SYNTHETIC APPROACHES TO THIATROPANES AND RELATED HOMOLOGUES

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A C K N O W L E D G E M E N T S

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C O N T E N T S

SUMMARY

The synthesis of 8-thiabicyclo[3.2.1]octanes, as structural mimics of the tropane alkaloids, was undertaken and, in particular, the feasibility of functional group modification at certain ring positions was investigated.

In Chapter 1, functional group changes were effected at C(6) and C(7) of 6,7-dichloro-8-thiabicyclo[3.2.1]octane (107) which reacted with weaker nucleophiles, such as water, alcohols, catechol, 1,2-diaminobenzene, ethanoic acid and ethanoate ion, forming substitution products with stereochemical retention, replacements generally being faster in the presence of zinc metal. Substitution did not proceed at all with the stronger nucleophiles AlH_4^-, $\bar{O}R$, I^-, or Et_3N. In presence of zinc, (107) underwent elimination with CN^-, 1,2-diaminoethane and glycine forming (114). With phenol/Zn, both substitution and elimiantion took place to yield (134). (107) underwent a novel stereospecific oxidation-dichlorination with NaOH forming (126). Similar reactivity was observed for the homologue, 7,8-dichloro-9-thiabicyclo[4.2.1]nonane (111), the reactivity of which is discussed in Chapter 2. (111) however, failed to react with NaOH. In Chapter 3, the addition of SCl_2 to cyclohepta-3,5-dienol (108) was investigated, as a synthetic approach to C(3)-oxygenated thiatropanes. The adduct (152) was formed as a single diastereoisomer but only in modest yield. (152) underwent esterification with tiglic acid (or acid chloride) in low yield forming

(156), as a sulphur analogue of the antiparkinson drug tropigline (14). Like (107) and (111), (152) underwent elimination with 1,2-diaminoethane/Zn forming (160) but (152) failed to react with $LiAlH_4$ or with NaOH.

Also discussed in Chapter 3, the attempts to place a methoxycarbonyl group at C(2) of the keto-thioether (110) via its enolate or enamines with pyrrolidine and morpholine were unsuccessful. (110) appears to be stereochemically hindered to reaction with these secondary amines but does form an oxine (162). The attempted methylation of the thioether bridges of (107) and (110) with CH_3I in neutral conditions was also unsuccessful.

I N T R O D U C T I O N

TROPANE ALKALOIDS AND RELATED COMPOUNDS - A REVIEW

The tropane alkaloids are a closely related group of nitrogenous compounds comprising natural products of the Convolvulaceae, Dioscoraceae, Erythroxylaceae and Solanaceae families together with a growing number of synthetic analogues.

They have attracted interest because of their pharmacological activity and reviews of the history, chemistry and pharmacology of the principal tropane alkaloids have been published in the years 1950[1], 1965[2], 1970[3] and 1977[4]. Selected tropane structures (1-38) are listed, in order of year of structural assignment, in Table 1. Some structures of synthetic origin are included.

The tropane alkaloids are frequently esters of common organic acids (atropic (39), benzoic (40) (see Scheme 6), cinnamic (41), ethanoic, (4-hydroxyphenyl)-ethanoic, isovaleric (42), mandelic (43), 4-methoxybenzoic, 2-methylbutanoic (44), 2-methylpropanoic, 2-phenylethanoic, tiglic (45), 3,4,5-trimethoxybenzoic, 3',4',5'-trimethoxycinnamic, tropic (46) (see Scheme 6), truxillic (47), veratric (48) and others) combined with one of a series of nitrogen-bridged bicyclic hydroxyamines (methylecgonine (49), nortropine (50), pseudotropine (51), scopine (52), tropine (53) (see Scheme 1) and others).

Tropine (53) is biogenetically formed[5] (Scheme 1) from acetate and ornithine (54). The latter is methylated at an early stage to α-N-methylornithine (55) which undergoes

δ-transamination to α-N-methylglutamic mono-aldehyde (56). Cyclisation affords the N-methylpyrrolinium salt (57) which combines with acetoacetate in a Mannich-like condensation. Oxidative decarboxylation of (58) leading to the substituted N-methyl pyrrolinium salt (59) is followed by a second cyclisation forming tropan-3-one-2-carboxylic acid (60). Tropine (53) is formed by decarboxylation of (60) followed by reduction of the resulting ketone, tropinone (61). Keto-acid (60) is also regarded[5] as the biogenetic precursor of ecgonine (2) and β-cocaine (8) (Scheme 2). Esterification of tropine (53) with tropic acid gives[5] (Scheme 3) hyoscyamine (4), the most widely distributed alkaloid of this group. Labelled at C-2, α-N-methylornithine (55) (see Scheme 1) was shown to be incorporated into the tropine moiety of hyoscyamine without loss of the N-methyl group and the configuration of the α-carbon was retained.

The administration of 1,4-^{14}C-putrescine (62) (Scheme 4) to Datura species yielded tropine (53) labelled at C-1 and C-5 which indicates an alternative biogenetic route to (53) via (59), not involving decarboxylation.

Hyoscyamine (4) was shown[5] (Scheme 5) to be a precursor of hyoscine (1), two intermediates in this interconversion being 6,7-dehydrohyoscyamine (63) and 6-hydroxyhyoscyamine (64). The tropic and moiety of hyoscyamine (4) and hyoscine (1) is derived (Scheme 6) from phenylalanine (65) by an intramolecular rearrangement of the side chain. 2-Phenylethanoic

acid (66) also serves as a precursor of tropic acid. However, since phenylalanine is a much more efficient precursor, it seems probable that the 2-phenylethanoic acid is converted to phenylalanine prior to its incorporation into tropic acid. The carboxylation of 2-phenylethanoic acid to phenyl pyruvic acid (67) and thence to phenylalanine has been demonstrated [6] in some bacteria. Phenylalanine was also found to be the source of the benzoic acid moiety of β-cocaine (8) (Scheme 6).

Tiglic acid esters of hydroxytropanes constitute a group of minor alkaloids of Datura and Duboisia species. In Datura ferox and Dinnoxia, 7-hydroxy-3,6-di(tiglyloxy)tropane (68) is formed (Scheme 7) in the roots and is then translocated to the leaves where hydrolysis occurs yielding meteloidine (3) and teloidine (28).

Tiglic acid (45) is derived[5] from isoleucine (69). The metabolic conversion (Scheme 8) of isoleucine to tiglic acid, via (70) and (44), has been established[6] in animals and, in principle, could be operative in plant cells. It may be significant that 2-methylbutanoic acid (44) is found esterified with tropane bases in some Duboisia species.

Nortropine (50) and pseudonortropine (71) were shown to be diastereoisomeric at C(3). Stereospecific intramolecular N → O acyl migration took place (Scheme 9) when N-acetyl-nor-pseudotropine hydrochloride (72) was heated giving O-acetyl-nor-pseudotropine hydrochloride (73) whereas N-acetyl

nortropine hydrochloride (75) failed to react under the same conditions. This behaviour is evidence for the cis or β configuration of the C(3) hydroxyl relative to the nitrogen bridge in nor-pseudotropine (71). The rearrangement requires a transitory ring closure to a 2-hydroxytetrahydro-1,3-oxazine (74) involving the boat form of the tropane skeleton in the transition state, in which the N-acyl and hydroxyl groups are in steric proximity.

The epimeric benzoates behaved similarly[3]. Norpseudotropine (71) reacted with p-nitrobenzaldehyde to form the tetrahydrooxazine (76), structurally related to intermediate (74), whereas nortropine (50), under the same conditions, afforded only N-p-nitrobenzoyl nortropine (77).

The same diastereoisomeric relationship between tropine (53) and pseudotropine (51) was first recognised by Willstäter[7] and the stereochemical assignments were substantiated much later by dipole measurements. Pseudotropine (51), in which the nitrogen bridge and hydroxyl substituent are cis, was shown to have a higher dipole moment (2.20[8] and 1.68[9] D) than tropine (53) (1.59[8] and < 0.4[9] D), in which the C(3) hydroxyl group is trans to the bridge.

The C-3 configurations of the tropan-3-ols was also verified[3] by comparing the rates of hydrolysis of the epimeric O-benzoyl and O-p-nitrobenzoyl tropan-3-ols and of their derived methiodides. Hydrolysis of the tropine esters

(endo or axial in the chair conformation (78) is stereochemically hindered by the C(6), C(7) endo and C(2), C(4) equatorial hydrogen atoms and was shown to proceed at slower rates than for the less hindered pseudotropine esters (79) (exo or equatorial at C(3)).

Tropine (53) and pseudotropine (51) can be separately obtained[3] (Scheme 10) by stereospecific reduction of tropinone (61): magnesium-hydrochloric acid reduction gave tropine (53) whereas pseudotropine (51) was formed[3] with sodium-ethanol. Tropinone (61), formed by CrO_3 oxidation of either (51) or (53) (Scheme 10), gave a mono-oxime and underwent bis α-nitrosation to (80), indicating the presence of two active methylene groups. Ring cleavage in sulphuric acid furnished N-methyl succinimide (81), an observation which provided evidence for the existence of the pyrrolidine ring as a structural unit of the tropanes.

The most pharmacologically important tropane alkaloids are atropine (4), scopolamine (1) and β-cocaine (8). Atropine (4) (Table 1), the optically inactive form of L-hyoscyamine, was first isolated by Mein[10] in 1833 from deadly nightshade, Atropa belladonna. L-Hyoscyamine is the most common tropane alkaloid found in solanaceous plants and was first isolated by Geiger[11] from henbane, Hyoscyamus niger L. L-Hyoscyamine is rarely isolated but rather is racemised to atropine during the isolation process. Prabably the most important action of atropine is concerned with antagonism of muscarinic

receptors (parasympathetic inhibition). These receptors are responsible for slowing of the heart-beat, constriction of the pupil of the eye, vasodilation and stimulation of secretions[12].

L-Scopolamine (1) (Table 1), was first isolated by Ladenbenburg[13] from Hyoscyamus , but can also be obtained as the major alkaloid from the leaves of Datura metel L, D. meteloides L, and D. fastuosa var alba. As with L. hyoscyamine, racemisation takes place readily with alkali. The racemic modification occurs naturally in Duboisia leichhardtii von Muell, which is the commercial source. A process for manufacture of scopolamine has been described[14].

β-Cocaine (8) (Table 1) was first isolated in 1862[15,16] and assigned the formula $C_{16}H_{20}O_4N$, but this was later revised to $C_{17}H_{21}O_4N$. It is the principal alkaloid of the various species of the genus Erythroxylon[1]. The outstanding property observed of β-cocaine was its ability to produce numbness of the tongue but it is also a central nervous system stimulant, creating euphoria. When Willstäter prepared (1896) a position isomer of cocaine, called α-cocaine (82), he observed that it produced no local anaesthetic action on the tongue[17] but later (1955) it was demonstrated in an intradermal infusion test[18] that α-cocaine was actually one-third to one eighth as strong as local anaesthetic as β-cocaine (8). Two years later it was proved that this isomer had the methoxycarbonyl group in the endo or α configuration and the

currently accepted structure of α-cocaine is (82). The recently (1975) prepared epimer (83) proved also to have no local anaesthetic action on the tongue but was one-third as active as β-cocaine (8) in the intradermal test[19] and lacked stimulant action.

Of the more recently isolated tropanes bellendine (12) (Table 1) bearing a fused γ-pyrone ring at C-2, C-3 is the first reported[20] alkaloid constituent of the Proteaceae (P. Bellendena montana) and this same source also furnished the structurally related epimers isobellendine (15) and cis-endo-dihydroisobellendine (16). Other alkaloids contained in the Proteaceace are the structurally simpler tropan-3,6-diol mono- and diesters, the 3-ethanoate (17), the 3-ethanoate-6-isobutanoate (18) and the 3-isobutanoate-6-ethanoate (19), the absolute configuration of these compounds has not been established.

Darlingine (20), a methylated form of bellendine, was isolated[21] from Darlingia ferruginea and from D. darlingiana. Ferrugine and ferruginine, minor constituents of the former/latter proved to be 2-α-benzoyltropane (21) and 2-ethanolytrop-2-ene (22).

New tropane alkaloids, recently isolated[22] from Schizanthus grahamii, are bis-tropanol esters of the diacids, mesaconic (84) and itaconic (85), namely, the schizanthines (36), (37) and (38).

The relationship between chemical structure and physiological activity remains a central theoretical problem of drug research and the tropanes have been found to afford useful model compounds for this work.

According to Levy and Hzard[23], a 1% solution of nortropine (50) causes a 72% contraction of the pupil of the enucleated eye of the frog. The α-epimer (50) has a myoptic effect which is not shown by the β-compound (71) but the α-epimer has no significant effect on the heart or blood vessels. Its parasympatholytic activity is also weak and uncertain. On the other hand, the β-epimer, nor-pseudotropine (71), strongly influences blood circulation, and unlike atropine (4), it increases blood pressure in animals without suprarenal gland (71). It increases the frequency of the heart beat and the systolic power.

The tropine ether (86) of benzhydrol and its aromatic ring substituion products were found to possess considerable antihistaminic activity[24,25]. The synthesis of these ethers was undertaken specifically to investigate such activity, since the simpler alkyl ethers of benzhydrol were known to be antihistamines. Strong and long-lasting effects were demonstrated especially by tropine benzhydryl ethers chlorinated in the para/ortho positions. For example, tropine-p-chlorobenzhydryl ether is capable of saving guinea-pig for 7 to 8 days from histamine bronchospasm. Even 0.1 g

of this compound is sufficient to protect the animal against a lethal dose of histamine. By contrast, the benzhydryl ether of scopoline (101) shows[26] no significant antihistaminic activity. Atropine (4) has a considerable central nervous effect in addition to its vegetative parasympatholytic action. Thus, higher doses of atropine brings about fits of rage, hallucination and, in general, a strong excitation of the central nervous system. Quaternization causes these effects to disappear, only the vegetative actions being retained. On the other hand, scopolamine (1) has strong depressive action and it has a limited use in calming raging patients suffering from mental disease.

On the basis of the observed central nervous effects of chloropromazine (87) the tropanes were derivatised with the chloropromazine ring system in the form of 9-phenothiazinyl-alkyl-nortropanes (88). Such compounds bearing an α-hydroxyl group at C-3 were more active than the β-epimers. Chloro-substitution in the phenothiazine ring produces increased activity whereas replacement of the tropane hydroxyl group by hydrogen is unfavourable.

The presence of a trimethoxybenzoyl group at C-3 of the tropane skeleton is again detrimental, although this structural unit makes a positive contribution to the central nervous action of other compounds such as reserpine and mescaline.

Pfeiffer[27] was the first to point out that the interprosthetic distances between the nitrogen atom and the alcoholic and carboxyl oxygen were 5 and 7 Å, respectively, both in acetylcholine and atropine (Fig. 1). He argued that the same interprosthetic distances occur in other parasympathomimetic compounds which can be antagonized by atropine, e.g. doryl (89), prostigmine bromide (90) and pilocarpine (91).

It was hypothesised that the 7 Å distance was important in the attachment of acetylcholine and, by implication, the tropanes, to both the nerve terminals and the cholinesterase. However, only the tropanes with α- configuration at C-3 possess the interprosthetic distances of 5 and 7 Å. Hence only the α- series should exhibit parasympatholytic activity while the β- series might be expected to be inactive. This is not borne out by experimental evidence which shows that both the α- and β-series affect, by blocking action, the sympathetic and parasympathetic ganglia in much the same way. They also display no selective affinity for the receptors of vegetative ganglia. It appears that ganglionic effects of the tropanes are determined primarily by the nature and steric position of the substituents on the quaternised nitrogen atom. For example, N-butyl derivatives of both the α- and β-tropan-3-ol esters possess considerable ganglion blocking action and also have the highest curare-like activity. The presence of a 3-α-acyloxy group, in the form of a simple aromatic acid ester or arylalkylhydroxy acid

ester, critically affects the selectivity of the curare-like agents but is not a prerequisite for this activity.

The occurrence of local anaesthetic activity is not limited to compounds bearing the 7-azabicyclo[3.2.1]octane skeleton. Such activity has also been reported[28,29,30] for the bispidines (3,7-diazabicyclo[3.3.1]nonanes) and for the structurally unrelated synthetic aromatic compounds, novocaine (procaine), benzocaine and xylocaine. Novocaine (92)[31], prepared by reaction of p-aminobenzoic acid with 2-(N,N-diethylamino)ethanol using sulphuric acid as catalyst, has about half the anaesthetic potency of β-cocaine (8) but is about one fourth as toxic.

Benzocaine (93), prepared[32] by reaction of p-nitrotoluene, $Na_2Cr_2O_7$ and ethanol, has local anaesthetic activity.

Xylocaine (94) was prepared[33] by the reaction of 2,6-dimethylbenzylamine with chloroethanoyl chloride and diethyl amine. Xylocaine is a good nerve blocking agent and shows local anaesthetic and antiarrhythmic activities.

Many derivatives of bispidine have now been prepared and many exhibit biological activity. A few recent examples are given in table (2). The most potent anaesthetic of the bispidines is (95)[29] (Table 2) which is about 3 times as active as procaine (92). p-Chlorobenzoate (96)[30] showed local anaesthetic activity but was also an antiarrythmic of the membrane depressive Ca^{2+} antagonist type.

Considering the physiological applications of the tropane alkaloids and the now customary biological screening of synthetic analogues of naturally-occurring compounds, it is surprising that very little research has been carried out on sulphur analogues of this system. On comparing the nitrogen and sulphur bridged bicyclo(3.2.1)octane systems (102) and (103) the following differences and similarities are noted:

1. Nitrogen is basic, sulphur is neutral.
2. Both nitrogen and sulphur are nucleophiles.
3. Nitrogen is 3-valent, sulphur can be 2,4 or 6 valent.
4. As monocations nitrogen is 4-coordinated and sulphur 3-coordinated.
5. The C-S bond length (1.8 Å) is 0.3 Å longer than the C-N bond (1.5 Å)
6. The singly-bonded C-N-C bond angle is $\sim 107^{o}$ and singly-bonded C-S-C bond angle is $\sim 90^{o}$.

The combination of 2 longer C-S bonds and the more acute S bond angle makes little difference to the C-1 and C-5 distance of (103) when compared with (102); hence, the thia- and aza-bicyclic systems are closely similar in shape. This similarity suggests that if 8-thiabicyclo (3.2.1)octanes and perhaps also the more easily obtained 9-thiabicyclo (4.2.1)octanes were given suitable functionality they might exhibit tropane-like activity.

Since 1955, several methods have been reported for synthesising compounds containing a sulphur bridge, one of which is the condensation of cyclic polyalkenes with sulphur dichloride. The reaction of sulphur dichloride with alkenes has been known for over a century but it was only comparatively recently that the synthetic utility of the reagent was fully realised. The trans addition of sulphur dichloride to carbon-carbon double bands is now believed[34] (Scheme 11) to proceed via formation of a Π– complex and a cyclic episulphonium cation (104), which is opened by chloride to give the Markovnikov adduct (105).

A direct method of synthesising compounds with a sulphur bridge is by the extension of the above process (Scheme 11) to transannular 1:1 condensation of sulphur dichloride with a cyclic diene (e.g. (106) Scheme 12). Since this condensation proceeds by two sequential trans additions, the product (107), a β,β'-dichlorothioether, contains two chlorine substituents cis to each other but trans to the sulphur bridge.

The reaction of sulphur dichloride with several substituted cycloheptadienes has been studied by McCabe and Routledge[35] to synthesise precursors to thia- analogues of biologically active tropone alkaloids. Using this approach chloride, ester, carbonyl groups and unsaturation have been introduced at potentially useful positions of the bicyclic framework. Routledge observed that[36] no bicyclic adduct

was formed between cyclohepta-3,5-dienol (108) and sulphur dichloride and this failure was ascribed to the competing reaction of sulphur dichloride with the nucleophilic hydroxyl group to give, after hydrolysis, an ester, e.g. (109), of a sulphur oxyacid. In the current work, it was proposed to examine this reaction in more detail, to isolate if possible and prove the structure of the sulphur-acid derivative and to alter reaction conditions to favour diene-sulphur dichloride interaction. It was hoped that this would provide a route to thia-tropan-3-ols (cf (53) and (51)) and derived esters (cf. (1), (3), (4) and (8)).

Routledge also found that (110) failed to α-acylate when treated with dimethyl carbonate/sodium hydride as a part of a synthetic route to a thia analogue of β-cocaine. It was planned to investigate alternative conditions under which the α-acylation could be successful.

To extend the adaptability of this approach to thiatropanes, it was proposed to attempt replacement or elimination reactions of the halogen substituents of 6,7-dichloro-8-thiabicyclo(3.2.1.)octane (107) (Scheme 12) to mimic the functionality of the epoxide (1), diol (3), alkene (13) and ether (25).

CHAPTER 1

6,7-Disubstituted 8-thiabicyclo[3.2.1]octanes

DISCUSSION

The synthetic approach of McCabe and Routledge[36] to thiatropanes, by addition of SCl_2 to the conjugated diene system of cyclohepta-1,3-diene (106) and its derivatives, was intended to allow for functional group modifications at C-6 and C-7 of the adducts (eg 107) involving the cis, vicinal chlorine substituents. It was, however, appreciated by them that such modifications were likely to be difficult to achieve since the chlorine substituents of the analagous 7,8-dichloro-9-thiabicyclo[4.2.1]nonane (111) had been reported[37] to be unreactive in comparison with the labile chlorine substituents (also both β to the thioether bridge) of the isomeric 2,6-dichloro-9-thia bicyclo[3.3.1]nonane (112). For example, (111) failed to undergo nucleophilic displacement with $LiAlH_4$ under conditions which readily converted (112) to 9-thiabicyclo [3.3.1]nonane (113).

Following on from Routledge's work, Heaney[38] was unable to effect dechlorination of (107), with Zn/EtOH, although he did achieve conversion of (107) to (114), in modest yield, using sodium in presence of anthracene[38]. Heaney also found that reaction of (107) with sodium hydroxide in 1,2-dimethoxyethene did not give diol (115), in contrast to the high-yielding conversion of the dichloride (112) to diol (116) under these conditions.

In the present work, it was proposed to examine the special reactivity of the β,β'-dichlorothioether moiety of (107) by exposing it to a series of nucleophiles of varying strength and basicity and to nucleophiles in acid solutions of varying strength. It was expected that discoveries arising from this study would lead to syntheses of 8-thiabicyclo-[3.2.1]octanes bearing the exact C-6, C-7 functionality of the tropanes (see Table 1) as well as creating a range of new derivatives for testing as potential therapeutic agents.

The starting point for the present study was the observation by Heaney[38] that attempted dechlorination of (107) with Zn/EtOH (see above), gave a liquid product which was tentatively assigned as 6,7-diethoxy-8-thiabicyclo[3.2.1]octane (117). A study of this apparent solvolysis reaction was undertaken.

Thus, the dichloride starting material (107) was re-synthesised in 70% yield by high-dilution reaction (Scheme 12) of cyclohepta-1,3-diene (106) with sulphur dichloride at -70°. The purified product, m.p. 188-189°, showed a molecular ion at m/e 196, 198 and 200 of intensity ratio 9:6:1 in the mass spectrum, conforming the presence of two chlorine atoms. The NMR spectrum (Fig 2) showed a characteristic double doublet of δ 4.85, corresponding to the two H-CCl protons and a slightly broadened singlet at δ 3.42 assigned as the bridgehead protons. The configuration of the chlorine atoms of (107) was substantited by the apparent NMR coupling of 4Hz (the larger of the two

couplings in the δ 4.85 double doublet) between H(5) and H(6) (or H(1)and H(7)), which corresponds to a dihedral angle of ca. 48° as calculated from the Karplus equation:

$$J_{AB} = 4 \text{ Hz} = 9 \text{ Cos}^2 \theta - 0.3 \text{ Hz}$$

A molecular model, with the chlorine atoms trans to the sulphur bridge and the six-membered ring in a chair conformation, possesses an H(5), H(6) dihedral angle of ca. 50°, close to the above predicted value.

The alternative possibility in which H(6) and H(7) are cis to the sulphur bridge would possess an H(5), H(6) and H(1), H(7) dihedral angle of ca. 90° which would result in a coupling constant close to zero Hz. This rationale is approximate since H(1) H(5), H(6) and H(7) constitute an A_2B_2 complex spin system[39] (not amenable to first-order analysis) and consideration has been given only to the intense central four peaks of the H(6), H(7) group, neglecting the low intensity satellites. There was no observable coupling between H(6) and H(7) (the ideal molecule has a mirror plane) as shown by double irradiation of H(1), H(5) at δ 3.42 which caused collapse of the H(6), H(7) absorption at δ 4.85 to a singlet. The assigned trans stereochemistry of the chlorine and sulphur atoms is consistent with the accepted <u>trans</u> addition mechanism of SCl_2 condensation with alkenes as discussed in the Introduction (see Schemes11 and 12).

Repeating Heaney's attempted dechlorination procedure[38], (107) and acid-washed zinc dust were refluxed in ethanol for ca. 8 days, during which time a colourless, water-soluble, amorphous

solid (zinc chloride) collected. The distilled liquid product, b.p. 115°/0.7 mm, gave microanalytical figures consistent with the molecular formula $C_{11}H_{20}O_2S$ and showed a mass spectral molecular ion at m/e 216. The IR spectrum possessed intense C-O stretching absorptions at 1192, 1112, 1050 cm^{-1} and the NMR spectrum (Fig. 3) showed prominent ethoxy absorptions as a quartet (4H) at δ 3.65 and a triplet (6H) at δ 1.25. The bridgehead and methylene signals at δ 3.27 and δ 1.1 - 2.4, of integrated intensities 1:3, confirmed that the bicyclic framework had remained intact. This firmly establishes the product to be 6,7-diethoxy-8-thiabicyclo[3.2.1]octane (117), formed quantitatively by solvolysis.

Although (117) was virtually the only product of the above reaction, the NMR spectrum of the crude product possessed a very small vinyl absorption (δ 6.13) indicating that dechlorination had taken place but only as a very minor process under these conditions. The small amount of (114) formed, being volatile, was lost during purification of (117).

An attempt was made to favour the dechlorination through activation of the zinc by formation of zinc-copper couple. (107) Was refluxed in ether with zinc-copper couple in presence of a small volume of dimethyl formamide. However, this procedure proved to be ineffective and the starting material was returned unreacted.

To assess the role of the zinc in the solvolysis process, (107) was refluxed in ethanol alone, monitoring the progress of the reaction by TLC. After 15 days, the starting material had been quantitatively converted to (112) and no alkene was formed.

The much slower time of the latter reaction, taken together with the observed formation of zinc chloride in the previous procedure, indicates that the zinc accelerates the reaction (ca. by a factor of 2), probably by weakening the C-Cl bonds, through tetrahedral coordination, as shown in Scheme 13. After initial sulphur-assisted C-Cl bond cleavage, the highly reactive bridged sulphonium intermediate (118) is attacked faster by ethanol from the solvent cage than the elimination of the second chlorine can occur.

The configuration of C-6 and C-7 of (117) is assumed to be the same as for (107) because the apparent coupling of ca. 5 Hz (the larger of the two couplings in the δ 4.18 double doublet) and hence the dihedral anglesbetween H(5) and H(6) (or H(1) and H(7)) are approximately the same in both compounds (see p 16). Thus, the substitution reaction of (107) with ethanol has occurred with stereochemical retention.

(107) behaved identically towards methanol. When a methanol solution of (107) was stirred under reflux with zinc dust, it was converted into 6,7-dimethoxy-8-thiabicyclo-[3.2.1]octane (119) in 95% yield in 6 days and only a minor

amount of alkene (114) was observed in the crude product. In the absence of zinc, complete conversion required 14 days (no alkene formed).

The structural assignment of (119) was established by its microanalytical data, consistent with the molecular formula, $C_9H_{16}O_2S$ and its spectroscopic properties. The molecular ion peak appeared at m/e 188 in the mass spectrum. The NMR spectrum (Fig. 4) showed a prominent methoxy singlet at δ 3.49 and the protons at C-6, C-7 appeared as a double doublet at δ 4.12. The larger coupling of 4 Hz within this group indicates, as above, that substitution has taken place with retention.

The reaction of (107) with methanol was repeated replacing zinc dust with sodium metal. In this case, (107) failed to react despite the presence of the stronger nucleophile $MeO^{\ominus}$. Nucleophilic substitution of this β,β'-dichlorosulphide system appears, therefore, to be disfavoured if the nucleophile is highly electron dense, cf. the attempted reduction of (111) with $LiAlH_4$. For comparison, $LiAlH_4$ treatment of (107) was undertaken but, after 24 h in refluxing tetrahydrofuran, the starting material remained unreacted.

As an extension of the reaction of (107) with the alcohol function, (107) was refluxed with 1,2-dihydroxyethane in presence of zinc. In 4 hours, a single crystalline product, $C_9H_{14}O_2S$, m.p. 40-42°, was formed in 79% yield. This showed a molecular ion at m/e 186 in the mass spectrum and the IR spectrum

possessed intense C-O stretching absorptions at 1237, 1112 and 1032 cm^{-1}. In addition to the bicyclic methylene (δ 2.5 - 1.4) and bridgehead (δ 3.3) signals, new peaks appeared in the NMR spectrum (Fig. 5) at δ 4.05 and 3.90, of integrated intensity ratio 2:1, which were assigned to H_2C-O- and HC-O- respectively. Thus, the structure of this product was established as (120), the stereochemical assignment being based on the similar appearance of H-C-O and bridgehead signals to those of (107), (117) and (119).

To assess the reactivity of (107) towards powerful nucleophiles which are not basic (cf. $MeO^{\ominus}$ above), the reactions of (107) with ethane-1,2-dithiol and with potassium cyanide were investigated.

The reaction of (107) with refluxing excess ethane-1,2-dithiol in the presence of zinc proceeded in an identical fashion to that with 1,2-dihydroxyethane and gave (121), m.p. 55 - 56° in 83% yield after 23 hours. (107) failed to react with ethane-1,2-dithiol when the reaction was conducted in refluxing 1,4-dioxan in absence of zinc.

In contrast to the substitution observed in the treatment of (107) with ethane-1,2-dithiol/zinc, reaction of (107) with potassium cyanide in the presence of zinc gave a single product containing no nitrogen. The IR spectrum did not possess C≡N stretching absorptions at ca. 2100-2200 cm^{-1} corresponding to the structure (122). The presence of vinylic absorptions (6.13, 2H, dd) in the NMR spectrum (Fig. 6)

together with bridgehead (δ 3.63, 2H) and methylenic (δ 2.3 - 1.5, 6H) signals confirmed the structure as the unsaturated sulphide (114). (107) failed to react with potassium cyanide when the reaction was carried out in the absence of zinc. These results suggest that the zinc complexes (Scheme 14) with the chlorine atoms of (107), the strong nucleophile $\overset{\ominus}{C}N$ supplying the remaining two ligands of a tetrahedral complex ((123), L = $\overset{\ominus}{C}N$). Sulphur-assisted expulsion of chloride ion, as previously proposed (see Scheme 13), is followed, in this case, by rapid elimination of the second chlorine, formally as a chloronium ion. It would appear that the high electron density of the chlorine atoms of (124) deter the electron rich $\overset{\ominus}{C}N$ ion, as a nucleophile, from approaching C(6), thus preventing substitution. By comparison, the approach of ethanol (see Scheme 13) to C(6) of (118) is not blocked in this way because of the much lower change density on the ethanol oxygen nucleophile.

In a manner similar to the solvolysis of (107) with alcohols, (107) reacted with water in neutral medium (aqueous tetrahydrofuran) in presence of zinc to give diol (115), m.p. 202 - 206° (sealed tube) after 3 days reflux. The single crystalline product, $C_7H_{12}O_2S$, formed in 75% yield, showed a molecular ion peak at m/e 160 in the mass spectrum and exhibited strong infrared bands at 3620, 3420, 1456, 1428 cm^{-1} due to O-H and C-O stretching. In additon to the bridgehead (δ 3.26) and methylene (δ 2.2 - 1.5) absorptions of the

bicyclic skeleton, the NMR spectrum (Fig. 7) showed an H-C-O resonance as a double doublet (like the H-C-Cl dd of (107)) at δ 4.45 and a broad, deuterium - exchangeable singlet at δ 3.0, due to the presence of hydroxyl substituents at C-6 and C-7. Thus solvolysis had occurred with stereochemical retention.

The diol was also formed when the reaction of (107) with water-tetrahydrofuran was re-run, in the absence of zinc (75% yield) or in the presence of a few drops of hydrochloric acid (3 M), whereas reflux of (107) in aqueous acetone in the presence of zinc for 40 hours gave only unreacted starting material.

It is noteworthy that the dichloride (107) undergoes solvolysis, with or without zinc, by all three of the weak nucleophiles, ethanol, methanol and water.

The reaction of (107) with formalin in presence of zinc was attempted in the hope that replacement of both chlorine substituents would take place with the hydrate of methanal, i.e. 1,1-dihydroxymethane, to give the acetal (125), cf. reaction with 1,2-dihydroxyethane (above). In the event, (125) was not formed but reaction of (107) with the excess water present occurred, forming again diol (115).

As a means of modifying the newly created C(6), C(7) diol functionality in the 8-thiabicyclo[3.2.1]octane system, an attempt was made to mono-dehydrate (115) by reflux in

aqueous tetrahydrofuran containing a few drops of 3 M hydrochloric acid. This treatment gave no reaction and, as yet, dehydration with other agents (e.g. H_3PO_4, H_2SO_4, p-TSA) has not been explored.

Following the failure of (107) to react with the strong nucleophile, $MeO^{\ominus}$, the reaction of (107) with $OH^{\ominus}$ was reinvestigated[37].

In accord with Heaney's observations[38], (107) was found to react with sodium hydroxide in aqueous dimethoxyethane to give a ca. 1:1 mixture of starting material and one product, which Heaney had previously established, after separation, to be the unsaturated sulphoxide (126). When the reaction was repeated in presence of zinc, the sulphoxide (126) was accompanied by the unsaturated sulphide (114), these structural assignments being made by NMR comparison with the pure components, without separation of the mixture. When the reaction of (107) with sodium hydroxide was carried out in aqueous dioxan, (126) was obtained as a single crystalline product (72% yield), m.p. 180 - 181° (lit.[38] 190 - 192°). The appearance of its molecular ion peak at m/e 142 in the mass spectrum and the presence of vinyl (δ 6.15), rather than hydroxyl, absorption in the NMR spectrum confirmed that the diol (115) (f.w. 160) had not been formed. The product possessed the bicyclic skeleton as shown by the bridgehead (δ 3.25) and methylene absorptions (δ 2.1 - 1.5), of integrated intensity ratio 1:3, in the NMR spectrum (Fig. 8) and the appearance of strong

IR bands at 1075 and 1055 cm^{-1} confirmed that the sulphur bridge existed as a sulphoxide. The product was thus the unsaturated sulphoxide (126). The sulphur configuration followed from the assignment of Heaney[38], who had isolated pure samples of the two sulphoxide diastreoisomers, which had different melting points and distinctive spectroscopic features. It is noteworthy that only one of the sulphoxide diastreoisomers is stereospecifically formed in the hydroxide treatment of (107) and oxidation at sulphur has apparently occurred in the absence of a formal oxidising agent.

A mechanism which accounts for these observations is given in Scheme 15. Sulphur-oxygen coordination is brought about by attack of $\overset{\ominus}{O}H$ on the bridged episulphonium ion (127); formed by spontaneous sulphur-assisted ionisation of (107) in the polar solvent. The sulphur-oxygen bond is exclusively formed anti to the new carbon-sulphur link. The resulting transient sulphurane (128) undergoes a Grob-like fragmentation[40] with elimination of the elements of HCl, forming that sulphoxide (126) in which the sulphinyl oxygen is anti with respect to the double bond formed.

This sequence is unusual because the nucleophile $(\overset{\ominus}{O}H)$ has attacked the episulphonium sulphur, the most electrophilic site, rather than the more usual ring opening process of attack at one of the two episulphonium ring carbons, which are stereochemically hindered in this system. The Grob-like fragmentation (Scheme 15) provides a rapid means to

alleviate ring strain in the unstable sulphurane without reversion to starting materials.

This elimination pathway would not necessarily be possible for all other nucleophiles, e.g. $MeO^{\ominus}$, in which case the sulphurane (129), if formed, (Scheme 16) would fragment most likely by reattachment of chloride ion and sulphur-oxygen bond cleavage with reversion to the starting materials. Attack on (127) from the α-face by $MeO^{\ominus}$ at C(6) (Scheme 17) is both stereochemically hindered (by the endo C(3)-H and the C(7)-Cl atoms) and strongly disfavoured by electron repulsion with the C(7) chlorine atom lone pairs. The alternative ring opening by attack of $MeO^{\ominus}$ at C-5 (Scheme 18) is likewise stereochemically hindered but is also unfavourable on account of the angle strain engendered in the developing four-membered ring product (130).

These considerations account for the failure (see above) of (107) to react with Na/MeOH and, by analogy with the highly electron dense $AlH_4^{\ominus}$ ion. It thus appears that sterically demanding and highly electron rich nucleophiles will be disinclined to effect replacements at C(6) and C(7) of (107) and will attack at S(8) only if the intermediate sulphurane can fragment to a stable product.

To examine the reactivity of (107) to nucleophiles which are weakly basic, reaction of (107) toward selected amines was investigated.

(107) was found to be inert to triethylamine in presence of zinc. In accord with the above considerations, triethylamine would be expected to be too sterically demanding to bring about substitution at C(6) and C(7) or to be an effective ligand to the zinc.

(107) Also failed to react with 1,2-diaminoethane alone, but in presence of zinc a rapid reaction took place, with the formation of zinc chloride, to give the alkene (114). This reaction has proceeded in a similar manner to that of (107) with $\overset{\ominus}{CN}$ (see Scheme 14 where L,L = $H_2NCH_2CH_2NH_2$). The close proximity of the two amino groups creates again high electron density (cf. $\overset{\ominus}{CN}$), as well as the chelate effect in this case, and, as before, substitution, which would have formed (131), is disfavoured. In contrast to the elimination reaction observed in the treatment of (107) with 1,2-diaminoethane, (107) underwent replacement with the weaker nitrogen nucleophile, 1,2-diaminobenzene. This reacted smoothly with (107) forming a single crystalline product (69%), m.p. 144-145°, which was separated from excess reagent by preparative t.l.c. The product showed a molecular ion at m/e 232 in the mass spectrum. It exhibited strong N-H(3365 cm^{-1}) and C-N(1265 cm^{-1}) stretching absortpion in the IR spectrum. New peaks appeared in the NMR spectrum (Fig. 9) at δ 6.66 and δ 4.09 of integrated intensity ratio 2:1, due to the aromatic protons and H-CN respectively and thus was assigned the structure (132). There was no evidence, in the crude product, of dechlorination having occurred.

Thus, as previously noted with the weak oxygen nucleophiles, ethanol, methanol, 1,2-dihydroxyethane and water, the less electron dense nitrogen nucleophiles react with (107) giving substitution products.

Since a marked difference in reactivity was observed for reaction of (107) with 1,2 diaminoethane and 1,2-diaminobenzene, although both are bases, the possibility was considered that (107) may behave differently to the neutral 1,2-dihydroxyethane (see above) and the weakly acidic 1,2-dihydroxybenzene and phenol.

Reflux of (107) in liquid catechol in presence of zinc for 2 hours, furnished a colourless crystalline product, (81%), m.p. 99 - 100°, which was separated from excess reagent by preparative t.l.c. The assigned structure of (133) was consistent with microanalytical figures, $C_{13}H_{14}O_2S$, and a molecular ion at m/e 234. The IR spectrum possessed intense C-O stretching absorptions at 1064, 1043 cm^{-1} and the NMR spectrum (Fig. 10) showed prominent aromatic peaks (4H) at δ 6.95. The bridgehead and methylene signals in the NMR spectrum (Fig. 10) at δ 3.52 and δ 1.5 - 2.5, of integrated intensities 1:3, confirmed the presence of the bicyclic framework. Once again the appearance of the H-CO signal as 4 peaks, embodying a larger coupling constant of 4 Hz (approximately the same as for (107)) with the bridgehead absorption, verified that the nucleophilic substitution had occurred with retention.

Reaction of (107) with phenol in presence of zinc furnished a colourless crystalline product (82%). The product showed a molecular ion at m/e 218 in the mass spectrum. The NMR spectrum (Fig. 11) of this product was complex. In addition to the broad bicyclic methylene absorptions (δ 2.4 - 1.1) and two different bridgehead signals at δ 4.4 (H-C(1)) and δ 3.62,(H-C(5)), new peaks appeared in the NMR spectrum at δ 6.6 - 7.3 and δ 5.60, of integrated intensity ratio 5:1. These were assigned to aromatic and vinyl protons respectively. Thus, the product was established as having the unsymmetrical structure (134). Speculative mechanistic considerations regarding the reaction of (107) with phenol are raised in Scheme 19. Substitution can take place by attachment of $PhO^{\ominus}$ (produced by reaction of PhOH with zinc) at C-6 of the episulphonium ion (127), formed by spontaneous sulphur-assisted ionisation of (107) as before. The intermediate (135) could undergo a second sulphur-assisted ionisation to give (136) but, because of the steric crowding and electron density repulsion previously alluded to in Scheme 13, the approach of a second $PhO^{\ominus}$ at C-7 of (136) is disfavoured, thus preventing the formation of the substitution product (137). Alternatively, (136) could undergo elimination to form alkene (134) but the bonds being broken, namely C(6)-H and C(7)-S, are syn to each other. It is more likely that a facile anti-elimination occurs directly from (135) (Scheme 19) in which the C-Cl bond is weakened by coordination with the zinc (formation of $ZnCl_2$ observed).

To examine the reaction of (107) to an acid of strength intermediate between phenols (p K∿10) and hydrochloric acid (see above), (107) was refluxed in glacial ethanoic acid for 6 days. This resulted in quantitative solvolysis and the structural assignment of the product as (138) was established by its microanalytical data consistent with the molecular formula, $C_{11}H_{16}O_4S$, and the molecular ion peak at m/e 244 in the mass spectrum. The NMR spectrum (Fig. 12) showed a prominent methyl singlet at δ 2.1 and the protons at C-6, C-7 appeared as a double doublet at δ 5.5. The larger coupling of 4 Hz within this group indicates, as above, that substitution has taken place with retention.

From treatment of (107) with acids of varying strengths, it can be concluded that replacement occurs with the phenolic weak acids, but, in some cases, the initial substitution maybe followed by elimination, instead of a second substitution, as a result of steric crowding. With the stronger acids, carboxylic acids as well as aqueous hydrochloric acid, solvolysis exclusively takes place.

Following from the observation of substitution reactions at C(6), C(7) in the treatment of (107) both with 1,2-diaminobenzene and with ethanoic acid, a dual substitution was attempted with the amino acid, glycine, to form the novel heterocycle (139). Reaction of (107) with glycine in refluxing dimethylformamide in presence of zinc gave a single product containing no nitrogen. The IR spectrum did not possess

C=O stretching corresponding to the structure (139). The presence of vinylic absorption (δ 6.13, 2H) in the NMR spectrum confirmed the formation of the alkene (114). Reaction of (107) with glycine was repeated in water in the presence of tin (II) chloride, replacing zinc as coordinating metal, in an attempt to favour substitution over elimination. However, this procedure failed to give either (139) or (114) but furnished instead the diol (115). As before, where water is in excess, solvolytic substitution of Cl for OH occurs but, in the case where glycine is the main reactant, the glycine behaves as a highly electron-rich ligand towards the zinc and brings about elimination (Scheme 14; L,L = H_2NCH_2COOH).

Substitution/elimination reactions were attempted by treatment of (107) with potassium iodide, magnesium iodide and sodium sulphide. It was hoped that (107) might undergo the Finkelstein[41] reaction in the presence of iodide ion to give the alkene (114) and with the strong nucleophile, S^{2-}, to give the thiirane (140). However, in all these attempts, the starting material was recovered unreacted.

EXPERIMENTAL SECTION

GENERAL EXPERIMENTAL

Proton NMR spectra were recorded on a Perkin-Elmer R52 spectrometer operating at 90 MHz and a varian XL100 spectrometer operating at 100 MHz. Spectra were recorded in deuteriochloroform with TMS as internal standard. Mass spectra were recorded on an AEI MS9 spectrometer and mass measurement on an AEI MS12 spectrometer. Infra red spectra were recorded on a Perkin-Elmer 983 instrument on CCl_4 solutions.

Melting points were recorded on a Reichart hot-stage apparatus and in sealed tubes on a Gallenkamp apparatus. Small scale vacuum distillations and sublimations were carried out on a Gallenkamp sublimation apparatus.

TLC plates were spread with 0.1 or 0.5 mm thickness of silica gel HF 254 and generally run in hexane:ether, 1:1. Analytical spots were visualised by iodine staining.

Sulphur dichloride was purified by distillation from PCl_3 and the fraction boiling at 58 - 60^{o} used immediately.

Commercial zinc dust was stirred in a beaker with 6% hydrochloric acid for 1 min and the acid decanted. The washing was repeated several times and the zinc was collected under suction, washed with several portions of water to neutrality, twice with 95% ethanol and three times with anhydrous ether. The zinc was spread out finely on a filter paper and stored in a desiccator (silica-gel drying agent) which had been flushed with nitrogen gas.

Reaction of 1,3-Cycloheptadiene (106) with Sulphur Dichloride[38]

(106) (9.4 g, 100 mmol) and sulphur dichloride (10.3 g, 100 mmol), each dissolved in dichloromethane (10 ml), were added simultaneously over 5 min to dichloromethane (100 ml) which was vigorously stirred at -70°. The stirred mixture was maintained at -70° for 15 min and allowed to come to room temperature. The solution was filtered and evaporated, leaving a yellow-brown sticky solid, which darkened on standing. Two isolation/purification procedures were followed as detailed below.

1. 1.312 g of the crude product was separated by preparative t.l.c. in ether-hexane 1:4. The upper band furnished pure 6,7-dichloro-8-thiabicyclo[3.2.1]octane (107) (0.995 g, 76%).

2. A solution of 5 g of the crude product in ether was evaporated to dryness under suction in presence of ca. 10 g t.l.c. silica gel HF254. The dried material was placed on top of a dry-packed column of silica gel (40 g total; 3 cm x 13 cm) contained in a porosity 3 column fitted with a vacuum side-arm. The column was eluted under suction with ether-hexane mixtures (60 ml each) of increasing polarity: 1:4, 3:7, 2:3 and 1:1. Eleven 20 ml fractions were collected and the column was then washed with ether (40 ml) (fraction 12). Combined fractions 2-4 (1.38 g) and 5-11 (0.68 g) (combined yield 41%) were separately crystallised from ether-hexane to give colourless prisms of (107), m.p. 188-189° (lit.[38] m.p. 105 - 107°) (Found: C, 42.67; H, 5.01. $C_7H_{12}Cl_2S$ requires C, 42.65; H, 5.11 %); m/e 200, 198, 196 (1:6:9, M), 163,

161 (M - Cl), 159, 129, 128, 127 (161 - H_2S), 126 (M - Cl_2), 125, 99, 97 (C_5H_5S), 93 (128 - Cl), 92, 91, (C_7H_7, base peak), 85, 81, 79 and 77 (91 - CH_2); $\nu_{max}^{(KBr)}$ 2955, 2942, 2921, 2878, 2842, 1461, 1434, 1349, 1250, 1042, 1000, 881, 766, 654 and 610 cm^{-1}; δ (CCl_4) 4.85 (dd, J ∿ 4 and 2.5 Hz, 2H; H - CCl), 3.42 (m, 2H; H - CS) and 2.4 - 1.5. (m, 6H: CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1.]octane (107) with Ethanol[38]

1. With Ethanol Alone. (107) (0.06 g, 0.3 mmol) was refluxed with stirring in ethanol (20 ml) for 15 d after which the solvent was removed under suction to give 6,7-diethoxy-8-thiabicyclo[3.2.1]octane (117) (0.065 g, 100%) as an oil, b.p. 115, 0.7 mm (Found: C, 60.93; H, 9.31. $C_{11}H_{20}O_2S$ requires C, 61.07; H, 9.32%); m/e 216 (M), 183 (M - SH), 170 (M - EtOH), 137 (183 - EtOH), 111 (183 - EtOCCH), 103, 100, 98, 91 (C_7H_7), 85 (111 - C_2H_2, base peak), 83, 79, 75 and 70; ν_{max} 2975, 2935, 2900, 2880, 2845, 1463, 1434, 1402, 1369, 1354, 1192, 1112, 1050, 967, 928 and 679 cm^{-1}; δ 4.18 (dd, J ∿ 5 and 2.5 Hz, 2H; H - CO), 3.65 (q, J ∿ 7 Hz, 4H; H_2C - O), 3.27 (m, 2H; H - CS), 2.4 - 1.1 (m, ca. 6H; CH_2) 1.28 (t, J ∿ 7 Hz, ca. 3H; Me) and 1.25 (t, J ∿ 7 Hz, ca. 3H; Me).

2. With Zinc Present. A mixture of (107) (0.098 g, 0.05 mmol), zinc dust (0.098 g, 1.5 mmol) and ethanol (10 ml) was refluxed with vigorous stirring for 8 d. The mixture was filtered through celite 535 and the filtrate evaporated and distilled to give (117) (0.087 g, 87%), which showed identical physical characteristics to those of the previous sample.

Attempted Dechlorinations of 6,7-Dichloro-8-thiabicyclo[3.2.1] (107)

1. With Zinc in Tetrahydrofuran. A solution of (107) (0.098 g, 0.5 mmol) in tetrahydrofuran (30 ml) was refluxed (bath temperature 100°) with vigorous stirring in presence of zinc dust (0.39 g, 6 mmol) for 7 d. The reaction mixture was filtered through celite 535 and the filtrate evaporated leaving a yellow solid, the NMR spectrum of which indicated only the presence of unreacted starting material.

2. With Zinc-Copper Couple[42] Zinc dust (4.92 g) was stirred magnetically for several minutes with 3% hydrochloric acid. (In a repeat attempt, 6% hydrochloric acid was used). The acid was decanted and the zinc washed three times with portions of 3% (or 6%) hydrochloric acid, five times with water, twice with 2% copper sulphate solution, five times with water, four times with absolute ethanol and five times with anhydrous diethyl ether. The Zn-Cu couple was quickly dried under suction in a Buchner funnel and stored in a desiccator over phosphorus pentoxide. A mixture of zinc-copper couple (0.13 g), (107) (0.197 g, 1 mmol), dimethylformamide (1 ml) and anhydrous ether (10 ml) was refluxed with stirring overnight. The reaction mixture was filtered through celite 535, washed with water, dried and evaporated to give unreacted starting material.

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Methanol

1. With Methanol Alone. (107) (0.065 g, 0.36 mmol) was refluxed with stirring in methanol (20 ml) for 14 d after which the methanol was removed under reduced pressure to give 6,7-dimethoxy-8-thiabicyclo[3.2.1]octane (119) (0.059 g, 95%) as a yellow oil. This distilled at 115°, 0.7 mm as a colourless oil (Found: C,57.21; H, 8.70. $C_9H_{16}O_2S$ requires C, 57.42; H, 8.57%); m/e 188 (M), 156 (M - MeOH), 155 (M - SH), 124 (156 - MeOH), 123 (155 - MeOH), 100 (156 - MeOCCH), 97 (C_5H_5S), 91 (C_7H_7), 85, 75 and 71; ν_{max} 2935, 2722, 1464, 1435, 1199, 1130, 1100, 1051, 1030, 1004, 957 and 683 cm^{-1}; δ 4.12 (dd, J ∿ 4 and 2.5 Hz; H - CO) 3.49 (s, 6H; Me), 3.34 (m, 2H; H - CS) and 2.2 - 1.2 (m, 6 H; CH_2).

2. With Zinc Dust Present. A mixture of (107) (0.98 g, 0.5 mmol), zinc dust (0.098 g, 1.5 mmol) and methanol (10 ml) was refluxed for 6d with vigorous stirring. The mixture was filtered through celite 535 and the filtrate evaporated and distilled to give (119) (0.087 g, 87%), identical to the product obtained in the absence of zinc.

Attempted Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Sodium Methoxide

Sodium metal (0.07 g, 3.26 mmol) was dissolved with stirring in 15 ml dry methanol and solid (107) (0.098 g, 0.5 mmol) was added. The solution was refluxed with vigorous stirring for 4 h. On cooling, the mixture was poured

into water and extracted with dichloromethane, the organic layer being dried and evaporated. NMR indicated only the presence of unreacted (107).

Attempted Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Lithium Aluminium Hydride

Lithium aluminium hydride (0.38 g, 10 mmol) in anhydrous tetrahydrofuran (ca. 10 ml) was added to a solution of (107) (0.098 g, 0.5 mmol) in the same solvent (10 ml) and the mixture refluxed for 24 h with stirring. On cooling, a few drops of saturated sodium sulphate was added, the solution filtered and the filtrate evaporated to give unreacted starting material.

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with 1,2-Dihydroxyethane and Zinc

A mixture of (107) (0.098 g, 0.5 mmol) zinc dust (0.98 g, 1.5 mmol) and 1,2-dihydroxyethane (20 ml) was refluxed with vigorous stirring for 4 h. The mixture was percolated through cotton wool into water and extracted with ether. The ether extract was washed several times with water, dried and evaporated to give 6,7-ethylenedioxy-8-thiabicyclo[3.2.1]octane (120) as a solid (0.073 g, 79%). Sublimation of this residue at 50°, 0.13 mm gave needles, m.p. 40 - 42° (Found: C, 57.92; H, 7.72, $C_9H_{14}O_2S$ requires C, 58.05; H, 7.58%); m/e 186 (M), 158 (M - C_2H_4), 153 (M - HS), 141 (M - C_2H_5O),

125, 111, 100, 97 (C_5H_5S), 83, 69 and 57 (base peak); ν_{max} 2975, 2930, 2865, 1460, 1434, 1237, 1112, 1032, 896 and 672 cm^{-1}; δ 4.00 (m, 4H; CH_2 - O), 3,85 - 3.25 (m, 4 H; H - CO and H - CS), 2.5 - 1.35 (m, 6H; CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with 1,2-Ethanedithiol

1. In Dioxan. A solution of (107) (0.12 g, 0.6 mmol) and 1,2-ethanedithiol (0.0954 g, 1 mmol) in dioxan (10 ml) was refluxed (bath temp. 120°) with stirring for 23 h. The reaction mixture was poured into ether and washed several times with sodium hydroxide (1 M) then with water to neutrality. The organic layer was dried and evaporated to give unreacted starting material.

2. In the Presence of Zinc. A mixture of (107) (0.098 g, 0.5 mmol), zinc dust (0.39 g, 6 mmol) and 1,2-ethanedithiol (3 ml) was refluxed (bath temp. 165°) with vigorous stirring for 23 h. The reaction mixture was filtered and the filtrate poured into ether and washed many times with sodium hydroxide (2 M) then with water to neutrality. The ether layer was dried and evaporated to give a yellow solid which was shown by t.l.c. in ether-hexane (1:9) to be a mixture of two compounds. The mixture was separated by preparative t.l.c. in ether-hexane (1:9). The band of R_f 0.71 contained 1,2-ethanedithiol. The band of R_f 0.56, extracted with boiling dichloromethane, gave the dithane derivative (121) (0.09 g, 83%). An analytical sample of (121) was prepared by short-

path sublimation at 50°, 0.1 mm giving pale yellow needles, m.p. 55 - 56°, (Found: C, 49.75; H, 6.71. $C_9H_{14}S_3$ requires C, 49.54; H, 6.4%); m/e 218 (M, base peak), 190 (M - C_2H_4), 185 (M - SH), 158 (190 - S), 157, 126 (158 - S), 125, 100 (126 - C_2H_2), 97 (C_5H_5S) and 91 (C_7H_7); ν_{max} 2915, 2825, 1452, 1429, 1335, 1225, 1210, 1182, 1151, 1040, 916, 880, 659 and 623 cm^{-1}; δ 3.78 (m, 2 H; H - $C_{6,7}$- S), 3.65 (m, 2 H; H - $C_{1,5}$ - S), 3.1 - 2.5 (m, 2H; SCH_2CH_2S) and 2.2 - 1.4 (m, 6 H; CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Potassium Cyanide

1. In the Absence of Zinc. A mixture of (107) (0.98 g, 0.5 mmol), potassium cyanide (0.65 g, 10 mmol) and dioxan (30 ml) was refluxed (bath temperature 120°) with vigorous stirring for 24 h. On cooling, the reaction mixture was poured into water and extracted with ether, the extract being washed with water, dried and evaporated leaving a yellow solid, the NMR spectrum of which indicated only the presence of unreacted starting material.

2. In the Presence of Zinc. A mixture of (107) (0.08 g, 0.4 mmol), zinc dust (0.8 g, 1.2 mmol) potassium cyanide (0.65 g, 10 mmol) and dioxan (30 ml) was refluxed with vigorous stirring at 120° (bath temperature) for 24 h. On cooling, the reaction mixture was filtered and the filtrate poured into ether and washed with water. The ether layer was dried and evaporated (some of this volatile product was

lost during rotary evaporation) to give a waxy solid (0.056 g), which was shown by t.l.c. in ether-petroleum spirit 1:1 to be mainly the alkene (114). Purification was effected by preparative t.l.c. in the same solvent. The band of R_f 0.22 gave solvent-derived aromatic impurity (0.04 g) and that of R_f 0.68 extracted with boiling dichloromethane, furnished 8-thiabicyclo[3.2.1]oct-6-ene (114) (0.04 g, 64%). An analytical sample of (114) as needles, m.p. 105 - 106° was prepared by short-path sublimation at 30° at water-pump pressure (Found: C, 66.59; H, 7.93. $C_7H_{10}S$ requires C, 66.62; H, 7.99%); m/e 126 (M), 125, 99 (125 - C_2H_2), 97 (C_5H_5S), 95 93 (M - SH), 91 (C_7H_7), 85 and 57 (base peak); ν_{max} 3055, 2950, 2905, 2842, 1604, 1449, 1432, 1333, 1052, 896, 719, 701 and 596 cm^{-1}; δ 6.13 (dd, J ∿ 3 and 2 Hz, 2 H; vinyl), 3.63 (m, 2 H; H - CS) and 2.3 - 1.5 (m, 6 H; CH_2)

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1.]octane (107) with Water

1. In Acetone with Zinc Present. A mixture of (107), zinc dust (0.165 g, 0.5 mmol), water (8 ml) and acetone (20 ml) was stirred under reflux for 40 h. The cooled mixture was filtered through celite 535 and the filtrate evaporated. The solid residue was unreacted starting material.

2. In Tetrahydrofuran with Zinc Present. A mixture of (107) (0.098 g, 0.05 mmol), zinc dust (0.39 g, 6 mmol), tetrahydrofuran (2 ml) and water (20 ml) refluxed with vigorous stirring for 3 d. On cooling, the mixture was filtered and the filtrate extracted with ether, the ether layer being dried and

evaporated leaving a colourless semisolid (0.066 g). This was purified by t.l.c. in ether-petroleum spirit 1:1. The band of R_f 0.29, extracted with boiling dichloromethane, gave 6,7-dihydroxy-8-thiabicyclo[3.2.1]octane (115) (0.06 g, 75%). Other bands contained only small amounts of material. An analytical sample of (115) was prepared as needles, m.p. ca. 202 - 206° (sealed-tube) by short-path sublimation at 40°, 0.07 mm (Found: C, 52.55; H, 7.60. $C_7H_{12}O_2S$ requires C, 52.49; H, 7.55%); m/e 160 (M), 142 (M - H_2O), 131, 114, (142 - CO), 113, 109 (142 - SH, 127 - H_2O), 101 100 (113 - CH, base peak), 97, 85, 83, 81, 79, 77, 67, and 65; ν_{max} 3620, 3420, 2935, 1456, 1428, 1372, 1076, 1060, 1034, 959, 890 and 670 cm^{-1}; δ 4.45 (dd, J ∿ 4 and 2.5 Hz, 2 H; H - CO), 3.26 (m, 2H; H - CS), 3.0 (bs, 2 H, deuterium exchangeable; OH) and 2.2 - 1.5 (m, 6 H; CH_2).

3. In the Absence of Zinc. A mixture of (107) (0.098 g, 0.5 mmol), tetrahydrofuran (2 ml) and water (30 ml) was refluxed with vigorous stirring at 100° (bath temperature) for 3 d. The reaction mixture was extracted with dichloromethane and the organic layer dried and evaporated to give (115) (0.06 g, 75%) as a colourless solid.

4. In the Presence of Hydrochloric Acid. A mixture of (107) (0.098 g, 0.5 mmol), tetrahydrofuran (2 ml), water (5 ml) and 3 drops of hydrochloric acid (3 M) was refluxed with stirring at 100° (bath temperature) for 4 d. On cooling, the reaction mixture was extracted with dichloromethane. The organic layer was dried and evaporated to give (115) (0.065 g, 82%) as a colourless solid.

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Formaldehyde and Zinc

A mixture of (107) (0.098 g, 0.5 mmol), tetrahydrofuran (2 ml), zinc dust (0.098 g, 1.5 mmol) and formalin (37 - 39% w/v) (20 ml) was refluxed with vigorous stirring for 3 d, the reaction mixture filtered and the filtrate extracted with ether and dried. Removal of solvent gave a colourless oil which was shown by t.l.c. to be a mixture mainly of starting material and the diol (115) but also containing three other minor products. The mixture was separated by preparative t.l.c. in ether-petroleum spirit 4:1. The band of R_f 0.64 gave, by NMR comparison, unreacted starting material (0.03 g) and that of R_f 0.32, extracted with boiling dichloromethane, gave (115) (0.032 g, 58% based on (107) consumed). The other bands contained materials (0.045 g in total) which were not bicyclic and were not further investigated.

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1.]octane (107) with Sodium Hydroxide

1. In Dimethoxyethane[37,43] (107) (1.97 g, 10 mmol) was dissolved in a mixture of dimethoxyethane (15 ml) and 10% aqueous sodium hydroxide (15 ml) and the solution refluxed for 20 h under nitrogen. The reaction mixture was filtered, the filtrate poured into dichloromethane and washed many times with water to neutrality. The organic layer was dried and evaporated to give a mixture (ca. 1:1) of (107) and 8-thiabicyclo[3.2.1]oct-6-ene-8-oxide (126).

2. In Dimethoxyethane with Zinc Present. A mixture of (107) (0.098 g, 0.5 mmol), zinc dust (1.3 g, 20 mmol), 10% aqueous sodium hydroxide (15 ml) and dimethoxyethane (15 ml) was refluxed (bath temp. 115°) with vigorous stirring under nitrogen for 20 h. The reaction mixture was filtered, the filtrate poured into dichloromethane and washed many times with water to neutrality. The organic layer was dried and evaporated to give a mixture (0.075 g) of (107) and (114).

This mixture was again treated with zinc dust (0.65 g, 10 mmol), 10% aqueous sodium hydroxide (5 ml) and dichloromethane (2 ml) and refluxed (bath temp. 100°) with stirring for a further 24 h. Work up as above gave a mixture (ca. 1:1) of the sulphoxide (126) and the sulphide (114).

3. In Dioxan. A mixture of (107) (0.081 g, 0:41 mmol), dioxan (2 ml) and 10% aqueous sodium hydroxide (7 ml) was refluxed (bath temp. 120°) with stirring for 24 h. The reaction mixture was poured into dichloromethane and washed many times with water. The organic layer was dried and evaporated to give (126) (0.042 g, 72%) as a solid, m.p. 180 - 181° (lit.[38] 190 - 92°); m/e 142 (M), 126 (M - 16), 94 (M - SO), 91, 79 (base peak) and 66; $\nu_{max}^{(KBr)}$ 3058, 2980, 2935, 2915, 1453, 1433, 1340, 1204, 1072, 1051, 1041, 818, 750 and 670 cm^{-1}. δ 6.11 (br. d, 2 H; vinyl), 3.25 (m, 2 H; H - CS), 2.4 - 2.0 (m, 2 H; CH_2) and 1.7 - 1.2 (m, 4 H; CH_2).

4. In Tetrahydrofuran.

(a) A mixture of (107) (0.098 g, 0.5 mmol), tetrahydrofuran (15 ml) and 10% sodium hydroxide (15 ml) was refluxed under nitrogen with vigorous stirring for 24 h. The reaction mixture was filtered and the filtrate extracted with dichloromethane. The organic layer was dried and evaporated leaving a yellow solid which was mainly starting material, as shown by NMR.

(b) A mixture of (107) (0.098 g, 0.5 mmol) tetrahydrofuran (2 ml) and 10% sodium hydroxide (7 ml) was refluxed with vigorous stirring for 24 h. The reaction mixture was filtered and the filtrate extracted with dichloromethane. The organic layer was dried and evaporated leaving a yellow solid, which was mainly starting material but a minor amount of an alkene was present.

Attempted Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Triethylamine

A mixture of (107) (0.098 g, 0.5 mmol), zinc dust (0.098 g, 1.5 mmol) and triethylamine (10 ml) was refluxed for 4 d. On cooling, the mixture was filtered through cotton wool into ether and the ether solution was washed many times with water, brine and dried. Evaporation gave a yellow solid the NMR of which indicated only the presence of unreacted starting material.

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with 1,2-Diaminoethane

1. With Zinc Present. A mixture of (107) (0.098 g, 0.5 mmol), zinc dust (0.39 g, 6 mmol) and 1,2-diaminoethane (30 ml) was refluxed with vigorous stirring at 120° (bath temperature) for 18 h. On cooling, the reaction solution was filtered, the filtrate poured into ether and washed with water to neutrality. The ether layer was dried and evaporated to give 8-thiabicyclo[3.2.1]oct-6-ene (114) as a waxy solid (0.053 g, 84%), identical to the sample prepared by reaction of (107) with potassium cyanide.

2. In the Absence of Zinc. A solution of (107) (0.098 g, 0.5 mmol) in 1,2-diaminoethane (30 ml) was refluxed with stirring at 120° (bath temperature) for 18 h. On cooling, the solution was poured into ether and washed with water to neutrality, dried and evaporated to give a yellow solid. The NMR showed this to be mainly starting material with a minor amount of alkene (114) (δ 6.15) present.

Reaction of 6,7-dichloro-8-thiabicyclo[3.2.1.]octane (107) with 1,2-Diaminobenzene and Zinc

(107) (0.098 g, 0.5 mmol) was heated at 120° (bath temperature) in 1,2-diaminobenzene liquid (5 g) and zinc dust (0.098 g, 1.5 mmol) was added. The mixture was heated at 120° with vigorous stirring for 8 h and cooled. The resulting solid was broken up and extracted several times with hot water by agitating over a steam bath. When the water extract had been

decanted, the remaining solid was washed out with ether and the solution dried and evaporated to give a red solid which was shows by t.l.c. in ether to be a mixture of 1,2-diaminobenzene and one product. The mixture was separated by preparative t.l.c. in ether. The band of R_f 0.26, extracted with boiling dichloromethane, gave 1,2-diaminobenzene (0.009 g) and that of R_f 0.9 gave (132) (0.08 g, 69%). An analytical sample of (132) was prepared by short-path distillation at 30°, 0.06 mm as a yellow solid, m.p. 144 - 145° (Found: C, 67.34; H, 6.74. $C_{13}H_{16}N_2S$ requires C, 67.22; H, 6.94%); m/e 232 (M, base peak), 199 (M - SH), 171, 164, 132 (M - C_5H_8S), 104 ($C_6H_4N_2$), 91, 85, and 77; ν_{max} 3365, 2920, 2860, 2845, 1601, 1502, 1450, 1286, 1265 and 1043 cm^{-1}; δ 6.66 (s, 4 H; Ar), 4.2 - 3.6 (ca. 2 H, deuterium exchangeable; NH), 4.09 (dd, J ∿ 3 and 2 Hz, 2 H; H - CN), 3.30 (m, 2 H; H - CS) and 2.4 - 1.5 (m, 6H: CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Catechol and Zinc

(107) (0.098 g, 0.5 mmol) was dissolved at 120° (bath temperature) in catechol liquid (5 g) and zinc dust (0.098 g, 1.5 mmol) was added. The mixture was heated at 120° with vigorous stirring for 2 h. On cooling, the reaction mixture was swirled with water and transferred to a separatory funnel containing ether. The ether extract was separated, dried and evaporated with gentle heating to give a solid product (133) (0.0944 g, 0.4 mmol, 81%), which was substantially pure,

as shown by NMR. An analytical sample of the product was prepared by short-path sublimation at 80°, 0.3 mm as colourless needles, m.p. 99 - 100° (Found: C, 66.72; H, 6.17. $C_{13}H_{14}O_2S$ requires C, 66.66; H, 6.02%); m/e 234 (M), 201 (M - SH), 134 (M - C_5H_8S), 110 ($C_6H_6O_2$) 109, 100 (C_5H_8S, base peak), 97, 92 (110 - H_2O), 91, 85, 79, 77, 67 (93 - C_2H_2), 66 and 65; ν_{max} 2920, 1592, 1487, 1251, 1084, 1043 and 970 cm^{-1}; δ 6.95 (m, 4 H; Ar), 4.71 (dd, J ∿ 4 and 2.5 Hz; H - CO) 3.52 (m, 2 H; H - CS), 2.5 - 1.5 (m, 6 H; CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Phenol and Zinc

(107) (0.098 g, 0.5 mmol) and zinc dust (0.098 g, 1.5 mmol) were added to phenol liquid (15 ml) at ca. 60° and the mixture refluxed (bath temperature 120°) with vigorous stirring for 4 h. On cooling, the mixture was rendered alkaline with sodium hydroxide solution and extracted with ether. The ether layer was washed with water to neutrality, dried and evaporated to give (134) as a solid (0.082 g, 82%). Sublimation of this residue at 50°, 15 mm gave needles, m.p. 64 - 65° (Found; C, 71.79; H, 6.51 $C_{13}H_{14}OS$ requires C, 71.54; H, 6.4%); m/e 218 (M), 185 (M - SH), 157 (185 - C_2H_4) 144, 131, 119, 118, 115, 107, 100 (C_5H_8S, base peak), 91 (C_7H_7), 85, 77 and 67; ν_{max} 3070, 3045, 3025, 2925, 2840. 1607, 1591, 1469, 1452, 1225, 1015, 987, 971, 831, 678 and 665 cm^{-1}; δ 7.3 - 6.6 (m, 5 H; Ar), 5.60 (dd, J ∿ 12 and 7 Hz; vinyl), 4.40 (dd, J ∿ 12 and 7 Hz; H - C(1)), 3.62 (m, 1 H; H - C (5)) and 2.4 - 1.1 (m, 6 H; CH_2).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Ethanoic Acid

A solution of (107) (0.098 g, 0.5 mmol) in glacial ethanoic acid (20 ml) was stirred under reflux at 120° (bath temperature) for 6 d. On cooling, the reaction solution was poured into water and extracted with ether, the extract being washed with saturated sodium bicarbonate, water to neutrality and dried. Removal of solvent gave 6,7-diacetoxy-8-thiabicyclo [3.2.1]octane (138) (0.121 g, 100%) as a yellow oil. Distillation of this at 40°, 0.06 mm gave a colourless oil which solidified immediately to needles, m.p. 55 - 56° (found: C, 54.32; H, 6.68. $C_{11}H_{15}O_4S$ requires C, 54.09; H, 6.60%); m/e 244 (M), 184 (M - AcOH), 151 (184 - SH), 124 (184 - AcOH), 108 (151 - Ac), 97 (C_5H_5S), 91 (C_7H_7) and 43 (base peak); ν_{max} 2910, 2830, 1739, 1368, 1240, 1220, 1060, 1046 and 901 cm^{-1}; 5.35 (dd, J ~ 4 and 3 Hz, 2 H; H - CO), 3.35 (m, 2 H; H - CS), 2.24 - 1.42 (m, ca. 6 H; CH_2) and 2.02 (s, ca. 6 H; Me).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107) with Glycine

1. In the Absence of Water. A mixture of (107) (0.098 g, 0.5 mmol) zinc dust (0.65 g, 10 mmol), glycine (0.37 g, 5 mmol) and dioxan (5 ml) was refluxed (bath temperature 120°) with vigorous stirring for 24 h. The reaction mixture was filtered and the filtrate poured into ether and washed with water. The ether layer was dried and evaporated to give starting material as a yellow solid.

2. In Aqueous Dimethylformamide. A mixture of (107) (0.098 g, 0.5 mmol), zinc dust (0.65 g, 10 mmol), glycine (0.37 g, 5 mmol), dimethylformamide (5 ml) and a few drops of water was refluxed (bath temperature 130°) with vigorous stirring for 15 h. Work-up as above gave 8-thiabicyclo[3.2.1]oct-6-ene (114)

3. In the Presence of Tin (II) Chloride. A mixture of (107) (0.196 g, 1 mmol), tin (II) chloride dihydrate (1.13 g, 5 mmol), glycine (0.37 g, 5 mmol) and water (3 ml) was refluxed (bath temperature 130°) with vigorous stirring for 21 h. The reaction mixture was poured into ether and washed with water. The organic layer was dried and evaporated to give 6,7-dihydroxy-8-thiabicyclo[3.2.1]octane (115) (0.15 g, 94%).

Attempted Dechlorinations of 6,7-Dichloro-8-thiabicyclo[3.2.1] octane (107) with Iodides

1. With Potassium Iodide.[41] A mixture of (107) (0.098 g, 0.5 mmol) and potassium iodide (1.66 g, 6 mmol) in dioxan (30 ml) was refluxed with vigorous stirring at 120° (bath temperature) for 6 days. On cooling, the reaction mixture was poured into water and extracted with ether. Drying and evaporation of the ether layer gave only unreacted starting material.

2. With Magnesium Iodide[44]. A mixture of magnesium turnings (0.024 g, 1 mmol) and dry ether (20 ml) was stirred under reflux for 15 m and iodine (0.033 g, 0.13 mmol) was added in small portions. When the mixture became virtually colourless, a solution of (107) (0.098 g, 0.5 mmol) in ether (10 ml) was added

and the mixture refluxed for 9 h. The reaction mixture was poured into ether and washed with water. The separated organic layer was dried and evaporated to leave unreacted starting material.

Attempted Reaction of 6,7-Dichloro-8-thiabicyclo(3.2.1)octane (107) with Sodium Sulphide

A mixture of (107) (0.098 g, 0.5 mmol), tetrahydrofuran (25 ml) and Na_2S9H_2O (0.78 g, 3.25 mmol) was refluxed with vigorous stirring (bath temperature, 100°) for 24 h, the reaction mixture filtered and the filtrate extracted with dichloromethane. The organic layer was dried and evaporated leaving a yellow solid, NMR of which indicated only the presence of the unreacted starting material.

The reaction was reattempted on the same scale, using twice the quantity of Na_2S9H_2O (1.46 g) and reducing the volume of tetrahydrofuran to 3 ml. However, no reaction took place.

CHAPTER 2

7,8-Disubstituted-9-thiabicyclo[4.2.1]nonanes

The reactions, discussed above, of 6,7-dichloro-8-thiabicyclo[3.2.1]octane (107) with electron-poor nucleophiles contradict the reported unreactivity of the cis-vic-dichloro system of the homologue, 7,8-dichloro-9-thiabicyclo[4.2.1]-nonane (111). To resolve this paradox, the reactivity of (111) towards conditions, found to be effective in bringing about reaction of (107), was investigated.

Thus, 7,8-dichloro-9-thiabicyclo[4.2.1]nonane (111) was reprepared by sulphur dichloride addition to 1,3-cycloocta diene (141) under high dilution at 0^{o} as a modification of a reported procedure[38].

(111) showed a 9:6:1 molecular ion group (m/e 210, 212, 214) characteristic of a dichloride, in the mass spectrum and possessed the same configuration as (107) of the C-Cl and C-S bonds as shown by the virtual identity in the NMR spectrum (Fig. 13) of the H(7), H(8) absorption at δ 4.84 (cf. H(6), H(7) of (107)(Fig. 2)in both chemical shift and appearance. The H - Cl signal of (111) collapsed to a singlet on double irradiation of the bridgehead signal (δ 3.65) indicating that (111) possesses, like (107), a plane of symmetry. A static model of (111) with the 7-membered ring as a pseudo-chair apparently does not have a plane of symmetry but the model is conformationally mobile and thermal averaging of the conformations may effectively create a mirror plane. In this model of (111) the observed dihedral angle between H(7) and H(6) (or H(8) and H(1)) of 35 - 40^{o} is close to the value of

40^{o} calculated from the Karplus equation, $J_{AB} = 9 \cos^2 \theta - 0.3$ Hz, with $J_{AB} = 5$ Hz, the larger of the two couplings observed in the H(7), H(8), double doublet.

(111) was found to undergo replacement reactions with ethanol and water in a manner similar to the solvolyses of (107) and comparable reaction times were necessary. In the reaction of (111) with methanol and zinc, elimination was found to compete favourably with substitution.

Reflux of (111) in ethanol in the presence of zinc gave 7,8-diethoxy-9-thiabicyclo[4.2.1]nonane (142) as an oil. This structure was assigned from a mass spectral molecular ion at m/e 230, the IR stretching bands of C-O at 1105, 1065, and 1045 cm^{-1} and the ethoxy absorption in the NMR spectrum (Fig. 14) at δ 1.25 (CH_3) and 3.9 - 3.4 (CH_2). The bridgehead signal (δ 3.9 - 3.4), coincident with the H_2C-O absorption, and the broad methylene envelope extending from δ 2.3 to 0.8 indicated the presence of the bicyclic framework. In this case, accurate measurement of coupling constants was not possible because of this coincidence of NMR absorptions.

As was found with (107), the crude product of reaction of (111) with ethanol and zinc showed a low-intensity vinyl absorption (δ 5.86) in the NMR spectrum indicating that dichlorination had occurred only to a very minor extent. Dechlorination of (111) did not take place in its reaction with ethanol in the absence of zinc. In this case, only (142) was quantitatively formed after the prolonged reaction time of 15 days.

With boiling methanol in the presence of zinc, (111) formed both 7,8-dimethoxy-9-thiabicyclo[4.2.1]nonane (143) (24%) and the elimination product, 9-thiabicyclo[4.2.1]non-7-ene (144) (36%), after 10 days. This was clearly shown by the appearance of two bridgehead signals, together with both vinyl and H - CO absorptions in the NMR spectrum of the crude reaction mixture. The products were separated by preparative t.l.c.

The solvolysis product (143), isolated from the band of R_f 0.6, gave microanalytical figures consistent with the molecular formula, $C_{10}H_{18}O_2S$, and showed a mass spectral molecular ion at m/e 202. The IR spectrum possessed intense C-O stretching absorptions at 1185, 1130 and 1090 cm^{-1} and the NMR spectrum (Fig. 15) showed methoxy absorptions as a singlet (6 H) at δ 3.5. The bridgehead and methylene signals at δ 3.0 and 2.1 - 1.65, of integrated intensities 1:4, confirmed the presence of the bicyclic framework. That the replacement had occurred with stereochemical retention was indicated by the appearance of the C(7) and C(8) absorptions as the characteristic double doublet, with the larger coupling constant of 5.5 Hz.

The structural assignment of the alkene (144), isolated from the band of R_f 0.71, was established from its molecular weight (m/e 140.0677) and three distinct NMR absorptions (Fig. 16) in the vinyl (δ 5.86), H - CS (δ 3.97) and saturated methylene (δ 2.1 - 1.3) regions in the intensity ratio of 1:1:4.

Absorptions associated with the presence of the $\Delta^{7.8}$ double bond appeared at 1623 and 690 cm^{-1} in the infrared spectrum.

Treatment of (111) with refluxing aqueous tetrahydrofuran in presence of zinc for 4 days furnished 7,8-dihydroxy-9-thia-bicyclo[4.2.1]nonane (145) as a colourless waxy solid m.p. 232 - 240° (sealed tube). This gave microanalytical figures corresponding to a molecular formula of $C_8H_{14}O_2S$ and showed a molecular ion at m/e 174 in the mass spectrum. (145) exhibited strong O - H (3620 cm^{-1}) and C - O (1060 cm^{-1}) stretching absorption in the IR spectrum and possessed a concentration-dependent deuterium-exchangeable hydroxyl absorption in the NMR spectrum (Fig. 17). The hydrolysis of (111) as with (107), had proceeded with stereochemical retention as indicated by the identical multiplicity and similar coupling of $J \sim$ 5.4 Hz shown by the H(7), H(8) absorption (δ 4.4) in both NMR spectra (Figs. 17 and 2).

Unlike the clean oxidation-dechlorination of (107) to (126) with sodium hydroxide in aqueous dioxan, (111) reacted sluggishly under these conditions to give a poor yield of a mixture after 24 hours. This showed only vinylic and methylenic absorptions at δ 5.1 - 6.4 and 0.6 - 2.7 but no peak due to sulphur bridgehead (usually ca. δ 3.6), One compound was separated from this mixture by t.l.c. and showed NMR absorption similar to the crude spectrum. Since the products of this reaction were not bicyclic, they were not further investigated.

(111) reacted in the same way as (107) towards 1,2-dioxyethylene. The novel dioxymethylene-fused heterocycle (146) was formed in 80% yield by overnight reflux of (111) in 1,2-dihydroxyethane in presence of zinc. The oily product, $C_{10}H_{16}O_2S$, exhibited a molecular ion at m/e 200 and strong C - O absorption at 1120 and 1105 cm^{-1} in the IR spectrum. In the H - CO region of the NMR spectrum (Fig. 18) the dioxy methylene absorptions appeared as a triplet (δ 3.5) and the new bridgehead protons as a sharp double doublet, the stereochemical assignment being based on the similar appearance of H - CO and bridgehead signals to those of (111) and (142). (111) behaved identically to (107) towards 1,2-diaminoethane and 1,2-diaminobenzene. (111) reacted with 1,2-diaminoethane in presence of zinc to give the alkene (144) (100% yield) whereas with the weaker nucleophile, 1,2-diaminobenzene, a dual substitution took place forming the new benzo-fused piperazine (147) (69% yield).

(147) m.p. 130 - 131°, separated from excess reagent by preparative t.l.c., showed a molecular ion at m/e 246 in the mass spectrum and gave strong amine absorption, N - H stretching at 3380 cm^{-1}, C - N stretching at 1275 cm^{-1}, in the IR spectrum. By comparison with starting material (107), the NMR spectrum (Fig. 19) of (147) possessed new absorptions at δ 6.7 and 4.15, of integrated intensity ratio 2:1, due to the presence of the aromatic and H - CN protons. This data, taken together with microanalytical figures corresponding to the molecular formula, $C_{14}H_{18}N_2S$, confirms the structural assignment of (147).

(111) reacted in the same way as (107) towards catechol and phenol. Reflux of (111) in liquid catechol in presence of zinc for 20 hours furnished a colourless crystalline product (100%), m.p. 98 - 99°, which was separated from excess reagent by t.l.c. The assigned benzo-dioxan structure (148) was consistent with microanalytical figures, $C_{14}H_{16}O_2S$ and a molecular ion at m/e 248. The IR spectrum possessed intense C - O stretching absorptions at 1090, 1061 cm^{-1} and the NMR spectrum (Fig. 20) showed prominent aromatic peaks (4 H) at δ 6.93 - 6.84. The bridgehead and methylene signals at δ 3.80 and δ 2.6 - 1.4 of integrated intensities 1:3 confirmed the presence of the bicyclic framework. Once again, the appearance of the H - CO signal as 4 peaks, embodying a larger coupling constant of 5.5 Hz (approximately the same as for (111) with the bridgehead absorption, verified that the nucleophilic substitution had occurred with retention.

Reaction of (111) with phenol in presence of zinc furnished a colourless crystalline product (77%), which showed a molecular ion at m/e 232 in the mass spectrum. The NMR spectrum (Fig. 21) of this product was complex. In addition to the broad bicyclic methylene absorptions (δ 2.6 - 1.5) and two different bridgehead signals at δ 4.2 (H - C(1)) and δ 4.8 (H - C(6)), new peaks appeared in the aromatic (δ 7.6 - 7.0) and vinyl (δ 5.9) regions, of integrated intensity ratio 5:1. Thus the product was established as having the unsymmetrical structure (149), formed in the same way (Scheme 19) as (134). To examine the reaction of (111) to an acid of

medium strength, (111) was refluxed in glacial ethanoic acid for 38 hours in presence of zinc This reaction furnished two compounds which were separated by preparative t.l.c. The band of R_f 0.85 gave the alkene (144) (30% yield) and that of R_f 0.17 furnished the substitution product (150, 70% yield) The latter showed a molecular ion peak at m/e 258 in the mass spectrum and intense ester carbonyl stretching absorption (1749 cm^{-1}) in the IR spectrum. Its NMR spectrum (Fig. 22) possessed a prominent methyl singlet at δ 2.06 and the protons at C(7), C(8), appeared as a double doublet at δ 5.37. Within this group the larger coupling of 5 Hz with the bridgehead protons (δ 3.61) indicates, as before, that substitution has taken place with retention.

To assess the role of zinc in the elimination process, (111), was refluxed in ethanoic acid alone. After 14 days, the starting material had been quantitatively converted to (150) and there was no alkene formed. These results suggest that the zinc complexes with the chlorine atoms of (111), the ethanoate ion. $CH_3C\overset{\ominus}{O}O$ (formed by the reaction of ethanoic acid with zinc) supplying the remaining two ligands of the tetrahedral complex. Sulphur assisted expulsion of chloride ion, as previously discussed, (Scheme 15) is followed in this case, by rapid elimination of the second chlorine forming the alkene (144), in competition with solvolysis.

From the above investigation, it can be deduced that the β,β'-dichlorosulphide function of (111) behaves similarly to that of (107) with the exception of the reactions with methanol-zinc and ethanoic acid-zinc. In these cases, (111) undergoes elimination as well as substitution, which is, by far, the major process for (107).

EXPERIMENTAL SECTION

Reaction of 1,3-Cyclooctadiene (141) with Sulphur Dichloride

From separate funnels, a solution of 1,3-cyclooctadiene (5 g, 46.29 mmol) in dichloromethane (40 ml) and a solution of sulphur dichloride (5.22 g, 50.67 mmol) in dichloromethane (40 ml) were added dropwise with stirring to methylene chloride (40 ml) over 1 h at 0^{o} and the reaction mixture allowed to warm to room temperature. Solvent was removed under suction to leave a yellow syrup (9.76 g). An analytical sample of 7,8-dichloro-9-thiabicyclo[3.3.1]nonane (111) was prepared by short-path sublimation of this syrup at 60^{o}, 0.05 mm to give a waxy solid, m.p. 138 - 140^{o}. Chromatographic purification was found to be more satisfactory. Thus, a solution of the above syrup (2.65 g) in dichloromethane was evaporated to dryness in the presence of t.l.c. silica gel GF 254 (8 g). The dried material was placed on top of a dry-packed column (3 cm x 13 cm) of silica gel (total 70 g), contained in a porosity 3 column with a vacuum side-arm. The column was washed under suction with hexane (200 ml, one fraction only). Removal of the hexane gave (111) as a pale yellow solid (1.45 g, 55%) which crystallised from hexane as colourless prisms, m.p. 168 - 169^{o} (lit.[37] m.p. 185.5 - 186.5^{o}). (Found; C, 45.60; H, 5.69. $C_8H_{12}Cl_2S$ requires C, 45.49; H, 5.68%) m/e 214, 212, 210 (1:6:9, M), 177, 175 (M - Cl, base peak), 141, 139 (175 - HCl), 105 (139 - H_2), 97, 79 and 77; ν_{max} 2930, 2875, 2855, 1455, 1448, 1437, 1255, 983, 960, 720 and 595 cm^{-1}; δ 4.85 (dd, J $\sim$ 5 and 2.5 Hz, 2 H; H - C Cl), 3.65 (m, 2 H; H - CS) and 2.6 - 1.3 (m, 8 H; CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Ethanol

1. With Ethanol Alone. (111) (0.06 g, 0.28 mmol) was refluxed with vigorous stirring in ethanol (20 ml) for 15 days, after which the solution was cooled and ethanol removed under reduced pressure to give 6,7-diethoxy-9-thiabicyclo[4.2.1]-octane (142) as a colourless oil b.p. 60°, 0.05 mm (Found m/e 230.1342. $C_{12}H_{22}O_2S$ requires 230.1340); m/e 230 (M), 197 (M - HS), 184 (M - EtOH), 151 (184 - HS), 125, 99, 85 and 69 (base peak); ν_{max} 2979, 2930, 2875, 1445, 1375, 1312, 1130, 1112, 1040 and 923 cm^{-1}. δ 4.1 (m, ca. 2 H; H - CO), 3.9 - 3.4 (m, ca. 6 H; H_2C - O and H - CS), 2.3 - 0.8 (m, CH_2) and 1.25 (superimposed on the CH_2 absorption, t, J ~ 6 Hz; CH_3)

2. With Zinc Present. A mixture of (111) (0.21 g, 1 mmol) zinc dust (0.39 g, 6 mmol) and ethanol (15 ml) was refluxed (bath temperature 100°) with vigorous stirring for 8 days. The reaction mixture was poured into ether and washed with water. The dried organic layer was evaporated to give (142) (0.229 g, 100%), which showed physical characteristics identical to the previous sample.

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Methanol and Zinc

A mixture of (111) (0.21 g, 1 mmol), zinc dust (0.65 g, 10 mmol) and methanol (20 ml) was refluxed at 100° (bath temperature) with vigorous stirring for 10 days. The reaction mixture was filtered and the filtrate poured into ether and

washed with water. The ether layer was dried and evaporated to give a colourless oil (0.180 g) which was shown by t.l.c. in ether-hexane 1:3 to be a mixture of two compounds. This was separated by preparative t.l.c. in the same solvent. The band of R_f 0.71, extracted with boiling dichloromethane, gave 9-thiabicyclo[4.2.1]non-7-ene (144) (0.062 g, 36%) and that of R_f 0.6 gave 7,8-dimethoxy-9-thiabicyclo[4.2.1]nonane (143) (0.042 g, 24%).

An analytical sample of (144) was prepared by short-path sublimation at 38° at water-pump pressure as colourless needles, m.p. 110 - 111° (lit.[45] m.p. 108 - 109°), (Found: 140.0677. $C_8H_{12}S$ requires 140.0660); m/e 140 (M), 111 (M - Et), 107 (M - HS), 105, 97 (C_5H_5S, base peak), 91 C_5H_5S and 84 (C_4H_4S); ν_{max} 3050, 2930, 2845, 1623, 1438, 1432, 1342, 1108, 951, 880 and 690 cm^{-1}; δ (100 MHz) 5.86 (J ∿ 5.5 and 2.5 Hz, 2 H; vinyl), 3.97 (m, 2 H; H - CS) and 2.1 - 1.3 (m, 8 H; CH_2).

An analytical sample of (143) was prepared by short-path distillation at 30° 0.1 mm as a colourless oil (Found: C, 59.25; H, 8.70. $C_{10}H_{18}O_2S$ requires C, 59.40; H, 8.91%); m/e 202 (M), 169 (M - SH), 137 (169 - MeOH), 111 (137 - C_2H_2) 109, 97 (111 - CH_2), and 40 (base peak); ν_{max} 2915, 2812, 1439, 1186, 1128, 1088, 1000 and 898 cm^{-1}; δ 4.05 (dd, J ∿ 5.5 and 2 Hz, 2H; H - CO), 3.5 (s; CH_3 and m; H - CS; 8 H) and 2.3 - 1.4 (m, 8 H; CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Water

A mixture of (111) (0.105 g, 0.5 mmol), tetrahydrofuran (2 ml) and water (5 ml) was refluxed (bath temperature 90°) with stirring for 4 d. The reaction mixture was poured into ether and the ether layer washed with water, dried and evaporated to give 7,8-dihydroxy-9-thiabicyclo[4.2.1]nonane (145) (0.076 g, 88%). An analytical sample was prepared by short-path sublimation at 60°, 0.15 mm giving colourless needles, m.p. 232 - 235°, (sealed tube) (Found: C, 55.26; H, 8.04. $C_8H_{14}O_2S$ requires C, 55.17; H, 8.04%); m/e 174 (M), 156 (M - H_2O), 141 (M - SH), 123 (156 - SH), 115, 114, 101, 99, 59, 57, 55 and 29 (base peak); ν_{max} 3620, 3360, 2920, 1440, 1380, 1060, 905 and 845 cm^{-1}; δ 4.4 (dd, J ~ 5.4 and 2.5 Hz, 2 H; H - CO), 3.5 (m, 2 H; H - CS) and 2.1 - 1.5 (m, 8 H; CH_2)

Attempted Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Sodium Hydroxide

1. In Dimethoxyethane. A mixture of (111) (0.105 g, 0.5 mmol), sodium hydroxide (4 ml, 10%) and dimethoxyethane (4 ml) was refluxed (bath temperature 100°) with vigorous stirring for 14 h. On cooling, the reaction mixture was poured into ether and washed with water to neutrality. The ether layer was evaporated to give the unreacted starting material.

2. In Dioxan. A mixture of (111) (0.1 g, 0.47 mmol), dioxan (2 ml) and sodium hydroxide (7 ml, 10%) was refluxed (bath temperature 120°) with stirring for 24 h. The reaction mixture was poured into ether and washed with water to neutrality. The ether layer was evaporated leaving a brown residue in low yield (0.03 g), the NMR of which showed vinyl (δ 5.1 - 6.4) and methylene absorptions (δ 0.6 - 2.7) but no signals at ca. δ 6.5 for bridgehead protons. An attempt was made to purify this by preparative t.l.c. in hexane. A prominent band at R_f 0.96, extracted with boiling dichloromethane, gave a colourless solid (0.102 g), the NMR of which was essentially the same as the crude material and its mass spectrum showed a peak of highest mass at m/e 244. Since this compound and the crude product were unlikely to be bicyclic substances, this reaction was not further investigated.

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with 1,2-Dihydroxyethane

A solution of (111) (0.21 g, 1 mmol) in 1,2-dihydroxyethane (10 ml) was refluxed with stirring for 24 h. On cooling, the reaction solution was poured into ether and washed with water. The ether layer was dried and evaporated to give 7,8-ethylenedioxy-9-thiabicyclo[4.2.1]nonane (146) (0.160 g, 80%) as a colourless oil, b.p. 38°, 0.1 mm (Found: C, 59.91; H, 8.50. $C_{10}H_{16}O_2S$ requires C, 59.98; H, 8.05%); m/e 200 (M), 186 (M - CH_2), 167 (M - SH), 153, 114, 99, 97, 86, 85 and 84..

ν_{max} 2920, 2860, 1740, 1440, 1120, 1105 and 910 cm^{-1}; δ (100 MHz) 3.86 (dd, J ~5 and 2.5 Hz, 2 H; H - CO), 3.5 (m, 6 H; H_2C - O and H - CS), 2.3 - 1.3 (m, 8 H; CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with 1,2-Diaminoethane

A mixture of (111) (0.21 g, 1 mmol), 1,2-diaminoethane (15 ml) and zinc dust (0.65 g, 10 mmol) was heated at 130° (bath temperature) with vigorous stirring for 20 h. The reaction mixture was filtered through celite 535 and the filtrate extracted with ether. The ether layer was washed with water, dried and evaporated to yield 9-thiabicyclo[4.2.1]non-7-ene (144) (0.13 g, 100%) as a yellow solid, which was substantially pure (by NMR). After sublimation, this showed physical characteristics indentical to the previous sample.

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with 1,2-Diaminobenzene

(111) (0.21 g, 1 mmol) was dissolved at 120° (bath temperature) in 1,2-diaminobenzene liquid (9 g) and zinc dust (0.65 g, 10 mmol) was added. The mixture was heated at 120° with vigorous stirring for 7 h and cooled. The resulting solid was broken up and extracted several times with hot water by agitating over a steam bath. When the water extract had been decanted, the remaining solid was washed out with ether and the solution dried and evaporated to give a red solid which was shown by t.l.c. in ether-hexane (1:1) to

be a mixture of 1,2-diaminobenzene and one product. The mixture was separated by preparative t.l.c. in ether. The band of R_f 0.42, extracted with boiling dichloromethane, gave 1,2-diaminobenzene (0.03 g) and that of R_f 0.85 gave (147) (0.15 g, 61%) as yellow needles, m.p. 130 - 131° (Found: m/e 246.1190. $C_{14}H_{18}N_2S$ requires 246.11906); m/e 246 (M), 213 (M - SH), 145, 132 ($C_8H_8N_2$, base peak) 119, 84 and 77; ν_{max} 3380, 2925, 2862, 1607, 1508, 1458, 1298, 1282, 1275, 1170, 1120 and 908 cm^{-1}; δ (poor resolution) 6.7 (m, 4 H; Ar), 4.15 (m, ca. 2 H; H - CN), 3.75 (m, ca. 4 H; H - CS and NH) and 2.5 - 1.5 (m, 8 H; CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Catechol and Zinc

(111) (0.21 g, 1 mmol) was dissolved at 120° in catechol liquid (5 g) and zinc dust (0.65 g, 10 mmol) was added. The mixture was stirred at 120° for 2 h, swirled with water and extracted with ether. The ether extract was washed with water, dried and evaporated to give (148) as a solid product (0.24 g, 100%) which was substantially pure as shown by NMR An analytical sample of (148) was prepared by short-path sublimation at 40°, 0.2 mm as colourless needles, m.p. 98 - 99°, (Found: C, 67.73; H, 6.47. $C_{14}H_{16}O_2S$ requires C, 67.73; H, 6.50%); m/e 248 (M, base peak), 215 (M - HS), 139 (M - $C_6H_5O_2$), 121, 114, 110 (C_6H_6S), 105, 97 (C_5H_5S), 91, 84 (C_4H_4S) and 77; ν_{max} 2930, 1605, 1505, 1490, 1270, 1258,

1149, 1090, 1061 and 912 cm^{-1}; δ 6.93 (bs, 2 H; Ar), 6.84 (bs, 2 H; Ar), 4.65 (dd, J ∿ 5.5 and 2.5 Hz; 2 H; H - CO), 3.80 (m, 2 H; H - CS), 2.6 - 2.2 and 1.9 - 1.4 (m, 8 H: CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Phenol and Zinc

(111) (0.210 g, 1 mmol) and zinc dust (0.065 g, 10 mmol) were added to phenol liquid (5 ml) at ca. 60° and the mixture heated at 130° (bath temperature) with vigorous stirring for 20 h. On cooling, the mixture was rendered alkaline with sodium hydroxide solution and extracted with ether. The decanted ether layer was washed with water to neutrality, dried and evaporated to give a brown solid (0.129 g) which was shown by t.l.c. in ether-hexane 1:1 to be a mixture. Separation was achieved by preparative t.l.c. in the same solvent. The band of R_f 0.93, extracted with boiling dichloromethane, gave (149) (0.100 g, 77%) and other bands contained only small amounts of material. An analytical sample of (149) was prepared by short-path sublimation at 43°, 0.05 mm to give colourless needles, m.p. 64 - 65° (Found: C, 72.38; H, 6.92. $C_{14}H_{16}OS$ requires C, 72.39; H, 6.94%); m/e 232 (M), 231, 148, 139 (M - PhO), 115 (M - PhOCCH), 114 (base peak), 112, 85, 83, (111 - C_2H_4) and 81; ν_{max} 2920, 1610, 1590, 1470, 1405, 1310, 1230, 1170, 1015, 1005, 915 and 885 cm^{-1}; δ (100 MHz) 7.6 - 7.0 (m, 5 H; Ar), 5.9 (m, 1 H; vinyl), 4.8 (m, 1 H; H - C(6)), 4.2 (m, 1 H; H - C(1)) and 2.6 - 1.5 (m, 8 H; CH_2).

Reaction of 7,8-Dichloro-9-thiabicyclo[4.2.1]nonane (111) with Ethanoic Acid

1. In the Absence of Zinc. (111) (0.21 g, 1 mmol) and ethanoic acid (10 ml) were heated at 100° (bath temperature) for 14 d. The reaction mixture was poured into ether and the ether extract washed with sodium hydroxide followed by water to neutrality. The organic layer was dried and evaporated to give 7,8-di(ethanoyloxy)-9-thiabicyclo[4.2.1]nonane (150) as a yellow oil (0.256 g, 99%). Distillation of this at 54°, 0.06 mm gave a colourless oil which immediately solidified to prisms, m.p. 68 - 69°, (Found: M 258.0910. $C_{12}H_{18}O_4S$ requires 258.0926); m/e 258 (M), 198 (M - AcOH), 156, 138 (198 - AcOH), 127, 123, 105 (138 - HS), 97 and 43 (base peak); ν_{max} 2930, 2850, 1749, 1368, 1244, 1223, 1060, 1046, 931 and 923 cm^{-1}; δ 5.37 (dd, J ∿ 5 and 2.5 Hz, 2 H; H - CO), 3.61 (m, 2 H; H - CS), 2.17 - 1.1 (m, ca. 8 H; CH_2) and 2.06 (s, ca. 6 H; CH_3).

2. In the Presence of Zinc. A mixture of (111) (0.21 g, 1 mmol), zinc dust (0.65 g, 10 mmol) and ethanoic acid (10 ml) was refluxed with vigorous stirring for 38 h. After filtration, the reaction mixture was worked up as above to give a yellow solid (0.2 g) which was shown by t.l.c. to be a mixture of two compounds. Separation was achieved by preparative t.l.c. in hexane. The band of R_f 0.85, extracted with boiling dichloromethane, furnished 9-thiabicyclo[4.2.1]non-7-ene (144) (0.042 g, 30%) and that of R_f 0.17 gave (150) (0.15 g, 70%).

CHAPTER 3

Approaches to 2,3-Disubstituted and 3,6,7-trisubstituted 8-Thiabicyclo(3.2.1)octanes

In Chapter 1, syntheses were undertaken of 8-thiabicyclo-[3.2.1]octanes, in which a number of medium to high yielding functional group modifications at C(6) and C(7) were demonstrated. To provide synthetic routes to thia-tropane structures by the SCl_2-cycloheptadiene addition route (Scheme 12) it would be necessary also to place an oxygen function at C(3), as the tropane alkaloids are commonly derivatives of tropan-3-ols.

The formation of such 3-hydroxy-8-thiabicyclo[3.2.1]-octanes could notionally be achieved by addition of SCl_2 to cyclohepta-3,5-dienol (108) forming (152), which could be structurally modified at C(3), C(6) and C(7). However, a serious limitation to this approach was apparently uncovered by Routledge[36], who was unable to obtain the adduct (152) (see Introduction)

It was proposed to seek conditions under which SCl_2 could be induced to condense with cyclohepta-3,5-dienol. If this proved difficult, SCl_2 condensation with selected esters of cyclohepta-3,5--dienol would be undertaken. Indeed, Routledge has already shown that the benzoate (153) was quantitatively formed by reaction of SCl_2 with 1-benzoyloxycyclohepta-3,5-diene (154). However, this route may not be applicable to non-aromatic unsaturated esters (e.g. tiglate), the double bonds of which would possibly compete with the diene system for the SCl_2.

Two further aims of this part of the project were to attempt methoxycarbonylation at C(2) of the known ketone (126) as an approach to the synthesis of thia-cocaine (155), and to investigate the methylation of the sulphur bridge of the 8-thiabicyclo[3.2.1]octanes.

Condensation of SCl_2 with (108), prepared from tropone (151), had been originally attempted by adding the two reactants simultaneously to a reservoir of dichloromethane over 2 minutes at - 70°. It was claimed[36] that the NMR spectrum of the crude product showed no absorptions characteristic of a bicyclic dichloro-thioether adduct. The reaction was repeated but the reaction time was increased from 2 to 20 minutes. The resulting mixture was light yellow but on removal of solvent it darkened considerably and difficulty was encountered in the isolation of colourless crystalline material. By a combination of solvent trituration, decolourisation with charcoal, small-scale short-path vacuum sublimation and thin layer chromatography, pure samples of (159) were obtained as colourless needles, m.p. 170 - 180° (with considerable sublimation from 90°). These showed an OH stretching absorption at 3310 cm^{-1}, characteristic H-CCl peaks at δ 4.8 ppm (Fig. 23) and a molecular ion grouping of 212, 214, 216 (9:6:1 in area) in the mass spectrum in accord with the molecular formula of $C_7H_{10}OCl_2S$, as derived from microanalysis.

Since two diastereoisomers of (152) are possible, its homogeneity was checked by t.l.c. and gas chromatography. In six different solvent systems, (152) ran as a single spot on t.l.c. A gas chromatogram of the trimethylsilyl derivative of (152) showed one large peak accompanied by a very small deflection indicating a minor amount of another substance. When analysed by GCMS, the minor component showed a molecular ion of m/e 292 and its mass spectrum bore no similarity to that of the major component (M 284, 286, 288; 9:6:1 by area). It was concluded that the minor compound was not the diastereoisomer of the major product, which was thus formed as a single diastereoisomer.

To ascertain the C(3) configuration of this single product, an analysis of the NMR couplings of the proton on C(3) with those of the adjacent methylene groups was undertaken.

On double irradiation at the bridgehead signal (δ 3.55), both methylene envelopes resolved into double doublets, that at δ 2.5 - 2.8 showing couplings of 5.6 and 13 Hz and that at δ 1.85, 10 and 13 Hz. The 13 Hz coupling was assigned to the geminal coupling between the axial and equatorial protons of the methylene groups. Thus, the H - C(3) proton shows two couplings, 10 and 5.6 Hz, with the methylene hydrogens, the former being of the amplitude of a 1,2-diaxial coupling and the latter of a 1,2-axial-equatorial coupling. This would immediately indicate an equatorial configuration (exo) of the C(3) hydroxyl group of (152), with the six-membered ring in

a chair conformation (Fig 24), allowing the H - C(3) (axial) to form a dihedral angle of 180° with the axial H - C(2), H - C(4) and of 60° with the equatorial H - C(2), H - C(4). However, inspection of a molecular model of (152) with the C(3) hydroxyl group axial (endo) shows that there would be a very severe non-bonded interaction between the hydroxyl group and the endo chlorine substituents if the six-membered ring were in the chair conformation (Fig. 25). Consequently, it is more likely that this diastereoisomer of the alcohol would exist with the six-membered ring in the boat conformation (Fig. 26). In this conformation, the same dihedral angles of 180° and 60° exist between the C(3) - H and the methylene protons. Based on this decoupling experiment, the C(3) hydroxyl configuration cannot be uniquely defined from the two possibilities, chair conformation with exo(equatorial) C(3) hydroxyl and boat conformation with endo C(3) hydroxyl.

The alternative two possibilities can definitely be ruled out, i.e. the chair conformation with endo (axial) C(3) hydroxyl (considered above) and the boat conformation with exo C(3) hydroxyl, both of which allow for equal amplitude of coupling of H - C(3) with the methylene protons, the dihedral angles subtended with both axial and equatorial methylene hydrogens being ca. 60°.

To establish the six-membered ring conformation, measurement was undertaken of the dihedral angles subtended between the bridgehead C - H bond and those of the methylene hydrogens.

Double irradiation at δ 4.8 (H - CCl) simplified the bridgehead multiplet (δ 3.55) to a broad double doublet embodying two main couplings of medium-low amplitude, 3.5 and 2 Hz, for the vicinal cyclohexane-like situation. This clearly establishes the six-membered ring as a chair conformation where H - C(1) (equatorial) forms dihedral angles of ca. 75° and 35° with axial and equatorial H - C(2) respectively, as measured on a model. The model shows that adoption of a boat conformation by the six-membered ring creates dihedral angles between H - C(1) and the methylene C - H bonds of ca. 95° and 10°, which would lead to one small and one large coupling (not observed).

The boat conformation with the C(3) alcohol endo is thus ruled out. It follows that (152) exists as one diastereoisomer with the C(3) hydroxyl group equatorial in a chair six-membered ring.

Having thus established the structure, homogeneity, configuration and conformation of the alcohol (152), its esterification with tiglic acid (45) was investigated with a view to forming a thia analogue of tropigline (14). Difficulties were anticipated in this esterification since it was recognised that both the alcohol and the acid components are stereochemically hindered. Tiglic acid was converted to its acid chloride using thionyl chloride and reacted with the alcohol (152). The crude reaction product was shown by t.l.c. to be a mixture of unreacted alcohol (152) and one other compound.

Separation was achieved by preparative t.l.c. in hexane-dichloromethane 1:1 and the band of R_f 0.75 contained the tiglyl ester (156) (26% yield). In addition to alcohol (152) from the band of R_f 0.25, other minor bands were present containing small amounts of material. The ester (156) was triturated with and crystallised from hexane mixed with a small amount of ether to produce colourless needles, m.p. 114 - 115°, which gave microanalysis figures consistent with the molecular formula $C_{12}H_{16}O_2Cl_2S$. The IR spectrum lacked the hydroxyl absorption 3310 cm^{-1} characteristic of the alcohol (152) but showed a peak at 1713 cm^{-1} due to an α, β unsaturated ester. The NMR spectrum (Fig. 27) showed a vinyl multiplet at δ 6.8, two kinds of methyl absorption, a singlet at δ 1.8, a doublet (J ∿ 3 Hz) at δ 1.72, and the C(3) proton resonance was shifted downfield relative to that of (152) to δ 5.35. No molecular ion was seen in the mass spectrum but peaks at 194, 196, 198 (9:6:1 by area) suggested that elimination of tiglic acid occurred immediately on bombardment with the electron beam to give the cation of the alkene (157).

Analysis of the NMR coupling constants of the bicyclic skeleton of (156) by double irradiation experiments allowed the same stereochemical conclusions to be drawn as for (152). Double irradiation of the bridgehead multiplet at δ 3.55 in the NMR spectrum caused collapse of the methylene envelopes into double doublets, that at δ 2.7 showing couplings of 5.6 and 13 Hz and that at δ 2.05 10 and 13 Hz.

These couplings are exactly the same as for the alcohol (152) and thus the configurational and conformational possibilities for (156) can be narrowed immediately to the two C(3) diastereoisomeric esters, exo ester (158) with the six-membered ring in a chair and endo ester (159) in a boat.

To distinguish between the two ring conformations, double irradiation of the H - CCl protons at δ 4.85 and of the H - CO protons at δ 5.35 was undertaken. In the former case, the sharpening of the bridgehead signal was insufficient to allow measurement of coupling constants. In the latter case, the two methylene envelopes resolved again into double doublets, that at δ 2.7 showing couplings of 6 and 13 Hz and that at δ 2.05 2 and 13 Hz. As with the alcohol (152), the bridgehead proton gives two couplings of medium amplitude, (i.e. 6 and 2 Hz), rather than one large and one small, with the methylene protons. Thus, as before, only the chair conformation with the C(3) substituent equatorial (exo) possesses the appropriate dihedral angles.

Esterification of (152) was also attempted by a modification of the Fisher-Speier method[46] of reflux with tiglic acid in toluene in presence of sulphuric acid as a dehydrating agent. The crude product obtained was shown by t.l.c. to be a mixture which was again separated by preparative t.l.c. to give the unreacted alcohol (152) and the tiglyl ester (156) (7% yield). Neither esterification method is thus efficient but no attempt was made to improve on this conversion.

Because of this low yield, the projected esterifications of (152) with mandelic and tropic acids (see above) were not undertaken in the present work.

In the knowledge that tropane-like esters based on 8-thiabicyclo[3.2.1]octane could be made, albeit in low yield, in two steps from cyclohepta-3,5-dienol (108), it was necessary to find out if the β,β'-dichlorothioether moiety of the intermediate dichloroalcohol (152) was capable of being modified in the same way as for (107) and (111). Thus (152) was refluxed with 1,2-diaminoethane in the presence of zinc and one product was quantitatively formed. The assignment of this as the novel unsaturated bicyclic thioether (160) was based on its mass spectral molecular ion at m/e 142, uncharacteristic of a dichloride, and the appearance of vinyl absorption as low-intensity IR absorptions, at 3060 and 1600 cm^{-1}, and a broadened singlet at δ 6.15 in the NMR spectrum (Fig. 28). The presence of the bicyclic skeleton was shown by the bridgehead (δ 3.85) and complex methylene multiplets (δ 2.6 - 1.5). The IR spectrum also showed OH and C - O bonds at 3620 (free), 3480 (bonded), 1049 and 1028 cm^{-1} and the H - CO proton absorption, centred at ca. δ 4.1 was partly obscured by the bridgehead signal. Thus, the dichloroalcohol (152) undergoes smooth dehalogenation in the same way as (107) and (111).

In contrast, (152) failed to react with sodium hydroxide in aqueous dimethoxyethane under nitrogen, even when the reaction time was extended to 28 hours. A possible explanation for this surprising result is that the intermediate sulphonium ion, required for the oxidation-dechlorination sequence depicted in Scheme 15 for (107), is stereochemically hindered by hydrogen-bonding (Scheme 20) with the C(3) exo hydroxyl group, the close approach of the hydrogen-bonded groups being facilitated by conformational inversion of the six-membered ring into the boat.

In agreement with the observed unreactivity of the halogens of (107) and (111) towards electron-dense nucleophiles, (152) was found to be inert to $LiAlH_4$, even when the reagent was present in large excess.

Having established that functional group changes could be achieved in the 8-thiabicyclo[3.2.1]octane ring system at C(3) and C(6), C(7) an investigation was initiated into the possibility of functionalising C(2) via enol derivatives of the ketone (110). (110) was made by the reported[47] procedure of replacement of a nitrogen bridge by a sulphur bridge by reaction of quaternised tropinone with sodium sulphide.

Thus tropinone (61) reacted with methyl iodide to give tropinone methiodide (161) as a fine colourless powder, m.p. 280 - 281° (lit.[48] m.p. 278°). Treatment of (161) with sodium sulphide nonahydrate in water furnished (110) as colourless needles, m.p. 143 - 146° (lit.[47] m.p. 155 - 156°).

The structure of this product was confirmed by the appearance of a strong carbonyl stretching absorption at 1713 cm^{-1} in the IR spectrum and a sulphur bridgehead signal at δ 3.81 in the NMR spectrum (Fig. 29). The latter also disclosed the presence of two different kinds of methylenic protons, i.e. those adjacent to carbonyl at δ 2.7 and those of the tetrahydrothiophene ring at δ 2.3 - 1.8, of equal integrated intensity.

α-Methoxycarbonylation of (110) was attempted by treatment with dimethyl carbonate - sodium methoxide but the starting material was returned unreacted.

An attempt was made to prepare the pyrrolodine enamine of (110) by reflux with pyrrolidine containing a few drops of pyridine in presence of 4 A molecular sieves but no reaction took place. Changing to acid catalysis, (110) was refluxed with morpholine in presence of a few crystals of p-toluene sulphonic acid[49] but (110) remained unchanged. The attempted reaction of (61) with pyrrolidine in the presence of the Lewis acid titanium (IV) chloride[50] was also unsuccessful.

It thus appears that the carbonyl group of (110) is stereochemically hindered towards the approach of the secondary amines pyrrolidine and morpholine. To check if this carbonyl group would be reactive to primary amines, (110) was refluxed with hydroxylamine in ethanol in presence of a small volume of pyridine. The oxime (162), m.p. 85 - 86°, was formed in 95% yield and purified by vacuum sublimation. (162) gave

microanalytical figures consistent with the molecular formula, $C_7H_{11}NOS$, and the molecular ion at m/e 157 in the mass spectrum. Hydroxyl stretching absorption appeared in the IR spectrum at 3590 (free) and 3260 cm^{-1} (bonded) and the imine double bond as a weak band at 1645 cm^{-1}. The methylenic absorptions in the NMR spectrum (Fig. 30) were complex and widely spread from δ 3.4 to 1.8 but the bridgehead signal was visible at δ 3.7 and the hydroxyl proton appeared downfield as a broad peak at δ 9.5. While (110) reacted easily with the primary amino group of hydroxylamine, no further attempt was made to prepare enamines by reaction with secondary amines.

In the previously described synthetic approaches to thiatropanes, no attempt was made to match the N - Me bridge of the tropanes by methylation of the sulphur atom of the 8-thiabicyclo-[3.2.1]octanes. As a first step towards the development of a generally applicable methylation procedure, the dichlorosulphide (107) and the ketosulphide (110) were separately treated with iodomethane under the conditions used to form tropinone methiodide (161) from tropinone (61) (see above). No precipitate of S-methyl sulphonium iodide collected and, on removal of solvent, the starting material was returned unchanged. In the current work, procedures using more reactive methylating agents, e.g. dimethyl sulphate or trimethyloxonium borofluoride, have not been investigated.

EXPERIMENTAL SECTION

Cycloheptatrienone (Tropone) (151)[51]

To a solution of potassium dihydrogen phosphate (13.5 g) in distilled water (33 ml) were added dioxan (330 ml), selenium dioxide (53. 0 g, 0.48 mmol) and cycloheptatriene (43.0, 0.46 mmol). The mixture was stirred at 90° for 15 h, filtered and the filtrate poured into water (750 ml). The mixture was extracted three times with dichloromethane and the extract washed with saturated sodium bicarbonate and brine, dried and evaporated leaving a dark brown oil (23.51 g). Distillation of this residue under reduced pressure (0.3 mm) gave (151) (14.42 g, 0.15 mmol, 33%), b.p. 65 - 68° (lit.[51] b.p. 91 - 92°, 4 mm); ν_{max} (liq. film) 3450, 3010, 1710, 1633, 1576, 1520, 1470, 1255, 1215, 895, 830, 780 and 580 cm^{-1}; δ 7.1 (complex m).

Cyclohepta-3,5-dienol (108)[52]

Sodium borohydride (1.401 g, 38.9 mmol) was added slowly to a solution of tropone (2.1 g, 19.8 mmol) in methanol (50 ml) causing immediate evolution of hydrogen. The mixture was stirred for 2 h at room temperature and residual sodium borohydride decomposed by the dropwise addition of glacial acetic acid (7 ml). The mixture was neutralised with saturated sodium carbonate solution and extracted with ether. The combined extracts were washed with brine, dried and evaporated. The brown oily residue was distilled to give, as a colourless oil (108) (1.12 g, 10.18 mmol, 51%), b.p. 30 - 36°, 0.1 mm (lit.[52] b.p. 45 - 52°, 6 mm); ν_{max} (liq. film) 3354, 3012, 2900, 1615, 1440, 1055, 1020, 990, 890, 835, 675 and 610 cm^{-1}; δ 5.9 (m, 4 H; vinyl), 4.3 (m, 1 H; H - CO), 2.55 (m, 4 H; CH_2)

Reaction of Cyclohepta-3,5-dienol (108) with Sulphur Dichloride

Cyclohepta-3,5-dienol (108) (1.1 g, 10 ml) and sulphur dichloride (1.13 g, 10.97 mmol) each dissolved in dichloromethane (10 ml), were added simultaneously over 5 m to dichloromethane (25 ml) which was vigorously stirred at -70° (bath temp.). The stirred mixture was maintained at -70° for 15 min and allowed to come to room temperature. The solution was evaporated leaving a yellow solid which was triturated with ether-dichloromethane to give 6,7-dichloro-8-thiabicyclo-[3.2.1]octan-3-ol (152) (1.5 g, 7 mmol, 70%), substantially pure by NMR. An analytical sample of (152) was prepared by short-path sublimation at 90°, 0.005 mm as colourless needles, m.p. 175 - 176°, (Found: C, 39.64; H, 4.67. $C_7H_{10}OSCl_2$ requires C, 39.46; H, 4.73%); m/e 216, 214, 212 (1:6:9;M), 179, 177 (M - Cl), 161, 159 (177 - H_2O), 143, 141, 113, 97 (C_5H_5S) and 45 (base peak); ν_{max}(KBr) 3310, 2940, 2919, 2854, 1450, 1437, 1350, 1045, 1032, 890, 847, 798, 772 and 613 cm^{-1}; δ 4.8 (dd, J ∿ 4 and 2.5 Hz, 2 H; H - CCl), 6.36 (septuplet, J ∿ 7 Hz, 1 H; H - CO), 3.56 (m, 2 H; H - CS), 2.8 - 2.5 (m, 2 H; CH_2), 2.0 - 1.7 (bt, J ∿ 12 Hz, ca. 2H; CH_2) and 1.74 (s, ca. 1 H; OH).

6,7-Dichloro-3-tiglyloxy-8-thiabicyclo[3.2.1]octane (156)

a) Tiglic acid (0.30 g, 3 mmol) was refluxed (bath temp. 80 - 120°), with freshly distilled thionyl chloride (0.393 g, 3.3 mmol) for 1 h and excess thionyl chloride was removed under suction. A solution of 6,7-dichloro-8-thiabicyclo[3.2.1]-octan-3-ol (152) (0.2130 g, 1 mmol) in dichloromethane was added

and the resulting solution refluxed for 16 h. On cooling, the reaction solution was poured into water and extracted with dichloromethane, the extract being washed with saturated sodium bicarbonate, water to neutrality and dried. Removal of solvent gave a brown solid (0.05 g) which was shown, by t.l.c. in dichloromethane-hexane (8:2), to contain alcohol (152) and two less polar compounds in unequal amounts. Preparative thin layer chromatography in dichloromethane-hexane (8:2) gave (156) (0.04 g 26%) from the band of R_f 0.75 and (152) (0.1 g) from the band of R_f 0.25.

b) A mixture of (152) (0.107 g, 0.5 mmol) and tiglic acid (0.1 g, 1 mmol) in toluene containing one drop of conc, sulphuric acid was refluxed for 3 h, during which time some charred material collected out of solution. The toluene was removed under suction and the residue, in dichloromethane, was washed with saturated sodium bicarbonate, water to neutrality and dried. Removal of solvent gave a brown semi-solid which was shown by t.l.c. in dichloromethane, hexane (1:1) to be a mixture of (152) and ester (156). The mixture was separated by thin layer chromatography in dichloromethane-hexane (1:1). The band of R_f 0.45, extracted with boiling dichloromethane, gave (156) (0.01 g, 7%) (based on alcohol reacted) as a pale yellow solid and the band of R_f 0.1 extracted with boiling ethyl acetate, contained alcohol (0.005 g). Other bands contained only small amounts of material.

c) Combined samples of the ester (156) (0.05 g) were washed with hexane-ether to remove colour and recrystallised from hexane (containing a little ether) as colourless needles, m.p. 114 - 115° , (Found: C, 48.54; H, 5.53. $C_{12}H_{16}O_2Cl_2S$ requires C, 48.83; H, 5.46%); m/e 298, 296, 294 (M, only seen after signal amplification), 198, 196, 194 (1:6:9; M - $C_5H_8O_2$; base peak 194), 165, 163, 161 (M - SH), 159, 125, 97 (C_5H_5S) and 91; ν_{max} 2955, 2930, 2855, 1713, 1615, 1262, 1153, 1134, 1073, 908, 892 and 618 cm^{-1}; δ 6.8 (m, 1 H; vinyl), 5.4 (septuplet, J ∿ 6 Hz, 1 H; H - CO), 4.74 (dd, J ∿ 4 and 2.5 Hz, 2 H; H - CCl), 3.52 (m, 2 H; H - CS), 2.85 - 2.5 (m, 2 H; CH_2), 2.15 - 1.5 (m, Ca. 2H; CH_2), 1.8 (s) and 1.75 (d, J ∿ 7 Hz) (together ca. 6 H; CH_3).

Reaction of 6,7-Dichloro-8-thiabicyclo[3.2.1]octan-3-ol (152) with 1,2-Diaminoethane

A mixture of (152) (0.1 g, 0.47 mmol), zinc dust (0.65 g, 10 mmol) and 1,2-diaminoethane (5 ml) was refluxed (bath temperature 120°) with vigorous stirring for 21 h. The reaction mixture was filtered and the filtrate poured into ether and washed with water. The separated organic layer was dried and evaporated to give 3-hydroxy-8-thiabicyclo[3.2.1]oct-6-ene (160) (0.066 g, 100%). An analytical sample of (160) was prepared by short-path sublimation at 70° at water pump pressure as colourless needles m.p. 119 - 120°, (Found: m/e 142.0462, $C_7H_{10}OS$ requires 142.04613); m/e 142 (M), 124 (M - H_2O), 97 (C_5H_5S, base peak) and 97 (C_7H_7); ν_{max} 3620, 3480, 3060, 2959

2910, 2844, 1600, 1328, 1098, 1049 and 1028 cm^{-1}; δ 6.15 (bs, 2 H; vinyl), 4.3 - 3.8 (m; H - CO), 3.85 (m; H - CS) (together 3 H) and 2.6 - 1.5 (m, ca 5H; CH_2 and OH).

Attempted Solvolysis of 6,7-Dichloro-8-thiabicyclo[3.2.1]octan-3-ol (152) with Sodium Hydroxide

A mixture of (152) (0.107 g, 0.5 mmol), dimethoxyethane (75 ml) and 10% aqueous sodium hydroxide (5 ml) was refluxed under nitrogen for 20 h. The reaction mixture was concentrated under suction and extracted with ethyl acetate. The ethyl acetate layer was dried and evaporated leaving a brown solid, the NMR of which indicated only the presence of unreacted starting material.

Attempted Reaction of 6,7-Dichloro-8-thiabicyclo[3,2,1]octan-3-ol (152) with Lithium Aluminium Hydride

Lithium aluminium hydride (0.285 g, 7.5 mmol) in anhydrous tetrahydrofuran was added to a solution of (152) (0.321 g, 1.5 mmol) in the same solvent (10 ml) and the mixture refluxed for 2 h with stirring. On cooling, a few drops of saturated sodium sulphate were added. The solution was filtered and the filtrate evaporated to give unreacted starting material.

Reaction of Tropinone (61) with Iodomethane[48]

Tropinone (61) (2.06 g, 14.8 mmol) was dissolved in absolute ethanol (12.5 ml) and iodomethane (2.75 g, 19.4 mmol) added dropwise with stirring. After stirring for 2 h, ether (37.5 ml) was added and the precipitated tropinone methiodide

(161) filtered and washed with ether. Recrystallisation from aqueous methanol gave needles (20.6 g, 9.25 mmol, 62%) m.p. 278 - 280° (lit.[48] m.p. 278°) ν_{max}^{KBr} 3015, 2940, 1725, 1460, 1320, 1260, 1205, 1115, 1025, 985, 925 and 460 cm^{-1}.

Reaction of Tropinone Methiodide (161) with Sodium Sulphide[47]

Tropinone methiodide (161) (1.04 g, 3.7 mmol) and sodium sulphide nonahydrate (2.8 g, 11.7 mmol) were dissolved in water (85 ml) and stirred at 85° for 2 h under nitrogen. On cooling, the solution was extracted with ether and the combined extracts washed with dilute hydrochloric acid and brine to neutrality. Drying and evaporation of solvent gave (110) as a yellow solid (0.34 g. 65%). This was decolourised by passing in ether through a short column of alumina (Grade O, basic) and recrystallised from methanol as needles, m.p. 143 - 145° (lit.[47] m.p. 155 - 156°); m/e 142 (M), 114 (M - CO), 109 (M - HS), 99 and 85 (C_4H_5S); ν_{max} 2960, 2942, 2908, 2872, 1713, 1404, 1331, 1206, 1041 and 980 cm^{-1}; δ 3.81 (m, 2 H; H - CS), 2.7 (m, 4 H; H - C(2), H - C(4) and 2.3 - 1.8 (m, 4 H; H - C(6) H - C(7)).

Attempted Reaction of 8-Thiabicyclo[3.2.1]octan-3-one(110) with Dimethyl Carbonate.

Cuttings of sodium metal (0.3 g, 13 mmol) were stirred for 30 m with 50 ml of dry ethanol. With stirring maintained, a solution of (110) (0.158 g, 1.11 mmol) in ethanol (10 ml) and, after 30 m, dimethycarbonate (1 ml) in ethanol (5 ml) were

added dropwise over several m. The mixture was refluxed (bath temperature 100°) with stirring for 4 h and the cloudy yellow suspension, on cooling, was poured into 100 ml dilute HCl. The mixture was extracted with ether and the separated ether layer washed with sodium carbonate, water, dried and evaporated to give a yellow solid, the NMR of which indicated only the presence of unchanged starting material.

Attempted Reaction of 8-Thiabicyclo[3.2.1]octan-3-one (110) with Pyrrolidine

(110) (0.142 g, 1 mmol), pyrrolidine (10 ml) and a few drops of pyridine were refluxed for 7 h in the presence of 4A molecular sieves. The reaction mixture was poured into ether and washed with water to neutrality. The organic layer was dried and evaporated to give a brown solid (0.121 g), the NMR of which indicated only the presence of unreacted starting material.

Attempted Reaction of 8-Thiabicyclo[3.2.1]octan-3-one (110) with Morpholine[49]

A solution of (110) (0.172 g, 1.21 mmol), 10 ml of morpholine and a few crystals of p-toluene sulfonic acid was heated to boiling (bath temperature 127°) in a round bottom flask (25 ml) to which was attached a distillation apparatus. The distillation of water began at once and ceased after 13 h. Most of the morpholine was distilled at atmospheric pressure. The reaction mixture was poured into ether and washed with water. The organic layer was dried and evaporated to give a

yellow solid (0.083 g) which was shown by t.l.c. in ether-hexane (1:1) to be a mixture. This mixture was separated by t.l.c. in ether-hexane (1:1). The band of R_f 0.71 extracted with boiling ethyl acetate gave (110) (0.034 g) and the band of R_f 0.41 apparently gave the same compound (110) (0.015 g). The latter band may have contained the morpholine enamine of (110) but this was hydrolysed by contact with the silica in presence of the boiling extraction solvent.

Attempted Reaction of Tropinone (61) with Pyrrolidine

A mixture of (61) (0.1 g, 0.72 mmol) and pyrrolidine (0.153 g, 2.15 mmol) in toluene was treated at 0 - 5° with titanium (IV)chloride (3 ml) and the mixture was refluxed for 7 h with slow separation of a solid. The mixture was allowed to stand at room temperature for 15 min, treated with pentane and filtered. Evaporation of the pentane gave a solid, the NMR of which showed only the presence of unreacted starting material.

Reaction of 8-Thiabicyclo[3.2.1]octan-3-one (124) with Hydroxylamine Hydrochloride

(124) (0.1 g, 0.7 mmol), hydroxylamine hydrochloride (0.1 g, 1.44 mmol) and pyridine (0.5 ml) were refluxed (bath temperature 100°) with vigorous stirring in ethanol (5 ml) for 25 h. The ethanol was removed under suction and the residue dissolved in ether. The ether solution was washed with water, dried and evaporated to give (113) as a yellow solid (0.05 g, 0.7 mmol, 95%). An analytical sample of (163) was prepared by

short-path sublimation at 40° at 0.1 mm as colourless prisms, m.p. 85 - 86°, (Found: C, 53.73; H, 7.07; N, 8.94. $C_7H_{11}NOS$ requires C, 53.47; H, 7.05; N, 8.91%); m/e 157 (M), 140 (157 - OH, base peak), 123 (140 - NH_3) 97 (C_5H_5S) and 85 (C_4H_5S); ν_{max} 3590, 3260, 2948, 2922, 2890, 2850, 1645, 1430, 1410, 1325, 1312, 1215, 1041, 981, 957, 936, 918 and 868 cm^{-1}; δ 9.5 (bs, 1 H; OH), 3.7 (m, ca. 2 H; H - CS), 3.6 - 3.3 (m, ca. 1 H; CH_2), 2.9 - 2.5 (m, ca. 2 H; CH_2) and 2.5 - 1.8 (m, ca. 5 H; CH_2).

Attempted Methylation of 6,7-Dichloro-8-thiabicyclo[3.2.1]octane (107)

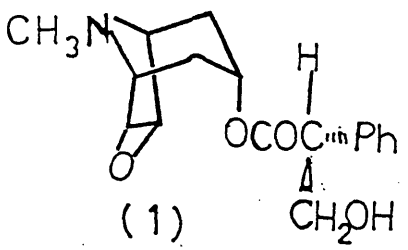
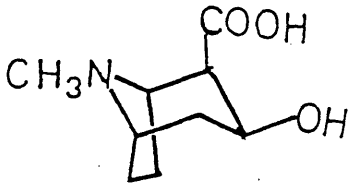
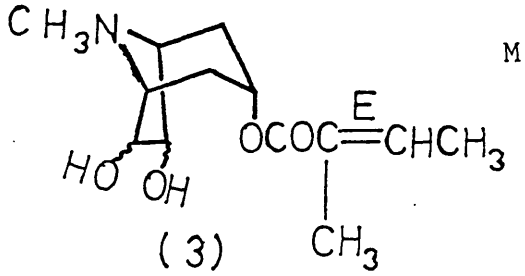
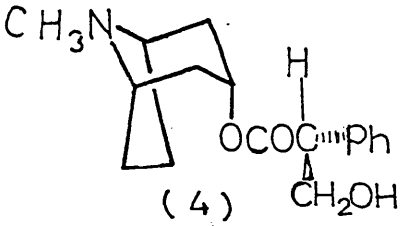
Iodomethane (0.165 g, 1.63 mmol) was added with stirring to (107) (0.197 g, 1 mmol) in absolute ethanol. After stirring for 2 h, ether (10 ml) was added and, since no precipitate appeared, the solvent was removed leaving a yellow solid, the NMR of which indicated only the presence of unreacted starting material.

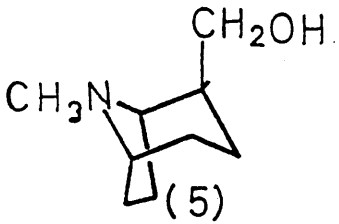
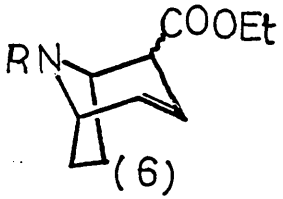
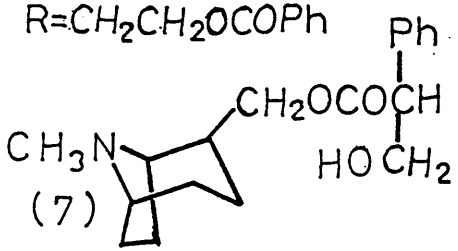
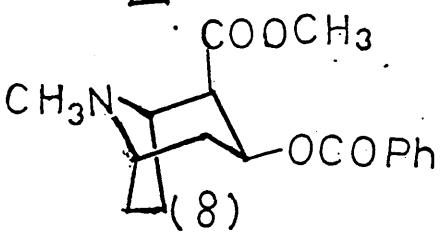
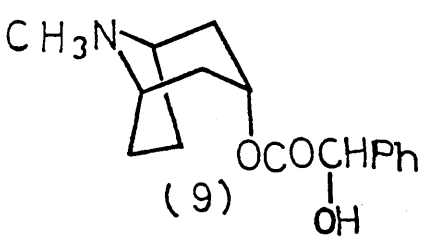
Attempted Methylation of 8-Thiabicyclo[3.2.1]octan-3-one (110)

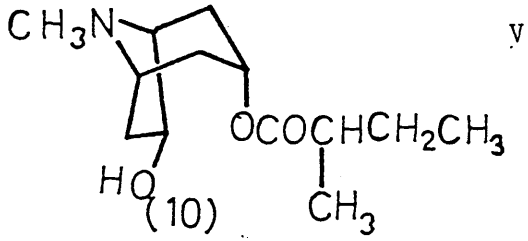
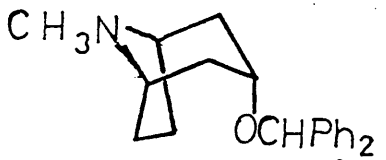
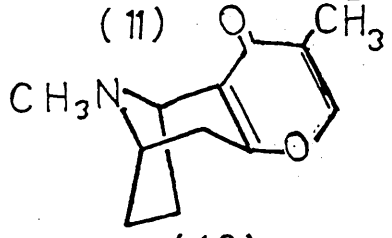
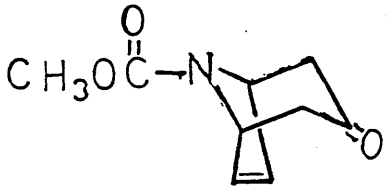
Iodomethane (0.165 g, 1.63 mmol) was added with stirring to (124) (0.142 g, 1 mmol) in absolute ethanol. After stirring for 2 h, ether (10 ml) was added and, since no precipitate appeared, the solvent was removed leaving a yellow solid, the NMR of which indicated only the presence of unreacted starting material.

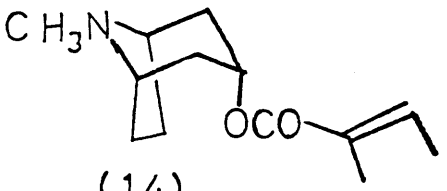
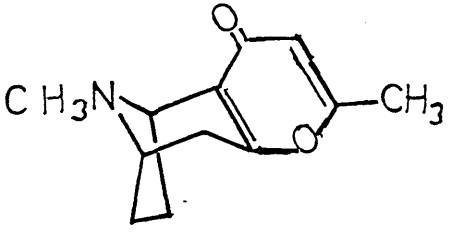
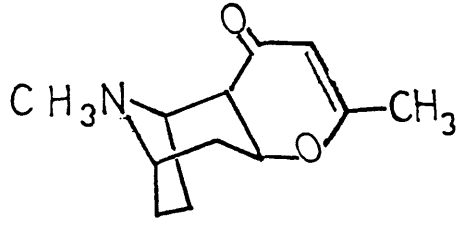
TABLE 1

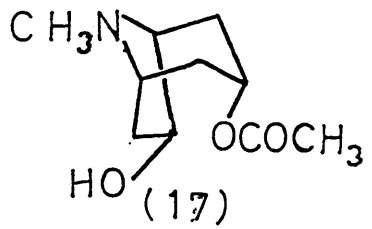
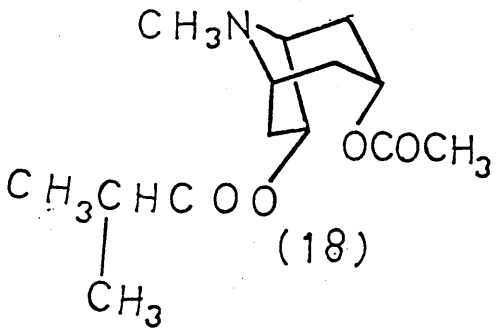
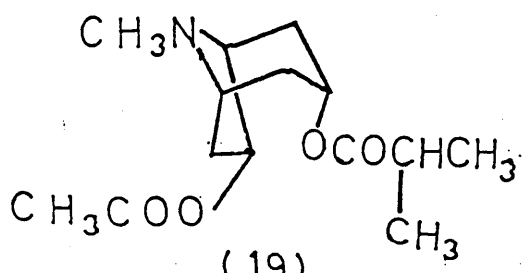
Table 1 Selected Tropanes, Natural and Synthetic, Arranged Approximately by Year of Structural Assignment.

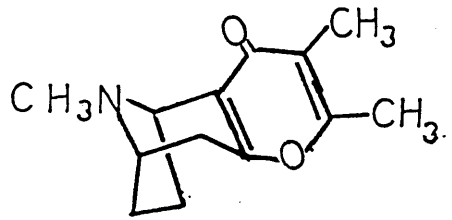
Structure	Name	Source	Activity	Year
 (1)	Scopolamine (Hyoscine)	Atropa, Datura, Hyoscyamus	Powerful narcotic, mydriatic	1880
 (2)	Ecgonine	Cocoa leaves	Similar to β-cocaine but less toxic. Not mydriatic.	1888
 (3)	Meteloidine	Datura meteloides	———	1901
 (4)	Atropine (L-Hyoscyamine)	Atropa belladonna	Antispasmodic, analgesic, anaesthetic, parasympatholytic.	1909

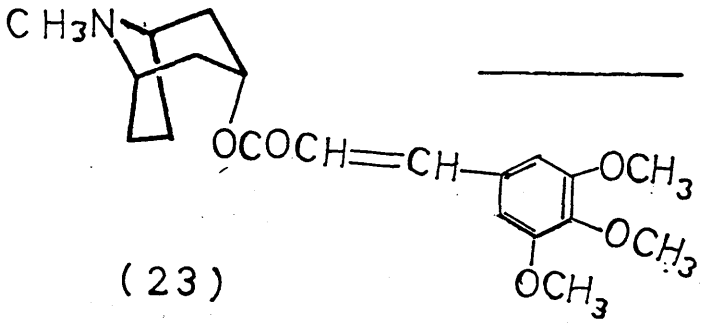
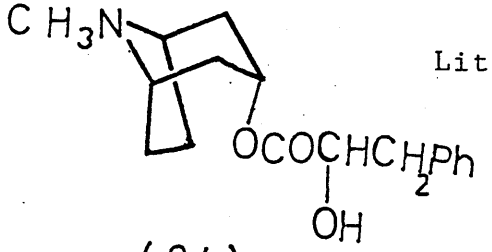
Structure	Name	Source	Activity	Year
 (5)	Homotropine	Synthetic	Local anaesthetic, mydriatic.	1918
 (6)	Eccaine	Synthetic	Non-toxic anaesthetic	1918
R=CH_2CH_2OCOPh  (7)	Mydriasin	Synthetic	Powerful mydriatic	1918
 (8)	β-Cocaine	Erythroxylon Coca.	Narcotic, analgesic, local anaesthetic	1923
 (9)	Homatropine	Synthetic	Cycloplegic, parasympatholytic, mydriatic.	1927

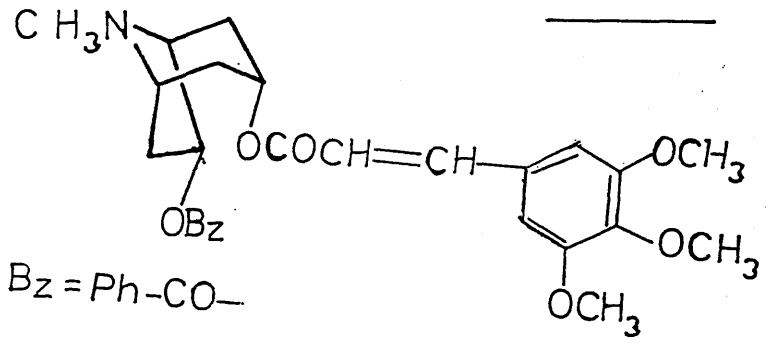
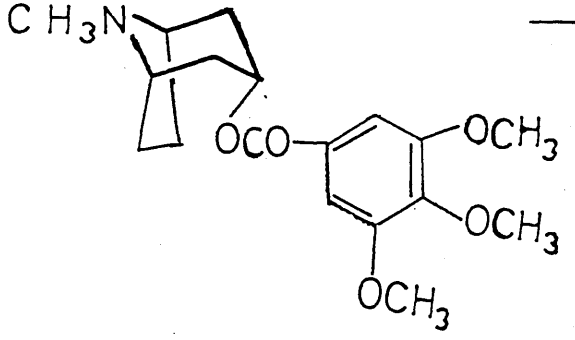
Structure	Name	Source	Activity	Year
 (10)	Valeroidine	Dubosia myoporoides		1937
 (11)	Benztropine	Synthetic	antispasmodic, antihistamine, parasympatholytic, used in treatment of Parkinson syndrome.	1953
 (12)	Bellendine	Proteaceae		1971
 (13)	———	Synthetic	———	1974

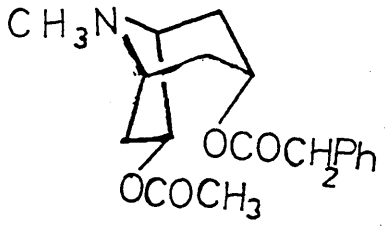
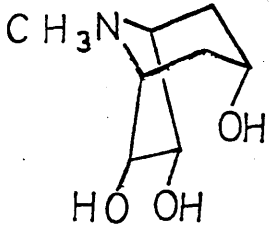
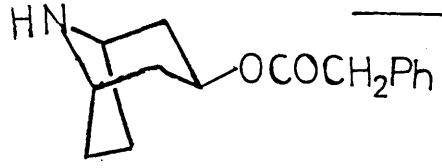
Structure	Name	Source	Activity	Year
 (14)	Tropigline	Physalis peruviana	Antiparkinsonian drug.	1974
 (15)	Isobellendine	Proteaceae	———	1975
 (16)	Cis-endo-Dihydro-iso-bellendine	Proteaceae	———	1975

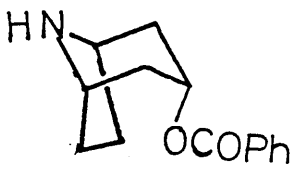
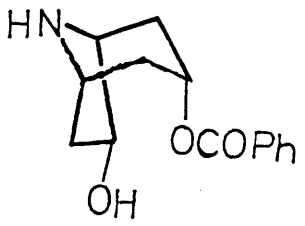
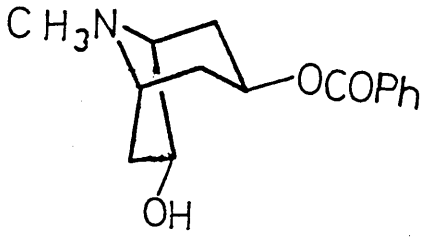
Structure	Name	Source	Activity	Year
 (17)	———	Proteaceae	———	1975
 (18)	———	Proteaceae	———	1975
 (19)	———	Proteaceae	———	1975

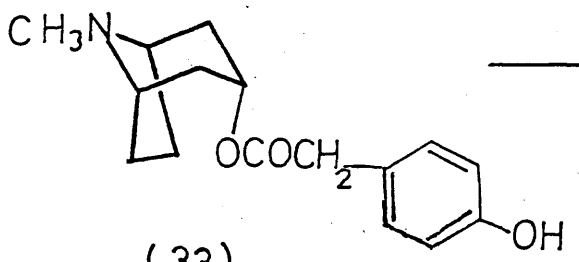
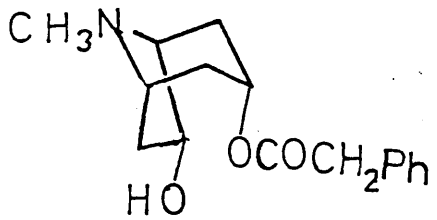
Structure	Name	Source	Activity	Year
 (20)	Darlingine	Darlingea ferruginea	———	1975
 (21)	Ferrugine	Darlingea ferruginea	———	1975
 (22)	Ferruginine	Darlingea ferruginea	———	1975

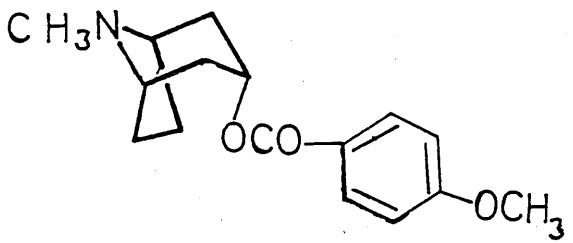
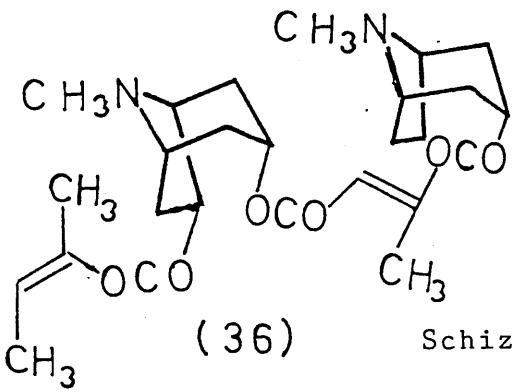
Structure	Name	Source	Activity	Year
 (23)	———	Erythroxylum ellipticum	———	1976
 (24)	Littorine	Datura innoxia	———	1976

Structure	Name	Source	Activity	Year
 (25)	———	Erythroxylum monogynum	———	1976
 (26)	———	Erythroxylum monogynum	———	1976

Structure	Name	Source	Activity	Year
 (27)	———	Erythroxylum dekintii	———	1986
 (28)	Teloidine	Erythroxylum dekintii	———	1986
 (29)	———	Erythroxylum dekintii	———	1986

Structure	Name	Source	Activity	Year
 (30)	———	Erythroxylum macrocarpum	———	1986
 (31)	———	Erythroxylum macrocarpum	———	1986
 (32)	———	Erythroxylum macrocarpum	———	1986

Structure	Name	Source	Activity	Year
 (33)	———	Erythroxylum hepericifolium	———	1986
 (34)	———	Erythroxylum hepericifolium	———	1986

Structure	Name	Source	Activity	Year
 (35)	Datumetine	Leaves of Datura metel	———	1986
 (36)	Schizanthine (-1)	Schizanthus grahamii	———	1987

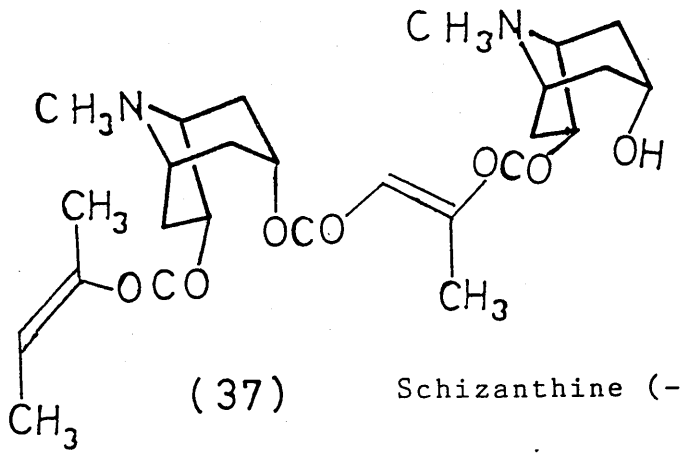
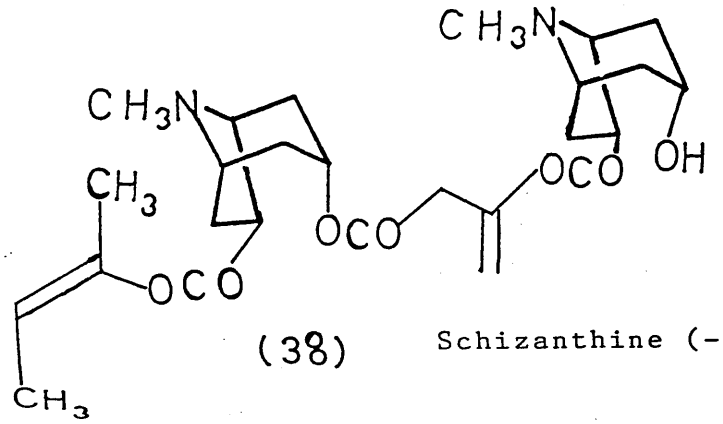
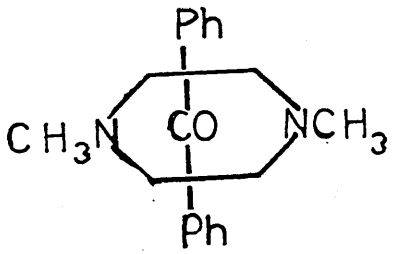
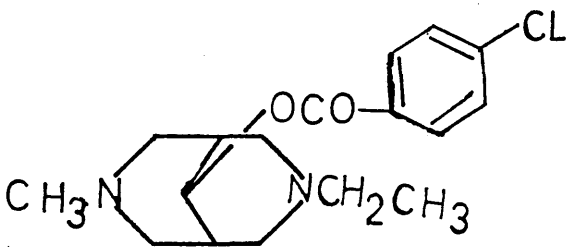
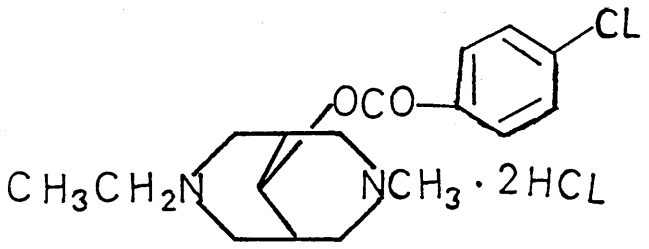
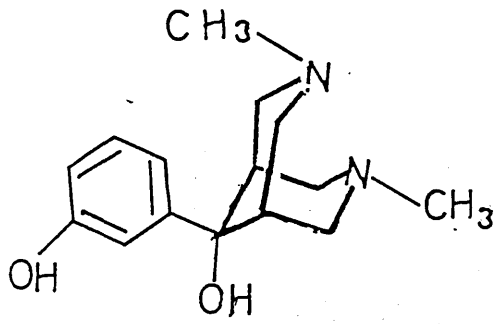
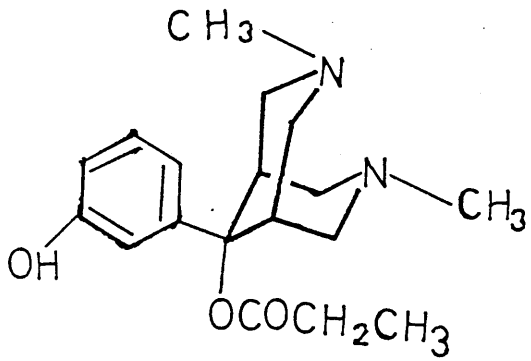
Structure	Name	Source	Activity	Year
 (37)	Schizanthine (-2)	Schizanthus grahamii	———	1987
 (38)	Schizanthine (-3)	Schizanthus grahamii	———	1987

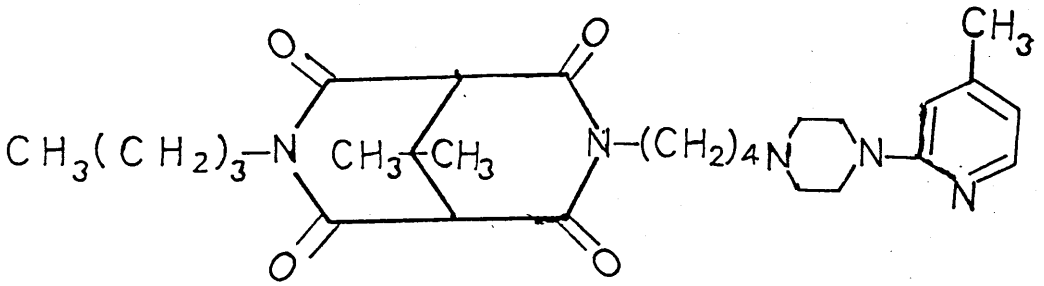
TABLE 2

Table 2 Selected Bispidines, Arranged Approximately by Year of Structural Assignment

Structure	Source	Activity	Year
 (95)	Synthetic	Local anaesthetic	1951
 (96)	Synthetic	Anaesthetic, Ca^{++} antagonist activity, neginotropic and chronotropic effect.	1982

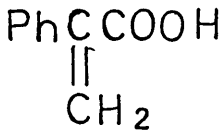
Structure	Source	Activity	Year
 (97)	Synthetic	suppressed the isoprenaline - triggered Ca^{2+} action potentials in the papillary muscle - depolarized with 25 mM K^+. Prolonged the action potential and decreased the slow diastolic depolarization rate in the sinus node. Had no effect on the resting potential but lengthened the initial phase repolarization.	1982

Structure	Source	Activity	Year
 (98)	Synthetic	Narcotic analgesic	1986
 (99)	Synthetic	Narcotic analgesic	1986

Structure	Source	Activity	Year
 (100)	Synthetic	Central nervous system agent.	1987

FORMULAE AND SCHEMES

(1) - (38) see Table 1

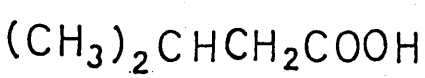


(39)

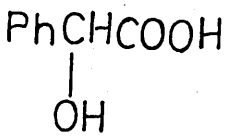
(40)

See Scheme 6

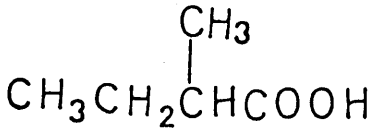
(41)



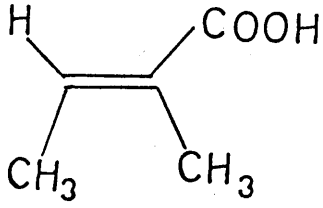
(42)



(43)



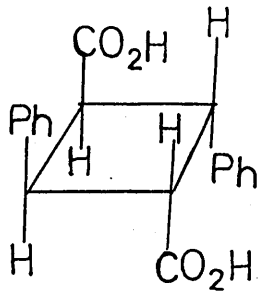
(44)



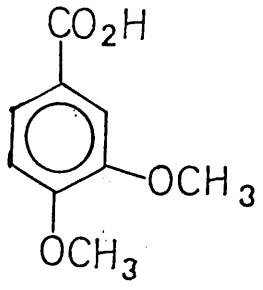
(45)

(46)

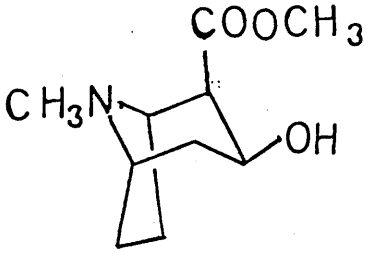
See Scheme 6



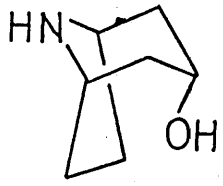
(47)



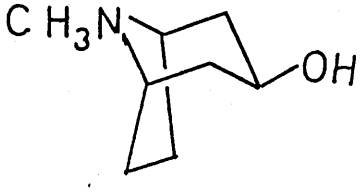
(48)



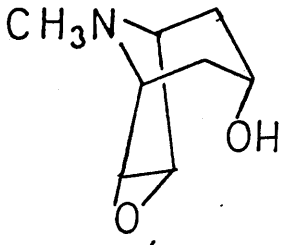
(49)



(50)



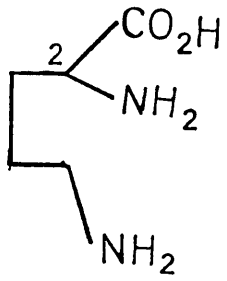
(51)



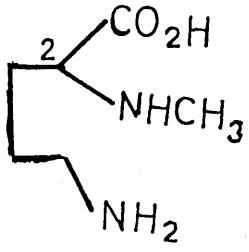
(52)

(53)

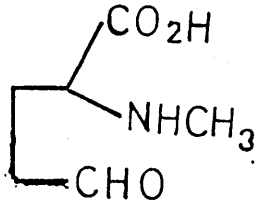
See Scheme 1



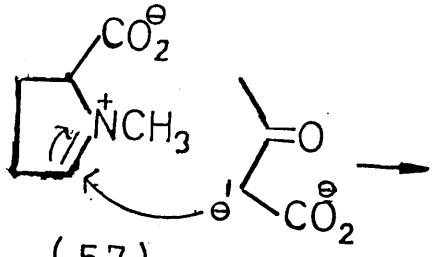
(54)



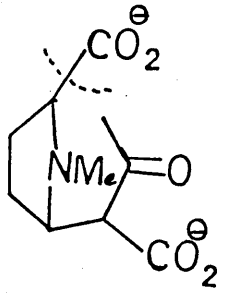
(55)



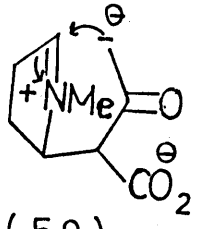
(56)



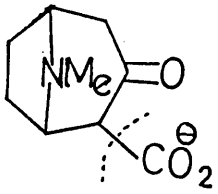
(57)



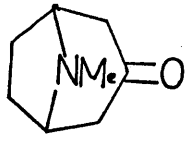
(58)



(59)



(60)



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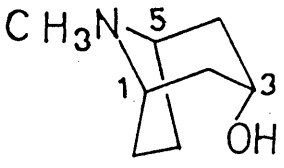
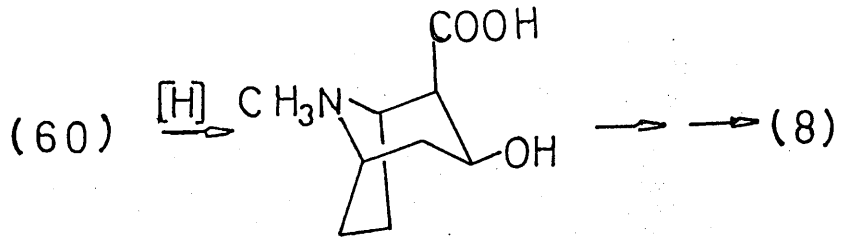


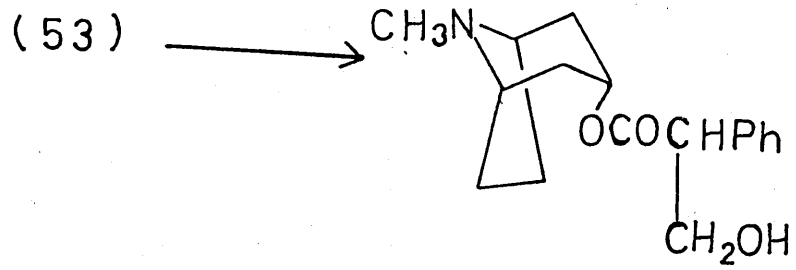
(53)

Scheme 2



(2)

Scheme 3



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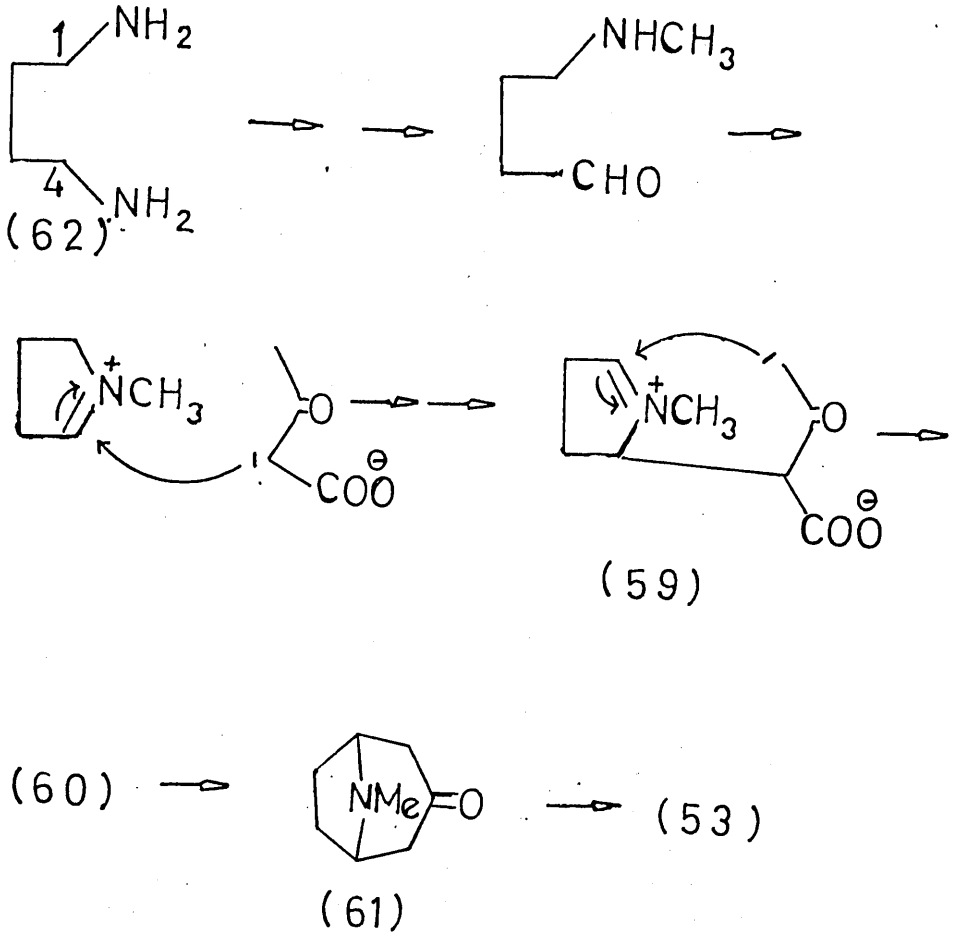
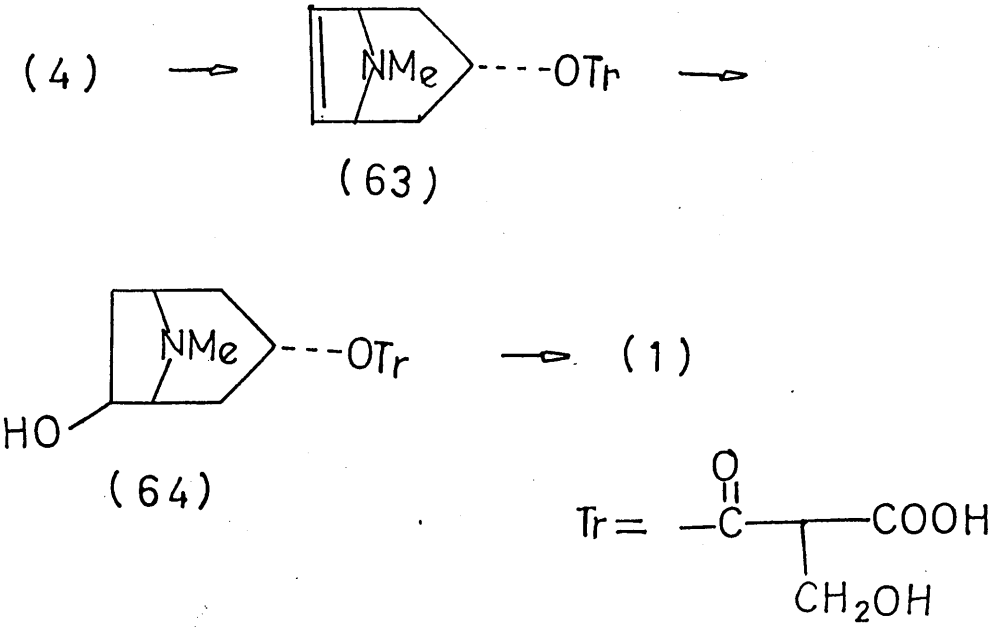
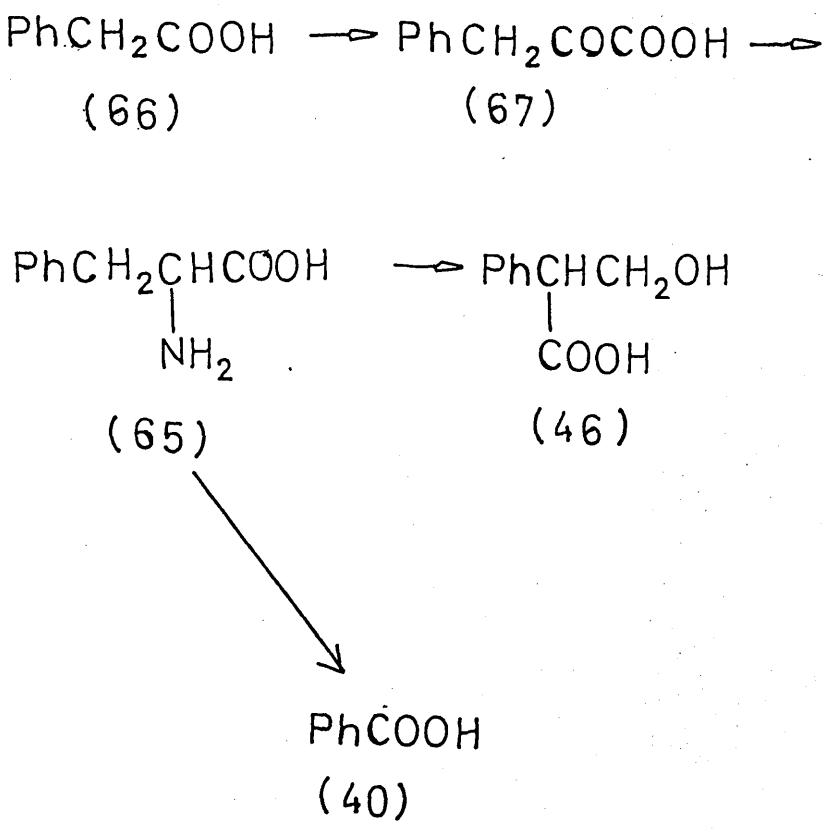
Scheme 4



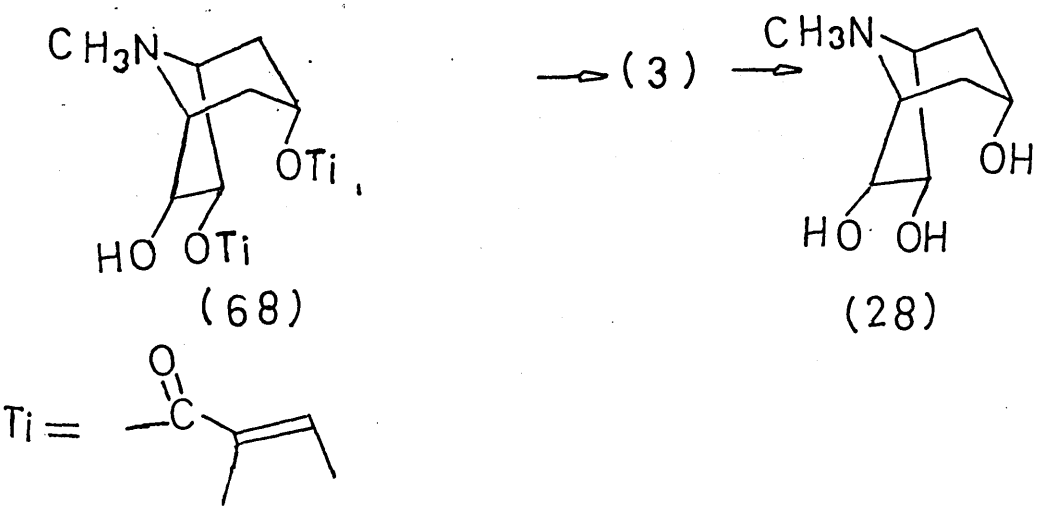
Scheme 5

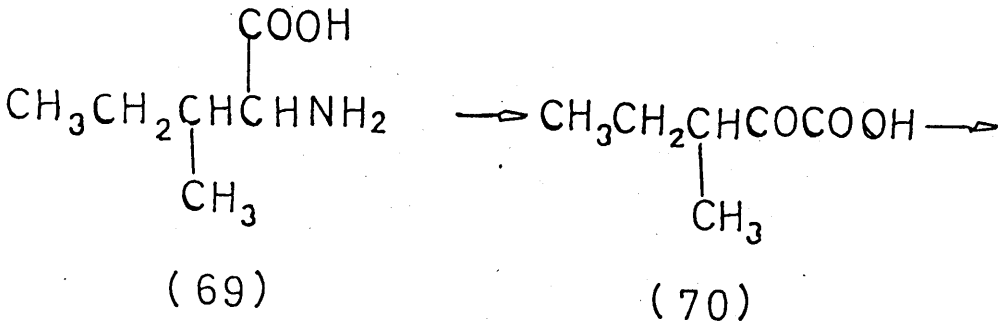


Scheme 6



Scheme 7





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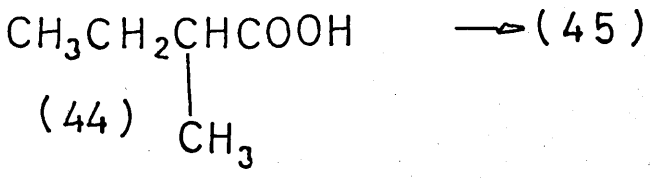

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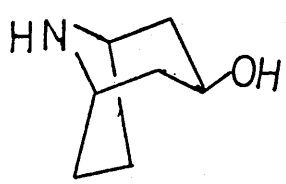

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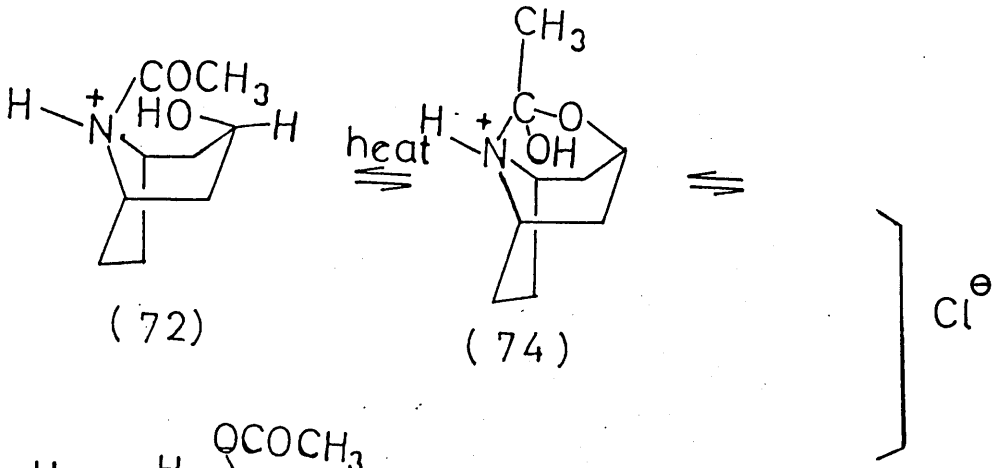

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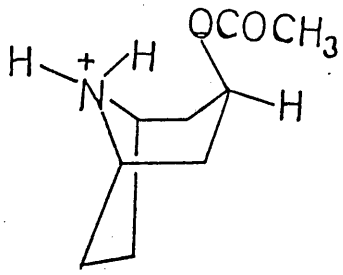

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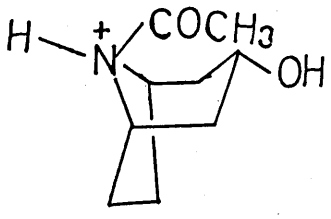

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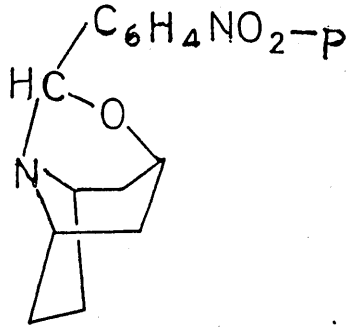

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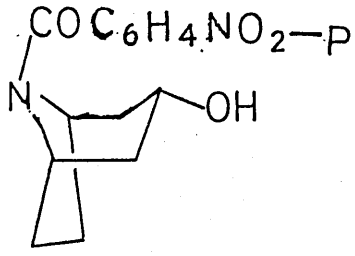

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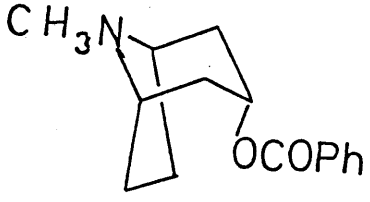

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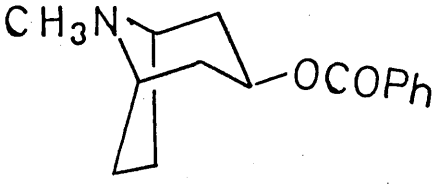

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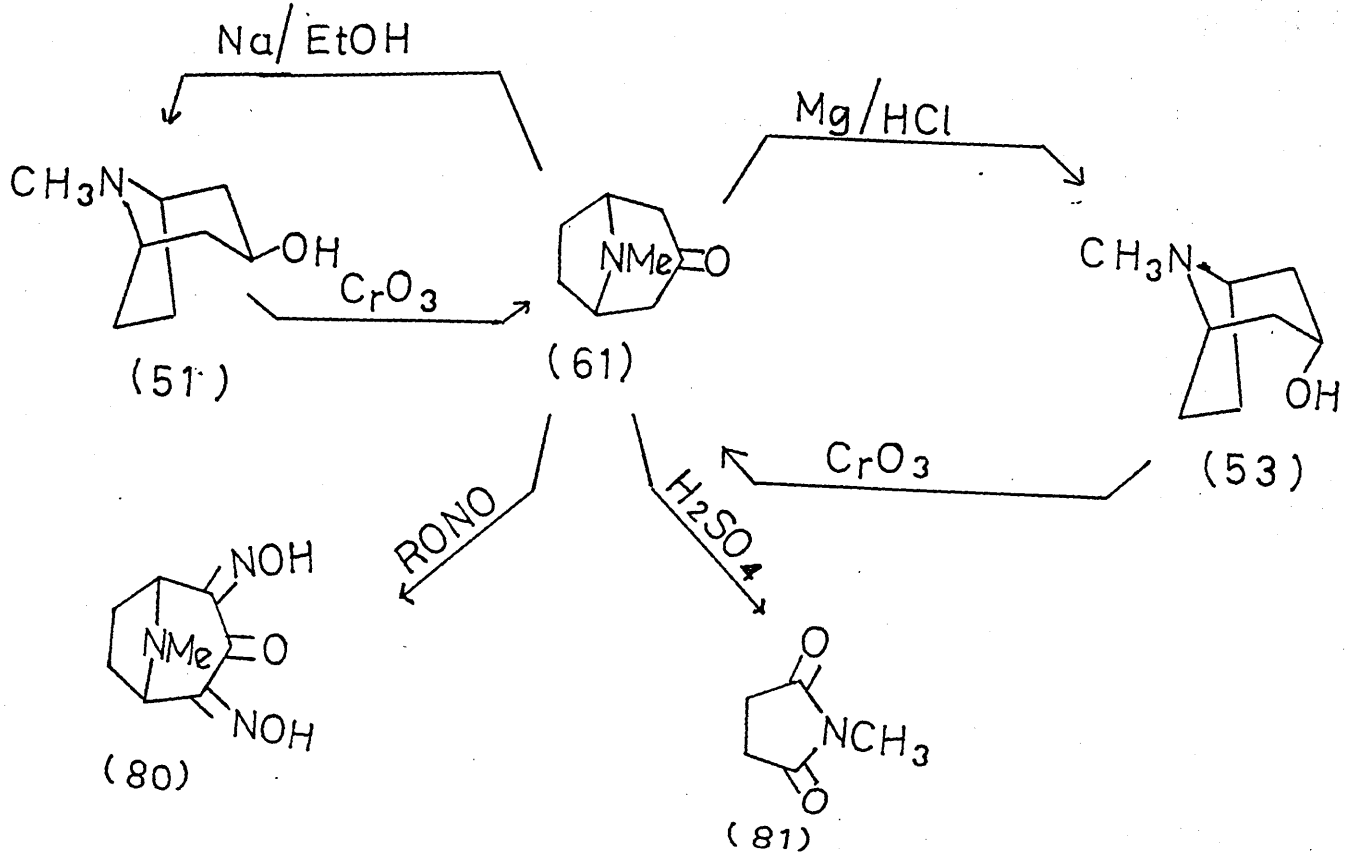
Scheme 10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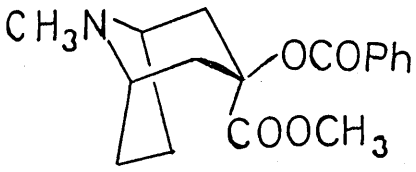
CH3N
OH
CrO3
(51)
NMe
O
(61)
Mg/HCl
CH3N
OH
(53)
CrO3
RONO
H2SO4
NOH
NMe
O
NOH
(80)
O
NCH3
O
(81)



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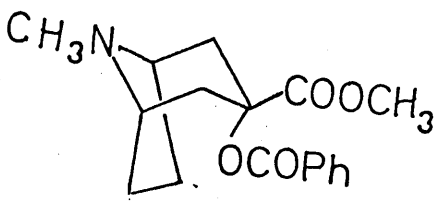

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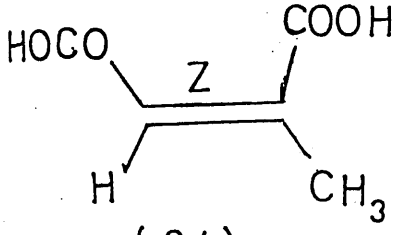

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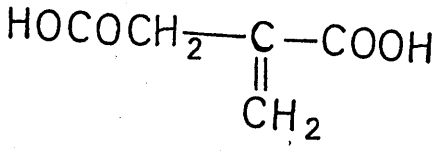

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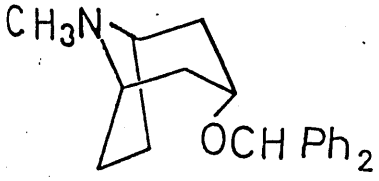

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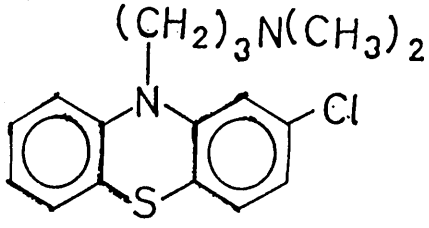

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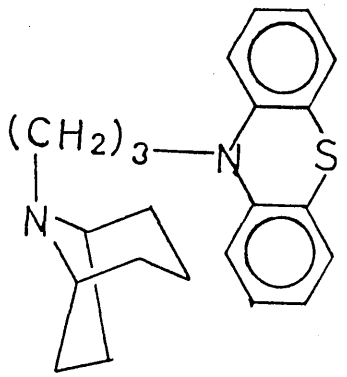

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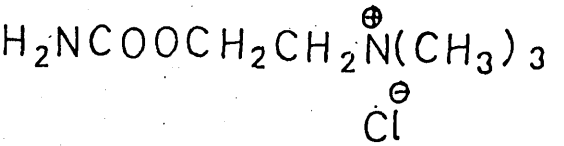

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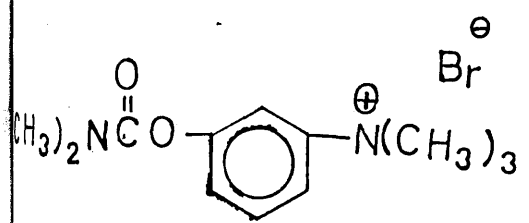

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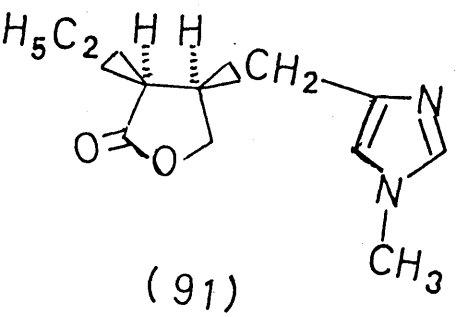

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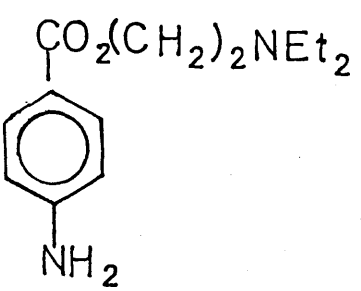

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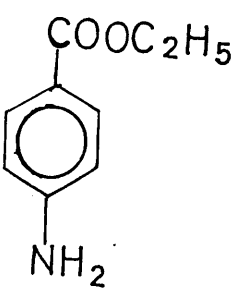

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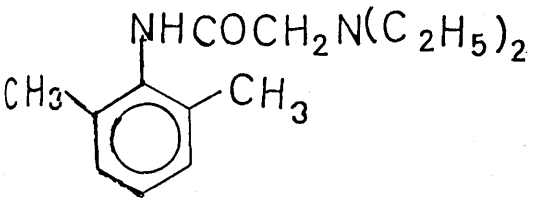

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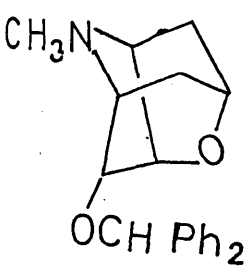
(95) - (100)

See Table 2



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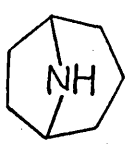

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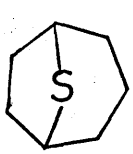

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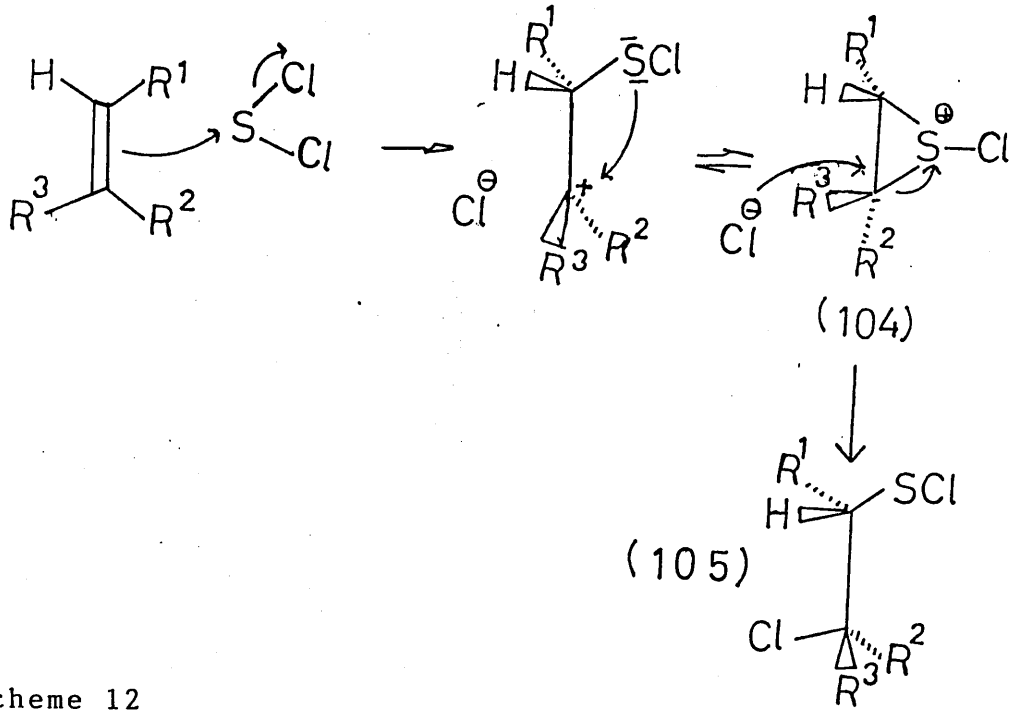
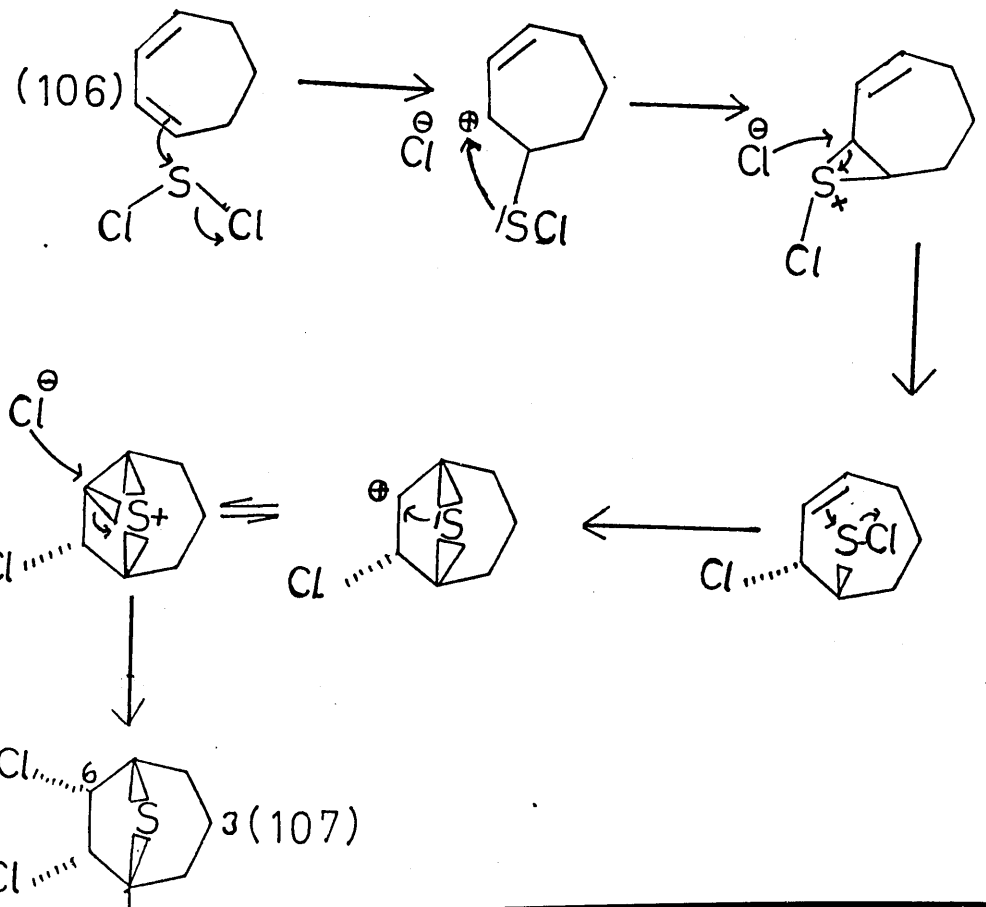
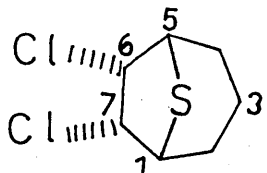
Scheme 11



Scheme 12





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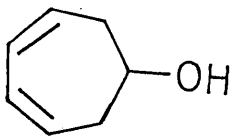

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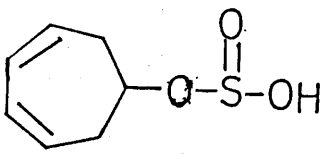

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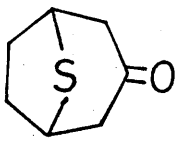

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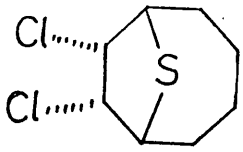

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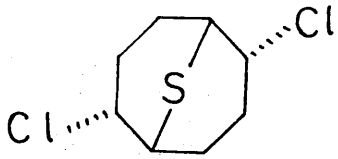

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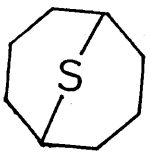

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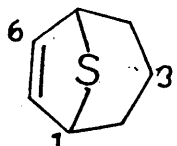

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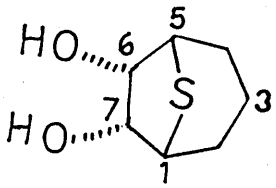

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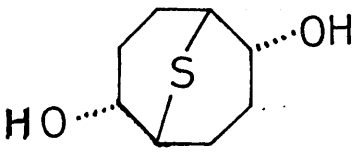

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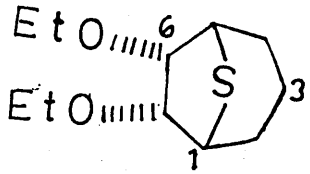

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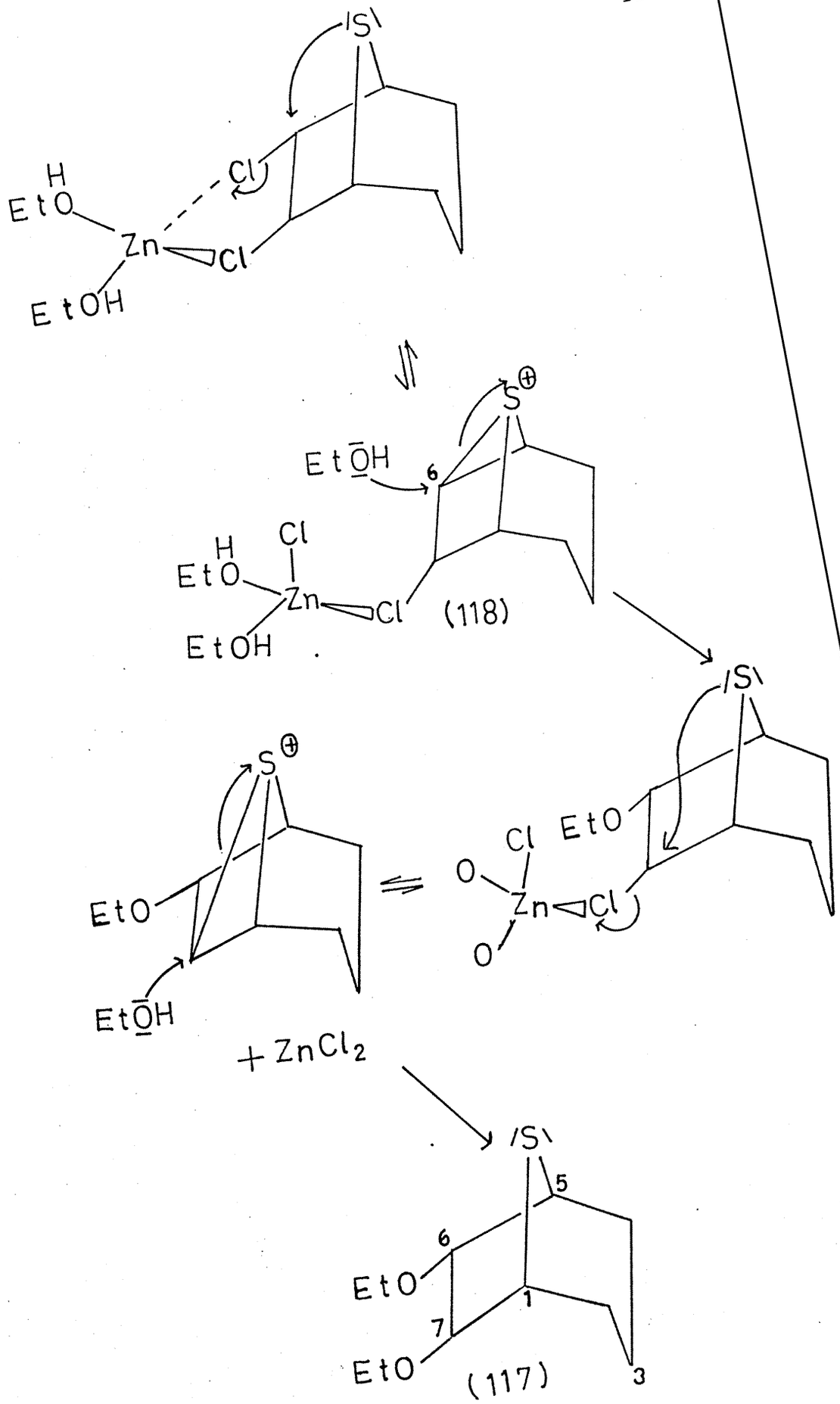
Scheme 13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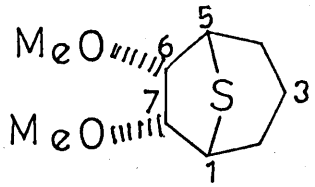
H
Zn
Cl
Cl
EtOH
EtO
H
Cl
Zn
Cl
EtOH
(118)
6
EtOH
EtO
Cl
O
Zn
Cl
O
EtO
EtOH
+ ZnCl2
EtO
EtO
(117)
1
3
5
6
7



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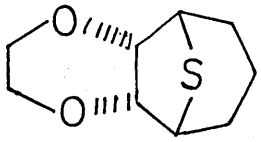

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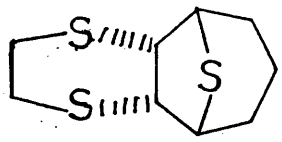

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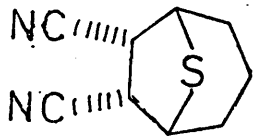

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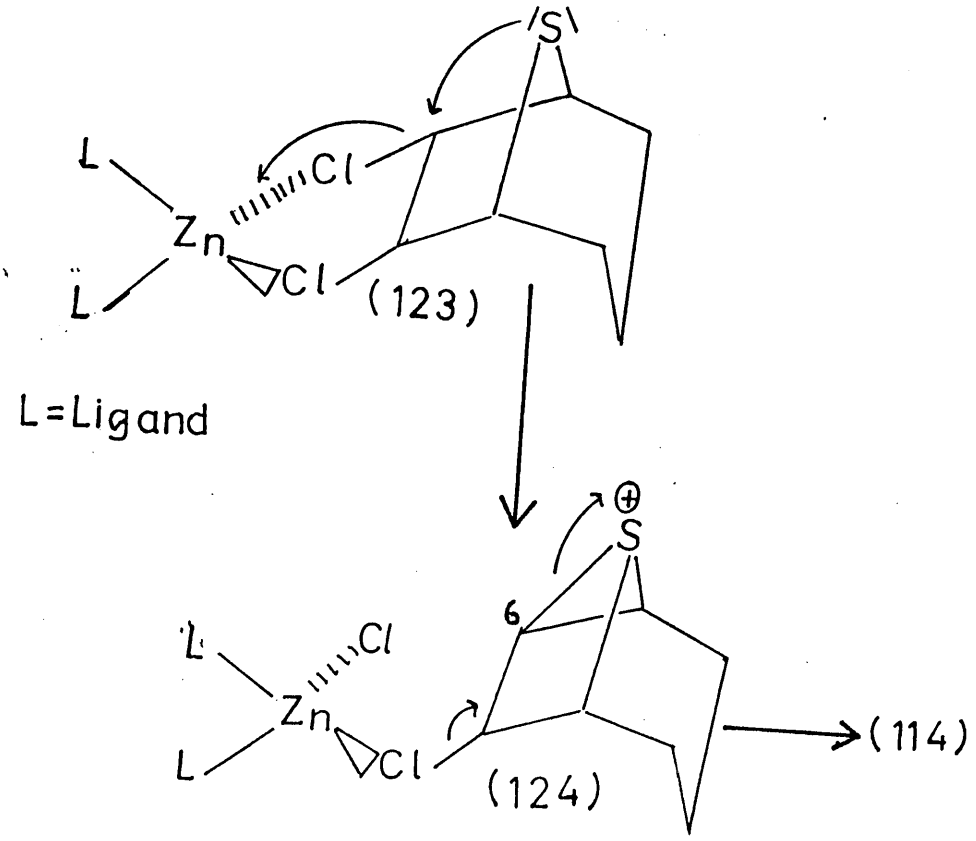
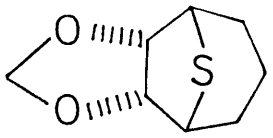
Scheme 14





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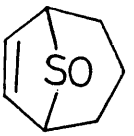

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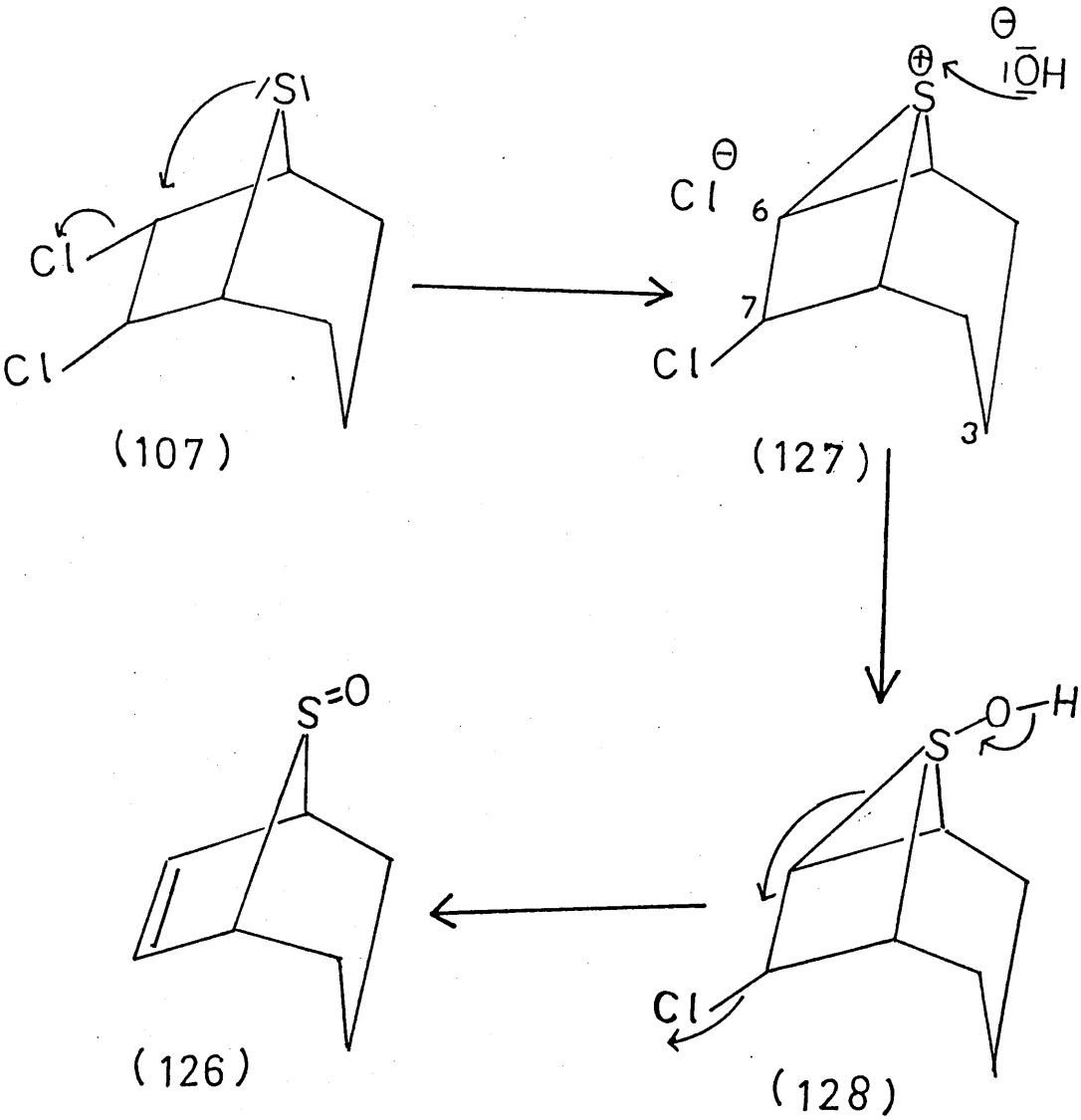
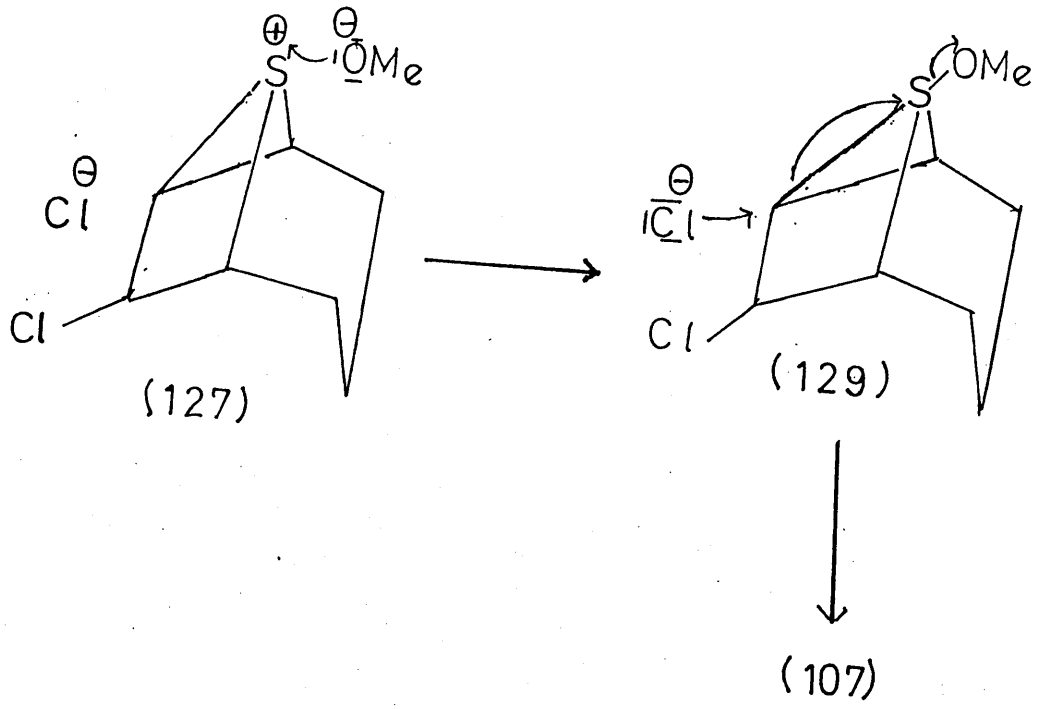
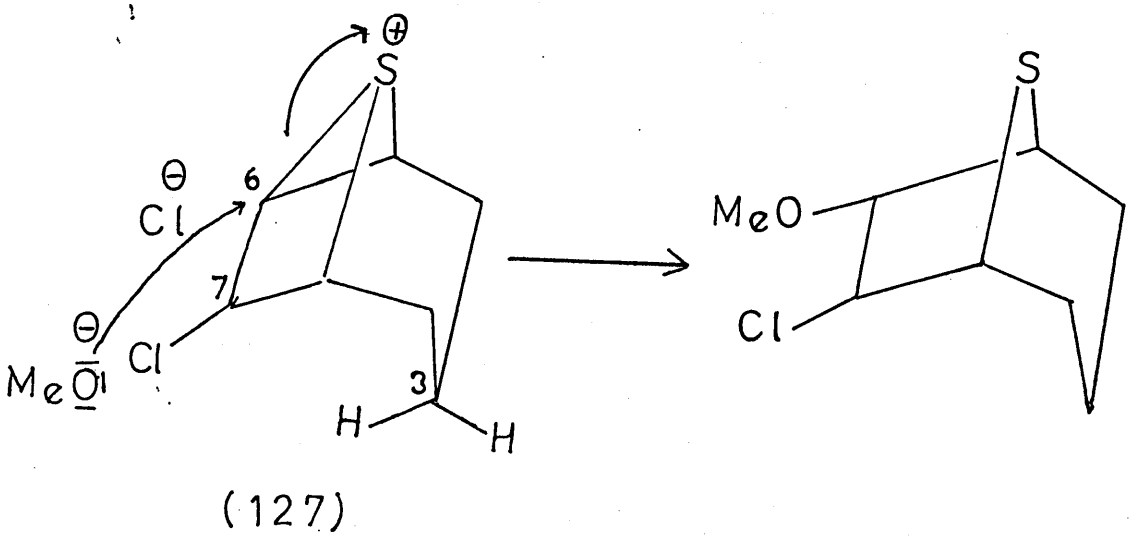
Scheme 15



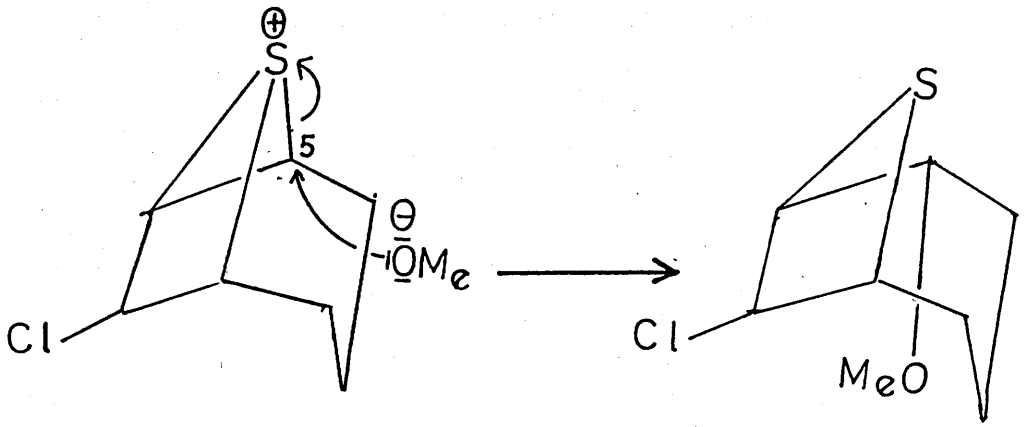
Scheme 16



Scheme 17



Scheme 18



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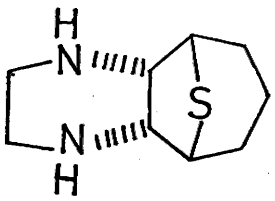

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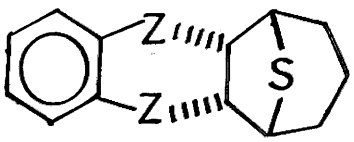
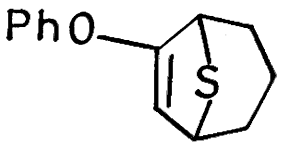


(132) Z = NH

(133) Z = O



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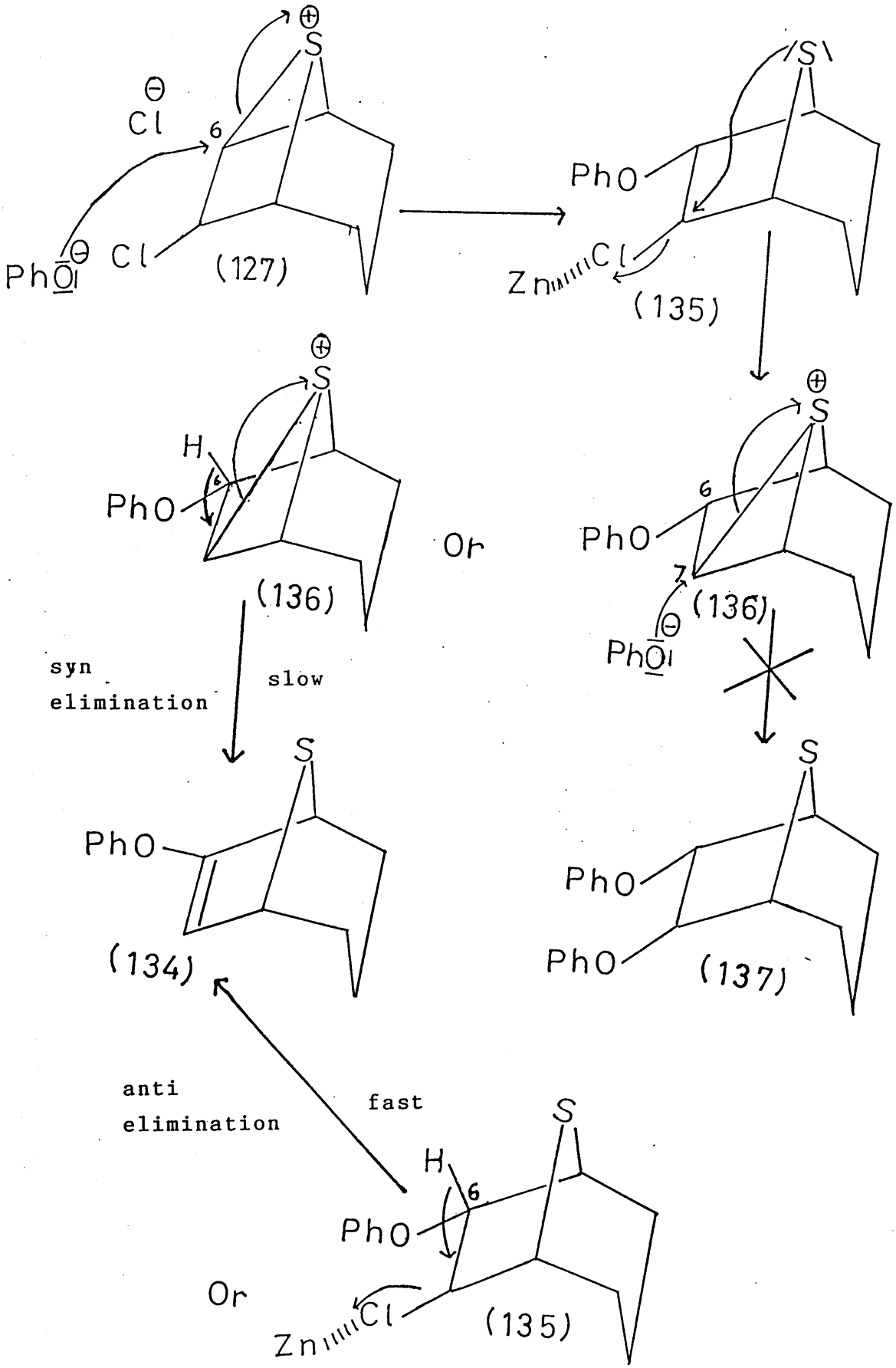
Scheme 19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syn
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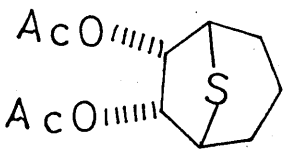
(135)



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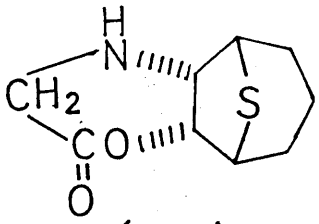

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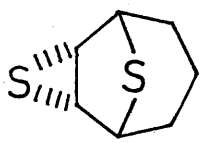

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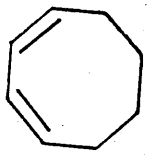

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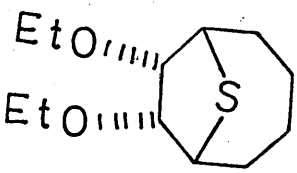

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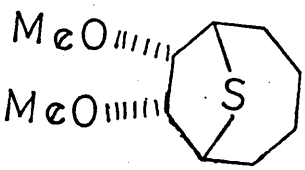

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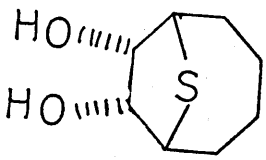

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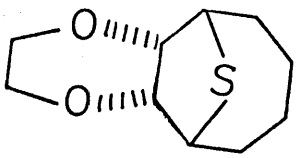

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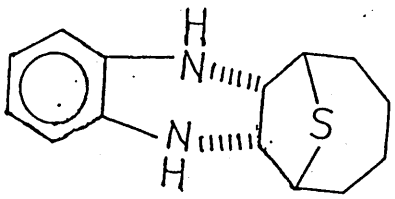

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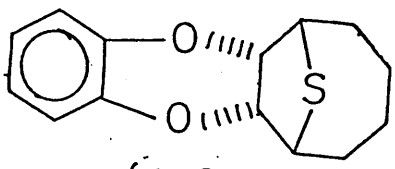

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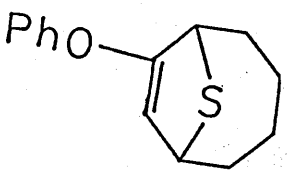

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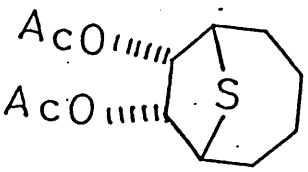

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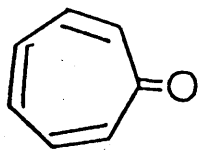

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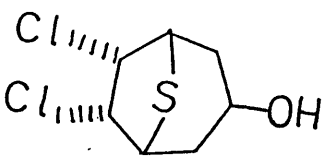

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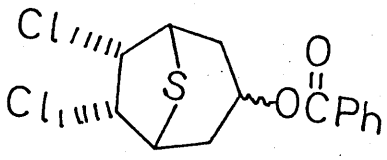

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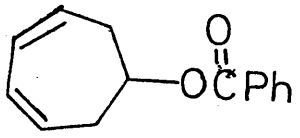

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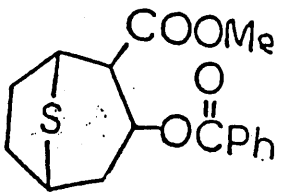

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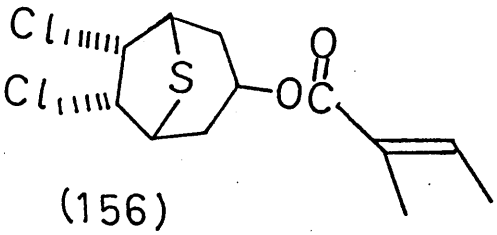

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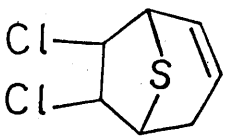

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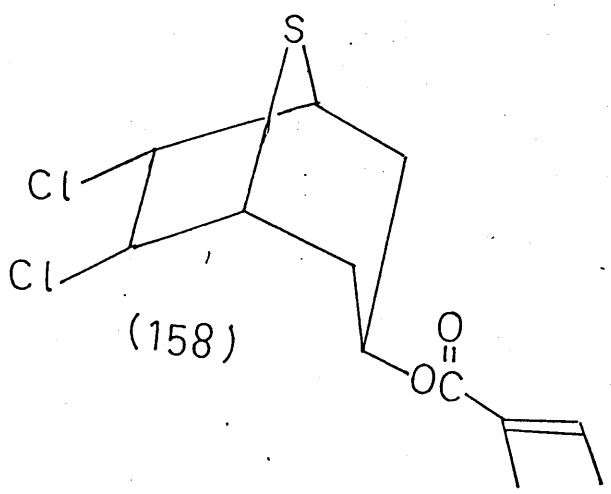

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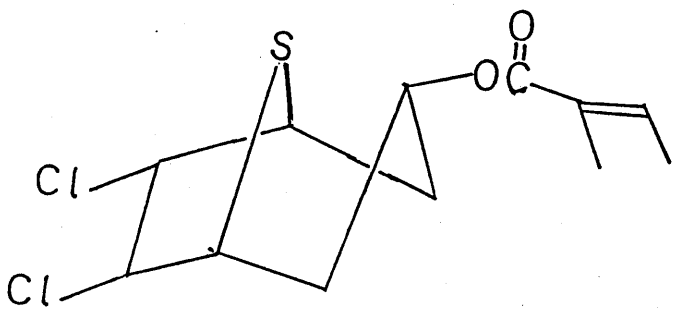

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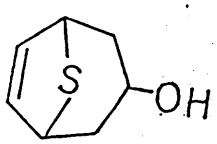

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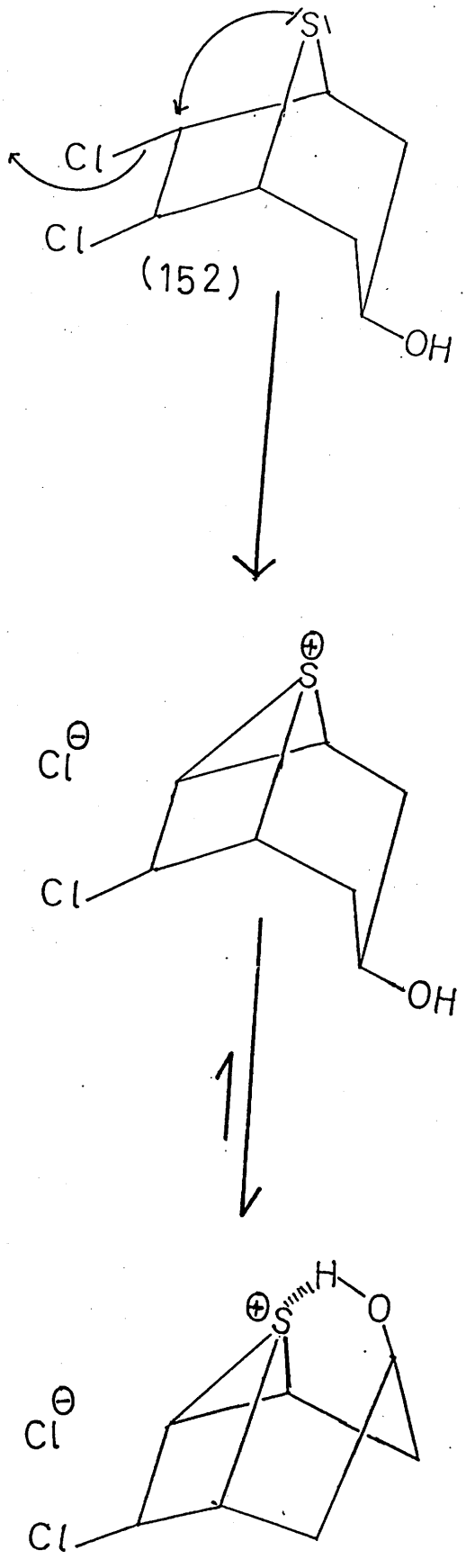
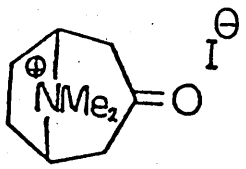
Scheme 20





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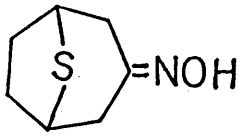

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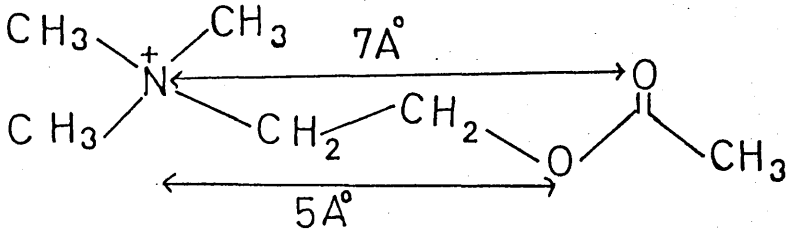
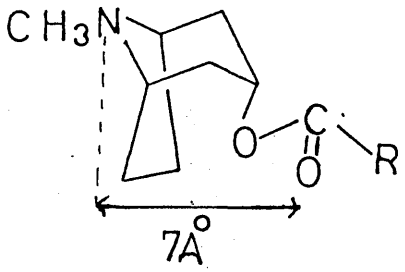
FIGURES

Fig. 1





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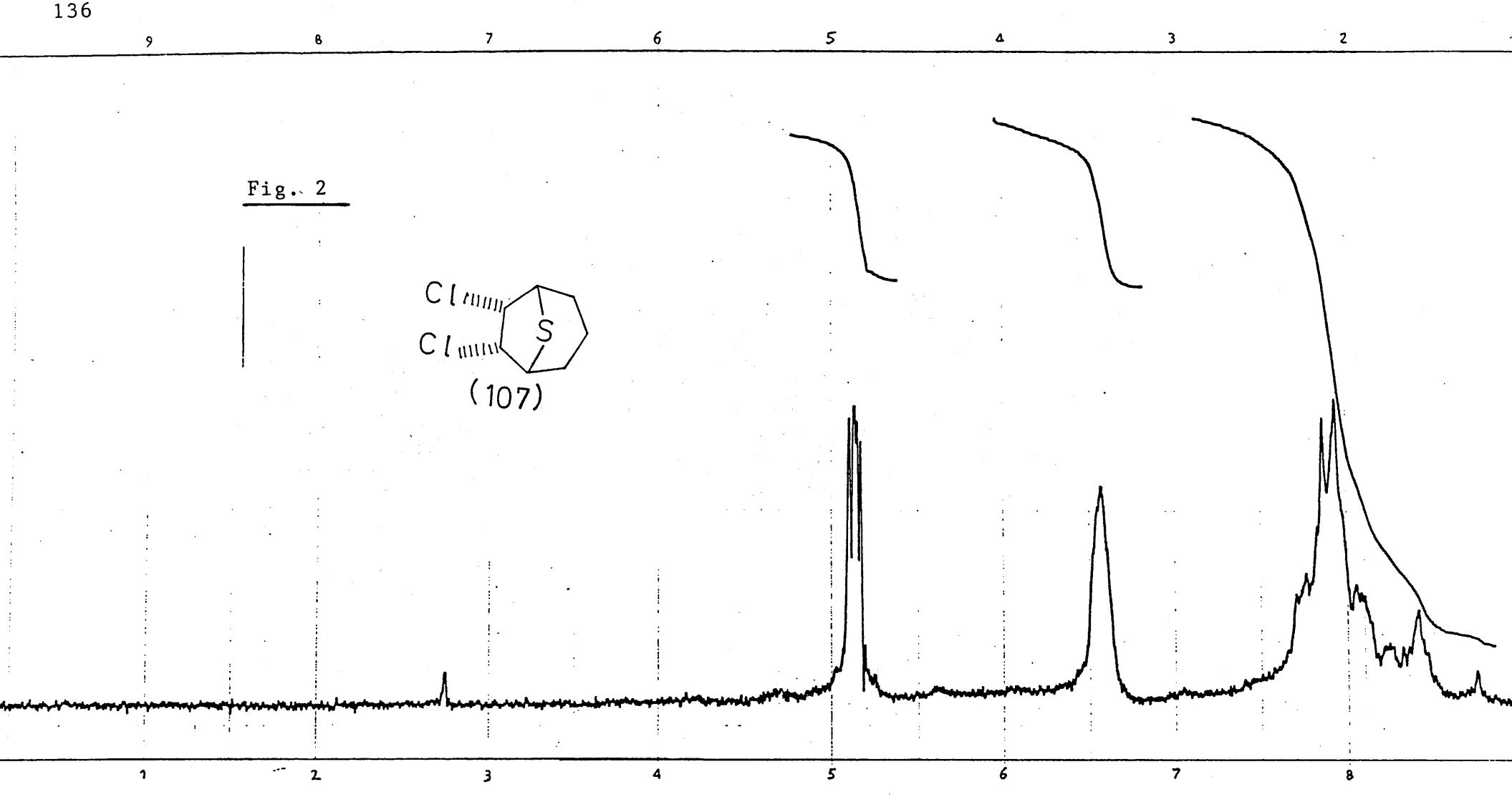


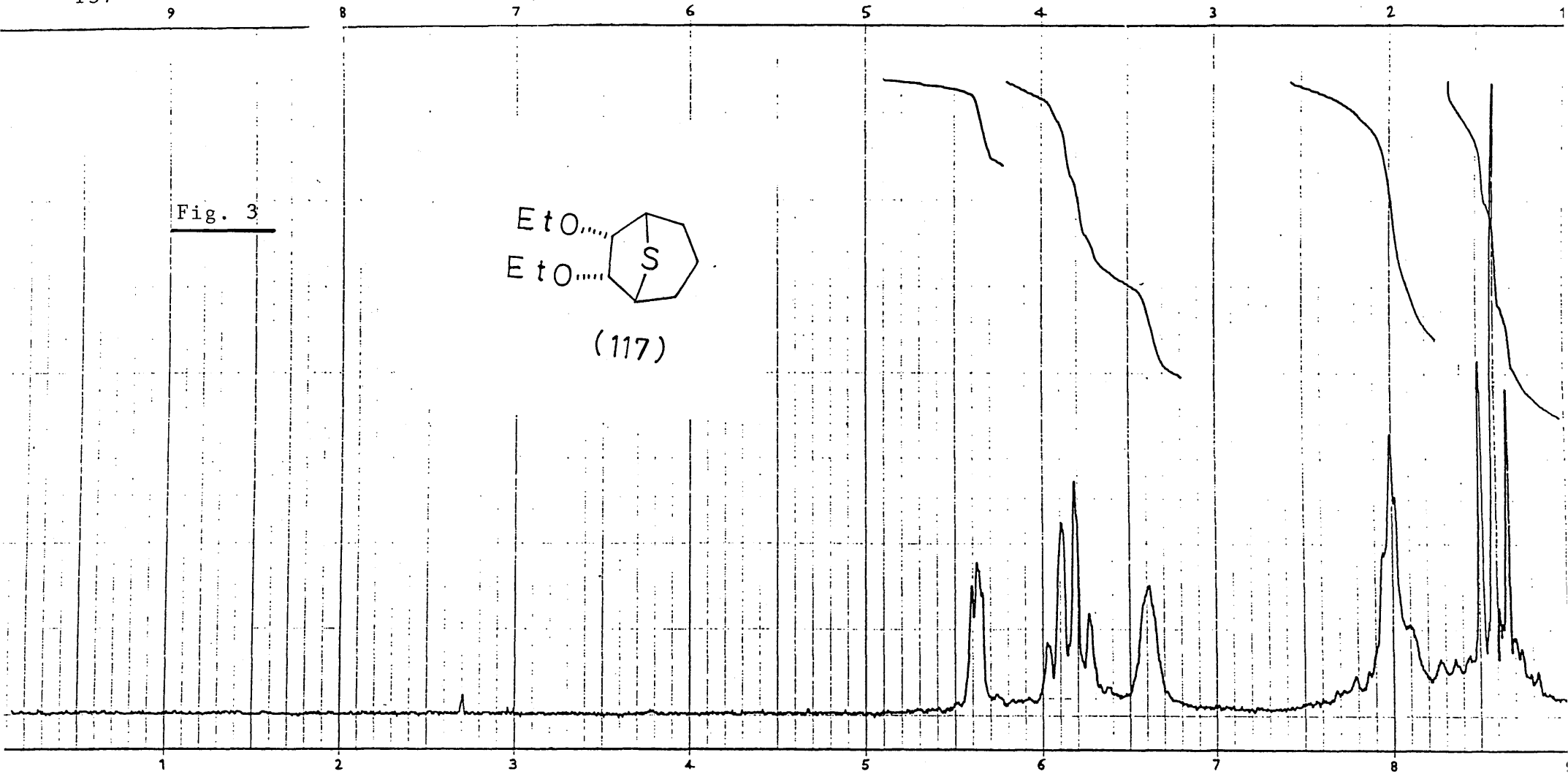
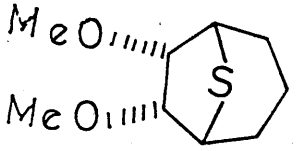


Fig. 3

Fig. 4



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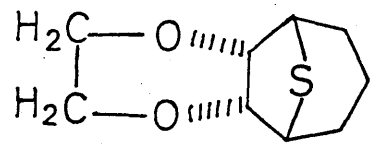

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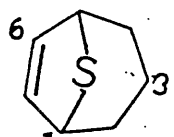

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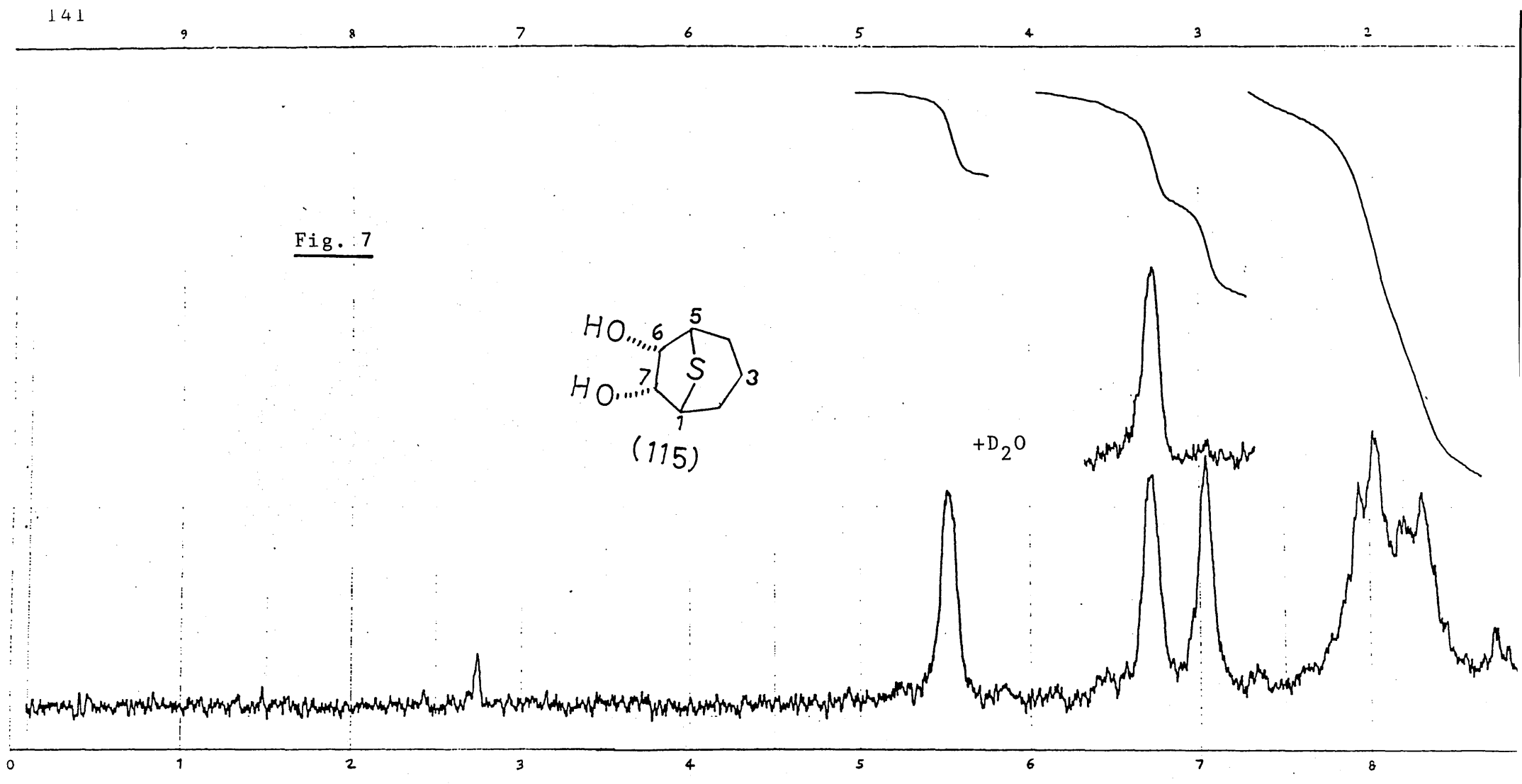

Fig. 7

Fig. 8

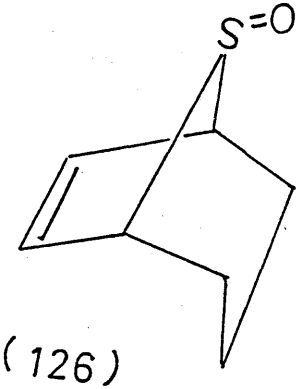

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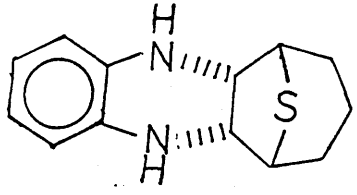
Fig. 9



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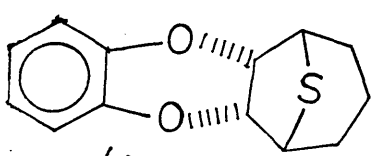

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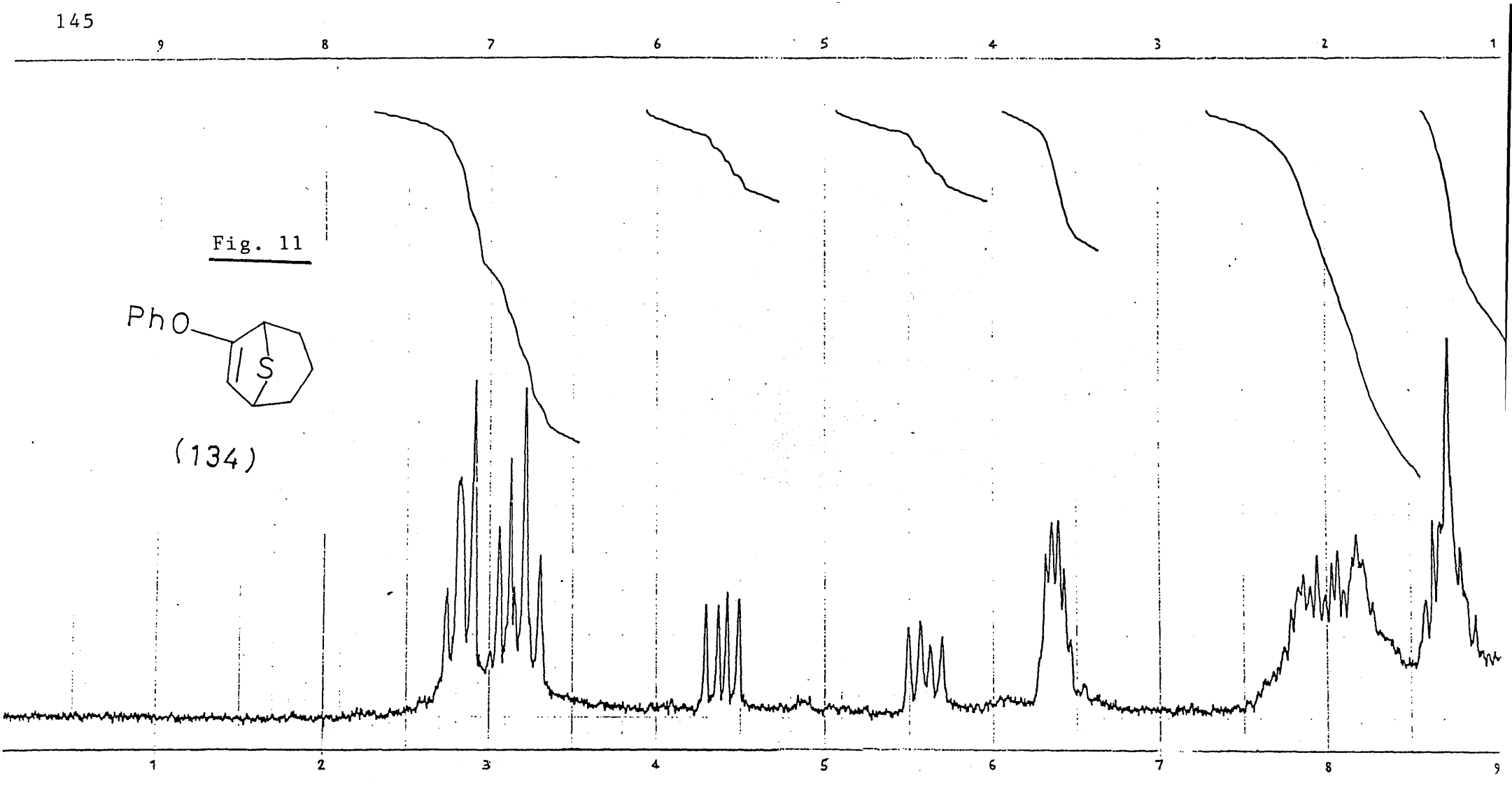
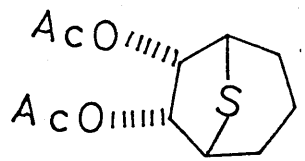


Fig. 11

(134)

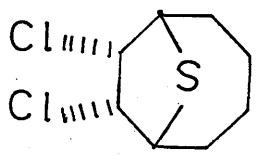
Fig. 12



(138)

Ac = CH_3CO

Fig. 13



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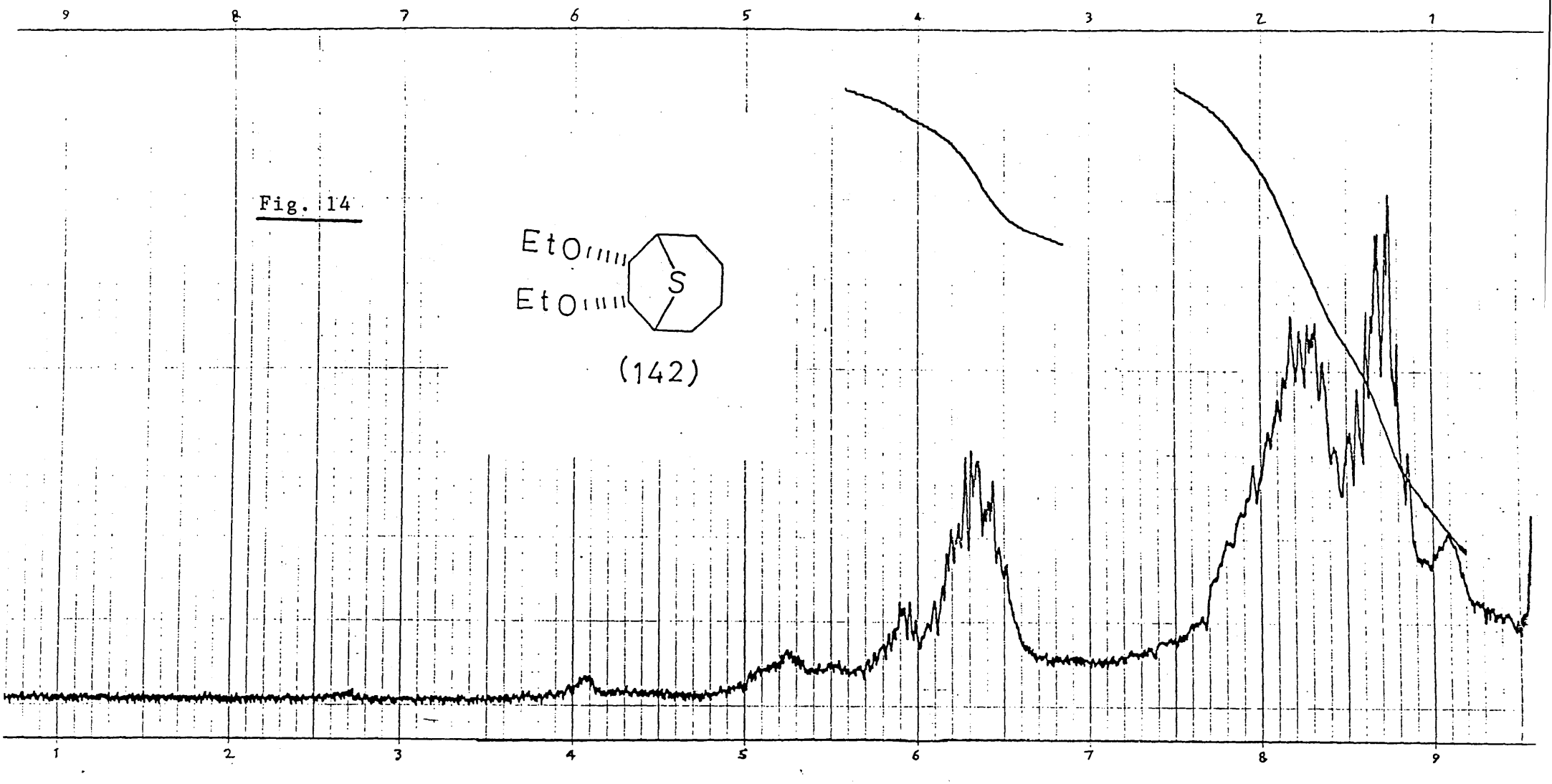


Fig. 14

(142)

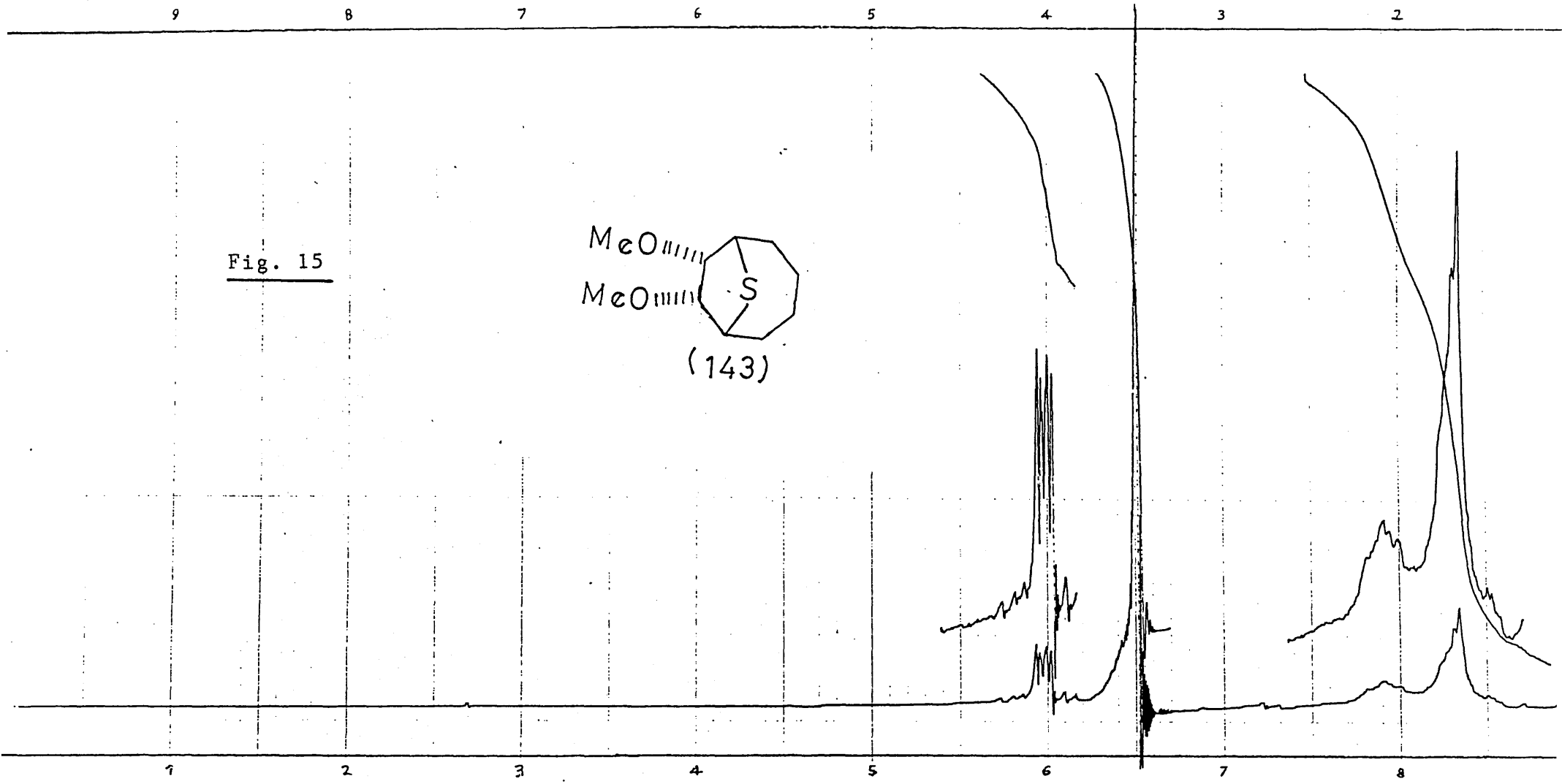


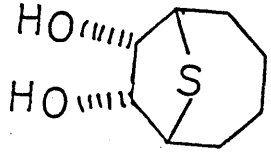
Fig. 15

(143)

Fig. 16

(144)

Fig. 17



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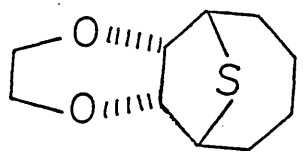

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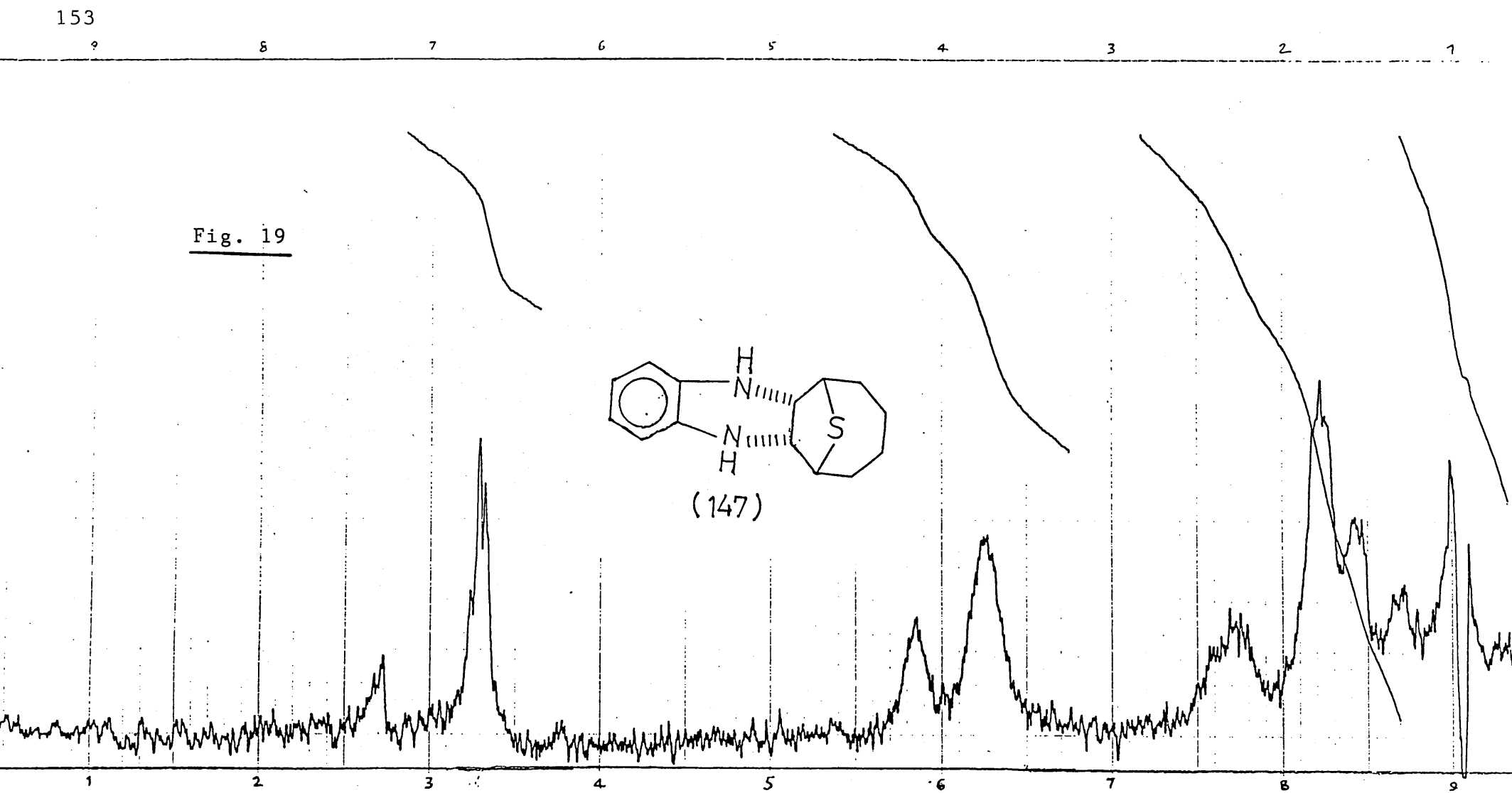

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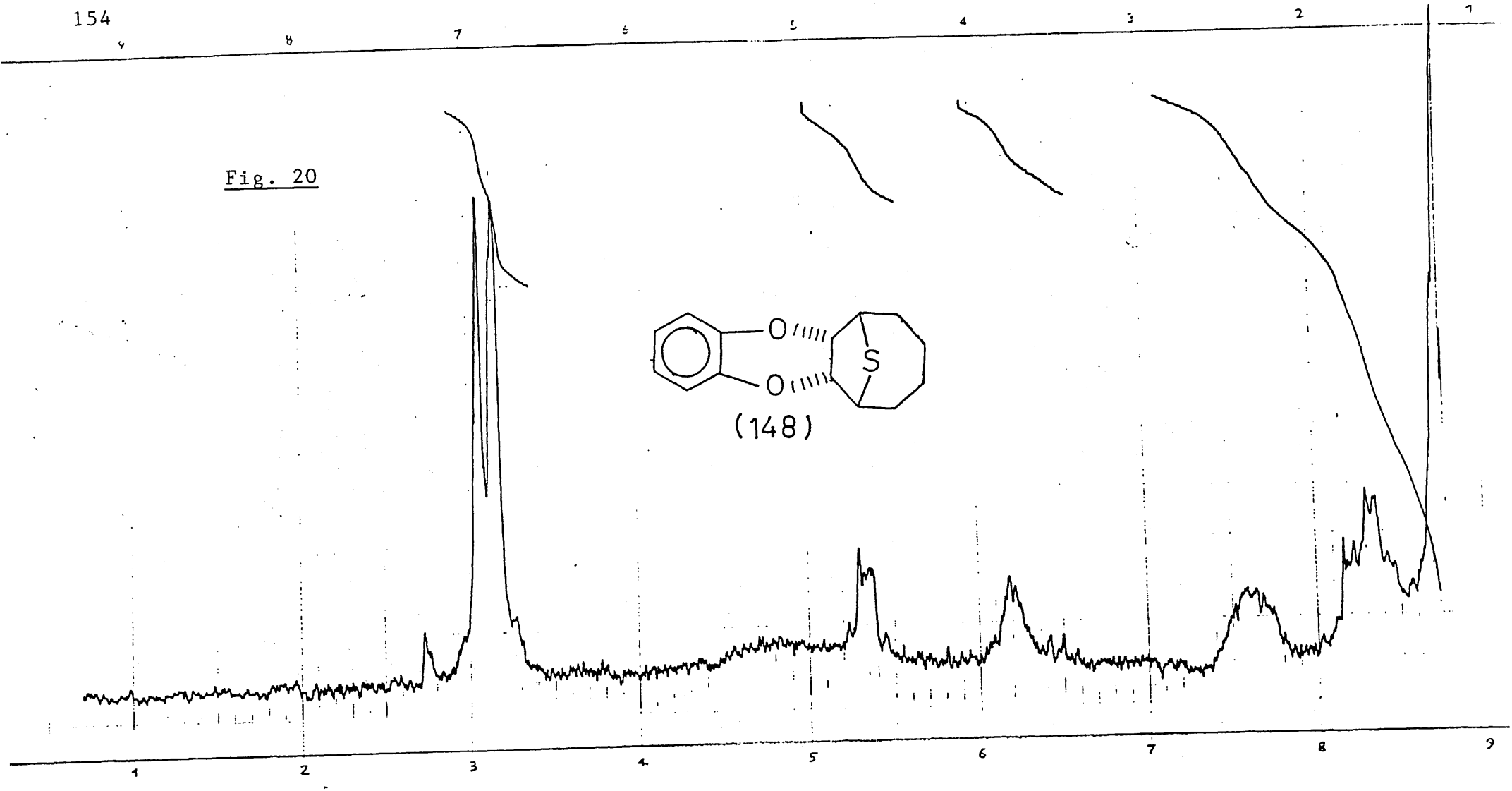

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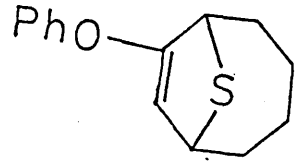

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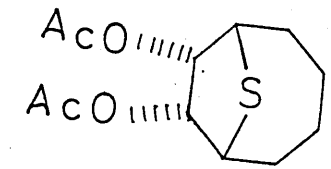

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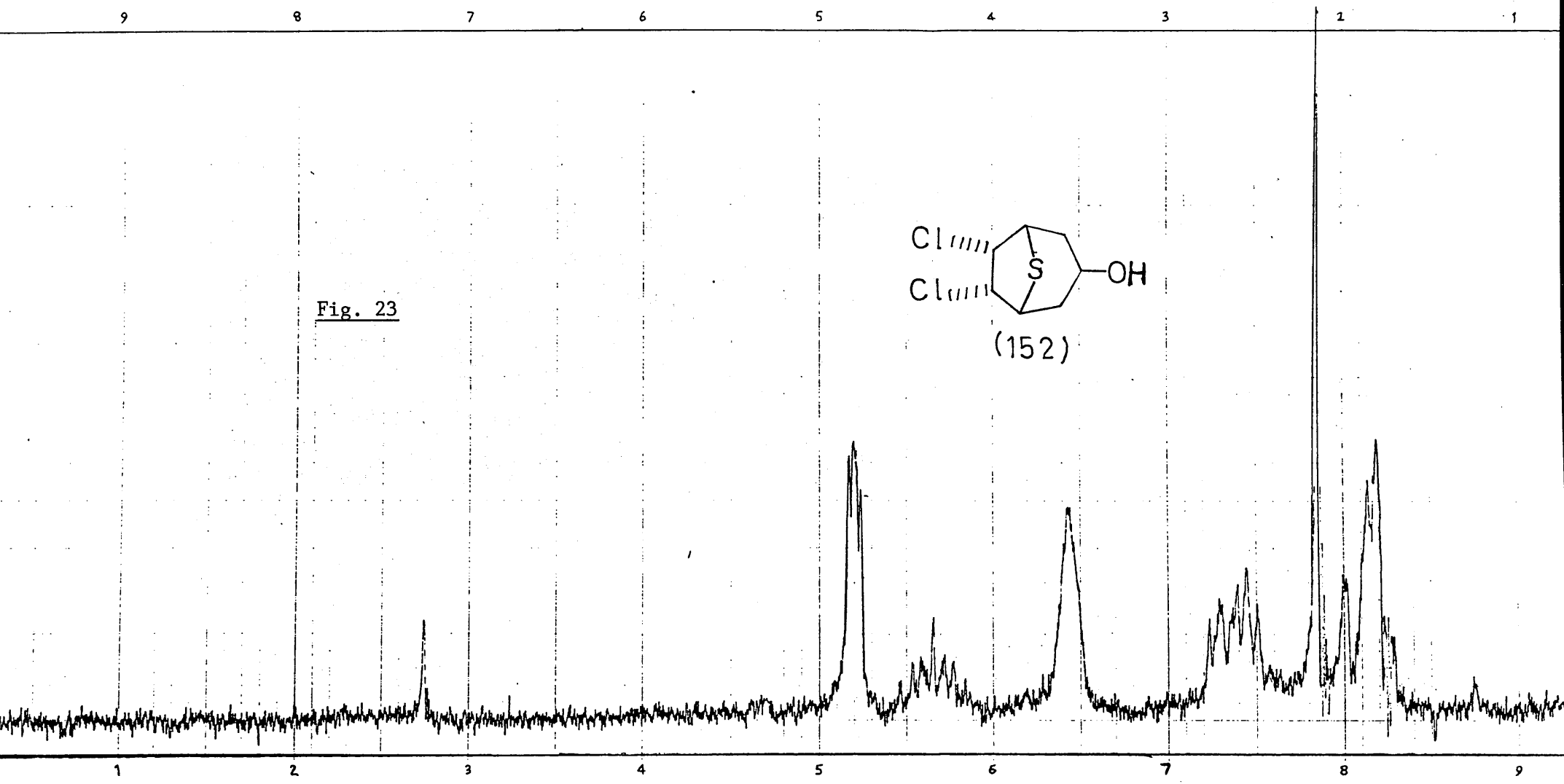
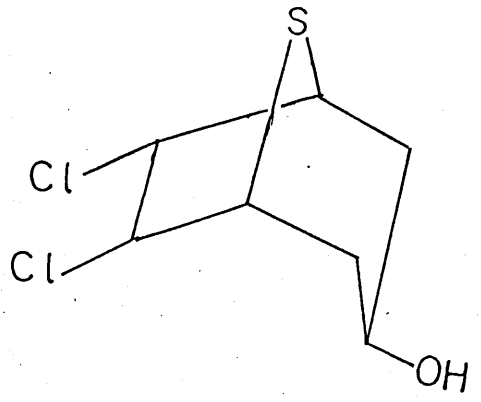


Fig. 23

(152)



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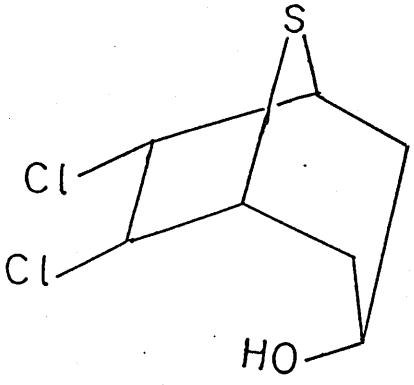

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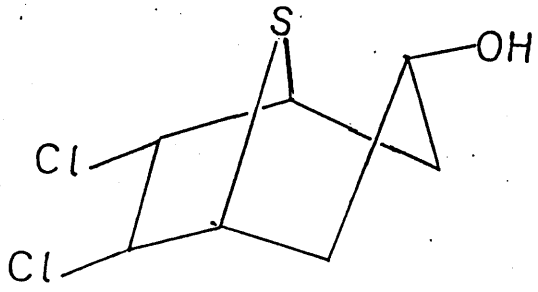

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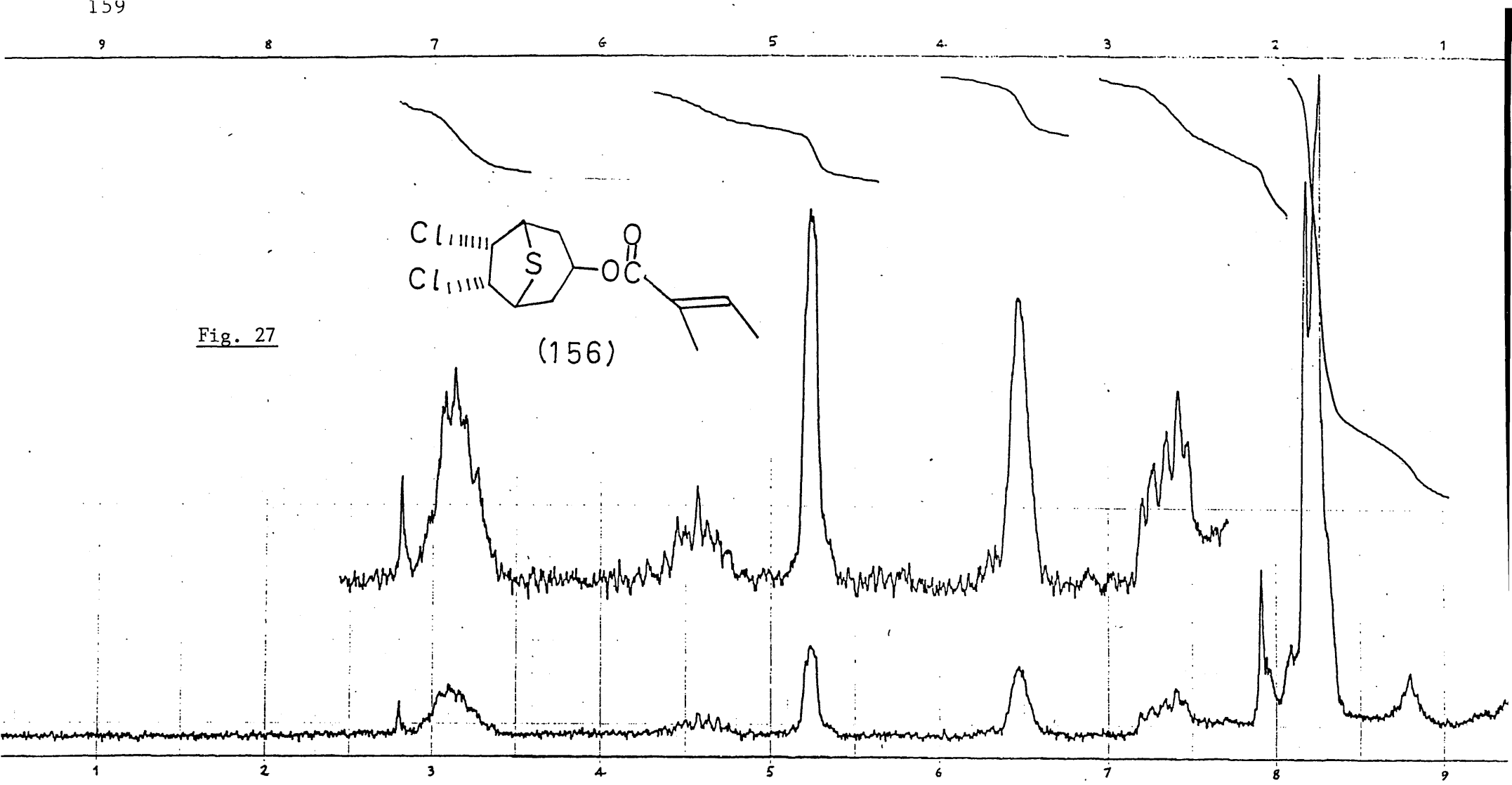


(156)

Fig. 27

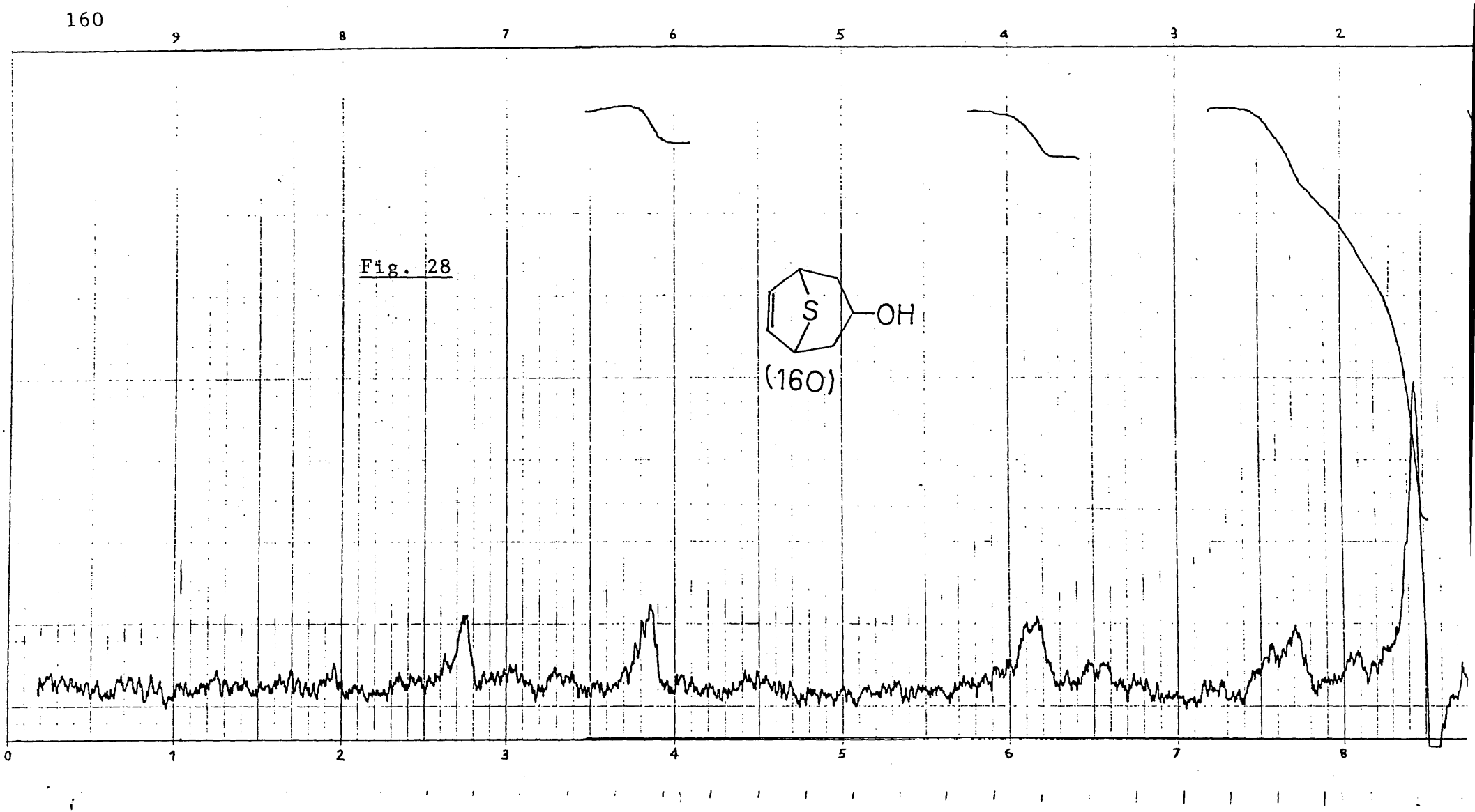
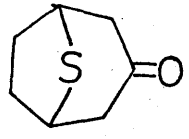


Fig. 28

(160)

Fig. 29



(110)

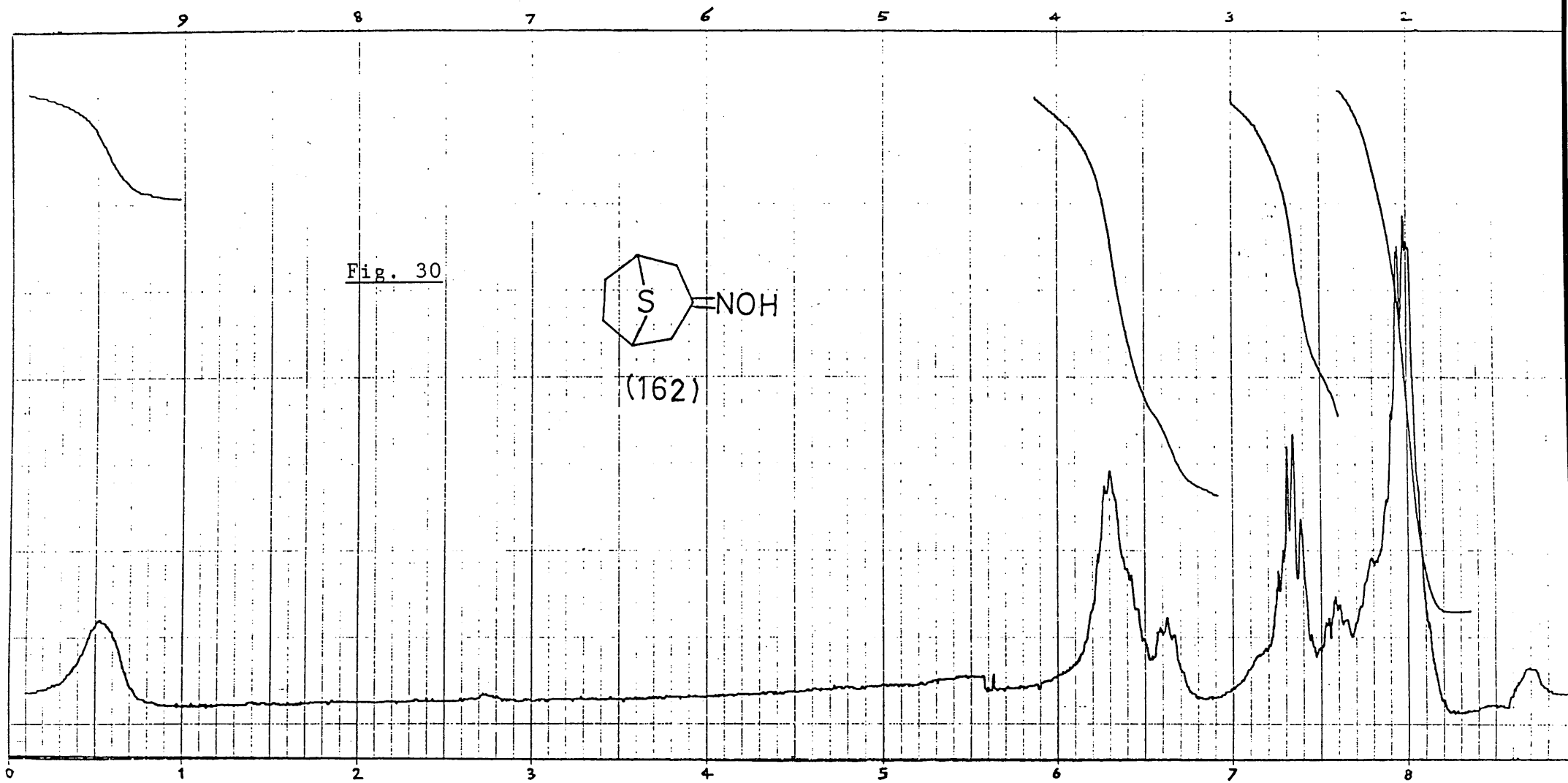


Fig. 30

(162)

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