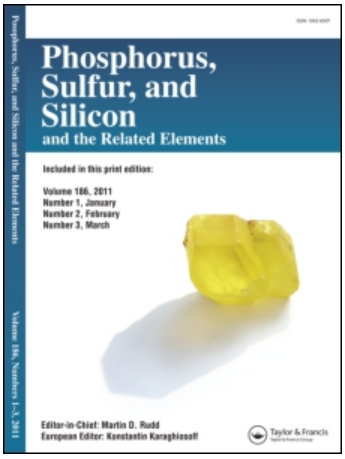

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Thioaldehydes in Synthesis

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THIOALDEHYDES IN SYNTHESIS

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Abstract Thioaldehydes, ZCHS, where Z is an electron-withdrawing group, have been prepared by base-mediated, 1,2-elimination reactions of sulfenyl derivatives, ZCH_2SX, where X is a heteroatomic leaving group, *e.g.* Cl, *N*-phthaloyl, SO_2Tol and SO_3Na. The transient thioaldehydes were trapped *in situ* with conjugated dienes to give Diels-Alder cycloadducts. The cycloadducts of anthracene, 9,10-dimethylanthracene and cyclopentadiene dissociate in toluene at 111°C and thereby serve as synthetically useful, auxiliary precursors of the labile thials. α-Alkylation of anthracene adducts provides precursors of thioketones and *S*-oxidation precursors of sulfines. Anthracene and cyclopentadiene adducts of unsaturated esters of thioxoacetic acid, $RO_2C.CHS$, have been used to study intramolecular ene cyclisations of thioaldehydes.

The Diels-Alder adducts of thioaldehydes have been used in the synthesis of new opiate analgesics, derived from thebaine, and of 6-thiashikimic acid, a sulfur analogue of the key intermediate in the biosynthesis of aromatic amino acids.

INTRODUCTION

It has long been known that simple thioaldehydes polymerise rapidly in the condensed state and are too reactive to be isolated or manipulated at ambient temperatures. The first well characterised thioaldehyde monomers were stabilised by strongly electron-donating groups[1] but, more recently, sterically stabilised thioaldehydes have been described. Thus, both 2,4,6-tri-*tert*-butylthiobenzaldehyde[2] and tris(trimethylsilyl)ethanethial[3] were obtained as monomers at room temperature, while 2,2-dimethylpropanethial[4] persisted as the monomer for some time in dilute solutions. Moreover, it has been shown during the past ten years that simple, transient thioaldehydes may be exploited in synthesis providing that they are generated and trapped *in situ* by suitable co-reactants. In 1982, Vedejs *et al.*[5] reported that thioaldehydes, generated by photolysis of phenacyl sulfides, may be trapped as Diels-Alder cycloadducts, and Baldwin and Lopez[6] described similar studies, employing the thermolysis of thiosulfinates to form the thioaldehydes. Soon after, we reported[7] the preparation of transient, dienophilic thioaldehydes by base-mediated, 1,2-elimination of sulfenyl derivatives. Since then, many new methods[8]

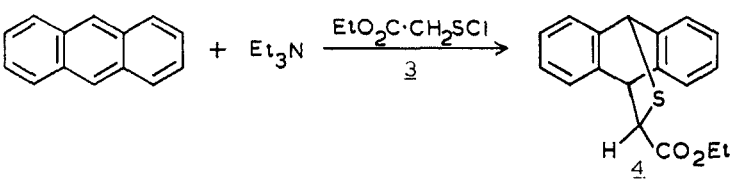
for the generation of reactive thials have been developed, and have recently been reviewed.[9] Further, α-silylthioketones,[10] the synthetic equivalents of thioaldehydes, have become readily accessible.

THIOALDEHYDES AS DIENOPHILES

Thioaldehydes, especially those ZCHS 2 having electron-withdrawing groups Z, are valuable heterodienophiles in synthesis. The thial π-bond is weak and reactive, the steric demands of mono-substituted dienophiles are small, and sulfur in the derived cycloadducts may be removed reductively or retained and used to facilitate further transformations, for example by enhancing the acidity of the adjacent, methine hydrogen. We have developed a range of methods for the preparation of the thioaldehydes 2 from sulphenyl derivatives 1 by 1,2-elimination, mediated, or

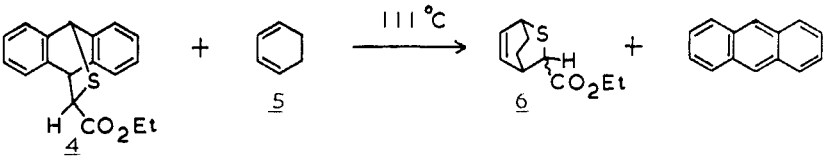
$$\underset{1}{ZCH_2SX} + Et_3N \longrightarrow \underset{2}{ZCHS} + Et_3\overset{+}{N}H\,X^-$$

catalysed, by triethylamine. Sulfenyl chlorides[7] (1 ; X=Cl) and phthalimides[11] (1 ; X=*N*-phthaloyl) were prepared from thiols or disulfides, whereas thiotosylates[12] (1; X=SO_2Tol) and thiosulfate *S*-esters,[13] Bunte salts (1 ; X=SO_3Na) were more conveniently prepared from sulfur-free precursors, the alkyl halides ZCH_2Br or ZCH_2Cl. The liberated thioaldehydes were trapped generally in good yields with simple acyclic or cyclic dienes. However, with sulfenyl chlorides (1 ; X=Cl) by-products sometimes arose from attack of the sulfenyl chloride on the diene, in competition with elimination to form the thioaldehydes. An alternative strategy employed the cycloadducts of anthracene, 9,10-dimethylanthracene, or cyclopentadiene as auxiliary precursors of the thioaldehydes, in the following way.

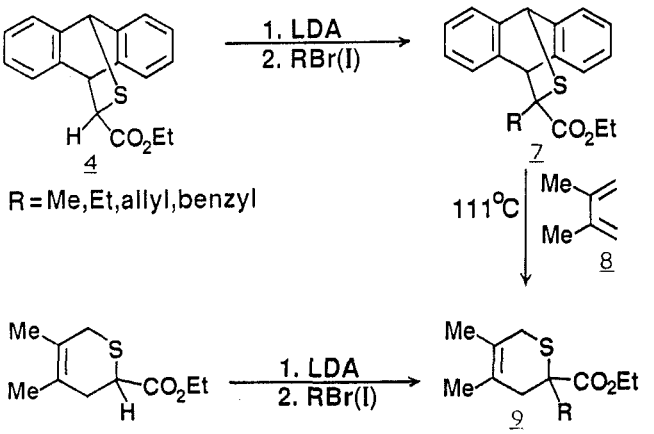


4

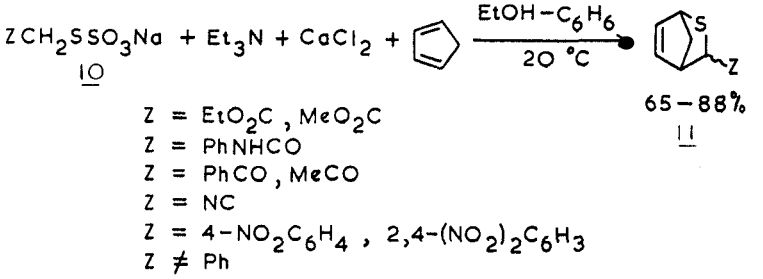
For example, addition of the sulfenyl chloride 3 to a mixture of anthracene and triethylamine in chloroform, with heating under reflux, gave the crystalline cycloadduct[7] 4 in 60-70% yield.[14] The adduct was stable at room temperature, but it dissociated into its components at a convenient rate when heated in toluene under



reflux (111°C). Thus, equimolecular amounts of the adduct 4 and cyclohexa-1,3-diene 5 gave, at 111°C, the cycloadduct 6, largely the *endo* isomer, in high yield, along with anthracene.[7] Recently,[15] alkylation of the anthracene cycloadduct 4 has been effected efficiently with lithium diisopropylamide (LDA) and a range of alkyl halides. Gratifyingly, the products 7 also undergo retro-Diels-Alder cleavage at 111°C, and thereby serve as auxiliary precursors for the corresponding, reactive thioketones, $RCSCO_2Et$. For example, the adducts 7 and 2,3-dimethylbuta-1,3-diene 8 gave the cycloadducts 9 of the diene efficiently.



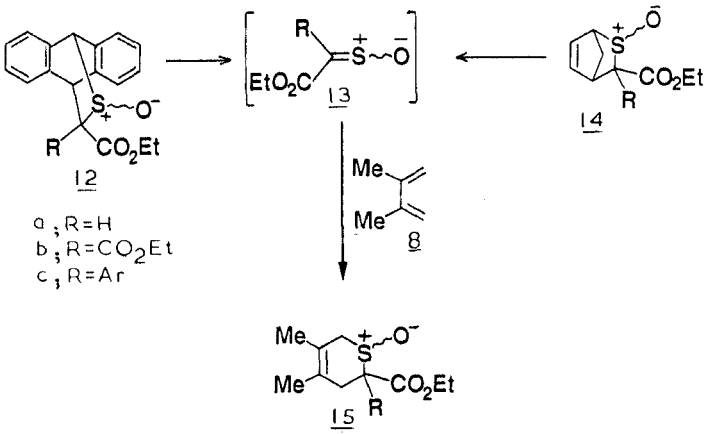
Cyclopentadiene is the cheapest and most reactive diene for use in Diels-Alder reactions. Also, strain in the bridged cycloadducts facilitates retro-Diels-Alder cleavage. The cycloadducts 11 of a range of thioaldehydes, ZCHS, were most conveniently prepared,[13] as mixtures of *endo* and *exo* isomers, from the crystalline Bunte salts 10. Calcium chloride was added to the reaction mixtures to remove the nucleophilic sulfite dianion formed by elimination. Elimination of the doubly charged leaving group, SO_3^{2-}, proceeds easily when the acidity of the methylene group is enhanced by an electron-withdrawing group, Z; the method failed for Z=Ph rather than 4-$NO_2C_6H_4$. Retro-Diels-Alder cleavage of all the



cyclopentadiene adducts 11 occurred in refluxing toluene, and thermal transfer of the liberated thioaldehydes to dimethylbutadiene was achieved in good yield, the only significant by-product being the volatile cyclopentadiene. When heated alone, the *endo* and *exo* cycloadducts (11; $Z=CO_2Et$) separately gave the same, *exo*-rich, equilibrium mixture by dissociation and recombination. The retro-Diels-Alder strategy for generating thioaldehydes reversibly from auxiliary precursors ensures that the concentration of the labile species remains very low. For this reason, polymerisation is not a serious problem even when the thioaldehyde is to be trapped by a relatively unreactive coreactant.

THIOALDEHYDE *S*-OXIDES (SULFINES)

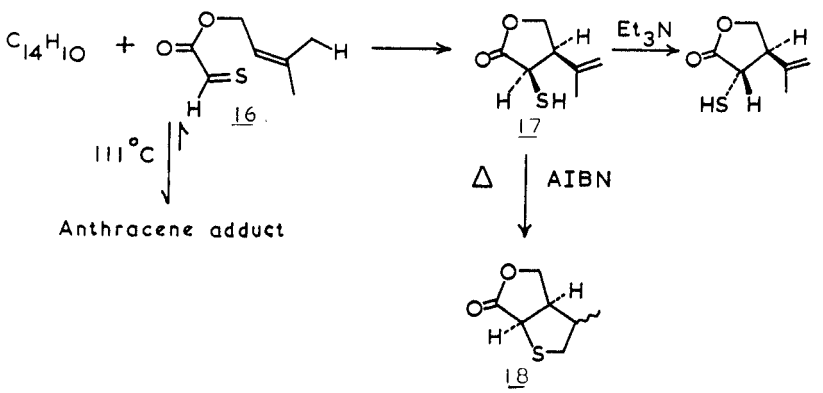
The chemistry of thiocarbonyl *S*-oxides, sulfines, has been extensively studied; ten methods for generating sulfines were listed in Zwanenburg' s authoritative 1982 review.[16] We reasoned that the *S*-oxides of the cycloadducts of thioaldehydes and



anthracene and cyclopentadiene might, like the corresponding sulfides, undergo thermal cleavage to liberate sulfines under 'clean' conditions. This proved to be so, indeed cleavage occurred at temperatures lower than those required for the sulfides.[17] For example, the *trans*-*S*-oxide 12a, when heated at 60°C with dimethylbutadiene 8, gave the *trans*-cycloadduct 15a of the sulfine 13a. The corresponding *cis*-*S*-oxide 12a required a higher temperature, 80°C, to effect retro-Diels-Alder cleavage. Similar results were obtained with the cyclopentadiene cycloadduct *S*-oxides 14, although complications can arise from intramolecular rearrangement[18,19] of *endo*-sulfoxides of the type 14. The cycloadducts[19] 12b and 14b of diethyl thioxomalonate *S*-oxide 13b also cleaved thermally, as did corresponding adducts[20] of aryl sulfines 13c. The retro-Diels-Alder route to sulfines should allow the chemistry of these labile species to be studied under conditions of controlled release in inert solvents.

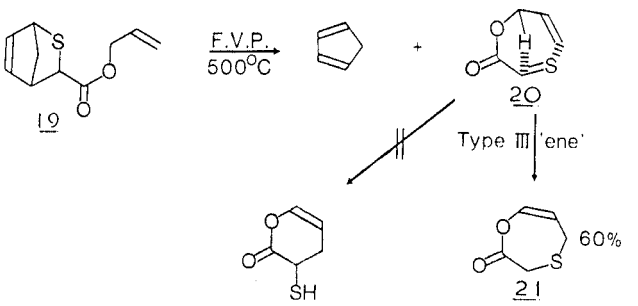
ENE REACTIONS

Baldwin and Lopez[6] first demonstrated the intermolecular ene reaction of a thioaldehyde. Thiobenzaldehyde, generated in the presence of β-pinene by thermolysis of *S*-benzyl phenylmethanethiosulfinate, gave ene products predomin-



antly by C-C bond formation. In contrast, we found[7] that ethyl thioxoacetate (2; Z=EtO2C), formed by cleavage of the anthracene adduct 4, reacted with β-pinene mainly by C-S bond formation. However, the outcome of intramolecular ene reactions was dictated, as expected, by the effects of ring size, the conformation of transition states and the accessibility of the obligatory, allylic hydrogen. The crystalline acids derived from the cycloadduct esters 4 and 6 were converted into

series of esters with various unsaturated alcohols. Thermolysis of these esters gave unsaturated thioxoacetates which then underwent intramolecular ene reactions. Allylic and homoallylic thioxoacetates, with appropriately placed allylic hydrogens, gave -mercaptolactones by Type I and Type II ene reactions.[14] For example, the prenyl derivative 16 gave the α-mercaptolactone 17 as the only significant product. The *cis*-configuration 17 was confirmed when the lactone was epimerised with triethylamine to form the stable *trans*-isomer. Radical-initiated cyclisation of the thiol 17 gave the bicyclic epimers 18. Other allylic or homoallylic thioxoacetate esters gave α-mercapto- γ- or δ-lactones by Type I or Type II intramolecular ene reactions. In contrast, thioxoacetate esters with terminal double bonds cyclised by Type III ene reactions to form 3-thia-alk-5-enolides.[21] In this study, flash vacuum pyrolysis (FVP) was required to accelerate the slow ene cyclisation and prevent retardation by recapture of the thioaldehyde by anthracene or cyclopentadiene. Thus, when the allyl ester 19 was subjected to FVP at 500°C and 10^{-3} mbar, the transient thioaldehyde 20 cyclised to give the thialactone 21 exclusively. A homologous series of cyclopentadiene derivatives gave thialactones with 6- to 11-membered rings in useful preparative yields (*ca.* 60%).

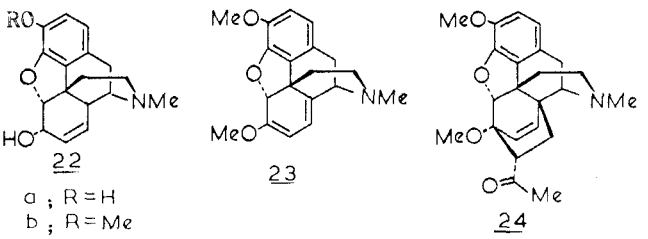


19 20 21

The recent application of thioaldehydes in two areas of natural product synthesis will now be described.

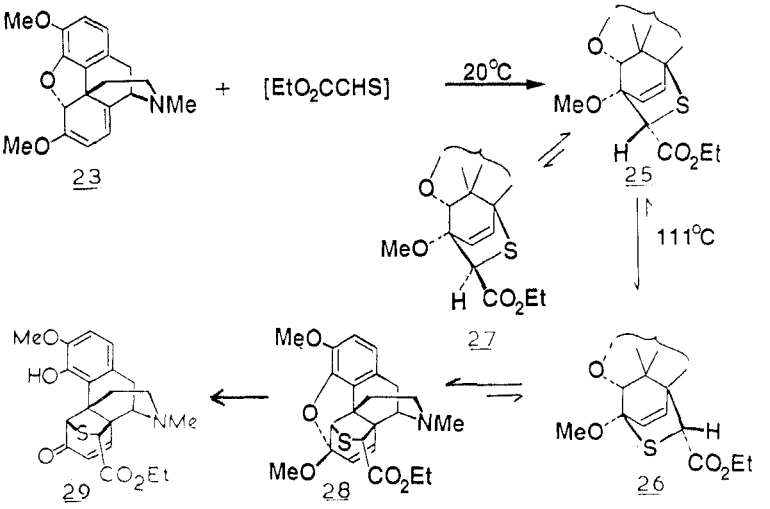
MORPHINE ALKALOIDS

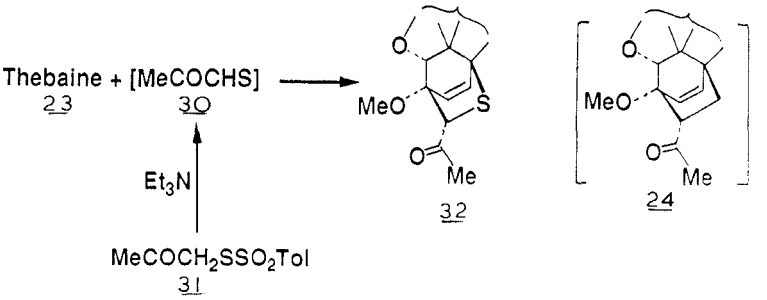
Morphine 22a and codeine 22b are still widely used as analgesics. However, many new, synthetic morphinan derivatives have partially replaced the traditional opiates 22 in modern medicine. Nevertheless, the search for more selective analgesics continues. The opium alkaloid thebaine 23 is an especially versatile starting material. In their seminal studies, Bentley *et al.* investigated the chemistry of



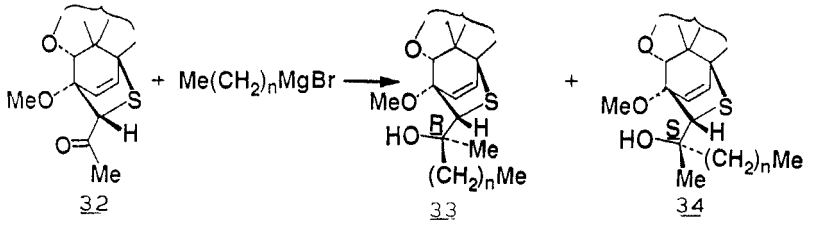
thevinone 24, the Diels-Alder adduct of thebaine 23 and methyl vinyl ketone. They prepared a series of potent analgesic, tertiary alcohols (thevinols) by treatment of thevinone 24 with Grignard reagents.[22] Clinically useful derivatives emerged from these investigations; etorphine in veterinary medicine and buprenorphine in man. The Diels-Alder reactions of thebaine with thioaldehydes were studied, in collaboration with Reckitt and Colman Ltd., in the hope of observing receptor, and perhaps functional, selectivity in the sulfur analogues of known analgesics.

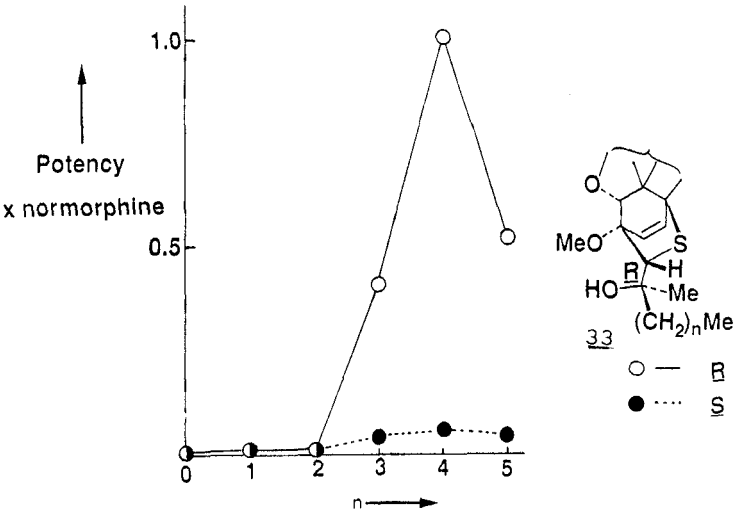
Ethyl thioxoacetate, generated from the sulfenyl chloride 3, was trapped *in situ* by thebaine 23 to give very largely a single regio- and stereo-isomer[7] 25. When this was heated in toluene under reflux, it rearranged, by dissociation and recombination, to afford the regioisomer 26 in good yield. The epimer 27 of 25 was observed as a transient species during this transformation.[23] However, prolonged heating in toluene generated a fourth isomer 28, the most stable of the thermally





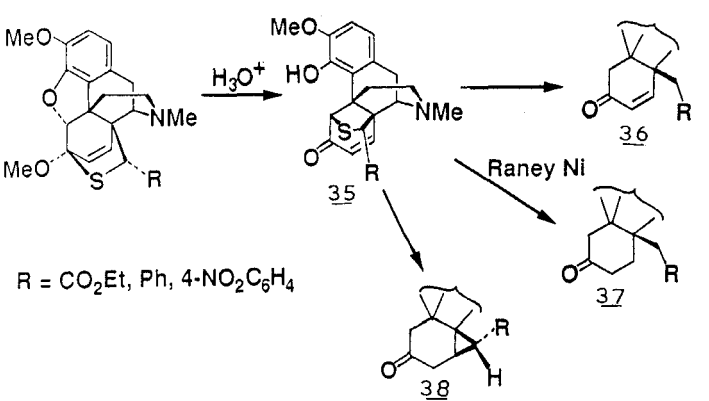
connected set. This acetal 28 was hydrolysed with acid to give the ketone 29, obtainable more directly from the isomer 26 under the same conditions. Similarly, thebaine and 2-oxopropanethial 30, generated from the thiotosylate 31, gave thiathevinone[23] 32 (*cf.* thevinone 24). Thiathevinone was then converted with a homologous series of Grignard reagents into the corresponding, epimeric 20*R*- 33 and 20*S*-thiathevinols 34. Unexpectedly, the epimers 33 and 34 were formed in similar amounts whereas thevinone 24 gave 20*R*-thevinols highly stereoselectively. The analgesic potencies of both series of thiathevinols were measured with guinea-pig ileum tissue preparations, employing *N*-normorphine as a standard. The results are illustrated in the Figure. The 20*R*-thiathevinols 33 were much more potent than their epimers 34, and potency in both series rose then fell with increasing chain length. In these respects, the new analgesics behaved like the original thevinols. However, replacement of a methylene group by sulfur caused a large reduction in overall analgesic potency. Nevertheless, the 20*R*-pentyl derivative (33; n=4) was about equipotent with normorphine, *i.e.* substantially more potent than codeine 22b, a more apposite standard for phenolic methyl ethers.



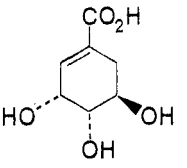


FIGURE

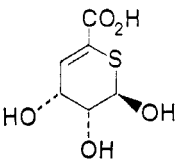
A related study[24] exploited rearranged cycloadducts of thebaine, of the types 26 and 28, as convenient intermediates for the preparation of 14β-alkyl or -aralkylcodeine derivatives. It was hoped that reductive desulfurisation would lead directly to compounds of the required type. However, treatment of the ester 26 with Raney nickel in ethanol gave complex mixtures arising from concurrent rearrangement, solvolysis and reduction. Better results were obtained with the rearranged enones 35. Again, mixtures were commonly observed but, with choice of conditions and the substituent R, it was possible to isolate major products, for example the phenols (36; R=CO_2Et), (37; R=CO_2Et) and (38; R=Ph). While



this work was in progress, Revesz *et al.*[25] reported related studies, leading from cycloadducts of *N*-cyclopropylmethyl-*N*-northebaine with thiobenzaldehyde and various alkanethials, to 14 -benzyl- and -alkyl-morphinans.



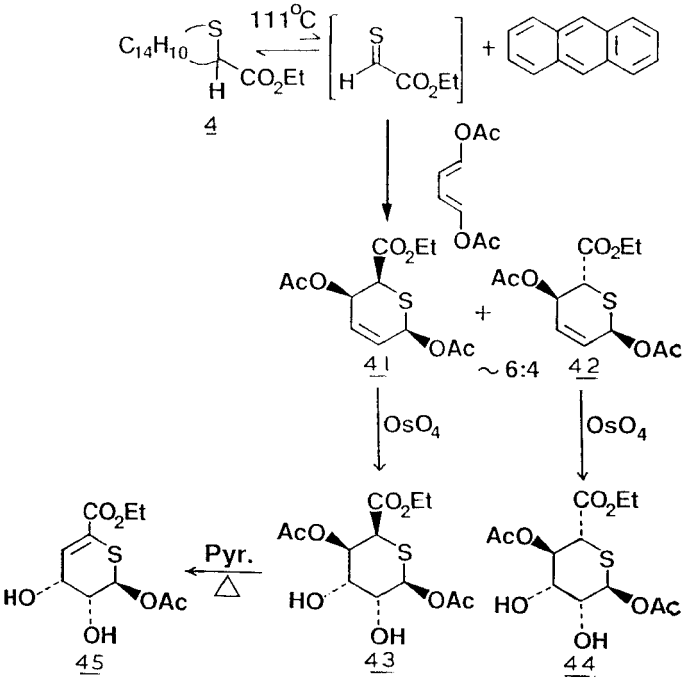
Shikimic acid
39



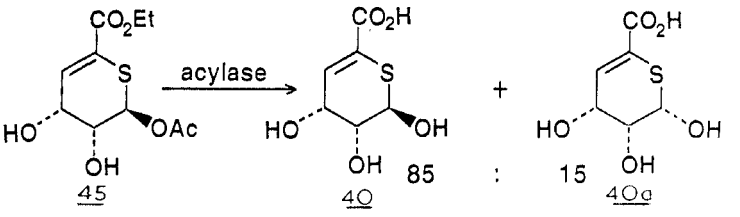
Thiashikimic acid
40

THIASHIKIMIC ACID

Shikimic acid 39 is a pivotal intermediate in the biosynthesis of aromatic amino acids from carbohydrates in organisms of the plant Kingdom.[26] In principle, structural analogues of shikimic acid might act as inhibitors for enzymes of the biosynthetic pathways and thereby have potential use in crop protection. We considered that 6-thiashikimic acid 40 would be an especially interesting analogue.



Replacement of the methylene group by sulfur would have the minimal effect on the shape, lipophilicity and functionality of shikimic acid and yet would radically affect its chemical reactivity; thiashikimic acid is a hemiacetal of an enethiol and lacks the hydrogen at position 6 which is removed later on the biosynthetic pathway. The synthesis of racemic thiashikimic acid was modelled on syntheses of shikimic acid itself.[27] Thus the anthracene adduct 4 was heated with 1,4-diacetoxybutadiene to give a mixture of cycloadducts 41 and 42 in good yield. Each was converted into the corresponding *cis*-diol with osmium tetroxide. The diol 43 underwent *trans*-elimination of acetic acid in hot pyridine to give the required ethyl ester acetate[28] 45. Attempts to hydrolyse the ester groups under even mild alkaline conditions led



to decomposition of the molecule. However, enzyme-catalysed hydrolysis gave thiashikimic acid[29] as a mixture of anomers 40 and 40a, which were stable at pH 7 and could be purified by HPLC. The anomer 40, having an axial 5-hydroxy group, was the major constituent (85%) of the equilibrium mixture. It is not yet known whether the product is still racemic; enzymic hydrolysis may have been stereoselective.

CONCLUSION

The route to thioaldehydes by 1,2-elimination of sulfenyl derivatives has been extended successfully to the preparation of selenoaldehydes.[30] Again, other methods[31] are now available for the study of these labile species. No doubt, both thio- and seleno-aldehydes will be exploited widely in organic synthesis in the future.

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