4-dinitrophenylhydrazone) was obtained from the chloropentane (XIII; R = Me, X = Cl). In contrast, 4-methoxyphenethyl chloride yielded β-*p*-methoxyphenylpropionaldehyde in 23% yield by an analogous process. The virtual failure of the secondary Grignard reagent to react with ethyl orthoformate is similar to the failure to obtain an aldehyde from the reaction of isopropyl-lithium with *NN*-dimethylformamide.[7]

Brown and McFarlin[8] have described an elegant method for the reduction of acid chlorides to aldehydes using lithium tri-t-butoxyaluminium hydride. When our work was done the method had not been applied to aliphatic acid chlorides, though a more recent paper[9] describes its successful application to some straight-chain aliphatic acid chlorides. We attempted reduction of α-ethyl-β-*p*-methoxyphenylbutyryl chloride by this reagent. The corresponding ethyl butenoate was obtained from 4-methoxyacetophenone and ethyl α-bromobutyrate, hydrolysed to the free acid, and reduced in alkaline solution with nickel-aluminium alloy. The chloride of the product failed to yield an identifiable product when treated with lithium tri-t-butoxyaluminium hydride.

The aldehyde (XI; R = Me) was eventually prepared by oxidising the corresponding alcohol with chromic anhydride in pyridine. The alcohol (XIV; X = OH) was obtained from the butenoate by catalytic hydrogenation followed by reduction with lithium aluminium hydride. The hydrogenation was very slow, owing to traces of sulphur impurities, even after treatment with Raney nickel. In subsequent runs initial reduction of the butenoate to the butenol before catalytic hydrogenation overcame this difficulty. An attempt to reduce the butenoate directly to the alcohol (XIV; X = OH) by an excess of lithium aluminium hydride gave only 2-ethyl-3-*p*-methoxyphenylbut-2-en-1-ol, which with manganese dioxide gave only a small yield of aldehyde, isolated as its 2,4-dinitrophenylhydrazone.

As expected, the aldehyde (XI; R = Me) reacted readily with zinc and ethyl α-bromoisobutyrate, to yield the hydroxy-ester (VI; R = H, R′ = Et, R″ = Me) which was dehydrated to the hex-3-ene (VII; R = H, R′ = Et, R″ = Me) by potassium hydrogen sulphate. 3-*p*-Methoxyphenylpropionaldehyde similarly yielded the hydroxy-ester (VI; R = R′ = R″ = H), but neither phosphorus oxychloride nor potassium hydrogen sulphate brought about the required dehydration.

A different approach to the synthesis of branched-chain acids related to doisynolic acid used malonic ester. 3-Chloromethyl- and 3-bromomethyl-2-*p*-methoxyphenylpentane (XIV; X = Cl and Br) were obtained from the alcohol (XIV; X = OH) by thionyl chloride and phosphorus tribromide respectively, and the chloride was converted into the iodide. The bromide and, better, the iodide with diethyl sodiomethylmalonate gave the diester (XV), whence hydrolysis gave a crystalline dicarboxylic acid in 57% yield. This decomposed at *ca.* 140° to the oily monocarboxylic acid (XVI; R = H), characterised as its ethyl ester.

The branched-chain hydroxy-esters (VI; R = R′ = R″ = H; and R = H, R′ = Et, R″ = Me), the unsaturated esters (X and VII, R = Me, R′ = Et, R″ = H; and VII, R = H, R′ = Et, R″ = Me), the malonate (XV), and the saturated ester (XVI; R = Et) were examined for œstrogenic activity on ovariectomized mice. The hydroxy-esters and the malonate were inactive at a dose of 5 mg. The most active compound was the saturated ester (XVI; R = Et) which was *ca.* 600 times less active than diethylstilbœstrol, *i.e.*, approximately equal in potency to the previously reported ester (II). Even after allowance for the fact that the compounds tested are mixtures of stereoisomers, it appears that further chain-branching in compounds of this type has no marked effect on œstrogenic potency.

Details of the biological tests will be reported elsewhere.

---

[7] Evans, *J.*, 1956, 4691.

[8] Brown and McFarlin, *J. Amer. Chem. Soc.*, 1956, **78**, 252.

[9] *Idem, ibid.*, 1958, **80**, 5372; Brown and Subba Rao, *ibid.*, p. 5377.

EXPERIMENTAL

Infrared spectra were determined on liquid films unless stated otherwise.

Reaction of Grignard Reagents with α-*Ethyl*-p-*methoxystyryl Methyl Ketone*.—(a) *Methylmagnesium bromide*. α-Ethyl-*p*-methoxystyryl methyl ketone (10·2 g.) in dry ether (30 c.c.) was added slowly with stirring to ethereal methylmagnesium bromide, made from magnesium (3·63 g.), cooled in ice–salt. Stirring was continued for a further 2 hr. and the solution poured into ice and concentrated hydrochloric acid. The ethereal layer was separated, the aqueous layer was further extracted with ether, and the combined ethereal solutions were washed and dried ($MgSO_4$). Distillation yielded 2-*ethyl*-1-p-*methoxyphenyl*-3-*methylbutadiene* (7·4 g.), b. p. 96—97°/0·1 mm., $\lambda_{\max.}$ 219 (ε 10,000), 275 mμ (ε 13,700) (Found: C, 83·4; H, 9·0. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%).

(b) *Methylmagnesium iodide in the presence of cuprous chloride*. Methylmagnesium iodide was prepared from magnesium (3·63 g.) and methyl iodide (21·5 g.) in dry ether (150 c.c.). Cuprous chloride (0·15 g.) was added, the solution cooled in ice–salt, and α-ethyl-*p*-methoxystyryl methyl ketone (12·75 g.) added during 30 min. The mixture was stirred for a further hr., left at room temperature overnight, then heated under reflux for 1 hr. Working up in the usual manner gave 3-*ethyl*-4-p-*methoxyphenylpentan*-2-*one* (1·6 g.), b. p. 102—104°/0·2 mm. (Found: C, 76·3; H, 8·9. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·1%). It yielded a *semicarbazone*, m. p. 167—168° (Found: C, 64·9; H, 8·2; N, 15·3. $C_{12}H_{23}O_2N_3$ requires C, 64·95; H, 8·3; N, 15·2%).

(c) *Ethylmagnesium bromide*. The ketone (71 g.) was treated with ethylmagnesium bromide, prepared from magnesium (25·3 g.) and ethyl bromide (125 g.), as described in (*a*). Distillation of the product yielded an oil (67·6 g.), b. p. 114—116°/0·2 mm. It rapidly decolorised permanganate in the cold and had $\nu_{\max.}$ 1709s (saturated C=O), no absorption at 1667 cm.$^{-1}$ (absence of C:C·C=O), $\lambda_{\max.}$ 225 ($E^{1\%}_{1\,\text{cm.}}$ 417) and 277 mμ ($E^{1\%}_{1\,\text{cm.}}$ 393) in ethanol. On microhydrogenation (Pd–C) 39·1 mg. absorbed 3·16 c.c., equivalent to 35·7% of 2-ethyl-1-*p*-methoxyphenyl-3-methylpenta-1,3-diene.

3-4′-*Methoxybenzylpentan*-2-*one*.—α-Ethyl-*p*-methoxystyryl methyl ketone (50 g.) in 95% alcohol (100 c.c.) was hydrogenated at atmospheric pressure in presence of 5% palladium–charcoal (1 g.). When the hydrogen uptake (7·5 l.) was complete, the catalyst was filtered off, the alcohol evaporated, and the residue in benzene (250 c.c.) added, with stirring, to a solution of sodium dichromate (34 g.) in acetic acid (25 c.c.), concentrated sulphuric acid (45 c.c.), and water (150 c.c.). Stirring was continued for 6 hr. at 25—30°. The benzene layer was separated and washed with water, dilute sodium hydroxide, and water. Distillation of the dried ($MgSO_4$) benzene solution gave 3-4′-*methoxybenzylpentan*-2-*one* (12·5 g.), b. p. 80—83°/0·1 mm. (Found: C, 76·0; H, 8·8. $C_{13}H_{18}O_2$ requires C, 75·75; H, 8·7%), $\nu_{\max.}$ 1712s cm.$^{-1}$.

An attempt to obtain 3-4′-methoxybenzylpentan-2-one by controlled hydrogenation of the styryl ketone with palladium–charcoal resulted in a mixture of the saturated ketone, unreduced starting material, and alcohol.

Ethyl 4-4′-*Methoxybenzyl*-3-*methylhex*-2-*ene*-2-*carboxylate*.—3-4′-Methoxybenzylpentan-2-one (10·2 g.) was mixed with ethyl α-bromopropionate (8·1 g.) and dry benzene (20 c.c.), and a little of the mixture (5 c.c.) added to zinc (3·5 g.). A trace of mercuric chloride was added and the mixture heated until reaction commenced. The remainder of the ketone–bromo-ester mixture was then added during 30 min. The mixture was stirred and heated under reflux for a further 2 hr. The cooled mixture was poured into ice-cold 20% sulphuric acid (40 c.c.), the benzene layer separated, and the aqueous layer extracted with benzene. The combined benzene solutions were washed with 5% sulphuric acid, 10% sodium carbonate solution, and water. Distillation of the dried ($MgSO_4$) benzene solution gave a mixture (4·15 g.), b. p. 138—144°/0·2 mm., of ethyl 3-hydroxy-4-4′-methoxybenzyl-3-methylhexane-2-carboxylate and 4-4′-methoxybenzyl-3-methylhex-2-ene-2-carboxylate.

The mixture (4·15 g.) was heated with iodine (0·07 g.) on the steam-bath for 30 min., and the product dissolved in ether and washed with thiosulphate solution. Distillation of the dried ($MgSO_4$) ethereal solution gave two fractions, b. p. 118—120°/0·05 mm. and 124—126°/0·05 mm., both of which were mixtures of the hydroxy- and the unsaturated ester, $\nu_{\max.}$ 3571m, 1739 sh, 1718s cm.$^{-1}$.

The combined fractions (2·4 g.) were heated at 190—200° for 15 min. with anhydrous potassium hydrogen sulphate (2·5 g.) in an atmosphere of nitrogen. The cooled material was extracted with ether, and the ethereal solution distilled, yielding *ethyl* 4-4′-*methoxybenzyl*-3-*methylhex*-2-*ene*-2-*carboxylate* (1·62 g.), b. p. 116—120°/0·1 mm. (Found: C, 74·55; H, 8·65. $C_{18}H_{26}O_3$ requires C, 74·5; H, 9·0%), $\nu_{max.}$ 1730s, no band at 3571 or 1739 cm.$^{-1}$, $\lambda_{max.}$ 225 (ε 11,700), 278 (ε 4720), and 284 mμ (ε 4450) in ethanol.

Ethyl-4-4′-*Methoxybenzyl*-2,3-*dimethylhex*-3-*ene*-2-*carboxylate*.—3-4′-Methoxybenzylpentan-2-one (39·6 g.) was treated with zinc (13·5 g.) and ethyl α-bromoisobutyrate (37·5 g.) in dry benzene (40 c.c.) in the usual way. The crude product (35·2 g.) was heated with anhydrous potassium hydrogen sulphate (20 g.) at 180° for 15 min., the mixture extracted with ether, and the ethereal solution distilled, to yield *ethyl* 4-4′-*methoxybenzyl*-2,3-*dimethylhex*-3-*ene*-2-*carboxylate* (4·87 g.), b. p. 124—126°/0·05 mm. (Found: C, 75·0; H, 8·85. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·2%), $\nu_{max.}$ 1736s cm.$^{-1}$, $\lambda_{max.}$ 225 (ε 13,180), 278 (ε 5470),and 284 mμ (ε 4970) in ethanol. Use of magnesium in place of zinc did not give the required product.

4-p-*Methoxyphenylhexan*-3-*ol*.—4-*p*-Methoxyphenylhexan-3-one [6] (36·3 g.) in dry ether (50 c.c.) was added gradually with stirring, at room temperature, to lithium aluminium hydride (1·9 g.) in ether (100 c.c.), then stirred and heated on a water-bath for 1 hr. The excess of hydride was decomposed by water, and the precipitate filtered off. The ethereal filtrate and the ether-washings of the precipitate were combined, dried ($MgSO_4$), and evaporated. Distillation of the residue gave 4-*p*-methoxyphenylhexan-3-ol (33·1 g.), b. p. 107—109°/0·5 mm. (Found: C, 75·05; H, 9·3. Calc. for $C_{13}H_{20}O_2$: C, 75·0; H, 9·6%). Rubin,[10] by using sodium and isopentyl alcohol, obtained a crystalline isomer, b. p. 100—105°/0·2 mm., m. p. 75—76°.

2-p-*Methoxyphenylpentan*-3-*one*.—Methyl iodide (191·5 g.) was added, with cooling and stirring, in 3 min., to a mixture of ethyl *p*-methoxybenzyl ketone [6] (80·0 g.) and sodium methoxide (48·5 g.) under nitrogen. After the initial reaction had subsided, the stirring was continued and the mixture heated on a steam-bath under a reflux condenser, further small quantities of methyl iodide being added if the mixture became too viscous. After 1 hr. the surplus methyl iodide was distilled off, water (200 c.c.) added, and the oil extracted with ether. The ethereal extract was washed with sodium thiosulphate solution and water, and dried ($MgSO_4$). Distillation yielded 2-*p*-methoxyphenylpentan-3-one (71·3 g.), b. p. 96°/0·4 mm.

2-p-*Methoxyphenylpentan*-3-*ol*.—2-*p*-Methoxyphenylpentan-3-one (71 g.), reduced with lithium aluminium hydride (4·0 g.) as described for the hexanone, gave 2-p-*methoxyphenylpentan*-3-*ol* (66·5 g.), b. p. 104—106°/0·5 mm. (Found: C, 74·1; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

3-*Bromo*-4-p-*methoxyphenylhexane*.—4-*p*-Methoxyphenylhexan-3-ol (36 g.) in carbon tetrachloride (50 c.c.) was cooled in an ice-bath, and phosphorus tribromide (17 g.) added gradually to the stirred solution. The mixture was stirred at room temperature for 2 days and then on a steam-bath for 1 hr. The solution was washed with water and then dried ($MgSO_4$). Distillation yielded 3-bromo-4-*p*-methoxyphenylhexane (36·4 g.), b. p. 114—116°/0·5 mm. (Found: Br, 29·1. Calc. for $C_{13}H_{19}OBr$: Br, 29·5%).

3-*Chloro*-2-p-*methoxyphenylpentane*.—2-*p*-Methoxyphenylpentan-3-ol (66 g.) in dry benzene (100 c.c.) was added, during 30 min., at room temperature, to a stirred solution of thionyl chloride (48·2 g.) in benzene (50 c.c.) containing one drop of pyridine. The mixture was heated on the steam-bath for 1 hr., cooled, and poured into iced water. The benzene layer was separated, washed successively with water, sodium hydrogen carbonate solution, and water, and dried ($CaCl_2$). Distillation yielded 3-*chloro*-2-p-*methoxyphenylpentane* (64·8 g.), b. p. 95—97°/0·5 mm. (Found: C, 67·6; H, 8·1; Cl 16·9. $C_{12}H_{17}OCl$ requires C, 67·8; H, 8·0; Cl 16·7%).

Reaction Between Ethyl Orthoformate and 1-*Ethyl*-2-p-*methoxyphenylpropylmagnesium Chloride*.—Ethyl orthoformate (19·6 g.) was added slowly to a solution, at −10°, of the Grignard reagent from 3-chloro-2-*p*-methoxyphenylpentane (34 g.) and magnesium (3·9 g.), in dry ether (100 c.c.). A crystal of iodine was needed to start the formation of the Grignard reagent. The mixture was stirred and heated on a water-bath for 6 hr., allowed to cool, and decomposed with ice and ammonium chloride. The aqueous layer was extracted with ether. The oily residue, from the distillation of the combined ether solutions, was boiled with 5N-hydrochloric acid (100 c.c.) for 1 hr., cooled, and extracted with ether. The ethereal extracts were washed with water, sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). Distillation gave, in addition to recovered ethyl orthoformate and chloride (13·3 g.), an oil (3·9 g.), b. p. 76—88°/0·6 mm. On reaction with 2,4-dinitrophenylhydrazine sulphate in alcohol this yielded 2-*ethyl*-3-p-*methoxyphenylbutyraldehyde* 2,4-*dinitrophenylhydrazone* (0·4 g.), m. p. 146—147° (Found:

---

[10] Rubin, *J. Amer. Chem. Soc.*, 1944, **66**, 2075.

C, 59·25; H, 5·85; N, 14·7. $C_{19}H_{22}O_5N_4$ requires C, 59·1; H, 5·7; N, 14·5%), $\lambda_{max.}$ 357 mμ (ε 26,600) in ethanol.

4-Methoxyphenethyl Alcohol.—(*a*) Reduction of ethyl *p*-methoxyphenylacetate (40 g.) in dry ether with lithium aluminium hydride (5 g.) in the usual manner gave 4-methoxyphenethyl alcohol (27·8 g.), b. p. 142°/12 mm., m. p. 23° (Shoesmith and Connor,[11] m. p. 24°).

Reduction of the free carboxylic acid was less successful, resulting in only a 50% yield.

(*b*) The alcohol was also obtained by a modification of the method of Plimmer, Short, and Hill,[12] whereby the duration of the reaction was considerably reduced. Ethylene oxide (32·2 g.) in ether (50 c.c.), cooled in ice–salt, was added slowly to cold ethereal *p*-methoxyphenylmagnesium bromide, prepared from *p*-bromoanisole (152 g.) and magnesium (19·5 g.). The mixture was then stirred and heated under reflux for 1 hr., dry benzene (300 c.c.) added, and the ether distilled. The resulting benzene solution was heated under reflux for 4 hr., then cooled, and a saturated solution of ammonium chloride added. The benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene solutions were dried (Na_2SO_4) and distilled, yielding 4-methoxyphenethyl alcohol (63 g.), b. p. 138—140°/10 mm.

4-Methoxyphenethyl Chloride.—4-Methoxyphenethyl alcohol (27·8 g.) in dry benzene (150 c.c.) was added during 1 hr., with stirring at room temperature, to thionyl chloride (25·8 g.) in benzene (100 c.c.) containing pyridine (0·2 c.c.). The mixture was heated on a water-bath for 1 hr. cooled, and poured into iced water. The oil was extracted into benzene, and the benzene solution washed with water, sodium hydrogen carbonate solution, and water. The dried ($CaCl_2$) benzene solution was distilled, yielding 4-methoxyphenethyl chloride (19·3 g.), b. p. 116—120°/8 mm. (lit.,[12] b. p. 100—105°/7 mm.).

3-p-Methoxyphenylpropionaldehyde.—Ethyl orthoformate (13·8 g.) was caused to react with 4-methoxyphenethylmagnesium chloride prepared from 4-methoxyphenethyl chloride (19·3 g.) and magnesium (2·75 g.) in dry ether (100 c.c.), and the product hydrolysed as described for the homologue. The aldehyde (5·0 g.), b. p. 140°/12 mm., was obtained (Found: C, 71·7; H, 7·25. Calc. for $C_{10}H_{12}O_2$: C, 73·2; H, 7.32%), having $\nu_{max.}$ 2740w and 1727s cm.$^{-1}$.

*Ethyl α-Ethyl-β-hydroxy-β-*p-*methoxyphenylbutyrate.*—4-Methoxyacetophenone (220 g.), ethyl α-bromobutyrate (286 g.), and dry benzene (300 c.c.) were mixed and a portion of the mixture (20 c.c.) added with stirring and heating under reflux, to zinc (110 g.) with a trace of mercuric chloride. When the reaction started, the remainder of the mixture was added gradually, and stirring and heating were continued for a further 2 hr. The cooled mixture was poured into 20% ice-cold sulphuric acid, the benzene layer separated, and the aqueous layer extracted with benzene. The combined benzene solutions were washed successively with water, dilute sodium carbonate solution, and water, and dried ($MgSO_4$). Distillation yielded the *hydroxy-ester* (105 g.), b. p. 132—134°/0·5 mm. (Found: C, 68·4; H, 8·35. $C_{15}H_{22}O_4$ requires C, 67·7; H, 8·3%).

*Dehydration of Ethyl α-Ethyl-β-hydroxy-β-*p-*methoxyphenylbutyrate.*—(*a*) The hydroxy-ester (105 g.) was heated on a steam-bath for 2 hr. with iodine (1·5 g.), dissolved in ether, washed with sodium thiosulphate solution and water, and dried ($MgSO_4$). Distillation yielded *ethyl 2-ethyl-3-*p-*methoxyphenylbut-2-enoate* (89 g.), b. p. 126—128°/0·5 mm. (Found: C, 72·4; H, 8·25. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%), $\nu_{max.}$ 1730s cm.$^{-1}$.

(*b*) The dried benzene solution from the reaction between 4-methoxyacetophenone (267 g.), ethyl α-bromobutyrate (347 g.), and zinc (139 g.) was not distilled but heated under reflux with phosphorus oxychloride (12 c.c.) for 1·5 hr. The cooled solution was washed successively with water, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and distilled. After distillation of unchanged ketone, a fraction of b. p. 124—134°/0·5 mm., containing only a little ketone, was obtained. Redistillation of this fraction through a column packed with Dixon gauze rings yielded the butenoate (160·5 g.), b. p. 132—134°/0·6 mm.

*α-Ethyl-β-*p-*methoxyphenylbutyric Acid.*—The above ester (40 g.) was heated under reflux with 20% alcoholic potassium hydroxide (150 c.c.) for 3 hr. Water (200 c.c.) was added, the mixture acidified to Congo Red, cooled, and extracted with ether. The residue, after evaporation of the ether, was dissolved in 10% aqueous sodium hydroxide (1 l.). The solution was heated at 90° and nickel–aluminium alloy (130 g.) added gradually with stirring. When this addition was complete, a further 150 c.c. of sodium hydroxide solution and 15 g. of alloy were added. The hot liquid was filtered under reduced pressure, and the precipitate washed

---

[11] Shoesmith and Connor, *J.*, 1927, 2230.

[12] Plimmer, Short, and Hill, *J.*, 1938, 694.

with hot water. The cooled filtrate was poured slowly, with vigorous stirring, into concentrated hydrochloric acid (500 c.c.). The organic acid was extracted from the co-precipitated sodium chloride with ether. Distillation of the ether left a sticky brown solid which recrystallised from 33% aqueous acetic acid and then from light petroleum (b. p. 80—100°), yielding needles of *α-ethyl-β-*p*-methoxyphenylbutyric acid* (10 g.), m. p. 81—82° (Found: C, 70·6; H, 8·1. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%), $\nu_{max.}$ (in Nujol mull) 1704s cm.$^{-1}$.

*α-Ethyl-β-*p*-methoxyphenylbutyryl Chloride.*—The above acid (7·1 g.) and thionyl chloride (8·1 g.) were kept at 60° for 10 hr. Distillation yielded the *acid chloride* (6·7 g.), b. p. 116—117°/0·5 mm. (Found: C, 65·1; H, 7·1. $C_{13}H_{17}O_2Cl$ requires C, 64·9, H, 7·1%).

*2-Ethyl-3-*p*-methoxyphenylbut-2-en-1-ol.*—Ethyl 2-ethyl-3-*p*-methoxyphenylbut-2-enoate (40 g.) was reduced with lithium aluminium hydride (3·5 g.) in ether (150 c.c.) to *2-ethyl-3-*p*-methoxyphenylbut-2-en-1-ol* (29·5 g.), b. p. 123—126°/0·5 mm. (Found: C, 75·15; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%).

*Oxidation of 2-Ethyl-3-*p*-methoxyphenylbut-2-en-1-ol with Manganese Dioxide.*—The alcohol (12·5 g.) in dry light petroleum (b. p. 60—80°; 300 c.c.) was stirred with freshly prepared manganese dioxide (30 g.), at room temperature for 5 days. The mixture was filtered, the precipitate washed with light petroleum, and the filtrate distilled, yielding, besides recovered alcohol (9·5 g.), a fraction (2·7 g.) of b. p. 112—120°/0·5 mm., shown by its infrared spectrum to be a mixture of unchanged alcohol and the αβ-unsaturated aldehyde ($\nu_{max.}$ 1672 cm.$^{-1}$). An attempt to isolate the aldehyde as its bisulphite compound was unsuccessful, but the mixture yielded *2-ethyl-3-*p*-methoxyphenylbutyraldehyde 2,4-dinitrophenylhydrazone*, m. p. 176—177° (Found: C, 58·8; H, 5·25; N, 14·6. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2; N, 14·6%), $\lambda_{max.}$ 396 mμ (ε 29,200) in ethanol.

*Ethyl α-Ethyl-β-*p*-methoxyphenylbutyrate.*—Ethyl 2-ethyl-3-*p*-methoxyphenylbut-2-enoate (89 g.) in 95% alcohol (100 c.c.) was heated on a steam-bath for 4 hr. with Raney nickel to remove sulphur-containing impurities. The Raney nickel was filtered off and the alcoholic solution of the ester shaken with platinum oxide (0·2 g.) and hydrogen at atmospheric pressure. Three days were required for the theoretical uptake of hydrogen, and fresh platinum oxide (0·1 g.) was added as required. The catalyst was filtered off and the filtrate distilled, yielding *ethyl α-ethyl-β-*p*-methoxyphenylbutyrate* (75 g.), b. p. 111—112°/0·2 mm. (Found: C, 72·4; H, 8·4. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%), $\nu_{max.}$ 1733s cm.$^{-1}$, $\lambda_{max.}$ 224·5 (ε 15,580), 275 mμ (ε 3160) in ethanol.

*2-Ethyl-3-*p*-methoxyphenylbutan-1-ol.*—(*a*) The foregoing ester (75 g.) was reduced in ether with lithium aluminium hydride (6·5 g.), giving *2-ethyl-3-*p*-methoxyphenylbutan-1-ol* (53 g.), b. p. 120—122°/0·4 mm. (Found: C, 75·15; H, 9·45. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6%), $\nu_{max.}$ 3333s cm.$^{-1}$. (*b*) 2-Ethyl-3-*p*-methoxyphenylbut-2-en-1-ol (36·3 g.) was hydrogenated at atmospheric pressure and temperature, in alcohol (100 c.c.), with 5% palladium–charcoal (1 g.). Hydrogen uptake was complete in 3 hr. Isolation in the usual way gave the saturated alcohol (29·4 g.), b. p. 124—126°/0·6 mm.

*2-Ethyl-3-*p*-methoxyphenylbutyraldehyde.*—Chromic anhydride (40·5 g.) in dry pyridine (400 c.c.) was added to a solution of the butyl alcohol (29·4 g.) in pyridine (400 c.c.). The mixture was shaken and left in a stoppered vessel overnight at room temperature, then poured into water (2 l.), and the solid material was filtered off through " Hyflo super-cel." The filtrate was extracted with ether, and the ether extract dried ($MgSO_4$). Distillation, and redistillation through an efficient column, yielded the *aldehyde* (10·6 g.), b. p. 109—110°/0·5 mm. (Found: C, 75·05; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%), $\nu_{max.}$ 2732w and 1730s cm.$^{-1}$ (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 146°).

*Ethyl 4-Ethyl-3-hydroxy-5-*p*-methoxyphenyl-2-methylhexane-2-carboxylate.*—The preceding aldehyde (10·6 g.), ethyl α-bromoisobutyrate (8·2 g.), and zinc (4·0 g.) amalgamated with a trace of mercuric chloride, were caused to react together in dry benzene (30 c.c.) in the usual way. Decomposition of the resulting complex with ice-cold 20% sulphuric acid (40 c.c.), extraction with benzene, and distillation of the benzene solution yielded *ethyl 4-ethyl-3-hydroxy-5-*p*-methoxyphenyl-2-methylhexane-2-carboxylate* (8·5 g.), b. p. 162—164°/0·5 mm. (Found: C, 71·1; H, 9·2. $C_{19}H_{30}O_4$ requires C, 70·8; H, 9·3%), $\nu_{max.}$ 3650m and 1736s cm.$^{-1}$.

*Ethyl 4-Ethyl-5-*p*-methoxyphenyl-2-methylhex-3-ene-2-carboxylate.*—Ethyl 4-ethyl-3-hydroxy-5-*p*-methoxyphenyl-2-methylhexane-2-carboxylate (6·0 g.) was heated with anhydrous potassium hydrogen sulphate (6 g.) for 30 min. at 190°. The organic material was extracted from the cooled mixture with ether and distilled, yielding fractions, b. p. 130—142°/0·5 mm.

(1·1 g.), 146—156°/0·5 mm. (1·0 g.), and 162—164°/0·5 mm. (3·3 g.), each of which was shown to contain a hydroxyl group by infrared analysis.

Two further treatments with potassium hydrogen sulphate yielded *ethyl* 4-*ethyl*-5-p-*methoxyphenyl*-2-*methylhex*-3-*ene*-2-*carboxylate* (0·7 g.), b. p. 135—145°/0·9 mm. (Found: C, 74·9; H, 9·1. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·2%), $\nu_{max.}$ 1733s cm.$^{-1}$.

Ethyl 3-*Hydroxy*-5-p-*methoxyphenyl*-2-*methylpentane*-2-*carboxylate and its Attempted Dehydration.*—3-*p*-Methoxyphenylpropionaldehyde (5 g.), ethyl α-bromoisobutyrate (5·95 g.), and zinc (3 g.) with a trace of mercuric chloride, reacted in benzene (40 c.c.) in the usual way. The complex was decomposed with ice-cold 20% sulphuric acid (40 c.c.), and the organic material taken into benzene. The benzene solution was dried ($MgSO_4$), and then heated under reflux for 1·5 hr. with phosphorus oxychloride (1·0 c.c.). The cooled product was washed with water and sodium hydrogen carbonate solution, and dried ($MgSO_4$). Distillation yielded *ethyl* 3-*hydroxy*-5-p-*methoxyphenyl*-2-*methylpentane*-2-*carboxylate* (2·5 g.), b. p. 152—154°/0·5 mm. (Found: C, 68·5; H, 8·5. $C_{16}H_{24}O_4$ requires C, 68·6; H, 8·75%), $\nu_{max.}$ 3560m, and 1724s cm.$^{-1}$. The low value for the carbonyl band is anomalous. The analytical figures preclude the material's being a mixture of hydroxy- and unsaturated ester.

Heating this hydroxy-ester (2·5 g.) with potassium hydrogen sulphate (2 g.) at 190° for 30 min. did not yield the unsaturated ester.

2-*Ethyl*-3-p-*methoxyphenylbutyl Bromide.*—Phosphorus tribromide (10 g.) was added gradually to a stirred solution of 2-ethyl-3-*p*-methoxyphenylbutan-1-ol (20 g.) in carbon tetrachloride (50 c.c.) at 0°. The mixture was left at room temperature for 5 days, then heated under a reflux for 1 hr., cooled, washed with water, and dried ($MgSO_4$). Distillation yielded the *bromide* (8·5 g.), b. p. 124—126°/0·5 mm. (Found: C, 59·3; H, 7·25; Br, 29·45. $C_{13}H_{19}OBr$ requires C, 57·6; H, 7·0; Br, 29·5%).

2-*Ethyl*-3-p-*methoxyphenylbutyl Chloride.*—2-Ethyl-3-*p*-methoxyphenylbutan-1-ol (20 g.) in dry benzene (100 c.c.) was added, at room temperature, during 30 min., to thionyl chloride (13·6 g.) in benzene (50 c.c.) containing one drop of pyridine. The mixture was heated on a steam-bath for 1 hr., allowed to cool, and poured into iced-water, the benzene layer was separated, and the aqueous layer was extracted with benzene. The combined benzene solutions were washed with water and sodium hydrogen carbonate solution and dried ($CaCl_2$). Distillation yielded the *chloride* (15·6 g.), b. p. 116—118°/0·7 mm. (Found: C, 68·5; H, 8·2. $C_{13}H_{19}OCl$ requires C, 68·9; H, 8·4%).

Diethyl 4-*Ethyl*-5-p-*methoxyphenylhexane*-2,2-*dicarboxylate.*—(*a*) Diethyl methylmalonate (4·9 g.) was added to a stirred solution, at 50—60°, of sodium ethoxide, prepared from sodium (0·61 g.) and dry ethanol (7·2 c.c.). The temperature was allowed to fall to *ca.* 35°, then 2-ethyl-3-*p*-methoxyphenylbutyl bromide (7·5 g.) was added, and the mixture was stirred overnight. The alcohol was distilled from the neutral mixture, water (10 c.c.) added, and the mixture acidified with acetic acid. Extraction with benzene and distillation of the dried ($MgSO_4$) extract yielded *diethyl* 4-*ethyl*-5-p-*methoxyphenylhexane*-2,2-*dicarboxylate* (4 g.), b. p. 166—168°/0·2 mm. (Found: C, 68·95; H, 8·6. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·8%).

(*b*) 2-Ethyl-3-*p*-methoxyphenylbutyl chloride (14 g.) was stirred and heated overnight with dry sodium iodide (11·3 g.) in dry acetone (100 c.c.). The acetone was distilled and the precipitate filtered off and washed with ether. The ether washings were added to the filtrate, and this ethereal solution was washed with sodium thiosulphate solution and water and dried ($MgSO_4$). Distillation yielded the iodide (11·2 g.), b. p. 122—126°/0·6 mm.

This iodide (9·4 g.) was added to an alcoholic solution of diethyl sodiomethylmalonate, prepared from sodium (0·65 g.), ethanol (10 c.c.), and diethyl methylmalonate (5·2 g.) as described above. On working up in the usual manner, diethyl 4-ethyl-5-*p*-methoxyphenylhexane-2,2-dicarboxylate (5·3 g.), b. p. 169—172°/0·5 mm., was obtained.

4-*Ethyl*-5-p-*methoxyphenylhexane*-2,2-*dicarboxylic Acid.*—The diethyl ester (4·6 g.) was heated under reflux for 4 hr. with 2N-alcoholic potassium hydroxide (50 c.c.). The cooled solution was diluted with water (150 c.c.) and acidified with hydrochloric acid. The brown viscous oil which separated was added to boiling light petroleum (b. p. 60—80°), in which it is only slightly soluble, and ethylene dichloride added to complete the dissolution. The solid white precipitate formed on cooling was recrystallised from 30% aqueous methanol, to yield 4-*ethyl*-5-p-*methoxyphenylhexane*-2,2-*dicarboxylic acid* (2·2 g.) (Found: C, 66·35; H, 7·6. $C_{17}H_{24}O_5$ requires C, 66·3; H, 7·8%).

Ethyl 4-*Ethyl*-5-p-*methoxyphenylhexane*-2-*carboxylate.*—The above dicarboxylic acid (2·1 g.)

was heated at 160° in nitrogen until the evolution of carbon dioxide ceased. The crude monocarboxylic acid (1·6 g.) did not crystallise.

Esterification by the Fischer–Spier method yielded *ethyl* 4-*ethyl*-5-p-*methoxyphenylhexane*-2-*carboxylate* (0·8 g.), b. p. 135—138°/0·5 mm. (Found: C, 74·1; H, 9·6. $C_{18}H_{28}O_3$ requires C, 74·0; H, 9·6%).

DEPARTMENT OF PHARMACOLOGY, THE UNIVERSITY OF LEEDS,
LEEDS, 2.

[*Received, May* 15*th*, 1959.]