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VITAMIN A ANALOGUES—IV*

ATTEMPTED SYNTHESIS OF 2,4,4-TRIMETHYL-TETRAHYDROTHIOPYRONE-3

J. L. BAAS†, A. DAVIES-FIDDER and H. O. HUISMAN
Laboratory for Organic Chemistry University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

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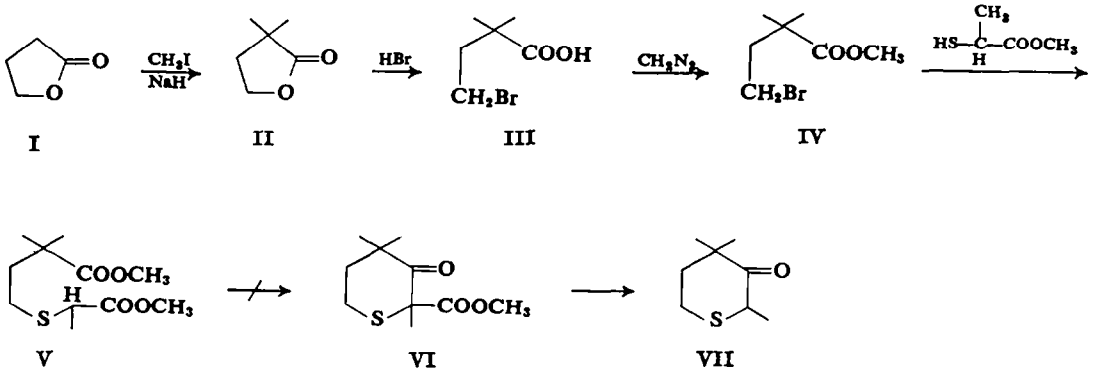
Abstract—In connection with investigations on the synthesis of 4-thia-vitamin A several attempts are described for the preparation of 2,4,4-trimethyltetrahydrothiopyrone-3.

IN CONNECTION with investigations on the synthesis of 4-thia-vitamin A[1] initially the synthesis of 2,4,4-trimethyltetrahydrothiopyrone-3 (VII)—which could be used as a starting material for the preparation of 4-thia-vitamin A—was undertaken.

A similar scheme has been utilized earlier in the vitamin A chemistry, for instance, Attenburrow[2] synthesized vitamin A starting with 2,6,6-trimethylcyclohexanone and, in an attempt to obtain some thiophene-ring analogues of vitamin A, Acheson[3] *et al.* synthesized perhydro-2,4,4-trimethyl-3-oxothiophene.

However, several attempts directed towards the synthesis of the thia-ketone VII were unsuccessful.

We started our studies with an attempt to prepare compound VII according to the following reaction scheme:



* Part III: P. K. Korver, C. Kruk, P. J. van der Haak, J. L. Baas and H. O. Huisman, *Tetrahedron* **22**, 277 (1966).

† Part of the Thesis of J. L. Baas, University of Amsterdam (1964).

[1] Part II: J. L. Baas, Mrs. A. Davies-Fidder, F. R. Visser and H. O. Huisman, *Tetrahedron* **22**, 265 (1966).

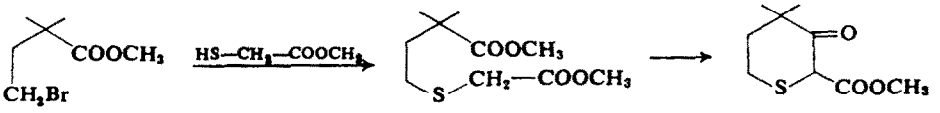
[2] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1904 (1952).

[3] R. M. Acheson, J. A. Barltrop, M. Hichens and R. E. Hichens, *J. Chem. Soc.* 650 (1961).

Several complicated methods are given in the literature for the preparation of α,α-dimethyl-γ-butyrolactone (II).[4–6] However, by direct methylation of γ-butyrolactone (I) the dimethyl derivative (II) could be obtained in a good yield.

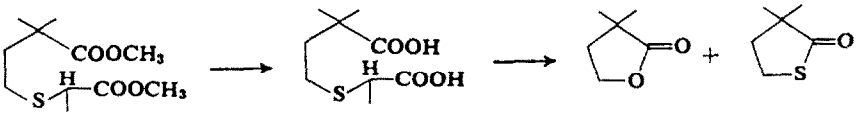
The lactone (II)[7] was converted with dry HBr into the acid (III) and the latter esterified to the ester (IV). By reacting IV with 1-thia-propionic acid methyl ester, under alkaline conditions, the diester (V) could be obtained in a high yield.

Attempts to carry out the Dieckmann cyclization reaction—under several conditions—in order to obtain compound VI, failed. This failure, in all probability, is due to steric factors, since cyclization of the corresponding diester VIII to IX proceeds in good yield. However, various attempts to methylate the keto ester IX were unsuccessful.



IV VIII IX

Another method to prepare cyclic ketones is via the pyrolysis of dicarboxylic acids.[8] To that purpose the diester V was saponified and the corresponding dicarboxylic acid X was isolated.

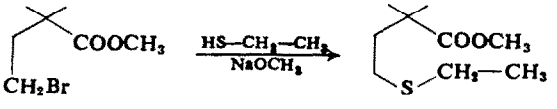


V X II XI

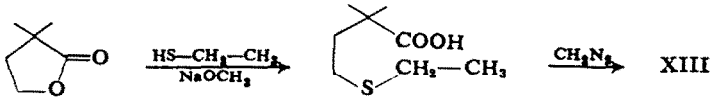
Pyrolysis of the potassium-, calcium- or barium-salts or the dicarboxylic acid itself, yielded in all cases two compounds—the lactone II and the thia-lactone XI—isolated from the reaction mixture by means of GLC.

Their structures were proved by IR spectroscopy and NMR spectrometry.

Another synthetic route leading to compound VII was based upon the cyclization of sulphone esters by an internal Claisen condensation.[8] For this purpose the sulphide ester XIII was prepared by two different ways:[9]



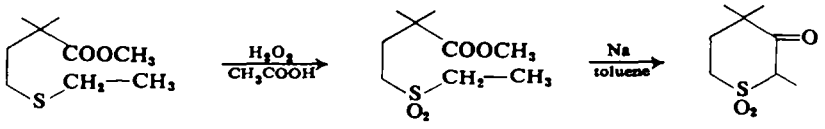
IV XIII



II XII XIII

[4] E. E. Blaise and A. Courtot, *Bull. Soc. Chim. Fr.* **3**, 35, 582 (1906).
[5] G. Blanc, *Bull. Soc. Chim. Fr.* **4**, 3, 288 (1908).
[6] B. E. Hudson and C. R. Hauser, *J. Amer. Chem. Soc.* **63**, 3156 (1941).
[7] D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.* **76**, 2753 (1954).
[8] W. E. Truce and R. H. Knospe, *J. Amer. Chem. Soc.* **77**, 5063 (1955).
[9] H. Plieninger, *Chem. Ber.* **83**, 265 (1950).

Compound XIII was converted into the corresponding sulphone XIV by oxidation with H_2O_2 in acetic acid[10] and cyclized to XV.[11]

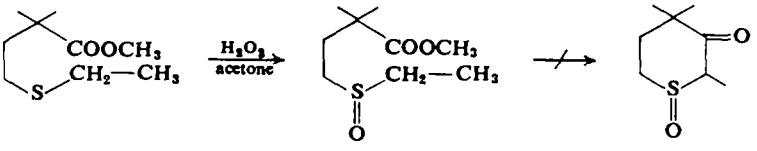


XIII XIV XV

Attempts to reduce the cyclic keto-sulphone XV failed.[12,13]

Cyanohydrin synthesis or lithium acetylide condensation with XV were also unsuccessful. This is probably due to steric hinderance of the surrounding methyl groups and the enolization of the ketone under the reaction conditions.

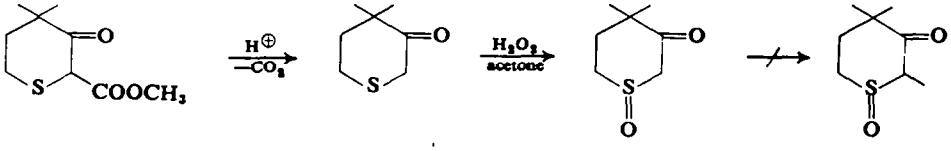
The following scheme which was also investigated was based upon the easy reduction of sulphoxides.[14] The sulphide ester XIII was converted into the sulphoxide ester XVI by H_2O_2 in acetone:[15]



XIII XVI

A cyclization reaction similar to the one carried out with the corresponding sulphone XIV failed. Several reaction conditions were investigated but in all experiments the starting sulphoxide ester XVI was recovered unchanged.

A final attempt to obtain compound VII started with the hydrolysis of the cyclic keto ester IX. After decarboxylation the cyclic keto sulphide XVII could be isolated and converted into the corresponding sulphoxide XVIII:



IX XVII XVIII

Methylation of XVIII however was unsuccessful; only a mixture of methylated products was isolated.

EXPERIMENTAL

IR spectra were taken with a Unicam SP 200 Spectrophotometer; NMR spectra were obtained with a Varian A 60 Analytical Spectrometer. The compounds were measured as 10% solutions in CCl_4.

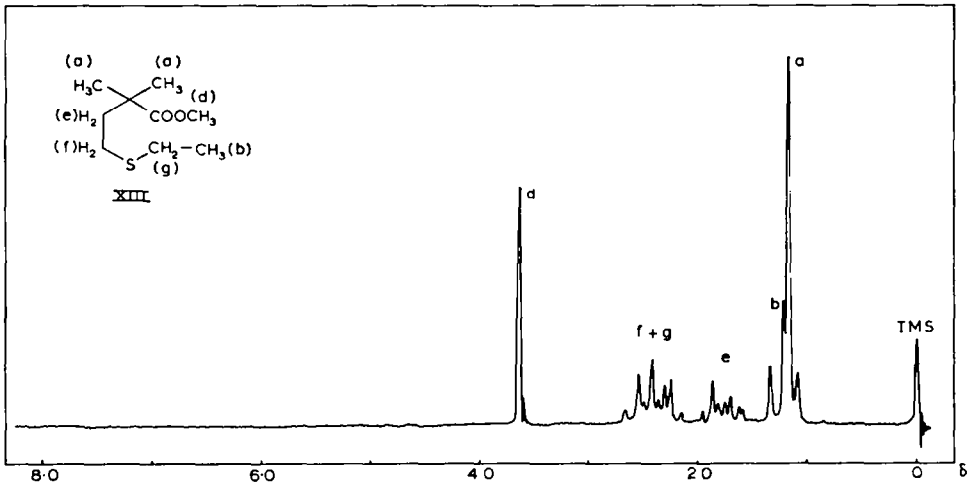
[10] C. G. Overberger, R. A. Gadea, J. A. Smith and I. C. Kogon, *J. Amer. Chem. Soc.* **75**, 2075 (1953).
[11] H. D. Becker and G. A. Russell, *J. Org. Chem.* **28**, 1896 (1963).
[12] W. G. Gaylord, *Reduction with complex metal hydrides.* p. 851. Interscience, New York (1956).
[13] F. G. Bordwell and W. H. McKellin, *J. Amer. Chem. Soc.* **74**, 2251 (1951).
[14] E. N. Karanlove and G. D. Gal'pern, *J. Gen. Chem. USSR* **29**, 2998 (1959).
[15] R. H. Eastman and R. M. Wagner, *J. Amer. Chem. Soc.* **71**, 4089 (1949).

Chemical shifts are given from the tetramethylsilane as an internal reference. Mass spectra were measured on a A.E.I. MS 2H spectrometer. The ionizing potential employed in all measurements was 70 eV.

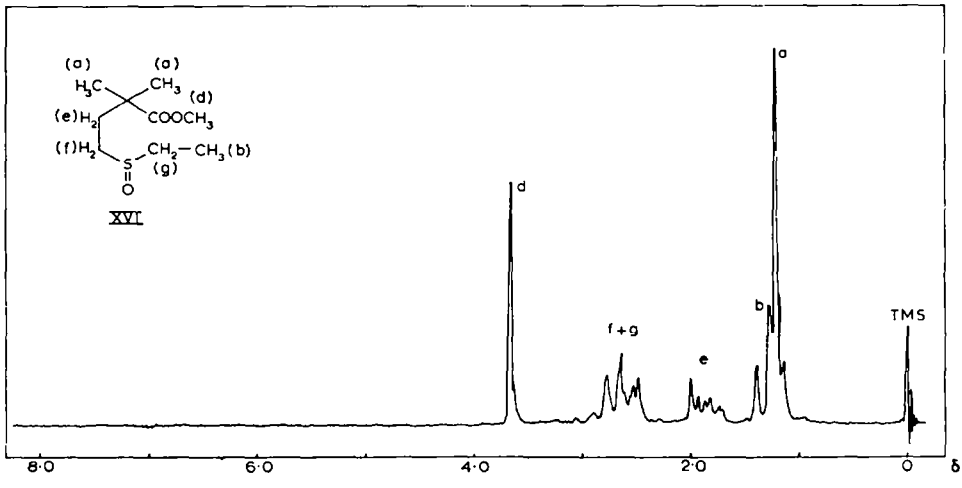
M.ps were determined with a Koffler microscope. Both m.ps and b.ps are uncorrected.

α,α-Dimethyl-γ-butyrolactone (II). A mixture of 86 g (1 mole) γ-butyrolactone (I) and 400 g (2·8 moles) MeI was added in 1·5 hr with stirring to a refluxing suspension of 120 g (2·5 moles) NaH (in oil) in 1000 ml dioxan. After 1 hr more boiling the mixture was poured into ice, acidified with dil. HCl, and extracted with ether for 3 days. After evaporation of the solvent the α,α-dimethyl-γ-butyrolactone was distilled, b.p. (10 mm) 74° (lit. (11 mm) 77°), yield 75 g = 65%. IR absorption spectrum (cap.): C=O 1760 cm^{-1}.

1,1-Dimethyl-3-bromobutyric acid (III). Dry HBr was passed through 228 g (2 moles) of II at room temp till constant wt. The mixture obtained was dissolved in pet. ether (40–60°) and this solution was cooled to −50° where upon white needles crystallized out. After filtering and recrystallization from

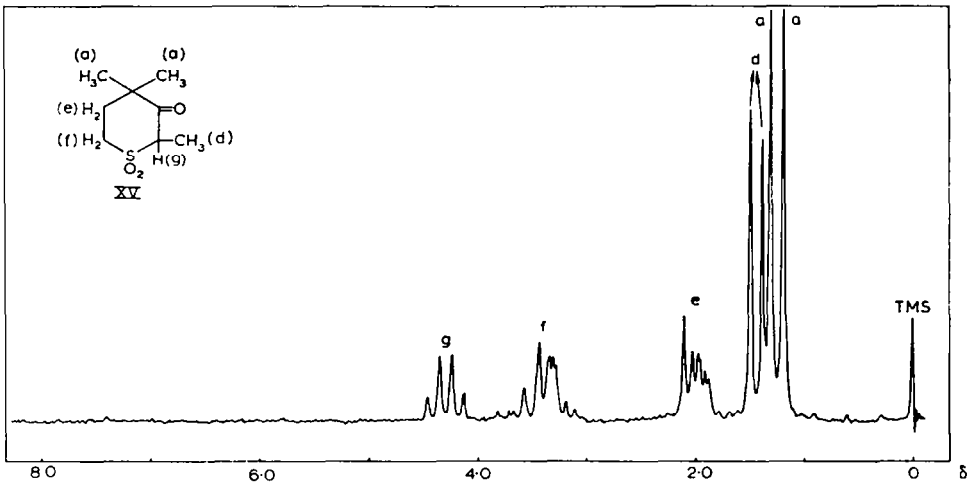


(a)

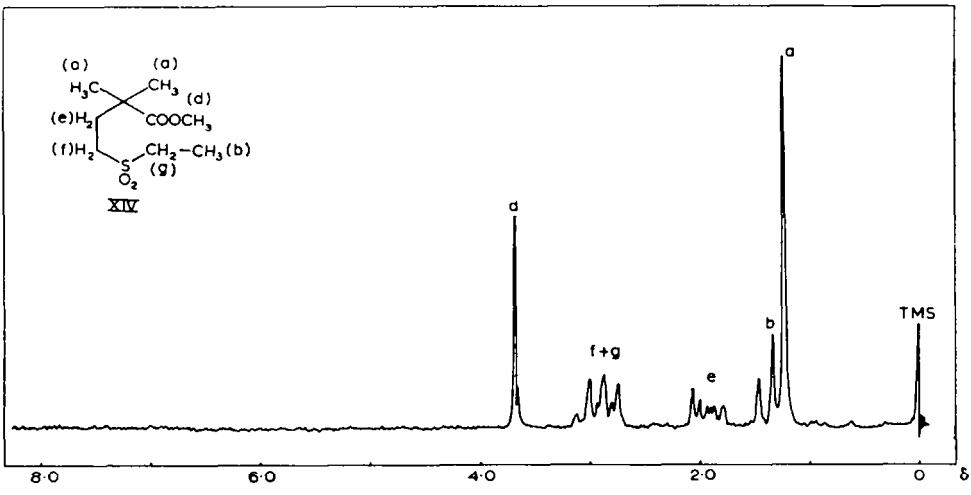


(b)

FIG. 1



(c)



(d)

FIG. 1 (contd.)

pet. ether (40–60°) 262 g (67%) of IV was isolated, m.p. 47–48° (lit. 48°). (Found: C, 36·9; H, 5·5; Calc. for $C_6H_{11}BrO_2$ (195.06): C, 36·92; H, 5·64%.)

1,1-*Dimethyl-3-bromobutyric acid methyl ester* (IV). Compound III (100 g; 0·51 mole) was added to a solution of diazomethane at 0°. The methyl ester was isolated by distillation, b.p. (9 mm) 79–81°, yield 92 g (86%).

6-*Methyl-3-thia-heptane-dicarboxylic acid methyl ester*-2,6 (V). Thiopropionic acid methyl ester (58 g; 0·5 mole) was added to a solution of 27 g MeONa in 150 ml MeOH and after boiling for 5 min this mixture was cooled and added with stirring to a solution of 91 g IV in 50 ml MeOH. After 1 hr refluxing the MeOH was evaporated and the residue poured into a mixture of ice and dil. HCl. After extraction with ether, drying over $MgSO_4$ and removing the solvent *in vacuo* the diester could be isolated by distillation, b.p. (1 mm) 109–112°, n_D^{24}: 1·4661, yield 83 g (75%). (Found: C, 53·0; H, 7·9; S, 12·7; Calc. for $C_{11}H_{20}O_4S$ (248·34): C, 53·22; H, 8·06; S, 12·90%.) The mol wt. found by mass spectrometry: 248. IR-absorption spectrum (cap.): C=O (ester-groups): 1720 and 1735cm^{-1}. NMR-spectrum: *gem*-dimethyl: $\delta = 1{\cdot}17$ (singlet); $-C(CH_3)_2-COOCH_3$: CH_3 (ester) $\delta = 3{\cdot}64$ (singlet);

—S—CH(CH_3)—$COOCH_3$: CH_3 (ester) $\delta = 3{\cdot}69$ (singlet); CH_3 $\delta = 1{\cdot}38$ (doublet); CH $\delta = 3{\cdot}33$ (quartet); —CH_2—CH_2—: $\delta = 1{\cdot}76$, $\delta = 2{\cdot}50$ ($A_2 - B_2$ system).[16]

6-Methyl-3-thia-heptane dicarboxylic acid-2,6 (X). The diester (V; 90 g) saponified with 50 g KOH in 90 ml water by shaking the mixture for 2 days. After removing non-acidic impurities by ether extraction, the water layer was acidified by cold dil. HCl, extracted with ether and after drying over $MgSO_4$ the solvent was evaporated, yielding 75 g (86%) X after recrystallization from ether, m.p. 57–58°. (Found: C, 48·9; H, 7·3; S, 14·5; Calc. for $C_9H_{16}O_4S$ (220·29): C, 49·06; H, 7·32; S, 14·55%.)

Pyrolytic experiments with dicarboxylic acid (X). The reactions were carried out by the pyrolysis of a mixture of the dicarboxylic acid X and $Ba(OH)_2$, KOH, CaO respectively and of the dicarboxylic acid itself at 300°. By ether extraction of the reaction mixture, a mixture of two compounds was isolated by GLC. (1·5 m silicon oil GE–SF 96 column, injection temp 200°, column temp 150°, gas speed 50 ml/min).

One of these compounds proved to be II, the other was the corresponding thio-lactone (XI) as shown by IR and NMR spectrometry. IR absorption spectrum: (of XI, cap.): C=O: 1690 cm^{-1}. (compare with lactone II: 1760 cm^{-1})

		XI	II
NMR-spectrum:	*gem*-dimethyl:	$\delta = 1{\cdot}11$ (singlet)	$\delta = 1{\cdot}12$ (singlet);
	—X—CH_2—:	X = S, $\delta = 3{\cdot}25$ (triplet)	X = O, $\delta = 4{\cdot}37$ (triplet);
	—CH_2—:	$\delta = 2{\cdot}08$ (triplet)	$\delta = 2{\cdot}15$ (triplet).

2-Methyl-5-thia-heptane-carboxylic acid methyl ester-2 (XIII). Ethyl sulphide (31 g; 0·15 mole) was, with stirring, added to a solution of 27 g MeONa. This mixture was added to a solution of IV and the resulting mixture refluxed for 1 hr. The reaction mixture was poured into ice, acidified by dil. HCl, extracted with ether and after drying over $MgSO_4$ and evaporation of the solvent the residue was distilled; b.p. (14 mm) 110–114°; yield 62 g (65%).

In a different method the solution of sodium ethylsulphide was evaporated and the residue added to dry benzene. This suspension was added at room temp to the lacetone II and then refluxed for 3 hr. The reaction product was poured into a mixture of ice and dil. HCl and extracted with ether.

After drying, the ether solution was added to a solution of diazomethane in ether. Upon evaporation of the solvent, the residue was distilled and 73 g (77%) of XIII was obtained. IR-absorption spectrum (cap.): C=O 1735 cm^{-1}. NMR-spectrum (Fig. 1a): *gem*-dimethyl: $\delta = 1{\cdot}15$ (singlet); methyl (ester): $\delta = 3{\cdot}61$ (singlet); —CH_2—CH_2—: $\delta = 1{\cdot}75$, $\delta = 2{\cdot}36$ ($A_2 - B_2$ system)[16]; —S—CH_2—CH_3: CH_3 $\delta = 2{\cdot}48$ (quartet), CH_3 $\delta = 1{\cdot}20$ (triplet).

2-Methyl-4-(ethylsulphonyl)-butane-carboxylic acid methyl ester-2 (XIV). A mixture of 95 g (0·05 mole) XIII, 150 ml H_2O_2 (30%), 150 ml acetic acid and 150 ml acetic anhydride was kept at room temp for 18 hr. The crystals were filtered off and recrystallized from ether, m.p. 60–61° (white needles), yield 78 g (70%). (Found: C, 48·5; H, 8·2; S, 14·3; Calc. for $C_9H_{18}O_4S$ (222·30): C, 48·61; H, 8·17; S, 14·42%.) IR absorption spectrum (tetra, 0·1 mm): C=O 1725 cm^{-1} SO_2 1130, 1309 cm^{-1}.

NMR spectrum (Fig. 1d): *gem*-dimethyl: $\delta = 1{\cdot}23$ (singlet); methyl (ester): $\delta = 3{\cdot}68$ (singlet); —CH_2CH_2—: $\delta = 1{\cdot}93$, $\delta = 2{\cdot}88$ ($A_2 - B_2$ system);[16] —SO_2—CH_2—CH_3: CH_2 $\delta = 2{\cdot}93$ (quartet) CH_3 $\delta = 1{\cdot}33$ (triplet).

1,1-Dioxo-2,4,4-trimethyl-1-thia-cyclohexanone-3 (XV). To a suspension of 5·7 g (0·25 mole) Na in toluene, a solution of 55 g (0·25 mole) XIV was added at room temp. Then the mixture was refluxed for 5 hr. After cooling it was poured into ice and acidified with cold dil. HCl. The cyclic keto-sulphone (XV) was isolated by extraction with benzene, followed by evaporation of the solvent and recrystallization from ether, m.p. 114–116°; yield 47 g (70%). (Found: C, 50·3; H, 7·4; S, 16·7; Calc. for $C_8H_{14}O_3S$ (190·26): C, 50·52; H, 7·42; S, 16·81%.)

IR absorption spectrum (KBr pellet): C=O 1700 cm^{-1}; SO_2 1129 and 1310 cm^{-1}. NMR spectrum (Fig. 1c): *gem*-dimethyl: $\delta = 1{\cdot}18$ and $\delta = 1{\cdot}30$ (singlets, these methyl groups are not equivalent); methyl: $\delta = 1{\cdot}43$ (doublet); —CH_2—CH_2—: $\delta = 1{\cdot}99$, $\delta = 3{\cdot}39$ ($A_2 - B_2$ system);[16] CH: $\delta = 4{\cdot}29$ (quartet).

2-Methyl-4-(ethylsulphinyl)-butane-carboxylic acid methyl ester-2 (XVI). The sulphide ester (XIII; 47·5 g; 0·25 mole) 250 ml acetone and 30 ml H_2O_2 (30%) were kept for 5 days at room temp. Benzene was added and the solvents evaporated. After distillation 45 g (84%) of XVI were obtained; b.p.

[16] Estimated centre of multiplet.

(0·07 mm) 108–112°. The mol. wt. (206) was determined by mass spectrometry. IR absorption spectrum (cap.): C=O 1720 cm^{-1}; S=O 1050 cm^{-1}. NMR spectrum (Fig. 1b): *gem*-dimethyl: δ = 1·21 (singlet); methyl (ester): δ = 3·65 (singlet); —CH_2—CH_2—: δ = 1·87, δ = 2·61 ($A_2 - B_2$ system);[16] —SO—CH_2—CH_3: CH_3 δ = 2·71 (quartet) CH_3 δ = 1·26 (triplet).

4,4-*Dimethyl*-3-*oxo*-1-*thia-cyclohexane carboxylic acid methyl ester*-2 (IX). Thioglycolic acid methyl ester (53 g; 0·5 mole) was added with stirring to a solution of 27 g MeONa in MeOH. After boiling for 15 min and cooling to room temp the mixture was slowly added to a solution of 104 g (0·5 mole) IV. The mixture was refluxed for 20 min and the MeOH evaporated. The residue was poured into a mixture of ice and dil. HCl and after extraction with ether and drying, the solvent was evaporated and VIII distilled, b.p. (0·2 mm) 112–114°; yield 82 g (70%).

Compound VIII was added to a boiling suspension of 16 g NaH in 150 ml benzene. After boiling 4 hr the reaction mixture was poured into ice. After acidifying with cooled dil. HCl the mixture was extracted with benzene and after drying and evaporating the solvent 49 g (70%) of IX was obtained, b.p. (0·1 mm) 114–116°. IR absorption spectrum (cap.): compound VIII, C=O 1720 and 1735 cm^{-1}; compound IX, C=O (ester) 1735 cm^{-1}; C=O 1700 cm^{-1}; C=O 1644 cm^{-1} (enol tautomer); C=C 1585 cm^{-1} (enol tautomer). NMR spectrum (IX): *gem*-dimethyl: δ = 1·22 (singlet); methyl (ester): δ = 3·77 (singlet); —CH_2—CH_2—: δ = 1·93 δ = 2·73 ($A_2 - B_2$ system);[16] —OH: δ = 5·65. Both IR and NMR spectra indicate that IX exists mainly as the enol-tautomer.

4,4-*Dimethyl*-1-*thia-cyclohexanone*-3 (XVII). Compound IX (40 g) was hydrolysed with 10% H_2SO_4 by boiling for 6 hr. After extraction and evaporation of the solvent, the residue was distilled, b.p. (14 mm) 106°; yield 23 g (80%). (Found: C, 58·2; H, 8·4; S, 22·3; Calc. for $C_7H_{12}OS$ (144·24): C, 58·28; H, 8·38; S, 22·23%). IR absorption spectrum (cap.): C=O 1705 cm^{-1}. NMR spectrum: *gem*-dimethyl: δ = 1·11 (singlet); —CH_2—CH_2—: δ = 2·17, δ = 2·78 (A_2–B_2 system);[16] —S—CH_2—CO—: δ = 3·19 (singlet).

4,4-*Dimethyl*-3-*oxo*-1-*thia-cyclohexane*-1-*oxide* (XVIII). The cyclic ketone (XVII; 4·3 g; 0·03 mole) and 2·5 g H_2O_2 (30%) were dissolved in acetone and kept at room temp for 2 days. After evaporation of the solvent the cyclic sulphoxide was obtained as a hygroscopic substance. IR absorption spectrum (cap.): C=O 1705 cm^{-1}; S=O 1040 cm^{-1}.

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