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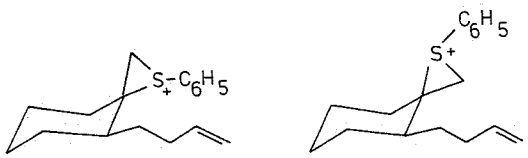
Abstract. Cyclization initiated by thiiranium ions was investigated. *Cis*-fused decalins were formed by a process involving inversion. In nitromethane a sulphonium salt **8** was formed. The reactions of **8** with nucleophilic reagent deviated from those of comparable compounds. It is expected that a product-controlled transition state accounts for this feature.

Introduction

Biomimetic polyene cyclization is considered as a synthetic tool with great potentiality. However, so far the applicability of this type of reaction has remained rather limited. The usefulness would be considerably improved if the versality could be enlarged and if the product formation could be well controlled. For these purposes an effective influence on the mode of reaction is required. In this connection some good results are obtained by geometrical means, especially in attempts to realize an asymmetric induction[1]. The alternative, interaction of heteroatom-containing groups with initiating or intermediate ions, has hardly been considered. Such involvement can be very effective, particularly in precluding side reactions. Moreover, participation in enzymic reactions may well occur, which results in differences in stereochemical outcome of enzymic and non-enzymic cyclizations[2].

The groups involved must form bonds with carbon which are stable enough to prevent isomerization and still allow of a cyclization reaction. These conditions seem to be well fulfilled by phenylthio groups. The participating ability of sulphur is well documented, especially when it is situated in the β position (*e.g.* as in mustard gas)[3]. In addition, *Lansbury* et al.[4] has demonstrated that phenylthio groups totally change the stereochemical outcome of an alkyne cyclization. The proposed mechanism includes the intermediacy of thiiranium ions and a nucleophilic attack on sulphur followed by insertion into the carbon-sulphur bond which results in a net retention of configuration with respect to the thiiranium ion as outlined in Scheme 1.

This mechanism is probably not correct because nucleophilic attack on sulphur usually leads to desulphurization. *In our opinion, it is more likely that the reaction proceeds with inversion.* In that case the phenylthio group acts as an active site enabling control over the stereochemistry and, most likely, over additional aspects of the cyclization reaction *(vide infra)*. Therefore, we decided to investigate the reactions of ions **1a** and **1b** in order to clarify the mechanism of the cyclization reaction induced *via* a thiiranium ion.

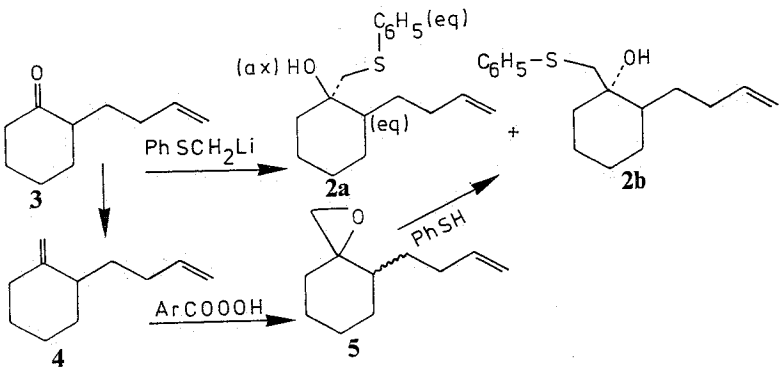


1a **1b**

Furthermore, the influence of participation in other respects such as five- or six-membered ring formation is considered.

Results

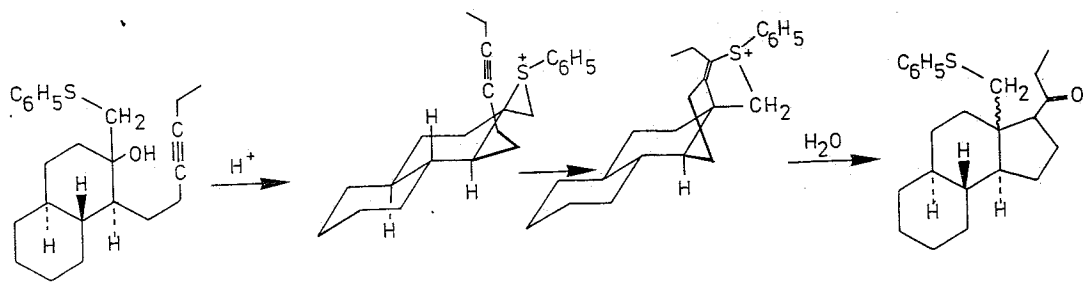
The alcohols **2a** and **2b** are the precursors for **1a** and **1b**, respectively. Synthesis of two mixtures (**2a**/**2b**) of unequal composition was accomplished in accordance with the reaction routes shown in Scheme 2.



Scheme 2

* Present address: Philips Duphar B.V., Postbus 2, 1380 AA Weesp, The Netherlands.

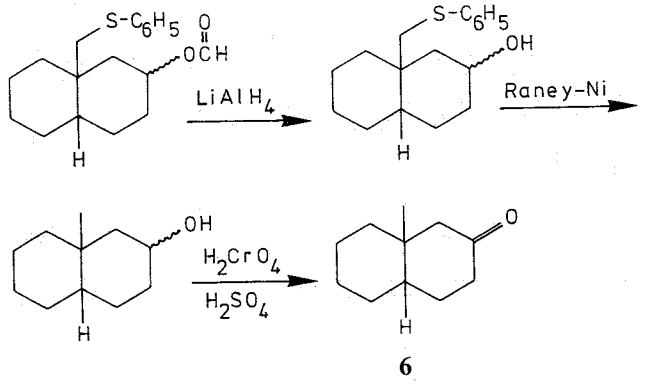
[1] *A. A. Macco*, Thesis, Eindhoven University of Technology, The Netherlands (1979).
[2] *W. A. J. de Loos*, Thesis, Eindhoven University of Technology, The Netherlands (1978).
[3] See for example:
W. H. Mueller, Angew. Chem. **81**, 475 (1969).
K. D. Gundermann, Angew. Chem. **75**, 1194 (1963).
[4] *P. T. Lansbury, T. R. Demmin, G. E. Dubois* and *V. R. Haddon*, J. Am. Chem. Soc. **97**, 394 (1975).



Scheme 1

Direct conversion of ketone **3** with phenylthiomethyllithium gave **2a** and **2b** in a ratio of 9/1. The alternative route *via* dialkene **4** afforded, after selective epoxidation and opening of the oxirane ring, **2a** and **2b** in a ratio of 1/4. The assignment of configuration of the two isomers, which could be distinguished by means of ^{13}C NMR, was based upon the followed synthetical route[5].

Formolyses were performed on both mixtures. After one hour at reflux temperature, the products were treated directly with $LiAlH_4$ and subsequently separated into an alkenic and an alcoholic fraction. The alcoholic fraction was desulphurized with Raney-Nickel and then oxidized with chromic acid (see Scheme 3), resulting in 8a-methyl-*cis*-β-decalone **6**.

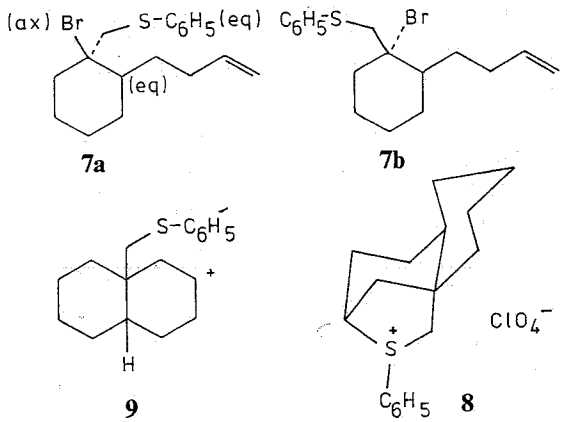


6

Scheme 3

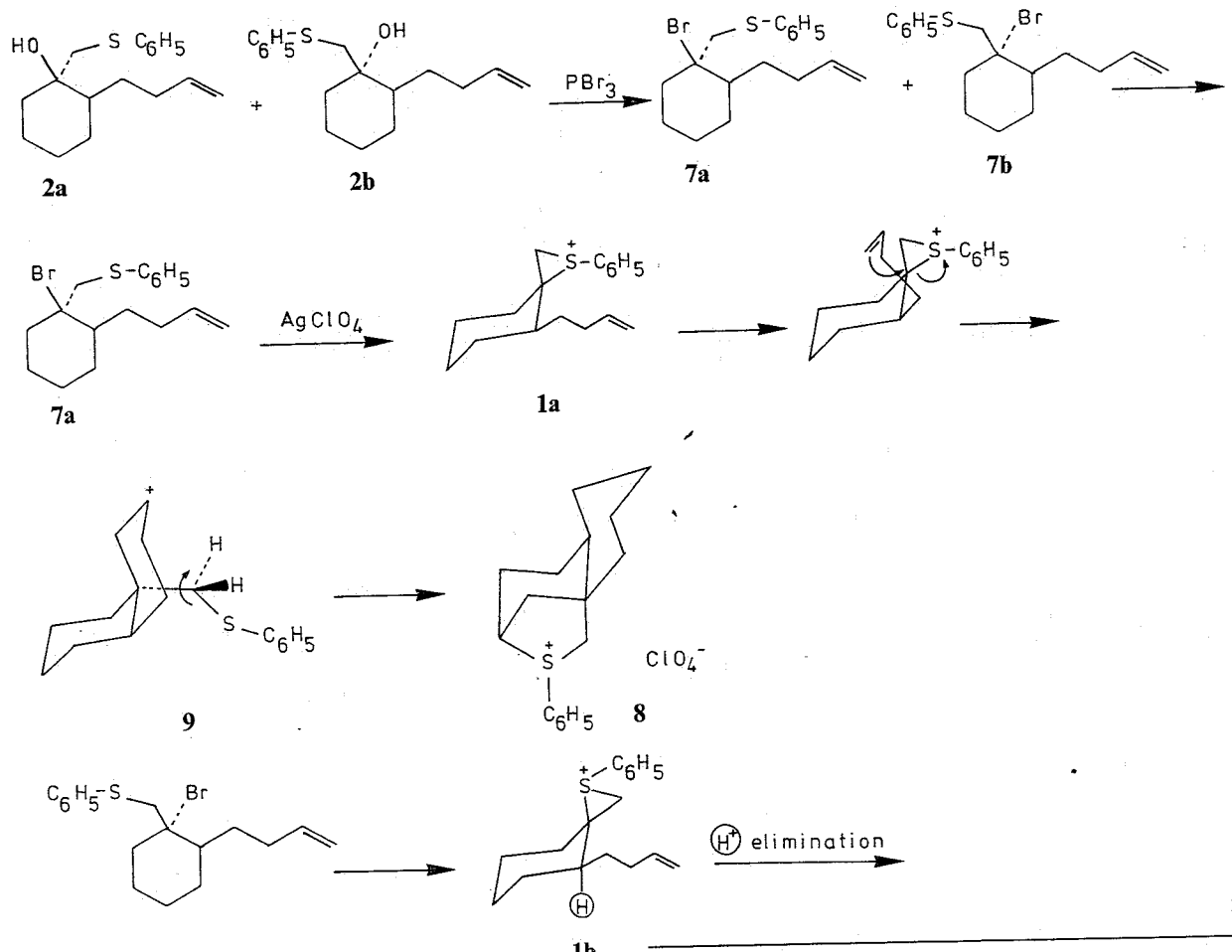
This compound was identical with a sample prepared according to literature[6]. In neither of the two formolyses was *trans*-ketone detected. The alkenic fraction contained cyclized and uncyclized products as could be seen by ^1H NMR.

In the alkenic region among other signals the characteristics of the terminal alkene were still observable, whereas the CH_2S resonances appeared at 3.5 ppm and at 3.0 ppm. Further exposure to the reaction conditions resulted in a decrease in the signals of the terminal alkene group and the peak at 3.5 ppm. Thus the uncyclized alkenes are reprotonated. The signal at 3.0 ppm conceivably arises from cyclized compounds. These results indicate that the ions **1a** and **1b** can equilibrate *via* the uncyclized alkenes prior to cyclization. In order to prevent the reprotonation and to investigate the cyclization of **1a** and **1b** separately, these ions had to be generated in the absence of acid. For this purpose **2a** and **2b** were converted into the corresponding bromides **7a** and **7b**, respectively.



7a **7b** **9** **8**

These compounds were brought to reaction with silver perchlorate in nitromethane containing $CaCO_3$ to prevent the formation of perchloric acid during the reaction. Under



2a **2b** **7a** **7b** **7a** **1a** **9** **8** **7b** **1b**

Scheme 6. Cyclization.

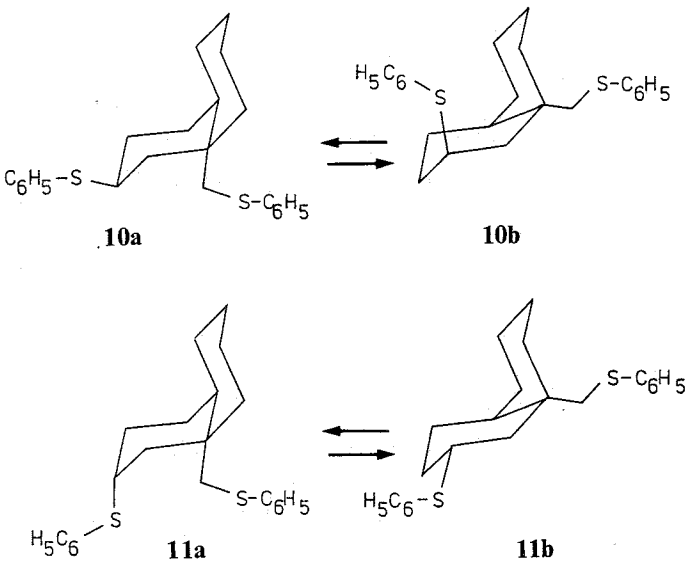
[5] Equatorial approach of phenylthiomethyllithium with respect to the carbonyl is favoured, as can be seen in the reaction of 4-*tert*-butyl ketone with this reagent.

[6] *A. J. Birch* and *R. Robinson*, J. Chem. Soc. 501 (1943).

these conditions the two isomers showed a different behaviour. Compound **7b** only gave uncyclized alkenes, while **7a** gave a mixture of cyclized and uncyclized alkenes and, in addition, a crystalline compound.

The most likely candidate for the latter compound is **8**, resulting from the cyclized compound **9** and intramolecular trapping of the secondary carbenium ion. It is noteworthy that treatment of the alcohols **2a** and **2b** with perchloric acid also afforded **8**. The ^{13}C NMR spectrum showed the correct multiplet structure. The carbons adjacent to the charged sulphur appeared at 67.8 ppm and 56.2 ppm with $^{13}C-^{1}H$ spin couplings of 155 Hz and 150 Hz, respectively. Furthermore, the signals at 51.2 ppm and 41.5 ppm for C(8a) and C(4a) are in good agreement with other *cis*-decalin (= *cis*-decahydronaphtalene) derivatives. In the ^{1}H NMR spectrum the signals for CH and CH_2 next to sulphur appeared at 4.53 (m) ppm and at 3.96 ppm. The phenyl hydrogens are located at 7.5 ppm, 0.5 ppm more downfield than in the phenylthio compounds.

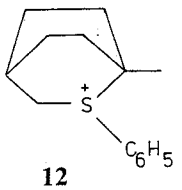
Reaction of **8** with potassium benzenethiolate gave **10**. The ^{13}C NMR spectrum of this compound is comparable with the one of 4a-methyl-*cis*-decalin in a frozen conformation, taking into account a large downfield effect of the phenylthio group on C(2), a 7 ppm downfield shift on C(1) and C(3), while the group at C(8a) in addition induces an upfield shift of 2 ppm at C(1), C(8) and C(4a) caused by *gauche* interactions. The isomeric structure **11** can be ruled out because in the most stable conformation of **11**, C(5) and C(6) should both be located near 22 ppm, whereas in this region only one signal was observed.



Scheme 4

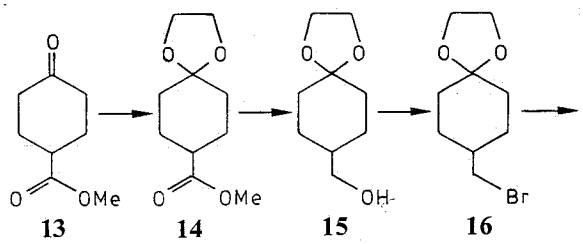
This ring opening *via* nucleophilic attack on the more substituted carbon is in disagreement with the expectation[11] that nucleophilic attack on the less substituted carbon is preferred. The ring opening resulting from attack on CH_2 should, however, give **11** in the strained conformation **11a**. Apparently, the high energy of this species is reflected in the transition state.

The reactions of the bromides **7a** *and* **7b** *with silver perchlorate clearly demonstrate that only* **1a** *undergoes cyclization and that in* **1b** *deprotonation is much faster than cyclization.* In the latter compound a *trans* elimination is allowed. The fact that sulphur is situated out of the cyclohexane ring may cause an acceleration of this reaction, because the orbital orientation of sulphur is presumably favourable for a concerned process. For this reason it was expected that elimination would be slower in compounds in which the sulphur is located in a position such as **12**.

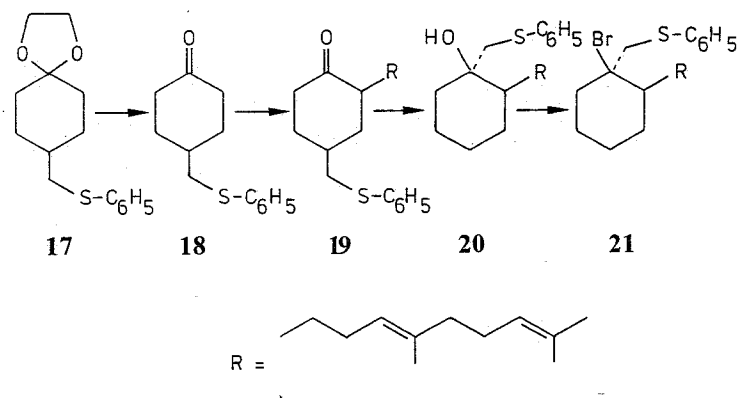


12

The location of the reaction centre is of interest because the cyclohexane ring is in a boat conformation and therefore offers the opportunity to simulate the enzymic cyclization to lanosterol. A special feature of this process is, besides the boat conformation of the B ring, that the formation of the C ring proceeds in an *anti-Markownikoff* way. Therefore bromide **21** was synthesized as outlined in Scheme 5.



13 **14** **15** **16**



17 **18** **19** **20** **21**

Scheme 5

The phenylthio group is needed for the synthesis of the bromide and for conversion to an intermediate like **12**. In a similar way, **21** was treated with silver perchlorate. The major product was alcohol **20**, presumably formed in the aqueous work-up[7]. No sulphonium compounds or compounds with aliphatic methyl groups were detected.

Discussion

There is no doubt that cyclization reactions are affected by participating groups. It seems likely that if the participating group is in the right orientation and highly reactive, the selective cyclization to *trans*-fused products may also proceed. Furthermore, an interference in a sequence of ring formations and then initiation of a new reaction will be possible as is demonstrated in the model compounds, in which cyclization is preceded by sulphur participation.

[11] *E. L. Elliel, R. O. Hutchins, R. Mebane* and *R. L. Willer*, J. Org. Chem. **41**, 1052 (1976).

[7] In a similar compound lacking the substituent at C(4) of the cyclohexane ring, cyclization gave a mixture of uncyclized alkenes and sulphonium ions. The structure of the latter compounds could not be completely clarified, but it appeared that one five-membered ring was formed.

A remarkable aspect of the formolyses is the formation of formates while the sulphur group is available as an intramolecular, nucleophilic group. The intermediacy of **8** can be excluded, because this compound is stable in formic acid. Apparently, the formate anion is close to the reactive carbon, indicating that the ion pair is not separated by the solvent. It has been demonstrated that collapse of such ion pairs is very rapid, perhaps proceeds even synchronously with the formation of the carbenium ion[8]. Furthermore, it must also be taken into account that for the formation of **8** a rotation – as indicated in Figure 1 – is required for trapping the carbenium ion by sulphur. Hence a concerted reaction is excluded.

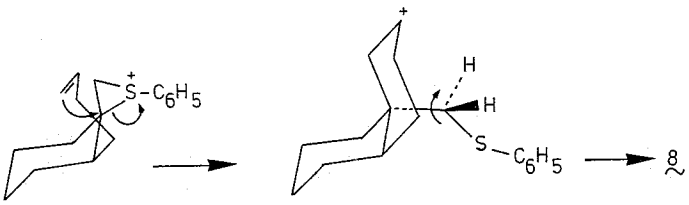


Fig. 1

The capture of carbenium ions formed by cyclization is probably more effective when the nucleophile is located in a position which is favourable for a concerted reaction.

Experimental part

General remarks

IR spectra were performed by a Perkin-Elmer 237 spectrometer. ^{1}H NMR spectra were recorded with a Varian EM 360A and a Varian T-60A spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured with a Varian HA100 spectrometer equipped with a Digilab FTS-NMR-3 pulsing and data system. Chemical shifts are reported relative to tetramethylsilane as external standard. Microanalyses were carried out in our laboratories by Messrs. *H. Eding* and *P. van den Bosch*.

2-(But-3-enyl)-1-(phenylthiomethyl)cyclohexanol (**2a** and **2b**) from *2-(but-3-enyl)cyclohexanone* (**3**)

2-(But-3-enyl)cyclohexanone was added to a stirred solution of phenylthiomethyllithium in THF at 0°C under nitrogen. The mixture was kept overnight at room temperature. Work-up of an ethereal extract afforded the crude product. Crystallization from pentane at −30°C gave the alcohols (94%). Pure samples were obtained by chromatography over silica gel using $CHCl_3$ as eluent, followed by recrystallization from pentane. IR: 3470 cm^{-1}. ^{1}H NMR: δ 3.13 (s, CH_2S); 4.7–5.1 (m, 2× olefin H); 5.3–6.2 (m, olefin H); 6.9–7.5 (m, Ar).

2-(But-3-enyl)methylenecyclohexane (**4**)

Ketone (**3**) (3.5 g, 23 mmol) was added to a stirred solution of methylenetriphenylphosphorane (29 mmol) in DMSO (45 ml) under nitrogen. After stirring for 2 h at 55°C the mixture was poured into water. Ethereal work-up afforded 3.0 g (85%) of **4**. ^{1}H NMR: δ 4.7–5.1 (m, 2× olefin H); 5.3–6.2 (m, olefin H); 4.3–4.7 (m, 2× olefin H).

4-(But-3-enyl)-1-oxaspiro[2.5]octane (**5**)

A solution of *m*-chloroperbenzoic acid (2.18 g, 0.013 mol) in CH_2Cl_2 (50 ml) was added to a stirred solution of diene **4** (1.5 g, 0.01 mol) in CH_2Cl_2 (60 ml). After 1 h at 0°C, excess peracid was destroyed by the addition of 5 ml of 10% aqueous sodium sulphite. After washing and drying, bulb to bulb distillation afforded 1.05 g (63%) of **5**. ^{1}H NMR: δ 4.7–5.2, 5.4–6.2 (see **2a** and **2b**); 2.3–2.8 (mixture of two AB quartets, epoxide); (m, 2× olefin H).

2-(But-3-enyl)-1-(phenylthiomethyl)cyclohexanol (**2a** *and* **2b**) *from* **5**

Epoxide **5** (1.05 g, 6.3 mmol) was added to an ice-cooled solution of benzenethiol (0.77 g, 7 mmol) and KOH (0.35 g, 6.3 mmol) in 80% aqueous methanol (30 ml). Stirring was continued for 1 h at 0°C and at room temperature overnight. Work-up of an ethereal extract followed by chromatography on silica gel gave 1.4 g (81%) of a mixture of **2a** and **2b**. Isomeric pure samples were obtained by chromatography under pressure [silica gel using hexane/ethyl acetate as eluent (9/1)].

Formolyses of **2a** *and* **2b** *and product characterization* (**6**)

A mixture of the alcohols (**2a**; **2b**: 2 g, 7.2 mmol) and formic acid (30 ml) containing acetic anhydride (3 ml) was refluxed for 1 h. The cooled solution was then poured into bicarbonate solution. After ethereal work-up the crude product was added to a stirred suspension of $LiAlH_4$ (1 g) in THF (40 ml). After hydrolysis, extraction with ether, drying and evaporation of the ether, the mixture was separated by chromatography on silica gel (pentane followed by chloroform) into an alkenic and an alcoholic fraction. The alcoholic fraction was added to 16 ml of Raney-nickel in 100 ml of methanol and refluxed for 18 h. After filtration the product was taken up in chloroform and washed with bicarbonate and water. Drying and concentration afforded 0.5 g of a mixture of alcohols. ^{1}H NMR: δ 0.90 and 0.95 (s, CH_3); 3.5–4.2 (m, CHO). A sample of these alcohols (0.15 g) in 7.5 ml of acetone was treated with an excess of Jones reagent. After 5 min, isopropyl alcohol was added. Ethereal work-up afforded, after purification by TLC, 0.11 g of ketone **6** which was identical (^{1}H and ^{13}C NMR) with a sample prepared by an alternative route[6]. No *trans* ketone [^{1}H NMR: δ 0.97 (CH_3)] was detected.

Cyclization of the alcohols **2a** *and* **2b** *with perchloric acid affording compound* **8**

To a stirred solution of the alcohols **2a** and **2b** (0.5 g, 1.8 mmol) in nitromethane under nitrogen was added 0.5 ml of perchloric acid (60%). After standing overnight the mixture was diluted with 30 ml of ether and washed with saturated bicarbonate solution. After stripping off the ether the nitromethane solution was extracted twice with hexane. Concentration of the hexane extract gave 0.21 g of a mixture of alkenes. ^{1}H NMR: δ 3.0 (m, SCH_2), 5.3–5.5 (m, olefin H). The nitromethane fraction was concentrated and the residue was taken up in hot ethanol. The product (0.22 g) crystallized on standing. M.p. 139.5–140.0°C (after recrystallization); anal. $C_{17}H_{23}ClO_4S$ (358.90): calcd C, 56.89; H, 6.46; Cl, 9.88; S, 9.94; found C, 56.95; H, 6.44; Cl, 9.88; S, 8.93.

1-Bromo-2-(but-3-enyl)-1-(phenylthiomethyl)cyclohexane (**7a** *and* **7b**)

To a stirred solution of alcohol **2a** or **2b** (2.15 g, 7.78 mmol) in ether (25 ml) was added an excess of PBr_3 (0.3 ml, 3.16 mmol) at room temperature. After standing overnight the solution was poured on to ice and bicarbonate. After extraction with ether and washing with bicarbonate and brine the solution was dried and concentrated to afford 2.33 g of bromide, which was contaminated with alkene (20%). The mixture was used directly or stored at −20°C. ^{1}H NMR: **7a**: δ 3.78 (AB quartet, CH_2S), 4.7–5.2 (m, 2× olefin H), 5.3–6.2 (m, olefin H), 6.9–7.6 (m, Ar); **7b**: 3.40 (s, CH_2S).

Sulphonium salt (**8**) *from reaction of* **7a** *and* **7b** *with* $AgClO_4$

In a typical experiment 0.5 g of **7a** and **7b** in nitromethane (15 ml) was added drop by drop with exclusion of light to a solution of $AgClO_4$ (0.45 g) in nitromethane (25 ml) in which $CaCO_3$ (100 mg) was suspended. After stirring for 15 min, the mixture was poured into 15 ml of a saturated bicarbonate solution overlaid with ether (25 ml). This mixture was stirred for 10 min and subsequently filtered over celite. The organic layer was washed with bicarbonate, dried and concentrated *in vacuo* to yield 0.45 g of product which consisted of two phases. The alkenic fraction was taken up in pentane. Concentration of the alkenic fraction afforded 0.332 g of a mixture of alkenes. The residue was taken up in hot ethanol. The sulphonium salt (0.115 g) crystallized on standing. The structure of the sulphonium salt was further confirmed by the ^{1}H NMR showing signals for CH and CH_2 next to the sulphur at 4.53 ppm (multiplet) and at 3.96 ppm (AB quartet with an extra coupling of 1 Hz at the downfield part). Furthermore, the ^{13}C NMR spectrum showed the correct number of singlets, doublets and triplets.

[8] *P. D. Bartlett, W. D. Closson* and *T. J. Cogdell*, J. Am. Chem. Soc. **87**, 1308 (1965).

Reaction of sulphonium salt **8** *with benzenethiolate giving* **10a** *and* **10b**

A solution of **8** (0.1 g, 0.28 mmol) in methanol (5 ml) was added to a stirred solution of benzenethiol (0.034 g, 0.31 mmol) and KOH (0.025 g, 0.45 mmol). After 2 h, water was added and work-up with ether followed by TLC afforded 95 mg (88%) of **10**. ^{1}H NMR: δ 3.10 (AB quartet, CH_2S); 2.9–3.6 (m, CHS).

Methyl 1,4-dioxaspiro[4,5]decane-8-carboxylate (**14**)

A solution of ketone **13** (10.5 g, 0.067 mol), prepared according to *Jung*[10], glycol and *p*-toluenesulphonic acid (0.1 g) was refluxed in 300 ml of benzene with continuous removal of water. When no more water separated the cooled solution was washed with bicarbonate and water. After drying and concentration, distillation afforded 12.5 g (93%) of **14**. B.p. (17 mm) 138–140°C. IR: 1740 cm^{-1}. ^{1}H NMR: δ 3.63 (s, CH_3O); 3.90 (s, dioxolanylidene).

8-(Hydroxymethyl)-1,4-dioxaspiro[4.5]decane (**15**)

A solution of ester **14** (10.0 g, 0.05 mol) in 50 ml of ether was added drop by drop to a stirred suspension of $LiAlH_4$ (1.75 g, 0.046 mol) in 200 ml of ether (under nitrogen). After the addition was complete, the mixture was refluxed for 1 h. The excess $LiAlH_4$ was destroyed by the subsequent addition of 1.75 ml of water, 1.75 ml of 15% NaOH and 1.75 ml of water. After filtration the resulting solution was washed with water and brine. Drying and concentration followed by distillation afforded 7.6 g (90%) of **15**. B.p. (8 mm) 138–142°C. IR: 3450 cm^{-1}. ^{1}H NMR: δ 3.90 (s, dioxolanylidene); 3.40 (d, CH_2OH).

8-(Bromomethyl)-1,4-dioxaspiro[4,5]decane (**16**)

To a solution of CBr_4 (20.3 g, 0.061 mol) (dried before use) and alcohol **15** (7.0 g, 0.04 mol) in 100 ml of benzene was added $P(C_6H_5)_3$ (7 g, 0.44 mol) in benzene. The mixture was stirred for 2 h and allowed to stand overnight. Pentane was added and the precipitated $O{=}P(C_6H_5)_3$ was removed by filtration. Concentration followed by chromatography on silica gel using hexane/ethyl acetate (3/1) as eluent gave 6.8 g (69%) of **16**. ^{1}H NMR: δ 3.90 (s, dioxolanylidene); 3.28 (d, CH_2Br).

8-(Phenylthiomethyl)-1,4-dioxaspiro[4,5]decane (**17**)

A solution of bromide **16** (6.5 g, 0.027 mol) was added to a sodium benzenethiolate solution (prepared *in situ* by the subsequent addition of Na (0.7 g, 0.030 mol) and benzenethiol (3.04 g, 0.033 mol)) in ethanol (50 ml). The mixture was left overnight, water was added and normal ethereal work-up afforded 8.5 g of **17** which was used without purification. ^{1}H NMR: δ 2.85 (d, CH_2S); 3.90 (s, dioxolanylidene); 7.1–7.5 (m, Ar).

4-(Phenylthiomethyl)cyclohexanone (**18**)

Sulphide **17** (8.5 g, crude product) was dissolved in a mixture of 200 ml of acetone and 75 ml of 10% HCl. The solution was refluxed for 1 h to afford after work-up with ether and chromatography on silica gel ($CHCl_3$ as eluent) 5.1 g of **18** (84% on the basis of bromide **16**). IR: 1710 cm^{-1}). ^{1}H NMR: δ 2.92 (d, CH_2S); 7.1–7.5 (m, Ar).

2-(4,8-Dimethylnona-3,6-dienyl)-4-(phenylthiomethyl)cyclohexanone (**19**)

Compound **19** was prepared in 35% yield by the method of *Harding* et al.[9]. The *cis* and *trans* isomers were formed in about equal amounts. Isomerization of 1 g of ketone in 50 ml of *t*-BuOH containing 0.1 g of *t*-BuOK for 2.5 h changed the ratio to 1/5 in favour of the *cis* isomer. Pure products were obtained by chromatography on silica gel using ethyl acetate/hexane (1/4) as eluent. ^{1}H NMR: *trans:* δ 1.58, 1.67, 5.02, 2.93 (d, CH_2S); 7.1–7.5 (m, Ar); *cis:* as for *trans* with 2.85 (d) instead of 2.93.

2-t-(4,8-Dimethylnona-3,6-dienyl)-4-c-bis(phenylthiomethyl)-1-r-cyclohexanol (**20**)

Prepared as for **2a** and **2b** from *cis* **19** in 43% yield. ^{1}H NMR: δ 1.58, 1.67, 5.02, 7.1–7.5 (as for **19**); 2.83 (d, CH_2S); 3.12 (AB quartet, CH_2S).

1-n-Bromo-2-t-(dimethylnona-3,8-dienyl)-4-c-bis(phenylthiomethyl)cyclohexane (**21**)

Prepared as for **7a** and **7b** (quantitatively). ^{1}H NMR: δ 1.58, 1.67, 5.02, 7.1–7.5 (as for **20**), 2.83 (d, CH_2S); 3.68 (AB quartet, CH_2S).

Formation of a bridged sulphonium ion (**12**) *from an open carbenium ion*

To a stirred solution of CH_3MgI, prepared from Mg (0.5 g, 0.021 mol) and CH_3I (2.5 g, 0.018 mol), in 20 ml of ether was added a solution of **18** (1 g, 0.0045 mol) in ether (5 ml). After 1 h at room temperature the mixture was poured over ice. Work-up of the ethereal extract afforded 1.1 g (quantitatively) of a mixture of (*cis* and *trans*) alcohols. ^{1}H NMR: δ 1.20 and 1.22 (s, CH_3); 2.83 (broad, CH_2S); 7.1–7.5 (m, Ar). The formation of a bridged sulphonium ion (**12**) from an open carbenium ion could be demonstrated by the reaction of a mixture of alcohols prepared from ketone **18**, with perchloric acid in CD_3NO_2. ^{1}H NMR: δ 7.77 (m, phenyl H); 3.87 (d, *J* 3 Hz CH_2 next to S); 1.21 (CH_3).

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Synthesis of fragments of human β-lipotropin, β_h-LPH. Part II†. The synthesis of β_h-LPH-(61–91), β_h-endorphin

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Abstract. The classical fragment condensation approach was used to synthesize the hentriacontapeptide human β-endorphin [β_h-LPH-(61–91)].

Introduction

Approximately at the same time but independently, several groups of investigators[1-6] were involved in isolating peptides, which showed opiate-like activity, from brain and pituitary tissue.

† Fort part I see: Recl. Trav. Chim. Pays-Bas **98**, 571 (1979).

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