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REACTIONS RELATED TO COENZYME B_{12} DEPENDENT REARRANGEMENTS: METAL MEDIATED FREE RADICAL ACYL MIGRATIONS IN METHYL AND CYCLOPROPYL SUBSTITUTED MODELS

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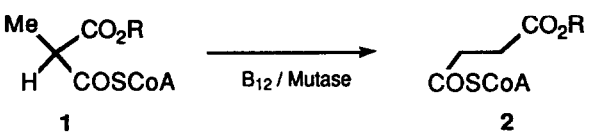
Abstract: – Free radicals generated from the methylmalonylcoenzyme A mutase model substrates (**3**) and (**4**) by chromium(II) reduction, or by pyrolysis of the analogous cobaloximes, underwent [1,2]-migration only in the acyl series (R = Ph, Me) and not the critical ester series (R = OEt, SBu). The mechanism of the migration was implied by incorporation into (**4**) of the cyclopropyl ring, the opening of which demonstrated the free radical nature of the rearranged intermediate.

In continuation of our studies on rearrangements related to B_{12} catalysed reactions[1], we have examined substances which are intended to mimic the free radical methylmalonylCoA (**1**, R = H) – succinylCoA (**2**, R = H) rearrangement (Scheme 1)[2] but avoid the problems that we had previously encountered with tin based propagation steps[1].

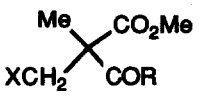


1 **2**

Scheme 1

These problems essentially derive from the slowness of the [1,2]-acyl, thiol ester or ester migration in the models (**3**)[3]. Thus tin hydride propagation was inefficient due to the rapid capture of the derived organic radicals by tin hydride before rearrangement, even under conditions of slow addition, and hexaalkylditin gave an unacceptable proportion of intractable stannylated products.

We needed, therefore, to generate radical precursors by methods which were clean and conducive to long radical lifetimes and in order to verify that any rearrangement observed was of a radical nature, it would be advantageous to incorporate a specific radical probe, in this study a cyclopropyl group[4], into the system.

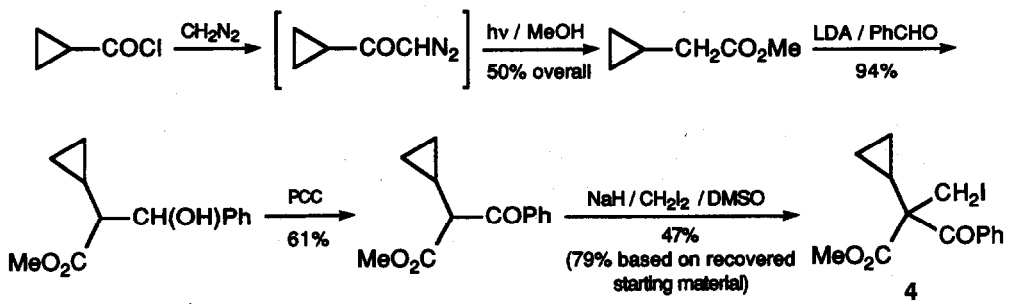


R = Ph, Me, SBu, OEt

3

The reported migration of the thiolester group in (3, R = SEt, X = Br), on reaction with zinc in methanol[5], was unrepeatable in our hands, although we could observe benzoyl group migration in (3, R = Ph, X = I) under these conditions. Consequently, we investigated the production of substrate radicals from (3, X = I) and the cyclopropyl analogue (4) *via* the use of other metals and now report our results with chromium and cobalt derived radicals.

The substrates (3) and potential products, both rearranged and unrearranged, were prepared as before[1], or by modifications of conventional routes (see Experimental). A number of routes to the cyclopropyl analogue (4) were examined, the preferred sequence is shown in Scheme 2.



LDA = lithium diisopropylamide; PCC = pyridinium chlorochromate.

Scheme 2

Chromium(II) is known to reduce iodides in the sequence shown in Scheme 3[6].

$$R_3C{-}X \rightarrow R_3C\cdot \rightarrow R_3C{-}Cr^{2+} \rightarrow R_3C{-}H$$

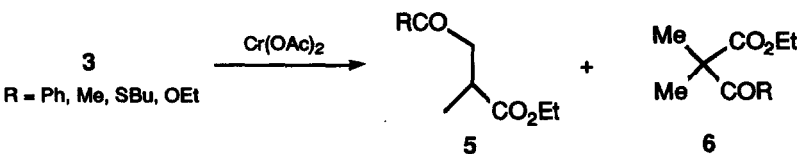
Scheme 3

It was considered that, provided the concentration of chromium(II) was kept low in order to minimise the second step, this process could produce the required radical from (3) under

conditions which would allow rearrangement to occur.

In the event, treatment of the iodides (3) with an excess of freshly prepared chromium(II) acetate in acetonitrile, in which the chromium(II) is largely insoluble, gave good yields (Table 1) of benzoyl and moderate yields of acetyl migration products (5) (Runs 1, 2) but again, no thiolester or oxyester migration (Runs 3, 4). In all runs, there was a good mass balance of isolated products, the remainder in each case being almost entirely the deiodinated unrearranged compounds (6). There was an additional component (≈ 1%), isolated from the products of Run 3, which was tentatively identified by spectral analysis (see Experimental) to be the deoxygenated compound S-butyl 2-methyl-4-oxothiolhexanoate (7). The manner of formation of this product remains to be resolved.

Table 1: Chromium(II) Reductions of Iodides (3)



5 6

Run No.	Substrate(3) R	Product(s) Rearranged (5) (%[a])	Unrearranged (6) (%)
1.	Ph	63	14
2.	Me	49	34
3.	SBu	0[b]	93[c]
4.	OEt	0[b]	100

[a] All yields refer to isolated material.

[b] No rearranged material was detectable by g.l.c.

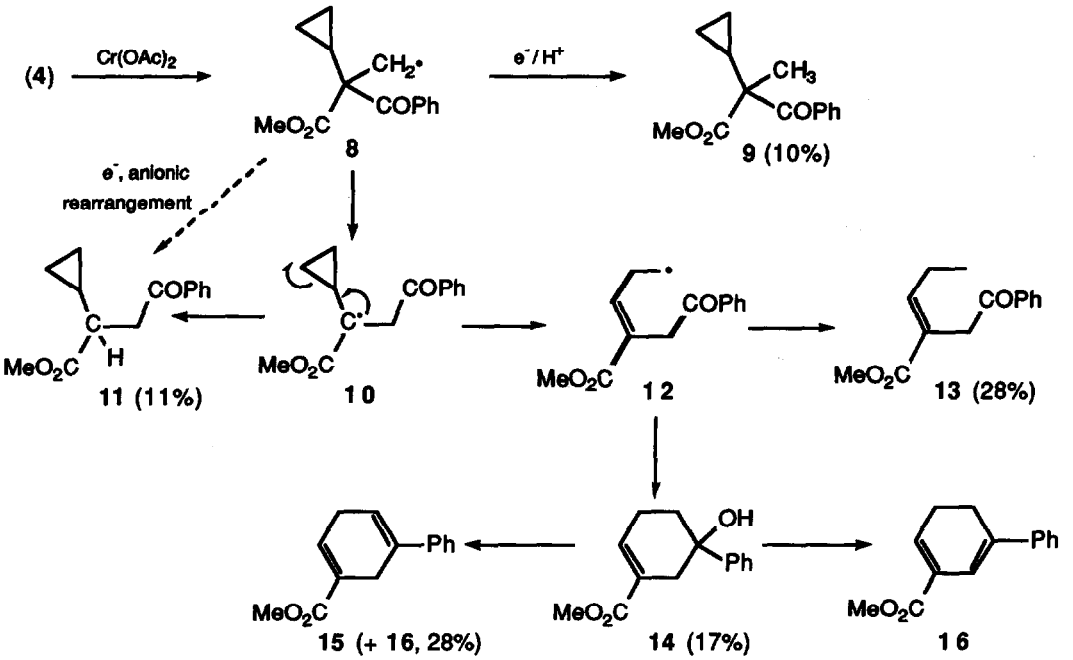
[c] Unchanged substrate (5%) was also recovered.

At this stage it was not certain that we were observing a radical, as opposed to an anionic, rearrangement. The reaction was therefore applied to the cyclopropyl analogue (4) and resulted a complex mixture of products (Scheme 4).

Despite this complexity, a good mass balance of isolated and identified material was obtained (94%) of which 73% was cyclopropyl ring opened products (13–16). Since these can only come from the rearranged radical (10)[4] *via* the initial radical (8), this provides very strong support for the postulate of a radical rearrangement process. The product ratios also imply that the radical acyl migration is 3–7 times faster than the second electron transfer (see below). The rearranged but unopened cyclopropyl product (11) could have arisen by either an anionic or a radical

process, dependent upon the relative rates of the radical rearrangement and radical reduction processes and the mechanism of its formation is undeterminable from these data.

From this experiment alone, it is not possible to determine the precise mode of quenching of any of the intermediates, but since the solvent and reagent are poor sources of hydrogen atoms, we propose that the intermediate and product radicals are further reduced to anions [or alkylchromium(III) species] prior to protonation as depicted in Scheme 3. Thus although the rearranged radical (12) could add reversibly to the benzoyl carbonyl group, the equilibrium generally lies in favour of the ring-opened radical[7] and we consider that it is the anion of (12) which cyclises to give the products (14–16).



Scheme 4

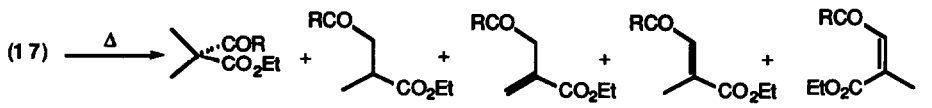
Rather than resolve these points at this stage, we sought a source of the radical intermediates which would not produce further reduction and turned to the use of alkylcobaloximes (17) which have been much used as cobalamin models[1,8]. These were prepared from the iodides (3) and (4) in generally good yield by standard procedures[9] (see Experimental).

Usually, the cobalt–carbon bond in cobaloximes has been homolysed by photolytic means[10] but we considered that vacuum pyrolysis[11] of cobaloximes (17) and (23), which cannot undergo simple thermal β-elimination of hydride, might be more effective for our purpose especially if carried out in the absence of solvent such that the products would distil out of the reaction as they were formed. The procedure adopted was to heat a finely ground sample of the cobaloxime at

150–160°C and 0.1–0.3 mmHg pressure for 45–60 min in a simple S-shaped glass tube, heated at one (closed) end and with a solid CO_2 cooled middle loop. In all case, the distillate contained pyridine and dimethylglyoxime together with the products of Co–C bond cleavage.

By this procedure, the alkylcobaloximes (17, R = Ph or Me) gave moderate to good yields of products (Table 2) and in agreement with our original concept, these were predominantly rearranged material, with only minor amounts of non-rearranged compounds being detectable.

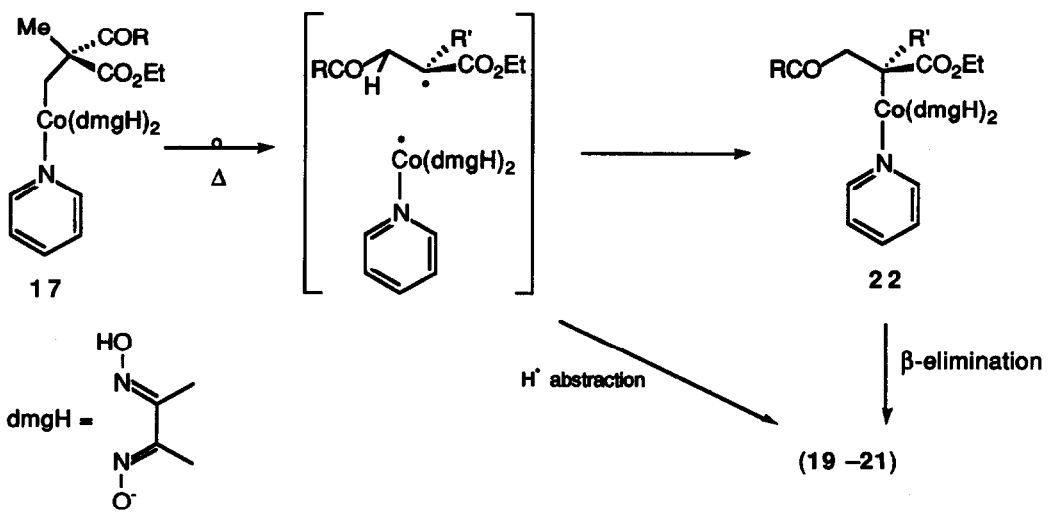
Table 2: Pyrolysis of Alkylcobaloximes (17).



	6	18	19	20	21
R = Ph	3%	5%	31%	39%	3%
R = Me	8%	2%	20%	24%	—[a]
R = SBu	trace[b]	—	—	—	—
R = OEt	48%	—	—	—	—

[a] No detectable quantities of product.

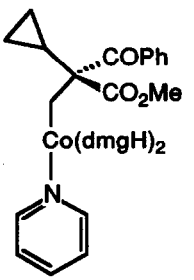
[b] G.l.c. analysis indicated the major volatiles to be butanethiol and dibutyldisulphide.



Scheme 5

It is noteworthy that most of the product arises from the loss of a hydrogen atom from the product radical [to give (19–21)] and cannot therefore be the result of disproportionation. This suggests that either the rearrangement is occurring within the coordination sphere of, or within close proximity to, the cobalt atom[12], (a fact which has notable implications for the enzymic process[2]) such that a resulting intermediate tertiary radical or alkyl complex (22, R' = Me) undergoes hydrogen abstraction or β-elimination[13] to give the observed products (19–21) (Scheme 5).

The thiolester and oxyester analogues (17, R = SBu and R = OEt), when treated similarly, gave volatile products which contained no rearranged compounds (by g.l.c. analysis). The oxyester (17, R = OEt) gave diethyl dimethylmalonate (6, R = OEt) (48%) as the only identifiable product and the thiol ester (17, R = SBu) produced little volatile material which contained a trace of the unrearranged reduced compound (6, R = SBu) and sulphur containing fragmentation products.



23

Finally, pyrolysis of the cyclopropyl substituted cobaloxime (23) gave a very low return (11%) of volatile products which were separated by flash chromatography into two fractions, a) principally unrearranged methyl 2-benzoyl-2-cyclopropylpropionate (by n.m.r. analysis) (14 mg, 3%) , and b) an inseparable mixture of methyl (*E*)-2-(2'-oxo-2'-phenylethyl)pent-2-enoate (13) and methyl (*E*)-2-(2'-oxo-2'-phenylethyl)penta-2,4-dienoate (24) (40 mg, 8%). This is consistent with the primary cobaloxime structure of the ring opened product and being more thermally stable and less prone to β-elimination than the tertiary cobaloximes (22) above. Although, as suggested above, a tertiary cobaloxime (22, R' = cyclopropyl) intermediate could be implicated and could ring open by the well established[14] cobalt mediated cyclopropylmethyl—butenyl rearrangement, the fact that no β-elimination product was observed, the highly hindered nature of tertiary cobaloximes (stable examples are extremely rare[15]) and the similarity of this to the chromium mediated reactions above, suggests that the rearrangement of radical (10) to (12) is faster than capture of cobalt(II).

However, this process remains restricted to the acyl series and we can detect no sign (by g.l.c.analysis) of rearrangement in the oxyester or the critical thiolester analogues. These results

are consistent with the theoretical prediction[16] that the ease of radical migration is in the order:—

$$HCO > COSH > CO_2H$$

There have now been many attempts to emulate the putative free radical [1,2]-thiolester shift of the methylmalonylcoenzyme A mutase reaction[2,3,10]. None have been successful in producing an efficient process and few have demonstrated an unambiguous radical migration. The results reported by us above and earlier[1], and those of other groups[2,3,10], show clearly that whilst a radical [1,2]-acyl migration is readily achieved, a free radical [1,2]-thiolester migration is not a facile process. If the mutase reaction is indeed a radical process, the cobalamin and/or the apoenzyme must play a decisive role in activating the reaction[2] in a manner which, with the possible exception of the Retey bridged cobaloxime[12b], has not been revealed by the model studies so far reported.

ACKNOWLEDGEMENT

We thank the SERC for financial support.

EXPERIMENTAL

For general details of solvents, reagents and equipment, see ref. 1.

Substrates and potential products not previously fully reported, or for which a significantly modified synthesis was necessary were:—

Methyl 2-Benzoylcyclopropylacetate. — Methyl cyclopropylacetate (1.14 g, 10 mmol) in THF (20 ml) was added to a solution of LDA (20 mmol) in THF (100 ml) at –78°C. The resulting solution was stirred at –78°C for 15 min before benzaldehyde (1.2 g, 11 mmol) in THF (10 ml) was added. The solution was allowed to warm to room temperature, extracted with ether and the ethereal layer dried and evaporated under reduced pressure. The residue was chromatographed over silica gel; elution with ethyl acetate–petrol (1 : 4) gave a diastereomeric mixture of alcohols (*ca* 1 : 1 by n.m.r. analysis) (2.07 g, 94%). The alcohols were dissolved in dichloromethane (100 ml), pyridinium chlorochromate (PCC) (12 g) was added and the mixture stirred at room temperature for 5 h. Ether (100 ml) was added and the mixture was stirred for a further 30 min before being filtered through Celite. The filtrate was evaporated and the residue chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the *title ester* as a colourless oil (1.24 g, 61%). A sample was distilled for analysis, b.p. 160°C / 6 mmHg; ν_{max} (neat) 1740, 1690 cm^{-1}; δ_H (250 MHz) 0.20 (1H, m), 0.42 (1H, m), 0.69 (2H, m), 1.57 (1H, m), 3.55 (1H, d, *J* 9.9 Hz), 3.70 (3H, s), 7.51 (3H, m), 7.96 (2H, m); *m/z* 218 (M^+, 4%), 105 (100), 77 (33), 51 (11). (Found: C, 71.48; H, 6.62. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%).

Methyl 2-Benzoyl-2-cyclopropyl-3-iodopropionate (4). — Methyl 2-benzoylcyclopropylacetate (1.00 g, 4.6 mmol) in DMSO (10 ml) was treated with a 60% suspension of sodium hydride in oil (240 mg, 6.0 mmol). The mixture was stirred until it became homogeneous, diiodomethane (0.65 ml, 8.0 mmol) was added and the mixture stirred at room temperature, in the dark, for 3 d. The reaction was worked up by ether extraction in the usual way and the crude product chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the

iodoester (4) (746 mg, 47%) as a colourless oil; ν_{max} (neat) 1735 and 1675 cm^{-1}; δ_H (250 MHz) 0.36 (2H, m), 0.73 (2H, m), 1.91 (1H, t t, *J* 6, 9 Hz), 3.62 and 3.66 (2H, AB q, *J* 10 Hz) 7.46 (3H, m) 7.85 (2H, m); *m/z* 358 (M^+, 4%), 231 (2), 105 (100) and 77 (21). Further elution gave starting material (414 mg, 41%).

Methyl 2-benzoyl-2-cyclopropylpropionate (9) — Methyl benzoylcyclopropylacetate (205 mg, 0.94 mmol) in methyl iodide (2 ml) was treated with a solution of sodium hydroxide (75 mg, 1.9 mmol) and tetrabutylammonium hydrogen sulphate (320 mg, 0.94 mmol) in water (2 ml). The mixture was stirred vigorously for 5 h at room temperature, extracted with ether as before, and chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the *ester* (9) as a colourless oil, (190 mg, 87%). A small sample was bulb-to-bulb distilled (at 70°C / 0.05 mmHg) for analysis; ν_{max} (neat) 1740 and 1690 cm^{-1}; δ_H (250 MHz) 0.28 (1H, m), 0.53 (3H, m), 1.25 (3H, s), 1.64 (1H, m), 3.65 (3H, s), 7.46 (3H, m), 7.84 (2H, m); *m/z* 232 (M^+, 0.1%), 105 (100) and 77 (28). (Found: C, 72.16; H, 6.95. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

2-(2-Ethoxycarbonylethyl)-2-phenyl-1,3-dioxolane. — Ethyl 4-oxo-4-phenylbutanoate[17] (40 g), 1,2-ethanediol (90 ml) and *p*-toluenesulphonic acid (1 g) in benzene (600 ml) were refluxed in a Dean-Stark apparatus for 2 d. The mixture was extracted with ether as before and distillation gave a colourless oil, b.p. 128–134°C / 0.2 mmHg, (lit.[18] b.p. 130°C / 0.2 mmHg) (35 g, 72%); ν_{max} (neat) 1734 cm^{-1}; δ_H (250 MHz) 1.22 (3H, t, *J* 7 Hz), 2.24 (2H, m), 2.42 (2H, m), 3.77 (2H, m), 3.99 (2H, m), 4.09 (2H, q, *J* 7 Hz), 7.28 (3H, m), 7.46 (2H, m); *m/z* 250 (M^+, 15%), 149 (100), 105 (38), 77 (16).

Ethyl 2-methyl-4-oxo-4-phenylbutanoate (5, R = Ph)[19]. — 2-(2-Ethoxycarbonylethyl)-2-phenyl-1,3-dioxolane (1.0 g, 4.0 mmol) in THF (5 ml) was added to a solution of LDA (4.0 mmol) in THF (25 ml) at –78°C. The solution was stirred at –78°C for 20 min and methyl iodide (0.25 ml, 4.0 mmol) was added. The solution was then allowed to warm to room temperature before being worked up by ether extraction as before. The crude product was dissolved in dichloromethane (30 ml) and added to a slurry prepared by treating silica gel (10 g) in dichloromethane (50 ml) with 15% aqueous sulphuric acid (1.5 ml) and stirring until the aqueous phase disappeared. The mixture was stirred vigorously overnight at room temperature before being filtered. The filtrate was evaporated and the residue chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the ester (5, R = Ph) as a colourless oil (0.70 g, 80%); ν_{max} (neat) 1729 and 1686 cm^{-1}; δ_H (250 MHz) 1.25 (3H, t, *J* 7.2 Hz), 1.28 (3H, d, *J* 7.2 Hz), 3.00 (1H, d d, *J* 4.9, 16.3 Hz), 3.12 (1H, m), 3.48 (1H, d d, *J* 7.2, 16.3 Hz), 4.15 (2H, q, *J* 7.2 Hz), 7.50 (3H, m), 7.96 (2H, m); *m/z* 220 (M^+, 4%), 175 (18), 146 (15), 121 (15), 105 (100), and 77 (36).

2-(2-Ethoxycarbonylpropyl)-2-methyl-1,3-dioxolane. — Ethyl levulinate ethylene ketal[20] (3.0 g, 16 mmol) in THF (10 ml) was added to a solution of LDA (16 mmol) in THF (100 ml) at –78°C. The resulting solution was then stirred at –78°C for 20 min before methyl iodide (1.0 ml, 16 mmol) in THF (5 ml) was added. The solution was allowed to warm to room temperature before being worked up *via* ether extraction as before and the crude product chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the dioxolane as a colourless oil (2.9 g, 90%). A sample was bulb-to-bulb distilled (55°C / 1 mmHg) for analysis; ν_{max} (neat) 1735 cm^{-1}; δ_H (250 MHz) 1.17 (3H, d, *J* 7.1 Hz), 1.26 (3H, t, *J* 7.1 Hz), 1.31 (3H, s), 1.67 (1H, d d, *J* 3.4, 14.4 Hz), 2.26 (1H, d d, *J* 10.0, 14.4 Hz), 2.60 (1H, m), 3.92 (4H, s), 4.12 (2H, q, *J* 7.1 Hz); *m/z* 187 (M^+–Me, 10%), 157 (14), 113 (16), 87 (100) and 43 (41). (Found: C, 59.13; H, 9.21. $C_{10}H_{18}O_4$ requires C, 59.39; H, 8.97%).

Ethyl 2-Methyl-4-oxopentanoate (5, R = Me)[21]. — 2-(2-Ethoxycarbonylpropyl)-2-methyl-1,3-

dioxolane (1.0 g) in dichloromethane (10 ml) was added to a slurry prepared by treating silica gel (10 g) in dichloromethane (50 ml) with 15% aqueous sulphuric acid (2 ml) and stirring until the aqueous phase had disappeared. The mixture was stirred vigorously overnight at room temperature before being filtered, the filtrate evaporated and the crude product was chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave the ketoester (5, R = Me) as a colourless oil (0.72 g, 92%); ν_{max} (neat) 1720 cm^{-1}; δ_H (250 MHz) 1.18 (3H, d, *J* 7.1 Hz), 1.26 (3H, t, *J* 7.1 Hz), 2.17 (3H, s), 2.48 (1H, d d, *J* 20.2, 7.4 Hz), 2.93 (2H, m), 4.13 (2H, q, *J* 7.1 Hz); *m/z* 158 (M^+, 2%), 113 (22), 101 (12), 73 (12) and 43 (100).

Ethyl 2-Benzoyl-2-methylpropionate (6, R = Ph)[22]. — This was prepared from ethyl 2-benzoylpropionate, by a method we reported previously[1] but modified by using 1.2 eq of sodium hydride, as a colourless oil, (84%); δ_H (90 MHz) 1.03 (3H, t, *J* 7 Hz), 1.55 (6H, s), 4.14 (2H, q, *J* 7 Hz), 7.42 (3H, m), 7.85 (2H, m).

Ethyl 2-Acetyl-2-methylpropionate (6, R = Me). — This was prepared from ethyl 2-methylacetoacetate, by the method reported previously[1] but modified by using 1.1 eq of sodium hydride, as a colourless oil, (92%), b.p. 182°C (lit.[23] b.p. 180–184°C), δ_H (90 MHz. $CDCl_3$) 1.27 (3H, t, *J* 7 Hz), 1.37 (6H, s), 2.18 (3H, s), 4.23 (2H, q, *J* 7 Hz).

General Procedure for the Reaction of Acyclic Iodides with Chromium(II) Acetate. — The iodide (1.0 g) in degassed acetonitrile (25 ml) was treated with freshly prepared chromium(II) acetate[6] (1.7 g) and the mixture refluxed under nitrogen. The reaction was monitored every 24 h by g.l.c. and more chromium(II) acetate (≈ 1.7 g portions) was added if substrate was still present.When the reaction was complete (2–4 d) the products were worked up by pouring the mixture into water and extracting with ether as before and the crude product chromatographed over silica gel. All products isolated from these reactions were identical with the authentic samples prepared by independent routes except for S-butyl 2-methyl-4-oxothiolhexanoate (7) which was identified on the basis of its n.m.r. spectrum {δ_H (250 MHz) 0.91 (3H, t, *J* 7.4 Hz), 1.05 (3H, t, *J* 7.4 Hz), 1.20 (3H, d, *J* 7.1 Hz) 1.43 (4H, m), 2.43 (2H, q, *J* 7.4 Hz), 2.46 (1H, d d, *J* 15, 6 Hz), 2.85 (1H, d t, *J* 13.5, 6.8 Hz), 2.86 (1H, d t, *J* 13.5, 6.8 Hz), 2.93 (1H, d d, *J* 15, 7.5 Hz), 3.17 (1H, m)}; and mass spectra {*m/z* 127 (M^+–SBu, 72%) 57 (100)}. The results of these reactions on the acyclic series are given in Table 1.

The Reaction of Methyl 2-Benzoyl-2-cyclopropyl-3-iodopropionate (4) *with Chromium(II) Acetate.* — The iodide (4) (730 mg) in degassed acetonitrile (25 ml) was treated with freshly prepared chromium(II) acetate in an identical manner to that described above for the acyclic series. After consumption of the substrate was complete (4 d) the mixture was worked up by ether extraction as before and the crude product chromatographed over silica gel. Elution with ethyl acetate–petrol (1 : 9) gave, in order of elution:—

a) an inseparable mixture possessing a complex n.m.r. spectrum consistent with it being a 1 : 1 mixture of methyl 5-phenylcyclohexa-1,4-dienecarboxylate (15) and methyl 5-phenylcyclohexa-1,5-dienecarboxylate (16) (120 mg, 28%). A small sample of the mixture was treated with DDQ in benzene to give, after chromatographic purification, methyl 3-phenylbenzoate, as colourless crystals, m.p. 47°C (lit.[24] m.p. 49–50°C); δ_H (250 MHz) 3.96 (3H, s), 7.52 (6H, m), 7.79 (1H, d, *J* 7.2 Hz), 8.03 (1H, d, *J* 7.5 Hz), 8.29 (1H, s); b) methyl 2-benzoyl-2-cyclopropylpropionate (9) (46 mg, 10%) identical to authentic material (*vide supra*); c) an inseparable mixture (185 mg) which, by n.m.r. analysis, consisted a 1 : 2.5 ratio of methyl 2-cyclopropyl-4-oxo-4-phenylbutanoate (11), (11%), δ_H (250 MHz) 0.19 (1H, m), 0.54 (3H, m), 0.97 (1H, m), 2.27 (1H, d t, *J* 4, 10 Hz), 3.22 (1H, d d, *J* 4, 18 Hz), 3.62 (1H, d d, *J* 10, 18 Hz), 3.73

(3H, s), 7.52 (3H, m), 7.99 (2H, m); and methyl *E*-2-(2-oxo-2-phenylethyl)pent-2-enoate (13), (28%), δ_H (250 MHz) 1.08 (3H, t, *J* 7.3 Hz), 2.18 (2H, quintet, *J* 7.3 Hz), 3.72 (3H, s), 4.02 (2H, s), 7.07 (1H, t, *J* 7.3 Hz), 7.52 (3H, m), 8.01 (2H, m); d) methyl 5-hydroxy-5-phenylcyclohex-1-enecarboxylate (14) as a colourless oil (80 mg, 17%). A sample was bulb-to-bulb distilled (140°C / 0.1 mmHg) for analysis; ν_{max} (neat) 3500 and 1710 cm^{-1}; δ_H (250 MHz) 1.88 (1H, s), 1.99 (2H, m), 2.27 (1H, m), 2.52 (1H, m), 2.64 and 2.76 (2H, br AB q, *J* ~18 Hz), 3.74 (3H, s), 7.10 (1H, m), 7.32 (3H, m), 7.49 (2H, m); *m/z* 232 (M^+, 10%), 200 (28), 172 (24), 120 (100), 105 (73), 78 (26), 77 (36), 43 (20). (Found: C, 72.15; H, 6.98. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

General Procedure for the Synthesis of Cobaloximes.[25] — Chloro(pyridine)cobaloxime (1 to 10 mmol) in DMF (10 ml) was cooled to –15°C and treated with sodium borohydride (1 eq) for 10 min. The iodide (0.95 eq) in DMF (0.5 ml) was added and the solution was allowed to warm to room temperature before being poured into water and extracted with dichloromethane. The bulk of the dichloromethane was removed under reduced pressure and the residue triturated with petrol or methanol, as appropriate, and the crystals collected. So prepared were:—

2-Benzoyl-2-ethoxycarbonylpropyl(pyridine)cobaloxime (17, R = Ph). — Recrystallised from dichloromethane–petrol (76%). An analytical sample was further recrystallised from methanol, as orange–red prisms, m.p. 195°C (dec); δ_H (250 MHz) 0.83 (3H, t, *J* 7.1 Hz), 1.51 (3H, s), 1.73 and 2.84 (2H, AB q, *J* 10.1 Hz), 1.78 (6H, s), 2.09 (6H, s), 3.91 (2H, q, *J* 7.1 Hz), 7.27 (2H, m), 7.41 (3H, m), 7.70 (1H, t t, *J* 7.7, 1.5 Hz), 7.84 (2H, m), 8.47 (2H, m), 18.25 (2H, s). (Found: C, 52.89; H, 5.75; N, 11.86. $C_{26}H_{34}CoN_5O_7$ requires C, 53.15; H, 5.83; N, 11.92%).

2-Acetyl-2-ethoxycarbonylpropyl(pyridine)cobaloxime (17, R = Me). — Recrystallised from acetonitrile (73%). An analytical sample was further recrystallised as red prisms, m.p. 200°C (dec); δ_H (250 MHz) 1.21 (3H, t, *J* 7.2 Hz), 1.25 (3H, s), 1.88 and 2.00 (2H, AB q, *J* 9.5 Hz), 2.05 (3H, s), 2.14 (12H, s), 4.07 (1H, d q, *J* 7.2, 10.7 Hz), 4.09 (1H, d q, *J* 7.2, 10.7 Hz), 7.31 (2H, m), 7.72 (1H, t t, *J* 7.3, 1.6 Hz), 8.51 (2H, m),18.0 (2H, br s). (Found: C, 48.16; H, 6.12; N, 13.28. $C_{21}H_{32}CoN_5O_7$ requires C, 48.00; H, 6.14; N, 13.33%).

2-Benzoyl-2-cyclopropyl-2-methoxycarbonylethyl(pyridine)cobaloxime (23). — Recrystallised methanol–dichloromethane as red prisms (58%), m.p. 190°C (dec); δ_H (250 MHz) 0.09 (2H, m), 0.44 (1H, m), 0.64 (1H, m), 1.77 (6H, s), 1.84 and 2.81 (2H, AB q, *J* 9.8 Hz), 1.97 (1H, t t, *J* 5.8, 8.3), 2.09 (6H, s), 3.31 (3H, s), 7.33 (5H, m), 7.67 (1H, t t, *J* 7.5, 1.5 Hz), 7.80 (2H, m), 8.48 (2H, m), 18.2 (2H, br s). (Found: C, 54.00; H, 5.74; N, 11.68. $C_{27}H_{34}CoN_5O_7$ requires C, 54.09; H, 5.72; N, 11.68%).

General Procedure for the Pyrolysis of the Cobaloximes. — Finely ground cobaloxime (500 mg) was pyrolysed at 150–160°C and 0.05 mmHg pressure for 45–60 min. The distillate was analysed by g.l.c. and chromatographed over silica gel for product isolation and identification. Pyridine and dimethylglyoxime were produced in all the pyrolyses but no attempt was made to isolate or quantify them. The results are presented in Table 2. The products were isolated by flash chromatography and compared with authentic material or fully characterised as necessary. Thus identified (in order of elution) were:—

[From 2-benzoyl-2-ethoxycarbonylpropyl(pyridine)cobaloxime (17, R = Ph)]:– a) Ethyl 2-benzoyl-2-methylpropionate (6, R = Ph) (5 mg, 3%); b) *ethyl (E)-2-methyl-4-oxo-4-phenylbut-2-enoate* (20, R = Ph) as a yellow oil b.p. 120°C (bath temperature)/0.3 mmHg (72 mg, 39%); ν_{max} (neat) 1720, 1670 and 1265 cm^{-1}; δ_H (250 MHz) 1.36 (3H, t, *J* 7.1 Hz), 2.19 (3H, d, *J* 1.5 Hz), 4.31 (2H, q, *J* 7.1 Hz), 7.55 (3H, m), 7.72 (1H, q, *J* 1.5 Hz), 7.97 (2H, m), *m/z* 218 (M^+, 16%),

173 (17), 172 (49), 145 (22), 144 (20), 105 (100), 77 (40). (Found: C, 71.38; H, 6.59. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%); c) an oil, the n.m.r. spectrum of which was consistent with ethyl (*Z*)-2-methyl-4-oxo-4-phenylbut-2-enoate (21, R = Ph) (5 mg, 3%); d) ethyl 2-methyl-4-oxo-4-phenylbutanoate (18, R = Ph) (9 mg, 5%); e) slightly impure ethyl 2-methylene-4-oxo-4-phenylbutanoate (19, R = Ph) (57 mg, 31%), identified on the basis of its n.m.r. spectrum. Attempts to further purify this material resulted in partial isomerisation to (20, R = Ph).

[From 2-acetyl-2-ethoxycarbonylpropyl(pyridine)cobaloxime (17, R = Me)]:– a) ethyl 2-acetyl-2-methylpropionate (6, R = Me) (12 mg, 8%); b) ethyl (*E*)-2-methyl-4-oxo-pent-2-enoate (20, R = Me) (36 mg, 24%); δ_H (90 MHz) 1.40 (3H, t, *J* 7 Hz), 2.29 (3H, d, *J* 1.5 Hz), 2.38 (3H, s), 4.33 (2H, q, *J* 7 Hz), 7.08 (1H, q, *J* 1.5 Hz); c) ethyl 2-methyl-4-oxopentanoate (18, R = Me) (3 mg, 2%); d) ethyl 2-methylene-4-oxopentanoate (19, R = Me) (30 mg, 20%), δ_H (90 MHz) 1.33 (3H, t, *J* 7 Hz), 2.26 (3H, s), 3.47 (2H, s), 4.25 (2H, q, *J* 7 Hz), 5.70 (1H, s), 6.40 (1H, s).

[From ethyl 2-butylthiocarbonyl-2-ethoxycarbonylpropyl(pyridine)cobaloxime (17, R = SBu)]:– a low recovery of volatile products was obtained. G.l.c. analysis indicated the major components to be butanethiol, dibutyl disulphide and a small amount of O-ethyl S-butyl dimethylmonothiolmalonate (6, R = SBu).

[From 2,2-bisethoxycarbonylpropyl(pyridine)cobaloxime (17, R = OEt)]:– diethyl malonate (6, R = OEt) (81 mg, 48%).

[From 2-benzoyl-2-cyclopropyl-2-methoxycarbonylethyl(pyridine)cobaloxime (23)]:– a) an impure fraction (by n.m.r. analysis) predominantly methyl 2-benzoyl-2-cyclopropylpropionate (9) (14 mg, 3%); b) a mixture (by n.m.r. analysis) of methyl (*E*)-2-(2'-oxo-2'-phenylethyl)pent-2-enoate (13) and methyl (*E*)-2-(2'-oxo-2'-phenylethyl)penta-2,4-dienoate (24) (40 mg, 8%).

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