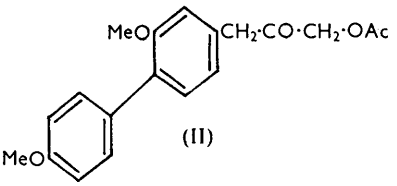
240. *Analogues of Cortical Hormones.*

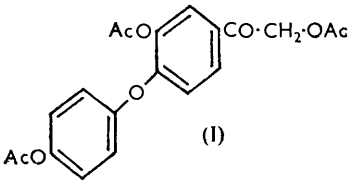
By Edward R. Clark and J. G. B. Howes.

2-3′-Acetoxyacetonyl*cyclo*pentanone (V) and 2-3′-acetoxyacetonyl-5-*p*-methoxyphenyl*cyclo*pentanone (IV; R = H) have been synthesized as analogues of 11-dehydrocorticosterone.

Walker [1] and Logemann [2] have synthesized simple analogues (I, II) of cortical hormones possessing phenolic groups in positions comparable with the 11-oxygen functions in certain of the natural hormones. Their compounds were physiologically inactive whereas the related structure (III),[3] not possessing this potential phenolic group, has proved effective for prolongation of the life of adrenalectomised animals. The 11-oxygen function is, however, essential if the hormone is to control protein and carbohydrate metabolism. It is not, of course, phenolic. The synthesis of compounds in which the analogous group is not phenolic might therefore be of interest.

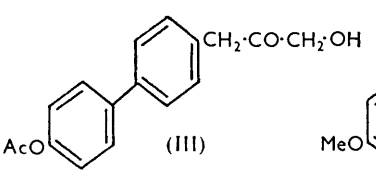


(II)



(I)

The *cyclo*pentanone (IV) was chosen for initial investigation, in preference to a *cyclo*hexane structure, since the introduction of the side chain would be facilitated. Synthesis of the single-ring analogue (V) was undertaken to gain experience of the steps involved.



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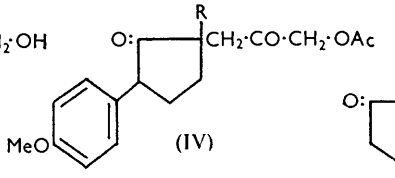
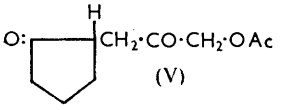


(IV)



(V)

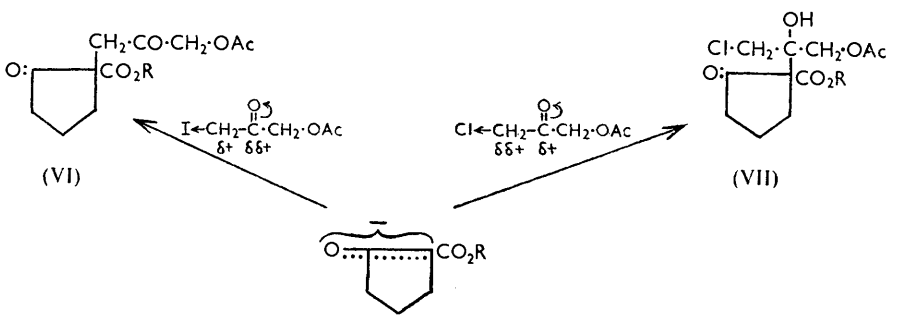
Reaction between α-halogeno-ketones and β-keto-esters does not always yield the *C*-subsitution product,[4] *O*-alkylation and aldol condensation being offered as explanations for the formation of alternative products. 1-Acetoxy-3-chloroacetone [5] (an improved method of isolation, including that of the co-formed 1 : 3-diacetoxyacetone, not isolated by the original workers, is described) reacted rapidly with the sodio-derivative of ethyl 2-oxo-*cyclo*pentanecarboxylate to yield only 9% (best) of the desired compound (VI; R = Et) together with a considerable amount of a non-distillable oil. 1-Acetoxy-3-iodoacetone (an unstable, non-distillable oil), on the other hand, reacted readily at 0° to give ethyl 1-3′-acetoxyacetonyl-2-oxo*cyclo*pentanecarboxylate (VI; R = Et) as the major product (72%), there being only a small amount of the by-product.

There is no reason to believe that the use of the chloride in place of the iodide will enhance the likelihood of *O*-substitution at the expense of *C*-substitution, both of which would occur more readily with the iodide. Here, therefore, the alternative product is due to aldol condensation to give the alcohol (VII; R = Et). Some support for this conclusion is found in the failure of 1-chloro-2 : 2-diethoxypropane [6] to react under similar conditions.

[1] Walker, *J.*, 1942, 347.
[2] Logemann, *Z. physiol. Chem.*, 1952, **290**, 61.
[3] Linnell, Mathieson, and Williams, *Nature*, 1951, **167**, 237.
[4] Feist, *Ber.*, 1902, **35**, 1545; Archer and Pratt, *J. Amer. Chem. Soc.*, 1944, **66**, 1656; Dunlop and Hurd, *J. Org. Chem.*, 1950, **15**, 1160.
[5] Hess and Fink, *Ber.*, 1915, **48**, 1986.
[6] Ewlampiew, *Ber.*, 1929, **62**, 2386.

Ketonic hydrolysis of the diketo-ester (VI; R = Et), followed by reacetylation of the product, gave the desired analogue (V). Better yields were obtained by the acid-catalysed decomposition of the corresponding *tert.*-butyl ester (VI; R = Bu^t) under anhydrous conditions.

Dieckmann cyclisation of di-*tert.*-butyl adipate occurred readily, to give the cyclic β-keto-ester in good yield (80%) if an excess of condensing agent was used. The 3′-acetoxyacetonyl derivative (VI; R = Bu^t) was thermally unstable at 15 mm., 2-3′-acetoxyacetonyl*cyclo*pentanone (V) being formed. Better yields were obtained when the decomposition was catalysed with toluene-*p*-sulphonic acid.

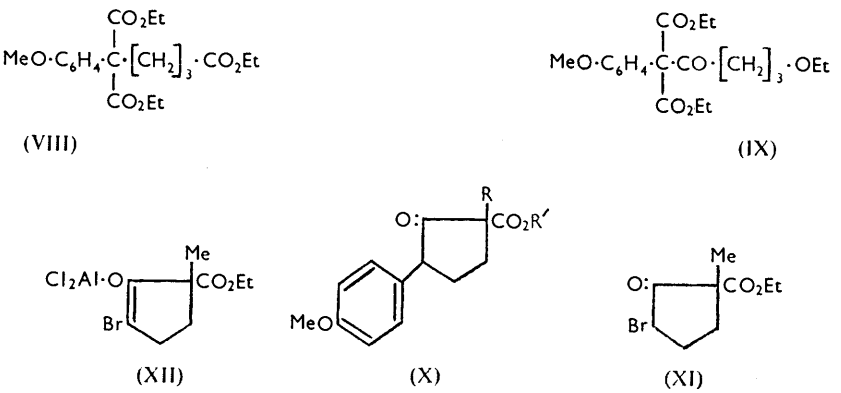


(VI) (VII)

The extension of this method to the synthesis of the two-ring analogue (IV; R = H) necessitated the synthesis of α-*p*-methoxyphenyladipic acid.

Reaction of γ-iodobutyronitrile with the sodio-derivative of *p*-methoxyphenylacetonitrile or *p*-methoxyphenylmalonate, followed by hydrolysis, failed to yield appreciable quantities of the desired acid (cf. Newman and Closson [7] and Case [8] who obtained α-methyl-α-phenyl- and α-phenyl-adipic acids respectively by analogous methods).

Ethyl γ-iodobutyrate with the sodiomalonate gave, however, an oil (70%) which on hydrolysis yielded the desired adipic acid (73%) together with some *p*-methoxyphenylacetic and *p*-methoxyphenylmalonic acid. These can only arise from the presence of the isomeric keto-ester (IX) together with the expected triester (VIII) in the product of condensation.



(VIII) (IX) (XII) (X) (XI)

Esterification of the derived adipate, followed by Dieckmann cyclisation and methylation, yielded ethyl 3-*p*-methoxyphenyl-1-methyl-2-oxo*cyclo*pentanecarboxylate (X; R = Me, R′ = Et). The tedious nature of this method of preparation led us to examine other possible routes.

[7] Newman and Closson, *J. Amer. Chem. Soc.*, 1944, **66**, 1553.
[8] Case, *ibid.*, 1933, **55**, 2927.

Berlande [9] obtained α-phenyladipic acid by oxidation of 3-phenyl*cyclo*hexene. Oxidation of the product of reaction between *p*-methoxyphenylmagnesium bromide and 3-bromo-*cyclo*hexene gave, however, a mixture of the required adipic acid and δ-anisoylvaleric acid. The ultraviolet absorption spectrum of the intermediate *cyclo*hexene indicated the presence of some of the conjugated isomer, thus accounting for the formation of the keto-acid. The experiments were abandoned because of the low yield of acids obtained and the failure to isolate a pure sample of 3-*p*-methoxyphenyl*cyclo*hexene (*i.e.*, one not possessing an absorption peak at 249 mμ).

Neutral permanganate oxidation of 2-*p*-methoxyphenyl*cyclo*hexanone gave δ-anisoylvaleric acid as the sole product.

Mason and Terry [10] and Richard [11] have successfully carried out Friedel–Crafts reactions between α-chloro-ketones and aromatic hydrocarbons. It seemed possible, therefore, that the dicyclic ester (X; R = Me, R′ = Et) might be obtained in a similar manner by using ethyl 3-bromo-1-methyl-2-oxo*cyclo*pentanecarboxylate (XI). This was readily produced by means of *N*-bromosuccinimide, but reaction with anisole and aluminium chloride failed to yield any dicyclic product (X; R = Me, R′ = Et): 64% of the bromo-compound (XI) was recovered together with a small amount of an unsaturated substance, presumably a *cyclo*pentenone. The formation of the *cyclo*pentene (XII) would explain the inert nature of the bromine and the vigorous evolution of hydrogen chloride which was observed during the reaction.

Since we attempted the above reaction Zaheer and his co-workers [12] have demonstrated the complex nature of the products which may be obtained by using aliphatic α-halogeno-ketones in reactions with aryl ethers and aluminium chloride.

Di-*tert.*-butyl α-*p*-methoxyphenyladipate, prepared *via* the di-acid chloride, was difficult to isolate in quantity since it could only be distilled in a short-path still. The product of Dieckmann cyclisation was even more unstable and could not be distilled even at 1×10^{-5} mm. A portion of the product, presumably the required cyclic keto-ester (X; R = H, R′ = Bu^t) (colour with neutral ferric chloride), was separated from unchanged adipate by extraction with alkali, but decomposition soon occurred on storage.

The isolation of this unstable substance was avoided by adding 1-acetoxy-3-iodoacetone to the crude sodio-derivative obtained on cyclising di-*tert.*-butyl α-*p*-methoxyphenyladipate. Catalytic decarboxylation of the product yielded a small amount of the desired material (IV; R = H). No crystalline carbonyl derivative could be obtained but infrared spectroscopy showed strong absorption peaks at 5·69, 5·79, and 5·86 μ, corresponding with cyclic, acetate, and aliphatic carbonyl groups. This resembles the behaviour of dehydrocorticosterone acetate except that the alicyclic carbonyl band has been displaced to a shorter wavelength with diminution of ring size.

Disubstituted β-keto-esters are very sensitive to metal alkoxides. The use of the crude sodio-derivative in the above reaction meant that such a compound (IV; R = CO_2Bu^t) was being exposed to sodium *tert.*-butoxide. Since, however, this stage of the reaction was completed at room temperature, alcoholysis was considered to be unlikely. In order to confirm this, and before the above experiments were carried out, diethyl α-*p*-methoxyphenyladipate was cyclised and 1-acetoxy-3-iodoacetone added to the crude sodium derivative. Ethyl 1-3′-acetoxyacetonyl-3-*p*-methoxyphenyl-2-oxo*cyclo*pentanecarboxylate (IV; R = CO_2Et) was isolated in 45% yield. Hydrolysis and reacetylation under the conditions described for the monocyclic analogue failed to yield any decarboxylated product (IV; R = H).

The authors are indebted to Professor G. A. H. Buttle and Dr. P. F. D'Arcy of the School of Pharmacy (University of London) for examining analogues (V) and (VI) for cortical activity. They were tested for their effects on the survival times of adrenalectomised mice subjected to cold stress. Conflicting results were obtained with compound (VI), the initial activity observed not being confirmed by later experiments. Compound

[9] Berlande, *Bull. Soc. chim. France*, 1942, **9**, 644.
[10] Mason and Terry, *J. Amer. Chem. Soc.*, 1940, **62**, 1622.
[11] Richard, *Compt. rend.*, 1935, **200**, 753.
[12] Zaheer *et al.*, *J.*, 1954, 3360; 1955, 1706.

(V) was inactive at a dose of 10 mg./17—20 g. mouse. The very low solubilities of compounds (IV; R = H and CO_2Et) in suitable media has so far prevented their biological examination.

Experimental

1-*Acetoxy*-3-*chloroacetone*.—1 : 3-Dichloroacetone (75 g.) was treated with fused potassium acetate (70 g.) in glacial acetic acid, as described by Hess and Fink.[5] The precipitated potassium chloride was filtered from the rapidly cooled mixture, washed with glacial acetic acid, and the acetic acid distilled from the resulting solution under a reduced pressure of nitrogen. Ether, added to the residue, precipitated further inorganic salts which were filtered off, and the ethereal solution was fractionally distilled under reduced pressure, yielding 1 : 3-dichloroacetone (3·8 g.), b. p. 78—84°/10 mm., 1-acetoxy-3-chloroacetone (30·7 g.), b.p. 100—103°/10 mm., and 1 : 3-diacetoxyacetone (23·7 g.), b. p. 118—122°/8 mm., m. p. 47° [from light petroleum (b. p. 40—60°)] (Found : C, 48·1; H, 5·7. Calc. for $C_7H_{10}O_5$: C, 48·3; H, 5·75%).

1-*Acetoxy*-3-*iodoacetone*.—1-Acetoxy-3-chloroacetone (5 g.) was added to a solution of anhydrous sodium iodide (6 g.) in dry acetone (25 c.c.), a white precipitate being formed immediately. After being kept at room temperature (12 hr.) the precipitate was filtered off and the acetone solution concentrated under reduced pressure in the cold. Anhydrous ether (50 c.c.) was added to the residue and the resulting precipitate of excess of sodium iodide filtered off. Distillation of the ether *in vacuo*, in the cold, yielded the iodo-compound (8·5 g.), somewhat contaminated with free iodine. Extensive decomposition, with the liberation of large quantities of free iodine, occurred above 60°. The product was used in the crude state in subsequent experiments.

tert.-*Butyl* 2-*Oxo*cyclo*pentanecarboxylate*.—A solution of di-*tert.*-butyl adipate (25·8 g.) [13] in anhydrous benzene (30 c.c.) was added to a stirred, refluxing suspension of sodamide [from sodium (3·3 g.)] in anhydrous benzene (100 c.c.). Stirring and heating were continued until the evolution of ammonia ceased (5 hr.). The semi-solid mixture was cooled and decomposed with ice-cold dilute acetic acid, the benzene layer separated, and the aqueous layer further extracted. Distillation of the washed and dried (Na_2SO_4) benzene solution yielded tert.-*butyl* 2-*oxo*cyclo*pentanecarboxylate* (14·7 g.), b. p. 107—109°/14 mm. (Found : C, 64·8; H, 9·1. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). It yielded a *semicarbazone*, m. p. 155° (from dilute alcohol) (Found : C, 54·5; H, 7·2; N, 17·0. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9; N, 17·4%).

A smaller yield of the keto-ester (10 g.) was obtained if powdered sodium (3·3 g.) was used as the condensing agent.

tert.-*Butyl* 1-3′-*Acetoxyacetonyl*-2-*oxo*cyclo*pentanecarboxylate* (VI; R = Bu^t).—The above keto-ester (10·65 g.) was added dropwise to a cold, stirred suspension of sodamide [from sodium (1·35 g.)] in anhydrous benzene (125 c.c.) under nitrogen. When the reaction slackened the mixture was heated under reflux until evolution of ammonia ceased (8 hr.). 1-Acetoxy-3-iodoacetone [from chloro-compound (8·8 g.)] was added with ice-cooling. Stirring was continued with cooling (5 hr.) and then at room temperature (16 hr.). The neutral mixture was poured into water (100 c.c.), the benzene layer separated, and the aqueous layer further extracted. The washed and dried (Na_2SO_4) benzene solution was distilled under reduced pressure, yielding tert.-*butyl* 1-3′-*acetoxyacetonyl*-2-*oxo*cyclo*pentanecarboxylate* (8·9 g.), b. p. 137—147°/0·04 mm. (Found : C, 60·15; H, 7·65. $C_{15}H_{22}O_6$ requires C, 60·4; H, 7·4%).

Attempted distillation, at 15 mm., of the crude product caused extensive decomposition. Subsequent careful fractionation gave appreciable amounts of 2-3′-*acetoxyacetonyl*cyclo*pentanone*, b. p. 89—96°/0·04 mm. (Found : C, 60·25; H, 7·45. $C_{10}H_{14}O_4$ requires C, 60·4; H, 7·1%), yielding a *disemicarbazone*, m. p. 187° (decomp.) (from 95% alcohol) (Found : C, 46·35; H, 6·8; N, 26·75. $C_{12}H_{20}O_4N_6$ requires C, 46·15; H, 6·4; N, 26·9%).

The corresponding ethyl ester was obtained similarly, except that the sodio-derivative of ethyl 2-oxo*cyclo*pentanecarboxylate (5·15 g.) was prepared by using powdered sodium in boiling benzene. *Ethyl* 1-3′-*acetoxyacetonyl*-2-*oxo*cyclo*pentanecarboxylate* (6·5 g.), b. p. 125—126°/0·05 mm., was obtained (Found : C, 57·9; H, 6·55. $C_{13}H_{18}O_6$ requires C, 57·75; H, 6·65%).

2-3′-*Acetoxyacetonyl*cyclo*pentanone* (V).—(*a*) *tert.*-Butyl 1-3′-acetoxyacetonyl-2-oxo*cyclo*pentanecarboxylate (8·1 g.) and toluene-*p*-sulphonic acid (0·2 g.) in anhydrous benzene (30 c.c.) were heated under reflux until effervescence ceased (3 hr.). The cooled solution was washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). Distillation under reduced pressure gave 2-3′-acetoxyacetonyl*cyclo*pentanone (3·6 g.), b. p. 92—104°/0·05 mm., yielding a disemicarbazone, m. p. and mixed m. p. 187° (decomp.).

[13] Backer and Homan, *Rec. Trav. chim.*, **1939**, **58**, 1048.

(*b*) Ethyl 1-3′-acetoxyacetonyl-2-oxo*cyclo*pentanecarboxylate (3 g.), potassium hydroxide (1·25 g.), and water (12·5 c.c.) were shaken (40 hr.), under nitrogen, at room temperature. Undissolved oil was extracted with ether, the aqueous layer acidified (hydrochloric acid), and the water distilled off under reduced pressure. Acetone-extraction of the residue and subsequent distillation of the acetone gave a residue which was dissolved in 1 : 1 pyridine–acetic anhydride (14 c.c.) and set aside for 24 hr. The solution was diluted with benzene (50 c.c.), washed with water, dried (Na_2SO_4), and distilled under reduced pressure, yielding the required diketone (0·6 g.), b. p. 101—104°/0·07 mm. [semicarbazone, m. p. and mixed m. p. 187° (decomp.)].

A similar result was obtained on using aqueous-alcoholic hydrochloric acid at 100°.

Ethyl γ-Iodobutyrate.—The procedure [14] for the oxidation of trimethylene chlorohydrin was applied to tetramethylene chlorohydrin.[15] γ-Chlorobutyric acid, b. p. 116—118°/14 mm., was obtained in varying yields (50—77·5%).

Fischer–Speier esterification yielded ethyl γ-chlorobutyrate, b. p. 63—66°/6 mm. (81%).

Later, γ-butyrolactone became available commercially and was readily converted (85% yield) into the desired ester by heating it with absolute alcohol saturated with hydrogen chloride.

The iodo-ester was formed from the chloro-compound by the action of sodium iodide in dry acetone; it had b. p. 94—99°/14 mm.

α-p-*Methoxyphenyladipic Acid.*—Diethyl *p*-methoxyphenylmalonate (100 g.) [16] was added to a stirred solution of sodium ethoxide [from sodium (8·6 g). and absolute alcohol (400 c.c.)] at 60°. The solution was cooled to −15° and ethyl γ-iodobutyrate (160 g.) added rapidly with stirring. Cooling was maintained for a further 6 hr., and the mixture allowed to attain room temperature, stirred for a further 36 hr., and finally heated to 45° (15 min.). The mixture was poured into water and extracted with benzene. Distillation of the dried (Na_2SO_4) extract yielded a mixture of triethyl 1-*p*-methoxyphenylbutane-1 : 1 : 4-tricarboxylate and the isomeric diethyl 5-ethoxy-1-*p*-methoxyphenyl-2-oxopentane-1 : 1-dicarboxylate (100 g.), b. p. 155—180°/0·03 mm., having a green fluorescence (Found : C, 63·4; H, 7·0. Calc. for $C_{20}H_{28}O_7$: C, 63·2; H, 7·4%), together with ethyl γ-iodobutyrate (72 g.) and diethyl *p*-methoxyphenylmalonate (15 g.).

Condensations carried out under reflux gave yields of only 20—27%.

The product was heated under reflux with 10% alcoholic potassium hydroxide (1 l.) for 3 hr., the mixture poured into water (1 l.), sufficient hydrochloric acid added to neutralise the excess of alkali, and the whole evaporated to *ca.* 500 c.c. and strongly acidified. After being kept overnight in the refrigerator the required diacid, together with some potassium chloride, was precipitated. Further evaporation of the mother-liquors gave further yields of product. The dried solid was extracted with hot acetone, evaporation of which yielded crude acid (76·5 g.). Recrystallisation from ethylene dichloride yielded α-p-*methoxyphenyladipic acid* (48·5 g.), m. p. 139—140° (Found : C, 61·8; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%).

Evaporation of the mother liquors of recrystallisation yielded an acidic oil (27·5 g.) which on re-esterification yielded ethyl *p*-methoxyphenylacetate (6·5 g.) and diethyl *p*-methoxyphenylmalonate (14·5 g.).

Diethyl α-p-*Methoxyphenyladipate.*—A solution of the above acid (33 g.) in absolute alcohol (120 c.c.) was saturated with dry hydrogen chloride and heated under reflux (3 hr.). Working up in the usual manner yielded the desired *ester* (38 g.), b. p. 150—152°/0·02 mm. (Found : C, 66·2; H, 7·9. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·8%).

Ethyl 3-p-*Methoxyphenyl*-2-*oxo*cyclo*pentanecarboxylate* (X; R = H, R′ = Et).—Diethyl α-*p*-methoxyphenyladipate (8 g.) was added to alcohol-free sodium ethoxide [from sodium (1·2 g.)] in anhydrous benzene (90 c.c.), and the mixture heated (3 hr.) under reflux (nitrogen atmosphere). The cooled solution was acidified with acetic acid, washed with water, dilute sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). After distillation of the benzene under nitrogen, the residue was distilled in a short-path still, yielding *ethyl* 3-p-*methoxyphenyl*-2-*oxo*cyclo*pentanecarboxylate* (4 g.) (bath-temp. 120—140°/1 × 10^{-5} mm.) as a greenish-yellow oil (Found : C, 68·5; H, 7·2. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

The oil gave a dark violet colour with alcoholic ferric chloride solution and yielded a *semicarbazone*, m. p. 133° (from 40% aqueous alcohol) (Found : C, 60·0; H, 6·3; N, 13·4. $C_{16}H_{21}O_4N_3$ requires C, 60·2; H, 6·6; N, 13·15%).

Powdered sodium was an equally effective cyclising agent. Pure keto-ester was also isolated by extraction of an ethereal solution of the crude product with N-sodium hydroxide, acidification, re-extraction, and evaporation of the dried ether *in vacuo* (Found : C, 68·65, H, 7·05%).

[14] Powell, Huntress, and Hershberg, *Org. Synth.*, 1932, Coll. Vol. I, p. 168.
[15] Star and Hixon, *Org. Synth.*, Coll. Vol. II, p. 571.
[16] Clark and Linnell, *J. Pharm. Pharmocol.*, 1949, **1**, 211.

Ethyl 3-p-*Methoxyphenyl*-1-*methyl*-2-*oxo*cyclo*pentanecarboxylate* (X; R = Me, R′ = Et).—The above keto-ester (10 g.), anhydrous benzene (50 c.c.), and powdered sodium (0·9 g.) were stirred and heated under reflux until all the sodium had dissolved (36 hr.). Methyl iodide (5·5 g.) was added dropwise and heating continued (30 hr.) until the mixture was neutral. Working up as above yielded on distillation (bath-temp. 136—140°/1 × 10^{-5} mm.) the required methylated *compound* (6·3 g.) (Found: C, 69·85; H, 7·45. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·25%).

Reaction between p-*Methoxyphenylmagnesium Bromide and* 3-*Bromo*cyclo*hexene, and Oxidation of the Product.*—3-Bromo*cyclo*hexene [17] (20 g.) was slowly added (1 hr.) to a stirred solution of *p*-methoxyphenylmagnesium bromide [from magnesium (3 g.), *p*-bromoanisole (23·2 g.), and ether (75 c.c.)], at −15°, and the mixture stirred and cooled for a further hour. Working up in the usual manner yielded a *p*-methoxyphenyl*cyclo*hexene (10 g.), b. p. 140°/9 mm. (Found: C, 83·3; H, 8·65. Calc. for $C_{13}H_{16}O$: C, 82·95; H, 8·5%). Ultraviolet absorption (in EtOH): $\lambda_{max.}$ 226 (ε 12,000), 249 (ε 1000), 278 (ε 2300), and 284 mμ. (ε 1900).

Oxidation of the derived *cyclo*hexene (5 g.) with potassium permanganate (11·2 g.) in the presence of magnesium sulphate (4 g.) in aqueous acetone, at room temperature, yielded 2 g. of acid, m. p. 122—128° (Found: equiv., 184, 185. Calc. for $C_{13}H_{16}O_5$: equiv., 126. Calc. for $C_{13}H_{16}O_4$: equiv., 236). Recrystallisation from a variety of sovlents failed to separate the constituent acids.

1-p-*Methoxyphenyl*cyclo*hexene* was obtained as a crystalline material, b. p. 153—156°/10 mm., m. p. 37° [from light petroleum (b. p. 40—60°)] (Braun[18] gives m. p. 35°) (Found: C, 82·5; H, 8·55. Calc. for $C_{13}H_{16}O$: C, 82·95; H, 8·5%), on distillation of the product of reaction between *p*-methoxyphenylmagnesium bromide and *cyclo*hexanone. Ultraviolet absorption (in EtOH): $\lambda_{max.}$ 254 mμ (ε 15,000).

2-p-*Methoxyphenyl*cyclo*hexanone.*—2-Chloro*cyclo*hexanone (15 g.) in anhydrous ether (25 c.c.) was added dropwise to a stirred solution of *p*-methoxyphenylmagnesium bromide [from magnesium (3 g.), *p*-bromoanisole (21·3 g.), and anhydrous ether (45 c.c.)]. The ether was distilled off, anhydrous benzene (60 c.c.) added to the residue, and the mixture heated under reflux (12 hr.) with stirring. The cooled product was poured into water (500 c.c.), the benzene layer separated, and the aqueous layer extracted with benzene. Distillation of the dried (Na_2SO_4) benzene solution yielded 2-p-*methoxyphenyl*cyclo*hexanone* (7 g.), b. p. 130—134°/0·05 mm., m. p. 89·5—90° [from light petroleum (b. p. 60—80°)] (Found: C, 76·4; H, 7·85. $C_{13}H_{16}O_2$ requires C, 76·45; H, 7·85%).

δ-p-*Anisoylvaleric Acid.*—To 2-*p*-methoxyphenyl*cyclo*hexanone (1 g.) in acetone at 40° was added an aqueous solution (23 c.c.) of potassium permanganate (1·6 g.) and magnesium sulphate (0·6 g.). After 15 min. the temperature was raised to 60° (maintained for 90 min.). The filtered mixture was evaporated to *ca.* 15 c.c. and acidified with hydrochloric acid. Recrystallisation of the crude product (0·9 g.) from benzene gave δ-*p*-anisoylvaleric acid [19] (0·7 g.), m. p. 127—127·5° (Found: equiv., 236. Calc. for $C_{13}H_{16}O_4$: equiv., 236).

Bromination of Ethyl 1-*Methyl*-2-*oxo*cyclo*pentanecarboxylate.*—Ethyl 1-methyl-2-oxo*cyclo*pentanecarboxylate (10 g.) in anhydrous carbon tetrachloride (30 c.c.) was heated under reflux with *N*-bromosuccinimide (10·5 g.), the solution being irradiated with a 100-w lamp. When bromination was complete (18 hr.) the succinimide was filtered off and the filtrate distilled yielding a colourless oil (10·3 g.), b. p. 126—127°/7 mm.

The material coloured quite rapidly on storage under nitrogen at 0°, the analytical figures (Found: C, 45·2; H, 5·4; Br, 29·5. Calc. for $C_9H_{13}O_3Br$: C, 43·4; H, 5·2; Br, 32·1%) indicated, however, that the product was essentially the required ethyl 3-bromo-1-methyl-2-oxo*cyclo*pentanecarboxylate (XI).

Di-tert.-*butyl* α-p-*Methoxyphenyladipate.*—α-*p*-Methoxyphenyladipic acid (5·0 g.) and redistilled thionyl chloride (7·2 g.) were heated at 55—60° under reflux until evolution of hydrogen chloride ceased (4 hr.). Excess of thionyl chloride was distilled off under a reduced pressure of dry nitrogen, and the crude acid chloride, dissolved in anhydrous benzene (10 c.c.), added slowly (45 min.) to a stirred, water-cooled mixture of redistilled anhydrous *tert.*-butyl alcohol (7·4 g.) and anhydrous pyridine (4·8 g.). The mixture was heated for 1 hr. at 50°, cooled, washed with 2N-sulphuric acid, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). The benzene was distilled under reduced pressure, leaving an orange-coloured

[17] Ziegler, Späth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80.
[18] Braun, *ibid.*, 1929, **472**, 57.
[19] Fuson, Kuykendall, and Wilhelm, *J. Amer. Chem. Soc.*, 1931, **53**, 4187.

viscous oil (6·1 g.). Distillation (bath-temp. 112—115°/1 × 10^{-5} mm.) gave *di*-tert.-*butyl* α-p-*methoxyphenyladipate* (3·3 g.) as a pale greenish solid, m. p. 51° (Found: C, 68·95; H, 8·65. $C_{21}H_{32}O_5$ requires C, 69·25; H, 8·8%).

If the acid chloride–alcohol stage was carried out at 100° for 3 hr. there was a 50% reduction in yield.

Determination of ester value showed the undistilled oil to contain >90% of the desired ester (Found: 91·8 and 91·3% ≡ 5·5 g.), and experiments conducted on the crude material, based on this figure, gave results equivalent to those obtained with the distilled product.

2-3′-*Acetoxyacetonyl*-5-p-*methoxyphenyl*cyclo*pentanone* (IV; R = H).—Di-*tert.*-butyl α-*p*-methoxyphenyladipate (13·3 g.), sodamide [from sodium (1·05 g.)], and anhydrous benzene (100 c.c.) were stirred, under nitrogen, at 45° (3 hr.) and then at 75° (3 hr.), evolution of ammonia then ceasing. 1-Acetoxy-3-iodoacetone [from the chloro-analogue (6·75 g.)] was added to the cooled (ice) solution, and stirring continued, with cooling (3 hr.), and then at room temperature (18 hr.). The neutral mixture was poured into water, the organic layer separated, and the aqueous solution extracted with ether. The combined benzene–ether solutions were extracted with 0·5N-sodium hydroxide, washed with water, and dried (Na_2SO_4).

The residue (4·0 g.) after distillation of the solvents was dissolved in anhydrous benzene (40 c.c.), and the solution heated under reflux (3 hr.) with a crystal of toluene-*p*-sulphonic acid. Working up in the normal manner yielded a dark, viscous, non-distillable oil (2·3 g.).

0·7 g. of this material was placed on a 20 × 2 cm. column of neutral alumina. Elution with 4 : 1 benzene–acetone removed a single yellow band. Evaporation of the solvent and short-path distillation (bath-temp. 135°/1 × 10^{-6} mm.) of the residue (0·35 g.) gave 2-3′-*acetoxyacetonyl*-5-p-*methoxyphenyl*cyclo*pentanone* (Found: C, 66·7; H, 7·3. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

Ethyl 1-3′-*Acetoxyacetonyl*-3-p-*methoxyphenyl*-2-*oxo*cyclo*pentanecarboxylate* (X; R = CH_2·CO·CH_2·OAc, R′ = Et).—Diethyl α-*p*-methoxyphenyladipate (8 g.) was cyclised as described above. To the deep-red solution of the sodium salt so formed was added 1-acetoxy-3-iodoacetone [from the chloro-analogue (3·9 g.)], and the mixture stirred for 3 hr. The neutral mixture was worked up as above, yielding an orange-yellow, viscous oil (6·2 g.), undistillable at 1 × 10^{-6} mm. The crude product (0·7 g.) was chromatographed on neutral alumina, 1 : 5 methanol–benzene eluting a single yellow band. Evaporation of the solvents gave ethyl 1-3′-*acetoxyacetonyl*-3-p-*methoxyphenyl*-2-*oxo*cyclo*pentanecarboxylate* (0·5 g.) (Found: C, 64·25; H, 6·6. $C_{20}H_{24}O_7$ requires C, 63·85; H, 6·4%).

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