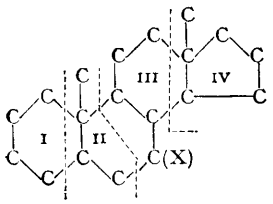
151. *Experiments on the Synthesis of Substances related to the Sterols. Part XLVI. The Synthetic Use of* 4-*Keto*-1 : 1-*dialkylpiperidinium Salts.*

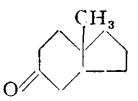
By H. M. E. Cardwell and F. J. McQuillin.

4-Keto-1 : 1-dimethylpiperidinium iodide has been shown to alkylate β-keto-esters (and ethyl malonate) yielding 1 : 5-diketones retaining the potentially reactive dimethylamino-group. The synthetical applications of these substances have been explored in two directions. Thus the product (VII) obtained from ethyl *cyclo*pentanonecarboxylate has been cyclised to the ketotetrahydroindane derivative (VIII), and the *cyclo*hexenone derivative obtained from ethyl acetoacetate has been shown by degradation to *m*-2-dimethylaminoethylphenol to have the structure (XI; R = CO_2Et, R′ = NMe_2). Further, the intermediate ethyl 8-dimethylamino-2 : 6-diketo-octane-3-carboxylate (X; R = CH_2·NMe_2), obtained from ethyl acetoacetate, has been shown to react, as its methiodide, with a second molecule of ethyl acetoacetate to yield a triketone (XVIII; R = H).

In Part XIV of this series (du Feu, McQuillin, and Robinson, *J.*, 1937, 53) it was suggested that the sterol skeleton might be dissected into α- and αα′-substituted acetone units, and that, starting from a methyl*cyclo*pentanone derivative constituting ring IV, the ætiocholane ring system might be synthesised by successive condensation with methyl vinyl ketone, ethyl vinyl ketone and again with methyl vinyl ketone. The direction which may be taken by the second step in this sequence is, however, ambiguous. Thus 5-keto-8-methylhexahydroindane (II) with 1-diethylaminopentan-3-one methiodide (as the equivalent of ethyl vinyl ketone) leads to a product which may be (III) or (IV) and the structure of which was not established (*idem*, *ibid.*; McQuillin and Robinson, *J.*, 1938, 1097; 1941, 586).



(I.)



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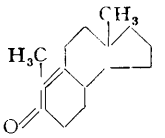

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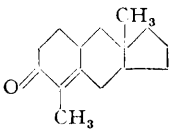

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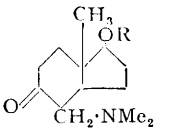
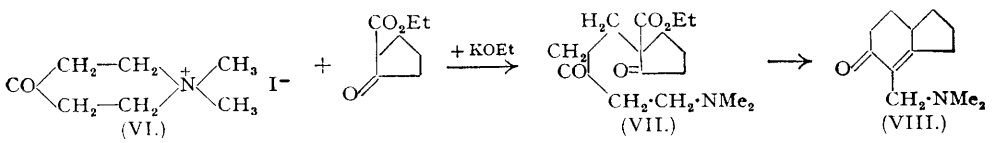


(V.)

A modified dissection of the sterol skeleton as in (I) offers a means of resolving this ambiguity. The addition of ring III is here envisaged as arising from condensation of the appropriate methyl*cyclo*pentanone with a divinyl ketone equivalent, such that the atom X (I) in the derived dicyclic substance carries a substituent capable of providing for closure of ring II. Thus testosterone or an isomer could in principle be synthesised from the β-dialkylamino-ketone (V) by using the method of Cook and Robinson (Part XXXI, *J.*, 1941, 391) and this amino-ketone could in turn be made by alkylation of the appropriate methyl*cyclo*pentanone with 4-keto-1 : 1-dimethylpiperidinium iodide (VI) followed by cyclisation and reduction. As a model we turned our attention in the first instance to the corresponding sequence starting from ethyl *cyclo*pentanone-2-carboxylate, *viz.* :

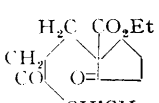


The iodide (VI) (Howton, *J. Org. Chem.*, 1945, **10**, 277) reacted readily with ethyl potassio-*cyclo*pentanonecarboxylate, but the basic product on attempted distillation lost dimethylamine to give *ethyl* 1-(3′-*ketopent*-4′-*enyl*)cyclo*pentan*-2-*one*-1-*carboxylate* (IX). Precipitation, however, of the crude basic product as the acid oxalates and fractional crystallisation gave the *hydrogen oxalate* of ethyl 1-(5′-dimethylamino-3′-ketoamyl)*cyclo*pentan-2-one-1-carboxylate (VII), m. p. 169—170°, in 5% yield. This base was also characterised as the *hydrochloride*, m. p. 200—202°, and *picrate*, m. p. 126—128°. Cyclisation of the crude basic product by means of hydrochloric acid in acetic acid (cf. Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469) gave 5-keto-4-dimethylaminomethyl-5 : 6 : 7 : 8-tetrahydroindane (VIII), isolated as the *hydrogen oxalate*, m. p. 120—124°, in 13% yield. In the above and all subsequent alkylations

excess alkalinity of the reaction mixture was avoided by slow addition of ethanolic potassium ethoxide to an ice-cold suspension of the metho-salt and keto-ester in benzene. Strong bases are known to catalyse the decomposition of β-dialkylamino-ketones [*e.g.*, (VII)] into vinyl ketones [*e.g.*, (IX)] and secondary amines (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206; Blicke, " Organic Reactions," Vol. 1). Contamination of the main product with cyclised material was also minimised by this method.

Ethyl malonate with 4-keto-1 : 1-dimethylpiperidinium iodide similarly gave ethyl 5-dimethylamino-3-ketoamylmalonate, $NMe_2 \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_2 \cdot CH_2 \cdot CH(CO_2Et)_2$ (*hydrogen oxalate*, m. p. 87—89°), in 25% yield.

In view of the difficulty encountered in isolating the products of these reactions in satisfactory yields, the alkylation of ethyl acetoacetate with 4-keto-1 : 1-dimethylpiperidinium iodide was investigated in detail. Prolonged fractional crystallisation of the oxalate of the basic product gave (*a*) the *hydrogen oxalate* of ethyl 8-dimethylamino-2 : 6-diketo-octane-3-carboxylate (X; R = $CH_2 \cdot NMe_2$), m. p. 109—110°, as major product, with (*b*) ethyl 4-(2′-dimethylaminoethyl)*cyclo*hex-3-en-2-one-1-carboxylate (XI; R = CO_2Et; R′ = NMe_2), *hydrogen oxalate*, m. p. 116—117°, in small amount, together with (*c*) dimethylamine hydrogen oxalate and (*d*) the *dihydrogen dioxalate* of 2 : 2′-bisdimethylaminodiethyl ketone, m. p. 155—156°, identified by independent preparation from dimethylamine and 2 : 2′-dichlorodiethyl ketone.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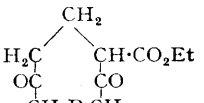
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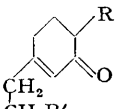
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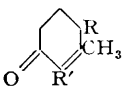
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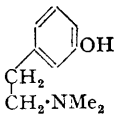

(XIII.)

The preparation of the latter ketone by aluminium chloride-catalysed addition of β-chloropropionyl chloride to ethylene (Catch, Elliott, Hey, and Jones, *J.*, 1948, 278) was improved by substitution of nitromethane as solvent for the customary excess of acid chloride. Nitromethane appears to be an excellent medium for this type of reaction, provided the derived chloro-ketone can be effectively separated from it by distillation.

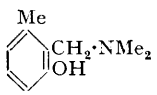
The structure of the *cyclo*hexenone (XI; R = CO_2Et; R′ = NMe_2), which was also prepared from the diketone (X; R = $CH_2 \cdot NMe_2$) by cyclisation with ice-cold sulphuric acid, was established by its hydrolysis and decarboxylation to 1-2′-dimethylaminoethyl*cyclo*hexen-3-one (XI; R = H; R′ = NMe_2) (isolated as the *hydrogen oxalate*, m. p. 135—136°) and by bromination and dehydrobromination of this substance by Knoevenagel's method (*Annalen*, 1894, **281**, 98; *Ber.*, 1893, **26**, 1951) to *m*-2-dimethylaminoethylphenol (XIII), identical with a synthetic specimen prepared from *m*-hydroxybenzaldehyde by a modification of the method given in D.R-P. 233,069 (Friedländer, Vol. 10, p. 1229). Before the identity of this aminophenol was established, an attempt was made to prepare the amino-xylenol (XIV) to be expected from the alternative formulation of the *cyclo*hexenone as (XII; R = CO_2Et or H; R′ = $CH_2 \cdot NMe_2$). Equimolecular proportions of *m*-cresol, formaldehyde, and dimethylamine gave a single product, which, however, was evidently the undesired *5-methyl-2-dimethylaminomethylphenol* (XV; R = Me), since hydrogenation afforded a xylenol giving no ferric chloride colour and which therefore cannot be *o*-3-xylenol. An analogous product obtained by Grillot and Gormerly (*J. Amer. Chem. Soc.*, 1945, **67**, 1968) from diethylamine, formaldehyde, and *m*-cresol was therefore most probably 5-methyl-2-diethylaminomethylphenol (XV; R = Et).

Alkylation of ethyl *cyclo*hexanonecarboxylate with 4-keto-1-methyl-1-ethylpiperidinium iodide gave ethyl 1-(5′-methylethylamino-3′-ketoamyl)*cyclo*hexan-2-one-1-carboxylate (XVI) isolated as the *hydrogen oxalate*, m. p. 95—97°, in 70% yield, but only after some difficulty (see p. 713). Numerous attempts to convert this diketone into the aminomethyl-tetralol (XVII) were unsuccessful, the only basic product isolated being methylethylamine.

The isolation of the unstable hydrogen oxalate of the diketone (XVI) in a yield of 70% confirmed our impression that alkylations of β-keto-esters with 4-keto-1 : 1-diethylpiperidinium iodides give the desired diketones in substantial quantities (over 60%) and that it is only the difficulty of freeing these compounds from by-products which has precluded these yields being achieved in general. With the analogous thioalkyl compounds (see following paper) isolation of the diketones is, however, easier, and we have therefore directed further work to a study of these substances.

The alkylation of ethyl acetoacetate described above was envisaged as the first step in a model synthesis of reduced analogues of doisynolic acid. The cyclisation of (X; R = $CH_2 \cdot NMe_2$)

to (XI; R = CO_2Et, R′ = NMe_2) rather than to the desired compound (XII; R = CO_2Et, R′ = CH_2·NMe_2) ruled out this method but there remained the possibility that the triketone (XVIII; R = H) might undergo double cyclisation to give the tetralol (XIX; R = H). The reaction mixture from ethyl acetoacetate and 4-keto-1-methyl-1-ethylpiperidinium iodide was therefore treated with an equivalent of methyl iodide and when the pH of the solution became constant a further molecule of ethyl potassio-acetoacetate was added. The alkali-soluble portion of the product was subjected to molecular distillation and *ethyl* 2 : 6 : 10-*triketoundecane*-3 : 9-*dicarboxylate* (XVIII; R = H) was isolated. The analogous *ethyl* 3 : 7 : 11-*triketotridecane*-4 : 10-*dicarboxylate* (XVIII; R = Me) was prepared from two equivalents of ethyl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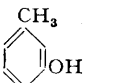
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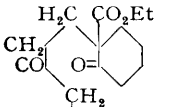
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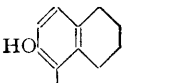
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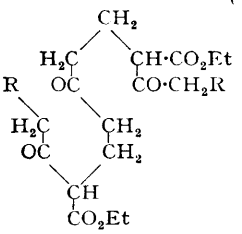
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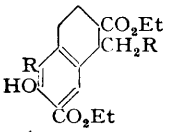
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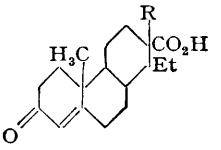
(XX.)

sodio-β-ketovalerate and one equivalent of 2 : 2′-dichlorodiethyl ketone. The doubly cyclised material in this case would have been the tetralol (XIX; R = Me), an excellent starting material for the synthesis of the reduced analogue of doisynolic acid (XX; R = H). Only preliminary and inconclusive experiments on the cyclisation of these triketones have been made, and this investigation has been temporarily suspended in view of the lack of activity in the capon comb tests of the compound (XX; R = Me) prepared from androstenedione (Heer and Miescher, *Helv. Chim. Acta*, 1947, **30**, 786).

The cyclisation of the diketone (X; R = CH_2·NMe_2) to the *cyclo*hexenone (XI; R = CO_2Et, R′ = NMe_2) rather than to (XII; R = CO_2Et, R′ = CH_2·NMe_2) deserves some discussion. There are few analogies to indicate the most probable direction of cyclisation of diketones of this type (X), and indeed the structure of our product was in doubt (until the reference compound had been prepared), for the ready decarboxylation and ferric chloride colour reaction were equally consistent with 2 : 7-cyclisation to (XII; R = CO_2Et, R_2′ = CH_2·NMe_2) by analogy with Hagemann's ester (XII; R = CO_2Et, R′ = H) which gives a violet colour with ferric chloride and is readily decarboxylated on hydrolysis (Hagemann, *Ber.*, 1893, **26**, 879; Rabe, *Annalen*, 1905, **342**, 339).

From condensation of ethyl acetoacetate with dimethylaminobutan-3-one by means of sodium ethoxide, Mannich and Fourneau (*Ber.*, 1938, **71**, 2090) obtained Hagemann's ester, a preparation evidently involving cyclisation of the diketone (X; R = H). This intermediate diketone, *ethyl* 2 : 6-*diketoheptane*-3-*carboxylate* has now been prepared from ethyl acetoacetate and the methiodide of diethylaminobutan-3-one, and its cyclisation under alkaline conditions to Hagemann's ester has been confirmed. Using 2-chlorodiethyl ketone with ethyl acetoacetate, Blaise and Maire (*Compt. rend.*, 1907, **144**, 572; *Bull. Soc. chim.*, 1908, **3**, 418) obtained the higher homologue (X; R = Me), cyclised under acid conditions to a product (semicarbazone, m. p. 207°) assigned the structure (XI; R = CO_2Et, R = H) on the grounds of its colour reaction with ferric chloride, solubility in alkali, and ready decarboxylation to a *cyclo*hexenone (semicarbazone, m. p. 204°), presumably (XI; R = R′ = H). Mousseron and Winternitz (*Bull. Soc. chim.*, 1945, **12**, 71; *Compt. rend.*, 1944, **219**, 132) prepared this ethyl*cyclo*hexenone by another route and confirmed the melting point of the semicarbazone; Clemo, Cocker, and Hornsby (*J.*, 1946, 616) assign the same structure to a ketone (semicarbazone, m. p. 191—192°), which may, however, be the corresponding 3-ethylidene*cyclo*hexanone. The alternative cyclisation of Blaise and Maire's product would lead to the known dimethylcarbethoxy*cyclo*hexenone (XII; R = CO_2Et, R′ = Me), semicarbazone, m. p. 204—205° (Cornubert and Maurel, *Bull. Soc. chim.*, 1931, **49**, 1515; Kötz, Blendermann, Mahnert, and Rosenbusch,

Annalen, 1913, **400**, 82), and to the dimethyl*cyclo*hexenone (XII; R = R′ = Me), semicarbazone, m. p. 225°, the structure of which has been established by dehydrogenation to *o*-3-xylenol (Smith and Rouault, *J. Amer. Chem. Soc.*, 1943, **65**, 631). The melting points of the semicarbazones in these two series are consistent with the structure (XI; R = CO_2Et, R′ = H) for Blaise and Maire's product although their original grounds for assigning this structure are evidently fallacious.

These examples and the exclusive 1 : 6-cyclisation in the present case (X; R = CH_2·NMe_2) suggest that the direction of cyclisation is determined by the known greater reactivity of the terminal methyl group as in the self-condensation of simple ketones (cf. Grignard and Colonge, *Compt. rend.*, 1930, **190**, 1349), and that it is only in the symmetrical example of Mannich and Fourneau that the influence of the β-keto-ester system is effective.

Experimental.

(M. p.s are uncorrected.)

Methyldi-(2-carbethoxyethyl)amine was prepared in 80—90% yield from ethyl acrylate and methylamine; b. p. 107—109°/0·3 mm. (*Org. Synth.*, **20**, 36, give b. p. 105—108°/3 mm.).

3-*Carbethoxy*-1-*methyl*-4-*piperidone methiodide* was prepared from 3-carbethoxy-1-methyl-4-piperidone (McElvain, *J. Amer. Chem. Soc.*, 1924, **46**, 1721) and methyl iodide in dry ether. It crystallised from *iso*propanol in colourless prisms, m. p. 138—139° (decomp.) (Found: N, 4·0; I, 38·6. $C_{10}H_{18}O_3NI$ requires N, 4·3; I, 38·8%).

1-*Methyl*-4-*piperidone* (Prill and McElvain, *ibid.*, 1933, **55**, 1233). The following modification of the method used by Fuson, Parham, and Reed (*ibid.*, 1946, **68**, 1239) for the preparation of the hydrochloride of the ethyl analogue was convenient. Sodium (17·5 g.) was powdered under boiling xylene with a Herschberg stirrer (*Org. Synth.*, Coll. Vol. II, 117). Methyldi-(2-carbethoxyethyl)amine (180—185 g.) was run in with vigorous stirring at such a rate that gentle refluxing was maintained. The mixture was stirred and refluxed until homogeneous (½—1 hour), cooled, and shaken with ice (200 g.) and concentrated hydrochloric acid (150 c.c.). The xylene layer was further extracted with ice-water (100 c.c.) containing a little hydrochloric acid. The combined aqueous extracts were extracted with ether and filtered through glass-wool. Concentrated hydrochloric acid (390 c.c.) was added, dissolved ether was removed on the steam-bath, and the mixture was refluxed until a few drops gave no colour with ferric chloride. The mixture was evaporated to dryness under reduced pressure by flash distillation or with a reversed air-leak to stop bumping, and the residue was dissolved in distilled water (100 c.c.). The solution was covered with ether, cooled to below 0°, and treated with anhydrous potassium carbonate (125 g.) and extracted four times with ether. The dried ethereal extracts were distilled; yield 35—53 g. (40—60%), b. p. 53—56°/5 mm. (Prill and McElvain, *loc. cit.*, give b. p. 56—58°/11 mm.). These authors and Howton (*J. Org. Chem.*, 1945, **10**, 277) reported that the free base polymerised on keeping at room temperature to give an ether-insoluble substance. The pure base, as prepared above, was stable indefinitely at 0°, and after 5 months' storage at room temperature in dry aldehyde-free ether only a small quantity of gum was deposited, and redistillation gave a 62% recovery of pure free base, characterised as methiodide and hydrogen oxalate. Howton (*loc. cit.*) reported that the latter salt was unsuitable for characterisation but gave no further details. 1-*Methyl*-4-*piperidone hydrogen oxalate* crystallised from ethanol–ether or *iso*propanol–ethanol in colourless, feathery rods, m. p. 122—123°, containing solvent of crystallisation which was removed at 50° in a vacuum (Found: N, 6·8. $C_6H_{11}ON,C_2H_2O_4$ requires N, 6·9%).

4-Keto-1 : 1-dimethylpiperidinium iodide was prepared in quantitative yield by adding excess of methyl iodide to the free base in ice-cold aldehyde-free ether and allowing it to stand for 7 days; the colourless, hygroscopic microcrystals, m. p. 186—188° (decomp.), recrystallised from methanol with a molecule of methyl alcohol, m. p. 189—190°. [Howton, *loc. cit.*, gives m. p. 187·6—188·0° (decomp.) and describes this compound as a hemiketal.] The molecule of methyl alcohol is tenaciously held but is slowly removed at 110°/0·1 mm. The methiodide crystallised from ethanol–ether with varying quantities of solvent of crystallisation which are difficult to remove, and from 96% aqueous acetone as colourless prisms of a *monohydrate* (Found: C, 30·7; H, 5·9; N, 5·0; I, 47·1. $C_7H_{14}ONI,H_2O$ requires C, 30·8; H, 5·9; N, 5·1; I, 46·7%). The *methiodide* is best prepared in a pure state in reasonably large crystals by adding methyl iodide to a refluxing solution of the piperidone in dry *iso*propanol; colourless prisms, m. p. 202—204° (decomp.) (Found: N, 5·2; I, 49·6. $C_7H_{14}ONI$ requires N, 5·5; I, 49·8%).

1-*Ethyl*-4-*piperidone* was prepared from 2 : 2′-dicarbethoxytriethylamine (195 g.) in the same manner as for 1-methyl-4-piperidone. Fuson, Parham, and Reed (*loc. cit.*) quote a yield of 82—87%, but this refers to the crude hydrochloride whose m. p. they do not record. The yield of free base (not previously described) was 40—60 g. (40—60%), b. p. 46—48°/1 mm.; it distilled at 38°/0·5 mm. (Found: N, 11·0. $C_7H_{13}ON$ requires N, 11·0%). This base was stable indefinitely at 0° and after 5 months' storage at room temperature had developed a yellow colour, but recovery of pure methiodide was over 80%. Its *hydrogen oxalate* crystallised in glistening flat prisms from moist acetone but had an indefinite m. p. (75—100°). Analysis indicated the presence of ½ mol. of water of crystallisation which could not be removed without decomposition (Found: C, 47·7, 47·8; H, 6·5, 6·2; N, 6·2. $C_7H_{13}ON,C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 47·8; H, 7·1; N, 6·2%).

4-*Keto*-1-*methyl*-1-*ethylpiperidinium iodide* was prepared in hot *iso*propanol (it could be crystallised from ethanol without becoming solvated only by rapidly chilling a hot solution); colourless prisms, m. p. 180—182° (decomp.), dependent on rate of heating (Found: N, 4·9; I, 47·2. $C_8H_{16}ONI$ requires N, 5·2; I, 47·2%). In admixture with the dimethyl analogue, the m. p. was 183—186° (decomp.).

4-*Keto*-1 : 1-*dimethylpiperidinium iodide* crystallised in pale yellow prisms from *iso*propanol; m. p.

156—160°, with sintering at 154° (Found: C, 38·1; H, 6·4; N, 4·9; I, 44·8. $C_9H_{18}ONI$ requires C, 38·2; H, 6·4; N, 5·0; I, 44·9%).

Ethyl 1-(5′-*Dimethylamino*-3′-*ketoamyl*)cyclo*pentan*-2-*one*-1-*carboxylate* (VII).—(A) 1-Methyl-4-piperidone (6·92 g.), benzene (150 c.c.), and methyl iodide (8·7 g.) were mixed and left for 3 days at room temperature. Ethyl *cyclo*pentan-2-one-1-carboxylate (8·56 g.) in benzene (100 c.c.) was added, and the mixture was stirred at 0° under nitrogen while potassium ethoxide (potassium 2·28 g., ethanol 27 c.c.) was run in during one hour. After 2 hours at 0° the mixture was filtered from potassium iodide, kept overnight at room temperature, and extracted with ice-cold 2N-hydrochloric acid. The acid layer was made alkaline with anhydrous potassium carbonate (below 5°), extracted several times with ether, and dried (Na_2SO_4); a stream of dry hydrogen chloride then precipitated a gummy hydrochloride which partly crystallised. The *hydrochloride* of (VII) crystallised in micro-needles (1·02 g., 5%) from ethanol–ether; m. p. 194—196° with sintering at 185°. After crystallisation from ethanol–ether and then *iso*propanol it melted at 200—202° (Found: C, 56·4; H, 8·6; N, 4·2; Cl, 11·1. $C_{15}H_{25}O_4N,HCl$ requires C, 56·4; H, 8·2; N, 4·4; Cl, 11·1%). The *picrate* crystallised in flat rods, m. p. 126—128·5°, with sintering at 124°, from *iso*propanol (Found: C, 49·3; H, 5·6; N, 11·1. $C_{15}H_{25}O_4N,C_6H_3O_7N_3$ requires C, 49·2; H, 5·5; N, 10·9).

(B) 4-Keto-1 : 1-dimethylpiperidinium iodide (52 g.), ethyl *cyclo*pentan-2-one-1-carboxylate (32 g.), and benzene (250 c.c.) were stirred at 0° under nitrogen while potassium ethoxide (potassium 7·4 g., ethanol 90 c.c.) was run in during one hour. The mixture was left for 4 days at room temperature, filtered from potassium iodide, and poured into ether (200 c.c.) containing anhydrous oxalic acid (24 g.). The gummy oxalates were washed with ether and fractionally crystallised from aqueous ethanol, and then from *iso*propanol. There were obtained: (i) 0·7 g. of colourless needles (from 85% aqueous ethanol), m. p. 152—153°, alone or admixed with the by-product from the acetoacetate alkylation (see below); (ii) 2·3 g. (3%) of colourless rods, from methanol, of the *hydrogen oxalate* of (VII), m. p. 169—170° (decomp.), with sintering at 165° (Found: C, 55·0; H, 7·2; N, 3·9. $C_{15}H_{25}O_4N,C_2H_2O_4$ requires C, 54·8; H, 7·2; N, 3·8%); and (iii) 3·35 g. of micro-plates from *iso*propanol, softening at 75° and slowly melting to a clear liquid at 110°. This substance could not be purified further by recrystallisation. Analysis (Found: C, 52·3, 51·8; H, 7·3, 7·3; N, 5·5, 5·2%) suggested that it was a mixture of the oxalate (ii) and the oxalate of a simpler base.

Ethyl 1-(3′-*Ketopent*-4′-*enyl*)cyclo*pentan*-2-*one*-1-*carboxylate* (IX).—The crude free base from method (B) (above) was distilled. There was pronounced decomposition and a neutral oil, b. p. 145—150°/0·5 mm., was collected; yield 17%, based on the original piperidone methiodide used. The oil was washed with dilute acid to remove any base and redistilled, the *ethyl* ester (IX) distilling at 138—144°/0·5 mm. (Found: C, 64·9, 65·1; H, 7·9, 7·9. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%). There was much residue in the distillation flask, indicating the ready polymerisation of this vinyl ketone.

5-*Keto*-4-*dimethylaminomethyl*-5 : 6 : 7 : 8-*tetrahydroindane* (VIII).—The reaction mixture from 4-keto-1 : 1-dimethylpiperidinium iodide (52 g.) and ethyl *cyclo*pentan-2-one-1-carboxylate (32 g.) as in method (B) (above) was extracted with ice-cold 2N-hydrochloric acid. The acid layer was made alkaline with anhydrous potassium carbonate (below 5°) and extracted with ether. The ether, after drying over sodium sulphate, was removed in a vacuum, and the residue was heated in a vacuum to 60°. The residual basic oil (42 g.) was heated under reflux under nitrogen with acetic acid (1200 c.c.) and concentrated hydrochloric acid (200 c.c.) for 8 hours. After removal of the solvents in a vacuum on the steam-bath, the residue was dissolved in water (50 c.c.) and extracted with ether to remove some gum. The aqueous layer was made alkaline with anhydrous potassium carbonate (below 5°) and extracted with ether. The ether extract after being dried (Na_2SO_4) was poured into ether (200 c.c.) containing anhydrous oxalic acid (16 g.). Fractional crystallisation of the acid oxalates from ethanol gave (i) 0·5 g., colourless needles (from aqueous ethanol), m. p. 149—151° alone or admixed with the by-product from the acetoacetate alkylation (see below); (ii) 1·7 g. of fern-like prisms (from ethanol), m. p. 145—147° alone or admixed with an authentic specimen of dimethylamine hydrogen oxalate, and (iii) 7·5 g.(13%) of irregular plates (from ethanol), m. p. 114—118°. After three recrystallisations from ethanol, the *hydrogen oxalate* of the ketone (VIII) melted at 120—121° with sintering at 115° (Found: C, 59·2; H, 7·4; N, 5·1. $C_{12}H_{19}ON,C_2H_2O_4$ requires C, 59·4; H, 7·4; N, 5·0%).

Ethyl 8-*Dimethylamino*-2 : 6-*diketo*-*octane*-3-*carboxylate*.—4-Keto-1 : 1-dimethylpiperidinium iodide (12·8 g.), ethyl acetoacetate (6·5 g.), and benzene (150 c.c.) were stirred at 0° under nitrogen while potassium ethoxide (potassium 1·85 g., ethanol 22 c.c.) was run in during one hour. After standing overnight at room temperature, the mixture was filtered from potassium iodide and diluted with ether (300 c.c.). A small amount of a cream-coloured solid, which rapidly deliquesced and went brown in air, was filtered off (this may have been the salt 4-keto-1 : 1-dimethylpiperidinium, ethyl acetoacetate). The filtrate was poured into ether (50 c.c.) containing anhydrous oxalic acid (5·5 g.). The gummy oxalate was washed with ether and extracted with 95% aqueous ethanol. On cooling, fine white needles (0·84 g.) separated, m. p. 148—150°. 2 : 2′-*Bisdimethylaminodiethyl ketone dihydrogen dioxalate* melted at 152—153° after two recrystallisations from aqueous ethanol. It gave a red colour with 2 : 4-dinitrophenylhydrazine but no colour with ferric chloride (Found: C, 44·3, 44·4; H, 7·0, 6·7; N, 8·1. $C_9H_{20}ON_2,2C_2H_2O_4$ requires C, 44·3; H, 6·8; N, 8·0%). The aqueous-alcoholic mother-liquors from this separation, on standing at 0°, deposited successive crops of white needles (total yield 3·73 g., 21%). The crude substance softened at 54° and slowly melted to a clear liquid at 113°. Repeated crystallisations from ethanol gave fine white needles of *ethyl* 8-*dimethylamino*-2 : 6-*diketo*-*octane*-3-*carboxylate hydrogen oxalate* (as X; R = $CH_2{\cdot}NMe_2$), softening at 72° and melting at 109—110°, but melting completely when put into a bath at 100°. It gave a dark green colour with alcoholic ferric chloride (Found: C, 51·8; H, 7·5; N, 3·7; OEt, 13·3. $C_{13}H_{23}O_4N,C_2H_2O_4$ requires C, 51·9; H, 7·2; N, 4·0; OEt, 13·0%). Large-scale runs gave lower yields and appreciable quantities of the oxalate of ethyl 4-(2′-dimethylaminoethyl)*cyclo*hex-3-en-2-one-1-carboxylate.

Ethyl 4-(2′-*Dimethylaminoethyl*)cyclo*hex*-3-*en*-2-*one*-1-*carboxylate* (XI; R = CO_2Et, R′ = NMe_2).—The foregoing acid oxalate of (X; R = $CH_2{\cdot}NMe_2$) (2·5 g.) was added slowly to well-stirred ice-cold concentrated sulphuric acid (20 c.c.). Stirring was continued until all the solid had dissolved (2 hours),

and the mixture was kept overnight at 0°. The mixture was poured into chopped ice (100 g.) and saturated with anhydrous potassium carbonate (below 10°). The liberated base was precipitated from ether as the acid oxalate. The *hydrogen oxalate* of (XI; R = CO_2Et, R′ = NMe_2) crystallised in colourless, slender rods from ethanol–ether; m. p. 116—117°, with sintering at 114°. It gave a deep green colour with alcoholic ferric chloride (Found: C, 54·7; H, 6·9; N, 4·1. $C_{13}H_{21}O_3N,C_2H_2O_4$ requires C, 54·7; H, 6·7; N, 4·3%). The *hydrochloride* crystallised in colourless micro-needles from ethanol; m. p. 142—143° with previous greying. It gave a deep green colour with alcoholic ferric chloride, and immediately decolorised neutral permanganate (Found: C, 56·4; H, 8·0; N, 5·0; Cl, 13·1. $C_{13}H_{21}O_3N,HCl$ requires C, 56·6; H, 8·0; N, 5·1; Cl, 12·9%). The *picrate* crystallised in light yellow rods from *iso*propanol; m. p. 122—123° (Found: C, 49·0; H, 5·2; N, 12·0. $C_{13}H_{21}O_3N,C_6H_3O_7N_3$ requires C, 48·7; H, 5·1; N, 12·0%).

1-(2′-*Dimethylaminoethyl*)cyclo*hex*-1-*en*-3-*one* (XI; R = H, R′ = NMe_2).—The foregoing hydrogen oxalate (2·27 g.) was refluxed for one hour with 20% hydrochloric acid (18 c.c.). The residue, after removal of solvent under reduced pressure, was taken up in a little water and made alkaline with potassium carbonate. The base was precipitated from ether as the *hydrogen oxalate*, which crystallised in long prisms (1·37 g., 77%) from ethanol–ether; m. p. 135—136° (Found: C, 56·0; H, 7·8; N, 5·6. $C_{10}H_{17}ON,C_2H_2O_4$ requires C, 56·0; H, 7·4; N, 5·5%).

m-(2-*Dimethylaminoethyl*)*phenol*.—The above oxalate (1·66 g.) in acetic acid (20 c.c.) was cautiously treated with bromine (1·04 g.) at 0°. The pale red solution on warming for 3 hours on the steam-bath evolved copious fumes of hydrogen bromide and went black. The residue after removal of solvent under reduced pressure was taken up in a little water and made alkaline with potassium carbonate. The liberated oil was extracted with ether, and the ether was then extracted three times with 2N-sodium hydroxide. The alkaline extracts were made acid with hydrochloric acid and non-basic phenolic products were removed with ether. The aqueous layer was then again made alkaline with potassium carbonate and the aminophenol was extracted with ether. The residue after removal of ether slowly crystallised in a vacuum desiccator. It was pressed on a plate, and the solid (0·2 g.) recrystallised three times from *cyclo*hexane. *m*-(2-Dimethylaminoethyl)phenol melted at 97·5—100° (D.R.-P. 233,069; Friedländer, Vol. 10, p. 1229, gives m. p. 103°). Mixed with an authentic specimen prepared from *m*-hydroxybenzaldehyde (m. p. 99—100·5°; for preparation see below), it melted at 98·5—100° (Found: N, 8·3. Calc. for $C_{10}H_{15}ON$: N, 8·5%).

2-m-*Methoxyphenylethylamine*.—*m*-Methoxy-ω-nitrostyrene (9·0 g.) (prepared from *m*-hydroxybenzaldehyde by the method of Gulland and Virden, *J.*, 1929, 1791), acetic acid (400 c.c.), concentrated sulphuric acid (10 c.c.), and platinum oxide (0·5 g.) were hydrogenated at 10 atm. at room temperature. Hydrogen absorption exceeded the theoretical by 10% in one hour. The solution was filtered from the catalyst, and water and excess of sodium acetate were added. The filtrate was evaporated to dryness under reduced pressure and the residue was treated with excess of 40% sodium hydroxide and extracted with ether. 2-*m*-Methoxyphenylethylamine hydrochloride was isolated in the usual manner and was identical with an authentic specimen prepared from *m*-methoxy-β-phenylpropionamide by Helfer's method (*Helv. Chim. Acta*, 1924, **7**, 945).

Trimethyl-2-m-*methoxyphenylethylammonium Iodide*.—2-*m*-Methoxyphenylethylamine hydrochloride (1·24 g.) was heated under reflux for 3 hours with potassium carbonate (1·37 g.), methyl iodide (2 c.c.), and methanol (20 c.c.). The required quaternary *iodide* crystallised in colourless plates from methanol or ethanol; m. p. 184—186° (Found: N, 4·3, 4·4; I, 39·9, 39·9. $C_{12}H_{20}ONI$ requires N, 4·4; I, 39·6%).

m-(2-*Dimethylaminoethyl*)*phenol*.—The above iodide was quite stable at 180—190° but at 200—220° in a vacuum it decomposed, mostly with loss of trimethylamine but to a small extent with loss of methyl iodide. After the heating, the flask was rinsed with ether, and the ether, after filtration, was removed. The residue was refluxed with decolorised constant-boiling hydriodic acid in a stream of nitrogen for 30 minutes. The solvent was removed under reduced pressure and the residue was shaken with water and ether. The aqueous layer was made alkaline with potassium carbonate and the amino-phenol was extracted with ether. The ether, after being dried (Na_2SO_4), was removed, and the residue slowly crystallised in a desiccator. After several recrystallisations from *cyclo*hexane it melted at 99—100·5° (Found: N, 8·7. Calc. for $C_{10}H_{15}ON$: N, 8·5%). In one experiment, demethylation with a sample of hydriodic acid containing considerable quantities of free iodine gave an *iodo*-2-m-*dimethylaminoethylphenol*, m. p. 132—133°, from ethanol–light petroleum (b. p. 40—60°) (Found: C, 40·8; H, 4·4. $C_{10}H_{14}ONI$ requires C, 41·2; H, 4·8%).

Ethyl 5-dimethylamino-3-ketoamylmalonate was prepared from 4-keto-1 : 1-dimethylpiperidinium iodide (12·8 g.) and ethyl malonate (8·0 g.) in the normal manner and isolated as the *hydrogen oxalate*; yield 4·8 g. (25%) of imperfect micro-needles, m. p. 82—86°. After two recrystallisations from acetone and two from ethyl acetate, this salt melted at 87—89° (Found: C, 50·6; H, 7·0; N, 4·0. $C_{14}H_{25}O_5N,C_2H_2O_4$ requires C, 50·9; H, 7·2; N, 3·7%).

Ethyl 1-(5′-*Methylethylamino*-3′-*ketoamyl*)cyclo*hexan*-2-*one*-1-*carboxylate* (XVI).—The isolation of this substance gave much trouble and the following directions must be followed precisely. 4-Keto-1-methyl-1-ethylpiperidinium iodide (54 g.), ethyl *cyclo*hexan-2-one-1-carboxylate (34 g.), and benzene (150 c.c.) were stirred at 0° under nitrogen while potassium ethoxide (potassium 7·4 g., ethanol 100 c.c.) was run in during one hour. The mixture was stirred at 0° for a further hour and then at room temperature for an hour. The mixture was filtered from potassium iodide and extracted with ice-cold 2N-hydrochloric acid. The aqueous layer was cooled to 0°, saturated with potassium carbonate, and extracted with ether, washed with a little saturated brine and dried (Na_2SO_4). The basic oil, after removal of ether and the residual ethanol in a vacuum (finally at 45°), was taken into toluene and filtered from some gum. The base was then re-extracted with ice-cold 2N-hydrochloric acid, liberated with potassium carbonate, and precipitated from the dried ethereal solution as the hydrogen oxalate, which slowly crystallised (56 g., 72%), m. p. 88—93°. It recrystallised in glistening micro-plates from ethanol–ether, *iso*propanol, or ethyl acetate. After four recrystallisations from ethyl acetate it melted at 93—94·5° and three consecutive and concordant analyses for carbon, hydrogen, and nitrogen suggested that it was contaminated with approximately 10% of methylethylamine oxalate. The free base was

prepared from this sample and treated with methyl iodide. The oily methiodide on recrystallisation from ethanol gave a very small quantity of trimethylethylammonium iodide, m. p. >300° (Found: C, 27·9; H, 6·3. Calc. for $C_5H_{14}NI$: C, 27·9; H, 6·5%). The free base on treatment with ethyl iodide gave a very small quantity of methyltriethylammonium iodide, m. p. >300° (Found: I, 52·0. Calc. for $C_7H_{18}NI$: I, 52·3%). This suggested that the substance was extremely unstable even as the *hydrogen oxalate*, which was therefore recrystallised from a lower-boiling solvent and, after three recrystallisations from acetone, was obtained pure, m. p. 95—97°, with softening at 94°. Analyses were slightly variable (Found: C, 56·6, 56·1, 57·6, 57·8, mean 57·0; H, 7·5, 7·4, 7·6, 7·7, mean 76. $C_{17}H_{29}O_4N,C_2H_2O_4$ requires C, 56·9; H, 7·7%).

2 : 2′-*Dicarbethoxydiethyl Ether*.—Hydrolytic esterification of 2 : 2′-dicyanodiethyl ether (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23) with ethanolic hydrogen chloride gave the *dicarbethoxyether*, b. p. 109°/1·2 mm., $n_D^{14°}$ 1·4324 (Found: C, 54·7; H, 8·2. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%). The parent *acid* crystallised from carbon disulphide in colourless rods, m. p. 62—63° (Found: C, 44·4; H, 6·4. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%). Wislicenus (*Annalen*, 1873, **166**, 39) described the disodium salt of this acid.

2 : 2′-*Dichlorodiethyl Ketone*.—The following modification of the method of Catch, Elliott, Hey, and Jones (*loc. cit.*) gave excellent results. Dry ethylene was passed into a well-stirred solution of aluminium chloride (33 g.) and β-chloropropionyl chloride (32 g.) in nitromethane (25 c.c.) at 0°. After 7 hours the net gain in weight was 4·5 g. (theory 7·0 g.). The reaction mixture was poured on to chopped ice and extracted with ether. The ether was washed with ice-cold aqueous sodium hydrogen carbonate and dried at 0° over sodium sulphate. The ether was removed in a vacuum, and the product distilled; yield 19·0 g., b. p. 78°/6 mm.—88°/1 mm. This liquid was saturated at 0° with dry hydrogen chloride and allowed to stand at 0° for 48 hours. On redistillation there were obtained 9·1 g., b. p. 72—73·5°/2 mm., $n_D^{16°}$ 1·4676, and 9·5 g., b. p. 73·5—77°/2 mm., $n_D^{16°}$ 1·4710 (Found: C, 38·2; H, 5·3; Cl, 46·2. Calc. for $C_5H_8OCl_2$: C, 38·7; H, 5·2; Cl, 45·8%) (Catch *et al.*, *loc. cit.*, give b. p. 74°/0·8 mm., $n_D^{18°}$ 1·4726). Both fractions were suitable for preparative work although the former contained some 2-chloroethyl vinyl ketone. The ketone when pure is quite stable at 0°, but at room temperature polymerises with loss of hydrogen chloride.

2 : 2′-*Bisdimethylaminodiethyl Ketone*.—2 : 2′-Dichlorodiethyl ketone (2 c.c.) was dropped slowly into excess of 25% aqueous dimethylamine. After 24 hours at room temperature the solution was cooled in ice, saturated with potassium carbonate, and extracted with ether. The *dihydrogen dioxalate* was recrystallised from aqueous ethanol; colourless needles, m. p. 155—156°. When mixed with a specimen (m. p. 152—153°) isolated from the alkylation of ethyl acetoacetate with 4-keto-1 : 1-dimethylpiperidinium iodide, the mixture melted at 154—156° (Found: C, 4·2, 44·4; H, 6·3, 6·8; N, 8·2, 8·1. $C_9H_{20}ON_2,C_4H_4O_8$ requires C, 44·3; H, 6·8; N, 8·0%).

Alkylation of Ethyl Acetoacetate (2 *Mols.*) *with* 4-*Keto*-1-*methyl*-1-*ethylpiperidinium Iodide* (1 *Mol.*).—The iodide (83 g.), ethyl acetoacetate (39 g.), and benzene (300 c.c.) were stirred at 0° under nitrogen while potassium ethoxide (potassium 11·7 g., ethanol 140 c.c.) was run in during 2½ hours. Stirring was continued for 1 hour at 0° and 2 hours at room temperature. Methyl iodide (42·6 g.) was then added. After two days the pH of the mixture had reached a constant value of 3·4. The mixture was cooled to 0°, and ethyl acetoacetate (39 g.), followed by potassium ethoxide (potassium 11·7 g., ethanol 140 c.c.), was run in with stirring during 2½ hours. After a further hour the mixture was extracted with ice-cold 2N-sulphuric acid, and the acid layer was extracted once with benzene. The combined benzene extracts were washed with water and then repeatedly extracted with ice-cold 2N-sodium hydroxide solution until the benzene layer gave no colour with ferric chloride. The alkaline extracts were immediately run into ice-cold 2N-sulphuric acid. The β-keto-ester was extracted with ether and dried (Na_2SO_4). The unchanged ethyl acetoacetate was removed by distillation under reduced pressure and the liquid was degassed at 140°/0·1 mm. A small portion decomposed on direct distillation at 0·03 mm. and a further portion was therefore subjected to molecular distillation and four fractions were collected: ((i) $n_D^{20°}$ 1·4745, (ii) $n_D^{20°}$ 1·4772, (iii) $n_D^{20°}$ 1·4755, (iv) $n_D^{20°}$ 1·4785. The fractions were nearly identical and probably consisted of *ethyl* 2 : 6 : 10-*triketoundecane*-3 : 9-*dicarboxylate* (XVIII; R = H) contaminated with some cyclised material [Found: (i) C, 61·0; H, 9·2; (ii) C, 61·2, 60·9; H, 7·7, 7·3; (iii) C, 60·4, 60·5; H, 7·5, 7·8; (iv) C, 60·5, 60·7; H, 7·1, 7·6. $C_{17}H_{26}O_7$ requires C, 59·7; H, 7·6%. $C_{17}H_{24}O_6$ requires C, 63·0; H, 7·4%]. Each fraction gave a violet ferric chloride colour and an oily 2 : 4-dinitrophenylhydrazone which could not be induced to crystallise.

Alkylation of Ethyl β-Ketovalerate (2 *Mols.*) *with* 2 : 2′-*Dichlorodiethyl Ketone* (1 *Mol.*).—Sodium (3·2 g.) was powdered under xylene and the xylene was replaced by ether (100 c.c.). Ethyl β-ketovalerate (20 g.) was added at 0° and the flask was kept at 0° for 3 days, by which time formation of the sodio-derivative was complete. The mixture was cooled to −78° and 2 : 2′-dichlorodiethyl ketone (14·4 g.) in ether (50 c.c.), precooled to −78°, was added. The flask was placed in a "Thermos" flask full of cellosolve–dry ice for 4 days, the temperature then having risen to 5°. The mixture was decomposed with ice and dilute hydrochloric acid, and the ethereal layer was washed with sodium hydrogen carbonate solution. After being dried (Na_2SO_4), the ether and a small quantity of xylene were removed under reduced pressure. The residual oil was taken up in ether, filtered from some gum, and extracted with ice-cold 2N-sodium hydroxide until the ethereal solution gave no ferric chloride colour. The alkaline extracts were immediately run into ice-cold 2N-sulphuric acid. The β-keto-ester was isolated with ether and low-boiling impurities were removed under vacuum (130°/0·1 mm.). The remaining golden oil darkened on keeping and decomposed on attempted distillation. It was probably substantially pure *ethyl* 3 : 7 : 11-*triketotridecane*-4 : 10-*dicarboxylate* (XVIII; R = Me) (Found: C, 62·1; H, 7·4. $C_{19}H_{30}O_7$ requires C, 61·6; H, 8·1%). It gave a deep red-brown colour with ethanolic ferric chloride and an oily 2 : 4-dinitrophenylhydrazone.

Ethyl 2 : 6-*Diketoheptane*-3-*carboxylate*.—Pure diethylaminobutan-3-one (14·3 g.) (Wilds and Shunk, *loc. cit.*) was cooled in ice and methyl iodide (14·2 g.) was added in about ten equal portions (with constant swirling). The methiodide crystallised on the walls of the flask. (This technique was used at the suggestion of Dr. J. W. Cornforth, see also Part XLVIII, *J.*, in the press.) After 2 hours, ethyl aceto-

acetate (11·7 g.) in benzene (100 c.c.) was added, and potassium ethoxide (potassium 3·7 g., ethanol 44 c.c.) was run in with stirring. After 3 hours at 0° the mixture was filtered from potassium iodide and concentrated to a small bulk on the steam-bath. The residue was extracted with ether, and the ether was washed with sodium hydrogen carbonate solution, dried, and distilled, giving 10·3 g. of *ethyl 2 : 6-diketoheptane-3-carboxylate*, b. p. 113—114°/2 mm. A small portion on redistillation gave the pure diketone, b. p. 101—102°/1 mm., $n_D^{15°}$ 1·4490 (Found : C, 59·9; H, 7·8. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%). With 2 : 4-dinitrophenylhydrazine and alcoholic sulphuric acid it gave a yellow derivative which was crystallised to constant m. p. from benzene; yellow rectangular prisms, m. p. 141—141·5° (sintering at 140°). Analyses were variable but the carbon analyses suggested that it was a *pyrazolone* (Found : C, 50·6, 50·1, 49·6; H, 4·6, 4·4, 4·5; N, 19·8, 19·8, 20·1, 21·1, 18·3, 18·6. $C_{14}H_{14}O_6N_4$ requires C, 50·3; H, 4·2; N, 16·8%). On cyclisation with dry sodium ethoxide in boiling benzene the diketone gave Hagemann's ester, identified as the semicarbazone, m. p. 169° (Rabe and Rahm, *Ber.*, 1905, **38**, 971, give m. p. 169°).

5-Methyl-2-dimethylaminomethylphenol.—Dimethylamine (25% aqueous solution, 32·4 g.) was added slowly with stirring to *m*-cresol (18 g.), followed by formaldehyde (30% aqueous solution, 16 g.). The mixture was stirred at room temperature for 1½ hours and then on the steam-bath for 2 hours. The cooled mixture was extracted with ether, and the ether then extracted with 2N-hydrochloric acid. The acid extract was treated with potassium carbonate and extracted with ether. The ether, after drying over sodium sulphate, was removed and the residual oil was distilled; yield 12·8 g., b. p. 58—61°/0·04 mm. The distillate solidified on cooling. The *phenol* crystallised from *n*-hexane at −50° in colourless prisms, m. p. 45—46·5° (sintering at 43—45°) (Found : C, 72·4; H, 8·7; N, 8·6. $C_{10}H_{15}ON$ requires C, 72·6; H, 9·1; N, 8·5%). This phenol gave a red colour with aqueous ferric chloride solution, the colour being discharged on acidification.

p-*Xylenol.*—The foregoing phenol (5·8 g.) in dioxan (50 c.c.) was hydrogenated for five hours over copper chromite (3·0 g.) at 128 atm./160°. The solution was filtered from copper chromite and distilled. *p*-Xylenol (3 g.), m. p. 75° (lit., m. p. 75°) was obtained. It gave no colour with alcoholic ferric chloride.

Analyses are by Drs. Weiler and Strauss and by Mr. A. Bennett.

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