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Cycloaddition of ethyl thioxoacetate and 1-methoxy-1,3-cyclohexadiene

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ABSTRACT

The objective of this work is to study the regio- and stereochemistry of the cycloadducts obtained from the treatment of thioxoacetate and 1-methoxy 1,3-cyclohexadiene and also from the retro-Diels Alder reaction of the anthracene cycloadduct with 1-methoxy 1,3-cyclohexadiene.

Keywords: *Diels Alder, cycloaddition, anthracene, 1-methoxy 1,3-cyclohexadiene, thioxoacetat*e.

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INTRODUCTION

The use of Bunte salts, for example the ethyl ester (**1**), as precursors of thioaldehydes, e.g. ethyl thioxoacetate[1] (**2**) (**scheme 1**) was described by the German chemist Hans Bunte [2].

This early work employed symmetrical dienes as trapping agents, the one exception being thebaine [3-5].

Gourlay and Kirby concluded that the route involving deoxygenation of ethylene ketals with sulphur dioxide in pyridine is recommended generally for the conversion of thebaine , in four steps, into 14-β-acylaminocodienones and show that no chromatographic purifications are necessary and yield of 70-80 % per step are usual [6-8].

Reaction of the anions of thebaine and 6-demethoxythebaine with carbonyl compounds as 2-propanone gave the 5β-(dimethylmethanol)-substituted analogues and three isomeric C-7- substituted morphinan-5,8-dienes respectively but no reaction took place with methanal [9].

Regioisomers was characterized and studied in biological media using 1,3-dipolar cycloaddition-retro-Diels-Alder [10-16].

The aim of the present study was to explore the regiochemistry and stereochemistry of the reaction of thioxoacetate ester with unsymmetrical conjugated dienes.

RESULTS AND DISCUSSION

The first of these studied was 1-metoxy-1,3-cyclohexadiene, a close analogue of thebaine.

Accordingly, when the Bunte salt (**1**) was treated in ethanol benzene at room temperature with equimolecular amounts of triethylamine and calcium chloride dihydrate, in the presence of one mole equivalent of 1-methoxy-1,3-cyclohexadiene (**3**), the cycloadducts (**4**) and (**5**) were obtained in 60% yield after five days (**scheme 2**).The endo:exo ratio was 4:1 as judged from integration of the olefinic signals in ^{1}H n.m.r spectrum of the reaction mixture.

The two isomers were separated on preparative silica t.l.c plates and were obtained in approximately the same ratio as determined by integration of the ^{1}H n.m.r spectrum.

The same esters (**4**) and (**5**) were obtained using the alternative method for generating ethyl thioxoacetate, that is by thermal dissociation of the anthracene adduct (**6**).Thus, the anthracene adduct (**6**) was heated under reflux in toluene with 1-methoxy-1,3-cyclohexadiene (1.3 mol equiv.) for 4h, by which time all the anthracene adduct had

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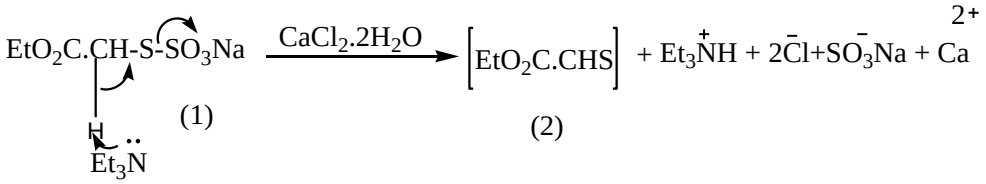
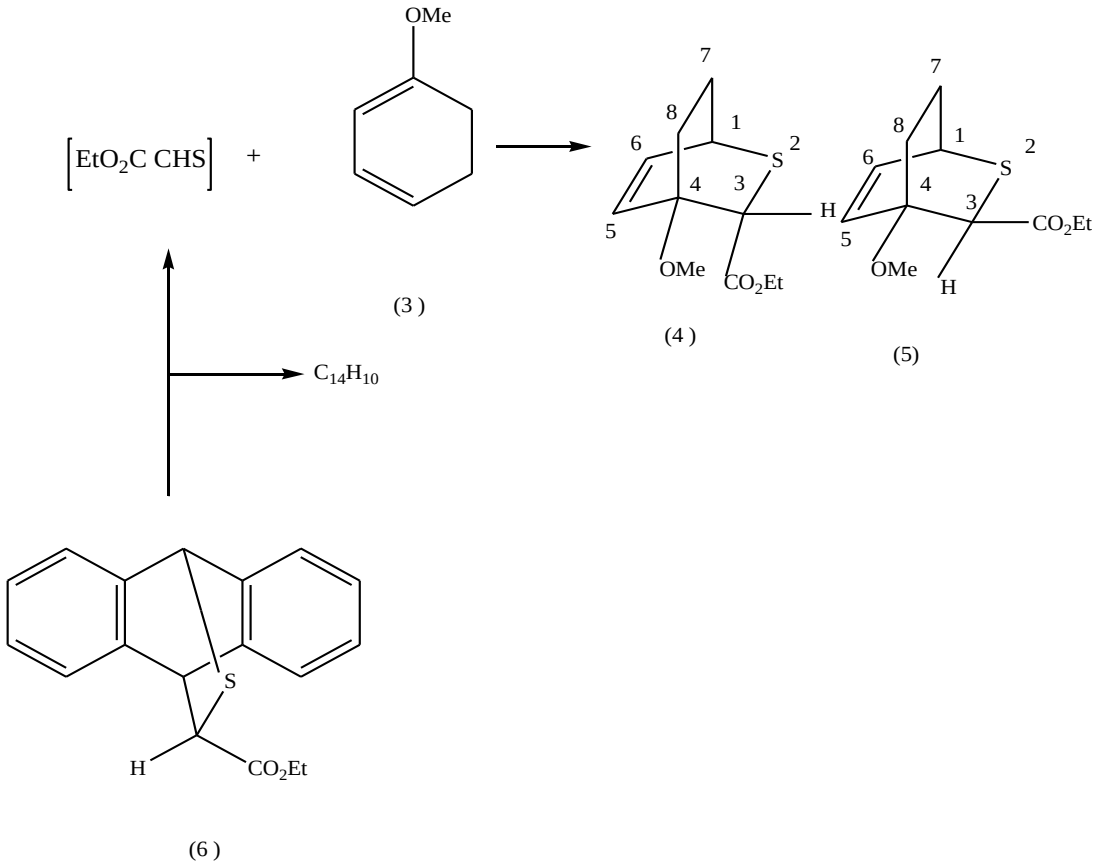
decomposed. The cycloadducts (**4**) and (**5**) were isolated in a combined yield of 68% and in essentially the same endo:exo ratio of 4:1.



Scheme 1



Scheme 2

The molecular formula of the adducts (**4**) and (**5**) was determined by accurate mass measurement. The fragmentation patterns were also useful and had some points of interest. The presence of the carbonyl groups was indicated by i.r. spectroscopy $\bar{\upsilon}_{max}$ 1735 cm^{-1}.

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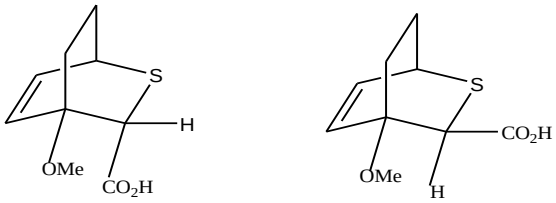
When the esters (**4**) and (**5**) were hydrolysed with 1.03 M sodium hydroxide in tetrahydrofuran at room temperature, the crystalline acids (**7**) and (**8**) were obtained in excellent yields, m.p. 114-115 °C and 124-125 °C respectively (**scheme 3**). Microanalysis supported the expected elemental composition, $C_9H_{12}O_3S$.

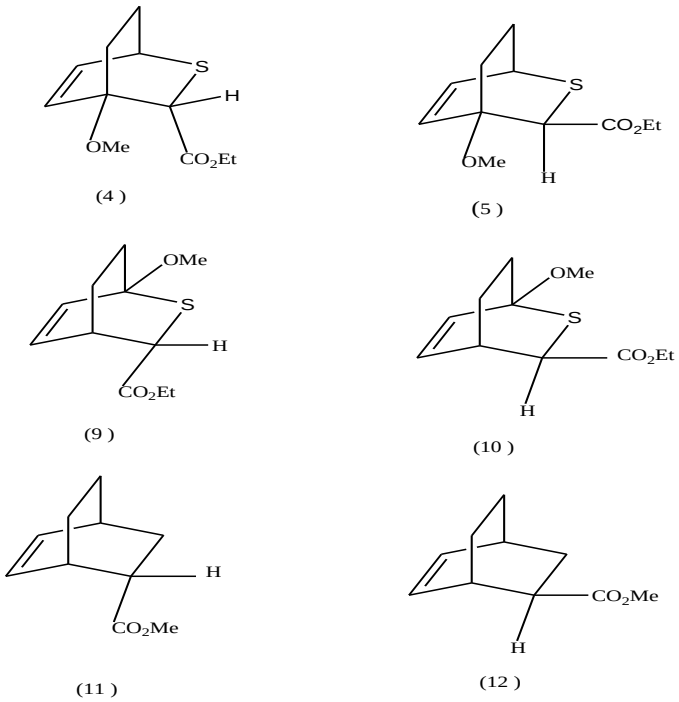
Mass spectroscopy with accurate mass measurement, confirmed this molecular formula for both acids and gave useful fragments. The i.r spectra showed carboxyl carbonyl bands at $\bar{\upsilon}_{max}$ 1715 cm^{-1} (endo-COOH) and 1705 cm^{-1} (exo-COOH). The ^1H n.m.r. spectra of the esters and the corresponding acids were closely similar, apart from the replacement of ethoxyl signals by broad hydroxyl signals.



(7) (8)

Scheme 3

Theoretically, four possible cycloadducts (**4**), (**5**), (**9**) and (**10**), can be formed from the addition of thioxoacetate (**2**) to the unsymmetrical diene 1-methoxy-1,3-cyclohexadiene (**3**) (**scheme 4**).



(4) (5) (9) (10) (11) (12)

Scheme 4

These adducts are two pairs of stereoisomers, the members of each pair being interconvertible, in principle, by epimerisation at C(3). We have shown the products to be (**4**) and (**5**) for the following reasons. First of all, when Ouellette and Booth [17] used base-catalysed epimerisation as an alternative method for confirming the relative stereochemistry of the esters (**11**) and (**12**) obtained from methyl accrylate and cyclohexadiene, the ratio of isomers at equilibrium was endo:exo,55:45. Using the procedure reported by Oullette and Booth, the major ester (**4**), prepared from the pure acid (**7**) was heated under reflux in 0.1 M sodium ethoxide for 1hour. The resulting mixture contained 40% of the minor ester (**5**). The minor ester was isolated and hydrolysed to the crystalline acid to establish its identity. To confirm that the reaction had reached equilibrium, the mixture of the esters (**4**) and (**5**) (4:1) was heated in sodium ethoxide for 24h.The proportion of the minor isomer was again 40%.The possibility that dissociation and recombination of the cycloadducts had occurred was excluded by heating the ester (**4**) in ethanol under reflux for 1h.The ester (**4**) was unchanged. Our results were essentially in agreement with those obtained by Oullette and Booth, who established the stereochemistry of there endo (major) acid by iodolactonisation [17].

This interconversion of the isomeric esters by epimerisation shows that they indeed have the same regiochemistry. The regiochemistry and stereochemistry of the isomers (**4**) and (**5**) and the derived acids (**7**) and (**8**), was confirmed by ^{1}H n.m.r spectroscopy aided by comparison with the corresponding cycloadducts of cyclohexadiene[2].The multiplicities of the signals for 3-H were particularly informative. The spectrum of the acid (**7**) derived from the major ester (**4**) showed only a fine-split doublet, *J* 0.8*Hz*, for 3-H, whereas vicinal coupling constants for the cyclohexadiene adducts were $J_{2,3}$ 3*Hz* (endo) and $J_{2,3}$ 2*Hz* (exo). Clearly the major product (**4**) must have the methoxy group at C(4) and the small splitting (0.8 *Hz*) must arise from long-range coupling. The spectrum of the minor product acid (**8**) showed a doublet *J* 2.2*Hz* for 3-H whereas that of the exo cycloadduct of cyclohexadiene showed a triplet *J* 2.1*Hz.* In both compounds, there must be a long-range (W) coupling between the endo 3-H and a proton in the ethano bridge.

The chemical shifts for protons in 1-methoxy-1,3-cyclohexadiene adducts were similar to those of the parent adducts. The stereochemistry of the endo cyclohexadiene adduct had been established unambiguously by conversion into bromolactone [2].

Bromolactonisation was therefore attempted at an early stage, to establish the stereochemistry of the adducts (**4**) and (**5**). Thus, the endo-exo mixture of the acids (**7**) and (**8**) was treated with bromine-water in aqueous sodium carbonate under conditions used successfully for the endo-acid of cyclohexadiene. Unexpectedly, the ^{1}H n.m.r spectrum of the total reaction product showed no significant signal for a methoxy group. The reaction was repeated with the same result and no identifiable product could be isolated from the reaction mixture.

Birch and Hill [18] reported a closely related reaction, namely addition of methyl accrylate to 1-methoxy-1,3-cyclohexadiene which occurred to give products, with the ester group (CO_2Me) adjacent to the methoxy group (OMe). That was in accord with other results

and theory. In their kinetically controlled reaction, they obtained the two isomers in an endo:exo ratio of 4:1. Base-catalysed equilibration resulted in an increase in the proportion of the exo-isomer (to 40%), this agrees with the equilibrium ratio observed for the corresponding thioaldehyde adducts (**4**) and (**5**) and therefore support the foregoing stereochemistry assignment.

In the hope of producing the other regioisomers, the endo-ester (**4**) was heated in benzene under reflux for 1h. Unfortunately, it remained unchanged. Therefore, the same ester (**4**) was heated in toluene under reflux. After 1h a mixture containing the endo (**4**) and exo isomer (**5**) was obtained, but no other compound was produced.

This result contrasts with that obtained with thebaine cycloadduct [3,4] under the same conditions, when isomerisation to the cycloadduct occurred in high yield. It appears that the missing regioisomers of methoxycyclohexadiene are less stable than of the corresponding isomer of thebaine.

CONCLUSION

According to molecular orbital calculations on simple thioaldehydes, it was concluded that the orientation of unsymmetrical electron rich diene depended upon the atomic coefficient of the LUMO of the thioaldehyde strongly electron-withdrawing groups enhance the electrophilic character of the sulphur i.e. they increase the atomic coefficient in the thioaldehydes, therefore the cycloaducts with the sulphur attached to the more electron-rich (i.e., higher coefficient in the HOMO) end of the diene are predominantly formed. Our results, methoxycyclohexadiene and ethyl thioxoacetate, which has an electron-withdrawing groups agrees with these theoretical arguments.

EXPERIMENTAL WORK

Preparation of Ethyl 4-Methoxy-2-thiabicyclo [2.2.2] oct.5-ene-3-carboxylate (4) and (5).

The Bunte salt (**1**) (1.73g, 7.75mmol) and calcium chloride dihydrate (1.15g, 7.75mmol) were dissolved in ethanol (30ml). 1-Methoxy-1,3-cyclohexadiene (**3**) (1.22g, 7.75 mmol) was added in benzene (25ml) to the salt mixture. The diene was used as a mixture of 1-methoxy-1,3-cyclohexadiene (70%) and 1-methoxy-1,4-cyclohexadiene (30%); the quantities cited are those corresponding to 1,3-diene. Triethylamine (0.79g, 7.75mmol) in benzene (2ml) was then added.The reaction mixture was stirred at room temperature for 5 days then was diluted with chloroform (50ml) and water (30ml). Dilute (5%) hydrochloric acid was added and the calcium sulphite had dissolved and the mixture had become clear. The organic layer was washed with aqueous sodium bicarbonate to remove the excess of hydrochloric acid, then it was washed with brine (10ml) water (20ml), and was dried with ($MgSo_4$) and evaporated to offer a mixture of the cycloadducts (**4**) and (**5**) (1.50g, 60%) as a yellow oil.This mixture was chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (80:20) gave the cycloadducts (1.42g, 56.2 %) as a yellow oil. The ^{1}H n.m.r spectrum showed the presence of the endo (4) and exo (**5**) isomers in the ratio of 4:1

based upon integration of the olefinic proton signals. The two isomers were separated on silica plates developed three times with light petroleum-ether (80:20) to offer the pure isomers (**4**) and (**5**) (ratio 4:1) the later having the higher R_F value. The major product, ethyl-4-methoxy-2-thiabicyclo[2.2.2]oct.5-ene-3-endo-carboxylate (**4**), was obtained as an oil (Found: m/z 228.0816. $C_{11}H_{16}O_3S$ requires M, 228.0821; $\bar{\upsilon}_{max}$ ($CHCl_3$ 1735 cm^{-1}; δ($CDCl_3$, 90 *MHz*) 1.27(t,*J7.0*Hz, OCH_2CH_3), 1.55-2-47(m, 7-and 8-CH_2), 3.43(S,4-OCH_3), 3.52 (m, 1-H), 4.14 (S, 3-H), 4.19(q,*J* 7.0*Hz*, OCH_2CH_3) and 6.20-6.75(m, 5-and 6-H). The minor product, ethyl 4-methoxy-2-thiabicyclo[2.2.2]oct.5-ene-3-exo-carboxylate(5) was obtained as an oil (Found: m/z 228.0815 $C_{11}H_{16}O_3S$ requires M, 228.0821; $\bar{\upsilon}_{max}$ ($CHCl_3$) 1735 cm^{-1}; δ($CDCl_3$, 90 *MHz*) 1.30(t, *J* 7.0*Hz*, OCH_2CH_3), 1.50-2.80(m, 7 and 8-CH_2), 3.5(S, 4-OCH_3), 3.5(m, 1-H), 3.83(S, 3-H), 4.28(q, *J*7.0 *Hz* OCH_2CH_3), and 6.30-6.70(m, 5-and 6-H).

Hydrolysis of the endo-ester (4)

1.03M sodium hydroxide (7ml) was added to a solution of the foregoing endo-ester (**4**) (0.40g, 1.75mmol) in tetrahydrofuran (5ml) and the mixture was stirred at room temperature overnight. After 24h, the solution was concentrated under reduced pressure with heating. The resulting aqueous solution was washed with ether (5x20ml) then acidified with 5% hydrochloric acid (10ml) and extracted with ether (5x20ml).The ethereal extracts were washed with brine (10ml), dried ($MgSo_4$) and evaporated under reduced pressure to give the pure 4-methoxy-2-thiabicyclo[2.2.2]oct.5-ene-3-endo-carboxylic acid (**7**) (0.31g, 90%) m.p 114-115 °C (from hexane).(Found: C, 54.00; H, 6.30; S, 16.30.$C_9H_{12}O_3S$ requires C, 53.98; H, 6.00; S, 16.01 %).(Found: m/z, 200.0510.$C_9H_{12}O_3S$ requires M 200.0507); $\bar{\upsilon}_{max}$ (KBr) 1725 cm^{-1}; δ($CDCl_3$, 200 *MHz*)2.24(1H,m) 1.62-1.92(3H,m)(7-and 8-CH_2), 3.46(S, 4-OMe), 3.53(dtd, *J* 6.8, 2.7, and 0.9 *Hz*, 1-H), 4.12(d, *J* 0.8*Hz*, 3-H), 6.22(dd, *J* 8.9 and 0.7 *Hz*, 5-H) and 6.60(dd, *J* 8.9 and 6.8 *Hz*, 6-H), 9,75(bs,CO_2H, exch, with D_2O).

Hydrolysis of the exo-ester (5)

The exo-ester (**5**) (0.22g, 1.1mmol) was hydrolysed as described for the endo-isomer to give 4-methoxy-2- thiabicyclo [2.2.2]oct.5-ene-3-exo-carboxylic acid (**8**) (0.169g, 88%), m.p.124-125°C(from hexane). 16.01%)(Found:m/z 200.0520. $C_9H_{12}O_3S$ requires M, 200.0507); $\bar{\upsilon}_{max}$ (KBr) 1705 cm^{-1}; δ($CDCl_3$, 200 *MHz*) 2.28-2.45 (2H, m), 1.76-1.94 (1H,m), and 1.57 (1H, ddd, *J*12.0, 8.0 and 2.0 *Hz*) (7-and 8-CH_2), 3.5 (S, 4-OMe), 3.5(m, 1-H), 3.84(d, *J* 2.2*Hz* , 3-H), 6.36(d,*J*8.9*Hz*, 5-H), and 6.60 (dd,*J* 8.9 and 6.8*Hz* 6-H), 8.52(bs, CO_2H, exch.with D_2O).

Thermal transfer of Ethyl thioxoacetate from the Anthracene cycloadduct to 1-Methoxy-1,3-cyclohexadiene.

The anthracene cycloadduct (**6**) (0.50g, 1.69mmol) and 1-methoxy-1,3-cyclohexadiene (0.235g, 1.3mol equiv) were heated in redistilled toluene (10ml) under reflux for 4h. The diene was used as a mixture of 1-methoxy-1,3-cyclohexadiene (70%) and 1-methoxy-1,4-cyclohexadiene (30%), the quantities cited are those corresponding to 1,3-diene. The toluene was evaporated under reduced pressure with heating to give a crude

mixture (0.737g) that was shown by ^{1}H n.m.r spectroscopy to contain the cycloaddct (**4**) and (**5**). The mixture was then chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (70:30) gave the cycloadducts (4) and (5) (0.26g, 67.5%) as a yellow oil; endo:exo ratio 4:1. The two isomers were separated on silica plates developed three times with light petroleum-ether (80:20). The ^{1}H n.m.r spectrum of each isomer agreed well with that of the compound obtained from the Bunte salt (**1**).

Hydrolysis of the endo-ester (4) and exo-ester (5) obtained from the transfer reaction.

The ester (**4**) (0.49g, 2.15mmol) was hydrolysed with aqeuous sodium hydroxide in tetrahydrofuran as described before to give the acid (7)(0.34g, 80 %), m.p 114-115 °C (from hexane). Similarly the ester (**5**) (0.056g, 0.245mmol) gave the acid (**8**) (0.041g, 83.4%), m.p.124-125 °C from (hexane). The ^{1}H n.m.r spectrum of each isomer agreed well with that of the compound obtained from the Bunt salt (**1**).

Esterification of 4-Methoxy-2- thiabicyclo [2.2.2]oct.5-ene-3-endo-carboxylic acid.

The acid (**7**) (0.22g, 0.96mmol) in dry ethanol was treated dropwise with redistilled acetyl chloride (0.785g, 1.00mmol), the mixture was kept at room temperature overnight, guarded by a drying tube. The solvents were evaporated under reduced pressure with heating to give the endo-ester (**4**) (0.23g, 92%) as a yellow oil. The ^{1}H n.m.r spectrum (90 *MHz*) showed that esterification had occurred without epimerisation.

Thermal isomerisation of the endo-ester (4).

The pure endo-ester (**4**) (0.20g, 0.88 mmol), prepared as described above from the pure acid (**7**) was heated in redistilled toluene (10ml) under reflux overnight. The toluene was evaporated under reduced pressure with heating to give a complex oily mixture (0.19g). The ^{1}H n.m.r spectrum showed the presence of same endo-ester (**4**), same exo-ester (**5**) and other unidentified products.

Attempted thermal isomerisation of the endo-ester (4) in benzene.

The pure endo-ester (**4**) was unchanged after being heated under reflux for 1.5h.

Attempted thermal isomerisation of the endo-ester (4) in ethanol.

The pure endo-ester (**4**) was unchanged after being heated in dry ethanol under reflux for 1h.

Attempted Bromolactonisation of the endo and exo-acid (7) and (8).

The mixture of acids (**7**) and (**8**) (0.12g, 0.60 mmol)was dissolved in 5% aqueous sodium carbonate (5 ml). Bromine-water was added dropwise with stirring at room

temperature until the colour of Bromine persisted. The mixture was extracted to give a gum (0.80g). The ^{1}H n.m.r spectrum showed no signal for a methoxy group.

Epimerisation of Ethyl 4-Methoxy-2-thiabicyclo [2.2.2]oct.5-ene-3-endo-carboxylate (4).

The endo-ester (**4**) (0.109g, 0.48 mmol) prepared from the pure acid (**7**) was heated under reflux in sodium ethoxide (10 ml, 0.1M) for 1h. The mixture was diluted with annalar chloroform (30 ml), then acidified with 5% hydrochloric acid, and extracted with chloroform. The extracts were washed with aqueous sodium bicarbonate, dried with ($MgSo_4$), and evaporated under reduced pressure with heating to give a mixture (0.106g) of the endo (**4**) and (**5**) isomers in the ratio of 6:4 as judged from integration of the ^{1}H n.m.r spectrum. The two isomers were separated on silica plates developed with light petroleum ether (80:20). Each isomer was hydrolysed with sodium hydroxide to give the corresponding acid, which gave the appropriate melting point.

Epimerisation of the mixture (4:1) of the endo (4) and exo-ester (5).

The mixture of esters (0.124g, 0.54mmol) was heated under reflux in sodium ethoxide (10ml, 0.1M) overnight. The reaction mixture was worked-up as before to give a mixture (0.116g) of the ester, endo:exo ratio 6:4.

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