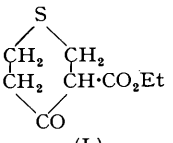
152. *Experiments on the Synthesis of Substances related to the Sterols. Part XLVII. The Synthetic Use of Thia*cyclo*hexan-4-one Methiodide.*

By H. M. E. Cardwell.

Thia*cyclo*hexan-4-one methiodide (III) has been shown to alkylate β-keto-esters yielding 1 : 5-diketones in which the potentially reactive methylthio-group is retained. Ethyl malonate and 2-nitropropane have similarly been alkylated.

By-products in these alkylation reactions have included *2-methylthioethyl vinyl ketone* and *2 : 2′-dimethylthiodiethyl ketone*. *Methyl-* and *ethyl-thiobutan-3-one* have been prepared.

In the preceding paper a possible method of elaborating the sterol skeleton, involving the alkylation of β-keto-esters with 4-keto-1 : 1-dialkylpiperidinium iodides, was outlined. The derived dialkylamino-diketones were unstable to distillation and their separation from by-products accordingly presented difficulties. There were reasons for expecting greater stability in the analogous alkylthio-compounds and their preparation from β-keto-esters and thia*cyclo*hexan-4-one methiodide (III) has now been studied.



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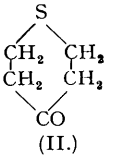

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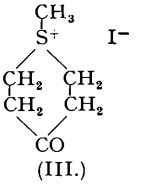


(III.)

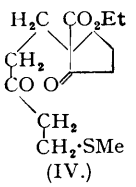
Thia*cyclo*hexan-4-one * (II) and the methiodide (III) were prepared by Bennett and Scorah (*J.*, 1927, 194), who obtained a 40% yield of the cyclic β-keto-ester (I) by treating 2 : 2′-dicarbethoxydiethyl sulphide with sodium ethoxide in ether in a freezing mixture, and an overall yield of 33% of the derived ketone (II). On a molar scale we found that this method gave erratic results and the yield of the keto-ester seldom exceeded 30%. Alternative methods of cyclisation were unsatisfactory. Pyrolysis of the lead and barium salts of the sulphide gave lead and barium sulphides, whilst potassium in liquid ammonia (and diethylaminomagnesium

* This nomenclature has been adopted at the suggestion of the Editor.

bromide in ether to a lesser extent) decomposed the ester to ethyl β-mercaptopropionate and presumably ethyl acrylate. Lower temperatures therefore favour fission at expense of cyclisation, whilst high temperatures (for instance, sodium in boiling benzene; Bennett and Scorah, *loc. cit.*) lead to formation of tar and sodium sulphide. The cyclic β-keto-ester (I) was finally prepared consistently in 40% yield on a molar scale by cyclisation with sodium ethoxide in ether at room temperature. The main by-product was a high-boiling β-keto-ester presumably formed by linear condensation of two or more molecules of the ester. Since the completion of this work, Fehnel and Carnack (*J. Amer. Chem. Soc.*, 1948, **70**, 1813) have reported the preparation of the corresponding methyl ester in 65% yield by cyclisation of 2 : 2′-dicarbomethoxydiethyl sulphide with sodium methoxide in boiling ether.

Thia*cyclo*hexan-4-one methiodide reacted smoothly with ethyl potassio-*cyclo*pentanonecarboxylate to give a 60% yield of *ethyl* (*5′-methylthio-3′-ketoamyl*)cyclo*pentan-2-one-1-carboxylate* (IV) (*disemicarbazone*, m. p. 194—195°). Unlike the analogous dimethylamino-compound (preceding paper), this diketone could be distilled under high vacuum with only minor decomposition.

Ethyl 5-methylthio-3-ketoamylmalonate, $CH_3{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$, and *2-nitro-7-methylthio-2-methylheptan-5-one*, $CH_3{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CMe_2{\cdot}NO_2$ (*4-phenylsemicarbazone*, m. p. 156—157°), were prepared similarly from ethyl malonate and 2-nitropropane, respectively. The generality of this alkylation reaction having been established, it was applied to methyl β-keto-α-methyladipate, as the first step in the projected sterol synthesis (see preceding paper). The product, *methyl 9-methylthio-3 : 7-diketo-4-carbomethoxy-4-methylnonane-1-carboxylate* (V), obtained in 70% yield, was an oil which could not be distilled without decomposition. It was contaminated with a small quantity of a substance of lower sulphur content (possibly the vinyl ketone). Preliminary attempts to cyclise this diketone or the diketone (IV) with retention of the carboxyl groups have been only partly successful. The bicarbonate washings from the preparation of the diketone (V), however, have yielded an acid (m. p. 99—99·5°). Analyses of this acid and of its p-*bromobenzylthiuronium* salt (m. p. 132—133°) agree with its formulation as a cyclised product (VI or VII; R = Me, R′ = H, or less likely R = H, R′ = Me, for tertiary are known to be more resistant to hydrolysis than primary carbomethoxy-groups). This acid immediately decolourised neutral permanganate and bromine water, but it gave no colour reaction with 2 : 4-dinitrophenylhydrazine, and a piperonylidene derivative could not be isolated. These observations suggest that it is *methyl 1-methyl-3-carboxymethyl-4-(2′-methylthioethyl)*cyclo*hex-3-en-2-one-1-carboxylate* (VII; R = Me, R′ = H). Walker (*J.*, 1935, 1585) has described an analogous cyclisation, ethyl sodio-α-*iso*propylacetoacetate and methyl 2-chloroethyl ketone giving directly the *cyclo*hexenone (IX), and the intermediate diketone (VIII) not being isolated. In the projected sterol synthesis the *cyclo*hexenone (VI) rather than (VII) is required and the cyclisation of the diketone (V) will therefore be further studied.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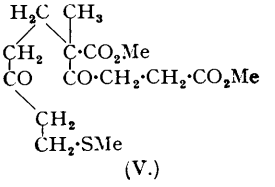
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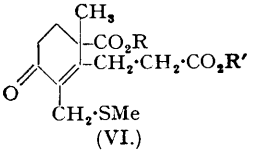
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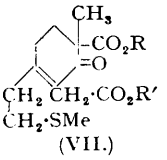
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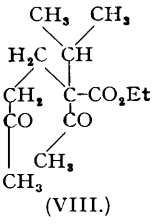
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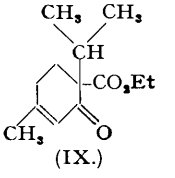
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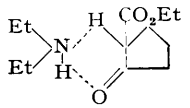
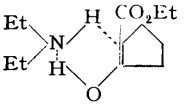
By-products in alkylations with thia*cyclo*hexan-4-one methiodide have included (*a*) a trace of thia*cyclo*hexan-4-one, (*b*) *2-methylthioethyl vinyl ketone* (*methiodide*, m. p. 116—117°), and (*c*) *2 : 2′-dimethylthiodiethyl ketone* (isolated as the *dimethiodide*, m. p. 126—128°). These compounds and the primary alkylation product account for 80—90% of the thia*cyclo*hexan-4-one methiodide

used in the reaction. The reaction therefore takes a very similar course to the analogous reaction with 4-keto-1 : 1-dialkylpiperidinium iodides, with the advantage, however, that the products are more stable and easier to isolate, and with the disadvantages that thia*cyclo*hexan-4-one is less accessible than the alkyl-4-piperidones, and that the alkylation products are more difficult to characterise.

The extension of this alkylation reaction to straight-chain β-alkylthio-ketones would have been a corollary to this work; these ketones have received little attention but the preparation of propylthiobutan-3-one from methyl vinyl ketone and propylthiol is described in U.S.P. 2,010,828. *Methylthiobutan-3-one* (2 : 4-*dinitrophenylhydrazone*, m. p. 94—95°) and *ethylthiobutan-3-one* (2 : 4-*dinitrophenylhydrazone*, m. p. 90—92°) have now been prepared from methyl 2-chloroethyl ketone and sodium thio-methoxide and -ethoxide, respectively. On treatment with methyl iodide they gave oily methiodides from which, in the former case, considerable quantities of trimethylsulphonium iodide were isolated. Their use as alkylating agents was not therefore explored.*

In the preparation of methyl β-keto-α-methyladipate (after Robinson and Seijo, *J.*, 1941, 582), pure methyl α-methylacetoacetate was required. It is conveniently prepared by methylation of methyl sodioacetoacetate in benzene, but if a sample free from all traces of methyl acetoacetate and methyl dimethylacetoacetate is required it may be prepared by methylation of *methyl β-diethylaminocrotonate* (compare Robinson, *J.*, 1916, **109**, 1038) and subsequent hydrolysis. In the preparation of the crotonate it was observed that diethylamine and methyl acetoacetate gave a colourless crystalline adduct which slowly liquefied with separation of water to give the crotonate. Similar crystalline adducts were obtained from ethylamine and diethylamine and ethyl *cyclo*pentanonecarboxylate. These adducts rapidly reverted in free air to the bases and β-keto-esters and were too unstable to give consistent analytical figures. They could

(X.)   (XI.)

be recrystallised from non-polar solvents. Mr. H. M. Powell has suggested that they may be double hydrogen-bonded compounds, the two canonical forms for the diethylamine–*cyclo*pentanonecarboxylate adduct being (X) and (XI). Alternatively, these compounds could be amino-alcohols of the aldehyde-ammonia type but their instability would be difficult to account for on this basis.

Experimental.

(M. p.s are uncorrected.)

2 : 2′-Dicarbethoxydiethyl sulphide was prepared in 94% yield by the method of Gershbein and Hurd (*J. Amer. Chem. Soc.*, 1947, **69**, 241) from ethyl acrylate (from which the polymerisation inhibitor had *not* been removed) and hydrogen sulphide with a trace of sodium methoxide. On treatment with methyl iodide it gave an oil from which *ethyl β-methylthiopropionate methiodide* was isolated; colourless prisms, m. p. 122° (decomp.; sintering at 108°) (Found : C, 28·9; H, 5·2; S, 11·1; I, 44·4. $C_7H_{15}O_2SI$ requires C, 29·0; H, 5·2; S, 11·0; I, 43·8%).

Ethyl β-Mercaptopropionate.—Potassium (12·5 g.) was dissolved in liquid ammonia (300 c.c.) and when the blue colour had disappeared the above sulphide (40 g.) was added slowly; after 3 hours' standing, excess of ammonium chloride was added, and the ammonia allowed to evaporate overnight. The residue was extracted with dry ether and distilled, b. p. 76—78°/20 mm. (Karrer and Schmid, *Helv. Chim. Acta*, 1944, **27**, 124, give b. p. 77·5°/20 mm.). There was negligible residue. It was characterised as the *chloromercuri*-derivative, from pyridine–ethanol, m. p. 131—133° (Found : Cl, 9·6; S, 8·6. $C_5H_9O_2SClHg$ requires Cl, 9·6; S, 8·7%).

*Thia*cyclo*hexan-4-one.*—The following modification of Bennett and Scorah's method (*J.*, 1927, 194) was used. To sodium ethoxide (from powdered sodium, 25 g., and ethanol, 55 g.) in ether (2 l.) 2 : 2′-dicarbethoxydiethyl sulphide (234 g.) in ether (1 l.) was run in with stirring during 6 hours. After a further 12 hours the mixture was decomposed with ice-cold 2N-hydrochloric acid. The ethereal layer was washed with aqueous sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled. After a small forerun of ethyl β-mercaptopropionate, the main fraction was collected at 82—130°/1—2 mm. The residual oil gave a deep blue-purple ferric chloride colour and decomposed on attempted distillation. The main fraction was heated under reflux with 2N-sulphuric acid (700 c.c.) for 5 hours, cooled, and extracted with ether. The ethereal extracts were washed with cold 5N-sodium carbonate solution and dried (Na_2SO_4). The thia*cyclo*hexan-4-one remaining after removal of the ether was recrystallised from light petroleum (b. p. 40—60°); yield 34 g., m. p. 61—62°, and of sufficient purity for preparative work (Bennett and Scorah, *loc. cit.*, give m. p. 65—66°).

*Ethyl thia*cyclo*hexan-4-one-3-carboxylate methiodide* was prepared from pure ethyl thia*cyclo*hexan-4-one-3-carboxylate (b. p. 110°/1 mm.). It crystallised from ethanol in prisms, m. p. 112—113° (decomp.) (Found : I, 38·3. $C_9H_{15}O_3SI$ requires I, 38·5%).

* But see note, p. 719.

*Thia*cyclo*hexan-4-one methiodide* crystallised from methanol–ether in colourless prisms, m. p. 82—85° (decomp.), with a molecule of methanol of crystallisation (Bennett and Scorah, *loc. cit.*, give m. p. 112—113° for the non-solvated methiodide) (Found: C, 29·2; H, 4·5; S, 11·4; I, 44·9; OMe, 12·4. $C_6H_{11}OSI,CH_3{\cdot}OH$ requires C, 29·0; H, 5·2; S, 11·0; I, 43·8; OMe, 10·7%).

*Ethyl (5′-Methylthio-3′-ketoamyl)*cyclo*pentan-2-one-1-carboxylate* (IV).—Thia*cyclo*hexan-4-one methiodide (29·0 g.), ethyl *cyclo*pentan-2-one-1-carboxylate (14·8 g.), and benzene (300 c.c.) were stirred at 0° under nitrogen whilst potassium ethoxide (potassium, 3·71 g.; ethanol, 45 c.c.) was run in during an hour. The mixture was stirred at 0° until neutral to bromothymol-blue, filtered from potassium iodide, and concentrated on the steam-bath until all the ethanol was removed. The residue was cooled, and benzene and ice-water added. The benzene layer was washed with ice-cold 2N-sodium hydroxide until free from *cyclo*pentanonecarboxylate and distilled. The *ethyl* ester (IV) was collected at 156°/0·005 mm. to 170°/0·03 mm.; yield 16·7 g. (58%). On redistillation it boiled at 140—144°/0·01 mm. as a pale yellow viscous oil, $n_D^{17°}$ 1·5002 (Found: C, 58·6; H, 7·5; S, 10·9. $C_{14}H_{22}O_4S$ requires C, 58·7; H, 7·7; S, 11·2%). The ester gave an oily mercuric chloride derivative, an oily platinic chloride derivative, and an oily methiodide from which a trace of trimethylsulphonium iodide was isolated (Found: S, 15·8; I, 62·1. Calc. for C_3H_9SI: S, 15·7; I, 62·3%). The *disemicarbazone* crystallised from aqueous alcohol in needles, m. p. 194—195° (decomp.) (Found: C, 48·4; H, 6·7; N, 21·1; S, 8·5, 7·8. $C_{16}H_{28}O_4N_6S$ requires C, 48·0; H, 7·0; N, 21·0; S, 8·0%). An isomeric *disemicarbazone* was isolated from another preparation; needles from aqueous ethanol, m. p. 201—203° (decomp.), mixed m. p. with other sample, 182—184° (Found: C, 48·2; H, 7·0%).

Attempted cyclisation. The ester (IV) (5 g.) was dissolved in syrupy phosphoric acid (*d* 1·82) (30 c.c.) and kept at room temperature for 24 hours. On dilution with water and extraction with ether a small fraction, b. p. 120—130°/0·005 mm., was collected; $n_D^{18°}$ 1·5184. Analysis (Found: C, 62·0; H, 9·1; S, 10·6. Calc. for $C_{14}H_{20}O_3S$: C, 62·7; H, 7·5; S, 11·9%. Calc. for $C_{14}H_{22}O_4S$: C, 58·7; H, 7·7; S, 11·2%) suggested that it was a mixture of cyclised and uncyclised material.

Ethyl 5-methylthio-3-ketoamylmalonate was prepared similarly from thia*cyclo*hexan-4-one methiodide (29 g.) and ethyl malonate (16 g.); yield 12·0 g.(42%), b. p. 144—150°/0·07 mm. On redistillation, it boiled at 125—134°/0·007 mm.; $n_D^{14°}$ 1·4762 (Found: C, 54·0; H, 7·6; S, 11·0. $C_{13}H_{22}O_5S$ requires C, 53·8; H, 7·6; S, 11·0%).

2-Nitro-7-methylthio-2-methylheptan-5-one was prepared similarly from thia*cyclo*hexan-4-one methiodide (29 g.) and 2-nitropropane (8·9 g.); yield 9·1 g. (41%), b. p. 128—140°/0·05 mm. On redistillation, it boiled at 105—108°/0·02 mm., $n_D^{14°}$ 1·4942 (Found: C, 49·9; H, 7·3; N, 6·4; S, 14·7. $C_9H_{17}O_3NS$ requires C, 49·3; H, 7·8; N, 6·4; S, 14·6%). Its *4-phenylsemicarbazone* crystallised from ethanol in micro-needles, m. p. 156—157° (Found: C, 54·7; H, 6·8; S, 8·9. $C_{16}H_{24}O_3N_4S$ requires C, 54·5; H, 68; S, 9·1%).

Methyl 9-Methylthio-3: 7-diketo-4-carbomethoxy-4-methylnonane-1-carboxylate (V).—Methyl β-keto-α-methyladipate (redistilled 50·5 g.), thia*cyclo*hexan-4-one methiodide (74 g.), and benzene (300 c.c.) were stirred in an ice-bath under nitrogen, whilst potassium methoxide (potassium 9·75 g., methanol 150 c.c.) was run in during 2 hours. After a further hour's stirring a few drops on dilution with water were neutral to bromothymol-blue. The solution was filtered and concentrated on the steam-bath until the temperature of the distillate reached 78°. The residue was diluted with benzene, filtered, and washed with aqueous sodium hydrogen carbonate solution. The organic layer was washed with ice-cold 2N-sodium hydroxide solution to remove unchanged β-keto-ester, then with dilute sulphuric acid and water. After drying (Na_2SO_4), the solvent was removed on the steam-bath and the residue was heated at 160—170°/0·1 mm. until the pressure started to fall. The residual pale yellow oil (60 g., 72%), $n_D^{18°}$ 1·4942, consisted of the *methyl* ester (V), contaminated with a substance of lower sulphur content, possibly the vinyl ketone (Found: C, 55·4; H, 6·9; S, 8·9. $C_{15}H_{24}O_6S$ requires C, 54·1; H, 7·5; S, 9·6%).

The methiodide, mercuric iodide–methiodide complex, auric chloride complex, platinic chloride and iodide complexes, 2 : 4-dinitrophenylhydrazone, and semicarbazone were all intractable oils. Attempted cyclisation of this substance with ice-cold sulphuric acid, syrupy phosphoric acid, or hydrogen bromide in acetic acid gave very little water-insoluble material.

*Methyl 1-Methyl-3-carboxymethyl-4-(2′-methylthioethyl)*cyclo*hex-3-en-2-one-1-carboxylate* (VII; R = Me, R′ = H).—The bicarbonate extracts from the preceding preparation were acidified with 2N-hydrochloric acid and extracted with ether. After drying over sodium sulphate and removal of solvent, the residual oil was crystallised from benzene–light petroleum (b. p. 60—80°). The *methyl* ester (VII; R = Me, R′ = H) crystallised in flattened needles, m. p. 99—99·5° [Found: C, 56·3, 56·2, 56·1; H, 6·6, 6·6, 6·4; S, 10·4; *M* (Rast), 286, 291; equiv., 276, 279. $C_{14}H_{20}O_5S$ requires C, 56·0; H, 6·7; S, 10·7%; *M* and equiv., 300]. The p-*bromobenzylthiuronium* salt crystallised in colourless needles, m. p. 132—133°, from *iso*propanol (Found: N, 5·1; S, 11·4. $C_{14}H_{19}O_5S,C_8H_{10}N_2SBr$ requires N, 5·1; S, 11·7%).

2-Methylthioethyl Vinyl Ketone.—Low-boiling fractions from a number of alkylations with thia*cyclo*hexan-4-one methiodide were combined and redistilled. The fraction boiling at 87—88°/15 mm. was collected; n_D^{15} 1·4935; it was impure *2-methylthioethyl vinyl ketone* (Found: C, 54·7; H, 7·5; S, 21·3. $C_6H_{10}OS$ requires C, 55·4; H, 7·7; S, 24·6%). The *methiodide* crystallised from ethanol in colourless rods, m. p. 116—117° (decomp.) (Found: C, 30·9; H, 4·8; S, 11·9; I, 46·7. $C_7H_{13}OSI$ requires C, 30·9; H, 4·8; S, 11·8; I, 46·7%).

2 : 2′-Dimethylthiodiethyl Ketone.—The intermediate fractions (b. p. 50—110°/0·1 mm.) from a number of alkylations with thia*cyclo*hexan-4-one methiodide were treated with methyl iodide. After two days at room temperature the mushy *methiodide* of the ketone was triturated with acetone and recrystallised from methanol to constant m. p.; it formed colourless prisms, m. p. 126—128° (decomp.) (dependent on rate of heating) (Found: C, 23·5; H, 4·2; S, 13·8; I, 54·8. $C_9H_{20}OS_2I_2$ requires C, 23·4; H, 4·3; S, 13·8; I, 55·0%). Mixed with the methiodide of 2-methylthioethyl vinyl ketone, it melted at 102—104°.

Methyl β-Keto-α-acetyl-α-methyladipate.—[This substance and methyl β-keto-α-methyladipate were prepared by Robinson and Seijo (*J.*, 1941, 582) but except for b. p.'s, no details were given.] Methyl α-methylacetoacetate (130 g.) in ether (300 c.c.) was added to powdered sodium (23 g.) in ether (1000 c.c.);

when the formation of the sodio-derivative was complete, methyl succinic half-ester chloride (150 g.) in ether (400 c.c.) was dropped in with stirring and ice cooling. After standing for 12 hours at room temperature, the mixture was heated under reflux until it was neutral or slightly acid to litmus. After cooling, the mixture was filtered from sodium chloride and distilled. *Methyl β-keto-α-acetyl-α-methyladipate* boiled at 117—120°/0·1 mm. (*idem, ibid.*, b. p. 135—137°/0·5 mm.). A sample on redistillation boiled at 118—120°/0·2 mm.; $n_D^{15°}$ 1·4572 (Found: C, 54·1; H, 6·5. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%).

Methyl β-Keto-α-methyladipate.—The foregoing acetyl ester (60 g.) in ether (350 c.c.) was saturated at 0° with dry ammonia. The acetamide which separated gradually liquefied, indicating that the alternative fission to methyl succinic half-ester amide occurred to an appreciable extent. The mixture was washed with water, dilute hydrochloric acid, and aqueous sodium hydrogen carbonate solution, dried, and distilled. *Methyl β-keto-α-methyladipate* distilled at 93—94°/0·1 mm.; $n_D^{16°}$ 1·4458 (*idem, ibid.*, b. p. 106—108°/0·3 mm.); yield 50% (Found: C, 53·5; H, 7·1. $C_9H_{14}O_5$ requires C, 53·5; H, 6·9%).

Methylthiobutan-3-one.—Methyl 2-chloroethyl ketone (50 g.) was added with cooling to sodium thiomethoxide (33 g.) in methanol (100 c.c.). The mixture was kept at room temperature for 2 days, and the methanol was removed on the steam-bath. The residue was extracted with ether, and the ether was washed with aqueous sodium hydrogen carbonate and dried. The residual liquid after removal of ether was carefully fractionated; yield 16·6 g., b. p. 75°/17 mm. On redistillation, *methylthiobutan-3-one*, a colourless mobile liquid of characteristic odour, boiled at 72—73°/16 mm.; $n_D^{15°}$ 1·4775 (Found: C, 50·9; H, 8·5. $C_5H_{10}OS$ requires C, 50·8; H, 8·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised in orange rods, m. p. 94—95° (Found: N, 18·2; S, 10·6. $C_{11}H_{14}O_4N_4S$ requires N, 18·8; S, 10·7%). On treatment with methyl iodide the ketone gave an oily methiodide from which considerable quantities of trimethylsulphonium iodide (m. p. 202—205°) were isolated.

Ethylthiobutan-3-one.—Ethylthiol (20·7 g.) was added to ice-cold sodium ethoxide (sodium 7·7 g., ethanol 250 c.c.), followed by methyl 2-chloroethyl ketone (36 g.). On working up as above, *ethylthiobutan-3-one* was obtained as a colourless mobile liquid of characteristic odour; b. p. 84°/19 mm., $n_D^{16°}$ 1·4738 (Found: C, 54·5; H, 8·6; S, 23·6. $C_6H_{12}OS$ requires C, 54·6; H, 9·1; S, 24·2%). The 2 : 4-*dinitrophenylhydrazone* crystallised in orange rods, m. p. 90—92° (Found: N, 17·9; S, 9·8. $C_{12}H_{16}O_4N_4S$ requires N, 17·9; S, 10·3%). The ketone gave an oily methiodide which gave oily iodoform, auric chloride, and mercuric iodide complexes.

Methyl β-Diethylaminocrotonate.—On mixing equimolecular quantities of diethylamine and methyl acetoacetate much heat was evolved and large prisms soon formed. On further standing the crystals dissolved and water separated. After three weeks at room temperature the mixture was diluted with ether, dried (Na_2SO_4), and distilled. The fraction, b. p. 142—144°/17 mm., was collected; yield 70%. On redistillation *methyl β-diethylaminocrotonate* boiled at 134—136°/14 mm.; $n_D^{19°}$ 1·5208 (Found: C, 63·5; H, 9·6; N, 8·1. $C_9H_{17}O_2N$ requires C, 63·2; H, 9·9; N, 8·2%).

Methyl α-Methylacetoacetate.—Methyl β-diethylaminocrotonate (40 g.) was refluxed with excess of methyl iodide for 10 hours. The mixture was then well shaken with ether to remove unchanged crotonate, and warmed with water (10 c.c.) for 20 minutes. The homogeneous solution was extracted repeatedly with ether, and the ethereal extracts dried (Na_2SO_4) and distilled. Methyl α-methylacetoacetate distilled at 72—73°/17 mm. (lit., b. p. 80°/20 mm.). Both the first and the last drop gave a pure blue colour with ferric chloride which is characteristic of monoalkylated acetoacetates. From the aqueous layer diethylamine hydriodide, m. p. 171—172° (lit., m. p. 172°), was recovered in almost quantitative yield.

Adducts formed from Amines and Ethyl cyclo*Pentanonecarboxylate.*—(*a*) *Ethylamine.* On mixing equimolecular proportions of ethylamine and ethyl *cyclo*pentan-2-one-1-carboxylate a white solid was formed. It crystallised in rosettes of long needles from *cyclo*hexane, m. p. 75—78° (sealed capillary), with sintering at 70°. In free air it rapidly reverted to ethylamine and the ester; it was too unstable for consistent analytical results to be achieved. On keeping in a sealed tube it liquefied with separation of water.

(*b*) *Diethylamine.* The complex which was similarly prepared in quantitative yield from diethylamine and the ester crystallised from light petroleum (b. p. 60—80°) in large colourless prisms, m. p. 67—68° (sealed capillary). In a sealed tube it slowly darkened but was still crystalline after 6 months.

Micro-analyses are by Drs. Weiler and Strauss and Mr. A. Bennett. I wish to thank Dr. F. J. McQuillin for the interest he has shown in this work and for many useful discussions.

Note, added August 23rd, 1948.—The alkylation of ethyl *cyclo*pentan-2-one-1-carboxylate with the oily methiodide of ethylthiobutan-3-one has now been accomplished, as follows. Ethylthiobutan-3-one (13·2 g.) was treated with excess of methyl iodide, and after 48 hours at room temperature the oily methiodide was washed with dry ether, dissolved in ethanol (40 c.c.), and added to ethyl *cyclo*pentan-2-one-1-carboxylate (15·6 g.) in benzene (150 c.c.). Potassium ethoxide (potassium 7·8 g., ethanol 90 c.c.) was added during 30 minutes to the stirred mixture at 0°. Stirring was continued at 0° for 3 hours and then at reflux temperature for 30 minutes. The mixture was decomposed with ice-water and extracted with ether. The extract, after being dried and distilled, gave *ethyl octan-7-one-1 : 4-dicarboxylate*, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$, b. p. 143—146/0·7 mm. (11·1 g., 34%). A pure sample boiled at 114—116°/0·01 mm.; $n_D^{21°}$ 1·4485 (Found: C, 61·8; H, 8·8. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%). The *semicarbazone* crystallised from *cyclo*hexane in colourless needles, m. p. 78—79° (Found: C, 55·5; H, 8·1; N, 13·0. $C_{15}H_{27}O_5N_3$ requires C, 54·8; H, 8·7; N, 12·7%). Ring-opening to substituted adipic esters as above has previously been observed in the alkylation of ethyl *cyclo*pentanone-1-carboxylate with benzyl chloride and ethyl maleate in the presence of alcoholic metal alkoxides (Duff and Ingold, *J.*, 1934, 87; Ghosh, *J. Indian Chem. Soc.*, 1947, **24**, 45).

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